

# ***N*-Heterocyclic Carbenes in Pd<sup>0</sup>-Catalyzed C(sp<sup>3</sup>)–H Activation**

**Inauguraldissertation**

zur

Erlangung der Würde eines Doktors der Philosophie

vorgelegt der

Philosophisch-Naturwissenschaftlichen Fakultät

der Universität Basel

von

Nadja Elena Niggli

Basel, 2022



Genehmigt von der Philosophisch-Naturwissenschaftlichen Fakultät auf Antrag von

Prof. Dr. Olivier Baudoin

Prof. Dr. Thomas R. Ward

Prof. Dr. Martin Albrecht

Basel, 14.12.2021

Prof. Dr. Marcel Mayor



## Acknowledgements

First, I would like to thank Prof. Dr. Olivier Baudoin for giving me the opportunity to pursue my PhD-studies during the last four years in his group. I am grateful for my personal and scientific development which I experienced during this time under his supervision. I appreciate the freedom he gave me in pursuing my projects and the fruitful discussions.

I would like to thank Prof. Dr. Thomas Ward for accepting to be my co-supervisor and for the constructive feedback he provided during our annual research meetings.

Then, I would like to thank Prof. Dr. Martin Albrecht for accepting to be the external referee for this PhD thesis.

Many thanks go to the former and present members of the Baudoin group, Marcus, Titou, Ke-Feng, Ronan, Weilong, Romain, Antonin, Yann, Pierre, David, Kevin, Stefania, Shu-Min, Marco, Anton, Takeru, Oleks, Rafael, Maria, Andrea, Soohee, and Matthew. I really appreciate the constructive discussions and the support I was allowed to experience during my time in this group. Also, I enjoyed the fun time we spent together during our lunch breaks, group excursions, and apéros.

Special thanks go to Shu-Min for creating a nice work environment in lab 202 and for all her moral support during difficult times.

Thanks to Diana, for her great work during her master thesis. Further thanks go to Thomas who worked with me during his Wahlpraktikum.

I would like to thank Stefania and Matthew for proofreading this thesis and for their helpful advice. I really appreciate your help and the time you have invested in supporting me.

I am grateful for all the nice people I got to know here in the department during the course of the last four years. I enjoyed talking to you and the support in all different kinds of matters. Merci dä Chäuerching Daniel, Raphi. Thomas und Pasci für ihri Hiuf bi mine NMR Problem, o wed Spektre nid immer optimau si gsi. I ha üsi Fүүrabebier im Chäuer immer gnosse! Thanks to the Mayor group and Björn for their hospitality and the nice times we spent together after work.

I am very grateful for the special moral support I received during the last year and while finishing my thesis, thank you, Stefania, Maria, Jovana, Bapu, and Camilo.

I danke mire Familie für au die Ungerstützig woni ha brcho i aune mögleche Aglägäheite. Ohni öich wäri nid woni hüt bi und das bedüdet mir sehr viu!

I danke ar Jovana, Bapu, Barbara, Sämi, Sara, Phippu, Anna und Vali für üsi Fründschaft womer sit afangs Studium hei und d'Zite womer zämä vrbringe bim Pizza ässä oder Aareböötle! Äs grosses Dankeschön ad Funny Bunnies Sheri, Nina, Caro, Domi, Döne, Kossi, Fabi und Oli, merci für öichi Fründschaft, bedingigslosi Ungerstützig und Vrständniss sit au dene Jahr wo mir üs scho kenne.

## Abstract

The direct functionalization of C(sp<sup>3</sup>)-H bonds by transition metals has emerged as an efficient strategy in the streamlined synthesis of valuable molecules. However, translating this reactivity to an asymmetric transformation has thus far been only moderately successful. A limited array of motifs was accessed in high enantioselectivity by Pd<sup>0</sup>-catalyzed C(sp<sup>3</sup>)-H arylation during the course of the last 10 years. In this thesis, we aimed to address this shortcoming with the development of new asymmetric methods for the construction of enantioenriched cyclic products. In the first project, different indanone products were synthesized in excellent yields and moderate enantioselectivity by C(sp<sup>3</sup>)-H arylation. Strikingly, IBiox-type ligands generally exhibited an exceptional reactivity and product selectivity compared to other classes of ligands. In addition, the IBiox ligands performed best in terms of enantioinduction, but still with limited stereoselectivity. Based on these findings, new IBiox-derived NHC ligands were designed with the intention to improve their stereoinducing properties in the envisioned C(sp<sup>3</sup>)-H arylation transformation. This plan was pursued in a second project wherein a new IBiox*t*BuMe<sub>4</sub> ligand was synthesized and successfully employed in the challenging desymmetrization of enantiotopic protons in the construction of indanes. In addition to this, the synthetic sequences towards two further ligands were initiated and are now close to completion. In parallel, new carboxylate bearing NHC-complexes were designed, synthesized, and characterized. Careful experimentation and analysis of the data revealed the delicate nature of these complexes which accounts for their unsatisfactory performance in the envisioned reactions. Interestingly, during the course of these investigations, a β-lactam product was identified arising from a new 1,4-Pd shift and subsequent C(sp<sup>3</sup>)-C(sp<sup>3</sup>) bond formation. This new reactivity was exemplified in the synthesis of biologically interesting β-lactams. In addition, mechanistic studies were performed to disclose the nature of this transformation. IBiox-type ligands showed a superior product selectivity for this novel reactivity and proved to be key to its success.

**Keywords:** C-C coupling, C-H activation, enantioselectivity, palladium, spirocycles, indanone, NHCs, bifunctional NHC-complexes, 1,4-Pd shift, β-lactam.

Nadja Elena Niggli  
Group of Prof. Dr. O. Baudoin  
Department of Chemistry  
University of Basel  
St. Johanns-Ring 19  
CH-4056 Basel  
Switzerland



## Published work during the PhD

- T. Miyakoshi,<sup>[+]</sup> **N. E. Niggli**,<sup>[+]</sup> O. Baudoin, Remote Construction of N-Heterocycles via 1,4-Palladium Shift-Mediated Double C–H Activation. *Angew. Chem. Int. Ed.* **2022**, ASAP. doi.org/10.1002/anie.202116101.  
<sup>[+]</sup>contributed equally.
- **N. E. Niggli**, O. Baudoin, Design of Chiral NHC-Carboxylates as Potential Ligands for Pd-Catalyzed Enantioselective C–H Activation. *Helv. Chim. Acta* **2021**, *104*, e2100015.
- R. Melot, M. Zuccarello, D. Cavalli, **N. Niggli**, M. Devereux, T. Bürgi, O. Baudoin, Palladium(0)-Catalyzed Enantioselective Intramolecular Arylation of Enantiotopic Secondary C–H Bonds. *Angew. Chem. Int. Ed.* **2021**, *60*, 7245–7250.



## Abbreviations

"t"	apparent triplet
%V <sub>bur</sub>	percentage of buried volume
%wt	weight percentage
Ac	acetyl
AcOH	acetic acid
Ad	adamantyl
Alk	alkyl
aq.	aqueous
Ar	aryl
atm	atmospheric pressure
B	base
BCB	benzyocyclobutane
BDE	bond dissociation energy
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
BOM	benzyloxymethyl-
BOX	bisoxazoline
Bu	butyl
c	concentration
cat.	catalytic
Cbz	benzyl carbamate
CDC	cross dehydrogenative coupling
cHex	cyclohexane
CMD	concerted metalation deprotonation process
CPME	cyclopentylmethyl ether
Cy	cyclohexyl
d.r.	diastereomeric ratio
DAST	diethylaminosulfur trifluoride
dba	<i>trans,trans</i> -dibenzylidenacetone
DCE	dichloroethane
DCM	dichloromethane
DFT	density functional theory
DG	directing group
DMAP	dimethylamino pyridine
DME	dimethoxyethane
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
%ee	enantiomeric excess
<i>e.g.</i>	<i>for example</i>
e.r.	enantiomeric ratio
EA	ethyl acetate
equiv.	equivalent
ESI-MS	electrospray ionisation coupled with mass spectrometry

Et	ethyl
FC	flash column chromatography
FG	functional group
GC	gas chromatography
GC-MS	gas chromatography coupled with mass spectrometry
HFIP	hexafluoro <i>isopropanol</i>
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectroscopy
<i>i</i> Pr	<i>iso</i> -propyl
IR	infrared
L	ligand
LiHMDS	lithium bis(trimethylsilyl)amide
<i>m</i>	<i>meta</i>
Me	methyl
MHz	megahertz
mol%	mol percent
MOM	methoxymethyl-
mp	melting point
Ms	mesyl
MS	molecular sieves
n.d.	not determined
NHC	<i>N</i> -heterocyclic carbene
NMM	<i>N</i> -methyl morpholine
NMR	nuclear magnetic resonance
<i>o</i>	<i>ortho</i>
<i>o</i> /n	overnight
OAc	acetate
OPiv	pivalate
OTf	triflate
<i>p</i>	<i>para</i>
PE	petroleum ether
pent	pentane
Ph	phenyl
Piv	pivaloyl
ppm	parts per million
quant.	quantitative
R <sub>f</sub>	retardation factor
rpm	rounds per minute
rt	room temperature
sat.	saturated
SM	starting material
TADDOL	$\alpha,\alpha,\alpha',\alpha'$ -tetraaryl-2,2-disubstituted 1,3-dioxolane-4,5-dimethanol
TBAB	tetrabutylammonium bromide
TBAC	tetrabutylammonium chloride

TBDPS	<i>tert</i> -butyldiphenylsilane
TBS	<i>tert</i> -butyldimethylsilane
<i>t</i> Bu	<i>tert</i> -butyl
TEP	Tolman electronic parameter
TES	triethylsilane
Tf	triflic/trifluoromethansulfonate
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilane
TMSOTf	trimethylsilyltrifluoromethansulfonate
tol	tolyl
UV	ultra violet
$\theta$	cone angle
$\pi$ -cin	$\pi$ -cinnamyl



## Table of Content

Acknowledgements .....	I
Abstract .....	III
Published Work during the PhD.....	V
Abbreviations .....	VII
1 General Introduction .....	1
1.1 C–H Activation.....	2
1.1.1 Palladium Catalyzed C–H Activation .....	3
1.1.2 Pd-Catalyzed C(sp <sup>3</sup> )–H Activation .....	3
1.1.3 Directed Pd-Catalyzed C(sp <sup>3</sup> )–H Activation.....	4
1.1.4 Chelate Directed Pd <sup>II</sup> -Catalyzed C(sp <sup>3</sup> )–H Activation.....	5
1.1.5 Oxidative Addition Directed Intramolecular C(sp <sup>3</sup> )–H Activation.....	6
1.1.6 Valuable Cyclic Products <i>via</i> Intramolecular Unactivated C(sp <sup>3</sup> )–H Arylation..	7
1.1.7 Mechanism .....	8
1.1.8 Site Selectivity in the Intramolecular C(sp <sup>3</sup> )–H Activation.....	10
1.2 Enantioselective Intramolecular C(sp <sup>3</sup> )–H Arylation.....	10
1.3 1,4-Pd Shift.....	13
1.3.1 C(sp <sup>2</sup> ) to C(sp <sup>2</sup> ) Shift.....	14
1.3.2 C(sp <sup>2</sup> ) to C(sp <sup>3</sup> ) Shift.....	15
1.4 Introduction <i>N</i> -Heterocyclic Carbenes .....	18
1.4.1 Carbenes .....	18
1.4.2 <i>N</i> -Heterocyclic Carbenes.....	19
1.4.3 NHCs as Ligands.....	20
1.4.4 Electronic Properties .....	20
1.4.5 Steric Properties .....	21
2 Aim of this Thesis .....	23
3 Towards the Enantioselective C(sp <sup>3</sup> )–H Arylation in the Synthesis of Spirocycles.....	25
3.1 Introduction .....	25

3.2	Aim of this Project.....	27
3.3	Results and Discussion .....	28
3.3.1	Substrate Synthesis for Axially Chiral Spirocycles .....	28
3.3.2	Substrate Evaluation towards the Synthesis of Axially Chiral Spirocycles.....	28
3.3.3	Substrate Evaluation towards the Synthesis of Central Chiral Spirocycles.....	31
3.3.4	Reaction Optimization.....	33
3.3.5	Mono C(sp <sup>3</sup> )-H Arylation: Substrate Modification.....	35
3.3.6	Investigation towards the Spirocyclization .....	37
3.3.7	Towards Enantioenriched Indanones .....	38
3.3.8	Substrate Synthesis and Evaluation.....	38
3.3.9	Reaction Condition Optimization.....	40
3.3.10	Substrate and Reaction Condition Optimization.....	42
3.4	Conclusion and Outlook .....	44
4	Towards the Synthesis of Novel IBiox-Type Ligands .....	45
4.1	Introduction .....	45
4.2	Aim of this Project.....	47
4.3	Computational Characterization of the Envisioned Ligands.....	48
4.4	Results and Discussion .....	49
4.4.1	Synthesis towards an <i>N</i> -Analog of the IBiox <i>t</i> Bu ligand .....	49
4.4.2	Synthesis of IBiox <i>t</i> BuMe <sub>4</sub> •HOTf.....	52
4.4.3	Evaluation of IBiox <i>t</i> BuMe <sub>4</sub> in Enantioselective C(sp <sup>3</sup> )-H Arylations .....	53
4.4.4	Towards the Synthesis of IBiox6 <i>t</i> Bu•HOTf .....	55
4.4.5	Towards the Synthesis of IBioxMe <sub>2</sub> OR•HOTf.....	58
4.5	Conclusion and Outlook .....	63
5	Design of Chiral NHC-Carboxylates as Potential Ligands for Pd-Catalyzed Enantioselective C-H Activation.....	65
5.1	Introduction .....	65
5.2	Results and Discussion .....	67

5.2.1	Synthesis of Carboxylate Bearing Imidazolium Salts.....	67
5.2.2	Evaluation of the new Bifunctional NHC-Precursors .....	68
5.2.3	Synthesis of well-defined Pd-Complexes .....	69
5.2.4	Evaluation of the Bifunctional Pd-Complexes.....	71
5.2.5	Other tested Substrates .....	74
5.3	Conclusion and Outlook .....	76
6	Synthesis of $\beta$ -Lactams <i>via</i> 1,4-Pd Shift-Mediated Double C(sp <sup>3</sup> )-H Activation.....	77
6.1	Introduction .....	77
6.2	Aim of this Project.....	79
6.3	Results and Discussion .....	81
6.3.1	Ligand Effect and Reaction Optimization.....	81
6.3.2	Substrate Modifications.....	83
6.3.3	Second Reaction Optimization.....	84
6.3.4	Reaction Scope .....	85
6.3.5	Preliminary Mechanistic Investigations .....	88
6.3.6	Expansion of the Methodology .....	90
6.4	Conclusion and Outlook .....	91
7	General Conclusion .....	93
8	References .....	97
9	Experimental Part.....	107
9.1	Towards the Enantioselective C(sp <sup>3</sup> )-H Arylation in the Synthesis of Spirocycles	108
9.2	Towards the Synthesis of Novel IBiox-Type Ligands .....	127
9.3	Design of Chiral NHC-Carboxylates as Potential Ligands for Pd-Catalyzed Enantioselective C-H Activation.....	140
9.3.1	Reaction optimization .....	140
9.3.2	Procedures .....	145
9.4	Synthesis of $\beta$ -Lactams <i>via</i> 1,4-Pd Shift-Mediated Double C(sp <sup>3</sup> )-H Activation ..	165
9.4.1	Reaction Optimization.....	165

9.4.2	NMR Studies with Deuterium-Labeled Substrates .....	167
9.4.3	Procedures .....	169
10	References Experimental Part .....	203
11	Experimental Data: NMR, HPLC traces and Crystallographic Data .....	205

## 1 General Introduction

The synthesis of urea and acetic acid by Friedrich Wöhler<sup>[1]</sup> in 1828 and Hermann Kolbe<sup>[2]</sup> in 1845, respectively, set the stage for the emerging field of organic chemistry. The subsequent rapid development in the field can be measured by the construction of increasingly complex molecules by synthetic chemists. In 1856, Sir William Perkin synthesized mauveine, a molecule which exhibited much greater complexity than what had previously been achieved.<sup>[3]</sup> Owing to the rapid developments that had taken place, a variety of natural products were synthesized, which allowed the confirmation of their molecular structures. In parallel, other valuable molecules such as indigo<sup>[4]</sup> and acetylsalicylic acid were successfully synthesized.<sup>[2]</sup> The new insights and possibilities which arose from this development not only resulted in the establishment of the dye and pharmaceutical industries, but also provided new powerful methods for the construction of highly complex molecules.<sup>[3]</sup> In these traditional approaches, molecules are assembled by functional group interconversion, which generally occurs over multiple steps. Although the complex targets were accessed, usually a significant number of transformations were required which is not efficient when considering the resource or time economy on a synthesis. The development of transition metal-catalyzed cross-coupling reactions has enabled significant progress to be made towards solving the aforementioned limitations and revolutionized synthetic chemistry. These coupling reactions enable previously hard to synthesize, or impossible, new bonds in a straightforward and selective manner.<sup>[5]</sup> Their importance for the scientific community is highlighted by the Nobel prizes rewarded for the development of metathesis reactions in 2005<sup>[6,7]</sup> and Pd-catalyzed cross-couplings in 2010.<sup>[8,9]</sup> The impact of these protocols can further be seen by their continuous development and application in academia and industries to date.<sup>[10–14]</sup>

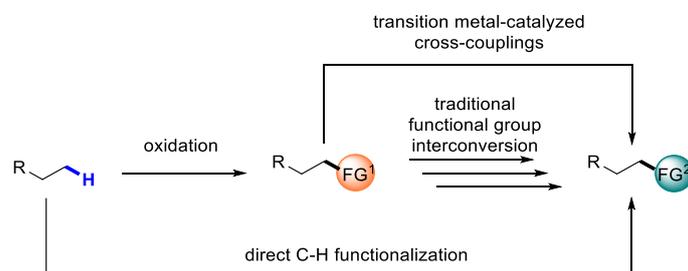


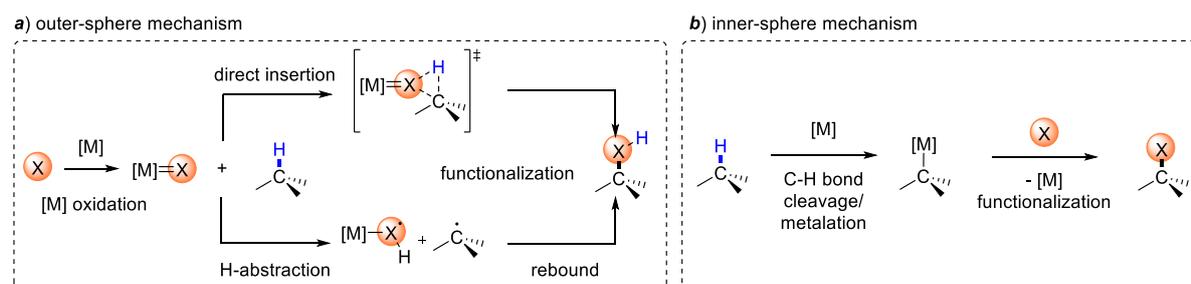
Figure 1. Functionalization of feedstock chemicals.

As a consequence of the required pre-functionalization and functional group interconversion in the traditional reactions and transition metal-catalyzed cross-couplings, these syntheses are less attractive from an economic point of view.<sup>[15]</sup> The ideal synthesis of a complex molecule of interest would arise from the direct functionalization of the cheapest and most abundant

feedstock chemicals (Figure 1). The direct activation of the ubiquitous “inert” C–H bonds in such chemicals would allow the construction of a higher complexity in a streamlined way, enabling a more step- and atom-economical synthesis while the generation of (super)stoichiometric waste generated during the functional group interconversions would be avoided. However, it has to be considered that the major challenge of such transformations is the strength of C–H bonds ( $C(\text{Ar})\text{--H} = 113 \text{ kcal/mol}$ ;  $\text{H}_3\text{CCH}_2\text{--H} = 101 \text{ kcal/mol}$ )<sup>[16]</sup> along with their ubiquity, which turns the selective activation of a specific bond very demanding.<sup>[17]</sup>

### 1.1 C–H Activation

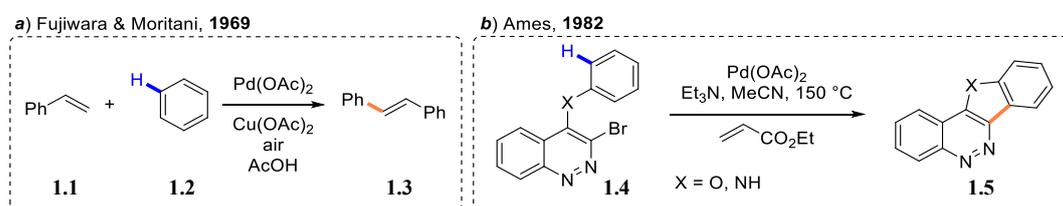
During the last decades, several approaches were elaborated for the direct functionalization of unactivated C–H bonds. In the transition metal-catalyzed version, two very different mechanisms are generally operating, as depicted in Scheme 1. The outer-sphere mechanism (**a**) is mimicking enzyme-catalyzed biological oxidation transformations, where a high oxidation state metal-complex  $[\text{M}]=\text{X}$  containing an active ligand X (carbene<sup>[18]</sup>, nitrene<sup>[19]</sup>, oxene<sup>[20]</sup>) is formed upon oxidation of the corresponding metal complex. In the second step, ligand X will react with a C–H bond, either *via* direct insertion or H-atom abstraction/radical rebound. In this reaction manifold, the substrate reacts directly with the coordinated ligand instead of the metal center. Typically, these reactions exhibit high selectivity for weaker C–H bonds such as benzylic, allylic,  $3^\circ$ , or  $\alpha$ - to heteroatom since it usually involves a radical and/or cationic character on the corresponding carbon. In contrast, the inner-sphere mechanism proceeds through a discrete organometallic species formed upon C–H bond cleavage by the metal complex (Scheme 1**b**). A subsequent functionalization of this species then affords the desired product. The selectivity of this process is directed by steric factors, the ligand environment, and the mechanism of the occurring C–H bond cleavage.<sup>[21]</sup> Traditionally, there are three different classifications of mechanism in operation in the C–H bond activation: oxidative addition for electron rich low valent transition metal-catalysts;  $\sigma$ -bond metathesis from electrophilic early transition metal-catalysts; and electrophilic activation catalyzed by late transition metal-complexes.<sup>[17]</sup>



Scheme 1. The two possible modes in transition metal-catalyzed C–H activation/functionalization.

### 1.1.1 Palladium Catalyzed C–H Activation

Palladium is one of the most prevalent catalysts employed in C–H functionalization. As an electron poor late transition metal, Pd<sup>II</sup> is the active species in this inner-sphere “electrophilic” activation of the C–H bond.<sup>[17]</sup> The first reports of transition metal-catalyzed C–H functionalization were published in the late 1960s and early 1970s.<sup>[22]</sup> In parallel to these reports, the first examples of Pd-catalyzed arene alkenylation in the synthesis of vinyl arenes **1.3** were disclosed by Fujiwara and Moritani (Scheme 2a).<sup>[23]</sup> About 10 years later, Ames demonstrated the intramolecular C(sp<sup>2</sup>)–H arylation initiated by oxidative addition of Pd<sup>0</sup> into the C(Ar)–Br bond (Scheme 2b).<sup>[24]</sup> Since these initial findings, Pd-catalyzed C–H functionalization of arenes has emerged as a powerful and well-established method.<sup>[25–30]</sup>

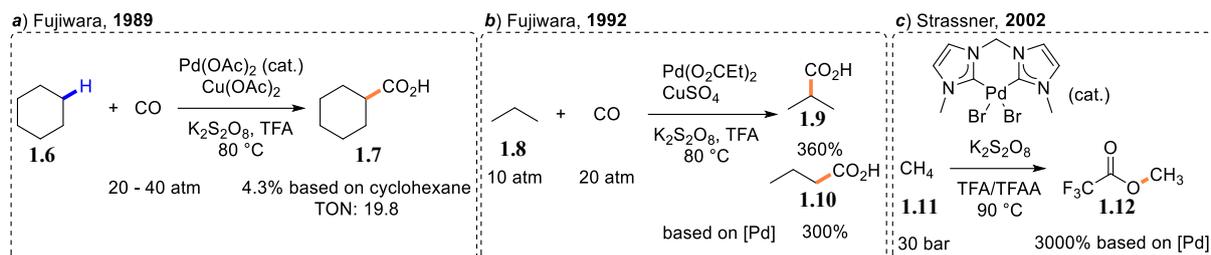


Scheme 2. Seminal reports in Pd-catalyzed C–H functionalization with the arene alkenylation by Fujiwara and Moritani (**a**) and Pd<sup>0</sup>-catalyzed C(sp<sup>2</sup>)–H arylation by Ames (**b**).

### 1.1.2 Pd-Catalyzed C(sp<sup>3</sup>)–H Activation

In the activation of C(sp<sup>2</sup>)–H bonds, the pre-coordination of the metal complex to the neighboring  $\pi$ -system facilitates C–H bond cleavage. In the case of C(sp<sup>3</sup>)–H bonds of alkanes, this beneficial coordination cannot occur.<sup>[31]</sup> Although C(sp<sup>3</sup>)–H bonds have a lower bond dissociation energy, the acidity of these bonds is lower as for C(sp<sup>2</sup>)–H bonds, and the alkyl–Pd–bond is weaker than the corresponding C(sp<sup>2</sup>)–Pd bond, which results in a more difficult transformation.<sup>[32]</sup> Nevertheless, earlier precedents in the transition metal-catalyzed functionalization of alkanes proved the feasibility of this process. As exemplified by the work of Fujiwara in 1989, an *in situ* formed electrophilic [Pd(TFA)]<sup>+</sup>-complex catalyzed the carboxylation of alkanes as shown in Scheme 3a.<sup>[33,34]</sup> In this reaction, the electrophilic Pd-species adds into the C–H bond with subsequent CO-insertion and terminal oxidation to deliver the observed carboxylic acids **1.7**. In this case, mono carboxylation proceeded in 4.3% yield starting from cyclohexane **1.6**, which was employed as solvent. In a similar fashion, the use of propane **1.8** as alkane source resulted in a mixture of *iso*-butyric acid **1.9** and butyric acid **1.10** in 360% and 300% yield, respectively, based on the engaged Pd (Scheme 3b).<sup>[35]</sup> A further successful example in the functionalization of methane **1.11** was reported by the Strassner group in 2002 (Scheme 3c).<sup>[36]</sup> The trifluoroacetic acid methyl ester **1.12** was obtained in 3000% yield calculated on the used Pd. As proposed by the authors, after initial C(sp<sup>3</sup>)–H activation, a

$[\text{Pd}(\text{CH}_3)(\text{TFA})]^+$ -complex is formed which is then oxidized by  $\text{Br}_2$ . Subsequent reductive elimination from the resulting  $\text{Pd}^{\text{IV}}$ -species furnishes the C–H functionalized product **1.12**.



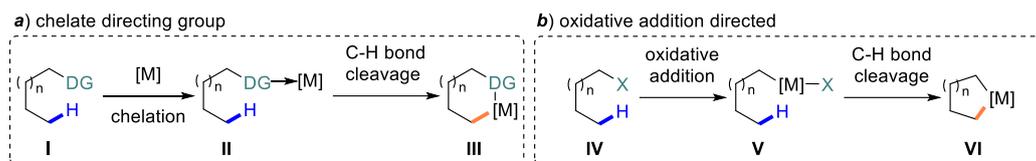
Scheme 3. Precedents of non-directed  $\text{C}(\text{sp}^3)\text{-H}$  functionalizations of simple alkanes.

Some of the major limitations in this direct functionalization of alkanes originate from the non-polar character of the hydrophobic alkanes which impedes the interactions with the weakly polar Pd-complexes. Therefore, a high excess of the alkane is required to overcome this low affinity and push the reaction towards product formation. A second major issue arises from the need for highly electrophilic Pd-species for this  $\text{C}(\text{sp}^3)\text{-H}$  bond activation. Consequently, the control of regio- and chemoselectivity along with the suppression of undesired over-functionalization becomes more difficult due to the involvement of this highly energetic catalyst. One approach to improve the reactivity and regioselectivity is the use of a pre-existing functional group with the ability to coordinate and direct the active  $\text{Pd}^{\text{II}}$ -species.<sup>[37]</sup>

### 1.1.3 Directed Pd-Catalyzed $\text{C}(\text{sp}^3)\text{-H}$ Activation

The use of pre-installed functional groups can help to direct the active Pd-species in close proximity to the C–H bond to be activated. This directing effect thereby facilitates the bond cleavage.<sup>[38]</sup> By applying this concept, a discrete palladacycle **III** or **VI** (Scheme 4) is formed after successful C–H activation following a directed inner-sphere reaction mechanism (Scheme 1*b*). The resulting palladacycle intermediates, most commonly 5- and 6-membered, are stable and, therefore, lower the energy barrier for this transformation. As a consequence of the stabilization of this reaction intermediate, the reactivity and selectivity of such directed processes increase and a subsequent functionalization can occur more readily.<sup>[32]</sup> There are two types of directivity: the first one arises from a non-covalent directing group, in which usually a strong  $\sigma$ -donor and/or  $\pi$ -acceptor of the substrate chelates the active  $\text{Pd}^{\text{II}}$ -species (Scheme 4*a*). Typical directing groups of this class contain nitrogen or sulfur atoms as well as carbonyls.<sup>[39,40]</sup> The second type of directivity originates from the oxidative addition of a  $\text{Pd}^0$ -species into a carbon-(pseudo)halogen bond. Thereby, the catalytically active  $\text{Pd}^{\text{II}}$ -species is formed and the C–H activation substrate becomes a part of the active complex (Scheme 4*b*).

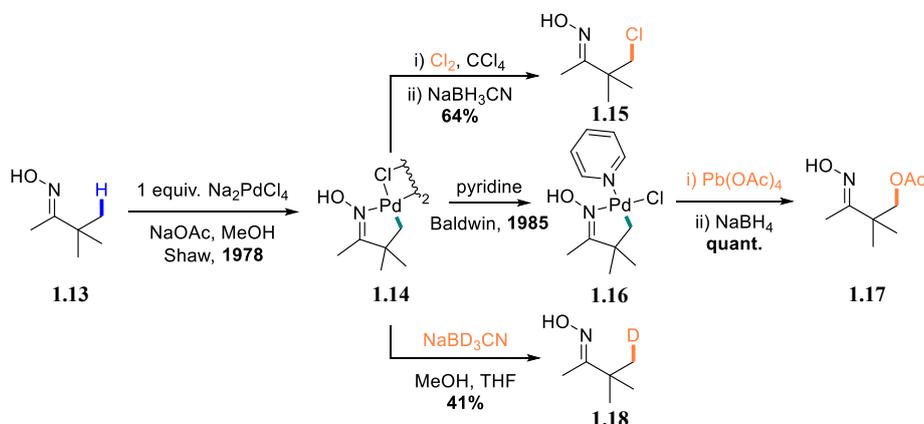
## General Introduction



Scheme 4. The two direction modes in the Pd-catalyzed inner sphere C-H metalation.

### 1.1.4 Chelate Directed Pd<sup>II</sup>-Catalyzed C(sp<sup>3</sup>)-H Activation

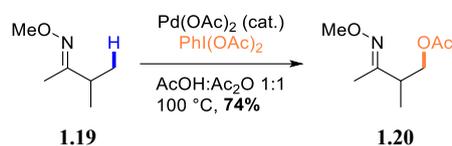
The cyclometalation process arising from a C(sp<sup>2</sup>)-H or C(sp<sup>3</sup>)-H activation is known since the 1960s.<sup>[31]</sup> However, due to the relative inertness of unactivated C(sp<sup>3</sup>)-H bonds, relatively few examples of stoichiometric studies are reported in the literature. The first example was presented by Shaw in 1978 as shown in Scheme 5.<sup>[41]</sup> The chloride-bridged dimeric 5-membered palladacycle **1.14** was obtained after the cleavage of the C-H bond occurring with the treatment of *tert*-butyl methyl ketone oxime **1.13** with stoichiometric Na<sub>2</sub>PdCl<sub>4</sub> and NaOAc. Further directing groups were evaluated in the formation of such cyclopalladation reactions. In addition to oximes, trialkyl phosphines,<sup>[42]</sup> pyridine<sup>[43,44]</sup> and *N,N*-dimethylamine<sup>[45]</sup> proved to be suitable for effecting the C(sp<sup>3</sup>)-H cleavage. In particular, stable five<sup>[42,44,45]</sup> and six-membered<sup>[43]</sup> palladacycles were obtained and characterized. In 1985, Baldwin and co-workers investigated the reactivity of the oxime-derived palladacycle **1.14** in stoichiometric studies (Scheme 5). The treatment of palladacycle **1.14** with Cl<sub>2</sub> and subsequent reduction of the chlorinated species with NaBH<sub>3</sub>CN afforded the mono-chlorinated product **1.15** in 64% yield. In the presence of pyridine, the dimeric palladacycle **1.14** was transformed into its corresponding monomer **1.16**. Oxidation of this species with Pb(OAc)<sub>4</sub> and subsequent reduction with NaBH<sub>4</sub> proceeded smoothly, furnishing the acetoxyated product **1.17** in quantitative yield. The exposure of **1.14** to NaBD<sub>3</sub>CN resulted in the mono-deuterated product **1.18** in 41% yield.<sup>[46]</sup>



Scheme 5. Stoichiometric studies in the oxime-directed C(sp<sup>3</sup>)-H activation and subsequent functionalizations.

In 2004, the first directed catalytic oxygenation of unactivated C(sp<sup>3</sup>)-H bonds was disclosed by Sanford and co-workers.<sup>[47]</sup> In order to achieve a productive reaction, the directing group

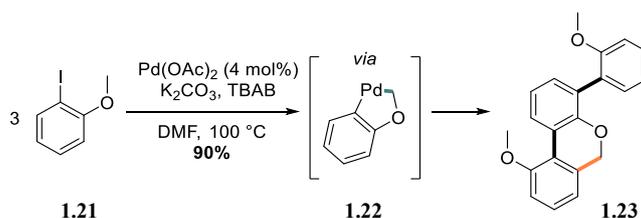
was changed to a less strongly coordinating oxime-ether to result in a thermodynamically less stable palladacycle (Scheme 6). This species was then further oxidized to a Pd<sup>IV</sup>-complex with PhI(OAc)<sub>2</sub>. Subsequent reductive elimination furnished the acetoxyated product. After these initial insights, many protocols were developed for such directed functionalizations employing a variety of directing groups, oxidants, and electrophiles.<sup>[32,37,48,49]</sup>



Scheme 6. First catalytic chelate directed C(sp<sup>3</sup>)-H functionalization by the Sanford group.

### 1.1.5 Oxidative Addition Directed Intramolecular C(sp<sup>3</sup>)-H Activation

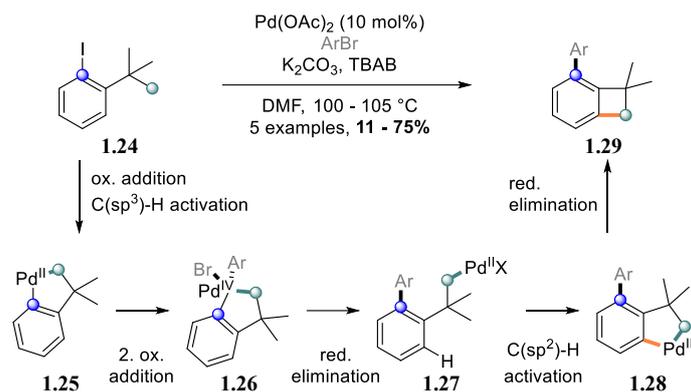
In 1992, Dyker reported the first oxidative addition promoted activation of a C(sp<sup>3</sup>)-H bond on a methoxy group as depicted in Scheme 7.<sup>[50]</sup> A trimerization of aryl iodide **1.21** was observed in 90% when it was treated with catalytic Pd(OAc)<sub>2</sub> in presence of an ammonium salt and K<sub>2</sub>CO<sub>3</sub> as the stoichiometric base in DMF at 100 °C. It was proposed that the cyclopalladated species **1.22** was an intermediate of this transformation.



Scheme 7. First reported oxidative addition directed C(sp<sup>3</sup>)-H activation by Dyker.

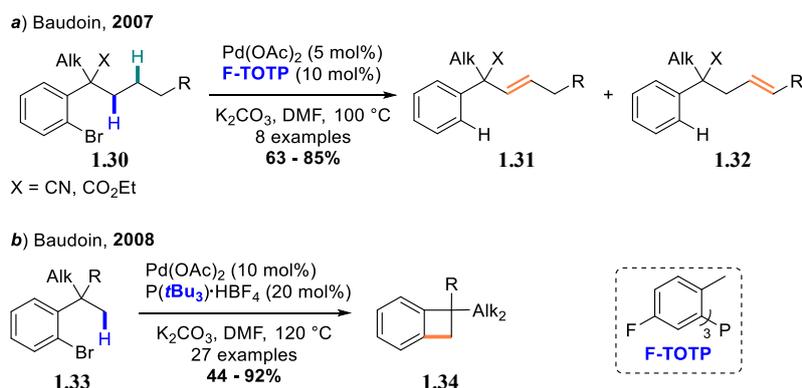
In a later report, 1,2-dihydrocyclobutanebenzene **1.29** derivatives were accessed under similar conditions when reacting 1-*tert*-butyl-2-iodobenzene **1.24** with aryl bromides. The proposed mechanism for this transformation is shown in Scheme 8. After the initial oxidative addition of the Pd<sup>0</sup> into the Ar-I bond, a C(sp<sup>3</sup>)-H bond activation at the *tert*-butyl group leads to palladacycle **1.25**. Subsequent oxidative addition of the Pd<sup>II</sup> into the Ar-Br bond results in a Pd<sup>IV</sup>-species **1.26** which reductively eliminates and generates alkyl-Pd<sup>II</sup>-species **1.27**. Following this, C(sp<sup>2</sup>)-H activation gives rise to a second palladacycle **1.28** which reductively eliminates to furnish the product **1.29** along with the regeneration of the catalytically active Pd<sup>0</sup>.<sup>[51]</sup>

## General Introduction



Scheme 8. Dyker's synthesis of 1,2-dihydrocyclobutanebenzene and proposed mechanism.

In 2003, the Baudoin group presented the synthesis of olefins and benzocyclobutenes (BCBs) *via* C(sp<sup>3</sup>)-H activation by engaging aryl halides with Pd(OAc)<sub>2</sub>, P(*o*-tol)<sub>3</sub> and K<sub>2</sub>CO<sub>3</sub> at 150 °C in DMF.<sup>[52]</sup> Remarkably, the employment of phosphine ligands in this transformation suppressed the self-condensation of the aryl-halide starting material as observed in Dyker's case.<sup>[51]</sup> The product selectivity was dictated by the nature of the starting materials where the desaturated products were observed unless a benzylic substituent was a methyl- instead of a larger alkyl group. In the former case, the corresponding BCB was observed. Further optimization of the reaction conditions allowed the efficient synthesis of olefins (**1.31/2**) employing the optimized F-TOTP (tris(5-bisfluoro-2-methylphenyl)phosphane) ligand with Pd(OAc)<sub>2</sub> and K<sub>2</sub>CO<sub>3</sub> in DMF at 100 °C (Scheme 9a). Remarkably, more challenging methylene positions were activated even under these relatively mild reaction conditions.<sup>[53]</sup> In contrast, Pd(OAc)<sub>2</sub>, P(*t*Bu)<sub>3</sub>•HBF<sub>4</sub> and K<sub>2</sub>CO<sub>3</sub> in DMF at 120 °C were found to be the optimal conditions for the activation of benzylic methyl groups in the synthesis of BCBs **1.34** (Scheme 9b).<sup>[54]</sup>

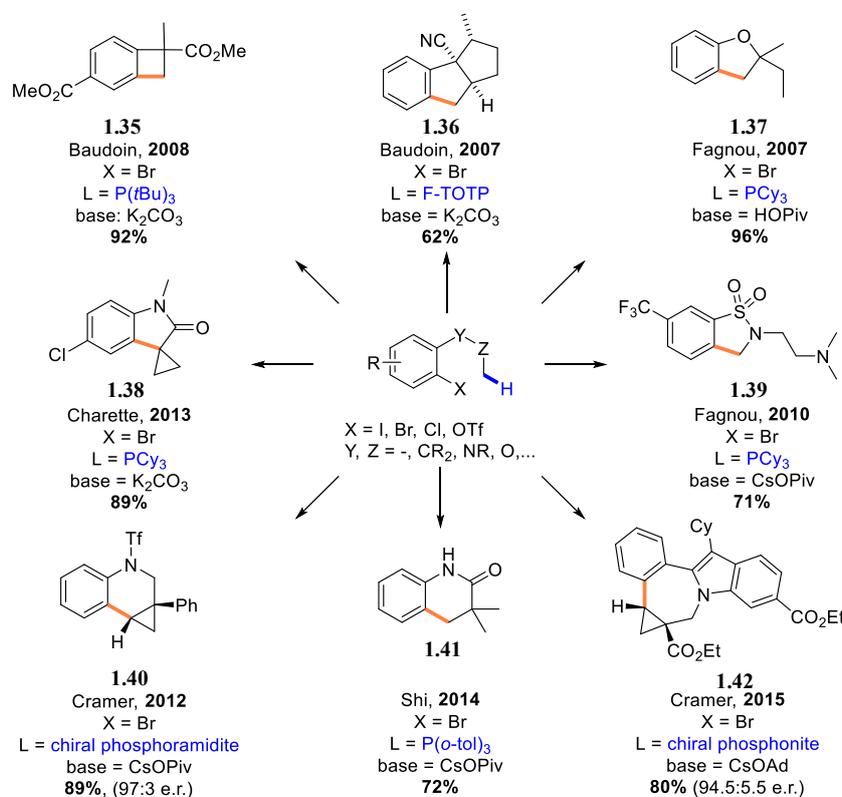


Scheme 9. Baudoin's synthesis of olefins and BCBs *via* C(sp<sup>3</sup>)-H activation.

### 1.1.6 Valuable Cyclic Products *via* Intramolecular Unactivated C(sp<sup>3</sup>)-H Arylation

After these initial results in the direct C(sp<sup>3</sup>)-H activation, various cyclic motifs were accessed in an efficient way under Pd<sup>0</sup>-catalysis (Scheme 10). For each of the cyclic systems, the reaction

conditions had to be adapted individually, highlighting the importance of the ligands and the CMD-promoting bases in these transformations. Following on from the previously discussed BCBs, various 5-membered cyclic system such as fused indanes **1.36**,<sup>[55,56]</sup> dihydrobenzofuranes **1.37**,<sup>[56,57]</sup> 2-indolinone **1.38**,<sup>[58–60]</sup> fused *N*-heterocycles,<sup>[61]</sup> indolines<sup>[62]</sup> and dihydrobenzothiazole **1.39**<sup>[56]</sup> can be assembled easily. Six-membered heterocycles such as tetrahydroquinoline **1.40**<sup>[63]</sup> and dihydroquinolinones **1.41**<sup>[64,65]</sup> can be forged along with the polyfused seven-membered product **1.42**<sup>[65]</sup> in an efficient way. Generally, methyl groups and cyclopropanes are activated more readily due to their higher reactivity compared to methylenes and methines. In some specific cases, methylene activation can be observed, however, this is generally the exception.<sup>[52,66–69]</sup>



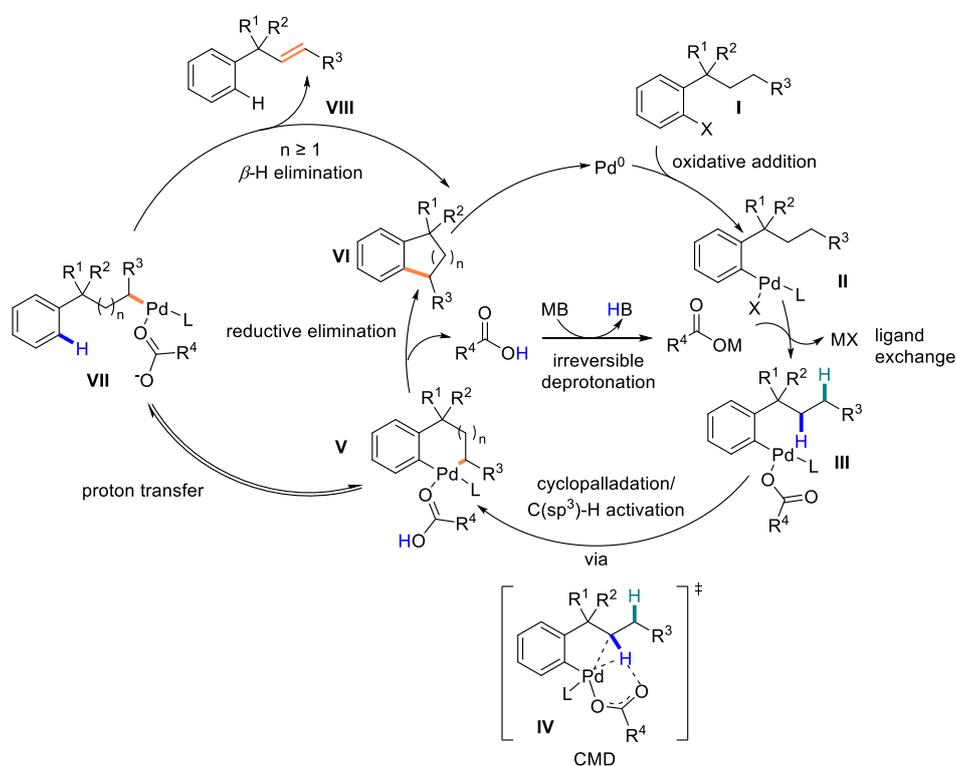
Scheme 10. Selected examples for the synthesis of valuable (hetero)cyclic motifs *via* C(sp<sup>3</sup>)-H arylation.

### 1.1.7 Mechanism

It was initially believed that the cyclometalation occurs *via* an electrophilic mechanism and proceeds through a Wheland (metal-arenium) intermediate in the activation of C(sp<sup>2</sup>)-H bonds. A subsequent proton transfer to one of the metal ligated acetates *via* a highly ordered six-membered transition state would then result in the isolated and characterized palladacycles.<sup>[38]</sup> However, observations of improved reactivity of electron deficient arenes coupled with inverse selectivity in the C(sp<sup>2</sup>)-H activation suggested a different mode of action. Further investigation by DFT calculations by Echavarren & Maseras,<sup>[70]</sup> MacGregor,<sup>[71]</sup> and Fagnou & Gorelsky<sup>[72]</sup>

## General Introduction

completely invalidated the hypothesis of this electrophilic mechanism. The combined findings strongly support a concerted metalation deprotonation process (CMD) occurring in the cleavage of the C–H bond. Thereby, an agostic interaction is formed and the carbonate or carboxylate ligand assists in the proton-transfer *via* a six-membered transition state.<sup>[73]</sup> DFT computational studies by Baudoin and Clot<sup>[54,74]</sup> in the synthesis of BCBs *via* C(sp<sup>3</sup>)–H activation revealed a CMD mechanism was likely taking place in the C(sp<sup>3</sup>)–H activation step, as reported in the C(sp<sup>2</sup>)–H activation. Additionally, DFT analyses of further C–C bond formations *via* C(sp<sup>3</sup>)–H activation mechanism proved that these processes also proceed *via* a CMD mechanism.<sup>[75,76]</sup> However, it has to be noted that the energy profiles of the transition states of each reaction is strongly dependent on modification of substrates, bases, and ligands and can vary in each case.



Scheme 11. Detailed mechanism in the formation of cyclic products and olefins *via* direct C(sp<sup>3</sup>)–H arylation and β-H elimination after 1,4-Pd shift, respectively.

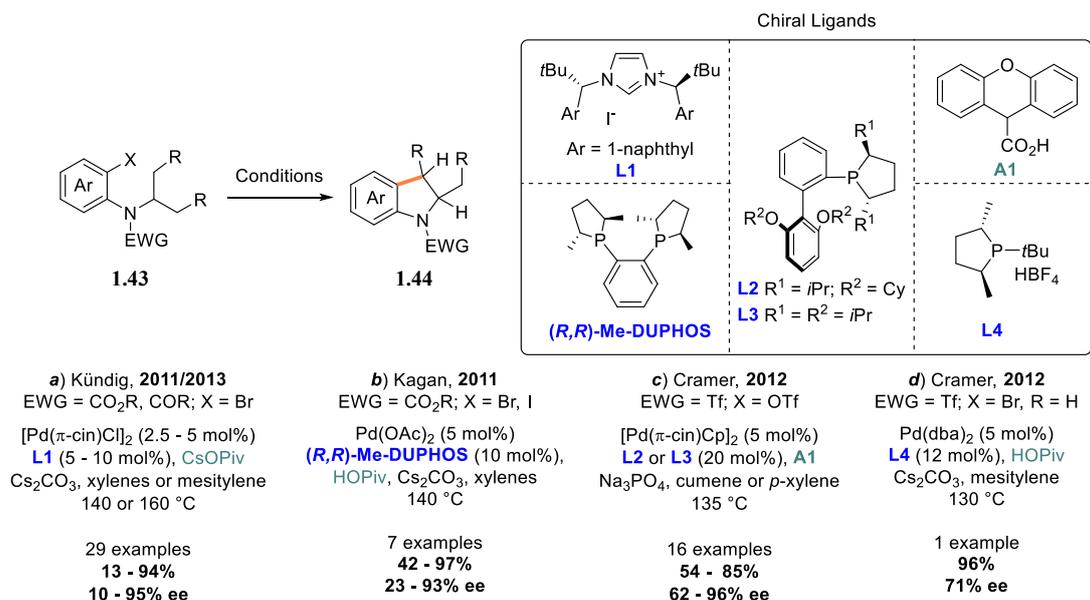
In general, the C(sp<sup>3</sup>)–H functionalization is initiated by oxidative addition of the Pd<sup>0</sup> into the aryl–(pseudo)halide bond resulting in a Pd<sup>II</sup>-complex **II** (Scheme 11). Ligand exchange of the (pseudo)halide with a carbonate or carboxylate and subsequent C(sp<sup>3</sup>)–H activation *via* CMD mechanism results in palladacycle **V**. At this point, there are two possible reactions pathways. In scenario 1, the carbonate/carboxylate ligand dissociates followed by reductive elimination forging the fused polycyclic product **VI** and the catalytically active Pd<sup>0</sup>-catalysts is regenerated. BCBs and other C(sp<sup>3</sup>)–H arylated products are formed upon this pathway. In scenario 2, a proton transfer from the protonated acetyl ligand/carbonate to the aryl in palladacycle **V** takes

place. The resulting  $\sigma$ -alkyl-Pd-species **VII** can then undergo a base assisted  $\beta$ -H elimination to result in the olefin products **VII** or undergoes a  $C(sp^2)$ -H activation to regenerate palladacycle **V**. If no  $\beta$ -H is available, the alkylpalladium species can undergo further functionalization. The pathway proceeding *via*  $\sigma$ -alkyl-Pd **VII** with following functionalization describes a 1,4-Pd shift.

### 1.1.8 Site Selectivity in the Intramolecular $C(sp^3)$ -H Activation

The evaluation of the  $C(sp^3)$ -H activations reported to date shows some general reactivity trends in this type of functionalization. Firstly, the type of C-H bond has a strong influence on the reactivity with cyclopropyl > methyl > methylene >> methine. Furthermore, the size of the formed intermediate palladacycle influences the reaction outcome by favoring the resulting cyclic products as following: 4-membered > 5-membered > 6-membered > 7-membered. However, it has to be considered that these are just general guidelines which can be overcome by ligand effects<sup>[66]</sup> and conformational strain.<sup>[77]</sup> Also, the addition of substituents can result in a Thorpe-Ingold effect and a better reactivity in the intramolecular cyclization.<sup>[78]</sup>

## 1.2 Enantioselective Intramolecular $C(sp^3)$ -H Arylation

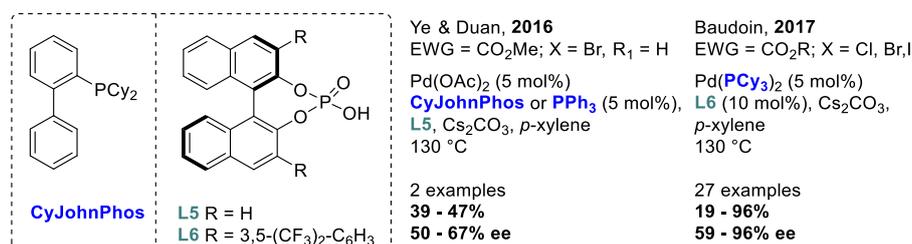


Scheme 12. Enantioselective construction of an indoline moiety under Pd<sup>0</sup>-catalyzed  $C(sp^3)$ -H arylation conditions.

Considering the mechanism of the Pd<sup>0</sup>-catalyzed  $C(sp^3)$ -H arylation shown in Scheme 11, a stereocontrolled reaction can be performed by using a chiral ligand or chiral carboxylate co-catalyst. Thereby, the irreversible deprotonation of the CMD-active carboxylate by an inorganic stoichiometric base renders the CMD-step enantiodetermining whilst the base-catalyst is regenerated.<sup>[79,80]</sup> The first Pd<sup>0</sup>/Pd<sup>II</sup>-catalyzed enantioselective  $C(sp^3)$ -H arylation towards enantioenriched indolines was disclosed by the Kündig group in 2011 (Scheme 12a). A chiral 2,2-dimethyl-1-arylpropane-1-amine derived NHC ligand **L1** was employed in combination

## General Introduction

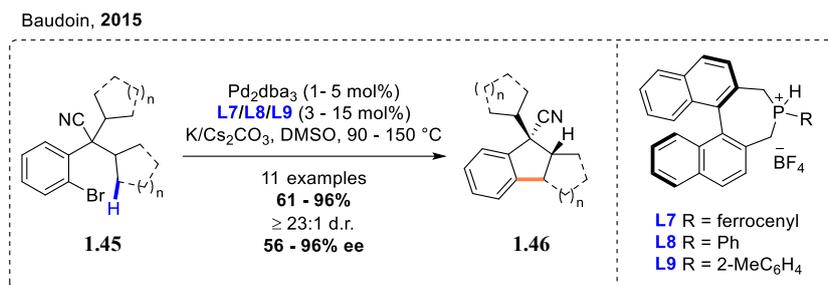
with cesium pivalate and cesium carbonate in apolar aromatic solvents. The indolines **1.44** were accessed in the desymmetrization of methylene groups with mostly excellent stereocontrol.<sup>[67]</sup> Moreover, a regiodivergent parallel kinetic resolution was reported in an expansion of this study.<sup>[66]</sup> In a similar fashion, high stereocontrol could be achieved employing (*R,R*)-**Me-DUPHOS** ligand along with pivalic acid and cesium carbonate in the methyl arylation by Kagan and co-workers (Scheme 12*b*).<sup>[81]</sup> A small library of indolines was obtained in satisfactory yield and enantioselectivity. In parallel, the Cramer group developed air stable monodentate phosphine ligands **L2/L3** which showed high enantioinduction in combination with achiral acid co-catalyst **A1** in the synthesis of a variety of indolines (Scheme 12*c-d*).<sup>[82]</sup> The concept of enantioinduction by a chiral base was proven by Kagan<sup>[81]</sup> and Cramer<sup>[82]</sup> independently in single examples and moderate enantioinduction. The concept was later explored by the Ye & Duan<sup>[83]</sup> and Baudoin<sup>[84]</sup> groups individually (Scheme 13). Both groups showed that the employment of BINOL-derived chiral phosphoric acids in combination with achiral ancillary ligands can result in moderate to high stereocontrol when employed in combination with achiral ancillary ligands in the synthesis of indolines **1.44**. In the work presented by the Baudoin group, a modest kinetic resolution was observed.<sup>[84]</sup>



Scheme 13. Chiral base controlled enantioselective synthesis of indolines.

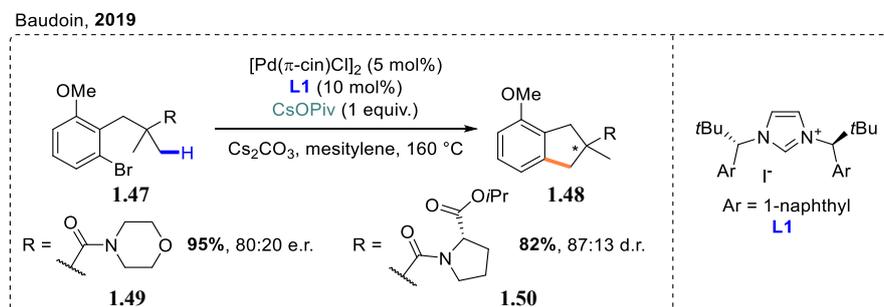
In addition, further cyclic motifs such as indanes **1.46**<sup>[69,85–87]</sup> and **6**-<sup>[63]</sup> and 7-membered *N*-heterocycles<sup>[65]</sup> were accessed with the application of various chiral ligands. Baudoin and co-workers implemented new chiral binepine ligands which showed remarkable activity and selectivity in the synthesis of enantioenriched fused bi- and tricyclic indanes **1.46** as depicted in Scheme 14.<sup>[69]</sup> Methyl activation was able to occur at low temperature (90 °C) when the aryl bromides **1.45** were submitted to Pd<sub>2</sub>dba<sub>3</sub>, binepine ligand **L7**, and K<sub>2</sub>CO<sub>3</sub> in DMSO. The fused tricyclic products arising from methylene activation were accessed in moderate to high enantioselectivities as single diastereoisomers with binepine ligands **L8-L9** under slightly adapted conditions.<sup>[69]</sup>

## General Introduction



Scheme 14. Enantioselective synthesis of indanes **1.46** with binepine ligands by Baudoin and co-workers.

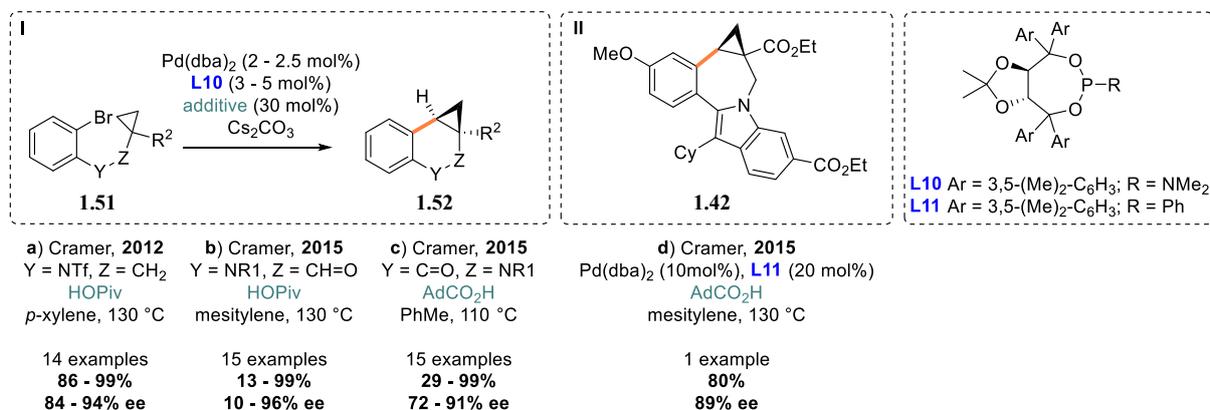
In 2019, the Baudoin group reported the construction of the bicyclic core of (Nor)illudalane sesquiterpenes *via* asymmetric Pd<sup>0</sup>-catalyzed C(sp<sup>3</sup>)-H arylation by the desymmetrization of two methyl groups (Scheme 15).<sup>[86,87]</sup> Optimum results were obtained with Kündig-type NHC-ligand **L1**<sup>[67]</sup> in combination with [Pd( $\pi$ -cin)Cl]<sub>2</sub>, CsOPiv as the CMD-mediating base and Cs<sub>2</sub>CO<sub>3</sub> in mesitylene at 160 °C. The highest enantioinduction on the model substrate was observed when the morpholine substrate was engaged under the optimized reaction conditions (**1.49**, 95%, 60% ee). Introducing the chiral *L*-proline auxiliary in the substrate further enhanced to the stereocontrol in comparable yield (**1.50**, 82%, 87:13 d.r.). Although only moderate stereoselectivity was achieved in this transformation, it is still remarkable considering the presence of only one highly symmetric quaternary stereocenter in the resulting product.



Scheme 15. Baudoin's study in the stereoselective synthesis of indanes in the total synthesis of (Nor)illudalane sesquiterpenes.

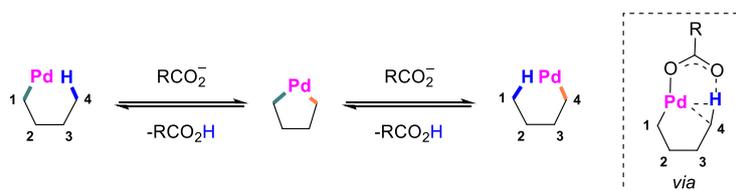
The synthesis of 6-membered cycles **1.52** *via* C-H activation is rare, since the reaction proceeds *via* a less favored 7-membered palladacycle. Nevertheless, in 2012 the Cramer group succeeded in the stereoselective arylation of the cyclopropane moiety forging the tetrahydroquinoline scaffold in high yield and excellent enantioselectivity (Scheme 16I, **a**).<sup>[63]</sup> In a follow up study in 2015, the group employed similar conditions in the synthesis of dihydroquinolones (**b**) and dihydroisoquinolones (**c**) through an enantioselective arylation of cyclopropanes.<sup>[65]</sup> All these six-membered heterocycles were accessed in high enantioselectivities by employing TADDOL-derived phosphoramidite ligand **L10** and pivalic or adamantane carboxylic acid as CMD-mediating base in combination with Cs<sub>2</sub>CO<sub>3</sub> and Pd(dba)<sub>2</sub> in apolar aromatic solvents at 110 - 130 °C. In addition, the method was further expanded to the construction of a 7-membered ring

system **1.42** (Scheme 16II, *d*). The 7-membered pentacyclic cyclopropyl indolbenzazepine-core **1.42** of BMS-791325 was constructed under similar conditions. The highest enantioinduction (89% ee) was achieved with TADDOL-derived phosphonite.<sup>[65]</sup>



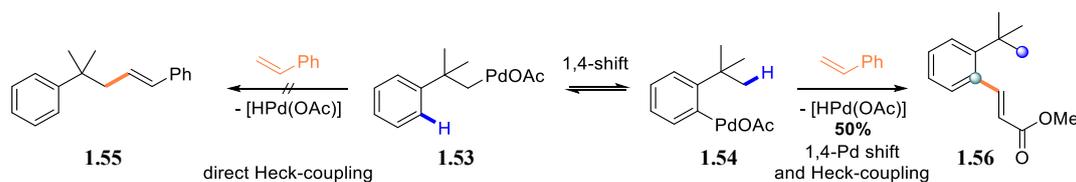
Scheme 16. Enantioselective synthesis of 6- and 7- membered rings *via* C(sp<sup>3</sup>)-H arylation.

### 1.3 1,4-Pd Shift



Scheme 17. Schematic representation of a 1,4-Pd shift.

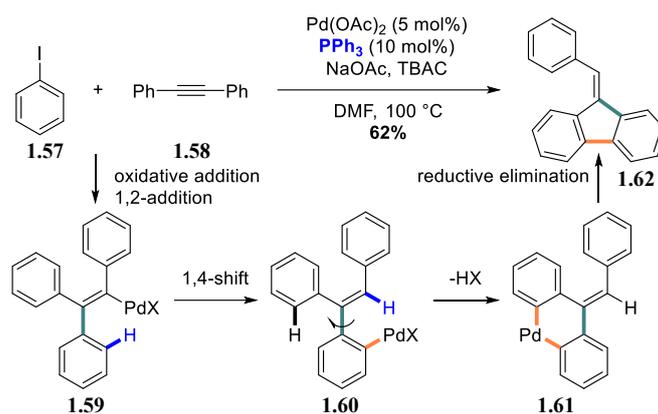
In the previous sections, an unusual functionalization reactivity was described in the seminal C(sp<sup>3</sup>)-H activation by Dyker (Scheme 8) and in the olefin synthesis by Baudoin and co-workers (Scheme 9*a*). Instead of the direct functionalization at the oxidative addition site, the palladium is migrating to another position *via* a C(sp<sup>3</sup>)-H activation event and proton transfer prior to further functionalization, the so-called 1,4-Pd shift. The first report of such a migration was reported by Heck in 1972.<sup>[88]</sup> When reacting styrene with 2-methyl-2-phenyl-1-propylpalladium acetate **1.53**, which was obtained after treatment of the corresponding mercury acetate with palladium acetate, the C(sp<sup>2</sup>)-H coupled product **1.56** was isolated in 50% yield instead of the expected alkylated styrene **1.55** (Scheme 18). From this point onwards, chemists understood that this new reaction manifold could be exploited in order to access new Pd-species which were hard or even impossible to synthesize and, therefore, allowing new disconnections in the construction of more complex molecules.<sup>[89-91]</sup>



Scheme 18. Heck's initial observation of a 1,4-Pd shift in 1972.

### 1.3.1 C(sp<sup>2</sup>) to C(sp<sup>2</sup>) Shift

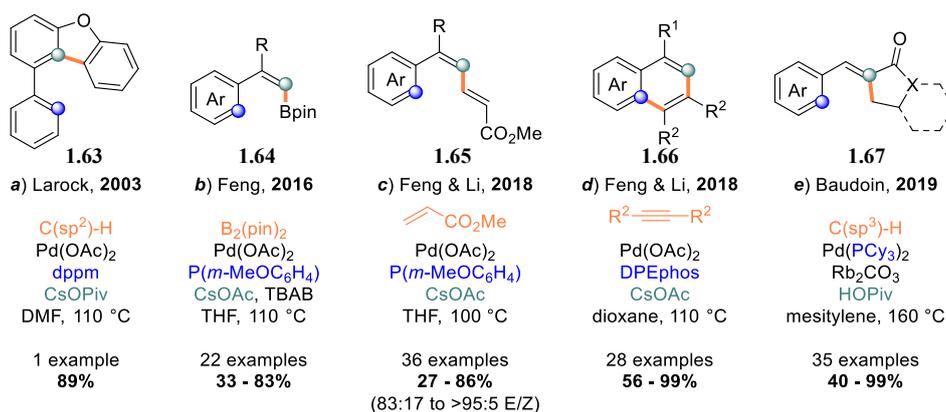
The first catalytic 1,4-Pd shift from a C(sp<sup>2</sup>) to another C(sp<sup>2</sup>) center was described in the synthesis of 9-alkylidene-substituted 9*H*-fluorene **1.62** by Larock in 2000 (Scheme 19).<sup>[92]</sup> An alkenyl-Pd intermediate **1.59** is thereby formed after initial oxidative addition and insertion across the triple bond. Subsequent 1,4-Pd shift and C(sp<sup>2</sup>)–H activation at the neighboring phenyl substituent results in a six-membered palladacycle **1.61**. Reductive elimination furnishes the fluorene product **1.62** in 62% yield. Crucial for the success of this domino-reaction was the employment of a phosphine ligand and NaOAc as the base.



Scheme 19. 1,4-Pd shift from aryl to vinyl by Larock in 2000.

In further studies, the influence of the electronics of the aryl groups, the steric properties together with the adjustment of the reaction conditions were shown to control the migratory behavior of the palladium.<sup>[93–96]</sup> After these initial insights and investigation on this reaction, this shift was further expanded to install new functionalities on a remote position from the original oxidative addition site. One of the first selective examples of a functionalization after an aryl-aryl shift was disclosed by Larock in 2003 (Scheme 20*a*). In this work, several fused polycycles **1.63** were obtained in good yields after a subsequent arylation *via* C(sp<sup>2</sup>)–H activation and reductive elimination of the newly formed aryl-Pd species.<sup>[97]</sup> Moreover, the Feng and Li group shifted the Pd from an aryl to a vinylic position and trapped the resulting  $\sigma$ -alkenyl-Pd-species with diboron reagents which gave rise to a series of vinylboronates **1.64** with excellent regioselectivity and broad functional group tolerance (Scheme 20*b*). Crucial for the reactivity and selectivity of this reaction was the use of the P(*m*-MeOC<sub>6</sub>H<sub>4</sub>)<sub>3</sub> ligand, CsOAc as the base and THF as solvent.<sup>[98]</sup> This methodology was further expanded to the subsequent trapping of the alkenyl-Pd species by a Heck reaction (Scheme 20*c*). In this case, the *gem*-disubstituted ethylenes were efficiently coupled with acrylates in a stereospecific manner.<sup>[99]</sup> In addition to these findings, the vinylpalladium species was shown to be able to insert into an alkyne bond (Scheme 20*d*). Subsequent C(sp<sup>2</sup>)–H activation and reductive elimination

furnished the corresponding poly-substituted naphthalenes **1.66** in good to excellent yield.<sup>[100]</sup> In 2019, our group showed that a 1,4-Pd shift  $\alpha$ - to an unsaturated ketone or amide after initial oxidative addition into an aryl halide bond can be trapped in a subsequent C(sp<sup>3</sup>)-H activation and reductive elimination (Scheme 20e). A broad range of arylidene  $\gamma$ -lactams and some indanones (**1.67**) were constructed in good to excellent yield with this simple and step-economic process.<sup>[101]</sup> In addition, the shifted Pd-species was involved in subsequent Heck reaction and C-H activation,<sup>[102]</sup> and benzannulations.<sup>[103]</sup> This selection of examples highlights the versatility of reactivities that can be achieved with the newly formed Pd-species.



Scheme 20. Selected examples of a 1,4-Pd shift from C(sp<sup>2</sup>) to C(sp<sup>3</sup>) and subsequent selective functionalization.

### 1.3.2 C(sp<sup>2</sup>) to C(sp<sup>3</sup>) Shift

Compared to the presented shift to a C(sp<sup>2</sup>)-position, migration to a C(sp<sup>3</sup>)-position is generally more challenging. The more sterically demanding environment, lower acidity of C(sp<sup>3</sup>)-H bonds, a weaker resulting Pd-C(sp<sup>3</sup>)-bond,<sup>[104,105]</sup> and no pre-coordination to a neighboring  $\pi$ -system make these bonds less susceptible towards activation. Moreover, the generated  $\sigma$ -alkylpalladium species is more prone to undergo protodemetalation or even  $\beta$ -H elimination. As a consequence, these species are harder to access, especially in a more traditional approach. However, by obtaining such discrete species in the course of a domino reaction, the alkylpalladium complex could potentially react faster than its decomposition allowing the discovery of new reactivities. The first successful catalytic C(sp<sup>2</sup>) to C(sp<sup>3</sup>) migration was described in the previously discussed precedents of Dyker in the 1990s (Scheme 7 and Scheme 8).<sup>[50,51,106]</sup> In 2007, the Baudoin group reported the synthesis of olefins **1.69** *via* desaturation of an alkane substituent (Figure 2b). The use of phosphine ligands prevented the self-condensation of the aryl halides observed by Dyker.<sup>[50,51,106]</sup> The new double bond is formed adjacent to a quaternary benzylic carbon center and it is believed to originate from a  $\beta$ -H elimination of the 1,4-shifted alkyl-palladium species as depicted in Scheme 11.<sup>[53]</sup> Starting from primary  $\alpha$ -benzylic substituents, the olefin is formed as the sole C-H activation product.

## General Introduction

However, the shift-pathway is suppressed by the sterically more demanding poly-substituted  $\alpha$ -benzylic carbon which upon reductive elimination results in the direct C–C bond formation. In addition, the occurrence of a 1,4-Pd shift was observed in the synthesis of BCBs **1.70** by the Baudoin group (Figure 2c).<sup>[54]</sup> Although these four membered cyclic compounds are the only products isolated along with the corresponding protodehalogenated reactants, the presence of a regiomer mixture starting from substrates bearing small substituents *para* to the bromide is indicative for an alkylpalladium species formed during the reaction. In 2019, Baudoin and co-workers developed a protocol which allows the formation of a C(sp<sup>3</sup>)–C(sp<sup>3</sup>) bond in the construction of 2,3-dihydrobenzofuranes and indolines (Figure 2d).<sup>[107]</sup> In this cross-dehydrogenative reaction,<sup>[108,109]</sup> the newly generated alkylpalladium species undergoes a second C(sp<sup>3</sup>)–H activation at a benzylic position or alpha to a carbonyl group before it reductively eliminates. The installation of a trifluoroacetyl group on the *N*-methyl aniline suppressed the well-known demethylation under Pd<sup>0</sup>-catalysis and permitted therefore the successful shift instead. It is assumed that the demethylation originates after 1,4-Pd shift and iminium formation.<sup>[110–112]</sup> The concept of the cross dehydrogenative coupling of two C(sp<sup>3</sup>)–H was then expanded to the synthesis of cyclopropanes **1.72** (Figure 2e).<sup>[113]</sup> Strikingly, starting from the substrates which were previously used in the synthesis of BCBs,<sup>[54]</sup> the selectivity of the reaction outcome could be changed completely by slight alteration of the reaction conditions. When submitting the substrate with KO*Piv* instead of the previously employed K<sub>2</sub>CO<sub>3</sub> in combination with Pd(PPh<sub>3</sub>)<sub>4</sub> in toluene, exclusive formation of cyclopropane was observed. Mechanistic studies revealed the preferred reductive elimination from the five-membered palladacycle in presence of carbonate. However, this process is disfavored with pivalate. Instead, a high-energetically four membered palladacycle is formed upon subsequent C(sp<sup>3</sup>)–H activation followed by reductive elimination to furnish the cyclopropane product.<sup>[113]</sup>

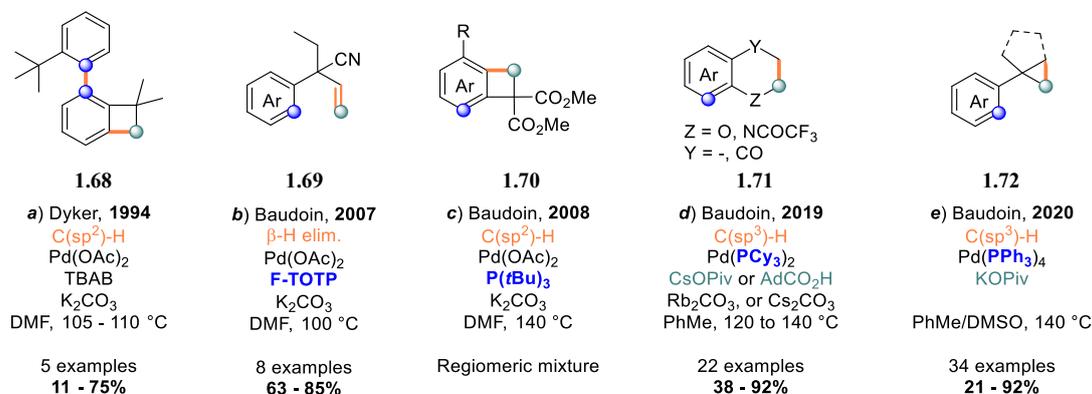


Figure 2. Selected examples of a subsequent C–H activation event after 1,4-Pd shift.

The 1,4-Pd shift was also extended to intermolecular reactions, in which the alkylpalladium species reacts with a variation of nucleophiles (Figure 3). An example of this was reported by

the Buchwald group, with the arylation of a *tert*-butyl group (**1.73**) in excellent yield when reacting 2,4,6-tri-*tert*-butylbromobenzene with phenyl boronic acid under their developed standard Suzuki-Miyaura coupling conditions,<sup>[114]</sup> while the expected biaryl product was not observed (Figure 3a). The shift is believed to be favored due to the steric congestion around the oxidative addition site. The same group further expanded this methodology to an intermolecular amination reaction (Figure 3b).<sup>[115]</sup> The employment of a **SIPr**-ligand in combination with NaOtBu as the base proved to be crucial for this effective transformation in presence of aniline derivatives. The regioselectivity is strongly dependent on the steric effect of the two *ortho*-substituents in regard to the oxidative addition site. In 2008, the Larock group disclosed the shift from an aryl to a benzylic position and subsequent C–O bond formation (Figure 3c).<sup>[116]</sup> The benzylic palladium species obtained after 1,4-shift was trapped with oxygen nucleophiles, such as carboxylates and phenoxides, to furnish the corresponding benzylic esters and ethers (**1.75**) after reductive elimination in good yield and excellent regioselectivity. Extended deuterium labeling studies in this transformation revealed the reversible nature of the Pd-shift. In a similar fashion, the Baudoin group recently reported the synthesis of amides and esters *via* carbonylative C(sp<sup>3</sup>)–H activation (Figure 3d).<sup>[117]</sup> Under similar conditions as for their cyclopropane synthesis,<sup>[113]</sup> a  $\sigma$ -alkylpalladium complex is formed upon treatment of the substrates after protonation of the corresponding 5-membered palladacycle. At this point, CO-insertion occurs with subsequent nucleophilic attack of the corresponding nucleophiles in the reaction media (amine or alcohol) and reductive elimination, providing the products **1.76** together with the regenerated Pd<sup>0</sup>-species. The indanone product arising from CO-insertion and direct reductive elimination was not observed as the nucleophilic addition was shown to be the faster of these two possible processes.

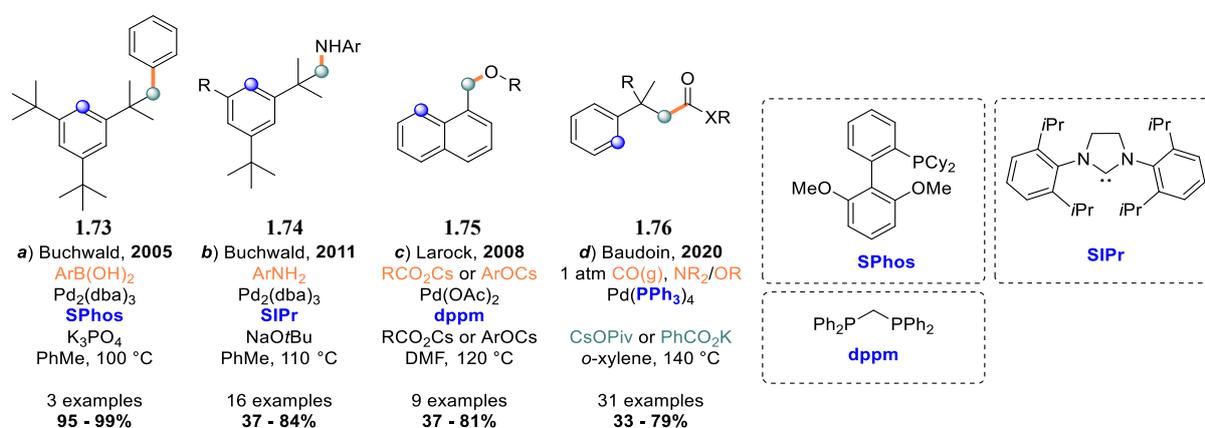
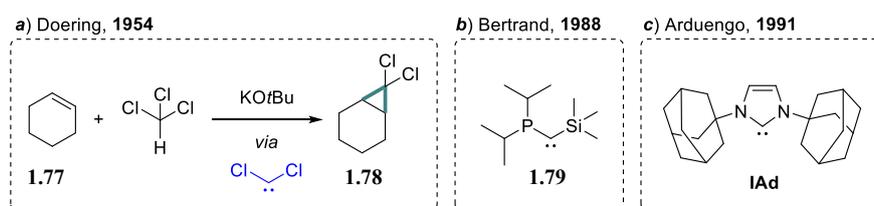


Figure 3. Selected examples of an intermolecular C(sp<sup>3</sup>)–H functionalization after 1,4-Pd shift.

## 1.4 Introduction *N*-Heterocyclic Carbenes

### 1.4.1 Carbenes

Carbenes are defined as neutral, divalent carbon atoms with only six valence electrons. First speculations about their existence were postulated by J. B. Duman in 1835.<sup>[118]</sup> However, it wasn't until in 1954, when the addition of dihalocarbenes into alkenes was reported by Doering, proving the occurrence of such neutral species (Scheme 21a).<sup>[119]</sup> Despite this success, carbenes were considered as highly elusive and reactive species, since all attempts at their isolation and unambiguous characterization were without success. In 1988, the first breakthrough in the synthesis and characterization of carbenes was disclosed by Bertrand and co-workers (Scheme 21b).<sup>[120]</sup> They reported the preparation and first isolation of a stabilized phosphine carbene **1.79**. Shortly thereafter, Arduengo and co-workers succeeded in the isolation of a bench-stable crystalline carbene, 1,3-diphenylimidazolidin-2-ylidene (**IAd**).<sup>[121]</sup> Since these initial studies, many more characteristics and reactivities of these carbene species were investigated.<sup>[122–124]</sup>



Scheme 21. First proof of an intermediate carbene species (a), first isolated carbene (b), first isolated bench-stable carbene (c).

Carbenes occur in two geometries. The linear *sp*-hybridized carbene has two degenerated *p*-orbitals ( $p_x, p_y$ ) resulting in a triplet ground state (Figure 4a). In case of the more common non-linear carbenes, the degeneracy of the two *p*-orbitals is broken as a consequence of its bent structure. As a result, the  $p_y$  is mostly unchanged whereas the  $p_x$  orbital acquires some *s* character due to the  $sp^2$ -type hybridization and is therefore called  $\sigma$ -orbital. Depending on the nature of the substituents, the bent carbene exists either in a singlet state with the two non-bonding electrons in the  $\sigma$ -orbital (HOMO) and an empty *p*-orbital (LUMO), or a triplet state with the two electrons in the two different orbitals with parallel spin. The multiplicity is strongly dependent on the substituents which therefore also dictates its stability and reactivity.

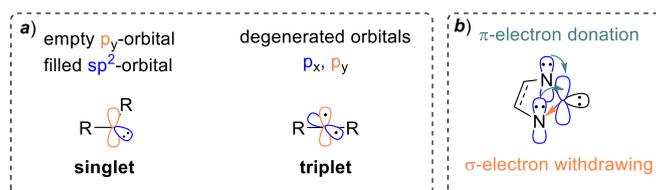
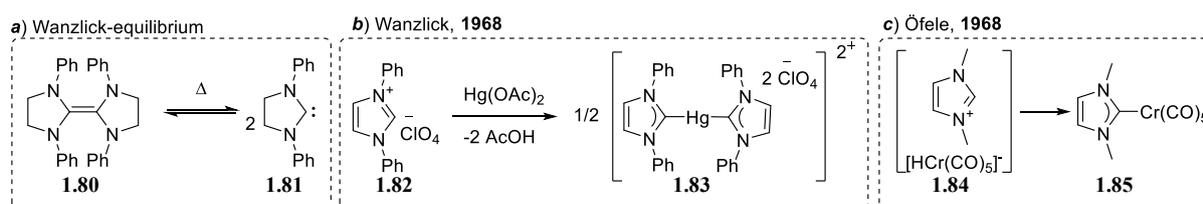


Figure 4. Representation of the two types of carbenes (a), the stabilization effect of the adjacent nitrogen atoms in NHCs (b).

### 1.4.2 *N*-Heterocyclic Carbenes

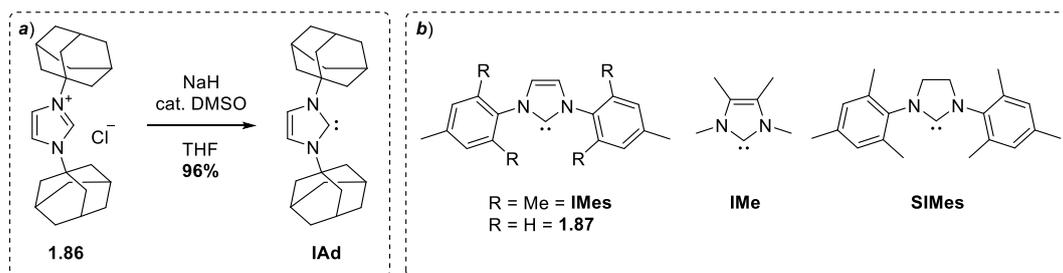
*N*-heterocyclic carbenes (NHCs) are a subclass of the previously described carbenes in which the divalent carbon atom is integrated in a *N*-heterocyclic scaffold. Their cyclic structure and the presence of an adjacent nitrogen atom to the carbon center strongly favors a singlet ground state. Additionally, the nitrogen atoms are stabilizing the carbene with electronic effects (Figure 4b). Thereby, their inductive  $\sigma$ -electron withdrawing effect lowers the HOMO of the carbene. Further, their  $\pi$ -electron donation into the empty carbene *p*-orbital results in an additional mesomeric stabilization.<sup>[125]</sup>



Scheme 22. Initial findings in the characterization of NHCs properties (a) and the first isolated NHC-metal complexes (b, c).

Initial investigations by Wanzlick demonstrated the *in situ* formation of free NHC **1.81** from the corresponding dimeric species **1.80** under thermolysis (Scheme 22a). Although all isolation attempts failed, the characterization of the reactivity of the *in situ* formed NHCs revealed a nucleophilic nature, which was not observed for other previously studied carbenes.<sup>[126]</sup> In the 1960s, however, Wanzlick & Schönherr<sup>[127]</sup> (Scheme 22b) and Öfele<sup>[128]</sup> (Scheme 22c) simultaneously reported the isolation and characterization of NHC-metal complexes. Finally, in 1991 Arduengo reported the isolation and characterization of the first crystalline and bench-stable carbene **IAd** which was obtained upon deprotonation of the imidazolium salt with dimsylv anion (Scheme 23a).<sup>[121]</sup> Initially, it was suggested that the steric hindrance of the adamantyl group is causing the outstanding stability of the isolated **IAd**. This theory was invalidated after the isolation and characterization of sterically less hindered NHCs such as **IMes** and **IME** (Scheme 23b). Their persistence derives from the electronic stabilization of these nucleophilic carbenes and can be further enhanced by the steric factors which result in their additional kinetic stabilization towards dimerization.<sup>[129]</sup> Furthermore, the isolation of the stable saturated carbene **SIMes** excluded the necessity of an aromatic core.<sup>[130]</sup> The simplicity of their preparation, their stable nature and the identification of many reactivities of these NHCs allow their application in a multitude of fields.<sup>[122,131–133]</sup> One of the most prominent fields in which they found a successful application is the organometallic chemistry. During the last decades, NHC-ancillary ligands have become a viable alternative of the more commonly applied phosphine ligands.<sup>[123,134–137]</sup>

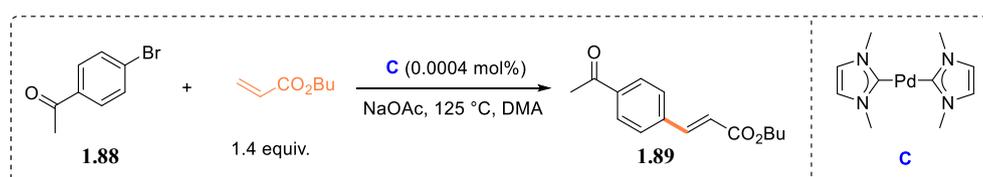
## General Introduction



Scheme 23. The synthesis of the first bench-stable NHC (**IAd**) (a). Isolated stable NHCs proving the electronic stabilization of such species (b).

### 1.4.3 NHCs as Ligands

Although the first NHC-metal complexes were already synthesized in the 1960s by Wanzlick<sup>[127]</sup> and Öfele,<sup>[128]</sup> they were employed the first time as ancillary ligands in a Pd-catalyzed Mizoroki-Heck reaction by Herrmann in 1995 (Scheme 24).<sup>[138]</sup> In a seminal example, 0.0004 mol% Pd/NHC complex **C** was sufficient for an efficient transformation. The high efficiency of the active complex was attributed to a high activity along with an outstanding long catalyst lifetime. From this moment on, it was believed that such electron rich NHCs, which bind with their  $sp^2$ -hybridized lone pair to the metal, were mimics of the strong  $\sigma$ -donor phosphine ligands.<sup>[139]</sup> However, chemists started to recognize that replacing phosphine ligands with NHCs often resulted in an improved catalyst activity and in some cases even in a complementary reactivity as showcased by the Grubbs 2<sup>nd</sup> generation catalyst.<sup>[140]</sup> Their outstanding performance and diverging reactivity to phosphines can mainly be explained in their differences in electronic- and steric properties.



Scheme 24. The first application of NHCs as ligands in transition-metal catalysis.

### 1.4.4 Electronic Properties

The electronic properties of ligands such as phosphines and NHCs are most commonly described by the Tolman electronic parameter (TEP).<sup>[141]</sup> Thereby, the ligands get ranked based on the infrared-stretching frequency of CO ligands in the corresponding  $[\text{Ni}(\text{CO})_3\text{L}]$  complexes (more recently, the less toxic  $\text{cis-}[\text{IrCl}(\text{CO})_2\text{L}]$  and  $\text{cis-}[\text{RhCl}(\text{CO})_2\text{L}]$  have been used).<sup>[142]</sup> The more electron donating ligands will increase the  $\pi$ -backbonding of the metal into the  $\pi^*$ -orbital of the CO-ligands resulting in a reduced stretching frequency. The different series (TEP, Ir, Rh), can be interconverted by the appropriate equations.<sup>[143,144]</sup> Generally, most of the NHCs show similar TEP values and are even lower than for the most electron rich phosphines. Furthermore, the range of TEP of phosphines values is much larger, as their substituents are

directly connected to the donor atom. For NHCs, the substituents are situated at the periphery of the ligand and therefore show much lower impact on the general electronic properties. Instead, the electronics of NHCs is mainly defined by their *N*-heterocyclic core. As for phosphine ligands, the nature of the M–NHC bond is dependent on the metal involved.<sup>[144]</sup> For  $d^8$  metals (*e.g.* Pd<sup>II</sup>), the average  $\pi$ -contribution in such NHC-complexes was calculated to be about 15%. For the more electron rich  $d^{10}$  metals,  $\pi$ -interactions contribute to about 20%. Furthermore, 75% of the  $\pi$ -interactions were calculated to originate from the  $M \rightarrow L \pi^*$ -backbonding.<sup>[144]</sup> Although perceivable  $\pi$ -bonding, the M–NHC bond is usually represented as a single bond which is also more representative of the ligand's rotation around the L–M bond. This relatively stable bond of NHCs compared to phosphines renders these complexes thermally and oxidatively more resistant. This property is usually expressed by a lower required catalyst loading and no need for excess of ligands compared to the metal-source. Furthermore, the reactions tend to be less sensitive towards oxygen as in the case of phosphine ligands.<sup>[145]</sup> Furthermore, the electron rich NHCs can facilitate challenging oxidative additions as in the case of Ar–Cl bonds.<sup>[146]</sup>

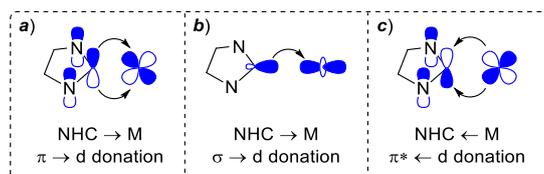


Figure 5. Contributions to the M–NHC bond:  $\pi$ -donation (a),  $\sigma$ -donation (b),  $\pi$ -backdonation (c).

### 1.4.5 Steric Properties

Comparing phosphine ligands and NHCs, a clear difference in their geometrical shape is apparent (Figure 6). Tertiary phosphine ligands have their substituents pointing away from the coordinated metal center and, therefore, are most commonly referred to as cone-shaped ligands. The geometry of NHCs is much more complex and often described as fan- or umbrella-shaped.<sup>[147]</sup> The *N*-substituents are generally more directed towards the metal center resulting in their presence in the coordination sphere and interactions with the substrate during catalysis. The cone-shaped phosphines are commonly described by their corresponding cone angle  $\theta$  (Figure 6). However, this model cannot appropriately represent a variety of geometrical shapes, such as in the case of NHCs. Nolan, Cavallo and co-workers introduced the buried volume ( $\%V_{bur}$ ) parameter to characterize such geometrically more flexible systems.<sup>[147]</sup> The percentage of a sphere ( $r = 3.5 \text{ \AA}$ ) occupied by a ligand coordinated to a metal center, which is located in the center of the sphere, is described by this parameter. For its determination, a M–L distance of 2.00 or 2.28  $\text{\AA}$  is employed. The steric impact of each ligand is thereby represented as a

single number. For a better representation of unsymmetrical ligands, the  $\%V_{\text{bur}}$  can be assigned for each quadrant around the metal center. For even better visualization of the steric profile of a complex and therefore gaining insights into the catalytic pocket, Cavallo and co-workers implemented the steric maps.<sup>[148]</sup> This tool allows the representation of the steric bulk *via* colored contours. Thereby, the surface of the ligands offered to the substrate is depicted which allows the description of catalyst-ligand interactions together with the catalytic pocket.  $\%V_{\text{bur}}$  and steric maps can be calculated based on the corresponding DFT-optimized structures or X-ray structures with the web application SambVca 2.0.<sup>[149]</sup> As a consequence, these methods are limited to the description of the thermodynamically most stable conformation in the gas phase of the ligand or its conformation which is favored in solid state, respectively.<sup>[150]</sup>

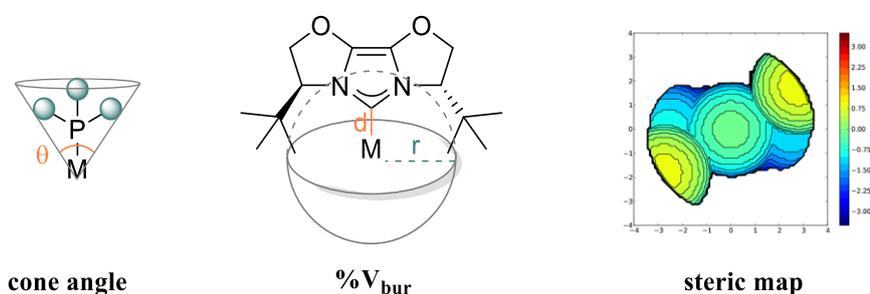


Figure 6. Descriptors of the steric properties of metal-complexes.

Since the initial studies, NHCs have become a viable class of ligands in transition metal-catalysis.<sup>[134,136,151]</sup> Their electronic and steric properties can be fine-tuned which allows an optimal ligand design for various transformations.<sup>[125]</sup> The strong NHC–M bond results often in high catalytic activity and long catalyst lifetimes. In addition, their strong  $\sigma$ -donor properties allow their use in challenging transformations, such as the oxidative addition into Ar–Cl bonds<sup>[146]</sup> and some general cross-coupling at room temperature.<sup>[135,152]</sup>

## 2 Aim of this Thesis

The Pd<sup>0</sup>-catalyzed C(sp<sup>3</sup>)-H arylation contributed to the revolution of the direct and efficient synthesis of (hetero)cyclic compounds. Since its emergence, it has become an important entity in the toolbox of organic chemists in the atom- and step-economic functionalization of C(sp<sup>3</sup>)-H bonds. Although major developments in this field were reported during the last two decades, there is still potential for further elaborations towards new reactivity and the broadening of its applicability. One of the most important aspects is the development of new ligands and catalysts to open the path to new reactions and chemical scaffolds. In particular, NHC ligands have been shown to exhibit complementary product selectivity to the traditionally more commonly employed phosphorus-based ligands in such reactions. The aim of this thesis was the further expansion of the repertoire of C(sp<sup>3</sup>)-H functionalization, with a special focus on the exploration of the unique properties of NHCs for such transformations.

Following the goal of broadening the application of this methodology, the first part of this thesis was dedicated to the development of new enantioselective transformations which allow access towards highly enantioenriched cyclic molecules. Enantiopure compounds have an immense impact in biology and our daily life. As a consequence, efficient and reliable methods for the construction and control of chiral centers are highly sought after. Although the Pd<sup>0</sup>-catalyzed C(sp<sup>3</sup>)-H arylation proved to be powerful in the construction of new C-C bonds, only a small variety of highly stereoselective versions thereof was reported up to these days. We envisioned the enantioselective synthesis of different valuable (hetero)cyclic products. The products were planned to be accessed *via* C(sp<sup>3</sup>)-H arylation of enantiotopic methyl groups. We intended to control the formed adjacent stereocenter upon desymmetrization by careful reaction conditions optimization with special focus on the choice and evaluation of known chiral ligands, especially NHCs. Furthermore, we considered the restricted access towards enantioenriched products *via* C(sp<sup>3</sup>)-H functionalization might originate from a lack of appropriate ligands for the envisioned desymmetrization. For this reason, we aspired the development of new catalysts which could improve the stereoinduction of the reaction. In addition to a remarkable reactivity and stereocontrol, IBiox ligands often showed an interesting product selectivity compared to other NHC- and phosphine ligands. Based on those interesting characteristics, we chose the IBiox-scaffold as template for a variation of modifications. In particular, we wanted to explore the synthesis of C<sub>2</sub>-symmetric-derivatives thereof. The four planned modifications consist of the homologation and bismethylation of the oxazoline rings, substitution of the oxygen atom in the

## Aim of this Thesis

core with nitrogen atoms, and the modification of the substituent at the stereogenic center. These alterations will influence the electronics and the steric profile of the ligands and, as consequence, their interactions with the substrates. In addition, the new ligands with the implemented modifications were planned to be evaluated in different enantioselective C(sp<sup>3</sup>)-H activation reactions. In a second approach, we aspired to design and synthesize new bifunctional NHC ligands. In a previous report, it was shown that carboxylate bearing phosphine ligands induce a better stereocontrol in C(sp<sup>2</sup>)-H arylations compared to their monofunctional analogs in combination with a base co-catalyst. This concept was translated into IBiox ligands to combine the beneficial electronic and steric properties of this class of ligands with the advantages of highly ordered transition state obtained by the bifunctionality. In contrast to the described bifunctional NHCs, the carboxylate-bearing side arm will be installed on the other side of the ligand as the stereocenter. Variations on the linker would result in a modified acidity and flexibility of the linker which can be fine-tuned for an optimal reaction outcome. Also, for this part, we envisioned exploring the applicability of these new ligands in enantioselective C-H functionalizations.

In the second part of this thesis, we aimed to investigate new reactions by exploiting the complementary reactivity of NHCs in C-H functionalizations. We were interested in exploring the performance of NHC-ligands in the context of 1,4-Pd shift. Therefore, our goal was to implement a new Pd-migration transformation in the synthesis of highly strained  $\beta$ -lactams. The new four-membered ring would be forged by the formation of a new C(sp<sup>3</sup>)-C(sp<sup>3</sup>) bond. The key to success in this envisioned project is to overcome the innate reactivity of the amide-substrate under C-H activation conditions which usually results in the well-explored direct  $\alpha$ -arylation towards oxindoles or C(sp<sup>2</sup>)-H arylation in the synthesis of dibenzazepinone. The feasibility of this ambitious project is strongly supported by the precedents in 1,4-Pd shift over *N*-Me groups together with the observed divergent product selectivity of NHCs in C-H functionalizations.

### 3 Towards the Enantioselective C(sp<sup>3</sup>)-H Arylation in the Synthesis of Spirocycles

#### 3.1 Introduction

Bicyclic hydrocarbons which are connected *via* one common carbon atom are defined as spirocycles.<sup>[153]</sup> The two connected rings lie in perpendicular planes resulting in a rigid structure with limited rotation and a potential axial symmetry when substituents are connected thereon. The first successful synthesis of such a spirane dates back to the 1890s<sup>[154]</sup> and has remained a formidable challenge since then. The spirocyclic motif is also of biological interest since this structural element can be found in many natural products.<sup>[155–157]</sup> Compared to their aromatic analogs,<sup>[158]</sup> spirocycles exhibit a lower conformational entropy penalty upon binding to the protein target<sup>[159]</sup> along with improved physical properties. These attributes often lead to superior bioactivities compared to the flat aromatic systems. Therefore, it is not surprising to see an increased presence of spirocycles in new pharmaceutically active molecules as a consequence of the progress in the development of synthetic routes towards such scaffolds.<sup>[159–161]</sup> Furthermore, axially chiral spirocycles exhibit a very high racemization barrier arising from the connection of the quaternary *sp*<sup>3</sup>-hybridized center which is an additional attractive characteristic of these compounds.<sup>[155]</sup> These interesting features were recognized by the chemical society and new chiral auxiliaries and ligands including phosphorus ligands<sup>[162]</sup> and Brønsted acids<sup>[163]</sup> comprising of a C<sub>2</sub>-symmetric axially chiral rigid spirocyclic motif were designed and successfully employed in asymmetric synthesis. The rigidity of such spirocyclic ligands along with their simple axial chirality distinguish them from other chiral ligands such as biaryl derivatives (BINOLS, BIPHENOL).

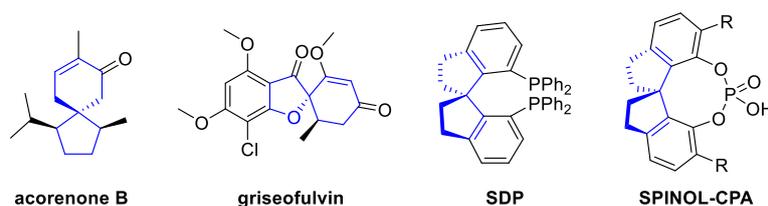


Figure 7. Spirocyclic scaffolds in natural products, drugs, ligands, and Brønsted acids (from left to right)

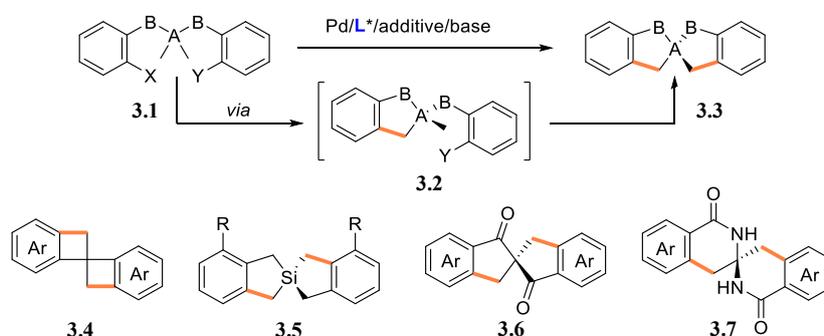
To date, most of the methods used for the construction of spirocyclic motifs include alkylations, metal-catalyzed transformations, ring closures, cycloadditions, radical-mediated bond formations, and rearrangements.<sup>[164,165]</sup> Usually, most of these transformations exhibit a low functional group tolerance which limits their application to the synthesis of simple spiranes. Furthermore, the enantioselective formation of these spirocyclic compounds not only suffers from the aforementioned limitations but also from the scarcely controlled formation of a

## Towards the Enantioselective C(sp<sup>3</sup>)-H Arylation in the Synthesis of Spirocycles

quaternary stereocenter. The stereoselective formation thereof is until now one of the biggest challenges for the organic chemistry community.<sup>[166]</sup> Consequently, the efficient and enantioselective construction of such axially chiral scaffolds is still a major limitation which needs to be addressed.

### 3.2 Aim of this Project

A way to overcome the limited access to axially chiral spirocycles could be found in the enantioselective Pd<sup>0</sup>-catalyzed C(sp<sup>3</sup>)-H activation. In this system, the quaternary stereocenter could be controlled by the desymmetrization of its two adjacent alkyl groups as shown in Scheme 25. After the stereodetermining initial C(sp<sup>3</sup>)-H arylation (intermediate **3.2**), a second C(sp<sup>3</sup>)-H functionalization could forge the desired enantioenriched spirocyclic motif (**3.3**). A similar concept was already validated in a Rh-catalyzed C(sp<sup>2</sup>)-H silylation by Kuninobu, Takai and co-workers in their synthesis of enantiomerically enriched spirostilbibfluorenes.<sup>[167]</sup> In this sense, we aimed to develop a Pd<sup>0</sup>-catalyzed enantioselective double C(sp<sup>3</sup>)-H arylation for the construction of “dimeric” axially chiral spirocycles. As seen in the previous chapter, Pd<sup>0</sup>-catalyzed C(sp<sup>3</sup>)-H arylation is a powerful and versatile tool in the atom-economic and efficient construction of (hetero)cyclic structures. In addition, some double C-H activations were previously reported.<sup>[168,169]</sup> These precedents strongly support the feasibility of the construction of a variety of different dimeric (hetero)cyclic spirocycles under Pd<sup>0</sup>-catalysis. Moreover, the various examples of enantioselective C(sp<sup>3</sup>)-H arylations presented in the previous chapter show the possibility of the stereocontrolled formation of the new quaternary stereocenters using chiral ligands or a chiral CMD-mediating base such as chiral phosphoric acids. We envisioned a variety of spirocycles being accessible from the corresponding dihalogenated precursor **3.1** as depicted in Scheme 25. Various spirocyclic products, such as **3.3**, with a stereogenic axis could be obtained by the introduction of different substituents at the B-position or on the aromatic ring where B = CH<sub>2</sub>. The herein presented examples constitute of cyclic motifs which were previously shown to be accessible *via* mono Pd<sup>0</sup>-catalyzed C(sp<sup>3</sup>)-H arylation.<sup>[53,54,56,64,78,170]</sup> This method would allow fast access to the highly value-added enantioenriched spirocycles which is a major limitation in the methodologies presented up to date.

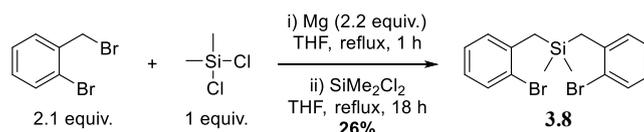


Scheme 25. Access towards axially chiral spirocyclic scaffolds *via* double C(sp<sup>3</sup>)-H activation under Pd<sup>0</sup>-catalysis.

### 3.3 Results and Discussion

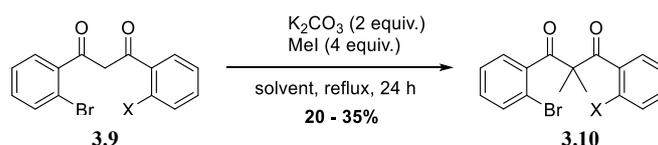
#### 3.3.1 Substrate Synthesis for Axially Chiral Spirocycles

In order to test the different desired C(sp<sup>3</sup>)-H arylations, the corresponding symmetric dihalogenated precursors had to be prepared in a first step. Therefore, the dibrominated silane substrate **3.8** was synthesized in 26% yield by the addition of *o*-bromobenzyl-magnesium species to dichlorodimethylsilane. The relatively low yield for this simple reaction is related to the difficult purification required.



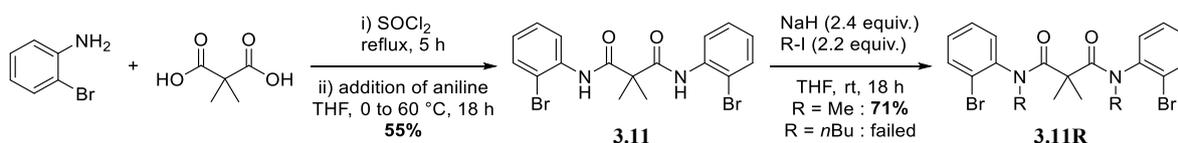
Scheme 26. Synthesis of symmetric silane **3.8**.

The substrate for the synthesis of the diindanone spirocycle **3.6** was easier to dictate and the corresponding dibromo, bromo-chloro, and monobromo analogs were synthesized upon treatment of the diketone species **3.9** (obtained after a 3 step sequence<sup>[171]</sup>) with K<sub>2</sub>CO<sub>3</sub> and MeI in refluxing toluene or acetone.



Scheme 27. Synthesis of the bismethylated diketone substrates from known intermediate **3.9**.

The bisamide substrate **3.11** for the envisioned synthesis of spiro lactam **3.7** was obtained in 55% yield by reacting 2,2-dimethylmalonyl dichloride with 2 equivalents of *o*-Br-aniline in THF at 60 °C (Scheme 28). Furthermore, bisamide **3.11** was deprotonated with NaH in THF and reacted with MeI yielding 71% of the symmetrical methylated tertiary amide **3.11Me**. With this alkylation, the effect of the *N*-alkyl substituent on the C(sp<sup>3</sup>)-H activation performance can be compared to the free NH, which was reported in the monocyclization towards dihydroquinolinones by Shi and co-workers.<sup>[64]</sup> Unfortunately, the alkylation with a longer alkyl chain to increase the solubility of the resulting alkylated bisamide failed (R = *n*Bu).



Scheme 28. Synthesis of the double C-H activation substrate **3.11**.

#### 3.3.2 Substrate Evaluation towards the Synthesis of Axially Chiral Spirocycles

During the last two decades, our group has established some standard conditions for substrate testing in Pd<sup>0</sup>-catalyzed C(sp<sup>3</sup>)-H arylation reactions as shown in Table 1.

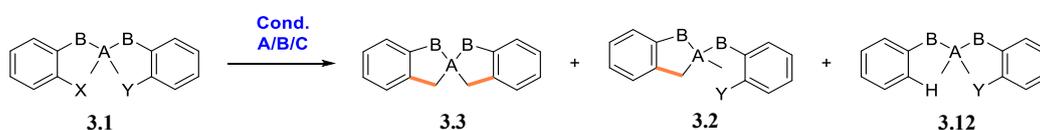
# Towards the Enantioselective C(sp<sup>3</sup>)-H Arylation in the Synthesis of Spirocycles

Table 1. Standard racemic C(sp<sup>3</sup>)-H arylation conditions.

Condition	
<b>A</b>	Pd(PR <sub>3</sub> ) <sub>2</sub> (10 mol%), Cs <sub>2</sub> CO <sub>3</sub> (1.1 equiv.), DMF, 140/160 °C, 18 h.
<b>B</b>	Pd(PR <sub>3</sub> ) <sub>2</sub> (10 mol%), CsOPiv (30 mol%), Cs <sub>2</sub> CO <sub>3</sub> (1.1 equiv.), mesitylene, 140/160 °C, 18 h.
<b>C</b>	[Pd(π-cin)Cl] <sub>2</sub> (5 mol%), IBioxMe <sub>4</sub> •HOTf (10 mol%), CsOPiv (1 equiv.), Cs <sub>2</sub> CO <sub>3</sub> (3 equiv.), mesitylene, 160 °C, 18 h.

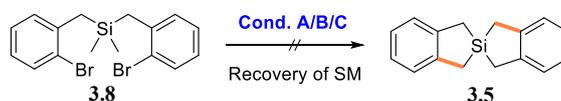
R = Ph, Cy, *t*Bu.

To assess the suitability of the synthesized dimeric precursors, all of them were subjected to the exact reported conditions. Together with the desired spirocyclic products **3.3**, we expect to obtain the monocyclized intermediate **3.2** with Y = Br, Cl, or H, and the most often observed protodehalogenated side product **3.12**.



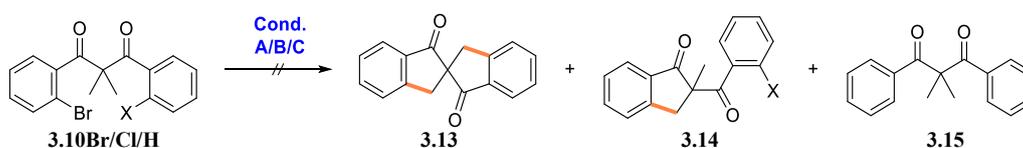
Scheme 29. Possible reaction products from the Pd<sup>0</sup>-catalyzed C(sp<sup>3</sup>)-H arylation conditions. X = Br, Cl; Y = Br, Cl.

Our investigations started with the use of the symmetrical dibenzylsilane **3.8**. Unfortunately, exclusive recovery of the starting material was observed in each case and no other species were observed by <sup>1</sup>H NMR or GC-MS.



Scheme 30. Full recovery of the dibromosilane **3.8** under C(sp<sup>3</sup>)-H arylation conditions.

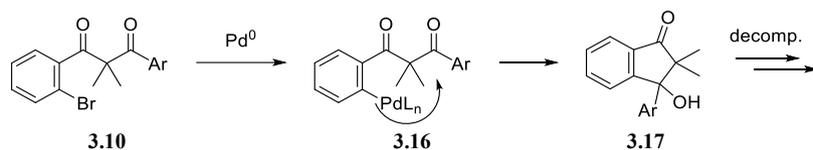
We then turned our attention towards the synthesis of diindanone spirocycle **3.13**. Therefore, the three different diketone substrates from **3.10** (Y = Br, Cl, H) were engaged under the standard reaction conditions. In the case of the double halogenated substrate **3.10Br** and **3.10Cl**, full decomposition was observed under cond. A with major decomposition under cond. C with some recovery of starting material. Some decomposition in case of **3.10Br**, but otherwise full recovery of the substrates was observed under cond. B. As we did not observe any productive reaction for these diketone substrates, we hypothesized that the poor performance under these typical C-H activation conditions may result from a deleterious effect on the two halogen atoms present in this substrate. It could also originate from the substrate scaffold itself.



Scheme 31. Standard C(sp<sup>3</sup>)-H activation conditions applied on the three different diketone-substrates **3.10**.

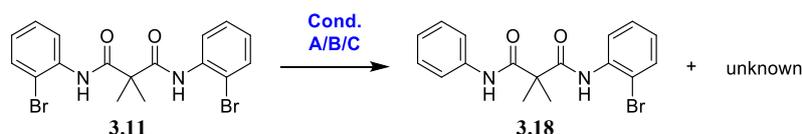
## Towards the Enantioselective C(sp<sup>3</sup>)-H Arylation in the Synthesis of Spirocycles

For this reason, the monobrominated substrate **3.10H** was submitted to the standard reaction conditions. The analysis of the obtained crude reaction mixtures revealed different levels of decomposition and to some extent recovery of the starting material. We speculate that the decomposition may have resulted from the addition of the Pd<sup>II</sup>-species, formed upon oxidative addition, to the ketone. The resulting alcohol **3.17** presumably decomposed further under the reaction conditions instead of undergoing the desired C(sp<sup>3</sup>)-H activation (Scheme 32).



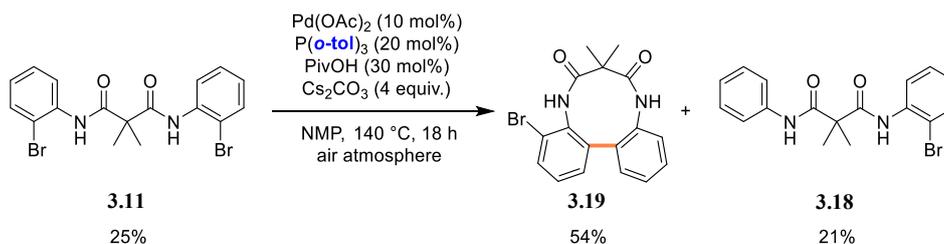
Scheme 32. Possible side reaction originating from the nucleophilic addition of the aryl-palladium **3.16** species into the ketone and further decomposition.

Bisamide **3.11** was tested under the standard conditions as depicted in Scheme 33. By doing so, only the monodebrominated species **3.18** was identified along with an unknown trace-compound which could not be analyzed. The *N*-methylated substrate did not result in any reactivity, most probably due to some solubility issues.



Scheme 33. Standard C(sp<sup>3</sup>)-H activation conditions applied on model bisamide substrate **3.11**.

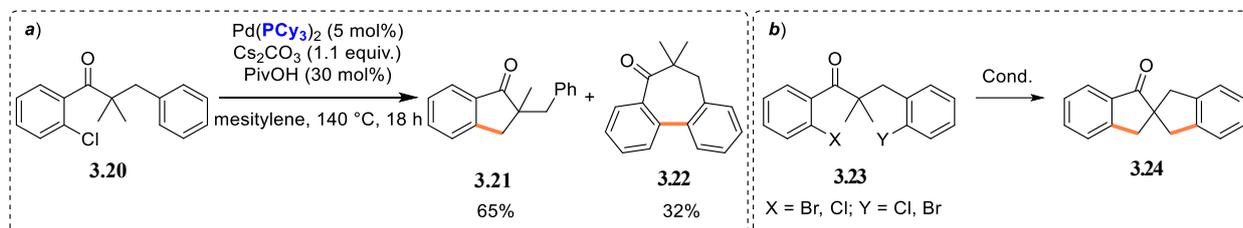
The bisamide substrate **3.11** was further engaged under the reported monocyclization conditions reported by the Shi group (Scheme 34).<sup>[64]</sup> Surprisingly, the involvement of P(*o*-tol)<sub>3</sub> ligand in NMP in combination with Pd(OAc)<sub>2</sub> under an atmosphere of air resulted in the formation of 9-membered bislactam **3.19** as the main product of an intramolecular C(sp<sup>2</sup>)-C(sp<sup>2</sup>) coupling. The only other products identified were the mono-dehalogenated **3.18** next to unreacted starting material **3.11**. A small screening revealed the best results for the 9-membered ring formation (**3.19**) in polar solvents in presence of air. However, no desired C(sp<sup>3</sup>)-H activation products were observed in any case.



Scheme 34. Unexpected formation of 9-membered bislactam **3.19** under the reported monocyclization conditions.

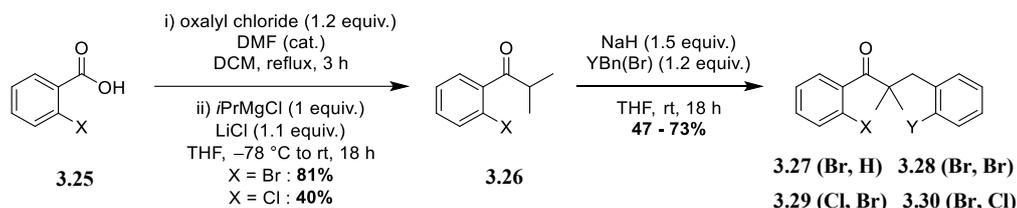
### 3.3.3 Substrate Evaluation towards the Synthesis of Central Chiral Spirocycles

After these unfruitful attempts in the synthesis of axially chiral spirocyclic compounds, we decided to start investigating unsymmetrical substrates which would result in central symmetric spirocycles instead. In a previous study, our group reported the synthesis of indanones *via* Pd<sup>0</sup>-catalyzed C(sp<sup>3</sup>)-H activation employing Pd(PCy<sub>3</sub>)<sub>2</sub> in combination with a pivalic acid co-catalyst and Cs<sub>2</sub>CO<sub>3</sub> in mesitylene at 140 °C.<sup>[56]</sup> In particular, a benzyl substituted indanone **3.21** was accessed in 65% along with the corresponding direct C(sp<sup>2</sup>)-H arylated product **3.22** in 32% yield (Scheme 35a). Installing a second halide on the other aromatic ring of **3.20** would allow access to the corresponding spirocycle **3.24** *via* two sequential C(sp<sup>3</sup>)-H activation events (Scheme 35b). Adding substituents on the right phenyl moiety would further permit the synthesis of central chiral spirocycles.



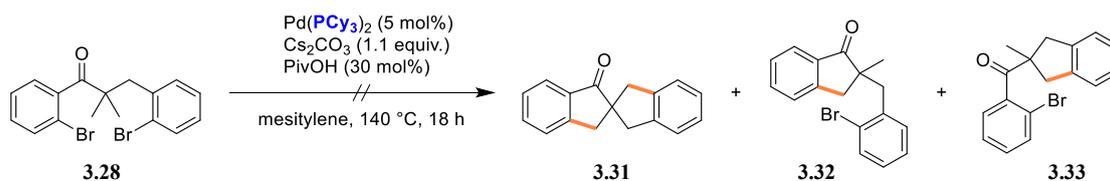
Scheme 35. a) Previous results in the synthesis of indanone **3.21** *via* Pd<sup>0</sup>-catalyzed C(sp<sup>3</sup>)-H activation of the Baudoin group. b) Envisioned spirocyclic product *via* two-fold C(sp<sup>3</sup>)-H activation

In order to test the feasibility of this double C(sp<sup>3</sup>)-H activation strategy, the suitable precursors were first synthesized (Scheme 36). The corresponding benzoyl halides of **3.25** were substituted with 2-propyl magnesium chloride in the presence of LiCl. A subsequent alkylation of the  $\alpha$ -position of the ketone with the corresponding benzyl bromides and NaH, resulted in the desired substrates (**3.27**, **3.28**, **3.29**, and **3.30**).



In a next step, the corresponding dibromo-substrate **3.28** was submitted to the reported mono-cyclization conditions (Scheme 37).<sup>[56]</sup> However, only a complex mixture was obtained and none of the products could be characterized. No desired C-H activation product was identified next to the unknown decomposition products.

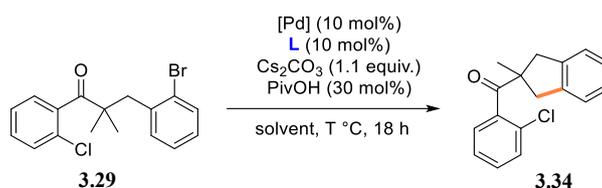
## Towards the Enantioselective C(sp<sup>3</sup>)-H Arylation in the Synthesis of Spirocycles



Scheme 37. Unsuccessful application of the described C(sp<sup>3</sup>)-H arylation conditions on dibromide **3.28**.

Suspecting the second bromide was causing this unproductive reaction, the corresponding ketones with Br and Cl- substituted substrates (**3.29** and **3.30**), respectively, were investigated. Engaging **3.29** with the chloride on the ketone-side under the standard C(sp<sup>3</sup>)-H conditions furnished the corresponding indanone **3.34** after mono C(sp<sup>3</sup>)-H arylation from the oxidative addition into the Ar-Br bond in 30% NMR yield (Table 2, entry 1). Running the reaction in DMF or replacing the ligand with *Pt*Bu<sub>3</sub> or PPh<sub>3</sub> resulted in strongly decreased yields (entries 2-4). Increasing the temperature to 160 °C (entry 5) or using NHC-ligands (entry 6) showed poor reactivity. Unfortunately, no spirocyclic product was observed in any of the reactions.

Table 2. Evaluation of the standard conditions on substrate **3.29**.



entry	[Pd]	ligand	base	temp [°C]	solvent	<sup>1</sup> H NMR yield <sup>a</sup>
1	Pd(PCy <sub>3</sub> ) <sub>2</sub>		Cs <sub>2</sub> CO <sub>3</sub>	140	mesitylene	30%
2	Pd(PCy <sub>3</sub> ) <sub>2</sub>		Cs <sub>2</sub> CO <sub>3</sub>	140	DMF	6%
3	Pd(PPh <sub>3</sub> ) <sub>4</sub>		Cs <sub>2</sub> CO <sub>3</sub>	140	mesitylene	7%
4	Pd( <i>Pt</i> Bu <sub>3</sub> ) <sub>2</sub>		Cs <sub>2</sub> CO <sub>3</sub>	140	mesitylene	2%
5	Pd(PCy <sub>3</sub> ) <sub>2</sub>		Cs <sub>2</sub> CO <sub>3</sub>	160	mesitylene	12%
6	[Pd(π-cin)Cl] <sub>2</sub>	IBioxMe <sub>4</sub> •HOTf	Cs <sub>2</sub> CO <sub>3</sub>	160	mesitylene	10%

<sup>a</sup> Determined with trichloroethylene as internal standard.

The same procedure was repeated with the substrate with interchanged Cl- and Br- on the ketone scaffold. Submission of ketone **3.30** under the described mono-cyclization conditions resulted in 44% of the indanone **3.35** and 33% yield of the corresponding 7-membered C(sp<sup>2</sup>)-H arylation product **3.36** (Table 3, entry 1). Exchanging the Pd(PCy<sub>3</sub>)<sub>2</sub> with Pd(PPh<sub>3</sub>)<sub>4</sub> or Pd(*Pt*Bu<sub>3</sub>)<sub>2</sub> resulted in a lower reactivity (entries 2 and 3). Increasing the temperature to 160 °C gave full conversion of the substrate **3.30** along with 56% of the indanone **3.35** and 37% of the 7-membered **3.36**, respectively (entry 4). Replacing mesitylene with DMF at 140 °C led to full conversion and 40% NMR yield of indanone **3.35** with a lower conversion towards **3.36** in 12% (entry 5). Interestingly, when NHC conditions were employed (entry 6) the formation of the 7-membered side product **3.36** was completely suppressed and the desired mono C(sp<sup>3</sup>)-H

## Towards the Enantioselective C(sp<sup>3</sup>)-H Arylation in the Synthesis of Spirocycles

activation product **3.35** was afforded in 51% <sup>1</sup>H NMR yield. Also, in this case, the spirocycle was never detected.

Table 3. Evaluation of the standard conditions on substrate **3.30**.

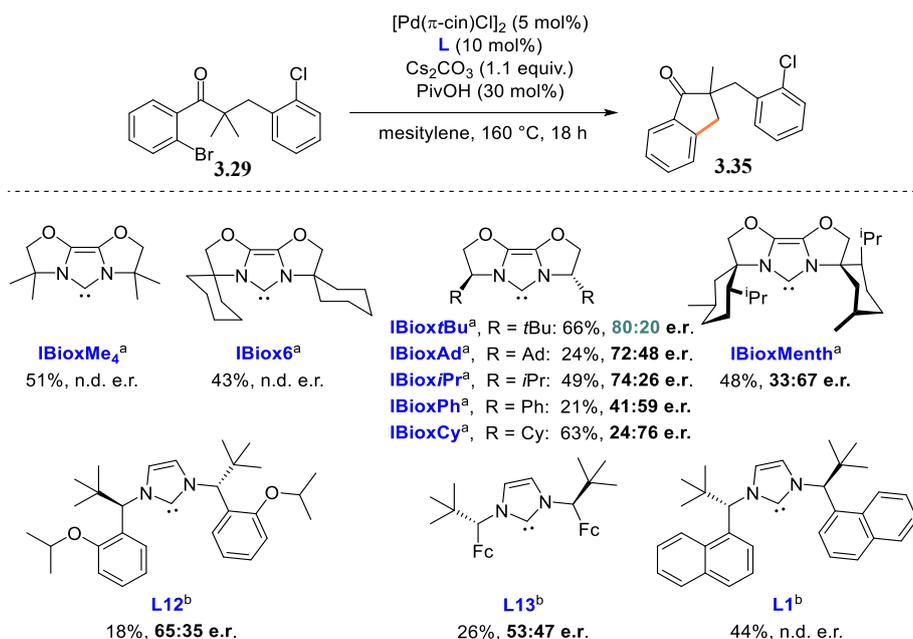
entry	[Pd]	ligand	temp [°C]	solvent	GC-MS ratio 3.30:3.35:3.36:3.37	<sup>1</sup> H NMR yield [%] 3.35/3.36 <sup>a</sup>
1	Pd( <b>PCy</b> <sub>3</sub> ) <sub>2</sub>		140	mesitylene	11:42:34:13	44/33
2	Pd( <b>PPh</b> <sub>3</sub> ) <sub>4</sub>		140	mesitylene	26:8:8:54	12/5
3	Pd( <b>PrBu</b> <sub>3</sub> ) <sub>2</sub>		140	mesitylene	19:15:0:47	n.d.
4	Pd( <b>PCy</b> <sub>3</sub> ) <sub>2</sub>		160	mesitylene	0:50:46:4	56/37
5	Pd( <b>PCy</b> <sub>3</sub> ) <sub>2</sub>		140	DMF	0:62:7:31	40/12
6	[Pd(π-cin)Cl] <sub>2</sub>	<b>IBioxMe</b> <sub>4</sub> <sup>c</sup>	160	mesitylene	0:66:0:11 <sup>b</sup>	51/0

<sup>a</sup> Determined with trichloroethylene as internal standard. <sup>b</sup> Unknown products observed in GC-MS. <sup>c</sup> Started from the HOTf salt.

### 3.3.4 Reaction Optimization

Encouraged by the decent yield and the full suppression of the C(sp<sup>2</sup>)-H activation product **3.36** under Pd/NHCs conditions, we started to investigate the influence of different NHC ligands on the reaction outcome as depicted in Scheme 38. A screening of various IBiox-type ligands<sup>[172-175]</sup> (**IBioxXX**) and Kündig-type NHCs<sup>[66,67,176]</sup> (**L1**, **L12**, **L13**) revealed an improved reactivity of the bulkier **IBiox<sup>t</sup>Bu** and **IBioxCy** with the formation of the indanone **3.35** in 66 and 63% yield, respectively. The indanones obtained in a reaction employing chiral ligands were isolated by flash column chromatography and analyzed by HPLC on a chiral stationary phase. The best performing ligand in terms of enantioinduction was again **IBiox<sup>t</sup>Bu** with an 80:20 e.r. Additionally, various chiral phosphines were tested under these reaction conditions, however, only very low conversion was observed in every case.

## Towards the Enantioselective C(sp<sup>3</sup>)-H Arylation in the Synthesis of Spirocycles

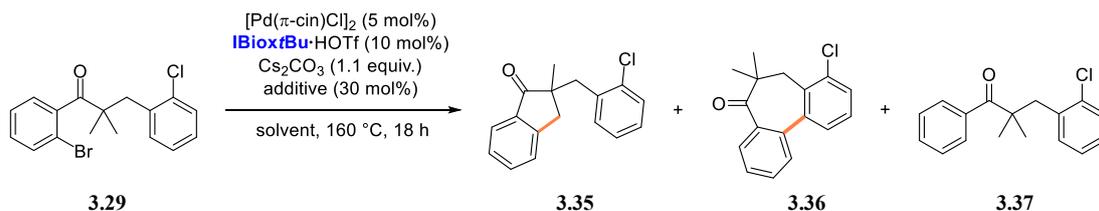


Scheme 38. Screening of NHC ligands in the synthesis of indanone **3.35**.<sup>a</sup> Started from the corresponding HOTf salt.<sup>b</sup> Started from the corresponding HI salt.

We decided to further optimize this mono C(sp<sup>3</sup>)-H activation in order to increase the yield and enantioselectivity of indanone **3.35**. The resulting aryl chloride **3.35** could then be employed in a subsequent C(sp<sup>3</sup>)-H activation which would result in enantioenriched spirocycles when installing a substituent on the remote phenyl group. Using bulkier CMD mediating bases such as adamantic acid instead of pivalic acid further improved the yield of indanone **3.35** to 76% without affecting the enantiomeric excess (Table 4, entry 2). Less sterically demanding additives such as mesitoic acid showed reduced reactivity and more than 70% of the substrate was recovered (entry 3). Employing other aromatic solvents such as cumene and *m*-xylene led to similar yields and enantioselectivities to mesitylene (entries 4-5). Polar solvents such as DMF (entry 6) favored the protodehalogenation over the C(sp<sup>3</sup>)-H activation although with only about 50% conversion of the reactant **3.29**. Etheral solvents like *n*Bu<sub>2</sub>O showed a beneficial effect on the formation of indanone **3.35** in 94% NMR yield, however, a small drop in e.r. (78:22) was measured (entry 7). Finally, a screening of the stoichiometric bases revealed K<sub>2</sub>CO<sub>3</sub> as optimal base, furnishing the indanone **3.35** in 99% <sup>1</sup>H NMR yield and 82:18 e.r. under the optimized conditions [Pd(π-cin)Cl]<sub>2</sub> (5 mol%), **IBiox<sup>t</sup>Bu**•HOTf (10 mol%), K<sub>2</sub>CO<sub>3</sub> (1.1 equiv.), adamantic acid (30 mol%), mesitylene, 160 °C, 18 h).

## Towards the Enantioselective C(sp<sup>3</sup>)-H Arylation in the Synthesis of Spirocycles

Table 4. Selected examples of the reaction optimization towards indanone **3.35**.



entry	additive	solvent	GC-MS ratio	<sup>1</sup> H NMR yield [%] <sup>a</sup>	e.r. <sup>b</sup>
			<b>3.29:3.35:3.36:3.37</b>	<b>3.35</b>	<b>3.35</b>
1	CsOPiv	mesitylene	0:84:0:10	66	80:20
2	AdCO <sub>2</sub> H	mesitylene	0:87:0:7	76	80:20
3	MesiCO <sub>2</sub> H	mesitylene	70:11:0:17	13	n.d.
4	AdCO <sub>2</sub> H	cumene	9:67:0:10	67	73:27
5	AdCO <sub>2</sub> H	<i>m</i> -xylene	0:85:2:0	72	80:20
6	AdCO <sub>2</sub> H	DMF	42:9:0:29	n.d.	n.d.
7	AdCO <sub>2</sub> H	<i>n</i> Bu <sub>2</sub> O	0:93:7:0	94	78:22
8	AdCO <sub>2</sub> H <sup>c</sup>	mesitylene	0:97:0:3	99	82:18

<sup>a</sup> Determined with trichloroethylene as internal standard. <sup>b</sup> Determined by HPLC on a chiral stationary phase. <sup>c</sup> With K<sub>2</sub>CO<sub>3</sub> instead of Cs<sub>2</sub>CO<sub>3</sub>.

Since the performed optimization did not show any improvement on the enantiomeric excess in this reaction, we employed enantiopure acids instead of the racemic adamantoic acid additive (conditions: Table 4, entry 8). Various amino acids and other chiral acids were tested (when available, both enantiomers were tested). The best three examples are summarized in Figure 8. The employed acids resulted in lower reactivity towards indanone **3.35** but comparable enantioinduction as in the case of the racemic adamantoic acid. Therefore, these chiral additives did not represent an improvement for the enantioselective formation of **3.35**.

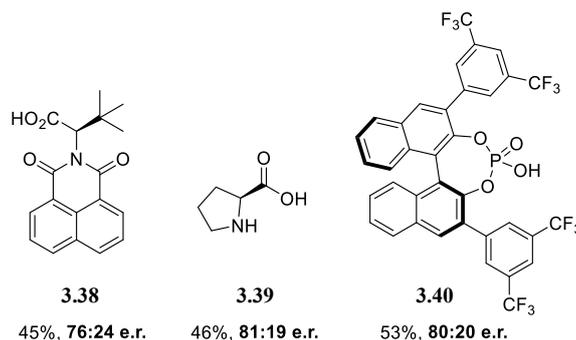


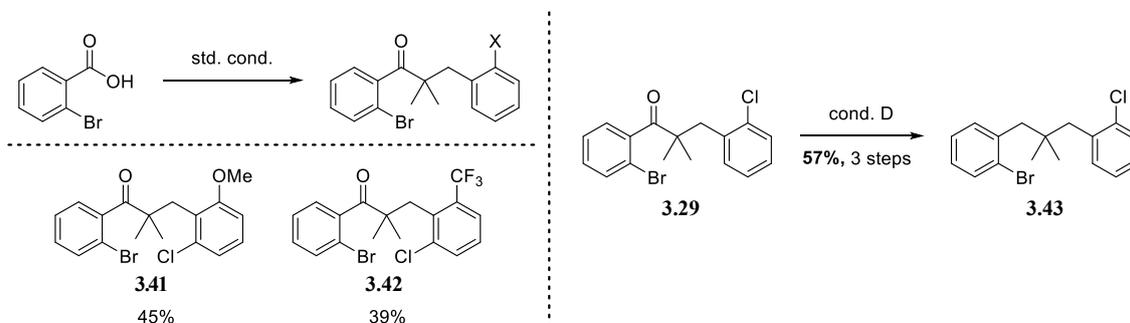
Figure 8. Selected examples of chiral acids in the enantioselective synthesis of indanone **3.35**. Only the matched cases are shown.

### 3.3.5 Mono C(sp<sup>3</sup>)-H Arylation: Substrate Modification

After this intensive screening without improving the enantiomeric excess, we turned our attention towards the modification of the reactant. Substrates bearing a second *ortho*-substituent on the remote aromatic ring were synthesized in the same manner with the corresponding benzyl

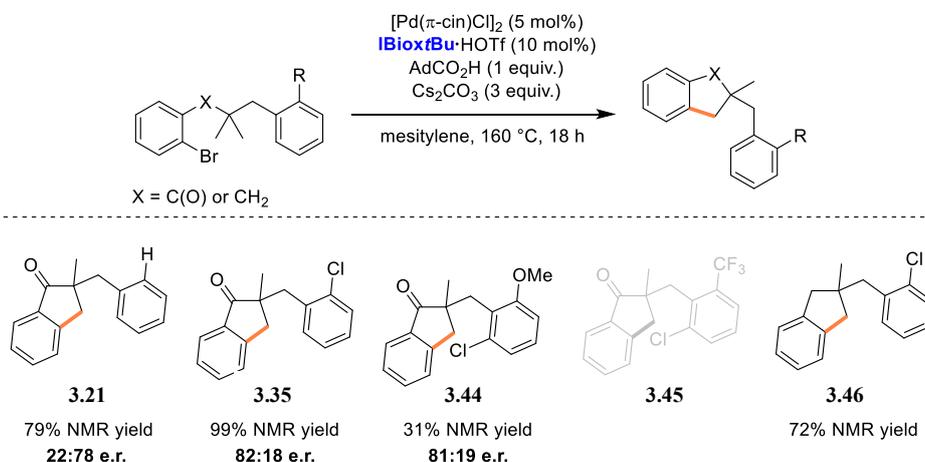
## Towards the Enantioselective C(sp<sup>3</sup>)-H Arylation in the Synthesis of Spirocycles

bromides (Scheme 39). In addition, the standard ketone substrate **3.29** was deoxygenated *via* reduction of the ketone to the alcohol with NaBH<sub>4</sub>, followed by methyl xanthate formation and Barton-McCombie deoxygenation in an overall yield of 57%. The resulting substrates were then engaged under the optimized C(sp<sup>3</sup>)-H activation conditions as summarized in Scheme 40.



Scheme 39. Left: Synthesis of bis-*ortho* substituted substrates. Right: synthesis of the deoxygenated derivative. Std. cond: *i*) oxalyl chloride (1.2 equiv.), DMF (cat.), DCM, reflux. *ii*) *i*PrMgCl (1.0 equiv.), LiCl (1.1 equiv.), THF, -78 °C to rt, 18 h. *iii*) NaH (1.5 equiv.), BnBr (1.2 equiv.), THF, rt, 18 h. cond. D: *i*) NaBH<sub>4</sub> (1.5 equiv.), MeOH, 0 °C, 30 min, 98%. *ii*) NaH (1.3 equiv.), CS<sub>2</sub> (1.3 equiv.), THF, reflux, 1.5 h, then MeI (1.3 equiv.), reflux, 18 h, quant. *iii*) *n*Bu<sub>3</sub>SnH (1.2 equiv.), AIBN (5 mol%), PhMe, reflux, 1 h, 59%

Starting from ketone **3.27** without any substituent on the remote aromatic ring resulted in 79% NMR yield of indanone **3.21** with a similar e.r. of 22:78 compared to the model system **3.35** (Scheme 40). The installation of a methoxy substituent on the second *ortho*-position of the side aromatic ring resulted in a drop of yield (31%) of indanone **3.44**, however with comparable 81:19 e.r. The CF<sub>3</sub>-substituted indanone **3.45** could not be obtained clean enough for adequate analysis. These results indicate that the substitution pattern on the remote aromatic ring does not seem to impact the enantioselectivity of the reaction. In contrast, the deoxygenated aryl bromide **3.43** furnished the corresponding indane **3.46** in 72% <sup>1</sup>H NMR yield, demonstrating the feasibility of indane synthesis under the herein optimized conditions.

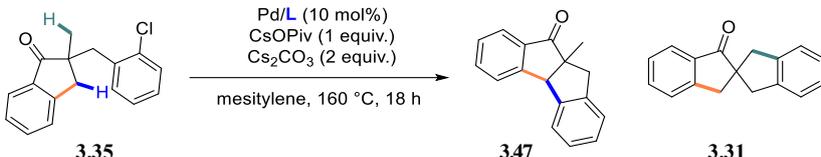


Scheme 40. Small substrate scope in the enantioselective synthesis of indanones and indane **3.46**.

### 3.3.6 Investigation towards the Spirocyclization

As every reaction parameter was optimized at this point and no further improvement in enantiomeric ratio was obtained, we continued to investigate the second C(sp<sup>3</sup>)-H activation step towards the desired spirocyclic product. Employing the two standard conditions with Pd(PCy<sub>3</sub>)<sub>2</sub> as catalyst (Table 5, entries 1 and 2) did not furnish any C-H activation products. However, submitting indanone **3.35** under standard NHC conditions (entry 3) resulted in the formation of the fused polycyclic product **3.47** in 44% yield without any trace of the desired spirocycle **3.31**.

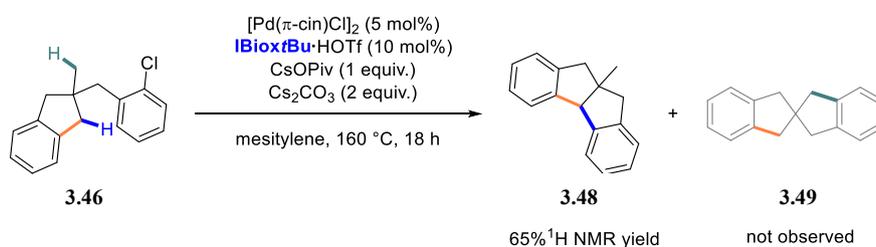
Table 5. Attempted spirocyclization *via* second C(sp<sup>3</sup>)-H arylation.



entry	Pd/L	solvent	<sup>1</sup> H NMR yield <sup>a</sup> <b>3.47:3.31</b>
1	Pd(PCy <sub>3</sub> ) <sub>2</sub>	mesitylene	0:0
2	Pd(PCy <sub>3</sub> ) <sub>2</sub>	DMF	0:0
3	Pd <sup>b</sup> /IBioxMe <sub>4</sub> <sup>c</sup>	mesitylene	44:0

<sup>a</sup> Determined with trichloroethylene as internal standard. <sup>b</sup> [Pd(π-cin)Cl]<sub>2</sub>. <sup>c</sup> HOTf salt.

The NHC conditions which led to a productive benzylic activation were further applied on indane **3.46**. Since the indanone and indane scaffolds have different angles in their five-membered cyclic systems, we hoped that this simple modification might favor the methyl activation instead of the methylene activation. However, the fused polycycle **3.48** was afforded as sole product in 65% <sup>1</sup>H NMR yield as shown in Scheme 41. As no spirocycle products were observed in any of these two reactions, we were discouraged about the selective formation of the spirocycles by simple reaction optimization. Therefore, no further investigations were undertaken in this project.



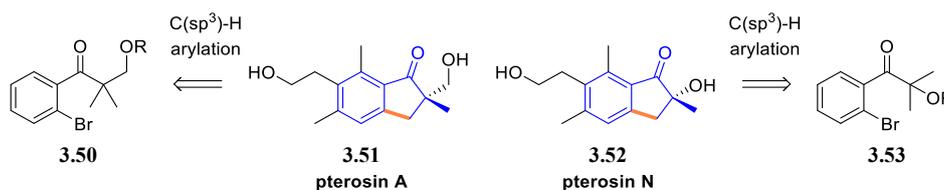
Scheme 41. Attempted spirocyclization from indane **3.46**.

### 3.3.7 Towards Enantioenriched Indanones

Although the spirocycles could not be accessed *via* our double C(sp<sup>3</sup>)-H activation strategy, we decided to build on our initial results in the formation of enantioenriched indanones. Indanones are a common motif in many natural products which exhibit interesting biological activities.<sup>[177]</sup> Their biological activity makes them also a privileged motif in drug discovery. Pterosins, a family of sesquiterpenes containing a 1-indanone core, are secondary metabolites that can be found in the bracken fern, *Pteridium aquilinum*.<sup>[178,179]</sup> Some members of this class of molecules, e.g. *pterosin A*, *B*, *K*, *L* as well as *pterosin N*, contain a well-defined quaternary stereocenter and can be seen as potential targets to be accessed by our previously described enantioselective C(sp<sup>3</sup>)-H arylation strategy. In particular, *pterosin A* with antidiabetic effects,<sup>[180]</sup> of which only racemic syntheses are reported up to date,<sup>[181,182]</sup> together with *pterosin N* of which only one enantioselective route is described,<sup>[183]</sup> are good potential candidates due to a possible desymmetrization of bismethylated ketone precursors **3.50** and **3.53**.

### 3.3.8 Substrate Synthesis and Evaluation

For initial studies to test the feasibility of this enantioselective transformation, we envisioned the synthesis of two model systems for *pterosin A* (**3.51**) and *pterosin N* (**3.52**) (Scheme 42). Each of which contains either a primary (**3.50**) or a tertiary alcohol (**3.53**) in their core structure, respectively. We expected an influence of the protecting groups of the alcohols on the resulting enantioselectivity and reactivity due to the different steric and electronic environments they provide.

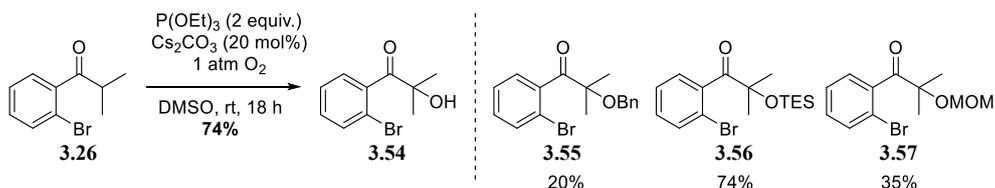


Scheme 42. Model systems for the synthesis of indanone-containing natural products *pterosin A* and *N*.

First, the model tertiary alcohol **3.53** towards *pterosin N* (**3.52**) was synthesized. For this purpose, ketone **3.26** was treated with triethylphosphite and catalytic amount of Cs<sub>2</sub>CO<sub>3</sub> under an O<sub>2</sub>-atmosphere affording the tertiary alcohol **3.54** in 74% yield (Scheme 43). We then synthesized different substrates in order to investigate the influence of the protecting group on the performance of the C-H activation step. Treatment of the alcohol with NaH and benzyl bromide resulted in 20% of the benzyl protected substrate **3.55**. A competing S<sub>N</sub>Ar reaction is the reason for this low yield. Furthermore, TES protection was performed under standard conditions (TESOTf and lutidine) furnishing 74% yield (**3.56**). Unfortunately, the sterically

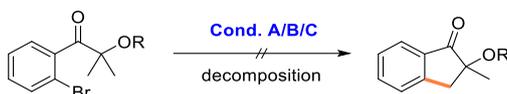
## Towards the Enantioselective C(sp<sup>3</sup>)-H Arylation in the Synthesis of Spirocycles

more demanding TBS-group could not be installed under these conditions. Treatment of the alcohol with MOMCl and DIPEA gave access to the MOM-protected substrate **3.57**.



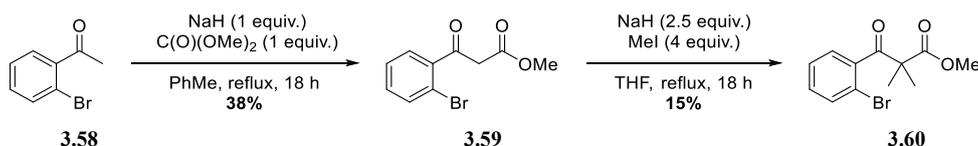
Scheme 43.  $\alpha$ -hydroxylation and subsequent protection in the synthesis of *pterosin N* model systems.

Submission of these three model systems under the three standard C–H activation conditions (Table 1, cond. A, B, C) resulted in decomposition along with some recovery of the corresponding substrate as determined by crude <sup>1</sup>H NMR spectroscopy (Scheme 44). We believe that the tertiary alcohol is relatively labile under these harsh reaction conditions which might be the reason for the observed decomposition.



Scheme 44. Evaluation of the protected tertiary alcohol substrates under standard C(sp<sup>3</sup>)-H arylation conditions.

Avoiding the presence of the potentially sensitive tertiary alcohol, we started to focus on the synthesis of model system **3.50** towards *pterosin A*. Initially, we decided to synthesize the corresponding  $\beta$ -keto-ester **3.60**, omitting the presence of any potentially labile hydroxyl group. The nucleophilic addition of the enolate from NaH mediated deprotonation of **3.58** on dimethylcarbonate followed by bismethylation with MeI and NaH afforded  $\beta$ -keto-ester **3.60** in 5.7% overall yield (Scheme 45).

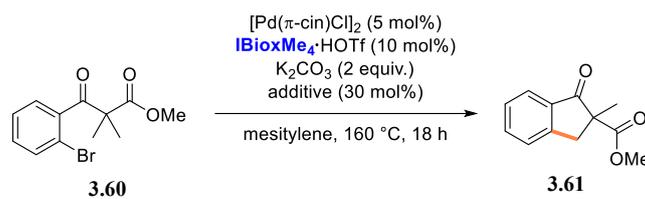


Scheme 45. Synthesis of bismethylated keto-ester **3.60**.

Employing the standard C–H activation with phosphine ligands on  $\beta$ -keto-ester **3.60** resulted in no reaction. Also, the optimized conditions for the efficient indanone formation with the **IBioxMe<sub>4</sub>** ligand failed and no reaction was observed (Table 6, entry 1). Interestingly, some reactivity could be obtained by replacing the adamantoic acid under NHC conditions with dibenzylphosphate (entry 2), however, the supposed product **3.61** was only observed in a low <sup>1</sup>H NMR yield of 13%.

## Towards the Enantioselective C(sp<sup>3</sup>)-H Arylation in the Synthesis of Spirocycles

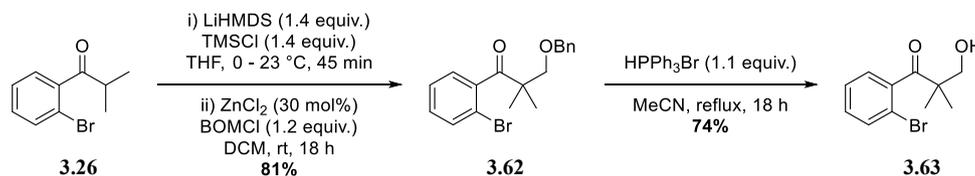
Table 6. Evaluation of the  $\beta$ -keto-ester substrate under C(sp<sup>3</sup>)-H arylation conditions.



entry	additive	<sup>1</sup> H NMR yield <sup>a</sup>
1	AdCO <sub>2</sub> H	0
2	(BnO) <sub>2</sub> PO <sub>2</sub> H	13

<sup>a</sup> Determined with trichloroethylene as internal standard.

In parallel, we investigated the model substrate **3.50** with the corresponding primary alcohol. The methylene linker and the nature of the primary alcohol could lead to a higher stability of this scaffold under the C-H activation conditions. Moreover, the alcohol might still be close enough for impacting the enantioselectivity of the reaction. Thus, the TMS enolate of **3.26** formed upon deprotonation with LiHMDS and trapping with TMSCl, was submitted to a ZnCl<sub>2</sub>-mediated alkylation with BOMCl in 81% yield (Scheme 46). Subsequently, the benzyl group of **3.62** was cleaved with HPPH<sub>3</sub>Br<sup>[184]</sup> yielding primary alcohol **3.63** in 74% yield. Deprotection of the benzyl ether **3.62** with Pd/C under an atmosphere of H<sub>2</sub> and in presence of ZnBr<sub>2</sub><sup>[185]</sup> (1 equivalent) resulted in an inseparable mixture of the free alcohol **3.63** and its debrominated derivative. Also, direct alkylation of ketone **3.26** with paraformaldehyde failed.



Scheme 46. Synthesis of primary alcohol **3.63**

### 3.3.9 Reaction Condition Optimization

Benzyl protected alcohol **3.62** was chosen as model substrate for a first reaction optimization, since it's the fastest to synthesize. Submission of this model substrate to the standard C(sp<sup>3</sup>)-H activation conditions (Table 1, cond. A, B, C) showed that phosphines and NHC ligands can efficiently promote this reaction (Table 7, entries 1-3).

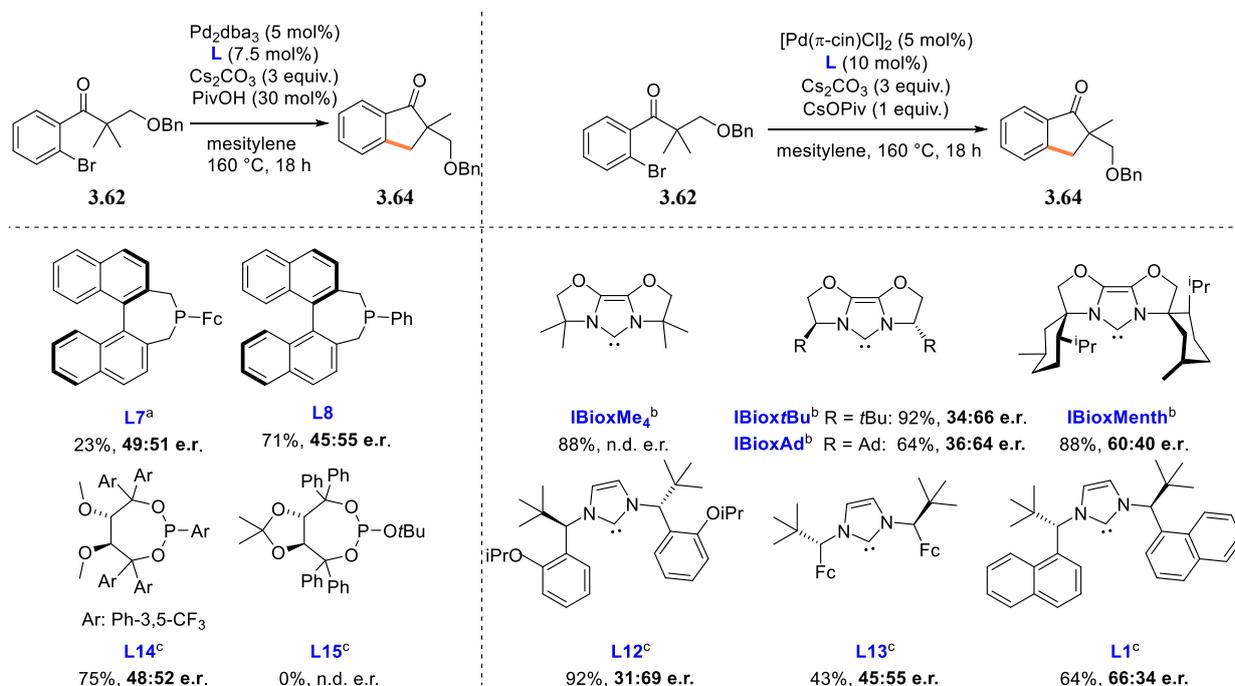
# Towards the Enantioselective C(sp<sup>3</sup>)-H Arylation in the Synthesis of Spirocycles

Table 7. Initial results in the racemic synthesis of indanone **3.64** via C(sp<sup>3</sup>)-H arylation.

entry	[Pd]	ligand	solvent	<sup>1</sup> H NMR yield <sup>a</sup>
1	Pd(PCy <sub>3</sub> ) <sub>2</sub>		mesitylene	99
2	Pd(PCy <sub>3</sub> ) <sub>2</sub>		DMF	60
3	[Pd(π-cin)Cl] <sub>2</sub>	IBioxMe <sup>b</sup>	mesitylene	88

<sup>a</sup> Determined with trichloroethylene as internal standard. <sup>b</sup> HOTf salt.

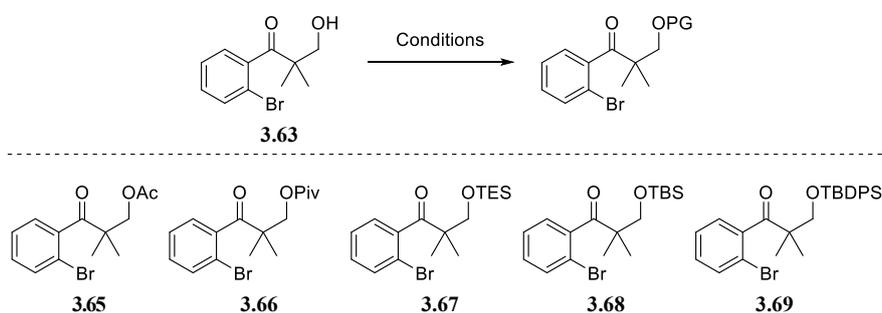
As we were interested in the enantioselective construction of the indanone core, we started to evaluate chiral phosphorus-based and NHC ligands in this reaction (Scheme 47). The employment of binatephos ligands (**L7** and **L8**) resulted in almost racemic indanone **3.64**. TADDOL derived phosphonites **L14** showed good reactivity, however, no enantioinduction was observed. Finally, phosphites **L15**<sup>[186]</sup> did not promote the reaction at all. On the other hand, the employment of chiral NHC ligands was more successful. The best performing ligands, **L12** and **IBioxfBu**, furnished indanone **3.64** in an excellent yield (both 92%) with 31:69 e.r. and 34:66 e.r., respectively. Screening of solvents, bases and additives did not show any improvement.



Scheme 47. Screening of chiral ligands in the enantioselective synthesis of indanone **3.64**.<sup>a</sup> HBF<sub>4</sub> salt. <sup>b</sup> HOTf salt. <sup>c</sup> HI salt.

### 3.3.10 Substrate and Reaction Condition Optimization

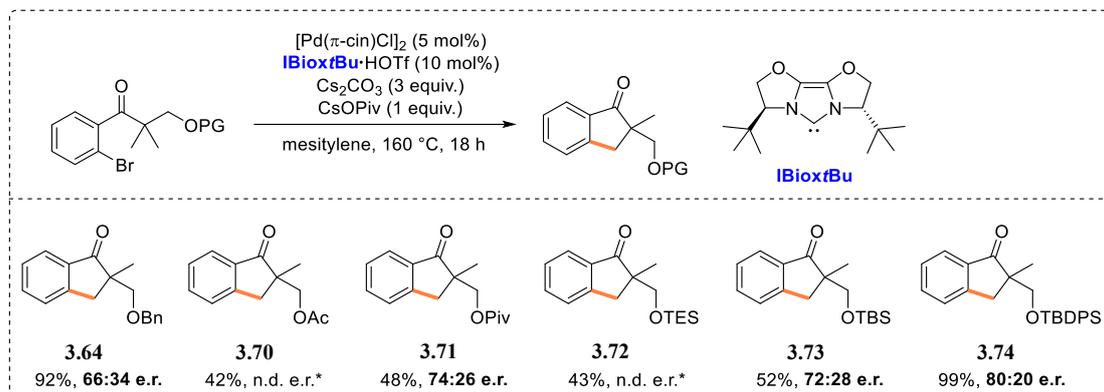
At this point, we were interested in the modification of the substrate to further increase the e.r. We questioned if the enantioselectivity could be affected by increasing the steric demand of the substrate. Firstly, we focused on the ketone. Unfortunately, the imine formation between ketone **3.62** and cyclohexylamine or the even less sterically demanding *o*-methylhydroxylamine failed. In both cases, no reaction was observed, not even under neat and anhydrous conditions at 130 °C (CyNH<sub>2</sub>). As the ketone functionality could not be further manipulated, we focused on the modification of the hydroxyl group. Different protecting groups were installed under standard reaction conditions. Thereby, a series of substrates with different steric impact (**3.65-3.69**) was accessed (Scheme 48).



Scheme 48. Library of differently protected primary alcohol substrates.

The previously evaluated best performing ligands **IBioxzBu** and **L12** were tested on each of the new substrates under standard conditions as shown in Scheme 49. However, **IBioxzBu** generally performed better and therefore only the corresponding results are discussed. Acetyl and pivaloyl groups resulted in a lower yield of the corresponding indanones **3.70** and **3.71** compared to the Bn-protected model substrate **3.64**. It seems that the ester groups are sensitive and partial decomposition occurred. However, an improved e.r. of 76:24 was obtained for pivaloyl protected **3.71** which might result from a better differentiation of the two enantiotopic methyl groups due to the sterically more demanding environment compared to the benzyl group. Unfortunately, the enantiomeric excess of the acetyl protected substrate could not be measured because of the moderate yield and difficulties in purification. Further, silane protected alcohols were investigated. The less sterically demanding TES group resulted in mediocre yields of 43% of **3.72**, similar to the yields of the previously discussed esters. Also, purification issues of **3.72** impeded the accurate determination of the enantiomeric excess. Luckily, by augmenting the steric demand with a TBDS group an improved yield was achieved (52%) compared to the less sterically demanding TES group. Moreover, the e.r. of the obtained indanone **3.73** increased to 72:28. Engaging the TBDPS protected alcohol **3.69** resulted in quantitative formation of the corresponding indanone **3.74**. Also the e.r. was improved compared to the Bn protected model

**3.64** with 80:20 e.r.. This substrate screening revealed TBDPS protected alcohol **3.69** as the best performing substrate.



\* these compounds could not be fully purified and therefore, no e.r. was measured.

Scheme 49. Evaluation of the different protected alcohols under the optimized reaction conditions. <sup>1</sup>H NMR yields were determined with trichloroethylene as internal standard. The e.r. was measured by normal phase HPLC analysis on a chiral stationary phase.

With the best substrate in hand, we undertook further optimization on this system. However, following an extensive screening of solvents, stoichiometric bases, additives, and concentration no improvement in the enantiomeric excess of the reaction was observed. A variety of chiral NHC ligands were tested again under the optimized reaction conditions on the TBDPS-protected alcohol **3.69**. However, no improvement in e.r. was achieved.

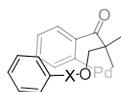
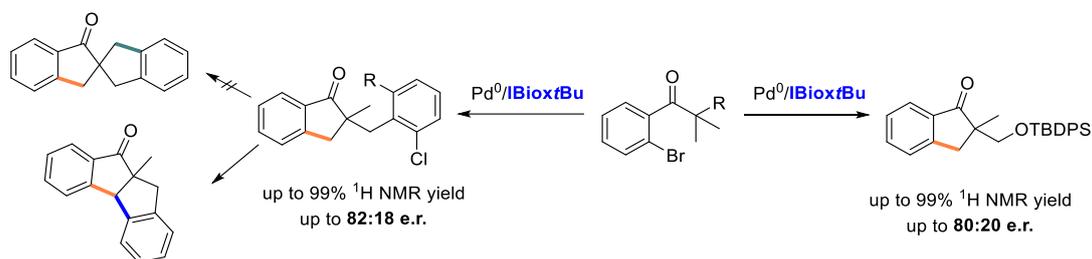


Figure 9. Probable  $\pi$ -stacking might result in a highly efficient C(sp<sup>3</sup>)-H arylation.

Since benzyl- and TBPDS-protected alcohols gave the best yields, we deduced a probable  $\pi$ -stacking occurring during the course of the reaction as proposed in Figure 9. This interaction might cause a favored transition state in this C(sp<sup>3</sup>)-H activation which would explain the high yield observed.

### 3.4 Conclusion and Outlook

Starting from various aryl bromide precursors, a highly efficient and streamlined synthesis of indanones was developed. The employment of IBiox-type ligands under Pd<sup>0</sup>-catalysis proved to be the best for the desymmetrization of the two methyl groups with moderate stereocontrol. A plateau of 80:20 e.r. was reached under optimized reaction conditions with the best performing **IBiox<sup>t</sup>Bu** ligand. Strikingly, the IBiox ligands successfully suppress the formation of the C(sp<sup>2</sup>)-H arylation side product, which was formed in a considerable amount under Pd/phosphine catalysis. Furthermore, the engagement of the benzylated indanones in a second C(sp<sup>3</sup>)-H activation resulted in the selective formation of a fused polycyclic system *via* the activation of the benzylic positions over the second methyl group. These results indicate a clear selectivity for the polyfused cycles, the synthesis of spirocycles *via* double C(sp<sup>3</sup>)-H activation turned out to be challenging under the applied reaction conditions. Nevertheless, in order to benefit from the obtained results, we modified the substrate to access a model system for the synthesis of indanones found in the family of pterodin natural products. Optimizations on the substrate and reaction conditions led to a highly efficient synthesis of the desired indanones, however, with a limited enantiomeric ratio of 80:20 under Pd<sup>0</sup>/IBiox catalysis.



Scheme 50. Developed syntheses of indanones under Pd<sup>0</sup>/IBiox<sup>t</sup>Bu catalysis.

In order to improve the enantioselectivity of these difficult reactions, new catalytic systems need to be developed. Preferably, new ligands exhibiting the high reactivity and selectivity for C(sp<sup>3</sup>)-H bonds as observed for IBiox ligands should be accessed. Therefore, a possible modification of the IBiox-core could be envisioned resulting in an altered steric demand of the ligands with similar electronic properties. These modifications might allow an enhanced differentiation of the enantiotopic methyl groups and, consequently, deliver the desired indanones in high enantioselectivity.

## 4 Towards the Synthesis of Novel IBiox-Type Ligands

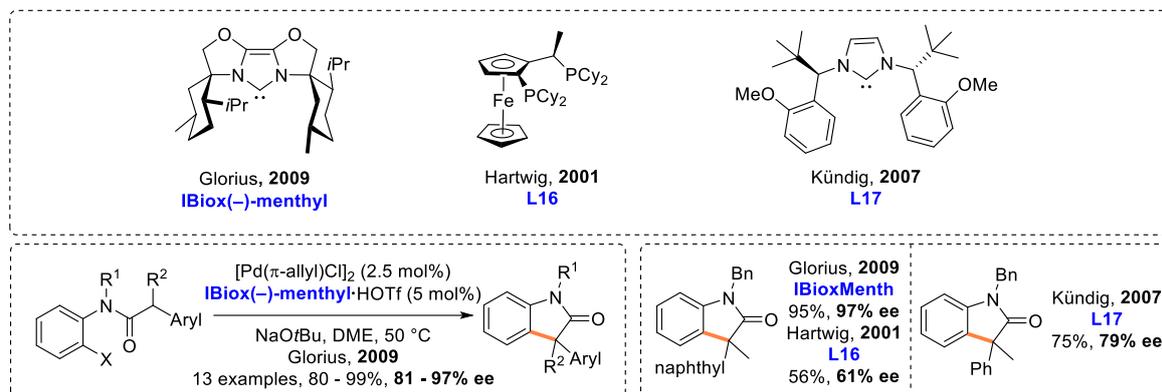
\*In collaboration with Diana Cavalli during the course of her Master Thesis.

### 4.1 Introduction

Asymmetric catalysis has evolved as a powerful method for the efficient and selective construction of chiral molecules which are of particular interests in biology, medicinal chemistry and related fields.<sup>[187]</sup> Of particular interest is the transition metal-catalyzed, enantioselective functionalization of C–H bonds, which allows a streamlined synthesis of such enantioenriched structures.<sup>[79]</sup> Although it is a powerful tool in the construction of such valuable molecules, a new catalytic system has to be developed for most classes of compounds. For example, various types of chiral ligands, including different phosphorus-based ligands such as phospholanes,<sup>[81]</sup> phosphoramidites,<sup>[82]</sup> and binepines<sup>[69]</sup> were required to access different motifs in high yield and enantioselectivity.<sup>[79,80]</sup> To broaden the applicability of such enantioselective C–H functionalizations, the Glorius group introduced a new class of oxazoline-derived NHC ligands.<sup>[172,173,175,188]</sup> One of these new chiral ligands, **IBiox(-)-menthyl** was employed in the enantioselective  $\alpha$ -arylation towards oxindoles (Scheme 51).<sup>[175]</sup> Thereby, this ligand proved superior to previously tested chiral phosphines and NHCs in regard of their reactivity and enantioselectivity.<sup>[189]</sup> Shortly before the report by Glorius, the Kündig group presented similar results for this transformation but employed a newly developed  $\alpha$ -alkylbenzylamine-derived imidazolylidine **L17** NHC ligand.<sup>[176]</sup> However, the **IBiox(-)-menthyl** ligand performed better in terms of stereocontrol in the case of sterically more demanding substrates than the NHC reported by the Kündig group.<sup>[176]</sup> The unique characteristics of the IBiox-family originate from the combination of the well-explored features of chiral bisoxazoline-scaffolds, a privileged motif in a variety of asymmetric catalysis,<sup>[187,190]</sup> with the favorable qualities of NHCs. The core of the IBiox ligands is defined by its tricyclic, rigid backbone which also determines their electronic properties. In general, this class of ligand has similar electronics compared to other typical NHCs as determined by their TEP values of 2048.6 to 2049.9  $\text{cm}^{-1}$  (IBiox)<sup>[188]</sup>, and 2051.5  $\text{cm}^{-1}$  (**IPr**<sup>[191]</sup>), respectively. As a consequence, IBiox ligands benefit, as most electron-rich NHCs, from a strong  $\sigma$ -donation. This property usually results in a strong M–NHC bond which often translates to excellent catalytic activities and complex stability. Their steric bulk can easily be modified by the substituents adjacent to the nitrogen atoms and originates from the initially employed (chiral) amino acids in their synthesis without affecting their electronic properties.<sup>[188]</sup> These highly interesting features

## Towards the Synthesis of Novel IBioX-Type Ligands

make IBioX a perfect candidate as ligands in other challenging transformations. Their steric properties can be fine-tuned which allows an optimal ligand design for each reaction.<sup>[125]</sup>



Scheme 51. New NHC ligands in the enantioselective  $\alpha$ -arylation.

## 4.2 Aim of this Project

IBioX ligands were demonstrated to perform best in terms of stereocontrol in the synthesis of enantioenriched indanones as shown in the previous paragraph. In addition, these ligands proved to be capable of suppressing the competing  $C(sp^2)$ -H arylation in similar reactions, which was commonly observed when phosphine ligands were employed. Keeping the advantages of this class of ligands in mind, we aimed to develop novel IBioX ligands. The modified IBioX ligands are supposed to retain their original reactivity and product selectivity while their stereoinduction is further improved by tuning their electronic and steric properties.

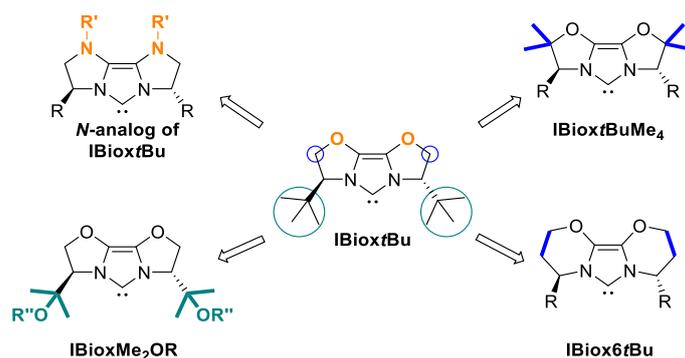


Figure 10. Envisioned modifications of the parent IBioXtBu ligand. R = *t*Bu

We envisioned the synthesis of a bisimidazoline analog (*N*-analog of IBioXtBu, Figure 10) of the parent IBioXtBu. Variation of R' will result in different electronic properties of the ligand as well as its different spatial arrangement. It is believed that this modification can result in an improved enantioinduction, which originates from higher flexibility compared to bisoxazolines. In particular, reported studies in which bisimidazoline ligands were employed in an asymmetric allylic alkylation of 1,3-bisaryl-2-propenyl acetate with malonate, showed an enhanced enantioinduction compared to their corresponding bisoxazoline ligands.<sup>[192]</sup> The second modification is the introduction of two methyl groups at the position  $\alpha$  to the oxygen of the oxazoline core, IBioXtBuMe<sub>4</sub>. Previously, Corey and Ishihara reported the beneficial effect of this bismethylation in their BOX ligand resulting in an enhanced enantioinduction in a Diels-Alder reaction compared to the corresponding non-methylated ligand.<sup>[193]</sup> Subsequently, Paquin and co-workers demonstrated a favorable effect of a bismethylation of an *i*Pr-PHOX ligand which resulted in improved stereocontrol in a Pd-catalyzed allylation in comparison to the non-methylated one.<sup>[194]</sup> A further modification consists of the replacement of the oxazoline with dihydro-oxazine, IBioX6tBu. Thereby, the angle of the substituents pointing toward the metal center changes along with the steric profile of the ligand. The ligand IBioXMe<sub>2</sub>OR, shows modification at the substituent adjacent to the nitrogen. By replacing a methyl of the *tert*-butyl

group with a hydroxyl group, the sterics of this substituent can be modulated by the installation of different protecting groups.

### 4.3 Computational Characterization of the Envisioned Ligands

In order to have a tool to compare the obtained enantioselectivities with the steric properties ( $\%V_{\text{bur}}$ ) of the corresponding ligands, the quadrant difference of percent of buried volume ( $\%V_{\text{bur}}(\text{QD})$ )<sup>1</sup> can be calculated. This method was applied to the known IBiox ligands, which were previously employed in such C–H arylation reactions (Figure 11). Strikingly, the highest enantioselectivities were obtained when the  $\%V_{\text{bur}}(\text{QD})$  was high, as shown for **IBiox*t*Bu** and **IBioxAd**. Ligands with lower  $\%V_{\text{bur}}(\text{QD})$  such as **IBioxMenth** (1.4), **IBiox*i*Pr** (14.0) and **IBioxCy** (14.1) yielded lower stereocontrol.

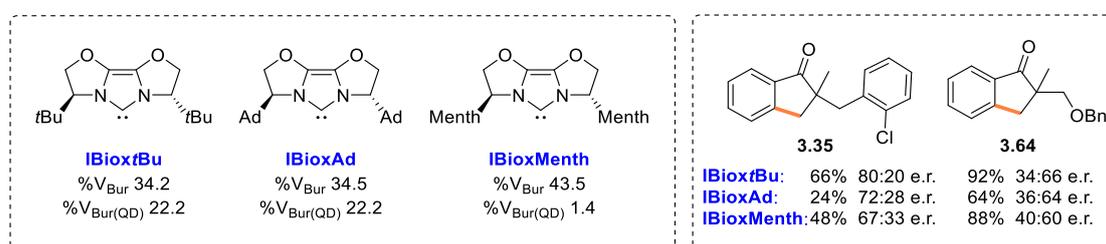


Figure 11. Steric characterization of **IBiox*t*Bu**, **IBioxAd** and **IBioxMenth** and the results of their application in the enantioselective synthesis of **3.35** and **3.64**.

Based on these findings, we postulated that in order to obtain better enantioselectivities in these transformations we needed to access IBiox ligands with favorable high  $\%V_{\text{bur}}(\text{QD})$ -values. The structure of the envisioned  $[\text{Pd}(\text{NHC})\pi\text{-allyl}]\text{Cl}$ -complexes with the NHC = **IBiox*t*BuMe<sub>4</sub>**, **IBioxMe<sub>2</sub>SiO**, and **IBiox6*t*Bu** were modeled by Michael Devereux (DFT calculations using BP86/TZVP as level of calculations). Based on these results, their  $\%V_{\text{bur}}$  and  $\%V_{\text{bur}}(\text{QD})$  were found as shown in Figure 12 by using the SambVca 2.1 web application.<sup>[149]</sup> On the basis of the assumption of the involvement of  $\%V_{\text{bur}}(\text{QD})$ , higher stereocontrol can be expected from the TMS-protected **IBioxMe<sub>2</sub>SiO** compared to the parent **IBiox*t*Bu**. The employment of **IBiox*t*BuMe<sub>4</sub>** and **IBiox6*t*Bu** would result in similar performance as the parental ligand.

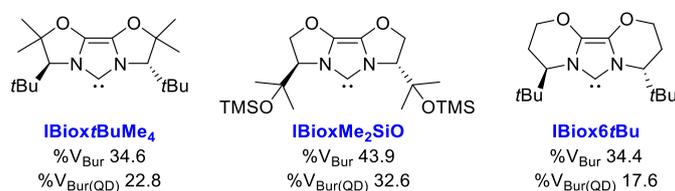


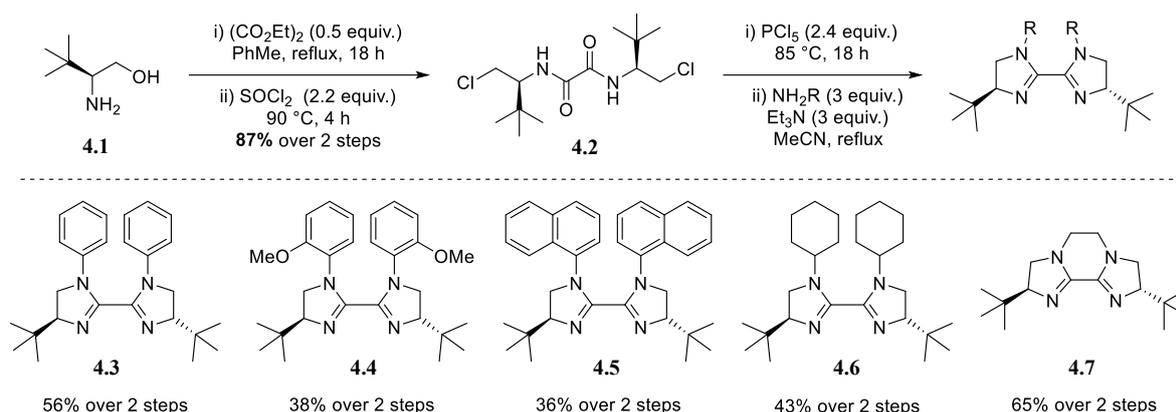
Figure 12. Calculated steric properties of the target ligands.

<sup>1</sup>  $\%V_{\text{bur}}(\text{QD}) = \frac{\Sigma \text{ most occupied quadrants} - \Sigma \text{ least occupied quadrants}}{2}$

## 4.4 Results and Discussion

### 4.4.1 Synthesis towards an *N*-Analog of the IBioX/Bu ligand

Five different bisimidazolines were synthesized following the described procedure of Song and co-workers as depicted in Scheme 52.<sup>[192]</sup> Thereby, (*L*)-*tert*-leucinol **4.1** was condensed with diethyl oxalate and further chlorinated with SOCl<sub>2</sub> resulting in bisamide **4.2** in 87% over two steps. Subsequent dehydration upon treatment with PCl<sub>5</sub> at 85 °C delivered an imidoyl chloride intermediate which was further reacted with the corresponding amines to furnish the substituted bisimidazolines **4.3-4.7**. The aniline derivative **4.3** was synthesized along with the 2-methoxy aniline **4.4** and naphthalene substituted amine **4.5** to investigate the electronic influence of the substituents and the enlarged aromatic surface which might lead to  $\pi$ -stacking with the ligand. In addition, the impact of the dihedral-angle on the scaffold can be evaluated. The more sterically demanding cyclohexyl derivative **4.6** along with the ethyl-linked fused tricyclic **4.7** were synthesized for further modification of their dihedral-angle.

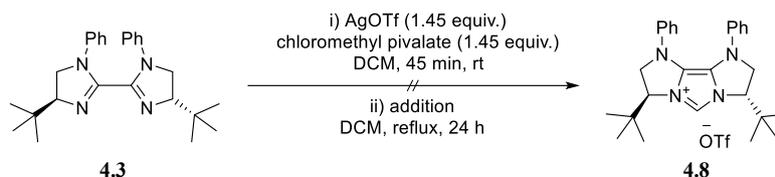


Scheme 52. Synthesis of five different optically pure bisimidazolines from (*L*)-*tert*-leucinol.

In order to access the *N*-analogs of the IBioX ligand, a final cyclization of the bisimidazolines was required. Following the well-established procedure reported by the Glorius group,<sup>[172]</sup> the chloride on the chloromethyl pivalate was exchanged with a triflate from AgOTf in the absence of light. The thereby formed triflated species was subsequently added to the phenyl-substituted bisimidazolines **4.3** and refluxed in DCM for 24 h (Scheme 53). After removal of the solvent, the crude <sup>1</sup>H NMR revealed two singlets with a chemical shift >8 ppm, which can originate from the desired imidazolium salt **4.8**. Unfortunately, after purification by flash column chromatography (DCM/MeOH system), the isolated fractions showed new species in the <sup>1</sup>H NMR spectrum and no signal with a chemical shift above 8 ppm. The presence of these unknown products after purification clearly indicates a decomposition occurring during this process. The reaction was repeated in CDCl<sub>3</sub> and the different steps were monitored by <sup>1</sup>H NMR by taking aliquots and their direct measurement. Usually, the characteristic highly shifted peaks

## Towards the Synthesis of Novel IBiox-Type Ligands

for the desired product were found as a minor product in the reaction mixture. Since the purification by flash column chromatography previously failed, recrystallization in DCM/Et<sub>2</sub>O was performed on this reaction mixture, however precipitation was not observed. As it is known that the stability of the resulting cyclized salt for some NHC-precursors is dependent on its corresponding counter ion, the crude containing the desired signals in its <sup>1</sup>H NMR was directly engaged with 10 equivalents of NaI in acetone for anion exchange. Unfortunately, the desired product was not observed.



Scheme 53. Attempted imidazolium synthesis under Glorius' condition.

Considering that the herein described bisimidazoline **4.3** seemed to be quite reactive and all of the starting material was consumed in less than 1 h at room temperature, we theorized that the substrate could be too reactive under the applied reaction conditions giving rise to the undesired side products. The pivalic species was therefore added at 0 °C to **4.3** and let warm to room temperature overnight. The crude NMR showed full conversion of the substrate and new signals in the <sup>1</sup>H NMR, however only traces of singlets at >8 ppm. Lowering the temperature to even -65 °C gave comparable results with the full consumption of the reactant in less than 1 h. In previous reports, different electrophiles were shown to result in the most efficient product formation in the cyclization of some NHC-precursors. The reported procedures with EtOCH<sub>2</sub>Cl with AgOTf and formaldehyde with HCl at 80 °C were tested on the bisimidazoline substrate.<sup>[195]</sup> None of these approaches led to the formation of the desired imidazolium salt **4.8**. At this point, we were wondering if the electronic nature or the conformation of the phenyl-substituted bisimidazoline might cause the impeded formation of the desired imidazolium salt **4.8**. Therefore, the cyclohexylamine derived **4.6** and ethylene-bridged **4.7** bisimidazoline were engaged under Glorius' conditions.<sup>[172]</sup> The cyclohexyl derivative resulted in the complete conversion of the reactant **4.6**, but no characteristic imidazolium peaks were observed in the spectrum of the crude. The ethylene-linked **4.7** resulted in a crude whose <sup>1</sup>H NMR spectrum shows an intense characteristic signal (Figure 13). The crude was submitted to a flash column chromatography purification on Alox since the previous decomposition of the phenyl-analog **4.8** on silica was observed. However, the isolated fractions, again, were not in agreement with the crude <sup>1</sup>H NMR, indicating decomposition during the purification process.

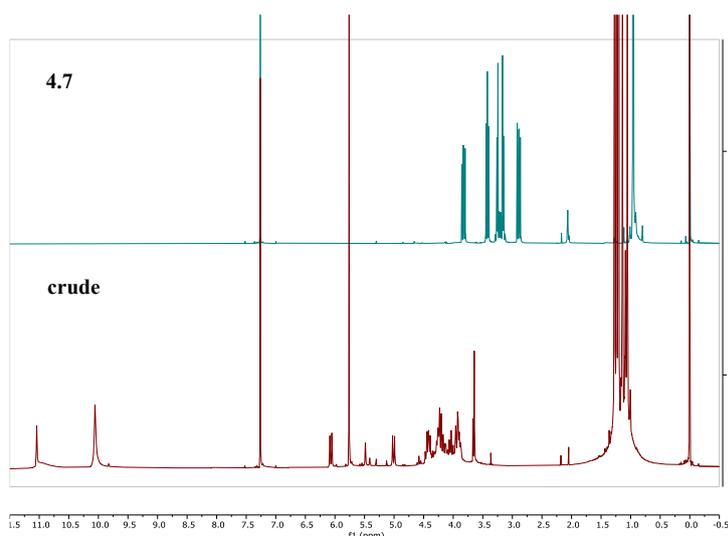
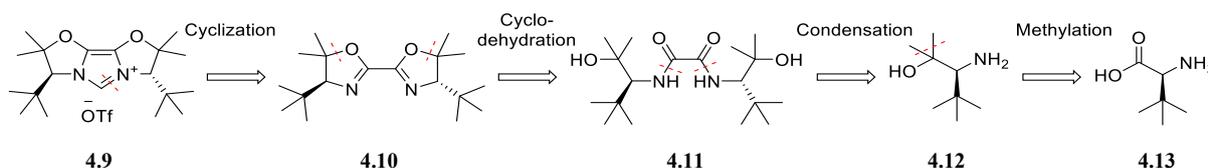


Figure 13.  $^1\text{H}$  NMR in  $\text{CDCl}_3$  of **4.7** and the crude after attempted cyclization under Glorius' conditions.

For a better understanding of what was taking place over the course of the reaction,  $^1\text{H}$  NMR studies were conducted. Usually, the maximum intensity of the characteristic singlet at about 9.5 – 10.0 ppm was observed in the course of the first hour after the addition of the electrophile at room temperature for all the tested substrates. In the case of  $\text{R} = \text{Ph}$  and  $= \text{Cy}$ , the intensity of this singlet decreased in 4 h and sometimes even fully disappeared. Knowing that only a low conversion of the more flexible substrates towards the desired imidazolium salt was observed, we were intrigued to understand the reason for its instability. Interestingly, the addition of 1 equivalent of methanol to the reaction after 40 min, resulted in the complete disappearance of the characteristic singlets for  $\text{R} = \text{Ph}$ , and in less than 1 min for the ethyl-linked diimidazoline **4.7**. This observation explains the decomposition obtained during the purification attempts wherein MeOH was used as one of the solvents. At this point, we deduced that the potentially formed imidazolium salts are sensitive towards any kind of nucleophiles, such as MeOH and  $\text{H}_2\text{O}$ , which would explain the observed decomposition in each case. The impossibility of reproducing the results in combination with the difficulty in working in a nucleophile-free environment under such reaction conditions prevented further studies on the optimization of the synthesis of this class of ligands.

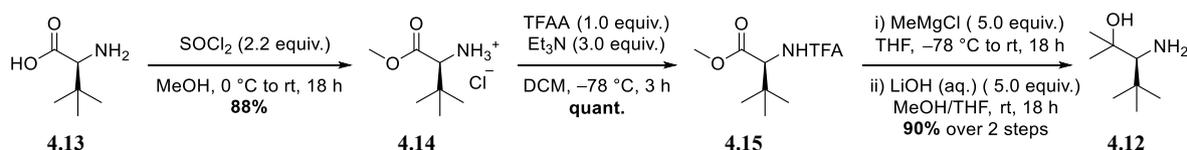
#### 4.4.2 Synthesis of IBiox*t*BuMe<sub>4</sub>•HOTf

We planned to synthesize the tetramethylated IBiox*t*BuMe<sub>4</sub> *via* a modified route reported by the Glorius group for the IBiox*t*Bu ligand as shown in Scheme 54.<sup>[172]</sup> Thereby, the desired imidazolium salt **4.9** could be obtained after imidazolium cyclization of bisoxazolin **4.10**. Cyclodehydration of the dimeric amide **4.11** would furnish the bicyclic oxazoline **4.10** *via* an S<sub>N</sub>1 mechanism. Instead of direct condensation of (*L*)-*tert*-leucine **4.1** with diethyl oxalate, the bismethylated (*L*)-*tert*-leucinol derivative could be obtained after methyl ester formation and subsequent methyl nucleophile addition to the carbonyl group at low temperature to avoid racemization.



Scheme 54. Retrosynthetic analysis of the IBiox*t*BuMe<sub>4</sub> ligand-precursor **4.9**.

Following this retrosynthetic plan, the hydrochloride salt of the methyl ester of (*L*)-*tert*-leucinol **4.14** was obtained upon treatment of (*L*)-*tert*-leucine with SOCl<sub>2</sub> and MeOH in 88% yield (Scheme 55). Subsequent TFA protection of the free amine group with trifluoroacetic anhydride and triethylamine as a base at -78 °C furnished the TFA-protected ester **4.15** in a quantitative yield. Bismethylation with methyl magnesium chloride at -78 °C proceeded smoothly without racemization of the α-position. Finally, the TFA group was cleaved with LiOH to afford the enantiopure amino alcohol **4.12** in 90% yield over two steps.

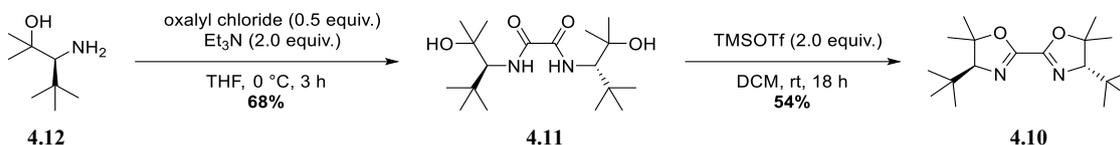


Scheme 55. Synthesis of bismethylated *tert*-leucinol **4.12**.

The subsequent engagement of the bismethylated amino alcohol **4.12** in the condensation with diethyl oxalate as described by the Glorius group for (*L*)-*tert*-leucinol<sup>[172]</sup> resulted in no success. However, replacing the diethyl oxalate with oxalyl chloride as a more reactive electrophile in the presence of Et<sub>3</sub>N at 0 °C allowed the synthesis of bisamide **4.11** in a 68% yield. In the bisoxazoline synthesis reported by Glorius,<sup>[172]</sup> the primary alcohol is transformed into the corresponding chloride followed by intramolecular substitution by the amide upon treatment with NaOH (Scheme 56). Since in our case the tertiary alcohol cannot be applied in such S<sub>N</sub>2-type reactions, we intended to perform the cyclization *via* a tertiary carbocation. In the first attempt, the tertiary alcohol was treated with excess methane sulfonic acid.<sup>[194]</sup> Unfortunately, this reaction resulted in the complete decomposition of the reactant. In order to circumvent the

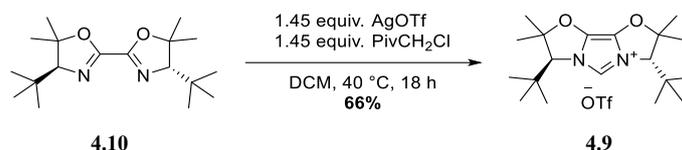
## Towards the Synthesis of Novel IBiox-Type Ligands

use of strong Brønsted acids which yielded decomposition products, various Lewis acids were further tested. TMSOTf was identified as the best reagent. Treatment of bisamide **4.11** with 2 equivalents of TMSOTf at room temperature yielded the tetramethylated bisoxazoline **4.10** in 54% yield.



Scheme 56. Synthesis of the tetramethylated bisoxazoline **4.10**.

Finally, submitting 70 mg of **4.10** under typical imidazolium cyclization conditions<sup>[172]</sup> resulted in a clean reaction (Scheme 57). Purification of the crude by flash column chromatography with a MeOH/DCM solvent system afforded 70 mg (66%) of the desired imidazolium salt **4.9**. However, when the reaction was performed on a bigger scale of 300 mg, no product was obtained.

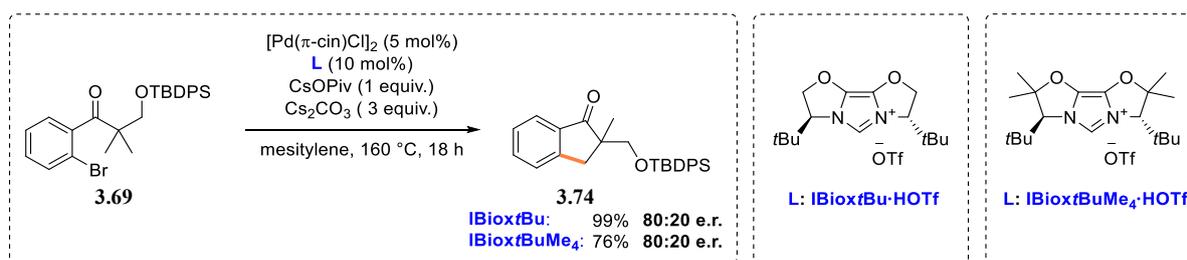


Scheme 57. Final cyclization towards **4.9**.

The reaction proceeded cleanly when repeated on a reduced scale of 100 mg. Purification of the crude on silica with MeOH/DCM system resulted in the imidazolium salt **4.9** as a mixture with a compound that was not observed in the crude. This purification issue was circumvented by recrystallization of the crude in a mixture of hexane and DCM at  $-25$  °C.

### 4.4.3 Evaluation of IBiox*t*BuMe<sub>4</sub> in Enantioselective C(sp<sup>3</sup>)-H Arylations

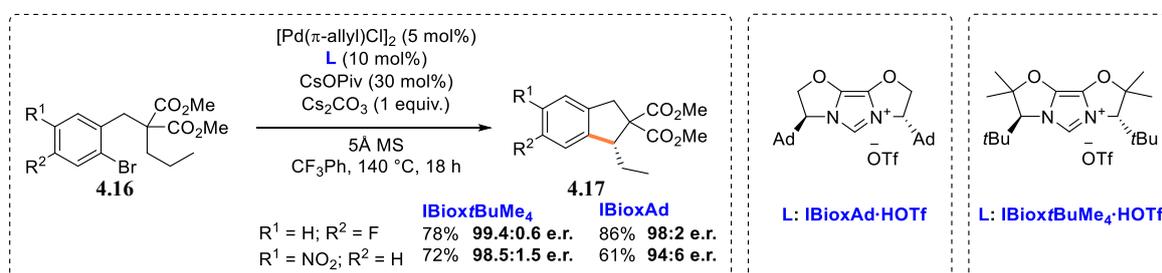
Having succeeded in the synthesis of the **IBiox*t*BuMe<sub>4</sub>•HOTf**, we were curious about its performance in the enantioselective Pd<sup>0</sup>-catalyzed C(sp<sup>3</sup>)-H activation. The ligand precursor was submitted to the optimized standard conditions with aryl bromide **3.69** as depicted in Scheme 58. Thereby, indanone **3.74** was observed in 97% <sup>1</sup>H NMR yield and finally isolated in 76% yield. Unfortunately, the enantiomeric ratio of the isolated product was 80:20, which is identical to the values obtained with the parental **IBiox*t*Bu**.



Scheme 58. Evaluation of the new **IBiox*t*BuMe<sub>4</sub>** ligand in the enantioselective synthesis of indanone **3.74**.

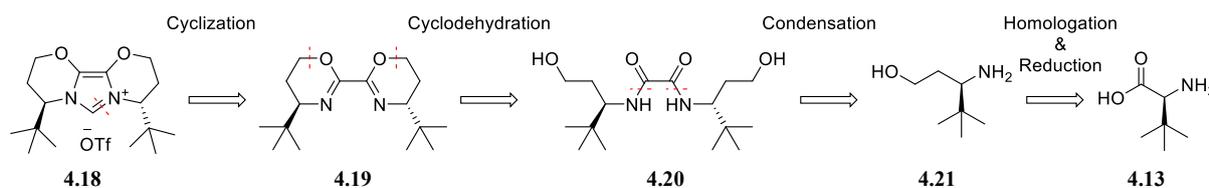
## Towards the Synthesis of Novel IBiox-Type Ligands

At the same time, an enantioselective desymmetrization of a methylene group was developed in our group. Taking that as the perfect opportunity to test our new ligand in this challenging transformation, we submitted the model substrate **4.16** under optimized conditions with **IBiox*t*BuMe<sub>4</sub>**. The corresponding indane **4.17** was isolated with a good yield of 78% which is similar to the one obtained with the reference **IBioxAd** ligand. Analysis of the enantiomeric ratio of the methylene activation product revealed an outstanding value of 99.4:0.6 e.r. which is even superior to the one previously obtained with the standard **IBioxAd** ligand (Scheme 59). The reaction was repeated with a differently substituted substrate to prove the general superiority of the new **IBiox*t*BuMe<sub>4</sub>** ligand over the known ones. Indeed, an improvement of e.r. of 98.5:1.5 was observed in addition to a slightly higher yield as shown in Scheme 59.<sup>[68]</sup>

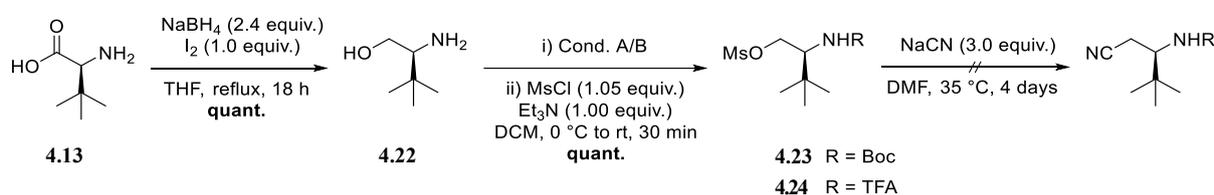


Scheme 59. Ligand effect in the asymmetric C(sp<sup>3</sup>)-H activation of methylene groups.

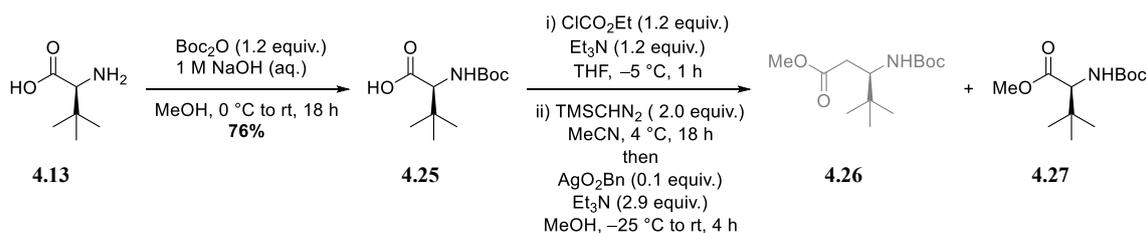
## 4.4.4 Towards the Synthesis of IBioX6tBu•HOTf



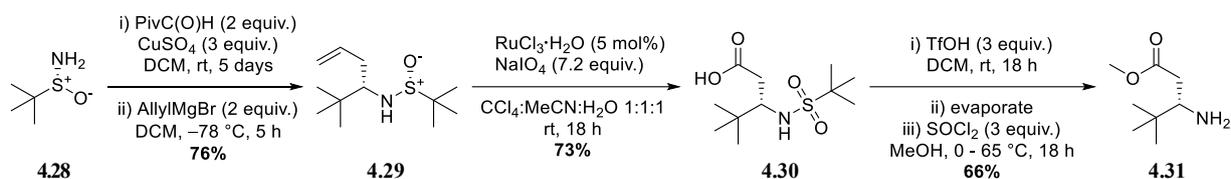
The desired homologated ligand precursor **4.18** was planned to be obtained following Glorius' route in the synthesis of **IBioXtBu•HOTf** as shown in Scheme 60.<sup>[172]</sup> The IBioX core could be synthesized by cyclization of the 1,2-dihydrooxazine **4.19** which can be accessed after cyclodehydration of **4.20**. This diol, in turn, could be afforded after condensation of diethyl oxalate with two molecules of amino alcohol **4.21** which is the product after homologation and subsequent reduction starting from (*L*)-*tert*-leucine **4.13**.



Initial attempts at the homologation started with the reduction of (*L*)-*tert*-leucine **4.13** to amino alcohol **4.22** with NaBH<sub>4</sub> and I<sub>2</sub> in quantitative yield (Scheme 61). Mono-protection of the primary amine with Boc-anhydride and Et<sub>3</sub>N followed by mesylation of the primary alcohol yielded the corresponding mesylate **4.23** in quantitative yield. This intermediate was further engaged with NaCN, however, only decomposition and some traces of the corresponding aziridine from an intramolecular S<sub>N</sub>2 were detected instead of the desired nitrile. As the intramolecular displacement of the mesyl group was favored over the nitrile formation, the TFA-protected mesylate **4.24** was synthesized in 59% yield over 2 steps from amino alcohol **4.22**. Although the diminished nucleophilicity avoided the formation of the aziridine side product, only decomposition of the reactant was detected, along with no traces of the desired nitrile.

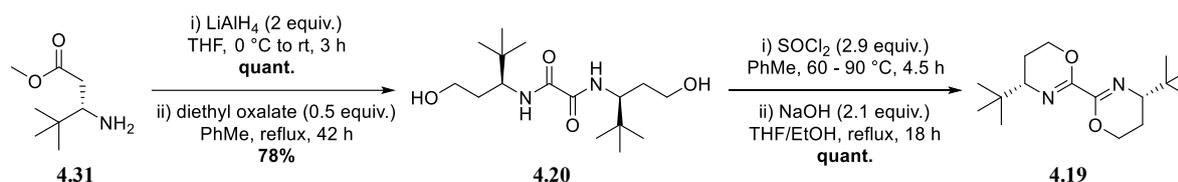


After these failed attempts in the homologation of *tert*-leucinol *via* a nitrile intermediate, we envisioned the application of the Arndt-Eistert homologation protocol. This procedure is well-established in the synthesis of  $\beta$ -amino acids avoiding racemization.<sup>[196]</sup> The sequence started with Boc-protection of **4.13** in 76% (Scheme 62). Submission of the resulting acid **4.25** to the reported conditions with TMSCHN<sub>2</sub><sup>[197]</sup> resulted only in the methyl ester **4.27** and no homologated ester **4.26** was observed. This undesired side product can be explained by the shielding of the *tert*-butyl group which impeded to addition to the desired carbonyl. Thereby, the TMSCHN<sub>2</sub> attacks the less sterically hindered carbonyl group of the formed anhydride which results in the undesired methyl ester **4.27**.



Scheme 63. Synthesis of homologated *tert*-leucine methyl ester **4.31** following Stoltz' procedure.

At this point, we decided to follow a reaction sequence of Stoltz and co-workers, in which the homologated *tert*-leucine was accessed in 98% ee (Scheme 63).<sup>[198]</sup> *Tert*-butanesulfinyl imine was formed starting from the corresponding Ellman sulfonamide **4.28** and pivalic aldehyde in the first step. Subsequent addition of allyl magnesium bromide at -78 °C was directed by the chiral directing group and proceeded in 76% yield. Oxidative cleavage of the resulting olefin and subsequent sulfonamide oxidation under Ru-catalysis resulted in the Bus-protected **4.30** in 73% yield. TfOH mediated Bus-deprotection followed by methyl ester formation in the presence of SOCl<sub>2</sub> and MeOH yielded homologated amino ester **4.31** in 66% yield over 2 steps.

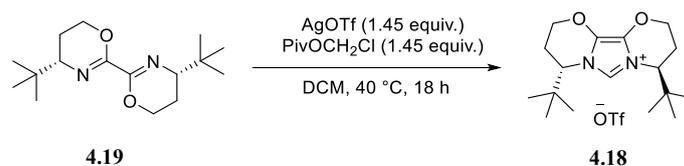


Scheme 64. Synthesis of bisoxazoline **4.19** from homologated amino ester **4.31**.

Reduction of the resulting ester **4.31** with LiAlH<sub>4</sub> proceeded in quantitative yield (Scheme 64). Subsequent condensation of the obtained amino alcohol **4.21** with diethyl oxalate required 42 h in toluene at 90 °C furnished diol **4.20** in 78% yield. Unfortunately, the use of oxalyl chloride resulted in unknown products and could not be used for a faster reaction. Consecutive chlorination of the diol with SOCl<sub>2</sub> and NaOH mediated cyclization allowed access to bisoxazoline **4.19** in a quantitative yield. Submitting the bisoxazoline under typical imidazolium cyclization conditions<sup>[172]</sup> showed some product formation in its crude <sup>1</sup>H NMR

## Towards the Synthesis of Novel IBiox-Type Ligands

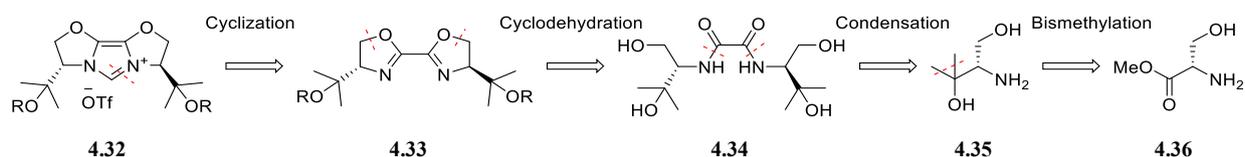
(Scheme 65). However, purification on silica gel with a MeOH/DCM solvent system resulted in decomposition. The reaction was not reproducible under the same conditions. In one case, the reaction proceeded relatively cleanly and small amounts of the desired imidazolium salt were obtained. In this case, a side product was precipitated in chloroform and the resulting filtrate was concentrated followed by the precipitation of the product in a mixture of hexane and diethyl ether. However, the obtained product was not obtained in a suitable purity to be tested in catalysis. Considering the small amount of product obtained, further purification was not possible and the synthesis of **IBiox6tBu** was discontinued.



Scheme 65. Attempted final imidazolium cyclization.

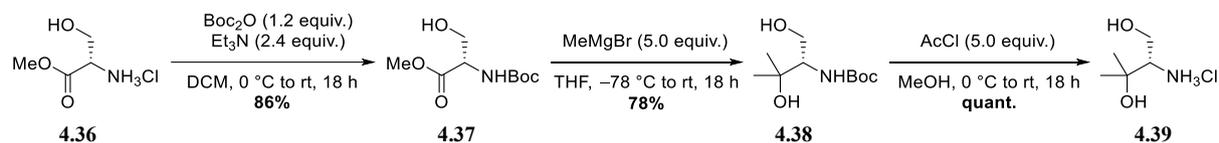
#### 4.4.5 Towards the Synthesis of IBioXMe<sub>2</sub>OR•HOTf

The retrosynthetic analysis of IBioXMe<sub>2</sub>OR-carbene precursor **4.32** is presented in Scheme 66. Thereby, the imidazolium salt **4.32** could be obtained after cyclization of **4.33** which could be accessed after cyclodehydration of bisamide **4.34**. This tetraol could arise from the condensation of diethyl oxalate with two molecules of amino alcohol **4.35** which could result after bisalkylation of (*L*)-serine methyl ester **4.36**.



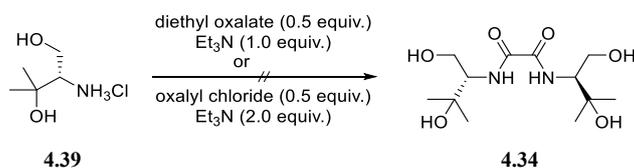
Scheme 66. Retrosynthetic analysis of IBioXMe<sub>2</sub>OR•HOTf **4.32**.

This planned synthetic sequence was initiated with Boc-protection of commercially available (*L*)-serine methyl ester **4.36** with Boc-anhydride in 86% yield (Scheme 67). Further treatment of **4.37** with 5 equivalents of MeMgBr at -78 °C furnished the desired bismethylated diol **4.38** in 78% yield and 99:1 e.r. as determined by GC on a chiral stationary phase. The direct use of aqueous HCl resulted in a clean Boc-deprotection. However, the formed amino alcohol **4.39** is very hygroscopic and the water could not be removed efficiently under reduced pressure. The presence of water could result in competitive hydrolysis during subsequent condensation. As consequence, Boc-deprotection was accomplished in a quantitative yield using acyl chloride in methanol for the *in situ* generation of HCl.



Scheme 67. Synthesis of bismethylated diol **4.39** from (*L*)-serine methyl ester hydrochloride **4.36**.

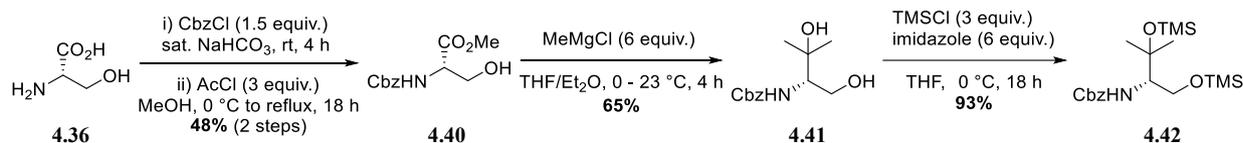
*In situ* deprotonation of the hydrochloride salt **4.39** with 1 equivalent of Et<sub>3</sub>N and the addition of diethyl oxalate or oxalyl chloride under the previously described conditions did not result in the formation of amido alcohol **4.34** (Scheme 68). We suggest that the presence of the free tertiary hydroxyl group is causing the impeded formation of the desired bisamide in a competitive intramolecular S<sub>N</sub>2 reaction, which is probably even further enhanced by the Thorpe-Ingold effect resulting from the two methyl substituents.



Scheme 68. Diethyl oxalate conditions: PhMe, 90 °C, 18 h. Oxalyl chloride conditions: DCM, 0 °C to rt, 2 h.

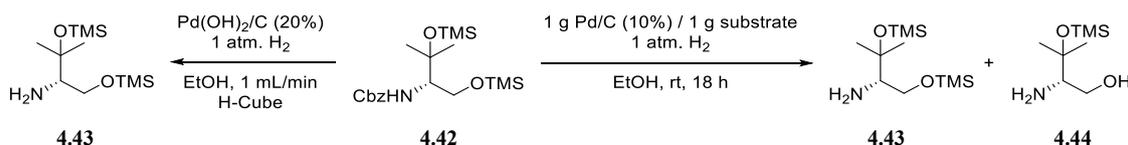
## Towards the Synthesis of Novel IBiox-Type Ligands

In order to avoid this competitive intramolecular reaction in place of the desired formation of bisamide **4.34**, we intended to selectively protect the tertiary alcohol. Following a described reaction sequence,<sup>[199]</sup> (*L*)-serine methyl ester **4.36** was submitted to Cbz protection and subsequent methyl ester formation under acid catalysis in 48% yield over two-step. The resulting primary alcohol **4.40** was treated with 6 equivalents of methyl magnesium bromide at 0 °C to afford the bismethylated diol **4.41** in 65% yield. Treatment with excess TMSCl and imidazole resulted in 93% of the intermediate **4.42**.



Scheme 69. Synthesis of protected diol **4.42**.

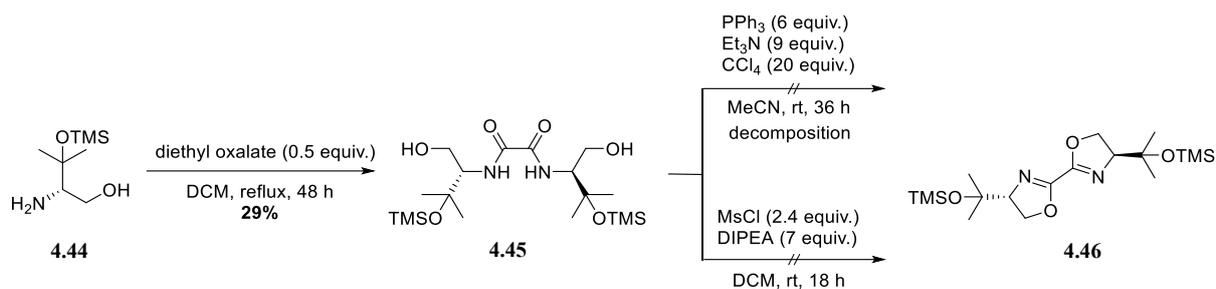
The reported procedure of the combined deprotection of the Cbz and TMS groups of the primary alcohol includes the use of 1 g 10% Pd/C for 1 g of the substrate. In order to avoid the handling of this amount of Pd/C, some trials with the H-Cube were conducted (Scheme 70). Using 20% Pd(OH)<sub>2</sub>/C resulted in the clean deprotection of the Cbz-group, however, both TMS groups were not touched (**4.43**). The mono-deprotection of the primary alcohol is most probably affected by the presence of some traces of HCl on the Pd/C which is not present in the cartridges of the flow system. Therefore, **4.42** was submitted under the described conditions which resulted in a mixture of **4.43** and the desired **4.44**. Due to the labile nature of the TMS groups, the separation of the two products was performed on silica gel which was previously deactivated with Et<sub>3</sub>N.



Scheme 70. Deprotection attempts towards primary alcohol **4.44**.

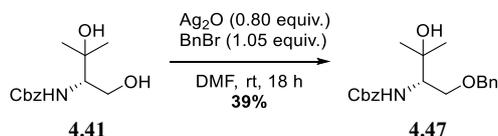
Reacting the obtained mono-protected **4.44** with diethyl oxalate resulted in the TMS-protected amido alcohol **4.45** but in moderate yield. Since the TMS group is labile towards acidic conditions, the typical chlorination and cyclization strategy could not be used on this substrate. Appel conditions applied on the diol resulted in decomposition (Scheme 71). Mesylation of the alcohol in the presence of DIPEA as the base furnished the deprotected tertiary alcohol. It seems that DIPEA•HCl salt is the active species in the deprotection mechanism. A possibility to circumvent this problem could be found in the use of mesityl-triflate, avoiding the potentially deleterious presence of chloride ions in the reaction.

## Towards the Synthesis of Novel IBioX-Type Ligands



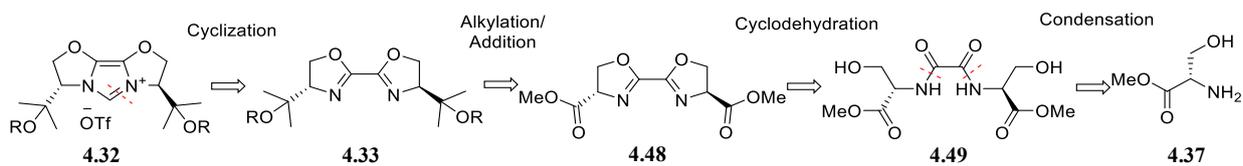
Scheme 71. Attempts towards the TMS protected bisoxazoline **4.46**.

Although the TMS protecting group is attractive due to its simple deprotection, it causes considerable problems in the synthesis of the desired bisoxazoline **4.46** mainly due to its instability. In order to gain more flexibility in the synthesis, we decided to change the protecting groups of the hydroxyl groups. We chose to install a benzyl group on the primary alcohol for its smooth deprotection along with the Cbz-group in one transformation. To this end, diol **4.41** was deprotonated with NaH followed by the addition of benzyl bromide. This reaction resulted in the formation of two unknown products. Changing to milder conditions employing Ag<sub>2</sub>O as base delivered tertiary alcohol **4.47** in 39% in after flash column chromatography (ca. 80% pure, Scheme 72). Optimization of the reaction and its purification might allow the installation of various protecting groups which can be tested towards the synthesis of bisoxazoline **4.33**.



Scheme 72. Benzyl protection of primary alcohol **4.41**.

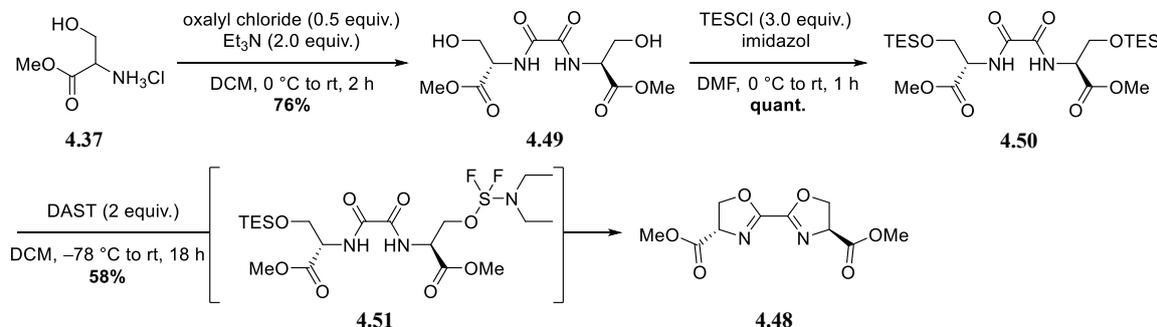
Despite the effort invested into this synthetic route, it shows low flexibility in the synthesis of different analogs defined by the alkylation of the ester in an early stage of the synthesis. Therefore, a more divergent route was designed as depicted in Scheme 73. Thereby, bisoxazoline **4.33** could arise after nucleophilic addition of the desired organometallic species to ester **4.48**. The bisoxazoline core then could be obtained after cyclodehydration from bisamide **4.49** resulting after condensation of diethyl oxalate with (*L*)-serine methyl ester **4.37**.



Scheme 73. New retrosynthetic analysis of IBioXMe<sub>2</sub>OR precursor **4.32**.

This new approach was started with the condensation of (*L*)-serine methyl ester **4.37** with oxalyl chloride in presence of Et<sub>3</sub>N in 76% yield (Scheme 74). The use of the less reactive diethyl oxalate did not deliver any product. Due to the presence of the acidic  $\alpha$ -position, strong basic

conditions such as the one reported by the Glorius group had to be avoided in the next cyclodehydration reaction. An alternative procedure is the cyclodehydration of  $\beta$ -hydroxy amides under mild conditions reported by the Wipf group.<sup>[200]</sup> The therein described DAST (dimethylaminosulfur trifluoride) mediated reaction can be performed at  $-78\text{ }^{\circ}\text{C}$  in the presence of a weak base ( $\text{K}_2\text{CO}_3$ ) for trapping of the HF side product suppressing any epimerization. Direct engagement of amido alcohol **4.49** under these described conditions was not successful due to the insolubility of the reactant in DCM. The high reactivity of DAST limits the solvent choice to relatively inert and apolar solvents, which is the limitation of this reaction when applied to polar substances like amido alcohol **4.49**. The use of further dehydrating agents such as Burgess reagent only resulted in direct elimination of the alcohol instead of the desired cyclodehydration. Inspired by the work of the Luedtke group,<sup>[201]</sup> the corresponding TES-protected derivative **4.50** was synthesized by treating bisamide **4.49** with TESCl and imidazole in quantitative yield. Engagement of the silyl ether **4.50** with 2 equivalents of DAST at  $-78\text{ }^{\circ}\text{C}$  furnished the desired cyclized **4.48** in 58% yield. The success of this protocol relies on the slow deprotection of the silyl ether by fluoride ions originating from the DAST. The resulting alkoxide adds to the electrophilic sulfur center (**4.51**) and a subsequent intramolecular substitution furnishes the oxazoline core and HF as side product (Scheme 74).



Scheme 74. Synthesis of **4.48** following Luedtke's procedure.

After the cyclodehydration was performed successfully, the alkylation was investigated in the next step. Performing the addition at  $-78\text{ }^{\circ}\text{C}$  and room temperature, respectively, failed due to the insolubility of diester **4.48**. Using an anhydrous saturated solution of LiCl in THF (0.5 M) as solvent improved the solubility of the bisoxazoline which might be a result of the coordination of the Li-ion by the substrate and the THF molecules. Performing the Grignard reaction in THF/LiCl showed no reactivity at  $-78\text{ }^{\circ}\text{C}$  due to precipitation of the substrate (Table 8, entry 1). Performing the reaction at  $-50$  and  $0\text{ }^{\circ}\text{C}$  seemed to result in traces of the desired alcohol (entries 2 and 3). However, all purification attempts failed to obtain a pure sample. *In situ* addition of electrophiles (MeI and TMSOTf, entry 4 and 5, respectively) did not result in

## Towards the Synthesis of Novel IBiox-Type Ligands

the corresponding ethers. Since the magnesium and lithium nucleophiles are known to be strong bases, a possible epimerization can occur as a side reaction that should be suppressed to preserve the enantiopurity of the substrate. The corresponding cerium nucleophiles were synthesized and engaged in this addition reaction, however, without any success and no product was obtained.

Table 8. Attempted tetramethylation of diester **4.48**.

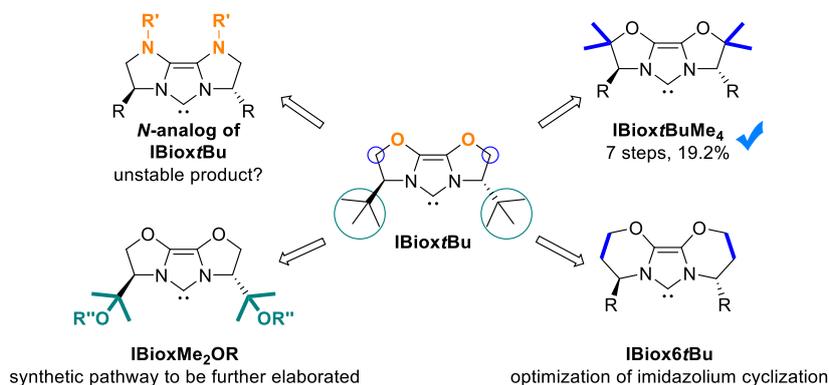


entry	nucleophile	temp.	solvent	comment
1	MeMgCl <sup>a</sup>	-78 °C	THF (0.5 M LiCl)	SM not soluble
2	MeMgCl <sup>a</sup>	-50 °C	THF (0.5 M LiCl)	Traces of probable product
3	MeMgCl <sup>a</sup>	0 °C	THF (0.5 M LiCl)	Traces of probable product
4	MeMgCl <sup>b</sup>	-50 °C	THF (0.5 M LiCl)	Addition of MeI after 5 h, decomp.
5	MeLi <sup>b</sup>	-50 °C	THF (0.5 M LiCl)	Addition of TMSOTf after 5 h, no product observed
6	MeMgCl-CeCl <sub>3</sub> <sup>b</sup>	0 °C	THF	Very slow reaction, no product observed
7	MeCeCl <sub>2</sub> <sup>b</sup>	-60 °C	THF	Only new polar compound observed, could not be isolated

<sup>a</sup> 4 equiv. <sup>b</sup> 4.5 equiv.

#### 4.5 Conclusion and Outlook

One of the four envisioned chiral ligand precursors, **IBiox*f*BuMe<sub>4</sub>**•HOTf was synthesized successfully in 7 steps and 19.2% overall yield from commercially available (*L*)-*tert*-leucine. The properties of this ligand were evaluated in two enantioselective C(sp<sup>3</sup>)-H activation reactions. In the synthesis of the indanone model substrate of the previous chapter, an excellent reactivity was obtained, however, the enantioinduction was the same as for the parental **IBiox*f*Bu** ligand (80:20 e.r.). Nevertheless, we were pleased to find the superiority of this ligand in the asymmetric synthesis of indanes in the desymmetrization of a methylene group compared to the best performing **IBiox*Ad*** ligand (99.6:0.4 e.r. compared to 98:2 e.r., respectively).



Scheme 75. Summary of the state of the syntheses of the four desired ligands.

The synthesis of the ***N*-analog of IBiox*f*Bu** turned out to be problematic. The final cyclization showed usually only traces of something which seemed to be the desired imidazolium salts. Furthermore, the resulting species was demonstrated to be unstable towards nucleophiles such as MeOH. The ethylene bridged substrate, however, was revealed to be more promising in the final cyclization. In this course, reproducibility issues limited further investigations. In a similar fashion, the **IBiox6*f*Bu** was accessed in trace amounts. The final cyclization proved to be irreproducible and decomposition was observed when the crude was treated with MeOH. A stable synthetic pathway was elaborated which allows access to the cyclization substrate from the corresponding homologated methyl ester<sup>[198]</sup> in 78% yield over 4 steps. In contrast, no successful synthetic route was found to deliver the **IBioxMe<sub>2</sub>OR**-precursor. Solubility seems to be the main problem in the synthesis of a highly modular synthesis of the bisoxazoline core. As there is still a need for new and more potent ligands in the asymmetric functionalization of C(sp<sup>3</sup>)-H bonds under Pd<sup>0</sup>-catalysis, more effort has to be put into the synthesis of the envisioned ligands. Firstly, the irreproducibility of the imidazolium cyclization needs to be further investigated along with the stability of the resulting products. After optimization of these steps, the homologated **IBiox6*f*Bu** would be readily synthesized. In the synthesis of **IBioxMe<sub>2</sub>OR** precursor, preferential conditions can be found which allow the bisalkylation of

## Towards the Synthesis of Novel IBiox-Type Ligands

the ester substituted bisoxazoline core. Different additives can be tested which coordinate to the bisoxazoline core to hopefully improve the solubility and the low reactivity towards its ester groups. Furthermore, other nucleophiles can be tested. Otherwise, the first route *via* the Bn-protection of the diol before the bisamide synthesis can be continued which most probably will result in the desired ligand precursor following the general described route. Further studies to overcome these limitations are still needed in order to test the ligands on some model systems of different C(sp<sup>3</sup>)-H activation projects in our group to evaluate their reactivity and stereinduction properties.

## 5 Design of Chiral NHC-Carboxylates as Potential Ligands for Pd-Catalyzed Enantioselective C–H Activation

Adapted from: N. E. Niggli, O. Baudoin, *Helv. Chim. Acta* **2021**, *104*, e2100015.

### 5.1 Introduction

In the past 20 years, transition metal-catalyzed C–H activation reactions have been established as powerful synthetic tools.<sup>[202]</sup> However, in order to cleave non-activated C–H bonds, a high kinetic barrier has to be overcome, hence requiring the use of highly reactive transition metal-catalysts.<sup>[203]</sup> In addition, the presence of multiple C–H bonds of similar strength and steric environment often results in chemo-, regio- and stereoselectivity issues. In the past years, a great number of strategies and catalysts were developed to address these problems, and an array of atom- and step-economical methods suitable for the synthesis or late stage modification of complex molecules were developed.<sup>[30,204–207]</sup> Despite intense recent developments, the control of enantioselectivity in C–H bond activation remains challenging and is still limited to certain motifs.<sup>[79,208,209]</sup> In 2011, the groups of Kündig<sup>[67]</sup> and Kagan<sup>[81]</sup> independently reported the first example of Pd<sup>0</sup>-catalyzed enantioselective C(sp<sup>3</sup>)–H activation initiated by oxidative addition and producing chiral indolines. A high enantioinduction was achieved using a chiral NHC or phosphine ligand, respectively. After these initial reports, diverse enantioselective transformations proceeding through Pd<sup>0</sup>-catalyzed C(sp<sup>3</sup>)–H activation were published.<sup>[80]</sup> Different classes of chiral ligands, including phosphoramidites,<sup>[210]</sup> phosphines,<sup>[82,85]</sup> phosphonites,<sup>[211]</sup> diazophospholidines,<sup>[212]</sup> and NHCs<sup>[67]</sup> were employed in order to reach a high enantioselectivity for different classes of products. Alternatively, the use of a chiral base in combination with an achiral ligand is also able to deliver enantioselectivity in Pd<sup>0</sup>/ Pd<sup>II</sup> catalyzed C(sp<sup>3</sup>)–H arylation.<sup>[81,82]</sup> By exploiting this concept, the Baudoin group reported a highly enantioselective synthesis of indolines using a chiral binol-derived phosphate in combination with an achiral phosphine ligand.<sup>[84]</sup> Despite important efforts, only a relatively small variety of cyclic systems can be accessed to date through enantioselective Pd<sup>0</sup>-catalyzed C(sp<sup>3</sup>)–H activation, and hence more broadly applicable chiral catalysts are still needed.

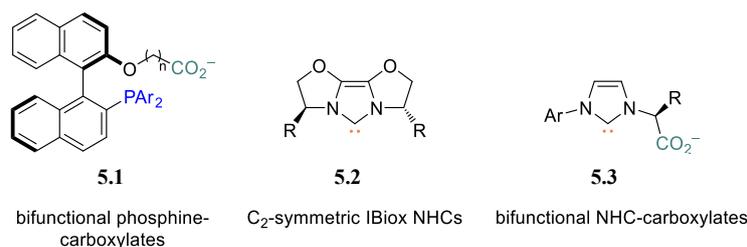
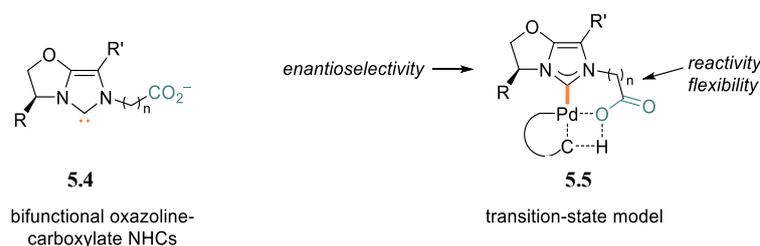


Figure 14. Known bifunctional phosphine-carboxylates and NHC-carboxylate ligands.

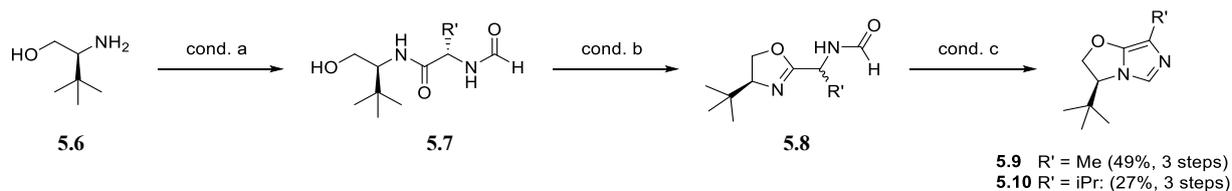
The Baudoin group recently showed the beneficial effect of bifunctional ligands in Pd<sup>0</sup>-catalyzed enantioselective desymmetrizing C(sp<sup>2</sup>)-H activation for the synthesis of 5,6-dihydrophenanthridines<sup>[213]</sup> and chiral warped molecules.<sup>[214]</sup> The designed phosphine ligands (**5.1**) based on a binaphthyl scaffold incorporate a carboxylate group, which acts as the base to promote the C-H activation step occurring through the concerted metalation-deprotonation (CMD) mechanism (Figure 14).<sup>[74]</sup> It is assumed that the high enantioinduction results from a highly ordered transition state, which allows this system to outperform the corresponding monofunctional ligands. However, the Baudoin group found that this bifunctional phosphine ligand was not sufficiently reactive to activate the stronger C(sp<sup>3</sup>)-H bonds. In parallel, Baudoin and co-workers recently reported that bisoxazoline-derived (IBiox)<sup>[172,175,188]</sup> NHC ligands (**5.2**) exhibit both a high reactivity and enantioselectivity in the challenging arylation of enantiotopic methylene C-H bonds.<sup>[68]</sup> Motivated by these results, we thought to exploit the outstanding reactivity of IBiox-type ligands in C(sp<sup>3</sup>)-H activation to design bifunctional ligands **5.4** incorporating both a chiral oxazoline ring and a carboxylate group. Amino acid-derived chiral NHC-carboxylates (**5.3**), wherein the stereogenic center and carboxylate group are located on the same side of the imidazole ring, were previously reported by Baslé, Mauduit and co-workers. These NHCs were employed in enantioselective Cu-catalyzed reactions<sup>[215,216]</sup> as well as in Rh-catalyzed C-H borylation,<sup>[217,218]</sup> hence demonstrating the potential of bifunctional NHC-carboxylate ligands in catalysis.<sup>[219-221]</sup> We surmised that ligand **5.4**, wherein the chiral substituent and the carboxylate group are located on opposite sides of the imidazole ring, would be well suited to the enantiodetermining C-H activation step (see the transition-state model **5.5** in Figure 15), with the rigid oxazoline ring providing enantioselectivity and the carboxylate arm providing both reactivity and sufficient flexibility to adapt to the substrate.

Figure 15. Envisioned bifunctional NHC **5.4**.

## 5.2 Results and Discussion

### 5.2.1 Synthesis of Carboxylate Bearing Imidazolium Salts

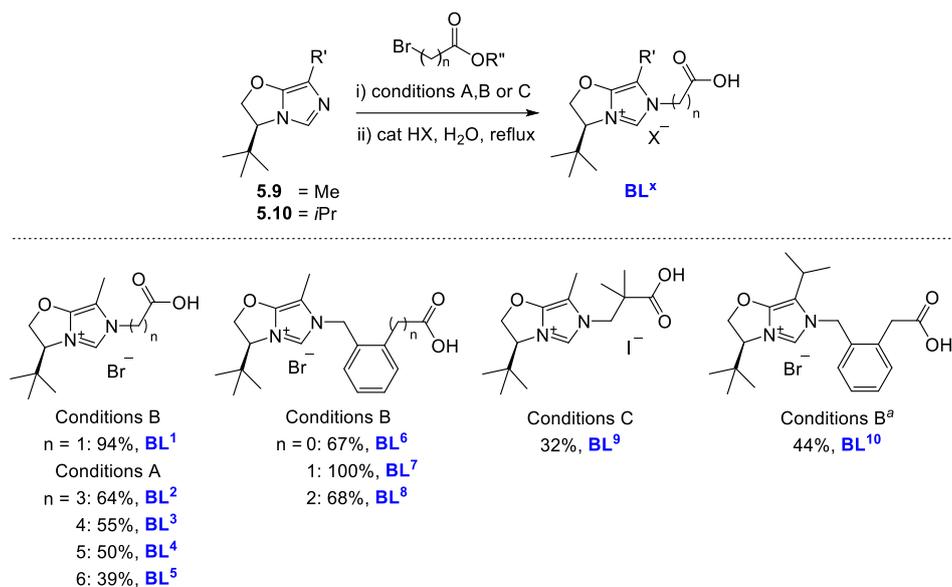
The oxazoline-fused imidazole cores of the target ligands (**5.9** and **5.10**) were synthesized in three steps from enantiopure *L-tert*-leucinol, taking inspiration from a precedent by Yoshida, Yanagisawa and co-workers (Scheme 76).<sup>[222]</sup> The R' substituent (R' = Me, *i*Pr) was previously shown to be necessary for the imidazole ring formation and serves as further handle to modulate the steric properties of the bifunctional ligand.



Scheme 76. Synthesis of the oxazolidine-fused imidazole core. a) Me: NMM (1.01 equiv.), formyl-*L*-alanine (1.00 equiv.), isobutyl chloroformate (1.01 equiv.), DCM, -15 °C, 15 min, then **5.6** (1.05 equiv.), -15 °C to 25 °C, 3 h, 85%. *i*Pr: NMM (1.10 equiv.), formyl-*L*-valine (1.10 equiv.), isobutyl chloroformate (1.01 equiv.), THF, -15 °C, 15 min, then **5.6** (1.00 equiv.), -15 °C to 25 °C, 16 h, 78%. b) Me: Et<sub>3</sub>N (4.30 equiv.), **5.7Me** (1.00 equiv.), DMAP (0.02 equiv.), *p*-toluenesulfonyl chloride (1.20 equiv.), DCM, 25 °C, 16 h, 92%. *i*Pr: Et<sub>3</sub>N (4.30 equiv.), **5.7*i*Pr** (1.00 equiv.), DMAP (0.02 equiv.), *p*-toluenesulfonyl chloride (1.01 equiv.), DCE, 25 °C, 1 h, then 84 °C, 16 h, 56%. c) Me: P<sub>2</sub>O<sub>5</sub> (2.0 equiv.), **5.8Me** (1.0 equiv.), toluene, 100 °C, 48 h, 63%. *i*Pr: P<sub>2</sub>O<sub>5</sub> (3.0 equiv.), **5.8*i*Pr** (1.0 equiv.), toluene, 100 °C, 48 h, 62%.

The installation of the carboxylic acid-bearing side arm from **5.9** required some optimization (Scheme 77). The linear alkyl linkers were installed upon stirring with excess alkyl bromide in acetonitrile during seven days at room temperature. More activated electrophiles (benzyl bromides or  $\alpha$ -bromoester) reacted at 70 °C in 16 h. Of note, the use of the corresponding carboxylic acids led to protonation, which further slowed down the alkylation rate, and increasing the temperature resulted in a slow degradation. In the case of linear alkyl bromides, elevated temperatures (> 40 °C) led to byproducts resulting from the deprotonation at the  $\alpha$ -position to the ester, and additives such as Et<sub>3</sub>N did not show any beneficial effect. Then, all of the corresponding esters were further hydrolyzed to give the desired NHC imidazolium salt precursors under acidic conditions. As a result, we obtained a library of five imidazolium salts (**BL**<sup>1</sup>–**BL**<sup>5</sup>) with a linear linker [(CH<sub>2</sub>)<sub>*n*</sub>CO<sub>2</sub>H, *n*=1, 3–6], three (**BL**<sup>6</sup>–**BL**<sup>8</sup>) incorporating a benzene ring with different chain lengths (CH<sub>2</sub>Ar(CH<sub>2</sub>)<sub>*n*</sub>CO<sub>2</sub>H, *n*=0–2), and a neopentyl linker mimicking pivalic acid (**BL**<sup>9</sup>) in moderate to excellent yields. In addition, analog **BL**<sup>10</sup> bearing an *isopropyl* group instead of a methyl group on the imidazolium ring was synthesized from **5.10**.

## New Bifunctional Pd-NHC-Complexes



Scheme 77. Synthesis of a library of NHC precursors. Conditions A: alkyl bromide (1.5 equiv.), MeCN, 25 °C, 7 days. Conditions B: alkyl- or benzyl bromide (1.1 equiv.), MeCN, 70 °C, 16 h. Conditions C: alkyl triflate (1.5 equiv.), MeCN, 70 °C, 16 h, then NaI (5 equiv.), acetone, 25 °C, 16 h.<sup>a</sup> 48 h at 70 °C.

### 5.2.2 Evaluation of the new Bifunctional NHC-Precursors

The synthesized imidazolium precursors were then evaluated in the Pd<sup>0</sup>-catalyzed desymmetrizing C(sp<sup>3</sup>)-H arylation leading to indolines, which was employed as a prototypical enantioselective reaction.<sup>[67,81,82,84]</sup> In many Pd-catalyzed reactions engaging NHC ligands, the imidazolium salt can be directly added to the mixture containing a Pd-source and a base, hence forming the active Pd<sup>0</sup>-NHC complex *in situ*.<sup>[136,137]</sup> Unfortunately, only a low reactivity and no enantioinduction were observed by simply engaging a mixture of the imidazolium salt, a Pd-source such as Pd<sub>2</sub>dba<sub>3</sub> and a carbonate base, despite extensive experimentation (Table 9, conditions A). Pd<sup>II</sup>-( $\pi$ -allyl) complexes are standard Pd-precatalysts in Pd/NHC-catalyzed C-H activation, but they need to be activated *in situ* to generate the active Pd<sup>0</sup>-NHC species. Typically, an additive such as pivalate<sup>[67,68,223]</sup> or *tert*-butoxide<sup>[224]</sup> is introduced for this purpose. Running the reaction with these additives slightly improved the yield, but the product was completely racemic (Table 9, conditions B). Various imidazolium salts of our library performed similarly in terms of reactivity and enantioselectivity.

## New Bifunctional Pd-NHC-Complexes

Table 9. First tries of the newly designed imidazole-carboxylate ligands in the enantioselective synthesis of indoline **5.12**.

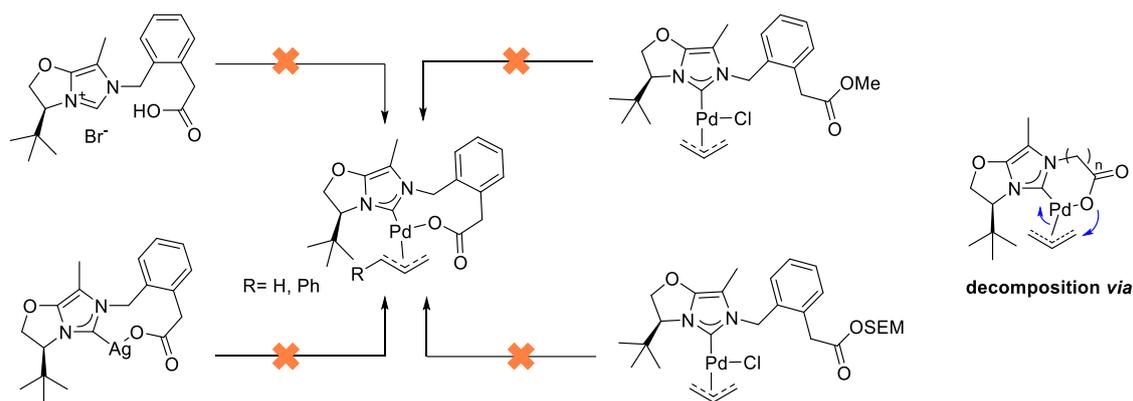
condition	[Pd]	ligand	base	additive
<b>A</b>	Pd <sub>2</sub> dba <sub>3</sub>	<b>BL<sup>x</sup></b>	K <sub>2</sub> CO <sub>3</sub> or Cs <sub>2</sub> CO <sub>3</sub>	-
<b>B</b>	[Pd(π-cin)Cl] <sub>2</sub>	<b>BL<sup>x</sup></b>	K <sub>2</sub> CO <sub>3</sub> or Cs <sub>2</sub> CO <sub>3</sub>	CsOPiv, KOPiv, CsOtBu, KOtBu.
<b>C</b>	Pd <sub>2</sub> dba <sub>3</sub> or [Pd(π-cin)Cl] <sub>2</sub>	Ag/ <b>BL<sup>x</sup></b>	K <sub>2</sub> CO <sub>3</sub> or Cs <sub>2</sub> CO <sub>3</sub>	CsOtBu

At this point, it was questioned whether the active complex was formed under the employed conditions, or if some undefined Pd-species were causing the low rate of product formation. The free carboxylate group in our newly designed ligand is the main difference with the IBiox ligands. Considering this, we presumed that this functional group was the reason for the impeded *in situ* Pd<sup>0</sup>-NHC complex formation. In order to facilitate this process, we turned our attention towards the synthesis of the corresponding Ag-NHC complexes, which are prone to undergo transmetalation with metals such as Pd.<sup>[225,226]</sup> We decided to test this approach in the synthesis of indoline **5.12** (Table 9, conditions **C**). To access the silver-NHC-complexes, imidazolium salts were charged with Ag<sub>2</sub>O in a catalysis tube in the dark and stirred for 2–24 h at room temperature. The crude Ag-complexes were then engaged in the reaction together with the substrate, a stoichiometric base, a Pd-source and an additive, and was stirred at 160 °C for 16 h. Unfortunately, low yields and almost no enantioselectivity (18%, 52:48 e.r. for **BL**<sup>7</sup>) were again observed using [Pd(π-cin)Cl]<sub>2</sub> as the Pd-source. Interestingly, using Pd<sub>2</sub>dba<sub>3</sub> as the precatalyst in combination with the Ag-NHC complex resulted in a noticeable enantioinduction (64:36 e.r. for **BL**<sup>7</sup>), albeit with a low yield (10%). In the latter case the active Pd-NHC complex was presumably formed, albeit in a very inefficient way.

### 5.2.3 Synthesis of well-defined Pd-complexes

These results led us to consider the synthesis of stable well-defined Pd-complexes with our newly developed NHC-carboxylate ligands. Unfortunately, all attempts at synthesizing [Pd(π-allyl)**BL**<sup>x</sup>] or [Pd(π-cin)**BL**<sup>x</sup>] complexes either directly from the imidazolium-carboxylic acid precursor or from a protected acid followed with deprotection failed and complex mixtures were observed. We concluded that the resulting carboxylate allyl complex is unstable, probably due to the intramolecular attack of the carboxylate onto the π-allyl ligand, initiating further decomposition (Scheme 78).

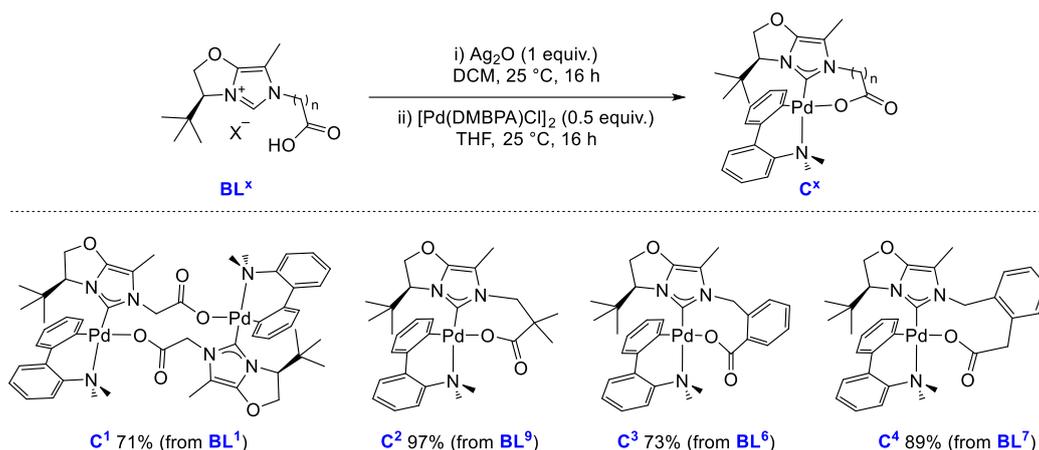
## New Bifunctional Pd-NHC-Complexes



Scheme 78. Attempts in the synthesis of the bifunctional  $[\text{Pd}(\pi\text{-allyl})\text{NHC}]$  complexes with the proposed initial decomposition.

We then became interested in the use of palladacycles as precatalyst instead of the more common  $\text{Pd}^{\text{II}}\text{NHC}$ -precomplexes. In a seminal work, Hermann and Beller successfully applied cyclopalladated phosphine ligands in the Mizoroki-Heck reaction.<sup>[227]</sup> Since this initial report, this class of Pd-precursors has emerged as an attractive stable and readily activated alternative to more commonly used Pd-precomplexes.<sup>[228–230]</sup> In particular, the Nolan group reported an **IPr**-palladacycle complex, which was employed as a very active precatalyst in the cross-coupling of aryl chlorides and amines as well as in the  $\alpha$ -arylation of ketones.<sup>[231]</sup> In this work, the *N,N*-dimethyl[1,1'-biphenyl]-2-amine (DMBPA) NHC-palladacycle was synthesized by reacting the free NHC with the corresponding Pd-dimer in good yield. Inspired by these results, we first generated the corresponding Ag-NHC complexes by treatment of the imidazolium salts with  $\text{Ag}_2\text{O}$ . The obtained crude silver complexes were directly engaged in the transmetalation with the DMBPA  $\mu$ -chloro dimeric Pd-complex in THF at room temperature overnight. Following this procedure, Pd-complexes **C**<sup>1</sup>–**C**<sup>4</sup> were isolated in good yields (Scheme 79). Other imidazolium salts described in Scheme 77 were also used as precursors but, despite repeated efforts, they afforded complex mixtures (as monitored by NMR), and the corresponding palladacyclic complexes could not be isolated and characterized without ambiguity.

## New Bifunctional Pd-NHC-Complexes



Scheme 79. Synthesis of bifunctional NHC-Pd<sup>II</sup> palladacyclic complexes **C**<sup>1</sup>-**C**<sup>4</sup>.

The single crystal X-ray diffraction analysis of complexes **C**<sup>1</sup> and **C**<sup>3</sup> was successfully performed and revealed dimeric and monomeric structures in the solid state, respectively (Figure 16). This observation is not surprising since the monomeric structure should be disfavored for a short linker due to strain and favored with a longer linker. In both complexes, the NHC ligand is located *trans* to the amino group and the carboxylate is bound to the Pd-center *trans* to the aryl ligand (NHC–Pd–O<sub>2</sub>C angles: 91.7°, **C**<sup>1</sup>; 88.8°, **C**<sup>3</sup>) in a standard square-planar geometry. The biphenyl scaffold is twisted, due to the steric bulk at the oxazoline ring, similar to previous observations with other NHC ligands.<sup>[231]</sup> Complexes **C**<sup>2</sup> and **C**<sup>4</sup> occurred as monomers similar to **C**<sup>3</sup>, as indicated by mass spectrometry, but did not afford crystals suitable for X-ray diffraction analysis.

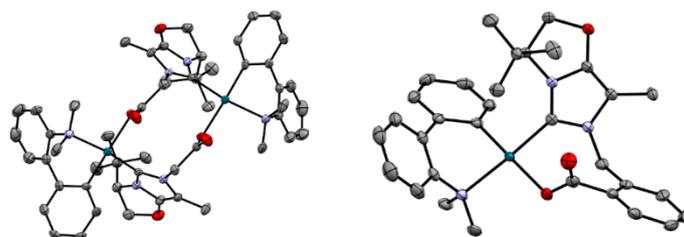


Figure 16. left: ORTEP representation of the X-ray crystal structure of the dimeric complex **C**<sup>1</sup> (ellipsoids shown at 50% probability). right: ORTEP representation of the X-ray crystal structure of complex **C**<sup>3</sup> (ellipsoids shown at 50% probability). H-atoms were omitted for clarity.

### 5.2.4 Evaluation of the Bifunctional Pd-Complexes

With these well-defined Pd<sup>II</sup>-complexes in hand, we turned our attention towards their application in enantioselective C(sp<sup>3</sup>)-H activation (Table 10). Running the standard reaction with 10 mol% of complex **C**<sup>4</sup> in the presence of 1.5 equiv. Cs<sub>2</sub>CO<sub>3</sub> and 10 mol% of CsOtBu as activator<sup>[215,231]</sup> at 160 °C in mesitylene for 16 h yielded 20% of almost racemic indoline (Table 10, entry 1). This low yield and the enantioinduction indicate again a possible inefficient generation of the active chiral Pd<sup>0</sup>-NHC complex. Examination of the solvent effect showed a

similar behavior in apolar aromatic solvents. A slight increase in yield was observed in ethers such as THF, Bu<sub>2</sub>O and anisole (entry 2), while full decomposition occurred in polar aprotic solvents (*e.g.*, DMSO, entry 3). However, the enantioselectivity did not improve noticeably in any case. We were curious to know if the originally employed *tert*-butoxide was suitable for the activation of the complex under the current reaction conditions. Omitting CsOtBu actually gave the same results, hence showing the inaptitude of this reagent at activating the precomplex (entry 4). Replacing cesium *tert*-butoxide with sodium formate resulted in low yield and formation of the racemic product (entry 5), and a similar result was obtained with diphenylaniline (entry 6). Hydrazine and morpholine were likewise unable to provide a more active catalyst, and only led to traces of product (entries 7 and 8). Surprisingly, the addition of 20 mol% HFIP increased the enantiomeric ratio to 78:22, albeit with a low yield (20%; entry 9). Encouraged by this result, we tried to optimize the reaction conditions. Various solvents were tested (*e.g.*, anisole, entry 10), but comparable results to mesitylene were at best obtained. Moreover, further variation of the employed stoichiometric base did not show any beneficial effect on the yield or enantioselectivity. At this point, we assumed that these unsuccessful results were again the result of the difficult generation of an active Pd<sup>0</sup>-NHC complex prior to the substrate oxidative addition.

Table 10. Effect of solvents and additives in the enantioselective C(sp<sup>3</sup>)-H arylation.

entry	solvent <sup>a</sup>	additive <sup>b</sup>	NMR yield [%] <sup>c</sup>	e.r. <sup>d</sup>
1	mesitylene	CsOtBu	20	55:45
2	anisole	CsOtBu	43	55:45
3	DMSO	CsOtBu	0	-
4	mesitylene	-	21	55:45
5	mesitylene	HCO <sub>2</sub> Na	16	52:48
6	mesitylene	Ph <sub>2</sub> NH	32	52:48
7	mesitylene	N <sub>2</sub> H <sub>2</sub>	<5	-
8	mesitylene	morpholine	<5	-
9	mesitylene	HFIP <sup>e</sup>	20	78:22
10	anisole	HFIP <sup>e</sup>	24	69:31

<sup>a</sup> 0.1 M. <sup>b</sup> 10 mol%. <sup>c</sup> Using trichloroethylene as internal standard.  
<sup>d</sup> Determined by HPLC on a chiral stationary phase. <sup>e</sup> 20 mol%.

To further investigate this preactivation, we performed some NMR experiments. Complex **C**<sup>1</sup> was dissolved in degassed C<sub>6</sub>D<sub>6</sub> and various activating agents were added in order to monitor the modification of the *N,N*-dimethylaniline motif. The addition of hydrazine, DIBAL-H, and LiHMDS resulted in the immediate full decomposition of the complex. As expected from the above results (Table 10, entry 4), the addition of CsOtBu did not result in any change, neither at room temperature nor at 70 °C. Interestingly, when HFIP was added, a visible change in the proton signals of the NHC core and HFIP was observed as shown in Figure 17. We propose that HFIP coordinates to the Pd-center and forms a hydrogen bond with the carboxylic group. This intermediate might stabilize the complex and therefore play a beneficial role in the Pd-complex activation.

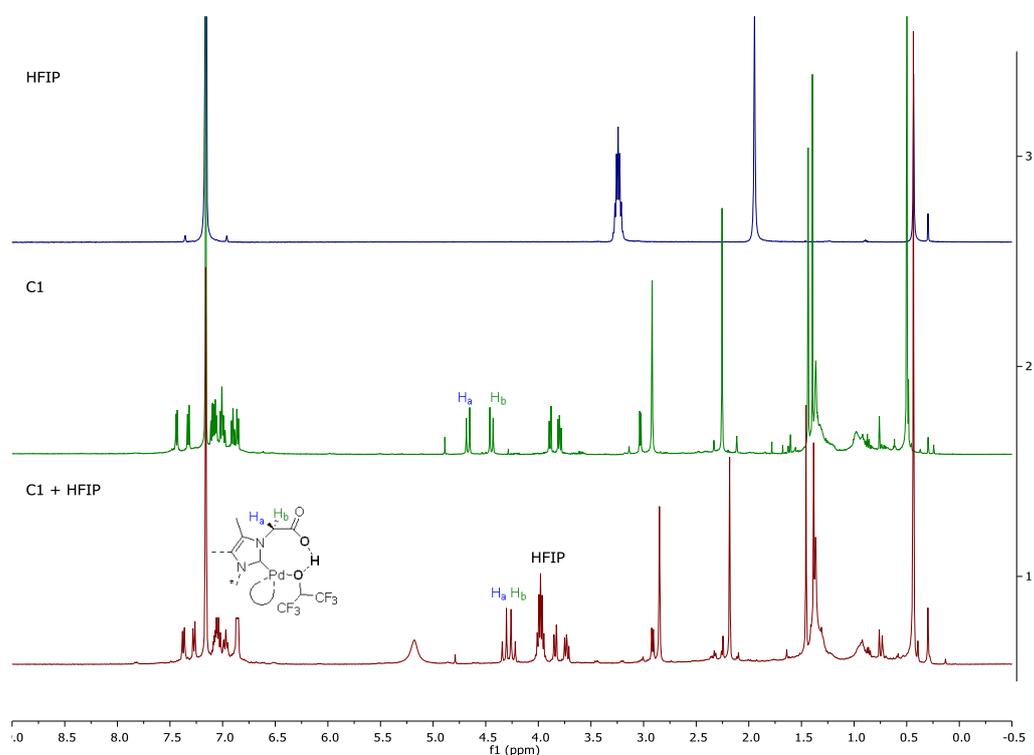


Figure 17. HFIP additive experiment by <sup>1</sup>H NMR in C<sub>6</sub>D<sub>6</sub>.

Finally, applying the optimized conditions to the four different complexes **C**<sup>1</sup> - **C**<sup>4</sup> gave low yields for **C**<sup>1</sup> and **C**<sup>4</sup> (13% and 20%, resp., Table 11, entries 1 and 4), whereas traces of product were observed with complexes **C**<sup>2</sup> and **C**<sup>3</sup> (entries 2 and 3). In addition, the enantioselectivity induced by **C**<sup>4</sup> was significantly higher than with **C**<sup>1</sup> (**C**<sup>4</sup>, e.r. 78:22; **C**<sup>1</sup>, e.r. 56:44). Therefore, the nature of the linker separating the carboxylate group from the imidazole core seems to have a significant effect on the catalyst performance.

## New Bifunctional Pd-NHC-Complexes

Table 11. Evaluation of the synthesized complexes in the enantioselective C(sp<sup>3</sup>)-H arylation.

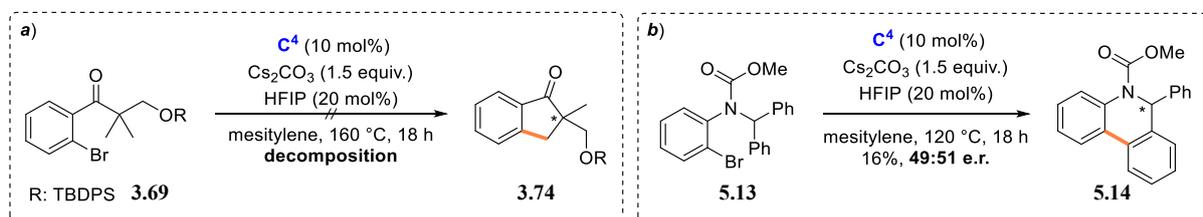
entry	complex	<sup>1</sup> H NMR yield [%] <sup>a</sup>	e.r. <sup>b</sup>
1	<b>C<sup>1</sup></b>	13	56:44
2	<b>C<sup>2</sup></b>	<5	n.d.
3	<b>C<sup>3</sup></b>	<5	n.d.
4	<b>C<sup>4</sup></b>	20	78:22

<sup>a</sup> Using trichloroethylene as internal standard. <sup>b</sup> Determined by HPLC on a chiral stationary phase.

Upon further analysis of the Pd-complexes, we realized that they decomposed in the solid state far below the reaction temperature (**C<sup>1</sup>**: 120 °C; **C<sup>2</sup>**: 80 °C; **C<sup>3</sup>**: 110 °C; **C<sup>4</sup>**: 90 °C). This degradation could explain the low reactivity observed under the applied reaction conditions. Unfortunately, reducing the reaction temperature to 140 °C resulted in traces of indoline **5.12**.

### 5.2.5 Other tested Substrates

During the course of this project, different C–H activation substrates were tested with the new bifunctional complexes under the optimized conditions as shown in Scheme 80. Submission of the indanone substrate **3.69** from the previous chapter under these conditions resulted in complete decomposition of the substrate and no indanone **3.74** was detected. At this point, we were curious to investigate the performance of the new complexes in the simpler activation of C(sp<sup>2</sup>)-H bonds. Therefore, amide **5.13** bearing two phenyl substituents was engaged under standard conditions at 120 °C. The resulting C(sp<sup>2</sup>)-arylated product **5.14** was obtained in a comparable yield of 16%, however completely racemic.

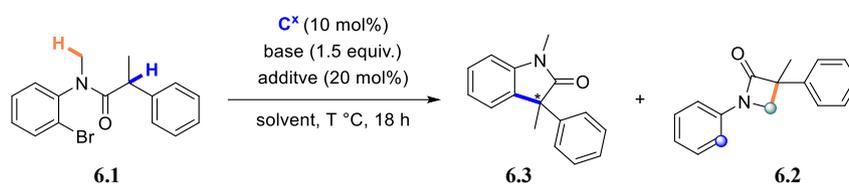


Scheme 80. Testing of **C<sup>4</sup>** under optimized reaction conditions on different C(sp<sup>3</sup>)-H (**a**) and C(sp<sup>2</sup>)-H (**b**) arylations.

In a last attempt, we hoped to find an application of our new bifunctional complexes in the well-established  $\alpha$ -arylation of amides towards the synthesis of oxindoles (Table 12).<sup>[172]</sup> As reference, performing the reaction under typical  $\alpha$ -arylation conditions consisting of [Pd( $\pi$ -allyl)Cl]<sub>2</sub> precomplex, the parental **IBioxzBu** ligand, and NaOtBu in DME at 50 °C gave the expected product **6.3** in 30% <sup>1</sup>H NMR yield (Table 12, entry 1). Repeating the reaction with **C<sup>4</sup>**

at 120 °C resulted in 82% <sup>1</sup>H NMR yield of the same product, but unfortunately almost completely racemic (entry 2). Interestingly, when the amide **6.1** was engaged under typical C(sp<sup>3</sup>)–H activation condition comprising of a [Pd(π-cin)Cl]<sub>2</sub> precomplex, the parental **IBioxzBu** ligand, the CsOPiv co-catalyst, and stoichiometric Cs<sub>2</sub>CO<sub>3</sub> in mesitylene at 160 °C, the oxindole product **6.3** was isolated in 50% yield along with 15% <sup>1</sup>H NMR yield of an unknown product with the same molecular mass as the C(sp<sup>3</sup>)–H arylation product **6.3**. A further analytical investigation suggested that this newly formed product was the corresponding β-lactam **6.2** arising from a 1,4-Pd shift to the methyl group adjacent to the nitrogen atom and subsequent C(sp<sup>3</sup>)–C(sp<sup>3</sup>)-bond formation upon activation of the α-hydrogen-bond and consecutive reductive elimination. Unfortunately, when applying the optimized conditions at 120 °C with **C<sup>4</sup>** as catalyst instead, only traces of the desired oxindole **6.3** were observed.

Table 12. Investigation in the application of **IBioxzBu** ligand and **C<sup>4</sup>** in the α-arylation of **6.1**.

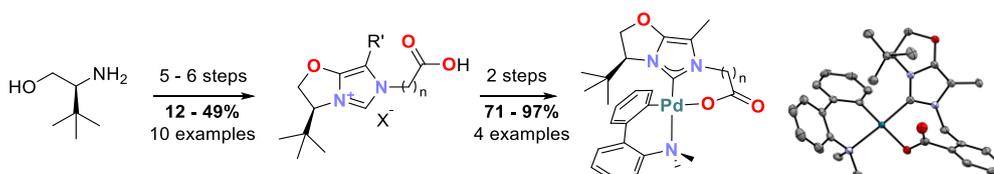


entry	complex	solvent	additive	base	temp. [°C]	<sup>1</sup> H NMR yield [%] <sup>a</sup> <b>6.3:6.2</b>
1	<b>IBioxzBu</b> <sup>b</sup> + [Pd(π-allyl)Cl] <sub>2</sub>	DME	none	NaOtBu	50	30:0
2	<b>C<sup>4</sup></b>	DME	none	NaOtBu	120	82:0
3	<b>IBioxzBu</b> <sup>b</sup> + [Pd(π-cin)Cl] <sub>2</sub>	mesitylene	CsOPiv <sup>c</sup>	Cs <sub>2</sub> CO <sub>3</sub>	160	55:15
4	<b>C<sup>4</sup></b>	mesitylene	HFIP	Cs <sub>2</sub> CO <sub>3</sub>	120	2:0

<sup>a</sup> Determined with trichloroethylene as internal standard. <sup>b</sup> Starting from **IBioxzBu**•HOTf. <sup>c</sup> 30 mol%.

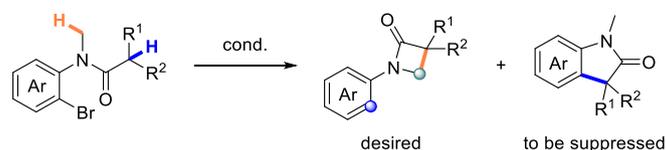
### 5.3 Conclusion and Outlook

A library of 10 imidazolium-carboxylic acids with different linkers (five linear, four incorporating a benzene ring, and one neopentyl) was synthesized from enantiopure *L*-tert-leucinol in five to six steps. Four well-defined Pd(DMBPA)NHC palladacycles were obtained from the corresponding imidazolium salts in good to excellent yield and were characterized. The direct use of the imidazolium salts in a prototypical Pd<sup>0</sup>-catalyzed C(sp<sup>3</sup>)-H arylation reaction only resulted in low reactivity and enantioinduction. Attempts at employing the corresponding Pd(DMBP)NHC palladacycles as precatalysts were modestly successful. HFIP was required as an additive to obtain the indoline product in moderate but significant enantioselectivity (e.r. 78:22), albeit in low yield. HFIP seems to form an H-bonding network, which stabilizes the complex and limits its decomposition. Further investigations revealed the thermal instability of these palladacycles, which likely explains their poor performance in C(sp<sup>3</sup>)-H activation performed at high temperatures. In light of these results, we believe that these bifunctional NHC precursors could find applications in enantioselective transformations performed under milder conditions, either as ligands<sup>[215–220]</sup> or as organocatalysts.<sup>[133,232,233]</sup>



Scheme 81. Established synthesis of new bifunctional NHC-ligands and complexes.

Different substrates were evaluated while testing of the new complexes. Interestingly, doing a reference reaction with the parental **IBioxzBu** ligand under typical C(sp<sup>3</sup>)-H activation conditions on an  $\alpha$ -arylation substrate towards oxindoles, a new side product was observed. This new compound was identified as a  $\beta$ -lactam-product arising from a 1,4-Pd-shift with subsequent C(sp<sup>3</sup>)-C(sp<sup>3</sup>) bond formation. This new reactivity has been explored and optimization and they will be presented in the next chapter.



Scheme 82. Envisioned synthesis of  $\beta$ -lactams *via* a 1,4-Pd shift mediated double C(sp<sup>3</sup>)-H activation.

## 6 Synthesis of $\beta$ -Lactams via 1,4-Pd Shift-Mediated Double C(sp<sup>3</sup>)-H Activation

### 6.1 Introduction

$\beta$ -lactams, four-membered lactams, exhibit broad biological activities and are therefore highly interesting scaffolds.<sup>[234–236]</sup> This motif is usually best known for its presence in many antibiotic drugs such as the naturally occurring *penicillin*<sup>[237,238]</sup> or the synthetic *aztreonam*<sup>[239]</sup> and the  $\beta$ -lactamase inhibitor *sulbactam*.<sup>[240]</sup> Moreover, the biologically active  $\beta$ -lactam core can be found in the cholesterol-lowering *ezetimibe*.<sup>[241]</sup> In addition to their biological interest,  $\beta$ -lactams are valuable reaction intermediates. The cyclic scaffold is prone to react with a variety of nucleophiles resulting in the corresponding ring-opened products such as  $\beta$ -amino acid derivatives.<sup>[242]</sup> Due to their highly attractive characteristics, a variety of synthetic methods have been developed to access such privileged four-membered motifs.<sup>[243–245]</sup> The most commonly employed synthetic strategies include [2+2] cycloadditions of a ketene and an imine in the Staudinger reaction,<sup>[246]</sup> the copper-catalyzed Kinugasa reaction<sup>[247,248]</sup> reacting alkynes with nitrones, together with the Reformatsky reaction by condensing a Zn-ester enolate with an imine.<sup>[249]</sup>

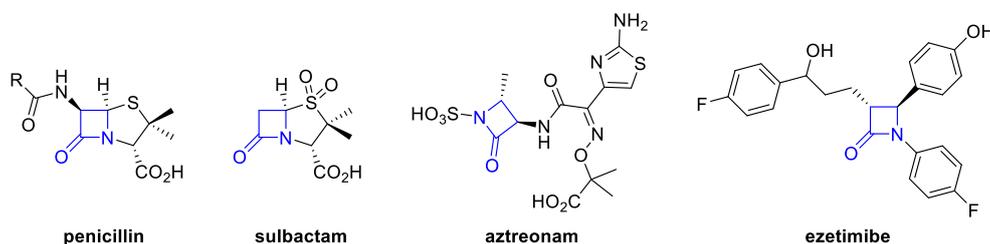
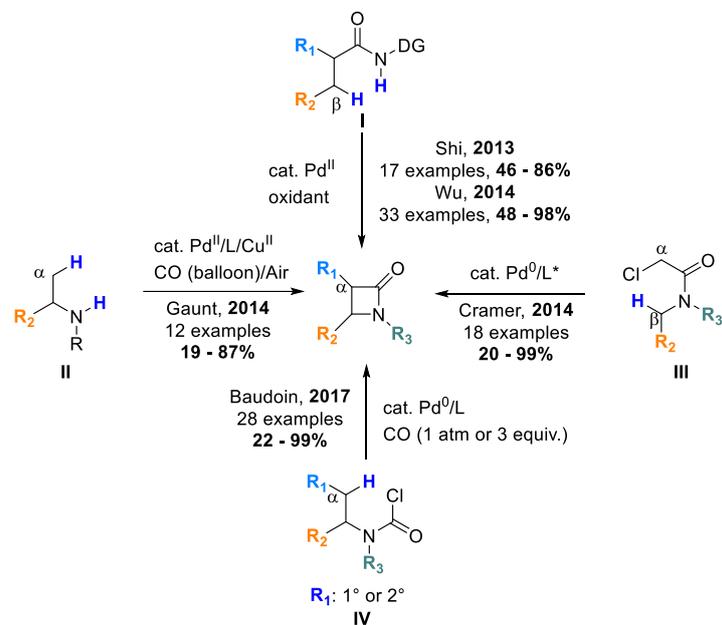


Figure 18. Selected examples of relevant  $\beta$ -lactam containing drugs.

During the last decade, palladium catalyzed C(sp<sup>3</sup>)-H activation has emerged as a powerful disconnection possibility for such  $\beta$ -lactams (Scheme 83). For instance, the Shi<sup>[250]</sup> and Wu<sup>[251]</sup> groups disclosed a pyridine- or quinolone-directed Pd<sup>II</sup>-catalyzed C(sp<sup>3</sup>)-H amidation (**I**) in the construction of the desired four-membered cyclic products. In both procedures, methylene positions were functionalized, and the employment of a stoichiometric oxidant was required. On the other hand, the Gaunt group published an elegant synthesis of the  $\beta$ -lactam moiety under Pd<sup>II</sup>-catalysis.<sup>[252]</sup> In this work, the formation of a strained four-membered palladacycle is directed by an aliphatic secondary amine **II** upon activation of a methyl group. Subsequent carbonylation under oxidative conditions (Cu- catalyst under an air/CO atmosphere) and reductive elimination forges the strained four-membered products. The Cramer group presented a protocol starting from electrophilic  $\alpha$ -chloroamides **III** under Pd<sup>0</sup>-catalysis, in which the use of external stoichiometric oxidants was omitted.<sup>[210]</sup> The employment of a chiral TADDOL-

## Synthesis of $\beta$ -Lactams *via* 1,4-Pd Shift-Mediated Double C(sp<sup>3</sup>)-H Activation

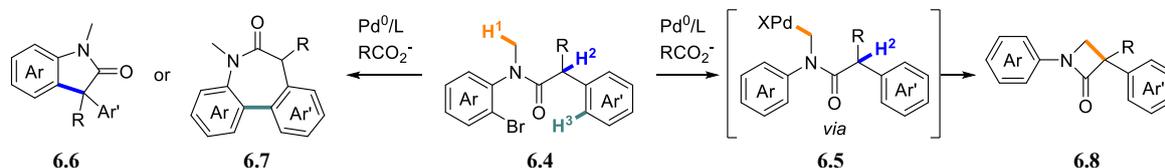
derived phosphoramidite ligand resulted in good reactivity and enantioselectivity in the functionalization of activated methylene positions adjacent to the nitrogen atom. Similarly, the Baudoin group developed a C(sp<sup>3</sup>)-H carbamoylation reaction starting from the corresponding carbamoyl chlorides **IV** under Pd<sup>0</sup>-catalysis.<sup>[211]</sup> In presence of CO-gas, methyl and unactivated methylene positions were successfully functionalized resulting in a variety of  $\beta$ -lactams.



Scheme 83. Precedents in the  $\beta$ -lactam synthesis *via* Pd-catalyzed C(sp<sup>3</sup>)-H activation.

## 6.2 Aim of this Project

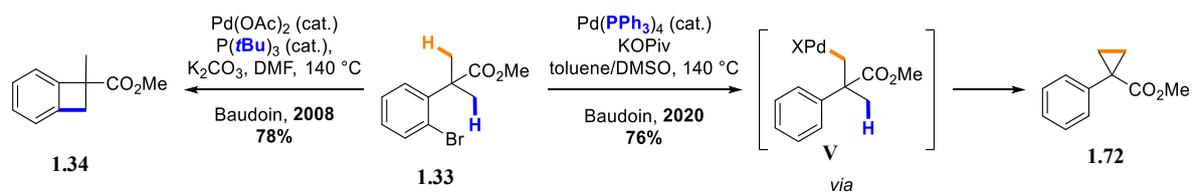
All of the herein presented Pd-catalyzed C(sp<sup>3</sup>)-H functionalizations towards the highly strained  $\beta$ -lactam either include sensitive substrates, the requirement for directing groups (that are difficult to remove), additional external oxidants, and/or the presence of CO-gas. All these factors make the individual streamlined reactions not very user-friendly in one way or another. To overcome those limitations, we aimed to develop a protocol to access this four-membered cyclic product under more convenient reaction conditions. We envisioned the construction of the  $\beta$ -lactam *via* a 1,4-Pd shift mediated double C(sp<sup>3</sup>)-H activation strategy as presented in Scheme 84. Starting from readily available and stable *N*-Me amide **6.4**, oxidative addition of Pd<sup>0</sup> into the aryl halide bond, followed by subsequent C(sp<sup>3</sup>)-H activation at the *N*-Me group (H<sup>1</sup>) and proton transfer, would furnish  $\sigma$ -alkylpalladium species **6.5**. In turn, this species could promote a second C(sp<sup>3</sup>)-H activation event at H<sup>2</sup>. Subsequent reductive elimination would then forge the strained four-membered cyclic product **6.8**. However, several aspects have to be considered. The direct arylation at H<sup>2</sup> and H<sup>3</sup> leading to oxindole **6.6**<sup>[189,253,254]</sup> and dibenzazepinone **6.7**,<sup>[255,256]</sup> respectively, are well-documented and efficient transformations. Consequentially, the direct activation of these more acidic C-H bonds must be suppressed to ensure the selective formation of the new quaternary carbon center in the desired  $\beta$ -lactams.



Scheme 84. Envisioned synthesis of the biologically relevant  $\beta$ -lactam motif *via* 1,4-Pd shift-mediated double C(sp<sup>3</sup>)-H activation.

For instance, our group already demonstrated the complete suppression of the direct C(sp<sup>3</sup>)-H arylation by careful optimization of the reaction conditions as shown in Scheme 85. By changing the ligand, bases, and solvent, cyclopropane **1.72** was obtained as sole product by the formation of a new C(sp<sup>3</sup>)-C(sp<sup>3</sup>) bond after 1,4-Pd shift (V), instead of the previously described direct arylation furnishing the corresponding BCB **1.34**.<sup>[54]</sup> Furthermore, the successful 1,4-Pd shift over a methyl position adjacent to a nitrogen atom was performed in the synthesis of indolines.<sup>[107]</sup> All these findings support the feasibility of the selective  $\beta$ -lactam synthesis *via* 1,4-Pd shift-mediated double C(sp<sup>3</sup>)-H activation which is going to be a new entry in the construction of challenging C(sp<sup>3</sup>)-C(sp<sup>3</sup>) bonds through cross-dehydrogenation.<sup>[109]</sup>

## Synthesis of $\beta$ -Lactams *via* 1,4-Pd Shift-Mediated Double C(sp<sup>3</sup>)-H Activation



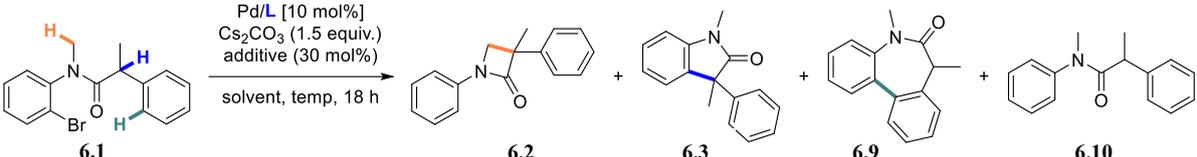
Scheme 85. Previous results demonstrating the selective 1,4-Pd shift over the direct C(sp<sup>3</sup>)-H arylation.

### 6.3 Results and Discussion

#### 6.3.1 Ligand Effect and Reaction Optimization

In the previously presented projects, it has been shown that the ligand has a pronounced influence on reaction selectivity. Since we believed that this ligand effect is the key parameter for the selectivity control in the functionalization of **6.1**, we started with the investigation of different catalytic systems as presented in Table 13. Initially, the  $\beta$ -lactam **6.2** was observed in 15% <sup>1</sup>H NMR yield under standard C(sp<sup>3</sup>)-H activation conditions with an **IBiox<sup>t</sup>Bu** ligand (entry 1). The previously employed 1,4-Pd shift functionalization conditions in the synthesis of cyclopropanes<sup>[113]</sup> and indolines<sup>[107]</sup> favored the formation of the dibenzazepinone **6.9** along with some oxindole **6.3** and only traces of the desired  $\beta$ -lactam **6.2** (entries 2 and 3). The model substrate **6.1** was then further reacted with various other ligands under standard C-H activation conditions, Pd/L (10 mol%), Cs<sub>2</sub>CO<sub>3</sub> (1.5 equiv.), CsOPiv (30 mol%) in mesitylene at 160 °C for 18 h. Fortunately, with the **IBiox6** ligand, the  $\beta$ -lactam **6.2** was observed for the first time in an improved <sup>1</sup>H NMR yield of 30% along with 31% oxindole **6.3**, 23% of dibenzazepinone **6.9** and 26% of the proto-dehalogenated **6.10** (entry 4). Other types of NHCs such as **IPr** resulted in the selective formation of the direct  $\alpha$ -arylation product **6.3** (entry 5). Kündig type ligand **L12** showed a low reactivity together with low selectivity in this transformation (entry 6).

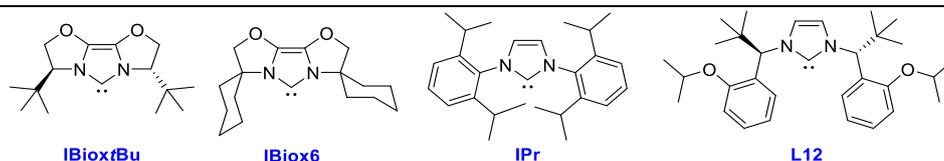
Table 13. Selected results of the initial investigation of the ligand effect.



entry	Pd/L	solvent	additive	base	temp [°C]	<sup>1</sup> H NMR yield <sup>a</sup> 6.1:6.2:6.3:6.9:6.10
1	Pd/ <b>IBiox<sup>t</sup>Bu</b> <sup>b</sup>	mesitylene	CsOPiv	Cs <sub>2</sub> CO <sub>3</sub>	160	0:15:55:0:0
2	Pd( <b>PPh</b> <sub>3</sub> ) <sub>4</sub>	PhMe:DMSO <sup>c</sup>	-	KOPiv <sup>d</sup>	140	0:1:25:64:0
3	Pd( <b>PCy</b> <sub>3</sub> ) <sub>2</sub>	mesitylene	AdCO <sub>2</sub> H	Rb <sub>2</sub> CO <sub>3</sub>	160	0:9:5:66:11
4	Pd/ <b>IBiox6</b> <sup>b</sup>	mesitylene	CsOPiv	Cs <sub>2</sub> CO <sub>3</sub>	160	0:30:31:23:26
5	Pd/ <b>IPr</b> <sup>b,e</sup>	mesitylene	CsOPiv	Cs <sub>2</sub> CO <sub>3</sub>	160	1:2:84:0:8
6	Pd <sup>b,e</sup> / <b>L12</b> <sup>f</sup>	mesitylene	CsOPiv	Cs <sub>2</sub> CO <sub>3</sub>	160	48:2:13:15:10

<sup>a</sup> Determined with trichloroethylene as internal standard. <sup>b</sup> Starting from [Pd( $\pi$ -cin)Cl]<sub>2</sub> and IBiox•HOTf salt.

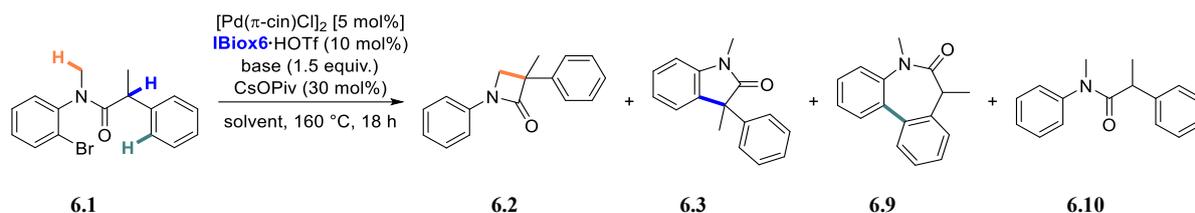
<sup>c</sup> 95:5. <sup>d</sup> 2 equiv. <sup>e</sup> IPr•HCl. <sup>f</sup> HI salt.



Building upon this initial result with **IBiox6** as ligand, the reaction conditions were optimized. In a first screening, the solvent effect was investigated. Apolar aromatic solvents generally resulted in a less favorable reaction selectivity as seen in the case of cumene in Table 14, entry 2. Ethereal solvents gave similar yields in the desired formation of **6.2** along with a slight decrease in the C(sp<sup>2</sup>)-H arylation product **6.9** (entries 3 and 4) compared to the initial reaction conditions (entry 1). When CF<sub>3</sub>Ph was used as solvent, the yield of  $\beta$ -lactam improved to 37%, and complete suppression of dibenzazepinone **6.9** was observed (entry 5). More polar solvents as represented by DMA showed a lower reactivity together with the favored formation of oxindole **6.3** (entry 6). After this optimization, cesium was shown to be the optimal counter cation for the carbonate bases after the evaluation of the stoichiometric base. K<sub>2</sub>CO<sub>3</sub> suppressed the formation of the desired **6.2** while the formation of the three undesired side products stayed constant (entry 7). Na<sub>2</sub>CO<sub>3</sub> and K<sub>3</sub>PO<sub>4</sub> instead, showed a much lower reactivity (entries 8 and 9). The use of strong bases such as LiHMDS and NaOtBu favored the direct  $\alpha$ -arylation with the almost exclusive formation of oxindole **6.3** (entries 10 and 11). These results are not surprising considering an enolate arylation mechanism being at play under such typical conditions.<sup>[189,253]</sup> Various cesium bases were further tested as a stoichiometric base, however no satisfying results were achieved. Also, the screening of different CMD-mediating bases led to no improvement. A second evaluation of IBiox ligands revealed the sterically less demanding **IBioxMe4** as optimal, furnishing an improved yield of 44% for  $\beta$ -lactam under the optimized conditions ([Pd( $\pi$ -cin)Cl]<sub>2</sub> (5 mol%), **IBioxMe4**•HOTf (10 mol%), CsOPiv (30 mol%) and Cs<sub>2</sub>CO<sub>3</sub> (1.5 equiv.) in CF<sub>3</sub>Ph at 160 °C for 18 h (entry 12). The formation of oxindole **6.3** and proto-dehalogenated **6.10** was decreased compared to the results obtained with **IBiox6**. Moreover, no dibenzazepinone **6.9** was observed.

## Synthesis of $\beta$ -Lactams via 1,4-Pd Shift-Mediated Double C(sp<sup>3</sup>)-H Activation

Table 14. Selected examples in the reaction optimization towards **6.2**.

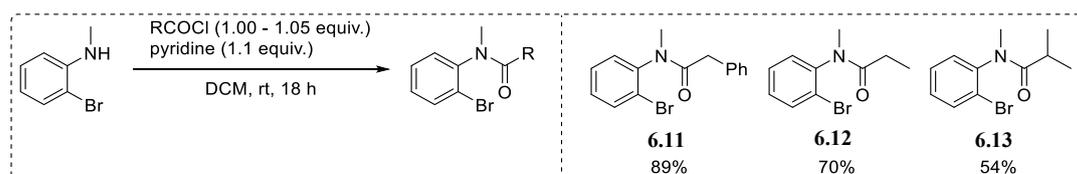


entry	solvent	base	<sup>1</sup> H NMR yield <sup>a</sup> <b>6.1:6.2:6.3:6.9:6.10</b>
1	mesitylene	Cs <sub>2</sub> CO <sub>3</sub>	0:30:31:23:26
2	cumene	Cs <sub>2</sub> CO <sub>3</sub>	0:10:27:14:10
3	<i>n</i> Bu <sub>2</sub> O	Cs <sub>2</sub> CO <sub>3</sub>	0:31:23:9:15
4	DME	Cs <sub>2</sub> CO <sub>3</sub>	0:32:41:10:13
5	CF <sub>3</sub> Ph	Cs <sub>2</sub> CO <sub>3</sub>	0:37:18:0:12
6	DMA	Cs <sub>2</sub> CO <sub>3</sub>	20:12:33:0:20
7	CF <sub>3</sub> Ph	K <sub>2</sub> CO <sub>3</sub>	0:8:20:30:20
8	CF <sub>3</sub> Ph	Na <sub>2</sub> CO <sub>3</sub>	71:0:10:0:13
9	CF <sub>3</sub> Ph	K <sub>3</sub> PO <sub>4</sub>	0:15:19:0:12
10	CF <sub>3</sub> Ph	LiHMDS	6:0:89:2:2
11	CF <sub>3</sub> Ph	NaOtBu	0:0:95:0:0
12	CF <sub>3</sub> Ph <sup>b</sup>	Cs <sub>2</sub> CO <sub>3</sub>	0:44:25:0:19

<sup>a</sup> Determined with trichloroethylene as internal standard. <sup>b</sup> With IBioxMe<sub>4</sub>•HOTf instead of IBiox6•HOTf.

### 6.3.2 Substrate Modifications

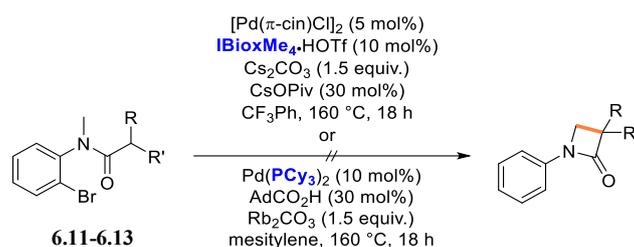
As the yield in this transformation on model amide **6.1** could not be further improved than 44% <sup>1</sup>H NMR yield, we were curious to find out if modifications on the substrates might promote the reaction selectivity. In a first approach, the influence of the substituent in the  $\alpha$ -position to the amide was investigated (R). Thus, amides with a methylene position  $\alpha$ - to the amide **6.11** and **6.12** were synthesized by reacting 2-bromo-*N*-methylaniline with the corresponding phenylacetyl- and propionyl chloride, respectively (Scheme 86). In the same manner, **6.13** was obtained from *isobutyryl* chloride to investigate the influence of the acidity at the tertiary position.



Scheme 86. Synthesis of the modified model substrates.

## Synthesis of $\beta$ -Lactams via 1,4-Pd Shift-Mediated Double C(sp<sup>3</sup>)-H Activation

All of these three modified substrates were engaged under the herein optimized 1,4-Pd shift conditions and the one presented in literature for the synthesis of indolines<sup>[107]</sup> (Table 13, entry 3). Unfortunately, none of the possible C-H activation products was identified in any of the reactions (Scheme 87) Scheme 87. Testing of the modified substrates under standard 1,4-Pd shift conditions.. In all the cases, the <sup>1</sup>H NMR spectra of the crude reaction was of difficult interpretation, indicating substrate or product decomposition. These results showed a strong substrate dependency in the formation of  $\beta$ -lactams. As consequence, these modifications of the substrate cannot be used for a more efficient reaction.



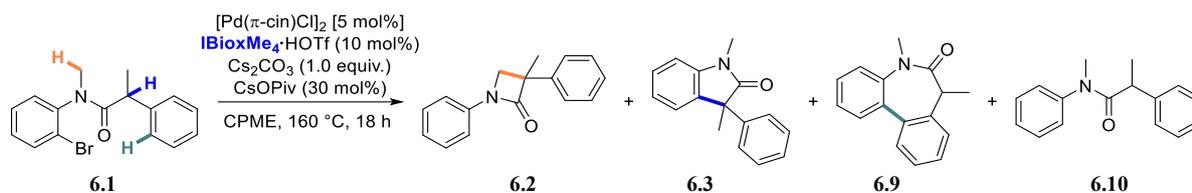
Scheme 87. Testing of the modified substrates under standard 1,4-Pd shift conditions.

### 6.3.3 Second Reaction Optimization

Being aware of these substrate limitations, we turned our attention back to reaction optimization. In general, the best reactivity and selectivity towards the desired **6.2** was observed in apolar aromatic and slightly polar solvents such as ethers and CF<sub>3</sub>Ph. Therefore, a second solvent screening was performed wherein more volatile solvents were tested. Performing these reactions in capped microwave vials revealed CPME (cyclopentyl methyl ether) as the optimal solvent which increased the yield of  $\beta$ -lactam **6.2** to 50% along with 35% oxindole **6.3** and 12% proto-dehalogenated **6.10** as observed by <sup>1</sup>H NMR and shown in Table 15, entry 2. Omitting the CMD-mediating pivalic species resulted in a decreased yield of 41% and an increase in proto-dehalogenation (22%) (entry 3). The previously elucidated reaction conditions resulted to still perform the best even after further optimization of all the reaction parameters (bases, additives, concentration, temperature). However, the amount of Cs<sub>2</sub>CO<sub>3</sub> could be reduced to 1 equivalent without affecting the reaction performance (entry 4). Lowering the temperature to 140 °C completely shut-down the reaction and 89% of the starting material was recovered (entry 5). The best conditions promoting this remote functionalization were found to be [Pd( $\pi$ -cin)Cl]<sub>2</sub> (5 mol%), IBioxMe<sub>4</sub>.HOTf (10 mol%), CsOPiv as CMD-mediating base (30 mol%) and Cs<sub>2</sub>CO<sub>3</sub> as stoichiometric base (1.0 equiv.) in CPME at 160 °C for 18 h. During the course of this reaction optimization, reproducibility issues arose. It was shown that running the reactions in a new microwave vial and in an oil bath instead of the catalysis metal blocks resulted in better reproducibility and all further experiments were performed in this setting.

## Synthesis of $\beta$ -Lactams via 1,4-Pd Shift-Mediated Double C(sp<sup>3</sup>)-H Activation

Table 15. Summarized second reaction optimization.

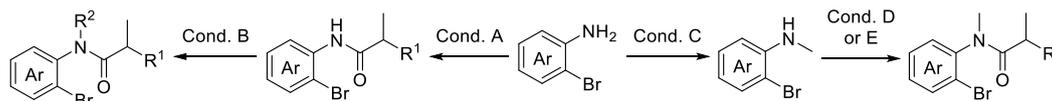


entry	deviation from optimized conditions		<sup>1</sup> H NMR yield <sup>a</sup>
			<b>6.1:6.2:6.3:6.9:6.10</b>
1	CF <sub>3</sub> Ph instead of CPME	Cs <sub>2</sub> CO <sub>3</sub> (1.5 equiv.)	0:44:25:0:19
2		Cs <sub>2</sub> CO <sub>3</sub> (1.5 equiv.)	0:50:35:0:12
3	No CsOPiv	Cs <sub>2</sub> CO <sub>3</sub> (1.5 equiv.)	0:41:24:0:22
4			0:52:29:0:23
5	140 °C		89:0:0:0

<sup>a</sup> Determined with trichloroethylene as internal standard.

### 6.3.4 Reaction Scope

The reaction was repeated on a 0.3 mmol scale on model substrate **6.1** under the best reaction conditions and furnished a separable 3:2 mixture of the desired  $\beta$ -lactam **6.2** and the directly arylated oxindole **6.3**. The remotely functionalized **6.2** was isolated in 51% yield. After these promising results, we started to explore the substrate scope for this 1,4-Pd shift promoted C(sp<sup>3</sup>)-H functionalization. The substrates were synthesized in a streamlined fashion starting from the corresponding *ortho*-bromo anilines as depicted in Scheme 88. Either the free aniline was reacted with the corresponding acyl chloride with subsequent alkylation promoted by NaH deprotonation of the secondary amide (Cond. A and B) or the aniline was methylated before the amide formation with the corresponding acyl chlorides (Cond. C, D, and E).

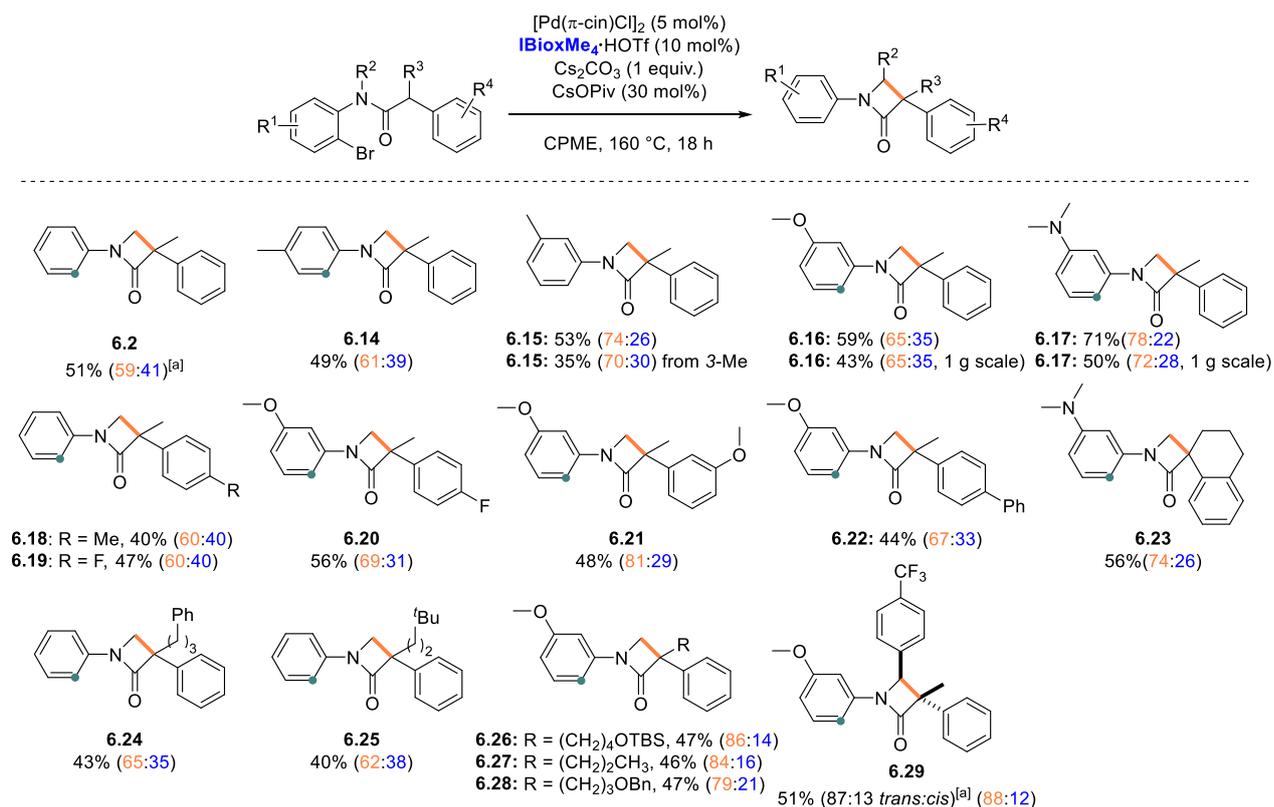


Scheme 88. Substrate Syntheses. Cond. A: RCO<sub>2</sub>H (1.1 equiv.), SOCl<sub>2</sub> (2.0 equiv.), reflux, 2 h. Then aniline (1.0 equiv.), Et<sub>3</sub>N (1.5 equiv.), DCM, rt, 2 h. Cond. B: NaH (1.0 equiv.), AlkI/BnBr (1.0 equiv.), THF, rt, 3 h. Cond. C: *n*BuLi (1.00 equiv.), MeI (1.05 equiv.), THF, -78 °C to rt. Cond. D: (COCl)<sub>2</sub>, RCO<sub>2</sub>H (1.3 equiv.), DMF (cat.), DCM, rt, 18 h. Cond. E: RCO<sub>2</sub>Cl (1.5 equiv.), Et<sub>3</sub>N (2.0 equiv.), DCM, rt, 18 h.

As shown in Scheme 89, a variety of electron-donating groups at the *meta*- and *para*-position to the nitrogen were well tolerated delivering the desired  $\beta$ -lactams in moderate to good yields **6.14** - **6.17**. Remarkably, having strong electron-donating groups (OMe, NMe<sub>2</sub>) at this position improves the yield significantly (**6.16** = 59% and **6.17** = 71%, respectively). In the next step, the influence of the initial substituent position was investigated. Submitting the 2-bromo-5-methylaniline derivative resulted in the corresponding  $\beta$ -lactam **6.15** in a moderate yield of 53%. In contrast, starting from the 2-bromo-3-methyl aniline derivative furnished **6.15** in only 35% yield with some unreacted substrate and more proto-dehalogenation. We suggest that this

lower yield arises from a more challenging oxidative addition. Furthermore, the substituents on the remote aryl ring at the  $\alpha$ -position to the amide group were examined (R<sup>4</sup>). Electron-donating (**6.18**, **6.21**) and -withdrawing groups (**6.19**, **6.20**), as well as a phenyl substituent (**6.22**), were well tolerated and the corresponding products isolated in a range of 40 - 48% yield. Interestingly, when starting from the corresponding tetrahydronaphthoic acid derivative, the spirocyclic  $\beta$ -lactam **6.23** was obtained in 56% isolated yield. In addition, replacing the methyl substituent at the position  $\alpha$ - to the amide group with a variety of functionalized alkyl chains (R<sup>3</sup>) was shown to be compatible under the applied reaction conditions and furnishing the corresponding  $\beta$ -lactams in moderate yields in a range from 40 - 47% (**6.24** - **6.28**). Thereby it was shown that phenyl substituents (**6.24**), longer alkyl chains (**6.25**, **6.27**) as well as TBS and benzyl protected primary alcohols were well tolerated. Pleasingly, the highly functionalized  $\beta$ -lactam **6.29** was isolated as a diastereomeric mixture in 51% yield by replacing the *N*-Me with an *N*-(*p*-trifluoromethylbenzyl) substituent (R<sup>2</sup>). 2D-NMR analyses revealed the *trans* diastereoisomer as the major product in a ratio of 87:13. Next to the formation of this densely functionalized product, this example also demonstrates the feasibility of a 1,4-Pd migration over an activated methylene position adjacent to a nitrogen atom. Unfortunately, starting from the *N*-ethylated substrate resulted in 41% of the olefin arising from the 1,4-shift and subsequent  $\beta$ -H elimination. Also, other activating groups adjacent to the 1,4-Pd shift position which suppress the  $\beta$ -H elimination, such as esters and CF<sub>3</sub> groups, were not stable under the employed reaction conditions. When scaling the reaction up to 1 g, the desired  $\beta$ -lactams **6.16** and **6.17** were isolated in 43% and 50% yield, respectively. Moreover, the structure of biphenyl analog **6.22** was unequivocally determined by X-ray diffraction analysis as presented in Figure 19.

## Synthesis of $\beta$ -Lactams via 1,4-Pd Shift-Mediated Double C(sp<sup>3</sup>)-H Activation



Scheme 89. Reaction scope in the synthesis of  $\beta$ -lactams via 1,4-Pd shift mediated double C(sp<sup>3</sup>)-H activation on a 0.3 mmol scale. Yields refer to the isolated  $\beta$ -lactam product. The ratios in the brackets refer to the  $\beta$ -lactam/oxindole products as determined by GCMS. The green dot indicates the initial position of the Br.<sup>[a]</sup> As determined by <sup>1</sup>H NMR.

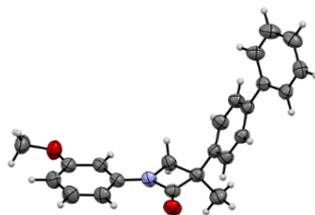
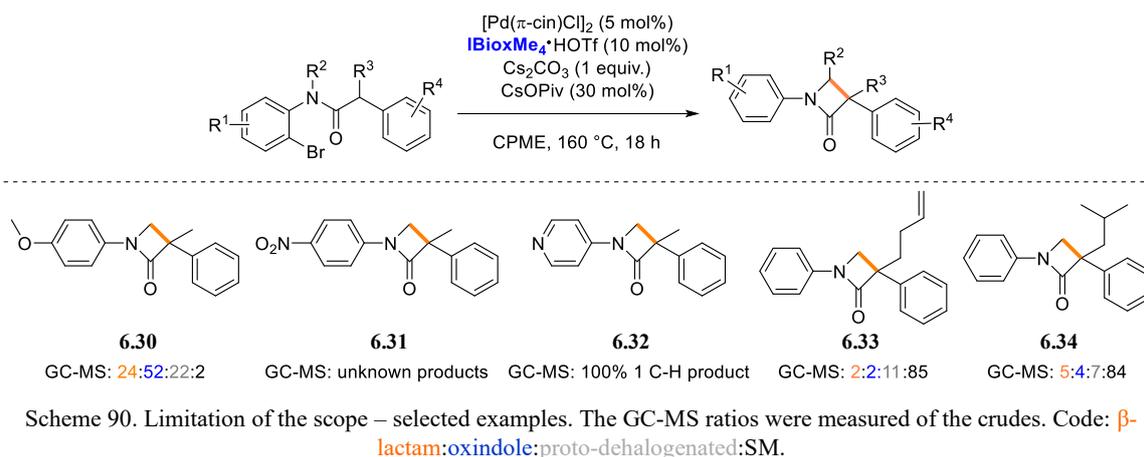


Figure 19. X-ray crystal structure of **6.22**. Thermal ellipsoids are shown at 50% probability

Some of the limitations for this transformation are shown in Scheme 90. Generally, electron donating groups *para* to the nitrogen substituent either favor the direct  $\alpha$ -arylation as shown in the case of **6.30** or shut down the reactivity. Electron-withdrawing substituents such as Cl and NO<sub>2</sub> are not tolerated on the aromatic moiety R<sup>1</sup> (**6.31**). A pyridine moiety at any part of the molecule either completely shuts down the reaction or results in the formation of an unknown C-H activation product (**6.32**). On the alkyl substituent (R<sup>3</sup>), olefins (**6.33**), and an *isopropyl* group two positions away from the activated center (**6.34**) almost fully inhibited the reaction.

## Synthesis of $\beta$ -Lactams *via* 1,4-Pd Shift-Mediated Double C(sp<sup>3</sup>)-H Activation

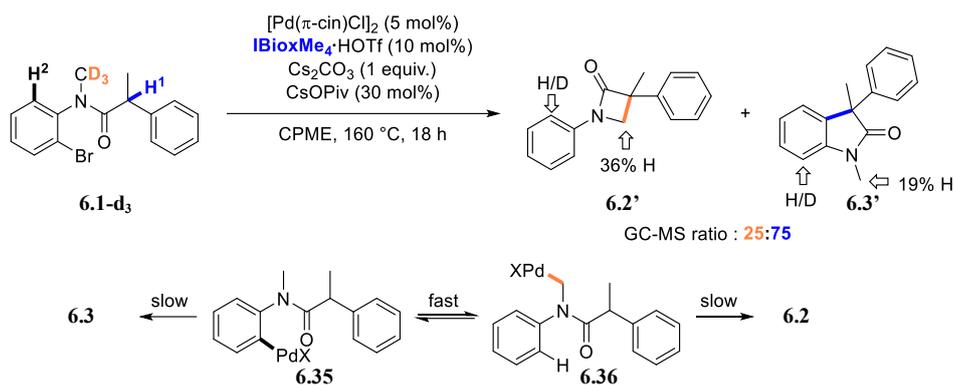


At this stage, we investigated further modifications on the substrate. Replacing the remote phenyl substituent ( $\alpha$ - to the amide) with a methyl-, *tert*-butyl ester, amide, or  $\beta$ -ketoamide did not result in the desired  $\beta$ -lactams. The methyl ester gave the corresponding decarboxylated oxindole, the other substrates did not lead to any productive reaction. Installing a benzyl group instead resulted only in traces of  $\beta$ -lactam while mostly starting material was recovered. Substituting the alkyl moiety R<sup>3</sup> with a second phenyl group furnished the direct C(sp<sup>2</sup>)-H activation product together with some recovered starting material.

### 6.3.5 Preliminary Mechanistic Investigations

Submitting the *N*-CD<sub>3</sub> **6.1-d<sub>3</sub>** under standard reaction conditions revealed deuterium incorporation in the aromatic ring of the  $\beta$ - (**6.2'**) and  $\gamma$ -lactams (**6.3'**), respectively, as observed by <sup>2</sup>H NMR experiments (Scheme 91). Unfortunately, the deuterium incorporation in the aromatic ring could not be quantified due to low incorporation and overlaps in the corresponding <sup>1</sup>H-NMR spectrum. Additionally, proton incorporation in the initial CD<sub>3</sub>-group was observed on both isolated cyclic products which are evidence for a reversible 1,4-Pd shift *via* C(sp<sup>3</sup>)-H activation and a fast equilibrium between the two occurring Pd-species **6.35** and **6.36**. These findings are in agreement with previous observations of our group.<sup>[101]</sup> The source of protons is not known, but we speculated the following possibilities: upon deprotonation of the acidic **H**<sup>1</sup>, from the reversible 1,4-shift (**H**<sup>2</sup>), and H<sub>2</sub>O traces in the reaction medium. The low incorporation of deuterium on the aromatic ring suggests dynamic deprotonation and reprotonation of the pivalic acid or carbonate being involved in the CMD-step after C-H activation. We assume that a Curtin-Hammett scenario is likely at play. Thereby, the trapping rate of the  $\sigma$ -aryl- and  $\sigma$ -alkylpalladium intermediates **6.35** and **6.36** by C-H functionalization at the  $\alpha$ -position to the amide is controlling the reaction selectivity and, as consequence, the ratio of the two arising cyclic products.

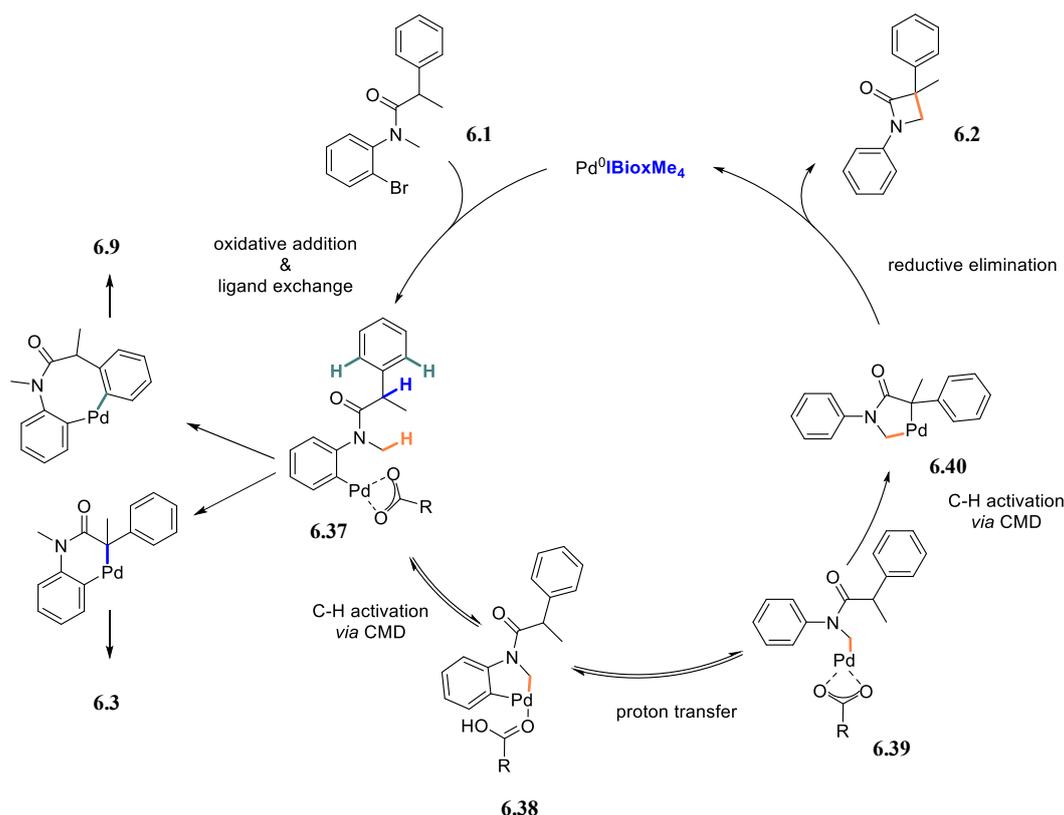
## Synthesis of $\beta$ -Lactams *via* 1,4-Pd Shift-Mediated Double C(sp<sup>3</sup>)-H Activation



Scheme 91. Deuterium labeling experiments.

Based on these findings we propose the catalytic cycle which is depicted in Scheme 92. The Pd<sup>II</sup>-species **6.37** is generated after oxidative addition of Pd<sup>0</sup> into the aryl bromide bond of **6.1** and ligand exchange with the pivalate. At this point, the ligand and reaction conditions dictate the course of the further reaction. Species **6.37** can undergo direct  $\alpha$ -arylation resulting in **6.3**, or direct C(sp<sup>2</sup>)-activation *via* CMD with subsequent reductive elimination furnishing dibenzazepinone **6.9**. However, these two pathways are disfavored under the optimized reaction conditions and **6.37** undergoes a first C(sp<sup>3</sup>)-H activation on the methyl group adjacent to the nitrogen atom resulting in palladacycle **6.38**. A subsequent proton transfer furnishes the  $\sigma$ -alkyl palladium species **6.39** which can undergo a second C(sp<sup>3</sup>)-H activation and reductive elimination while forging the desired four membered cyclic product **6.2** while regenerating the catalytically active Pd<sup>0</sup>. The 1,4-Pd shift was shown to be in equilibrium.

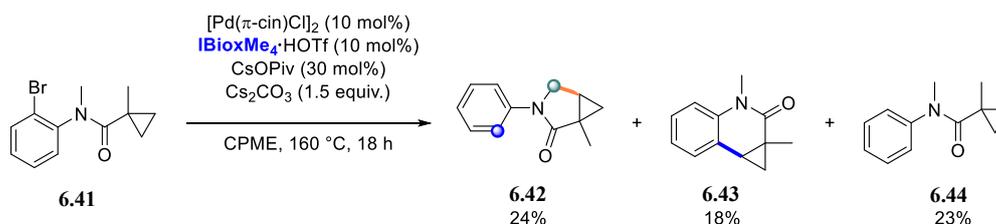
## Synthesis of $\beta$ -Lactams via 1,4-Pd Shift-Mediated Double $C(sp^3)$ -H Activation



Scheme 92. The proposed catalytic cycle for the herein developed 1,4-Pd shift mediated synthesis of  $\beta$ -lactam. Ligands were omitted for clarity.

### 6.3.6 Expansion of the Methodology

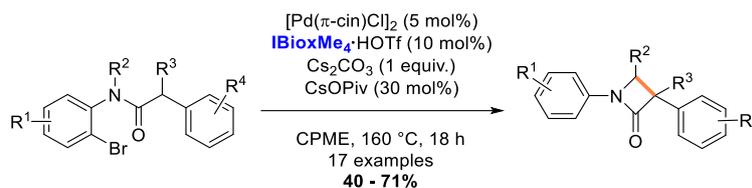
At this point, we postulated whether this 1,4-shift mediated  $C(sp^3)$ - $C(sp^3)$  bond formation methodology could be expanded with the trapping of the formed  $\sigma$ -alkylpalladium with the functionalization of less reactive  $C(sp^3)$ -H bonds. For this purpose, *N*-methylated amide **6.41** was submitted under the optimized conditions of the  $\beta$ -lactam synthesis. Fortunately, the desired cyclopropane fused lactam **6.42** was observed in 24%  $^1H$  NMR yield together with the direct arylated cyclopropane **6.43**<sup>[65]</sup> and 23% of the protodehalogenated **6.44** (Scheme 93). These initial results support the feasibility of this transformation. Further optimization of the reaction conditions and the substrates might allow the selective synthesis of such fused bicyclic amides.



Scheme 93. Initial result in the construction of cyclopropane fused lactam **6.42** via 1,4-Pd mediated double  $C(sp^3)$ -H activation.

## 6.4 Conclusion and Outlook

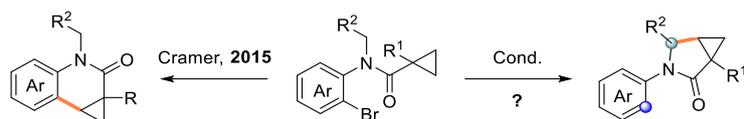
In conclusion, a 1,4-Pd shift mediated double C(sp<sup>3</sup>)–H activation in the synthesis of  $\beta$ -lactams was disclosed in this chapter. Starting from simple and readily accessible starting materials, a scope of 17  $\beta$ -lactams was accessed in moderate to good yield tolerating a variation of substituents on the aromatic cores and the alkyl moiety. A new all-carbon quaternary center was created during this process while an additional C(sp<sup>3</sup>)–C(sp<sup>3</sup>) bond is formed. Careful reaction condition optimization allowed a high product selectivity in this delicate transformation. Crucial for its product selectivity was the use of an **IBioxMe<sub>4</sub>** ligand together with CPME as a reaction medium. In contrast, the employment of phosphine- and other types of NHC (*e.g.* **IPr**) ligands favored dibenzazepinone and oxindole products, respectively. Furthermore, the first shift over a benzylic position adjacent to the nitrogen was presented which furnished a highly functionalized  $\beta$ -lactam core in moderate yield. The structure of the four membered cyclic products was unequivocally confirmed by X-ray crystallographic analysis. Deuterium labeling experiments proved the reversible nature of the occurring 1,4-Pd shift.



Scheme 94. Summary of the reaction scope.

In this project, the  $\sigma$ -alkylpalladium intermediate formed after a 1,4-Pd shift was trapped *via* second C(sp<sup>3</sup>)–H activation  $\alpha$ - to an amide bypassing the potential direct C(sp<sup>3</sup>)–H  $\alpha$ -arylation. This concept could be further expanded to the activation and functionalization of less acidic C(sp<sup>3</sup>)–H groups. In 2015, the Cramer group reported the synthesis of dihydroquinolones *via* intramolecular C(sp<sup>3</sup>)–H arylation of a cyclopropane moiety (Scheme 95).<sup>[65]</sup> Careful reaction optimization similar to the work presented in this chapter might lead to the selective 1,4-Pd shift to the position adjacent to the nitrogen atom with subsequent C(sp<sup>3</sup>)–C(sp<sup>3</sup>) bond formation upon activation of the cyclopropane moiety instead, as shown in Scheme 95. The thereby forged motif with a cyclopropane fused to a lactam or pyrrolidine (after reduction)<sup>[257]</sup> is a common structural scaffold found in pharmacophores<sup>[258,259]</sup> and some biologically active natural products.<sup>[260,261]</sup> Initial observations under the herein described reaction conditions proved the feasibility of this 1,4-Pd-shift mediated functionalization and are a suitable starting point for the further development of this reaction.

## Synthesis of $\beta$ -Lactams *via* 1,4-Pd Shift-Mediated Double C(sp<sup>3</sup>)-H Activation

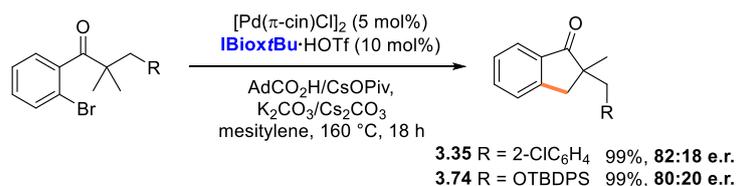


Scheme 95. Potential new reactivity in the 1,4-Pd-shift mediated double C(sp<sup>3</sup>)-H activation.

Also, an enantioselective version of the  $\beta$ -lactam synthesis could be envisioned. However, the lower selectivity of sterically more demanding IBiox ligands might cause a major limitation in this transformation. A broad ligand screening, reaction optimization, and probably the design and application of new ligands might be necessary to achieve a high product selectivity together with a good enantioinduction.

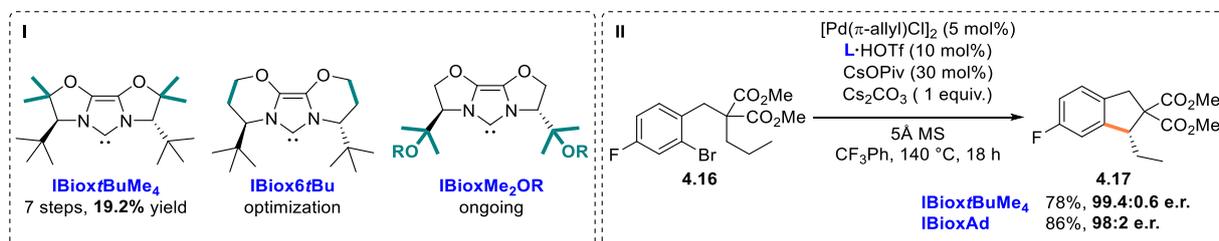
## 7 General Conclusion

During the first part of this thesis, new insights were gained in enantioselective C(sp<sup>3</sup>)-H arylation reactions. Indanones were accessed in good to excellent yields after substrate and reaction condition optimization. Moderate enantioselectivities (ca. 80:20 e.r.) were achieved with the best performing **IBiox*t*Bu** ligand as shown in Scheme 96. Interestingly, the use of IBiox ligands suppressed a competitive C(sp<sup>2</sup>)-H arylation, which was observed as side reaction when phosphine ligands were employed on the benzylated substrates.



Scheme 96. The herein developed enantioselective indanone synthesis *via* C(sp<sup>3</sup>)-H activation.

Based on these promising results, we elaborated on the IBiox ligand scaffold to further improve the enantiocontrol in the envisioned C(sp<sup>3</sup>)-H arylation reactions. The herein designed and synthesized **IBiox*t*BuMe<sub>4</sub>** ligand showed superior enantioinduction compared to the previously best performing well studied **IBiox*Ad*** in the synthesis of highly enantioenriched indanes (**4.17**, up to 99.4:0.6 e.r.) (Scheme 97). In addition, the synthetic sequence towards the promising ligand **IBiox*6t*Bu** was explored with only the optimization of the last cyclization step remaining. The synthetic route towards **IBiox*Me<sub>2</sub>OR*** requires further elaboration towards its completion. Considering the excellent results obtained with the **IBiox*t*BuMe<sub>4</sub>** ligand, we are convinced that the herein described ligands can be fine-tuned with further modification and optimization. We are optimistic to access new highly enantioenriched cyclic products when employing these optimized ligands, which could not be accessed using previously reported ligands.

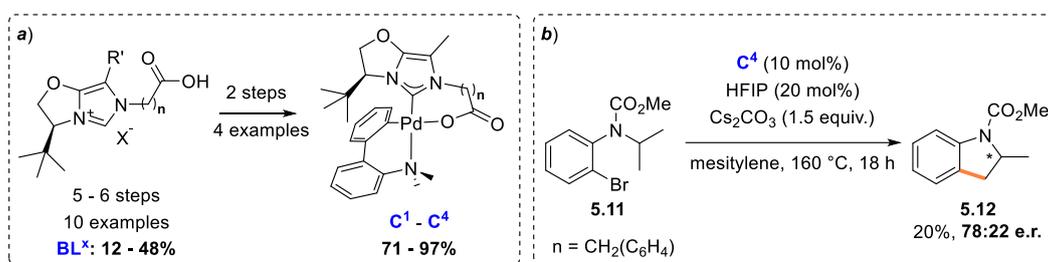


Scheme 97. I: Novel NHC-ligands. II: Application of the new **IBiox*t*BuMe<sub>4</sub>** in the enantioselective C(sp<sup>3</sup>)-H arylation.

In parallel, a strategy towards a bifunctional NHC-ligand was pursued, which could result in a higher stereoiduction arising from a highly ordered transition-state in the enantiodetermining C-H activation step. A library of 10 imidazolium-carboxylates (**BL<sup>X</sup>**) was synthesized starting from enantiopure (*L*)-*tert*-leucinol. In addition, four of the obtained imidazolium salts were

## General Conclusion

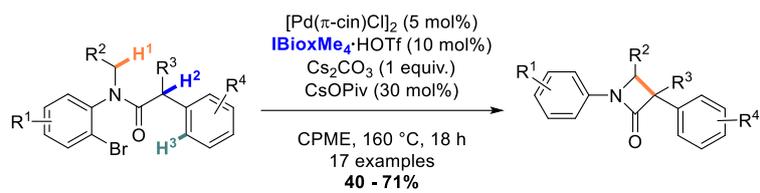
further transformed into their corresponding Pd(DMBPA)NHC palladacycles (**C<sup>x</sup>**) in good to excellent yield (Scheme 98a). The direct engagement of the NHC-precursors with Pd-sources resulted in low reactivity and racemic product formation in a prototypical Pd<sup>0</sup>-catalyzed C(sp<sup>3</sup>)–H arylation reaction. However, the engagement of the synthesized Pd(DMBP)NHC palladacycles as precatalysts under carefully optimized reaction conditions resulted in a modest enantioselectivity in the investigated indoline synthesis (78:22 e.r.), albeit in low yield (Scheme 98b). HFIP was found to be a necessary additive, presumably due to its ability to stabilize the complex through an H-bonding network. Further characterization of the complexes revealed their thermal instability at elevated temperatures. As a consequence of this instability, these highly promising bifunctional ligands and complexes cannot be employed under such forcing C(sp<sup>3</sup>)–H arylation conditions. However, transformations requiring milder conditions can benefit from the herein described new ligands and complexes.



Scheme 98. Synthesis of the new bifunctional complexes (**C<sup>x</sup>**) and their employment in the enantioselective synthesis of indolines.

In the second part of this thesis, we focused on the exploration of new reactivities under Pd<sup>0</sup>-catalyzed C(sp<sup>3</sup>)–H activation. We demonstrated the successful synthesis of a library of 17  $\beta$ -lactams in moderate to good yield employing a 1,4-Pd shift mediated double C–H activation (Scheme 99). In addition, the first example of a 1,4-Pd shift over an activated methylene position adjacent to a nitrogen atom was described resulting in a highly functionalized  $\beta$ -lactam. In this newly developed process, a challenging C(sp<sup>3</sup>)–C(sp<sup>3</sup>) bond was formed while forging the highly strained  $\beta$ -lactam ring. Key to the success of this reaction was the employment of **IBioxMe<sub>4</sub>** ligand in CPME as the reaction medium, thereby, the direct  $\alpha$ -arylation (**H<sup>2</sup>**) was disfavored and the direct C(sp<sup>2</sup>)–H arylation (**H<sup>3</sup>**) was completely suppressed. Further mechanistic studies revealed a fast equilibrium between the  $\sigma$ -aryl and  $\sigma$ -alkyl-Pd species and as consequence its reversible nature. This new entry in the C(sp<sup>3</sup>)–C(sp<sup>3</sup>)-bond formation *via* 1,4-Pd shift can potentially be further explored in the synthesis of larger *N*-heterocycles while functionalizing less activated C(sp<sup>3</sup>)–H bonds.

## General Conclusion



Scheme 99. New synthesis of  $\beta$ -lactams *via* a 1,4-Pd shift mediated double C–H activation.

## General Conclusion

## 8 References

- [1] F. Wöhler, *Ann. Phys.* **1828**, *88*, 253–256.
- [2] H. Kolbe, *Ann. Chem. Pharm.* **1845**, *54*, 145–188.
- [3] K. C. Nicolaou, *Isr. J. Chem.* **2018**, *58*, 104–113.
- [4] A. Baeyer, A. Emmerling, *Ber. Dtsch. Chem. Ges.* **1878**, *11*, 1296–1297.
- [5] C. C. C. Johansson Seechurn, M. O. Kitching, T. J. Colacot, V. Snieckus, *Angew. Chem. Int. Ed.* **2012**, *51*, 5062–5085.
- [6] R. R. Schrock, *Angew. Chem. Int. Ed.* **2006**, *45*, 3748–3759.
- [7] R. H. Grubbs, *Angew. Chem. Int. Ed.* **2006**, *45*, 3760–3765.
- [8] A. Suzuki, *Angew. Chem. Int. Ed.* **2011**, *50*, 6722–6737.
- [9] E. Negishi, *Angew. Chem. Int. Ed.* **2011**, *50*, 6738–6764.
- [10] L. J. Oxtoby, J. A. Gurak, S. R. Wisniewski, M. D. Eastgate, K. M. Engle, *Trends in Chemistry* **2019**, *1*, 572–587.
- [11] X. Ma, B. Murray, M. R. Biscoe, *Nat Rev Chem* **2020**, *4*, 584–599.
- [12] S. E. Hooshmand, B. Heidari, R. Sedghi, R. S. Varma, *Green Chem.* **2019**, *21*, 381–405.
- [13] I. Maluenda, O. Navarro, *Molecules* **2015**, *20*, 7528–7557.
- [14] K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem. Int. Ed.* **2005**, *44*, 4442–4489.
- [15] J. B. Hendrickson, *J. Am. Chem. Soc.* **1975**, *97*, 5784–5800.
- [16] S. J. Blanksby, G. B. Ellison, *Acc. Chem. Res.* **2003**, *36*, 255–263.
- [17] F. Roudesly, J. Oble, G. Poli, *Journal of Molecular Catalysis A: Chemical* **2017**, *426*, 275–296.
- [18] M. P. Doyle, R. Duffy, M. Ratnikov, L. Zhou, *Chem. Rev.* **2010**, *110*, 704–724.
- [19] M.-L. Louillat, F. W. Patureau, *Chem. Soc. Rev.* **2014**, *43*, 901–910.
- [20] A. E. Shilov, A. A. Shteinman, *Coord. Chem. Rev.* **1977**, *24*, 97–143.
- [21] A. R. Dick, M. S. Sanford, *Tetrahedron* **2006**, *62*, 2439–2463.
- [22] J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem. Int. Ed.* **2012**, *51*, 8960–9009.
- [23] Y. Fujiwara, I. Moritani, S. Danno, R. Asano, S. Teranishi, *J. Am. Chem. Soc.* **1969**, *91*, 7166–7169.
- [24] D. E. Ames, D. Bull, *Tetrahedron* **1982**, *38*, 383–387.
- [25] V. Ritleng, C. Sirlin, M. Pfeffer, *Chem. Rev.* **2002**, *102*, 1731–1770.
- [26] D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174–238.
- [27] W. Hagui, H. Doucet, J. F. Soulé, *Chem* **2019**, *5*, 2006–2078.
- [28] D. Y. K. Chen, S. W. Youn, *Chem. Eur. J.* **2012**, *18*, 9452–9474.
- [29] L. McMurray, F. O'Hara, M. J. Gaunt, *Chem. Soc. Rev.* **2011**, *40*, 1885–1898.
- [30] O. Baudoin, *Angew. Chem. Int. Ed.* **2020**, *59*, 17798–17809.

## References

- [31] A. E. Shilov, G. B. Shul'pin, N. N. Semenov, *Chem. Rev.* **1997**, *97*, 2879–2932.
- [32] J. C. K. Chu, T. Rovis, *Angew. Chem. Int. Ed.* **2018**, *57*, 62–101.
- [33] Y. Fujiwara, K. Takkai, J. Watanabe, Y. Uchida, H. Taniguchi, *Chem. Lett.* **1989**, *18*, 1687–1688.
- [34] C. Jia, T. Kitamura, Y. Fujiwara, *Acc. Chem. Res.* **2001**, *34*, 633–639.
- [35] T. Nishiguchi, K. Nakata, K. Takai, Y. Fujiwara, *Chem. Lett.* **1992**, *21*, 1141–1142.
- [36] M. Muehlhofer, T. Strassner, W. A. Herrmann, *Angew. Chem. Int. Ed.* **2002**, *41*, 1745–1747.
- [37] J. He, M. Wasa, K. S. L. Chan, Q. Shao, J. Q. Yu, *Chem. Rev.* **2017**, *117*, 8754–8786.
- [38] A. D. Ryabov, *Chem. Rev.* **1990**, *90*, 403–424.
- [39] C. Sambigiato, D. Schönbauer, R. Blicck, T. Dao-Huy, G. Pototschnig, P. Schaaf, T. Wiesinger, M. F. Zia, J. Wencel-Delord, M. Schnürch, *Chem. Soc. Rev.* **2018**, *47*, 6603–6743.
- [40] G. Rousseau, B. Breit, *Angew. Chem. Int. Ed.* **2011**, *50*, 2450–2494.
- [41] A. G. Constable, W. S. McDonald, L. C. Sawkins, B. L. Shaw, *J. Chem. Soc., Chem. Commun.* **1978**, *23*, 1061–1062.
- [42] N. A. Al-Salem, D. H. Empsall, R. Markham, B. L. Shaw, B. Weeks, *J. Chem. Soc., Dalton Trans.* **1979**, *12*, 1972–1982.
- [43] Y. Fuchita, K. Hiraki, T. Uchiyama, *J. Chem. Soc., Dalton Trans.* **1983**, 897–899.
- [44] K. Hiraki, Y. Fuchita, Y. Matsumoto, *Chem. Lett.* **1984**, *13*, 1947–1948.
- [45] Y. Fuchita, K. Hiraki, Y. Matsumoto, *J. Organomet. Chem.* **1985**, *280*, c51–c54.
- [46] J. E. Baldwin, R. H. Jones, C. Najera, M. Yus, *Tetrahedron* **1985**, *41*, 699–711.
- [47] L. v. Desai, K. L. Hull, M. S. Sanford, *J. Am. Chem. Soc.* **2004**, *126*, 9542–9543.
- [48] O. Baudoin, *Chem. Soc. Rev.* **2011**, *40*, 4902–4911.
- [49] G. Rouquet, N. Chatani, *Angew. Chem. Int. Ed.* **2013**, *52*, 11726–11743.
- [50] G. Dyker, *Angew. Chem. Int. Ed.* **1992**, *31*, 1023–1025.
- [51] G. Dyker, *Angew. Chem. Int. Ed.* **1994**, *33*, 103–105.
- [52] O. Baudoin, A. Herrbach, F. Guéritte, *Angew. Chem. Int. Ed.* **2003**, *42*, 5736–5740.
- [53] J. Hitce, P. Retailleau, O. Baudoin, *Chem. Eur. J.* **2007**, *13*, 792–799.
- [54] M. Chaumontet, R. Piccardi, N. Audic, J. Hitce, J. L. Peglion, E. Clot, O. Baudoin, *J. Am. Chem. Soc.* **2008**, *130*, 15157–15166.
- [55] J. Hitce, O. Baudoin, *Adv. Synth. Catal.* **2007**, *349*, 2054–2060.
- [56] S. Rousseaux, M. Davi, J. Sofack-Kreutzer, C. Pierre, C. E. Kefalidis, E. Clot, K. Fagnou, O. Baudoin, *J. Am. Chem. Soc.* **2010**, *132*, 10706–10716.
- [57] M. Lafrance, S. I. Gorelsky, K. Fagnou, *J. Am. Chem. Soc.* **2007**, *129*, 14570–14571.
- [58] C. L. Ladd, D. Sustac Roman, A. B. Charette, *Org. Lett.* **2013**, *15*, 1350–1353.

## References

- [59] C. Tsukano, M. Okuno, Y. Takemoto, *Angew. Chem. Int. Ed.* **2012**, *51*, 2763–2766.
- [60] C. Tsukano, M. Okuno, Y. Takemoto, *Chem. Lett.* **2013**, *42*, 753–755.
- [61] H. Ren, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 3462–3465.
- [62] T. Watanabe, S. Oishi, N. Fujii, H. Ohno, *Org. Lett.* **2008**, *10*, 1759–1762.
- [63] T. Saget, N. Cramer, *Angew. Chem. Int. Ed.* **2012**, *51*, 12842–12845.
- [64] J.-X. Yan, H. Li, X.-W. Liu, J.-L. Shi, X. Wang, Z.-J. Shi, *Angew. Chem.* **2014**, *126*, 5045–5049.
- [65] J. Pedroni, T. Saget, P. A. Donets, N. Cramer, *Chem. Sci.* **2015**, *6*, 5164–5171.
- [66] D. Katayev, M. Nakanishi, T. Bürgi, E. P. Kündig, *Chem. Sci.* **2012**, *3*, 1422–1425.
- [67] M. Nakanishi, D. Katayev, C. Besnard, E. P. Kündig, *Angew. Chem. Int. Ed.* **2011**, *50*, 7438–7441.
- [68] R. Melot, M. Zuccarello, D. Cavalli, N. Niggli, M. Devereux, T. Bürgi, O. Baudoin, *Angew. Chem. Int. Ed.* **2021**, *60*, 7245–7250.
- [69] P. M. Holstein, M. Vogler, P. Larini, G. Pilet, E. Clot, O. Baudoin, *ACS Catal.* **2015**, *5*, 4300–4308.
- [70] D. García-Cuadrado, A. A. C. Braga, F. Maseras, A. M. Echavarren, *J. Am. Chem. Soc.* **2006**, *128*, 1066–1067.
- [71] D. L. Davies, S. M. A. Donald, S. A. Macgregor, *J. Am. Chem. Soc.* **2005**, *127*, 13754–13755.
- [72] M. Lafrance, C. N. Rowley, T. K. Woo, K. Fagnou, *J. Am. Chem. Soc.* **2006**, *128*, 8754–8756.
- [73] D. Lapointe, K. Fagnou, *Chem. Lett.* **2010**, *39*, 1118–1126.
- [74] O. Baudoin, *Acc. Chem. Res.* **2017**, *50*, 1114–1123.
- [75] L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315–1345.
- [76] S. Rousseaux, S. I. Gorelsky, B. K. W. Chung, K. Fagnou, *J. Am. Chem. Soc.* **2010**, *132*, 10692–10705.
- [77] P. M. Holstein, D. Dailier, J. Vantourout, J. Shaya, A. Millet, O. Baudoin, *Angew. Chem.* **2016**, *128*, 2855–2859.
- [78] S. Janody, R. Jazzar, A. Comte, P. M. Holstein, J.-P. Vors, M. J. Ford, O. Baudoin, *Chem. Eur. J.* **2014**, *20*, 11084–11090.
- [79] C. G. Newton, S. G. Wang, C. C. Oliveira, N. Cramer, *Chem. Rev.* **2017**, *117*, 8908–8976.
- [80] O. Vyhivskiy, A. Kudashev, T. Miyakoshi, O. Baudoin, *Chem. Eur. J.* **2021**, *27*, 1231–1257.
- [81] S. Anas, A. Cordi, H. B. Kagan, *Chem. Commun.* **2011**, *47*, 11483–11485.
- [82] T. Saget, S. J. Lemouzy, N. Cramer, *Angew. Chem. Int. Ed.* **2012**, *51*, 2238–2242.
- [83] Z. Song, L. Junzhu, Y. Jinxing, D. Wei-liang, *Chin. J. Org. Chem.* **2016**, *36*, 752–759.
- [84] L. Yang, R. Melot, M. Neuburger, O. Baudoin, *Chem. Sci.* **2017**, *8*, 1344–1349.

## References

- [85] N. Martin, C. Pierre, M. Davi, R. Jazzar, O. Baudoin, *Chem. Eur. J.* **2012**, *18*, 4480–4484.
- [86] R. Melot, M. V. Craveiro, T. Bürgi, O. Baudoin, *Org. Lett.* **2019**, *21*, 812–815.
- [87] R. Melot, M. V. Craveiro, O. Baudoin, *J. Org. Chem.* **2019**, *84*, 12933–12945.
- [88] R. F. Heck, *J. Organomet. Chem.* **1972**, *37*, 389–396.
- [89] S. Ma, Z. Gu, *Angew. Chem. Int. Ed.* **2005**, *44*, 7512–7517.
- [90] A. Rahim, J. Feng, Z. Gu, *Chin. J. Chem.* **2019**, *37*, 929–945.
- [91] F. Shi, R. C. Larock, *Top Curr Chem* **2010**, *292*, 123–164.
- [92] Q. Tian, R. C. Larock, *Org. Lett.* **2000**, *2*, 3329–3332.
- [93] G. Karig, M.-T. Moon, N. Thasana, T. Gallagher, *Org. Lett.* **2002**, *4*, 3115–3118.
- [94] M. A. Campo, R. C. Larock, *J. Am. Chem. Soc.* **2002**, *124*, 14326–14327.
- [95] M. A. Campo, H. Zhang, T. Yao, A. Ibdah, R. D. McCulla, Q. Huang, J. Zhao, W. S. Jenks, R. C. Larock, *J. Am. Chem. Soc.* **2007**, *129*, 6298–6307.
- [96] Q. Huang, M. A. Campo, T. Yao, Q. Tian, R. C. Larock, *J. Org. Chem.* **2004**, *69*, 8251–8257.
- [97] M. A. Campo, Q. Huang, T. Yao, Q. Tian, R. C. Larock, *J. Am. Chem. Soc.* **2003**, *125*, 11506–11507.
- [98] T. J. Hu, G. Zhang, Y. H. Chen, C. G. Feng, G. Q. Lin, *J. Am. Chem. Soc.* **2016**, *138*, 2897–2900.
- [99] T.-J. Hu, M.-Y. Li, Q. Zhao, C.-G. Feng, G.-Q. Lin, *Angew. Chem. Int. Ed.* **2018**, *130*, 5973–5977.
- [100] D. Wei, T.-J. Hu, C.-G. Feng, G.-Q. Lin, *Chin. J. Chem.* **2018**, *36*, 743–748.
- [101] R. Rocaboy, O. Baudoin, *Org. Lett.* **2019**, *21*, 1434–1437.
- [102] Q. Huang, R. C. Larock, *Tetrahedron Lett.* **2009**, *50*, 7235–7238.
- [103] S. K. Bhunia, A. Polley, R. Natarajan, R. Jana, *Chem. Eur. J.* **2015**, *21*, 16786–16791.
- [104] P. E. M. Siegbahn, *J. Phys. Chem.* **1995**, *99*, 12723–12729.
- [105] J. A. Martinho Simoes, J. L. Beauchamp, *Chem. Rev.* **1990**, *90*, 629–688.
- [106] G. Dyker, *Chem. Ber.* **1994**, *127*, 739–742.
- [107] R. Rocaboy, I. Anastasiou, O. Baudoin, *Angew. Chem. Int. Ed.* **2019**, *58*, 14625–14628.
- [108] B. V. Varun, J. Dhineshkumar, K. R. Bettadapur, Y. Siddaraju, K. Alagiri, K. R. Prabhu, *Tetrahedron Lett.* **2017**, *58*, 803–824.
- [109] S. A. Girard, T. Knauber, C. J. Li, *Angew. Chem. Int. Ed.* **2014**, *53*, 74–100.
- [110] R. Rocaboy, D. Dailier, F. Zellweger, M. Neuburger, C. Salomé, E. Clot, O. Baudoin, *Angew. Chem. Int. Ed.* **2018**, *57*, 12131–12135.
- [111] T. Harayama, T. Sato, A. Hori, H. Abe, Y. Takeuchi, *Synthesis* **2004**, 1446–1456.
- [112] D. Solé, L. Vallverdú, X. Solans, M. Font-Bardia, *Chem. Commun.* **2005**, 2738–2740.

## References

- [113] A. Clemenceau, P. Thesmar, M. Gicquel, A. le Flohic, O. Baudoin, *J. Am. Chem. Soc.* **2020**, *142*, 15355–15361.
- [114] T. E. Barder, S. D. Walker, J. R. Martinelli, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 4685–4696.
- [115] J. Pan, M. Su, S. L. Buchwald, *Angew. Chem.* **2011**, *123*, 8806–8810.
- [116] T. Kesharwani, R. C. Larock, *Tetrahedron* **2008**, *64*, 6090–6102.
- [117] T. Čarný, R. Rocaboy, A. Clemenceau, O. Baudoin, *Angew. Chem. Int. Ed.* **2020**, *59*, 18980–18984.
- [118] D. Bourissou, O. Guerret, F. P. Gabbaï, G. Bertrand, *Chem. Rev.* **2000**, *100*, 39–92.
- [119] W. von E. Doering, A. K. Hoffmann, *J. Am. Chem. Soc.* **1954**, *76*, 6162–6165.
- [120] A. Igau, H. Grutzmacher, A. Baceiredo, G. Bertrand, *J. Am. Chem. Soc.* **1988**, *110*, 6463–6466.
- [121] A. J. Arduengo, R. L. Harlow, M. Kline, *J. Am. Chem. Soc.* **1991**, *113*, 361–363.
- [122] D. Enders, O. Niemeier, A. Henseler, *Chem. Rev.* **2007**, *107*, 5606–5655.
- [123] P. de Frémont, N. Marion, S. P. Nolan, *Coord. Chem. Rev.* **2009**, *253*, 862–892.
- [124] D. Zhu, L. Chen, H. Fan, Q. Yao, S. Zhu, *Chem. Soc. Rev.* **2020**, *49*, 908–950.
- [125] M. N. Hopkinson, C. Richter, M. Schedler, F. Glorius, *Nature* **2014**, *510*, 485–496.
- [126] H. W. Wanzlick, *Angew. Chem. Int. Ed.* **1962**, *1*, 75–80.
- [127] H. -W Wanzlick, H. -J Schönherr, *Angew. Chem. Int. Ed.* **1968**, *7*, 141–142.
- [128] K. Öfele, *J. Organomet. Chem.* **1968**, *12*, 42–43.
- [129] A. J. Arduengo, H. V. R. Dias, R. L. Harlow, M. Kline, *J. Am. Chem. Soc.* **1992**, *114*, 5530–5534.
- [130] A. J. Arduengo, J. R. Goerlich, W. J. Marshall, *J. Am. Chem. Soc.* **1995**, *117*, 11027–11028.
- [131] X. Bugaut, F. Glorius, *Chem. Soc. Rev.* **2012**, *41*, 3511–3522.
- [132] A. Grossmann, D. Enders, *Angew. Chem. Int. Ed.* **2012**, *51*, 314–325.
- [133] N. Marion, S. Díez-González, S. P. Nolan, *Angew. Chem. Int. Ed.* **2007**, *46*, 2988–3000.
- [134] R. D. J. Froese, C. Lombardi, M. Pompeo, R. P. Rucker, M. G. Organ, *Acc. Chem. Res.* **2017**, *50*, 2244–2253.
- [135] N. Marion, O. Navarro, J. Mei, E. D. Stevens, N. M. Scott, S. P. Nolan, *J. Am. Chem. Soc.* **2006**, *128*, 4101–4111.
- [136] E. A. B. Kantchev, C. J. O'Brien, M. G. Organ, *Angew. Chem. Int. Ed.* **2007**, *46*, 2768–2813.
- [137] Q. Zhao, G. Meng, S. P. Nolan, M. Szostak, *Chem. Rev.* **2020**, *120*, 1981–2048.
- [138] W. A. Herrmann, M. Alison, J. Fischer, C. Köcher, G. R. J. Artus, *Angew. Chem. Int. Ed.* **1995**, *34*, 2371–2374.

## References

- [139] K. Öfele, W. A. Herrmann, D. Mihailios, M. Elison, E. Herdtweck, W. Scherer, J. Mink, *J. Organomet. Chem.* **1993**, *459*, 177–184.
- [140] T. M. Trnka, R. H. Grubbs, *Acc. Chem. Res.* **2001**, *34*, 18–29.
- [141] C. A. Tolman, *Chem. Rev.* **1977**, *77*, 313–348.
- [142] H. V. Huynh, *Chem. Rev.* **2018**, *118*, 9457–9492.
- [143] T. Dröge, F. Glorius, *Angew. Chem. Int. Ed.* **2010**, *49*, 6940–6952.
- [144] H. Jacobsen, A. Correa, A. Poater, C. Costabile, L. Cavallo, *Coord. Chem. Rev.* **2009**, *253*, 687–703.
- [145] C. M. Crudden, D. P. Allen, *Coord. Chem. Rev.* **2004**, *248*, 2247–2273.
- [146] A. F. Littke, G. C. Fu, *Angew. Chem. Int. Ed.* **2002**, *41*, 4176–4211.
- [147] H. Clavier, S. P. Nolan, *Chem. Commun.* **2010**, *46*, 841–861.
- [148] A. Poater, F. Ragone, R. Mariz, R. Dorta, L. Cavallo, *Chem. Eur. J.* **2010**, *16*, 14348–14353.
- [149a] L. Falivene, R. Credendino, A. Poater, A. Petta, L. Serra, R. Oliva, V. Scarano, L. Cavallo, *Organometallics* **2016**, *35*, 2286–2293.
- [149b] L. Falivene, Z. Cao, A. Petta, L. Serra, A. Poater, R. Oliva, V. Scarano, L. Cavallo, *Nat. Chem.* **2019**, *11*, 872–879.
- [150] A. Gómez-Suárez, D. J. Nelson, S. P. Nolan, *Chem. Commun.* **2017**, *53*, 2650–2660.
- [151] F. Glorius, *N-Heterocyclic Carbenes in Catalysis - An Introduction*. In: *Topics in Organometallic Chemistry*. Springer, **2006**.
- [152] N. Hadei, E. A. B. Kantchev, C. J. O'Brien, M. G. Organ, *J. Org. Chem.* **2005**, *70*, 8503–8507.
- [153] A. Baeyer, *Ber. Dtsch. Chem. Ges.* **1900**, *33*, 3771–3775.
- [154] A. P. Krapcho, *Synthesis* **1974**, 383–419.
- [155] S. Kotha, A. C. Deb, K. Lahiri, E. Manivannan, *Synthesis* **2009**, 165–193.
- [156] L. K. Smith, I. R. Baxendale, *Org. Biomol. Chem.* **2015**, *13*, 9907–9933.
- [157] E. Chupakhin, O. Babich, A. Prosekov, L. Asyakina, M. Krasavin, *Molecules* **2019**, *24*, 4165–4202.
- [158] M. Aldeghi, S. Malhotra, D. L. Selwood, A. W. E. Chan, *Chem Biol Drug Des* **2014**, *83*, 450–461.
- [159] Y. Zheng, C. M. Tice, S. B. Singh, *Bioorg. Med. Chem. Lett.* **2014**, *24*, 3673–3682.
- [160] G. Müller, T. Berkenbosch, J. C. J. Benningshof, D. Stumpfe, J. Bajorath, *Chem. Eur. J.* **2017**, *23*, 703–710.
- [161] K. Hiesinger, D. Dar'in, E. Proschak, M. Krasavin, *J. Med. Chem.* **2021**, *64*, 150–183.
- [162] J.-H. Xie, Q.-L. Zhou, *Acc. Chem. Res.* **2008**, *41*, 581–593.
- [163] A. Rahman, X. Lin, *Org. Biomol. Chem.* **2018**, *16*, 4753–4777.

## References

- [164] A. Ding, M. Meazza, H. Guo, J. W. Yang, R. Rios, *Chem. Soc. Rev.* **2018**, *47*, 5946–5996.
- [165] R. Rios, *Chem. Soc. Rev.* **2012**, *41*, 1060–1074.
- [166] Y. Liu, S.-J. Han, W.-B. Liu, B. M. Stoltz, *Acc. Chem. Res.* **2015**, *48*, 740–751.
- [167] Y. Kunitobu, K. Yamauchi, N. Tamura, T. Seiki, K. Takai, *Angew. Chem. Int. Ed.* **2013**, *52*, 1520–1522.
- [168] C. Pierre, O. Baudoin, *Org. Lett.* **2011**, *13*, 1816–1819.
- [169] R. Rocaboy, D. Dailler, O. Baudoin, *Org. Lett.* **2018**, *20*, 772–775.
- [170] Y. Liang, W. Geng, J. Wei, K. Ouyang, Z. Xi, *Org. Biomol. Chem.* **2012**, *10*, 1537–1542.
- [171] G. Markopoulos, L. Henneicke, J. Shen, Y. Okamoto, P. G. Jones, H. Hopf, *Angew. Chem. Int. Ed.* **2012**, *51*, 12884–12887.
- [172] F. Glorius, G. Altenhoff, R. Goddard, C. Lehmann, *Chem. Commun.* **2002**, *22*, 2704–2705.
- [173] G. Altenhoff, R. Goddard, C. W. Lehmann, F. Glorius, *J. Am. Chem. Soc.* **2004**, *126*, 15195–15201.
- [174] G. Altenhoff, R. Goddard, C. W. Lehmann, F. Glorius, *Angew. Chem. Int. Ed.* **2003**, *42*, 3690–3693.
- [175] S. Würtz, C. Lohre, R. Fröhlich, K. Bergander, F. Glorius, *J. Am. Chem. Soc.* **2009**, *131*, 8344–8345.
- [176] E. P. Kündig, T. M. Seidel, Y. Jia, G. Bernardinelli, *Angew. Chem. Int. Ed.* **2007**, *46*, 8484–8487.
- [177] N. Ahmed, *Synthetic Advances in the Indane Natural Product Scaffolds as Drug Candidates: A Review*. In *Studies in Natural Products Chemistry*, Elsevier, **2016**.
- [178] K. Yoshihira, M. Fukuoka, M. Kuroyanagi, S. Natori, M. Umeda, T. Morohoshi, M. Enomoto, M. Saito, *Chem. Pharm. Bull.* **1978**, *26*, 2346–2364.
- [179] M. Fukuoka, M. Kuroyanagi, K. Yoshihira, S. Natori, *Chem. Pharm. Bull.* **1978**, *26*, 2365–2385.
- [180] F.-L. Hsu, C.-F. Huang, Y.-W. Chen, Y.-P. Yen, C.-T. Wu, B.-J. Uang, R.-S. Yang, S.-H. Liu, *Diabetes* **2013**, *62*, 628–638.
- [181] K.-M. E. Ng, T. C. McMorris, *Can. J. Chem.* **1984**, *62*, 1945–1953.
- [182] S. C. Hsu, M. Narsingam, Y. F. Lin, F. L. Hsu, B. J. Uang, *Tetrahedron* **2013**, *69*, 2572–2576.
- [183] H. H. Wu, S. C. Hsu, F. L. Hsu, B. J. Uang, *Eur. J. Org. Chem.* **2014**, 4351–4355.
- [184] M. Ramanathan, D. R. Hou, *Tetrahedron Lett.* **2010**, *51*, 6143–6145.
- [185] G. Wu, M. Huang, M. Richards, M. Poirier, X. Wen, R. W. Draper, *Synthesis* **2003**, 1657–1660.
- [186] J. Pedroni, N. Cramer, *Chem. Commun.* **2015**, *51*, 17647–17657.
- [187] A. K. Ghosh, P. Mathivanan, J. Cappiello, *Tetrahedron: Asymmetry* **1998**, *9*, 1–45.

## References

- [188] S. Würtz, F. Glorius, *Acc. Chem. Res.* **2008**, *41*, 1523–1533.
- [189] S. Lee, J. F. Hartwig, *J. Org. Chem.* **2001**, *66*, 3402–3415.
- [190] G. Desimoni, G. Faita, K. A. Jørgensen, *Chem. Rev.* **2006**, *106*, 3561–3651.
- [191] R. A. Kelly, H. Clavier, S. Giudice, N. M. Scott, E. D. Stevens, J. Bordner, I. Samardjiev, C. D. Hoff, L. Cavallo, S. P. Nolan, *Organometallics* **2008**, *27*, 202–210.
- [192] X. Q. Hao, Y. N. Dong, B. Gao, K. Li, X. M. Zhao, Y. Xu, M. P. Song, *Tetrahedron Asymmetry* **2015**, *26*, 1360–1368.
- [193] E. J. Corey, K. Ishihara, *Tetrahedron Lett.* **1992**, *33*, 6807–6810.
- [194] E. Bélanger, M.-F. Pouliot, J.-F. Paquin, *Org. Lett.* **2009**, *11*, 2201–2204.
- [195] J.-N. Levy, C. M. Latham, L. L. Roisin, N. Kandziora, P. di Fruscia, A. J. P. White, S. Woodward, M. J. Fuchter, *Org. Biomol. Chem.* **2012**, *10*, 512–515.
- [196] J. Podlech, D. Seebach, *Liebigs Annalen* **1995**, *1995*, 1217–1228.
- [197] J. Cesar, M. Sollner Dolenc, *Tetrahedron Lett.* **2001**, *42*, 7099–7102.
- [198] M. Liniger, Y. Liu, B. M. Stoltz, *J. Am. Chem. Soc.* **2017**, *139*, 13944–13949.
- [199] V. A. Toussaint, *Boron-Bridged Bis(Oxazolines) and Their Use in Copper-Catalyzed Reactions*, University of Basel, Basel, **2008**.
- [200] A. J. Phillips, Y. Uto, P. Wipf, M. J. Reno, D. R. Williams, *Org. Lett.* **2000**, *2*, 1165–1168.
- [201] M. Brandstätter, F. Roth, N. W. Luedtke, *J. Org. Chem.* **2015**, *80*, 40–51.
- [202] J. F. Hartwig, *J. Am. Chem. Soc.* **2016**, *138*, 2–24.
- [203] T. Gensch, M. J. James, T. Dalton, F. Glorius, *Angew. Chem. Int. Ed.* **2018**, *57*, 2296–2306.
- [204] K. Godula, D. Sames, *Science* **2006**, *312*, 67–72.
- [205] J. Wencel-Delord, F. Glorius, *Nat. Chem.* **2013**, *5*, 369–375.
- [206] J. Börgel, T. Ritter, *Chem* **2020**, *6*, 1877–1887.
- [207] D. J. Abrams, P. A. Provencher, E. J. Sorensen, *Chem. Soc. Rev.* **2018**, *47*, 8925–8967.
- [208] T. Kumar Achar, S. Maiti, S. Jana, D. Maiti, *ACS Catal.* **2020**, *10*, 13748–13793.
- [209] T. G. Saint-Denis, R.-Y. Zhu, G. Chen, Q.-F. Wu, J.-Q. Yu, *Science* **2018**, *359*, eaao4798.
- [210] J. Pedroni, M. Boghi, T. Saget, N. Cramer, *Angew. Chem. Int. Ed.* **2014**, *53*, 9064–9067.
- [211] D. Dailier, R. Rocaboy, O. Baudoin, *Angew. Chem. Int. Ed.* **2017**, *56*, 7218–7222.
- [212] J. Pedroni, N. Cramer, *J. Am. Chem. Soc.* **2017**, *139*, 12398–12401.
- [213] L. Yang, M. Neuburger, O. Baudoin, *Angew. Chem. Int. Ed.* **2018**, *57*, 1394–1398.
- [214] D. Savary, O. Baudoin, *Angew. Chem. Int. Ed.* **2021**, *60*, 5136–5140.
- [215] C. Jahier-Diallo, M. S. T. Morin, P. Queval, M. Rouen, I. Artur, P. Querard, L. Toupet, C. Crévisy, O. Baslé, M. Mauduit, *Chem. Eur. J.* **2015**, *21*, 993–997.

## References

- [216] R. Tarrieu, A. Dumas, J. Thongpaen, T. Vives, T. Roisnel, V. Dorcet, C. Crévisy, O. Baslé, M. Mauduit, *J. Org. Chem.* **2017**, *82*, 1880–1887.
- [217] J. Thongpaen, T. E. Schmid, L. Toupet, V. Dorcet, M. Mauduit, O. Baslé, *Chem. Commun.* **2018**, *54*, 8202–8205.
- [218] J. Thongpaen, R. Manguin, V. Dorcet, T. Vives, C. Duhayon, M. Mauduit, O. Baslé, *Angew. Chem.* **2019**, *131*, 15388–15392.
- [219] E. Peris, *Chem. Rev.* **2018**, *118*, 9988–10031.
- [220] B. Ramasamy, P. Ghosh, *Eur. J. Inorg. Chem.* **2016**, *2016*, 1448–1465.
- [221] J. Thongpaen, R. Manguin, O. Baslé, *Angew. Chem. Int. Ed.* **2020**, *59*, 10242–10251.
- [222] K. Yoshida, S. Horiuchi, T. Takeichi, H. Shida, T. Imamoto, A. Yanagisawa, *Org. Lett.* **2010**, *12*, 1764–1767.
- [223] S. T. Kim, M. H. Baik, *Chem. Commun.* **2020**, *56*, 13868–13871.
- [224] M. S. Viciu, R. F. Germaneau, O. Navarro-Fernandez, E. D. Stevens, S. P. Nolan, *Angew. Chem. Int. Ed.* **2002**, *41*, 1760–1763.
- [225] H. M. J. Wang, I. J. B. Lin, *Organometallics* **1998**, *17*, 972–975.
- [226] Q. X. Liu, L. X. Zhao, X. J. Zhao, Z. X. Zhao, Z. Q. Wang, A. H. Chen, X. G. Wang, *J. Organomet. Chem.* **2013**, *731*, 35–48.
- [227] W. A. Herrmann, C. Brossmer, K. Öfele, C.-P. Reisinger, T. Priermeier, M. Beller, H. Fischer, *Angew. Chem. Int. Ed.* **1995**, *34*, 1844–1848.
- [228] J. Dupont, C. S. Consorti, J. Spencer, *Chem. Rev.* **2005**, *105*, 2527–2571.
- [229] H. Li, C. C. C. Johansson Seechurn, T. J. Colacot, *ACS Catal.* **2012**, *2*, 1147–1164.
- [230] A. Bruneau, M. Roche, M. Alami, S. Messaoudi, *ACS Catal.* **2015**, *5*, 1386–1396.
- [231] M. S. Viciu, R. A. Kelly, E. D. Stevens, F. Naud, M. Studer, S. P. Nolan, *Org. Lett.* **2003**, *5*, 1479–1482.
- [232] M. Zhao, Y.-T. Zhang, J. Chen, L. Zhou, *Asian J. Org. Chem.* **2018**, *7*, 54–69.
- [233] X.-Y. Chen, Z.-H. Gao, S. Ye, *Acc. Chem. Res.* **2020**, *53*, 690–702.
- [234] W. Qin, M. Panunzio, S. Biondi, *Antibiotics* **2014**, *3*, 193–215.
- [235] P. W. Smith, F. Zuccotto, R. H. Bates, M. Santos Martinez-Martinez, K. D. Read, C. Peet, O. Epemolu, *ACS Infect. Dis.* **2018**, *4*, 1439–1447.
- [236] K. Bush, P. A. Bradford, *Nat. Rev. Microbiol.* **2019**, *17*, 295–306.
- [237] C. L. Tooke, P. Hinchliffe, E. C. Bragginton, C. K. Colenso, V. H. A. Hirvonen, Y. Takebayashi, J. Spencer, *J. Mol. Biol.* **2019**, *431*, 3472–3500.
- [238] A. Fleming, *Br. J. Exp. Pathol.* **1929**, *10*, 226–236.
- [239] R. J. Duma, *Ann. Intern. Med.* **1987**, *106*, 766–767.

## References

- [240] M. A. Totir, M. S. Helfand, M. P. Carey, A. Sheri, J. D. Buynak, R. A. Bonomo, P. R. Carey, *Biochemistry* **2007**, *46*, 8980–8987.
- [241] D. A. Burnett, M. A. Caplen, H. R. Davis, R. E. Burrier, J. W. Clader, *J. Med. Chem.* **1994**, *37*, 1733–1736.
- [242] C. Palomo, M. Oiarbide, *Top. Heterocycl. Chem.* **2010**, *22*, 211–259.
- [243] S. Hosseyni, A. Jarrahpour, *Org. Biomol. Chem.* **2018**, *16*, 6840–6852.
- [244] C. R. Pitts, T. Lectka, *Chem. Rev.* **2014**, *114*, 7930–7953.
- [245] A. Kamath, I. Ojima, *Tetrahedron* **2012**, *68*, 10640–10664.
- [246] R. Tuba, *Org. Biomol. Chem.* **2013**, *11*, 5976–5988.
- [247] J. Marco-Contelles, *Angew. Chem. Int. Ed.* **2004**, *43*, 2198–2200.
- [248] S. Stecko, B. Furman, M. Chmielewski, *Tetrahedron* **2014**, *70*, 7817–7844.
- [249] H. Gilman, M. Speeter, *J. Am. Chem. Soc.* **1943**, *65*, 2255–2256.
- [250] Q. Zhang, K. Chen, W. Rao, Y. Zhang, F. J. Chen, B. F. Shi, *Angew. Chem. Int. Ed.* **2013**, *52*, 13588–13592.
- [251] W. W. Sun, P. Cao, R. Q. Mei, Y. Li, Y. L. Ma, B. Wu, *Org. Lett.* **2014**, *16*, 480–483.
- [252] A. McNally, B. Haffemayer, B. S. L. Collins, M. J. Gaunt, *Nature* **2014**, *510*, 129–133.
- [253] K. H. Shaughnessy, B. C. Hamann, J. F. Hartwig, *J. Org. Chem.* **1998**, *63*, 6546–6553.
- [254] L. Ackermann, R. Vicente, N. Hofmann, *Org. Lett.* **2009**, *11*, 4274–4276.
- [255] C. G. Newton, E. Braconi, J. Kuziola, M. D. Wodrich, N. Cramer, *Angew. Chem.* **2018**, *130*, 11206–11210.
- [256] T. Saget, N. Cramer, *Angew. Chem. Int. Ed.* **2013**, *52*, 7865–7868.
- [257] X. Ren, A. L. Chandgude, R. Fasan, *ACS Catal.* **2020**, *10*, 2308–2313.
- [258] J. W. Epstein, H. J. Brabander, W. J. Fanshawe, C. M. Hofmann, T. C. McKenzie, S. R. Safir, A. C. Osterberg, D. B. Cosulich, F. M. Lovell, *J. Med. Chem.* **1981**, *24*, 481–490.
- [259] F. Micheli, P. Cavanni, D. Andreotti, R. Arban, R. Benedetti, B. Bertani, M. Bettati, L. Bettelini, G. Bonanomi, S. Braggio, R. Carletti, A. Checchia, M. Corsi, E. Fazzolari, S. Fontana, C. Marchioro, E. Merlo-Pich, M. Negri, B. Oliosi, E. Ratti, K. D. Read, M. Roscic, I. Sartori, S. Spada, G. Tedesco, L. Tarsi, S. Terreni, F. Visentini, A. Zocchi, L. Zonzini, R. di Fabio, *J. Med. Chem.* **2010**, *53*, 4989–5001.
- [260] S. Gomi, D. Ikeda, H. Nakamura, H. Naganawa, F. Yamashita, K. Hotta, S. Kondo, Y. Okami, H. Umezawa, Y. Iitaka, *J. Antibiot.* **1984**, *37*, 1491–1494.
- [261] T. Furuta, M. Koike, M. Abe, *Agric. Biol. Chem.* **1982**, *46*, 1921–1922.

## 9 Experimental Part

All reactions were performed in pre-dried glassware under positive pressure of argon unless otherwise mentioned. All reactions involving air-sensitive materials were carried out in pre-dried glassware under an argon atmosphere by using Schlenk techniques employing double-line argon-vacuum lines and working in an argon-filled glovebox. Analytical thin layer chromatography (TLC) was performed using pre-coated Merck silica gel 60 F254 plates (0.25 mm). Visualization of the developed chromatogram was performed by UV absorbance (254 nm) or TLC stains (KMnO<sub>4</sub> and phosphomolybdic acid). Flash column chromatography (FC) was performed using Silicycle SiliaFlash P60 (230-400 mesh) with the indicated solvent system. Anhydrous solvents were obtained from a solvent purification system equipped with activated alumina and copper columns. The solvents were degassed by three cycles of freeze-pump-thaw and stored in single-necked flasks equipped with a J-Young PTFE valve (or similar) when necessary. Chemical reagents were purchased from Merck (Sigma-Aldrich), Acros Organics, Alfa Aesar, Apollo scientific and Fluorochem and used as received without further purification unless otherwise stated. HPLC analyses were performed using a Shimadzu Prominence system with SIL-20A auto sample, CTO-20AC column oven, LC-20AD pump system, DGU-20A3 degasser and SPD-M20A Diode Array or UV/VIS detector. The following chiral column from Daicel Chemical Industries was used: OJ-H (Chiralcel®) in 4.6 x 250 mm size. Melting points were obtained on a Büchi melting point M-565, and are uncorrected. IR spectra were recorded on an ATR Varian Scimitar 800 and are reported in reciprocal centimeters (cm<sup>-1</sup>). Nuclear magnetic resonance spectra were recorded on a Bruker Advance 400 (400 MHz) and Advance 500 (500 MHz) in deuterated chloroform (residual peaks <sup>1</sup>H δ 7.26 ppm, <sup>13</sup>C δ 77.16 ppm), deuterated acetonitrile (residual peaks <sup>1</sup>H δ 1.94 ppm, <sup>13</sup>C δ 1.32 ppm) or deuterated dichloromethane (residual peaks <sup>1</sup>H δ 5.32 ppm, <sup>13</sup>C δ 54.00 ppm) unless otherwise noted. Data are reported in parts per million (ppm) as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintuplet, sept = septuplet, m = multiplet and br = broad signal), coupling constants in Hz and integration. High resolution mass spectra were recorded by Dr. M. Pfeffer and S. Mittelheisser (Department of Chemistry, University of Basel) on a Bruker maXis 4G QTOF ESI mass spectrometer. Optical rotations were measured on an Anton Paar MCP 100 Polarimeter in a 0.7 mL micro cuvette (cell length 100mm) with NaD-Line (λ = 589 nm). The concentration (c) was given in g/100 mL. X-ray crystallographic analyses were performed by Dr. A. Prescimone (Department of Chemistry, University of Basel).

## 9.1 Towards the Enantioselective C(sp<sup>3</sup>)-H Arylation in the Synthesis of Spirocycles

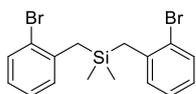
### General Procedure 1

NaH (60%, 1.5 equiv.) was added to a solution of **3.26** (1.0 equiv.) in dry THF under Ar at room temperature and the resulting mixture was stirred at the same temperature for 6 h. The corresponding benzyl bromide (1.2 equiv.) was added and stirred at room temperature for 18 h. The reaction was carefully quenched by addition of H<sub>2</sub>O followed by three times extraction with Et<sub>2</sub>O. The combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude was purified by FC to afford the corresponding benzylated products.

### General Procedure 2

Aryl bromide (0.1 mmol) was charged into a catalysis tube equipped with a magnetic stirring bar. The tube was introduced into the glovebox and was subsequently charged with Cs<sub>2</sub>CO<sub>3</sub> (3.0 equiv.), adamantic acid (1.0 equiv.), [Pd( $\pi$ -cin)Cl]<sub>2</sub> (5 mol%), and IBiox*t*Bu•HOTf (10 mol%). The vial was closed with a rubber septum and taken out of the glovebox. Dry and degassed mesitylene (1 mL/0.1 mmol) was added into the tube under Ar and the tube capped with the corresponding cap. The tube was inserted into a preheated catalysis block at 160 °C and was stirred for 18 h. Then, the reaction was cooled down to room temperature and diluted with EtOAc, filtered over a plug of *Celite* and the solvent evaporated under reduced pressure. The crude was analyzed by GC-MS or <sup>1</sup>H NMR (1 mL CDCl<sub>3</sub>/0.1 mmol + 0.1 mmol trichloroethylene as internal standard). After analysis, the solvent was evaporated under reduced pressure and the crude purified by FC.

### bis(2-bromobenzyl)dimethylsilane (**3.8**)



Chemical Formula: C<sub>16</sub>H<sub>18</sub>Br<sub>2</sub>Si  
Molecular Weight: 398.21

A dry two neck flask was equipped with a reflux condenser, a stirring bar and Mg-turnings (414 mg, 17.1 mmol, 2.2 equiv.). Dry THF (15 mL) was added under Ar followed by a crystal of I<sub>2</sub>. 2-bromobenzyl bromide (4.01 g, 16.3 mmol, 2.1 equiv.) was slowly added. After complete addition, the reaction mixture was refluxed for 30 min and then cooled down to room temperature. Dichlorodimethylsilane (1.00 g, 7.8 mmol, 1 equiv.) was added and the resulting reaction mixture stirred under reflux for 18 h. After cooling down to room temperature, aqueous HCl (1 N) was carefully added to quench the reaction and the mixture was extracted three times with Et<sub>2</sub>O. The combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under

## Experimental Part

reduced pressure. The crude was purified by FC (PE) to afford the title compound **3.8** (800 mg, 2.0 mmol, 26%) as a colorless oil.

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.50 (dd,  $J = 8.0, 1.3$  Hz, 1H), 7.15 ("t"d,  $J = 7.5, 1.4$  Hz, 1H), 7.03 (dd,  $J = 7.7, 1.8$  Hz, 1H), 6.98 – 6.86 (m, 1H), 2.41 (s, 2H), 0.03 (s, 3H).

$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  140.2, 132.96, 129.9, 127.3, 125.9, 123.8, 25.8, -2.7.

### (Z)-1,3-bis(2-bromophenyl)-3-hydroxyprop-2-en-1-one (3.9Br)

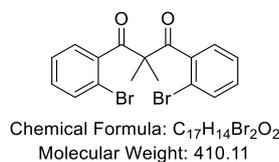


Prepared following literature.<sup>[1]</sup>

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.72 – 7.68 (m, 1H), 7.66 (dd,  $J = 8.0, 1.2$  Hz, 1H), 7.61 (dd,  $J = 7.7, 1.7$  Hz, 1H), 7.48 – 7.45 (m, 1H), 7.43 – 7.39 (m, 2H), 7.37 (dd,  $J = 7.5, 1.5$  Hz, 1H), 7.35 – 7.30 (m, 1H), 6.58 (s, 1H).

$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  187.6, 185.2, 137.9, 135.5, 134.2, 132.2, 132.1, 132.0, 130.9, 130.4, 130.3, 127.6, 127.1, 120.5, 103.4.

### 1,3-bis(2-bromophenyl)-2,2-dimethylpropane-1,3-dione (3.10Br)

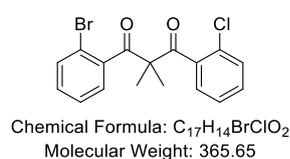


A mixture of **3.9Br** (200 mg, 0.52 mmol, 1 equiv.),  $\text{K}_2\text{CO}_3$  (145 mg, 1.05 mmol, 2 equiv.) and MeI (0.13 mL, 2.10 mmol, 4 equiv.) in dry toluene (2 mL) was refluxed for 24 h under Ar. The reaction mixture was cooled down to room temperature and  $\text{H}_2\text{O}$  was added to the mixture. The phase was extracted three times with  $\text{Et}_2\text{O}$ . The combined organic phases were washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated under reduced pressure. The crude was purified by FC (EtOAc/cHex) to afford the title compound **3.10Br** (78 mg, 0.19 mmol, 35%) as a white solid.

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.63 – 7.59 (m, 2H), 7.38 – 7.32 (m, 4H), 7.28 (ddd,  $J = 8.1, 6.5, 2.8$  Hz, 2H), 1.60 (s, 6H).

$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  205.0, 141.2, 133.4, 130.9, 127.1, 127.1, 118.6, 63.6, 23.4.

### 1-(2-bromophenyl)-3-(2-chlorophenyl)-2,2-dimethylpropane-1,3-dione (3.10Cl)

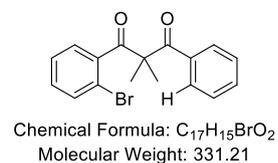


Obtained from R. Melot. Prepared according to **3.10Br**  
 $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.61 (dd,  $J = 7.9, 1.1$  Hz, 1H), 7.42 (dd,  $J = 8.0, 1.2$  Hz, 1H), 7.38 – 7.30 (m, 4H), 7.30 – 7.26 (m, 2H), 1.58 (s, 6H).

## Experimental Part

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 204.8, 204.7, 141.3, 139.1, 133.5, 130.9, 130.8, 130.3, 130.1, 127.1, 127.1, 127.0, 126.6, 118.6, 63.2, 23.2.

### 1-(2-bromophenyl)-2,2-dimethyl-3-phenylpropane-1,3-dione (3.10H)

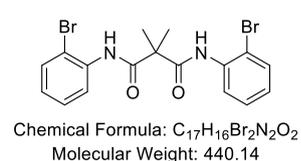


A mixture of **3.9H**<sup>[2]</sup> (2.50 g, 8.4 mmol, 1 equiv.), K<sub>2</sub>CO<sub>3</sub> (3.48 g, 25.2 mmol, 3 equiv.) and MeI (3.58 g, 25.2 mmol, 3 equiv.) in dry acetone (50 mL) was refluxed for 24 h under Ar. The reaction mixture was cooled down to room temperature and H<sub>2</sub>O was added to the mixture. The phase was extracted three times with Et<sub>2</sub>O. The combined organic phases were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude was purified by FC (EtOAc/cHEX 5:95) to afford the title compound **3.10H** (1.00 g, 3.01 mmol, 36%) as a yellow oil. <sup>13</sup>C NMR in agreement with reported data.<sup>[3]</sup>

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.97 – 7.93 (m, 2H), 7.60 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.55 – 7.50 (m, 1H), 7.46 – 7.41 (m, 2H), 7.19 (d, *J* = 7.7, 1.7 Hz, 1H), 7.13 (“t”d, *J* = 7.6, 1.3 Hz, 1H), 7.00 (dd, *J* = 7.7, 1.7 Hz, 1H), 1.62 (s, 6H).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 202.6, 198.5, 139.7, 136.2, 134.5, 133.2, 131.5, 129.4, 128.8, 126.9, 126.8, 120.5, 62.2, 24.4.

### N<sup>1</sup>,N<sup>3</sup>-bis(2-bromophenyl)-2,2-dimethylmalonamide (3.11)



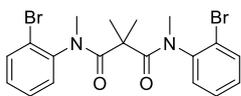
A mixture of dimethylmalonic acid (2.00 g, 15.1 mmol, 1 equiv.) and SOCl<sub>2</sub> (11 mL, 151 mmol, 10 equiv.) was refluxed under Ar for 5 h. The mixture was cooled down to room temperature, and the volatiles removed under reduced pressure. The obtained crude acyl chloride was dissolved in dry THF (5 mL) and slowly added to a solution of *o*-Bromoaniline (10.39 g, 60.4 mmol, 4 equiv.) in dry THF (120 mL) at 0 °C under Ar. The resulting reaction mixture was stirred under reflux for 18 h. The reaction mixture was cooled down to room temperature and the solvent removed under reduced pressure. The crude was redissolved in MeOH (20 mL). Amberlyst 15 was added and the resulting mixture stirred at room temperature for 15 min. The mixture was filtered over a plug of *Celite* and the filtrate concentrated under reduced pressure to afford the title compound **3.11** (3.65 g, 15.1 mmol, 55%) as a white solid.

**<sup>1</sup>H NMR** (250 MHz, CDCl<sub>3</sub>) δ 8.93 (bs, 2H), 8.34 (dd, *J* = 8.3, 1.6 Hz, 2H), 7.55 (dd, *J* = 8.0, 1.5 Hz, 2H), 7.32 (“t”d, *J* = 8.3, 7.9, 1.5 Hz, 2H), 7.00 (“t”d, *J* = 7.7, 1.6 Hz, 2H), 1.76 (s, 6H).

**<sup>13</sup>C NMR** (63 MHz, CDCl<sub>3</sub>) δ 171.4, 135.5, 132.5, 128.4, 125.8, 122.3, 114.4, 51.9, 24.2.

## Experimental Part

### *N*<sup>1</sup>,*N*<sup>3</sup>-bis(2-bromophenyl)-*N*<sup>1</sup>,*N*<sup>3</sup>,2,2-tetramethylmalonamide (**3.11Me**)



Chemical Formula: C<sub>17</sub>H<sub>16</sub>Br<sub>2</sub>N<sub>2</sub>O<sub>2</sub>  
Molecular Weight: 440.14

NaH (60%, 120 mg, 3.0 mmol, 2.6 equiv.) was added to a solution of **3.11** (500 mg, 1.1 mmol, 1.0 equiv.) in dry THF (5 mL) under Ar at room temperature. After stirring for 15 min, MeI (400 mg, 2.4 mmol, 2.4 equiv.) was added and the mixture stirred at the same temperature for 72 h. The reaction was carefully quenched with the addition of H<sub>2</sub>O. The resulting mixture was extracted five times with EtOAc. The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude was purified by FC (EtOAc/cHex) to afford the title compound **3.11Me** (379 mg, 0.8 mmol, 71%) as a white solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.72 – 7.65 (m, 1H), 7.44 – 7.34 (m, 1H), 7.25 – 7.14 (m, 2H), 3.45 – 3.40 (m, 3H), 1.72 – 1.63 (m, 3H).

### 4-chloro-7,7-dimethyl-5,9-dihydro-6H-dibenzo[f,h][1,5]diazonine-6,8(7H)-dione (**3.19**)



Chemical Formula: C<sub>17</sub>H<sub>15</sub>ClN<sub>2</sub>O<sub>2</sub>  
Molecular Weight: 314.77

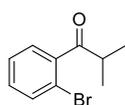
A catalysis tube was charged with bisamide **3.11** (88 mg, 0.2 mmol, 1.0 equiv.) and a magnetic stirring bar and was introduced into a glovebox. Pd(OAc)<sub>2</sub> (4.5 mg, 0.02 mmol, 10 mol%), P(*o*-tol)<sub>3</sub> (12.6 mg, 0.04 mmol, 10 mol%), PivOH (6.2 mg, 0.06 mmol, 30 mol%) and Cs<sub>2</sub>CO<sub>3</sub> (132 mg, 0.4 mmol, 2 equiv.) were added and the tube sealed with a rubber septum and removed from the glovebox. The septum was removed and let stand under air for 10 min before dry NMP (2 mL) were added and the tube was sealed with an appropriate cap and inserted into a preheated catalysis block at 140 °C. After reacting under stirring for 18 h, the vial was cooled down to room temperature, diluted with EtOAc, filtered over Alox and concentrated under reduced pressure. The crude was dissolved in CDCl<sub>3</sub> (2 mL) and trichloroethylene (0.1 mmol) was added as internal standard. The yield was determined by <sup>1</sup>H NMR (54%, 0.18 mmol).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.59 – 7.53 (m, 1H), 7.48 – 7.37 (m, 4H), 7.31 – 7.23 (m, 2H), 3.10 (s, 2H), 1.26 (s, 6H).

<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 212.07, 141.5, 140.0, 138.1, 135.3, 134.9, 131.7, 129.3, 129.0, 128.6, 128.6, 128.5, 128.3, 55.0, 39.5.

## Experimental Part

### 1-(2-bromophenyl)-2-methylpropan-1-one (3.26Br)



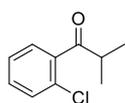
Chemical Formula: C<sub>10</sub>H<sub>11</sub>BrO  
Molecular Weight: 227.10

Following a slightly adapted procedure.<sup>[4]</sup> 2-Bromobenzoic acid (10.0 g, 49.4 mmol, 1 equiv.), oxalyl chloride (5.7 mL, 60.0 mmol, 1.2 equiv.) and DMF (2 drops) were refluxed in dry DCM (20 mL) under Ar for 3 h. The mixture was cooled down to room temperature and the volatiles removed under reduced pressure. The crude acyl chloride was dissolved in dry THF (50 mL), anhydrous LiCl (2.3 g, 55 mmol, 1.1 equiv.) was added and the mixture was cooled down to –78 °C before *i*PrMgCl (2 M, 26.3 mL, 52.5 mmol, 1.05 equiv.) was added by dropping funnel over 1 h. After complete addition, the reaction mixture was allowed to slowly warm to room temperature overnight. The reaction was quenched by slow addition of aqueous HCl (1 N) and extracted five times with Et<sub>2</sub>O. The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude was purified by distillation under reduced pressure (ca. 10<sup>-1</sup> mbar, 120 °C) to afford the title compound **3.26Br** (9.2 g, 40.7 mmol, 81%) as a yellow oil. NMR data in agreement with reported data.<sup>[4]</sup>

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.62 – 7.57 (m, 1H), 7.35 (ddd, *J* = 8.0, 7.1, 1.2 Hz, 1H), 7.32 – 7.24 (m, 2H), 3.32 (hept, *J* = 6.9 Hz, 1H), 1.20 (d, *J* = 6.8 Hz, 6H).

<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 208.8, 142.2, 133.5, 131.2, 128.3, 127.4, 118.8, 40.3, 18.3.

### 1-(2-chlorophenyl)-2-methylpropan-1-one (3.26Cl)



Chemical Formula: C<sub>10</sub>H<sub>11</sub>ClO  
Molecular Weight: 182.65

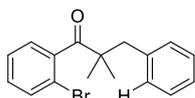
Following a slightly adapted procedure.<sup>[4]</sup> 2-Chlorobenzoic acid (2.50 g, 15.6 mmol, 1 equiv.), oxalyl chloride (1.8 mL, 18.7 mmol, 1.2 equiv.) and DMF (2 drops) were refluxed in dry DCM (5 mL) under Ar for 3 h. The mixture was cooled down to room temperature and the volatiles removed under reduced pressure. The crude acyl chloride was dissolved in dry THF (20 mL), anhydrous LiCl (0.73 g, 16.4 mmol, 1.1 equiv.) was added and the mixture was cooled down to –78 °C before *i*PrMgCl (2 M, 8.2 mL, 16.4 mmol, 1.05 equiv.) was added dropwise by dropping funnel over 1 h. After complete addition, the reaction mixture was allowed to slowly warm to room temperature overnight. The reaction was quenched by slow addition of aqueous HCl (1 N) and extracted five times with Et<sub>2</sub>O. The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude was purified by distillation under reduced pressure (ca. 10<sup>-1</sup> mbar, 80 °C) to afford the title compound **3.26Cl** (1.14 g, 6.3 mmol, 40%) as a colorless oil. NMR data in agreement with reported data.<sup>[5]</sup>

## Experimental Part

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.40 (ddd, J = 7.9, 1.3, 0.6 Hz, 1H), 7.38 – 7.28 (m, 3H), 3.33 (hept, J = 6.9 Hz, 1H), 1.19 (d, J = 6.9 Hz, 6H).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 208.3, 140.0, 131.2, 130.7, 130.4, 128.5, 126.9, 40.4, 18.3.

### 1-(2-bromophenyl)-2,2-dimethyl-3-phenylpropan-1-one (3.27)



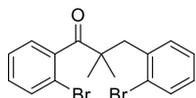
Chemical Formula: C<sub>17</sub>H<sub>16</sub>BrClO  
Molecular Weight: 351.67

Obtained according to literature. [6]

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.56 – 7.51 (m, 1H), 7.33 – 7.24 (m, 3H), 7.24 – 7.16 (m, 4H), 6.67 – 6.59 (m, 1H), 3.00 (s, 2H), 1.24 (s, 6H).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 211.8, 142.9, 137.6, 133.1, 131.2, 130.0, 128.2, 126.8, 126.7, 126.0, 117.7, 49.4, 45.7, 25.1.

### 1,3-bis(2-bromophenyl)-2,2-dimethylpropan-1-one (3.28)



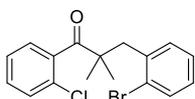
Chemical Formula: C<sub>17</sub>H<sub>16</sub>Br<sub>2</sub>O  
Molecular Weight: 396.12

Following **General Procedure 1** reacting **3.26Br** (150 mg, 0.66 mmol, 1.0 equiv.) with NaH (60%, 40 mg, 1.00 mmol, 1.5 equiv.) and 2-bromobenzyl bromide (248 mg, 1.00 mmol, 1.5 equiv.) in THF (6 mL) afforded the title compound **3.28** (122 mg, 0.31 mmol, 47%) as a colorless oil after FC (EtOAc/cHex 2:98, R<sub>f</sub>: 0.50 in EtOAc/cHex 5:95).

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.60 – 7.55 (m, 2H), 7.32 – 7.27 (m, 2H), 7.26 – 7.21 (m, 2H), 7.12 – 7.07 (m, 1H), 7.02 – 6.97 (m, 1H), 3.29 (s, 2H), 1.28 (s, 6H).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 211.4, 142.6, 137.6, 133.3, 133.3, 133.0, 130.1, 128.3, 127.1, 126.9, 126.6, 126.2, 118.0, 50.3, 42.9, 24.9.

### 3-(2-bromophenyl)-1-(2-chlorophenyl)-2,2-dimethylpropan-1-one (3.29)



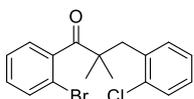
Chemical Formula: C<sub>17</sub>H<sub>16</sub>BrClO  
Molecular Weight: 351.67

Following **General Procedure 1** reacting **3.26Cl** (500 mg, 2.74 mmol, 1.0 equiv.) with NaH (60%, 132 mg, 3.29 mmol, 1.2 equiv.) and 2-bromobenzyl bromide (753 mg, 3.01 mmol, 1.1 equiv.) in THF (14 mL) afforded the title compound **3.29** (704 mg, 2.00 mmol, 73%) as a colorless oil after FC (Et<sub>2</sub>O/PE 4:96, R<sub>f</sub>: 0.28).

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.59 – 7.55 (m, 1H), 7.41 – 7.37 (m, 1H), 7.33 – 7.27 (m, 2H), 7.26 – 7.22 (m, 2H), 7.12 – 7.07 (m, 1H), 7.01 – 6.98 (m, 1H), 3.28 (s, 2H), 1.26 (s, 6H).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 211.2, 140.5, 137.7, 133.3, 133.0, 130.1, 130.0, 129.6, 128.3, 127.2, 126.5, 126.4, 126.2, 50.5, 42.8, 24.8.

**1-(2-bromophenyl)-3-(2-chlorophenyl)-2,2-dimethylpropan-1-one (3.30)**



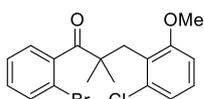
Chemical Formula: C<sub>17</sub>H<sub>16</sub>BrClO  
Molecular Weight: 351.67

Following **General Procedure 1** reacting **3.26Br** (3.09 g, 13.6 mmol, 1.0 equiv.) with NaH (60%, 0.65 g, 16.3 mmol, 1.2 equiv.) and 2-chlorobenzyl bromide (3.07 g, 15.0 mmol, 1.1 equiv.) in THF (25 mL) afforded the title compound **3.30** (3.34 g, 9.5 mmol, 70%) as a light-yellow oil after FC (Et<sub>2</sub>O/PE 2:98).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.67 – 7.61 (m, 1H), 7.48 – 7.41 (m, 1H), 7.38 – 7.32 (m, 2H), 7.31 – 7.27 (m, 1H), 7.27 – 7.22 (m, 2H), 7.06 – 7.01 (m, 1H), 3.32 (s, 2H), 1.33 (s, 6H).

<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 211.4, 142.6, 135.8, 135.6, 133.2, 133.2, 130.1, 129.9, 128.1, 126.9, 126.5, 126.1, 117.9, 50.2, 40.7, 24.8.

**1-(2-bromophenyl)-3-(2-chloro-6-methoxyphenyl)-2,2-dimethylpropan-1-one (3.41)**



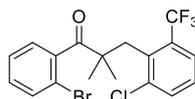
Chemical Formula: C<sub>18</sub>H<sub>18</sub>BrClO<sub>2</sub>  
Molecular Weight: 381.69

Following **General Procedure 1** reacting **3.26Br** (500 mg, 2.2 mmol, 1.0 equiv.) with NaH (60%, 106 mg, 2.6 mmol, 1.2 equiv.) and 2-(bromomethyl)-1-chloro-3-methoxybenzene (570 mg, 2.4 mmol, 1.1 equiv.) in THF (5 mL) afforded the title compound **3.41** (374 mg, 1.0 mmol, 45%) as a light-yellow oil after FC (Et<sub>2</sub>O/PE 6:94).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.62 – 7.56 (m, 1H), 7.36 – 7.32 (m, 2H), 7.26 – 7.22 (m, 1H), 7.14 (“t”, J = 8.1 Hz, 1H), 7.01 (dd, J = 8.1, 1.1 Hz, 1H), 6.76 (dd, J = 8.3, 1.0 Hz, 1H), 3.71 (s, 3H), 3.30 (s, 2H), 1.23 (s, 6H).

<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 210.8, 159.3, 143.0, 136.6, 133.3, 130.0, 128.1, 126.9, 126.3, 125.0, 122.1, 118.5, 109.0, 55.3, 50.0, 35.1, 25.2.

**1-(2-bromophenyl)-3-(2-chloro-6-(trifluoromethyl)phenyl)-2,2-dimethylpropan-1-one (3.42)**



Chemical Formula: C<sub>18</sub>H<sub>15</sub>BrClF<sub>3</sub>O  
Molecular Weight: 419.67

Following **General Procedure 1** reacting **3.26Br** (500 mg, 2.2 mmol, 1.0 equiv.) with NaH (60%, 106 mg, 2.6 mmol, 1.2 equiv.) and 2-(bromomethyl)-1-chloro-3-(trifluoromethyl)benzene (806 mg, 2.9 mmol, 1.3 equiv.) in THF (5 mL) afforded the title compound **3.42** (362 mg, 0.9 mmol, 39%) as a light-yellow oil after FC (Et<sub>2</sub>O/PE 2:98).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.65 – 7.57 (m, 3H), 7.37 – 7.20 (m, 4H), 3.66 (d, J = 1.4 Hz, 2H), 1.23 (s, 6H).

## Experimental Part

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  209.2, 141.5, 137.9, 135.8, 133.5, 133.40, 132.1 (q,  $J = 29.5$  Hz), 130.2, 128.5, 132.1 (q,  $J = 87.2$  Hz), 127.7, 126.9, 126.5, 125.7 (q,  $J = 5.8$  Hz), 118.9, 49.1, 35.5, 25.9.

### 1-bromo-2-(3-(2-chlorophenyl)-2,2-dimethylpropyl)benzene (3.43)

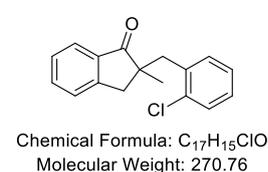


$\text{NaBH}_4$  (71 mg, 1.88 mmol, 1.5 equiv.) was added to a solution of **3.30** (440 mg, 1.25 mmol, 1.0 equiv.) in MeOH (12.5 mL) under Ar at 0 °C. The resulting reaction mixture was stirred at the same temperature for 1 h before sat. aqueous  $\text{NH}_4\text{Cl}$  was added. The mixture was extracted twice with  $\text{Et}_2\text{O}$  and the combined organic phase dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated under reduced pressure to afford the crude alcohol as a colorless viscous oil (435 mg, 1.23 mmol, 98%). The crude alcohol (435 mg, 1.23 mmol, 1 equiv.) was dissolved in dry THF (15 mL) under Ar.  $\text{NaH}$  (60%, 64 mg, 1.60 mmol, 1.3 equiv.) and  $\text{CS}_2$  (0.10 mL, 1.60 mmol, 1.3 equiv.) were added and the resulting reaction mixture refluxed for 1.5 h. The reaction mixture was cooled down to room temperature and MeI (0.12 mL, 1.84 mmol, 1.5 equiv.) was added before the resulting reaction mixture was refluxed for 18 h. The reaction was carefully quenched by addition of  $\text{H}_2\text{O}$  and extracted three times with  $\text{Et}_2\text{O}$ . The combined organic layers were washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated under reduced pressure. The crude was purified by FC ( $\text{Et}_2\text{O}/\text{PE}$  2:98) to afford the corresponding xanthate (560 mg, 1.24 mmol, quant.) as a yellow viscous oil. The obtained xanthate (534 mg, 1.20 mmol, 1.0 equiv.) was added to a mixture of  $n\text{Bu}_3\text{SnH}$  (419 mg, 1.44 mmol, 1.2 equiv.) and AIBN (9.9 mg, 0.06 mmol, 5 mol%) in toluene (12 mL). The resulting reaction mixture was refluxed for 1 h. The solvent was evaporated, and the crude purified by FC (PE) to afford the title compound **3.43** (237 mg, 0.70 mmol, 59%) as a colorless oil.

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.59 – 7.54 (m, 1H), 7.36 (dd,  $J = 7.4, 1.8$  Hz, 1H), 7.24 – 7.20 (m, 3H), 7.20 – 7.12 (m, 2H), 7.09 – 7.03 (m, 1H), 2.91 (s, 2H), 2.88 (s, 2H), 0.96 (s, 6H).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  138.9, 137.0, 135.5, 133.2, 133.0, 132.8, 129.8, 127.8, 127.6, 126.7, 126.5, 126.1, 47.4, 45.2, 38.4, 26.4.

### 2-(2-chlorobenzyl)-2-methyl-2,3-dihydro-1H-inden-1-one (3.35)



Aryl bromide **3.30** (35.2 mg, 0.1 mmol, 1 equiv.) was charged into a catalysis tube equipped with a magnetic stirring bar. The tube was introduced into the glovebox and was subsequently charged with  $\text{K}_2\text{CO}_3$  (27.6 mg, 0.2 mmol, 2 equiv.), adamantic acid (5.4 mg, 0.03 mmol, 30

## Experimental Part

mol%),  $[\text{Pd}(\pi\text{-cin})\text{Cl}]_2$  (2.6 mg, 0.005 mmol, 5 mol%), and IBioxtBu•HOTf (3.6 mg, 0.01 mmol, 10 mol%). The vial was closed with a rubber septum and taken out of the glovebox. Dry and degassed mesitylene (1 mL) was added into the tube under Ar and the tube capped with the corresponding cap. The tube was inserted into a preheated catalysis block at 160 °C and was reacted under stirring for 18 h. Then, the reaction was cooled down to room temperature and diluted with EtOAc, filtered over a plug of *Celite* and the solvent evaporated under reduced pressure. The crude was analyzed by GC-MS and  $^1\text{H}$  NMR (1 mL  $\text{CDCl}_3$ /0.1 mmol + 0.1 mmol trichloroethylene as internal standard). **3.35** was observed in quantitative  $^1\text{H}$  NMR yield. After analysis, the solvent was evaporated under reduced pressure and the crude purified by FC to afford an analytically pure sample.

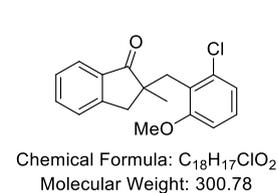
The reaction was performed on 1 mmol scale by reacting aryl bromide **3.30** (352 mg, 1.0 mmol, 1 equiv.) with  $\text{K}_2\text{CO}_3$  (276 mg, 2.0 mmol, 2 equiv.), adamantoic acid (54 mg, 0.3 mmol, 30 mol%),  $[\text{Pd}(\pi\text{-cin})\text{Cl}]_2$  (26 mg, 0.05 mmol, 5 mol%), and IBioxtBu•HOTf (3.6 mg, 0.1 mmol, 10 mol%) in mesitylene (10 mL) to afford the title compound **3.35** (156 mg, 0.57 mmol, 57%) as a yellow oil.

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.77 – 7.73 (m, 1H), 7.52 (td,  $J = 7.5, 1.3$  Hz, 1H), 7.37 – 7.29 (m, 3H), 7.19 – 7.15 (m, 1H), 7.10 – 7.03 (m, 2H), 3.24 (d,  $J = 17.2$  Hz, 1H), 3.18 (s, 2H), 2.81 (d,  $J = 17.2$  Hz, 1H), 1.31 (s, 3H).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  210.7, 152.9, 136.1, 135.7, 135.0, 134.9, 132.2, 129.7, 128.0, 127.5, 126.8, 126.7, 124.4, 51.2, 39.1, 38.9, 25.5.

**HPLC separation:** Chiralcel OD-H; 99:1 (*n*hexane/*i*PrOH), 1.5 mL/min, 239 nm,  $t_r(\text{major}) = 17.2$  min,  $t_r(\text{minor}) = 30.2$  min, 82:18 e.r.

### 2-(2-chloro-6-methoxybenzyl)-2-methyl-2,3-dihydro-1H-inden-1-one (3.44)



The title compound **3.44** (31%  $^1\text{H}$  NMR yield) was obtained as yellow oil following **General Procedure 2** by reacting aryl bromide **3.41** (38.2, 0.1 mmol, 1.0 equiv.),  $\text{Cs}_2\text{CO}_3$  (99 mg, 0.3 mmol, 3.0 equiv.), adamantoic acid (18 mg, 0.1 mmol, 1.0 equiv.),  $[\text{Pd}(\pi\text{-cin})\text{Cl}]_2$  (2.6 mg, 0.005 mmol, 5 mol%), and IBioxtBu•HOTf (4.2 mg, 0.01 mmol, 10 mol%) in mesitylene (1 mL). The crude was purified by FC ( $\text{Et}_2\text{O}/\text{PE}$  5:95) to obtain a clean sample to determine the e.r. by chiral HPLC.

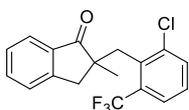
## Experimental Part

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.77 – 7.73 (m, 1H), 7.53 – 7.47 (m, 1H), 7.35 – 7.27 (m, 2H), 7.08 – 7.03 (m, 1H), 6.98 – 6.94 (m, 1H), 6.61 – 6.57 (m, 1H), 3.57 (s, 3H), 3.25 – 3.14 (m, 3H), 2.76 (d, *J* = 17.0 Hz, 1H), 1.31 (s, 3H).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 210.0, 159.0, 152.3, 136.2, 136.1, 134.4, 128.0, 127.2, 126.4, 125.5, 124.0, 121.8, 108.5, 55.0, 50.6, 40.5, 35.2, 24.5.

**HPLC separation:** Chiralcel OJ-H; 99:1 (*n*hexane/*i*PrOH), 1 mL/min, 239 nm, *t*<sub>r</sub>(major) = 16.6 min, *t*<sub>r</sub>(minor) = 19.3 min, 81:19 e.r.

### 2-(2-chloro-6-(trifluoromethyl)benzyl)-2-methyl-2,3-dihydro-1H-inden-1-one (3.45)



Chemical Formula: C<sub>18</sub>H<sub>14</sub>ClF<sub>3</sub>O  
Molecular Weight: 338.75

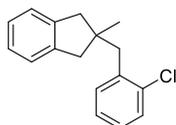
The title compound **3.45** (25% <sup>1</sup>H NMR yield) was obtained as yellow oil following **General Procedure 2** by reacting aryl bromide **3.42** (42 mg, 0.1 mmol, 1 equiv.), Cs<sub>2</sub>CO<sub>3</sub> (99 mg, 0.3 mmol, 3.0 equiv.), adamantoic acid (18 mg, 0.1 mmol, 1.0 equiv.), [Pd(*π*-cin)Cl]<sub>2</sub> (2.6 mg, 0.005 mmol, 5 mol%), and IBioxtBu•HOTf (4.2 mg, 0.01 mmol, 10 mol%) in mesitylene (1 mL). The crude was purified by FC (Et<sub>2</sub>O/PE 2:98). No suitable conditions were found to successfully separate the two enantiomers by chiral HPLC.

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.78 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.58 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.54 – 7.46 (m, 2H), 7.38 – 7.33 (m, 1H), 7.27 – 7.23 (m, 2H), 3.83 (d, *J* = 15.0 Hz, 1H), 3.22 (d, *J* = 15.0 Hz, 1H), 2.78 (d, *J* = 17.3 Hz, 1H), 2.61 (d, *J* = 17.3 Hz, 1H), 1.39 (s, 3H).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 210.2, 152.3, 137.6, 137.0, 137.0, 134.9, 134.8, 133.5, 131.7 (q, *J* = 29.4 Hz), 127.8, 127.6, 126.5, 125.0 (q, *J* = 5.9 Hz), 124.7, 49.1, 39.4, 36.2, 28.6.

**<sup>19</sup>F NMR** (471 MHz, CDCl<sub>3</sub>) δ -58.7.

### 2-(2-chlorobenzyl)-2-methyl-2,3-dihydro-1H-indene (3.46)



Chemical Formula: C<sub>17</sub>H<sub>17</sub>Cl  
Molecular Weight: 256.77

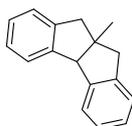
The title compound **3.46** (72% <sup>1</sup>H NMR yield) was obtained as yellow oil following **General Procedure 2** by reacting aryl bromide **3.43** (33.8 mg, 0.1 mmol, 1 equiv.), Cs<sub>2</sub>CO<sub>3</sub> (99 mg, 0.3 mmol, 3.0 equiv.), adamantoic acid (18 mg, 0.1 mmol, 1.0 equiv.), [Pd(*π*-cin)Cl]<sub>2</sub> (2.6 mg, 0.005 mmol, 5 mol%), and IBioxtBu•HOTf (4.2 mg, 0.01 mmol, 10 mol%) in mesitylene (1 mL). The crude was purified by FC (PE) to obtain an analytically pure sample.

## Experimental Part

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.38 – 7.35 (m, 1H), 7.27 – 7.24 (m, 1H), 7.21 – 7.14 (m, 4H), 7.14 – 7.11 (m, 2H), 3.01 (d, *J* = 15.4 Hz, 2H), 2.99 (s, 2H), 2.63 (d, *J* = 15.3 Hz, 2H), 1.12 (s, 3H).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 143.1, 137.6, 135.3, 132.6, 129.8, 127.6, 126.4, 126.2, 124.9, 45.8, 45.7, 42.8, 26.5.

### 9a-methyl-4b,9,9a,10-tetrahydroindeno[1,2-a]indene (3.48)

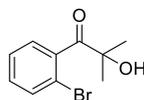


Chemical Formula: C<sub>17</sub>H<sub>16</sub>  
Molecular Weight: 220.32

The title compound **3.48** (65% <sup>1</sup>H NMR yield) was obtained as yellow oil following **General Procedure 2** by reacting aryl chloride **3.46** (27.1 mg, 0.1 mmol, 1 equiv.), Cs<sub>2</sub>CO<sub>3</sub> (99 mg, 0.3 mmol, 3.0 equiv.), adamantic acid (18 mg, 0.1 mmol, 1.0 equiv.), [Pd(π-cin)Cl]<sub>2</sub> (2.6 mg, 0.005 mmol, 5 mol%), and IBiox/Bu•HOTf (4.2 mg, 0.01 mmol, 10 mol%) in mesitylene (1 mL). The crude decomposed while purified on silica by FC.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.50 – 7.44 (m, 2H), 7.32 – 7.21 (m, 6H), 4.30 (s, 1H), 3.09 – 2.97 (m, 4H), 1.49 (s, 3H).

### 1-(2-bromophenyl)-2-hydroxy-2-methylpropan-1-one (3.54)

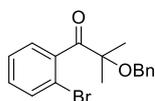


Chemical Formula: C<sub>10</sub>H<sub>11</sub>BrO<sub>2</sub>  
Molecular Weight: 243.10

Triethylphosphite (2.28 mL, 13.2 mmol, 2.0 equiv.) was added to a mixture of **3.26Br** (1.50 g, 6.6 mmol, 1.0 equiv.) and Cs<sub>2</sub>CO<sub>3</sub> (0.44 g, 1.3 mmol, 20 mol%) in dry DMSO (26.1 mL) under Ar. The atmosphere of the reaction was exchanged with O<sub>2</sub> by bubbling O<sub>2</sub> through the solution for 5 min. Then, a balloon of O<sub>2</sub> was connected to the flask with a needle and the reaction stirred at room temperature for 18 h. The solution was then diluted with Et<sub>2</sub>O, and washed three times with brine. The organic phase was then dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude was purified by FC (EtOAc/pent 30:70) to afford the title compound **3.54** (1.20 g, 4.9 mmol, 74%) as a yellow oil.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.64 – 7.60 (m, 1H), 7.36 (td, *J* = 7.5, 1.2 Hz, 1H), 7.30 (dd, *J* = 7.7, 1.9 Hz, 1H), 7.29 – 7.26 (m, 1H), 3.30 (bs, 1H), 1.54 (s, 6H).

### 2-(benzyloxy)-1-(2-bromophenyl)-2-methylpropan-1-one (3.55)



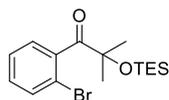
Chemical Formula: C<sub>17</sub>H<sub>17</sub>BrO<sub>2</sub>  
Molecular Weight: 333.23

Benzyl bromide (0.12 mL, 1.04 mmol, 1.2 equiv.) was added to a mixture of alcohol **3.54** (210 mg, 0.86 mmol, 1.0 equiv.) and NaH (60%, 25 mg, 1.04 mmol, 1.2 equiv.) in dry THF (2 mL) under Ar. The resulting mixture was stirred at the same temperature for 18 h before it

## Experimental Part

was carefully quenched with H<sub>2</sub>O. The resulting mixture was three times extracted with Et<sub>2</sub>O, washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude was purified by FC (Et<sub>2</sub>O/pent 5:95) to afford the title compound **3.55** (60 mg, 0.18 mmol, 20%) as a yellow oil.

### 1-(2-bromophenyl)-2-methyl-2-((triethylsilyl)oxy)propan-1-one (**3.56**)



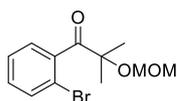
Chemical Formula: C<sub>16</sub>H<sub>25</sub>BrO<sub>2</sub>Si  
Molecular Weight: 357.36

2,6-lutidine (0.27 mL, 2.3 mmol, 1.5 equiv.) was added to a solution of alcohol **3.54** (400 mg, 1.7 mmol, 1.0 equiv) in dry DCM (3.3 mL) at -78 °C under Ar. After stirring for 5 min, TESOTf (0.39 mL, 1.7 mmol, 1.1 equiv.) was added and the resulting reaction mixture was allowed to warm to room temperature and stirred for 18 h. The mixture was quenched with sat. NH<sub>4</sub>Cl, and extracted three times with DCM. The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude was purified by FC (Et<sub>2</sub>O/pent 2:98) to afford the title compound **3.56** (413 mg, 1.2 mmol, 74%) as a colorless oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.57 – 7.50 (m, 1H), 7.34 – 7.21 (m, 2H), 7.25 – 7.15 (m, 1H), 1.55 (s, 6H), 0.78 (t, *J* = 7.9 Hz, 9H), 0.48 (q, *J* = 7.9 Hz, 6H).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 210.2, 142.0, 132.7, 130.1, 127.5, 126.3, 118.6, 28.5, 6.9, 6.6.

### 1-(2-bromophenyl)-2-(methoxymethoxy)-2-methylpropan-1-one (**3.57**)



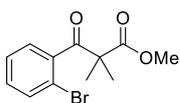
Chemical Formula: C<sub>12</sub>H<sub>15</sub>BrO<sub>3</sub>  
Molecular Weight: 287.15

To an ice-cooled solution of alcohol **3.54** (350 mg, 1.44 mmol, 1.0 equiv.) and DIPEA (0.30 mL, 1.73 mmol, 1.2 equiv.) in dry DCM (5.5 mL) under Ar was added dropwise MOMCl (0.13 mL, 1.73 mmol, 1.2 equiv.). The resulting mixture was stirred at room temperature for 18 h. Sat. NH<sub>4</sub>Cl was added and the mixture extracted three times with Et<sub>2</sub>O. The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude was purified by FC (Et<sub>2</sub>O/pent 15:85) to afford the title compound **3.57** (146 mg, 0.51 mmol, 35%) as a yellow oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.62 – 7.53 (m, 1H), 7.39 – 7.35 (m, 1H), 7.35 – 7.30 (m, 1H), 7.28 – 7.22 (m, 1H), 4.70 (s, 2H), 3.27 (s, 3H), 1.58 (s, 6H).

## Experimental Part

### methyl 3-(2-bromophenyl)-2,2-dimethyl-3-oxopropanoate (3.60)

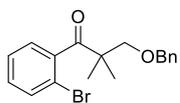


Chemical Formula: C<sub>12</sub>H<sub>13</sub>BrO<sub>3</sub>  
Molecular Weight: 285.14

NaH (60%, 0.60 g, 15.1 mmol, 1.0 equiv.) followed by dimethylcarbonate (1.27 mL, 15.1 mmol, 1.0 equiv.) were added to a solution of 2-bromoacetophenone (3.00 g, 15.1 mmol, 1.0 equiv.) in dry toluene (60 mL) under Ar. The resulting reaction mixture was stirred under reflux for 18 h. After cooling down to room temperature, H<sub>2</sub>O was carefully added to quench the excess NaH. The resulting mixture was extracted three times with Et<sub>2</sub>O, washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to afford the crude **3.59** (1.48 g, 5.8 mmol 38%) as a reddish oil. The crude was engaged in the next reaction without further purification. NaH (60%, 0.58 g, 14.4 mg, 2.5 equiv.) was added to a solution of **3.59** (1.48 g, 5.77 mmol, 1.0 equiv.) in dry THF (6 mL) under Ar. After 5 min of stirring at the same temperature, MeI (1.44 mL, 23.1 mmol, 4.0 equiv.) was added and the resulting mixture was refluxed under Ar for 18 h. After cooling down to room temperature, H<sub>2</sub>O was carefully added to quench the excess NaH. The resulting mixture was extracted three times with Et<sub>2</sub>O, the organic phase washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude was purified by FC (10 – 15% Et<sub>2</sub>O in pentane) to afford the title compound **3.60** (0.26 g, 0.9 mmol, 16%) as a yellow oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.60 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.31 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.28 – 7.24 (m, 1H), 7.21 (dd, *J* = 7.5, 1.8 Hz, 1H), 3.71 (s, 3H), 1.53 (s, 6H).

### 3-(benzyloxy)-1-(2-bromophenyl)-2,2-dimethylpropan-1-one (3.62)



Chemical Formula: C<sub>18</sub>H<sub>19</sub>BrO<sub>2</sub>  
Molecular Weight: 347.25

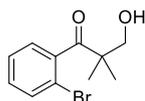
A solution of LiHMDS (7.03 g, 42.0 mmol, 1.2 equiv.) in dry THF (42 mL) was added slowly to an ice cooled solution of **3.26Br** (7.94 g, 35.0 mmol, 1.0 equiv.) in dry THF (40 mL) under Ar. The resulting reaction mixture was warmed to room temperature and stirred for 30 min before TMSCl (4.2 mL, 49.0 mmol, 1.4 equiv.) was added dropwise. After 15 min at the same temperature, the solvent was removed under reduced pressure and the crude filtered through a pad of *Celite* (eluent Et<sub>2</sub>O). The filtrate was concentrated under reduced pressure and the resulting residue dissolved in dry DCM (200 mL). Anhydrous ZnCl<sub>2</sub> (1.43 g, 10.5 mmol, 30 mol%) and BOMCl (60%, 8.2 mL, 35.4 mmol, 1.01 equiv.) were subsequently added under Ar and the resulting mixture stirred at room temperature for 18 h. The reaction was quenched by addition of sat. aqueous NH<sub>4</sub>Cl and was extracted three times with Et<sub>2</sub>O. The combined organic phases were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced

## Experimental Part

pressure. The crude was purified by FC (Et<sub>2</sub>O/PE 4:96) to afford the benzyl ether **3.62** (9.88 g, 28.4 mmol, 81%) as a colorless oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.57 – 7.52 (m, 1H), 7.38 – 7.28 (m, 6H), 7.25 – 7.23 (m, 1H), 7.23 – 7.17 (m, 1H), 4.53 (s, 2H), 3.54 (s, 2H), 1.28 (s, 6H).

### 1-(2-bromophenyl)-3-hydroxy-2,2-dimethylpropan-1-one (3.63)



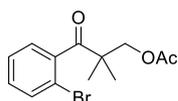
Chemical Formula: C<sub>11</sub>H<sub>13</sub>BrO<sub>2</sub>  
Molecular Weight: 257.13

The benzyl ether **3.62** (65% purity, 4.00 g, 7.5 mmol, 1.0 equiv.) was dissolved in anhydrous MeCN (15.8 mL) under Ar. Triphenylphosphine hydrobromide (7.16 g, 8.3 mmol, 1.1 equiv.) was added and the resulting mixture stirred under reflux for 18 h. The reaction was cooled down to room temperature, poured into Et<sub>2</sub>O (100 mL) and filtered. The filtrate was concentrated under reduced pressure. The resulting crude was purified by FC (Et<sub>2</sub>O/PE 40:60) to afford the title compound **3.63** (1.42 g, 5.5 mmol, 74%) as a colorless oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.60 – 7.56 (m, 1H), 7.34 ("t"d, *J* = 7.5, 1.2 Hz, 1H), 7.28 – 7.21 (m, 2H), 3.72 (s, 2H), 2.05 (d, *J* = 15.7 Hz, 1H), 1.27 (s, 6H).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 212.1, 141.9, 133.3, 130.4, 127.0, 126.4, 118.1, 70.1, 50.5, 22.3.

### 3-(2-bromophenyl)-2,2-dimethyl-3-oxopropyl acetate (3.65)

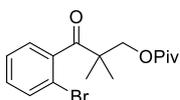


Chemical Formula: C<sub>13</sub>H<sub>15</sub>BrO<sub>3</sub>  
Molecular Weight: 299.16

Acetyl chloride (0.15 mL, 2.04 mmol, 1.5 equiv.) was added dropwise to a solution of alcohol **3.63** (350 mg, 1.36 mmol, 1.0 equiv.) and Et<sub>3</sub>N (0.38 mL, 2.72 mmol, 2.0 equiv.) in dry THF (3.3 mL). Sat. NaHCO<sub>3</sub> was added and the mixture extracted three times with Et<sub>2</sub>O and the organic phase washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude was purified by FC (Et<sub>2</sub>O/pent 5:95) to afford the title compound **3.65** (305 mg, 1.02 mmol, 75%) as a yellow viscous oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.61 – 7.57 (m, 1H), 7.37 – 7.31 (m, 1H), 7.28 – 7.23 (m, 1), 7.20 – 7.15 (m, 1H), 4.20 (s, 2H), 2.07 (s, 3H), 1.30 (s, 6H).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 209.2, 170.8, 142.1, 133.3, 130.4, 127.0, 126.2, 118.0, 70.2, 48.3, 22.7, 21.0.

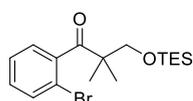
**3-(2-bromophenyl)-2,2-dimethyl-3-oxopropyl pivalate (3.66)**

Chemical Formula: C<sub>16</sub>H<sub>21</sub>BrO<sub>3</sub>  
Molecular Weight: 341.25

A solution of LiHMDS (1 M, 13.2 mL, 13.2 mmol, 1.2 equiv) was added dropwise to a stirred solution of ketone **3.26Br** (2.50 g, 11 mmol, 1.0 equiv.) in dry THF (22mL) at 0 °C under Ar. The mixture was stirred for 15 min at room temperature before KI (2.00 g, 12.1 mmol 1.1 equiv.) and chloromethyl pivalate (1.90 mL, 13.2 mmol, 1.2 equiv.) were added subsequently. The resulting mixture was stirred at the same temperature for 2 h before the reaction was quenched by careful addition of sat. NH<sub>4</sub>Cl. The reaction mixture was extracted three times with Et<sub>2</sub>O. The combined organic phases were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude was purified by FC (Et<sub>2</sub>O/pent 6:94) to afford the title compound **3.66** (2.46 g, 7.22 mmol, 66%) as a yellow oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.62 – 7.55 (m, 1H), 7.38 – 7.30 (m, 1H), 7.28 – 7.22 (m, 1H), 7.21 – 7.18 (m, 1H), 4.21 (s, 2H), 1.31 (s, 6H), 1.21 (s, 9H).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 208.5, 178.3, 141.9, 133.4, 130.4, 127.0, 126.4, 118.2, 69.6, 48.8, 39.0, 27.3, 22.5.

**1-(2-bromophenyl)-2,2-dimethyl-3-((triethylsilyl)oxy)propan-1-one (3.67)**

Chemical Formula: C<sub>17</sub>H<sub>27</sub>BrO<sub>2</sub>Si  
Molecular Weight: 371.39

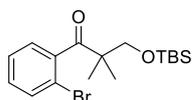
To a solution of alcohol **3.63** (400 mg, 1.56 mmol, 1.0 equiv) in dry DCM (3 mL) at 0 °C under Ar was added subsequently TESCl (0.90 mL, 2.03 mmol, 1.3 equiv.) and imidazole (212 mg, 3.12 mmol, 2.0 equiv.). The resulting reaction mixture was stirred at room temperature overnight. Sat. NH<sub>4</sub>Cl was added and the mixture extracted three times with DCM and the combined organic phases were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude was purified by FC (Et<sub>2</sub>O/pent 2:98) to afford the title compound **3.67** (210 mg, 0.57 mmol, 36%) as a yellow viscous oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.56 – 7.53 (m, 1H), 7.35 – 7.32 (m, 1H), 7.32 – 7.27 (m, 1H), 7.24 – 7.18 (m, 1H), 3.67 (s, 2H), 1.22 (s, 6H), 0.96 (t, *J* = 7.9 Hz, 9H), 0.68 – 0.56 (m, 6H).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 212.2, 141.9, 133.3, 130.4, 127.0, 126.4, 118.1, 70.1, 50.5, 22.3, 6.9, 6.6.

## Experimental Part

### 1-(2-bromophenyl)-3-((tert-butyldimethylsilyloxy)-2,2-dimethylpropan-1-one (3.68)

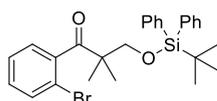


Chemical Formula: C<sub>17</sub>H<sub>27</sub>BrO<sub>2</sub>Si  
Molecular Weight: 371.39

To a solution of alcohol **3.63** (130 mg, 0.51 mmol, 1.0 equiv) in dry DCM (1 mL) at 0 °C under Ar was added subsequently TBSCl (0.12 mL, 0.66 mmol, 1.3 equiv.) and imidazole (68.9 mg, 1.01 mmol, 2.0 equiv.). The resulting mixture was stirred at room temperature overnight. Sat. NH<sub>4</sub>Cl was added and the mixture extracted three times with DCM and the organic phase washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude was purified by FC (Et<sub>2</sub>O/pent 5:95) to afford the title compound **3.68** (120 mg, 0.32 mmol, 64%) as a yellow viscous oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.50 – 7.46 (m, 1H), 7.27 – 7.21 (m, 2H), 7.18 – 7.12 (m, 1H), 3.62 (s, 2H), 1.16 (s, 6H), 0.84 (s, 9H), 0.00 (s, 6H).

### 1-(2-bromophenyl)-3-((tert-butyldiphenylsilyloxy)-2,2-dimethylpropan-1-one (3.69)



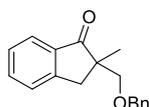
Chemical Formula: C<sub>27</sub>H<sub>31</sub>BrO<sub>2</sub>Si  
Molecular Weight: 495.53

To a solution of **3.63** (1.42 g, 5.52 mmol, 1.0 equiv.) in dry DCM (5.5 mL) under Ar at 0 °C was added TBDPSCl (1.97 g, 7.18 mmol, 1.3 equiv.) followed by imidazole (0.56 g, 8.28 mmol, 1.5 equiv.). The resulting mixture was allowed to warm to room temperature and was stirred at this temperature for 2 h. H<sub>2</sub>O was added, and the mixture extracted three times with DCM. The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude was purified by FC (Et<sub>2</sub>O/PE 2:98) to afford the title compound **3.69** (2.14 g, 4.32 mmol, 78%) as a colorless oil.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.69 – 7.63 (m, 4H), 7.58 – 7.52 (m, 1H), 7.47 – 7.42 (m, 2H), 7.42 – 7.37 (m, 4H), 7.31 – 7.27 (m, 1H), 7.24 – 7.19 (m, 2H), 3.75 (s, 2H), 1.24 (s, 6H), 1.09 (s, 9H).

<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 210.5, 142.6, 135.9, 133.3, 133.1, 130.1, 129.9, 127.9, 126.7, 126.7, 118.0, 71.1, 50.8, 27.1, 22.5, 19.5.

### 2-((benzyloxy)methyl)-2-methyl-2,3-dihydro-1H-inden-1-one (3.64)



Chemical Formula: C<sub>18</sub>H<sub>18</sub>O<sub>2</sub>  
Molecular Weight: 266.34

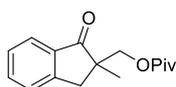
Aryl bromide **3.62** (34.7 mg, 0.1 mmol, 1 equiv.) was charged into a catalysis tube equipped with a magnetic stirring bar. The tube was introduced into the glovebox and was subsequently charged with Cs<sub>2</sub>CO<sub>3</sub> (99 mg, 0.3 mmol, 3 equiv.), CsOPiv (23 mg, 0.1 mmol, 1.0 equiv.), [Pd( $\pi$ -cin)Cl]<sub>2</sub> (2.6 mg, 0.005 mmol, 5 mol%), and IBiox*t*Bu•HOTf (4.2 mg, 0.01 mmol, 10

## Experimental Part

mol%). The vial was closed with a rubber septum and taken out of the glovebox. Dry and degassed mesitylene (1 mL) was added into the tube under Ar and the tube capped with the corresponding cap. The tube was inserted into a preheated catalysis block at 160 °C and was reacted under stirring for 18 h. Then, the reaction was cooled down to room temperature and diluted with EtOAc, filtered over a plug of *Celite* and the solvent evaporated under reduced pressure. The crude was analyzed by GC-MS and <sup>1</sup>H NMR (1 mL CDCl<sub>3</sub>/0.1 mmol + 0.1 mmol trichloroethylene as internal standard) to afford the title compound **3.64** (92% <sup>1</sup>H NMR yield, 0.1 mmol).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.79 – 7.75 (m, 1H), 7.59 (td, *J* = 7.5, 1.3 Hz, 1H), 7.47 – 7.43 (m, 1H), 7.39 – 7.34 (m, 2H), 7.32 – 7.24 (m, 2H), 7.22 – 7.17 (m, 2H), 4.52 – 4.37 (m, 2H), 3.68 (d, *J* = 8.8 Hz, 1H), 3.51 – 3.40 (m, 2H), 2.87 (d, *J* = 17.1 Hz, 1H), 1.19 (s, 3H).

### (2-methyl-1-oxo-2,3-dihydro-1H-inden-2-yl)methyl pivalate (**3.71**)

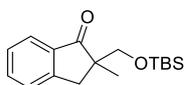


Chemical Formula: C<sub>16</sub>H<sub>20</sub>O<sub>3</sub>  
Molecular Weight: 260.33

Aryl bromide **3.66** (34.7 mg, 0.1 mmol, 1 equiv.) was charged into a catalysis tube equipped with a magnetic stirring bar. The tube was introduced into the glovebox and was subsequently charged with Cs<sub>2</sub>CO<sub>3</sub> (99 mg, 0.3 mmol, 3 equiv.), CsOPiv (23 mg, 0.1 mmol, 1.0 equiv.), [Pd( $\pi$ -cin)Cl]<sub>2</sub> (2.6 mg, 0.005 mmol, 5 mol%), and IBiox $t$ Bu•HOTf (4.2 mg, 0.01 mmol, 10 mol%). The vial was closed with a rubber septum and taken out of the glovebox. Dry and degassed mesitylene (1 mL) was added into the tube under Ar and the tube capped with the corresponding cap. The tube was inserted into a preheated catalysis block at 160 °C and was reacted under stirring for 18 h. Then, the reaction was cooled down to room temperature and diluted with EtOAc, filtered over a plug of *Celite* and the solvent evaporated under reduced pressure. The crude was analyzed by GC-MS and <sup>1</sup>H NMR (1 mL CDCl<sub>3</sub>/0.1 mmol + 0.1 mmol trichloroethylene as internal standard) to afford the title compound **3.71** (48% <sup>1</sup>H NMR yield, 0.48 mmol).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.74 – 7.69 (m, 1H), 7.59 – 7.55 (m, 1H), 7.46 – 7.42 (m, 1H), 7.36 – 7.31 (m, 1H), 3.80 (d, *J* = 9.3 Hz, 1H), 3.53 (d, *J* = 9.3 Hz, 1H), 3.39 (d, *J* = 17.0 Hz, 1H), 2.82 (d, *J* = 17.1 Hz, 1H), 0.98 (s, 3H), 0.68 (s, 9H).

### 2-(((tert-butyldimethylsilyl)oxy)methyl)-2-methyl-2,3-dihydro-1H-inden-1-one (**3.73**)



Chemical Formula: C<sub>17</sub>H<sub>26</sub>O<sub>2</sub>Si  
Molecular Weight: 290.48

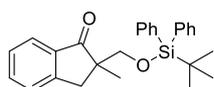
Aryl bromide **3.68** (37.1 mg, 0.1 mmol, 1 equiv.) was charged into a catalysis tube equipped with a magnetic stirring bar. The tube was introduced into the glovebox and was subsequently charged with Cs<sub>2</sub>CO<sub>3</sub> (99 mg, 0.3 mmol, 3 equiv.), CsOPiv (23 mg, 0.1 mmol, 1.0 equiv.), [Pd( $\pi$ -cin)Cl]<sub>2</sub>

## Experimental Part

(2.6 mg, 0.005 mmol, 5 mol%), and IBioxtBu•HOTf (4.2 mg, 0.01 mmol, 10 mol%). The vial was closed with a rubber septum and taken out of the glovebox. Dry and degassed mesitylene (1 mL) was added into the tube under Ar and the tube capped with the corresponding cap. The tube was inserted into a preheated catalysis block at 160 °C and was reacted for 18 h. Then, the reaction was cooled down to room temperature and diluted with EtOAc, filtered over a plug of *Celite* and the solvent evaporated under reduced pressure. The crude was analyzed by GC-MS and <sup>1</sup>H NMR (1 mL CDCl<sub>3</sub>/0.1 mmol + 0.1 mmol trichloroethylene as internal standard) to afford the title compound **3.73** (52% <sup>1</sup>H NMR yield, 0.1 mmol).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.74 – 7.68 (m, 1H), 7.59 – 7.54 (m, 1H), 7.46 – 7.42 (m, 1H), 7.36 – 7.30 (m, 1H), 3.80 (d, *J* = 9.3 Hz, 1H), 3.53 (d, *J* = 9.3 Hz, 1H), 3.39 (d, *J* = 17.0 Hz, 1H), 2.82 (d, *J* = 16.9 Hz, 1H), 1.15 (s, 3H), 0.68 (s, 9H), 0.00 (s, 3H), -0.09 (s, 3H).

### 2-(((tert-butyldiphenylsilyloxy)methyl)-2-methyl-2,3-dihydro-1H-inden-1-one (3.74)



Chemical Formula: C<sub>27</sub>H<sub>30</sub>O<sub>2</sub>Si  
Molecular Weight: 414.62

Aryl bromide **3.69** (49.6 mg, 0.1 mmol, 1 equiv.) was charged into a catalysis tube equipped with a magnetic stirring bar. The tube was introduced into the glovebox and was subsequently charged with Cs<sub>2</sub>CO<sub>3</sub> (99 mg, 0.3 mmol, 3 equiv.), CsOPiv (23 mg, 0.1 mmol, 1.0 equiv.), [Pd( $\pi$ -cin)Cl]<sub>2</sub> (2.6 mg, 0.005 mmol, 5 mol%), and IBioxtBu•HOTf (4.2 mg, 0.01 mmol, 10 mol%). The vial was closed with a rubber septum and taken out of the glovebox. Dry and degassed mesitylene (1 mL) was added into the tube under Ar and the tube capped with the corresponding cap. The tube was inserted into a preheated catalysis block at 160 °C and was reacted under stirring for 18 h. Then, the reaction was cooled down to room temperature and diluted with EtOAc, filtered over a plug of *Celite* and the solvent evaporated under reduced pressure. The crude was analyzed by GC-MS and <sup>1</sup>H NMR (1 mL CDCl<sub>3</sub>/0.1 mmol + 0.1 mmol trichloroethylene as internal standard) to afford the title compound **3.74** (99% <sup>1</sup>H NMR yield, 0.1 mmol). The crude was purified by FC Et<sub>2</sub>O/cHex 4:96), to afford an analytically pure sample (31 mg, 0.76 mmol, 76%). The enantiomeric ratio was then determined by HPLC using a chiral stationary phase.

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.80 – 7.76 (m, 1H), 7.63 – 7.58 (m, 1H), 7.55 – 7.51 (m, 4H), 7.50 – 7.46 (m, 1H), 7.43 – 7.31 (m, 7H), 3.97 – 3.91 (m, 1H), 3.60 – 3.55 (m, 1H), 3.49 – 3.42 (m, 1H), 2.92 – 2.84 (m, 1H), 1.13 (s, 3H), 0.82 (s, 9H).

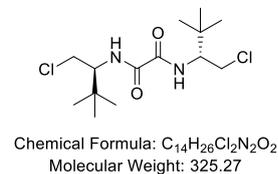
**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 210.2, 153.8, 137.1, 135.8, 135.7, 134.8, 133.6, 133.2, 129.8, 129.8, 127.8, 127.8, 127.3, 126.5, 124.1, 69.5, 51.6, 38.6, 26.7, 20.1, 19.3.

## Experimental Part

**HPLC separation:** Chiralcel OD-H; 99:1 (*n*hexane/*i*PrOH), 1 mL/min, 239 nm,  $t_r(\text{minor}) = 4.7$  min,  $t_r(\text{major}) = 6.3$  min, 20:80 e.r.

## 9.2 Towards the Synthesis of Novel IBio-Type Ligands

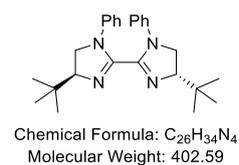
### N<sup>1</sup>-((*R*)-1-chloro-3,3-dimethylbutan-2-yl)-N<sup>2</sup>-((*S*)-1-chloro-3,3-dimethylbutan-2-yl)oxalamide (**4.2**)



Following reported procedure.<sup>[7]</sup> Ethyl oxalate (2.76 mL, 20.3 mmol, 1.0 equiv.) was added to a solution of (*S*)-*tert*-leucinol **4.1** (7.72 g, 40.3 mmol, 2.0 equiv.) in dry toluene (200 mL) under Ar at room temperature and then refluxed for 18 h. The reaction mixture was cooled down to room temperature, and ca. 50% of the toluene was evaporated under reduced pressure. SOCl<sub>2</sub> (3.22 mL, 44.4 mmol, 2.2 equiv.) was added and the resulting mixture stirred under reflux for 4 h. The mixture was cooled down to room temperature and an aqueous solution KOH (20 wt%) was added and extracted three times with DCM. The combined organic phases were washed with sat. NaHCO<sub>3</sub>, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The orange crude product **4.2** (5.73 g, 17.6 mmol, 87%) was used in the next step without further purification.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.48 (d, *J* = 10.7 Hz, 1H), 4.08 – 3.91 (m, 1H), 3.82 (dd, *J* = 11.6, 3.3 Hz, 1H), 3.49 (dd, *J* = 11.6, 9.4 Hz, 1H), 1.00 (s, 9H).

### 4*S*,4'*S*)-4,4'-di-*tert*-butyl-1,1'-diphenyl-4,4',5,5'-tetrahydro-1*H*,1'*H*-2,2'-biimidazole (**4.3**)



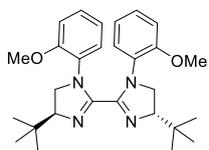
PCl<sub>5</sub> (1229 mg, 5.9 mmol, 2.4 equiv.) was added to a solution of **4.2** (2.00 g, 6.2 mmol, 1.0 equiv.) in dry toluene (40 mL) under Ar and the resulting mixture stirred at 85 °C for 18 h before the solvent was removed under reduced pressure. The resulting crude imidoyl chloride was dissolved in dry acetonitrile (40 mL) and Et<sub>3</sub>N (2.56 mL, 18.5 mmol, 3.0 equiv.) followed by aniline (2.3 mL, 24.6 mmol, 4.0 equiv.) were added. The resulting reaction mixture was stirred under reflux for 4 days before it was cooled down to room temperature. The solvent was removed under reduced pressure and the crude purified by FC (20 -100% EtOAc in *c*Hex) to afford the title compound **4.3** (1.39 g, 3.45 mmol, 56%) as a beige solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.04 – 6.97 (m, 4H), 6.91 – 6.84 (m, 2H), 6.63 – 6.56 (m, 4H), 4.05 (dd, *J* = 13.3, 10.1 Hz, 2H), 3.61 (dd, *J* = 13.3, 9.1 Hz, 2H), 3.49 (dd, *J* = 10.0, 9.1 Hz, 2H), 1.07 (s, 18H).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 153.7, 139.7, 128.3, 123.2, 119.3, 74.6, 52.2, 33.9, 26.8.

## Experimental Part

### (4S,4'S)-4,4'-di-tert-butyl-1,1'-bis(2-methoxyphenyl)-4,4',5,5'-tetrahydro-1H,1'H-2,2'-biimidazole (4.4)



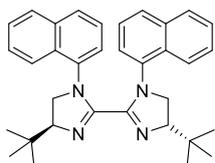
Chemical Formula: C<sub>26</sub>H<sub>38</sub>N<sub>4</sub>  
Molecular Weight: 406.62

PCl<sub>5</sub> (3.07 g, 14.8 mmol, 2.4 equiv.) was added to a solution of **4.2** (3.07 g, 14.8 mmol, 1.0 equiv.) in dry toluene (50 mL) under Ar and the resulting mixture stirred at 85 °C for 18 h before the solvent was removed under reduced pressure. The crude was engaged in the next step without further purification. The crude imidoyl chloride (400 mg, 1.1 mmol, 1.0 equiv.) was dissolved in dry acetonitrile (8.2 mL) and Et<sub>3</sub>N (0.47 mL, 3.3 mmol, 3.0 equiv.) followed by *ortho*-anisidine (630 mg, 4.4 mmol, 4.0 equiv.) were added. The resulting reaction mixture was stirred under reflux for 3 days before it was cooled down to room temperature. The solvent was removed under reduced pressure and the crude purified by FC (Alox, 100% EtOAc) to afford the title compound **4.4** (194 mg, 0.42 mmol, 38%) as a yellow sticky oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.18 – 7.12 (m, 2H), 7.11 – 7.04 (m, 2H), 6.82 – 6.75 (m, 2H), 6.73 – 6.67 (m, 2H), 3.93 (t, *J* = 10.8 Hz, 2H), 3.58 (s, 6H), 3.56 – 3.40 (m, 4H), 0.80 (s, 18H).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 154.7, 154.0, 130.2, 127.4, 126.4, 120.1, 110.6, 75.3, 55.0, 52.7, 34.1, 26.2.

### (4S,4'S)-4,4'-di-tert-butyl-1,1'-di(naphthalen-1-yl)-4,4',5,5'-tetrahydro-1H,1'H-2,2'-biimidazole (4.5)



Chemical Formula: C<sub>34</sub>H<sub>38</sub>N<sub>4</sub>  
Molecular Weight: 502.71

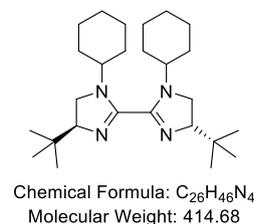
PCl<sub>5</sub> (3.07 g, 14.8 mmol, 2.4 equiv.) was added to a solution of **4.2** (3.07 g, 14.8 mmol, 1.0 equiv.) in dry toluene (50 mL) under Ar and the resulting mixture stirred at 85 °C for 18 h before the solvent was removed under reduced pressure. The crude was engaged in the next step without further purification. The crude imidoyl chloride (400 mg, 1.1 mmol, 1.0 equiv.) was dissolved in dry acetonitrile (8.2 mL) and Et<sub>3</sub>N (0.47 mL, 3.3 mmol, 3.0 equiv.) followed by *ortho*-1-naphthylamine (0.50 mL, 4.4 mmol, 4.0 equiv.) were added. The resulting reaction mixture was stirred under reflux for 2 days before it was cooled down to room temperature. The solvent was removed under reduced pressure and the crude purified by FC (Alox, 10-30% EtOAc in *c*Hex) to afford the title compound **4.5** (200 mg, 0.39 mmol, 36%) as an orange sticky oil. The product occurred as a mixture of rotamers.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.67 – 7.55 (m, 1H), 7.55 – 7.40 (m, 2H), 7.40 – 7.30 (m, 1H), 7.04 – 6.89 (m, 1H), 6.58 – 6.41 (m, 1H), 6.25 – 6.03 (m, 1H), 4.34 – 4.17 (m, 1H), 3.80 – 3.64 (m, 1H), 3.30 – 3.08 (m, 1H), 1.02 (s, 9H).

## Experimental Part

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  156.7, 138.7, 134.1, 129.6, 127.3, 126.7, 125.5, 125.3, 122.3, 122.1, 55.1, 34.7, 30.1, 26.6.

### (4*S*,4'*S*)-4,4'-di-tert-butyl-1,1'-dicyclohexyl-4,4',5,5'-tetrahydro-1*H*,1'*H*-2,2'-biimidazole (4.6)

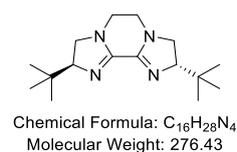


$\text{PCl}_5$  (1.65 g, 7.9 mmol, 2.4 equiv.) was added to a solution of **4.2** (1.07 g, 3.3 mmol, 1.0 equiv.) in dry toluene (47 mL) under Ar and the resulting mixture stirred at 85 °C for 18 h before the solvent was removed under reduced pressure. The crude imidoyl chloride was dissolved in dry acetonitrile (25 mL) and  $\text{Et}_3\text{N}$  (1.4 mL, 9.9 mmol, 3.0 equiv.) followed by cyclohexylamine (2.2 mL, 19.8 mmol, 6.0 equiv.) were added. The resulting reaction mixture was stirred under reflux for 2 days before it was cooled down to room temperature. The solvent was removed under reduced pressure and the crude purified by FC (Alox, 10-100% EtOAc in cHex) to afford the title compound **4.6** (594 mg, 1.43 mmol, 43%) as an orange sticky oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.88 – 3.71 (m, 2H), 3.34 (dd,  $J = 11.8, 9.3$  Hz, 1H), 3.15 (t,  $J = 9.6$  Hz, 1H), 2.04 – 1.92 (m, 1H), 1.82 – 1.69 (m, 2H), 1.64 – 1.54 (m, 1H), 1.52 – 1.29 (m, 3H), 1.28 – 1.12 (m, 2H), 1.06 (tt,  $J = 12.9, 3.5$  Hz, 1H), 0.91 (s, 9H).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  156.4, 74.3, 54.1, 44.7, 34.7, 31.6, 31.1, 26.3, 25.9, 25.9, 25.6.

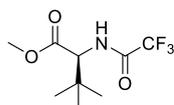
### (2*S*,9*S*)-2,9-di-tert-butyl-2,3,5,6,8,9-hexahydrodiimidazo[1,2-*a*:2',1'-*c*]pyrazine (4.7)



$\text{PCl}_5$  (3.07 g, 14.8 mmol, 2.4 equiv.) was added to a solution of **4.2** (3.07 g, 14.8 mmol, 1.0 equiv.) in dry toluene (50 mL) under Ar and the resulting mixture stirred at 85 °C for 18 h before the solvent was removed under reduced pressure. The crude was engaged in the next step without further purification. The crude imidoyl chloride (400 mg, 1.1 mmol, 1.0 equiv.) was dissolved in dry acetonitrile (8.2 mL) and  $\text{Et}_3\text{N}$  (0.47 mL, 3.3 mmol, 3.0 equiv.) followed by ethylenediamine (0.22 mL, 3.3 mmol, 3.0 equiv.) were added. The resulting reaction mixture was stirred under reflux for 4.5 h before it was cooled down to room temperature. The solvent was removed under reduced pressure and the crude purified by FC (Alox, EtOAc/cHex) to afford the title compound **4.7** (196 mg, 0.71 mmol, 65%) as an off white solid.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.87 – 3.78 (m, 2H), 3.43 (dd,  $J = 9.9, 9.1$  Hz, 2H), 3.28 – 3.13 (m, 4H), 2.90 (dd,  $J = 12.5, 9.1$  Hz, 2H), 0.96 (s, 9H).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  154.5, 75.7, 53.1, 45.8, 33.6, 26.7.

**Methyl *N*-TFA *L*-*tert*-leucinate (4.15)**

Chemical Formula: C<sub>9</sub>H<sub>14</sub>F<sub>3</sub>NO<sub>3</sub>  
Molecular Weight: 241.21

Et<sub>3</sub>N (3.8 mL, 27.7 mmol, 3.0 equiv.) was added under Ar to a solution of (*L*)-*tert*-leucine methyl ester hydrochloride (1.68 g, 9.23 mmol, 1.0 equiv.) in dry DCM (20 mL) and the reaction mixture was cooled down to  $-78$  °C. Trifluoroacetic anhydride (1.3 mL, 9.23 mmol, 1.0 equiv.) was added dropwise and the solution was stirred at  $-78$  °C for 3 h. The reaction was quenched with sat. NaHCO<sub>3</sub> at  $-78$  °C and was allowed to warm to room temperature. The aqueous phase was extracted three times with DCM, the combined organic phase was washed with water, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure affording the crude *N*-TFA *L*-*tert*-leucine **4.15** (2.23 g, 9.23 mmol, quant.) as a yellow oil.

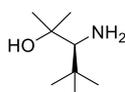
<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 6.81 (d, *J* = 9.0 Hz, 1H), 4.49 (d, *J* = 9.5 Hz, 1H), 3.78 (s, 3H), 1.00 (s, 9H).

<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 170.7, 157.0 (q, <sup>2</sup>*J*<sub>CF</sub> = 37.5 Hz), 115.9 (q, <sup>1</sup>*J*<sub>CF</sub> = 287.9 Hz), 60.5, 52.5, 35.5, 26.5.

<sup>19</sup>F {<sup>1</sup>H} NMR (471 MHz, CDCl<sub>3</sub>) δ  $-75.8$ .

R<sub>f</sub> = 0.69 (DCM)

[α]<sub>D</sub><sup>20</sup>: +27.3 (c 1.00, CHCl<sub>3</sub>)

**(*S*)-3-amino-2,4,4-trimethylpentan-2-ol (4.12)**

Chemical Formula: C<sub>8</sub>H<sub>19</sub>NO  
Molecular Weight: 145.25

Methyl magnesium chloride (3.0 M in THF, 21 mL, 62 mmol, 5.0 equiv.) was added dropwise at  $-78$  °C under Ar to a solution of *N*-TFA *L*-*tert*-leucine **4.15** (3.00 g, 12.4 mmol, 1.0 equiv.) in dry THF (50 mL). The reaction mixture was allowed to warm to room temperature overnight. The reaction was carefully quenched with sat. NH<sub>4</sub>Cl and then water was added to dissolve the formed salt. The aqueous phase was extracted with Et<sub>2</sub>O, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and the solvent removed under reduced pressure. The crude product was dissolved in a solution of aqueous LiOH (2.0 M, 30 mL, 5.0 equiv.), MeOH (30 mL) and THF (30 mL) and then stirred at room temperature overnight. The organic solvents were removed under reduced pressure and the aqueous phase was extracted with DCM three times. The combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub> and the solvent was removed under reduced pressure affording (*S*)-3-amino-2,4,4-trimethylpentan-2-ol **4.12** (1.62 g, 11.2 mmol, 90%) as a yellow oil. The analytical data are in agreement with the reported analysis.<sup>[8]</sup>

## Experimental Part

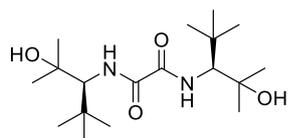
$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  2.34 (s, 1H), 1.30 (s, 3H), 1.13 (s, 3H), 1.00 (s, 9H).

$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  72.4, 68.5, 35.1, 30.1, 28.9, 25.9.

R<sub>f</sub>: 0.05 (MeOH/DCM 10:90)

$[\alpha]_{\text{D}}^{20}$ : +19.5 (c 1.00,  $\text{CHCl}_3$ )

### (*S*)-*N,N'*-Bis[2-hydroxy-2,4,4-trimethylpentan-3-yl]oxalamide (**4.11**)



$\text{C}_{18}\text{H}_{36}\text{N}_2\text{O}_4$   
M = 344,50 g·mol<sup>-1</sup>

Triethylamine (3.8 mL, 27.5 mmol, 4.0 equiv.) was added to a solution of (*S*)-3-amino-2,4,4-trimethylpentan-2-ol **4.12** (2.00 g, 13.8 mmol, 2.0 equiv.) in dry THF (100 mL) under Ar and the resulting reaction mixture cooled down to 0 °C. A solution of oxalyl chloride (0.65 mL, 6.88 mmol, 1.0 equiv.) in dry THF (50 mL) was added dropwise to the mixture, which was stirred at this temperature for 3 h. The triethylamine salt in the solution was then filtered off and the solvent removed under reduced pressure. The resulting solid was washed with hexane and diethyl ether to afford (*S*)-*N,N'*-bis[2-hydroxy-2,4,4-trimethylpentan-3-yl]oxalamide **4.11** (1.61 g, 4.67 mmol, 68%) as a white powder.

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.86 (d, J = 11.0 Hz, 2H), 3.66 (d, J = 11.0 Hz, 2H), 1.81 (s, 2H), 1.39 (s, 6H), 1.26 (s, 6H), 1.07 (s, 18H).

$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  160.1, 74.7, 64.6, 36.1, 30.4, 29.7, 28.9.

IR (neat):  $\nu$  (cm<sup>-1</sup>) 3371, 2972, 2605, 1666, 1504, 1377, 1159.

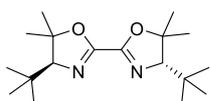
HRMS (ESI): Calcd for  $\text{C}_{18}\text{H}_{36}\text{N}_2\text{O}_4$  [M+Na]<sup>+</sup>: 367.2567 found: 367.2568.

R<sub>f</sub>: 0.20 (MeOH/DCM 5:95)

Sublimation Point: 192 °C

$[\alpha]_{\text{D}}^{20}$ : -36.3 (c 1.00,  $\text{CHCl}_3$ )

### (4*S*,4'*S*)-4,4'-di-*tert*-butyl-5,5,5',5'-tetramethyl-4,4',5,5'-tetrahydro-2,2'-bioxazole (**4.10**)



Chemical Formula:  $\text{C}_{18}\text{H}_{32}\text{N}_2\text{O}_2$   
Molecular Weight: 308.47

A solution of trimethylsilyl trifluoromethanesulfonate (1.05 mL, 5.8 mmol, 2.0 equiv.) in dry DCM (43 mL) was added dropwise under Ar to a solution of (*S*)-*N,N'*-bis[2-hydroxy-2,4,4-trimethylpentan-3-yl]oxalamide **4.11** (1.00 g, 2.9 mmol, 1.0 equiv.) in dry DCM (140 mL) and the resulting reaction mixture was stirred at room temperature for 18 h. The reaction was quenched with sat.  $\text{NaHCO}_3$  and the aqueous phase extracted with DCM three times, the

## Experimental Part

combined organic phases were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude was purified by FC (EtOAc/cHex 10:90, R<sub>f</sub>: 0.31) affording (4*S*,4'*S*)-4,4'-di-*tert*-butyl-5,5,5',5'-tetramethyl-4,4',5,5'-tetrahydro-2,2'-bioxazole **4.10** (480 mg, 1.56 mmol, 54%) as a white powder.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 3.56 (s, 2H), 1.52 (s, 6H), 1.50 (s, 6H), 1.09 (s, 18H).

<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): δ 154.0, 89.2, 83.3, 34.1, 30.7, 27.9, 23.2.

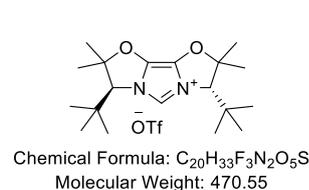
IR (neat): ν (cm<sup>-1</sup>) 2961, 2358, 1615, 1365, 1197, 1093.

HRMS (ESI): Calcd for C<sub>18</sub>H<sub>32</sub>N<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup>: 309.2537 found: 309.2541.

mp: 174 °C

[α]<sub>D</sub><sup>20</sup>: -40.2 (c 1.00, CHCl<sub>3</sub>)

### (3*S*,7*S*)-3,7-di-*tert*-butyl-2,2,8,8-tetramethyl-2,3,7,8-tetrahydroimidazo[4,3-*b*:5,1-*b'*]bis(oxazole)-4-ium triflate (IBioxtBuMe<sub>4</sub> HOTf) (**4.9**)



Chloromethyl pivalate (48 μL, 329 μmol, 1.45 equiv.) was added under Ar to a suspension of AgTOF (84.6 mg, 329 μmol, 1.45 equiv.) in dry DCM (750 μL) and the reaction mixture was stirred in the dark for 1 h. The supernatant was then added under Ar to (4*S*,4'*S*)-4,4'-di-*tert*-butyl-5,5,5',5'-tetramethyl-4,4',5,5'-tetrahydro-2,2'-bioxazole **4.10** (70 mg, 227 μmol, 1.0 equiv.) and the mixture was refluxed for 18 h. After the solution was cooled down to room temperature, the reaction was quenched with methanol and the solvent removed under reduced pressure. The crude was purified by FC (MeOH/DCM 3:97, R<sub>f</sub>: 0.27) affording IBioxtBu<sub>2</sub>Me<sub>4</sub> HOTf **4.9** (70 mg, 149 μmol, 66%) as a yellow solid.

**Important:** Since purification on silica led to decomposition the crude was purified later by recrystallization from a mixture of DCM and nHex at -25 °C. If the crude is clean enough, the crude was dissolved in Et<sub>2</sub>O and sonicated until the product precipitated. The solvent was removed and the solid dried under HV.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.77 (s, 1H), 4.42 (s, 2H), 1.78 (s, 6H), 1.56 (s, 6H), 1.17 (s, 18H).

<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): 125.0, 119.5, 99.6, 76.1, 34.6, 29.4, 27.1, 23.7.

<sup>19</sup>F {<sup>1</sup>H} NMR (471 MHz, CDCl<sub>3</sub>) δ - 78.25.

## Experimental Part

**IR** (neat):  $\nu$  (cm<sup>-1</sup>) 3124, 2979, 2360, 1737, 1511, 1258, 1168, 1030.

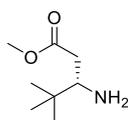
**HRMS** (ESI): Calcd for C<sub>19</sub>H<sub>33</sub>N<sub>2</sub>O<sub>2</sub><sup>+</sup> [M]<sup>+</sup>: 321.2537 found: 321.2542.

**mp**: 136 °C

**[ $\alpha$ ]<sub>D</sub><sup>20</sup>**: + 48.1 (c 0.66, CHCl<sub>3</sub>)

### **methyl (S)-3-amino-4,4-dimethylpentanoate (4.31)**

Following a modified procedure.<sup>[9]</sup>



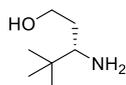
Chemical Formula: C<sub>8</sub>H<sub>17</sub>NO<sub>2</sub>  
Molecular Weight: 159.23

TfOH (6.9 mL, 78 mmol, 3.0 equiv.) was added at 0 °C to a solution of **4.30**<sup>[9]</sup> (6.89 g, 26 mmol 1 equiv.) in dry DCM (260 mL) under Ar. The reaction was allowed to warm to room temperature and was stirred at this temperature for 18 h. H<sub>2</sub>O (10 mL) was added and the solvent completely removed under reduced pressure. The dry crude was re-dissolved in MeOH (260 mL) and the solution cooled down to 0 °C. SOCl<sub>2</sub> (11.3 mL, 156 mmol, 6 equiv.) was added dropwise under Ar. The reaction mixture was allowed to slowly warm to ambient temperature and was further stirred at the same temperature for 18 h. The MeOH was evaporated under reduced pressure and the residue taken up in H<sub>2</sub>O and the organic impurities were removed by extraction with Et<sub>2</sub>O. Sat. K<sub>2</sub>CO<sub>3</sub> solution was then added to the aqueous phase until pH = 12 was reached. This basic aqueous phase was then extracted five times with Et<sub>2</sub>O. The combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to afford the title compound **4.31** (2.76 g, 17.3 mmol, 66%) as a yellow oil. The compound was directly engaged in the next reaction without further purification. Analytical data in agreement with the literature.<sup>[9]</sup>

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>)  $\delta$  3.69 (s, 3H), 2.92 (dd, *J* = 10.9, 2.6 Hz, 1H), 2.55 (dd, *J* = 15.3, 2.6 Hz, 1H), 2.12 (dd, *J* = 15.3, 10.9 Hz, 1H), 0.89 (s, 9H).

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>)  $\delta$  174.2, 57.4, 51.8, 37.8, 34.2, 26.1.

### **(S)-3-amino-4,4-dimethylpentan-1-ol (4.53)**



Chemical Formula: C<sub>7</sub>H<sub>17</sub>NO  
Molecular Weight: 131.22

A solution of ester **4.31** (807 mg, 5.1 mmol, 1 equiv.) in dry THF (1 mL) was added dropwise to a suspension of LiAlH<sub>4</sub> (385 mg, 10.1 mmol, 1 equiv.) in dry THF (20 mL) at 0 °C under Ar. The resulting reaction mixture was allowed to warm to room temperature and was stirred for 3 h. The reaction mixture was cooled down to 0 °C and carefully diluted with Et<sub>2</sub>O. H<sub>2</sub>O (0.4

## Experimental Part

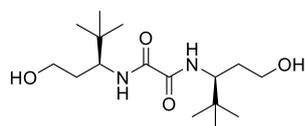
mL) was carefully added followed by aq. KOH (20 wt%, 0.4 mL) and again H<sub>2</sub>O (1.2 mL). The resulting mixture was stirred at room temperature for 18 h before it was filtered over *Celite* and eluted with Et<sub>2</sub>O. The organic solvent was evaporated under reduced pressure to afford the title compound **4.53** (688 mg, 5.1 mmol, quant.) as a colorless oil. <sup>13</sup>C NMR in agreement with the literature.<sup>[10]</sup>

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 3.88 – 3.75 (m, 2H), 2.51 (dd, *J* = 11.3, 2.1 Hz, 1H), 1.72 – 1.62 (m, 1H), 1.41 – 1.31 (m, 1H), 0.86 (s, 9H).

<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 64.2, 63.3, 34.8, 31.9, 25.9.

[α]<sub>D</sub><sup>20</sup>: -6.8 (c 0.79, CHCl<sub>3</sub>)

### *N*<sup>1</sup>,*N*<sup>2</sup>-bis((*S*)-1-hydroxy-4,4-dimethylpentan-3-yl)oxalamide (**4.20**)



Chemical Formula: C<sub>16</sub>H<sub>32</sub>N<sub>2</sub>O<sub>4</sub>  
Molecular Weight: 316.44

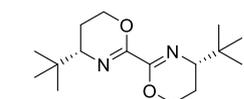
Dimethyl oxalate (0.23 mL, 1.7 mmol 1 equiv.) was added under Ar to a solution of **4.53** (435 mg, 3.3 mmol, 2.0 equiv.) in dry toluene (33 mL). The resulting reaction mixture was stirred at 100 °C for 48 h. After allowing to cool down to room temperature, the solvent was removed under reduced pressure and the crude purified by FC (MeOH/DCM 5:95, R<sub>f</sub>: 0.15) to afford the title compound **4.20** (410 mg, 1.3 mmol, 78%) as a colorless crystalline solid.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.41 (d, *J* = 10.6 Hz, 2H), 3.86 – 3.77 (m, 2H), 3.67 (ddd, *J* = 11.8, 5.7, 3.3 Hz, 2H), 3.51 – 3.38 (m, 2H), 2.08 – 1.96 (m, 2H), 1.50 – 1.34 (m, 2H), 0.98 (s, 18H).

<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 160.4, 59.3, 55.5, 33.9, 32.5, 26.6.

[α]<sub>D</sub><sup>20</sup>: -24.4 (c 1.07, CHCl<sub>3</sub>)

### (4*S*,4'*S*)-4,4'-di-*tert*-butyl-5,5',6,6'-tetrahydro-4*H*,4'*H*-2,2'-bi(1,3-oxazine) (**4.19**)



Chemical Formula: C<sub>16</sub>H<sub>28</sub>N<sub>2</sub>O<sub>2</sub>  
Molecular Weight: 280.41

SOCl<sub>2</sub> (0.26 mL, 2.9 mmol, 2.9 equiv.) was added dropwise to a solution of **4.20** (390 mg, 1.2 mmol, 1 equiv.) in dry toluene (12.4 mL) under Ar. The resulting reaction mixture was stirred at 60 °C for 45 min before it was heated to 90 °C for additional 3.5 h. The reaction mixture was then cooled down to room temperature and all volatiles were removed under reduced pressure. The obtained crude was directly dissolved in dry THF (24.2 mL) and treated with NaOH (103 mg, 2.6 mmol, 2.1 equiv. in 5.5 mL EtOH). The resulting mixture was stirred under reflux for 18 h. After cooling to room temperature, the solvents were removed under

## Experimental Part

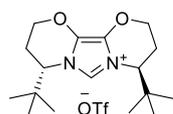
reduced pressure. The resulting crude was re-dissolved in Et<sub>2</sub>O and washed with aqueous Na<sub>2</sub>CO<sub>3</sub> (10 wt%). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to afford the title compound **4.19** (345 mg, 1.2 mmol, quant.) as an orange solid.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 4.36 (ddd, *J* = 10.9, 4.6, 2.3 Hz, 1H), 4.14 (ddd, *J* = 12.3, 10.8, 2.8 Hz, 1H), 3.14 (dd, *J* = 11.0, 5.0 Hz, 1H), 1.91 – 1.81 (m, 1H), 1.80 – 1.67 (m, 1H), 0.96 (s, 9H).

<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 149.7, 65.4, 61.1, 34.5, 26.4, 22.8.

[α]<sub>D</sub><sup>20</sup>: -43.1 (c 0.79, CHCl<sub>3</sub>)

### (4*S*,8*S*)-4,8-di-tert-butyl-3,4,9,10-tetrahydro-2*H*,8*H*-imidazo[4,3-*b*:5,1-*b'*]bis([1,3]oxazine)-5-ium trifluoromethanesulfonate (IBiox6*t*Bu HOTf) (**4.18**)



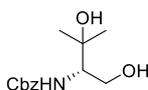
Chemical Formula: C<sub>18</sub>H<sub>29</sub>F<sub>3</sub>N<sub>2</sub>O<sub>5</sub>S  
Molecular Weight: 442.49

Chloromethyl pivalate (74 μL, 0.51 mmol, 1.45 equiv.) was added to a suspension of AgOTf (132 mg, 0.51 mmol, 1.45 equiv.) in dry DCM (1.2 mL) under Ar and the reaction mixture was stirred in the dark for 1 h. The supernatant was then added to **4.19** (100 mg, 0.035 mmol, 1.0 equiv.) under Ar and the mixture refluxed for 18 h. After the solution was cooled down to room temperature and the solvent removed under reduced pressure. The residue was dissolved in a minimal amount of DCM and precipitated with hexane. All solvent was removed under reduced pressure. CHCl<sub>3</sub> was added and the precipitate was filtered off. All solvent was evaporated to afford the title compound **4.18** (35 mg, 0.085 mmol, 23%) as a brown sticky oil in ca. 80-90% purity.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.24 (s, 1H), 4.59 – 4.52 (m, 2H), 4.52 – 4.43 (m, 2H), 4.34 – 4.26 (m, 2H), 2.45 – 2.30 (m, 4H), 1.10 (s, 18H).

<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ -78.39.

### benzyl (*S*)-(1,3-dihydroxy-3-methylbutan-2-yl)carbamate (**4.41**)

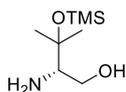


Chemical Formula: C<sub>13</sub>H<sub>19</sub>NO<sub>4</sub>  
Molecular Weight: 253.30

Synthesized according to literature.<sup>[11]</sup>

### (*S*)-2-amino-3-methyl-3-((trimethylsilyl)oxy)butan-1-ol (**4.44**)

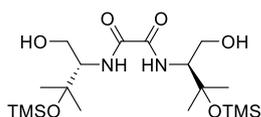
## Experimental Part



Chemical Formula:  $C_8H_{21}NO_2Si$   
Molecular Weight: 191.35

Synthesized according to literature.<sup>[11]</sup>

### *N,N'*-bis((*S*)-1-hydroxy-3-methyl-3-(trimethylsilyloxy)butan-2-yl)oxalamide (**4.45**)

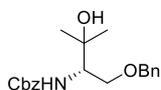


Chemical Formula:  $C_{18}H_{40}N_2O_6Si_2$   
Molecular Weight: 436.70

A mixture of **4.44** (251 mg, 1.31 mmol, 2 equiv.) and ethyl oxalate (0.09 mL, 0.66 mmol, 1 equiv.) in dry DCM (6.6 mL) was refluxed for 18 h under Ar. After cooling to room temperature and  $Et_3N$  (0.2 mL, 1.44 mmol, 2.2 equiv.) was added and the reaction mixture washed with sat. aqueous  $NaHCO_3$ . The organic phase was dried over  $Na_2SO_4$ , filtered and concentrated under reduced pressure. The crude was purified by FC (acetone/pentane 20:80 + 5%  $Et_3N$ ) to afford the title compound **4.45** (85 mg, 0.20 mmol, 30%) was a yellow oil.

$^1H$  NMR (250 MHz,  $CDCl_3$ )  $\delta$  8.00 (d,  $J = 9.0$  Hz, 1H), 3.96 (d,  $J = 7.5$  Hz, 1H), 3.88 – 3.64 (m, 2H), 3.02 (d,  $J = 8.4$  Hz, 1H), 1.39 (s, 3H), 1.30 (s, 3H), 0.18 (s, 9H).

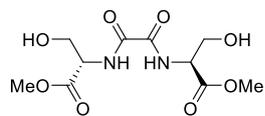
### benzyl (*S*)-(1-(benzyloxy)-3-hydroxy-3-methylbutan-2-yl)carbamate (**4.47**)



Chemical Formula:  $C_{20}H_{25}NO_4$   
Molecular Weight: 343.42

Following a reported procedure.<sup>[12]</sup>  $Ag_2O$  (155 mg, 0.67 mmol, 0.8 equiv.) was added to a well stirred solution of **4.41** and benzyl bromide (0.11 mL, 0.88 mmol, 1.05 equiv.) in DMF (0.7 mL) under Ar in the dark (flask wrapped in Al-foil). The reaction mixture was stirred at room temperature for 18 h before the precipitate was filtered off. The filtrate was diluted with  $CHCl_3$  and the solution was stored in the fridge for 12 h and filtered again. Pyridine (0.2 mL) was added and the solution was washed successively with  $H_2O$ , aqueous HCl (20 wt%),  $H_2O$ , sat. aqueous  $NaHCO_3$  and brine. The organic layer was dried over  $Na_2SO_4$ , filtered and concentrated under reduced pressure. The crude was purified by FC (EtOAc/cHex 25:75) to afford the title compound **4.47** (109 mg, 0.33 mmol, 39%) as a colorless oil.

$^1H$  NMR (250 MHz,  $CDCl_3$ )  $\delta$  7.41 – 7.27 (m, 10H), 5.64 (d,  $J = 9.1$  Hz, 1H), 5.12 (s, 2H), 4.70 (d,  $J = 5.3$  Hz, 1H), 4.60 – 4.38 (m, 2H), 3.90 (dd,  $J = 9.9, 2.8$  Hz, 1H), 3.64 (ddd,  $J = 17.8, 9.5, 2.6$  Hz, 2H), 3.15 (s, 1H), 1.29 (s, 3H), 1.19 (s, 3H).

**(S)-N,N'-Bis(2-hydroxy-1-methoxycarbonyl)ethyl)oxamide (4.49)**

Chemical Formula: C<sub>10</sub>H<sub>16</sub>N<sub>2</sub>O<sub>8</sub>  
Molecular Weight: 292.24

A suspension of *L*-Serine methyl ester hydrochloride (10.0 g, 64.4 mmol, 2.0 equiv.) and triethylamine (18.0 mL, 129 mmol, 4.0 equiv.) in dry DCM (210 mL) was cooled in an ice-bath under Ar. Oxalyl chloride (3.0 mL, 32.2 mmol, 1.0 equiv.) in dry DCM (40 mL) was added dropwise to the reaction mixture, which was allowed to warm up to room temperature and stirred for 2 h. The white solid was filtered off and the solvent removed under reduced pressure. To the obtained white solid was added THF (200 mL) and the mixture was cooled to 0 °C for 1 h. The undissolved salt was filtered off and the solution dried under reduced pressure obtaining **4.49** (7.13 g, 24.4 mmol, 76%) as a white solid.

<sup>1</sup>H NMR (500 MHz, DMSO) δ 8.72 (d, *J* = 8.1 Hz, 1H), 5.19 (dd, *J* = 6.9, 5.4 Hz, 1H), 4.46 – 4.38 (m, 1H), 3.85 – 3.78 (m, 1H), 3.78 – 3.71 (m, 1H), 3.67 (s, 3H).

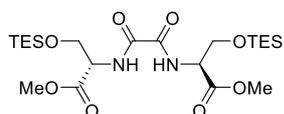
<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) 170.0, 159.4, 60.7, 55.1, 52.2.

IR (neat): ν (cm<sup>-1</sup>) 3281, 2956, 1733, 1658, 1513, 1437, 1217, 1065.

HRMS (ESI): Calcd for C<sub>10</sub>H<sub>16</sub>N<sub>2</sub>O<sub>8</sub>Na [M+Na]<sup>+</sup>: 315.0799 found: 315.0797.

mp: 125 °C

[α]<sub>D</sub><sup>20</sup>: – 8.6 (*c* 1.0, MeOH)

**methyl N-(2-(((S)-1-methoxy-1-oxo-3-((triethylsilyl)oxy)propan-2-yl)amino)-2-oxoacetyl)-O-(triethylsilyl)-L-serinate (4.50)**

Chemical Formula: C<sub>22</sub>H<sub>44</sub>N<sub>2</sub>O<sub>8</sub>Si<sub>2</sub>  
Molecular Weight: 520.77

Chlorotriethylsilane (8.6 mL, 51.3 mmol, 3.0 equiv.) was added dropwise to a solution of **4.49** (5.00 g, 17.1 mmol, 1.0 equiv.) and imidazole (5.82 g, 85.5 mmol, 5.0 equiv.) in dry DMF (34 mL) at 0 °C under Ar. The reaction mixture was allowed to warm to room temperature and was stirred for 1 h. The mixture was then diluted with Et<sub>2</sub>O (40 mL) and washed with aqueous citric acid (10 wt%) first and half brine afterwards. The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced. The crude was purified by FC (EtOAc/cHex, 20:80, R<sub>f</sub> = 0.32) to afford the title compound **4.50** (8.36 g, 16.1 mmol, 94%) as a faint yellow oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 8.09 (d, *J* = 8.78 Hz, 2 H), 4.64 – 4.61 (m, 2 H), 4.14 – 4.61 (m, 2 H), 3.87 – 3.84 (m, 2 H), 3.76 (s, 6 H), 0.97 – 0.91 (m, 18 H), 0.60 – 0.56 (m, 12 H).

## Experimental Part

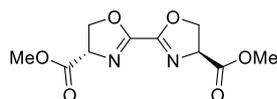
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ) 169.8, 159.1, 63.1, 54.7, 52.7, 6.7, 4.3.

IR (neat):  $\nu$  ( $\text{cm}^{-1}$ ) 3402, 2955, 2878, 1750, 1682, 1502, 1240, 1240, 1108, 1013.

HRMS (ESI): Calcd for  $\text{C}_{22}\text{H}_{44}\text{N}_2\text{O}_8\text{Si}_2\text{Na}$   $[\text{M}+\text{Na}]^+$ : 543.2528 found: 543.2532.

$[\alpha]_{\text{D}}^{20}$ : +22.4 ( $c$  1.0,  $\text{CHCl}_3$ )

### dimethyl (4*S*,4'*S*)-4,4',5,5'-tetrahydro-[2,2'-bioxazole]-4,4'-dicarboxylate (4.48)



Chemical Formula:  $\text{C}_{10}\text{H}_{12}\text{N}_2\text{O}_6$   
Molecular Weight: 256.21

DAST (2.50 mL, 19.2 mmol, 2.0 equiv.) was added dropwise to a solution of **4.50** (5.0 g, 4.9 mL, 9.6 mmol, 1.0 equiv.) in DCM (100 mL, 0.1 M) at  $-78$  °C under Ar. The reaction mixture was then allowed to warm to room temperature overnight and quenched with sat.  $\text{NaHCO}_3$  in MeOH. The solvent was removed under reduced pressure and the crude was purified by FC (MeOH/DCM 2:98,  $R_f$ : 0.21) to afford the title compound **4.48** (1.43 g, 5.58 mmol, 58%) as a white solid.

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) 4.98 – 4.94 (m, 2 H), 4.75 – 4.71 (m, 2 H), 4.64 – 4.60 (m, 2 H), 3.80 (s, 3H).

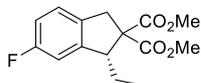
$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ) 170.2, 156.9, 70.7, 68.8, 53.1.

IR (neat):  $\nu$  ( $\text{cm}^{-1}$ ) 2956, 2361, 1735, 1609, 1434, 1340, 1206, 1147.

HRMS (ESI): Calcd for  $\text{C}_{10}\text{H}_{12}\text{N}_2\text{O}_6\text{Na}$   $[\text{M}+\text{Na}]^+$ : 279.0588 found: 279.0592.

$[\alpha]_{\text{D}}^{20}$ :  $-118.9^\circ$  ( $c$  1.0  $\text{CHCl}_3$ )

### dimethyl (*R*)-1-ethyl-6-fluoro-1,3-dihydro-2*H*-indene-2,2-dicarboxylate (4.17)



Chemical Formula:  $\text{C}_{15}\text{H}_{17}\text{FO}_4$   
Molecular Weight: 280.30

Aryl bromide **4.16** (36.1 mg, 0.1 mmol, 1 equiv.) was charged into a catalysis tube equipped with a magnetic stirring bar. The tube was introduced into the glovebox and was subsequently charged with powdered 5 Å MS (25 mg),  $\text{Cs}_2\text{CO}_3$  (32.6 mg, 0.1 mmol, 1 equiv.), CsOPiv (7.0 mg, 0.03 mmol, 30 mol%),  $[\text{Pd}(\pi\text{-allylCl})]_2$  (1.9 mg, 0.005 mmol, 5 mol%), and IBiox*t*BuMe<sub>4</sub>•HOTf (4.7 mg, 0.01 mmol, 10 mol%). The vial was closed with a rubber septum and taken out of the glovebox. Dry and degassed  $\text{CF}_3\text{Ph}$  (1 mL/0.1 mmol) was added into the tube under Ar and the tube capped with the corresponding stopper. The tube was inserted into a preheated catalysis block at 140 °C and was reacted under stirring for 18 h. Then, the reaction was cooled down to room temperature and diluted with EtOAc, filtered over a plug of *Celite*

## Experimental Part

and the solvent evaporated under reduced pressure. The crude was analyzed by GC-MS or  $^1\text{H}$  NMR (1 mL  $\text{CDCl}_3$ /0.1 mmol + 0.1 mmol trichloroethylene as internal standard) and purified by preparative HPLC chromatography (EtOAc/hexane) to yield dimethyl (*R*)-1-ethyl-6-fluoro-1,3-dihydro-2*H*-indene-2,2-dicarboxylate **4.17** (23 mg, 78  $\mu\text{mol}$ , 78%) as a white crystalline solid. The enantiomeric ratio was then determined by HPLC using a chiral stationary phase.

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.13 – 7.07 (m, 1H), 6.94 – 6.89 (m, 1H), 6.89 – 6.81 (m, 1H), 3.80 – 3.73 (m, 5H), 3.70 – 3.67 (m, 3H), 3.26 (dd,  $J = 16.1, 2.1$  Hz, 1H), 1.56 – 1.53 (m, 1H), 1.47 – 1.37 (m, 1H), 0.97 (td,  $J = 7.4, 2.1$  Hz, 3H).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  (ppm) 172.2, 170.3, 162.2 (d,  $J = 243.6$  Hz), 146.5 (d,  $J = 7.9$  Hz), 134.5 (d,  $J = 2.6$  Hz), 125.4 (d,  $J = 8.7$  Hz), 114.1 (d,  $J = 22.4$  Hz), 112.2 (d,  $J = 22.6$  Hz), 66.1, 53.1, 52.7, 51.5 (d,  $J = 2.1$  Hz), 38.3, 23.9, 11.7

$^{19}\text{F}$  NMR (471 MHz,  $\text{CDCl}_3$ )  $\delta$  -116.6.

IR (neat):  $\nu$  ( $\text{cm}^{-1}$ ) 2961, 2928, 1728, 1484, 1437, 1237, 1159, 875

HRMS (ESI): Calcd for  $\text{C}_{15}\text{H}_{17}\text{FNaO}_4$  [ $\text{M}+\text{Na}$ ] $^+$  : 303.1003, found 303.1004

HPLC separation: Chiralcel OD-H; 99.5:0.5 (*n*hexane/*i*PrOH), 0.5 mL/min, 215 nm,  $t_r$ (minor) = 420.2 min,  $t_r$ (major) = 23.1 min, 99.4:0.6 e.r.

R<sub>f</sub>: 0.26 (EtOAc/pent 5:95)

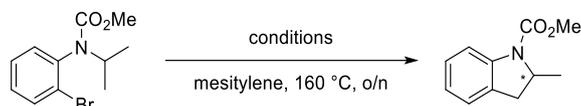
mp: 106 °C

$[\alpha]_{\text{D}}^{20}$ :  $-188.4^\circ$  ( $c = 1.16$ ,  $\text{CHCl}_3$ )

### 9.3 Design of Chiral NHC-Carboxylates as Potential Ligands for Pd-Catalyzed Enantioselective C–H Activation

#### 9.3.1 Reaction optimization

##### Pd-source screening and investigation of the influence of preformed Ag-NHC complex

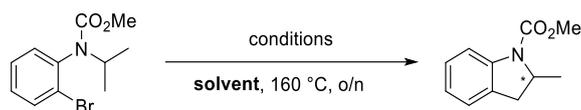


Pd source [0.1 eq [Pd]]	ligand	base [1.5 eq]	additive [0.1 eq]	[Ag] [0.1 eq]	NMR yield [%] <sup>a</sup>	e.r. <sup>b</sup>
[Pd( $\pi$ -cin)Cl] <sub>2</sub>	<b>IBioxMe<sub>4</sub></b>	Cs <sub>2</sub> CO <sub>3</sub>	CsOPiv [1 eq.]	-	65	-
[Pd( $\pi$ -cin)Cl] <sub>2</sub>	<b>IBiox<sup>t</sup>Bu</b>	Cs <sub>2</sub> CO <sub>3</sub>	CsOPiv [0.3 eq.]	-	46	10:90
[Pd( $\pi$ -cin)Cl] <sub>2</sub>	<b>L<sub>7</sub></b>	Cs <sub>2</sub> CO <sub>3</sub>	CsO <sup>t</sup> Bu	Ag <sub>2</sub> O	18	52:48
[Pd( $\pi$ -cin)Cl] <sub>2</sub>	<b>L<sub>7</sub></b>	K <sub>2</sub> CO <sub>3</sub>	KO <sup>t</sup> Bu	Ag <sub>2</sub> O	traces	n.d.
Pd <sub>2</sub> dba <sub>3</sub>	<b>L<sub>7</sub></b>	Cs <sub>2</sub> CO <sub>3</sub>	CsO <sup>t</sup> Bu	Ag <sub>2</sub> O	10	<b>36:64</b>
Pd <sub>2</sub> dba <sub>3</sub>	<b>L<sub>7</sub></b>	K <sub>2</sub> CO <sub>3</sub>	KO <sup>t</sup> Bu	Ag <sub>2</sub> O	0	n.d.
[Pd( $\pi$ -cin)Cl] <sub>2</sub>	<b>L<sub>7</sub></b>	Cs <sub>2</sub> CO <sub>3</sub>	CsO <sup>t</sup> Bu	Ag <sub>2</sub> O*	10	n.d.
Pd <sub>2</sub> dba <sub>3</sub>	<b>L<sub>7</sub></b>	Cs <sub>2</sub> CO <sub>3</sub>	CsO <sup>t</sup> Bu	Ag <sub>2</sub> O*	7	n.d.
Pd <sub>2</sub> dba <sub>3</sub>	<b>L<sub>7</sub></b>	Cs <sub>2</sub> CO <sub>3</sub>	-	Ag <sub>2</sub> O*	7	n.d.
<b>C<sup>4</sup></b>	-	K <sub>2</sub> CO <sub>3</sub>	KO <sup>t</sup> Bu	-	5	n.d.
<b>C<sup>4</sup></b>	-	Cs <sub>2</sub> CO <sub>3</sub>	CsO <sup>t</sup> Bu	-	20	45:55
<b>C<sup>4</sup></b>	-	K <sub>2</sub> CO <sub>3</sub>	KO <sup>i</sup> Pr	-	10	n.d.

<sup>a</sup> Trichloroethylene as internal standard, <sup>b</sup> Determined by HPLC on chiral stationary phase, \* No preformation of the NHC complex, all mixed and directly engaged.

## Experimental Part

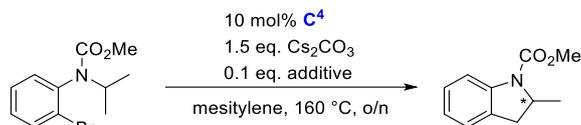
### Solvent effect

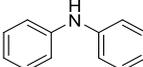


complex [0.1 eq]	base [1.5 eq]	additive [0.1 eq]	solvent [0.1 M]	temp [°C]	NMR yield [%] <sup>a</sup>	e.r. <sup>b</sup>	Comment
<b>C<sup>4</sup></b>	Cs <sub>2</sub> CO <sub>3</sub>	CsO <sup>t</sup> Bu	mesitylene	160	20	45:55	
<b>C<sup>4</sup></b>	Cs <sub>2</sub> CO <sub>3</sub>	CsO <sup>t</sup> Bu	mesitylene:DMSO 95:5	160	8	n.d.	
<b>C<sup>4</sup></b>	Cs <sub>2</sub> CO <sub>3</sub>	CsO <sup>t</sup> Bu	mesitylene:DMSO 90:10	160	7	n.d.	
<b>C<sup>4</sup></b>	Cs <sub>2</sub> CO <sub>3</sub>	CsO <sup>t</sup> Bu	mesitylene:DMSO 80:20	160	8	n.d.	
<b>C<sup>4</sup></b>	Cs <sub>2</sub> CO <sub>3</sub>	CsO <sup>t</sup> Bu	mesitylene:DMSO 60:40	160	5	n.d.	
<b>C<sup>4</sup></b>	Cs <sub>2</sub> CO <sub>3</sub>	CsO <sup>t</sup> Bu	DMSO	160	-	n.d.	decomposition
<b>C<sup>4</sup></b>	Cs <sub>2</sub> CO <sub>3</sub>	CsO <sup>t</sup> Bu	anisole	160	43	45:55	
<b>C<sup>4</sup></b>	Cs <sub>2</sub> CO <sub>3</sub>	CsO <sup>t</sup> Bu	DME	160	traces	n.d.	
<b>C<sup>4</sup></b>	Cs <sub>2</sub> CO <sub>3</sub>	CsO <sup>t</sup> Bu	dioxane	160	0	n.d.	
<b>C<sup>4</sup></b>	Cs <sub>2</sub> CO <sub>3</sub>	CsO <sup>t</sup> Bu	THF	140	18	43:57	
<b>C<sup>4</sup></b>	Cs <sub>2</sub> CO <sub>3</sub>	CsO <sup>t</sup> Bu	<i>n</i> Bu <sub>2</sub> O	160	10	42:58	
<b>C<sup>4</sup></b>	Cs <sub>2</sub> CO <sub>3</sub>	CsO <sup>t</sup> Bu	cumene	160	27	45:55	
<b>C<sup>4</sup></b>	Cs <sub>2</sub> CO <sub>3</sub>	CsO <sup>t</sup> Bu	trifluorotoluene	160	17	46:54	
<b>C<sup>4</sup></b>	Cs <sub>2</sub> CO <sub>3</sub>	CsO <sup>t</sup> Bu	xylenes	160	23	45:55	
<b>C<sup>4</sup></b>	Cs <sub>2</sub> CO <sub>3</sub>	CsO <sup>t</sup> Bu	benzotrifluoride	160	0	n.d.	
<b>C<sup>4</sup></b>	Cs <sub>2</sub> CO <sub>3</sub>	CsO <sup>t</sup> Bu	PhCl	160	36	47:53	
<b>C<sup>4</sup></b>	Cs <sub>2</sub> CO <sub>3</sub>	CsO <sup>t</sup> Bu	1,2-Cl <sub>2</sub> Ph	160	19	47:53	

<sup>a</sup> Trichloroethylene as internal standard. <sup>b</sup> Determined by HPLC on chiral stationary phase

### Additives for activation – screening

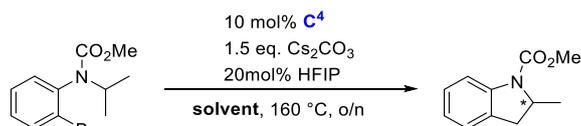


additive [10mol%]	NMR yield [%] <sup>a</sup>	e.r. <sup>b</sup>	comment
KO <sup>t</sup> Bu	5	n.d.	K <sub>2</sub> CO <sub>3</sub> as stoichiometric base
CsO <sup>t</sup> Bu	20	45:55	-
KO <sup>i</sup> Pr	10	n.d.	K <sub>2</sub> CO <sub>3</sub> as stoichiometric base
-	21	45:55	42% SM
HCO <sub>2</sub> Na	16	48:52	41% SM
N <sub>2</sub> H <sub>2</sub>	0	n.d.	66% SM
HFIP [0.2 eq]	20	22:78	56% SM
HFIP 5vol%	0	n.d.	61% SM
	32	48:52	
PhI	29	50:50	55% SM
	4	n.d.	58% SM

<sup>a</sup> Trichloroethylene as internal standard. <sup>b</sup> Determined by HPLC on chiral stationary phase.

## Experimental Part

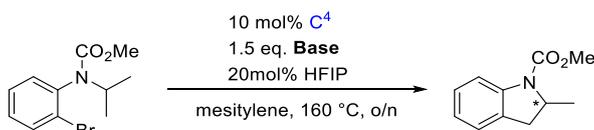
### Solvent screening with the best additives



solvent	temp	Additive	<sup>1</sup> H NMR yield <sup>a</sup>	e.r. <sup>b</sup>
mesitylene	160	HFIP [0.2 eq.]	20	<b>22:78</b>
anisole	160	HFIP [0.2 eq.]	24	31:69
THF	140	HFIP [0.2 eq.]	11	33:67
<i>n</i> Bu <sub>2</sub> O	160	HFIP [0.2 eq.]	21	24:76
cumene	160	HFIP [0.2 eq.]	30	49:51
2-MeTHF	160	HFIP [0.2 eq.]	12	24:76
CPME	160	HFIP [0.2 eq.]	32*	<b>22:78</b>
DME	160	HFIP [0.2 eq.]	0	-
PhCF <sub>3</sub>	160	HFIP [0.2 eq.]	24	40:60
xylenes	160	HFIP [0.2 eq.]	24	34:66
<i>o</i> -xylene	160	HFIP [0.2 eq.]	23	39:61
<i>m</i> -xylene	160	HFIP [0.2 eq.]	27	36:64
<i>p</i> -xylene	160	HFIP [0.2 eq.]	16	32:68
PhCl	160	HFIP [0.2 eq.]	24	35:65
1,2-Cl <sub>2</sub> Ph	160	HFIP [0.2 eq.]	traces	n.d.

<sup>a</sup> Trichloroethylene as internal standard. <sup>b</sup> Determined by HPLC on chiral stationary phase.  
\*Irreproducible yield.

### Base screening

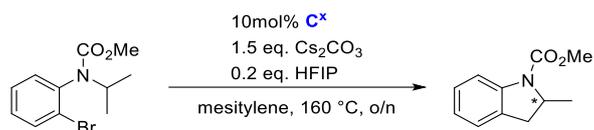


base	temp [° C]	<sup>1</sup> H NMR yield <sup>a</sup>	e.r. <sup>b</sup>
Cs <sub>2</sub> CO <sub>3</sub>	160	20	<b>22:78</b>
CsOAc	160	10	n.d.
Dibenzylphosphate	160	0	n.d.
K <sub>3</sub> PO <sub>4</sub>	160	traces	n.d.
K <sub>2</sub> CO <sub>3</sub>	160	12	<b>26:74</b>
Rb <sub>2</sub> CO <sub>3</sub>	160	12	40:60
Na <sub>2</sub> CO <sub>3</sub>	160	traces	n.d.
Guanidine Carbonate	160	0	n.d.

<sup>a</sup> Trichloroethylene as internal standard. <sup>b</sup> Determined by HPLC on chiral stationary phase.

## Experimental Part

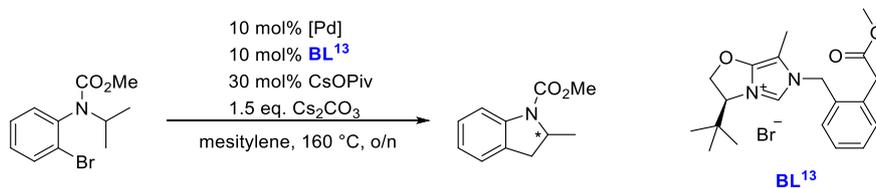
### Testing of the different Bifunctional Pd<sup>II</sup>-complexes



complex	solvent	temp [°C]	<sup>1</sup> H NMR yield [%] <sup>a</sup>	e.r. <sup>b</sup>
C <sup>1</sup>	Mesitylene	160	13	44:56
C <sup>2</sup>	Mesitylene	160	>5	n.d.
C <sup>3</sup>	Mesitylene	160	>5	n.d.
C <sup>4</sup>	Mesitylene	160	20	22:78
C <sup>1</sup>	Mesitylene	140	traces	n.d.
C <sup>4</sup>	Mesitylene	140	6	n.d.
C <sup>1</sup>	Mesitylene	120	0	n.d.
C <sup>4</sup>	Mesitylene	120	0	n.d.

<sup>a</sup> Trichloroethylene as internal standard. <sup>b</sup> Determined by HPLC on chiral stationary phase.

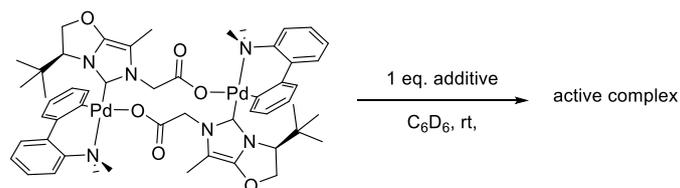
### Application of the corresponding iminium ester as Ligand



Pd-source	NMR yield [%] <sup>a</sup>	e.r. <sup>b</sup>
[Pd( $\pi$ -cinnamyl)Cl] <sub>2</sub>	6	n.d.
Pd <sub>2</sub> dba <sub>3</sub>	25	45:55

## Experimental Part

### NMR Experiments: Preactivation of the complexes



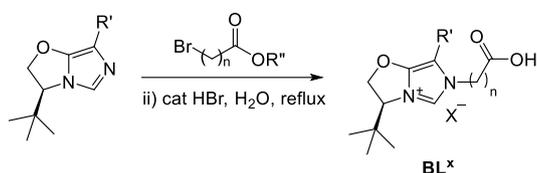
additive	time	temp. [°C]	Comment
N <sub>2</sub> H <sub>4</sub>	5 min	rt	1 M in THF
DIBAL-H	5 min	rt	1 M in toluene
LiHMDS	5 min	rt	1 M in THF, solvent evaporated then addition of C <sub>6</sub> D <sub>6</sub> and complex
HFIP	5 min	rt	A new adduct formed
<sup>t</sup> BuOK	5min, 1.5 h	rt	Nothing happened
<sup>t</sup> BuOK	5min, 1.5 h	70	Nothing happened
PhNHPPh	5 min	rt	Nothing happened
PhNHPPh	o/n	70	Nothing happened
PhNHPPh	o/n	120	Nothing happened

## Experimental Part

### 9.3.2 Procedures

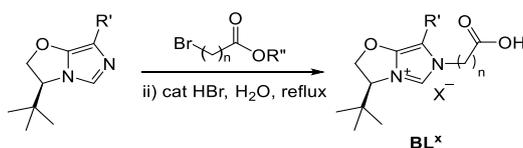
Methyl (2-bromophenyl)(isopropyl)carbamate (**5.11**),<sup>[13]</sup> [Pd(DMBPA)Cl]<sub>2</sub>,<sup>[14]</sup> CsO<sup>t</sup>Bu,<sup>[15]</sup> and (*S*)-2-Amino-3,3-dimethylbutan-1-ol (**5.6**)<sup>[16]</sup> were synthesized according to literature.

#### General Procedure 3: Imidazole alkylation



Bromo alkylester (1.5 equiv.) was added to a 0.36 M solution of imidazole (**5.9**, 1.0 equiv.) in dry MeCN under Ar. The reaction mixture was stirred for 7 days or to completion at 25 °C. The solvent was removed under reduced pressure. A minimal amount of DCM was added to dissolve the crude mixture, and Et<sub>2</sub>O was added to precipitate the product (usually orange sticky oil). The solvent was removed and the residue further dried. Then, H<sub>2</sub>O (0.1 M imidazolium solution) and 2 drops of HBr (48 wt% in H<sub>2</sub>O, cat.) were added to the crude mixture and the mixture was refluxed for 3 h. The mixture was allowed to cool down to 25 °C and the water was removed under reduced pressure. The crude mixture was again dissolved in a minimum amount of DCM and precipitated with Et<sub>2</sub>O. The solvent was removed and the obtained residue washed again with Et<sub>2</sub>O. All solvent residues were removed under reduced pressure to afford the corresponding carboxyl-imidazolium salts. If needed, the obtained products were further purified by FC (MeOH/ CH<sub>2</sub>Cl<sub>2</sub>/AcOH 10:90:1).

#### General Procedure 4: Imidazole alkylation



Activated bromo alkyl- or benzyl ester (1.1 equiv.) was added to a 0.36 M solution of imidazole (**5.9** or **5.10**, 1.0 equiv.) in dry MeCN under Ar. The reaction mixture was stirred for 16 h at 70 °C. The solvent was removed under reduced pressure. A minimal amount of DCM was added to dissolve the crude mixture, and Et<sub>2</sub>O was added to precipitate the product (usually orange sticky oil or off white solid). The solvent was removed and the residue further dried. Then, H<sub>2</sub>O (0.1 M imidazolium solution) and 2 drops of HBr (48 wt% in H<sub>2</sub>O, cat) were added to the crude mixture and the mixture was refluxed for 2 to 48 h. The mixture was allowed to cool down to 25 °C, and the water was removed under reduced pressure. The crude mixture

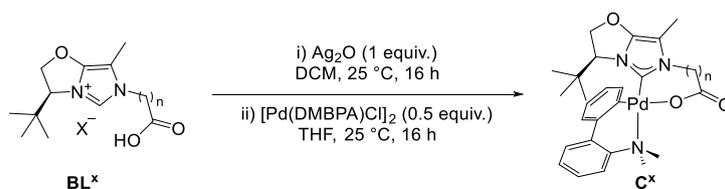
## Experimental Part

was again dissolved in a minimum amount of DCM and precipitated with Et<sub>2</sub>O. The solvent was removed and the obtained residue washed again with Et<sub>2</sub>O. All solvent residues were removed under reduced pressure to afford the corresponding carboxyl-imidazolium salts. If needed, the obtained products were further purified by FC (MeOH/CH<sub>2</sub>Cl<sub>2</sub>/AcOH 10:90:1).

### General Procedure 5: C–H activation protocol with Ag-NHC complex

In the dark, Ag<sub>2</sub>O (0.1 equiv.) was added to the corresponding **BL<sup>x</sup>** (0.1 equiv.) in a catalysis tube covered with aluminum foil in the glovebox. The tube was closed with a septum and removed from the glovebox. Dry DCM (1 mL /0.1 mmol **BL<sup>x</sup>**) was added under argon and the resulting mixture was stirred at 25 °C for 16 h. The reaction mixture was filtered over *Celite* and the solvent removed under reduced pressure. The crude mixture was transferred into a new catalysis tube, which was then introduced into the glovebox. Substrate (1.0 equiv.), Cs<sub>2</sub>CO<sub>3</sub> (1.5 equiv.), Pd-source (10 mol% Pd), and additive (10 mol%) were charged into the tube containing the crude Ag-NHC complex which was then sealed. The tube was taken out of the glovebox and dry and degassed solvent (1 mL/ 0.1 mmol substrate) was added. The reaction mixture was stirred at 160 °C for 16 h. The reaction mixture was allowed to cool down to 25 °C, filtered over a plug of *Celite*, and the solvent removed under reduced pressure. <sup>1</sup>H NMR yields were determined of the crude mixture. After further purification by FC, the e.r. was determined by HPLC on chiral stationary phase.

### General procedure 6: Complex formation

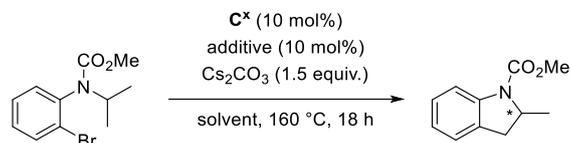


Following a modified procedure.<sup>[17]</sup>In the dark, Ag<sub>2</sub>O (1.0 equiv.) was added to the corresponding imidazolium salt (**BL<sup>x</sup>**, 1.0 equiv.) in a reaction flask covered in aluminium foil in the glovebox. The flask was sealed with a septum, and removed from the glovebox. Dry DCM was added and the resulting reaction mixture was stirred at 25 °C under Ar for 16 h. The reaction mixture was filtered over *Celite*, and the solvent removed under reduced pressure. Pd-dimer<sup>[14]</sup> (0.5 equiv.) was added to the crude mixture, and the flask was evacuated and backfilled with Ar three times. Dry THF was added and the resulting suspension stirred at 25 °C for 16 h. The crude was filtered over a plug of *Celite* and all solvents were removed under reduced

## Experimental Part

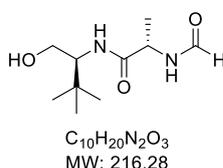
pressure. Hexane was added to precipitate the product. The product was filtered and washed with hexane.

### General Procedure 7: C–H activation protocol with C<sup>x</sup>



In the glovebox, substrate (1.0 equiv.), Cs<sub>2</sub>CO<sub>3</sub> (1.5 equiv.), complex (C<sup>x</sup>, 10 mol%), and solid additive (10 mol%) were charged into a microwave vial. The vial was sealed and taken out of the glovebox. Dry and degassed solvent (1 mL/ 0.1 mmol substrate), and liquid additives (10- or 20 mol%) were added. The reaction mixture was stirred at 160 °C for 16 h. The reaction mixture was allowed to cool down to 25 °C, filtered over a plug of *Celite*, and the solvent was removed under reduced pressure. <sup>1</sup>H NMR yields were determined of the crude mixture. After further purification by FC, the e.r. was determined by HPLC on chiral stationary phase.

### (S)-2-Formamido-N-((S)-1-hydroxy-3,3-dimethylbutan-2-yl)propanamide (5.7Me)



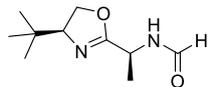
*N*-Methylmorpholine (0.99 mL, 9.04 mmol, 1.01 equiv.) was added to a suspension of formyl-*L*-alanine (prepared following a known procedure<sup>[18]</sup>) (1.05 g, 8.95 mmol, 1.00 equiv) in dry CH<sub>2</sub>Cl<sub>2</sub> (20 mL) under Ar and was stirred at 25 °C until a homogeneous mixture was observed. The resulting reaction mixture was cooled down to -15 °C and isobutyl chloroformate (1.19 mL, 9.04 mmol, 1.01 equiv.) was added dropwise. After 15 min at the same temperature, (*S*)-2-amino-3,3-dimethylbutan-1-ol (**5.6**, 1.10 g, 9.39 mmol, 1.05 equiv.) was added. The resulting reaction mixture was allowed to warm to 25 °C and stirred for further 3 h at this temperature. The solvent was removed under reduced pressure. The crude mixture was purified by FC (gradient, acetone/DCM 1:1 to 1:0, (R<sub>F</sub> = 0.20 acetone/CH<sub>2</sub>Cl<sub>2</sub> 1:1)), affording the title compound **5.7Me** (1.64 g, 7.58 mmol, 85%) as a colorless solid. NMR data are consistent with literature data.<sup>[18]</sup>

<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 8.23 (d, *J* = 7.7 Hz, 1H), 7.96 (s, 1H), 7.46 (d, *J* = 9.5 Hz, 1H), 4.45 – 4.38 (m, 1H), 4.37 (t, *J* = 5.3 Hz, 1H), 3.59 – 3.52 (m, 2H), 3.32 – 3.26 (m, 1H), 1.20 (d, *J* = 6.9 Hz, 3H), 0.84 (s, 9H).

<sup>13</sup>C NMR (126 MHz, DMSO-*d*<sub>6</sub>) δ 171.9, 160.6, 60.5, 58.6, 47.0, 33.7, 26.8, 18.6.

[α]<sub>D</sub><sup>20</sup>: -54.0 (c 1.01, MeOH).

***N*-((*S*)-1-((*S*)-4-(*tert*-Butyl)-4,5-dihydrooxazol-2-yl)ethyl)formamide (**5.8Me**)**



C<sub>10</sub>H<sub>18</sub>N<sub>2</sub>O<sub>2</sub>  
MW: 198.27

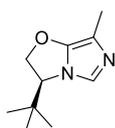
Et<sub>3</sub>N (4.80 mL, 34.20 mmol, 4.30 equiv.) was added dropwise to a suspension of (*S*)-2-formamido-*N*-((*S*)-1-hydroxy-3,3-dimethylbutan-2-yl)propanamide (**5.7Me**, 1.72 g, 7.95 mmol, 1.00 equiv.), DMAP (0.02 g, 0.12 mmol, 0.02 equiv.), and *p*-toluenesulfonyl chloride (1.82 g, 9.54 mmol, 1.20 equiv.) in dry CH<sub>2</sub>Cl<sub>2</sub> (88 mL) under Ar. The resulting mixture was stirred at 25 °C for 16 h. The mixture was diluted with DCM and washed with sat. NaHCO<sub>3</sub>. The phases were separated and the aqueous phase extracted twice with DCM. The combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude mixture was purified by FC (EtOAc, R<sub>f</sub> = 0.18) affording the title compound **5.8Me** (1.45 g, 7.31 mmol, 92%) as a yellow oil as a diastereomeric mixture (d.r. 8.9:1.1). <sup>13</sup>C NMR spectrum is consistent with literature data.[7]

<sup>1</sup>H NMR (400 MHz, chloroform-*d*) δ 8.18 (s, 1H), 6.65 (bs, 1H), 4.71 (p, *J* = 7.0 Hz, 1H), 4.24 (t, *J* = 9.4 Hz, 1H), 4.14 (t, *J* = 8.3 Hz, 1H), 3.87 – 3.79 (m, 1H), 1.43 (d, *J* = 6.9 Hz, 3H), 0.87 (s, 9H).

<sup>13</sup>C NMR (101 MHz, chloroform-*d*) δ 167.2, 160.4, 75.4, 69.9, 42.7, 33.7, 25.8, 19.4.

[α]<sub>D</sub><sup>20</sup>: -87.7 (c 1.63, CH<sub>2</sub>Cl<sub>2</sub>) of the diastereomeric mixture.

**(*S*)-3-(*tert*-Butyl)-7-methyl-2,3-dihydroimidazo[5,1-*b*]oxazole (**5.9**)**



C<sub>10</sub>H<sub>16</sub>N<sub>2</sub>O  
MW: 180.25

P<sub>2</sub>O<sub>5</sub> (6.64 g, 46.8 mmol, 2.0 equiv.) was added to a solution of *N*-((*S*)-1-((*S*)-4-(*tert*-butyl)-4,5-dihydrooxazol-2-yl)ethyl)formamide (**5.8Me**, 4.63 g, 23.4 mmol, 1.0 equiv.) in dry toluene (260 mL) under Ar and was then stirred at 100 °C for 48 h. The resulting mixture was allowed to cool down to 25 °C and the solvent was decanted. 1 M HCl (65 mL) was added to the crude mixture. After all solid has dissolved, a 20wt% aqueous solution of KOH was added until the mixture had a pH of 12. The resulting mixture was extracted with DCM three times. The combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude mixture was purified by FC (silica gel, EtOAc, R<sub>f</sub> = 0.12) affording the title compound **5.9** (2.66 g, 14.8 mmol, 63%) as a yellow oil. <sup>13</sup>C NMR is consistent with literature data.<sup>[19]</sup>

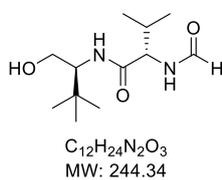
<sup>1</sup>H NMR (500 MHz, chloroform-*d*) δ 7.06 (s, 1H), 4.92 (dd, *J* = 9.1, 8.1 Hz, 1H), 4.80 (dd, *J* = 9.2, 4.3 Hz, 1H), 4.09 (dd, *J* = 8.0, 4.3 Hz, 1H), 2.07 (s, 3H), 0.98 (s, 9H).

<sup>13</sup>C NMR (126 MHz, chloroform-*d*) δ 149.3, 122.7, 105.3, 78.5, 65.1, 33.9, 25.6, 11.1.

## Experimental Part

$[\alpha]_D^{20}$ : +17.6 (c 1.17, CHCl<sub>3</sub>).

### (*S*)-2-Formamido-N-((*S*)-1-hydroxy-3,3-dimethylbutan-2-yl)-3-methylbutanamide (**5.7iPr**)



*N*-Methylmorpholine (2.43 mL, 22.1 mmol, 1.10 equiv.) was added to a suspension of formyl-*L*-valine (prepared following procedure<sup>[18]</sup>) (2.77 g, 21.1 mmol, 1.10 equiv.) in dry THF (70 mL) under Ar and was stirred at 25 °C until a homogeneous mixture was observed. The resulting reaction mixture was cooled down to -15 °C and isobutyl chloroformate (2.55 mL, 19.4 mmol, 1.01 equiv.) was added dropwise. After 15 min at the same temperature, (*S*)-2-amino-3,3-dimethylbutan-1-ol **5.6** (2.25 g, 19.2 mmol, 1.00 equiv.) was added. The resulting reaction mixture was allowed to warm to 25 °C and stirred at the same temperature for 16 h. The solvent was evaporated under reduced pressure before water (25 mL) was added. The precipitate was filtered off, washed with water, and EtOAc and further dried to afford the title compound **5.7iPr** (3.67 g, 15.0 mmol, 78%) as a colorless powder.

<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 8.14 (d, *J* = 9.0 Hz, 1H), 8.03 (d, *J* = 1.8 Hz, 1H), 7.53 (d, *J* = 9.5 Hz, 1H), 4.33 (bs, 1H), 4.30 – 4.24 (m, 1H), 3.61 (ddd, *J* = 9.5, 7.9, 3.9 Hz, 1H), 3.55 (dt, *J* = 10.7, 3.1 Hz, 1H), 3.28 (qd, *J* = 9.1, 8.3, 4.4 Hz, 1H), 1.95 (sept, *J* = 6.7 Hz, 1H), 0.88 (d, *J* = 6.8 Hz, 3H), 0.86 – 0.82 (m, 12H).

<sup>13</sup>C NMR (126 MHz, DMSO-*d*<sub>6</sub>) δ 170.8, 160.8, 60.6, 58.5, 56.4, 33.7, 30.5, 26.9, 19.3, 18.1.

IR (neat): ν (cm<sup>-1</sup>) 3342, 3260, 3096, 2965, 2890, 2361, 1650, 1580, 1393, 1238, 670, 629.

HRMS (ESI): Calcd for C<sub>12</sub>H<sub>24</sub>N<sub>2</sub>NaO<sub>3</sub> [M+H]<sup>+</sup>: 267.1679, found 267.1684.

mp: 204 °C.

$[\alpha]_D^{20}$ : -44.9 (c 1.04, MeOH).

### *N*-((*S*)-1-((*S*)-4-(*tert*-Butyl)-4,5-dihydrooxazol-2-yl)-2-methylpropyl)formamide (**5.8iPr**)



Et<sub>3</sub>N (4.45 mL, 31.70 mmol, 4.30 equiv.) was added dropwise to a suspension of (*S*)-2-formamido-*N*-((*S*)-1-hydroxy-3,3-dimethylbutan-2-yl)-3-methylbutanamide **5.7iPr** (1.80 g, 7.37 mmol, 1.00 equiv.), DMAP (0.01 g, 0.11 mmol, 0.02 equiv.), and *p*-toluenesulfonyl chloride (1.42 g, 7.44 mmol, 1.01 equiv.) in dry DCE (255 mL) under Ar. The resulting mixture was stirred for 1 h at 25 °C, then refluxed for 16 h. The reaction mixture was cooled down to 25 °C, diluted with DCM and

## Experimental Part

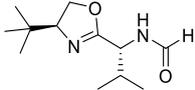
washed with sat. NaHCO<sub>3</sub>. The phases were separated and the aqueous phase extracted twice with DCM. The combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude mixture was purified by FC (EtOAc, R<sub>f</sub> = 0.24) affording the title compound **5.8iPr** (0.93 g, 4.12 mmol, 56%) as a yellow oil (diastereomeric mixture, d.r. 82:18).

### Major:

**<sup>1</sup>H NMR** (500 MHz, chloroform-*d*) δ 8.25 (s, 1H), 6.35 (d, *J* = 8.6 Hz, 1H), 4.68 (ddt, *J* = 8.8, 4.8, 0.8 Hz, 1H), 4.21 (dd, *J* = 10.1, 8.8 Hz, 1H), 4.11 (dd, *J* = 8.8, 7.8 Hz, 1H), 3.84 (ddd, *J* = 10.1, 7.8, 0.8 Hz, 1H), 2.16 (pd, *J* = 6.9, 4.7 Hz, 1H), 0.95 (d, *J* = 6.9 Hz, 3H), 0.93 (d, *J* = 6.9 Hz, 3H), 0.87 (s, 9H).

**<sup>13</sup>C NMR** (126 MHz, chloroform-*d*) δ 165.8, 160.7, 75.4, 69.5, 51.3, 33.8, 31.6, 25.9, 18.9, 17.9.

### Minor:

 **<sup>1</sup>H NMR** (500 MHz, chloroform-*d*) δ 8.04 (d, *J* = 11.9 Hz, 1H), 6.04 – 5.95 (m, 1H), 4.28 – 4.23 (m, 1H), , 4.06 (dd, *J* = 13.7, 8.7 Hz, 1H), 3.95 (dd, *J* = 10.0, 6.3 Hz, 1H), 3.88 (dd, *J* = 9.3, 1.2 Hz, 1H), 2.08 – 2.02 (m, 1H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.98 – 0.95 (m, 3H), 0.88 (s, 9H).

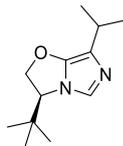
**<sup>13</sup>C NMR** (126 MHz, chloroform-*d*) δ 164.9, 163.8, 75.8, 69.4, 56.3, 33.7, 31.9, 26.0, 19.3, 17.8.

**IR (neat):** ν (cm<sup>-1</sup>) 3261, 2961, 2873, 2361, 2340, 1664, 1531, 1479, 1386, 1210, 985, 641.

**HRMS** (ESI): Calcd for C<sub>12</sub>H<sub>23</sub>N<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup>: 227.1754, found 227.1753.

**[α]<sub>D</sub><sup>20</sup>:** -81.1 (c 0.99, CHCl<sub>3</sub>) of the diastereomeric mixture.

### **(S)-3-(tert-Butyl)-7-isopropyl-2,3-dihydroimidazo[5,1-b]oxazole (5.10)**

  
P<sub>2</sub>O<sub>5</sub> (382 mg, 2.69 mmol, 3.0 equiv.) was added to a solution of *N*-((*S*)-1-((*S*)-4-(*tert*-butyl)-4,5-dihydrooxazol-2-yl)-2-methylpropyl)formamide **5.8iPr** (203 mg, 0.89 mmol, 1.0 equiv.) in dry toluene (11 mL) under Ar and was then stirred at 100 °C for 48 h. The resulting mixture was allowed to cool down to 25 °C and the solvent was decanted. 1 M HCl (3.8 mL) was added to the crude mixture. After all solid has dissolved, a 20wt% aqueous solution of KOH was added until the mixture had a pH

C<sub>12</sub>H<sub>23</sub>N<sub>2</sub>O  
MW: 208.31

## Experimental Part

of 12. The resulting mixture was extracted with DCM three times. The combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude mixture was purified by FC (EtOAc, R<sub>f</sub> = 0.17) affording the title compound **5.10** (116 mg, 0.56 mmol, 62%) as a yellow oil.

**<sup>1</sup>H NMR** (400 MHz, chloroform-*d*) δ 7.15 (s, 1H), 4.92 (t, *J* = 8.8 Hz, 1H), 4.80 (dd, *J* = 9.2, 4.2 Hz, 1H), 4.09 (ddd, *J* = 8.0, 4.2, 1.3 Hz, 1H), 2.83 (sept, *J* = 7.3, 6.8 Hz, 1H), 1.23 (d, *J* = 7.3, 6.8 Hz, 6H), 0.98 (s, 9H).

**<sup>13</sup>C NMR** (126 MHz, chloroform-*d*) δ 148.2, 122.6, 115.9, 78.5, 65.0, 34.0, 26.3, 25.7, 22.1, 22.1.

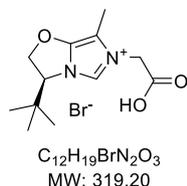
**IR (neat):** ν (cm<sup>-1</sup>) 2967, 2905, 2361, 2340, 1700, 1633, 1470, 1386, 1066, 364.

**HRMS (ESI):** Calcd for C<sub>12</sub>H<sub>21</sub>N<sub>2</sub> [M+H]<sup>+</sup>: 209.1648, found 209.1653.

**mp:** 47 °C.

**[α]<sub>D</sub><sup>20</sup>:** +24.4 (c 0.96, MeCN).

### **(S)-3-(*tert*-Butyl)-6-(carboxymethyl)-7-methyl-2,3-dihydroimidazo[5,1-*b*]oxazol-6-ium bromide (BL<sup>1</sup>)**



The title compound **BL<sup>1</sup>** (159 mg, 0.46 mmol, 92%) was obtained as an off-white solid following **general procedure 4** using the corresponding imidazole **5.9** (90 mg, 0.50 mmol, 1.0 equiv.) and ethyl bromoacetate (0.06 mL, 0.55 mmol, 1.1 equiv.) as alkylating agent. The hydrolysis took 2 h under reflux.

**<sup>1</sup>H NMR** (500 MHz, acetonitrile-*d*<sub>3</sub>) δ 8.60 (s, 1H), 5.13 – 4.96 (m, 4H), 4.69 (dd, *J* = 8.1, 4.0 Hz, 1H), 2.10 (s, 3H), 0.99 (s, 9H).

**<sup>13</sup>C NMR** (126 MHz, acetonitrile-*d*<sub>3</sub>) δ 167.5, 148.7, 127.1, 104.4, 79.8, 68.3, 49.5, 34.6, 25.3, 7.0.

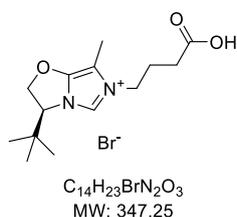
**IR (neat):** ν (cm<sup>-1</sup>) 2966, 2353, 1740, 1688, 1541, 1195, 768.

**HRMS (ESI):** Calcd for C<sub>12</sub>H<sub>19</sub>N<sub>2</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 239.1390, found 239.1394.

**mp:** > 90 °C decomposition.

**[α]<sub>D</sub><sup>20</sup>:** +37.4 (c 0.68, MeCN).

**(S)-3-(tert-Butyl)-6-(3-carboxypropyl)-7-methyl-2,3-dihydroimidazo[5,1-b]oxazol-6-ium bromide (BL<sup>2</sup>)**



The title compound **BL<sup>2</sup>** (478 mg, 0.51 mmol, 64%) was obtained as an orange viscous oil following **general procedure 3** using the corresponding imidazole (**5.9**, 144 mg, 0.80 mmol, 1.0 equiv.) and ethyl 4-bromobutyrate (0.17 mL, 1.20 mmol, 1.5 equiv.) as alkylating agent. The hydrolysis took 3 h under reflux. An analytically pure sample was obtained after FC (MeOH/CH<sub>2</sub>Cl<sub>2</sub>/AcOH 10:90:1, R<sub>f</sub>: 0.07).

**<sup>1</sup>H NMR** (500 MHz, acetonitrile-*d*<sub>3</sub>) δ 10.35 (bs, 1H), 8.61 (s, 1H), 5.07 (dd, *J* = 9.6, 8.2 Hz, 1H), 5.00 (dd, *J* = 9.5, 4.1 Hz, 1H), 4.64 (dd, *J* = 8.2, 4.2 Hz, 1H), 4.21 – 4.09 (m, 2H), 2.46 (t, *J* = 6.4 Hz, 2H), 2.16 (s, 3H), 2.13 – 2.02 (m, 2H), 0.99 (s, 9H).

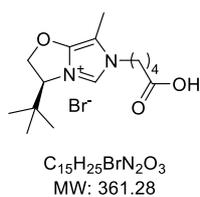
**<sup>13</sup>C NMR** (126 MHz, acetonitrile-*d*<sub>3</sub>) δ 173.9, 149.2, 125.9, 103.7, 79.8, 68.1, 48.1, 34.5, 31.2, 25.6, 25.4, 7.2.

**IR** (neat): ν (cm<sup>-1</sup>) 3378, 2960, 2353, 1720, 1691, 1538, 1538, 1384, 1189.

**HRMS** (ESI): Calcd for C<sub>14</sub>H<sub>23</sub>N<sub>2</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 267.1703, found 267.1706.

[α]<sub>D</sub><sup>20</sup>: +67.5 (c 0.52, MeCN).

**(S)-3-(tert-Butyl)-6-(carboxymethyl)-6,6,6,7-tetramethyl-3,6-dihydro-2H-6l6-imidazo[4,3-b]oxazol-4-ium bromide (BL<sup>3</sup>)**



The title compound **BL<sup>3</sup>** (180 mg, 0.50 mmol, 52%) was obtained as an orange viscous oil following **general procedure 3** using the corresponding imidazole (**5.9**, 171 mg, 0.94 mmol, 1.0 equiv.) and methyl 5-bromovalerate (0.20 mL, 1.42 mmol, 1.5 equiv.) as alkylating agent. The hydrolysis took 3

h under reflux. An analytically pure sample was obtained after FC (MeOH/DCM/AcOH 10:90:1, R<sub>f</sub>: 0.21).

**<sup>1</sup>H NMR** (400 MHz, acetonitrile-*d*<sub>3</sub>) δ 9.47 (bs, 1H), 8.39 (s, 1H), 5.11 – 5.00 (m, 2H), 4.61 (dd, *J* = 7.9, 4.4 Hz, 1H), 4.11 – 4.05 (m, 2H), 2.40 (t, *J* = 7.2 Hz, 2H), 2.17 (s, 3H), 1.86 (p, *J* = 7.3 Hz, 2H), 1.63 (p, *J* = 15.3, 7.5 Hz, 2H), 1.01 (s, 9H).

**<sup>13</sup>C NMR** (126 MHz, acetonitrile-*d*<sub>3</sub>) δ 174.5, 149.2, 125.6, 103.6, 79.7, 68.1, 48.6, 34.6, 33.8, 29.3, 25.4, 22.1, 7.2.

## Experimental Part

**HRMS** (ESI): Calcd for  $C_{15}H_{25}N_2O_3$   $[M-Br]^+$ : 281.1860, found 281.1863.

**IR** (neat):  $\nu$  ( $cm^{-1}$ ) 3385, 2962, 1723, 1683, 1539, 1475, 1374, 1195, 633.

$[\alpha]_D^{20}$ : +29.1 (c 0.51, MeCN).

### **(S)-3-(tert-Butyl)-6-(carboxymethyl)-6,6,6,6,7-pentamethyl-3,6-dihydro-2H-617-imidazo[4,3-b]oxazol-4-ium bromide (BL<sup>4</sup>)**



The title compound **BL<sup>4</sup>** (155 mg, 0.41 mmol, 50%) was obtained as an orange viscous oil following **general procedure 3** using the corresponding imidazole **5.9** (48 mg, 0.82 mmol, 1.0 equiv.) and methyl 6-bromohexanoate (0.20 mL, 1.23 mmol, 1.5 equiv.) as alkylating agent. The hydrolysis took 3 h under reflux. An analytically pure sample was obtained after FC (MeOH/ $CH_2Cl_2$ /AcOH 10:90:1,  $R_f$ : 0.18).

**<sup>1</sup>H NMR** (400 MHz, acetonitrile- $d_3$ )  $\delta$  8.49 (s, 1H), 5.11 – 4.97 (m, 2H), 4.63 (dd,  $J = 8.0, 4.3$  Hz, 1H), 4.13 – 3.99 (m, 2H), 2.33 (t,  $J = 7.3$  Hz, 2H), 2.14 (s, 3H), 1.86 – 1.76 (m, 2H), 1.63 (dtd,  $J = 14.9, 7.6, 2.6$  Hz, 2H), 1.42 – 1.31 (m, 2H), 0.99 (s, 9H).

**<sup>13</sup>C NMR**: (101 MHz, acetonitrile- $d_3$ )  $\delta$  174.9, 149.2, 125.6, 103.6, 79.7, 68.1, 48.7, 34.6, 34.2, 29.6, 26.0, 25.3, 24.8, 7.1.

**HRMS** (ESI): Calcd for  $C_{16}H_{27}N_2O_3$   $[M-Br]^+$ : 295.2016, found 295.2020.

**IR** (neat):  $\nu$  ( $cm^{-1}$ ) 2970, 2905, 2362, 2340, 1726, 1683, 1539, 1395, 1054, 761.

$[\alpha]_D^{20}$ : +36.8 (c 0.52, MeCN).

### **(S)-3-(tert-Butyl)-6-(carboxymethyl)-6,6,6,6,6,7-hexamethyl-3,6-dihydro-2H-618-imidazo[4,3-b]oxazol-4-ium bromide (BL<sup>5</sup>)**



The title compound **BL<sup>5</sup>** (123 mg, 0.31 mmol, 38%) was obtained as an orange viscous oil following **general procedure 3** using the corresponding imidazole **5.9** (147 mg, 0.82 mmol, 1.0 equiv.) and ethyl 7-bromoheptanoate (0.24 mL, 1.22 mmol, 1.5 equiv.) as alkylating agent. The hydrolysis took 3 h under reflux. An analytically pure sample was obtained after FC (MeOH/DCM/AcOH 10:90:1,  $R_f$ : 0.16).

## Experimental Part

**<sup>1</sup>H NMR** (400 MHz, acetonitrile-*d*<sub>3</sub>) δ 9.37 (bs, 1H), 8.37 (s, 1H), 5.09 – 4.97 (m, 2H), 4.60 (dd, *J* = 8.0, 4.3 Hz, 1H), 4.03 (td, *J* = 7.1, 3.4 Hz, 2H), 2.30 (t, *J* = 7.3 Hz, 2H), 2.14 (s, 3H), 1.79 (p, *J* = 7.2 Hz, 2H), 1.57 (p, *J* = 7.2 Hz, 2H), 1.42 – 1.30 (m, 4H), 0.99 (s, 9H).

**<sup>13</sup>C NMR** (101 MHz, acetonitrile-*d*<sub>3</sub>) δ 175.1, 149.2, 125.7, 103.5, 79.7, 68.1, 48.8, 34.5, 34.4, 29.8, 28.9, 26.2, 25.4, 25.3, 7.2.

**IR (neat):** ν (cm<sup>-1</sup>) 3380, 2953, 2352, 2341, 1719, 1691, 1537, 1465, 1383, 1189, 676.

**HRMS (ESI):** Calcd for C<sub>17</sub>H<sub>29</sub>N<sub>2</sub>O<sub>3</sub> [M-Br]<sup>+</sup>: 309.2173, found 309.2177.

[α]<sub>D</sub><sup>20</sup>: +31.9 (c 0.57, MeCN).

### Methyl 2-(bromomethyl)benzoate (**5.15**)

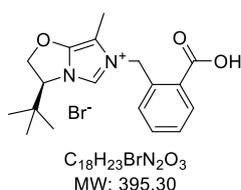


NBS (1.77g, 10.0 mmol, 1.00 equiv.) and BPO (0.04 g, 0.2 mmol, 0.02 equiv.) were added to a solution of methyl 2-methylbenzoate (1.50 g, 10.0 mmol, 1.00 equiv.) in CCl<sub>4</sub> (30 mL). The resulting mixture was refluxed for 5 h. After cooling down to 25 °C, the reaction mixture was diluted with water. The phases were separated and the aqueous phase was extracted twice with DCM. The combined organic phases were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude mixture was purified by FC (Et<sub>2</sub>O/*n*-pent 5:95, R<sub>f</sub> = 0.40) affording the title compound **5.15** (2.27 g, 9.9 mmol, 99%) as a yellow oil. NMR spectra are consistent with literature data.<sup>[20]</sup>

**<sup>1</sup>H NMR** (400 MHz, chloroform-*d*) δ 7.99 – 7.94 (m, 1H), 7.52 – 7.44 (m, 2H), 7.40 – 7.34 (m, 1H), 4.96 (s, 2H), 3.94 (s, 3H).

**<sup>13</sup>C NMR** (101 MHz, chloroform-*d*) δ 167.1, 139.3, 132.7, 131.8, 131.4, 129.2, 128.7, 52.4, 31.7.

### (*S*)-3-(*tert*-Butyl)-6-(2-carboxybenzyl)-7-methyl-2,3-dihydroimidazo[5,1-*b*]oxazol-6-ium bromide (**BL**<sup>6</sup>)



The title compound **BL**<sup>6</sup> (275 mg, 0.69 mmol, 98%) was obtained as a yellow solid following **general procedure 4** using the corresponding imidazole **5.9** (127 mg, 0.71 mmol, 1.0 equiv.) and methyl 2-(bromomethyl)benzoate **5.15** (178 mg, 0.78 mmol, 1.1 equiv.) as alkylating agent. The hydrolysis took 24 h under reflux.

## Experimental Part

**<sup>1</sup>H NMR** (400 MHz, acetonitrile-*d*<sub>3</sub>) δ 8.32 (s, 1H), 8.11 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.66 – 7.59 (m, 1H), 7.56 – 7.50 (m, 1H), 7.15 (dd, *J* = 7.7, 1.2 Hz, 1H), 5.68 (s, 2H), 5.15 – 5.00 (m, 2H), 4.65 (dd, *J* = 8.0, 3.9 Hz, 1H), 2.03 (s, 3H), 0.98 (s, 9H).

**<sup>13</sup>C NMR** (101 MHz, acetonitrile-*d*<sub>3</sub>) δ 168.0, 149.3, 135.7, 134.2, 134.2, 132.8, 130.0, 130.0, 126.4, 104.3, 79.8, 68.2, 51.2, 34.6, 25.3, 7.3.

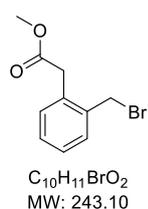
**IR (neat):** ν (cm<sup>-1</sup>) 3377, 2964, 2361, 1684, 1538, 1475, 1201, 747, 647.

**HRMS (ESI):** Calcd for C<sub>18</sub>H<sub>23</sub>N<sub>2</sub>O<sub>3</sub> [M-Br]<sup>+</sup>: 315.1703, found 315.1706.

**mp:** > 80 °C decomposition.

**[α]<sub>D</sub><sup>20</sup>:** +29.4 (c 0.46, MeCN).

### Methyl 2-(2-(bromomethyl)phenyl)acetate (**5.16**)<sup>[21]</sup>

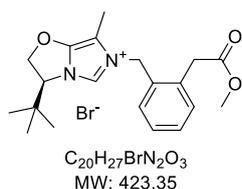


Thionyl bromide (0.35 mL, 4.55 mmol, 1.3 equiv.) was added dropwise to a stirred solution of 3-isochromanone (500 mg, 3.37 mmol, 1.0 equiv.) in dry MeOH (0.45 mL) and dry toluene (25 mL) at 25 °C under Ar. After 1 h, the mixture was carefully poured into an excess of an aqueous 20wt% NaHCO<sub>3</sub> solution and the resulting mixture was stirred for 10 min before it was transferred into a separating funnel. The phases were separated and the aqueous phase was extracted twice with DCM. The two organic layers were washed independently with water. The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure to afford the title compound **5.16** (623 mg, 2.56 mmol, 76%) as a yellow oil.

**<sup>1</sup>H NMR** (400 MHz, chloroform-*d*) δ 7.39 – 7.35 (m, 1H), 7.32 – 7.23 (m, 3H), 4.59 (s, 2H), 3.81 (s, 2H), 3.71 (s, 3H).

**<sup>13</sup>C NMR** (101 MHz, chloroform-*d*) δ 171.6, 136.5, 133.4, 131.4, 130.8, 129.3, 128.2, 52.4, 38.3, 31.9.

### (*S*)-3-(*tert*-Butyl)-6-(2-(2-methoxy-2-oxoethyl)benzyl)-7-methyl-2,3-dihydroimidazo[5,1-*b*]oxazol-6-ium bromide (**5.17**)



The title compound **5.17** (252 mg, 0.62 mmol, 99%) was obtained as a yellow solid following the first part of **general procedure 4** using the corresponding imidazole **5.9** (106 mg, 0.59 mmol, 1.0 equiv.) and methyl

## Experimental Part

2-(2-(bromomethyl)phenyl)acetate **5.16** (80% purity, 185 mg, 0.65 mmol, 1.1 equiv.) as alkylating agent.

**<sup>1</sup>H NMR**: (400 MHz, chloroform-*d*)  $\delta$  9.90 (s, 1H), 7.36 – 7.22 (m, 3H), 6.95 – 6.87 (m, 1H), 5.78 – 5.63 (m, 2H), 5.20 – 5.11 (m, 1H), 4.97 – 4.89 (m, 2H), 3.86 – 3.76 (m, 2H), 3.67 (s, 3H), 2.01 (s, 3H), 1.07 (s, 9H).

**<sup>13</sup>C NMR** (126 MHz, chloroform-*d*)  $\delta$  171.5, 148.4, 132.4, 132.3, 131.8, 129.2, 128.6, 127.8, 127.1, 102.9, 78.7, 67.5, 52.5, 49.9, 38.8, 34.0, 25.6, 7.3.

**IR (neat)**:  $\nu$  (cm<sup>-1</sup>) 2962, 2361, 2341, 1733, 1682, 1539, 1457, 1197, 168, 630.

**HRMS** (ESI): Calcd for C<sub>20</sub>H<sub>27</sub>N<sub>2</sub>O<sub>3</sub> [M-Br]<sup>+</sup>: 343.2016, found 343.2022.

**mp**: 48 °C.

**[ $\alpha$ ]<sub>D</sub><sup>20</sup>**: +37.0 (c 0.57, CHCl<sub>3</sub>).

### **(S)-3-(tert-Butyl)-6-(2-(carboxymethyl)benzyl)-7-methyl-2,3-dihydroimidazo[5,1-b]oxazol-6-ium bromide (BL<sup>7</sup>)**



The title compound (**BL<sup>7</sup>**, 672 mg, 1.64 mmol, 99%) was obtained as a yellow solid following **general procedure 4** using the corresponding imidazole (**5.9**, 295 mg, 1.64 mmol, 1.0 equiv.) and methyl 2-(2-(bromomethyl)phenyl)acetate (**5.16**, 80% purity, 548 mg, 1.80 mmol, 1.1 equiv.) as alkylating agent. The hydrolysis took 2 h under reflux.

**<sup>1</sup>H NMR** (500 MHz, acetonitrile-*d*<sub>3</sub>)  $\delta$  8.34 (s, 1H), 7.45 – 7.27 (m, 3H), 7.10 – 6.99 (m, 1H), 5.44 – 5.27 (m, 2H), 5.13 (dd, *J* = 9.5, 8.2 Hz, 1H), 5.03 (dd, *J* = 9.6, 4.0 Hz, 1H), 4.68 (dd, *J* = 8.2, 4.0 Hz, 1H), 3.89 – 3.76 (m, 2H), 2.03 (s, 3H), 0.99 (s, 9H).

**<sup>13</sup>C NMR** (126 MHz, acetonitrile-*d*<sub>3</sub>)  $\delta$  172.4, 149.4, 134.8, 133.0, 132.8, 130.1, 129.1, 129.0, 126.3, 104.3, 79.9, 68.3, 50.4, 39.2, 34.5, 25.3, 7.4.

**IR (neat)**:  $\nu$  (cm<sup>-1</sup>) 2963, 2924, 2361, 2340, 1720, 1684, 15399, 1457, 1373, 1196, 781, 630.

**HRMS** (ESI): Calcd for C<sub>19</sub>H<sub>25</sub>N<sub>2</sub>O<sub>3</sub> [M-Br]<sup>+</sup>: 329.1860, found 329.1865.

**mp**: >120 °C decomposition.

**[ $\alpha$ ]<sub>D</sub><sup>20</sup>**: +52.4 (c 0.54, CHCl<sub>3</sub>).

**Methyl 3-(2-(bromomethyl)phenyl)propanoate (5.18)**

*m*-Chloroperbenzoic acid (70% purity, 3.37 g, 13.7 mmol, 2.0 equiv.) was added to a solution of  $\beta$ -tetralone (1.00 g, 6.8 mmol, 1.0 equiv.) in dry DCM (14 mL) under Ar. The resulting reaction mixture was stirred at 25 °C for 16 h. The precipitate was filtered off and the filtrate was washed with sat.  $Na_2SO_3$  solution, followed by sat.  $NaHCO_3$  solution. The organic phase was dried over  $Na_2SO_4$ , filtered and concentrated under reduced pressure. The obtained white solid was dissolved in dry toluene (20 mL) and dry MeOH (0.45 mL) under Ar. Thionyl bromide (0.35 mL, 0.7 equiv.) was added dropwise. After 1 h of stirring at 25 °C, the mixture was carefully poured into an excess of an aqueous 20wt%  $NaHCO_3$  solution and the resulting mixture was stirred for 10 min before it was transferred into a separating funnel. The phases were separated and the aqueous phase was extracted twice with DCM. The two organic layers were washed independently with water. The combined organic layers were dried over  $Na_2SO_4$ , filtered, and concentrated under reduced pressure. The crude mixture was purified by FC ( $Et_2O$ /cyclohexane 1:9) to afford a mixture of the title compound **5.18** and its regioisomer (82:18, 500 mg, 1.94 mmol, 28%) as a colorless oil.

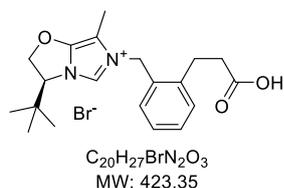
$^1H$  NMR (400 MHz, chloroform-*d*)  $\delta$  7.34 (dd,  $J = 7.8, 1.6$  Hz, 1H), 7.30 – 7.23 (m, 1H), 7.23 – 7.18 (m, 2H), 4.58 (s, 2H), 3.70 (s, 3H), 3.08 (dd,  $J = 8.7, 7.1$  Hz, 2H), 2.76 – 2.67 (m, 2H).

$^{13}C$  NMR (126 MHz, chloroform-*d*)  $\delta$  173.3, 139.6, 135.8, 130.9, 129.6, 129.4, 127.2, 51.9, 34.9, 31.6, 27.3.

**Regioisomer: methyl 2-(2-(2-bromoethyl)phenyl)acetate:**

$^1H$  NMR (500 MHz, chloroform-*d*)  $\delta$  7.29 – 7.24 (m, 4H), 3.70 (s, 3H), 3.69 (s, 2H), 3.54 (dd,  $J = 8.5, 7.4$  Hz, 2H), 3.21 (dd,  $J = 8.4, 7.4$  Hz, 2H).

$^{13}C$  NMR (126 MHz, chloroform-*d*)  $\delta$  173.3, 139.6, 135.8, 130.9, 129.6, 129.4, 127.2, 51.9, 34.9, 31.6, 27.3.

**(S)-3-(tert-Butyl)-6-(2-(2-carboxyethyl)benzyl)-7-methyl-2,3-dihydroimidazo[5,1-b]oxazol-6-ium bromide (BL<sup>8</sup>)**

The title compound **BL<sup>8</sup>** (111 mg, 0.25 mmol, 68%) was obtained as an orange solid following **general procedure 4** using the corresponding imidazole **5.9** (67 mg, 0.37 mmol, 1.0 equiv.) and methyl 3-(2-

## Experimental Part

(bromomethyl)phenyl)propanoate **5.18** (82% purity, 163 mg, 0.52 mmol, 1.5 equiv.) as alkylating agent. The hydrolysis took 2 h under reflux.

**<sup>1</sup>H NMR** (500 MHz, chloroform-*d*)  $\delta$  9.33 (s, 1H), 7.35 – 7.27 (m, 2H), 7.27 – 7.19 (m, 1H), 6.90 (d,  $J$  = 7.7 Hz, 1H), 5.68 – 5.54 (m, 2H), 5.20 (t,  $J$  = 8.7 Hz, 1H), 5.06 (dd,  $J$  = 8.1, 3.6 Hz, 1H), 4.91 (dd,  $J$  = 9.3, 3.5 Hz, 1H), 3.00 (t,  $J$  = 7.4 Hz, 2H), 2.70 (ddt,  $J$  = 48.4, 15.3, 7.4 Hz, 2H), 2.06 (s, 3H), 1.05 (s, 9H).

**<sup>13</sup>C NMR** (126 MHz, chloroform-*d*)  $\delta$  174.5, 148.6, 139.3, 130.8, 130.6, 129.6, 127.7, 127.5, 126.9, 103.1, 78.9, 67.5, 50.2, 36.1, 34.0, 27.8, 25.6, 7.6.

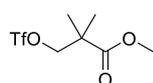
**IR (neat):**  $\nu$  (cm<sup>-1</sup>) 3385, 2963, 2923, 2361, 2341, 1724, 1682, 1538, 1454, 1374, 1195, 760, 630.

**HRMS (ESI):** Calcd for C<sub>20</sub>H<sub>27</sub>N<sub>2</sub>O<sub>3</sub> [M-Br]<sup>+</sup>: 343.2016, found 343.2023.

**mp:** 96 °C.

**$[\alpha]_D^{20}$ :** +27.5 (c 0.53, CHCl<sub>3</sub>).

### Methyl 2,2-dimethyl-3-(((trifluoromethyl)sulfonyl)oxy)propanoate (**5.19**)



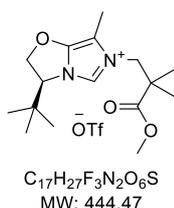
C<sub>7</sub>H<sub>11</sub>F<sub>3</sub>O<sub>5</sub>S  
MW: 264.22

Tf<sub>2</sub>O (1.65 mL, 9.84 mmol, 1.3 equiv.) was added dropwise to a solution of methyl hydroxypivalate (1.00 g, 7.57 mmol, 1.0 equiv.) and 2,6-lutidine (1.32 mL, 11.4 mmol, 1.5 equiv.) in dry DCM (21 mL) at -78 °C under Ar. The reaction was stirred for 3 h at the same temperature before it was allowed to warm to 25 °C. The reaction was quenched by addition of sat. NH<sub>4</sub>Cl. The two phases were separated and the aqueous phase was extracted twice with DCM. The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude mixture was purified by FC (EtOAc/petroleum ether 30:70, R<sub>f</sub> = 0.85) to afford the title compound **5.19** (1.47 g, 5.58 mmol, 73%) as a colorless oil.

**<sup>1</sup>H NMR** (500 MHz, chloroform-*d*)  $\delta$  4.50 (s, 2H), 3.74 (s, 3H), 1.30 (s, 6H).

**<sup>13</sup>C NMR** (126 MHz, chloroform-*d*)  $\delta$  174.3, 118.8 (q,  $J$  = 319.7 Hz), 81.1, 52.7, 43.2, 21.9.

**<sup>19</sup>F NMR** (471 MHz, chloroform-*d*)  $\delta$  -74.5.

**(S)-3-(tert-Butyl)-6-(3-methoxy-2,2-dimethyl-3-oxopropyl)-7-methyl-2,3-dihydroimidazo[5,1-b]oxazol-6-ium trifluoromethanesulfonate (5.20)**

Methyl 2,2-dimethyl-3-(((trifluoromethyl)sulfonyl)oxy)propanoate **5.19** (220 mg, 0.83 mmol, 1.5 equiv.) was added to (*S*)-3-(*tert*-butyl)-7-methyl-2,3-dihydroimidazo[5,1-*b*]oxazole **5.9** (100 mg, 0.56 mmol, 1.0 equiv.) in dry MeCN (1.5 mL) under Ar. The reaction mixture was stirred at 70 °C for 16 h.

The solvent was removed under reduced pressure. A minimal amount of DCM was added to dissolve the crude mixture, and Et<sub>2</sub>O was added to precipitate the product. The solvent was removed and the residue further dried to afford the title compound **5.20** (157 mg, 0.35 mmol, 63%) as an orange viscous oil.

<sup>1</sup>H NMR (400 MHz, chloroform-*d*) δ 8.65 (s, 1H), 5.12 (dd, *J* = 9.3, 8.1 Hz, 1H), 4.92 (dd, *J* = 9.3, 3.3 Hz, 1H), 4.80 (dd, *J* = 8.1, 3.4 Hz, 1H), 4.32 (d, *J* = 14.6 Hz, 1H), 4.17 (d, *J* = 14.6 Hz, 1H), 3.75 (s, 3H), 2.16 (s, 3H), 1.33 (s, 3H), 1.29 (s, 3H), 1.03 (s, 9H).

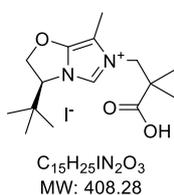
<sup>13</sup>C NMR (101 MHz, chloroform-*d*) δ 175.5, 148.2, 127.5, 103.1, 78.7, 67.4, 54.6, 53.0, 44.3, 34.1, 25.4, 23.5, 23.3, 7.6.

<sup>19</sup>F NMR (376 MHz, chloroform-*d*) δ -78.5.

IR (neat): ν (cm<sup>-1</sup>) 2972, 2361, 2340, 1731, 1539, 1477, 1278, 1159, 1031, 642.

HRMS (ESI): Calcd for C<sub>16</sub>H<sub>27</sub>N<sub>2</sub>O<sub>3</sub> [M-OTf]<sup>+</sup>: 295.2016, found 295.2020.

[α]<sub>D</sub><sup>20</sup>: +16.9 (c 0.97, CHCl<sub>3</sub>).

**(S)-3-(tert-Butyl)-6-(2-carboxy-2-methylpropyl)-7-methyl-2,3-dihydroimidazo[5,1-b]oxazol-6-ium iodide (BL<sup>9</sup>)**

NaI (416 mg, 2.78 mmol, 5 equiv.) was added to a solution of (*S*)-3-(*tert*-butyl)-6-(3-methoxy-2,2-dimethyl-3-oxopropyl)-7-methyl-2,3-dihydroimidazo[5,1-*b*]oxazol-6-ium trifluoromethanesulfonate **5.20** (157 mg, 0.35 mmol, 1 equiv.) in acetone (3 mL). The resulting reaction mixture was

stirred at 25 °C for 16 h. The solvent was removed under reduced pressure and the crude filtered over a plug of *Celite* (eluent DCM). The solvent was evaporated and H<sub>2</sub>O (1 mL) was added. 2 drops HI (57 wt% in H<sub>2</sub>O, cat.) were added to the reaction mixture. The resulting mixture was refluxed for 48 h. After cooling down to 25 °C, the water was removed under reduced pressure.

## Experimental Part

The crude mixture was purified by FC (MeOH/DCM/AcOH 10/90/1,  $R_f = 0.16$ ) to afford the title compound **BL**<sup>9</sup> (144 mg, 0.35 mmol, 98%) as an orange viscous oil.

<sup>1</sup>H NMR (400 MHz, acetonitrile-*d*<sub>3</sub>)  $\delta$  8.32 (s, 1H), 5.09 – 4.99 (m, 2H), 4.62 (dd,  $J = 7.6, 4.2$  Hz, 1H), 4.30 – 4.13 (m, 2H), 2.15 (s, 3H), 1.26 (s, 3H), 1.25 (s, 3H), 0.98 (s, 9H).

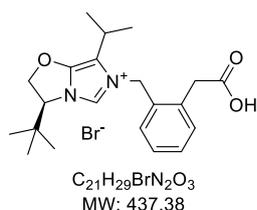
<sup>13</sup>C NMR (126 MHz, acetonitrile-*d*<sub>3</sub>)  $\delta$  176.9, 149.0, 126.7, 104.6, 79.8, 68.3, 54.9, 44.7, 34.7, 25.4, 23.4, 23.3, 7.8.

IR (neat):  $\nu$  (cm<sup>-1</sup>) 3703, 2960, 2923, 2853, 2361, 2340, 765, 630.

HRMS (ESI): Calcd for C<sub>15</sub>H<sub>25</sub>N<sub>2</sub>O<sub>3</sub> [M-I]<sup>+</sup>: 281.1860, found 281.1863.

$[\alpha]_D^{20}$ : +13.4 (c 0.37, CHCl<sub>3</sub>).

### (*S*)-3-(*tert*-Butyl)-6-(2-(carboxymethyl)benzyl)-7-isopropyl-2,3-dihydroimidazo[5,1-b]oxazol-6-ium bromide (**BL**<sup>10</sup>)



Methyl 2-(2-(bromomethyl)phenyl)acetate **5.16** (193 mg, 0.79 mmol, 1.1 equiv.) was added to a solution of (*S*)-3-(*tert*-butyl)-7-isopropyl-2,3-dihydroimidazo[5,1-b]oxazole **5.10** (150 mg, 0.72 mmol, 1.0 equiv.) in dry acetonitrile (2 mL) under Ar. The reaction mixture was stirred at 70 °C for 48 h. The solvent was removed under reduced pressure. A minimal amount of DCM was added to dissolve the crude mixture, and Et<sub>2</sub>O was added to precipitate the product. The solvent was removed and the residue further dried. Then, H<sub>2</sub>O (0.1 M imidazolium solution) and 2 drops of HBr (48 wt% in H<sub>2</sub>O, cat) were added to the crude mixture and the mixture was refluxed for 36 h. The mixture was allowed to cool down to 25 °C, and the water was removed under reduced pressure. The crude mixture was purified by FC (MeOH/DCM/AcOH 10:90:1,  $R_f = 0.08$ ) to obtain the title compound **BL**<sup>10</sup> (138 mg, 0.31 mmol, 44%) as a yellow viscous oil.

<sup>1</sup>H NMR (400 MHz, methanol-*d*<sub>4</sub>)  $\delta$  8.64 (s, 1H), 7.40 - 7.37 (m, 2H), 7.37 – 7.31 (m, 1H), 6.97 (d,  $J = 7.4$  Hz, 1H), 5.50 (s, 2H), 5.16 (d,  $J = 6.0$  Hz, 2H), 4.71 (t,  $J = 6.1$  Hz, 1H), 3.76 (s, 2H), 2.91 (sept,  $J = 6.8$  Hz, 1H), 1.20 (d,  $J = 6.9$  Hz, 3H), 1.18 (d,  $J = 6.9$  Hz, 3H), 1.04 (s, 9H).

<sup>13</sup>C NMR (126 MHz, methanol-*d*<sub>4</sub>)  $\delta$  175.1, 149.3, 135.4, 133.9, 132.9, 130.3, 129.1, 128.4, 126.9, 114.5, 114.5, 80.2, 68.6, 50.7, 34.9, 25.4, 24.6, 21.7, 21.1.

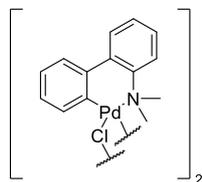
IR (neat):  $\nu$  (cm<sup>-1</sup>) 3388, 2968, 2361, 2340, 1602, 1539, 1373, 722.

## Experimental Part

**HRMS** (ESI): Calcd for  $C_{21}H_{29}N_2O_3$   $[M-Br]^+$ : 357.2173, found 357.2176.

$[\alpha]_D^{20}$ : +29.4 (c 0.47, MeOH).

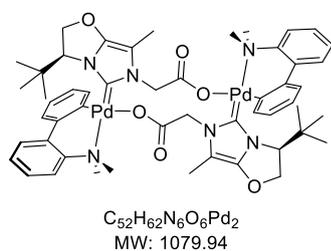
### **[Pd(DMBPA)Cl]<sub>2</sub>**



A solution of *N,N*-dimethyl-[1,1'-biphenyl]-2-amine (2.00 g, 10.2 mmol, 1.1 equiv.) in acetic acid (5 mL) was slowly added to a stirred solution of  $Pd(OAc)_2$  (2.01 g, 9.3 mmol, 1.0 equiv.) in acetic acid (111 mL) at room temperature. A color change to dark purple was observed after ca. 10 min.

The reaction was stirred for 48 h at the same temperature before the precipitated aceto-bridged dimeric cyclopalladate was filtered off and washed subsequently with pentane and  $Et_2O$ . After drying of the product under HV overnight, the obtained product was added to a mixture of LiCl (5.88 g, 139 mmol, 10 equiv.) in  $H_2O$  (55 mL) and acetone (110 mL). The resulting mixture was stirred at room temperature for 48 h.  $H_2O$  was added to precipitate the product and dissolve the salts. The mixture was filtered and subsequently washed with EtOH and  $Et_2O$  to afford the crude  $[Pd(DMBPA)Cl]_2$  as a light green solid. The crude product was directly engaged in the next reactions without further purification.

### **Complex C<sup>1</sup>**



The title compound **C<sup>1</sup>** (72.2 mg, 0.13 mmol, 71%) was obtained as a beige solid following **general procedure 6** using **BL<sup>1</sup>** (60 mg, 0.19 mmol, 1.0 equiv.), and  $Ag_2O$  (43.6 mg, 0.19 mmol, 1.0 equiv.) in dry DCM (18 mL) followed by Pd-dimer (63.6 mg, 0.09 mmol, 0.5 equiv.) in dry THF (5 mL). Single crystals suitable for X-ray

characterization were obtained by recrystallization from a mixture of DCM and hexane by solvent layering and slow diffusion.

**<sup>1</sup>H NMR** (500 MHz, methylene chloride- $d_2$ )  $\delta$  7.55 – 7.50 (m, 1H), 7.35 (dd,  $J = 7.7, 1.3$  Hz, 1H), 7.31 – 7.24 (m, 3H), 7.10 (td,  $J = 7.3, 1.6$  Hz, 1H), 6.91 – 6.83 (m, 2H), 4.71 (d,  $J = 15.5$  Hz, 1H), 4.59 (dd,  $J = 9.1, 1.2$  Hz, 1H), 4.47 (dd,  $J = 9.1, 6.9$  Hz, 1H), 4.37 (d,  $J = 15.6$  Hz, 1H), 3.12 (dd,  $J = 6.9, 1.2$  Hz, 1H), 3.02 (s, 3H), 2.57 (s, 3H), 2.09 (s, 3H), 0.68 (s, 9H).

**<sup>13</sup>C NMR** (126 MHz, methylene chloride- $d_2$ )  $\delta$  170.7, 156.2, 151.8, 148.2, 148.1, 142.5, 141.7, 139.2, 130.7, 128.0, 126.7, 126.4, 126.2, 125.5, 117.7, 100.6, 77.7, 66.7, 53.2, 52.2, 48.4, 34.7, 26.9, 8.2.

**IR** (neat)  $\nu$  ( $cm^{-1}$ ): 2961, 2924, 2361, 2340, 1711, 1617, 1468, 1393, 1256, 1058, 633, 604.

## Experimental Part

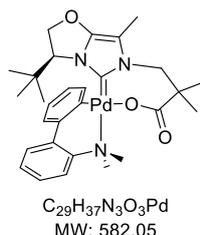
**HRMS** (ESI): Calcd for  $C_{52}H_{63}N_6O_6Pd_2$   $[M+H]^+$ : 1079.2876, found 1079.2872.

**mp**: >120 °C decomposition.

$[\alpha]_D^{20}$ : +101.7 (c 0.77,  $CH_2Cl_2$ ).

Structure characterized by X-ray analysis.

### Complex **C**<sup>2</sup>



The title compound **C**<sup>2</sup> (115 mg, 0.20 mmol, 97%) was obtained as a beige solid following **general procedure 6** using **BL**<sup>9</sup> (83.0 mg, 0.20 mmol, 1.0 equiv.), and  $Ag_2O$  (47.0 mg, 0.20 mmol, 1.0 equiv.) in dry DCM (20 mL) followed by Pd-dimer (68.6 mg, 0.10 mmol, 0.5 equiv.) in dry THF (10 mL).

**<sup>1</sup>H NMR** (500 MHz, methylene chloride-*d*<sub>2</sub>)  $\delta$  7.53 (dd,  $J = 7.7, 1.7$  Hz, 1H), 7.33 (dd,  $J = 7.6, 1.5$  Hz, 1H), 7.31 – 7.23 (m, 3H), 7.13 – 7.04 (m, 1H), 6.82 (td,  $J = 7.4, 1.5$  Hz, 1H), 6.45 (d,  $J = 7.5$  Hz, 1H), 5.31 (d,  $J = 13.8$  Hz, 1H), 4.54 (dd,  $J = 9.1, 1.5$  Hz, 1H), 4.31 (dd,  $J = 9.1, 7.2$  Hz, 1H), 3.66 – 3.62 (m, 1H), 2.84 – 2.79 (m, 1H), 2.62 (s, 3H), 2.12 (s, 3H), 1.41 (s, 3H), 1.30 (s, 3H), 1.06 (s, 3H), 0.70 (s, 9H).

**<sup>13</sup>C NMR** (126 MHz, methylene chloride-*d*<sub>2</sub>)  $\delta$  182.3, 157.9, 150.4, 148.5, 148.3, 142.5, 141.6, 138.8, 130.4, 128.1, 126.7, 126.4, 126.0, 125.4, 117.8, 101.4, 77.8, 66.0, 58.0, 52.3, 48.7, 34.7, 30.7, 27.0, 26.7, 24.2, 8.7.

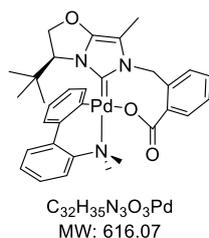
**IR** (neat):  $\nu$  ( $cm^{-1}$ ) 3678, 2964, 2923, 2361, 2341, 1591, 1559, 1462, 1393, 1258, 1058, 736.

**HRMS** (ESI): Calcd for  $C_{29}H_{38}N_3O_3Pd$   $[M+H]^+$ : 582.1954, found 582.1952.

**mp**: >80 °C decomposition.

$[\alpha]_D^{20}$ : +84.0 (c 0.78,  $CH_2Cl_2$ ).

### Complex **C**<sup>3</sup>



The title compound **C**<sup>3</sup> (57.0 mg, 0.09 mmol, 73%) was obtained as a beige solid following **general procedure 6** using **BL**<sup>6</sup> (50.0 mg, 0.13 mmol, 1.0 equiv.), and  $Ag_2O$  (29.2 mg, 0.13 mmol, 1.0 equiv.) in dry  $CH_2Cl_2$  (12 mL) followed by Pd-dimer (42.6 mg, 0.06 mmol, 0.5 equiv.) in dry THF (6 mL). Single crystals suitable for X-ray characterization were obtained by slow

evaporation of solvent from a THF/hexane mixture.

## Experimental Part

**<sup>1</sup>H NMR** (500 MHz, methylene chloride-*d*<sub>2</sub>) δ 7.57 – 7.51 (m, 2H), 7.41 – 7.38 (m, 1H), 7.35 – 7.26 (m, 6H), 7.05 (t, *J* = 7.5 Hz, 1H), 6.79 (t, *J* = 7.3 Hz, 1H), 6.51 (d, *J* = 14.1 Hz, 1H), 6.41 (d, *J* = 7.5 Hz, 1H), 4.90 (d, *J* = 14.1 Hz, 1H), 4.49 (d, *J* = 9.0 Hz, 1H), 4.22 (t, *J* = 8.1 Hz, 1H), 3.05 (s, 3H), 2.88 (d, *J* = 7.0 Hz, 1H), 2.55 (s, 3H), 2.03 (s, 3H), 0.76 (s, 9H).

**<sup>13</sup>C NMR**: due to some impurities and overlapping of some signals, the <sup>13</sup>C could not be assigned to the structure.

**IR (neat)**: ν (cm<sup>-1</sup>) 2957, 2925, 2854, 2362, 2339, 1705, 1605, 1563, 1438, 1382, 1257, 942, 739.

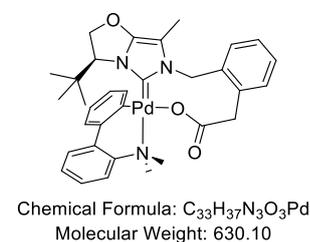
**HRMS (ESI)**: Calcd for C<sub>32</sub>H<sub>36</sub>N<sub>3</sub>O<sub>3</sub>Pd [M+H]<sup>+</sup>: 616.1798, found 616.1799.

**mp**: >110 °C decomposition.

**[α]<sub>D</sub><sup>20</sup>**: -29.5 (c 0.42, CH<sub>2</sub>Cl<sub>2</sub>).

Structure characterized by X-ray analysis.

### Complex C<sup>4</sup>



The title compound C<sup>4</sup> (35.2 mg, 0.056 mmol, 89%) was obtained as an off-white solid following **general procedure 6** using **L<sup>7</sup>** (25.7 mg, 0.063 mmol, 1.0 equiv.), Ag<sub>2</sub>O (14.6 mg, 0.063 mmol, 1.0 equiv.) in dry CH<sub>2</sub>Cl<sub>2</sub> (7 mL), followed by Pd-dimer (21.2 mg, 0.032 mmol, 0.5 equiv.) in dry THF (3.5 mL).

**<sup>1</sup>H NMR**: (500 MHz, methylene chloride-*d*<sub>2</sub>) δ 7.57 – 7.51 (m, 1H), 7.44 (dd, *J* = 7.2, 2.0 Hz, 1H), 7.39 – 7.31 (m, 3H), 7.30 – 7.19 (m, 3H), 7.15 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.01 – 6.96 (m, 1H), 6.80 – 6.74 (m, 1H), 6.19 (d, *J* = 7.5 Hz, 1H), 5.38 (d, *J* = 14.4 Hz, 1H), 5.02 (d, *J* = 14.2 Hz, 1H), 4.47 (d, *J* = 9.0 Hz, 1H), 4.10 (t, *J* = 8.0 Hz, 1H), 3.78 – 3.60 (m, 2H), 2.78 (d, *J* = 6.1 Hz, 1H), 2.74 (s, 3H), 2.19 (s, 3H), 2.15 (s, 3H), 0.73 (s, 9H).

**<sup>13</sup>C NMR** (126 MHz, methylene chloride-*d*<sub>2</sub>) δ 176.0, 157.7, 149.0, 148.7, 148.5, 142.4, 141.6, 139.1, 138.3, 135.9, 132.1, 131.9, 130.3, 129.1, 128.1, 127.3, 126.4, 126.2, 125.5, 125.1, 117.6, 102.2, 78.2, 66.2, 51.3, 50.3, 48.2, 44.1, 34.5, 26.4, 8.8.

**IR (neat)**: ν (cm<sup>-1</sup>) 2960, 2924, 2362, 2340, 1716, 1592, 1391, 1058, 783.

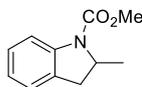
**HRMS (ESI)**: Calcd for C<sub>33</sub>H<sub>38</sub>N<sub>3</sub>O<sub>3</sub>Pd [M+H]<sup>+</sup>: 630.1955, found 630.1956.

**mp**: >90 °C decomposition.

## Experimental Part

$[\alpha]_D^{20}$ :  $-50.1$  (c 0.61,  $\text{CH}_2\text{Cl}_2$ ).

### Methyl 2-methylindoline-1-carboxylate (5.12)



Chemical Formula:  $\text{C}_{11}\text{H}_{13}\text{NO}_2$   
Molecular Weight: 191.23

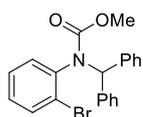
The title compound **5.12** was obtained following **general procedure 7** using aryl bromide **5.11** (13.6 mg, 0.050 mmol, 1 equiv.),  $\text{Cs}_2\text{CO}_3$  (24.7 mg, 0.075 mmol, 1.5 equiv), complex **4** (**C**<sup>4</sup>, 3.2 mg, 0.005 mmol, 0.1 equiv.), and HFIP (1  $\mu\text{L}$ , 0.01 mmol, 0.2 equiv.) in mesitylene (0.5 mL). The crude mixture was purified by FC ( $\text{Et}_2\text{O}$ /petroleum ether 8:92, R<sub>f</sub>: 0.28) affording a light yellow oil. <sup>1</sup>H NMR yield: 20%. All analytical data are consistent with literature data.<sup>[13]</sup> Racemic **5.12** was synthesized according to literature from **5.11**.<sup>[13]</sup>

<sup>1</sup>H NMR (400 MHz, chloroform-*d*)  $\delta$  7.81 (bs, 1H), 7.23 – 7.12 (m, 2H), 6.97 (t,  $J = 7.4$  Hz, 1H), 4.62 – 4.48 (m, 1H), 3.85 (s, 3H), 3.36 (dd,  $J = 15.9, 9.5$  Hz, 1H), 2.63 (dd,  $J = 15.9, 2.4$  Hz, 1H), 1.30 (d,  $J = 6.4$  Hz, 3H).

<sup>13</sup>C NMR (126 MHz, chloroform-*d*)  $\delta$  153.7, 141.6, 130.1, 127.6, 125.1, 122.8, 115.5, 55.5, 52.5, 36.0, 21.3.

**HPLC separation:** Chiralcel OJ-H; 99:1 (*n*hexane/*i*PrOH), 1 mL/min, 243 nm,  $t_r(\text{minor}) = 9.7$  min,  $t_r(\text{major}) = 10.7$  min, 22:78 e.r.

### methyl benzhydryl(2-bromophenyl)carbamate (5.13)



Chemical Formula:  $\text{C}_{21}\text{H}_{18}\text{BrNO}_2$   
Molecular Weight: 396.28

Synthesized according to literature.<sup>[22]</sup>

<sup>1</sup>H NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.42 – 7.30 (m, 5H), 7.30 – 7.24 (m, 1H), 7.23 – 7.18 (m, 1H), 7.15 – 7.02 (m, 6H), 6.96 (td,  $J = 7.7, 1.7$  Hz, 1H), 6.72 (s, 1H), 3.70 (s, 3H).

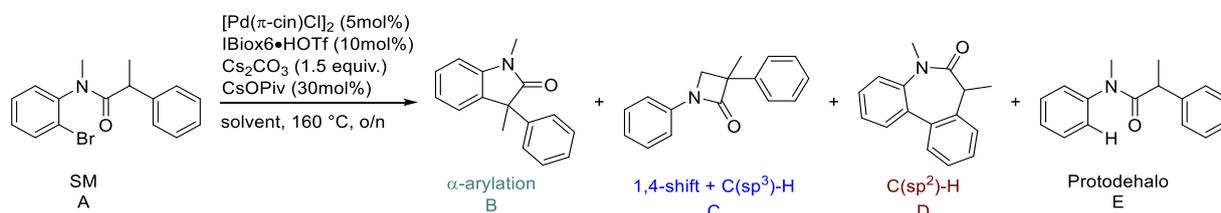
<sup>13</sup>C NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  156.1, 141.0, 139.2, 137.3, 133.1, 131.1, 130.6, 128.8, 128.4, 127.8, 127.8, 127.7, 127.5, 127.2, 126.3, 67.0, 53.5.

## Experimental Part

### 9.4 Synthesis of $\beta$ -Lactams *via* 1,4-Pd Shift-Mediated Double C(sp<sup>3</sup>)-H Activation

#### 9.4.1 Reaction Optimization

##### Solvent Screening



entry	solvent	<sup>1</sup> H NMR yield [%] <sup>[a]</sup>
1	Mesitylene	0:31:30:23:26
2	Xylenes	67:7:3:0:23
3	nBu <sub>2</sub> O	0:23:31:9:15
4	Cumene	0:27:10:14:10
5	CF <sub>3</sub> Ph	0:18:37:0:12
6	Anisole	65:9:6:0:5
7	DMA	20:33:12:0:20
8	DMSO	43:11:0:0:0
9	Benzonitrile	0:29:18:4:22
10	DME	0:41:32:10:13
11	1,2Cl <sub>2</sub> Ph	0:7:0:29:21

[a] with trichloroethylene as internal standard.

##### Stoichiometric Base Screening

entry	base	<sup>1</sup> H NMR yield [%] <sup>[a]</sup>
1	Cs <sub>2</sub> CO <sub>3</sub>	0:18:37:0:12
2	K <sub>2</sub> CO <sub>3</sub>	0:20:8:30:20
3	Na <sub>2</sub> CO <sub>3</sub>	71:10:0:0:13
4	Rb <sub>2</sub> CO <sub>3</sub>	0:33:37:0:0
5	KHCO <sub>3</sub>	0:15:10:20:17
6	Guanidine carbonate	82:15:0:5:0
7	Li <sub>2</sub> CO <sub>3</sub>	100:0:0:0:0
8	K <sub>3</sub> PO <sub>4</sub>	0:19:15:0:12
9	KHMDS	0:36:0:0:0
10	LiHMDS	6:89:0:2:2
11	NaOtBu	0:95:0:0:0
12	Cs <sub>2</sub> CO <sub>3</sub> <sup>[b]</sup>	0:25:44:0:19

[a] with trichloroethylene as internal standard. [b] with IBioxMe<sub>4</sub>.

## Experimental Part

### Base Screening with IBioxMe<sub>4</sub>

entry	base	<sup>1</sup> H NMR Yield [%] <sup>[a]</sup>
<b>1</b>	<b>Cs<sub>2</sub>CO<sub>3</sub></b>	<b>0:24:52:0:15</b>
2	K <sub>2</sub> CO <sub>3</sub>	0:29:19:0:20
3	Na <sub>2</sub> CO <sub>3</sub>	92:0:0:0:5
4	Rb <sub>2</sub> CO <sub>3</sub>	0:48:33:0:17
5	KHCO <sub>3</sub>	x:27:15:x:21
6	Guanidine carbonate	102:0:0:0:0
7	Li <sub>2</sub> CO <sub>3</sub>	98:0:0:0:0
8	K <sub>3</sub> PO <sub>4</sub>	0:37:25:0:28
9	CsOH	0:0:7:x:x
10	CsOPiv	13:0:4:0:34
11	CsO <sup>t</sup> Bu	0:47:6:0:38
12	CsOAc	74:0:0:0:30
13	CsTFA	24:8:5:0:9

[a] with trichloroethylene as internal standard

### Additive Screening with IBioxMe<sub>4</sub>

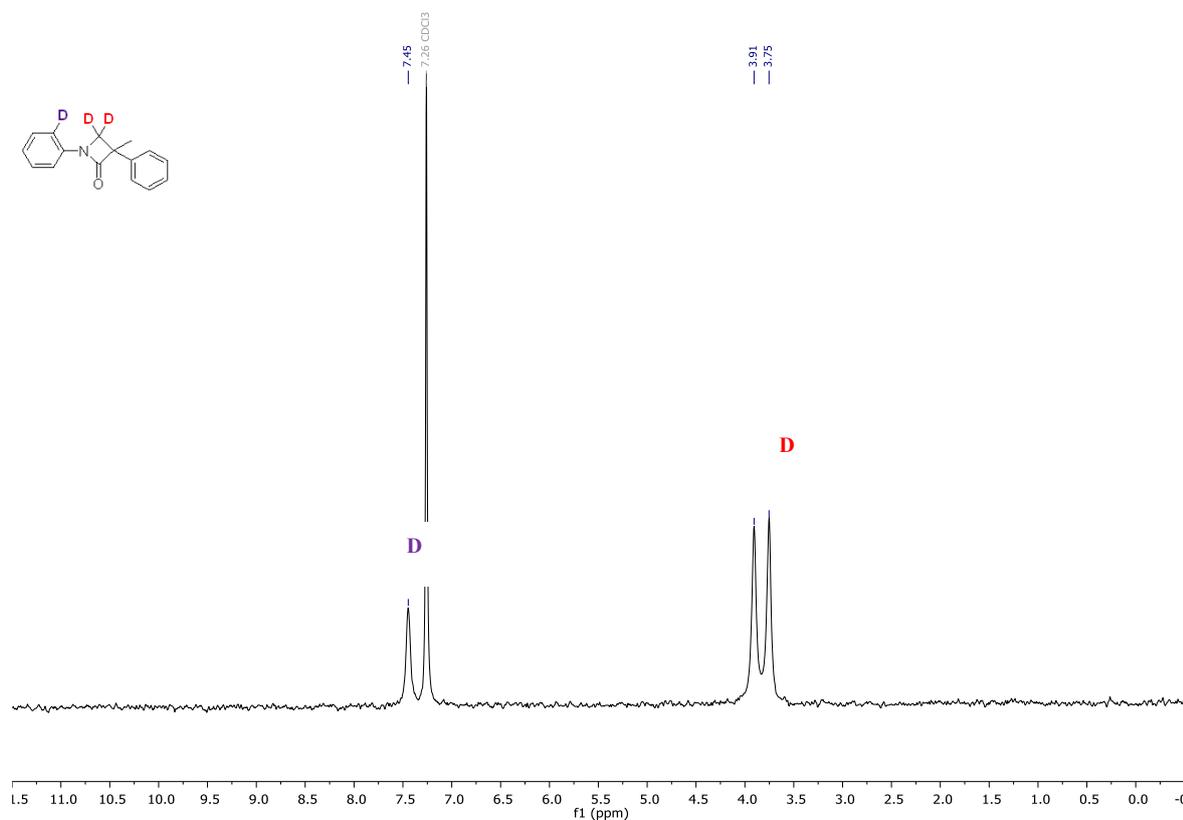
entry	additive	<sup>1</sup> H NMR yield [%] <sup>[a]</sup>
<b>1</b>	<b>CsOPiv</b>	<b>0:41:51:0:9</b>
2	CsOAc	87:0:0:0:14
3	CsTFA	0:21:47:0:24
4	Cesium decanoate	0:40:45:0:15
5	Adamantoic acid	0:33:43:0:20
6	dibenzylphosphate	0:56:39:0:26

[a] with trichloroethylene as internal standard

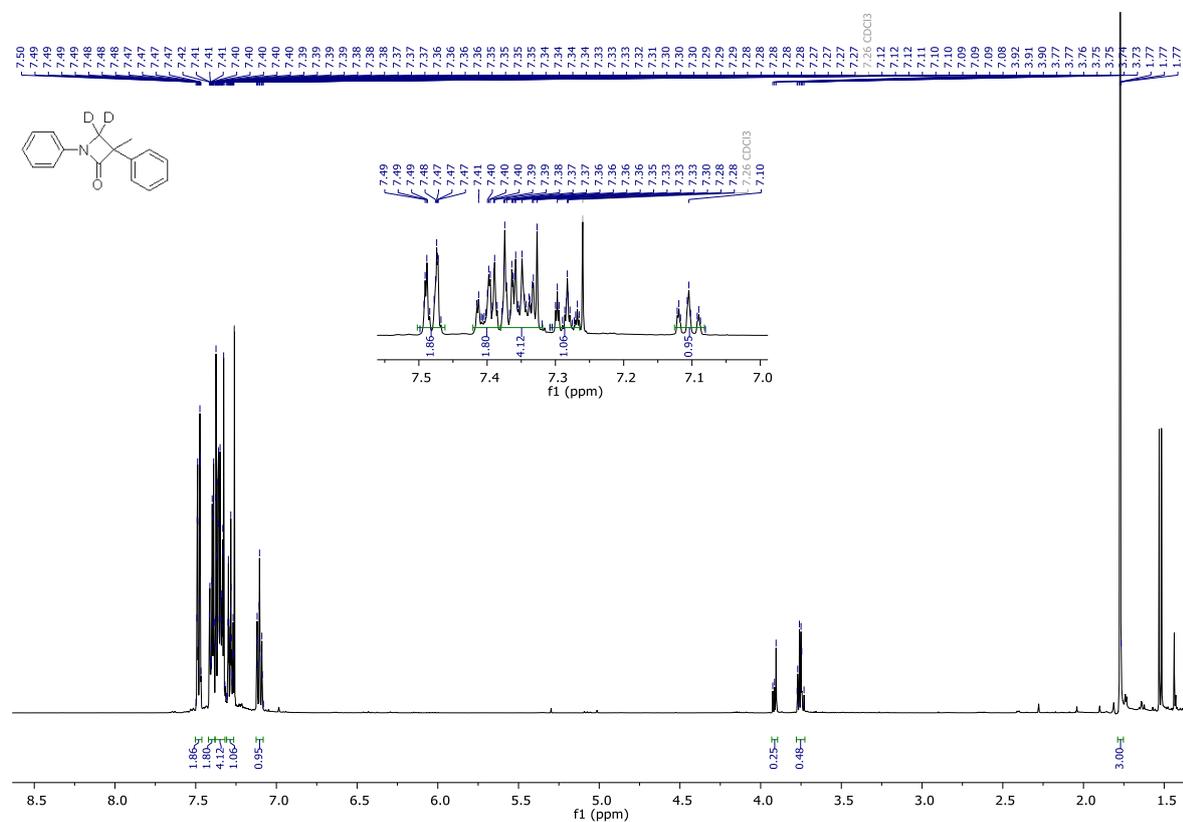
## Experimental Part

### 9.4.2 NMR Studies with Deuterium-Labeled Substrates

$^2\text{H}$  NMR (92 MHz,  $\text{CHCl}_3$ ) with  $\text{CDCl}_3$  as residual solvent

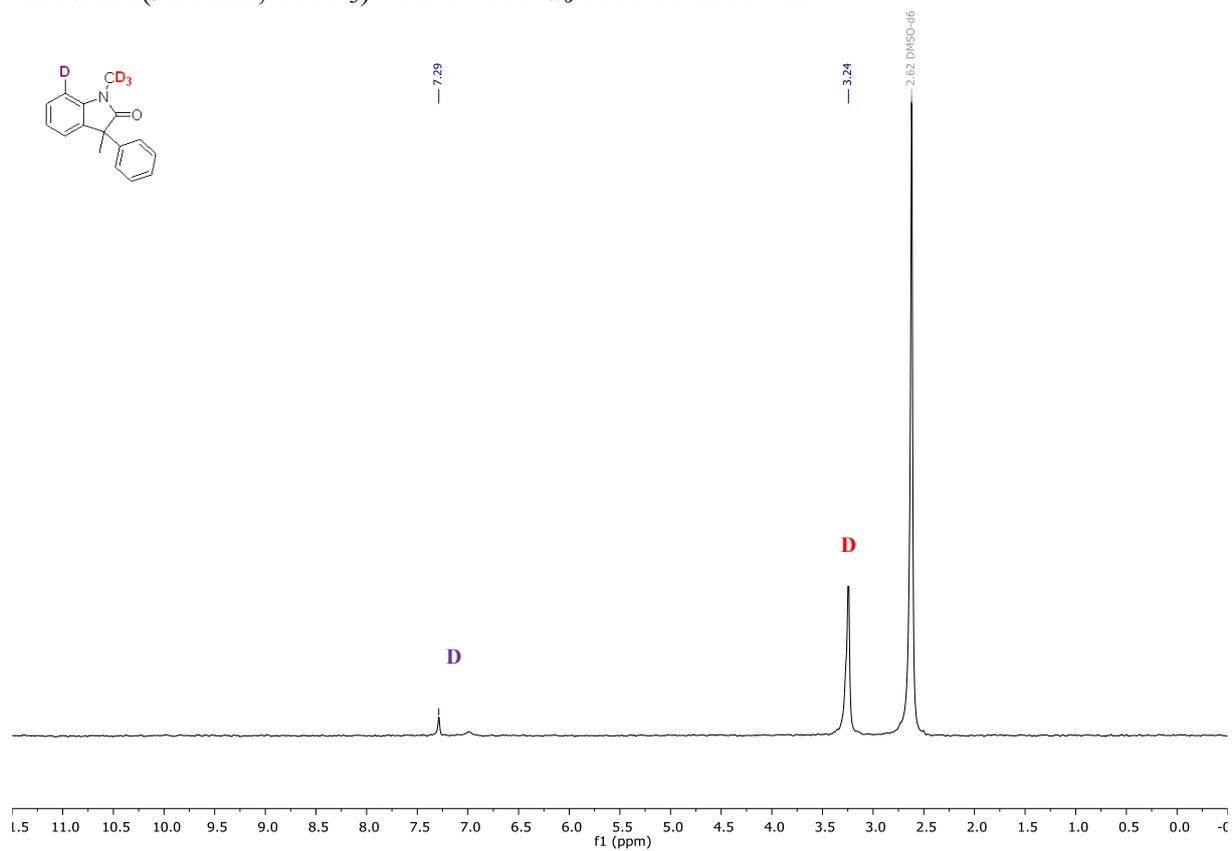


$^1\text{H}$  NMR (400 MHz, Chloroform-*d*).

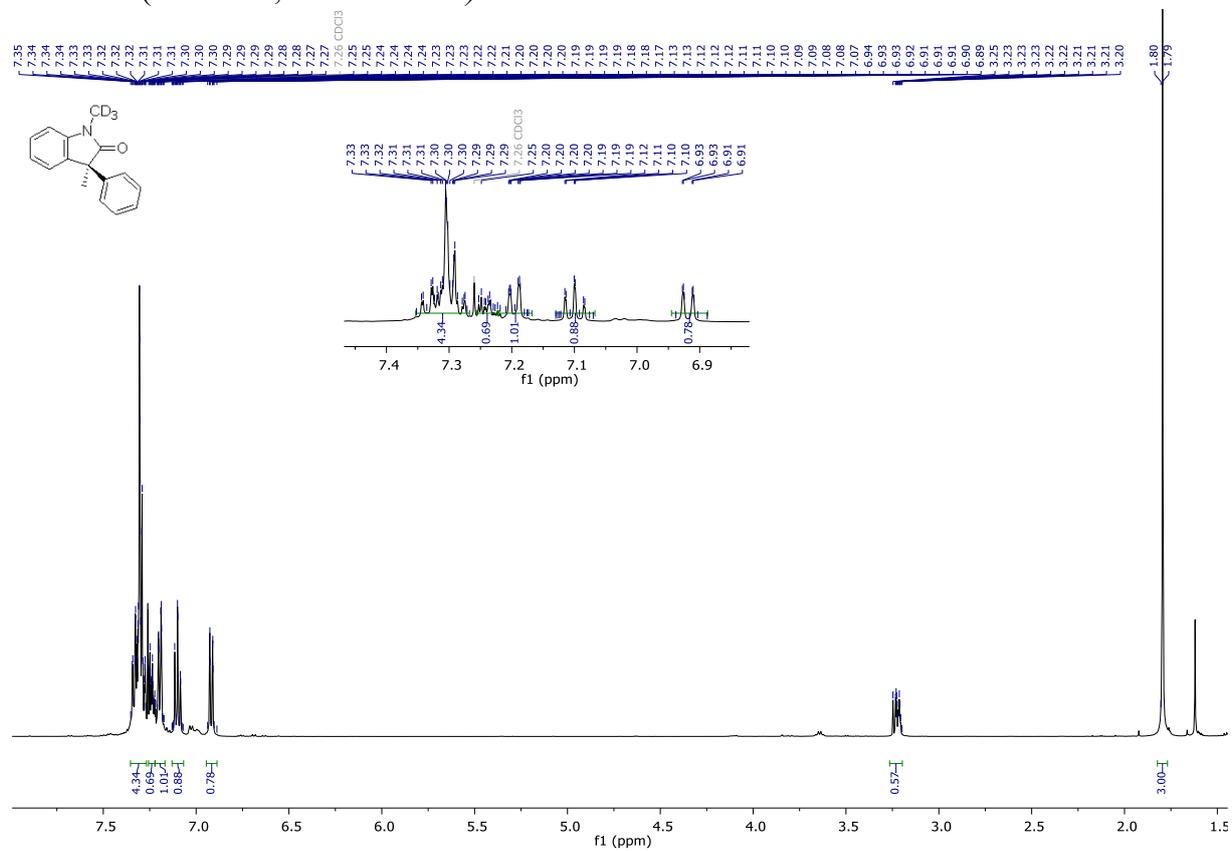


## Experimental Part

$^2\text{H}$  NMR (92 MHz,  $\text{CHCl}_3$ ) with  $\text{DMSO-}d_6$  as residual solvent



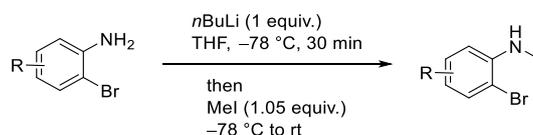
$^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )



## Experimental Part

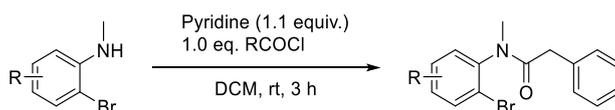
### 9.4.3 Procedures

#### General Procedure 8



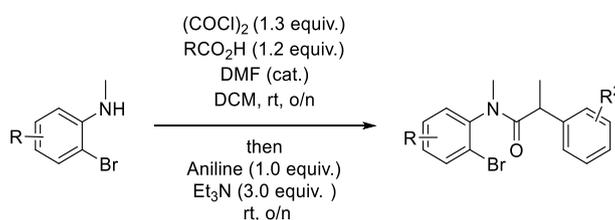
*n*BuLi (2.5 M in hexanes, 1.0 equiv.) was added dropwise to a solution of the corresponding aniline (1.1 equiv.) in dry THF at  $-78\text{ }^\circ\text{C}$  under Ar and stirred at the same temperature for 30 min before MeI (1.05 equiv.) was added. The resulting mixture was allowed to warm to room temperature overnight. H<sub>2</sub>O was added carefully to quench the reaction. The reaction mixture was diluted with Et<sub>2</sub>O and the aqueous phase extracted three times with Et<sub>2</sub>O. The combined organic phases were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude was purified by FC (EtOAc/cHex) to afford the methylated aniline.

#### General procedure 9



Pyridine (1.1 equiv.) was added dropwise to a stirred solution of the corresponding aniline (1.0 equiv.) and phenylacetyl chloride (1.0 equiv.) in dry DCM (0.22 M) at room temperature under Ar. The resulting mixture was stirred at the same temperature for 3 h. Then, sat. aqueous NH<sub>4</sub>Cl was added and extracted three times with DCM. The combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude was purified by FC (EtOAc/cHex) to afford the corresponding amides.

#### General Procedure 10

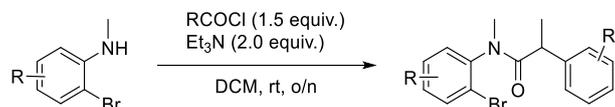


2 drops of DMF were added to the corresponding acid (1.2 equiv.) and oxalyl chloride (1.3 equiv.) in dry DCM (0.25 M) under Ar. The resulting mixture was stirred at room temperature for 16 h before the corresponding aniline (1.0 equiv.) was added followed by dropwise addition of Et<sub>3</sub>N (3.0 equiv.) and further stirred at room temperature for 16 h. Sat. aqueous NH<sub>4</sub>Cl was added and extracted three times with DCM. The combined organic layers were dried over

## Experimental Part

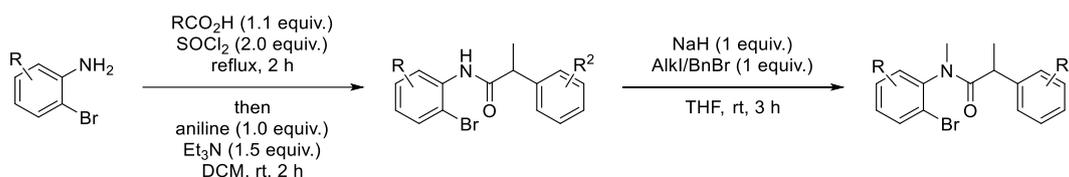
Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude was purified by FC (EtOAc/cHex or Et<sub>2</sub>O/PE) to afford the desired amide.

### General Procedure 11



Acyl chloride (1.5 equiv.) was added dropwise to a mixture of the corresponding aniline (1.0 equiv.) and Et<sub>3</sub>N (2.0 equiv.) in dry DCM (0.33 M). The resulting mixture was stirred at room temperature for 16 h. Sat. aqueous NH<sub>4</sub>Cl was added and extracted three times with DCM. The combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude was purified by FC (EtOAc/cHex or Et<sub>2</sub>O/PE) to afford the desired amide.

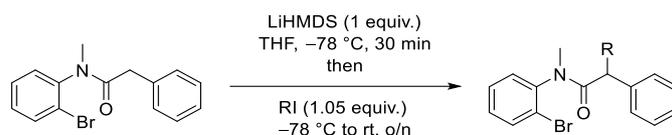
### General Procedure 12



The corresponding tertiary acid (1.1 equiv.) and SOCl<sub>2</sub> (2.0 equiv.) were refluxed for 2 h. The excess SOCl<sub>2</sub> was removed under reduced pressure. The resulting acetyl chloride was dissolved in dry DCM (0.43 M) under Ar. Subsequently, the corresponding aniline (1.0 equiv.) was added followed by dropwise addition of Et<sub>3</sub>N (1.5 equiv.). The resulting mixture was stirred at room temperature for 2 h or upon completion. The mixture was quenched with sat. aqueous NH<sub>4</sub>Cl and extracted three times with DCM. The combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure to afford the crude amide. The resulting crude amide was dissolved in dry THF (0.25 M) and NaH (60%, 1.0 equiv.) was added under Ar. After stirring at room temperature for 30 min, MeI (1.0 equiv.) was added and the mixture stirred for 3 h or until completion. The reaction was quenched by careful addition of H<sub>2</sub>O. The mixture was extracted three times with Et<sub>2</sub>O. The combined organic phases were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude was purified by FC (EtOAc/cHex) to afford the desired tertiary amides.

## Experimental Part

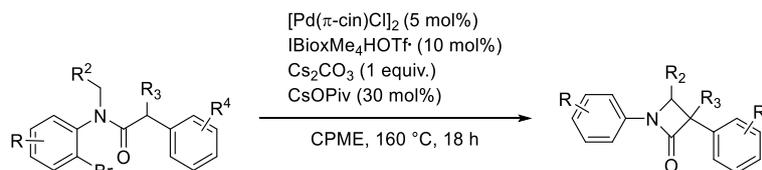
### General Procedure 13



The corresponding amide (1.00 equiv.) was dissolved in anhydrous THF (0.33 M) under argon. The mixture was cooled down to  $-78\text{ }^{\circ}\text{C}$  and stirred for 5 min. LiHMDS (1 M, 1.00 equiv.) was added and the resulting mixture stirred for further 15 min at the same temperature before the alkyl iodide (1.05 equiv.) was added. The resulting mixture was allowed to warm to room temperature and stirred at this temperature for 3 h. The reaction was quenched by addition of  $\text{H}_2\text{O}$  and was extracted three times with  $\text{Et}_2\text{O}$ . The combined organic layers were washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated under reduced pressure. The crude was purified by FC (EtOAc/cHex) to afford the desired alkylated amide.

### General Procedure 14

#### 0.1 – 0.3 mmol scale



A microwave vial (0.5-2 mL for 0.1 mmol scale and 10-20 mL for 0.3 mmol scale) was charged with the corresponding amide (0.30 mmol, 1.00 equiv.) and stirring bar. The vial was introduced into a glovebox and subsequently charged with  $\text{Cs}_2\text{CO}_3$  (97.0 mg, 0.30 mmol, 1.00 equiv.), CsOPiv (21.1 mg, 0.09 mmol, 0.30 equiv.),  $[\text{Pd}(\pi\text{-cinnamyl})\text{Cl}]_2$  (7.8 mg, 0.015 mmol, 0.05 equiv.), and IBioxMe<sub>4</sub>HOTf (10.8 mg, 0.03 mmol, 0.10 equiv.) before the vial was sealed with the corresponding metal cap and taken out of the glovebox. Dry and degassed CPME (3.0 mL) was added through the septum of the cap and the charged vial was inserted into a preheated oil bath at  $160\text{ }^{\circ}\text{C}$ . The reaction was stirred (ca. 600 rpm) at this temperature for 18 h before it was allowed to cool down to room temperature and filtered through a pad of *Celite* (eluted with EtOAc). The filtrate was concentrated under reduced pressure. The resulting crude was purified by FC (EtOAc/cHex) to afford the desired  $\beta$ -lactam.

For the analysis of the reaction mixture on 0.1 mmol scale: the crude was dissolved in  $\text{CDCl}_3$  (1 mL) and trichloroethylene (9  $\mu\text{L}$ , 0.1 mmol, 1 equiv.) was added as internal standard. The crude mixture was analyzed by GCMS and  $^1\text{H}$  NMR spectroscopy.

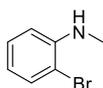
## Experimental Part

### 3 mmol scale

A 100 mL pressure flask was charged with the corresponding amide (2.87 mmol, 1.00 equiv.) and stirring bar. The flask was introduced into a glovebox and charged subsequently with  $\text{Cs}_2\text{CO}_3$  (947 mg, 2.87 mmol, 1.00 equiv.), CsOPiv (201 mg, 0.86 mmol, 0.30 equiv.),  $[\text{Pd}(\pi\text{-cinnamyl})\text{Cl}]_2$  (52 mg, 0.01 mmol, 0.035 equiv.), and IBioxMe<sub>4</sub>·HOTf (72 mg, 0.07 mmol, 0.07 equiv.). Dry CPME (29 mL, directly out of the new anhydrous Sigma Aldrich bottle) was added before the flask was sealed with the corresponding stopper and taken out of the glovebox. The content was stirred at room temperature for 5 min before it was inserted into a preheated oil bath at 160 °C. The reaction was stirred (ca 600 rpm) at this temperature for 18 h before it was allowed to cool down to room temperature and filtered through a pad of *Celite* (eluted with EtOAc). The filtrate was concentrated under reduced pressure. The crude was purified by FC (EtOAc/cHex) to afford the desired  $\beta$ -lactam.



Left picture: starting material before C-H activation in 100 mL pressure flask.  
Right picture: after C-H activation at 160 °C o/n.

**2-bromo-*N*-methylaniline (6.45)**

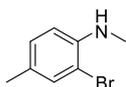
Chemical Formula: C<sub>7</sub>H<sub>8</sub>BrN  
Molecular Weight: 186.05

Following **General Procedure 8**, *o*-Bromoaniline (6.00 mL, 55.0 mmol, 1.00 equiv.) was reacted with *n*BuLi (2.5 M in hexanes, 22.0 mL, 55.0 mmol, 1.00 equiv.), and MeI (3.6 mL, 57.8 mmol, 1.05 equiv.) in dry THF (113 mL) to afford the title compound **6.45** (9.11 g, 48.9 mmol, 89%) as a yellow oil. Analytical data are in agreement with the literature.<sup>[23]</sup>

<sup>1</sup>H NMR (500 MHz, Chloroform-*d*) δ 7.41 (d''t'', *J* = 7.9, 1.5 Hz, 1H), 7.20 (dd''t'', *J* = 8.4, 7.3, 1.5 Hz, 1H), 6.65 – 6.52 (m, 2H), 4.34 (s, 1H), 2.89 (s, 3H).

<sup>13</sup>C NMR (126 MHz, Chloroform-*d*) δ 146.1, 132.4, 128.7, 117.7, 110.8, 109.7, 30.7.

R<sub>f</sub> = 0.47 (EtOAc/cHex 5:95)

**2-bromo-*N*,4-dimethylaniline (6.46)**

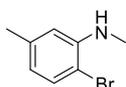
Chemical Formula: C<sub>8</sub>H<sub>10</sub>BrN  
Molecular Weight: 200.08

Following **General Procedure 8**, 2-Bromo-4-Methylaniline (2.12 g, 11.4 mmol, 1.10 equiv.) was reacted with *n*BuLi (2.5 M in hexanes, 4.14 mL, 10.4 mmol, 1.00 equiv.), and MeI (0.67 mL, 10.9 mmol, 1.05 equiv.) in dry THF (21 mL) to afford the title compound **6.46** (1.92 g, 9.59 mmol, 93%) as a yellow oil. Analytical data are in agreement with the literature.<sup>[24]</sup>

<sup>1</sup>H NMR (400 MHz, Chloroform-*d*) δ 7.27 – 7.25 (m, 1H), 7.02 (dd, *J* = 8.2, 1.2 Hz, 1H), 6.54 (d, *J* = 8.2 Hz, 1H), 4.18 (bs, 1H), 2.87 (d, *J* = 5.2 Hz, 3H), 2.23 (s, 3H).

<sup>13</sup>C NMR (101 MHz, Chloroform-*d*) δ 143.9, 132.8, 129.2, 127.3, 110.9, 109.6, 31.0, 20.2.

R<sub>f</sub> = 0.62 (Et<sub>2</sub>O/petroleum ether 10:90)

**2-bromo-*N*,5-dimethylaniline (6.47)**

Chemical Formula: C<sub>8</sub>H<sub>10</sub>BrN  
Molecular Weight: 200.08

Following **General Procedure 8**, 2-Bromo-5-Methylaniline (2.10 g, 11.4 mmol, 1.10 equiv.) was reacted with *n*BuLi (2.5 M in hexanes, 4.14 mL, 10.4 mmol, 1.00 equiv.), and MeI (0.67 mL, 10.9 mmol, 1.05 equiv.) in dry THF (21 mL) to afford the title compound **6.47** (1.93 g, 9.65 mmol, 93%) as a yellow oil. Analytical data are in agreement with the literature.<sup>[24]</sup>

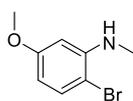
<sup>1</sup>H NMR (500 MHz, Chloroform-*d*) δ 7.30 (d, *J* = 7.9 Hz, 1H), 6.46 (d, *J* = 1.9 Hz, 1H), 6.45 – 6.38 (m, 1H), 4.29 (bs, 1H), 2.90 (d, *J* = 3.3 Hz, 3H), 2.31 (s, 3H).

<sup>13</sup>C NMR (126 MHz, Chloroform-*d*) δ 145.8, 138.6, 132.0, 118.6, 111.7, 106.6, 30.7, 21.6.

## Experimental Part

$R_f = 0.43$  (EtOAc/cHex 5:95)

### 2-bromo-5-methoxy-*N*-methylaniline (6.48)



Chemical Formula:  $C_8H_{10}BrNO$   
Molecular Weight: 216.08

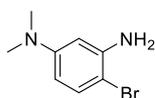
Following **General Procedure 8**, 2-Bromo-5-Methoxyaniline (2.15 g, 10.6 mmol, 1.05 equiv.) was reacted with *n*BuLi (2.5 M, 4.04 mL, 10.1 mmol, 1.00 equiv.), and MeI (0.66 mL, 10.6 mmol, 1.05 equiv.) in dry THF (21 mL) to afford the title compound **6.48** (1.93 g, 9.65 mmol, 93%) as a yellow oil. Analytical data are in agreement with the literature.<sup>[25]</sup>

$^1H$  NMR (400 MHz, Chloroform-*d*)  $\delta$  7.29 (d,  $J = 8.5$  Hz, 1H), 6.21 – 6.13 (m, 2H), 4.33 (bs, 1H), 3.79 (s, 3H), 2.88 (d,  $J = 5.1$  Hz, 3H).

$^{13}C$  NMR (101 MHz, Chloroform-*d*)  $\delta$  160.5, 146.9, 132.5, 102.5, 101.0, 97.7, 55.5, 30.7

$R_f = 0.3$  (EtOAc/cHex 5:95)

### 4-bromo-*N*<sup>1</sup>,*N*<sup>1</sup>-dimethylbenzene-1,3-diamine (6.49)



Chemical Formula:  $C_8H_{11}BrN_2$   
Molecular Weight: 215.09

Was synthesized following literature procedures: Nitration<sup>[26]</sup> followed by reduction.<sup>[27]</sup> Analytical data are in agreement with the literature.

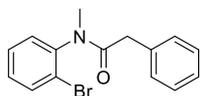
$^1H$  NMR (400 MHz, Chloroform-*d*)  $\delta$  7.20 (d,  $J = 8.8$  Hz, 1H), 6.12 (d,  $J = 2.8$  Hz, 1H), 6.08 (dd,  $J = 8.8, 2.9$  Hz, 1H), 3.97 (bs, 2H), 2.89 (s, 6H).

$^{13}C$  NMR (101 MHz, Chloroform-*d*)  $\delta$  151.2, 144.5, 132.7, 105.3, 99.8, 97.1, 40.8.

$R_f = 0.23$  (EtOAc/cHex 20:80)

## Substrate Synthesis

### *N*-(2-bromophenyl)-*N*-methyl-2-phenylacetamide (6.50)



Chemical Formula:  $C_{15}H_{14}BrNO$   
Molecular Weight: 304.19

Following **General Procedure 9**, **6.45** (3.00 g, 16.1 mmol, 1.0 equiv.) was reacted with phenylacetyl chloride (2.15 mL, 16.1 mmol, 1.0 equiv.) and pyridine (1.43 mL, 17.7 mmol, 1.1 equiv.) in dry DCM (74 mL) to afford the title compound **6.50** (4.46 g, 16.6 mmol, 91%) as a white solid. Analytical data are in agreement with literature.<sup>[28]</sup>

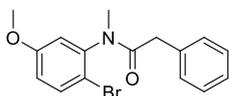
$^1H$  NMR (400 MHz, Chloroform-*d*)  $\delta$  7.69 (dd,  $J = 8.0, 1.4$  Hz, 1H), 7.33 (“t”d,  $J = 7.6, 1.5$  Hz, 1H), 7.30 – 7.11 (m, 5H), 7.08 – 6.99 (m, 2H), 3.42 (d,  $J = 14.9$  Hz, 1H), 3.31 (d,  $J = 14.9$  Hz, 1H), 3.20 (s, 3H).

## Experimental Part

$^{13}\text{C}$  NMR (101 MHz, Chloroform-*d*)  $\delta$  170.9, 142.6, 135.0, 134.0, 130.4, 130.0, 129.3, 128.9, 128.4, 126.7, 123.7, 41.2, 36.2.

$R_f$  = 0.17 (EtOAc/cHex 20:80)

### *N*-(2-bromo-5-methoxyphenyl)-*N*-methyl-2-phenylacetamide (6.51)



Chemical Formula:  $\text{C}_{16}\text{H}_{16}\text{BrNO}_2$   
Molecular Weight: 334.21

Following **General Procedure 9, 6.48** (400 mg, 1.85 mmol, 1.0 equiv.) was reacted with phenylacetyl chloride (0.27 mL, 1.85 mmol, 1.0 equiv.) and pyridine (0.16 mL, 2.04 mmol, 1.1 equiv.) in dry DCM (8.5 mL) to afford the title compound **6.51** (542 mg, 1.62 mmol, 87%) as a white solid.

$^1\text{H}$  NMR (500 MHz, Chloroform-*d*)  $\delta$  7.55 (d,  $J$  = 8.9 Hz, 1H), 7.26 – 7.17 (m, 3H), 7.08 – 7.04 (m, 2H), 6.82 (dd,  $J$  = 8.9, 3.0 Hz, 1H), 6.59 (d,  $J$  = 3.0 Hz, 1H), 3.68 (s, 3H), 3.47 (d,  $J$  = 14.9 Hz, 1H), 3.33 (d,  $J$  = 14.9 Hz, 1H), 3.19 (s, 3H).

$^{13}\text{C}$  NMR (126 MHz, Chloroform-*d*)  $\delta$  170.9, 159.9, 143.2, 135.3, 134.1, 129.4, 128.4, 126.8, 116.3, 115.6, 113.7, 55.7, 41.4, 36.1.

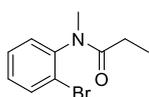
**IR** (neat):  $\nu$  ( $\text{cm}^{-1}$ ) 3062, 2936, 2846, 1765, 1590, 1478, 1370, 1226, 1117, 696.

**HRMS** (ESI): Calcd for  $\text{C}_{16}\text{H}_{17}\text{BrNO}_2$   $[\text{M}+\text{H}]^+$ : 334.0437, found: 334.0439.

$R_f$  = 0.17 (EtOAc/cHex 30:70)

**mp**: 95 °C

### *N*-(2-bromophenyl)-*N*-methylpropionamide (6.12)

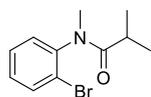


Chemical Formula:  $\text{C}_{10}\text{H}_{12}\text{BrNO}$   
Molecular Weight: 242.12

Following **General Procedure 9, 6.45** (500 mg, 2.69 mmol, 1.00 equiv.) was reacted with propionyl chloride (0.25 mL, 2.82 mmol, 1.05 equiv.) and pyridine (0.24 mL, 2.96 mmol, 1.10 equiv.) in dry DCM (11.5 mL) to afford the title compound **6.12** (460 mg, 1.9 mmol, 70%) as a white solid.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.68 (dd,  $J$  = 7.9, 1.5 Hz, 1H), 7.42 – 7.35 (m, 1H), 7.30 – 7.20 (m, 2H), 3.19 (s, 3H), 1.97 (q,  $J$  = 7.5 Hz, 2H), 1.05 (t,  $J$  = 7.4 Hz, 3H).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  173.8, 143.0, 134.0, 130.0, 129.8, 129.1, 123.7, 35.9, 27.5, 9.6.

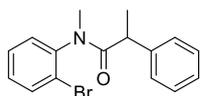
***N*-(2-bromophenyl)-*N*-methylisobutyramide (6.13)**

Chemical Formula: C<sub>11</sub>H<sub>14</sub>BrNO  
Molecular Weight: 256.14

Following **General Procedure 9**, **6.45** (500 mg, 2.69 mmol, 1.00 equiv.) was reacted with isobutyryl chloride (0.24 mL, 2.82 mmol, 1.05 equiv.) and pyridine (0.24 mL, 2.96 mmol, 1.10 equiv.) in dry DCM (11.5 mL) to afford the title compound **6.13** (378 mg, 1.48 mmol, 54%) as a white solid.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.62 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.35 – 7.28 (m, 1H), 7.24 – 7.14 (m, 2H), 3.11 (s, 3H), 2.19 (dq, *J* = 13.4, 6.7 Hz, 1H), 1.02 (d, *J* = 6.7 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 3H).

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 177.45, 143.04, 133.99, 129.82, 129.70, 128.99, 123.72, 36.01, 31.76, 20.02, 19.52.

***N*-(2-bromophenyl)-*N*-methyl-2-phenylpropanamide (6.52)**

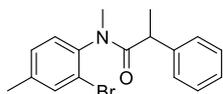
Chemical Formula: C<sub>16</sub>H<sub>16</sub>BrNO  
Molecular Weight: 318.21

Following **General Procedure 11**, methyl-aniline **6.45** (1.00 g, 5.37 mmol, 1.0 equiv.) was reacted with 2-phenylacetyl chloride (95%, 1.43 g, 8.06 mmol, 1.5 equiv.) and Et<sub>3</sub>N (1.51 mL, 10.7 mmol, 2.0 equiv.) in dry DCM (15 mL). The crude was purified by FC (0-15% EtOAc in cHex) to afford the desired amide **6.52** (1.46 g, 4.60 mmol, 86%) as a light yellow viscous oil which occurs as a conformational mixture. Analytical data are in agreement with the literature.<sup>[23]</sup>

**<sup>1</sup>H NMR** (500 MHz, Chloroform-*d*) δ 7.71 (dd, *J* = 7.9, 1.5 Hz, 0.66H), 7.58 (dd, *J* = 8.0, 1.4 Hz, 0.24H), 7.45 – 7.41 (m, 0.24H), 7.36 (dd, *J* = 7.8, 1.7 Hz, 0.24H), 7.28 – 7.25 (m, 0.24H), 7.24 – 7.14 (m, 4.61H), 7.03 – 6.99 (m, 0.51H), 6.97 – 6.94 (m, 1.41H), 6.70 (dd, *J* = 7.7, 1.7 Hz, 0.67H), 3.53 (q, *J* = 6.9 Hz, 0.26H), 3.34 (q, *J* = 6.9 Hz, 0.75H), 3.19 (s, 0.79H), 3.17 (s, 2.06H), 1.43 (d, *J* = 6.9 Hz, 2.15H), 1.41 (d, *J* = 7.0 Hz, 0.80H).

**<sup>13</sup>C NMR** (126 MHz, Chloroform-*d*) δ 174.1, 173.9, 142.7, 142.4, 141.8, 140.8, 134.2, 133.7, 131.0, 130.2, 129.9, 129.8, 128.8, 128.6, 128.5, 128.3, 128.2, 127.6, 126.9, 126.8, 124.4, 123.4, 44.2, 43.4, 36.3, 36.3, 20.8, 20.3.

**R<sub>f</sub>** = 0.42 (EtOAc/cHex 20:80)

***N*-(2-bromo-4-methylphenyl)-*N*-methyl-2-phenylpropanamide (6.53)**

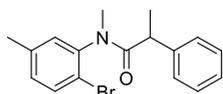
Chemical Formula: C<sub>17</sub>H<sub>18</sub>BrNO  
Molecular Weight: 332.24

Following **General Procedure 11**, 2-phenylpropionyl chloride (95%, 700 mg, 3.95 mmol 1.5 equiv.) was reacted with methyl-aniline **6.46** (527 mg, 2.63 mmol, 1.0 equiv.) and Et<sub>3</sub>N (0.74 mL, 5.26 mmol, 2.0 equiv.) in dry DCM (7.6 mL). The crude was purified by FC (Et<sub>2</sub>O/PE 15:85) to afford the amide **6.53** (603 mg, 1.82 mmol, 69%) as a yellow viscous oil which occurs as a conformational mixture. Analytical data are in agreement with the literature.<sup>[29]</sup>

**<sup>1</sup>H NMR** (500 MHz, Chloroform-*d*) δ 7.53 – 7.52 (m, 0.70H), 7.42- 7.41 (m, 0.25H), 7.23 – 7.15 (m, 3.39H), 7.08 – 7.04 (m, 0.48H), 7.02 – 6.95 (m, 2.16H), 6.61 (d, *J* = 7.9 Hz, 0.67H), 3.54 (q, *J* = 7.0 Hz, 0.25H), 3.37 (q, *J* = 6.9 Hz, 0.71H), 3.16 (s, 0.74H), 3.14 (s, 2.20H), 2.40 (s, 0.75H), 2.37 (s, 2.07H). 1.43 (d, *J* = 6.9 Hz, 2.15H), 1.40 (d, *J* = 7.0 Hz, 0.76H).

**<sup>13</sup>C NMR** (126 MHz, Chloroform-*d*) δ 174.4, 174.1, 141.9, 140.9, 140.3, 140.2, 140.1, 139.8, 134.5, 134.1, 130.5, 129.7, 129.5, 129.3, 128.5, 128.3, 128.2, 127.7, 126.8, 126.8, 123.8, 123.4, 44.0, 43.2, 36.4, 36.4, 21.0, 21.0, 20.8, 20.2.

**R<sub>f</sub>** = 0.48 (EtOAc/cHex 20:80)

***N*-(2-bromo-5-methylphenyl)-*N*-methyl-2-phenylpropanamide (6.54)**

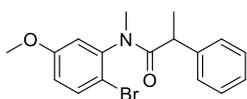
Chemical Formula: C<sub>17</sub>H<sub>18</sub>BrNO  
Molecular Weight: 332.24

Following **General Procedure 11**, methyl-aniline **6.47** (582 mg, 2.91 mmol, 1.0 equiv.) was reacted with 2-phenylacetyl chloride (95%, 775 mg, 4.37 mmol, 1.5 equiv.) and Et<sub>3</sub>N (0.82 mL, 5.82 mmol, 2.0 equiv.) in dry DCM (8.4 mL). The crude was purified by FC (0-15% EtOAc in PE) to afford the desired amide **6.54** (710 mg, 2.14 mmol, 73%) as a white solid which occurs as a conformational mixture. Analytical data are in agreement with the literature.<sup>[29]</sup>

**<sup>1</sup>H NMR** (500 MHz, Chloroform-*d*) δ 7.55 (d, *J* = 8.2 Hz, 0.71H), 7.44 (d, *J* = 8.2 Hz, 0.22H), 7.22 – 7.14 (m, 3.13H), 7.08 – 7.05 (m, 0.22H), 7.04 (dd, *J* = 7.8, 1.8 Hz, 0.44H), 7.02 – 6.99 (m, 0.78H), 6.94 – 6.91 (m, 1.46H), 6.39 (dd, *J* = 2.2, 0.8 Hz, 0.71H), 3.54 (q, *J* = 7.0 Hz, 0.22H), 3.32 (q, *J* = 6.9 Hz, 0.78H), 3.17 (s, 0.68H), 3.15 (s, 2.32H), 2.39 (d, *J* = 0.7 Hz, 0.63H), 2.10 (d, *J* = 0.7 Hz, 2.28H), 1.41 (m, 1.43 – 1.40 3H).

**<sup>13</sup>C NMR** (126 MHz, Chloroform-*d*) δ 174.1, 173.8, 142.4, 142.1, 141.9, 140.8, 139.1, 138.8, 133.7, 133.1, 131.9, 130.7, 130.7, 130.5, 128.4, 128.3, 128.2, 127.6, 126.8, 126.7, 120.7, 120.0, 44.4, 43.3, 36.3, 36.2, 21.0, 20.7, 20.7, 20.3.

**R<sub>f</sub>** = 0.48 (EtOAc/cHex 20:80)

***N*-(2-bromo-5-methoxyphenyl)-*N*-methyl-2-phenylpropanamide (6.55)**

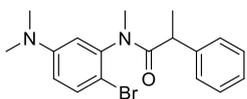
Chemical Formula: C<sub>17</sub>H<sub>18</sub>BrNO<sub>2</sub>  
Molecular Weight: 348.24

Following **General Procedure 11**, 4-methoxy-aniline **6.48** (350 mg, 1.62 mmol, 1.0 equiv.) was reacted with 2-phenylacetyl chloride (95%, 345 mg, 1.94 mmol, 1.2 equiv.) and Et<sub>3</sub>N (0.34 mL, 2.43 mmol, 1.5 equiv.) in dry DCM (4.6 mL). The crude was purified by FC (0-20% EtOAc in cHex) to afford the desired amide **6.55** (258 mg, 0.74 mmol, 46%) as a white solid which occurs as a conformational mixture. Analytical data are in agreement with the literature.<sup>[29]</sup>

**<sup>1</sup>H NMR** (400 MHz, Chloroform-*d*) δ 7.54 (d, *J* = 8.9 Hz, 0.71H), 7.46 (d, *J* = 8.8 Hz, 0.18H), 7.24 – 7.14 (m, 2.78H), 7.09 – 7.04 (m, 0.38H), 7.01 – 6.94 (m, 1.53H), 6.83 (dd, *J* = 8.8, 3.0 Hz, 0.19H), 6.78 (dd, *J* = 8.9, 3.0 Hz, 0.74H), 6.13 (d, *J* = 3.0 Hz, 0.71H), 3.86 (s, 0.57H), 3.57 (q, *J* = 7.0 Hz, 0.20H), 3.47 (s, 2.25H), 3.36 (q, *J* = 6.9 Hz, 0.74H), 3.17 (s, 0.55H), 3.16 (s, 2.22H), 1.42 (d, *J* = 6.9 Hz, 2.93H).

**<sup>13</sup>C NMR** (101 MHz, Chloroform-*d*) δ 174.1, 173.7, 159.9, 159.5, 143.3, 142.9, 142.3, 140.8, 134.4, 133.8, 128.6, 128.3, 128.2, 127.6, 126.9, 126.8, 117.1, 115.9, 115.5, 115.4, 114.5, 113.7, 55.9, 55.5, 44.4, 43.3, 36.2, 36.2, 20.8, 20.3.

**R<sub>f</sub>** = 0.31 (EtOAc/cHex 20:80)

***N*-(2-bromo-5-(dimethylamino)phenyl)-*N*-methyl-2-phenylpropanamide (6.56)**

Chemical Formula: C<sub>18</sub>H<sub>21</sub>BrN<sub>2</sub>O  
Molecular Weight: 361.28

Following **General Procedure 11**, 2-phenylpropionic acid (0.28 mL, 2.05 mmol 1.1 equiv.), SOCl<sub>2</sub> (0.27 mL; 3.71 mmol, 2.0 equiv.), **6.49** (400 mg, 1.86 mmol, 1.0 equiv.), and Et<sub>3</sub>N (0.39 mL, 2.79 mmol, 1.5 equiv.) in dry DCM (5.4 mL) were reacted to the amide. The crude amide was further reacted with NaH (60%, 75 mg, 1.86 mmol, 1.0 equiv.) and MeI (0.12 mL, 1.86 mmol, 1.0 equiv.) in dry THF (7.5 mL) and purified by FC to afford the title compound **6.56** (525 mg, 1.45 mmol, 78%) as a beige solid which occurs as a conformational mixture.

**<sup>1</sup>H NMR** (500 MHz, Chloroform-*d*) δ 7.44 (d, *J* = 8.9 Hz, 0.74H), 7.39 – 7.36 (m, 0.18H), 7.24 – 7.12 (m, 3.43H), 7.04 – 6.99 (m, 1.64H), 6.63 – 6.58 (m, 0.38H), 6.54 (dd, *J* = 9.0, 3.1 Hz, 0.85H), 5.94 (d, *J* = 3.1 Hz, 0.79H), 3.63 (q, *J* = 7.0 Hz, 0.18H), 3.42 (q, *J* = 6.9 Hz, 0.84H), 3.17 (s, 0.61H), 3.16 (s, 2.53H), 3.00 (s, 1.03H), 2.71 (s, 4.70H), 1.46 – 1.40 (m, 2.89H).

**<sup>13</sup>C NMR** (126 MHz, Chloroform-*d*) δ 174.42, 173.88, 150.80, 150.45, 142.59, 142.44, 141.09, 133.94, 133.37, 128.44, 128.37, 128.22, 127.77, 126.79, 126.60, 114.61, 113.72, 113.57, 113.06, 108.19, 44.19, 43.06, 40.59, 40.29, 36.24, 36.21, 20.82, 20.32.

## Experimental Part

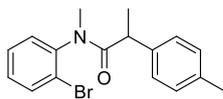
**IR (neat):**  $\nu$  ( $\text{cm}^{-1}$ ) 3027, 2929, 2873, 2810, 1663, 1593, 1494, 1375, 633.

**HRMS (ESI):** Calcd for  $\text{C}_{18}\text{H}_{22}\text{BrN}_2\text{O}$   $[\text{M}+\text{H}]^+$ : 361.0910, found: 361.0916.

**R<sub>f</sub>** = 0.29 (EtOAc/cHex 20:80)

**mp:** 113 °C

### ***N*-(2-bromophenyl)-*N*-methyl-2-(*p*-tolyl)propanamide (6.57)**



Chemical Formula:  $\text{C}_{17}\text{H}_{18}\text{BrNO}$   
Molecular Weight: 332.24

In a first step, the tertiary acid was synthesized. 2 drops of HCl (37%, cat) were added to 4-tolylacetic acid (3.00 g, 20.0 mmol, 1.0 equiv.) in MeOH (10.0 mL) and refluxed for 1 h. The solvent was evaporated under reduced pressure and the residue taken up in  $\text{Et}_2\text{O}$  and dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure to afford the methyl ester (2.95 g, 18.2 mmol, 91%) as a colorless oil which was directly engaged in the next step. The ester (1.00 g, 6.09 mmol, 1.00 equiv.) was added to a solution of LiHMDS (1.02 g, 6.09 mmol, 1.00 equiv.) in dry THF (18 mL) under Ar at  $-78$  °C and the resulting yellow solution was stirred for 30 min at the same temperature before MeI (0.40 mL, 6.39 mmol, 1.05 equiv.) was added. The resulting mixture was stirred for 15 min more at the same temperature before it was allowed to warm to room temperature. The reaction was quenched by addition of sat. aqueous  $\text{NH}_4\text{Cl}$  and extracted three times with  $\text{Et}_2\text{O}$ . The combined organic phase was washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated under reduced pressure. The crude was dissolved in a mixture of THF/ $\text{H}_2\text{O}$ /MeOH (16 mL, 1/1/1), then LiOH (146 mg, 6.09 mmol, 1.00 equiv.) was added and the mixture stirred at room temperature for 3 days.  $\text{Et}_2\text{O}$  was added and the phases were separated. The aqueous phase was acidified with conc. HCl to pH = 1 and extracted three times with DCM. The combined DCM phase was washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated under reduced pressure. The crude was directly engaged in the next step without further purification.

Following **General procedure 12**, the crude acid (317 mg, 1.93 mmol, 1.2 equiv.) was reacted with oxalyl chloride (0.20 mL, 2.09 mmol, 1.3 equiv.) in dry DCM (4.0 mL) before aniline **6.45** (300 mg, 1.00 mmol 1.0 equiv.) and  $\text{Et}_3\text{N}$  (0.68 mL, 4.83 mmol, 3.0 equiv.) were added. The crude was purified by FC (0-15% EtOAc in cHex) to afford the title compound **6.57** (367 mg, 1.10 mmol, 69%) as a yellow viscous oil which occurs as a conformational mixture.

**$^1\text{H}$  NMR** (400 MHz, Chloroform-*d*)  $\delta$  7.71 (dd,  $J$  = 7.7, 1.8 Hz, 0.65H), 7.60 (dd,  $J$  = 8.0, 1.5 Hz, 0.23H), 7.43 ("t"d,  $J$  = 7.6, 1.5 Hz, 0.24H), 7.35 (dd,  $J$  = 7.8, 1.8 Hz, 0.24H), 7.28 (d,  $J$  =

## Experimental Part

1.8 Hz, 0.08H), 7.25 – 7.15 (m, 1.63H), 7.00 (d,  $J = 7.8$  Hz, 1.63H), 6.95 – 6.90 (m, 0.52H), 6.88 – 6.83 (m, 1.50H), 6.75 (dd,  $J = 7.5, 2.0$  Hz, 0.69H), 3.48 (q,  $J = 7.0$  Hz, 0.25H), 3.31 (q,  $J = 6.9$  Hz, 0.74H), 3.18 (s, 0.71H), 3.16 (s 2.24H), 2.29 (s, 2.09H), 1.41 (d,  $J = 6.9$  Hz, 2.23H), 1.39 (d,  $J = 7.0$  Hz, 0.78H).

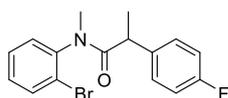
$^{13}\text{C}$  NMR (101 MHz, Chloroform-*d*)  $\delta$  174.3, 174.1, 142.8, 142.5, 138.8, 137.8, 136.4, 136.4, 134.2, 133.6, 131.1, 130.2, 129.8, 129.8, 129.2, 129.0, 128.8, 128.6, 128.0, 127.5, 124.3, 123.9, 43.7, 42.9, 36.3, 36.3, 21.2, 21.2, 20.8, 20.3.

**IR (neat):**  $\nu$  ( $\text{cm}^{-1}$ ) 3062, 3027, 2936, 2864, 1636, 1378, 770.

**HRMS (ESI):** Calcd for  $\text{C}_{17}\text{H}_{19}\text{BrNO}$   $[\text{M}+\text{H}]^+$ : 332.0645, found: 332.0642.

**R<sub>f</sub>** = 0.31 (EtOAc/cHex 20:80)

### ***N*-(2-bromophenyl)-2-(4-fluorophenyl)-*N*-methylpropanamide (6.58)**



Chemical Formula:  $\text{C}_{16}\text{H}_{15}\text{BrFNO}$   
Molecular Weight: 336.20

Methyl 4-fluorophenylacetate (2.00 g, 11.9 mmol, 1.00 equiv.) was dissolved in dry THF (12 mL) and added to a solution of LiHMDS (1.02 g, 6.09 mmol, 1.00 equiv.) in dry THF (18 mL) under Ar at  $-78$  °C. The resulting yellow solution was stirred for 30 min at the same temperature before MeI (0.78 mL, 12.5 mmol, 1.05 equiv.) was added. The mixture was stirred for 15 min more at the same temperature before it was allowed to warm to room temperature. The reaction was quenched by addition of sat. aqueous  $\text{NH}_4\text{Cl}$  and extracted three times with  $\text{Et}_2\text{O}$ . The combined organic phase was washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated under reduced pressure. The crude was dissolved in a mixture of THF/ $\text{H}_2\text{O}$ /MeOH (18 mL, 1/1/1), then LiOH (428 mg, 17.9 mmol, 1.50 equiv.) was added and the mixture stirred at room temperature for 3 days.  $\text{Et}_2\text{O}$  was added and the phases were separated. The aqueous phase was acidified with conc. HCl to pH = 1 and extracted three times with DCM. The combined DCM phase was washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated under reduced pressure to afford the corresponding acid (1.81 g, 10.7 mmol, 90%). The crude was directly engaged in the next step without further purification. 2 drops of DMF were added the corresponding acid (543 mg, 3.23 mmol, 1.2 equiv.) and oxalyl chloride (0.33 mL, 3.50 mmol, 1.3 equiv.) in dry DCM (6.6 mL) under Ar. The resulting mixture was stirred at room temperature for 16 h before 2-bromo-*N*-methylaniline **6.45** (500 mg, 2.69 mmol, 1.0 equiv.) was added.  $\text{Et}_3\text{N}$  (1.13 mL, 8.07 mmol, 3.0 equiv.) was added dropwise to the mixture which was further stirred at room temperature for 16 h. Sat. aqueous  $\text{NH}_4\text{Cl}$  was added and extracted three times with DCM. The combined

## Experimental Part

organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude was purified by FC (0-15% EtOAc/cHex) to afford the corresponding amide **6.58** (549 mg, 1.63 mmol, 61%) as a yellow viscous oil which occurs as a conformational mixture.

<sup>1</sup>H NMR (500 MHz, Chloroform-*d*) δ 7.71 (dd, *J* = 7.8, 1.7 Hz, 0.52H), 7.60 (dd, *J* = 8.0, 1.4 Hz, 0.23H), 7.43 (“t”d, *J* = 7.6, 1.4 Hz, 0.27H), 7.35 (dd, *J* = 7.8, 1.7 Hz, 0.28H), 7.29 – 7.26 (m, 0.23H), 7.26 – 7.17 (m, 1.32H), 7.00 – 6.96 (m, 0.54H), 6.94 – 6.85 (m, 2.90H), 6.73 (dd, *J* = 7.5, 1.9 Hz, 0.56H), 3.50 (q, *J* = 7.0 Hz, 0.29H), 3.33 (q, *J* = 6.9 Hz, 0.66H), 3.18 (s, 0.99H), 3.16 (s, 2.00H), 1.41 (d, *J* = 6.9 Hz, 2.39H), 1.38 (d, *J* = 7.0 Hz, 1.03H).

<sup>13</sup>C NMR (126 MHz, Chloroform-*d*) δ 173.8, 173.6, 161.9 (d, *J* = 244.6 Hz), 161.7 (d, *J* = 244.9 Hz), 142.5, 142.2, 137.4 (d, *J* = 3.2 Hz), 136.4 (d, *J* = 3.3 Hz), 134.1, 133.7, 130.7, 130.1, 129.8, 129.8, 129.5 (d, *J* = 8.0 Hz), 129.0 (d, *J* = 7.9 Hz), 128.7, 128.5, 124.1, 123.7, 115.2 (d, *J* = 21.2 Hz), 115.0 (d, *J* = 21.3 Hz), 43.3, 42.5, 36.2, 36.2, 20.7, 20.2.

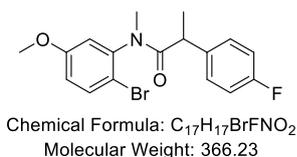
<sup>19</sup>F{<sup>1</sup>H} NMR (376 MHz, Chloroform-*d*) δ -116.23, -116.43.

IR (neat): ν (cm<sup>-1</sup>) 3062, 2975, 2932, 1663, 1508, 1377, 1223, 1130, 839, 765, 632.

HRMS (ESI): Calcd for C<sub>16</sub>H<sub>16</sub>BrFNO [M+H]<sup>+</sup>: 336.0394, found: 336.0393.

R<sub>f</sub> = 0.32 (EtOAc/cHex 20:80)

### *N*-(2-bromo-5-methoxyphenyl)-2-(4-fluorophenyl)-*N*-methylpropanamide (**6.59**)



Methyl 4-fluorophenylacetate (2.00 g, 11.9 mmol, 1.00 equiv.) was dissolved in dry THF (12 mL) and added to a solution of LiHMDS (1.02 g, 6.09 mmol, 1.00 equiv.) in dry THF (18 mL) under Ar at -78 °C. The resulting yellow solution was stirred for 30 min at the same temperature before MeI (0.78 mL, 12.5 mmol, 1.05 equiv.) was added. The mixture was stirred for 15 min more at the same temperature before it was allowed to warm to room temperature. The reaction was quenched by addition of sat. aqueous NH<sub>4</sub>Cl and extracted three times with Et<sub>2</sub>O. The combined organic phase was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure. The crude was dissolved in a mixture of THF/H<sub>2</sub>O/MeOH (18 mL, 1/1/1), then LiOH (428 mg, 17.9 mmol, 1.50 equiv.) was added and the mixture stirred at room temperature for 3 days. Et<sub>2</sub>O was added and the phases were separated. The aqueous phase was acidified with conc. HCl to pH = 1 and extracted three times with DCM. The combined DCM phase was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure to afford the corresponding acid (1.81 g, 10.7 mmol, 90%). The crude acid (110 mg, 6.54 mmol,

## Experimental Part

1.1 equiv.) and  $\text{SOCl}_2$  (0.87 mL, 12.0 mmol, 2.0 equiv.) were refluxed for 2 h before all the volatiles were removed under reduced pressure. The resulting crude acyl chloride was dissolved in dry DCM (5.4 mL) before 2-bromo-5-methoxyaniline (1.21 g, 6.0 mmol, 1 equiv.) followed by  $\text{Et}_3\text{N}$  (1.26 mL, 9.0 mmol, 1.5 equiv.) were added at 0 °C under Ar. The reaction was stirred at room temperature for 18 h before sat. aqueous  $\text{NH}_4\text{Cl}$  was added and extracted three times with DCM. The combined organic phase was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure and purified by FC (25% EtOAc in cHex) to afford the amide (1.41 g, 4.0 mmol, 67%) as a yellow viscous oil. The pure amide (400 mg, 1.20 mmol, 1.0 equiv.) was dissolved in dry THF (7.5 mL) before NaH (60%, 48 mg, 1.20 mmol, 1 equiv.) was added under Ar. After stirring of the reaction mixture for 15 min, MeI (0.19 mL, 1.20 mmol, 1.0 equiv.) was added and the resulting mixture stirred at room temperature for 4 h. The reaction was carefully quenched by addition of  $\text{H}_2\text{O}$ , and extracted three times with  $\text{Et}_2\text{O}$ . The combined organic layers were washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The crude was purified by FC (0-25% EtOAc in cHex) to afford the amide **6.59** (173 mg, 0.46 mmol, 39%) as a colorless viscous oil which occurs as a conformational mixture.

**$^1\text{H}$  NMR** (400 MHz, Chloroform-*d*)  $\delta$  7.55 (d,  $J = 8.9$  Hz, 0.69H), 7.47 (d,  $J = 8.8$  Hz, 0.25H), 7.07 – 7.01 (m, 0.44H), 6.98 – 6.86 (m, 3.59H), 6.84 (dd,  $J = 8.8, 3.0$  Hz, 0.24H), 6.80 (dd,  $J = 8.9, 3.0$  Hz, 0.68H), 6.19 (d,  $J = 3.0$  Hz, 0.77H), 3.85 (s, 0.75H), 3.58 – 3.52 (m, 2.41H), 3.36 (q,  $J = 6.9$  Hz, 0.72H), 3.16 (s, 0.92H), 3.16 (s, 1.82H), 1.42 – 1.38 (m, 3.00H).

**$^{13}\text{C}$  NMR** (126 MHz, Chloroform-*d*)  $\delta$  174.0, 173.6, 162.0 (d,  $J = 244.6$  Hz), 161.9 (d,  $J = 245.0$  Hz), 160.0, 159.6, 143.2, 142.9, 137.9 (d,  $J = 3.2$  Hz), 136.6 (d,  $J = 3.2$  Hz), 134.4, 133.9, 129.7 (d,  $J = 8.0$  Hz), 129.2 (d,  $J = 7.9$  Hz), 116.8, 115.9, 115.6, 115.4, 115.4 (d,  $J = 32.9$  Hz), 115.1 (d,  $J = 21.2$  Hz), 114.3, 113.7, 55.9, 55.6, 43.5, 42.5, 36.2, 36.2, 20.9, 20.5.

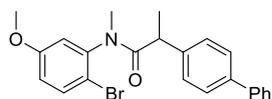
**$^{19}\text{F}\{^1\text{H}\}$  NMR** (376 MHz, Chloroform-*d*)  $\delta$  -116.25, -116.47.

**IR (neat):**  $\nu$  ( $\text{cm}^{-1}$ ) 2972, 2935, 1664, 1590, 1477, 1224, 775.

**HRMS (ESI):** Calcd for  $\text{C}_{17}\text{H}_{18}\text{BrFNO}_2$   $[\text{M}+\text{H}]^+$ : 366.0499, found: 366.0496.

**$R_f$**  = 0.26 (EtOAc/cHex 28:80)

**mp:** 74 °C

**2-([1,1'-biphenyl]-4-yl)-N-(2-bromo-5-methoxyphenyl)-N-methylpropanamide (6.60)**

Chemical Formula: C<sub>23</sub>H<sub>22</sub>BrNO<sub>2</sub>  
Molecular Weight: 424.34

In a first step, the tertiary acid was synthesized. 2 drops of HCl (37%, cat.) were added to 4-biphenylacetic acid (2.50 g, 11.8 mmol, 1.0 equiv.) in MeOH (6.0 mL) and refluxed for 1 h. The solvent was evaporated under reduced pressure and the residue taken up in Et<sub>2</sub>O and dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to afford the methyl ester (2.58 g, 11.4 mmol, 96%) as a colourless oil and directly engaged in the next step.

The ester (1.50 g, 6.63 mmol, 1.00 equiv.) was dissolved in dry THF (14 mL) under Ar and cooled down to -78 °C. LiHMDS (1 M in THF, 6.63 mL, 6.63 mmol, 1.00 equiv.) was added dropwise and the resulting yellow solution stirred for 30 min at the same temperature before MeI (0.43 mL, 6.96 mmol, 1.05 equiv.) was added. The resulting mixture was stirred for 15 min more at the same temperature before it was allowed to warm to room temperature. The reaction was quenched by addition of sat. aqueous NH<sub>4</sub>Cl and extracted three times with Et<sub>2</sub>O. The combined organic phase was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure. The crude was dissolved in a mixture of THF/H<sub>2</sub>O/MeOH (12 mL, 1/1/1), then LiOH (476 mg, 19.9 mmol, 3.00 equiv.) was added and the mixture stirred at room temperature for 16 h. Et<sub>2</sub>O was added and the phases were separated. The aqueous phase was acidified with conc. HCl to pH = 1 and extracted three times with DCM. The combined DCM phase was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure. The crude was directly engaged in the next step without further purification.

Following **General procedure 10**, the crude acid (300 mg, 1.33 mmol, 1.2 equiv.) was reacted with oxalyl chloride (0.14 mL, 1.43 mmol, 1.3 equiv.), in dry DCM (4.4 mL) before aniline **6.48** (238 mg, 1.10 mmol 1.0 equiv.) and Et<sub>3</sub>N (0.46 mL, 3.3 mmol, 3.0 equiv.) were added. The crude was purified by FC (0-20% EtOAc in cHex) to afford the desired amide **6.60** (125 mg, 0.29 mmol, 27%) as a light yellow viscous oil which occurs as a conformational mixture.

**<sup>1</sup>H NMR** (400 MHz, Chloroform-*d*) δ 7.58 – 7.51 (m, 2.85H), 7.51 – 7.38 (m, 4.15H), 7.36 – 7.30 (m, 1.14H), 7.18 – 7.14 (m, 0.46H), 7.07 – 7.02 (m, 1.58H), 6.91 (d, *J* = 3.0 Hz, 0.20H), 6.85 (dd, *J* = 8.8, 3.0 Hz, 0.23H), 6.80 (dd, *J* = 8.9, 3.0 Hz, 0.80H), 6.19 (d, *J* = 3.0 Hz, 0.73H), 3.87 (s, 0.56H), 3.62 (q, *J* = 7.0 Hz, 0.21H), 3.47 – 3.38 (m, 2.90H), 3.19 (s, 3.00H), 1.46 (d, *J* = 6.9 Hz, 3.00H).

## Experimental Part

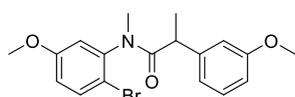
$^{13}\text{C}$  NMR (101 MHz, Chloroform-*d*)  $\delta$  173.7, 159.6, 142.9, 141.4, 140.9, 139.8, 133.8, 128.9, 128.1, 127.4, 127.3, 127.1, 117.2, 115.4, 113.7, 55.5, 44.1, 36.2, 20.8. Only major rotamer described.

**IR (neat):**  $\nu$  ( $\text{cm}^{-1}$ ) 3029, 2971, 2932, 1664, 1589, 1478, 1374, 1286, 1225, 1126, 1120, 759, 630.

**HRMS (ESI):** Calcd for  $\text{C}_{23}\text{H}_{23}\text{BrNO}_2$   $[\text{M}+\text{H}]^+$ : 424.0907, found: 424.0900.

$R_f = 0.28$  (EtOAc/cHex 20:80)

### *N*-(2-bromo-5-methoxyphenyl)-2-(3-methoxyphenyl)-*N*-methylpropanamide (**6.61**)



Chemical Formula:  $\text{C}_{18}\text{H}_{20}\text{BrNO}_3$   
Molecular Weight: 378.27

The tertiary acid was prepared in a first step: LDA was freshly prepared by adding *n*BuLi (2.5 M in hexanes, 5.06 mL, 12.6 mmol, 2.1 equiv.) dropwise to diisopropylamine (1.79 mL, 12.6 mmol 2.1 equiv.) in dry THF (18 mL) at 0 °C under Ar. After stirring for 30 min at the same temperature, the mixture was cooled down to  $-78$  °C and 3-methoxyphenylacetic acid (1.00 g, 6.02 mmol 1.0 equiv.) was added. After stirring for further 30 min at this temperature, MeI (0.41 mL, 6.61 mmol 1.1 equiv) was added and the resulting mixture was warmed to room temperature and kept for 2 h. The reaction was quenched by addition of aqueous HCl (1 M), extracted three times with  $\text{Et}_2\text{O}$ , dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The crude acid was directly engaged in the next step. Following **General Procedure 12**, the crude acid (392 mg, 2.18 mmol 1.1 equiv.),  $\text{SOCl}_2$  (0.29 mL; 3.96 mmol, 2.0 equiv.), 2-Bromo-5-Methoxyaniline (400 mg, 1.86 mmol, 1.0 equiv.),  $\text{Et}_3\text{N}$  (0.39 mL, 2.79 mmol, 1.5 equiv.) in dry DCM (5.4 mL) were reacted to the amide. The crude amide was further reacted with NaH (60%, 79 mg, 1.98 mmol, 1.0 equiv.), MeI (0.12 mL, 1.96 mmol, 1.0 equiv.) in dry THF (7.5 mL) and purified by FC (0-30% EtOAc/cHex) to afford the title compound **6.61** (215 mg, 0.57 mmol, 29%) as a yellow viscous oil which occurs as a conformational mixture.

$^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  7.54 (d,  $J = 8.9$  Hz, 0.67H), 7.46 (d,  $J = 8.8$  Hz, 0.19H), 7.14 – 7.08 (m, 1.00H), 6.88 (d,  $J = 3.0$  Hz, 0.17H), 6.83 (dd,  $J = 8.8, 3.0$  Hz, 0.20H), 6.79 (dd,  $J = 8.9, 3.0$  Hz, 0.78H), 6.72 (ddd,  $J = 8.3, 2.6, 1.00$  Hz, 1.00H), 6.66 – 6.61 (m, 0.39H), 6.58 – 6.54 (m, 0.79H), 6.53 – 6.49 (m, 0.76H), 6.19 (d,  $J = 3.0$  Hz, 0.74H), 3.85 (s, 0.55H), 3.75 (s, 0.62H), 3.73 (s, 2.38H), 3.55 (q,  $J = 7.1$  Hz, 0.24H), 3.50 (s, 2.29H), 3.33 (q,  $J = 6.8$  Hz, 0.86H), 3.17 (s, 0.58H), 3.16 (s, 2.75H), 1.42 (m, 3.00H).

## Experimental Part

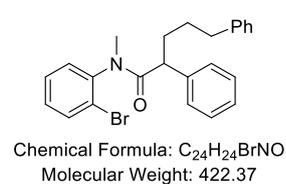
$^{13}\text{C}$  NMR (101 MHz, Chloroform-*d*)  $\delta$  173.9, 173.5, 159.9, 159.8, 159.6, 159.5, 143.7, 143.3, 142.9, 142.3, 134.3, 133.7, 129.5, 129.2, 120.7, 110.0, 117.0, 115.9, 115.6, 115.5, 114.5, 113.7, 113.6, 113.0, 112.7, 112.6, 55.9, 55.5, 55.3, 55.3, 44.5, 43.4, 36.2, 36.2, 20.7, 20.2.

**IR (neat):**  $\nu$  ( $\text{cm}^{-1}$ ) 2967, 2935, 2836, 1664, 1590, 1478, 1374, 1284, 1225, 1050.

**HRMS (ESI):** Calcd for  $\text{C}_{18}\text{H}_{21}\text{BrNO}_3$   $[\text{M}+\text{H}]^+$ : 378.0699, found: 378.0694.

$R_f$  = 0.34 (EtOAc/cHex 30:70)

### *N*-(2-bromophenyl)-*N*-methyl-2,5-diphenylpentanamide (6.62)



Ethyl phenylacetate (1.00 g, 6.09 mmol, 1.00 equiv.) was added to a solution of LiHMDS (1.02 g, 6.09 mmol, 1.00 equiv.) in dry THF (18 mL) under Ar at  $-78$  °C. and the resulting yellow solution was stirred for 30 min at the same temperature before 3-iodopropylbenzene (1.03 mL, 6.39 mmol, 1.05 equiv.) was added. The resulting mixture was stirred for 15 min more at the same temperature before it was allowed to warm to room temperature. The reaction was quenched by addition of sat. aqueous  $\text{NH}_4\text{Cl}$  and extracted three times with  $\text{Et}_2\text{O}$ . The combined organic phase was washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated under reduced pressure. The crude was dissolved in a mixture of THF/ $\text{H}_2\text{O}$ /MeOH (16 mL, 1/1/1), then LiOH (146 mg, 6.09, 1.00 equiv.) was added and the mixture stirred at room temperature for 3 days.  $\text{Et}_2\text{O}$  was added and the phases were separated. The aqueous phase was acidified with conc. HCl to pH = 1 and extracted three times with DCM. The combined DCM phase was washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated under reduced pressure. The crude was directly engaged in the next step without further purification.

Following **General procedure 10**, the crude acid (491 mg, 1.93 mmol, 1.2 equiv.) was reacted with oxalyl chloride (0.20 mL, 2.09 mmol, 1.3 equiv.), in dry DCM (4.0 mL) before aniline **6.45** (300 mg, 1.00 mmol 1.0 equiv.) and  $\text{Et}_3\text{N}$  (0.68 mL, 4.83 mmol, 3.0 equiv.) were added. The crude was purified by FC (8% EtOAc in cHex) to afford the desired amide **6.62** (139 mg, 0.33 mmol, 20%) as a colorless viscous oil which occurs as a conformational mixture.

$^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  7.70 (dd,  $J$  = 8.0, 1.5 Hz, 0.68H), 7.56 (dd,  $J$  = 7.9, 1.4 Hz, 0.26H), 7.43 – 7.37 (m, 0.26H), 7.28 (“t”,  $J$  = 1.8 Hz, 0.29H), 7.25 – 7.07 (m, 8.00H), 6.95 (dd,  $J$  = 6.6, 3.0 Hz, 0.50H), 6.91 (dd,  $J$  = 6.6, 2.9 Hz, 1.38H), 6.60 (dd,  $J$  = 7.8, 1.7 Hz, 0.71H), 3.33 (t,  $J$  = 7.4 Hz, 0.29H), 3.17 (s, 0.79H), 3.16 – 3.11 (m, 2.92H), 2.63 – 2.43.54 (m, 2.00H), 2.20 – 2.06 (m, 0.87H), 1.81 – 1.58 (m, 1.00H), 1.65 – 1.55 (m, 1.53H), 1.52 – 1.38 (m, 1.00H).

## Experimental Part

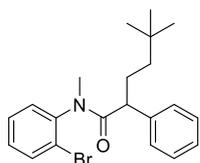
**$^{13}\text{C}$  NMR** (101 MHz, Chloroform-*d*)  $\delta$  173.1, 142.5, 142.2, 140.3, 133.7, 131.3, 129.9, 128.6, 128.5, 128.5, 128.3, 128.1, 126.9, 125.7, 123.6, 50.3, 36.3, 35.9, 35.1, 29.6. Only major rotamer described.

**IR (neat):**  $\nu$  ( $\text{cm}^{-1}$ ) 3060, 3026, 2930, 2856, 1664, 1477, 1377, 1123, 730, 630.

**HRMS** (ESI): Calcd for  $\text{C}_{24}\text{H}_{25}\text{BrNO}$   $[\text{M}+\text{H}]^+$ : 422.1114, found: 422.1114.

**R<sub>f</sub>** = 0.48 (EtOAc/cHex 20:80)

### *N*-(2-bromophenyl)-*N*,5,5-trimethyl-2-phenylhexanamide (**6.63**)



Chemical Formula:  $\text{C}_{21}\text{H}_{26}\text{BrNO}$   
Molecular Weight: 388.35

A mixture of 1-bromo-3,3-dimethylbutane (500 mg, 30.3 mmol, 1.0 equiv.) and NaI (908 g, 6.06 mmol, 2.0 equiv.) in acetone (3 mL) was stirred at room temperature for 16 h. The reaction mixture was filtered over *Celite* and the solvent removed under reduced pressure. The crude alkyl iodide was used without further purification in the next step.

Following **General Procedure 13**, amide **6.50** (400 mg, 1.31 mmol, 1.0 equiv.) was reacted with LiHMDS (1 M in THF, 1.31 mL, 1.31 mmol, 1.0 equiv.), and the previously synthesized alkyl iodide (306 mg, 1.44 mmol, 1.1 equiv.). The crude was purified by FC (0-10% EtOAc in cHex) to afford the title compound **6.63** (375 mg, 0.97 mmol, 74%) as a yellow viscous oil which occurs as a conformational mixture.

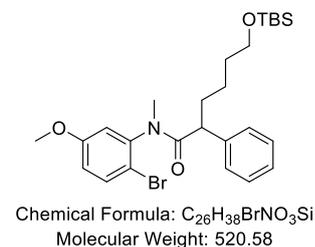
**$^1\text{H}$  NMR** (400 MHz, Chloroform-*d*)  $\delta$  7.71 (dd,  $J = 7.9, 1.5$  Hz, 0.65H), 7.58 (dd,  $J = 8.0, 1.4$  Hz, 0.24H), 7.44 (“t”d,  $J = 7.6, 1.4$  Hz, 0.24H), 7.34 (dd,  $J = 7.8, 1.7$  Hz, 0.23H), 7.29 – 7.27 (m, 0.16H), 7.28 – 7.11 (m, 4.50H), 6.99 – 6.93 (m, 2.13H), 6.64 (dd,  $J = 7.8, 1.7$  Hz, 0.67H), 3.23 (t,  $J = 7.4$  Hz, 0.28H), 3.19 (s, 0.81H), 3.16 (s, 2.22H), 3.04 (t,  $J = 7.3$  Hz, 0.73H), 2.14 – 1.95 (m, 1.00H), 1.75 – 1.54 (m, 1.00H), 1.19 (td,  $J = 13.0, 4.4$  Hz, 0.75H), 1.06 (td,  $J = 12.9, 4.5$  Hz, 0.28H), 1.00 – 0.86 (m, 1.00H), 0.81 (s, 9.00H).

**$^{13}\text{C}$  NMR** (101 MHz, Chloroform-*d*)  $\delta$  173.4, 173.3, 142.7, 142.4, 140.6, 139.5, 134.2, 133.7, 131.3, 130.6, 129.8, 129.8, 128.7, 128.6, 128.5, 128.4, 128.3, 128.1, 126.9, 126.8, 124.6, 123.6, 51.1, 50.2, 42.3, 42.1, 36.2, 36.2, 30.7, 30.4, 30.4, 29.4.

**IR (neat):**  $\nu$  ( $\text{cm}^{-1}$ ) 2955, 2866, 1665, 1477, 1377, 1292, 1129, 1030, 764.

**HRMS** (ESI): Calcd for  $\text{C}_{21}\text{H}_{27}\text{BrNO}$   $[\text{M}+\text{H}]^+$ : 388.1271, found: 388.1266.

**R<sub>f</sub>** = 0.48 (EtOAc/cHex 20:80)

***N*-(2-bromo-5-methoxyphenyl)-6-((*tert*-butyldimethylsilyl)oxy)-*N*-methyl-2-phenylhexanamide (6.64)**

Following **General Procedure 13**, amide **6.51** (800 mg, 2.39 mmol, 1.0 equiv.) was reacted with NaHMDS (1 M in THF, 2.39 mL, 1.39 mmol, 1.0 equiv.), and *tert*-butyl(4-iodobutoxy)dimethylsilane (0.68 mL, 2.63 mmol, 1.1 equiv.). The crude was purified by FC (0-5% EtOAc in cHex) to afford the title compound **6.64** (817 mg, 0.167 mmol, 70%) as a colorless viscous oil which occurs as a conformational mixture.

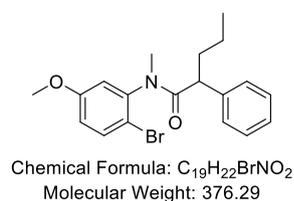
**<sup>1</sup>H NMR** (400 MHz, Chloroform-*d*) δ 7.54 (d, *J* = 8.9 Hz, 0.76H), 7.44 (d, *J* = 8.8 Hz, 0.18H), 7.23 – 7.14 (m, 3.27H), 7.03 – 7.00 (m, 0.36H), 6.97 – 6.92 (m, 1.74H), 6.87 (d, *J* = 2.9 Hz, 0.19H), 6.83 (dd, *J* = 8.8, 3.0 Hz, 0.21H), 6.78 (dd, *J* = 8.9, 3.0 Hz, 0.77H), 6.04 (d, *J* = 3.0 Hz, 0.83H), 3.85 (s, 0.60H), 3.55 – 3.50 (m, 2.18H), 3.43 (s, 2.48H), 3.39 (t, *J* = 7.5 Hz, 0.25H), 3.17 (s, 0.56H), 3.17 – 3.11 (m, 3.60H), 2.14 – 3.01 (m, 1.00H), 1.76 – 1.61 (m, 0.59H), 1.55 – 1.37 (m, 2.22H), 1.34 – 1.10 (m, 1.91H), 0.85 (s, 1.74H), 0.85 (s, 7.48H), 0.01 – -0.02 (m, 6.00H).

**<sup>13</sup>C NMR** (101 MHz, Chloroform-*d*) δ 173.0, 159.4, 142.7, 140.9, 133.8, 128.5, 128.1, 126.8, 117.2, 115.4, 113.5, 63.2, 55.4, 50.6, 36.1, 35.2, 32.9, 26.1, 24.2, 18.5, -5.1, -5.1. Only major rotamer described.

**IR** (neat): ν (cm<sup>-1</sup>) 2950, 2931, 2857, 1666, 1591, 1477, 1254, 1102, 836, 633.

**HRMS** (ESI): Calcd for C<sub>26</sub>H<sub>39</sub>BrNO<sub>3</sub>Si [M+H]<sup>+</sup>: 520.1877, found: 520.1873.

**R<sub>f</sub>** = 0.48 (EtOAc/cHex 20:80)

***N*-(2-bromo-5-methoxyphenyl)-*N*-methyl-2-phenylpentanamide (6.65)**

Following **General Procedure 13**, amide **6.51** (350 mg, 1.05 mmol, 1.0 equiv.) was reacted with LiHMDS (1 M in THF, 1.05 mL, 1.05 mmol, 1.0 equiv.), and *n*propyl iodide (0.11 mL, 1.16 mmol, 1.1 equiv.). The crude was purified by FC (0-20% EtOAc in cHex) to afford the title compound **6.65** (467 mg, 0.97 mmol, 72%) as a white solid which occurs as a conformational mixture.

**<sup>1</sup>H NMR** (400 MHz, Chloroform-*d*) δ 7.54 (d, *J* = 8.9 Hz, 0.74H), 7.46 (d, *J* = 8.7 Hz, 0.17H), 7.23 – 7.14 (m, 3.00H), 7.06 – 7.01 (m, 0.40H), 7.00 – 6.93 (m, 1.59H), 6.89 – 6.82 (m, 0.36H),

## Experimental Part

6.79 (dd,  $J = 8.9, 3.0$  Hz, 0.74H), 6.06 (d,  $J = 3.0$  Hz, 0.74H), 3.85 (s, 0.61H), 3.47 – 3.37 (m, 2.75H), 3.22 – 3.09 (m, 3.86H), 2.14 – 1.96 (m, 1.00H), 1.75 – 1.66 (m, 0.16H), 1.65 – 1.52 (m, 1.00H), 1.36 – 1.22 (m, 0.74H), 1.21 – 1.08 (m, 1.00H), 0.87 – 0.79 (m, 3.00H).

$^{13}\text{C}$  NMR (101 MHz, Chloroform-*d*)  $\delta$  173.1, 159.4, 142.8, 141.0, 133.8, 128.5, 128.1, 126.8, 117.2, 115.5, 113.5, 55.4, 50.4, 37.7, 36.1, 21.2, 14.2. Only major rotamer described.

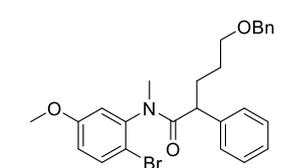
**IR (neat):**  $\nu$  ( $\text{cm}^{-1}$ ) 2956, 2933, 2870, 1661, 1589, 1476, 1373, 1225, 1018, 601.

**HRMS (ESI):** Calcd for  $\text{C}_{19}\text{H}_{23}\text{BrNO}_2$   $[\text{M}+\text{H}]^+$ : 376.0907, found: 376.0908.

$R_f = 0.47$  (EtOAc/cHex 30:70)

**mp:** 81 °C

### 5-(benzyloxy)-*N*-(2-bromo-5-methoxyphenyl)-*N*-methyl-2-phenylpentanamide (6.66)



Chemical Formula:  $\text{C}_{26}\text{H}_{28}\text{BrNO}_3$   
Molecular Weight: 482.42

A mixture of ((3-Bromopropoxy)methyl)benzene (1.5 mL, 8.5 mmol, 1.0 equiv.) and NaI (2.55 g, 17 mmol, 2.0 equiv.) in acetone (8.5 mL) was stirred at room temperature for 16 h. The reaction mixture was filtered over *Celite* and the solvent removed under reduced pressure. The crude alkyl iodide was used without purification in the next step.

Following **General Procedure 13**, amide **6.51** (450 mg, 1.35 mmol, 1.0 equiv.) was reacted with LiHMDS (1 M in THF, 1.35 mL, 1.35 mmol, 1.0 equiv.), and the previously synthesized alkyl iodide (410 mg, 1.49 mmol, 1.1 equiv.). The crude was purified by FC (0-20% EtOAc in cHex) to afford the title compound **6.66** (467 mg, 0.97 mmol, 72%) as a yellow viscous oil which occurs as a conformational mixture.

$^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  7.51 (d,  $J = 8.9$  Hz, 0.82H), 7.43 (d,  $J = 8.8$  Hz, 0.17H), 7.34 – 7.26 (m, 8.69H), 7.24 (d,  $J = 3.8$  Hz, 0.15H), 7.22 – 7.15 (m, 2.88H), 7.04 – 6.98 (m, 0.40H), 6.97 – 6.90 (m, 1.69H), 6.87 – 6.80 (m, 0.37H), 6.77 (dd,  $J = 8.9, 3.0$  Hz, 0.81H), 6.03 (d,  $J = 3.0$  Hz, 0.75H), 4.50 – 4.37 (m, 2.29H), 3.80 (s, 0.58H), 3.49 – 3.32 (m, 4.95H), 3.22 – 3.11 (m, 4.37H), 2.19 – 2.07 (m, 1.00H), 1.86 – 1.69 (m, 0.82H), 1.68 – 1.59 (m, 1.06H), 1.56 – 1.39 (m, 0.76H).

$^{13}\text{C}$  NMR (101 MHz, Chloroform-*d*)  $\delta$  172.8, 159.4, 142.6, 140.7, 138.8, 133.7, 128.5, 128.4, 128.1, 127.8, 127.6, 126.9, 117.2, 115.4, 113.5, 73.0, 70.5, 55.4, 50.4, 36.1, 32.1, 28.2.

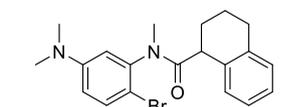
**IR (neat):**  $\nu$  ( $\text{cm}^{-1}$ ) 3028, 2938, 2857, 1667, 1590, 1478, 1372, 1226, 1116, 1019.

## Experimental Part

**HRMS** (ESI): Calcd for C<sub>26</sub>H<sub>29</sub>BrNO<sub>3</sub> [M+H]<sup>+</sup>: 482.1325, found: 482.1320.

**R<sub>f</sub>** = 0.22 (EtOAc/cHex 20:80)

### ***N*-(2-bromo-5-(dimethylamino)phenyl)-*N*-methyl-1,2,3,4-tetrahydronaphthalene-1-carboxamide (6.67)**



Chemical Formula: C<sub>20</sub>H<sub>23</sub>BrN<sub>2</sub>O  
Molecular Weight: 387.32

Following **General Procedure 12**, 1,2,3,4-tetrahydronaphthalene-1-carboxylic acid (361 mg, 2.05 mmol 1.1 equiv.), SOCl<sub>2</sub> (0.27 mL; 3.71 mmol, 2.0 equiv.), **6.49** (400 mg, 1.86 mmol, 1.0 equiv.), and Et<sub>3</sub>N (0.39 mL, 2.79 mmol, 1.5 equiv.) in dry DCM (5.4 mL) were reacted

to the amide. The crude amide was further reacted with NaH (60%, 75 mg, 1.86 mmol, 1.0 equiv.), MeI (0.12 mL, 1.86 mmol, 1.0 equiv.) in dry THF (7.5 mL) and purified by FC (0-30% EtOAc in cHex) to afford the title compound **6.67** (340 mg, 0.94 mmol, 51%) as a white solid which occurs as a conformational mixture.

**<sup>1</sup>H NMR** (500 MHz, Chloroform-*d*) δ 7.46 (d, *J* = 6.2 Hz, 0.46H), 7.44 (d, *J* = 6.2 Hz, 0.46H), 7.37 – 7.33 (m, 0.45H), 7.14 – 7.08 (m, 2.17H), 7.08 – 6.99 (m, 0.90H), 6.72 (d, *J* = 3.1 Hz, 0.49H), 6.62 (d, *J* = 3.0 Hz, 0.44H), 6.58 (dd, *J* = 8.9, 3.0 Hz, 0.42H), 6.55 (dd, *J* = 9.0, 3.1 Hz, 0.43H), 3.73 – 3.60 (m, 1.00H), 3.31 (s, 1.53H), 3.27 (s, 1.43H), 2.97 (s, 3.00H), 2.93 (s, 3.00H), 2.90 – 2.80 (m, 0.57H), 2.68 (t, *J* = 5.2 Hz, 0.60H), 2.64 (t, *J* = 5.2 Hz, 0.41H), 2.16 – 1.83 (m, 2.00H), 1.60 – 1.49 (m, 0.69H).

**<sup>13</sup>C NMR** (126 MHz, Chloroform-*d*) δ 175.98, 175.72, 150.86, 150.80, 143.36, 143.11, 137.95, 137.52, 136.14, 135.37, 134.00, 133.95, 129.76, 129.57, 129.14, 127.73, 126.40, 126.36, 125.89, 125.78, 113.75, 113.54, 113.25, 113.04, 107.98, 107.96, 43.39, 43.33, 40.56, 40.41, 36.34, 36.27, 29.46, 29.32, 28.44, 27.63, 21.56, 21.40.

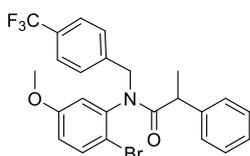
**IR** (neat): ν (cm<sup>-1</sup>) 3022, 2921, 2810, 1661, 1593, 1494, 1361, 1127, 634.

**HRMS** (ESI): Calcd for C<sub>20</sub>H<sub>24</sub>BrN<sub>2</sub>O [M+H]<sup>+</sup>: 387.1067, found: 387.1069.

**R<sub>f</sub>** = 0.10 (EtOAc/cHex 20:80)

**mp**: 168 °C

***N*-(2-bromo-5-methoxyphenyl)-2-phenyl-*N*-(4-(trifluoromethyl)benzyl)propanamide (6.68)**



Chemical Formula: C<sub>24</sub>H<sub>21</sub>BrF<sub>3</sub>NO<sub>2</sub>  
Molecular Weight: 492.34

Following **General Procedure 12**, 2-phenylpropionic acid (0.40 mL, 2.94 mmol 1.1 equiv.), SOCl<sub>2</sub> (0.39 mL; 5.34 mmol, 2.0 equiv.), 2-bromo-5-methoxyaniline (540 mg, 2.67 mmol, 1.0 equiv.), Et<sub>3</sub>N (0.56 mL, 4.01 mmol, 1.5 equiv.) in dry DCM (5.4 mL) were reacted. The crude was purified by FC (0-10% EtOAc in cHex) to afford the intermediate amide (814 mg, 2.43 mmol, 91%) as a yellow viscous oil. The pure amide (400 mg, 1.20 mmol, 1.0 equiv) was further reacted with NaH (60%, 48 mg, 1.20 mmol, 1.0 equiv.), 4-trifluoromethylbenzyl bromide (0.19 mL, 1.20 mmol, 1.0 equiv.) in dry THF (7.5 mL) and purified by FC (0-10% EtOAc in cHex) to afford the title compound **6.68** (437 mg, 0.89 mmol, 74%) as a light yellow viscous oil which occurs as a conformational mixture.

**<sup>1</sup>H NMR** (400 MHz, Chloroform-*d*) δ 7.56 – 7.51 (m, 1.12H), 7.48 – 7.44 (m, 1.71H), 7.37 – 7.33 (m, 0.43H), 7.27 – 7.22 (m, 2.00H), 7.22 – 7.18 (m, 0.72H), 7.13 – 7.08 (m, 0.41H), 6.97 – 6.88 (m, 1.54H), 6.81 (dd, *J* = 8.9, 3.0 Hz, 0.21H), 6.74 (dd, *J* = 8.9, 3.0 Hz, 0.80H), 6.38 (d, *J* = 3.0 Hz, 0.17H), 5.66 (d, *J* = 14.6 Hz, 0.23H), 5.61 (d, *J* = 14.6 Hz, 0.81H), 5.53 (d, *J* = 3.0 Hz, 0.72H), 4.08 (d, *J* = 14.6 Hz, 0.76H), 3.99 (d, *J* = 14.5 Hz, 0.20H), 3.66 (s, 0.54H), 3.54 (q, *J* = 7.0 Hz, 0.18H), 3.39 (q, *J* = 6.9 Hz, 0.74H), 3.20 (s, 2.24H), 1.46 (d, *J* = 6.9 Hz, 2.27H), 1.43 (d, *J* = 7.0 Hz, 0.68H).

**<sup>13</sup>C NMR** (101 MHz, Chloroform-*d*) δ 173.7, 158.8, 141.8, 141.3 (q, *J* = 1.4 Hz), 140.5, 133.6, 129.2, 129.2, 128.5, 127.4, 126.8, 125.2 (q, *J* = 3.8 Hz), 124.6 (q, *J* = 271.8 Hz), 117.1, 116.5, 113.8, 55.0, 51.4, 44.7, 20.6.

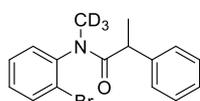
**<sup>19</sup>F{<sup>1</sup>H} NMR** (376 MHz, Chloroform-*d*) δ -62.46, -62.49.

**IR (neat):** ν (cm<sup>-1</sup>) 3028, 2978, 2932, 1668, 1591, 1478, 1326, 1168, 1125, 1067, 701.

**HRMS (ESI):** Calcd for C<sub>24</sub>H<sub>22</sub>BrF<sub>3</sub>NO<sub>2</sub> [M+H]<sup>+</sup>: 492.0781, found: 492.0778.

**R<sub>f</sub>** = 0.48 (EtOAc/cHex 20:80)

***N*-(2-bromophenyl)-*N*-(methyl-*d*<sub>3</sub>)-2-phenylpropanamide (6.1-*d*<sub>3</sub>)**



Chemical Formula: C<sub>16</sub>H<sub>13</sub>D<sub>3</sub>BrNO  
Molecular Weight: 321.23

Thionyl chloride (0.36 mL, 3.78 mmol, 1.3 equiv.) was added to 2-phenylpropionic acid (524 mg, 3.49 mmol, 1.2 equiv.) and in dry DCM (8.2 mL) under Ar. The resulting mixture was refluxed for 2 h.

## Experimental Part

After cooling to room temperature, the volatiles were removed under reduced pressure. The crude acid was dissolved in dry THF (8.2 mL) before the *o*-bromoaniline (500 mg, 2.91 mmol, 1.0 equiv.) was added. Et<sub>3</sub>N (0.48 mL, 8.7 mmol, 3.0 equiv.) was added dropwise to the mixture which was further stirred at room temperature for 16 h. Sat. aqueous NH<sub>4</sub>Cl was added and extracted three times with DCM. The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude was purified by FC (0-10% EtOAc in cHex). The obtained amide (300 mg, 0.99 mmol, 1.0 equiv.) was dissolved in dry THF (5.5 mL) and NaH (60%, 39.4 mg, 0.99 mmol, 1.0 equiv.) was added under Ar. After 15 min, CD<sub>3</sub>I (0.06 mL, 0.99 mmol, 1 equiv.) was added and the resulting mixture stirred at room temperature for 1 h. The reaction was carefully quenched by addition of H<sub>2</sub>O, and extracted with Et<sub>2</sub>O. The combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude was purified by FC (0-20% EtOAc in cHex) to afford the title compound **6.1-d<sub>3</sub>** (310 mg, 0.97 mmol, 98%) as a yellow viscous oil which occurs as a conformational mixture.

**<sup>1</sup>H NMR** (400 MHz, Chloroform-*d*) δ 7.71 (dd, *J* = 7.9, 1.6 Hz, 0.69H), 7.58 (dd, *J* = 8.0, 1.4 Hz, 0.24H), 7.43 (“t”d, *J* = 7.5, 1.4 Hz, 0.28H), 7.36 (dd, *J* = 7.8, 1.8 Hz, 0.26H), 7.28 (d, *J* = 1.8 Hz, 0.08H), 7.24 (d, *J* = 1.7 Hz, 0.19H), 7.23 – 7.14 (m, 4.00H), 7.03 – 6.98 (m, 0.50H), 6.98 – 6.93 (m, 1.50H), 6.71 (dd, *J* = 7.7, 1.8 Hz, 0.70H), 3.53 (q, *J* = 6.9 Hz, 0.28H), 3.34 (q, *J* = 6.9 Hz, 0.74H), 1.43 (d, *J* = 6.9 Hz, 2.16H), 1.41 (d, *J* = 7.0 Hz, 0.84H).

**<sup>13</sup>C NMR** (101 MHz, Chloroform-*d*) δ 173.9, 173.9, 142.4, 142.4, 141.8, 140.8, 134.2, 133.7, 131.0, 130.3, 129.9, 129.8, 128.9, 128.6, 128.5, 128.3, 128.2, 127.6, 126.9, 126.8, 124.4, 123.9, 44.2, 43.4, 20.8, 20.3.

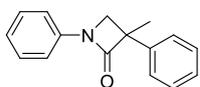
**IR (neat):** ν (cm<sup>-1</sup>) 3061, 3028, 2974, 2931, 1662, 1475, 1386, 1281, 1011, 763, 700, 632.

**HRMS (ESI):** Calcd for C<sub>16</sub>H<sub>14</sub>BrD<sub>3</sub>NO [M+H]<sup>+</sup>: 321.0676, found: 321.0679.

**R<sub>f</sub>** = 0.40 (EtOAc/cHex 20:80)

### β-Lactam Synthesis

#### 3-methyl-1,3-diphenylazetididin-2-one (6.2)



Chemical Formula: C<sub>16</sub>H<sub>15</sub>NO  
Molecular Weight: 237.30

Following **General Procedure 14**, amide **6.52** (99.5 mg, 0.3 mmol, 1.0 equiv.) was engaged. The crude was purified by FC (10% EtOAc in cHex) to afford the title compound **6.2** (36.8 mg, 0.16 mmol, 51%) as an orange viscous oil which solidified after a while upon standing.

## Experimental Part

**<sup>1</sup>H NMR** (500 MHz, Chloroform-*d*) δ 7.51 – 7.45 (m, 2H), 7.44 – 7.37 (m, 2H), 7.41 – 7.31 (m, 4H), 7.32 – 7.24 (m, 1H), 7.12 – 7.08 (m, 1H), 3.92 (d, *J* = 5.5 Hz, 1H), 3.76 (d, *J* = 5.5 Hz, 1H), 1.77 (s, 3H).

**<sup>13</sup>C NMR** (126 MHz, Chloroform-*d*) δ 168.8, 140.8, 138.6, 129.3, 128.9, 127.4, 126.1, 124.1, 116.6, 57.5, 53.7, 23.7.

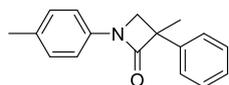
**IR (neat):** ν (cm<sup>-1</sup>) 3061, 2995, 1745, 1600, 1502, 1389, 1155, 756.

**HRMS (ESI):** Calcd for C<sub>16</sub>H<sub>16</sub>NO [M+H]<sup>+</sup>: 238.1226, found: 238.1224.

**R<sub>f</sub>** = 0.59 (EtOAc/cHex 20:80)

**mp:** 77 °C

### 3-methyl-3-phenyl-1-(*p*-tolyl)azetid-2-one (6.14)



Chemical Formula: C<sub>17</sub>H<sub>17</sub>NO  
Molecular Weight: 251.33

Following **General Procedure 14**, amide **6.53** (99.7 mg, 0.3 mmol, 1.0 equiv.) was engaged. The crude was purified by FC (10% EtOAc in cHex) to afford the title compound **6.14** (37.0 mg, 0.15 mmol, 49%) as an orange powder.

**<sup>1</sup>H NMR** (400 MHz, Chloroform-*d*) δ 7.50 – 7.45 (m, 2H), 7.40 – 7.34 (m, 2H), 7.32 – 7.27 (m, 3H), 7.17 – 7.12 (m, 2H), 3.89 (d, *J* = 5.4 Hz, 1H), 3.74 (d, *J* = 5.4 Hz, 1H), 2.32 (s, 3H), 1.76 (s, 3H).

**<sup>13</sup>C NMR** (101 MHz, Chloroform-*d*) δ 168.5, 140.9, 136.2, 133.7, 129.8, 128.9, 127.4, 126.1, 116.5, 57.4, 53.7, 23.7, 21.1.

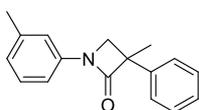
**IR (neat):** ν (cm<sup>-1</sup>) 3033, 2965, 2923, 2890, 2360, 2339, 1741, 1516, 1390, 1157.

**HRMS (ESI):** Calcd for C<sub>17</sub>H<sub>18</sub>NO [M+H]<sup>+</sup>: 252.1383, found: 252.1379.

**R<sub>f</sub>** = 0.48 (EtOAc/cHex 10:90)

**mp:** 74 °C

### 3-methyl-3-phenyl-1-(*m*-tolyl)azetid-2-one (6.15)



Chemical Formula: C<sub>17</sub>H<sub>17</sub>NO  
Molecular Weight: 251.33

Following **General Procedure 14**, amide **6.54** (99.7 mg, 0.3 mmol, 1.0 equiv.) was engaged. The crude was purified by FC (10% EtOAc in cHex) to afford the title compound **6.15** (40.4 mg, 0.16 mmol, 54%) as a beige solid.

## Experimental Part

**<sup>1</sup>H NMR** (400 MHz, Chloroform-*d*)  $\delta$  7.51 – 7.46 (m, 2H), 7.41 – 7.35 (m, 2H), 7.31 – 7.26 (m, 2H), 7.23 (“t”,  $J = 7.7$  Hz, 1H), 7.18 – 7.14 (m, 1H), 6.95 – 6.90 (m, 1H), 3.90 (d,  $J = 5.5$  Hz, 1H), 3.75 (d,  $J = 5.5$  Hz, 1H), 2.36 (s, 3H), 1.77 (s, 3H).

**<sup>13</sup>C NMR** (101 MHz, Chloroform-*d*)  $\delta$  168.8, 140.8, 139.4, 138.5, 129.1, 128.8, 127.4, 126.1, 124.9, 117.31, 113.6, 57.4, 53.8, 23.7, 21.6.

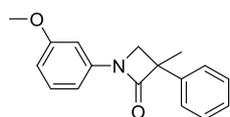
**IR (neat):**  $\nu$  (cm<sup>-1</sup>) 2965, 2922, 2360, 2337, 1740, 1599, 1486, 1380.

**HRMS** (ESI): Calcd for C<sub>17</sub>H<sub>18</sub>NO [M+H]<sup>+</sup>: 252.1383, found: 252.1380.

**R<sub>f</sub>** = 0.62 (EtOAc/cHex 20:80)

**mp:** 69 °C

### 1-(3-methoxyphenyl)-3-methyl-3-phenylazetid-2-one (6.16)



Chemical Formula: C<sub>17</sub>H<sub>17</sub>NO<sub>2</sub>  
Molecular Weight: 267.33

Following **General Procedure 14**, amide **6.55** (104.0 mg, 0.3 mmol, 1.0 equiv.) was engaged. The crude was purified by FC (12% EtOAc in cHex) to afford the title compound **6.16** (47.2 mg, 0.18 mmol, 59%) as an orange viscous oil.

2.87 mmol scale: 1000 mg amide resulted in 325 mg **6.16** (43%) of the title compound as an orange viscous oil.

**<sup>1</sup>H NMR** (400 MHz, Chloroform-*d*)  $\delta$  7.50 – 7.44 (m, 2H), 7.40 – 7.33 (m, 2H), 7.30 – 7.20 (m, 2H), 7.08 (“t”,  $J = 2.2$  Hz, 1H), 6.89 (ddd,  $J = 8.0, 2.0, 0.9$  Hz, 1H), 6.65 (ddd,  $J = 8.4, 2.5, 0.9$  Hz, 1H), 3.90 (d,  $J = 5.5$  Hz, 1H), 3.82 (s, 3H), 3.75 (d,  $J = 5.5$  Hz, 1H), 1.76 (s, 3H).

**<sup>13</sup>C NMR** (101 MHz, Chloroform-*d*)  $\delta$  168.9, 160.4, 140.7, 139.7, 130.1, 128.9, 127.4, 126.1, 110.2, 108.6, 102.5, 57.4, 55.5, 53.9, 23.7.

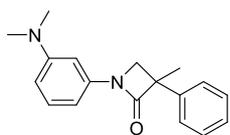
**IR (neat):**  $\nu$  (cm<sup>-1</sup>) 2964, 2361, 2340, 1744, 1601, 1495, 1389, 1228, 1173, 769.

**HRMS** (ESI): Calcd for C<sub>17</sub>H<sub>18</sub>NO<sub>2</sub> [M+H]<sup>+</sup>: 268.1332, found: 268.1330.

**R<sub>f</sub>** = 0.41 (EtOAc/cHex 20:80)

## Experimental Part

### 1-(3-(dimethylamino)phenyl)-3-methyl-3-phenylazetididin-2-one (6.17)



Chemical Formula: C<sub>18</sub>H<sub>20</sub>N<sub>2</sub>O  
Molecular Weight: 280.37

Following **General Procedure 14**, amide **6.56** (108.0 mg, 0.3 mmol, 1.0 equiv.) was engaged. The crude was purified by FC (10% EtOAc in cHex) to afford the title compound **6.17** (60.0 mg, 0.21 mmol, 71%) as an orange viscous oil.

2.77 mmol scale: 1000 mg amide resulted in 386 mg **6.17** (50%) of the title compound as an orange viscous oil.

**<sup>1</sup>H NMR** (400 MHz, Chloroform-*d*) δ 7.52 – 7.44 (m, 2H), 7.41 – 7.32 (m, 2H), 7.32 – 7.23 (m, 1H), 7.19 (“t”, *J* = 8.1 Hz, 1H), 6.96 (“t”, *J* = 2.2 Hz, 1H), 6.59 (ddd, *J* = 7.9, 1.9, 0.9 Hz, 1H), 6.51 – 6.46 (m, 1H), 3.90 (d, *J* = 5.5 Hz, 1H), 3.75 (d, *J* = 5.5 Hz, 1H), 2.96 (s, 6H), 1.76 (s, 3H).

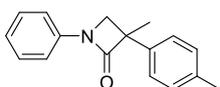
**<sup>13</sup>C NMR** (101 MHz, Chloroform-*d*) δ 168.9, 151.4, 141.0, 139.5, 129.7, 128.9, 127.3, 126.1, 108.6, 104.27, 101.1, 57.1, 53.9, 40.6, 23.7.

**IR (neat):** ν (cm<sup>-1</sup>) 2964, 2923, 2890, 2361, 2340, 1741, 1604, 1504, 1446, 1393, 1347, 1179, 765, 701.

**HRMS (ESI):** Calcd for C<sub>18</sub>H<sub>21</sub>N<sub>2</sub>O [M+H]<sup>+</sup>: 281.1648, found 281.1657.

**R<sub>f</sub>** = 0.23 (EtOAc/cHex 20:80)

### 3-methyl-1-phenyl-3-(*p*-tolyl)azetididin-2-one (6.18)



Chemical Formula: C<sub>17</sub>H<sub>17</sub>NO  
Molecular Weight: 251.33

Following **General Procedure 14**, amide **6.57** (99.7 mg, 0.3 mmol, 1.0 equiv.) was engaged. The crude was purified by FC (10% EtOAc in cHex) to afford the title compound **6.18** (30.0 mg, 0.12 mmol, 40%) as an off white solid.

**<sup>1</sup>H NMR** (400 MHz, Chloroform-*d*) δ 7.42 – 7.30 (m, 6H), 7.21 – 7.15 (m, 2H), 7.12 – 7.07 (m, 1.4 Hz, 1H), 3.88 (d, *J* = 5.4 Hz, 1H), 3.74 (d, *J* = 5.5 Hz, 1H), 2.34 (s, 3H), 1.75 (s, 3H).

**<sup>13</sup>C NMR** (101 MHz, Chloroform-*d*) δ 169.0, 138.6, 137.8, 137.1, 129.6, 129.3, 126.0, 124.1, 116.6, 57.2, 53.8, 23.7, 21.2.

**IR (neat):** ν (cm<sup>-1</sup>) 2922, 2861, 1747, 1600, 1503, 1388.

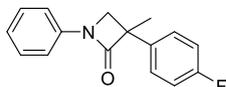
**HRMS (ESI):** Calcd for C<sub>17</sub>H<sub>18</sub>NO [M+H]<sup>+</sup>: 252.1383, found: 252.1379.

## Experimental Part

$R_f = 0.57$  (EtOAc/cHex 20:80)

mp: 107 °C

### 3-(4-fluorophenyl)-3-methyl-1-phenylazetid-2-one (6.19)



Chemical Formula:  $C_{16}H_{14}FNO$   
Molecular Weight: 255.29

Following **General Procedure 14**, amide **6.58** (101.0 mg, 0.3 mmol, 1.0 equiv.) was engaged. The crude was purified by FC (10% EtOAc in cHex) to afford the title compound **6.19** (36.0 mg, 0.14 mmol, 47%) as an off white solid.

$^1H$  NMR (500 MHz, Chloroform-*d*)  $\delta$  7.48 – 7.41 (m, 2H), 7.43 – 7.36 (m, 2H), 7.39 – 7.31 (m, 2H), 7.13 – 7.09 (m, 1H), 7.09 – 7.02 (m, 2H), 3.87 (d,  $J = 5.5$  Hz, 1H), 3.76 (d,  $J = 5.5$  Hz, 1H), 1.75 (s, 3H).

$^{13}C$  NMR (126 MHz, Chloroform-*d*)  $\delta$  168.6, 162.1 (d,  $J = 246.1$  Hz), 138.4, 136.6 (d,  $J = 3.3$  Hz), 129.3, 127.8 (d,  $J = 8.0$  Hz), 124.2, 116.6, 115.8 (d,  $J = 21.5$  Hz), 56.9, 53.8, 23.8.

$^{19}F\{^1H\}$  NMR (376 MHz, Chloroform-*d*)  $\delta$  -115.14.

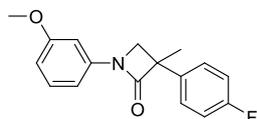
IR (neat):  $\nu$  ( $cm^{-1}$ ) 2361, 2339, 1745, 1600, 1504, 1309, 1228, 721.

HRMS (ESI): Calcd for  $C_{16}H_{14}FNNaO$   $[M+H]^+$ : 278.0952, found: 278.0948.

$R_f = 0.56$  (EtOAc/cHex 20:80)

mp: 94 °C

### 3-(4-fluorophenyl)-1-(3-methoxyphenyl)-3-methylazetid-2-one (6.20)



Chemical Formula:  $C_{17}H_{16}FNO_2$   
Molecular Weight: 285.32

Following **General Procedure 14**, amide **6.59** (110.0 mg, 0.3 mmol, 1.0 equiv.) was engaged. The crude was purified by FC (8% EtOAc in cHex) to afford the title compound **6.20** (48.3 mg, 0.17 mmol, 56%) as an orange viscous oil.

$^1H$  NMR (400 MHz, Chloroform-*d*)  $\delta$  7.49 – 7.39 (m, 2H), 7.24 (“t”,  $J = 8.1$  Hz, 1H), 7.11 – 7.00 (m, 3H), 6.89 (ddd,  $J = 8.0, 2.0, 1.0$  Hz, 1H), 6.67 (ddd,  $J = 8.3, 2.5, 0.9$  Hz, 1H), 3.86 (d,  $J = 5.5$  Hz, 1H), 3.82 (s, 3H), 3.75 (d,  $J = 5.6$  Hz, 1H), 1.74 (s, 3H).

$^{13}C$  NMR (101 MHz, Chloroform-*d*)  $\delta$  168.6, 162.1 (d,  $J = 246.1$  Hz), 160.5, 139.6, 136.5 (d,  $J = 3.3$  Hz), 130.2, 127.8 (d,  $J = 8.0$  Hz), 115.8 (d,  $J = 21.4$  Hz), 110.3, 108.6, 102.6, 56.8, 55.5, 54.0, 23.8 (d,  $J = 0.9$  Hz).

## Experimental Part

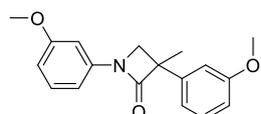
$^{19}\text{F}\{^1\text{H}\}$  NMR (376 MHz, Chloroform-*d*)  $\delta$  -115.12.

**IR (neat):**  $\nu$  ( $\text{cm}^{-1}$ ) 2965, 2929, 2894, 2383, 1744, 1603, 1496, 1390, 1228, 1160, 1041, 838, 775, 688.

**HRMS (ESI):** Calcd for  $\text{C}_{17}\text{H}_{17}\text{FNO}_2$   $[\text{M}+\text{H}]^+$ : 286.1238, found: 286.1234.

$R_f$  = 0.38 (EtOAc/cHex 20:80)

### 1,3-bis(3-methoxyphenyl)-3-methylazetid-2-one (6.21)



Chemical Formula:  $\text{C}_{18}\text{H}_{19}\text{NO}_3$   
Molecular Weight: 297.35

Following **General Procedure 14**, amide **6.61** (113.0 mg, 0.3 mmol, 1.0 equiv.) was engaged. The crude was purified by FC (12% EtOAc in cHex) to afford the title compound **6.21** (43.1 mg, 0.15 mmol, 48%) as a yellow viscous oil.

$^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  7.29 (“t”,  $J$  = 8.2 Hz, 1H), 7.24 (“t”,  $J$  = 8.2 Hz, 1H), 7.08 (“t”,  $J$  = 2.2 Hz, 1H), 7.08 – 7.00 (m, 2H), 6.88 (ddd,  $J$  = 7.9, 2.0, 0.9 Hz, 1H), 6.82 (ddd,  $J$  = 8.2, 2.4, 1.0 Hz, 1H), 6.66 (ddd,  $J$  = 8.3, 2.5, 0.9 Hz, 1H), 3.90 (d,  $J$  = 5.5 Hz, 1H), 3.82 (s, 3H), 3.82 (s, 3H), 3.73 (d,  $J$  = 5.5 Hz, 1H), 1.76 (s, 3H).

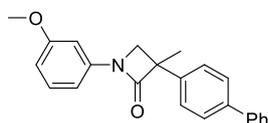
$^{13}\text{C}$  NMR (101 MHz, Chloroform-*d*)  $\delta$  168.8, 160.5, 160.0, 142.4, 139.7, 130.1, 129.9, 118.4, 112.7, 112.0, 110.2, 108.6, 102.5, 57.4, 55.5, 55.4, 53.9, 23.8.

**IR (neat):**  $\nu$  ( $\text{cm}^{-1}$ ) 2967, 2894, 2361, 2340, 1746, 1603, 1496, 1390, 1291, 1234, 1176, 1045.

**HRMS (ESI):** Calcd for  $\text{C}_{18}\text{H}_{20}\text{NO}_3$   $[\text{M}+\text{H}]^+$ : 298.1438, found: 298.1431.

$R_f$  = 0.28 (EtOAc/cHex 20:80)

### 3-([1,1'-biphenyl]-4-yl)-1-(3-methoxyphenyl)-3-methylazetid-2-one (6.22)



Chemical Formula:  $\text{C}_{23}\text{H}_{21}\text{NO}_2$   
Molecular Weight: 343.43

Following **General Procedure 14**, amide **6.60** (127 mg, 0.3 mmol, 1.0 equiv.) was engaged. The crude was purified by FC (12% EtOAc in cHex) to afford the title compound **6.22** (45.5 mg, 0.13 mmol, 44%) as an orange viscous oil that turned into a yellow solid. Suitable crystals for X-ray diffraction analysis were obtained by dissolving the sample in  $\text{Et}_2\text{O}$  and let stand at room temperature open to air.

$^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  7.62 – 7.51 (m, 6H), 7.46 – 7.40 (m, 2H), 7.37 – 7.31 (m, 1H), 7.28 – 7.24 (“t”,  $J$  = 8.1 Hz, 1H), 7.10 (“t”,  $J$  = 2.2 Hz, 1H), 6.90 (ddd,  $J$  = 7.9, 1.9,

## Experimental Part

0.9 Hz, 1H), 6.66 (ddd,  $J = 8.4, 2.5, 0.9$  Hz, 1H), 3.93 (d,  $J = 5.5$  Hz, 1H), 3.82 (s, 3H), 3.77 (d,  $J = 5.5$  Hz, 1H), 1.80 (s, 3H).

$^{13}\text{C}$  NMR (101 MHz, Chloroform-*d*)  $\delta$  168.8, 160.5, 140.7, 140.4, 139.7, 139.7, 130.1, 128.9, 127.6, 127.5, 127.2, 126.5, 110.2, 108.6, 102.6, 57.2, 55.5, 53.9, 23.6.

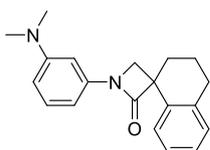
IR (neat):  $\nu$  ( $\text{cm}^{-1}$ ) 2964, 2892, 2361, 2340, 1744, 1601, 1494, 1388, 1228, 768.

HRMS (ESI): Calcd for  $\text{C}_{23}\text{H}_{22}\text{NO}_2$   $[\text{M}+\text{H}]^+$ : 344.1645, found: 344.1639.

$R_f = 0.30$  (EtOAc/petroleum ether 20:80)

mp: 112 °C

### 1-(3-(dimethylamino)phenyl)-3',4'-dihydro-2'H-spiro[azetidine-3,1'-naphthalen]-2-one (6.23)



Chemical Formula:  $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}$   
Molecular Weight: 306.41

Following **General Procedure 14**, amide **6.67** (116.0 mg, 0.3 mmol, 1.0 equiv.) was engaged. The crude was purified by FC (12% EtOAc in cHex) to afford the title compound **6.22** (51.9 mg, 0.17 mmol, 56%) as a light orange solid.

$^1\text{H}$  NMR (500 MHz, Chloroform-*d*)  $\delta$  7.31 – 7.26 (m, 1H), 7.22 (“t”,  $J = 8.0$  Hz, 1H), 7.20 – 7.14 (m, 2H), 7.17 – 7.10 (m, 1H), 7.00 (t,  $J = 2.2$  Hz, 1H), 6.63 (ddd,  $J = 7.8, 1.7, 0.6$  Hz, 1H), 6.52 (ddd,  $J = 8.4, 2.6, 0.9$  Hz, 1H), 3.74 (dd,  $J = 5.6, 0.9$  Hz, 1H), 3.69 (d,  $J = 5.6$  Hz, 1H), 2.98 (s, 6H), 2.90 – 2.82 (m, 2H), 2.34 – 2.24 (m, 1H), 2.18 – 2.06 (m, 2H), 1.88 – 1.73 (m, 1H).

$^{13}\text{C}$  NMR (126 MHz, Chloroform-*d*)  $\delta$  169.8, 151.5, 139.5, 137.6, 134.2, 129.8, 129.6, 127.5, 126.8, 126.5, 108.6, 104.3, 101.1, 57.2, 56.8, 40.6, 30.7, 29.6, 20.6.

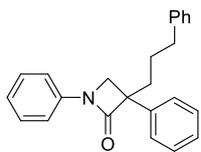
IR (neat):  $\nu$  ( $\text{cm}^{-1}$ ) 2930, 2873, 2803, 1745, 1604, 1504, 1389, 1347, 1178, 633.

HRMS (ESI): Calcd for  $\text{C}_{20}\text{H}_{23}\text{N}_2\text{O}$   $[\text{M}+\text{H}]^+$ : 307.1805, found: 307.1808.

$R_f = 0.33$  (EtOAc/cHex 20:80)

mp: 115 °C

### 1,3-diphenyl-3-(3-phenylpropyl)azetid-2-one (6.24)



Chemical Formula: C<sub>24</sub>H<sub>23</sub>NO  
Molecular Weight: 341.45

Following **General Procedure 14**, amide **6.62** (127 mg, 0.3 mmol, 1.0 equiv.) was engaged. The crude was purified by FC (10% EtOAc in cHex) to afford the title compound **6.24** (44.3 mg, 0.13 mmol, 43%) as an orange viscous oil.

**<sup>1</sup>H NMR** (400 MHz, Chloroform-*d*) δ 7.49 – 7.42 (m, 2H), 7.40 – 7.27 (m, 7H), 7.25 – 7.21 (m, 2H), 7.19 – 7.13 (m, 1H), 7.13 – 7.04 (m, 3H), 3.88 (d, *J* = 5.6 Hz, 1H), 3.78 (d, *J* = 5.6 Hz, 1H), 2.60 (t, *J* = 7.6 Hz, 2H), 2.14 – 2.02 (m, 2H), 1.88 – 1.71 (m, 1H), 1.71 – 1.57 (m, 1H).

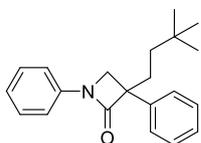
**<sup>13</sup>C NMR** (101 MHz, Chloroform-*d*) δ 168.2, 141.8, 139.7, 138.4, 129.3, 128.7, 128.5, 128.5, 127.4, 126.8, 126.0, 124.1, 116.5, 61.6, 51.0, 37.5, 36.0, 26.8.

**IR (neat):** ν (cm<sup>-1</sup>) 3027, 2940, 1742, 1600, 1501, 1386, 1155, 700.

**HRMS (ESI):** Calcd for C<sub>24</sub>H<sub>24</sub>NO [M+H]<sup>+</sup>: 342.1852, found: 342.1847.

**R<sub>f</sub>** = 0.55 (EtOAc/cHex 20:80)

### 3-(3,3-dimethylbutyl)-1,3-diphenylazetid-2-one (6.25)



Chemical Formula: C<sub>21</sub>H<sub>25</sub>NO  
Molecular Weight: 307.44

Following **General Procedure 14**, amide **6.63** (117 mg, 0.3 mmol, 1.0 equiv.) was engaged. The crude was purified by FC (10% EtOAc in cHex) to afford the title compound **6.26** (36.7 mg, 0.12 mmol, 40%) as a yellow solid.

**<sup>1</sup>H NMR** (500 MHz, Chloroform-*d*) δ 7.50 – 7.46 (m, 2H), 7.41 – 7.31 (m, 6H), 7.31 – 7.26 (m, 1H), 7.09 (“tt”, *J* = 7.3, 1.2 Hz, 1H), 3.90 (d, *J* = 5.5 Hz, 1H), 3.78 (d, *J* = 5.6 Hz, 1H), 2.05 – 1.98 (m, 2H), 1.31 (ddd, *J* = 13.2, 9.9, 7.4 Hz, 1H), 1.23 – 1.15 (m, 1H), 0.84 (s, 9H).

**<sup>13</sup>C NMR** (126 MHz, Chloroform-*d*) δ 168.4, 139.9, 138.5, 129.3, 128.7, 127.3, 126.8, 124.0, 116.5, 61.7, 50.9, 38.5, 33.0, 30.2, 29.4.

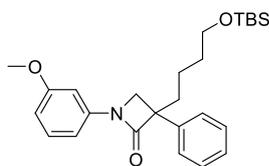
**IR (neat):** ν (cm<sup>-1</sup>) 2954, 2363, 2341, 1744, 1600, 1502, 1386, 1155, 700.

**HRMS (ESI):** Calcd for C<sub>21</sub>H<sub>26</sub>NO [M+H]<sup>+</sup>: 308.2009, found: 308.2005.

**R<sub>f</sub>** = 0.76 (EtOAc/cHex 20:80)

**mp:** 108 °C

**3-(4-((tert-butyldimethylsilyloxy)butyl)-1-(3-methoxyphenyl)-3-phenylazetidin-2-one**  
**(6.26)**



Chemical Formula:  $C_{26}H_{37}NO_3Si$   
Molecular Weight: 439.67

Following **General Procedure 14**, amide **6.64** (156.0 mg, 0.3 mmol, 1.0 equiv.) was engaged. The crude was purified by FC (10% EtOAc in cHex) to afford the title compound **6.26** (61.5 mg, 0.14 mmol, 47%) as a yellow viscous oil.

**$^1H$  NMR** (400 MHz, Chloroform-*d*)  $\delta$  7.51 – 7.44 (m, 2H), 7.40 – 7.33 (m, 2H), 7.30 – 7.25 (m, 1H), 7.22 (“t”,  $J$  = 8.1 Hz, 1H), 7.07 (“t”,  $J$  = 2.2 Hz, 1H), 6.86 (ddd,  $J$  = 8.0, 2.0, 0.9 Hz, 1H), 6.64 (ddd,  $J$  = 8.3, 2.5, 0.9 Hz, 1H), 3.90 (d,  $J$  = 5.6 Hz, 1H), 3.81 (s, 3H), 3.80 (d,  $J$  = 5.6 Hz, 1H), 3.58 – 3.52 (m, 2H), 2.10 – 1.99 (m, 2H), 1.54 – 1.42 (m, 3H), 1.41 – 1.25 (m, 1H), 0.84 (s, 9H), -0.01 (s, 6H).

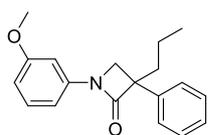
**$^{13}C$  NMR** (101 MHz, Chloroform-*d*)  $\delta$  168.4, 160.4, 139.7, 139.6, 130.1, 128.7, 127.3, 126.8, 110.2, 108.5, 102.4, 62.9, 61.7, 55.5, 51.2, 37.8, 32.9, 26.1, 21.4, 18.5, -5.2.

**IR (neat):**  $\nu$  ( $cm^{-1}$ ) 2931, 2893, 2867, 2360, 2340, 1746, 1601, 1495, 1483, 1386, 1228, 1157, 1099, 837, 775.

**HRMS** (ESI): Calcd for  $C_{26}H_{38}NO_3Si$   $[M+H]^+$ : 440.2615, found: 440.2611.

$R_f$  = 0.51 (EtOAc/cHex 20:80)

**1-(3-methoxyphenyl)-3-phenyl-3-propylazetidin-2-one (6.27)**



Chemical Formula:  $C_{19}H_{21}NO_2$   
Molecular Weight: 295.38

Following **General Procedure 14**, amide **6.65** (113 mg, 0.3 mmol, 1.0 equiv.) was engaged. The crude was purified by FC (12% EtOAc in cHex) to afford the title compound **6.27** (40.8 mg, 0.14 mmol, 46%) as a yellow viscous oil.

**$^1H$  NMR** (400 MHz, Chloroform-*d*)  $\delta$  7.46 – 7.41 (m, 2H), 7.35 – 7.29 (m, 2H), 7.26 – 7.21 (m, 1H), 7.18 (“t”,  $J$  = 8.1 Hz, 1H), 7.03 (“t”,  $J$  = 2.2 Hz, 1H), 6.83 (ddd,  $J$  = 8.0, 2.0, 1.0 Hz, 1H), 6.60 (ddd,  $J$  = 8.3, 2.5, 0.9 Hz, 1H), 3.85 (d,  $J$  = 5.6 Hz, 1H), 3.77 (s, 3H), 3.76 (d,  $J$  = 5.6 Hz, 1H), 2.03 – 1.90 (m, 2H), 1.49 – 1.36 (m, 1H), 1.35 – 1.20 (m, 1H), 0.86 (t,  $J$  = 7.3 Hz, 3H).

**$^{13}C$  NMR** (101 MHz, Chloroform-*d*)  $\delta$  168.5, 160.4, 139.8, 139.6, 130.1, 128.7, 127.3, 126.7, 110.1, 108.5, 102.4, 61.8, 55.5, 51.2, 40.2, 18.4, 14.3.

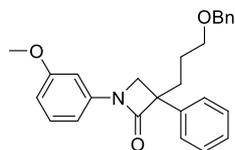
**IR (neat):**  $\nu$  ( $cm^{-1}$ ) 2959, 2933, 1739, 1600, 1494, 1383, 1226, 1127, 1039, 850, 771, 702.

## Experimental Part

**HRMS (ESI):** Calcd for C<sub>19</sub>H<sub>22</sub>NO<sub>2</sub> [M+H]<sup>+</sup>: 296.1645, found: 296.1642.

**R<sub>f</sub>** = 0.45 (EtOAc/cHex 20:80)

### 3-(3-(benzyloxy)propyl)-1-(3-methoxyphenyl)-3-phenylazetidin-2-one (6.28)



Chemical Formula: C<sub>26</sub>H<sub>27</sub>NO<sub>3</sub>  
Molecular Weight: 401.51

Following **General Procedure 14**, amide **6.66** (145.0 mg, 0.3 mmol, 1.0 equiv.) was engaged. The crude was purified by FC (12% EtOAc in cHex) to afford the title compound **6.28** (56.3 mg, 0.14 mmol, 47%) as an orange viscous oil.

**<sup>1</sup>H NMR** (400 MHz, Chloroform-*d*) δ 7.50 – 7.45 (m, 2H), 7.39 – 7.33 (m, 2H), 7.33 – 7.26 (m, 6H), 7.22 (“t”, *J* = 8.1 Hz, 1H), 7.06 (“t”, *J* = 2.2 Hz, 1H), 6.86 (ddd, *J* = 7.9, 2.0, 0.9 Hz, 1H), 6.64 (ddd, *J* = 8.4, 2.5, 0.9 Hz, 1H), 4.44 (s, 2H), 3.88 (d, *J* = 5.6 Hz, 1H), 3.81 (s, 3H), 3.80 (d, *J* = 5.6 Hz, 1H), 3.44 (td, *J* = 6.3, 1.3 Hz, 2H), 2.19 – 2.11 (m, 2H), 1.83 – 1.71 (m, 1H), 1.68 – 1.57 (m, 1H).

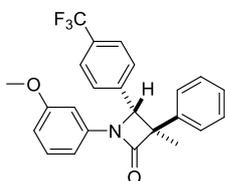
**<sup>13</sup>C NMR** (101 MHz, Chloroform-*d*) δ 168.3, 160.4, 139.6, 139.5, 138.5, 130.1, 128.8, 128.5, 127.8, 127.7, 127.4, 126.8, 110.2, 108.5, 102.4, 73.1, 70.1, 61.4, 55.5, 51.3, 34.7, 25.5.

**IR (neat):** ν (cm<sup>-1</sup>) 2947, 2858, 2361, 2352, 1742, 1601, 1495, 1386, 1277, 1158, 1100, 1041, 741.

**HRMS (ESI):** Calcd for C<sub>26</sub>H<sub>28</sub>NO<sub>3</sub> [M+H]<sup>+</sup>: 402.2064, found: 402.2058.

**R<sub>f</sub>** = 0.35 (EtOAc/cHex 20:80)

### 1-(3-methoxyphenyl)-3-methyl-3-phenyl-4-(4-(trifluoromethyl)phenyl)azetidin-2-one (6.29)



Chemical Formula: C<sub>24</sub>H<sub>20</sub>F<sub>3</sub>NO<sub>2</sub>  
Molecular Weight: 411.42

Following **General Procedure 14**, amide **6.68** (148 mg, 0.3 mmol, 1.0 equiv.) was engaged. The crude was purified by FC (10% EtOAc in cHex) to separate the major diastereoisomer (56.0 mg, 0.14 mmol, 45%) as yellow viscous oil from the minor one and an unknown impurity. The mixed fraction containing the minor diastereoisomer was further purified by prep TLC (5% EtOAc in cHex) to afford the pure minor diastereoisomer (7.7 mg, 0.02 mmol, 6%) as a yellow viscous oil. Combined yield of 63.7 mg, 0.16 mmol, 51% of **6.29**.

## Experimental Part

### Major Diastereoisomer

**<sup>1</sup>H NMR** (500 MHz, Chloroform-*d*) δ 7.71 – 7.66 (m, 2H), 7.56 – 7.49 (m, 2H), 7.49 – 7.44 (m, 2H), 7.46 – 7.38 (m, 2H), 7.37 – 7.29 (m, 1H), 7.16 (“t”, *J* = 8.2 Hz, 1H), 7.07 (“t”, *J* = 2.2 Hz, 1H), 6.73 (ddd, *J* = 8.0, 2.0, 0.9 Hz, 1H), 6.64 (ddd, *J* = 8.3, 2.5, 0.9 Hz, 1H), 5.27 (s, 1H), 3.77 (s, 3H), 1.22 (s, 3H).

**<sup>13</sup>C NMR** (126 MHz, Chloroform-*d*) δ 169.0, 160.4, 141.3, 139.4, 138.4, 130.8 (q, *J* = 32.7 Hz), 130.2, 129.2, 127.8, 127.5, 126.1 (q, *J* = 3.8 Hz), 126.0, 123.0 (q, *J* = 272.2 Hz), 110.2, 109.6, 103.6, 66.7, 63.0, 55.5, 19.8.

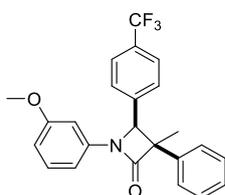
**<sup>19</sup>F{<sup>1</sup>H} NMR** (471 MHz, Chloroform-*d*) δ -62.60

**IR (neat):** ν (cm<sup>-1</sup>) 2970, 2929, 2840, 1753, 1602, 1494, 1383, 1325, 1248, 1168, 1126, 1068.

**HRMS (ESI):** Calcd for C<sub>24</sub>H<sub>21</sub>F<sub>3</sub>NO<sub>2</sub> [M+H]<sup>+</sup>: 412.1519, found: 412.1511.

**R<sub>f</sub>** = 0.55 (EtOAc/cHex 20:80)

### Minor Diastereoisomer



Chemical Formula: C<sub>24</sub>H<sub>20</sub>F<sub>3</sub>NO<sub>2</sub>  
Molecular Weight: 411.42

**<sup>1</sup>H NMR** (500 MHz, Chloroform-*d*) δ 7.36 – 7.31 (m, 2H), 7.15 (“t”, *J* = 8.2 Hz, 1H), 7.13 – 7.10 (m, 2H), 7.08 (“t”, *J* = 2.3 Hz, 1H), 7.09 – 7.01 (m, 5H), 6.75 (ddd, *J* = 8.0, 2.0, 0.9 Hz, 1H), 6.63 (ddd, *J* = 8.3, 2.5, 0.9 Hz, 1H), 5.08 (s, 1H), 3.77 (s, 3H), 1.94 (s, 3H).

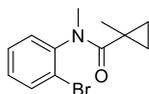
**<sup>13</sup>C NMR** (126 MHz, Chloroform-*d*) δ 169.0, 160.4, 139.8, 138.7, 137.0, 130.3 (q, *J* = 32.4 Hz), 130.1, 128.3, 127.7, 127.3, 127.3, 125.4 (q, *J* = 3.8 Hz), 124.7 (q, *J* = 272.4 Hz), 110.3, 109.5, 103.6, 68.4, 65.3, 55.5, 24.4.

**<sup>19</sup>F{<sup>1</sup>H} NMR** (471 MHz, Chloroform-*d*) δ -62.71.

**IR (neat):** ν (cm<sup>-1</sup>) 2958, 2923, 2857, 1751, 1603, 1495, 1326, 1125, 702, 630.

**HRMS (ESI):** Calcd for C<sub>24</sub>H<sub>20</sub>F<sub>3</sub>NNaO<sub>2</sub> [M+Na]<sup>+</sup>: 434.1338, found: 434.1332.

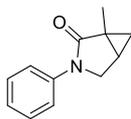
**R<sub>f</sub>** = 0.35 (EtOAc/cHex 20:80)

**N-(2-bromophenyl)-N,1-dimethylcyclopropane-1-carboxamide (6.41)**

Chemical Formula: C<sub>12</sub>H<sub>14</sub>BrNO  
Molecular Weight: 268.15

Following **General Procedure 11**, methyl-aniline **6.45** (500 mg, 2.69 mmol, 1.0 equiv.) was reacted with 1-Methylcyclopropane-1-carboxylic acid (323 mg, 3.23 mmol, 1.2 equiv.) and Et<sub>3</sub>N (0.95 mL, 6.73 mmol, 2.5 equiv.) in dry DCM (5 mL). The crude was purified by FC (0-30% EtOAc in cHex) to afford the desired amide **6.41** (517 mg, 1.93 mmol, 72%) as a white crystalline solid which occurs as a conformational mixture. Analytical data are in agreement with the literature.<sup>[30]</sup>

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.67 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.39 – 7.34 (m, 1H), 7.32 – 7.26 (m, 1H), 7.21 (td, *J* = 7.7, 1.8 Hz, 1H), 3.20 (s, 3H), 1.38 – 0.21 (m, 7H).

**1-methyl-3-phenyl-3-azabicyclo[3.1.0]hexan-2-one (6.42)**

Chemical Formula: C<sub>12</sub>H<sub>13</sub>NO  
Molecular Weight: 187.24

Following **General Procedure 14**, amide **6.41** (26.8 mg, 0.1 mmol, 1.0 equiv.) was engaged. The crude was purified by FC (10% EtOAc in cHex) to afford the title compound **6.42** (24% NMR yield) as a yellow viscous oil.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.58 – 7.53 (m, 2H), 7.36 – 7.30 (m, 2H), 7.11 – 7.07 (m, 1H), 3.99 (dd, *J* = 9.9, 5.8 Hz, 1H), 3.65 (d, *J* = 9.9 Hz, 1H), 1.83 (ddd, *J* = 7.5, 5.8, 4.0 Hz, 1H), 1.43 (s, 3H), 1.00 (dd, *J* = 7.5, 4.6 Hz, 1H), 0.85 – 0.80 (m, 1H).

**10 References Experimental Part**

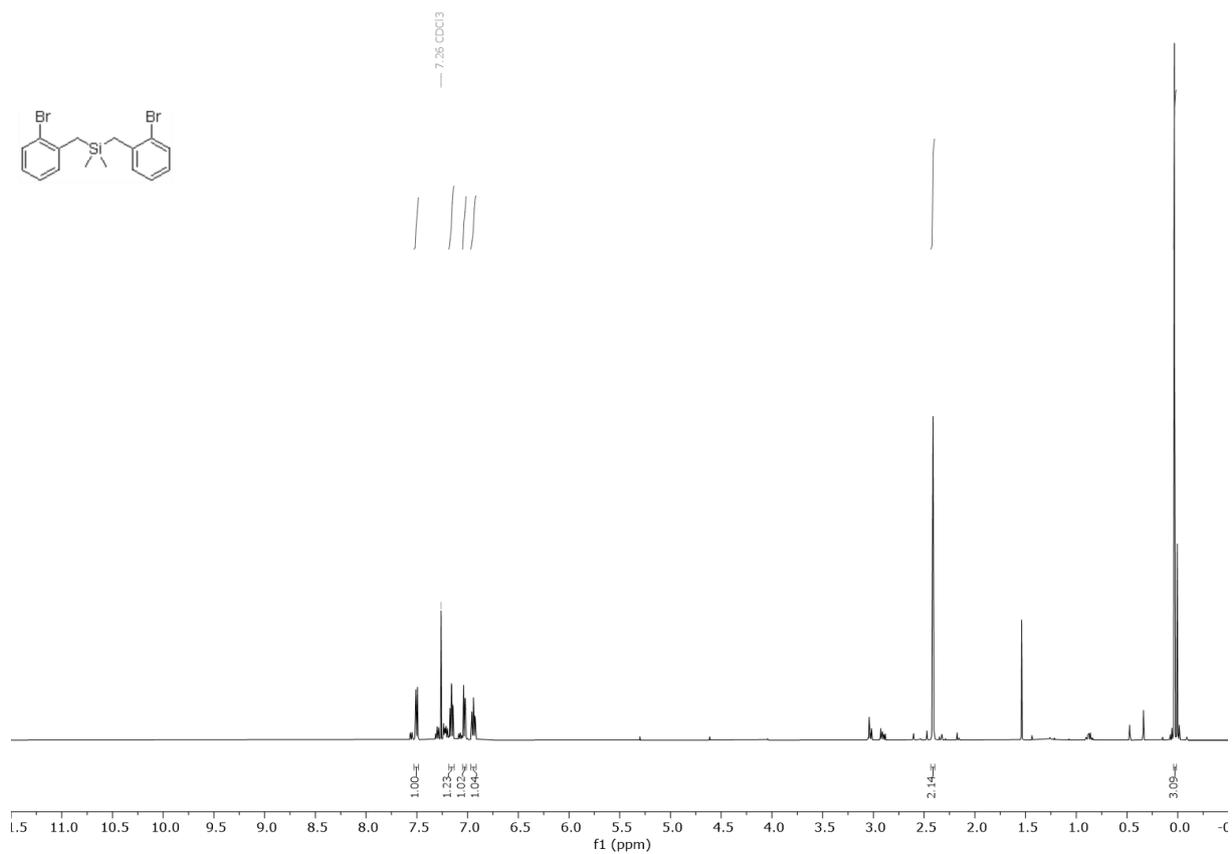
- [1] G. Markopoulos, L. Henneicke, J. Shen, Y. Okamoto, P. G. Jones, H. Hopf, *Angew. Chem. Int. Ed.* **2012**, *51*, 12884–12887.
- [2] H. Zhang, D. Feng, H. Sheng, X. Ma, J. Wan, Q. Tang, *RSC Adv.* **2014**, *4*, 6417–6423.
- [3] W. Adam, C. van Barneveld, J.-S. Gerke, F. G. Klärner, *J. Chem. Soc., Perkin Trans. 2* **1999**, 2723–2728.
- [4] S. Janody, R. Jazzar, A. Comte, P. M. Holstein, J.-P. Vors, M. J. Ford, O. Baudoin, *Chem. Eur. J.* **2014**, *20*, 11084–11090.
- [5] H. Yoshida, Y. Mimura, J. Ohshita, A. Kunai, *Chem. Commun.* **2007**, 2405–2407.
- [6] S. Rousseaux, M. Davi, J. Sofack-Kreutzer, C. Pierre, C. E. Kefalidis, E. Clot, K. Fagnou, O. Baudoin, *J. Am. Chem. Soc.* **2010**, *132*, 10706–10716.
- [7] X. Q. Hao, Y. N. Dong, B. Gao, K. Li, X. M. Zhao, Y. Xu, M. P. Song, *Tetrahedron Asymmetry* **2015**, *26*, 1360–1368.
- [8] Y. Kohari, Y. Okuyama, E. Kwon, T. Furuyama, N. Kobayashi, T. Otuki, J. Kumagai, C. Seki, K. Uwai, G. Dai, T. Iwasa, H. Nakano, *J. Org. Chem.* **2014**, *79*, 9500–9511.
- [9] M. Liniger, Y. Liu, B. M. Stoltz, *J. Am. Chem. Soc.* **2017**, *139*, 13944–13949.
- [10] D. Belmessieri, C. Joannesse, P. A. Woods, C. MacGregor, C. Jones, C. D. Campbell, C. P. Johnston, N. Duguet, C. Concellón, R. A. Bragg, A. D. Smith, *Org. Biomol. Chem.* **2011**, *9*, 559–570.
- [11] V. A. Toussaint, *Boron-Bridged Bis(Oxazolines) and Their Use in Copper-Catalyzed Reactions*, University of Basel, Basel, **2008**.
- [12] G. D. Monarche, M. C. di Giovanni, F. Maggio, D. Misiti, G. Zappia, *Synthesis* **1995**, 1155–1158.
- [13] L. Yang, R. Melot, M. Neuburger, O. Baudoin, *Chem. Sci.* **2017**, *8*, 1344–1349.
- [14] J. Dupont, M. Pfeffer, M. A. Rotteveel, A. de Clan, J. Fischer, *Organometallics* **1989**, *8*, 1116–1118.
- [15] A. v. Lygin, O. v. Larionov, V. S. Korotkov, A. de Meijere, *Chem. Eur. J.* **2009**, *15*, 227–236.
- [16] C. A. M. Cariou, B. M. Kariuki, J. S. Snaith, *Org. Biomol. Chem.* **2008**, *6*, 3337–3348.
- [17] M. S. Viciu, R. A. Kelly, E. D. Stevens, F. Naud, M. Studer, S. P. Nolan, *Org. Lett.* **2003**, *5*, 1479–1482.
- [18] B. H. Rotstein, D. J. Winterheimer, L. M. Yin, C. M. Deber, A. K. Yudin, *Chem. Commun.* **2012**, *48*, 3775–3777.

- [19] E. L. Ingalls, G. A. Holtzen, W. Kaminsky, F. E. Michael, *J. Organomet. Chem.* **2017**, *832*, 9–11.
- [20] L. W. Judd, A. P. Davis, *Chem. Commun.* **2010**, *46*, 2227–2229.
- [21] A. Elkamhawy, J. Park, A. H. E. Hassan, A. N. Pae, J. Lee, B. G. Park, S. Paik, J. Do, J.-H. Park, K. D. Park, B. Moon, W. K. Park, H. Cho, D. Y. Jeong, E. J. Roh, *Eur. J. Pharm. Sci.* **2017**, *104*, 366–381.
- [22] L. Yang, M. Neuburger, O. Baudoin, *Angew. Chem. Int. Ed.* **2018**, *57*, 1394–1398.
- [23] S. Würtz, C. Lohre, R. Fröhlich, K. Bergander, F. Glorius, *J. Am. Chem. Soc.* **2009**, *131*, 8344–8345.
- [24] N. Probst, G. Grelier, N. Ghermani, V. Gandon, M. Alami, S. Messaoudi, *Org. Lett.* **2017**, *19*, 5038–5041.
- [25] G. Sun, Z. Wang, Z. Luo, Y. Lin, Z. Deng, R. Li, J. Zhang, *J. Org. Chem.* **2020**, *85*, 10584–10592.
- [26] P. Zhang, M. Cedilote, T. P. Cleary, M. E. Pierce, *Tetrahedron Lett.* **2007**, *48*, 8659–8664.
- [27] C. Fischer, C. Sparr, *Angew. Chem. Int. Ed.* **2018**, *57*, 2436–2440.
- [28] A. Bunescu, T. Piou, Q. Wang, J. Zhu, *Org. Lett.* **2015**, *17*, 334–337.
- [29] Y.-X. Jia, D. Katayev, G. Bernardinelli, T. M. Seidel, E. P. Kündig, *Chem. Eur. J.* **2010**, *16*, 6300–6309.
- [30] J. Pedroni, T. Saget, P. A. Donets, N. Cramer, *Chem. Sci.* **2015**, *6*, 5164–5171.

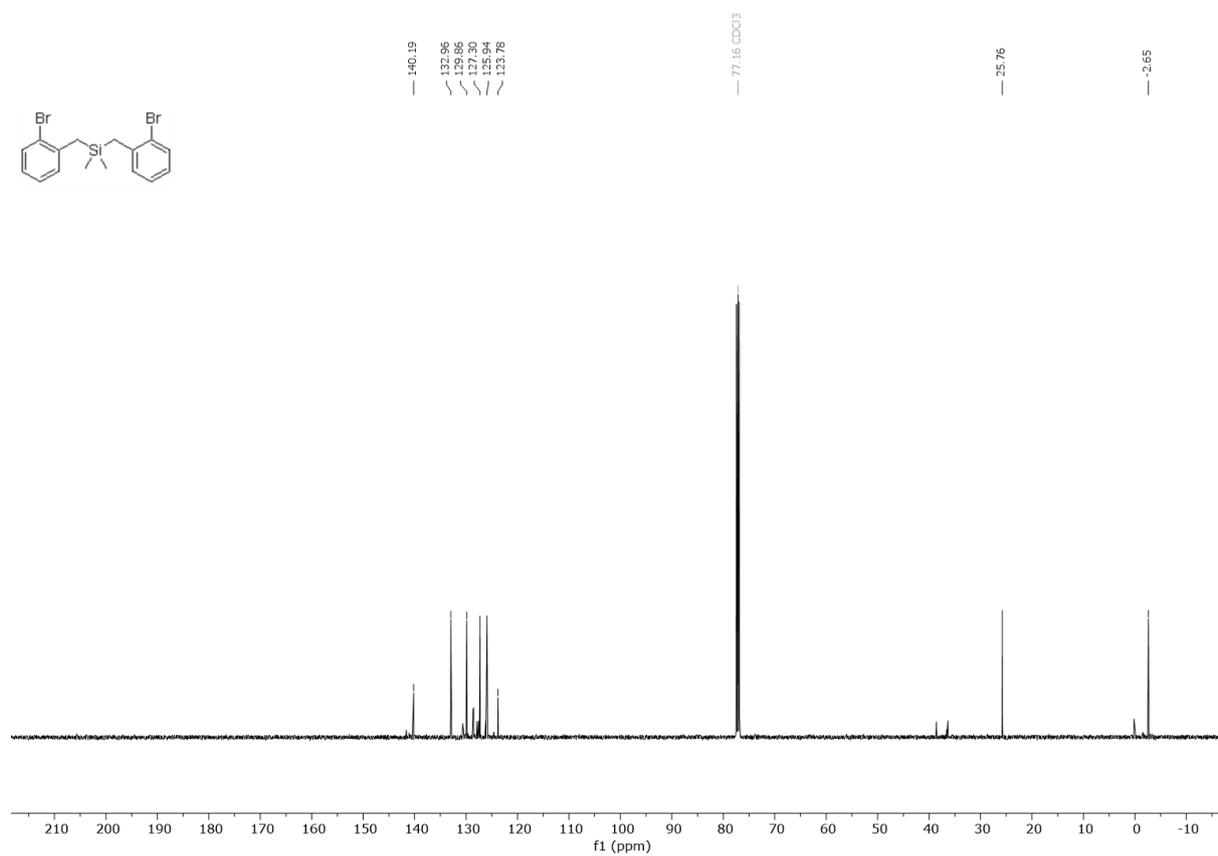
## **11 Experimental Data:** NMR, HPLC traces and Crystallographic Data

bis(2-bromobenzyl)dimethylsilane (**3.8**)

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )

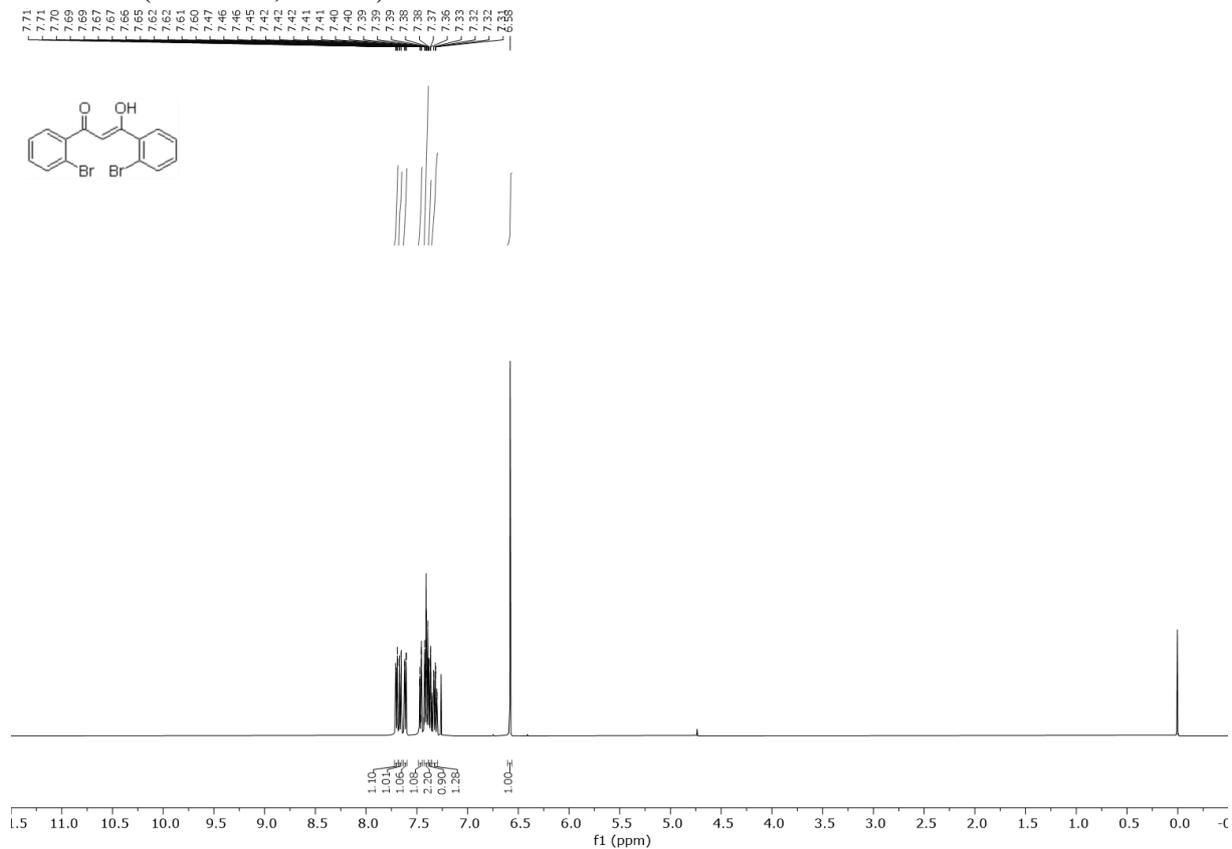


$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )

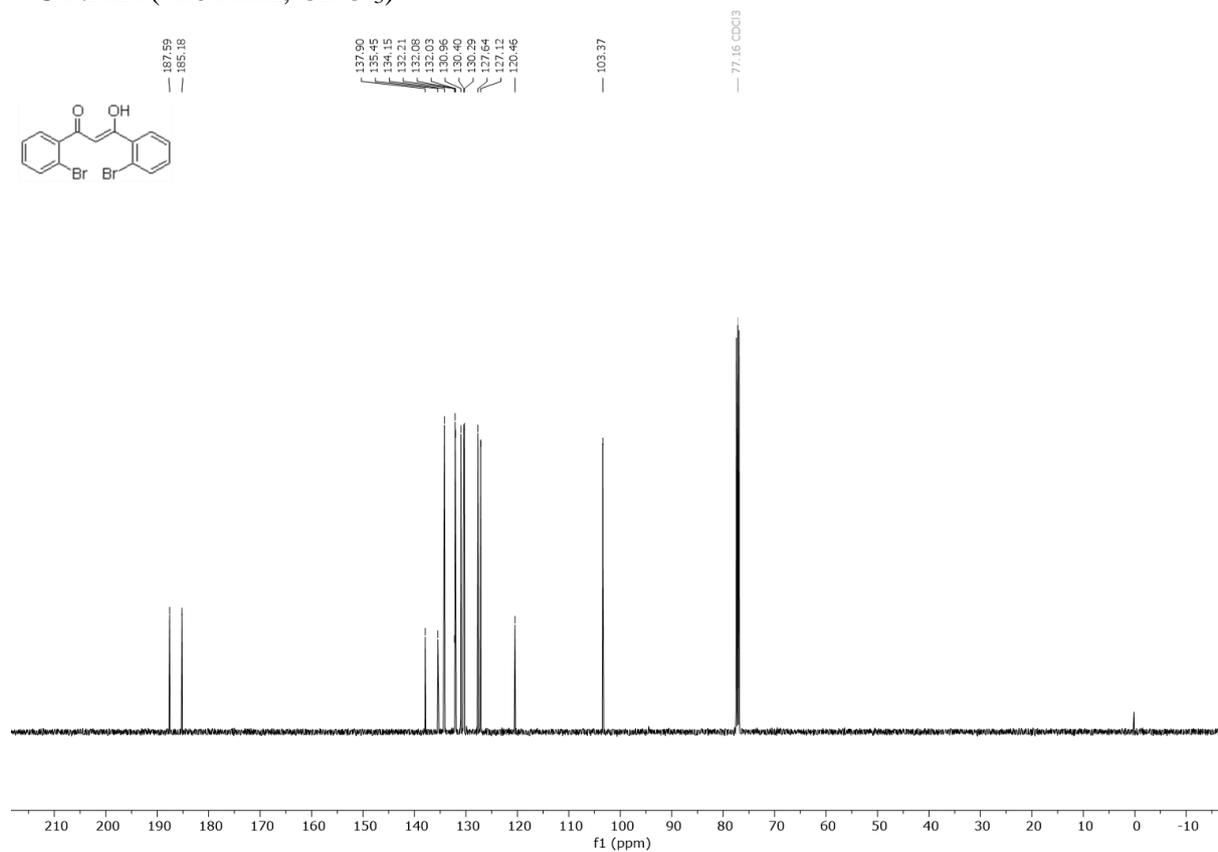


(Z)-1,3-bis(2-bromophenyl)-3-hydroxyprop-2-en-1-one (**3.9Br**)

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)

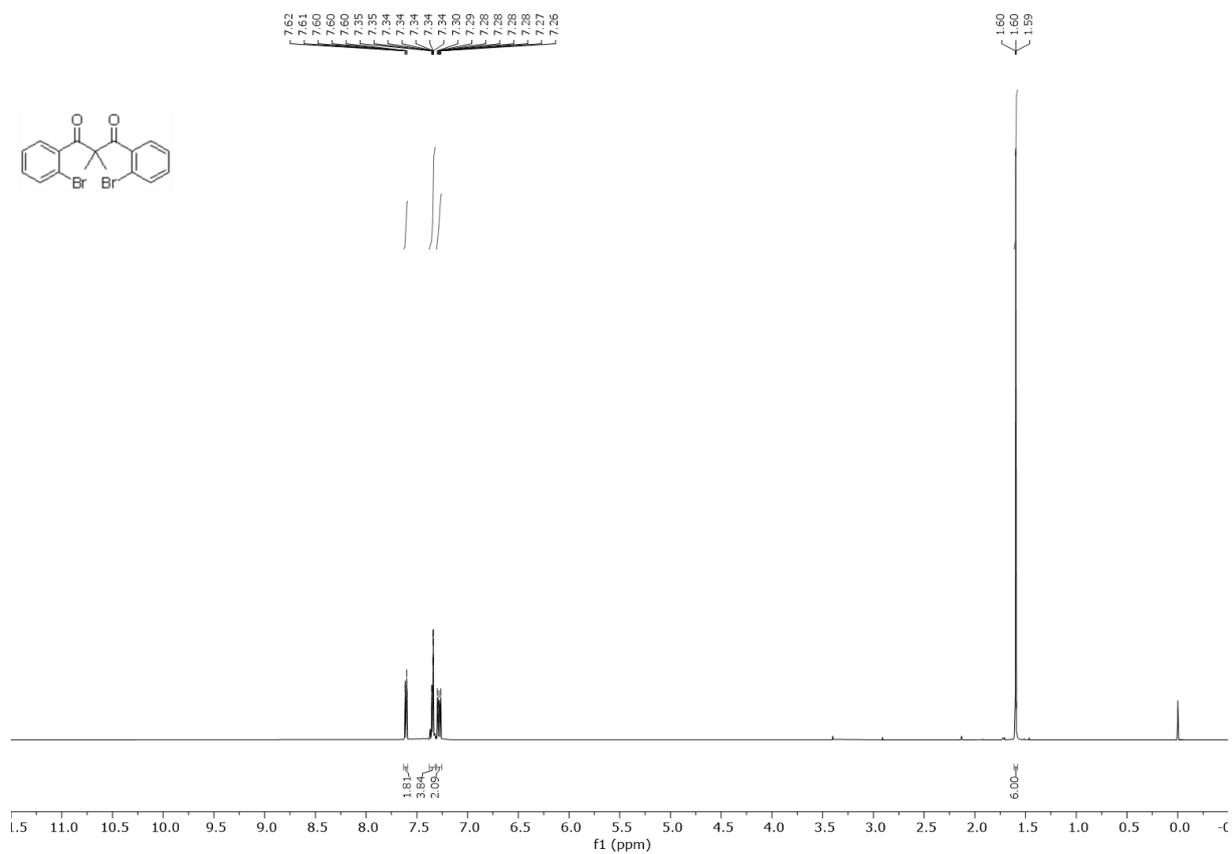


<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)

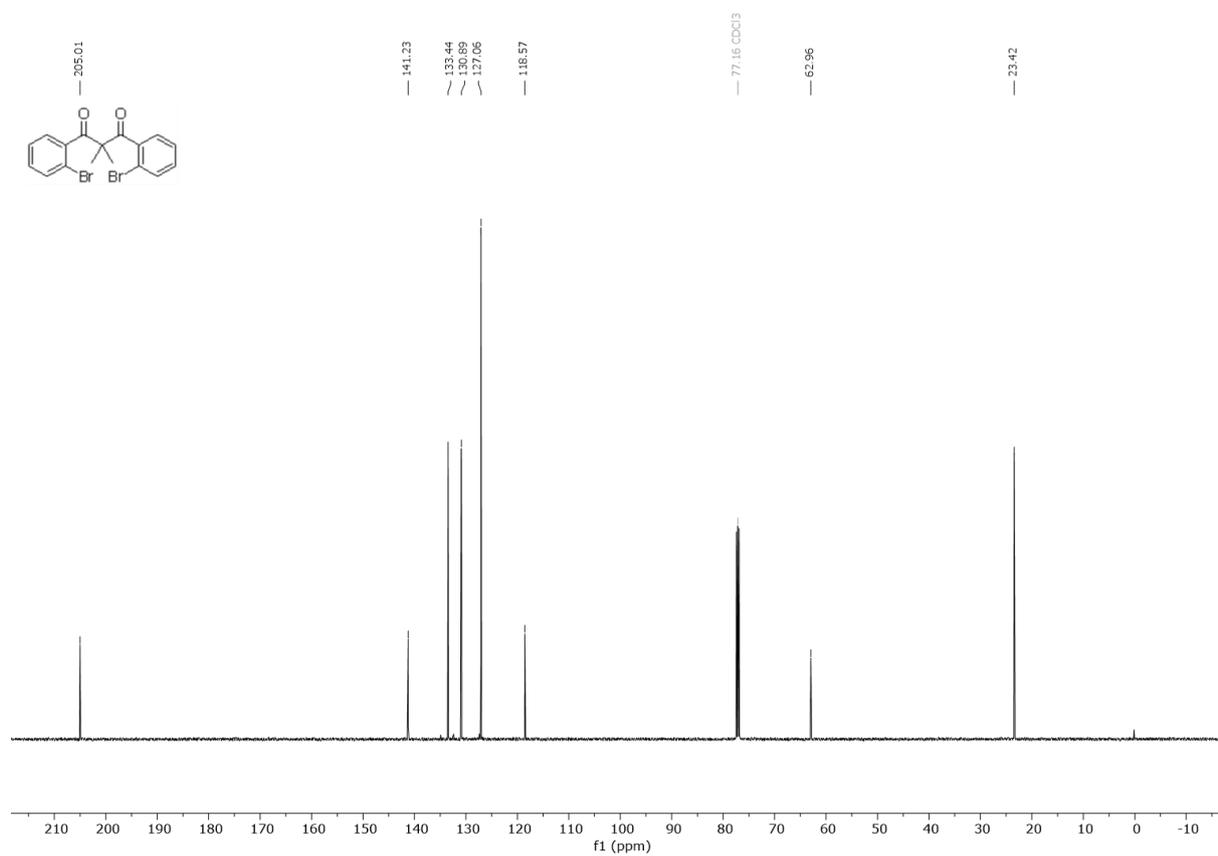


# 1,3-bis(2-bromophenyl)-2,2-dimethylpropane-1,3-dione (**3.10Br**)

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )

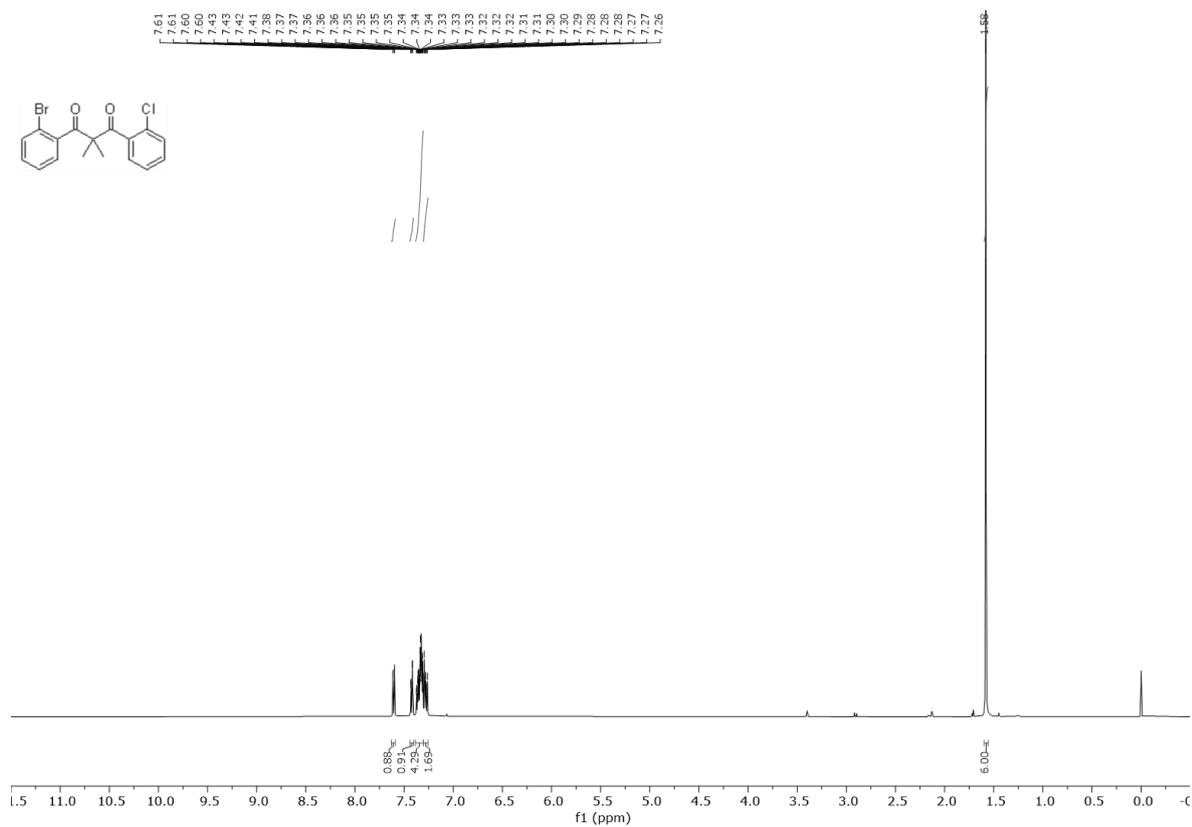


$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )

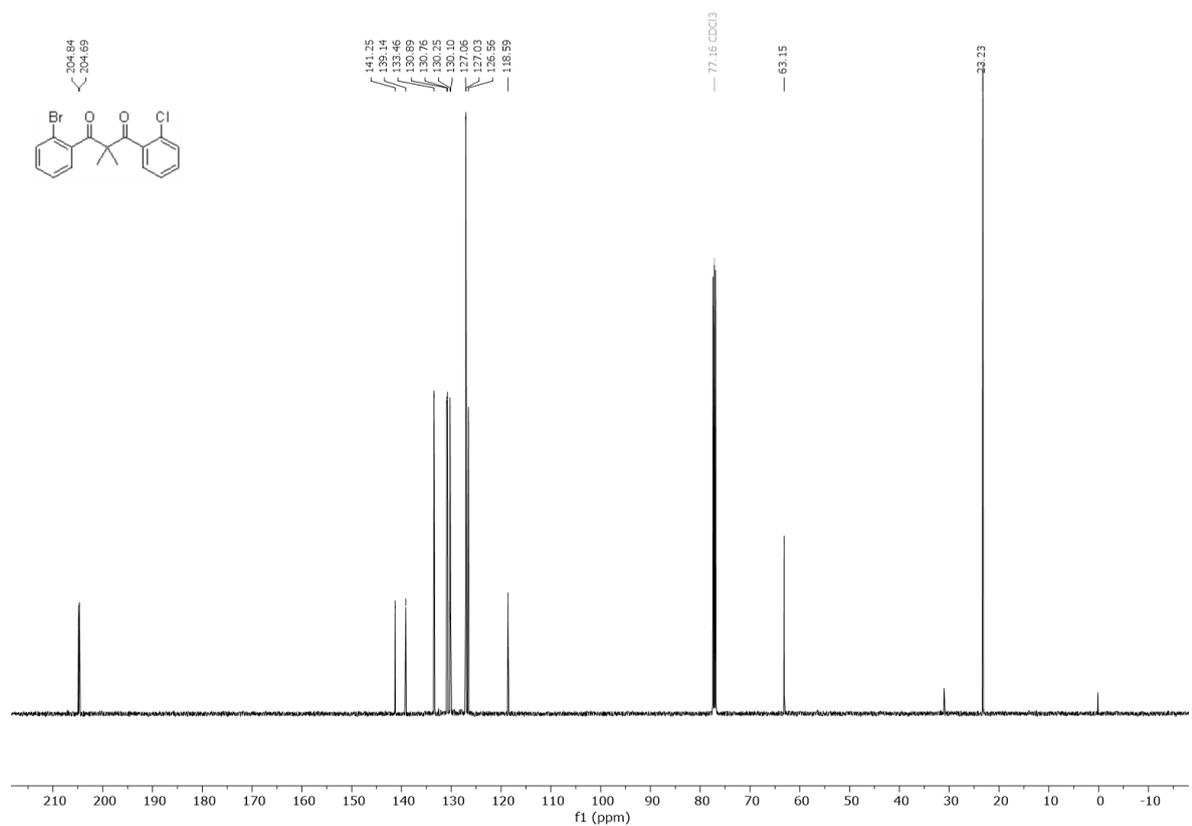


1-(2-bromophenyl)-3-(2-chlorophenyl)-2,2-dimethylpropane-1,3-dione (**3.10Cl**)

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )



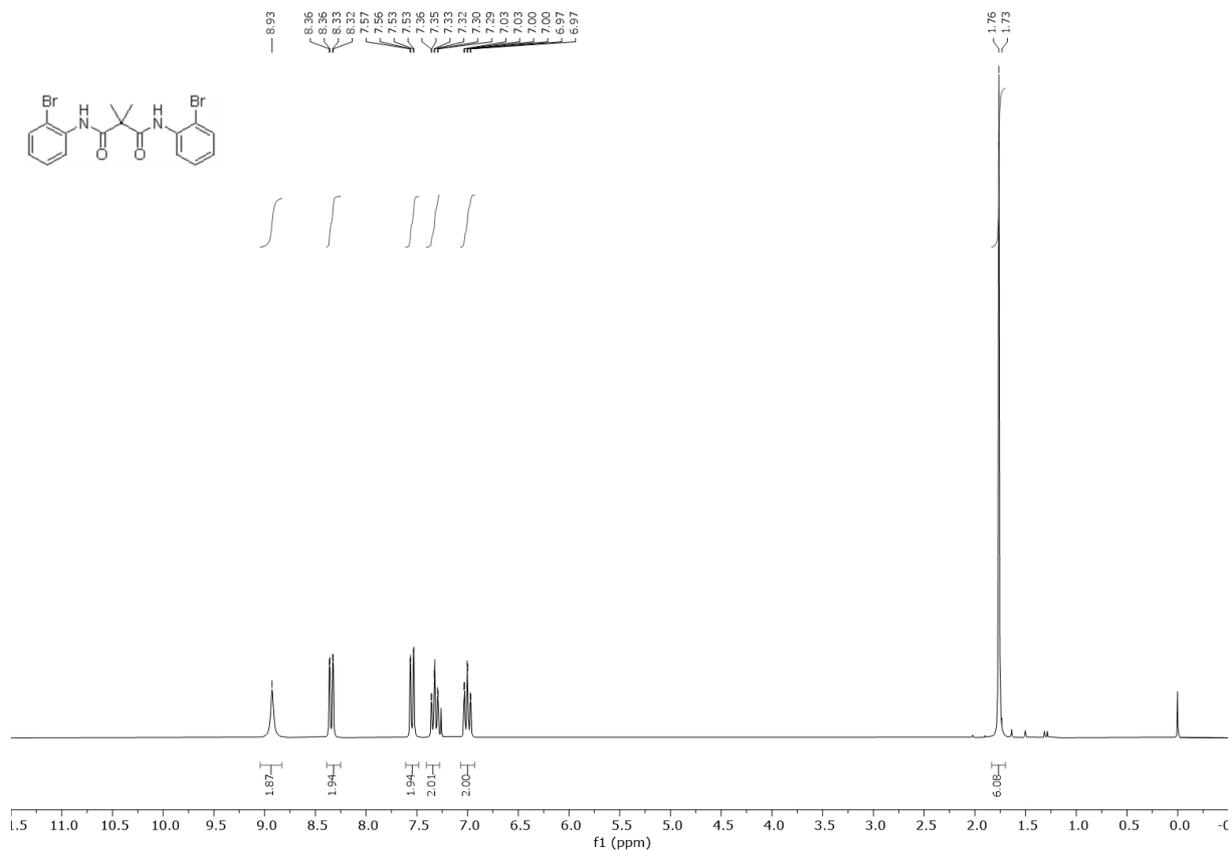
$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )



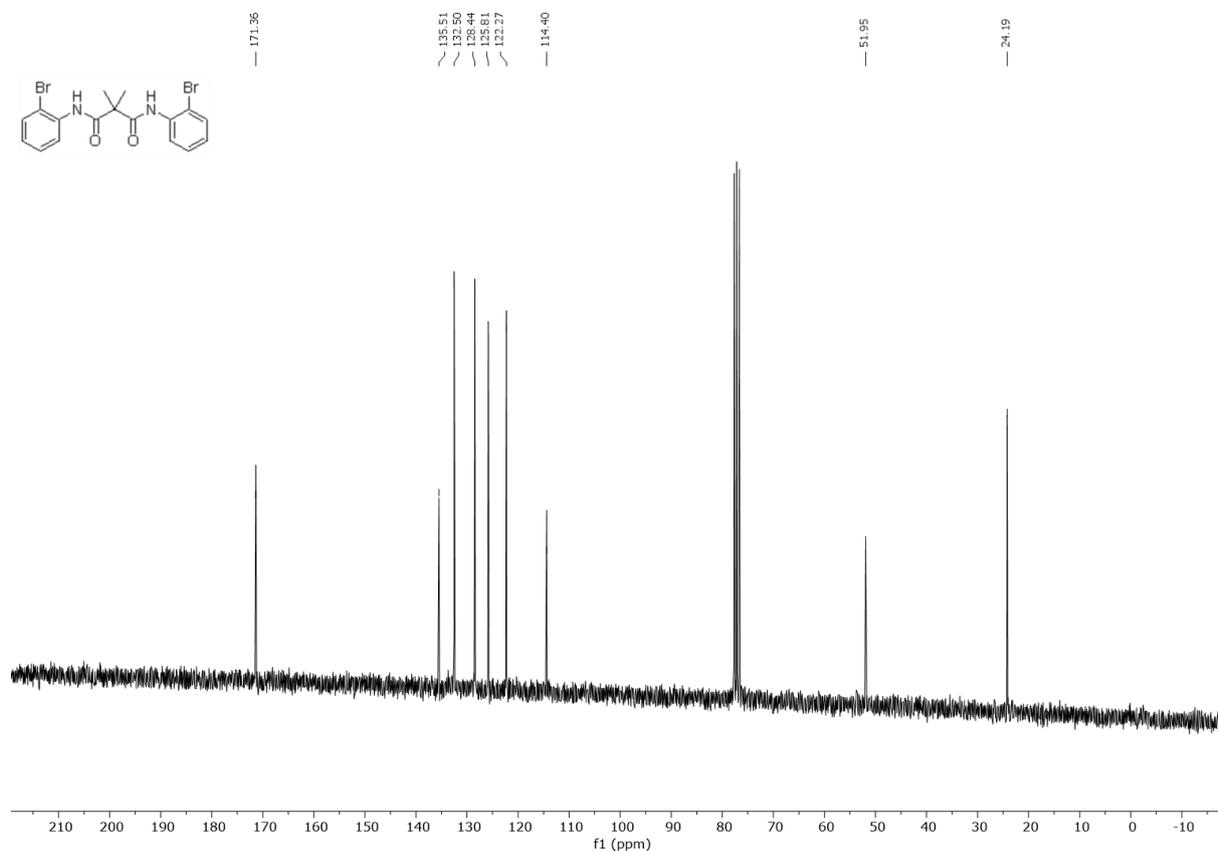


*N*<sup>1</sup>,*N*<sup>3</sup>-bis(2-bromophenyl)-2,2-dimethylmalonamide (**3.11**)

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>)

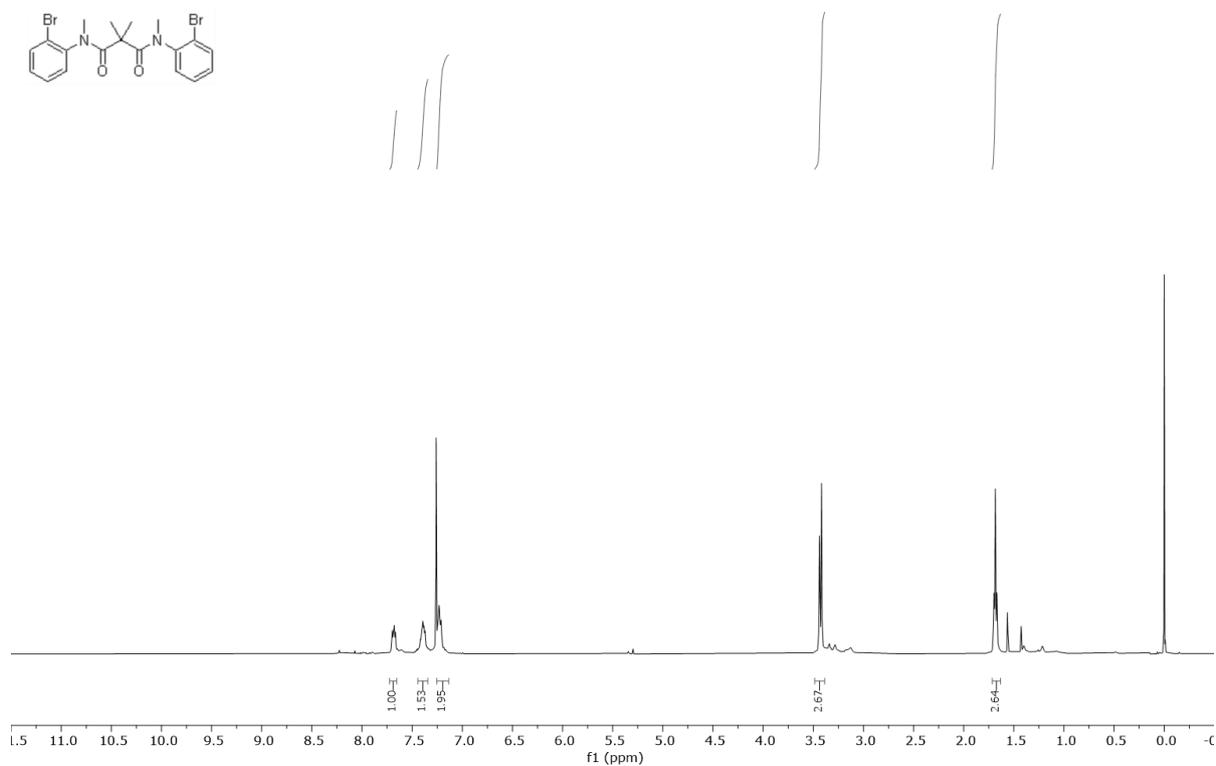


<sup>13</sup>C NMR (63 MHz, CDCl<sub>3</sub>)



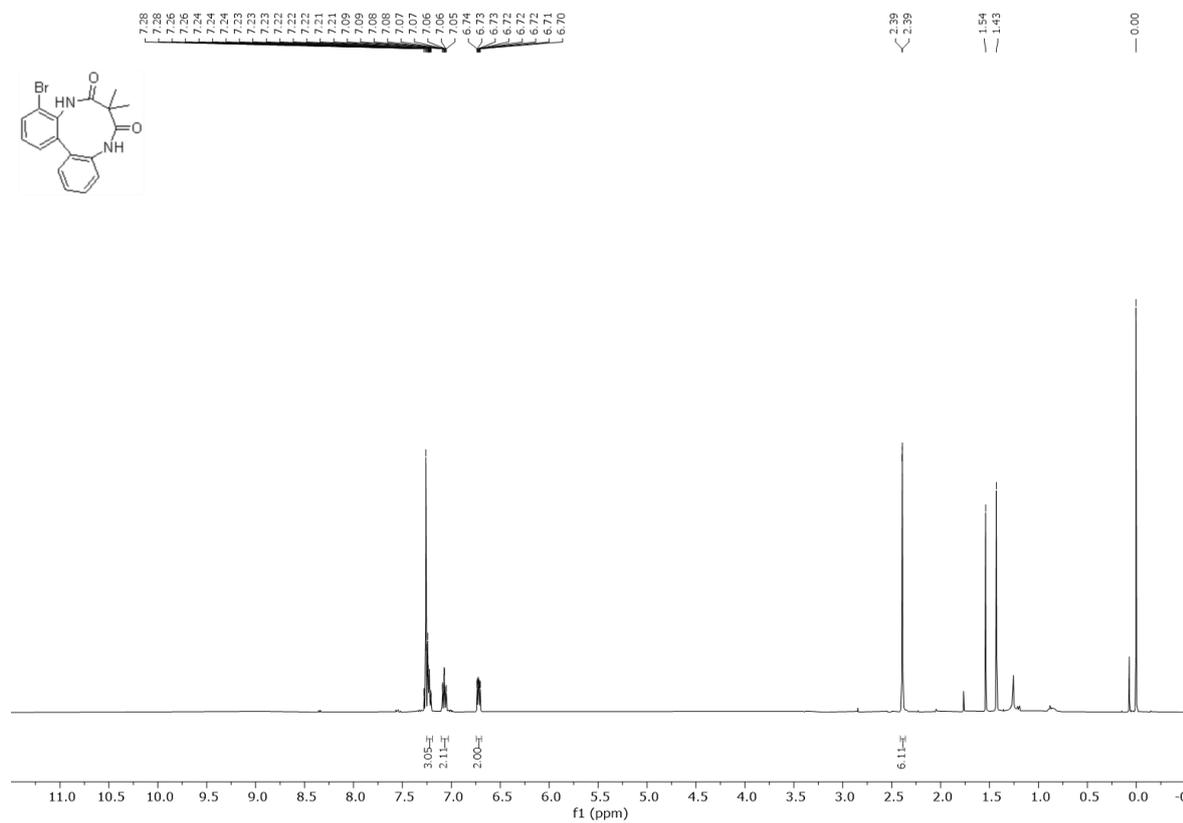
*N*<sup>1</sup>,*N*<sup>3</sup>- bis(2-bromophenyl)-*N*<sup>1</sup>,*N*<sup>3</sup>,2,2-tetramethylmalonamide (**3.11Me**)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)



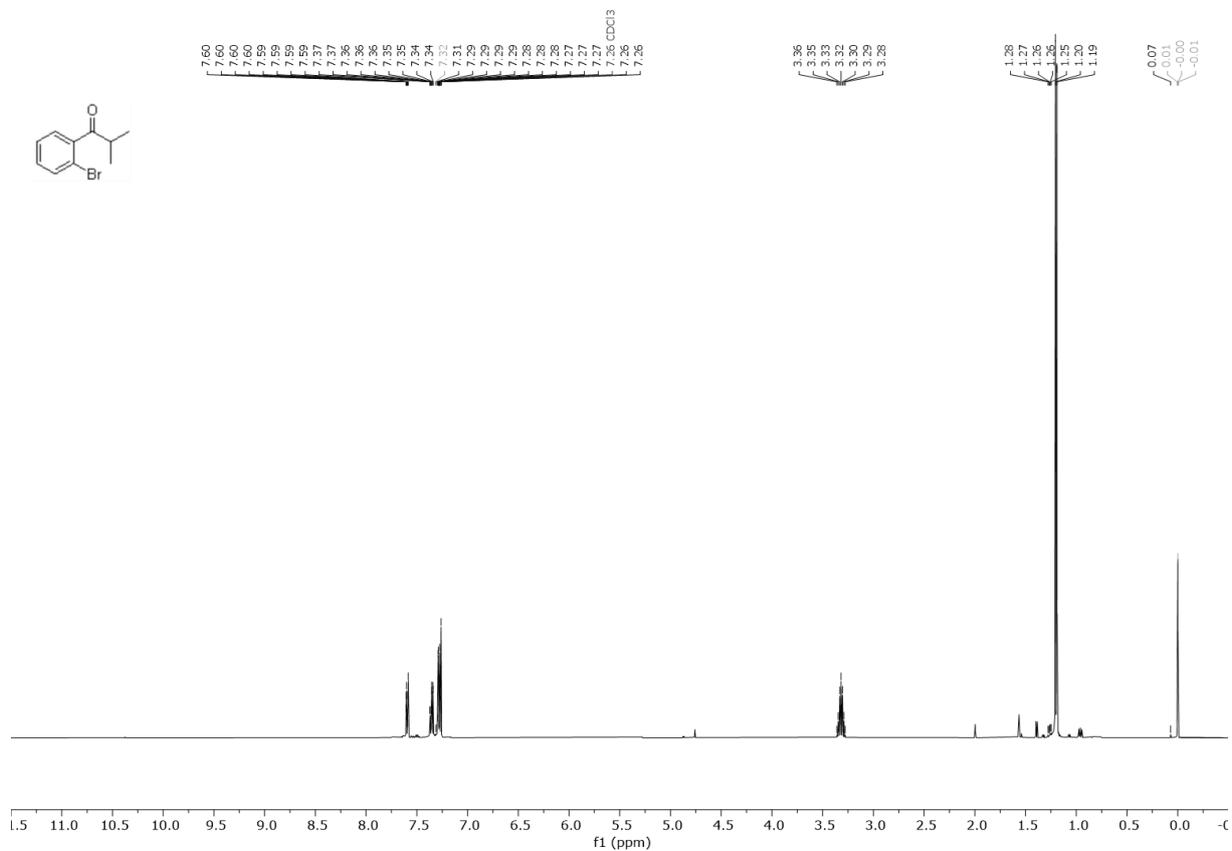
4-bromo-7,7-dimethyl-5,9-dihydro-6H-dibenzo[f,h][1,5]diazonine-6,8(7H)-dione (**3.19**)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)

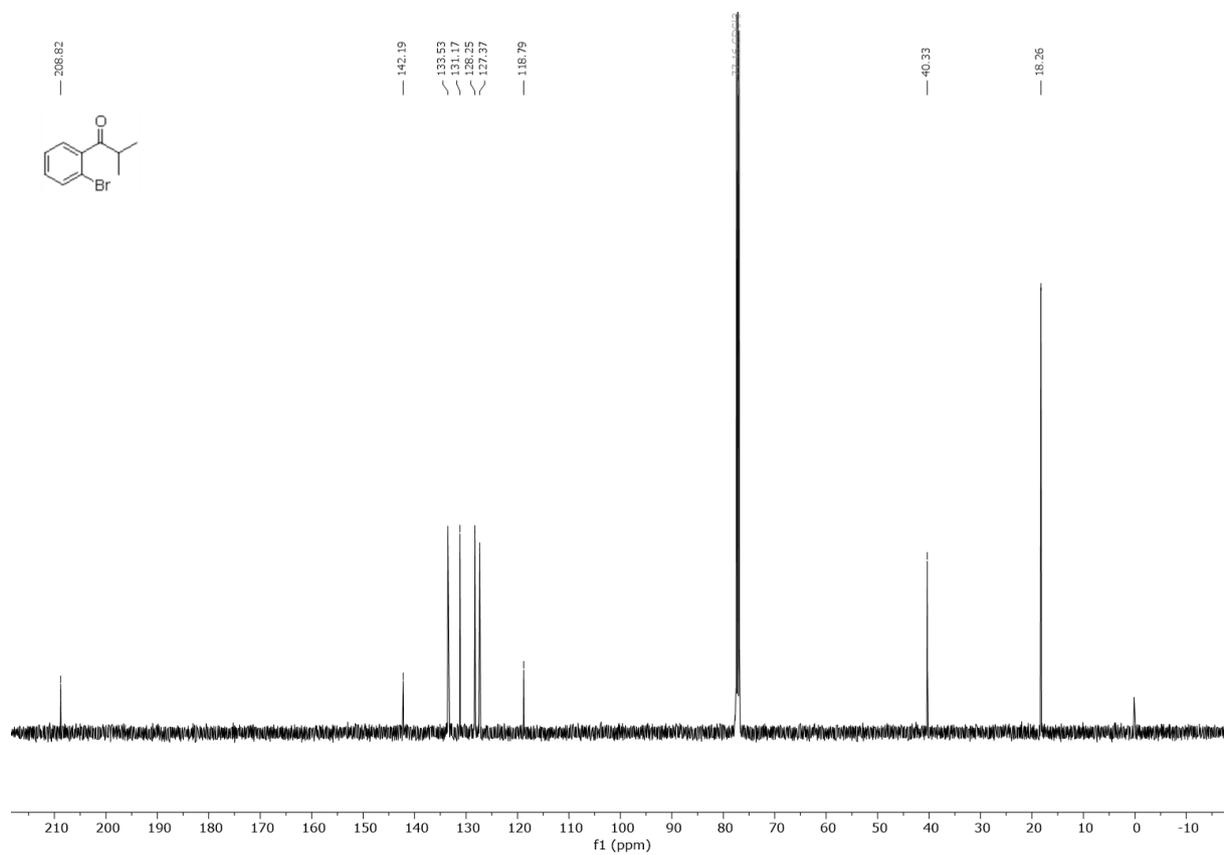


1-(2-bromophenyl)-2-methylpropan-1-one (**3.26Br**)

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )

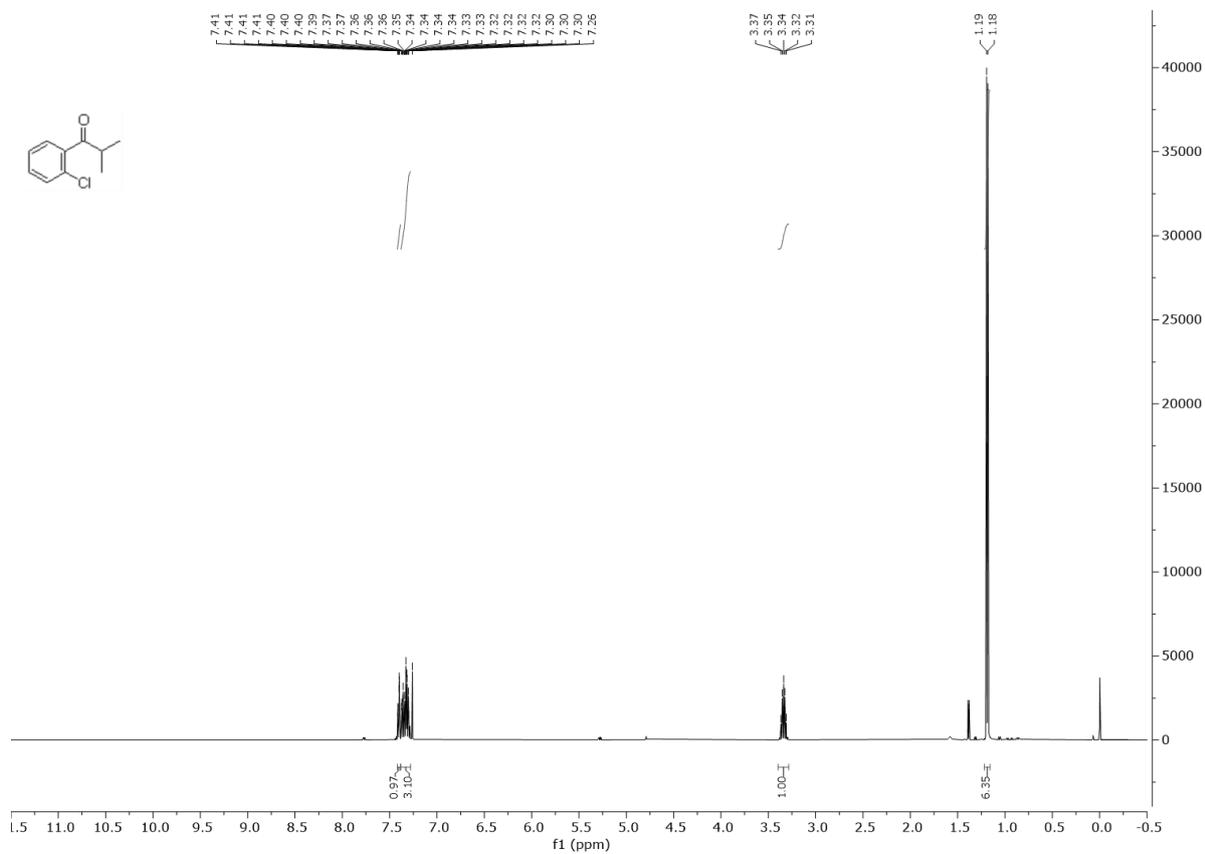


$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )

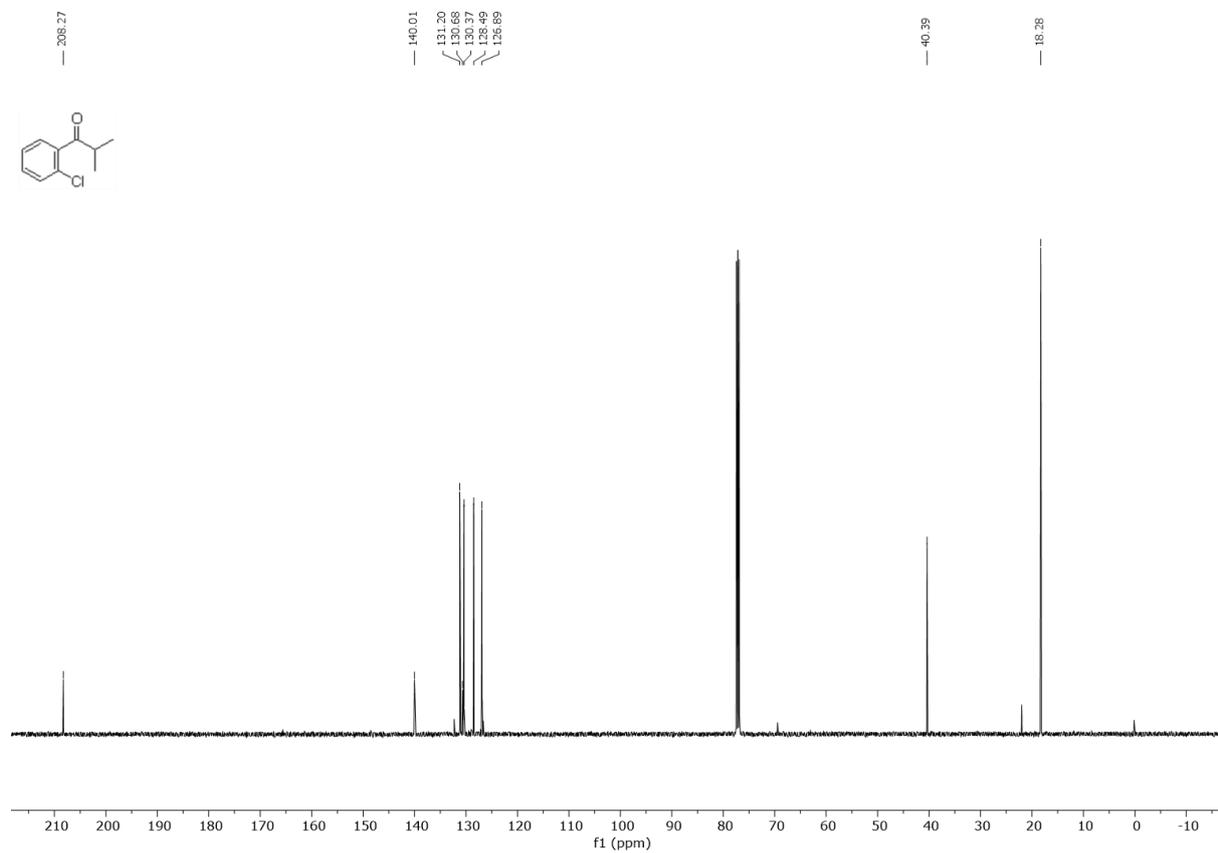


# 1-(2-chlorophenyl)-2-methylpropan-1-one (3.26Cl)

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )

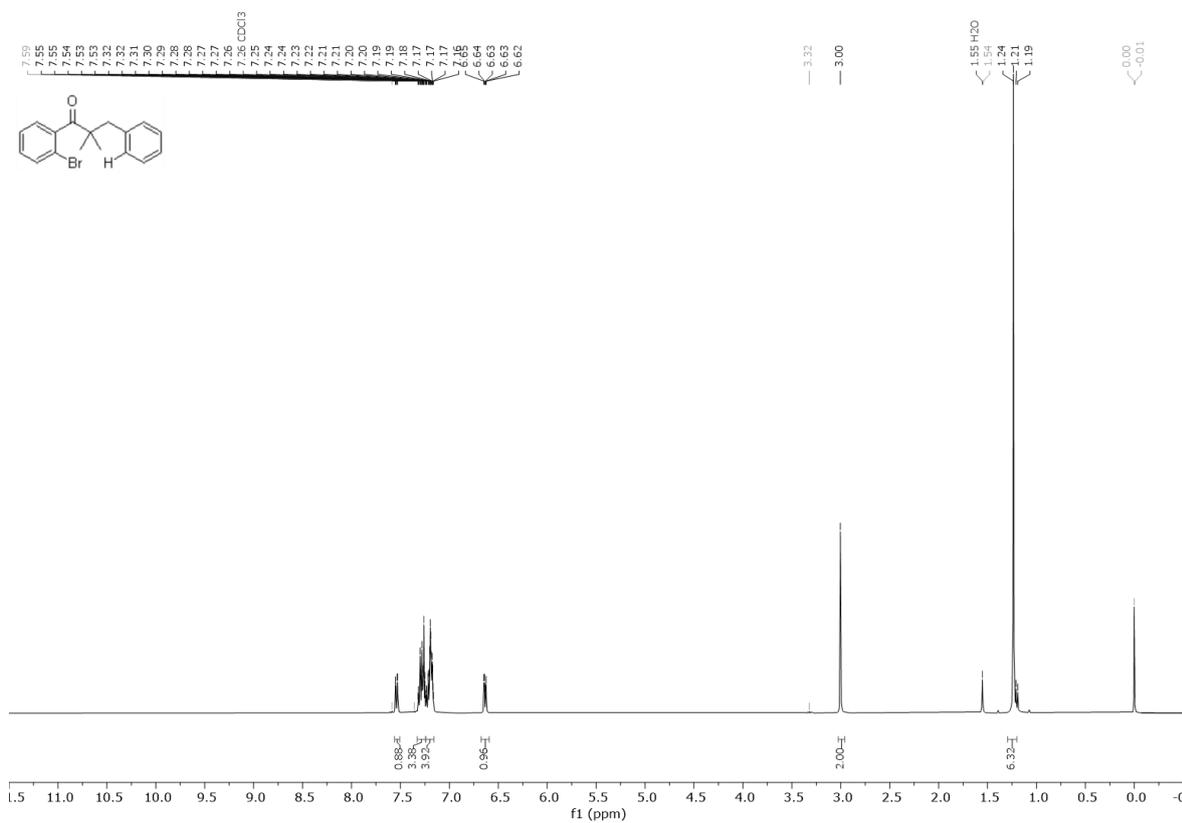


$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )

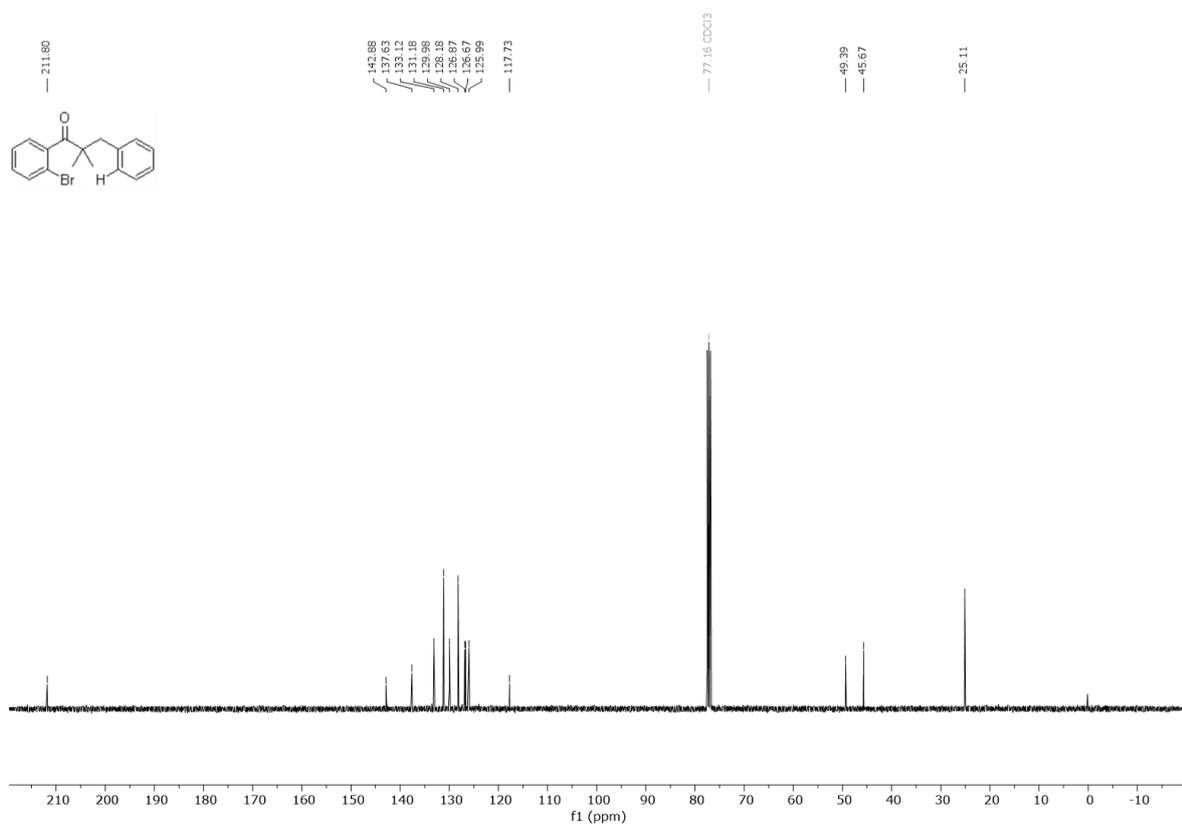


# 1-(2-bromophenyl)-2,2-dimethyl-3-phenylpropan-1-one (**3.27**)

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )

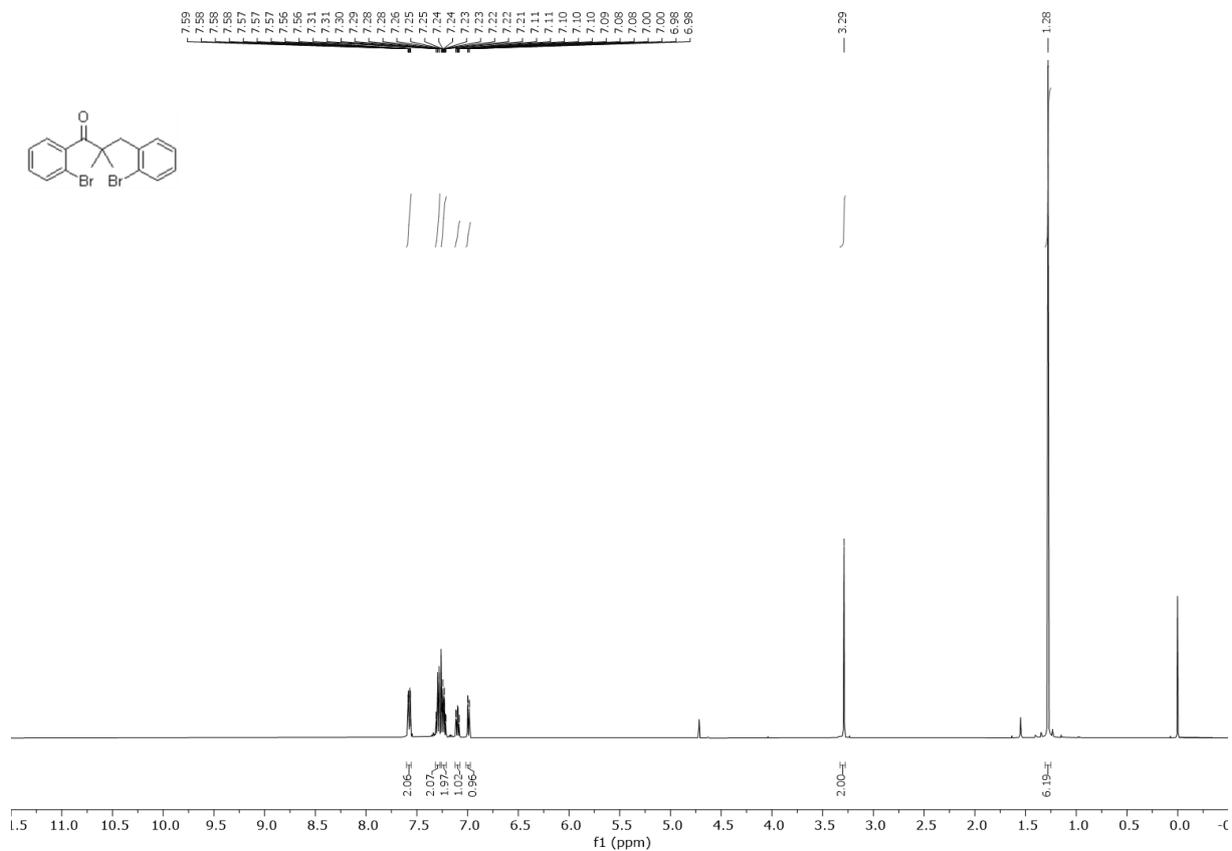


$^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )

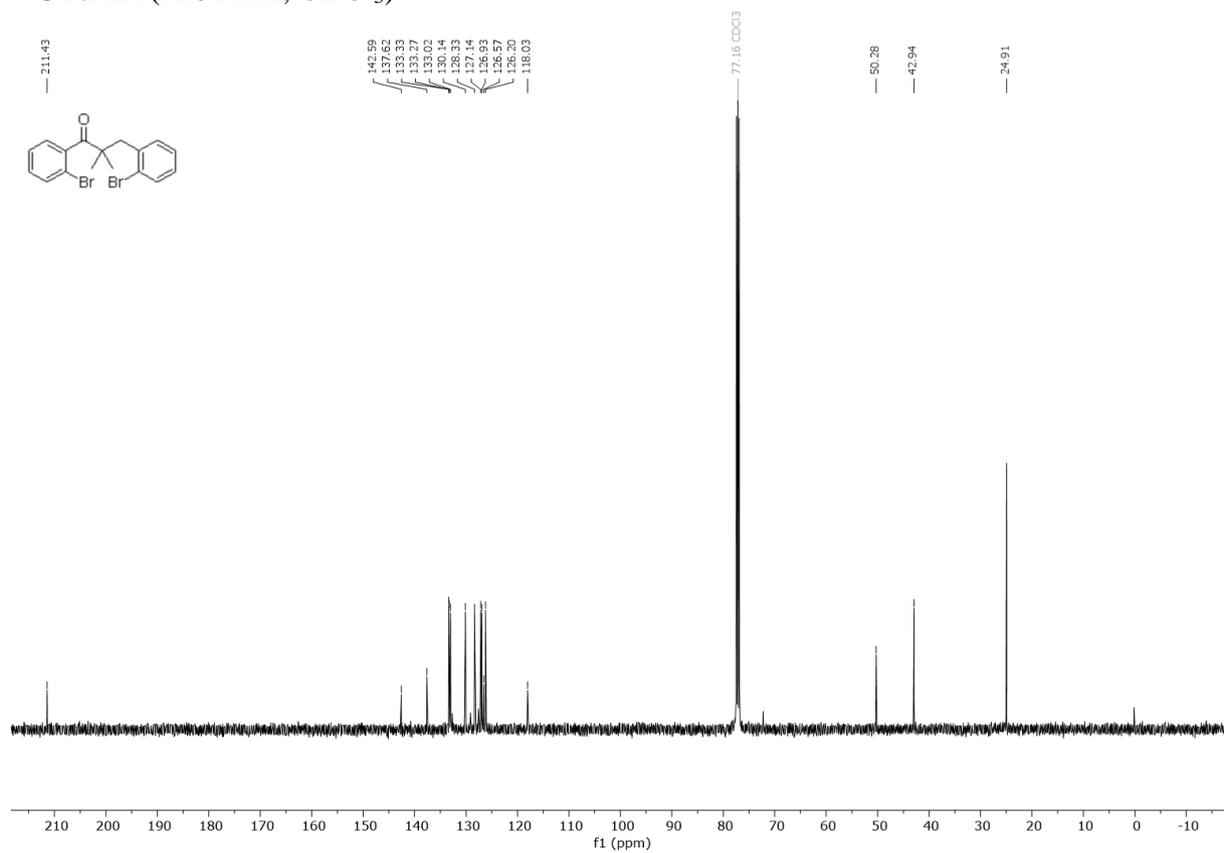


1,3-bis(2-bromophenyl)-2,2-dimethylpropan-1-one (**3.28**)

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )

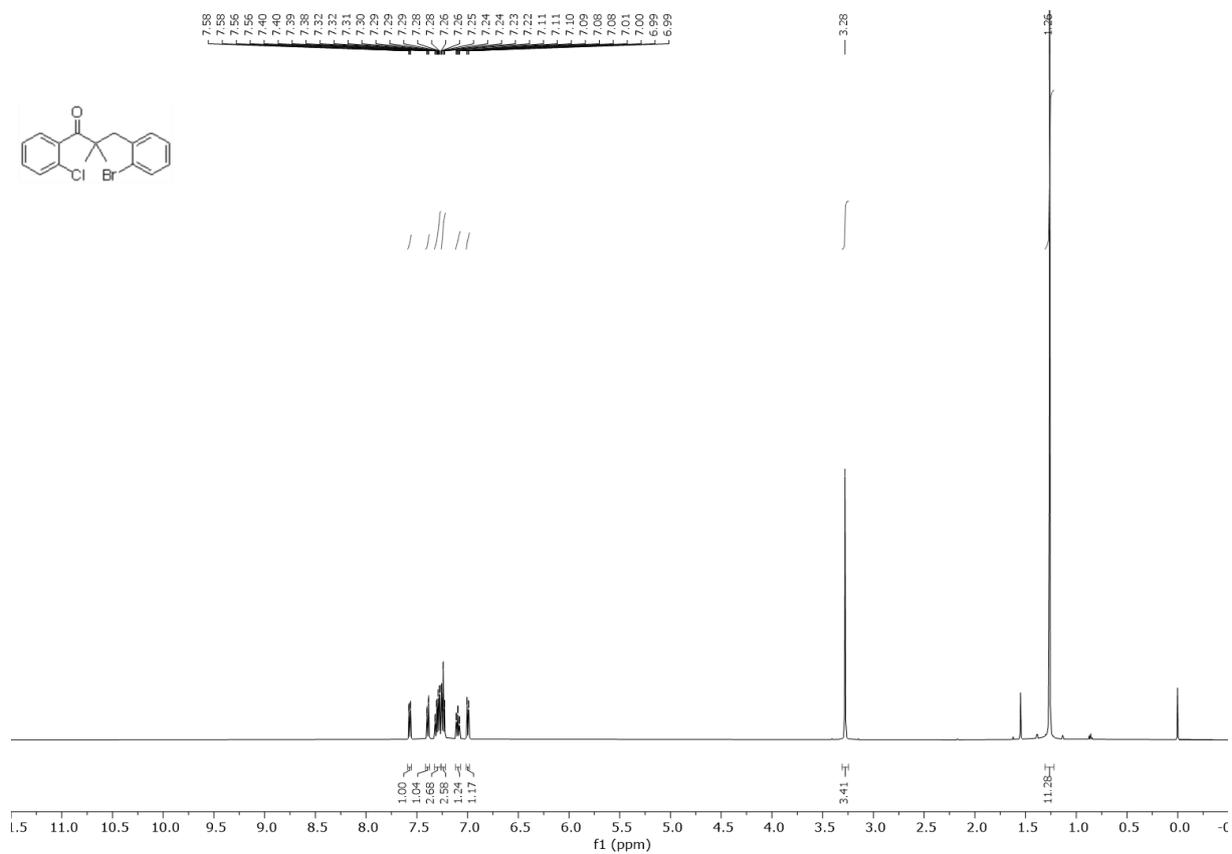


$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )

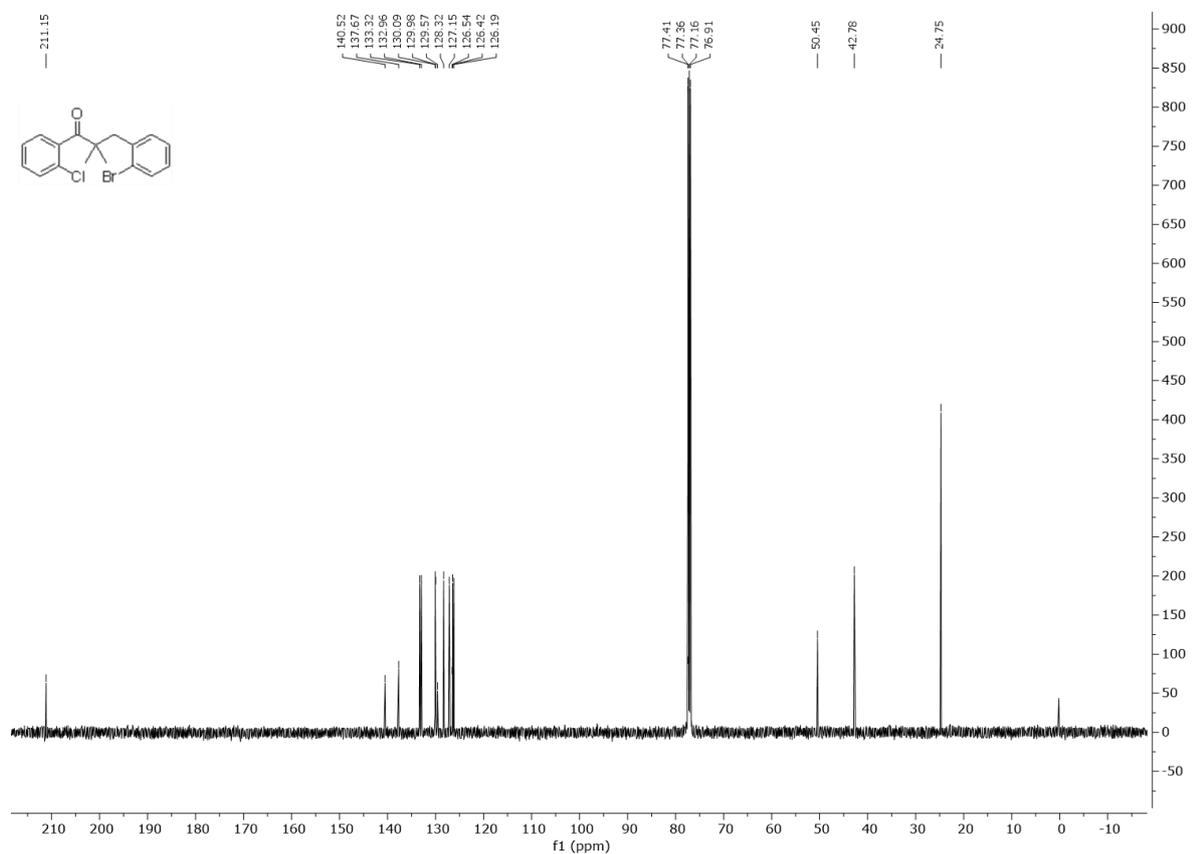


3-(2-bromophenyl)-1-(2-chlorophenyl)-2,2-dimethylpropan-1-one (**3.29**)

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )

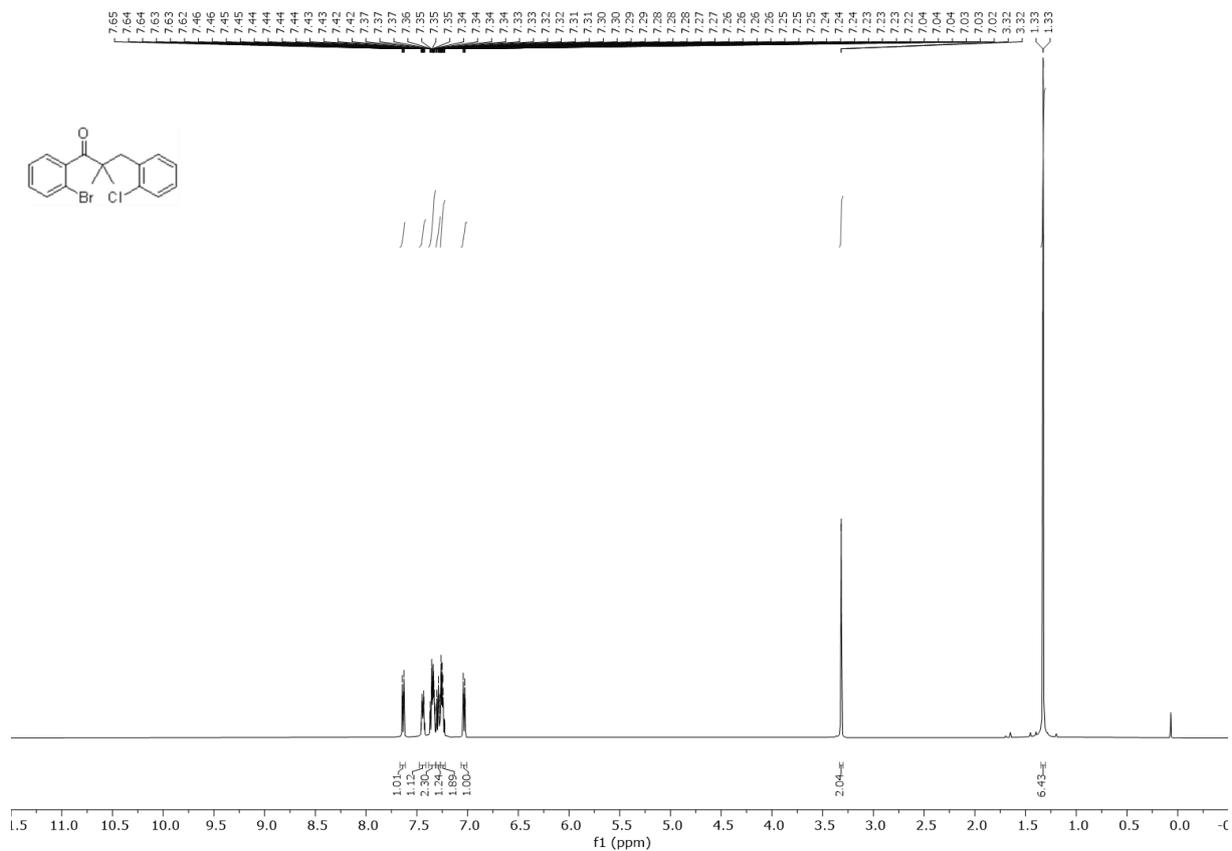


$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )

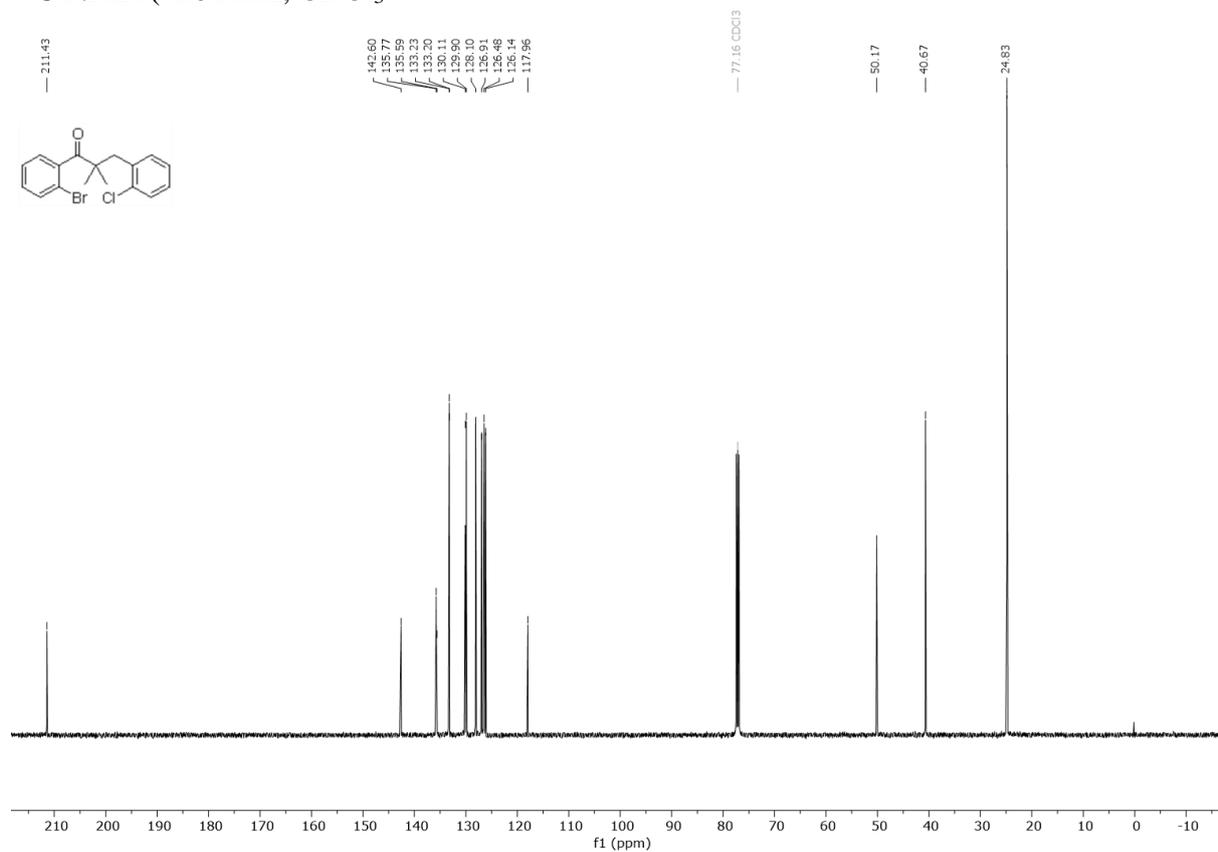


1-(2-bromophenyl)-3-(2-chlorophenyl)-2,2-dimethylpropan-1-one (**3.30**)

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )



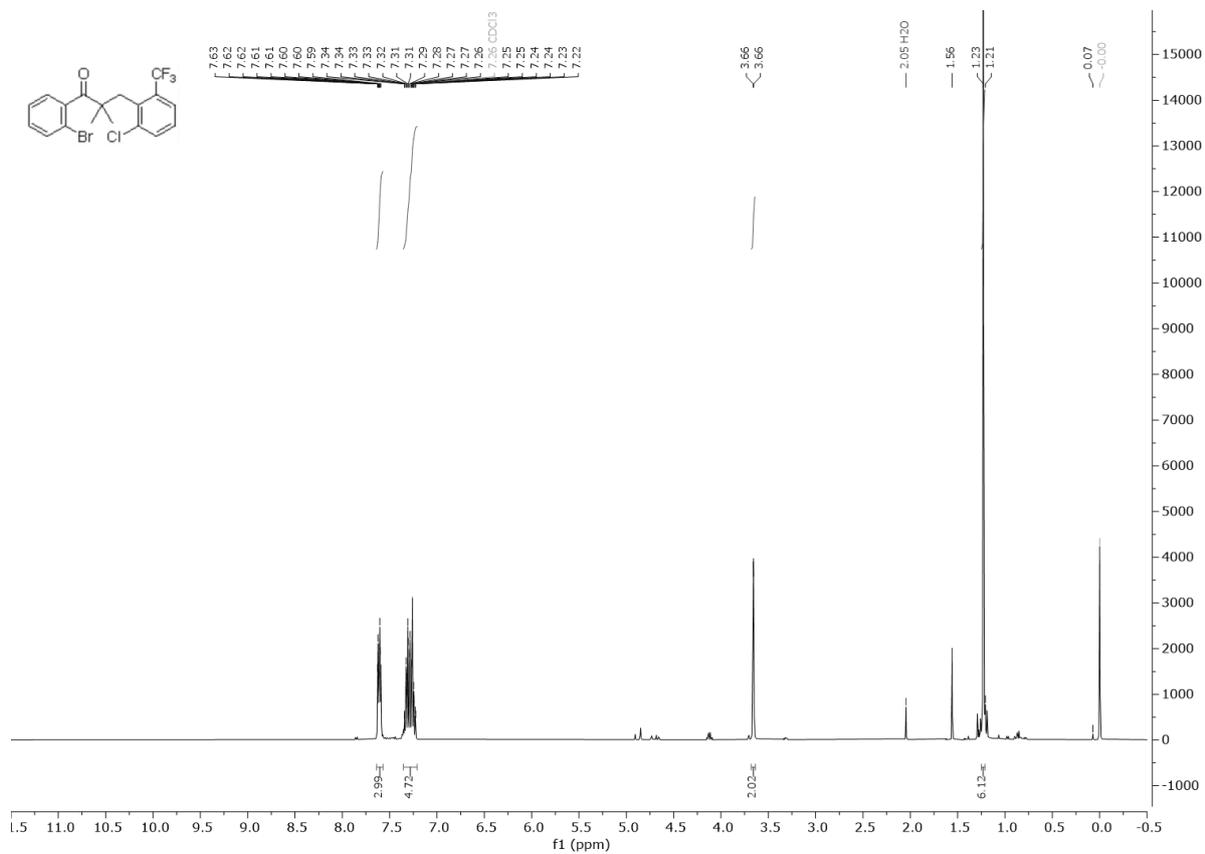
$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )



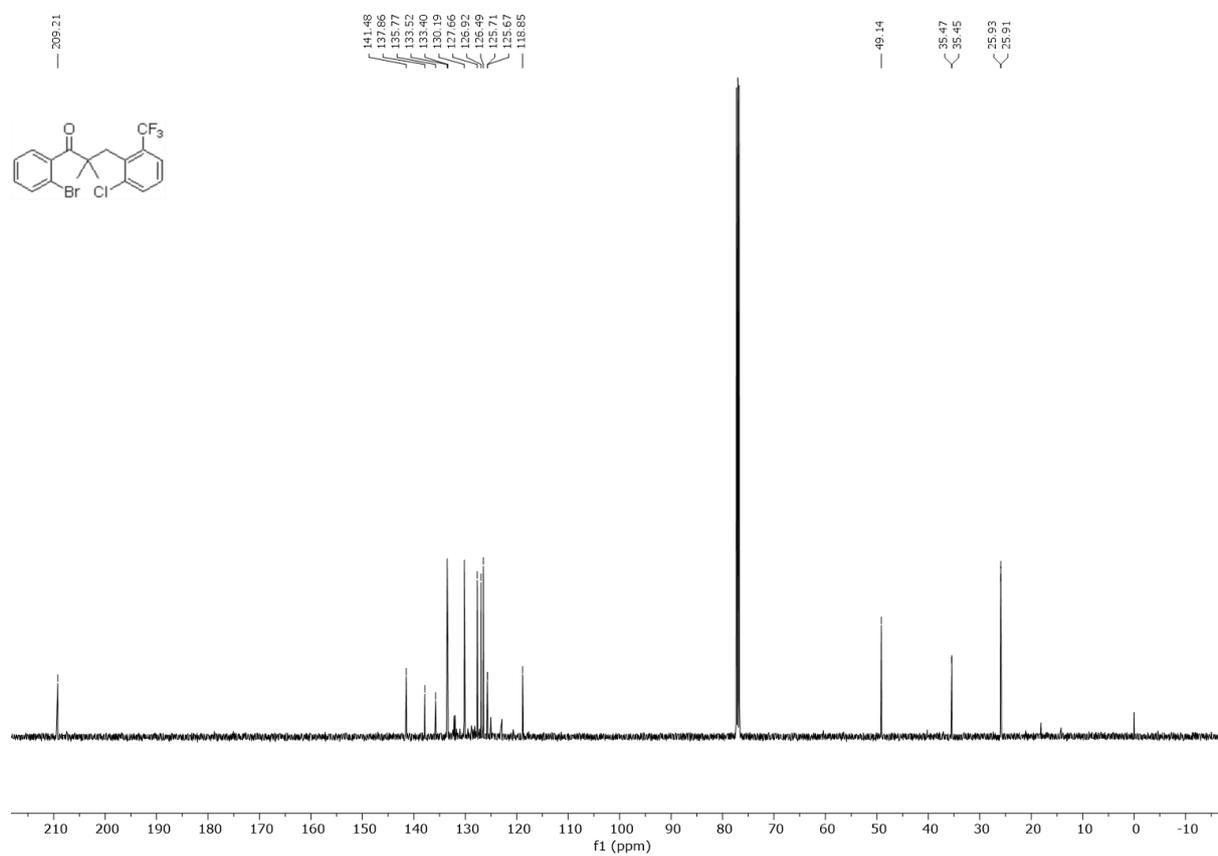


1-(2-bromophenyl)-3-(2-chloro-6-(trifluoromethyl)phenyl)-2,2-dimethylpropan-1-one (**3.42**)

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )

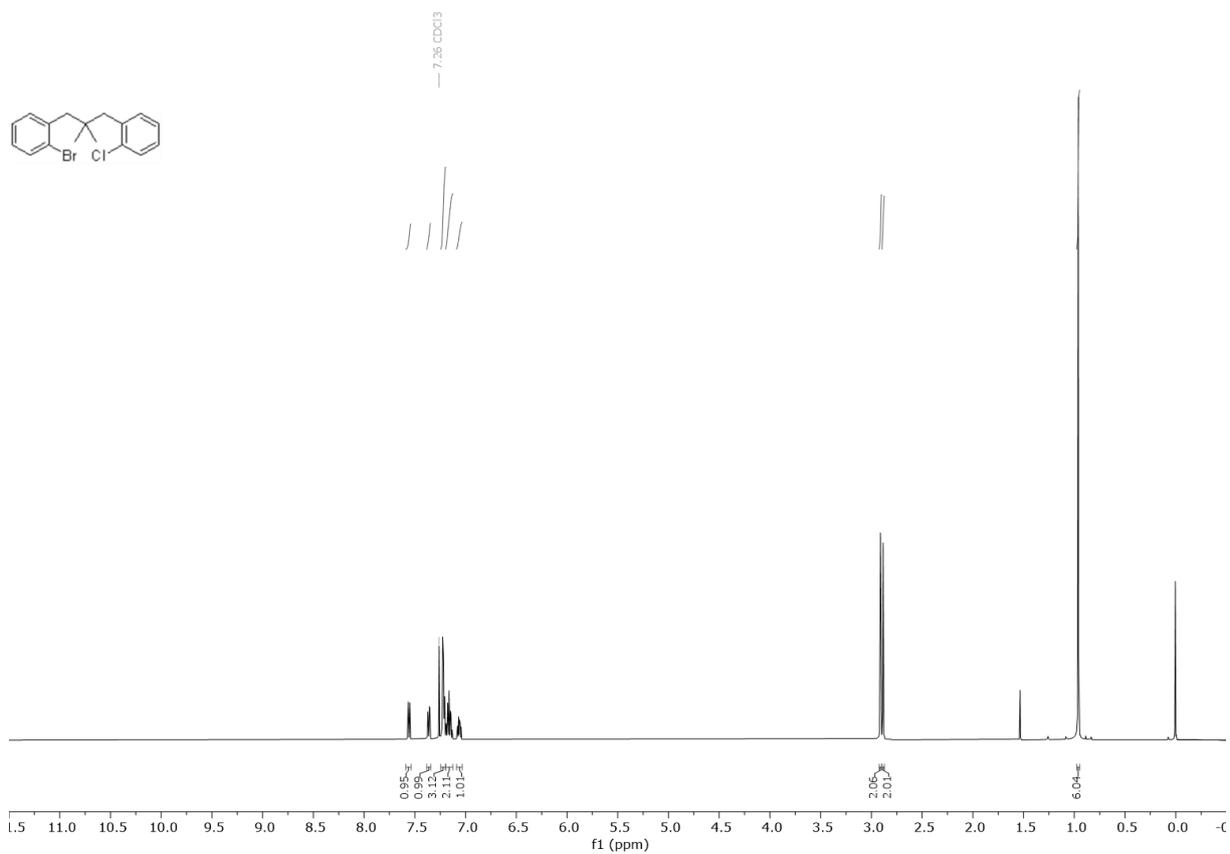


$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )

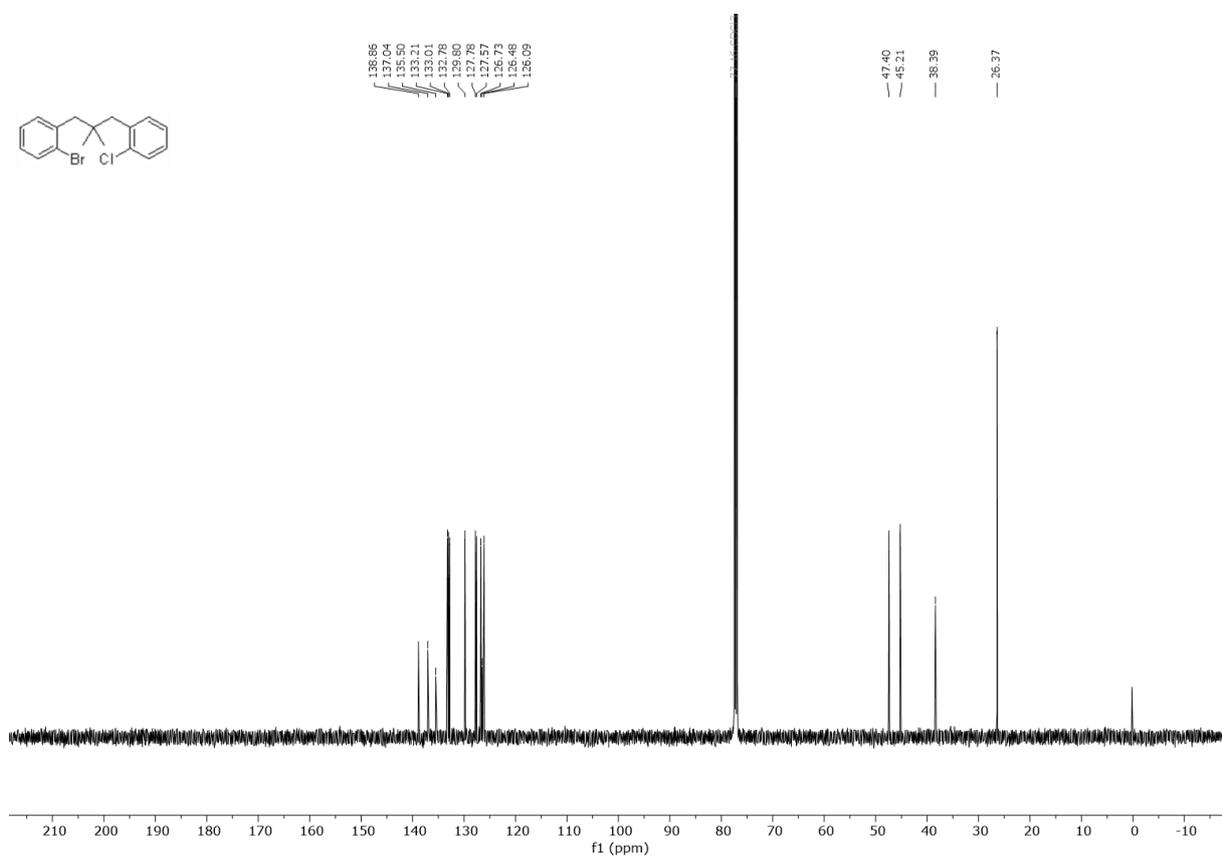


1-bromo-2-(3-(2-chlorophenyl)-2,2-dimethylpropyl)benzene (**3.43**)

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )

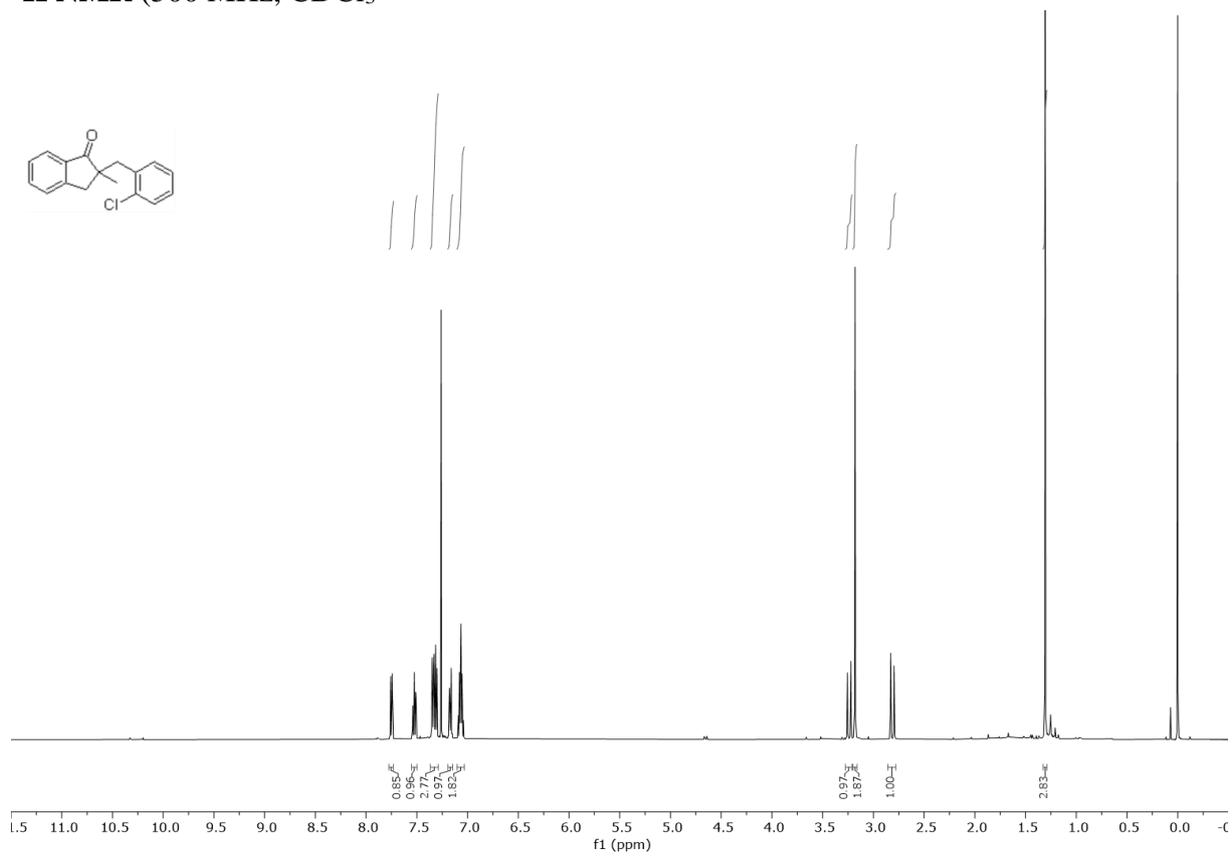


$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )

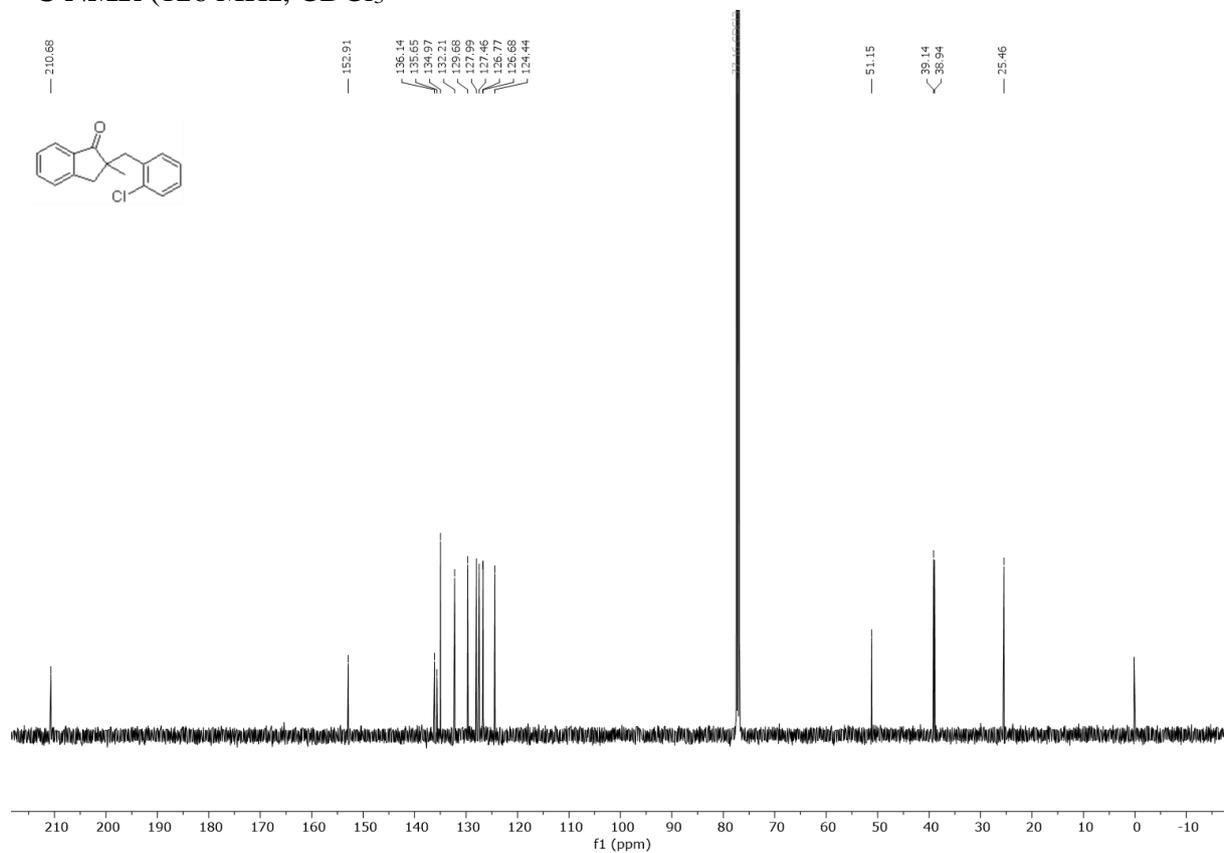


2-(2-chlorobenzyl)-2-methyl-2,3-dihydro-1H-inden-1-one (3.35)

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )



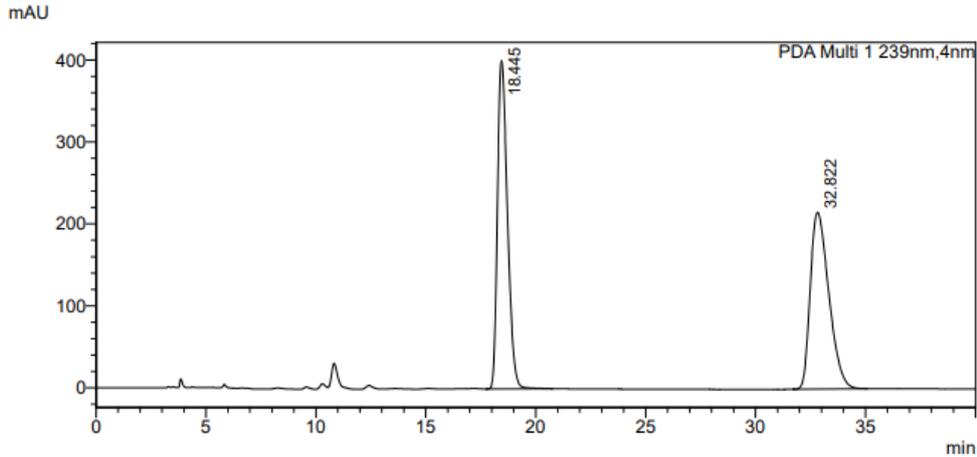
$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )



**<Sample Information>**

Sample Name : nn913  
Sample ID :  
Data Filename : NN913RAC\_run\_col2\_IC\_99\_1\_1mL.lcd  
Method Filename : run\_col2\_IC\_99\_1\_1mL\_40min.lcm  
Batch Filename : batch-913-914.lcb  
Vial # : 1-36  
Injection Volume : 15 uL  
Date Acquired : 28.11.2018 15:49:21  
Date Processed : 14.12.2018 17:41:28  
Sample Type : Unknown  
Acquired by : System Administrator  
Processed by : System Administrator

**<Chromatogram>**



**<Peak Table>**

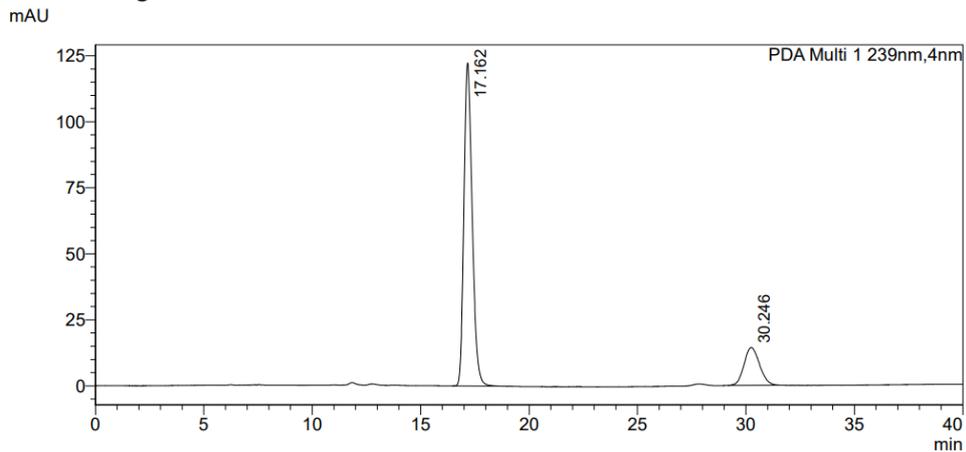
PDA Ch1 239nm

Peak#	Ret. Time	Area	Height	Area%
1	18.445	12652603	400283	49.980
2	32.822	12662871	215543	50.020
Total		25315474	615826	100.000

**<Sample Information>**

Sample Name : NN989  
Sample ID :  
Data Filename : NN989OJH\_99\_1\_1.5mL\_run.lcd  
Method Filename : run\_col5\_OJH\_99\_1\_1mL\_40min.lcm  
Batch Filename : NN986\_987\_989.lcb  
Vial # : 1-38  
Injection Volume : 1 uL  
Date Acquired : 18.12.2018 15:00:04  
Date Processed : 20.10.2021 16:01:34  
Sample Type : Unknown  
Acquired by : System Administrator  
Processed by : System Administrator

**<Chromatogram>**



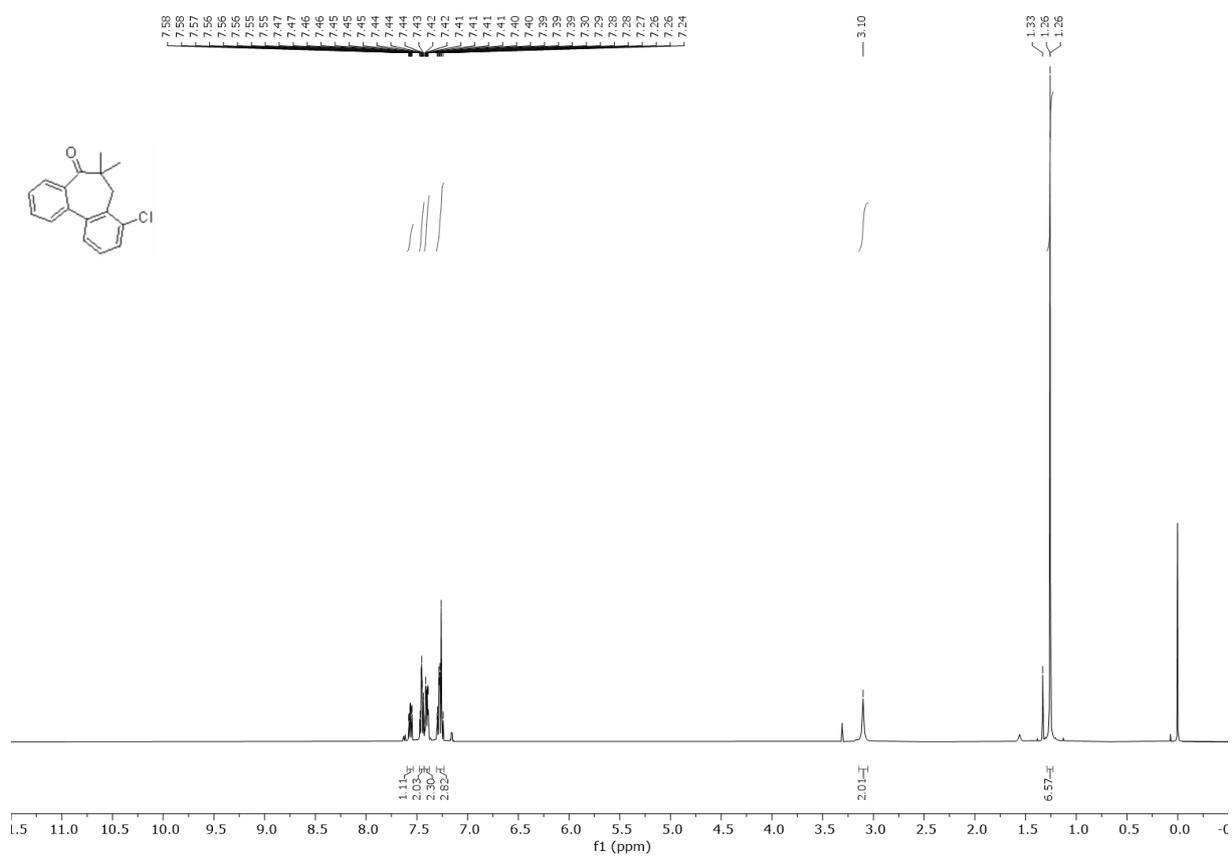
**<Peak Table>**

PDA Ch1 239nm

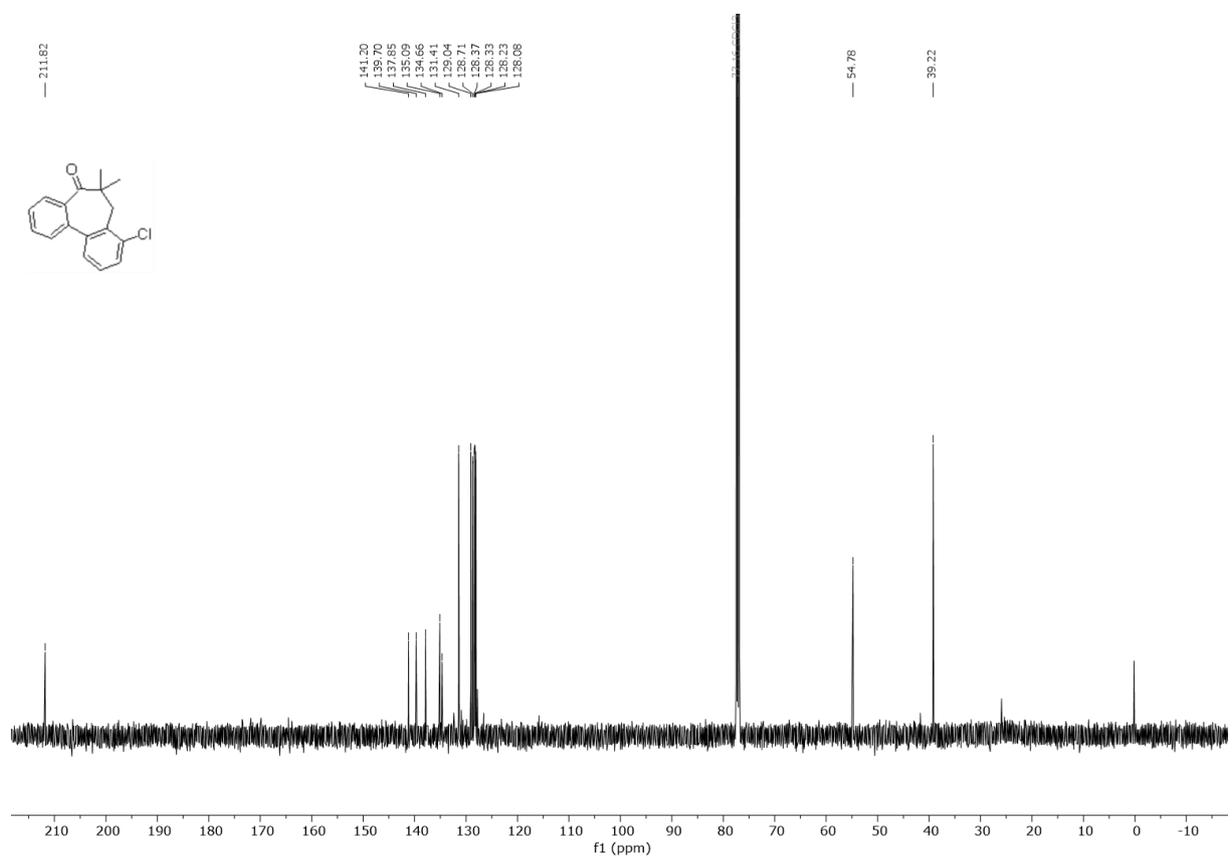
Peak#	Ret. Time	Area	Height	Area%
1	17.162	3260616	122329	82.047
2	30.246	713475	14355	17.953
Total		3974090	136684	100.000

8-chloro-6,6-dimethyl-6,7-dihydro-5H-dibenzo[a,c][7]annulen-5-one (**3.36**)

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )

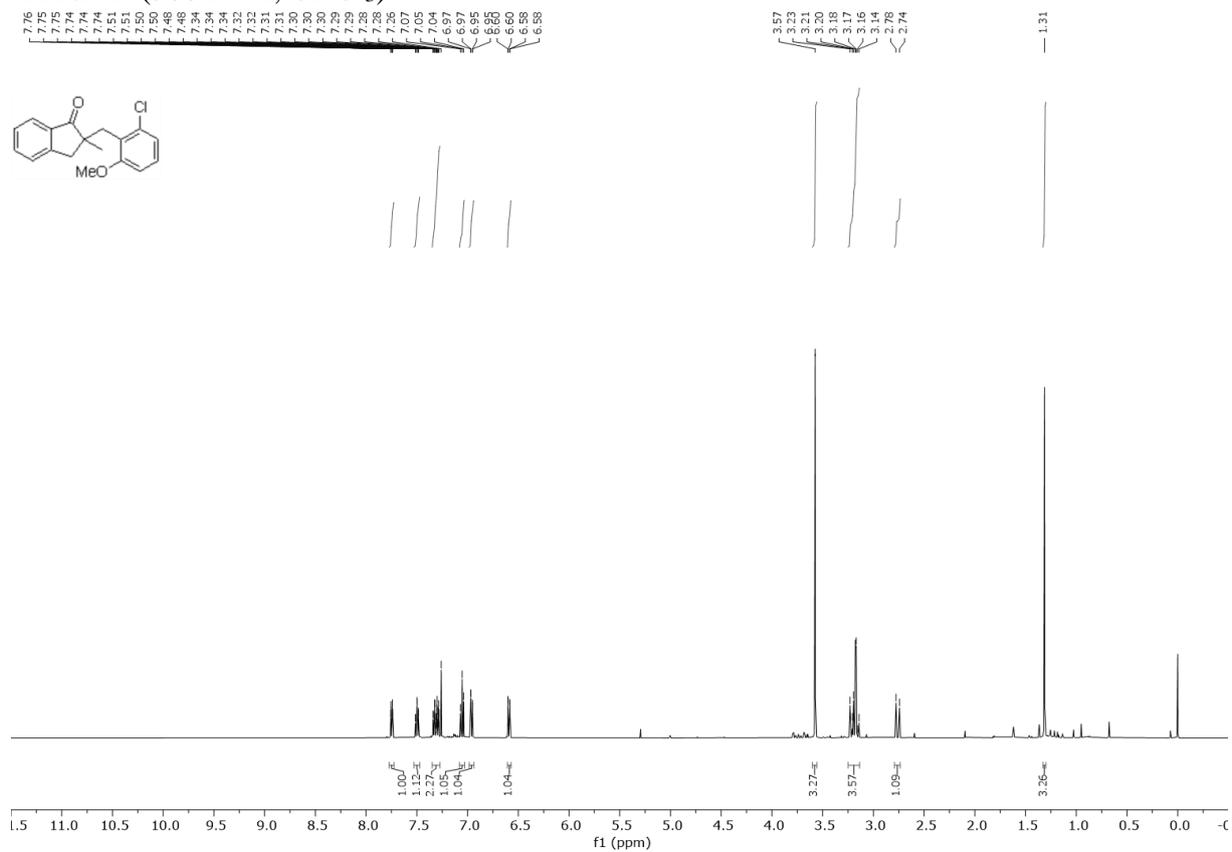


$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )

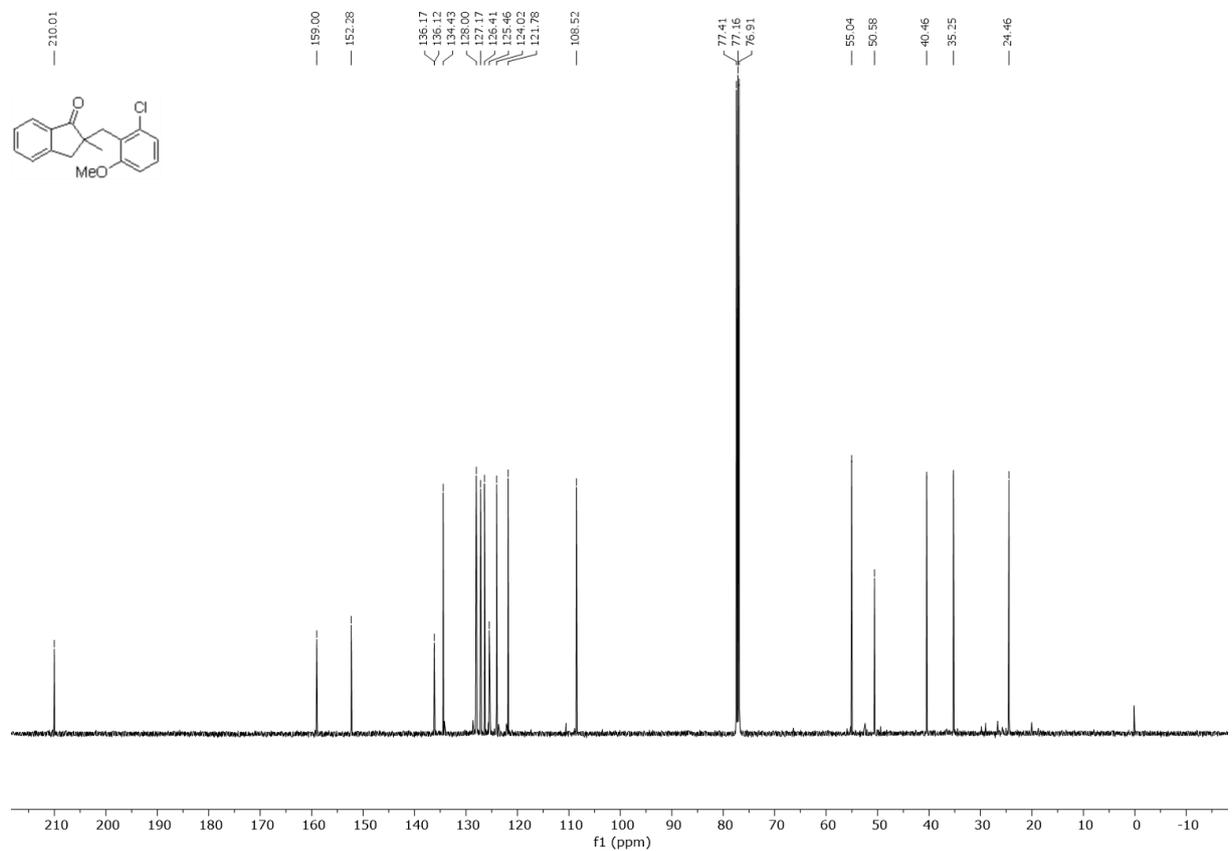


2-(2-chloro-6-methoxybenzyl)-2-methyl-2,3-dihydro-1H-inden-1-one (**3.44**)

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)



<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)

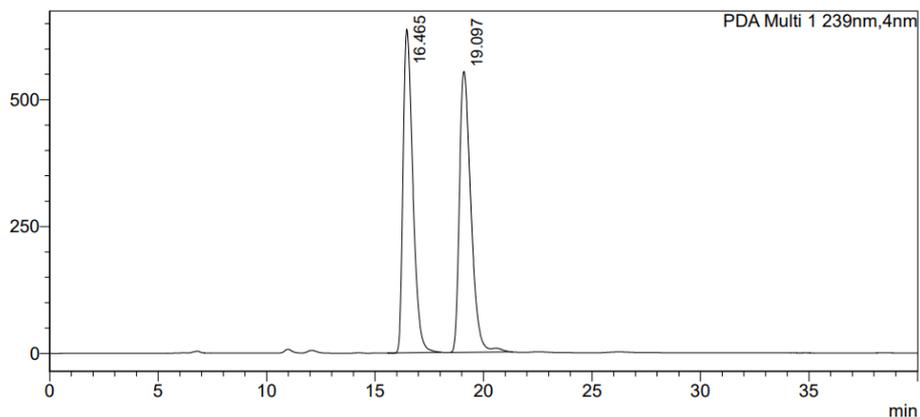


### <Sample Information>

Sample Name : NN972rac  
Sample ID :  
Data Filename : NN972 racOJH 99\_1\_1mL run.lcd  
Method Filename : Run-col5-OJH\_98\_2\_1mL\_40min.lcm  
Batch Filename : NN972rac.lcb  
Vial # : 1-37  
Injection Volume : 4 uL  
Date Acquired : 13.12.2018 14:26:38  
Date Processed : 20.10.2021 15:37:58  
Sample Type : Unknown  
Acquired by : System Administrator  
Processed by : System Administrator

### <Chromatogram>

mAU



### <Peak Table>

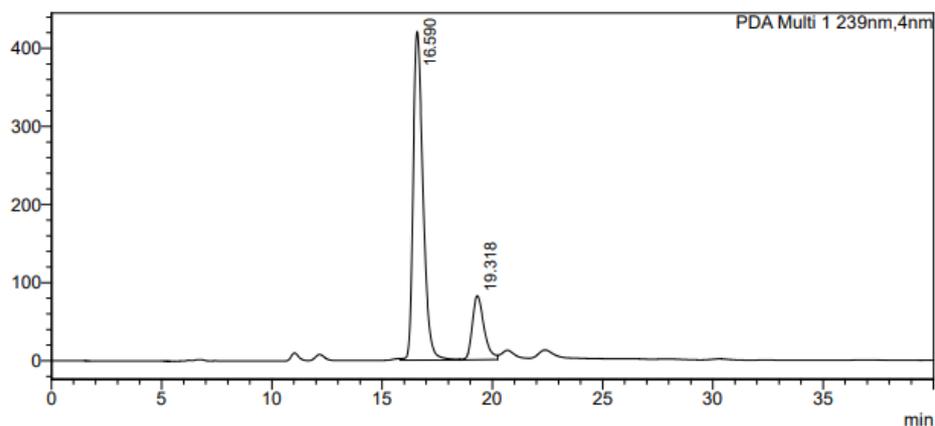
Peak#	Ret. Time	Area	Height	Area%
1	16.465	19913075	637724	49.354
2	19.097	20434576	553995	50.646
Total		40347651	1191720	100.000

### <Sample Information>

Sample Name : NN974  
Sample ID :  
Data Filename : NN974OJH 99\_1\_1mL run.lcd  
Method Filename : Run-col5-OJH\_98\_2\_1mL\_40min.lcm  
Batch Filename : NN974.lcb  
Vial # : 1-37  
Injection Volume : 3 uL  
Date Acquired : 13.12.2018 15:52:27  
Date Processed : 17.12.2018 09:26:08  
Sample Type : Unknown  
Acquired by : System Administrator  
Processed by : System Administrator

### <Chromatogram>

mAU

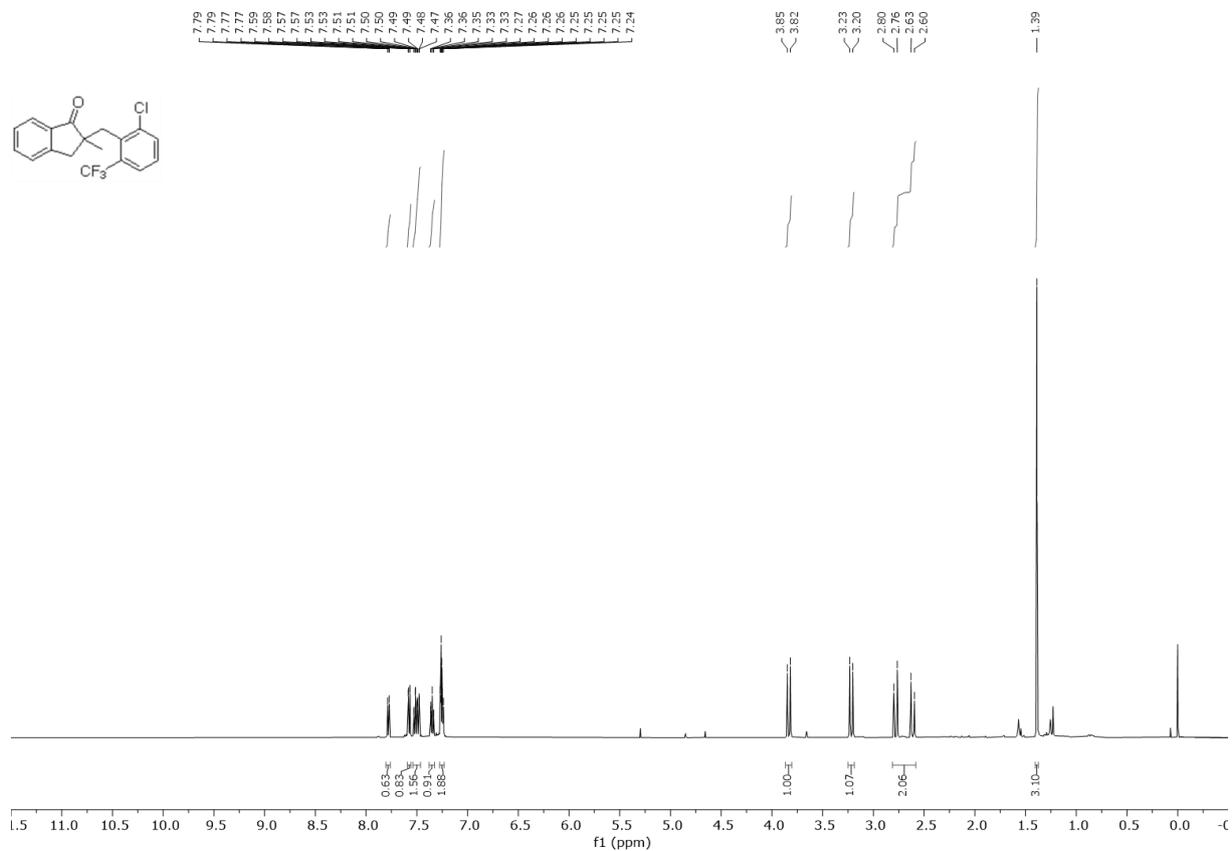


### <Peak Table>

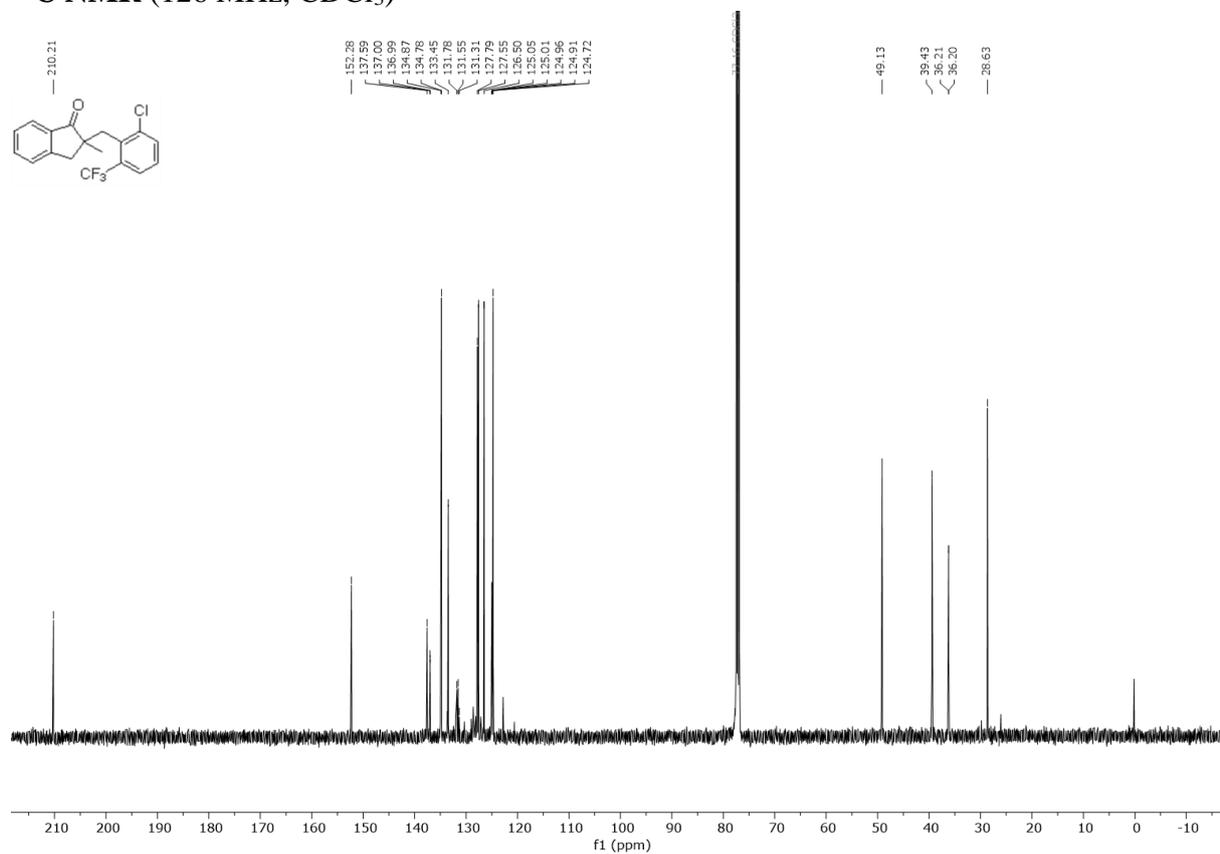
Peak#	Ret. Time	Area	Height	Area%
1	16.590	13102085	420951	81.170
2	19.318	3039513	81973	18.830
Total		16141597	502924	100.000

2-(2-chloro-6-(trifluoromethyl)benzyl)-2-methyl-2,3-dihydro-1H-inden-1-one (**3.45**)

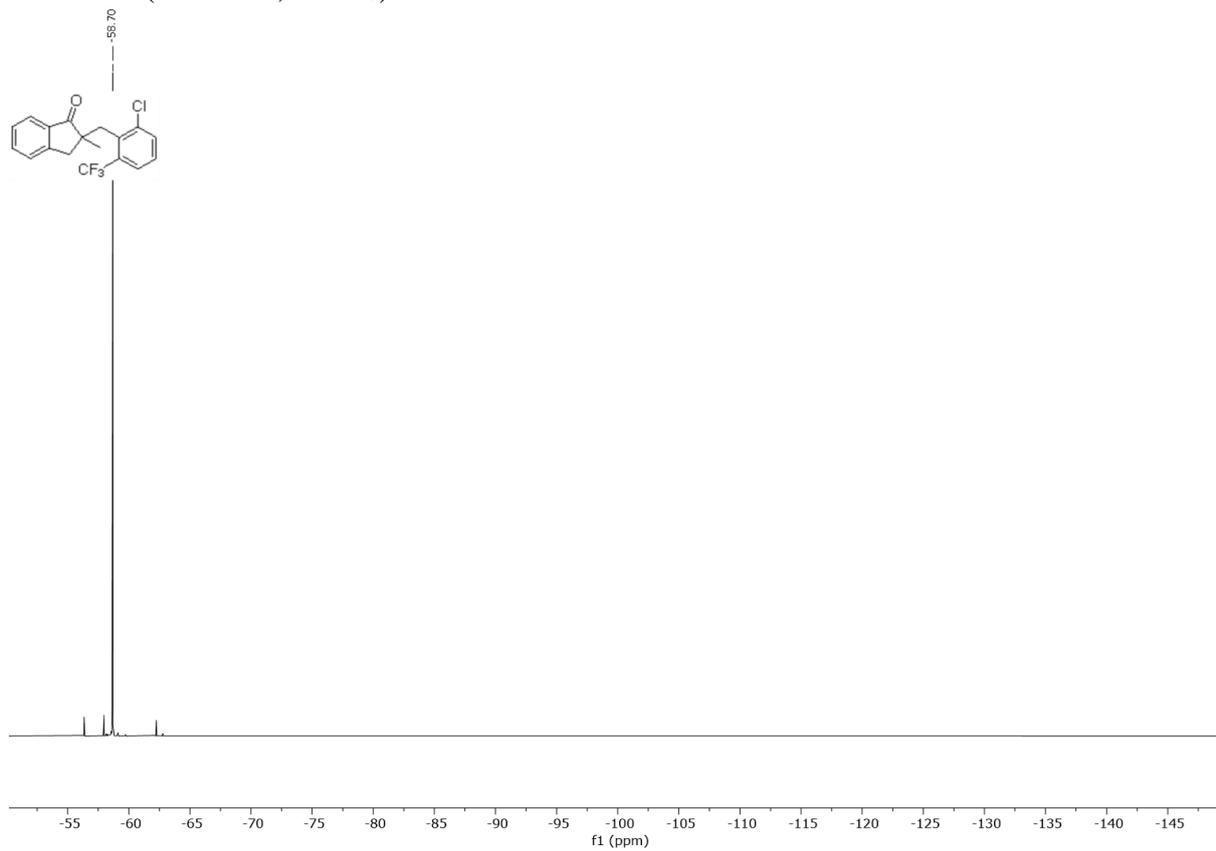
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )



$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )

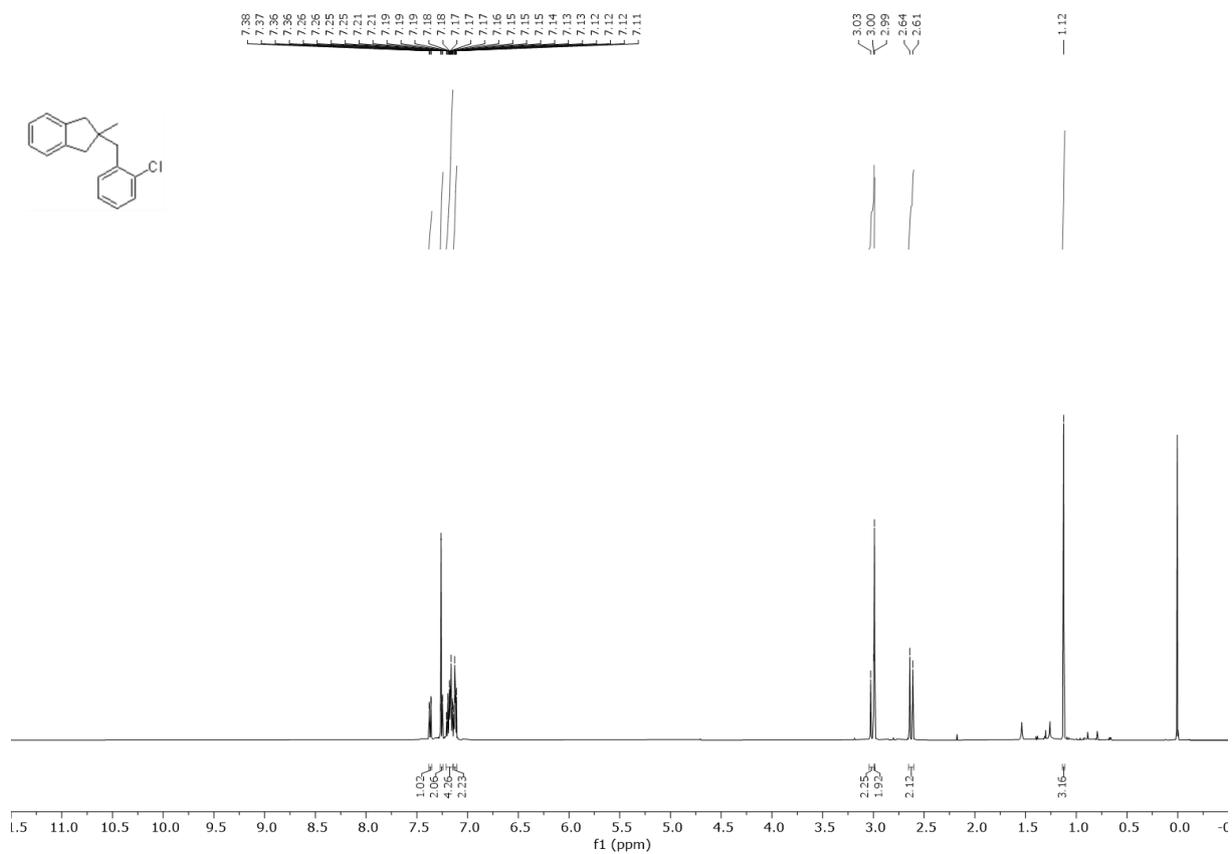


**$^{19}\text{F}$  NMR (471 MHz,  $\text{CDCl}_3$ )**

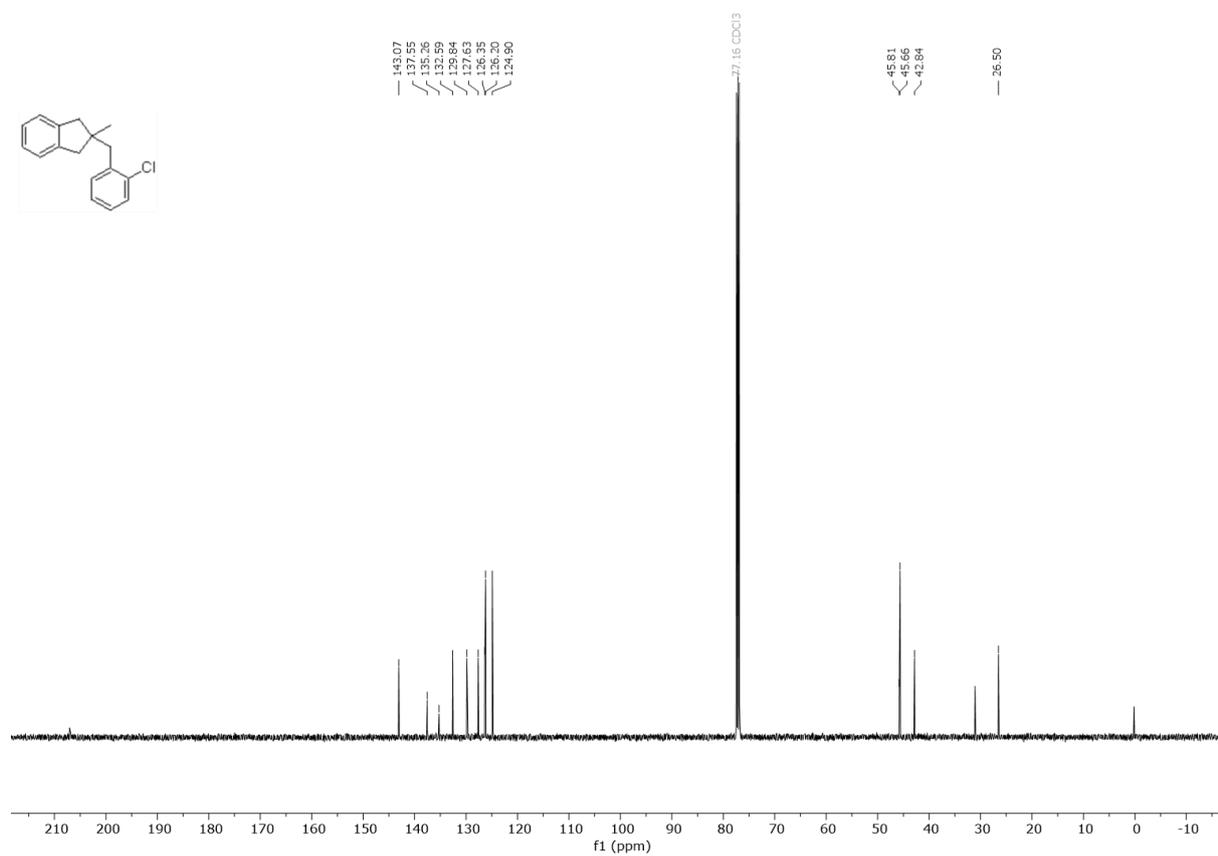


2-(2-chlorobenzyl)-2-methyl-2,3-dihydro-1H-indene (**3.46**)

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )

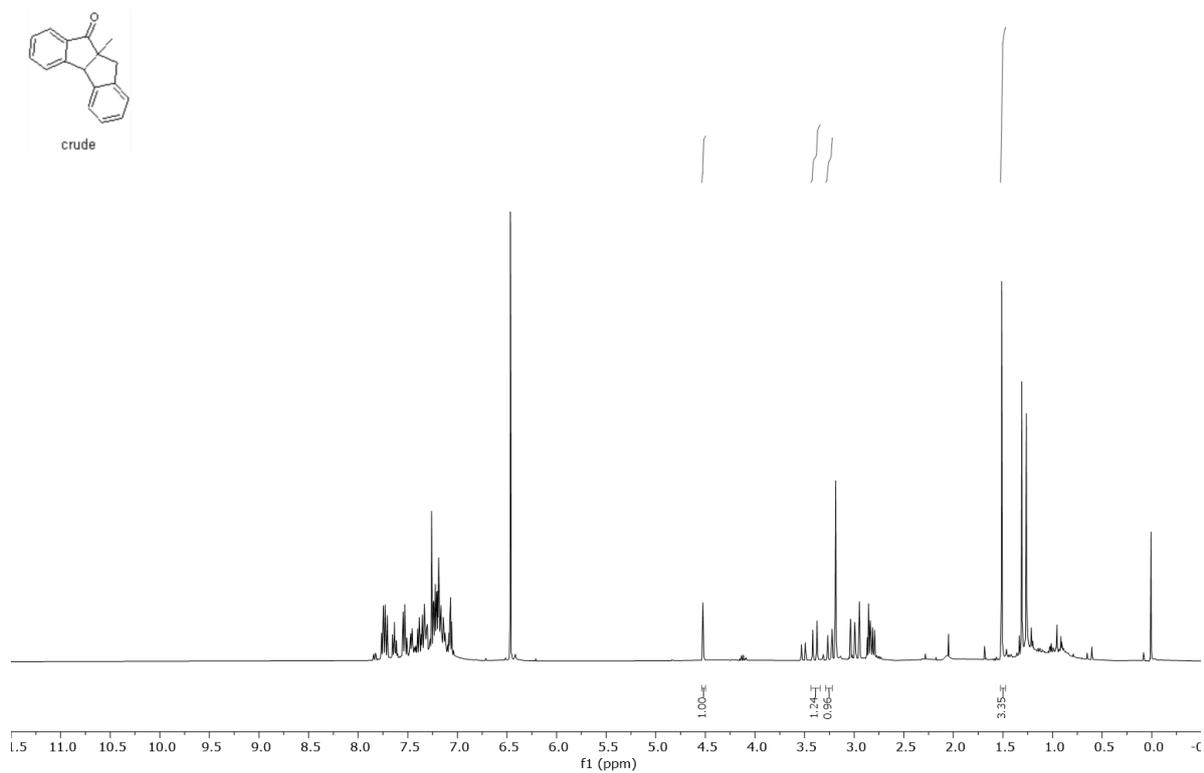


$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )



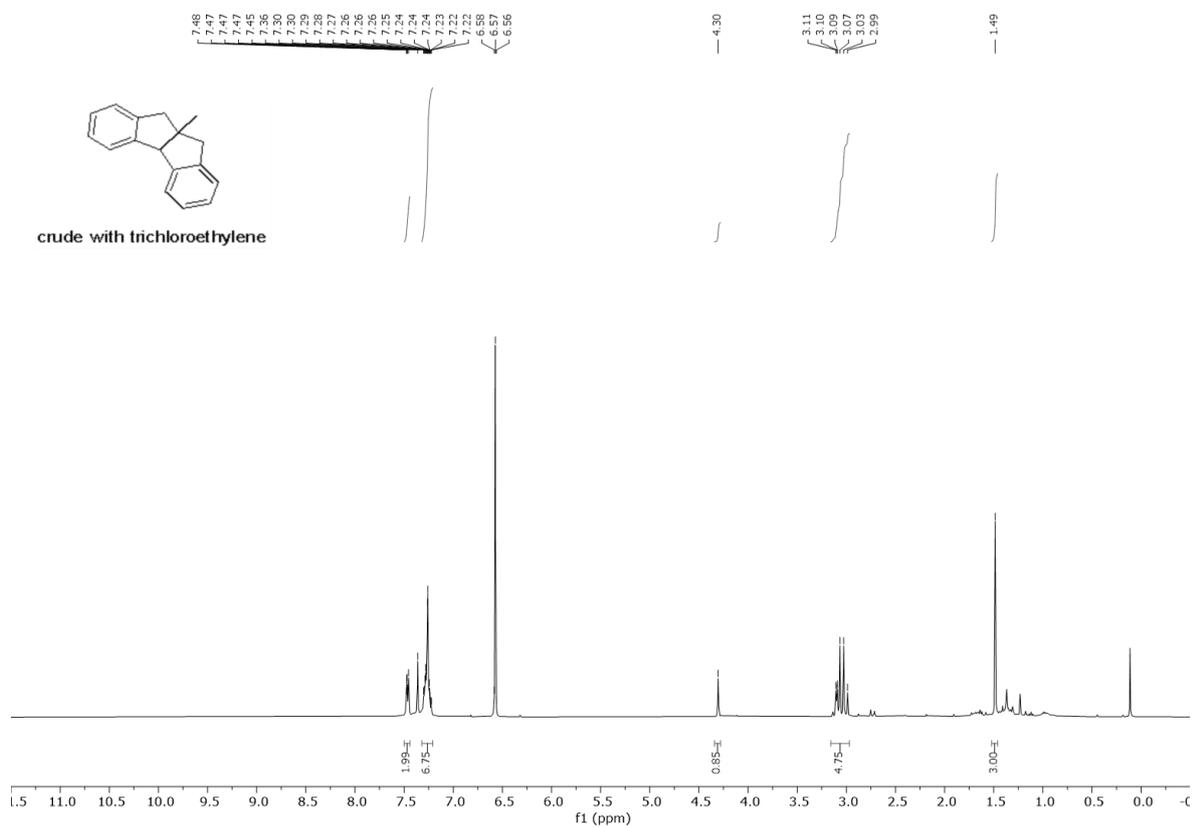
(3.47)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)



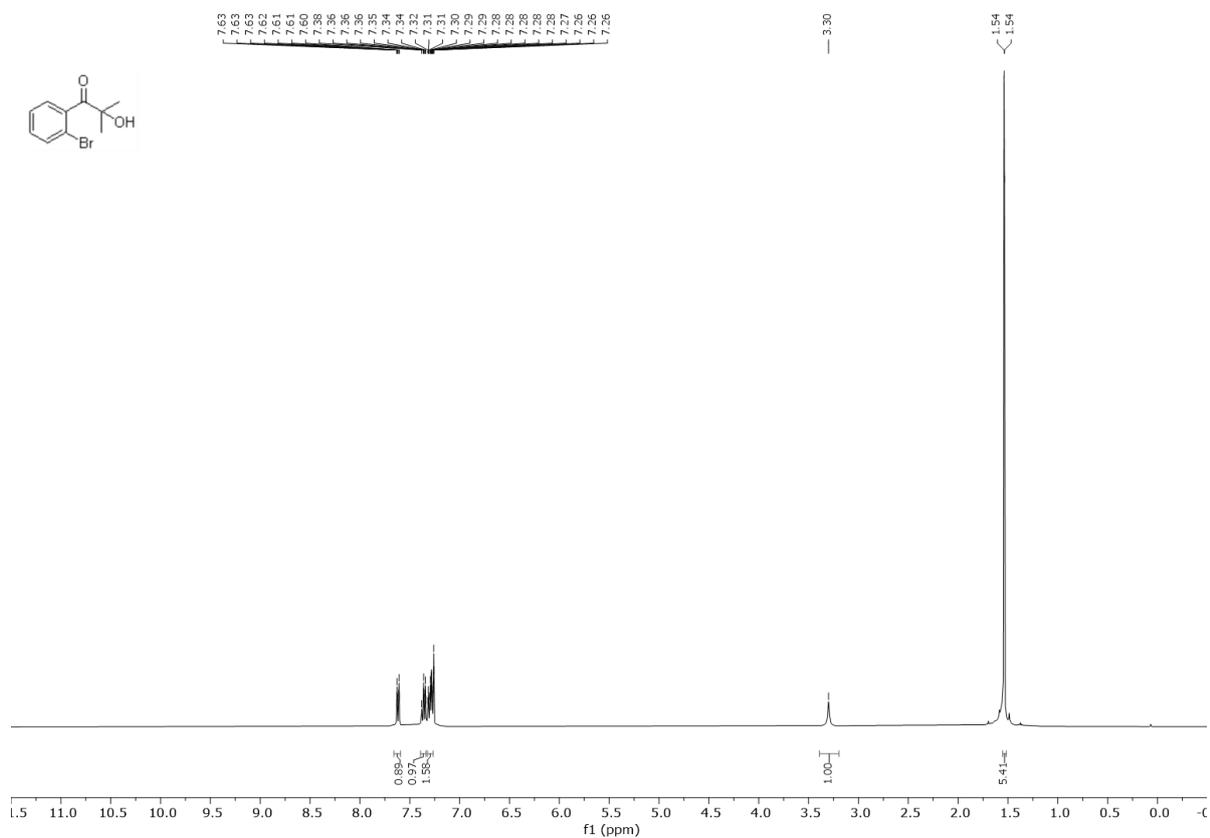
9a-methyl-4b,9,9a,10-tetrahydroindeno[1,2-a]indene (3.48)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)



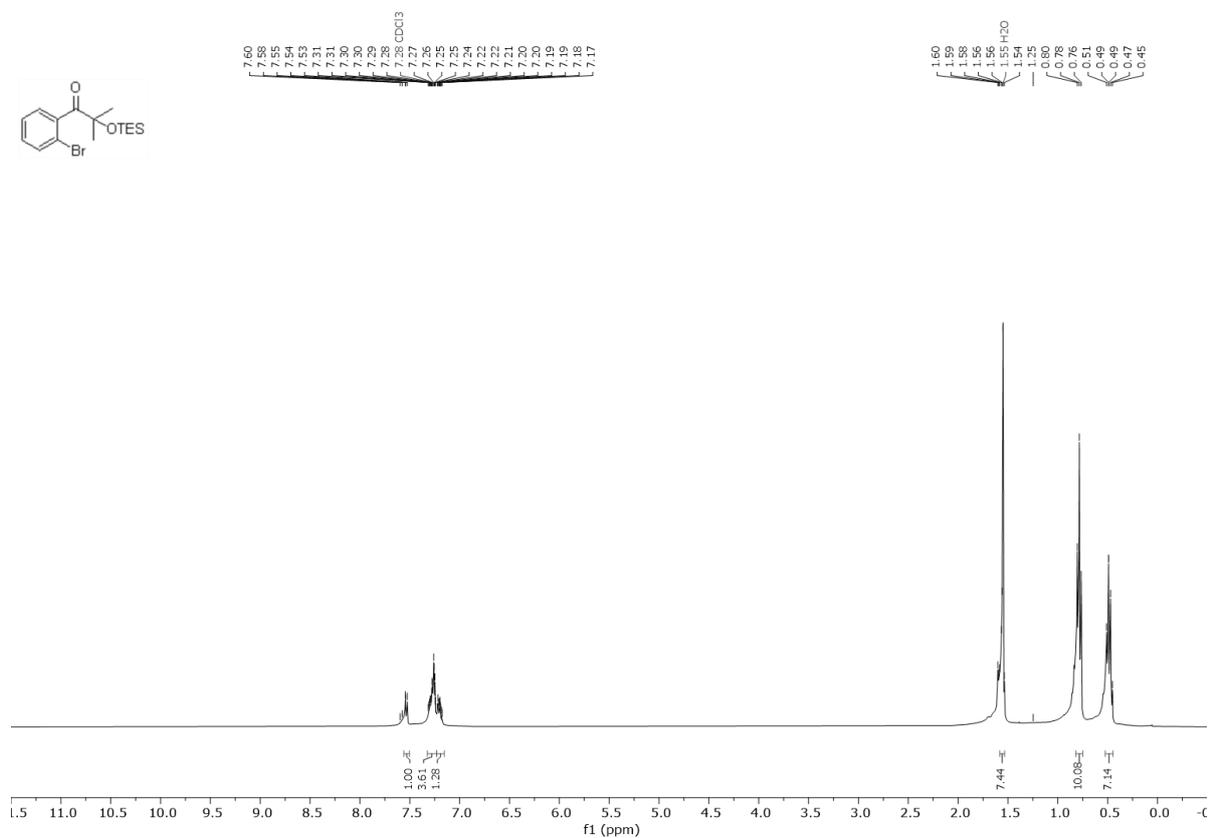
1-(2-bromophenyl)-2-hydroxy-2-methylpropan-1-one (**3.54**)

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )

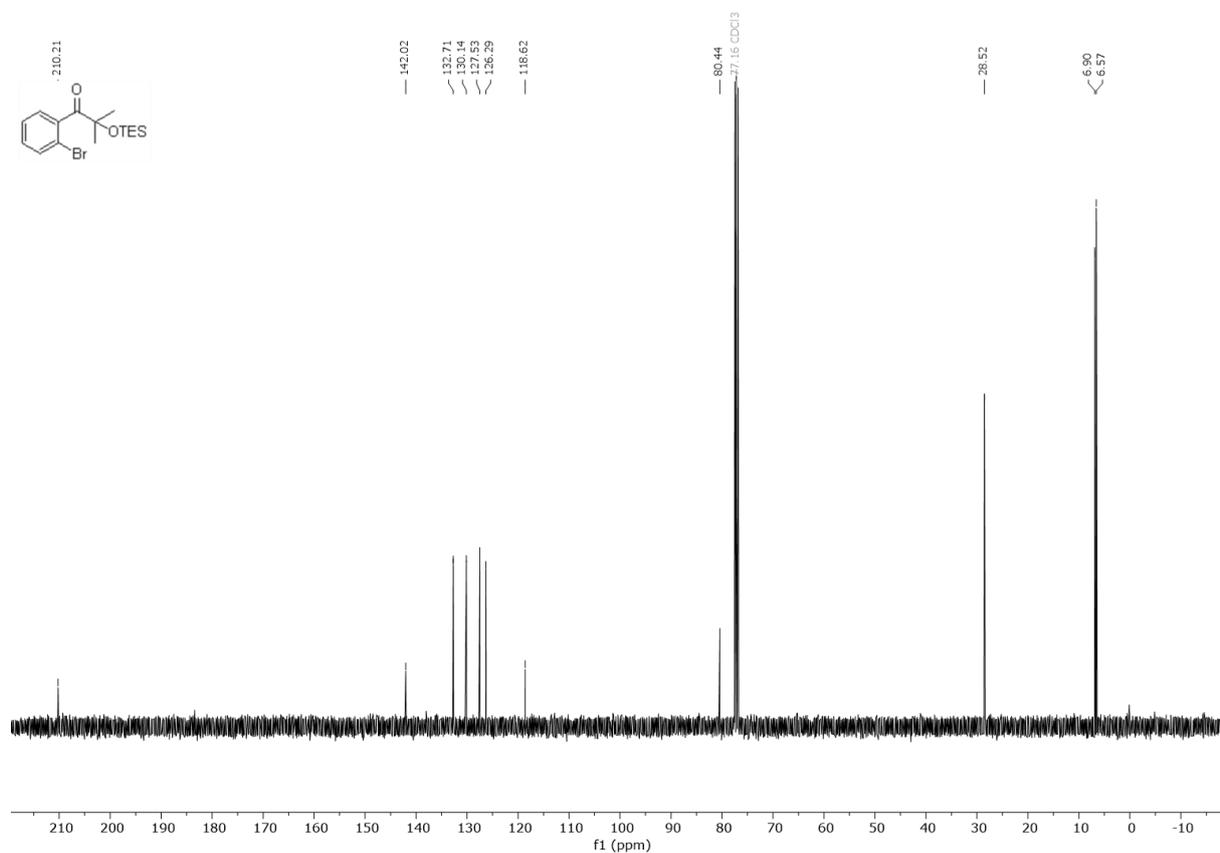


1-(2-bromophenyl)-2-methyl-2-((triethylsilyloxy)propan-1-one (**3.56**)

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )



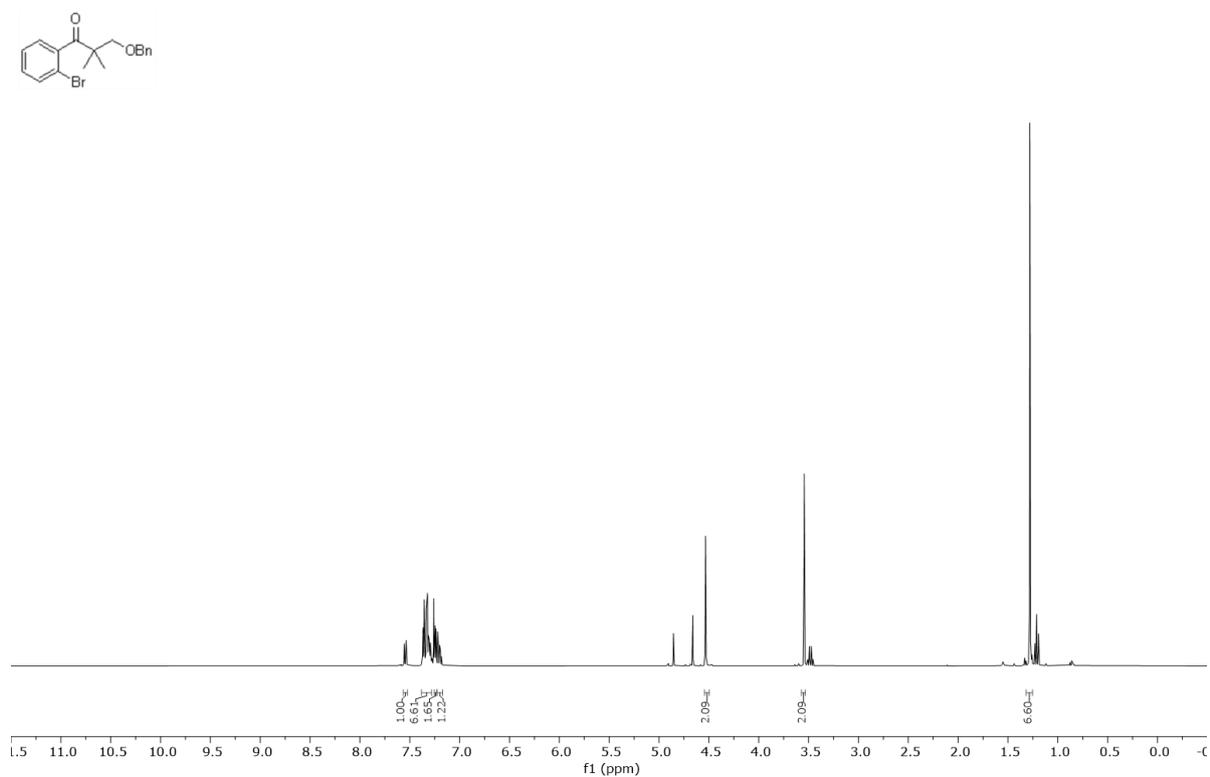
$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )





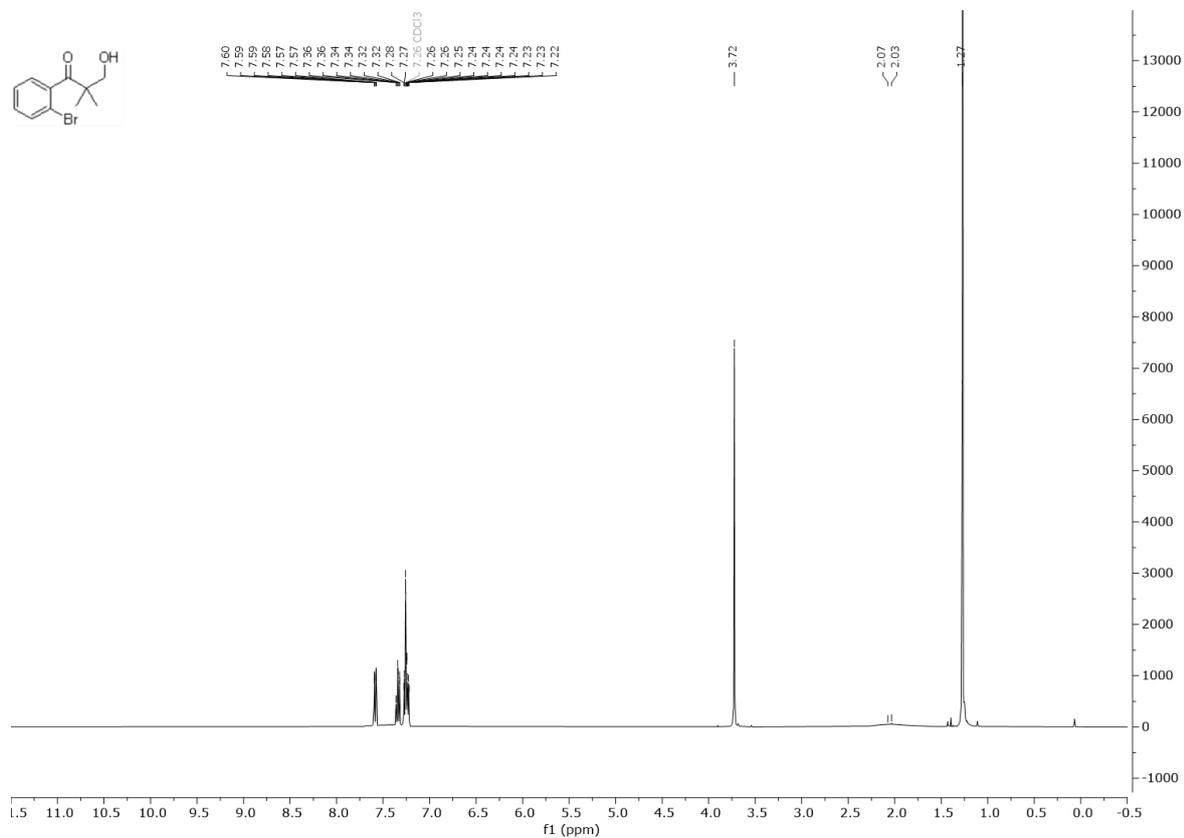
3-(benzyloxy)-1-(2-bromophenyl)-2,2-dimethylpropan-1-one (**3.62**)

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )



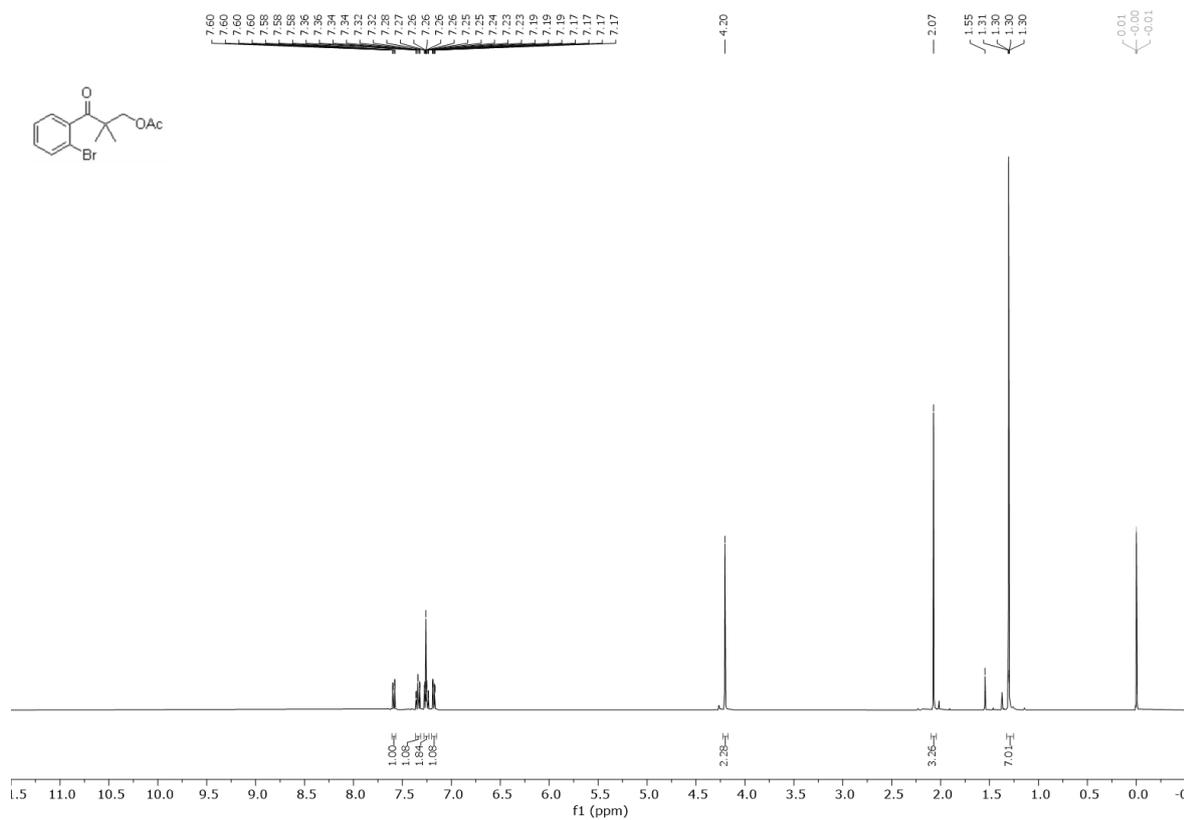
1-(2-bromophenyl)-3-hydroxy-2,2-dimethylpropan-1-one (**3.63**)

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )

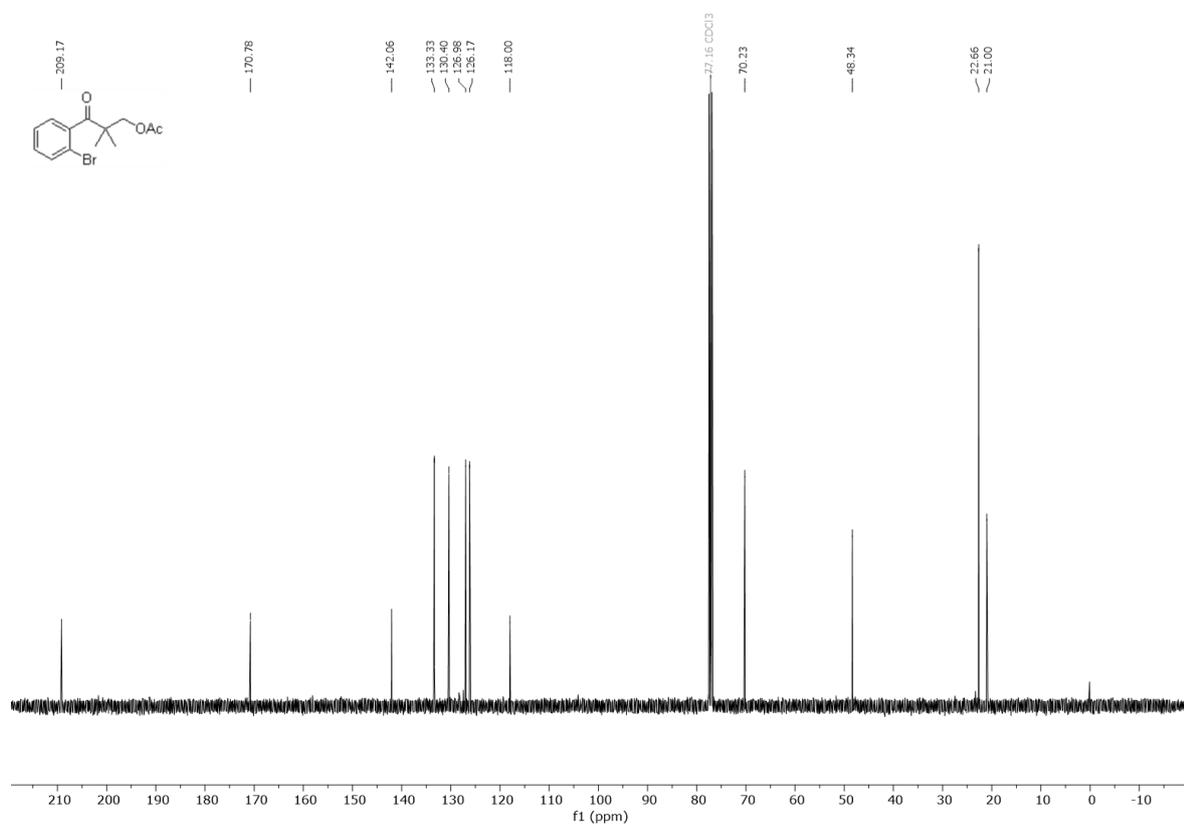


### 3-(2-bromophenyl)-2,2-dimethyl-3-oxopropyl acetate (3.65)

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )

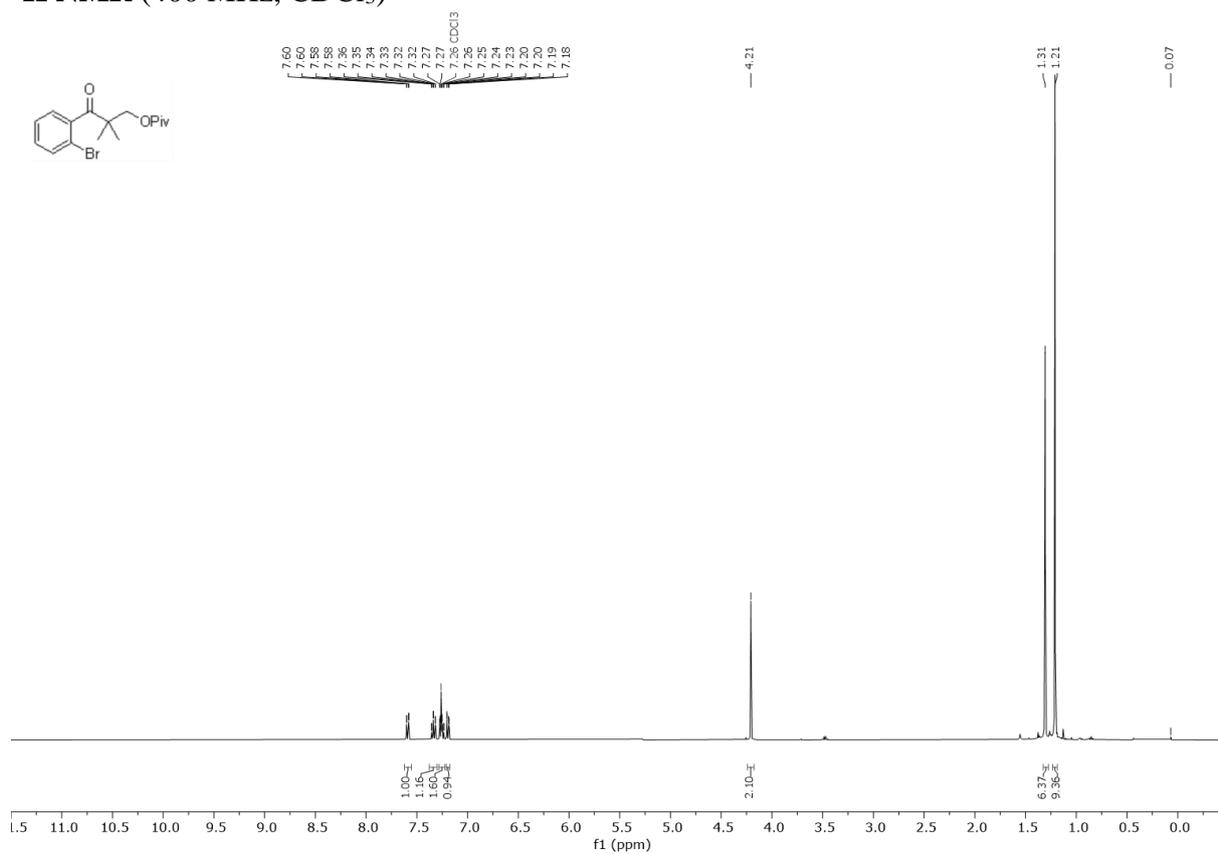


$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )

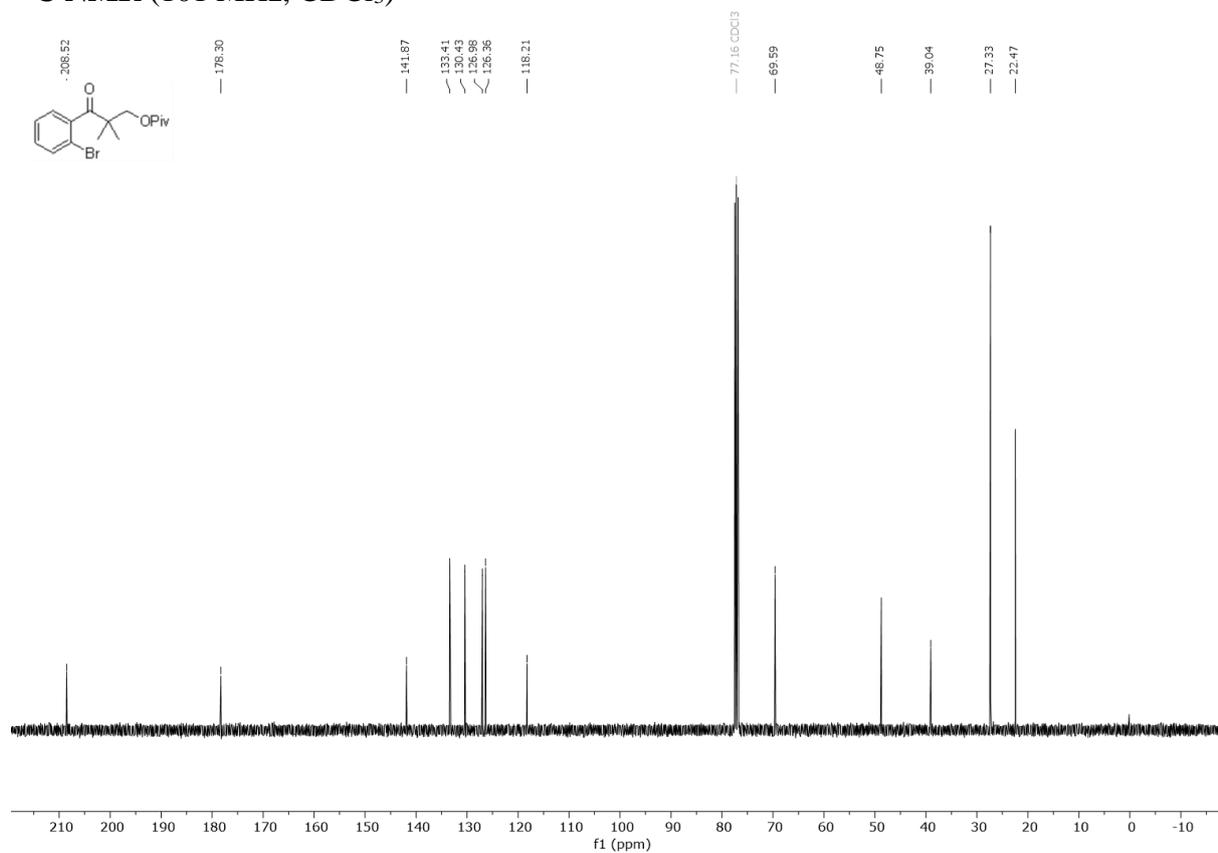


3-(2-bromophenyl)-2,2-dimethyl-3-oxopropyl pivalate (**3.66**)

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )

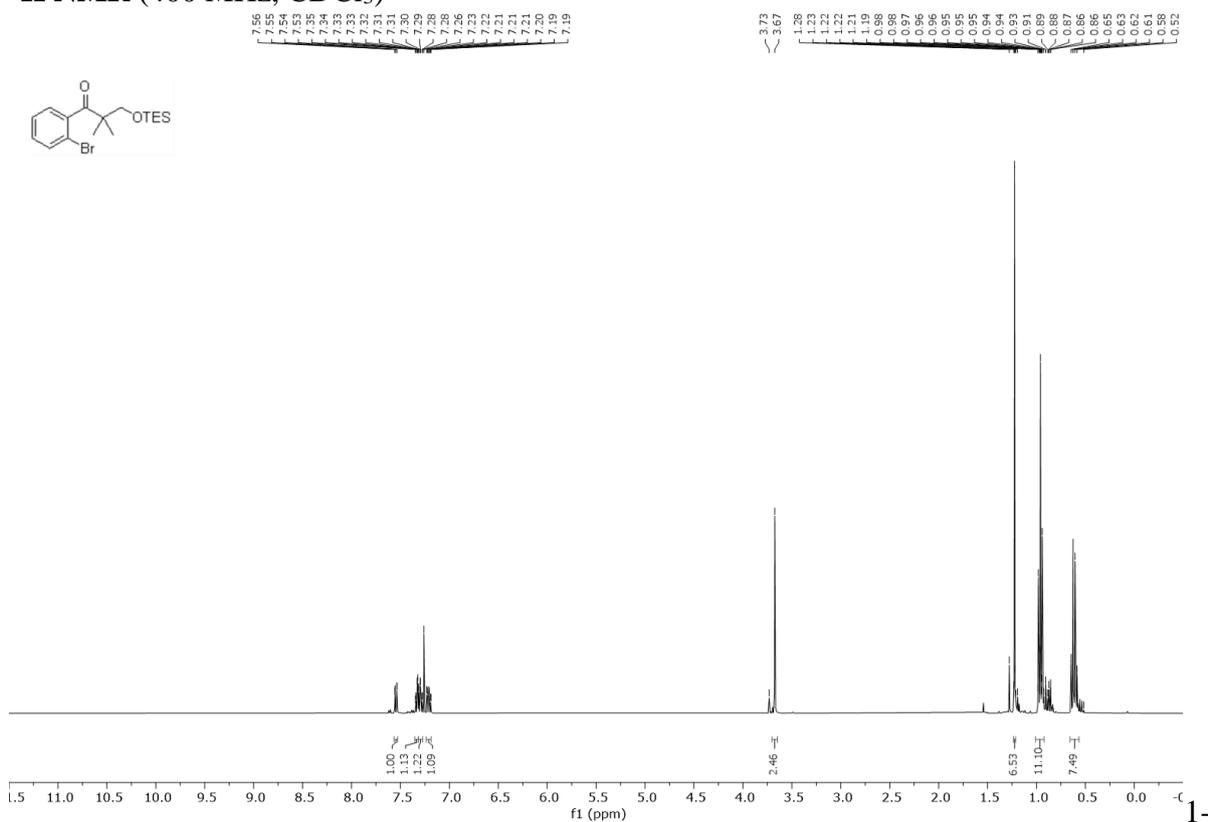


$^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )

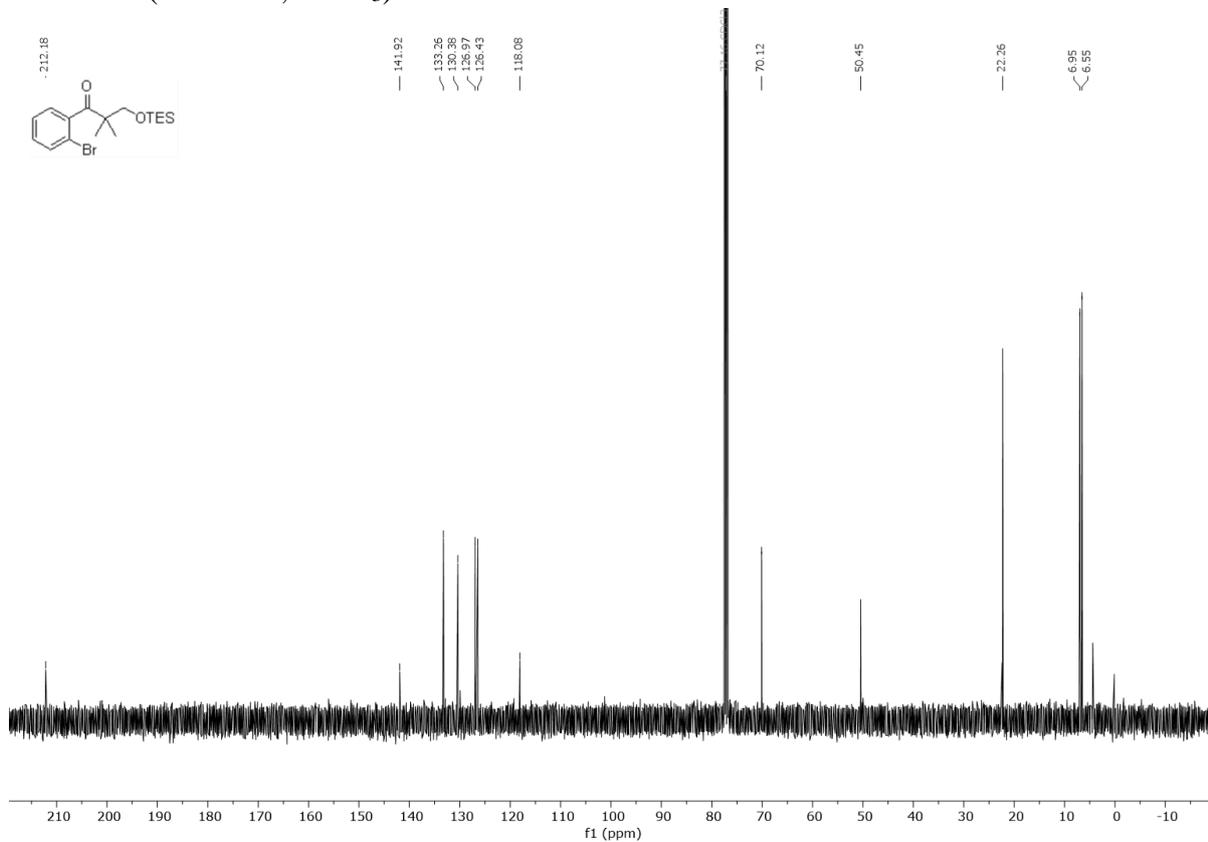


1-(2-bromophenyl)-2,2-dimethyl-3-((triethylsilyloxy)propan-1-one (**3.67**)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)

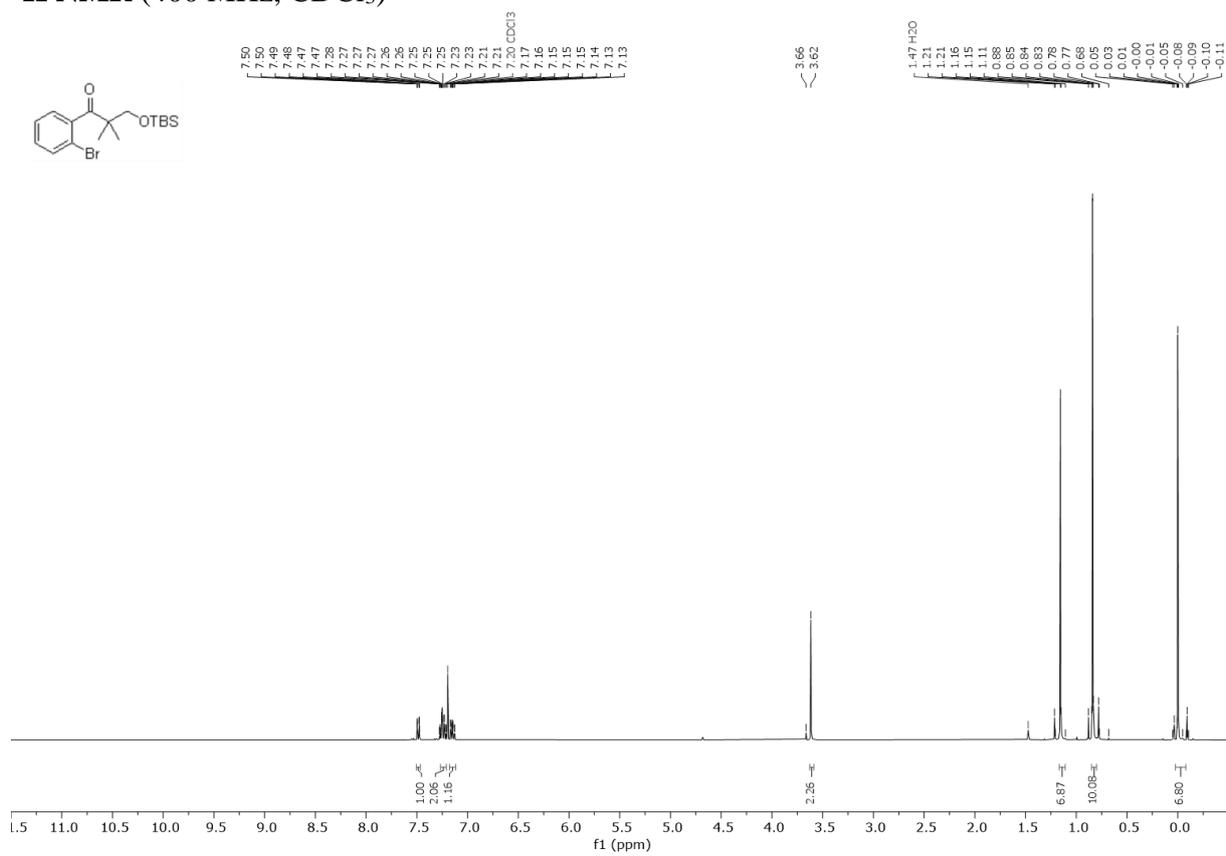


<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)



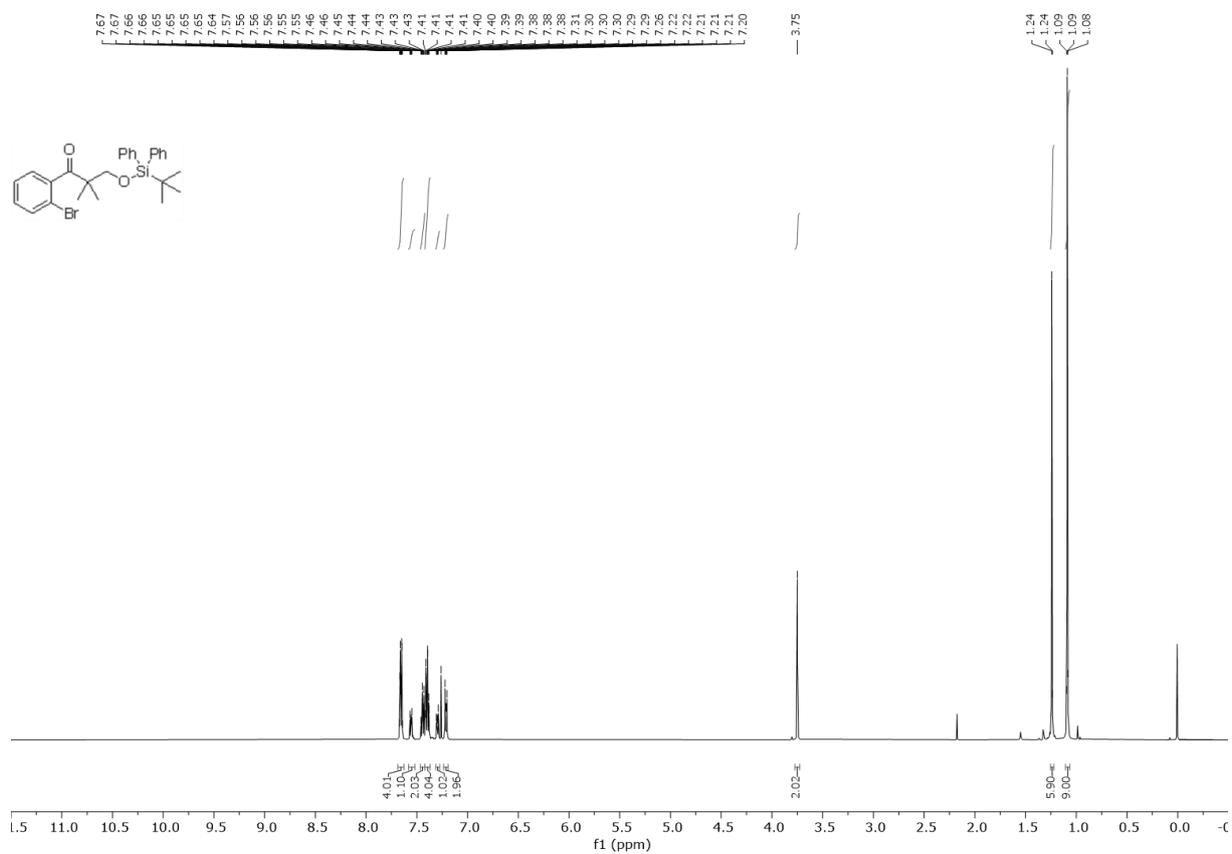
(2-bromophenyl)-3-((tert-butyl dimethylsilyl)oxy)-2,2-dimethylpropan-1-one (**3.68**)

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )

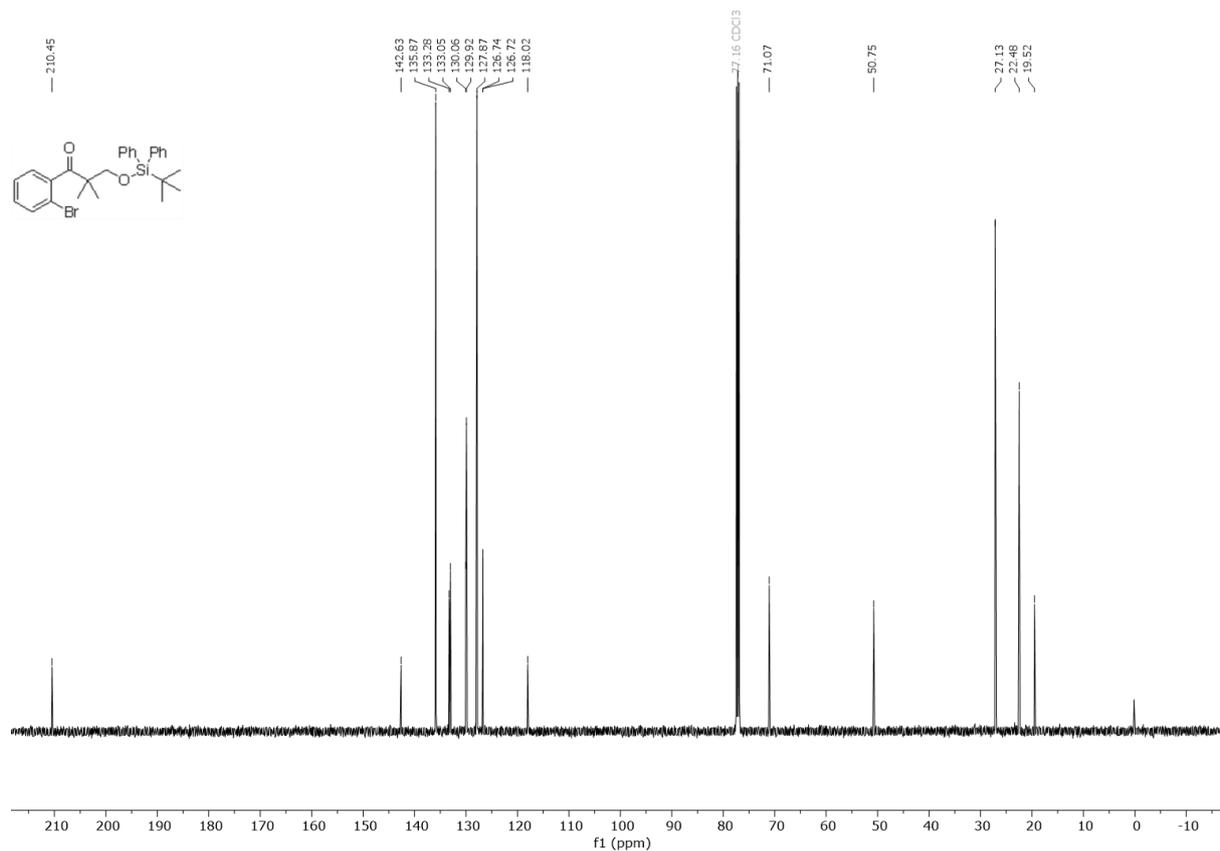


1-(2-bromophenyl)-3-((tert-butyl-diphenylsilyl)oxy)-2,2-dimethylpropan-1-one (**3.69**)

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$

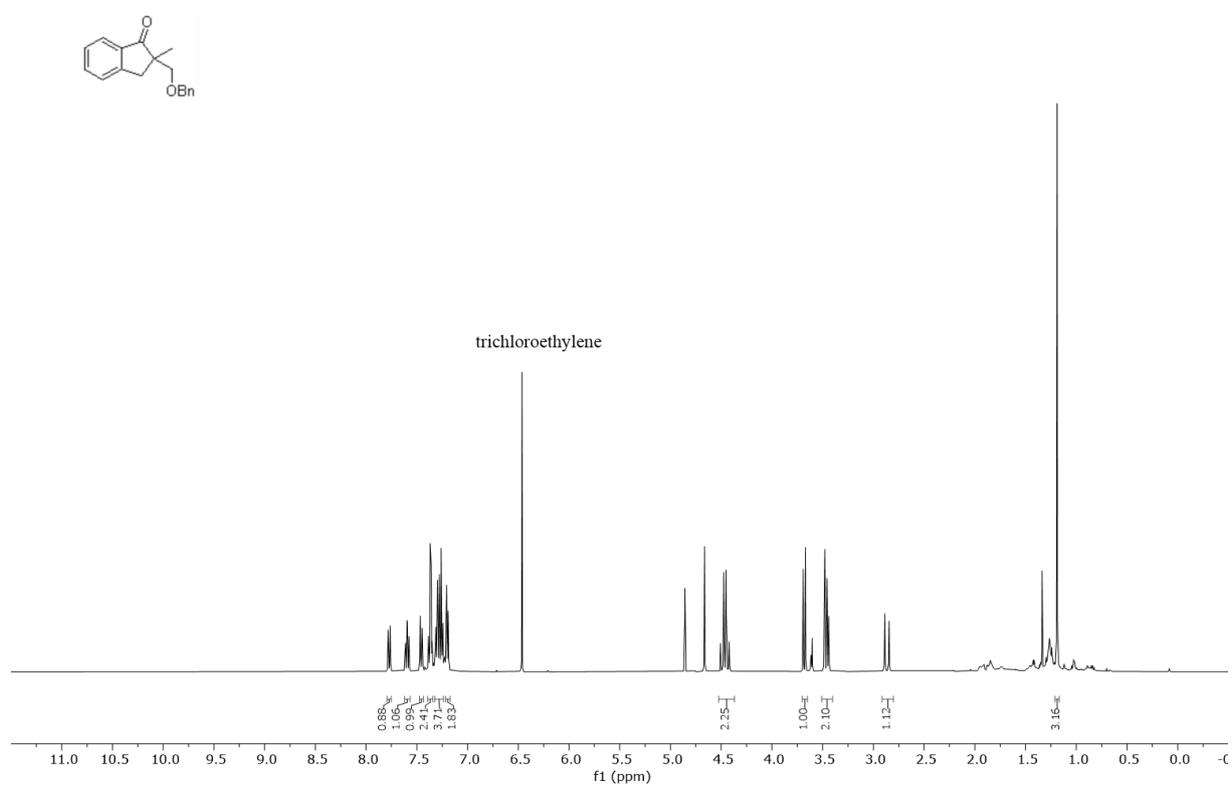


$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )

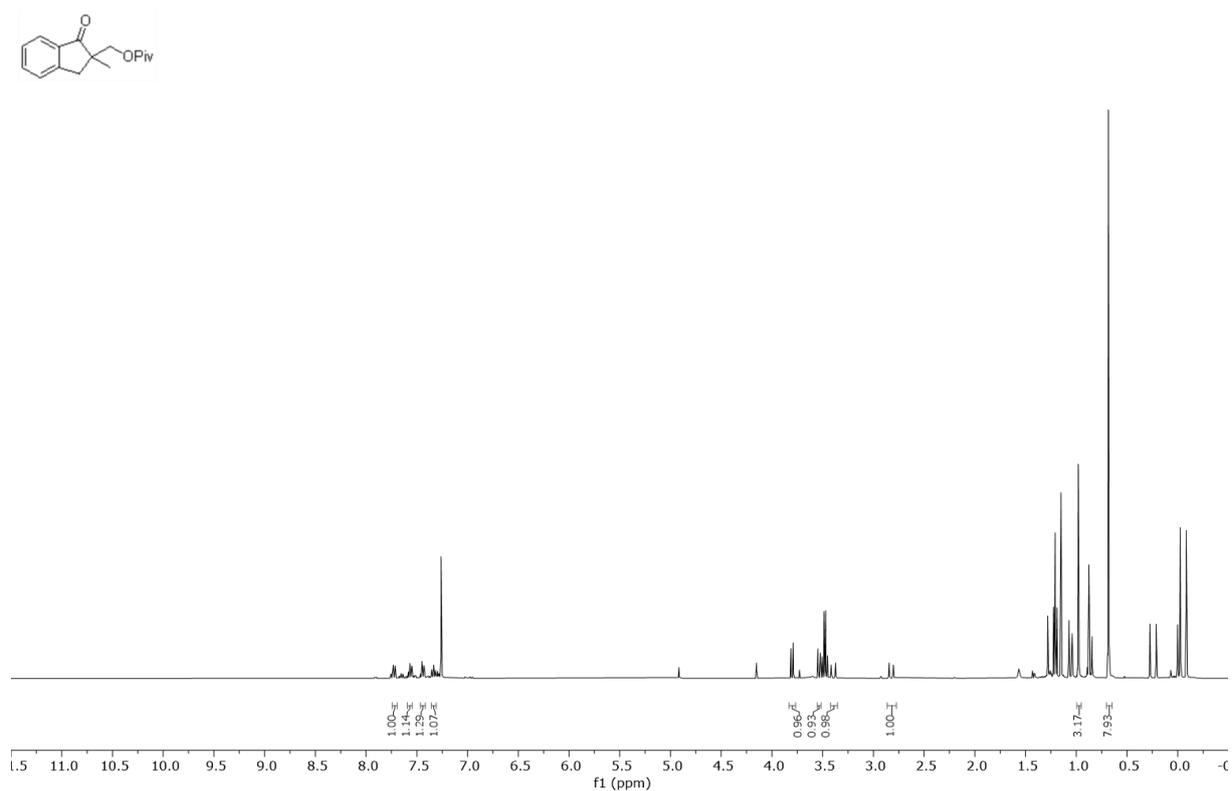


2-((benzyloxy)methyl)-2-methyl-2,3-dihydro-1H-inden-1-one (**3.64**)

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )

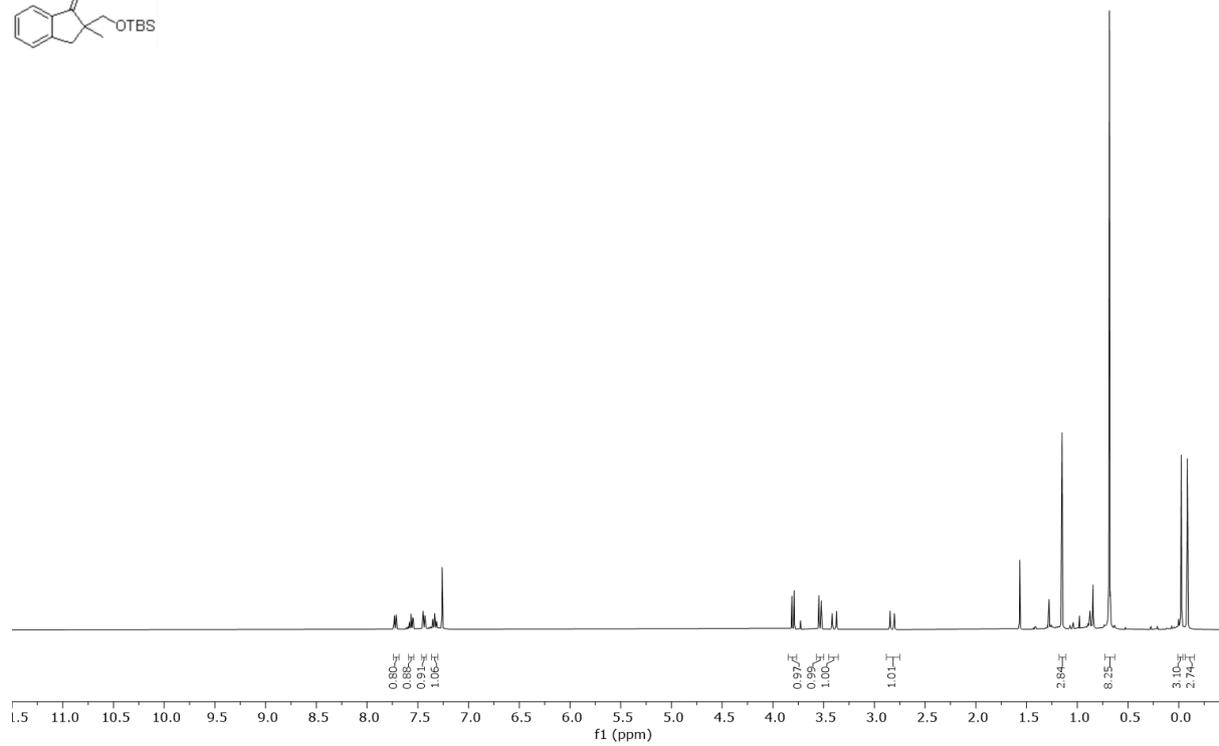
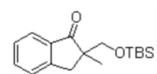


(2-methyl-1-oxo-2,3-dihydro-1H-inden-2-yl)methyl pivalate (**3.71**)



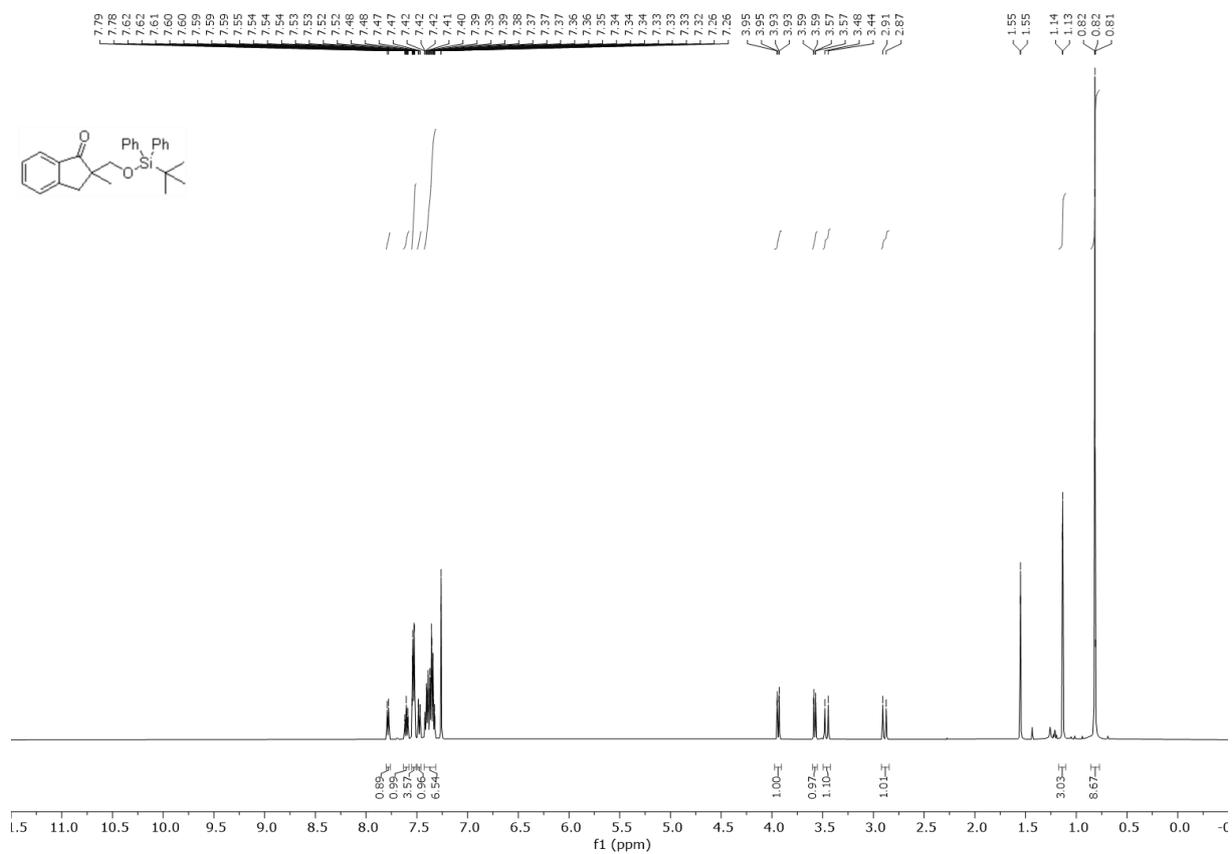
2-(((tert-butyldimethylsilyl)oxy)methyl)-2-methyl-2,3-dihydro-1H-inden-1-one (**3.73**)

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )

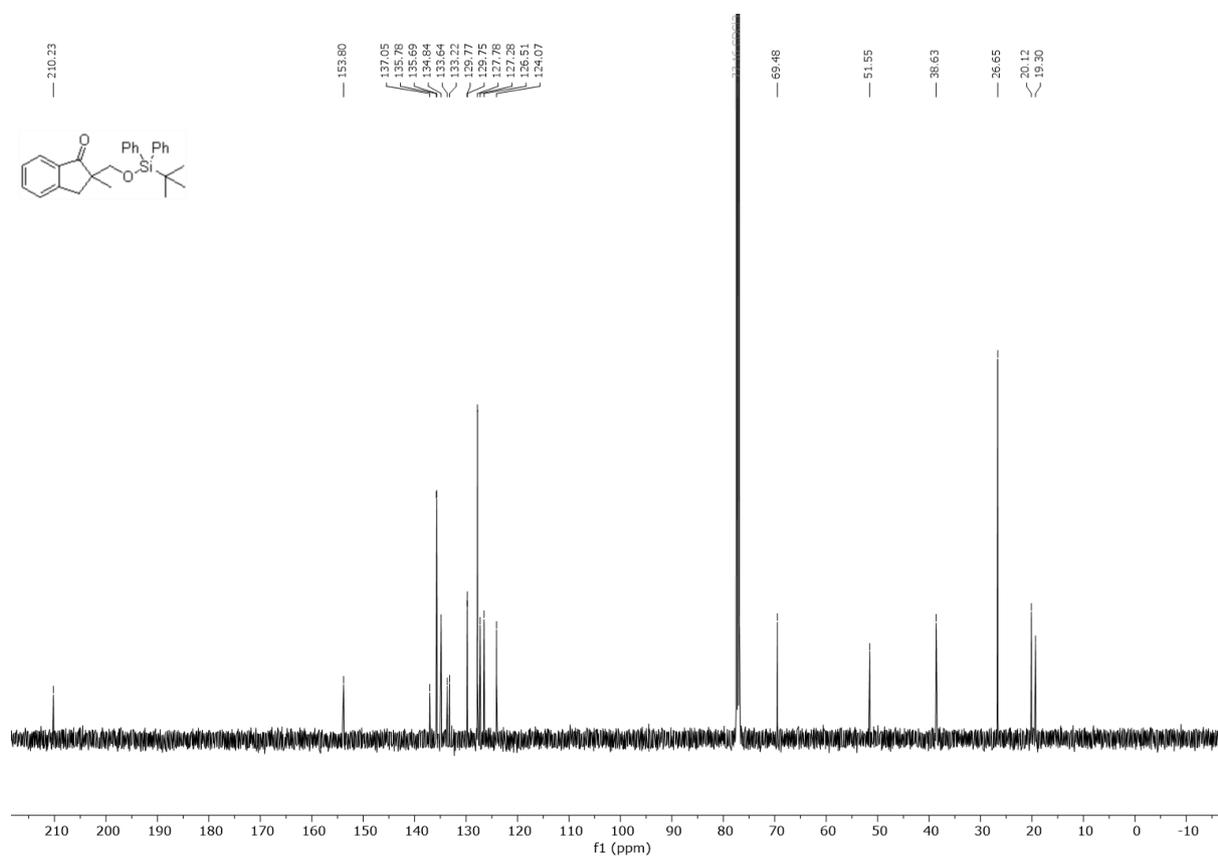


2-(((tert-butyl)phenylsilyloxy)methyl)-2-methyl-2,3-dihydro-1H-inden-1-one (**3.74**)

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )



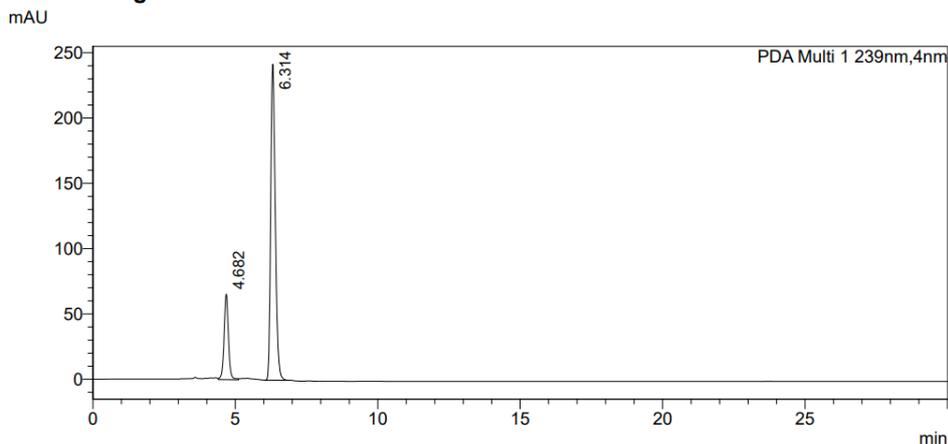
$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )



**<Sample Information>**

Sample Name : NN1381  
Sample ID :  
Data Filename : NN1381\_run\_ODH\_99\_1\_1mL\_30min.lcd  
Method Filename : run\_col1\_ODH\_99\_1\_1mL\_30min.lcm  
Batch Filename : NN-1381-85.lcb  
Vial # : 1-36  
Injection Volume : 1 uL  
Date Acquired : 17.05.2019 17:20:08  
Date Processed : 20.10.2021 14:58:49  
Sample Type : Unknown  
Acquired by : System Administrator  
Processed by : System Administrator

**<Chromatogram>**



**<Peak Table>**

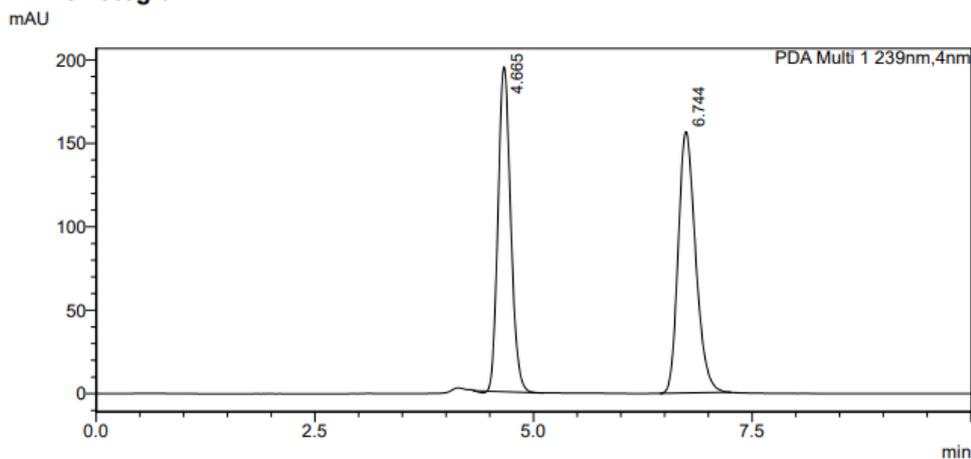
PDA Ch1 239nm

Peak#	Ret. Time	Area	Height	Area%
1	4.682	698574	65680	20.367
2	6.314	2731415	242047	79.633
Total		3429989	307727	100.000

**<Sample Information>**

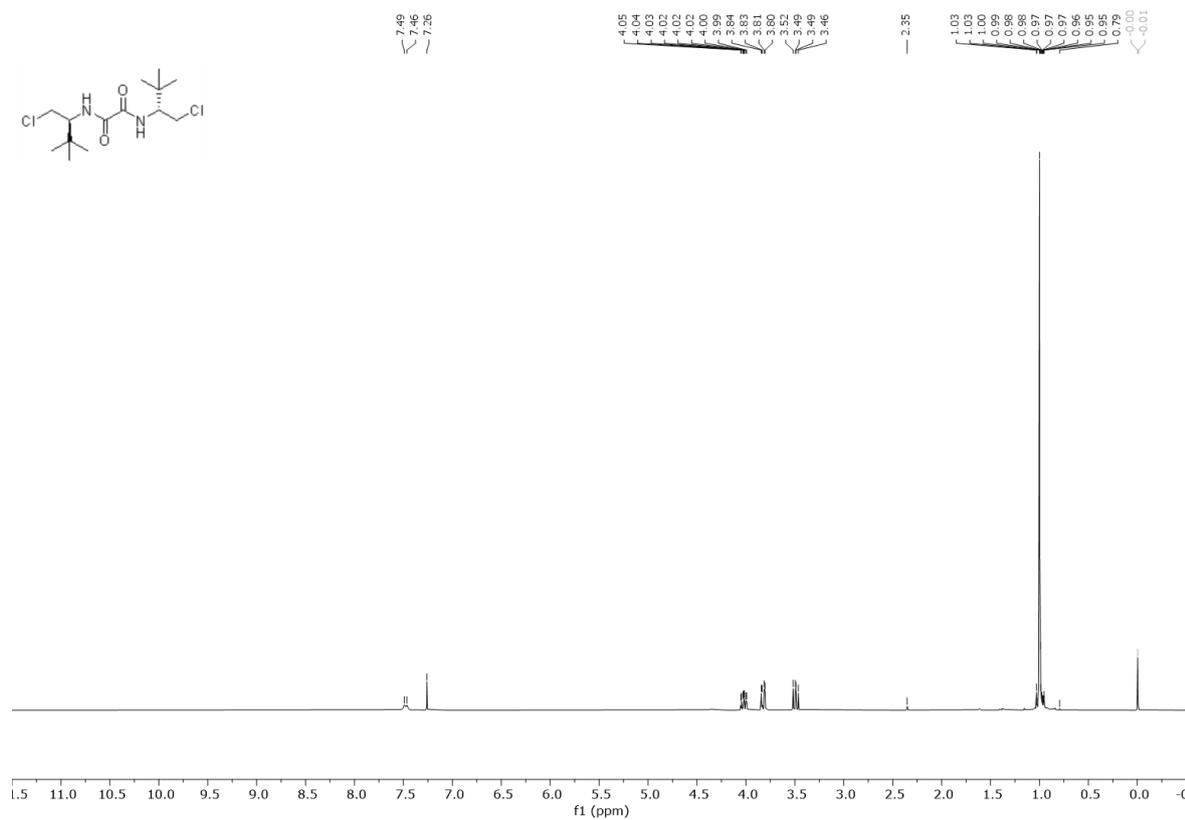
Sample Name : NN1827  
Sample ID :  
Data Filename : NN1827\_run\_ODH\_99\_1\_1mL\_10min004.lcd  
Method Filename : run\_col1\_ODH\_99\_1\_1mL\_10min.lcm  
Batch Filename : NN1825-27.lcb  
Vial # : 1-38  
Injection Volume : 1 uL  
Date Acquired : 14.01.2020 01:17:01  
Date Processed : 20.10.2021 15:15:20  
Sample Type : Unknown  
Acquired by : System Administrator  
Processed by : System Administrator

**<Chromatogram>**



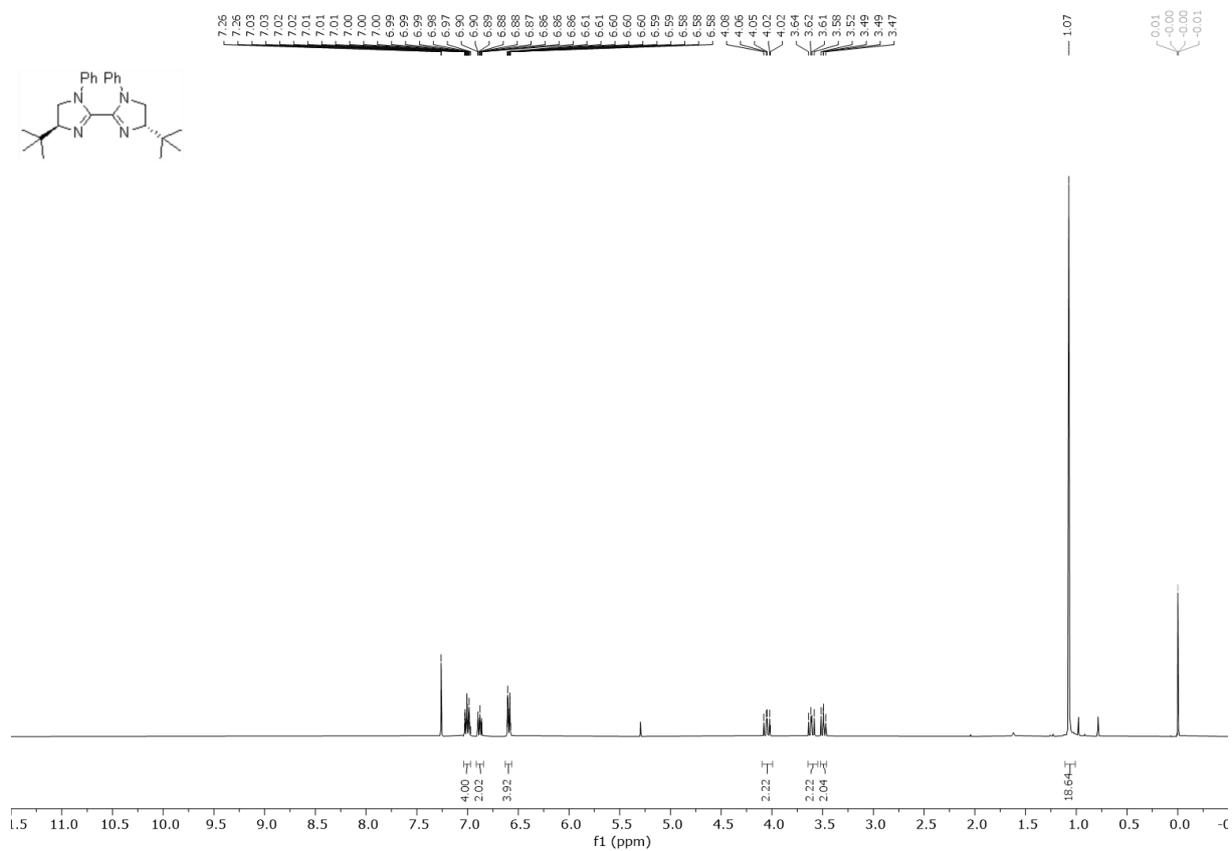
Peak#	Ret. Time	Area	Height	Area%
1	4.665	1952211	194685	47.358
2	6.744	2170052	156615	52.642
Total		4122263	351301	100.000

**N<sup>1</sup>-((S)-1-chloro-3,3-dimethylbutan-2-yl)-N<sup>2</sup>-((S)-1-chloro-3,3-dimethylbutan-2-yl)oxalamide (4.2), <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)**

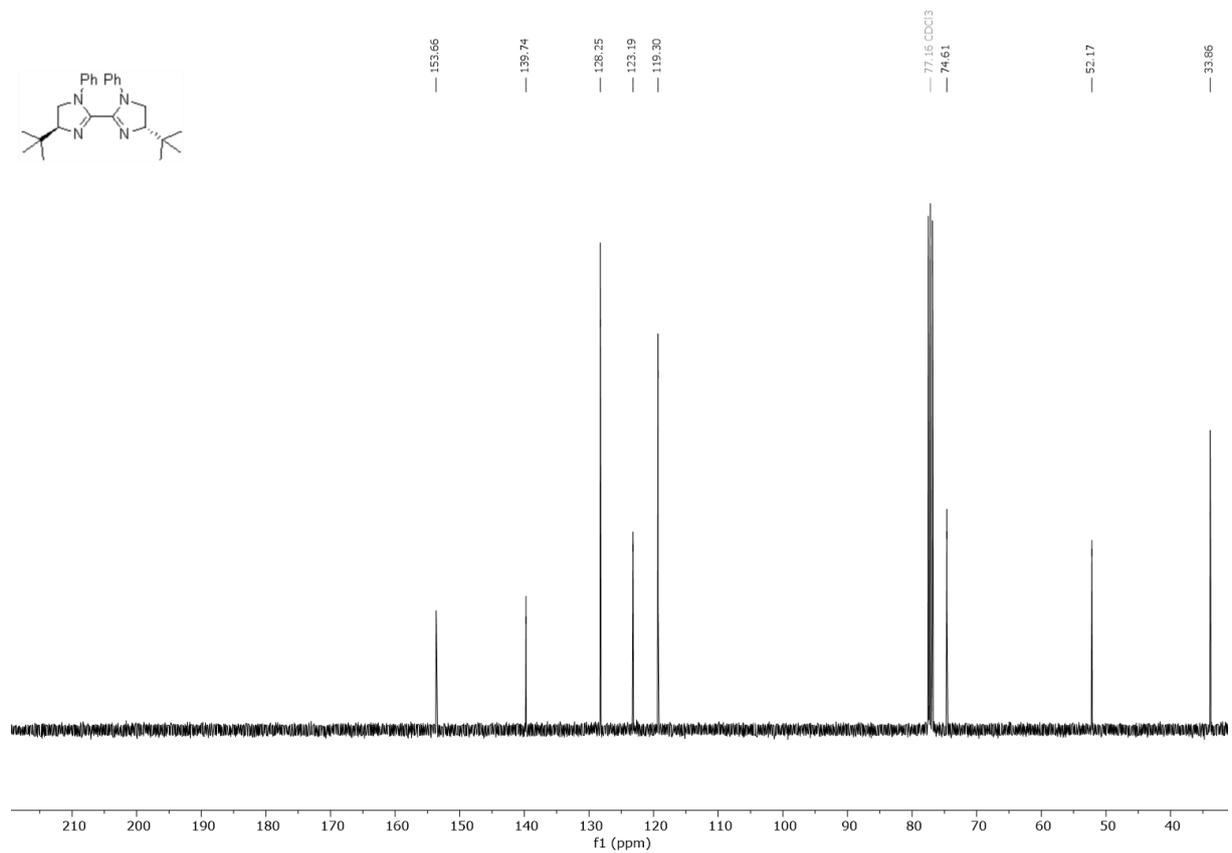


(4S,4'S)-4,4'-di-tert-butyl-1,1'-diphenyl-4,4',5,5'-tetrahydro-1H,1'H-2,2'-biimidazole (**4.3**)

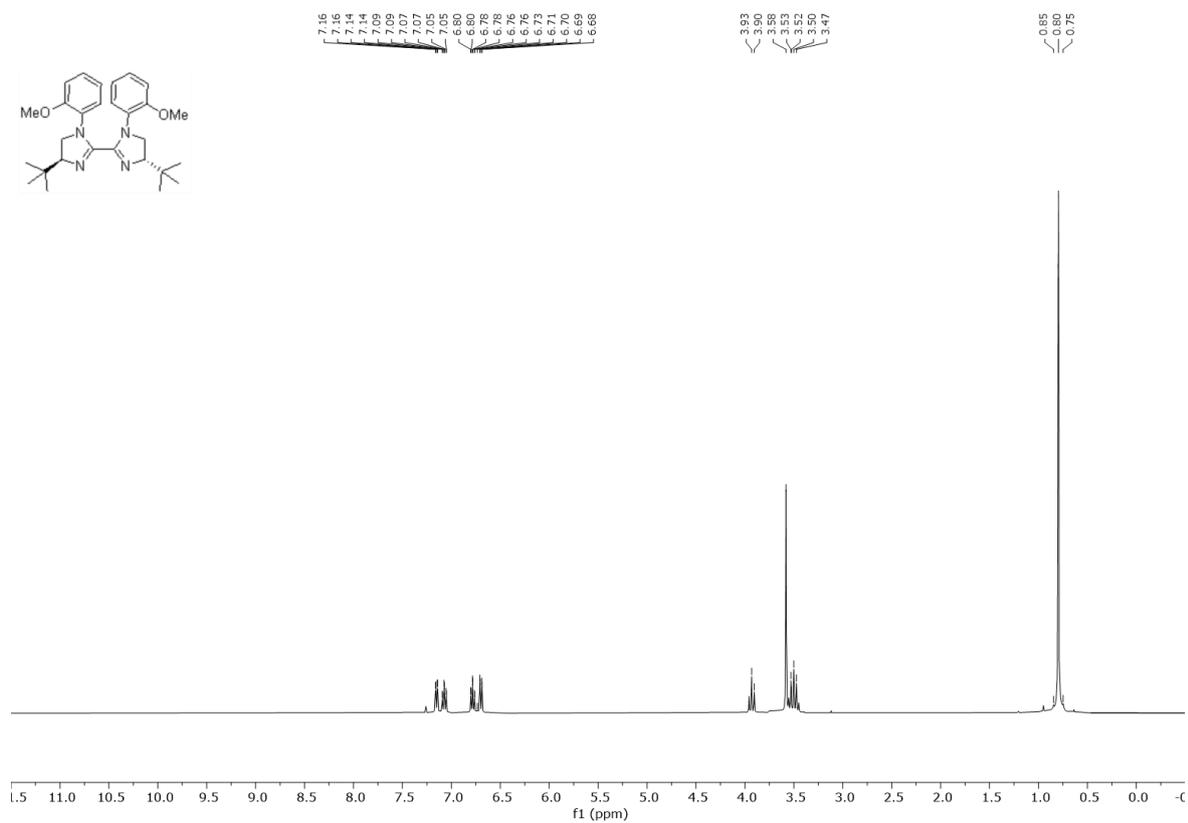
$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )



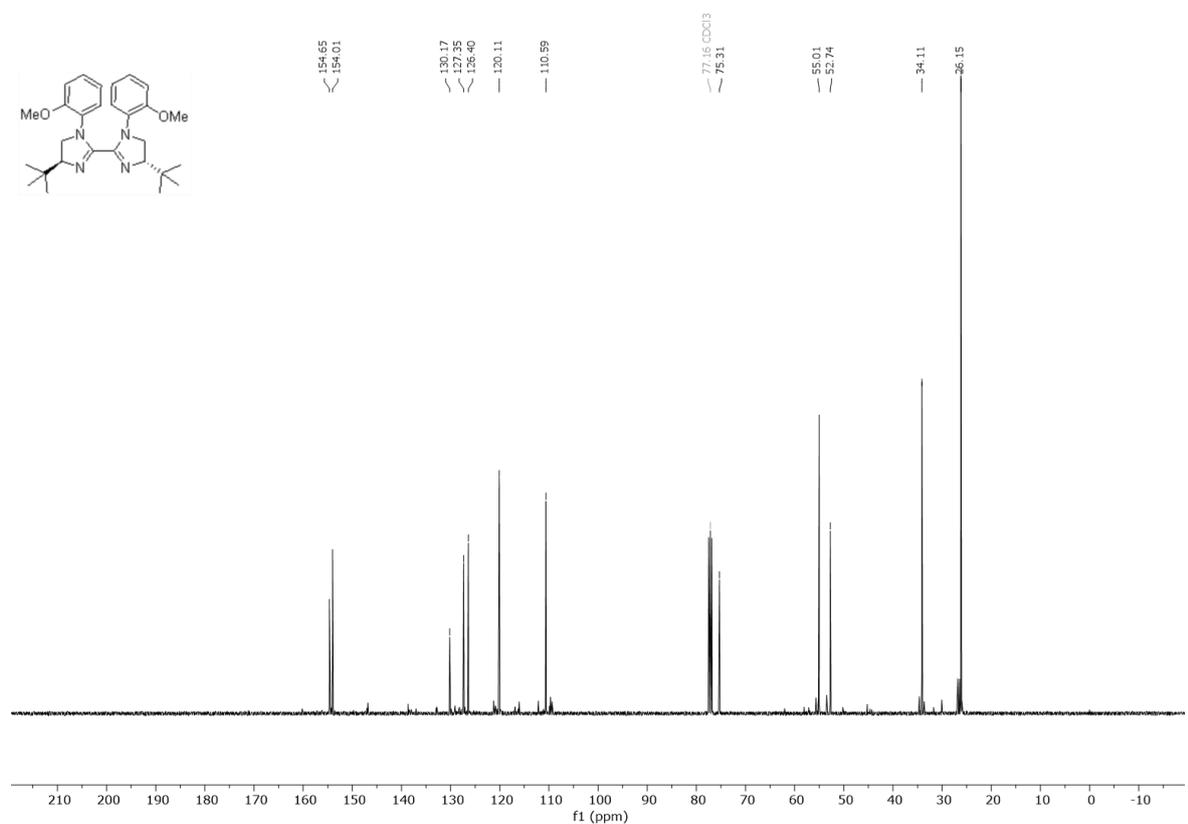
$^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )



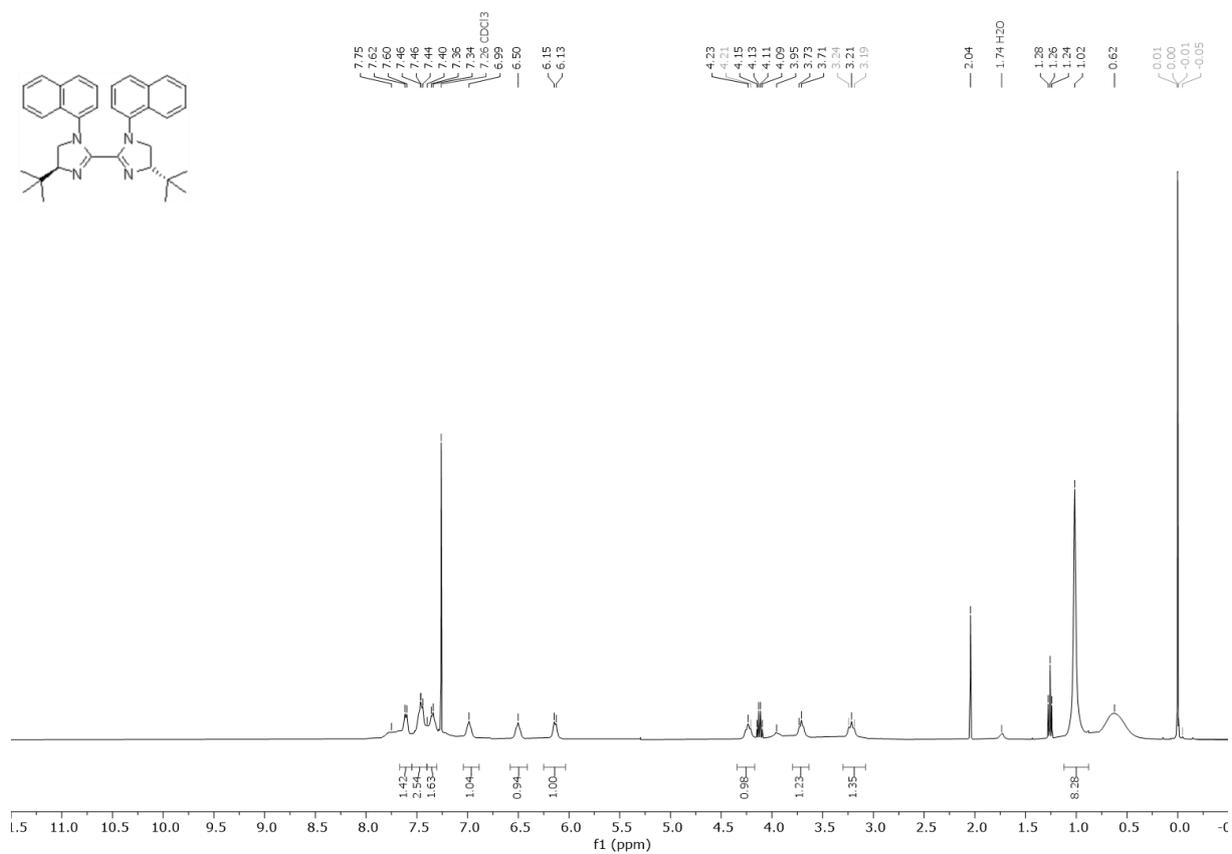
(4*S*,4'*S*)-4,4'-di-*tert*-butyl-1,1'-bis(2-methoxyphenyl)-4,4',5,5'-tetrahydro-1*H*,1'*H*-2,2'-biimidazole (**4.4**),  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )



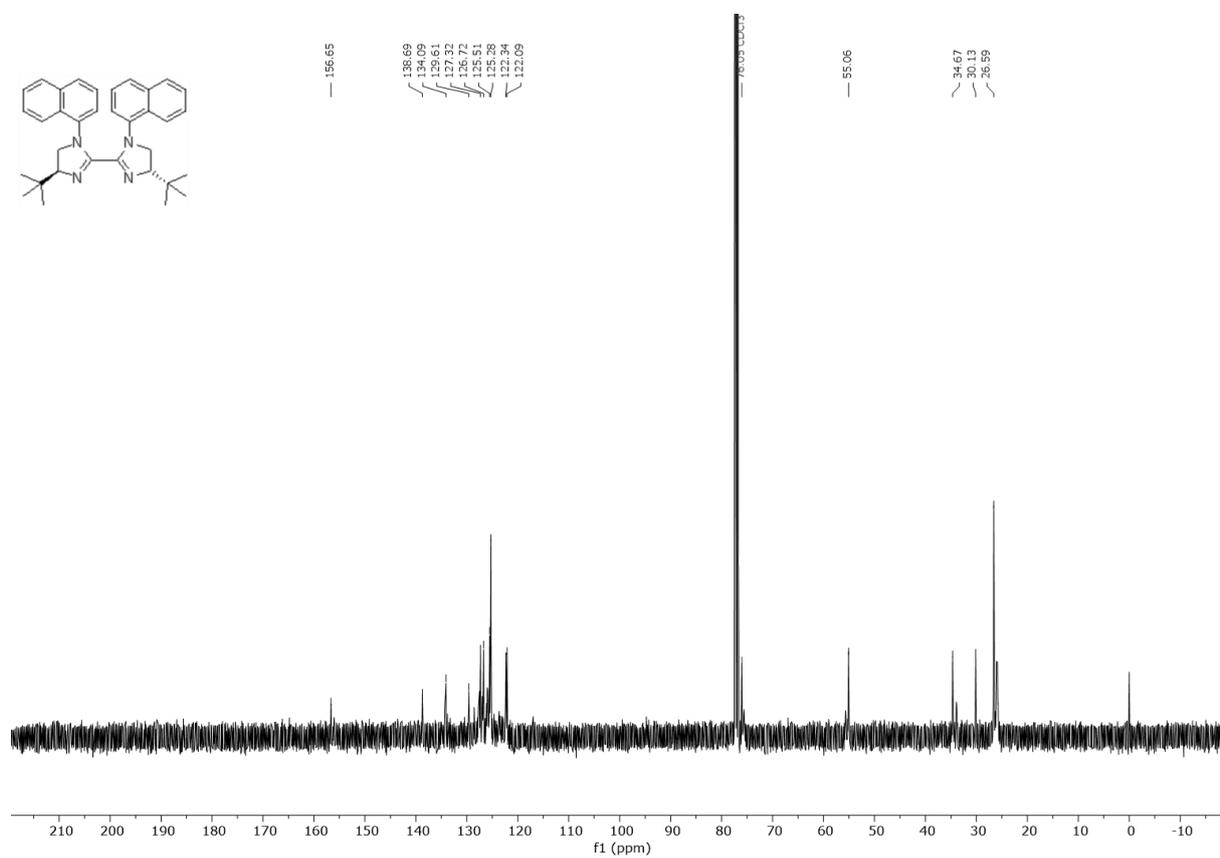
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )



(4*S*,4'*S*)-4,4'-di-tert-butyl-1,1'-di(naphthalen-1-yl)-4,4',5,5'-tetrahydro-1*H*,1'*H*-2,2'-biimidazole (**4.5**), <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)

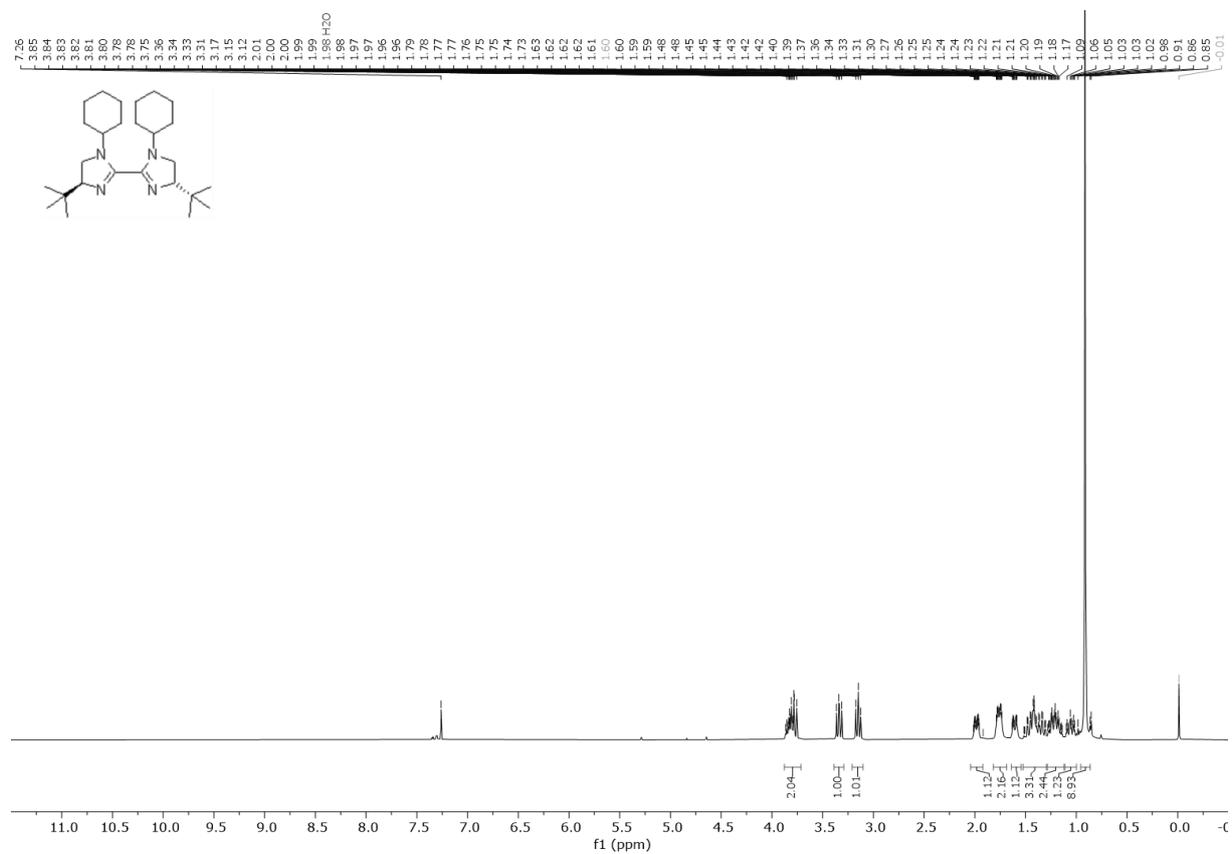


<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)

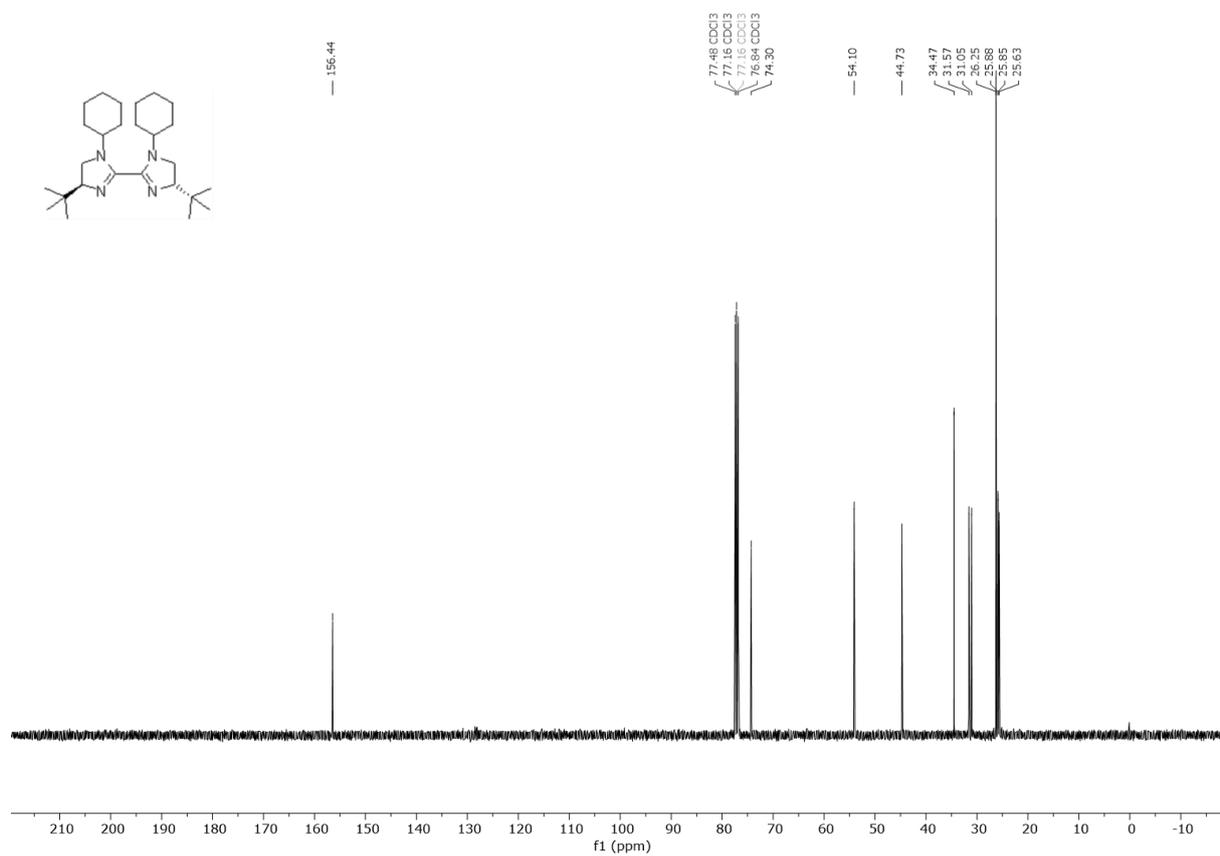


(4*S*,4'*S*)-4,4'-di-tert-butyl-1,1'-dicyclohexyl-4,4',5,5'-tetrahydro-1*H*,1'*H*-2,2'-biimidazole (**4.6**),

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)

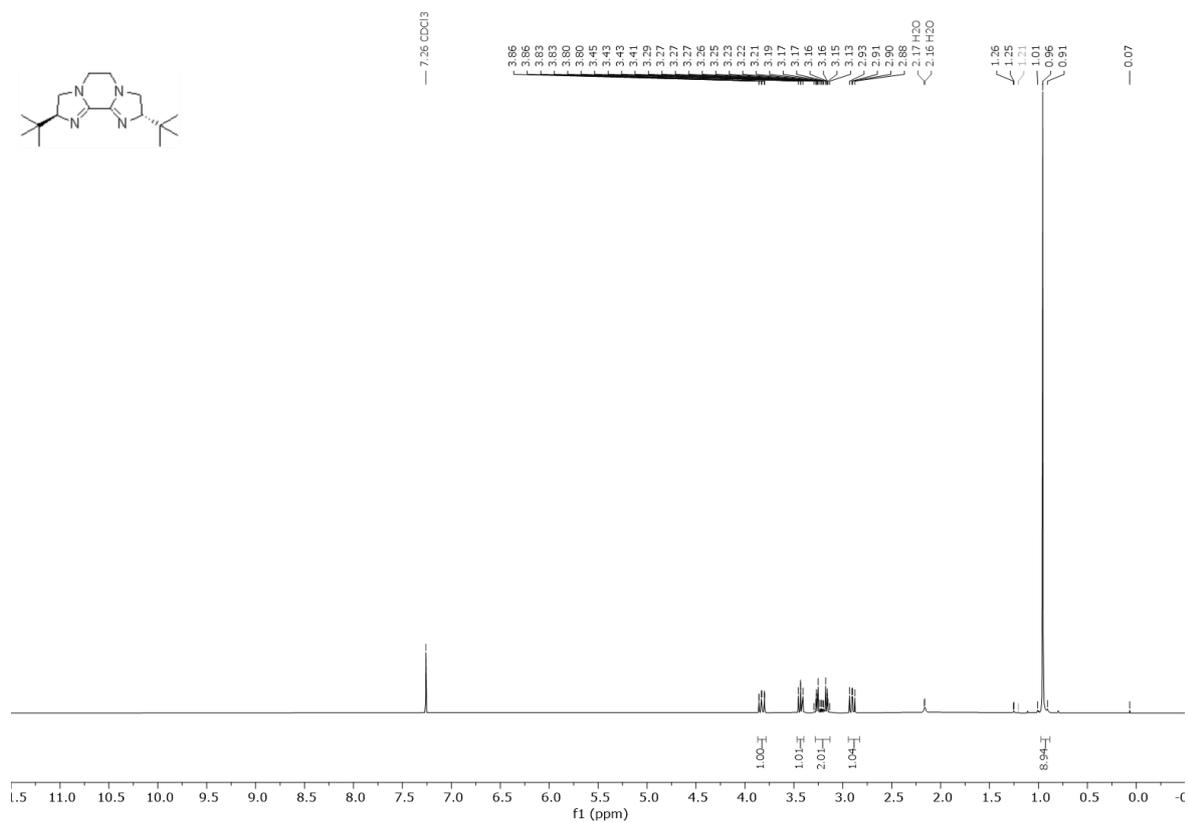


<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)

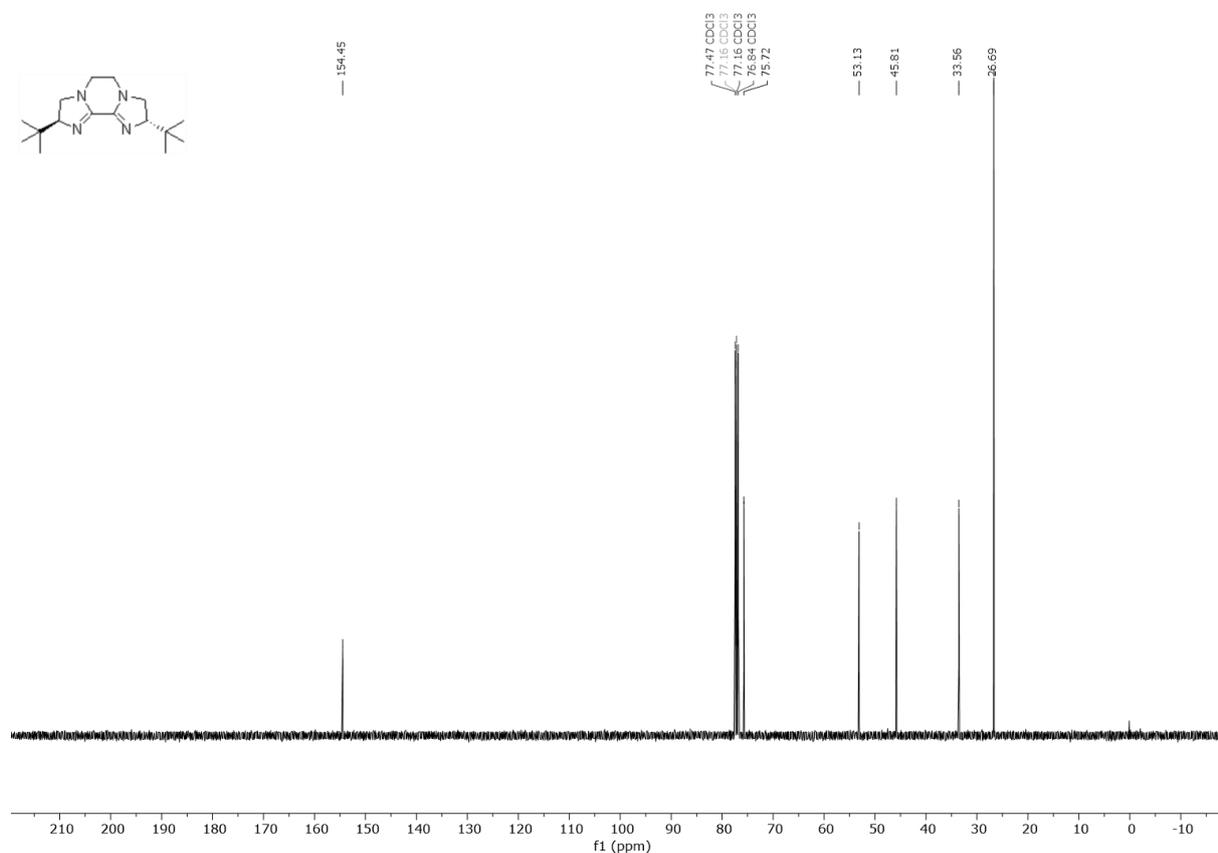


(2*S*,9*S*)-2,9-di-tert-butyl-2,3,5,6,8,9-hexahydroimidazo[1,2-*a*:2',1'-*c*]pyrazine (**4.7**)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)

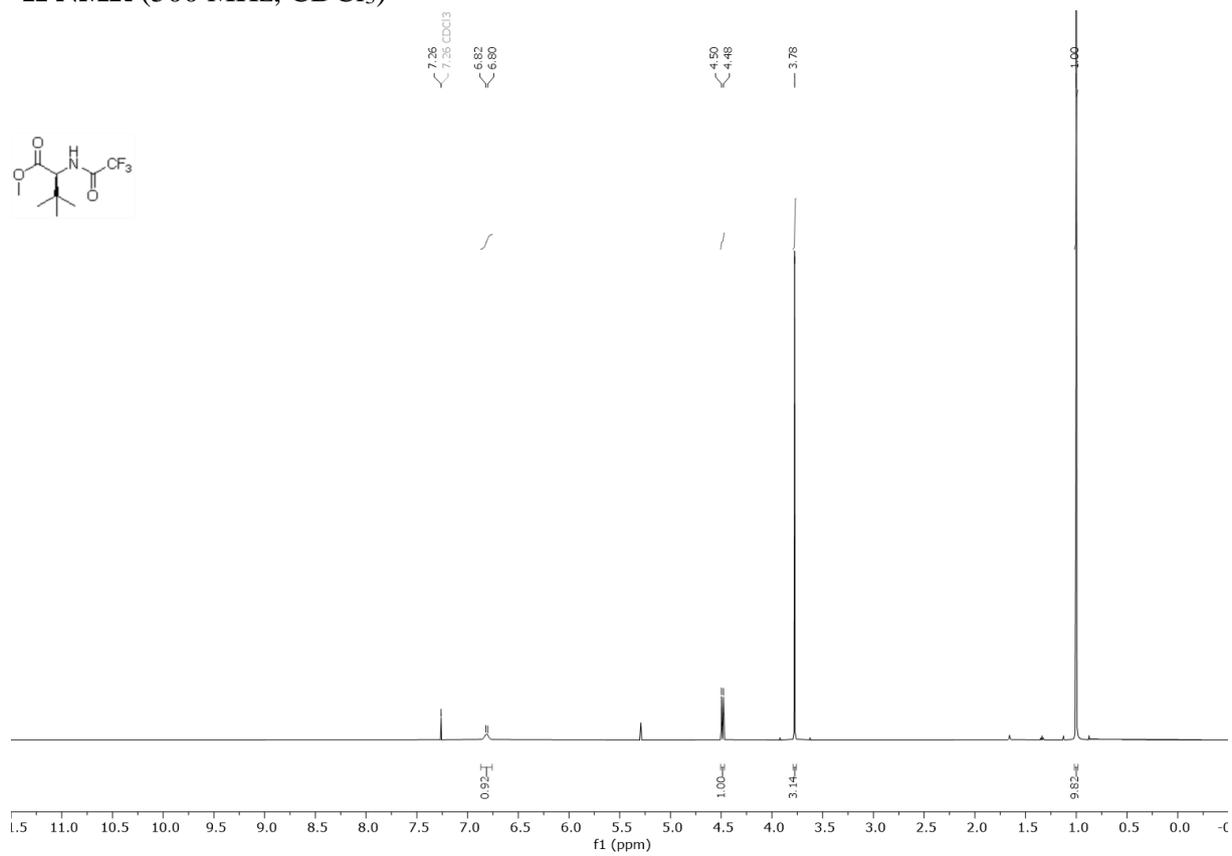


<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)

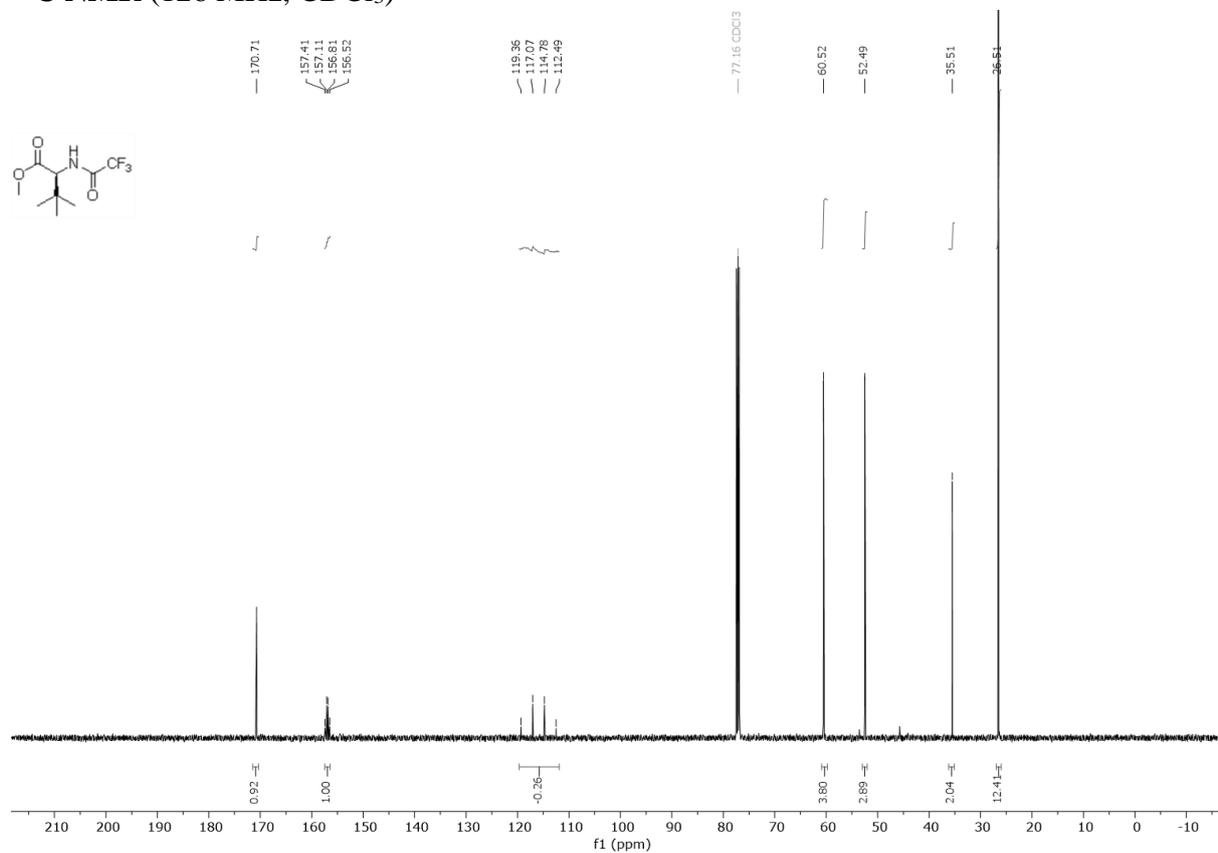


Methyl *N*-TFA *L*-*tert*-leucinate (**4.15**)

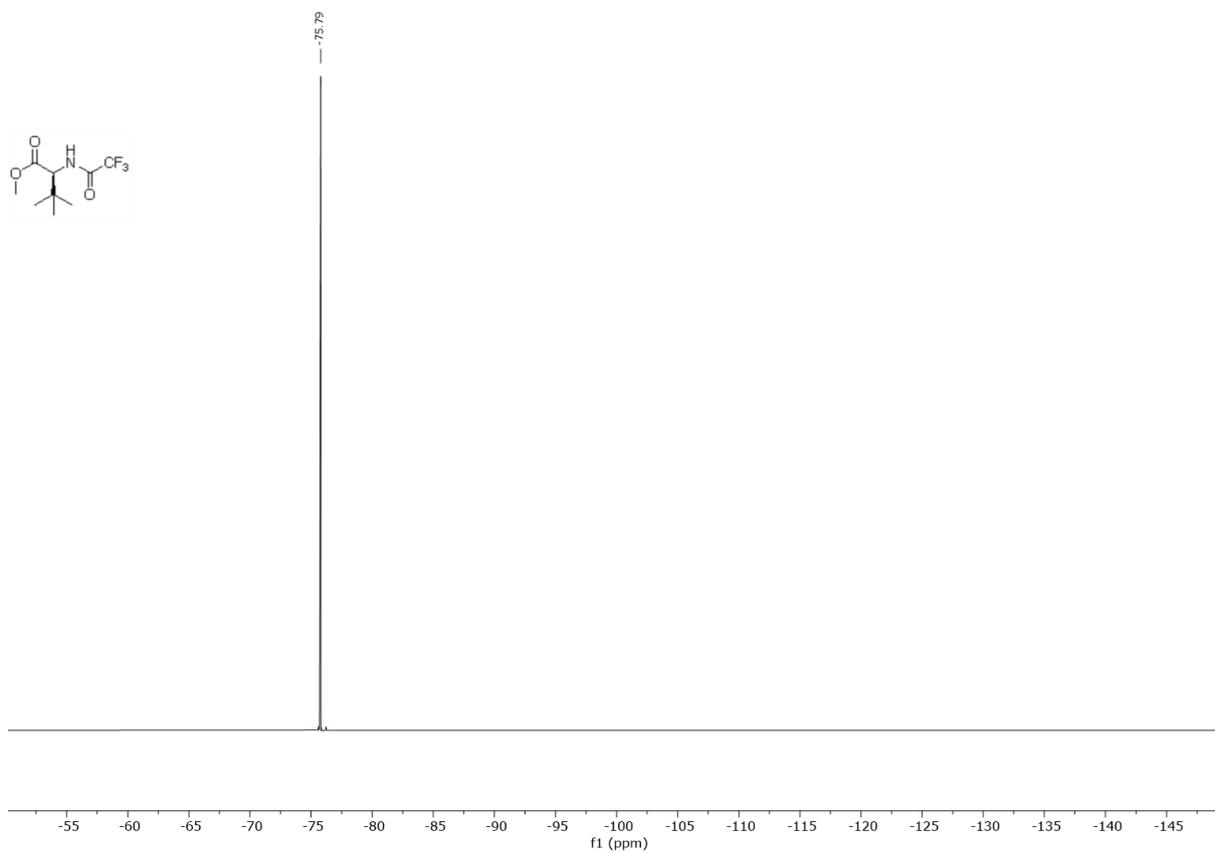
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )



$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )

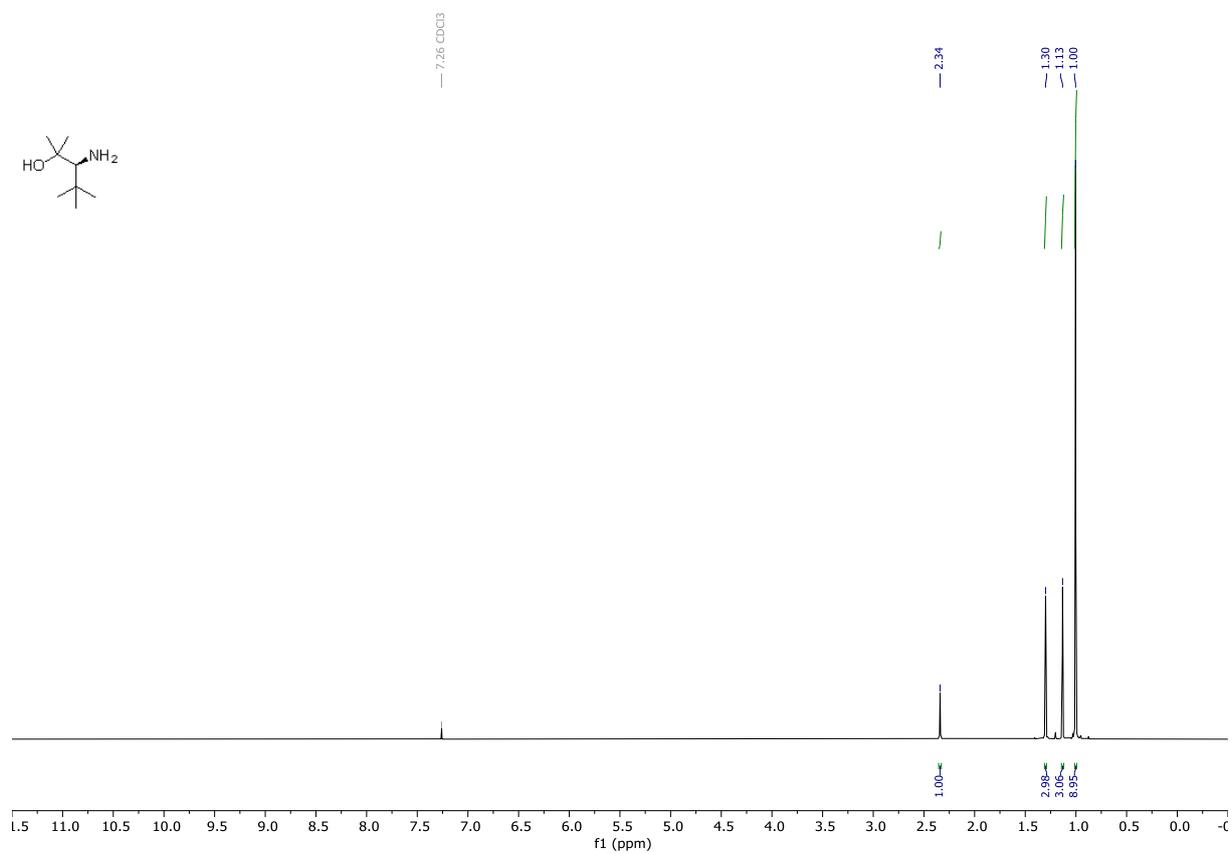


**$^{19}\text{F}$  { $^1\text{H}$ } NMR (471 MHz,  $\text{CDCl}_3$ )**

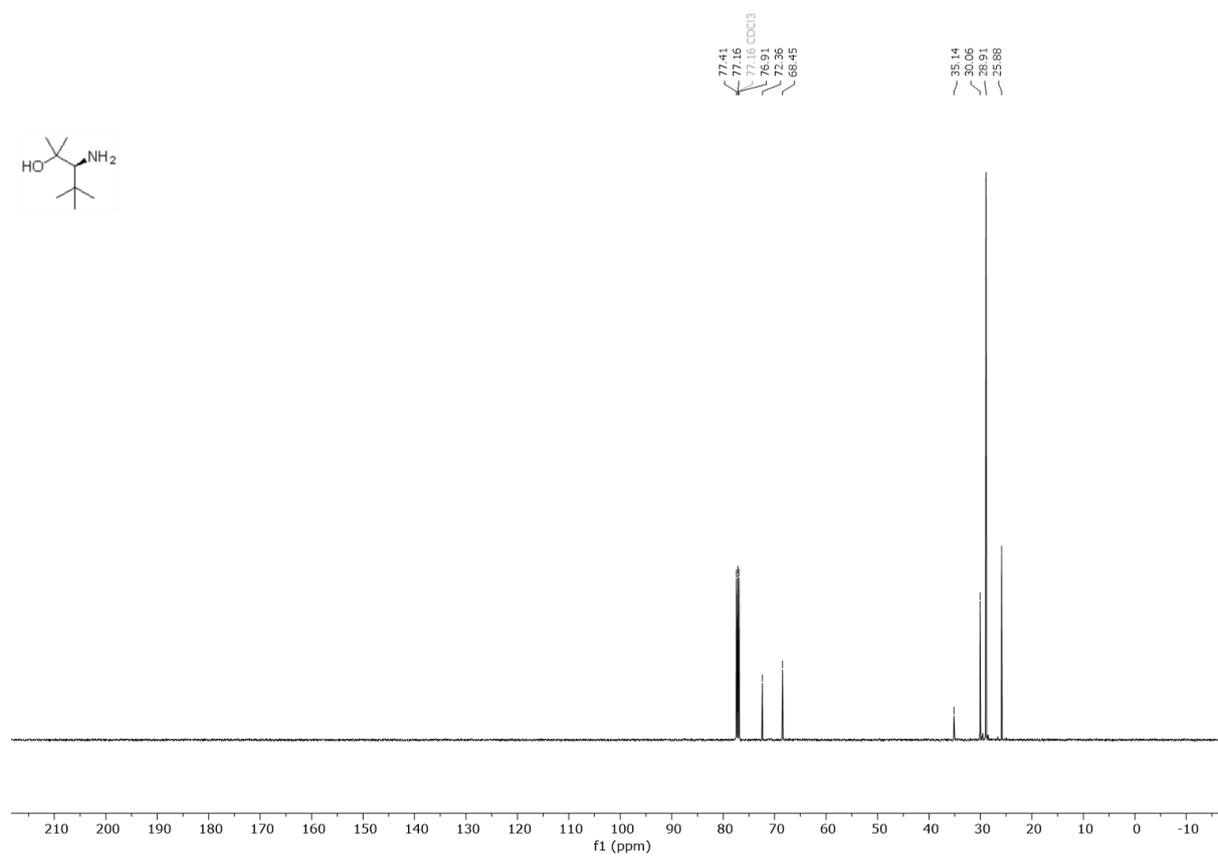


(S)-3-amino-2,4,4-trimethylpentan-2-ol (**4.12**)

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )

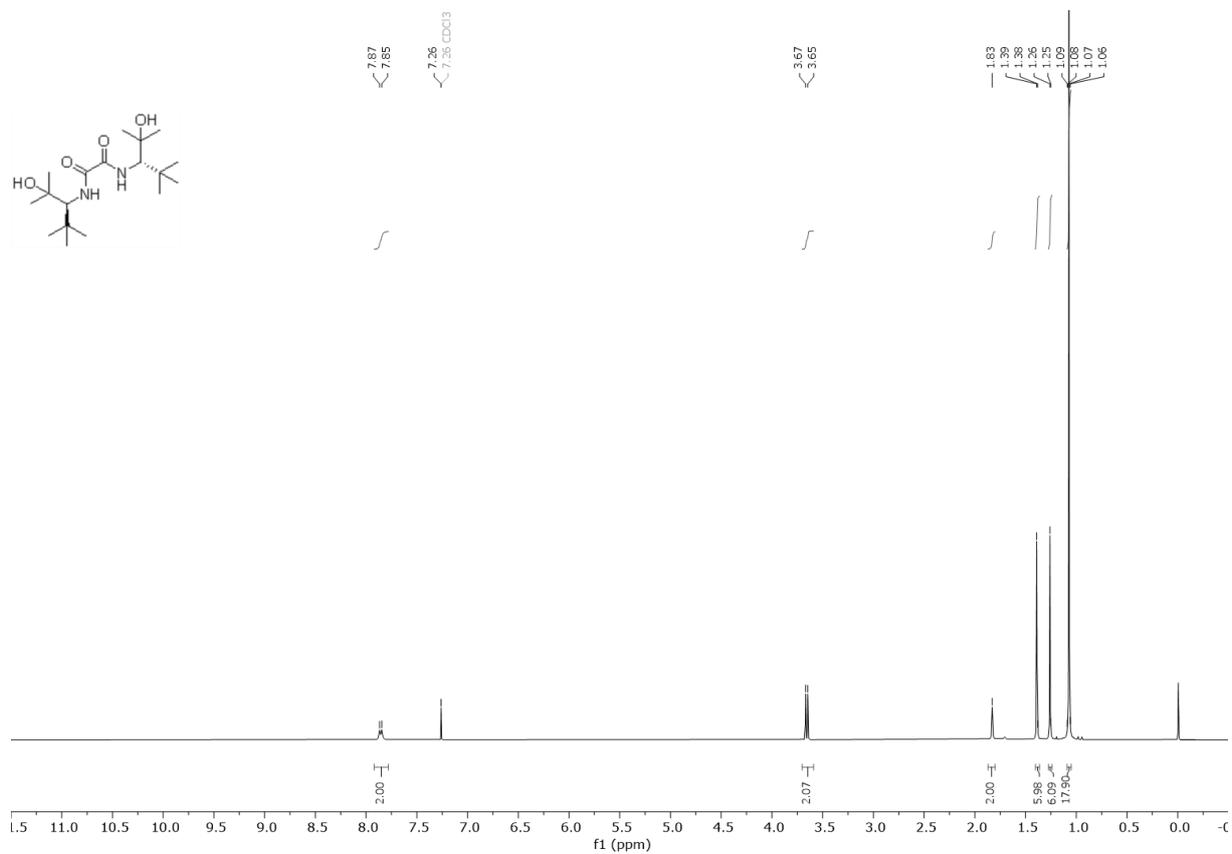


$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )

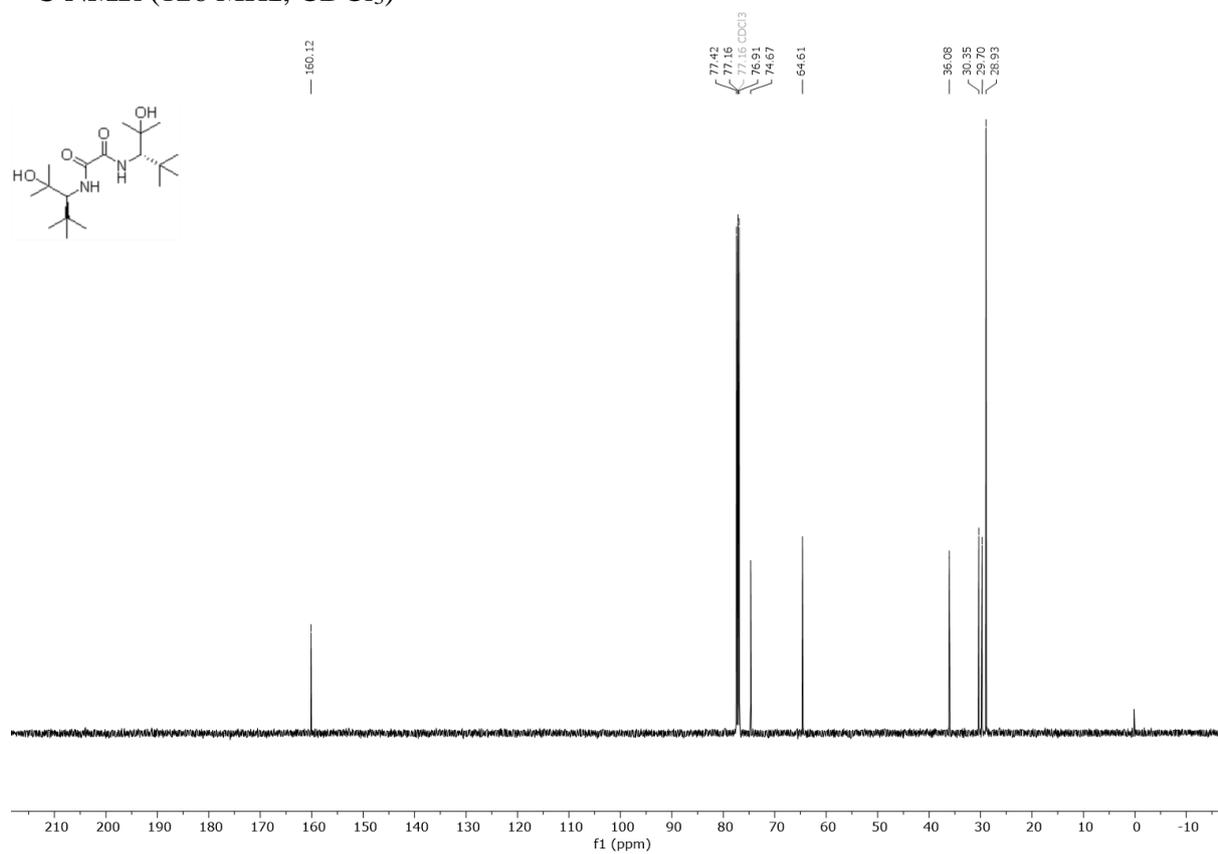


(S)-N,N'-Bis[2-hydroxy-2,4,4-trimethylpentan-3-yl]oxalamide (**4.11**)

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )

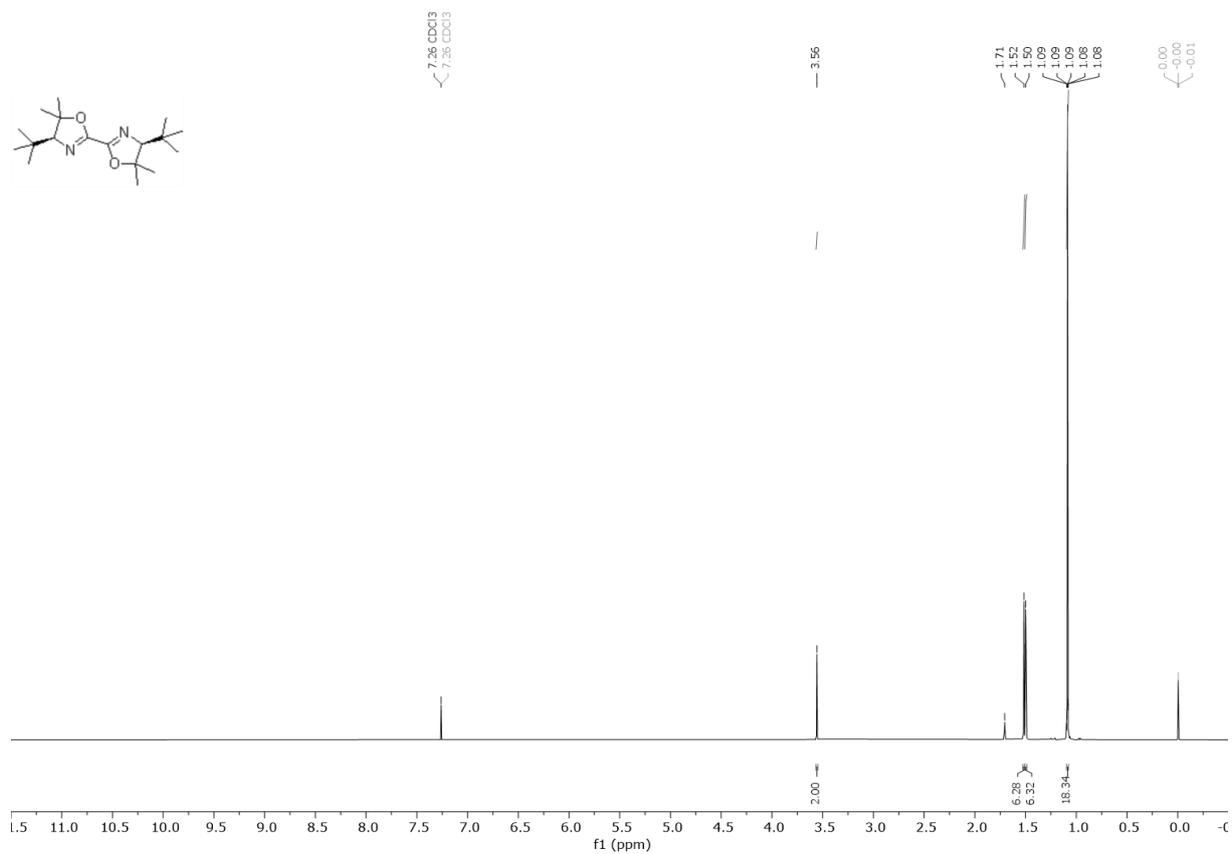


$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )

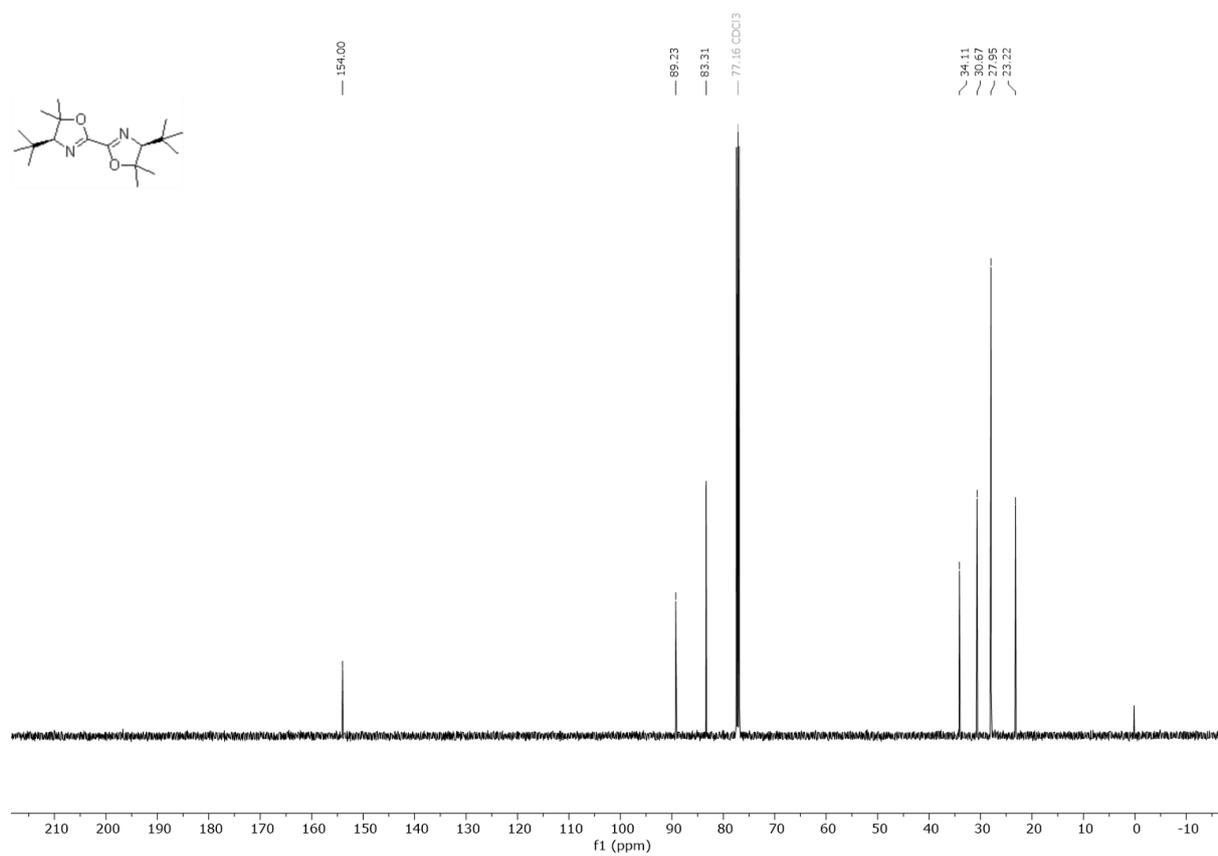


(4*S*,4'*S*)-4,4'-di-*tert*-butyl-5,5,5',5'-tetramethyl-4,4',5,5'-tetrahydro-2,2'-bioxazole (**4.10**)

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)

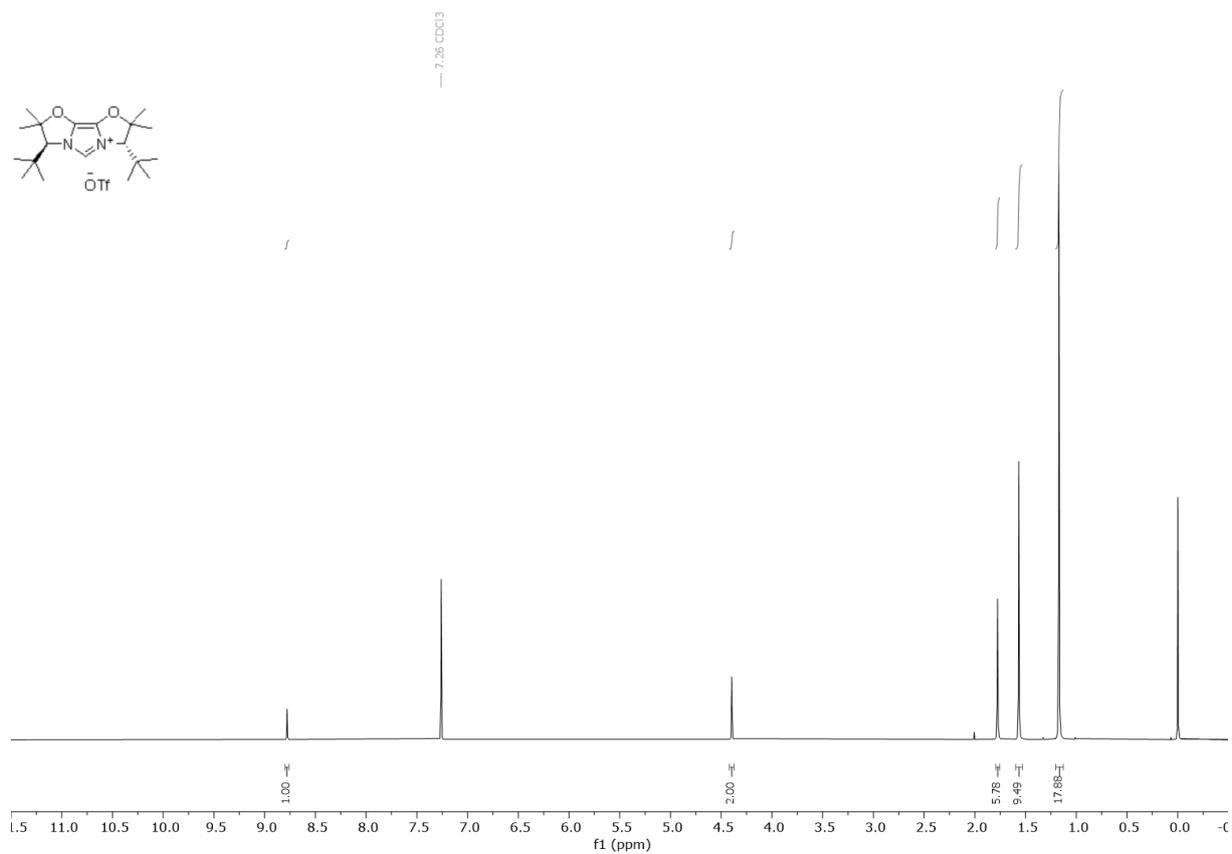


<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)

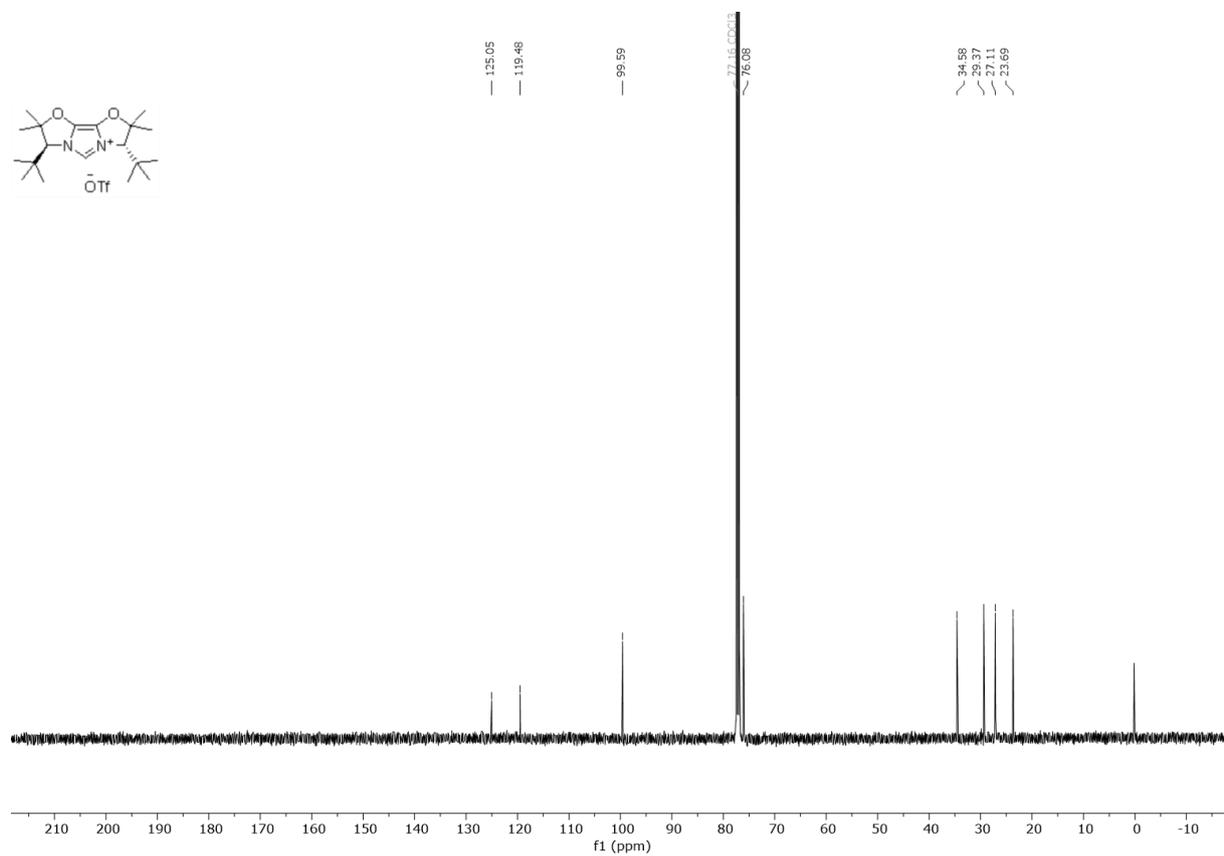


IBiox*t*BuMe<sub>4</sub> HOTf (**4.9**)

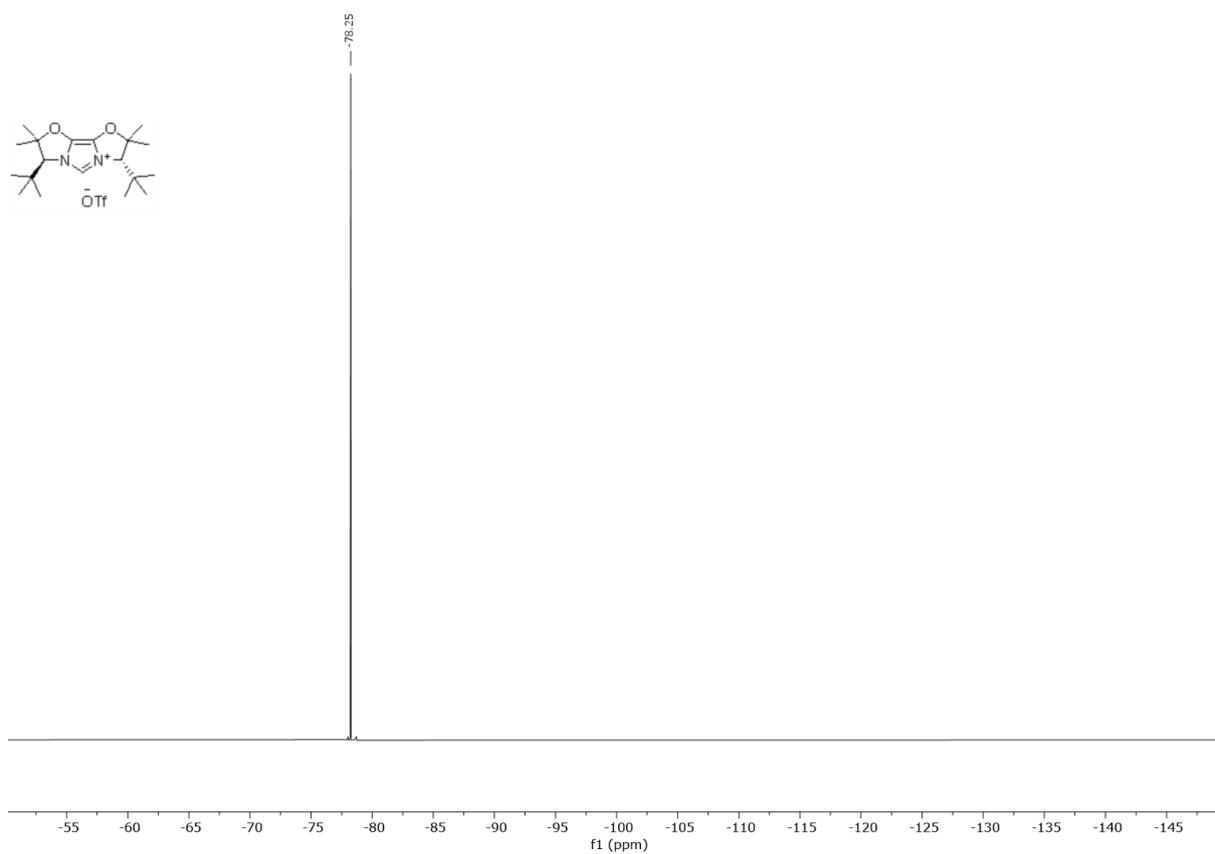
<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)



<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)

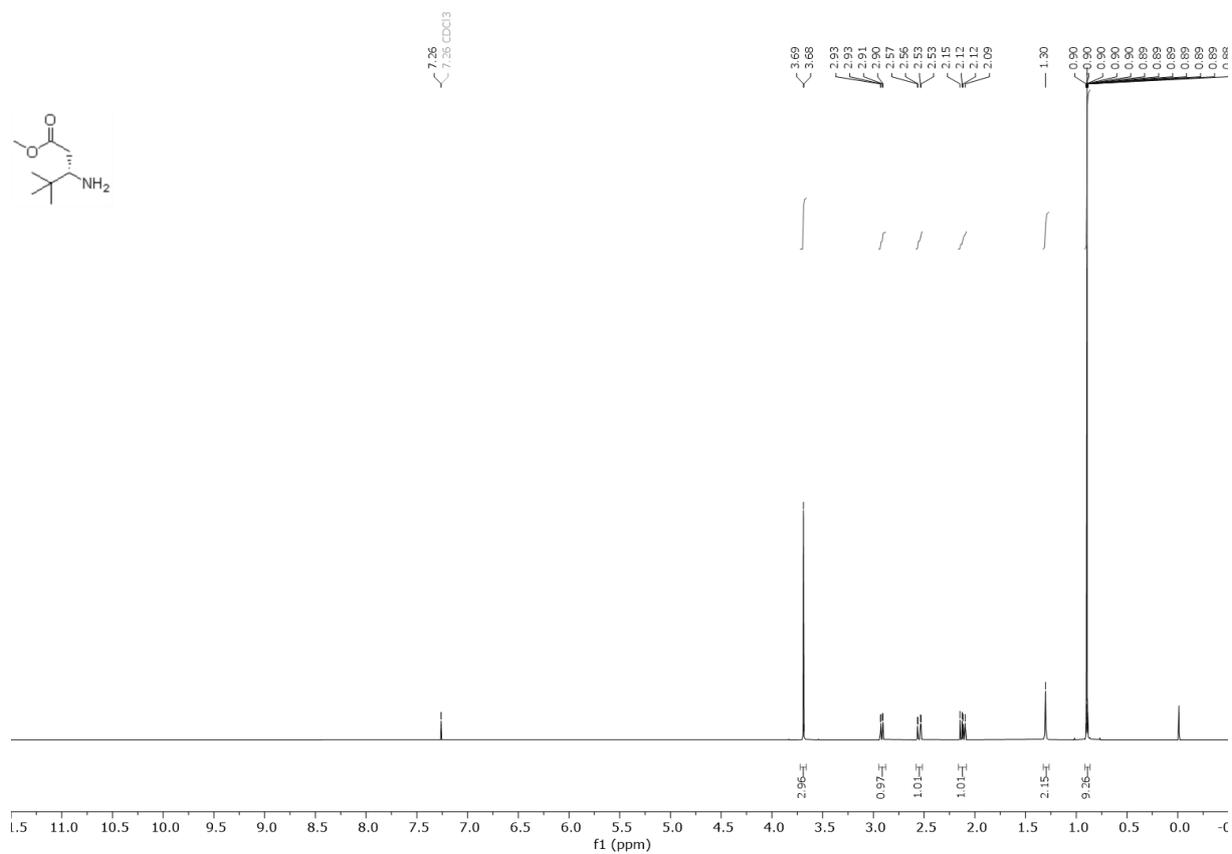


**$^{19}\text{F}$  { $^1\text{H}$ } NMR (471 MHz,  $\text{CDCl}_3$ )**

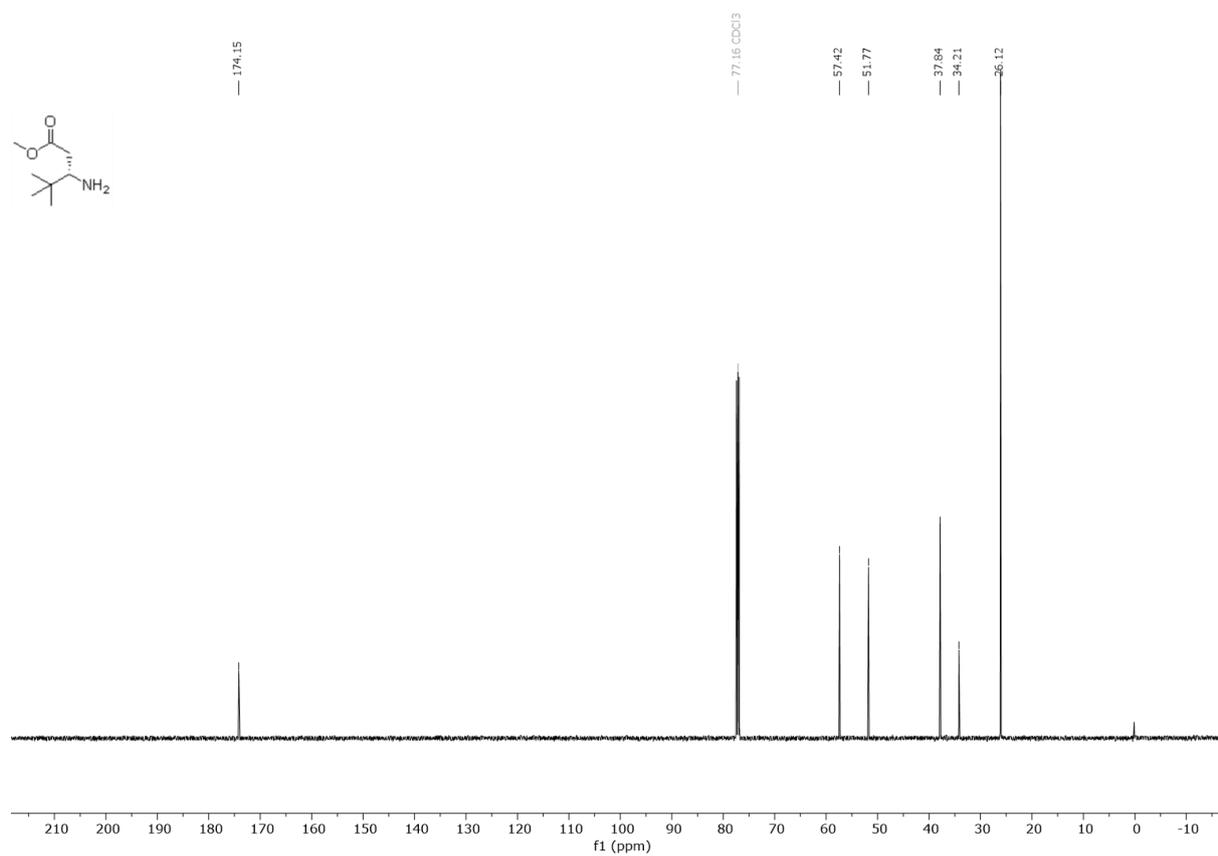


methyl (S)-3-amino-4,4-dimethylpentanoate (**4.31**)

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )

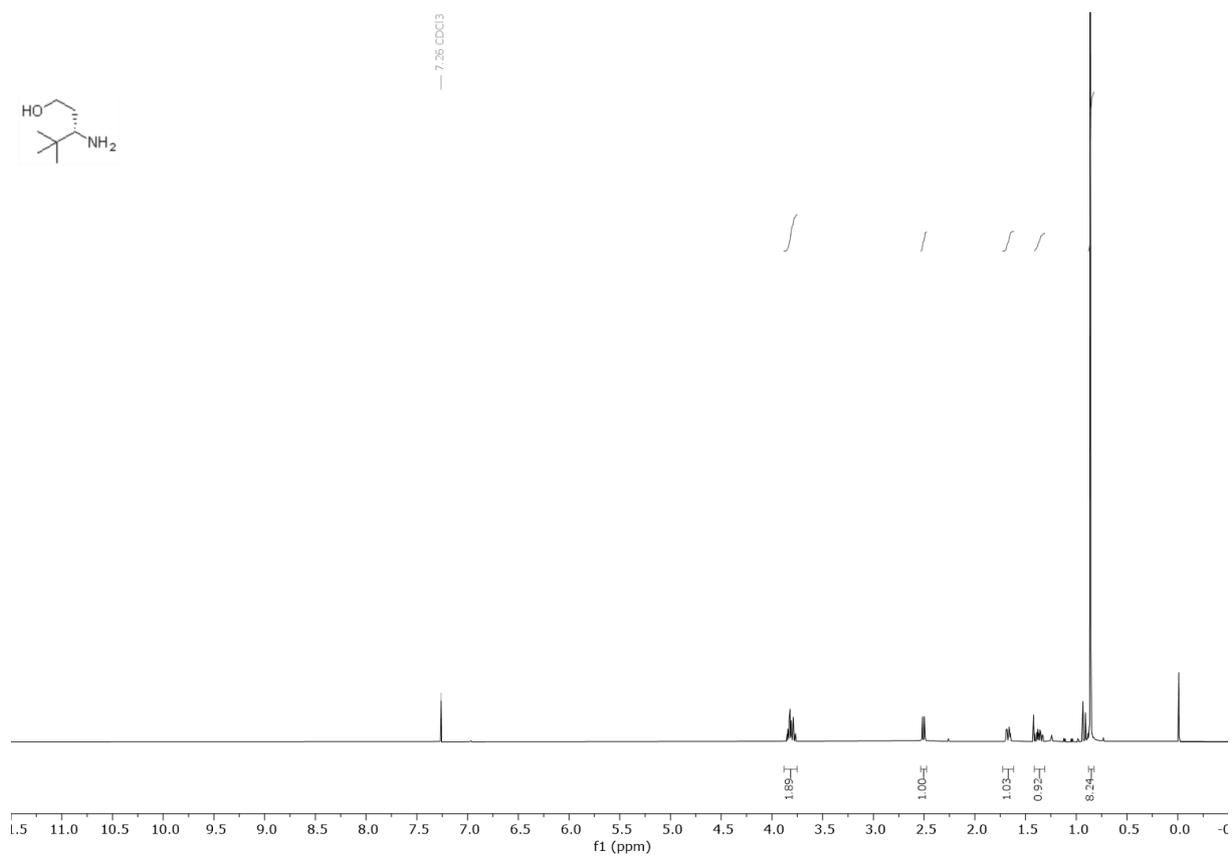


$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )

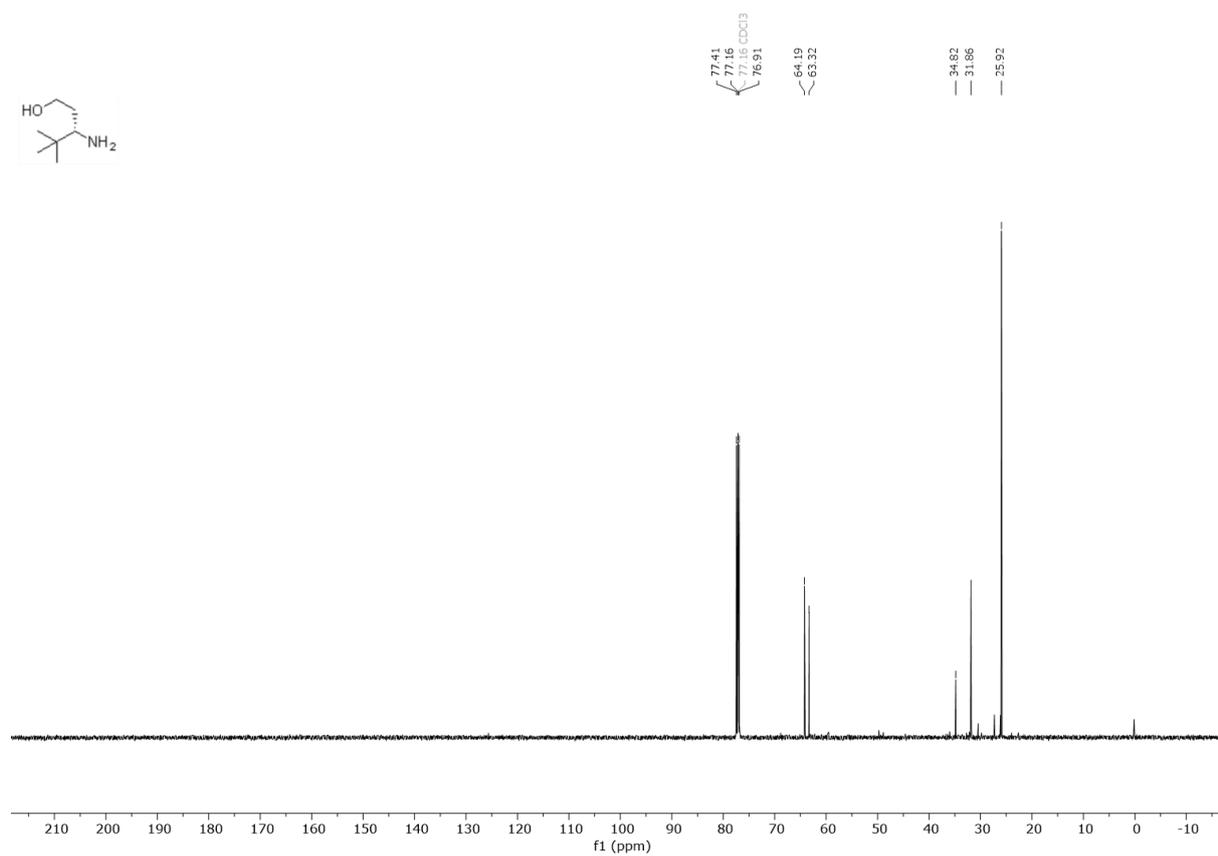


(S)-3-amino-4,4-dimethylpentan-1-ol (**4.53**)

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )

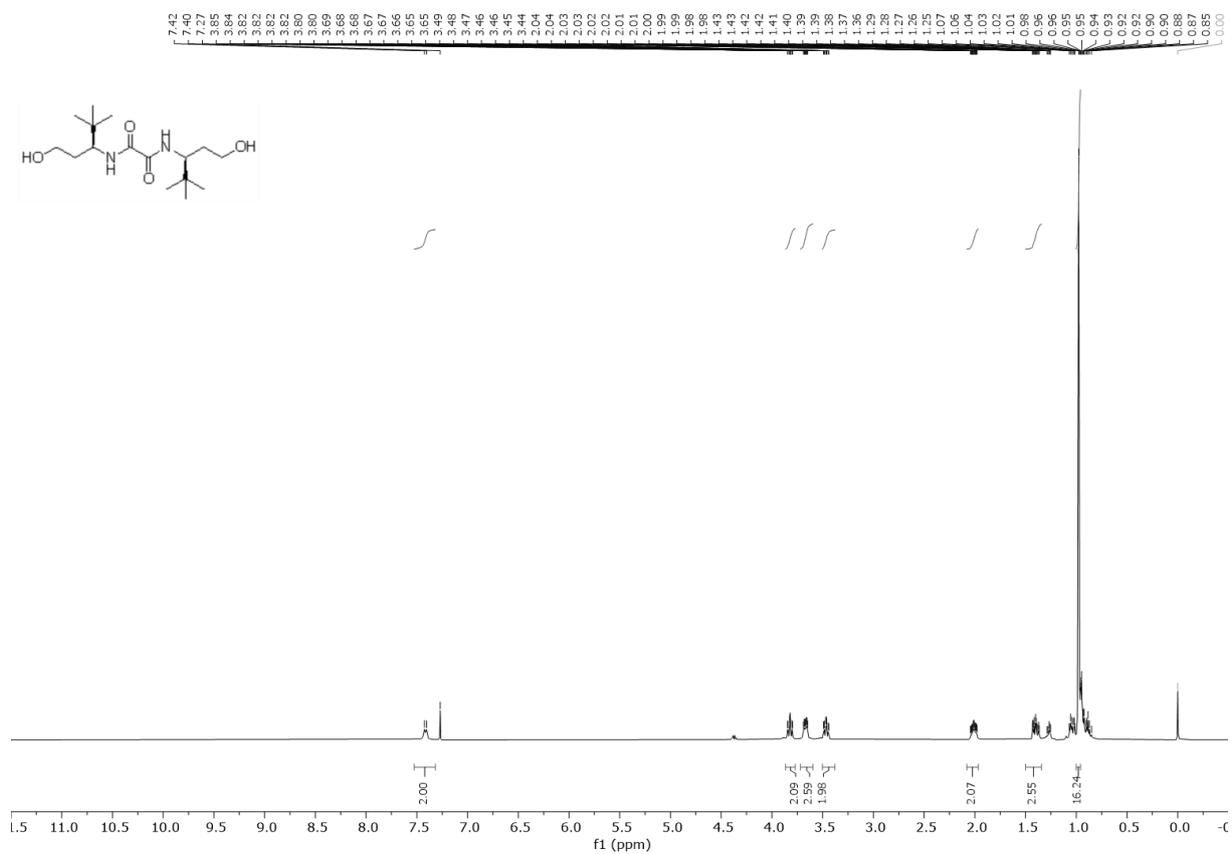


$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )

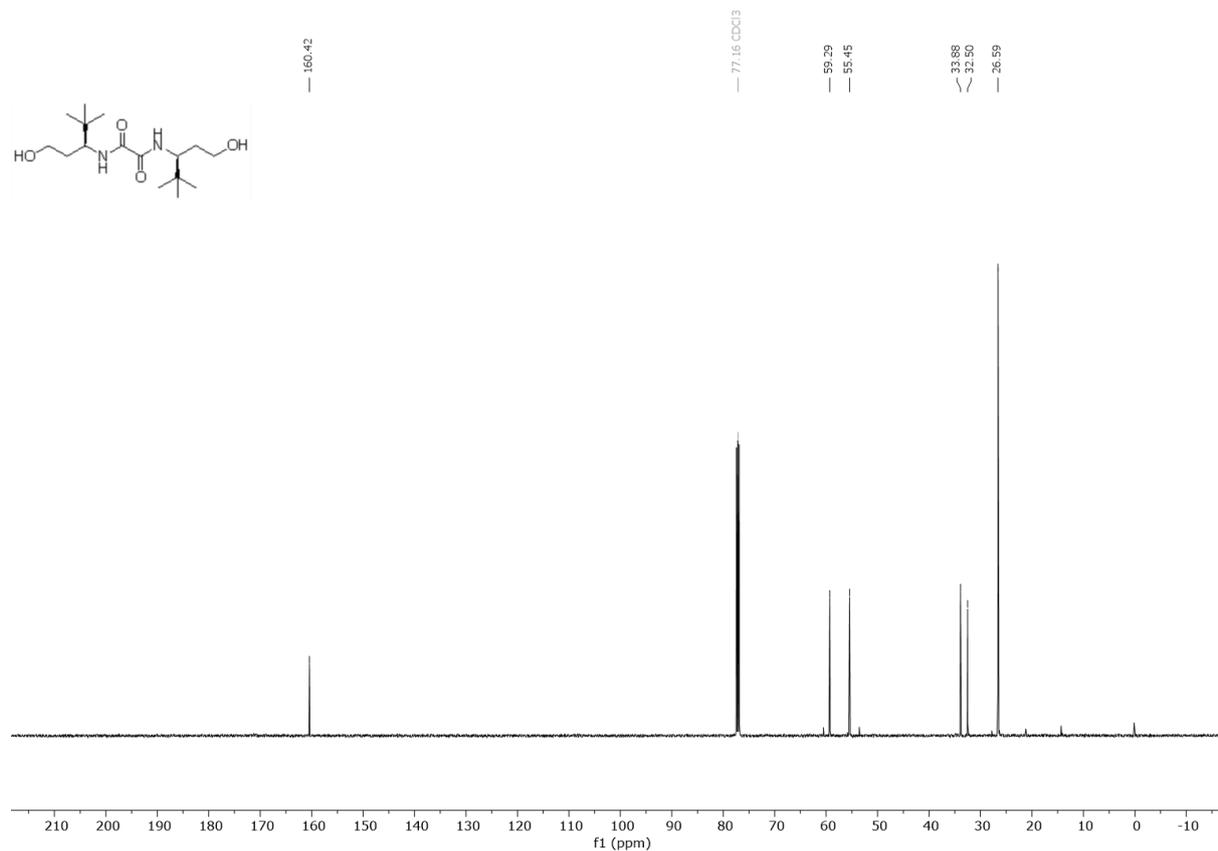


*N*<sup>1</sup>,*N*<sup>2</sup>-bis((S)-1-hydroxy-4,4-dimethylpentan-3-yl)oxalamide (**4.20**)

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)

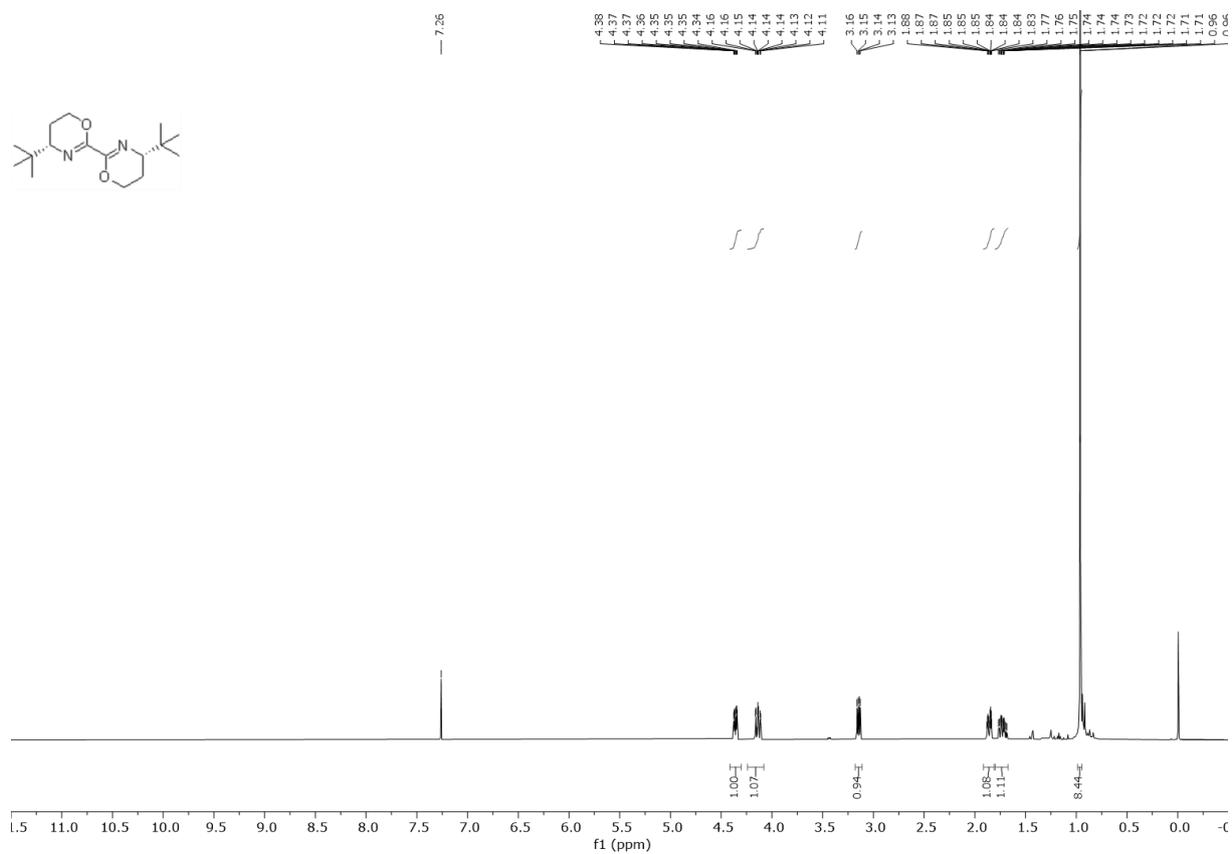


<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)

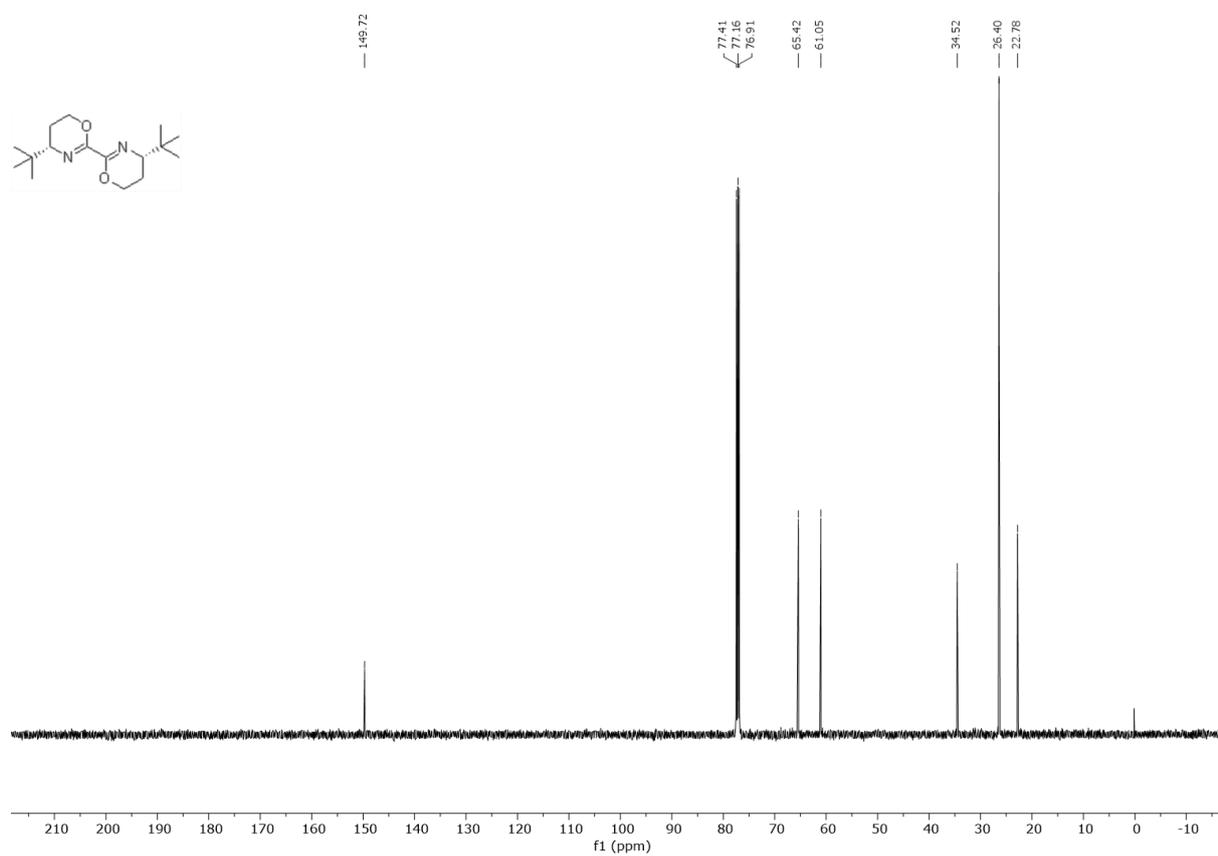


(4*S*,4'*S*)-4,4'-di-*tert*-butyl-5,5',6,6'-tetrahydro-4*H*,4'*H*-2,2'-bi(1,3-oxazine) (**4.19**)

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)

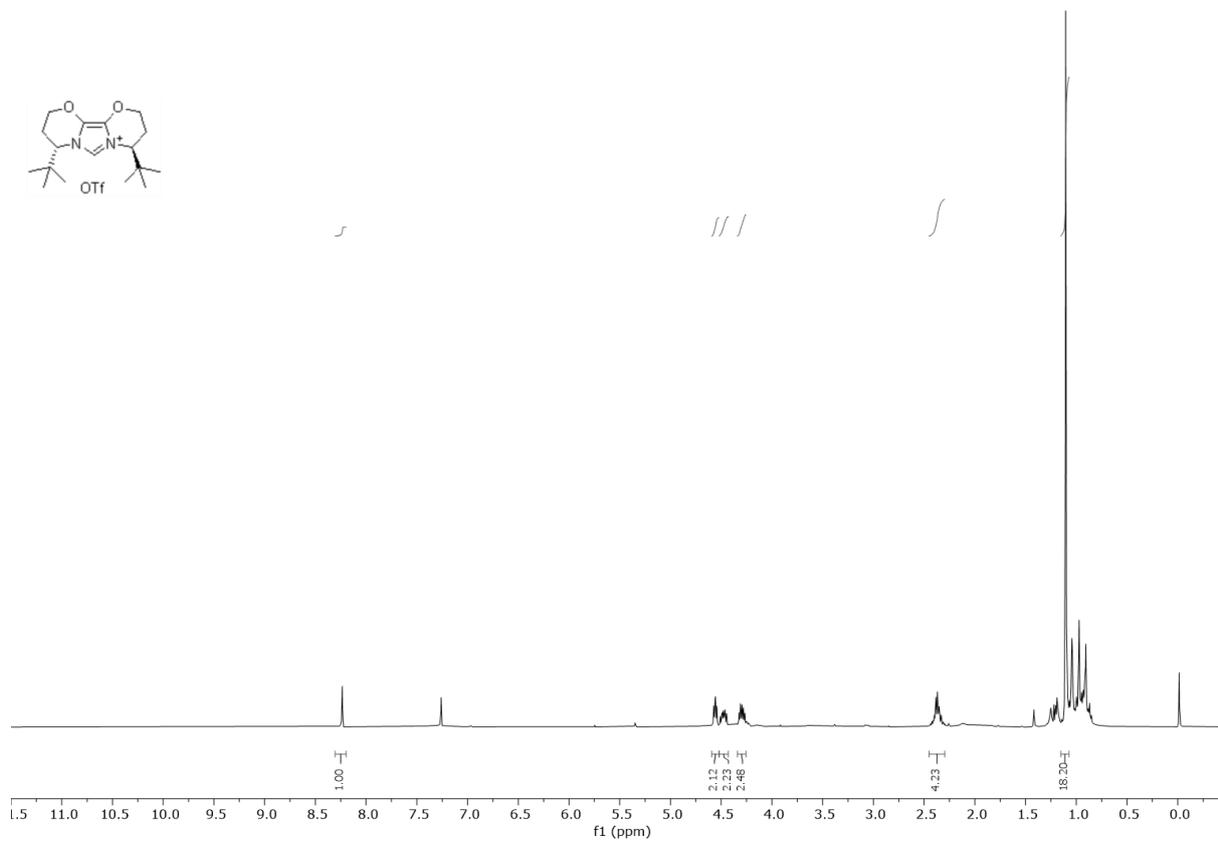


<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)

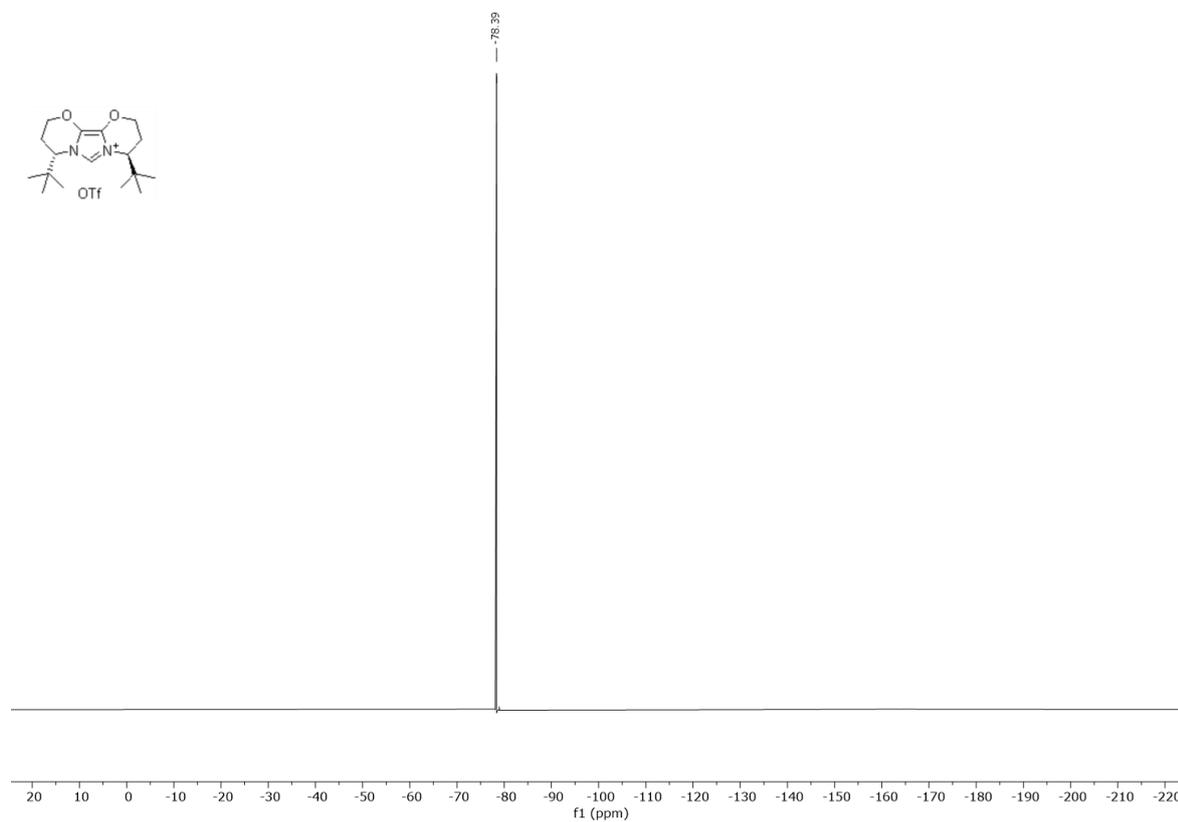


IBiox6tBu HOTf (**4.18**)

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )

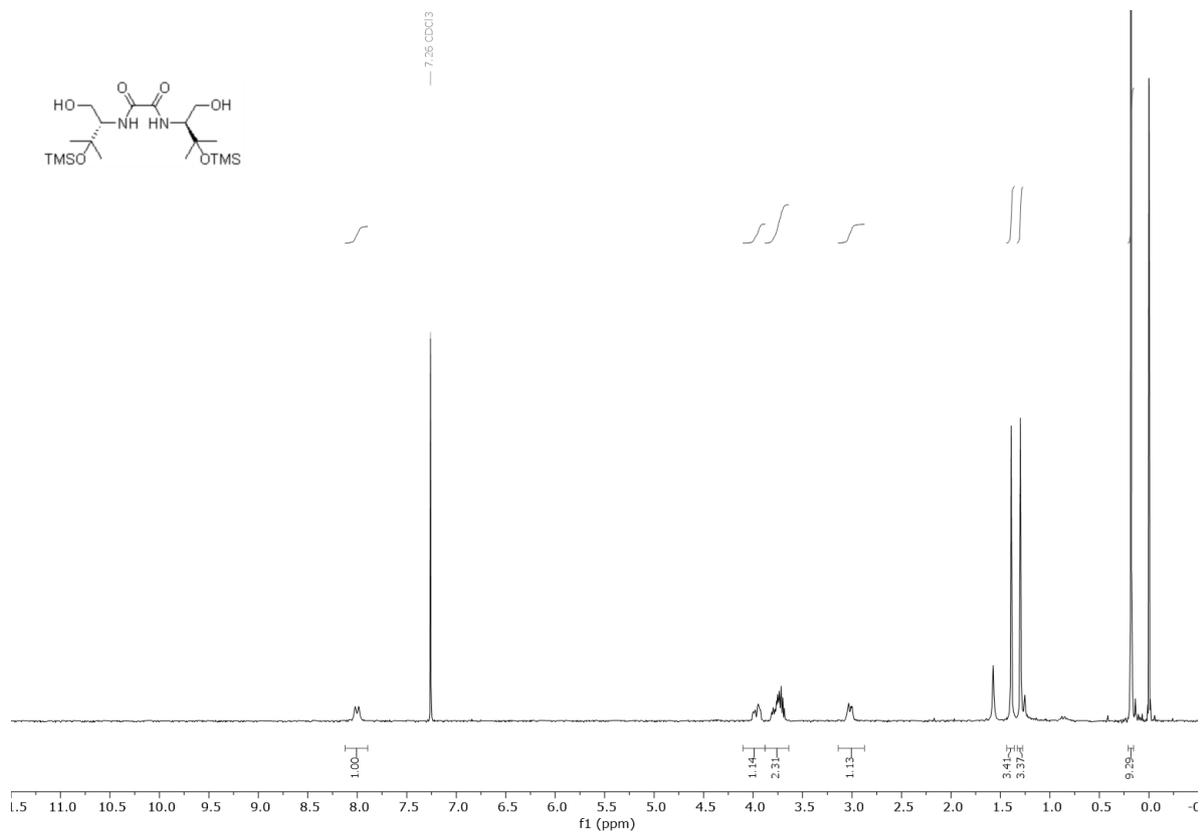


$^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )

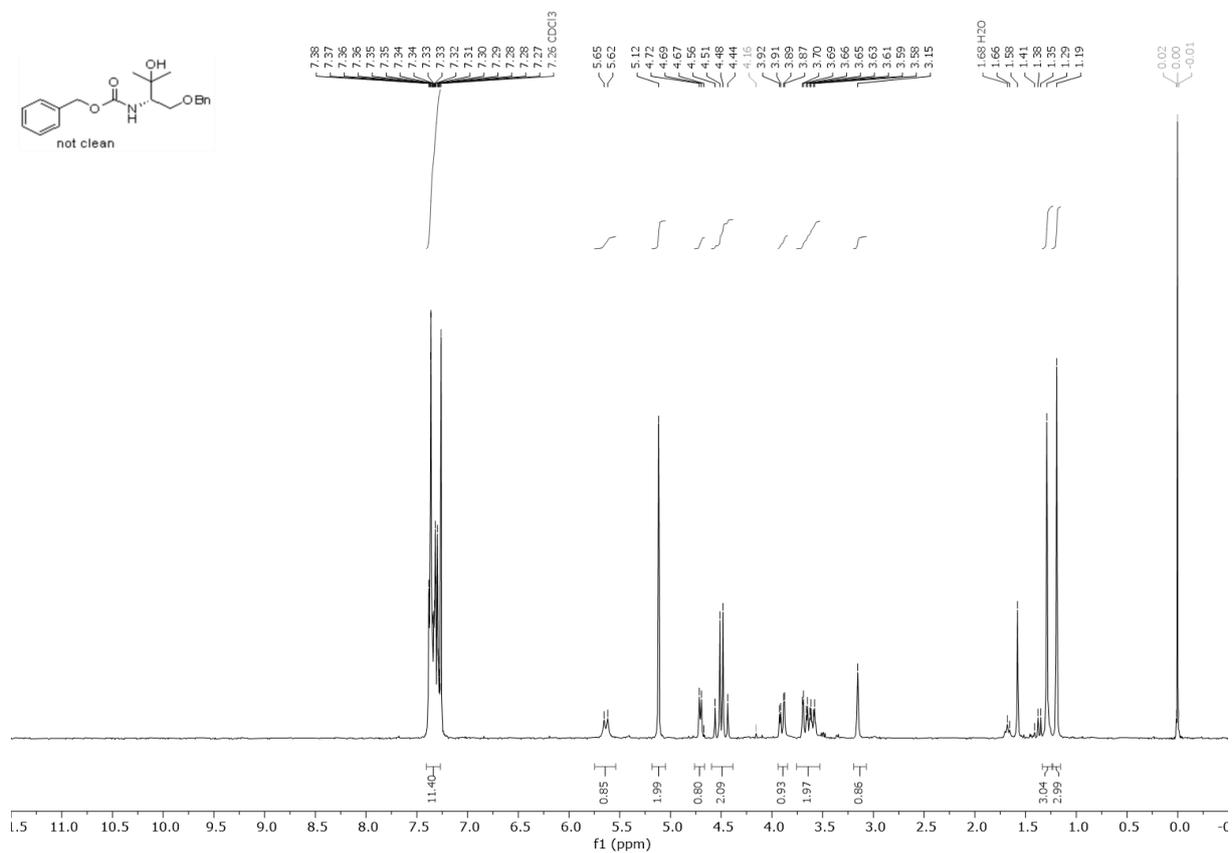


*N*<sup>1</sup>,*N*<sup>2</sup>-bis((*S*)-1-hydroxy-3-methyl-3-((trimethylsilyl)oxy)butan-2-yl)oxalamide (**4.45**)

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>)

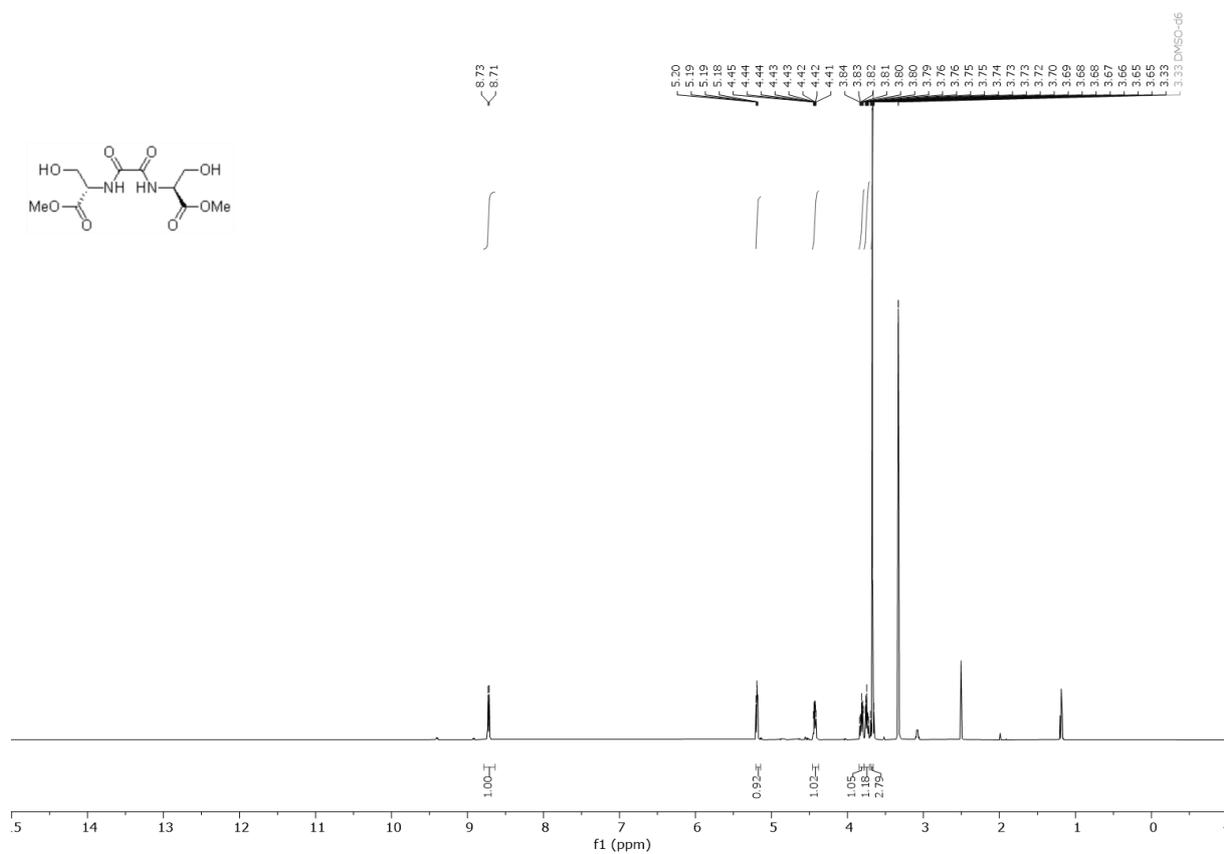


benzyl (*S*)-(1-(benzyloxy)-3-hydroxy-3-methylbutan-2-yl)carbamate (**4.47**)

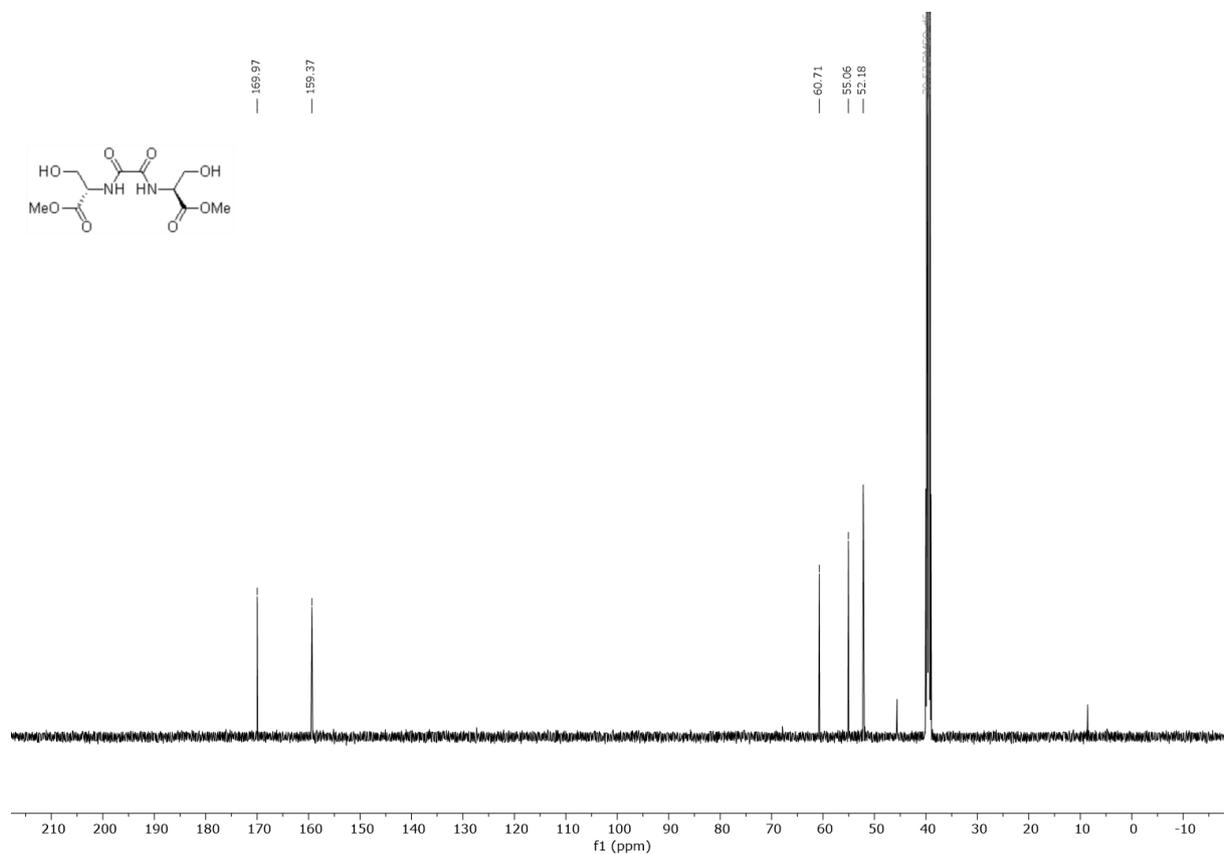


(S)-N,N'-Bis(2-hydroxy-1-methoxycarbonyl)ethyl)oxamide (**4.49**)

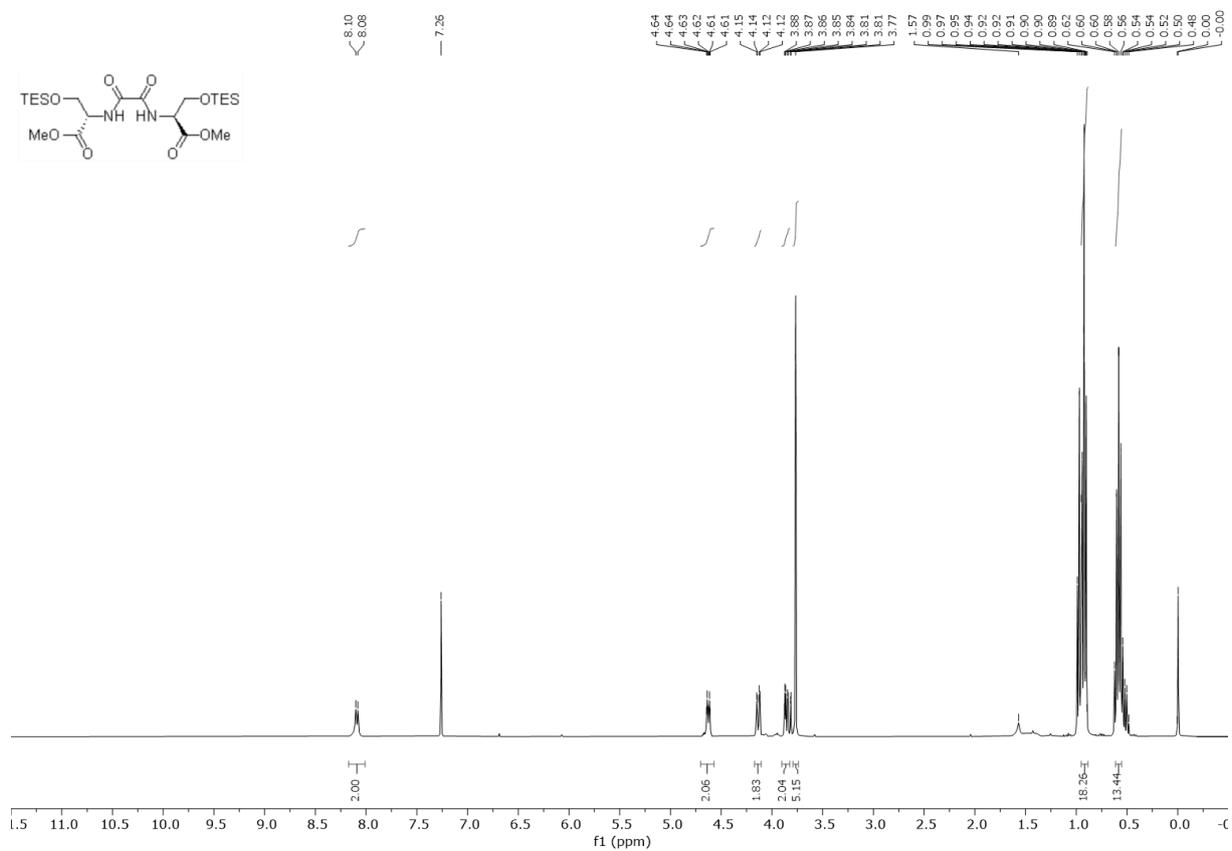
<sup>1</sup>H NMR (500 MHz, DMSO)



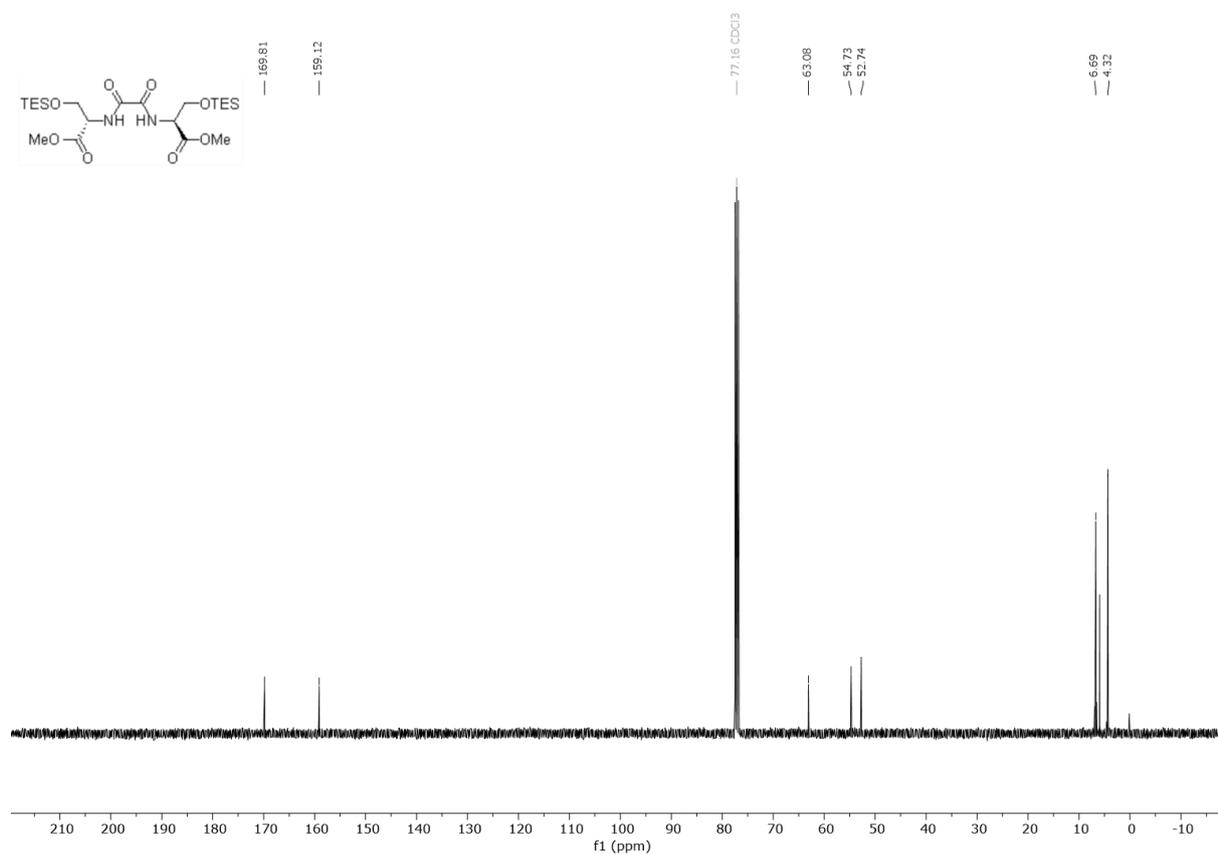
<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)



methyl N-(2-(((S)-1-methoxy-1-oxo-3-((triethylsilyl)oxy)propan-2-yl)amino)-2-oxoacetyl)-O-(triethylsilyl)-L-serinate (**4.50**),  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )

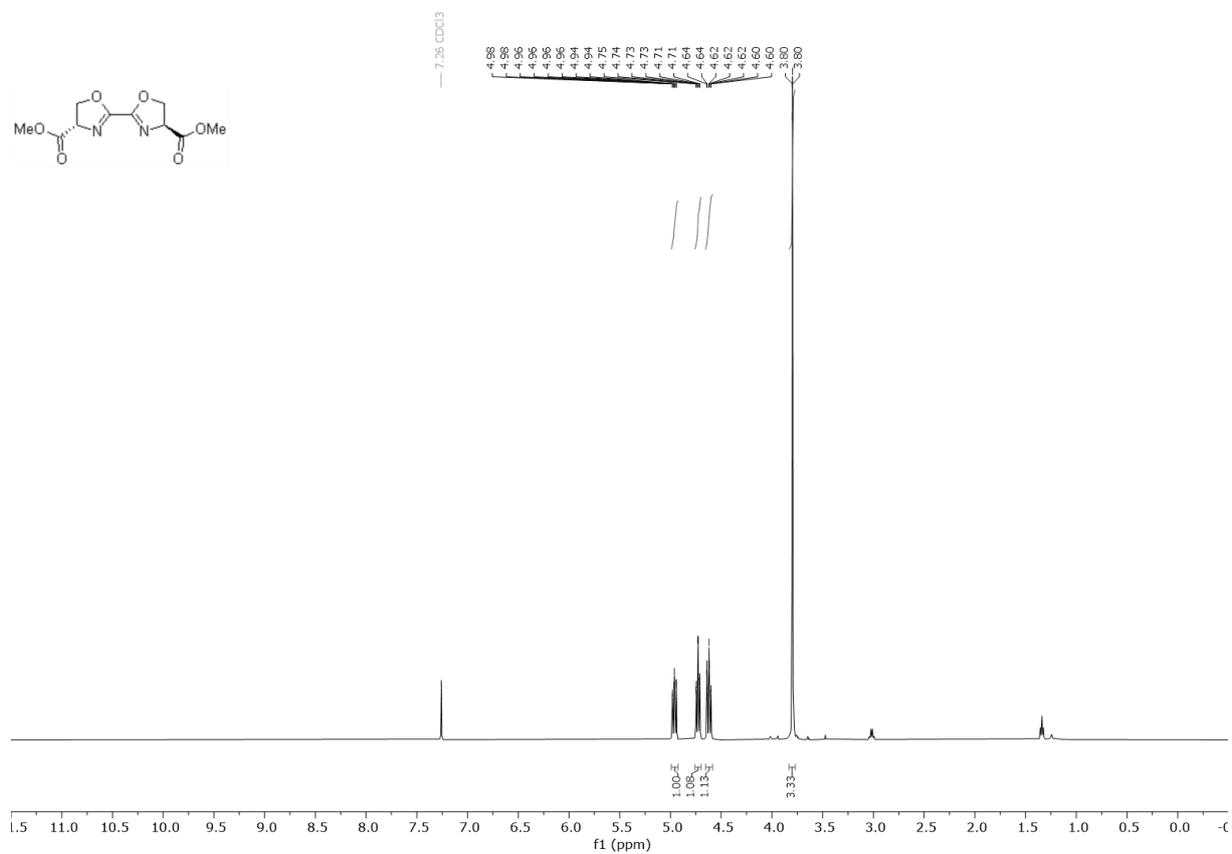


$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )

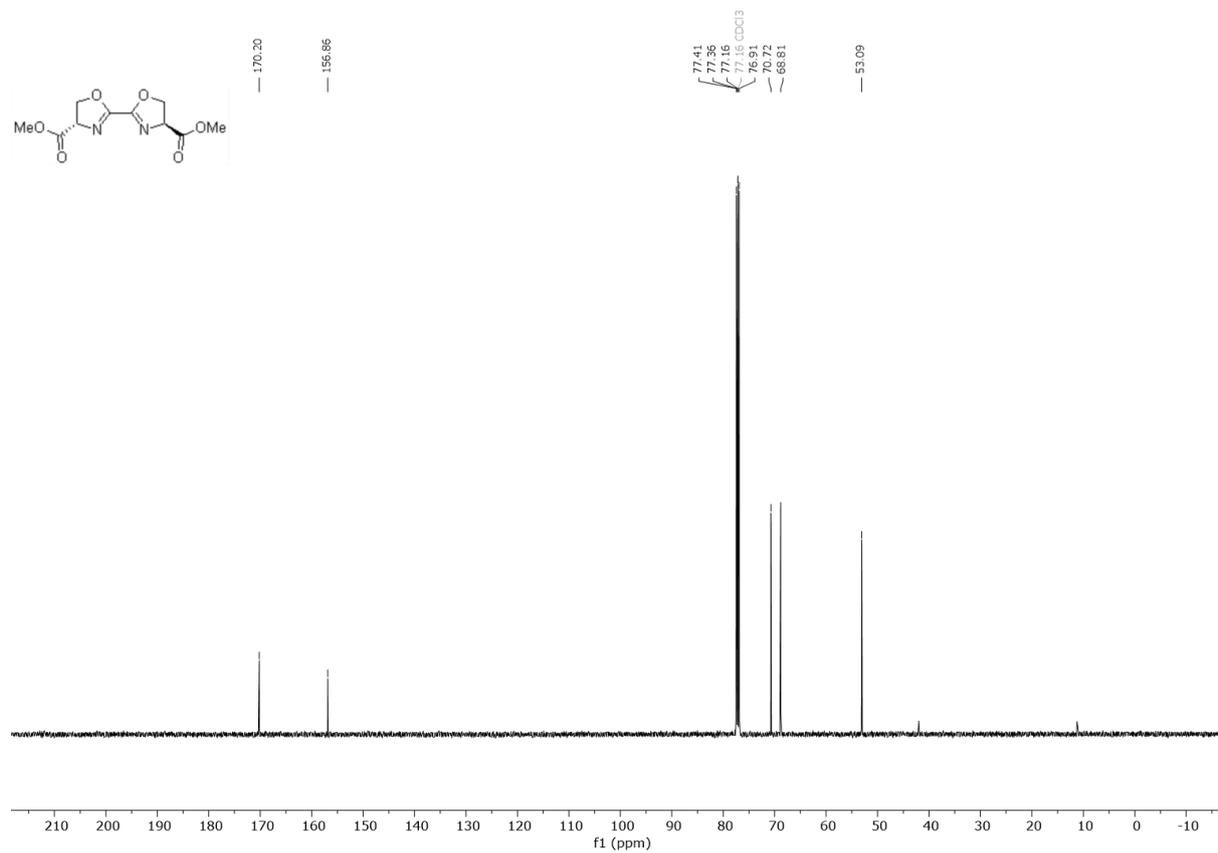


dimethyl (4*S*,4'*S*)-4,4',5,5'-tetrahydro-[2,2'-bioxazole]-4,4'-dicarboxylate (**4.48**)

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )

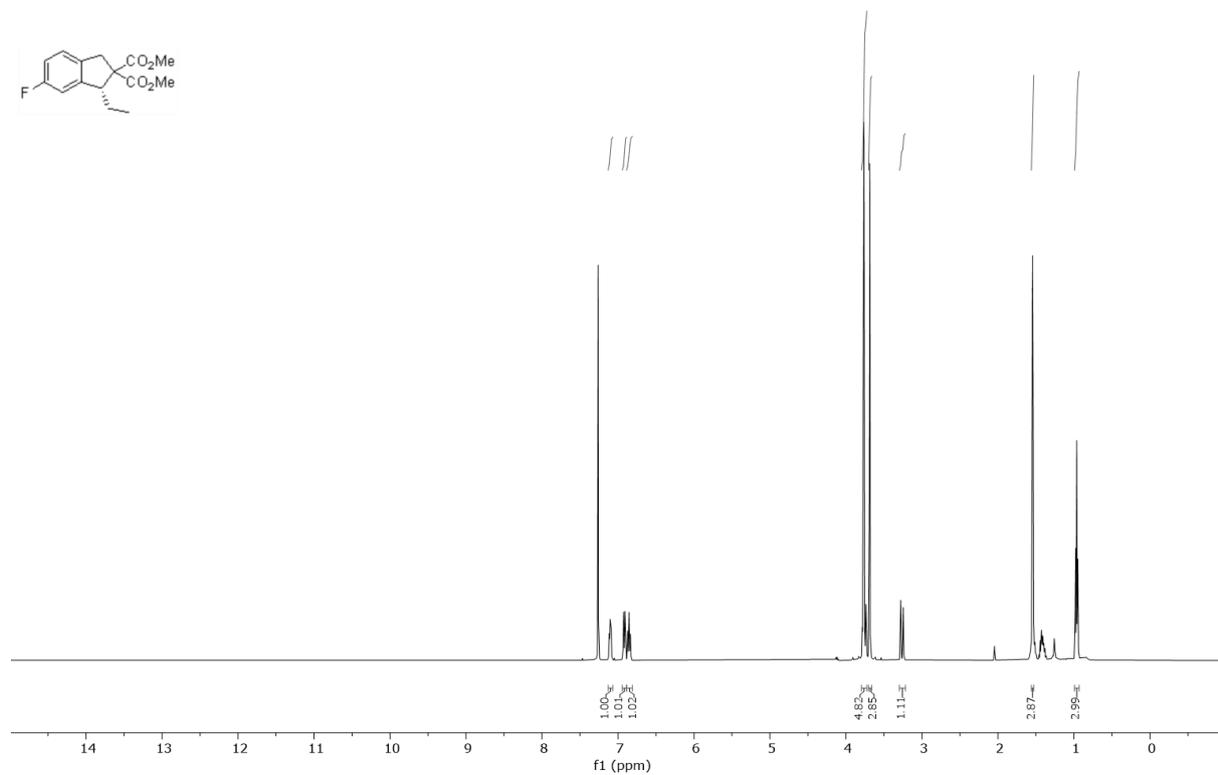


$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )

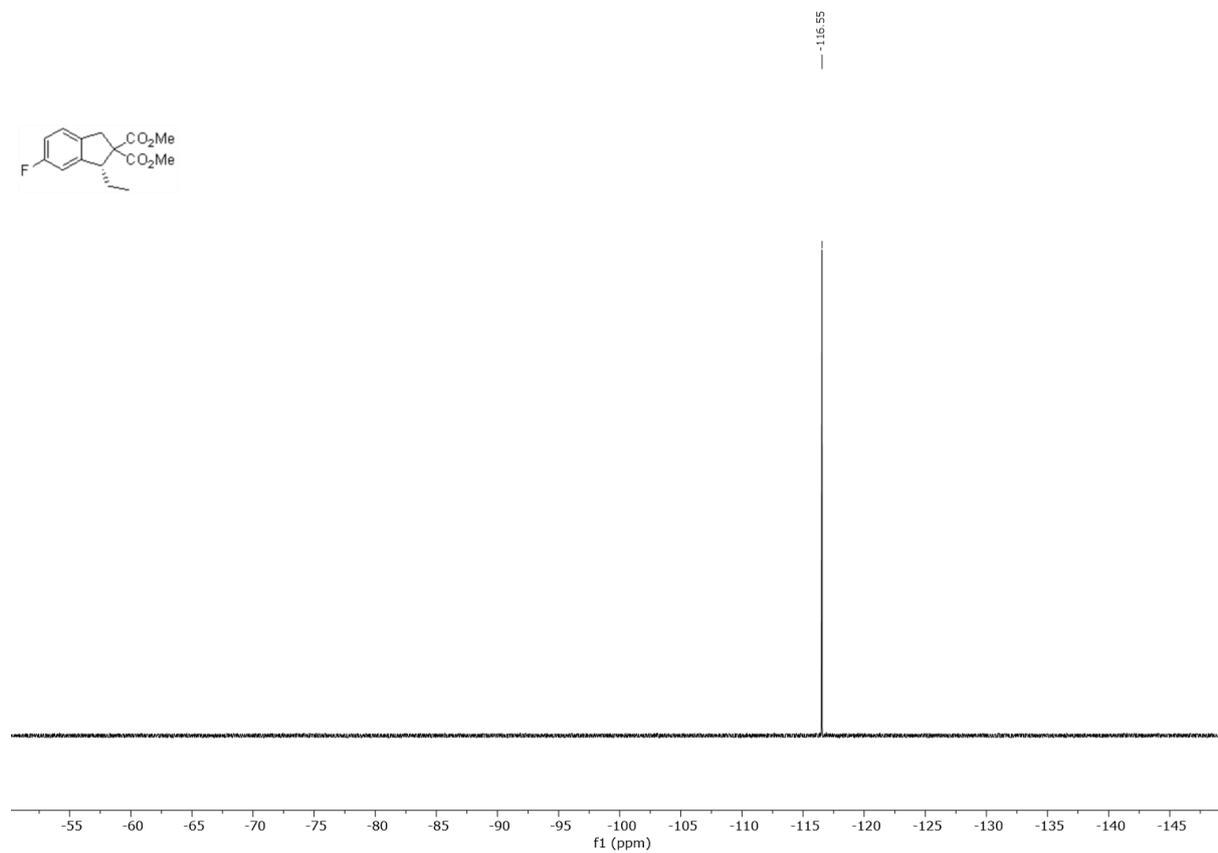


dimethyl (*R*)-1-ethyl-6-fluoro-1,3-dihydro-2*H*-indene-2,2-dicarboxylate (**4.17**)

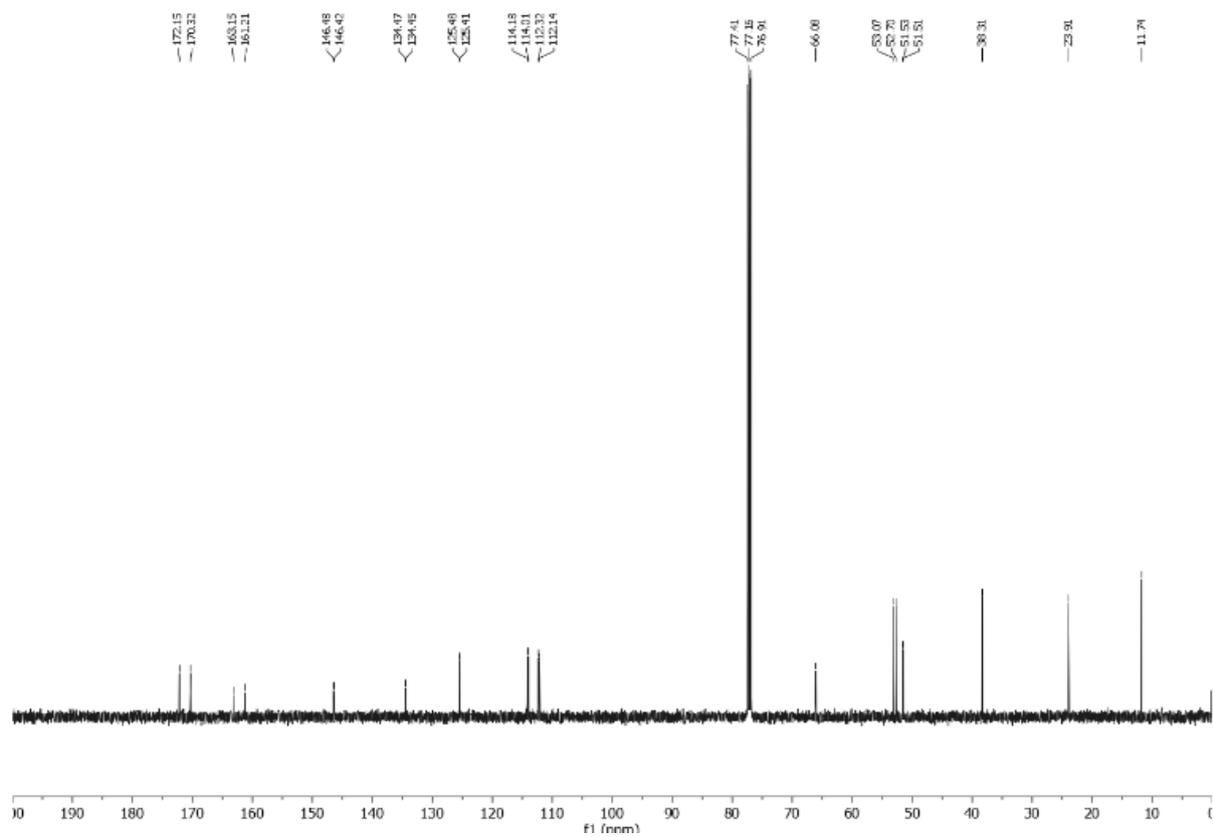
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )



$^{19}\text{F}$  NMR (471 MHz,  $\text{CDCl}_3$ )

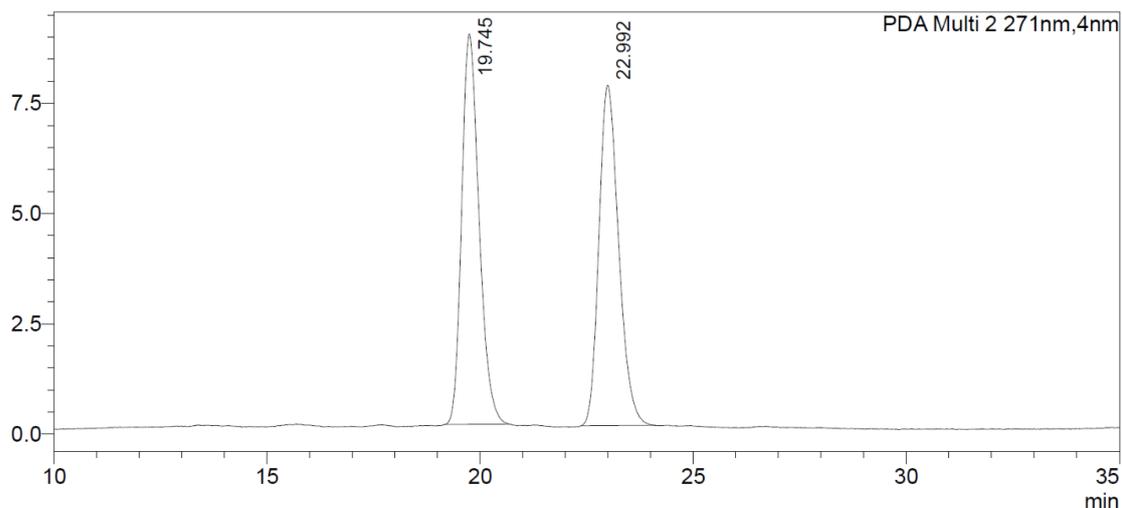


$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )



### <Chromatogram>

mAU



### <Peak Table>

PDA Ch2 271nm

Peak#	Ret. Time	Area	Area%
1	19.745	251628	50.261
2	22.992	249015	49.739
Total		500643	100.000



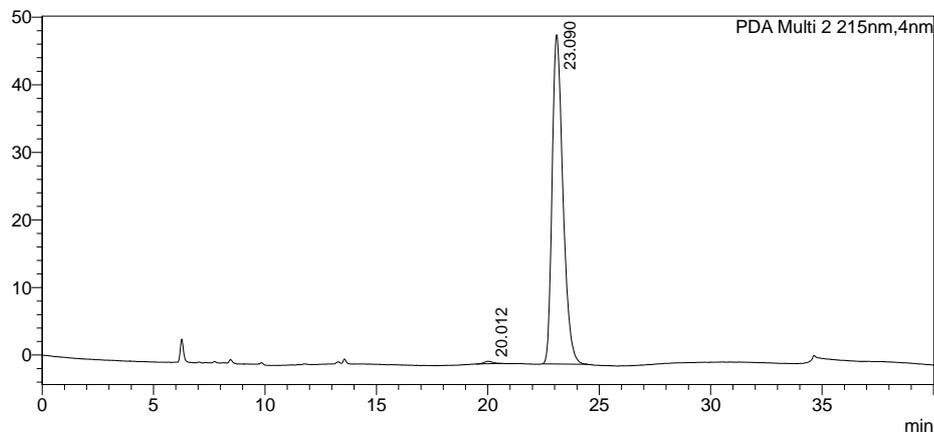
## Analysis Report

### <Sample Information>

Sample Name : CAV176  
Sample ID :  
Data Filename : CAV176\_run\_col1\_ODH\_99.5\_0.5\_0.5mL\_40min.lcd  
Method Filename : run\_col1\_ODH\_99.5\_0.5\_0.5mL\_40min.lcm  
Batch Filename : CAV175\_CAV176\_C1ODH\_99.5\_0.5\_0.5mL\_40min.lcb  
Vial # : 1-62 Sample Type : Unknown  
Injection Volume : 2 uL  
Date Acquired : 12.02.2020 19:02:11 Acquired by : System Administrator  
Date Processed : 13.02.2020 07:55:46 Processed by : System Administrator

### <Chromatogram>

mAU



### <Peak Table>

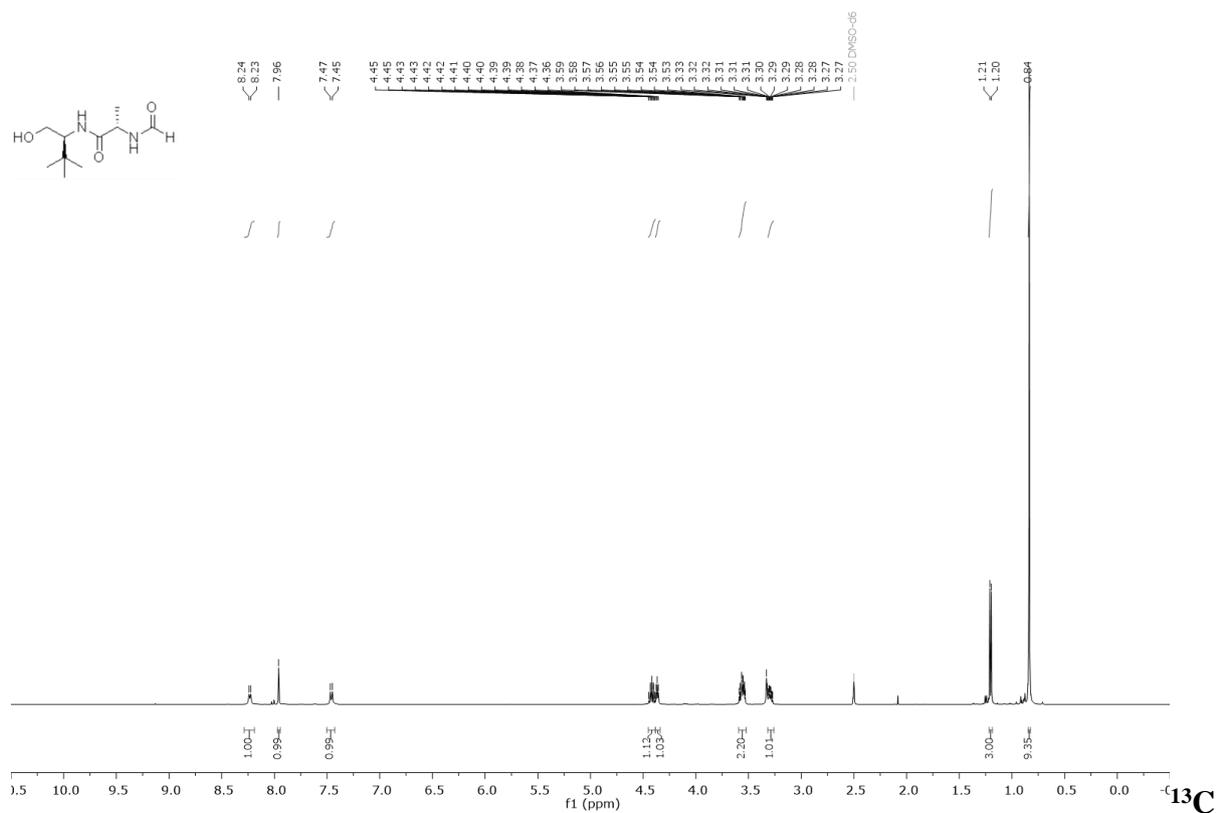
PDA Ch2 215nm

Peak#	Ret. Time	Area	Area%
1	20.012	9948	0.601
2	23.090	1646492	99.399
Total		1656440	100.000

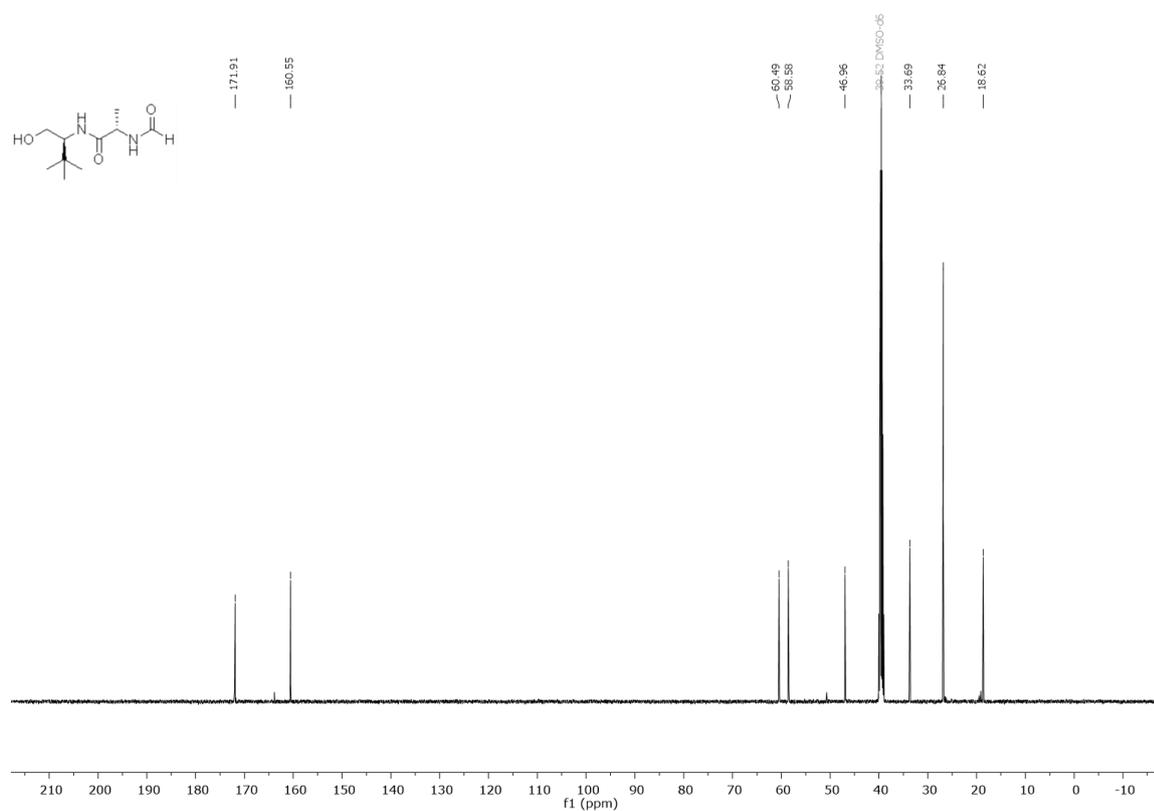


(S)-2-formamido-N-((S)-1-hydroxy-3,3-dimethylbutan-2-yl)propanamide (**5.7Me**)

$^1\text{H}$  NMR (500 MHz, DMSO- $d_6$ )

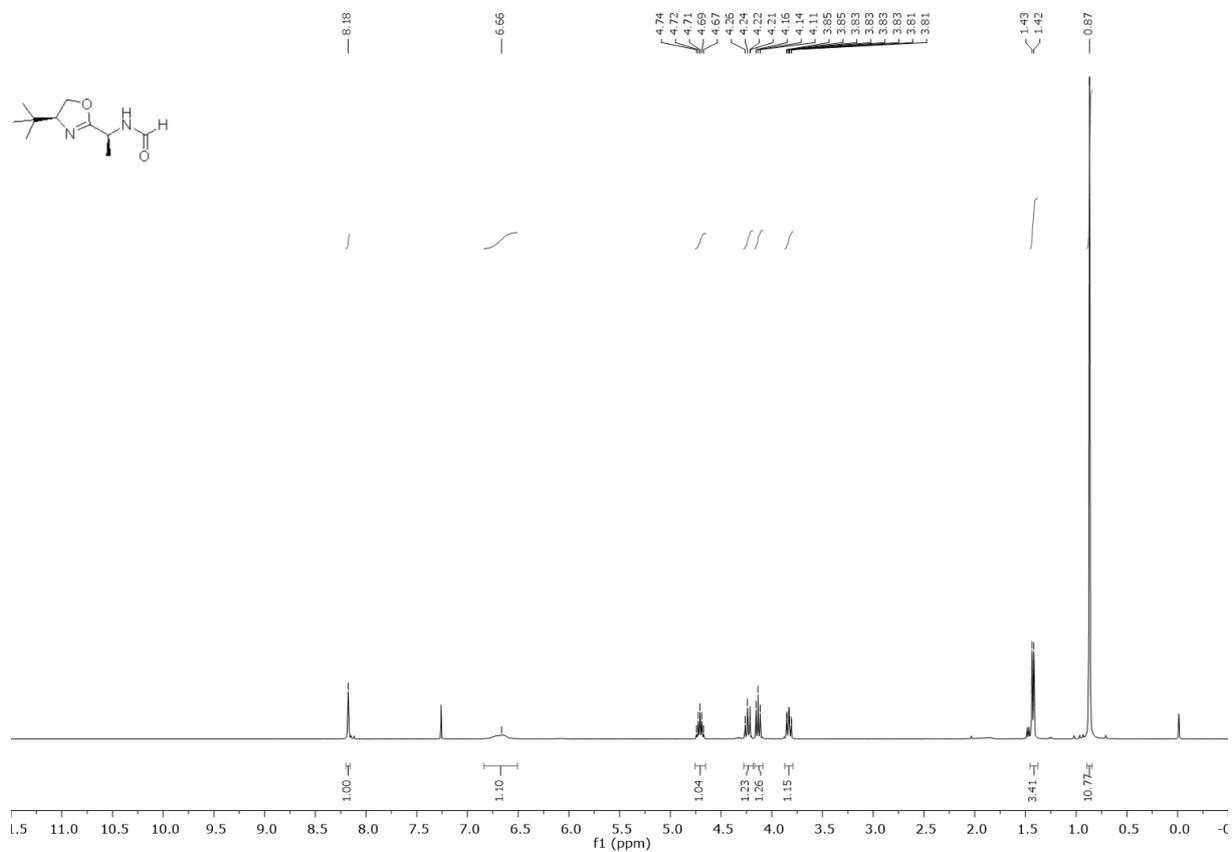


$^{13}\text{C}$  NMR (126 MHz, DMSO- $d_6$ )

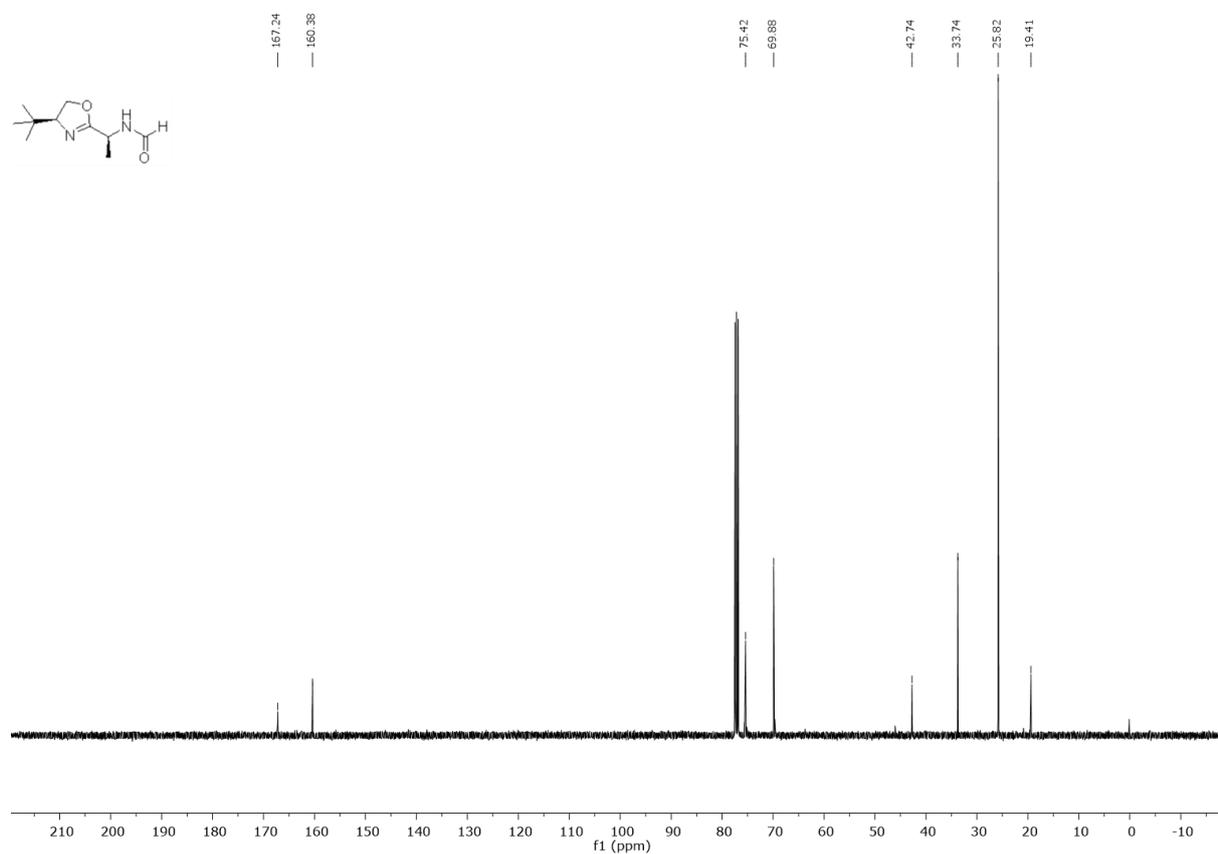


*N*-((*S*)-1-((*S*)-4-(*tert*-butyl)-4,5-dihydrooxazol-2-yl)ethyl)formamide (**5.8Me**)

$^1\text{H}$  NMR (400 MHz, chloroform-*d*)

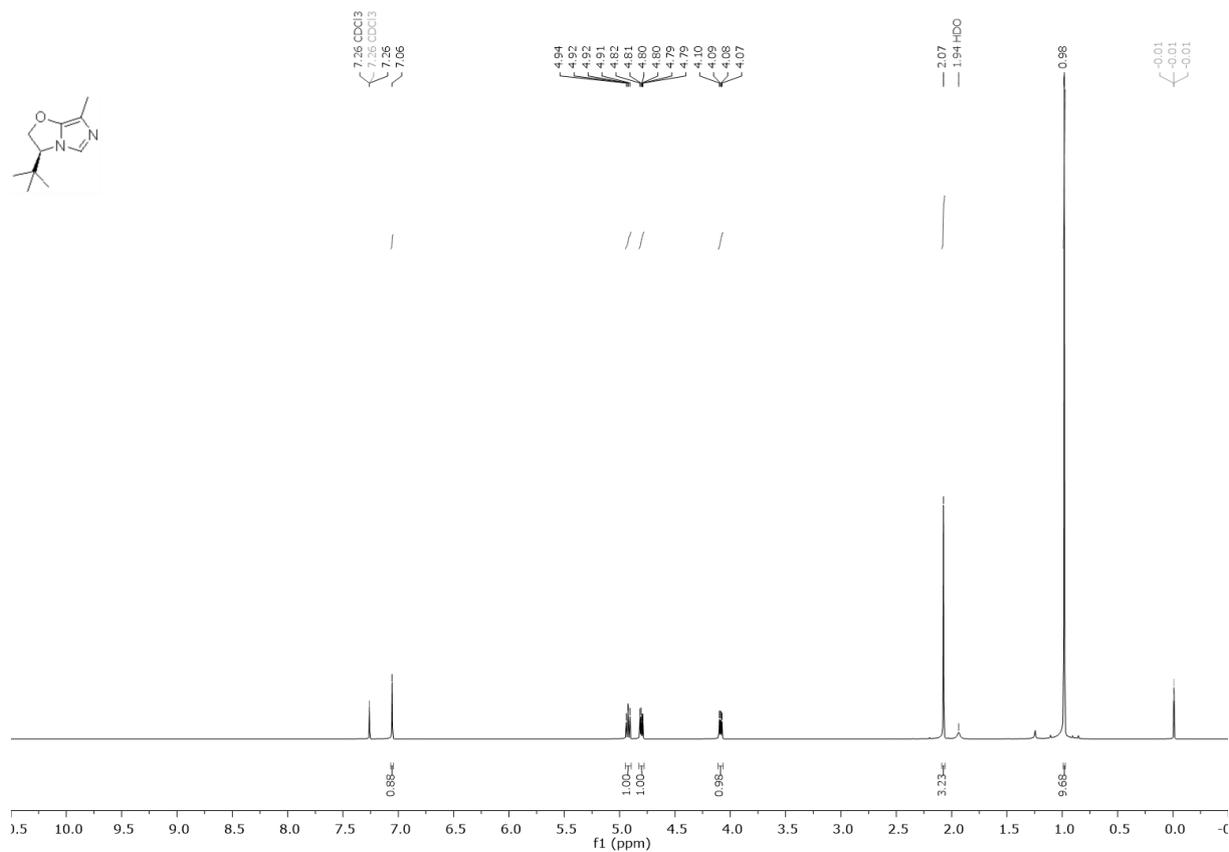


$^{13}\text{C}$  NMR (101 MHz, chloroform-*d*)

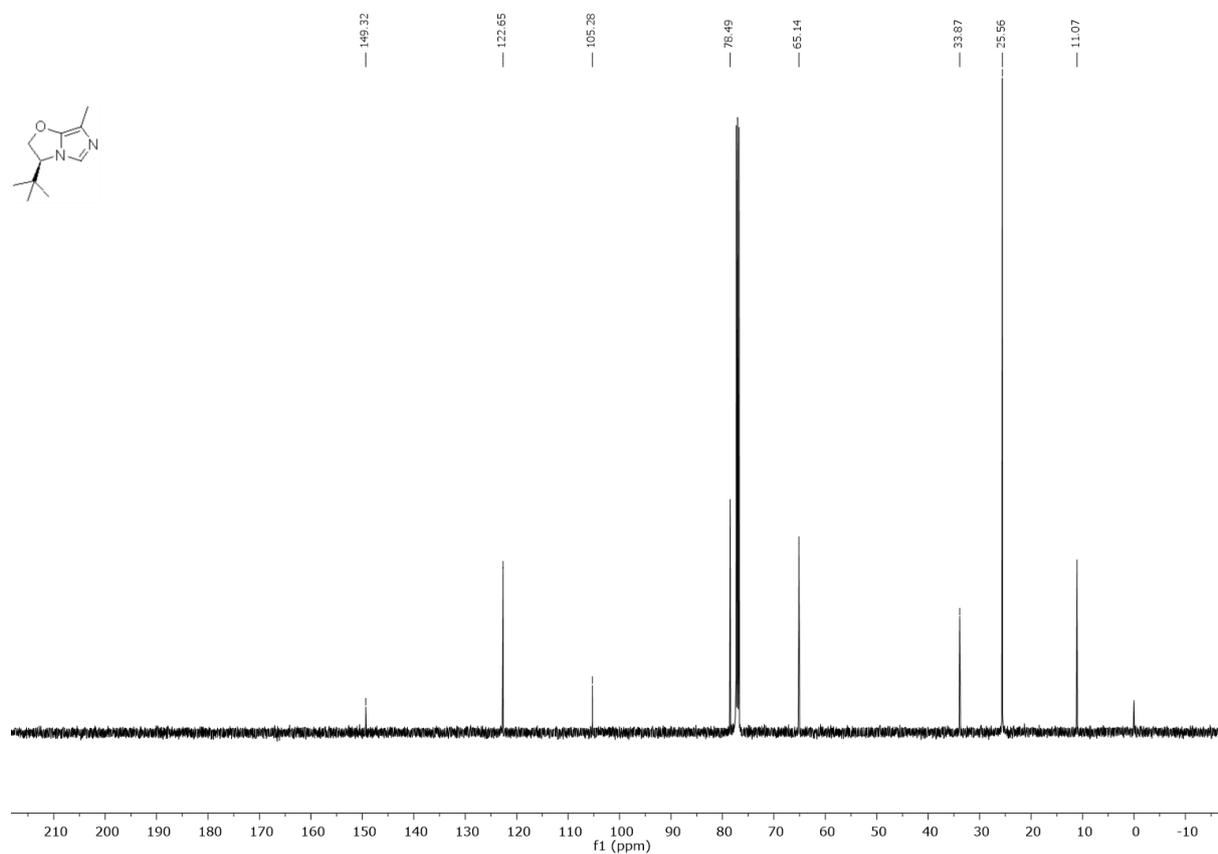


(S)-3-(tert-butyl)-7-methyl-2,3-dihydroimidazo[5,1-b]oxazole (**5.9**)

<sup>1</sup>H NMR (500 MHz, chloroform-d)

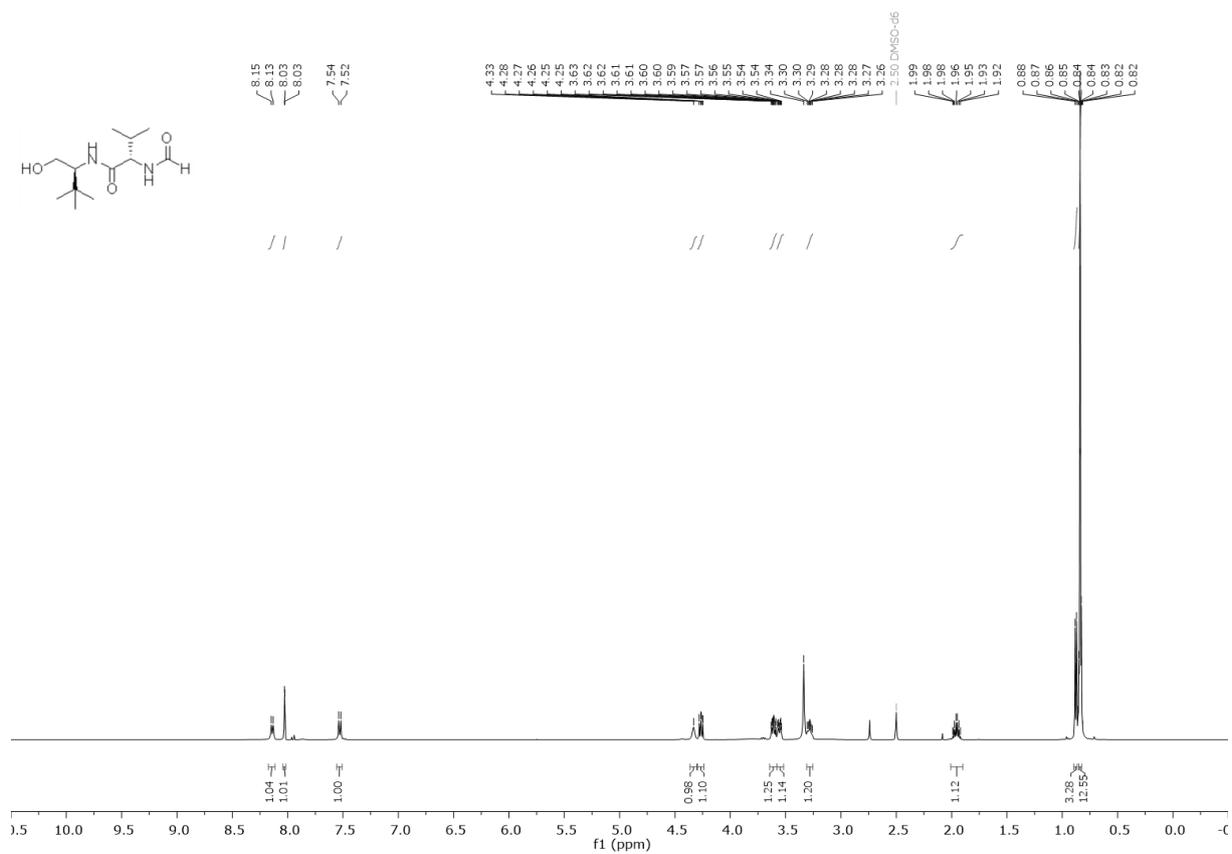


<sup>13</sup>C NMR (126 MHz, chloroform-d)

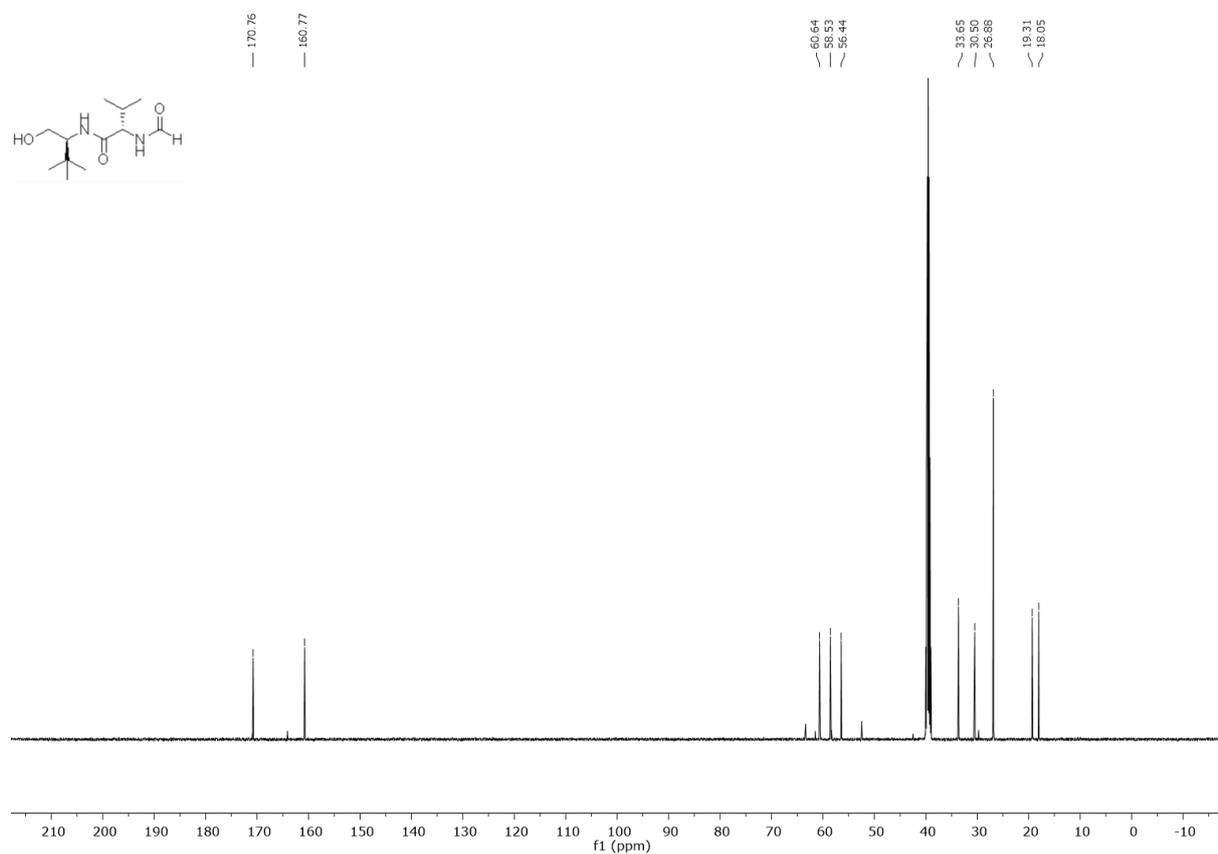


(S)-2-formamido-N-((S)-1-hydroxy-3,3-dimethylbutan-2-yl)-3-methylbutanamide (**5.7iPr**)

$^1\text{H}$  NMR (500 MHz,  $\text{DMSO-}d_6$ )

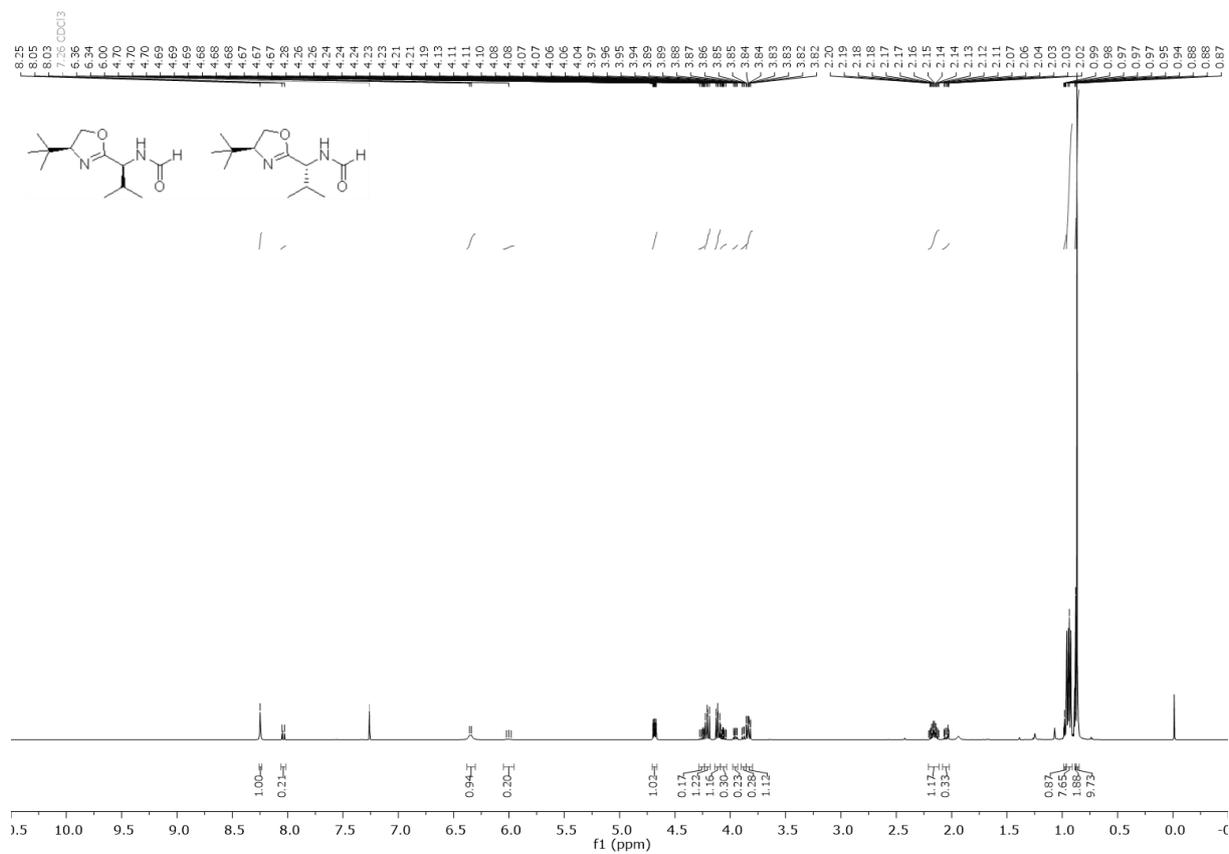


$^{13}\text{C}$  NMR (126 MHz,  $\text{DMSO-}d_6$ )

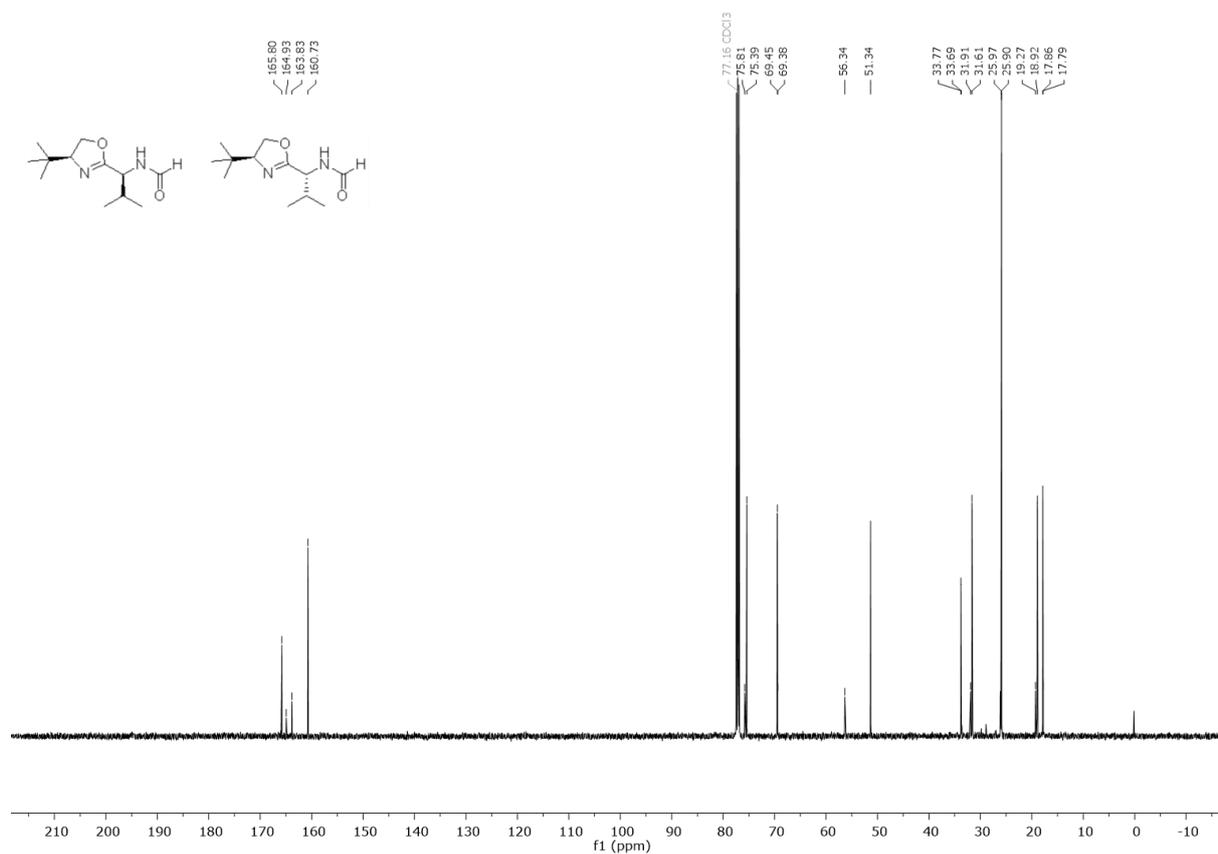


N-((S)-1-((S)-4-(*tert*-butyl)-4,5-dihydrooxazol-2-yl)-2-methylpropyl)formamide (**5.8iPr**)

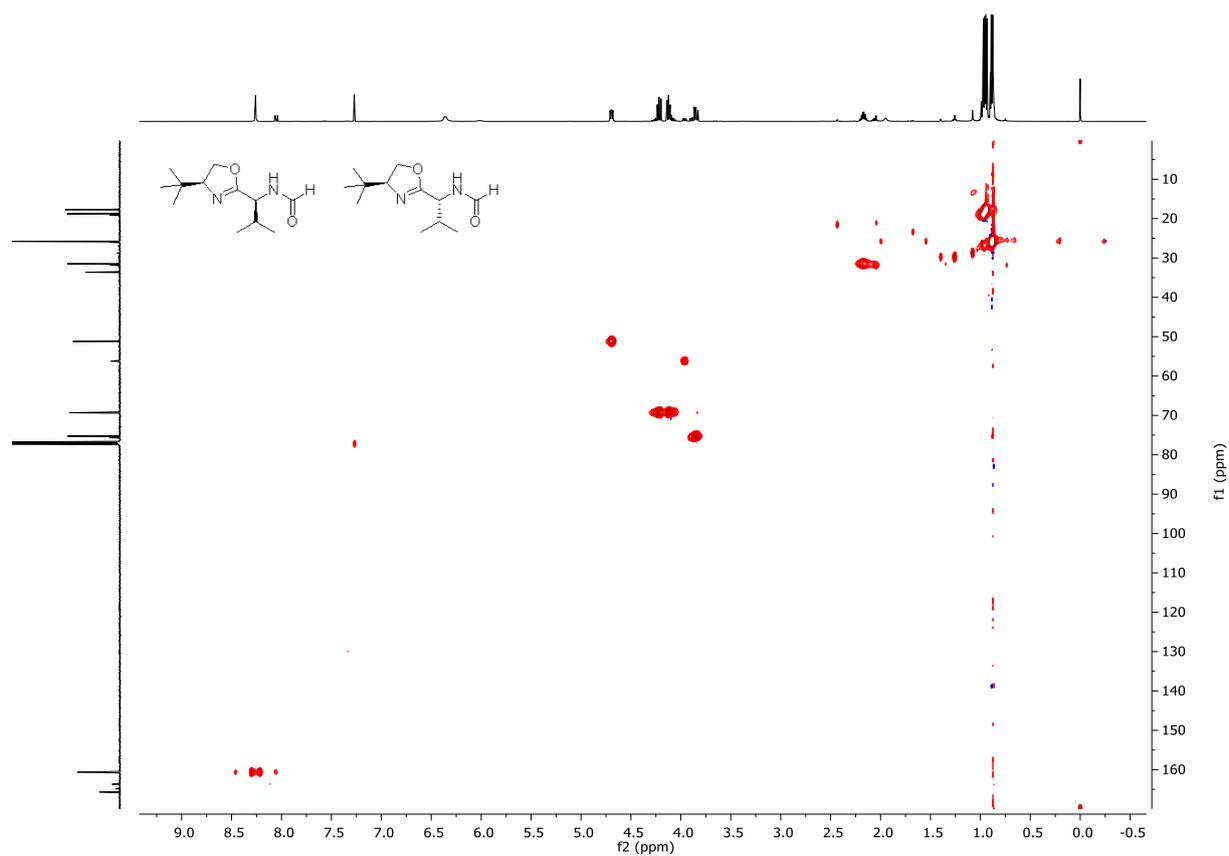
$^1\text{H}$  NMR (500 MHz, chloroform-*d*)



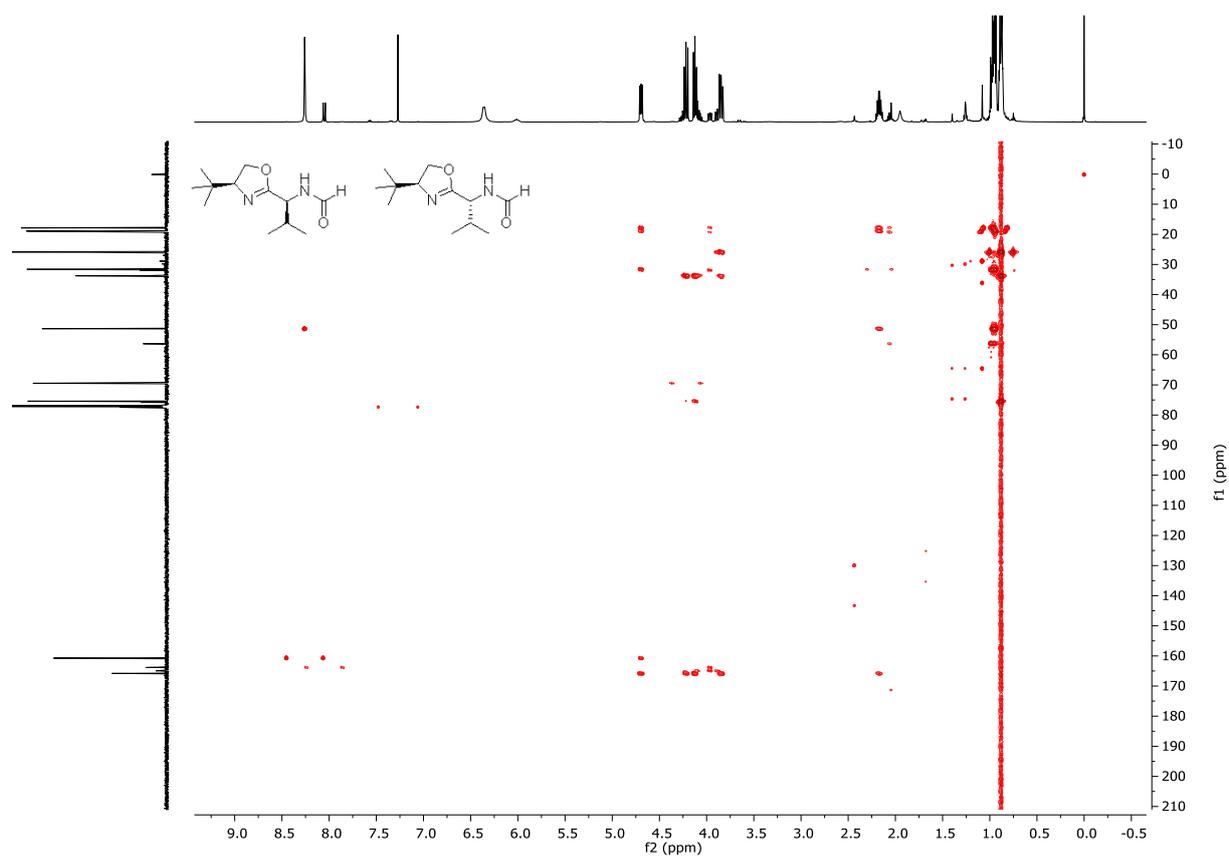
$^{13}\text{C}$  NMR (126 MHz, chloroform-*d*)



### HMQC

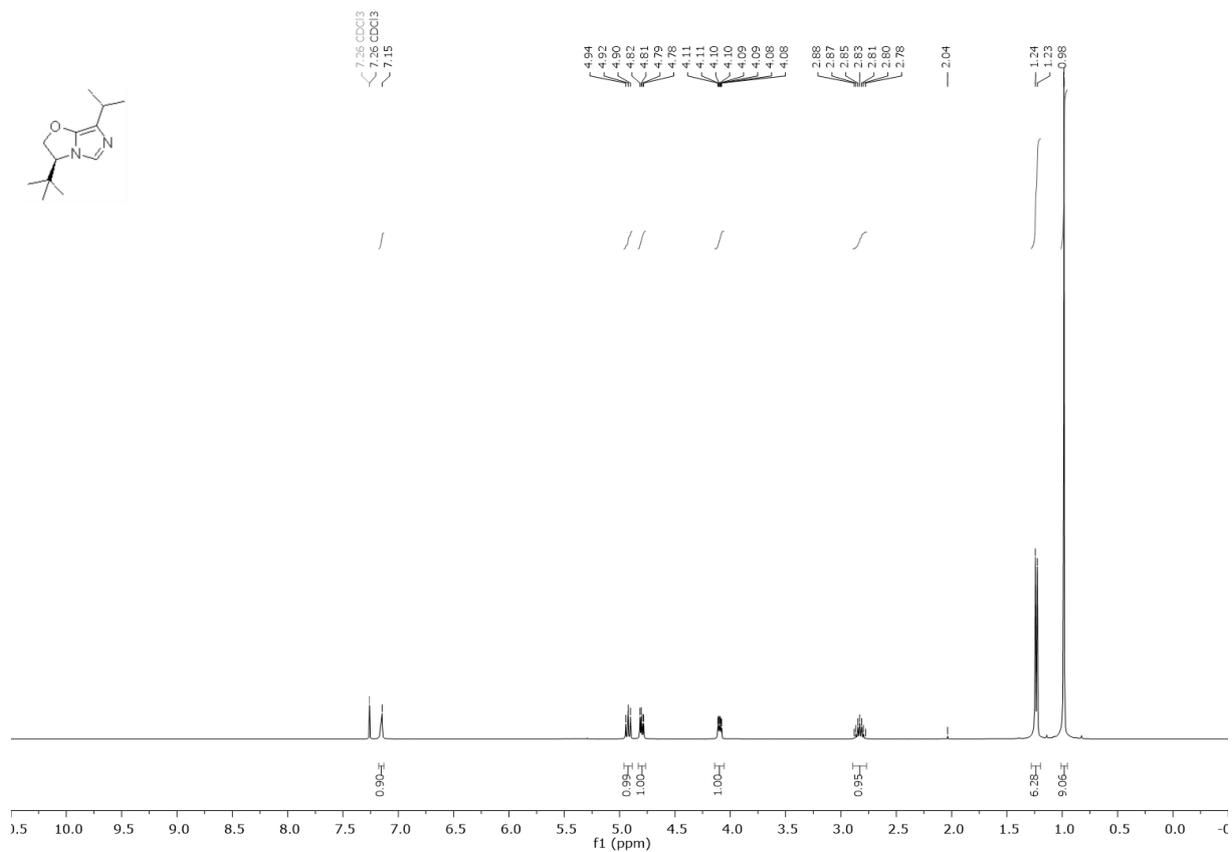


### HMBC

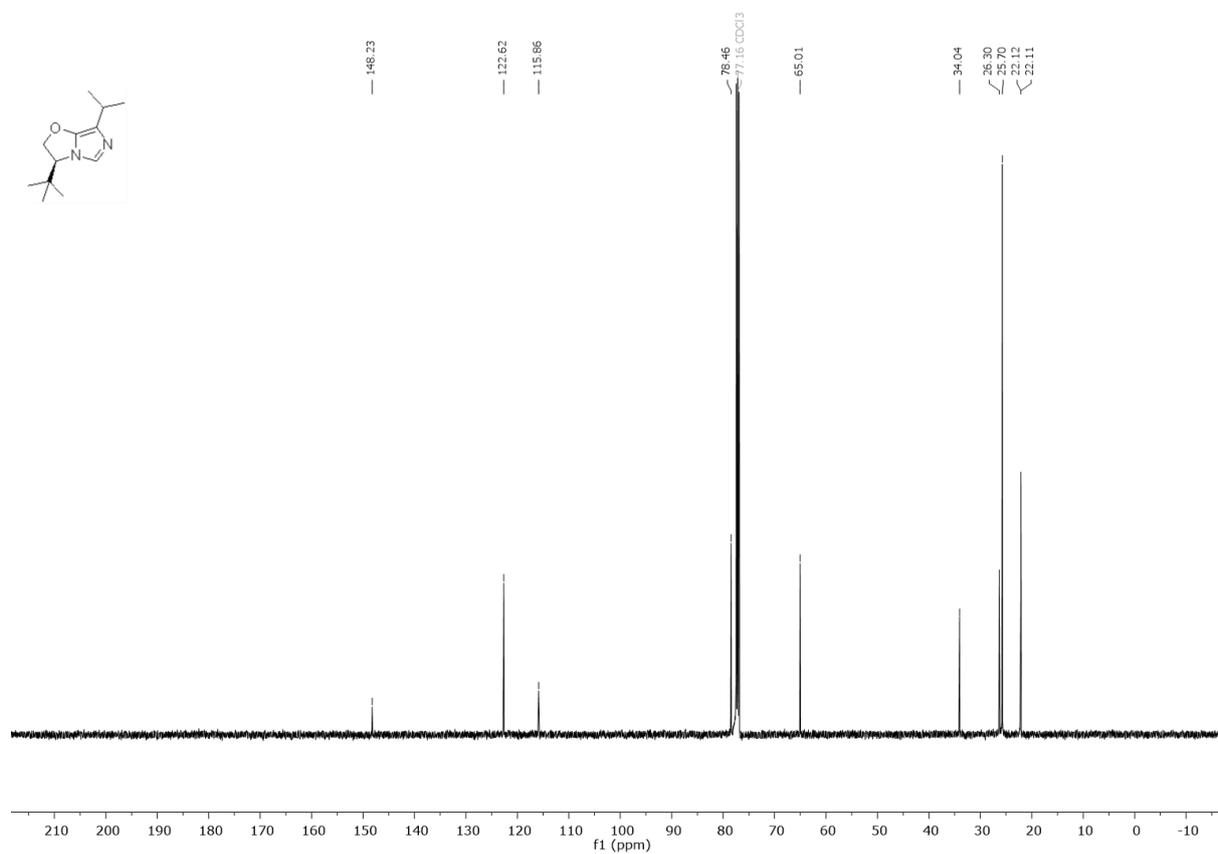


(S)-3-(*tert*-butyl)-7-isopropyl-2,3-dihydroimidazo[5,1-b]oxazole (**5.10**)

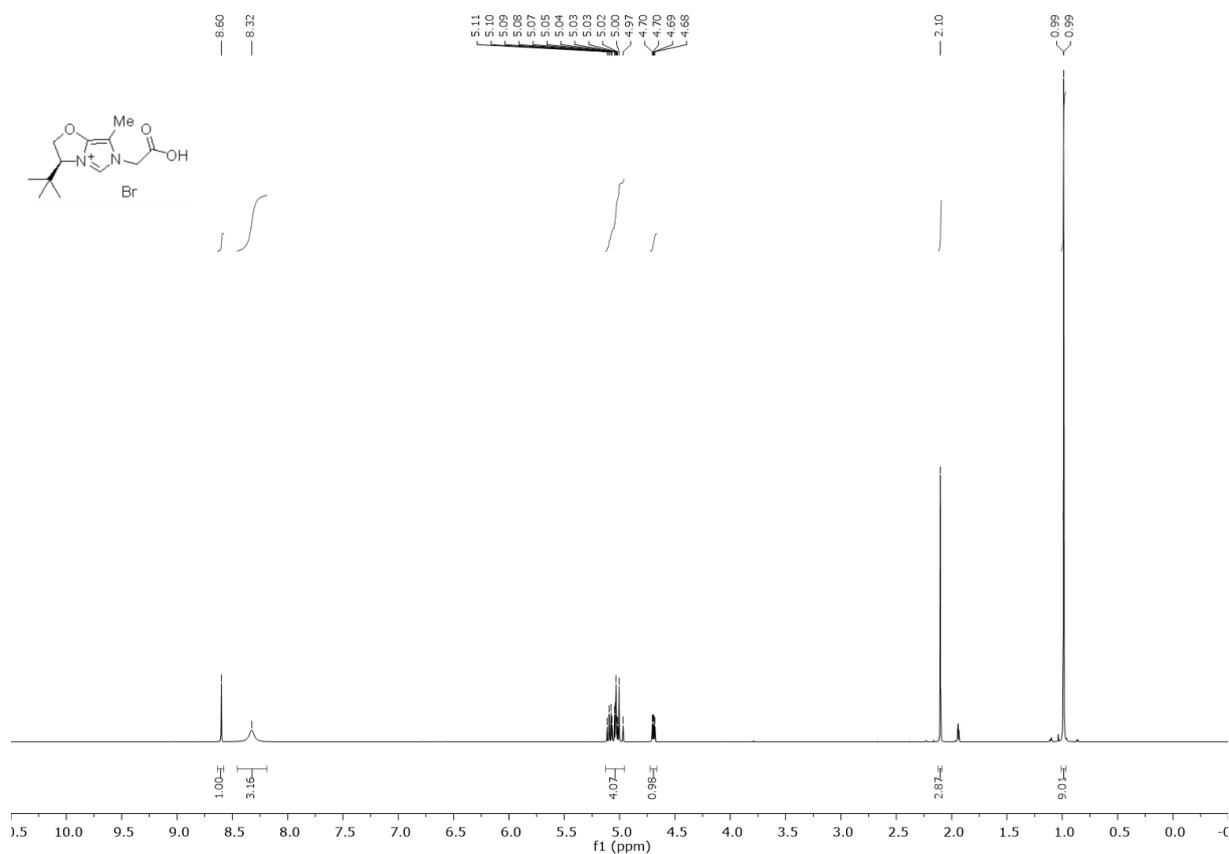
$^1\text{H}$  NMR (400 MHz, chloroform-*d*)



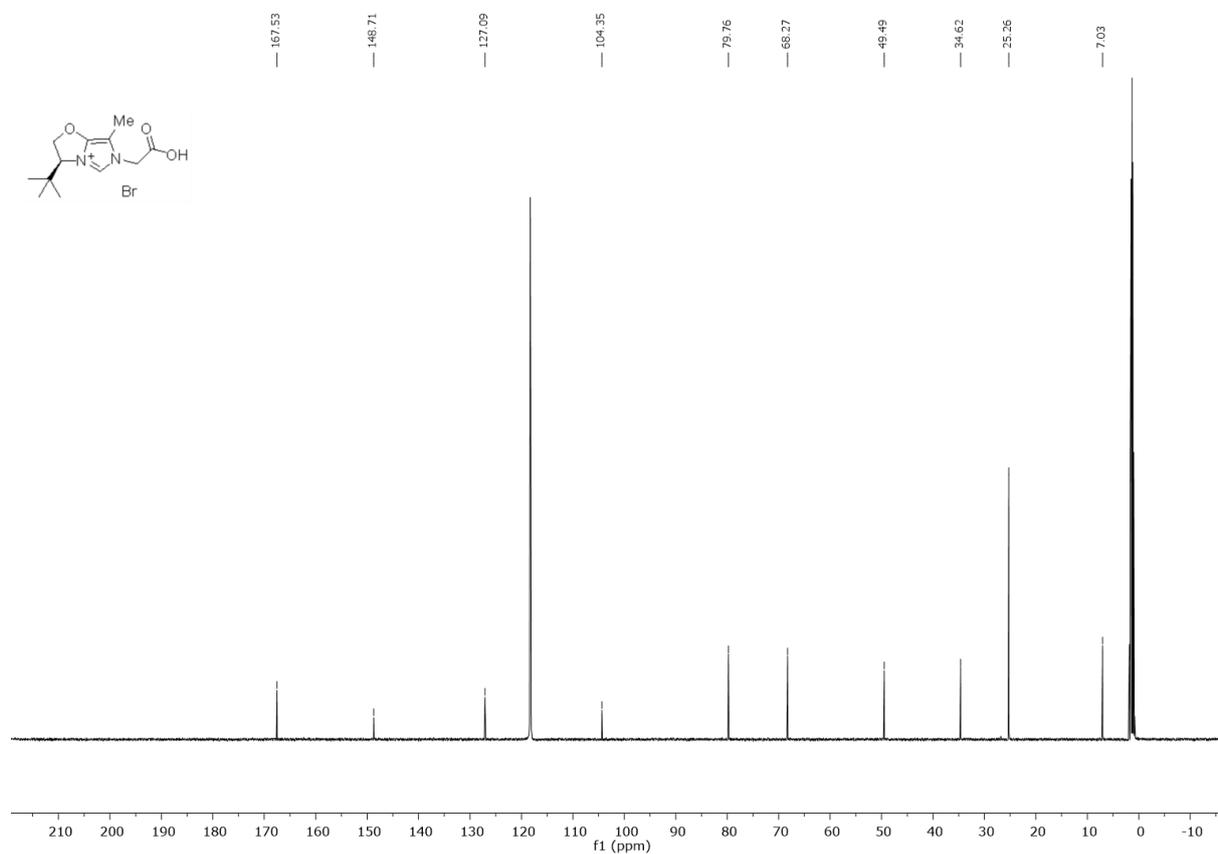
$^{13}\text{C}$  NMR (126 MHz, chloroform-*d*)



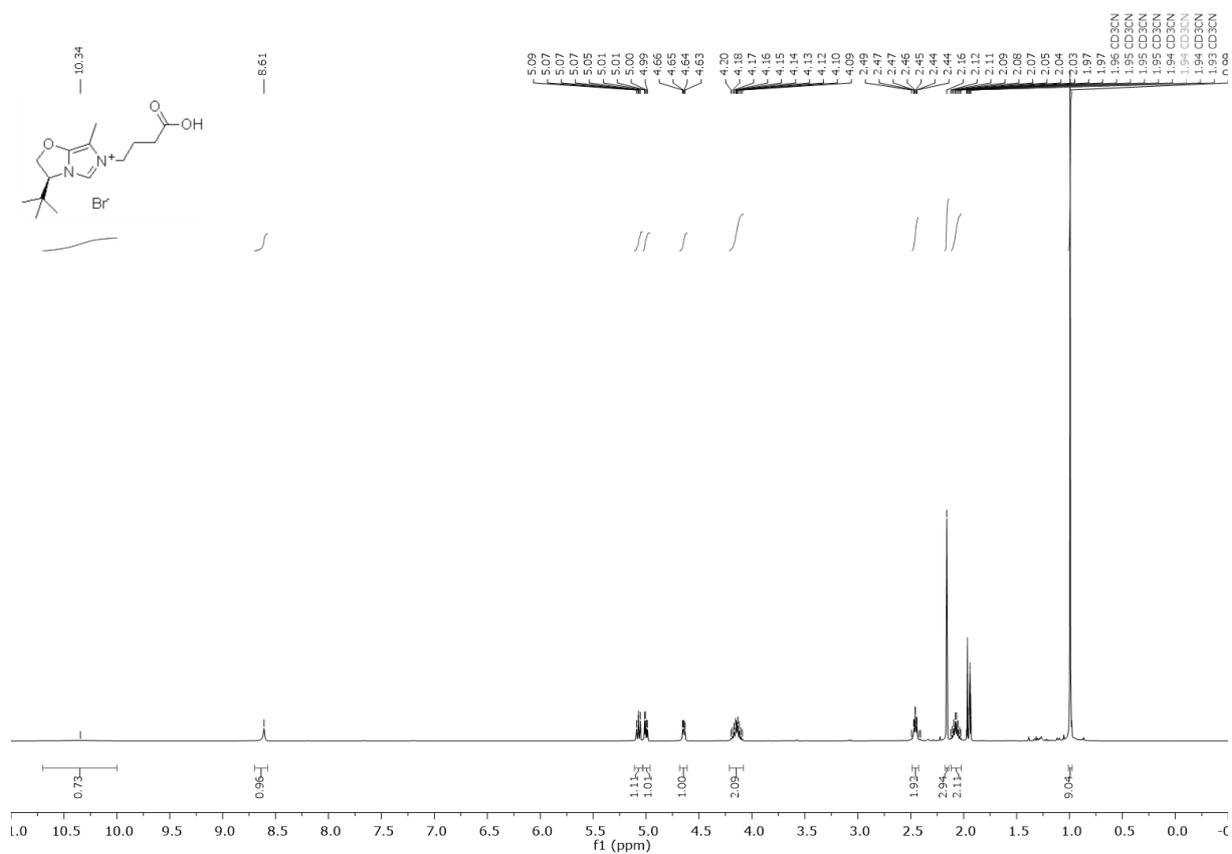
(*S*)-3-(tert-butyl)-6-(carboxymethyl)-7-methyl-2,3-dihydroimidazo[5,1-b]oxazol-6-ium bromide (**BL**<sup>1</sup>). <sup>1</sup>H NMR (500 MHz, acetonitrile-*d*<sub>3</sub>)



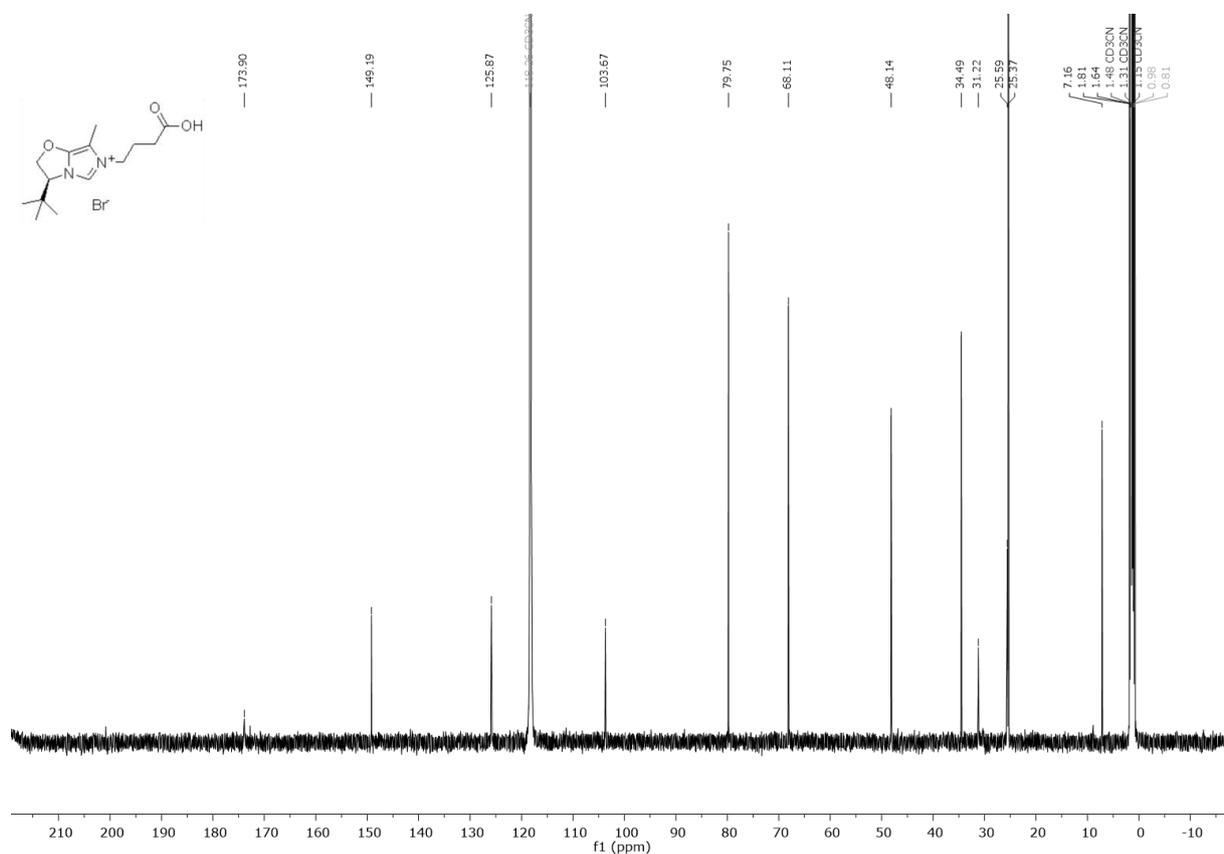
<sup>13</sup>C NMR (126 MHz, acetonitrile-*d*<sub>3</sub>)



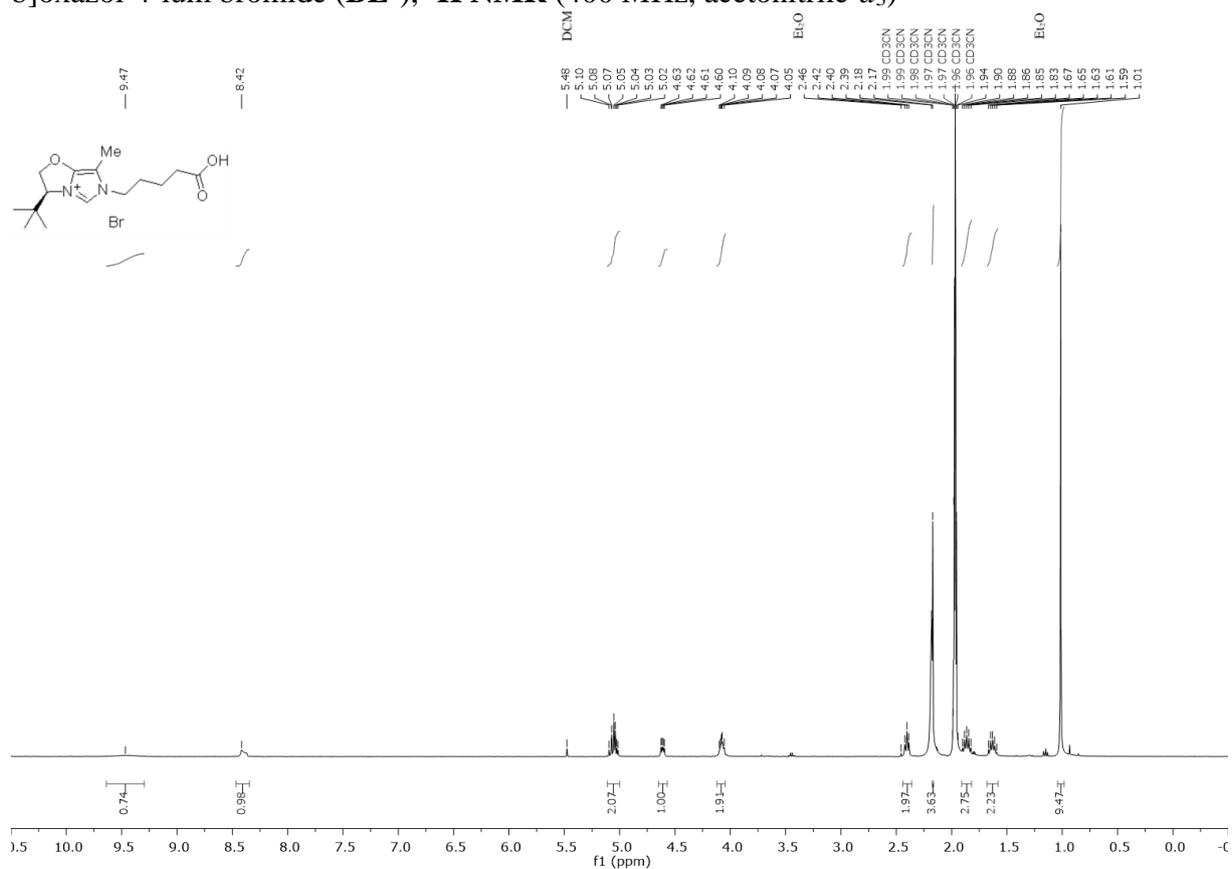
(S)-3-(tert-butyl)-6-(3-carboxypropyl)-7-methyl-2,3-dihydroimidazo[5,1-b]oxazol-6-ium bromide (**BL**<sup>2</sup>), <sup>1</sup>H NMR (500 MHz, acetonitrile-*d*<sub>3</sub>)



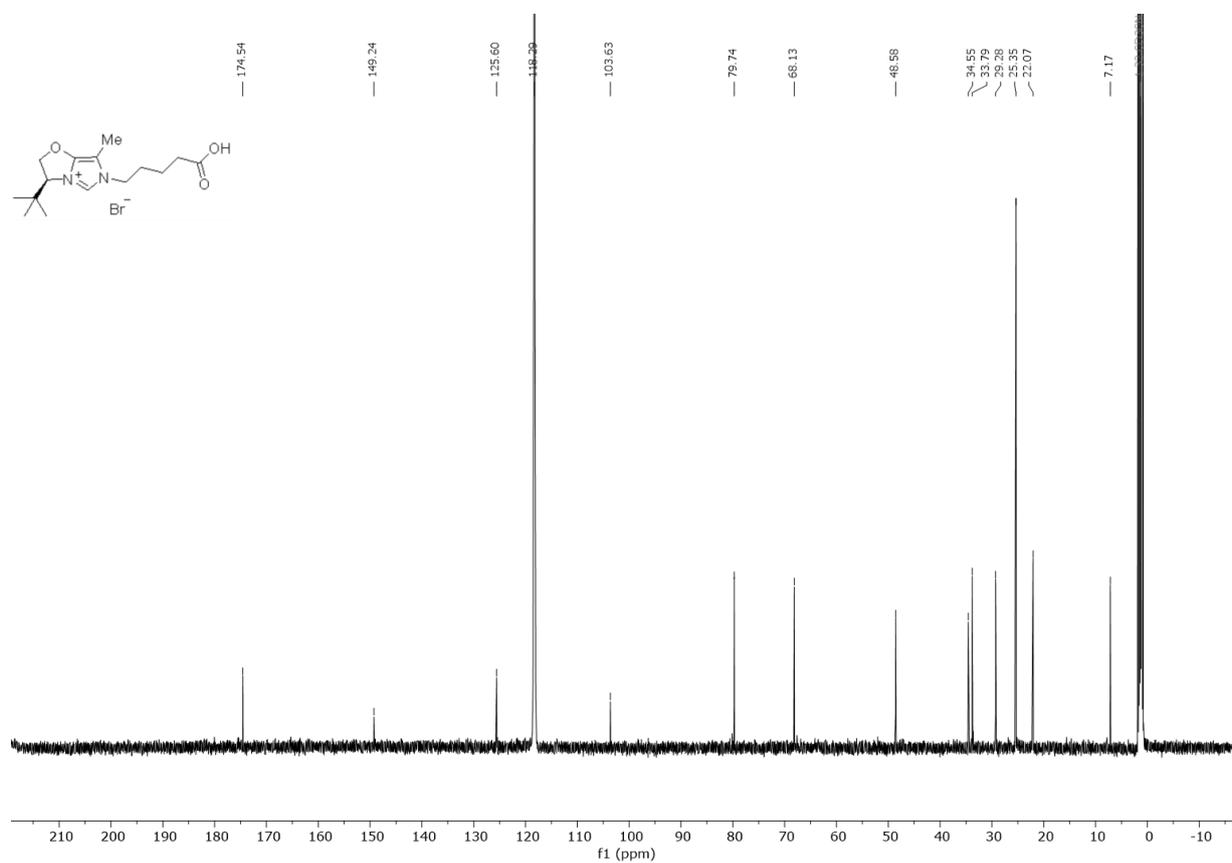
<sup>13</sup>C NMR (126 MHz, acetonitrile-*d*<sub>3</sub>)



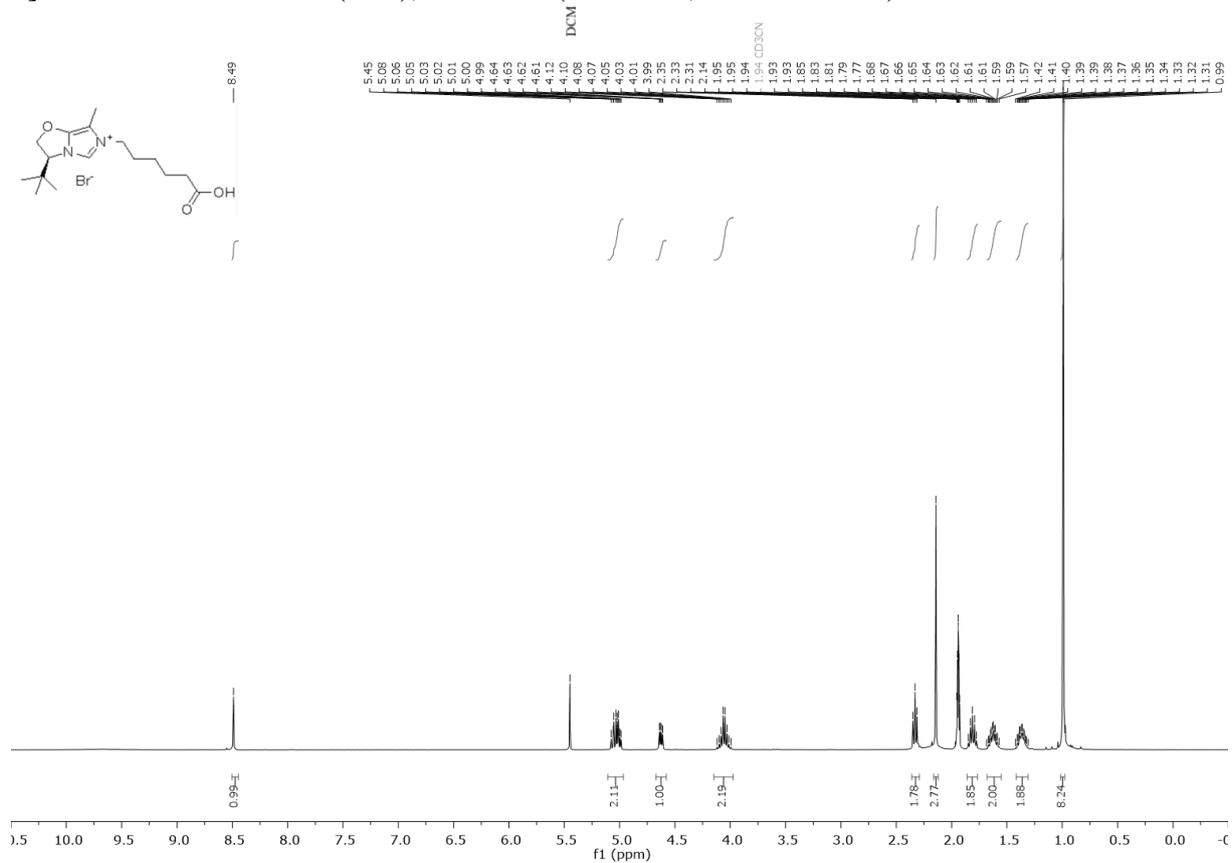
(S)-3-(tert-butyl)-6-(carboxymethyl)-6,6,6,7-tetramethyl-3,6-dihydro-2H-6l6-imidazo[4,3-b]oxazol-4-ium bromide (**BL<sup>3</sup>**), <sup>1</sup>H NMR (400 MHz, acetonitrile-*d*<sub>3</sub>)



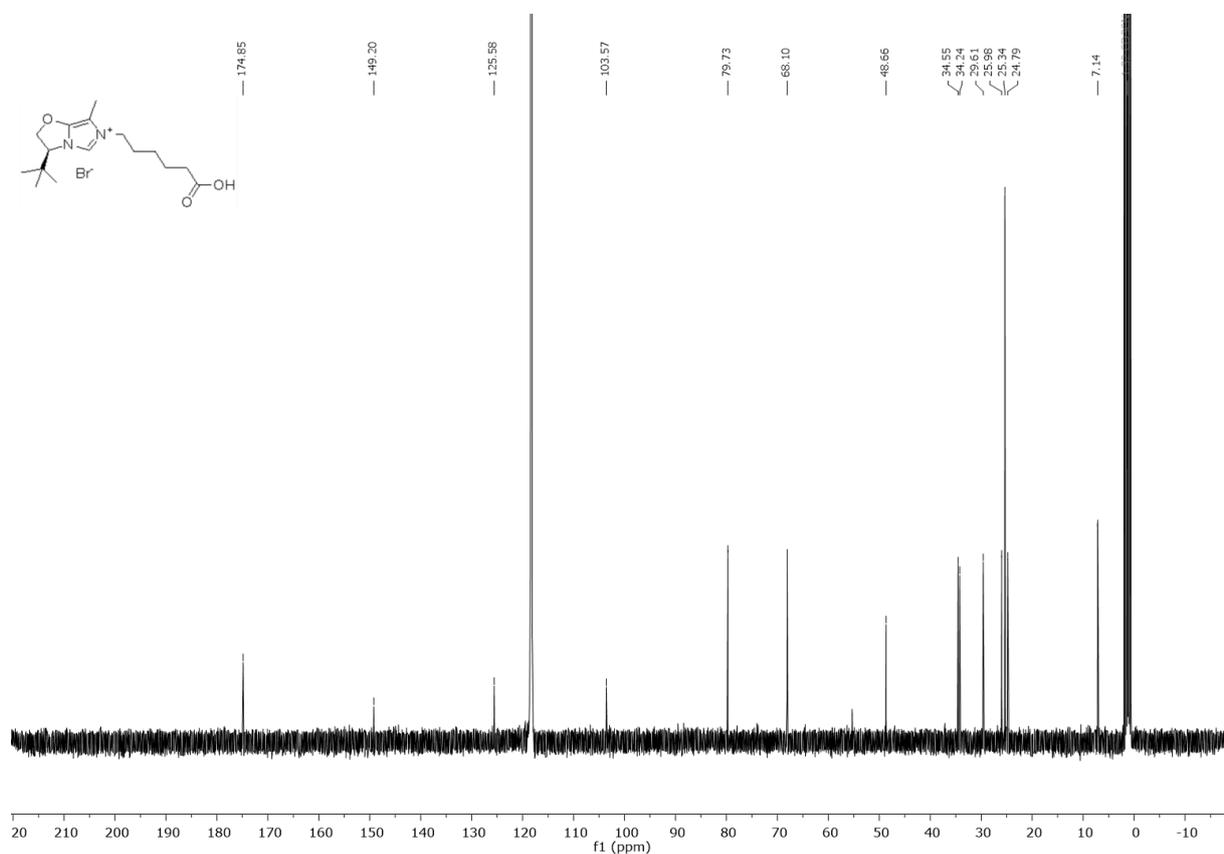
<sup>13</sup>C NMR (126 MHz, acetonitrile-*d*<sub>3</sub>)



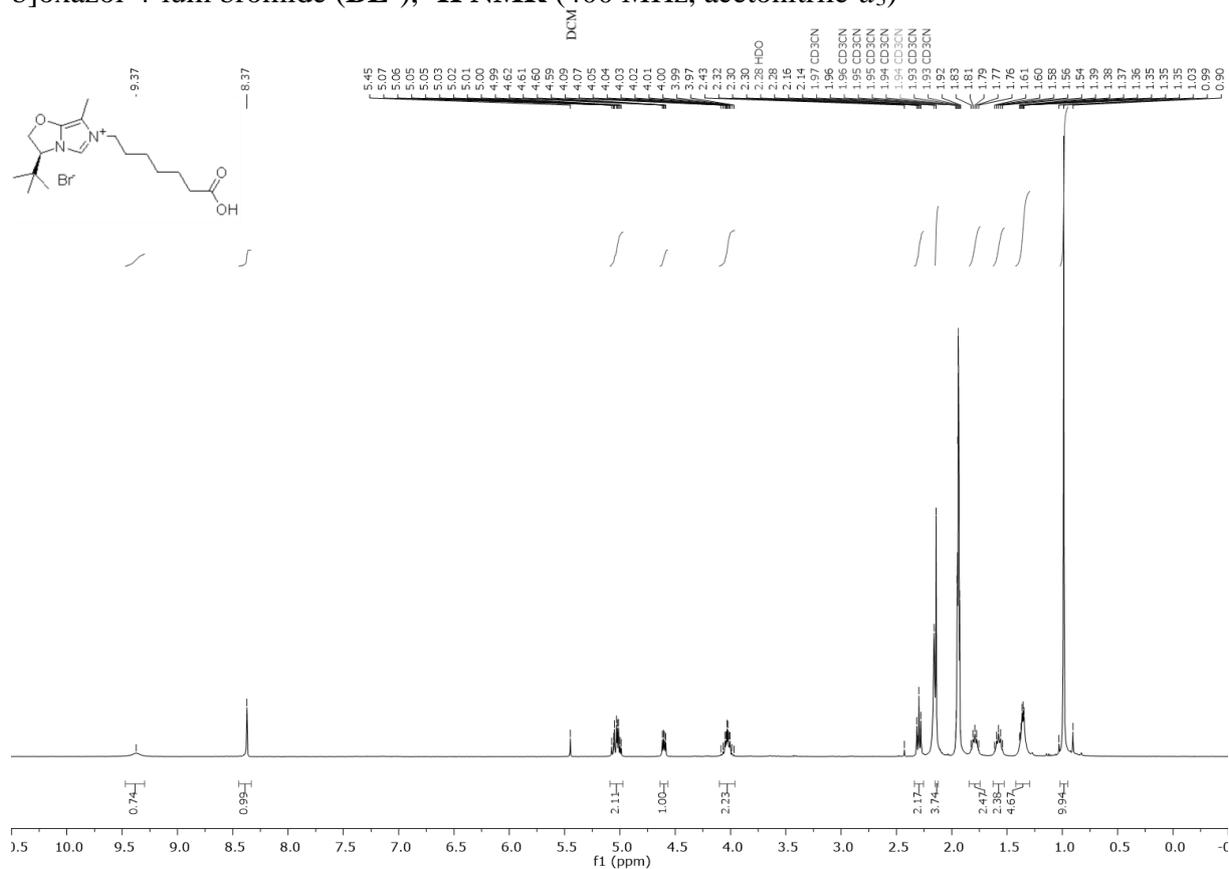
(S)-3-(tert-butyl)-6-(carboxymethyl)-6,6,6,7-pentamethyl-3,6-dihydro-2H-6l7-imidazo[4,3-b]oxazol-4-ium bromide (**BL<sup>4</sup>**), <sup>1</sup>H NMR (400 MHz, acetonitrile-*d*<sub>3</sub>)



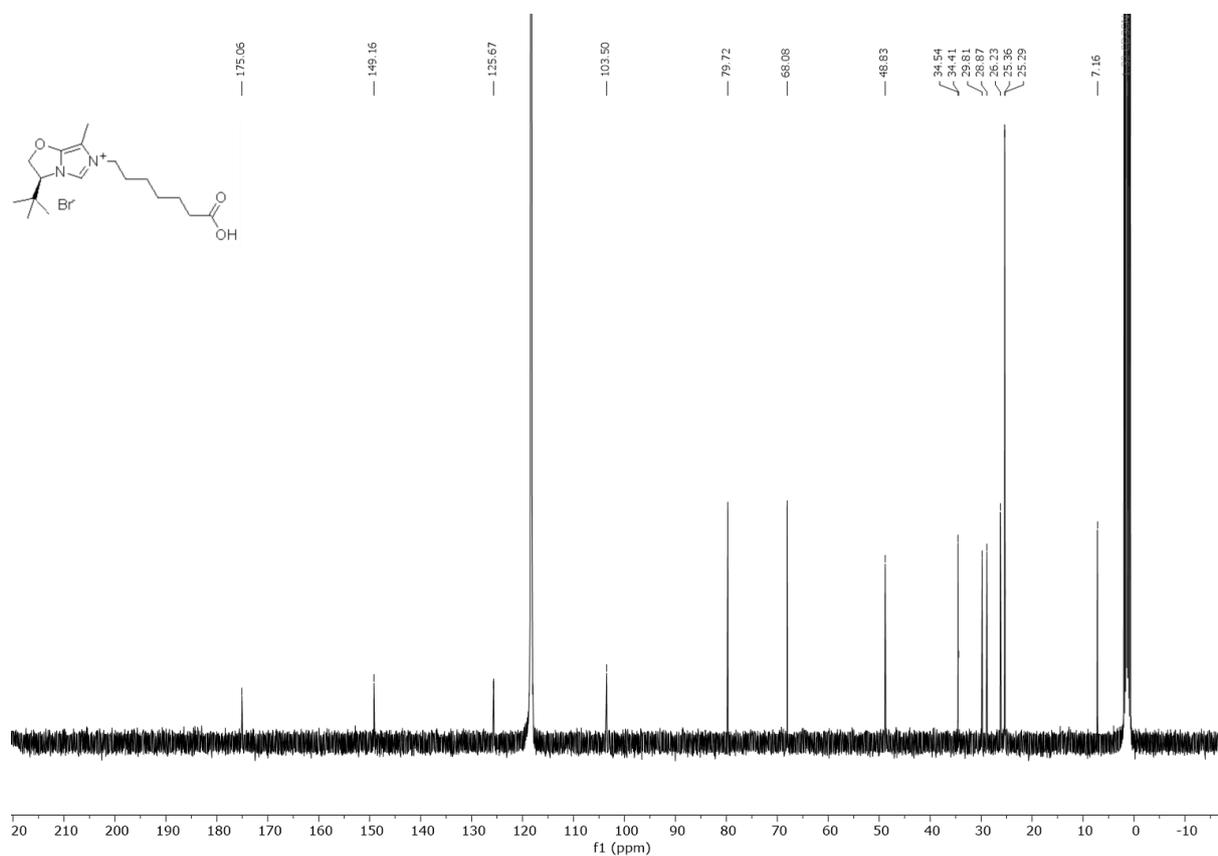
<sup>13</sup>C NMR: (101 MHz, acetonitrile-*d*<sub>3</sub>)



(*S*)-3-(tert-butyl)-6-(carboxymethyl)-6,6,6,6,7-hexamethyl-3,6-dihydro-2H-6l8-imidazo[4,3-b]oxazol-4-ium bromide (**BL<sup>5</sup>**), <sup>1</sup>H NMR (400 MHz, acetonitrile-*d*<sub>3</sub>)

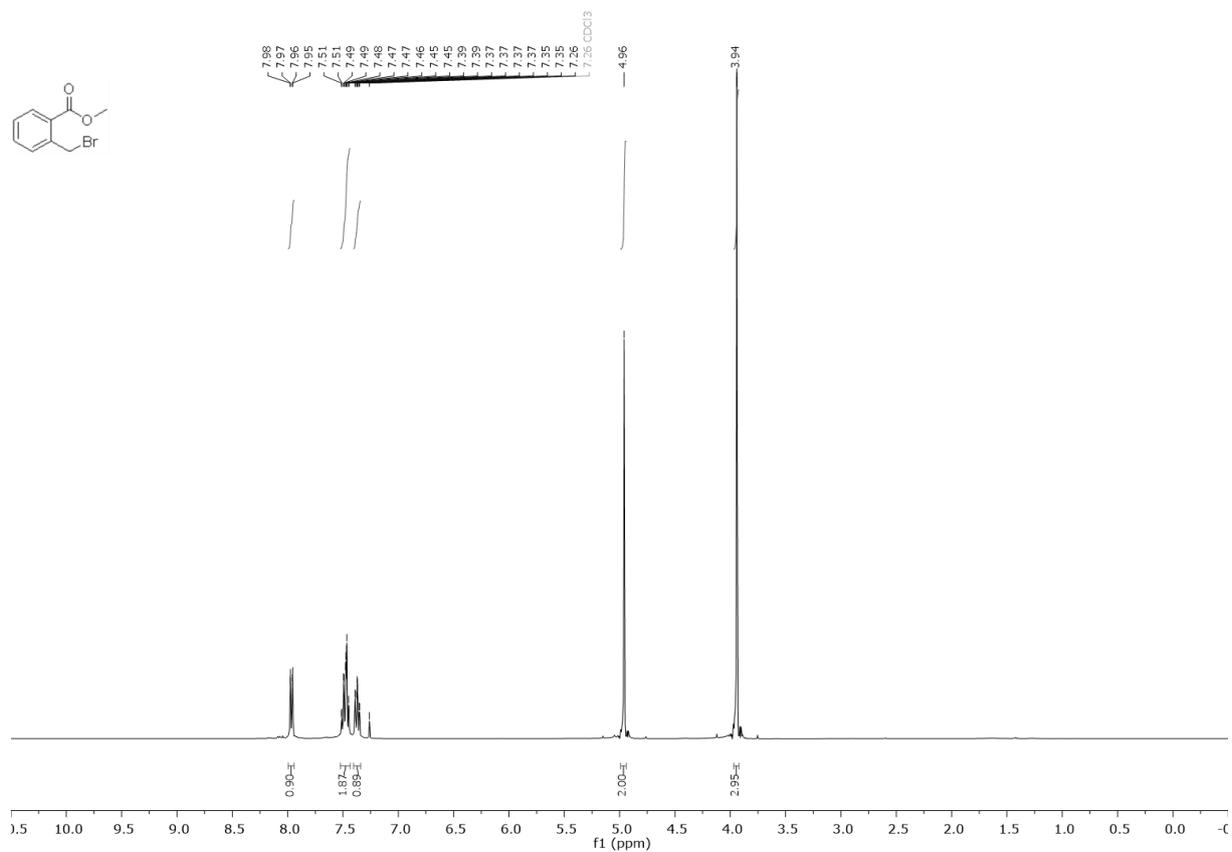


<sup>13</sup>C NMR (101 MHz, acetonitrile-*d*<sub>3</sub>)

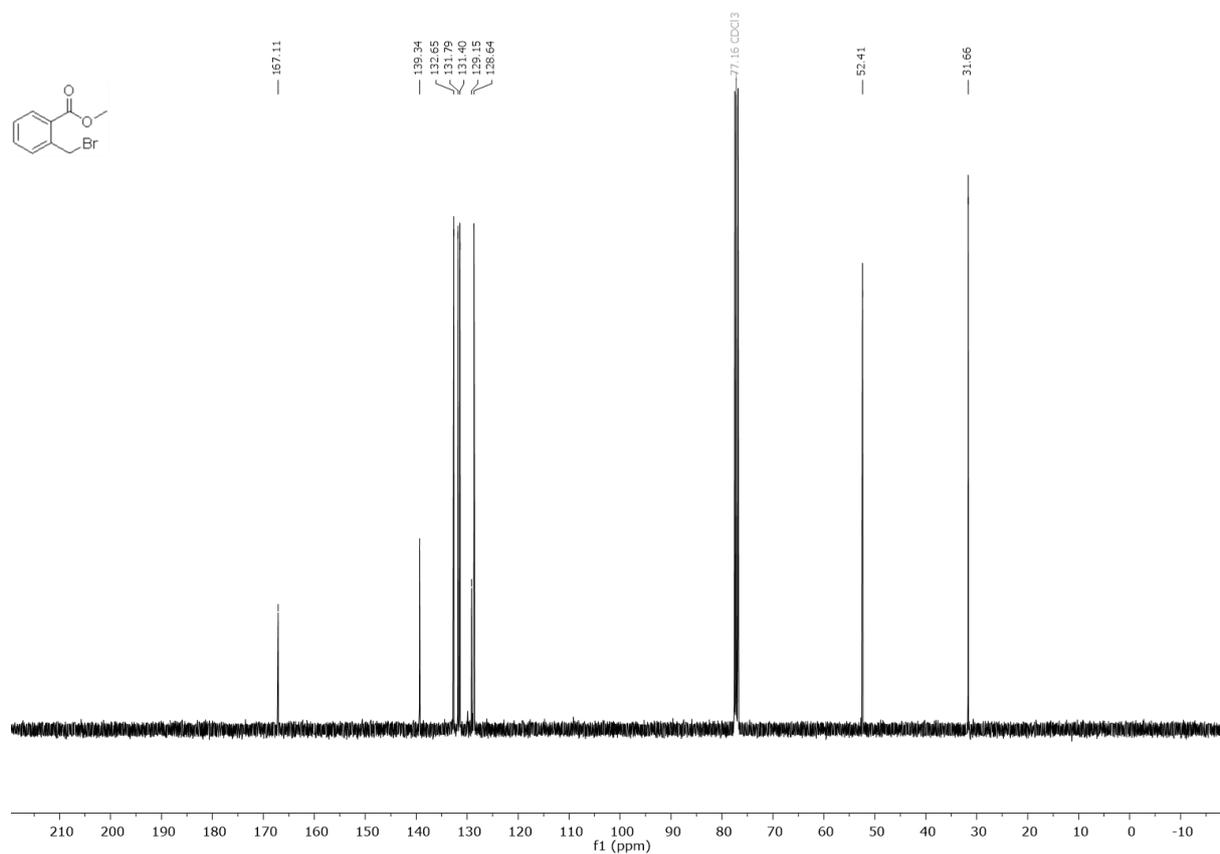


methyl 2-(bromomethyl)benzoate (**5.15**)

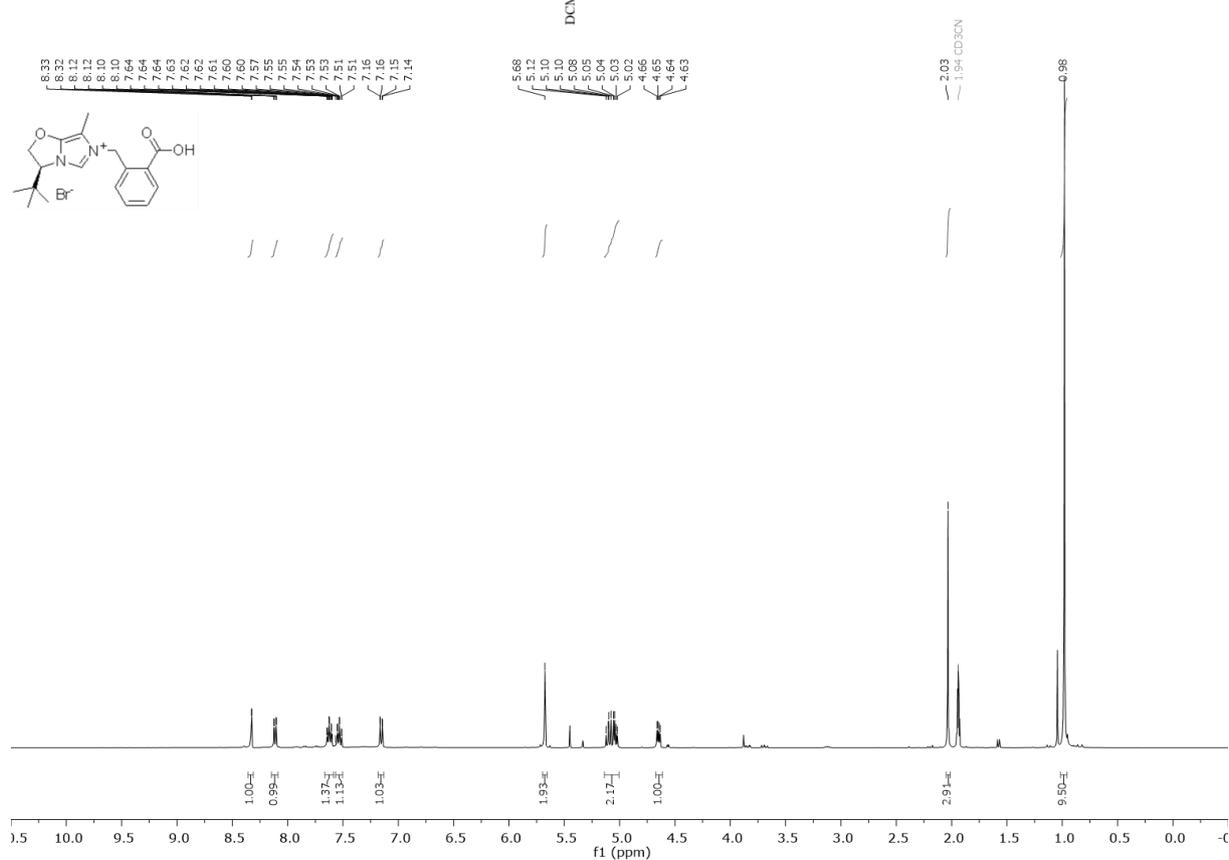
$^1\text{H}$  NMR (400 MHz, chloroform-*d*)



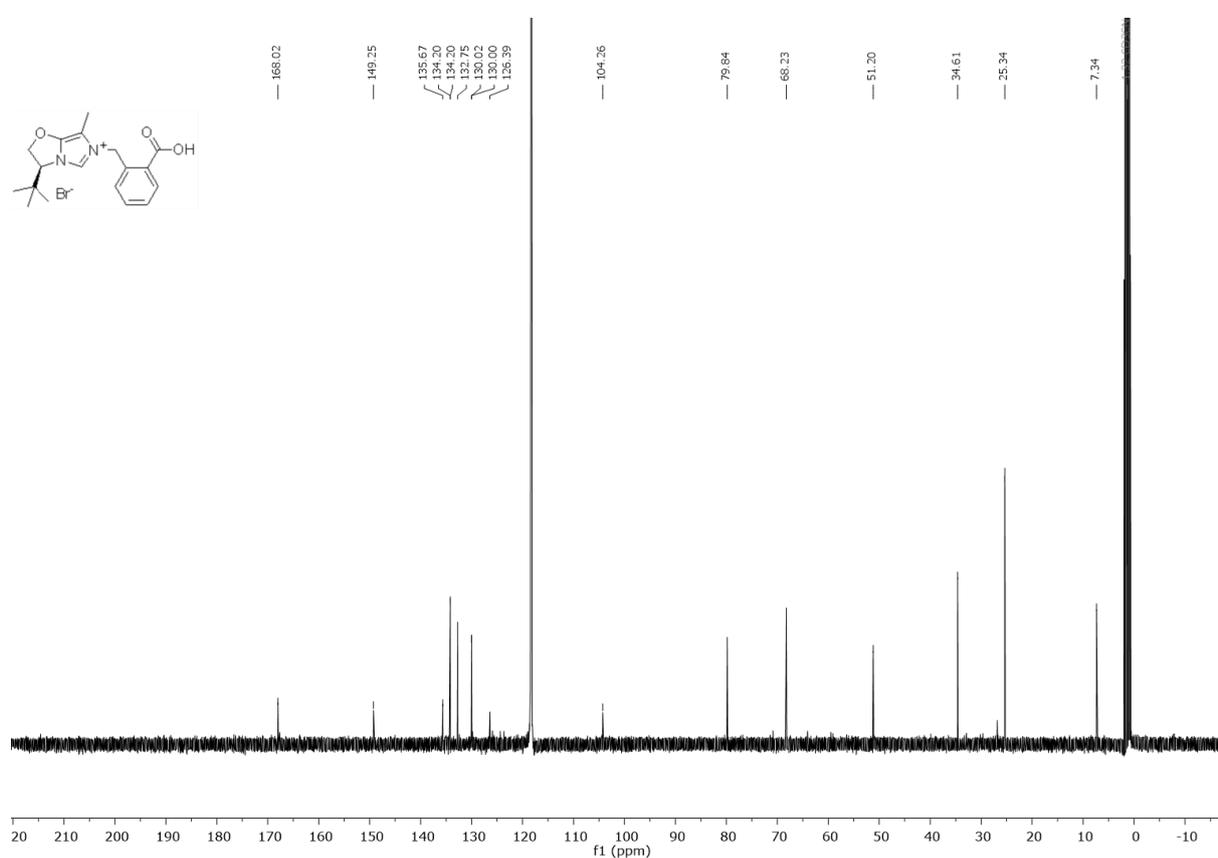
$^{13}\text{C}$  NMR (101 MHz, chloroform-*d*)



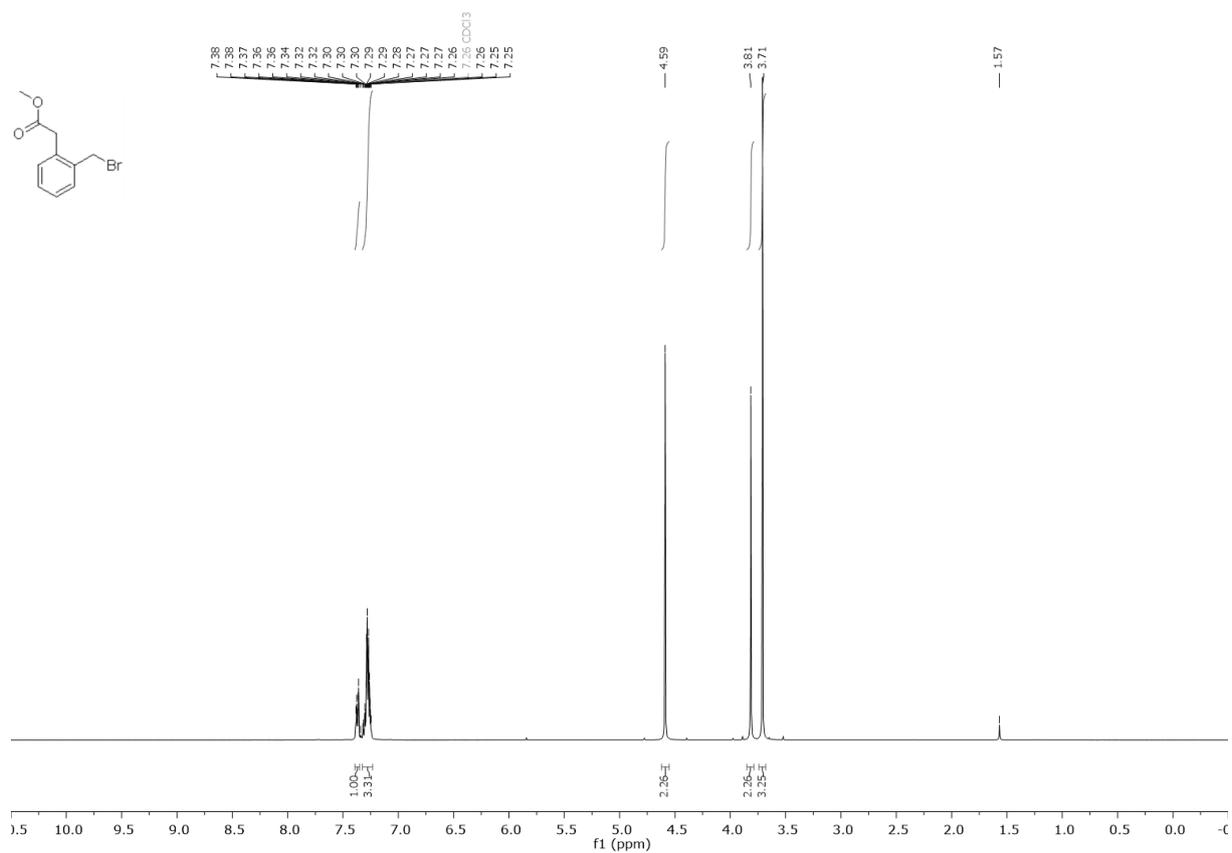
(*S*)-3-(*tert*-butyl)-6-(2-carboxybenzyl)-7-methyl-2,3-dihydroimidazo[5,1-*b*]oxazol-6-ium bromide (**BL**<sup>6</sup>), <sup>1</sup>H NMR (400 MHz, acetonitrile-*d*<sub>3</sub>)



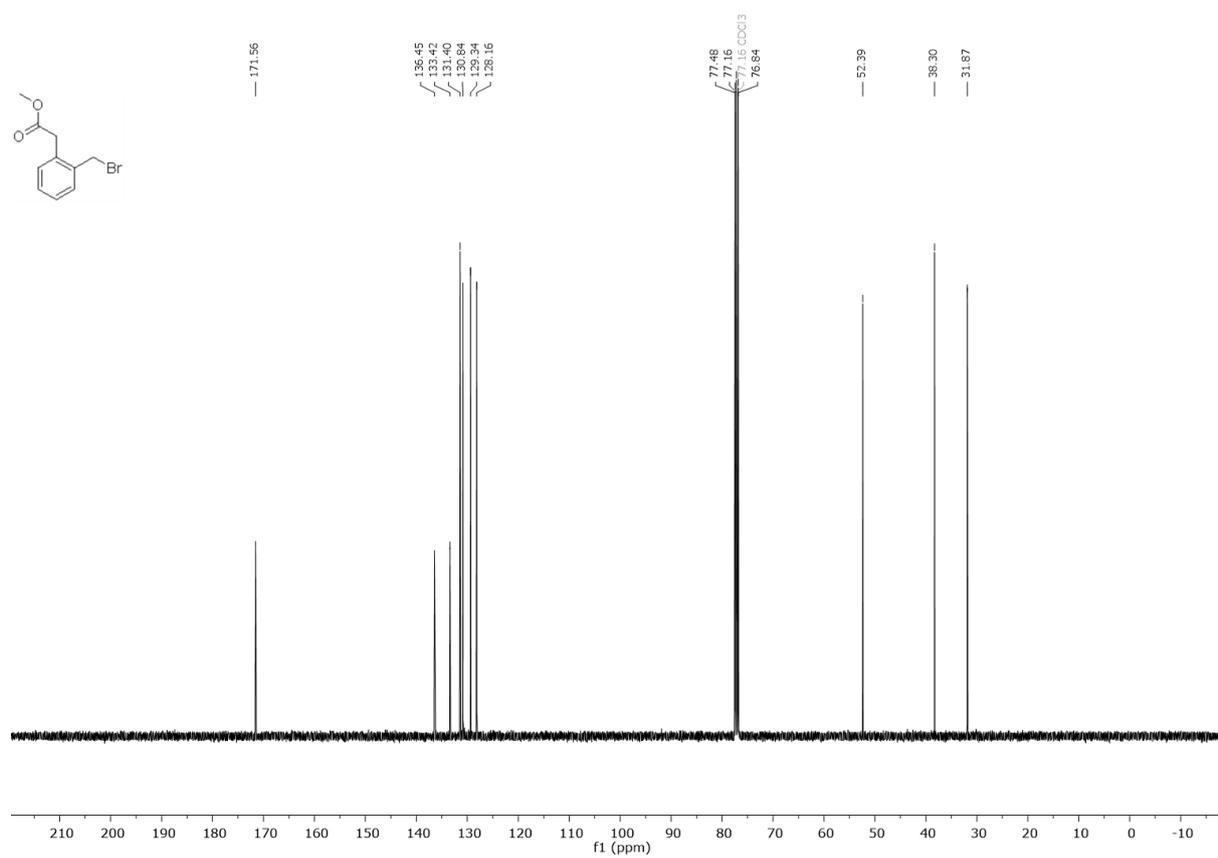
<sup>13</sup>C NMR (101 MHz, acetonitrile-*d*<sub>3</sub>)



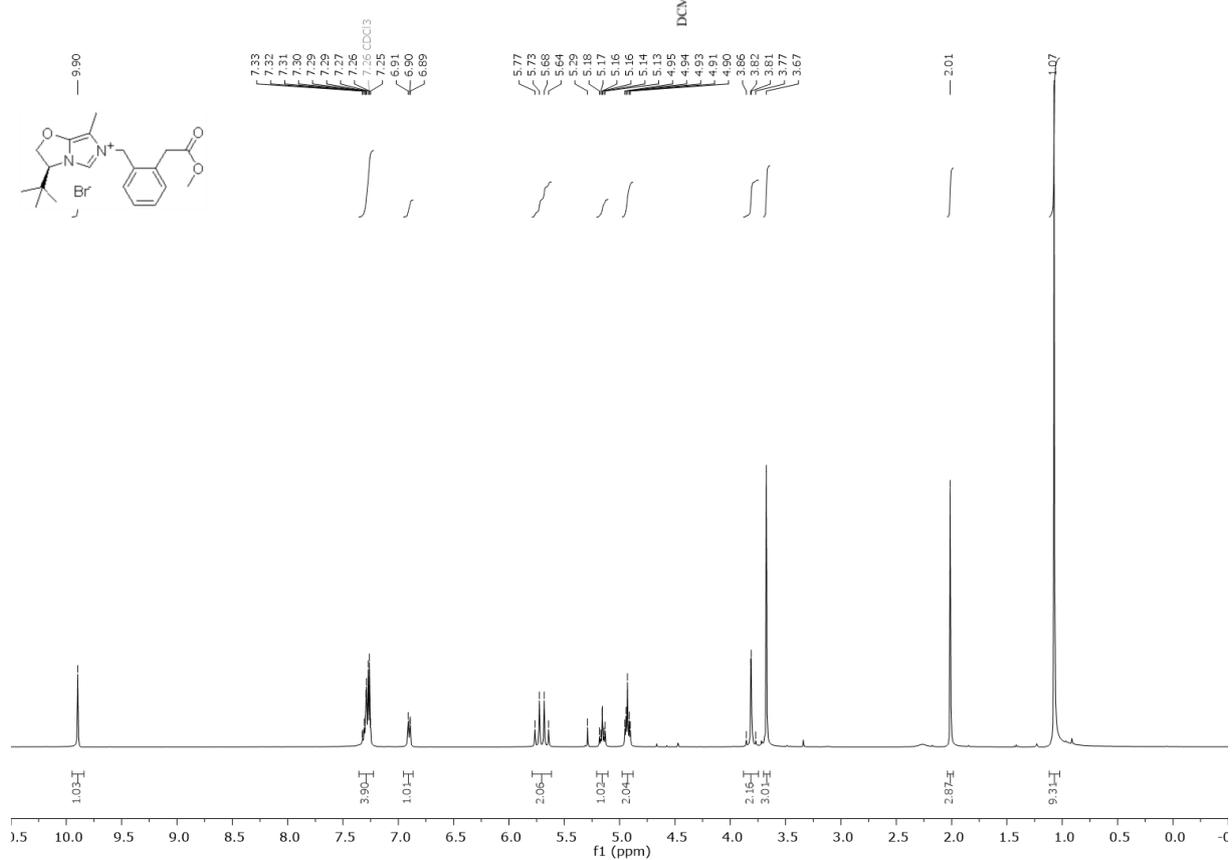
methyl 2-(2-(bromomethyl)phenyl)acetate (**5.16**),  $^1\text{H NMR}$  (400 MHz, chloroform-*d*)



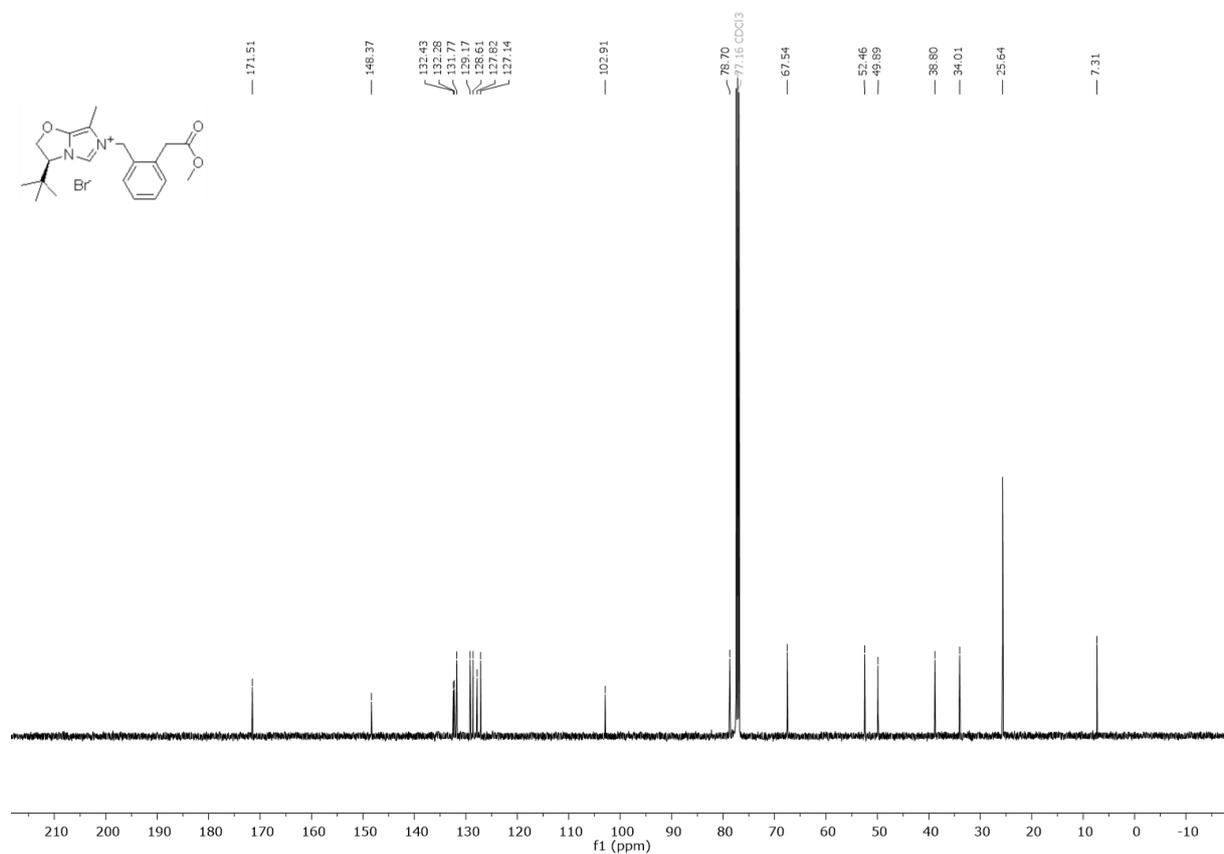
$^{13}\text{C NMR}$  (101 MHz, chloroform-*d*)



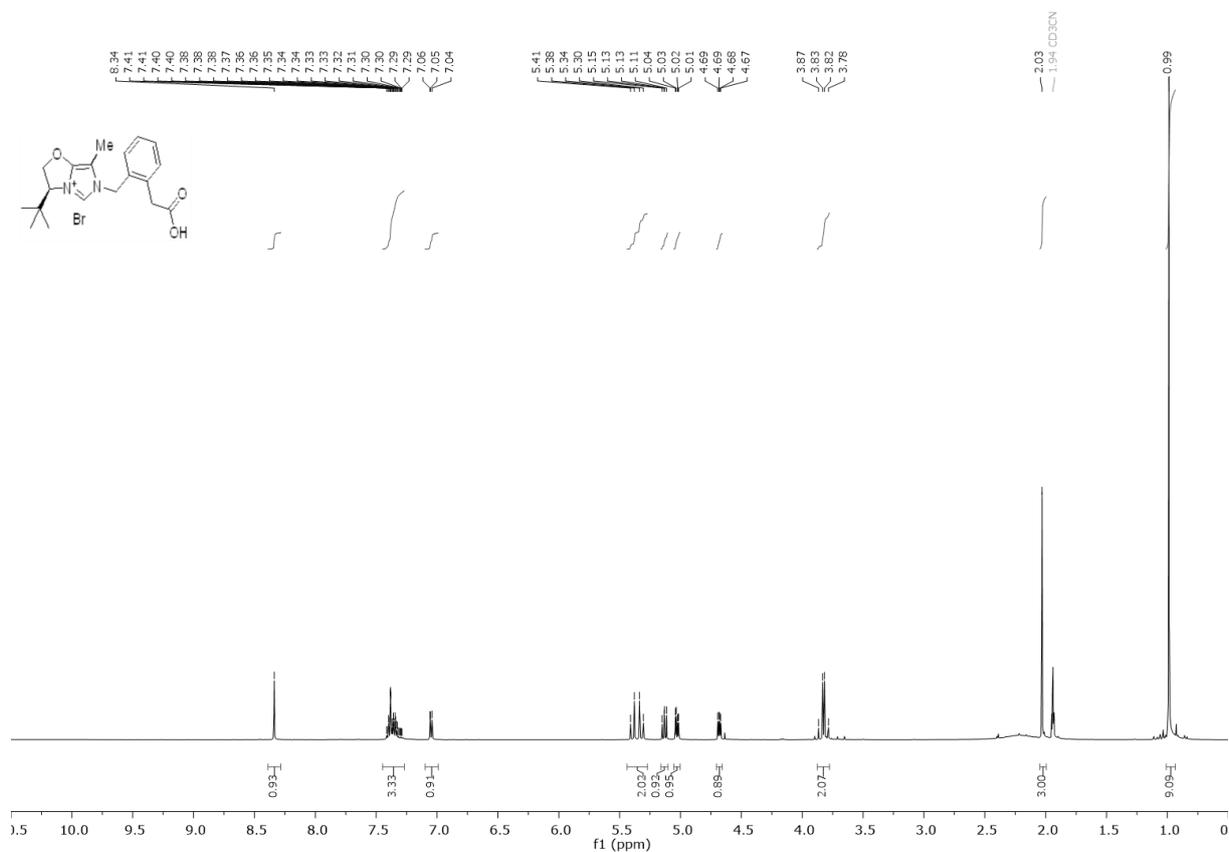
(*S*)-3-(*tert*-butyl)-6-(2-(2-methoxy-2-oxoethyl)benzyl)-7-methyl-2,3-dihydroimidazo[5,1-*b*]oxazol-6-ium bromide (**5.17**),  $^1\text{H NMR}$ : (400 MHz, chloroform-*d*)



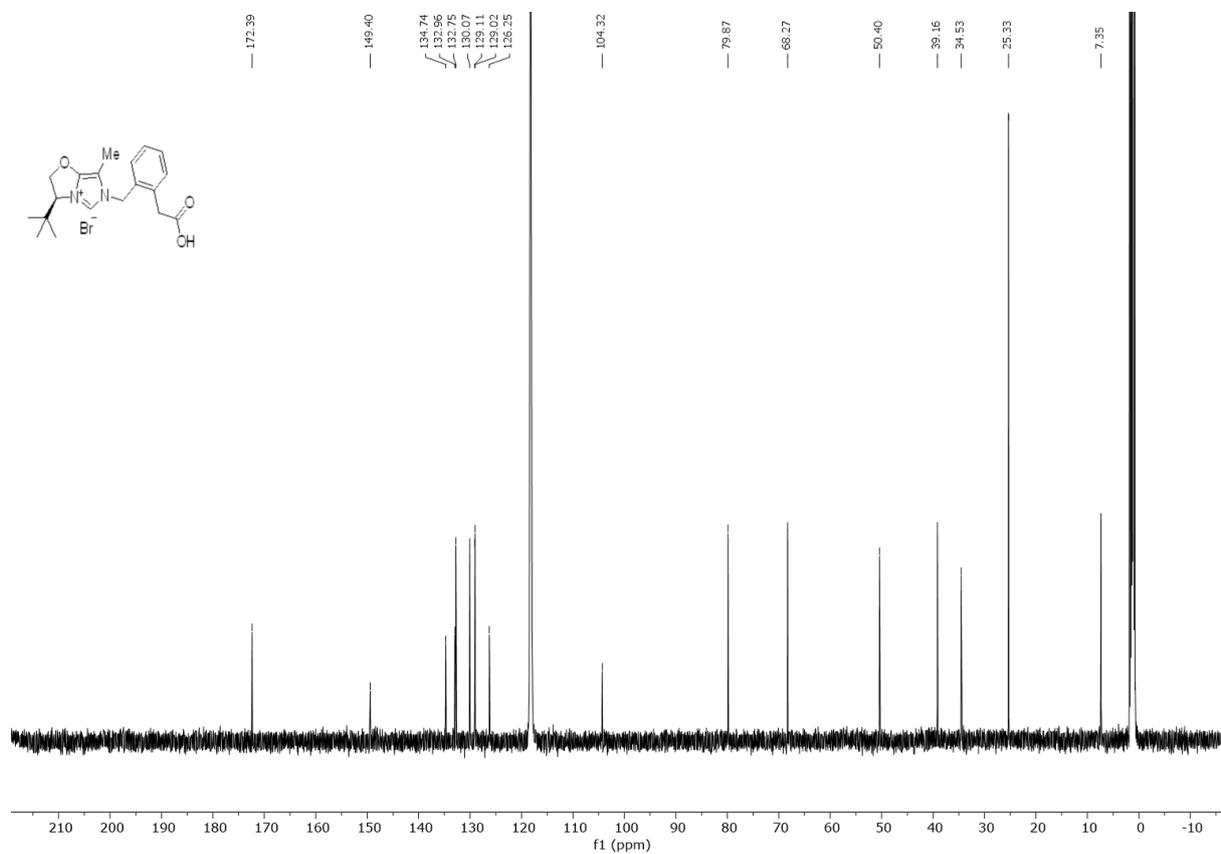
$^{13}\text{C NMR}$  (126 MHz, chloroform-*d*)



(S)-3-(tert-butyl)-6-(2-(carboxymethyl)benzyl)-7-methyl-2,3-dihydroimidazo[5,1-b]oxazol-6-ium bromide (**BL**<sup>7</sup>), <sup>1</sup>H NMR (500 MHz, acetonitrile-*d*<sub>3</sub>)

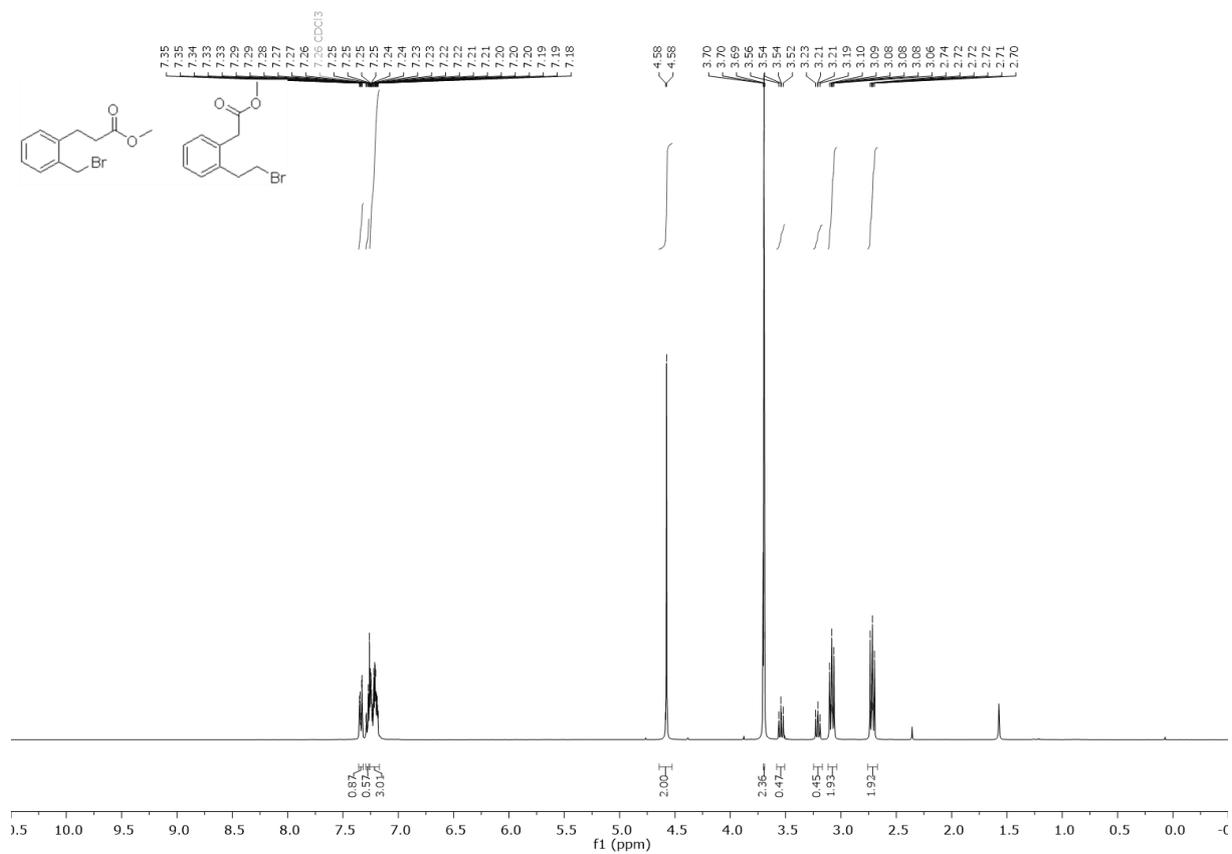


<sup>13</sup>C NMR (126 MHz, acetonitrile-*d*<sub>3</sub>)

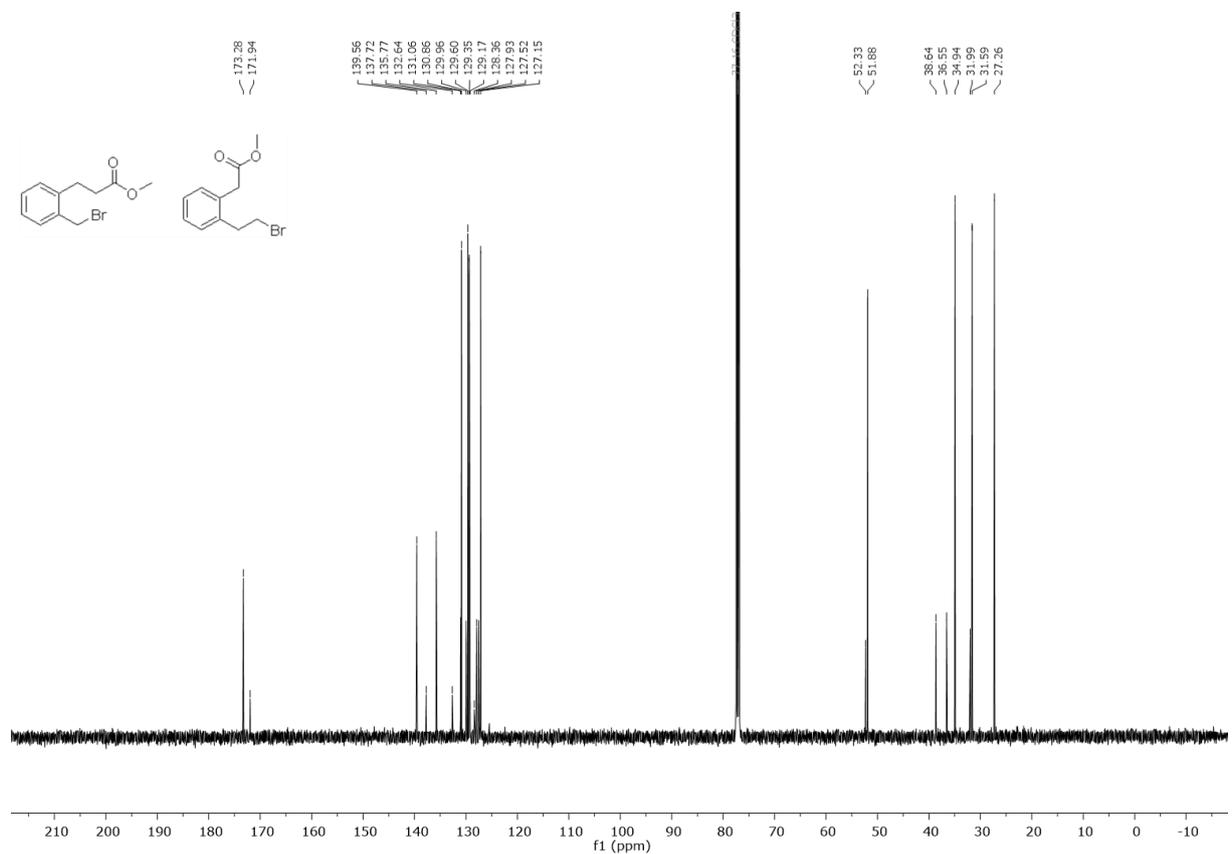


methyl 3-(2-(bromomethyl)phenyl)propanoate (**5.18**)

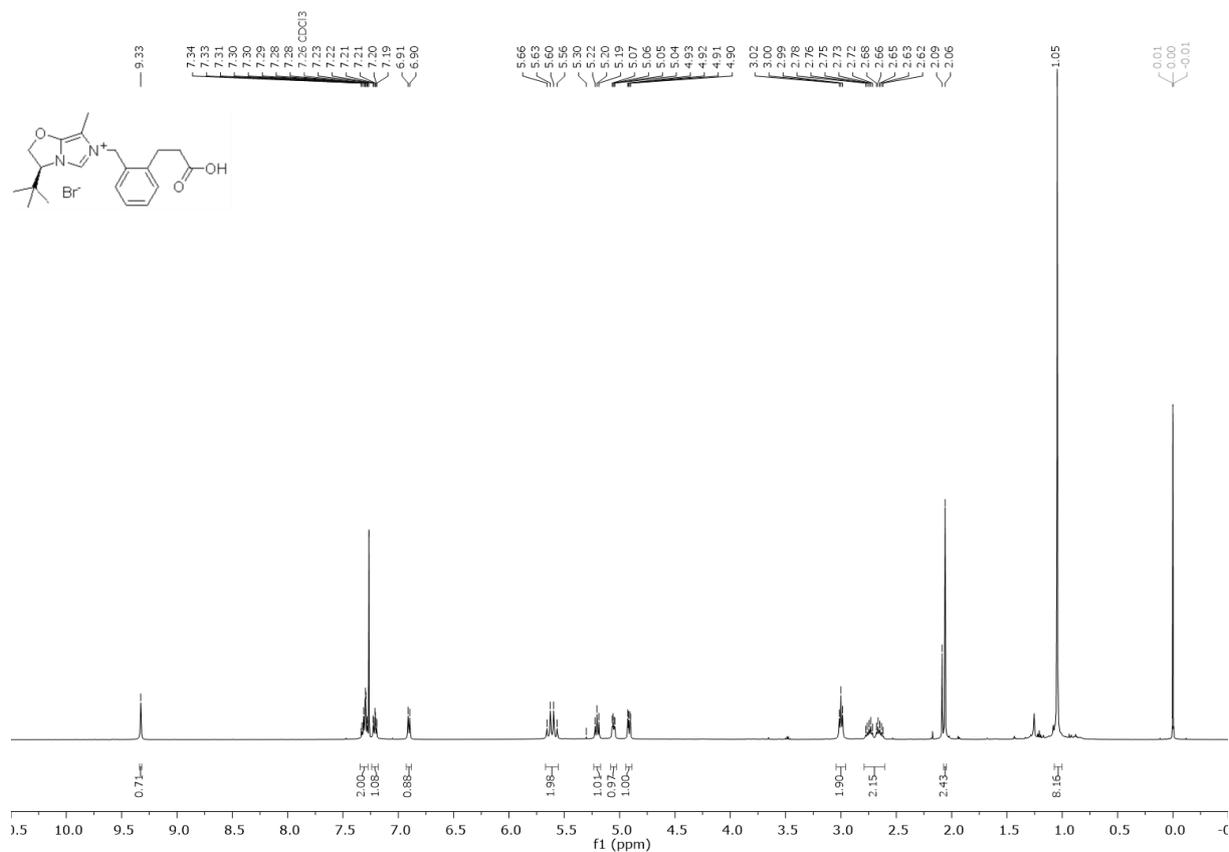
$^1\text{H NMR}$  (400 MHz, chloroform-*d*)



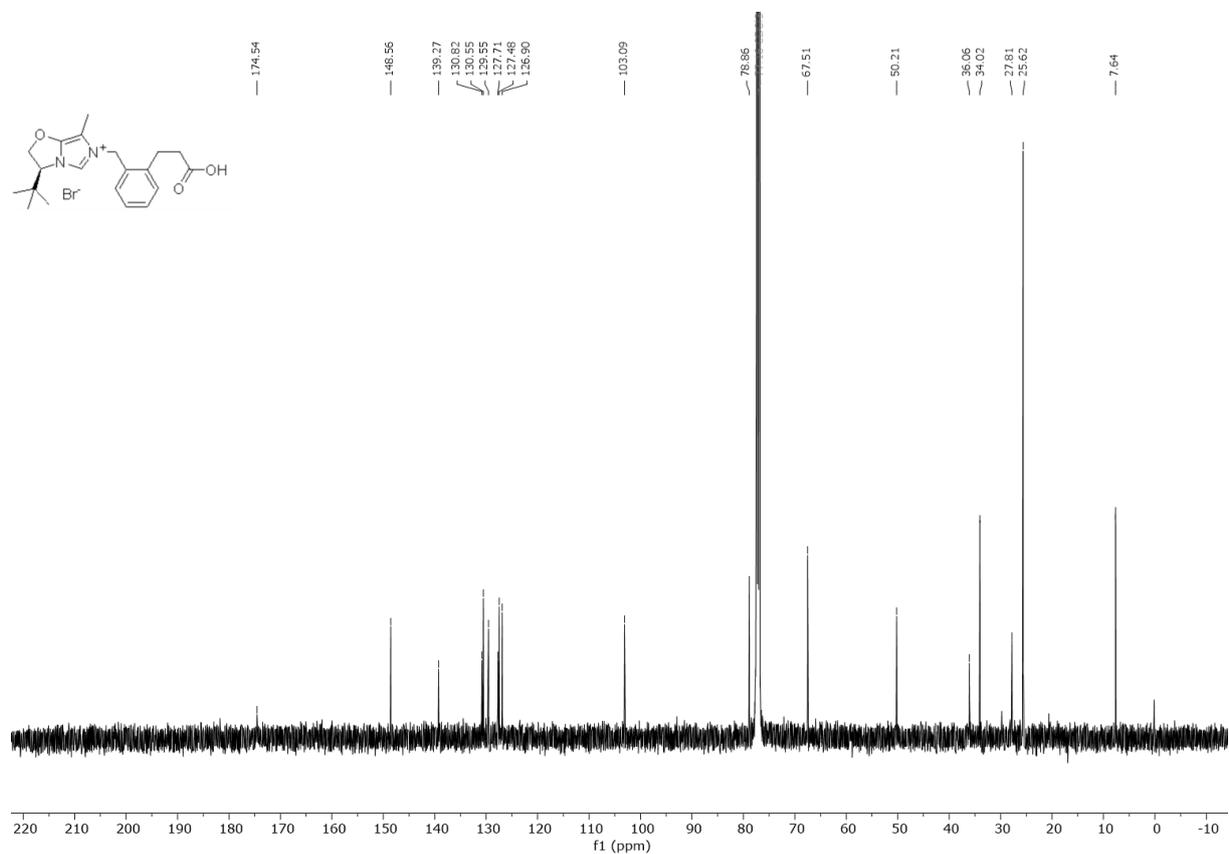
$^{13}\text{C NMR}$  (126 MHz, chloroform-*d*)



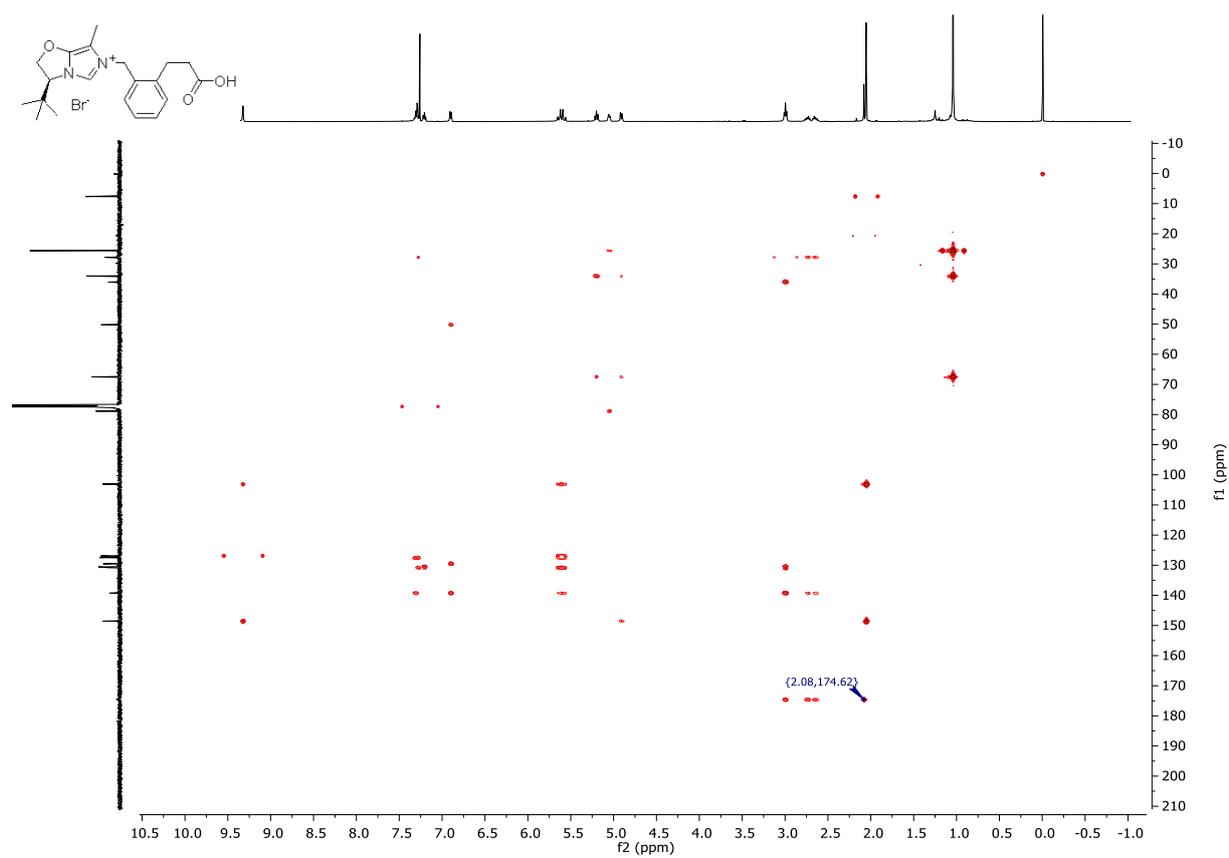
(*S*)-3-(tert-butyl)-6-(2-(2-carboxyethyl)benzyl)-7-methyl-2,3-dihydroimidazo[5,1-b]oxazol-6-ium bromide (**BL**<sup>8</sup>), <sup>1</sup>H NMR (500 MHz, chloroform-*d*)



<sup>13</sup>C NMR (126 MHz, chloroform-*d*)

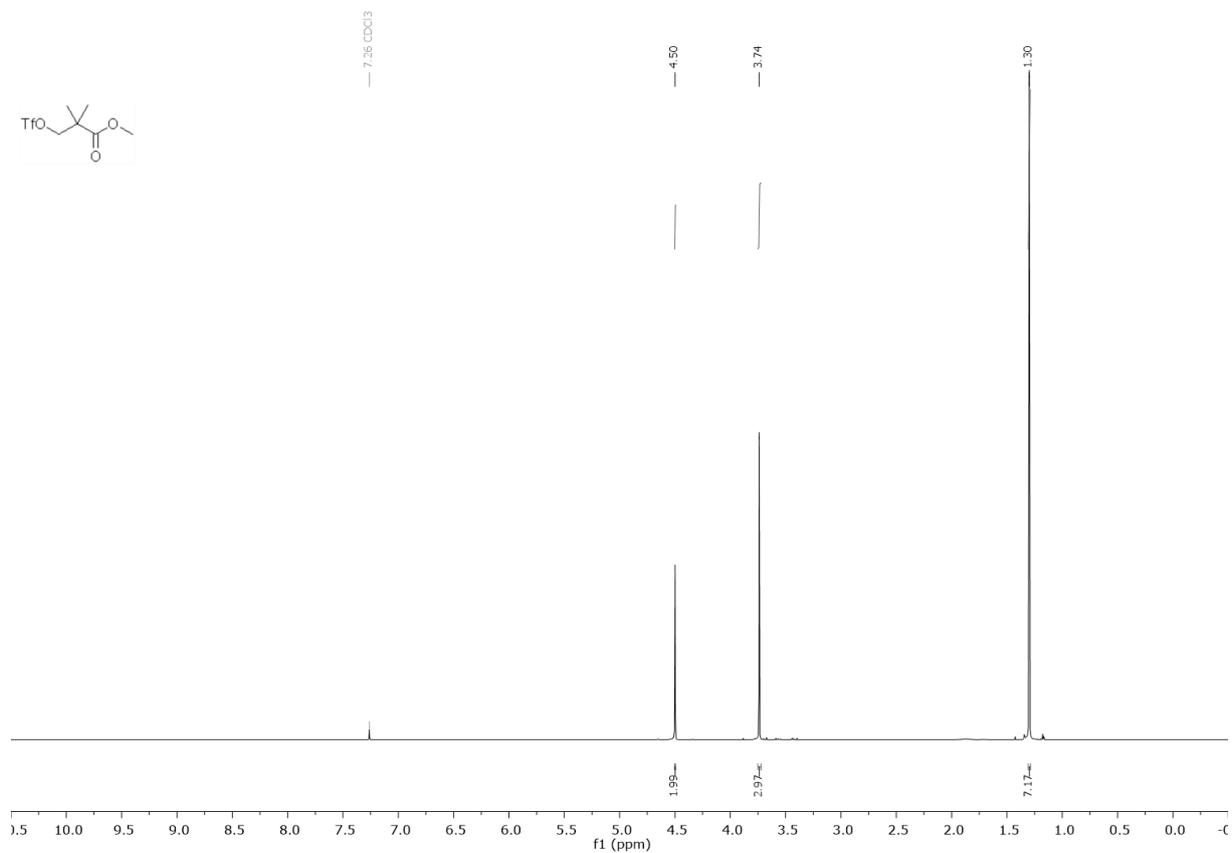


# HMBC

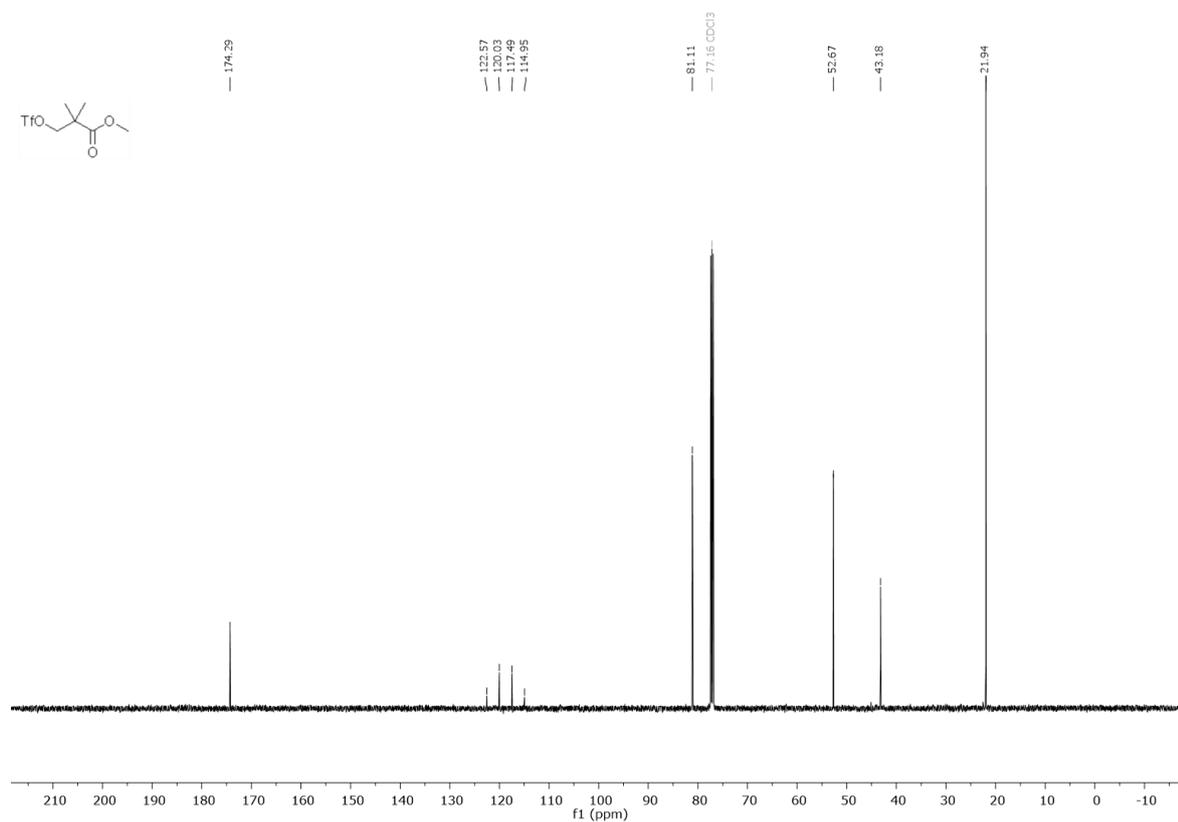


methyl 2,2-dimethyl-3-(((trifluoromethyl)sulfonyl)oxy)propanoate (**5.19**)

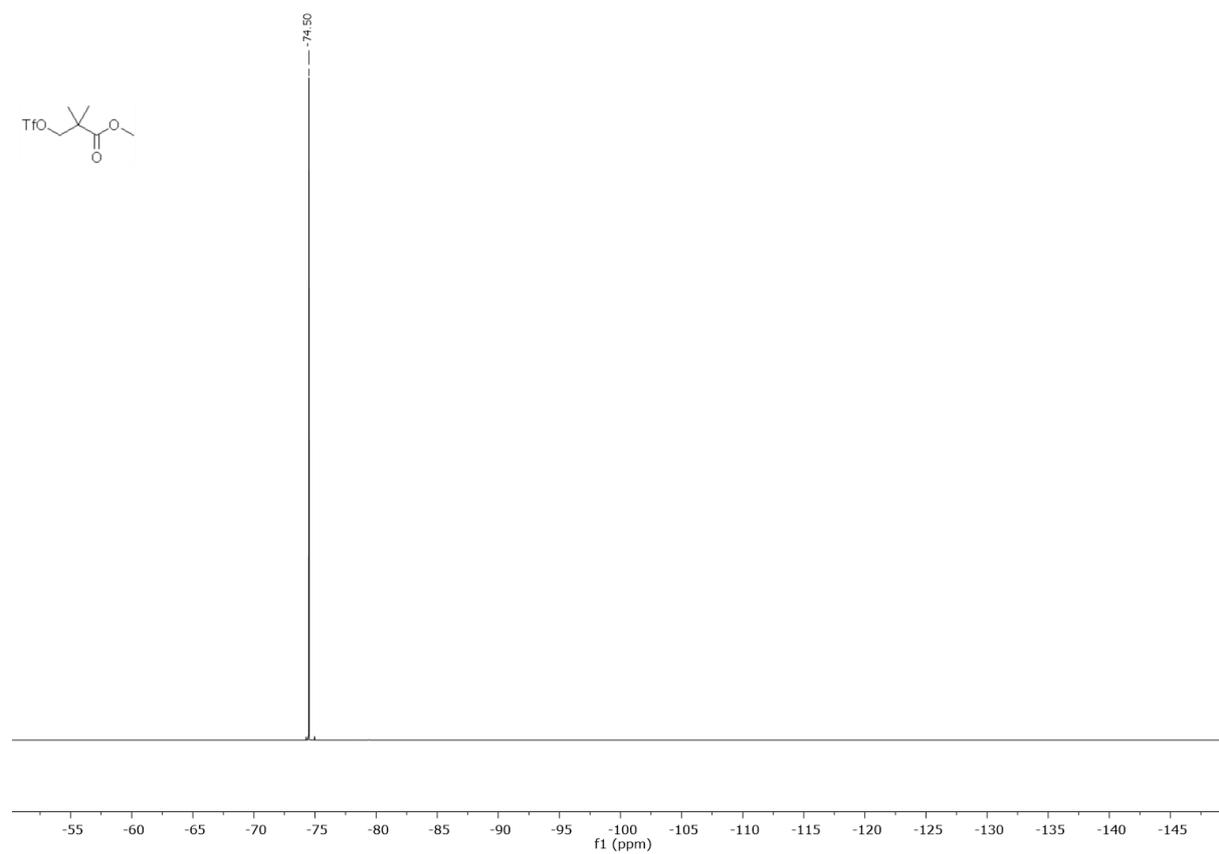
$^1\text{H}$  NMR (500 MHz, chloroform-*d*)



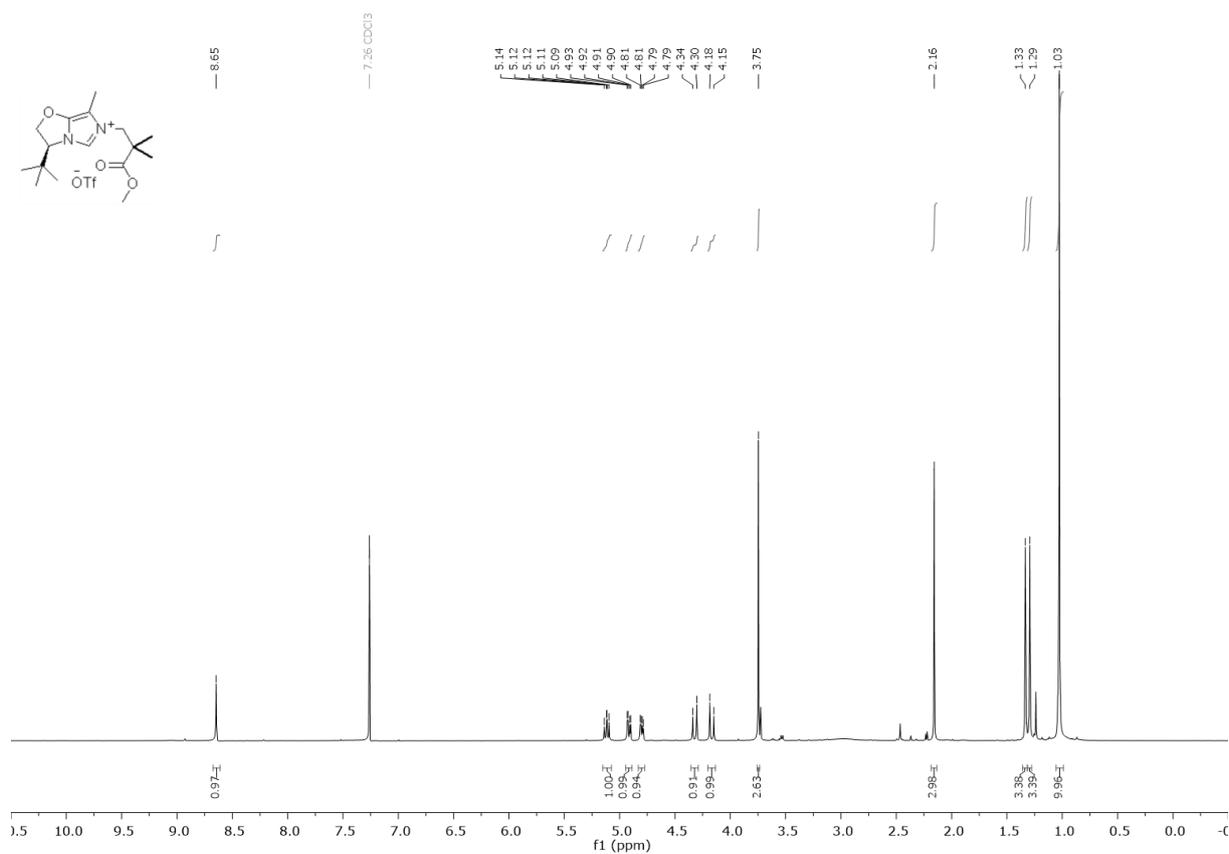
$^{13}\text{C}$  NMR (126 MHz, chloroform-*d*)



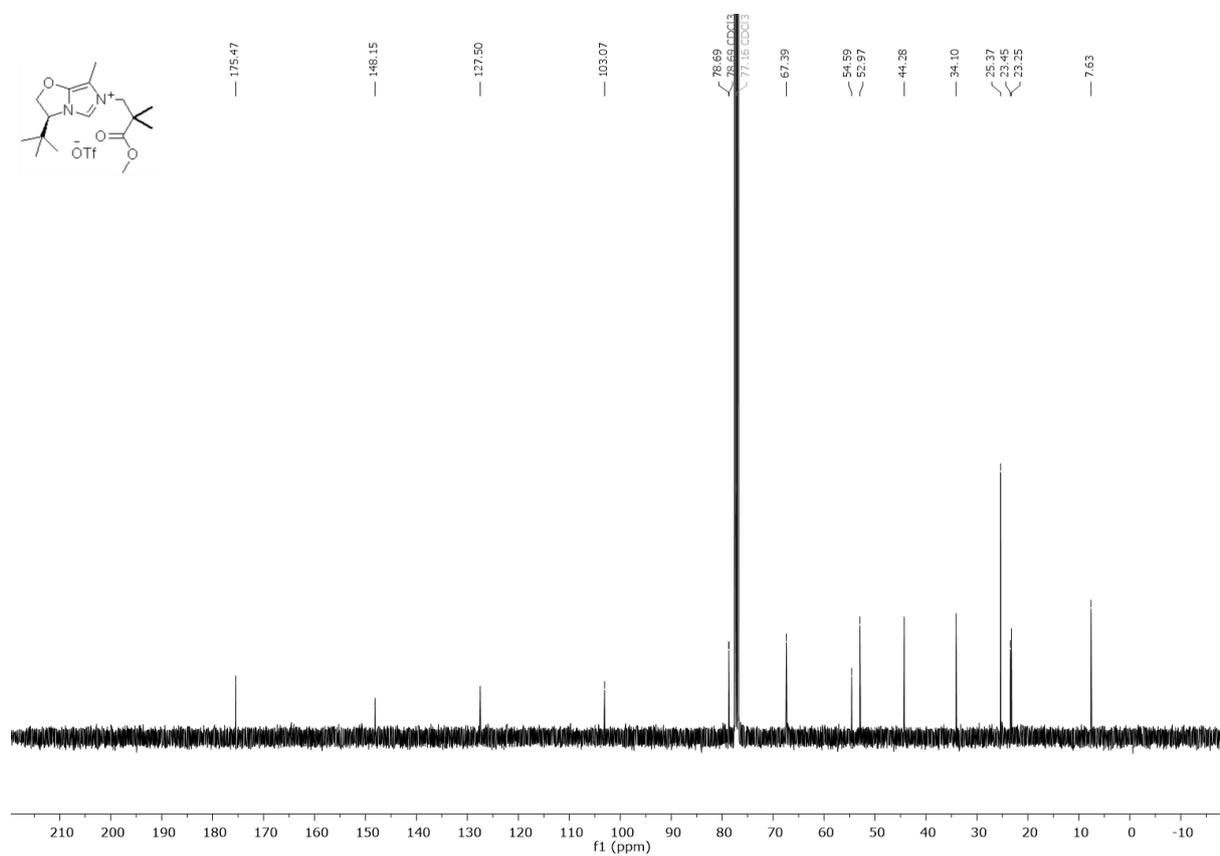
**$^{19}\text{F}$  NMR** (471 MHz, chloroform-*d*)  $\delta$  -74.5.



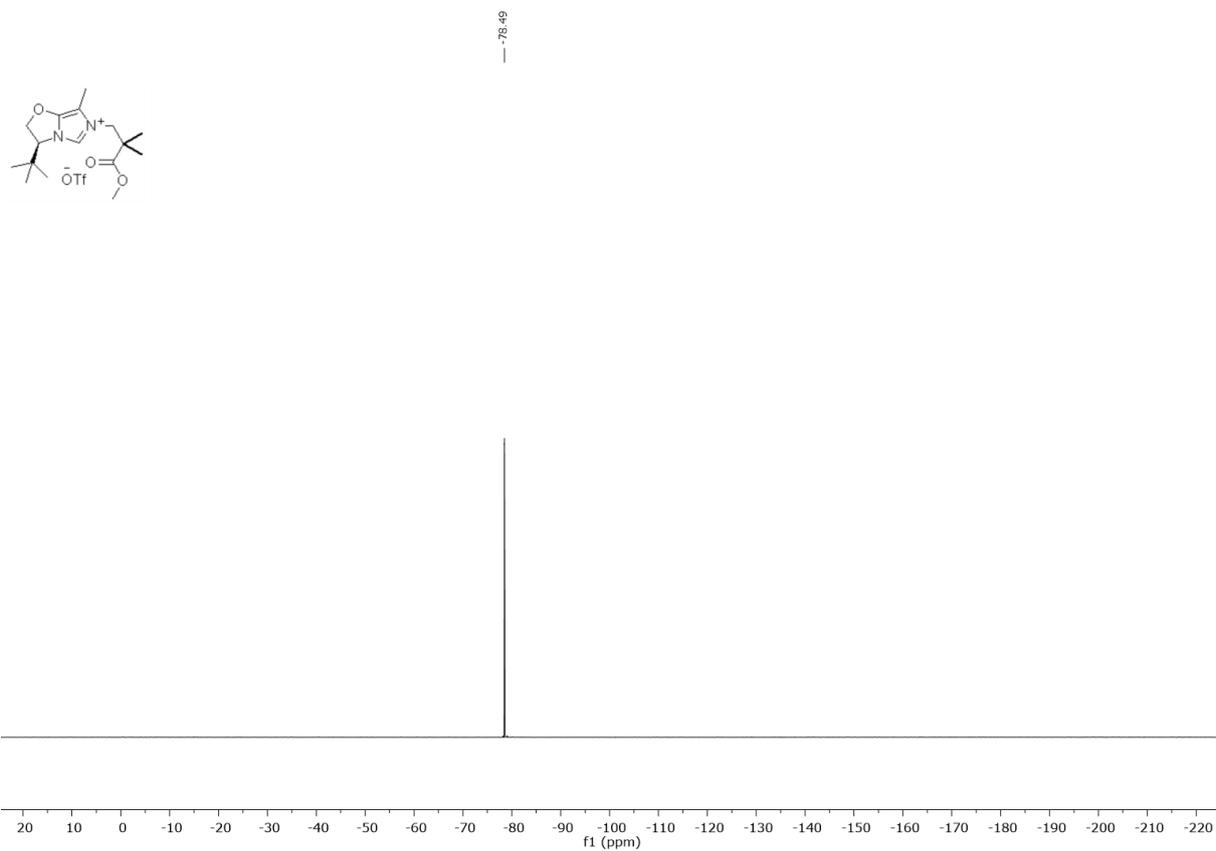
(*S*)-3-(tert-butyl)-6-(3-methoxy-2,2-dimethyl-3-oxopropyl)-7-methyl-2,3-dihydroimidazo[5,1-*b*]oxazol-6-ium trifluoromethanesulfonate (**5.20**),  $^1\text{H}$  NMR (400 MHz, chloroform-*d*)



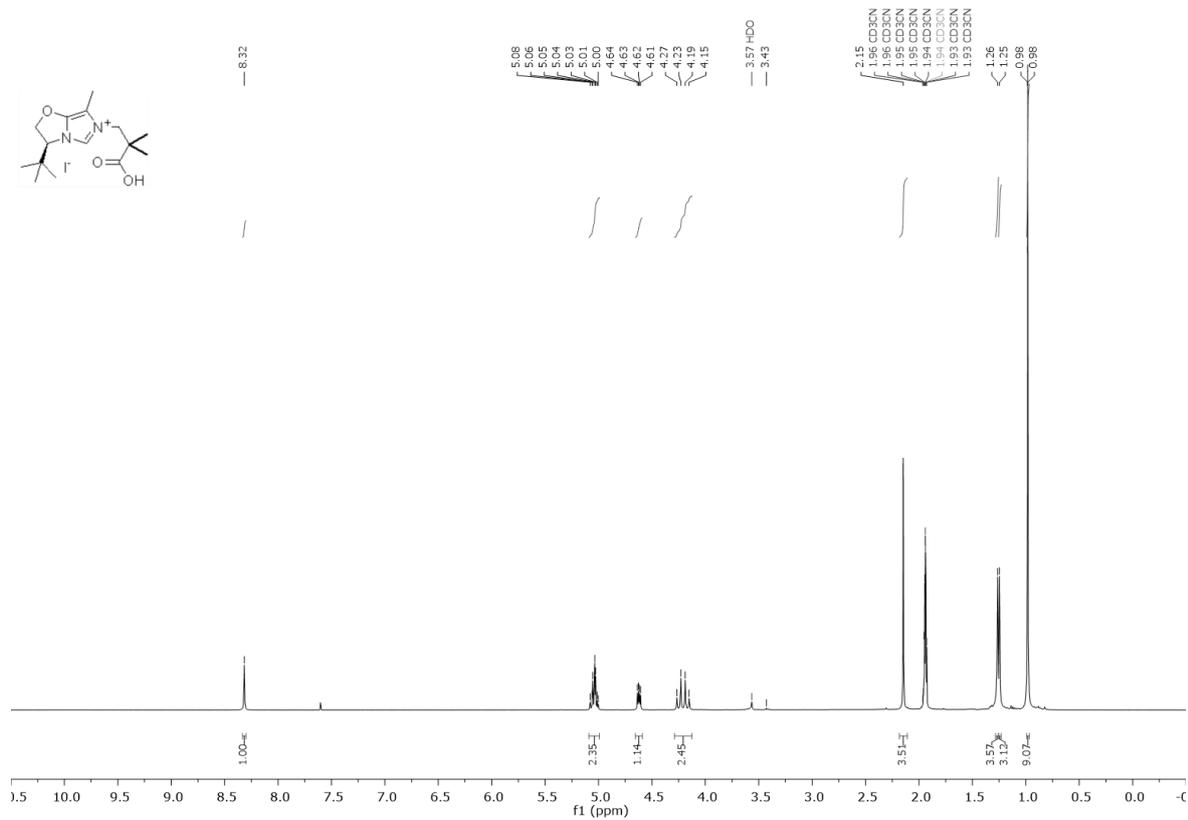
$^{13}\text{C}$  NMR (101 MHz, chloroform-*d*)



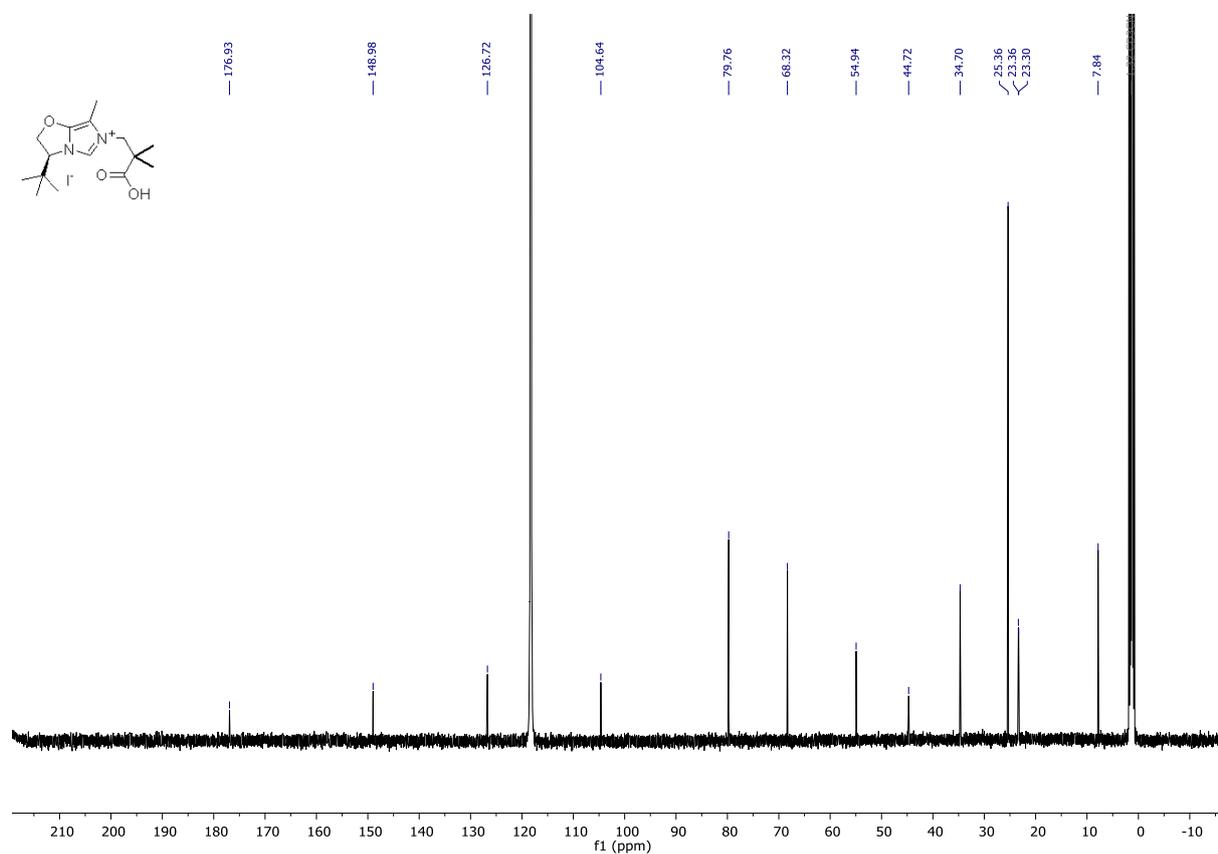
**$^{19}\text{F}$  NMR (376 MHz, chloroform-*d*)**



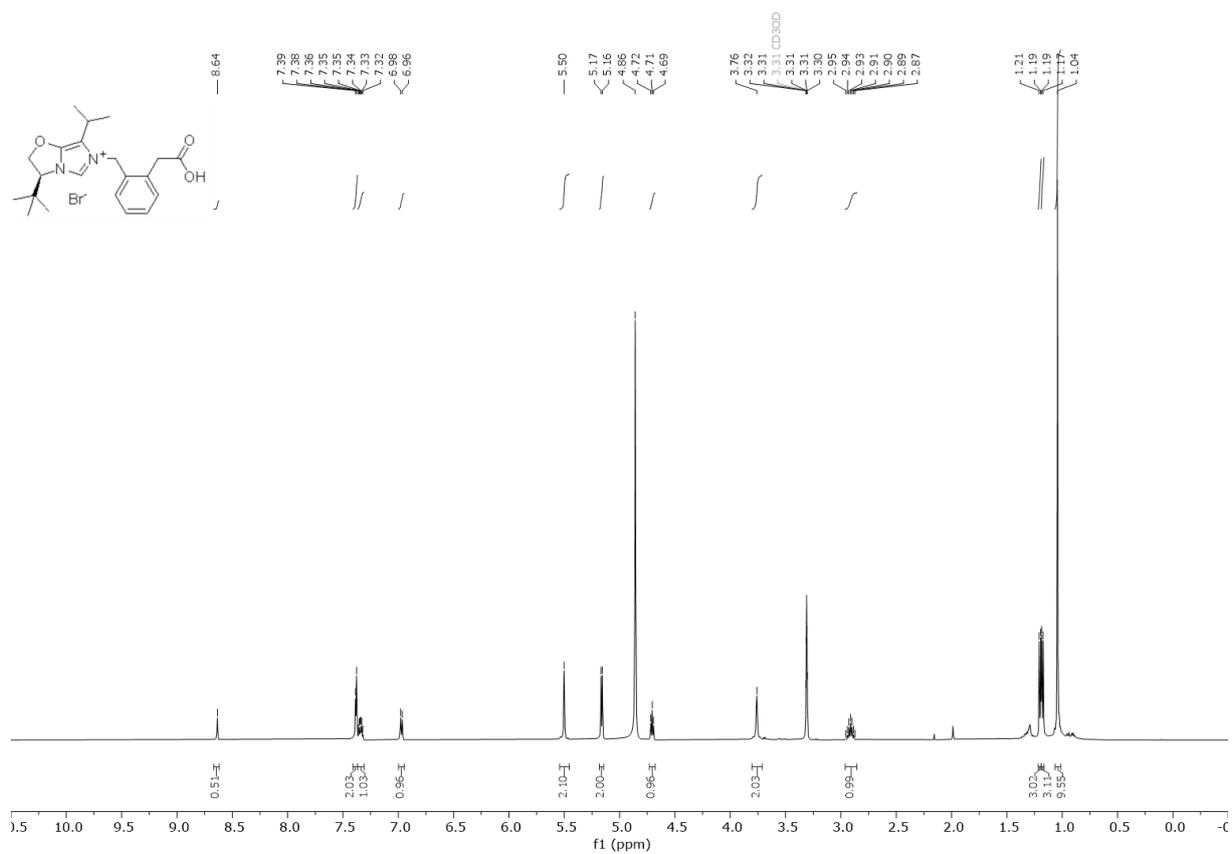
(*S*)-3-(*tert*-butyl)-6-(2-carboxy-2-methylpropyl)-7-methyl-2,3-dihydroimidazo[5,1-*b*]oxazol-6-ium iodide (**BL**<sup>9</sup>), <sup>1</sup>H NMR (400 MHz, chloroform-*d*)



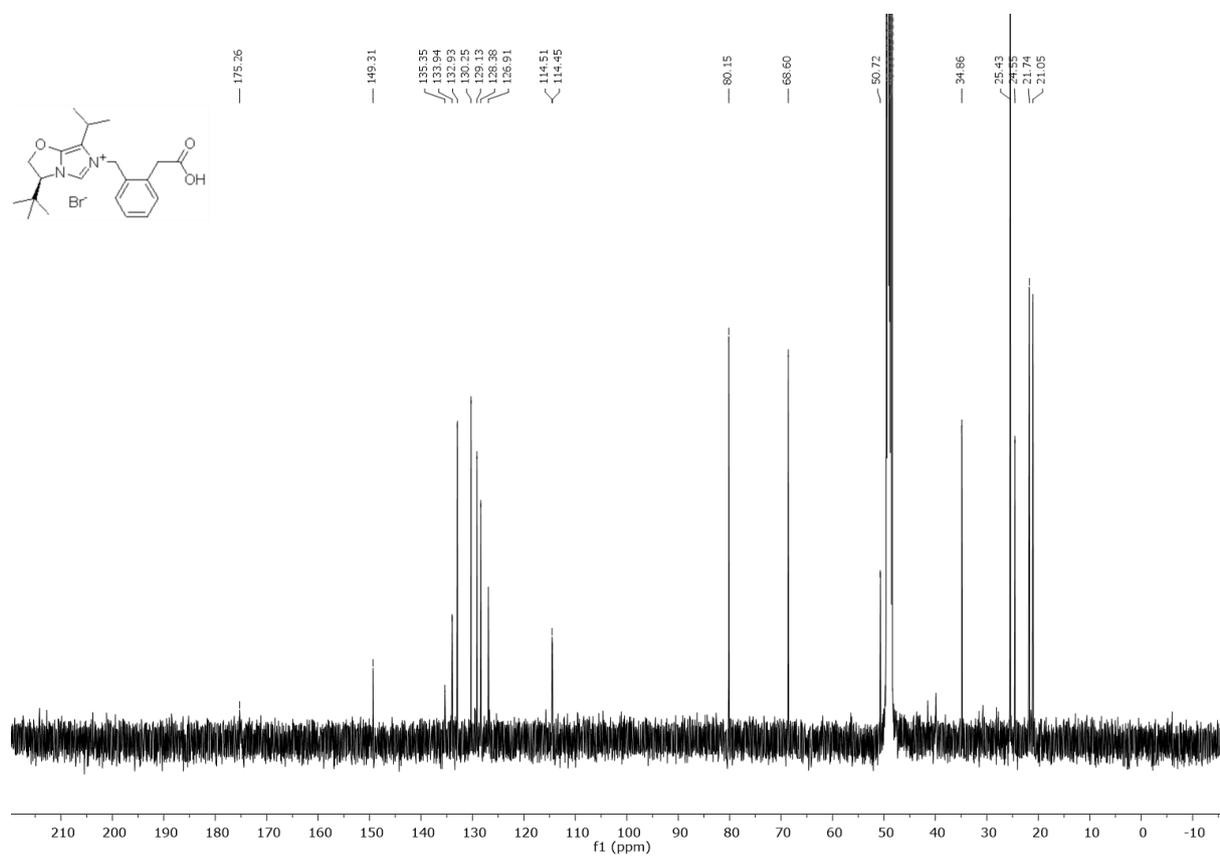
<sup>13</sup>C NMR (126 MHz, acetonitrile-*d*<sub>3</sub>)



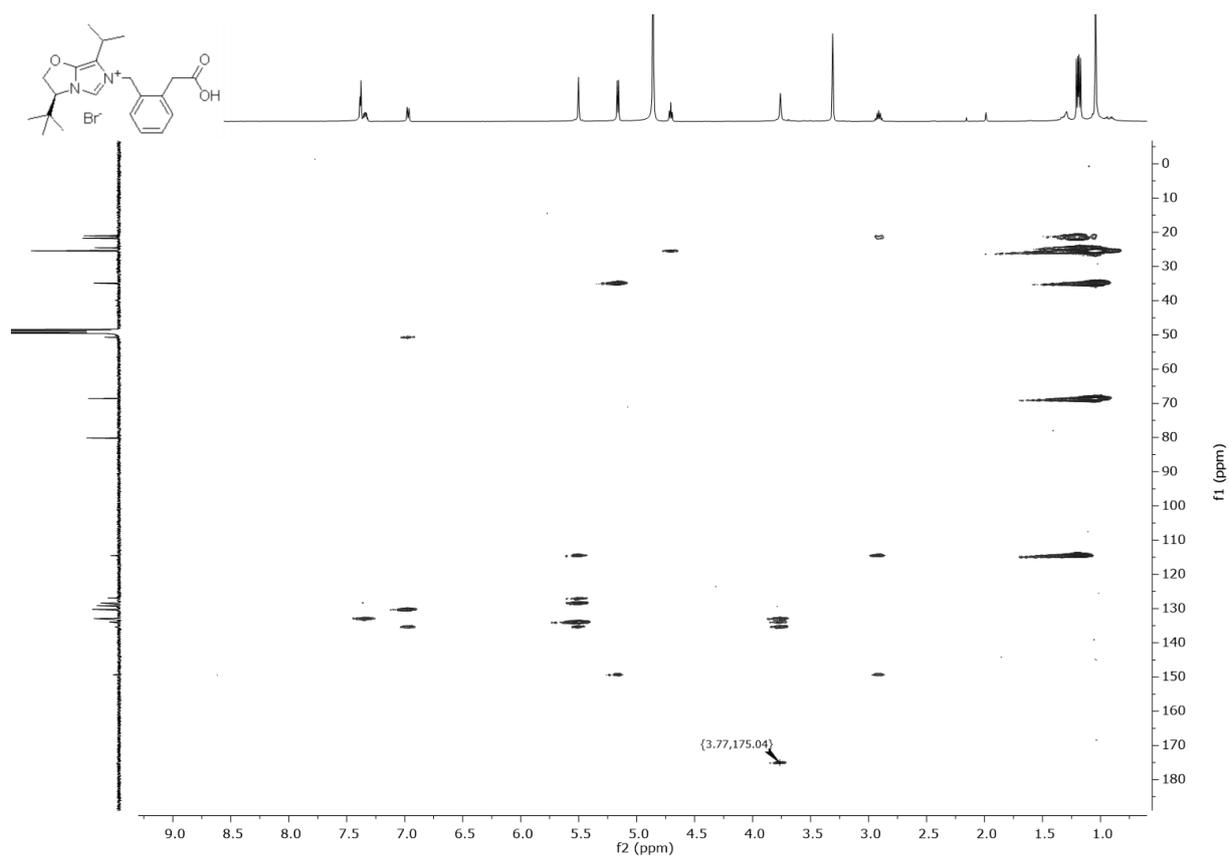
(S)-3-(tert-butyl)-6-(2-(carboxymethyl)benzyl)-7-isopropyl-2,3-dihydroimidazo[5,1-b]oxazol-6-ium bromide (**BL<sup>10</sup>**), <sup>1</sup>H NMR (400 MHz, methanol-d<sub>4</sub>)



<sup>13</sup>C NMR (126 MHz, methanol-d<sub>4</sub>)

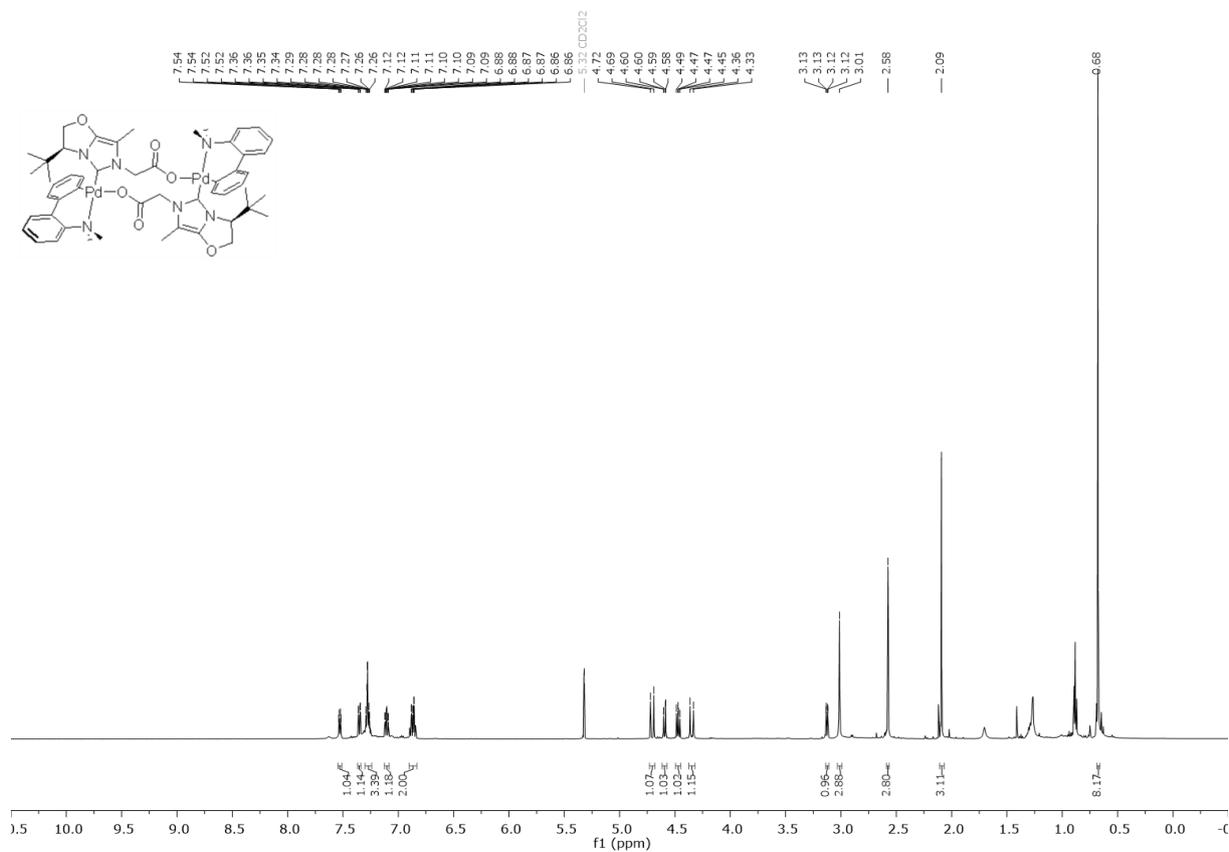


# HMBC

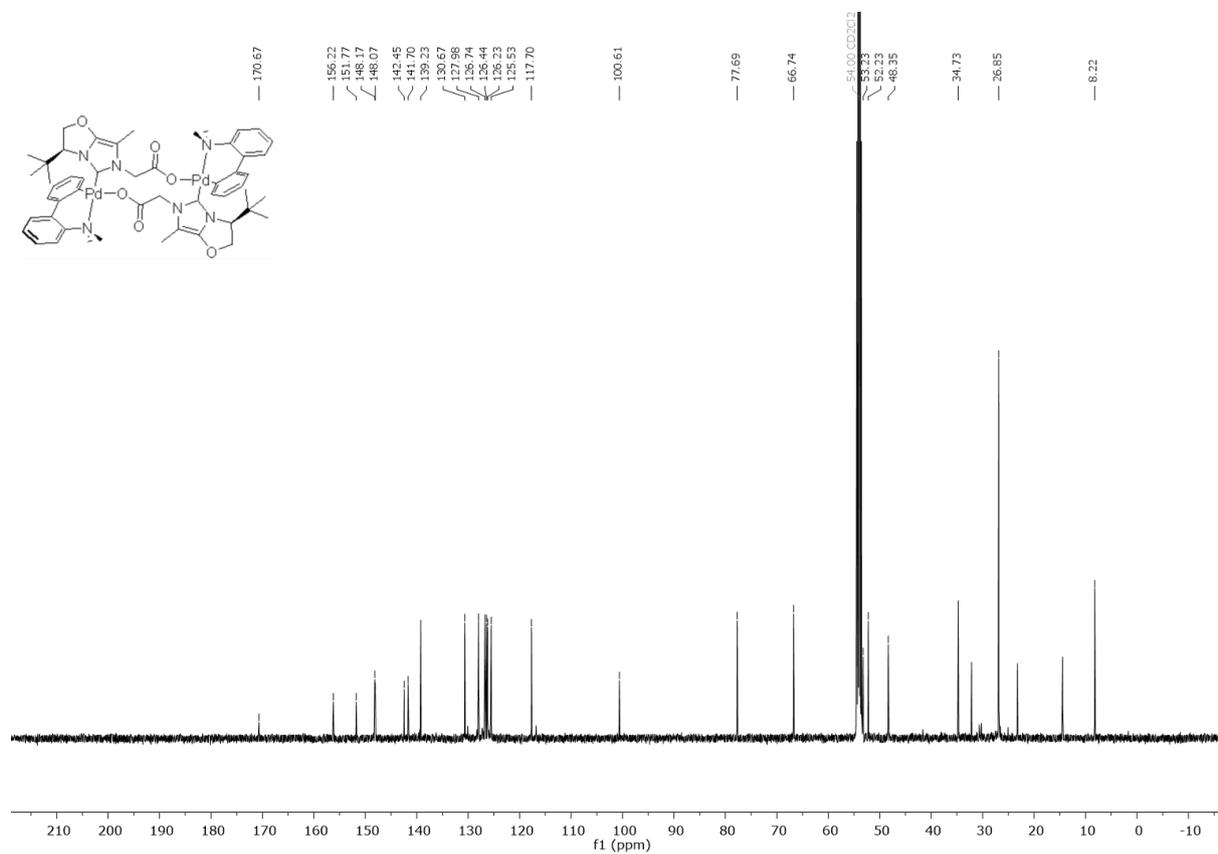


# Complex 1 (C<sup>1</sup>)

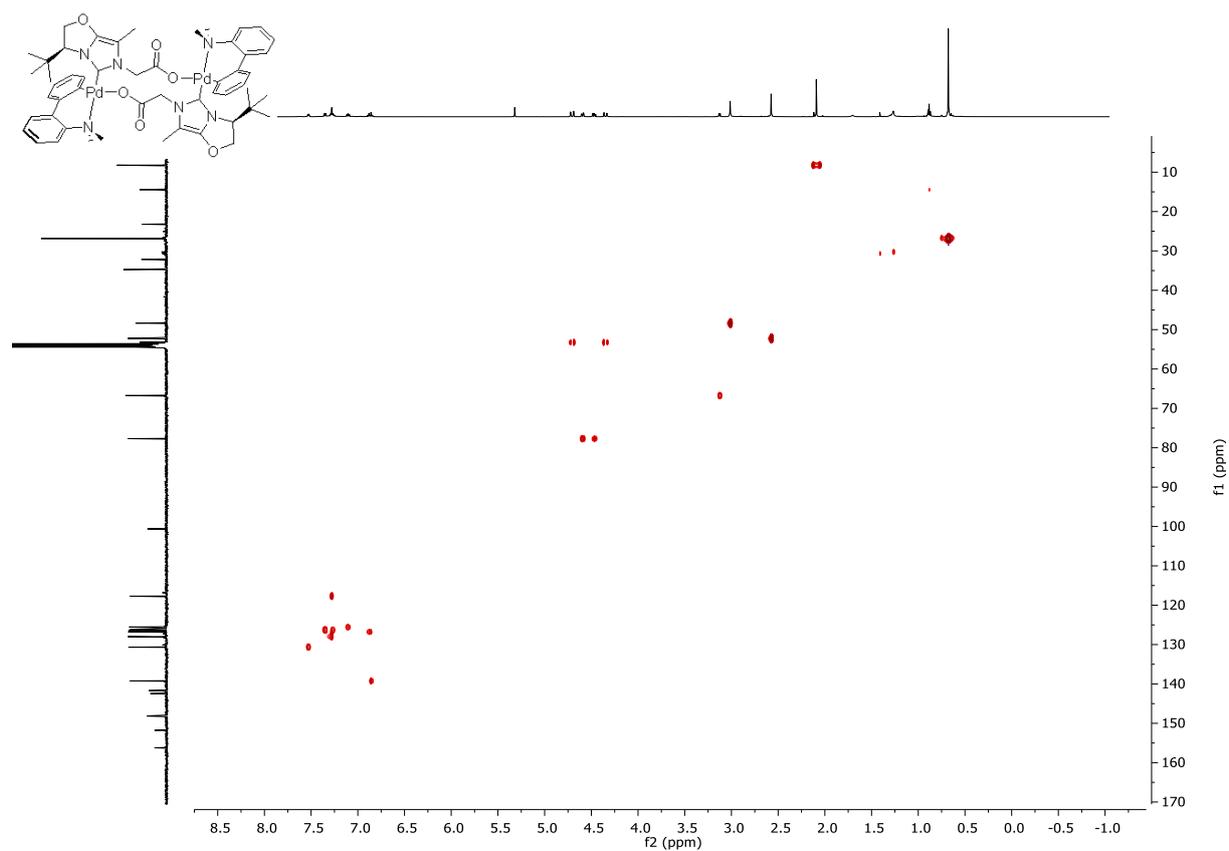
<sup>1</sup>H NMR (500 MHz, methylene chloride-d<sub>2</sub>)



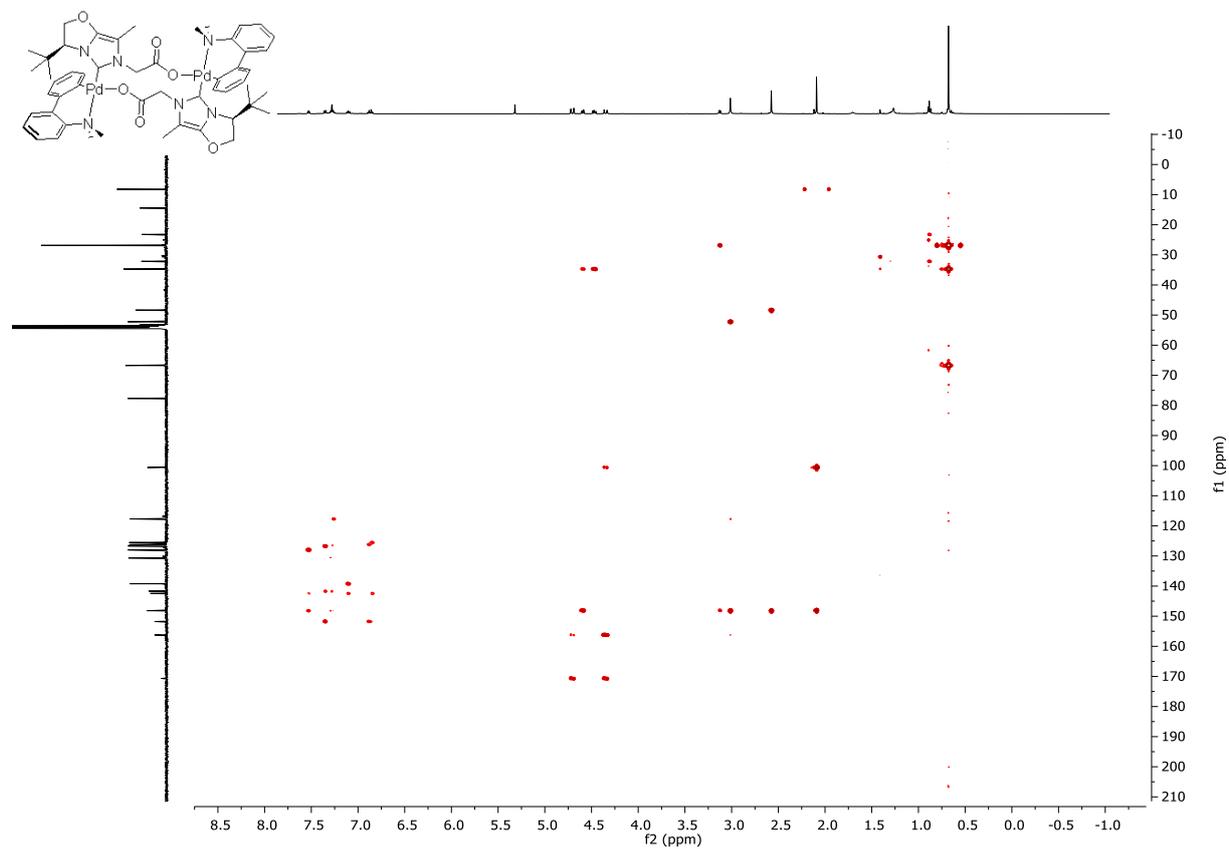
<sup>13</sup>C NMR (126 MHz, methylene chloride-d<sub>2</sub>)



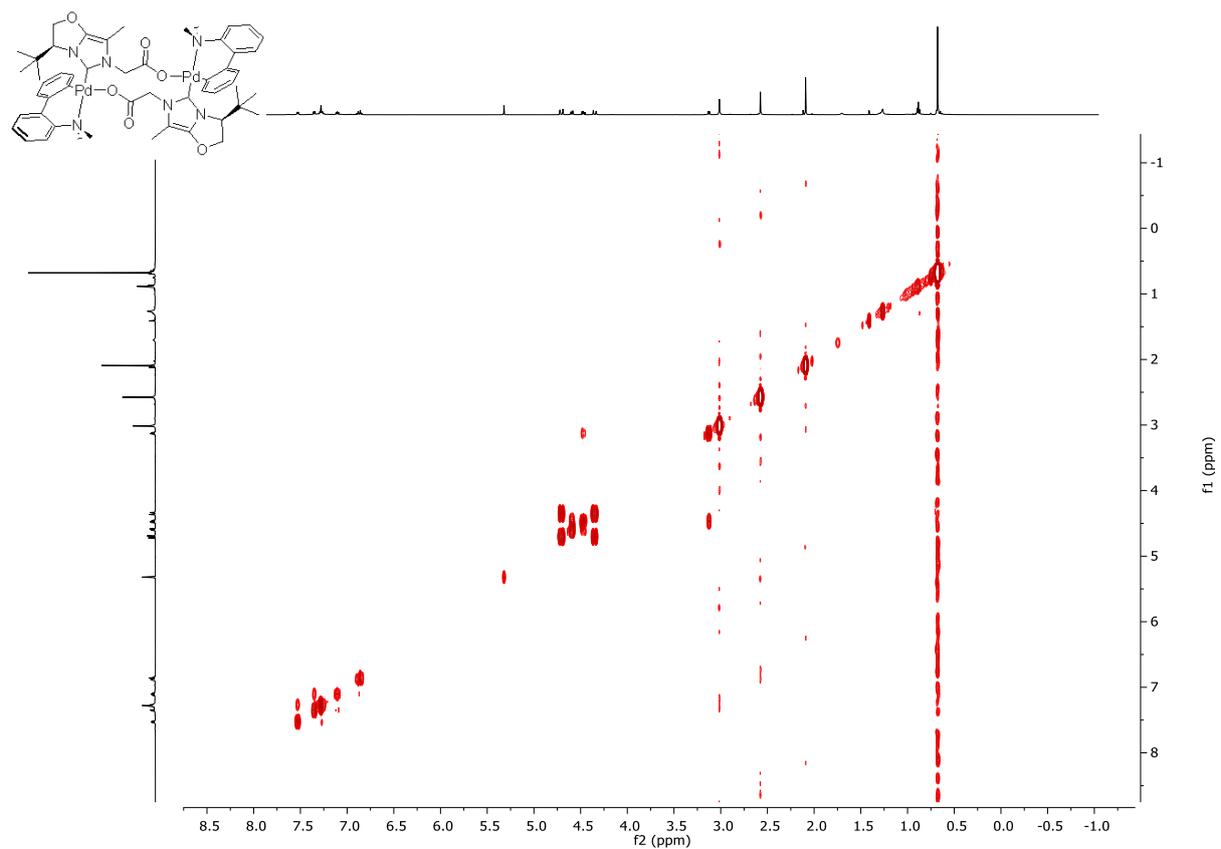
# HMQC



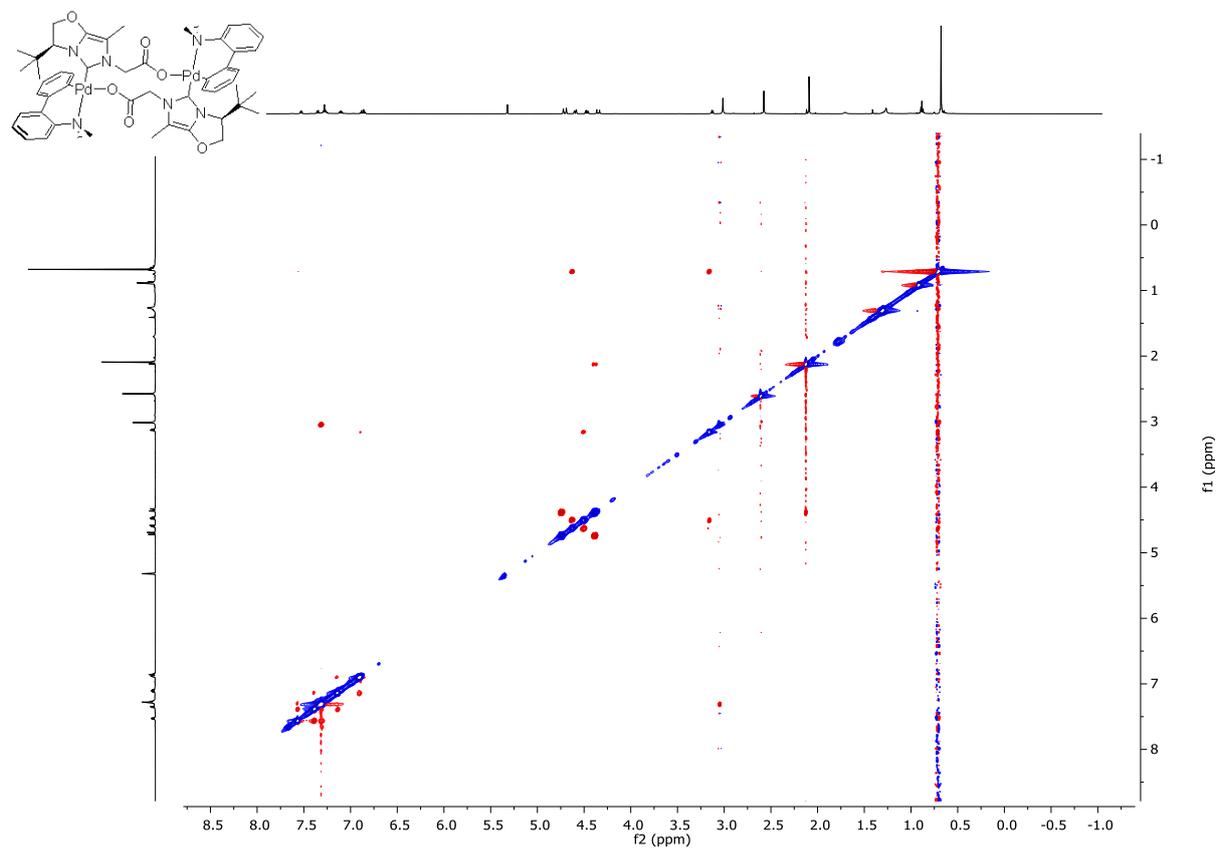
# HMBC



# COSY

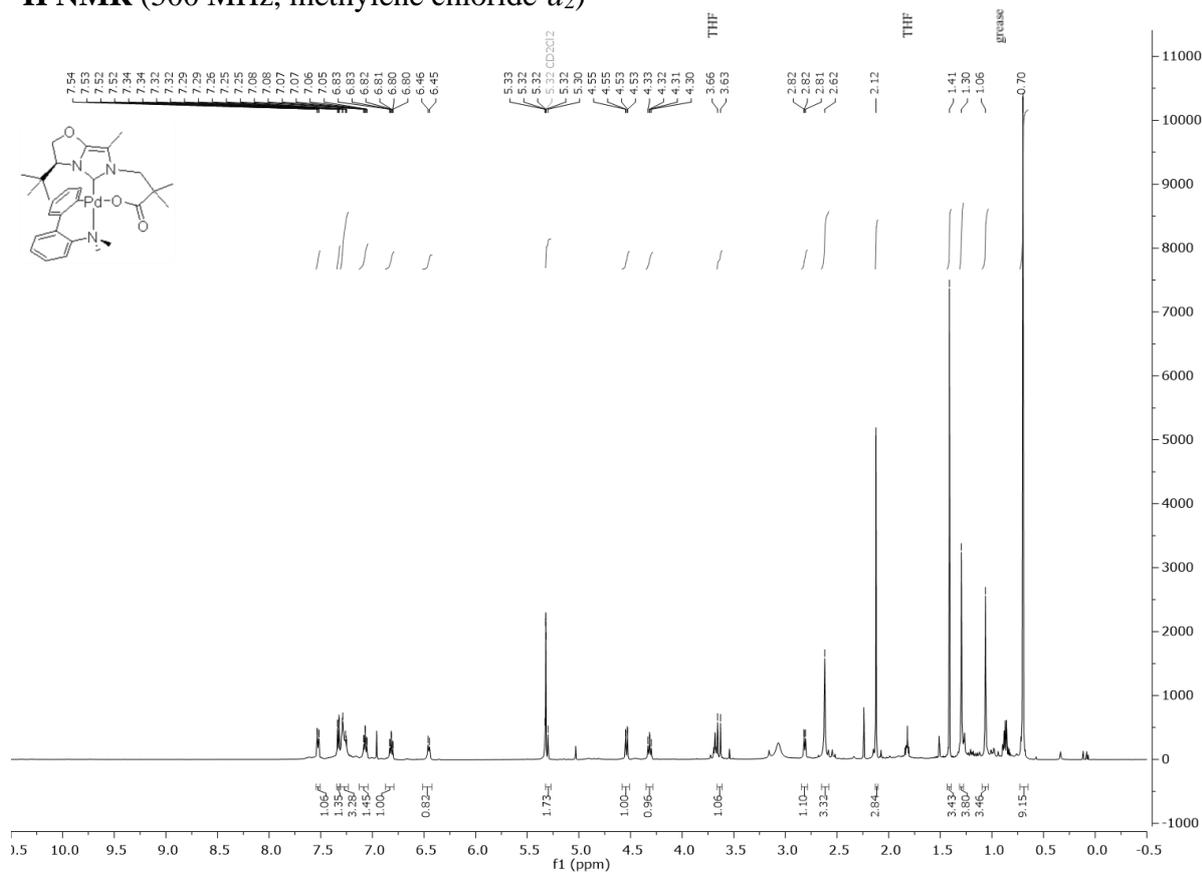


# NOESY

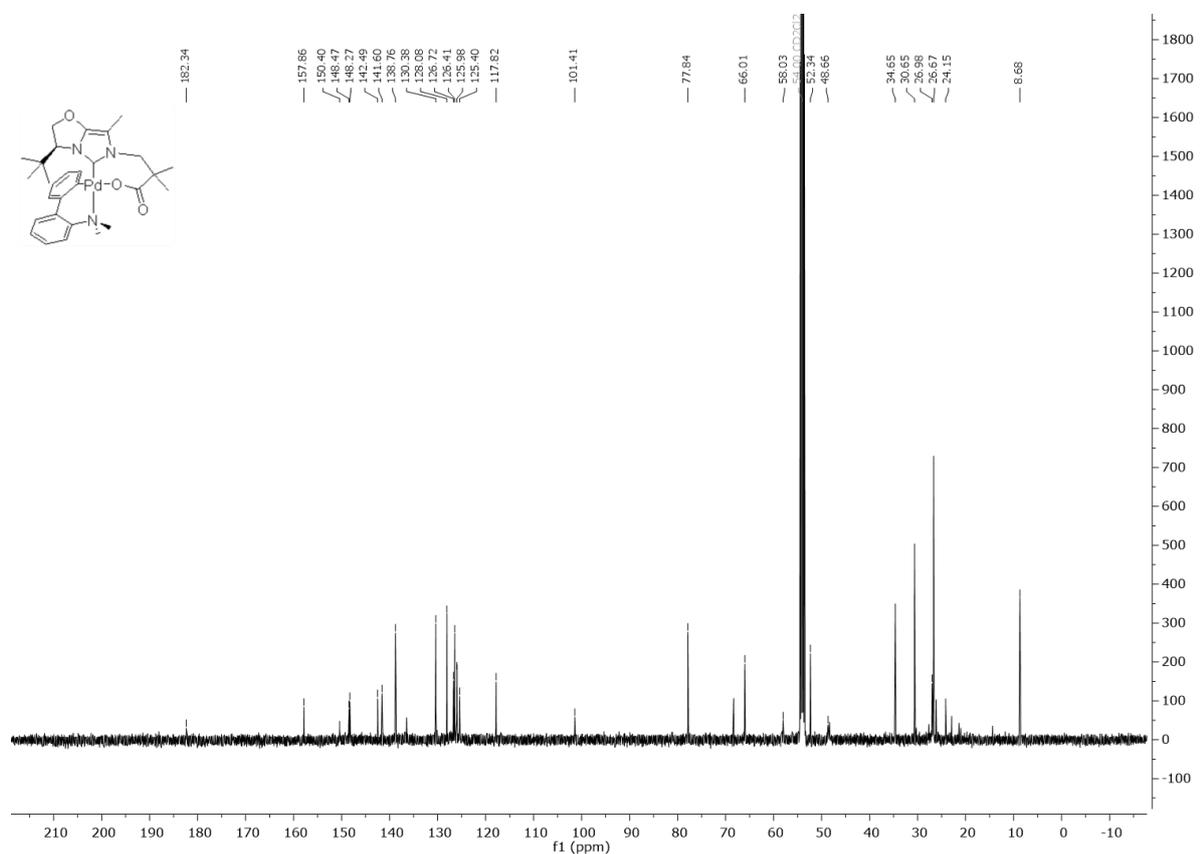


# Complex 2 (C<sup>2</sup>)

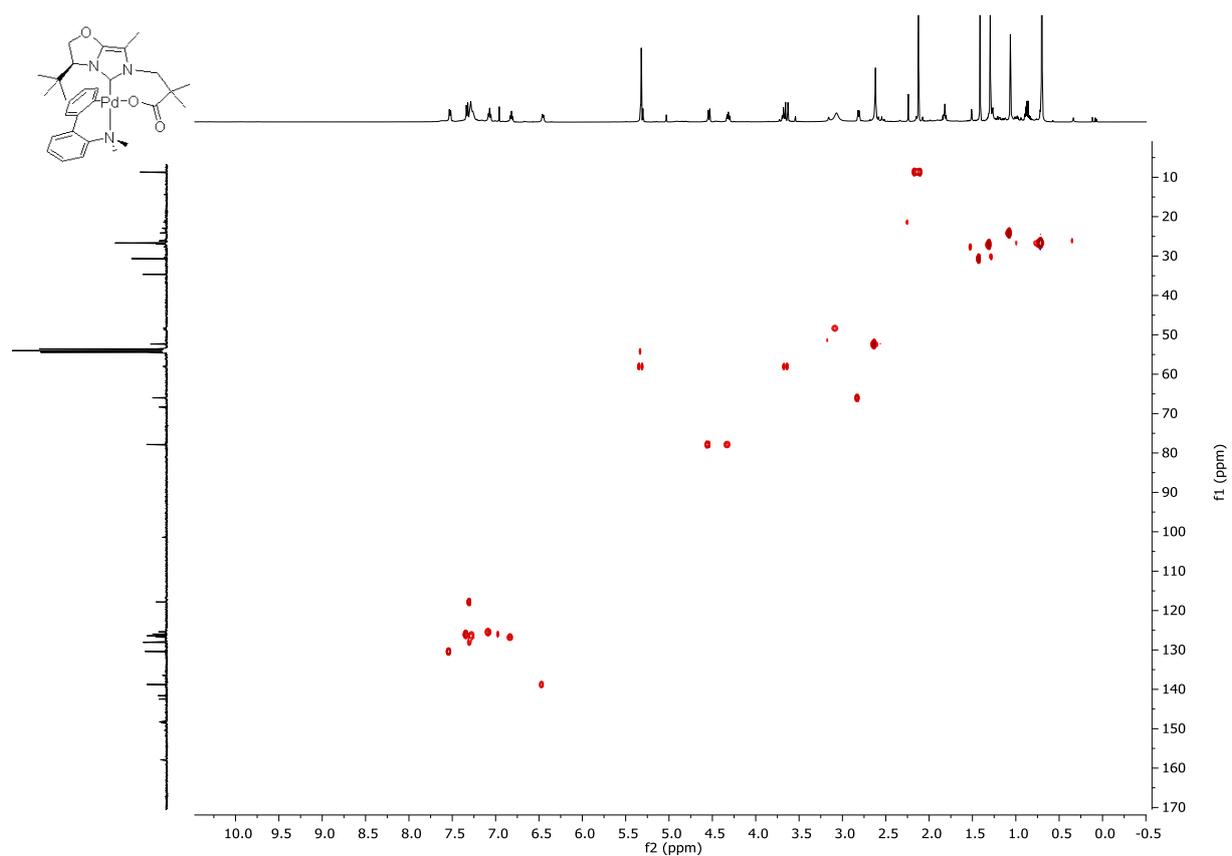
## <sup>1</sup>H NMR (500 MHz, methylene chloride-d<sub>2</sub>)



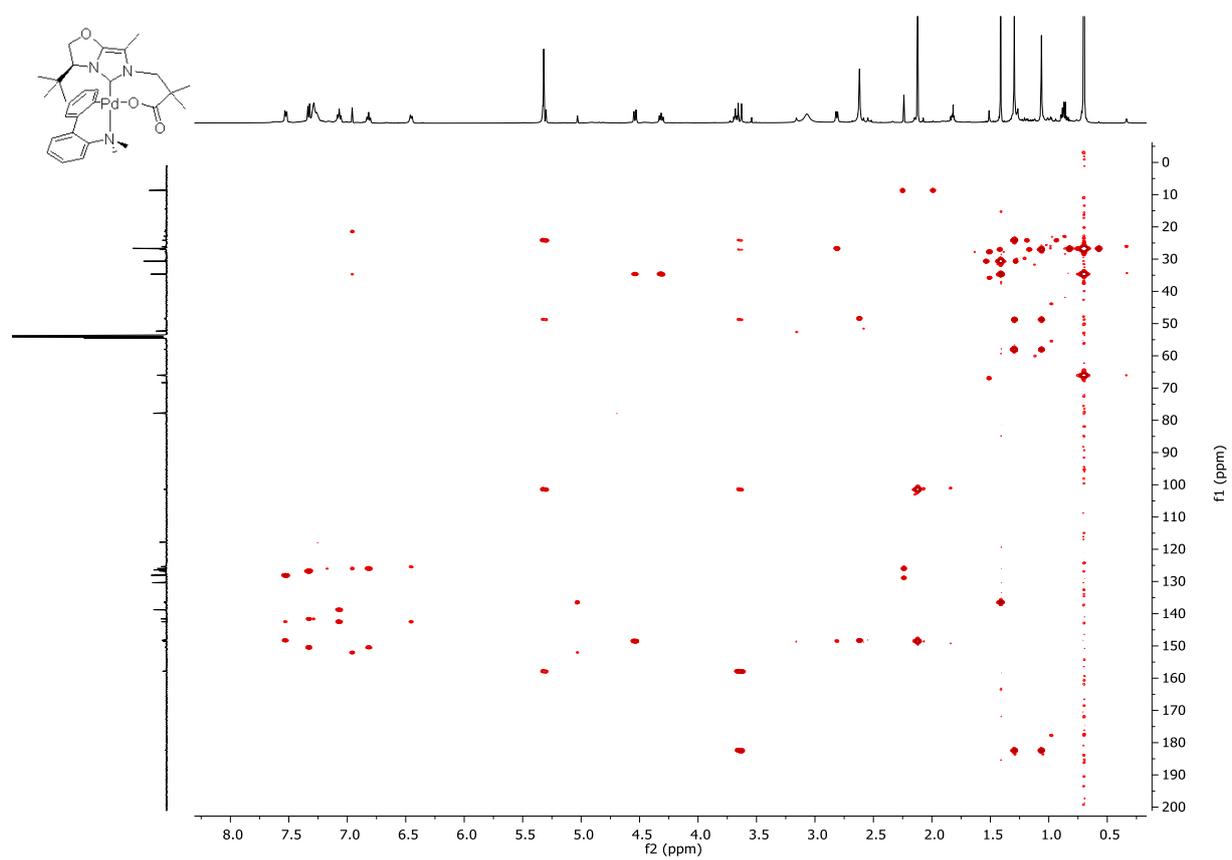
## <sup>13</sup>C NMR (126 MHz, methylene chloride-d<sub>2</sub>)



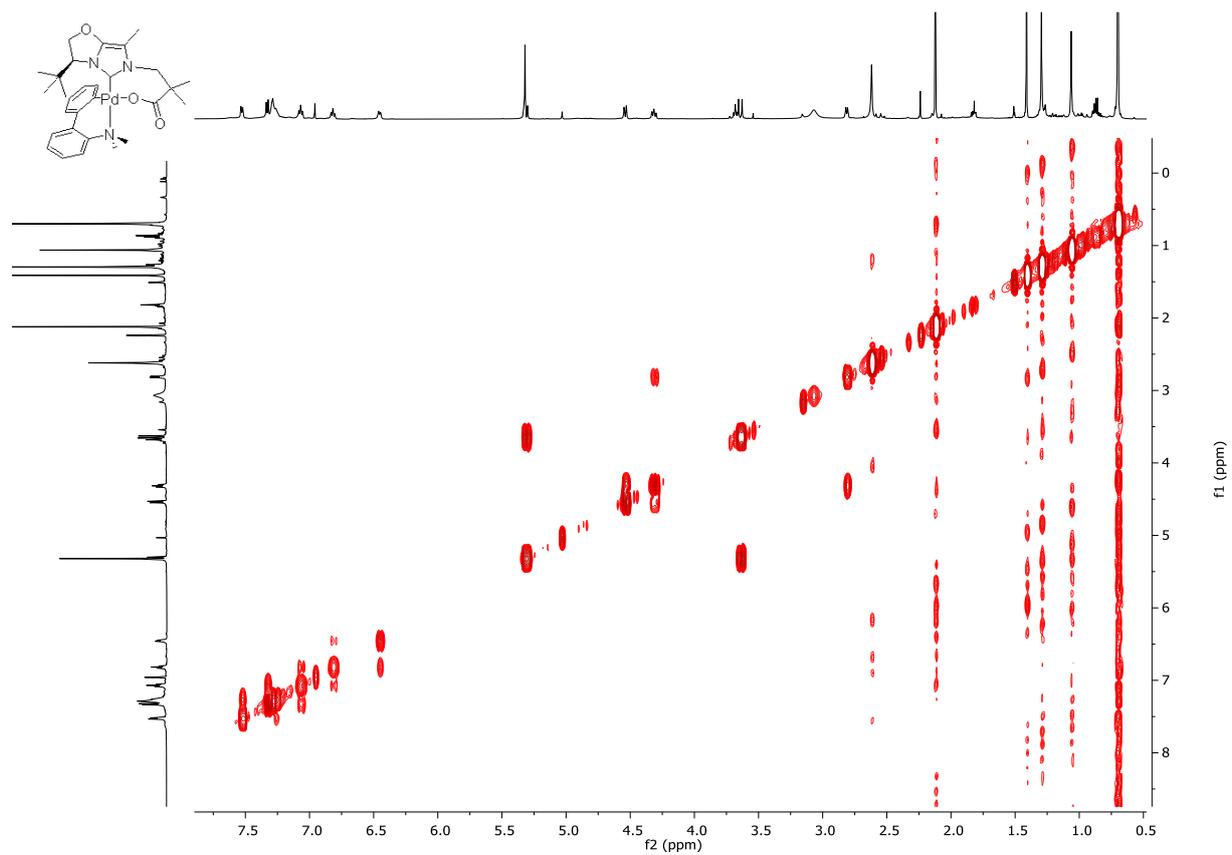
# HMQC



# HMBC

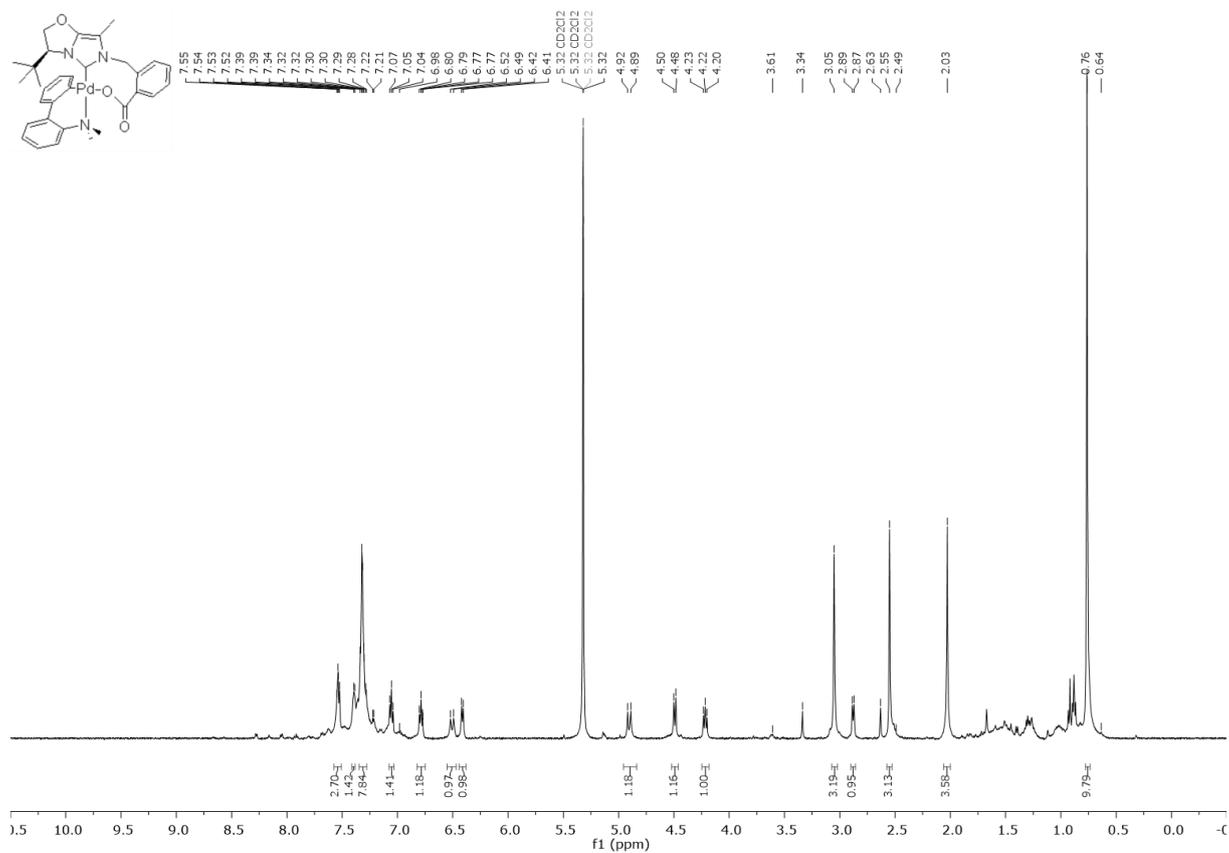


# COSY



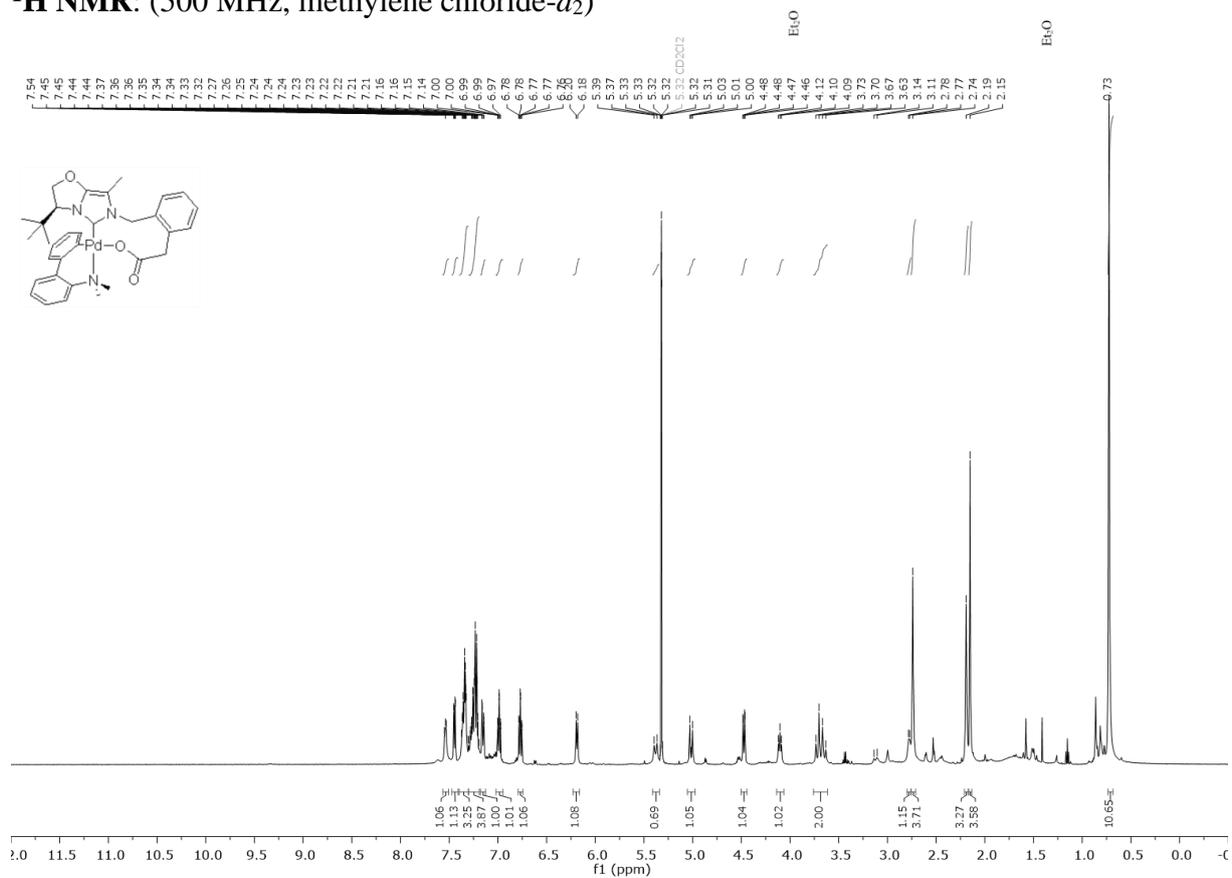
# Complex 3 (C<sup>3</sup>)

<sup>1</sup>H NMR (500 MHz, methylene chloride-d<sub>2</sub>)

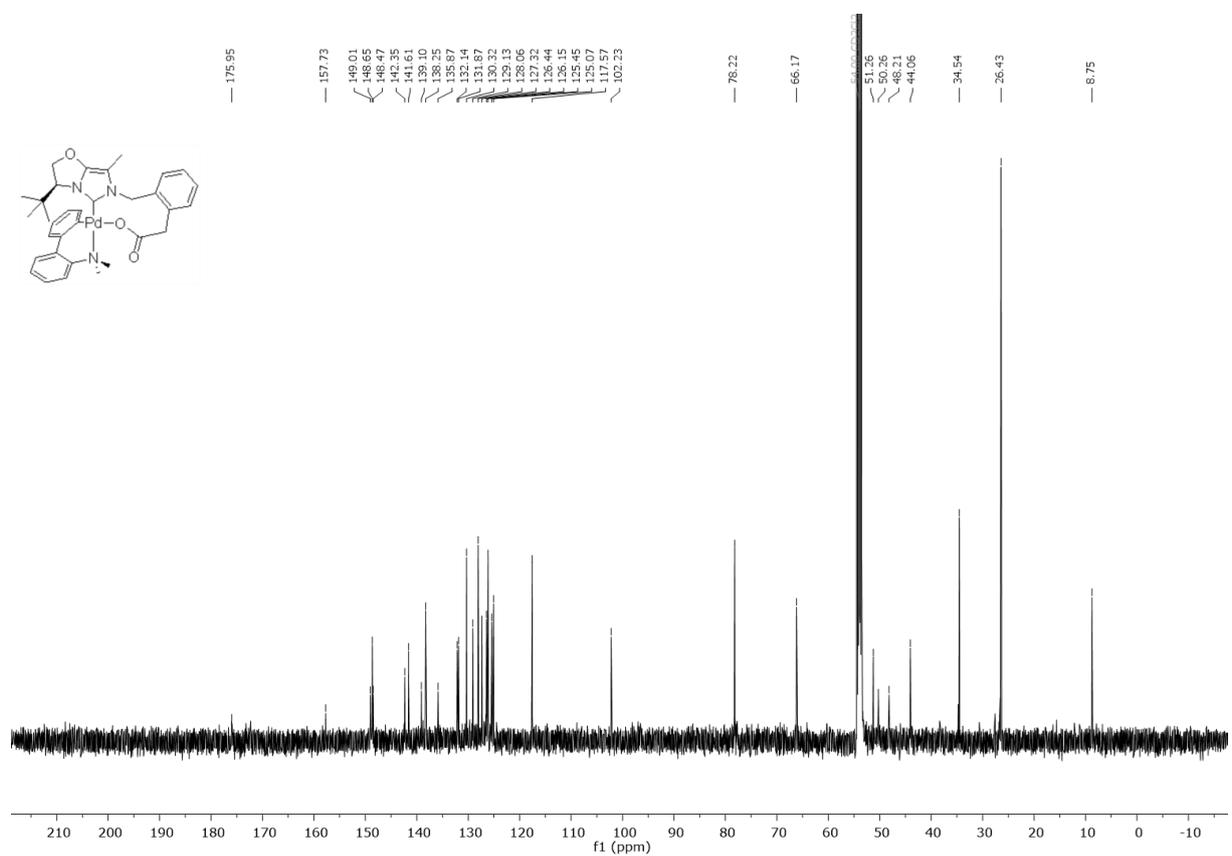


# Complex 4 (C<sup>4</sup>)

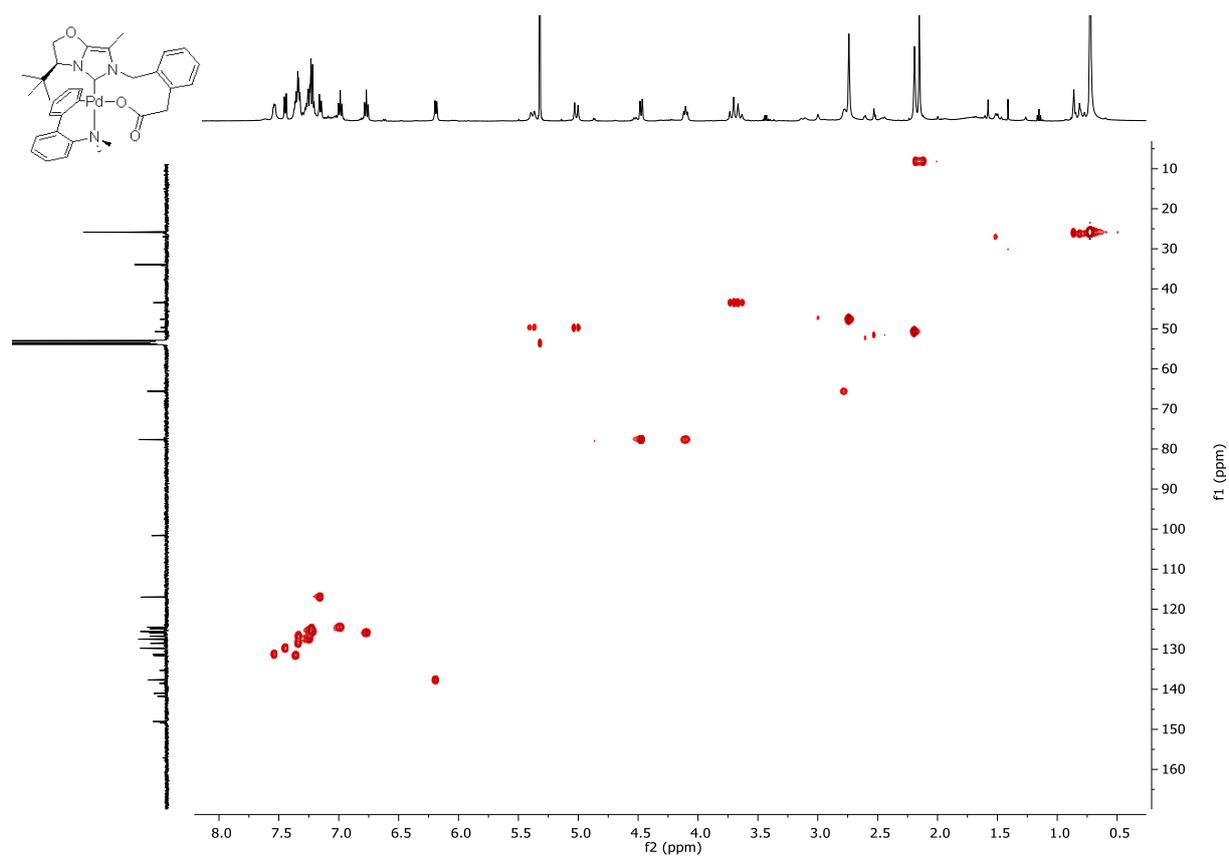
<sup>1</sup>H NMR: (500 MHz, methylene chloride-d<sub>2</sub>)



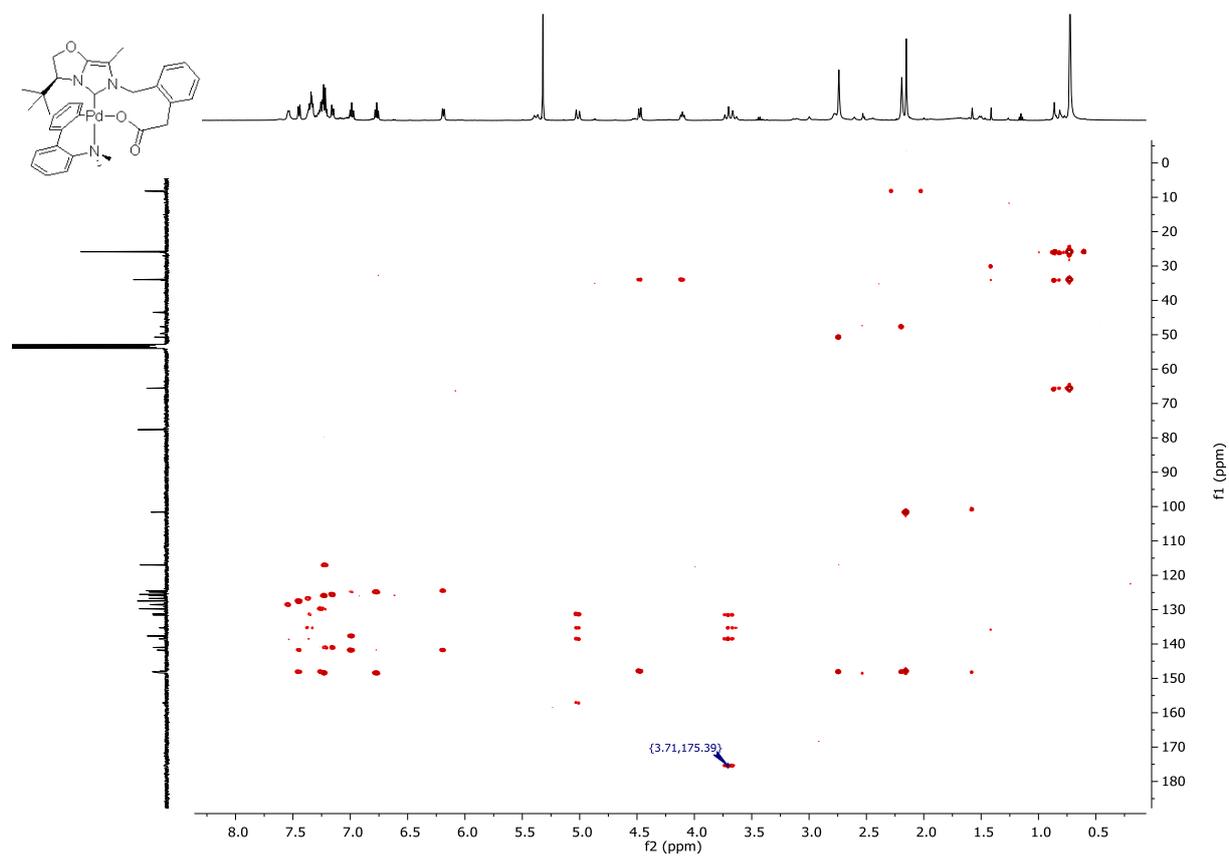
<sup>13</sup>C NMR (126 MHz, methylene chloride-d<sub>2</sub>)



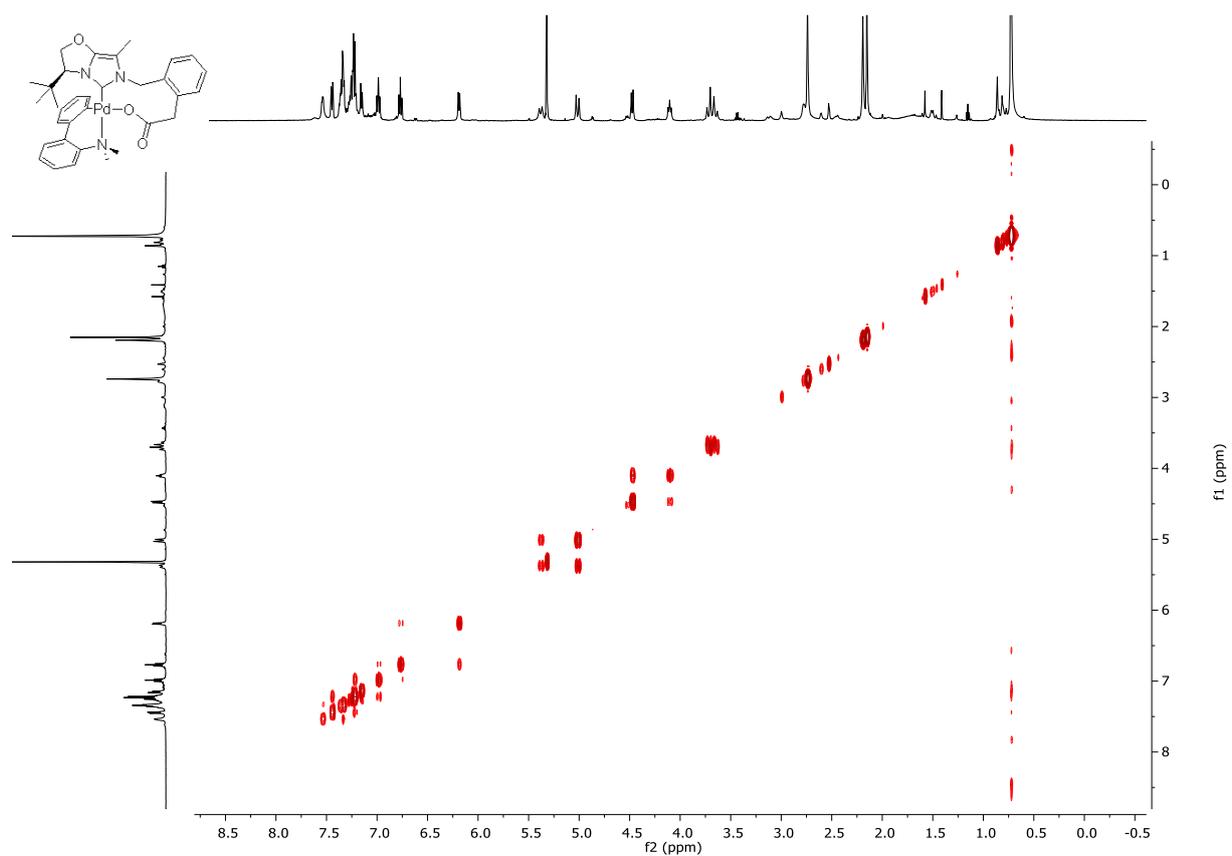
# HMQC



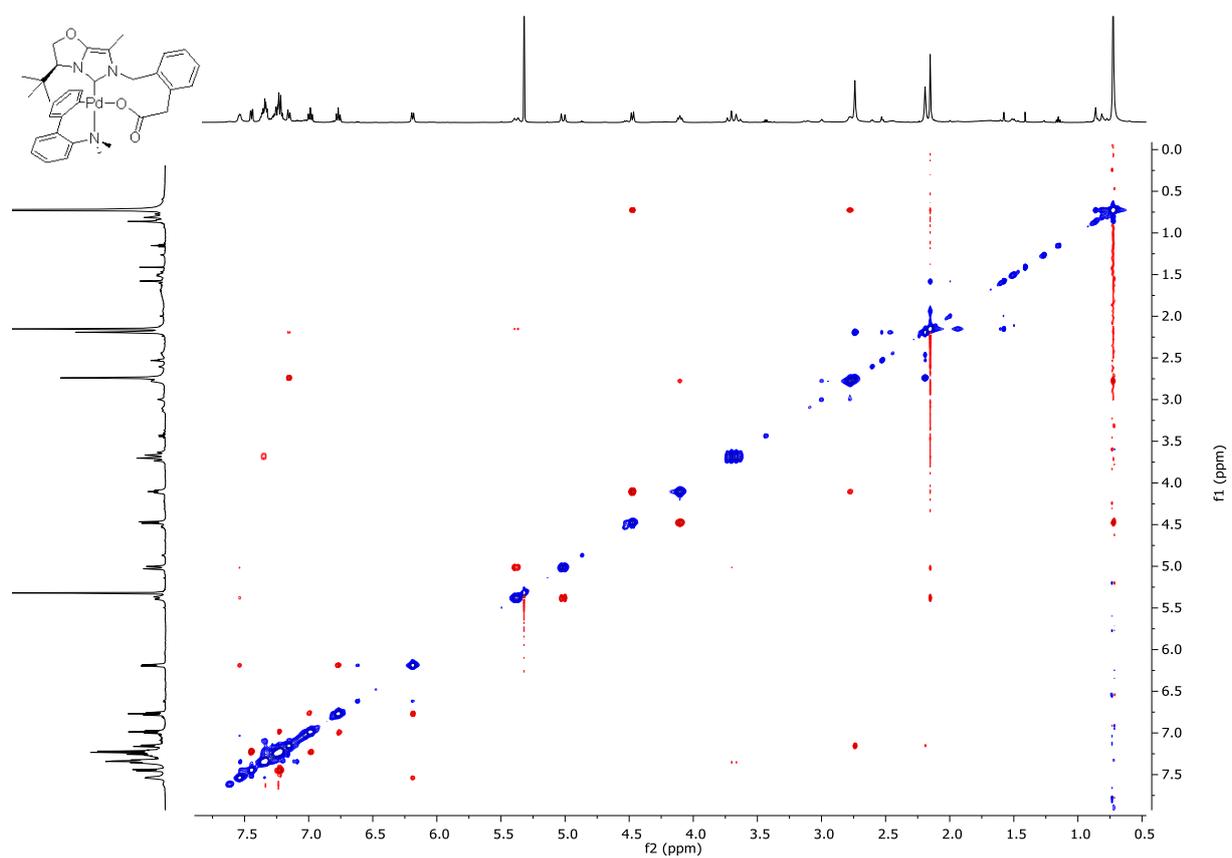
# HMBC



# COSY

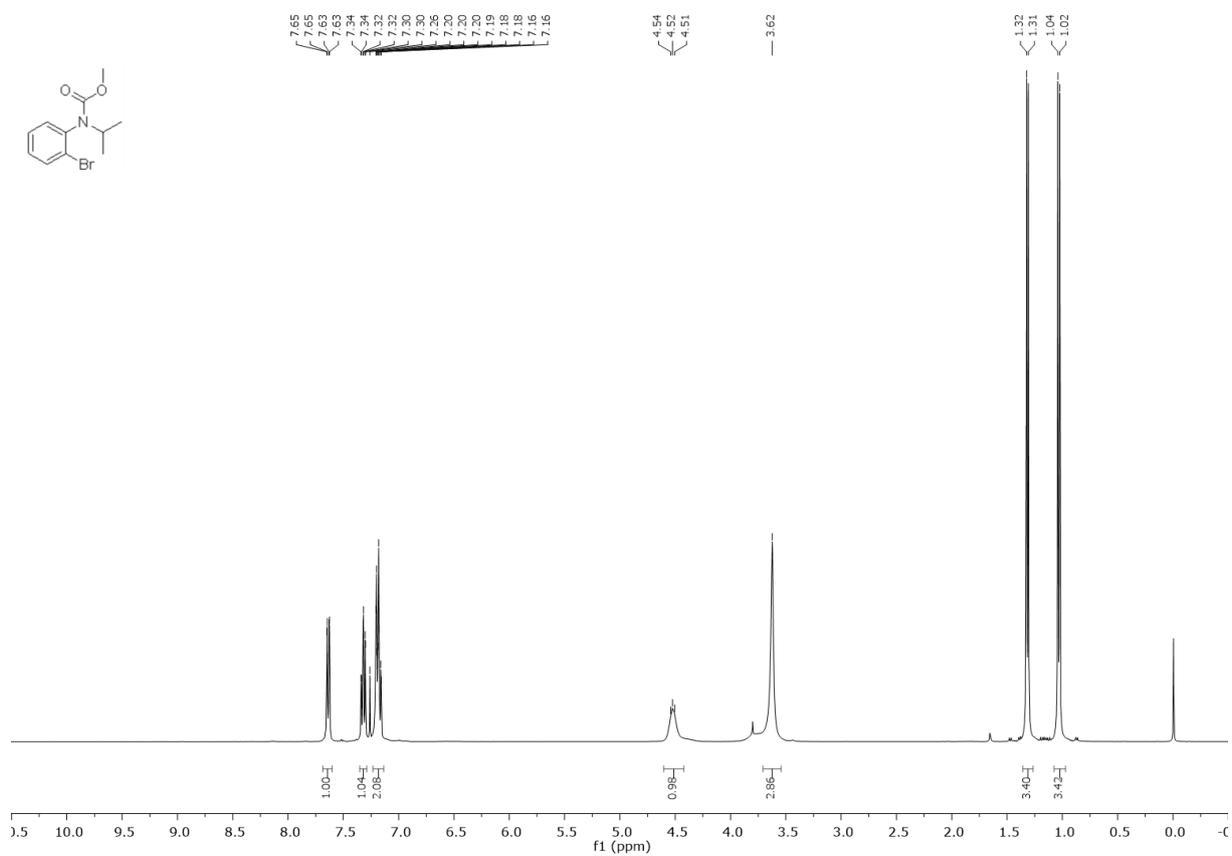


# NOESY

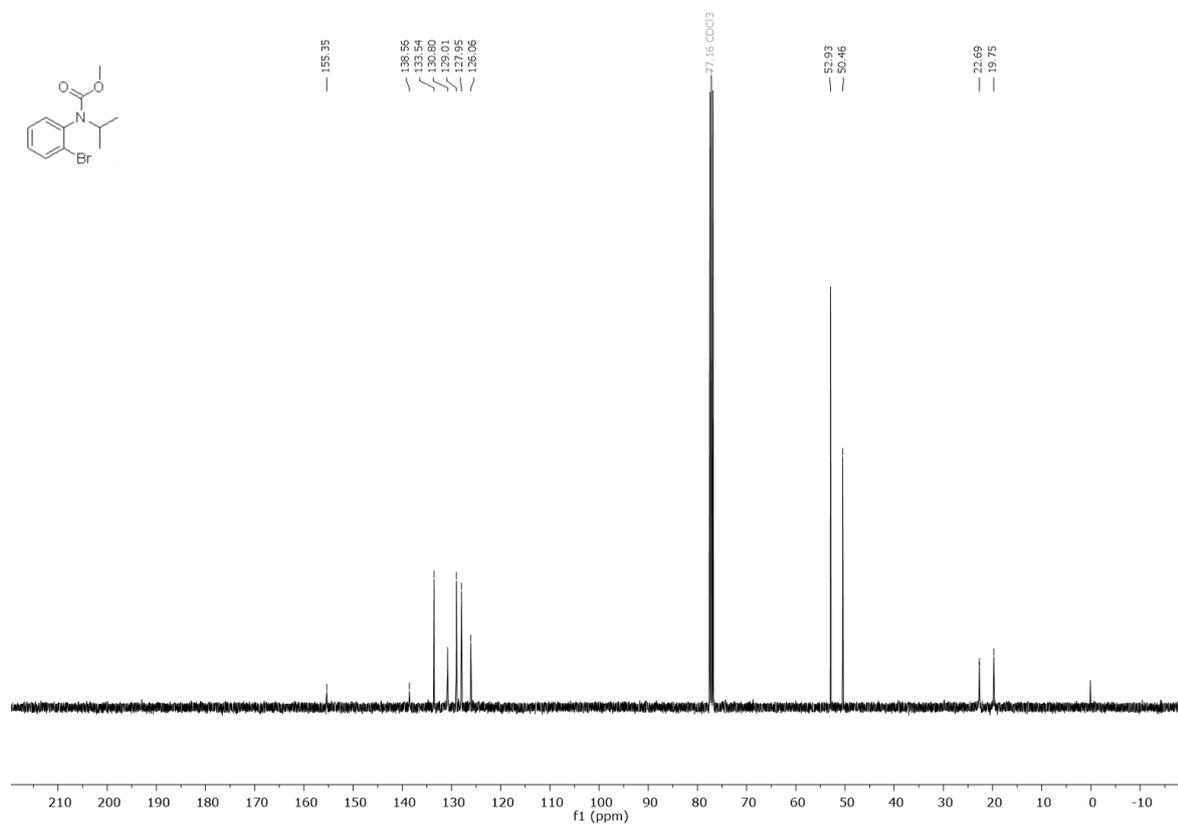


methyl (2-bromophenyl)(isopropyl)carbamate (**5.11**)

$^1\text{H}$  NMR (400 MHz, chloroform-*d*)

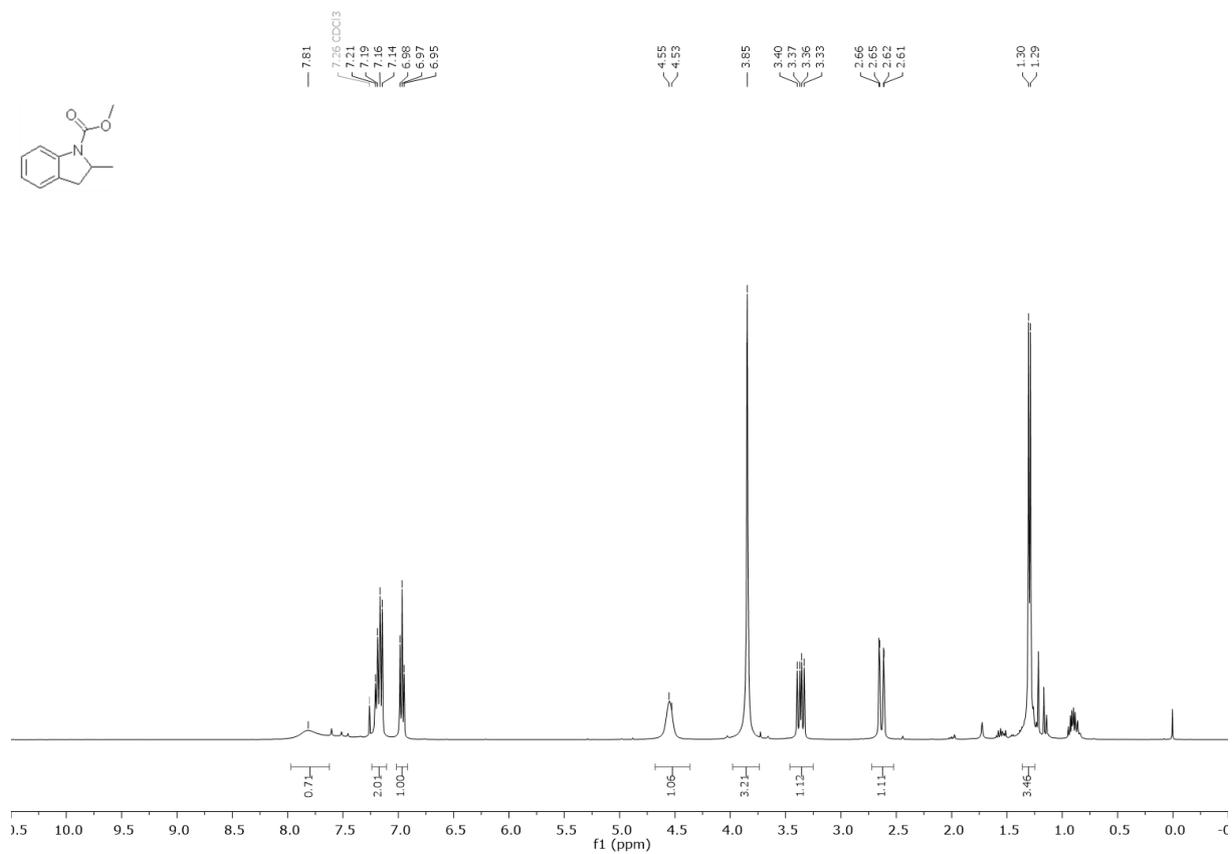


$^{13}\text{C}$  NMR (126 MHz, chloroform-*d*)

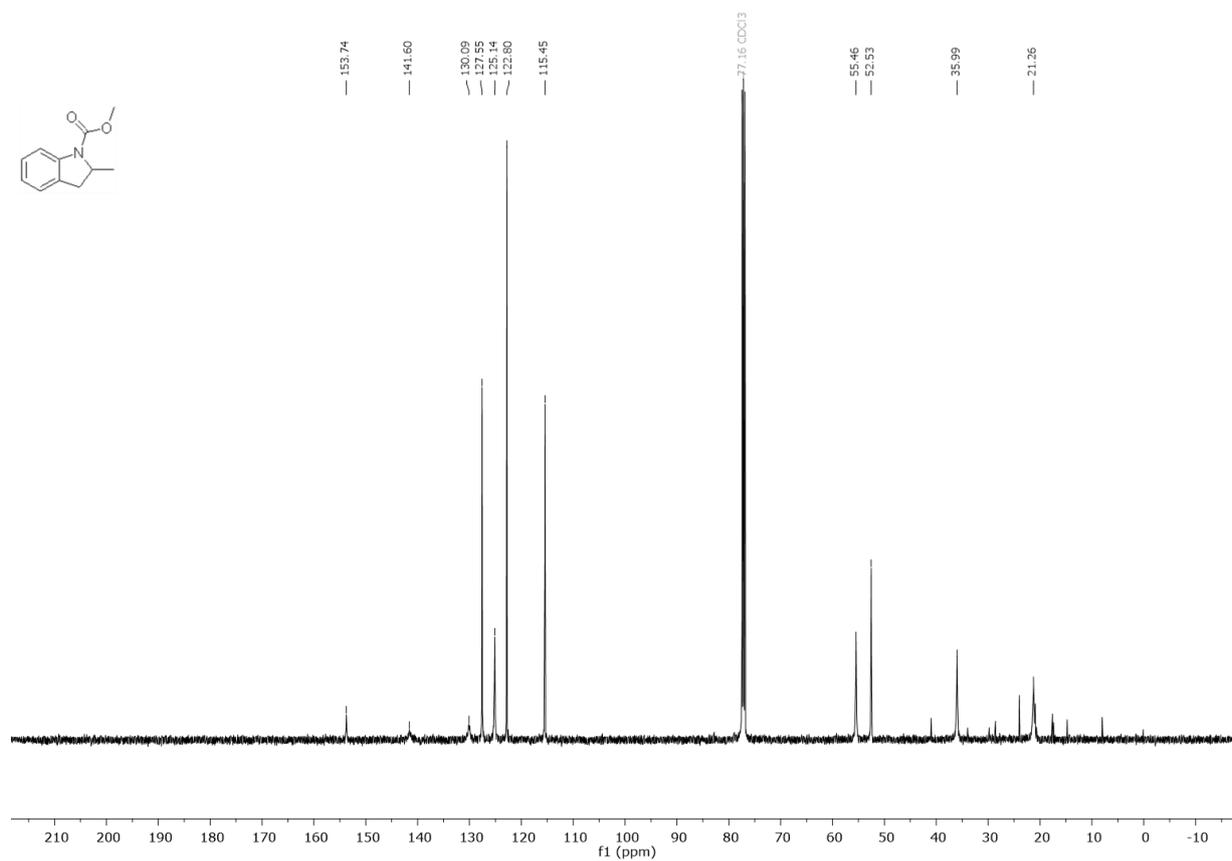


methyl 2-methylindoline-1-carboxylate (**5.12**)

$^1\text{H}$  NMR (400 MHz, chloroform-*d*)



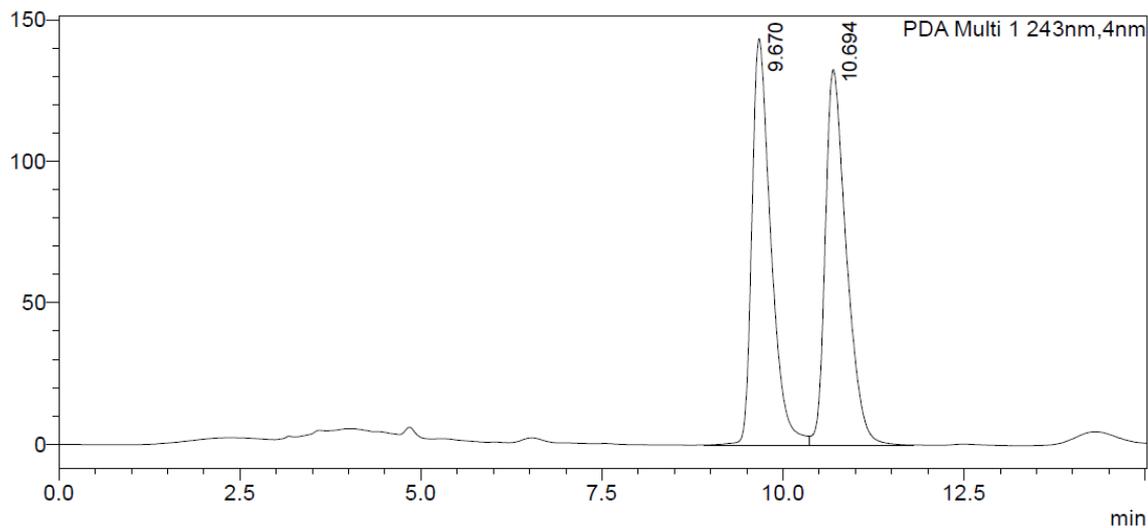
$^{13}\text{C}$  NMR (126 MHz, chloroform-*d*)



## HPLC traces

racemic (5.12)

mAU



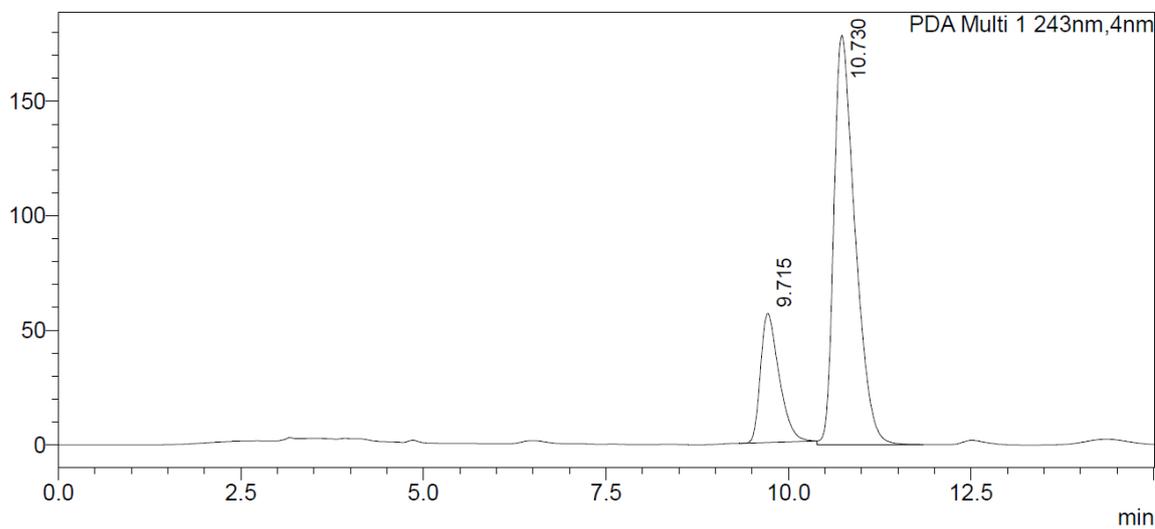
### <Peak Table>

PDA Ch1 243nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	9.670	2626554	143462	49.371			
2	10.694	2693458	132590	50.629		V	
Total		5320012	276052				

With C<sup>4</sup> (5.12)

mAU



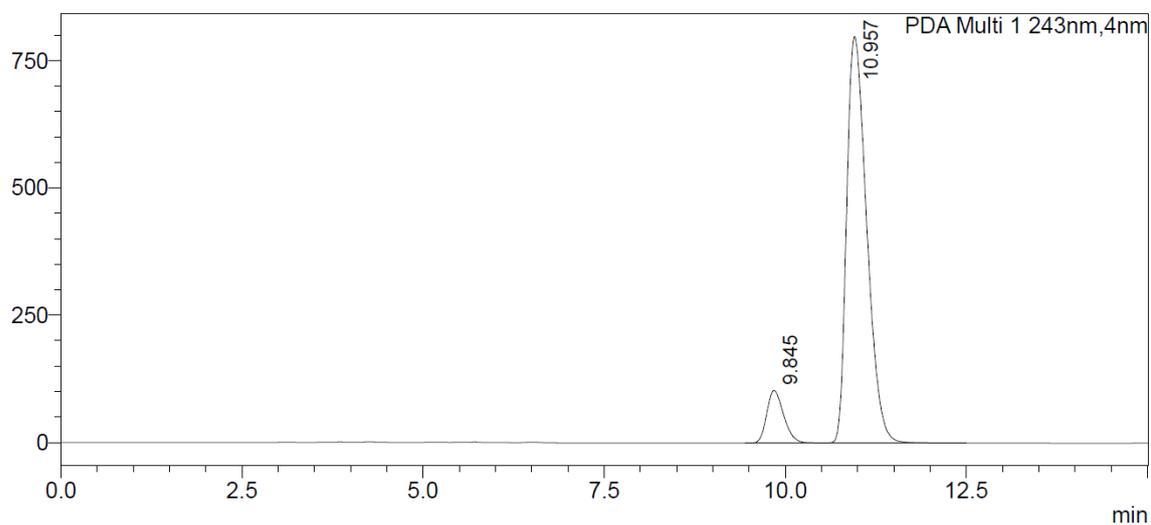
### <Peak Table>

PDA Ch1 243nm

Peak#	Ret. Time	Area	Height	Area%
1	9.715	995157	56349	21.600
2	10.730	3612116	178797	78.400
Total		4607273	235146	100.000

With IBiox/Bu (Parental NHC) (5.12)

mAU



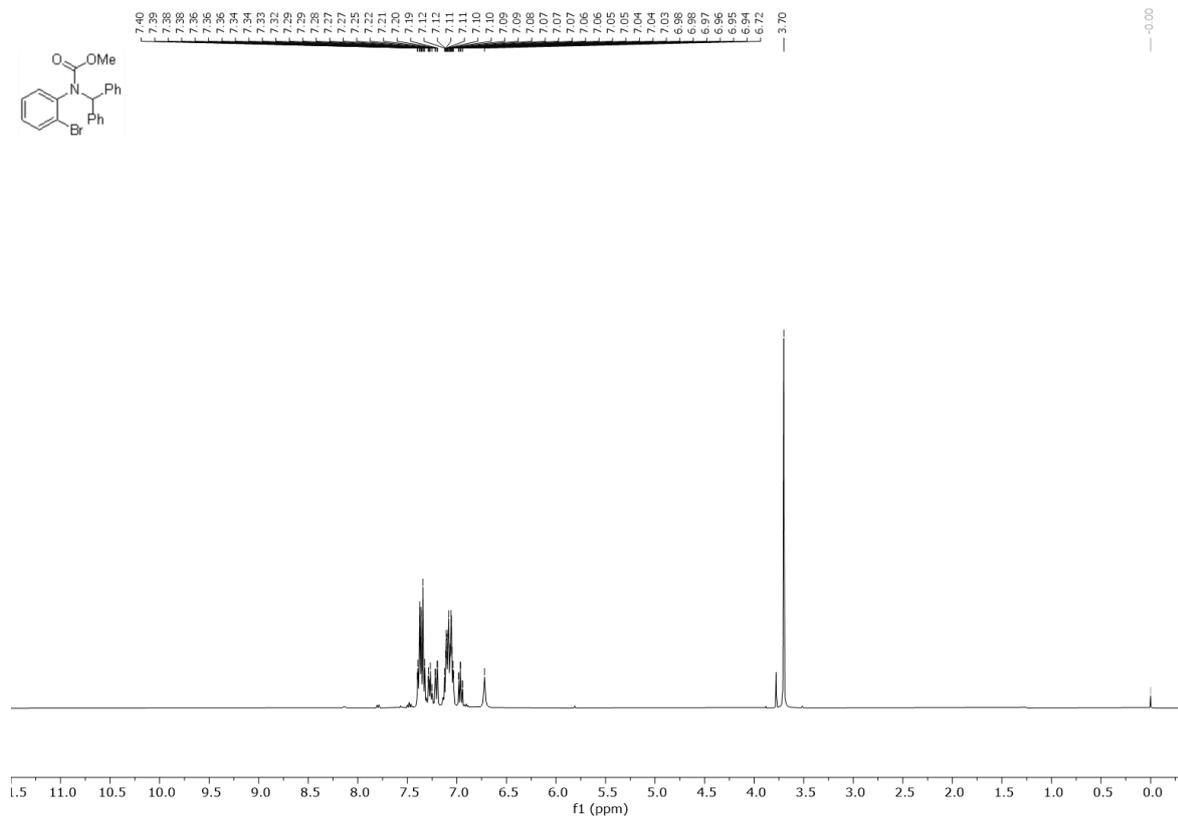
**<Peak Table>**

PDA Ch1 243nm

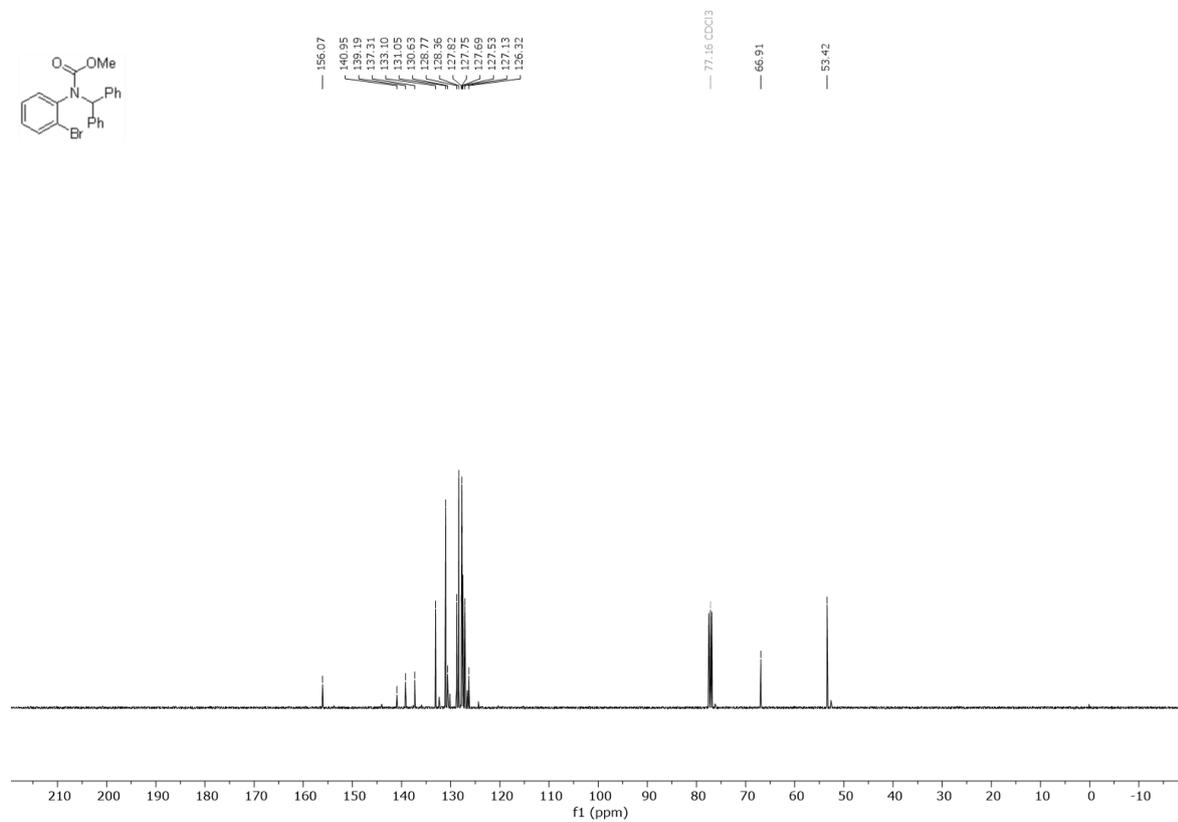
Peak#	Ret. Time	Area	Height	Area%
1	9.845	1692202	103535	9.894
2	10.957	15411777	799348	90.106
Total		17103980	902884	100.000

methyl benzhydryl(2-bromophenyl)carbamate (**5.13**)

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )



$^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )



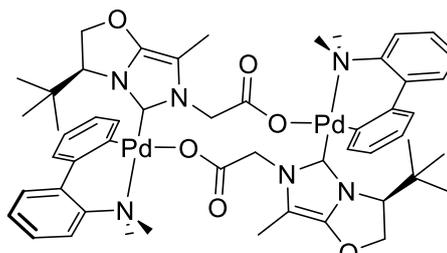
## X-ray structures

### X-ray Structure of Complex 1 (C<sup>1</sup>)

Checkcif for C<sup>1</sup>

checkCIF/PLATON report

Structure factors have been supplied for datablock(s) nn1872\_150k



THIS REPORT IS FOR GUIDANCE ONLY. IF USED AS PART OF A REVIEW PROCEDURE FOR PUBLICATION, IT SHOULD NOT REPLACE THE EXPERTISE OF AN EXPERIENCED CRYSTALLOGRAPHIC REFEREE.

No syntax errors found. CIF dictionary Interpreting this report

Datablock: nn1872\_150k

---

Bond precision:	C-C = 0.0110 A	Wavelength=1.34143
Cell:	a=9.2397(4)	b=17.6859(7) c=18.1004(7)
	alpha=89.960(3)	beta=90.186(3) gamma=90.207(3)
Temperature:	150 K	
	Calculated	Reported
Volume	2957.8(2)	2957.8(2)
Space group	P 1	P 1
Hall group	P 1	P 1
C52 H62 N6 O6 Pd2, C H2		
C52 H62 N6 O6 Pd2, C H2		
Moiety formula		C12, 0.5[C1H2CL2],
C12 [+ solvent]		
0.5[C1H2CL2]		
C53 H64 C12 N6 O6 Pd2 [+ solvent]		
Sum formula		C54 H66 C14 N6 O6 Pd2

Mr	1164.81	1249.72
Dx,g cm-3	1.308	1.403
Z	2	2
Mu (mm-1)	4.134	4.647
F000	1196.0	1280.0
F000'	1199.62	
h,k,lmax	11,22,22	11,22,22
Nref	25188[ 12594]	16470
Tmin,Tmax	0.529,0.658	0.019,0.849
Tmin'	0.474	

Correction method= # Reported T Limits: Tmin=0.019 Tmax=0.849  
AbsCorr = MULTI-SCAN

Data completeness= 1.31/0.65 Theta(max)= 58.189

R(reflections)= 0.0424( 16091) wR2(reflections)= 0.1209( 16470)

S = 1.090 Npar= 1319

The following ALERTS were generated. Each ALERT has the format  
**test-name\_ALERT\_alert-type\_alert-level**. Click on the hyperlinks  
for more details of the test.

---

### Alert level B

PLAT112_ALERT_2_B ADDSYM Detects New (Pseudo) Symm. Elem	21	100 %Fit
PLAT112_ALERT_2_B ADDSYM Detects New (Pseudo) Symm. Elem	21	100 %Fit
PLAT112_ALERT_2_B ADDSYM Detects New (Pseudo) Symm. Elem	2	100 %Fit
PLAT113_ALERT_2_B ADDSYM Suggests Possible Pseudo/New Space Group		P21212 Check
PLAT915_ALERT_3_B No Flack x Check Done: Low Friedel Pair Coverage		34 %
PLAT934_ALERT_3_B Number of (Iobs-Icalc)/Sigma(W) > 10 Outliers ..		8 Check
PLAT987_ALERT_1_B The Flack x is >> 0 - Do a BASF/TWIN Refinement		Please Check

---

### Alert level C

PLAT155_ALERT_4_C The Triclinic Unitcell is NOT Reduced .....		Please Do !
PLAT220_ALERT_2_C NonSolvent Resd 1 C Ueq(max) / Ueq(min) Range		3.4 Ratio
PLAT342_ALERT_3_C Low Bond Precision on C-C Bonds .....		0.01102 Ang.
PLAT790_ALERT_4_C Centre of Gravity not Within Unit Cell: Resd. #		1 Note
C52 H62 N6 O6 Pd2		
PLAT911_ALERT_3_C Missing FCF Refl Between Thmin & STh/L=	0.600	26 Report
PLAT918_ALERT_3_C Reflection(s) with I(obs) much Smaller I(calc) .		133 Check
PLAT977_ALERT_2_C Check Negative Difference Density on H72		-0.31 eA-3

**Alert level G**

FORMU01\_ALERT\_1\_G There is a discrepancy between the atom counts in the  
 \_chemical\_formula\_sum and \_chemical\_formula\_moiety. This is usually  
 due to the moiety formula being in the wrong format. Atom count  
 from \_chemical\_formula\_sum: C54 H66 Cl4 N6 O6 Pd2

Atom count from \_chemical\_formula\_moiety: C53.5 H65 Cl3 N6 O6 Pd2

FORMU01\_ALERT\_2\_G There is a discrepancy between the atom counts in the  
 \_chemical\_formula\_sum and the formula from the \_atom\_site\* data.

Atom count from \_chemical\_formula\_sum: C54 H66 Cl4 N6 O6 Pd2

Atom count from the \_atom\_site data: C53 H64 Cl2 N6 O6 Pd2

ABSMU01\_ALERT\_1\_G Calculation of \_exptl\_absorpt\_correction\_mu not  
 performed for this radiation type. CELLZ01\_ALERT\_1\_G Difference between formula  
 and atom\_site contents detected. CELLZ01\_ALERT\_1\_G ALERT: Large difference may  
 be due to a symmetry error - see SYMMG tests From the

CIF: \_cell\_formula\_units\_Z 2

From the CIF: \_chemical\_formula\_sum C54 H66 Cl4 N6 O6 Pd2

TEST: Compare cell contents of formula and atom\_site data

	atom	Z*formula	cif sites	diff
C	108.00	106.00	2.00	
	H	132.00	128.00	4.00
	Cl	8.00	4.00	4.00
N	12.00	12.00	0.00	
O	12.00	12.00	0.00	
	Pd	4.00	4.00	0.00

PLAT033\_ALERT\_4\_G Flack x Value Deviates > 3.0 \* sigma from Zero . 0.034 Note  
 PLAT041\_ALERT\_1\_G Calc. and Reported SumFormula Strings Differ Please Check  
 PLAT051\_ALERT\_1\_G Mu(calc) and Mu(CIF) Ratio Differs from 1.0 by . 11.05 %  
 PLAT068\_ALERT\_1\_G Reported F000 Differs from Calcd (or Missing)... Please Check  
 PLAT154\_ALERT\_1\_G The s.u.'s on the Cell Angles are Equal ..(Note) 0.003 Degree  
 PLAT300\_ALERT\_4\_G Atom Site Occupancy of Cl1 Constrained at 0.5 Check  
 PLAT300\_ALERT\_4\_G Atom Site Occupancy of Cl2 Constrained at 0.5 Check  
 PLAT300\_ALERT\_4\_G Atom Site Occupancy of Cl105 Constrained at 0.5 Check  
 PLAT300\_ALERT\_4\_G Atom Site Occupancy of H10L Constrained at 0.5 Check  
 PLAT300\_ALERT\_4\_G Atom Site Occupancy of H10M Constrained at 0.5 Check  
 PLAT300\_ALERT\_4\_G Atom Site Occupancy of Cl3 Constrained at 0.5 Check  
 PLAT300\_ALERT\_4\_G Atom Site Occupancy of Cl4 Constrained at 0.5 Check  
 PLAT300\_ALERT\_4\_G Atom Site Occupancy of Cl106 Constrained at 0.5 Check  
 PLAT300\_ALERT\_4\_G Atom Site Occupancy of H10P Constrained at 0.5 Check  
 PLAT300\_ALERT\_4\_G Atom Site Occupancy of H10Q Constrained at 0.5 Check  
 PLAT300\_ALERT\_4\_G Atom Site Occupancy of Cl5 Constrained at 0.5 Check  
 PLAT300\_ALERT\_4\_G Atom Site Occupancy of Cl6 Constrained at 0.5 Check  
 PLAT300\_ALERT\_4\_G Atom Site Occupancy of Cl107 Constrained at 0.5 Check  
 PLAT300\_ALERT\_4\_G Atom Site Occupancy of H10N Constrained at 0.5 Check  
 PLAT300\_ALERT\_4\_G Atom Site Occupancy of H10O Constrained at 0.5 Check  
 PLAT300\_ALERT\_4\_G Atom Site Occupancy of Cl7 Constrained at 0.5 Check  
 PLAT300\_ALERT\_4\_G Atom Site Occupancy of Cl8 Constrained at 0.5 Check  
 PLAT300\_ALERT\_4\_G Atom Site Occupancy of Cl108 Constrained at 0.5 Check  
 PLAT300\_ALERT\_4\_G Atom Site Occupancy of H10R Constrained at 0.5 Check  
 PLAT300\_ALERT\_4\_G Atom Site Occupancy of H10S Constrained at 0.5 Check  
 PLAT302\_ALERT\_4\_G Anion/Solvent/Minor-Residue Disorder (Resd 3 ) 100% Note  
 PLAT302\_ALERT\_4\_G Anion/Solvent/Minor-Residue Disorder (Resd 4 ) 100% Note  
 PLAT302\_ALERT\_4\_G Anion/Solvent/Minor-Residue Disorder (Resd 5 ) 100% Note  
 PLAT302\_ALERT\_4\_G Anion/Solvent/Minor-Residue Disorder (Resd 6 ) 100% Note  
 PLAT304\_ALERT\_4\_G Non-Integer Number of Atoms in ..... (Resd 3 ) 2.50 Check  
 PLAT304\_ALERT\_4\_G Non-Integer Number of Atoms in ..... (Resd 4 ) 2.50 Check  
 PLAT304\_ALERT\_4\_G Non-Integer Number of Atoms in ..... (Resd 5 ) 2.50 Check  
 PLAT304\_ALERT\_4\_G Non-Integer Number of Atoms in ..... (Resd 6 ) 2.50 Check  
 PLAT398\_ALERT\_2\_G Deviating C-O-C Angle From 120 for O1 104.8 Degree

PLAT398_ALERT_2_G	Deviating	C-O-C	Angle From 120 for O4	104.1	Degree
PLAT398_ALERT_2_G	Deviating	C-O-C	Angle From 120 for O7	103.8	Degree
PLAT398_ALERT_2_G	Deviating	C-O-C	Angle From 120 for O10	103.5	Degree
PLAT606_ALERT_4_G	VERY LARGE	Solvent	Accessible VOID(S) in Structure	!	Info
PLAT790_ALERT_4_G	Centre of Gravity not Within Unit Cell:	Resd.	#	2	Note
	C52 H62 N6 O6 Pd2				
PLAT790_ALERT_4_G	Centre of Gravity not Within Unit Cell:	Resd.	#	3	Note
	C H2 C12				
PLAT790_ALERT_4_G	Centre of Gravity not Within Unit Cell:	Resd.	#	4	Note
	C H2 C12				
PLAT790_ALERT_4_G	Centre of Gravity not Within Unit Cell:	Resd.	#	5	Note
	C H2 C12				
PLAT790_ALERT_4_G	Centre of Gravity not Within Unit Cell:	Resd.	#	6	Note
	C H2 C12				
PLAT791_ALERT_4_G	Model has Chirality at C19		(Chiral SPGR)	S	Verify
PLAT791_ALERT_4_G	Model has Chirality at C46		(Chiral SPGR)	S	Verify
PLAT791_ALERT_4_G	Model has Chirality at C72		(Chiral SPGR)	S	Verify
PLAT791_ALERT_4_G	Model has Chirality at C98		(Chiral SPGR)	S	Verify
PLAT794_ALERT_5_G	Tentative Bond Valency for Pd1	(II)	.	1.75	Info
PLAT794_ALERT_5_G	Tentative Bond Valency for Pd2	(II)	.	1.74	Info
PLAT794_ALERT_5_G	Tentative Bond Valency for Pd3	(II)	.	1.73	Info
PLAT794_ALERT_5_G	Tentative Bond Valency for Pd4	(II)	.	1.77	Info
PLAT868_ALERT_4_G	ALERTS Due to the Use of _smtbx_masks	Suppressed		!	Info
PLAT912_ALERT_4_G	Missing # of FCF Reflections Above STh/L=	0.600		360	Note
PLAT933_ALERT_2_G	Number of OMIT Records in Embedded .res File ...			14	Note
PLAT984_ALERT_1_G	The C-f' =	0.0148	Deviates from the B&C-Value	0.0137	Check
PLAT984_ALERT_1_G	The N-f' =	0.0253	Deviates from the B&C-Value	0.0241	Check
PLAT984_ALERT_1_G	The O-f' =	0.0412	Deviates from the B&C-Value	0.0389	Check
PLAT984_ALERT_1_G	The Pd-f' =	0.0665	Deviates from the B&C-Value	0.0375	Check
PLAT985_ALERT_1_G	The Pd-f" =	3.1314	Deviates from the B&C-Value	3.1039	Check

---

0 **ALERT level A** = Most likely a serious problem - resolve or explain

7 **ALERT level B** = A potentially serious problem, consider carefully

8 **ALERT level C** = Check. Ensure it is not caused by an omission or oversight

64 **ALERT level G** = General information/check it is not something unexpected

14 ALERT type 1 CIF construction/syntax error, inconsistent or missing data

13 ALERT type 2 Indicator that the structure model may be wrong or deficient

5 ALERT type 3 Indicator that the structure quality may be low

43 ALERT type 4 Improvement, methodology, query or suggestion

4 ALERT type 5 Informative message, check

---

## Validation response form

Please find below a validation response form (VRF) that can be filled in and pasted into your CIF.

```
# start Validation Reply Form
_vrf_PLAT155_nn1872_150k
; PROBLEM: The Triclinic Unitcell is NOT Reduced ..... Please Do
!
RESPONSE: ...
;
_vrf_PLAT220_nn1872_150k
;
```

```

PROBLEM: NonSolvent Resd 1 C Ueq(max) / Ueq(min) Range 3.4 Ratio RESPONSE:
...
;
_vrf_PLAT342_nn1872_150k
; PROBLEM: Low Bond Precision on C-C Bonds ..... 0.01102
Ang.
RESPONSE: ...
;
_vrf_PLAT790_nn1872_150k
;
PROBLEM: Centre of Gravity not Within Unit Cell: Resd. # 1 Note RESPONSE:
...
;
_vrf_PLAT911_nn1872_150k
;
PROBLEM: Missing FCF Refl Between Thmin & STh/L= 0.600 26 Report RESPONSE:
...
;
_vrf_PLAT918_nn1872_150k
;
PROBLEM: Reflection(s) with I(obs) much Smaller I(calc) . 133 Check RESPONSE:
...
;
_vrf_PLAT977_nn1872_150k
; PROBLEM: Check Negative Difference Density on H72 -0.31 eA-
3 RESPONSE: ...
;
_vrf_PLAT978_nn1872_150k
;
PROBLEM: Number C-C Bonds with Positive Residual Density. 0 Info RESPONSE:
...
;
# end Validation Reply Form

```

---

It is advisable to attempt to resolve as many as possible of the alerts in all categories. Often the minor alerts point to easily fixed oversights, errors and omissions in your CIF or refinement strategy, so attention to these fine details can be worthwhile. In order to resolve some of the more serious problems it may be necessary to carry out additional measurements or structure refinements. However, the purpose of your study may justify the reported deviations and the more serious of these should normally be commented upon in the discussion or experimental section of a paper or in the "special\_details" fields of the CIF. checkCIF was carefully designed to identify outliers and unusual parameters, but every test has its limitations and alerts that are not important in a particular case may appear. Conversely, the absence of alerts does not guarantee there are no aspects of the results needing attention. It is up to the individual to critically assess their own results and, if necessary, seek expert advice.

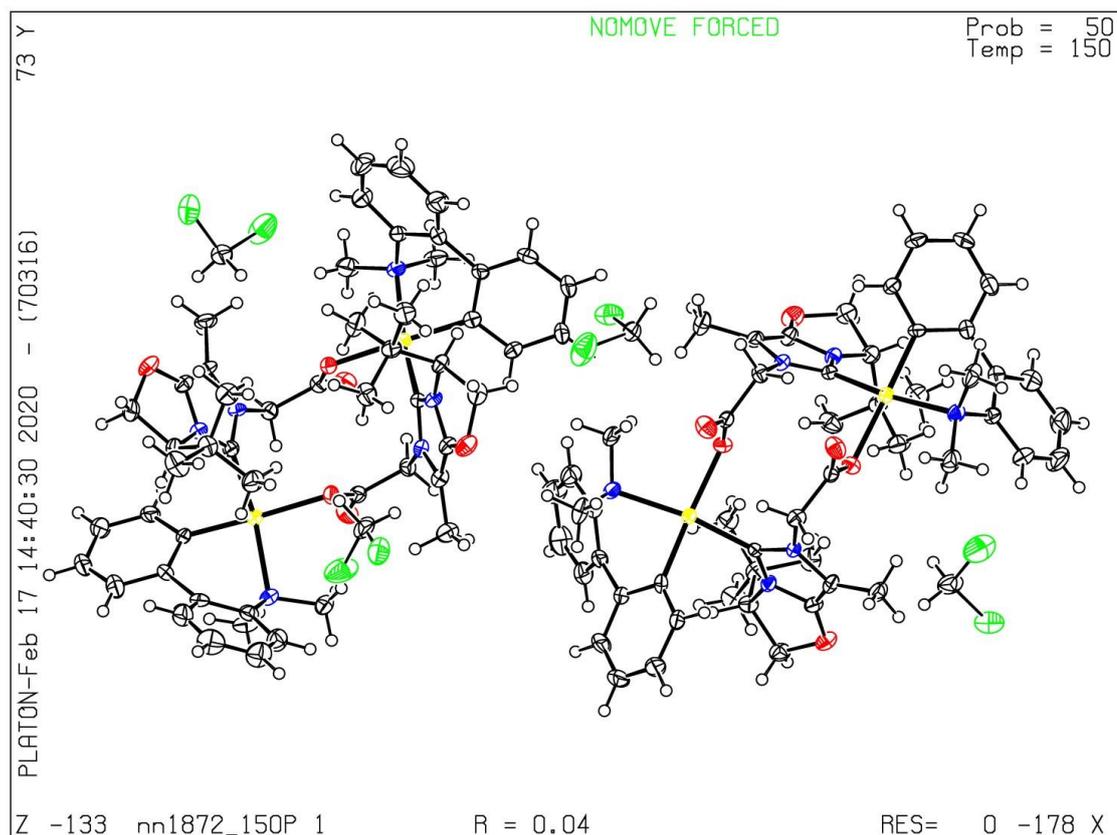
### **Publication of your CIF in IUCr journals**

A basic structural check has been run on your CIF. These basic checks will be run on all CIFs submitted for publication in IUCr journals (*Acta Crystallographica*, *Journal of Applied Crystallography*, *Journal of Synchrotron Radiation*); however, if you intend to submit to *Acta Crystallographica Section C* or *E* or *IUCrData*, you should make sure that full publication checks are run on the final version of your CIF prior to submission.

### **Publication of your CIF in other journals**

Please refer to the *Notes for Authors* of the relevant journal for any special instructions relating to CIF submission.

**PLATON version of 22/12/2019; check.def file version of 13/12/2019 Datablock  
nn1872\_150k - ellipsoid plot**

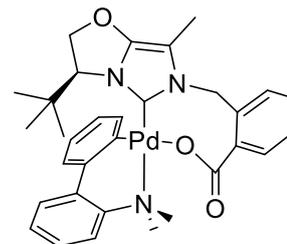


## X-ray Structure of complex 3 (C<sup>3</sup>)

Checkcif for C<sup>3</sup>

### checkCIF/PLATON report

Structure factors have been supplied for datablock(s)  
nn1929\_150k\_0m



THIS REPORT IS FOR GUIDANCE ONLY. IF USED AS PART OF A REVIEW PROCEDURE FOR PUBLICATION, IT SHOULD NOT REPLACE THE EXPERTISE OF AN EXPERIENCED CRYSTALLOGRAPHIC REFEREE.

No syntax errors found. CIF dictionary Interpreting this report

### Datablock: nn1929\_150k\_0m

---

Bond precision:	C-C = 0.0041 Å	Wavelength=1.54178
Cell:	a=9.9298(10)	b=13.7729(14) c=10.4444(11)
	alpha=90	beta=92.180(2) gamma=90
Temperature:	150 K	
	Calculated	Reported
Volume	1427.4(3)	1427.4(3)
Space group	P 21	P 1 21 1
Hall group	P 2yb	P 2yb
Moiety formula	C32 H35 N3 O3 Pd	C32 H35 N3 O3 Pd
Sum formula	C32 H35 N3 O3 Pd	C32 H35 N3 O3 Pd
Mr	616.03	616.03
Dx, g cm <sup>-3</sup>	1.433	1.433
Z	2	2
Mu (mm <sup>-1</sup> )	5.539	5.539
F000	636.0	636.0
F000'	637.85	
h, k, lmax	12, 16, 12	12, 16, 12
Nref	5435[ 2838]	4471
Tmin, Tmax	0.424, 0.460	0.540, 0.753
Tmin'	0.287	

Correction method= # Reported T Limits: Tmin=0.540 Tmax=0.753

AbsCorr = MULTI-SCAN

Data completeness= 1.58/0.82    Theta(max)= 70.143

R(reflections)= 0.0197( 4468)    wR2(reflections)= 0.0425( 4471)

S = 1.038                                  Npar= 358

---

The following ALERTS were generated. Each ALERT has the format **test-name\_ALERT\_alert-type\_alert-level**.

Click on the hyperlinks for more details of the test.

---

 **Alert level B**

PLAT987\_ALERT\_1\_B The Flack x is >> 0 - Do a BASF/TWIN Refinement                  Please Check

---

 **Alert level C**

PLAT090\_ALERT\_3\_C Poor Data / Parameter Ratio (Zmax > 18) .....                  7.59 Note  
PLAT911\_ALERT\_3\_C Missing FCF Refl Between Thmin & STh/L=    0.600                  43 Report  
PLAT915\_ALERT\_3\_C No Flack x Check Done: Low Friedel Pair Coverage                  67 %

---

 **Alert level G**

PLAT033\_ALERT\_4\_G Flack x Value Deviates > 3.0 \* sigma from Zero .                  0.054 Note  
PLAT232\_ALERT\_2\_G Hirshfeld Test Diff (M-X) Pdl                  --C23                  .                  6.2 s.u.  
PLAT398\_ALERT\_2\_G Deviating C-O-C                  Angle From 120 for O3                  104.9 Degree  
PLAT791\_ALERT\_4\_G Model has Chirality at C27                  (Chiral SPGR)                  S Verify  
PLAT794\_ALERT\_5\_G Tentative Bond Valency for Pdl                  (II)                  .                  1.84 Info  
PLAT912\_ALERT\_4\_G Missing # of FCF Reflections Above STh/L=    0.600                  77 Note  
PLAT913\_ALERT\_3\_G Missing # of Very Strong Reflections in FCF ....                  1 Note  
PLAT961\_ALERT\_5\_G Dataset Contains no Negative Intensities .....                  Please Check  
PLAT978\_ALERT\_2\_G Number C-C Bonds with Positive Residual Density.                  5 Info

---

0 **ALERT level A** = Most likely a serious problem - resolve or explain  
1 **ALERT level B** = A potentially serious problem, consider carefully  
  3 **ALERT level C** = Check. Ensure it is not caused by an omission or oversight  
  9 **ALERT level G** = General information/check it is not something unexpected

  1 ALERT type 1 CIF construction/syntax error, inconsistent or missing data  
  3 ALERT type 2 Indicator that the structure model may be wrong or deficient  
  4 ALERT type 3 Indicator that the structure quality may be low  
    3 ALERT type 4 Improvement, methodology, query or suggestion  
    2 ALERT type 5 Informative message, check

---

It is advisable to attempt to resolve as many as possible of the alerts in all categories. Often the minor alerts point to easily fixed oversights, errors and omissions in your CIF or refinement strategy, so attention to these fine details can be worthwhile. In order to resolve some of the more serious problems it may be necessary to carry out additional measurements or structure refinements. However, the purpose of your study may justify the reported deviations and the more serious of these should normally be commented upon in the discussion or experimental section of a paper or in the "special\_details" fields of the CIF. checkCIF was carefully designed to identify outliers and unusual parameters, but every test

has its limitations and alerts that are not important in a particular case may appear. Conversely, the absence of alerts does not guarantee there are no aspects of the results needing attention. It is up to the individual to critically assess their own results and, if necessary, seek expert advice.

### Publication of your CIF in IUCr journals

A basic structural check has been run on your CIF. These basic checks will be run on all CIFs submitted for publication in IUCr journals (*Acta Crystallographica*, *Journal of Applied Crystallography*, *Journal of Synchrotron Radiation*); however, if you intend to submit to *Acta Crystallographica Section C* or *E* or *IUCrData*, you should make sure that full publication checks are run on the final version of your CIF prior to submission.

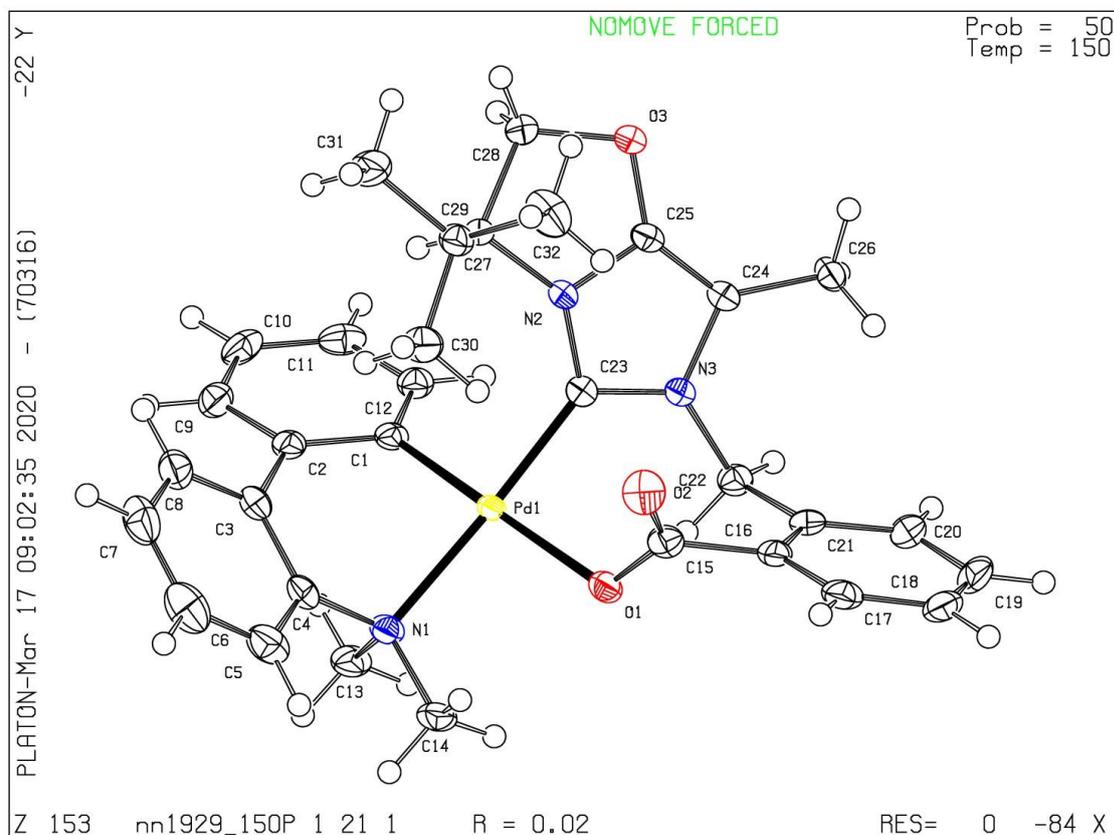
### Publication of your CIF in other journals

Please refer to the *Notes for Authors* of the relevant journal for any special instructions relating to CIF submission.

---

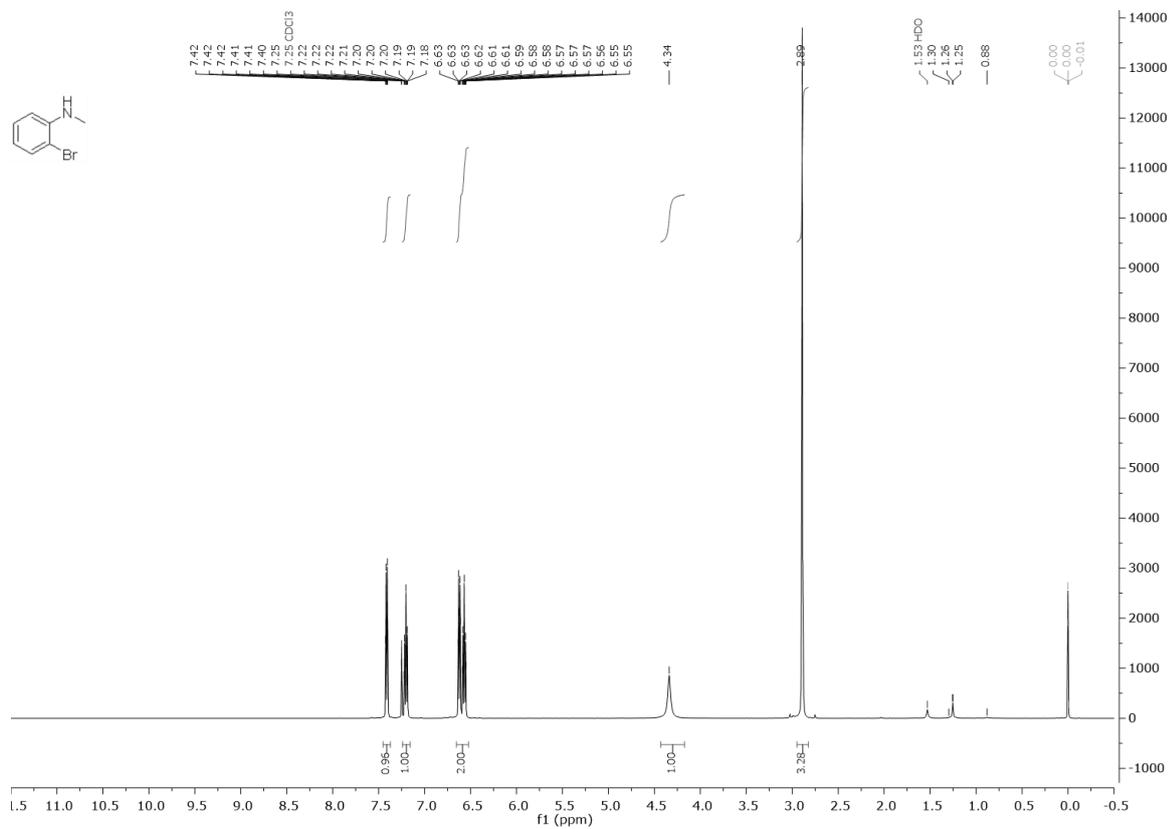
### PLATON version of 22/12/2019; check.def file version of 13/12/2019

Datablock nn1929\_150k\_0m - ellipsoid plot

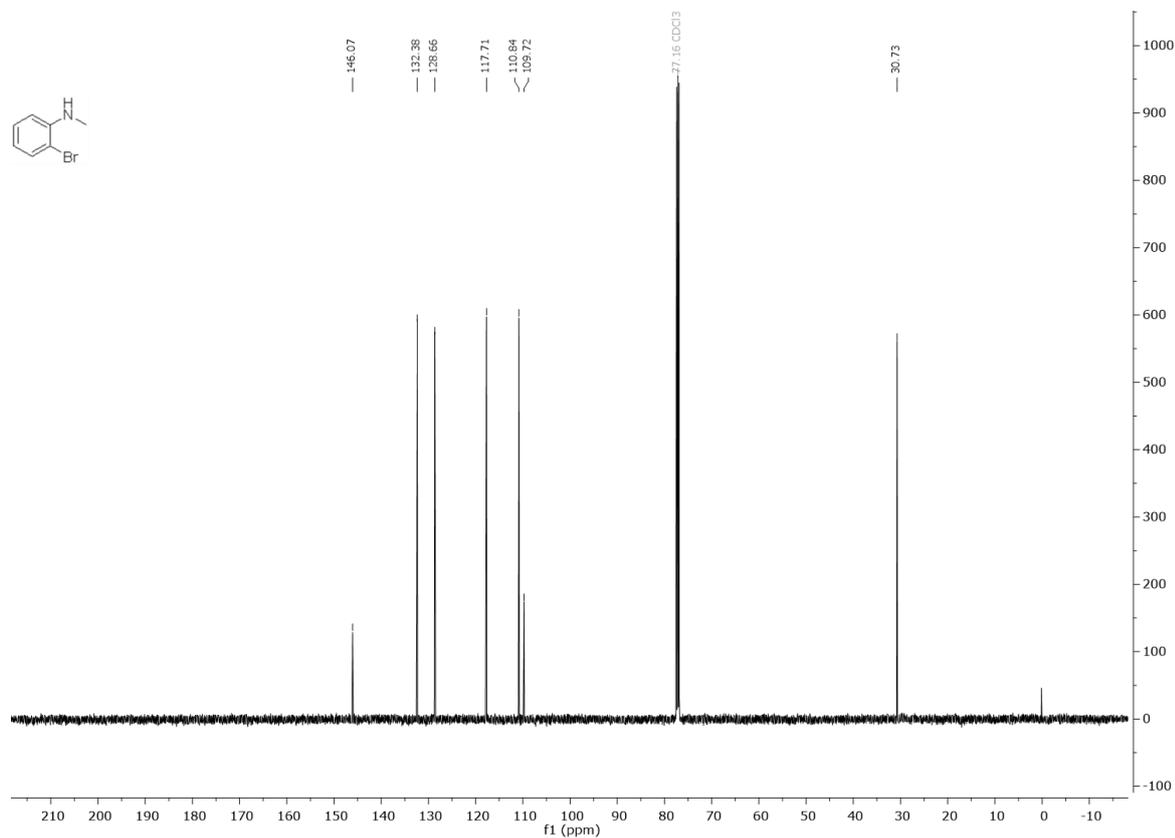


## NMR spectra $\beta$ -lactam part

2-bromo-*N*,5-dimethylaniline (**6.45**),  $^1\text{H}$  NMR (500 MHz, Chloroform-*d*)

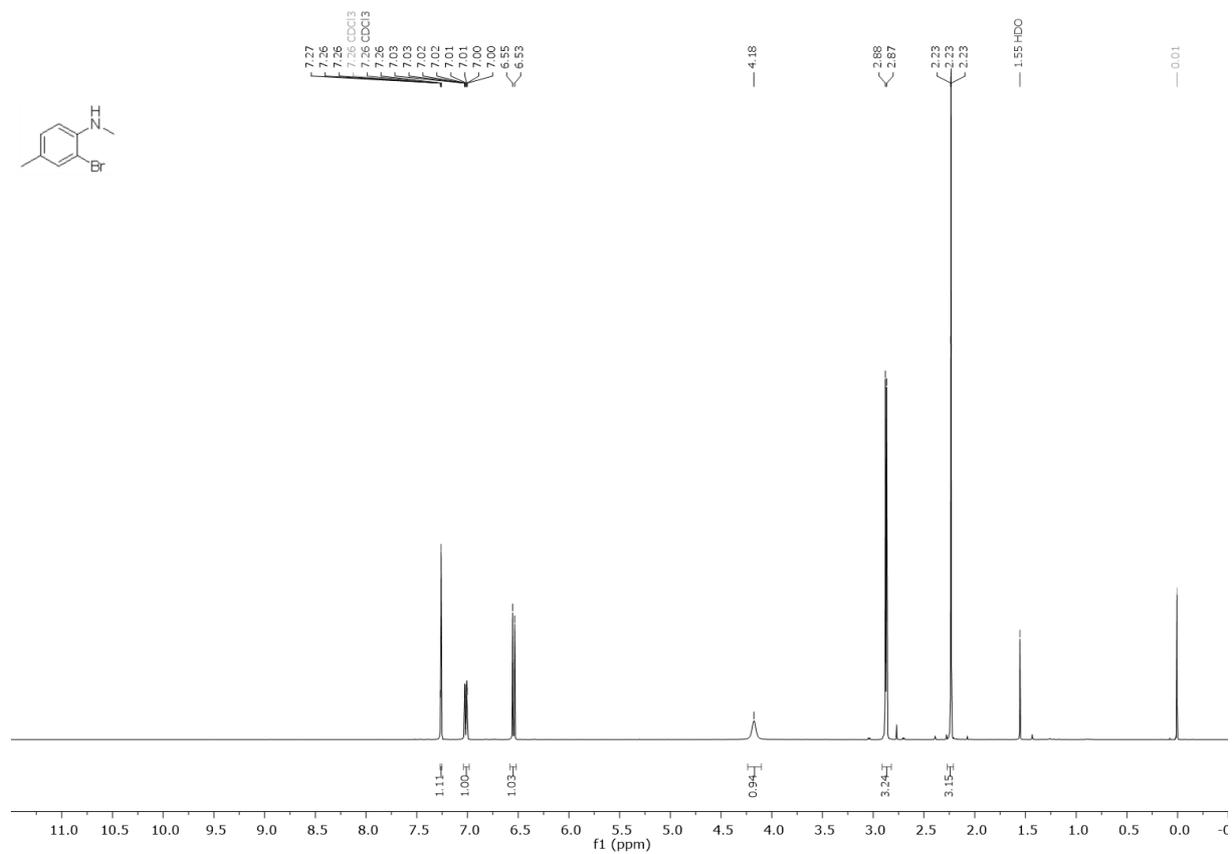


$^{13}\text{C}$  NMR (126 MHz, Chloroform-*d*)

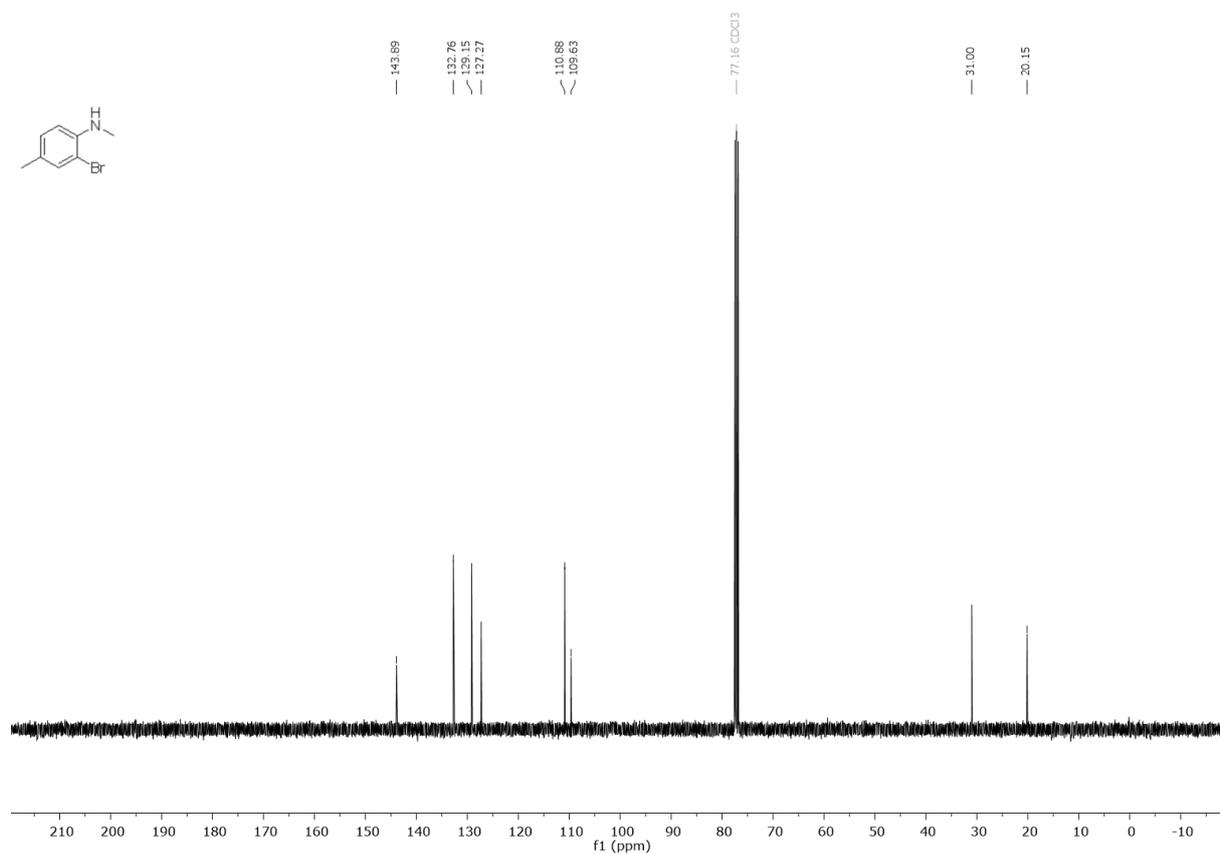


## 2-bromo-*N*,4-dimethylaniline (**6.46**)

$^1\text{H}$  NMR (400 MHz, Chloroform-*d*)

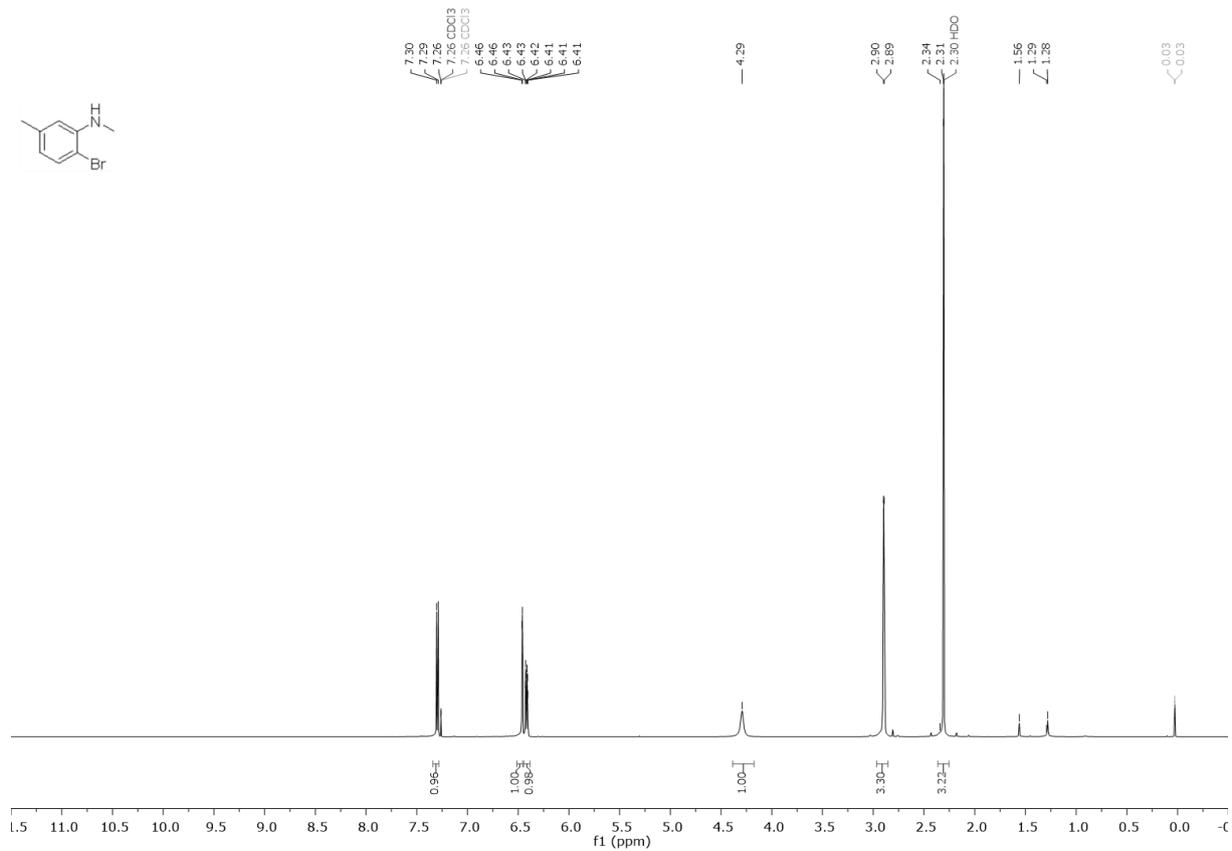


$^{13}\text{C}$  NMR (101 MHz, Chloroform-*d*)

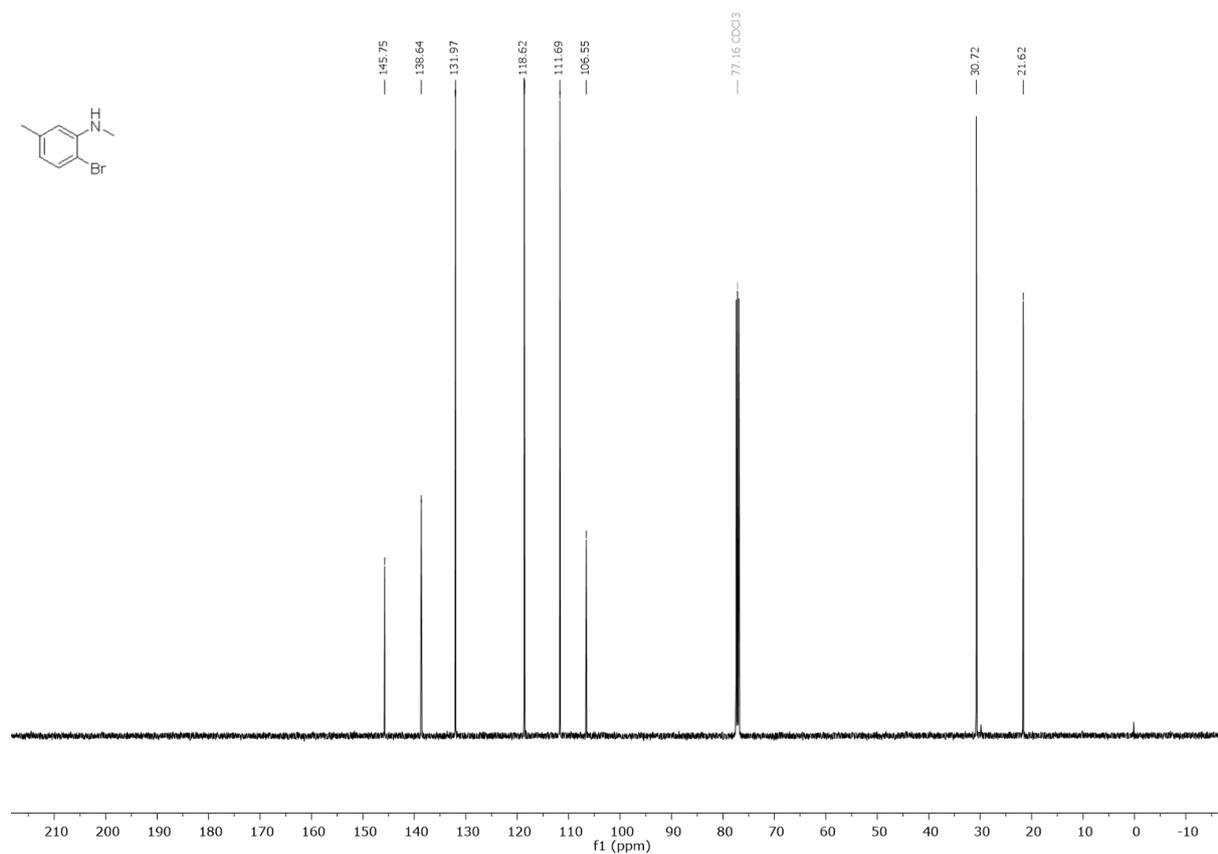


### 2-bromo-*N*,5-dimethylaniline (**6.47**)

$^1\text{H}$  NMR (500 MHz, Chloroform-*d*)

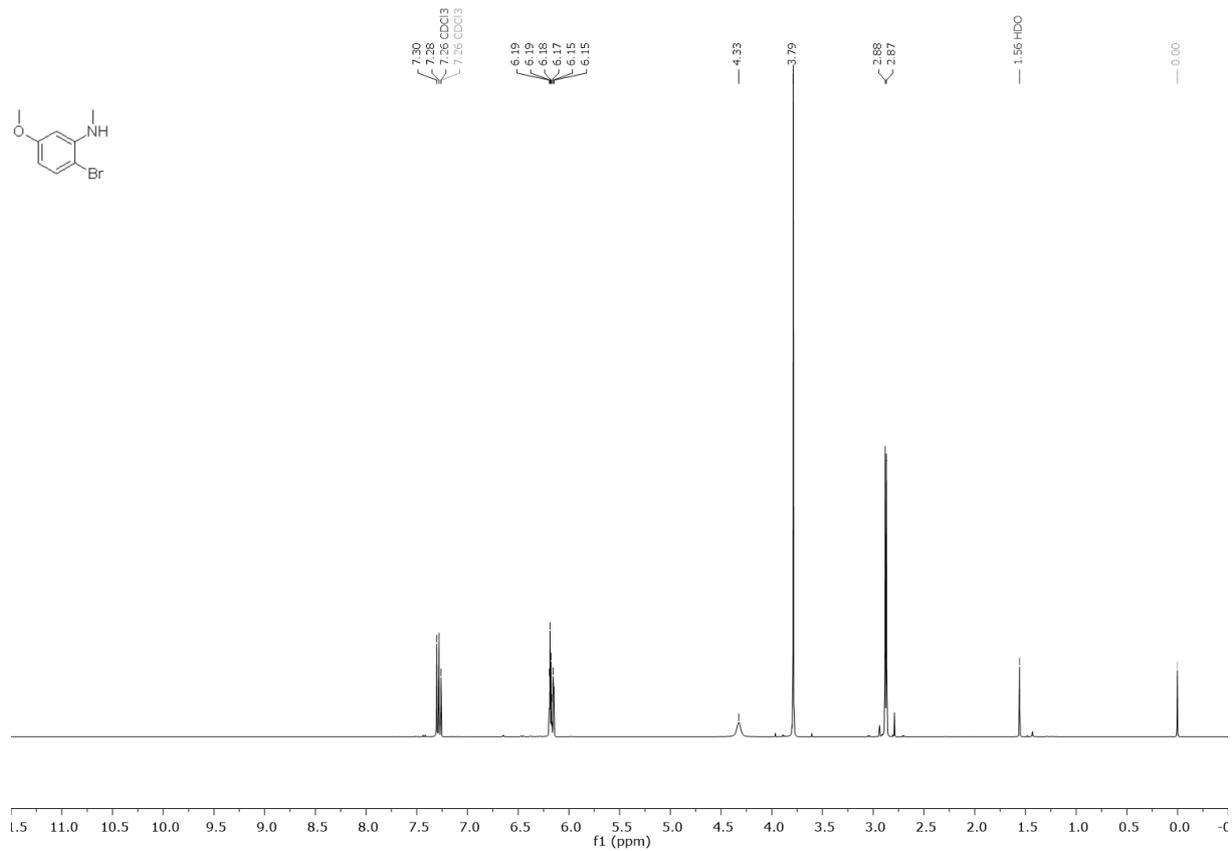


$^{13}\text{C}$  NMR (126 MHz, Chloroform-*d*)

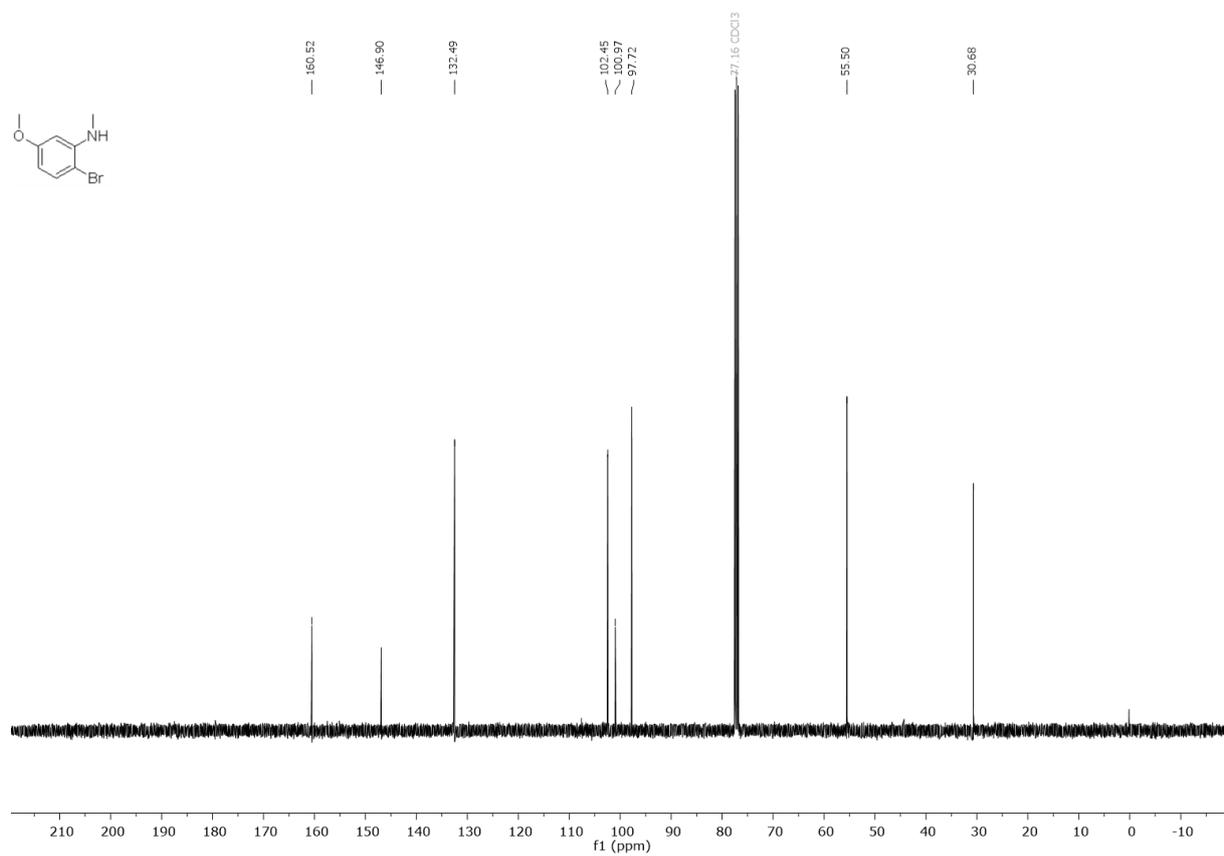


## 2-bromo-5-methoxy-*N*-methylaniline (**6.48**)

$^1\text{H}$  NMR (400 MHz, Chloroform-*d*)

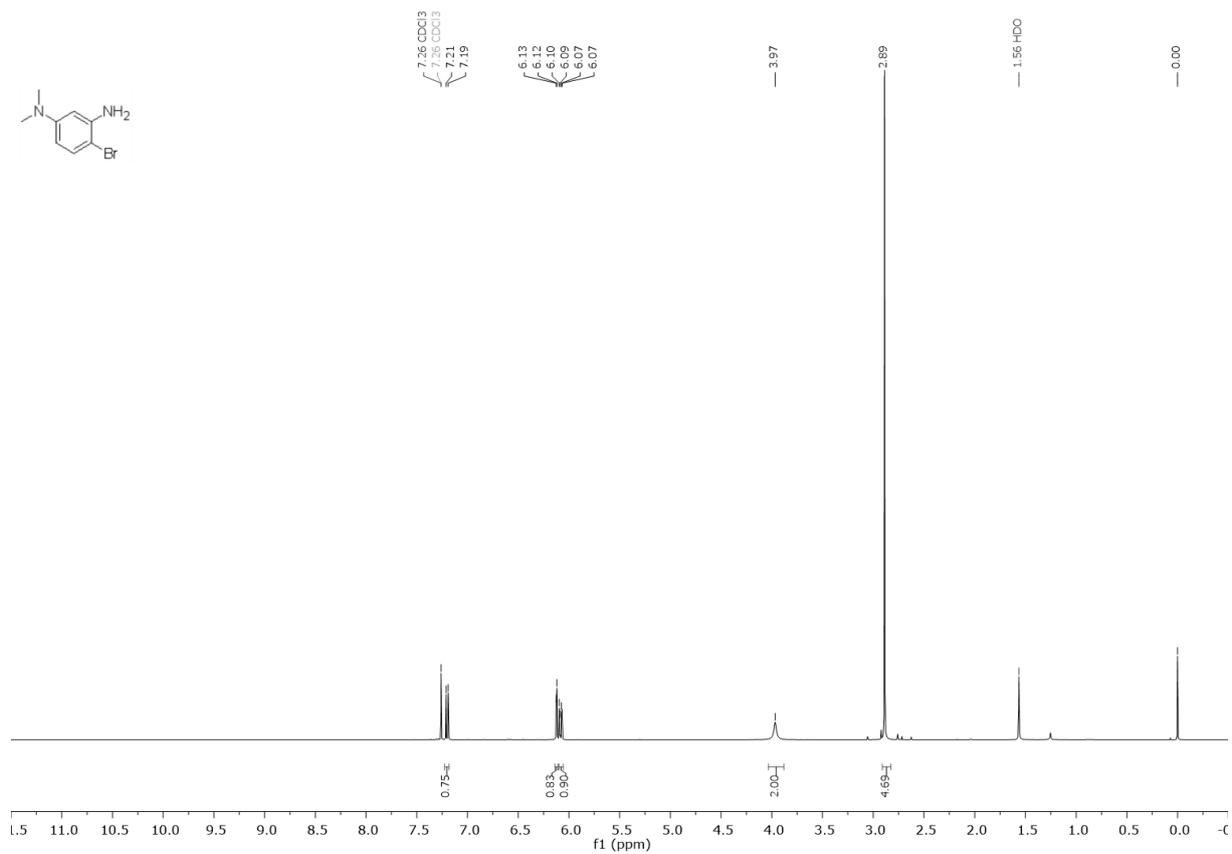


$^{13}\text{C}$  NMR (101 MHz, Chloroform-*d*)

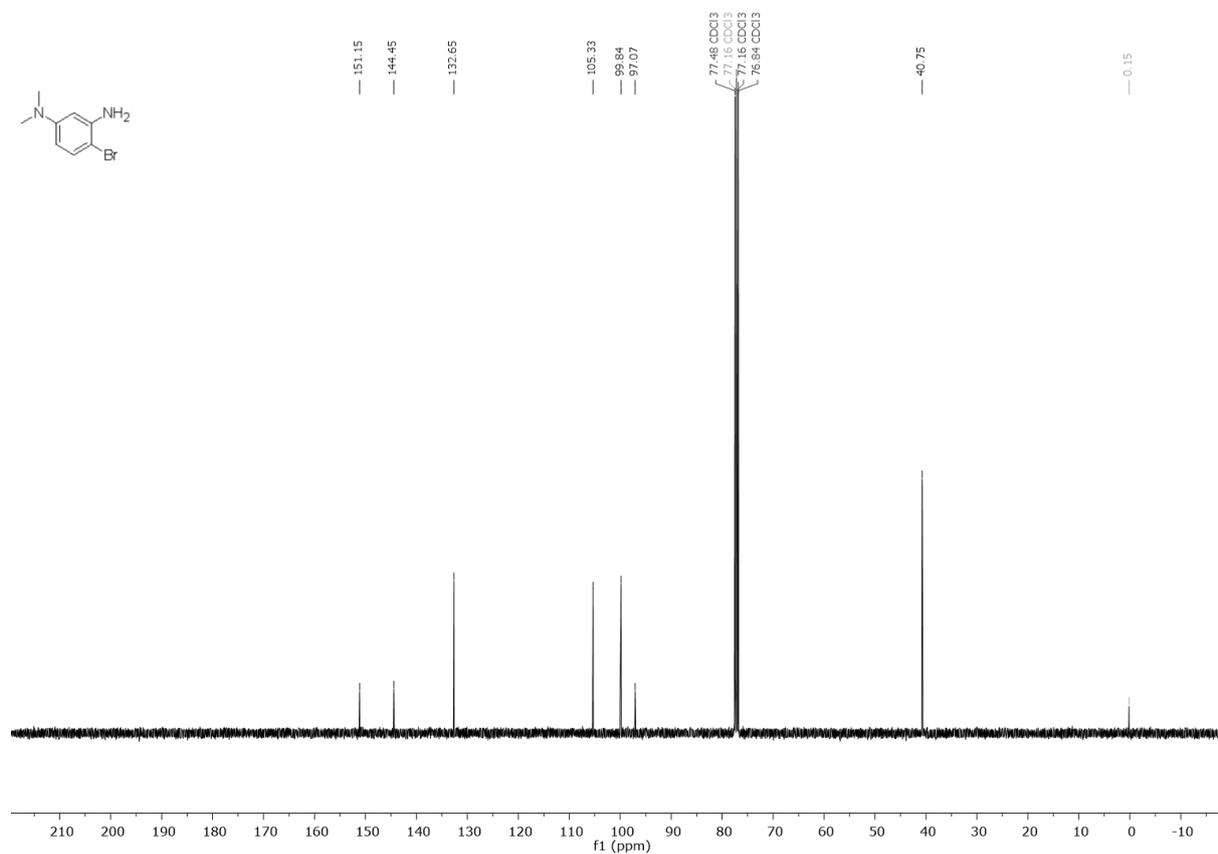


4-bromo-*N,N*-dimethylbenzene-1,3-diamine (**6.49**)

$^1\text{H}$  NMR (400 MHz, Chloroform-*d*)

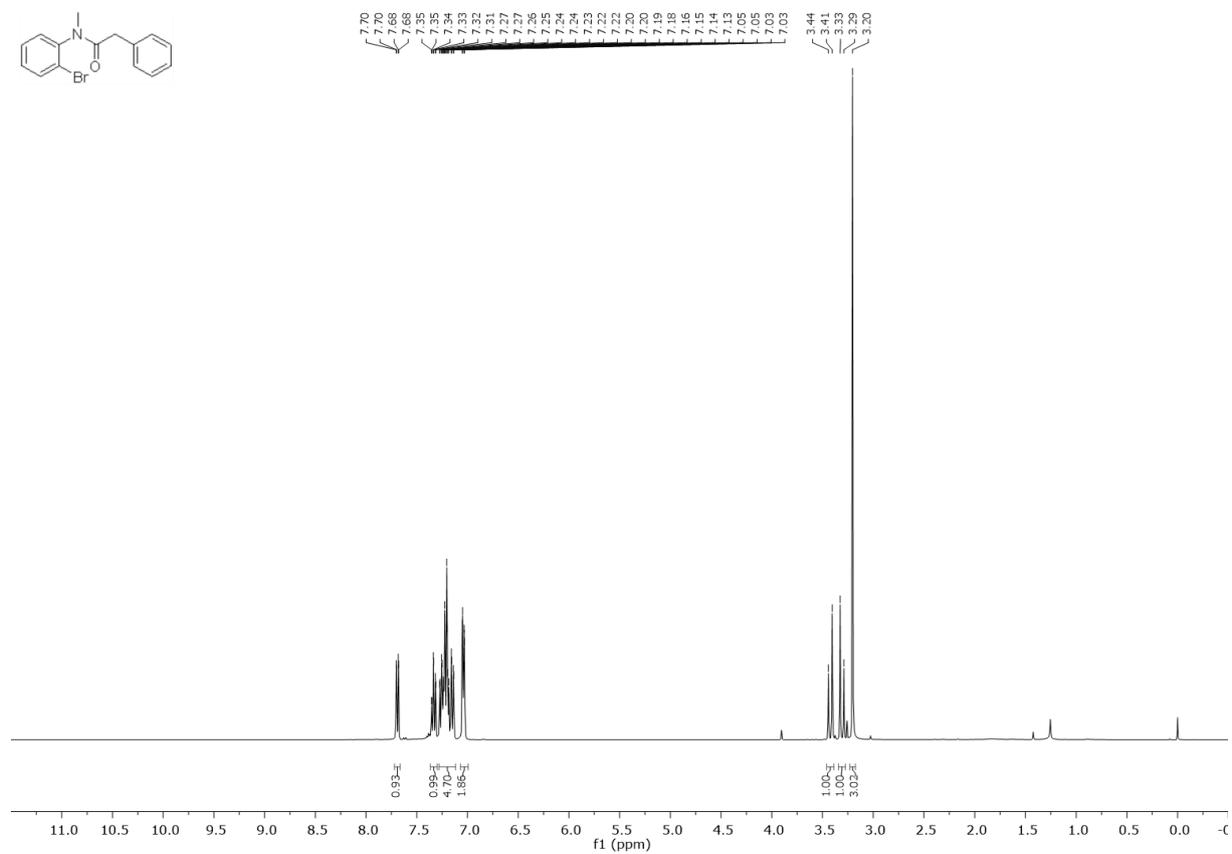


$^{13}\text{C}$  NMR (101 MHz, Chloroform-*d*)

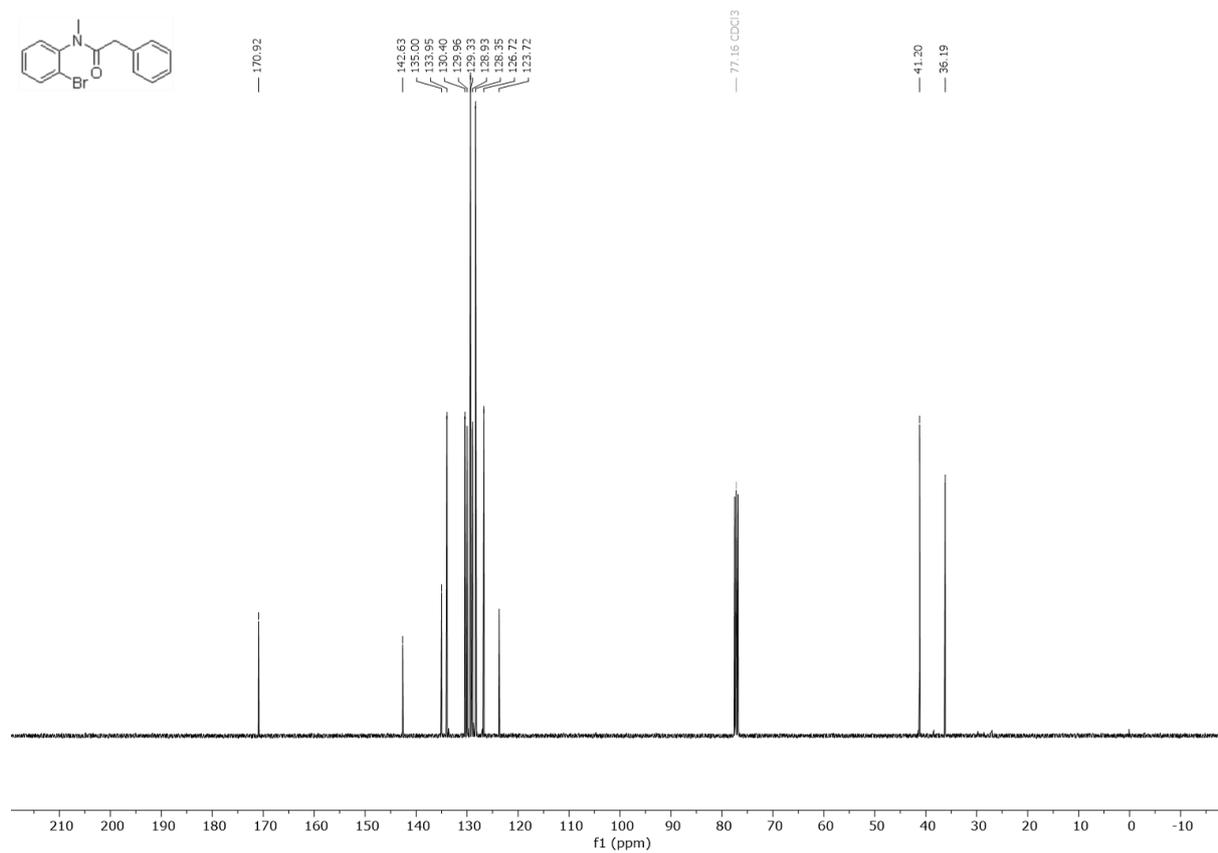


*N*-(2-bromophenyl)-*N*-methyl-2-phenylacetamide (**6.50**)

<sup>1</sup>H NMR (400 MHz, Chloroform-*d*)

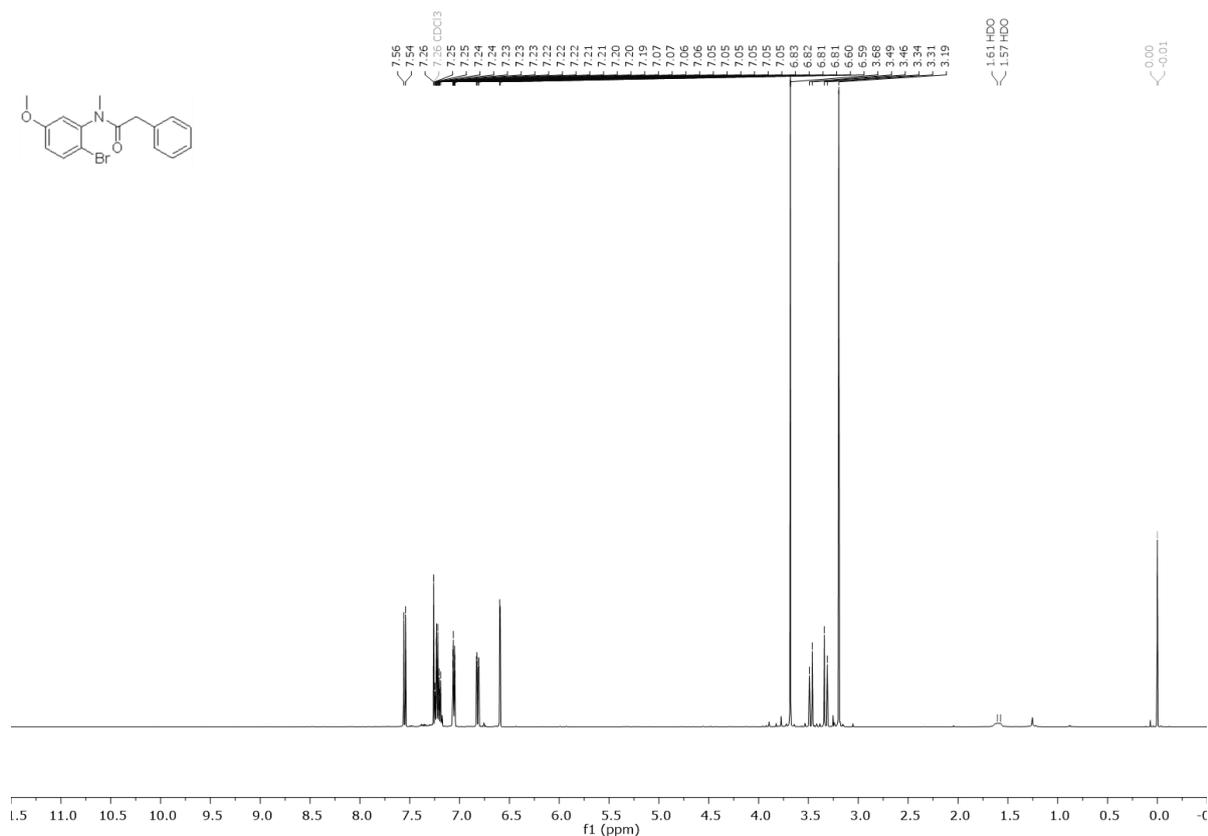


<sup>13</sup>C NMR (101 MHz, Chloroform-*d*)

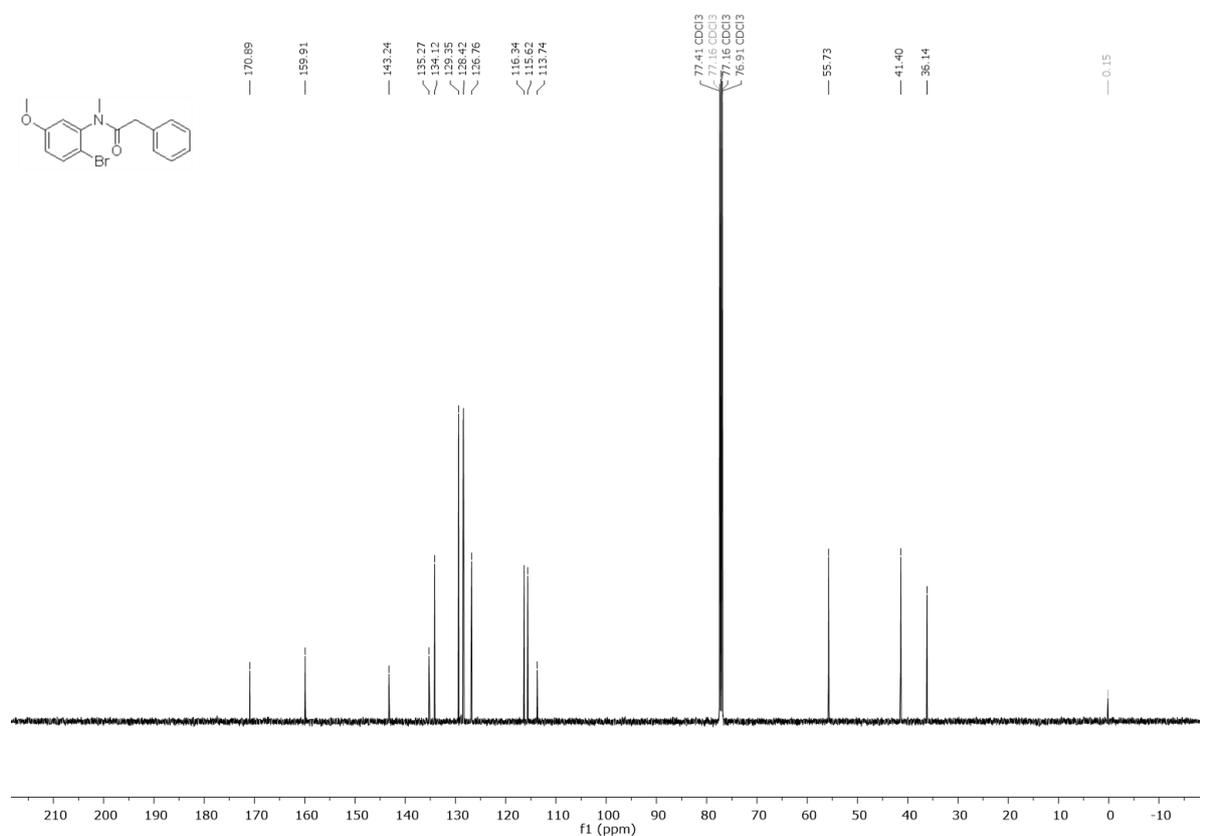


*N*-(2-bromo-5-methoxyphenyl)-*N*-methyl-2-phenylacetamide (**6.51**)

<sup>1</sup>H NMR (500 MHz, Chloroform-*d*)

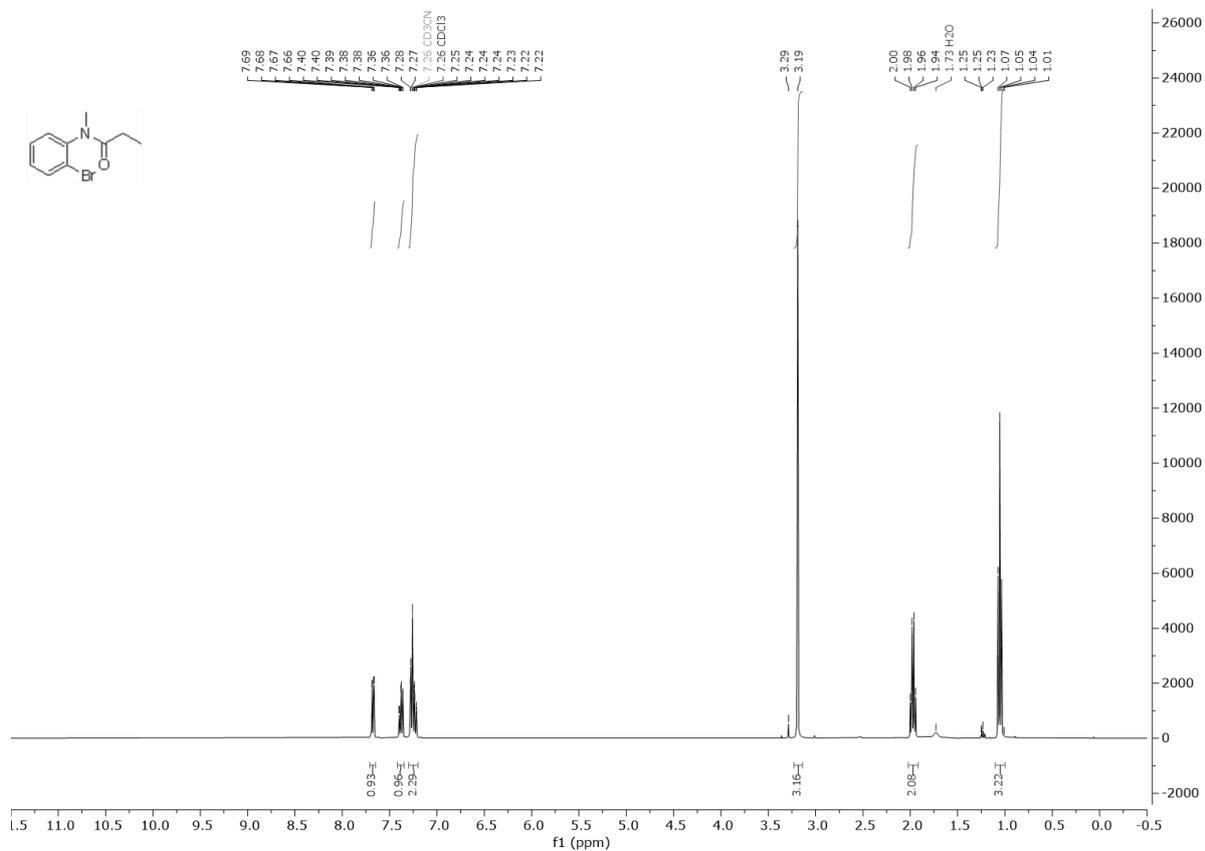


<sup>13</sup>C NMR (126 MHz, Chloroform-*d*)

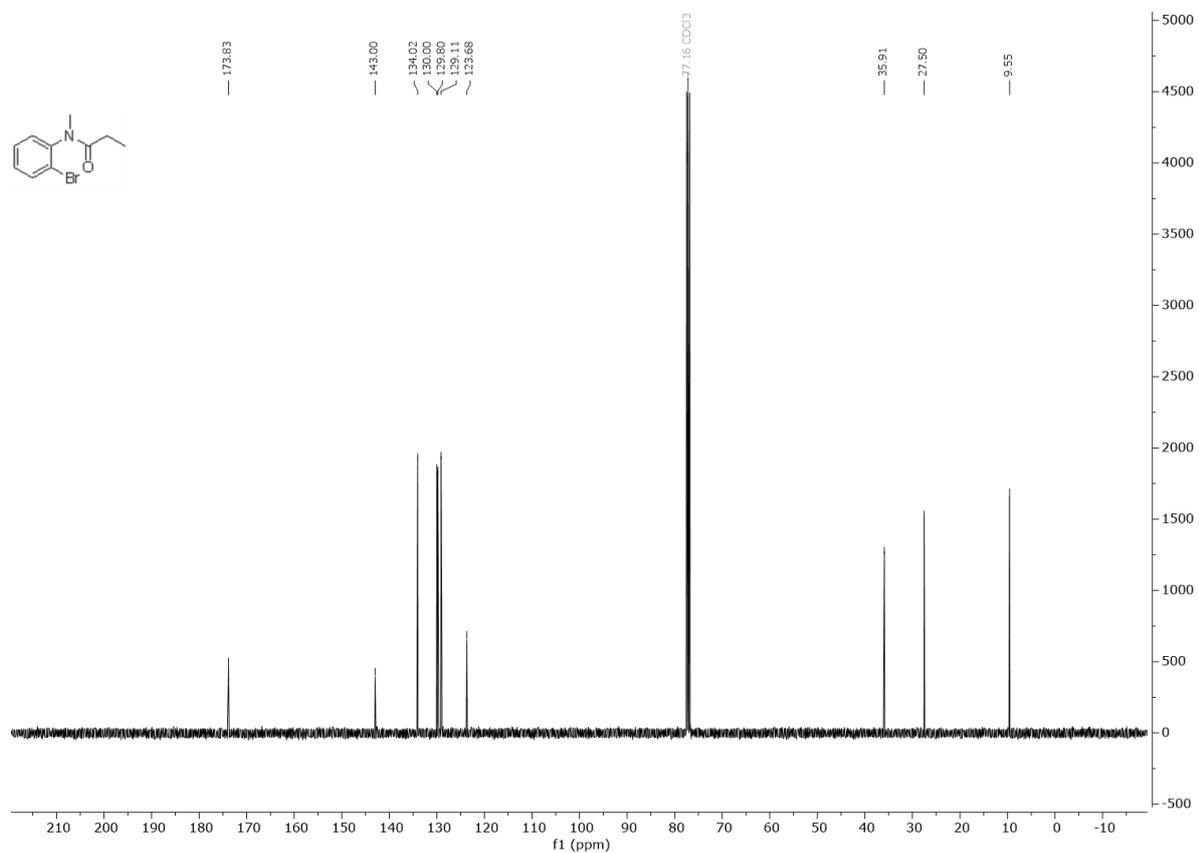


# N-(2-bromophenyl)-N-methylpropionamide (6.12)

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )

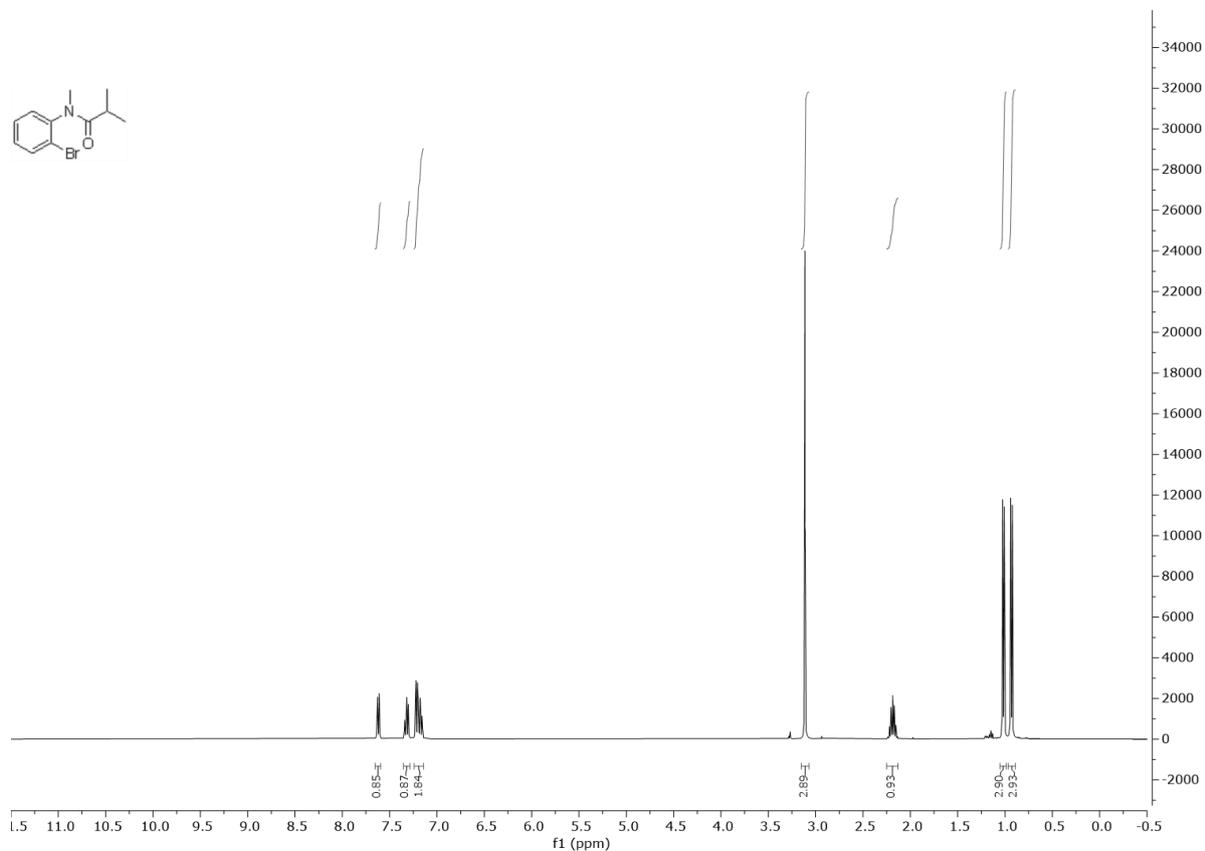


$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )

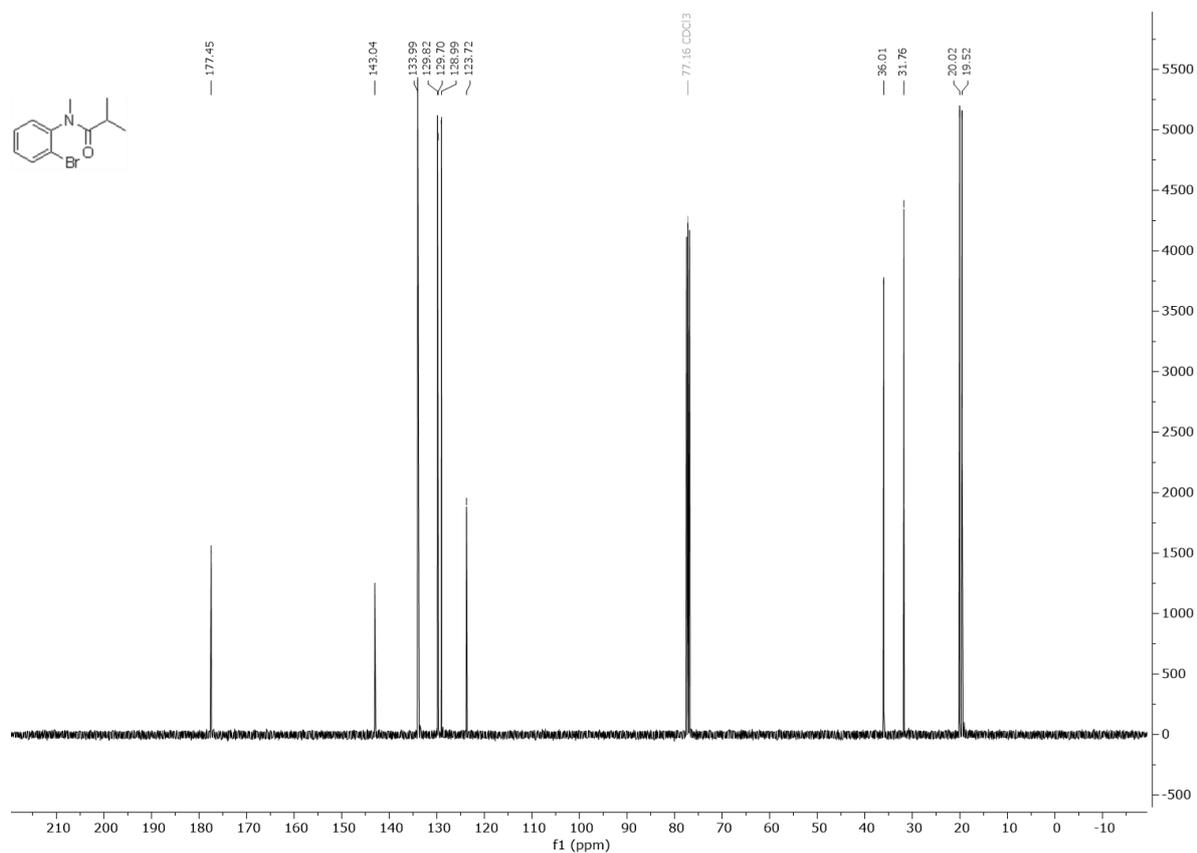


*N*-(2-bromophenyl)-*N*-methylisobutyramide (**6.13**)

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )



$^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )

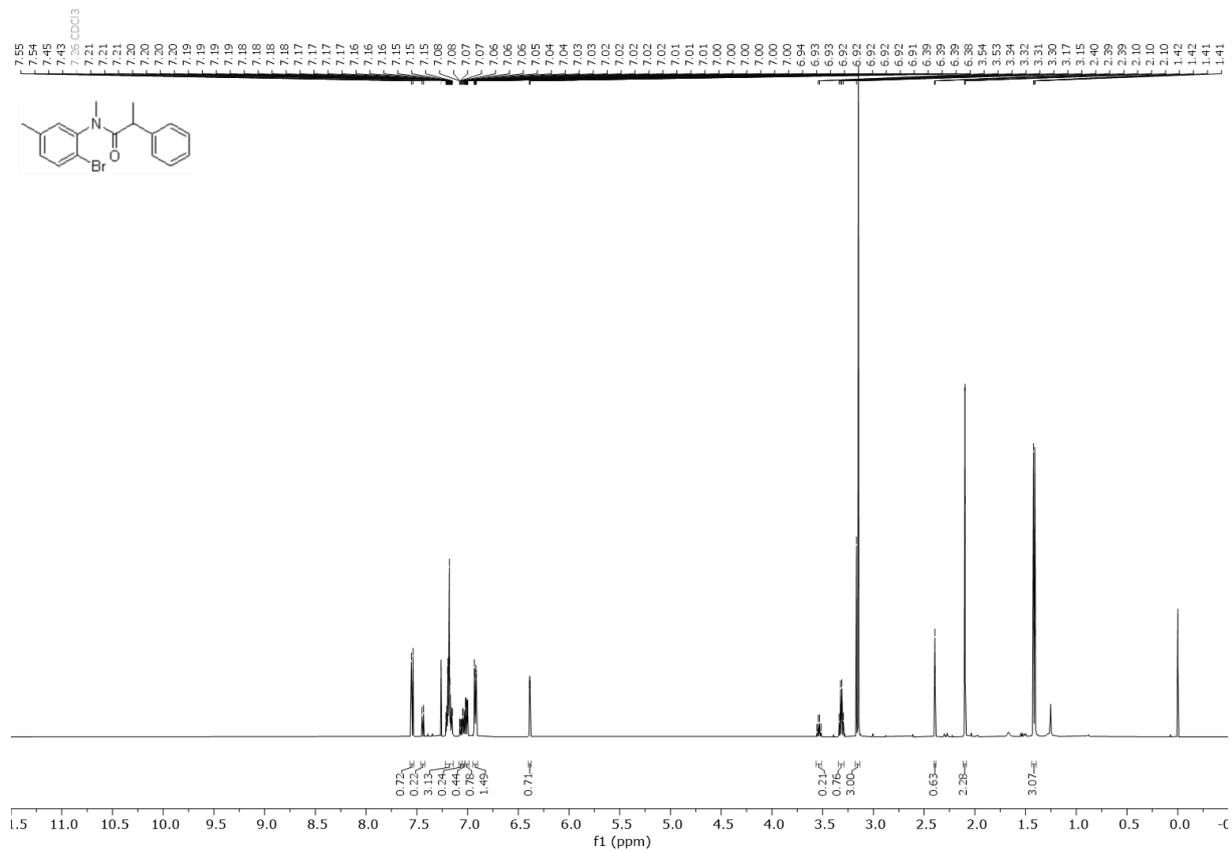




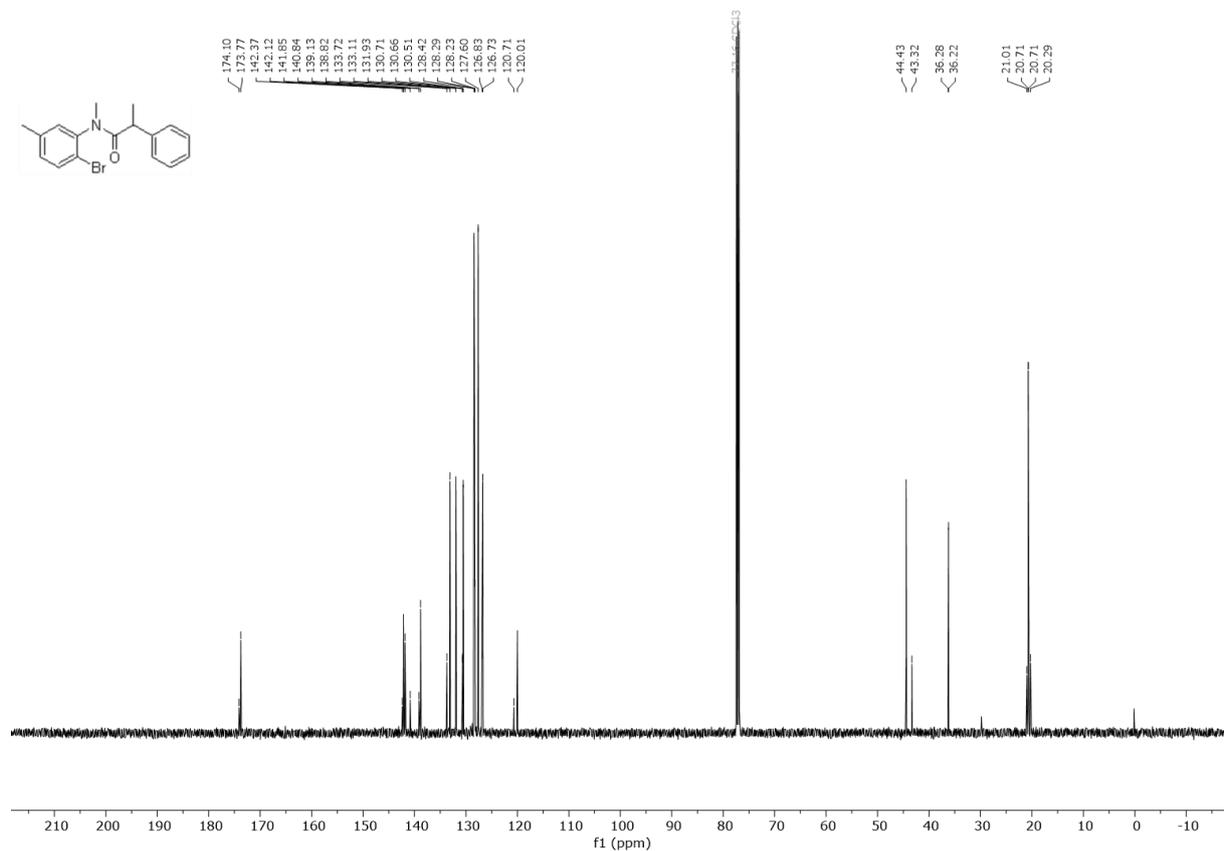


*N*-(2-bromo-5-methylphenyl)-*N*-methyl-2-phenylpropanamide (**6.54**)

<sup>1</sup>H NMR (500 MHz, Chloroform-*d*)

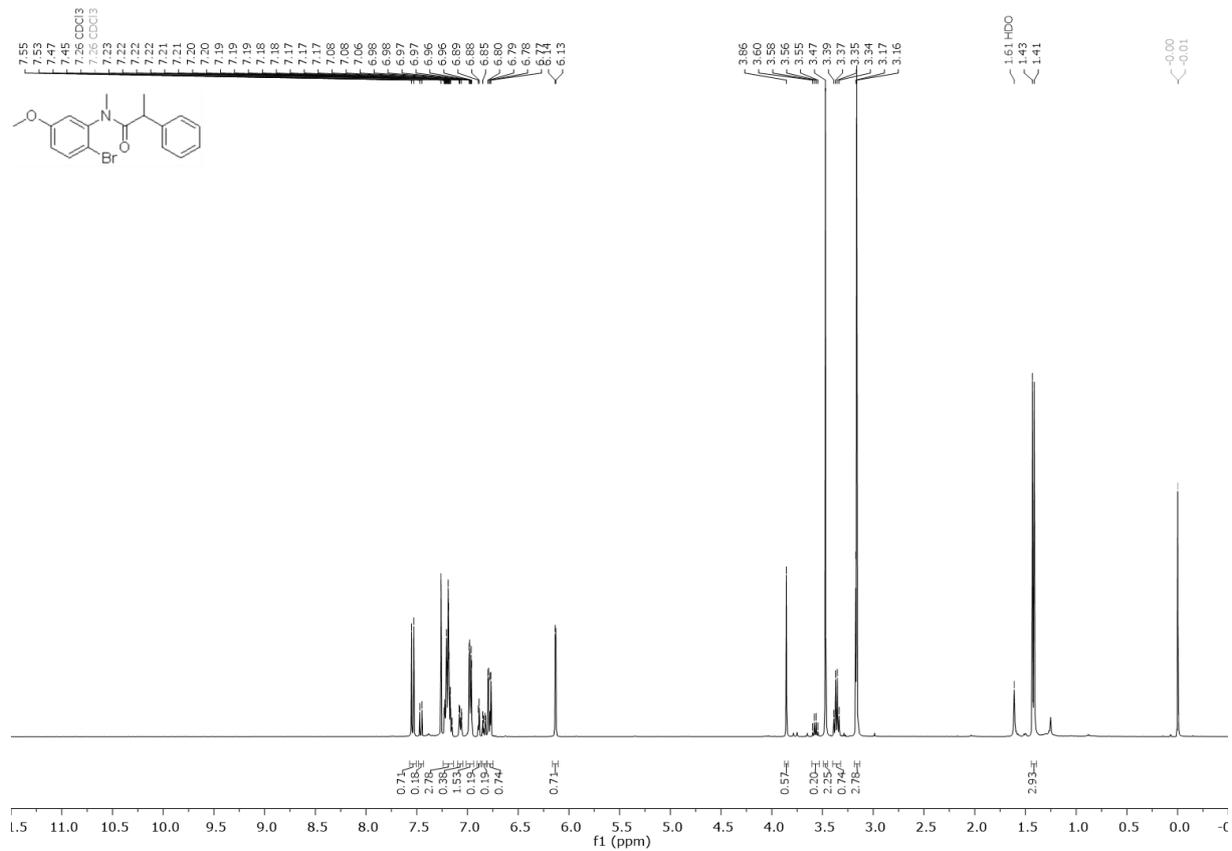


<sup>13</sup>C NMR (126 MHz, Chloroform-*d*)

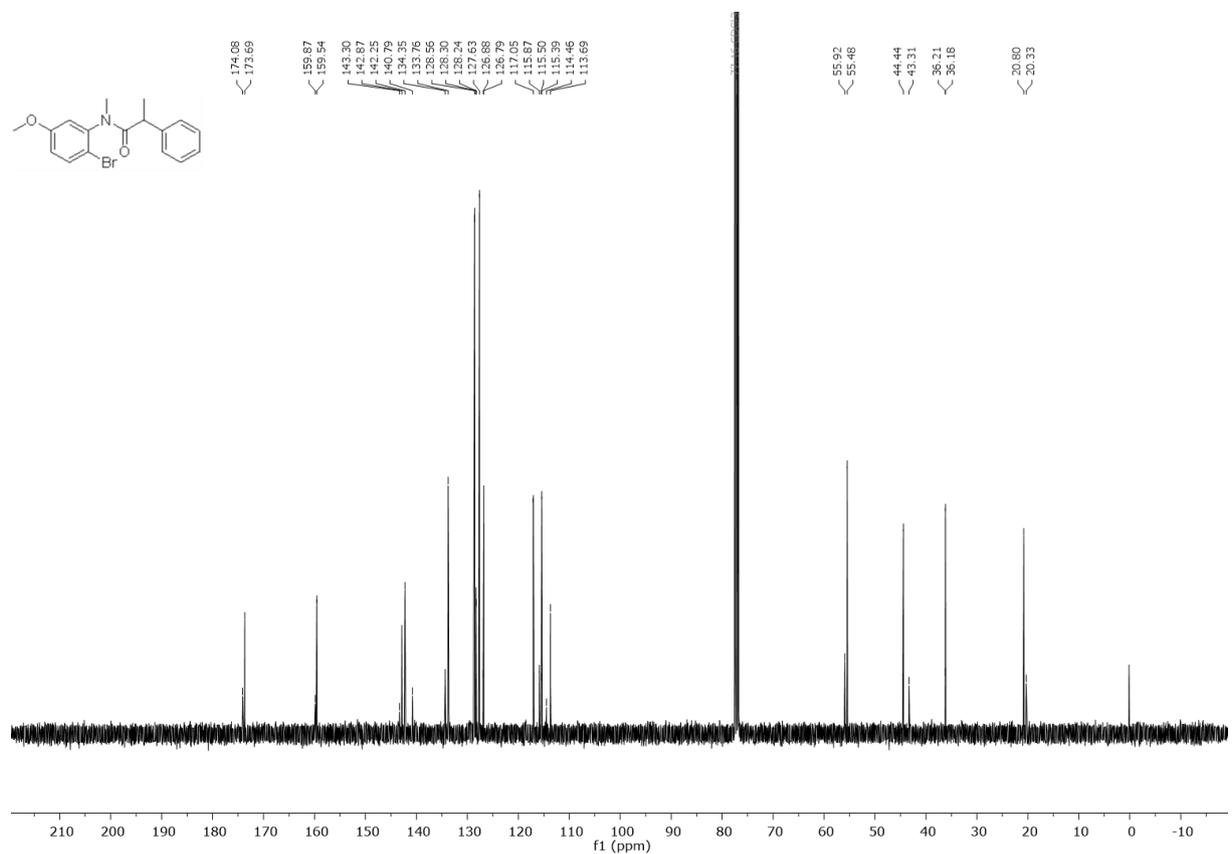


*N*-(2-bromo-5-methoxyphenyl)-*N*-methyl-2-phenylpropanamide (**6.55**)

<sup>1</sup>H NMR (400 MHz, Chloroform-*d*)



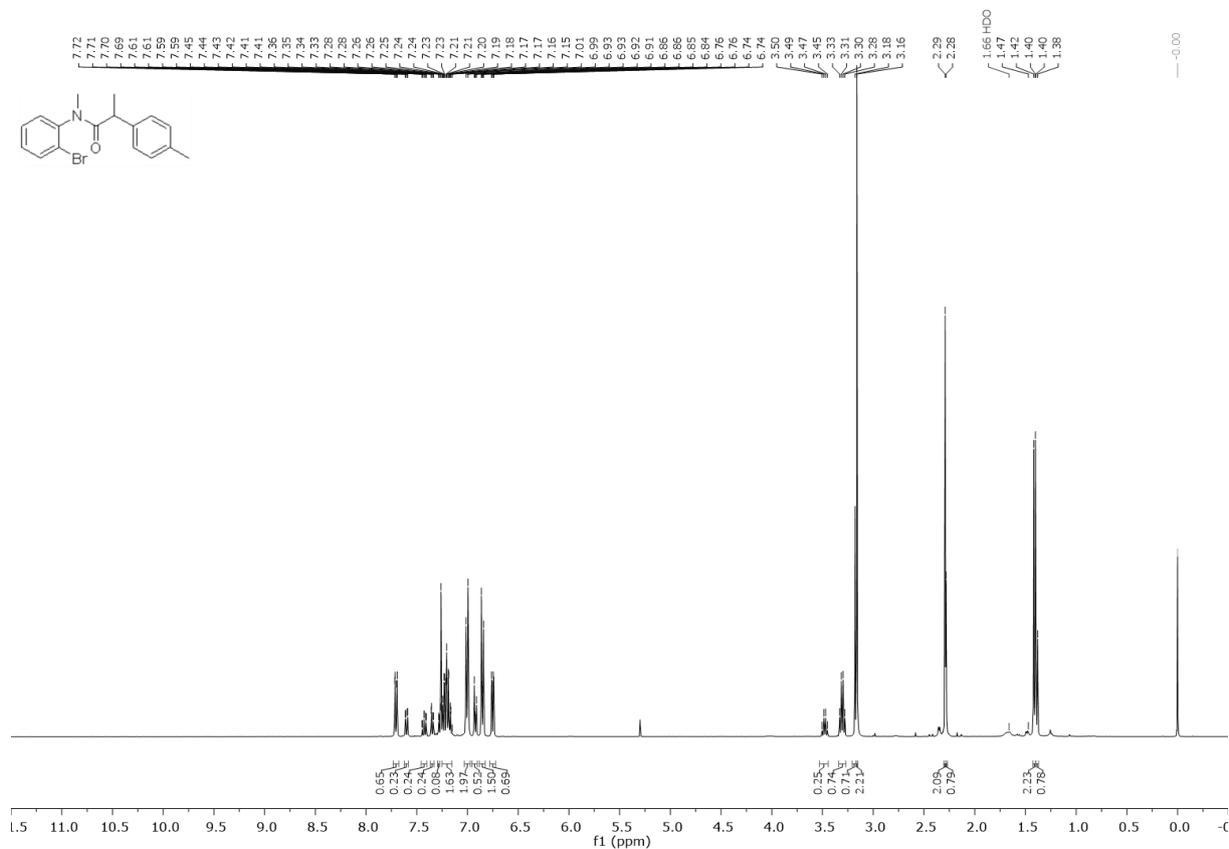
<sup>13</sup>C NMR (101 MHz, Chloroform-*d*)



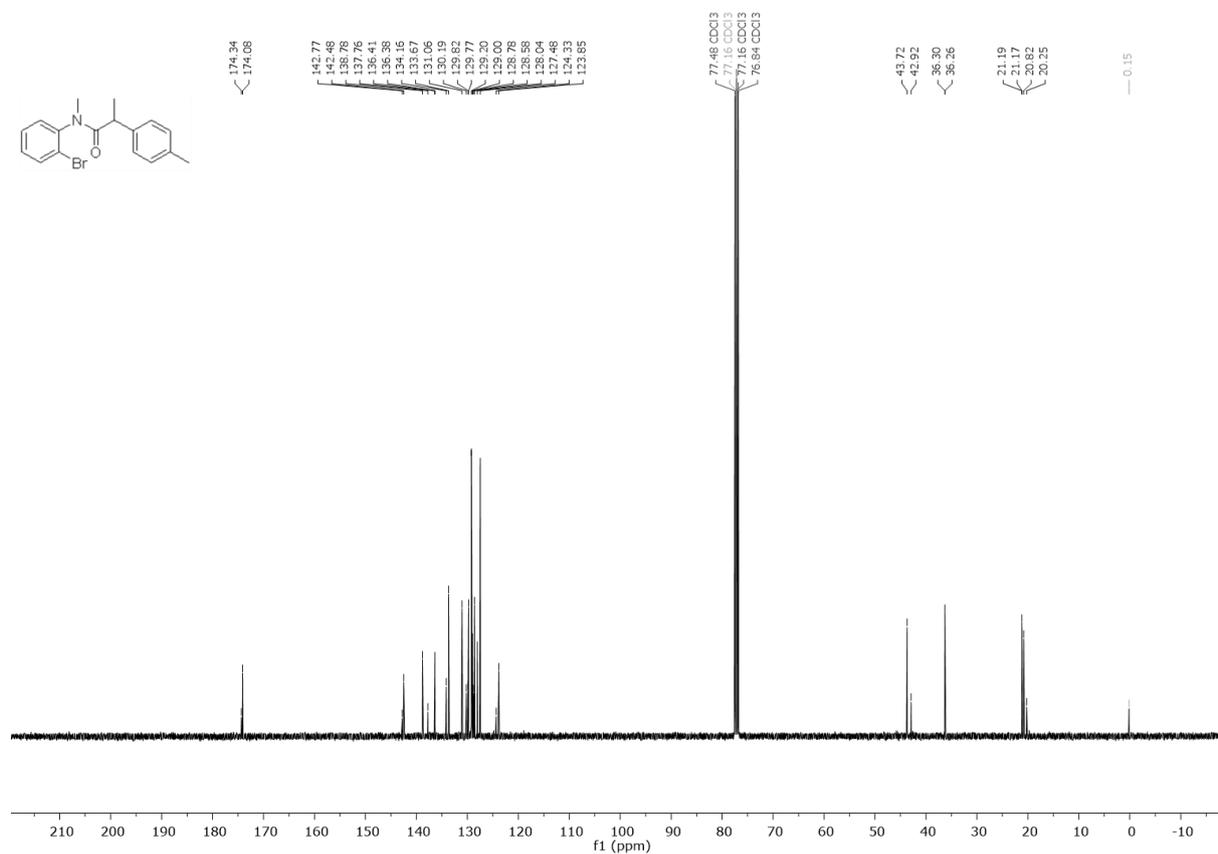


*N*-(2-bromophenyl)-*N*-methyl-2-(*p*-tolyl)propanamide (**6.57**)

<sup>1</sup>H NMR (400 MHz, Chloroform-*d*)

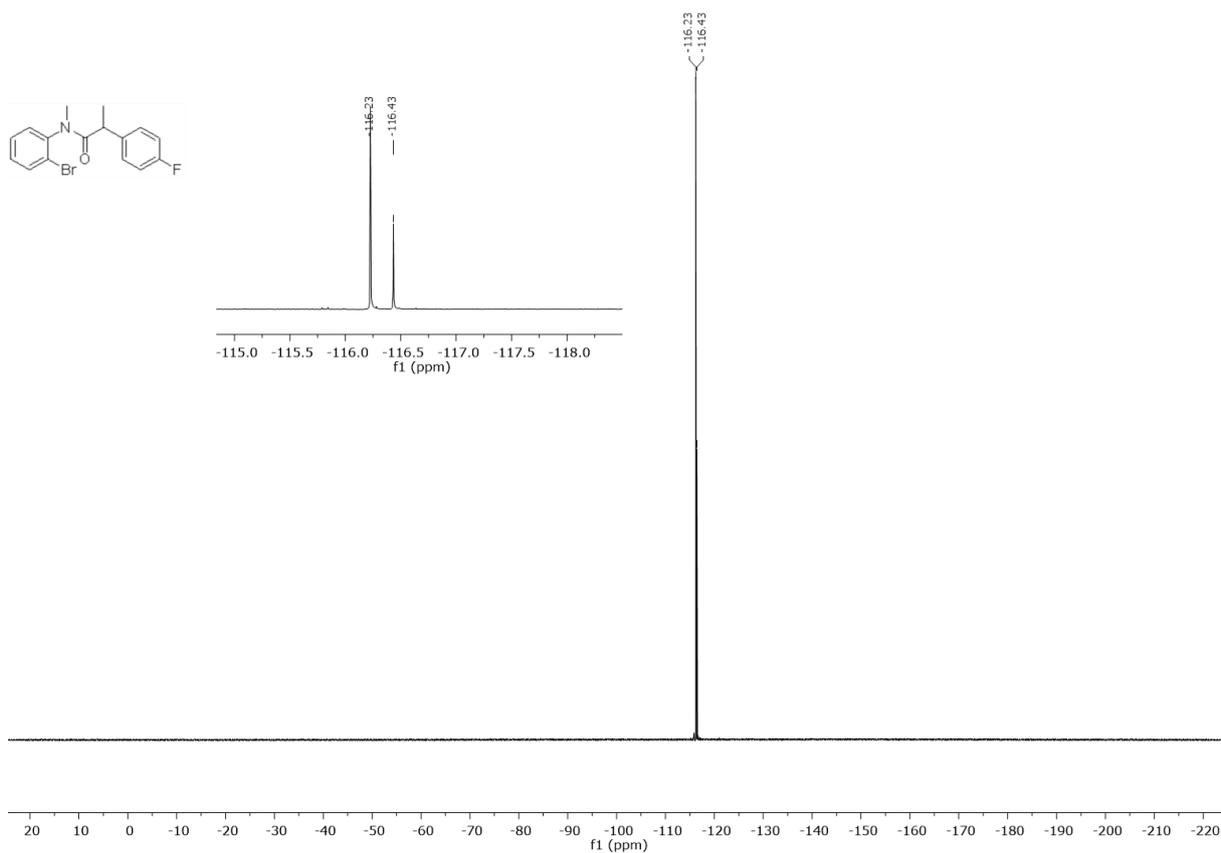


<sup>13</sup>C NMR (101 MHz, Chloroform-*d*)



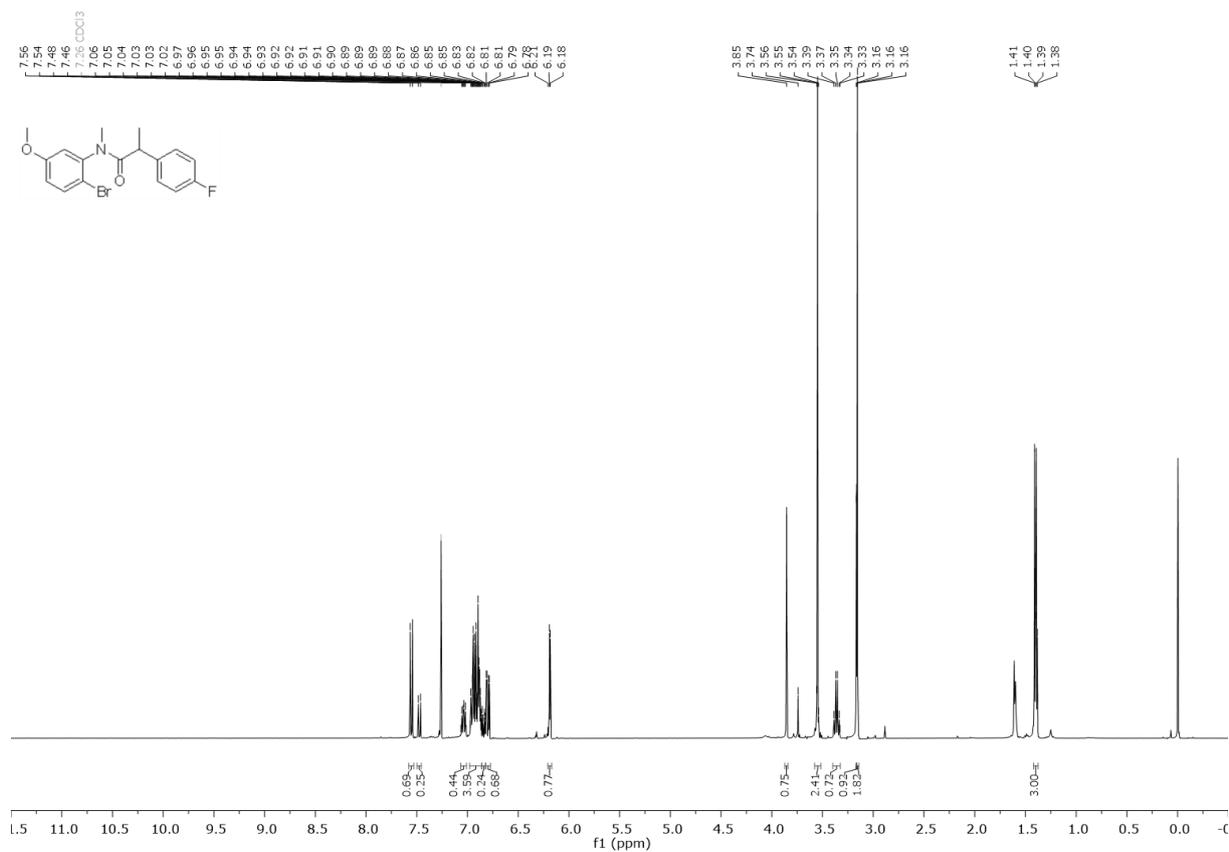


**$^{19}\text{F}\{^1\text{H}\}$  NMR (376 MHz, Chloroform-*d*)**

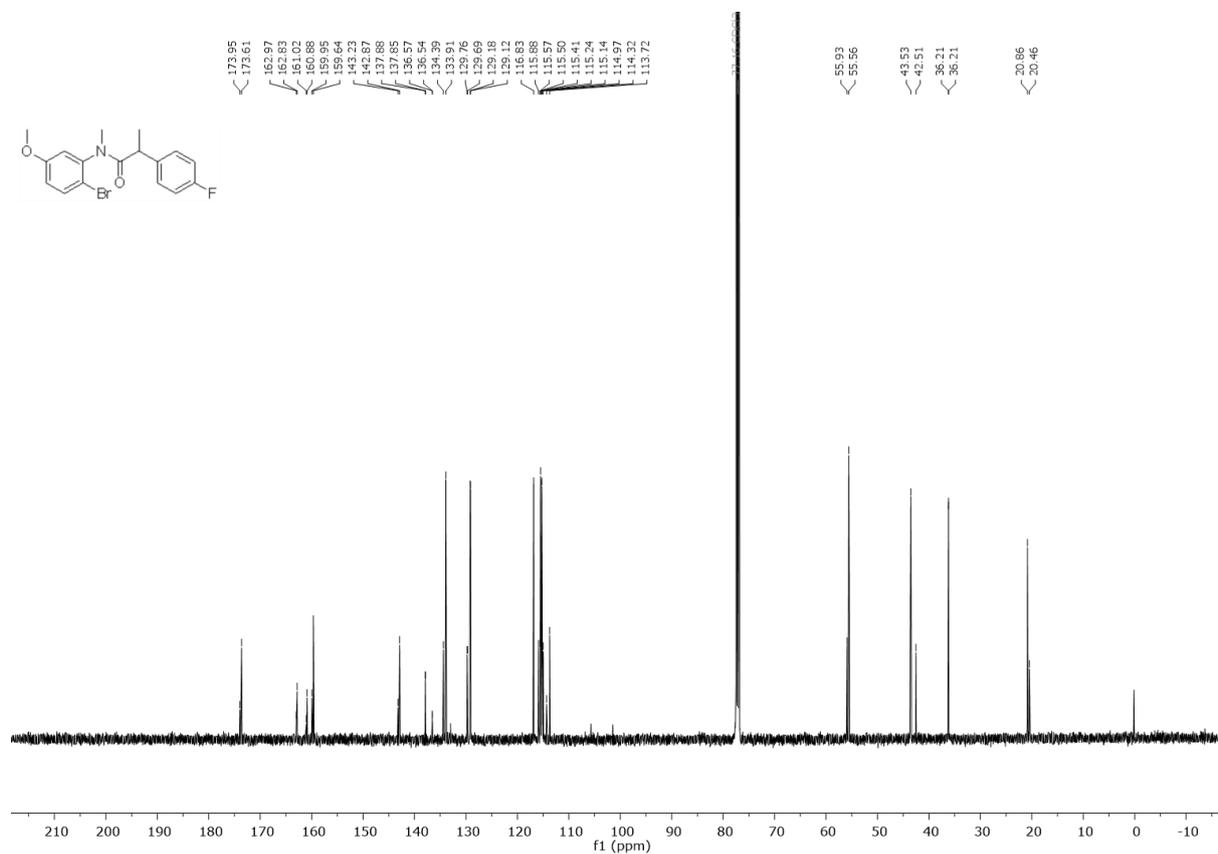


*N*-(2-bromo-5-methoxyphenyl)-2-(4-fluorophenyl)-*N*-methylpropanamide (**6.59**)

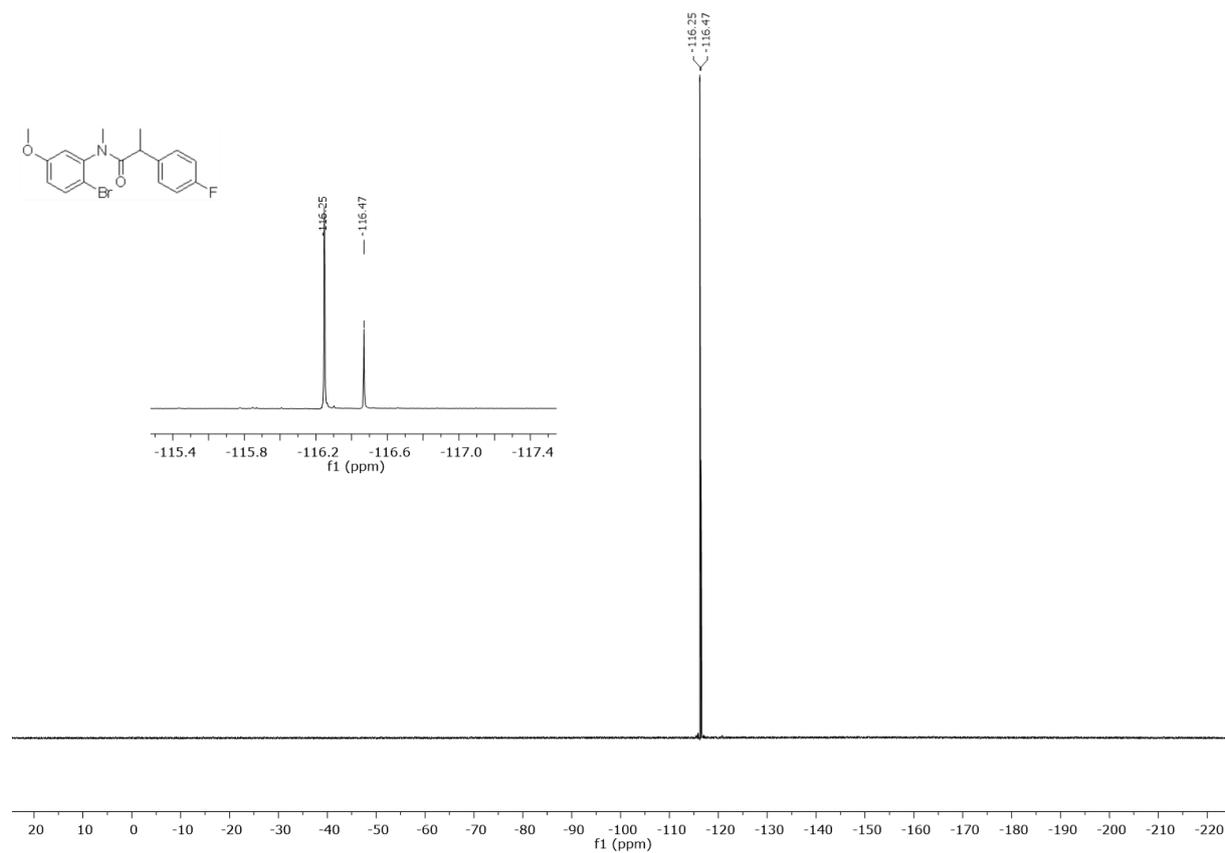
<sup>1</sup>H NMR (400 MHz, Chloroform-*d*)



<sup>13</sup>C NMR (126 MHz, Chloroform-*d*)

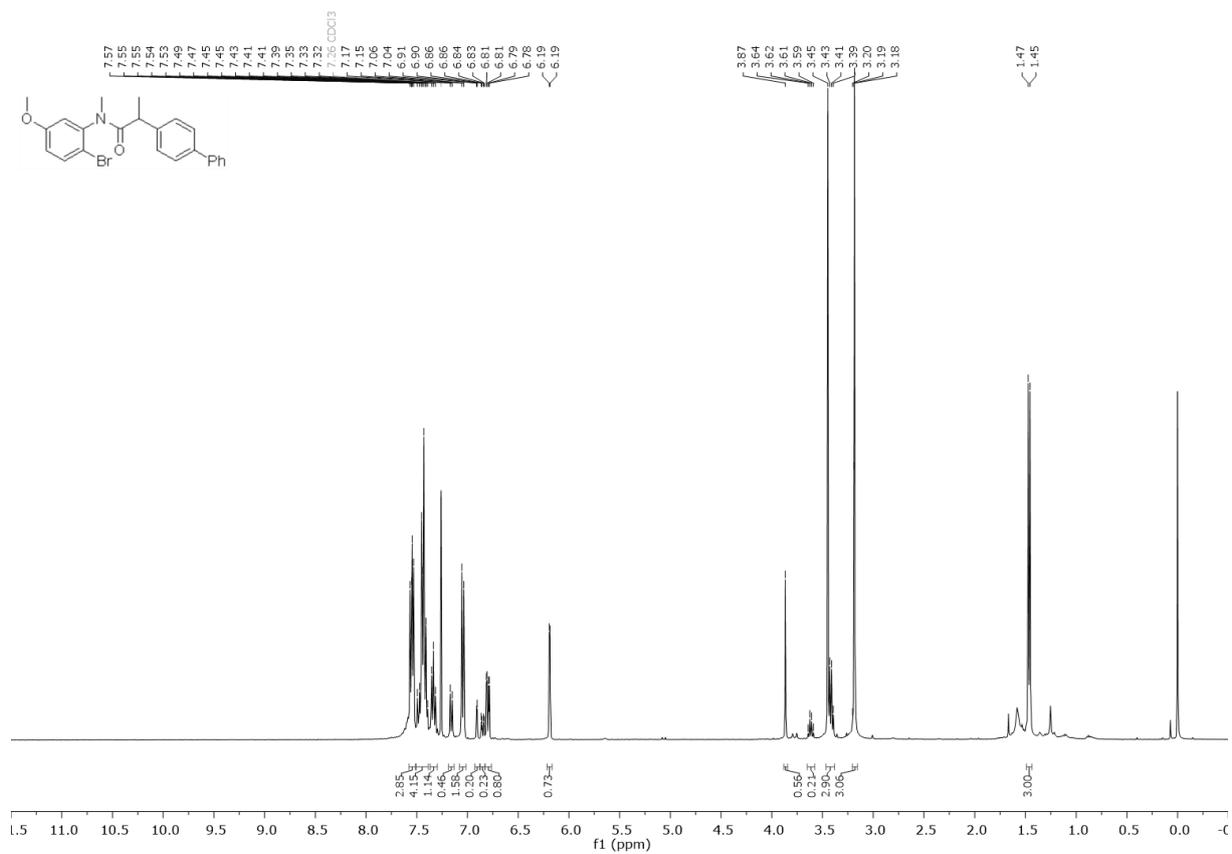


$^{19}\text{F}\{^1\text{H}\}$  NMR (376 MHz, Chloroform-*d*)

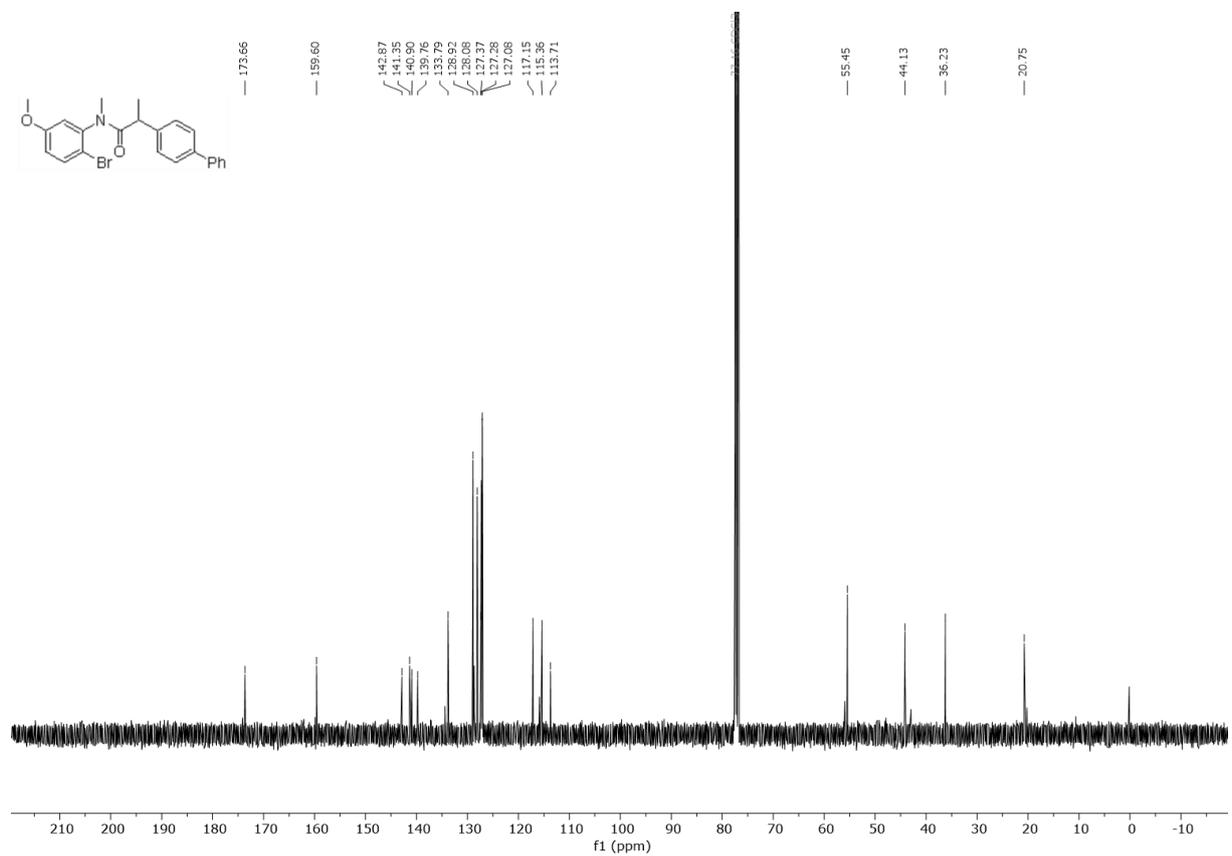


2-([1,1'-biphenyl]-4-yl)-*N*-(2-bromo-5-methoxyphenyl)-*N*-methylpropanamide (**6.60**)

<sup>1</sup>H NMR (400 MHz, Chloroform-*d*)

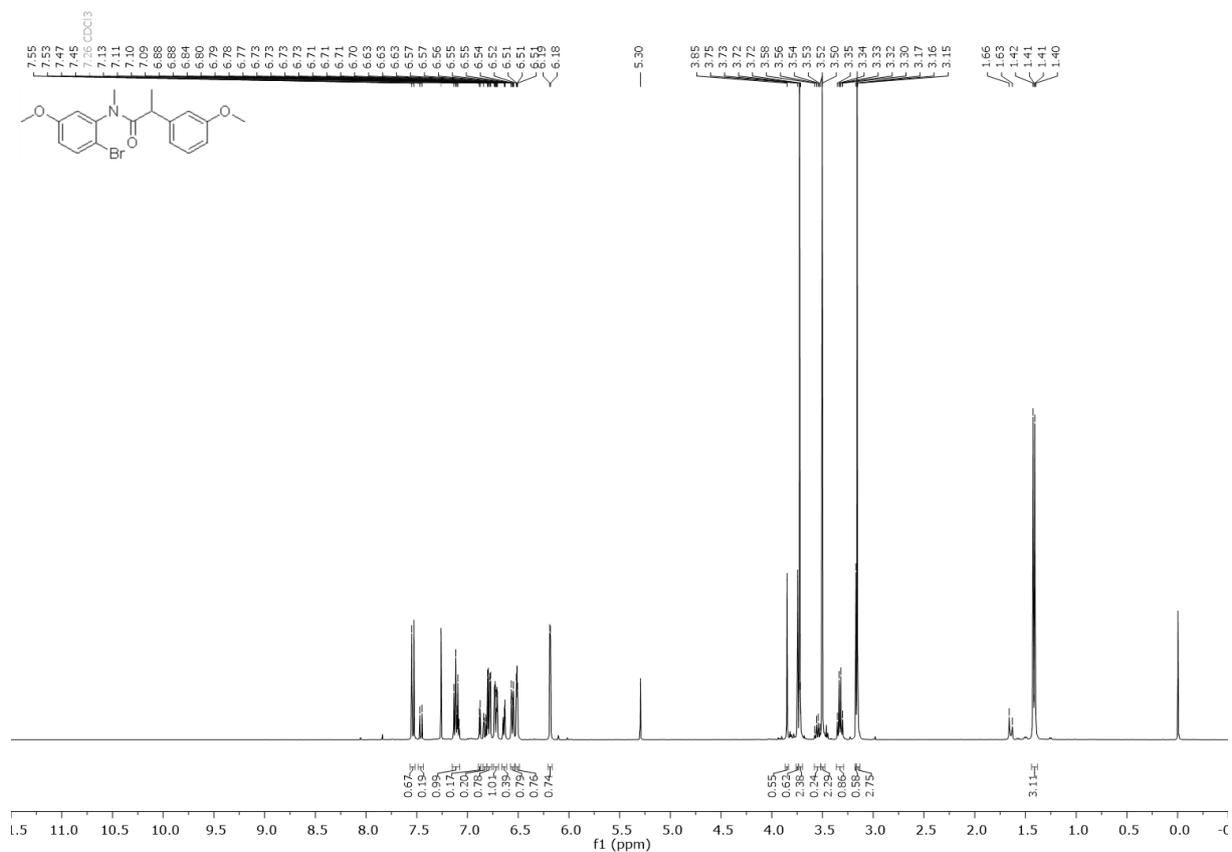


<sup>13</sup>C NMR (101 MHz, Chloroform-*d*)

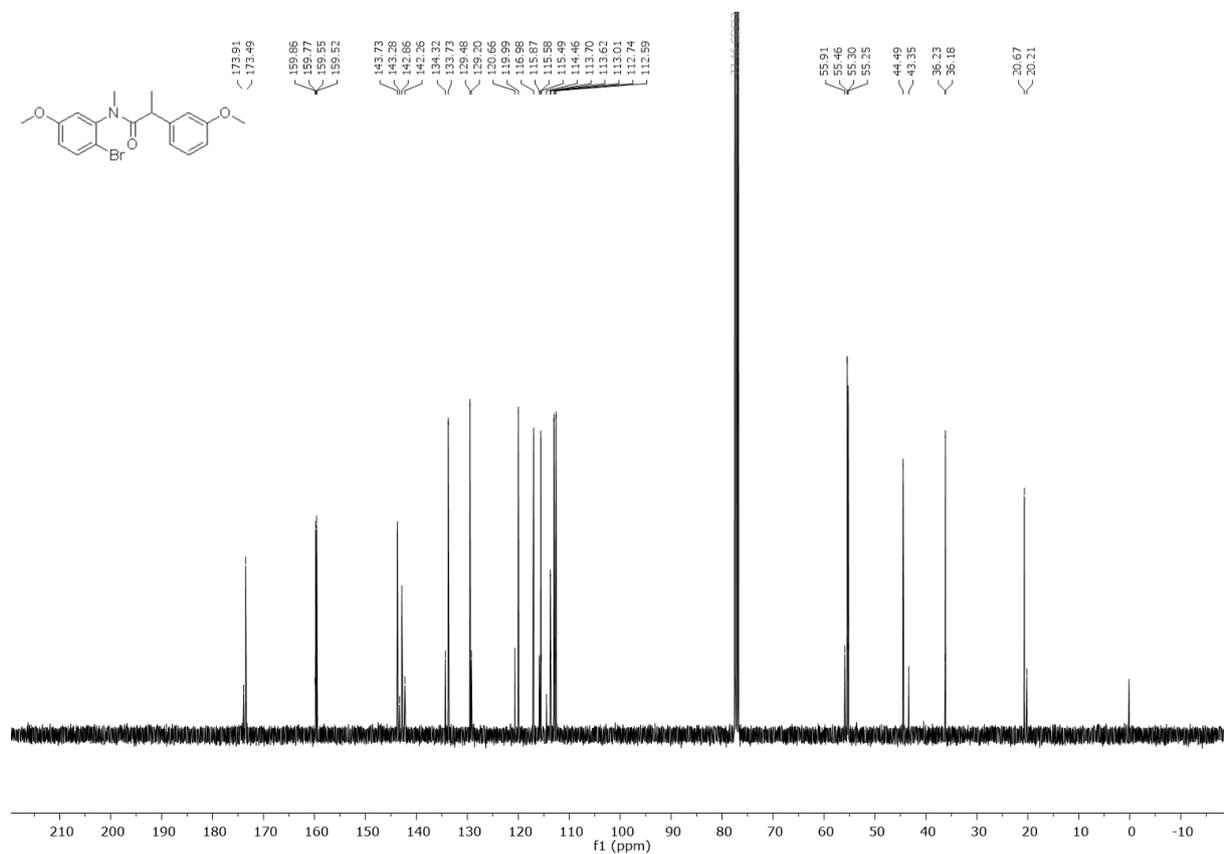


*N*-(2-bromo-5-methoxyphenyl)-2-(3-methoxyphenyl)-*N*-methylpropanamide (**6.61**)

<sup>1</sup>H NMR (400 MHz, Chloroform-*d*)



<sup>13</sup>C NMR (101 MHz, Chloroform-*d*)





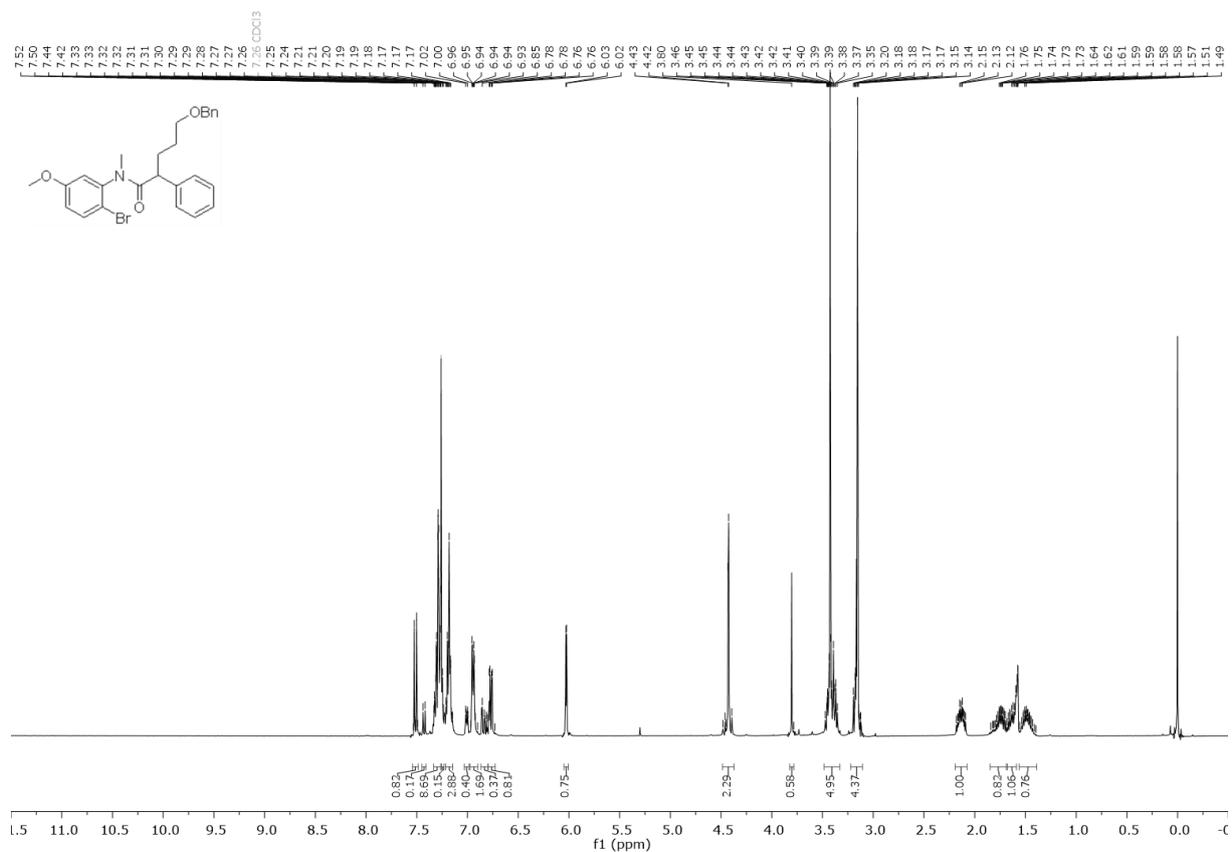




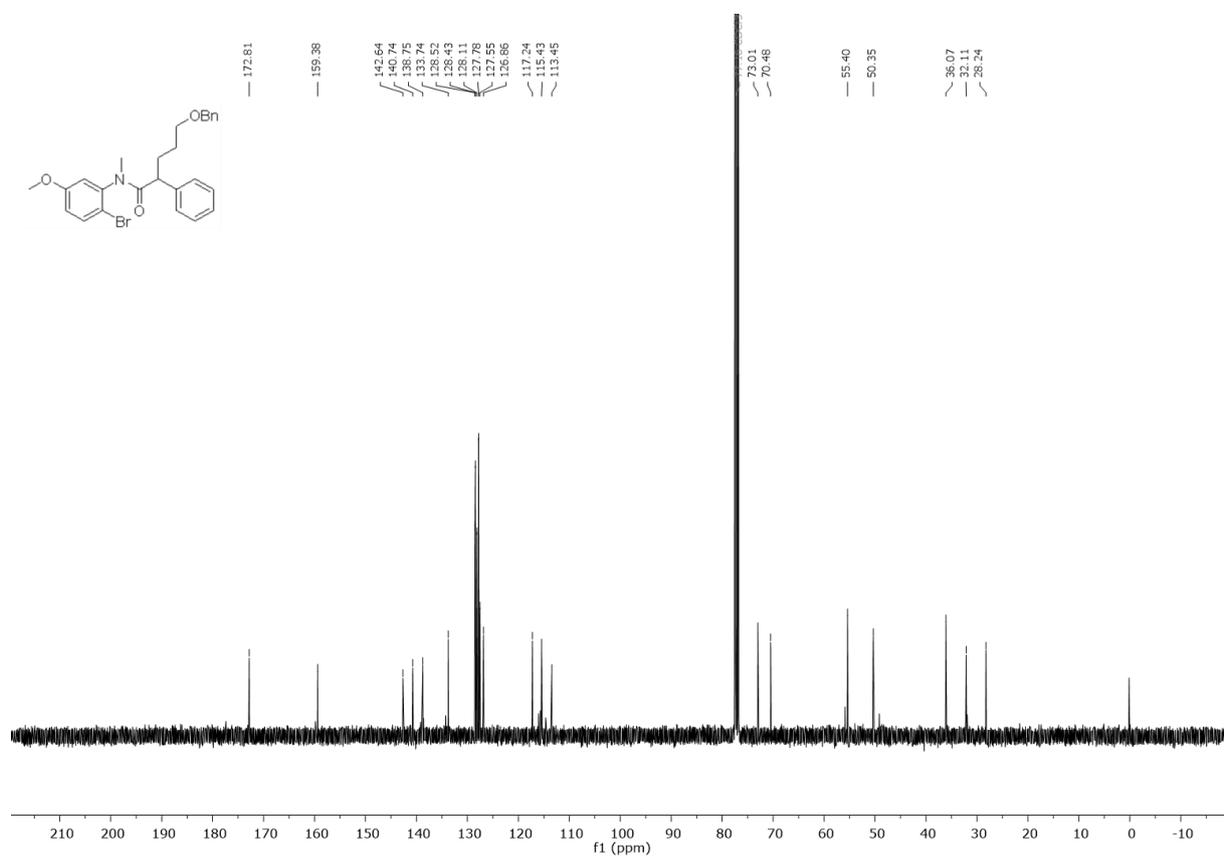


5-(benzyloxy)-*N*-(2-bromo-5-methoxyphenyl)-*N*-methyl-2-phenylpentanamide (**6.66**)

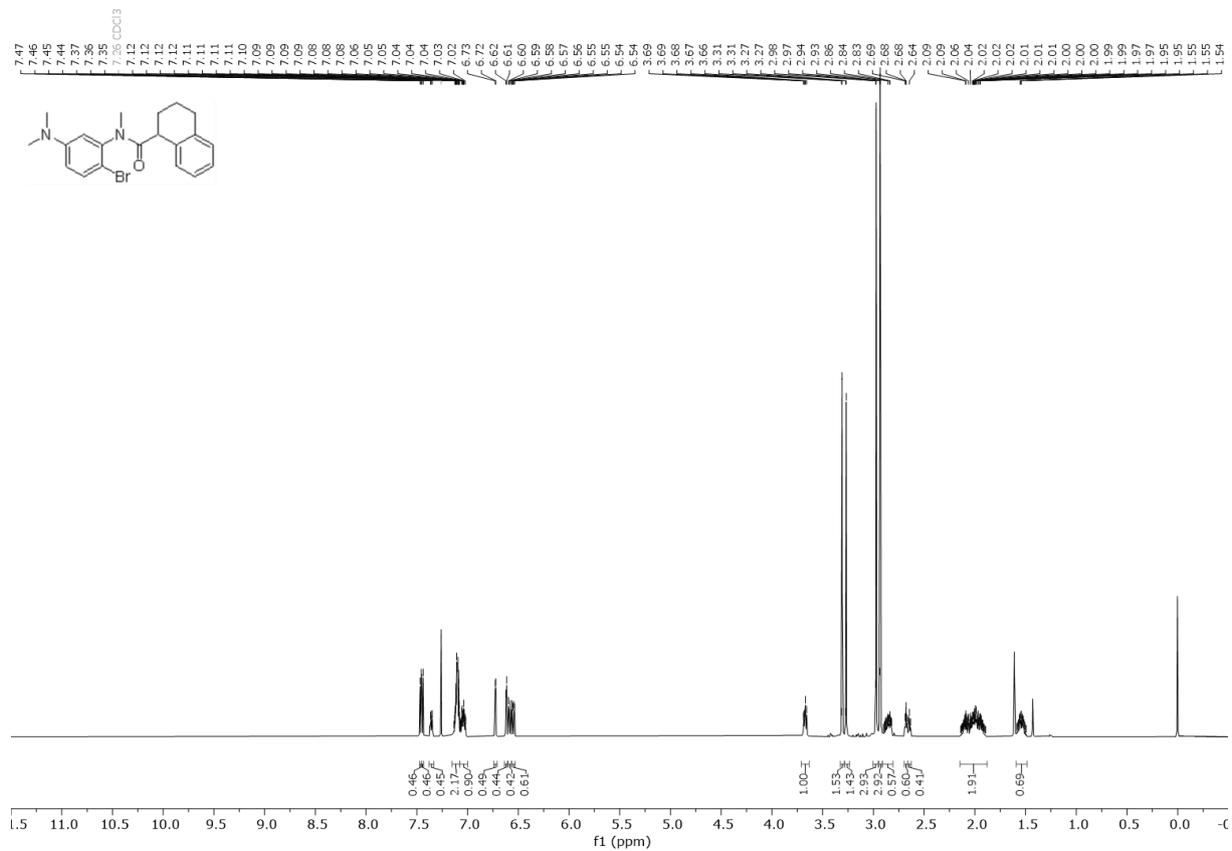
$^1\text{H}$  NMR (400 MHz, Chloroform-*d*)



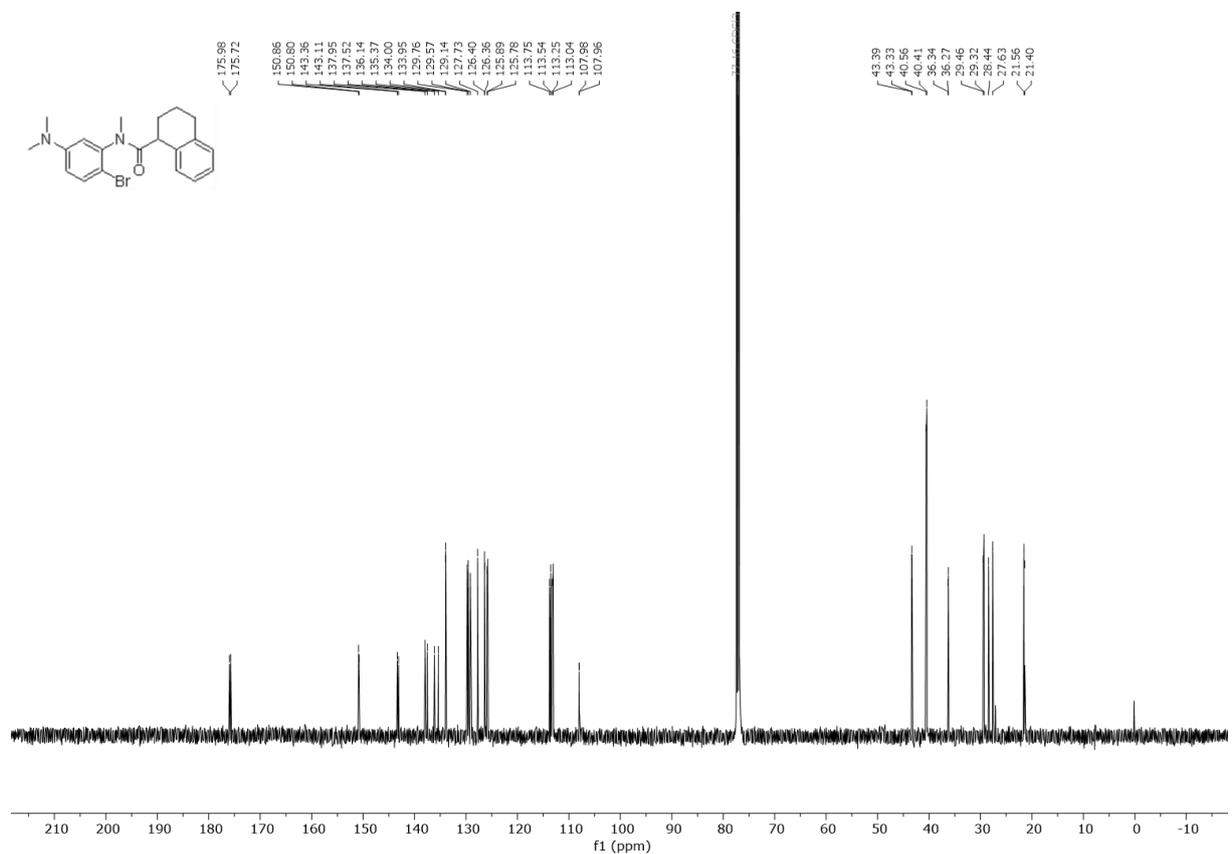
$^{13}\text{C}$  NMR (101 MHz, Chloroform-*d*)



*N*-(2-bromo-5-(dimethylamino)phenyl)-*N*-methyl-1,2,3,4-tetrahydronaphthalene-1-carboxamide (**6.67**),  $^1\text{H}$  NMR (500 MHz, Chloroform-*d*)

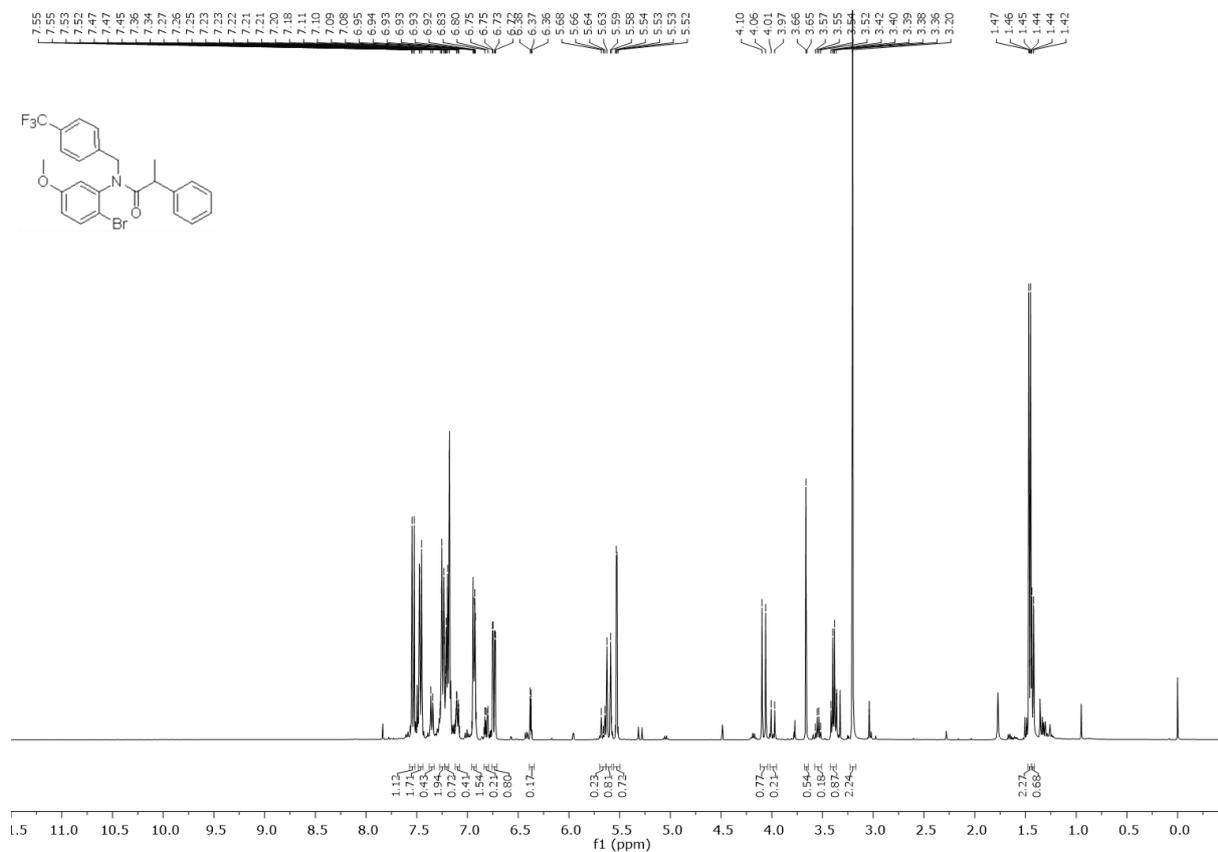


$^{13}\text{C}$  NMR (126 MHz, Chloroform-*d*)

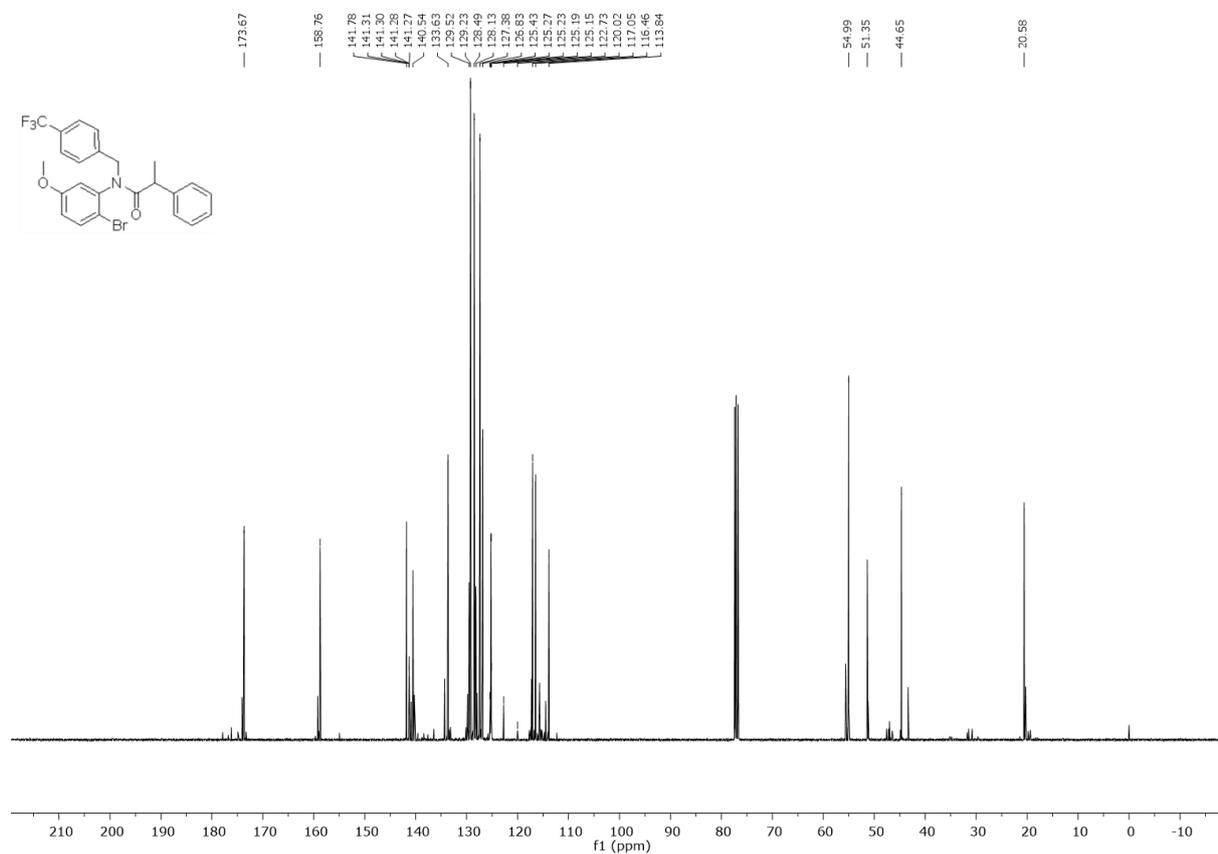


*N*-(2-bromo-5-methoxyphenyl)-2-phenyl-*N*-(4-(trifluoromethyl)benzyl)propanamide (**6.68**)

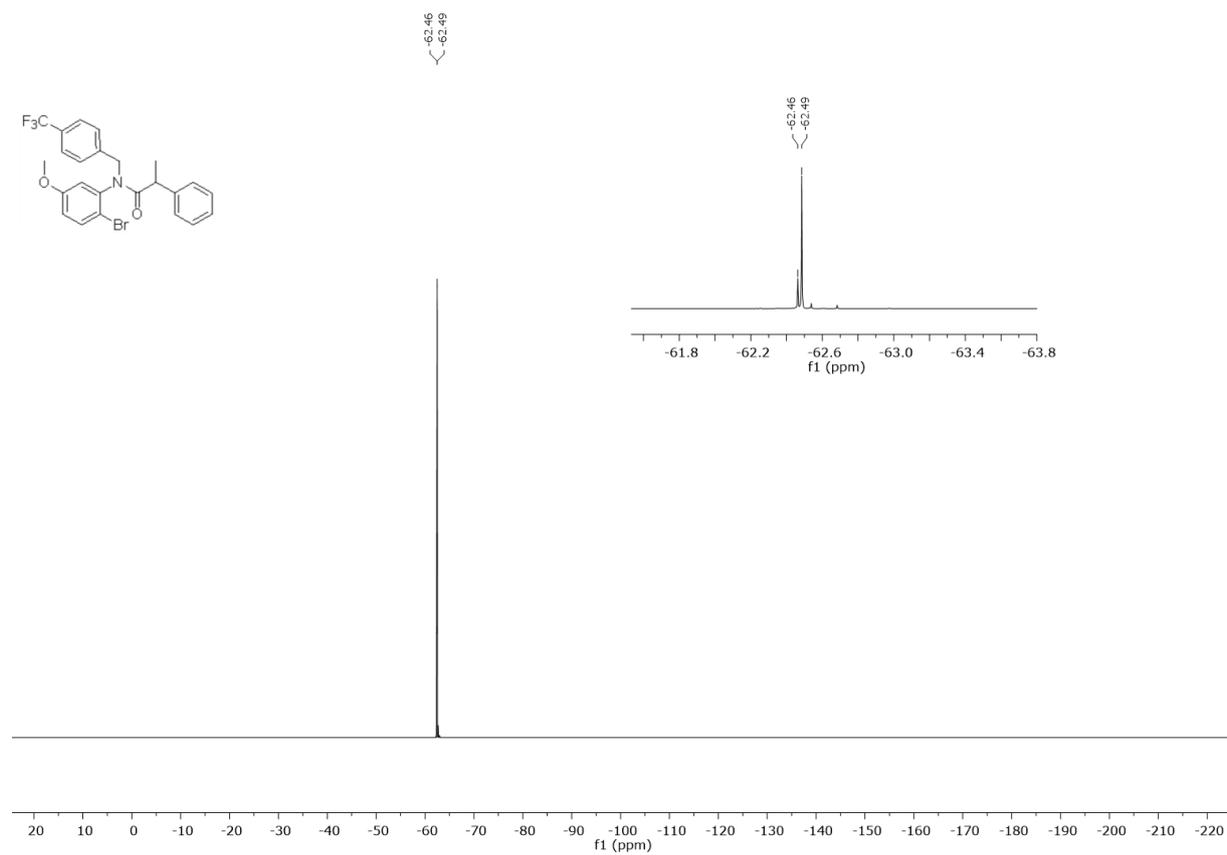
<sup>1</sup>H NMR (400 MHz, Chloroform-*d*)



<sup>13</sup>C NMR (101 MHz, Chloroform-*d*)

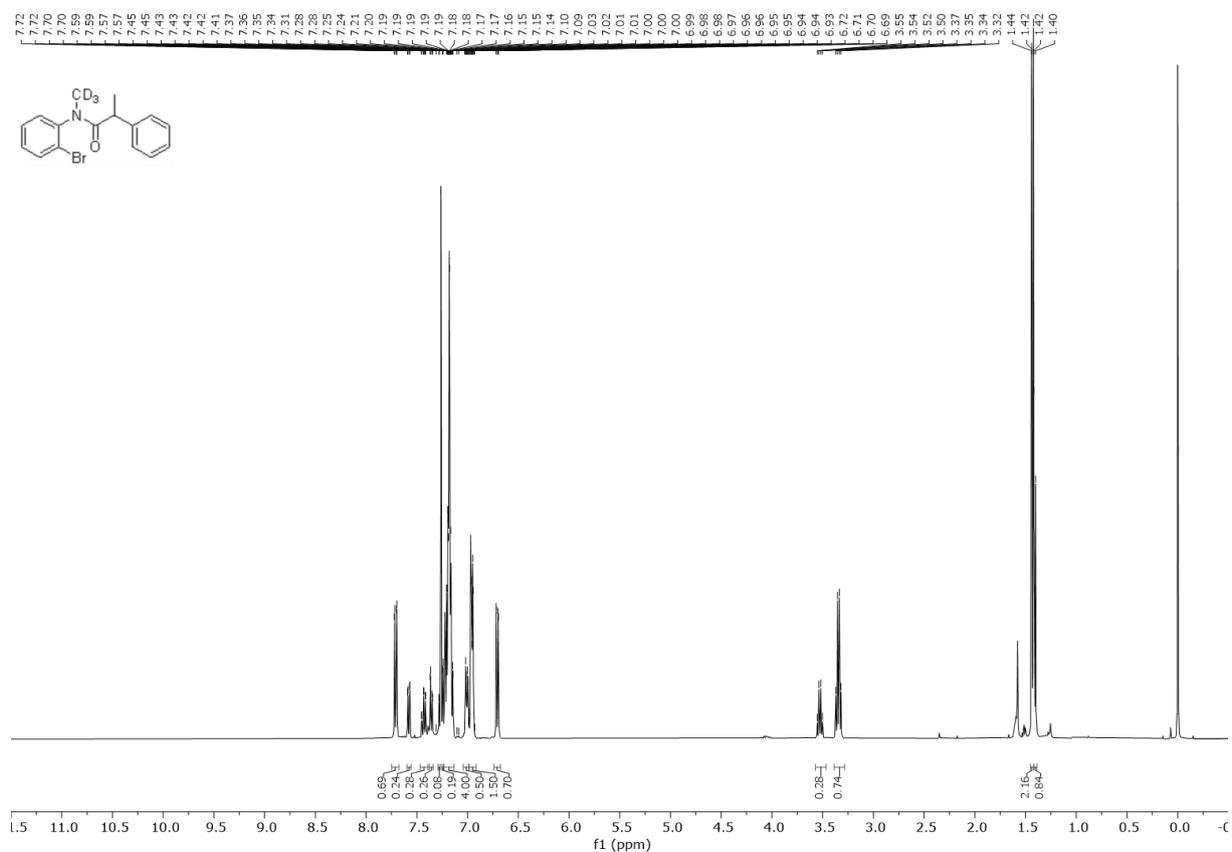


**$^{19}\text{F}\{^1\text{H}\}$  NMR (376 MHz, Chloroform-*d*)**

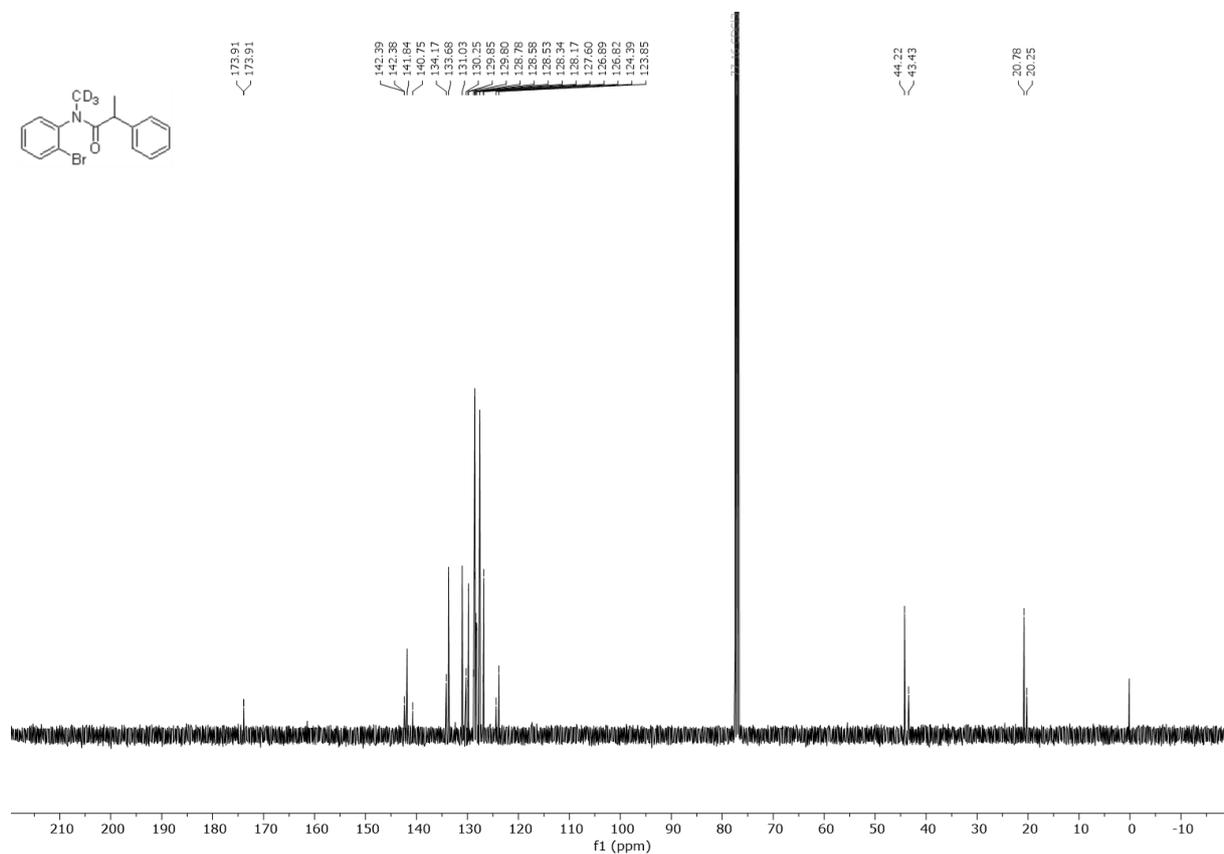


*N*-(2-bromophenyl)-*N*-(methyl-d<sub>3</sub>)-2-phenylpropanamide (**6.1-d<sub>3</sub>**)

<sup>1</sup>H NMR (400 MHz, Chloroform-*d*)

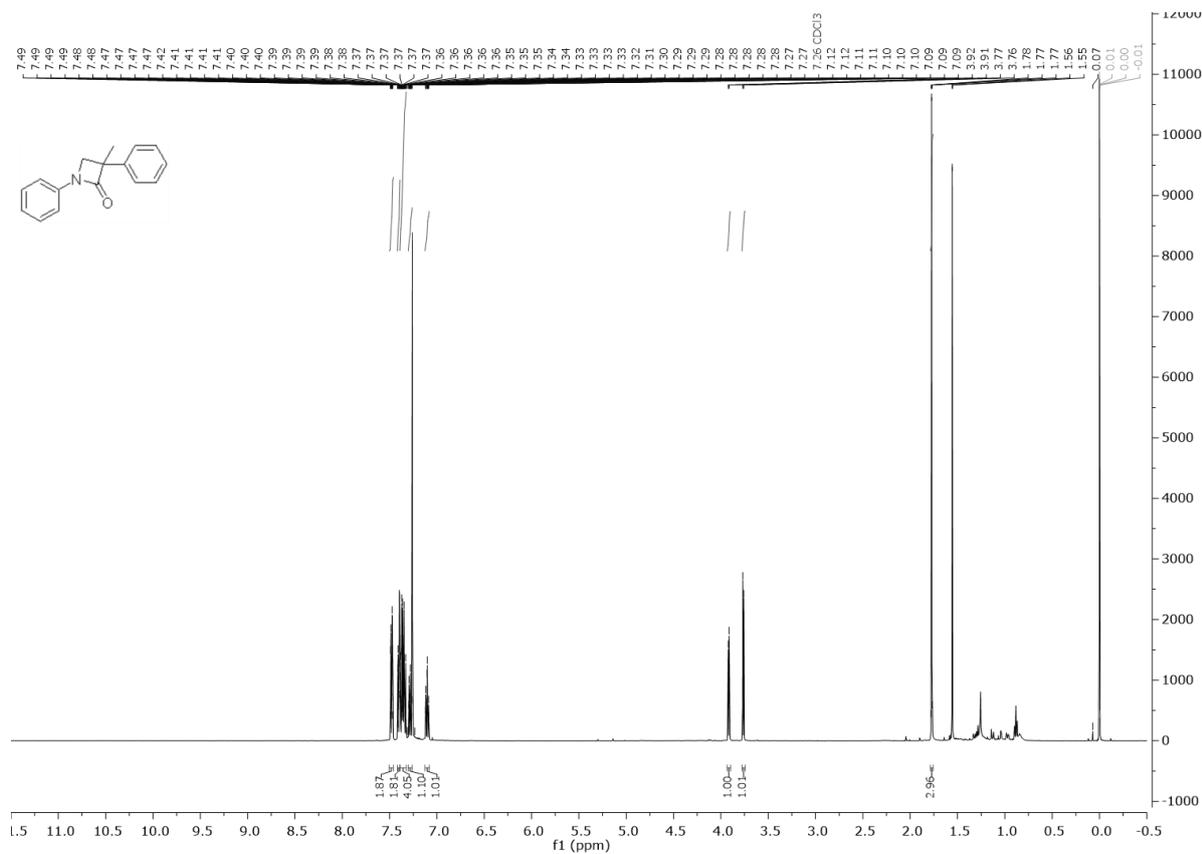


<sup>13</sup>C NMR (101 MHz, Chloroform-*d*)



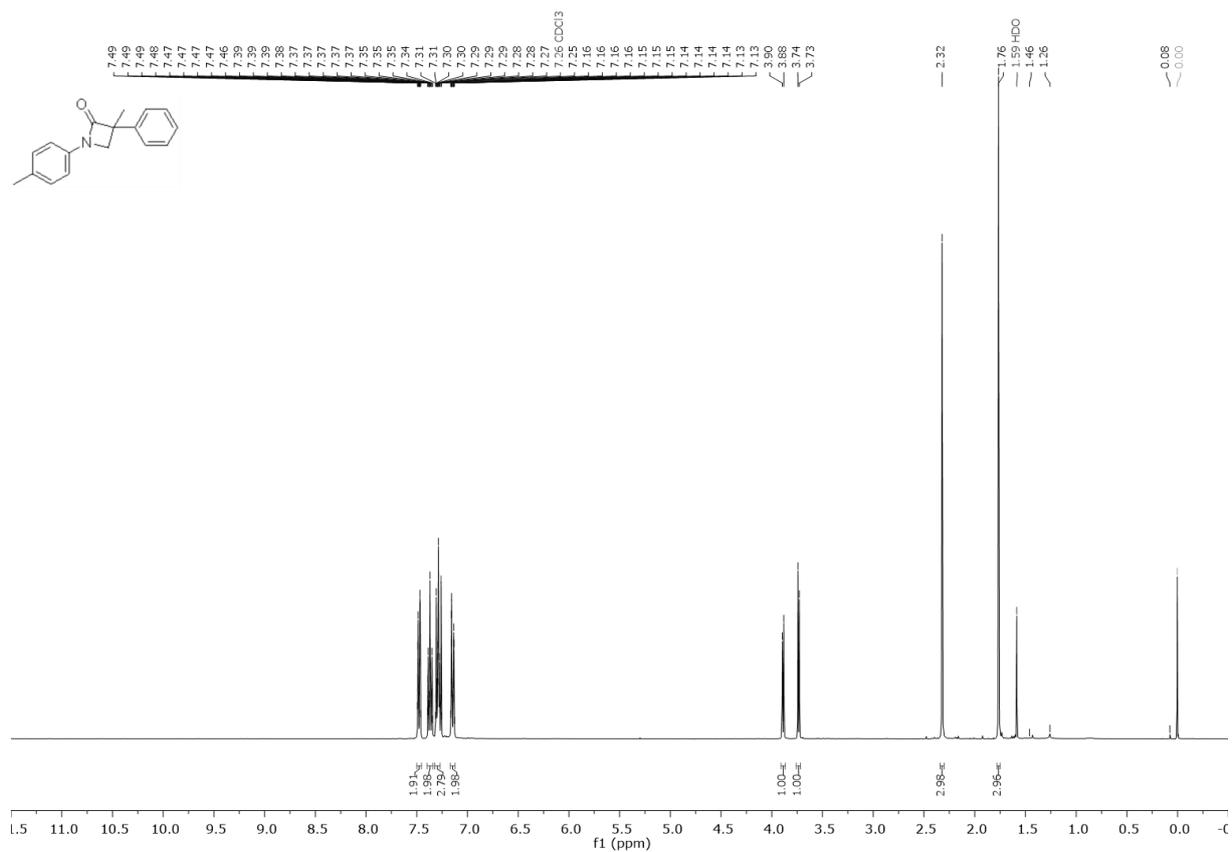
### 3-methyl-1,3-diphenylazetidin-2-one (**6.2**)

$^1\text{H}$  NMR (500 MHz, Chloroform-*d*)

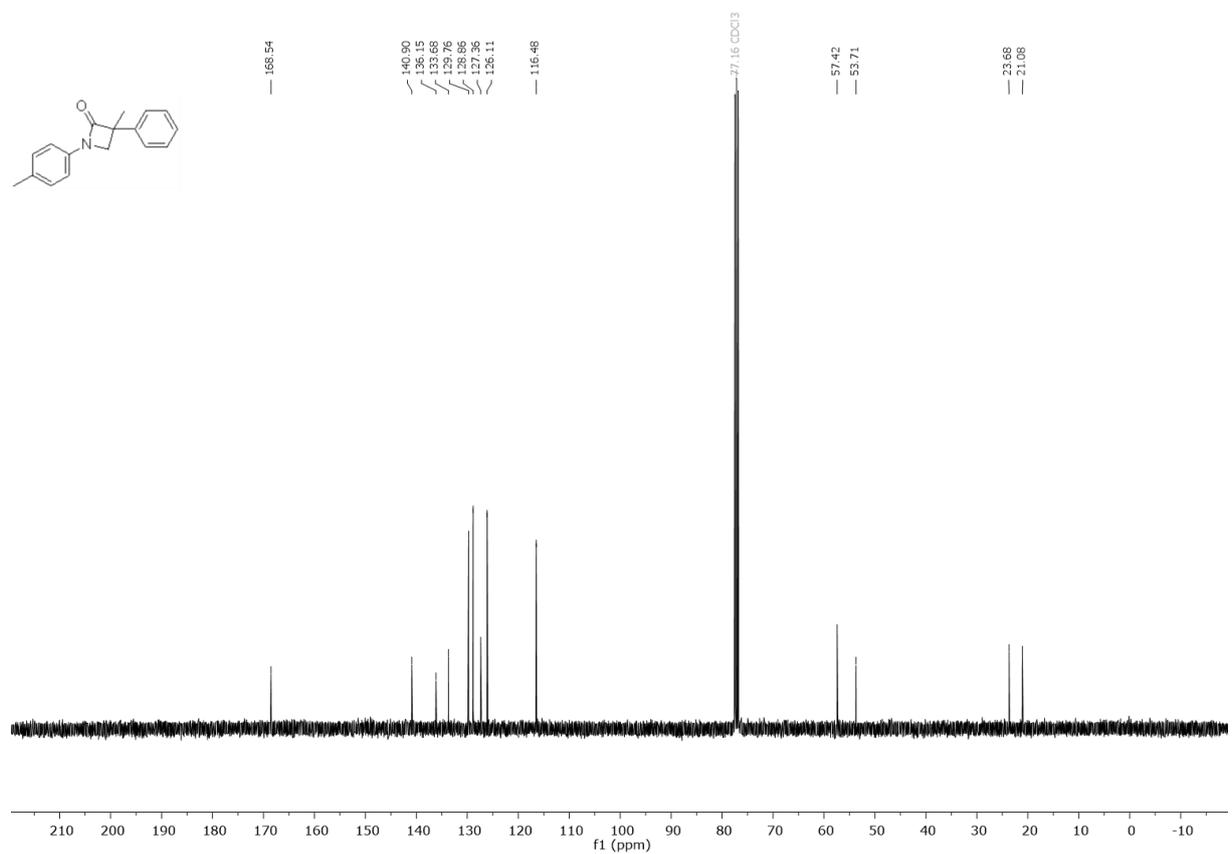


### 3-methyl-3-phenyl-1-(p-tolyl)azetidion-2-one (**6.14**)

$^1\text{H}$  NMR (400 MHz, Chloroform-*d*)

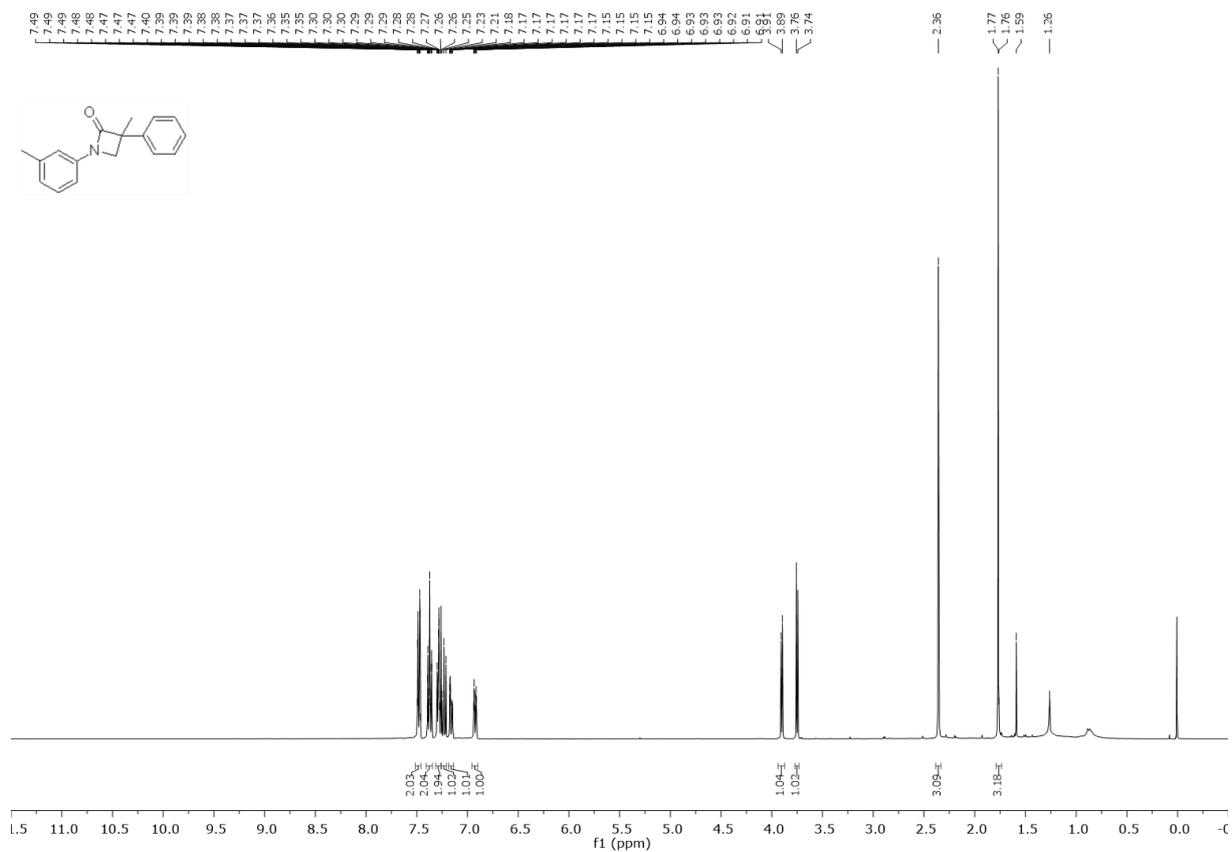


$^{13}\text{C}$  NMR (101 MHz, Chloroform-*d*)

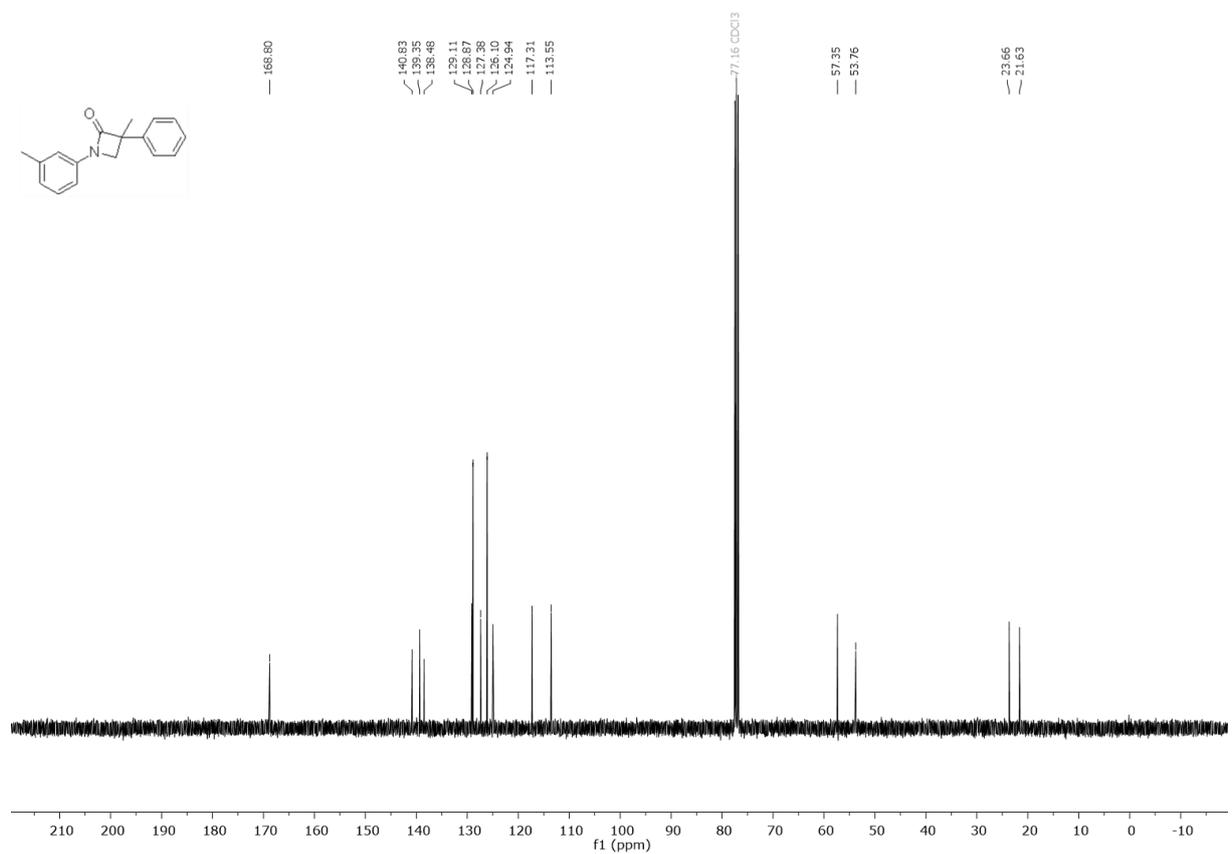


### 3-methyl-3-phenyl-1-(m-tolyl)azetid-2-one (**6.15**)

<sup>1</sup>H NMR (400 MHz, Chloroform-d)

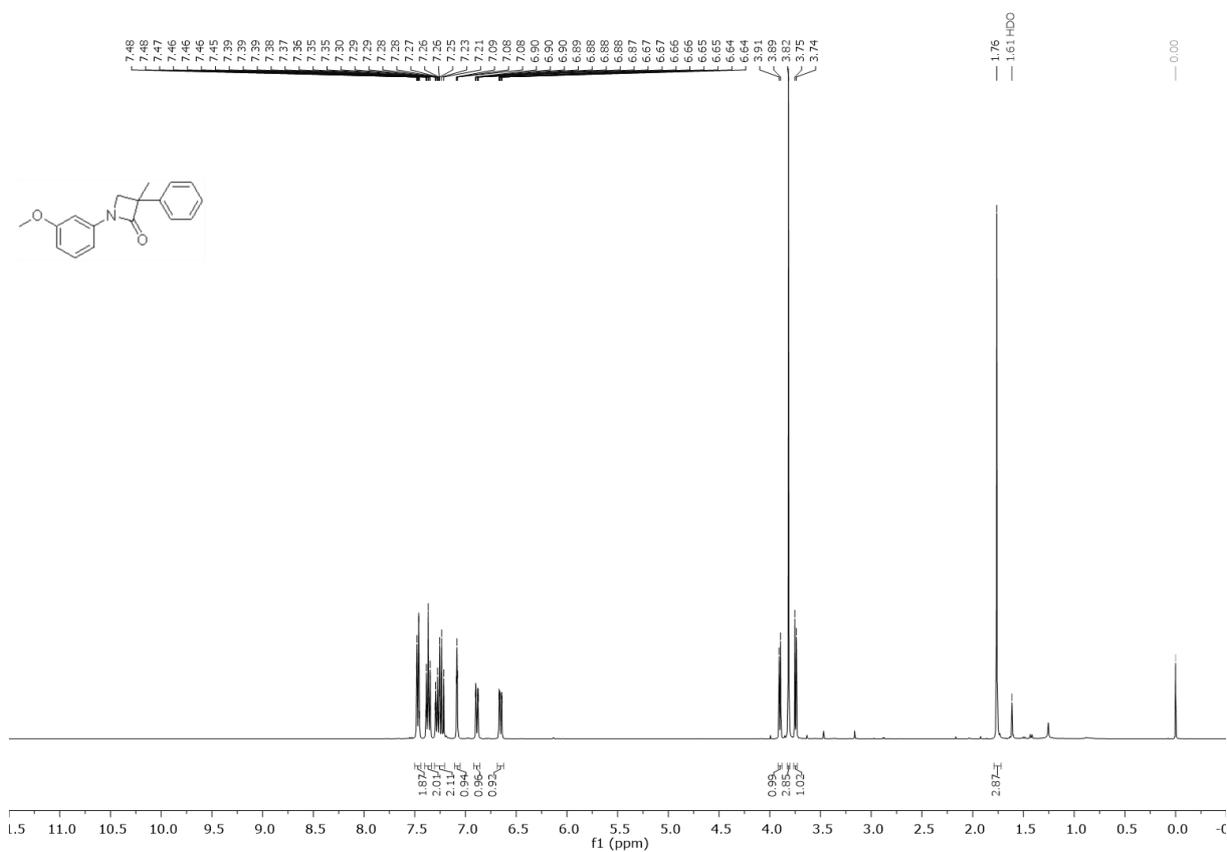


<sup>13</sup>C NMR (101 MHz, Chloroform-d)

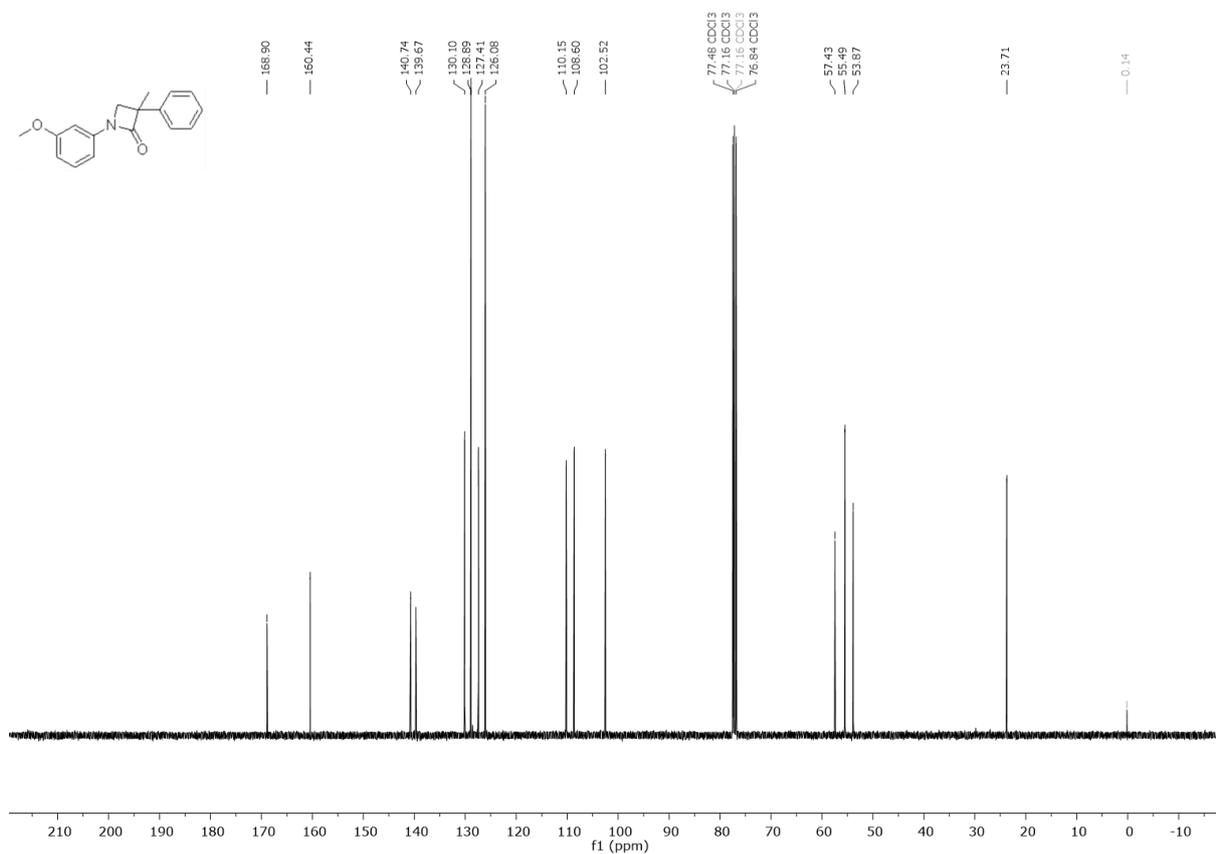


1-(3-methoxyphenyl)-3-methyl-3-phenylazetidin-2-one (**6.16**)

<sup>1</sup>H NMR (400 MHz, Chloroform-*d*)

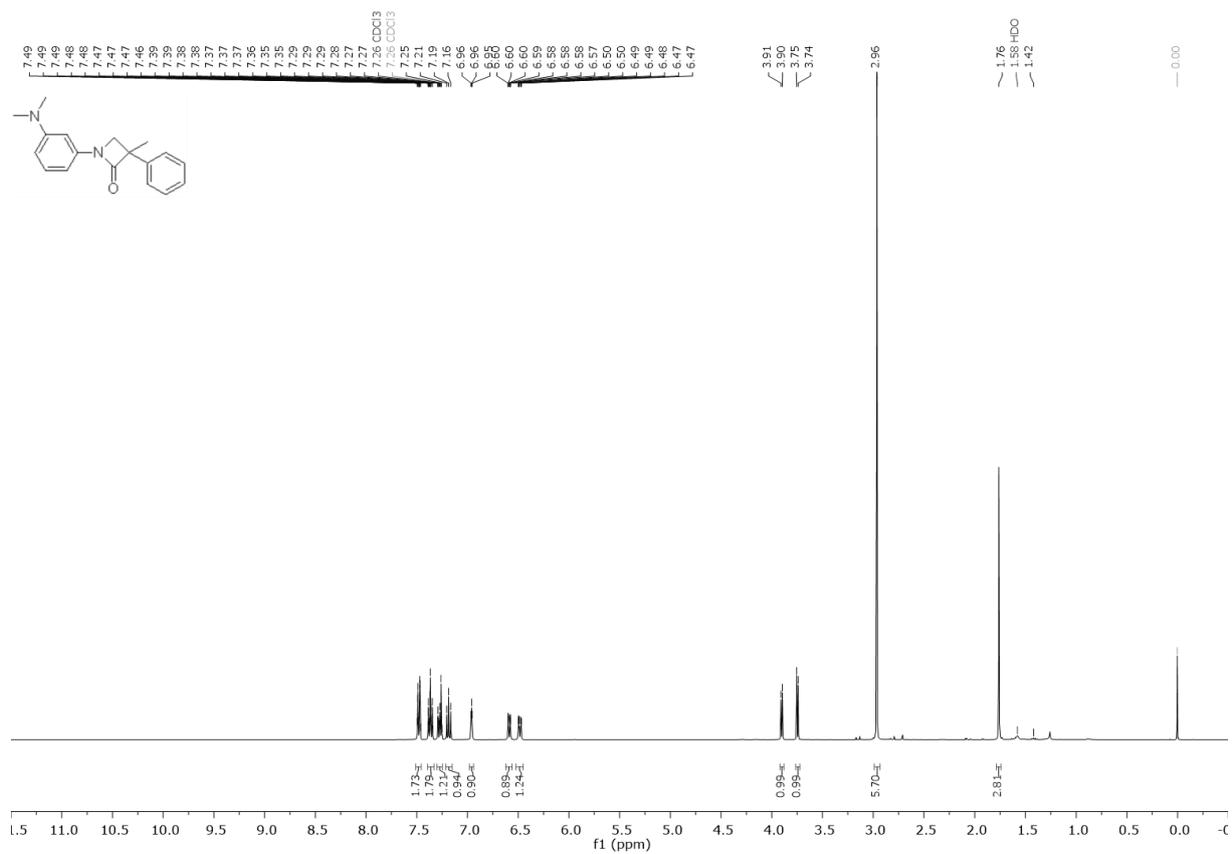


<sup>13</sup>C NMR (101 MHz, Chloroform-*d*)

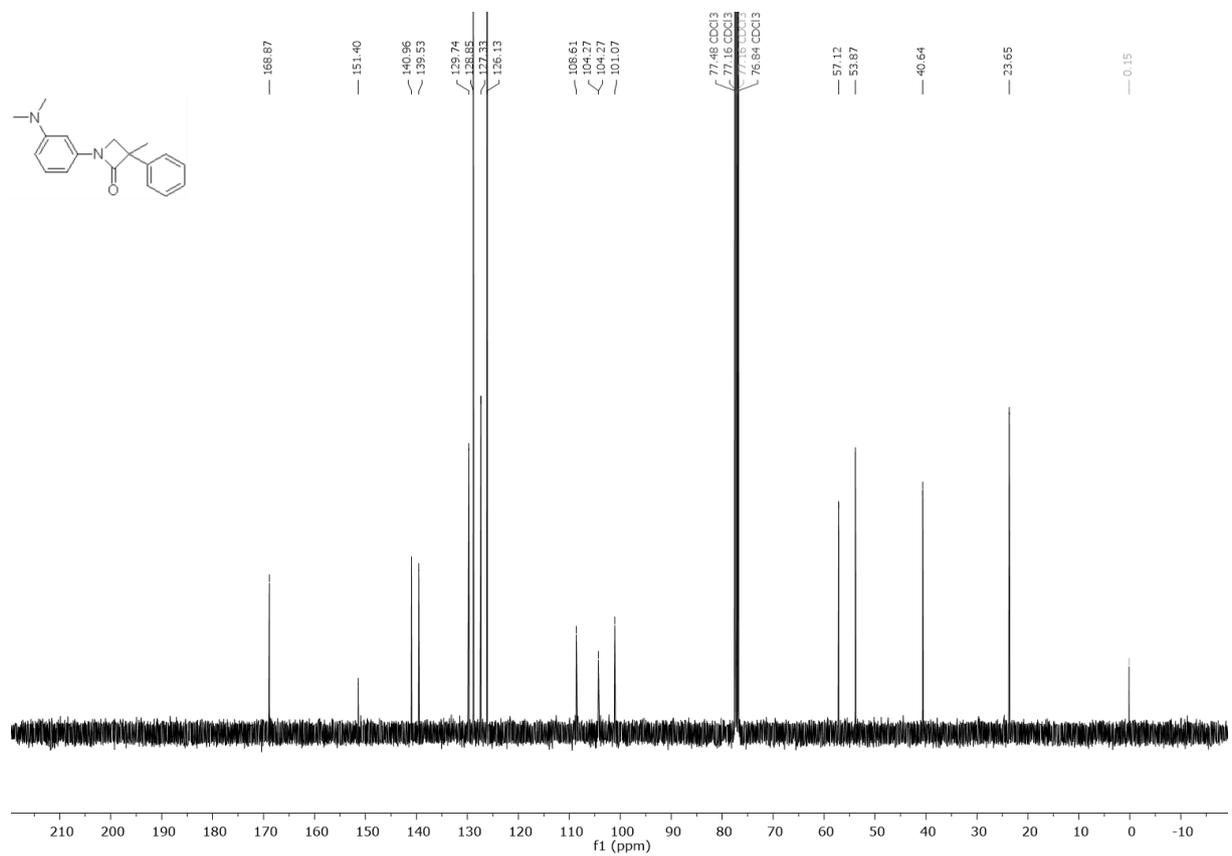


1-(3-(dimethylamino)phenyl)-3-methyl-3-phenylazetidin-2-one (**6.17**)

$^1\text{H}$  NMR (400 MHz, Chloroform-*d*)

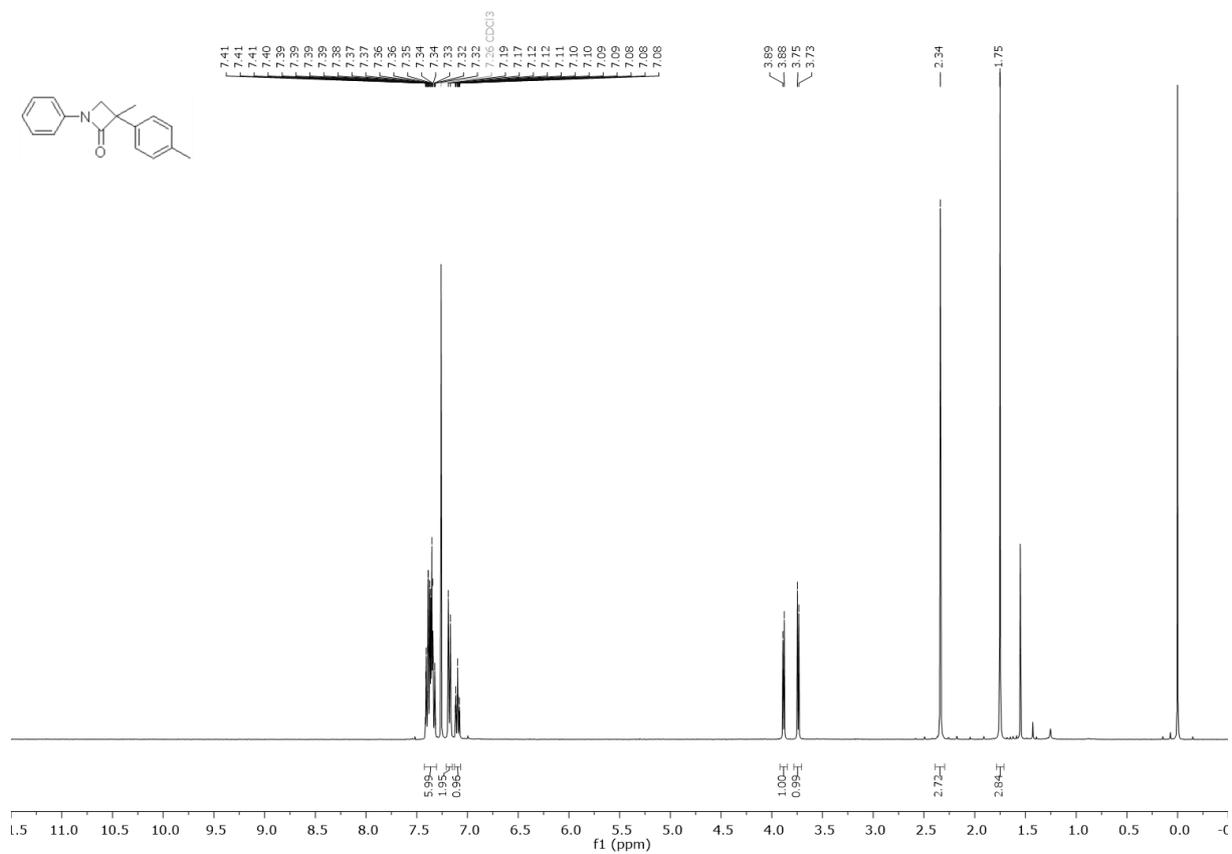


$^{13}\text{C}$  NMR (101 MHz, Chloroform-*d*)

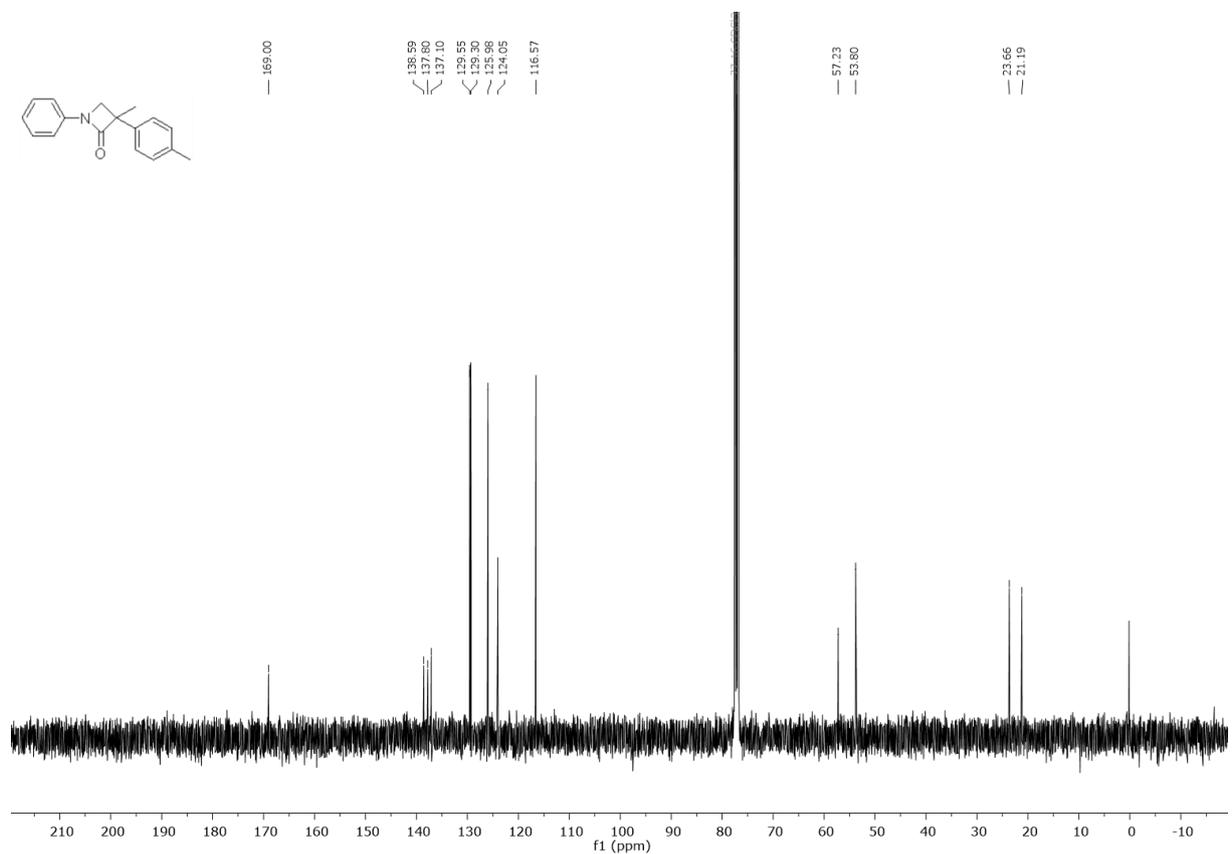


### 3-methyl-1-phenyl-3-(p-tolyl)azetid-2-one (**6.18**)

$^1\text{H}$  NMR (400 MHz, Chloroform-*d*)

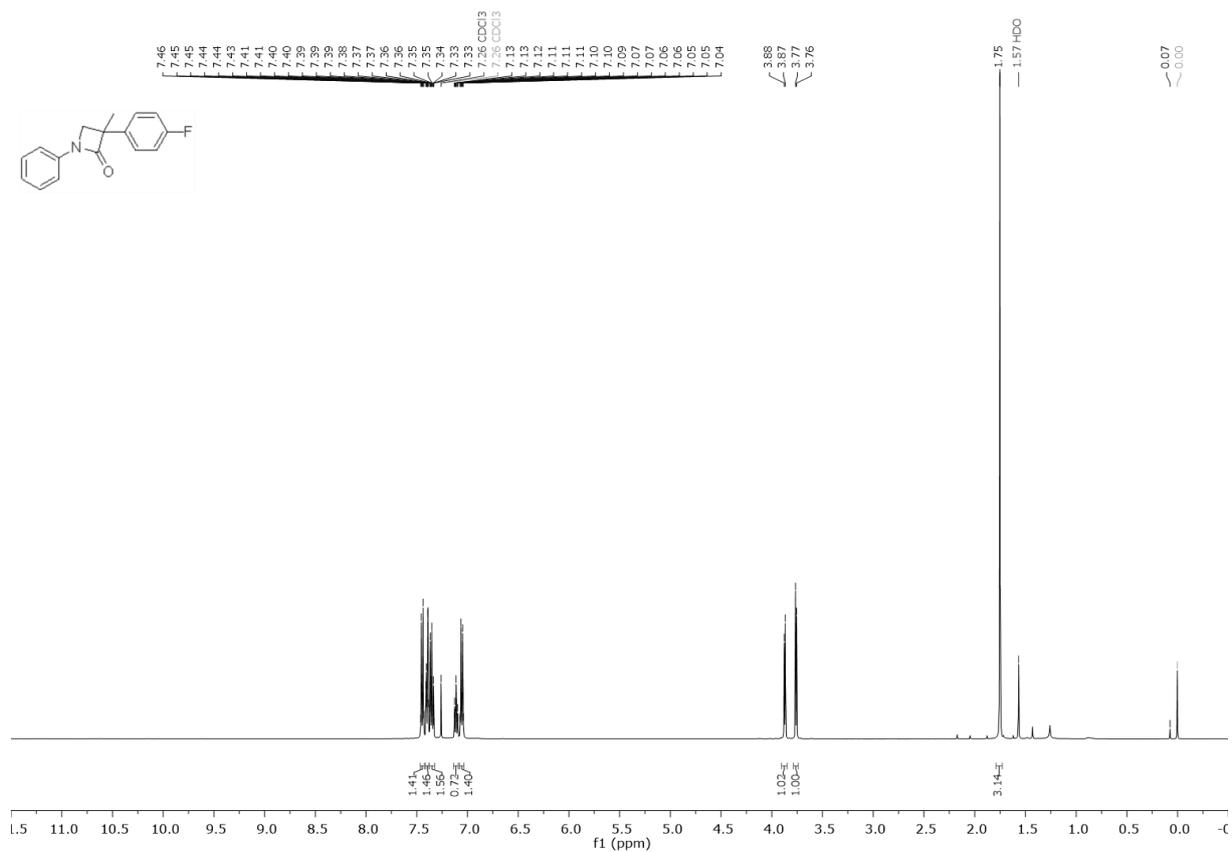


$^{13}\text{C}$  NMR (101 MHz, Chloroform-*d*)

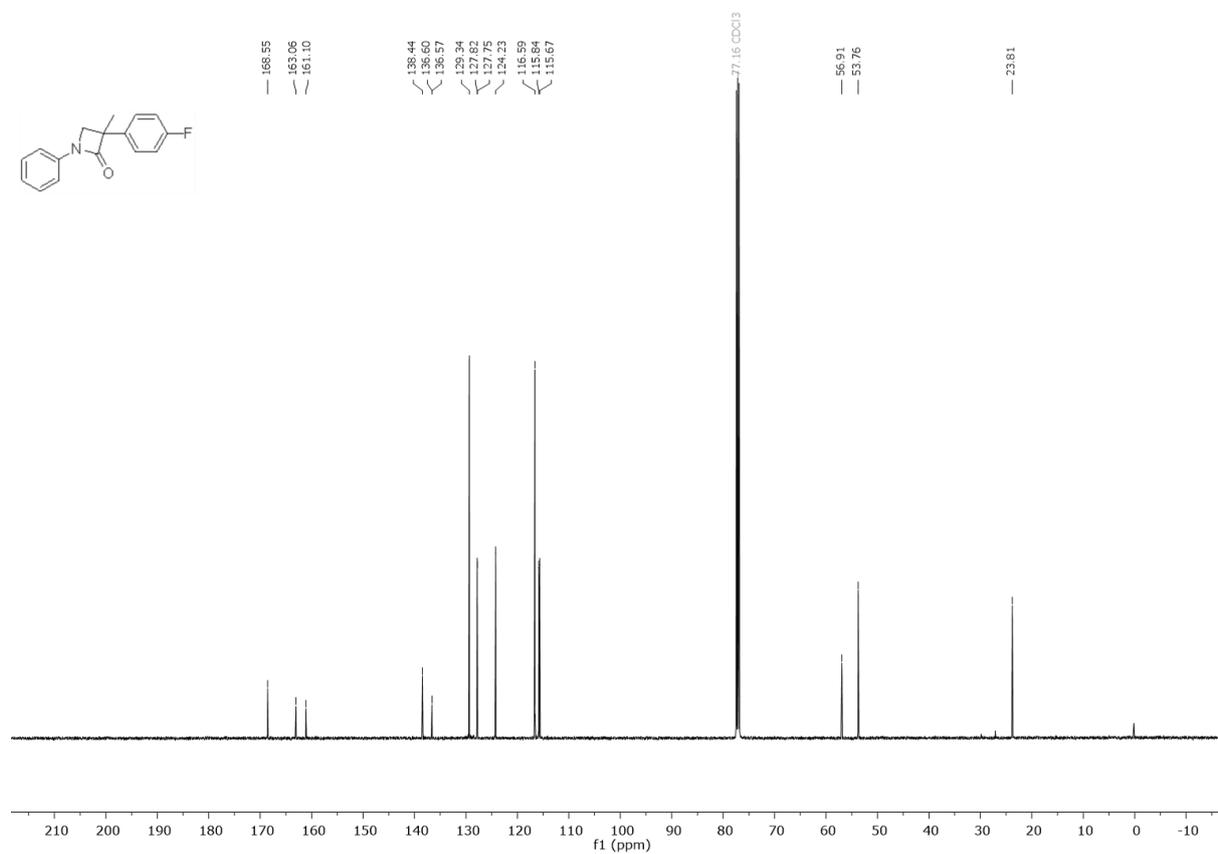


### 3-(4-fluorophenyl)-3-methyl-1-phenylazetidin-2-one (**6.19**)

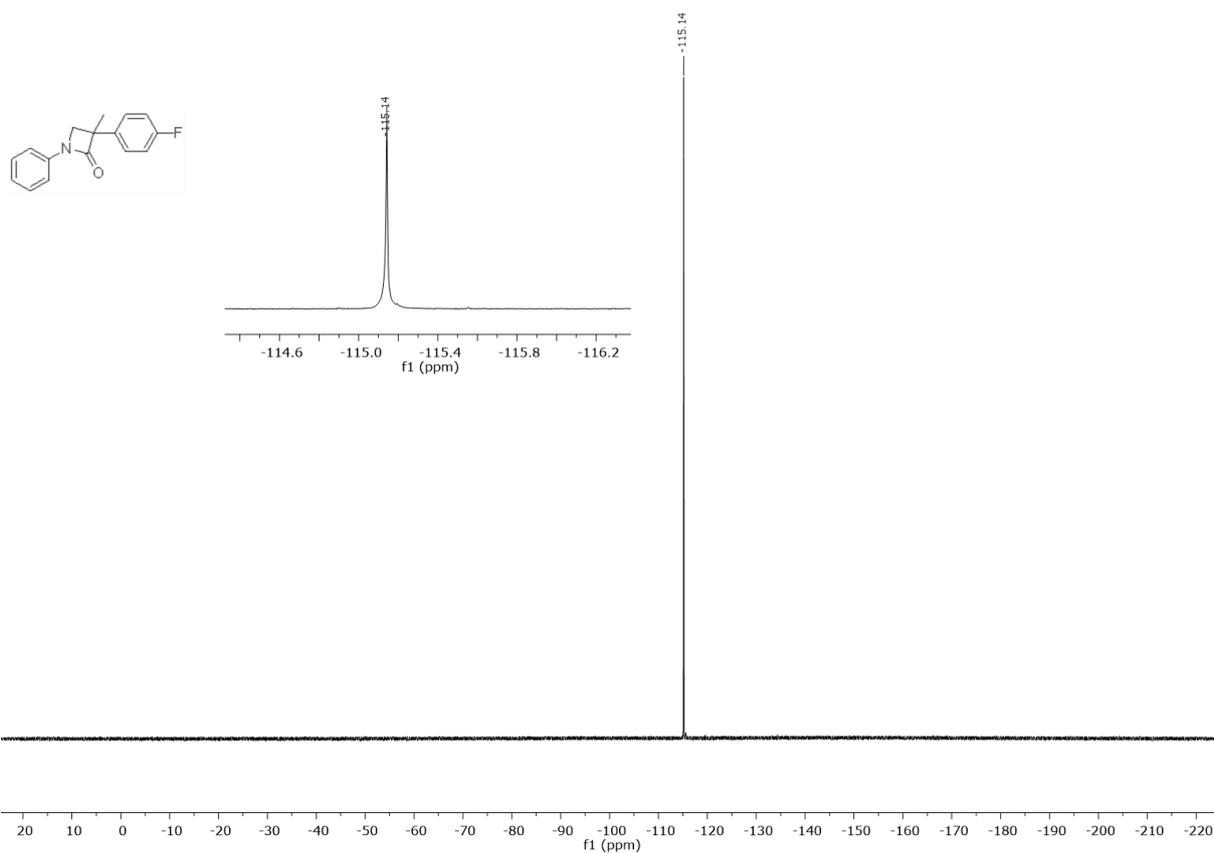
$^1\text{H}$  NMR (500 MHz, Chloroform-*d*)



$^{13}\text{C}$  NMR (126 MHz, Chloroform-*d*)

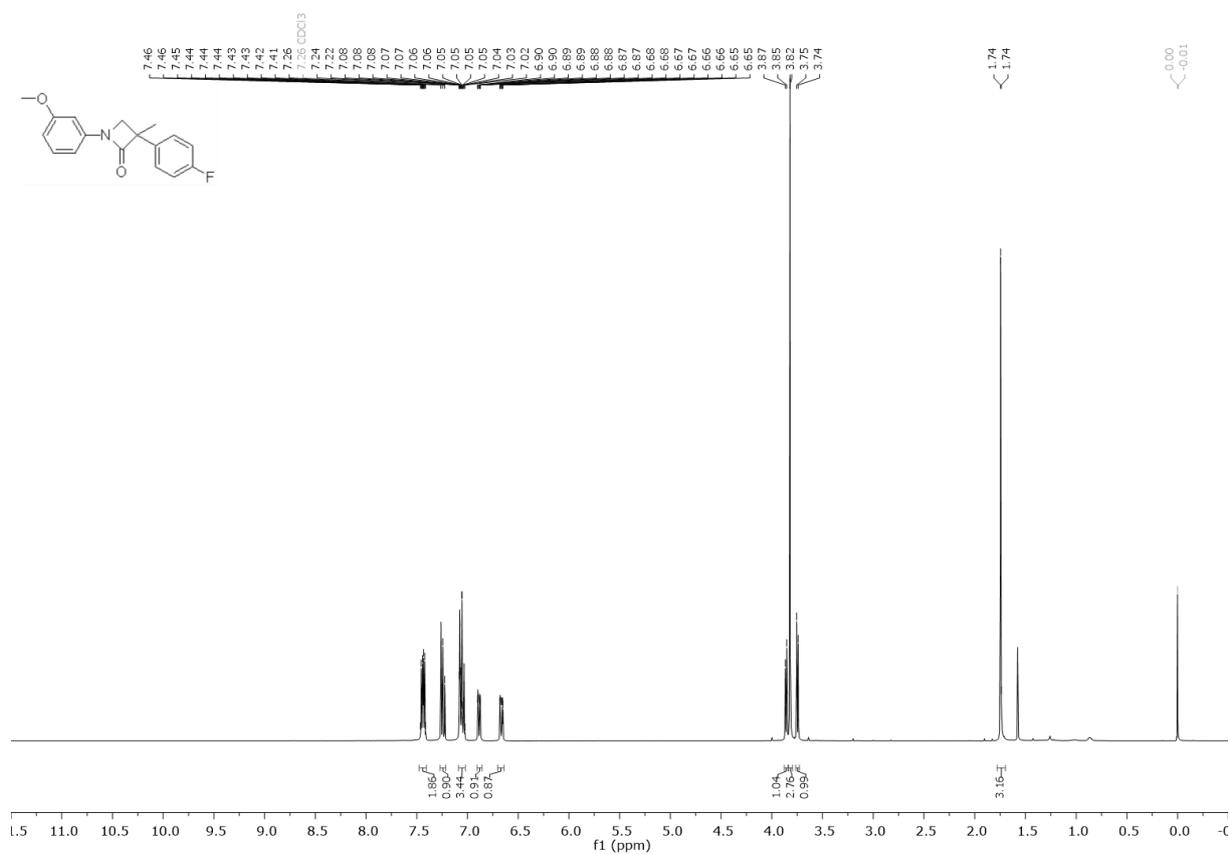


**$^{19}\text{F}\{^1\text{H}\}$  NMR (376 MHz, Chloroform-*d*)**

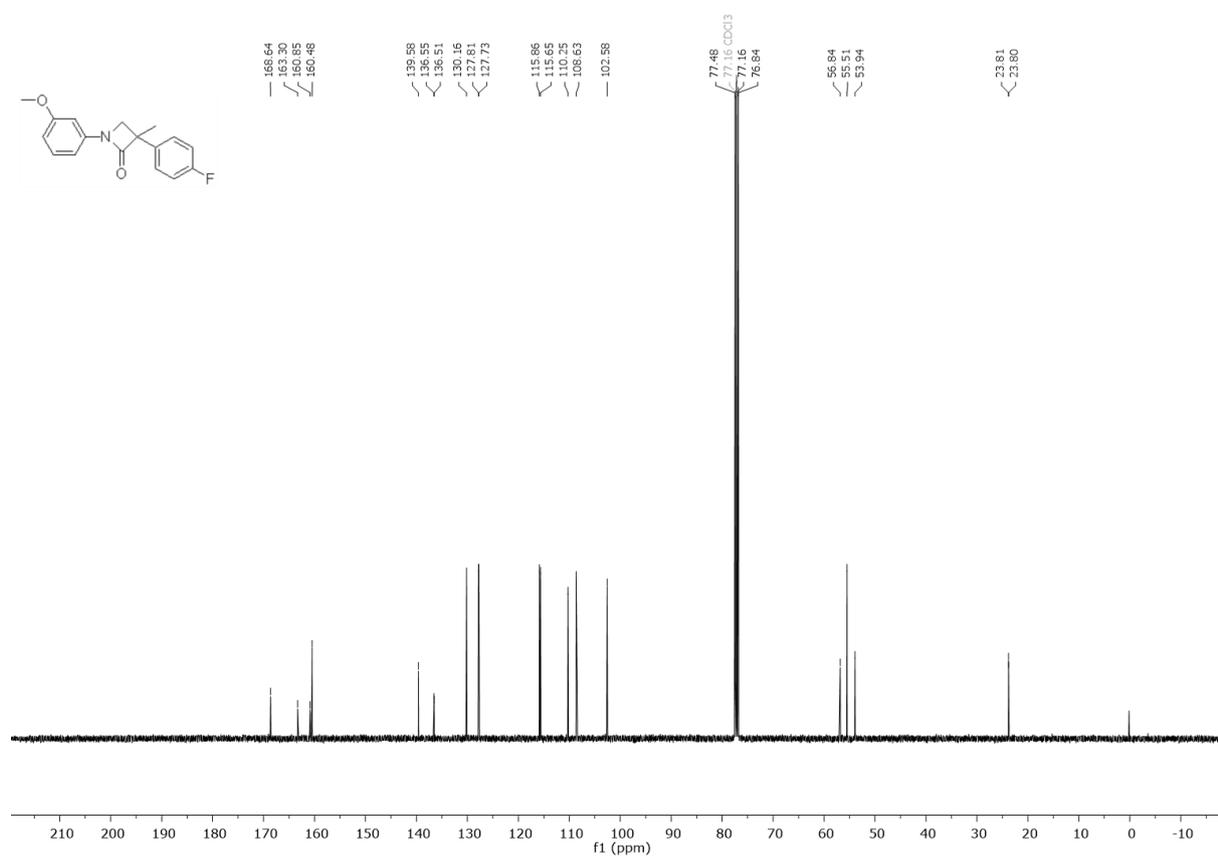


3-(4-fluorophenyl)-1-(3-methoxyphenyl)-3-methylazetidin-2-one (**6.20**)

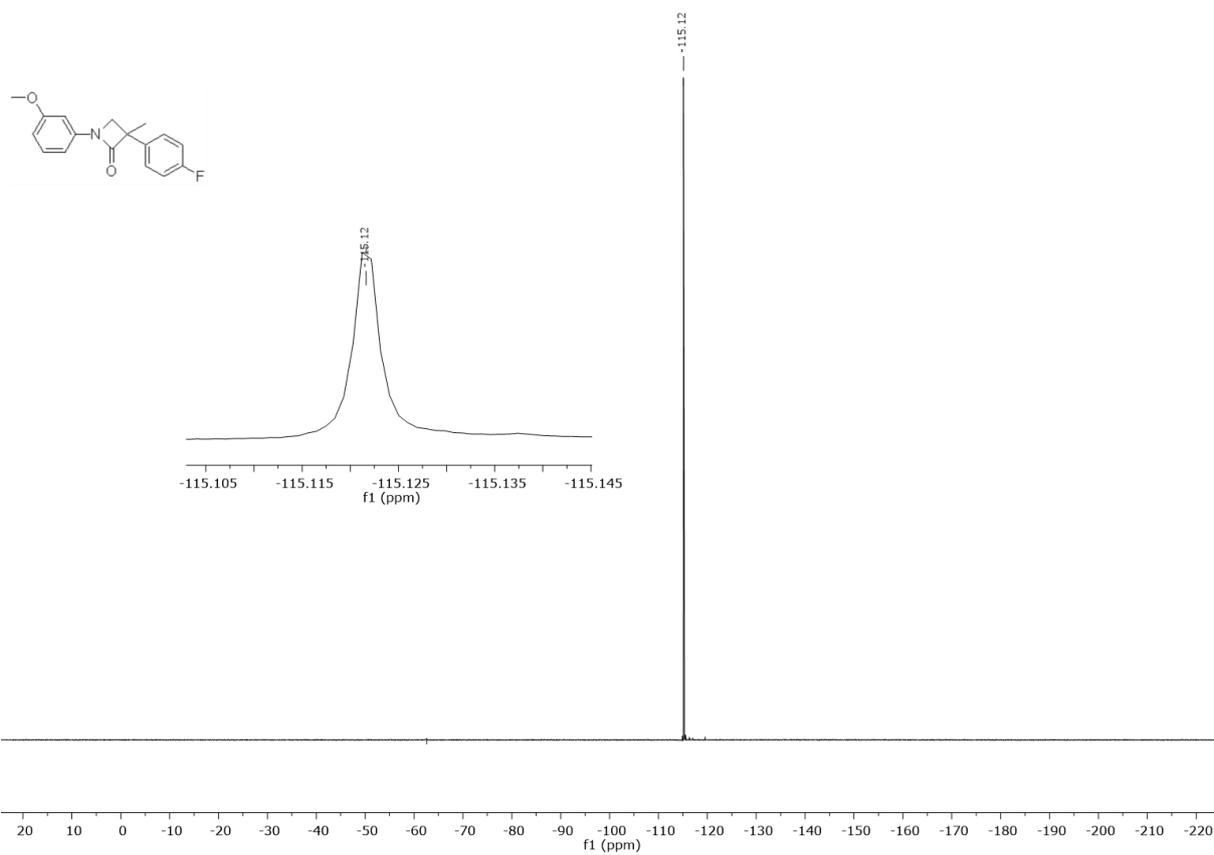
<sup>1</sup>H NMR (400 MHz, Chloroform-d)



<sup>13</sup>C NMR (101 MHz, Chloroform-d)

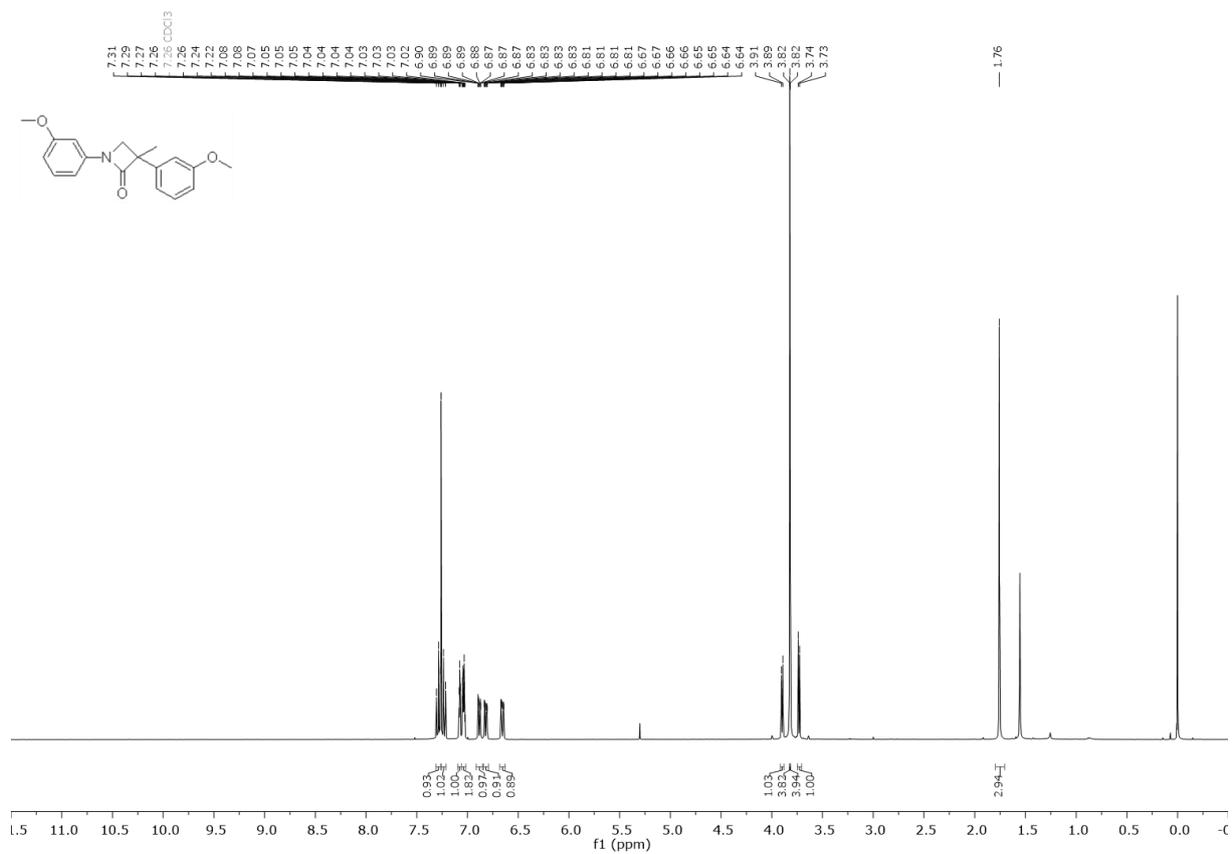


$^{19}\text{F}\{^1\text{H}\}$  NMR (376 MHz, Chloroform-d)  $\delta$  -115.12.

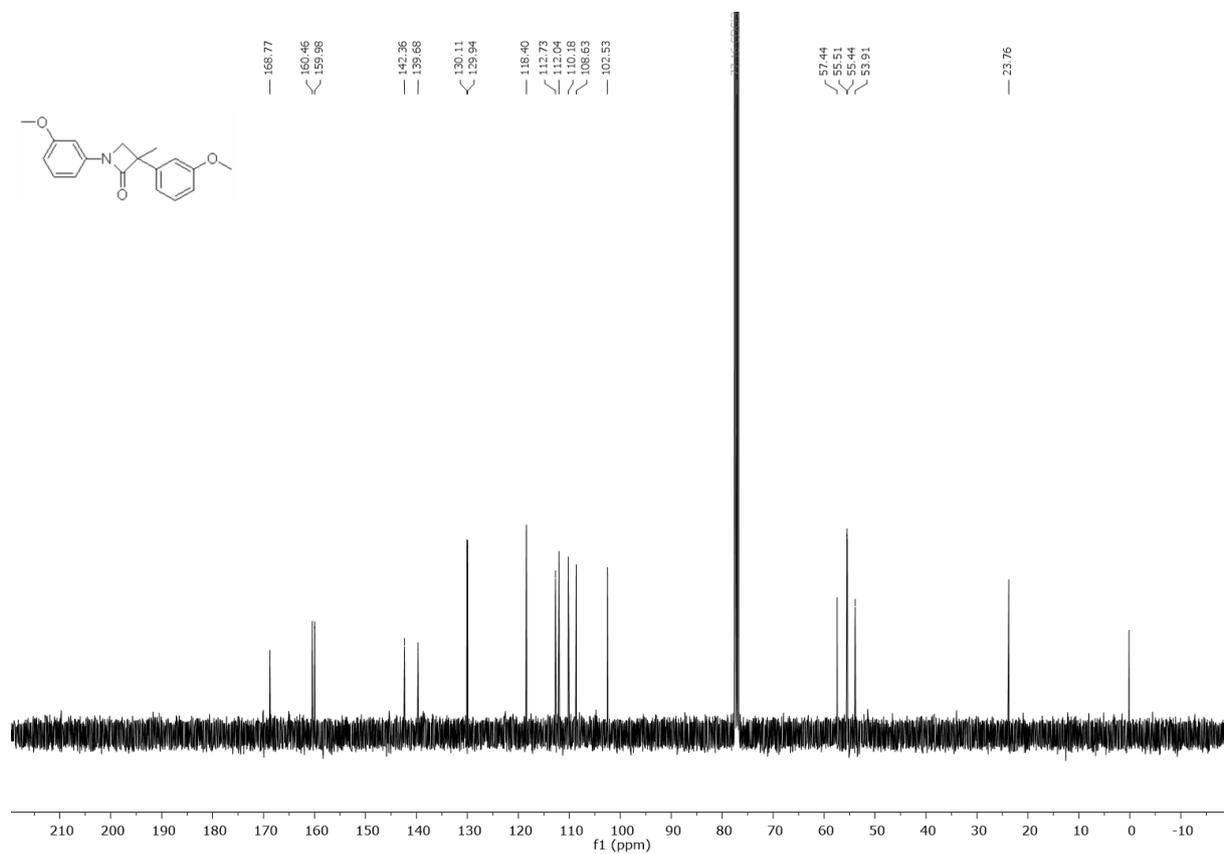


# 1,3-bis(3-methoxyphenyl)-3-methylazetidin-2-one (**6.21**)

<sup>1</sup>H NMR (400 MHz, Chloroform-*d*)



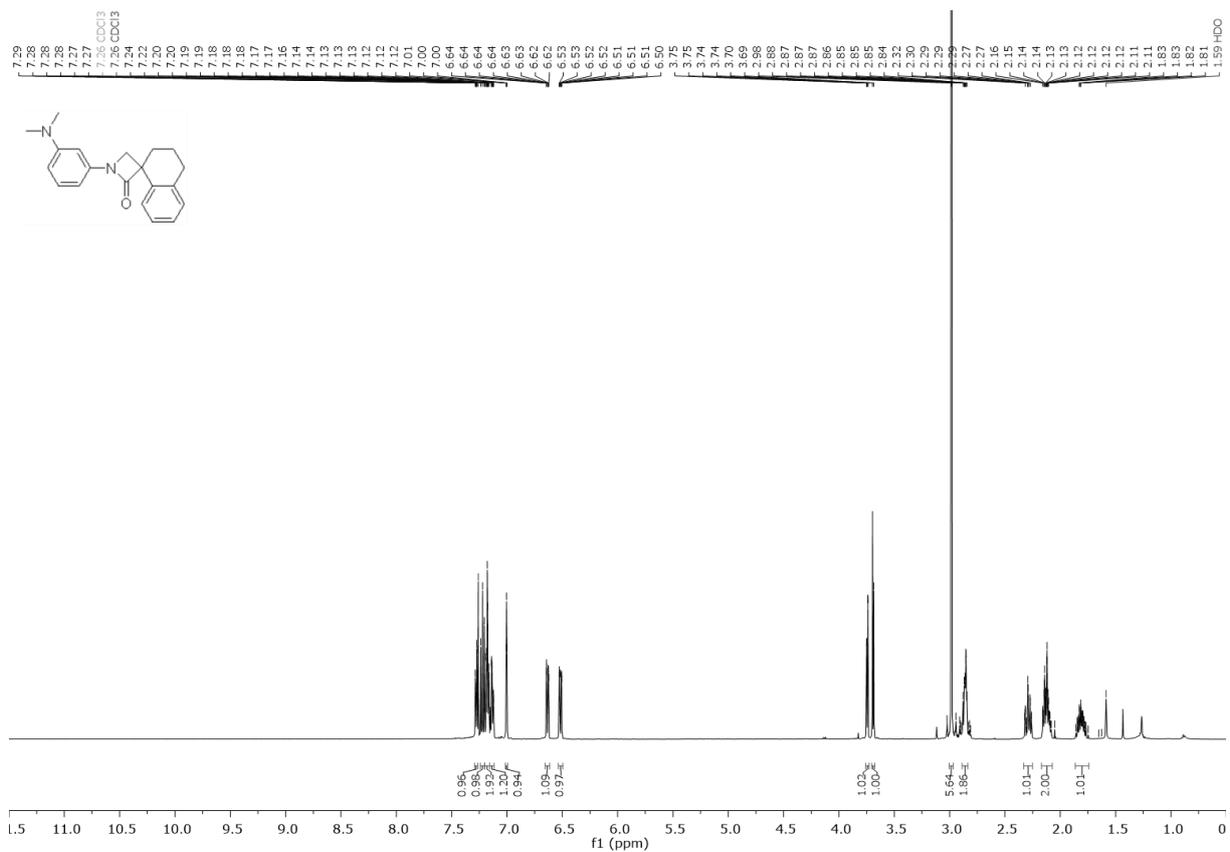
<sup>13</sup>C NMR (101 MHz, Chloroform-*d*)



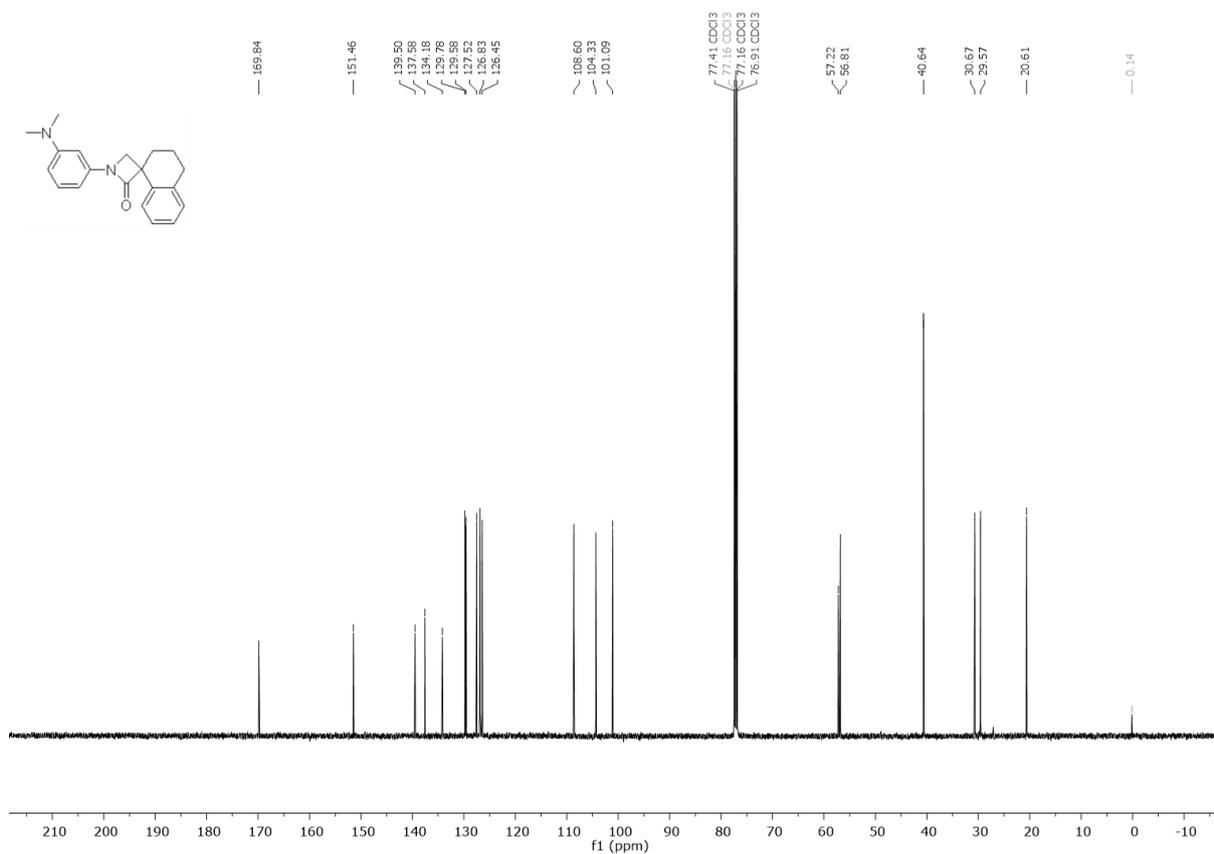


1-(3-(dimethylamino)phenyl)-3',4'-dihydro-2'H-spiro[azetidine-3,1'-naphthalen]-2-one (**6.23**),

$^1\text{H}$  NMR (500 MHz, Chloroform-*d*)

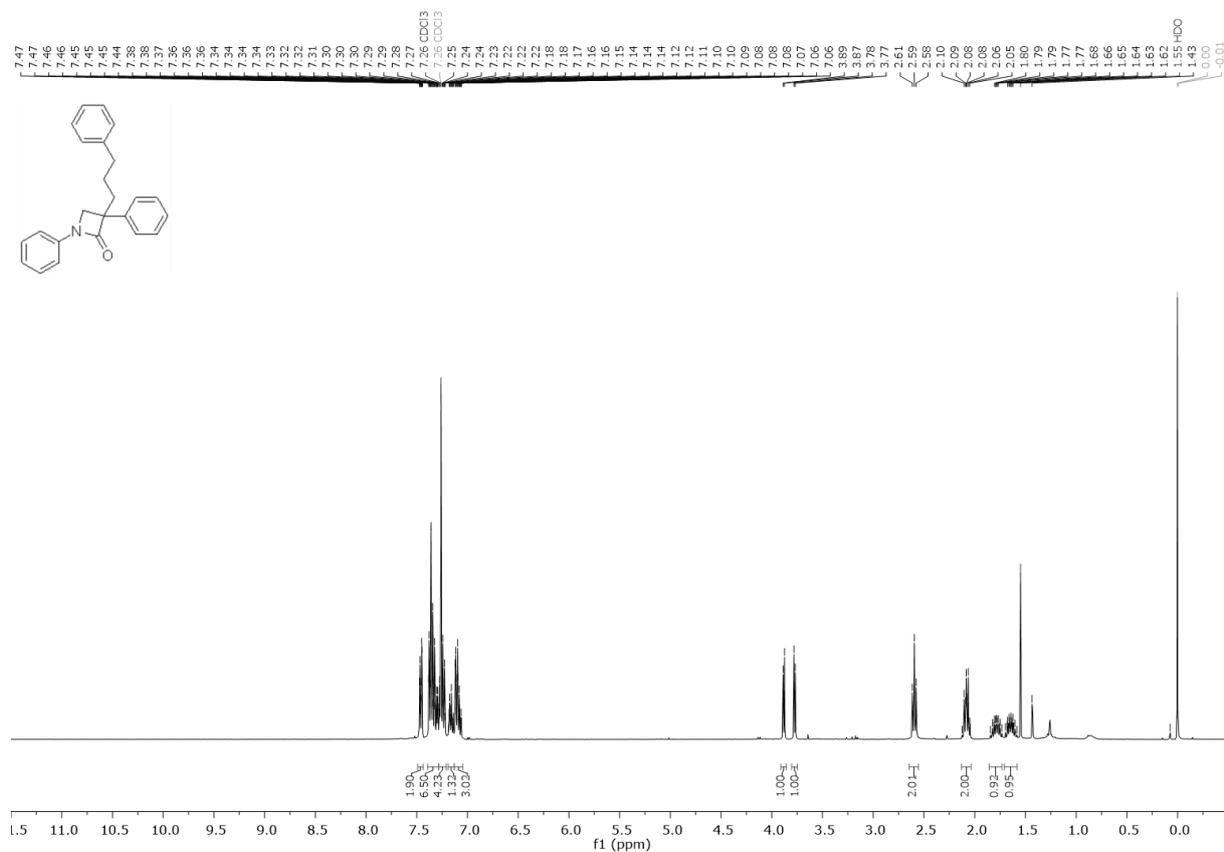


$^{13}\text{C}$  NMR (126 MHz, Chloroform-*d*)

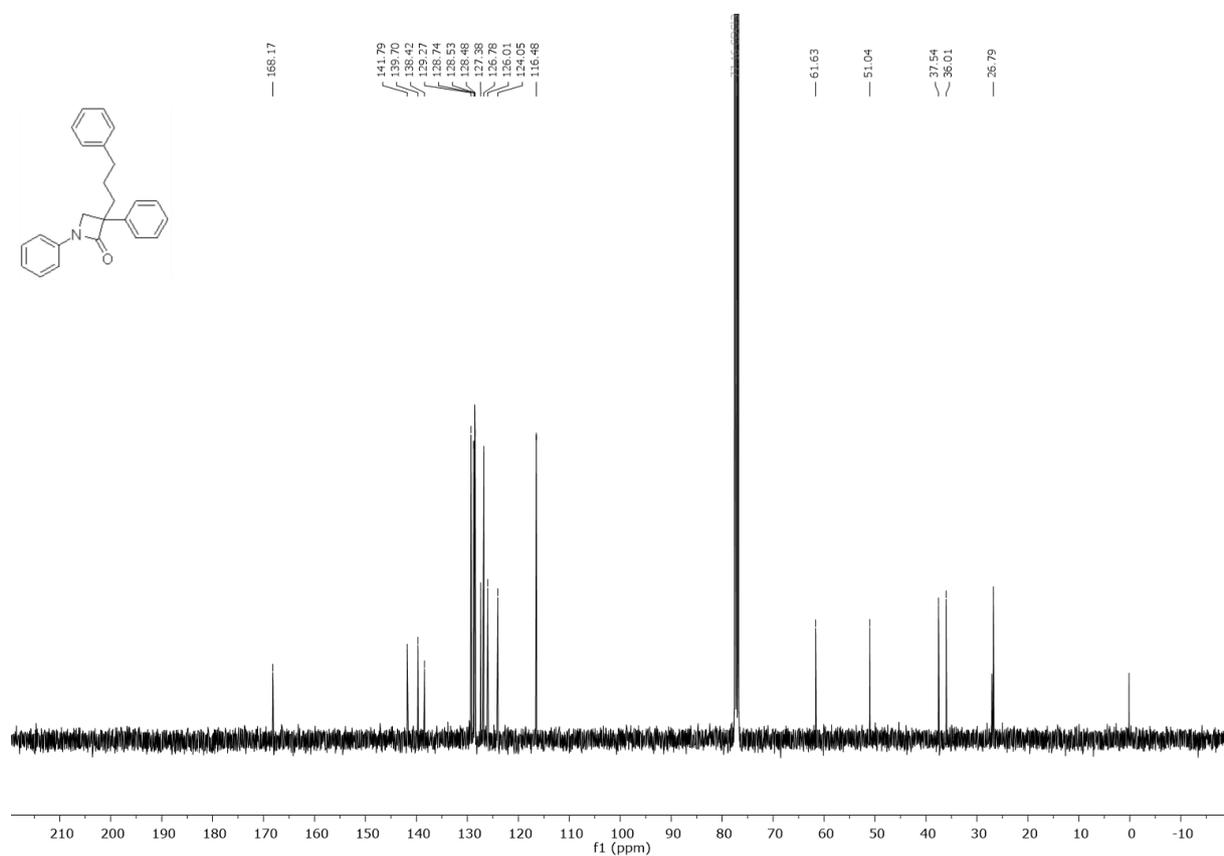


# 1,3-diphenyl-3-(3-phenylpropyl)azetid-2-one (6.24)

$^1\text{H}$  NMR (400 MHz, Chloroform-*d*)

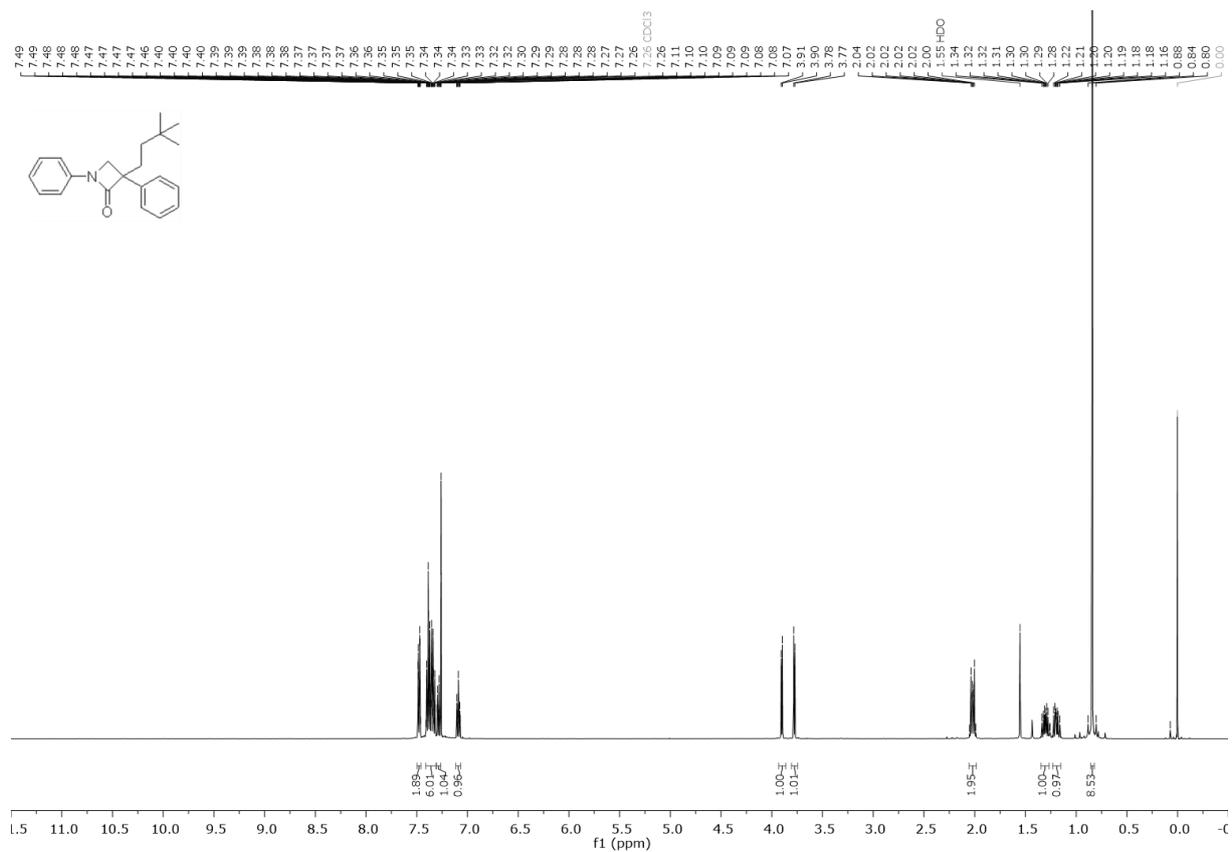


$^{13}\text{C}$  NMR (101 MHz, Chloroform-*d*)

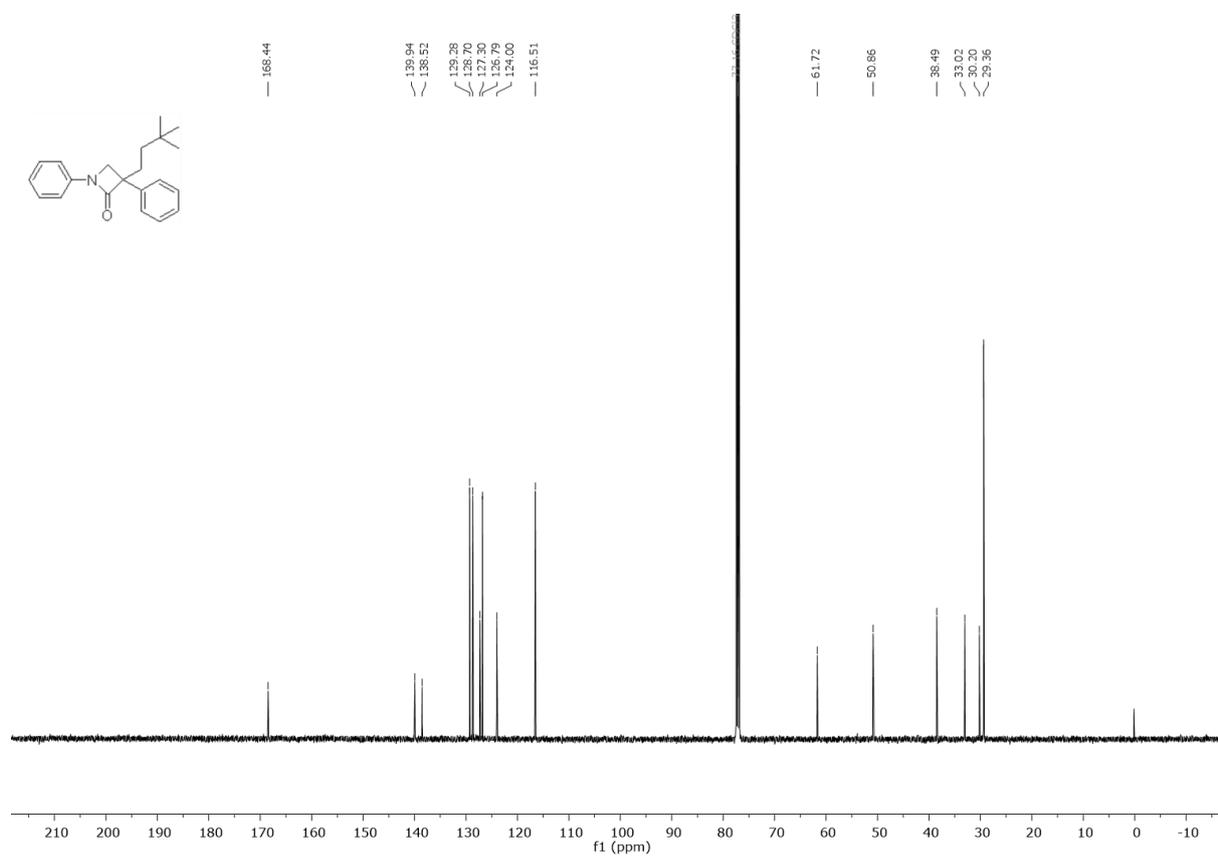


### 3-(3,3-dimethylbutyl)-1,3-diphenylazetidin-2-one (6.25)

$^1\text{H NMR}$  (500 MHz, Chloroform-*d*)

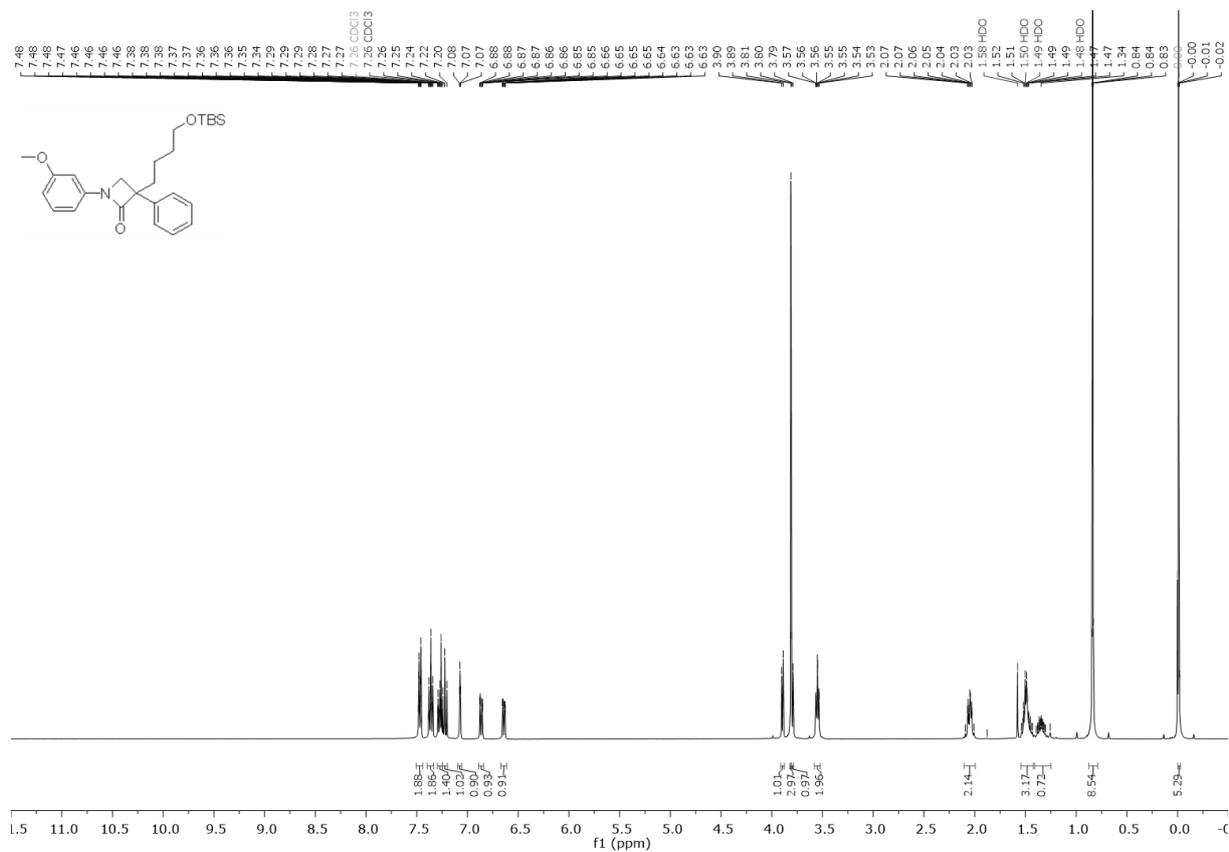


$^{13}\text{C NMR}$  (126 MHz, Chloroform-*d*)



3-(4-((tert-butyldimethylsilyloxy)butyl)-1-(3-methoxyphenyl)-3-phenylazetidin-2-one (**6.26**),

$^1\text{H}$  NMR (400 MHz, Chloroform-*d*)

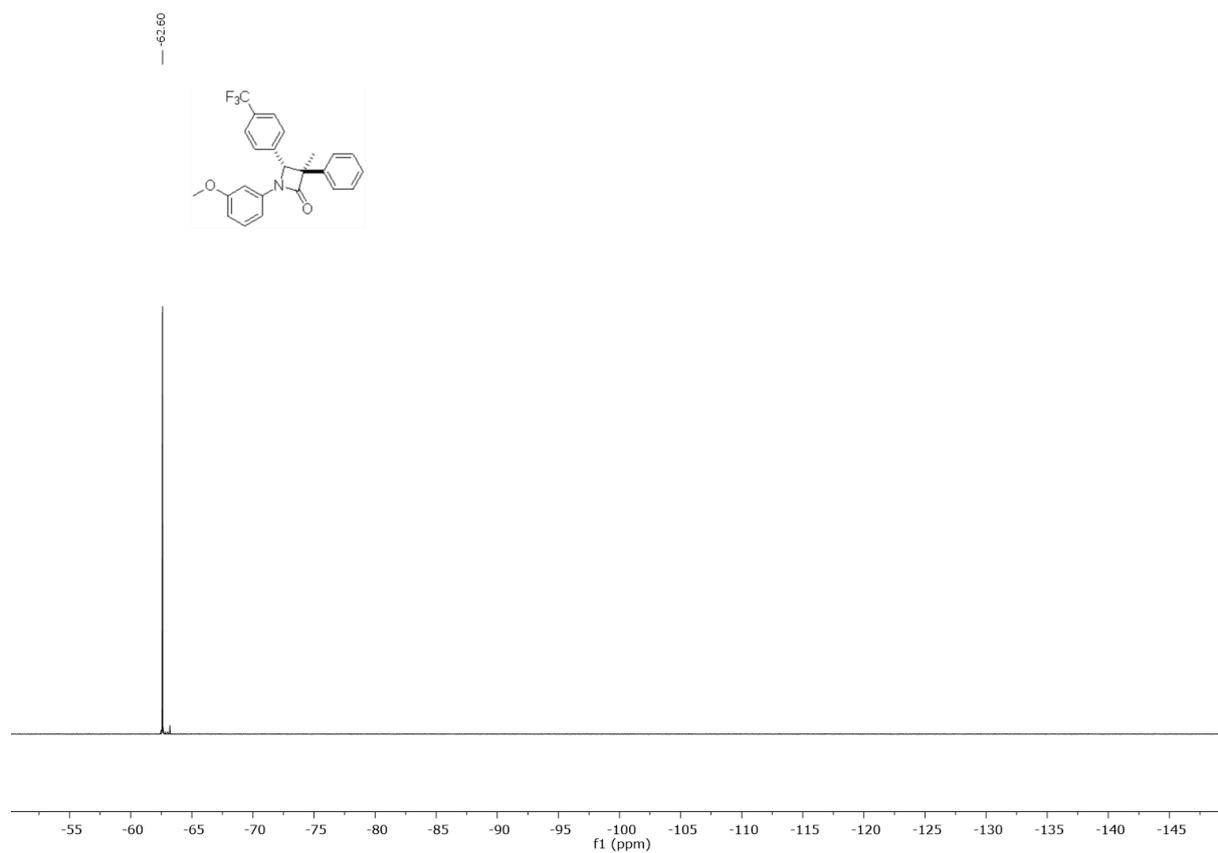




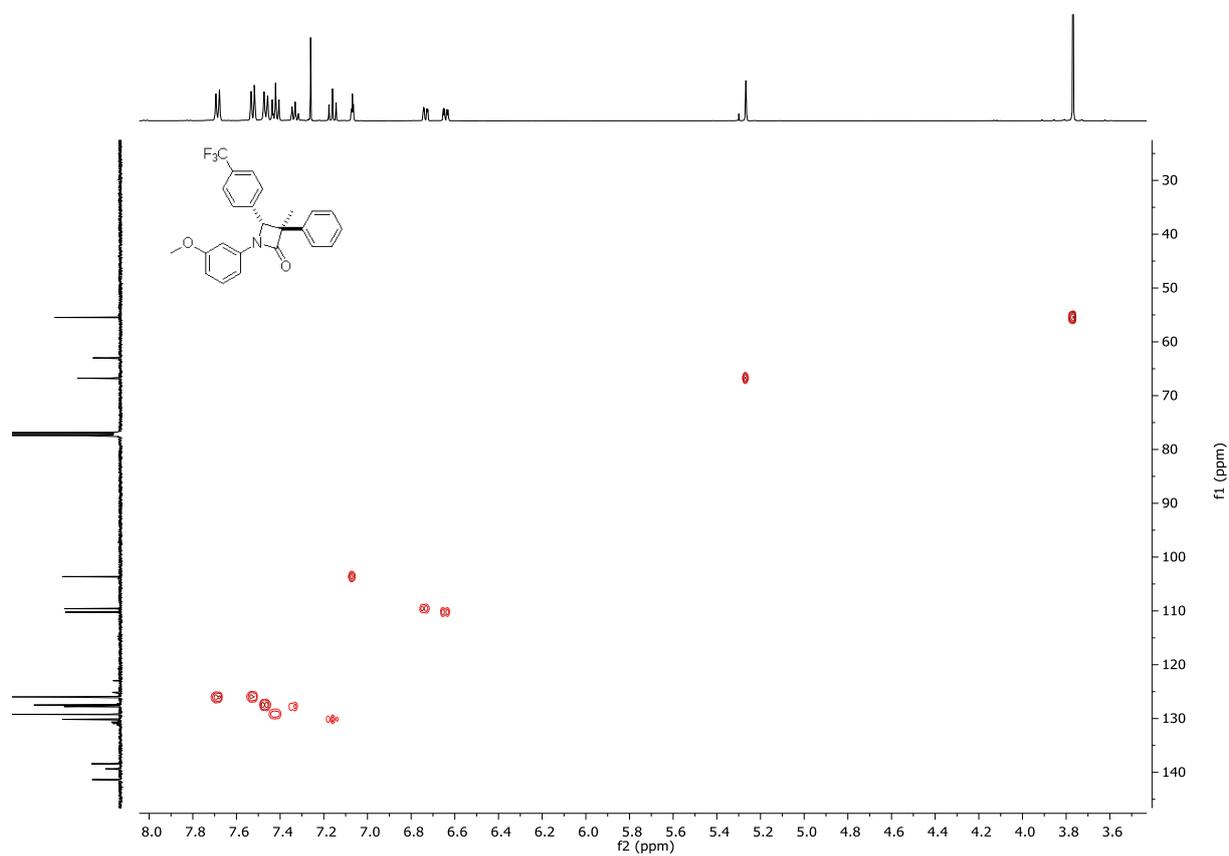




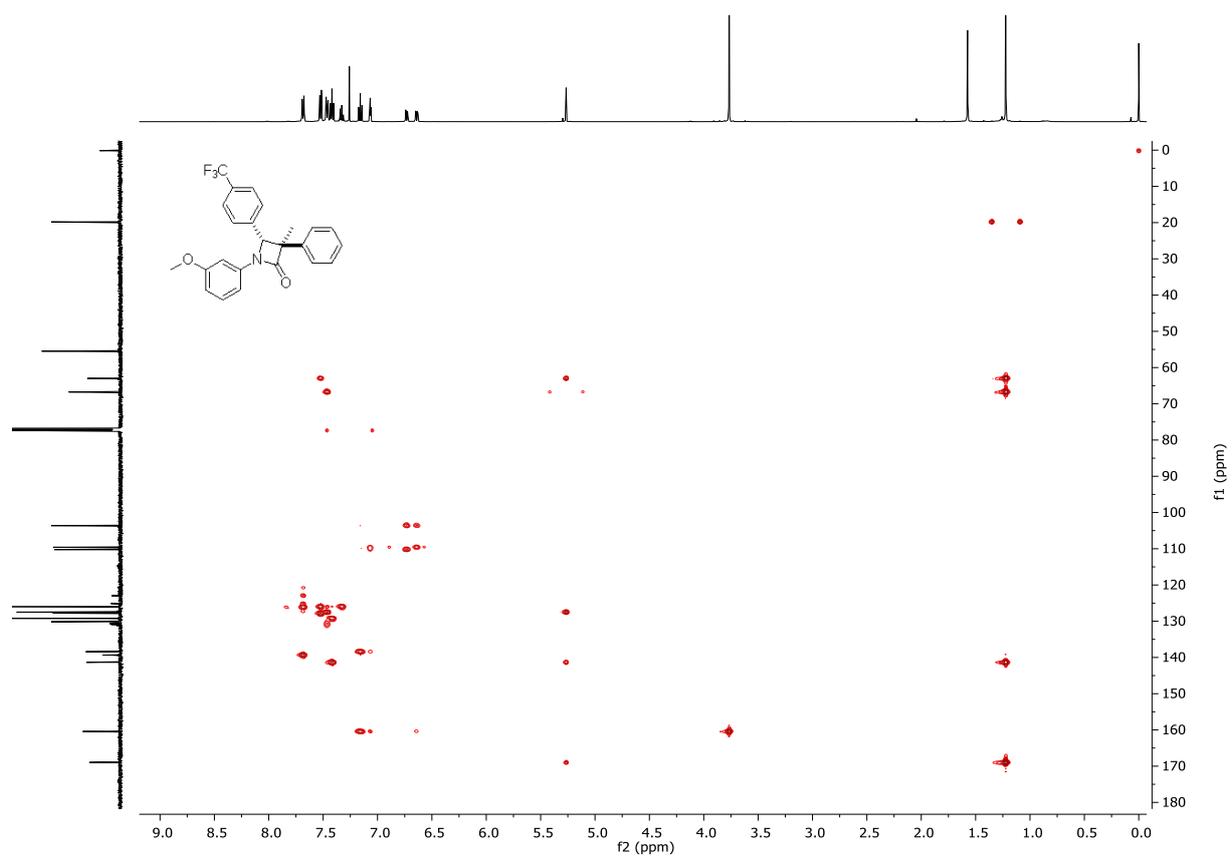
# $^{19}\text{F}\{^1\text{H}\}$ NMR (471 MHz, Chloroform-d)



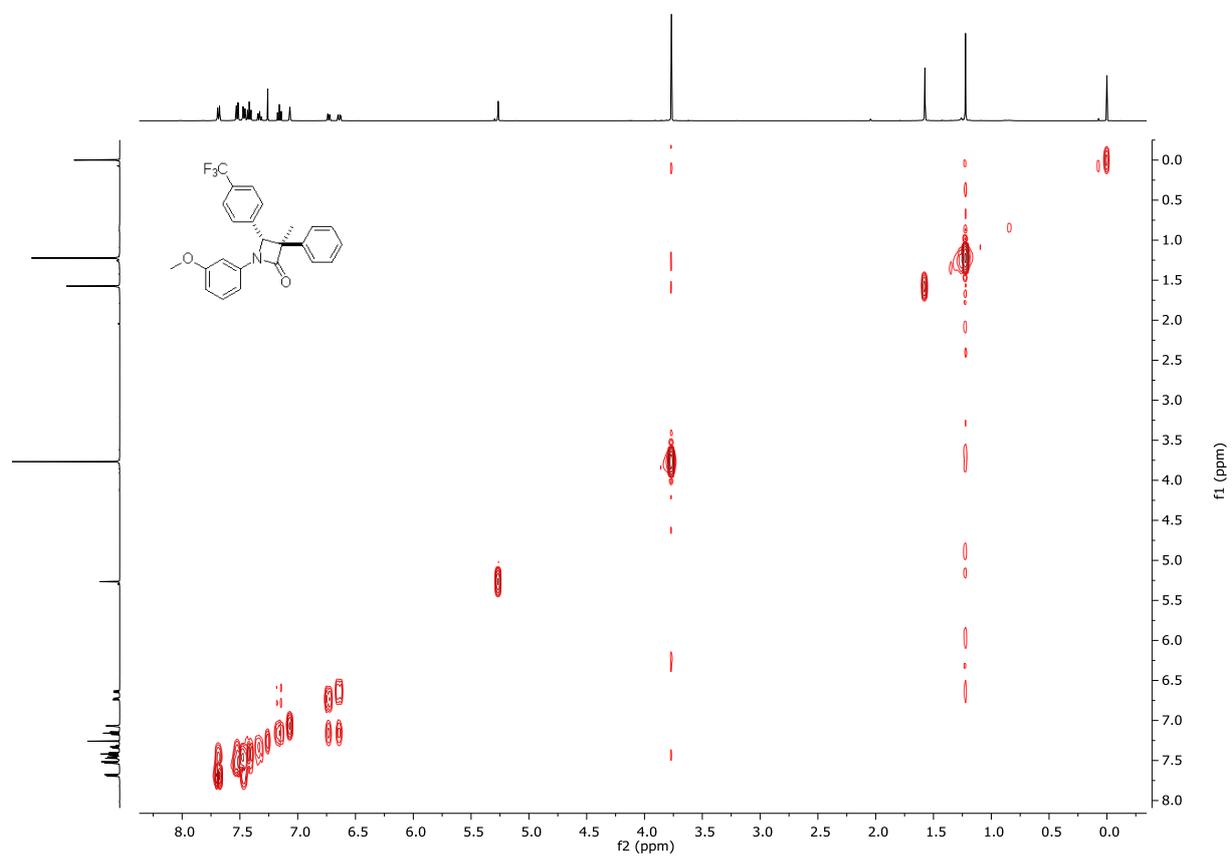
## HMQC



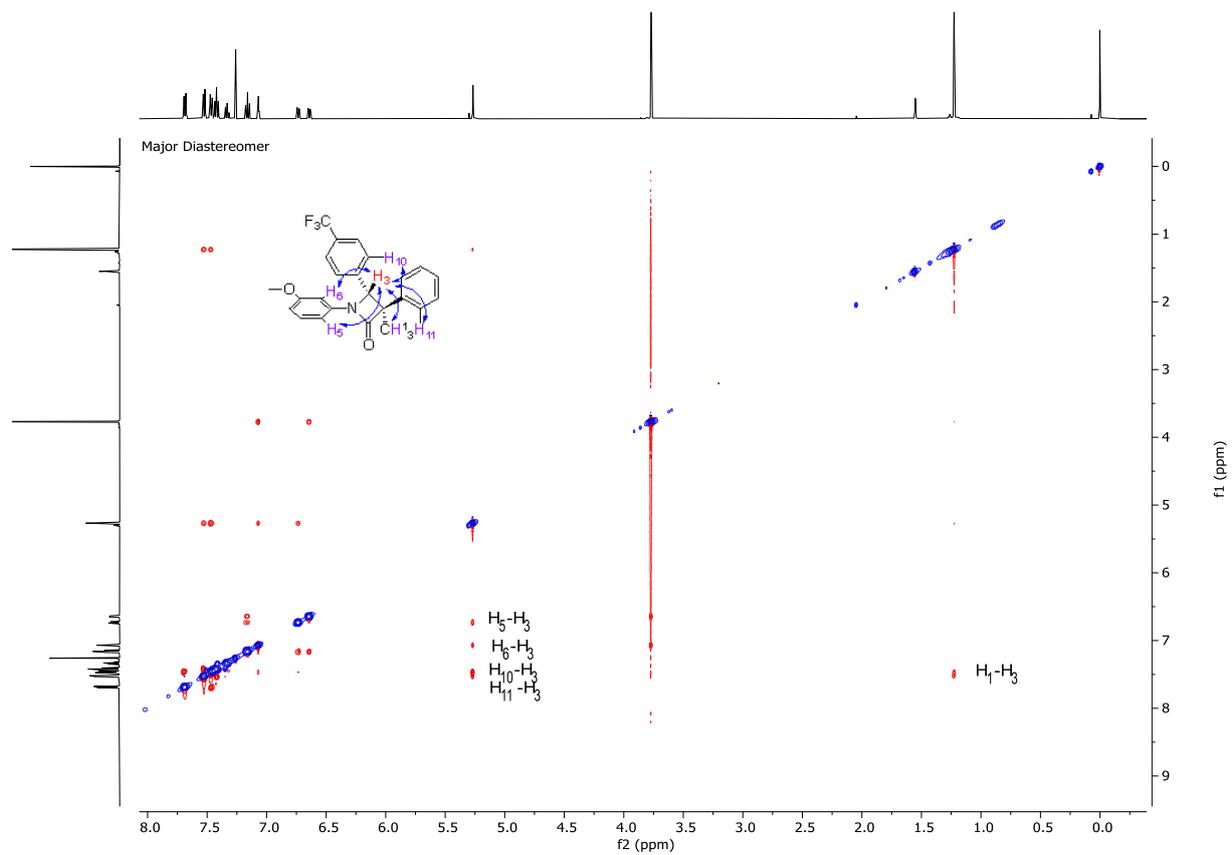
# HMBC



# COSY

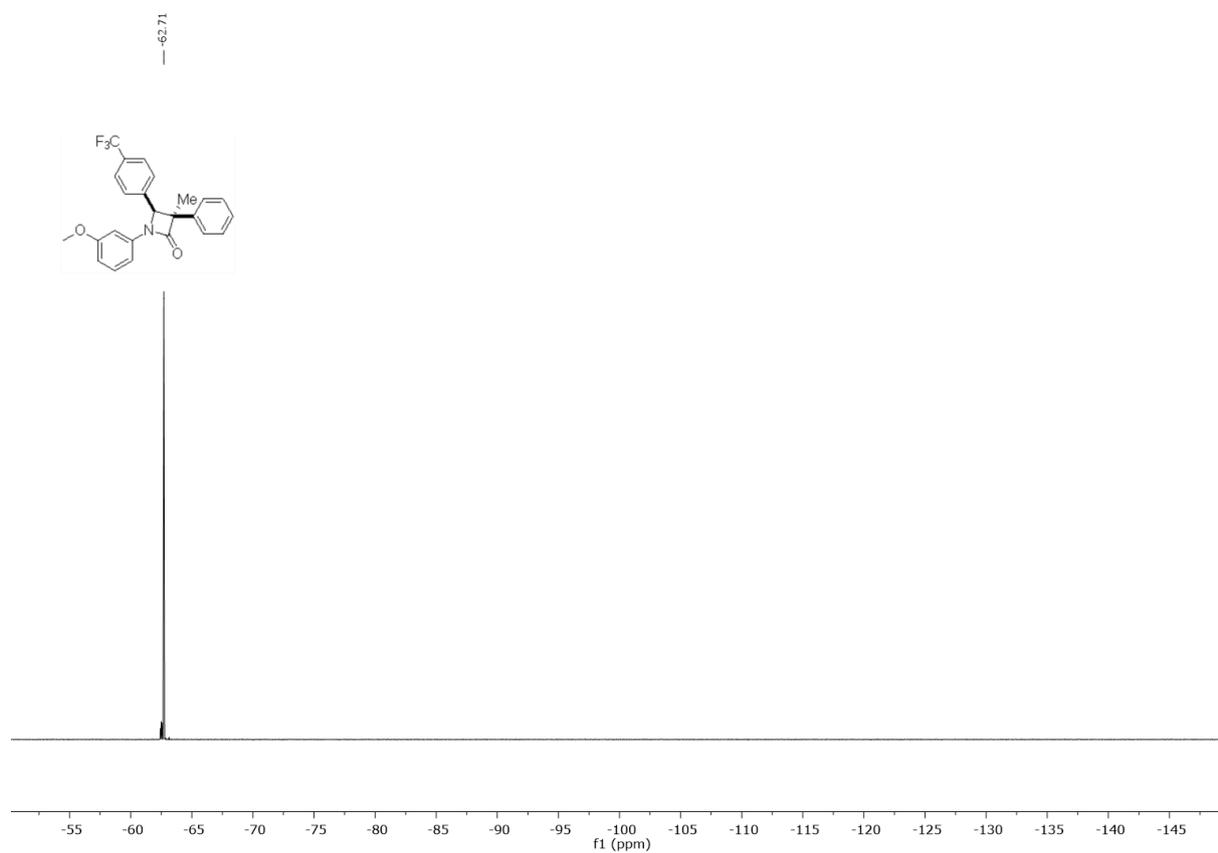


# NOESY

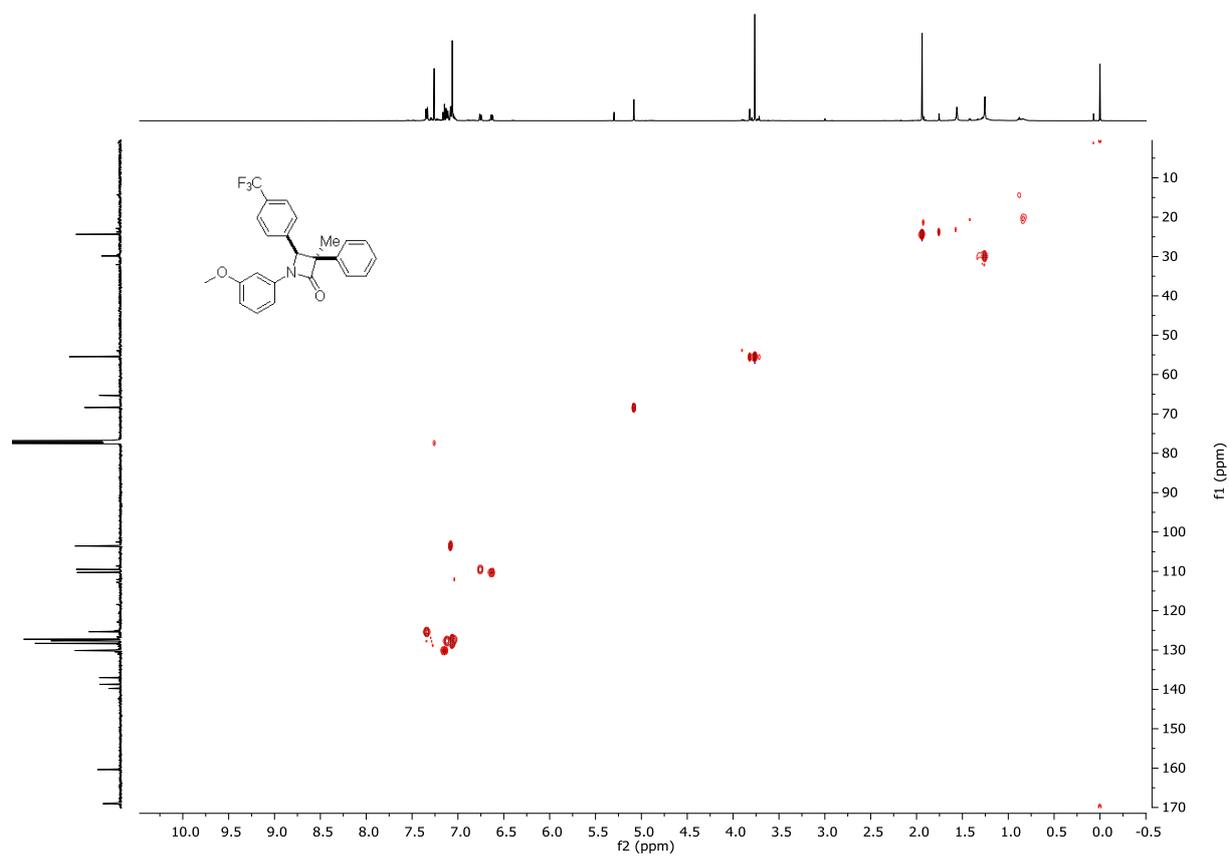




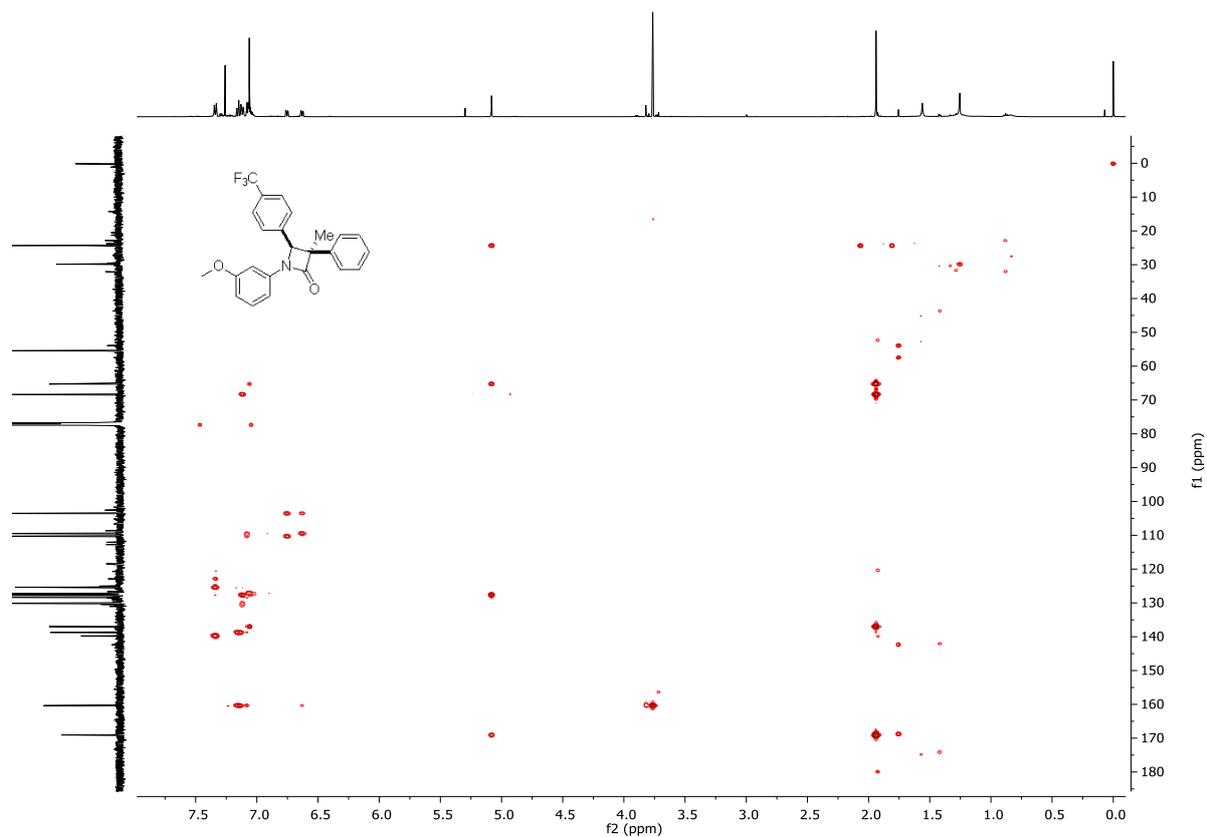
# $^{19}\text{F}\{^1\text{H}\}$ NMR (471 MHz, Chloroform-*d*)



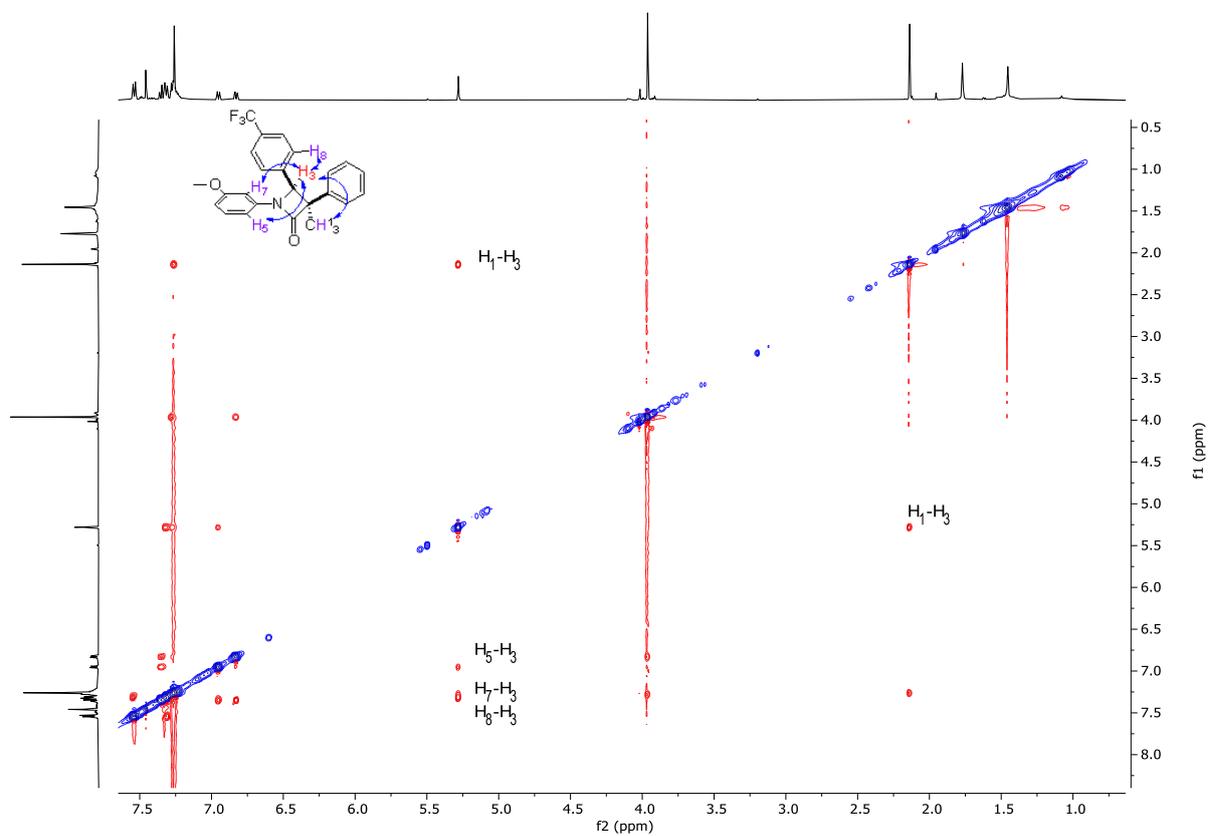
## HMQC



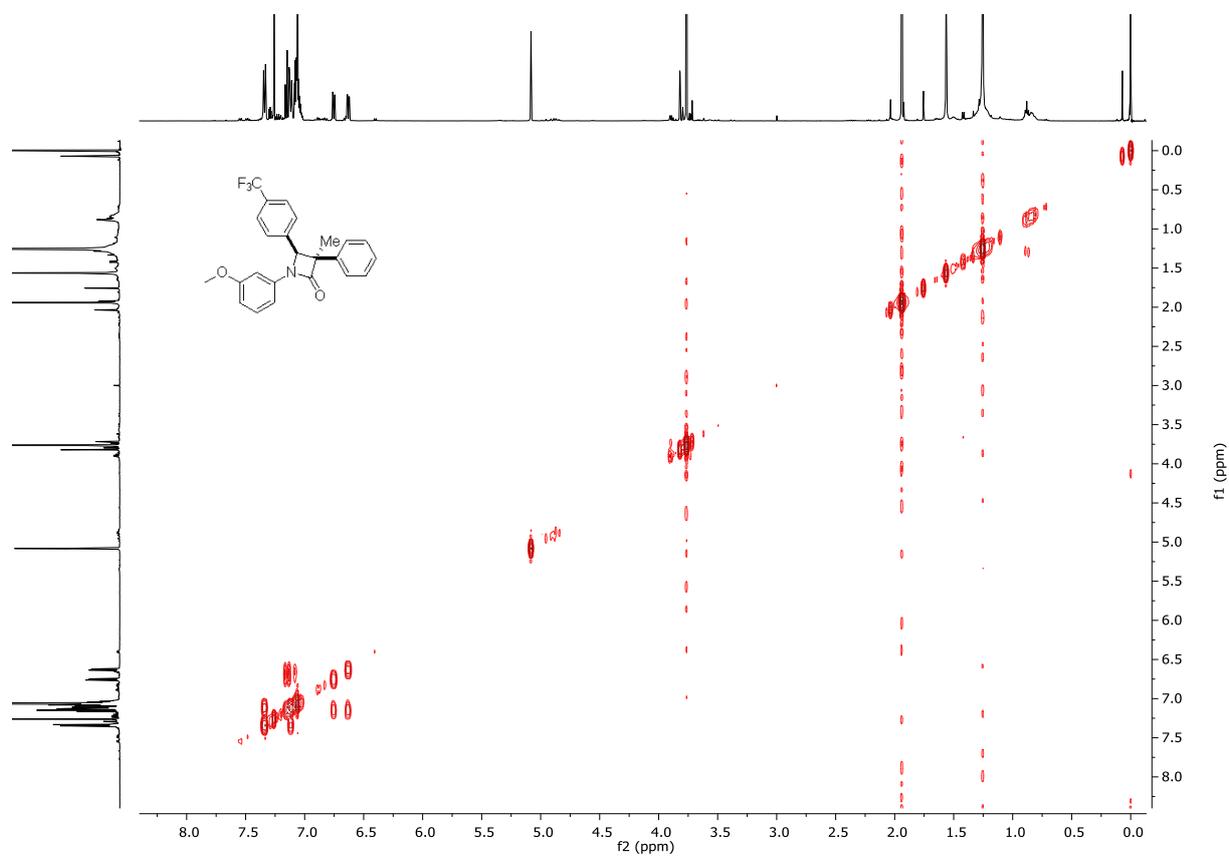
# HMBC



# NOESY

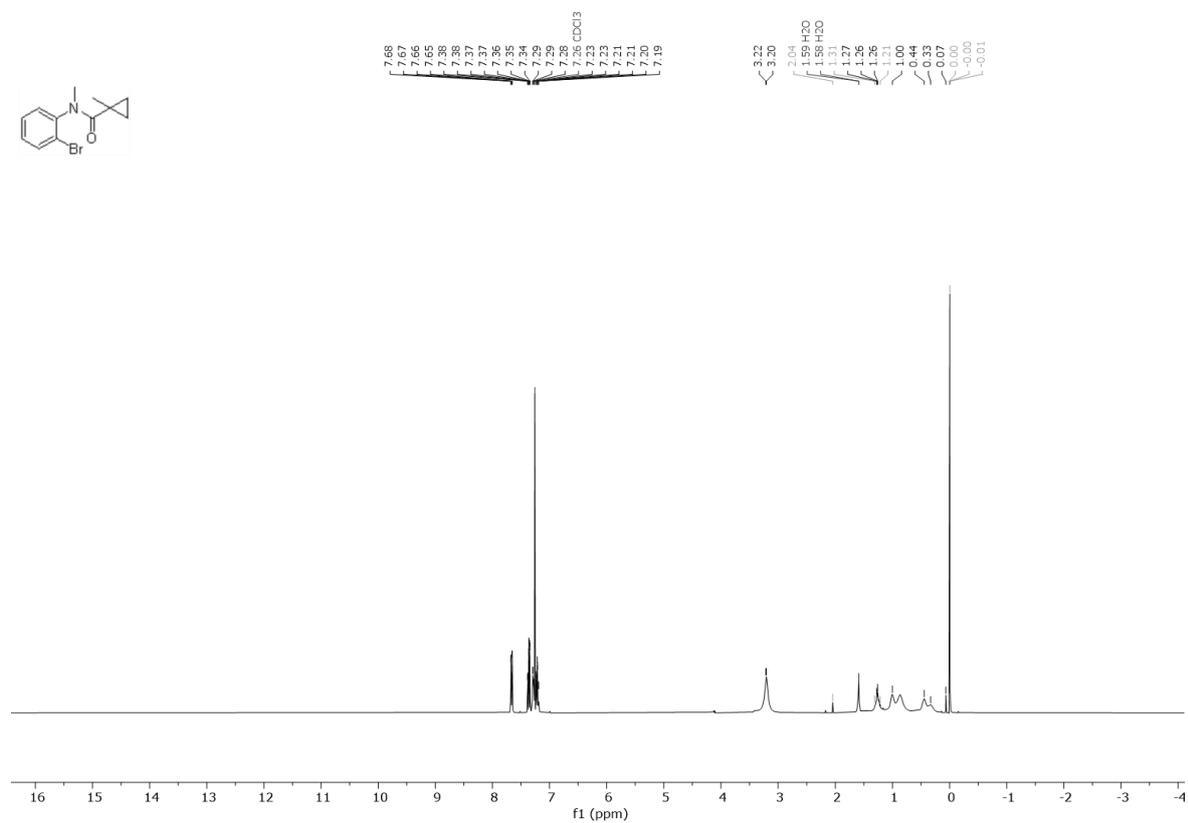


# COSY



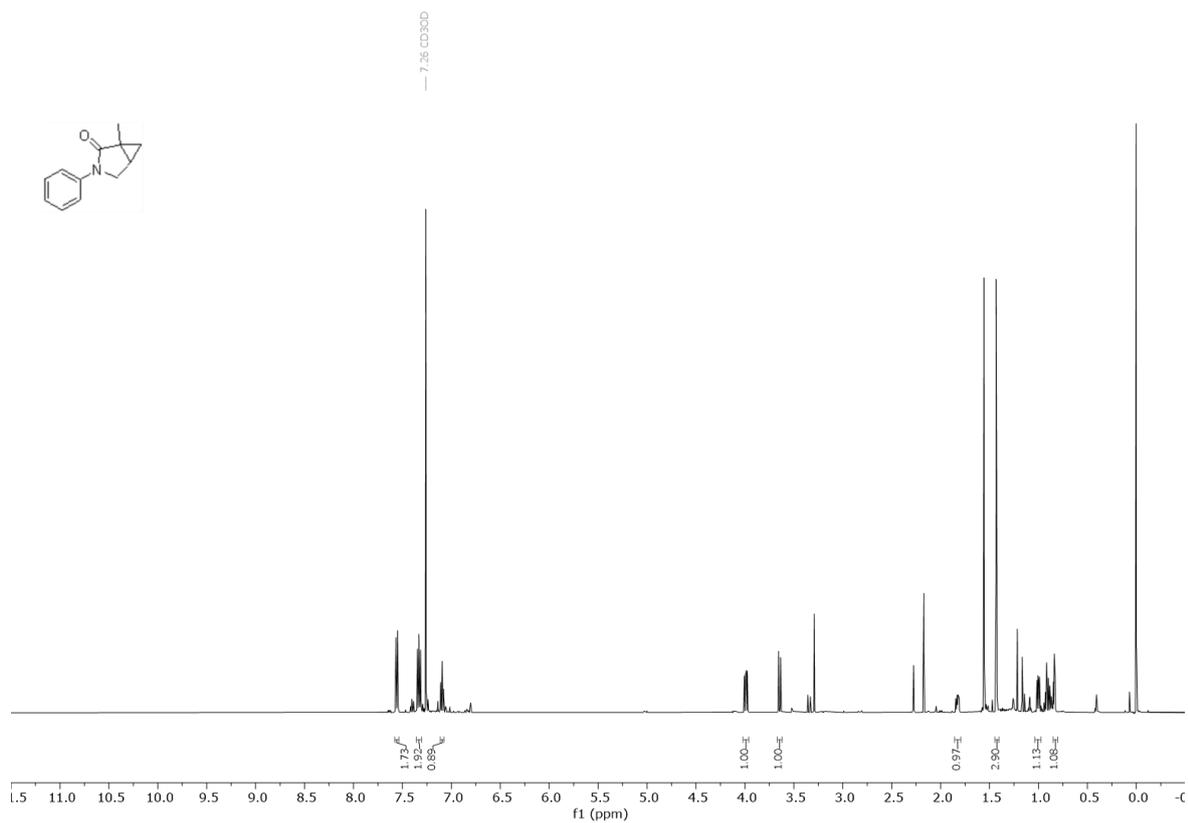
N-(2-bromophenyl)-N,1-dimethylcyclopropane-1-carboxamide (**6.41**)

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )



1-methyl-3-phenyl-3-azabicyclo[3.1.0]hexan-2-one (**6.48**)

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )



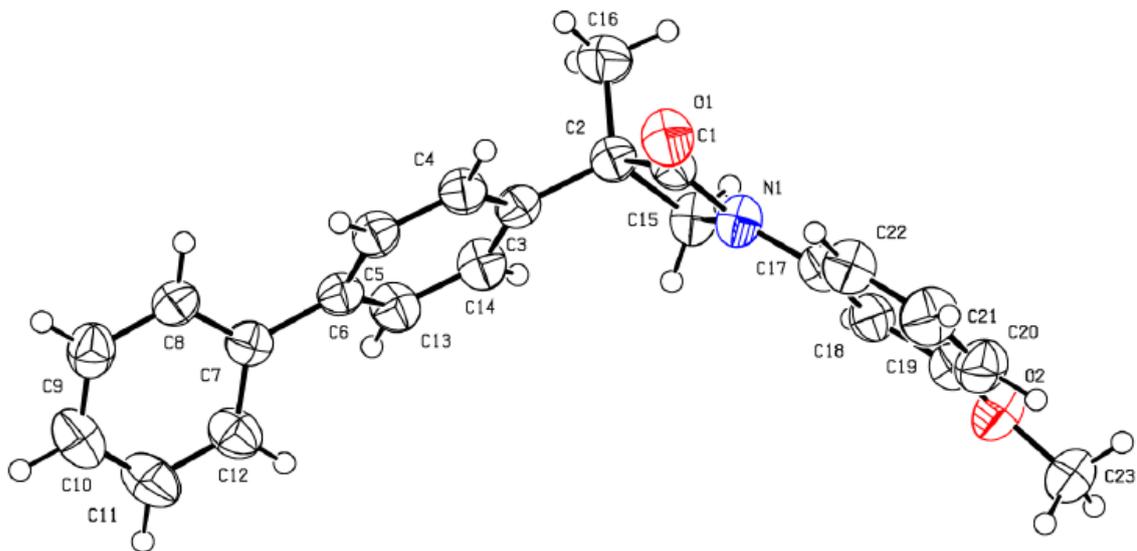


-6 Y

NOMOVE FORCED

Prob = 50  
Temp = 150

PLATON-Jul 8 08:55:43 2021 - (30621)



Z 154

nn2921\_150k

P 1 21/c 1

R = 0.04

RES= 0 -78 X