Asymmetric Palladium(0)-Catalyzed C(sp^3)-H Arylation and Natural Product Synthesis

Inauguraldissertation

zur

Erlangung der Würde eines Doktors der Philosophie

vorgelegt der

Philosophisch-Naturwissenschaftlichen Fakultät

der Universität Basel

von

Romain Melot

Aus Frankreich

BASEL, 2020

Genehmigt von der Philosophisch-Naturwissenschaftlichen Fakultät

auf Antrag von

Prof. Dr. Olivier BAUDOIN

Prof. Dr. Nicolai CRAMER

Basel, den 15. October 2019

Prof. Dr. Martin Spiess

Acknowledgments

First, I would like to thank Prof. Dr. Olivier Baudoin who gave me the opportunity to join his research group four years ago when he got his position in Basel. I am really thankful for the fruitful discussions that we had together and for the knowledge that I have learned during these years. I am grateful for the confidence that he placed in me to conduct my research and for his support when I was looking for a postdoctoral position.

I also thank Prof. Dr. Nicolai Cramer for accepting to co-examinate my thesis and Prof. Dr. Denis Gillingham for chairing the Ph.D. defense.

Je tiens à remercier les membres du groupe que j'ai rejoint en 2015 pour mon master lorsque nous étions encore à Lyon et qui, pour certains, étaient quelques mois, voire années, à Bâle également. Tout d'abord Alexis, merci de m'avoir encadré durant mon stage de master, pour ta grande humanité et pour tous les conseils que tu m'as donnés professionnellement et personnellement, j'espère que ton tout nouveau poste de CR à Montpellier t'apportera le meilleur à toi et ta petite famille. Merci Greg pour ta bienveillance, ta gentillesse et tes précieux conseils, j'ai rarement autant rigolé qu'avec toi. Merci David, dit petit poulet dans le métier, tu étais toujours là quand un problème se présentait au laboratoire et tu avais toujours une solution pour le résoudre, j'ai beaucoup appris grâce à toi. On a travaillé tard ensemble au labo et tu étais toujours prêt à aller manger un MacDo après. Merci Titou, on a bien profité ensemble, au Paso on a bien bu, et je ne compte pas le nombre de parties de billard que l'on a faites ensemble. Aller se détendre au bord du Rhin, c'était une bonne activité aussi. Et également merci pour toutes ces discussions que l'on a eues ensemble au sujet de la vie ou de la science et pour tout le reste. Merci Stéphanie, tu étais toujours partante pour sortir et faire quelque chose et on à bien rigolé. Merci Antho, on ne t'a pas beaucoup revu, mais tu faisais partie de la bande. Et merci aux autres membres du groupe de Lyon, Ke-Feng, Maria et enfin Lei avec qui j'ai travaillé pour mon premier projet de thèse.

Je tiens également à remercier mes collègues de Bâle. Merci David, dit boulanger, on a bossé plus de trois ans côtes à côtes au labo et on s'est bien amusé, on a bien rigolé, discuté et on s'est bien engueulé aussi, mais il n'y avait jamais de méchanceté. Je te souhaite le meilleur pour ta fin de thèse. Merci Yann et Diana pour tous les bons moments autour d'une bière ou d'un café et pour votre convivialité. Thank you, Marcus, working with you for one year was really

Asymmetric Palladium(0)-Catalyzed C(sp^3)-H Arylation and Natural Product Synthesis

Abstract

Over the last decades, C(sp^3)-H activation has emerged as a powerful tool for building structural complexity in a step-economical manner. In this context, our group developed diverse methodologies and applied them to the synthesis of natural products, bioactive molecules and valuable building blocks.

More recently, our group was attracted, as others, by the development of asymmetric versions of such reactions. In this regard, the synthesis of enantioenriched indanes through asymmetric palladium-catalyzed C(sp^3)-H arylation was described using a chiral binepine ligand for chiral induction. This work motivated us to develop other asymmetric reactions and apply them to the synthesis of interesting compounds.

In this optic, we first investigated the use of a chiral anion as an alternative to the classic approach using chiral NHC or phosphorylated ligands. This led to the development of a new methodology for the synthesis of enantioenriched indolines.

We then elaborated a divergent asymmetric synthesis of three (nor)illudalanes sesquiterpenes using C(sp^3)-H arylation as the key step, which demonstrates the potential of such transformations to access chiral natural products.

Finally, we are actually developing a new methodology for the asymmetric C(sp^3)-H arylation of unactivated methylene positions to prepare valuable indanes related to potential natural product targets.

Keywords: C-H functionalization, C-H activation, asymmetric catalysis, palladium, total synthesis, indolines, indanes

Romain Melot

Prof. Dr. Olivier Baudoin

Department of Chemistry

University of Basel

St. Johanns-Ring 19

CH-4056 Basel, Switzerland

Published work during the Ph.D.

R. Melot, M. Craveiro, O. Baudoin, Total Synthesis of (Nor)illudalane Sesquiterpenes Based on a C(sp^3)–H Activation Strategy. *J. Org. Chem.* **2019**, *xx*, xxxx-xxxx

R. Melot,[‡] M. Craveiro,[‡] T. Bürgi, O. Baudoin, Divergent Enantioselective Synthesis of (Nor)illudalane Sesquiterpenes via Pd^0-Catalyzed Asymmetric C(sp^3)–H Activation. *Org. Lett.* **2019**, *21*(3), 812-815 ([‡]contributed equally)

L. Yang, R. Melot, M. Neuburger, O. Baudoin, Palladium(0)-Catalyzed Asymmetric C(sp^3)-H Arylation Using a Chiral Binol-Derived Phosphate and an Achiral Ligand. *Chem. Sci.* **2017**, *8*, 1344-1349

Abbreviations

*	Chiral
Ac	Acetyl
Ad	Adamantyl
AIBN	Azobisisobutyronitrile
All	Allyl
Ar	Aromatic
Asp	Aspartic acid
B	Base
BINOL	1,1′-bi(2-naphthol)
Bn	Benzyl
Boc	*tert*-butyloxycarbonyl
BPA	BINOL Phosphoric Acid
BPin	Pinacolboryl
Bz	Benzoyl
CAAC	Cyclic Alkyl Amino Carbene
CMD	Concerted Metalation-Deprotonation
COD	1,4-cyclooctadiene
conv.	conversion
Coord.	Coordination
Cp	Cyclopentadienyl
CPME	Cyclopentyl methyl ether
Cy	Cyclohexyl
Cyp	Cyclopentyl
Cys	Cysteine
d.r.	diastereomeric ratio
DABAL-Me$_3$	Bis(trimethylaluminum)-1,4-diazabicyclo[2.2.2]-octane
dba	Dibenzylideneacetone
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEE	1,2-diethoxyethane
DFT	Density Functional Theory
DG	Directing Group
DMAc	*N,N*-dimethylacetamide

DMBA	2,2-dimethylbutanoic acid
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
DMSO	Dimethylsulfoxide
dtbbpy	4,4′-Di-tert-butyl-2,2′-dipyridyl
e.r.	enantiomeric ratio
EDG	Electron Donating Group
Et	Ethyl
EWG	Electron Withdrawing Group
Fc	Ferrocenyl
GC-MS	Gas Chromatography - Mass Spectrometry
HAT	Hydrogen Atom Transfer
HetAr	Heteroaromatic
HFIP	1,1,1,3,3,3-Hexafluoro-2-propanol
His	Histidine
HPLC	High-Performance Liquid Chromatography
IAd	1,3-di-1-adamantylimidazolium
IBiox	Imidazolium Bisoxazoline
*i*Bu	Isobutyl
IMes	1,3-bis(2,4,6-trimethylphenyl)imidazolinium
Ind	Indanyl
*i*Pr	Isopropyl
IPr	1,3-bis(2,6-diisopropylphenyl)imidazolium
L	Ligand
LDA	Lithium diisopropylamide
Me	Methyl
Mes	Mesityl
MOM	Methoxymethyl
MS	Molecular Sieves
NADPH	Nicotinamide adenine dinucleotide phosphate
NBS	*N*-bromosuccinimide
*n*Bu	*n*-butyl
NHC	*N*-heterocyclic carbene
NMR	Nuclear Magnetic Resonance
NOESY	Nuclear Overhauser Effect SpectroscopY

Ns	Nitrobenzenesulfonyl
O.A.	Oxidative Addition
Ox.	Oxidation
PG	Protecting Group
Ph	Phenyl
Piv	Pivaloyl
R.E.	Reductive Elimination
RCM	Ring-Closing Metathesis
SpiCy	Spirocyclohexyl
T°C	Temperature
TADDOL	$\alpha,\alpha,\alpha',\alpha'$-tetraaryl-2,2-disubstituted 1,3-dioxolane-4,5-dimethanol
^{t}Bu	*tert*-butyl
Tf	Triflate
TFA	Trifluoroacetic acid
TFE	2,2,2-Trifluoroethanol
THF	Tetrahydrofurane
TIPS	Triisopropylsilyl
TM	Transmetalation
TMB	Trimethoxybenzyl
tol	Tolyl
Ts	Tosyl
VCD	Vibrational Circular Dichroism
π-All	π-allyl
π-cin	π-cinnamyl

Table of Contents

1. General Introduction

1.1. From the Concept of Chirality in Chemistry to Asymmetric Synthesis

1.1.1. Early History of Chirality in Chemistry

The history of chirality in Chemistry began in the nineteenth century with the discovery of the rotation of linearly polarized light. The French physicist F. J. D. Arago observed in 1811 that quartz can induce this rotation.[1] Few years later, in 1820, the English astronomer Sir J. F. W. Herschel observed that quartz can adopt crystalline structures that are mirror images of each other.[2] When linearly polarized light passes through those two types of quartz, an equal amount of rotation is measured, but in opposite directions. In the meantime, in 1815, J. B. Biot discovered that certain liquids and vapors of organic substances can rotate the axis of polarized light as well.[3] This was first observed for oil of turpentine, and then for plenty of other liquids like sugars or tartaric acid solutions.

Later, L. Pasteur made a discovery which is considered as the foundation of stereochemistry.[4] Before he began his experiments on this subject, it was already well-known that tartaric acid was optically active and dextrorotatory in solution. Nevertheless, an isomeric compound of tartaric acid, discovered during the production of natural tartaric acid, and called at that time paratartaric acid, did not show the same optical activity. L. Pasteur observed that crystals of sodium ammonium paratartrate present two distinct structures, which are mirror images of each other. In solution, those two types of crystals present an equal optical activity, but in opposite directions. L. Pasteur proposed that tartaric acid should exist in two chiral forms and concluded that paratartaric acid is an equimolar mixture thereof.

J. H. van't Hoff[5] and J. A. Le Bel,[6] in 1874, proposed that the optical activity of organic compounds may be linked to a tetrahedral geometry of carbon atoms. Indeed, if the 4 atoms linked to a carbon are different, the obtained tetrahedron can exist in two different structures, mirror images of each other. Later, A. Werner similarly proposed an octahedral arrangement for metal complexes showing optical activity.[7]

Since these important discoveries, the chemistry community disclosed that molecular chirality plays a key role in science and technology. Two enantiomers can have extremely different properties, like flavor or odor for example, due to chiral recognition.[8,9] Unfortunately,

these differences can as well transform a useful drug into a terrible poison.[10–12] In regard of the importance of chiral molecules, the field of asymmetric synthesis has become a fundamental topic in research and chemists have now been working intensively since decades on the development of effective ways to control stereochemistry.

1.1.2. Asymmetric Synthesis
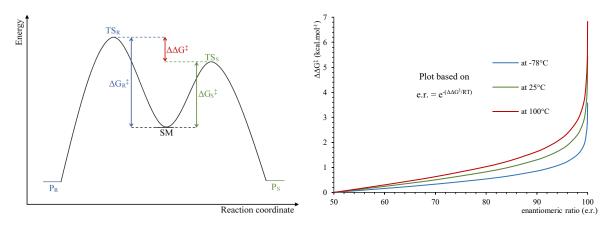
Since the beginning of the twentieth century, researchers have developed many smart strategies to isolate or prepare enantioenriched compounds. The first one, introduced by L. Pasteur, is the isolation of enantioenriched crystals from a racemic mixture.[4] This method is called spontaneous resolution. Besides the important results that this method gave in the early age of asymmetric chemistry, this type of resolution is only possible for a reduced number of compounds. Later, chemists found that resolution of racemates is also possible by formation of ionic or covalent bond with an enantiopure substance, usually an abundant natural molecule. The formed diastereomeric mixture can then be separated via crystallization or chromatography, and the introduced bond cleaved to release the enantioenriched product.[13] This method is still broadly used and convenient on large scale for separation by crystallization, but not general.[14] More recently, a lot of efforts have been made to directly separate enantiomers by chromatography using a chiral stationary phase. This is now the method of choice for the analysis of enantiomeric mixtures.[15] However, the separation of enantiomers via this way is generally limited to small amounts of material.

A more synthetic approach for the preparation of enantioenriched compounds consists in the use of naturally abundant chiral molecules (chiral pool) and further modifications via known synthetic methods.[14] This strategy proved to be useful, but cannot be applied to every synthetic problem. Hence, chemists developed methodologies using chiral reagents or chiral auxiliaries as new ways to prepare enantioenriched compounds.[16] These synthetic tools have become highly popular and are now part of the knowledge that every synthetic chemist should handle. Nevertheless, major drawbacks of such methods are the stochiometric use of a chiral molecule or the additional steps required for installation and removal of an auxiliary. For these reasons, organic chemists turned their attention to asymmetric catalysis as an alternative to other methods. Theoretically, asymmetric catalysis is an ideal solution for synthesizing optically active compounds by chirality multiplication using small amounts of homemade catalysts.[17,18]

General Introduction

1.2. Asymmetric Catalysis

1.2.1. Fundamentals

Catalysis consists in increasing the rate of a reaction by addition of a small amount of catalyst regenerated in the end of the reaction without modification of the overall standard Gibbs energy. In asymmetric catalysis, the objective is to tune carefully a chiral catalyst to induce an energy differentiation in diastereomeric transition states (prochiral substrate-catalyst complex) (**Figure 1.1, left**). This differentiation is induced by the combination of both an ideal three-dimensional arrangement and a suitable kinetic. The enantioselectivity of a catalyzed reaction is exponentially related to the free energy of activation difference ($\Delta\Delta G^{\ddagger}$) (**Figure 1.1, right**). Besides careful control of the enantio-determining step, the catalyst must be well-designed to allow all other steps of the catalytic cycle.[19,20]
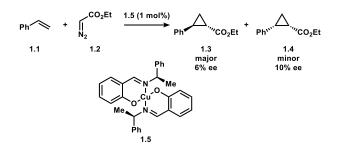
Figure 1.1. *Left – simplified profile of an asymmetric catalysed reaction (one step). Right – free energy of activation as a function of the enantiomeric ratio at different temperatures.*

Relatively to overall activation barriers or individual bond energies,[21] the values of $\Delta\Delta G^{\ddagger}$ necessary to achieve high enantioselectivities are small (**Figure 1.1, right**). Nevertheless, such differentiations are difficult to achieve and require a precise identification of the involved interactions.
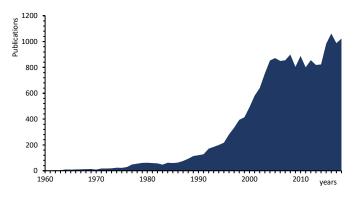
Despite the fact that many beautiful examples of enantioselective reactions can be found in bio- or organocatalysis, this introduction will be focused on metal-based asymmetric catalysis, for the sake of conciseness. The use of a catalyst based on the combination of a metal with chiral ligands constitute a powerful strategy. Indeed, the flexibility of such systems is broad. The range of available metals with their different properties combined with the variety of possible chiral ligands allows a considerable number of possibilities. This explains the popularity of this field since the middle of the twentieth century.

General Introduction

1.2.2. Major Contributions

Despite early examples of asymmetric syntheses of polymers by Natta in the sixties, the first example of asymmetric organometallic catalysis was the cyclopropanation of alkenes described by H. Nozaki, R. Noyori *et al.* in 1966.[22] Although only low enantioselectivity was achieved (6% ee) using a Salen-copper catalyst (**Scheme 1.1**), this result initiated further investigations in this field. Since this decade, the area of asymmetric catalysis has never stopped growing (**Figure 1.2**).

Scheme 1.1. Seminal work on copper-catalyzed asymmetric cyclopropanation.
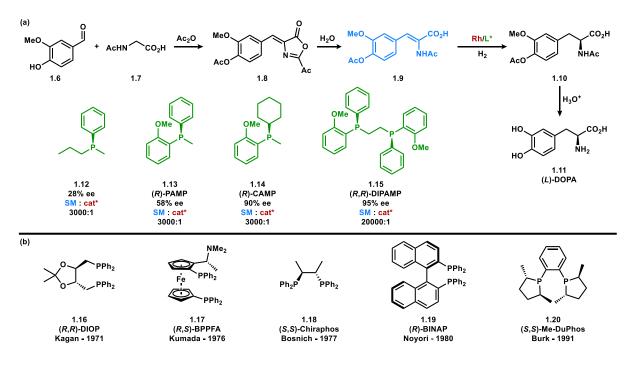
Figure 1.2. SciFinder® results for asymmetric catalysis – publications per year.

Asymmetric hydrogenation is certainly one of the subjects that impacted the most this domain, thanks to the extensive work of R. Noyori, W. S. Knowles, H. Kagan and others.[23] Indeed, the development of C_2-symmetrical diphosphine ligands, like DIOP (**Scheme 1.2b**), which was introduced by Kagan,[24] was a great advancement and inspiration to induce effectively enantioselectivity. This early age of asymmetric hydrogenation culminated in 1975 with the famous Monsanto process for L-dopa.[25] Knowles developed the hydrogenation of **1.9** with rhodium and DIPAMP with excellent enantioselectivity (**Scheme 1.2a**). This was the first industrial application of asymmetric synthesis and the first milestone in this field.
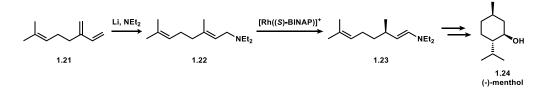
Another major contributor to the popularity of asymmetric methodologies is K. B. Sharpless. His work on the functionalization of olefins is now part of the classics in enantioselective

synthesis. In 1980, he developed the asymmetric epoxidation of allylic alcohols, using a combination of titanium and tartrate esters.[26] This method proved to be broadly applicable and predictable with a simple model despite a non-obvious enantiodetermining dititanium transition-state. Moreover, enantioselective dihydroxylation[27] and aminohydroxylation[28] are also important parts of his legacy to organic chemistry.

Scheme 1.2. *(a) Synthesis of L-DOPA by Knowles and Monsanto. (b) Examples of other diphosphine ligands.*

The development, in 1980, of BINAP (**Scheme 1.2b**) by R. Noyori[29] is also another breakthrough in this history. The combination of this ligand with ruthenium gave impressive results in the hydrogenation of unsaturated substrates such as alkenes or carbonyls. Additionally, BINAP with rhodium allowed the effective isomerization of allyl amines to enamines. For instance, this found an industrial application in the synthesis of (-)-menthol (**Scheme 1.3**), known as the Takasago process.[29,30]

Scheme 1.3. *Takasago process for the industrial synthesis of (-)-menthol.*

There are many other excellent chemists who contributed to the notoriety of this field and that should be cited here. As examples, B. M. Trost, E. N. Jacobsen, H. Yamamoto, M. Shibasaki, D. MacMillan, or A. Pfaltz and his work on the development of new ligand classes,

such as semicorins, bisoxazolines or PHOX.[31,32] All the work done by those giants of asymmetric catalysis constituted solid foundations and an inspiration for our contemporary research.

1.3. Metal-Catalyzed C-H Bond Functionalization
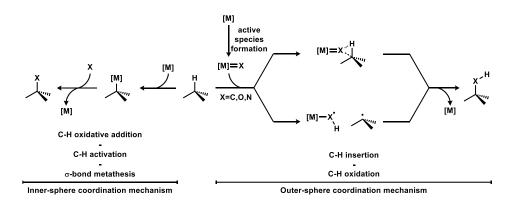
1.3.1. Generalities

The direct functionalization of C-H bonds is one of the long-standing objectives in organic synthesis. Indeed, C-H bonds are the most common bonds found in organic materials. Direct functionalization of this type of bonds would avoid classical functional groups manipulations and bring to more atom-economical processes. Most reactions developed in organic synthesis take advantage of polarized or polarizable reactive bonds. In contrast, aliphatic or aromatic C-H bonds are intrinsically stable due to their low polarization and strong σ-bond character.[33] Nevertheless, the cleavage of such bonds in alkanes or arenes is commonly used since thousands of years to generate energy via combustion. Even in organic synthesis, radical cleavage, carbene insertion or metalation with strongly basic reagents have been known for a long time. Thus, the challenge in the development of reactions for C-H bond functionalization is to conduct this type of transformations selectively. The selectivity of the previously enounced transformations can be predicted thanks to electronic or steric factors. However, selectivity becomes a challenge when a non-reactive C-H bond must be functionalized preferentially to another or when multiple reactive C-H bonds are present. One solution found to solve this issue was to use a preinstalled functional group to selectively generate a reactive species. This reactive species will then react with a close C-H bond for further functionalization.[34–36] This strategy was used for radical shift and carbene intramolecular C-H insertion. Moreover, such methods were successfully applied in total synthesis.[37,38] Over the time, metal-catalysis has emerged as an elegant solution and toolbox for C-H functionalization. Different reactivities were observed and further developed to promote a wide range of transformations.[39]

1.3.2. Classification

Metal-catalyzed C-H functionalization can be divided into five major groups: 1) C-H oxidation; 2) C-H insertion; 3) C-H oxidative addition; 4) C-H activation; 5) σ-bond metathesis. The first two involve an outer-sphere coordination mechanism, without formation of a carbon-metal bond, but only via coordination of the oxo-metal or carbenoid/nitrenoid-metal species. The last three imply an inner-sphere coordination mechanism, with formation of a carbon-metal

bond generated via direct oxidative addition, C-H activation or σ-bond metathesis (**Scheme 1.4**).[39,40]

Scheme 1.4. Different groups of metal catalyzed C-H functionalization.
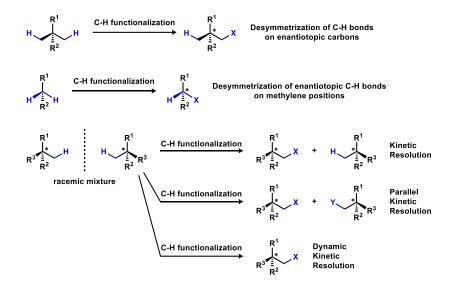
These different types of C-H functionalization possess their own particularities, advantages and drawbacks due to distinct mechanisms and related interactions. In the next part, we will discuss the application of these different strategies for asymmetric $C(sp^3)$-H functionalization. Moreover, we will focus on enantioselective metal-catalyzed $C(sp^3)$-H functionalization reactions in which the generated stereocenter results from the $C(sp^3)$-H bond cleavage exclusively. Therefore, diastereoselective reactions, $C(sp^2)$-H functionalization and enantioselective reactions relying on another enantio-determining step will not be discussed.

1.4. Asymmetric Metal-Catalyzed C-H Functionalization

1.4.1. Generalities

In asymmetric catalyzed $C(sp^3)$-H functionalization, the generation of chiral centers can be divided into three categories.[41,42] First, the desymmetrization of $C(sp^3)$-H bonds located on two enantiotopic carbons. In this case, the obtained stereocenter is created in an adjacent position to the activated site. Secondly, the desymmetrization of the two enantiotopic hydrogen atoms of a methylene position with generation of the chiral center directly at the activated site. The last one consists in the resolution of a racemic mixture. This third category contains only few examples that can be divided in three subcategories. In the case of pure kinetic resolution, only one enantiomer of the racemic starting material is functionalized, and the other enantiomer can be recovered enantioenriched and unchanged. Secondly, parallel kinetic resolution, where both enantiomers react to form two different enantioenriched products, and finally, dynamic kinetic resolution, where the racemic mixture is transformed to only one enantiomer. At the time this
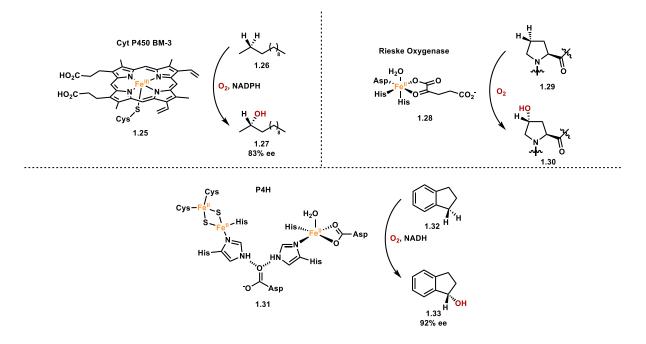
manuscript was written and to the best of our knowledge there was no reported example of dynamic kinetic resolution corresponding to the criteria of this introduction (**Scheme 1.5**).

Scheme 1.5. *Different categories of asymmetric C(sp³)-H functionalization reactions.*
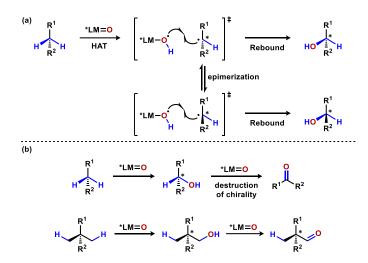
1.4.2. C(sp³)-H Oxidation

C-H oxidation is a biomimetic approach for C-H functionalization. Indeed, this strategy is directly inspired from naturally occurring metalloenzymes that catalyze C-H oxidation. There are many examples of metalloenzymes able to oxidize C-H bonds with an impressive level of chemo- and enantioselectivity (**Scheme 1.6**).[43–45] Thus, it is not surprising that chemists took the opportunity to reproduce those properties to build new synthetic tools.[46]

Scheme 1.6. *Examples of C-H oxidation by metalloenzymes.*

General Introduction

C-H oxidation occurs via an outer-sphere mechanism composed of two major steps. First, a hydrogen atom transfer (HAT) to a metal-oxo complex proceeds to form a radical pair. Then, after a fast O-rebinding, the oxidized product is formed. Enantioselectivity in this process comes from both steps. Besides the enantioselectivity of the first HAT step, the radical lifetime, and the enantioselectivity of the rebound may have a determining effect on the overall stereoselectivity of the reaction. Indeed, depending on the nature of the radical intermediate, racemization can occur prior to rebounding (**Scheme 1.7a**). Moreover, in this type of systems, the necessity to use a strong oxidant capable to oxidize aliphatic C-H bonds induces the risk of possible overoxidation. For this reason, asymmetric C-H oxidation of enantiotopic protons of a methylene position is more challenging than desymmetrization. Indeed, in desymmetrization, overoxidation would lead to the corresponding carbonyl with an adjacent stereocenter untouched (**Scheme 1.7b**).
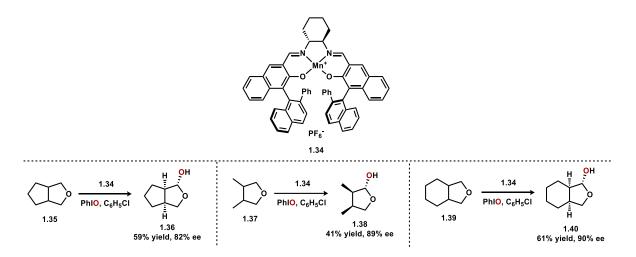
***Scheme 1.7**. (a) General mechanism of C-H oxidation. (b) Overoxidation issue in asymmetric C-H oxidation.*

Selectivity of C-H oxidation is controlled by the HAT process and depends on many factors. Moreover, structural properties play a key role due to radical stabilization. However, selectivity also depends on other electronic effects and interactions, such as torsional and 1,3-diaxial strains, as well as on the solvent and Lewis acid used.[47,48]
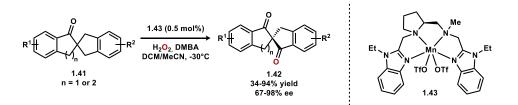
The first example of desymmetrization via C-H oxidation was reported by T. Katsuki in 1998.[49] C-H oxidation of tetrahydrofuran and tetrahydropyran derivatives was reported using 2 mol% of Mn-salen complex **1.34** and iodosobenzene as stochiometric oxidant in chlorobenzene at -30°C. The corresponding enantioenriched lactols were isolated in 41-61% yield with 82-90% ee (**Scheme 1.8**). Only small amounts of overoxidized lactones were observed probably

due to steric congestion in the adjacent position. T. Katsuki then applied this methodology to pyrolidines with a broader scope.[50]
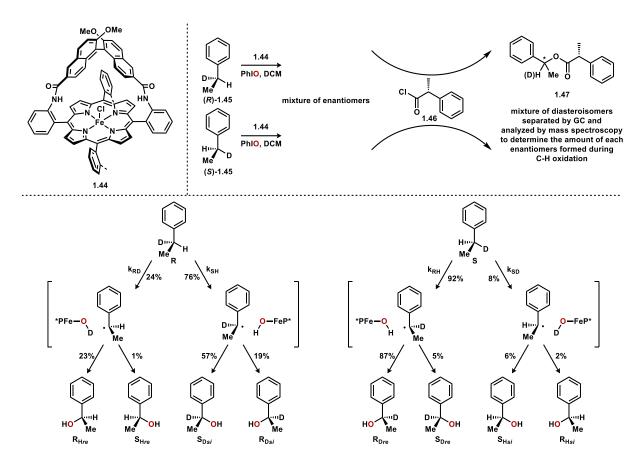
Scheme 1.8. Desymmetrizing C-H oxidation using Mn-salen complex.

Different methodologies were developed for the desymmetrization of indane derivatives to form the corresponding enantioenriched indanone products via enantioselective C-H overoxidation.[46] For example, Nam and Sun prepared enantioenriched spiroindanones using catalyst **1.43** with hydrogen peroxide as stochiometric oxidant in presence of 2,2-dimethylbutanoic acid (DMBA) (**Scheme 1.9**). This report presents a highly site- and enantioselective C-H oxidation under mild conditions and a low catalyst loading.[51]
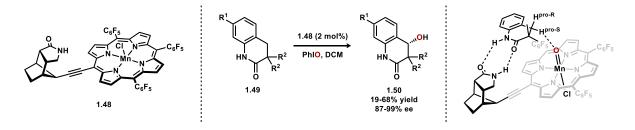
Scheme 1.9. Synthesis of spirocyclic indanones via enantioselective C-H oxidation.

Besides other examples of desymmetrization, J. Groves, a pioneer in the field of asymmetric C-H oxidation described the enantioselective functionalization of enantiotopic methylenes protons. His first reports were published in 1989 and 1990 and present the oxidation of benzylic positions using chiral iron porphyrin catalyst **1.44**.[52] Despite moderate yields and enantioselectivities, a relevant study was done with deuterated ethylbenzene indicating that HAT is the enantiodetermining step of this process (**Scheme 1.10**). Moreover, a strong isotope effect of 6.4 was accompanied with a higher racemization rate of the unfavored radical.
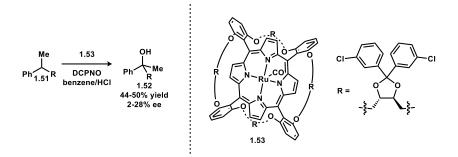
Scheme 1.10*. C-H oxidation of enantiopure deuterium-labeled ethylbenzene and analysis (spectroscopy, each enantiomer).*

Since this discovery, asymmetric C-H oxidation of benzylic positions has been extensively studied by different groups. For example, T. Bach described recently the enantioselective C-H oxidation of 3,4-dihydroquinolones using a Mn porphyrin complex. In this case, the incorporation of a chiral template, able to interact via H-bonding with the substrate, on the porphyrin ligand was determining to achieve high enantioselectivity (**Scheme 1.11**).[53]

Scheme 1.11*. Asymmetric C-H oxidation of 3,4-dihydroquinolones.*
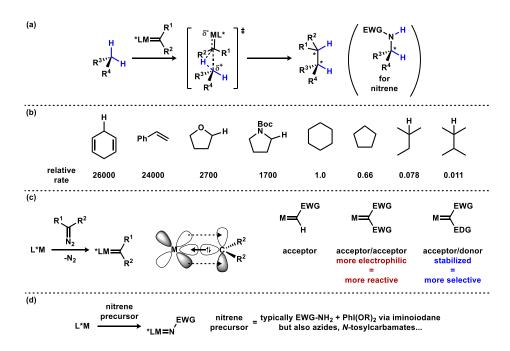
Kinetic resolution is underrepresented in this field. The first report was published by Z. Gross in 1999. Resolution of tertiary alkanes was examined using chiral Ru porphyrin complex **1.53** and 2,6-dichloropyridine *N*-oxide. However, moderate enantiomeric excess were observed.[54]

***Scheme 1.12**. Kinetic resolution of alkanes via C-H oxidation.*

1.4.3. C(sp³)-H Insertion

Asymmetric C-H insertion is an important field in enantioselective C-H functionalization.[55–57] As for C-H oxidation, C-H insertion also proceeds via an outer-sphere mechanism. After formation of a metal carbenoid or nitrenoid, C-H insertion occurs via a 3-centers transition-state (**Scheme 1.13a**). Due to the formation of a partial positive charge on the activated site during C-H insertion, this type of transformations occurs preferentially at carbocation-stabilizing positions. However, steric interactions play a crucial role as well and more accessible C-H bonds are more prone to react (**Scheme 1.13b**).
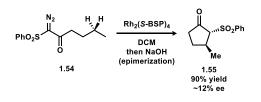
***Scheme 1.13**. (a) C-H insertion mechanism. (b) Relative rates of reactivity in C-H insertion with $Rh_2(DOSP)_4$. (c) Metal carbenoids formation – type of carbenoids. (d) Metal nitrenoids formation.*
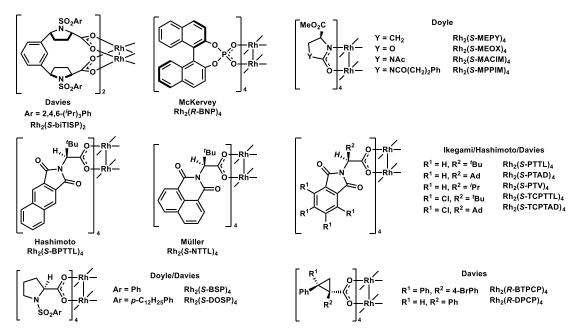
In intramolecular cases, formation of 5-membered rings is favored for carbenoids and carbamate nitrenoids, whereas 6-membered rings are preferentially formed for sulfamate nitrenoids. The nature of the employed carbene precursor is also determining for the observed reactivity and the corresponding metal carbenoids can be divided into three groups: 1) acceptor;

2) acceptor/acceptor; 3) acceptor/donor. Acceptor refers to electron withdrawing groups and, in contrary, donor refers to electrondonating groups. Acceptors amplify the electrophilic character and the reactivity of carbenoids, whereas donors stabilize carbenoids and improve their selectivity (**Scheme 1.13c**). In the case of carbenoids with two different substituents, up to two stereocenters are created during C-H insertion. Therefore, diastereomeric mixtures are formed. Due to the additional diastereoselectivity issues, the outcome of such transformations is more difficult to control. A well-designed catalyst is required to force the approach of the substrate from one selected face of the carbenoid and to control the regioselectivity.[58] Nevertheless, this particularity allows the formation of a stereocenter, even in the case of C-H insertion into a non-prochiral position.

In 1990, M. McKervey was the first to report an enantioselective C-H insertion using the prolinate dirhodium complex Rh$_2$(*S*-BSP)$_4$ (**Scheme 1.14**).[59] Only one reaction was described with high yield and moderate enantioselectivity (90%, 12% ee). Nevertheless, this result brought interest for asymmetric carbenoid C-H insertion.
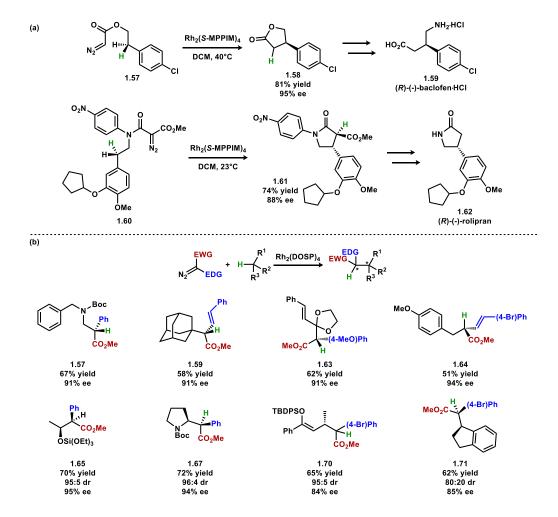
Scheme 1.14. First example of asymmetric carbenoid C-H insertion
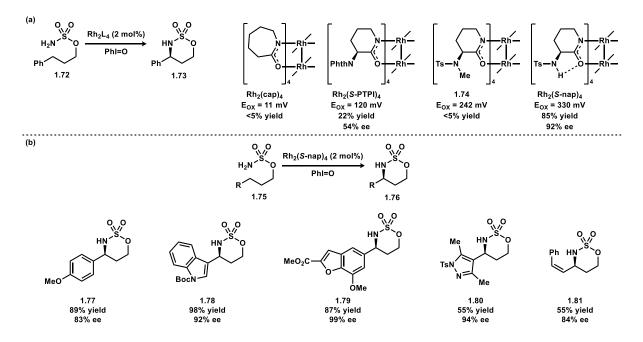
Scheme 1.15. Selected examples of dirhodium catalysts for carbenoid C-H insertion.

General Introduction

During the following years, different major contributors in this field concentrated their efforts on the development of new chiral catalysts to improve enantio-, diastereo- and chemoselectivity. Their attention was mainly focused on amino acid-based dirhodium catalysts (**Scheme 1.15**), which are also effective for enantioselective cyclopropanation.[60] However, other metals, such as copper[61–64] or iridium[65] also proved efficient to promote carbenoid C-H insertion. The first good results were obtained for intramolecular C-H insertion[66–75] and were successfully applied to the synthesis of active molecules (**Scheme 1.16a**).[76,77] Then Rh$_2$(DOSP)$_4$, developed by H. Davies, found broad applications in intermolecular carbenoid C-H insertion and became one of the most general catalyst in this field (**Scheme 1.16b**).[58] Moreover, enantioselectivity and diastereoselectivity are well rationalized with this catalyst thanks to extensive studies by H. Davies. In addition, more recent reports present impressive chemoselectivity for specific C-H bond functionalization of complex molecules in intermolecular asymmetric carbenoid C-H insertion thanks to fine catalyst and carbenoid precursor design.[78–82]

Scheme 1.16. *(a) Representative applications of intramolecular carbenoid C-H insertion. (b) Selected examples of intermolecular carbenoid C-H insertion with Rh$_2$(DOSP)$_4$ as catalyst.*

Enantioselective C-H amination via insertion appeared later than the previously discussed chemistry. In 1997, P. Müller described the asymmetric amination of indane using $Rh_2(BNP)_4$ and excess NsN=IPh leading to the corresponding indanol in 71% yield and 33% ee.[83] Then, similar intermolecular and intramolecular reactions were examined by the same group and the Davies group.[84–86] However, the obtained ee were generally below 80% and an excess of substrate or oxidant was necessary. In complement, P. Dauban recently described a general and efficient methodology for the intermolecular amination of benzylic positions using a similar strategy.[87] One major breakthrough came in 2011 with the work of J. Du Bois and his design of a chiral dirhodium catalyst with higher redox potential and more donating ligands to stabilize nitrene intermediates (**Scheme 1.17a**).[88] This allowed excellent levels of reactivity and enantioselectivity. Even allylic C-H amination, for which competitive aziridination is usually observed, was described (**Scheme 1.17b**). Ruthenium complexes also proved efficient for enantioselective C-H amination, but, in this case, the mechanistic pathway is not always clear.[89,90] Indeed, a radical C-H abstraction pathway with fast rebinding is also reasonable as for C-H oxidation. Moreover, S. Chang, G. He and G. Chen recently reported a highly enantioselective intramolecular C-H amination methodology via nitrene insertion with iridium for the preparation of a variety of γ-lactams.[91,92]
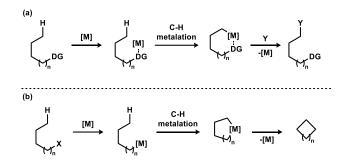
Scheme 1.17. (a) Catalyst design based on redox potential. (b) Selected examples of the reaction scope.

1.4.4. C(sp³)-H Activation via Oxidative Addition
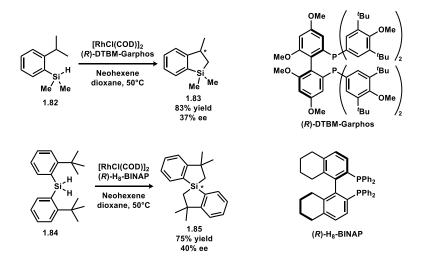
In the next two parts, the described processes will occur via metalation of C-H bonds. For this type of transformations, two strategies are used, namely non-directed and directed C-H

metalation. Metalation can be directed via coordination of the metal to a Lewis basic functional group of the substrate or by oxidative addition (**Scheme 1.18**). Hence, the metal is placed in close proximity to the targeted C-H bonds, resulting in a lower activation barrier and a better selectivity for the metalation step compared to non-directed cases.

Scheme 1.18. Strategies for directed C-H metalation via: (a) coordination or (b) oxidative addition.
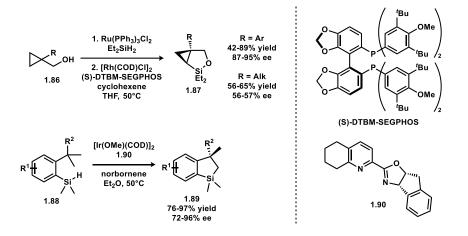
Oxidative addition in unactivated C-H bonds is one possibility for C-H metalation and was observed since early ages of organometallic chemistry with a wide range of metals.[20,40] The C-H oxidative addition process occurs via the same interactions that the one responsible for the H-H oxidative addition. First, a σ-complex is formed between the metal center and a C-H bond via donation of the σ-orbital into a metal orbital and back-donation of metal orbitals to the σ*-orbital. Then, oxidative addition proceeds through a flow of electrons from the C-H σ-bond to the metal and from π-orbitals of the metal C-H σ*-orbital. Despite many interesting examples of methodologies taking advantage of this process,[93–95] only few examples of asymmetric reactions have been described.

Scheme 1.19. Asymmetric dehydrogenative silylation reported by Murai and Takai.
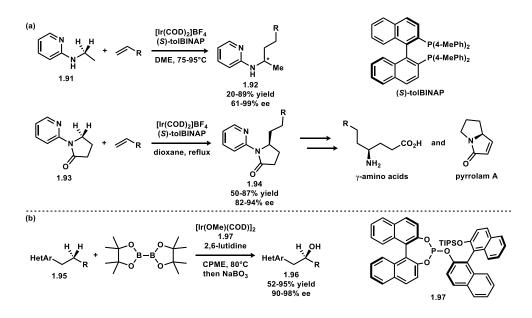
One of them was reported by M. Murai and K. Takai in 2015, in the context of dehydrogenative silylation with rhodium and phosphine ligands.[96] In this case, oxidative

addition into the Si-H bond serves to direct the subsequent oxidative addition into the C-H bond of one enantiotopic methyl group. A moderate enantioselectivity was observed for desymmetrization of substrates **1.82** and **1.84** using different chiral diphosphines (**Scheme 1.19**). One year later, J. Hartwig developed a similar process for the dehydrogenative enantioselective silylation of cyclopropanes using Rhodium and (*S*)-DTBM-SEGPHOS.[97] The reaction proved to be effective with a wide range of cyclopropanes bearing an aromatic substituent, but gave lower enantioselectivity with alkyl moieties. The same group also generalized the desymmetrization of isopropyl groups previously introduced by Murai and Takai using iridium and *N*,*N*-ligand **1.90 (Scheme 1.20)**.[98] The mechanism of this reaction was further examined by G. Huang.[99] In this study, the C-H oxidative addition was demonstrated to be both the enantio- and rate-determiming step, in accordance with the observed enantiomeric excess and kinetic isotope effect.

Scheme 1.20. Improvement of asymmetric dehydrogenative silylation by Hartwig.

T. Shibata took advantage of a pyridine directing group for the alkylation of 2-(ethylamino)pyridine and *N*-(2-pyridyl)-γ-butyrolactam in α-position to the nitrogen using iridium combined with (*S*)-tolBINAP. This methodology was applicable to diverse substrates and alkene partners (**Scheme 1.21a**).[100–102] Moreover, the synthesis of γ-amino acids and pyrrolam A were described using this strategy. Similarly, M. Sawamura explored the enantioselective C-H borylation of methylene positions using pyridine as a directing group. In a first report, they showed a moderate induction using rhodium or iridium combined with a BINOL derived phosphoramidites,[103] first introduced by J. Hartwig.[104] More recently, the same group described a more efficient system using iridium and the bis(BINOL)-based phosphite **1.98**.[105] These conditions gave excellent yields and enantioselectivities for diverse substrates with nitrogen-based heteroaromatic directing groups (**Scheme 1.21b**).
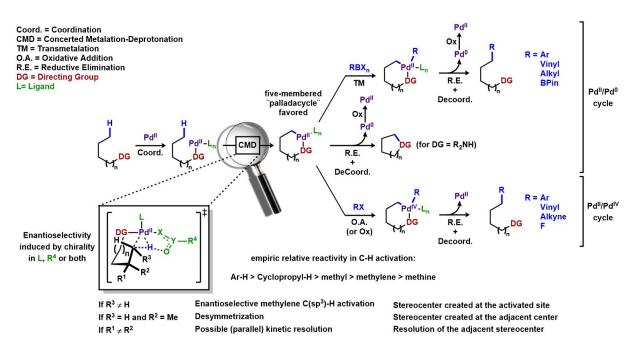
Scheme 1.21. *(a) Asymmetric directed C-H alkylation of 2-aminopyridine derivatives. (b) Enantioselective directed C-H borylation of methylene positions.*

1.4.5. Base mediated C(sp³)-H Activation

First of all, C-H activation is a term widely employed for a range of different reactions. It is generally admitted that this term refers to reactions between a transition-metal complex and a C-H bond with formation of a new metal-carbon bond. Here, this expression will refer to metalation via assisted C-H bond cleavage usually named CMD for concerted metalation-deprotonation or AMLA for ambiphilic metal-ligand activation.[106–114] In this process, the oxidation state of the metal stays unchanged in contrary to previous part examples. Nevertheless, reactions discussed in part 1.4.4 can be classified as C-H activation processes as well.
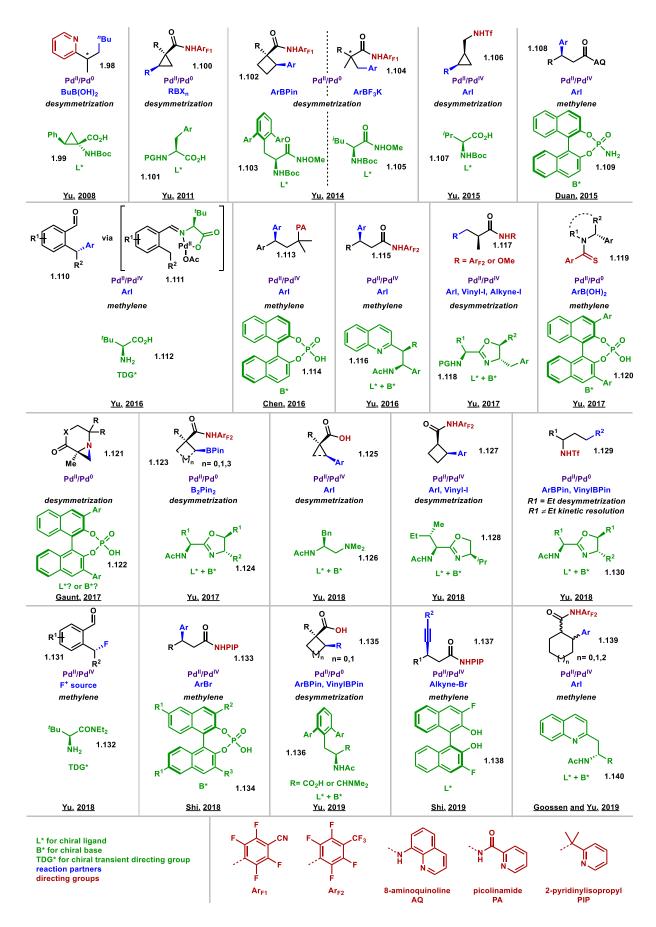
As previously discussed for C-H oxidative addition, two main strategies are used in enantioselective C(sp³)-H activation, one via coordination of the metal to the substrate, usually called directed, and the other via oxidative addition. Palladium is the most commonly used metal for asymmetric transformations of this kind. This is true for both approaches due to the ability of Pd(II) to effectively promote CMD processes with C(sp³)-H bonds, although other metals[115–117] can form competent catalysts. In the case of directed C-H activation, a source of Pd(II) is used. After coordination to the substrate via a directing group, C-H activation occurs leading to the corresponding alkyl-palladium(II) intermediate. Then, different pathways are possible (**Scheme 1.22**). The first one is a transmetalation with a nucleophile followed by reductive elimination, decoordination of the formed Pd(0) and release of the functionalized product. In this case, an oxidant is needed to regenerate Pd(II) and close the catalytic cycle. The

second one is the direct reductive elimination with formation of a bond between the activated position and the directing group, again an oxidant is needed to oxidized Pd(0) to Pd(II). The third one is an oxidative addition into an electrophilic reagent to form a Pd(IV) intermediate followed by reductive elimination, decoordination of Pd(II) and formation of the product.

Scheme 1.22. *Mechanisms and information about directed C(sp^3)-H activation via Pd^{II}/Pd^0 and Pd^{II}/Pd^{IV} pathways.*
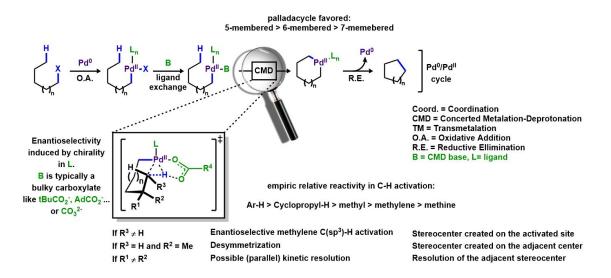
J.-Q. Yu is the most prolific contributor in enantioselective directed C(sp^3)-H activation. Since 2008, both desymmetrization and methylene enantioselective reactions have been developed for a wide range of substrates and reaction partners (**Scheme 1.23**).[118–134] In complement, B.-F. Shi extended those asymmetric methods to aryl bromide and alkyne bromide partners.[135,136] Moreover, the use of the "transient directing group" concept in asymmetric C(sp^3)-H activation by J.-Q. Yu in 2016 opened new opportunities.[129] Prior to that a classical chiral ligand strategy was generally used, even if the use of a chiral CMD base for enantioselective directed C(sp^3)-H activation was meanwhile introduced by W.-L. Duan[137] and G. Chen.[138] Besides, conjoint work of J.-Q. Yu and K. Houk on mechanistic calculations[130,131] suggests that acetylated ligands participate in the CMD process as deprotonating agents. Therefore, this type of ligands could be classified as bifunctional. In 2017, M. Gaunt reported an example of enantioselective amination via intramolecular reductive elimination between the amine directing group and the activated site using a BINOL-derived chiral phosphoric acid.[139] In this case, the exact role of the chiral phosphoric acid could not be clearly elucidated and it might act as a classical ligand or as the CMD base.

Scheme 1.23. *Major contributions in enantioselective directed C(sp³)-H activation.*

General Introduction

One example of kinetic resolution has been presented in this field by J.-Q. Yu in the context of an enantiotopic carbons desymmetrization methodology using a Pd(II)/Pd(0) system with an acetyl protected amino oxazoline (APAO) ligand and a NHTf directing group. Indeed, six 2-substituted propyl amines were resolved with excellent enantiomeric excess and moderate yields.[122] A recent collaboration between J.-Q. Yu and L. Gooßen presented an interesting methodology for the enantio- and diastereoswitchable C-H arylation of methylene groups in cycloalkanes controlled by both reaction partners and a fine choice of the ligand. This method allowed an unprecedented access to the four possible chiral products via one reaction.[126]
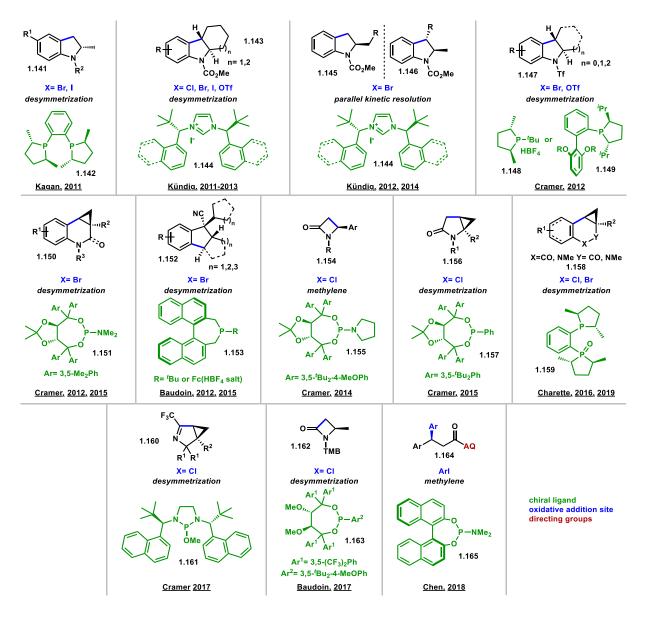
The second approach via oxidative addition is complementary to the first one. Indeed, C(sp^3)-H activation via this way is the method of choice for the preparation of cyclic enantioenriched products for which coordination allows intermolecular reactions. A typical catalytic cycle starts with oxidative addition into a carbon-halogen or pseudohalogen bond, typically an aryl halide, aryl triflate, alkenyl halide or a 2-chlorocabonyl. Then, the halide on the palladium is exchanged for a base, typically a bulky carboxylate like pivalate. Then, metalation occurs through CMD process forming the corresponding palladacycle, which undergoes reductive elimination to regenerate Pd(0) and release the corresponding cyclized product (**Scheme 1.24**). A substochiometric amount of CMD base is generally used in combination with a stochiometric amount of an inorganic base to regenerate the CMD base after C-H activation.

Scheme 1.24. *Mechanism and information about oxidative addition induced C(sp^3)-H activation via Pd^0/Pd^{II} pathway.*

Major contributions in this field are presented in **Scheme 1.25**. The first enantioselective reactions based on this strategy were developed by P. Kündig[140,141] and H. Kagan[142] in 2011 for the synthesis of indolines. Their work relies on the desymmetrization of enantiotopic carbons.

General Introduction

The methodology of P. Kündig using a bulky chiral NHC, inspired from H. Herrmann NHC,[143] proved to be more effective and general than the use of Me-DUPHOS by H. Kagan. Moreover, the work of P. Kündig covers the desymmetrization of two enantiotopic methylene carbons, even though the activation of methylene C-H bond is known to be challenging. In addition, the scope of the reaction was extended and presented in another report with mechanistic experiments and calculations.[144] P. Kündig also reported the only example of parallel kinetic resolution in $C(sp^3)$-H activation with the same catalytic system, also in the context of indolines synthesis.[145,146]

Scheme 1.25. *Major contributions in enantioselective oxidative addition induced $C(sp^3)$-H activation.*

A similar indolines synthesis was reported in 2012 by N. Cramer. He introduced a new family of phosphine ligands inspired from a Buchwald-type backbone and containing a C_2-symmetric chiral phospholane moiety.[147,148] In this case, triflates were used as oxidative addition sites and

General Introduction

both enantiotopic methyl and methylene carbons were functionalized with success. The same group reported the use of TADDOL-derived phosphoramidite and phosphonite ligands for different cyclizations.[149–152] The first one was the synthesis of enantioenriched tetrahydroquinolones[149] via desymmetrization of gem-disubstituted cyclopropyls in 2012. This methodology was extended few years later to the synthesis of dihydroisoquinolones.[151] A similar example was recently reported by A. Charette using BozPhos, the monophosphine oxide analogue of Me-DUPHOS.[153,154] The second one was the synthesis of β- and γ-lactams from α-chloroamides.[150,152] In the case of β-lactams,[150] desymmetrization of enantiotopic protons on a benzylic position was achieved in high yields and enantioselectivities. For γ-lactams,[152] chirality came from the desymmetrization of the enantiotopic carbons of a gem-disubstituted cyclopropyl similarly to the previous example. In 2012, our group reported the synthesis of enantioenriched indanes via the desymmetrization of isopropyl groups using binepine ligands with high diastereoselectivities and promising enantioselectivities.[155] After extensive ligand synthesis and screening, higher enantioselectivities and excellent diastereoselectivities could be reported. Furthermore, this system could be used for the desymmetrization of cycloalkanes leading to indanes containing up to three adjacent stereocenters. In complement, calculations were done to rationalize the enantio- and diasteroselective outcome of this transformation.[156] N. Cramer reported an interesting example of cyclopropyl desymmetrization using non-classical trifluoroacetimidoyl chloride as oxidative addition sites combined with a new family of chiral alkoxy diazaphospholidines inspired from the NHCs developed by P. Kündig. In the context of β-lactams synthesis from carbamoyl chloride,[157] our group showed the possible desymmetrization of two enantiotopic methyl groups using an elaborated TADDOL-derived phosphonite with good induction and yield on one example. Unfortunately, this method was less efficient for other substrates.[158]

A recent intriguing example was reported by G. Chen in the context of enantioselective directed $C(sp^3)$-H arylation.[159] This methodology seems really similar to classical directed C-H arylations discussed previously. However, mechanistic investigations tend to indicate that this transformation occurs through an unusual Pd(0)/Pd(II) pathway. The proposed mechanism, accordingly, is similar to intramolecular C-H arylation through oxidative addition, but in an intermolecular fashion. If this pathway is confirmed in the future, this would open a new type of enantioselective $C(sp^3)$-H arylation in the frontier of both fields.

General Introduction

1.5. Research Aim and Work Described in This Thesis

As Shown in the previous parts, over the last thirty years, metal-catalyzed enantioselective $C(sp^3)$-H functionalization has emerged as an incredibly powerful tool for a variety of transformations. Our research group topics in C-H functionalization bring us to the limits of possible chiral or non-chiral transformations by exploring or improving new or existing concepts. We aim to develop new methods and apply them to the synthesis of natural products, bioactive molecules and valuable building blocks.

In this thesis, we will first discuss a chiral CMD-base approach for the enantioselective synthesis of indolines via $C(sp^3)$-H arylation. At the time, in 2015-2016, this approach had never been used effectively even in directed C-H activation and appeared to be an interesting alternative to the classical chiral ligand strategy.

The second part will be dedicated to the divergent synthesis of (nor)illudalane sesquiterpenes based on a $C(sp^3)$–H activation strategy. Both racemic and enantioselective syntheses will be discussed.
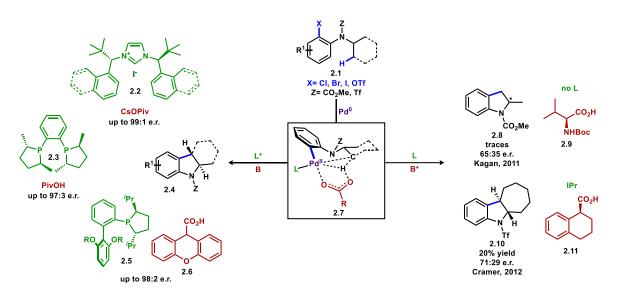
Finally, in the third part, promising results on enantioselective indanes synthesis via activation of enantiopic protons of a methylene position will be presented. This methodology could be potentially applied to the synthesis of different natural products and scaffolds of interest.

General Introduction

General Introduction

Palladium(0)-Catalyzed Asymmetric C(sp3)-H Arylation: the Chiral Anion Approach

2. Palladium(0)-Catalyzed Asymmetric C(sp^3)-H Arylation: the Chiral Anion Approach

∗ *Work done in collaboration with Dr. Lei Yang during his postodoctoral stay in our group.*

2.1. Introduction

As presented previously, the racemic synthesis of indolines described by H. Ohno[160] inspired the development of several enantioselective C(sp^3)-H activation reactions and indolines became targets of choice for this kind of transformations. Considering the CMD transition-state, different groups proposed methodologies based on chiral ligands.[140–142,144–148] Indeed, this strategy proved worthwhile and gave impressive results. Nevertheless, knowing the implication of a base in this transition-state, the use of a chiral base could also effect asymmetric induction. Actually, this opportunity was explored by H. Kagan[142] and N. Cramer[148] and was mentioned as foot notes in their early reports on the enantioselective synthesis of indolines (**Scheme 2.1**). H. Kagan observed traces of indoline product **2.7** with 65:35 e.r. when 50 mol% of *N*-Boc-*L*-valine was used instead of pivalic acid even in absence of a phosphine ligand. N. Cramer observed the formation of indoline **2.10** in 20% yield and 71:29 e.r., in the context of methylene carbons desymmetrization, using chiral carboxylic acid **2.11** combined with IPr NHC ligand instead of **2.6**.

***Scheme 2.1**. Overview of the results obtained for the enantioselective synthesis of indolines via C(sp^3)-H arylation using chiral ligands or chiral CMD bases.*

Based on these results, we decided to investigate in more details the synthesis of chiral indolines via C(sp^3)-H activation using a chiral base. In order to increase our chances to find a

Palladium(0)-Catalyzed Asymmetric C(sp3)-H Arylation: the Chiral Anion Approach

Brønsted base which would induce high levels of enantioselectivity and allow a smooth reactivity, we needed a family of bases with tunable steric, electronic and acidobasic properties. These features are comparable to the ones required to develop a new family of ligands.

R^1 and R^2 tunable to modify electronic and steric properties and interactions
Modification of Y to adjust the pKa
possible partial aromatic reduction to modify dihedral angle (θ)
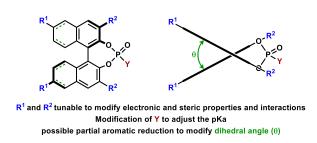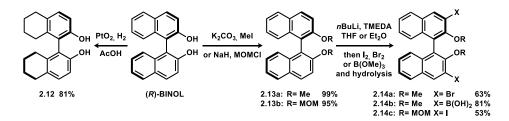
Figure 2.1. Possible modifications of BPAs.

We turned our attention toward BINOL-derived phosphoric acids (BPAs) combined with an inorganic base. Indeed, this type of Brønsted acids are known to be highly tunable (**Figure 2.1**) and proved to be effective in cooperative palladium catalysis.[161–163] Moreover, as we started this work, W.-L. Duan reported the use of a BPA derivative in enantioselective directed C(sp^3)-H arylation.[137] This comforted us in our choice. Of note, while this work was ongoing and almost complete, the same group reported the use of the simplest BPA for the desymmetrization of ferrocene via C(sp^2)-H arylation.[164] In this context, they extended their methodology to the synthesis of two indolines and obtained up to 47% yield and 83:17 e.r..
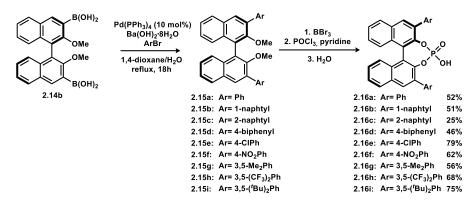
2.2. Preparation of Binol-Derived Phosphoric Acids

For this project, we first synthetized a library of BPAs following known routes.[165-175] Binol derivatives with different scafolds were prepared as precursors (**Scheme 2.2**). Then, (*R*)-BINOL was protected with methyl iodide or MOMCl. The obtained ethers were subjected to double ortho-lithiation and the lithiated species obtained quenched with different reagents to yield the corresponding 3,3'-bromide **2.14a**, boronic acid **2.14b** and iodide **2.14c**. We also reduced (*R*)-BINOL to the corresponding (*R*)-H$_8$-BINOL **2.12** by hydrogenation.
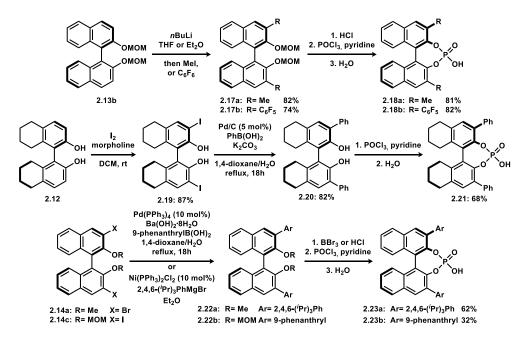
Scheme 2.2. Preparation of BPA precursors.

Palladium(0)-Catalyzed Asymmetric C(sp3)-H Arylation: the Chiral Anion Approach

We then engaged boronic acid **2.14b** into Suzuki cross-couplings with a variety of aryl bromides. The corresponding arylated products were demethylated with BBr$_3$, phosphorylated with POCl$_3$ and finally quenched with water to yield phosphoric acids **2.16a-i** (**Scheme 2.3**).

2.15a: Ar= Ph
2.15b: Ar= 1-naphtyl
2.15c: Ar= 2-naphtyl
2.15d: Ar= 4-biphenyl
2.15e: Ar= 4-ClPh
2.15f: Ar= 4-NO$_2$Ph
2.15g: Ar= 3,5-Me$_2$Ph
2.15h: Ar= 3,5-(CF$_3$)$_2$Ph
2.15i: Ar= 3,5-(^{t}Bu)$_2$Ph

2.16a: Ar= Ph   52%
2.16b: Ar= 1-naphtyl   51%
2.16c: Ar= 2-naphtyl   25%
2.16d: Ar= 4-biphenyl   46%
2.16e: Ar= 4-ClPh   79%
2.16f: Ar= 4-NO$_2$Ph   62%
2.16g: Ar= 3,5-Me$_2$Ph 56%
2.16h: Ar= 3,5-(CF$_3$)$_2$Ph 68%
2.16i: Ar= 3,5-(^{t}Bu)$_2$Ph 75%

Scheme 2.3. Preparation of BPAs bearing different aromatic substituents in 3,3' positions.

For some substituents, other procedures were used. **2.13b** was lithiated and quenched with methyl iodide and hexafluorobenzene to yield **2.17a,b** respectively, which were then transformed to the corresponding BPAs following the usual procedure. In the case of 9-phenantryl, **2.14c** proved to be a better partner for the Suzuki cross-coupling and a nickel-catalyzed Kumada cross-coupling was used to incorporate 2,4,6-tris(1-methylethyl)phenyl. To prepare the hydrogenated version of **2.16a**, H$_8$-BINOL was iodinated and subjected to the same route as its unsaturated analogue (**Scheme 2.4**).

2.17a: R= Me   82%
2.17b: R= C$_6$F$_5$ 74%

2.18a: R= Me   81%
2.18b: R= C$_6$F$_5$ 82%

2.12

2.19: 87%

2.20: 82%

2.21: 68%

2.14a: R= Me   X= Br
2.14c: R= MOM   X= I

2.22a: R= Me   Ar= 2,4,6-(^{i}Pr)$_3$Ph
2.22b: R= MOM Ar= 9-phenanthryl

2.23a: Ar= 2,4,6-(^{i}Pr)$_3$Ph 62%
2.23b: Ar= 9-phenanthryl   32%

Scheme 2.4. Preparation of other BPAs.

Palladium(0)-Catalyzed Asymmetric C(sp3)-H Arylation: the Chiral Anion Approach

With this range of BPAs in hands, we started our investigations for the synthesis of indolines using conditions based on the methodology developed by H. Ohno and coworkers.

2.3. First Hit and Optimization

Substrate **2.24a-Br** was chosen for preliminary studies (**Table 2.1**) and prepared as described in previous reports.[160] Under H. Ohno conditions, except for the replacement of pivalic acid with **2.16a-c,h**, full conversion was observed in all cases by GC-MS (entries 1-4). After isolation and HPLC analysis using a chiral stationary phase, it turned out that the indolines formed in presence of **2.16a-c** were completely racemic. A slight excess of 54:46 e.r. was observed in the case of **2.16h**. We also ran the reaction without ligand as H. Kagan. Only traces of product were observed under these conditions (entry 5). Using free tricyclohexylphosphine instead of its tetrafluoroborate salt, similar results were observed (entry 6). We suspected that acetate ligands of the palladium source could competitively participate in the CMD process and thus lead to racemic products. Therefore, we changed $Pd(OAc)_2$ and $PCy_3 \cdot HBF_4$ for well-defined $Pd(PCy_3)_2$. We were pleased to observe indoline formation with 82:18 e.r. (entry 7). However, significant amounts of starting material and proto-debrominated byproduct were observed. Decreasing the amount of BPA to 10 mol% and increasing the reaction time to 24h resulted in similar induction and higher conversion (entry 8).
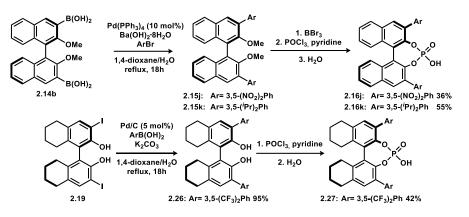
Table 2.1. Preliminary screening based on H. Ohno conditions.						

Entry[a]	Ar	[Pd]	Ligand	Time (h)	Yield of 2.25a (%)[b]	e.r. of **2.25a**[c]
1	Ph (**2.16a**)	$Pd(OAc)_2$	$PCy_3 \cdot HBF_4$	12	86	50:50
2	1-naphtyl (**2.16b**)	$Pd(OAc)_2$	$PCy_3 \cdot HBF_4$	12	52	50:50
3	2-naphtyl (**2.16c**)	$Pd(OAc)_2$	$PCy_3 \cdot HBF_4$	12	76	50:50
4	3,5-$(CF_3)_2$Ph (**2.16h**)	$Pd(OAc)_2$	$PCy_3 \cdot HBF_4$	12	86	54:46
5	2-naphtyl (**2.16b**)	$Pd(OAc)_2$	-	12	traces[d]	-
6	2-naphtyl (**2.16b**)	$Pd(OAc)_2$	PCy_3	12	68	50:50
7	3,5-$(CF_3)_2$Ph (**2.16h**)	$Pd(PCy_3)_2$	-	12	31	82:18
8[e]	3,5-$(CF_3)_2$Ph (**2.16h**)	$Pd(PCy_3)_2$	-	24	50	80:20

*[a]Reaction carried on 0.2 mmol of **2.24a-Br**. [b]Isolated yield. [c]Determined by HPLC using a chiral phase. [d]Estimated by GC-MS analysis. [e]10 mol% of chiral phosphoric acid was used.*

Palladium(0)-Catalyzed Asymmetric C(sp3)-H Arylation: the Chiral Anion Approach

Based on those last conditions, we screened different BPAs of our library (**Table 2.2**). All BPAs gave poor induction (up to 57:43 e.r.) except **2.16h** (entry 8). Moreover, no clear reactivity- or enantioselectivity-structure relationship could be deduced.
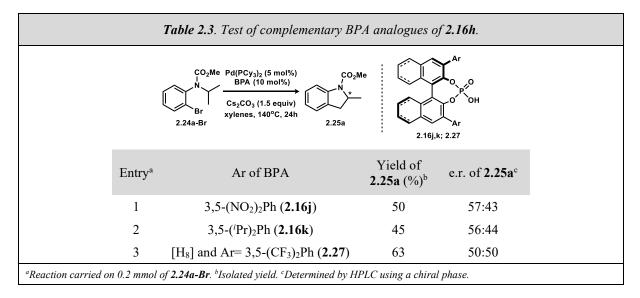
	Table 2.2. Screening of BPAs.		

Entry[a]	R	Yield of 2.25a (%)[b]	e.r. of **2.25a**[c]
1	Ph (**2.16a**)	65	50:50
2	1-naphtyl (**2.16b**)	71	53:47
3	2-naphtyl (**2.16c**)	68	54:46
4	4-biphenyl (**2.16d**)	52	53:47
5	4-ClPh (**2.16e**)	47	54:46
6	4-NO$_2$Ph (**2.16f**)	34	54:46
7	3,5-Me$_2$Ph (**2.16g**)	39	57:43
8	**3,5-(CF$_3$)$_2$Ph (2.16h)**	**50**	**80:20**
9	3,5-(^{t}Bu)$_2$Ph (**2.16i**)	63	55:45
10	Me (**2.18a**)	80	52:48
11	C$_5$F$_6$ (**2.18b**)	31	50:50
12	[H$_8$] and R= Ph (**2.21**)	52	50:50
13	2,4,6-(^{i}Pr)$_3$Ph (**2.23a**)	21	56:44
14	9-phenanthryl (**2.23b**)	71	52:48
15	(R)-VAPOL-P(O)OH	79	50:50

[a]*Reaction carried on 0.2 mmol of* **2.24a-Br**. [b]*Isolated yield.* [c]*Determined by HPLC using a chiral phase.*

As 3,5-trifluoromethyl substituents seemed to be essential for enantioselectivity, we decided to prepare a range of new 3,3'-disubstituted BPAs to understand this effect (**Scheme 2.5**).

Palladium(0)-Catalyzed Asymmetric C(sp3)-H Arylation: the Chiral Anion Approach

Scheme 2.5. Preparation of complementary BPA analogues of 2.16h.

BPAs bearing isopropyl and nitro groups in place of trifluoromethyl were synthetized to mimic the steric or electronic properties of **2.16h**. In complement, we also prepared the partially hydrogenated analogue of **2.16h** to see the influence of the dihedral angle on the reaction outcome. After reaction in presence of these new BPAs, we observed in all cases lower enantioselectivity than when **2.16h** was used (**Table 2.3**). These results indicate that dihedral angle plays a key role in the enantioselectivity like the 3,5-bis(trifluoromethyl)phenyl substituents whose effect remains unclear.

	Table 2.3. Test of complementary BPA analogues of 2.16h.		
Entry[a]	Ar of BPA	Yield of **2.25a** (%)[b]	e.r. of **2.25a**[c]
1	3,5-(NO$_2$)$_2$Ph (**2.16j**)	50	57:43
2	3,5-(^{i}Pr)$_2$Ph (**2.16k**)	45	56:44
3	[H$_8$] and Ar= 3,5-(CF$_3$)$_2$Ph (**2.27**)	63	50:50

[a]*Reaction carried on 0.2 mmol of 2.24a-Br.* [b]*Isolated yield.* [c]*Determined by HPLC using a chiral phase.*
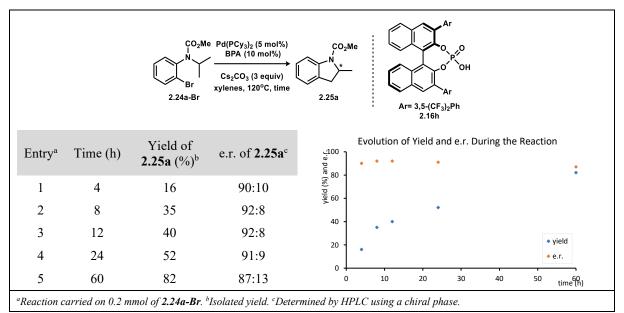
We then decided to investigate the effect of the stochiometric base (**Table 2.4**, entries 1-7). When changing cesium carbonate for lower alkali counter cations (entries 1-4), racemic mixtures were obtained in all cases, even if Rb$_2$CO$_3$ gave a higher yield. The use of cesium hydroxide resulted in similar enantioselectivity compared to cesium carbonate, but with a decreased reactivity (entry 5). For both cesium pivalate and potassium acetate, racemic products were isolated (entries 6,7), certainly because of competitive action in the CMD process as observed in preliminary investigations. Decreasing the temperature of the reaction to 120°C

had a benefic effect on enantioselectivity at the expense of reactivity (entry 8). We suspected that the low solubility of cesium carbonate in xylenes could be responsible for the incomplete deprotonation of BPA, which could account for the lower reactivity. Thus, we doubled the amount of cesium carbonate and observed a better conversion. Nevertheless, when the reaction was pushed to full conversion, an erosion of e.r. was observed (entries 9-10). We hypothesized that this erosion could come from the background reaction in which carbonate act as the CMD base without participation of BPA.
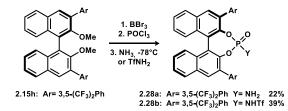
Table 2.4. Screening of different bases.						
Entry[a]	Base	n (equiv.)	T (°C)	Time (h)	Yield of 2.25a (%)[b]	e.r. of **2.25a**[c]
1	Li_2CO_3	1.5	140	24	0	-
2	Na_2CO_3	1.5	140	24	0	-
3	K_2CO_3	1.5	140	24	26	51:49
4	Rb_2CO_3	1.5	140	24	73	50:50
5	CsOH	1.5	140	24	29	79:21
6	CsOPiv	1.5	140	24	63	50:50
7	KOAc	1.5	140	24	16	50:50
8	**Cs_2CO_3**	**1.5**	**120**	**40**	**24**	**87:13**
9	**Cs_2CO_3**	**3**	**120**	**24**	**55**	**88:12**
10	**Cs_2CO_3**	**3**	**120**	**40**	**73**	**83:17**

[a]*Reaction carried on 0.2 mmol of* ***2.24a-Br***. [b]*Isolated yield*. [c]*Determined by HPLC using a chiral phase*.

To check our hypothesis, we ran a batch of 5 reactions and stopped them after different reaction times (**Table 2.5**). Once again, we observed that a longer reaction time led to full conversion, but to lower e.r.. Thus, we decided to stop our reactions after 24h, even if full conversion could not be reached.
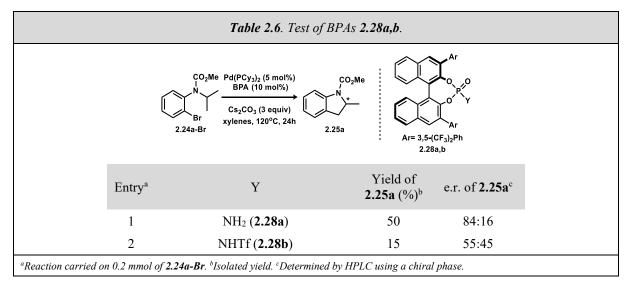
Table 2.5. Evolution of yield and e.r. during the reaction.

Palladium(0)-Catalyzed Asymmetric C(sp3)-H Arylation: the Chiral Anion Approach

Entry[a]	Time (h)	Yield of 2.25a (%)[b]	e.r. of 2.25a[c]
1	4	16	90:10
2	8	35	92:8
3	12	40	92:8
4	24	52	91:9
5	60	82	87:13

[a]Reaction carried on 0.2 mmol of **2.24a-Br**. [b]Isolated yield. [c]Determined by HPLC using a chiral phase.

At this stage, we decided to prepare phosphoramidate analogues of **2.16h** (**Scheme 2.6**) to see the influence of the pKa on the reaction efficiency. We observed that using both new analogues resulted in lower reactivity and enantioselectivity (**Table 2.6**).
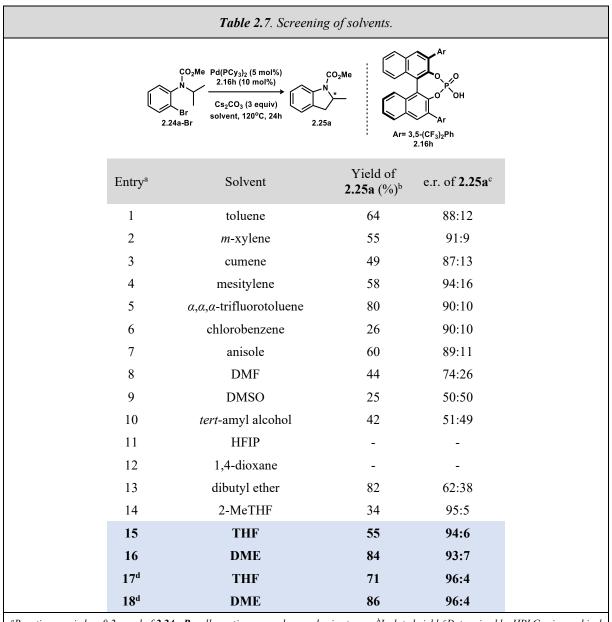
Scheme 2.6. *Preparation of BPA analogues of 2.16h with different acidity.*

Table 2.6. *Test of BPAs **2.28a,b**.*

Entry[a]	Y	Yield of 2.25a (%)[b]	e.r. of 2.25a[c]
1	NH₂ (**2.28a**)	50	84:16
2	NHTf (**2.28b**)	15	55:45

[a]Reaction carried on 0.2 mmol of **2.24a-Br**. [b]Isolated yield. [c]Determined by HPLC using a chiral phase.
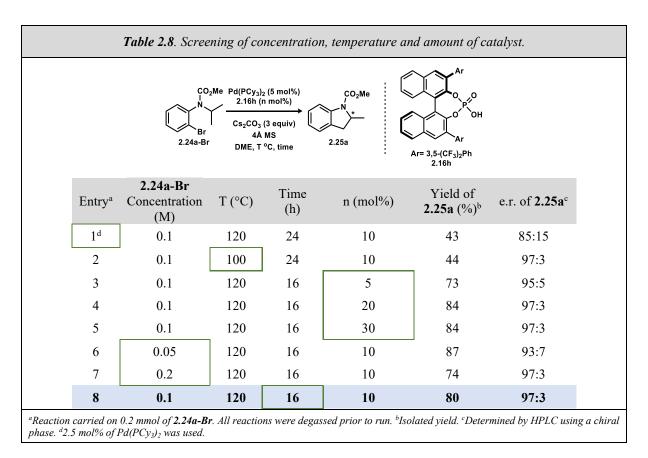
We then turned our attention to an extensive solvent screening (**Table 2.7**). It turned out that other aromatic solvents (entries 1-7) gave similar results as xylenes. In all cases, full conversion could not be achieved, even if α,α,α-trifluorotoluene seemed really promising since we observed almost full conversion and a good isolated yield of 80%. Polar and protic solvents

Palladium(0)-Catalyzed Asymmetric C(sp3)-H Arylation: the Chiral Anion Approach

(entries 8-11) gave average yields and lower enantioselectivities. This may be due to carbonate dissolution and its participation in the CMD. 1,4-dioxane gave complete conversion to the proto-debrominated product (entry 12). However, other ethers gave interesting results (entries 13-16). Dibutyl ether led to full conversion, but low induction. 2-MeTHF, THF and DME gave the best e.r. obtained so far and full conversion in the case of DME. Moreover, addition of 4Å molecular sieve in the reaction led to both better isolated yield and enantioselectivity (entries 17,18). We decided to keep those final conditions for further investigations.

Table 2.7. Screening of solvents.

Entry[a]	Solvent	Yield of 2.25a (%)[b]	e.r. of 2.25a[c]
1	toluene	64	88:12
2	*m*-xylene	55	91:9
3	cumene	49	87:13
4	mesitylene	58	94:16
5	*α,α,α*-trifluorotoluene	80	90:10
6	chlorobenzene	26	90:10
7	anisole	60	89:11
8	DMF	44	74:26
9	DMSO	25	50:50
10	*tert*-amyl alcohol	42	51:49
11	HFIP	-	-
12	1,4-dioxane	-	-
13	dibutyl ether	82	62:38
14	2-MeTHF	34	95:5
15	**THF**	**55**	**94:6**
16	**DME**	**84**	**93:7**
17[d]	**THF**	**71**	**96:4**
18[d]	**DME**	**86**	**96:4**

[a]Reaction carried on 0.2 mmol of **2.24a-Br**, all reactions were degassed prior to run. [b]Isolated yield. [c]Determined by HPLC using a chiral phase. [d]50 mg of 4Å molecular sieve powder was added.

Palladium(0)-Catalyzed Asymmetric C(sp3)-H Arylation: the Chiral Anion Approach

We then wanted to determine the limits of our system concerning the minimum catalyst loading, temperature, concentration and time (**Table 2.8**). When the Pd(PCy$_3$)$_2$ loading was halved, both yield and e.r. decreased significantly (entry 1). Reactivity suffered from a lower temperature of 100°C, even if the enantioselectivity remained stable (entry 2). Increasing the amount of BPA gave similar results (entries 4,5), but with only 5 mol% of BPA lower yield and enantioselectivity were observed (entry 3). The concentration of 0.1 M used since the beginning of this optimization seems to be optimal and offers the best compromise between reactivity and induction (entries 6,7). Finally, the reaction time could be reduced to 16h with only slightly lower yield (entry 8).

Table 2.8. Screening of concentration, temperature and amount of catalyst.

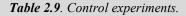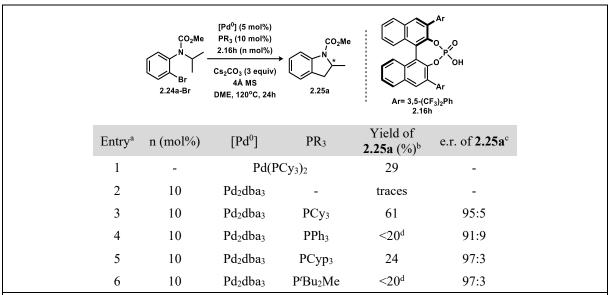| Entry[a]	2.24a-Br Concentration (M)	T (°C)	Time (h)	n (mol%)	Yield of 2.25a (%)[b]	e.r. of 2.25a[c]
1[d]	0.1	120	24	10	43	85:15
2	0.1	100	24	10	44	97:3
3	0.1	120	16	5	73	95:5
4	0.1	120	16	20	84	97:3
5	0.1	120	16	30	84	97:3
6	0.05	120	16	10	87	93:7
7	0.2	120	16	10	74	97:3
8	0.1	120	16	10	80	97:3

[a]Reaction carried on 0.2 mmol of **2.24a-Br**. All reactions were degassed prior to run. [b]Isolated yield. [c]Determined by HPLC using a chiral phase. [d]2.5 mol% of Pd(PCy$_3$)$_2$ was used.

We finally ran few control experiments (**Table 2.9**). Without BPA, product formation was still observed (entry 1), which confirms that a slow background reaction takes place, probably with carbonate, to lead to a racemic product. No reaction occurred in the absence of a phosphine ligand (entry 2) and PCy$_3$ furnished the highest reactivity (entry 3) among all the tested monophosphines (entries 4-6).
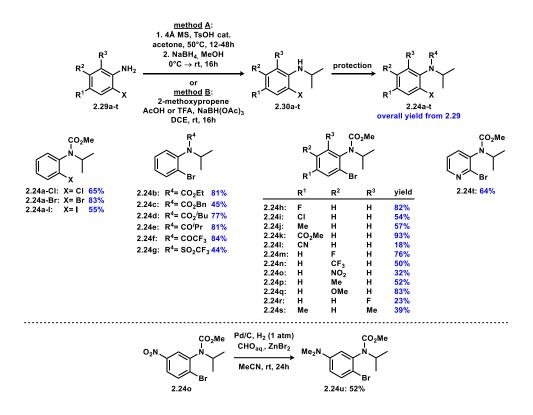
Table 2.9. Control experiments.

Palladium(0)-Catalyzed Asymmetric C(sp3)-H Arylation: the Chiral Anion Approach

Entry[a]	n (mol%)	[Pd⁰]	PR₃	Yield of 2.25a (%)[b]	e.r. of 2.25a[c]
1	-	Pd(PCy₃)₂		29	-
2	10	Pd₂dba₃	-	traces	-
3	10	Pd₂dba₃	PCy₃	61	95:5
4	10	Pd₂dba₃	PPh₃	<20[d]	91:9
5	10	Pd₂dba₃	PCyp₃	24	97:3
6	10	Pd₂dba₃	PᵗBu₂Me	<20[d]	97:3

[a]Reaction carried on 0.2 mmol of **2.24a-Br**. All reactions were degassed prior to run. [b]Isolated yield. [c]Determined by HPLC using a chiral phase. [d]Estimated by GC-MS analysis.

2.4. Scope and Limitations
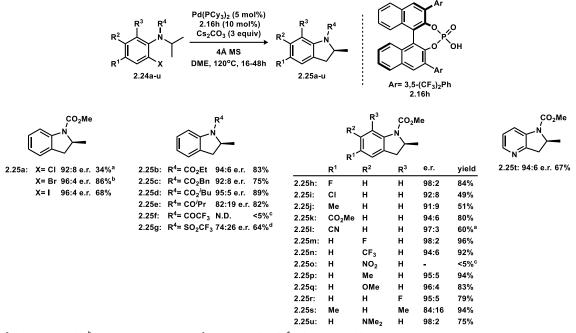
We then prepared a range of *N*-protected-*N*-isopropyl-o-bromoanilines from o-bromoanilines via known methods (**Scheme 2.7**).[160,176,177] We used two different procedures for reductive amination. In most cases we used a two-step sequence via condensation of acetone with a catalytic amount of acid in presence of a desiccant followed by reduction with sodium borohydride. For some difficult substrates, we used the other one-pot procedure using 2-methoxypropene and sodium triacetoxyborohydride. The corresponding alkylated anilines were then protected using different classic procedures. In the case of **2.24u**, reductive methylation by hydrogenation of **2.24o** was performed.

Palladium(0)-Catalyzed Asymmetric C(sp3)-H Arylation: the Chiral Anion Approach

method A:
1. 4Å MS, TsOH cat.
acetone, 50°C, 12-48h
2. NaBH$_4$, MeOH
0°C → rt, 16h

or

method B:
2-methoxypropene
AcOH or TFA, NaBH(OAc)$_3$
DCE, rt, 16h

2.29a-t → 2.30a-t

protection → 2.24a-t
overall yield from 2.29

2.24a-Cl: X= Cl 65%
2.24a-Br: X= Br 83%
2.24a-I: X= I 55%

2.24b: R^4= CO$_2$Et 81%
2.24c: R^4= CO$_2$Bn 45%
2.24d: R^4= CO$_2^i$Bu 77%
2.24e: R^4= CO^{i}Pr 81%
2.24f: R^4= COCF$_3$ 84%
2.24g: R^4= SO$_2$CF$_3$ 44%

2.24t: 64%

	R^1	R^2	R^3	yield
2.24h:	F	H	H	82%
2.24i:	Cl	H	H	54%
2.24j:	Me	H	H	57%
2.24k:	CO$_2$Me	H	H	93%
2.24l:	CN	H	H	18%
2.24m:	H	F	H	76%
2.24n:	H	CF$_3$	H	50%
2.24o:	H	NO$_2$	H	32%
2.24p:	H	Me	H	52%
2.24q:	H	OMe	H	83%
2.24r:	H	H	F	23%
2.24s:	Me	H	Me	39%

2.24o

Pd/C, H$_2$ (1 atm)
CHO$_{aq.}$, ZnBr$_2$
MeCN, rt, 24h

2.24u: 52%

Scheme 2.7. Preparation of substrates bearing an isopropyl moiety 2.24a-u.

All corresponding racemic indolines were prepared successfully from these substrates using conditions developed by H. Ohno. With all racemic references for chiral HPLC analysis in hand, we engaged these substrates in the enantioselective transformation under the previously optimized conditions (**Scheme 2.8**). We first explored the tolerance of the reaction for different halogens as oxidative addition site. Iodide **2.24a-I** led to same enantioselectivity than bromide **2.24a-Br**, but with lower yield. In the case of chloride **2.24a-Cl**, the temperature had to be increased to regain some reactivity at the expense of the enantioselectivity. Moreover, for both chloride and iodide, full conversion could not be achieved and a larger amount of proto-debrominated byproduct was observed. Of note, reaction on **2.24a-Br** could be performed on 1.36 g (5 mmol) of substrate with similar results. All tested carbamates gave excellent enantioselectivity and yield. However, the use of other protecting groups resulted in lower induction and even complete shutdown of the reactivity in the case of the trifluoroacetamide protecting group. The reaction seems to tolerate a wide range of electron donating and withdrawing substituents on the aromatic. In most cases, excellent reactivity and enantioselectivity were obtained. Substrates containing strongly coordinating groups such as nitrile or dimethyl amine, which could potentially poison the metal-catalyst reacted as well. Nevertheless substrate **2.24o** bearing a nitro group was unreactive, even if the reaction performed correctly under the conditions described by H. Ohno. Reaction on substrate **2.25i,j,s**
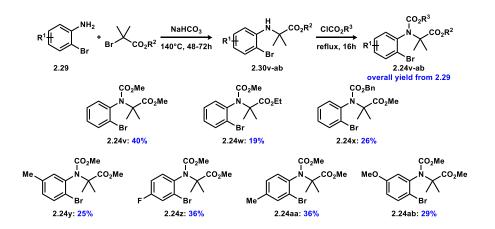
proved to be more challenging and led to lower yields and/or enantioselectivity. Interestingly, the pyridine moiety of **2.24t** was well tolerated and azaindoline **2.25t** could be formed in acceptable yield and good enantioselectivity.

	R^1	R^2	R^3	e.r.	yield
2.25h:	F	H	H	98:2	84%
2.25i:	Cl	H	H	92:8	49%
2.25j:	Me	H	H	91:9	51%
2.25k:	CO_2Me	H	H	94:6	80%
2.25l:	CN	H	H	97:3	60%[a]
2.25m:	H	F	H	98:2	96%
2.25n:	H	CF_3	H	94:6	92%
2.25o:	H	NO_2	H	-	<5%[c]
2.25p:	H	Me	H	95:5	94%
2.25q:	H	OMe	H	96:4	83%
2.25r:	H	H	F	95:5	79%
2.25s:	Me	H	Me	84:16	94%
2.25u:	H	NMe_2	H	98:2	75%

2.25a: X= Cl 92:8 e.r. 34%[a]
X= Br 96:4 e.r. 86%[b]
X= I 96:4 e.r. 68%

2.25b: R^4= CO_2Et 94:6 e.r. 83%
2.25c: R^4= CO_2Bn 92:8 e.r. 75%
2.25d: R^4= $CO_2{}^iBu$ 95:5 e.r. 89%
2.25e: R^4= CO^iPr 82:19 e.r. 82%
2.25f: R^4= $COCF_3$ N.D. <5%[c]
2.25g: R^4= SO_2CF_3 74:26 e.r. 64%[d]

2.25t: 94:6 e.r. 67%

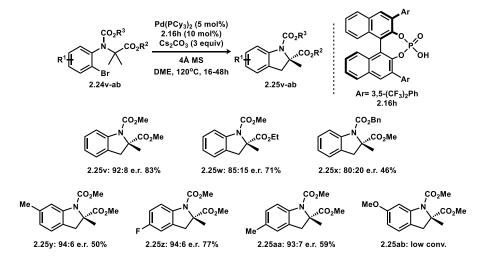[a]Performed at 140°C. [b]Performed on 5 mmol scale. [c]Estimated by GCMS. [d]Performed at 100°C.

Scheme 2.8. *Scope of the reaction with substrates bearing an isopropyl moiety.*

All examples discussed so far, bear a trisubstituted stereocenter and are close to reported work using different chiral ligands. To expand this work, we explored some new substrates containing a tetrasubstituted center instead of an isopropyl group. For this, we prepared a range of new substrates from some anilines used before via alkylation with α-bromoisobutyrate and subsequent protection (**Scheme 2.9**).[178]

Palladium(0)-Catalyzed Asymmetric C(sp3)-H Arylation: the Chiral Anion Approach

Scheme 2.9. *Preparation of substrates bearing a tetrasubstituted center **2.24v-ab**.*
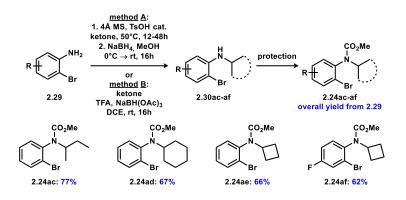
We then engaged substrates **2.24v-ab** under the previously established conditions and we were pleased to observe the formation of the corresponding indolines. We observed that the size of the carbamate and ester impact drastically the outcome of the reaction. Indeed, smaller methoxy substituents in **2.24v** seem to give a better reactivity and enantioselectivity compared to ethyl and benzyl analogues **2.24w,x**. Methyl and fluorine moieties on the aromatic (**2.24y-aa**) were well tolerated, but gave lower reactivities. Nevertheless, the introduction of a methoxy substituent (**2.24ab**) led to poor conversion. Overall, using our system, reactions on substrates bearing a tetrasubstituted center appear to be more challenging that on the corresponding substrates containing a trisubstituted center, even if those substrates react perfectly under H. Ohno conditions. However, this synthetic route presents a simple access to valuable amino acids building blocks.

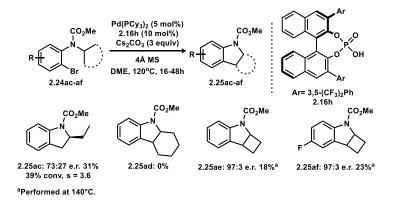**Scheme 2.10**. *Scope of the reaction with substrates bearing a tetrasubstituted center.*

As chiral indolines synthesis proved to be efficient with different chiral ligands through methylene activation on six-membered and larger rings, we thought about the possibility to

Palladium(0)-Catalyzed Asymmetric C(sp3)-H Arylation: the Chiral Anion Approach

extend our work to this type of systems. Moreover, we considered the possibility to activate methylenes on cyclobutanes. Indeed, despite the work of K. Fagnou and coworkers on indolines the synthesis of indolines bearing a fused cyclobutane moiety,[179] an asymmetric version has never been described. In complement, we also wanted to test the ability of our system to promote the kinetic resolution of racemic substrates. In regard to these perspectives, compounds **2.24ac-af** bearing an activable methylene position were prepared in good overall yield from **2.29** (**Scheme 2.11**).
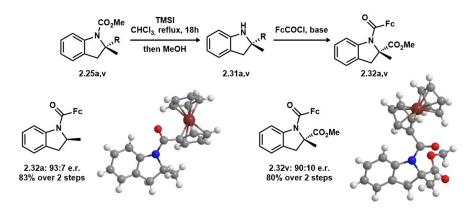
Scheme 2.11. *Preparation of substrates bearing a stereocenter or a cyclic moiety.*

As discussed in the introduction, examples of resolution in C(sp^3)-H remain rare. In our case, with substrate **2.24ac**, we observed a modest resolution. **2.25ac** arising from activation of the methyl group was the only product observed without traces of methylene activation or tetrahydroquinoline product. Our conditions failed to effectively promote the activation of methylene cyclohexyl positions and a poor reactivity was observed for cyclobutane substrates, even at 140°C. Moreover, the purification of product **2.25ae,af** proved to be difficult, which explains the low isolated yields. However, products **2.24ae,af** showed an excellent enantiomeric ratio of 97:3 (**Scheme 2.12**).

Scheme 2.12. *Scope of the reaction with substrates bearing a cyclic moiety and kinetic resolution.*

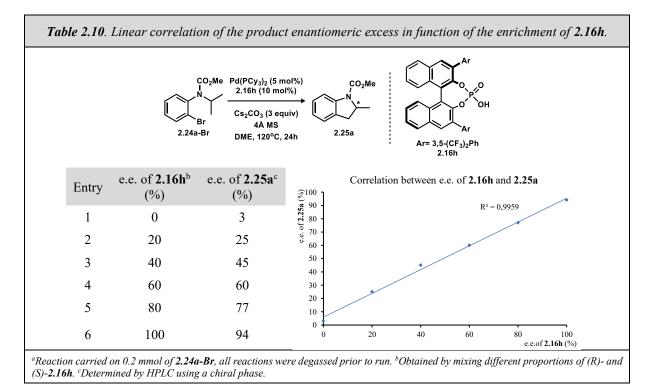# Palladium(0)-Catalyzed Asymmetric C(sp3)-H Arylation: the Chiral Anion Approach

We first assigned the configuration of the created stereocenter by comparison with previous reports. However, we wanted to confirm this attribution by X-ray crystallography. Unfortunately, most prepared compounds were isolated as oils and the few solids that we obtained did not give suitable crystals. In this regard, we decided to derivatize our indoline with a ferrocene group. Indeed, this strategy had previously been used with success by our group.[180] Thus, we cleaved the carbamate group on **2.25a,v** using trimethylsilyl iodide[181] to obtain the corresponding free indolines and we then derivatized the latter as ferrocenecarboxamides.[182–184] Suitable crystals were obtained easily and analyzed using X-ray diffraction analysis, which confirmed us the *S* configuration for both products.
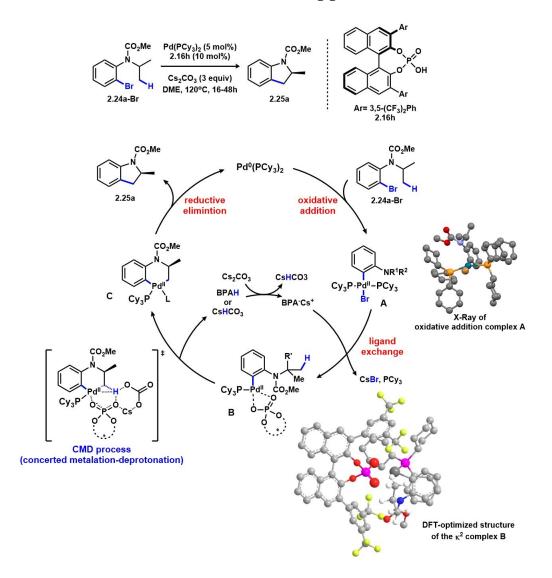

Scheme 2.13. *Ferrocene derivatization and crystal structures.*

Palladium(0)-Catalyzed Asymmetric C(sp3)-H Arylation: the Chiral Anion Approach

2.5. Mechanistic considerations

Since the beginning of this work, we assumed that BPA played the role of the base involved in the CMD transition-state. To confirm our hypothesis, a batch of reactions with different mixture of (**R**)- and (**S**)-**2.16h** was run. A linear correlation between the enrichment of **2.15h** and of the isolated indoline (**Table 2.10**) was observed. This suggests that a single molecule of BPA is involved in the enantiodetermining transition-state.

Table 2.10. Linear correlation of the product enantiomeric excess in function of the enrichment of **2.16h**.

Entry	e.e. of **2.16h**[b] (%)	e.e. of **2.25a**[c] (%)
1	0	3
2	20	25
3	40	45
4	60	60
5	80	77
6	100	94

[a]Reaction carried on 0.2 mmol of **2.24a-Br**, all reactions were degassed prior to run. [b]Obtained by mixing different proportions of (R)- and (S)-**2.16h**. [c]Determined by HPLC using a chiral phase.

Moreover, DFT-optimized structure of the κ^2 complex **B** with the optimal BPA **2.16h** (vide infra) indicates close interactions of both carbamate and isopropyl moieties with the aromatic groups present in 3,3' positions of **2.16h**. Nevertheless, the unique effect of the CF_3 substituents remains unclear as discussed before. We then ran the reaction using a stochiometric amount of the cesium salt of **2.16h** in absence of cesium carbonate. In this case, no formation of the expected indoline was observed.

Palladium(0)-Catalyzed Asymmetric C(sp3)-H Arylation: the Chiral Anion Approach

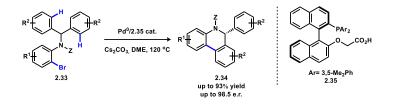*Scheme 2.14. Proposed catalytic cycle of the transformation.*

Furthermore, as shown during the optimization, potassium or rubidium carbonate led to a racemic product. These observations, combined with the slow background reaction observed when using only cesium carbonate as base, indicate that BPA forms a cluster with carbonate and cesium during the deprotonation. The implication of this type of clusters was proposed in different theorical mechanistic studies regarding transformations involving CMD transition-states.[185,186] Nevertheless, without other experiments and extended DFT calculations, the exact interactions responsible for the observed induction remain unclear. Thus, at this point, the mechanism illustrated in **Scheme 2.14** can be proposed. The first step of the reaction involves the classic oxidative addition into the C-Br bond to form complex **A**, the structure of which was confirmed by X-ray analysis after isolation of the complex. The following ligand exchange leads to complex **B**, which undergoes CMD process via a base-counteranion relay to form

palladacycle **C**. After reductive elimination, the enantioenriched indoline is formed and the active Pd(0) catalyst is regenerated.

2.6. Conclusion

In summary, we have developed a new methodology for the synthesis of highly enantioenriched indolines via enantioselective $C(sp^3)$-H arylation. Moreover, a chiral anion approach was used instead of classical chiral ligands approaches. This work constitutes the first asymmetric methodology for $C(sp^3)$-H arylation cyclisation based on this strategy. Both trisubstituted and tetrasubstituted stereocenters were generated efficiently with a wide range of substrates and interesting amino acid scaffolds were prepared. We hope that this approach will be applied in complement to the use of chiral ancillary ligands for the development of new interesting methodologies.

Furthermore, this work conduced our group to study the development of new ligands bearing both functionalities: a phosphine to serve as an ancillary ligand and a carboxylate base for the CMD process. We like to call them "bifunctional" ligands. This was demonstrated by the preparation of bifunctional ligand **2.35** composed of a chiral binaphtyl scaffold combined with a phosphine and a carboxylic acid moiety. This ligand proved to be highly efficient for asymmetric intramolecular $C(sp^2)$-H arylation.[187]
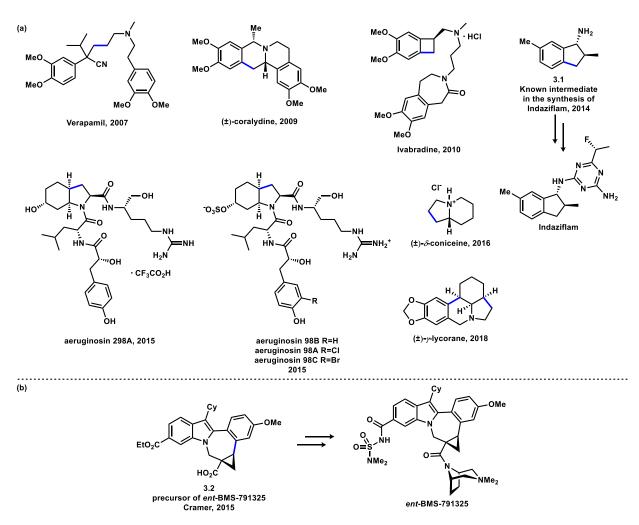
Scheme 2.15. *Recently published work by our group using bifunctional ligands.*

Palladium(0)-Catalyzed Asymmetric C(sp3)-H Arylation: the Chiral Anion Approach

Palladium(0)-Catalyzed Asymmetric C(sp3)-H Arylation: the Chiral Anion Approach

3. Total Synthesis of (Nor)illudalane Sesquiterpenes Based on a C(sp³)-H Activation Strategy

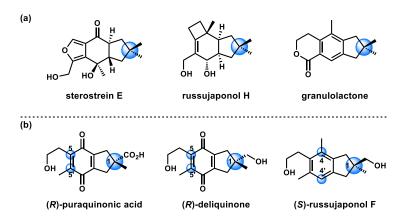∗ *Work done in collaboration with Dr. Marcus Craveiro during his postdoctoral stay in our group.*

3.1. Introduction

Although non-asymmetric C(sp³)-H activation has proven to be a powerful tool for the synthesis of natural or bioactive products (**Figure 3.1a**),[188,189] applications of asymmetric version of these reactions are rare. Even if excellent results have been reported for oxidative addition initiated asymmetric C(sp³)-H activation reactions, only one application in bioactive molecule synthesis has been described so far. Indeed, N. Cramer presented the synthesis of a precursor of *ent*-BMS-791325, a hepatitis C virus NS5B replicase inhibitor (**Figure 3.1b**).[151]

Figure 3.1. a) Applications of C(sp3)-H activation to the synthesis of natural or bioactive products described by our group. (b) Only application of asymmetric C(sp³)-H activation, presented by N. Cramer.

Total Synthesis of (Nor)illudalane Sesquiterpenes Based on a C(sp3)-H Activation Strategy
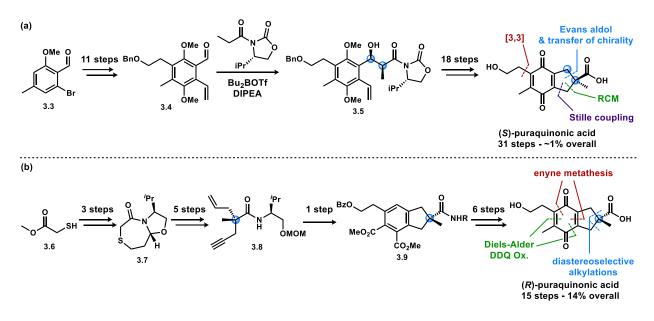
This lack of applications motivated us to find new potential targets. In this context we turned our attention to some natural products of the family of illudalane and norilludalane sesquiterpenes, which are generally isolated from mycelial cultures of woody mushrooms. These compounds are usually composed of two geminal methyl groups on a cyclopentane ring fused with diverse scaffolds (**Figure 3.2a**).[190–192] Nevertheless, some members of this family possess a quaternary stereocenter, resulting from the oxidation of one of the geminal methyl groups to a hydroxymethyl or a carboxylic acid group. This is notably the case for the benzoquinones puraquinonic acid[193] and deliquinone,[194] and the indane russujaponol F[195] (**Figure 3.2b**). In addition to a polysubstituted aromatic or benzoquinone core, the most intriguing feature of these molecules is probably the highly symmetric quaternary stereocenter resulting from substituents located three or four carbons away. Such quaternary stereocenters constitute an interesting synthetic challenge.[196–204]

Figure 3.2. (a) Examples of (nor)illudalanes with a gem-dimethyl group. (b) (Nor)illudalane targets featuring a quaternary stereocenter.
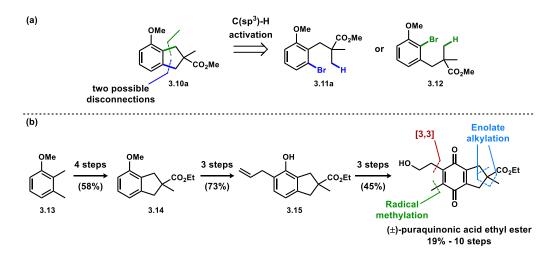
Despite its moderate structural complexity, only two enantioselective syntheses of puraquinonic acid have been reported and none for russujaponol F and deliquinone. D. L. J. Clive and coworkers reported the first synthesis of (*S*)-puraquinonic acid in 31 steps using an Evans aldol reaction as the enantio-determining step (**Scheme 3.1a**).[205] This strategy required a large number of functional group interconversions and manipulations. In addition, this work established the absolute configuration of natural puraquinonic acid as (*R*) upon comparison with a natural sample. More recently, Gleason and coworkers disclosed a much more efficient synthesis of (*R*)-puraquinonic acid (**Scheme 3.1b**).[206] The quaternary stereocenter was constructed at the beginning of the synthesis via sequential diastereoselective alkylations using a valine-derived chiral auxiliary. Then, the indane core was built using an elegant and effective combination of enyne metathesis and Diels−Alder cycloaddition, followed by oxidation with DDQ in a one-pot procedure. After functional group manipulations, cleavage of the chiral

Total Synthesis of (Nor)illudalane Sesquiterpenes Based on a C(sp3)-H Activation Strategy

auxiliary and oxidation of the aromatic ring to the corresponding benzoquinone, this approach yielded enantiopure (*R*)-puraquinonic acid in 12 steps and 20% overall yield from the in-house auxiliary,[207] or 15 steps and 14% from (*S*)-valinol.

Scheme 3.1. *Previous Enantioselective Total Syntheses of Puraquinonic Acid.*

We thought that C(sp^3)-H activation could be used to access this type of scaffold in a simpler and more general way. Indeed, we based our retrosynthetic analysis on the disconnection of one of the two C(sp^2)-C(sp^3) bonds of indane **3.10a** (**Scheme 3.2a**). This bond would be built through asymmetric C(sp^3)-H arylation with creation of the quaternary stereocenter via desymmetrization of the two enantiotopic C-H bonds in **3.11a** or **3.12**. The construction of these two substrates should not be problematic. Moreover, the following steps to complete the synthesis would be similar to the one employed in the racemic synthesis of racemic puraquinonic acid ethyl ester and deliquinone reported by G. A. Kraus (**Scheme 3.2b**).[208]
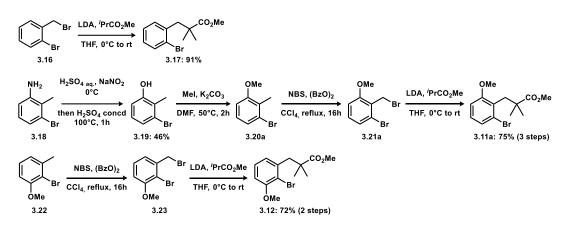
Scheme 3.2. *(a) Retrosynthetic analysis. (b) Total synthesis of puraquinonic acid ethyl ester by G. A. Kraus.*

Total Synthesis of (Nor)illudalane Sesquiterpenes Based on a C(sp3)-H Activation Strategy

Considering the work done by our group to generate quaternary stereocenters in the context of indane and indoline synthesis,[155,156] we thought that formation of **3.10** would be challenging. Indeed, in both precedents the intramolecular C−H arylation was likely favored by a strong Thorpe-Ingold effect. Moreover, we already exposed, in chapter 2, that the generation of tetrasubstituted stereocenters to form indolines proved to be significantly more difficult than the creation of trisubstituted stereocenters.

3.2. Preliminary Screening
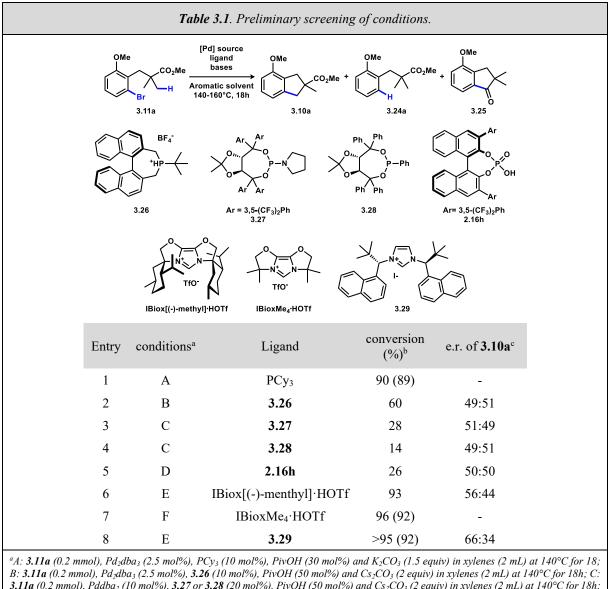
We first prepared three substrates for a preliminary screening of conditions (**Scheme 3.3**). Substrate **3.17** was prepared to probe the effect of the methoxy group on the reactivity. We prepared **3.11a** in large quantities for our main screening, expecting that placing the methoxy group in meta-position to the bromine atom would lead to a better reactivity compared to **3.12**.

Scheme 3.3. *Preparation of substrates **3.11a**, **3.12** and **3.17**.*

We then started a screening of conditions to evaluate the reactivity of **3.11a** in C(sp^3)-H arylation (**Table 3.1**). We found that classic conditions using a palladium(0) source and tricyclohexylphosphine gave mainly the expected product **3.10a** (entry 1) contaminated with 5-10% of the unseparable protodebrominated product. Moreover, we observed the formation of indanone **3.25** resulting from the nucleophilic attack of the organopalladium intermediate onto the ester.[209] With the reactivity of **3.11a** established, we then screened different families of chiral ligands to evaluate their potential induction. We tested ligands available in our library and while Binepines, phosphoramidites, phosphonites and BPAs all gave racemic products, IBiox[(-)-menthyl]·HOTf,[210] developed by F. Glorius gave a really good conversion accompanied with a low induction. Motivated by the results obtained with this NHC ligand, we prepared the non-chiral IBioxMe$_4$·HOTf[211], which gave better results than tricyclohexylphosphine. Indeed, the formation of both **3.24a** and **3.25** byproducts was almost

suppressed and indane **3.10a** was isolated in 92% yield. We then prepared NHC **3.29** developed by P. Kündig.[212,213] This ligand proved to be highly efficient and led to **3.10a** in 92% yield with a promising induction (66:34 e.r.).
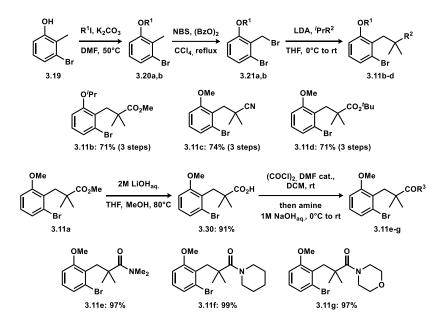

Table 3.1. *Preliminary screening of conditions.*

Entry	conditions[a]	Ligand	conversion (%)[b]	e.r. of **3.10a**[c]
1	A	PCy₃	90 (89)	-
2	B	**3.26**	60	49:51
3	C	**3.27**	28	51:49
4	C	**3.28**	14	49:51
5	D	**2.16h**	26	50:50
6	E	IBiox[(-)-menthyl]·HOTf	93	56:44
7	F	IBioxMe₄·HOTf	96 (92)	-
8	E	**3.29**	>95 (92)	66:34

[a]*A:* ***3.11a*** *(0.2 mmol), Pd₂dba₃ (2.5 mol%), PCy₃ (10 mol%), PivOH (30 mol%) and K₂CO₃ (1.5 equiv) in xylenes (2 mL) at 140°C for 18; B:* ***3.11a*** *(0.2 mmol), Pd₂dba₃ (2.5 mol%),* ***3.26*** *(10 mol%), PivOH (50 mol%) and Cs₂CO₃ (2 equiv) in xylenes (2 mL) at 140°C for 18h; C:* ***3.11a*** *(0.2 mmol), Pddba₂ (10 mol%),* ***3.27*** *or* ***3.28*** *(20 mol%), PivOH (50 mol%) and Cs₂CO₃ (2 equiv) in xylenes (2 mL) at 140°C for 18h; D:* ***3.11a*** *(0.2 mmol), Pd(PCy₃)₂ (10 mol%),* ***2.16h*** *(10 mol%), Cs₂CO₃ (1.5 equiv) in xylenes (2 mL) at 140°C for 18h; E:* ***3.11a*** *(0.2 mmol), [Pd(π-cin)Cl]₂ (2.5 mol%), NHC (5 mol%), CsOPiv (1 equiv), Cs₂CO₃ (1.5 equiv), in mesitylene (2 mL) at 160°C for 18h. F:* ***3.11a*** *(0.2 mmol), [Pd(π-cin)Cl]₂ (5 mol%), NHC (10 mol%), CsOPiv (1 equiv), Cs₂CO₃ (1.5 equiv), in mesitylene (2 mL) at 160°C for 18h.* [b]*Conversion of the aryl bromide to the indane product estimated by GC−MS analysis, yield of isolated product in parentheses.* [c]*Determined by HPLC using a chiral phase.*

We then engaged **3.12** and **3.17** using IBioxMe₄·HOTf as ligand to evaluate their reactivity. We observed that **3.12** led to a poor conversion. This lack of reactivity could be explained by a sterically difficult oxidative addition. Nevertheless, under the same condition **3.17** led to the corresponding indane **3.10a** with a conversion of 95%, which indicates that the methoxy substituent is not necessary to enhance the reactivity. We decided to base our optimization on the results obtained with substrate **3.11a** and NHC **3.29**.
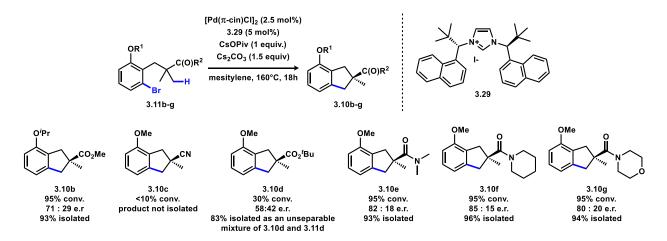
Total Synthesis of (Nor)illudalane Sesquiterpenes Based on a C(sp3)-H Activation Strategy

3.3. Optimization of Asymmetric Conditions

We then wanted to explore the impact of the substrate structure on the enantioselectivity of the reaction. In this regard, we prepared a range of new analogues of **3.11a** by modification of the ether and ester parts (**Scheme 3.4**).
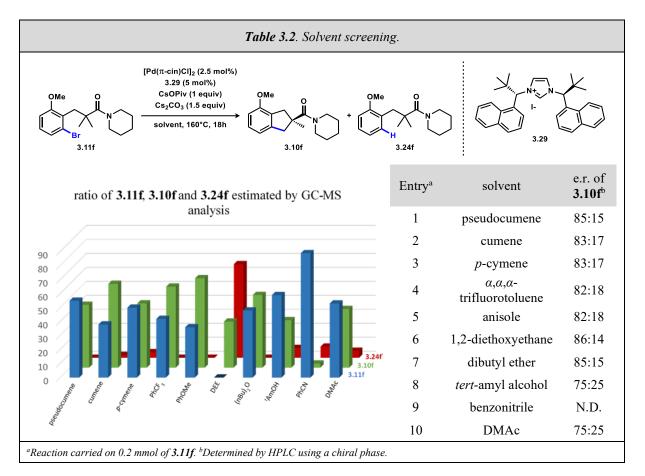

*Scheme 3.4. Preparation of substrates **3.11b-g**.*

We then engaged these substrates under the previously established conditions. Under non-asymmetric conditions, all products were isolated in satisfactory yields to serve as references for chiral HPLC analysis. Of note, compared to the results obtained with the ester **3.11a**, we observed the formation of indanone **3.25** in a larger amount for substrates **3.11e-g** when tricyclohexylphosphine was used. However, using IBioxMe4·HOTf, clean reactions and high yields could be obtained.
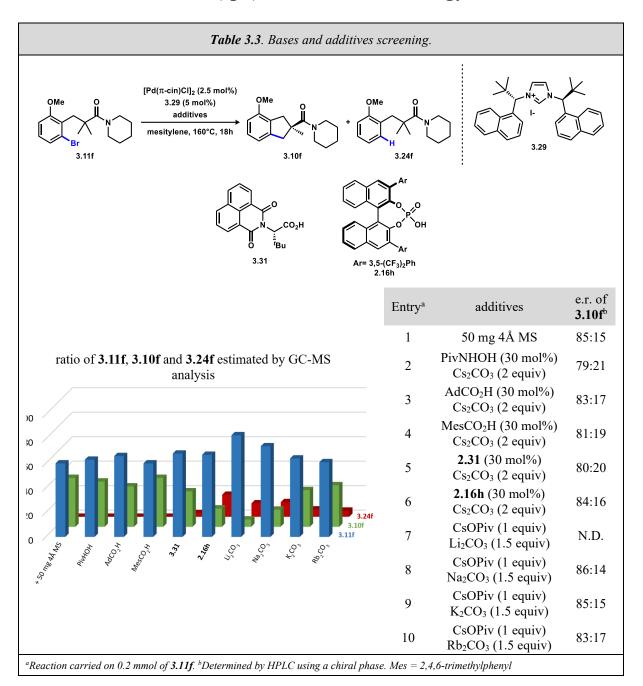
*Scheme 3.5. Test of asymmetric C(sp³)-H arylation on substrates **3.11b-g**.*

Total Synthesis of (Nor)illudalane Sesquiterpenes Based on a C(sp3)-H Activation Strategy

Under asymmetric conditions using **3.29** as ligand (**Scheme 3.5**), substrate **3.11b** bearing an isopropyl moiety gave a good reactivity and a slightly higher e.r.. However, this minor improvement was not judged sufficient in regard to the expected cleavage issues at a later stage of the synthesis. Changing the methyl ester for a nitrile or a tert-butyl ester led to lower yields and enantioselectivities. Nevertheless, changing from an ester to an amide allowed to increase significantly the induction with a maximum of 85:15 e.r. in the case of piperidine amide. Few other amides were prepared. However, in all cases the enantioselectivity was lower.

Table 3.2. Solvent screening.		

Entry[a]	solvent	e.r. of **3.10f**[b]
1	pseudocumene	85:15
2	cumene	83:17
3	*p*-cymene	83:17
4	α,α,α-trifluorotoluene	82:18
5	anisole	82:18
6	1,2-diethoxyethane	86:14
7	dibutyl ether	85:15
8	*tert*-amyl alcohol	75:25
9	benzonitrile	N.D.
10	DMAc	75:25

[a]Reaction carried on 0.2 mmol of **3.11f**. [b]Determined by HPLC using a chiral phase.
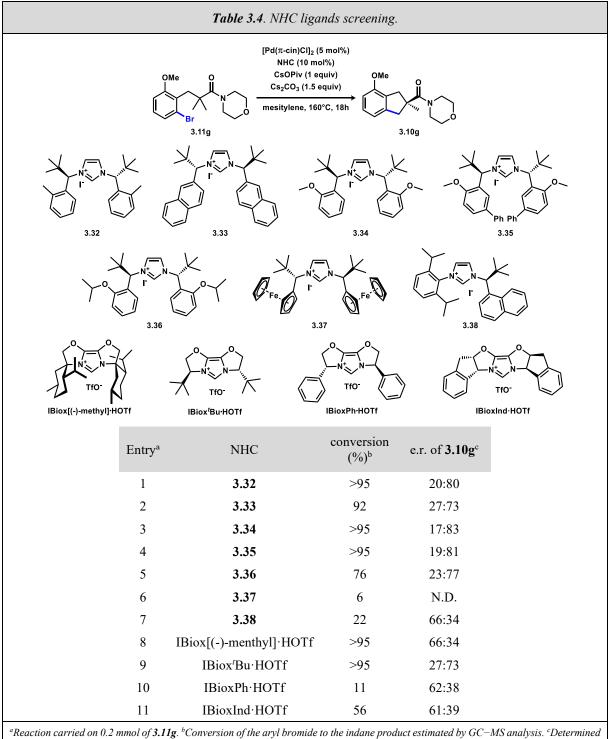
At this point, we decided to examine the reaction conditions and we screened a range of different solvents using **3.11f** as substrate (**Table 3.2**). All tested aromatic, ether, polar protic or aprotic solvents gave similar or lower enantioselectivity compared to mesitylene. Moreover, in almost every case, full conversion could not be achieved and 1,2-diethoxyethane (DEE, entry 6) was the only solvent leading to full conversion, but with the formation of a significant amount of protodebrominated product. We then tested different additives or bases (**Table 3.3**), but in all situations low conversions were observed. Besides, induction remained at a similar or lower level.

Total Synthesis of (Nor)illudalane Sesquiterpenes Based on a C(sp3)-H Activation Strategy

Table 3.3. *Bases and additives screening.*

ratio of **3.11f**, **3.10f** and **3.24f** estimated by GC-MS analysis

Entry[a]	additives	e.r. of **3.10f**[b]
1	50 mg 4Å MS	85:15
2	PivNHOH (30 mol%) Cs_2CO_3 (2 equiv)	79:21
3	$AdCO_2H$ (30 mol%) Cs_2CO_3 (2 equiv)	83:17
4	$MesCO_2H$ (30 mol%) Cs_2CO_3 (2 equiv)	81:19
5	**2.31** (30 mol%) Cs_2CO_3 (2 equiv)	80:20
6	**2.16h** (30 mol%) Cs_2CO_3 (2 equiv)	84:16
7	CsOPiv (1 equiv) Li_2CO_3 (1.5 equiv)	N.D.
8	CsOPiv (1 equiv) Na_2CO_3 (1.5 equiv)	86:14
9	CsOPiv (1 equiv) K_2CO_3 (1.5 equiv)	85:15
10	CsOPiv (1 equiv) Rb_2CO_3 (1.5 equiv)	83:17

[a]*Reaction carried on 0.2 mmol of **3.11f**.* [b]*Determined by HPLC using a chiral phase. Mes = 2,4,6-trimethylphenyl*

At this point, we suspected some reproducibility issues, which was confirmed by running a control experiment using the previously established conditions. Indeed, a 1:1 ratio of product and starting material was obtained instead of full conversion. The e.r. was also lower than expected (82:18). We investigated every parameter of the reaction, we bought new commercial batches of catalyst and bases, we prepared a new batch of substrate and ligand, but we never regained good conversions and enantioselectivities. The only solution that we found was to double the loading of palladium and ligand. Therefore, as we do not know when these reproducibility issues started, it is difficult to evaluate the validity of this screening of conditions. Moreover, we figured out that the cleavage of the amide part was only successful

71
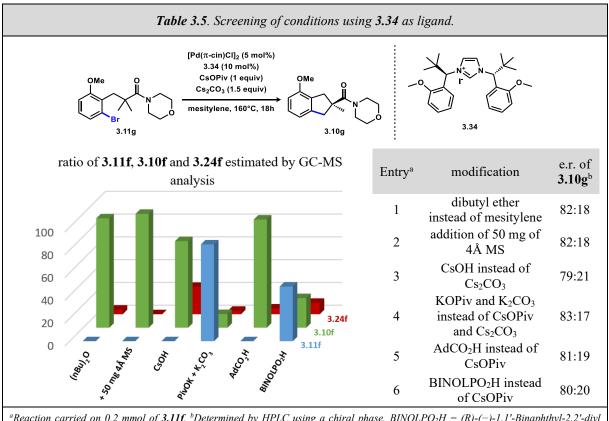
for the morpholine amide product **2.10g**. Thus, we decided to continue our investigations on substrate **2.11g**.

We prepared a range of NHC ligands from the Hermann-Kündig[212–214] and IBiox[215–217] families using known methods. We then tested these ligands in C(sp^3)-H arylation of **2.11g** (**Table 3.4**).

	Table 3.4. NHC ligands screening.

Entry[a]	NHC	conversion (%)[b]	e.r. of **3.10g**[c]
1	**3.32**	>95	20:80
2	**3.33**	92	27:73
3	**3.34**	>95	17:83
4	**3.35**	>95	19:81
5	**3.36**	76	23:77
6	**3.37**	6	N.D.
7	**3.38**	22	66:34
8	IBiox[(-)-menthyl]·HOTf	>95	66:34
9	IBiox^{t}Bu·HOTf	>95	27:73
10	IBioxPh·HOTf	11	62:38
11	IBioxInd·HOTf	56	61:39

[a]Reaction carried on 0.2 mmol of **3.11g**. [b]Conversion of the aryl bromide to the indane product estimated by GC−MS analysis. [c]Determined by HPLC using a chiral phase.

Total Synthesis of (Nor)illudalane Sesquiterpenes Based on a C(sp3)-H Activation Strategy

We observed that the presence of an ortho substituent on the aromatic moieties was essential to achieve better enantioselectivity (entry 2 compared to entries 1, 3-4). This had already been observed by P. Kündig.[213] Moreover, increasing the size of these ortho substituents as in **3.36** resulted in a negative effect on both the enantioselectivity and the reactivity (entry 5). Ferrocene analogue **3.37** gave low conversion and the e.r. was not determined (entry 6). Unsymmetrical NHC **3.38** led as well to lower conversion and induction (entry 7). IBiox[(-)-menthyl]·HOTf (entry 8) induced excellent conversion and better enantioselectivity than with methyl ester **3.11a**, but the positive effect of the amide was less important with this ligand. A better e.r. was obtained using IBiox^{t}Bu·HOTf (entry 9), but still inferior than with Hermann-Kundig type NHCs. Finally, the last two IBiox ligands led to poor results (entries 10,11). As **3.34** induced the best enantioselectivity, we screened few modifications of reaction conditions using this ligand (**Table 3.5**). Changing from mesitylene to dibutyl ether or adding some 4Å molecular sieves did not modify the reaction outcome (entries 1,2). Other bases led to decreased reactivity and/or enantioselectivity (entries 3-6). At this point, we renounced to perform any further optimization or new ligand synthesis. We envisaged the possibility to introduce a chiral center on the substrate as a source of internal induction. In this regard, we selected proline as a cheap and readily available enantiopure building block.

***Table 3.5**. Screening of conditions using **3.34** as ligand.*

ratio of **3.11f**, **3.10f** and **3.24f** estimated by GC-MS analysis

Entry[a]	modification	e.r. of **3.10g**[b]
1	dibutyl ether instead of mesitylene	82:18
2	addition of 50 mg of 4Å MS	82:18
3	CsOH instead of Cs$_2$CO$_3$	79:21
4	KOPiv and K$_2$CO$_3$ instead of CsOPiv and Cs$_2$CO$_3$	83:17
5	AdCO$_2$H instead of CsOPiv	81:19
6	BINOLPO$_2$H instead of CsOPiv	80:20
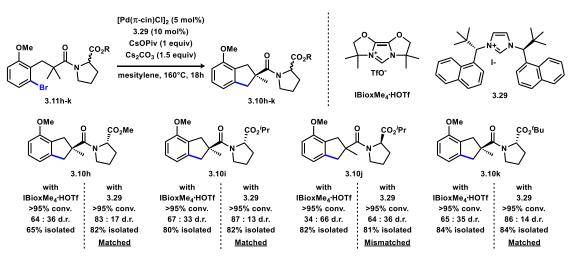
*[a]Reaction carried on 0.2 mmol of **3.11f**. [b]Determined by HPLC using a chiral phase. BINOLPO$_2$H = (R)-(−)-1,1'-Binaphthyl-2,2'-diyl hydrogenphosphate*

Total Synthesis of (Nor)illudalane Sesquiterpenes Based on a C(sp3)-H Activation Strategy

Thus, we prepared a few amides derived from proline (**Scheme 3.6**).

Scheme 3.6. *Preparation of proline derived substrates **3.11h-k**.*

We then engaged these new substrates in C(sp^3)-H arylation using IBioxMe$_4$·HOTf or **3.29** (**Scheme 3.7**). In all cases, when using the non-chiral NHC IBioxMe$_4$, we observed internal induction from the proline moiety in a range of 64:36 to 67:33 d.r.. Modifying the ester part of the proline does not seem to have a major impact on the diastereoselectivity. The use of **3.29** resulted in a matched induction with *L*-proline derivatives (**3.11h,i,k**). Whereas the isopropyl ester gave the best observed diastereoselectivity (87:13 d.r.), smaller or larger esters gave lower diastereomeric ratio. In complement, we observed the corresponding mismatch effect on the *D*-proline based substrate **3.11j**, for which external induction overcomes internal induction. Substrate **3.11i** gave at this point the best induction that we never achieved.
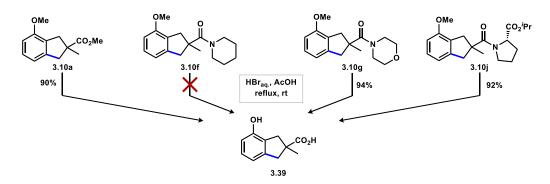
Scheme 3.7. *Asymmetric C(sp3)-H arylation of **3.10h-k**.*

Moreover, proline amides are cleavable under acidic conditions as observed previously for the corresponding morpholine amide. Unfortunately, we never managed to separate the two diastereoisomers of the products using available purification methods, even by preparative HPLC. We stopped our investigations with these results because we observed that an

intermediate in the synthesis could be enriched by recrystallization and we thought that this level of induction would be high enough in this regard.
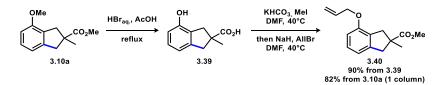
3.4. Racemic Synthesis: First Route

As exposed in the introduction, we based our synthesis on the work done by G. A. Kraus. We took racemic indane **3.10a** to explore the following steps. First, we cleaved both ester and methoxy substituents using aqueous HBr in refluxing acetic acid (**Scheme 3.8**). We used these conditions instead of the selective cleavage of the methoxy substituent described by G. A. Kraus, because they proved to be efficient for amides **3.10g,j** as well and so, potentially applicable to our enantioenriched material. Nevertheless, cleavage of piperidine amide **3.10f** gave low conversion. We observed that **3.39** is poorly soluble in chloroform, which made us think that this compound could be potentially recrystallized for enrichment.
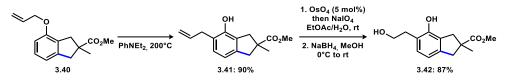
Scheme 3.8. Full deprotection overview.

We then used a sequential one-pot alkylation/allylation procedure inspired from the literature.[218] Taking advantage of the pKa difference between the phenol and carboxylic acid parts (**Scheme 3.9**), we first deprotonated the carboxylic acid using potassium hydrogenocarbonate and alkylated it using methyl iodide. Then, after evaporation of the remaining methyl iodide by bubbling argon through the reaction, sodium hydride was added followed by allyl bromide. The reported procedure describes this reaction using potassium carbonate. However, sodium hydride proved to be a more efficient base in our case. The corresponding fully protected product **3.40** was isolated in 90% yield. In a second pass, we isolated this compound in 82% yield from **3.10a** with only one purification.
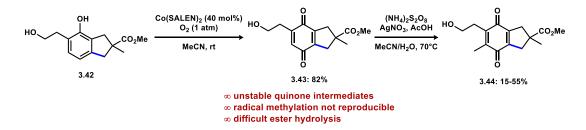
Scheme 3.9. Deprotection of 3.10a and sequential alkylation/allylation.

Total Synthesis of (Nor)illudalane Sesquiterpenes Based on a C(sp3)-H Activation Strategy

Afterward, compound **3.40** was submitted to high temperature to initiate a Claisen rearrangement. G. A. Kraus described this reaction on the ethyl ester analogue in DMF. Nevertheless, they could not reach full conversion. We observed the same result using DMF, even under microwave heating. Whereas decalin gave a worst result, we found that using *N,N*-diethylaniline as solvent led to full conversion and clean reaction. Under these conditions, **3.41** was isolated in 90% yield (**Scheme 3.10**).

Scheme 3.10. *Claisen rearrangement, Lemieux−Johnson oxidation and reduction.*

We then engaged **3.41** under ozonolysis conditions as described by G. A. Kraus. Unfortunately, we could not reproduce the reported results. Indeed, we obtained low yields (ca. 20%) along with starting material decomposition. We assume that the free phenol undergoes oxidation to the benzoquinone which then degrades. This ozonolysis problem was already discussed by D. L. J. Clive on a similar intermediate and they found that the Lemieux−Johnson oxidation gave better results.[219] Thus, we used classic Lemieux−Johnson oxidation conditions followed by reduction to produce indane **3.42** in an excellent yield of 87% over two steps. Subsequently, **3.42** was oxidized using salcomine under oxygen atmosphere, as described, yielding the corresponding unstable benzoquinone **3.43** in 82% yield (**Scheme 3.11**). We then engaged the former compound under radical methylation conditions.
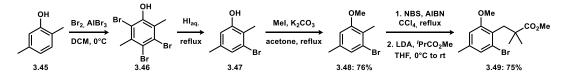
Scheme 3.11. *Oxidation to benzoquinone and radical methylation.*

At this point, we again encountered issues to reproduce the results obtained by G. A. Kraus. Indeed, we never achieved a yield higher than 55%, even after multiple attempts, even though the expected yields should have been above 60-65%. Moreover, benzoquinone **3.44** proved to be relatively unstable as **3.43**. We anyway isolated some material to continue our synthesis. There, we arrived at the same point as G. A. Kraus, who never described the final saponification,

Total Synthesis of (Nor)illudalane Sesquiterpenes Based on a C(sp3)-H Activation Strategy

which would lead to puraquinonic acid. Unfortunately, probably as G. A. Kraus, we never managed to saponify ester **3.44** to obtain racemic puraquinonic acid. We ran out of material and turned our attention to other possible strategies. Nevertheless, these results gave us important information to design a more efficient plan. Indeed, we encountered three major problems during this synthesis: (1) instability of benzoquinone intermediates; (2) low yield and irreproducibility of the radical methylation; (3) impossibility to hydrolyze the ester on the benzoquinone. These problems led us to conclude that the saponification had to be performed prior to the oxidation to benzoquinone. This also precludes the introduction of the methyl group via radical methylation, which would be likely incompatible with the carboxylic acid moiety. Therefore, this methyl group has to be installed earlier in the synthesis. Besides, a late-stage oxidation of the phenol to the benzoquinone would be more adapted in light of stability issues.

3.5. Racemic Synthesis: Second Route

For this second route, we chose to start our synthesis with the methyl group already present from the beginning. Thus, we first considered two possible ways to prepare the methylated analogue of **3.11a**. The first one (**Scheme 3.12**), which had already been partially described,[220] started from cheap phenol **3.45**, which was fully brominated and then selectively debrominated at the ortho and para positions of the hydroxy group using hydroiodic acid to yield **3.47**. The former compound was then methylated to lead to anisole **3.48** in 76% yield from **3.45**. Then, selective radical bromination of **3.48** was performed to yield the corresponding benzyl bromide,[221] which had to be used directly in the next step due to stability issues. Alkylation of methyl isobutyrate with the former performed well and led to **3.49** in 75% yield over two steps.

Scheme 3.12. first effective way to prepare 3.49.
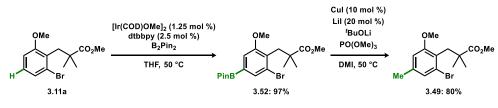
Even if this sequence proved to be efficient, some drawbacks could be noticed. The first two steps imply harsh conditions and are inelegant in terms of atom economy. Moreover, even though the benzylic bromination was quite selective, the product resulting from the undesired isomer was difficult to separate from **3.49** after alkylation. For these reasons, we considered another way to prepare **3.49**. Indeed, based on precedent work by M. Lautens,[222] we thought that lithiation/formylation of **3.50** could be achieved to obtain **3.51** (**Scheme 3.13**), which would be easily converted to the corresponding benzyl bromide and to **3.49**. Unfortunately, despite

77

Total Synthesis of (Nor)illudalane Sesquiterpenes Based on a C(sp3)-H Activation Strategy

our efforts to find suitable conditions, we never managed to obtain **3.51** by this way, probably due to the generation of the unstable benzyne.
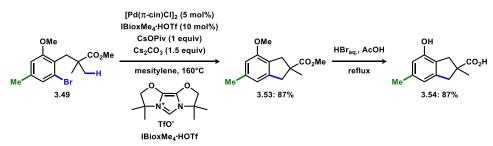
*Scheme 3.13. Unsuccessful lithiation/formylation of **3.50**.*

More recently, thanks to a report published by J. Hartwig, we found an attractive way to build a bridge between our first and second routes. Indeed, we considered a sequence of iridium-catalyzed C(sp^2)-H borylation and copper-catalyzed methylation.[223] The C-H borylation of ester **3.11a** should be selective for the least hindered position, as demonstrated by J. Hartwig for di- and trisubstituted arenes,[224,225] and the Cu-catalyzed methylation of the corresponding boronate would lead to the desired aryl bromide **3.49**. We applied this approach (**Scheme 3.14**) and boronate **3.52** was obtained in 97% yield. The copper-catalyzed methylation also performed well and yielded **3.49** in 80% yield. The global sequence from 3-bromo-2-methylphenol **3.19** (see **Scheme 3.3**) is as effective as the previous one from 2,5-xylenol **3.45**, with an overall yield of 58% for the same number of steps. In addition, boronate intermediate **3.52** could be potentially used as a platform to prepare different analogues of the targeted natural products.[226–230]
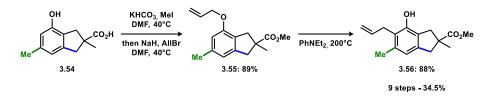
*Scheme 3.14. second effective way to prepare **3.49**.*

With **3.49** in hand, we planned to follow the same sequence that we used in the first route. We engaged **3.49** under C(sp^3)-H arylation conditions using IBioxMe$_4$·HOTf as ligand, which led to indane **3.53** in 87% yield (**Scheme 3.15**). The former was fully deprotected furnishing **3.54** in 87% yield. We observed the same propensity of **3.54** to crystallize in chloroform as for **3.39**.
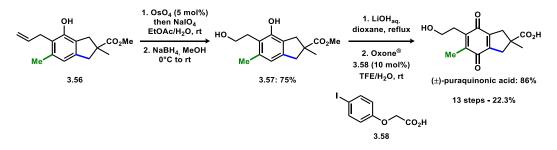
*Scheme 3.15. C(sp^3)-H arylation of **3.49** and full deprotection.*

Total Synthesis of (Nor)illudalane Sesquiterpenes Based on a C(sp3)-H Activation Strategy

One-pot sequential double alkylation of **3.54** was performed to obtain **3.55** in 89% yield followed by a Claisen rearrangement leading to **3.56** in 88% yield (**Scheme 3.16**). This 9-step sequence from 3-bromo-2-methylphenol **3.19** allowed the preparation of **3.56** in 34.5% overall yield.
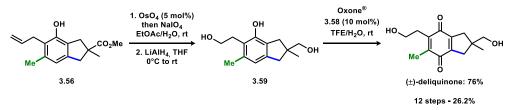
Scheme 3.16. Sequential alkylation and Claisen rearrangement.

We then engaged **3.56** under Lemieux−Johnson oxidation conditions. The crude material obtained was reduced with sodium borohydride to obtain indane **3.57** in 75% yield (**Scheme 3.17**). Saponification of the former was performed without any problem to obtain the corresponding carboxylic acid. Final oxidation of the phenol to the corresponding benzoquinone proved to be ineffective using salcomine and oxygen as in the first route. We found that this oxidation can be performed smoothly using conditions developed by T. Yakura[231] to obtain racemic puraquinonic acid in 86% yield over two steps. Overall, racemic puraquinonic acid was prepared in thirteen steps in a good global yield of 22.3%.

Scheme 3.17. Final steps to obtain racemic puraquinonic acid.
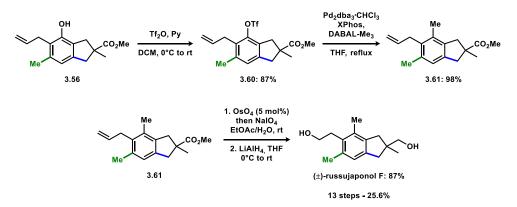
The synthesis of this racemic natural product was an important milestone in this project. At this point, we reasoned that compound **3.56** could serve as an advanced common intermediate for the divergent synthesis of other natural products, deliquinone and russujaponol F for instance.

Scheme 3.18. Final steps to obtain racemic deliquinone.

Total Synthesis of (Nor)illudalane Sesquiterpenes Based on a C(sp3)-H Activation Strategy

In this regard, after Lemieux-Johnson oxidation of **3.56**, we used lithium aluminum hydride instead of sodium borohydride to obtain fully reduced product **3.59** (**Scheme 3.18**). As previously, this compound was oxidized using Oxone and **3.58** to yield racemic deliquinone in 76% yield over three steps. Overall, racemic deliquinone was prepared in twelve steps and 26.2% yield.
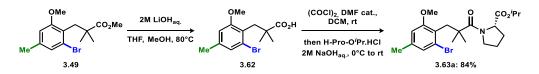
We then turned our attention to the synthesis of russujaponol F, which had never been explored in the literature. For this, we converted phenol **3.56** to the corresponding triflate in view of a Pd^0-catalyzed cross-coupling for methyl incorporation. We then ran this cross-coupling under conditions developed by S. Woodward[232] using the air-stable DABAL-Me$_3$ [DABCO-bis(trimethylaluminum)] complex. These efficient and convenient conditions furnished **3.61** in excellent yield (98%) (**Scheme 3.19**). Racemic russujaponol F could be obtained in 87% yield from this intermediate, using the same steps as for the synthesis of **3.59**. Overall, racemic russujaponol F was prepared in thirteen steps in a good global yield of 25.6%. Moreover, this work describes the first synthesis of racemic russujaponol F.

Scheme 3.19. Final steps to obtain racemic russujaponol F.
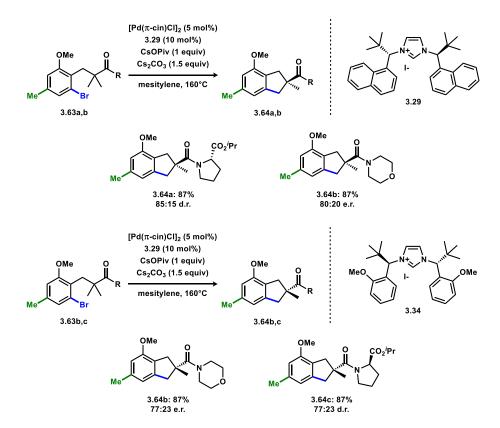
3.6. Asymmetric Synthesis

Based on the investigations on the enantioselectivity discussed in subchapter 3.3, we prepared the methylated analogue of **3.10i**. For this, **3.49** was saponified and converted to amide **3.63** in 84% yield over two steps using previously established conditions (**Scheme 3.20**).

Scheme 3.20. preparation of 3.63a.

Total Synthesis of (Nor)illudalane Sesquiterpenes Based on a C(sp3)-H Activation Strategy

3.63a was then engaged under asymmetric C(sp^3)-H arylation conditions and gave the best results when NHC **3.29** was used with a d.r. of 85:15 and 87% yield (**Scheme 3.21**). We observed that, in this case, morpholine amide analogue **3.63b** gave rise to 80:20 e.r. using 1-naphtyl NHC **3.29** and 77:23 using o-methoxyphenyl NHC **3.34**. Moreover, we observed that this lower e.r. rendered the enantioenrichment by recrystallization more difficult. When substrate **3.63c** was engaged using NHC **3.34**, a lower d.r. was observed than when **3.63a** was used in presence of **3.29**.

Scheme 3.21. *Asymmetric C(sp^3)-H arylation on substrates **3.63a-c**.*

3.64 was then engaged under deprotection conditions leading to **3.54** in 92% yield. We then investigated different recrystallization conditions for enantioenrichement. To determine the e.r. we had to convert both crystals and mother liquor residue to **3.55**. Indeed, no suitable HPLC conditions were found to determine the excess of **3.54**.
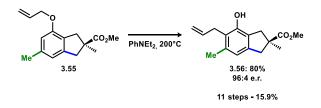
Scheme 3.22. *Deprotection and alkylation/allylation.*

We observed that crystalline material was in fact racemic and the mother liquor enantioenriched. We established that slow crystallization from chloroform and cyclohexane

Total Synthesis of (Nor)illudalane Sesquiterpenes Based on a C(sp3)-H Activation Strategy
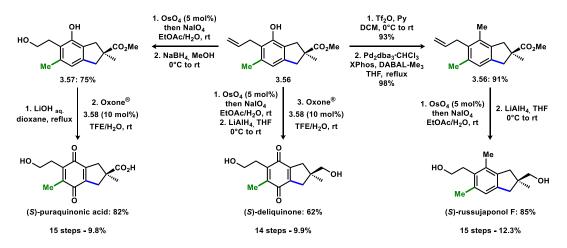
provided a greatly improved e.r. of 96:4 with a yield of 57% from **3.64**. This enantioenriched material was then engaged under alkylation conditions to obtain **3.55** in 82% yield. To establish the absolute configuration of the formed tetrasubstituted stereocenter we wanted to isolate a crystal for X-Ray analysis, but enantioenriched **3.54** was isolated as a waxy solid. We prepared numerous derivatives of this product containing a ferrocene moiety, as this strategy proved to be effective for different projects of our group in the past. Nevertheless, none of them formed suitable crystals. In complement some nitro derivatives were prepared without more success. We then prepared Mosher's amide derivatives of **3.54** after Curtius rearrangement. NOESY NMR analysis of these compounds indicated that the major enantiomer had a (*S*) configuration. This was further confirmed by vibrational circular dichroism (VCD) analysis of another derivative conducted in collaboration with T. Bürgi. More details about this can be found in the experimental part.

We then followed the route established for the racemic synthesis. Claisen rearrangement led to intermediate **3.56** in 80% yield with an unchanged e.r. of 96:4. This compound was prepared in 15.6% overall yield in eleven steps.

*Scheme 3.23. Claisen rearrangement on enantioenriched **3.55**.*
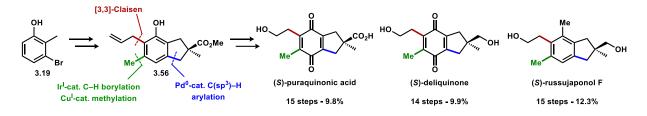
This common intermediate was then converted to the three enantioenriched natural products (**Scheme 3.24**). (*S*)-puraquinonic acid was obtained in an overall yield of 9.8% over 15 steps, (*S*)-deliquinone in 9.9% over 14 steps and (*S*)-russujaponol F in 12.3% over 15 steps. We measured the specific rotation of synthetic puraquinonic acid, deliquinone and russujaponol F and found +1.4, +0.9 and +2.1 respectively. The reported specific rotations of the natural products in the same solvents are -2.2 for (*R*)-puraquinonic acid, -0.5 for (*R*)-deliquinone, and +1.3 for (*S*)-russujaponol F. Hence, our values are consistent with the ones expected for the (S) enantiomers of these three compounds. Moreover, this is in accordance with previously enounced NMR and VCD analyses. Therefore, we prepared natural russujaponol F, ent-puraquinonic acid, and ent-deliquinone.

Total Synthesis of (Nor)illudalane Sesquiterpenes Based on a C(sp3)-H Activation Strategy

Scheme 3.24. *Final steps to obtain enantioenriched (S)-puraquinonic acid, (S)-deliquinone and (S)-russujaponol F.*

3.7. Conclusion

In conclusion, three (nor)illudalane sesquiterpenes were synthesized in racemic and enantioenriched forms from a common indane intermediate (**Scheme 3.25**). The latter was obtained by Ir- catalyzed C-H borylation and Pd^0-catalyzed C(sp^3)-H arylation as key steps, and an asymmetric version of the C-H arylation allowed the construction of the isolated, highly symmetric quaternary stereocenter. This work constitutes the first application of Pd^0-catalyzed enantioselective C(sp^3)-H activation to natural product synthesis and highlights the potential, but also the challenges, associated with this strategy.

Scheme 3.25. *Overview of asymmetric synthesis of (S)-puraquinonic acid, (S)-deliquinone and (S)-russujaponol F.*
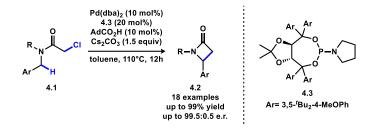
Nevertheless, despite all our efforts, the key asymmetric C(sp^3)-H arylation was not highly enantioselective, which constrained us to enrich an intermediate by recrystallization. This strongly decreased the global yield compared to the racemic synthesis. However, this strategy remains interesting to access such structures thanks to its generality and relative simplicity compared to previously reported work.

Total Synthesis of (Nor)illudalane Sesquiterpenes Based on a C(sp3)-H Activation Strategy

Total Synthesis of (Nor)illudalane Sesquiterpenes Based on a C(sp3)-H Activation Strategy

4. Construction of Indanes via Asymmetric C(sp^3)-H Activation of Methylene Positions

∗ *Work ongoing in collaboration with Marco Zuccarello during his master thesis and current PhD in our group.*

4.1. Introduction
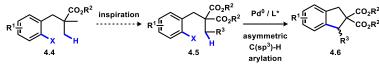
As exposed in the introduction of this thesis, the desymmetrization of enantiotopic carbons via asymmetric intramolecular C(sp^3)-H arylation has been largely explored. In contrast, the creation of stereocenters via the desymmetrizing activation of one of the two enantiotopic protons of a methylene position is rarer. Indeed, only one report by N. Cramer describes such a transformation (**Scheme 4.1**).[150] This work describes the selective activation of a benzylic position using *α*-chloroacetamides as oxidative addition sites leading to the formation of *β*-lactams in high yield and enantioselectivity. This was achieved using a combination of palladium(0), a fine tuned TADDOL-based phosphoramidite ligand and adamantyl carboxylic acid.

Scheme 4.1. Synthesis of β-lactams via asymmetric C(sp^3)-H activation of benzylic positions.

In this report, one example where R is an ethyl group demonstrates that benzylic positions are relatively easy to activate compared to unactivated methylene positions. Actually, no formation of the *β*-lactam resulting from the activation of the ethyl group was mentioned in this paper. Indeed, the activation of nonactivated methylene protons is empirically known to be more challenging than the ones of methyl, benzylic or cyclopropyl positions based on experimental observations. Therefore, we wanted to explore this type of interesting transformations to develop a new useful methodology. We thought that substrates **4.5** inspired from **4.4** used previously for the total synthesis of (nor)illudalanes would constitute a good starting point (**Scheme 4.2**). Indeed, these substrates can be easily prepared by the sequential double alkylation of malonate esters. Moreover, the corresponding indanes **4.6** obtained after

Construction of Indanes via Asymmetric C(sp3)-H Activation of Methylene Positions

asymmetric C(sp^3)-H arylation could constitute interesting intermediates for the synthesis of different natural products.

Scheme 4.2. *Proposed substrates inspired from our previous project and corresponding indanes after C(sp^3)-H arylation.*

Indeed, we found in the literature a range of prenylated chalcones isolated from *desmodium renifolium* and *streblus indicus*. Renifolin A-H[233] and indidene A-C[234] present similar structures composed of a trans-disubstituted indane and an oxygenated aromatic moiety installed on a side chain or directly linked to the aromatic part of the indane.
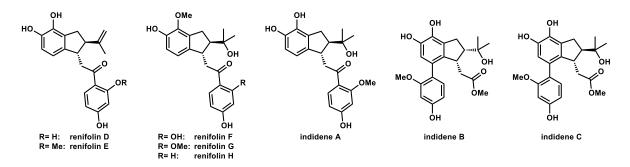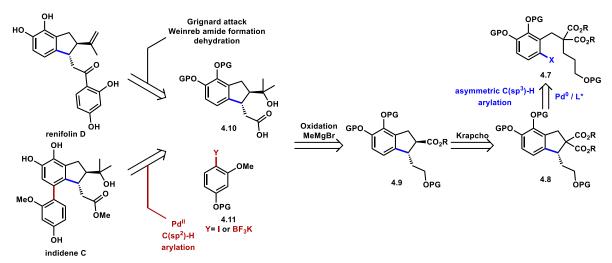
Figure 4.1. *Range of potential targets using this methodology.*

As examples, retrosynthetic analyses for renifolin D and indidene C are presented in **Scheme 4.3**. Indane **4.8** would be constructed using the developed Pd^0-catalyzed asymmetric C(sp^3)-H arylation. Then Krapcho mono-decarboxylation of the malonate unit should lead to the thermodynamically favored *trans*-indane **4.9**. Afterward, oxidation of the side chain and dimethylation would conduce to intermediate **4.10**, which would be the common intermediate of our divergent synthesis.
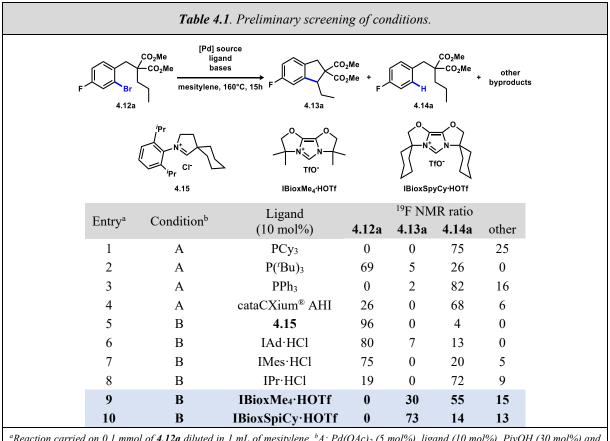
Scheme 4.3. *Retrosynthetic analysis for renofolin D and indidene C*

Construction of Indanes via Asymmetric C(sp3)-H Activation of Methylene Positions

Renifolin D would be obtained by addition of a Grignard reagent (Grignard formed from **4.11**) on the corresponding Weinreb amide and subsequent dehydration (using Burgess reagent for example). Indidene C would be prepared by $C(sp^2)$-H arylation using the carboxylic acid located on the side chain as directing group, based on the work described by J.-Q. Yu.[235] In addition, some protection/deprotection steps would be for sure necessary.

4.2. First Hit and Optimization
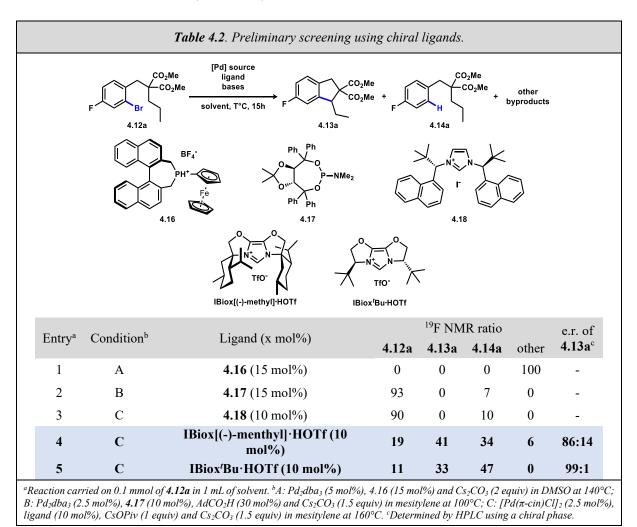
We envisaged to conduct our optimization using ^{19}F NMR for quantification. For this reason, we chose substrate **4.12a** bearing a fluorine on the aromatic as our model substrate. This substrate was prepared easily by sequential alkylation of dimethyl malonate using 2-bromobenzyl bromide and *n*-propyl iodide. The corresponding proto-debrominated product **4.14a** was also prepared by hydrogenation of **4.12a** to determine its shift in ^{19}F NMR. We initiated our screening by testing different phosphines under classic conditions for $C(sp^3)$-H arylation (**Table 4.1**, entries 1-4). With tricyclohexylphosphine and cataCXium® AHI (di(1-adamantanyl)-n-butyl-phosphonium iodide) the formation of the desired indane was not observed (entries 1,4).

Table 4.1. Preliminary screening of conditions.

Entry[a]	Condition[b]	Ligand (10 mol%)	4.12a	4.13a	4.14a	other
			^{19}F NMR ratio			
1	A	PCy$_3$	0	0	75	25
2	A	P(^{t}Bu)$_3$	69	5	26	0
3	A	PPh$_3$	0	2	82	16
4	A	cataCXium® AHI	26	0	68	6
5	B	**4.15**	96	0	4	0
6	B	IAd·HCl	80	7	13	0
7	B	IMes·HCl	75	0	20	5
8	B	IPr·HCl	19	0	72	9
9	**B**	**IBioxMe$_4$·HOTf**	**0**	**30**	**55**	**15**
10	**B**	**IBioxSpiCy·HOTf**	**0**	**73**	**14**	**13**
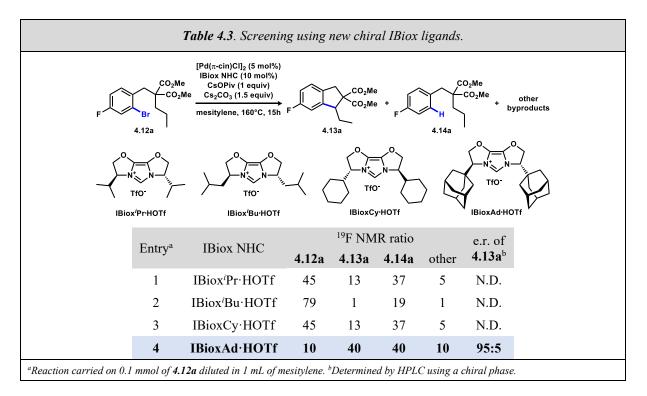
[a]Reaction carried on 0.1 mmol of **4.12a** diluted in 1 mL of mesitylene. [b]A: Pd(OAc)$_2$ (5 mol%), ligand (10 mol%), PivOH (30 mol%) and Cs$_2$CO$_3$ (2 equiv); B: [Pd(π-cin)Cl]$_2$ (2.5 mol%), ligand (10 mol%), CsOPiv (1 equiv) and Cs$_2$CO$_3$ (1.5 equiv).

Construction of Indanes via Asymmetric C(sp3)-H Activation of Methylene Positions

The major product obtained was **4.14a** along with multiple byproducts. We observed by GC-MS analysis the formation of different decarboxylated byproducts related to starting material **4.12a** and proto-debrominated byproduct **4.14a**. This degradation is probably due to the high reaction temperature of 160°C. When tri-*tert*-butylphosphine or triphenylphosphine were used as ligands, traces of product were observed (entries 2,3). We then turned our attention to different NHC ligands as they proved to be efficient in our previous project. CAAC **4.15** gave low conversion (entry 5), probably due to its unstability at this high temperature. When common NHC ligands IAd·HCl, IMes·HCl and IPr·HCl were used, we observed either low conversion or proto-debrominated product formation (entries 6-8). Then, IBioxMe4·HOTf was tested and for the first time a significant amount (30%) of indane **4.13a** was obtained. Motivated by this result, we prepared IBioxSpiCy·HOTf as described by F. Glorius.[211] This ligand increases significatively the efficiency of the reaction leading to 73% of **4.13a** in ^{19}F NMR.

Following these promising results using IBiox-type NHC, we tested some other chiral ligands under described conditions (**Table 4.2**).

Entry[a]	Condition[b]	Ligand (x mol%)	4.12a	4.13a	4.14a	other	e.r. of 4.13a[c]
			^{19}F NMR ratio				
1	A	**4.16** (15 mol%)	0	0	0	100	-
2	B	**4.17** (15 mol%)	93	0	7	0	-
3	C	**4.18** (10 mol%)	90	0	10	0	-
4	C	**IBiox[(-)-menthyl]·HOTf (10 mol%)**	19	41	34	6	86:14
5	C	**IBiox^tBu·HOTf (10 mol%)**	11	33	47	0	99:1

Table 4.2. Preliminary screening using chiral ligands.

[a]Reaction carried on 0.1 mmol of **4.12a** in 1 mL of solvent. [b]A: Pd2dba3 (5 mol%), 4.16 (15 mol%) and Cs2CO3 (2 equiv) in DMSO at 140°C; B: Pd2dba3 (2.5 mol%), **4.17** (10 mol%), AdCO2H (30 mol%) and Cs2CO3 (1.5 equiv) in mesitylene at 100°C; C: [Pd(π-cin)Cl]2 (2.5 mol%), ligand (10 mol%), CsOPiv (1 equiv) and Cs2CO3 (1.5 equiv) in mesitylene at 160°C. [c]Determined by HPLC using a chiral phase.

Construction of Indanes via Asymmetric C(sp3)-H Activation of Methylene Positions

Using binepine **4.16** as ligand led to complete conversion to the mono-decarboxylated analogue of **4.12a**, probably because DMSO used as solvent is known to promote Krapcho reaction (entry 1). Phosphoramidite ligand **4.17** and Herrmann-Kündig type NHC **4.18** gave low conversion without traces of indane **4.13a** (entries 2,3). As for the non-asymmetric conditions, only IBiox-type NHC gave some reactivity (entries 4,5). Indeed, IBiox[(-)-menthyl]·HOTf and IBiox^{t}Bu·HOTf led to 41% and 33% of the desired indane. Moreover, we were really pleased to observe a really high induction (99:1 e.r.) with IBiox^{t}Bu·HOTf. The use of IBiox[(-)-menthyl]·HOTf resulted in a lower induction with 86:14 e.r.. Considering the impact of the substitutents' size observed for achiral IBiox, we wanted to test a range of bulky chiral analogues. In this regard, we prepared described IBiox^{i}Pr·HOTf and its new analogues IBiox^{i}Bu·HOTf, IBioxCy·HOTf and IBioxAd·HOTf following established routes.[215,216]

Table 4.3. Screening using new chiral IBiox ligands.

Entry[a]	IBiox NHC	^{19}F NMR ratio				e.r. of 4.13a[b]
		4.12a	**4.13a**	**4.14a**	other	
1	IBiox^{i}Pr·HOTf	45	13	37	5	N.D.
2	IBiox^{i}Bu·HOTf	79	1	19	1	N.D.
3	IBioxCy·HOTf	45	13	37	5	N.D.
4	**IBioxAd·HOTf**	**10**	**40**	**40**	**10**	**95:5**

[a]Reaction carried on 0.1 mmol of **4.12a** diluted in 1 mL of mesitylene. [b]Determined by HPLC using a chiral phase.

We then tested these ligands in the studied reaction (**Table 4.3**). These results seem to confirm that the reactivity depends on the steric bulk of the ligand. Indeed, IBiox bearing a smaller group (entries 1-3) led to lower conversion compared to bulkier IBiox (entries 4 of **Table 4.3** and entries 4,5 of **Table 4.3**). Moreover, IBioxAd·HOTf gave the best compromise between reactivity and enantioselectivity with 40% of **4.13a** in ^{19}F NMR and 95:5 e.r.. We decided to continue our screening with IBioxAd·HOTf as ligand. We then modified some parameters of the reaction: the amount of cesium carbonate, the temperature and the concentration (**Table 4.4**).

Construction of Indanes via Asymmetric C(sp3)-H Activation of Methylene Positions

Table 4.4. Influence of the amount of cesium carbonate, temperature and concentration.

Entry[a]	Cs$_2$CO$_3$ (n equiv)	T (°C)	Concentration (M)	^{19}F NMR ratio				e.r. of 4.13a[b]
				4.12a	4.13a	4.14a	other	
1	1.5	120	0.1	9	36	43	12	N.D.
2	**1.5**	**140**	**0.1**	**0**	**54**	**38**	**7**	**98:2**
3	**2**	**160**	**0.1**	**0**	**60**	**25**	**15**	**98:2**
4	3	160	0.1	0	63	24	13	N.D.
5	2	120	0.1	69	7	20	4	N.D.
6	2	140	0.1	0	49	42	9	N.D.
7	**1.5**	**160**	**0.2**	**0**	**60**	**28**	**12**	**98:2**
8	1.5	160	0.05	6	53	35	6	98:2
9	1.5	120	0.2	7	36	47	10	N.D.
10	1.5	140	0.2	0	59	35	6	N.D.

[a]Reaction carried on 0.1 mmol of **4.12a**. [b]Determined by HPLC using a chiral phase.
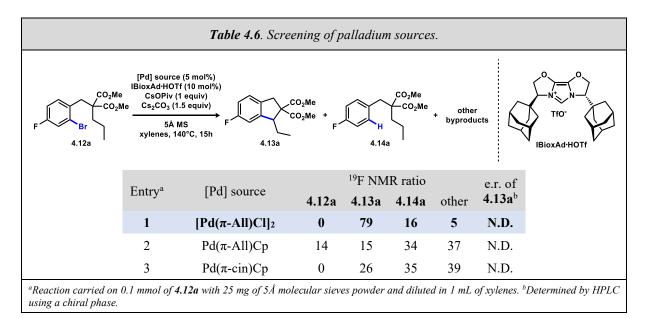
At 120°C, the same results were obtained than at 160°C (entry 1 compared to entry 4 of **Table 4.3**). Nevertheless, at 140°C, full conversion and a higher ratio of 54% of indane **4.13a** were observed (entry 2). Increasing the amount of cesium carbonate to 2 equivalents resulted as well in a better ratio of **4.13a** (60%, entry 3). However, the use of 3 equivalents of cesium carbonate did not lead to further improvement (entry 4). We then tried to combine both effects without success (entries 5,6). When the concentration was increased to 0.2 M, a higher ratio of product was obtained (60%, entry 7), but when the concentration was halved no significant impact was observed (entry 8). We tried again to combine the beneficial effects of a lower temperature and a higher concentration, but similar results were observed (entries 9,10). However, in this set of reactions, the enantiomeric ratio seems to be stable, when measured (entries 2,3,7,8). We then continued our investigations (**Table 4.5**). At 140°C, using xylenes instead of mesitylene (entry 1), a better ratio of **4.13a** was observed compared to entry 2 of **Table 4.4**. When pivalic acid was used instead of cesium pivalate, similar ratios of product were observed at 160°C in mesitylene or 140°C in xylenes (entries 2,4). Nevertheless, at 140°C in mesitylene full conversion was not achieved (entry 3). When different carboxylic acids or carboxylates were used instead of pivalates or pivalic acid, inferior results were obtained (entries 5-9). As xylenes seem to be beneficial for the reaction outcome, we continued our

Construction of Indanes via Asymmetric C(sp3)-H Activation of Methylene Positions

screening with this solvent. Addition of 5Å molecular sieves powder gave a significantly better result with 80% of indane **4.13a** in ^{19}F NMR (entry 12). However, 3Å and 4Å molecular sieves led to worse results (entries 10,11). We also tried to decrease the amount of cesium pivalate, but lower ratios of **4.13a** (entries 13,14) were obtained. When *o*-xylene, *p*-xylene or dibutyl ether were used instead of mesitylene, we observed as well decreased ratios of **4.13a**. Moreover, in this series as well, the e.r. remained stable at 98:2.

***Table 4.5**. Screening of solvents, temperature and carboxylate or carboxylic acid.*

Entry[a]	acid or base (x equiv)	Cs$_2$CO$_3$ (y equiv)	Solvent	T (°C)	^{19}F NMR ratio				e.r. of 4.13a[b]
					4.12a	**4.13a**	**4.14a**	other	
1	CsOPiv (1 equiv)	1.5	xylenes	140	0	62	33	5	98:2
2	PivOH (0.3 equiv)	2	mesitylene	160	0	65	24	11	98:2
3	PivOH (0.3 equiv)	2	mesitylene	140	23	31	38	7	98:2
4	PivOH (0.3 equiv)	2	xylenes	140	0	57	37	6	98:2
5	CsOAc (1 equiv)	1.5	mesitylene	160	43	14	41	2	N.D.
6	CF$_3$CO$_2$Cs (1 equiv)	1.5	mesitylene	160	10	51	39	0	N.D.
7	AdCO$_2$H (0.3 equiv)	2	mesitylene	160	43	22	33	2	N.D.
8	MesCO$_2$H (0.3 equiv)	2	mesitylene	160	0	33	51	16	N.D.
9	CF$_3$CO$_2$Cs (1 equiv)	1.5	mesitylene	140	76	0	24	0	N.D.
10[c]	CsOPiv (1 equiv)	1.5	xylenes	140	18	15	32	35	N.D.
11[d]	CsOPiv (1 equiv)	1.5	xylenes	140	4	36	31	29	N.D.
12[e]	**CsOPiv (1 equiv)**	**1.5**	**xylenes**	**140**	**0**	**80**	**18**	**2**	**98:2**
13[e]	CsOPiv (0.3 equiv)	1.5	xylenes	140	0	72	20	8	N.D.
14[e]	CsOPiv (0.3 equiv)	2	xylenes	140	0	71	26	3	N.D.
15[e]	CsOPiv (1 equiv)	1.5	*o*-xylene	140	0	77	20	3	N.D.
16[e]	CsOPiv (1 equiv)	1.5	*p*-xylene	140	0	74	24	2	N.D.
17[e]	CsOPiv (1 equiv)	1.5	dibutyl ether	140	0	57	39	4	N.D.

*[a]Reaction carried on 0.1 mmol of **4.12a** diluted in 1 mL of solvent. [b]Determined by HPLC using a chiral phase. [c]25 mg of 3Å molecular sieve powder was added. [d]25 mg of 4Å molecular sieves powder was added. [e]25 mg of 5Å molecular sieves powder was added.*

We were pleased with the results of entry 12. Nevertheless, product **4.13a** and **4.14a** proved to be unseparable by column chromatography. Thus, we decided to do a second round of optimization to try to reduce the formation of this undesired byproduct.

Construction of Indanes via Asymmetric C(sp3)-H Activation of Methylene Positions

Table 4.6. *Screening of palladium sources.*

Entry[a]	[Pd] source	4.12a	4.13a	4.14a	other	e.r. of 4.13a[b]
1	**[Pd(π-All)Cl]₂**	**0**	**79**	**16**	**5**	**N.D.**
2	Pd(π-All)Cp	14	15	34	37	N.D.
3	Pd(π-cin)Cp	0	26	35	39	N.D.

*[a]Reaction carried on 0.1 mmol of **4.12a** with 25 mg of 5Å molecular sieves powder and diluted in 1 mL of xylenes. [b]Determined by HPLC using a chiral phase.*

We tested few other palladium sources instead of [Pd(π-cin)Cl]₂ (**Table 4.6**). [Pd(π-All)Cl]₂ led to similar results (entry 1). We also prepared Pd(π-All)Cp and Pd(π-cin)Cp complexes which both gave a lower ratio of indane **4.13a** (entries 2,3). We chose to continue our screening with [Pd(π-All)Cl]₂. Indeed, this complex can be easily prepared and the use of a homemade complex allows to control its purity and prevents reproducibility issues.

We then screened a range of acids to replace cesium pivalate. Nevertheless, all tested acids proved to be less efficient than cesium pivalate (**Table 4.7**).

Table 4.7. *Screening of acids.*

Entry[a]	Acid	4.12a	4.13a	4.14a	other	e.r. of 4.13a[b]
1	xanthanoic acid	87	0	11	2	N.D.
2	dibenzyl phosphate	88	3	8	1	N.D.
3	PivNHOH	66	4	14	16	N.D.
4	AdCO₂H	91	5	3	1	N.D.
5	MesCO₂H	67	14	14	5	N.D.
6	AcOH	88	1	8	3	N.D.
7	hexanoic acid	2	61	30	7	N.D.

*[a]Reaction carried on 0.1 mmol of **4.12a** with 25 mg of 5Å molecular sieves powder and diluted in 1 mL of xylenes. [b]Determined by HPLC using a chiral phase.*

Construction of Indanes via Asymmetric C(sp3)-H Activation of Methylene Positions

Afterward, some other stochiometric bases were used in place of cesium carbonate (**Table 4.8**). However, none of them led to better results.

	Table 4.8. Screening of stochiometric base.					

			^{19}F NMR ratio			e.r. of
Entry[a]	base	**4.12a**	**4.13a**	**4.14a**	other	**4.13a**[b]
1	K_2CO_3	35	4	17	44	N.D.
2	Rb_2CO_3	0	35	18	47	N.D.
3	K_3PO_4	45	12	18	25	N.D.
4	CsOH	57	3	32	8	N.D.

[a]Reaction carried on 0.1 mmol of **4.12a** with 25 mg of 5Å molecular sieves powder and diluted in 1 mL of xylenes. [b]Determined by HPLC using a chiral phase.

The next step was an extensive screening of solvents (**Table 4.9**). We first tested a range of aromatic solvents (entries 1-6). Anisole, pseudocumene, cumene and *p*-cymene did not lead to full conversion. Moreover, high amounts of proto-debrominated byproduct were observed (entries 1-4). Toluene gave a slightly lower proportion of **4.13a** than xylenes (entry 5). Nevertheless, the use of *α,α,α*-trifluorotoluene as solvent resulted in the formation of the expected indane in 84%. Ether solvents gave worse results with maximum 60% of product formation with dibutyl ether (entries 7-9). With *tert*-amyl alcohol the product was not observed (entry 10). In diethyl carbonate, proto-debrominated compound **4.14a** was the major product (entry 11). Finally, polar solvents such as DMF and DMSO led to complete monodecarboxylation of **4.12a** (entries 12,13). We kept *α,α,α*-trifluorotoluene as the best solvent to continue our investigations.

We prepared the well-defined precatalyst Pd(IBioxAd)(π-All)Cl using conditions described by P. Kündig (**Scheme 4.4**).[214] We expected that this complex could lead to a cleaner reaction outcome. We then conducted the last screening of our optimization (**Table 4.10**). When the amounts of cesium pivalate and cesium carbonate were decreased to 30 mol% and 1 equivalent respectively, we observed 89% of **4.13a** in ^{19}F NMR (entry 1). When the reaction was run using the well-defined precatalyst, a similar result was observed (entry 2). Moreover, in both cases, an e.r. of 98:2 was measured.

Construction of Indanes via Asymmetric C(sp3)-H Activation of Methylene Positions

| | | | Table 4.9. Screening of solvents. | | | | |

Entry[a]	solvent	^{19}F NMR ratio				e.r. of 4.13a[b]
		4.12a	4.13a	4.14a	other	
1	anisole	57	11	21	11	N.D.
2	pseudocumene	20	40	36	4	N.D.
3	cumene	7	24	37	32	N.D.
4	*p*-cymene	22	4	55	19	N.D.
5	toluene	0	76	21	3	N.D.
6	**α,α,α-trifluorotoluene**	**0**	**84**	**14**	**2**	**N.D.**
7	CPME	0	45	34	21	N.D.
8	1,4-dioxane	31	25	23	21	N.D.
9	dibutyl ether	0	60	33	7	N.D.
10	*tert*-amyl alcohol	40	0	26	34	N.D.
11	diethyl carbonate	11	30	50	9	N.D.
12	DMSO	0	0	0	100	N.D.
13	DMF	0	0	0	100	N.D.

[a]*Reaction carried on 0.1 mmol of 4.12a with 25 mg of 5Å molecular sieves powder and diluted in 1 mL of solvent.* [b]*Determined by HPLC using a chiral phase.*

We then tested other Ibiox NHC under these optimized conditions. IBiox*t*Bu·HOTf proved to be less efficient and led to 81% of the expected product (entry 3). Achiral IBioxMe$_4$·HOTf and IBioxSpiCy·HOTf gave good results (entries 4,5), which provides us with conditions for the preparation of racemic indanes. In complement, we conducted two control experiments. When the reaction was carried out without cesium carbonate, only traces of proto-debrominated product were observed along with starting material (entry 6). Moreover, running the reaction without cesium pivalate resulted as well in a lower conversion, but 9% of product were observed along with 26% of **4.14a** (entry 7).
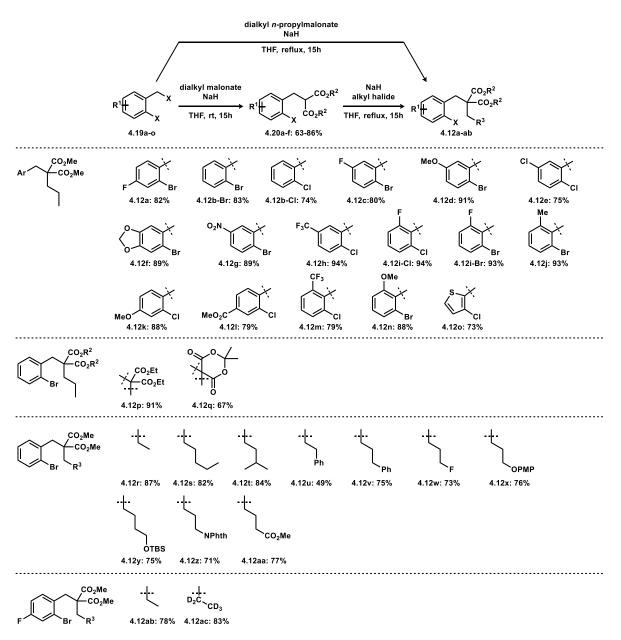
Scheme 4.4. *Preparation of a well-defined precatalyst from IBioxAd·HOTf.*

Construction of Indanes via Asymmetric C(sp3)-H Activation of Methylene Positions

Table 4.10. Final optimization.

Entry[a]	[Pd] source	IBiox NHC	^{19}F NMR ratio				e.r. of 4.13a[b]
			4.12a	**4.13a**	**4.14a**	**other**	
1	[Pd(π-All)Cl]$_2$	IBioxAd·HOTf	0	89	8	3	98:2
2	Pd(IBioxAd)(π-All)Cl		0	86	9	5	98:2
3	[Pd(π-All)Cl]$_2$	IBiox^{t}Bu·HOTf	0	81	9	10	N.D.
4	[Pd(π-All)Cl]$_2$	IBioxMe$_4$·HOTf	0	83	9	8	-
5	[Pd(π-All)Cl]$_2$	IBioxSpiCy·HOTf	0	89	5	6	-
6[c]	[Pd(π-All)Cl]$_2$	IBioxAd·HOTf	96	0	4	0	N.D.
7[d]	[Pd(π-All)Cl]$_2$	IBioxAd·HOTf	56	9	26	9	N.D.

[a]*Reaction carried on 0.1 mmol of **4.12a** with 25 mg of 5Å molecular sieves powder and diluted in 1 mL of α,α,α-trifluorotoluene.* [b]*Determined by HPLC using a chiral phase.* [c]*Carried without Cs$_2$CO$_3$.* [d]*Carried without CsOPiv.*

These results seem to indicate that both pivalate and carbonate are involved in the catalytic process, maybe by forming a cluster as proposed previously in the discussion about the mechanistic studies conducted with BPA (subchapter 2.5).
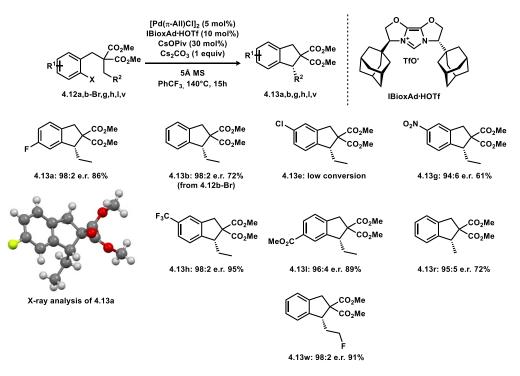
4.3. Scope and limitations

With the optimized conditions in hand, we prepared a variety of substrates in order to explore the scope of this transformation (**Scheme 4.5**). In this regard, we used two similar procedures. The first one in which malonate was first benzylated and then alkylated using a range of alkyl halides. The other one was the benzylation of commercial dialkyl *n*-propylmalonates. By those ways, a range of seventeen substrates with different substituents on the aromatic part were prepared. We also prepared one diethyl malonate substrate and one Meldrum's acid derivative. Then, nine substrates bearing different alkyl chains were prepared, either pure alkyl or functionalized chains. In complement, we prepared two substrates with a fluorine on the aromatic and an ethyl chain deuterated or not, in prevision of kinetic experiments, that we plan to monitor by ^{19}F NMR, to determine a possible kinetic isotope effect.

Construction of Indanes via Asymmetric C(sp3)-H Activation of Methylene Positions

Scheme 4.5. *Preparation of substrates.*

We then started to investigate the scope of our transformation using these substrates. With all substrates tested so far, we observed the formation of the corresponding proto-debrominated byproducts in a range of 5-15% (determined by GC-MS). Unfortunately, the latter cannot be separated from the expected indanes using classical column chromatography. We turned our attention to reversed-phase preparative HPLC without much more success. However, better results were obtained with a normal phase column, although purifications remain tricky. Here, we present the first products that we could purify (**Scheme 4.6**). Other experiments are ongoing.

Construction of Indanes via Asymmetric C(sp3)-H Activation of Methylene Positions
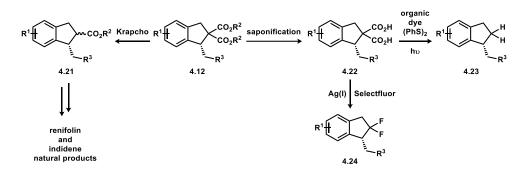
Scheme 4.6. *Preliminary scope, reactions carried on 0.2 mmol.*

The substrate used during the optimization led to indane **4.12a**, which was isolated in 86% yield with 98:2 e.r.. Moreover, this indane was crystalized and its structure determined by X-ray crystallography. Nevertheless, the flack parameter indicates a 3:1 ratio between the two enantiomers in the crystal. Thus the exact configuration remains uncertain. Changing the aromatic properties with electro-withdrawing groups seems to be well tolerated (**4.13g,h,l**) as well as changing bromine for chloride as oxidative addition site (**4.13h,l**). However, putting another chlorine on the aromatic shuts down the reaction, probably due to competitive oxidative addition which leads to an unproductive palladium(II) complex. A shorter chain resulted in a slightly lower 95:5 e.r. with a good isolated yield of 72%. In this case, we observed, by GC-MS analysis, traces of a byproduct resulting from the activation of the terminal methyl position. Addition of a fluorine on the chain is also tolerated. Indeed, indane **4.13w** was isolated in 91% yield with 98:2 e.r.. Other substrates were already tested and showed good results by GC-MS analysis. Nevertheless, conditions for their purification were not found yet.

4.4. Conclusion and Outlooks

In conclusion, the development of a new methodology for indanes synthesis via asymmetric C(sp^3)-H arylation of unactivated methylenes by desymmetrization of two enantiotopic protons is on a good way. At this point, preliminary results seem really promising. The main drawback remains the difficulties of purification. After mono-decarboxylation, the obtained indanes could

Construction of Indanes via Asymmetric C(sp3)-H Activation of Methylene Positions

be used, as discussed previously, as intermediates in the synthesis of different natural products. Moreover, a recent methodology developed by D. A. Nicewicz[236] could be applied on **4.13** derivatives for complete bis-decarboxylation to obtain the corresponding indanes **4.23** (**Scheme 4.7**). Similarly, a recent report by J.-P. Chen[237] describes a method for the Ag-catalyzed chemoselective decarboxylative mono- and gemdifluorination of malonic acid derivatives. These few examples of post-functionalization demonstrate that malonate derivatives constitute an excellent platform for further modifications.
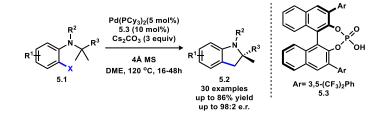
Scheme 4.7. *Possible post-functionalization of the obtained indanes*

Construction of Indanes via Asymmetric C(sp3)-H Activation of Methylene Positions

Construction of Indanes via Asymmetric C(sp3)-H Activation of Methylene Positions

5. General Conclusion

Over the past thirty years, impressive work has been accomplished for the selective and asymmetric functionalization of $C(sp^3)$-H bonds using a range of metal-catalyzed transformations. These new methods constitute an interesting toolbox which provides rapid access to molecular complexity in an atom- and step economical manner. In this context, my Ph.D was oriented toward the development of new asymmetric methodologies for $C(sp^3)$-H arylation and their application to the total synthesis of natural products.
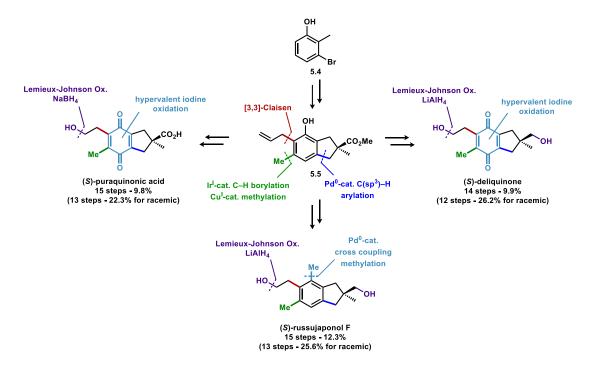
We first developed a new methodology for the synthesis of enantioenriched indolines (**Scheme 5.1**). Instead of the well-developed approach using chiral phosphorylated or NHC ligands, we used a chiral BINOL-based phosphate, in combination with tricyclohexylphosphine, for asymmetric induction. We were able to achieve high yields and enantioselectivity for a broad range of substrates. Moreover, we extended this method to the creation of tetrasubstituted stereocenters, which furnishes valuable amino acid derivatives. In complement, we applied our conditions on cyclobutyl derivatives leading to the corresponding fused indolines in medium yield and high enantioselectivity. Finally, we observed modest kinetic resolution of one substrate.

Scheme 5.1. *Synthesis of enantioenriched indolines via C(sp³)-H arylation using BPA for asymmetric induction.*
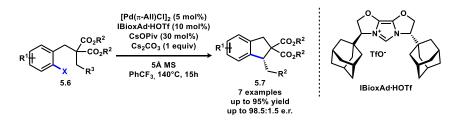
In a second part, we performed the divergent total synthesis of three (nor)illudalanes sesquiterpenes in racemic and enantioselective fashions using $C(sp^3)$-H arylation. For this, we had to perform an extensive screening of conditions to accomplish sufficient induction during the $C(sp^3)$-H arylation key step. Due to an unsatisfying enantiomeric ratio, we recrystallized one intermediate to prepare highly enantioenriched natural products. Moreover, we applied an iridium-catalyzed $C(sp^2)$-H borylation strategy, recently developed by J. Hartwig, and a subsequent copper-catalyzed methylation to the preparation of our C-H activation precursor. This work demonstrates the potential of asymmetric $C(sp^3)$-H arylation in total synthesis.

Scheme 5.2. *Total synthesis of (S)-puraquinonic acid, (S)-deliquinone and (S)-russujaponol F.*

Finally, we present here preliminary results of a new methodology for the contruction of indanes via enantioselective $C(sp^3)$-H arylation of unactivated methylene positions through the desymmetrization of two enantiotopic protons. This work is still in progress, but seems really promising. Moreover, we plan to apply this new reaction to the synthesis of different natural products from the renifolin and indidene families.

Scheme 5.3. *Synthesis of enantioenriched indanes via $C(sp^3)$-H arylation through desymmetrization of two enantiotopic protons on an unactivated methylene position*

General Conclusion

General Conclusion

6. Experimental Section

6.1. General Information

Techniques:

All reactions involving air-sensitive material were carried out in predried glassware under an argon atmosphere by using Schlenk techniques employing double-line argon-vacuum lines and working in an argon-filled glovebox. An oil bath was used as heating source unless otherwise noted. Analytical thin layer chromatography (TLC) was performed using precoated Merck silica gel 60 F254 plates (0.25 mm). Visualization of the developed chromatogram was performed by UV absorbance (254 nm) or TLC stains (KMnO4 and Phosphomolybdic acid). Flash chromatography was performed using Silicycle SiliaFlash P60 (230−400 mesh) with the indicated solvent system, using gradients of increasing polarity in most cases.

Chemicals:

Anhydrous solvents were purchased from Acros Organics or Sigma-Aldrich. The solvents were degassed by three cycles of freeze−pump−thaw and storing in single-necked flasks equipped with a JYoung PTFE valve when necessary. Palladium complexes were purchased from Sigma-Aldrich or Strem. All other chemical reagents were purchased from Sigma-Aldrich, Acros Organics, Alfa Aesar, Apollo scientific and Fluorochem and used as received without further purification unless otherwise stated.

Instrumentation:

GC-MS analyses were performed with a Shimadzu QP2010SB GC−MS apparatus on a Rtx-5 ms-LowBleed column lined with a mass (EI) detection system. HPLC analyses were performed using a Shimadzu Prominence system with SIL-20A auto sample, CTO-20AC column oven, LC-20AD pump system, DGU20A3 degasser and SPD-M20A Diode Array or UV/vis detector. The following chiral columns from Daicel Chemical Industries were used: OD-H (Chiralcel), OJ-H (Chiralcel), IA (Chiralpak), AD-H (Chiralpak) in 4.6 × 250 mm size. HPLC purifications were performed using a Shimadzu system with SIL-20AC auto sample, CTO-20AC column oven, LC-20AP pump system and SPD-M20A Diode Array or UV/vis detector. The following columns were used: Reprosher 100 Si, 5 or 10 μm, in 20 × 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

Experimental Section

centimeters (cm−1). Nuclear magnetic resonance spectra were recorded on a Bruker Advance 400 (400 MHz), Advance 500 (500 MHz) and Advance 600 (600 MHz) in deuterated chloroform (residual peaks ^1H δ 7.26 ppm, ^{13}C δ 77.16 ppm) unless otherwise noted. ^{19}F NMR spectra were referenced to external $CFCl_3$. 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 brs = broad singlet), coupling constant in Hz and integration. High resolution mass spectra were recorded by Dr. H. Nadig, 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 a PerkinElmer 341 Polarimeter in a 1 mL micro cuvette (cell length 100 mm) with NaD-Line (λ = 589 nm). The concentration (c) was given in g/100 mL.

Experimental Section

Experimental Section

Experimental Section
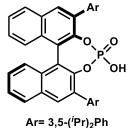
6.2. Chapter 2

6.2.1. BPA

(*R*)-(-)-VAPOL hydrogenphosphate was purchased from Sigma-Aldrich. All other chiral phosphoric acids were prepared in accordance with literature procedures and spectroscopic data were consistent with those previously reported.[162–172] Except **2.16k** which was never described:

(*R*)-3,3'-bis[2,5-di(trifluoromethyl)phenyl]-1,1'-binaphthyl-2,2'-diylphosphoric   acid (2.16k):

Prepared according to literature procedures from (2,2'-dimethoxy-[1,1'-binaphthalene]-3,3'-diyl)diboronic acid (**2.14b**) and 3,5-diisopropyl-1-bromophenyl. Suzuki cross coupling and cleavage of methoxy groups lead to corresponding BINOL derivative (917 mg, 1.51 mmol, 61% yield over 2 steps). Then the BINOL was subjected to phosphorylation with $POCl_3$ and hydrolyzed using pyridine and water to obtain **2.16k** as a white solid (782 mg, 1.17 mmol, 90% yield over two steps).

Ar= 3,5-(^{i}Pr)$_2$Ph
2.16k
$C_{44}H_{45}O_4P$
M= 668,81 g.mol^{-1}

^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 8.07 (brs, 1H), 7.99 (s, 2H), 7.96 (d, *J* = 8.2 Hz, 2H), 7.50 (ddd, *J* = 7.9, 6.6, 1.1 Hz, 2H), 7.37 (d, *J* = 8.5 Hz, 2H), 7.30 (ddd, *J* = 8.4, 6.8, 1.2 Hz, 2H), 7.27 (s, 2H), 7.27 (s, 2H), 6.96 (t, *J* = 1.6 Hz, 2H), 2.79 (hept, *J* = 6.9 Hz, 4H), 1.09 (d, *J* = 6.9 Hz, 12H), 1.06 (d, *J* = 6.9 Hz, 12H).

^{13}C NMR (126 MHz, CDCl$_3$): δ (ppm) 148.8, 145.0, 144.9, 136.9, 135.0, 135.0, 132.0, 132.0, 131.6, 131.5, 128.4, 127.3, 126.4, 125.9, 125.7, 123.9, 122.6, 122.6, 34.2, 24.2, 23.8

31P NMR (162 MHz, CDCl$_3$): δ (ppm) 2.5

IR (neat): ν (cm^{-1}) 2960, 2870, 1598, 1224, 1179, 1019, 872, 749
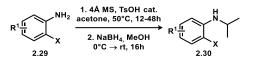
HRMS (ESI): Calcd for C$_{44}$H$_{45}$NaO$_4$P [M+Na]$^+$: 691.2948, found 691.2937

Mp: 218-222°C

[α]$_D^{20}$: -294.5° (c = 1.15, CHCl$_3$)

Experimental Section
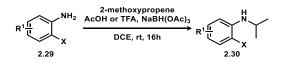
6.2.2. Substrates

General procedure A:
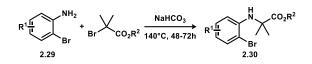
Molecular sieves (4 Å, 2.0 g/mmol), TsOH·H$_2$O (0.2 equiv) were added to a solution of o-haloarylamine (1.0 equiv) in dry acetone (5 mL/mmol) and the resulting mixture was vigorously stirred at 50°C for 12-48 h. It was filtered and the filtrate was evaporated to afford the crude imine. NaBH$_4$ (3.0 equiv) was added at 0°C to a solution of this oil in methanol. The reaction mixture was stirred overnight, during which time the ice bath warmed up to ambient temperature. Then 1.0 M aq. NaOH solution was added and the reaction was stirred for 10 min. The resulting mixture was extracted with DCM and the combined organic layers were dried over anhydrous Na$_2$SO$_4$. After removal of solvents, the crude product was purified by flash column chromatography using EtOAc–pentane mixture as eluent.

General procedure B:
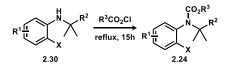
To a stirred solution of o-haloarylamine (1.0 equiv) in DCE (2-3 mL/mmol) under argon, 2-methoxypropene (1.5 equiv), AcOH or TFA (1.0 equiv) and NaBH(OAc)$_3$ (1.5 equiv) were added sequentially. After stirring at room temperature overnight, the reaction mixture was quenched with an aqueous 1M NaOH solution and extracted with DCM. The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, and concentrated under reduced pressure. If necessary, the crude product was purified by flash column chromatography using EtOAc–pentane mixture as an eluent.

Experimental Section

General procedure C:

2.29   2.30

A mixture of o-bromoarylamine (1.0 equiv), sodium bicarbonate (1.5 equiv) and 2-bromo-2-methylpropanoate (1.68 equiv) was heated at 140°C for 48-72 h. The reaction mixture was then cooled down to room temperature and directly purified by flash column chromatography on silica gel using EtOAc–pentane mixture as eluent.

General procedure D:

2.30   2.24
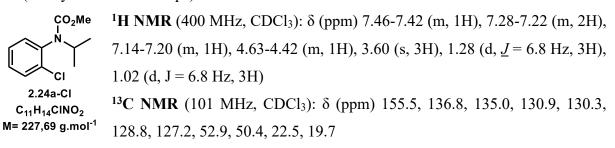
A mixture of *N*-alkyl-o-bromoarylamine in chloroformate (2-3 mL/mmol) was heated under reflux overnight. The mixture was then poured into water and extracted with DCM. The combined organic layers were dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The crude material was purified by flash column chromatography using EtOAc–pentane mixture as eluent.

Methyl (2-chlorophenyl)(isopropyl)carbamate (2.24a-Cl):

Obtained according to the **General procedure A** and **General procedure D**, as a slight yellow oil (65% yield over two steps).

^{1}**H NMR** (400 MHz, CDCl$_3$): δ (ppm) 7.46-7.42 (m, 1H), 7.28-7.22 (m, 2H), 7.14-7.20 (m, 1H), 4.63-4.42 (m, 1H), 3.60 (s, 3H), 1.28 (d, *J* = 6.8 Hz, 3H), 1.02 (d, J = 6.8 Hz, 3H)

^{13}**C NMR** (101 MHz, CDCl$_3$): δ (ppm) 155.5, 136.8, 135.0, 130.9, 130.3, 128.8, 127.2, 52.9, 50.4, 22.5, 19.7

2.24a-Cl
C$_{11}$H$_{14}$ClNO$_2$
M= 227,69 g.mol^{-1}

IR (neat): ν (cm^{-1}) 2977, 2953, 1700, 1480, 1440, 1319, 1095, 756

HRMS (ESI): Calcd for C$_{11}$H$_{14}$^{35}ClNNaO$_2$ [M+Na]$^+$: 250.0605, found 250.0605

# Experimental Section
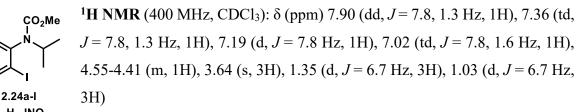
Methyl (2-bromophenyl)(isopropyl)carbamate (2.24a-Br):

Obtained according to the **General procedure A** and **General procedure D**, as a white solid (83% yield over two steps).

^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.63 (dd, J = 7.9, 1.5 Hz, 1H), 7.31 (td, J = 7.9, 1.5 Hz, 1H), 7.22-7.13 (m, 2H), 4.58-4.42 (m, 1H), 3.61 (s, 3H), 1.31 (d, J = 6.8 Hz, 3H), 1.02 (d, J = 6.8 Hz, 3H)

^{13}C NMR (101 MHz, CDCl$_3$): δ (ppm) 155.3, 138.5, 133.5, 130.8, 129.0, 127.9, 126.0, 52.9, 50.4, 22.6, 19.7

2.24a-Br
C$_{11}$H$_{14}$BrNO$_2$
M= 272,14 g.mol^{-1}

IR (neat): ν (cm^{-1}) 2977, 2951, 1693, 1323, 1096, 763

HRMS (ESI): Calcd for C$_{11}$H$_{14}$^{79}BrNNaO$_2$ [M+Na]$^+$: 294.0100, found 294.0103

Mp: 49-51°C

Methyl (2-iodophenyl)(isopropyl)carbamate (2.24a-I):

Obtained according to the **General procedure A** and **General procedure D**, as a slight yellow solid (55% yield over two steps).

^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.90 (dd, J = 7.8, 1.3 Hz, 1H), 7.36 (td, J = 7.8, 1.3 Hz, 1H), 7.19 (d, J = 7.8 Hz, 1H), 7.02 (td, J = 7.8, 1.6 Hz, 1H), 4.55-4.41 (m, 1H), 3.64 (s, 3H), 1.35 (d, J = 6.7 Hz, 3H), 1.03 (d, J = 6.7 Hz, 3H)

2.24a-I
C$_{11}$H$_{14}$INO$_2$
M= 319,14 g.mol^{-1}

^{13}C NMR (101 MHz, CDCl$_3$): δ (ppm) 155.1, 142.1, 139.9, 129.8, 129.1, 128.9, 103.5, 52.9, 50.5, 22.9, 19.9

IR (neat): ν (cm^{-1}) 2974, 2948, 1694, 1439, 1334, 1323, 1091, 761

HRMS (ESI): Calcd for C$_{11}$H$_{14}$INNaO$_2$ [M+Na]$^+$: 341.9961, found 341.9965

Mp: 72-75°C

Ethyl (2-bromophenyl)(isopropyl)carbamate (2.24b):

Obtained according to the **General procedure A** and **General procedure D**, as a colorless viscous oil (81% yield over two steps).

^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.63 (dd, J = 7.9, 1.4 Hz, 1H), 7.31 (ddd, J = 7.9, 7.4, 1.4 Hz, 1H), 7.23-7.15 (m, 2H), 4.61-4.46 (m, 1H), 4.23-3.95 (m, 2H), 1.31 (d, J = 6.7 Hz, 3H), 1.16-1.09 (m, 2H), 1.03 (d, J = 6.7 Hz, 3H)

2.24b
C$_{12}$H$_{16}$BrNO$_2$
M= 286,17 g.mol^{-1}

^{13}C NMR (101 MHz, CDCl$_3$): δ (ppm) 154.7, 138.5, 133.3, 130.7, 128.8, 127.8, 125.9, 61.4, 50.0, 22.6, 19.6, 14.6

Experimental Section

IR (neat): ν (cm^{-1}) 2977, 2934, 1698, 1443, 1309, 1086, 752

HRMS (ESI): Calcd for $C_{12}H_{16}C^{79}BrNNaO_2$ [M+Na]$^+$: 308.0257, found 308.0260

Benzyl (2-bromophenyl)(isopropyl)carbamate (2.24c):

Obtained according to the **General procedure A** and **General procedure D**, as a white solid (45% yield over two steps).

2.24c
$C_{17}H_{18}BrNO_2$
M= 348,24 g.mol^{-1}

^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.64 (d, *J* = 7.8 Hz, 1H), 7.49-7.10 (m, 8H), 5.32-5.01 (m, 2H), 4.63-4.40 (m, 1H), 1.33 (d, *J* = 6.7 Hz, 3H), 1.05 (d, *J* = 6.7 Hz, 3H)

^{13}C NMR (101 MHz, CDCl$_3$): δ (ppm) 154.7, 138.4, 136.8, 133.5, 130.9, 129.0, 128.3, 127.9, 127.7, 127.4, 126.0, 67.1, 50.5, 22.6, 19.7

IR (neat): ν (cm^{-1}) 2980, 1691, 1404, 1307, 1085, 688

HRMS (ESI): Calcd for $C_{17}H_{18}^{79}BrNNaO_2$ [M+Na]$^+$: 370.0413, found 370.0416

Mp: 56-58°C

Isobutyl (2-bromophenyl)(isopropyl)carbamate (2.24d):

Obtained according to the **General procedure A** and **General procedure D**, as a colorless viscous oil (77% yield over two steps).

2.24d
$C_{14}H_{20}BrNO_2$
M= 314,22 g.mol^{-1}

^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.63 (d, *J* = 7.9 Hz, 1H), 7.33-7.28 (m, 1H), 7.25-7.13 (m, 2H), 4.63-4.28 (m, 1H), 4.11-3.70 (m, 2H), 1.80-1.64 (m, 1H), 1.31 (d, *J* = 6.7 Hz, 3H), 1.05 (d, *J* = 6.7 Hz, 3H), 0.71 (s, 6H)

^{13}C NMR (101 MHz, CDCl$_3$): δ (ppm) 155.0, 138.7, 133.4, 131.0, 128.9, 127.8, 126.2, 71.7, 50.0, 28.0, 22.7, 19.8, 19.1

IR (neat): ν (cm^{-1}) 2960, 2874, 1697, 1314, 1087, 763

HRMS (ESI): Calcd for $C_{14}H_{20}^{79}BrNNaO_2$ [M+Na]$^+$: 336.0570, found 336.0575

Experimental Section

_N_-(2-bromophenyl)-_N_-isopropylisobutyramide (2.24e):
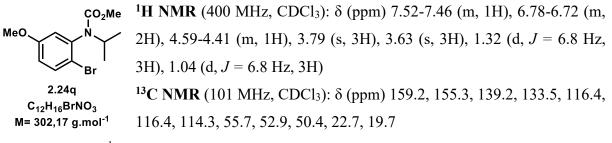
Obtained according to the **General procedure A** and **General procedure D**, as a white solid (81% yield over two steps). Spectroscopic data are consistent with those previously reported.[144]

^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.71-7.67 (m, 1H), 7.40-7.35 (m, 1H), 7.26-7.21 (m, 2H), 4.85 (sept, _J_ = 6.7 Hz, 1H), 2.10 (sept, _J_ = 6.7 Hz, 1H), 1.23 (d, _J_ = 6.5 Hz, 3H), 1.12 (d, _J_ = 6.5 Hz, 3H), 0.96 (d, _J_ = 6.7 Hz, 3H), 0.90 (d, _J_ = 6.7 Hz, 3H)

2.24e
C$_{13}$H$_{18}$BrNO
M= 284,20 g.mol^{-1}

^{13}C NMR (101 MHz, CDCl$_3$): δ (ppm) 177.0, 139.2, 134.0, 131.3, 129.6, 128.3, 126.7, 47.9, 32.9, 22.3, 20.1, 19.4, 19.3

_N_-(2-bromophenyl)-2,2,2-trifluoro-_N_-isopropylacetamide (2.24f):

_N_-isopropyl-2-bromoaniline (Obtained according to the **General procedure A**) was mixed with TFAA (5 equiv) and NEt$_3$ (1.5 equiv), the mixture was stirred overnight at ambient temperature. Then the crude was concentrated under reduce pressure and purified by flash column chromatography with a mixture of pentane and AcOEt to give **2.24f** as a white solid (84% yield over two steps).

^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.68 (dd, _J_ = 8.0, 1.6 Hz, 1H), 7.37 (td, _J_ = 7.7, 1.6 Hz, 1H), 7.29 (td, _J_ = 7.7, 1.6 Hz, 1H), 7.24 (dd, _J_ = 7.7, 0.9 Hz, 1H), 4.59 (sept, _J_ = 6.7 Hz, 1H), 1.34 (d, _J_ = 6.7 Hz, 3H), 1.12 (d, _J_ = 6.7 Hz, 3H)

2.24f
C$_{11}$H$_{11}$BrF$_3$NO
M= 310,11 g.mol^{-1}

^{13}C NMR (101 MHz, CDCl$_3$): δ (ppm) 156.6 (q, _J_ = 35.4 Hz), 136.1, 133.9, 131.7, 130.8, 128.0, 125.8, 116.0 (q, _J_ = 289.0 Hz), 52.7, 21.1, 18.8

^{19}F NMR (376 MHz, CDCl$_3$): δ (ppm) -69.13

IR (neat): ν (cm^{-1}) 2985, 1682, 1473, 1187, 1146, 1110, 736, 700, 552

HRMS (ESI): Calcd for C$_{11}$H$_{11}$^{79}BrF$_3$NNaO [M+Na]$^+$: 331.9868, found 331.9868

Mp: 40-42°C

Experimental Section

N-(2-bromophenyl)-1,1,1-trifluoro-N-isopropylmethanesulfonamide (2.24g):

Obtained according to the describe procedure of the Cramer group, as a white solid (44% yield over two steps). Spectroscopic data are consistent with those previously reported.[147]

2.24g
C$_{10}$H$_{11}$BrF$_3$NO$_2$S
M= 346,16 g.mol^{-1}
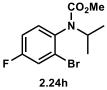
^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.74 (dd, J = 8.2, 1.5 Hz, 1H), 7.38 (ddd, J = 8.2, 6.9, 1.5 Hz, 1H), 7.33-7.27 (m, 2H), 4.55 (hept, J = 6.7 Hz, 1H), 1.32 (d, J = 6.7 Hz, 3H), 1.31 (d, J = 6.7 Hz, 3H)

^{13}C NMR (101 MHz, CDCl$_3$): δ (ppm) 134.8, 133.4, 133.3, 131.1, 128.1, 128.0, 120. (q, J = 323.8 Hz), 56.6, 22.2, 22.1

^{19}F NMR (376 MHz, CDCl$_3$): δ (ppm) -74.86

Methyl (2-bromo-4-fluorophenyl)(isopropyl)carbamate (2.24h):

Obtained according to the **General procedure B** and **General procedure D**, as a colorless viscous oil (82% yield over two steps).

2.24h
C$_{11}$H$_{13}$BrFNO$_2$
M= 290,13 g.mol^{-1}

^{1}H NMR (400 MHz, CDCl$_3$): 7.38 (dd, J = 8.0, 2.9 Hz, 1H), 7.16 (dd, J = 8.7, 5.6 Hz, 1H), 7.03 (ddd, J = 8.7, 7.7, 2.9 Hz, 1H), 4.59-4.40 (m, 1H), 3.62 (s, 3H), 1.29 (d, J = 6.8 Hz, 3H), 1.03 (d, J = 6.8 Hz, 3H)

^{13}C NMR (101 MHz, CDCl$_3$): δ (ppm) 161.3 (d, J = 251.5 Hz), 155.3, 134.8, 131.5 (d, J = 5.7 Hz), 126.5 (d, J = 10.0 Hz), 120.8 (d, J = 25.2 Hz), 115.0 (d, J = 21.9 Hz), 53.0, 50.4, 22.6, 19.8
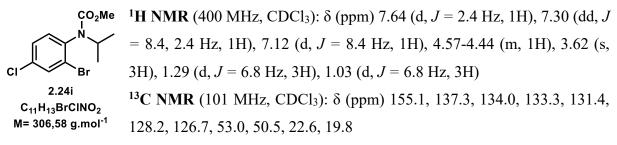
^{19}F NMR (376 MHz, CDCl$_3$): δ (ppm) 112.22 (m).

IR (neat): ν (cm^{-1}) 2980, 2957, 1696, 1442, 1314, 1257, 1094, 587

HRMS (ESI): Calcd for C$_{11}$H$_{13}$^{79}BrFNNaO$_2$ [M+Na]$^+$: 312.0006, found 312.0007

Methyl (2-bromo-4-chlorophenyl)(isopropyl)carbamate (2.24i):

Obtained according to the **General procedure A** and **General procedure D**, as a white solid (54% yield over two steps).

2.24i
C$_{11}$H$_{13}$BrClNO$_2$
M= 306,58 g.mol^{-1}

^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.64 (d, J = 2.4 Hz, 1H), 7.30 (dd, J = 8.4, 2.4 Hz, 1H), 7.12 (d, J = 8.4 Hz, 1H), 4.57-4.44 (m, 1H), 3.62 (s, 3H), 1.29 (d, J = 6.8 Hz, 3H), 1.03 (d, J = 6.8 Hz, 3H)

^{13}C NMR (101 MHz, CDCl$_3$): δ (ppm) 155.1, 137.3, 134.0, 133.3, 131.4, 128.2, 126.7, 53.0, 50.5, 22.6, 19.8

IR (neat): ν (cm^{-1}) 3058, 2981, 2948, 1693, 1440, 1322, 1094, 766, 514

HRMS (ESI): Calcd for C$_{11}$H$_{13}$^{79}Br^{35}ClNNaO$_2$ [M+Na]$^+$: 327.9710, found 327.9709

Experimental Section

Mp: 43-45 °C

Methyl (2-bromo-4-methylphenyl)(isopropyl)carbamate (2.24j):

Obtained according to the **General procedure A** and **General procedure D**, as a colorless oil (57% yield over two steps).

2.24j
$C_{12}H_{16}BrNO_2$
M= 286,17 g.mol^{-1}
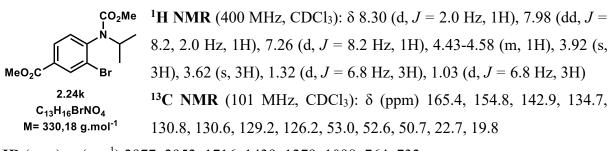
^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.44 (s, 1H), 7.12-7.02 (m, 2H), 4.58-4.42 (m, 1H), 3.60 (s, 3H), 2.33 (s, 3H), 1.28 (d, J = 6.8 Hz, 3H), 1.01 (d, J = 6.8 Hz, 3H)

^{13}C NMR (101 MHz, CDCl$_3$): δ (ppm) 155.4, 139.2, 135.6, 133.9, 130.3, 128.6, 125.5, 52.8, 50.2, 22.6, 20.8, 19.7

IR (neat): ν (cm^{-1}) 2978, 2949, 1696, 1440, 1318, 1094, 766

HRMS (ESI): Calcd for $C_{12}H_{16}$^{79}BrNNaO$_2$ [M+Na]$^+$: 308.0257, found 308.0258

Methyl 3-bromo-4-(isopropyl(methoxycarbonyl)amino)benzoate (2.24k):
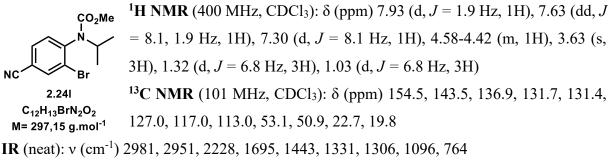
Obtained according to the **General procedure B** and **General procedure D**, as a colorless oil (93% yield over two steps).

2.24k
$C_{13}H_{16}BrNO_4$
M= 330,18 g.mol^{-1}

^{1}H NMR (400 MHz, CDCl$_3$): δ 8.30 (d, J = 2.0 Hz, 1H), 7.98 (dd, J = 8.2, 2.0 Hz, 1H), 7.26 (d, J = 8.2 Hz, 1H), 4.43-4.58 (m, 1H), 3.92 (s, 3H), 3.62 (s, 3H), 1.32 (d, J = 6.8 Hz, 3H), 1.03 (d, J = 6.8 Hz, 3H)

^{13}C NMR (101 MHz, CDCl$_3$): δ (ppm) 165.4, 154.8, 142.9, 134.7, 130.8, 130.6, 129.2, 126.2, 53.0, 52.6, 50.7, 22.7, 19.8

IR (neat): ν (cm^{-1}) 2977, 2952, 1716, 1439, 1279, 1098, 764, 732

HRMS (ESI): Calcd for $C_{13}H_{16}$^{79}BrNNaO$_4$ [M+Na]$^+$: 352.0155, found 352.0153

Methyl (2-bromo-4-cyanophenyl)(isopropyl)carbamate (2.24l):

Obtained according to the **General procedure A** and **General procedure D**, as a white solid (18% yield over two steps).

2.24l
$C_{12}H_{13}BrN_2O_2$
M= 297,15 g.mol^{-1}

^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.93 (d, J = 1.9 Hz, 1H), 7.63 (dd, J = 8.1, 1.9 Hz, 1H), 7.30 (d, J = 8.1 Hz, 1H), 4.58-4.42 (m, 1H), 3.63 (s, 3H), 1.32 (d, J = 6.8 Hz, 3H), 1.03 (d, J = 6.8 Hz, 3H)

^{13}C NMR (101 MHz, CDCl$_3$): δ (ppm) 154.5, 143.5, 136.9, 131.7, 131.4, 127.0, 117.0, 113.0, 53.1, 50.9, 22.7, 19.8

IR (neat): ν (cm^{-1}) 2981, 2951, 2228, 1695, 1443, 1331, 1306, 1096, 764

HRMS (ESI): Calcd for $C_{12}H_{13}$^{79}BrN$_2$NaO$_2$ [M+Na]$^+$: 319.0053, found 319.0053

Experimental Section

Mp: 125-127°C

Methyl (2-bromo-5-fluorophenyl)(isopropyl)carbamate (1m):

Obtained according to the **General procedure B** and **General procedure D**, as a white solid (76% yield over two steps).
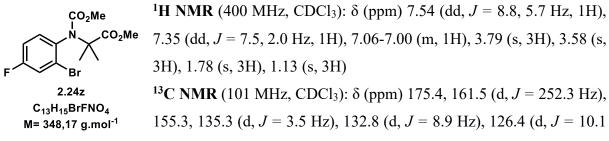
CO_2Me

2.24m

$C_{11}H_{13}BrFNO_2$

M= 290,13 g.mol^{-1}

^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.62-7.56 (m, 1H), 6.98-6.91 (m, 2H), 4.58-4.42 (m, 1H), 3.65 (s, 3H), 1.32 (d, J = 6.8 Hz, 3H), 1.05 (d, J = 6.8 Hz, 3H)

^{13}C NMR (101 MHz, CDCl$_3$): δ (ppm) 161.7 (d, J = 248.7 Hz), 155.0, 139.9, 134.1 (d, J = 8.6 Hz), 120.6 (d, J = 3.9 Hz), 118.3 (d, J = 22.0 Hz), 116.3 (d, J = 22.1 Hz), 53.0, 50.6, 22.7, 19.7

^{19}F NMR (376 MHz, CDCl$_3$): δ (ppm) -113.33 to -113.41 (m)

IR (neat): ν (cm^{-1}) 2976, 1699, 1441, 1332, 1318, 1096, 819, 764, 598

HRMS (ESI): Calcd for C$_{12}$H$_{16}$^{79}BrNNaO$_2$ [M+Na]$^+$: 312.0006, found 312.0008

Mp: 58-61°C

Methyl (2-bromo-5-(trifluoromethyl)phenyl)(isopropyl)carbamate (2.24n):

Obtained according to the **General procedure B** and **General procedure D**, as a white solid (50% yield over two steps).
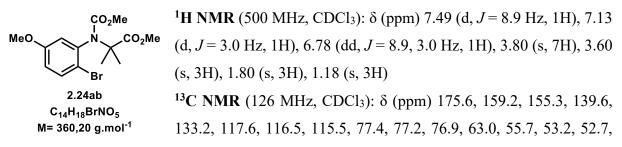
CO_2Me

2.24n

$C_{12}H_{13}BrF_3NO_2$

M= 340,14 g.mol^{-1}

^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.77 (d, J = 8.3 Hz, 1H), 7.46-7.41 (m, 2H), 4.59-4.45 (m, 1H), 3.64 (s, 3H), 1.33 (d, J = 6.8 Hz, 3H), 1.04 (d, J = 6.8 Hz, 3H)

^{13}C NMR (101 MHz, CDCl$_3$): δ (ppm) 154.9, 139.5, 134.2, 130.7 (q, J = 33.3 Hz), 130.4, 127.6, 125.7, 123.5 (q, J = 272.5 Hz), 53.1, 50.7, 22.7, 19.8

^{19}F NMR (376 MHz, CDCl$_3$): δ (ppm) -62.69 (s).

IR (neat): ν (cm^{-1}) 2982, 2954, 1700, 1442, 1319, 1114, 1077, 846

HRMS (ESI): Calcd for C$_{12}$H$_{13}$^{79}BrF$_3$NNaO$_2$ [M+Na]$^+$: 361.9974, found 361.9978

Mp: 89-92°C

Experimental Section
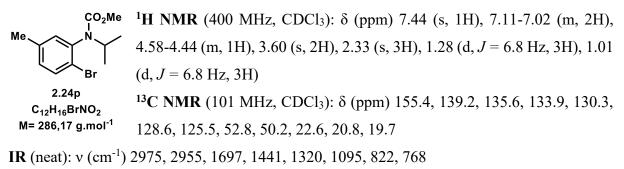
Methyl (2-bromo-5-nitrophenyl)(isopropyl)carbamate (2.24o):

Obtained according to the **General procedure B** and **General procedure D**, as a white solid (32% yield over two steps).

2.24o
$C_{11}H_{13}BrN_2O_4$
M= 317,14 g.mol^{-1}

^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 8.12-7.99 (m, 2H), 7.89-7.79 (m, 1H), 4.64-4.41 (m, 1H), 3.64 (s, 3H), 1.37 (d, J = 6.7 Hz, 3H), 1.06 (d, J = 6.9 Hz, 3H).

^{13}C NMR (126 MHz, CDCl$_3$): δ (ppm) 154.6, 147.5, 140.1, 134.3, 134.2, 125.6, 123.6, 53.2, 50.9, 22.7, 19.9

IR (neat): ν (cm^{-1}) 2982, 2952, 1701, 1519, 1443, 1322, 1258, 1104, 1044, 766, 739

HRMS (ESI): Calcd for $C_{11}H_{13}{}^{79}BrN_2NaO_4$ [M+Na]$^+$: 338.9951, found 338.9953

Mp: 94-96°C

Methyl (2-bromo-5-methylphenyl)(isopropyl)carbamate (2.24p):

Obtained according to the **General procedure A** and **General procedure D**, as white solid (52% yield over two steps).

2.24p
$C_{12}H_{16}BrNO_2$
M= 286,17 g.mol^{-1}

^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.44 (s, 1H), 7.11-7.02 (m, 2H), 4.58-4.44 (m, 1H), 3.60 (s, 2H), 2.33 (s, 3H), 1.28 (d, J = 6.8 Hz, 3H), 1.01 (d, J = 6.8 Hz, 3H)

^{13}C NMR (101 MHz, CDCl$_3$): δ (ppm) 155.4, 139.2, 135.6, 133.9, 130.3, 128.6, 125.5, 52.8, 50.2, 22.6, 20.8, 19.7

IR (neat): ν (cm^{-1}) 2975, 2955, 1697, 1441, 1320, 1095, 822, 768

HRMS (ESI): Calcd for $C_{12}H_{16}{}^{79}BrNNaO_2$ [M+Na]$^+$: 308.0257, found 308.0257

Mp: 46-48°C

Methyl (2-bromo-5-methoxyphenyl)(isopropyl)carbamate (2.24q):

Obtained according to the **General procedure A** and **General procedure D**, as a white solid (83% yield over two steps).

2.24q
$C_{12}H_{16}BrNO_3$
M= 302,17 g.mol^{-1}

^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.52-7.46 (m, 1H), 6.78-6.72 (m, 2H), 4.59-4.41 (m, 1H), 3.79 (s, 3H), 3.63 (s, 3H), 1.32 (d, J = 6.8 Hz, 3H), 1.04 (d, J = 6.8 Hz, 3H)

^{13}C NMR (101 MHz, CDCl$_3$): δ (ppm) 159.2, 155.3, 139.2, 133.5, 116.4, 116.4, 114.3, 55.7, 52.9, 50.4, 22.7, 19.7

IR (neat): ν (cm^{-1}) 2983, 2953, 1697, 1445, 1320, 1308, 1218, 1097

Experimental Section

HRMS (ESI): Calcd for $C_{12}H_{16}{}^{79}BrNNaO_3$ [M+Na]$^+$: 324.0206, found 324.0205

Mp: 55-57°C

Methyl (2-bromo-6-fluorophenyl)(isopropyl)carbamate (2.24r):

Obtained according to the **General procedure B** and **General procedure D**, as a white solid (23% yield over two steps).

2.24r
$C_{11}H_{13}BrFNO_2$
M= 290,13 g.mol^{-1}

^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.41 (d, J = 7.9 Hz, 1H), 7.20-7.05 (m, 2H), 4.37-4.15 (m, 1H), 3.60 (s, 3H), 1.32 (dd, J = 6.7, 1.8 Hz, 3H), 1.15 (d, J = 6.7 Hz, 3H)

^{13}C NMR (101 MHz, CDCl$_3$): δ (ppm) 160.0 (d, J = 251.4 Hz), 155.0, 129.6 (d, J = 8.8 Hz), 128.7 (d, J = 3.5 Hz), 127.0, 115.6 (d, J = 22.0 Hz), 53.0, 51.9, 21.4, 20.2

^{19}F NMR (376 MHz, CDCl$_3$): δ (ppm) -112.56 to -112.71 (m)
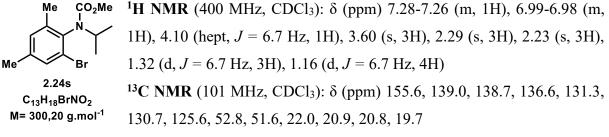
IR (neat): ν (cm^{-1}) 2977, 2951, 1707, 1440, 1089, 866, 768

HRMS (ESI): Calcd for $C_{12}H_{13}{}^{79}BrN_2NaO_2$ [M+Na]$^+$: 312.0006, found 312.0007

Mp: 48-49°C

Methyl (2-bromo-4,6-dimethylphenyl)(isopropyl)carbamate (2.24s):

Obtained according to the **General procedure B** and **General procedure D**, as a colorless viscous oil (39% yield over two steps).

2.24s
$C_{13}H_{18}BrNO_2$
M= 300,20 g.mol^{-1}

^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.28-7.26 (m, 1H), 6.99-6.98 (m, 1H), 4.10 (hept, J = 6.7 Hz, 1H), 3.60 (s, 3H), 2.29 (s, 3H), 2.23 (s, 3H), 1.32 (d, J = 6.7 Hz, 3H), 1.16 (d, J = 6.7 Hz, 4H)

^{13}C NMR (101 MHz, CDCl$_3$): δ (ppm) 155.6, 139.0, 138.7, 136.6, 131.3, 130.7, 125.6, 52.8, 51.6, 22.0, 20.9, 20.8, 19.7

IR (neat): ν (cm^{-1}) 2972, 2950, 1706, 1439, 1339, 1316, 1087

HRMS (ESI): Calcd for $C_{13}H_{18}{}^{79}BrNNaO_2$ [M+Na]$^+$: 322.0413, found 322,0416

Experimental Section

Methyl (2-bromopyridin-3-yl)(isopropyl)carbamate (1t):

Obtained according to the **General procedure B** and **General procedure D**, as a colorless viscous oil (64% yield over two steps).

Mixture or rotamers:

^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 8.25 (dd, J = 4.7, 1.8 Hz, 2/3 H), 8.22 (dd, J = 4.7, 1.8 Hz, 1/3 H), 7.48-7.41 (m, 2H), 7.22 (dd, J = 7.8, 4.7 H, dd, J = 7.8, 4.7 Hz superimposed, 1H), 4.55-4.35 (m, 2H), 3.53 (s, 4H), 1.21 (d, J = 6.8 Hz, 1H), 1.18 (d, J = 6.7 Hz, 2H), 0.97 (d, J = 6.8 Hz, 3H, d, J = 6.8 Hz superimposed, 3H)

^{13}C NMR (101 MHz, CDCl$_3$): δ (ppm) 154.8, 152.3, 148.3, 148.0, 145.8, 139.2, 138.5, 136.0, 133.6, 122.9, 122.7, 52.8, 50.4, 50.3, 22.5, 22.3, 19.7

IR (neat): ν (cm^{-1}) 2978, 2951, 1703, 1401, 1316, 1097, 1077, 768

HRMS (ESI): Calcd for C$_{10}$H$_{13}$^{79}BrN$_2$NaO$_2$ [M+Na]$^+$: 295.0053, found 295.0052

Structure label:
2.24t
C$_{10}$H$_{13}$BrN$_2$O$_2$
M= 273,13 g.mol^{-1}

Methyl (2-bromo-5-(dimethylamino)phenyl)(isopropyl)carbamate (2.24u):

2.24o (1.0 g, 3.2 mmol) was dissolved in MeCN (70 mL), then ZnBr (3.6 g, 16.0 mmol, 5 equiv) and a 37 % aqueous formaldehyde solution (12 mL) were added. After the addition of 10 % Pd/C (341 mg, 0.32 mmol, 10 mol%), the solution was purged with hydrogen and stirred under hydrogen atmosphere (1 bar) for 24 h. Then the reaction was filtered through a short pad of celite and concentrated under reduced pressure. The residue was purified by flash column chromatography using an EtOAc-pentane mixture to give **2.24u** as a white solid (520 mg, 1.65 mmol, 52 %).

^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.40 (d, J = 8.8 Hz, 1H), 6.56-6.47 (m, 2H), 4.57-4.45 (m, 1H), 3.64 (s, 3H), 2.94 (s, 6H), 1.33 (d, J = 6.7 Hz, 3H), 1.05 (d, J = 6.7 Hz, 3H)

^{13}C NMR (101 MHz, CDCl$_3$): δ (ppm) 155.6, 150.2, 138.6, 133.2, 114.5, 112.9, 111.4, 52.9, 50.3, 40.5, 22.9, 19.7

Structure label:
2.24u
C$_{13}$H$_{19}$BrN$_2$O$_2$
M= 315,21 g.mol^{-1}

IR (neat): ν (cm^{-1}) 2978, 2923, 1705, 1690, 1440, 1317, 1098

HRMS (ESI): Calcd for C$_{12}$H$_{16}$^{79}BrNNaO$_2$ [M+Na]$^+$: 337.0522, found 337.0524

Mp: 66-69°C

Experimental Section

Methyl 2-((2-bromophenyl)(methoxycarbonyl)amino)-2-methylpropanoate (2.24v):

Obtained according to the **General procedure C** and **General procedure D**, as a white solid (40% yield over two steps).

2.24v
$C_{13}H_{16}BrNO_4$
M= 330,18 g.mol^{-1}

^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.65-7.58 (m, 1H), 7.56-7.51 (m, 1H), 7.35-7.29 (m, 1H), 7.21-7.14 (m, 1H), 3.78 (s, 3H), 3.56 (s, 3H), 1.77 (s, 3H), 1.14 (s, 3H)

^{13}C NMR (101 MHz, CDCl$_3$): δ (ppm) 175.5, 155.2, 138.9, 133.2, 132.1, 129.5, 127.9, 126.0, 62.9, 53.2, 52.7, 26.0, 24.9

IR (neat): ν (cm^{-1}) 2960, 2930, 1733, 1703, 1337, 1267, 1151, 1088, 756

HRMS (ESI): Calcd for $C_{13}H_{16}{}^{79}BrNNaO_4$ [M+Na]$^+$: 352.0155, found 352,0160

Mp: 71-73°C

Ethyl 2-((2-bromophenyl)(methoxycarbonyl)amino)-2-methylpropanoate (2.24w):

Obtained according to the **General procedure C** and **General procedure D**, as a colorless oil (19% yield over two steps).

2.24w
$C_{14}H_{18}BrNO_4$
M= 344,21 g.mol^{-1}

^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.59 (dd, J = 8.9, 1.4 Hz, 1H), 7.52 (dd, J = 7.9, 1.6 Hz, 1H), 7.29 (td, J = 7.7, 1.4 Hz, 1H), 7.18-7.12 (m, 1H), 4.22 (q, J = 7.2 Hz, 2H), 3.53 (s, 3H), 1.75 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H), 1.12 (s, 3H)

^{13}C NMR (101 MHz, CDCl$_3$): δ (ppm) 174.7, 155.1, 138.9, 133.1, 131.9, 129.3, 127.8, 125.9, 62.8, 61.3, 53.0, 25.9, 24.7, 14.2

IR (neat): ν (cm^{-1}) 2982, 2956, 1735, 1711, 1337, 1147, 1092, 729

HRMS (ESI): Calcd for $C_{14}H_{18}{}^{79}BrNNaO_4$ [M+Na]$^+$: 366.0311, found 366.0312

Methyl 2-(((benzyloxy)carbonyl)(2-bromophenyl)amino)-2-methylpropanoate (2.24x):

Obtained according to the **General procedure C** and **General procedure D**, as a colorless oil (26% yield over two steps).

2.24x
$C_{19}H_{20}BrNO_4$
M= 406,28 g.mol^{-1}
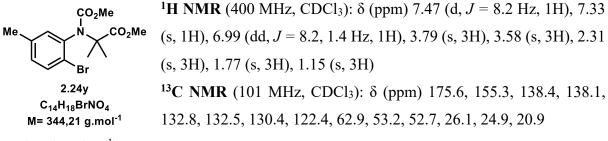
^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.64 (dd, J = 8.0, 1.5 Hz, 1H), 7.56 (dd, J = 8.0, 1.5 Hz, 1H), 7.39-7.29 (m, 2H), 7.25-7.16 (m, 5H), 7.13-7.08 (m, 2H), 5.06 (s, 2H), 3.77 (s, 3H), 1.82 (s, 3H), 1.17 (s, 3H)

^{13}C NMR (101 MHz, CDCl$_3$): δ (ppm) 175.5, 154.6, 138.9, 136.7, 133.3, 132.1, 129.5, 128.3, 127.9, 127.7, 127.2, 126.1, 67.2, 63.0, 52.7, 26.0, 24.9

IR (neat): ν (cm^{-1}) 2993, 2950, 1740, 1707, 1295

Experimental Section

HRMS (ESI): Calcd for $C_{19}H_{20}{}^{79}BrNNaO_4$ [M+Na]$^+$: 428.0468, found 428.0474

Methyl 2-((2-bromo-5-methylphenyl)(methoxycarbonyl)amino)-2-methylpropanoate (2.24y):

Obtained according to the **General procedure C** and **General procedure D**, as a white solid (25% yield over two steps).

Me — [structure] CO$_2$Me, N, CO$_2$Me, Br

2.24y
$C_{14}H_{18}BrNO_4$
M= 344,21 g.mol^{-1}

^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.47 (d, J = 8.2 Hz, 1H), 7.33 (s, 1H), 6.99 (dd, J = 8.2, 1.4 Hz, 1H), 3.79 (s, 3H), 3.58 (s, 3H), 2.31 (s, 3H), 1.77 (s, 3H), 1.15 (s, 3H)

^{13}C NMR (101 MHz, CDCl$_3$): δ (ppm) 175.6, 155.3, 138.4, 138.1, 132.8, 132.5, 130.4, 122.4, 62.9, 53.2, 52.7, 26.1, 24.9, 20.9

IR (neat): ν (cm^{-1}) 2994, 2954, 1742, 1707, 1333, 1142, 1096

HRMS (ESI): Calcd for $C_{14}H_{18}{}^{79}BrNNaO_4$ [M+Na]$^+$: 366.0311, found 366.0318

Mp: 98-99°C

Methyl 2-((2-bromo-4-fluorophenyl)(methoxycarbonyl)amino)-2-methylpropanoate (2.24z):

Obtained according to the **General procedure C** and **General procedure D**, as a white solid (36% yield over two steps).

F — [structure] CO$_2$Me, N, CO$_2$Me, Br

2.24z
$C_{13}H_{15}BrFNO_4$
M= 348,17 g.mol^{-1}

^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.54 (dd, J = 8.8, 5.7 Hz, 1H), 7.35 (dd, J = 7.5, 2.0 Hz, 1H), 7.06-7.00 (m, 1H), 3.79 (s, 3H), 3.58 (s, 3H), 1.78 (s, 3H), 1.13 (s, 3H)

^{13}C NMR (101 MHz, CDCl$_3$): δ (ppm) 175.4, 161.5 (d, J = 252.3 Hz), 155.3, 135.3 (d, J = 3.5 Hz), 132.8 (d, J = 8.9 Hz), 126.4 (d, J = 10.1 Hz), 120.3 (d, J = 25.2 Hz), 115.1 (d, J = 21.9 Hz), 63.0, 53.2, 52.7, 26.1, 24.9

^{19}F NMR (376 MHz, CDCl$_3$): δ (ppm) -111.33 (s)

IR (neat): ν (cm^{-1}) 2996, 2954, 1736, 1703, 1335, 1094

HRMS (ESI): Calcd for $C_{13}H_{15}{}^{79}BrFNNaO_4$ [M+Na]$^+$: 370.0061, found 370.0061

Mp: 86-87°C

Experimental Section

Methyl 2-((2-bromo-4-methylphenyl)(methoxycarbonyl)amino)-2-methylpropanoate (2.24aa):

Obtained according to the **General procedure C** and **General procedure D**, as a white solid (36% yield over two steps).

2.24aa
$C_{14}H_{18}BrNO_4$
M= 344,21 g.mol^{-1}

^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.44 (s, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.11 (d, J = 8.0 Hz, 1H), 3.78 (s, 3H), 3.58 (s, 3H), 2.34 (s, 3H), 1.76 (s, 3H), 1.15 (s, 3H)

^{13}C NMR (101 MHz, CDCl$_3$): δ (ppm) 175.6, 155.4, 139.8, 136.1, 133.7, 131.5, 128.7, 125.5, 62.9, 53.2, 52.6, 26.0, 24.8, 20.9

IR (neat): ν (cm^{-1}) 2996, 2954, 1740, 1708, 1336, 1094

HRMS (ESI): Calcd for C$_{14}$H$_{18}$^{79}BrNNaO$_4$ [M+Na]$^+$: 366.0311, found 366.0313

Mp: 105-107°C

Methyl 2-((2-bromo-5-methoxyphenyl)(methoxycarbonyl)amino)-2-methylpropanoate (2.24ab):

Obtained according to the **General procedure C** and **General procedure D**, as a white solid (29% yield over two steps).

2.24ab
$C_{14}H_{18}BrNO_5$
M= 360,20 g.mol^{-1}

^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 7.49 (d, J = 8.9 Hz, 1H), 7.13 (d, J = 3.0 Hz, 1H), 6.78 (dd, J = 8.9, 3.0 Hz, 1H), 3.80 (s, 7H), 3.60 (s, 3H), 1.80 (s, 3H), 1.18 (s, 3H)

^{13}C NMR (126 MHz, CDCl$_3$): δ (ppm) 175.6, 159.2, 155.3, 139.6, 133.2, 117.6, 116.5, 115.5, 77.4, 77.2, 76.9, 63.0, 55.7, 53.2, 52.7, 26.0, 24.9

IR (neat): ν (cm^{-1}) 3087, 3002, 2953, 2845, 1746, 1699, 1443, 1343, 1265, 1143, 1087, 772

HRMS (ESI): Calcd for C$_{14}$H$_{18}$^{79}BrNNaO$_5$ [M+Na]$^+$: 382.0261, found 382.0266

Mp: 114-116°C

Experimental Section

Methyl (2-bromophenyl)(sec-butyl)carbamate (2.24ac):

Obtained according to the **General procedure A** and **General procedure D**, as a colorless oil (77% yield over two steps). Spectroscopic data are consistent with those previously reported.[145]

^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.63 (dd, J = 7.9, 3.7 Hz, 1H), 7.35-7.28 (m, 1H), 7.23-7.12 (m, 2H), 4.44-4.02 (m, 1H), 3.63 (s, 3H), 1.86-1.71 (m, 1H), 1.61-1.47 (m, 1H), 1.34 (d, J = 6.7 Hz, 1H), 1.04-0.96 (m, 4H), 0.89 (t, J = 7.4 Hz, 1H)

^{13}C NMR (101 MHz, CDCl$_3$): δ (ppm) 155.6, 155.1, 139.5, 138.3, 133.4, 130.4, 128.8, 128.7, 127.9, 126.1, 125.6, 57.4, 55.8, 52.8, 52.7, 29.7, 26.8, 19.2, 16.7, 11.6, 11.1

Methyl (2-bromophenyl)(cyclobutyl)carbamate (2.24ae):

Obtained according to the **General procedure B** and **General procedure D**, as a white solid (66% yield over two steps). Spectroscopic data are consistent with those previously reported.[179]

^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.65 (dd, J = 7.9, 1.6 Hz, 1H), 7.35 (td, J = 7.6, 1.6 Hz, 1H), 7.20 (td, J = 7.9, 1.6 Hz, 1H), 7.16 (d, J = 7.6 Hz, 1H), 4.83-4.71 (m, 1H), 3.61 (s, 3H), 2.24-2.09 (m, 2H), 1.90 (quint, J = 10.0 Hz, 1H), 1.84-1.70 (m, 1H), 1.65-1.44 (m, 2H)

^{13}C NMR (101 MHz, CDCl$_3$): δ (ppm) 155.4, 138.2, 133.4, 131.6, 129.2, 128.1, 125.9, 53.0, 52.6, 29.5, 28.5, 15.2

Methyl (2-bromo-4-fluorophenyl)(cyclobutyl)carbamate (2.24af):

Obtained according to the **General procedure B** and **General procedure D**, as a pale viscous oil (62% yield over two steps).

^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.35 (dd, J = 7.8, 2.9 Hz, 1H), 7.16-7.07 (m, 1H), 7.03 (ddd, J = 8.7, 7.8, 2.9 Hz, 1H), 4.81-4.66 (m, 1H), 3.57 (s, 3H), 2.21-2.05 (m, 2H), 1.84 (quint, J = 10.0 Hz, 1H), 1.78-1.66 (m, 1H), 1.61-1.43 (m, 2H)

^{13}C NMR (101 MHz, CDCl$_3$): δ (ppm) 161.3 (d, J = 251.7 Hz), 155.2, 134.4, 132.2 (d, J = 8.1 Hz), 126.2 (d, J = 9.6 Hz), 120.5 (d, J = 25.3 Hz), 115.0 (d, J = 22.0 Hz), 52.9, 52.4, 29.3, 28.4, 15.0

^{19}F NMR (376 MHz, CDCl$_3$): δ (ppm) -111.87 to -111.95 (m)

IR (neat): ν (cm^{-1}) 2979, 2950, 1706, 1489, 1441, 1321, 1294, 878

Experimental Section

HRMS (ESI): Calcd for $C_{12}H_{13}{}^{79}BrFNNaO_2$ [M+Na]$^+$: 324.0006, found 324.0006

Experimental Section
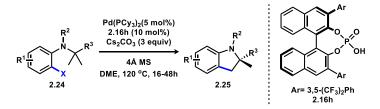
6.2.3. Products

General procedure E: Representative procedure for the racemic synthesis of indolines

2.24 (0.2 mmol) was weight in a reaction tube which was transferred in glovebox. Then Pd(OAc)$_2$ (2.3 mg, 0.01 mmol, 5 mol%), PCy$_3$·HBF$_4$ (7.4 mg, 0.02 mmol, 10 mol%), pivalic acid (6.1 mg, 0.06 mmol, 30 mol%) and cesium carbonate (98 mg, 0.3 mmol, 1.5 equiv) were added. The tube was sealed with a rubber septum, taken out of the glovebox and degassed dry xylenes (2 mL) was added under argon. The rubber septum was replaced with a Teflon screw cap and the reaction mixture was introduced in an oil bath or an aluminum block preheated at 140°C under stirring. After 14-24h, the reaction mixture was cooled down to room temperature and was directly purified by flash column chromatography on silica gel using EtOAc–pentane mixture as eluent to afford the desired racemic indoline **2.25**.

General procedure F: Representative procedure for the asymmetric C(sp^3)–H arylation

2.24 (0.2 mmol) was weight into a 25 mL J-Young tube which was transferred in glovebox. Then Pd(PCy$_3$)$_2$ (6.7 mg, 0.01 mmol, 5 mol%), **2.16h** (15.4 mg, 0.02 mmol, 10 mol%), cesium carbonate (195 mg, 0.6 mmol, 3 equiv) and 4Å molecular sieves powder (50 mg) were added. The tube was sealed and taken out of the glovebox, afterward dry DME (2 mL) was added under argon. The reaction mixture was degassed by three freeze-pump-thaw cycles and then introduced in a 120°C preheated oil bath under stirring. After required time, the reaction mixture was cooled to room temperature and diluted with ethyl acetate followed by filtration through a short pad of celite. The filtrate was concentrated under reduced pressure and purified by flash column chromatography on silica gel using EtOAc–pentane mixture as eluent to afford the desired enantioenriched indoline **2.25**.

Experimental Section

Methyl (*S*)-2-methylindoline-1-carboxylate (2.25a):

Small scale synthesis:

The title compound was prepared according to the **General procedure F** (0.2 mmol scale, 120 °C/24 h) and purified by chromatography to give **2.25a** as a slight yellow oil (32.7 mg, 0.171 mmol, 86% yield).

Gram scale synthesis:

2.24 (1.36 g, 5 mmol) was weight into a 100 mL J-Young tube which was transferred in glovebox. Then Pd(PCy$_3$)$_2$ (385 mg, 0.25 mmol, 5 mol%), **2.16h** (385 mg, 0.5 mmol, 10 mol%), cesium carbonate (4.9 g, 15 mmol, 3 equiv) and 4Å molecular sieves powder (1.25 g) were added. The tube was sealed and taken out of the glovebox, afterward dry DME (40 mL) was added under argon. The reaction mixture was degassed by three freeze-pump-thaw cycles and then introduced in a 120°C preheated oil bath under stirring. After 24h, the reaction mixture was cooled to room temperature and diluted with ethyl acetate followed by filtration through a short pad of Celite. The filtrate was concentrated under reduced pressure and purified by flash column chromatography (silica gel, pentane/EtOAc 30:1 as eluent) affording **2.25a** (825 mg, 4.32 mmol, 86%) as a slight yellow oil. Spectroscopic data are consistent with those previously reported.[142]

2.25a
C$_{11}$H$_{13}$NO$_2$
M= 191,23 g.mol^{-1}

^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.80 (bs, 1H), 7.22-7.12 (m, 2H), 6.96 (td, *J* = 7.4, 1.0 Hz, 1H), 4.62-4.48 (m, 1H), 3.85 (s, 3H), 3.36 (dd, *J* = 15.9, 9.6 Hz, 1H), 2.63 (dd, *J* = 15.9, 2.1 Hz, 1H), 1.30 (d, *J* = 6.4 Hz, 3H)

^{13}C NMR (101 MHz, CDCl$_3$): δ (ppm) 153.7, 141.5, 130.1, 127.5, 125.1, 122.8, 115.4, 55.4, 52.5, 35.9, 21.2

IR (neat): ν (cm^{-1}) 2953, 2926, 1703, 1485, 1389, 753
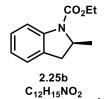
HRMS (ESI): Calcd for C$_{11}$H$_{13}$NNaO$_2$ [M+Na]$^+$: 214.0844, found 214,0837

[α]$_D^{20}$: +40.8° (c = 1.46, CHCl$_3$)

HPLC separation: Chiralcel® OJ-H; 99:1 (*n*-heptane/*i*-PrOH), 1.0 mL.min^{-1}, 243 nm, t_R (minor) = 9.6 min, t_R (major) = 10.6 min, 96:4 e.r.

Experimental Section

Ethyl (*S*)-2-methylindoline-1-carboxylate (2.25b):

The title compound was prepared according to the **General procedure F** (0.2 mmol scale, 120 °C/16 h) and purified by chromatography to give **2.25b** as a colorless oil (34.1 mg, 0.166 mmol, 83% yield).

2.25b
$C_{12}H_{15}NO_2$
M= 205,26 g.mol⁻¹

¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.81 (bs, 1H), 7.23-7.12 (m, 2H), 6.96 (td, *J* = 7.4, 1.0 Hz, 1H), 4.64-4.47 (m, 1H), 4.30 (q, *J* = 7.0 Hz, 2H), 3.37 (dd, *J* = 15.9, 9.6 Hz, 2H), 2.63 (dd, *J* = 15.9, 2.0 Hz, 1H), 1.37 (t, *J* = 7.0 Hz, 3H), 1.30 (d, *J* = 6.3 Hz, 3H)

¹³C NMR (101 MHz, CDCl₃): δ (ppm) 153.3, 141.6, 130.2, 127.5, 125.1, 122.7, 115.5, 61.4, 55.4, 35.9, 21.2, 14.8

IR (neat): ν (cm⁻¹) 2978, 2929, 1698, 1484, 1280, 1053, 748

HRMS (ESI): Calcd for C₁₂H₁₅NNaO₂ [M+Na]⁺: 228.1000, found 228,0995

[α]$_D^{20}$: +40.1° (c = 0.85, CHCl₃)

HPLC separation: Chiralcel® OJ-H; 99:1 (*n*-heptane/*i*-PrOH), 1.0 mL.min⁻¹, 243 nm, *t*$_R$ (minor) = 8.3 min, *t*$_R$ (major) = 9.4 min, 94:6 e.r.

Benzyl (*S*)-2-methylindoline-1-carboxylate (2.25c):

The title compound was prepared according to the **General procedure F** (0.2 mmol scale, 120 °C/24 h) and purified by chromatography to give **2.25c** as a colorless oil (40.1 mg, 0.150 mmol, 75% yield).

2.25c
$C_{17}H_{17}NO_2$
M= 267,33 g.mol⁻¹

¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.89 (bs, 1H), 7.51-7.31 (m, 5H), 7.24-7.13 (m, 2H), 6.98 (t, *J* = 7.4 Hz, 1H), 5.31 (s, 2H), 4.69-4.51 (m, 1H), 3.38 (dd, *J* = 15.9, 9.6 Hz, 1H), 2.65 (dd, *J* = 15.9, 2.1 Hz, 1H), 1.32 (d, *J* = 6.3 Hz, 3H)

¹³C NMR (101 MHz, CDCl₃): δ (ppm) 153.0, 141.6, 136.5, 130.1, 128.7, 128.3, 128.2, 127.6, 125.2, 122.9, 115.6, 67.1, 55.5, 36.0, 21.4

IR (neat): ν (cm⁻¹) 3033, 2958, 1701, 1484, 1403, 1282, 753

HRMS (ESI): Calcd for C₁₇H₁₇NNaO₂ [M+Na]⁺: 290.1157, found 290,1152

[α]$_D^{20}$: +25.7° (c = 1.10, CHCl₃)

HPLC separation: Chiralcel® OJ-H; 99:1 (*n*-heptane/*i*-PrOH), 1.0 mL.min⁻¹, 243 nm, *t*$_R$ (major) = 17.9 min, *t*$_R$ (minor) = 21.7 min, 92:8 e.r.

Experimental Section
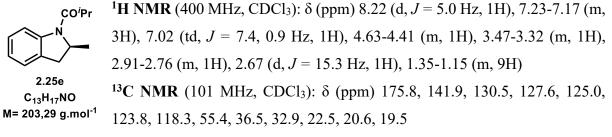
Isobutyl (*S*)-2-methylindoline-1-carboxylate (2.25d):

The title compound was prepared according to the **General procedure F** (0.2 mmol scale, 120 °C/16 h) and purified by chromatography to give **2.25d** as a colorless oil (41.3 mg, 0.177 mmol, 89% yield).

2.25d
$C_{14}H_{19}NO_2$
M= 233,31 g.mol^{-1}

^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.82 (bs, 1H), 7.22-7.12 (m, 2H), 6.96 (td, *J* = 7.4, 1.0 Hz, 1H), 4.66-4.43 (m, 1H), 4.03 (d, *J* = 6.2 Hz, 2H), 3.38 (dd, *J* = 15.9, 9.6 Hz, 1H), 2.64 (dd, *J* = 15.9, 1.8 Hz, 1H), 2.13-1.95 (m, 1H), 1.32 (d, *J* = 6.4 Hz, 3H), 1.01 (d, *J* = 6.7 Hz, 6H)

^{13}C NMR (101 MHz, CDCl$_3$): δ (ppm) 153.4, 141.7, 130.1, 127.6, 125.1, 122.7, 115.5, 71.7, 55.4, 36.0, 28.1, 21.4, 19.4

IR (neat): ν (cm^{-1}) 2960, 2927, 1701, 1485, 1407, 1281, 751

HRMS (ESI): Calcd for $C_{14}H_{19}NNaO_2$ [M+Na]$^+$: 256.1313, found 256,1304

[α]$_D^{20}$: +32.1° (c = 1.20, CHCl$_3$)

HPLC separation: Chiralcel® OJ-H; 99.5:0.5 (*n*-heptane/*i*-PrOH), 0.5 mL.min^{-1}, 243 nm, t_R (minor) = 13.8 min, t_R (major) = 15.2 min, 94.5:5.5 e.r.

**(*S*)-2-methyl-1-(2-methylindolin-1-yl)propan-1-one (2.25e):**

The title compound was prepared according to the **General procedure F** (0.2 mmol scale, 120 °C/16 h) and purified by chromatography to give **2.25e** as a colorless oil (33.3 mg, 0.164 mmol, 82% yield). Spectroscopic data are consistent with those previously reported.[144]

2.25e
$C_{13}H_{17}NO$
M= 203,29 g.mol^{-1}

^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 8.22 (d, *J* = 5.0 Hz, 1H), 7.23-7.17 (m, 3H), 7.02 (td, *J* = 7.4, 0.9 Hz, 1H), 4.63-4.41 (m, 1H), 3.47-3.32 (m, 1H), 2.91-2.76 (m, 1H), 2.67 (d, *J* = 15.3 Hz, 1H), 1.35-1.15 (m, 9H)

^{13}C NMR (101 MHz, CDCl$_3$): δ (ppm) 175.8, 141.9, 130.5, 127.6, 125.0, 123.8, 118.3, 55.4, 36.5, 32.9, 22.5, 20.6, 19.5

IR (neat): ν (cm^{-1}) 2966, 2929, 1651, 1479, 1404, 1270, 759
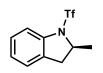
HRMS (ESI): Calcd for $C_{13}H_{17}NNaO$ [M+Na]$^+$: 226.1208, found 226,1202

[α]$_D^{20}$: +21.1° (c = 1.30, CHCl$_3$)

HPLC separation: Chiralcel® OJ-H; 99:1 (*n*-heptane/*i*-PrOH), 1.0 mL.min^{-1}, 254 nm, t_R (minor) = 8.8 min, t_R (major) = 12.0 min, 81.5:18.5 e.r.

Experimental Section

(*S*)-2-methyl-1-((trifluoromethyl)sulfonyl)indoline (2.25g):

The title compound was prepared according to the **General procedure F** (0.2 mmol scale, 100 ºC/24 h) and purified by chromatography to give **2.25g** as a colorless oil (34 mg, 0.128 mmol, 64% yield). Spectroscopic data are consistent with those previously reported.[147]

2.25g
$C_{10}H_{10}F_3NO_2S$
M= 265,25 g.mol^{-1}

^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.46 (d, *J* = 8.1 Hz, 1H), 7.27-7.19 (m, 2H), 7.17-7.11 (m, 1H), 4.81-4.64 (m, 1H), 3.52 (dd, *J* = 15.9, 9.2 Hz, 1H), 2.73 (dd, *J* = 15.9, 1.8 Hz, 1H), 1.44 (d, *J* = 6.5 Hz, 3H)

^{13}C NMR (101 MHz, CDCl$_3$): δ (ppm) 138.6, 130.8, 128.2, 126.0, 125.7, 120.3 (q, *J* = 325.6 Hz), 115.8, 61.0, 36.4, 22.9

^{19}F NMR (376 MHz, CDCl$_3$): δ (ppm) -73.97 (bs)

IR (neat): ν (cm^{-1}) 2926, 2857, 1395, 1223, 1189, 1145, 610
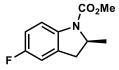
HRMS (ESI): Calcd for $C_{10}H_{10}F_3NNaO_2S$ [M+Na]$^+$: 288.0282, found 288,0277

$[\alpha]_D^{20}$: +16.1° (c = 1.35, CHCl$_3$)

HPLC separation: Chiralcel® OJ-H; 99.5:0.5 (*n*-heptane/*i*-PrOH), 0.5 mL.min^{-1}, 229 nm, t_R (major) = 11.4 min, t_R (minor) = 12.0 min, 74:26 e.r.

Methyl (*S*)-5-fluoro-2-methylindoline-1-carboxylate (2.25h):

The title compound was prepared according to the **General procedure F** (0.2 mmol scale, 120 ºC/18 h) and purified by chromatography to give **2.25h** as a colorless oil (35.3 mg, 0.169 mmol, 84% yield).

2.25h
$C_{11}H_{12}FNO_2$
M= 209,22 g.mol^{-1}

^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.75 (bs, 1H), 6.90-6.81 (m, 2H), 4.62-4.48 (s, 1H), 3.83 (s, 3H), 3.35 (ddd, *J* = 16.2, 9.6, 1.1 Hz, 1H), 2.60 (dd, *J* = 16.2, 1.8 Hz, 1H), 1.29 (d, *J* = 6.4 Hz, 3H)

^{13}C NMR (101 MHz, CDCl$_3$): δ (ppm) 159.1 (d, *J* = 240.5 Hz), 153.6, 137.4, 132.0, 116.1 (d, *J* = 8.2 Hz), 113.8 (d, *J* = 22.9 Hz), 112.4 (d, *J* = 24.0 Hz), 55.8, 52.6, 36.0, 21.3

^{19}F NMR (376 MHz, CDCl$_3$): δ (ppm) -121.21 (s)

IR (neat): ν (cm^{-1}) 2955, 2855, 1702, 1486, 1389

HRMS (ESI): Calcd for $C_{11}H_{12}FNNaO_2$ [M+Na]$^+$: 232.0750, found 232,0741

$[\alpha]_D^{20}$: +47.3° (c = 1.50, CHCl$_3$)

HPLC separation: Chiralcel® OJ-H; 99:1 (*n*-heptane/*i*-PrOH), 1.0 mL.min^{-1}, 240 nm, t_R (major) = 11.0 min, t_R (minor) = 12.4 min, 97.5:2.5 e.r.

Experimental Section

Methyl (*S*)-5-chloro-2-methylindoline-1-carboxylate (2.25i):

The title compound was prepared according to the **General procedure F** (0.2 mmol scale, 120 °C/32 h) and purified by chromatography to give **2.25i** as a colorless oil (22.3 mg, 0.099 mmol, 49% yield).

2.25i
$C_{11}H_{12}ClNO_2$
M= 225,67 g.mol^{-1}
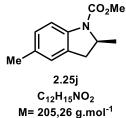
¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.73 (bs, 1H), 7.16-7.09 (m, 2H), 4.65-4.47 (m, 1H), 3.84 (s, 3H), 3.34 (dd, *J* = 16.2, 9.6 Hz, 1H), 2.61 (dd, *J* = 16.2, 2.0 Hz, 1H), 1.28 (d, *J* = 6.3 Hz, 3H)

¹³C NMR (101 MHz, CDCl₃): δ (ppm) 153.6, 140.3, 132.1, 127.7, 127.5, 125.3, 116.3, 55.8, 52.7, 35.8, 21.2

IR (neat): ν (cm^{-1}) 2955, 2927, 1704, 1480, 1383, 763

HRMS (ESI): Calcd for $C_{11}H_{12}{}^{35}ClNNaO_2$ [M+Na]$^+$: 248.0454, found 248,0447

$[α]_D^{20}$: +39.4° (c = 0.95, CHCl₃)

HPLC separation: Chiralpak® IA; 99:1 (*n*-heptane/*i*-PrOH), 1.0 mL.min^{-1}, 249 nm, t_R (minor) = 11.0 min, t_R (major) = 13.4 min, 92:8 e.r.

Methyl (*S*)-2,5-dimethylindoline-1-carboxylate (2.25j):

The title compound was prepared according to the **General procedure F** (0.2 mmol scale, 120 °C/32 h) and purified by chromatography to give **2.25j** as a colorless oil (21.1 mg, 0.103 mmol, 51% yield).

2.25j
$C_{12}H_{15}NO_2$
M= 205,26 g.mol^{-1}

¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.70 (bs, 1H), 7.02-6.92 (m, *J* = 9.5 Hz, 2H), 4.59-4.46 (m, 1H), 3.83 (s, 3H), 3.33 (dd, *J* = 15.9, 9.5 Hz, 1H), 2.59 (dd, *J* = 15.9, 1.8 Hz, 1H), 2.30 (s, 3H), 1.28 (d, *J* = 6.3 Hz, 3H)

¹³C NMR (101 MHz, CDCl₃): δ (ppm) 153.8, 139.3, 132.4, 130.1, 128.0, 125.9, 115.2, 55.5, 52.5, 36.0, 29.8, 21.0

IR (neat): ν (cm^{-1}) 2921, 2853, 1705, 1493, 1386, 1282, 762
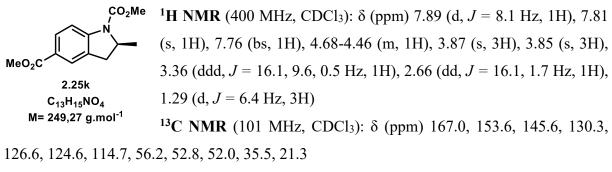
HRMS (ESI): Calcd for $C_{12}H_{15}NNaO_2$ [M+Na]$^+$: 228.0995, found 228,0991

$[α]_D^{20}$: +25.8° (c = 1.10, CHCl₃)

HPLC separation: Chiralpak® IA; 99:1 (*n*-heptane/*i*-PrOH), 1.0 mL.min^{-1}, 245 nm, t_R (minor) = 14.8 min, t_R (major) = 19.1 min, 91:9 e.r.

Experimental Section

Dimethyl (*S*)-2-methylindoline-1,5-dicarboxylate (2.25k):

The title compound was prepared according to the **General procedure F** (0.2 mmol scale, 120 °C/36 h) and purified by chromatography to give **2.25k** as a slight viscous yellow oil (40.1 mg, 0.161 mmol, 80% yield).

2.25k
$C_{13}H_{15}NO_4$
M= 249,27 g.mol^{-1}

¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.89 (d, *J* = 8.1 Hz, 1H), 7.81 (s, 1H), 7.76 (bs, 1H), 4.68-4.46 (m, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.36 (ddd, *J* = 16.1, 9.6, 0.5 Hz, 1H), 2.66 (dd, *J* = 16.1, 1.7 Hz, 1H), 1.29 (d, *J* = 6.4 Hz, 3H)

¹³C NMR (101 MHz, CDCl₃): δ (ppm) 167.0, 153.6, 145.6, 130.3, 126.6, 124.6, 114.7, 56.2, 52.8, 52.0, 35.5, 21.3

IR (neat): ν (cm^{-1}) 2953, 2854, 1707, 1384, 1267, 769
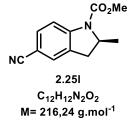
HRMS (ESI): Calcd for $C_{13}H_{15}NNaO_4$ [M+Na]$^+$: 272.0893, found 272,0894

[α]$_D^{20}$: +48.7° (c = 1.00, CHCl₃)

HPLC separation: Chiralpak® IA; 99:1 (*n*-heptane/*i*-PrOH), 1.0 mL.min^{-1}, 275 nm, t_R (minor) = 31.2 min, t_R (major) = 45.6 min, 94:6 e.r.

Methyl (*S*)-5-cyano-2-methylindoline-1-carboxylate (2.25l):

The title compound was prepared according to the **General procedure F** (0.2 mmol scale, 140 °C/48 h) and purified by chromatography to give **2.25l** as a white solid (26 mg, 0.120 mmol, 60% yield).

2.25l
$C_{12}H_{12}N_2O_2$
M= 216,24 g.mol^{-1}

¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.82 (bs, 1H), 7.49 (d, *J* = 8.4 Hz, 1H), 7.41 (s, 1H), 4.69-4.44 (m, 1H), 3.87 (s, 3H), 3.37 (dd, *J* = 16.3, 9.7 Hz, 1H), 2.68 (dd, *J* = 16.3, 2.0 Hz, 1H), 1.31 (d, *J* = 6.4 Hz, 3H)

¹³C NMR (101 MHz, CDCl₃): δ (ppm) 153.4, 132.9, 131.3, 128.7, 119.6, 115.7, 105.7, 56.2, 53.1, 35.5, 21.3

IR (neat): ν (cm^{-1}) 2923, 2852, 2221, 1710, 1383, 1277, 758

HRMS (ESI): Calcd for $C_{12}H_{12}N_2NaO_2$ [M+Na]$^+$: 239.0791, found 239,0789

Mp: 88-90 °C

[α]$_D^{20}$: +58.6° (c = 1.12, CHCl₃)

HPLC separation: Chiralpak® IA; 99:1 (*n*-heptane/*i*-PrOH), 1.0 mL.min^{-1}, 269 nm, t_R (minor) = 25.4 min, t_R (major) = 30.2 min, 97:3 e.r.

Experimental Section

Methyl (*S*)-6-fluoro-2-methylindoline-1-carboxylate (2.25m):

The title compound was prepared according to the **General procedure F** (0.2 mmol scale, 120 °C/18 h) and purified by chromatography to give **2.25m** as a colorless oil (40.2 mg, 0.192 mmol, 96% yield).

2.25m
$C_{11}H_{12}FNO_2$
M= 209,22 g.mol^{-1}

^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.53 (bs, 1H), 7.07-7.02 (m, 1H), 6.64 (tdd, *J* = 9.0, 8.2, 1.7 Hz, 1H), 4.64-4.50 (m, 1H), 3.84 (s, 3H), 3.30 (dd, *J* = 15.7, 9.6 Hz, 1H), 2.59 (d, *J* = 15.7 Hz, 1H), 1.29 (d, *J* = 6.3 Hz, 3H)

^{13}C NMR (101 MHz, CDCl$_3$): δ (ppm) 162.7 (d, *J* = 241.4 Hz), 153.4, 142.7, 125.4 (d, *J* = 9.5 Hz), 109.0 (d, *J* = 22.8 Hz), 103.6 (d, *J* = 28.9 Hz), 56.4, 52.6, 35.2, 21.1

^{19}F NMR (376 MHz, CDCl$_3$): δ (ppm) δ -112.64 (s)

IR (neat): ν (cm^{-1}) 2954, 2860, 1707, 1494, 1444, 1388, 1295
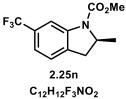
HRMS (ESI): Calcd for C$_{11}$H12FNNaO$_2$ [M+Na]$^+$: 232.0744, found 232,0743

[α]$_D^{20}$: +31.1° (c = 1.17, CHCl$_3$)

HPLC separation: Chiralcel® OD-H; 99:1 (*n*-heptane/*i*-PrOH), 1.0 mL.min^{-1}, 241 nm, t_R (major) = 6.20 min, t_R (minor) = 6.80 min, 98:2 e.r.

Methyl (*S*)-2-methyl-6-(trifluoromethyl)indoline-1-carboxylate (2.25n):

The title compound was prepared according to the **General procedure F** (0.2 mmol scale, 120 °C/18 h) and purified by chromatography to give **2.25n** as a white solid (47.6 mg, 0.184 mmol, 92% yield).

2.25n
$C_{12}H_{12}F_3NO_2$
M= 259,23 g.mol^{-1}

^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 8.09 (bs, 1H), 7.23 (bs, 2H), 4.68-4.52 (m, 1H), 3.87 (s, 3H), 3.40 (dd, *J* = 16.7, 9.7 Hz, 1H), 2.69 (d, *J* = 16.7 Hz, 1H), 1.31 (d, *J* = 6.4 Hz, 3H)

^{13}C NMR (101 MHz, CDCl$_3$): δ (ppm) 153.6, 130.2 (q, *J* = 31.3 Hz), 125.3, 124.4 (q, *J* = 272.2 Hz), 119.9 (q, *J* = 4.0 Hz), 112.4 (q, *J* = 4.0 Hz), 55.9, 52.9, 35.9, 21.2

^{19}F NMR (376 MHz, CDCl$_3$): δ (ppm) -62.17 (s)

IR (neat): ν (cm^{-1}) 2959, 2922, 1706, 1290, 819

HRMS (ESI): Calcd for C$_{12}$H$_{12}$F$_3$NNaO$_2$ [M+Na]$^+$: 282.0712, found 282,0711

Mp: 62-64 °C

[α]$_D^{20}$: + 32.5° (c = 1.38, CHCl$_3$)

Experimental Section

HPLC separation: Chiralcel® OD-H; 99:1 (*n*-heptane/*i*-PrOH), 1.0 mL.min^{-1}, 246 nm, t_R (major) = 5.5 min, t_R (minor) = 6.0 min, 97.5:2.5 e.r.

Methyl (*S*)-2,6-dimethylindoline-1-carboxylate (2.25p):

The title compound was prepared according to the **General procedure F** (0.2 mmol scale, 120 °C/20 h) and purified by chromatography to give **2.25p** as a white solid (38.7 mg, 0.189 mmol, 94% yield).

2.25p
C$_{12}$H$_{15}$NO$_2$
M= 205,26 g.mol^{-1}

^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.68 (bs, 1H), 7.03 (d, *J* = 7.5 Hz, 2H), 6.79 (dd, *J* = 7.5, 0.6 Hz, 2H), 4.60-4.48 (m, 1H), 3.84 (s, 3H), 3.31 (dd, *J* = 15.7, 9.5 Hz, 1H), 2.58 (dd, *J* = 15.8, 1.2 Hz, 1H), 2.34 (s, 3H), 1.28 (d, *J* = 6.3 Hz, 3H)

^{13}C NMR (101 MHz, CDCl$_3$): δ (ppm) 153.8, 141.6, 137.5, 127.2, 124.8, 123.5, 116.2, 55.8, 52.5, 35.7, 21.8, 21.3

IR (neat): ν (cm^{-1}) 2925, 2855, 1698, 1373, 1277, 1134, 803, 759

HRMS (ESI): Calcd for C$_{12}$H$_{15}$NNaO$_2$ [M+Na]$^+$: 228.0995, found 228,0993

Mp: 84-86 °C
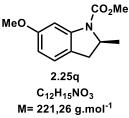
[α]$_D^{20}$: +33.8° (c = 1.16, CHCl$_3$)

HPLC separation: Chiralpak® IA; 99:1 (*n*-heptane/*i*-PrOH), 1.0 mL.min^{-1}, 224 nm, t_R (minor) = 8.3 min, t_R (major) = 10.3 min, 96:4 e.r.

Methyl (*S*)-6-methoxy-2-methylindoline-1-carboxylate (2.25q):

The title compound was prepared according to the **General procedure F** (0.2 mmol scale, 120 °C/20 h) and purified by chromatography to give **2.25q** as a colorless oil (36.7 mg, 0.166 mmol, 83% yield).

2.25q
C$_{12}$H$_{15}$NO$_3$
M= 221,26 g.mol^{-1}

^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.50 (bs, 1H), 7.02 (d, *J* = 8.2 Hz, 1H), 6.52 (dd, *J* = 8.2, 2.4 Hz, 1H), 4.46-4.62 (m, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 3.28 (ddd, *J* = 15.5, 9.5, 1.1 Hz, 1H), 2.55 (dd, *J* = 15.5, 2.1 Hz, 1H), 1.28 (d, *J* = 6.3 Hz, 3H)

^{13}C NMR (101 MHz, CDCl$_3$): δ (ppm) 159.7, 153.7, 142.6, 125.3, 121.8, 109.0, 101.4, 56.4, 55.6, 52.6, 35.3, 21.3

IR (neat): ν (cm^{-1}) 2953, 2857, 1704, 1386, 1296, 764

HRMS (ESI): Calcd for C$_{12}$H$_{15}$NNaO$_3$ [M+Na]$^+$: 244.0944, found 244,0945

[α]$_D^{20}$: +22.5° (c = 1.30, CHCl$_3$)

Experimental Section

HPLC separation: Chiralpak® IA; 99:1 (*n*-heptane/*i*-PrOH), 1.0 mL.min⁻¹, 244 nm, t_R (minor) = 11.6 min, t_R (major) = 13.0 min, 96:4 e.r.

Methyl (*S*)-7-fluoro-2-methylindoline-1-carboxylate (2.25r):
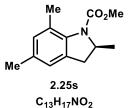
The title compound was prepared according to the **General procedure F** (0.2 mmol scale, 120 °C/18 h) and purified by chromatography to give **2.25r** as a slight yellow oil (33.1 mg, 0.158 mmol, 79% yield).

2.25r
$C_{11}H_{12}FNO_2$
M= 209,22 g.mol⁻¹

¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.02-6.90 (m, 3H), 4.67 (dqd, J = 8.5, 6.6, 1.4 Hz, 1H), 3.82 (s, 3H), 3.42 (dd, J = 15.8, 8.5 Hz, 1H), 2.52 (d, J = 15.8 Hz, 1H), 1.26 (d, J = 6.6 Hz, 3H)

¹³C NMR (101 MHz, CDCl₃): δ (ppm) 154.1, 151.9 (d, J = 252.1 Hz), 135.6 (d, J = 2.8 Hz), 127.9 (d, J = 9.9 Hz), 125.1 (d, J = 7.0 Hz), 120.8 (d, J = 3.3 Hz), 116.0 (d, J = 21.2 Hz), 57.9, 53.1, 36.7 (d, J = 1.7 Hz), 21.2

¹⁹F NMR (376 MHz, CDCl₃): δ (ppm) -117.60 to -117.71 (m)

IR (neat): ν (cm⁻¹) 2955, 2926, 1704, 1484, 1381, 762

HRMS (ESI): Calcd for $C_{11}H_{12}FNNaO_2$ [M+Na]⁺: 232.0744, found 232,0744

[α]$_D^{20}$: +64.5° (c = 1.14, CHCl₃)

HPLC separation: Chiralcel® OJ-H; 99:1 (*n*-heptane/*i*-PrOH), 1.0 mL.min⁻¹, 242 nm, t_R (minor) = 14.6 min, t_R (major) = 15.5 min, 95.5:4.5 e.r.

Methyl (*S*)-2,5,7-trimethylindoline-1-carboxylate (2.25s):

The title compound was prepared according to the **General procedure F** (0.2 mmol scale, 120 °C/18 h) and purified by chromatography to give **2.25s** as a slight yellow oil (41.1 mg, 0.187 mmol, 94% yield).

2.25s
$C_{13}H_{17}NO_2$
M= 219,28 g.mol⁻¹

¹H NMR (400 MHz, CDCl₃): δ (ppm) 6.85 (s, 2H), 4.70 (dqd, J = 7.6, 6.6, 0.9 Hz, 1H), 3.78 (s, 3H), 3.35 (dd, J = 15.5, 8.4 Hz, 1H), 2.38 (d, J = 15.5 Hz, 1H), 2.28 (s, 3H), 2.25 (s, 3H), 1.21 (d, J = 6.6 Hz, 3H)

¹³C NMR (101 MHz, CDCl₃): δ (ppm) 155.0, 137.6, 134.2, 133.2, 130.6, 127.9, 123.2, 58.1, 52.6, 36.7, 21.2, 21.0, 20.1

IR (neat): ν (cm⁻¹) 2953, 2922, 1710, 1439, 1366, 1262

HRMS (ESI): Calcd for $C_{13}H_{17}NNaO_2$ [M+Na]⁺: 242,1151, found 242,1155

[α]$_D^{20}$: +12.0° (c = 1.18, CHCl₃)

Experimental Section

Methyl (*S*)-2-methyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine-1-carboxylate (2.25t):

The title compound was prepared according to the **General procedure F** (0.2 mmol scale, 120 °C/24 h) and purified by chromatography to give **2.25t** as a slight yellow oil (25.8 mg, 0.134 mmol, 67% yield).

2.25t
$C_{10}H_{12}N_2O_2$
M= 192,22 g.mol^{-1}

¹H NMR (400 MHz, CDCl$_3$): δ (ppm) 8.11 (dd, *J* = 5.0, 1.4 Hz, 1H), 7.98 (bs, 1H), 7.06 (dd, *J* = 7.9, 5.0 Hz, 1H), 4.64-4.47 (m, 1H), 3.85 (s, 3H), 3.48 (ddd, *J* = 17.0, 9.8, 0.8 Hz, 1H), 2.77 (dd, *J* = 17.0, 2.7 Hz, 1H), 1.34 (d, *J* = 6.4 Hz, 3H)

¹³C NMR (101 MHz, CDCl$_3$): δ (ppm) 153.9, 152.6, 143.6, 136.3, 122.1, 121.7, 54.1, 52.8, 38.2, 21.6

IR (neat): ν (cm^{-1}) 2957, 2928, 1706, 1445, 1293, 764
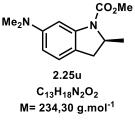
HRMS (ESI): Calcd for $C_{10}H_{13}N_2O_2$ [M+H]$^+$: 193.0977, found 193.0972

[α]$_D^{20}$: +9.9° (c = 0.80, CHCl$_3$)

Methyl (*S*)-6-(dimethylamino)-2-methylindoline-1-carboxylate (2.25u):

The title compound was prepared according to the **General procedure F** (0.2 mmol scale, 120 °C/18 h) and purified by chromatography to give **2.25u** as a colorless oil (35.3 mg, 0.151 mmol, 75% yield).

2.25u
$C_{13}H_{18}N_2O_2$
M= 234,30 g.mol^{-1}

¹H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.40 (bs, 1H), 7.00 (d, *J* = 8.2 Hz, 1H), 6.38 (dd, *J* = 8.2, 2.4 Hz, 1H), 4.61-4.44 (m, 1H), 3.83 (s, 3H), 3.27 (ddd, *J* = 15.2, 9.4, 0.8 Hz, 1H), 2.94 (s, 6H), 2.53 (dd, *J* = 15.2, 1.9 Hz, 1H), 1.28 (d, *J* = 6.3 Hz, 3H)

¹³C NMR (101 MHz, CDCl$_3$): δ (ppm) 153.8, 151.0, 125.2, 107.6, 100.9, 56.2, 52.4, 41.3, 35.2, 21.4

IR (neat): ν (cm^{-1}) 2854, 2796, 1704, 1508, 1387, 1055, 763

HRMS (ESI): Calcd for $C_{13}H_{18}N_2NaO_2$ [M+H]$^+$: 235.1441, found 235.1440

[α]$_D^{20}$: - 2.9° (c = 1.31, CHCl$_3$)

Experimental Section
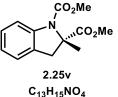
HPLC separation: Chiralcel® OJ-H; 99:1 (*n*-heptane/*i*-PrOH), 1.0 mL.min⁻¹, 312 nm, t_R (minor) = 15.2 min, t_R (major) = 19.1 min, 94.5:5.5 e.r.

Dimethyl (*S*)-2-methylindoline-1,2-dicarboxylate (2.25v):

The title compound was prepared according to the **General procedure F** (0.2 mmol scale, 120 °C/20 h) and purified by chromatography to give **2.25v** as a colorless oil (41.5 mg, 0.166 mmol, 83% yield).

2.25v
$C_{13}H_{15}NO_4$
M= 249,27 g.mol⁻¹

Mixture of two rotamers, description of the major:

¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.93 (bs, 1H), 7.17-7.27 (m, 1H), 7.18-7.08 (m, 2H), 6.99 (t, *J* = 7.4 Hz, 1H), 3.99-3.67 (m, 6H), 3.46 (d, *J* = 16.1 Hz, 1H), 3.04 (d, *J* = 16.1 Hz, 1H), 1.69 (d, *J* = 1.8 Hz, 3H)

¹³C NMR (101 MHz, CDCl₃): δ (ppm) 173.8, 152.9, 142.1, 128.1, 123.2, 115.2, 67.7, 52.7, 42.9, 23.7

IR (neat): ν (cm⁻¹) 2952, 2855, 1745, 1703, 1486, 1370, 764
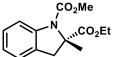
HRMS (ESI): Calcd for $C_{13}H_{15}NNaO_4$ [M+Na]⁺: 272.0893, found 272,0891

[α]$_D^{20}$: -10.0° (c = 0.90, CHCl₃)

HPLC separation: Chiralpak® IA; 99:1 (*n*-heptane/*i*-PrOH), 1.0 mL.min⁻¹, 241 nm, t_R (major) = 22.4 min, t_R (minor) = 26.9 min, 92:8 e.r.

2-ethyl 1-methyl (*S*)-2-methylindoline-1,2-dicarboxylate (2.25w):

The title compound was prepared according to the **General procedure F** (0.2 mmol scale, 120 °C/24 h) and purified by chromatography to give **2.25w** as a colorless oil (37.6 mg, 0.143 mmol, 71% yield).

2.25w
$C_{14}H_{17}NO_4$
M= 263,29 g.mol⁻¹

Mixture of two rotamers, description of the major:

¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.93 (bs, 1H), 7.28-7.17 (m, 1H), 7.12 (d, *J* = 7.3 Hz, 1H), 7.00 (t, *J* = 7.3 Hz, 1H), 4.34-4.09 (m, 2H), 3.77 (s, 3H), 3.45 (d, *J* = 16.1 Hz, 1H), 3.03 (d, *J* = 16.1 Hz, 1H), 1.68 (s, 3H), 1.24 (t, *J* = 7.1 Hz, 7H)

¹³C NMR (101 MHz, CDCl₃): δ (ppm) 173.3, 142.3, 128.1, 127.3, 124.6, 123.2, 115.3, 67.8, 61.6, 52.5, 43.0, 23.5, 14.3

IR (neat): ν (cm⁻¹) 2982, 2855, 1738, 1704, 1371, 1240, 754

HRMS (ESI): Calcd for $C_{14}H_{17}NNaO_4$ [M+Na]⁺: 286.1050, found 286,1051

[α]$_D^{20}$: -13.7° (c = 1.15, CHCl₃)

Experimental Section

HPLC separation: Chiralcel® OJ-H; 99:1 (*n*-heptane/*i*-PrOH), 1.0 mL.min⁻¹, 241 nm, t_R (major) = 23.9 min, t_R (minor) = 27.4 min, 85:15 e.r.

1-benzyl 2-methyl (*S*)-2-methylindoline-1,2-dicarboxylate (2.25x):

The title compound was prepared according to the **General procedure F** (0.2 mmol scale, 120 ºC/17 h) and purified by chromatography to give **2.25x** as a colorless oil (30 mg, 0.092 mmol, 46% yield).
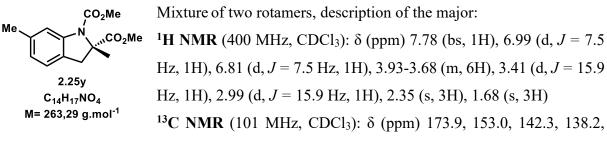
2.25x
$C_{19}H_{19}NO_4$
M= 325,36 g.mol⁻¹

Mixture of two rotamers, description of the major:

¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.98 (d, *J* = 6.6 Hz, 1H), 7.47-6.95 (m, 8H), 5.40-5.30 (m, *J* = 11.1 Hz, 2H), 3.46 (d, *J* = 16.2 Hz, 1H), 3.42 (s, 3H), 3.04 (d, *J* = 16.2 Hz, 1H), 1.70 (s, 3H)

¹³C NMR (101 MHz, CDCl₃): δ (ppm) 173.6, 152.2, 142.2, 140.9, 135.8, 128.7, 128.4, 128.1, 127.1, 124.5, 123.3, 115.4, 67.7, 67.4, 52.5, 43.0, 23.7

IR (neat): ν (cm⁻¹) 3033, 2949, 1744, 1703, 1397, 753

HRMS (ESI): Calcd for $C_{19}H_{19}NNaO_4$ [M+Na]⁺: 348.1206, found 348,1208

[α]$_D^{20}$: -22.6° (c = 1.36, CHCl₃)

HPLC separation: Chiralpak® IA; 97:3 (*n*-heptane/*i*-PrOH), 1.0 mL.min⁻¹, 242 nm, t_R (major) = 18.9 min, t_R (minor) = 31.7 min, 80:20 e.r.

Dimethyl (*S*)-2,6-dimethylindoline-1,2-dicarboxylate (2.25y):

The title compound was prepared according to the **General procedure F** (0.2 mmol scale, 120 ºC/20 h) and purified by chromatography to give **2.25y** as a pale viscous oil (26.5 mg, 0.101 mmol, 50% yield).

2.25y
$C_{14}H_{17}NO_4$
M= 263,29 g.mol⁻¹

Mixture of two rotamers, description of the major:

¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.78 (bs, 1H), 6.99 (d, *J* = 7.5 Hz, 1H), 6.81 (d, *J* = 7.5 Hz, 1H), 3.93-3.68 (m, 6H), 3.41 (d, *J* = 15.9 Hz, 1H), 2.99 (d, *J* = 15.9 Hz, 1H), 2.35 (s, 3H), 1.68 (s, 3H)
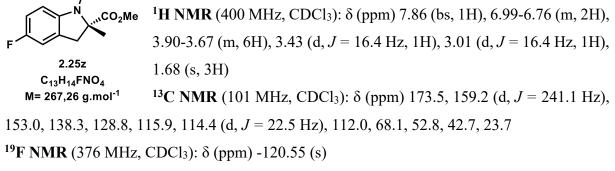
¹³C NMR (101 MHz, CDCl₃): δ (ppm) 173.9, 153.0, 142.3, 138.2, 124.6, 124.2, 123.9, 116.0, 68.0, 52.7, 42.6, 23.6, 21.8

IR (neat): ν (cm⁻¹) 2954, 2860, 1745, 1701, 1369, 1070, 752

HRMS (ESI): Calcd for $C_{14}H_{17}NNaO_4$ [M+Na]⁺: 286.1050, found 286,1049

[α]$_D^{20}$: -10.0° (c = 1.00, CHCl₃)

Experimental Section

Dimethyl (*S*)-5-fluoro-2-methylindoline-1,2-dicarboxylate (2.25z):

The title compound was prepared according to the **General procedure F** (0.2 mmol scale, 120 °C/17 h) and purified by chromatography to give **2.25z** as a colorless oil (41.2 mg, 0.154 mmol, 77% yield).

Mixture of two rotamers, description of the major:

2.25z
$C_{13}H_{14}FNO_4$
M= 267,26 g.mol⁻¹

¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.86 (bs, 1H), 6.99-6.76 (m, 2H), 3.90-3.67 (m, 6H), 3.43 (d, *J* = 16.4 Hz, 1H), 3.01 (d, *J* = 16.4 Hz, 1H), 1.68 (s, 3H)

¹³C NMR (101 MHz, CDCl₃): δ (ppm) 173.5, 159.2 (d, *J* = 241.1 Hz), 153.0, 138.3, 128.8, 115.9, 114.4 (d, *J* = 22.5 Hz), 112.0, 68.1, 52.8, 42.7, 23.7

¹⁹F NMR (376 MHz, CDCl₃): δ (ppm) -120.55 (s)

IR (neat): ν (cm⁻¹) 2954, 2854, 1745, 1707, 1487, 1372, 1257, 764

HRMS (ESI): Calcd for $C_{13}H_{14}FNNaO_4$ [M+Na]⁺: 290.0799, found 290,0800

[α]²⁰_D: -5.9° (c = 1.00, CHCl₃)
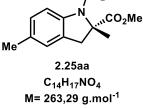
HPLC separation: Chiralpak® IA; 99:1 (*n*-heptane/*i*-PrOH), 1.0 mL.min⁻¹, 238 nm, t_R (major) = 22.5 min, t_R (minor) = 25.3 min, 93.5:6.5 e.r.

Dimethyl (*S*)-2,5-dimethylindoline-1,2-dicarboxylate (2.25aa):

The title compound was prepared according to the **General procedure F** (0.2 mmol scale, 120 °C/22 h) and purified by chromatography to give **2.25aa** as a pale viscous oil (31.1 mg, 0.118 mmol, 59% yield).

Mixture of two rotamers, description of the major:

2.25aa
$C_{14}H_{17}NO_4$
M= 263,29 g.mol⁻¹

¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.79 (bs, 1H), 7.07-6.96 (m, 1H), 6.93 (s, 1H), 3.90-3.67 (m, 6H), 3.42 (d, *J* = 16.2 Hz, 1H), 3.00 (d, *J* = 16.2 Hz, 1H), 2.29 (s, 3H), 1.68 (s, 3H)

¹³C NMR (101 MHz, CDCl₃): δ (ppm) 173.9, 152.9, 139.9, 132.8, 128.6, 127.2, 125.2, 115.0, 67.7, 52.7, 42.9, 23.6, 20.9

IR (neat): ν (cm⁻¹) 2953, 2857, 1745, 1705, 1493, 1361, 1073, 763

HRMS (ESI): Calcd for $C_{14}H_{17}NNaO_4$ [M+Na]⁺: 286.1050, found 286,1052
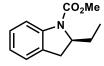
[α]²⁰_D: -3.4° (c = 1.00, CHCl₃)

Experimental Section

HPLC separation: Chiralpak® IA; 97:3 (*n*-heptane/*i*-PrOH), 1.0 mL.min^{-1}, 243 nm, t_R (major) = 23.3 min, t_R (minor) = 33.9 min, 93:7 e.r.

(*S*)-methyl 2-ethylindoline-1-carboxylate (2.25ac):

The title compound was prepared according to the **General procedure F** (0.2 mmol scale, 120-C/24 h) and purified by chromatography to give **2.25ac** as a colorless oil (12.6 mg, 0.061 mmol, 31% yield). NMR spectroscopic data are consistent with those previously reported.[142] **2.25ac** was assigned a (*S*) absolute configuration by comparison of HPLC data with those previously reported.[145]

2.25ac
$C_{12}H_{15}NO_2$
M= 205,26 g.mol^{-1}

^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.72 (bs, 1H), 7.19- 7.13 (m, 2H), 6.95 (td, J = 7.4, 1.0 Hz, 1H), 4.39 (m, 1H), 3.84 (s, 3H), 3.28 (dd, J = 16.1, 9.7 Hz, 1H), 2.76 (dd, J = 16.1, 2.2 Hz, 1H), 1.78 (m, 1H), 1.67-1.49 (m, 1H), 0.88 (t, J = 7.5 Hz, 3H)
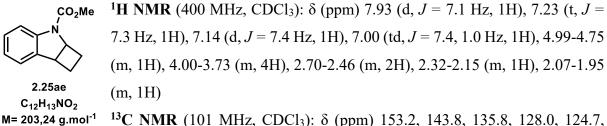
^{13}C NMR (101 MHz, CDCl$_3$): δ (ppm) 153.9, 142.0, 130.5, 127.4, 124.9, 122.8, 115.4, 60.7, 52.5, 32.9, 27.4, 9.1

[α]$_D^{20}$: +26.3° (c = 0.96, CHCl$_3$)

HPLC separation: Chiralpak® AD-H; 99:1 (*n*-heptane/*i*-PrOH), 0.5 mL.min^{-1}, 243 nm, t_R (minor) = 20.6 min, t_R (major) = 26.4 min, 73:27 e.r.

Methyl 2,2a-dihydro-1*H*-cyclobuta[b]indole-3(7b*H*)-carboxylate (2.25ae):

The title compound was prepared according to the **General procedure F** (0.5 mmol scale, 140 °C/48 h) and purified by chromatography to give **2.25ae** as a slight yellow oil (18 mg, 0.089 mmol, 18% yield).

2.25ae
$C_{12}H_{13}NO_2$
M= 203,24 g.mol^{-1}

^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.93 (d, J = 7.1 Hz, 1H), 7.23 (t, J = 7.3 Hz, 1H), 7.14 (d, J = 7.4 Hz, 1H), 7.00 (td, J = 7.4, 1.0 Hz, 1H), 4.99-4.75 (m, 1H), 4.00-3.73 (m, 4H), 2.70-2.46 (m, 2H), 2.32-2.15 (m, 1H), 2.07-1.95 (m, 1H)

^{13}C NMR (101 MHz, CDCl$_3$): δ (ppm) 153.2, 143.8, 135.8, 128.0, 124.7, 123.1, 115.4, 58.5, 52.5, 41.1, 29.4, 26.8

IR (neat): ν (cm^{-1}) 2947, 2853, 1702, 1386, 1062, 747
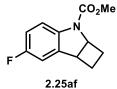
HRMS (ESI): Calcd for $C_{12}H_{13}NNaO_2$ [M+Na]$^+$: 226.0838, found 226,0838

[α]$_D^{20}$: -39.2° (c = 1.00, CHCl$_3$)

Experimental Section

Methyl 6-fluoro-2,2a-dihydro-1*H*-cyclobuta[b]indole-3(7b*H*)-carboxylate (2.25af):

The title compound was prepared according to the **General procedure F** (0.5 mmol scale, 140 °C/48 h) and purified by chromatography to give **2.25af** as a white solid (25 mg, 0.113 mmol, 23% yield).

2.25af
C$_{12}$H$_{12}$FNO$_2$
M= 221,23 g.mol^{-1}

^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.85 (dd, *J* = 7.4, 4.1 Hz, 1H), 6.90 (t, *J* = 8.6 Hz, 1H), 6.84 (dd, *J* = 8.1, 2.3 Hz, 1H), 5.01-4.77 (m, 1H), 3.96-3.69 (m, 4H), 2.67-2.43 (m, 2H), 2.32-2.15 (m, 1H), 2.07-1.94 (m, 1H)

^{13}C NMR (101 MHz, CDCl$_3$): δ (ppm) 159.3 (d, *J* = 240.9 Hz), 153.2, 139.8, 137.6, 116.1, 114.2 (d, *J* = 22.7 Hz), 111.9 (d, *J* = 24.0 Hz), 58.9, 52.6, 41.1, 29.4, 26.7

^{19}F NMR (376 MHz, CDCl$_3$): δ (ppm) -120.88 (s)

IR (neat): ν (cm^{-1}) 2994, 2951, 2920, 2851, 1705, 1248, 1071, 853, 751

HRMS (ESI): Calcd for C$_{12}$H$_{12}$FNNaO$_2$ [M+Na]$^+$: 244.0744, found 244,0745
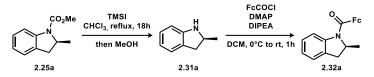
Mp: 57-60 °C
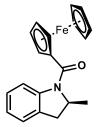
[α]$_D^{20}$: -29.4° (c = 0.50, CHCl$_3$)

Experimental Section

6.2.4. Ferrocene derivatization

(S)-2-methylindoline-1-Ferrocenoyl (2.32a):

Under argon, TMSI (602 μL, 4.24 mmol, 10 equiv) was added to a solution of **2.25a** (81 mg, 93.5:6.5 e.r., 0.424 mmol, 1.0 equiv) in CHCl$_3$ (10 mL at room temperature. The reaction mixture was refluxed overnight, then MeOH (10 mL) was added and the reaction was refluxed during 3 h. After this time, the solvent was removed under reduced pressure and ammonia hydroxide (10 mL, 28% NH$_3$ in H$_2$O) was added to the residue. Once the phases were separated, the aqueous layer was extracted with CH$_2$Cl$_2$ and the combined organic layers were dried over Na$_2$SO$_4$. After removing the solvent under reduced pressure, the crude amine **2.31a** was obtained as a colorless viscous oil, which was directly used in the next step. A round-bottom flask equipped with a magnetic stir bar was charged with crude **2.31a** and DCM (4 mL) was added and the mixture was cooled to 0°C. DMAP (5.2 mg, 0.0424 mmol, 10 mol%) was added, followed by DIPEA (210 μL, 1.27 mmol, 3.0 equiv) to give a clear solution. Then ferrocene carboxylic acid chloride (0.466 mmol, 116 mg, 1.1 equiv) in DCM (1 mL) was added. The reaction was warmed to room temperature and stirred for 1 hour. The reaction mixture was concentrated under reduced pressure to give the crude product, which was purified by flash column chromatography (silica gel, pentane/EtOAc 4:1 as eluent) affording **2.32a** (121.3 mg, 0.35 mmol, 93:7 e.r., 83%, two steps) as an orange solid. Suitable crystals for X-ray diffraction analysis were obtained from dichloromethane and pentane as solvent and anti-solvent, respectively.
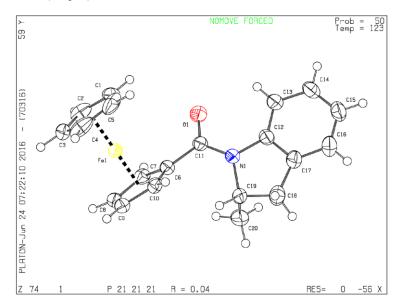
2.32a
C$_{20}$H$_{19}$FeNO
M= 345,22 g.mol^{-1}
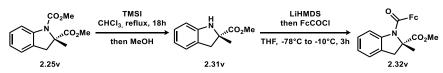
^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.78 (bs, 1H), 7.21 (d, J = 7.4 Hz, 1H), 7.14 (t, J = 6.9 Hz, 1H), 7.01 (t, J = 7.4 Hz, 1H), 4.97-4.86 (m, 1H), 4.83-4.71 (m, J = 10.2 Hz, 2H), 4.41-4.35 (m, 2H), 4.26 (s, 4H), 3.39 (dd, J = 15.5, 8.6 Hz, 1H), 2.64 (d, J = 15.5 Hz, 1H), 1.29 (d, J = 6.4 Hz, 3H)

^{13}C NMR (101 MHz, CDCl$_3$): δ (ppm) 168.6, 142.5, 131.0, 127.2, 125.3, 123.7, 118.0, 79.4, 72.8, 71.0, 70.4, 70.2, 70.0, 69.7, 56.6, 36.7, 21.7

IR (neat): ν (cm^{-1}) 2958, 2920, 1632, 1385, 756, 480

HRMS (ESI): Calcd for C$_{20}$H$_{19}$FeNNaO [M+H]$^+$: 346.0894, found 346.0889

Mp: 130-133 °C

[α]$_D^{20}$: +13.9° (c = 1.09, CHCl$_3$)

Experimental Section

HPLC separation: Chiralcel® OJ-H; 97:3 (*n*-heptane/*i*-PrOH), 1.0 mL.min^{-1}, 272 nm, t_R (minor) = 15.1 min, t_R (major) = 17.1 min, 93:7 e.r.

Methyl (*S*)-2-methylindoline-2-carboxylate-1-ferrocenoyl (2.32v):

Under argon, TMSI (542 μL, 3.8 mmol, 10 equiv) was added to a solution of **2.25u** (94 mg, 0.38 mmol, 90:10 e.r., 1.0 equiv) in CHCl$_3$ (10 mL) at room temperature. The reaction mixture was refluxed overnight, then MeOH (10 mL) was added and the reaction was refluxed during 3 h. After this time, the solvent was removed under reduced pressure and ammonia hydroxide (10 mL, 28% NH$_3$ in H$_2$O) was added to the residue. Once the phases were separated, the aqueous layer was extracted with CH$_2$Cl$_2$ and the combined organic layers were dried over Na$_2$SO$_4$. After removing the solvent under reduced pressure, the crude amine **2.31v** was obtained as a colorless viscous oil, which was directly used in the next step. To a solution of the crude amine **2.31v** in dry THF (5 mL) was added LiHMDS (0.45 mmol, 450 μL, 1.0 M in THF, 1.2 equiv) dropwise at -78 °C under argon. The mixture was stirred for 10 min at -78 °C, then for 20 min at -10 °C. At this time, ferrocene carboxylic acid chloride (0.45 mmol, 112 mg, 1.2 equiv) was added in one portion and the mixture was stirred at -10 °C for 3 h. The reaction was quenched with saturated solution of NH$_4$Cl and extracted three times with ethyl acetate. The organic layers were combined and washed with water, brine, dried over Na$_2$SO$_4$, and finally concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, pentane/EtOAc 10:1 as eluent) to yield **2.32v** (122 mg, 0.3 mmol,

Experimental Section

90:10 e.r., 80%, two steps) as an orange solid. Suitable crystals for X-ray diffraction analysis were obtained from diethyl ether and pentane as solvent and anti-solvent, respectively.

2.32v
C$_{22}$H$_{21}$FeNO$_3$
M= 403,26 g.mol^{-1}

^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.15-7.10 (m, 1H), 6.94-6.85 (m, 2H), 6.61-6.55 (m, 1H), 4.81 (dt, J = 2.5, 1.3 Hz, 1H), 4.63 (dt, J = 2.5, 1.2 Hz, 1H), 4.41 (td, J = 2.5, 1.3 Hz, 1H), 4.31 (td, J = 2.5, 1.3 Hz, 1H), 4.26 (s, 4H), 3.81 (s, 3H), 3.45 (d, J = 15.6 Hz, 1H), 2.93 (d, J = 15.6 Hz, 1H), 1.73 (s, 3H)

^{13}C NMR (101 MHz, CDCl$_3$): δ (ppm) 173.5, 169.2, 142.2, 129.7, 126.7, 125.3, 123.0, 115.6, 79.2, 72.2, 70.6, 70.3, 70.2, 69.8, 69.3, 52.8, 41.9, 21.7

IR (neat): ν (cm^{-1}) 2924, 2853, 1740, 1318, 747, 482

HRMS (ESI): Calcd for C$_{22}$H$_{21}$FeNNaO$_3$ [M+Na]$^+$: 426.0763, found 426,0761

Mp: 61-63 °C

[α]$_D^{20}$: -163° (c = 1.00, CHCl$_3$)
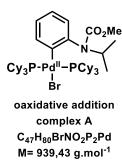
HPLC separation: Chiralpak® IA; 99:1 (*n*-heptane/*i*-PrOH), 1.0 mL.min^{-1}, 210 nm, t_R (major) = 16.1 min, t_R (minor) = 20.6 min, 90:10 e.r
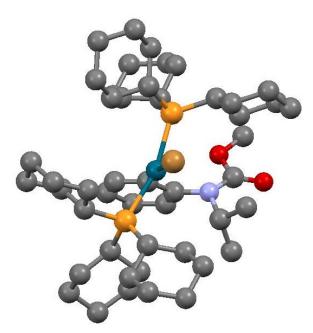
6.2.5. Oxidative addition complex

Oxidative addition complex A:

In an oven-dry catalysis tube was charged **2.24a-Br** (61.2 mg, 0.225 mmol, 1.5 equiv). The tube was then transferred in glovebox and Pd(PCy$_3$)$_2$ was added and the tube was closed with a septum. Then, outside of the glove box, dry and degassed toluene (3 mL) was added. After 24h of stirring at room temperature, the solvent was removed under vacuum using a Schlenk line. The obtained residual solid was then washed three time with a small amount of cold, dry and degassed diethyl ether and dry under high vacuum to obtained oxidative addition complex **A** as a white solid (82.3 mg, 0.088 mmol, 58%). Suitable crystals for X-ray analysis were obtained by evaporation of a solution of the obtained solid in diethyl ether.

oaxidative addition
complex A
C$_{47}$H$_{80}$BrNO$_2$P$_2$Pd
M= 939,43 g.mol^{-1}

¹H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.62 (d, J = 7.4 Hz, 1H), 6.83 (d, J = 7.1 Hz, 1H), 6.77 (t, J = 7.2 Hz, 1H), 6.70 (brs, 1H), 4.58 (sept, J = 6.8 Hz, 1H), 3.52 (brs, 3H), 2.24-0.55 (m, 72H)

³¹P NMR (162 MHz, CDCl$_3$): δ (ppm) 21.8, 19.4, 17.7, 15.3

Solid state structure of complex A (hydrogens are hiden for more clarity).

Experimental Section

Experimental Section

6.3. Chapter 3

6.3.1. Ligands

For C$_2$ symetrical Herrmann-Kundig type NHCs:

3.32 was graciously furnished by Pr. E. P. Kündig, **3.29**, **3.33-3.36** and **3.38** were prepared as reported.[212,213]

For C$_2$ symetrical and achiral IBiox-type NHCs:

All IBiox-type ligands were prepared as reported.[215–217]
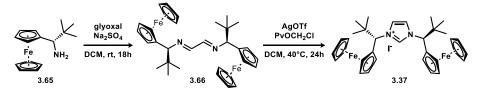
For Binepine ligand:

3.26 was previously prepared in our group.[156]

For TADDOL phosphoramidite/phosphonite ligands:
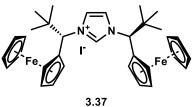
3.27, **3.28** were previously prepared as reported.[238,239]

1,3-bis((S)-2,2-dimethyl-1-ferrocenylpropyl)-1H-imidazol-3-ium iodide (3.37):

Chiral amine **3.65** was prepared as described.[240] A round-bottom 2-neck flask under nitrogen atmosphere was charged with an aq. soln. of glyoxal (40%) (0.21 mL, 1.84 mmol, 1 equiv), DCM (7 mL) and vigorously stirred with 1.4 g of freshly dehydrated Na$_2$SO$_4$ for 10 minutes. After the addition of formic acid (98%) (10 µL, 0.26 mmol, 14mol%) and **3.65** (1.0 g, 3.68 mmol, 2 equiv) the reaction mixture was allowed to stir for 5 minutes followed by addition of another 1.4 g of Na$_2$SO$_4$. After18 h of stirring at room temperature, the reaction mixture was filtered through a glass frit and Na$_2$SO$_4$ was washed with DCM. The organic solvents were removed with rotary evaporator to yield the crude diimine **3.66**. Then a dry 25 mL Schlenk tube under nitrogen atmosphere was charged with AgOTf (651 mg, 2.53 mmol, 1.5 equiv), 10 mL of DCM and chloromethylpivalate (0.37 mL, 2.53 mmol, 1.5 equiv). The mixture was stirred for 45 min. in the absence of light. The resulting suspension was transferred under nitrogen, via a cannula equiped with a filter, into a 25 mL dry Schlenk tube preloaded with the **3.66** (1.0 g, 1.69 mmol, 1 equiv). This mixture was stirred in absence of light at 40 °C for 24 h. After cooling to rt, the solvent was evaporated using a rotavap. Flash chromatography (Et$_2$O/CH$_2$Cl$_2$ 1:1) afforded a brown product. This was taken up in dry acetone (25 mL). NaI (280 mg, 1.86 mmol, 1.1 equiv) was added and the mixture was stirred overnight. Volatiles were removed via a

Experimental Section

rotavap. The residue was taken up in a small amount of CHCl₃ and filtered through a pad of celite. The above procedure (acetone, NaI, etc) was repeated. Two column chromatography (DCM/MeOH) afforded **3.37** (217 mg, 0.31 mmol, 18%) as a brown-orange solid.

3.37

$C_{33}H_{41}Fe_2IN_2$

M= 704,30 g.mol^{-1}

Mixture of rotamers, description of the major:

¹H NMR (500 MHz, CDCl₃): δ (ppm) 10.81 (s, 1H), 7.69 (s, 2H), 5.89 (s, 2H), 4.48 (s, 2H), 4.34-4.21 (m, 6H), 4.08 (s, 10H), 1.03 (s, 18H)

¹³C NMR (126 MHz, CDCl₃): 137.0, 122.0, 82.9, 71.6, 70.4, 69.4, 69.4, 67.9, 66.9, 36.9, 27.5

IR (neat): ν (cm⁻¹) 3089, 2957, 2871, 1747, 1701, 1445, 1367, 1141, 1106, 1002, 827, 770

HRMS (ESI): Calcd for $C_{33}H_{41}Fe_2N_2$ [M]⁺: 577.1964, found 577.1971

Mp: 180 °C (decomposition)

$[\alpha]_D^{20}$: +101.8° (c = 1.04, CHCl₃)

Experimental Section

6.3.2. Model Substrates

Methyl 3-(2-bromophenyl)-2,2-dimethylpropanoate (3.17):

A solution of LDA (8.4 mmol, 1.05 equiv) in THF (17 mL) was prepared from diisopropylamine (1.18 mL, 8.4 mmol, 1.05 equiv) and 2.5 M ^{n}BuLi in hexane (3.36 mL, 8.4 mmol, 1.05 equiv), stirred at 0°C during 15 min. To the LDA solution, methyl isobutyrate (0.92 mL, 8 mmol, 1 equiv) was added dropwise at 0 °C and the mixture was stirred at the same temperature for 45 min. Then 2-bromobenzyl bromide (2 g, 8 mmol, 1 equiv) in THF (8 mL) was added slowly to the solution always at 0 °C. The mixture was stirred for 16 h with the ice bath warming to room temperature. Water was then added to the reaction at 0 °C. The mixture was extracted three times with Et$_2$O; the combined organic layers were washed with brine. The organic layer was dried over MgSO$_4$, filtered, concentrated under a vacuum and purified by column chromatography (Cy/AcOEt: 95/5 to 90/10) to yield **3.17** (1.97 g, 7.26 mmol, 91%) as a colorless oil.

3.17

C$_{12}$H$_{15}$BrO$_2$

M= 271,15 g.mol^{-1}

^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm) 7.54 (dd, J = 8.0, 1.3 Hz, 1H), 7.20 (td, J = 7.5, 1.3 Hz, 1H), 7.13 (dd, J = 7.8, 1.8 Hz, 1H), 7.06 (ddd, J = 7.9, 7.2, 1.8 Hz, 1H), 3.69 (s, 3H), 3.12 (s, 2H), 1.24 (s, 6H)

^{13}C NMR (126 MHz, CDCl$_3$) δ (ppm) 178.0, 137.9, 133.2, 131.5, 128.2, 127.2, 126.2, 52.0, 44.4, 44.4, 25.1

IR (neat): ν (cm^{-1}) 2977, 2950, 1728, 1469, 1192, 1134, 1024, 749

HRMS (ESI): Calcd for C$_{13}$H$_{17}$^{79}BrNaO$_3$ [M+Na]$^+$: 323.0253, found 323.0257

Rf: 0.35 in a 90:10 mixture of pentane and ethyl acetate

3-Bromo-2-methylphenol (3.19):
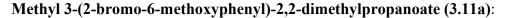
Freshly distilled 3-bromo-2-methylaniline (70 g, 376 mmol) was added to an aqueous 1M solution of sulfuric acid (451 mL, 451 mmol) at 0° C under vigorous stirring (formation of a white suspension of anilinium). Then a saturated solution of sodium nitrite (31.1 g, 451 mmol) in water was added dropwise at -5°C. After stirring at -5° C for 20 min (most of the solid is dissolve at this point), concentrated sulfuric acid (14 mL, 258 mmol) was added and the solution
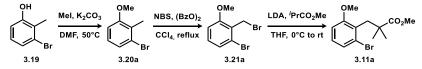
was heated at 100°C for 1 h. The mixture was then diluted with water, extracted with Et$_2$O, dried and concentrated to yield a black slurry. The residue was purified by sublimation under vacuum (0.1 mbar), and the obtained orange solid was recrystallized with cyclohexane to yield **3.19** as a white crystalline solid (32 g, 171 mmol, 46 % yield).

3.19
C$_7$H$_7$BrO
M= 187,04 g.mol^{-1}

^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm) 7.14 (dd, J = 8.0, 1.1 Hz, 1H), 6.92 (td, J = 8.0, 0.5 Hz, 1H), 6.71 (ddd, J = 8.0, 1.1, 0.5 Hz, 1H), 4.87 (s, 1H), 2.34 (s, 3H)

^{13}C NMR (126 MHz, CDCl$_3$) δ (ppm) 154.5, 127.6, 126.2, 125.1, 124.6, 114.2, 15.7

IR (neat): ν (cm^{-1}) 3283, 1435, 1241, 998, 762

GCMS (EI): Calcd for C$_7$H$_7$^{79}BrO [M]$^{+\bullet}$: 186, found 186

Rf: 0.25 in a 85:15 mixture of pentane and ethyl acetate

Mp: 96-98 °C

Methyl 3-(2-bromo-6-methoxyphenyl)-2,2-dimethylpropanoate (3.11a):

3-bromo-2-methylphenol (**3.19**) (17.8 g, 95 mmol) was dissolved in DMF (240 mL) and K$_2$CO$_3$ (39.4 g, 285 mmol, 3 equiv) was added, the mixture was then stirred during 5 min at room temperature. After this period, methyl iodide (29.6 mL, 475 mmol, 5 equiv) was added in one portion and the reaction was stirred at 50°C during 2h. The reaction was then diluted with water, extracted with EtOAc and concentrated to yield the corresponding anisole which was used in the next step without further purification. This anisole was mixed with N-bromosuccinimide (17.75 g, 100 mmol, 1.05 equiv) and benzoyl peroxide (75%) (1.23 g, 3.8 mmol, 4 mol%) in CCl$_4$ (190 mL) and was heated to reflux and stirred overnight. The reaction mixture was then cooled to room temperature and filtered. The filtrate was diluted with DCM and washed successively with 2M NaOH, water and brine. The organic layer was dried over MgSO$_4$, filtered and concentrated under reduced pressure to give the corresponding benzyl bromide which was used in the next step without further purification. A solution of LDA (100 mmol, 1.05 equiv) in THF (190 mL) was prepared from diisopropylamine (14 mL, 100 mmol, 1.05 equiv) and 2.5 M ^{n}BuLi in hexane (40 mL, 100 mmol, 1.05 equiv), stirred at 0°C during 15 min. To the LDA solution, methyl isobutyrate (10.9 mL, 95 mmol, 1 equiv) was added dropwise at 0°C and the mixture was stirred at the same temperature for 45 min. The Benzyl bromide, obtained

previously, in THF (95 mL) was added slowly to the solution always at 0°C. The mixture was stirred for 16 h with the ice bath warming to room temperature. Water was then add to the reaction at 0°C. The mixture was extracted three times with Et$_2$O, the combined organic layers were washed with brine. The organic layer was dried over MgSO$_4$, filtered, concentrated under vacuum purified by column chromatography (Cy/AcOEt: 95/5 to 90/10) to yield **3.11a** as a colorless oil (21.4 g, 71 mmol, 75% over 3 steps) that solidified upon standing.

3.11a
C$_{13}$H$_{17}$BrO$_3$
M= 301,18 g.mol^{-1}
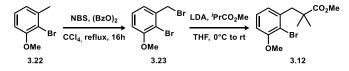
^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm) 7.16 (dd, J = 8.1, 1.1 Hz, 1H), 7.04 (t, J = 8.1 Hz, 1H), 6.76 (dd, J = 8.1, 1.1 Hz, 1H), 3.74 (s, 3H), 3.67 (s, 3H), 3.18 (s, 2H), 1.21 (s, 6H)

^{13}C NMR (126 MHz, CDCl$_3$) δ (ppm) 178.3, 159.1, 128.4, 127.4, 127.3, 125.2, 109.3, 55.6, 51.8, 43.4, 39.3, 25.6

IR (neat): ν (cm^{-1}) 2980, 1716, 1265, 1146, 1029, 771

HRMS (ESI): Calcd for C$_{13}$H$_{17}$^{79}BrNaO$_3$ [M+Na]$^+$: 323.0253, found 323.0251

Rf: 0.22 in a 90:10 mixture of pentane and ethyl acetate
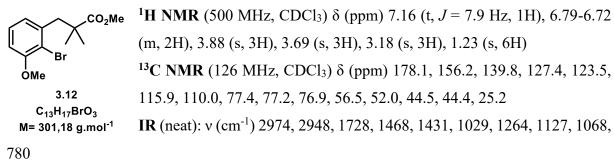
Mp: 42-44 °C

Methyl 3-(2-bromo-3-methoxyphenyl)-2,2-dimethylpropanoate (3.12):
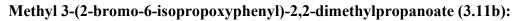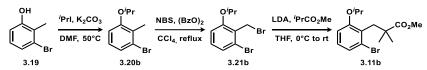
2-Bromo-1-methoxy-3-methylbenzene (**3.22**) (1.16 g, 5.77 mmol) was mixed with *N*-bromosuccinimide (1.08 g, 6.06 mmol, 1.05 equiv) and benzoyl peroxide (75%) (75 mg, 0.23 mmol, 4 mol%) in CCl$_4$ (13 mL) and was heated to reflux and stirred overnight. The reaction mixture was then cooled to room temperature and filtered. The filtrate was diluted with DCM and washed successively with 2M NaOH, water and brine. The organic layer was dried over MgSO$_4$, filtered and concentrated under reduced pressure to give the corresponding benzyl bromide which was used in the next step without further purification. A solution of LDA (6.06 mmol, 1.05 equiv) in THF (12 mL) was prepared from diisopropylamine (0.85 mL, 6.06 mmol, 1.05 equiv) and 2.5 M ^{n}BuLi in hexane (2.43 mL, 6.06 mmol, 1.05 equiv), stirred at 0°C during 15 min. To the LDA solution, methyl isobutyrate (0.66 mL, 5.77 mmol, 1 equiv) was added dropwise at 0°C and the mixture was stirred at the same temperature for 45 min. The Benzyl bromide, obtained previously, in THF (6 mL) was added slowly to the solution always at 0°C. The mixture was stirred for 16 h with the ice bath warming to room temperature. Water was then add to the reaction at 0°C. The mixture was extracted three times with Et$_2$O, the combined

organic layers were washed with brine. The organic layer was dried over MgSO$_4$, filtered, concentrated under vacuum purified by column chromatography (Cy/AcOEt: 95/5 to 90/10) to yield **3.12** (1.35 g, 4.48 mmol, 78%) as a colorless oil.

3.12
C$_{13}$H$_{17}$BrO$_3$
M= 301,18 g.mol^{-1}

^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm) 7.16 (t, J = 7.9 Hz, 1H), 6.79-6.72 (m, 2H), 3.88 (s, 3H), 3.69 (s, 3H), 3.18 (s, 3H), 1.23 (s, 6H)

^{13}C NMR (126 MHz, CDCl$_3$) δ (ppm) 178.1, 156.2, 139.8, 127.4, 123.5, 115.9, 110.0, 77.4, 77.2, 76.9, 56.5, 52.0, 44.5, 44.4, 25.2

IR (neat): ν (cm^{-1}) 2974, 2948, 1728, 1468, 1431, 1029, 1264, 1127, 1068, 780
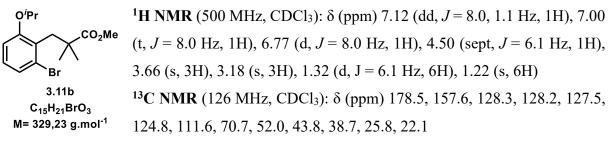
HRMS (ESI): Calcd for C$_{13}$H$_{17}$^{79}BrNaO$_3$ [M+Na]$^+$: 323.0253, found 323.0257

Rf: 0.24 in a 90:10 mixture of pentane and ethyl acetate

Methyl 3-(2-bromo-6-isopropoxyphenyl)-2,2-dimethylpropanoate (3.11b):

Obtained using the same procedure than for **3.11a** with isopropyl iodide instead of methyl iodide. **3.11b** was obtained as a colorless liquid (410 mg, 1.25 mmol, 71% over three steps).

3.11b
C$_{15}$H$_{21}$BrO$_3$
M= 329,23 g.mol^{-1}

^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 7.12 (dd, J = 8.0, 1.1 Hz, 1H), 7.00 (t, J = 8.0 Hz, 1H), 6.77 (d, J = 8.0 Hz, 1H), 4.50 (sept, J = 6.1 Hz, 1H), 3.66 (s, 3H), 3.18 (s, 3H), 1.32 (d, J = 6.1 Hz, 6H), 1.22 (s, 6H)

^{13}C NMR (126 MHz, CDCl$_3$): δ (ppm) 178.5, 157.6, 128.3, 128.2, 127.5, 124.8, 111.6, 70.7, 52.0, 43.8, 38.7, 25.8, 22.1
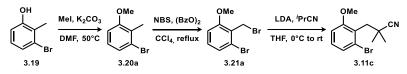
IR (neat): ν (cm^{-1}) 2977, 1729, 1444, 1258, 1139, 962

HRMS (ESI): Calcd for C$_{15}$H$_{21}$^{79}BrNaO$_3$ [M+Na]$^+$: 351.0566, found 351.0566

Rf: 0.40 in a 90:10 mixture of pentane and ethyl acetate

3-(2-bromo-6-methoxyphenyl)-2,2-dimethylpropanenitrile (3.11c):
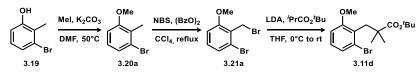
Obtained using the same procedure than for **3.11a** with isobutyronitrile instead of methyl isobutyrate. **3.11c** was obtained as a colorless liquid (494 mg, 1.84 mmol, 74% over three steps).

3.11c
$C_{12}H_{14}BrNO$
M= 268,15 g.mol^{-1}

^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 7.19 (dd, J = 8.1, 1.1 Hz, 1H), 7.10 (t, J = 8.1 Hz, 1H), 6.84 (dd, J = 8.1, 1.1 Hz, 1H), 3.82 (s, 3H), 3.17 (s, 3H), 1.45 (s, 6H)

^{13}C NMR (126 MHz, CDCl$_3$): δ (ppm) 159.2, 129.3, 127.0, 125.4, 125.3, 125.3, 109.8, 55.6, 38.9, 33.9, 27.9

IR (neat): ν (cm^{-1}) 2977, 1462, 1271, 1033, 774
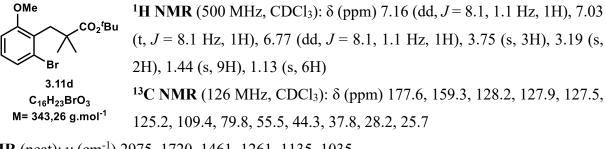
HRMS (ESI): Calcd for $C_{12}H_{14}{}^{79}BrNaO$ [M+Na]$^+$: 290.0151, found 290.0149

Rf: 0.27 in a 90:10 mixture of pentane and ethyl acetate

Tert-butyl 3-(2-bromo-6-methoxyphenyl)-2,2-dimethylpropanoate (3.11d):

Obtained using the same procedure than for **3.11a** with tert-butylisobutyrate instead of methyl isobutyrate. **3.11d** was obtained as a colorless liquid (856 mg, 2.49 mmol, 71% over three steps).

3.11d
$C_{16}H_{23}BrO_3$
M= 343,26 g.mol^{-1}

^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 7.16 (dd, J = 8.1, 1.1 Hz, 1H), 7.03 (t, J = 8.1 Hz, 1H), 6.77 (dd, J = 8.1, 1.1 Hz, 1H), 3.75 (s, 3H), 3.19 (s, 2H), 1.44 (s, 9H), 1.13 (s, 6H)

^{13}C NMR (126 MHz, CDCl$_3$): δ (ppm) 177.6, 159.3, 128.2, 127.9, 127.5, 125.2, 109.4, 79.8, 55.5, 44.3, 37.8, 28.2, 25.7
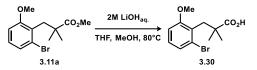
IR (neat): ν (cm^{-1}) 2975, 1720, 1461, 1261, 1135, 1035

HRMS (ESI): Calcd for $C_{16}H_{23}{}^{79}BrNaO_3$ [M+Na]$^+$: 365.0723, found 365.0725

Rf: 0.42 in a 90:10 mixture of pentane and ethyl acetate

Experimental Section
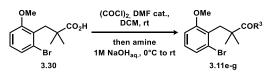
3-(2-bromo-6-methoxyphenyl)-2,2-dimethylpropanoic acid (3.30):

3.11a (12.3 g, 40.9 mmol) was dissolved in a mixture THF (70 mL), MeOH (70 mL) and 2M aqueous LiOH (70 mL). The reaction was then heat at 80°C for 6 hours. After cooling to room temperature, the organic solvents were removed under reduced pressure. The obtained aqueous solution was washed with diethyl ether, acidified to pH<0 and extracted three times with DCM. The combined organic layers were then dried over MgSO$_4$, filtered and concentrated under reduced pressure to yield **3.30** (10.7 g, 37.2 mmol, 91% yield) as a yellow solid.

3.30
C$_{12}$H$_{15}$BrO$_3$
M= 287,15 g.mol^{-1}

^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 7.17 (dd, J = 8.1, 1.1 Hz, 1H), 7.05 (t, J = 8.1 Hz, 1H), 6.77 (dd, J = 8.1, 1.1 Hz, 1H), 3.72 (s, 3H), 3.24 (s, 2H), 1.23 (s, 6H)

^{13}C NMR (126 MHz, CDCl$_3$): δ (ppm) 184.6, 159.1, 128.5, 127.3, 127.0, 125.2, 109.2, 55.0, 43.2, 39.3, 25.3

IR (neat): ν (cm^{-1}) 2971, 1687, 1265, 1033, 764

HRMS (ESI): Calcd for C$_{12}$H$_{15}$^{79}BrNaO$_3$ [M+Na]$^+$: 309.0097, found 309.0094

Rf: 0.26 in a 70:30 mixture of pentane and ethyl acetate

Mp: 122-124°C
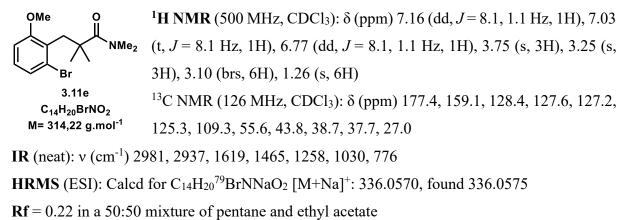
General procedure G: Amide formation

3.30 was dissolved in dry DCM (10 mL per mmol), then oxalyl chloride (1.1 equiv) was added, follow by few drops of DMF to initiate the reaction. After 1 hour of stirring at room temperature, the reaction was cooled to 0°C and the amine (free base or salt, 3 equiv) and aqueous 1M NaOH (10 equiv) were added in one portion. The mixture was vigorously stirred for 16 hours with the ice bath warming to room temperature. The organic layer was then separated, washed with 2M HCl, dried over MgSO$_4$, filtered and concentrated under reduced pressure. Crude material was then purified by flash column chromatography to yield the corresponding pure amide.

3-(2-bromo-6-methoxyphenyl)-*N*,*N*,2,2-tetramethylpropanamide (3.11e):

From **3.30** and HNMe$_2$·HCl using **General procedure G**. **3.11e** was obtained as a colorless oil that solidified upon standing (240 mg, 0.764 mmol, 97%).

OMe O

NMe$_2$

Br

3.11e
C$_{14}$H$_{20}$BrNO$_2$
M= 314,22 g.mol^{-1}

^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 7.16 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.03 (t, *J* = 8.1 Hz, 1H), 6.77 (dd, *J* = 8.1, 1.1 Hz, 1H), 3.75 (s, 3H), 3.25 (s, 3H), 3.10 (brs, 6H), 1.26 (s, 6H)

^{13}C NMR (126 MHz, CDCl$_3$): δ (ppm) 177.4, 159.1, 128.4, 127.6, 127.2, 125.3, 109.3, 55.6, 43.8, 38.7, 37.7, 27.0

IR (neat): ν (cm^{-1}) 2981, 2937, 1619, 1465, 1258, 1030, 776

HRMS (ESI): Calcd for C$_{14}$H$_{20}$^{79}BrNNaO$_2$ [M+Na]$^+$: 336.0570, found 336.0575

Rf = 0.22 in a 50:50 mixture of pentane and ethyl acetate

Mp = 62-64°C

3-(2-bromo-6-methoxyphenyl)-2,2-dimethyl-1-(piperidin-1-yl)propan-1-one (3.11f):

From 3.30 and piperidine using **General procedure G**. **3.11f** was obtained as a colorless oil that solidified upon standing (490 mg, 1.38 mmol, 99%).

OMe O

N

Br

3.11f
C$_{17}$H$_{24}$BrNO$_2$
M= 354,29 g.mol^{-1}

^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 7.16 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.03 (t, *J* = 8.1 Hz, 1H), 6.77 (dd, *J* = 8.1, 1.1 Hz, 1H), 3.75 (s, 3H), 3.70-3.65 (m, 4H), 3.24 (s, 2H), 1.71-1.64 (m, 3H), 1.64-1.56 (m, 3H), 1.21 (s, 6H)

^{13}C NMR (126 MHz, CDCl$_3$): δ (ppm) 176.2, 159.2, 128.4, 127.8, 127.3, 125.3, 109.3, 55.6, 46.6, 43.7, 37.4, 27.0, 26.3, 25.0

IR (neat): ν (cm^{-1}) 2935, 2854, 1611, 1415, 1265, 1028, 774

HRMS (ESI): Calcd for C$_{17}$H$_{24}$^{79}BrNNaO [M+Na]$^+$: 376.0883, found 376.0883

Rf: 0.25 in a 70:30 mixture of pentane and ethyl acetate

Mp: 96-98°C

Experimental Section

3-(2-bromo-6-methoxyphenyl)-2,2-dimethyl-1-morpholinopropan-1-one (3.11g):

From **3.30** and morpholine using **General procedure G**. **3.11g** was obtained as a colorless oil that solidified upon standing (480 mg, 1.35 mmol, 97%).
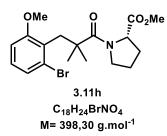
^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 7.17 (dd, J = 8.1, 1.1 Hz, 1H), 7.05 (t, J = 8.1 Hz, 1H), 6.78 (dd, J = 8.1, 1.1 Hz, 1H), 3.76 (s, 3H), 3.77-3.72 (m, 4H), 3.73-3.69 (m, 4H), 3.23 (s, 2H), 1.23 (s, 6H)

^{13}C NMR (126 MHz, CDCl$_3$): δ (ppm) 176.6, 159.0, 128.6, 127.4, 127.2, 125.4, 109.4, 67.1, 55.7, 46.2, 43.6, 37.5, 27.0

3.11g
C$_{16}$H$_{22}$BrNO$_3$
M= 356,26 g.mol^{-1}

IR (neat): ν (cm^{-1}) 2946, 2846, 1624, 1269, 1111, 1031, 775

HRMS (ESI): Calcd for C$_{16}$H$_{22}$^{79}BrNNaO$_3$ [M+Na]$^+$: 378.0675, found 378.0677

Rf: 0.24 in a 50:50 mixture of pentane and ethyl acetate

Mp: 86-88°C

Methyl (3-(2-bromo-6-methoxyphenyl)-2,2-dimethylpropanoyl)-*L*-prolinate (3.11h):

From **3.30** and H-*L*-Pro-OMe·HCl using **General procedure G**. **3.11h** was obtained as a wax (368 mg, 0.924 mmol, 89%).

^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 7.15 (d, J = 8.1 Hz, 1H), 7.03 (t, J = 8.1 Hz, 1H), 6.77 (d, J = 8.1 Hz, 1H), 4.54-4.46 (m, 1H), 3.84-3.67 (m, 2H), 3.74 (s, 3H), 3.71 (s, 3H), 3.25 (d, J = 13.5 Hz, 1H), 3.19 (d, J = 13.5 Hz, 1H), 2.20-2.09 (m, 1H), 2.09-2.00 (m, 1H), 1.94-1.79 (m, 2H), 1.29 (s, 3H), 1.18 (s, 3H)

3.11h
C$_{18}$H$_{24}$BrNO$_4$
M= 398,30 g.mol^{-1}

^{13}C NMR (126 MHz, CDCl$_3$): 176.4, 173.6, 159.2, 128.4, 127.4, 127.2, 125.3, 109.4, 61.3, 55.5, 52.1, 48.5, 44.0, 36.9, 28.0, 26.4, 26.1, 25.4
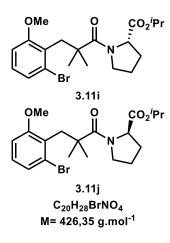
IR (neat): ν (cm^{-1}) 2948, 1743, 1622, 1397, 1159, 1031

HRMS (ESI): Calcd for C$_{18}$H$_{24}$^{79}BrNNaO$_4$ [M+Na]$^+$: 420.0781, found 420.0788

Rf: 0.24 in a 60:40 mixture of pentane and ethyl acetate

[α]$_D^{20}$: - 44.7° (c = 0.70, CHCl$_3$)

Experimental Section

Isopropyl (3-(2-bromo-6-methoxyphenyl)-2,2-dimethylpropanoyl)-*L*-prolinate (3.11i) and isopropyl (3-(2-bromo-6-methoxyphenyl)-2,2-dimethylpropanoyl)-*D*-prolinate (3.11j):

From **3.30** and H-*L*-Pro-O^{i}Pr·HCl or H-*D*-Pro-O^{i}Pr·HCl respectively using **General procedure G**. Obtained as colorless oils that solidified upon standing **3.11i** (698 mg, 1.64 mmol, 90%), **3.11j** (279 mg, 0.655 mmol, 93%).

3.11i

3.11j

C$_{20}$H$_{28}$BrNO$_4$

M= 426,35 g.mol^{-1}

^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 7.15 (dd, J = 8.1, 1.1 Hz, 1H), 7.03 (t, J = 8.1 Hz, 1H), 6.77 (dd, J = 8.1, 1.1 Hz, 1H), 5.02 (sept, J = 6.2 Hz, 1H), 4.53-4.42 (m, 1H), 3.85-3.67 (m, 2H), 3.74 (s, 3H), 3.27 (d, J = 13.5 Hz, 1H), 3.19 (d, J = 13.5 Hz, 1H), 2.21-2.09 (m, 1H), 2.09-1.97 (m, 1H), 1.93-1.76 (m, 2H), 1.31 (s, 3H), 1.25 (d, J = 6.2 Hz, 3H), 1.21 (d, J = 6.2 Hz, 3H), 1.19 (s, 3H)

^{13}C NMR (126 MHz, CDCl$_3$): δ (ppm) 176.6, 172.4, 159.2, 128.4, 127.3, 127.2, 125.3, 109.4, 68.2, 61.7, 55.5, 48.6, 44.1, 36.9, 28.0, 26.4, 26.1, 25.5, 21.9, 21.8

IR (neat): ν (cm^{-1}) 2975, 1742, 1627, 1401, 1177, 1035, 781

HRMS (ESI): Calcd for C$_{20}$H$_{28}$^{79}BrNNaO$_4$ [M+Na]$^+$: 448.1094, found 448.1097
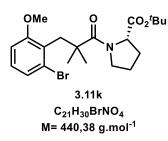
Rf: 0.32 in a 60:40 mixture of pentane and ethyl acetate

Mp: 88-90°C

3.11i [α]$_D^{23}$: - 23.7° (c = 1.05, CHCl$_3$)

3.11j [α]$_D^{23}$: + 22.8° (c = 0.50, CHCl$_3$)

Tert-butyl (3-(2-bromo-6-methoxyphenyl)-2,2-dimethylpropanoyl)-*L*-prolinate (3.11k):

From **3.30** and H-*L*-Pro-O^{t}Bu·HCl using **General procedure G**. **3.11h** was obtained as a wax (344 mg, 0.781 mmol, 89%).

3.11k

C$_{21}$H$_{30}$BrNO$_4$

M= 440,38 g.mol^{-1}

^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 7.16 (dd, J = 8.1, 1.1 Hz, 1H), 7.03 (t, J = 8.1 Hz, 1H), 6.77 (dd, J = 8.1, 1.1 Hz, 1H), 4.44-4.35 (m, 1H), 3.75 (s, 3H), 3.81-3.67 (m, 2H), 3.26 (d, J = 13.5 Hz, 1H), 3.19 (d, J = 13.5 Hz, 1H), 2.20-2.08 (m, 1H), 2.08-1.96 (m, 1H), 1.91-1.75 (m, 2H), 1.45 (s, 9H), 1.30 (s, 3H), 1.19 (s, 3H)
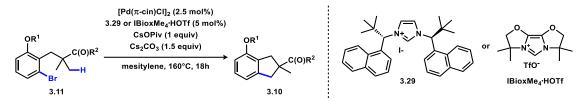
^{13}C NMR (126 MHz, CDCl$_3$): δ (ppm) 176.0, 172.3, 159.2, 128.4, 127.5, 127.3, 125.3, 109.3, 80.7, 62.2, 55.5, 48.5, 44.0, 37.0, 28.1, 28.1, 26.4, 26.3, 25.5

IR (neat): ν (cm^{-1}) 2974, 1736, 1623, 1365, 1148, 1033, 772

HRMS (ESI): Calcd for C$_{21}$H$_{30}$^{79}BrNNaO$_4$ [M+Na]$^+$: 462.1250, found 462.1253

Experimental Section

Rf: 0.28 in a 70:30 mixture of pentane and ethyl acetate

$[\alpha]_D^{23}$: - 34.6° (c = 2.40, CHCl$_3$)

Experimental Section

6.3.3. Model Products

General procedure H: Representative procedure for the asymmetric C(sp^3)–H arylation

In an oven dry catalysis tube, substrate (0.2 mmol) was introduced. Then the tube was transferred in glovebox and [Pd(π-cin)Cl]$_2$ (5.2 mg, 10 μmol, 5 mol%), **3.29** (11.8 mg, 20 μmol, 10 mol%), cesium pivalate (46.8 mg, 0.2 mmol, 1 equiv) and cesium carbonate (97.7 mg, 0.3 mmol, 1.5 equiv) were introduced and the tube was close with a septum. Outside of the glovebox, mesitylene (2 mL) was added. The reaction was stirred at room temperature for 10 min, then, under pressure of argon, the septum was rapidly exchange for a screw cap. The tube was then introduced in a 160°C preheated aluminium block and stirred at this temperature for 18 hours. After this period the reaction was coolded to room temperature, diluted with DCM (1 mL), filtered over a pad of celite (washed three times with 1 mL of DCM). The crude material was analyzed by GC-MS and then concentrated and purified by flash column chromatography to yield the corresponding indane product. Enantiomeric/diastereomeric ratio were then determined by HPLC using a chiral stationary phase.

Racemic materials were obtained following the same procedure, using IBioxMe$_4$·HOTf as ligand.

Methyl (*S*)-4-methoxy-2-methyl-2,3-dihydro-1*H*-indene-2-carboxylate (3.10a):

Small scale synthesis:

From **3.11a** using **General procedure H**. **3.10a** was obtained as a yellow liquid (40.5 mg, 0.184 mmol, 92%).

Gram scale synthesis of racemic material:

In an oven dry Schlenk tube, **3.11a** (1.36 g, 4.5 mmol) was introduced. Then the Schlenk tube was transferred in glovebox and [Pd(π-cin)Cl]$_2$ (117 mg, 0.23 mmol, 5 mol%), IBioxMe$_4$·HOTf (161 mg, 0.45 mmol, 10 mol%), cesium pivalate (1.05 g, 4.5 mmol, 1 equiv) and cesium carbonate (2.20 g, 6.75 mmol, 1.5 equiv) were introduced and the tube was close with a septum. Outside of the glovebox, mesitylene (45 mL) was added. The reaction was stirred at room temperature for 10 min. The tube was then introduced in a 160°C preheated oil bath and stirred at this temperature for 18 hours. After this period the reaction was cooled to room temperature,

Experimental Section

filtered over a pad of celite (washed with DCM). The crude material was analyzed by GC-MS and then concentrated and purified by flash column chromatography (Cy/AcOEt: 95/5 to 90/10) to yield **3.10a** (915 mg, 4.15 mmol, 92%) as a yellowish oil.

3.10a
$C_{13}H_{16}O_3$
M= 220,27 g.mol^{-1}

^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 7.15 (t, J = 7.8 Hz, 1H), 6.81 (d, J = 7.8 Hz, 1H), 6.68 (d, J = 7.8 Hz, 1H), 3.82 (s, 3H), 3.72 (s, 3H), 3.50 (d, J = 16.0 Hz, 1H), 3.39 (d, J = 16.4 Hz, 1H), 2.84 (d, J = 16.4 Hz, 1H), 2.82 (d, J = 16.0 Hz, 1H), 1.37 (s, 3H)

^{13}C NMR (126 MHz, CDCl$_3$): δ (ppm) 178.3, 156.3, 143.3, 128.9, 128.2, 117.1, 108.2, 55.3, 52.2, 49.4, 44.5, 41.0, 25.6

IR (neat): ν (cm^{-1}) 2950, 1730, 1590, 1261, 1075, 766

HRMS (ESI): Calcd for C$_{13}$H$_{16}$NaO$_3$ [M+Na]$^+$: 243.0992, found 243.0990

Rf: 0.21 in a 95:5 mixture of pentane and ethyl acetate

HPLC separation: Chiralcel$^®$ OJ-H; 99:1 (*n*-heptane/*i*-PrOH), 0.8 mL.min^{-1}, 204 nm, t_R (major) = 16.4 min, t_R (major) = 18.1 min, 66:34 e.r.

Methyl (*S*)-4-isopropoxy-2-methyl-2,3-dihydro-1*H*-indene-2-carboxylate (3.10b):

From **3.11b** using **General procedure H**. **3.10b** was obtained as a yellow liquid (46.2 mg, 0.186 mmol, 93%).

3.10b
$C_{15}H_{20}O_3$
M= 248,32 g.mol^{-1}

^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) δ 7.11 (t, J = 7.8 Hz, 1H), 6.79 (d, J = 7.8 Hz, 1H), 6.69 (d, J = 7.8 Hz, 1H), 4.51 (sept, J = 6.1 Hz, 1H), 3.72 (s, 3H), 3.50 (d, J = 16.0 Hz, 1H), 3.37 (d, J = 16.3 Hz, 1H), 2.85 (d, J = 16.3 Hz, 1H), 2.81 (d, J = 16.0 Hz, 1H), 1.36 (s, 3H), 1.33 (d, J = 6.1 Hz, 3H), 1.32 (d, J = 6.1 Hz, 3H)

^{13}C NMR (126 MHz, CDCl$_3$): δ (ppm) 178.4, 154.8, 143.4, 130.4, 128.0, 117.0, 111.5, 70.4, 52.2, 49.3, 44.5, 41.2, 25.6, 22.4, 22.4

IR (neat): ν (cm^{-1}) 2976, 1732, 1477, 1259, 1111, 766

HRMS (ESI): Calcd for C$_{15}$H$_{20}$NaO$_3$ [M+Na]$^+$: 271.1305, found 271.1305

Rf: 0.26 in a 95:5 mixture of pentane and ethyl acetate

HPLC separation: Chiralcel$^®$ OJ-H; 99:1 (*n*-heptane/*i*-PrOH), 0.8 mL.min^{-1}, 221 nm, t_R (major) = 7.5 min, t_R (minor) = 8.8 min, 71:29 e.r.

Experimental Section
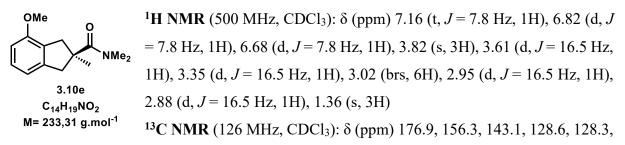
Tert-butyl (S)-4-methoxy-2-methyl-2,3-dihydro-1H-indene-2-carboxylate (3.10d):

From **3.11d** using **General procedure H**. **3.10d** was obtained as a yellow oil mixed with a significant amount of protodebrominated byproduct (12.6 mg, 0.048 mmol, 24%). NMR data are given from the racemate.

3.10d
$C_{16}H_{22}O_3$
M= 262,35 g.mol^{-1}

^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 7.14 (t, J = 7.8 Hz, 1H), 6.81 (d, J = 7.8 Hz, 1H), 6.68 (d, J = 7.8 Hz, 1H), 3.82 (s, 3H), 3.46 (d, J = 16.0 Hz, 1H), 3.32 (d, J = 16.3 Hz, 1H), 2.80 (d, J = 16.3 Hz, 1H), 2.76 (d, J = 16.0 Hz, 1H), 1.46 (s, 9H), 1.32 (s, 3H)

^{13}C NMR (126 MHz, CDCl$_3$): δ (ppm) 177.0, 156.3, 143.6, 129.1, 128.1, 117.2, 108.1, 80.3, 77.4, 77.2, 76.9, 55.3, 50.1, 44.3, 41.0, 28.2, 25.6

IR (neat): ν (cm^{-1}) 2974, 1721, 1260, 1112, 1076, 767

HRMS (ESI): Calcd for $C_{16}H_{22}NaO_3$ [M+Na]$^+$: 285.1461, found 285.1463

Rf: 0.32 in a 95:5 mixture of pentane and ethyl acetate

HPLC separation: Chiralcel® OJ-H; 99.5:0.5 (n-heptane/i-PrOH), 0.8 mL.min^{-1}, 220 nm, t_R (major) = 7.3 min, t_R (minor) = 8.3 min, 58:42 e.r.

(S)-4-methoxy-N,N,2-trimethyl-2,3-dihydro-1H-indene-2-carboxamide (3.10e):

From **3.11e** using **General procedure H**. **3.10e** was obtained as a wax (44.3 mg, 0.19 mmol, 95%).

3.10e
$C_{14}H_{19}NO_2$
M= 233,31 g.mol^{-1}

^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 7.16 (t, J = 7.8 Hz, 1H), 6.82 (d, J = 7.8 Hz, 1H), 6.68 (d, J = 7.8 Hz, 1H), 3.82 (s, 3H), 3.61 (d, J = 16.5 Hz, 1H), 3.35 (d, J = 16.5 Hz, 1H), 3.02 (brs, 6H), 2.95 (d, J = 16.5 Hz, 1H), 2.88 (d, J = 16.5 Hz, 1H), 1.36 (s, 3H)

^{13}C NMR (126 MHz, CDCl$_3$): δ (ppm) 176.9, 156.3, 143.1, 128.6, 128.3, 117.2, 108.0, 55.2, 49.5, 45.9, 41.7, 37.9, 26.5
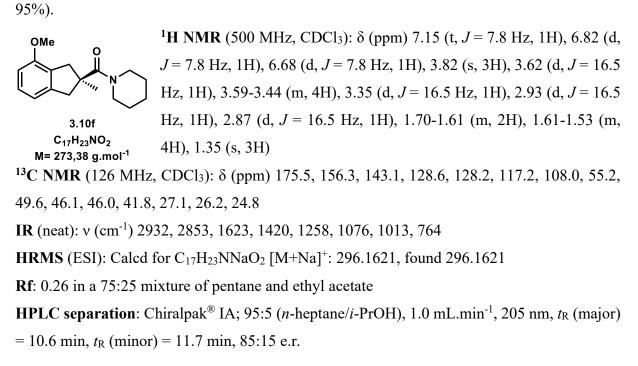
IR (neat): ν (cm^{-1}) 2935, 1620, 1263, 1075, 766

HRMS (ESI): Calcd for $C_{14}H_{19}NNaO_2$ [M+Na]$^+$: 256.1308, found 256.1309

Rf: 0.25 in a 50:50 mixture of pentane and ethyl acetate
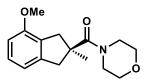
HPLC separation: Chiralcel® OJ-H; 95:5 (n-heptane/i-PrOH), 1.0 mL.min^{-1}, 204 nm, t_R (minor) = 16.7 min, t_R (major) = 18.5 min, 82:18 e.r.

Experimental Section

(*S*)-(4-methoxy-2-methyl-2,3-dihydro-1*H*-inden-2-yl)(piperidin-1-yl)methanone (3.10f):

From **3.11f** using **General procedure H**. **3.10f** was obtained as a wax (51.9 mg, 0.19 mmol, 95%).

3.10f
$C_{17}H_{23}NO_2$
M= 273,38 g.mol⁻¹

¹H NMR (500 MHz, CDCl₃): δ (ppm) 7.15 (t, *J* = 7.8 Hz, 1H), 6.82 (d, *J* = 7.8 Hz, 1H), 6.68 (d, *J* = 7.8 Hz, 1H), 3.82 (s, 3H), 3.62 (d, *J* = 16.5 Hz, 1H), 3.59-3.44 (m, 4H), 3.35 (d, *J* = 16.5 Hz, 1H), 2.93 (d, *J* = 16.5 Hz, 1H), 2.87 (d, *J* = 16.5 Hz, 1H), 1.70-1.61 (m, 2H), 1.61-1.53 (m, 4H), 1.35 (s, 3H)

¹³C NMR (126 MHz, CDCl₃): δ (ppm) 175.5, 156.3, 143.1, 128.6, 128.2, 117.2, 108.0, 55.2, 49.6, 46.1, 46.0, 41.8, 27.1, 26.2, 24.8

IR (neat): ν (cm⁻¹) 2932, 2853, 1623, 1420, 1258, 1076, 1013, 764

HRMS (ESI): Calcd for $C_{17}H_{23}NNaO_2$ [M+Na]⁺: 296.1621, found 296.1621

Rf: 0.26 in a 75:25 mixture of pentane and ethyl acetate

HPLC separation: Chiralpak® IA; 95:5 (*n*-heptane/*i*-PrOH), 1.0 mL.min⁻¹, 205 nm, t_R (major) = 10.6 min, t_R (minor) = 11.7 min, 85:15 e.r.

(*S*)-(4-methoxy-2-methyl-2,3-dihydro-1*H*-inden-2-yl)(morpholino)methanone (3.10g):

From **3.11g** using **General procedure H**. **3.10g** was obtained as a wax (52.3 mg, 0.19 mmol, 95%).

3.10g
$C_{16}H_{21}NO_3$
M= 275,35 g.mol⁻¹

¹H NMR (500 MHz, CDCl₃): δ (ppm) 7.17 (t, *J* = 7.8 Hz, 1H), 6.82 (d, *J* = 7.5 Hz, 1H), 6.69 (d, *J* = 8.1 Hz, 1H), 3.82 (s, 3H), 3.70-3.66 (m, 4H), 3.64-3.56 (m, 4H), 3.60 (d, *J* = 16.5 Hz, 1H), 3.33 (d, *J* = 16.5 Hz, 1H), 2.93 (d, *J* = 16.5 Hz, 1H), 2.88 (d, *J* = 16.5 Hz, 1H), 1.36 (s, 3H)

¹³C NMR (126 MHz, CDCl₃): δ (ppm) 175.9, 156.3, 142.7, 128.5, 128.2, 117.2, 108.1, 67.0, 55.2, 49.2, 46.0, 45.4, 41.8, 27.2

IR (neat): ν (cm⁻¹) 2961, 2926, 2852, 1626, 1416, 1264, 1113, 765

HRMS (ESI): Calcd for $C_{16}H_{21}NNaO_3$ [M+Na]⁺: 298.1414, found 298.1417

Rf: 0.25 in a 50:50 mixture of pentane and ethyl acetate

HPLC separation: Chiralpak® IA; 95:5 (*n*-heptane/*i*-PrOH), 1.0 mL.min⁻¹, 205 nm, t_R (major) = 14.5 min, t_R (minor) = 15.6 min, 82:18 e.r.

Experimental Section

Methyl ((*S*)-4-methoxy-2-methyl-2,3-dihydro-1*H*-indene-2-carbonyl)-*L*-prolinate (3.10h):

From **3.11h** using **General procedure H**. **3.10h** was obtained as a wax (52.1 mg, 0.164 mmol, 82%).

3.10h
$C_{18}H_{23}NO_4$
M= 317,39 g.mol^{-1}

Description of major diastereoisomer:

^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 7.15 (t, *J* = 7.8 Hz, 1H), 6.82 (d, *J* = 7.8 Hz, 1H), 6.68 (d, *J* = 7.8 Hz, 1H), 4.54 (dd, *J* = 8.5, 4.8 Hz, 1H), 3.82 (s, 3H), 3.72 (s, 3H), 3.77-3.63 (m, 2H), 3.61 (d, *J* = 16.2 Hz, 1H), 3.38 (d, *J* = 16.4 Hz, 1H), 2.94 (d, *J* = 16.4 Hz, 1H), 2.87 (d, *J* = 16.2 Hz, 1H), 2.22-2.13 (m, 1H), 2.12- 2.04 (m, 1H), 2.01- 1.86 (m, 2H), 1.36 (s, 3H)

^{13}C NMR (126 MHz, CDCl$_3$): δ (ppm) 176.1, 173.4, 156.4, 143.1, 128.6, 128.2, 117.2, 108.1, 60.6, 55.3, 52.2, 49.6, 47.8, 44.8, 40.7, 28.3, 25.9, 25.4

IR (neat): ν (cm^{-1}) 2953, 1743, 1623, 1401, 1264, 1173, 1075, 766

HRMS (ESI): Calcd for C$_{18}$H$_{23}$NNaO$_4$ [M+Na]$^+$: 340.1519, found 340.1520

Rf: 0.25 in a 60:40 mixture of pentane and ethyl acetate
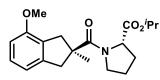
HPLC separation: with IBioxMe$_4$·HOTf Chiralpak$^®$ IA; 95:5 (*n*-heptane/*i*-PrOH), 1.0 mL.min^{-1}, 205 nm, t_R (major) = 22.2 min, t_R (minor) = 25.8 min, 64:36 d.r.

With **3.29** Chiralpak$^®$ IA; 95:5 (*n*-heptane/*i*-PrOH), 1.0 mL.min^{-1}, 205 nm, t_R (major) = 22.2 min, t_R (minor) = 25.9 min, 83:17 d.r.

Isopropyl ((*S*)-4-methoxy-2-methyl-2,3-dihydro-1*H*-indene-2-carbonyl)-*L*-prolinate (3.10i):

From **3.11i** using **General procedure H**. **3.10i** was obtained as a wax (56.7 mg, 0.164 mmol, 82%).

3.10i
$C_{20}H_{27}NO_4$
M= 345,44 g.mol^{-1}

Description of major diastereoisomer:

^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 7.15 (t, *J* = 7.8 Hz, 1H), 6.81 (d, *J* = 7.8 Hz, 1H), 6.68 (d, *J* = 7.8 Hz, 1H), 5.03 (hept, *J* = 6.2 Hz, 1H), 4.49 (dd, *J* = 8.6, 4.8 Hz, 1H), 3.81 (s, 3H), 3.76-3.60 (m, 2H), 3.60 (d, *J* = 16.2 Hz, 1H), 3.39 (d, *J* = 16.4 Hz, 1H), 2.94 (d, *J* = 16.4 Hz, 1H), 2.86 (d, *J* = 16.2 Hz, 1H), 2.21-2.11 (m, 1H), 2.12-2.00 (m, 1H), 1.99-1.83 (m, 2H), 1.35 (s, 3H), 1.26 (d, *J* = 6.2 Hz, 3H), 1.19 (d, *J* = 6.2 Hz, 3H)

^{13}C NMR (126 MHz, CDCl$_3$): δ (ppm) 175.9, 172.3, 156.4, 143.2, 128.6, 128.2, 117.2, 108.1, 68.3, 61.0, 55.3, 49.7, 47.8, 44.7, 40.7, 28.3, 25.9, 25.4, 21.9, 21.8

IR (neat): ν (cm^{-1}) 2977, 1735, 1625, 1401, 1264, 1185, 1107, 1076, 767

HRMS (ESI): Calcd for $C_{20}H_{27}NNaO_4$ $[M+Na]^+$: 368.1832, found 368.1834
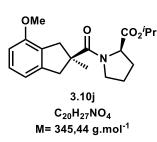
Rf: 0.27 in a 70:30 mixture of pentane and ethyl acetate

HPLC separation: with IBioxMe$_4$·HOTf Chiralpak® IA; 95:5 (*n*-heptane/*i*-PrOH), 1.0 mL.min^{-1}, 205 nm, t_R (major) = 14.8 min, t_R (minor) = 18.3 min, 66:34 d.r.

With **3.29** Chiralpak® IA; 95:5 (*n*-heptane/*i*-PrOH), 1.0 mL.min^{-1}, 205 nm, t_R (major) = 14.8 min, t_R (minor) = 18.3 min, 87:13 d.r.

Isopropyl ((S)-4-methoxy-2-methyl-2,3-dihydro-1*H*-indene-2-carbonyl)-*D*-prolinate (3.10j):

From **3.11j** using **General procedure H**. **3.10j** was obtained as a wax (56.0 mg, 0.162 mmol, 81%).

3.10j
$C_{20}H_{27}NO_4$
M= 345,44 g.mol^{-1}

Description of major diastereoisomer:

¹H NMR (500 MHz, CDCl$_3$): δ (ppm) 7.15 (t, *J* = 7.8 Hz, 1H), 6.82 (d, *J* = 7.8 Hz, 1H), 6.68 (d, *J* = 7.8 Hz, 1H), 5.04 (hept, *J* = 6.2 Hz, 1H), 4.49 (dd, *J* = 8.6, 4.8 Hz, 1H), 3.81 (s, 3H), 3.76-3.60 (m, 2H), 3.61 (d, *J* = 16.2 Hz, 1H), 3.33 (d, *J* = 16.4 Hz, 1H), 2.95 (d, *J* = 16.4 Hz, 1H), 2.86 (d, *J* = 16.2 Hz, 1H), 2.21-2.11 (m, 1H), 2.12-2.00 (m, 1H), 1.99-1.83 (m, 2H), 1.37 (s, 3H), 1.26 (d, *J* = 6.2 Hz, 3H), 1.21 (d, *J* = 6.2 Hz, 3H)

¹³C NMR (126 MHz, CDCl$_3$): δ (ppm) 175.9, 172.2, 156.3, 143.2, 128.5, 128.2, 117.2, 108.0, 68.3, 60.9, 55.2, 49.9, 47.8, 45.0, 40.3, 28.3, 25.8, 25.1, 21.9, 21.8

IR (neat): ν (cm^{-1}) 2977, 1735, 1625, 1401, 1264, 1185, 1107, 1076, 767

HRMS (ESI): Calcd for $C_{20}H_{27}NNaO_4$ $[M+Na]^+$: 368.1836, found 368.1834
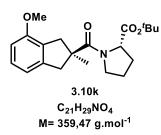
Rf: 0.27 in a 70:30 mixture of pentane and ethyl acetate

HPLC separation: with IBioxMe$_4$·HOTf Chiralpak® IA; 95:5 (*n*-heptane/*i*-PrOH), 1.0 mL.min^{-1}, 205 nm, t_R (minor) = 14.6 min, t_R (major) = 16.0 min, 36:64 d.r.

With **3.29** Chiralpak® IA; 95:5 (*n*-heptane/*i*-PrOH), 1.0 mL.min^{-1}, 205 nm, t_R (major) = 14.6 min, t_R (minor) = 16.6 min, 63:37 d.r.

Experimental Section

Tert-butyl ((*S*)-4-methoxy-2-methyl-2,3-dihydro-1*H*-indene-2-carbonyl)-*L*-prolinate (3.10k):

From **3.11k** using **General procedure H**. **3.10k** was obtained as a wax (60.4 mg, 0.168 mmol, 84%).

3.10k
C$_{21}$H$_{29}$NO$_4$
M= 359,47 g.mol^{-1}

Description of major diastereoisomer:

^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 7.14 (t, *J* = 7.8 Hz, 1H), 6.81 (d, *J* = 7.8 Hz, 1H), 6.67 (d, *J* = 7.8 Hz, 1H), 4.42 (dd, *J* = 8.5, 4.8 Hz, 1H), 3.81 (s, 3H), 3.75-3.56 (m, 2H), 3.61 (d, *J* = 16.3 Hz, 1H), 3.38 (d, *J* = 16.4 Hz, 1H), 2.94 (d, *J* = 16.4 Hz, 1H), 2.86 (d, *J* = 16.3 Hz, 1H), 2.19-2.09 (m, 1H), 2.11-1.98 (m, 1H), 1.96-1.82 (m, 2H), 1.44 (s, 9H), 1.35 (s, 3H)

^{13}C NMR (126 MHz, CDCl$_3$): δ (ppm) 175.7, 172.0, 156.4, 143.2, 128.7, 128.1, 117.2, 108.1, 80.9, 61.5, 55.3, 49.7, 47.7, 44.8, 40.7, 28.3, 28.1, 25.9, 25.4

IR (neat): ν (cm^{-1}) 2973, 1735, 1625, 1151, 1076, 766

HRMS (ESI): Calcd for C$_{21}$H$_{29}$NNaO$_4$ [M+Na]$^+$: 382.1989, found 382.1988
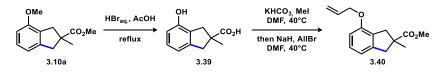
Rf: 0.33 in a 70:30 mixture of pentane and ethyl acetate

HPLC separation: with IBioxMe$_4$·HOTf Chiralpak$^®$ IA; 95:5 (*n*-heptane/*i*-PrOH), 1.0 mL.min^{-1}, 205 nm, t_R (major) = 11.0 min, t_R (minor) = 14.6 min, 62:38 e.r.

With **3.29** Chiralpak$^®$ IA; 95:5 (*n*-heptane/*i*-PrOH), 1.0 mL.min^{-1}, 205 nm, t_R (major) = 10.8 min, t_R (minor) = 14.6 min, 83:17 e.r.

Experimental Section

6.3.4. First Route – Racemic

Methyl 4-(allyloxy)-2-methyl-2,3-dihydro-1*H*-indene-2-carboxylate (3.40):

3.10a (911 mg, 4.14 mmol) was dissolved in glacial acetic acid (11 mL) and 48% aqueous hydrobromic acid (54 mL). The reaction mixture was refluxed for 2 h. After this period, the reaction was diluted with water and extracted with DCM. The organic layer was dried over MgSO4 and concentrated under a vacuum. Two portions of toluene were added and evaporated to remove excess of AcOH. The crude product was then diluted in DMF (6 mL) and KHCO3 (1.12 g, 12.42 mmol, 3 equiv) was added. The suspension was stirred 10 min at room temperature, and then methyl iodide (0.77 mL, 12.42 mmol, 3 equiv) was added. The mixture was stirred at 40 °C until total consumption of starting material (approximately 3 h). To remove the excess of iodomethane, the reaction was heated to 65 °C under a flow of argon for 15 min. After this period, the temperature was lowered to 40 °C, and then NaH (300 mg, 12.42 mmol, 3 equiv) and allyl bromide (1.07 mL, 12.42 mmol, 3 equiv) were added successively carefully. The reaction mixture was stirred for 30 min and then cooled with an ice bath, and then water was added. The reaction was extracted three times with DCM. The combined organic phases were dried over MgSO4, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography (Cy/AcOEt: 90/10) leading to 30 as a light yellow oil (835 mg, 3.39 mmol, 82% over 2 steps).

3.40
C$_{15}$H$_{18}$O$_3$
M= 246,31 g.mol^{-1}

^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 7.12 (t, *J* = 7.8 Hz, 1H), 6.81 (d, *J* = 7.5 Hz, 1H), 6.67 (d, *J* = 8.1 Hz, 1H), 6.06 (ddt, *J* = 17.3, 10.4, 5.1 Hz, 1H), 5.42 (dq, *J* = 17.3, 1.6 Hz, 1H), 5.27 (dq, *J* = 10.4, 1.6 Hz, 1H), 4.54 (dt, *J* = 5.1, 1.6 Hz, 2H), 3.72 (s, 3H), 3.51 (d, *J* = 16.0 Hz, 1H), 3.42 (d, *J* = 16.4 Hz, 1H), 2.89 (d, *J* = 16.4 Hz, 1H), 2.82 (d, *J* = 16.0 Hz, 1H), 1.38 (s, 3H)
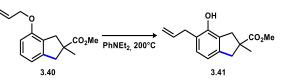
^{13}C NMR (63 MHz, CDCl$_3$) δ (ppm) 178.3, 155.3, 143.4, 133.6, 129.3, 128.1, 117.3, 117.2, 109.5, 68.7, 52.2, 49.4, 44.5, 41.1, 25.6

IR (neat): ν (cm^{-1}) 2950, 1730, 1590, 1480, 1262, 1112, 1061, 767 cm^{-1}
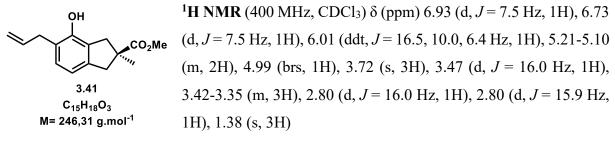
HRMS (ESI): Calcd for C$_{15}$H$_{18}$NaO$_3$ [M+Na]$^+$: 269.1148, found 269.1151

Rf: 0.33 in a 90:10 mixture of pentane and ethyl acetate

Experimental Section

Methyl 5-allyl-4-hydroxy-2-methyl-2,3-dihydro-1*H*-indene-2-carboxylate (31):

A sealed tube charged with **3.40** (409 mg, 1.66 mmol) and *N,N*-diethylaniline (3 mL) was heated under stirring at 200 °C for 24 h. After this period, the reaction was poured into 1 M HCl and extracted three times with DCM. The combined organic layers were dried over MgSO4, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography (Cy/AcOEt: 90/10) leading to **3.41** (368 mg, 1.49 mmol, 90%) as a yellow oil.

3.41
C$_{15}$H$_{18}$O$_3$
M= 246,31 g.mol^{-1}

^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 6.93 (d, *J* = 7.5 Hz, 1H), 6.73 (d, *J* = 7.5 Hz, 1H), 6.01 (ddt, *J* = 16.5, 10.0, 6.4 Hz, 1H), 5.21-5.10 (m, 2H), 4.99 (brs, 1H), 3.72 (s, 3H), 3.47 (d, *J* = 16.0 Hz, 1H), 3.42-3.35 (m, 3H), 2.80 (d, *J* = 16.0 Hz, 1H), 2.80 (d, *J* = 15.9 Hz, 1H), 1.38 (s, 3H)
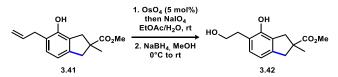
^{13}C NMR (63 MHz, CDCl$_3$) δ (ppm) 178.4, 150.8, 141.8, 137.0, 129.2, 127.3, 123.3, 116.9, 116.3, 52.3, 49.9, 44.2, 40.3, 35.0, 25.5

IR (neat): ν (cm^{-1}) 3460, 2952, 1712, 1445, 1284, 1209, 1114, 913

HRMS (ESI): Calcd for C$_{15}$H$_{18}$NaO$_3$ [M+Na]$^{+}$: 269.1148, found 269.1147
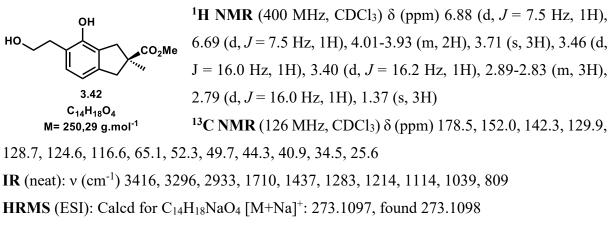
Rf: 0.20 in a 85:15 mixture of pentane and ethyl acetate

Methyl 4-hydroxy-5-(2-hydroxyethyl)-2-methyl-2,3-dihydro-1*H*-indene-2-carboxylate (3.41):
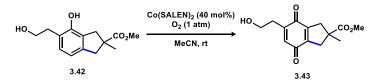
In a round-bottom flask containing a stirred biphasic solution of **3.41** (441 mg, 1.79 mmol) in EtOAc (20 mL) and water (12 mL) was added OsO$_4$ (23 mg, 90.5 µmol, 5 mol %). After 5 min, NaIO$_4$ (957 mg, 4.48 mmol, 2.5 equiv) was added in two portions separated by 5 min. The solution was vigorously stirred for 3 h at room temperature. The layers were separated and the aqueous phase was extracted twice with ethyl acetate. The combined organic layers were dried over MgSO4, filtered and concentrated under reduced pressure. The crude material was diluted in MeOH (20 mL) and cooled to 0 °C. After this, NaBH$_4$ (205 mg, 5.42 mmol, 3 equiv) was added and the reaction was allowed to reach room temperature. After 30 min, H$_2$O was added

and the reaction was extracted three times with ethyl acetate. The combined organic phases were dried over MgSO$_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography (Cy/AcOEt: 60/40) leading to **3.42** (389 mg, 1.55 mmol, 87%) as a light-yellow oil.

3.42
C$_{14}$H$_{18}$O$_4$
M= 250,29 g.mol^{-1}

^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 6.88 (d, J = 7.5 Hz, 1H), 6.69 (d, J = 7.5 Hz, 1H), 4.01-3.93 (m, 2H), 3.71 (s, 3H), 3.46 (d, J = 16.0 Hz, 1H), 3.40 (d, J = 16.2 Hz, 1H), 2.89-2.83 (m, 3H), 2.79 (d, J = 16.0 Hz, 1H), 1.37 (s, 3H)

^{13}C NMR (126 MHz, CDCl$_3$) δ (ppm) 178.5, 152.0, 142.3, 129.9, 128.7, 124.6, 116.6, 65.1, 52.3, 49.7, 44.3, 40.9, 34.5, 25.6

IR (neat): ν (cm^{-1}) 3416, 3296, 2933, 1710, 1437, 1283, 1214, 1114, 1039, 809

HRMS (ESI): Calcd for C$_{14}$H$_{18}$NaO$_4$ [M+Na]$^+$: 273.1097, found 273.1098
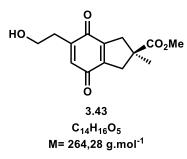
Rf: 0.19 in a 70:30 mixture of pentane and ethyl acetate

Methyl 5-(2-hydroxyethyl)-2-methyl-4,7-dioxo-2,3,4,7-tetrahydro-1H-indene-2-carboxylate (3.43):

In a round-bottom flask, **3.42** (250 mg, 1.0 mmol) and Salcomine (130 mg, 0.4 mmol, 40 mol %) were mixed in acetonitrile (13 mL). Oxygen was bubbled through the stirred suspension during 5 min. Then the reaction was stirred under oxygen atmosphere during 24 h. After this period, acetonitrile was removed under reduced pressure and the crude was purified by flash chromatography (Cy/AcOEt: 50/50) leading to **3.43** (218 mg, 0.82 mmol, 82%) as a yellow oil.

3.43
C$_{14}$H$_{16}$O$_5$
M= 264,28 g.mol^{-1}

^{1}H NMR (600 MHz, CDCl$_3$) δ (ppm) 6.58 (t, J = 1.2 Hz, 1H), 3.82 (t, J = 5.5 Hz, 2H), 3.72 (s, 3H), 3.38-3.31 (m, 2H), 2.74-2.69 (m, 2H), 2.68 (tt, J = 6.0, 1.0 Hz, 2H), 1.74 (brs, 1H), 1.39 (s, 3H)
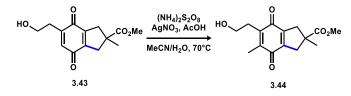
^{13}C NMR (151 MHz, CDCl$_3$) δ (ppm) 186.3, 185.9, 177.0, 146.6, 146.2, 146.0, 134.5, 61.2, 52.6, 47.3, 42.5, 42.2, 32.6, 26.1

IR (neat): ν (cm^{-1}) 3492, 3447, 2955, 1729, 1650, 1268, 1211, 1039, 851
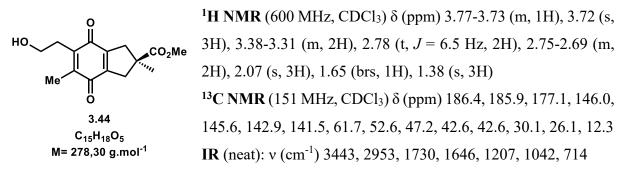
HRMS (ESI): Calcd for C$_{14}$H$_{16}$NaO$_5$ [M+Na]$^+$: 287.0890, found 287.0886

Rf: 0.23 in a 50:50 mixture of pentane and ethyl acetate

Experimental Section

Methyl 5-(2-hydroxyethyl)-2,6-dimethyl-4,7-dioxo-2,3,4,7-tetrahydro-1*H*-indene-2-carboxylate (3.44):

3.43   3.44

A solution of **3.43** (90.6 mg, 0.343 mmol), acetic acid (63.0 mg, 60 µL, 3 equiv) in acetonitrile/H_2O 1:1 (1 mL) was heated at 70 °C. Subsequently, silver nitrate (17.5 mg, 0.103 mmol, 0.3 equiv) and ammonium persulfate (102 mg, 0.446 mmol, 1.3 equiv) were added and the reaction was stirred for 2 h. After this period, the solution was diluted with ethyl acetate (15 mL). The organic layer was washed with water (10 mL), dried over $MgSO_4$ and concentrated under a vacuum. The crude was purified by flash chromatography (Cy/AcOEt: 50/50) leading to **3.44** (52 mg, 0.187 mmol, 55%) as a yellow oil.

3.44
$C_{15}H_{18}O_5$
M= 278,30 g.mol^{-1}

^{1}H NMR (600 MHz, CDCl$_3$) δ (ppm) 3.77-3.73 (m, 1H), 3.72 (s, 3H), 3.38-3.31 (m, 2H), 2.78 (t, *J* = 6.5 Hz, 2H), 2.75-2.69 (m, 2H), 2.07 (s, 3H), 1.65 (brs, 1H), 1.38 (s, 3H)

^{13}C NMR (151 MHz, CDCl$_3$) δ (ppm) 186.4, 185.9, 177.1, 146.0, 145.6, 142.9, 141.5, 61.7, 52.6, 47.2, 42.6, 42.6, 30.1, 26.1, 12.3

IR (neat): ν (cm^{-1}) 3443, 2953, 1730, 1646, 1207, 1042, 714
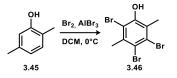
HRMS (ESI): Calcd for $C_{15}H_{18}NaO_5$ [M+Na]$^+$: 301.1046, found 301.1042

Rf: 0.25 in a 50:50 mixture of pentane and ethyl acetate

Experimental Section

6.3.5. Second route

2,4,5-tribromo-3,6-dimethylphenol (3.46):
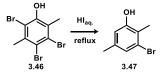
A modification of the procedure of Gould was used.[220] Aluminum (4.01 g, 0.15 mol, 0.45 equiv) was cautiously added in small portions to bromine (100 mL, 1.94 mol, 5.8 equiv) cooled to 0 °C, and the mixture was stirred for 20 min. A solution of 2,5-dimethylphenol (**3.45**) (40.3 g, 330 mmol) in DCM (200 mL) was added over 2 h, and the mixture was stirred for additional 2 h at 0 °C. (Caution! A copious amount of HBr is evolved in this reaction which can be trapped by a water trap connected to an aqueous sodium carbonate scrubber). The reaction was then diluted at 0 °C with DCM (200 mL) and water (200 mL). Then a 5% aqueous $NaHSO_3$ solution was added until the color of bromine disappeared. The phases were separated, the aqueous layer was extracted twice with DCM, and the combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure to yield **3.46** (115 g, 320 mmol) as a white solid which was used in the next step without further purification. Spectroscopic data are consistent with those previously reported.[220]

3.46

$C_8H_7Br_3O$

M= 358,86 g.mol^{-1}

^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 5.83 (s, 1H), 2.66 (s, 3H), 2.47 (s, 3H)

^{13}C NMR (101 MHz, CDCl$_3$): δ (ppm) 149.9, 136.2, 128.2, 125.3, 118.4, 112.7, 26.5, 19.1

IR (neat): ν (cm^{-1}) 3491, 1365, 1444, 1032, 654

HRMS (ESI): Calcd for C_8H_6^{79}Br$_3$O [M-H]$^-$: 354.7974, found 354.7976

Rf = 0.39 in a 90:10 mixture of pentane and ethyl acetate

Mp = 179-182°C

3-bromo-2,5-dimethylphenol (3.47):
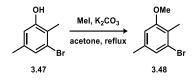
A modification of the procedure of Gould was used.[220]g A suspension of the **3.46** (115 g, 320 mmol) in aqueous HI (57%, 250 mL) was heated at reflux under argon for 16 h and cooled. TBME (500 mL) was added, and at 0 °C under stirring, $NaHSO_3$ (40%, 900 mL) was added dropwise. The layers were separated, and the aqueous layer was extracted twice with TBME

Experimental Section
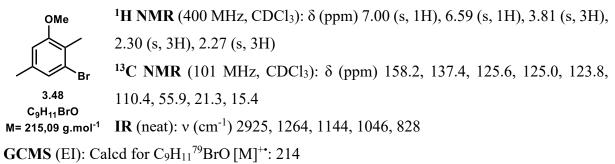
(300 mL). The combined organic phases were dried over MgSO$_4$, filtered, and concentrated under reduced pressure to yield **3.47** (54.7 g, 272 mmol) nearly pure as a light brown solid which was used in the next step without further purification. Spectroscopic data are consistent with those previously reported.[220]

1H NMR (400 MHz, CDCl$_3$): δ (ppm) 6.98 (s, 1H), 6.54 (s, 1H), 4.73 (s, 1H), 2.29 (s, 3H), 2.24 (s, 3H)

13C NMR (101 MHz, CDCl$_3$): δ (ppm) 154.1, 137.8, 125.8, 125.7, 121.3, 115.1, 20.78, 15.3

IR (neat): ν (cm^{-1}) 3306, 2921, 1399, 1272, 1124, 1007, 814

HRMS (ESI): Calcd for C$_8$H$_8$^{79}BrO [M-H]$^-$: 198.9764, found 198.9765

Rf: 0.29 in a 85:15 mixture of pentane and ethyl acetate

Mp: 85-88°C

1-bromo-3-methoxy-2,5-dimethylbenzene (3.48):
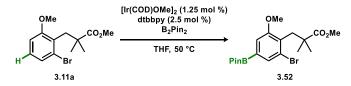
3.47 (54.4 g, 271 mmol) was dissolved in acetone (500 mL), then potassium carbonate (56.0 g, 405 mmol, 1.5 equiv) and methyl iodide (51.0 mL, 115 g, 810 mmol, 3.0 equiv) were added. The resulting dark brown mixture was stirred under reflux for 24 h; after 12 h, another equivalent of methyl iodide (16.0 mL, 270 mmol, 1.0 equiv) was added. The dark brown suspension was concentrated carefully under reduced pressure. The residue was diluted with diethyl ether (700 mL) and water (500 mL) and the layers were separated. The aqueous phase was extracted twice with diethyl ether (200 mL). The combined organic phases were washed twice with water (200 mL), then with brine (100 mL), dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The crude material was obtained as a brown liquid which was distilled under reduced pressure to give **3.48** as a colorless liquid (53.47 g, 249 mmol, 76% over 3 steps). Spectroscopic data are consistent with those previously reported.[220]

1H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.00 (s, 1H), 6.59 (s, 1H), 3.81 (s, 3H), 2.30 (s, 3H), 2.27 (s, 3H)

13C NMR (101 MHz, CDCl$_3$): δ (ppm) 158.2, 137.4, 125.6, 125.0, 123.8, 110.4, 55.9, 21.3, 15.4

IR (neat): ν (cm^{-1}) 2925, 1264, 1144, 1046, 828

GCMS (EI): Calcd for C$_9$H$_{11}$^{79}BrO [M]$^{+\bullet}$: 214

Experimental Section
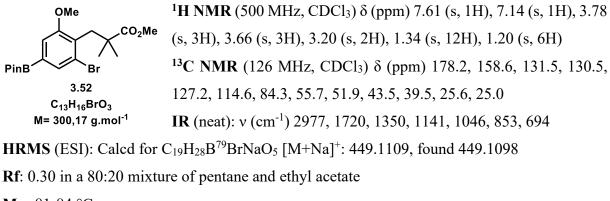
Rf: 0.53 in a 95:5 mixture of pentane and ethyl acetate

Bp: 54-59°C at 0.1 mbar

Methyl 3-(2-bromo-6-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-2,2-dimethylpropanoate (3.52):
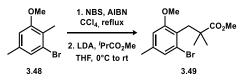
In an oven dry Schlenk tube, **3.11a** (1.0 g, 3.32 mmol), 4,4′-di-*tert*-butyl- 2,2′-dipyridyl (22.3 mg, 83 µmol, 2.5 mol %) and Bis(pinacolato)- diboron (843 mg, 3.32 mmol, 1 equiv) were charged. Then, this Schlenk tube was transferred in a glovebox, and [Ir(COD)OMe]$_2$ (27.5 mg, 41.5 µmol, 1.25 mol %) was added. The tube was closed with a septum and transferred outside of the glovebox. The reaction was diluted with THF (10 mL) and heated at 50 °C during 48 h. Afterward, THF was removed under a vacuum, and the crude was purified by column chromatography to yield **3.52** as a white solid (1.38 g, 3.23 mmol, 97% yield).

3.52
C$_{13}$H$_{16}$BrO$_3$
M= 300,17 g.mol^{-1}

^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm) 7.61 (s, 1H), 7.14 (s, 1H), 3.78 (s, 3H), 3.66 (s, 3H), 3.20 (s, 2H), 1.34 (s, 12H), 1.20 (s, 6H)

^{13}C NMR (126 MHz, CDCl$_3$) δ (ppm) 178.2, 158.6, 131.5, 130.5, 127.2, 114.6, 84.3, 55.7, 51.9, 43.5, 39.5, 25.6, 25.0

IR (neat): ν (cm^{-1}) 2977, 1720, 1350, 1141, 1046, 853, 694

HRMS (ESI): Calcd for C$_{19}$H$_{28}$B^{79}BrNaO$_5$ [M+Na]$^+$: 449.1109, found 449.1098

Rf: 0.30 in a 80:20 mixture of pentane and ethyl acetate

Mp: 81-84 °C
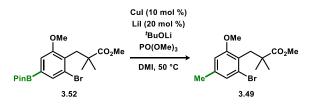
Methyl 3-(2-bromo-6-methoxy-4-methylphenyl)-2,2-dimethylpropanoate (3.49):
From 3.48:
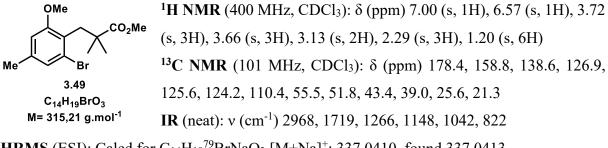
35 (3.50 g, 16.3 mmol) was dissolved in tetrachloromethane (20 mL) and N-bromosuccinimide (3.77 g, 21.2 mmol, 1.32 equiv) was added followed by AIBN (321 mg, 1.86 mmol, 12 mol %). The resulting light-yellow suspension was stirred under refluxed overnight. The reaction mixture was cooled in an ice bath, filtered and washed with a minimal amount of cold DCM.

173

Experimental Section

The filtrate was concentrated under reduced pressure to give an orange oil which was used without further purification. A solution of LDA (25.3 mmol, 1.55 equiv) in THF (25 mL) was prepared from freshly distilled diisopropylamine (25.3 mmol, 1.55 equiv) and 2.5 M (titrated) *n*-BuLi in hexane (10.1 mL, 25.3 mmol, 1.55 equiv), mixed for 15 min at 0 °C. To the LDA solution, methyl isobutyrate (24.5 mmol, 1.5 equiv) was added dropwise at 0 °C and the mixture was stirred at 0 °C for 45 min. Freshly prepared crude 3-bromo-2- bromomethyl-5-methyl-methoxybenzene from the previous step was diluted in THF (16 mL) and added slowly to the LDA solution at 0 °C. The mixture was slowly warmed to room temperature and stirred for 16 h. The reaction was quenched at 0 °C with water (30 mL). The mixture was extracted three times with diethyl ether (30 mL); the combined organic layers were washed with brine, dried over MgSO$_4$, filtered and then concentrated in vacuum to give the crude ester. The crude material was purified by flash column chromatography to yield 36 as a colorless oil, which crystallized on standing (3.85 g, 12.2 mmol, 75% yield over 2 steps).
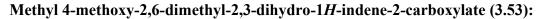
From 3.52:
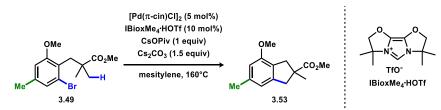
in an oven dry Schlenk tube, **3.52** (1.28 g, 3 mmol) was introduced. Then, this Schlenk tube was transferred in a glovebox, and CuI (57 mg, 0.3 mmol, 10 mol %), LiI (80 mg, 0.6 mmol, 20 mol %) and tBuOLi (480 mg, 6 mmol, 2 equiv) were added. The tube was closed with a septum and transferred outside of the glovebox. The reaction was diluted with DMI (4.5 mL) and trimethyl phosphate (0.73 mL, 6 mmol, 2 equiv) was added. The mixture was heated at 50 °C during 16 h. The reaction was quenched by H$_2$O, extracted by toluene. The organic layer was condensed, and the residue was purified by flash column chromatography to yield **3.49** as a colorless oil, which crystallized on standing (759 mg, 2.41 mmol, 80% yield).

¹H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.00 (s, 1H), 6.57 (s, 1H), 3.72 (s, 3H), 3.66 (s, 3H), 3.13 (s, 2H), 2.29 (s, 3H), 1.20 (s, 6H)

¹³C NMR (101 MHz, CDCl$_3$): δ (ppm) 178.4, 158.8, 138.6, 126.9, 125.6, 124.2, 110.4, 55.5, 51.8, 43.4, 39.0, 25.6, 21.3

IR (neat): ν (cm^{-1}) 2968, 1719, 1266, 1148, 1042, 822

HRMS (ESI): Calcd for C$_{14}$H$_{19}$^{79}BrNaO$_3$ [M+Na]$^+$: 337.0410, found 337.0413

Rf: 0.26 in a 90:10 mixture of pentane and ethyl acetate

Mp: 63-65°C

Experimental Section

Methyl 4-methoxy-2,6-dimethyl-2,3-dihydro-1*H*-indene-2-carboxylate (3.53):
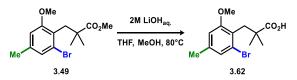
In an oven dry catalysis tube, **3.49** (506 mg, 1.15 mmol) was introduced. Then the tube was transferred in a glovebox, and [Pd(π-cin)Cl]₂ (29.8 mg, 57.5 μmol, 5 mol %), IBioxMe₄·HOTf (67.7 mg, 115 μmol, 10 mol %), cesium pivalate (269 mg, 1.15 mmol, 1 equiv) and cesium carbonate (562 mg, 1.72 mmol, 1.5 equiv) were introduced, and the tube was closed with a septum. Outside of the glovebox, mesitylene (6 mL) was added. The reaction was stirred at room temperature for 10 min, and then, under pressure of argon, the septum was rapidly exchanged for a screw cap. The tube was then introduced in a 160 °C preheated aluminum heating block and stirred at this temperature for 18 h. After this period the reaction was cooled to room temperature, diluted with DCM (6 mL), filtered over a pad of Celite (washed three times with 6 mL of DCM). The crude material was analyzed by GC-MS, then concentrated and purified by flash column chromatography to yield **3.53** as a yellowish liquid (361 mg, 1.00 mmol, 87%).

3.53
C₁₄H₁₈O₃
M= 234,30 g.mol⁻¹

¹H NMR (500 MHz, CDCl₃): δ (ppm) 6.64 (s, 1H), 6.50 (s, 1H), 3.80 (s, 7H), 3.71 (s, 6H), 3.45 (d, *J* = 16.0 Hz, 3H), 3.33 (d, *J* = 16.1 Hz, 3H), 2.79 (d, *J* = 16.1 Hz, 3H), 2.76 (d, *J* = 16.0 Hz, 3H), 2.33 (s, 8H), 1.36 (s, 6H)

¹³C NMR (126 MHz, CDCl₃): δ (ppm) 178.4, 156.0, 143.3, 138.3, 125.9, 117.7, 109.4, 77.4, 77.2, 76.9, 55.3, 52.2, 49.5, 44.4, 40.8, 25.6, 21.8

IR (neat): ν (cm⁻¹) 2950, 2843, 1730, 1593, 1461, 1317, 1199, 1111, 1083, 829

HRMS (ESI): Calcd for C₁₄H₁₈NaO₃ [M+Na]⁺: 257.1154, found 257.1148

Rf: 0.38 in a 95:5 mixture of pentane and ethyl acetate

3-(2-bromo-6-methoxy-4-methylphenyl)-2,2-dimethylpropanoic acid (3.62):

3.49 (3.5 g, 11.1 mmol) was dissolved in a mixture of THF (20 mL), MeOH (20 mL) and 2 M aqueous LiOH (20 mL). The reaction was then heated at 80 °C for 6 h. After cooling to room

Experimental Section

temperature, the organic solvents were removed under reduced pressure. The obtained aqueous solution was washed with diethyl ether, acidified to pH < 0 and extracted three times with DCM. The combined organic layers were then dried over MgSO$_4$, filtered and concentrated under reduced pressure to yield **3.62** as a yellow solid, which was engaged in the next step without further purifications.

3.62
C$_{13}$H$_{17}$BrO$_3$
M= 301,18 g.mol^{-1}
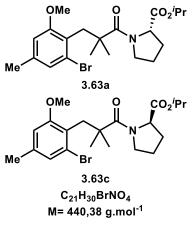
^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.01 (s, 1H), 6.57 (s, 1H), 3.69 (s, 3H), 3.19 (s, 2H), 2.29 (s, 3H), 1.22 (s, 6H).

^{13}C NMR (63 MHz, CDCl$_3$): δ (ppm) 184.9, 158.8, 138.7, 126.9, 125.6, 123.8, 110.4, 54.9, 43.2, 39.1, 25.2, 21.3

IR (neat): ν (cm^{-1}) 2974, 2939, 1691, 1271, 1159, 1045, 830

HRMS (ESI): Calcd for C$_{13}$H$_{17}$^{79}BrNaO$_3$ [M+Na]$^+$: 323.0253, found 323.0259

Rf: 0.30 in a 70:30 mixture of pentane and ethyl acetate

Mp: 100-103°C

Isopropyl (3-(2-bromo-6-methoxy-4-methylphenyl)-2,2-dimethylpropanoyl)-*L*-prolinate (3.63a) and isopropyl (3-(2-bromo-6-methoxy-4-methylphenyl)-2,2-dimethylpropanoyl)-*D*-prolinate (3.63c):

From **3.62** and H-*L*-Pro-O^{i}Pr·HCl or H-*D*-Pro-O^{i}Pr·HCl respectively using **General procedure G**. Obtained as colorless oils that solidified upon standing **3.63a** (4.25 g, 9.66 mmol, 87%), **3.63b** (142 mg, 0.32 mmol, 81%).

3.63a

3.63c
C$_{21}$H$_{30}$BrNO$_4$
M= 440,38 g.mol^{-1}

^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 6.99 (s, 1H), 6.58 (s, 1H), 5.02 (sept, *J* = 6.3 Hz, 1H), 4.51-4.42 (m, 1H), 3.87-3.67 (m, 2H), 3.73 (s, 3H), 3.21 (d, *J* = 13.6 Hz, 1H), 3.13 (d, *J* = 13.6 Hz, 1H), 2.28 (s, 3H), 2.20-2.09 (m, 1H), 2.09-1.97 (m, 1H), 1.95-1.76 (m, 2H), 1.29 (s, 3H), 1.25 (d, *J* = 6.3 Hz, 3H), 1.21 (d, *J* = 6.3 Hz, 3H), 1.17 (s, 3H)

^{13}C NMR (126 MHz, CDCl$_3$): δ (ppm) 176.4, 172.5, 158.9, 138.6, 126.9, 125.7, 124.2, 110.5, 68.1, 61.6, 55.5, 48.5, 44.1, 36.5, 28.0, 26.4, 26.0, 25.4, 21.9, 21.8, 21.2

IR (neat): ν (cm^{-1}) 2977, 2932, 1741, 1615, 1400, 1161, 1040, 833

HRMS (ESI): Calcd for C$_{21}$H$_{30}$^{79}BrNNaO$_4$ [M+Na]$^+$: 462.1250, found 462.1257

Mp: 75-79°C
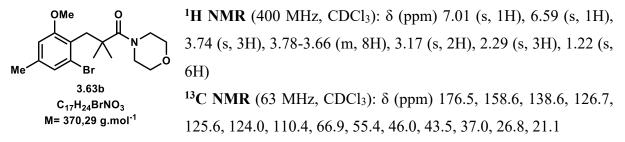
Rf: 0.24 in a 70:30 mixture of pentane and ethyl acetate

3.63a [α]$_D^{23}$: - 39.4° (c = 1.00, CHCl$_3$)

Experimental Section

3.63c $[α]_D^{23}$: + 38.1° (c = 0.80, CHCl$_3$)

3-(2-bromo-6-methoxy-4-methylphenyl)-2,2-dimethyl-1-morpholinopropan-1-one (3.63b):

From **3.62** and morpholine using **General procedure G**. **3.63b** was obtained as a wax (2.09 g, 5.65 mmol, 63% yield).

3.63b
C$_{17}$H$_{24}$BrNO$_3$
M= 370,29 g.mol^{-1}

^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.01 (s, 1H), 6.59 (s, 1H), 3.74 (s, 3H), 3.78-3.66 (m, 8H), 3.17 (s, 2H), 2.29 (s, 3H), 1.22 (s, 6H)

^{13}C NMR (63 MHz, CDCl$_3$): δ (ppm) 176.5, 158.6, 138.6, 126.7, 125.6, 124.0, 110.4, 66.9, 55.4, 46.0, 43.5, 37.0, 26.8, 21.1
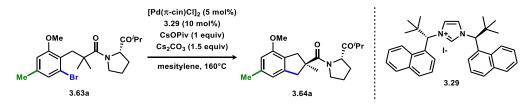
IR (neat): ν (cm^{-1}) 2966, 2854, 1629, 1406, 1268, 1115, 1041, 831
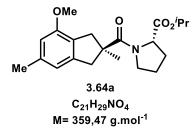
HRMS (ESI): Calcd for C$_{17}$H$_{24}$^{79}BrNNaO$_3$ [M+Na]$^+$: 378.0832, found 392.0828

Rf: 0.26 in a 50:50 mixture of pentane and ethyl acetate

Isopropyl ((*S*)-4-methoxy-2,6-dimethyl-2,3-dihydro-1*H*-indene-2-carbonyl)-*L*-prolinate (3.64a):

In an oven dry catalysis tube, **3.63a** (506 mg, 1.15 mmol) was introduced. Then the tube was transferred in a glovebox, and [Pd(π-cin)Cl]$_2$ (29.8 mg, 57.5 μmol, 5 mol %), L3 (67.7 mg, 115 μmol, 10 mol %), cesium pivalate (269 mg, 1.15 mmol, 1 equiv) and cesium carbonate (562 mg, 1.72 mmol, 1.5 equiv) were introduced, and the tube was close with a septum. Outside of the glovebox, mesitylene (6 mL) was added. The reaction was stirred at room temperature for 10 min, and then, under pressure of argon, the septum was rapidly exchange for a screw cap. The tube was then introduced in a 160 °C preheated aluminum heating block and stirred at this temperature for 18 h. After this period the reaction was cooled to room temperature, diluted with DCM (6 mL), filtered over a pad of Celite (washed three times with 6 mL of DCM). The crude material was analyzed by GC-MS, then concentrated and purified by flash column chromatography to yield **3.64a** as a wax (361 mg, 1.00 mmol, 87%).

Experimental Section

^{**1**}**H NMR** (500 MHz, CDCl$_3$): δ (ppm) 6.64 (s, 1H), 6.50 (s, 1H), 5.02 (sept, *J* = 6.2 Hz, 1H), 4.48 (dd, *J* = 8.6, 4.8 Hz, 1H), 3.79 (s, 3H), 3.78-3.59 (m, 2H), 3.56 (d, *J* = 16.3 Hz, 1H), 3.33 (d, *J* = 16.2 Hz, 1H), 2.89 (d, *J* = 16.2 Hz, 1H), 2.80 (d, *J* = 16.3 Hz, 1H), 2.33 (s, 3H), 2.21-2.10 (m, 1H), 2.09-2.00 (m, 1H), 1.97-1.81 (m, 2H), 1.34 (s, 3H), 1.25 (d, *J* = 6.2 Hz, 3H), 1.19 (d, *J* = 6.2 Hz, 3H)

3.64a
C$_{21}$H$_{29}$NO$_4$
M= 359,47 g.mol^{-1}

^{**13**}**C NMR** (126 MHz, CDCl$_3$): δ (ppm) 175.9, 172.2, 156.1, 143.1, 138.2, 125.6, 117.7, 109.2, 68.2, 60.9, 55.2, 49.7, 47.7, 44.7, 40.4, 28.3, 25.9, 25.4, 21.9, 21.8, 21.8

IR (neat): ν (cm^{-1}) 2976, 1736, 1626, 1400, 1185, 1108, 1085, 830

HRMS (ESI): Calcd for C$_{21}$H$_{29}$NNaO$_4$ [M+Na]$^+$: 382.1989, found 382.1994
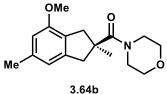
Rf: 0.29 in a 70:30 mixture of pentane and ethyl acetate

HPLC separation: with IBioxMe$_4$·HOTf Chiralpak® IA; 95:5 (*n*-heptane/*i*-PrOH), 1.0 ml.min^{-1}, 205 nm, *t*$_R$ (major) = 12.8 min, *t*$_R$ (minor) = 22.2 min, 66:34 e.r.

With **3.29** Chiralpak® IA; 95:5 (*n*-heptane/*i*-PrOH), 1.0 ml.min^{-1}, 205 nm, *t*$_R$ (major) = 12.8 min, *t*$_R$ (minor) = 21.7 min, 85:15 e.r.

(*S*)-(4-methoxy-2,6-dimethyl-2,3-dihydro-1*H*-inden-2-yl)(morpholino)methanone (3.64b):

From **3.63b** using **General procedure H**. **3.64b** was obtained as a wax (50.4 mg, 0.17 mmol, 87%).

3.64b
C$_{17}$H$_{23}$NO$_3$
M= 289,38 g.mol^{-1}

^{**1**}**H NMR** (500 MHz, CDCl$_3$): δ (ppm) 6.65 (s, 1H), 6.51 (s, 1H), 3.80 (s, 3H), 3.71-3.64 (m, 4H), 3.64-3.53 (m, 4H), 3.55 (d, *J* = 16.7 Hz, 1H), 3.27 (d, *J* = 16.4 Hz, 1H), 2.88 (d, *J* = 16.4 Hz, 1H), 2.82 (d, *J* = 16.7 Hz, 1H), 2.33 (s, 3H), 1.35 (s, 3H)

^{**13**}**C NMR** (126 MHz, CDCl$_3$): δ (ppm) 176.1, 156.1, 142.7, 138.6, 125.2, 117.7, 109.3, 67.0, 55.2, 49.2, 46.0, 41.6, 27.3, 21.8
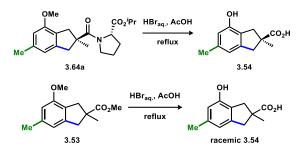
IR (neat): ν (cm^{-1}) 2922, 2854, 1627, 1415, 1114, 1031, 850

HRMS (ESI): Calcd for C$_{16}$H$_{21}$NNaO$_3$ [M+Na]$^+$: 312.1570, found 312.1571
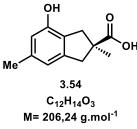
Rf: 0.26 in a 50:50 mixture of pentane and ethyl acetate

HPLC separation: Chiralpak® IA; 95:5 (*n*-heptane/*i*-PrOH), 1.0 mL.min^{-1}, 207 nm, *t*$_R$ (major) = 12.2 min, *t*$_R$ (minor) = 13.7 min, 80:20 e.r.

Experimental Section

(*S*)-4-hydroxy-2,6-dimethyl-2,3-dihydro-1*H*-indene-2-carboxylic acid (3.54):

To **3.64a** (931 mg, 2.59 mmol) was added glacial acetic acid (8 mL) and 48% aqueous hydrobromic acid (40 mL). The reaction mixture was refluxed for 2 h. After this period, the reaction was diluted with water (50 mL) and extracted with DCM (3 × 50 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure. Two portions of toluene (10 mL) were added and evaporated to remove the last traces of AcOH. The crude material was purified by flash chromatography using cyclohexane/EtOAc (6:4) affording 45 (491 mg, 2.38 mmol, 92%) as a light yellow solid. Then the product was enantioenriched by recrystallization as follows: the purified product was solubilized under heating in a mixture of CHCl₃ and cyclohexane (3:1) (proportion 40 mg/mL). The solution was then stored at room temperature for 4 days for crystallization. After separation, nearly racemic crystals (187 mg, 0.908 mmol, 35%) and concentrated enantioenriched mother liquor (304 mg, 1.47 mmol, 57%) were engaged in the next step to measure the enantiomeric ratio by HPLC using a chiral stationary phase. Racemic material was prepared using the same procedure from racemic **3.53** (890 mg, 3.80 mmol), glacial acetic acid (12 mL) and 48% aqueous hydrobromic acid (58 mL) to yield racemic **3.54** (682 mg, 3.31 mmol, 87%).

3.54
$C_{12}H_{14}O_3$
M= 206,24 g.mol⁻¹

¹H NMR (500 MHz, DMSO-d6): δ (ppm) 12.24 (bs, 1H), 9.03 (bs, 1H), 6.45 (s, 1H), 6.39 (s, 1H), 3.27 (d, *J* = 16.3 Hz, 1H), 3.16 (d, *J* = 16.3 Hz, 1H), 2.60 (d, *J* = 16.3 Hz, 1H), 2.63 (d, *J* = 16.3 Hz, 1H), 2.16 (s, 3H), 1.25 (s, 3H)

¹³C NMR (126 MHz, DMSO-d6): δ (ppm) 178.7, 153.3, 143.2, 136.9, 123.9, 116.0, 113.7, 48.8, 43.8, 40.2, 25.1, 21.0

IR (neat): ν (cm⁻¹) 3282, 2924, 1696, 1306, 1121, 835
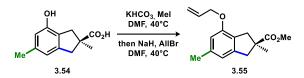
HRMS (ESI): Calcd for $C_{12}H_{14}NaO_3$ [M+Na]⁺: 229.0835, found 229.0838

Rf: 0.25 in a 60:40 mixture of pentane and ethyl acetate

Mp: 160-163°C

[α]$_D^{23}$: + 6.9° (c = 0.57, CHCl₃)

Experimental Section
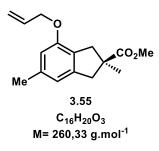
Methyl (*S*)-4-(allyloxy)-2,6-dimethyl-2,3-dihydro-1*H*-indene-2-carboxylate (3.55):

3.54 (304 mg, 1.47 mmol) was dissolved in DMF (12 mL) and $KHCO_3$ (442 g, 4.41 mmol, 3 equiv) was added. The suspension was stirred for 10 min at room temperature, and then iodomethane (0.28 mL, 4.41 mmol, 3 equiv) was added. The mixture was stirred at 40 °C until total consumption of starting material (approximately 3 h). To remove the excess of iodomethane, the reaction was heated to 65 °C under a flow of argon for 15 min. After this period, the temperature was lowered to 40 °C, then NaH (106 mg, 4.41 mmol, 3 equiv) and allyl bromide (0.40 mL, 4.41 mmol, 3 equiv) were added successively carefully. The reaction mixture was stirred for 30 min and then cooled with an ice bath, and then water (30 mL) was added. The reaction was extracted three times with DCM (15 mL); the combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography using cyclohexane/EtOAc (9:1) leading to **3.55** as a light-yellow oil (315 mg, 1.21 mmol, 82%). Racemic material was prepared using the same procedure from racemic **3.54** (650 mg, 3.15 mmol), $KHCO_3$ (947 mg, 9.45 mmol, 3 equiv), iodomethane (0.59 mL, 9.45 mmol, 3 equiv), NaH (227 mg, 9.45 mmol, 3 equiv) and allyl bromide (0.82 mL, 9.45 mmol, 3 equiv) to yield racemic **3.55** (730 mg, 2.80 mmol, 89%).

3.55
$C_{16}H_{20}O_3$
M= 260,33 g.mol^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 6.65 (s, 1H), 6.50 (s, 1H), 6.06 (ddt, *J* = 17.2, 10.5, 5.1 Hz, 1H), 5.42 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.27 (dq, *J* = 10.5, 1.6 Hz, 1H), 4.53 (dt, *J* = 5.1, 1.6 Hz, 2H), 3.72 (s, 3H), 3.47 (d, *J* = 16.1 Hz, 1H), 3.37 (d, *J* = 16.1 Hz, 1H), 2.84 (d, *J* = 16.1 Hz, 1H), 2.77 (d, *J* = 16.1 Hz, 1H), 2.32 (s, 3H), 1.37 (s, 3H)

^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) 178.3, 155.1, 143.3, 138.1, 133.7, 126.3, 117.9, 117.1, 110.6, 68.7, 52.2, 49.5, 44.4, 40.8, 25.6, 21.8

IR (neat): ν (cm^{-1}) 2926, 1730, 1591, 1315, 1112, 1073, 829
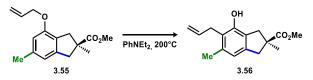
HRMS (ESI): Calcd for $C_{16}H_{20}NaO_3$ [M+Na]$^+$: 283.1305, found 283.1307

Rf: 0.25 in a 95:5 mixture of pentane and ethyl acetate
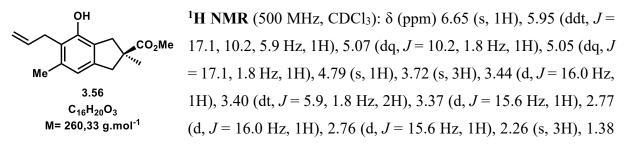
[α]$_D^{23}$: + 5.2° (c = 1.00, $CHCl_3$)

HPLC separation: Chiralpak® IA; 99:1 (*n*-heptane/*i*-PrOH), 1.0 ml.min^{-1}, 208 nm, t_R (major) = 5.0 min, t_R (minor) = 6.1 min, 96:4 e.r.

Experimental Section

Methyl (*S*)-5-allyl-4-hydroxy-2,6-dimethyl-2,3-dihydro-1*H*-indene-2-carboxylate (3.56):

A sealed tube charged with **3.55** (204 mg, 0.784 mmol) and *N,N*-diethylaniline (3 mL) was heated under stirring at 200 °C for 24 h. After this period, the reaction was poured into 1 M HCl (30 mL) and extracted three times with DCM (30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography using cyclohexane/EtOAc (9:1) leading to **3.56** (163 mg, 0.626 mmol, 80%) as a yellow oil which solidified on standing. Racemic material was prepared using the same procedure from racemic **3.55** (700 mg, 2.69 mmol) to yield racemic **3.56** (616 mg, 2.37 mmol, 88%).

3.56
$C_{16}H_{20}O_3$
M= 260,33 g.mol^{-1}

¹H NMR (500 MHz, CDCl₃): δ (ppm) 6.65 (s, 1H), 5.95 (ddt, *J* = 17.1, 10.2, 5.9 Hz, 1H), 5.07 (dq, *J* = 10.2, 1.8 Hz, 1H), 5.05 (dq, *J* = 17.1, 1.8 Hz, 1H), 4.79 (s, 1H), 3.72 (s, 3H), 3.44 (d, *J* = 16.0 Hz, 1H), 3.40 (dt, *J* = 5.9, 1.8 Hz, 2H), 3.37 (d, *J* = 15.6 Hz, 1H), 2.77 (d, *J* = 16.0 Hz, 1H), 2.76 (d, *J* = 15.6 Hz, 1H), 2.26 (s, 3H), 1.38 (s, 3H)

¹³C NMR (126 MHz, CDCl₃): δ (ppm) 178.2, 150.6, 1401.0, 136.8, 136.0, 124.6, 121.6, 118.9, 115.5, 52.3, 49.8, 44.3, 40.3, 30.8, 25.6, 20.0

IR (neat): ν (cm⁻¹) 3464, 2929, 1712, 1195, 1113, 909

HRMS (ESI): Calcd for $C_{16}H_{20}NaO_3$ [M+Na]⁺: 283.1305, found 283.1308
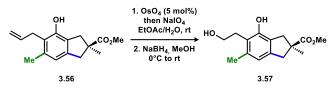
Rf: 0.25 in a 85:15 mixture of pentane and ethyl acetate

Mp: 65-67°C
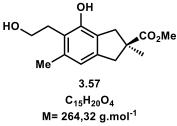
[α]$_D^{23}$: + 10.8° (c = 1.00, CHCl₃)

HPLC separation: Chiralpak® IA; 97:3 (*n*-heptane/*i*-PrOH), 1.0 ml.min⁻¹, 208 nm, t_R (minor) = 14.6 min, t_R (major) = 16.8 min, 96:4 e.r.

Experimental Section

Methyl (*S*)- 4-hydroxy-5-(2-hydroxyethyl)-2,6-dimethyl-2,3-dihydro-1*H*-indene-2-carboxylate (3.57):

In a round-bottom flask containing a stirred biphasic solution of **3.56** (102 mg, 0.392 mmol) in EtOAc (10 mL) and water (5 mL) was added OsO_4 (5.0 mg, 19.6 μmol, 5 mol %). After 5 min, $NaIO_4$ (210 mg, 0.98 mmol, 2.5 equiv) was added in two portions separated by 5 min. The solution was vigorously stirred for 3 h at room temperature. The layers were separated and the aqueous phase was extracted twice with ethyl acetate (6 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was diluted in MeOH (10 mL) and cooled to 0 °C. After this, $NaBH_4$ (44.5 mg, 1.18 mmol, 3 equiv) was added and the reaction was allowed to reach room temperature. After 30 min, H_2O was added and the reaction was extracted three times with ethyl acetate (6 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography using cyclohexane/ EtOAc (6:4) leading to **3.57** (78 mg, 0.295 mmol, 75%) as a light yellow oil. Racemic material was prepared using the same procedure from racemic **3.56** (257 mg, 0.987 mmol), OsO_4 (12.5 mg, 49.4 μmol, 5 mol %), $NaIO_4$ (528 mg, 2.47 mmol, 2.5 equiv) and $NaBH_4$ (112 mg, 2.96 mmol, 3 equiv) to yield racemic **3.57** (195 mg, 0.737 mmol, 75%).

3.57
$C_{15}H_{20}O_4$
M= 264,32 g.mol^{-1}

^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 6.63 (s, 1H), 3.95 – 3.86 (m, 2H), 3.71 (s, 3H), 3.42 (d, *J* = 16.0 Hz, 1H), 3.37 (d, *J* = 16.0 Hz, 1H), 2.88 (dd, *J* = 6.4, 4.6 Hz, 2H), 2.82 (d, *J* = 16.0 Hz, 1H), 2.75 (d, *J* = 16.0 Hz, 1H), 2.24 (s, 3H), 1.36 (s, 3H)

^{13}C NMR (126 MHz, CDCl$_3$): δ (ppm) 178.6, 151.9, 141.3, 136.1, 126.2, 123.1, 118.7, 64.0, 52.2, 49.6, 44.3, 40.9, 29.4, 25.6, 20.3
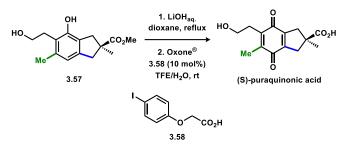
IR (neat): ν (cm^{-1}) 3313, 2924, 1722, 1188, 1110, 905

HRMS (ESI): Calcd for $C_{15}H_{20}NaO_4$ [M+Na]$^+$: 287.1254, found 287.1256

Rf: 0.26 in a 70:30 mixture of pentane and ethyl acetate

$[α]_D^{23}$: + 1.5° (c = 1.00, CHCl$_3$)

Experimental Section
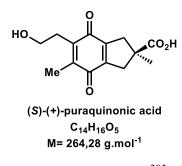
(*S*)-(+)-puraquinonic acid:

Title compound was made following a procedure of Yakura.[231] In a round-bottom flask equipped with a condenser, **3.57** (66 mg, 0.25 mmol) and LiOH (157 mg, 3.75 mmol, 15 equiv) in 1,4-dioxane/H_2O (1:1, 6 mL) were refluxed for 1.5 h. After this period, the mixture was acidified with 1 M HCl and extracted three times with EtOAc (15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was diluted in a mixture of 2,2,2-trifluoroethanol/H_2O (1:2, 3 mL). Then Oxone (305 mg, 0.992 mmol, 4 equiv) and 4-iodophenoxyacetic acid (7.0 mg, 24.8 μmol, 10 mol %) were added at room temperature. The reaction mixture was stirred until total consumption of starting material (approximately 1 h), then EtOAc and water were added (5 mL each). The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography using DCM/MeOH (93:7) leading to **(*S*)-(+)-puraquinonic acid** (54.0 mg, 0.204 mmol, 82% over two steps) as a yellow oil. Racemic material was prepared using the same procedure from racemic **3.57** (29.2 mg, 0.110 mmol), LiOH (39.7 mg, 1.66 mmol, 15 equiv), Oxone (135.8 mg, 0.442 mmol, 4 equiv) and 4-iodophenoxyacetic acid (3.1 mg, 11.0 μmol, 10 mol %) to yield racemic **puraquinonic acid** (25.1 mg, 0.095 mmol, 86%)

(*S*)-(+)-puraquinonic acid
$C_{14}H_{16}O_5$
M= 264,28 g.mol^{-1}
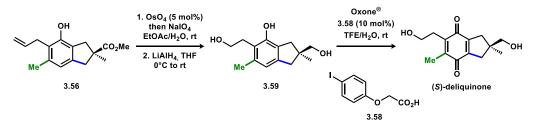
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 3.76 (t, *J* = 6.4 Hz, 2H), 3.41-3.34 (m, 2H), 2.79 (t, *J* = 6.4 Hz, 2H), 2.77-2.71 (m, 2H), 2.07 (s, 3H), 1.42 (s, 3H)

^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) 186.4, 185.9, 181.7, 145.9, 145.5, 143.0, 141.5, 61.6, 47.1, 42.5, 42.4, 30.0, 25.8, 12.4

Spectroscopic data are consistent with those previously reported for synthetic material.[205]
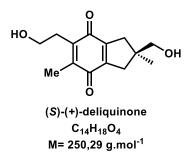
IR (neat): ν (cm^{-1}) 3394, 2925, 1706, 1221, 1172, 1103, 914

HRMS (ESI): Calcd for $C_{14}H_{16}NaO_5$ [M+Na]$^+$: 287.0890, found 287.0891

Rf: 0.12 in a 95:5 mixture of DCM and methanol

$[α]_D^{23}$: + 1.4° (c = 0.50, $CHCl_3$)

Experimental Section

Reported value for the natural material (R): $[\alpha]_D^{22}$: - 2.2° (c = 0.55, CHCl$_3$)[205]

(S)-(+)-deliquinone:

In a round-bottom flask containing a stirred biphasic solution of **3.56** (114 mg, 0.438 mmol) in EtOAc (14 mL) and water (7 mL) was added OsO$_4$ (5.57 mg, 21.9 μmol, 5 mol %). After 5 min, NaIO$_4$ (234 mg, 1.10 mmol, 2.5 equiv) was added in two portions separated by 5 min. The solution was vigorously stirred for 3 h at room temperature. The layers were separated and the aqueous layer was extracted twice with EtOAc (8 mL). The combined organic layers were dried over MgSO$_4$, filtered and concentrated under reduced pressure. The crude material was diluted in dry THF (10 mL) and cooled to 0 °C. After this, LiAlH$_4$ (49.9 mg, 1.31 mmol, 3 equiv) was added and the reaction was allowed to reach room temperature. After 1 h, H$_2$O was added and the reaction was extracted three times with ethyl acetate (8 mL). The combined organic phases were dried over MgSO$_4$, filtered and concentrated under reduced pressure. Then, the crude material was diluted in a mixture of 2,2,2-trifluoroethanol/H$_2$O (1:2, 9 mL). Then Oxone (541 mg, 1.76 mmol, 4 equiv) and 4-iodophenoxyacetic acid (12.2 mg, 44.0 μmol, 10 mol %) were added at room temperature. The reaction mixture was stirred until total consumption of the starting material (approximately 1 h), and then EtOAc and water were added (10 mL each). The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over MgSO$_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography using DCM/ MeOH (93:7) leading to **(S)-(+)-deliquinone** (62.7 mg, 0.276 mmol, 62% over two steps) as a yellow oil. Racemic material was prepared using the same procedure from racemic **3.56** (220 mg, 0.845 mmol), OsO$_4$ (11.1 mg, 43.7 μmol, 5 mol %), NaIO$_4$ (450 mg, 2.10 mmol, 2.5 equiv), LiAlH$_4$ (98.0 mg, 2.58 mmol, 3 equiv), Oxone (1,04 g, 3.38 mmol, 4 equiv) and 4-iodophenoxyacetic acid (22.1 mg, 84.5 μmol, 10 mol %) to yield racemic **deliquinone** (153 mg, 0.647 mmol, 76%)

Experimental Section

(S)-(+)-deliquinone
$C_{14}H_{18}O_4$
M= 250,29 g.mol⁻¹

¹H NMR (500 MHz, CDCl₃): δ (ppm) 3.74 (t, *J* = 6.5 Hz, 2H), 3.49 (s, 2H), 2.87-2.80 (m, 2H), 2.78 (t, *J* = 6.5 Hz, 2H), 2.53-2.47 (m, 2H), 2.06 (s, 3H), 1.75 (brs, 1H), 1.69 (brs, 1H), 1.16 (s, 3H)

¹³C NMR (126 MHz, CDCl₃): δ (ppm) 187.0, 186.4, 147.2, 146.8, 142.8, 141.4, 70.2, 61.7, 43.0, 40.8, 40.7, 30.1, 25.0, 12.3

Spectroscopic data are consistent with those previously reported for natural material.[194]

IR (neat): ν (cm⁻¹) 3395, 2925, 1644, 1249, 1033
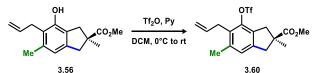
HRMS (ESI): Calcd for $C_{14}H_{18}NaO_4$ [M+Na]⁺: 273.1097, found 273.1095

Rf: 0.28 in a 95:5 mixture of DCM and methanol

[α]²³_D: + 0.9° (c = 1.00, CHCl3)

Reported value for the natural material (R): **[α]²²_D**: - 0.5° (c = 0.6, CHCl3)[194]

Methyl (S)-5-allyl-2,6-dimethyl-4-(((trifluoromethyl)sulfonyl)oxy)-2,3-dihydro-1H-indene-2-carboxylate (3.60):

To a solution of **3.56** (58.1 mg, 0.223 mmol) in DCM (1.2 mL), pyridine (54 µL, 0.669 mmol, 3 equiv) and trifluoromethanesulfonic anhydride (41 µL, 0.245 mmol, 1.1 equiv) were added. The reaction mixture was stirred at room temperature during 6 h. The reaction was then concentrated and purified by flash column chromatography to yield **3.60** (80.9 mg, 0.206 mmol, 93%) as a colorless liquid. Racemic material was prepared using the same procedure from racemic **3.56** (50 mg, 0.192 mmol), pyridine (47 µL, 0.576 mmol, 3 equiv) and trifluoromethanesulfonic anhydride (36 µL, 0.211 mmol, 1.1 equiv) to yield racemic **3.60** (87.1 mg, 0.167 mmol, 87%).

3.60
$C_{17}H_{19}F_3O_5S$
M= 392,39 g.mol⁻¹
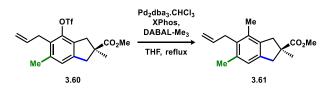
¹H NMR (500 MHz, CDCl₃): δ (ppm) 7.03 (s, 1H), 5.83 (ddt, *J* = 17.1, 10.1, 5.8 Hz, 1H), 5.04 (dq, *J* = 10.1, 1.7 Hz, 1H), 4.89 (dq, *J* = 17.1, 1.7 Hz, 1H), 3.72 (s, 3H), 3.54 (d, *J* = 16.3 Hz, 1H), 3.49 (d, *J* = 16.1 Hz, 1H), 3.45 (dt, *J* = 5.8, 1.7 Hz, 2H), 2.95 (d, *J* = 16.3 Hz, 1H), 2.82 (d, *J* = 16.1 Hz, 1H), 2.30 (s, 2H), 1.37 (s, 3H)

¹³C NMR (126 MHz, CDCl₃): δ (ppm) 177.3, 144.3, 142.9, 139.0, 134.4, 132.0, 129.2, 126.7, 118.7 (q, *J* = 319.8 Hz), 116.0, 52.4, 50.1, 44.1, 41.9, 31.2, 25.0, 19.9

Experimental Section

¹⁹F NMR (376 MHz, CDCl₃) δ (ppm) -73.8

IR (neat): ν (cm⁻¹) 2955, 1735, 1405, 1206, 1137, 817

HRMS (ESI): Calcd for $C_{17}H_{19}F_3NaO_5S$ [M+Na]⁺: 415.0798, found 415.0795

Rf: 0.25 in a 95:5 mixture of pentane and ethyl acetate

[α]$_D^{23}$: + 4.0° (c = 1.09, CHCl₃)

Methyl (*S*)-5-allyl-2,4,6-trimethyl-2,3-dihydro-1*H*-indene-2-carboxylate (3.61):

Title compound was made following a procedure of Woodward.[232] In an oven dry catalysis tube, **3.60** (80 mg, 0.204 mmol) was introduced. Then the tube was transferred in a glovebox, and [Pd₂dba₃·CHCl₃] (5.3 mg, 5.1 μmol, 2.5 mol %) and XPhos (5.0 mg, 10.2 μmol, 5 mol %) were introduced, and the tube was closed with a septum. Outside of the glovebox, THF (2.5 mL) and DABAL-Me₃ (41.8 mg, 0.163 mmol, 0.8 equiv, as a solution in 0.8 mL of THF) were added. The septum was rapidly exchanged for a screw cap. The tube was then introduced in a 75 °C preheated aluminum heating block and stirred at this temperature for 4 h. After this period the reaction was cooled to room temperature, quenched with 2 M HCl (2 mL), and extracted three times with diethyl ether (3 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography to yield **3.61** as a colorless liquid (51.7 mg, 0.200 mmol, 98%). Racemic material was prepared using the same procedure from racemic **3.60** (50.2 mg, 0.128 mmol), [Pd₂dba₃·CHCl₃] (3.3 mg, 3.2 μmol, 2.5 mol %), XPhos (3.2 mg, 6.4 μmol, 5 mol %) and DABAL-Me₃ (26.3 mg, 0.102 mmol, 0.8 equiv) to yield racemic **3.61** (32.4 mg, 0.167 mmol, 98%).

3.61
$C_{17}H_{22}O_2$
M= 258,36 g.mol⁻¹
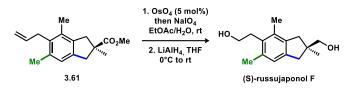
¹H NMR (500 MHz, CDCl₃): δ (ppm) 6.88 (s, 1H), 5.88 (ddt, *J* = 17.1, 10.1, 5.7 Hz, 1H), 4.99 (dq, *J* = 10.1, 1.8 Hz, 1H), 4.88 (dq, *J* = 17.1, 1.8 Hz, 1H), 3.72 (s, 3H), 3.46 (d, J = 15.9 Hz, 1H), 3.40 (d, *J* = 15.9 Hz, 1H), 3.38 (dt, *J* = 5.7, 1.8 Hz, 3H), 2.79 (d, *J* = 15.9 Hz, 1H), 2.78 (d, *J* = 15.9 Hz, 1H), 2.27 (s, 3H), 2.18 (s, 3H), 1.37 (s, 3H)
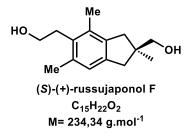
¹³C NMR (126 MHz, CDCl₃): δ (ppm) 178.5, 138.8, 138.3, 135.8, 135.3, 134.3, 132.7, 124.0, 114.9, 52.2, 49.1, 44.3, 43.7, 33.7, 25.8, 20.3, 16.0

Experimental Section

IR (neat): ν (cm^{-1}) 2931, 1732, 1208, 1112, 911

HRMS (ESI): Calcd for C$_{17}$H$_{22}$NaO$_2$ [M+Na]$^+$: 281.1512, found 281.1508

Rf: 0.33 in a 95:5 mixture of pentane and ethyl acetate

[α]$_D^{23}$: + 9.4° (c = 1.05, CHCl$_3$)

(*S*)-(+)-russujaponol F:

In a round-bottom flask containing a stirred biphasic solution of **3.61** (51.7 mg, 0.200 mmol) in EtOAc (4 mL) and water (2 mL) was added OsO$_4$ (2.5 mg, 10.0 μmol, 5 mol %). After 5 min, NaIO$_4$ (107 mg, 0.500 mmol, 2.5 equiv) was added in two portions separated by 5 min. The solution was vigorously stirred for 3 h at room temperature. The layers were separated and the aqueous layer was extracted twice with EtOAc (5 mL). The combined organic layers were dried over MgSO$_4$, filtered and concentrated under reduced pressure. The crude material was diluted in dry THF (5 mL) and cooled to 0 °C. After this, LiAlH$_4$ (22.8 mg, 0.600 mmol, 3 equiv) was added and the reaction was allowed to reach room temperature overnight. After this period, H$_2$O was added and the reaction was extracted three times with ethyl acetate (5 mL). The combined organic phases were dried over MgSO$_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography to yield **(*S*)-(+)-russujaponol F** as a colorless oil (39.8 mg, 0.170 mmol, 85%). Racemic material was prepared using the same procedure from racemic **3.61** (20.5 mg, 0.079 mmol), OsO$_4$ (1.0 mg, 4.0 μmol, 5 mol %), NaIO$_4$ (42.5 mg, 0.199 mmol, 2.5 equiv) and LiAlH$_4$ (9.1 mg, 0.238 mmol, 3 equiv) to yield racemic **russujaponol F** (16.2 mg, 0.069 mmol, 87%).

^{1}H NMR (400 MHz, C$_5$D$_5$N): δ (ppm) 6.90 (s, 1H), 5.76 (bs, 2H), 3.99 (t, *J* = 7.6 Hz, 2H), 3.75 (s, 2H), 3.18 (d, *J* = 15.9 Hz, 1H), 3.15 (t, *J* = 7.6 Hz, 2H), 3.09 (d, *J* = 15.8 Hz, 1H), 2.71 (d, *J* = 15.8 Hz, 1H), 2.60 (d, *J* = 15.9 Hz, 1H), 2.37 (s, 3H), 2.24 (s, 3H), 1.35 (s, 3H)

^{13}C NMR (126 MHz, C$_5$D$_5$N): δ (ppm) 140.9, 140.7, 135.3, 134.1, 133.3, 125.0, 70.3, 62.0, 45.4, 43.9, 43.1, 34.5, 25.6, 20.9, 16.5

Spectroscopic data are consistent with those previously reported for natural material.[195]

Experimental Section

^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 6.86 (s, 1H), 3.74 (t, J = 7.5 Hz, 2H), 3.52 (s, 2H), 2.95 (t, J = 7.5 Hz, 2H), 2.88 (d, J = 16.0 Hz, 1H), 2.84 (d, J = 16.0 Hz, 1H), 2.63 (d, J = 16.0 Hz, 1H), 2.59 (d, J = 16.0 Hz, 1H), 2.32 (s, 3H), 2.22 (s, 3H), 1.18 (s, 3H)

^{13}C NMR (126 MHz, CDCl$_3$): δ (ppm) 140.3, 139.8, 135.3, 133.2, 132.3, 124.4, 71.1, 62.1, 44.3, 43.1, 42.4, 32.9, 24.6, 20.5, 16.2

IR (neat): ν (cm^{-1}) 3313, 2920, 2867, 1460, 1037
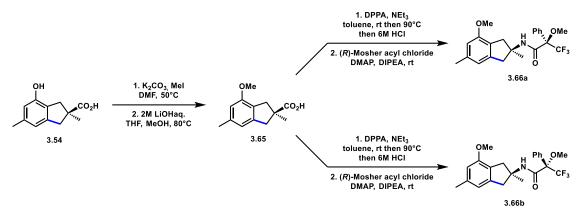
HRMS (ESI): Calcd for C$_{15}$H$_{22}$NaO$_2$ [M+Na]$^+$: 257.1512, found 257.1514

Rf: 0.23 in a 50:50 mixture of pentane and ethyl acetate

[α]$_D^{23}$: + 1.0° (c = 1.07, CHCl$_3$)

[α]$_D^{20}$: + 2.1° (c = 0.53, MeOH)
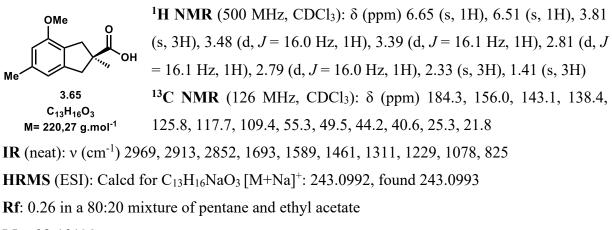
Reported value for the natural material (S): **[α]$_D^{25}$**: + 1.3° (c = 3.1, MeOH)[195]

Experimental Section

6.3.6. Determination of Configuration - VCD and NOESY

(S)-4-methoxy-2,6-dimethyl-2,3-dihydro-1H-indene-2-carboxylic acid (3.65):

3.54 (120 mg, 0.58 mmol) was dissolved in DMF (5 mL) and K_2CO_3 (401 mg, 2.9 mmol, 5 equiv) was added, the mixture was then stirred during 5 min at room temperature. After this period, methyl iodide (0.18 mL, 2.9 mmol, 5 equiv) was added in one portion and the reaction was stirred at 50°C during 2h. The reaction was then diluted with water, extracted with EtOAc and concentrated to yield 11', which was used in the next step without further purification. 11' was dissolved in a mixture of THF (1.5 mL), MeOH (1.5 mL) and 2M aqueous LiOH (1.5 ml). The reaction was then heat at 80°C for 6 hours. After cooling to room temperature, the organic solvents were removed under reduced pressure. The obtained aqueous solution was washed with diethyl ether, acidified to pH<0 and extracted three times with DCM. The combined organic layers were then dry over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography to yield the corresponding pure **3.65** (105 mg, 0.48 mmol, 82%) as a white solid.

3.65

$C_{13}H_{16}O_3$

M= 220,27 g.mol^{-1}

[1H] NMR (500 MHz, CDCl$_3$): δ (ppm) 6.65 (s, 1H), 6.51 (s, 1H), 3.81 (s, 3H), 3.48 (d, J = 16.0 Hz, 1H), 3.39 (d, J = 16.1 Hz, 1H), 2.81 (d, J = 16.1 Hz, 1H), 2.79 (d, J = 16.0 Hz, 1H), 2.33 (s, 3H), 1.41 (s, 3H)

[13C] NMR (126 MHz, CDCl$_3$): δ (ppm) 184.3, 156.0, 143.1, 138.4, 125.8, 117.7, 109.4, 55.3, 49.5, 44.2, 40.6, 25.3, 21.8

IR (neat): ν (cm^{-1}) 2969, 2913, 2852, 1693, 1589, 1461, 1311, 1229, 1078, 825

HRMS (ESI): Calcd for $C_{13}H_{16}NaO_3$ [M+Na]$^+$: 243.0992, found 243.0993

Rf: 0.26 in a 80:20 mixture of pentane and ethyl acetate

Mp: 98-101°C

[α]$_D^{20}$: + 3.6° (c = 0.38, CHCl$_3$)

Experimental Section

VCD experiments:

IR and vibrational circular dichroism (VCD) spectra were recorded on a Bruker PMA 50 accessory coupled to a Tensor 27 Fourier transform infrared spectrometer. A photoelastic modulator (Hinds PEM 90) set at l/4 retardation was used to modulate the handedness of the circular polarized light. Demodulation was performed by a lock-in amplifier (SR830 DSP). An optical low-pass filter (< 1800 cm^{-1}) in front of the photoelastic modulator was used to enhance the signal/noise ratio. A solution of 8 mg in 200 µl CDCl$_3$ of 12b was prepared and measured in a transmission cell equipped with CaF$_2$ windows and a 200 mm spacer. The VCD spectrum of the pure solvent served as the reference and was subtracted from the VCD spectrum of the compound in order to eliminate artefacts. For both the sample and the reference, ca. 40'000 scans at 4 cm^{-1} resolution were averaged.

Calculations:

Density functional theory (DFT) as implemented in Gaussian09 was used to study the conformation and to calculate the corresponding IR and VCD spectra. The calculations were performed using the b3pw91 functional and a 6-31+G(d,p) basis set. The solvent was considered with a polarizable continuum model for chloroform, as implemented in Gaussian09, Revision C.01. Prior to the calculation of the spectra all degrees of freedom were completely relaxed. IR and VCD spectra were constructed from calculated dipole and rotational strengths assuming Gaussian band shape with a half-width at half-maximum of 4 cm^{-1}. Frequencies were scaled by a factor of 0.97. To calculate the Boltzmann distribution of the different conformers a thermal free energy correction was applied.
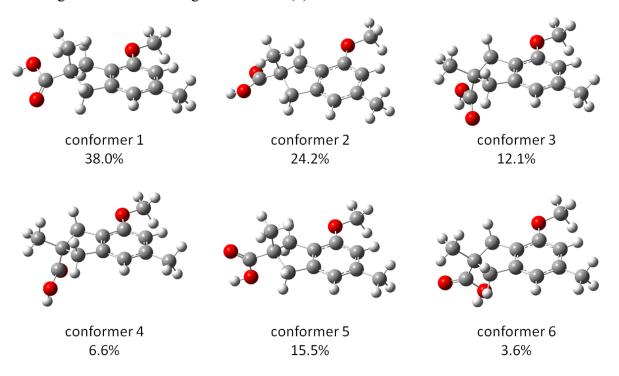
Conformational search:

A systematic conformation search of **3.65** was done. Conformational degrees of freedom are the orientation of the methyl group (methoxy), the orientation of the acid group and the five-membered ring, which is not planar. For the methoxy group only one conformation was considered because the other conformations are high up in energy and therefore not populated at room temperature. In total six conformers were found (**Figure 6.1**) differing in the orientation of the acid group and the conformation at the five-membered ring.

Assignment of absolute configuration:

As is evident from the comparison of the calculated VCD spectra of the individual conformers (**Figure 6.4**) the sign of many bands depends on the conformation. Therefore, the calculated

Experimental Section

VCD spectrum depends on the Boltzmann weights and hence the relative free energy of the conformers, which is challenging to calculate accurately. However, there are some bands that have the same sign for all conformers (marked in **Figure 6.4** and **Figure 6.5**). Based on these bands and the overall shape of the VCD spectrum the absolute configuration can be assigned. The comparison between experiment and calculations show that the sample analyzed has the same absolute configuration as the enantiomer considered in the calculations. Therefore, we can assign the absolute configuration as the (*S*)-enantiomer.

conformer 1
38.0%

conformer 2
24.2%

conformer 3
12.1%

conformer 4
6.6%

conformer 5
15.5%

conformer 6
3.6%

*Figure 6.1. Six conformers of **3.65** found by the systematic conformational search. The numbers show the fractions of the respective conformer according to a Boltzmann distribution at room temperature.*
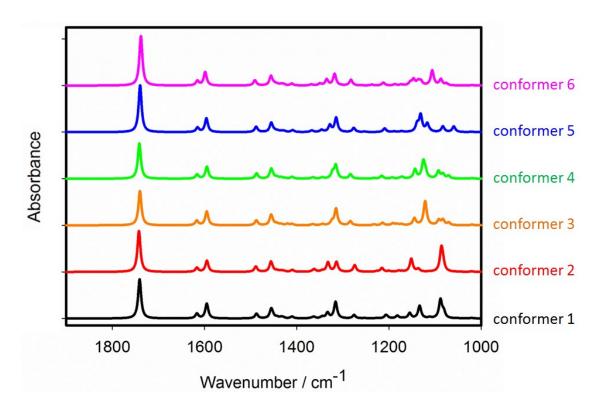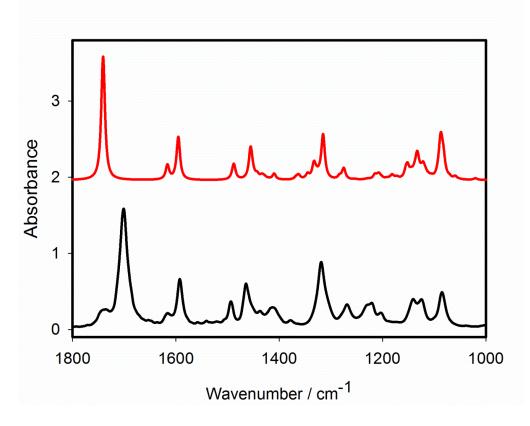
Figure 6.2. *Calculated infrared spectra for the six conformers. Frequencies are scaled by 0.97.*

Figure 6.3. *Comparison between experimental (black) and calculated (red) infrared spectra of **3.65**. The calculated spectrum is the linear combination (Boltzmann weighted) of the spectra of the conformers. Frequencies are scaled by 0.97 for the calculated spectrum.*

Experimental Section
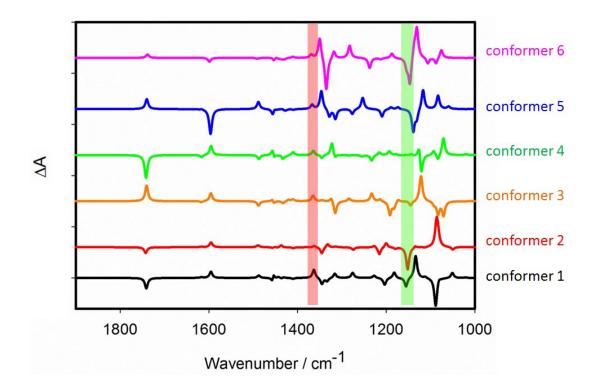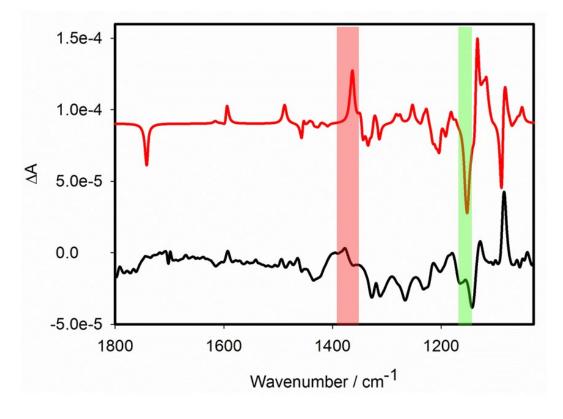
Figure 6.4. *Calculated VCD spectra for the six conformers. Frequencies are scaled by 0.97. The green and red areas mark bands that show the same sign for all conformers. These bands are particularly meaningful for the assignment of the absolute configuration because the sign does not depend on distribution of conformers (Boltzmann factors).*
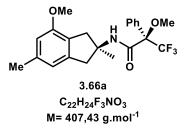
Figure 6.5. *Comparison between experimental (black) and calculated (red) VCD spectra of **3.65**. The calculated spectrum is the linear combination (Boltzmann weighted) of the spectra of the conformers. Frequencies are scaled by 0.97 for the calculated spectrum. The green and red areas mark bands that show the same sign for all conformers (see **Figure 6.4**).*

Experimental Section

(*R*)-3,3,3-trifluoro-2-methoxy-*N*-((*S*)-4-methoxy-2,6-dimethyl-2,3-dihydro-1*H*-inden-2-yl)-2-phenylpropanamideacid (3.66a) and (*S*)-3,3,3-trifluoro-2-methoxy-*N*-((*S*)-4-methoxy-2,6-dimethyl-2,3-dihydro-1*H*-inden-2-yl)-2-phenylpropanamideacid (3.66b):

3.65 (100 mg, 0.46 mmol) was suspended in toluene (4.0 mL). Triethylamine (77 µL, 0.552 mmol, 1.2 equiv) was added, followed by the addition of diphenylphosphonic azide (103 µL, 0.46 mmol, 1 equiv). The mixture was stirred at room temperature for 2 hours. Then the mixture was heated at 90°C for 1 hour. The mixture was cooled down and poured into ice-cold 6M aqueous HCl (4 mL) and stirred overnight. The aqueous layer was collected, cooled down at 0°C, basified with 2M NaOH, and extracted three times with DCM (5 mL). The combined organic phases were dried over MgSO$_4$, filtered and concentrated under reduced pressure to give the corresponding crude amine (60.1 mg, 0.314 mmol, 68%). After NMR analysis, the crude amine was considered enough pure to be engaged in the next step.

(*R*)- or (*S*)-Mosher acid (16.7 mg, 0.072 mmol, 1.1 equiv) was dissolved in dry DCM (0.85 mL), then oxalyl chloride (7 µL, 0.075 mmol, 1.15 equiv) was added, follow by one drops of a 10% solution of DMF in DCM to initiate the reaction. After 1 hour of stirring at room temperature, crude amine (12.4 mg, 0.065 mmol), NEt$_3$ (34 µL, 0.195 mmol, 3 equiv) and a crystal of DMAP were added. The mixture was stirred for 16 hours at room temperature. The reaction was then concentrated under reduced pressure and purified by flash column chromatography to yield the corresponding pure **3.66a** (15.6 mg, 0.038 mmol, 59%) and **3.66b** (18.9 mg, 0.046 mmol, 71%) amides as colorless waxes.

3.66a
C$_{22}$H$_{24}$F$_3$NO$_3$
M= 407,43 g.mol^{-1}

^{1}H NMR (600 MHz, CDCl$_3$): δ (ppm) 7.54-7.49 (m, 2H), 7.41-7.36 (m, 3H), 6.84 (s, 1H), 6.63 (s, 1H), 6.50 (s, 1H), 3.79 (s, 3H), 3.35 (d, *J* = 16 Hz, 1H), 3.35-3.34 (m, 3H), 3.11 (d, *J* = 16.0 Hz, 1H), 3.05 (d, *J* = 16.0 Hz, 1H), 3.01 (d, *J* = 16.0 Hz, 1H), 2.32 (s, 3H), 1.55 (s, 3H)
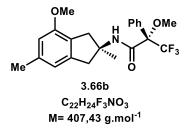
^{13}C NMR (126 MHz, CDCl$_3$): δ (ppm) 165.9, 156.0, 143.0, 138.4, 133.1, 129.5, 128.6, 127.7, 125.1, 124.0 (q, *J* = 290.0 Hz), 117.8, 109.5, 84.1 (q, *J* = 25.8 Hz), 61.5, 55.3, 55.0, 46.3, 43.2, 29.9, 25.7, 21.9

^{19}F NMR (376 MHz, CDCl$_3$): δ (ppm) -68.8

IR (neat): ν (cm^{-1}) 3415, 2926, 2848, 1694, 1510, 1159, 1081, 833

HRMS (ESI): Calcd for C$_{22}$H$_{24}$F$_3$NNaO$_3$ [M+Na]$^+$: 430.1600, found 430.1601

Rf: 0.32 in a 90:10 mixture of pentane and ethyl acetate

[α]$_D^{20}$: + 24.2° (c = 0.13, CHCl$_3$)

Experimental Section

3.66b
C$_{22}$H$_{24}$F$_3$NO$_3$
M= 407,43 g.mol^{-1}

^{1}H NMR (600 MHz, CDCl$_3$): δ (ppm) 7.51-7.47 (m, 2H), 7.40-7.34 (m, 3H), 6.87 (s, 1H), 6.62 (s, 1H), 6.50 (s, 1H), 3.79 (s, 3H), 3.37-3.35 (m, 3H), 3.31 (d, J = 16.0 Hz, 1H), 3.15 (d, J = 16.0 Hz, 1H), 3.03 (d, J = 16.0 Hz, 1H), 3.02 (d, J = 16.0 Hz, 1H), 2.33 (s, 3H), 1.56 (s, 3H)

^{13}C NMR (126 MHz, CDCl$_3$): δ (ppm) 165.8, 156.0, 142.9, 138.4, 133.0, 129.5, 128.6, 127.8, 125.2, 124.0 (q, J = 289.9 Hz), 117.8, 109.5, 84.1 (q, J = 25.9 Hz), 61.4, 55.3, 55.0, 46.2, 43.2, 25.9, 21.8.

^{19}F NMR (376 MHz, CDCl$_3$): δ (ppm) δ -68.8
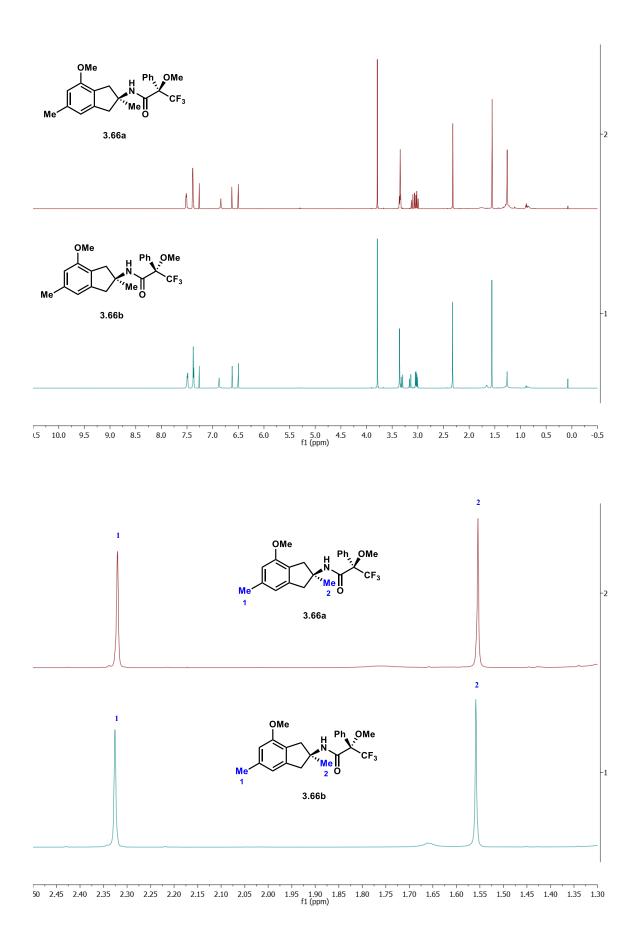
IR (neat): ν (cm^{-1}) 3416, 2926, 2847, 1694, 1509, 1158, 1081, 833
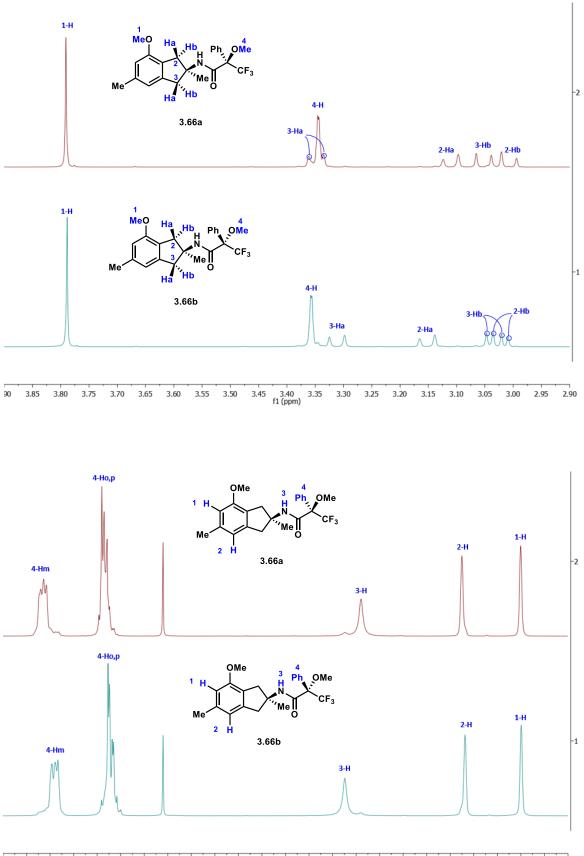
HRMS (ESI): Calcd for C$_{22}$H$_{24}$F$_3$NNaO$_3$ [M+Na]$^+$: 430.1600, found 430.1600

Rf: 0.32 in a 90:10 mixture of pentane and ethyl acetate

[α]$_D^{20}$: + 9.4° (c = 0.18, CHCl$_3$)

NOESY NMR Analysis:

Experimental Section
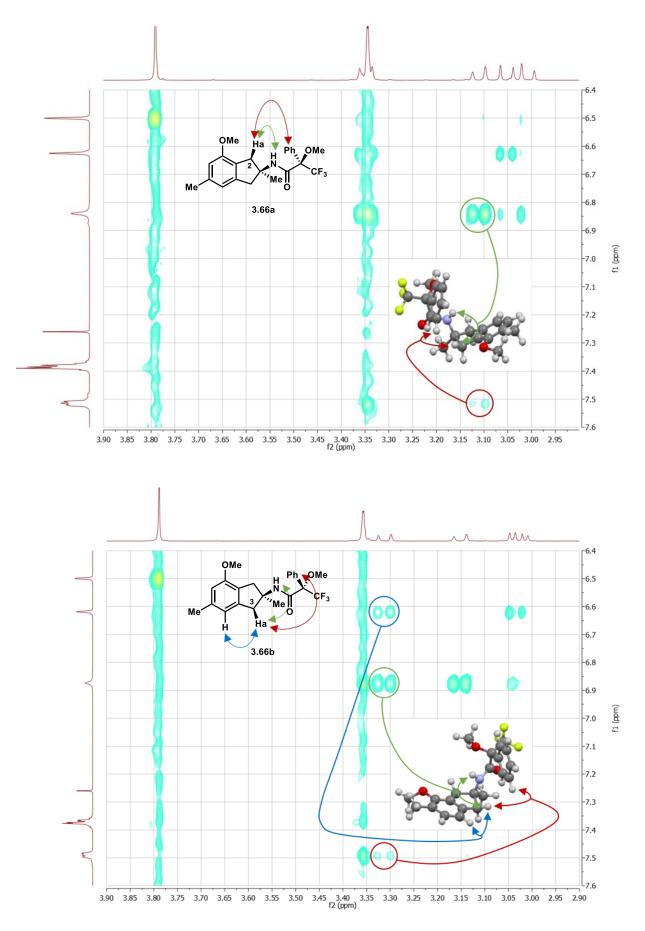
Figure 6.6. *NOESY of Mosher amide.*

Experimental Section

For **3.66a**, a correlation between the benzylic proton 2-Ha (identified by its correlation with the NH and the absence of correlation with the aromatic proton) and the meta proton of the phenyl group of the mosher amide part can be observed.

In the case of **3.66b**, a similar correlation can be observed between the benzylic proton 3-Ha (identified by its correlation with the NH and the aromatic proton) and the meta proton of the phenyl group of the mosher amide.

Precedent calculations on Mosher amides[241] indicate that the more stable conformer of such amides shows a synperiplanar relationship between the CF_3 and the carbonyl groups.

This indicates that the quaternary stereocenter constructed during the enantioselective $C(sp^3)$-H arylation step has the (*S*) configuration.

Experimental Section

Experimental Section

Experimental Section

6.4. Chapter 4
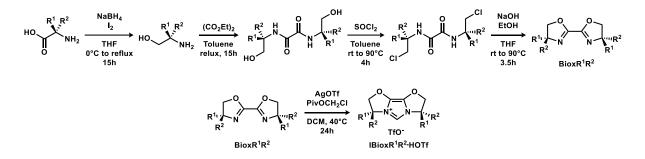
6.4.1. Ligands

For TADDOL phosphoramidite/phosphonite ligands:

4.17 was previously prepared as reported.[238,239]

For C$_2$ symetrical Herrmann-Kundig type NHCs:

All IBiox-type ligands were prepared as reported[210,211,215,216] from different amino acids according to the following sequence:

General procedure I: reduction of the amino acids

the amino acid (1 equiv), and NaBH$_4$ (3 equiv), and THF (4 mL/mmol of amino acid) were added to a dry round-bottom flask and cooled to 0 °C. A solution I$_2$ (1 equiv) in THF (2 mL/mmol of I$_2$) was added dropwise, allowing the mixture to turn white after each drop. Following the addition, the mixture was heated to reflux for 15 hours. The reaction mixture was then cooled to 0 °C and quenched slowly with MeOH. The solvents were removed in vacuo, and the remaining solid was dissolved in 20% aqueous solution of KOH and stirred at 50 °C for 1.5 hours. The mixture was cooled to room temperature, extracted with EtOAc, and the combined organic extracts were dried over MgSO$_4$ and filtered. The solvent was removed in vacuo, and the crude material aminoalcohol taken forward.

General procedure J: bisoxazoline synthesis

Aminoalcohol (2.1 equiv) and diethyloxalate (1.0 equiv) were stirred at reflux in toluene (2.5 mL/mmol of aminoalcohol) overnight. The reaction was then concentrated. The obtained solid was washed with petroleum ether and dried to afford the desired oxalamide which was used without further purification. SOCl$_2$ (2.9 equiv) was added to a suspension of the previously obtained oxalamide (1 equiv) in toluene (10 mL/mmol of oxalamide) at 60 °C. The solution

Experimental Section

was stirred at this temperature for 1 h and then 3 h at 90 °C. After this time, the reaction was quenched with methanol and concentrated. The residue was taken in DCM and vigorously washed with a 20% (w/v) aqueous solution of KOH. Layers were separated and the aqueous layer was extracted with DCM. The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated to yield the desired chlorooxalamide taken forward. To a solution of the previously obtained chlorooxalamide (1 equiv) in THF (20 mL/mmol of chlorooxalamide) a solution of NaOH (2.1 equiv) in ethanol (3 mL/mmol of NaOH) was added. After stirring at ambient temperature for 30 min the mixture was heated at 90 °C for 3 h. The solvent was evaporated, and the residue taken up in MTBE, washed with a saturated aqueous solution of Na_2CO_3 and dried over $MgSO_4$. After concentration, the crude was purified by flash column chromatography (cyclohexane/EtOAc) to yield the desired bisoxazoline.
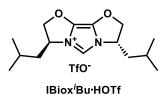
General procedure K: cyclization for NHC formation

To a suspension of AgOTf (1.45 equiv) in DCM (4.5 mL/mmol of bisoxazoline) was added chloromethyl pivalate (1.45 equiv) and the resulting suspension was stirred for 45 min in the dark. The supernatant was transferred via syringe to the bioxazoline (1 equiv) and the resulting solution was stirred in a sealed tube in the dark at 40 °C for 24 h. After the solution was cooled to room temperature, the solvent was evaporated in vacuo. The resulting oil was chromatographed on silica gel (DCM/MeOH) to afford the corresponding IBiox·HOTf.

All described compounds shown spectroscopic data in accordance with reported ones.

Here is the data of new bisoxazolines and IBiox NHC:

($3S$,$7S$)-3,7-diisobutyl-2,3,7,8-tetrahydroimidazo[4,3-b:5,1-b']bis(oxazole)-4-ium triflate (IBiox^{i}Bu·HOTf):

From **Biox^{i}Bu** (obtained from **_L_-leucine** using **General procedures I and J**) using **General procedures K. IBiox^{i}Bu·HOTf** was obtained as a wax (178 mg, 0.43 mmol, 15%).

IBiox^{i}Bu·HOTf
$C_{16}H_{25}F_3N_2O_5S$
M= 414,44 g.mol^{-1}

^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 8.57 (s, 1H), 5.15 (dd, J = 8.8, 7.4 Hz, 2H), 4.98-4.92 (m, 2H), 4.66 (dd, J = 8.8, 6.2 Hz, 2H), 2.10-2.02 (m, 2H), 1.76-1.66 (m, 4H), 1.00 (d, J = 6.4 Hz, 6H), 1.00 (d, J = 6.4 Hz, 6H)

^{13}C NMR (126 MHz, CDCl$_3$): δ (ppm) 125.7, 120.8 (q, J = 320.2 Hz), 115.3, 82.2, 58.0, 41.7, 25.3, 22.5, 22.2

^{19}F NMR (471 MHz, CDCl$_3$): δ (ppm) -78.4.
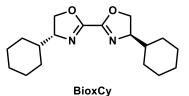
IR (neat): ν (cm^{-1}) 2962, 1731, 1525, 1469, 1253, 1153, 1028, 635.

Experimental Section

HRMS (ESI): Calcd for $C_{15}H_{25}N_2O_2^+$ [M]$^+$: 265.1911, found 265.1912

[α]$_D^{20}$: +51.8° (c = 0.75, CHCl$_3$)

(4*R*,4'*R*)-4,4'-dicyclohexyl-4,4',5,5'-tetrahydro-2,2'-bioxazole (BioxCy):

From ***D*-cyclohexylglycine** using **General procedures I and J**. **BioxCy·HOTf** was obtained as a white solid (2.91 g, 9.56 mmol, 72%).

BioxCy
C$_{18}$H$_{28}$N$_2$O$_2$
M= 304,22 g.mol^{-1}

^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 4.42 (dd, *J* = 9.8, 8.3 Hz, 2H), 4.14 (dd, *J* = 9.8, 8.3 Hz, 2H), 4.08 (td, *J* = 9.4, 6.7 Hz, 2H), 2.00-1.93 (m, 2H), 1.78-1.64 (m, 6H), 1.59-1.47 (m, 4H), 1.29-1.14 (m, 6H), 1.11-0.98 (m, 4H)

^{13}C NMR (126 MHz, CDCl$_3$): δ (ppm) 154.6, 72.4, 71.4, 42.5, 29.7, 29.1, 26.5, 26.4, 26.0.

IR (neat): ν (cm^{-1}) 3285, 2922, 2851, 1611, 1449, 1104, 949, 889, 719, 627

HRMS (ESI): Calcd for $C_{18}H_{28}NaO_2$ [M+Na]$^+$: 327.2043, found 327.2044
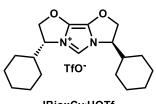
Rf: 0.63 in pure ethyl acetate

Mp: 104°C

[α]$_D^{20}$: +138 ° (c = 0.70, CHCl$_3$)

(3*R*,7*R*)-3,7-dicyclohexyl-2,3,7,8-tetrahydroimidazo[4,3-b:5,1-b']bis(oxazole)-4-ium triflate (IBioxCy·HOTf):

From **BioxCy** using **General procedures K. IBioxCy·HOTf** was obtained as a white solid (367 mg, 0.78 mmol, 24%).
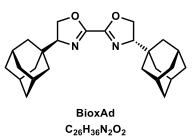
IBioxCy·HOTf
C$_{20}$H$_{29}$F$_3$N$_2$O$_5$S
M= 466,52 g.mol^{-1}

^{1}H NMR (250 MHz, CDCl$_3$): δ (ppm) 8.72 (s, 1H), 5.05 (dd, *J* = 10.1, 8.8 Hz, 2H), 4.91-4.80 (m, 4H), 2.03-1.89 (m, 2H), 1.87-1.66 (m, 9H), 1.36-1.09 (m, 9H), 1.04-0.86 (m, 2H)

^{13}C NMR (126 MHz, CDCl$_3$): δ (ppm) 125.8, 120.8 (q, *J* = 320.3 Hz), 116.4, 79.5, 63.8, 40.68, 28.3, 27.5, 25.8, 25.5, 25.4

^{19}F NMR (376 MHz, CDCl$_3$): δ (ppm) -78.5

IR (neat): ν (cm^{-1}) 2928, 2855, 1730, 1432, 1254, 1151, 1029, 635

HRMS (ESI): Calcd for $C_{19}H_{29}N_2O_2^+$ [M]$^+$: 317.2224, found 317.2219

Rf: 0.37 in a 95:5 mixture of DCM and methanol

Mp: 86°C

[α]$_D^{20}$: -67.2 ° (c = 0.93, CHCl$_3$)

Experimental Section

(4*S*,4'*S*)-4,4'-diadamantyl-4,4',5,5'-tetrahydro-2,2'-bioxazole (BioxAd):

From *L*-adamantylglycine (prepared as described in the literature[242]) using **General procedures I and J**. **BioxAd·HOTf** was obtained as a white solid (1.54 g, 3.77 mmol, 65%).

BioxAd
C₂₆H₃₆N₂O₂
M= 408,59 g.mol⁻¹

¹H NMR (500 MHz, CDCl₃): δ (ppm) 4.31 (dd, *J* = 9.9, 8.8 Hz, 2H) 4.29 (dd, *J* = 9.9, 8.8 Hz, 2H), 3.90 (t, *J* = 9.9 Hz, 2H), 2.02-1.97 (m, 6H), 1.74-1.63 (m, 18H), 1.46-1.40 (m, 6H)

¹³C NMR (126 MHz, CDCl₃): δ (ppm) 154.5, 77.0, 68.2, 38.7, 37.1, 35.6, 28.3

IR (neat): ν (cm⁻¹) 2899, 1614, 1449, 1114, 945, 870, 655

HRMS (ESI): Calcd for C₅₂H₇₂N₄O₄ [2M+Na]⁺: 839.5446, found 839.5447

Rf: 0.75 in pure ethyl acetate

Mp: 199-202°C
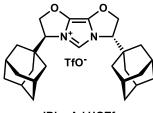
[α]²⁰_D: -159 ° (c = 0.68, CHCl₃)

(3*S*,7*S*)-3,7-diadamantyl-2,3,7,8-tetrahydroimidazo[4,3-b:5,1-b']bis(oxazole)-4-ium triflate (IBioxAd·HOTf):

From **BioxAd** using **General procedures K**. **IBioxAd·HOTf** was obtained as a white solid (1.45 g, 2.54 mmol, 65%).

IBioxAd·HOTf
C₂₈H₃₇F₃N₂O₅S
M= 570,67 g.mol⁻¹

¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.65 (s, 1H), 5.05 (dd, *J* = 9.4, 3.4 Hz, 2H), 4.99 (dd, *J* = 9.4, 7.5 Hz, 2H), 4.60 (dd, *J* = 7.5, 3.4 Hz, 2H), 2.13-2.07 (m, 6H), 1.77-1.64 (m, 18H), 1.57-1.49 (m, 6H)

¹³C NMR (126 MHz, CDCl₃): δ (ppm) 126.0, 120.8 (q, *J* = 320.1, Hz) 117.8, 77.5, 68.7, 37.6, 36.3, 35.8, 27.7

¹⁹F NMR (471 MHz, CDCl₃): δ (ppm) -78.4

IR (neat): ν (cm⁻¹) 2903, 2851, 1731, 1612, 1517, 1451, 1256, 1151, 1029, 635

HRMS (ESI): Calcd for C₂₇H₃₇N₂O₂⁺ [M]⁺: 421.2850, found 421.2847

Rf: 0.40 in a 95:5 mixture of DCM and methanol

Mp: 188°C

[α]²⁰_D: +69.7° (c = 0.34, CHCl₃)

Experimental Section

Pd(IBioxAd)(π-All)Cl:

In glovebox, [Pd(π- allyl)Cl]₂ (32 mg, 0.88 mmol, 1.0 equiv.), **IBioxAd·HOTf** (100 mg, 0.175 mmol, 2.0 equiv.) and sodium *tert*-butoxide (16.8 mg, 0.175 mmol, 2.0 equiv.) were placed into a dried catalysis tube. Dimethoxyethane (DME) (3.5 mL, freshly distilled over Na and benzophenone) was added and the mixture was stirred at rt for 24 h and then quenched with aqueous NH₄Cl and extracted with DCM. The combined organic phases were washed with water, brine, and dried over MgSO₄. The resulting crude product was purified by flash column chromatography (EtOAc/pentane) to give **Pd(IBioxAd)(π-All)Cl** as a white solid (82 mg, 0.136 mmol, 78%). This complex shown by 1H NMR to consist of a 1: 0.7 mixture of *endo*- and *exo*-isomers similarly to what was observed by Kündig for similar complexes.

Pd(IBioxAd)(π-All)Cl
$C_{30}H_{41}ClN_2O_2Pd$
M= 603,54 g.mol⁻¹

Description of major isomer:
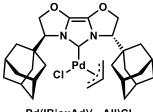
¹H NMR (600 MHz, CDCl₃): δ (ppm) 5.17-5.08 (m, 1H), 4.96 (d, J = 9.1 Hz, 1H), 4.85 (d, J = 9.0 Hz, 1H), 4.75 (dd, J = 9.0, 7.0 Hz, 1H), 4.69 (dd, J = 9.0, 7.0 Hz, 1H), 4.65 (d, J = 6.8 Hz, 1H), 4.09 (dd, J = 7.4, 1.9 Hz, 1H), 3.74 (d, J = 6.8 Hz, 1H), 3.37 (d, J = 6.7 Hz, 1H), 3.17 (d, J = 13.4 Hz, 1H), 2.48 (d, J = 11.6 Hz, 1H), 2.23-1.34 (m, 30H).

¹³C NMR (151 MHz, CDCl₃): δ (ppm) 158.4, 125.7, 125.4, 113.4, 77.0, 76.2, 70.5, 67.9, 66.0, 47.8, 38.9, 36.8, 36.7, 36.6, 36.5, 28.2, 28.2, 28.1, 27.1

IR (neat): ν (cm⁻¹) 2900, 2848, 1759, 1448, 1418, 1346, 1223, 1202, 913, 861

HRMS (ESI): Calcd for $C_{30}H_{41}ClN_2NaO_2Pd^+$ [M+Na]⁺: 625.1792, found 625.1772

HRMS (ESI): Calcd for $C_{30}H_{41}N_2O_2Pd^+$ [M-Cl]⁺: 567.2209, found 567.2201

Rf: 0.12 in a 75:25 mixture of pentane and ethyl acetate
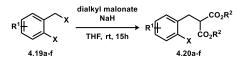
Mp: decomposition upon heating

[α]$_D^{20}$: +214.3° (c = 0.81, CHCl₃)

Experimental Section

6.4.2. Substrates

General procedure L: benzylation of dimethyl malonate

Dimethyl malonate (1.4 equiv) was diluted in THF (1 mL/mmol of dimethyl malonate) and added to a suspension of 100% sodium hydride (1.2 equiv) in THF (1 mL/mmol of sodium hydride) and the mixture was stirred for 30 min at room temperature. Then, a solution of the benzyl bromide (1.0 equiv) in THF (2 mL/mmol of benzyl halide) was added dropwise and the mixture was stirred overnight at room temperature. The reaction was then quenched by addition of H_2O and brine. The phases were separated, and the aqueous layer was extracted with diethyl ether. The combined organic phases were washed with brine and dried over Na_2SO_4. After evaporation of the volatiles the crude product was purified by distillation under high vacuum to yield the corresponding dimethyl benzylmalonate.

Dimethyl 2-(2-bromo-4-fluorobenzyl)malonate (4.20a):

From **dimethyl malonate** and **2-bromo-4-fluorobenzyl bromide** using **General procedures L. 4.20a** was obtained as a white solid (8.00 g, 25.08 mmol, 84%).

^1H NMR (500 MHz, CDCl$_3$): δ (ppm) 7.29 (dd, $^3J_{HF}$ = 8.2, 2.6 Hz, 1H), 7.22 (dd, J = 8.6, 6.0 Hz, 1H), 6.94 (ddd, J = 8.2, 8.3, 2.6 Hz, 1H), 3.83 (t, J = 7.8 Hz, 1H), 3.70 (s, 6H) 3.31 (d, J = 7.8 Hz, 2H)

^{13}C NMR (126 MHz, CDCl$_3$): δ (ppm) 169.0, 161.6 (d, J = 250.2 Hz), 133.0 (d, J = 3.6 Hz), 132.4 (d, J = 8.3 Hz), 124.5 (d, J = 9.5 Hz), 120.3 (d, J = 24.4 Hz), 114.7 (d, J = 20.9 Hz), 52.8, 51.4, 34.5

^{19}F NMR (471 MHz, CDCl$_3$): δ (ppm) -113.4

IR (neat): ν (cm^{-1}) 3007, 2955, 1731, 1596, 1277, 1226, 1153, 856, 777

HRMS (ESI): Calcd for $C_{12}H_{12}{}^{79}BrFNaO_4$ [M+Na]$^+$: 340.9795, found 340.9796

Rf: 0.17 in a 95:5 mixture of pentane and ethyl acetate

Mp: 61-62°C

Experimental Section

Dimethyl 2-(2-bromobenzyl)malonate (4.20b-Br):

From **dimethyl malonate** and **2-bromobenzyl bromide** using **General procedures L**. **4.20b-Br** was obtained as a colorless liquid (15.44 g, 51.27 mmol, 86%). The measured spectrometric data was in full accordance with the reported data.[243]

4.20b-Br
$C_{12}H_{13}BrO_4$
M= 301,14 g.mol^{-1}

^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.56-7.52 (m, 1H), 7.25-7.19 (m, 2H), 7.12-7.07 (m, 1H), 3.88 (t, $J = 7.8$ Hz, 1H), 3.70 (s, 6H), 3.34 (d, $J = 7.8$ Hz, 2H)

^{13}C NMR (101 MHz, CDCl$_3$): δ (ppm) 169.2, 137.1, 133.1, 131.5, 128.8, 127.6, 124.7, 52.8, 51.4, 35.3

Dimethyl 2-(2-chlorobenzyl)malonate (4.20b-Cl):

From **dimethyl malonate** and **2-chlorobenzyl bromide** using **General procedures L**. **4.20b-Cl** was obtained as a colorless liquid (4.62 g, 18.01 mmol, 74%). The measured spectrometric data was in full accordance with the reported data.[244]

4.20b-Cl
$C_{12}H_{13}ClO_4$
M= 256,68 g.mol^{-1}

^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 7.37-7.32 (m, 1H), 7.25-7.21 (m, 1H), 7.20-7.14 (m, 2H), 3.85 (t, $J = 7.8$ Hz, 1H), 3.69 (s, 6H), 3.34 (d, $J = 7.8$ Hz, 2H)

^{13}C NMR (126 MHz, CDCl$_3$): δ (ppm) 169.2, 135.4, 134.3, 131.5, 129.8, 128.6, 127.0, 52.7, 51.3, 32.9

Dimethyl 2-(2-bromo-5-fluorobenzyl)malonate (4.20c):

From **dimethyl malonate** and **2-bromo-5-fluorobenzyl bromide** using **General procedures L**. **4.20c** was obtained as a colorless liquid (3.88 g, 12.17 mmol, 77%).

4.20c
$C_{12}H_{12}BrFO_4$
M= 319,13 g.mol^{-1}
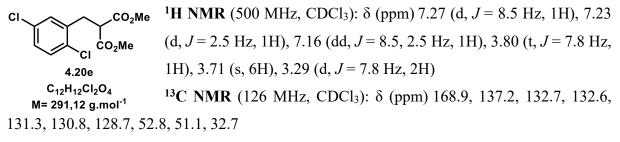
^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 7.48 (dd, $J = 8.8, 5.3$ Hz, 1H), 6.98 (dd, $J = 9.2, 3.1$ Hz, 1H), 6.84 (ddd, $J = 8.3, 8.3, 3.1$ Hz, 1H), 3.84 (t, $J = 7.7$ Hz, 1H), 3.72 (s, 6H), 3.31 (d, $J = 7.7$ Hz, 2H)

^{13}C NMR (126 MHz, CDCl$_3$): δ (ppm) 168.9, 161.9 (d, $J = 247.3$ Hz), 139.2 (d, $J = 7.7$ Hz), 134.2 (d, $J = 8.2$ Hz), 118.7 (d, $J = 3.2$ Hz), 118.5 (d, $J = 23.0$ Hz), 116.0 (d, $J = 22.3$ Hz), 52.9, 51.26, 35.2 (d, $J = 1.4$ Hz)

^{19}F NMR (471 MHz, CDCl$_3$): δ (ppm) -114.6

IR (neat): ν (cm^{-1}) 2955, 1734, 1470, 1236, 1150, 1030, 875, 811

HRMS (ESI): Calcd for $C_{12}H_{12}{}^{79}BrFNaO_4$ [M+Na]$^+$: 340.9795, found 340.9796

Rf: 0.22 in a 95:5 mixture of pentane and ethyl acetate

Experimental Section

Dimethyl 2-(2-bromo-5-methoxybenzyl)malonate (4.20d):

From **dimethyl malonate** and **2-bromo-5-methoxybenzyl bromide** using **General procedures L**. **4.20d** was obtained as a colorless liquid (3.74 g, 11.28 mmol, 63%).

MeO — (structure) — CO_2Me / CO_2Me / Br

4.20d

$C_{13}H_{15}BrO_5$

M= 331,16 g.mol^{-1}

^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 7.40 (d, J = 8.8 Hz, 1H), 6.78 (d, J = 3.1 Hz, 1H), 6.66 (dd, J = 8.8, 3.1 Hz, 1H), 3.85 (t, J = 7.8 Hz, 1H), 3.75 (s, 3H), 3.70 (s, 6H), 3.29 (d, J = 7.8 Hz, 2H)

^{13}C NMR (126 MHz, CDCl$_3$): δ (ppm) 169.1, 159.0, 138.0, 133.6, 117.0, 115.0, 114.6, 77.4, 77.2, 76.9, 55.6, 52.7, 51.4, 35.4

IR (neat): ν (cm^{-1}) 2954, 2840, 1734, 1474, 1436, 1239, 1152, 1022, 808

GC-MS (EI): Calcd for C$_{13}$H$_{15}$^{79}BrO$_5$ [M]$^{+•}$: 330, found 330

Rf: 0.18 in a 90:10 mixture of pentane and ethyl acetate

Dimethyl 2-(2,5-dichlorobenzyl)malonate (4.20e):

From **dimethyl malonate** and **2,5-dichlorobenzyl bromide** using **General procedures L**. **4.20e** was obtained as a colorless liquid (4.80 g, 16.47 mmol, 79%).

Cl — (structure) — CO_2Me / CO_2Me / Cl

4.20e

$C_{12}H_{12}Cl_2O_4$

M= 291,12 g.mol^{-1}

^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 7.27 (d, J = 8.5 Hz, 1H), 7.23 (d, J = 2.5 Hz, 1H), 7.16 (dd, J = 8.5, 2.5 Hz, 1H), 3.80 (t, J = 7.8 Hz, 1H), 3.71 (s, 6H), 3.29 (d, J = 7.8 Hz, 2H)

^{13}C NMR (126 MHz, CDCl$_3$): δ (ppm) 168.9, 137.2, 132.7, 132.6, 131.3, 130.8, 128.7, 52.8, 51.1, 32.7

IR (neat): ν (cm^{-1}) 2955, 2846, 1735, 1468, 1436, 1228, 1153, 1048, 814

HRMS (EI): Calcd for C$_{12}$H$_{12}$^{35}Cl$_2$NaO$_4$ [M+Na]$^+$: 313.0005, found 313.0005

Rf: 0.34 in a 90:10 mixture of pentane and ethyl acetate

Dimethyl 2-((6-bromobenzo[*d*][1,3]dioxol-5-yl)methyl)malonate (4.20f):

From **dimethyl malonate** and **5-bromo-6-(bromomethyl)benzo[*d*][1,3]dioxole** using **General procedures L**. **4.20f** was obtained as a colorless oil (2.97 g, 8.61 mmol, 84%).

O / O — (structure) — CO_2Me / CO_2Me / Br

4.20f

$C_{13}H_{13}BrO_6$

M= 345,15 g.mol^{-1}

^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 6.98 (s, 1H), 6.73 (s, 1H), 5.94 (s, 2H), 3.79 (t, J = 7.7 Hz, 1H), 3.71 (s, 6H), 3.24 (d, J = 7.7 Hz, 2H)

^{13}C NMR (126 MHz, CDCl$_3$): δ (ppm) 169.1, 147.6, 147.4, 130.0, 114.9, 113.0, 111.1, 101.9, 77.4, 77.2, 76.9, 52.8, 51.6, 35.1

IR (neat): ν (cm^{-1}) 2955, 2902, 1732, 1478, 1229, 1147, 1035, 931

GC-MS (EI): Calcd for C$_{13}$H$_{13}$^{79}BrO$_6$ [M]$^{+•}$: 344, found 344

Rf: 0.16 in a 90:10 mixture of pentane and ethyl acetate

Experimental Section

General procedure M: alkylation of dimethyl benzylmalonate

In a 10-20 mL microwave reaction vial, **4.20** (1 equiv) was diluted in THF (3 mL/mmol of dimethyl benzylmalonate), then sodium hydride (60% in mineral oil, 1.2 equiv) was added in one portion and the mixture was stirred for 30 min at room temperature. Then, the choose alkyl halide (1.4 equiv) was added. If solid, the alkyl halide was added as a solution in THF. The vial was then sealed and transferred in an 80°C preheated aluminum block. After overnight stirring at this temperature, the reaction was quenched by addition of H_2O and brine. The phases were separated, and the aqueous layer was extracted with diethyl ether or ethyl acetate. The combined organic phases were washed with brine and dried over Na_2SO_4. After evaporation of the volatiles the crude product was purified by flash column chromatography (pentane/EtOAc) to yield the corresponding product **4.12**.

Dimethyl 2-(2-bromo-4-fluorobenzyl)-2-propylmalonate (4.12a):

From **4.20a** and ***n*-propyl iodide** using **General procedures M**. **4.12a** was obtained as a colorless oil (842 mg, 2.42 mmol, 82%).

^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 7.30-7.26 (m, 1H), 7.15 (dd, J = 8.7, 6.0 Hz, 1H), 6.94 (ddd, J = 8.7, 7.8, 2.7 Hz, 1H), 3.70 (s, 6H), 3.42 (s, 2H), 1.85-1.78 (m, 2H), 1.36-1.25 (m, 2H), 0.92 (t, J = 7.3 Hz, 3H)

^{13}C NMR (126 MHz, CDCl$_3$): δ (ppm) 171.7, 161.2 (d, J = 250.3 Hz), 132.5 (d, J = 3.7 Hz), 132.2 (d, J = 8.3 Hz), 125.9 (d, J = 9.3 Hz), 120.2 (d, J = 24.2 Hz), 114.6 (d, J = 20.9 Hz), 59.1, 52.5, 37.1, 35.3, 18.2, 14.4

^{19}F NMR (471 MHz, CDCl$_3$): δ (ppm) -113.7

IR (neat): ν (cm^{-1}) 2958, 1730, 1599, 1487, 1211, 1120, 857, 731

HRMS (ESI): Calcd for C$_{15}$H$_{18}$^{79}BrFNaO$_4$ [M+Na]$^+$: 383.0265, found 383.0266

Rf: 0.17 in a 95:5 mixture of pentane and ethyl acetate

Experimental Section

Dimethyl 2-(2-bromobenzyl)-2-propylmalonate (4.12b-Br):

From **4.20b-Br** and ***n*-propyl iodide** using **General procedures M**. **4.12b-Br** was obtained as a white solid (1.90 g, 5.54 mmol, 82%).

4.12b-Br
$C_{15}H_{19}BrO_4$
M= 343,22 g.mol^{-1}

^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 7.53 (dd, J = 8.0, 1.2 Hz, 1H), 7.20 (td, J = 7.5, 1.3 Hz, 1H), 7.14 (dd, J = 7.8, 1.8 Hz, 1H), 7.07 (ddd, J = 8.0, 7.3, 1.8 Hz, 1H), 3.70 (s, 6H), 3.47 (s, 2H), 1.85-1.79 (m, 2H), 1.37-1.26 (m, 2H), 0.92 (t, J = 7.3 Hz, 3H)

^{13}C NMR (126 MHz, CDCl$_3$): δ (ppm) 171.8, 136.5, 133.2, 131.4, 128.6, 127.4, 126.1, 59.1, 52.5, 37.8, 35.1, 18.2, 14.4

IR (neat): ν (cm^{-1}) 2956, 2874, 1731, 1436, 1200, 754
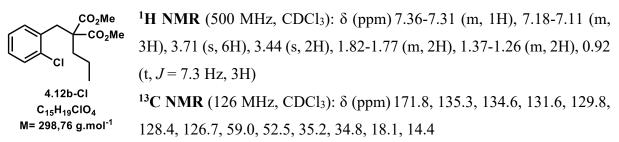
HRMS (ESI): Calcd for $C_{15}H_{19}^{79}BrNaO_4$ [M+Na]$^+$: 365.0359, found 365.0363

Rf: 0.34 in a 90:10 mixture of pentane and ethyl acetate

Mp: 71-73°C

Dimethyl 2-(2-chlorobenzyl)-2-propylmalonate (4.12b-Cl):

From **4.20b-Cl** and ***n*-propyl iodide** using **General procedures M**. **4.12b-Cl** was obtained as a colorless oil (432 mg, 1.44 mmol, 74%).

4.12b-Cl
$C_{15}H_{19}ClO_4$
M= 298,76 g.mol^{-1}

^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 7.36-7.31 (m, 1H), 7.18-7.11 (m, 3H), 3.71 (s, 6H), 3.44 (s, 2H), 1.82-1.77 (m, 2H), 1.37-1.26 (m, 2H), 0.92 (t, J = 7.3 Hz, 3H)

^{13}C NMR (126 MHz, CDCl$_3$): δ (ppm) 171.8, 135.3, 134.6, 131.6, 129.8, 128.4, 126.7, 59.0, 52.5, 35.2, 34.8, 18.1, 14.4
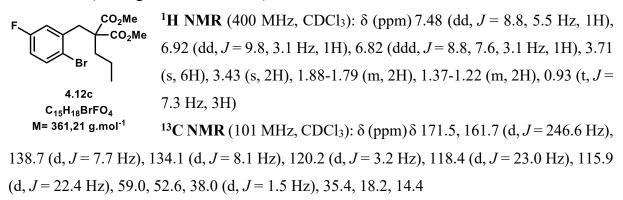
IR (neat): ν (cm^{-1}) 2956, 2874, 1732, 1439, 1211, 1120, 1048, 751

GC-MS (EI): Calcd for $C_{15}H_{19}^{35}ClO_4$ [M]$^{+\bullet}$: 298, found 298

Rf: 0.35 in a 90:10 mixture of pentane and ethyl acetate

Experimental Section

Dimethyl 2-(2-bromo-5-fluorobenzyl)-2-propylmalonate (4.12c):

From **4.20c** and ***n*-propyl iodide** using **General procedures M**. **4.12c** was obtained as a colorless oil (900 mg, 2.49 mmol, 80 %).

^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.48 (dd, J = 8.8, 5.5 Hz, 1H), 6.92 (dd, J = 9.8, 3.1 Hz, 1H), 6.82 (ddd, J = 8.8, 7.6, 3.1 Hz, 1H), 3.71 (s, 6H), 3.43 (s, 2H), 1.88-1.79 (m, 2H), 1.37-1.22 (m, 2H), 0.93 (t, J = 7.3 Hz, 3H)

^{13}C NMR (101 MHz, CDCl$_3$): δ (ppm) δ 171.5, 161.7 (d, J = 246.6 Hz), 138.7 (d, J = 7.7 Hz), 134.1 (d, J = 8.1 Hz), 120.2 (d, J = 3.2 Hz), 118.4 (d, J = 23.0 Hz), 115.9 (d, J = 22.4 Hz), 59.0, 52.6, 38.0 (d, J = 1.5 Hz), 35.4, 18.2, 14.4

^{19}F NMR (376 MHz, CDCl$_3$): δ (ppm) -114.8
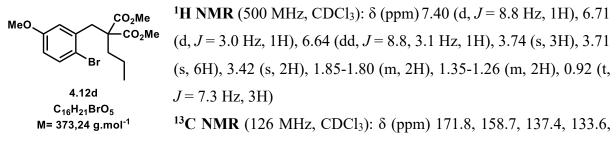
IR (neat): ν (cm^{-1}) 2957, 1731, 1579, 1469, 1213, 1155, 1032, 812, 701

HRMS (ESI): Calcd for C$_{15}$H$_{18}$^{79}BrFNaO$_4$ [M+Na]$^+$: 388.0265, found 388.0261

Rf: 0.20 in a 95:5 mixture of pentane and ethyl acetate

Dimethyl 2-(2-bromo-5-methoxybenzyl)-2-propylmalonate (4.12d):

From **4.20d** and ***n*-propyl iodide** using **General procedures M**. **4.12d** was obtained as a colorless oil (511 mg, 1.37 mmol, 91%).

^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 7.40 (d, J = 8.8 Hz, 1H), 6.71 (d, J = 3.0 Hz, 1H), 6.64 (dd, J = 8.8, 3.1 Hz, 1H), 3.74 (s, 3H), 3.71 (s, 6H), 3.42 (s, 2H), 1.85-1.80 (m, 2H), 1.35-1.26 (m, 2H), 0.92 (t, J = 7.3 Hz, 3H)

^{13}C NMR (126 MHz, CDCl$_3$): δ (ppm) 171.8, 158.7, 137.4, 133.6, 117.0, 116.5, 114.4, 59.1, 55.4, 52.5, 37.9, 35.0, 18.2, 14.4
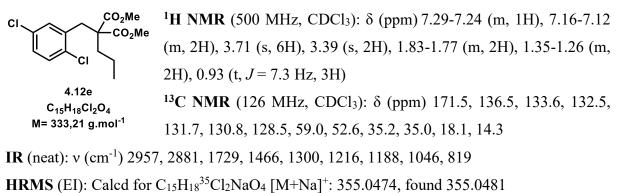
IR (neat): ν (cm^{-1}) 2957, 2875, 1731, 1469, 1238, 1213, 810

GC-MS (EI): Calcd for C$_{16}$H$_{21}$^{79}BrO$_5$ [M]$^{+•}$: 372, found 372

Rf: 0.24 in a 90:10 mixture of pentane and ethyl acetate

Experimental Section

Dimethyl 2-(2,5-dichlorobenzyl)-2-propylmalonate (4.12e):

From **4.20e** and ***n*-propyl iodide** using **General procedures M**. **4.12e** was obtained as a white solid (432 mg, 1.30 mmol, 75%).

4.12e
$C_{15}H_{18}Cl_2O_4$
M= 333,21 g.mol^{-1}

¹H NMR (500 MHz, CDCl₃): δ (ppm) 7.29-7.24 (m, 1H), 7.16-7.12 (m, 2H), 3.71 (s, 6H), 3.39 (s, 2H), 1.83-1.77 (m, 2H), 1.35-1.26 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H)

¹³C NMR (126 MHz, CDCl₃): δ (ppm) 171.5, 136.5, 133.6, 132.5, 131.7, 130.8, 128.5, 59.0, 52.6, 35.2, 35.0, 18.1, 14.3

IR (neat): ν (cm^{-1}) 2957, 2881, 1729, 1466, 1300, 1216, 1188, 1046, 819

HRMS (EI): Calcd for $C_{15}H_{18}{}^{35}Cl_2NaO_4$ [M+Na]$^+$: 355.0474, found 355.0481
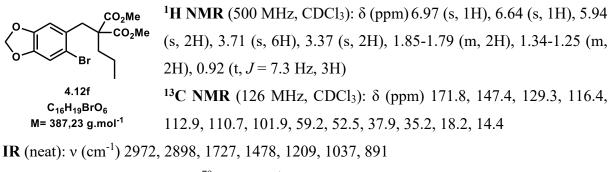
Rf: 0.46 in a 90:10 mixture of pentane and ethyl acetate

Mp: 45-47°C

Dimethyl 2-((6-bromobenzo[*d*][1,3]dioxol-5-yl)methyl)-2-propylmalonate (4.12f):

From **4.20f** and ***n*-propyl iodide** using **General procedures M**. **4.12f** was obtained as a white solid (497 mg, 1.28 mmol, 89%).

4.12f
$C_{16}H_{19}BrO_6$
M= 387,23 g.mol^{-1}

¹H NMR (500 MHz, CDCl₃): δ (ppm) 6.97 (s, 1H), 6.64 (s, 1H), 5.94 (s, 2H), 3.71 (s, 6H), 3.37 (s, 2H), 1.85-1.79 (m, 2H), 1.34-1.25 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H)

¹³C NMR (126 MHz, CDCl₃): δ (ppm) 171.8, 147.4, 129.3, 116.4, 112.9, 110.7, 101.9, 59.2, 52.5, 37.9, 35.2, 18.2, 14.4

IR (neat): ν (cm^{-1}) 2972, 2898, 1727, 1478, 1209, 1037, 891
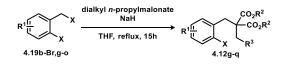
GC-MS (EI): Calcd for $C_{16}H_{19}{}^{79}BrO_6$ [M]$^{+•}$: 386, found 386

Rf: 0.25 in a 90:10 mixture of pentane and ethyl acetate

Mp: 94-96°C

Experimental Section

General procedure N: alkylation of dialkyl *n*-propylmalonate

In a 10-20 mL microwave reaction vial, dialkyl *n*-propylmalonate (1 equiv) was diluted in THF (3 mL/mmol of dimethyl *n*-propylmalonate), then sodium hydride (60% in mineral oil, 1.1 equiv) was added in one portion and the mixture was stirred for 30 min at room temperature. Then, the choose benzyl bromide (1.2 equiv) was added. If solid, the alkyl halide was added as a solution in THF. The vial was then sealed and transferred in an 80°C preheated aluminum block. After overnight stirring at this temperature, the reaction was quenched by addition of H_2O and brine. The phases were separated, and the aqueous layer was extracted with diethyl ether or ethyl acetate. The combined organic phases were washed with brine and dried over Na_2SO_4. After evaporation of the volatiles the crude product was purified by flash column chromatography (pentane/EtOAc) to yield the corresponding product **4.12**.

Dimethyl 2-(2-bromo-5-nitrobenzyl)-2-propylmalonate (4.12g):

From **dimethyl *n*-propylmalonate** and **2-bromo-5-nitrobenzyl bromide** using **General procedures N. 4.12g** was obtained as a white solid (690 mg, 1.78 mmol, 89%).

¹H NMR (500 MHz, CDCl₃): δ (ppm) 8.08 (d, *J* = 2.7 Hz, 1H), 7.93 (dd, *J* = 8.8, 2.7 Hz, 1H), 7.72 (d, *J* = 8.8 Hz, 1H), 3.74 (s, 6H), 3.53 (s, 2H), 1.84-1.80 (m, 2H), 1.39-1.29 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H)

¹³C NMR (126 MHz, CDCl₃): δ (ppm) 171.2, 147.1, 138.8, 134.0, 133.3, 126.2, 123.1, 59.0, 52.8, 38.0, 35.5, 18.2, 14.3

IR (neat): ν (cm⁻¹) 2965, 2877, 1737, 1527, 1338, 1216, 1040, 809, 738

HRMS (ESI): Calcd for C₁₅H₁₈⁷⁹BrNNaO₆ [M+Na]⁺: 410.0210, found 410.0210

Rf: 0.28 in a 90:10 mixture of pentane and ethyl acetate

Mp: 79-81°C

Experimental Section

Dimethyl 2-(2-chloro-5-(trifluoromethyl)benzyl)-2-propylmalonate (4.12h):

From **dimethyl *n*-propylmalonate** and **2-chloro-5-(trifluoromethyl)benzyl bromide** using **General procedures N**. **4.12h** was obtained as a colorless oil (689 mg, 1.88 mmol, 94%).

4.12h
$C_{16}H_{18}ClF_3O_4$
M= 366,76 g.mol^{-1}

^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 7.48-7.45 (m, 1H), 7.44-7.40 (m, 2H), 3.71 (s, 6H), 3.47 (s, 2H), 1.82-1.75 (m, 2H), 1.40-1.26 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H)

^{13}C NMR (126 MHz, CDCl$_3$): δ (ppm) 171.4, 139.1 (q, *J* = 1.5 Hz), 135.8, 130.3, 129.2 (q, *J* = 32.8 Hz), 128.7 (q, *J* = 3.8 Hz), 125.2 (q, *J* = 3.7 Hz), 123.8 (q, *J* = 272.2 Hz), 59.0, 52.6, 35.2, 34.9, 18.1, 14.2

^{19}F NMR (235 MHz, CDCl$_3$): δ (ppm) -62.7

IR (neat): ν (cm^{-1}) 2960, 2877, 1734, 1326, 1122, 1083, 828

HRMS (ESI): Calcd for $C_{16}H_{18}^{35}ClF_3NaO_4$ [M+Na]$^+$: 389.0738, found 389.0744

Rf: 0.44 in a 90:10 mixture of pentane and ethyl acetate

Dimethyl 2-(2-chloro-6-fluorobenzyl)-2-propylmalonate (4.12i-Cl):

From **dimethyl *n*-propylmalonate** and **2-chloro-6-fluorobenzyl bromide** using **General procedures N**. **4.12i-Cl** was obtained as a colorless oil (593 mg, 1.87 mmol, 94%).

4.12i-Cl
$C_{15}H_{18}ClFO_4$
M= 316,75 g.mol^{-1}

^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 7.20-7.11 (m, 2H), 6.97-6.91 (m, 1H), 3.72 (s, 6H), 3.50 (d, *J* = 2.0 Hz, 2H), 1.74-1.68 (m, 2H), 1.36-1.26 (m, 2H), 0.90 (t, *J* = 7.3 Hz, 3H)

^{13}C NMR (126 MHz, CDCl$_3$): δ (ppm) 171.8, 162.3 (d, *J* = 248.1 Hz), 136.6 (d, *J* = 6.3 Hz), 129.0 (d, *J* = 10.0 Hz), 125.6 (d, *J* = 3.3 Hz), 123.0 (d, *J* = 19.2 Hz), 114.0 (d, *J* = 24.0 Hz), 58.0, 52.5 (d, *J* = 0.8 Hz), 34.7 (d, *J* = 1.1 Hz), 29.9 (d, *J* = 0.9 Hz), 18.1 (d, *J* = 2.1 Hz), 14.4

^{19}F NMR (235 MHz, CDCl$_3$): δ (ppm) -109.1

IR (neat): ν (cm^{-1}) 2957, 2876, 1731, 1453, 1215, 1121, 923, 775

GC-MS (EI): Calcd for $C_{15}H_{18}^{35}ClFO_4$ [M]$^{+\bullet}$: 316, found 316

Rf: 0.35 in a 90:10 mixture of pentane and ethyl acetate

Experimental Section

Dimethyl 2-(2-bromo-6-fluorobenzyl)-2-propylmalonate (4.12i-Br):

From **dimethyl *n*-propylmalonate** and **2-bromo-6-fluorobenzyl bromide** using **General procedures N**. **4.12i-Br** was obtained as a colorless oil (675 mg, 1.87 mmol, 93%).

4.12i-Br
$C_{15}H_{18}BrFO_4$
M= 361,21 g.mol^{-1}

^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 7.36 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.08 (td, *J* = 8.2, 5.9 Hz, 1H), 6.97 (ddd, *J* = 9.6, 8.3, 1.2 Hz, 1H), 3.72 (s, 6H), 3.55 (d, *J* = 2.1 Hz, 2H), 1.77-1.71 (m, 2H), 1.37-1.27 (m, 2H), 0.89 (t, *J* = 7.3 Hz, 3H)

^{13}C NMR (126 MHz, CDCl$_3$): δ (ppm) 171.8, 162.0 (d, *J* = 249.2 Hz), 129.5 (d, *J* = 9.7 Hz), 129.0 (d, *J* = 3.3 Hz), 127.0 (d, *J* = 5.5 Hz), 124.9 (d, *J* = 19.0 Hz), 114.7 (d, *J* = 24.0 Hz), 58.1, 52.5, 35.0 (d, *J* = 1.0 Hz), 32.8, 18.3 (d, *J* = 1.8 Hz), 14.4

^{19}F NMR (235 MHz, CDCl$_3$): δ (ppm) -107.4

IR (neat): ν (cm^{-1}) 2957, 2876, 1730, 1447, 1244, 1216, 1120, 1039, 774

GC-MS (EI): Calcd for $C_{15}H_{18}^{79}BrFO_4$ [M]$^{+\bullet}$: 360, found 360

Rf: 0.34 in a 90:10 mixture of pentane and ethyl acetate

Dimethyl 2-(2-bromo-6-methylbenzyl)-2-propylmalonate (4.12j):

From **dimethyl *n*-propylmalonate** and **2-bromo-6-methylbenzyl bromide** using **General procedures N**. **4.12j** was obtained as a white solid (581 mg, 1.86 mmol, 93%).

4.12j
$C_{16}H_{21}BrO_4$
M= 357,24 g.mol^{-1}

^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 7.22-7.15 (m, 1H), 7.06-7.00 (m, 2H), 3.59 (s, 2H), 3.57 (s, 6H), 2.33 (s, 3H), 1.97-1.92 (m, 2H), 1.34-1.24 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H)

^{13}C NMR (126 MHz, CDCl$_3$): δ (ppm) 172.2, 140.5, 136.2, 134.5, 129.0, 127.7, 127.3, 58.9, 52.3, 37.7, 33.7, 21.2, 18.3, 14.5

IR (neat): ν (cm^{-1}) 2959, 2874, 1721, 1449, 1251, 1207, 1110, 951, 776
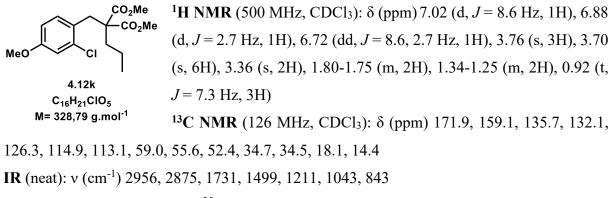
GC-MS (EI): Calcd for $C_{16}H_{21}^{79}BrO_4$ [M]$^{+\bullet}$: 356, found 356

Rf: 0.37 in a 90:10 mixture of pentane and ethyl acetate

Mp: 70-72°C

Experimental Section

Dimethyl 2-(2-chloro-4-methoxybenzyl)-2-propylmalonate (4.12k):

From **dimethyl *n*-propylmalonate** and **2-chloro-4-methoxybenzyl bromide** using **General procedures N**. **4.12k** was obtained as a colorless oil (578 mg, 1.76 mmol, 88%).

4.12k
$C_{16}H_{21}ClO_5$
M= 328,79 g.mol^{-1}

^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 7.02 (d, *J* = 8.6 Hz, 1H), 6.88 (d, *J* = 2.7 Hz, 1H), 6.72 (dd, *J* = 8.6, 2.7 Hz, 1H), 3.76 (s, 3H), 3.70 (s, 6H), 3.36 (s, 2H), 1.80-1.75 (m, 2H), 1.34-1.25 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H)

^{13}C NMR (126 MHz, CDCl$_3$): δ (ppm) 171.9, 159.1, 135.7, 132.1, 126.3, 114.9, 113.1, 59.0, 55.6, 52.4, 34.7, 34.5, 18.1, 14.4

IR (neat): ν (cm^{-1}) 2956, 2875, 1731, 1499, 1211, 1043, 843
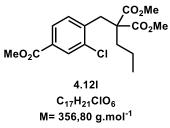
GC-MS (EI): Calcd for $C_{16}H_{21}{}^{35}ClO_5$ [M]$^{+•}$: 328, found 328

Rf: 0.24 in a 90:10 mixture of pentane and ethyl acetate

Dimethyl 2-(2-chloro-4-(methoxycarbonyl)benzyl)-2-propylmalonate (4.12l):

From **dimethyl *n*-propylmalonate** and **2-chloro-4-(methoxycarbonyl)benzyl bromide** using **General procedures N**. **4.12l** was obtained as a white solid (565 mg, 1.58 mmol, 79%).

4.12l
$C_{17}H_{21}ClO_6$
M= 356,80 g.mol^{-1}

^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 8.01 (d, *J* = 1.7 Hz, 1H), 7.81 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.24 (d, *J* = 8.1 Hz, 1H), 3.90 (s, 3H), 3.69 (s, 6H), 3.47 (s, 2H), 1.84-1.76 (m, 2H), 1.36-1.25 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H)

^{13}C NMR (126 MHz, CDCl$_3$): δ (ppm) 171.5, 165.9, 140.0, 135.6, 131.7, 130.8, 130.4, 127.7, 58.9, 52.6, 52.5, 35.4, 35.2, 18.1, 14.3

IR (neat): ν (cm^{-1}) 2969, 2875, 1736, 1712, 1285, 1215, 1122, 1051, 761

HRMS (ESI): Calcd for $C_{17}H_{21}{}^{35}ClNaO_6$ [M+Na]$^+$: 379.0919, found 379.0926

Rf: 0.20 in a 90:10 mixture of pentane and ethyl acetate

Mp: 70-72°C

Experimental Section
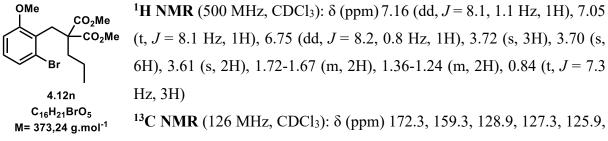
Dimethyl 2-(2-chloro-6-(trifluoromethyl)benzyl)-2-propylmalonate (4.12m):

From **dimethyl *n*-propylmalonate** and **2-chloro-6-(trifluoromethyl)benzyl bromide** using **General procedures N**. **4.12m** was obtained as a colorless oil (670 mg, 1.69 mmol, 79%).

^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 7.55 (t, *J* = 8.0 Hz, 2H), 7.31-7.24 (m, 1H), 3.73 (s, 2H), 3.55 (s, 6H), 1.96-1.91 (m, 2H), 1.35-1.25 (m, 2H), 0.90 (t, *J* = 7.3 Hz, 3H)

^{13}C NMR (126 MHz, CDCl$_3$): δ (ppm) 171.5, 137.9, 135.6 (q, *J* = 1.4 Hz), 133.2 (q, *J* = 1.1 Hz), 131.8 (q, *J* = 29.6 Hz), 128.0, 125.0 (q, *J* = 6.0 Hz), 123.8 (q, *J* = 274.4 Hz), 58.6, 52.3, 39.4, 34.8 (q, *J* = 2.0 Hz), 18.5, 14.5

^{19}F NMR (235 MHz, CDCl$_3$): δ (ppm) -58.6

IR (neat): ν (cm^{-1}) 2970, 1929, 2856, 1728, 1437, 1281, 1256, 1202, 1161, 1098, 759

GC-MS (EI): Calcd for C$_{16}$H$_{18}$^{35}ClF$_3$O$_4$ [M]$^{+•}$: 366, found 366

Rf: 0.34 in a 90:10 mixture of pentane and ethyl acetate

Dimethyl 2-(2-bromo-6-methoxybenzyl)-2-propylmalonate (4.12n):

From **dimethyl *n*-propylmalonate** and **2-bromo-6-methoxybenzyl bromide** using **General procedures N**. **4.12n** was obtained as a colorless oil (632 mg, 1.69 mmol, 85%).

^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 7.16 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.05 (t, *J* = 8.1 Hz, 1H), 6.75 (dd, *J* = 8.2, 0.8 Hz, 1H), 3.72 (s, 3H), 3.70 (s, 6H), 3.61 (s, 2H), 1.72-1.67 (m, 2H), 1.36-1.24 (m, 2H), 0.84 (t, *J* = 7.3 Hz, 3H)

^{13}C NMR (126 MHz, CDCl$_3$): δ (ppm) 172.3, 159.3, 128.9, 127.3, 125.9, 125.4, 109.2, 58.1, 55.7, 52.3, 35.5, 33.6, 18.4, 14.5
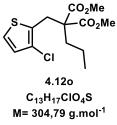
IR (neat): ν (cm^{-1}) 2954, 2874, 2839, 1729, 1462, 1433, 1264, 1218, 1033, 766

GC-MS (EI): Calcd for C$_{16}$H$_{21}$^{79}BrO$_5$ [M]$^{+•}$: 372, found 372

Rf: 0.17 in a 90:10 mixture of pentane and ethyl acetate

Experimental Section

Dimethyl 2-((3-chlorothiophen-2-yl)methyl)-2-propylmalonate (4.12o):

From **dimethyl *n*-propylmalonate** and **2-(bromomethyl)-3-chlorothiophene** using **General procedures N**. **4.12o** was obtained as a yellow oil (510 mg, 1.67 mmol, 73%).

4.12o
$C_{13}H_{17}ClO_4S$
M= 304,79 g.mol^{-1}

^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 7.15 (d, *J* = 5.4 Hz, 1H), 6.85 (d, *J* = 5.4 Hz, 1H), 3.74 (s, 6H), 3.48 (s, 2H), 1.89-1.80 (m, 2H), 1.35-1.26 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H)

^{13}C NMR (126 MHz, CDCl$_3$): δ (ppm) 171.3, 131.0, 127.5, 125.3, 124.3, 58.9, 52.7, 34.4, 30.7, 17.9, 14.3

IR (neat): ν (cm^{-1}) 2958, 2875, 1732, 1436, 1286, 1219, 1123, 1042, 926, 709

GC-MS (EI): Calcd for $C_{13}H_{17}{}^{35}ClO_4S$ [M]$^{+•}$: 304, found 304

Rf: 0.34 in a 90:10 mixture of pentane and ethyl acetate

Diethyl 2-(2-bromobenzyl)-2-propylmalonate (4.12p):

From **diethyl *n*-propylmalonate** and **2-bromobenzyl bromide** using **General procedures N**. **4.12p** was obtained as a colorless liquid (679 mg, 1.83 mmol, 91%).

4.12p
$C_{17}H_{23}BrO_4$
M= 371,27 g.mol^{-1}
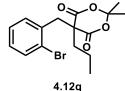
^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 7.54-7.50 (m, 1H), 7.21-7.16 (m, 2H), 7.10-7.02 (m, 1H), 4.22-4.10 (m, 4H), 3.47 (s, 2H), 1.85-1.79 (m, 2H), 1.40-1.28 (m, 2H), 1.21 (t, *J* = 7.1 Hz, 3H), 0.92 (t, *J* = 7.3 Hz, 3H)

^{13}C NMR (126 MHz, CDCl$_3$): δ (ppm) 171.4, 136.8, 133.2, 131.5, 128.5, 127.3, 126.2, 61.4, 58.9, 37.6, 35.1, 18.1, 14.4, 14.1

IR (neat): ν (cm^{-1}) 2964, 2874, 1728, 1469, 1442, 1209, 1185, 1121, 1031, 861, 750

GC-MS (EI): Calcd for $C_{17}H_{23}{}^{79}BrO_4$ [M]$^{+•}$: 370, found 370

Rf: 0.42 in a 90:10 mixture of pentane and ethyl acetate

5-(2-bromobenzyl)-2,2-dimethyl-5-propyl-1,3-dioxane-4,6-dione (4.12q):

From ***n*-propyl Meldrum's acid** and **2-bromobenzyl bromide** using **General procedures N**. **4.12q** was obtained as a colorless liquid (900 mg, 2.53 mmol, 67%).

4.12q
$C_{16}H_{19}BrO_4$
M= 355,23 g.mol^{-1}

^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 7.55 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.28 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.24 (td, *J* = 7.5, 1.3 Hz, 1H), 7.10 (ddd, *J* = 8.0, 7.3, 1.9 Hz, 1H), 3.54 (s, 2H), 2.20-2.12 (m, 2H), 1.61 (s, 3H), 1.34-1.24 (m, 2H), 1.09 (s, 3H), 0.94 (t, *J* = 7.2 Hz, 3H)

^{13}C NMR (126 MHz, CDCl$_3$): δ (ppm) 168.6, 134.9, 133.7, 132.5, 129.5, 127.7, 125.7, 105.8, 56.0, 43.5, 42.0, 30.1, 29.0, 19.1, 14.1

IR (neat): ν (cm^{-1}) 2968, 2936, 2876, 1766, 1732, 1267, 1197, 1026, 1003, 936, 749

Experimental Section

GC-MS (EI): Calcd for $C_{16}H_{19}{}^{79}BrO_4$ [M]$^{+\bullet}$: 354, found 354

Rf: 0.22 in a 95:5 mixture of pentane and ethyl acetate

Mp: 71-73°C

Dimethyl 2-(2-bromobenzyl)-2-ethylmalonate (4.12r):
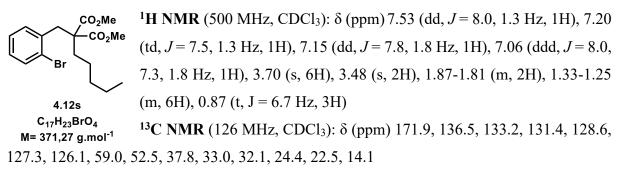
From **4.20b-Br** and **ethyl iodide** using **General procedures M**. **4.12r** was obtained as a colorless oil (2.85 g, 8.66 mmol, 87%).

4.12r
$C_{14}H_{17}BrO_4$
M= 329,19 g.mol^{-1}

^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.53 (dd, J = 8.0, 1.4 Hz, 1H) 7.23-7.14 (m, 2H), 7.09-7.04 (m, 1H), 3.71 (s, 6H), 3.47 (s, 2H), 1.93 (q, J = 7.5 Hz, 2H), 0.93 (t, J = 7.5 Hz, 3H)

^{13}C NMR (101 MHz, CDCl$_3$): δ (ppm) 171.7, 136.4, 133.22, 131.4, 128.6, 127.4, 126.1, 59.5, 52.5, 37.4, 26.1, 9.4

IR (neat): ν (cm^{-1}) 2951, 1729, 1435, 1223, 1125, 1026, 745

HRMS (ESI): Calcd for $C_{14}H_{17}{}^{79}BrNaO_4$ [M+Na]$^+$: 351.0202, found 351.0206

Rf: 0.31 in a 95:5 mixture of pentane and ethyl acetate

Dimethyl 2-(2-bromobenzyl)-2-pentylmalonate (4.12s):

From **4.20b-Br** and ***n*-pentyl iodide** using **General procedures M**. **4.12s** was obtained as a slightly yellow oil (506 mg, 1.36 mmol, 82%).

4.12s
$C_{17}H_{23}BrO_4$
M= 371,27 g.mol^{-1}

^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 7.53 (dd, J = 8.0, 1.3 Hz, 1H), 7.20 (td, J = 7.5, 1.3 Hz, 1H), 7.15 (dd, J = 7.8, 1.8 Hz, 1H), 7.06 (ddd, J = 8.0, 7.3, 1.8 Hz, 1H), 3.70 (s, 6H), 3.48 (s, 2H), 1.87-1.81 (m, 2H), 1.33-1.25 (m, 6H), 0.87 (t, J = 6.7 Hz, 3H)

^{13}C NMR (126 MHz, CDCl$_3$): δ (ppm) 171.9, 136.5, 133.2, 131.4, 128.6, 127.3, 126.1, 59.0, 52.5, 37.8, 33.0, 32.1, 24.4, 22.5, 14.1

IR (neat): ν (cm^{-1}) 2954, 2862, 1731, 1435, 1255, 1199, 1125, 1030, 750

GC-MS (EI): Calcd for $C_{17}H_{23}{}^{79}BrO_4$ [M]$^{+\bullet}$: 370, found 370

Rf: 0.36 in a 90:10 mixture of pentane and ethyl acetate

Experimental Section
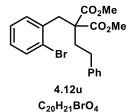
Dimethyl 2-(2-bromobenzyl)-2-isopentylmalonate (4.12t):

From **4.20b-Br** and **isopentyl iodide** using **General procedures M**. **4.12t** was obtained as a slightly yellow oil (515 mg, 1.39 mmol, 84%).

4.12t
$C_{17}H_{23}BrO_4$
M= 371,27 g.mol^{-1}

^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 7.53 (dd, J = 8.0, 1.2 Hz, 1H), 7.22-7.18 (m, 1H), 7.16 (dd, J = 7.8, 2.0 Hz, 1H), 7.06 (ddd, J = 8.0, 7.1, 2.0 Hz, 1H), 3.70 (s, 6H), 3.48 (s, 2H), 1.90-1.84 (m, 2H), 1.57-1.45 (m, 1H), 1.19-1.12 (m, 2H), 0.87 (d, J = 6.6 Hz, 6H)

^{13}C NMR (126 MHz, CDCl$_3$): δ (ppm) 171.9, 136.5, 133.2, 131.4, 128.6, 127.3, 126.1, 59.0, 52.5, 37.8, 33.5, 31.2, 28.5, 22.6

IR (neat): ν (cm^{-1}) 2954, 2871, 1731, 1435, 1265, 1239, 1205, 1133, 1030, 750

GC-MS (EI): Calcd for $C_{17}H_{23}{}^{79}BrO_4$ [M]$^{+•}$: 370, found 370

Rf: 0.36 in a 90:10 mixture of pentane and ethyl acetate

Dimethyl 2-(2-bromobenzyl)-2-phenethylmalonate (4.12u):

From **4.20b-Br** and **(2-iodoethyl)benzene** using **General procedures M**, a second addition of NaH and alkyl iodide was necessary, and the reaction was stirred at 80°C overnight again. **4.12u** was obtained as a slightly yellow oil (330 mg, 0.82 mmol, 49%).

4.12u
$C_{20}H_{21}BrO_4$
M= 405,29 g.mol^{-1}

^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 7.56-7.52 (m, 1H), 7.29-7.25 (m, 2H), 7.24-7.15 (m, 5H), 7.08 (ddd, J = 8.0, 6.3, 2.8 Hz, 1H), 3.73 (s, 6H), 3.59 (s, 2H), 2.69-2.60 (m, 2H), 2.24-2.17 (m, 2H)

^{13}C NMR (126 MHz, CDCl$_3$): δ (ppm) 171.6, 141.3, 136.3, 133.3, 131.3, 128.7, 128.5, 128.5, 127.5, 126.2, 126.1, 59.0, 52.6, 38.1, 34.7, 31.1

IR (neat): ν (cm^{-1}) 2951, 1730, 1435, 1199, 1173, 1026, 748, 699

GC-MS (EI): Calcd for $C_{20}H_{21}{}^{79}BrO_4$ [M]$^{+•}$: 404, found 404

Rf: 0.28 in a 90:10 mixture of pentane and ethyl acetate

Experimental Section
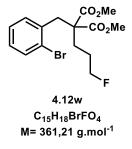
Dimethyl 2-(2-bromobenzyl)-2-(3-phenylpropyl)malonate (4.12v):

From **4.20b-Br** and **(2-iodopropyl)benzene** using **General procedures M**. **4.12v** was obtained as a slightly yellow oil (522 mg, 1.25 mmol, 75%).

1H NMR (500 MHz, CDCl$_3$): δ (ppm) 7.57-7.51 (m, 1H), 7.30-7.25 (m, 2H), 7.21-7.14 (m, 4H), 7.10-7.03 (m, 2H), 3.70 (s, 6H), 3.48 (s, 2H), 2.61 (t, J = 7.7 Hz, 2H), 1.95-1.88 (m, 2H), 1.68-1.56 (m, 2H)

13C NMR (126 MHz, CDCl$_3$): δ (ppm) 171.7, 141.9, 136.3, 133.2, 131.4, 128.6, 128.6, 128.5, 127.4, 126.1, 126.0, 58.9, 52.6, 37.7, 36.0, 32.5, 26.7

4.12v
C$_{21}$H$_{23}$BrO$_4$
M= 419,32 g.mol^{-1}

IR (neat): ν (cm^{-1}) 3026, 2950, 2862, 1730, 1435, 1200, 1168, 1089, 1026, 748, 699

GC-MS (EI): Calcd for C$_{21}$H$_{23}$^{79}BrO$_4$ [M]$^{+•}$: 418, found 418

Rf: 0.26 in a 90:10 mixture of pentane and ethyl acetate

Dimethyl 2-(2-bromobenzyl)-2-(3-fluoropropyl)malonate (4.12w):

From **4.20b-Br** and **1-fluoro-3-iodopropane** using **General procedures M**. **4.12w** was obtained as a white solid (435 mg, 1.20 mmol, 73%).

1H NMR (500 MHz, CDCl$_3$): δ (ppm) 7.54 (dd, J = 8.0, 1.3 Hz, 1H), 7.21 (td, J = 7.5, 1.3 Hz, 1H), 7.15 (dd, J = 7.8, 1.8 Hz, 1H), 7.08 (ddd, J = 8.0, 7.3, 1.8 Hz, 1H), 4.42 (dt, J = 47.2, 6.0 Hz, 2H), 3.73 (s, 6H), 3.50 (s, 2H), 2.00-1.92 (m, 2H), 1.79-1.66 (m, 2H)

4.12w
C$_{15}$H$_{18}$BrFO$_4$
M= 361,21 g.mol^{-1}

13C NMR (126 MHz, CDCl$_3$): δ (ppm) 171.5, 136.1, 133.3, 131.4, 128.8, 127.5, 126.1, 83.8 (d, J = 166.1 Hz), 58.7, 52.7, 38.0, 28.9 (d, J = 5.9 Hz), 26.1 (d, J = 20.1 Hz)

19F NMR (235 MHz, CDCl$_3$): δ (ppm) -218.7

IR (neat): ν (cm^{-1}) 2955, 2904, 1730, 1436, 1201, 1027, 752
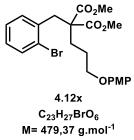
HRMS (ESI): Calcd for C$_{15}$H$_{18}$^{79}BrFNaO$_4$ [M+Na]$^+$: 383.0265, found 383.0270

Rf: 0.22 in a 90:10 mixture of pentane and ethyl acetate

Mp: 66-68°C

Experimental Section

Dimethyl 2-(2-bromobenzyl)-2-(3-((4-methoxybenzyl)oxy)propyl)malonate (4.12x):

From **4.20b-Br** and **3-(4-methoxyphenoxy)-1-iodopropane** using **General procedures M**. **4.12x** was obtained as a slightly yellow oil (590 mg, 1.27 mmol, 76%).
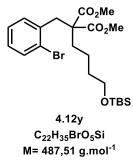
^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 7.54 (dd, J = 8.0, 1.1 Hz, 1H), 7.23-7.17 (m, 2H), 7.08 (ddd, J = 8.0, 6.7, 2.3 Hz, 1H), 6.86-6.78 (m, 4H), 3.90 (t, J = 6.4 Hz, 2H), 3.76 (s, 3H), 3.72 (s, 6H), 3.52 (s, 2H), 2.06-2.00 (m, 2H), 1.82-1.74 (m, 2H)

^{13}C NMR (126 MHz, CDCl$_3$): δ (ppm) 171.6, 153.9, 153.1, 136.2, 133.3, 131.5, 128.7, 127.4, 126.1, 115.6, 114.8, 68.4, 58.8, 55.9, 52.6, 37.8, 29.6, 25.0

IR (neat): ν (cm^{-1}) 2951, 1730, 1507, 1227, 1032, 824, 749

GC-MS (EI): Calcd for C$_{23}$H$_{27}$^{79}BrO$_6$ [M]$^{+•}$: 478, found 478

Rf: 0.12 in a 90:10 mixture of pentane and ethyl acetate

Dimethyl 2-(2-bromobenzyl)-2-(4-((tert-butyldimethylsilyl)oxy)butyl)malonate (4.12y):

From **4.20b-Br** and *tert*-**butyl(4-iodobutoxy)dimethylsilane** using **General procedures M**. **4.12y** was obtained as a slightly yellow oil (610 mg, 1.25 mmol, 75%).

^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 7.53 (dd, J = 8.0, 1.3 Hz, 1H), 7.22-7.17 (m, 1H), 7.15 (dd, J = 7.8, 1.9 Hz, 1H), 7.06 (ddd, J = 8.0, 7.2, 1.9 Hz, 1H), 3.70 (s, 6H), 3.59 (t, J = 6.3 Hz, 2H), 3.48 (s, 2H), 1.89-1.82 (m, 2H), 1.55-1.47 (m, 2H), 1.40-1.30 (m, 2H), 0.88 (s, 9H), 0.03 (s, 6H)

^{13}C NMR (126 MHz, CDCl$_3$): δ (ppm) 171.8, 136.4, 133.2, 131.4, 128.6, 127.4, 126.1, 62.8, 59.0, 52.5, 37.7, 33.1, 32.7, 26.1, 21.2, 18.4, -5.2

IR (neat): ν (cm^{-1}) 2952, 2858, 1735, 1436, 1252, 1099, 835, 775, 750

GC-MS (EI): Calcd for C$_{22}$H$_{35}$^{79}BrO$_5$Si [M]$^{+•}$: 486, found 486

Rf: 0.37 in a 90:10 mixture of pentane and ethyl acetate

Experimental Section

Dimethyl 2-(2-bromobenzyl)-2-(3-(1,3-dioxoisoindolin-2-yl)propyl)malonate (4.12z):

From **4.20b-Br** and *N*-(3-bromopropyl)phtalimide using **General procedures M**. **4.12z** was obtained as a white solid (576 mg, 1.18 mmol, 71%).

Structure label:
CO$_2$Me
CO$_2$Me
Br
NPhth
4.12z
C$_{23}$H$_{22}$BrNO$_6$
M= 488,33 g.mol^{-1}
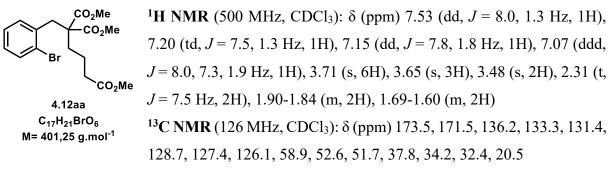
^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 7.85-7.81 (m, 2H), 7.74-7.69 (m, 2H), 7.51 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.17 (td, *J* = 7.4, 1.3 Hz, 1H), 7.12 (dd, *J* = 7.7, 1.9 Hz, 1H), 7.04 (ddd, *J* = 8.0, 7.2, 1.9 Hz, 1H), 3.70 (s, 6H), 3.67 (t, *J* = 7.3 Hz, 2H), 3.46 (s, 2H), 1.93-1.86 (m, 2H), 1.76-1.65 (m, 2H)

^{13}C NMR (126 MHz, CDCl$_3$): δ (ppm) 171.4, 168.4, 136.1, 134.1, 133.3, 132.3, 131.5, 128.7, 127.4, 126.1, 123.3, 58.8, 52.7, 38.0, 37.8, 29.9, 24.2

IR (neat): ν (cm^{-1}) 2952, 2869, 1711, 1394, 1271, 1179, 1053, 943, 717

GC-MS (EI): Calcd for C$_{23}$H$_{22}$^{79}BrNO$_6$ [M]$^{+\bullet}$: 487, found 487

Rf: 0.22 in a 75:25 mixture of pentane and ethyl acetate

Mp: 124-126°C

Trimethyl 5-(2-bromophenyl)pentane-1,4,4-tricarboxylate (4.12aa):

From **4.20b-Br** and **methyl 4-iodobutyrate** using **General procedures M**. **4.12aa** was obtained as a slightly yellow oil (514 mg, 1.28 mmol, 77%).

Structure label:
CO$_2$Me
CO$_2$Me
Br
CO$_2$Me
4.12aa
C$_{17}$H$_{21}$BrO$_6$
M= 401,25 g.mol^{-1}

^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 7.53 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.20 (td, *J* = 7.5, 1.3 Hz, 1H), 7.15 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.07 (ddd, *J* = 8.0, 7.3, 1.9 Hz, 1H), 3.71 (s, 6H), 3.65 (s, 3H), 3.48 (s, 2H), 2.31 (t, *J* = 7.5 Hz, 2H), 1.90-1.84 (m, 2H), 1.69-1.60 (m, 2H)

^{13}C NMR (126 MHz, CDCl$_3$): δ (ppm) 173.5, 171.5, 136.2, 133.3, 131.4, 128.7, 127.4, 126.1, 58.9, 52.6, 51.7, 37.8, 34.2, 32.4, 20.5

IR (neat): ν (cm^{-1}) 2953, 1729, 1435, 1199, 1166, 1026, 751

GC-MS (EI): Calcd for C$_{17}$H$_{21}$^{79}BrO$_6$ [M]$^{+\bullet}$: 400, found 400

Rf: 0.34 in a 75:25 mixture of pentane and ethyl acetate

Experimental Section

Dimethyl 2-(2-bromo-4-fluorobenzyl)-2-ethylmalonate (4.12ab):

From **4.20a** and **ethyl iodide** using **General procedures M**. **4.12ab** was obtained as a colorless oil (842 mg, 2.42 mmol, 78%).

^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.30-7.25 (m, 1H), 7.18 (dd, $J =$ 8.7, 6.0 Hz, 1H), 6.94 (ddd, $J =$ 8.7, 7.8, 2.7 Hz, 1H), 3.70 (s, 6H), 3.42 (s, 2H), 1.92 (q, $J =$ 7.5 Hz, 2H), 0.93 (t, $J =$ 7.5 Hz, 3H)

^{13}C NMR (126 MHz, CDCl$_3$): δ (ppm) 171.6, 161.2 (d, $J =$ 250.4 Hz), 132.4 (d, $J =$ 3.79 Hz) 132.2 (d, $J =$ 8.2 Hz), 125.9 (d, $J =$ 9.0 Hz), 120.2 (d, $J =$ 24.2 Hz), 114.6 (d, $J =$ 20.8 Hz), 59.5, 52.5, 36.8, 26.4, 9.4

^{19}F NMR (471 MHz, CDCl$_3$): δ (ppm) -113.7

IR (neat): ν (cm^{-1}) 2952, 1729, 1599, 1487, 1221, 1115, 1032, 879, 778

HRMS (ESI): Calcd for C$_{14}$H$_{16}$^{79}BrFNaO$_4$ [M+Na]$^{+}$: 369.0108, found 369.0111

Rf: 0.23 in a 95:5 mixture of pentane and ethyl acetate

Dimethyl 2-(2-bromo-4-fluorobenzyl)-2-(ethyl-*d$_5$*)malonate (4.12ac):

From **4.20a** and **iodoethane-*d$_5$*** using **General procedures M**. **4.12ac** was obtained as a slightly yellow oil (934 mg, 2.65 mmol, 83%).

^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.27 (dd, $J =$ 8.2, 2.6 Hz, 1H), 7.17 (dd, $J =$ 8.7, 6.1 Hz, 1H), 6.97-6.90 (m, 1H), 3.70 (s, 6H), 3.41 (s, 2H)

^{13}C NMR (126 MHz, CDCl$_3$): δ (ppm) 171.6, 161.2 (d, $J =$ 250.3 Hz), 132.4 (d, $J =$ 3.7 Hz), 132.2 (d, $J =$ 8.3 Hz), 125.9 (d, $J =$ 9.3 Hz), 120.2 (d, $J =$ 24.1 Hz), 114.6 (d, $J =$ 20.7 Hz), 59.3, 52.5, 36.7, 26.0-25.1 (m), 8.8-7.8 (m)

^{19}F NMR (471 MHz, CDCl$_3$): δ (ppm) -113.7
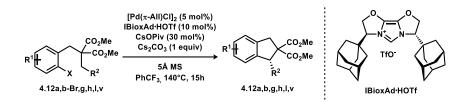
IR (neat): ν (cm^{-1}) 2953, 1729, 1600, 1488, 1227, 1069, 1033, 882, 859, 831

GC-MS (EI): Calcd for C$_{14}$H$_{11}$D$_5$^{79}BrFO$_4$ [M]$^{+•}$: 351, found 351

Rf: 0.23 in a 95:5 mixture of pentane and ethyl acetate

Experimental Section

6.4.3. Products

General procedure O: Representative procedure for the asymmetric C(sp^3)–H arylation

In an 2-5 mL microwave reaction vial, substrate (0.2 mmol) was introduced. Then the tube was transferred in glovebox and [Pd(π-All)Cl]$_2$ (3.7 mg, 10 μmol, 5 mol%), **IBioxAd·HOTf** (11.4 mg, 20 μmol, 10 mol%), cesium pivalate (14 mg, 60 μmol, 30 mol%), cesium carbonate (65 mg, 0.2 mmol, 1 equiv) and 5Å molecular sieves powder (50 mg) were introduced and the vial was then sealed. Outside of the glovebox, α,α,α-trifluorotoluene (2 mL) was added. The reaction was stirred at room temperature for 10 min. The vial was then introduced in a 140°C preheated aluminium block and stirred at this temperature for 15 hours. After this period the reaction was coolded to room temperature, diluted with DCM (1 mL), filtered over a pad of celite (washed three times with 1 mL of DCM). The crude material was analyzed by GC-MS and then concentrated and purified by preparative HPLC chromatography (EtOAc/hexane) to yield the corresponding indane product. Enantiomeric ratio were then determined by HPLC using a chiral stationary phase.

Racemic materials were obtained following the same procedure, using IBioxSpiCy·HOTf as ligand.

Dimethyl (*R*)-1-ethyl-6-fluoro-1,3-dihydro-2*H*-indene-2,2-dicarboxylate (4.13a):

From **4.12a** using **General procedures O**. **4.13a** was obtained as a white solid (48.2 mg, 0.172 mmol, 86%).

^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 7.10 (dd, J = 8.2, 5.2 Hz, 1H), 6.91 (dd, J = 8.9, 2.4 Hz, 1H), 6.85 (td, J = 8.8, 2.5 Hz, 1H), 3.76 (s, 3H), 3.79-3.73 (m, 2H), 3.69 (s, 3H), 3.26 (d, J = 16.3 Hz, 1H), 1.62-1.49 (m, 1H), 1.46-1.36 (m, 1H), 0.96 (t, J = 7.4 Hz, 3H)

^{13}C NMR (126 MHz, CDCl$_3$): δ (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}F NMR (471 MHz, CDCl$_3$): δ (ppm) -116.6

Experimental Section

IR (neat): ν (cm^{-1}) 2961, 2928, 1728, 1484, 1437, 1237, 1159, 875
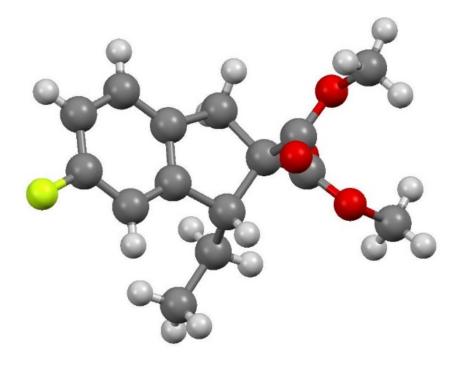
HRMS (ESI): Calcd for C$_{15}$H$_{17}$FNaO$_4$ [M+Na]$^+$: 303.1003, found 303.1004

Rf: 0.26 in a 95:5 mixture of cyclohexane and ethyl acetate

Mp: 104-107°C

[α]$_D^{20}$: -188.4° (c = 1.16, CHCl$_3$)

HPLC separation: Chiralcel$^®$ OD-H; 99.5:0.5 (*n*-heptane/*i*-PrOH), 0.5 ml.min^{-1}, 271 nm, t_R (minor) = 20.5 min, t_R (major) = 23.6 min, 98:2 e.r.

Experimental Section

Dimethyl (*R*)-1-ethyl-1,3-dihydro-2*H*-indene-2,2-dicarboxylate (4.13b):

From **4.12b-Br** using **General procedures O**. **4.13b** was obtained as a colorless oil (38 mg, 0.145 mmol, 72%).

4.13b
$C_{15}H_{18}O_4$
M= 262,31 g.mol^{-1}

^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.25-7.13 (m, 4H), 3.82 (d, *J* = 16.5 Hz, 1H), 3.80 (dd, *J* = 9.7, 4.9 Hz, 1H), 3.76 (s, 3H), 3.68 (s, 3H), 3.32 (d, *J* = 16.5 Hz, 1H), 1.61-1.48 (m, 1H), 1.47-1.34 (m, 1H), 0.97 (t, *J* = 7.4 Hz, 3H)

^{13}C NMR (101 MHz, CDCl$_3$): δ (ppm) 172.3, 170.7, 144.3, 139.1, 127.2, 126.7, 125.0, 124.5, 65.7, 53.0, 52.6, 51.5, 39.0, 24.1, 11.8

IR (neat): ν (cm^{-1}) 2958, 2933, 1729, 1234, 1152, 1072, 942, 759

HRMS (ESI): Calcd for $C_{15}H_{18}NaO_4$ [M+Na]$^+$: 285.1097, found 285.1103

Rf: 0.32 in a 90:10 mixture of cyclohexane and ethyl acetate
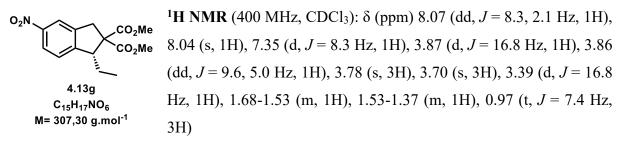
[α]$_D^{20}$: -208.3° (c = 1.01, CHCl$_3$)

HPLC separation: Chiralcel® OD-H; 99.5:0.5 (*n*-heptane/*i*-PrOH), 0.5 ml.min^{-1}, 266 nm, t_R (minor) = 19.3 min, t_R (major) = 23.0 min, 98:2 e.r.

Dimethyl (*R*)-1-ethyl-5-nitro-1,3-dihydro-2H-indene-2,2-dicarboxylate (4.13g):

From **4.12g** using **General procedures O**. **4.13g** was obtained as a colorless oil (37.5 mg, 0.122 mmol, 61%).

4.13g
$C_{15}H_{17}NO_6$
M= 307,30 g.mol^{-1}

^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 8.07 (dd, *J* = 8.3, 2.1 Hz, 1H), 8.04 (s, 1H), 7.35 (d, *J* = 8.3 Hz, 1H), 3.87 (d, *J* = 16.8 Hz, 1H), 3.86 (dd, *J* = 9.6, 5.0 Hz, 1H), 3.78 (s, 3H), 3.70 (s, 3H), 3.39 (d, *J* = 16.8 Hz, 1H), 1.68-1.53 (m, 1H), 1.53-1.37 (m, 1H), 0.97 (t, *J* = 7.4 Hz, 3H)

^{13}C NMR (126 MHz, CDCl$_3$): δ (ppm) 171.6, 169.8, 152.1, 147.8, 141.0, 125.4, 122.7, 119.9, 65.6, 53.3, 52.9, 51.4, 38.7, 23.7, 11.7

IR (neat): ν (cm^{-1}) 2955, 2879, 1728, 1522, 1430, 1341, 1248, 1216, 1158, 1086, 1056, 859, 751

HRMS (ESI): Calcd for $C_{15}H_{17}NNaO_6$ [M+Na]$^+$: 330.0948, found 330.0946

Rf: 0.22 in a 93:7 mixture of cyclohexane and ethyl acetate

[α]$_D^{20}$: -185.3° (c = 1.07, CHCl$_3$)

HPLC separation: Chiralcel® OD-H; 95:5 (*n*-heptane/*i*-PrOH), 0.5 ml.min^{-1}, 295 nm, t_R (minor) = 19.9 min, t_R (major) = 23.8 min, 94:6 e.r.

Experimental Section

Dimethyl (*R*)-1-ethyl-5-(trifluoromethyl)-1,3-dihydro-2*H*-indene-2,2-dicarboxylate (4.13h):

From **4.12h** using **General procedures O**. **4.13h** was obtained as a colorless oil (62.2 mg, 0.190 mmol, 95%).

4.13h
$C_{16}H_{17}F_3O_4$
M= 330,30 g.mol^{-1}

^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 7.44 (d, *J* = 8.5 Hz, 1H), 7.43 (s, 1H) 7.32 (d, *J* = 8.5 Hz, 1H), 3.85 (d, *J* = 16.8 Hz, 1H), 3.84 (dd, *J* = 9.8, 4.9 Hz, 1H), 3.78 (s, 3H), 3.69 (s, 3H), 3.36 (d, *J* = 16.8 Hz, 1H), 1.63-1.51 (m, 1H), 1.48-1.36 (m, 1H), 0.97 (t, *J* = 7.4 Hz, 3H)

^{13}C NMR (126 MHz, CDCl$_3$): δ (ppm) 171.9, 170.1, 148.4, 140.0, 129.7 (q, *J* = 32.1 Hz), 125.2, 124.5 (q, *J* = 272.0 Hz), 124.0 (q, *J* = 3.8 Hz), 121.5 (q, *J* = 3.7 Hz), 65.6, 53.2, 52.8, 51.4, 38.8, 23.8, 11.7

^{19}F NMR (471 MHz, CDCl$_3$): δ (ppm) -62.1

IR (neat): ν (cm^{-1}) 2975, 2877, 1731, 1436, 1327, 1252, 1153, 1114, 1065, 834

HRMS (ESI): Calcd for C$_{16}$H$_{17}$F$_3$NaO$_4$ [M+Na]$^+$: 353.0971, found 353.0973

Rf: 0.28 in a 95:5 mixture of cyclohexane and ethyl acetate
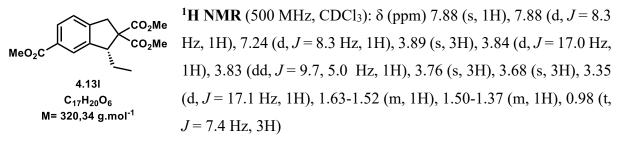
[α]$_D^{20}$: -161.2° (c = 1.23, CHCl$_3$)

HPLC separation: Chiralcel® OD-H; 99.5:0.5 (*n*-heptane/*i*-PrOH), 0.5 ml.min^{-1}, 214 nm, t_R (minor) = 16.3 min, t_R (major) = 18.6 min, 98:2 e.r.

Trimethyl (*R*)-3-ethyl-1,3-dihydro-2*H*-indene-2,2,5-tricarboxylate (4.13l):

From **4.12l** using **General procedures O**. **4.13l** was obtained as a colorless oil (57.1 mg, 0.178 mmol, 89%).

4.13l
$C_{17}H_{20}O_6$
M= 320,34 g.mol^{-1}

^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 7.88 (s, 1H), 7.88 (d, *J* = 8.3 Hz, 1H), 7.24 (d, *J* = 8.3 Hz, 1H), 3.89 (s, 3H), 3.84 (d, *J* = 17.0 Hz, 1H), 3.83 (dd, *J* = 9.7, 5.0 Hz, 1H), 3.76 (s, 3H), 3.68 (s, 3H), 3.35 (d, *J* = 17.1 Hz, 1H), 1.63-1.52 (m, 1H), 1.50-1.37 (m, 1H), 0.98 (t, *J* = 7.4 Hz, 3H)

^{13}C NMR (126 MHz, CDCl$_3$): δ (ppm) 172.0, 170.3, 167.3, 144.8, 144.7, 129.1, 129.0, 126.1, 124.5, 65.6, 53.1, 52.7, 52.2, 51.2, 39.2, 24.0, 11.8

IR (neat): ν (cm^{-1}) 2970, 2929, 2856, 1728, 1719, 1437, 1256, 1161, 1098, 866, 759

HRMS (ESI): Calcd for C$_{17}$H$_{20}$NaO$_6$ [M+Na]$^+$: 343.1152, found 343.1158

Rf: 0.25 in a 90:10 mixture of cyclohexane and ethyl acetate

[α]$_D^{20}$: -169.2° (c = 1.22, CHCl$_3$)

Experimental Section

Dimethyl (*R*)-1-methyl-1,3-dihydro-2*H*-indene-2,2-dicarboxylate (4.13r):

From **4.12r** using **General procedures O**. **4.13r** was obtained as a colorless oil (36.7 mg, 0.148 mmol, 74%).

^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.24-7.11 (m, 4H), 4.04 (q, *J* = 7.2 Hz, 1H), 3.77 (d, *J* = 16.6 Hz, 1H), 3.73 (s, 3H), 3.73 (s, 3H), 3.31 (d, *J* = 16.6 Hz, 1H), 1.23 (d, *J* = 7.2 Hz, 3H)

^{13}C NMR (101 MHz, CDCl$_3$): δ (ppm) 172.3, 170.9, 145.5, 139.1, 127.2, 127.2, 124.2, 123.5, 64.9, 52.9, 52.5, 45.2, 39.2, 16.7

C$_{14}$H$_{16}$O$_4$
M= 248,28 g.mol^{-1}

IR (neat): ν (cm^{-1}) 2956, 1730, 1434, 1243, 1158, 1073, 1047, 754

HRMS (ESI): Calcd for C$_{14}$H$_{16}$NaO$_4$ [M+Na]$^+$: 271.0941, found 271.0945
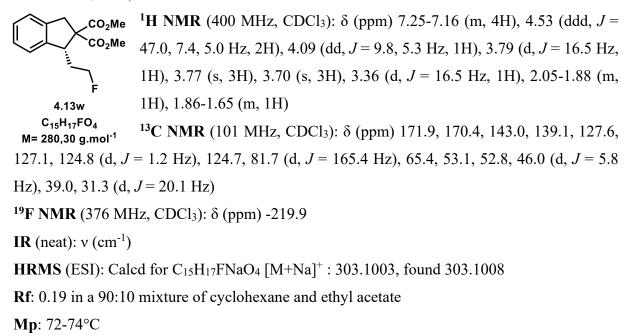
Rf: 0.28 in a 90:10mixture of cyclohexane and ethyl acetate

[α]$_D^{20}$: -194.9° (c = 1.13, CHCl$_3$)

Dimethyl (*R*)-1-(2-fluoroethyl)-1,3-dihydro-2H-indene-2,2-dicarboxylate (4.13w):

From **4.12w** using **General procedures O**. **4.13w** was obtained as a colorless oil (51.0 mg, 0.182 mmol, 91%).

^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.25-7.16 (m, 4H), 4.53 (ddd, *J* = 47.0, 7.4, 5.0 Hz, 2H), 4.09 (dd, *J* = 9.8, 5.3 Hz, 1H), 3.79 (d, *J* = 16.5 Hz, 1H), 3.77 (s, 3H), 3.70 (s, 3H), 3.36 (d, *J* = 16.5 Hz, 1H), 2.05-1.88 (m, 1H), 1.86-1.65 (m, 1H)

C$_{15}$H$_{17}$FO$_4$
M= 280,30 g.mol^{-1}

^{13}C NMR (101 MHz, CDCl$_3$): δ (ppm) 171.9, 170.4, 143.0, 139.1, 127.6, 127.1, 124.8 (d, *J* = 1.2 Hz), 124.7, 81.7 (d, *J* = 165.4 Hz), 65.4, 53.1, 52.8, 46.0 (d, *J* = 5.8 Hz), 39.0, 31.3 (d, *J* = 20.1 Hz)

^{19}F NMR (376 MHz, CDCl$_3$): δ (ppm) -219.9

IR (neat): ν (cm^{-1})

HRMS (ESI): Calcd for C$_{15}$H$_{17}$FNaO$_4$ [M+Na]$^+$: 303.1003, found 303.1008

Rf: 0.19 in a 90:10 mixture of cyclohexane and ethyl acetate

Mp: 72-74°C

Experimental Section

$[\alpha]_D^{20}$: -176.6° (c = 1.99, CHCl$_3$)

HPLC separation: Chiralcel® OD-H; 99:1 (*n*-heptane/*i*-PrOH), 0.5 ml.min^{-1}, 211 nm, t_R (minor) = 22.5 min, t_R (major) = 27.8 min, 98:2 e.r.

Experimental Section

Experimental Section

References

1. M. Arago, in *Mémoires La Cl. Des Sci. Mathématiques Phys. l'Institut Impérial Fr.*, **1811**, pp. 93–134.

2. J. F. W. Herschel, *Trans. Cambridge Philos. Soc.* **1822**, *1*, 43–51.

3. J. B. Biot, *Bull. des Sci. par la Société Philomatique Paris* **1815**, 190–192.

4. L. Pasteur, *Ann. Chim. Phys.* **1850**, *28*, 56–99.

5. J. H. van't Hoff, *Arch. Néerlandaises des Sci. Exactes Nat.* **1874**, *9*, 445–454.

6. J.-A. Le Bel, *Bull. la Société Chim. Paris* **1874**, *22*, 337–347.

7. W. G. Jackson, J. A. McKeon, S. Cortez, *Inorg. Chem.* **2004**, *43*, 6249–6254.

8. V. Tuan, G. Chuang, M. Otagiri, *Wiley Intersci.* **2006**, *18*, 159–166.

9. T. J. Leitereg, D. G. Guadagni, J. Harris, T. R. Mon, R. Teranishi, *J. Agric. Food Chem.* **1971**, *19*, 785–787.

10. I. A. Jaffe, K. Altman, P. Merryman, *J. Clin. Invest.* **1964**, *43*, 1869–1873.

11. J. P. and C. S. J. Hyttel, K. P. Bøgesø, *J. Neural Transm.* **1992**, *88*, 157–160.

12. A. W. and H. F. A. Ulla Lepolaa, *Int. Clin. Psychopharmacol.* **2004**, *19*, 149–155.

13. H. B. Kagan, K. Gopalaiah, *New J. Chem.* **2011**, *35*, 1933.

14. J. Crosby, *Tetrahedron* **1991**, *47*, 4789–4846.

15. H. Aboul-Enein, I. Ali, *Chiral Separations By Liquid Chromatography And Related Technologies*, **2010**.

16. E. M. Carreira, L. Kvaerno, *Classics in Stereoselective Synthesis*, **2009**.

17. R. Noyori, *Asymmetric Catalysis In Organic Synthesis*, **1994**.

18. E. N. Jacobsen, A. Pfaltz, H. Yamamoto, *Comprehensive Asymmetric Catalysis I-III*, **2001**.

19. Q. Peng, F. Duarte, R. S. Paton, *Chem. Soc. Rev.* **2016**, *45*, 6093–6107.

20. J. F. Hartwig, *Organotransition Metal Chemistry - From Bonding to Catalysis*, **2010**.

References

21. S. W. Benson, *J. Chem. Educ.* **1965**, *42*, 502.

22. H. Nozaki, S. Moriuti, H. Takaya, R. Noyori, *Tetrahedron Lett.* **1966**, *7*, 5239–5244.

23. W. S. Knowles, R. Noyori, *Acc. Chem. Res.* **2007**, *40*, 1238–1239.

24. T. P. Dang, H. B. Kagan, *J. Chem. Soc. D Chem. Commun.* **1971**, *7*, 481.

25. W. S. Knowles, *Angew. Chemie Int. Ed.* **2002**, *41*, 1998.

26. K. B. Sharpless, *Angew. Chemie Int. Ed.* **2002**, *41*, 2024.

27. M. M. Heravi, V. Zadsirjan, M. Esfandyari, T. B. Lashaki, *Tetrahedron: Asymmetry* **2017**, *28*, 987–1043.

28. J. A. Bodkin, M. D. McLeod, *J. Chem. Soc. Perkin 1* **2002**, *24*, 2733–2746.

29. R. Noyori, *Angew. Chemie Int. Ed.* **2002**, *41*, 2008.

30. M. Emura, H. Matsuda, *Chem. Biodivers.* **2014**, *11*, 1688–1699.

31. A. Pfaltz, *Acc. Chem. Res.* **1993**, *26*, 339–345.

32. A. Pfaltz, J. Blankenstein, R. Hilgraf, E. Hörmann, S. McIntyre, F. Menges, M. Schönleber, S. P. Smidt, B. Wüstenberg, N. Zimmermann, *Adv. Synth. Catal.* **2003**, *345*, 33–43.

33. A. E. Shilov, G. B. Shul'pin, *Chem. Rev.* **1997**, *97*, 2879–2932.

34. N. Candeias, C. Afonso, *Curr. Org. Chem.* **2009**, *13*, 763–787.

35. L. Stateman, K. Nakafuku, D. Nagib, *Synthesis (Stuttg).* **2018**, *50*, 1569–1586.

36. S. Chiba, H. Chen, *Org. Biomol. Chem.* **2014**, *12*, 4051–4060.

37. S. Masamune, *J. Am. Chem. Soc.* **1964**, *86*, 290–291.

38. R. M. Cory, F. R. McLaren, *J. Chem. Soc. Chem. Commun.* **1977**, 587.

39. A. R. Dick, M. S. Sanford, *Tetrahedron* **2006**, *62*, 2439–2463.

40. J. F. Hartwig, *J. Am. Chem. Soc.* **2016**, *138*, 2–24.

41. C. G. Newton, S. Wang, C. C. Oliveira, N. Cramer, *Chem. Rev.* **2017**, *117*, 8908–8976.

42. T. G. Saint-Denis, R.-Y. Zhu, G. Chen, Q.-F. Wu, J.-Q. Yu, *Science (80-.).* **2018**, *359*, eaao4798.

References

43. K. L. Gorres, R. T. Raines, *Anal. Biochem.* **2009**, *386*, 181–185.

44. M. W. Peters, P. Meinhold, A. Glieder, F. H. Arnold, *J. Am. Chem. Soc.* **2003**, *125*, 13442–13450.

45. L. P. Wackett, L. D. Kwart, D. T. Gibson, *Biochemistry* **1988**, *27*, 1360–1367.

46. M. Milan, M. Bietti, M. Costas, *Chem. Commun.* **2018**, *54*, 9559–9570.

47. M. Salamone, M. Bietti, *Acc. Chem. Res.* **2015**, *48*, 2895–2903.

48. V. Dantignana, M. Milan, O. Cussó, A. Company, M. Bietti, M. Costas, *ACS Cent. Sci.* **2017**, *3*, 1350–1358.

49. A. Miyafuji, T. Katsuki, *Tetrahedron* **1998**, *54*, 10339–10348.

50. T. Punniyamurthy, A. Miyafuji, T. Katsuki, *Tetrahedron Lett.* **1998**, *39*, 8295–8298.

51. B. Qiu, D. Xu, Q. Sun, C. Miao, Y. Lee, X. Li, W. Nam, W. Sun, *ACS Catal.* **2018**, *8*, 2479–2487.

52. J. T. Groves, P. Viski, *J. Am. Chem. Soc.* **1989**, *111*, 8537–8538.

53. F. Burg, M. Gicquel, S. Breitenlechner, A. Pöthig, T. Bach, *Angew. Chemie Int. Ed.* **2018**, *57*, 2953–2957.

54. Z. Gross, S. Ini, *Org. Lett.* **1999**, *1*, 2077–2080.

55. H. M. L. Davies, R. E. J. Beckwith, *Chem. Rev.* **2003**, *103*, 2861–2904.

56. H. M. L. Davies, J. R. Manning, *Nature* **2008**, *451*, 417–424.

57. M. P. Doyle, R. Duffy, M. Ratnikov, L. Zhou, *Chem. Rev.* **2010**, *110*, 704–724.

58. H. M. L. Davies, D. Morton, *Chem. Soc. Rev.* **2011**, *40*, 1857.

59. M. Kennedy, M. A. McKervey, A. R. Maguire, G. H. P. Roos, *J. Chem. Soc., Chem. Commun.* **1990**, 361–362.

60. F. G. Adly, A. Ghanem, *Chirality* **2014**, *26*, 692–711.

61. H. Lim, G. A. Sulikowski, *J. Org. Chem.* **1995**, *60*, 2326–2327.

62. C. J. Flynn, C. J. Elcoate, S. E. Lawrence, A. R. Maguire, *J. Am. Chem. Soc.* **2010**, *132*, 1184–1185.

References

63. L. A. Clarke, A. Ring, A. Ford, A. S. Sinha, S. E. Lawrence, A. R. Maguire, *Org. Biomol. Chem.* **2014**, *12*, 7612–7628.

64. T. A. Brouder, C. N. Slattery, A. Ford, U. B. R. Khandavilli, E. Skořepová, K. S. Eccles, M. Lusi, S. E. Lawrence, A. R. Maguire, *J. Org. Chem.* **2019**, *84*, 7543–7563.

65. A. G. Schafer, S. B. Blakey, *Chem. Soc. Rev.* **2015**, *44*, 5969–5980.

66. S. Hashimoto, N. Watanabe, S. Ikegami, *Tetrahedron Lett.* **1990**, *31*, 5173–5174.

67. M. P. Doyle, A. Van Oeveren, L. J. Westrum, M. N. Protopopova, T. W. Clayton, *J. Am. Chem. Soc.* **1991**, *113*, 8982–8984.

68. M. P. Doyle, M. N. Protopopova, W. R. Winchester, K. L. Daniel, *Tetrahedron Lett.* **1992**, *33*, 7819–7822.

69. N. McCarthy, M. A. McKervey, T. Ye, M. McCann, E. Murphy, M. P. Doyle, *Tetrahedron Lett.* **1992**, *33*, 5983–5986.

70. A. Padwa, D. J. Austin, A. T. Price, M. A. Semones, M. P. Doyle, M. N. Protopopova, W. R. Winchester, A. Tran, *J. Am. Chem. Soc.* **1993**, *115*, 8669–8680.

71. M. P. Doyle, A. B. Dyatkin, G. H. P. Roos, F. Canas, D. A. Pierson, A. van Basten, P. Mueller, P. Polleux, *J. Am. Chem. Soc.* **1994**, *116*, 4507–4508.

72. M. P. Doyle, A. B. Dyatkin, J. S. Tedrow, *Tetrahedron Lett.* **1994**, *35*, 3853–3856.

73. M. P. Doyle, Q.-L. Zhou, C. E. Raab, G. H. P. Roos, *Tetrahedron Lett.* **1995**, *36*, 4745–4748.

74. M. P. Doyle, A. B. Dyatkin, M. N. Protopopova, C. I. Yang, C. S. Miertschin, W. R. Winchester, S. H. Simonsen, V. Lynch, R. Ghosh, *Recl. des Trav. Chim. des Pays-Bas* **1995**, *114*, 163–170.

75. M. P. Doyle, A. V Kalinin, D. G. Ene, *J. Am. Chem. Soc.* **1996**, *118*, 8837–8846.

76. M. Anada, S. Hashimoto, *Tetrahedron Lett.* **1998**, *39*, 79–82.

77. M. Anada, O. Mita, H. Watanabe, S. Kitagaki, S. Hashimoto, *Synlett* **1999**, *1999*, 1775–1777.

78. D. M. Guptill, H. M. L. Davies, *J. Am. Chem. Soc.* **2014**, *136*, 17718–17721.

References

79.   C. Qin, H. M. L. Davies, *J. Am. Chem. Soc.* **2014**, *136*, 9792–9796.

80.   J. He, L. G. Hamann, H. M. L. Davies, R. E. J. Beckwith, *Nat. Commun.* **2015**, *6*, 5943.

81.   K. Liao, S. Negretti, D. G. Musaev, J. Bacsa, H. M. L. Davies, *Nature* **2016**, *533*, 230–234.

82.   K. Liao, T. C. Pickel, V. Boyarskikh, J. Bacsa, D. G. Musaev, H. M. L. Davies, *Nature* **2017**, *551*, 609–613.

83.   I. Nägeli, C. Baud, G. Bernardinelli, Y. Jacquier, M. Moraon, P. Müller, *Helv. Chim. Acta* **1997**, *80*, 1087–1105.

84.   C. Fruit, P. Müller, *Tetrahedron: Asymmetry* **2004**, *15*, 1019–1026.

85.   C. Fruit, P. Müller, *Helv. Chim. Acta* **2004**, *87*, 1607–1615.

86.   R. P. Reddy, H. M. L. Davies, *Org. Lett.* **2006**, *8*, 5013–5016.

87.   A. Nasrallah, V. Boquet, A. Hecker, P. Retailleau, B. Darses, P. Dauban, *Angew. Chemie Int. Ed.* **2019**, *58*, 8192–8196.

88.   D. N. Zalatan, J. Du Bois, *J. Am. Chem. Soc.* **2008**, *130*, 9220–9221.

89.   J. Liang, S. Yuan, J. Huang, W.-Y. Yu, C.-M. Che, *Angew. Chemie Int. Ed.* **2002**, *41*, 3465–3468.

90.   E. Milczek, N. Boudet, S. Blakey, *Angew. Chemie Int. Ed.* **2008**, *47*, 6825–6828.

91.   Y. Park, S. Chang, *Nat. Catal.* **2019**, *2*, 219–227.

92.   H. Wang, Y. Park, Z. Bai, S. Chang, G. He, G. Chen, *J. Am. Chem. Soc.* **2019**, *141*, 7194–7201.

93.   F. Kakiuchi, S. Murai, *Acc. Chem. Res.* **2002**, *35*, 826–834.

94.   D. A. Colby, A. S. Tsai, R. G. Bergman, J. A. Ellman, *Acc. Chem. Res.* **2012**, *45*, 814–825.

95.   J. F. Hartwig, *Acc. Chem. Res.* **2012**, *45*, 864–873.

96.   M. Murai, H. Takeshima, H. Morita, Y. Kuninobu, K. Takai, *J. Org. Chem.* **2015**, *80*, 5407–5414.

97.   T. Lee, J. F. Hartwig, *Angew. Chemie Int. Ed.* **2016**, *55*, 8723–8727.

References

98.   B. Su, T. Zhou, P. Xu, Z. Shi, J. F. Hartwig, *Angew. Chemie Int. Ed.* **2017**, *56*, 7205–7208.

99.   M. Zhang, J. Liang, G. Huang, *J. Org. Chem.* **2019**, *84*, 2372–2376.

100.   S. Pan, Y. Matsuo, K. Endo, T. Shibata, *Tetrahedron* **2012**, *68*, 9009–9015.

101.   Y. Tahara, M. Michino, M. Ito, K. S. Kanyiva, T. Shibata, *Chem. Commun.* **2015**, *51*, 16660–16663.

102.   S. Pan, K. Endo, T. Shibata, *Org. Lett.* **2011**, *13*, 4692–4695.

103.   R. L. Reyes, T. Harada, T. Taniguchi, K. Monde, T. Iwai, M. Sawamura, *Chem. Lett.* **2017**, *46*, 1747–1750.

104.   T. Ohmura, J. F. Hartwig, *J. Am. Chem. Soc.* **2002**, *124*, 15164–15165.

105.   R. L. Reyes, T. Iwai, S. Maeda, M. Sawamura, *J. Am. Chem. Soc.* **2019**, *141*, 6817–6821.

106.   C. E. Kefalidis, M. Davi, P. M. Holstein, E. Clot, O. Baudoin, *J. Org. Chem.* **2014**, *79*, 11903–11910.

107.   A. Lei, W. Liu, C. Liu, M. Chen, *Dalt. Trans.* **2010**, *39*, 10352.

108.   M. Chaumontet, R. Piccardi, N. Audic, J. Hitce, J.-L. Peglion, E. Clot, O. Baudoin, *J. Am. Chem. Soc.* **2008**, *130*, 15157–15166.

109.   M. Lafrance, S. I. Gorelsky, K. Fagnou, *J. Am. Chem. Soc.* **2007**, *129*, 14570–14571.

110.   L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315–1345.

111.   D. García-Cuadrado, P. de Mendoza, A. A. C. Braga, F. Maseras, A. M. Echavarren, *J. Am. Chem. Soc.* **2007**, *129*, 6880–6886.

112.   D. García-Cuadrado, A. A. C. Braga, F. Maseras, A. M. Echavarren, *J. Am. Chem. Soc.* **2006**, *128*, 1066–1067.

113.   D. L. Davies, S. M. A. Donald, S. A. Macgregor, *J. Am. Chem. Soc.* **2005**, *127*, 13754–13755.

114.   D. Lapointe, K. Fagnou, *Chem. Lett.* **2010**, *39*, 1118–1126.

115.   S. Greßies, F. J. R. Klauck, J. H. Kim, C. G. Daniliuc, F. Glorius, *Angew. Chemie Int. Ed.* **2018**, *57*, 9950–9954.

References

116. S. Fukagawa, Y. Kato, R. Tanaka, M. Kojima, T. Yoshino, S. Matsunaga, *Angew. Chemie Int. Ed.* **2019**, *58*, 1153–1157.

117. D. Sekine, K. Ikeda, S. Fukagawa, M. Kojima, T. Yoshino, S. Matsunaga, *Organometallics* **2019**, acs.organomet.9b00407.

118. B. F. Shi, N. Maugel, Y. H. Zhang, J. Q. Yu, *Angew. Chemie - Int. Ed.* **2008**, *47*, 4882–4886.

119. M. Wasa, K. M. Engle, D. W. Lin, E. J. Yoo, J.-Q. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 19598–19601.

120. Q.-F. Wu, X.-B. Wang, P.-X. Shen, J.-Q. Yu, *ACS Catal.* **2018**, *8*, 2577–2581.

121. P.-X. Shen, L. Hu, Q. Shao, K. Hong, J.-Q. Yu, *J. Am. Chem. Soc.* **2018**, *140*, 6545–6549.

122. Q. Shao, Q.-F. Wu, J. He, J.-Q. Yu, *J. Am. Chem. Soc.* **2018**, *140*, 5322–5325.

123. Y. Park, Z. L. Niemeyer, J.-Q. Yu, M. S. Sigman, *Organometallics* **2018**, *37*, 203–210.

124. H. Park, P. Verma, K. Hong, J.-Q. Yu, *Nat. Chem.* **2018**, *10*, 755–762.

125. L. Hu, P.-X. Shen, Q. Shao, K. Hong, J. X. Qiao, J.-Q. Yu, *Angew. Chemie Int. Ed.* **2019**, *58*, 2134–2138.

126. M. S. Andrä, L. Schifferer, C. H. Pollok, C. Merten, L. J. Gooßen, J. Yu, *Chem. – A Eur. J.* **2019**, chem.201902046.

127. K.-J. Xiao, D. W. Lin, M. Miura, R.-Y. Zhu, W. Gong, M. Wasa, J.-Q. Yu, *J. Am. Chem. Soc.* **2014**, *136*, 8138–8142.

128. K. S. L. Chan, H.-Y. Fu, J.-Q. Yu, *J. Am. Chem. Soc.* **2015**, *137*, 2042–2046.

129. F.-L. Zhang, K. Hong, T.-J. Li, H. Park, J.-Q. Yu, *Science (80-.).* **2016**, *351*, 252–256.

130. G. Chen, W. Gong, Z. Zhuang, M. S. Andrä, Y.-Q. Chen, X. Hong, Y.-F. Yang, T. Liu, K. N. Houk, J.-Q. Yu, *Science (80-.).* **2016**, *353*, 1023–1027.

131. Y.-F. Yang, G. Chen, X. Hong, J.-Q. Yu, K. N. Houk, *J. Am. Chem. Soc.* **2017**, *139*, 8514–8521.

132. Q.-F. Wu, P.-X. Shen, J. He, X.-B. Wang, F. Zhang, Q. Shao, R.-Y. Zhu, C. Mapelli, J.

References

X. Qiao, M. A. Poss, et al., *Science (80-.).* **2017**, *355*, 499–503.

133. P. Jain, P. Verma, G. Xia, J.-Q. Yu, *Nat. Chem.* **2017**, *9*, 140–144.

134. J. He, Q. Shao, Q. Wu, J. Yu, *J. Am. Chem. Soc.* **2017**, *139*, 3344–3347.

135. S.-Y. Yan, Y.-Q. Han, Q.-J. Yao, X.-L. Nie, L. Liu, B.-F. Shi, *Angew. Chemie Int. Ed.* **2018**, *57*, 9093–9097.

136. Y.-Q. Han, Y. Ding, T. Zhou, S.-Y. Yan, H. Song, B.-F. Shi, *J. Am. Chem. Soc.* **2019**, *141*, 4558–4563.

137. S.-B. Yan, S. Zhang, W.-L. Duan, *Org. Lett.* **2015**, *17*, 2458–2461.

138. H. Wang, H.-R. Tong, G. He, G. Chen, *Angew. Chemie Int. Ed.* **2016**, *55*, 15387–15391.

139. A. P. Smalley, J. D. Cuthbertson, M. J. Gaunt, *J. Am. Chem. Soc.* **2017**, *139*, 1412–1415.

140. M. Nakanishi, D. Katayev, C. Besnard, E. P. Kündig, *Angew. Chemie Int. Ed.* **2011**, *50*, 7438–7441.

141. M. Nakanishi, D. Katayev, C. Besnard, E. P. Kündig, *Chim. Int. J. Chem.* **2012**, *66*, 241–243.

142. S. Anas, A. Cordi, H. B. Kagan, *Chem. Commun.* **2011**, *47*, 11483.

143. W. A. Herrmann, C. Köcher, L. J. Gooßen, G. R. J. Artus, *Chem. - A Eur. J.* **1996**, *2*, 1627–1636.

144. E. Larionov, M. Nakanishi, D. Katayev, C. Besnard, E. P. Kündig, *Chem. Sci.* **2013**, *4*, 1995.

145. D. Katayev, M. Nakanishi, T. Bürgi, E. P. Kündig, *Chem. Sci.* **2012**, *3*, 1422.

146. D. Katayev, E. Larionov, M. Nakanishi, C. Besnard, E. P. Kündig, *Chem. - A Eur. J.* **2014**, *20*, 15021–15030.

147. P. A. Donets, T. Saget, N. Cramer, *Organometallics* **2012**, *31*, 8040–8046.

148. T. Saget, S. J. Lemouzy, N. Cramer, *Angew. Chemie Int. Ed.* **2012**, *51*, 2238–2242.

149. T. Saget, N. Cramer, *Angew. Chemie Int. Ed.* **2012**, *51*, 12842–12845.

150. J. Pedroni, M. Boghi, T. Saget, N. Cramer, *Angew. Chemie Int. Ed.* **2014**, *53*, 9064–9067.

References

151. J. Pedroni, T. Saget, P. A. Donets, N. Cramer, *Chem. Sci.* **2015**, *6*, 5164–5171.

152. J. Pedroni, N. Cramer, *Angew. Chemie Int. Ed.* **2015**, *54*, 11826–11829.

153. C. L. Ladd, A. B. Charette, *Org. Lett.* **2016**, *18*, 6046–6049.

154. C. Mayer, C. L. Ladd, A. B. Charette, *Org. Lett.* **2019**, *21*, 2639–2644.

155. N. Martin, C. Pierre, M. Davi, R. Jazzar, O. Baudoin, *Chem. - A Eur. J.* **2012**, *18*, 4480–4484.

156. P. M. Holstein, M. Vogler, P. Larini, G. Pilet, E. Clot, O. Baudoin, *ACS Catal.* **2015**, *5*, 4300–4308.

157. J. Pedroni, N. Cramer, *J. Am. Chem. Soc.* **2017**, *139*, 12398–12401.

158. D. Dailler, R. Rocaboy, O. Baudoin, *Angew. Chemie Int. Ed.* **2017**, *56*, 7218–7222.

159. H.-R. Tong, S. Zheng, X. Li, Z. Deng, H. Wang, G. He, Q. Peng, G. Chen, *ACS Catal.* **2018**, *8*, 11502–11512.

160. T. Watanabe, S. Oishi, N. Fujii, H. Ohno, *Org. Lett.* **2008**, *10*, 1759–1762.

161. R. J. Phipps, G. L. Hamilton, F. D. Toste, *Nat. Chem.* **2012**, *4*, 603–614.

162. M. Mahlau, B. List, *Angew. Chemie Int. Ed.* **2013**, *52*, 518–533.

163. S. M. Inamdar, V. S. Shinde, N. T. Patil, *Org. Biomol. Chem.* **2015**, *13*, 8116–8162.

164. S. Zhang, J. Lu, J. Ye, W. Duan, *Chinese J. Org. Chem.* **2016**, *36*, 752.

165. K. B. Simonsen, K. V. Gothelf, K. A. Jørgensen, *J. Org. Chem.* **1998**, *63*, 7536–7538.

166. D. Uraguchi, M. Terada, *J. Am. Chem. Soc.* **2004**, *126*, 5356–5357.

167. T. Kano, T. Yurino, K. Maruoka, *Angew. Chemie Int. Ed.* **2013**, *52*, 11509–11512.

168. T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew. Chemie Int. Ed.* **2004**, *43*, 1566–1568.

169. R. I. Storer, D. E. Carrera, Y. Ni, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2006**, *128*, 84–86.

170. N. V Sewgobind, M. J. Wanner, S. Ingemann, R. de Gelder, J. H. van Maarseveen, H. Hiemstra, *J. Org. Chem.* **2008**, *73*, 6405–6408.

References

171. P. Jiao, D. Nakashima, H. Yamamoto, *Angew. Chemie Int. Ed.* **2008**, *47*, 2411–2413.

172. P. Jiao, D. Nakashima, H. Yamamoto, *Angew. Chemie - Int. Ed.* **2008**, *47*, 2411–2413.

173. G. Pousse, A. Devineau, V. Dalla, L. Humphreys, M.-C. Lasne, J. Rouden, J. Blanchet, *Tetrahedron* **2009**, *65*, 10617–10622.

174. N. Momiyama, H. Nishimoto, M. Terada, *Org. Lett.* **2011**, *13*, 2126–2129.

175. W. Hu, J. Zhou, X. Xu, W. Liu, L. Gong, in *Org. Synth.*, John Wiley & Sons, Inc., Hoboken, NJ, USA, **2011**, pp. 406–417.

176. T. J. Reddy, M. Leclair, M. Proulx, *Synlett* **2005**, 583–586.

177. L. Weber, D. Eickhoff, J. Kahlert, L. Böhling, A. Brockhinke, H.-G. Stammler, B. Neumann, M. A. Fox, *Dalt. Trans.* **2012**, *41*, 10328.

178. R. Labrecque, L. C. Ciobanu, R. Labrecque, L. C. Ciobanu, *Non-Steroidal Antiandrogens and Selective Androgen Receptor Modulators with a Pyridyl Moiety*, **2015**, US 2015/0175576 A1.

179. S. Rousseaux, B. Liégault, K. Fagnou, *Chem. Sci.* **2012**, *3*, 244–248.

180. P. M. Holstein, J. J. Holstein, E. C. Escudero-Adán, O. Baudoin, A. M. Echavarren, *Tetrahedron: Asymmetry* **2017**, *28*, 1321–1329.

181. I. Ugarriza, U. Uria, L. Carrillo, J. L. Vicario, E. Reyes, *Chem. - A Eur. J.* **2014**, *20*, 11650–11654.

182. S. W. Wright, R. L. Dow, L. D. McClure, D. L. Hageman, *Tetrahedron Lett.* **1996**, *37*, 6965–6968.

183. J. Zhao, Z. Wei, X. Zeng, X. Liu, *Dalt. Trans.* **2012**, *41*, 11125.

184. C. Dockendorff, P. W. Faloon, M. Yu, W. Youngsaye, M. Penman, T. J. F. Nieland, P. P. Nag, T. A. Lewis, J. Pu, M. Bennion, et al., *ACS Med. Chem. Lett.* **2015**, *6*, 375–380.

185. T. M. Figg, M. Wasa, J.-Q. Yu, D. G. Musaev, *J. Am. Chem. Soc.* **2013**, *135*, 14206–14214.

186. W. Feng, T. Wang, D. Liu, X. Wang, Y. Dang, *ACS Catal.* **2019**, *9*, 6672–6680.

187. L. Yang, M. Neuburger, O. Baudoin, *Angew. Chemie Int. Ed.* **2018**, *57*, 1394–1398.

References

188.   O. Baudoin, *Acc. Chem. Res.* **2017**, *50*, 1114–1123.

189.   R. Rocaboy, D. Dailler, O. Baudoin, *Org. Lett.* **2018**, *20*, 772–775.

190.   K. Yoshikawa, Y. Matsumoto, H. Hama, M. Tanaka, H. Zhai, Y. Fukuyama, S. Arihara, T. Hashimoto, *Chem. Pharm. Bull. (Tokyo).* **2009**, *57*, 311–314.

191.   M. Isaka, U. Srisanoh, M. Sappan, S. Supothina, T. Boonpratuang, *Phytochemistry* **2012**, *79*, 116–120.

192.   T. Kokubun, A. Scott-Brown, G. C. Kite, M. S. J. Simmonds, *J. Nat. Prod.* **2016**, *79*, 1698–1701.

193.   U. Becker, G. Erkel, T. Anke, O. Sterner, *Nat. Prod. Lett.* **1997**, *9*, 229–236.

194.   M. Clericuzio, F. Han, F. Pan, Z. Pang, O. Sterner, *Acta Chem. Scand.* **1998**, *52*, 1333–1337.

195.   K. Yoshikawa, A. Kaneko, Y. Matsumoto, H. Hama, S. Arihara, *J. Nat. Prod.* **2006**, *69*, 1267–1270.

196.   K. Fuji, *Chem. Rev.* **1993**, *93*, 2037–2066.

197.   E. J. Corey, A. Guzman-Perez, *Angew. Chemie Int. Ed.* **1998**, *37*, 388–401.

198.   I. Vargas-Baca, D. Mitra, H. J. Zulyniak, J. Banerjee, H. F. Sleiman, *Angew. Chemie Int. Ed.* **2001**, *40*, 4629–4632.

199.   I. Denissova, L. Barriault, *Tetrahedron* **2003**, *59*, 10105–10146.

200.   B. M. Trost, C. Jiang, *Synthesis (Stuttg).* **2006**, 369–396.

201.   P. G. Cozzi, R. Hilgraf, N. Zimmermann, *European J. Org. Chem.* **2007**, *2007*, 5969–5994.

202.   M. Bella, T. Gasperi, *Synthesis (Stuttg).* **2009**, *2009*, 1583–1614.

203.   C. Hawner, A. Alexakis, *Chem. Commun.* **2010**, *46*, 7295.

204.   E. V. Prusov, *Angew. Chemie Int. Ed.* **2017**, *56*, 14356–14358.

205.   D. L. J. Clive, M. Yu, M. Sannigrahi, *J. Org. Chem.* **2004**, *69*, 4116–4125.

206.   E. A. Tiong, D. Rivalti, B. M. Williams, J. L. Gleason, *Angew. Chemie Int. Ed.* **2013**, *52*, 3442–3445.

References

207. A. Arpin, J. M. Manthorpe, J. L. Gleason, *Org. Lett.* **2006**, *8*, 1359–1362.

208. G. A. Kraus, P. K. Choudhury, *J. Org. Chem.* **2002**, *67*, 5857–5859.

209. L. G. Quan, M. Lamrani, Y. Yamamoto, *J. Am. Chem. Soc.* **2000**, *122*, 4827–4828.

210. S. Würtz, C. Lohre, R. Fröhlich, K. Bergander, F. Glorius, *J. Am. Chem. Soc.* **2009**, *131*, 8344–8345.

211. G. Altenhoff, R. Goddard, C. W. Lehmann, F. Glorius, *J. Am. Chem. Soc.* **2004**, *126*, 15195–15201.

212. D. Katayev, Chiral N -Heterocyclic Carbene (NHC) Ligands in Pd-Catalyzed Cross-Coupling Reactions, University of geneva, **2012**.

213. D. Katayev, Y.-X. Jia, A. K. Sharma, D. Banerjee, C. Besnard, R. B. Sunoj, E. P. Kündig, *Chem. - A Eur. J.* **2013**, *19*, 11916–11927.

214. Y. X. Jia, D. Katayev, G. Bernardinelli, T. M. Seidel, E. P. Kündig, *Chem. - A Eur. J.* **2010**, *16*, 6300–6309.

215. F. Glorius, *Method for Producing Imidazolium Salts*, **2005**, US 2005/0240025 A1.

216. F. Glorius, G. Altenhoff, R. Goddard, C. Lehmann, *Chem. Commun.* **2002**, *2*, 2704–2705.

217. J.-N. Levy, C. M. Latham, L. Roisin, N. Kandziora, P. Di Fruscia, A. J. P. White, S. Woodward, M. J. Fuchter, *Org. Biomol. Chem.* **2012**, *10*, 512–515.

218. W. Guo, J. Li, N. Fan, W. Wu, P. Zhou, C. Xia, *Synth. Commun.* **2005**, *35*, 145–152.

219. S. Hisaindee, D. L. . Clive, *Tetrahedron Lett.* **2001**, *42*, 2253–2255.

220. M. P. Gore, S. J. Gould, D. D. Weller, *J. Org. Chem.* **1992**, *57*, 2774–2783.

221. Y. Hirano, K. Tokudome, H. Takikawa, K. Suzuki, *Synlett* **2016**, *28*, 214–220.

222. H. Weinstabl, M. Suhartono, Z. Qureshi, M. Lautens, *Angew. Chemie Int. Ed.* **2013**, *52*, 5305–5308.

223. Z.-T. He, H. Li, A. M. Haydl, G. T. Whiteker, J. F. Hartwig, *J. Am. Chem. Soc.* **2018**, *140*, 17197–17202.

224. T. Ishiyama, J. Takagi, J. F. Hartwig, N. Miyaura, *Angew. Chemie Int. Ed.* **2002**, *41*,

References

3056–3058.
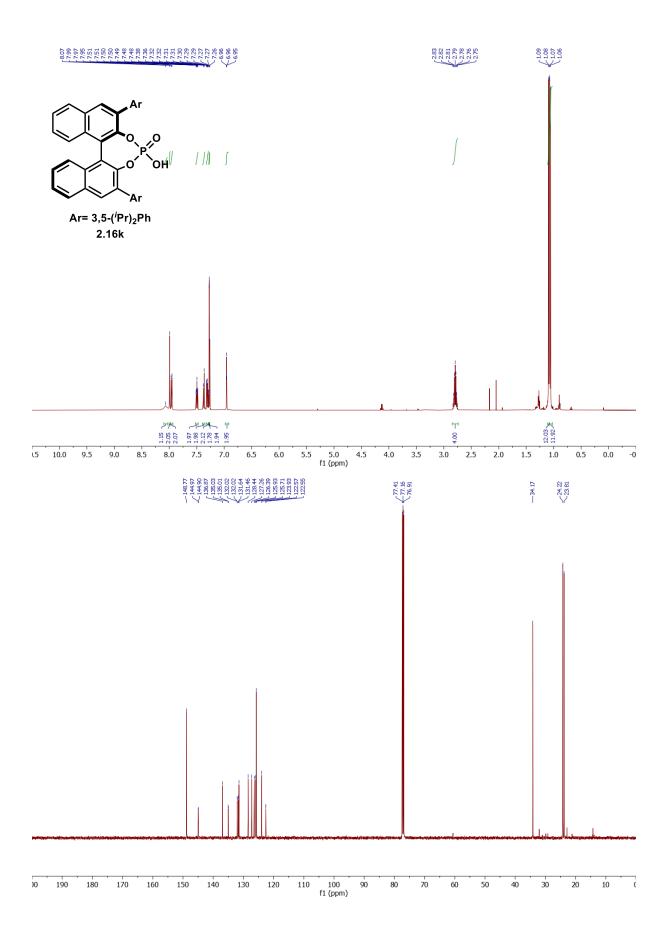
225. T. Ishiyama, J. Takagi, K. Ishida, N. Miyaura, N. R. Anastasi, J. F. Hartwig, *J. Am. Chem. Soc.* **2002**, *124*, 390–391.

226. J. M. Murphy, C. C. Tzschucke, J. F. Hartwig, *Org. Lett.* **2007**, *9*, 757–760.

227. C. C. Tzschucke, J. M. Murphy, J. F. Hartwig, *Org. Lett.* **2007**, *9*, 761–764.

228. C. W. Liskey, X. Liao, J. F. Hartwig, *J. Am. Chem. Soc.* **2010**, *132*, 11389–11391.

229. B. M. Partridge, J. F. Hartwig, *Org. Lett.* **2013**, *15*, 140–143.

230. P. S. Fier, J. Luo, J. F. Hartwig, *J. Am. Chem. Soc.* **2013**, *135*, 2552–2559.

231. T. Yakura, T. Konishi, *Synlett* **2007**, *2007*, 0765–0768.

232. T. Cooper, A. Novak, L. D. Humphreys, M. D. Walker, S. Woodward, *Adv. Synth. Catal.* **2006**, *348*, 686–690.

233. Y.-P. Li, Y.-C. Yang, Y.-K. Li, Z.-Y. Jiang, X.-Z. Huang, W.-G. Wang, X.-M. Gao, Q.-F. Hu, *Phytochem. Lett.* **2014**, *9*, 41–45.

234. R. He, X. Huang, Y. Zhang, L. Wu, H. Nie, D. Zhou, B. Liu, S. Deng, R. Yang, S. Huang, et al., *J. Nat. Prod.* **2016**, *79*, 2472–2478.

235. D.-H. Wang, K. M. Engle, B.-F. Shi, J.-Q. Yu, *Science (80-.)*. **2010**, *327*, 315–319.

236. J. D. Griffin, M. A. Zeller, D. A. Nicewicz, *J. Am. Chem. Soc.* **2015**, *137*, 11340–11348.

237. Z. Wang, C. Y. Guo, C. Yang, J. P. Chen, *J. Am. Chem. Soc.* **2019**, *141*, 5617–5622.

238. T. Saget, Enantioselective Palladium(0)-Catalyzed C-H Arylations, Ecole Polytechnique Fédérale de Zurich, **2014**.

239. J. Pedroni, Pd(0)-Catalysed C-H Functionalisations for the Enantioselective Synthesis of N-Heterocycles, Ecole Polytechnique Fédérale de Lausanne, **2017**.

240. T. Fukuda, A. Takehara, N. Haniu, M. Iwao, *Tetrahedron Asymmetry* **2000**, *11*, 4083–4091.

241. J. M. Seco, E. Quiñoá, R. Riguera, *Chem. Rev.* **2004**, *104*, 17–118.

242. D. J. Augeri, J. A. Robl, D. A. Betebenner, D. R. Magnin, A. Khanna, J. G. Robertson, A. Wang, L. M. Simpkins, P. Taunk, Q. Huang, et al., *J. Med. Chem.* **2005**, *48*, 5025–

References
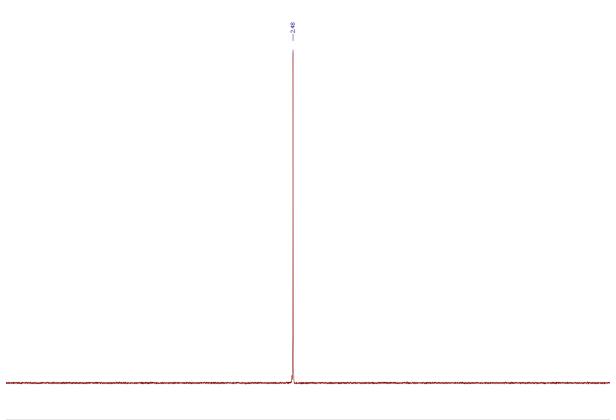
5037.

243.   N. Nella, E. Parker, J. Hitce, P. Larini, R. Jazzar, O. Baudoin, *Chem. - A Eur. J.* **2014**, *20*, 13272–13278.

244.   T. Takuwa, T. Minowa, H. Fujisawa, T. Mukaiyama, *Chem. Lett.* **2004**, *33*, 8–9.

References
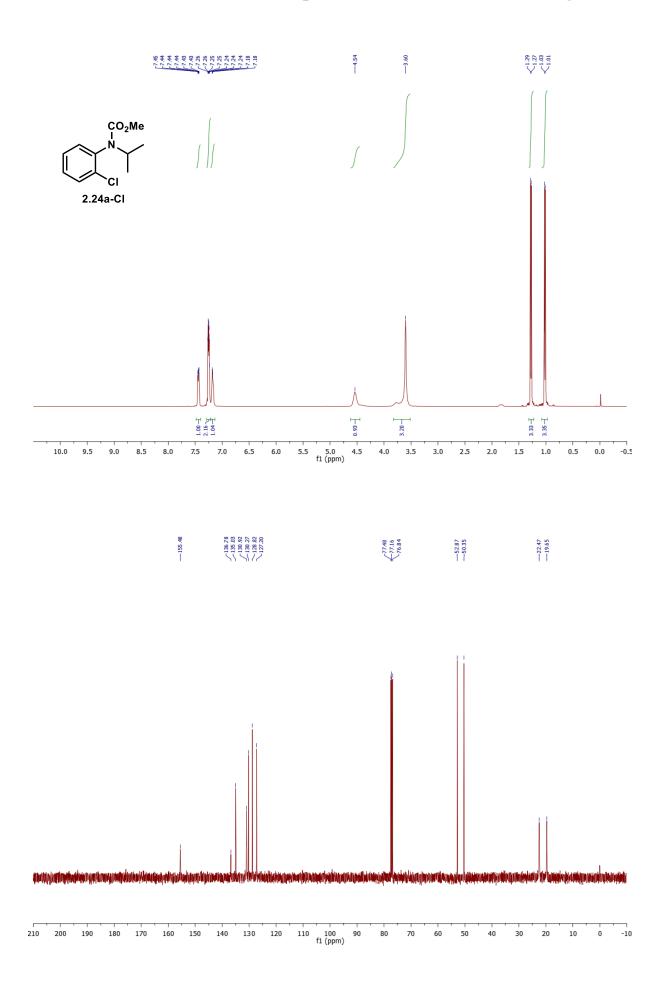
References

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

Ar= 3,5-(^{i}Pr)$_2$Ph

2.16k

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

2.24a-Cl

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

2.24a-Br

2.24a-I

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

2.24b

2.24c

CO$_2^i$Bu

2.24d

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

2.24f

-69.13

f1 (ppm)

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

112.19
112.21
112.22
112.24

10   0   -10   -20   -30   -40   -50   -60   -70   -80   -90   -100   -110   -120   -130   -140   -150   -160   -170   -180   -190   -200   -21(
f1 (ppm)

Structure label: 2.24i

^{1}H NMR peaks: 7.64, 7.64, 7.31, 7.30, 7.29, 7.28, 7.26, 7.13, 7.11, 4.51, 3.62, 1.30, 1.28, 1.03, 1.02

Integrations: 1.00, 1.09, 1.10, 1.06, 3.26, 3.48, 3.53

^{13}C NMR peaks: 155.11, 137.30, 134.01, 133.26, 131.40, 128.21, 126.65, 77.48, 77.16, 76.84, 53.00, 50.45, 22.64, 19.77

2.24j

2.24k

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

2.24n

-62.69

20	10	0	-10	-20	-30	-40	-50	-60	-70	-80	-90	-100	-110	-120	-130	-140	-150	-160	-170	-180	-190	-200	-210	-220

f1 (ppm)

2.24o

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

2.24q

2.24r

2.24t

CO₂Me
N
CO₂Me
Br

2.24v

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

2.24y

2.24z

-111.33

f1 (ppm)

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

2.24af

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

2.25a

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

mAU

PDA Multi 2 243nm,4nm

9.888
10.930

<Peak Table>

PDA Ch2 243nm
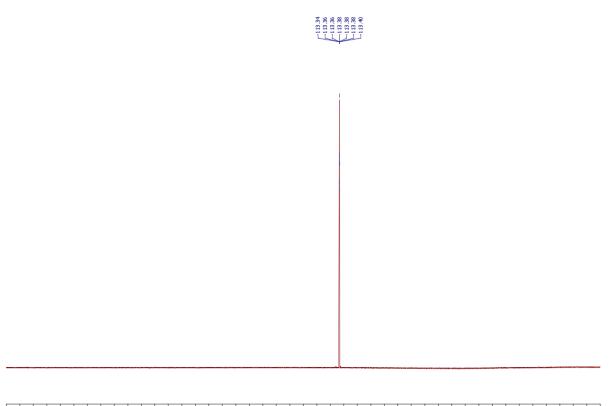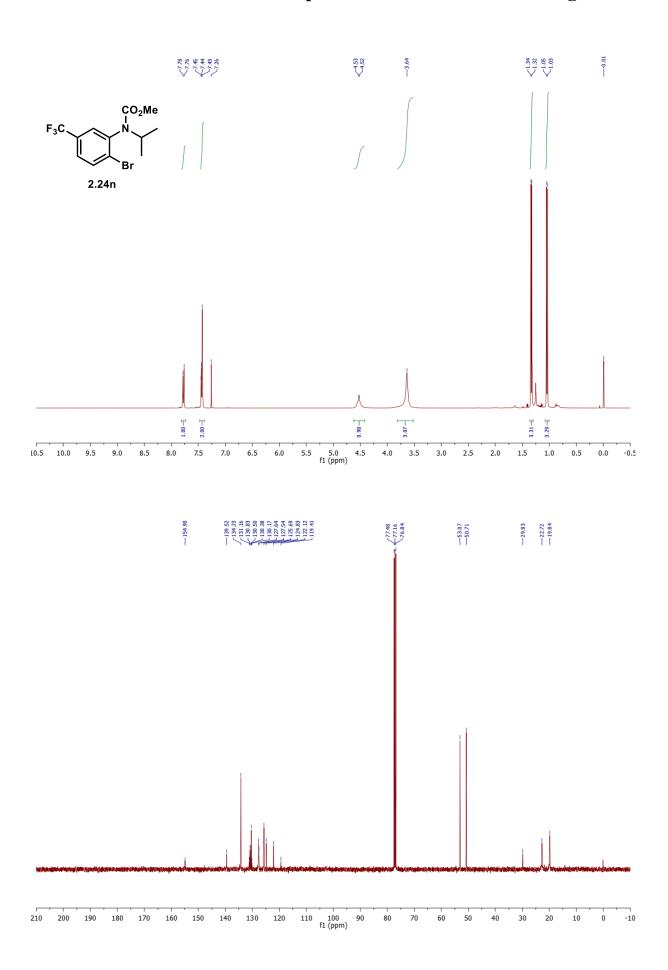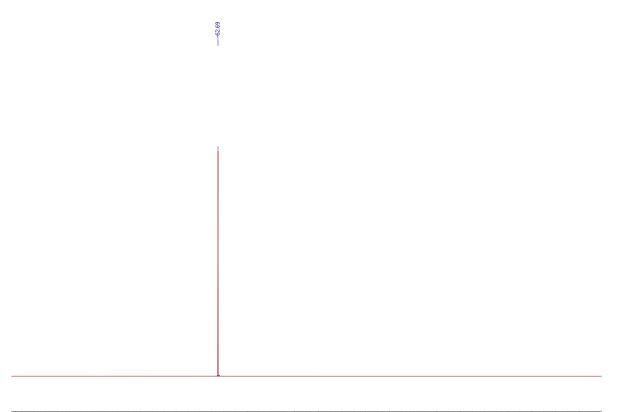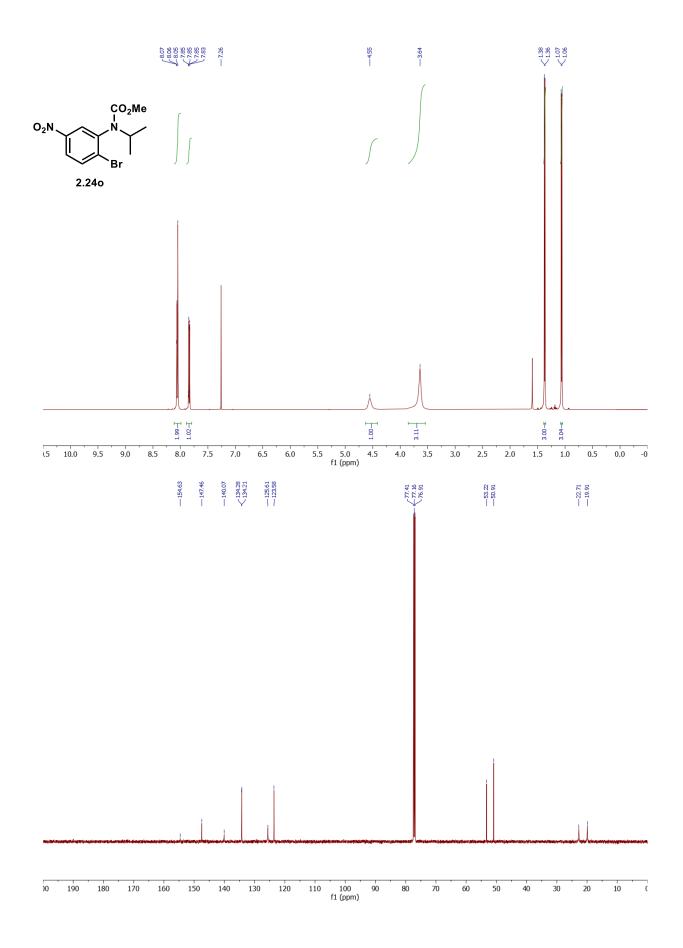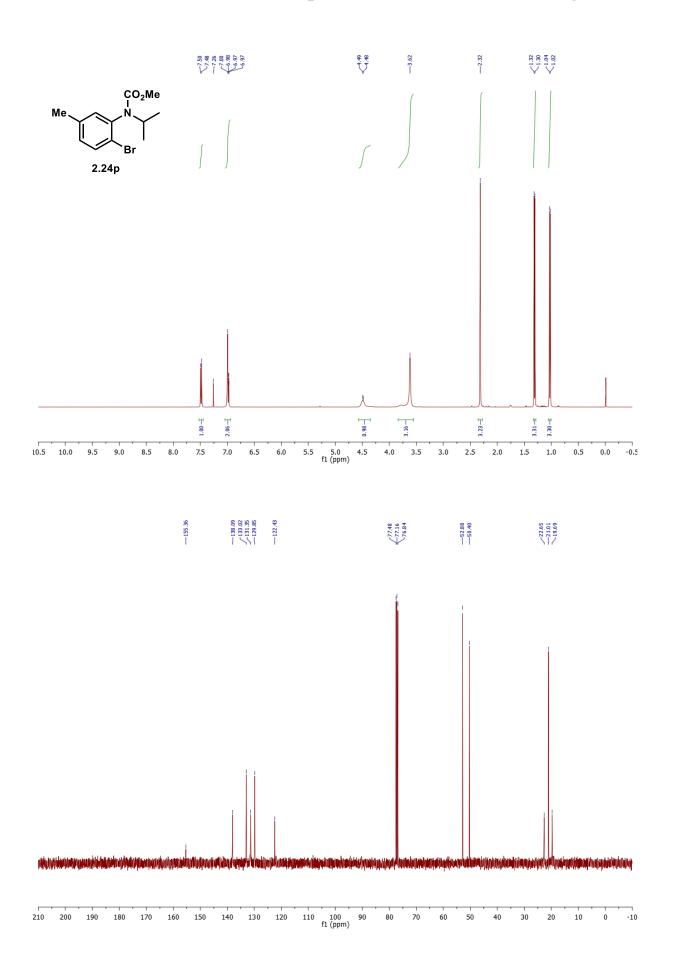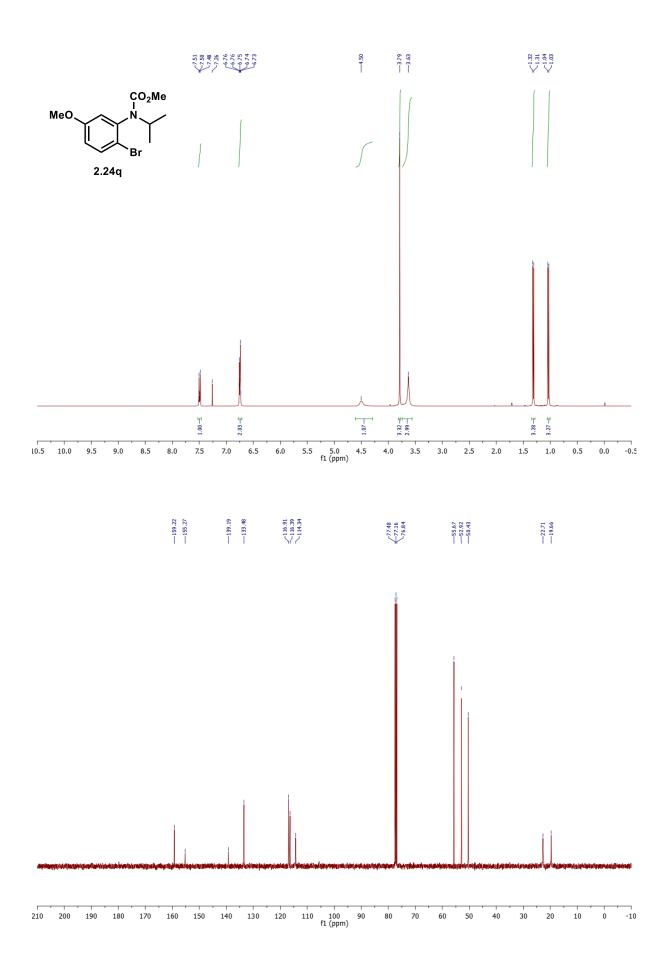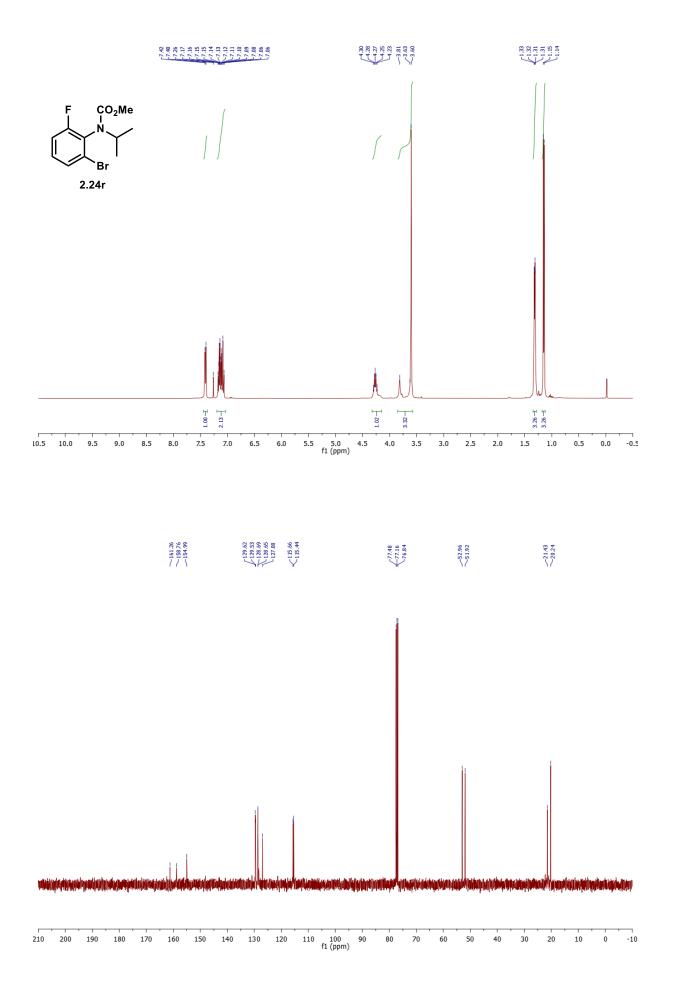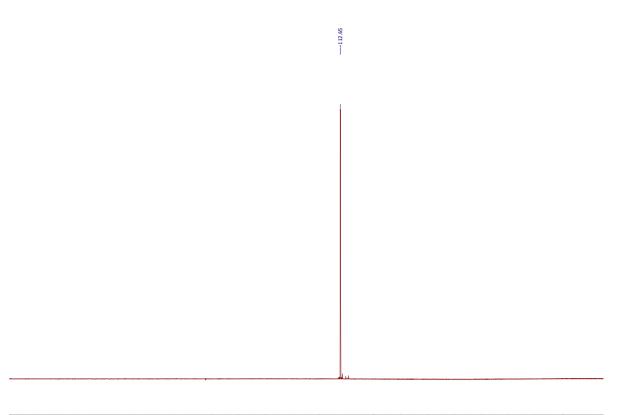
Peak#	Ret. Time	Area	Height	Area%
1	9.888	24265404	1591847	49.017
2	10.930	25238882	1495620	50.983
Total		49504286	3087467	100.000

mAU

PDA Multi 2 243nm,4nm

11.113

10.022

<Peak Table>

PDA Ch2 243nm

Peak#	Ret. Time	Area	Height	Area%
1	10.022	58166	4319	3.619
2	11.113	1548946	103968	96.381
Total		1607112	108287	100.000

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

Gram scale (5 mmol):

<Peak Table>

PDA Ch2 243nm

Peak#	Ret. Time	Area	Height	Area%
1	9.575	88777	6793	3.521
2	10.571	2432462	165708	96.479
Total		2521239	172501	100.000

From **2.24a-Cl**:
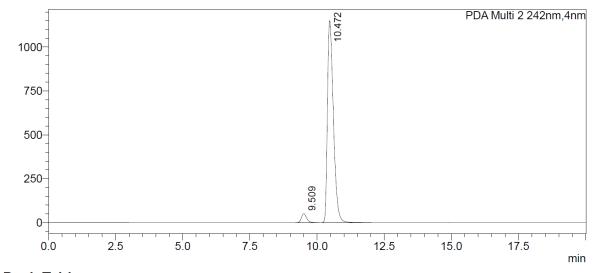
<Peak Table>

PDA Ch2 242nm
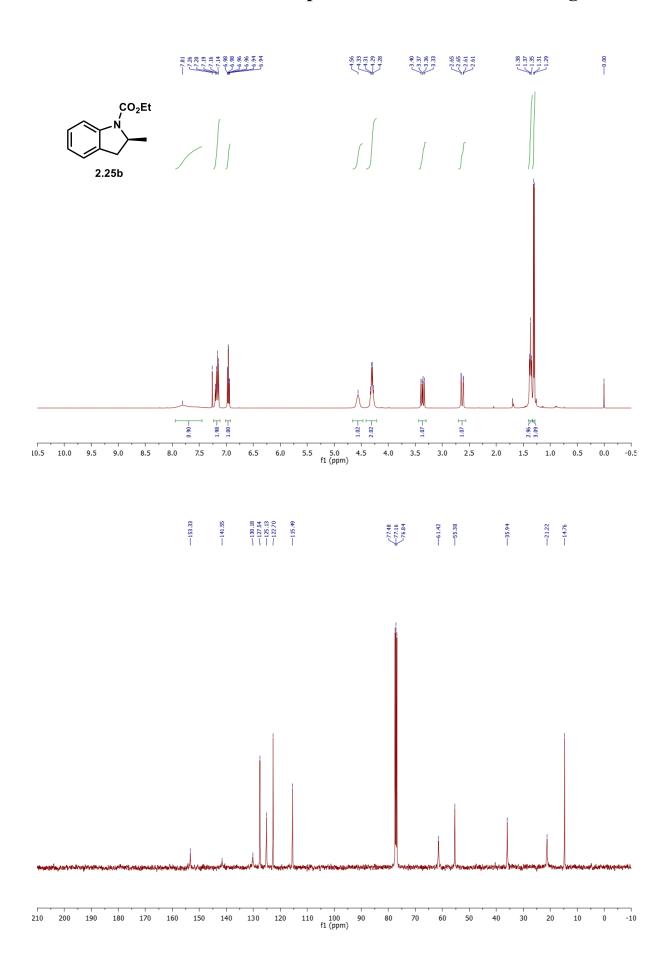
Peak#	Ret. Time	Area	Height	Area%
1	9.591	1570580	117053	8.529
2	10.584	16844490	1083280	91.471
Total		18415070	1200333	100.000

From **2.24a-I**:

mAU

PDA Multi 2 242nm,4nm

<Peak Table>

PDA Ch2 242nm
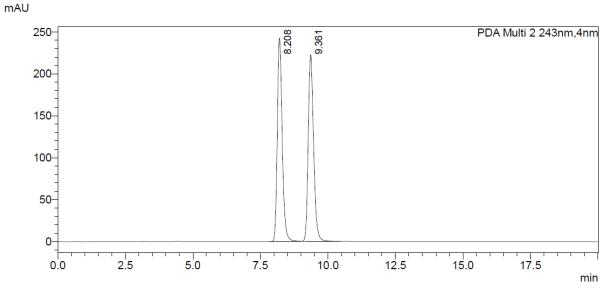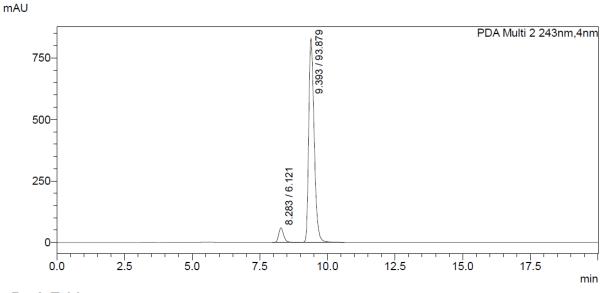
Peak#	Ret. Time	Area	Height	Area%
1	9.509	684830	51133	3.722
2	10.472	17716701	1150815	96.278
Total		18401531	1201947	100.000

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

2.25b

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

mAU

PDA Multi 2 243nm,4nm

\<Peak Table\>

PDA Ch2 243nm
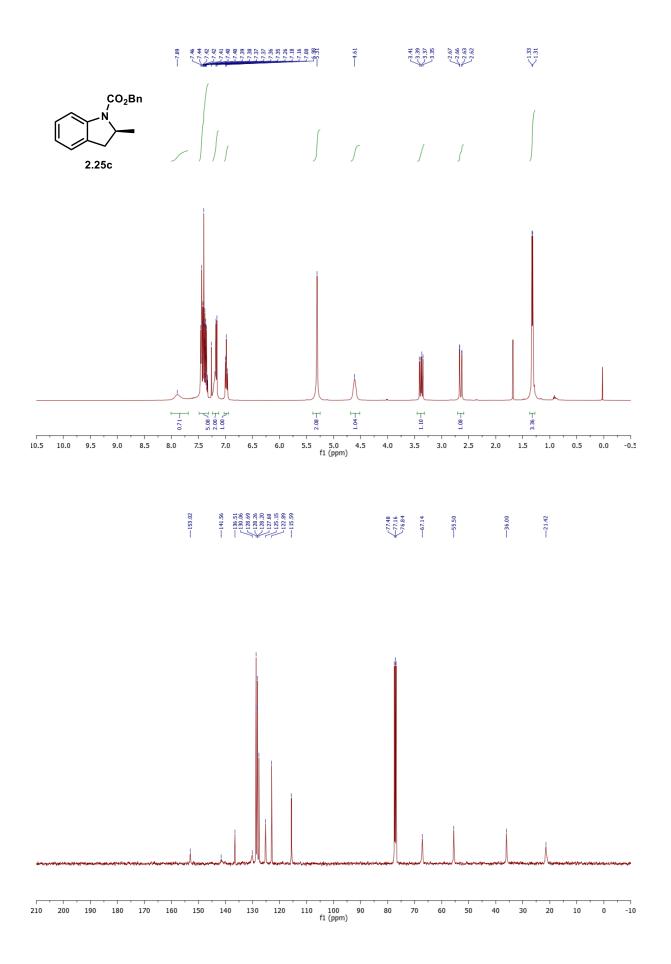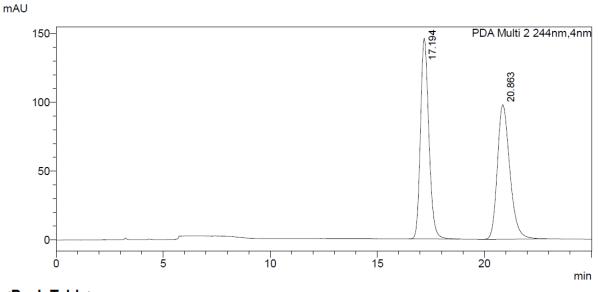
Peak#	Ret. Time	Area	Height	Area%
1	8.208	3075134	242442	49.975
2	9.361	3078236	222441	50.025
Total		6153370	464883	100.000

mAU

PDA Multi 2 243nm,4nm

\<Peak Table\>

PDA Ch2 243nm

Peak#	Ret. Time	Area	Height	Area%
1	8.283	753891	59486	6.121
2	9.393	11561909	829587	93.879
Total		12315801	889073	100.000

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

2.25c

<Peak Table>

PDA Ch2 244nm
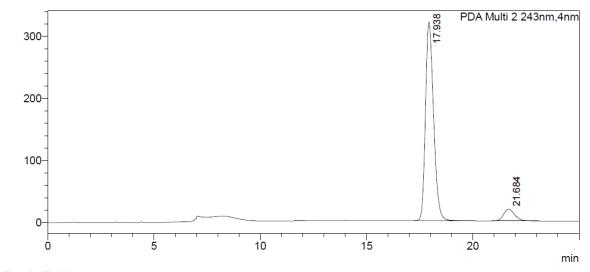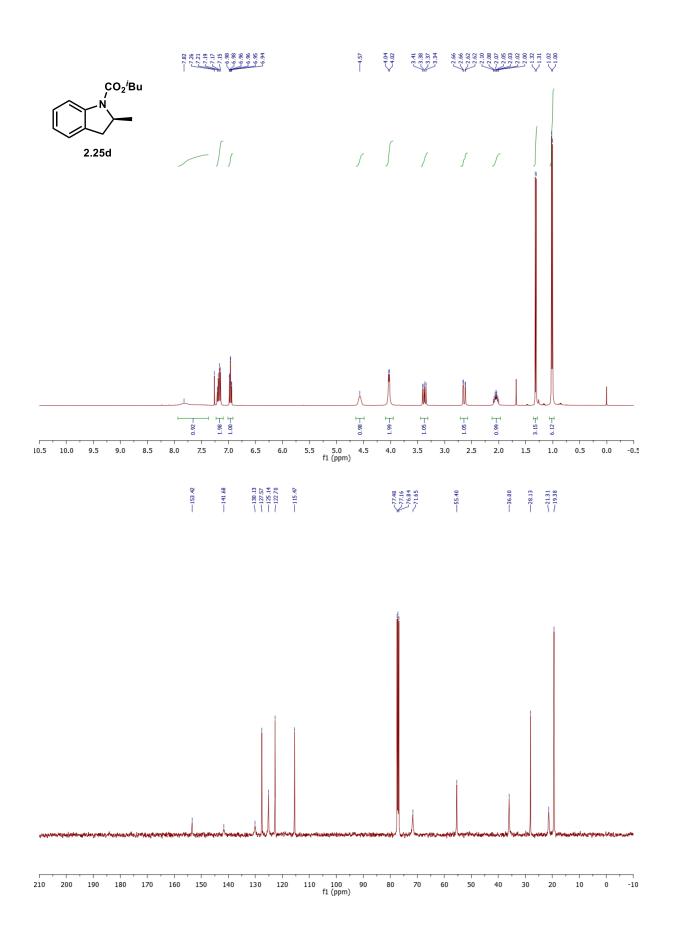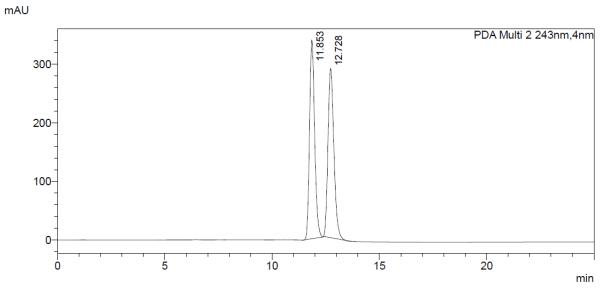
Peak#	Ret. Time	Area	Height	Area%
1	17.194	3972368	145545	50.154
2	20.863	3947941	97514	49.846
Total		7920309	243059	100.000

<Peak Table>

PDA Ch2 243nm
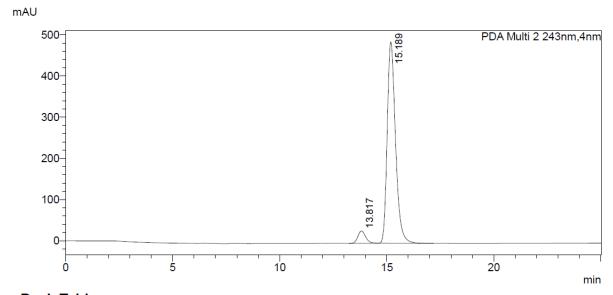
Peak#	Ret. Time	Area	Height	Area%
1	17.938	8483025	319782	92.342
2	21.684	703458	19002	7.658
Total		9186483	338784	100.000

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

2.25d

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

mAU

PDA Multi 2 243nm,4nm

<Peak Table>

PDA Ch2 243nm
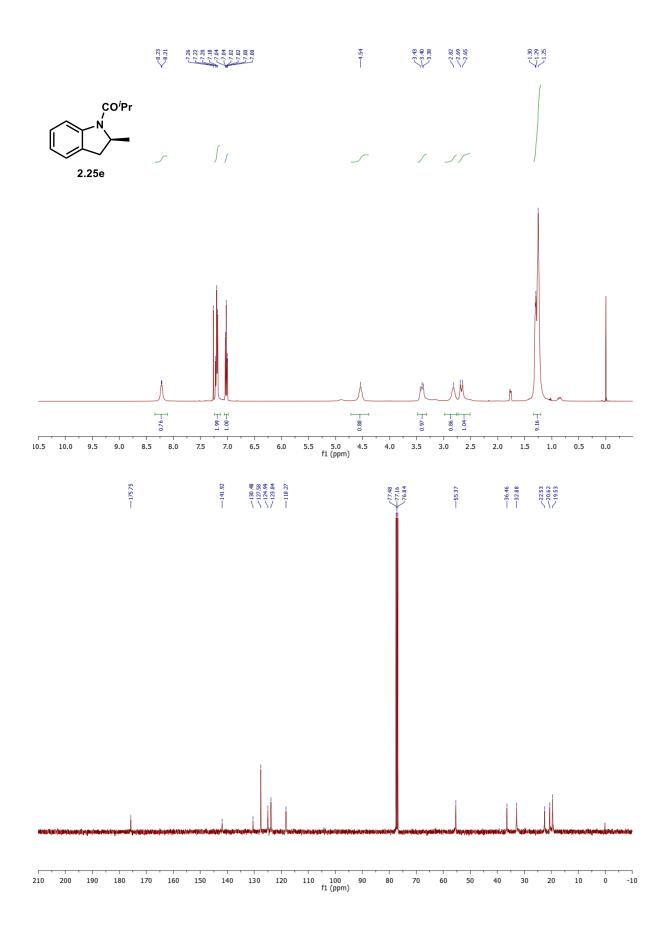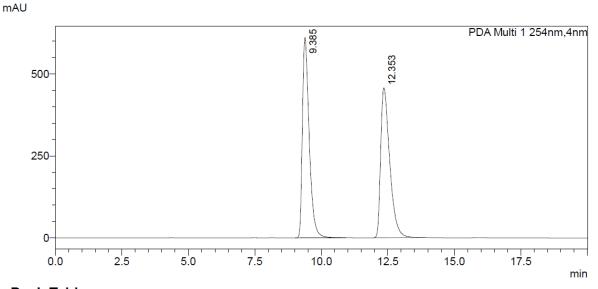
Peak#	Ret. Time	Area	Height	Area%
1	11.853	5603938	338509	50.240
2	12.728	5550466	288814	49.760
Total		11154404	627323	100.000

mAU

PDA Multi 2 243nm,4nm

<Peak Table>

PDA Ch2 243nm
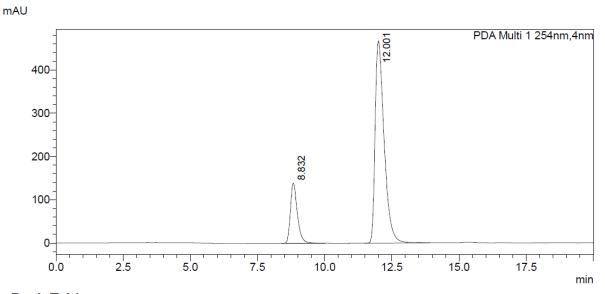
Peak#	Ret. Time	Area	Height	Area%
1	13.817	757360	30144	5.428
2	15.189	13195955	488695	94.572
Total		13953315	518839	100.000

2.25e

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

mAU

PDA Multi 1 254nm,4nm

9.385

12.353

<Peak Table>

PDA Ch1 254nm
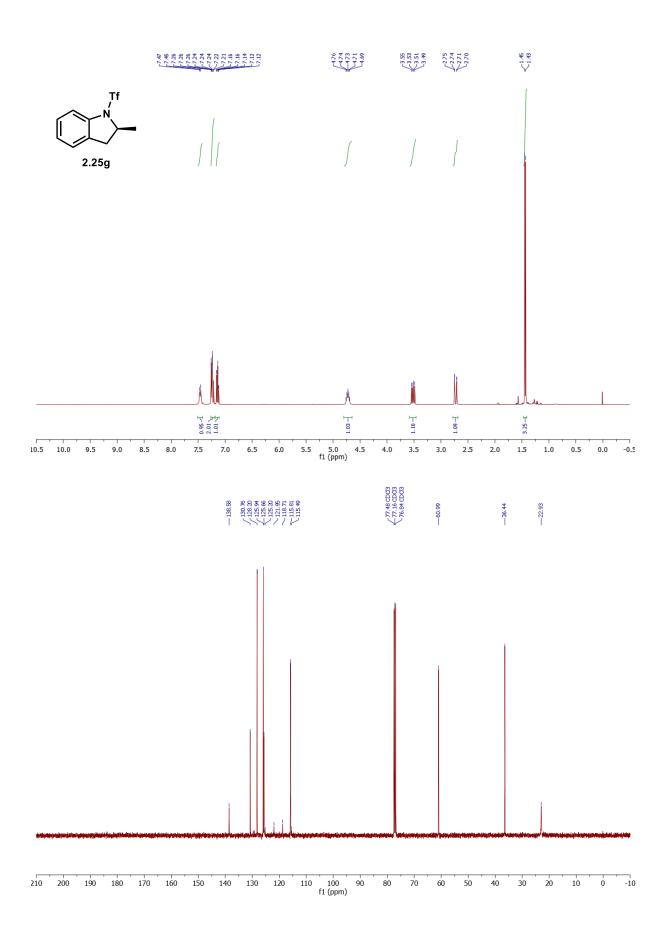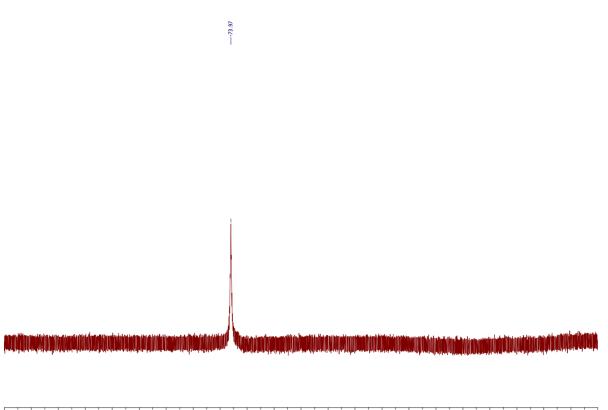
Peak#	Ret. Time	Area	Height	Area%
1	9.385	10875515	611160	50.149
2	12.353	10810916	457455	49.851
Total		21686431	1068615	100.000

mAU

PDA Multi 1 254nm,4nm

12.001

8.832

<Peak Table>

PDA Ch1 254nm
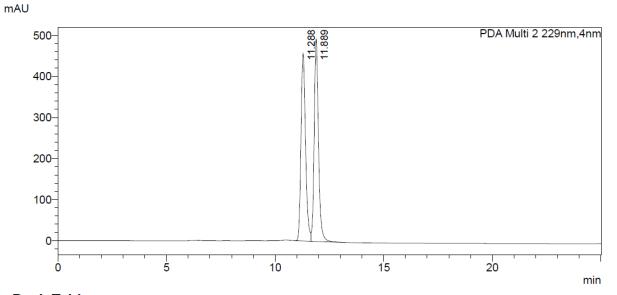
Peak#	Ret. Time	Area	Height	Area%
1	8.832	2492245	138925	18.590
2	12.001	10914480	467498	81.410
Total		13406724	606422	100.000
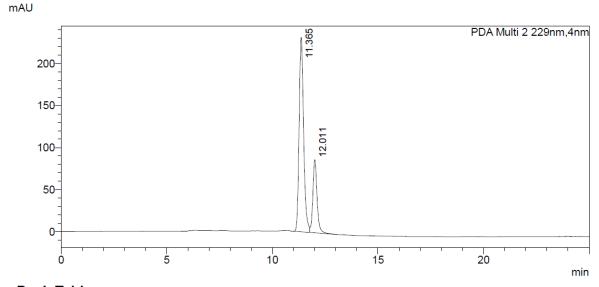
-73.97

f1 (ppm)

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

mAU

PDA Multi 2 229nm,4nm

<Peak Table>

PDA Ch2 229nm
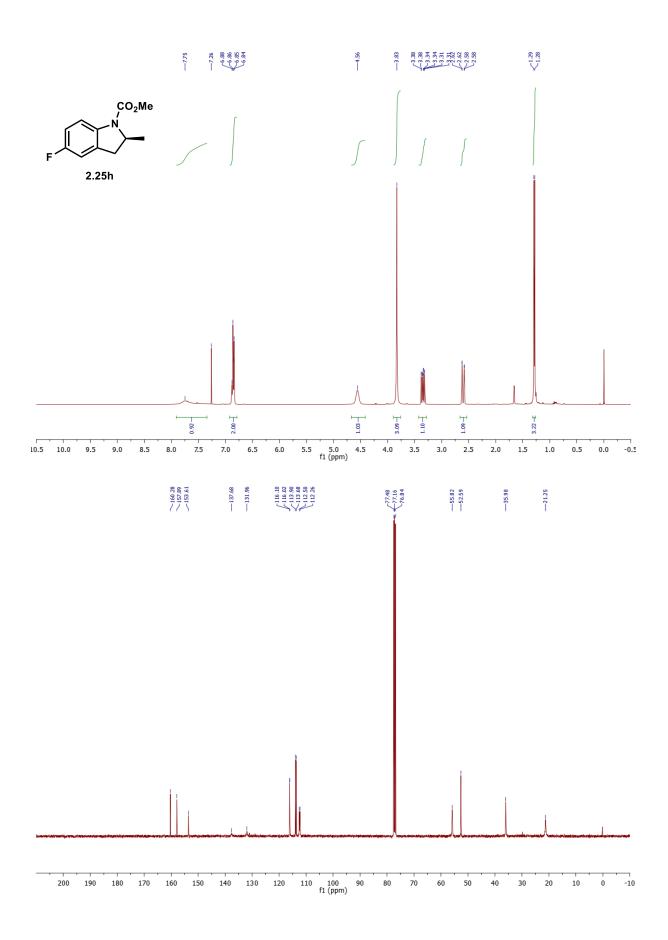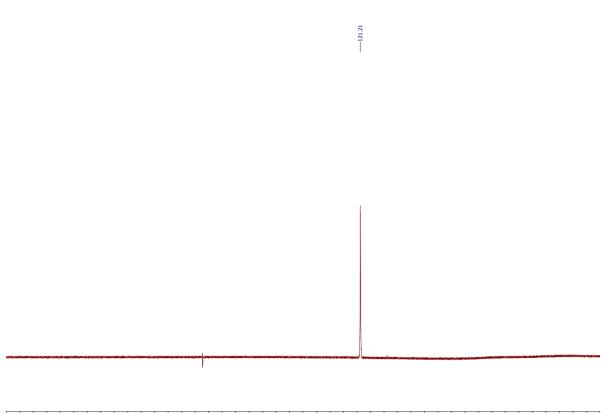
Peak#	Ret. Time	Area	Height	Area%
1	11.288	6695079	456641	49.706
2	11.889	6774408	493005	50.294
Total		13469487	949646	100.000

mAU

PDA Multi 2 229nm,4nm

<Peak Table>

PDA Ch2 229nm
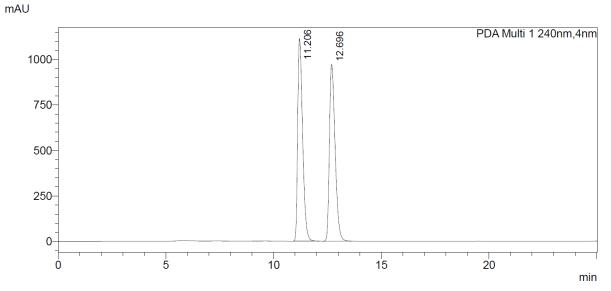
Peak#	Ret. Time	Area	Height	Area%
1	11.365	3432550	231122	74.065
2	12.011	1201934	86878	25.935
Total		4634483	318000	100.000
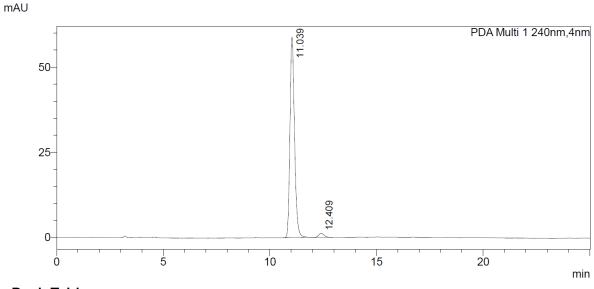
1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

-121.21

f1 (ppm)

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

mAU

PDA Multi 1 240nm,4nm

11.206
12.696

<Peak Table>

PDA Ch1 240nm
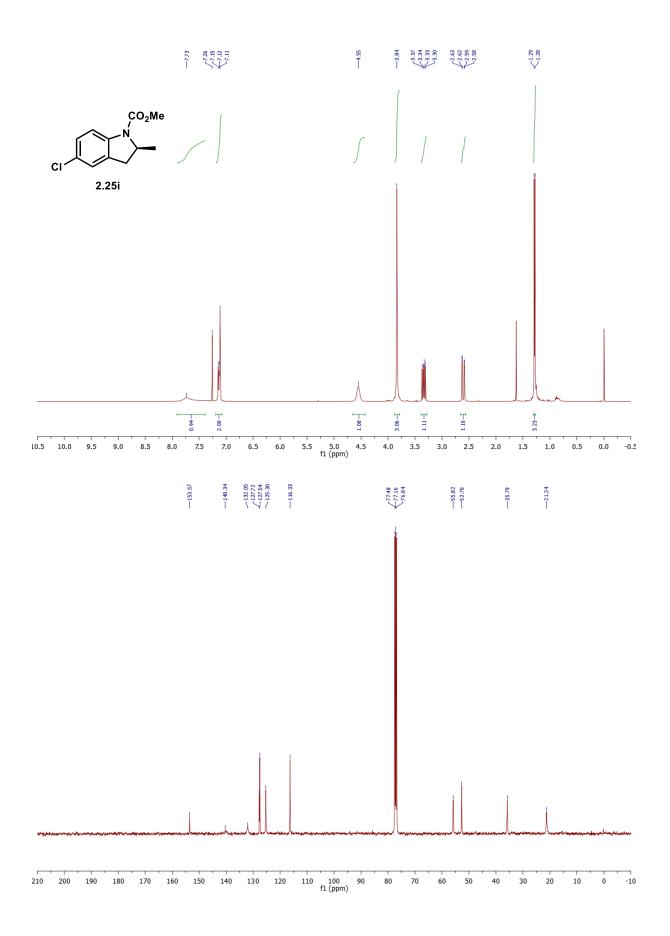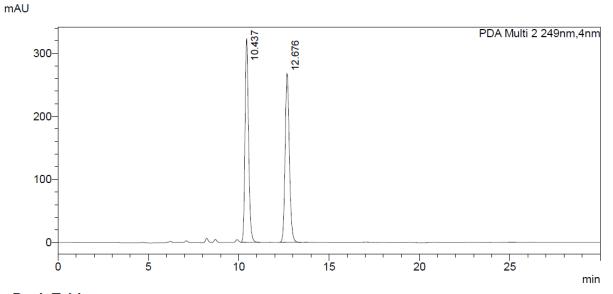
Peak#	Ret. Time	Area	Height	Area%
1	11.206	17693224	1113742	49.793
2	12.696	17840493	972153	50.207
Total		35533718	2085895	100.000

mAU

PDA Multi 1 240nm,4nm

11.039
12.409

<Peak Table>

PDA Ch1 240nm

Peak#	Ret. Time	Area	Height	Area%
1	11.039	870376	58780	97.663
2	12.409	20832	1218	2.337
Total		891207	59998	100.000

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

2.25i

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

mAU

PDA Multi 2 249nm,4nm

10.437

12.676

<Peak Table>

PDA Ch2 249nm
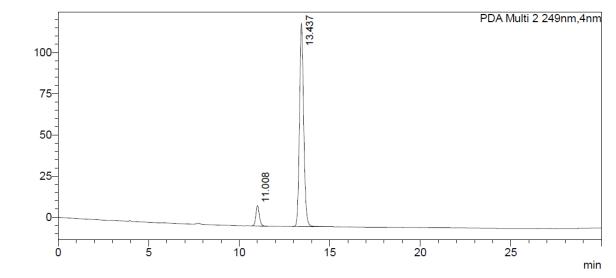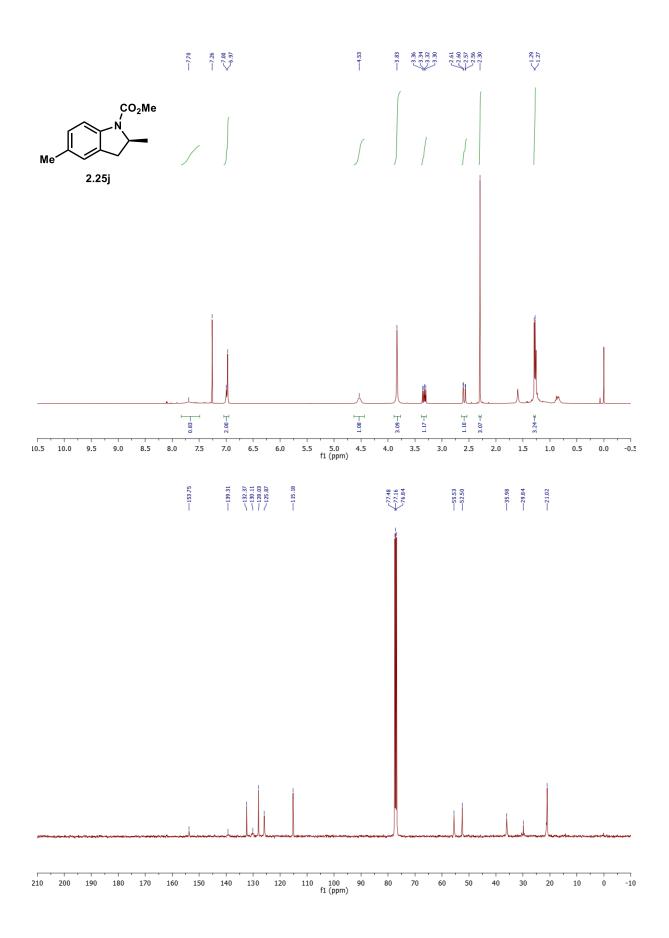
Peak#	Ret. Time	Area	Height	Area%
1	10.437	4360101	322560	49.957
2	12.676	4367691	267644	50.043
Total		8727791	590203	100.000

mAU

PDA Multi 2 249nm,4nm

13.437

11.008

<Peak Table>

PDA Ch2 249nm
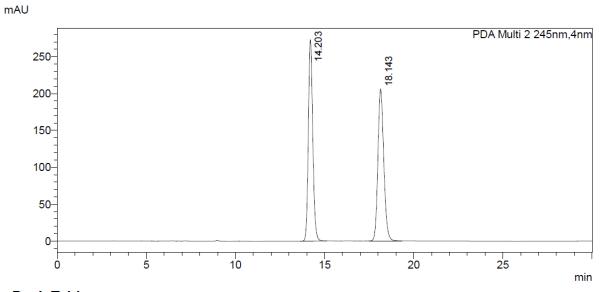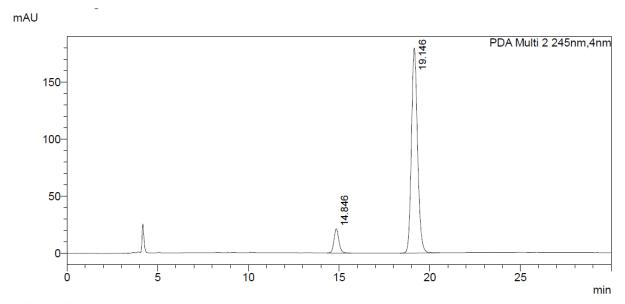
Peak#	Ret. Time	Area	Height	Area%
1	11.008	167659	12415	7.762
2	13.437	1992355	123055	92.238
Total		2160014	135470	100.000

2.25j

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

mAU

PDA Multi 2 245nm,4nm

<Peak Table>

PDA Ch2 245nm
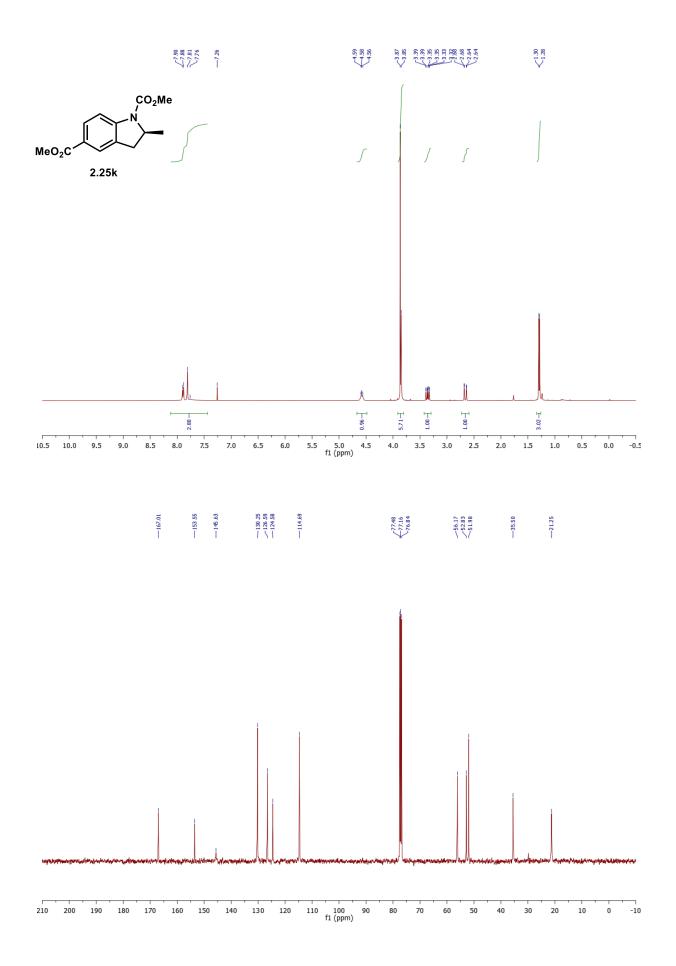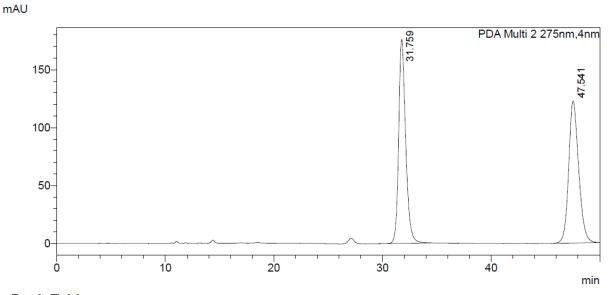
Peak#	Ret. Time	Area	Height	Area%
1	14.203	4700330	273014	49.947
2	18.143	4710359	205910	50.053
Total		9410688	478924	100.000

mAU

PDA Multi 2 245nm,4nm

<Peak Table>

PDA Ch2 245nm
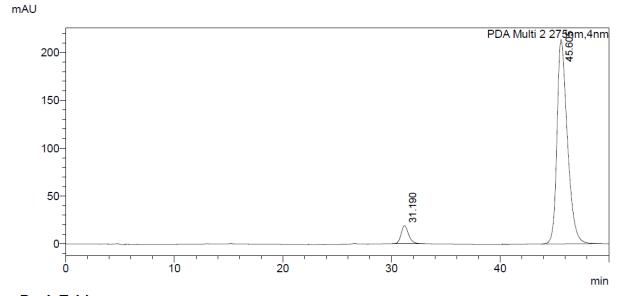
Peak#	Ret. Time	Area	Height	Area%
1	14.846	398759	21230	8.631
2	19.146	4221449	179579	91.369
Total		4620207	200809	100.000

2.25k

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

mAU

PDA Multi 2 275nm,4nm

31.759

47.541

\<Peak Table\>

PDA Ch2 275nm
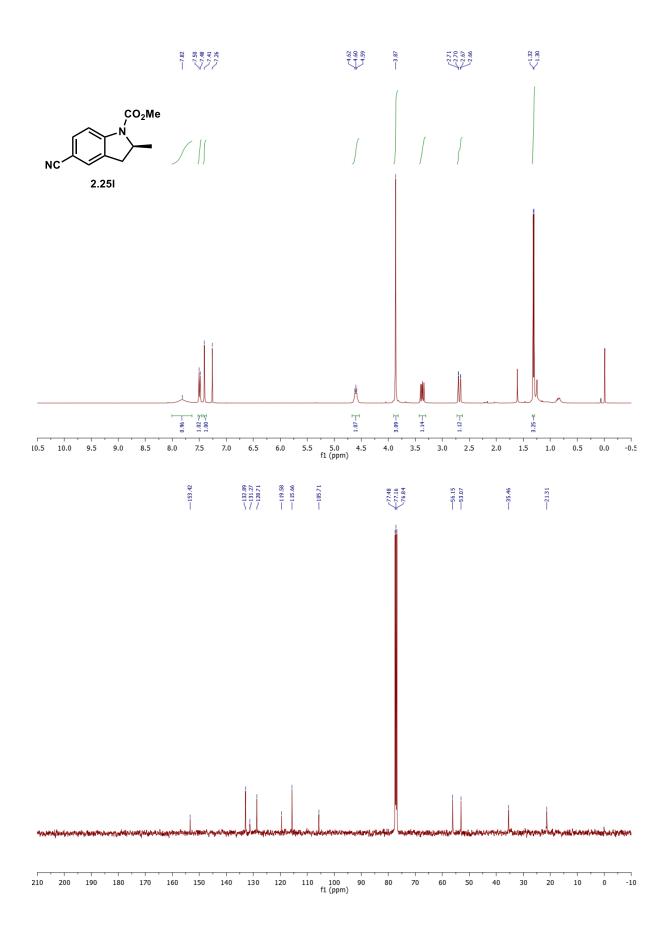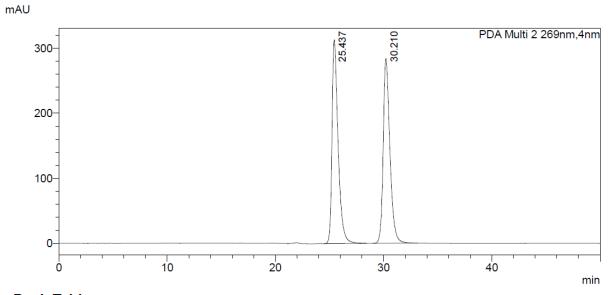
Peak#	Ret. Time	Area	Height	Area%
1	31.759	7867113	176070	50.102
2	47.541	7835040	122622	49.898
Total		15702153	298692	100.000

mAU

PDA Multi 2 275nm,4nm

31.190

45.605

\<Peak Table\>

PDA Ch2 275nm
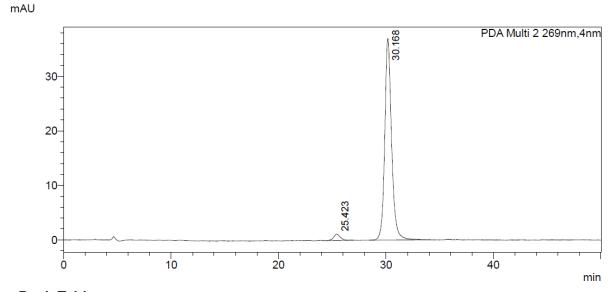
Peak#	Ret. Time	Area	Height	Area%
1	31.190	933992	19138	6.164
2	45.605	14218564	213398	93.836
Total		15152557	232536	100.000

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

mAU

PDA Multi 2 269nm,4nm

<Peak Table>

PDA Ch2 269nm
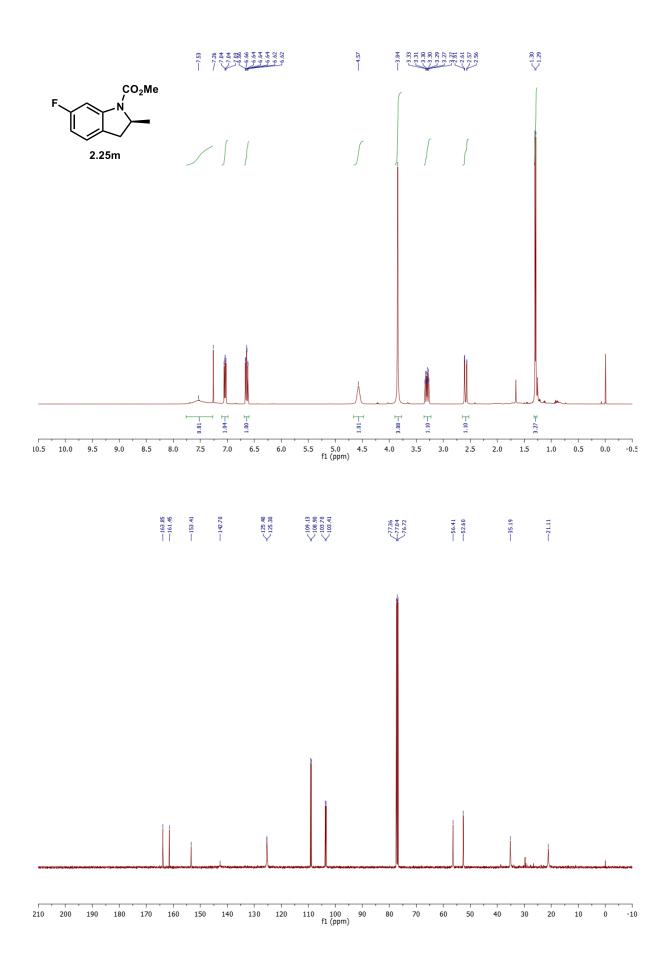
Peak#	Ret. Time	Area	Height	Area%
1	25.437	12195863	313214	50.009
2	30.210	12191331	284154	49.991
Total		24387194	597368	100.000

mAU

PDA Multi 2 269nm,4nm

<Peak Table>

PDA Ch2 269nm
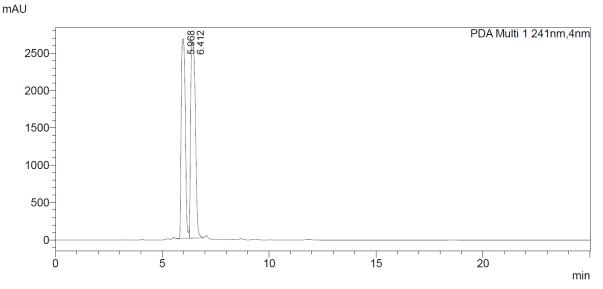
Peak#	Ret. Time	Area	Height	Area%
1	25.423	51142	1175	3.035
2	30.168	1634066	36960	96.965
Total		1685208	38135	100.000
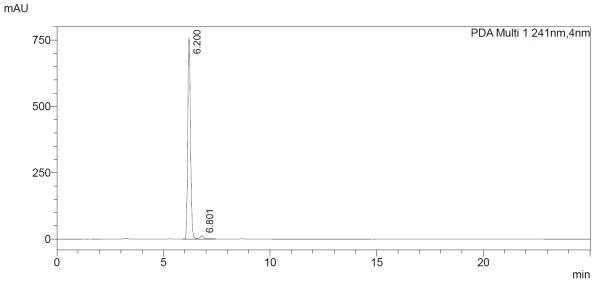
1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

—112.64

10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

mAU

PDA Multi 1 241nm,4nm

<Peak Table>

PDA Ch1 241nm
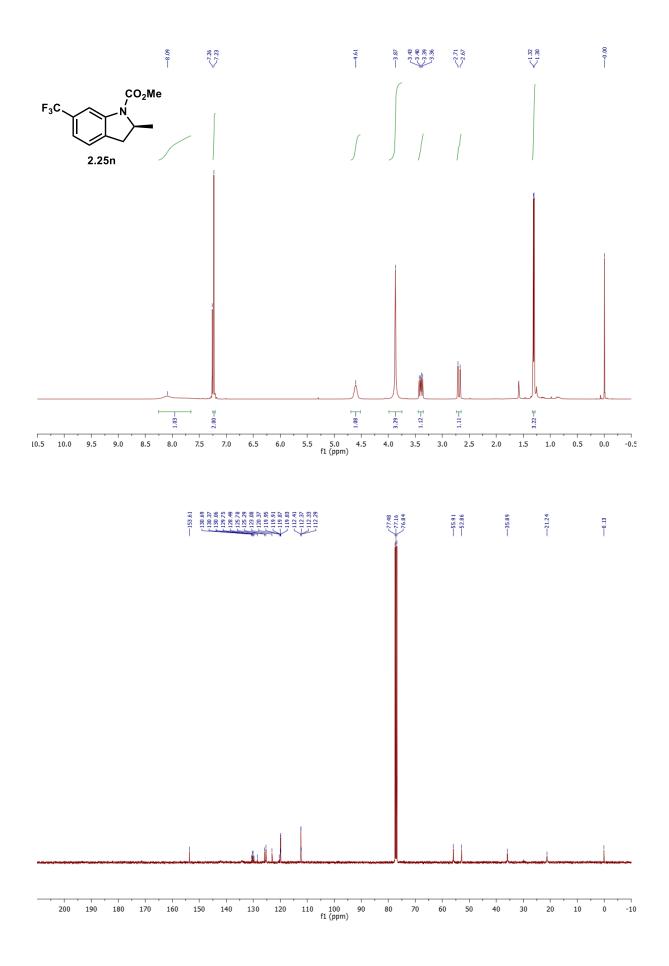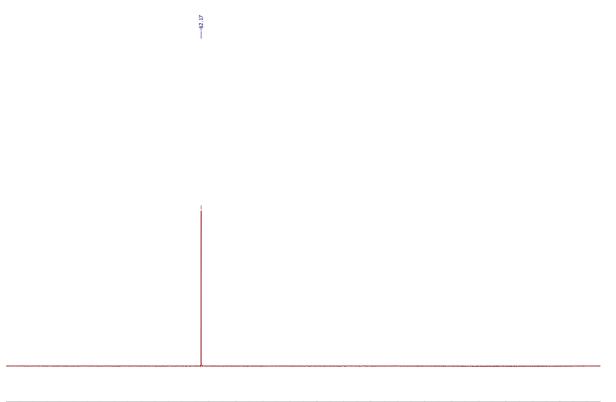
Peak#	Ret. Time	Area	Height	Area%
1	5.968	34934094	2672998	46.494
2	6.412	40203252	2614261	53.506
Total		75137346	5287258	100.000

mAU

PDA Multi 1 241nm,4nm

<Peak Table>

PDA Ch1 241nm
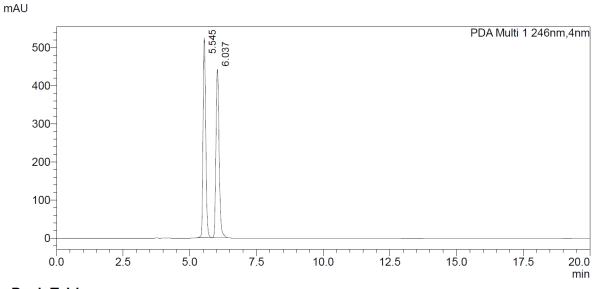
Peak#	Ret. Time	Area	Height	Area%
1	6.200	6856929	758418	97.945
2	6.801	143845	11676	2.055
Total		7000775	770094	100.000

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

317

-62.17

f1 (ppm)

<Peak Table>

PDA Ch1 246nm
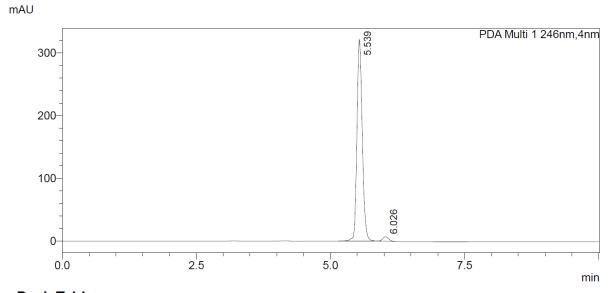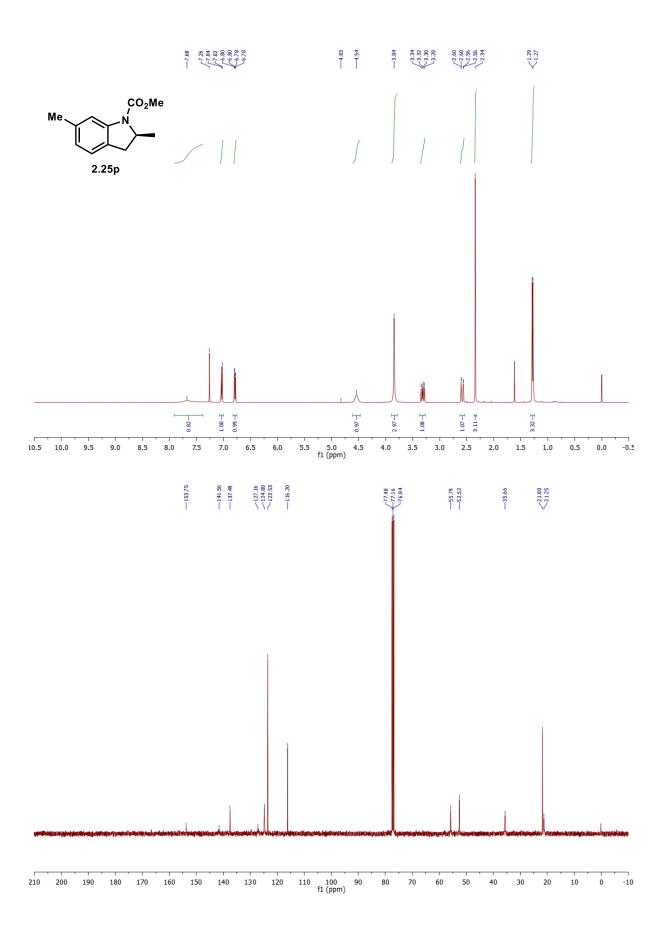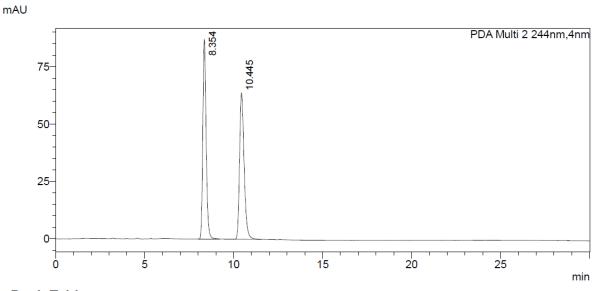
Peak#	Ret. Time	Area	Height	Area%
1	5.545	3614807	524285	49.928
2	6.037	3625271	442363	50.072
Total		7240077	966648	100.000

<Peak Table>

PDA Ch1 246nm
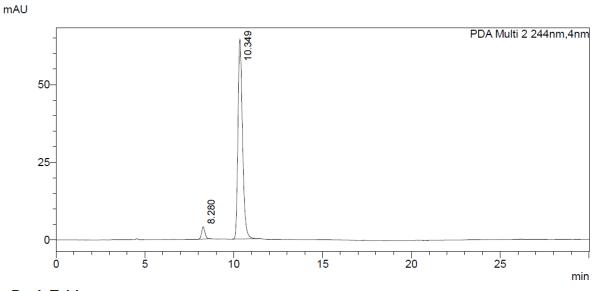
Peak#	Ret. Time	Area	Height	Area%
1	5.539	2218612	321543	97.663
2	6.026	53090	7055	2.337
Total		2271702	328597	100.000

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

2.25p

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

mAU

<Peak Table>

PDA Ch2 244nm
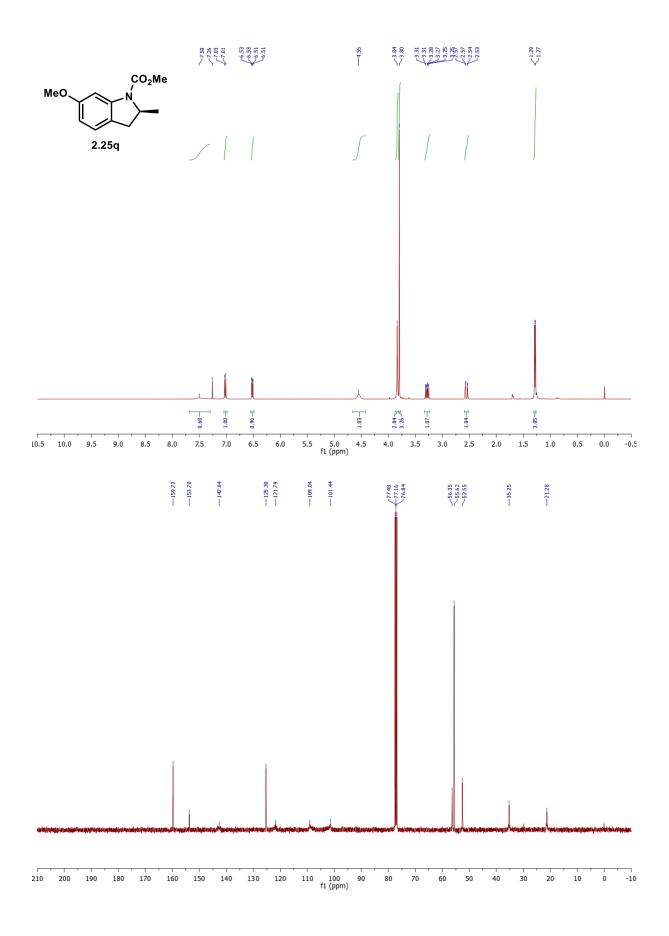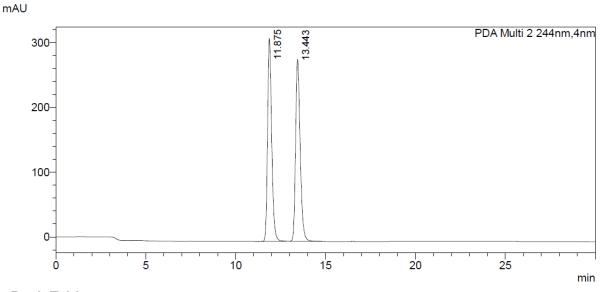
Peak#	Ret. Time	Area	Height	Area%
1	8.354	1133948	86846	50.063
2	10.445	1131106	63778	49.937
Total		2265054	150624	100.000

mAU

<Peak Table>

PDA Ch2 244nm
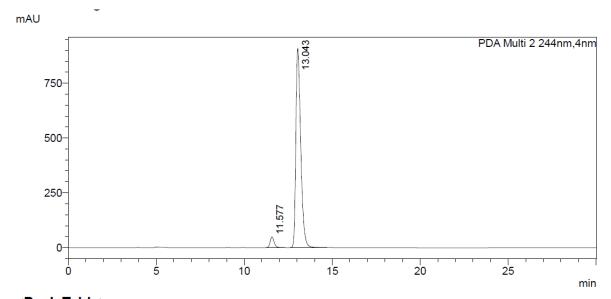
Peak#	Ret. Time	Area	Height	Area%
1	8.280	51873	3920	4.331
2	10.349	1145831	64250	95.669
Total		1197703	68170	100.000

MeO — (structure: methyl 6-methoxy-2-methylindoline-1-carboxylate)

2.25q

1H NMR peaks: 7.50, 7.26, 7.03, 7.01, 6.53, 6.53, 6.51, 6.51, 4.55, 3.84, 3.80, 3.31, 3.31, 3.28, 3.27, 3.25, 3.25, 2.57, 2.54, 2.53, 1.29, 1.27

Integrations: 0.68, 1.00, 0.96, 1.03, 2.84, 3.26, 1.07, 1.04, 3.05

13C NMR peaks: 159.72, 153.70, 142.64, 125.30, 121.79, 109.04, 101.44, 77.48, 77.16, 76.84, 56.35, 55.62, 52.55, 35.25, 21.28

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

mAU

PDA Multi 2 244nm,4nm

<Peak Table>

PDA Ch2 244nm
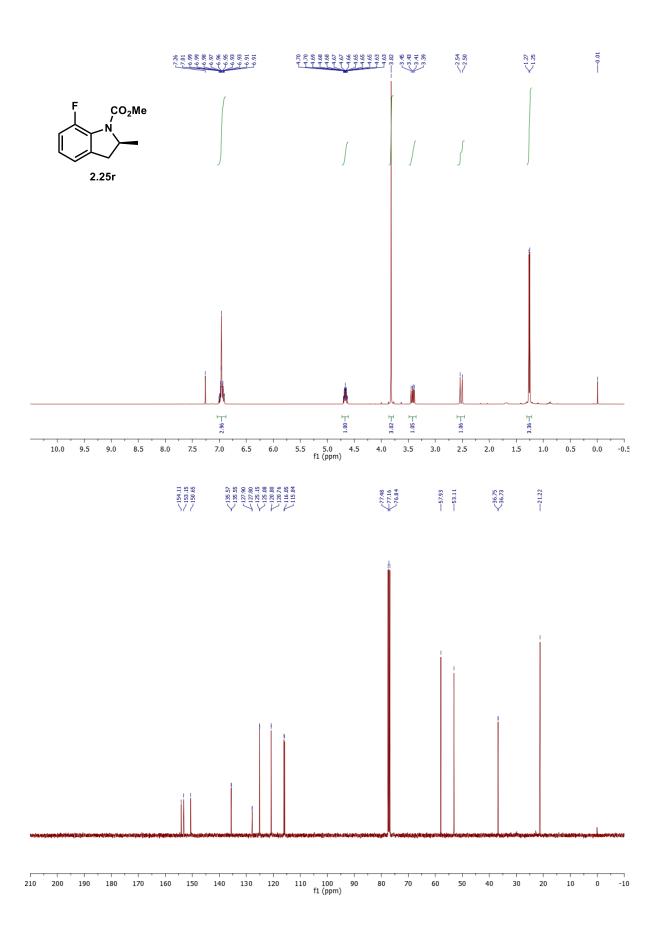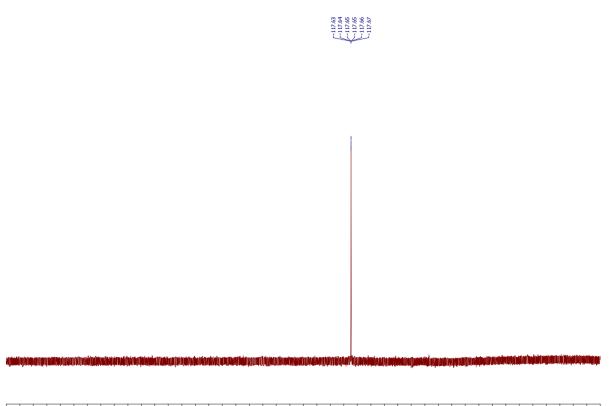
Peak#	Ret. Time	Area	Height	Area%
1	11.875	5010149	313411	49.973
2	13.443	5015631	280866	50.027
Total		10025781	594277	100.000

mAU

PDA Multi 2 244nm,4nm

<Peak Table>

PDA Ch2 244nm
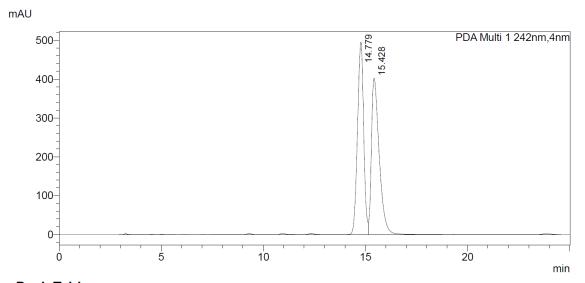
Peak#	Ret. Time	Area	Height	Conc.	Area%
1	11.577	771295	49148	4.210	4.210
2	13.043	17547455	907407	95.790	95.790
Total		18318750	956555		100.000
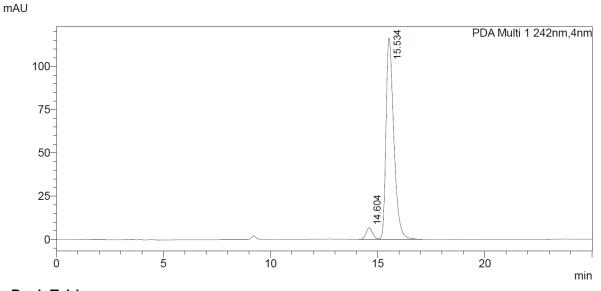
2.25r

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

mAU

PDA Multi 1 242nm,4nm

<Peak Table>

PDA Ch1 242nm
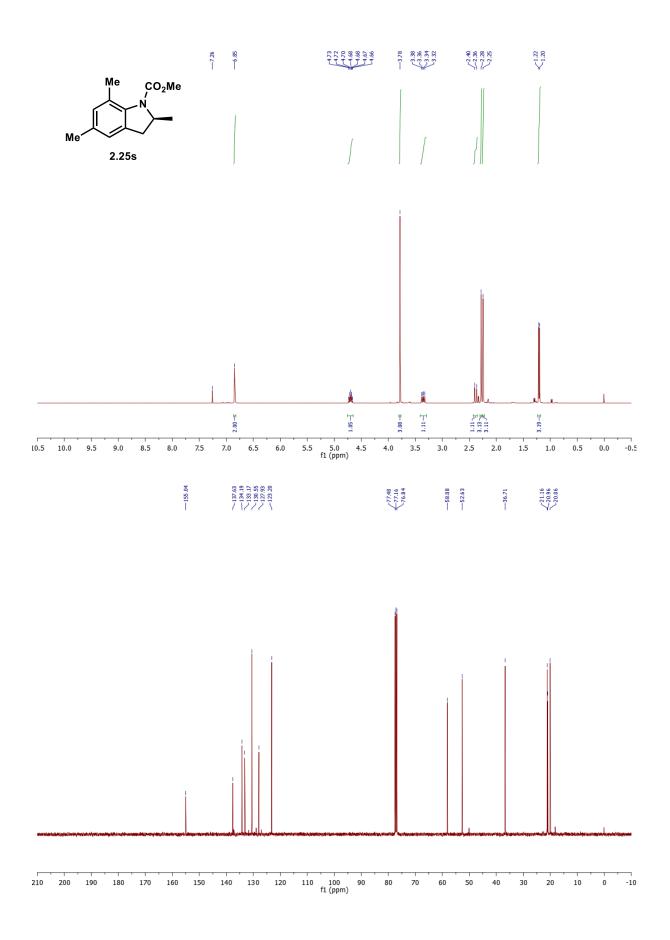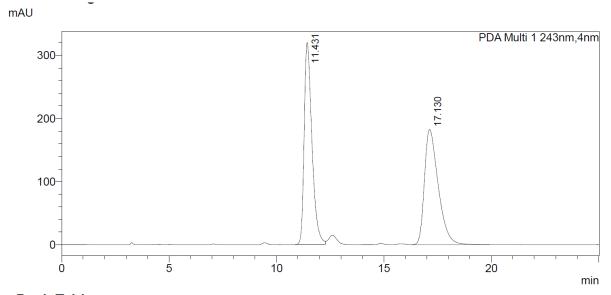
Peak#	Ret. Time	Area	Height	Area%
1	14.779	10551527	495275	49.491
2	15.428	10768496	402795	50.509
Total		21320023	898070	100.000

mAU

PDA Multi 1 242nm,4nm

<Peak Table>

PDA Ch1 242nm
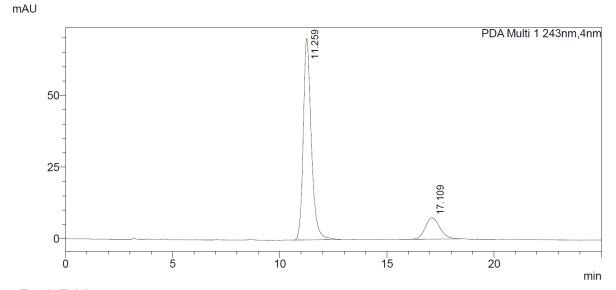
Peak#	Ret. Time	Area	Height	Area%
1	14.604	140604	6620	4.549
2	15.534	2950336	116399	95.451
Total		3090940	123020	100.000

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

mAU

PDA Multi 1 243nm,4nm

11.431

17.130

<Peak Table>

PDA Ch1 243nm
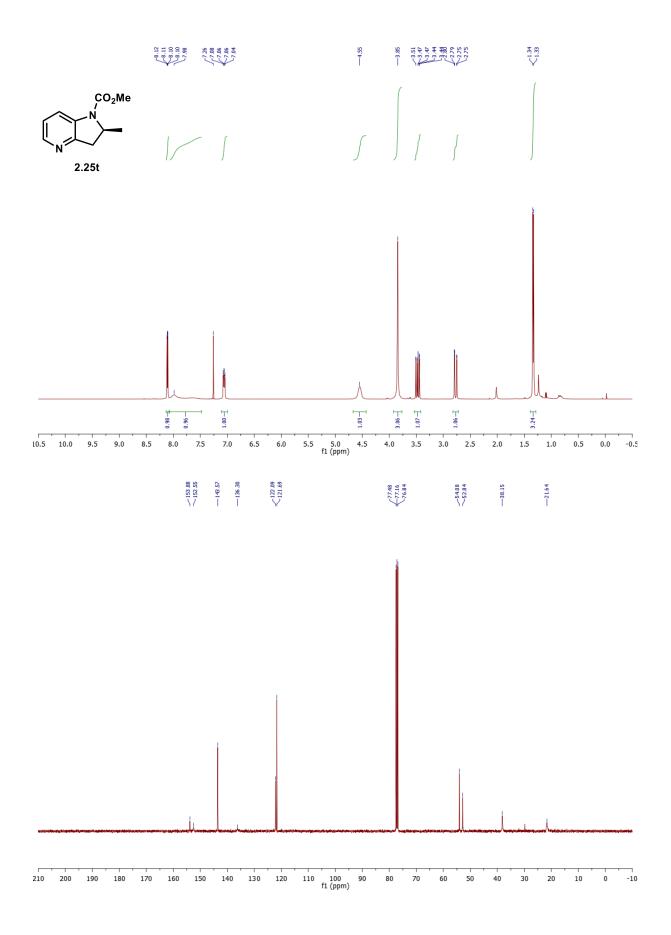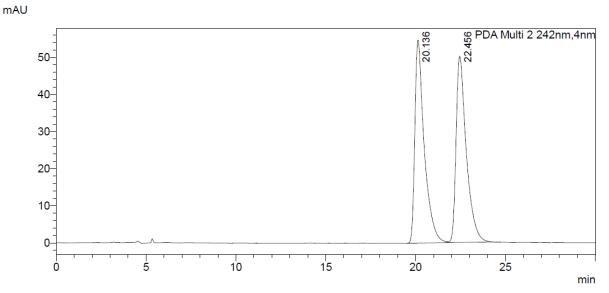
Peak#	Ret. Time	Area	Height	Area%
1	11.431	8043518	320070	49.788
2	17.130	8112132	182525	50.212
Total		16155651	502596	100.000

mAU

PDA Multi 1 243nm,4nm

11.259

17.109

<Peak Table>

PDA Ch1 243nm
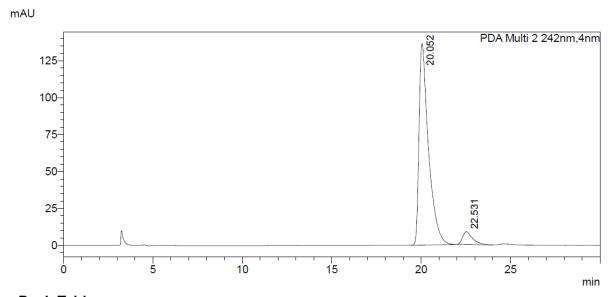
Peak#	Ret. Time	Area	Height	Area%
1	11.259	1829198	70201	84.073
2	17.109	346518	7402	15.927
Total		2175716	77602	100.000

2.25t

<Peak Table>

PDA Ch2 242nm
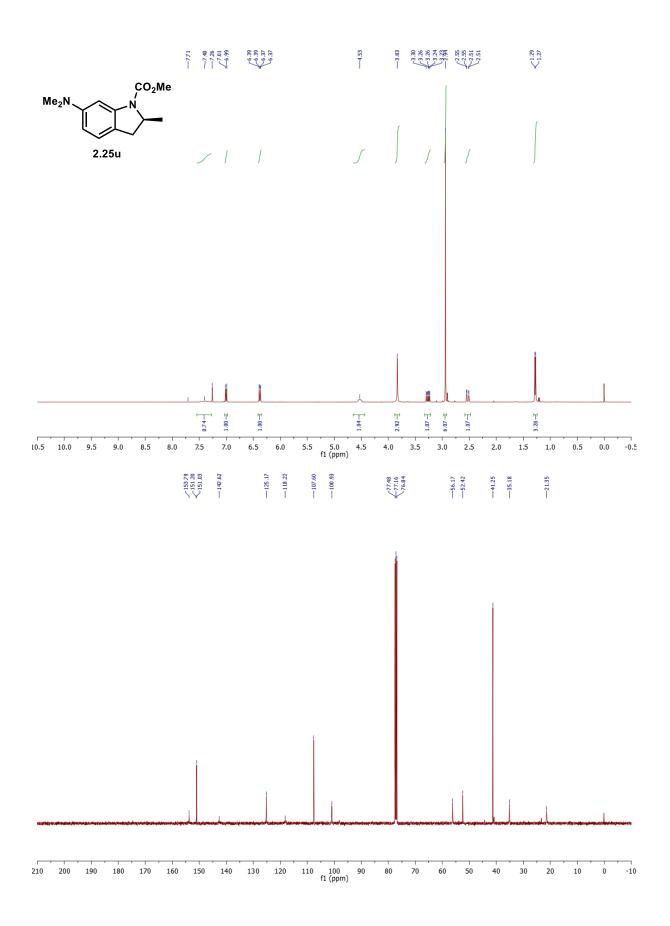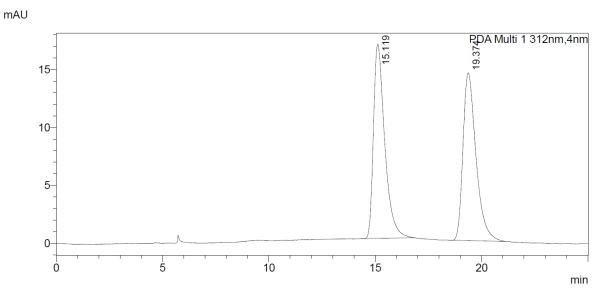
Peak#	Ret. Time	Area	Height	Area%
1	20.136	1989381	54691	50.087
2	22.456	1982484	50165	49.913
Total		3971865	104856	100.000

<Peak Table>

PDA Ch2 242nm

Peak#	Ret. Time	Area	Height	Area%
1	20.052	5008295	136294	93.767
2	22.531	332899	8621	6.233
Total		5341194	144915	100.000

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

mAU

PDA Multi 1 312nm,4nm

15.119

19.374

<Peak Table>

PDA Ch1 312nm
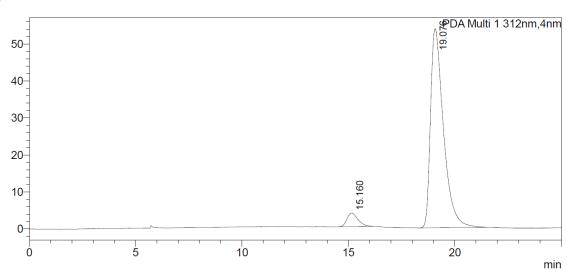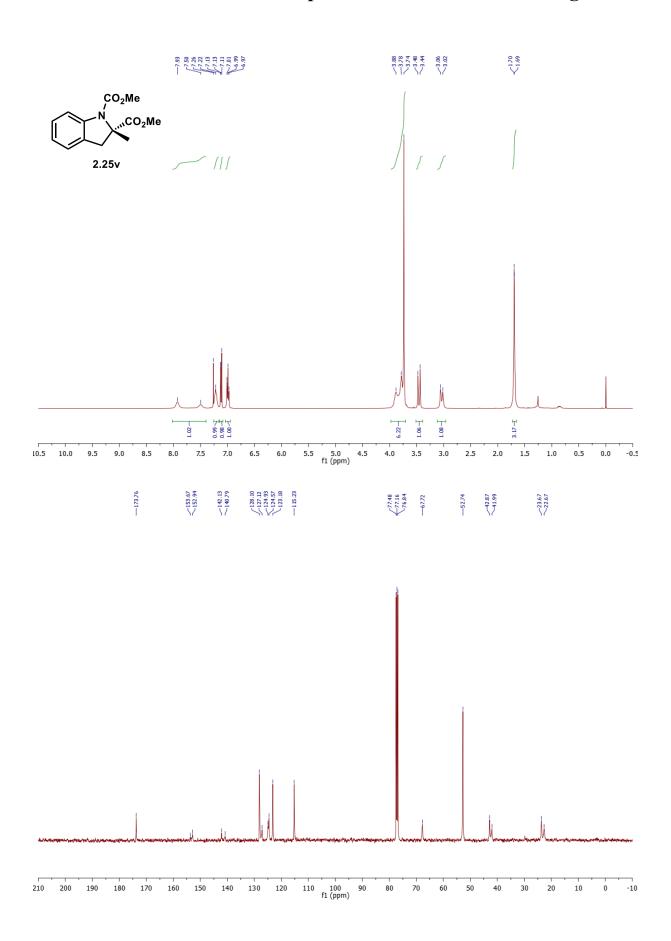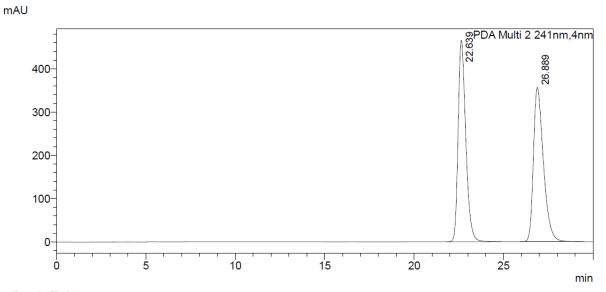
Peak#	Ret. Time	Area	Height	Area%
1	15.119	616790	16762	50.014
2	19.374	616441	14482	49.986
Total		1233231	31244	100.000

mAU

PDA Multi 1 312nm,4nm

19.076

15.160

<Peak Table>

PDA Ch1 312nm
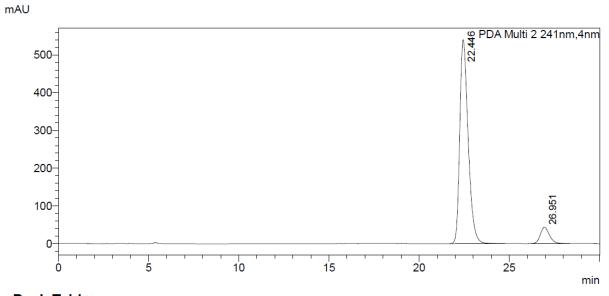
Peak#	Ret. Time	Area	Height	Area%
1	15.160	131325	3690	5.467
2	19.076	2270769	53789	94.533
Total		2402095	57480	100.000

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

mAU

PDA Multi 2 241nm,4nm

22.639

26.889

```
0    5    10    15    20    25    min
```

<Peak Table>

PDA Ch2 241nm
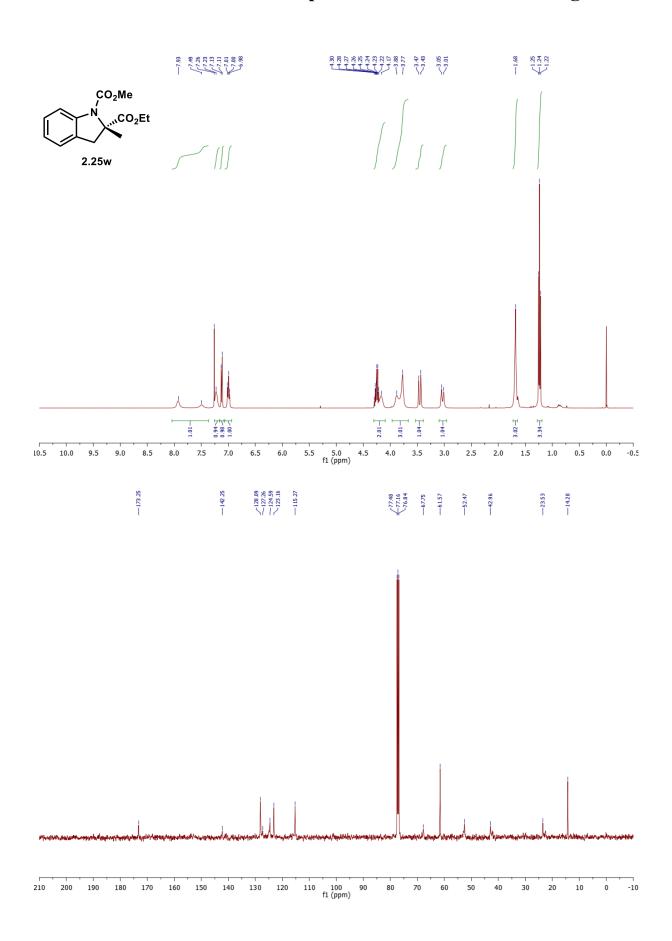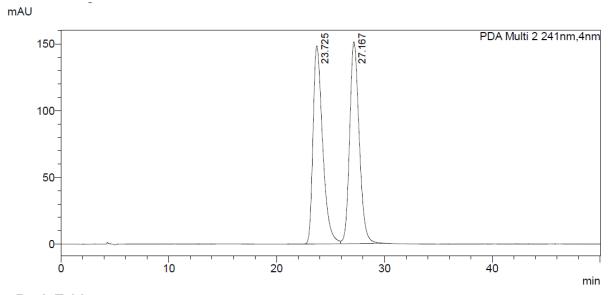
Peak#	Ret. Time	Area	Height	Area%
1	22.639	13795045	464981	49.980
2	26.889	13806168	355961	50.020
Total		27601213	820942	100.000

mAU

PDA Multi 2 241nm,4nm

22.446

26.951

```
0    5    10    15    20    25    min
```

<Peak Table>

PDA Ch2 241nm
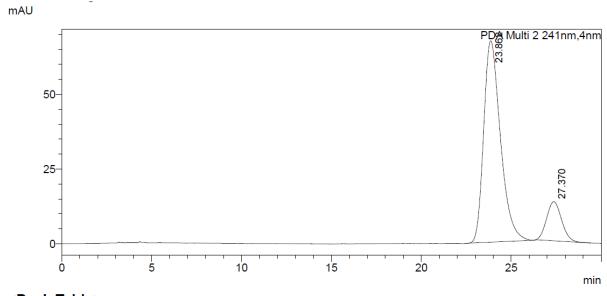
Peak#	Ret. Time	Area	Height	Area%
1	22.446	17440591	540449	91.902
2	26.951	1536726	43398	8.098
Total		18977317	583847	100.000

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

CO2Me

N

CO2Et

2.25w

f1 (ppm)

f1 (ppm)

<Peak Table>

PDA Ch2 241nm
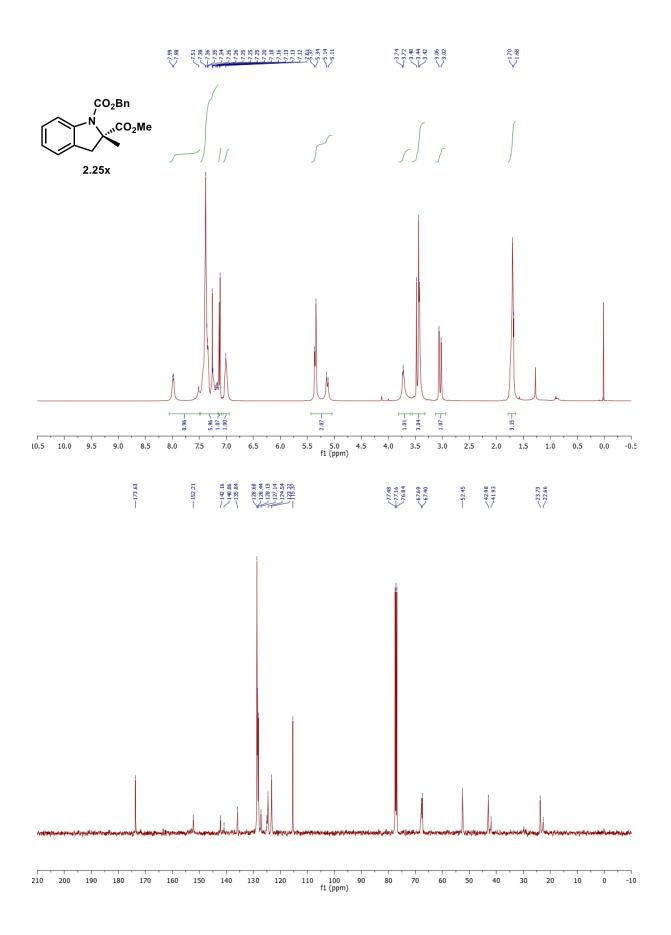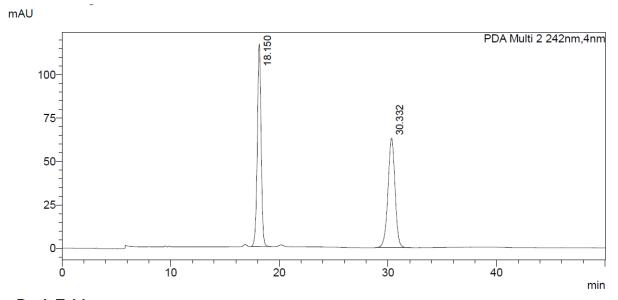
Peak#	Ret. Time	Area	Height	Area%
1	23.725	9192792	148374	49.636
2	27.167	9327585	151262	50.364
Total		18520377	299636	100.000

<Peak Table>

PDA Ch2 241nm
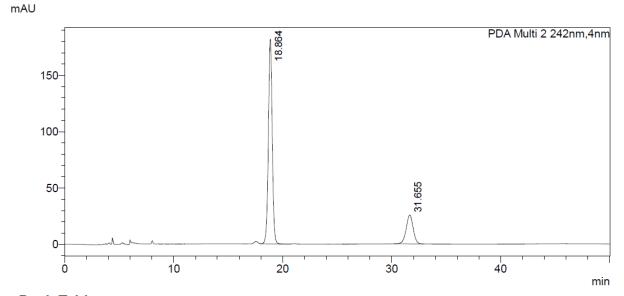
Peak#	Ret. Time	Area	Height	Area%
1	23.862	4366582	67415	85.165
2	27.370	760595	13115	14.835
Total		5127177	80529	100.000

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

mAU

PDA Multi 2 242nm,4nm

18.150

30.332

<Peak Table>

PDA Ch2 242nm
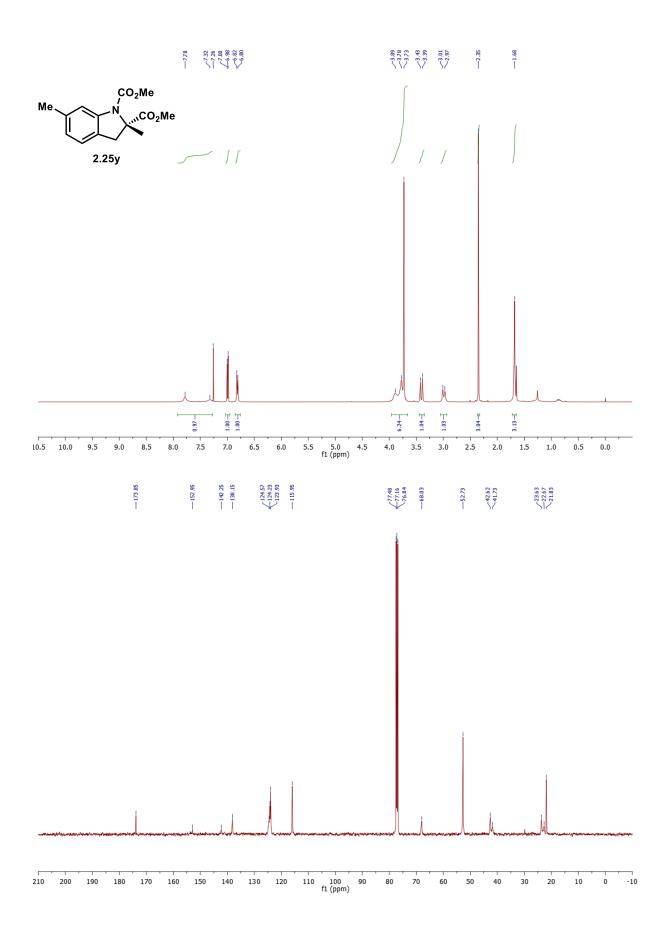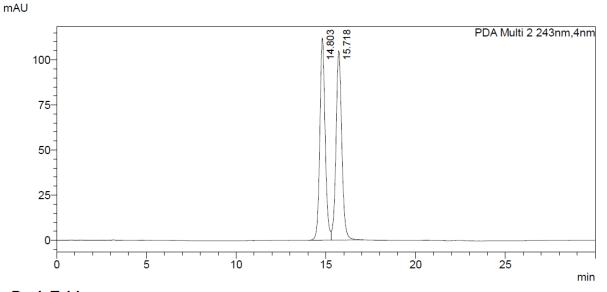
Peak#	Ret. Time	Area	Height	Area%
1	18.150	2834687	116518	49.882
2	30.332	2848120	63117	50.118
Total		5682807	179635	100.000

mAU

PDA Multi 2 242nm,4nm

18.864

31.655

<Peak Table>

PDA Ch2 242nm
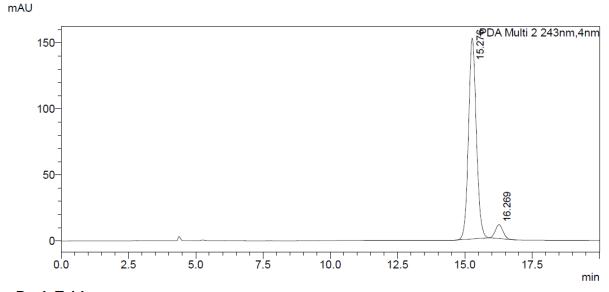
Peak#	Ret. Time	Area	Height	Area%
1	18.864	4455643	181857	79.605
2	31.655	1141547	25683	20.395
Total		5597190	207539	100.000

338

2.25y

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

mAU

PDA Multi 2 243nm,4nm

14.803
15.718

<Peak Table>

PDA Ch2 243nm
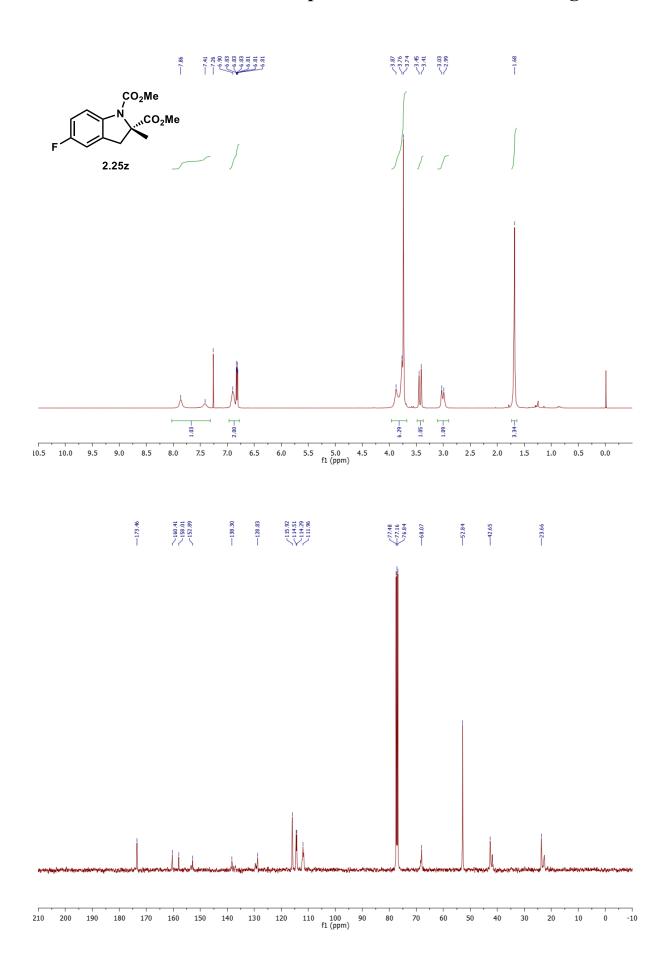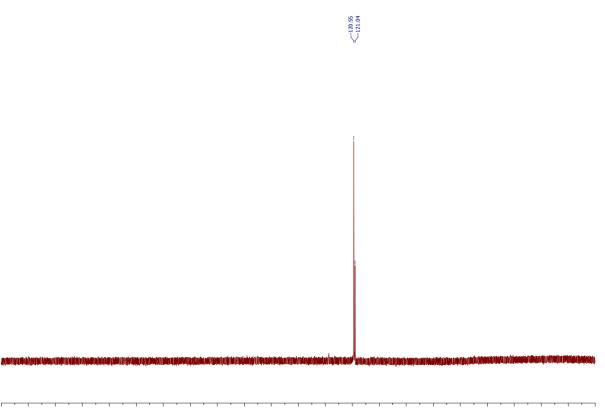
Peak#	Ret. Time	Area	Height	Area%
1	14.803	2318719	112054	49.623
2	15.718	2353956	104882	50.377
Total		4672675	216936	100.000

mAU

PDA Multi 2 243nm,4nm

15.276
16.269

<Peak Table>

PDA Ch2 243nm
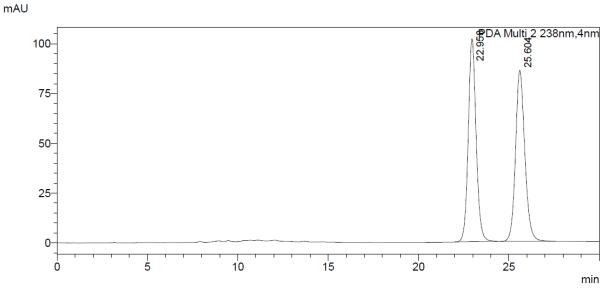
Peak#	Ret. Time	Area	Height	Area%
1	15.276	3087051	152101	93.724
2	16.269	206704	10486	6.276
Total		3293755	162588	100.000
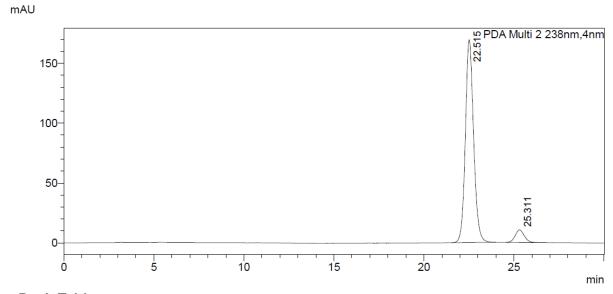
1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

2.25z

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

mAU

PDA Multi 2 238nm,4nm

<Peak Table>

PDA Ch2 238nm
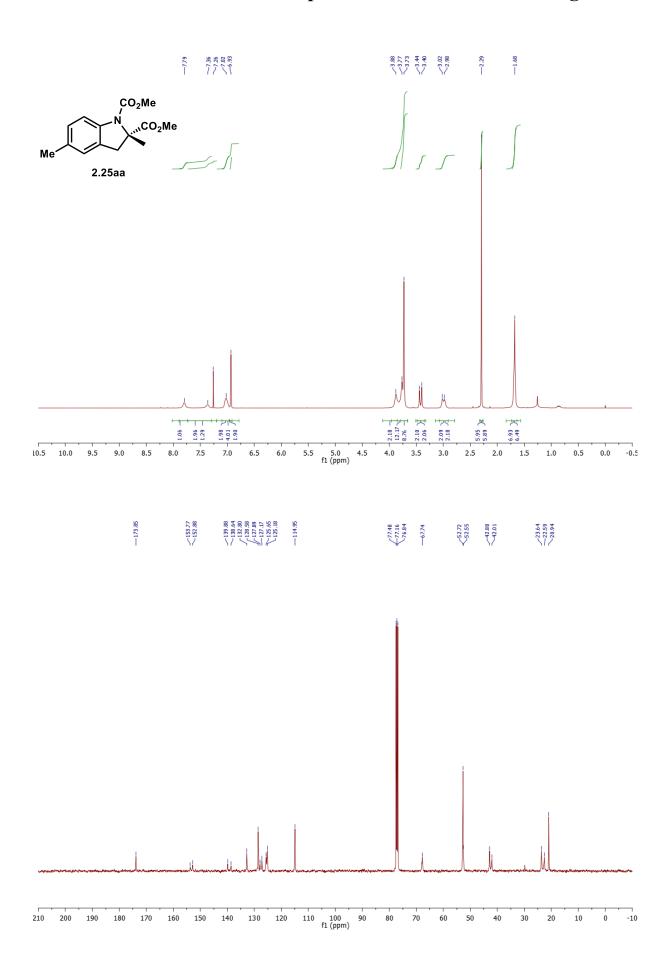
Peak#	Ret. Time	Area	Height	Area%
1	22.958	3087898	101883	50.068
2	25.604	3079454	85857	49.932
Total		6167351	187739	100.000

mAU

PDA Multi 2 238nm,4nm

<Peak Table>

PDA Ch2 238nm
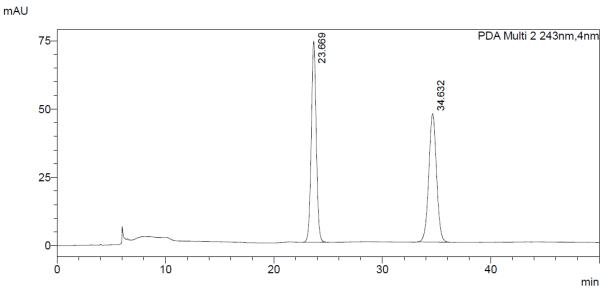
Peak#	Ret. Time	Area	Height	Area%
1	22.515	5370517	169261	93.505
2	25.311	373022	10558	6.495
Total		5743539	179820	100.000

2.25aa

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

mAU

PDA Multi 2 243nm,4nm

23.669

34.632

min

<Peak Table>

PDA Ch2 243nm
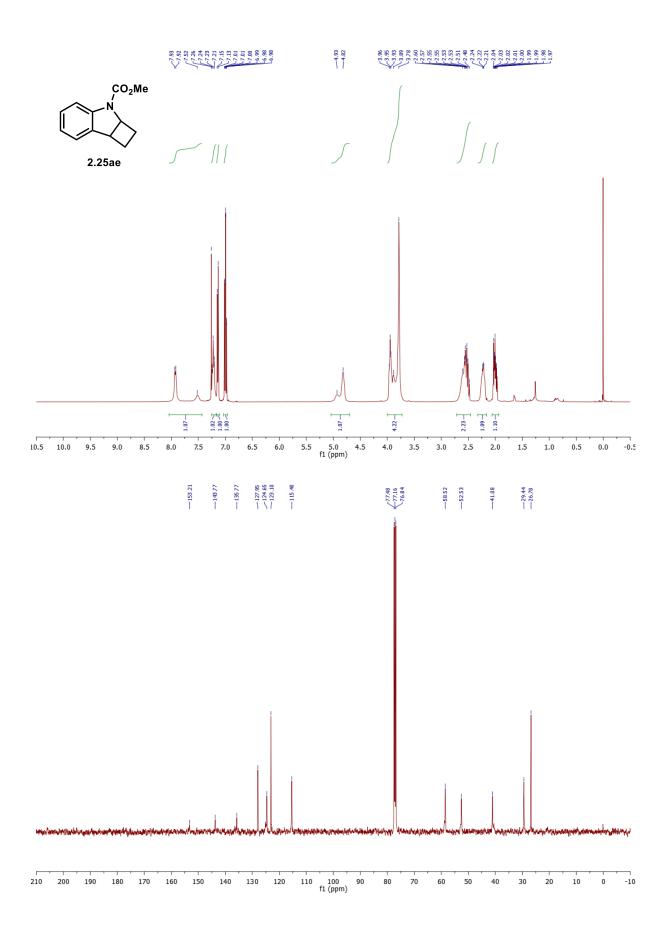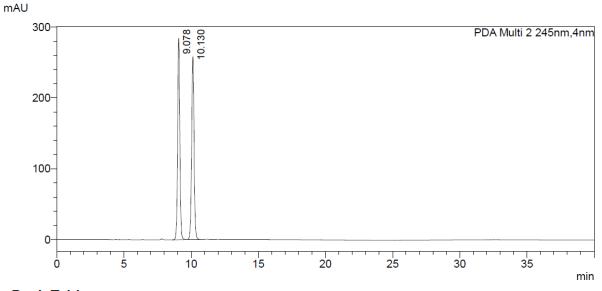
Peak#	Ret. Time	Area	Height	Area%
1	23.669	2345104	73597	50.090
2	34.632	2336675	46991	49.910
Total		4681779	120588	100.000

mAU

PDA Multi 2 243nm,4nm

23.266

33.923

min

<Peak Table>

PDA Ch2 243nm
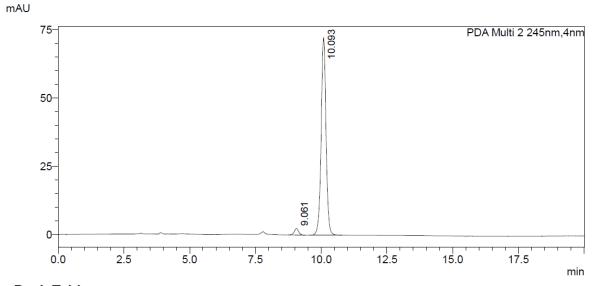
Peak#	Ret. Time	Area	Height	Area%
1	23.266	7666168	248757	92.588
2	33.923	613704	12505	7.412
Total		8279872	261262	100.000

2.25ae

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

mAU

PDA Multi 2 245nm,4nm

<Peak Table>

PDA Ch2 245nm
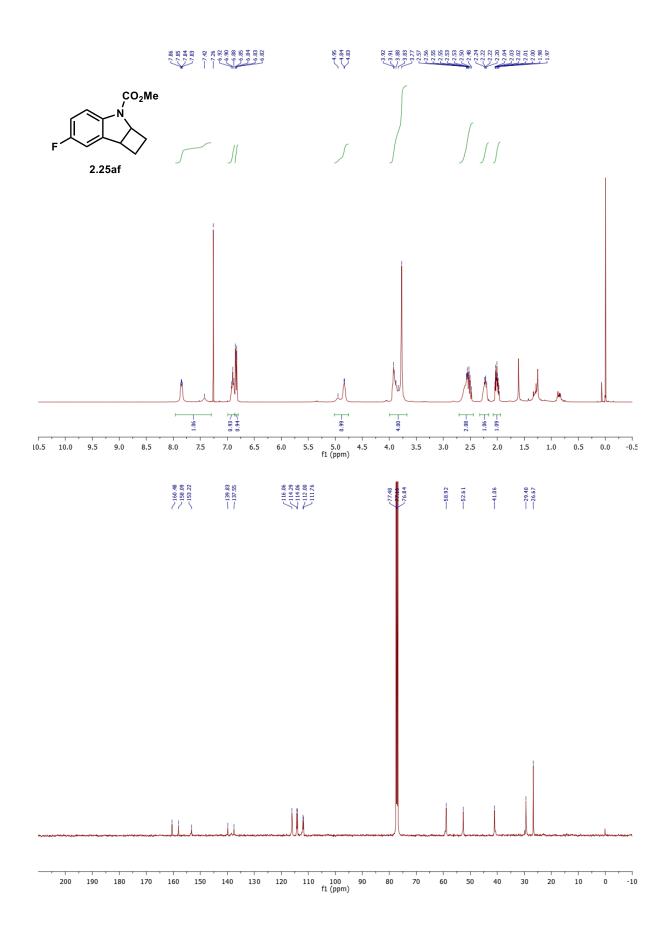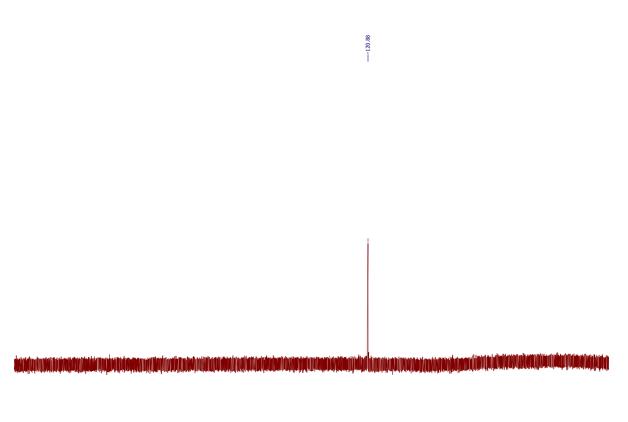
Peak#	Ret. Time	Area	Height	Area%
1	9.078	3237008	284756	49.930
2	10.130	3246137	257569	50.070
Total		6483145	542325	100.000

mAU

PDA Multi 2 245nm,4nm

<Peak Table>

PDA Ch2 245nm
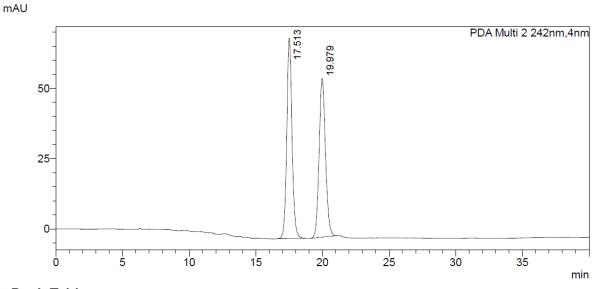
Peak#	Ret. Time	Area	Height	Area%
1	9.061	27525	2365	2.878
2	10.093	928984	72297	97.122
Total		956509	74661	100.000
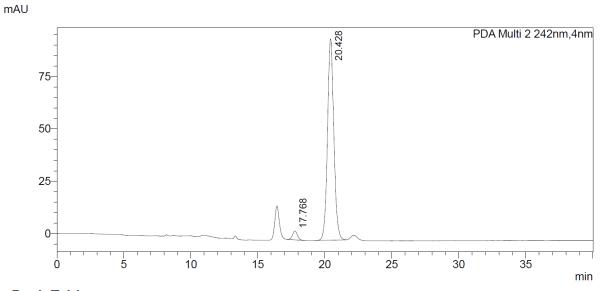
1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

2.25af

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

mAU

PDA Multi 2 242nm,4nm

<Peak Table>

PDA Ch2 242nm
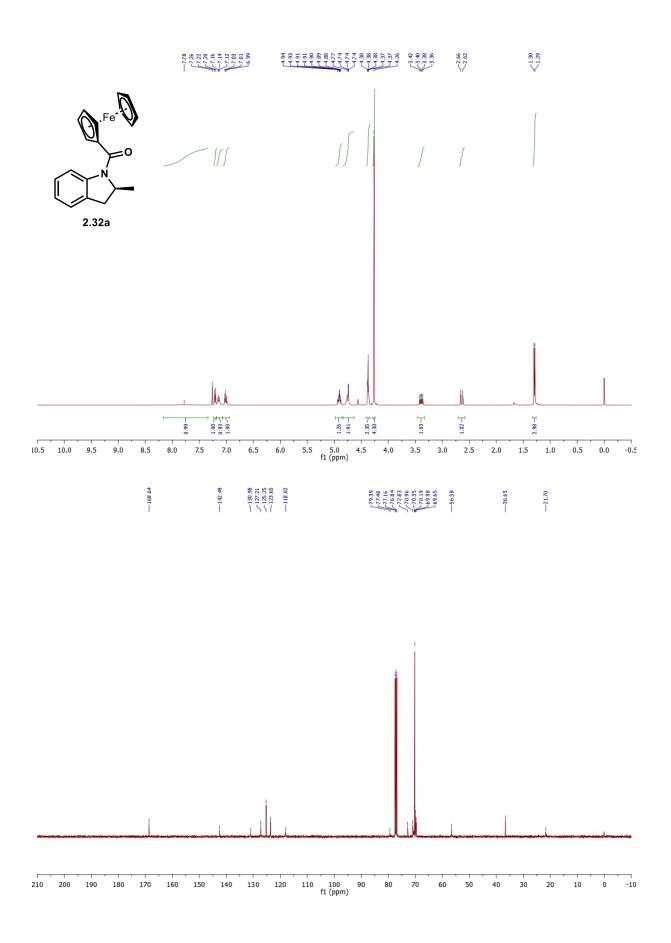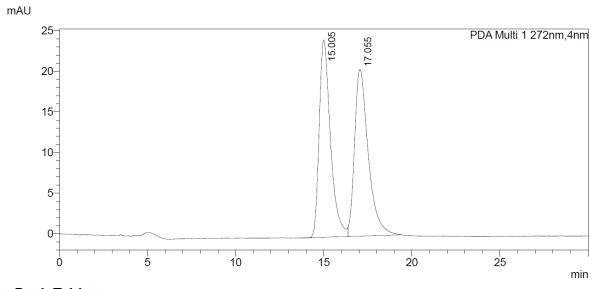
Peak#	Ret. Time	Area	Height	Area%
1	17.513	1951867	71317	50.961
2	19.979	1878217	56480	49.039
Total		3830085	127797	100.000

mAU

PDA Multi 2 242nm,4nm

<Peak Table>

PDA Ch2 242nm
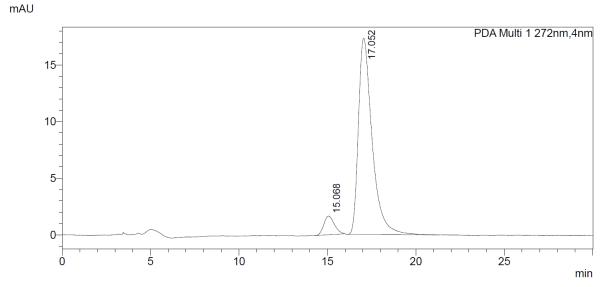
Peak#	Ret. Time	Area	Height	Area%
1	17.768	109127	4288	3.344
2	20.428	3153935	96029	96.656
Total		3263063	100317	100.000

2.32a

mAU

\<Peak Table\>

PDA Ch1 272nm
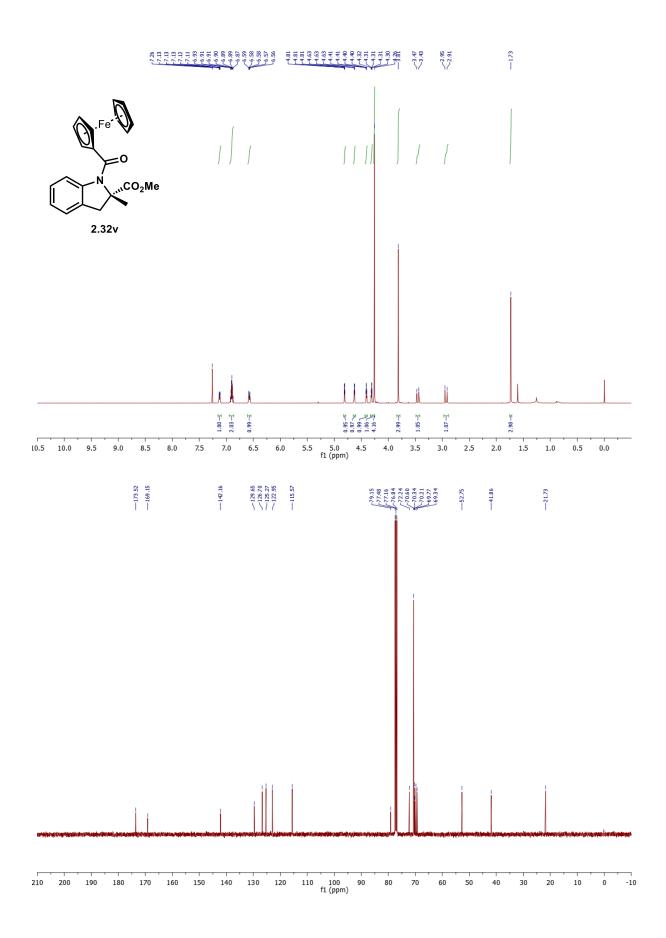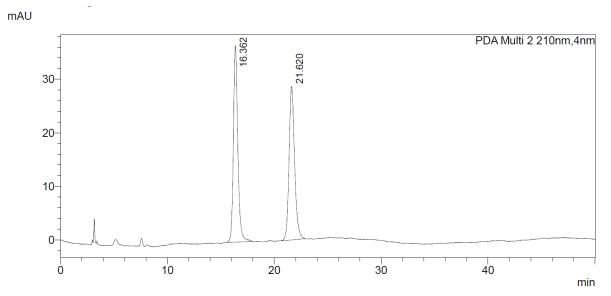
Peak#	Ret. Time	Area	Height	Area%
1	15.005	1079571	24285	49.315
2	17.055	1109556	20528	50.685
Total		2189126	44813	100.000

mAU

\<Peak Table\>

PDA Ch1 272nm
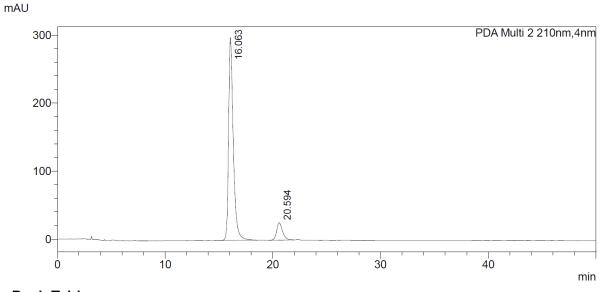
Peak#	Ret. Time	Area	Height	Area%
1	15.068	68103	1660	6.793
2	17.052	934391	17339	93.207
Total		1002495	18999	100.000

2.32v

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

mAU

PDA Multi 2 210nm,4nm

\<Peak Table\>

PDA Ch2 210nm
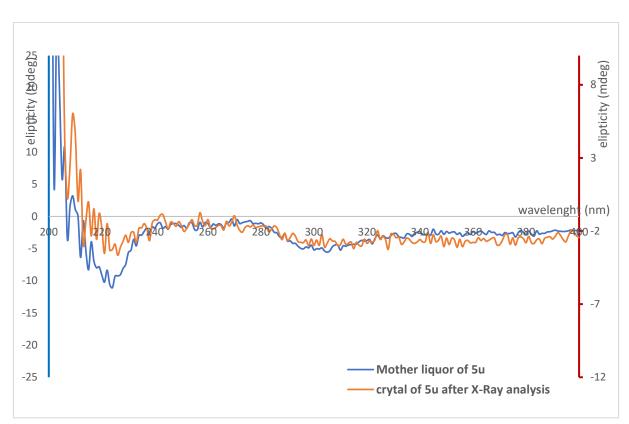
Peak#	Ret. Time	Area	Height	Area%
1	16.362	1055774	36701	50.551
2	21.620	1032763	28656	49.449
Total		2088537	65357	100.000

mAU

PDA Multi 2 210nm,4nm

\<Peak Table\>

PDA Ch2 210nm
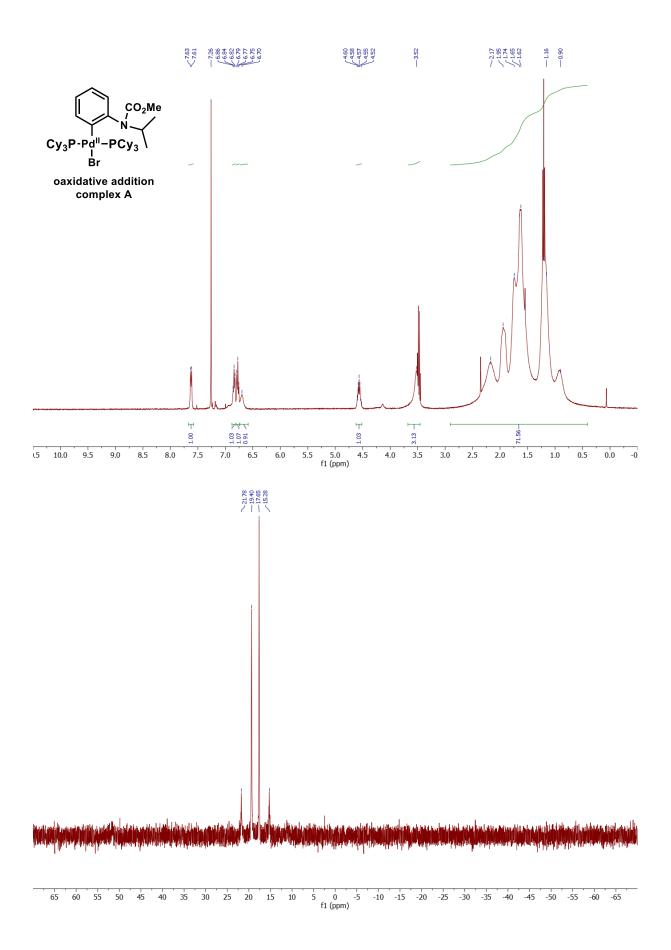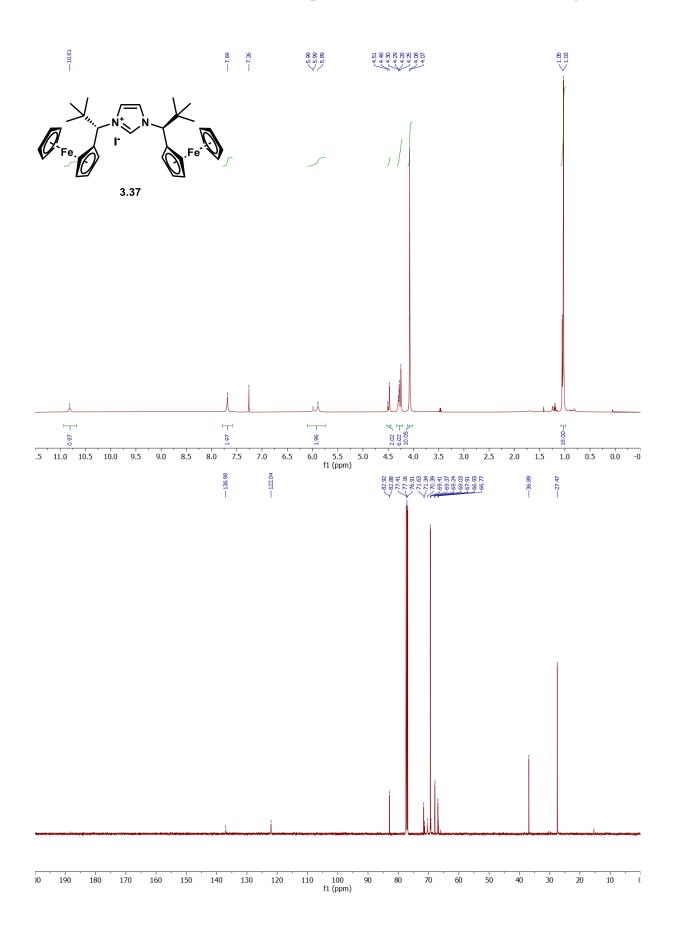
Peak#	Ret. Time	Area	Height	Area%
1	16.063	9039482	297723	90.238
2	20.594	977888	25561	9.762
Total		10017370	323283	100.000

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms
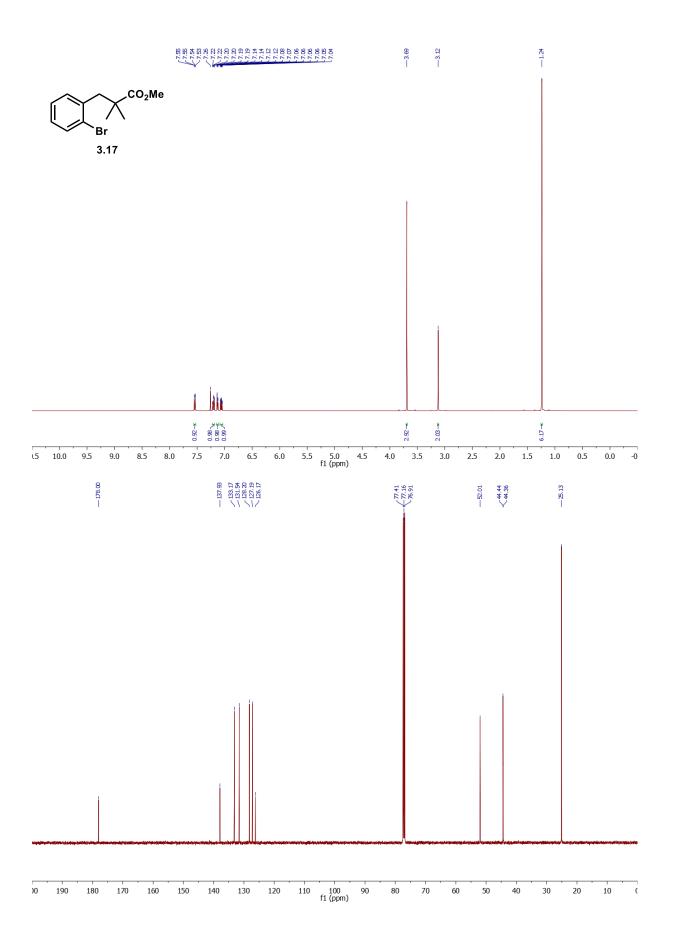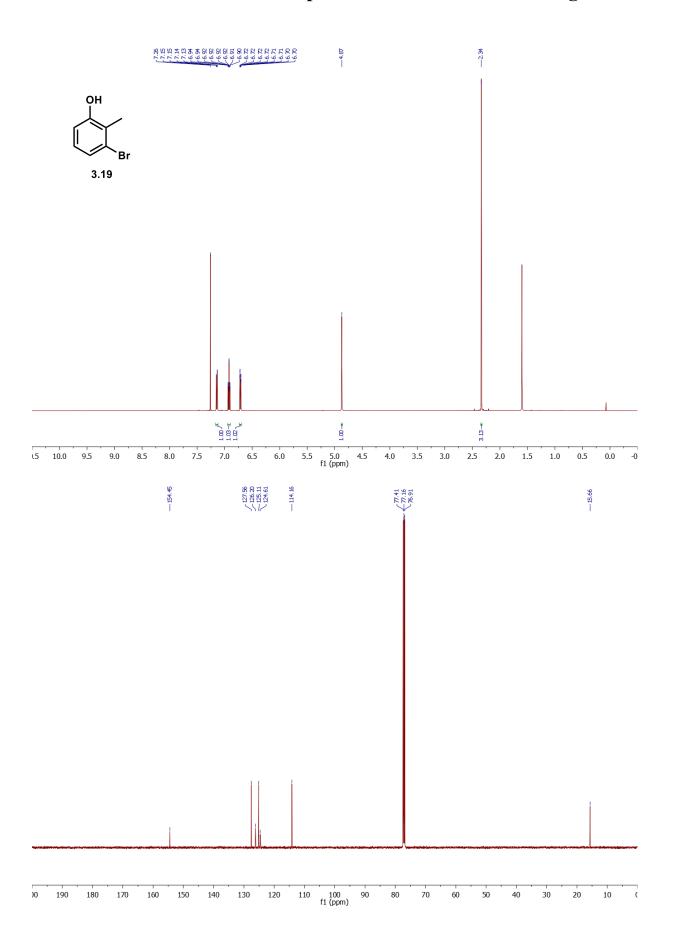
Circular dichroism spectrum of 2.32v
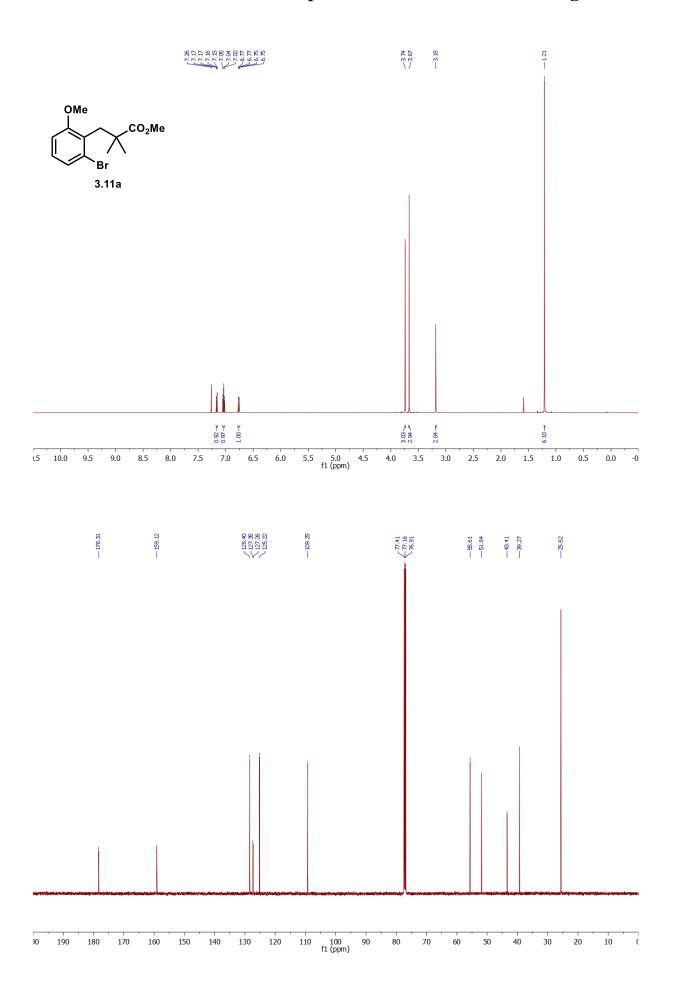
To avoid assigning the absolute configuration to the minor enantiomer, the circular dichroism spectrum of the solution prepared from the same single crystal of **2.32v**, which was analyzed by X-ray diffraction, was measured. It showed the same Cotton effect as the corresponding mother liquor, thereby showing that the major enantiomer was indeed analyzed by X-ray diffraction.

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

oaxidative addition
complex A

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

3.37

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

3.19

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

360

3.12

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

O*i*Pr

CO₂Me

Br

3.11b

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

3.11d

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

3.11e

3.11f

3.11g

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

3.11h

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

3.11i

370

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

OMe

O

CO₂ᵗBu

N

Br

3.11k

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

3.10a

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

<Chromatogram>

mAU

<Peak Table>

PDA Ch1 204nm

Peak#	Ret. Time	Area	Height	Area%
1	15.378	13244631	605367	49.545
2	17.306	13488147	548481	50.455
Total		26732778	1153849	100.000

<Chromatogram>

mAU

<Peak Table>

PDA Ch1 204nm
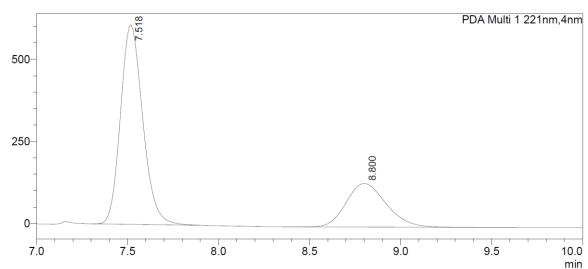
Peak#	Ret. Time	Area	Height	Area%
1	16.389	18602975	764148	66.255
2	18.088	9474922	374671	33.745
Total		28077896	1138819	100.000

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

O*i*Pr

CO₂Me

3.10b

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

<Chromatogram>

mAU

PDA Multi 2 221nm,4nm

<Peak Table>

PDA Ch2 221nm

Peak#	Ret. Time	Area	Height	Area%
1	7.546	3837875	449258	51.959
2	8.745	3548433	238485	48.041
Total		7386308	687743	100.000

<Chromatogram>

mAU

PDA Multi 1 221nm,4nm

<Peak Table>
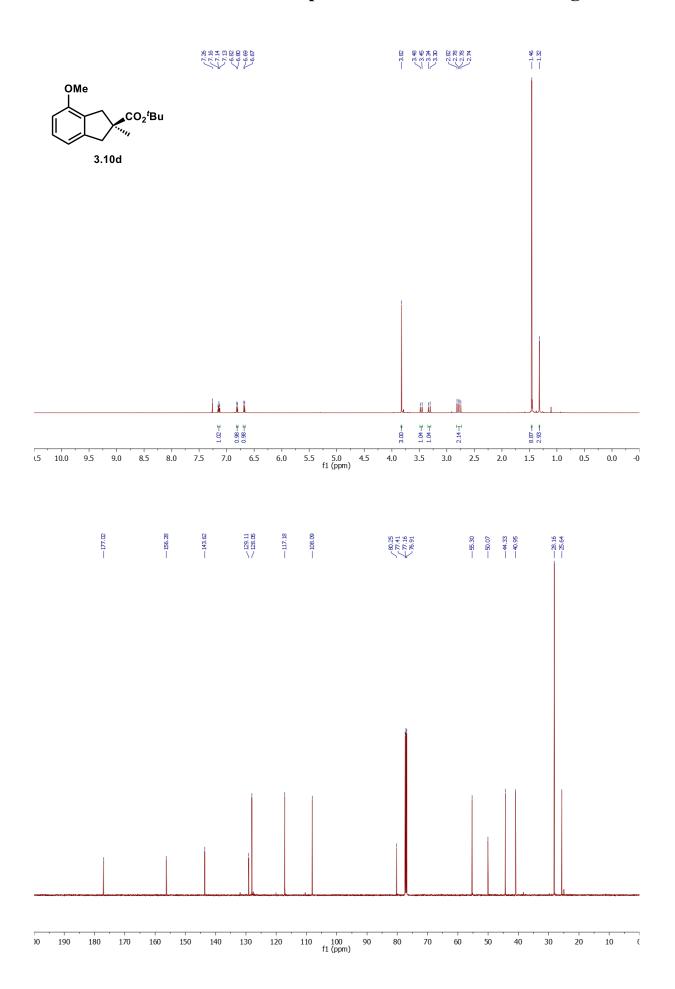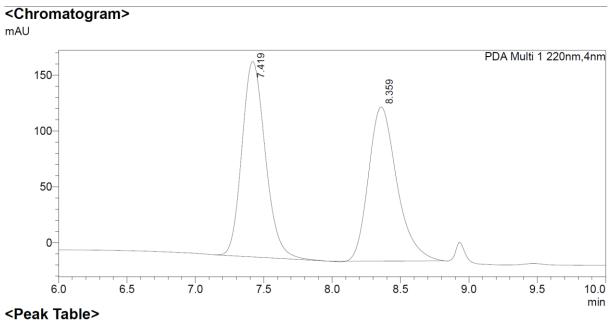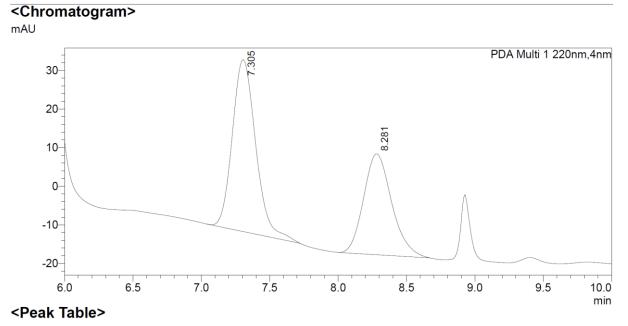
PDA Ch1 221nm

Peak#	Ret. Time	Area	Height	Area%
1	7.518	5163269	608571	71.677
2	8.800	2040244	133058	28.323
Total		7203513	741629	100.000

3.10d

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

\<Chromatogram\>

mAU

PDA Multi 1 220nm,4nm

7.419

8.359

\<Peak Table\>

PDA Ch1 220nm
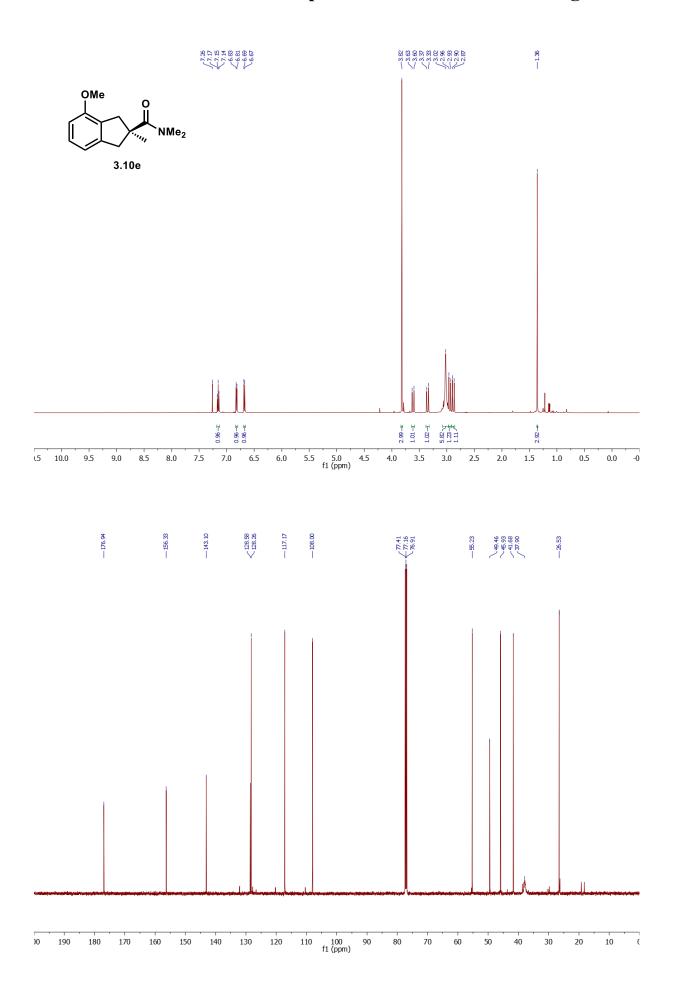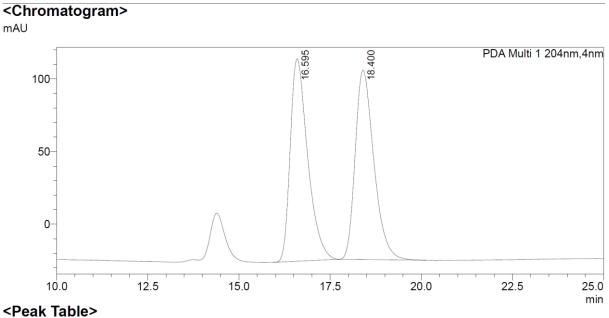
Peak#	Ret. Time	Area	Height	Area%
1	7.419	2089215	174899	51.140
2	8.359	1996092	137969	48.860
Total		4085306	312868	100.000

\<Chromatogram\>

mAU

PDA Multi 1 220nm,4nm

7.305

8.281

\<Peak Table\>

PDA Ch1 220nm

Peak#	Ret. Time	Area	Height	Area%
1	7.305	528165	44606	58.558
2	8.281	373780	26135	41.442
Total		901946	70741	100.000

3.10e

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

\<Chromatogram\>

mAU

PDA Multi 1 204nm,4nm

\<Peak Table\>

PDA Ch1 204nm
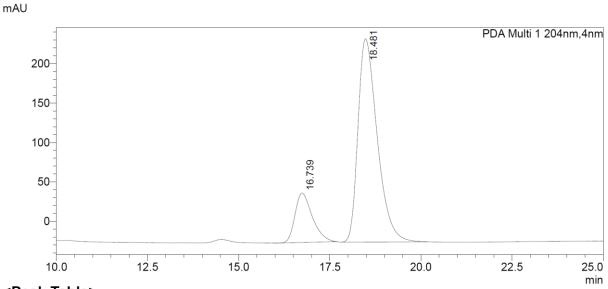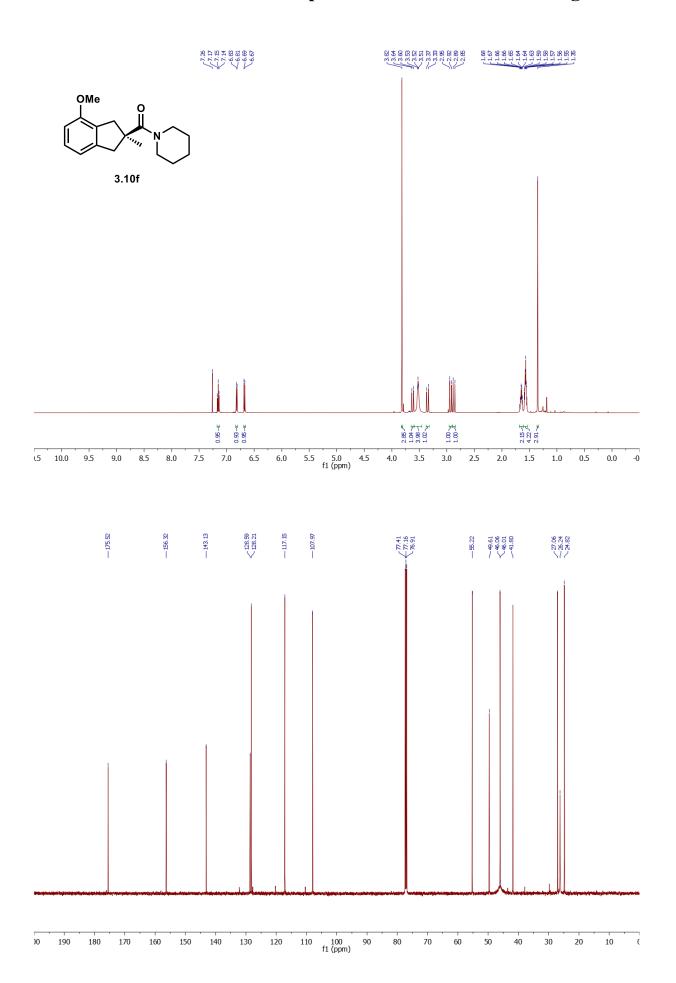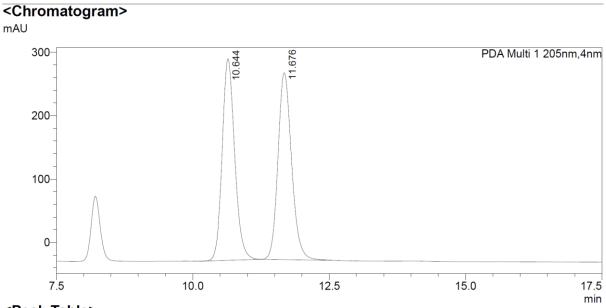
Peak#	Ret. Time	Area	Height	Area%
1	16.595	4643805	139542	50.005
2	18.400	4642939	130497	49.995
Total		9286745	270039	100.000

\<Chromatogram\>

mAU

PDA Multi 1 204nm,4nm

\<Peak Table\>

PDA Ch1 204nm
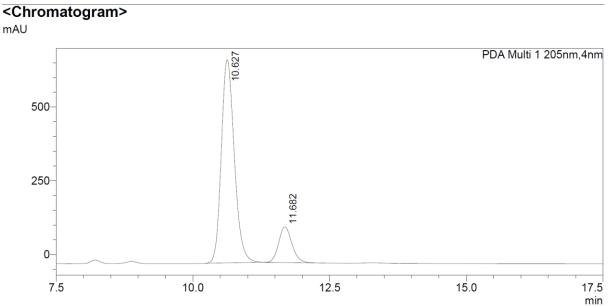
Peak#	Ret. Time	Area	Height	Area%
1	16.739	2072684	62758	17.953
2	18.481	9472399	258124	82.047
Total		11545084	320882	100.000

3.10f

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

\<Chromatogram\>

mAU

PDA Multi 1 205nm,4nm

\<Peak Table\>

PDA Ch1 205nm
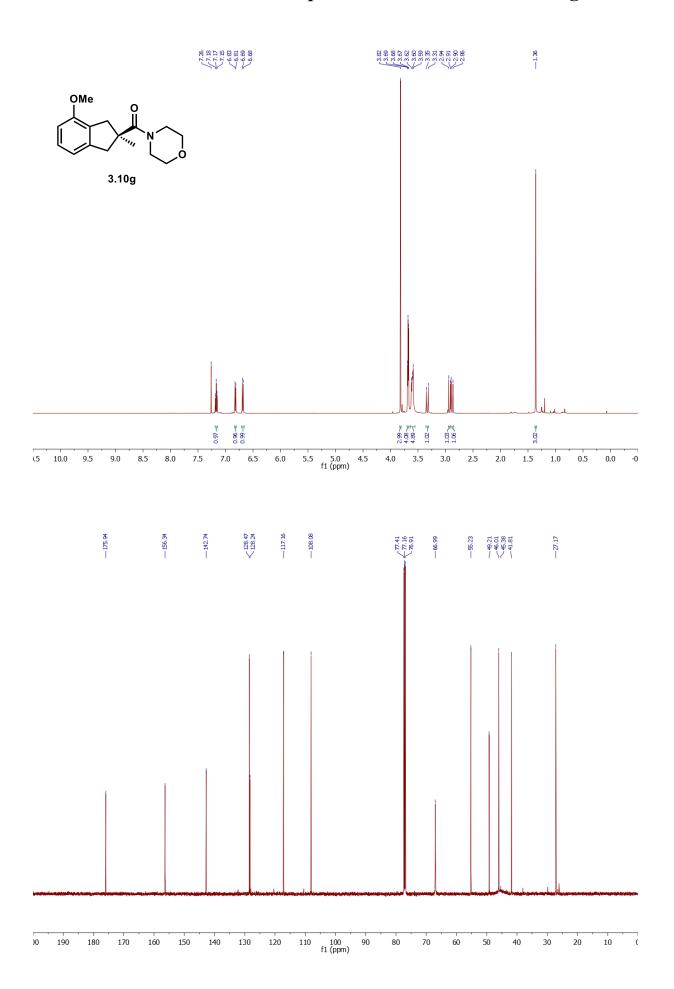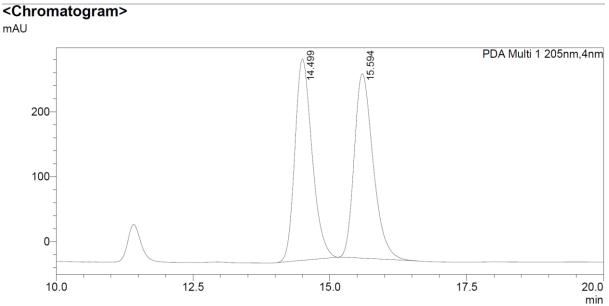
Peak#	Ret. Time	Area	Height	Area%
1	10.644	5075261	317900	49.733
2	11.676	5129706	294590	50.267
Total		10204967	612490	100.000

\<Chromatogram\>

mAU

PDA Multi 1 205nm,4nm

\<Peak Table\>

PDA Ch1 205nm

Peak#	Ret. Time	Area	Height	Area%
1	10.627	11395909	688748	84.796
2	11.682	2043259	121147	15.204
Total		13439168	809895	100.000

3.10g

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

<Chromatogram>

mAU

PDA Multi 1 205nm,4nm

14.499
15.594

<Peak Table>

PDA Ch1 205nm
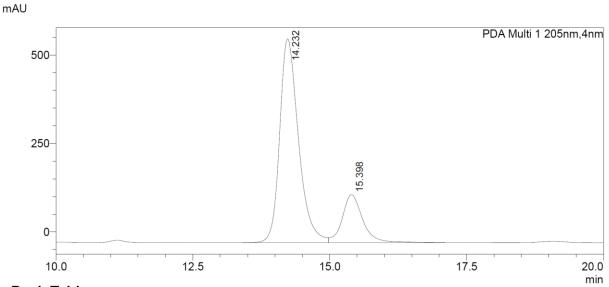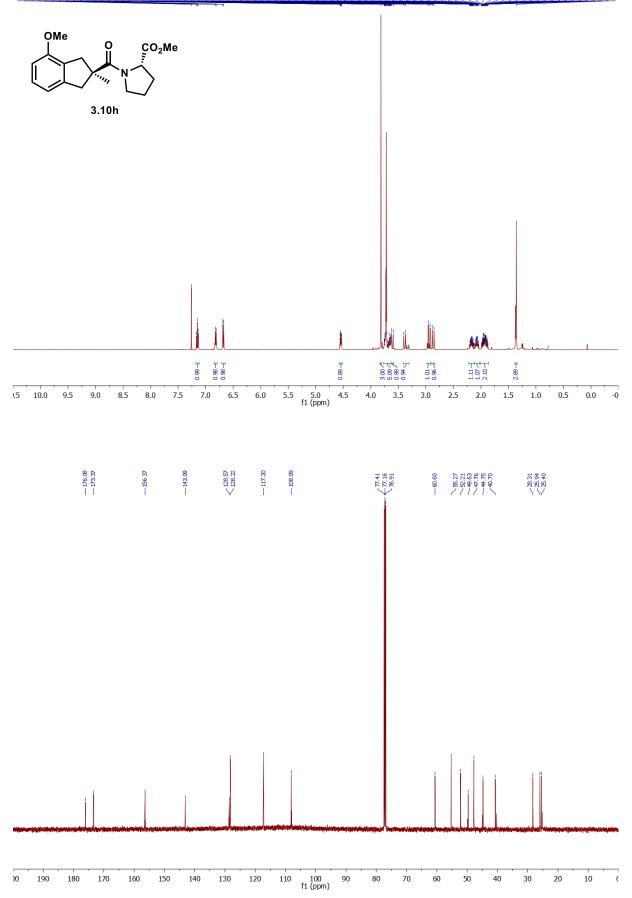
Peak#	Ret. Time	Area	Height	Area%
1	14.499	6779738	309557	49.841
2	15.594	6822886	283529	50.159
Total		13602624	593086	100.000

<Chromatogram>

mAU

PDA Multi 1 205nm,4nm

14.232
15.398

<Peak Table>

PDA Ch1 205nm
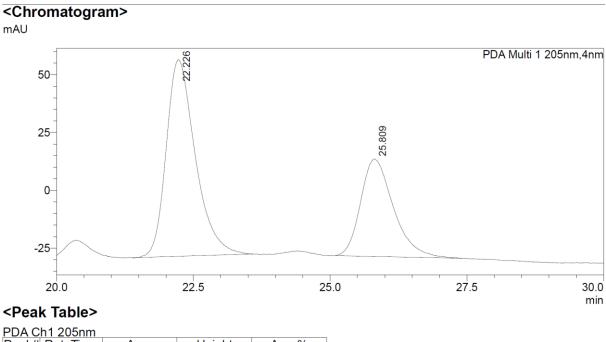
Peak#	Ret. Time	Area	Height	Area%
1	14.232	13766237	575649	79.675
2	15.398	3511859	135317	20.325
Total		17278096	710966	100.000

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

3.10h

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

With **IBioxMe₄·HOTf**:

\<Chromatogram\>

mAU

\<Peak Table\>

PDA Ch1 205nm
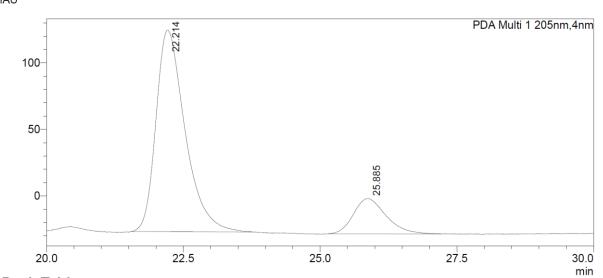
Peak#	Ret. Time	Area	Height	Area%
1	22.226	3144929	85062	64.131
2	25.809	1758950	42187	35.869
Total		4903879	127248	100.000

With **3.29**:

\<Chromatogram\>

mAU

\<Peak Table\>

PDA Ch1 205nm
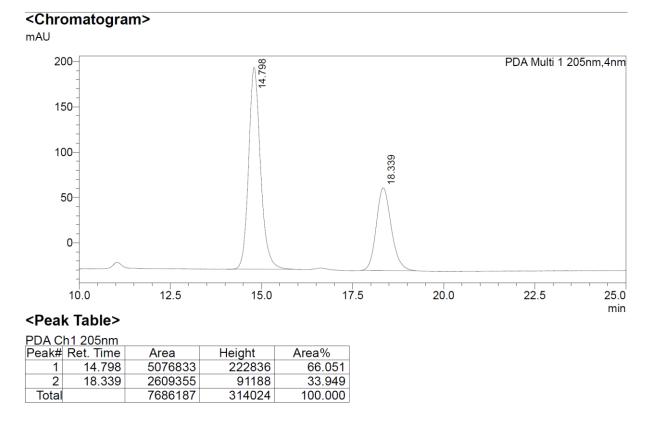
Peak#	Ret. Time	Area	Height	Area%
1	22.214	5609402	151676	83.579
2	25.885	1102089	26596	16.421
Total		6711492	178272	100.000

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

3.10i

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

From **3.11i** with **IBioxMe₄·HOTf**:

\<Chromatogram\>

mAU

PDA Multi 1 205nm,4nm

14.798

18.339

\<Peak Table\>

PDA Ch1 205nm

Peak#	Ret. Time	Area	Height	Area%
1	14.798	5076833	222836	66.051
2	18.339	2609355	91188	33.949
Total		7686187	314024	100.000
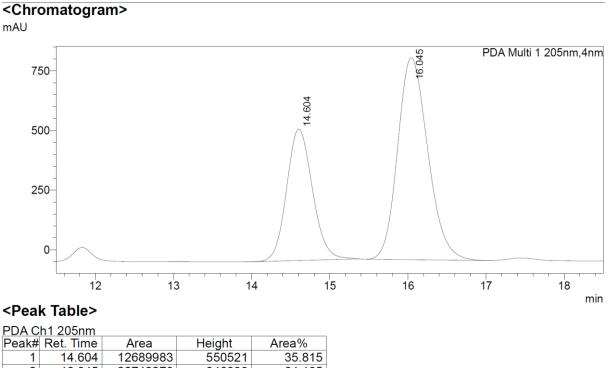
From **3.11i** with **3.29**:

\<Chromatogram\>

mAU

PDA Multi 1 205nm,4nm

14.772

18.344

\<Peak Table\>

PDA Ch1 205nm
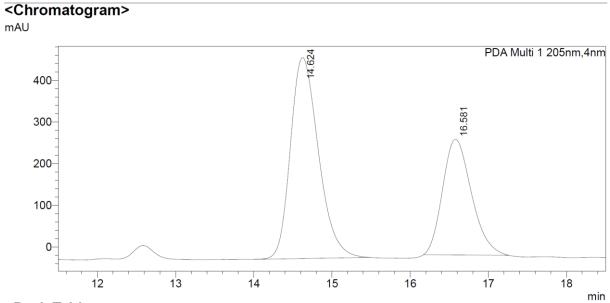
Peak#	Ret. Time	Area	Height	Area%
1	14.772	5842523	253013	87.058
2	18.344	868569	34187	12.942
Total		6711092	287200	100.000

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

From **3.11j** with **IBioxMe₄·HOTf**:

<Chromatogram>

mAU

<Peak Table>

PDA Ch1 205nm
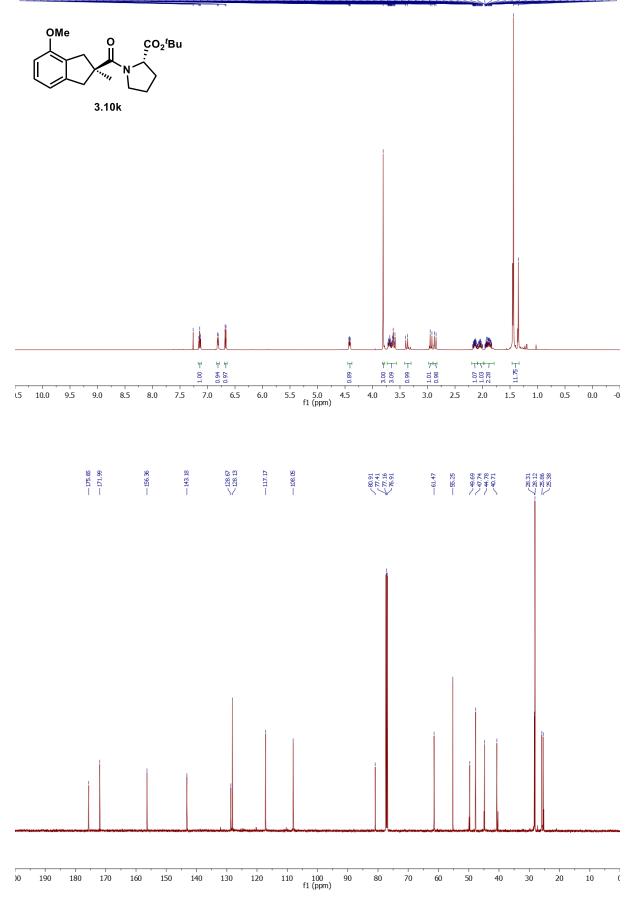
Peak#	Ret. Time	Area	Height	Area%
1	14.604	12689983	550521	35.815
2	16.045	22742276	846939	64.185
Total		35432258	1397460	100.000

From **3.11i** with **3.29**:

<Chromatogram>

mAU

<Peak Table>

PDA Ch1 205nm
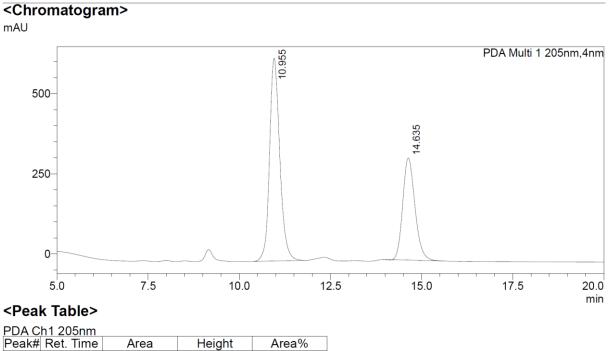
Peak#	Ret. Time	Area	Height	Area%
1	14.624	12018865	482571	62.798
2	16.581	7119918	277521	37.202
Total		19138783	760093	100.000

3.10k

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

With **IBioxMe₄·HOTf**:

\<Chromatogram\>

mAU

\<Peak Table\>

PDA Ch1 205nm
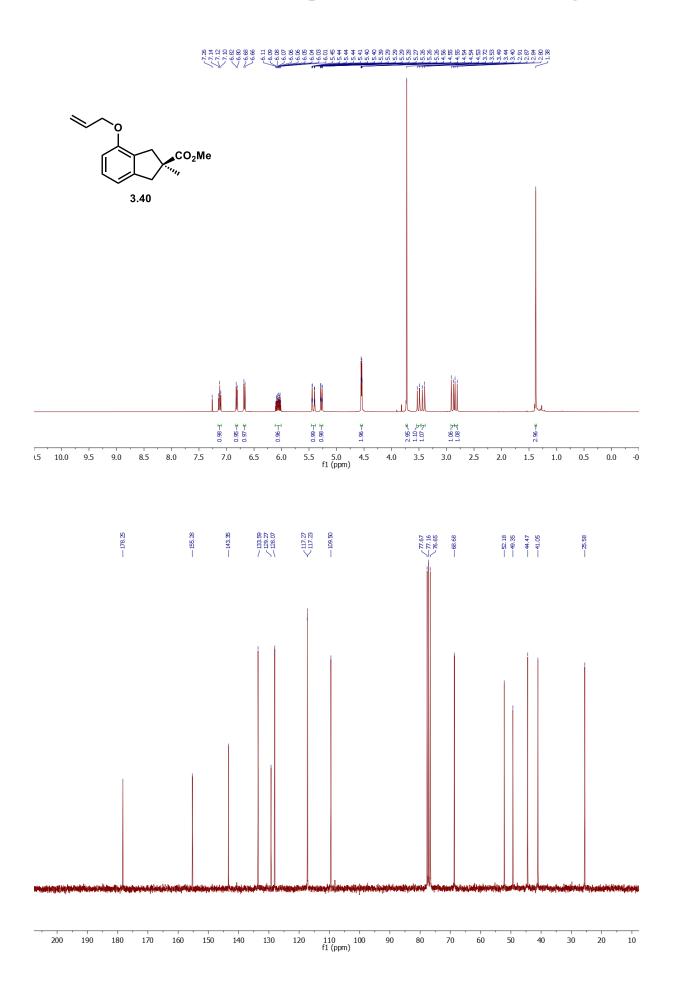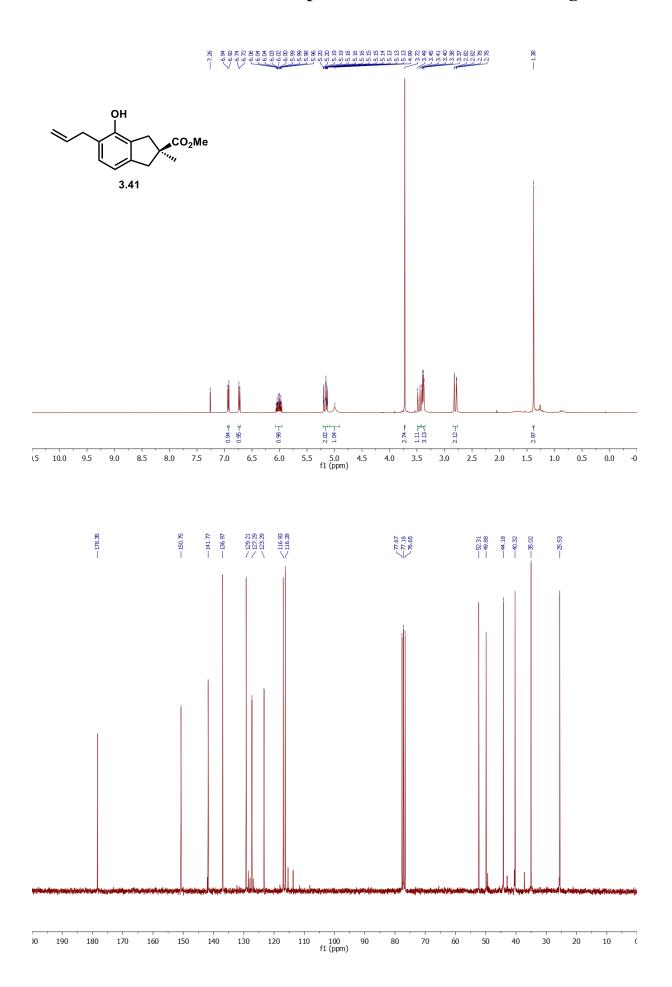
Peak#	Ret. Time	Area	Height	Area%
1	10.955	12332499	633593	62.397
2	14.635	7432194	319044	37.603
Total		19764693	952637	100.000

With **3.29**:

\<Chromatogram\>

mAU

\<Peak Table\>

PDA Ch1 205nm
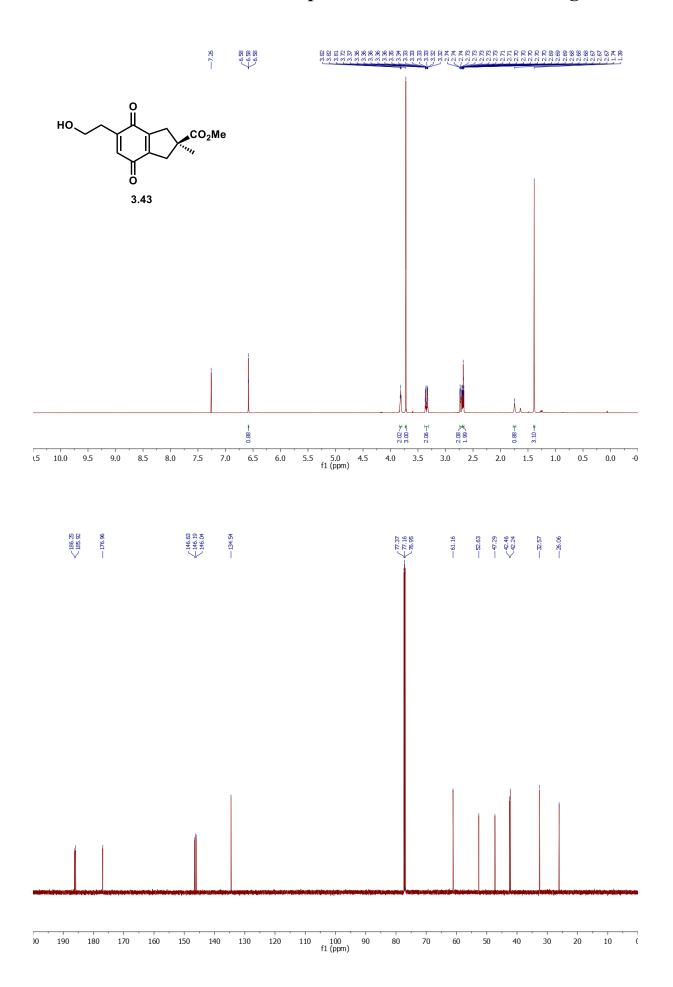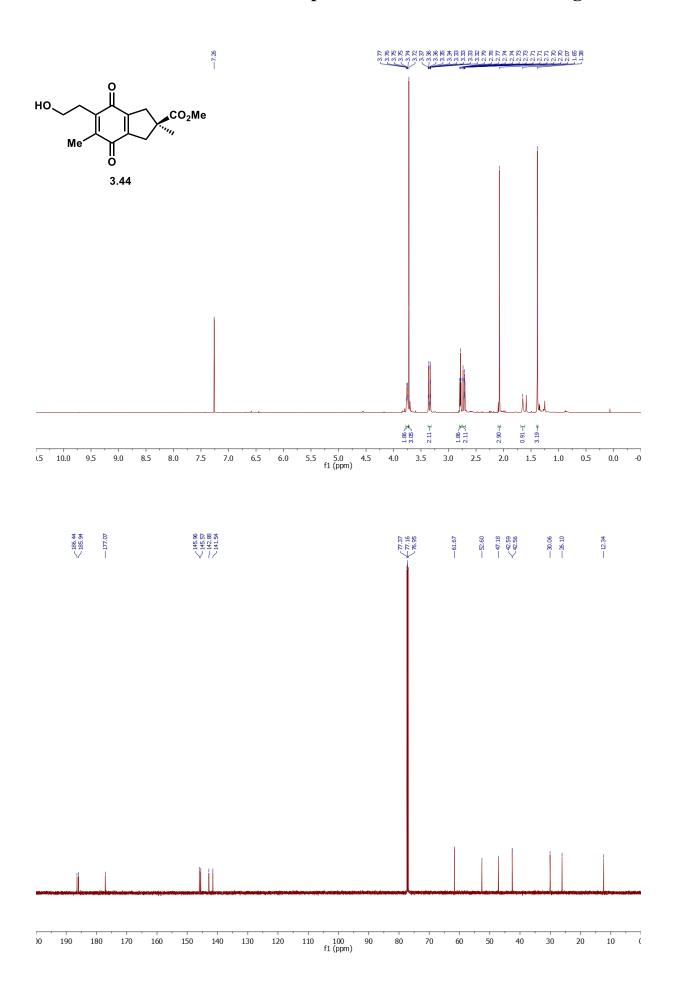
Peak#	Ret. Time	Area	Height	Area%
1	10.750	6616798	365456	83.192
2	14.558	1336847	60107	16.808
Total		7953645	425563	100.000

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

3.40

3.41

3.43

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

3.44

3.46

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

3.53

3.63a

3.63b

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

3.64a

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

From **3.63a** with **IBioxMe4·HOTf**:

\<Chromatogram\>

\<Peak Table\>

PDA Ch1 205nm
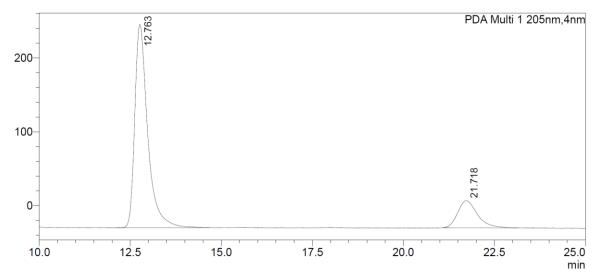
Peak#	Ret. Time	Area	Height	Area%
1	12.798	7298418	292502	66.186
2	22.161	3728758	97388	33.814
Total		11027177	389891	100.000

From **3.63a** with **3.29**:

\<Chromatogram\>

\<Peak Table\>

PDA Ch1 205nm
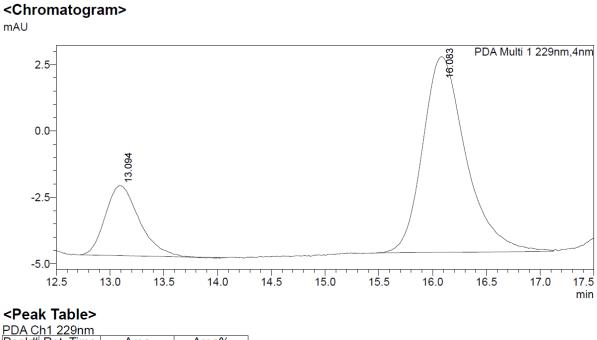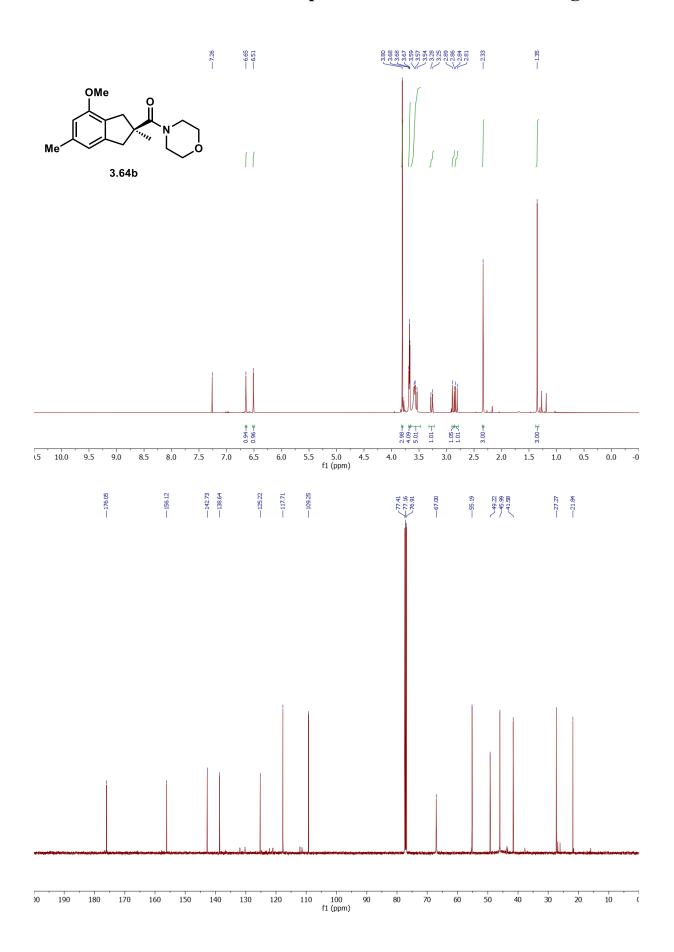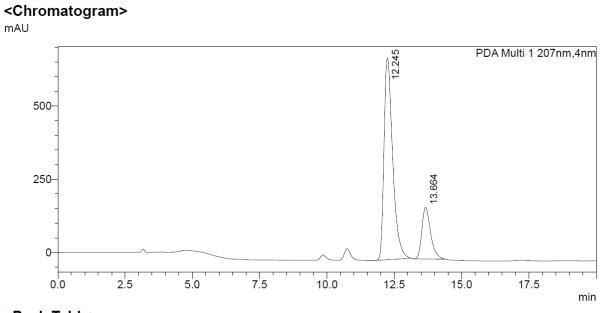
Peak#	Ret. Time	Area	Height	Area%
1	12.763	6790822	274912	85.107
2	21.718	1188296	34696	14.893
Total		7979119	309609	100.000

From **3.63c** with **3.34**:

<Chromatogram>

mAU

PDA Multi 1 229nm,4nm

<Peak Table>

PDA Ch1 229nm
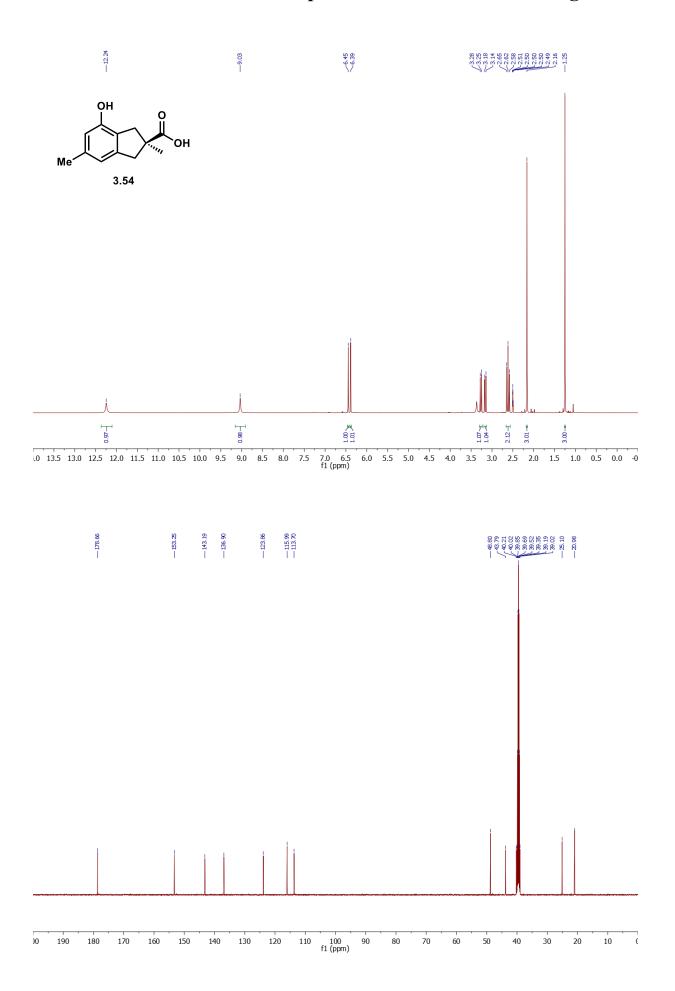
Peak#	Ret. Time	Area	Area%
1	13.094	57718	21.891
2	16.083	205946	78.109
Total		263664	100.000

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

3.64b

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

<Chromatogram>

mAU

PDA Multi 1 207nm,4nm

<Peak Table>

PDA Ch1 207nm
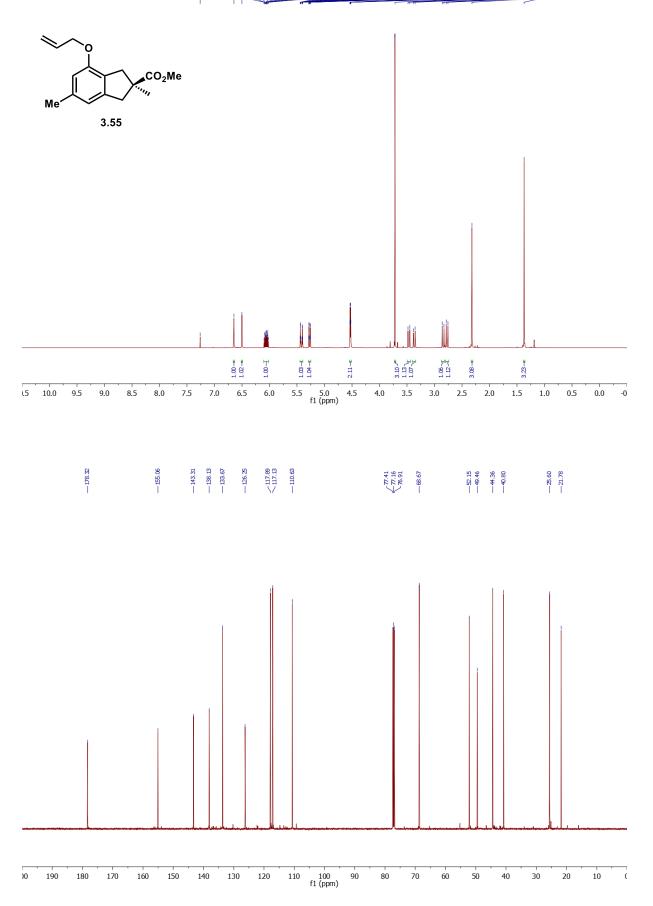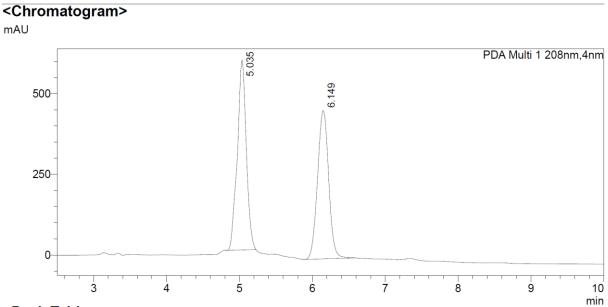
Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	12.245	79.447	15359729	687450	0.000		M
2	13.664	20.553	3973564	175978	0.000		M
Total		100.000	19333293	863427			

409

3.54

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

3.55

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

<Chromatogram>

mAU

PDA Multi 1 208nm,4nm

5.035

6.149

<Peak Table>

PDA Ch1 208nm
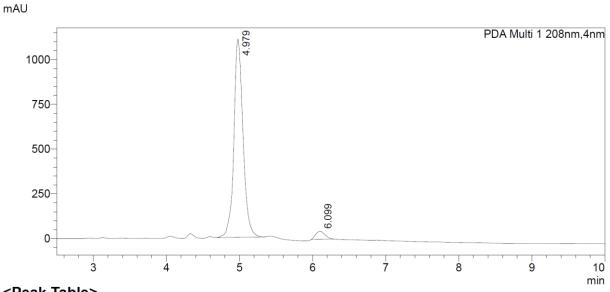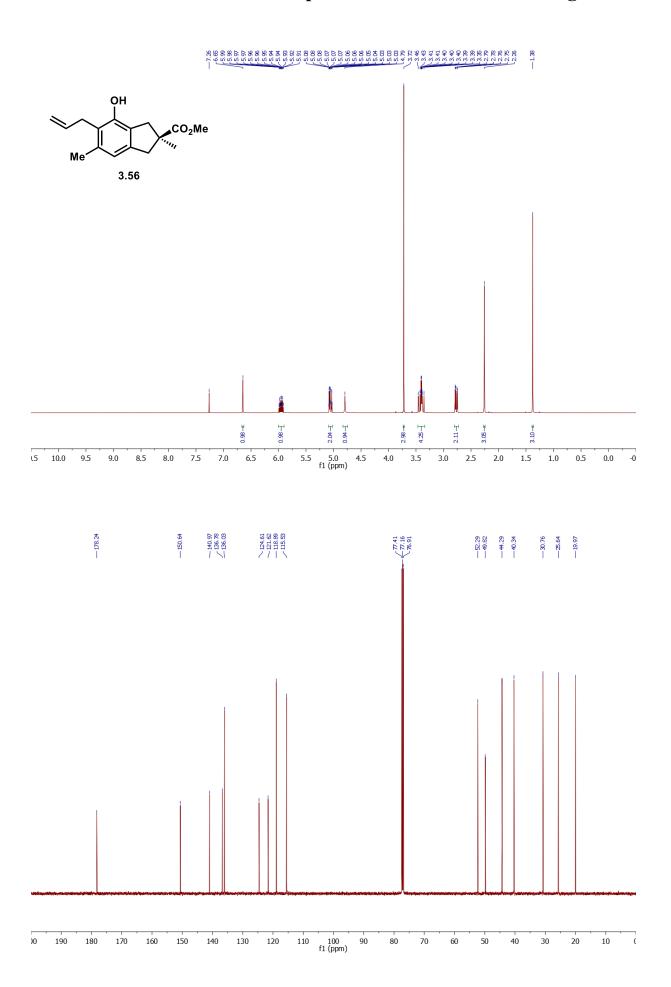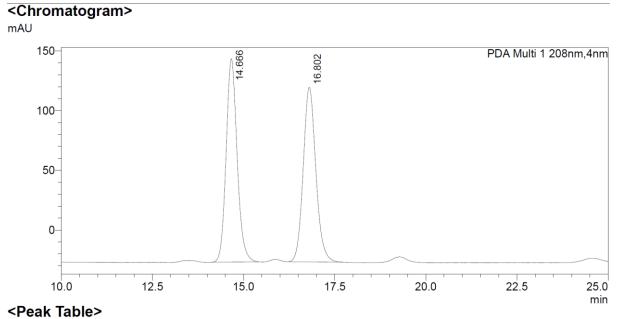
Peak#	Ret. Time	Area	Height	Area%
1	5.035	5058195	588405	50.908
2	6.149	4877789	459125	49.092
Total		9935984	1047530	100.000

<Chromatogram>

mAU

PDA Multi 1 208nm,4nm

4.979

6.099

<Peak Table>

PDA Ch2 225nm

Peak#	Ret. Time	Area	Height	Area%
1	4.979	3389276	439702	95.732
2	6.097	151099	15414	4.268
Total		3540375	455117	100.000

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

3.56

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

\<Chromatogram\>

mAU

PDA Multi 1 208nm,4nm

\<Peak Table\>

PDA Ch1 208nm
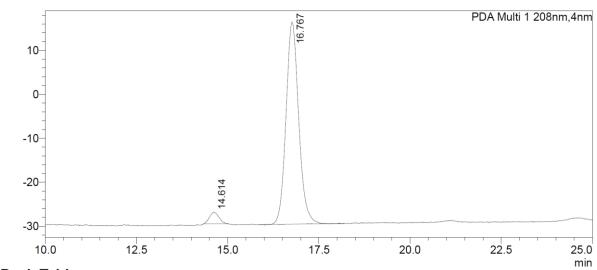
Peak#	Ret. Time	Area	Height	Area%
1	14.666	3577396	170451	50.347
2	16.802	3528036	146378	49.653
Total		7105432	316829	100.000

\<Chromatogram\>

mAU

PDA Multi 1 208nm,4nm

\<Peak Table\>

PDA Ch1 208nm
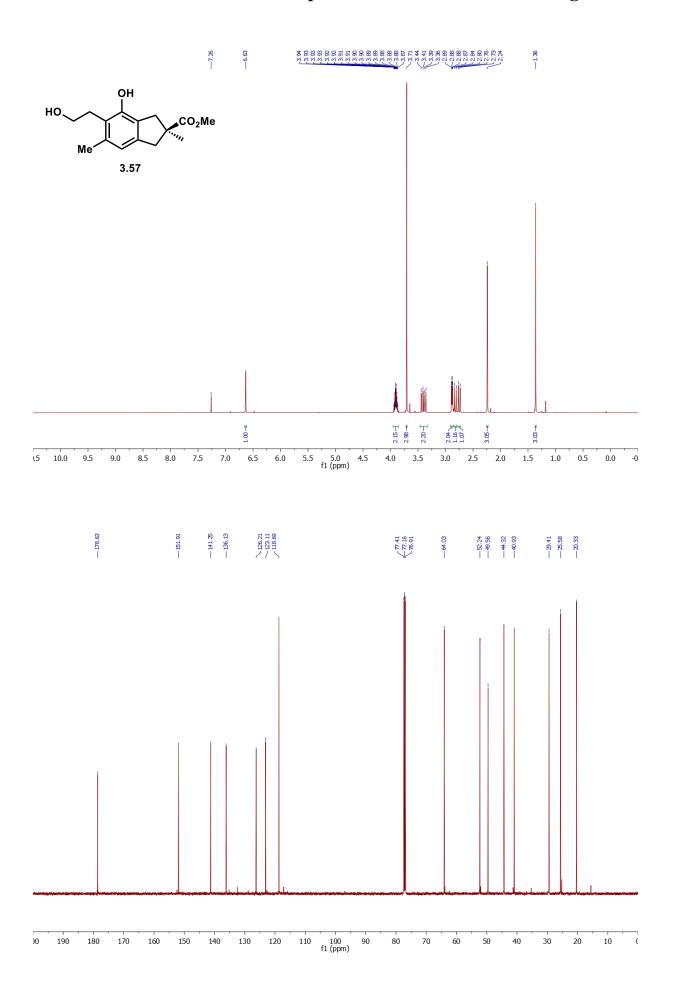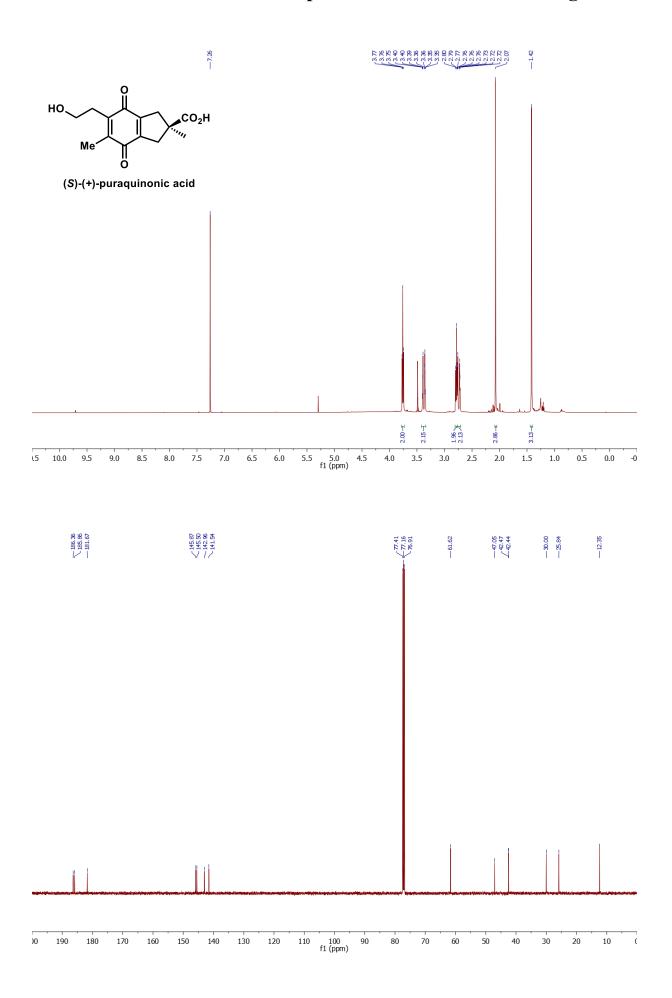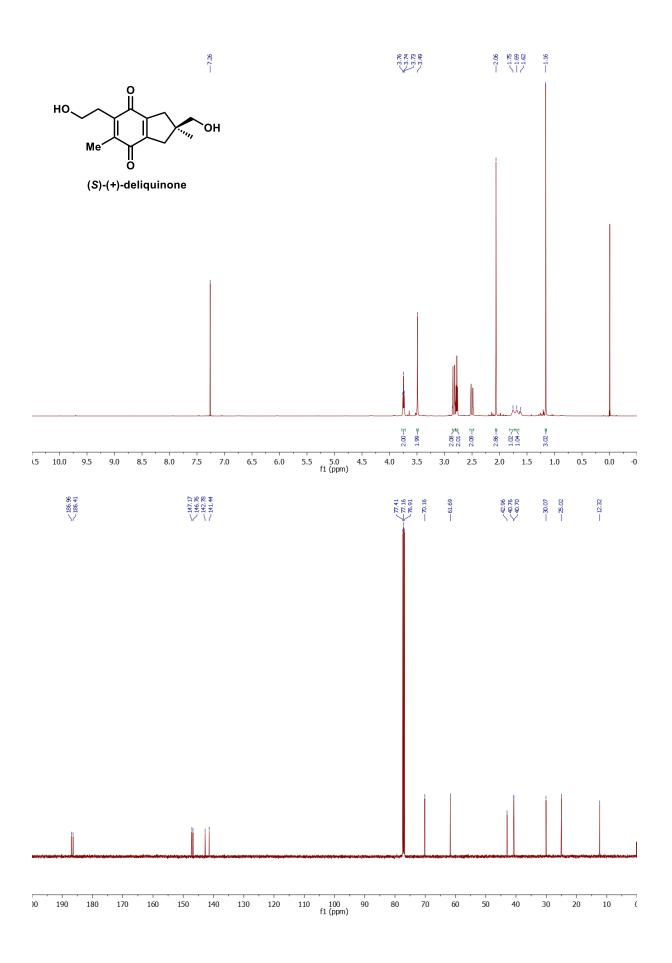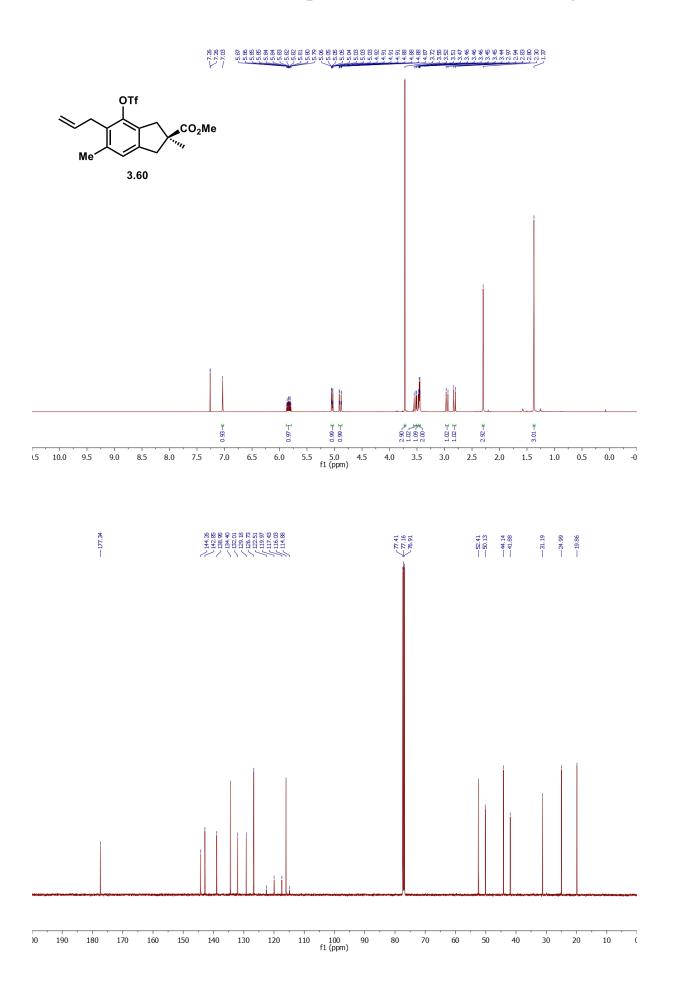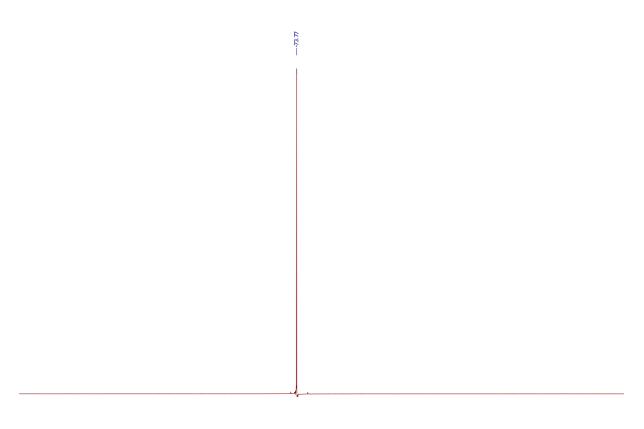
Peak#	Ret. Time	Area	Height	Area%
1	14.614	47308	2670	4.077
2	16.767	1113046	46025	95.923
Total		1160354	48696	100.000

414

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

(S)-(+)-puraquinonic acid

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

(S)-(+)-deliquinone

3.60

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

(S)-(+)-russujaponol F
(in C$_5$D$_5$N)

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

(S)-(+)-russujaponol F
(in CDCl₃)

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

3.66a

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

IBiox^{i}Bu·HOTf

-78.43

f1 (ppm)

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

BioxCy

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

IBioxCy·HOTf

—78.48

20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220
f1 (ppm)

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

BioxAd

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

IBioxAd·HOTf

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

-78.38

-55 -60 -65 -70 -75 -80 -85 -90 -95 -100 -105 -110 -115 -120 -125 -130 -135 -140 -145
f1 (ppm)

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

Pd(IBioxAd)(π-All)Cl

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

-114.58

f1 (ppm)

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

MeO, CO₂Me

Br CO₂Me

4.20d

7.41
7.39
7.26
6.79
6.78
6.67
6.66
6.65
6.65
3.87
3.85
3.83
3.75
3.70
3.28
3.30

0.98
1.00
1.00
1.00
3.00
6.01
2.02

f1 (ppm)

169.11
159.01
137.97
133.59
117.02
114.95
114.55
77.41
77.16
76.91
55.56
52.74
51.43
35.40

f1 (ppm)

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

Cl · · CO₂Me · CO₂Me · Cl · **4.20e**

7.28, 7.26, 7.26, 7.23, 7.17, 7.16, 7.15, 7.15

3.82, 3.80, 3.79, 3.71, 3.30, 3.28

0.97, 1.00, 0.99

1.00, 6.05, 2.17

f1 (ppm)

168.90

137.16, 132.73, 132.58, 131.34, 130.82, 128.67

77.41, 77.16, 76.91

52.84, 51.06

32.69

f1 (ppm)

4.20f

4.12a

-113.64

20   10   0   -10   -20   -30   -40   -50   -60   -70   -80   -90   -100   -110   -120   -130   -140   -150   -160   -170   -180   -190   -200   -210   -220
f1 (ppm)

4.12b-Br

4.12b-Cl

4.12c

-114.79

f1 (ppm)

4.12d

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

454

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

455

4.12g

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

458

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

4.12i-Cl

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

4.12i-Br

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

4.12j

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

4.12k

4.12l

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

4.12o

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

4.12p

4.12q

4.12r

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

4.12t

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

4.12v

4.12w

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

4.12x

4.12y

4.12z

4.12aa

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

CO$_2$Me
CO$_2$Me
F
Br
4.12ab

-113.66

-55 -60 -65 -70 -75 -80 -85 -90 -95 -100 -105 -110 -115 -120 -125 -130 -135 -140 -145
f1 (ppm)

-113.66

-101 -102 -103 -104 -105 -106 -107 -108 -109 -110 -111 -112 -113 -114 -115 -116 -117 -118 -119 -120 -121 -122 -123 -124 -125 -126 -127 -128 -129 -1
f1 (ppm)
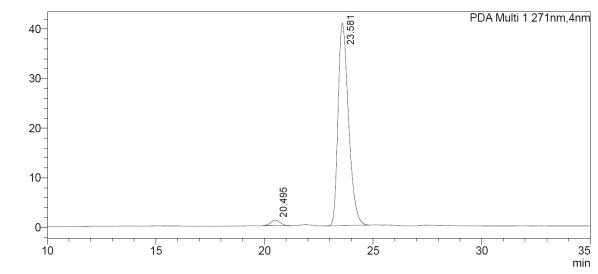
1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

4.13a

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

<Chromatogram>

mAU

PDA Multi 2 271nm,4nm

19.745

22.992

<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

<Chromatogram>

mAU

PDA Multi 1 271nm,4nm

23.581

20.495

<Peak Table>
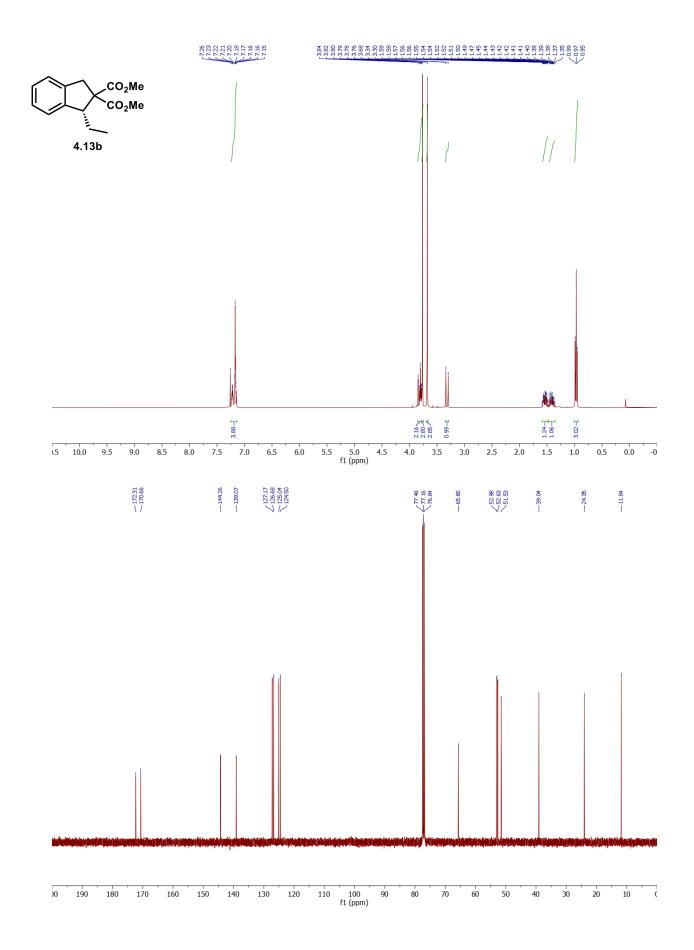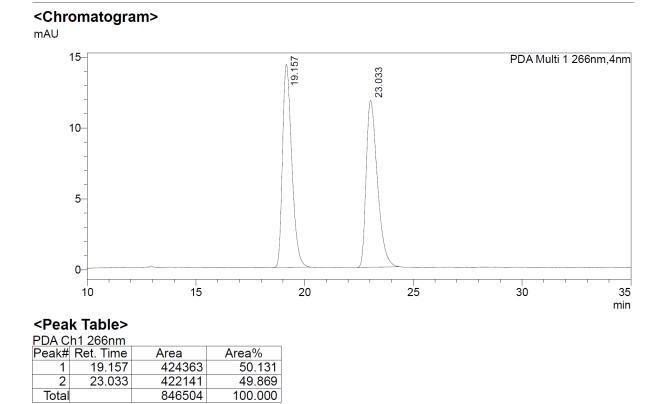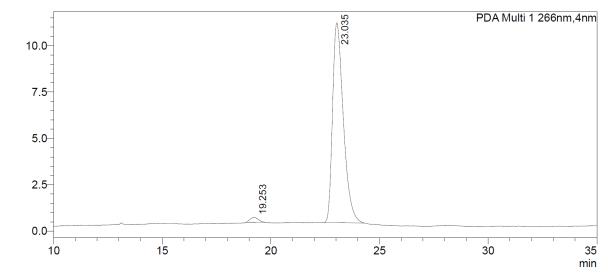
PDA Ch1 271nm

Peak#	Ret. Time	Area	Area%
1	20.495	33920	2.415
2	23.581	1370586	97.585
Total		1404507	100.000

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

4.13b

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

<Chromatogram>

mAU

PDA Multi 1 266nm,4nm

<Peak Table>

PDA Ch1 266nm

Peak#	Ret. Time	Area	Area%
1	19.157	424363	50.131
2	23.033	422141	49.869
Total		846504	100.000

<Chromatogram>

mAU

PDA Multi 1 266nm,4nm

<Peak Table>

PDA Ch1 266nm
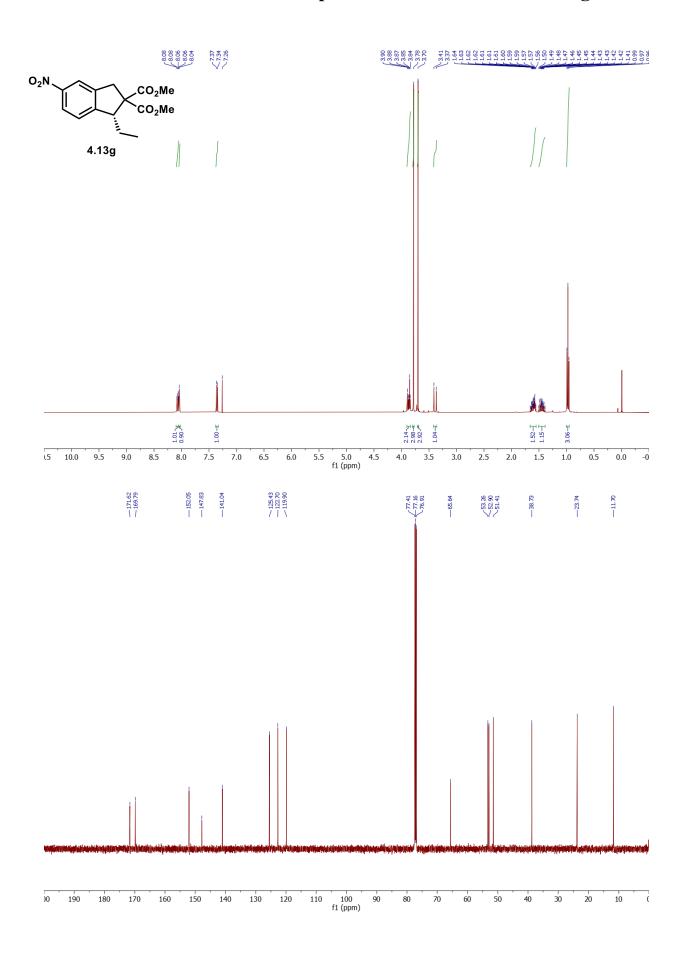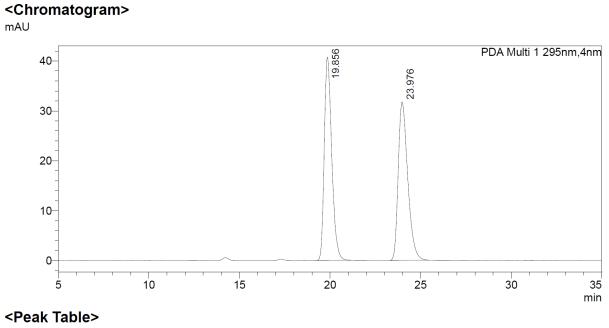
Peak#	Ret. Time	Area	Area%
1	19.253	7030	1.852
2	23.035	372496	98.148
Total		379526	100.000

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

4.13g

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

<Chromatogram>

mAU

<Peak Table>

PDA Ch1 295nm
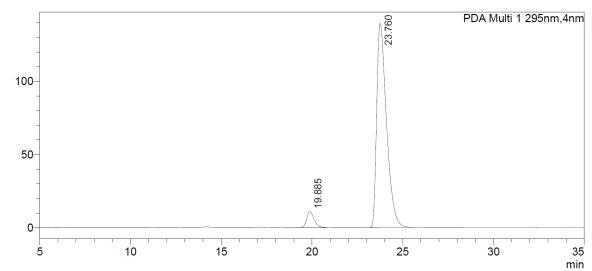
Peak#	Ret. Time	Area	Area%
1	19.856	1163701	50.094
2	23.976	1159338	49.906
Total		2323039	100.000

<Chromatogram>

mAU

<Peak Table>

PDA Ch1 295nm
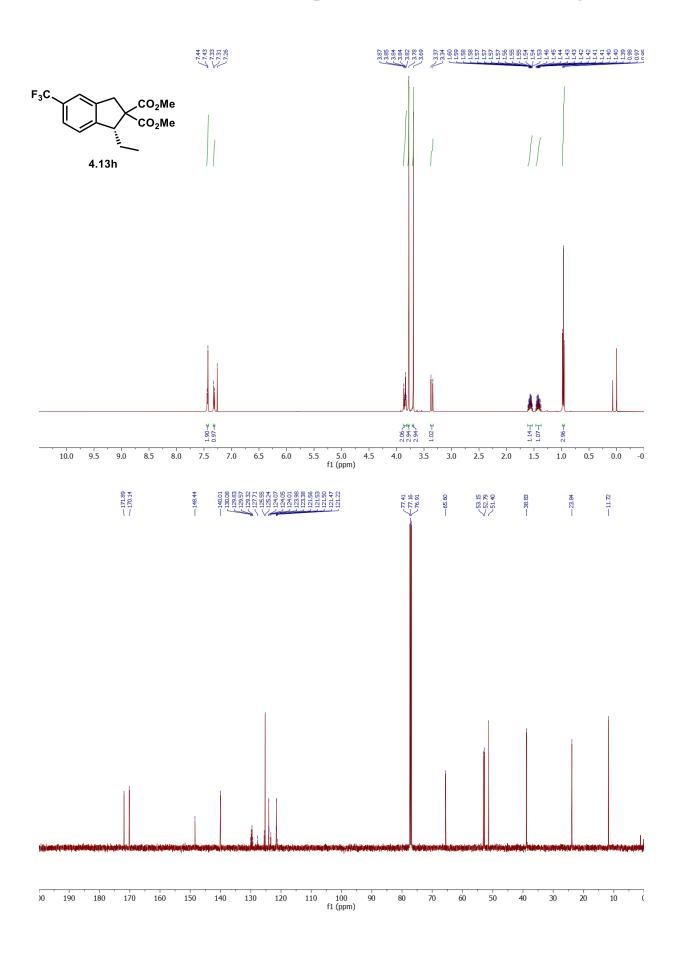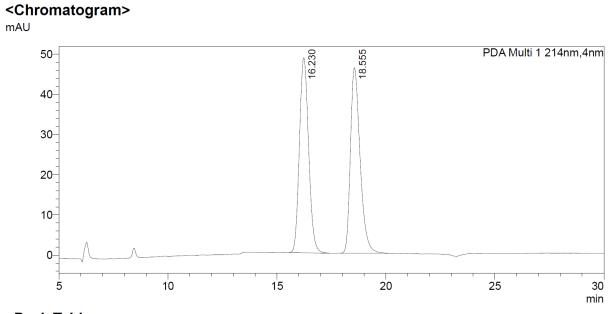
Peak#	Ret. Time	Area	Area%
1	19.885	309244	5.581
2	23.760	5231662	94.419
Total		5540906	100.000

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

4.13h

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

\<Chromatogram\>

mAU

\<Peak Table\>
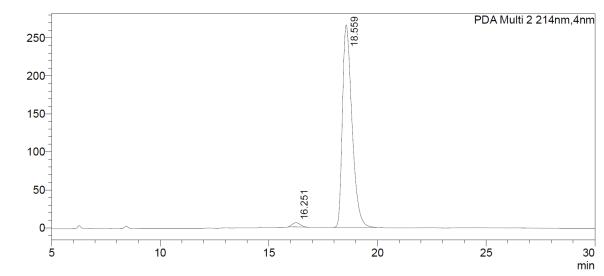
PDA Ch1 214nm

Peak#	Ret. Time	Area	Area%
1	16.230	1426260	50.032
2	18.555	1424463	49.968
Total		2850723	100.000

\<Chromatogram\>

mAU

\<Peak Table\>
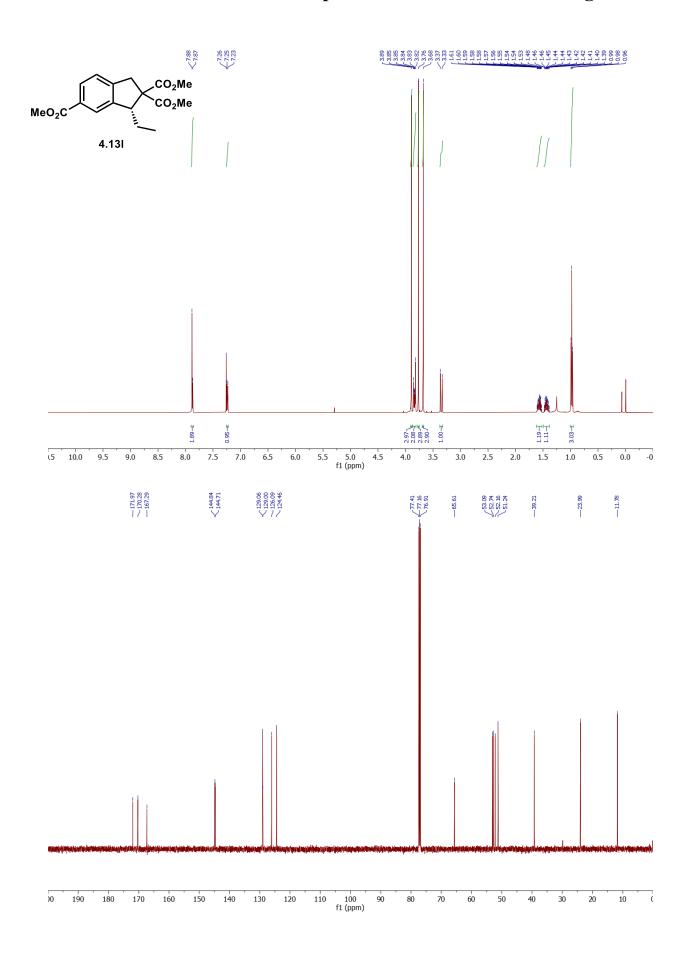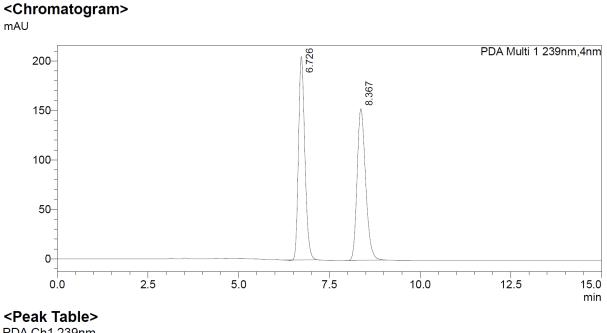
PDA Ch2 214nm

Peak#	Ret. Time	Area	Area%
1	16.251	142760	1.718
2	18.559	8167949	98.282
Total		8310709	100.000

4.13I

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

\<Chromatogram\>

mAU

\<Peak Table\>

PDA Ch1 239nm
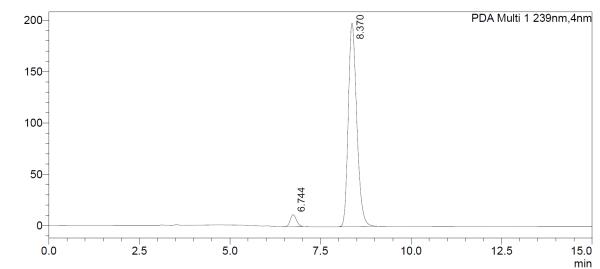
Peak#	Ret. Time	Area	Area%
1	6.726	2504582	49.929
2	8.367	2511716	50.071
Total		5016298	100.000

\<Chromatogram\>

mAU

\<Peak Table\>

PDA Ch1 239nm
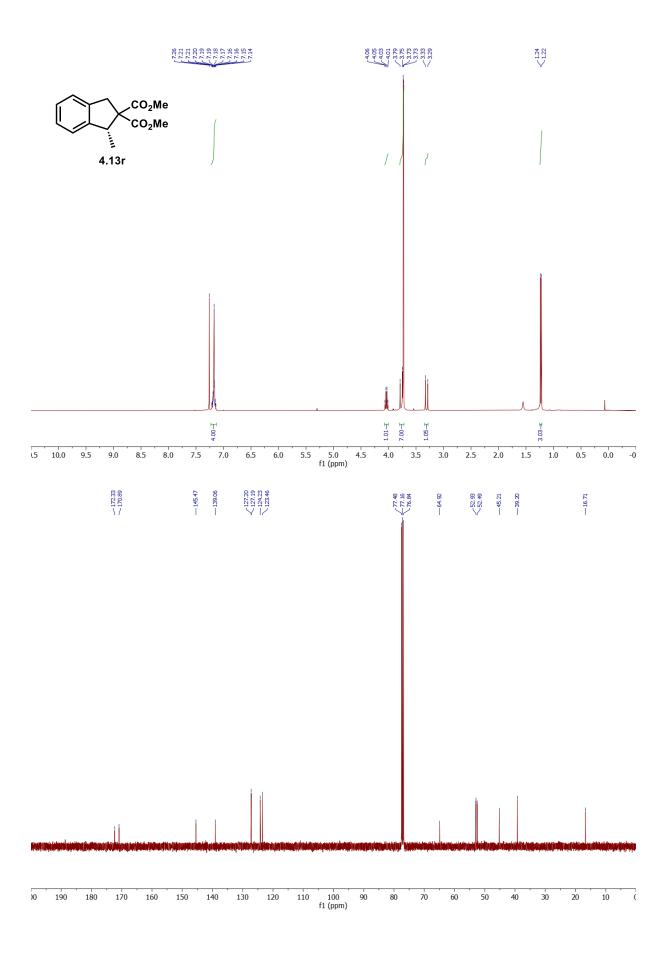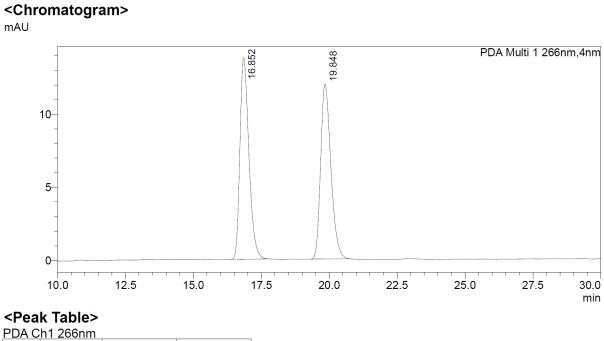
Peak#	Ret. Time	Area	Area%
1	6.744	136318	4.037
2	8.370	3239989	95.963
Total		3376307	100.000

4.13r

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

\<Chromatogram\>

mAU

PDA Multi 1 266nm,4nm

16.852

19.848

\<Peak Table\>

PDA Ch1 266nm
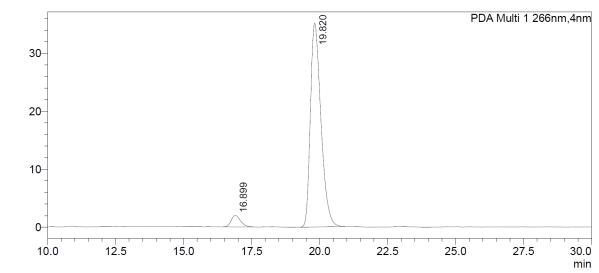
Peak#	Ret. Time	Area	Area%
1	16.852	316995	50.293
2	19.848	313305	49.707
Total		630301	100.000

\<Chromatogram\>

mAU

PDA Multi 1 266nm,4nm

19.820

16.899

\<Peak Table\>

PDA Ch1 266nm
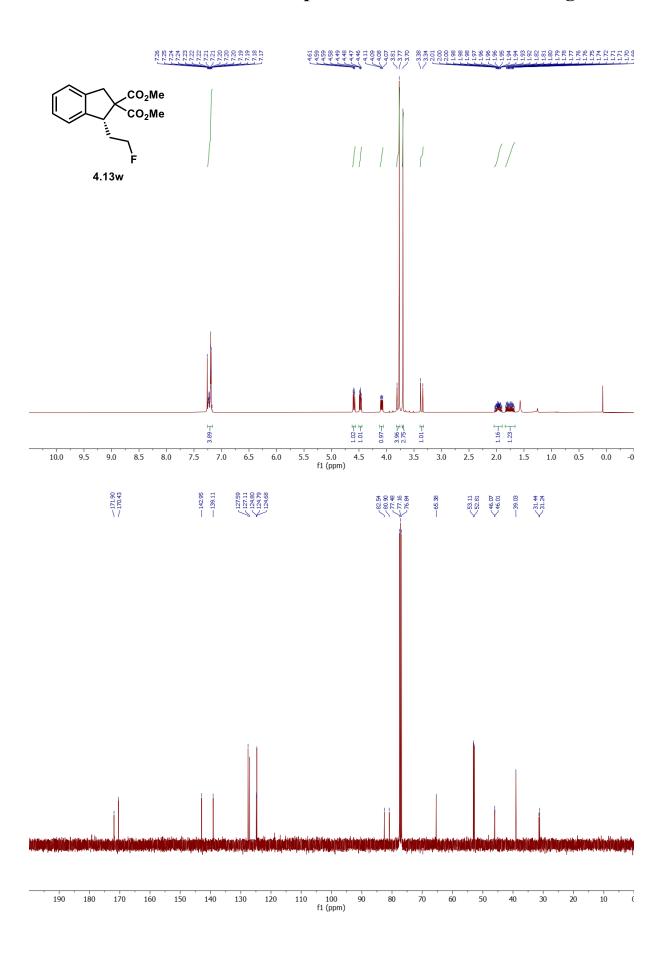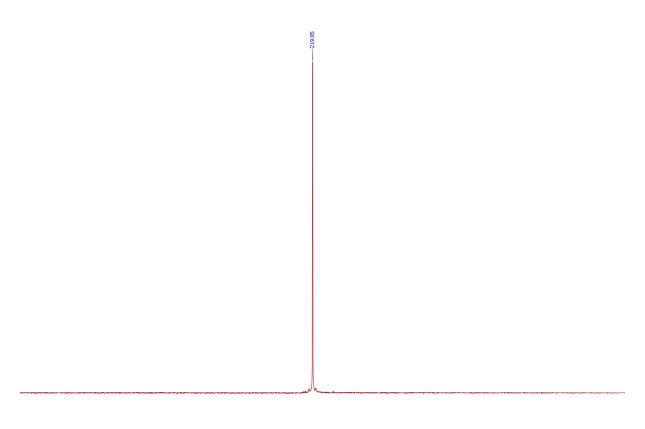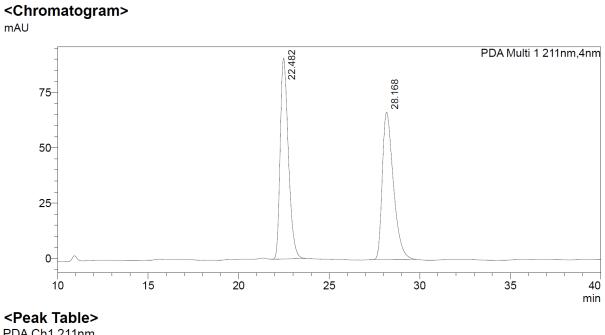
Peak#	Ret. Time	Area	Area%
1	16.899	47679	4.779
2	19.820	950060	95.221
Total		997738	100.000
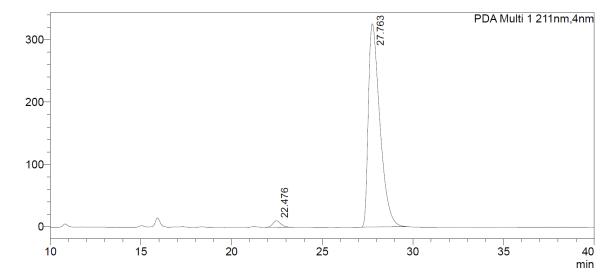
4.13w

1H, 13C, 19F, 31P NMR Spectra and HPLC Chromatograms

<Chromatogram>

mAU

PDA Multi 1 211nm,4nm

<Peak Table>

PDA Ch1 211nm

Peak#	Ret. Time	Area	Area%
1	22.482	2849460	50.106
2	28.168	2837403	49.894
Total		5686863	100.000

<Chromatogram>

mAU

PDA Multi 1 211nm,4nm

<Peak Table>

PDA Ch1 211nm

Peak#	Ret. Time	Area	Area%
1	22.476	313085	2.128
2	27.763	14398888	97.872
Total		14711973	100.000