Ring construction by palladium(0)-catalyzed C(sp^3)–H activation

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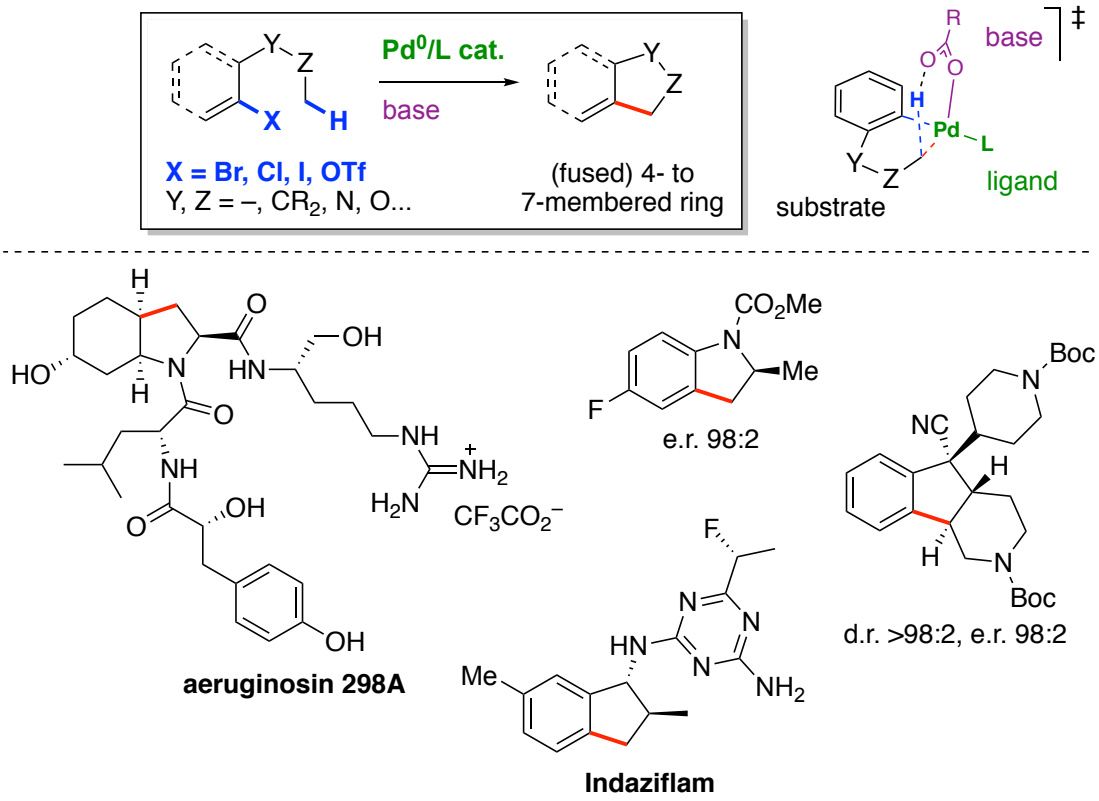
CONSPECTUS: The catalytic activation and functionalization of unactivated C(sp^3)–H bonds of alkyl groups has been more recently explored than the functionalization of C(sp^2)–H bonds, but has undergone intense development in recent years. In particular, a variety of directing groups as well as native functional groups have been employed in combination with palladium(II) catalysis in order to perform a variety of intermolecular, and to some extent intramolecular reactions. In parallel, inspired by precedents in C(sp^2)–H arylation, our group and others have developed a different approach, which is the focus of this Account. This strategy relies on the use of oxidative addition of a carbon–leaving group bond to palladium(0) to induce intramolecular C(sp^3)–H activation and the subsequent formation of a C(sp^2)–C(sp^3) or C(sp^3)–C(sp^3) bond. Since our first publication in 2003, the construction of olefins and, more interestingly, of an array of valuable monocyclic and polycyclic systems has been reported according to this principle. (Hetero)aryl bromides were initially employed as reactants, but the scope was later expanded to include (hetero)aryl chlorides and triflates, alkenyl bromides, carbamoyl chlorides and α-chloroamides. Mechanistic studies enabled a better understanding of the C–H activation step, which was

proposed to occur through Ambiphilic Metal-Ligand Activation-6 (AMLA-6), also known as Concerted Metalation Deprotonation (CMD), and a better rationalization of the observed selectivity patterns. Moreover, the wealth of accumulated experimental data indicate that the number of atoms separating the C–H bond from Pd and the type of C–H bond are the main factors controlling the site-selectivity of the C–H bond cleavage. Recent efforts have been devoted to the development of enantioselective reactions. To this purpose, two different strategies have been employed: a chiral ancillary ligand in combination with an achiral base, and a chiral base in combination with an achiral ligand, and allowed for the achievement of high enantioselectivities in the construction of both tri- and tetrasubstituted stereocenters. On the other hand, the current C–H activation-based ring-forming method was applied to the synthesis of pharmacologically active substances and agrochemicals, as well as complex natural products such as the aeruginosins, thereby demonstrating its great potential for step-economical organic synthesis.



1. INTRODUCTION

Although originating as early as the first half of the 20th century,[1,2] transition-metal-catalyzed C–H bond functionalization has exponentially developed since the turn of the 21th century, with the emergence of numerous methods to generate new carbon–carbon and carbon–heteroatom bonds from various types of C–H bonds.[3,4] In many cases the reaction substrates are readily accessible, thereby leading to valuable functionalized products in a step-economical manner. The power of these catalytic methods has been already acknowledged by a broad community of chemists and translated into numerous applications in the synthesis of natural products, pharmacologically active substances, and organic functional materials.[5,6] Among all categories of C–H bonds, C(sp^3)–H bonds of alkyl groups have been recognized as particularly challenging to activate and functionalize since they do not benefit from the precoordination of the transition-metal to neighboring π or π* orbitals. Despite this obstacle, C(sp^3)–H activation – herein defined as the

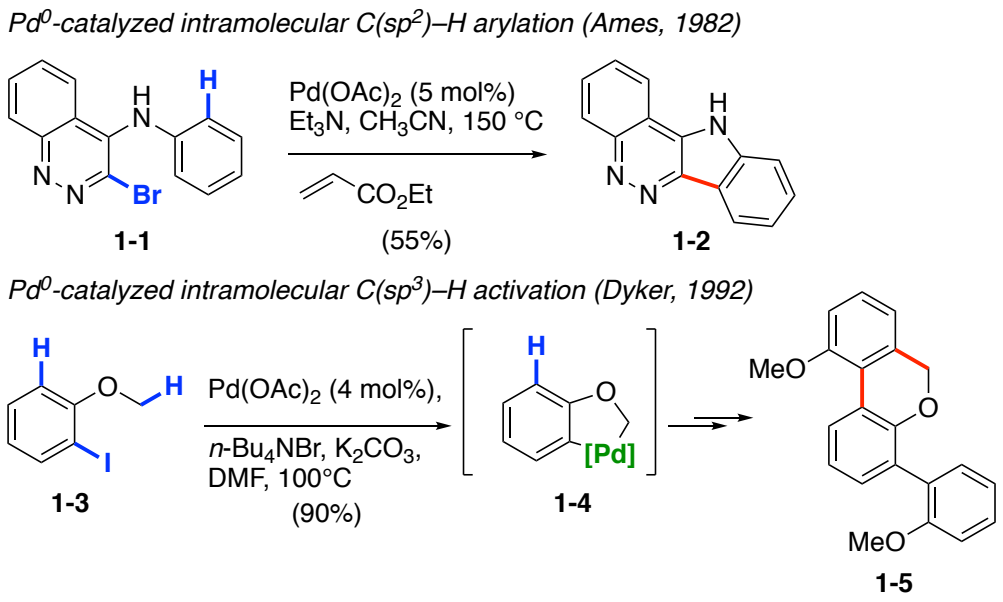
elementary step in the catalytic cycle of a C(sp^3)–H functionalization reaction wherein the C(sp^3)–H bond is cleaved and the metal–C(sp^3) bond is formed – has been found to take place via several mechanisms.[7] One such activation mode is the concerted metalation-deprotonation (CMD) mechanism,[8] also known as ambiphilic metal-ligand activation (AMLA),[9] which has been first reported for C(sp^2)–H bond activation.[10] This mechanism involves the cleavage of the C–H bond by a divalent base, typically a carbonate or carboxylate, bound to an electrophilic transition-metal. Among the latter, palladium(II) has proven particularly efficient and versatile in *intramolecular* C(sp^3)–H activation, leading to overall catalytic inter- or intramolecular functionalization. Two main sets of methods have been developed in the past decade: those initiated by the coordination of a Pd^{II} complex to a Lewis-basic heteroatom, belonging to a so-called directing group,[7,11,12] and oxidative addition of a carbon–leaving group bond to a Pd^0 complex. The second category has been the main focus of our work and constitutes the subject of the current account.

2. DEVELOPMENT OF PALLADIUM(0)-CATALYZED INTRAMOLECULAR C(SP3)–H FUNCTIONALIZATION

2.1. Inspiration and Early Work

At the outset of our work, we were inspired by two sets of precedents (Scheme 1, top). First, intramolecular, 'direct' C(sp^2)–H arylations, pioneered from 1982 by Ames,[13] employing a Pd^0 catalyst and a stoichiometric base similar to the Mizoroki-Heck reaction, were already well developed.[14] However, it was only in 2006 that concerted metalation-deprotonation was proposed independently by Echavarren and Maseras,[15] and Fagnou[16] for intra- and intermolecular reactions, respectively, as the predominant mechanism for the C–H bond cleavage step, instead of the

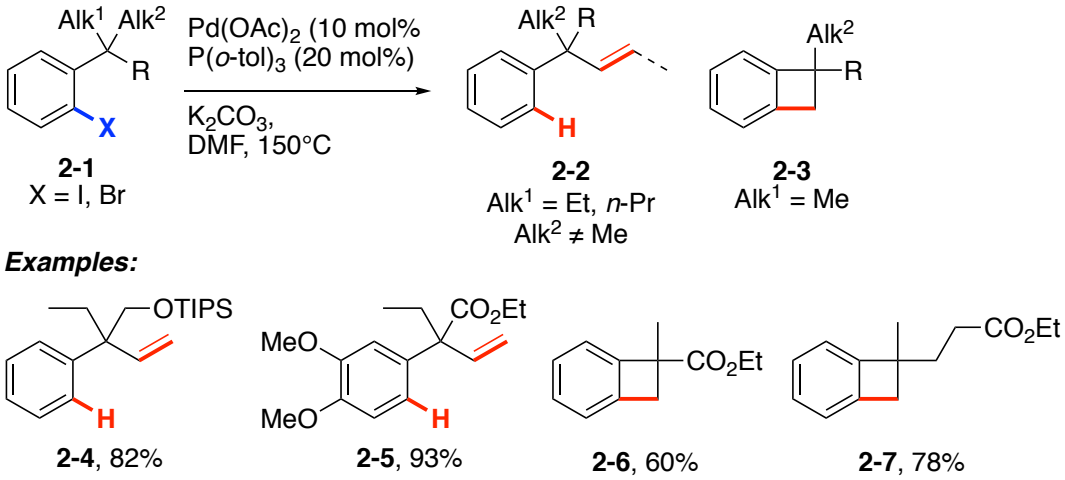
previously proposed electrophilic aromatic substitution. Second, a series of articles published by Dyker from 1992 indicated the feasibility of the translation of Pd^0-catalyzed C(sp^2)–H arylation to C(sp^3)–H bonds (Scheme 1, bottom).[17] Polycyclic compounds such as **1-5** were obtained under Heck-type conditions through self-condensation of three molecules of aryl iodide **1-3**. The proposed mechanism starts with oxidative addition to an in situ-generated Pd^0 species, followed by intramolecular activation of a primary C(sp^3)–H bond at the methoxy group to give palladacycle **1-4**. The latter undergoes a series of steps including a second C–H activation and probable Pd^{IV} intermediates, similar to the Catellani reaction.[18] This work demonstrated the feasibility of catalytic reactions proceeding by Pd^0-catalyzed intramolecular C(sp^3)–H activation.



Scheme 1. Inspirational Work

In 2003, we reported that the use of a phosphine ligand allows to avoid the self-condensation of the aryl halide, presumably by suppressing competitive oxidative addition to Pd^{II} intermediates (Scheme 2).[19] Two different products were obtained depending on the benzylic alkyl substituents

on substrates **2-1**: olefin products **2-2** from substrates bearing linear alkyl groups, and benzocyclobutenes **2-3** from substrates bearing at least one methyl group. Tri-*o*-tolylphosphine (TOTP) was found to be the best ligand to obtain both types of products, arising from C(sp^3)-H activation and either β-H elimination (**2-2**) or C–C reductive elimination (**2-3**), from aryl iodides or bromides. At this point, the exact mechanism and origins of product selectivity were not clear, but these findings triggered subsequent studies aiming at generalizing this method and gaining a clearer mechanistic picture.

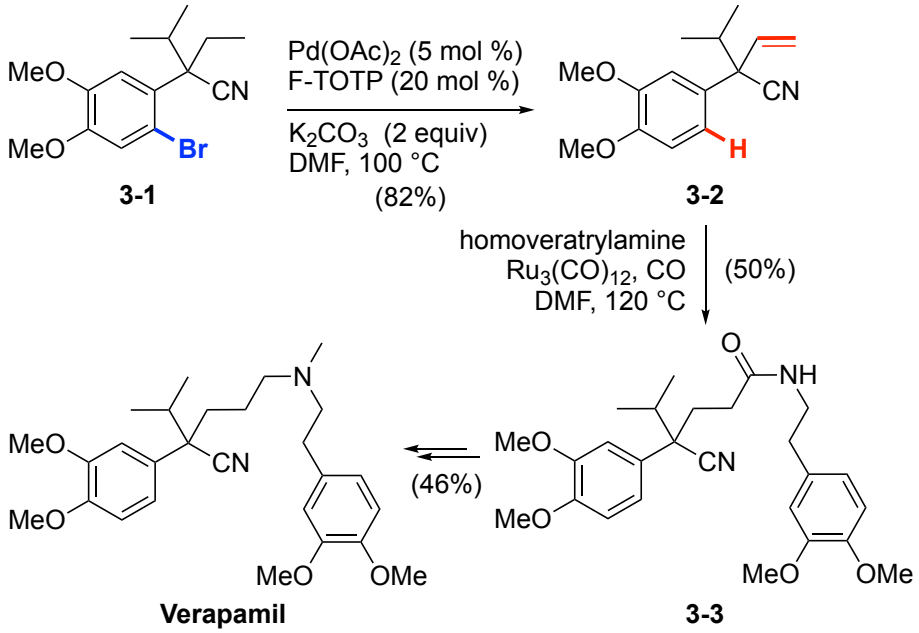


Scheme 2. Initial Results

2.2. Generalization

After some experimentation, it appeared that further optimizing the synthesis of olefins and benzocyclobutenes required to use two different types of ligands. First, we showed that the more electron-deficient tri(5-fluoro-2-methylphenyl)phosphine (F-TOTP) allowed to synthesize olefins more efficiently at a lower temperature (100 °C) compared to TOTP.[20] These improved conditions were applied to the synthesis of the antihypertensive drug Verapamil (Scheme 3). The ethyl group of **3-1** underwent selective C–H activation and dehydrogenation vs. the isopropyl

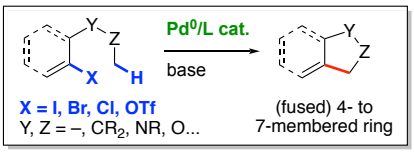
group to give alkene **3-2**, which was hydroformylated in the presence of homoveratrylamine under reoptimized conditions to give amide **3-3**. The latter provided Verapamil in two steps, hence completing the first application of this Pd^0-catalyzed $C(sp^3)$–H activation chemistry. A subsequent study showed that this olefin synthesis could be coupled to an intramolecular Heck reaction in a cascade fashion to access original indenes and *exo*-methylenebenzocyclobutenes.[21]



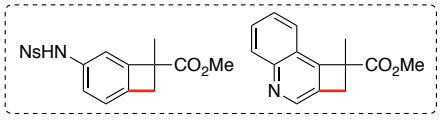
Scheme 3. Optimized Olefin Synthesis and Application to the Synthesis of Verapamil

Scheme 4 summarizes, in chronological, but non-comprehensive way, examples from our group and other groups for the synthesis of a variety of ring systems using the Pd^0-catalyzed $C(sp^3)$–H activation approach. On our side, we showed that benzocyclobutenes are synthesized from (hetero)aryl bromides with better yields and broader scope using P(*t*-Bu)$_3$ as the ligand (see **4-1**).[22] Through a collaboration with the Fagnou group, we showed that the same reaction, as well as the formation of fused 5-membered rings such as indanes, dihydrobenzofurans (**4-6**), indolines (**4-7**), and indanones can be performed from readily available (hetero)aryl chlorides instead of

bromides.[23] More complex tricyclic systems relevant to natural product synthesis were also constructed from bicyclic precursors (**4-5**, **4-12**)[20,23,24] or by a double C(sp^3)–H arylation from dihalogenated precursors (**4-9**).[25] We also found that alkenyl bromides are competent reaction substrates, leading to more saturated ring systems relevant to alkaloid synthesis (**4-11**, **4-15**).[26] Major contributions from other groups including Knochel (**4-4**),[27] Fagnou (**4-6**, **4-8**),[28] Fujii and Ohno (**4-7**),[29] Takemoto (**4-10**),[30] Charette (**4-13**, **4-21**),[31] Cramer (**4-3**, **4-14**, **4-17**, **4-19**, **4-20**),[32] and Shi (**4-18**)[33] further expanded the scope and demonstrated the generality of this approach to construct a variety of carbocyclic and heterocyclic systems.[34] Several important observations should be made: 1. the initial oxidative addition to Pd^0 may occur from a variety of precursors, including not only (hetero)aryl halides or triflates, but also alkenyl bromides (**4-11**, **4-15**, **4-21**) or triflates, carbamoyl chlorides (**4-10**), and α-chloroamides (**4-3**, **4-14**); 2. chemoselectivity is very good, functional groups such as esters (**4-1**, **4-2**, etc.), nitriles (**4-5**), nitro (**4-6**), chloride (**4-13**), and even free amides (**4-18**) being tolerated; 3. the most common types of activated C–H bonds are those of methyl groups and cyclopropanes, with cases of methylenes being rarer, in line with selectivities observed in directed Pd^{II}-catalyzed reactions;[7] 4. four- to seven-membered rings can be formed, but 5-membered rings are by far the most widespread; 5. enantioselectivity can be achieved using a chiral catalyst (**4-3**, **4-14**, **4-17**, **4-19**, **4-20**, *vide infra*).

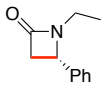


Examples of 4-membered rings:



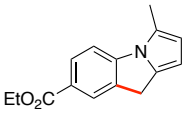
4-1 (72%)
X = Br
L = P(*t*-Bu)$_3$
base = K_2CO_3
Baudoin, 2008

4-2 (63%)
X = Cl
L = P(*t*-Bu)$_3$
base = K_2CO_3
Baudoin, 2010

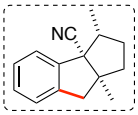


4-3 (74%, e.r. 98:2)
X = Cl
L = chiral phosphoramidite
base = $AdCO_2Cs$[a]
Cramer, 2014

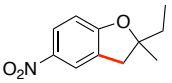
Examples of 5-membered rings:



4-4 (81-83%)
X = Br or I
L = P(*p*-tol)$_3$
base = AcOCs
Knochel, 2006

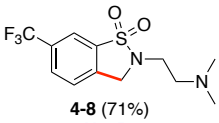


4-5 (62-79%)
X = Br or Cl
L = F-TOTP or $PCyp_3$
base = K_2CO_3
Baudoin, 2007, 2010

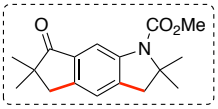


4-6 (84-85%)
X = Br or Cl
L = PCy_3
base = PivOCs[a]
Fagnou, 2007, 2010

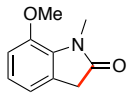
4-7 (83-99%)
X = Br or Cl
L = PCy_3
base = PivOCs[a]
Ohno, 2008



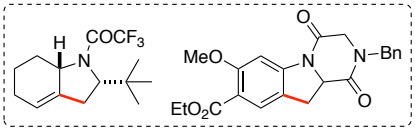
4-8 (71%)
X = Br
L = PCy_3
base = PivOCs[a]
Fagnou, 2010



4-9 (75%)
X = Cl
L = PCy_3
base = PivOCs[a]
Baudoin, 2011

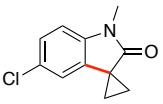


4-10 (88%)
X = Cl
L = $Ad_2P(n\text{-Bu})$
base = PivNHOCs[a]
Takemoto, 2012

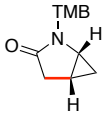


4-11 (71%)
X = Br
L = PCy_3
base = PivORb[a]
Baudoin, 2012

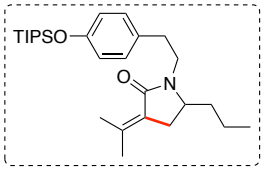
4-12 (82%)
X = Br
L = PCy_3
base = PivOK/Na[a]
Baudoin, 2012



4-13 (89%)
X = Br
L = PCy_3
base = AcOK[a]
Charette, 2013

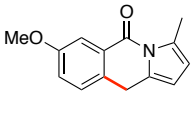


4-14 (99%, e.r. 96:4)
X = Cl
L = chiral phosphonite
base = $AdCO_2Cs$[a]
Cramer, 2015

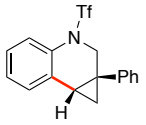


4-15 (70%)
X = Br
L = PPh_3
base = PivOCs[a]
Baudoin, 2016

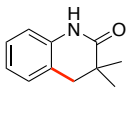
Examples of 6- and 7-membered rings:



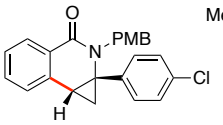
4-16 (80%)
X = Br
L = P(*p*-tol)$_3$
base = Cs_2CO_3
Knochel, 2006



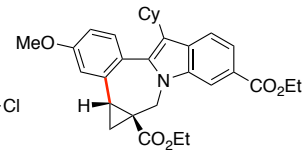
4-17 (89%, e.r. 97:3)
X = Br
L = chiral phosphoramidite
base = PivOCs[a]
Cramer, 2012



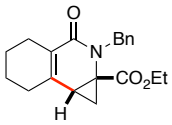
4-18 (60-72%)
X = Br, I
L = P(*o*-tol)$_3$
base = PivOCs[a]
Z.-J. Shi, 2014



4-19 (99%, e.r. 95:5)
X = Br
L = chiral phosphoramidite
base = $AdCO_2Cs$[a]
Cramer, 2015



4-20 (80%, e.r. 94.5:5.5)
X = Br
L = chiral phosphonite
base = $AdCO_2Cs$[a]
Cramer, 2015



4-21 (98%)
X = Br
L = PCy_3
base = AcOK[a]
Charette, 2016

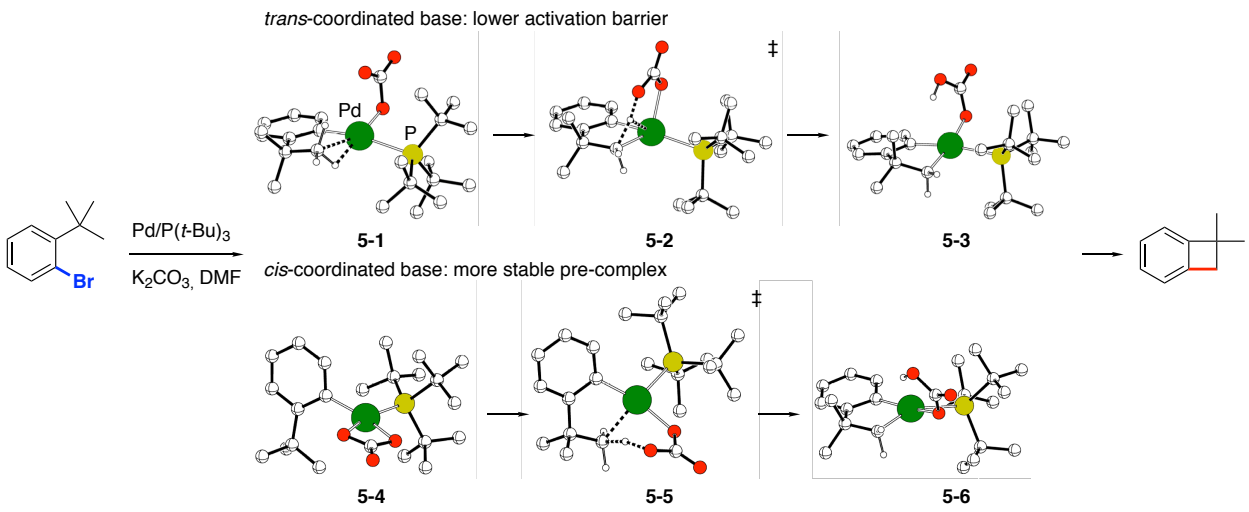
[a] Generated in situ from cat. PivOH, PivNHOH, $AdCO_2H$ or AcOH and stoichiometric Cs_2CO_3, Rb_2CO_3 or K_2CO_3. Ns = *p*-nitrophenylsulfonyl; Bn = benzyl; TMB = 2,4,6-trimethoxybenzyl; TIPS = triisopropylsilyl; Tf = trifluoromethanesulfonyl; PMB = *p*-methoxybenzyl.

Scheme 4. Construction of Various Cyclic Systems by Pd^0-Catalyzed C(sp^3)–H Activation Reactions

3. MECHANISM AND SELECTIVITY

3.1. Mechanism of the C–H Activation Step

Mechanistic investigations allowed us to characterize the C(sp^3)–H activation step and study selectivity factors. In particular, a complete analysis of the reaction pathway leading to benzocyclobutenes was performed through DFT calculations employing different ligands and bases.[22,23,35] Three transition states (TSs) were located for the base-induced C–H activation step (Scheme 5): two TSs corresponding to a proton abstraction by the base coordinated *trans* (**5-2**) or *cis* (**5-5**) to the activated C–H bond (AMLA-6 mechanism), and one TS for intermolecular proton abstraction. With P(*t*-Bu)$_3$ as the ligand and carbonate as the base, i. e. the experimental system,[22] the intermolecular proton abstraction occurs with a much higher activation barrier than the intramolecular abstraction ($\Delta G^{\ddagger}_{inter} - \Delta G^{\ddagger}_{intra}$ >20 kcal mol^{-1}), partly due to the high associated entropy cost (*ca*. 10 kcal mol^{-1}), and was subsequently ruled out. The *trans* activation mode starts with agostic complex **5-1** and generates a rather distorted TS (**5-2**). The *cis* activation mode, also proposed by Fagnou and Gorelsky,[28a,b] occurs from a more stable (ΔG = –21.3 kcal mol^{-1}) κ^2-carbonate pre-complex (**5-4**), but the *cis*-AMLA-6 TS is associated to a higher activation barrier ($\Delta\Delta G^{\ddagger}$= 13.6 kcal mol^{-1}) than the *trans*-AMLA-6, mainly due to the disruption of the strong κ^2 carbonate coordination. Computing these pathways with PMe_3 instead of P(*t*-Bu)$_3$ or AcO^- and HCO_3^- instead of CO_3^{2-} significantly altered the energy profiles and led to different trends.[35] These studies led us to the conclusion that the *trans* and *cis* geometries are both accessible based on the reaction substrate and conditions, and are both worth considering in mechanistic studies.



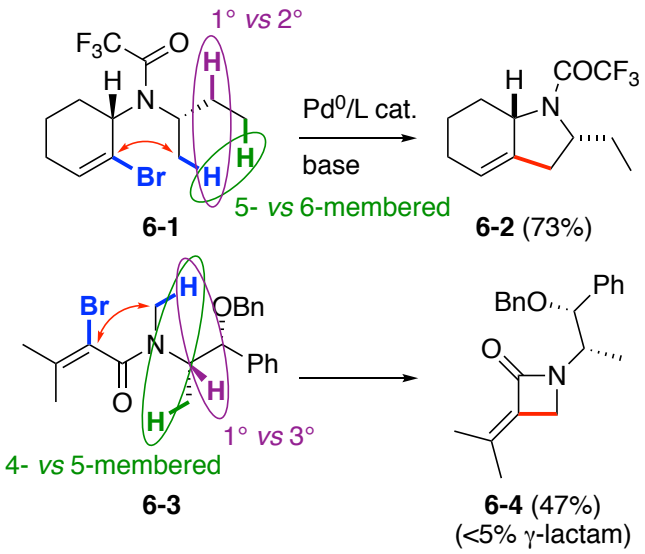
Scheme 5. Two Accessible Geometries for the C(sp^3)–H Activation Step Leading to Benzocyclobutenes

In the *cis*-AMLA-6 pathway, some degree of agostic interaction with the cleaved C–H bond is only present at the transition state (**5-5**, Pd–H 1.940 Å), whereas in the *trans* pathway the pre-complex **5-1** features a clear agostic interaction (Pd–H 1.878 Å). In the latter case, the cleaved C–H bond on the methyl group is not the agostic bond but is a geminal C–H bond, which has a more pronounced protic character, as also described by Macgregor.[36] This feature may contribute to explain the lack of reactivity of methines, which lack a geminal C–H bond, in these reactions,[23] with the exception of cyclopropanes.

3.2. Site-selectivity of the C–H Activation Step

According to the wealth of experimental data accumulated in recent years by our group and others, two main factors control the selectivity of the C–H bond cleavage (Scheme 6): 1. for a given type of C–H bond, the number of atoms between Pd and the C–H bond, which translates into the following preference for the formation of cyclic products: 4-membered > 5-membered > 6-membered > 7-membered; 2. the type of C–H bond, with: cyclopropyl > methyl > methylene

>> methine. These are general guidelines, but of course crossed selectivities are also observed, e. g. 5-membered/methyl > 4-membered/methylene (**4-15**, Scheme 4). In addition, other factors such as ring strain, conformational effects[26b] and last but not least ligand effects[37] can alter the usual selectivity.



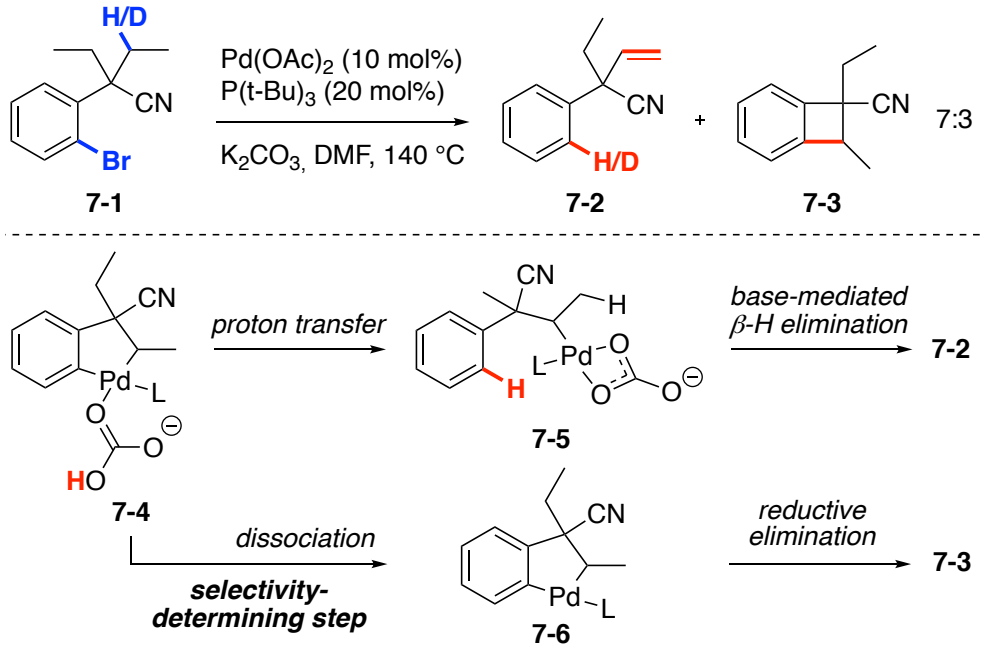
Scheme 6. Illustration of Typically Observed C–H Activation Selectivities[a]

[a] In substrate **6-1**, the 1° C–H bond in blue is preferentially activated compared to the equidistant 2° C–H bond in purple and the more remote 1° C–H bond in green; in **6-3**, the 1° C–H bond in blue is preferentially activated compared to the equidistant 3° C–H bond in purple and the more remote 1° C–H bond in green.

3.3. Other Steps Controlling Product Selectivity

In addition to the C–H activation step, the subsequent mechanistic steps can also affect the product selectivity. This is typically illustrated by the formation of a mixture of olefin **7-2** and benzocyclobutene **7-3** from aryl bromide **7-1** (Scheme 7).[38] Deuterium-labeling experiments showed that the two products arise from the activation of the same methylene C–H bonds. Through DFT calculations, it was proposed that palladacycle **7-4**, generated in the C–H

activation step, undergoes either proton transfer to give acyclic intermediate **7-5**, which gives rise to olefin **7-2** by a non-classical carbonate-mediated β-H elimination[39] or by dissociation of bicarbonate and reductive elimination to give cyclic product **7-3**. The high energy barrier of the strain-building reductive elimination leading to **7-3** ($\Delta G^{\ddagger}$= 27.4 kcal mol^{-1}) allows the opening of the proton transfer pathway leading to olefin **7-2** ($\Delta G^{\ddagger}$ = 24.3 kcal mol^{-1}), a phenomenon which does not *a priori* occur in the formation of larger (≥ 5-membered) rings, for which energy barriers of *ca*. 10-15 kcal mol^{-1} are typically obtained.[23] Kinetic simulations indicated that the rate of bicarbonate dissociation actually controls the product selectivity.

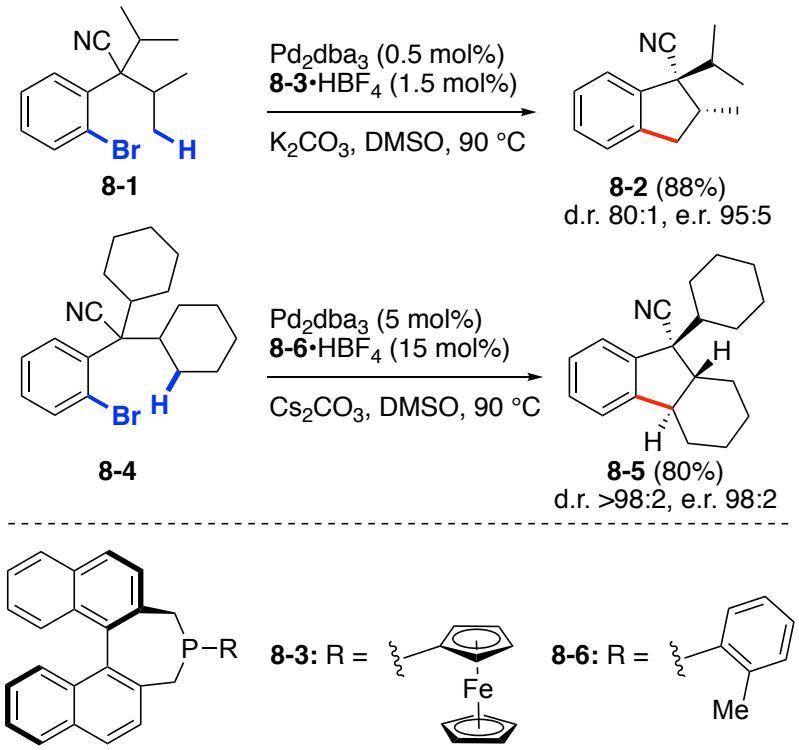


Scheme 7. Selectivity Control beyond the C–H Activation Step

4. ENANTIOSELECTIVE REACTIONS

The first example of an enantioselective Pd^{0}-catalyzed C(sp^{3})–H activation reaction was reported in 2011 by Kündig and co-workers.[40] Employing C2-symmetric *N*-heterocyclic carbenes (NHCs),

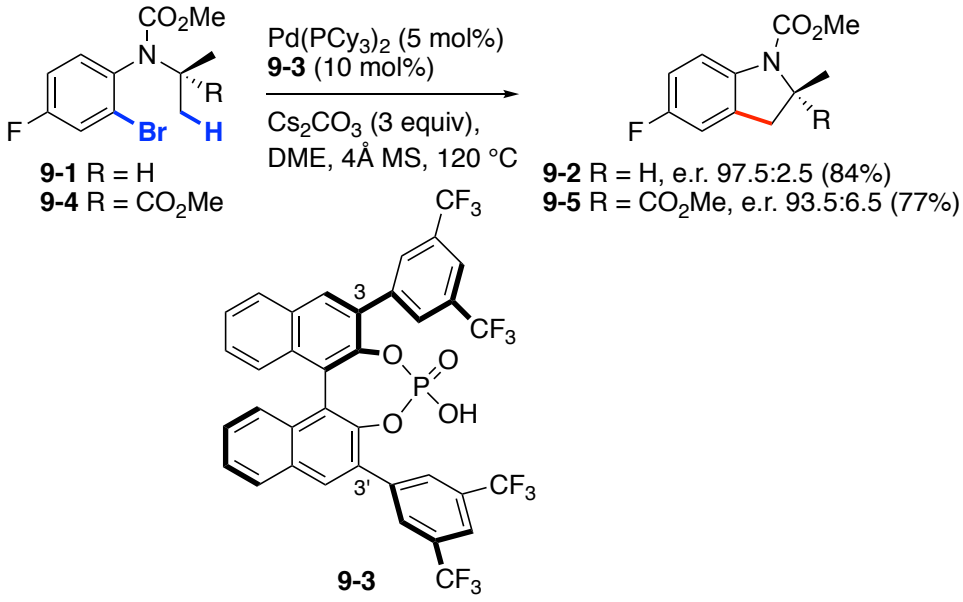
they were able to achieve very high enantioselectivities (e.r. up to 99.5:0.5) for the intramolecular arylation of 2° C–H bonds leading to fused indolines, three years after the racemic version reported by Fujii and Ohno.[29] Shortly after, Kagan[41] and Cramer[42] reported similar enantioselective indoline-forming reactions using chiral phosphines instead of NHCs, with the latter employing aryl triflates instead of bromides. In parallel, we studied the diastereo- and enantioselective synthesis of indanes, the racemic version of which was initially reported in 2007 (Scheme 8).[20] The precursor **8-1** contains 4 stereotopic methyl groups, leading to the generation of two adjacent stereocenters in product **8-2**. Initially, we were able to achieve high d.r. but moderate e.r. employing Beller's *t*-Bu-Binepine[43] as the chiral phosphine ligand.[44] After significant experimentation, we were able to improve the enantioselectivity by tuning the phosphorus substituent and the reaction conditions.[45] Compound **8-2** was obtained in high yield and high diastereo- and enantioselectivity using the new ferrocenylbinepine **8-3** as the ligand, introduced as the bench-stable phosphonium salt, and K_2CO_3 as the base in DMSO, without carboxylic acid additive. The catalyst formed from Pd_2dba_3 and **8-3** was found to be more active than catalysts formed from achiral phosphines, and loadings as low as 1 mol% Pd/1.5 mol% ligand could be employed at a relatively mild temperature (90 °C). The more challenging and rarer activation of 2° bonds was also achieved starting from precursor **8-4** but required further tuning the ligand and base: using *o*-tolylbinepine **8-6** and cesium carbonate, polycyclic product **8-5** was obtained in high stereoselectivity. Remarkably, the achiral substrate **8-4** now contains 8 activable stereotopic C–H bonds, hence leading to 3 adjacent stereocenters in **8-5**, which are almost completely controlled in this process. Computational studies pointed to the importance of C–H···π and π-stacking noncovalent interactions between the substrate and one naphthyl ring of the ligand to better stabilize the TS leading to the major enantiomer.



Scheme 8. Diastereo- and Enantioselective Arylation of Primary and Secondary C–H Bonds Using a Chiral Phosphine and an Achiral Base

Considering the AMLA mechanism of the C–H activation step, it was reasonable to assume that a chiral base combined with an achiral ancillary ligand would constitute a viable alternative to the chiral ligand/achiral base approach for enantioselective C(sp^3)–H activation reactions. To some extent, this was already demonstrated by the Yu group in palladium(II)-catalyzed intermolecular reactions using chiral monoprotected aminoacids as ligands.[46] Previous attempts in Pd^0-catalyzed reactions had been performed with chiral carboxylic acids,[41,42] but with limited success. From the structural analysis of putative C–H activation precursors [PdArL(base)], we hypothesized that Binol-derived phosphates would represent particularly suitable chiral bases. Indeed, they could be able to discriminate enantiotopic alkyl groups through stabilizing noncovalent interactions with their extended aromatic surface at the 3 or 3'-position (Scheme 9).

After extensive optimization, we found that the commercially available phosphoric acid **9-3** (10 mol%), in combination with stoichiometric Cs_2CO_3 and the well-defined $Pd(PCy_3)_2$ complex (5 mol%) allowed us to achieve levels of enantioselectivities comparable to those observed with chiral NHC or phosphine ligands for the synthesis of indolines bearing a trisubstituted stereocenter (**9-2**).[47,48] The 3,3'-substituents of the Binol-derived phosphate had a marked effect on the enantioselectivity. The same system was applied to the generation of more crowded tetrasubstituted stereocenters (**9-5**), albeit with reduced enantioselectivity.



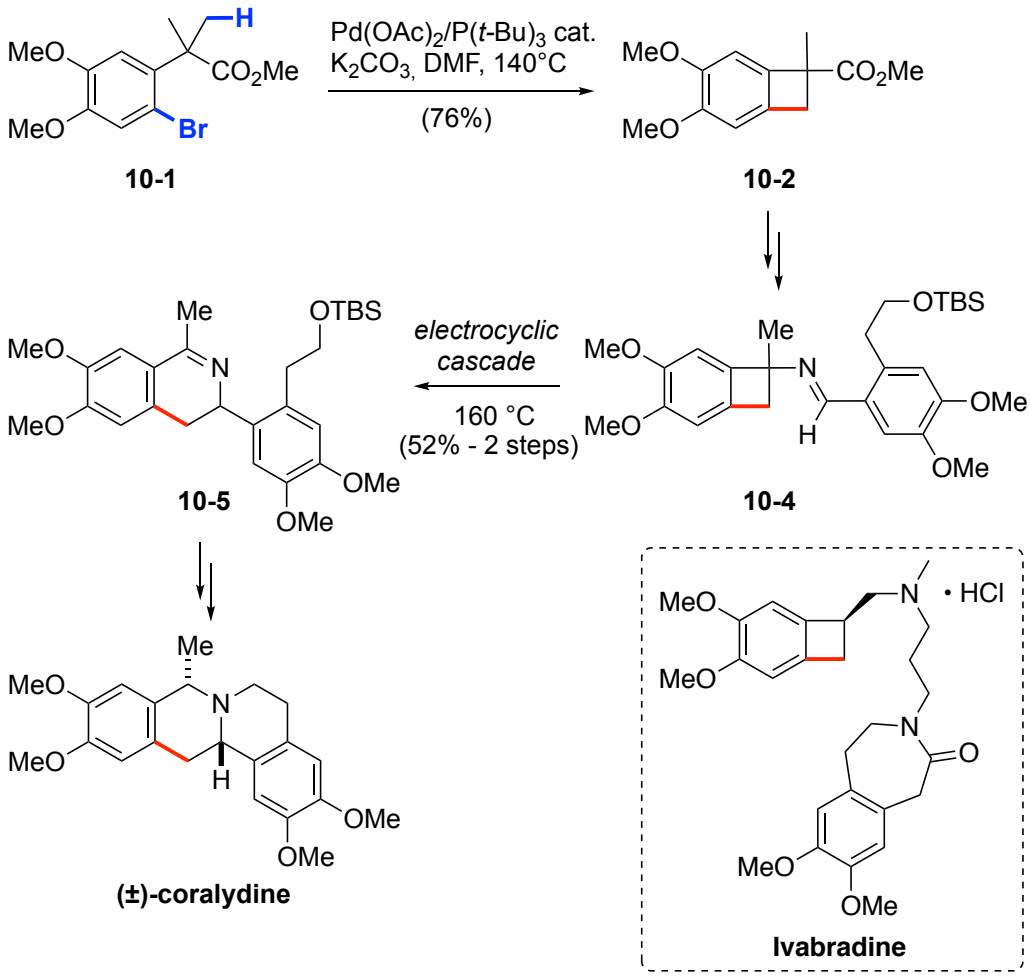
Scheme 9. Enantioselective Arylation of Primary C–H Bonds Using a Chiral Base and an Achiral Phosphine

The above studies demonstrate that enantioselective C(sp^3)–H activation is a powerful method to efficiently control single or multiple stereocenters and access valuable chiral compounds in a straightforward manner (see also examples from the Cramer group, Scheme 4).[32] Two conceptually different chiral catalysts can be employed, and hence this method offers a great

degree of tunability to achieve high enantioselectivities in the discrimination of both stereotopic methyl groups (**8-1**, **9-1**, **9-4**) and secondary C–H bonds (**8-4**).

5. APPLICATION TO THE SYNTHESIS OF BIOACTIVE MOLECULES AND NATURAL PRODUCTS

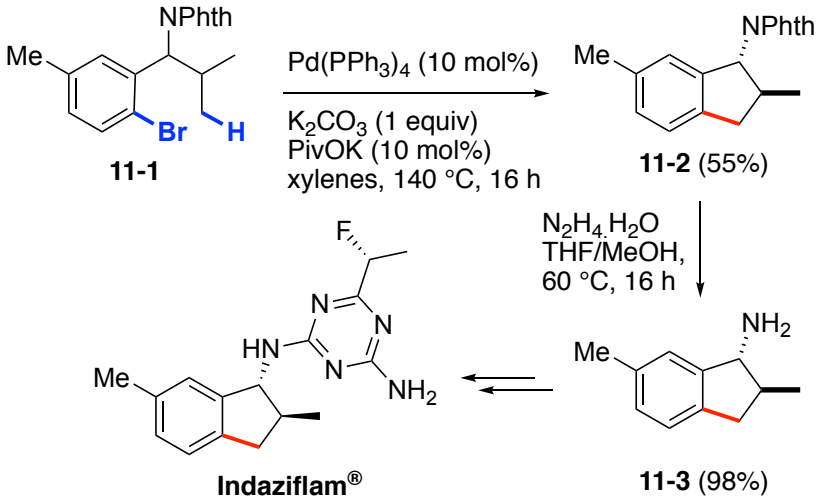
Benzocyclobutenes are both original scaffolds for drug discovery and useful intermediates for natural product synthesis.[49] Through a collaboration with medicinal chemists at Servier, we showed that our C–H activation method was applicable to the synthesis of the cardiotonic drug Ivabradine (Scheme 10, bottom right).[22] On the other hand, we employed benzocyclobutenes in two types of pericyclic reactions, namely Diels-Alder cycloadditions[50] and electrocyclic reactions.[51] The second method was applied to the racemic synthesis of the tetrahydroprotoberberin alkaloid coralydine (Scheme 10). Benzocyclobutene **10-2** was constructed by C(sp^3)–H arylation from compound **10-1**, which can be readily accessed by electrophilic bromination. After hydrolysis of the ester, Curtius rearrangement and imine condensation, imine **10-4** was thermolyzed to give 3,4-dihydroisoquinoline **10-5** through an electrocyclic ring-opening/6-π electrocyclization cascade. The synthesis of coralydine was completed through imine reduction, alcohol deprotection and Mitsunobu cyclization.



Scheme 10. Applications of Benzocyclobutenes Obtained by C(sp^3)–H Arylation: Ivabradine and Coralydine

Indanes are other important substructures for the synthesis of complex molecules. Through a collaboration with Bayer CropScience,[52] we developed specific conditions to generate an array of 1-indanols and 1-indanamines. We recognized that the synthesis of such indanes possessing a trisubstituted benzylic carbon would be particularly challenging. Indeed, previous studies indicated that tetrasubstitution was required at this position,[20,23] presumably due to Thorpe-Ingold effects favoring the rate-limiting C–H activation step. Surprisingly, the simple and small ligand triphenylphosphine was found to provide the most active catalyst for this transformation,

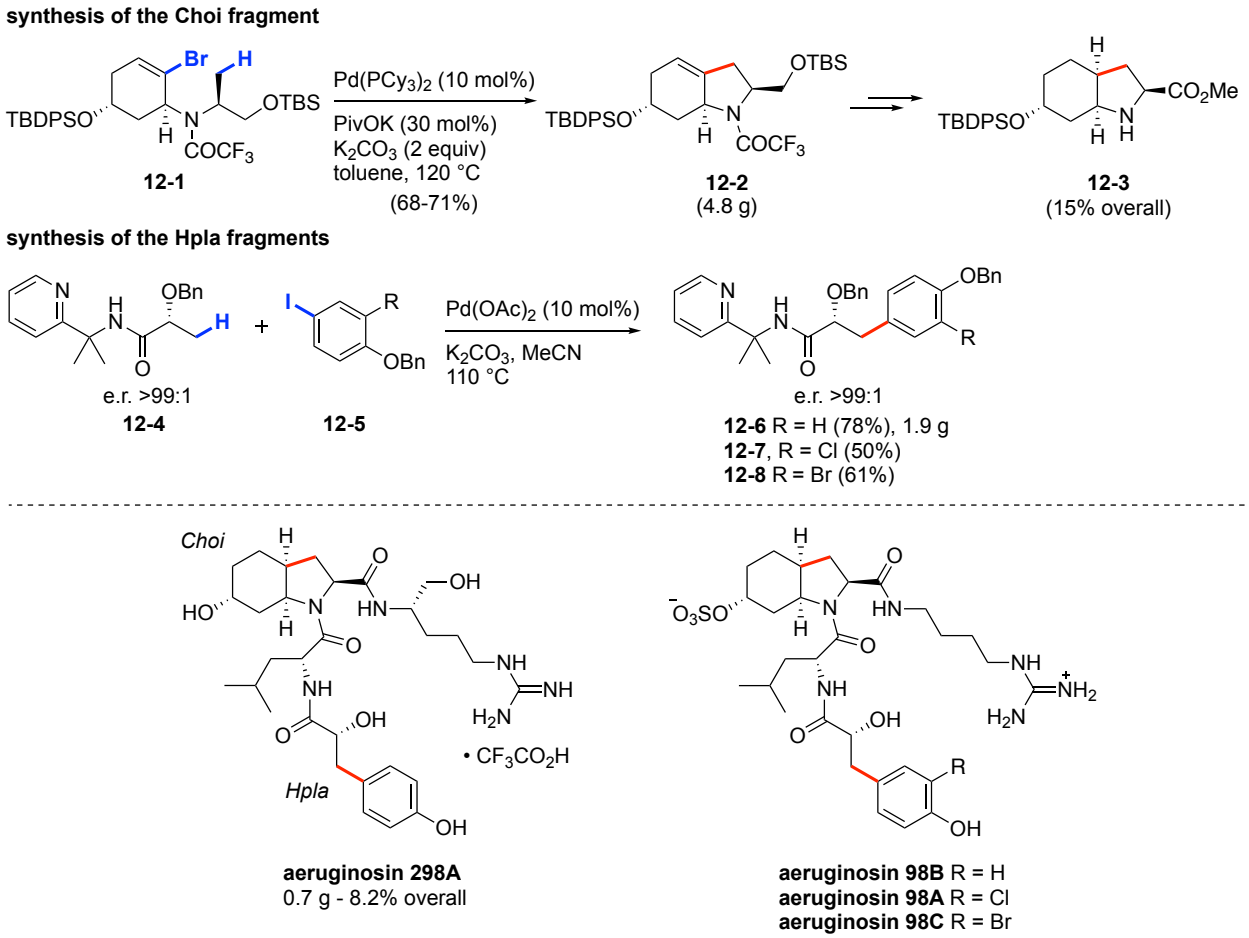
furnishing moderate to high yields for indanols and indanamines with a trisubstituted benzylic carbon. This method was applied to the synthesis of the herbicide Indaziflam® (Scheme 11). The C–H activation at diastereotopic methyl groups of **11-1** occurred with moderate yield due to the absence of a strong angle compression effect but with complete *trans* diastereoselectivity. After cleavage of the phthalimide group, the indanamine **11-3**, a known intermediate in the industrial synthesis of Indaziflam, was obtained.



Scheme 11. Application of Indanes Obtained by C(sp³)–H Arylation: Indaziflam

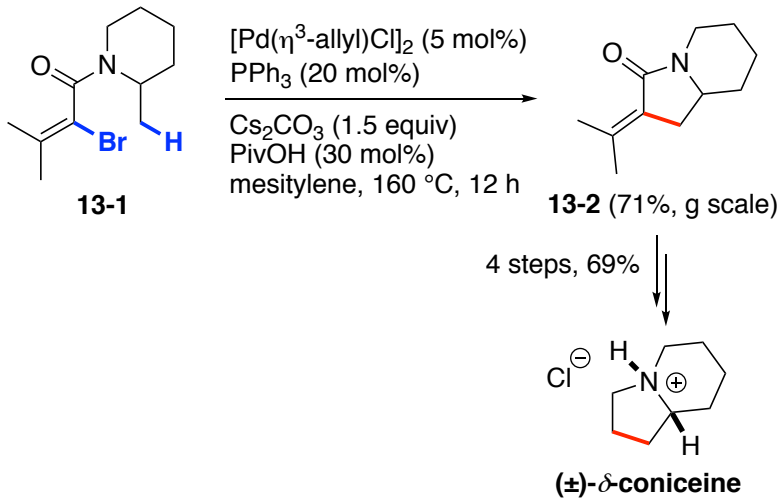
More recently, we reported the total synthesis of aeruginosins, toxic secondary metabolites isolated from marine sponges and cyanobacterial waterblooms,[53] by employing two C(sp³)–H activation reactions as key steps (Scheme 12).[54] The common 2-carboxy-6-hydroxyoctahydroindole (Choi) fragment of the four targeted congeners was synthesized efficiently and on multigram scale by application of our previously described C(sp³)–H alkenylation method,[26a] starting from the chiral pool (L-alaninol). The enantiomerically pure intermediate **12-2** was then converted to the aminoester fragment **12-3** using heterogeneous hydrogenation and standard functional group manipulations. The three required

hydroxyphenyllactic acid (Hpla) fragments **12-6-12-8** were constructed in a straightforward manner from methyl D-lactate by applying the intermolecular palladium(II)-catalyzed C–H arylation chemistry initially developed by Daugulis.[55] B.-F. Shi's pyridine-based bidentate directing group[56] was found to be optimal to achieve good yields and avoid the epimerization of the sensitive lactate stereocenter during its removal, which was performed under mild conditions upon treatment with $NOBF_4$. With the two sets of key fragments in hand, we were able to complete the total synthesis of aeruginosins 298A and 98A-C through a precise sequence of peptide couplings and deprotections. Aeruginosin 298A was obtained on an unprecedented scale (0.7 g) and with the highest overall yield (8.2% for 17 steps) to date, thereby further demonstrating the potential of C–H activation methods to streamline the synthesis of complex molecules.[57]



Scheme 12. Total Synthesis of Aeruginosins

Finally, the recently reported construction of α-alkylidene-γ-lactams (**13-2**) by C(sp^3)–H alkenylation from acyclic bromoalkenes (**13-1**) was applied to the synthesis of the simple bicyclic alkaloid δ-coniceine (Scheme 13).[26b]



Scheme 13. Synthesis of δ-Coniceine

6. SUMMARY AND OUTLOOK

This Account reviews, from the perspective of our own work, the development of Pd^0-catalyzed $C(sp^3)$–H activation reactions leading to olefins and, even more interestingly, to a variety of ring systems from 4- to 7-membered. This method proved powerful in constructing original cyclic scaffolds, some of which have already found applications in the synthesis of pharmacologically active substances and natural products. Future efforts should be dedicated to the development of more efficient catalysts, including chiral ones for enantioselective reations, and to further applications in the synthesis of complex molecules possessing cyclic fragments. Another direction could aim at further simplifying reaction substrates, and hence improving the overall step-economy, through the development of cross-dehydrogenative methods. Such methods relying on an initial C–H palladation instead of C–X oxidative addition, have been first investigated by the Fagnou,[58] then by our group,[59] but so far have limited scope and efficiency.

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Notes

The authors declare no competing financial interest.

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BIOGRAPHY

Olivier Baudoin completed his PhD in 1998 in the group of Jean-Marie Lehn in Paris. After a post-doctoral stay with K. C. Nicolaou in the Scripps Research Institute, he joined ICSN, Gif-sur-Yvette, in 1999 as a CNRS researcher, where he became fully independent in 2004. In 2006, he became a Professor at Université Claude Bernard Lyon 1 and was promoted to First Class in 2011. In 2015, he moved to the University of Basel where he is currently Full Professor of Chemistry. His current research focuses on the development of new synthetic methods to

functionalize C(sp^3)-H bonds using transition-metal catalysis, and their application in the synthesis of natural products and active ingredients.

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