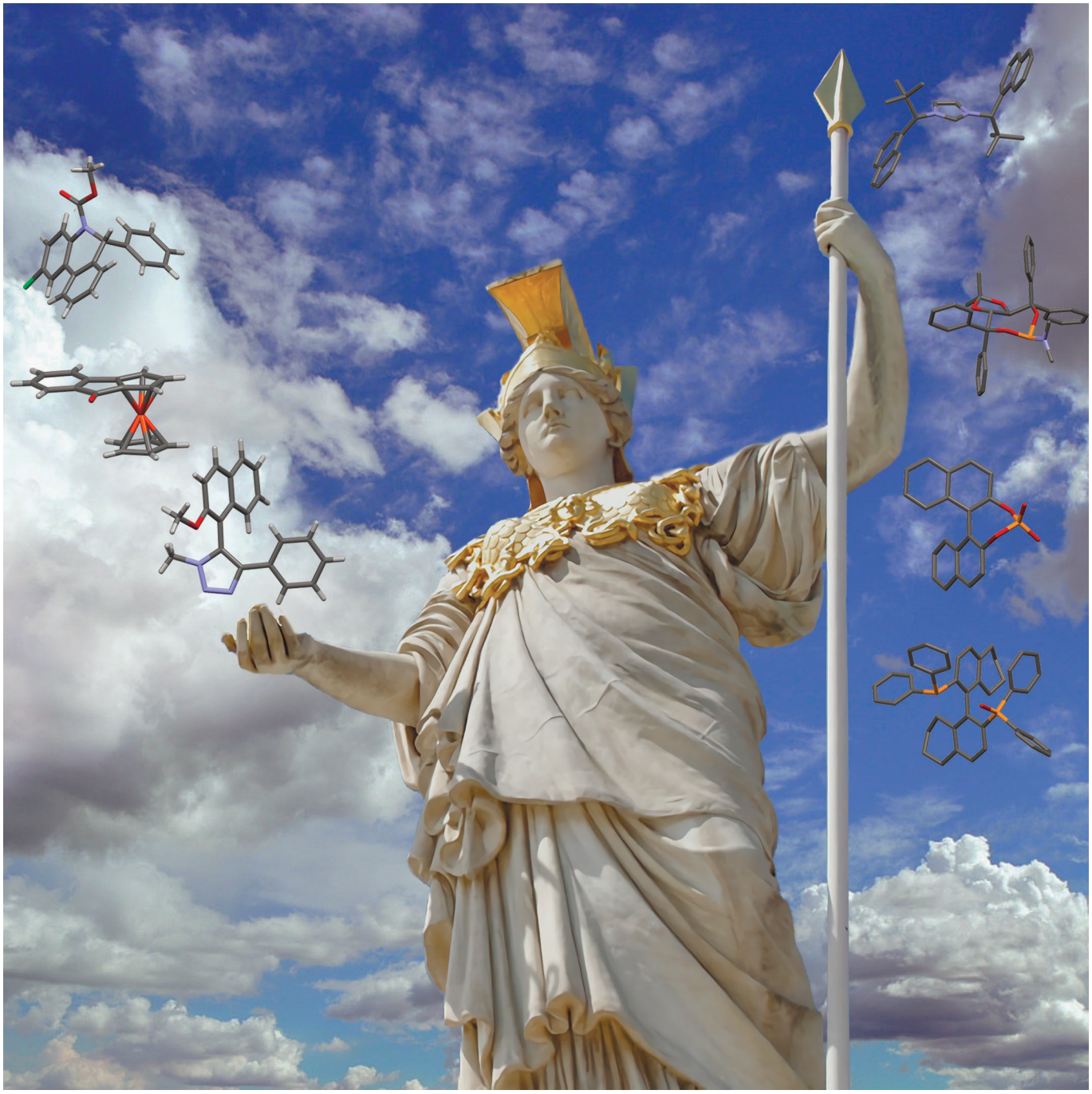
Chiral Catalysts for Pd^0-Catalyzed Enantioselective C–H Activation

Oleksandr Vyhivskyi, Anton Kudashev, Takeru Miyakoshi, and Olivier Baudoin*[a]



Abstract: In the past few decades, processes that involve transition-metal catalysis have represented a major part of the synthetic chemist's toolbox. Recently, the interest has shifted from the well-established cross-coupling reactions to C–H bond functionalization, thus making it a current frontier of transition-metal-catalyzed reactions. Constant progress in this field has led to the discovery of enantioselective methods to generate and control various types of stereogenic elements, thereby demonstrating its high value to generate scalemic chiral molecules. The present review is dedicated to enantioselective Pd^0-catalyzed C–H activation, which may be considered as an evolution of Pd^0-catalyzed cross-couplings, with a focus on the different chiral ligands and catalysts that enable these transformations.

Introduction

Transition-metal catalysis affords some of the most powerful synthetic methodologies for the formation of carbon–carbon or carbon–heteroatom bonds.[1] Over the last twenty years, these reactions were extended to the enantioselective construction of σ-bonds,[2] thereby increasing their broad applicability. Nowadays, cross-coupling reactions are still the gold standard for bond formation at the industrial scale.[3] However, despite their high efficiency and generality, these methods require the presence of functional groups on both coupling partners. These have to be introduced by pre-functionalization steps, thus limiting the atom- and step-economical character, and therefore the sustainability of cross-coupling reactions.

C–H bond activation and functionalization provides interesting solutions to this problem.[4] In these reactions, one or both coupling partners contain C–H bonds instead of C–X (X = leaving group) or C–M (M = main group metal) bonds, thereby offering improved atom- and step-economy over traditional cross-couplings. In the past few years, a great variety of transition metals have proved to be effective catalysts in C–H activation-based cross-coupling reactions. In particular, palladium has arguably been proven as the leading transition metal applicable to a great diversity of C–H bond transformations.[5] Its unique versatility mirrors the diversity of catalytic modes that this metal may adopt, including Pd^0/Pd^{II}, Pd^{II}/Pd^0, Pd^{II}/Pd^{IV}, redox neutral Pd^{II}, and $Pd^0/Pd^{II}/Pd^{IV}$. Similar to cross-coupling reactions, a number of stereoselective C–H functionalization reactions have been developed, and were already the subject of several recent reviews.[6] Herein, we will focus on Pd^0-catalyzed enantioselective C–H functionalization, which can be regarded as an offspring of Pd^0-catalyzed cross-coupling owing to the similarity of mechanisms and the fact that the ligands employed in the former were usually introduced in the context of the latter.

[a] *O. Vyhivskyi, A. Kudashev, T. Miyakoshi, Prof. Dr. O. Baudoin*
Department of Chemistry
University of Basel
St. Johanns-Ring 19, 4056 Basel (Switzerland)
E-mail: olivier.baudoin@unibas.ch

Typical catalytic cycles of Pd^0-catalyzed C–H activation reactions start, similar to cross-couplings, with the oxidative addition of a C–X bond [X = (pseudo)halogen] to the active Pd^0 catalyst, leading to the formation of intermediate **I** (Figure 1). Further ligand exchange with a suitable base, hereafter referred to as "active base", leads to complex **II**. Then, intramolecular C–H activation occurs, and generally proceeds through the base-mediated concerted metalation–deprotonation mechanism.[7] In most cases (but not all), this step is the enantiodetermining step, and therefore it is possible to induce enantioselectivity by using either a chiral ligand or a chiral active base, which control the orientation of substituents and the directionality of the palladium–carbon bond formation in transition state **III**. Then, the protonated base decoordinates to provide diorganopalladium intermediate **IV**, and the active base may be regenerated by a by-standing stoichiometric base, hence allowing the former to operate as a catalyst. Finally, reductive elimination from **IV** releases the desired product and regenerates the active Pd^0 complex.

A careful catalyst design, usually evolved from cross-coupling reactions and adapted to the mechanistic specificities of C–H activation, allows the control of a variety of stereogenic elements (center, plane, axis), which are usually key to the function of organic molecules. To better highlight this design and evolution over the past years, we organized the present

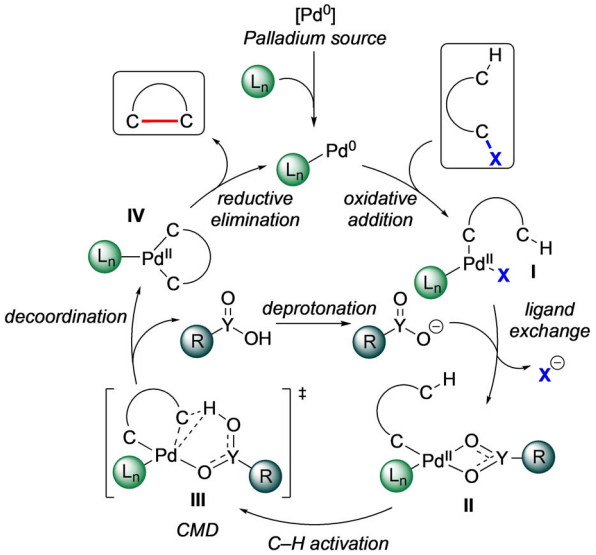


Figure 1. General mechanism of Pd^0/Pd^{II}-catalyzed C–H functionalization.

review according to the types of employed chiral ligands, taking into account the reported literature until May 2020.

Monodentate Ligands

Among all existing ligand classes, monodentate ligands show, by far, the greatest number of applications in modern palladium-catalyzed cross-couplings.[8] By extension, monodentate ligands also showed their efficacy in enantioselective Pd-catalyzed C–H functionalization. In addition to factors that favor cross-couplings, the C–H activation step, which is usually enantiodetermining, is indeed favored by monodentate ligands. In the intramolecular concerted metalation–deprotonation (CMD) mechanism, these ligands allow the metal center to keep a coordination site available for the Pd···CH agostic interaction that precedes the C–H bond cleavage (see transition state **III**, Figure 1).[7]

Phosphorus-containing ligands

Phosphorus-containing ligands are among the most studied and widely employed ligands in coordination chemistry. Their electronic and steric properties can be easily controlled by functionalization of substituents, which makes these ligands highly effective in various chemical reactions.[9] In 1967, Strohmeier and Müller[10] classified the electron-donating and -withdrawing properties of phosphine ligands (L) by measuring the shift of the infrared frequency of CO stretches, ν_{CO}, in monoligated nickel complexes $[Ni(CO)_3L]$. This approach was extended by Tolman in 1970,[11] leading to the famous "Tolman electronic parameter" (TEP). In 1970, Tolman also described a method to measure the apparent size of phosphine ligands and introduced the cone angle (θ) by using Corey–Pauling–Koltun molecular models.[12] He defined the cone angle as the "apex angle of a cylindrical cone, centered 2.28 Å away from the center of the phosphorus atom, which just touches the van der Waals radii of the outermost atoms of the model".[13] Since then, the TEP and Tolman cone angle have been widely utilized in the design of new ligands and catalytic methodologies. In addition to these original parameters, the electronic properties of phosphorus compounds can be assessed by measuring ν_{CO} vibrations for various metal carbonyl complexes,[14] $^1J_{P,Se}$ coupling constants of the corresponding phosphoselenides through ^{31}P NMR spectroscopy,[15] and by DFT calculations based on Gusev's method,[16] etc. The cone angle, in turn, has been completed by the solid angle, which is of great benefit for highly rotationally hindered and disymmetric phosphines.[17] To provide the reader with an overview of steric and electronic features of monodentate phosphorus ligands, including chiral ones, we created a qualitative map, based on recent literature (Figure 2).[9,18] The variation of ligand steric and electronic properties is central to optimizing reactivity and selectivity. It is, for instance, possible to change electronic effects without largely affecting the steric effects and vice versa. Moreover, the availability of large libraries of phosphorus-based ligands, their high modularity and generally good stability make these ligands well suited for the activation of strong bonds such as C–H bonds, which sometimes require harsh conditions.

Oleksandr Vyhivskyi obtained his specialist degree in chemistry from the Lomonosov Moscow State University. During that time, he conducted his graduate work under the supervision of Dr. Alexander V. Finko and Prof. Elena K. Beloglazkina. In 2019, he joined the group of Prof. Olivier Baudoin for PhD studies. Currently, his research interests are focused on the application of transition-metal catalysis in total synthesis.

Anton Kudashev obtained his BSc in Chemistry from the Igor Sikorsky Kyiv Polytechnic Institute in 2017, followed by MSc degree under supervision of A. A. Fokin in 2019. Currently, he is undertaking his PhD studies at the University of Basel under the supervision of Prof. O. Baudoin. His research interests lay in the field of transition-metal-catalyzed C–H activation.

Takeru Miyakoshi graduated from Yamagata University, Japan, in 2017. He obtained his Master's degree under the guidance of Prof. H. Konno at Yamagata University in 2019, and he is currently pursuing his PhD studies under the supervision of Prof. O. Baudoin at the University of Basel, working on Pd^0-catalyzed C–H activation.

Olivier Baudoin obtained his PhD in 1998 under the supervision of Prof. J.-M. Lehn and Dr. M.-P. Teulade-Fichou at Collège de France, Paris. After a post-doctoral position with K. C. Nicolaou at the Scripps Research Institute, La Jolla (USA), he was recruited as CNRS researcher at the Institut de Chimie des Substances Naturelles (France) in 1999, where he became a group leader in 2004. In 2006, he was appointed as Professor at the University of Lyon and since 2015 he has been a Full Professor at the University of Basel (Switzerland). He received the CNRS Bronze Medal in 2005, the Young Professor Award from the French Chemical Society, Organic Chemistry Division in 2010, and was a Junior Member of the Institut Universitaire de France from 2009–2014. His recent research focuses on the development of new methods to form C–C bonds by Pd-catalyzed C–H activation and migratory cross-couplings, and their application to complex molecule synthesis.

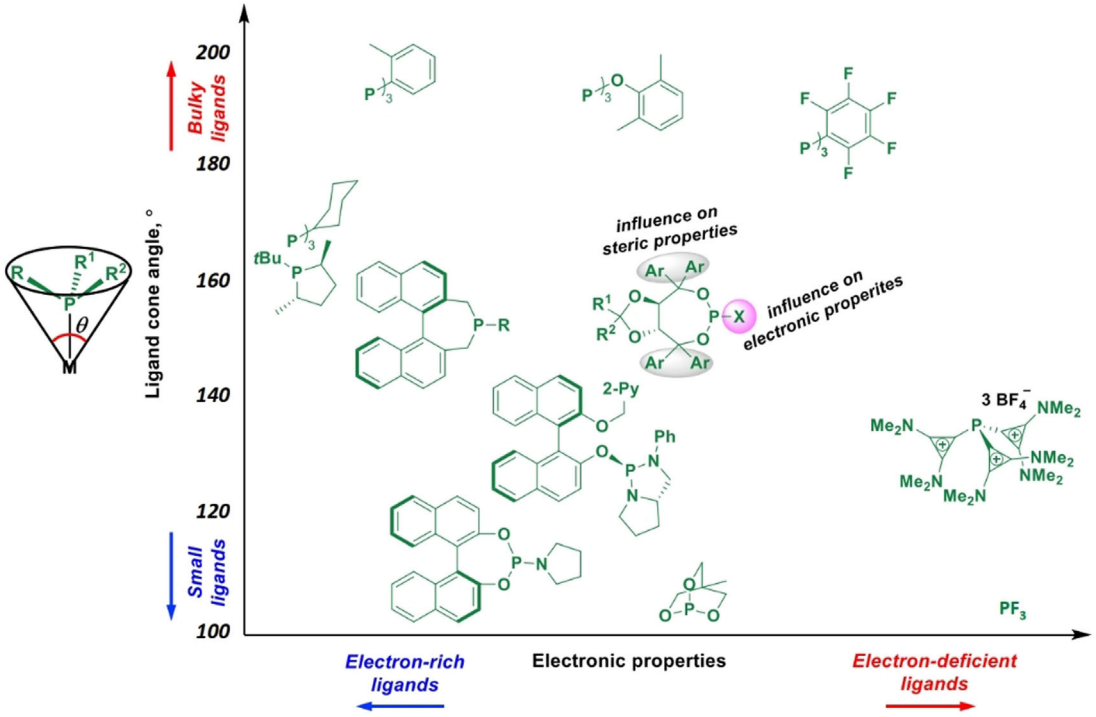
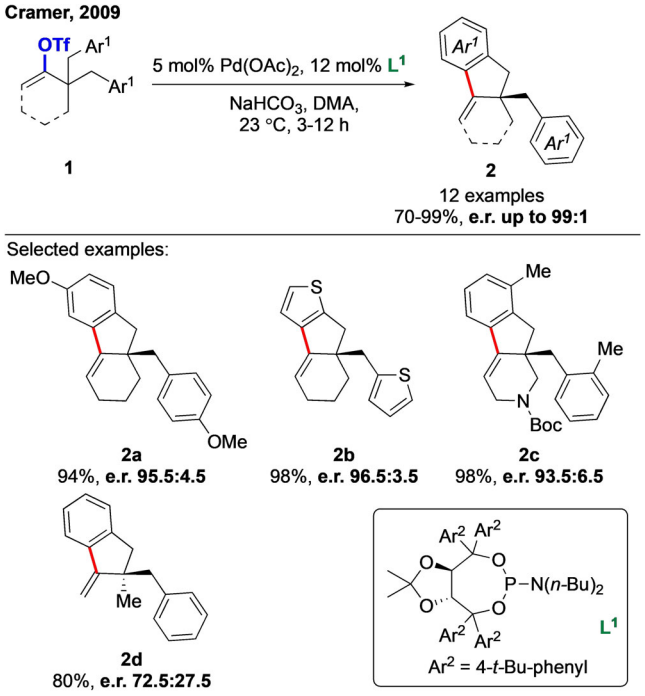


Figure 2. Electronic and steric features of various monodentate phosphorus ligands.

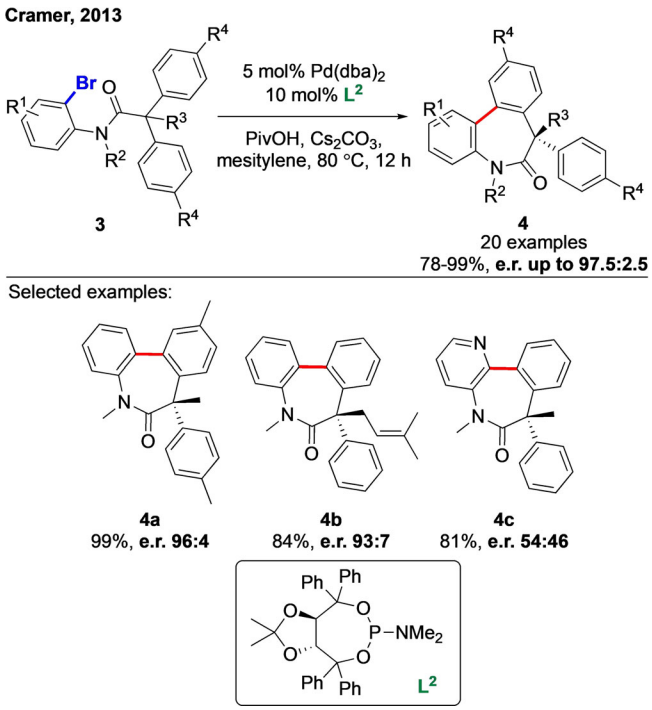
Phosphoramidites

Phosphoramidites,[19] besides being the first class of ligands employed in enantioselective Pd^0-catalyzed C–H activation, are also the most frequently employed ligands for this type of reactions.[20] Similar to their phosphonite analogs (see below), these modular and rather electron-neutral ligands are based on a C_2-symmetric chiral diol backbone such as TADDOL,[21] BINOL,[22] or SPINOL[23] to induce high levels of enantioselectivity. The catalytic system reported by Cramer and co-worker in 2009, employing a TADDOL-phosphoramidite ligand, is the first successful example of enantioselective Pd^0-catalyzed C–H activation.[24] In this work, bis-benzylated vinyl triflates **1** underwent intramolecular C–H alkenylation, leading to the formation of (fused) indanes **2** (Scheme 1). The enantioselectivity arises from the discrimination between the two enantiotopic benzylic substituents, one of which is preferentially alkenylated whereas the other one remains intact, thus generating a quaternary stereocenter. Phosphoramidite $\mathbf{L^1}$ was the ligand of choice for this C(sp^2)–H alkenylation, outperforming other phosphorus-based ligands. The optimization studies revealed a significant dependence of the yield and enantioselectivity on the solvent, with highly polar, aprotic dimethylacetamide (DMA) being the most efficient. The reaction showed high efficiencies and levels of enantioinduction, and tolerated structural variations at the benzylic groups (**2a**,**b**) and the cyclic vinyl triflate (**2c**). Of note, an acyclic vinyl triflate was compatible, but furnished a lower enantioselectivity (**2d**).

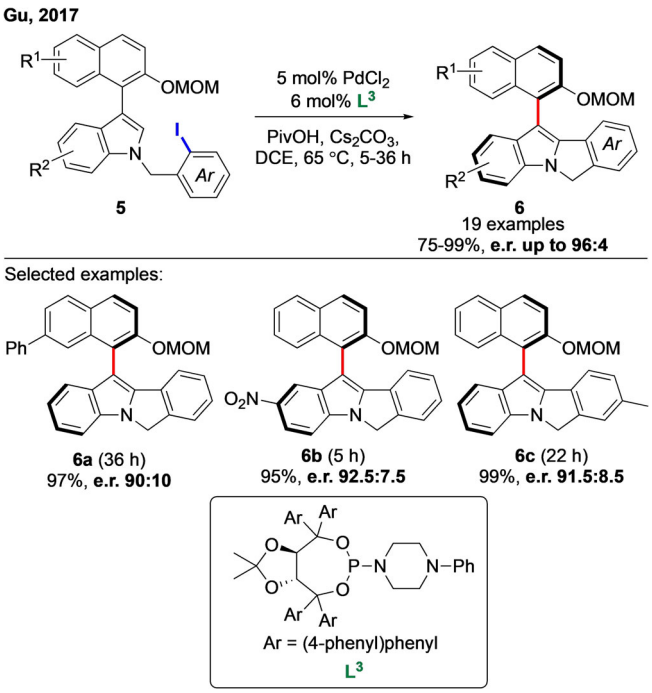
Palladium-catalyzed intramolecular C–H activation most often involves the formation of five- to seven-membered palladacycle intermediates. However, products arising from the reductive elimination of larger palladacycles are also accessible. Indeed, in 2013, Saget and Cramer reported a desymmetrizing C(sp^2)–H arylation to yield a high variety of dibenzazepinones **4** with excellent enantioselectivities (Scheme 2).[25] This reaction occurs through the formation of an eight-membered pallada-



Scheme 1. Indane synthesis by desymmetrizing C(sp^2)–H alkenylation in the presence of phosphoramidite $\mathbf{L^1}$.



Scheme 2. Desymmetrizing C–H arylation by using phosphoramidite **L²** for the synthesis of dibenzazepinones.

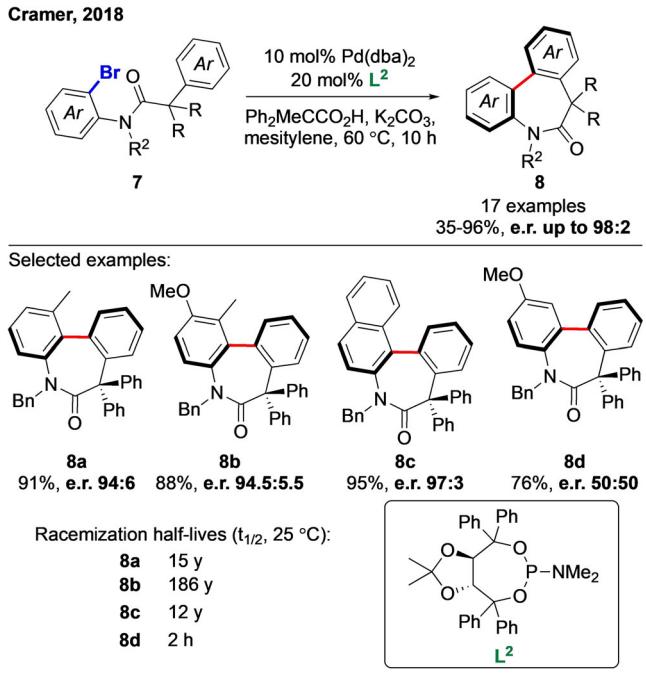


Scheme 3. Atroposelective C–H arylation catalyzed by using phosphoramidite **L³**.

cycle, which, in turn, forms the seven-membered cyclic product containing a quaternary stereocenter. During the optimization, the simple TADDOL-based phosphoramidite **L²** was revealed as the optimal ligand. Of note, if the carboxylic acid additive was omitted, the reaction proceeded sluggishly, affording the product in trace amounts. This result confirmed the superior role of carboxylates such as pivalate as active bases in Pd-catalyzed C–H activation reactions.[26] The reaction tolerated various aryl moieties (**4a**), side chains (**4b**), as well as heteroaromatics (**4c**), although with a significant decrease of enantioselectivity for the latter. Additional tests were performed with substrates containing potentially competitive C(sp^2)–H and C(sp^3)–H sites for six- and seven-membered palladacycle formation, but the products arising from eight-membered palladacycles were exclusively formed. This was attributed to the favorable alignment of the substituents induced by the tethering group in the C–H activation step.

The success of reactions that generate atropisomerism heavily depends on the stability of the formed stereogenic axis. Bulky substituents enforce such configurational stability, preventing the rotation along this axis. In 2017, Gu and co-workers reported a C–H arylation protocol enabling the control of biaryl axes (Scheme 3).[27,28] The construction of a C–C bond between the aryl iodide and the C2 position of the indole in substrate **5** led to a drastic increase of the racemization barrier of the biaryl axis. The configuration of the latter was efficiently controlled through the use of chiral phosphoramidite **L³**, containing biphenyl substituents at the TADDOL backbone and a piperazine moiety on phosphorus. A variety of substituents on both sides of the biaryl axis were well tolerated (**6a–c**).

A conceptually different entry into the field of atropo-enantioselective Pd^0-catalyzed C–H arylation for the formation of biaryl axes was reported by Cramer and co-workers in 2018.[29] This investigation was motivated by a preliminary computational analysis, which identified dibenzodiazepinone **7** as a promising lead (Scheme 4). Similarly to the previous study



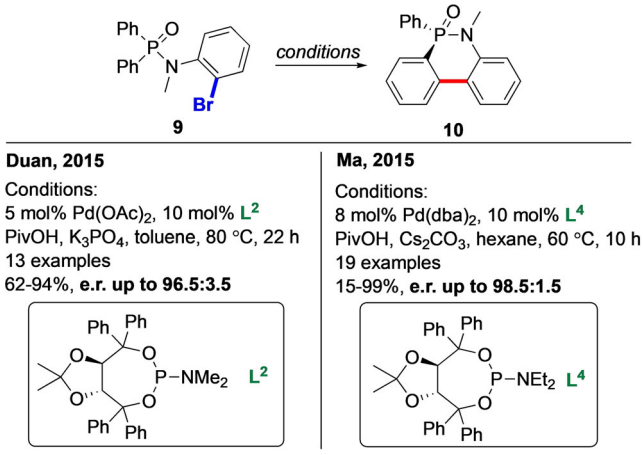
Scheme 4. Intramolecular atropo-enantioselective C–H arylation with phosphoramidite **L²**.

from this group (see Scheme 2),[25] phosphoramidite **L²** was found to be optimal for this process. A variety of substitution patterns were well tolerated (**8a**–**8c**), provided that a substituent was present at the *ortho* position of the biaryl axis to prevent racemization (**8a** vs. **8d**).

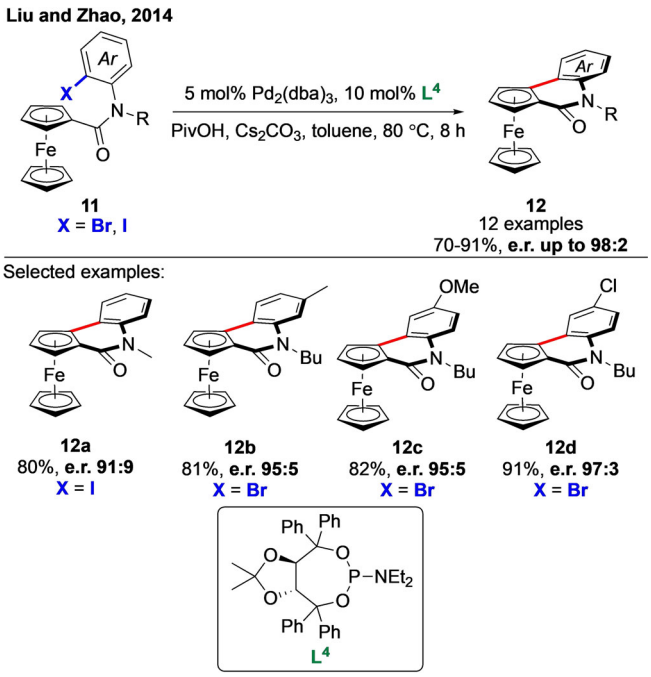
In addition to carbon stereocenters and biaryl axes, phosphoramidites are also capable of mediating enantioselective reactions that generate P stereogenic centers. Indeed, in 2015, the groups of Duan[30] and Ma[31] concurrently disclosed the enantioselective desymmetrization of phosphinic amides via C(sp²)–H arylation (Scheme 5). Simple TADDOL-based phosphoramidites **L²** and **L⁴** excelled in this reaction, providing cyclized products **10** with high degrees of enantioselectivity (e.r. > 95:5).

Another major application of C–H activation using chiral phosphoramidites is found in the synthesis of planar chiral ferrocenes.[32] This reactivity was simultaneously discovered by the Gu[33] (discussed later) and Liu–Zhao[34] groups in 2014 (Scheme 6). The approach undertaken by Zhao and co-workers utilized again the simple phosphoramidite **L⁴**, which provided high enantioselectivities across a broad scope of aryl and nitrogen substituents (**12a**–**d**). Both aryl bromides (**12b**–**d**) and iodides (**12a**) were suitable reactants for this transformation.

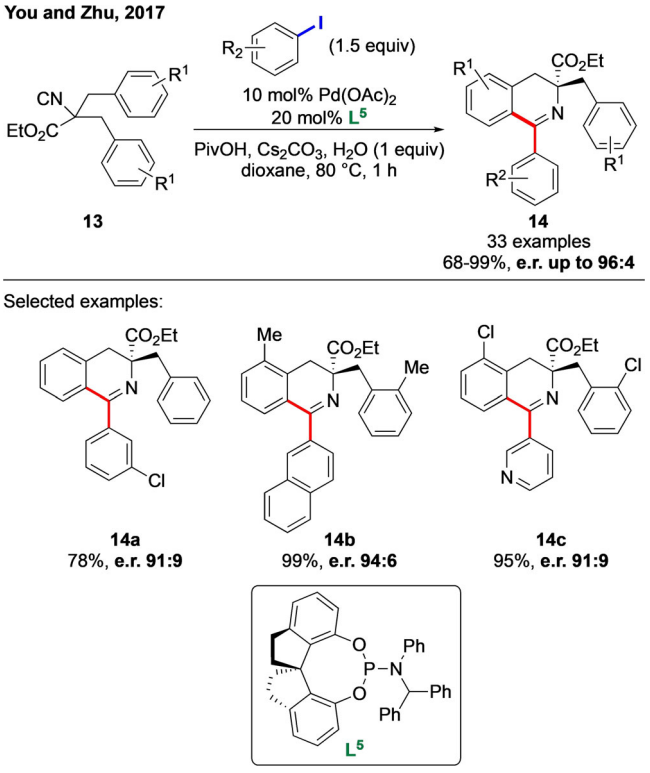
Domino reactions including a C(sp²)–H activation step offer fast access to complex molecules from simple precursors.[35] In this context, You, Zhu, and co-workers disclosed a desymmetrizing C(sp²)–H imidoylation protocol (Scheme 7).[36] Mechanistically, the oxidative addition of the aryl iodide to the palladium catalyst is followed by carbopalladation of the isocyanide group and intramolecular desymmetrizing C–H arylation. In this case, SPINOL-derived phosphoramidite **L⁵** outperformed BINOL- and TADDOL-derived phosphoramidites as well as diphosphines, providing valuable 3,4-dihydroisoquinolines **14** in high yield and good enantioselectivity. This protocol was compatible with a variety of modifications of aryl moieties on both reaction partners (**14a**–**c**). Notably, the addition of small amounts of water improved the yield without affecting the enantioselectivity of the process.



Scheme 5. Desymmetrizing C–H arylation for the synthesis of phosphinic amides enabled by phosphoramidites **L²** and **L⁴**.



Scheme 6. Synthesis of planar chiral ferrocenes catalyzed by Pd⁰/phosphoramidite **L⁴**.



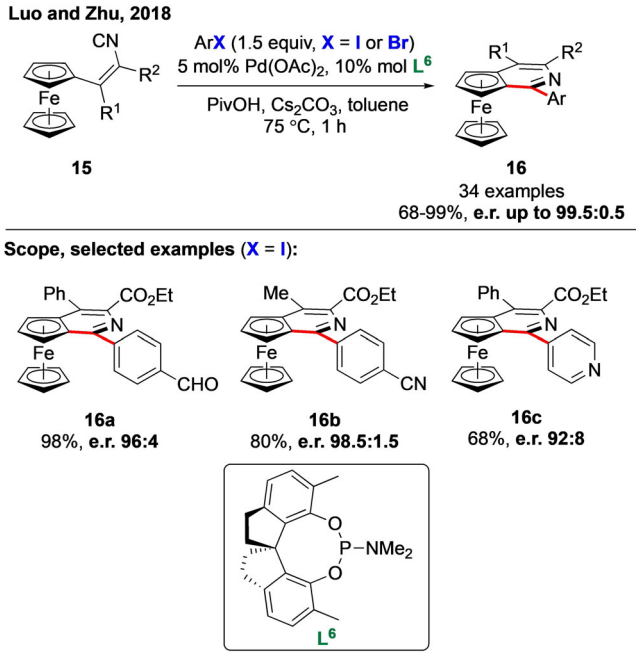
Scheme 7. Domino desymmetrizing C(sp²)–H imidoylation with SPINOL-based phosphoramidite **L⁵**.

In 2018, Luo, Zhu, and co-workers extended this imidoylation protocol to the synthesis of planar chiral ferrocenes.[37] By using another SPINOL-based phosphoramidite **L⁶**, they gener-

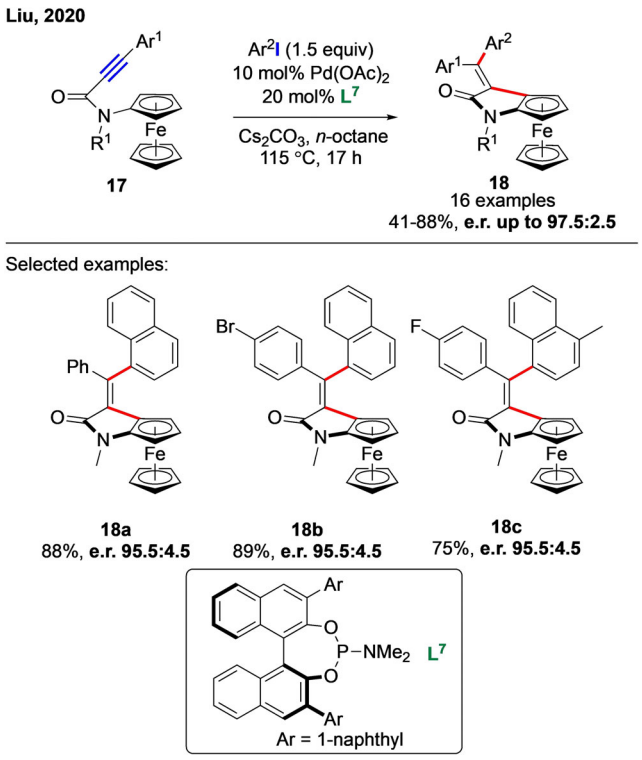
ated chiral pyridoferrocenes with high yields and enantioselectivities (Scheme 8). Interestingly, two flanking methyl substituents on the SPINOL backbone were crucial for both the reactivity and stereoinduction, as unsubstituted ligands furnished an inactive catalyst. The developed protocol was tolerant to various substituents of the isocyanide as well as on the aryl electrophile (**16a**–**16c**).

The ability of organopalladium complexes to insert into triple bonds was utilized in the synthesis of chiral fused heterocycloferrocenes.[38] In a similar vein, Liu and co-workers recently reported a domino *syn*-carbopalladation/C–H alkenylation reaction for the synthesis of fused pyrrolidinone-ferrocenes **18** with planar chirality (Scheme 9).[39] This reaction was enabled by ligand **L**^{7}, a member of the BINOL-derived MonoPhos-family of phosphoramidites.[40] As in the previous example (see Scheme 8), flanking substituents at the 3,3′-positions of the BINOL scaffold were crucial for the enantioinduction, and unsubstituted scaffolds afforded low enantioselectivities. The developed protocol tolerated a number of substituents on the aryl moiety connected to the triple bond, as well as on the aryl halide coupling partner.

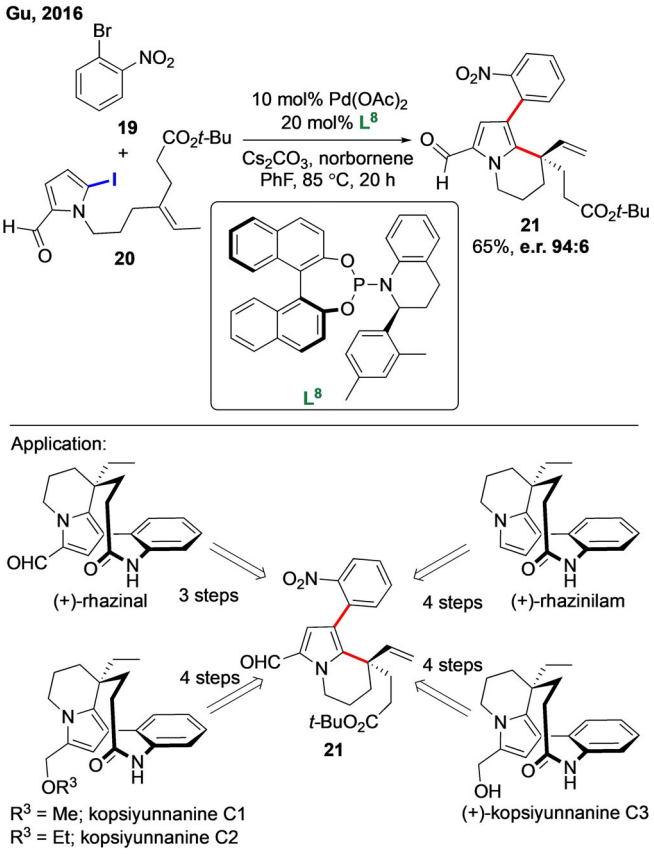
The Catellani reaction is a powerful multicomponent process including a C(sp^2)–H activation step, which allows the rapid construction of polysubstituted aromatic rings.[41] In 2016, Gu and co-workers reported the first enantioselective version of this reaction, in the course of a total synthesis of the rhazinilam family of natural products (Scheme 10).[42] In this case, the intramolecular alkene carbopalladation, occurring after C–H arylation with aryl bromide **19**, is the enantiodetermining step of the reaction. After testing simple chiral mono- and diphosphines such as MOP, BINAP, and DIOP, the authors focused on the optimization of phosphoramidite ligands. Although several phosphoramidites bearing an acyclic amino group furnished



Scheme 8. Synthesis of pyridoferrocenes by using phosphoramidite **L**^{6}.



Scheme 9. Domino carbopalladation/C–H alkenylation reaction for the synthesis of fused ferrocenes by employing 3,3′-disubstituted MonoPhos-type ligands.



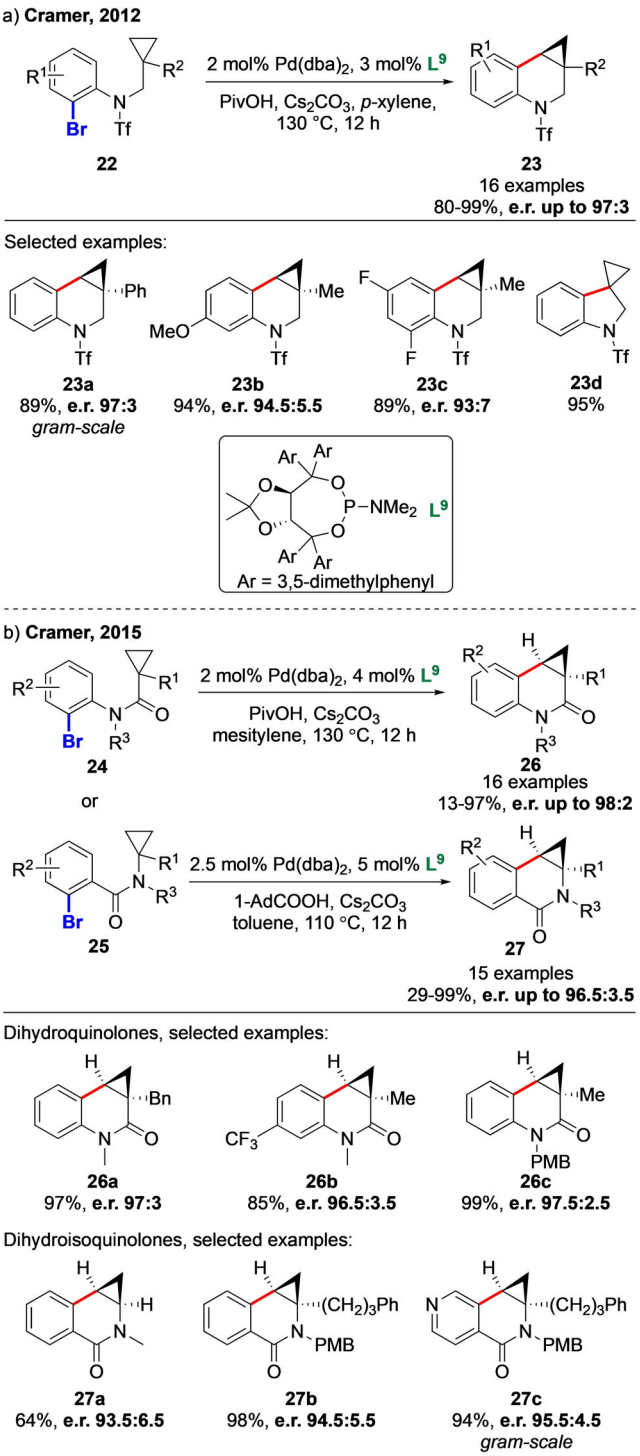
Scheme 10. Enantioselective Catellani reaction using phosphoramidite **L**^{8} and application to the total synthesis of rhazinilam and congeners.

satisfactory yields, the enantioselectivity was usually poor. Further screening revealed that phosphoramidites bearing a cyclic amine resulted in superior yields and enantioselectivities. Finally, ligands containing an α-stereogenic tetrahydroquinoline ring[43] performed the best, with **L⁸** providing the desired product **21** in 65% yield and an e.r. of 94:6. This key intermediate was then converted to rhazinilam and several congeners in an efficient manner. Subsequent to this work, another example of the enantioselective Catellani reaction catalyzed by a bidentate phosphoramidite-olefin ligand was reported by Zhou and co-workers (27%, e.r. 89:11).[44,45]

Cyclopropane C–H bonds display reactivities close to sp^2 C–H bonds vis-a-vis palladium complexes. In 2012, Saget and Cramer reported the enantioselective synthesis of cyclopropane-fused tetrahydroquinolines **23**,[46] as the first example from a series of papers on the enantioselective activation of cyclopropane C–H bonds by Pd^0/Pd^{II} catalysis (Scheme 11 a). For this transformation, the introduction of bulky 3,5-dimethylphenyl groups on the TADDOL backbone (ligand **L⁹**) was crucial to achieve high yields and enantiomeric ratios. Remarkably, the reaction also occurred nicely at low catalyst loadings (down to 2 mol%). In addition, it tolerated a wide variety of substitution patterns on the cyclopropane and aromatic fragments (**23 a**–**c**). Of note, a cyclopropane containing a tertiary carbon ($R^2 = H$) selectively underwent C–H arylation at this proximal position to provide the achiral spirocyclic product (**23 d**). The enantioselective activation of cyclopropane C–H bonds was later extended to substrates containing amide linkers (**24**–**25**, Scheme 11 b).[47] The same phosphoramidite ligand **L⁹** was found to promote the cyclization of both anilide (**24**) and amide (**25**) compounds with high enantioselectivity and yield across a wide range of substrates.

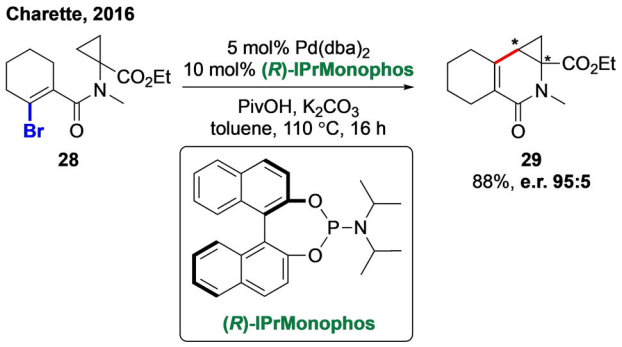
In 2016, Charette and co-worker reported a conceptually related intramolecular C–H alkenylation of cyclopropanes (Scheme 12).[48] Although this study mostly focused on the non-enantioselective cyclization employing PCy_3 as a ligand, the authors reported one example of an enantioselective reaction. By using (*R*)-IPrMonophos, they obtained the desired fused cyclopropane **29** in 88% yield and with an e.r. of 95:5 from amide **28**.

Alkyl C–H bonds are generally less reactive than sp^2 and cyclopropane C–H bonds towards the activation by palladium complexes.[5a,49] In addition, secondary C(sp^3)–H are less reactive than primary ones and therefore their enantioselective functionalization is particularly challenging. In this context, the Cramer group reported an intramolecular C(sp^3)–H alkylation of benzylic secondary C–H bonds for the synthesis of biologically important β-lactams **31** from the corresponding α-chloroamides **30** (Scheme 13).[50] In this rare case of methylene activation, the chiral catalyst discriminates the enantiotopic hydrogen atoms on the secondary position, and a stereogenic center is created at the activated C–H bond. A careful adjustment of its steric properties revealed phosphoramidite **L¹⁰** as the most efficient ligand for this transformation. This protocol tolerated various nitrogen substituents, although an optimal enantioselectivity was obtained with a *t*Bu group, as well as functional groups on the phenyl ring (**31 a**–**d**). However, starting materials containing heteroarenes (furan, thiophene, and indole) underwent competitive C(sp^2)–H alkylation, leading to the formation of achiral piperidin-2-ones.

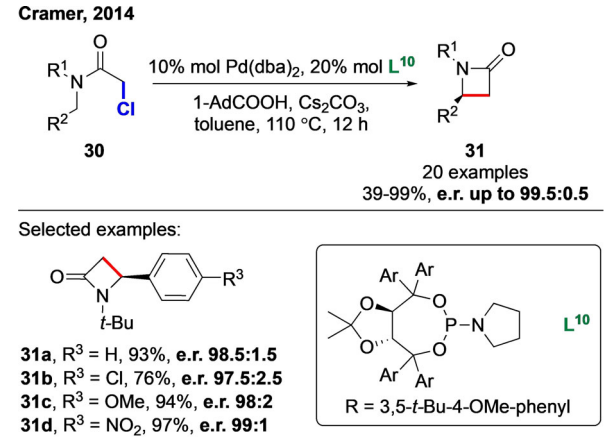


Scheme 11. Intramolecular C–H arylation of cyclopropanes with TADDOL-phosphoramidite **L⁹**.

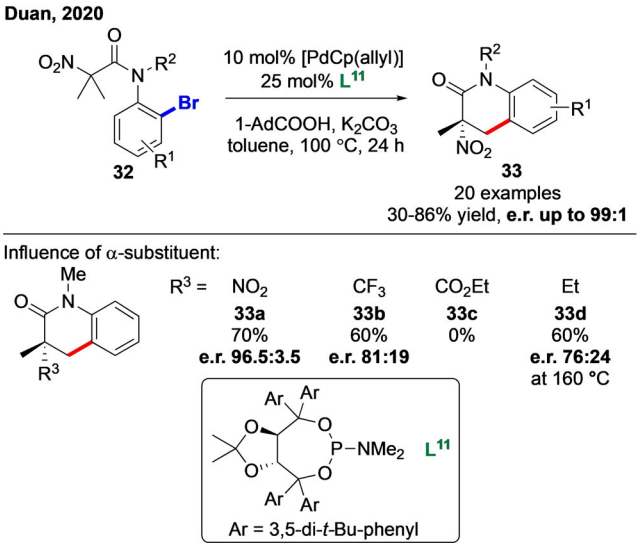
More recently, Duan and co-workers reported a novel Pd^0-catalyzed desymmetrization of methyl groups for the synthesis of scalemic dihydroquinolinones **33** (Scheme 14).[51] Phosphoramidite **L¹¹** was found to be the optimal ligand for this transfor-



Scheme 12. Enantioselective C–H alkenylation of cyclopropanes by using (*S*)-IPrMonophos.



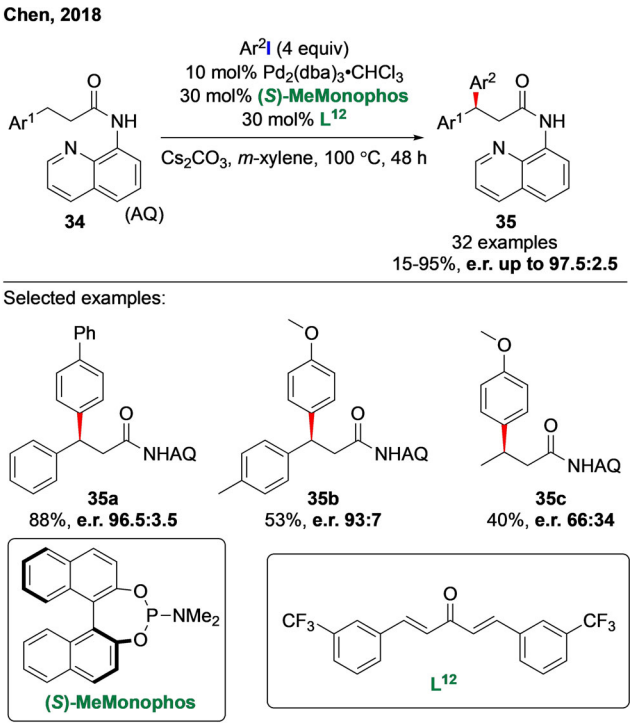
Scheme 13. Intramolecular C(sp^3)–H alkylation to synthesize β-lactams mediated by phosphoramidite **L**^{10}.



Scheme 14. Phosphoramidite **L**^{11} for the desymmetrization of activated methyl groups.

mation, outperforming various bidentate phosphines and other phosphoramidites, and leading to the cyclized products **33** in good yields and excellent stereoselectivities. The presence of an electron-withdrawing group at the α-position of the amide, affecting the acidity of the activated methyl groups, was crucial to provide the product in high yields and with high levels of enantioselectivity. Among these, the nitro group (**33 a**) outperformed other substituents (**33 b**–**d**).

Whereas intramolecular Pd^0-catalyzed enantioselective C–H activation is well developed and represented by a tremendous number of examples, intermolecular versions are much less common. In 2018, Chen and co-workers reported the first example of Pd^0-catalyzed intermolecular enantioselective C(sp^3)–H arylation.[52] To this purpose, they employed the well-established aminoquinoline (AQ) directing group[53] and (*S*)-MeMonophos as the chiral ligand (Scheme 15). Generally, bidentate directing groups (DGs) exhibit superior reactivity to monodentate DGs in palladium-catalyzed C–H activation reactions.[54] However, owing to the potential saturation of the coordination sphere of Pd with bidentate DGs, it is particularly challenging to develop enantioselective Pd^0-catalyzed reactions by using an external chiral ligand. A first screening revealed that the enantioselectivity of the β-C(sp^3)–H arylation could be significantly improved in the presence of a CF_3-disubstituted dba (dba = dibenzylideneacetone) ligand (**L**^{12}), which might help to stabilize Pd^0 species in the reaction mixture. The optimized catalytic system including both (*S*)-MeMonophos and **L**^{12} allowed the arylation of benzylic C(sp^3)–H bonds in a highly enantioselective manner. The reaction tolerated a wide array of substitution patterns on both coupling partners (**35 a**–**b**) and was also extended to non-benzylic methylene groups such as in **35 c**, albeit with a significant decrease of yield and enantioselectivi-

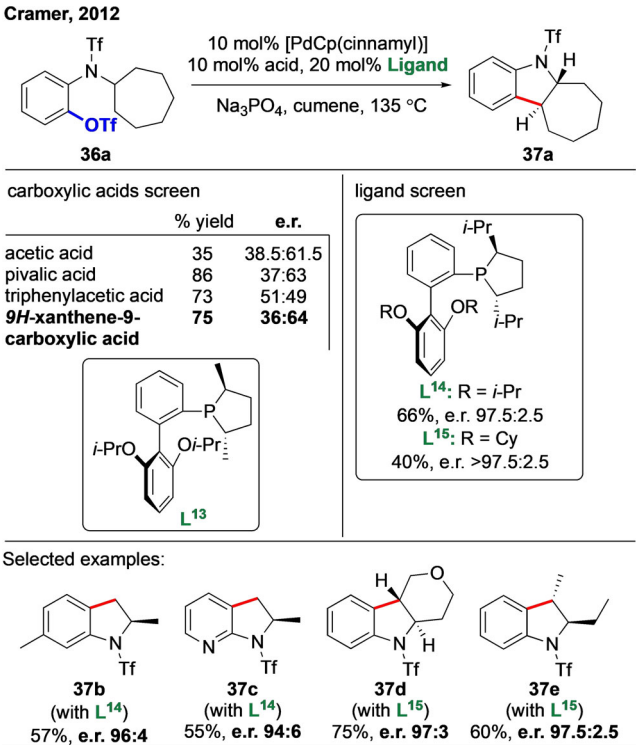


Scheme 15. Intermolecular enantioselective C(sp^3)–H arylation by using a bidentate directing group and (*S*)-MeMonophos.

ty, thereby illustrating the challenge of functionalizing non-activated methylenes. On the basis of experimental and theoretical mechanistic studies, the authors concluded that this reaction mainly occurs through the Pd^0/Pd^{II} catalytic mode, rather than the Pd^{II}/Pd^{IV} pathway that usually operates with bidentate DGs. In addition, the calculations indicated that the AQ directing group is coordinated in a monodentate mode during the enantiodetermining C–H activation step, hence allowing the chiral ligand to bind to Pd and exert its enantioinductive effect.

Phosphines

Chiral monodentate phosphines, which are usually more electron-rich than phosphoramidites (see Figure 2), have been successfully employed in various transition-metal-catalyzed enantioselective reactions such as hydrogenation.[40,55] In 2012, by combining a Buchwald-type biarylphosphine scaffold with a C_2-symmetric phospholane,[56] Cramer and co-workers designed a set of efficient chiral ligands, named SagePhos, for the enantioselective Pd^0-catalyzed C(sp^3)–H arylation leading to indolines (Scheme 16).[57] By using ligand **L^{13}**, they first examined the effect of carboxylic acids of various steric bulk, and found that 9*H*-xanthene-9-carboxylic acid provided the best enantioselectivity together with a good yield. Additional ligand modifications revealed that **L^{14}** or **L^{15}** furnished chiral indoline **37 a** with high enantiomeric ratios. By using this combination of bulky carboxylic acid and chiral phosphine, a variety of (fused) indoline products were obtained with a high enantioselectivity (**37 b**–**e**).

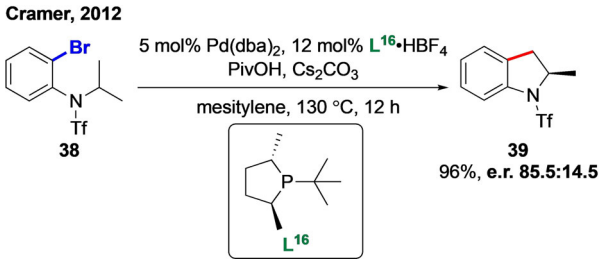


Scheme 16. Phospholane-biarylphosphine ligands in enantioselective indoline synthesis by C(sp^3)–H arylation.

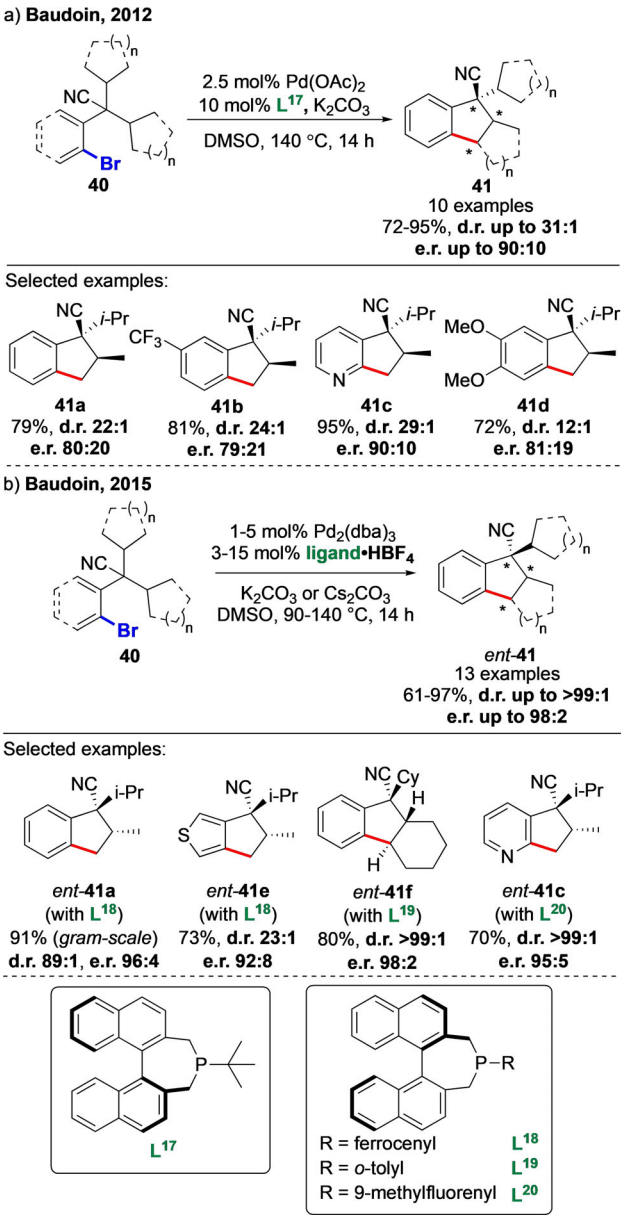
In the same year, in the search for chiral versions of the popular electron-rich, monodentate phosphines PCy_3 and $P(tBu)_3$, Cramer and co-workers reported the synthesis of C_2-symmetric phospholane ligands and their evaluation in the above indoline synthesis through C(sp^3)–H arylation (Scheme 17).[18f] Of all prepared phosphines, **L^{16}** performed the best, providing the target indoline **39** with an e.r. of 85.5:14.5 and an excellent yield (96%). The electronic and steric properties of **L^{16}** were indeed found to be similar to those of PCy_3 by comparing the CO stretching frequencies of *trans*-[RhCl(CO)(PR_3)$_2$] complexes (1941 vs. 1940 cm^{-1}, respectively) and buried volumes (29.8–30.9% vs. 31.8%).

In addition to these efforts and to seminal work by Kündig and Kagan (see below), our group reported in 2012 the use of Binepines, a class of chiral monophosphines initially developed for asymmetric hydrogenations,[18e] for enantioselective intramolecular C(sp^3)–H arylations furnishing chiral indanes **41** (Scheme 18 a).[58] Initially employing *tert*-butyl-substituted Binepine **L^{17}**, a screening of conditions revealed DMSO as the optimal solvent, in contrast to more commonly used aromatic solvents for such transformations. Together with $Pd(OAc)_2$ as the palladium source, these conditions minimized the ligand-free background reactivity, hence providing indanes containing two adjacent stereocenters with high yields and diastereoselectivities, but moderate enantioselectivities. In 2015, a more thorough study was reported, with the improvement of the enantioselectivity and expansion of the methodology (Scheme 18 b).[59] The investigations revealed three Binepines as optimal ligands. Phosphine **L^{18}**, containing a bulky ferrocenyl substituent, was shown to be effective for the arylation of primary C(sp^3)–H bonds, thus providing *cis*-indanes in high yield, enantio- and diastereoselectively (*ent*-**41 a**, *ent*-**41 e**). For the challenging methylene activation, *o*-tolyl-substituted Binepine **L^{19}** outperformed **L^{18}**, providing a set of tricyclic indanes containing three adjacent stereocenters in a diastereo- and enantiocontrolled manner (*ent*-**41 f**). Finally, Binepine **L^{20}** was found to be the most efficient ligand for a pyridine-containing substrate (*ent*-**41 c**). DFT calculations pointed to the importance of London dispersion forces between the substrate and ligand as the origin of the enantioselectivity.

Another interesting class of phosphine ligands used in enantioselective Pd^0-catalyzed C(sp^2)–H activations is based on the P-stereogenic benzooxaphosphole scaffold, namely AntPhos-

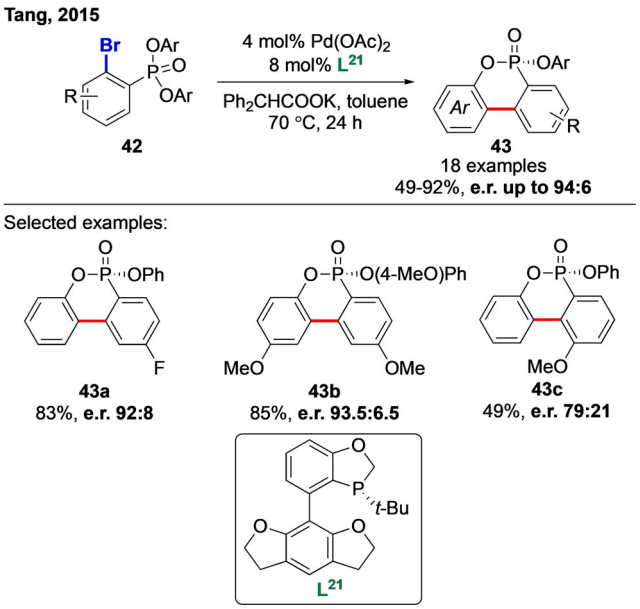


Scheme 17. Phospholane ligand **L^{16}** in enantioselective C(sp^3)–H arylation.



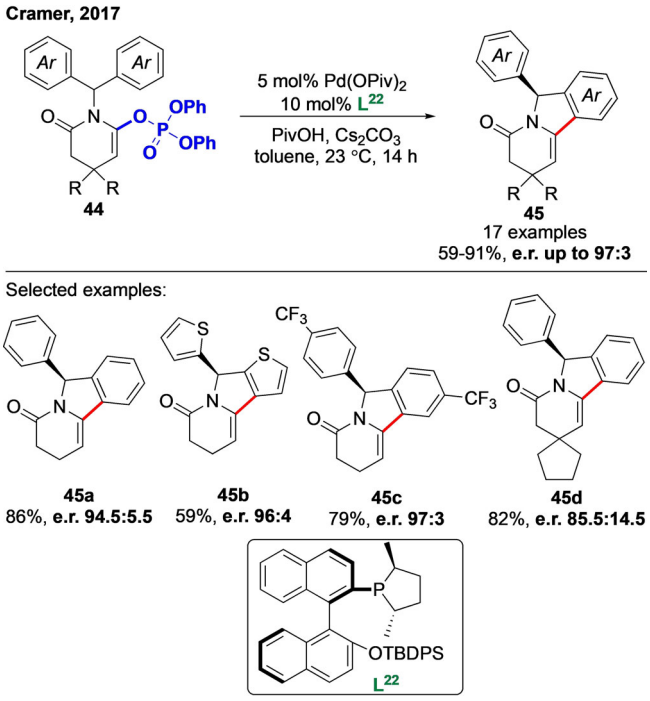
Scheme 18. Pd^0/Binepine-catalyzed intramolecular C(sp^3)–H arylation for the synthesis of (fused) indanes.

type ligands.[60] In 2015, the Tang group reported a desymmetrizing C(sp^2)–H arylation reaction for the synthesis of P-stereogenic compounds, employing AntPhos **L^{21}** (Scheme 19).[61] These investigations revealed a substantial dependence of the yield and enantiomeric ratio on the solvent. In ether solvents, such as dioxane or THF, the reaction was sluggish, in contrast to apolar, low-coordinating solvents such as toluene or even cyclohexane. The choice of active base was also dictated by these considerations, with potassium diphenyl acetate proving to be optimal. The reported conditions allowed access to P-stereogenic biarylphosphonates **43** in good yields and high e.r. values. This protocol tolerated diverse substituents (**43 a**–**c**), although substitution at the *ortho*-position to the biaryl bond induced both a lower yield and enantioselectivity (**43 c**).



Scheme 19. AntPhos-type ligand in desymmetrizing C(sp^2)–H arylation.

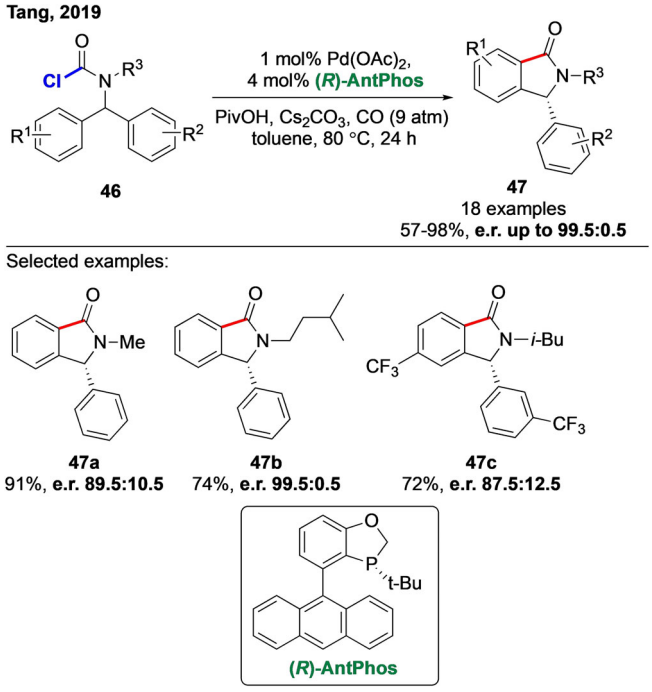
In 2017, Cramer and co-worker modified the abovementioned SagePhos-type scaffold (see Scheme 16) for another type of desymmetrization via C(sp^2)–H bond activation, wherein they employed ketene aminal phosphates as substrates (Scheme 20).[62] By replacing the biphenyl with a binaphthyl scaffold, phosphine **L^{22}** was identified as an optimal ligand for this transformation. This protocol allowed the construction of elaborate indolizine-based systems with high enantioselectivities and yields, while tolerating various substitutions on the



Scheme 20. Binaphthylphosphine ligand **L^{22}** in enantioselective C(sp^2)–H alkenylation with phosphates as electrophilic coupling partners.

aryl rings (**45 a–c**) and, to a certain extent on the dihydropyridone (**45 d**), albeit with a reduced enantioselectivity.

In addition to the construction of P-stereogenic centers (see Scheme 19), the AntPhos family of ligands was employed in enantioselective C(sp^2)–H carbamoylation (Scheme 21).[63] The reaction, developed by Tang and co-workers, required a pressure of carbon monoxide and allowed the desymmetrization of two phenyl substituents, giving rise to chiral isoindolinones **47** in the presence of (*R*)-AntPhos and $Pd(OAc)_2$ as the palladium source. Interestingly, the nitrogen substituent had a significant impact on the enantioselectivity, with larger alkyl groups furnishing better enantioinduction. With such substituents, high enantioselectivities and yields were obtained for a variety of isoindolinones **47**.

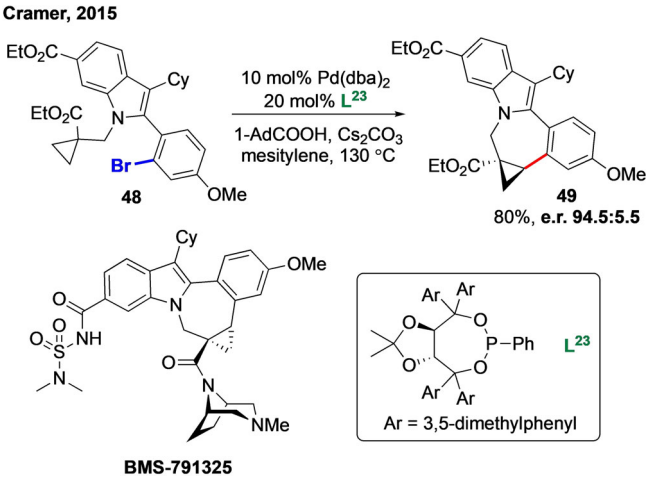


Scheme 21. Desymmetrizing C(sp^2)–H carbamoylation using AntPhos.

Phosphonites

Phosphonites[64] are valuable electron-deficient complements to phosphoramidites and phosphines for enantioselective Pd^0-catalyzed C–H activation. Usually, this class of ligands is based on C_2-symmetric chiral diol precursors similar to phosphoramidites. Both the chiral core and the aryl substituent on phosphorus can be easily tuned to modulate the catalytic activity.

In the course of their work on cyclopropane C–H arylation (see Scheme 11),[47] Cramer and co-workers tried to apply the developed method involving phosphoramidite **L^9** to the synthesis of the pentacyclic core of BMS-791325, a potential hepatitis C antiviral agent[65] (Scheme 22). Despite the successful use of phosphoramidite **L^9** for the general reaction, further studies revealed that the intramolecular cyclization of cyclopropane **48** was best accomplished in the presence of phosphonite **L^{23}**, possessing the same TADDOL-based backbone as **L^9** but with a

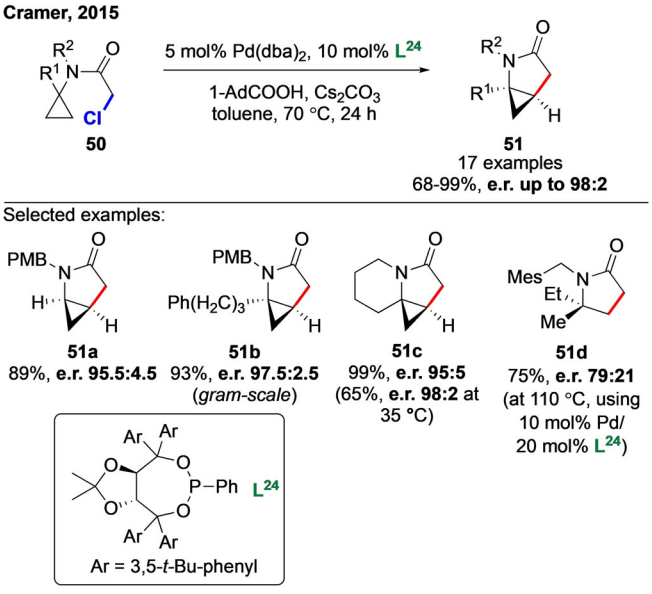


Scheme 22. Synthesis of the BMS-791325 core by C–H arylation employing phosphonite **L^{23}**.

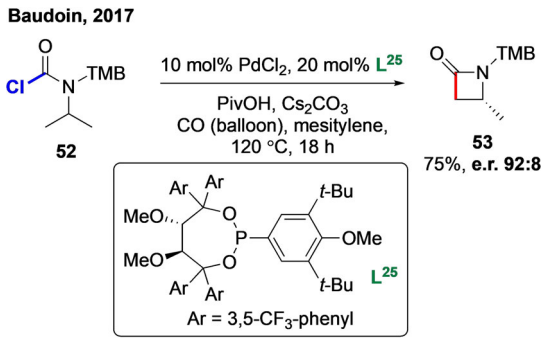
phenyl substituent on the phosphorus instead of the dimethylamino group. This ligand afforded compound **49** in 80% yield and very good enantioselectivity (e.r. 94.5:5.5).

In 2015, Pedroni and Cramer also reported the enantioselective C–H alkylation of cyclopropanes **50** to yield bicyclic γ-lactams **51** (Scheme 23).[66] In this work, the bulkier phosphonite **L^{24}** was the optimal ligand to form azabicyclo[3.1.0]hexanes with a variety of substituents on the cyclopropane ring (**51 a–b**) and with fused rings of different sizes (**51 c**), with high yields and e.r. values. Remarkably, the reaction could be conducted at temperatures as low as 35 °C (**51 c**). However, the challenging desymmetrization of the enantiotopic methyl groups was less efficient (**51 d**).

In 2017, our group employed C(sp^3)–H carbamoylation to synthesize β-lactams (Scheme 24).[67] After extensive screening



Scheme 23. Synthesis of cyclopropane-fused γ-lactams by enantioselective C–H alkylation using phosphonite **L^{24}**. PMB = *p*-methoxybenzyl.



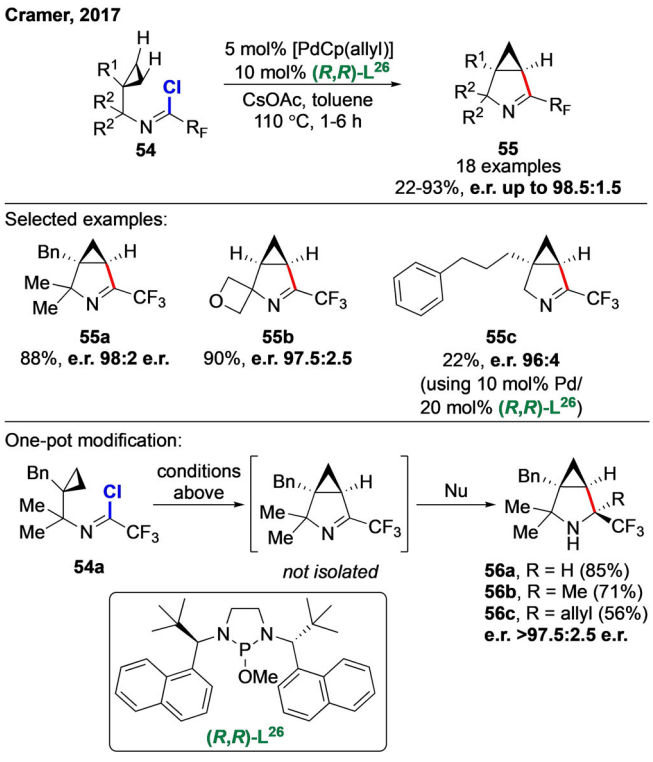
Scheme 24. Enantioselective synthesis of a β-lactam by C–H carbamoylation in the presence of phosphonite **L**^{25}. TMB = 2,4,6-trimethoxybenzyl.

and ligand optimization at the TADDOL backbone and phosphorus aryl substituent, phosphinite **L**^{25} was found to be optimal to provide β-lactam **53** with an e.r. of 92:8. This example further illustrates that the enantioselective desymmetrization of unactivated methyl groups remains challenging.

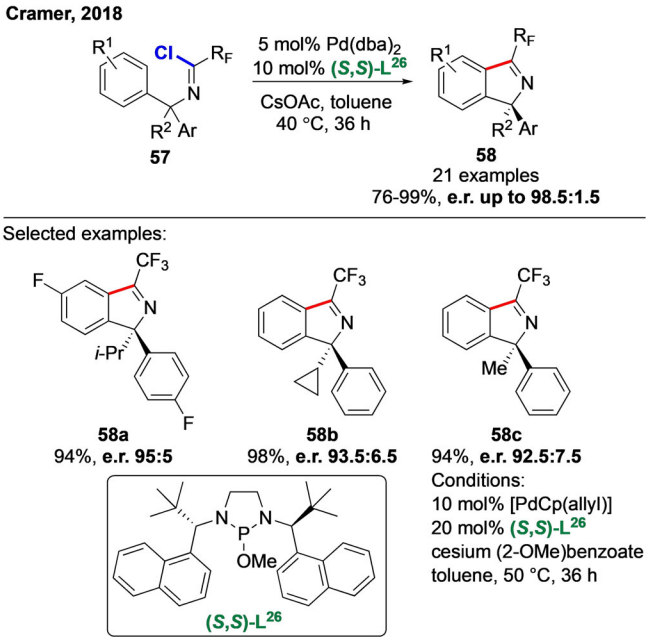
Diazaphospholidines

Diazaphospholidines[68] represent an interesting emerging class of chiral ligands for enantioselective C–H activation. In 2017, Cramer and co-worker reported the application of diazaphospholidine (*R*,*R*)-**L**^{26} to the synthesis of functionalized bicyclic pyrrolines **55** (Scheme 25).[69] Both previously described phosphonites and phosphoramidites failed to provide good enantioselectivities, whereas diazaphospholanes, which are structurally related to N-heterocyclic carbenes (NHCs), excelled, with bulky **L**^{26} being the most efficient. Substrates with an assortment of substituents on the cyclopropane (**55a**, **55c**) and in the α-position to the nitrogen atom (**55b**) were well tolerated. Interestingly, the obtained pyrrolines could be further functionalized in a one-pot fashion, leading to densely functionalized pyrrolidines (**56a**–**c**) in good yields and excellent diastereo- and enantioselectivity.

Later, this approach was further extended by the same group to the desymmetrization of aryl C(sp^2)–H bonds (Scheme 26).[70] By using diazaphospholane (*S*,*S*)-**L**^{26}, they developed a protocol that allows the enantioselective construction of 1*H*-isoindoles bearing quaternary stereocenters. The developed procedure tolerated a variety of substitution patterns on the aryl fragments (**58a**), as well as on the five-membered ring (**58b**). Additionally, with some modifications to the reaction conditions, products with smaller substituents could be formed in good enantioselectivity (**58c**).



Scheme 25. C–H imidoylation of cyclopropanes in the presence of diazaphospholidine **L**^{26} and one-pot functionalization.



Scheme 26. Desymmetrizing C(sp^2)–H functionalization for the synthesis of 1*H*-isoindoles by using diazaphospholidine **L**^{26}.

N-heterocyclic carbenes

NHCs represent a powerful class of ligands for C–H bond activation.[71] Their steric and electronic properties, which are comprehensively discussed elsewhere,[72] show the following features compared with phosphorus ligands:

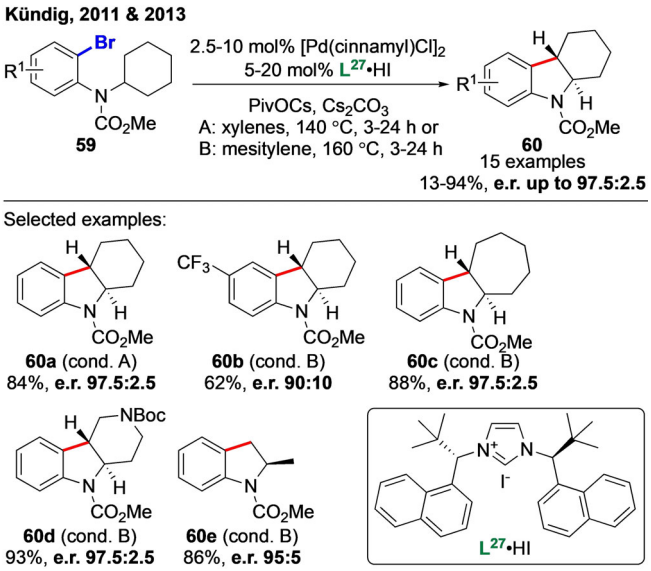
i) The main steric parameter used for NHCs is the buried volume (%V_{bur}), whereas phosphorus ligands are usually classified by their cone or bite angle;

ii) The Tolman electronic parameter, deduced from IR CO stretching frequencies of M(NHC)(CO)$_x$ complexes, such as IrCl(CO)$_2$(NHC), shows much stronger electron-donating properties for NHCs compared with phosphorus ligands;

iii) NHCs form highly stable bonds with transition metals owing to strong σ-donation and significant π-back-bonding. These bonds are usually stronger than with P ligands.

A comparative electronic and steric analysis of NHCs is represented by the Tolman-like map in Figure 3. Values of ν_{CO} are based on calculations by Gusev[73] for $Ni(CO)_3(NHC)$ complexes together with values determined by the Nolan group.[74] NHCs are capable of forming very stable complexes with palladium, which is a particularly interesting feature in the context of the activation of strong C(sp^3)–H bonds, which typically require high temperatures. In addition, thanks to their special electronic and steric properties, they facilitate the different steps of the catalytic cycle. One of the key applications for these ligands is the activation of methylene C(sp^3)–H bonds, a challenging task that only a few catalytic systems are able to perform.

In 2011, Kündig and co-workers pioneered enantioselective Pd^0-catalyzed C(sp^3)–H bond functionalization, establishing a protocol for the enantioselective desymmetrizing arylation of methylene C–H bonds giving rise to fused indolines **60** (Scheme 27).[75] Building on the previously discovered reactivity of C2-symmetric NHCs, initially developed by the groups of Enders and Hermann,[76] in intramolecular α-arylation of amides,[77] they showed that the Pd-NHC complex, formed in situ from imidazolium iodide **L^{27}**•HI, was particularly robust and efficient for this transformation. Through this protocol, fused indolines were synthesized in very good yields and enantioselectivities, and in a *trans*-diastereoselective fashion, despite the employed high temperature (140–160 °C). Varied substitution patterns were tolerated (**60 a**,**b**), as well as both six- and seven-membered (**60 c**) fused rings. The scope was later extended to other fused six-membered rings (**60 d**) and to the desymmetrization of methyl groups (**60 e**), in all cases with excellent enantioselectivities.[78] Detailed DFT calculations were performed, which validated the proposed pivalate-mediated CMD mechanism and reproduced well the experimentally observed stereoselectivities.



Scheme 27. Pd/NHC-catalyzed C(sp^3)–H arylation leading to (fused) indolines.

At the same time, Kündig and co-workers discovered that racemic substrates underwent parallel kinetic resolution (PKR), that is, the parallel transformation of each enantiomer of the starting material into two enantioenriched regioisomers

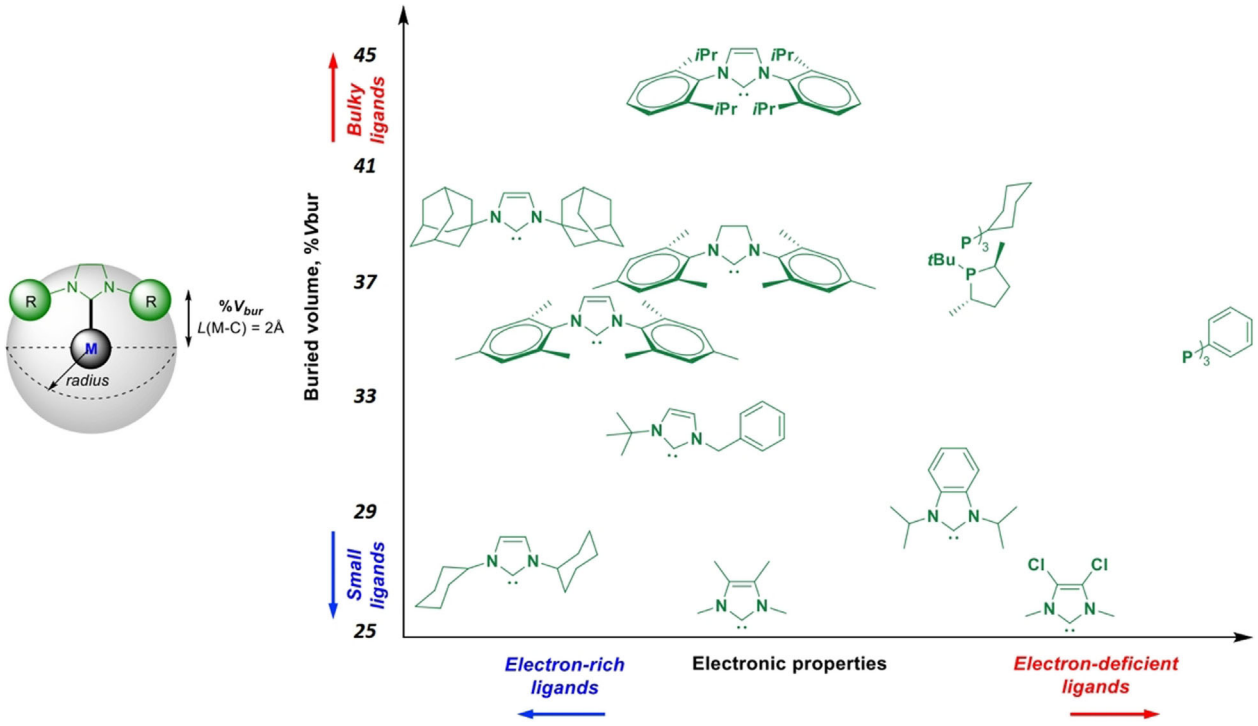
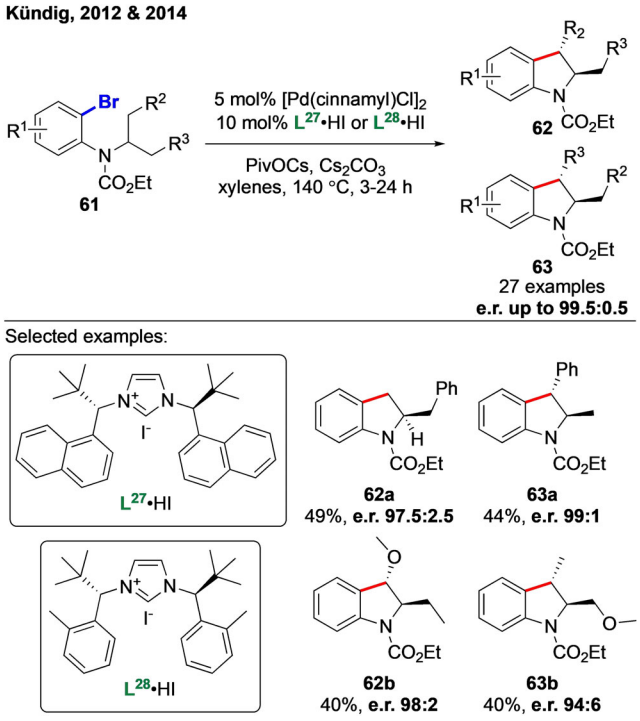


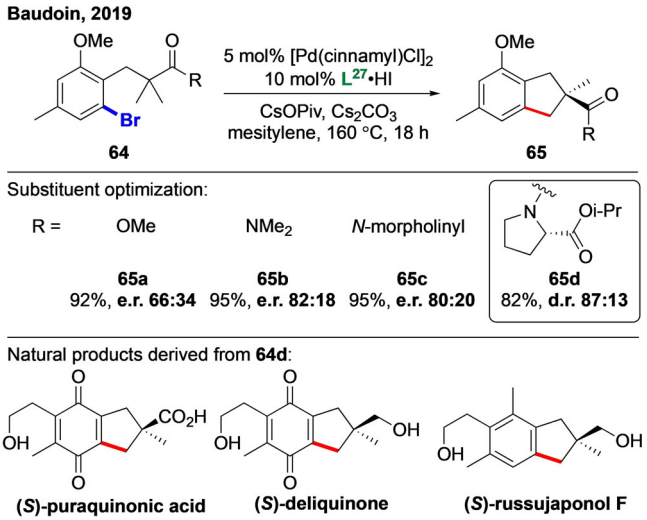
Figure 3. Electronic and steric features of various N-heterocyclic carbenes.

(Scheme 28).[79] Indeed, racemic aryl bromides **61** provided approximately 1:1 mixtures of indoline regioisomers **62** and **63** in almost quantitative yield and high enantiomeric ratios upon differentiation of the two alkyl groups by the catalyst, formed from NHC precursor **L**^{27}•HI or **L**^{28}•HI. This remarkably efficient PKR displayed high enantioselectivities across a broad range of substrates, wherein both primary and secondary C–H bonds were reactive. The observed selectivities were rationalized with the help of DFT calculations.

The desymmetrization of methyl groups by asymmetric C(sp^3)–H arylation was employed as the key step in the enantioselective synthesis of (nor)illudalane sesquiterpenes reported by our group (Scheme 29).[80] (Nor)illudalane sesquiterpenes, such as puraquinonic acid, deliquinone, and russujaponol F, are bioactive secondary metabolites isolated from various species of edible mushrooms, which were shown to induce the differentiation of leukemia HL-60 cells.[81] The aforementioned NHC **L**^{27} was found to be the most efficient chiral ligand for this transformation. The stereoselectivity of the process depended heavily on the nature of the carboxylic group, with a (*S*)-proline-derived amide (**65 d**) providing an enhanced stereoselectivity compared with achiral precursors (**65 a**–**c**). Of note, a matched effect between the (*S*)-prolinamide and the NHC was observed (d.r. 87:13), with the (*R*)-prolinamide/**L**^{27} combination providing a mismatched case (d.r. 66:34). After cleavage of the prolinamide group in intermediate **65 d** and recrystallization to improve the optical purity, the synthesis of the (*S*)-enantiomers of puraquinonic acid, deliquinone, and russujaponol F was completed. This work represented the first application of enantioselective Pd^0-catalyzed C(sp^3)–H activation in natural product synthesis.



Scheme 28. Parallel kinetic resolution in the C(sp^3)–H arylation catalyzed by Pd/NHCs.



Scheme 29. Desymmetrizing C(sp^3)–H arylation with NHC **L**^{27} and application to the total synthesis of (nor)illudalane sesquiterpenes.

Bidentate and Hemilabile Ligands

The vast majority of ligands employed in Pd^0-catalyzed enantioselective C–H functionalization are monodentate. However, the use of bidentate or hemilabile ligands, which have proven efficient in a wide array of other transformations, offers another option to solve challenging problems when monodentate ligands fail. In general, bidentate ligands have a high affinity towards the coordination of metal catalysts, hence stabilizing intermediates and avoiding premature catalyst decomposition. In addition, they allow the suppression of *cis*–*trans* equilibria, which may take place in tricoordinate species with monodentate ligands, hence potentially accelerating the catalytic cycles. Similar to monodentate ligands, the electronic properties of bidentate ligands can be evaluated by comparing IR stretching frequencies of the corresponding nickel carbonyl complexes,[82] or by calculations of bond dissociation energies.[83] In contrast, the steric properties of bidentate ligands are usually expressed as the bite angle,[84] whereas monodentate ligands are usually characterized by the Tolman cone angle.

As mentioned in the Introduction (Figure 1), typical catalytic cycles of Pd^0-catalyzed C–H functionalizations start with oxidative addition, and a further ligand exchange with the active base furnishes complex **II**, which usually undergoes C–H activation via the intramolecular base-induced CMD. However, in the presence of a bidentate ligand, a free coordination site is lacking for the binding of a C–H bond, which is in principle required for its cleavage. However, two main scenarios can be envisaged in this case (Figure 4):

i) The bidentate ligand acts as a hemilabile ligand, which dissociates to form monoligated intermediate **II a**, from which intramolecular CMD can occur in the usual way with an internal base (**III a**) to give the diorganopalladacycle **IV**;

ii) The bidentate ligand remains bonded in a κ^2 mode and C–H activation occurs from a cationic complex **II b** with an external base and by intermolecular CMD (**III b**), as initially proposed by Echavarren, Maseras, and co-workers.[85]

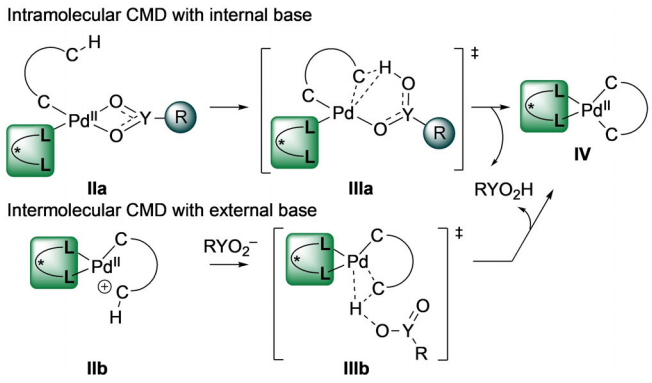


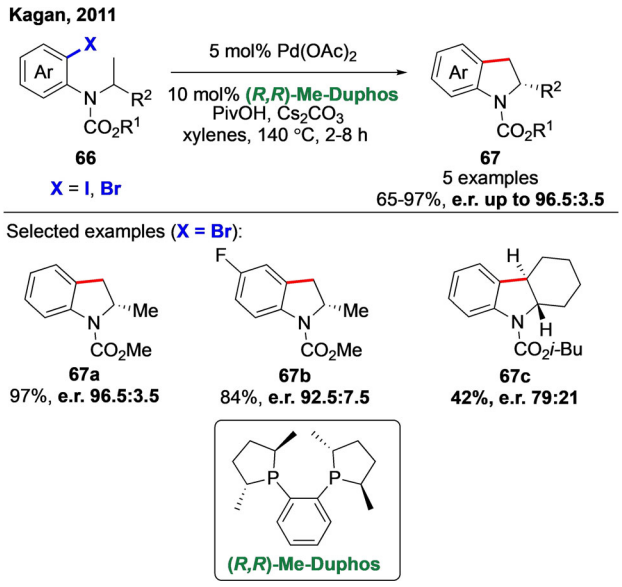
Figure 4. C–H activation with chiral bidentate ligands.

Chiral P,P- and P,P(O)-ligands

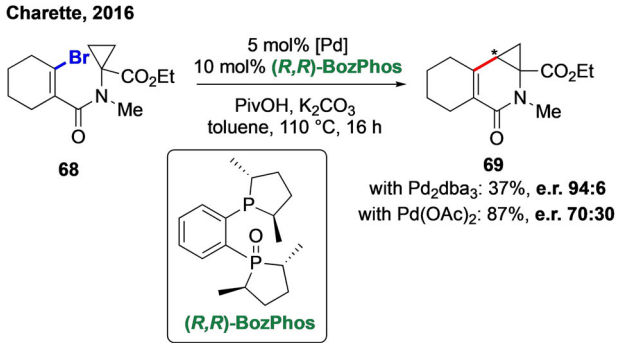
Despite the fact that diphosphine ligands were employed in various Pd-catalyzed C–H activation reactions, their exact role remained unknown for a long time. In 2015, in the context of a mechanistic investigation of Pd^0-catalyzed C–H arylations mediated by Xantphos, Blackmond and co-workers revealed that the monooxidation of the P,P-ligand, which leads to corresponding bis-phosphine mono-oxide (BPMO), is crucial for the formation of the active catalyst.[86] As a result, Xantphos monooxide performs as a hemilabile P,O-ligand, which affords additional coordination for an internal CMD base (Figure 4). As a consequence, and knowing that the reduction of Pd^{II} precatalysts such as $Pd(OAc)_2$ is accompanied by the oxidation of a phosphine in the corresponding monooxide,[87] chiral P,P-ligands reported thereafter in conjunction with a palladium(II) source should not likely be considered as the actual ligands that participate in the catalytic cycle. Therefore, although the involvement of BPMOs as the actual ligands in these reactions has not been unambiguously established, we will present bisphosphine and BPMO ligands together in this section.

In 2011, and concurrent to the work of Kündig[75] and Cramer,[57] Kagan and co-workers reported the enantioselective synthesis of indolines by intramolecular C(sp^3)–H arylation.[88] They employed commercially available (*R*,*R*)-Me-Duphos for the desymmetrization of methyl and cyclohexyl groups and obtained indolines in moderate to good yields and enantioselectivities (Scheme 30). In particular, whereas the desymmetrization of methyl groups provided good results (**67a**,**b**), the desymmetrization of a cyclohexyl group was much less efficient (**67c**), in contrast to examples by Kündig and Cramer.

In 2016, Charette and co-workers employed the BPMO (*R*,*R*)-BozPhos derived from (*R*,*R*)-Me-Duphos for the synthesis of a fused cyclopropane via C–H alkenylation (Scheme 31).[48] The catalyst formed from Pd_2dba_3 and (*R*,*R*)-BozPhos afforded the product **69** in 94:6 e.r., albeit with a low yield. Of note, when $Pd(OAc)_2$ was employed, the reactivity was significantly improved but the enantioselectivity decreased. BozPhos, similar to other P,O-ligands, possesses two main properties: 1) being an electron-rich ligand, it may allow the oxidative addition of challenging substrates, such as aryl chlorides; 2) it may adopt a monodentate or bidentate binding mode, and in the latter



Scheme 30. Synthesis of (fused) indolines by C(sp^3)–H arylation by using (*R*,*R*)-Me-Duphos.

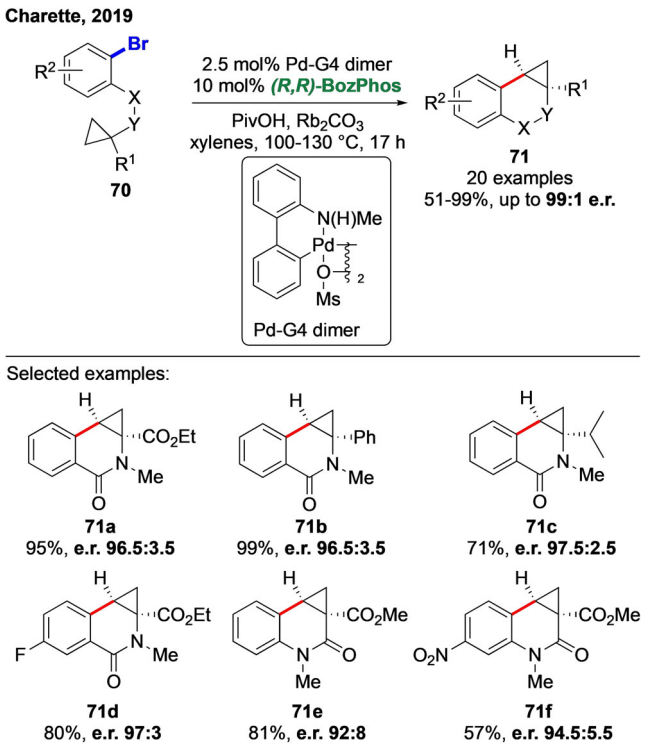


Scheme 31. Initial studies with BozPhos as the chiral ligand for intramolecular C–H alkenylation.

case possesses a soft (phosphorus) and a hard (oxygen) coordinating atom.

Three years later, the same group reported the application of BozPhos to the enantioselective synthesis of cyclopropane-fused dihydroisoquinolones and dihydroquinolones (Scheme 32).[89] They used benzamide **70a** as a model substrate for the reaction optimization. Several Pd sources were evaluated and Buchwald's fourth-generation palladium dimer (Pd-G4)[90] resulted in an excellent yield and enantioselectivity. This reaction yielding dihydroisoquinolones (**71a**–**d**) tolerated a variety of substituents at the aromatic moiety as well as at the cyclopropane. Interestingly, it could also be employed to synthesize dihydroquinolones with a very good enantioselectivity (**71e**,**f**).

In 2012, Shintani, Hayashi, and co-workers reported an enantioselective approach towards Si-stereocenters via C(sp^2)–H arylation/desymmetrization of triarylsilanes with the electron-rich Josiphos-type ligand **L**[29] to yield dibenzosiloles (**73**) with high enantioselectivities (Scheme 33a).[91] Interestingly, an isomer



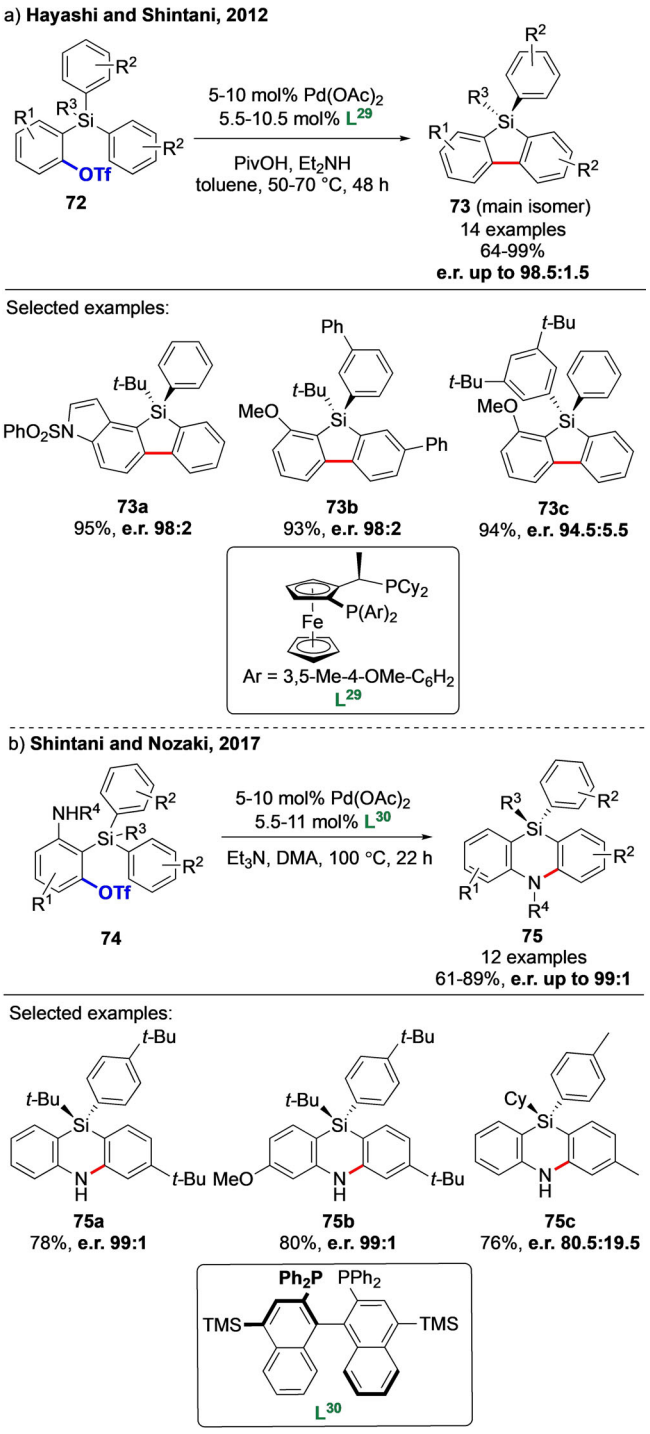
Scheme 32. Application of (*R*,*R*)-BozPhos to the enantioselective C–H arylation of cyclopropanes.

arising from a 1,5-Pd shift was also formed under the optimized conditions as a minor product. Among various products obtained through this method, dibenzosilole **73 a** derived from 5-indolyl triflate was obtained in 95 % combined yield and 98:2 e.r. Moreover, a substrate containing *meta*-phenyl groups underwent C–H arylation at the less hindered site (**73 b**).

In 2017, as follow-up research, Nozaki, Shintani, and coworkers reported the enantioselective synthesis of Si-stereogenic 5,10-dihydrophenazasilines **75** via enantioselective 1,5-palladium migration and intramolecular C–N bond formation, employing TMS-substituted (*R*)-BINAP (**L^{30}**) as the chiral ligand (Scheme 33 b).[92] Various substituents were well tolerated on the different aromatic rings (**75 a**,**b**), as well as on the silicon atom (**75 c**). Mechanistic investigations indicated that the 1,5-palladium migration step is enantiodetermining but not turnover-limiting.

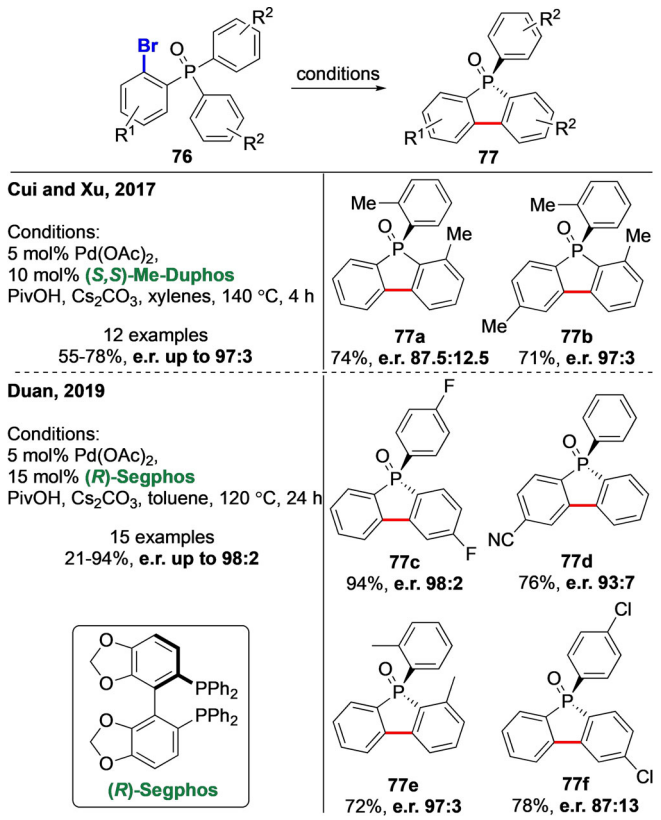
In 2017 and 2019, the groups of Cui and Xu[93] and Duan[94] developed a procedure for the enantioselective construction of P-stereogenic dibenzophospholes **77** (Scheme 34). Although very similar, these two approaches employed different diphosphine ligands, that is, (*S*,*S*)-Me-Duphos in the report by Cui and Xu and (*R*)-Segphos in the work by Duan, which both afforded high enantioselectivities, although a somewhat higher functional group tolerance was demonstrated by the latter (**77 d**, **77 f**).

In addition to carbon, silicon, and phosphorus stereocenters, bis-phosphines have also proven to be efficient chiral ligands for the generation of metallocenes with planar chirality. In 2014, the groups of Q. Gu and You[95] and Kang and Z. Gu[96] in-

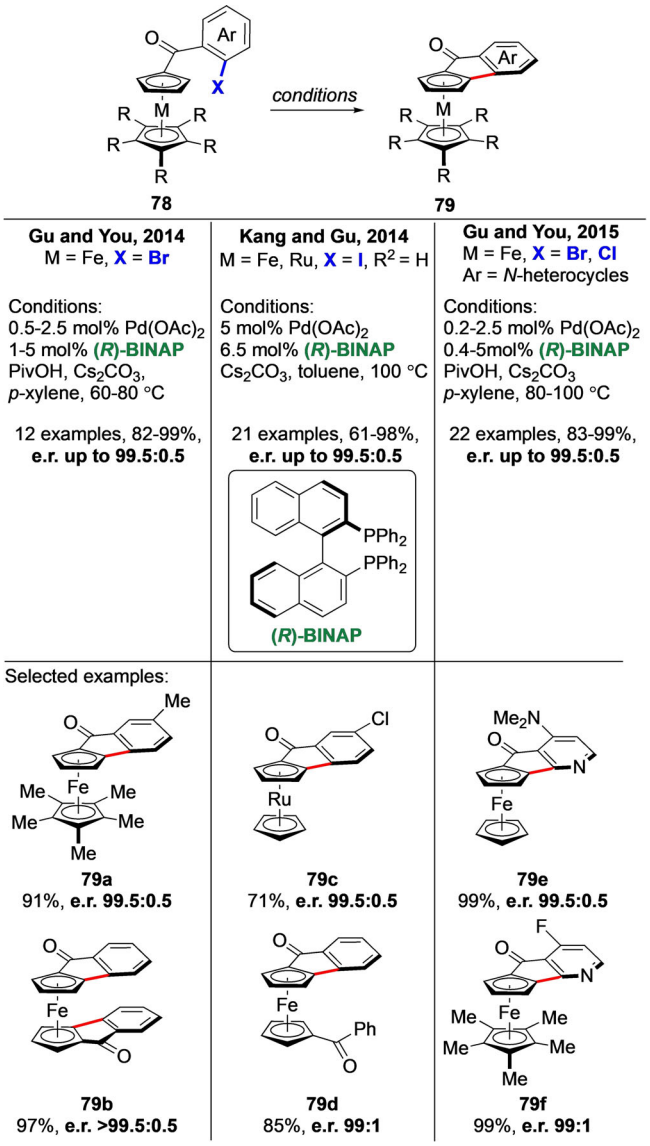


Scheme 33. Formation of Si-stereogenic centers by C(sp^2)–H arylation (a) and 1,5-Pd shift/C(sp^2)–H amination (b) using chiral diphosphines.

dependently reported the intramolecular Pd^0-catalyzed C(sp^2)–H arylation of metallocenes in the presence of (*R*)-BINAP (Scheme 35). In Gu and You's report, ferrocenes possessing a pentamethylcyclopentadienyl (Cp*) ring were also suitable reactants, giving rise to the arylated product **79 a** in excellent enantioselectivity. This result highlights the advantages of the method, as the same type of product could not be achieved through a previously reported Pd^{II}-catalyzed C–H arylation



Scheme 34. Synthesis of P-stereogenic dibenzophospholes by using chiral bis-phosphines.



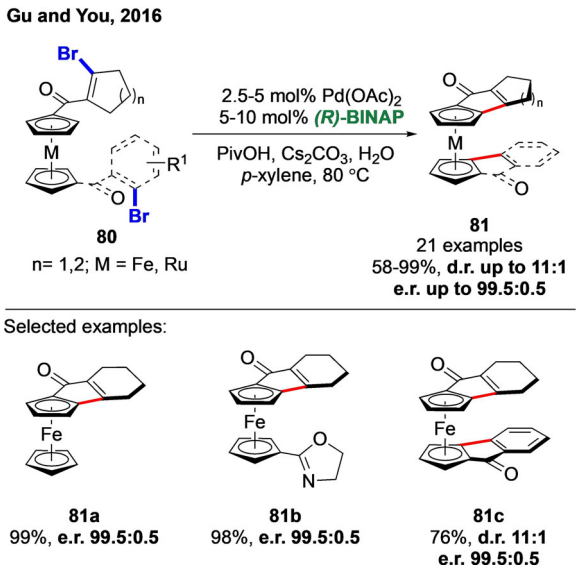
Scheme 35. (*R*)-BINAP-mediated enantioselective routes to metallocenes with planar chirality.

method employing mono-N-protected amino acid ligands (MPAAs).[97] In addition, C_2-symmetric planar chiral ferrocene **79 b** was obtained in excellent yield and enantioselectivity. The protocol developed by Kang and Gu allows derivatization of ruthenocenes in addition to ferrocenes, such as **79 c**, and tolerates other unprotected carbonyl moieties (**79 d**). The Gu–You group later extended this methodology towards N-heterocyclic derivatives at very low catalyst loadings (0.2 mol %).[98] For instance, this strategy provided an efficient access to a planar chiral DMAP **79 e**. Substrates with a fluorine atom on the pyridine ring (**79 f**) were also highly reactive under the optimized conditions. Moreover, the obtained products could be easily transformed into pyridine *N*-oxides, which were used in the asymmetric opening of *meso* epoxides with up to 83:17 e.r.

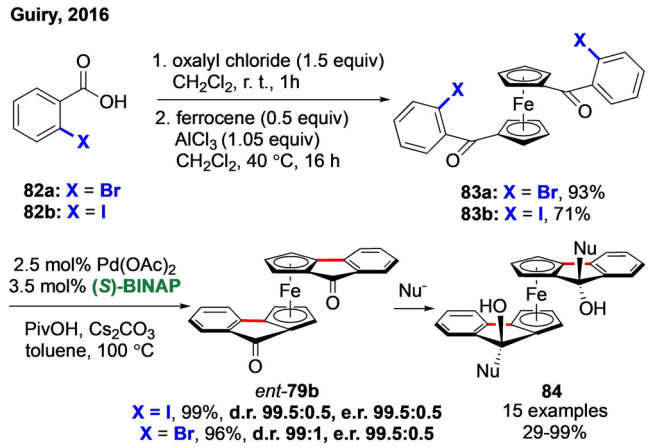
In 2016, the same group additionally showed that (*R*)-BINAP is a suitable ligand for the related intramolecular C(sp^2)–H alkenylation reaction (Scheme 36).[99] The addition of water in the reaction mixture was found to be crucial for the reproducibility, hence providing product **81 a** in 99 % yield and 99.5:0.5 e.r. Products with coordinating groups such as oxazoline (**81 b**) were obtained in excellent yield and enantioselectivity. Furthermore, the enantioselective and diastereoselective synthesis of planar chiral ferrocenes (**81 c**) was achieved via a cascade of C–H alkenylation and arylation.

Shortly after, Guiry and co-workers employed a similar methodology for the synthesis of novel chiral ferrocenyl diols (**84**, Scheme 37).[100] They applied cheap and readily available starting materials **82 a**,**b** to develop a high-yielding, chromatography-free procedure towards the synthesis of ferrocene derivative *ent*-**79 b**. The diketone *ent*-**79 b** underwent nucleophilic attack by 15 different nucleophiles such as sodium borohydride, organolithium and Grignard reagents, or the Ruppert–Prakash reagent to generate the corresponding diols **84**. The latter were successfully employed as chiral catalysts in hetero-Diels–Alder reactions.

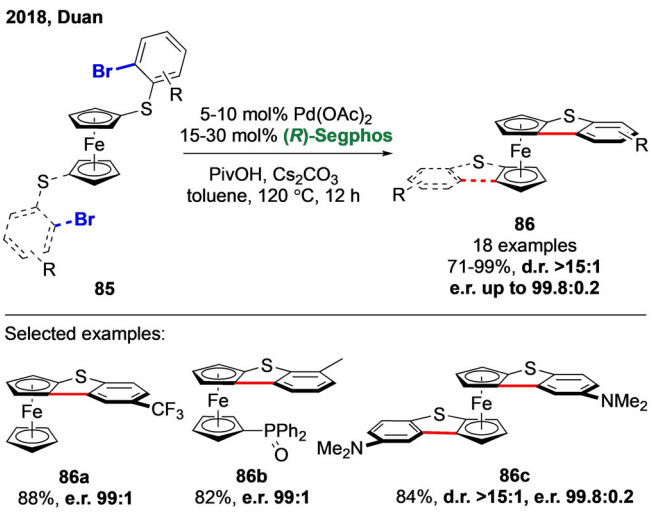
Finally, Duan and co-workers reported the enantioselective C–H arylation of ferrocenyl aryl thioethers **85** for the synthesis of planar chiral benzothiophene-fused ferrocenes **86** (Scheme 38).[101] During the optimization study, replacing BINAP with the more electron-rich bis-phosphine Segphos increased the yield and enantioselectivity. Various electron-rich or electron-deficient groups on the aryl ring were well tolerated (**86 a**,**b**), and a double C–H arylation resulted in the formation of **86 c** in 84 % yield, high diastereo- and enantioselectivity.



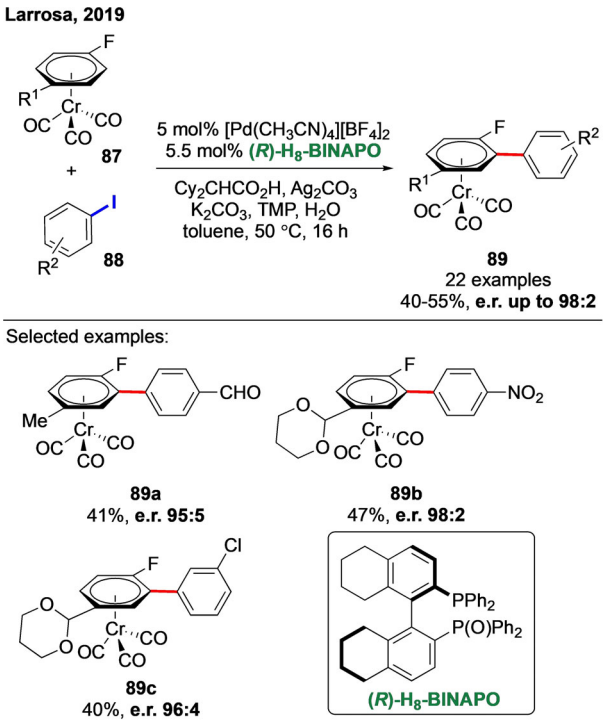
Scheme 36. Diastereo- and enantioselective C–H alkenylation of ferrocenes employing (*R*)-BINAP.



Scheme 37. Synthesis of chiral ferrocenyl diols by using a double C(sp^2)–H arylation in the presence of (*S*)-BINAP.



Scheme 38. Synthesis of planar chiral benzothiophene-fused ferrocenes by C(sp^2)–H arylation using Segphos.



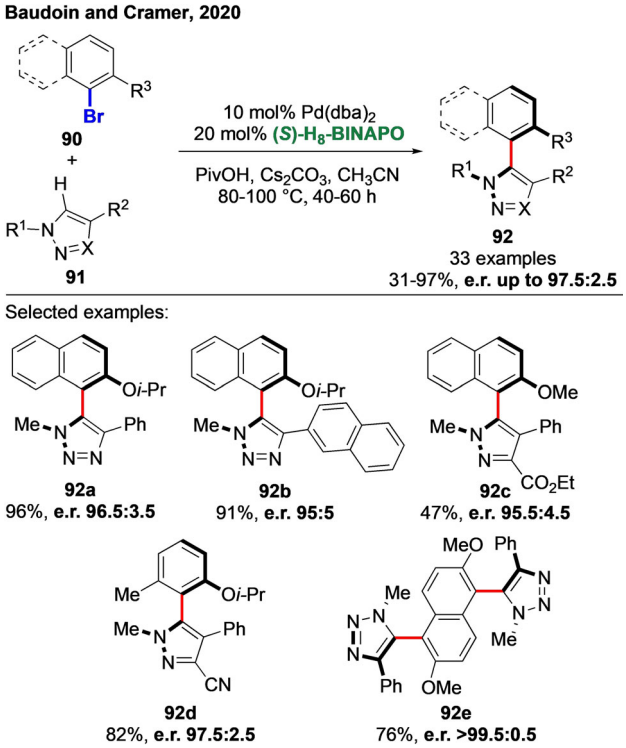
Scheme 39. C–H arylation of (η^6-arene)chromium complexes by using H_8-BINAPO.

Of note, the authors employed the bidentate P,S-ligand, obtained by reduction of phosphine oxide **86b**, for Suzuki–Miyaura cross-coupling between substituted 2-bromonaphthalene and *o*-methoxyphenylboronic acid, to give the corresponding axially chiral biaryl product in moderate enantioselectivity (e.r. 72.5:27.5).

In 2019, Larrosa and co-workers reported the first Pd^0-catalyzed *intermolecular* enantioselective C–H functionalization of metallocenes (Scheme 39).[102] Prochiral (η^6-arene)chromium complexes **87** underwent enantioselective C–H arylation with aryl iodides in the presence of a chiral BPMO ligand to provide planar chiral compounds. During the optimization of the reaction conditions, it was found that Segphos, possessing a smaller bite angle than BINAP, led to a decreased enantioselectivity. On the other hand, DIOP, possessing a larger bite angle, also led to a reduced enantiomeric ratio, suggesting that biarylphosphines were the ligands of choice for this transformation. Finally, the optimal ligand was found to be H_8-BINAPO. The developed conditions were compatible with a high variety of functional groups and substitution patterns on both reaction partners (**89a**–**c**). Mechanistic studies showed that the reaction proceeds through a Pd/Ag bimetallic double catalytic cycle where the C–H activation is carried out by Ag and not by Pd.

In 2020, Baudoin, Cramer, and co-workers reported the straightforward construction of stereogenic biaryl axes by *intermolecular* C–H arylation of heteroarenes, again by using H_8-

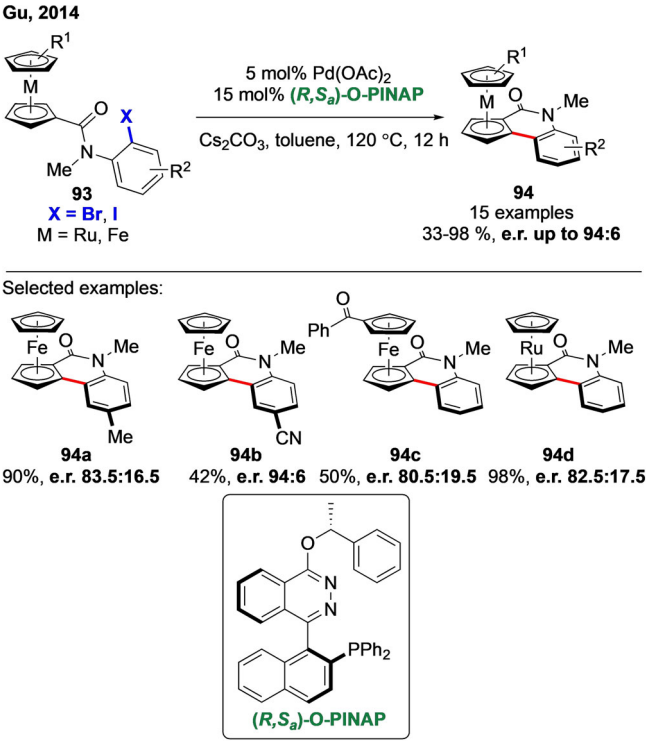
BINAPO as the chiral ligand.[103] This reaction provided atropisomeric (hetero)biaryls in excellent yield and e.r. values of up to 97.5:2.5 (Scheme 40). This method was found to be efficient for a range of disubstituted triazoles (**92a**,**b**) and trisubstituted pyrazoles (**92c**,**d**). Moreover, various sterically hindered aryl bromides could be employed, including naphthol (**92a**–**c**) and phenol (**92d**) derivatives. The reported conditions also enabled a double atroposelective C–H arylation, providing control over two stereogenic axes (**92e**) with outstanding diastereo- and enantioselectivity. A rough correlation was found between the enantioselectivity and the ligand biaryl dihedral angle, indicating that reductive elimination is the enantiodetermining step whereas a kinetic study revealed that the C–H bond cleavage is rate-determining.



Scheme 40. Atropo-enantioselective synthesis of (hetero)biaryls with H_8-BINAPO as the chiral ligand.

Chiral P,N-ligands

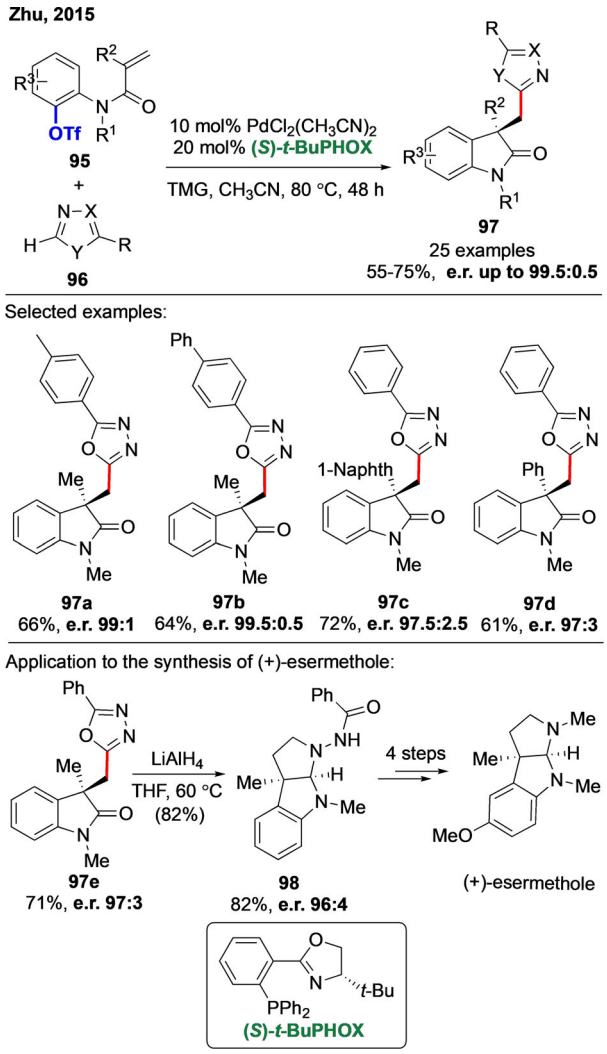
Bidentate phosphorus–nitrogen ligands provide an interesting handle to tune the electron density and steric environment of the metal center.[104] In 2014, Gu and co-workers reported that Carreira's (R,S_a)-*O*-PINAP[105] was a suitable ligand for the intramolecular C–H arylation of 2-halophenylferrocene carboxamides **93** towards quinolinometallocenes **94** with planar chirality (Scheme 41).[33] The products were generally obtained in moderate enantioselectivity. In addition to ferrocenes (**94a**–**c**), ruthenocenes were also competent substrates, providing the corresponding product **94d** in excellent yield and with an e.r. of 82.5:17.5.



Scheme 41. Synthesis of planar chiral quinolinometallocenes by using a chiral P,N-ligand.

In 2015, Zhu and co-workers reported the first asymmetric domino Heck/intermolecular direct arylation towards the synthesis of 3,3-disubstituted oxindoles bearing a quaternary stereocenter (Scheme 42).[106] Different classes of chiral ligands were examined, and the authors discovered that the PHOX-type ligands[107] provided a superior reactivity. (*S*)-*t*BuPHOX was selected as the optimal ligand in combination with $PdCl_2(CH_3CN)_2$ and 1,1,3,3-tetramethylguanidine (TMG) as the base, providing outstanding enantioselectivities towards 2-aryloxadiazoles (**97**). In this case, the carbopalladation step occurring prior to C–H activation is the enantiodetermining step generating the quaternary stereocenter. This domino reaction afforded the corresponding oxindole products (**97a**–**d**) in good yield and excellent enantioselectivity. This method was applied to the enantioselective synthesis of the alkaloid (+)-esermethole. The reductive cyclization of oxindole **97e** (e.r. 97:3), mediated by $LiAlH_4$ at 60 °C, provided the rearranged skeleton **98**, found in the natural product, in 82% yield.

Two years after their report on the first enantioselective Catellani reaction (see Scheme 10),[42] Gu and co-workers established efficient conditions for the atropo-enantioselective synthesis of axially chiral biaryls **102** by a Catellani-type reaction between a naphthyl bromide (**99**), boronic acid (**100**), and chloromethyl ether (**101**; Scheme 43).[108] In contrast to the previous Catellani reaction where carbopalladation was enantiodetermining, the enantiodetermining step of the current reaction is either the transmetalation between the naphthylpalladium intermediate and boronic acid **100** or the subsequent reductive elimination. A thorough ligand screening revealed the su-

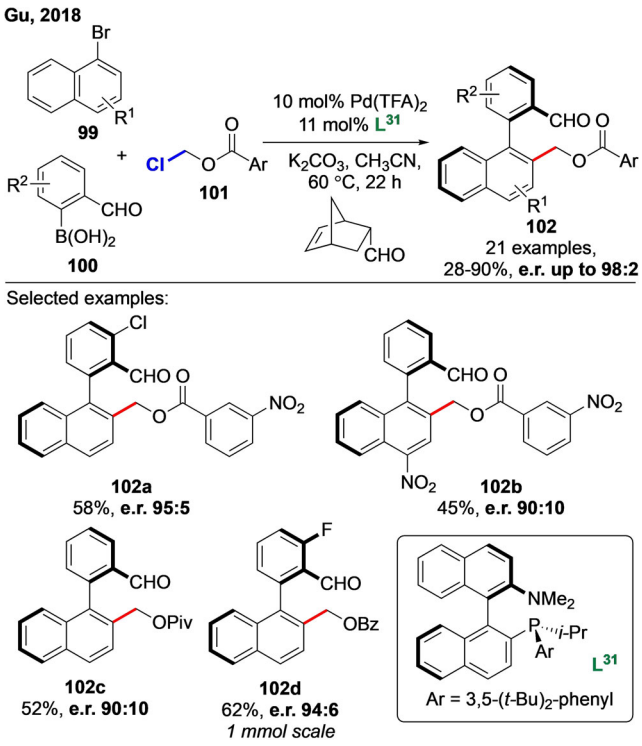


Scheme 42. Enantioselective domino Heck/intermolecular C–H arylation assisted by (*S*)-*t*BuPHOX.

perior activity of phosphine **L**^{31} bearing both a stereogenic axis and a stereogenic phosphorus atom. In combination with a norbornene carboxaldehyde analog, this ligand showed very good levels of enantioselectivity across a number of biaryl products. A number of functional groups were well tolerated (**102 a**–**c**) and scalability was demonstrated (**102 d**). The carbaldehyde and primary alcohol groups in the products could be further transformed without loss of enantiopurity, hence opening the way to interesting synthetic applications.

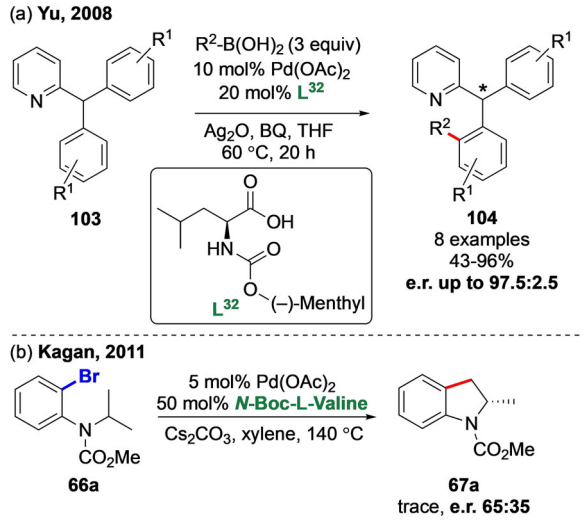
Chiral Bases and Bifunctional Ligands

In the late 1970s, Sokolov had already uncovered the role of acetate anions in the cyclopalladation of ferrocenes, hence prefiguring the now well-established CMD mechanism.[109] Moreover, the use of *N*-acetylvaline led to enantioenriched palladacycles with up to 79% *ee*, which showed for the first time that MPAAs can act both as chiral ligands and active bases in enantioselective C–H activation.[110] In 2008, Yu and co-workers reported the first catalytic enantioselective Pd^{II}-catalyzed C(sp^2)–



Scheme 43. Atropo-enantioselective Catellani reaction by using P,N-ligand **L**^{31}.

H activation in the presence of MPAAs (Scheme 44 a).[111] This discovery opened a prolific area in Pd^{II}-catalyzed enantioselective C–H activation, with the development of new generations of bifunctional ligands.[112] In addition, in the course of the previously mentioned work from Kagan and co-workers (see Scheme 30),[88] these authors discovered that the indoline product **67 a** was formed in trace amounts but with a significant e.r. of 65:35 by using Pd(OAc)$_2$ and *N*-Boc-L-valine without an ancillary ligand (Scheme 44 b). In addition to Yu's investiga-

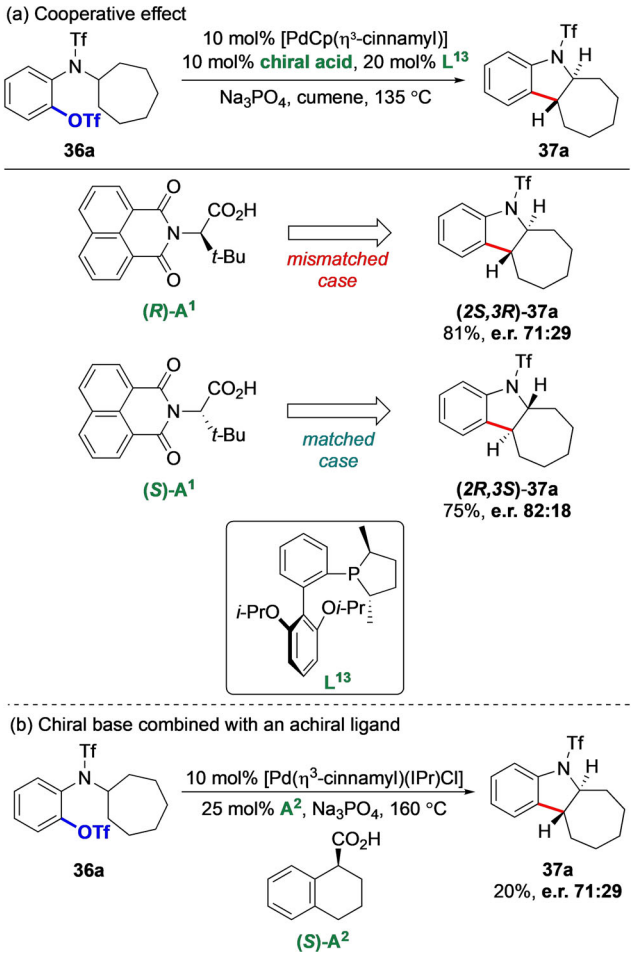


Scheme 44. Pioneering work on the use of chiral carboxylates in Pd-catalyzed C–H activation.

tions, this result opened the way for the use of chiral bases instead of chiral ligands in Pd^0-catalyzed enantioselective C–H activation.

Chiral bases

Enantioselective C–H activation reactions occurring through an enantiodetermining CMD mechanism provide several opportunities for the enhancement of reactivity and selectivity. In addition to modifications of the ancillary ligand, introducing stereogenic elements on the active base should afford new handles for the control of enantioselectivity. In 2012, Cramer and co-workers hypothesized that chiral carboxylates could act synergistically with chiral ligands to enhance the enantioselectivity in Pd^0-catalyzed transformations (Scheme 45).[57] Indeed, the (*S*) enantiomer of chiral carboxylic acid **A**[1] showed a matched effect with chiral phosphine **L**[13], whereas the (*R*) enantiomer led to a mismatched situation. Moreover, carrying out the corresponding reaction in the presence of (*S*)-1,2,3,4-tetrahydro-1-naphthoic acid **A**[2] and an achiral NHC ligand (IPr), they isolated the indoline product **37 a** with a low yield but substantial enantio-enrichment (e.r. 71:29), hence confirming carboxylates as promising chiral bases for such reactions.

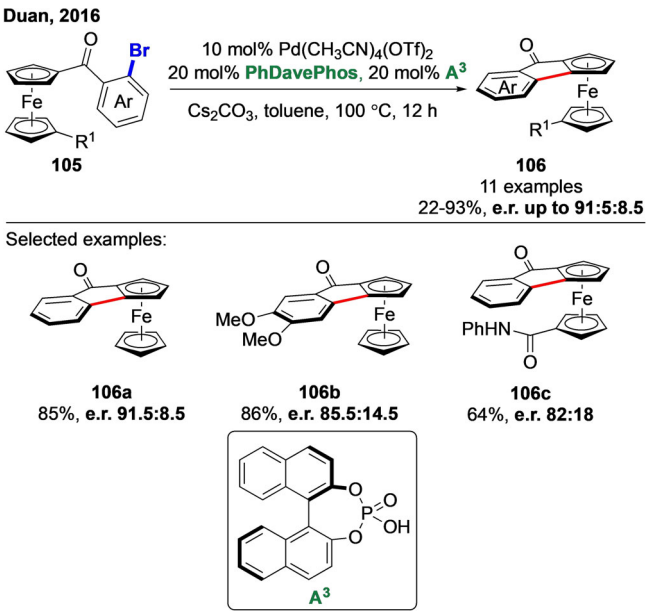


Scheme 45. Effect of chiral carboxylates in conjunction with chiral and achiral ligands in enantioselective C(sp^3)–H arylation.

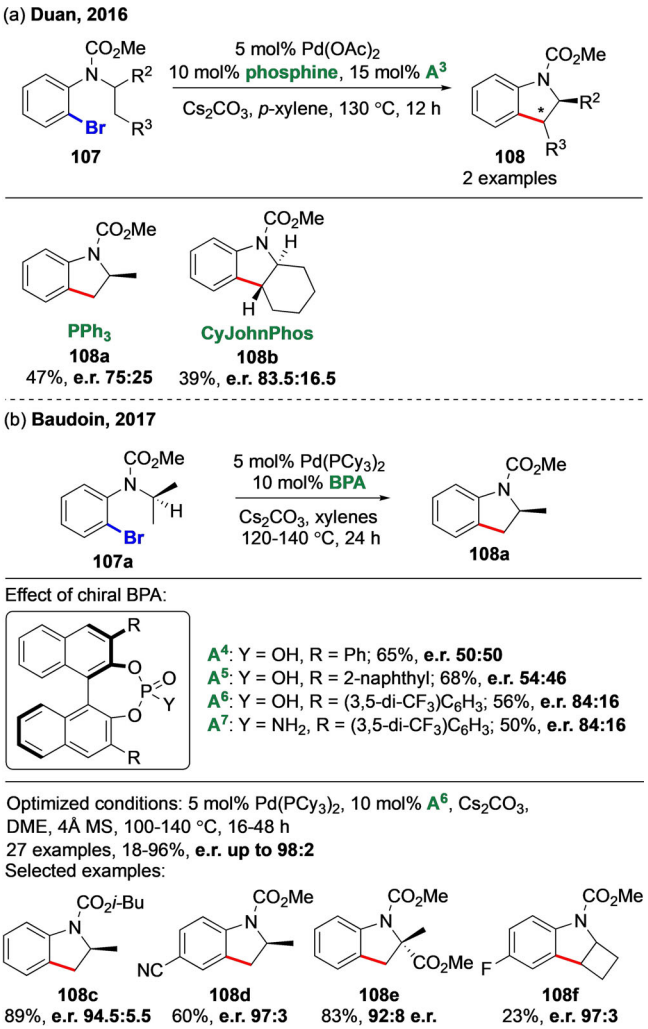
Another promising class of chiral bases for enantioselective Pd^0-catalyzed C–H activation is constituted by chiral BINOL-derived phosphates.[113] Despite the fact that chiral phosphoric acids are widely used in asymmetric organocatalysis,[114] the application of their conjugate base in enantioselective C–H activation remained unknown until 2015, when Duan and co-workers reported the first example of enantioselective Pd^{II}-catalyzed C–H activation in the presence of BINOL-derived phosphoric acids (BPAs) and amides, with moderate enantioselectivities.[115] Shortly after, the groups of Duan[116] and Baudoin[117] independently reported enantioselective Pd^0-catalyzed C–H arylation reactions in the presence of chiral BPAs and achiral phosphine ligands. The former mainly focused on C(sp^2)–H arylations whereas the second focused on C(sp^3)–H arylations. Duan and co-workers were the first to observe that the combination of a commercially available biarylphosphine and a chiral BPA is a great tool for the intramolecular C(sp^2)–H arylation of ferrocenes (Scheme 46).[116] A small library of planar chiral ferrocenes (**106**) were indeed obtained in moderate to excellent yields and up to 91.5:8.5 e.r., by using PhDavePhos as the ligand [PhDavePhos = 2-diphenylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl], BPA **A**[3] as the precursor of the active chiral phosphate, and $Pd(CH_3CN)_4(OTf)_2$ as the palladium source (Scheme 46).

In the same article, Duan and co-workers disclosed their attempts to perform enantioselective C(sp^3)–H arylation towards the synthesis of indolines **108** (Scheme 47 a).[116] Application of the commercially available CyJohnPhos [CyJohnPhos = 2-(dicyclohexylphosphino)biphenyl] or PPh_3 in conjunction with chiral BPA **A**[3] and $Pd(OAc)_2$ as the palladium source resulted in moderate yields and enantioselectivities (two examples).

A more comprehensive study was later published by Baudoin and co-workers (Scheme 47 b).[117] By using the well-defined palladium complex [$Pd(PCy_3)_2$], they showed that 3,3′-dis-



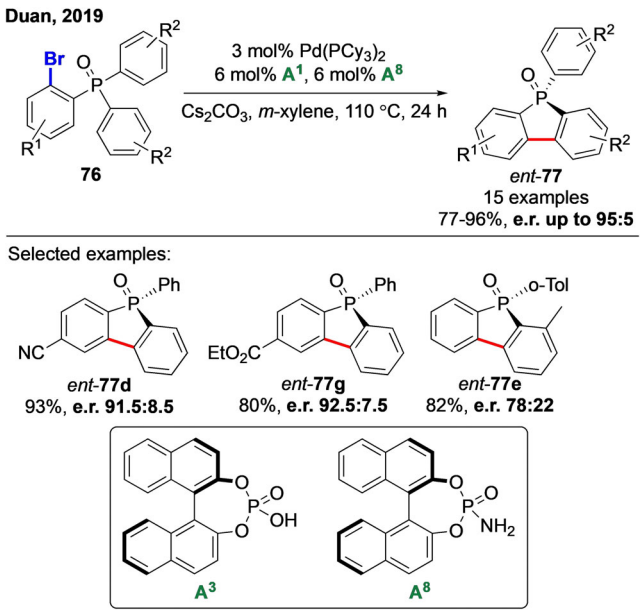
Scheme 46. Chiral phosphate-assisted C(sp^2)–H arylation towards ferrocenes with planar chirality.



Scheme 47. Effect of chiral carboxylates in conjunction with chiral and achiral ligands in enantioselective C(sp^3)–H arylation.

ubstituted BPAs were required to achieve high enantioselectivity in this transformation. In particular, CPA **A⁶** was found to be the optimal precatalyst, and in combination with stoichiometric cesium carbonate and in the presence of molecular sieves, N-protected indolines **108** were obtained in up to 96% yield and 98:2 e.r. The developed conditions tolerated a great variety of functional groups (**108c**,**d**) and more bulky products with a tetrasubstituted stereocenter were also efficiently accessed (**108e**). Interestingly, the rare cyclobutane-fused indoline **108f** could be synthesized, albeit with a much reduced yield. Of note, they also observed a modest kinetic resolution from one racemic substrate (31%, e.r. 73:27), different to the PKR reported by Kündig (see Scheme 28).[79]

In addition to using SegPhos as a chiral ligand for the synthesis of P-stereogenic compounds through aryl desymmetrization (see Scheme 34), Duan and co-workers reported the use of a chiral base in combination with an achiral phosphine (Scheme 48).[94] They observed high levels of stereoinduction for unsubstituted BINOL-derived acids and amides in combination with the well-defined $Pd(PCy_3)_2$ complex, and showed that, in this case, increasing the steric hindrance on the bi-



Scheme 48. Combined catalytic system for the synthesis of P-stereogenic compounds by desymmetrizing C–H arylation.

naphthyl scaffold had a negative impact on the enantioselectivity. Furthermore, the phosphine ligand did not have a major influence on the enantioselectivity, as an e.r. of 91:9 was observed when using $Pd(CH_3CN)_2Cl_2$ as the Pd source and without added phosphine. Further optimization of the reaction conditions showed that a 1:1 combination of **A³** and **A⁸** resulted in a significant enhancement of the enantioselectivity, and that the catalyst loading could be reduced.

Bifunctional ligands

In previous chapters, we discussed the application of the chiral ancillary ligand/achiral base and chiral base/achiral ligand approaches in enantioselective reactions wherein the C–H activation step is enantiodetermining and occurs through the CMD mechanism. An emerging alternative approach consists of designing so-called bifunctional ligands combining these two elements in a single chiral catalyst (Figure 5). Pioneered by the Yu group, this methodology is more developed for enantioselective Pd^{II}-catalyzed reactions, employing MPAAs and more

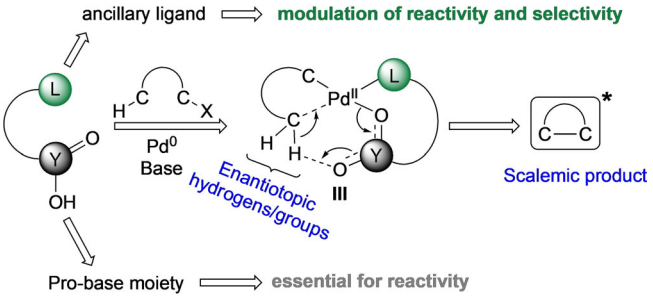
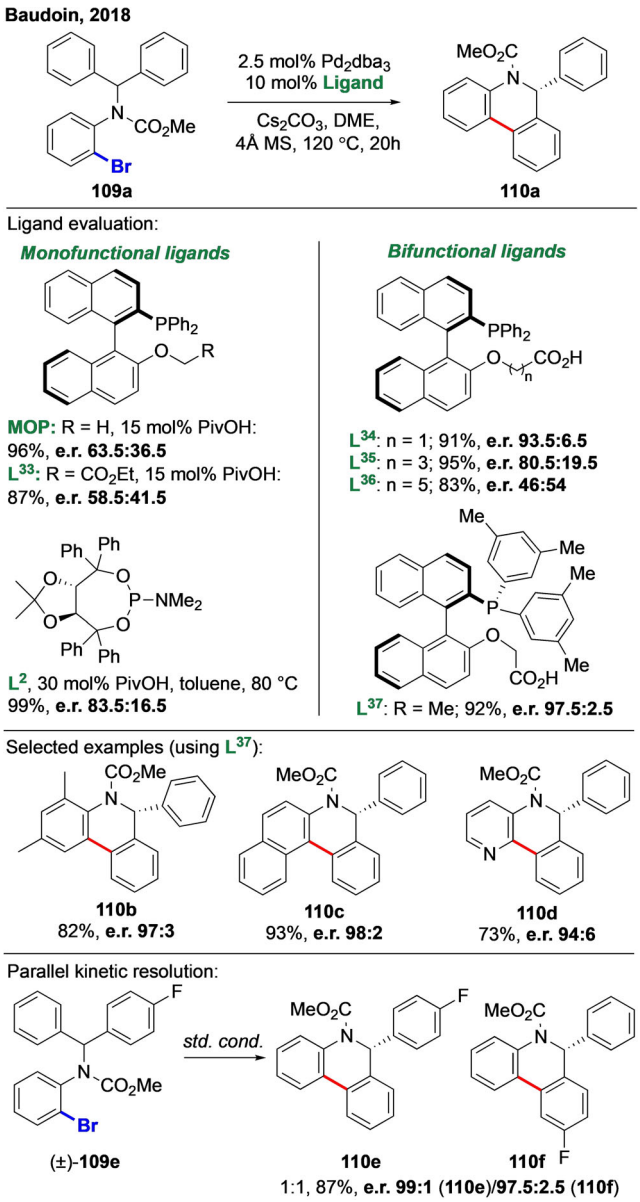


Figure 5. Bifunctional ligands in Pd^0-catalyzed enantioselective C–H functionalization.

recent generation ligands.[6d,112] Mechanistic investigations of MPAA-assisted C–H activation revealed that both the nitrogen atom and the carboxyl moiety coordinate palladium, and that the C–H bond cleavage may occur through two different pathways, called "internal ligand-assisted" and "external base-assisted".[118] The former involves proton abstraction by the N-protecting group (carbamate or amide) whereas in the latter an external base such as acetate assists the deprotonation.

In contrast to Pd^{II} catalysis, the use of bifunctional ligands in Pd^{0}-catalyzed C–H activation has remained unknown for a long time. In 2018, our group reported the first example of Pd^{0}-catalyzed intramolecular C–H arylation using a bifunctional ligand.[119] The design of the latter was based on MOP-type ligands,[120] with a chiral binaphthyl scaffold substituted on one side with a phosphine and on the other with a carboxylic acid (Scheme 49). Monofunctional ligands such as MOP, an ester-substituted MOP (**L**[33]), but also other classic chiral ligands such as TADDOL-based phosphoramidite **L**[2], BINAP, and NHCs, provided lower enantioselectivities in combination with an external carboxylic acid. Further investigations revealed that the distance between the carboxylic group and the binaphthalene scaffold was important for the enantioselectivity (**L**[34]–**L**[36]), with an optimum for MOP–acetic acid hybrid ligand **L**[34]. Additional adjustments of the phosphorus aryl substituents allowed not only the yield to be improved, but also the enantioselectivity to be increased (**L**[37], e.r. 97.5:2.5). A control experiment with the potassium salt of **L**[37] in stoichiometric amount without added carbonate furnished a similar result, hence further indicating the bifunctional nature of the ligand. With the optimal conditions, a great variety of 5,6-dihydrophenantridines **110** were obtained in good yield and excellent enantioselectivity, thus highlighting the benefit of bifunctional ligands for Pd^{0}-catalyzed C–H activation. The reaction tolerated a great deal of substituents on the different aromatic rings (**110 b**–**d**). Finally, racemic substrates (e.g., **109 e**), which contain three different aryl rings, were reacted and 1:1 mixtures of highly enantioenriched regioisomeric products (**110 e**–**110 f**) were obtained, hence demonstrating that the current catalytic system is also capable of performing efficient parallel kinetic resolution (PKR).



Scheme 49. Bifunctional ligands in desymmetrizing enantioselective C(sp^2)–H activation.

Conclusion

C–H bond functionalization is one of the most rapidly growing fields in current organic synthesis. The diversity, efficiency, and atom- and step-economical character of the developed methods made them powerful tools for the construction of various bonds, and have sparked applications in the synthesis of natural products and active pharmaceutical ingredients. Recent years have seen the emergence of an array of enantioselective C–H functionalization reactions, among which Pd^{0}-catalyzed reactions have played an active part. Figure 6 provides a chronological picture highlighting some of the most important milestones in this field.

Despite these advances, a number of important challenges remain to be addressed. For instance, intramolecular enantioselective C–H arylations are limited to the formation of five- to seven-membered rings and both smaller and larger rings are lacking in the reaction portfolio. In addition, the enantioselective functionalization of the less reactive C(sp^3)–H bonds remains limited. Furthermore, intermolecular reactions are underdeveloped, in contrast to Pd^{II}-catalyzed reactions. Finally, applications to the synthesis of complex functional organic molecules such as natural products are still scarce. Given the impressive development rate of this field, we believe that some of these standing issues will be solved in the near future thanks to the design of new chiral catalysts and a better understanding of their mode of action.

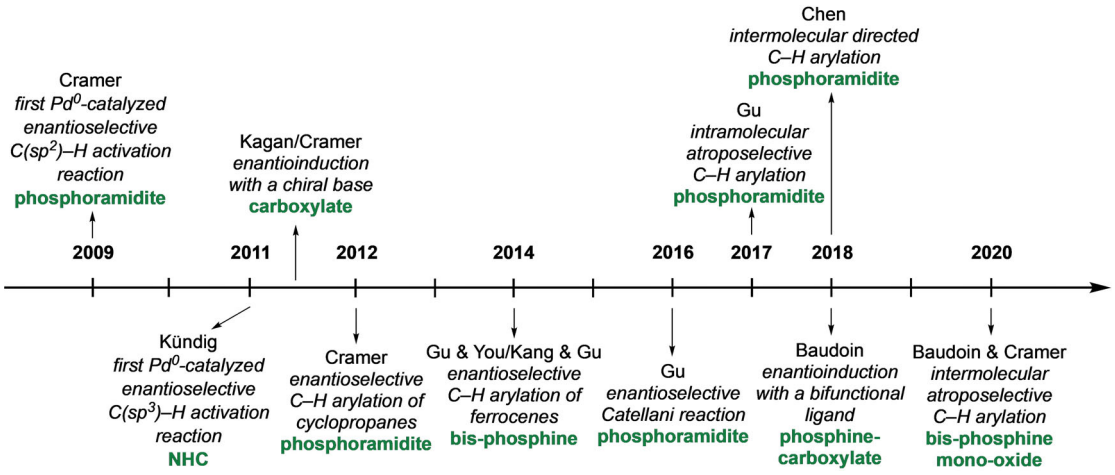


Figure 6. Timeline indicating important milestones in Pd^0-catalyzed enantioselective C–H activation, with the type of chiral catalyst used.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: asymmetric catalysis · C–H activation · chiral ligands · enantioselective reactions

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