



Chiral Transient Directing Groups in Transition-Metal-Catalyzed Enantioselective C–H Bond Functionalization

Maria Lapuh, Sara Mazeh, Tatiana Besset

► To cite this version:

Maria Lapuh, Sara Mazeh, Tatiana Besset. Chiral Transient Directing Groups in Transition-Metal-Catalyzed Enantioselective C–H Bond Functionalization. *ACS Catalysis*, 2020, 10 (21), pp.12898-12919. 10.1021/acscatal.0c03317 . hal-03004636

HAL Id: hal-03004636

<https://hal.science/hal-03004636>

Submitted on 8 Dec 2020

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Chiral Transient Directing Groups in Transition Metal-Catalyzed Enantioselective C–H Bond Functionalization

Maria I. Lapuh, [‡] Sara Mazeh, [‡] Tatiana Besset*

Normandie Univ, INSA Rouen, UNIROUEN, CNRS, COBRA (UMR 6014), 76000 Rouen, France.

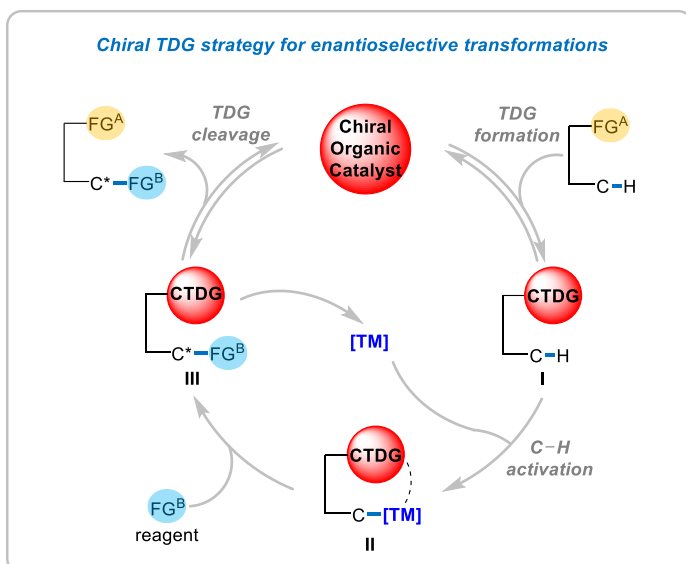
E-mail: tatiana.besset@insa-rouen.fr

Abstract: Transition metal-catalyzed C–H bond functionalization has known a rapid evolution in the last years, offering new strategies for reaching high molecular complexity in a step- and atom-economical way. Despite the indisputable advances, selectivity issues still remain given the ubiquity of C–H bonds on molecules, thus several approaches have been developed to tackle this challenge. Among them, the use of a transient directing group has emerged as an effective tool, circumventing the need of extra synthetic steps to install and then cleave a directing group on the molecule. More recently, this strategy has been successfully applied to the even more challenging transition metal-catalyzed enantioselective C–H bond functionalization. This review will highlight and discuss the main advances made in the use of a chiral transient directing group for the enantioselective functionalization of C(sp²)–H and C(sp³)–H bonds by transition metal catalysis.

1. INTRODUCTION

In the last decades, the transition metal-catalyzed C–H bond functionalization has emerged as a powerful strategy for achieving unprecedented transformations in a step- and atom-economical way.¹ This was illustrated, for instance, by the huge number of applications of this synthetic tool for the preparation of highly complex molecules.² Despite the unarguably advances, some limitations still remain: the selectivity is one of the most relevant challenges to be addressed since C–H bonds are ubiquitous on a molecule. This issue has been elegantly circumvented with the aid of a directing group (DG), which is able to coordinate to the metal center and to place it close to the C–H bond to be functionalized.³ Hence, various monodentate and bidentate directing groups have been efficiently used for the selective functionalization of different positions over aromatic⁴ and aliphatic derivatives.⁵ Nevertheless, solutions to avoid the extra synthetic steps required to install and cleave the directing group on the molecules were needed. Therefore, several strategies have arisen, such as the use of traceless directing groups⁶ and transient mediators.^{7,8} More recently, other promising alternatives emerged, based on the use of non-covalent interactions between the substrates and designed catalysts^{5e,9} and transient directing groups (TDGs).^{10,11} Since the pioneering example described by Jun and co-workers in 1997,¹² the latter strategy was successfully applied in several transition metal-catalyzed regioselective C–H bond functionalization, appearing as a modern and sustainable solution. Encouraged by this new synthetic tool, the scientific community showed a real endeavor towards the design and the use of chiral transient directing groups to achieve the highly challenging enantioselective C–H bond functionalization.^{1a,13} Indeed, the chiral transient directing group (CTDG) strategy, which relied on the reversible and temporary formation of a chiral directing group from a functional group, was particularly appealing. Taking benefit from the fact that the transient directing group also played the role of a chiral ligand, the number of species in the reaction media remained limited, reducing the possibilities for side reactions. Conceptually, a suitable functional group (FG^A) on the substrate would first react with a chiral organic catalyst to afford the aforementioned CTDG (I). After its coordination with the transition metal center in a monodentate or bidentate fashion, the metallacycle II would be formed. This latter would then react with the coupling partner leading to the species III and allowing the regeneration of the transition metal catalyst. A final hydrolysis would release the product along with the organo-catalyst (Scheme 1).

Scheme 1. The chiral transient directing group strategy in transition metal-catalyzed C–H bond activation reactions.



The aim of this review is to showcase and discuss the recent advances made in the cutting-edge C–H activation field based on the use of chiral transient directing groups to address transition metal-catalyzed enantioselective C–H bond functionalization. First, major advances regarding the atroposelective C(sp²)–H functionalization for the synthesis of enantioenriched chiral biaryls will be described. Then, the application of the transient directing group strategy to the preparation of enantioenriched heterocycles and carbocycles along with miscellaneous reactions will be highlighted. Finally, a last part of the review will be dedicated to the recent developments on the transition metal-catalyzed enantioselective C(sp³)–H bond functionalization.

2. Asymmetric C(sp²)-H bond activation for atropisomer synthesis

2.1. from biaryl derivatives

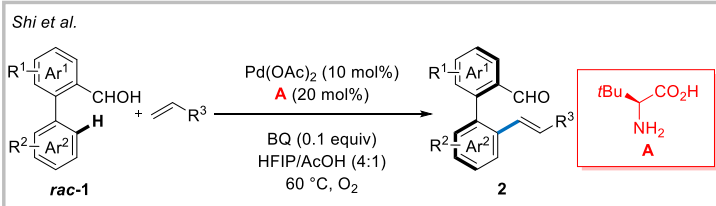
Given the significance and the abundance of the axially chiral biaryls in bioactive natural products,¹⁴ advanced material sciences,¹⁵ chiral ligands¹⁶ and catalysts,¹⁷ groundbreaking advances were made towards a straightforward access to these scaffolds.^{14c,18} Existing methods to synthesize such derivatives generally relied on stereoselective cross-coupling reactions,¹⁹ asymmetric cycloadditions,²⁰ transition metal-catalyzed atroposelective C–H bond functionalization,²¹ among others.²² Recently, the chiral transient directing group strategy appeared as a potent tool for the atroposelective synthesis of chiral biaryls. Therefore, the major advances made to access these high-value added axially chiral biaryl backbones thanks to this approach will be highlighted and discussed in this section.

a) Olefination and allylation reactions

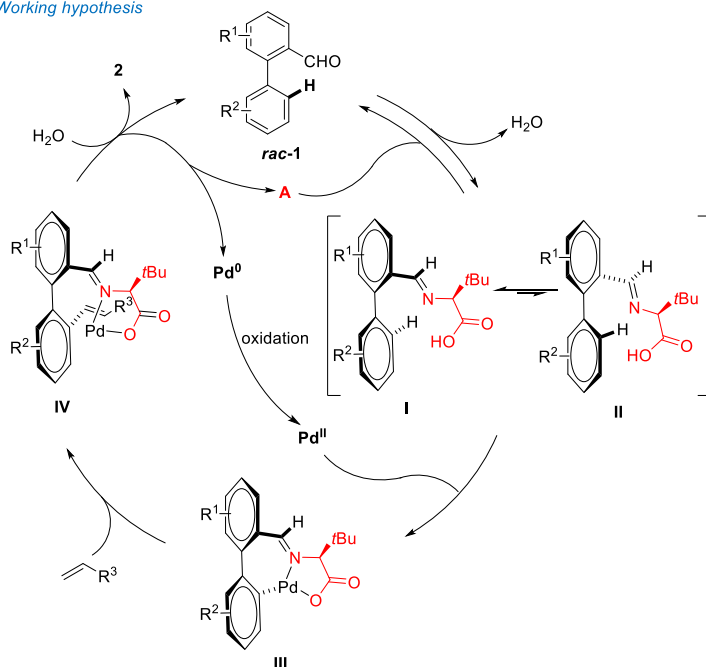
In 2017, Shi and co-workers studied the chiral transient directing group-assisted Pd-catalyzed atroposelective olefination of biaryl aldehydes based on the following working hypothesis²³ First, reaction of the racemic biaryl aldehyde (*rac*-1) with the chiral amino acid A would reversibly afford the two imines I and II. Then, formation of the axially enantioenriched biaryl palladacycle III derived from the diastereoisomer imine I would take place, presumably driven by steric interactions. The latter intermediate III would then undergo a Heck-type reaction with the alkene. After a reductive elimination and an *in situ* hydrolysis, the enantioenriched product 2 would be released along with the organocatalyst A. Finally, the palladium (II) catalyst would be regenerated after oxidation. Using the readily available chiral amino acid, L-*tert*-leucine (A), as a pivotal transient directing group precursor, a panel of aromatic aldehydes (*rac*-1) were olefinated through a dynamic kinetic resolution pathway (Scheme 2). When using substrates bearing electron-donating groups, the expected alkenylated products (2a-d) were obtained in yields up to 94% and high enantioselectivities (up to >99%). The transformation was tolerant to functional groups such as a halogen (1e) and an ester (1f). Pleasingly, a styrene derivative was a suitable coupling partner as showed by the synthesis of the compound 2g. In the case of biaryl derivatives bearing bulky

substituents at both 6- and 2'-positions, the reaction proceeded *via* a kinetic resolution pathway, furnishing the enantiopure products (2h-k) in 30-45% yields along with the enantioenriched starting biaryl aldehydes (1h-k). It is worth to mention that in this case the reaction also went smoothly with other acrylate and electron-poor styrene derivatives as demonstrated with the synthesis of compounds 2l-n.

Scheme 2. Pd(II)-catalyzed atroposelective C–H olefination reaction by using a chiral transient directing group.

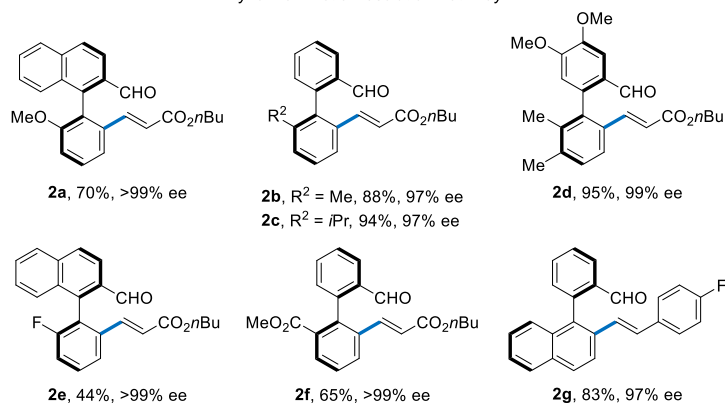


Working hypothesis

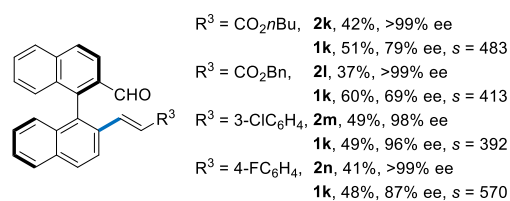
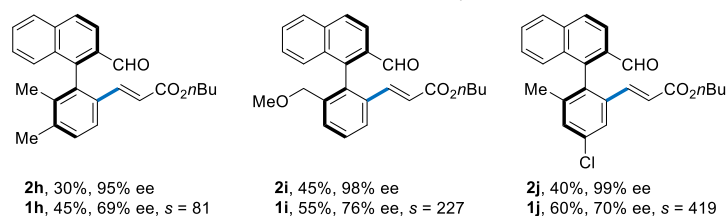


Selected examples

Dynamic Kinetic Resolution Pathway

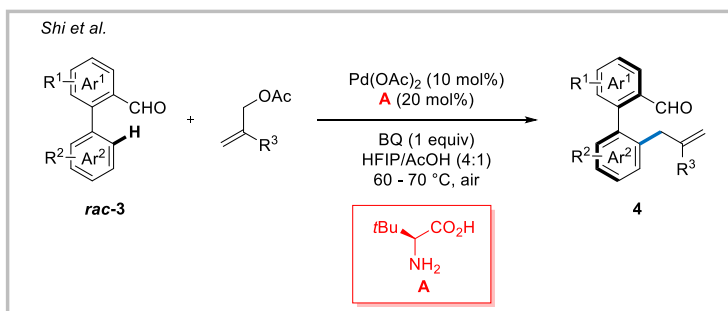


Kinetic Resolution Pathway

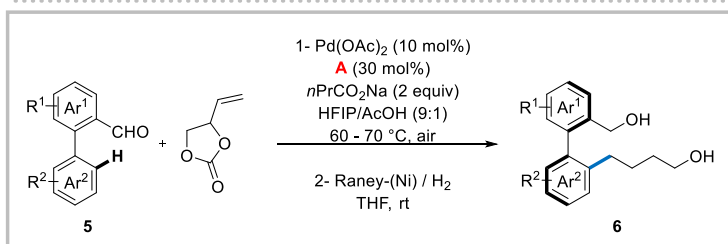
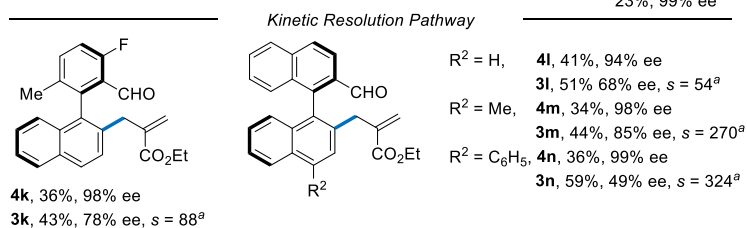
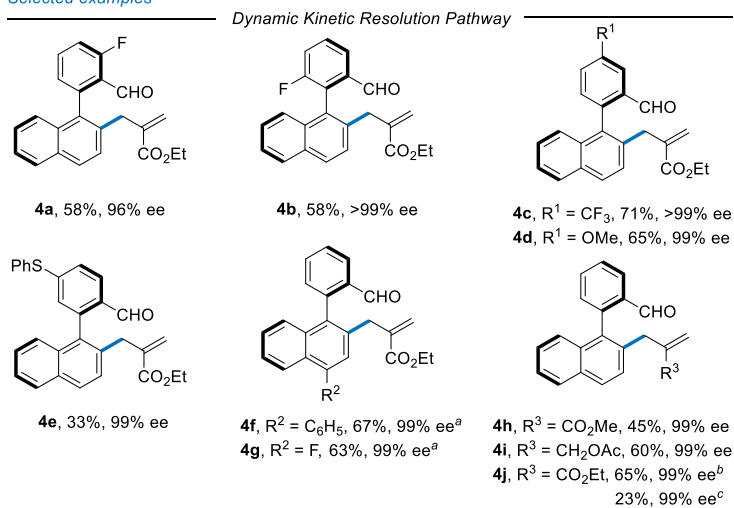


A year later, a Pd-catalyzed asymmetric allylation of biaryl aldehydes *via* a (dynamic) kinetic resolution reaction was developed by the same group (Scheme 3).²⁴ Using the L-*tert*-leucine (A) as a chiral organo-catalyst, an array of biaryl aldehydes *rac*-3 was functionalized with the allylic acetate reagent in the presence of benzoquinone in a HFIP/AcOH mixture. It turned out that the presence of an oxidant under acidic reaction conditions was crucial for the efficiency of the reaction. With substrates bearing a substituent at either the phenyl (3a-e) or the naphthyl part (3f-g), the corresponding allylated products were obtained efficiently through a dynamic kinetic resolution pathway in yields ranging between 33% and 71% and in high enantioselectivities (96% to >99% ee). Allylated biaryls bearing either halogens or electron-withdrawing groups (4a-c) as well as electron-donating groups (4d-f) were efficiently synthesized. In addition, the substitution pattern did not have a significant impact on the outcome of the reaction (4a, 4b and 4g). Worth mentioning that other coupling partners were also successfully used (4h-i) and replacing the leaving group of the allylation reagent with OBz or OBoc led to the corresponding product (4j) in 65% and 23% yields, respectively. With 2'- and 6-disubstituted racemic biaryls, the reaction proceeded in the presence of the allylic acetate reagent *via* a kinetic resolution process, affording the enantioenriched allylated products (4k-n) along with the enantioenriched starting materials (3k-n). Then, a Pd-catalyzed olefination of non-C2-symmetric biaryl aldehydes was achieved using the vinyl ethylene carbonate followed by a reduction step, offering an efficient access to the corresponding diols 6a-g in moderate to good yields and high enantioselectivities (>99%) (Scheme 3).

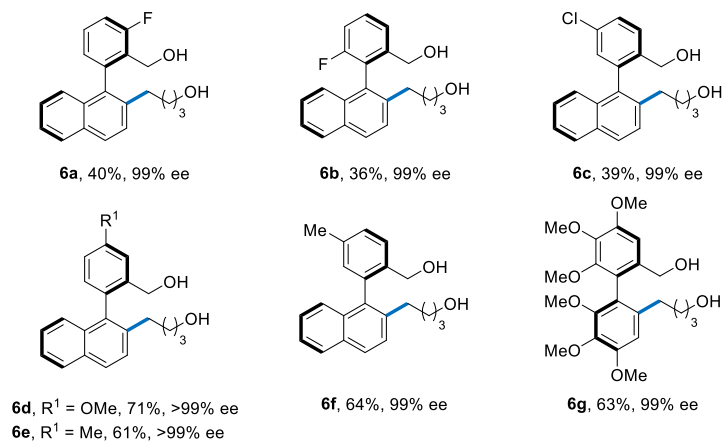
Scheme 3. Synthesis of axially chiral biaryls via a Pd(II)-catalyzed asymmetric allylation reaction.



Selected examples



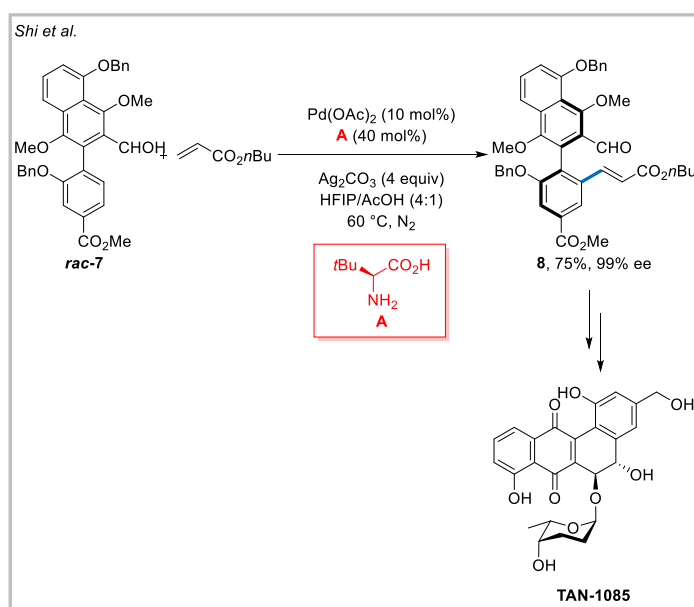
Selected examples



^a A (30 mol%). ^b The leaving group of the coupling partner (OAc) was replaced by a OBz group. ^c The leaving group of the coupling partner (OAc) was replaced by a OBoc group.

Applying the enantioselective C–H functionalization strategy to natural products synthesis,^{2a,c,d,k,25} the group of Shi reported a concise and highly enantioselective total synthesis of TAN-1085,²⁶ an angucycline antibiotic isolated from *Streptomyces* species (Scheme 4).²⁷ Taking benefit from their pioneering work,²³ a scalable and efficient construction of the axially chiral biaryl scaffold 8 was achieved in 75% yield with a high level of enantioselectivity (99% ee).

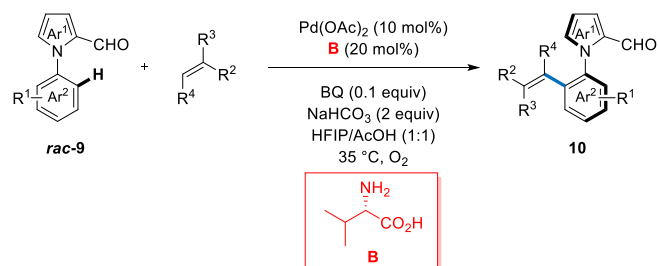
Scheme 4. Application of the transient directing group strategy to access a key intermediate 8 for the total synthesis of TAN-1085.



In 2019, Zhang and Xie extended this appealing strategy to the synthesis of unprecedented N–C axially chiral *N*-arylindoles by means of a transition metal-catalyzed atroposelective C–H alkenylation reaction (Scheme 5).²⁸ Using a catalytic amount of Pd(OAc)₂ and L-Valine (B) in the presence of benzoquinone, the olefination of a panel of aryl-1*H*-indole-2-carbaldehyde derivatives *rac*-9 with the *n*-butyl acrylate was achieved in a high regio- and stereocontrol leading to the corresponding alkenylated products 10a-g. Various *N*-arylindoles bearing electron-donating and electron-withdrawing groups at either the indole (9a-c) or the phenyl part (9d-g) were functionalized in good yields *via* a desymmetrization process. The transformation also went smoothly with a phenyl vinyl sulfone, a styrene derivative and with the 3-methylenedihydrofuran-2(3*H*)-one affording the compounds 10h-j. Moreover, a dynamic kinetic resolution pathway was reported allowing the functionalization of *N*-arylindoles bearing a halogen or an alkyl chain in good yields with excellent enantioselectivities (10k-l). The transformation was not restricted to the use of the *n*-butyl acrylate as several olefins were suitable (10m-n). The olefination of the bulkier substrates *rac*-11a-i with various activated olefins as coupling partners was achieved in the presence of L-*tert*-leucine and silver triflate *via* a kinetic resolution process furnishing a range of enantioenriched heterobiaryl derivatives in moderate to good yields and excellent enantioselectivities (12a-i).

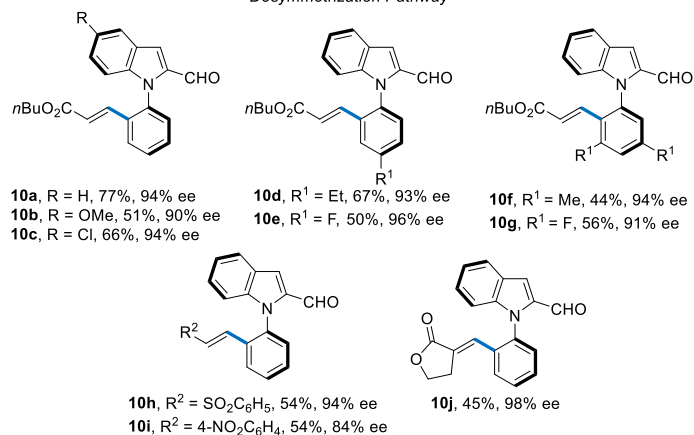
Scheme 5. Atroposelective Pd(II)-catalyzed olefination of *N*-arylindoles.

Zhang, Xie et al.

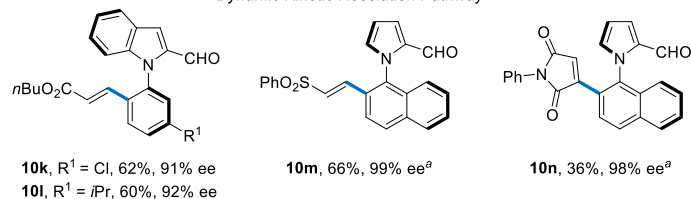


Selected examples

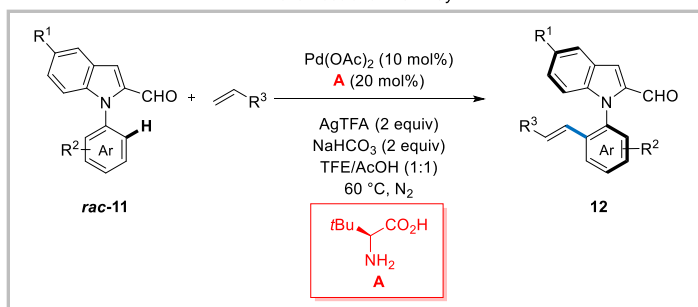
Desymmetrization Pathway



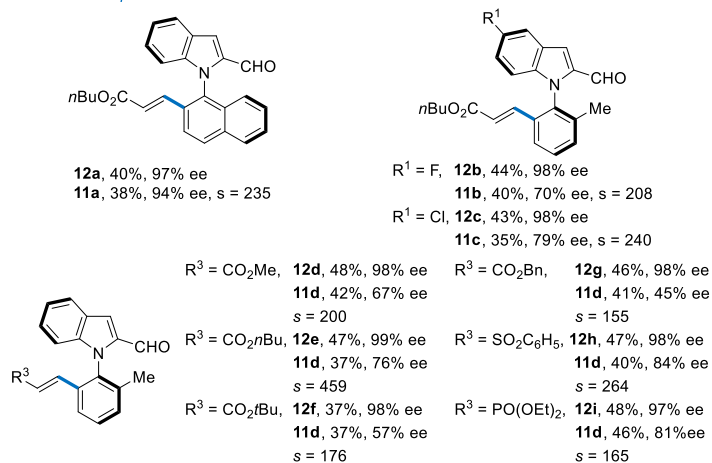
Dynamic Kinetic Resolution Pathway



Kinetic Resolution Pathway



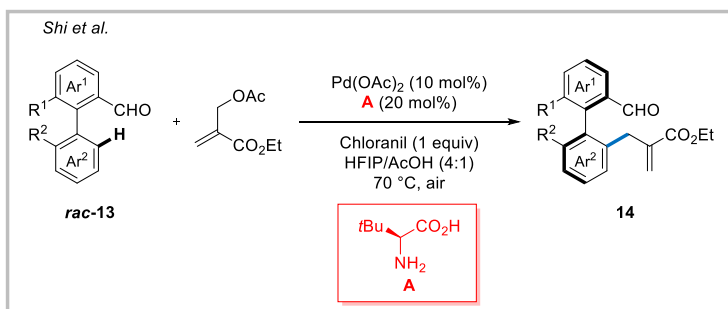
Selected examples



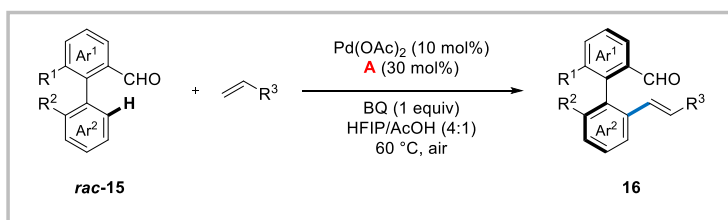
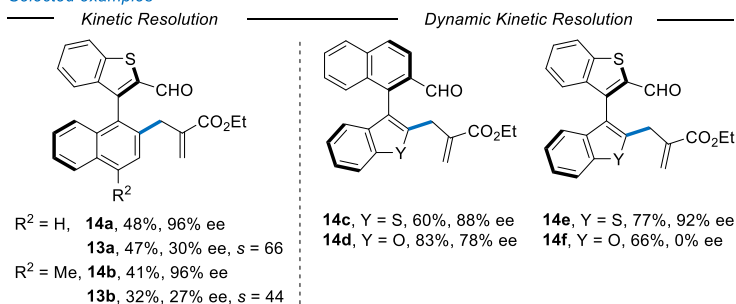
^a Pd(OAc)₂ (10 mol%), A (20 mol%), AgTFA (2 equiv), NaHCO₃ (2 equiv), TFE/AcOH (1:1), 60 °C, N₂.

The same year, the Shi group depicted the atroposelective Pd-catalyzed allylation and olefination of biaryl aldehydes, offering a straightforward access to the challenging five-membered axially chiral biaryls (Scheme 6).²⁹ For this purpose, a catalytic amount of L-*tert*-leucine and Pd(OAc)₂ along with chloranil as the oxidant were used for the allylation of a broad range of heterocycles *rac*-13 with the allylic acetate reagent leading to enantioenriched atropoisomers featuring a heteroaryl part. Importantly, it is worth to mention that the position of the heteroarenes on the biaryl scaffold did have an influence on the mechanism pathway involved in the transformation. When the benzothiophene was at the upper part of the biaryls (13a-b), the transformation proceeded via a kinetic resolution affording the expected products (14a-b) in good yields and high selectivities. While for substrates bearing heteroarenes in the lower part (13c-d), the enantiopure allylated biaryls (14c-d) were obtained through a dynamic kinetic resolution pathway in moderate to good yields. The synthesis of the allylated 3,3'-bisbenzothiophene (14e) was straightforward (77% yield, 92% ee), while no enantioselectivity was observed with a biaryl bearing a benzothiophene and a benzofuran residue (14f). This approach was then applied to the alkenylation of heteroarenes with various acrylate derivatives and styrene under similar reaction conditions. While a set of biaryls bearing a benzothiophene part (15a-e) were functionalized *via* a kinetic resolution process, the olefination of the benzofuran-based biaryl 15f and the 3,3'-bisbenzothiophene 15g proceeded according to a dynamic kinetic resolution pathway.

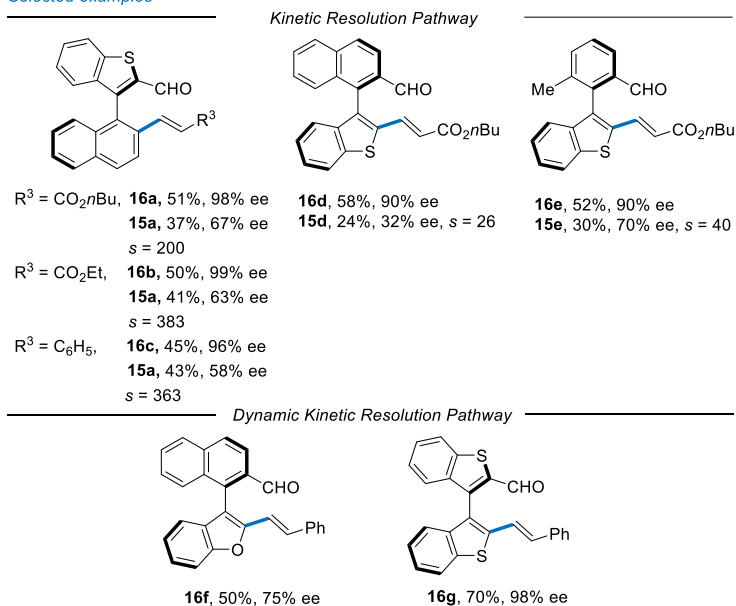
Scheme 6. Synthesis of enantioenriched atropoisomers featuring a heteroaryl part by Pd(II)-catalysis.



Selected examples



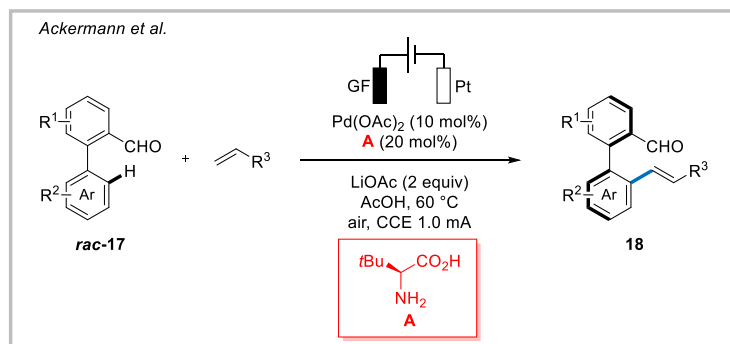
Selected examples



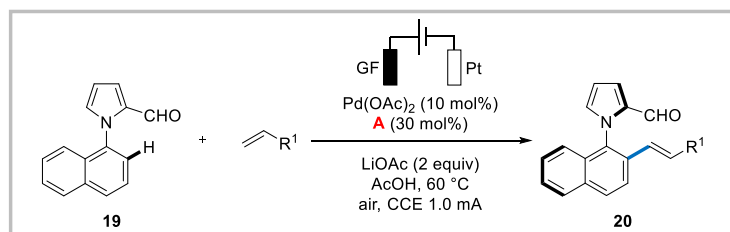
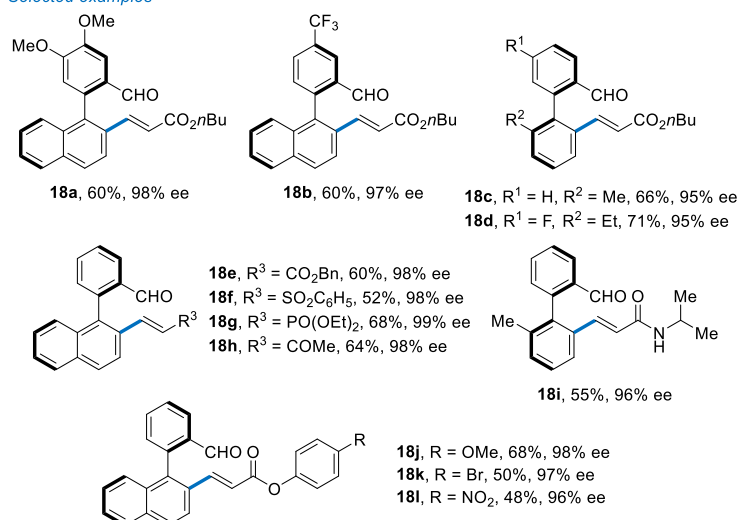
This year, the Ackermann group described the first atroposelective palladoelectro-catalyzed olefination of biaryl aldehydes by C–H bond activation under mild reaction conditions (Scheme 7).³⁰ A panel of biaryl derivatives **rac-17** was olefinated using the *L*-*tert*-Leucine as chiral organo-catalyst and LiOAc as the electrolyte, furnishing the corresponding products in moderate to good yields (up to 71%) and high enantioselectivities (up to 98% ee). Both electron-rich (**17a**) and electron-poor (**17b**) substrates reacted well under these conditions showcasing the robustness of this approach. Besides, disubstituted biphenyls proved to be suitable substrates for this functionalization (**17c-d**). Notably, a series of electron-deficient olefins was successfully used as coupling partners offering an atroposelective access to the corresponding biaryls in up to 68% yield (**18e-l**). More interestingly, this transformation turned out to be efficient also with *N*-arylpyrrole

derivatives. Hence, an access to N–C axially chiral heteroaryls 20a-e was achieved in a complete regio- and stereoselective manner. Finally, the strategy was further applied to access key compounds such as chiral BINOLs, dicarboxylic acids and helicenes.

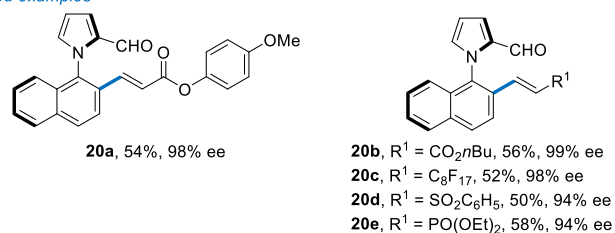
Scheme 7. Electrochemical enantioselective olefination of biaryl aldehydes by Pd(II)-catalyzed C–H bond activation using the chiral transient directing group strategy.



Selected examples



Selected examples

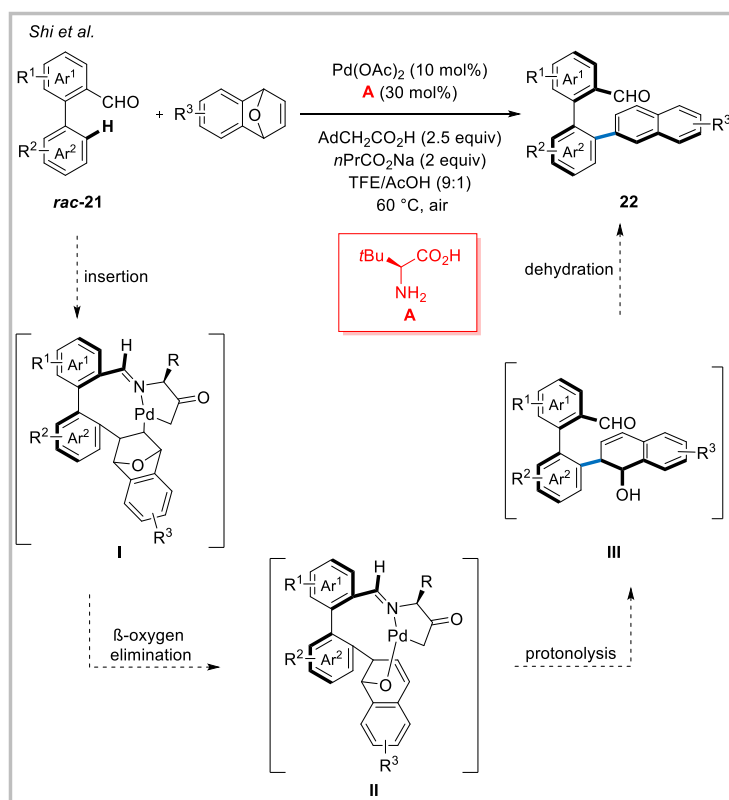


b) Naphthylation reaction

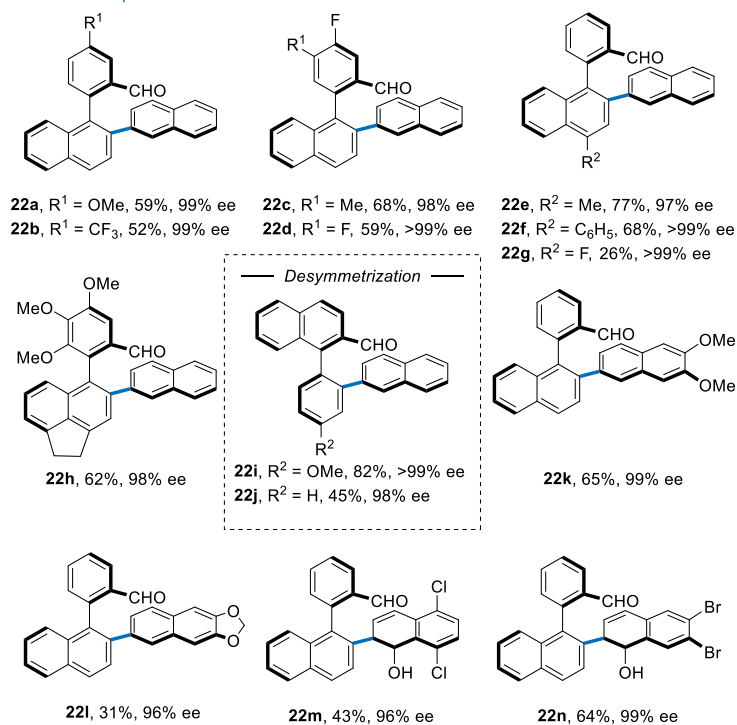
In 2019, the Shi group reported the atroposelective Pd-catalyzed *ortho* C–H naphthylation of racemic biaryl aldehydes *rac*-21 with 7-oxabenzonorboranadienes (Scheme 8)³¹ leading to key scaffolds, known to be efficient chiral catalysts.^{17d,32} For this transformation, a four-step process was designed: insertion of a 7-oxabenzonorboranadiene derivative within the palladacycle intermediate (I) followed by a β-oxygen elimination would lead to the intermediate II. The latter would then undergo a protonolysis to afford the dihydronaphthol III, which after a dehydration step would furnish the expected product

22. By employing *L-tert*-leucine, 1-adamantaneacetic acid and sodium butyrate, an array of the desired naphthylated products (22a-h) was obtained efficiently in good yields and enantioselectivities. Indeed, this reaction was compatible with substrates bearing at the aryl ring either an electron-donating functional group (21a) or an electron-withdrawing one (21b) and with difunctionalized substrates (21c-d). Also, the methodology was successfully applied to substrates with electron-rich naphthyl parts (21e-f). Nonetheless, a lower reactivity was observed once the naphthalene ring is functionalized with an electron-withdrawing group (22g). Besides, an access to the chiral poly-substituted biaryl compound 22h was possible by this methodology. Notably, the desymmetrization of prochiral substrates was achieved in good to moderate yields and high enantioselectivities (22i-j). When several analogues of the 7-oxabenzonorboranadiene were used, the desired products (22k-l) were successfully synthesized with electron-rich partners in contrast to electron-poor ones, which only afforded the dihydronaphthol products (22m-n).

Scheme 8. Atroposelective Pd(II)-catalyzed *ortho* C–H naphthylation of biaryl aldehydes.



Selected examples

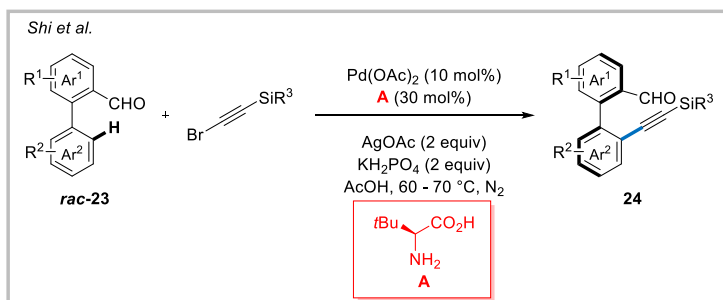


c) Alkynylation reaction

Aiming at having an efficient access towards advanced intermediates for the synthesis of the bioactive dibenzocyclooctadiene lignans,³³ Shi *et al.* developed a novel Pd-catalyzed C–H alkynylation reaction in the presence of a TIPS-protected alkynyl bromide (Scheme 9).³⁴ The approach displayed a high functional group tolerance since products bearing electron-withdrawing groups and halogens (24a–c) as well as electron-donating groups (24d–e) were obtained

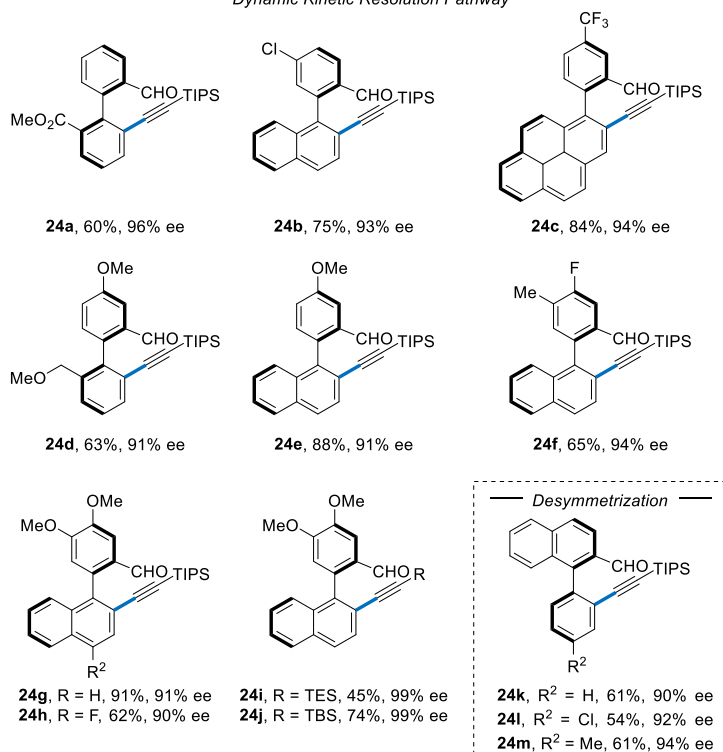
through a dynamic kinetic resolution process. Poly-substituted biaryl aldehydes 23f-h also underwent this reaction successfully. Moreover, different silylated-protected alkynyl bromides turned out to be suitable for this transformation leading to the corresponding compounds 24i-j in up to 74% yield and high selectivities (up to 99% ee). Furthermore, prochiral substrates were desymmetrized in good yields and high enantioselectivities (24k-m) and both halogenated 23l and alkylated biaryl aldehydes 23m were suitable substrates. In case of biaryl aldehydes, substituted at both 6- and 2'-positions (25a-d), the Pd-catalyzed alkynylation reaction proceeded *via* a kinetic resolution pathway under slightly modified reaction conditions (Scheme 9).

Scheme 9. Atroposelective synthesis of alkynylated biaryl scaffolds.

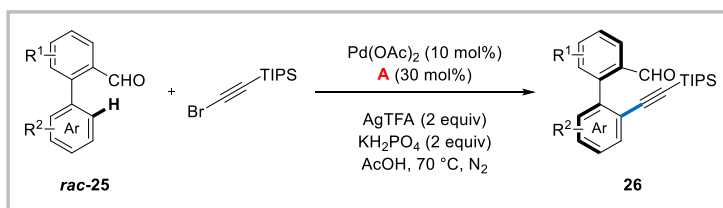


Selected examples

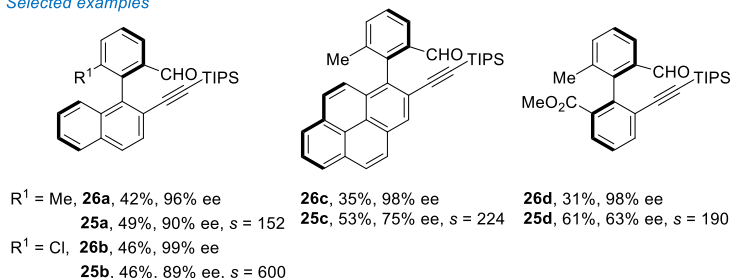
Dynamic Kinetic Resolution Pathway



Kinetic Resolution Pathway



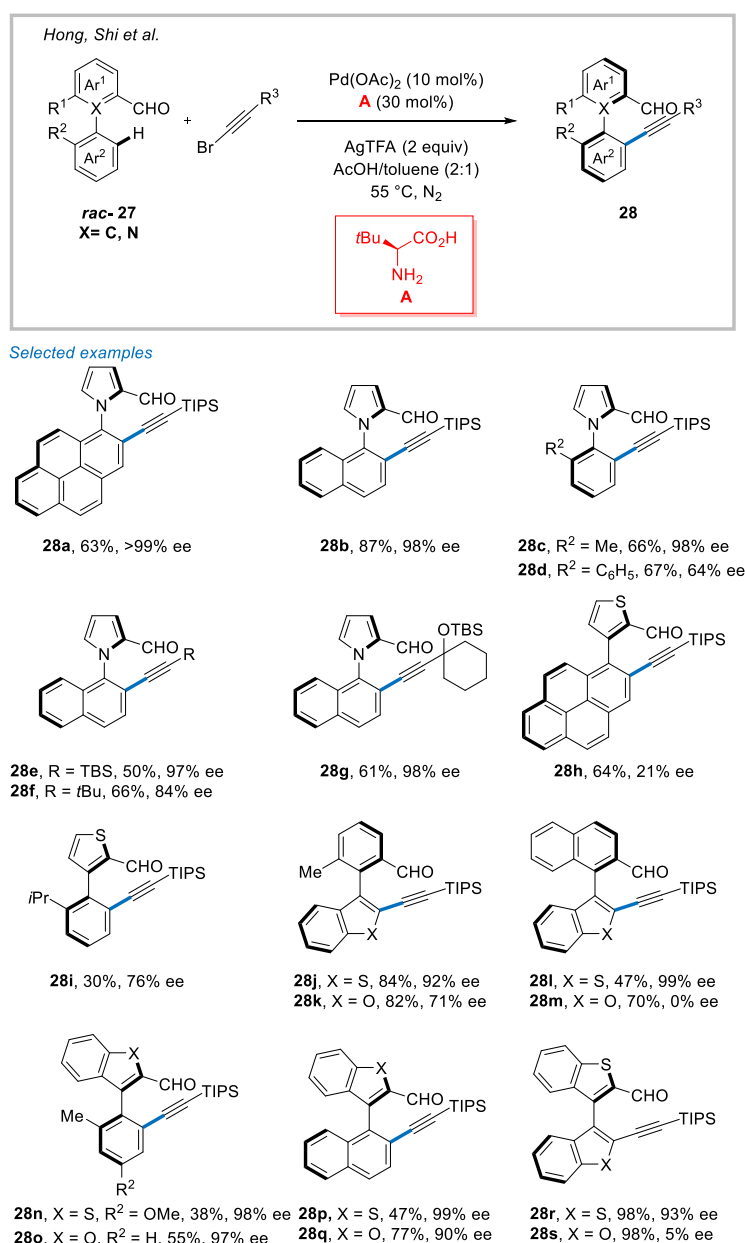
Selected examples



Then, the same group extended their methodology to the challenging atroposelective alkynylation of biaryls featuring at least one five-membered heteroarene (Scheme 10).³⁵ Under Palladium catalysis, the enantioselective alkynylation of various biaryl aldehydes bearing a C–N and a C–C chiral axis with a TIPS-protected alkyne bromide was realized in an efficient manner. Different *N*-arylpyrroles were functionalized (**28a-d**) and different alkynes were efficient partners in the reaction (**28e-g**), albeit *N*-arylindoles were unreactive. The alkynylation of the thiophene derivatives (**27h,i**) was achieved

in moderate to good yields and with enantiomeric excesses ranging from 21% to 76%. Moreover, replacing the benzothiophene in the lower part by a benzofuran had a deleterious effect on the enantioselectivity (28j vs 28k and 28l vs 28m), whereas the nature of the heteroaryl in the upper part of the biaryls had no significant impact on the outcome of the reaction (28n-q). Interestingly, with this approach, the alkynylation of substrates having two five-membered heteroarenes was possible and it turned out that the enantioselectivity of the reaction was dependent on the nature of the heteroarene in the lower part (28r vs 28s).

Scheme 10. Pd(II)-catalyzed alkynylation of five-membered containing biaryls by C–H bond activation.

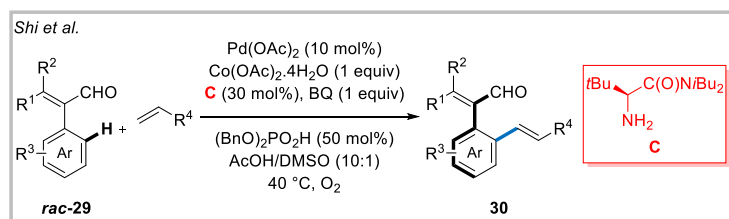


2.2 from styrene derivatives

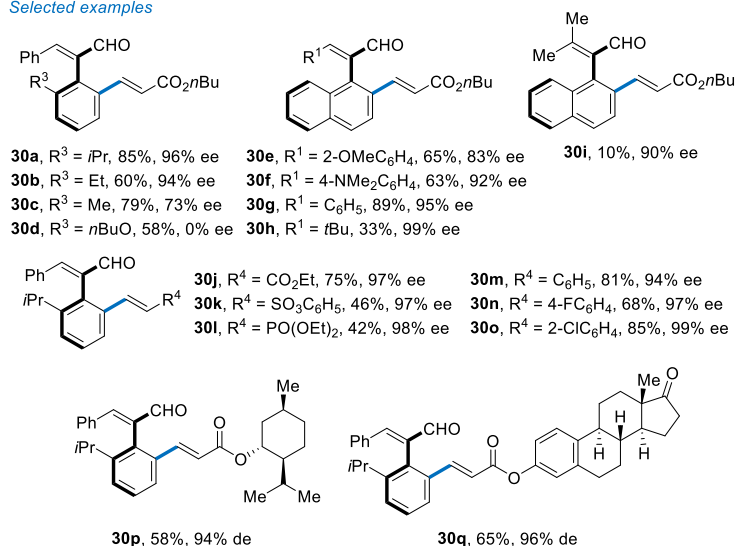
Recently in 2020, Shi and co-workers investigated the challenging synthesis of axially chiral styrenes. To that purpose, the Pd-catalyzed atroposelective C–H olefination of racemic styrenes (*rac*-29) using the bulky amino acid C was developed in the presence of benzoquinone and cobalt acetate in a mixture of AcOH and DMSO, this latter presumably acting as a ligand (Scheme 11).³⁶ With substrates bearing a substituent at the *ortho* position, the expected products were obtained

with a good enantiocontrol (30a-c) except in the case of 30d. By replacing the aryl part by a naphthyl one, the olefination of several derivatives (30e-i) went smoothly. Moreover, several activated olefins and styrenes were suitable coupling partners leading to the synthesis of axially chiral compounds (30j-o) in high enantioselectivities. Interestingly, using acrylates derived from natural products, an access to added-value styrenes (30p-q) was possible with high diastereomeric excesses. Notably, axially chiral styrenes 30 were oxidized to the corresponding carboxylic acids, which showed higher efficiency as chiral ligands in the Co(III)-catalyzed enantioselective (sp^3)-H amidation of a thioamide compared to their biaryl counterparts.

Scheme 11. Synthesis of axially chiral styrenes *via* the transient directing group strategy.



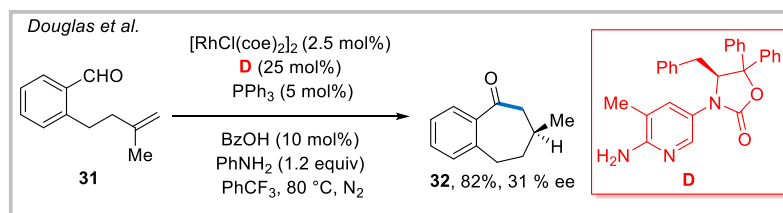
Selected examples



3. Asymmetric synthesis of chiral carbocycles and heterocycles by C–H bond activation

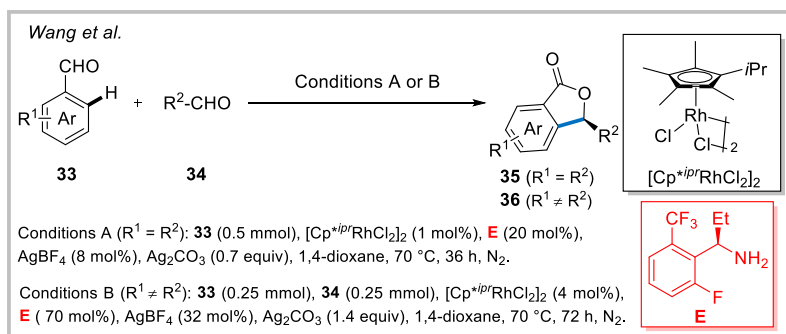
The preparation of chiral carbocycles and heterocycles through transition metal-catalyzed direct C–H bond activation has been considerably studied in the last decades. Indeed, the use of Rhodium complexes, especially those containing cyclopentadienyl (Cp)-derived ligands, allowed many successful enantioselective transformations employing different strategies to induce asymmetry.^{13g,37} In contrast, the utilization of chiral transient directing groups to this end is still in its infancy despite the indisputable advances made in the recent years. In 2012, in the course of their study regarding the Rh(I)-catalyzed intramolecular hydroacylation of disubstituted alkenes, Douglas and co-workers provided the first example applied to the enantioselective cyclization of the aldehyde 31.³⁸ To this purpose, a chiral derivative of 2-amino-3-picoline (D) was used to achieve the *in situ* formation of the aldimine species from 31 (Scheme 12). Although a unique example was depicted with a modest enantioselectivity, this seminal work paved the way for further developments in catalytic asymmetric transformations using the chiral transient directing group strategy. Note that a theoretical mechanistic study was then published by Zhang, Lei and co-workers in 2014.³⁹

Scheme 12. Rh(I)-catalyzed enantioselective hydroacylation using a chiral TDG.



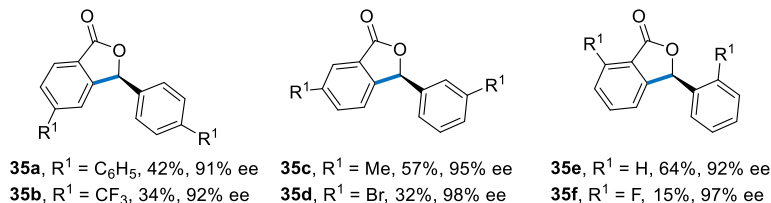
In 2019, Wang and co-workers took benefit from the use of cyclopentadienyl-containing Rh(III) catalysts for the asymmetric synthesis of phthalides.⁴⁰ By employing a combination of the $[\text{Cp}^*\text{RhCl}_2]_2$ catalyst and the chiral amine **E**, a methodology was developed for the enantioselective homo- and hetero-coupling of benzaldehyde derivatives, offering an access to a large panel of chiral phthalides (yields up to 73% and enantiomeric excesses ranging from 61% to 99.9 %, Scheme 13).⁴¹ For compounds **35a-f**, resulting from a homocoupling reaction, the best yields were obtained with phenyl- and alkyl-substituted aromatic aldehydes (**33a** and **33c**) as well as benzaldehyde (**33e**). On the contrary, the presence of a CF_3 group (**33b**) or halogens (**33d** and **33f**) had a deleterious effect on the outcome of the reaction. Notably, when *meta*-substituted aldehydes reacted, the functionalization at the less hindered position occurred (**35c-d**). Regarding the heterocoupling reactions (**36a-i**), the observed selectivity stemmed from the fact that the transition metal-catalyzed C–H bond activation event was favored with substrates substituted with electron-neutral or electron-donating groups (alkyl, phenyl, OBn), which then reacted with aromatic aldehydes bearing electron-withdrawing substituents (halogens, CF_3 , SO_2Me , CO_2Et , NO_2). Hence, a selective access to only one of the four potential products was possible in most cases. Moreover, heterocoupling of 2,4-dimethoxybenzaldehyde with aliphatic aldehydes was also achieved, leading to the corresponding products **36j-l** with good to high enantioselectivities. Regarding the mechanism of the transformation, a plausible pathway was suggested to explain the observed enantioselectivities for both homo- and hetero-couplings. First, the precatalyst $[\text{Cp}^*\text{RhCl}_2]_2$ would react with the silver tetrafluoroborate to afford the active species $[\text{Cp}^*\text{Rh}^{\text{III}}]$. Then, the rhodacycle **II** formation would take place from the aldimine **I** via a reversible C–H activation event, followed by the coordination of the second coupling partner (intermediate **III**). Subsequently, the intermediate **IV** would be obtained after a stereoselective addition of the arene to the second aldehyde, followed by an intramolecular attack of the resulting alkoxide at the imine carbon. After a β -hydride elimination, a Rh(I) species would be released, which after oxidation with the silver salt would regenerate the active Rh(III) catalyst along with the imine **V**. This latter would be easily hydrolyzed to provide the desired chiral phthalides **35** or **36** and the organo-catalyst.

Scheme 13. Rh(III)-catalyzed preparation of chiral phthalides from aldehydes using a chiral TDG.

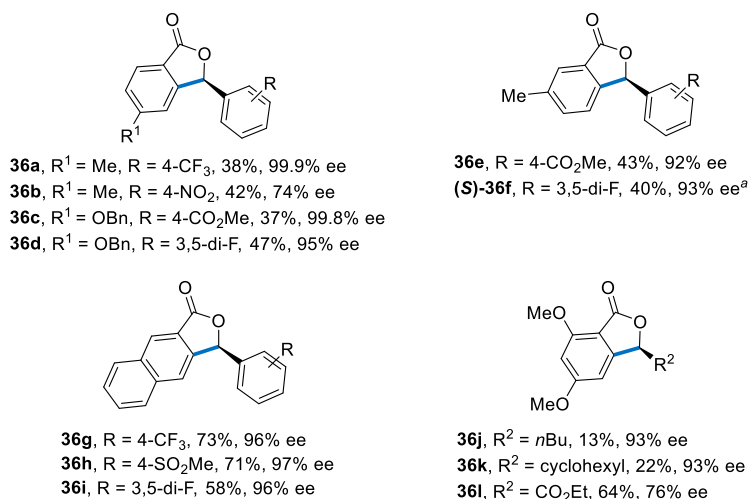


Selected examples

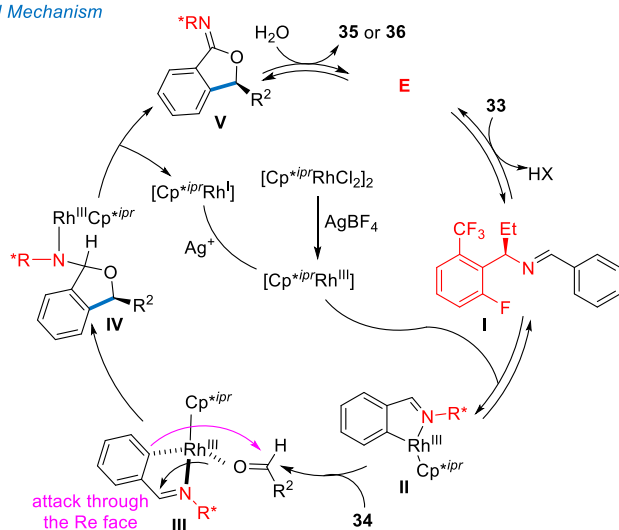
Homocoupling reactions



Heterocoupling reactions



Proposed Mechanism

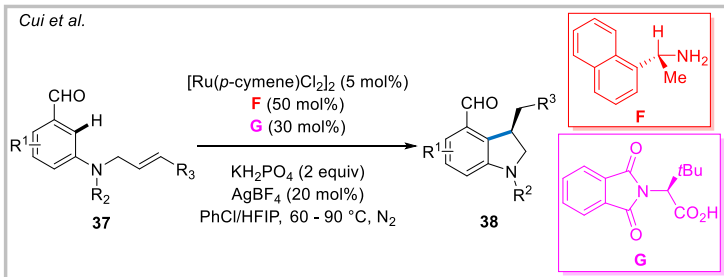


^a Absolute configuration determined by X-ray diffraction.

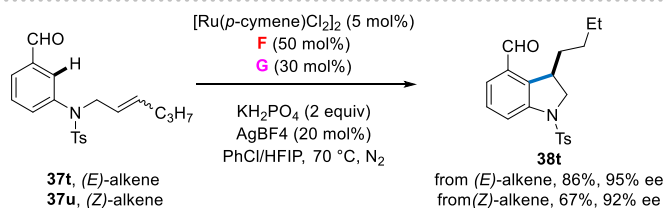
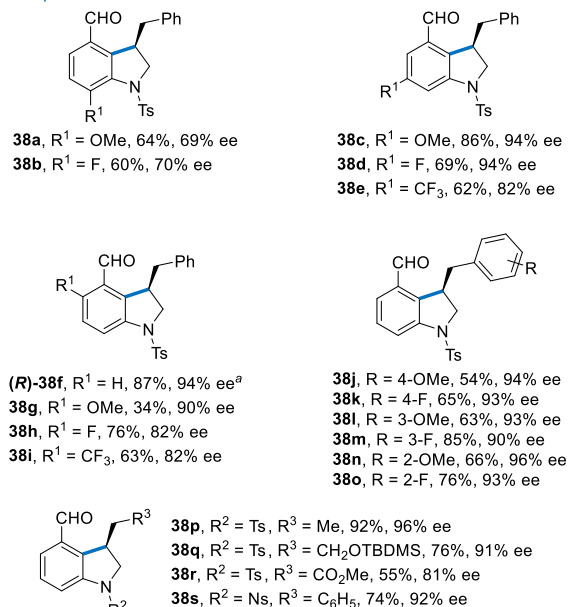
In contrast to Rhodium based-catalysts, Ruthenium ones have been less employed in asymmetric C–H activation reactions.^{21b,42} In 2019, Cui and co-workers reported the first Ruthenium-catalyzed synthesis of chiral indoline derivatives by means of the chiral transient directing group strategy. Using the $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ catalyst combined with the chiral amine F and an additional chiral acid G, the enantioselective intramolecular hydroarylation of aromatic aldehydes 37 was achieved leading to *N*-Tosyl protected indoline derivatives with yields up to 92% and enantiomeric excesses between 69% and 96% (Scheme 14).⁴³ Several benzaldehyde derivatives 37a-i bearing either an electron-donating (OMe, 37a, 37c, 37g) or an electron-withdrawing (CF_3 , 37e and 37h) group were functionalized with moderate to high yields. The substitution pattern on the aromatic aldehydes did not have a strong impact on the outcome of the reaction, except in the presence of a methoxy group at the *ortho* position, as the corresponding product 38g was isolated in only 34% yield with a high enantiomeric excess. The substitution over the alkene counterpart was also investigated (37j-r) and it turned out that various (*E*)-styrenyl groups containing both electron-donating and electron-withdrawing groups (OMe and F, among others) were suitable (37j-o). Moreover, alkenes substituted with different substituents (Me, CH_2OTBDMS , CO_2Et , 37p-r) were well tolerated. Note that the nitrogen-protecting group was not only restricted to tosyl, since the *N*-nosyl indoline 38s was synthesized. Notably, when both *E* and *Z* diastereoisomers of the same alkene were employed as substrates (37t-u), the same product 38t was obtained with high enantiomeric excesses (91% and 92%, respectively), showing that the alkene geometry did not have any influence on the stereocontrol of the transformation. The following plausible mechanism was suggested for the enantioselective synthesis of indoline scaffolds (Scheme 14). First, the active catalyst species $(\text{Ru}(p\text{-cymene})(\text{O}_2\text{CR}^*)_2)$ would be generated from $(\text{Ru}(p\text{-cymene})(\text{Cl}_2)_2)$ followed by the formation of the ruthenacycle II from the transient aldimine I through a reversible C–H activation step. Coordination of the alkene to the Ruthenium metal center would lead to the cationic intermediate III as an ion pair with the chiral carboxylate G, crucial for the efficiency and the enantioselectivity of the reaction. Then, the insertion of the alkene would occur selectively through the less hindered face of the chiral imine (intermediate IV) presumably due to its conformationally rigid structure. Finally, the product 38f would be obtained after the hydrolysis of the aldimine V and F would be regenerated along with the Ruthenium-based catalyst.

Scheme 14. Preparation of chiral indolines through an enantioselective Ru(II)-catalyzed intramolecular hydroarylation.

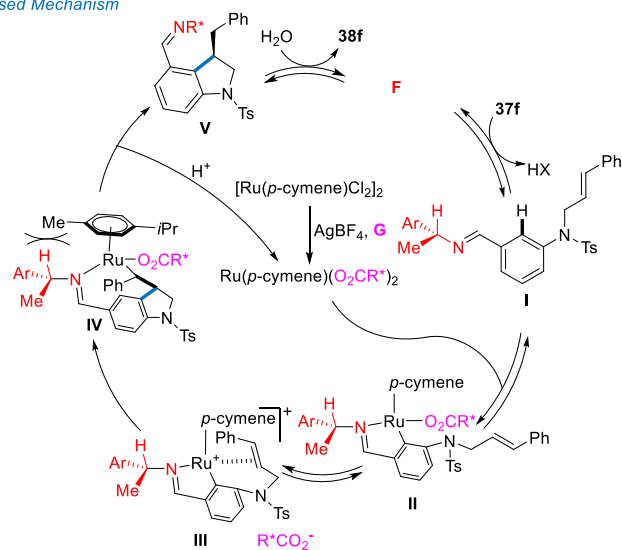
Cui et al.



Selected examples



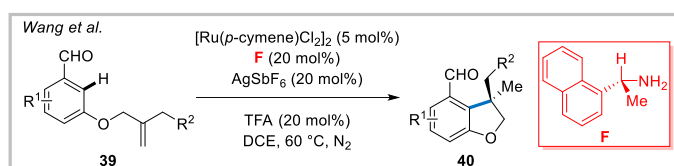
Proposed Mechanism



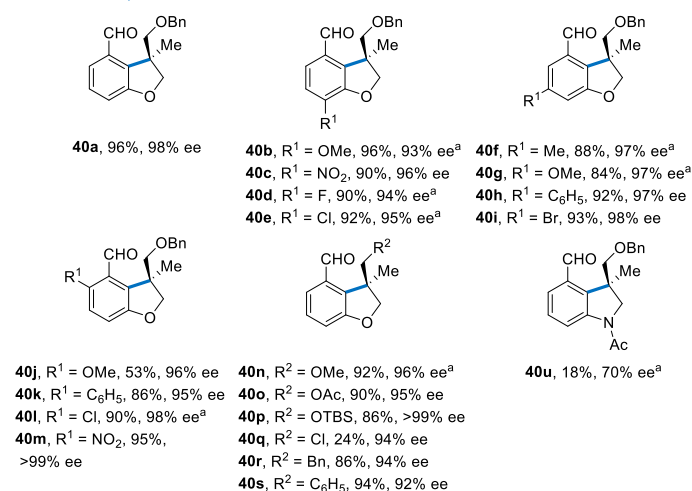
^a Absolute configuration determined by X-ray diffraction.

In 2020, Wang and co-workers reported another application of the chiral transient directing group strategy in a Ru-catalyzed transformation for the synthesis of 2,3-dihydrobenzofurans through an asymmetric intramolecular hydroarylation reaction.⁴⁴ To this end, the combination of [Ru(*p*-cymene)Cl₂]₂ catalyst with the chiral amine **F** and trifluoroacetic acid were found to be the best for this transformation. Several olefin-tethered aromatic aldehydes were smoothly converted into the corresponding 2,3-dihydrobenzofurans **40** with yields up to 98% and enantiomeric excesses up to >99% (Scheme 15). The reaction proceeded successfully with an unsubstituted aldehyde **39a** as well as with aromatic aldehydes bearing halogens, electron-donating (eg. OMe, Me) and electron-withdrawing groups (NO₂), either at the *para*-, *meta*- or *ortho*-position (**39b-m**). Nevertheless, the presence of a methoxy group at the *ortho* position led to a lower yield (**40j**). Substrates **39n-s**, bearing various substituents at the allylic position were also tested, leading to the expected products **40n-s** with very good yields and enantioselectivities, except for the chlorine-containing product **40q**. Extension of their methodology to the synthesis of the indoline derivative **40u** turned out to be feasible but less efficient (18% yield, 70% ee). A similar mechanism to the one depicted in the Scheme 14 was suggested for this transformation, although the use of a chiral acid was not required to improve yields and enantioselectivities.

Scheme 15. Synthesis of chiral 2,3-dihydrobenzofuranes through a Ru(II)-catalyzed enantioselective intramolecular hydroarylation.



Selected examples



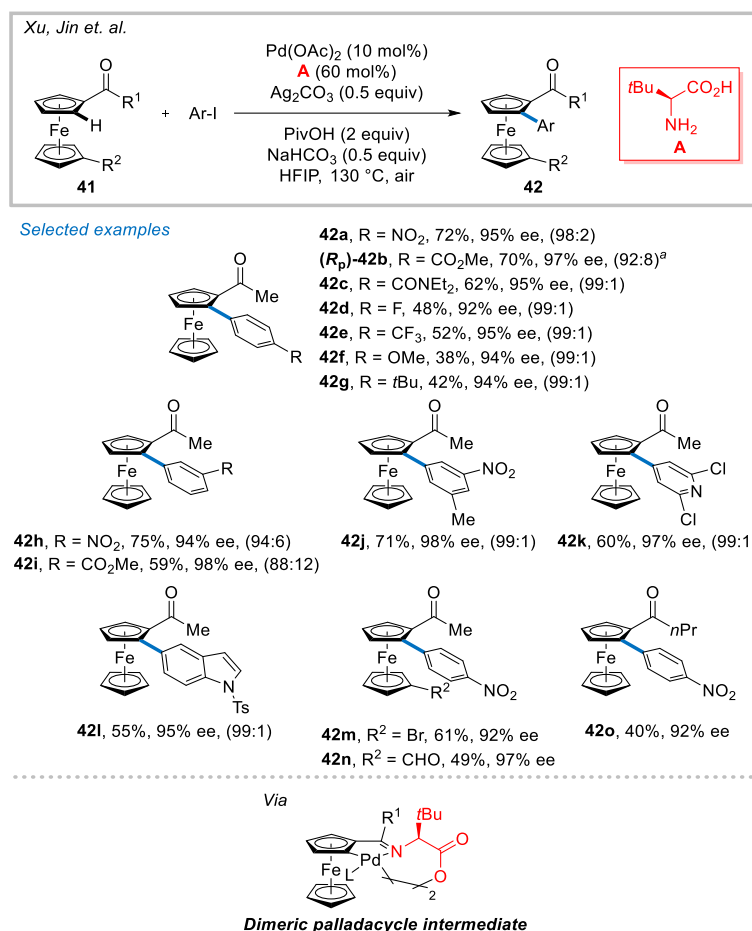
^a **F** (40 mol%), TFA (40 mol%).

4. Application of the chiral transient directing group strategy for miscellaneous reactions

In 2018, Xu, Jin and co-workers applied the chiral transient directing group strategy in the enantioselective C(sp²)-H arylation of ferrocenyl ketones by Palladium catalysis in order to obtain enantioenriched planar-chiral ferrocenes with yields up to 75%, enantiomeric excesses ranging from 92% to 98% and a ratio of mono- vs di-functionalized products between 88:12 and 99:1 (Scheme 16).⁴⁵ It was found that the reaction of the acetylferrocene with the 1-iodo-4-nitrobenzene was successfully achieved using the *L*-*tert*-leucine as the transient directing group precursor leading to the corresponding product **42a**. Both the pivalic acid and the sodium bicarbonate were essential for the efficiency and the enantioselectivity of the transformation. In particular, the pivalic acid had a dual function as it promoted the transient aldimine formation and played a key role in the rate determining C-H cleavage event. The arylation of **41** was also realized with an array of *para*- and *meta*-substituted aryl iodides (**42b-i**); electron-deficient ones being more efficient coupling partners (**42b-e** and **42h-i**). Aryl iodides bearing electron-donating substituents (OMe, *t*Bu) led to the expected products **42f-g** in lower yields. Note that the reaction went smoothly with disubstituted aryl iodides containing one electron-withdrawing group as demonstrated

with the compound 42j. Additionally, when heteroaryl iodides were used, the expected products 42k-l were obtained in moderate to good yields and high enantioselectivities (up to 97% ee). Notably, in all the cases, an excellent selectivity towards the monoarylation was observed. Substituents over the ferrocene ring were also tolerated, affording the corresponding arylated products 42m-n with moderate to good yields. Finally, the *n*-propyl ketone 41o led to the arylated product 42o in 40% yield and 92% enantiomeric excess. It is worth mentioning that a dimeric palladacycle intermediate was presumably formed in the course of the transformation.

Scheme 16. Enantioselective Pd(II)-catalyzed C(sp²)-H arylation of ferrocenyl ketones.



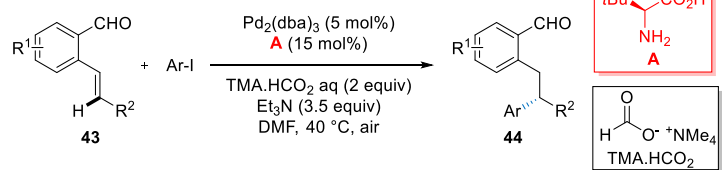
Ratio of mono:di arylated products are indicated in parenthesis. ^a The absolute configuration was assigned to *R_p* on the basis of X-ray diffraction.

In 2020, Liu, Engle and co-workers reported another application of the chiral transient directing group strategy for the enantioselective Pd-catalyzed β -hydroarylation of alkenyl benzaldehydes.⁴⁶ It is worth to mention that the enantioselective β -hydroarylation of substituted alkenyl arenes⁴⁷ is still underdeveloped compared to the asymmetric α -hydroarylation reaction.⁴⁸ Using *L*-tert-leucine and in the presence of a hydride donor (TMA.HCO₂), the Pd(0)-catalyzed reductive hydroarylation of alkenyl benzaldehydes with a panel of (hetero)aromatic iodides was achieved with yields up to 94% and enantiomeric excesses between 92% and >99% (Scheme 17). The reaction of the (*E*)-2-(prop-1-en-1-yl)benzaldehyde with several aryl iodides bearing electron-donating groups, electron-withdrawing ones and halogens led to the

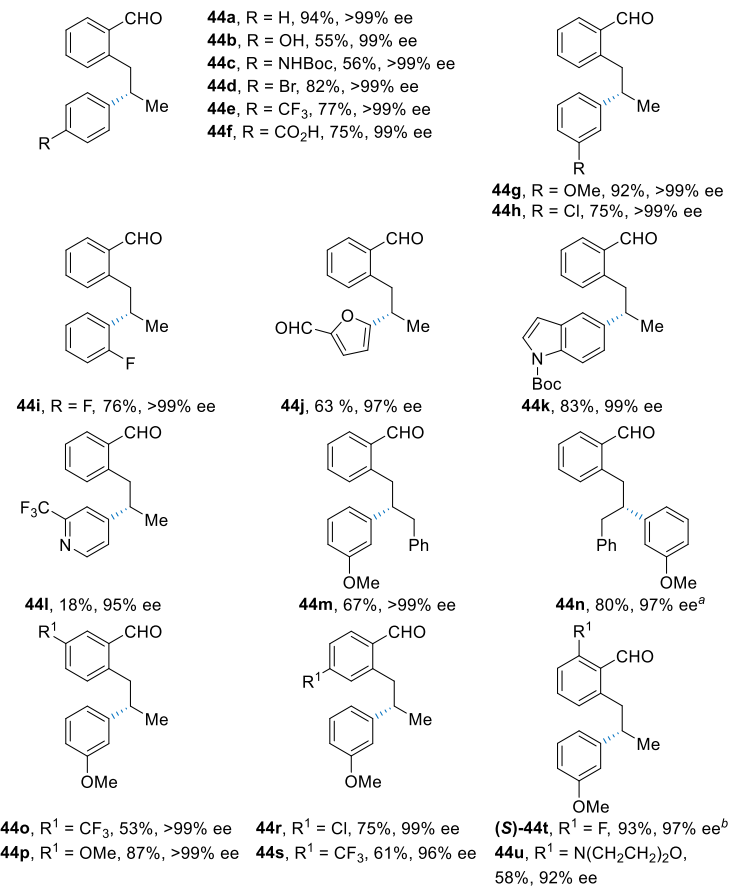
corresponding products 44a-i in moderate to excellent yields. Interestingly, various functional groups were tolerated such as a hydroxyl group (44b), a *N*-Boc-protected amine (44c) and a free carboxylic acid (44f). Heteroaryl iodides were suitable as well (44j-l), although the pyridine derivative 44l was synthesized with a very low yield. Regarding the alkene part, both *E* and *Z* isomers were hydroarylated and it turned out that *E* alkenes gave the best enantiomeric excesses but with lower yields (44m-n). Moreover, when the size of the substituent on the alkene part was increased, lower yields were generally obtained (44g vs. 44m). Finally, benzaldehydes with different substitution patterns were tested leading to the corresponding products 44o-u in good yields. Note that *ortho*-substituted benzaldehyde derivatives 43t-u were also functionalized. The authors suggested the following pathway for the enantioselective hydroarylation. First, aldimine I formation followed by the coordination to the Pd(0) would lead to the species II, which would undergo an oxidative addition with the aryl iodide to afford the intermediate III. Then, the enantioselective carbopalladation would take place (intermediate IV), which would be the key step for enantioinduction. Subsequently, the formate salt would coordinate to the metal center (intermediate V) and after a decarboxylation reaction, a Pd-H species VI would be obtained. A final reductive elimination would regenerate the Pd(0)-catalyst and would furnish VII, which after hydrolysis would release the product 44a along with L-*tert*-leucine (A).

Scheme 17. Pd(0)-catalyzed enantioselective reductive Heck arylation of alkenyl benzaldehydes.

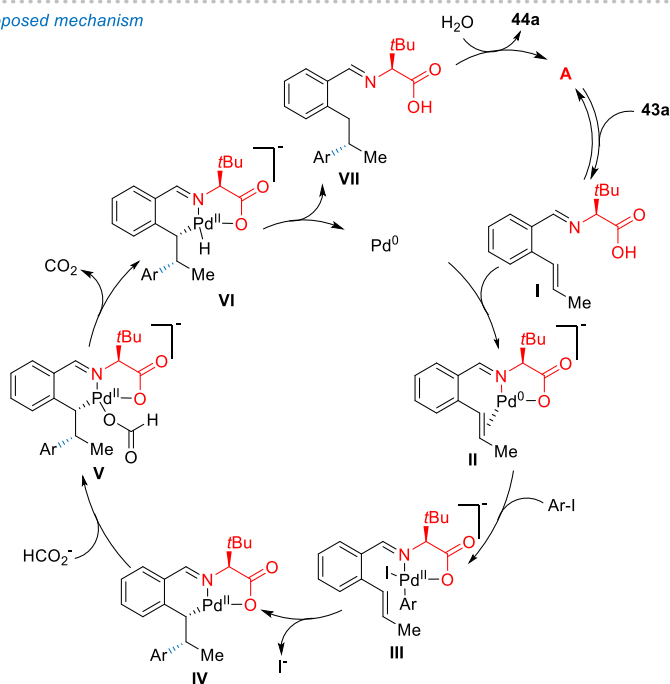
Liu, Engle et al.



Selected examples



Proposed mechanism



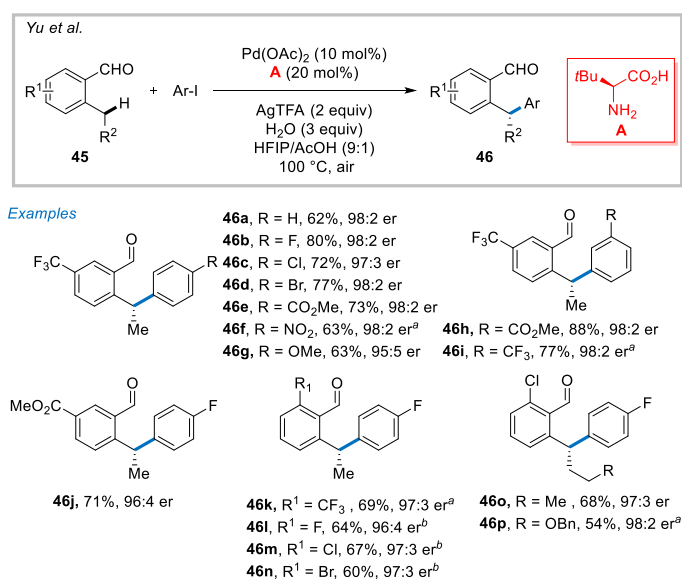
^aFrom *Z*-alkene. ^bThe absolute configuration was assigned through X-ray diffraction.

5. Enantioselective functionalization of C(sp³)–H bonds

Despite their lower reactivity in comparison with C(sp²)–H bonds, groundbreaking advances were made in the enantioselective functionalization of C(sp³)–H bonds by transition metal catalysis in the last decades.^{1a,13g,h,k} Among the existing approaches employed, the use of chiral ligands in Pd-catalyzed directed C–H bond functionalization reactions was broadly exploited.⁴⁹ Therefore, the quest for new approaches to reach highly challenging asymmetric transformations was particularly attractive. In this context, although restricted so far to handful of examples, the use of the chiral transient directing group strategy turned out to be an efficient tool as highlighted in this section.

In 2016, Yu and co-workers pioneered the use of a chiral transient directing group for achieving the Pd-catalyzed enantioselective arylation of benzylic C(sp³)–H bonds.⁵⁰ In the course of their study related to the arylation of C(sp³) centers of ketones and aldehydes by Pd-catalysis, the authors developed a methodology for the preparation of enantioenriched products by using *L*-*tert*-leucine (**A**) with yields up to 88% and enantiomeric ratios between 95:5 and 98:2 (Scheme 18). Taking benefit from the steric interactions between the bulky *tert*-butyl group of the *L*-*tert*-leucine and the benzylic R² group, good enantiomeric ratios were reached for this transformation. With this approach, an array of *meta*- and *para*-substituted aryl iodides was successfully employed for the functionalization of the 2-ethyl-5-(trifluoromethyl)benzaldehyde. Halogens as well as different electron-withdrawing (CO₂Me, NO₂, CF₃) and electron-donating groups (OMe) were well tolerated, as demonstrated with the synthesis of compounds **46a-i**. Several *ortho*- and *meta*-substituted benzaldehydes were suitable substrates in the reaction with 4-fluoroiodobenzene and the corresponding products **46j-n** were obtained in 60–71% yields and enantiomeric ratios up to 97:3. Note that the transformation turned out to be tolerant to functional groups such as an ester (**46j**) and halogens (**46l-n**). Moreover, the substituent over the benzylic position (R²) was not restricted to a methyl group since substrates bearing other alkyl chains were also smoothly functionalized (**46o-p**). Note that later in 2018, Dang and co-workers reported a theoretical study to get more insight about the regio- and stereoselectivity observed for the Pd-catalyzed arylation of aldehydes and ketones by C(sp³)–H activation using the chiral transient directing group strategy.⁵¹

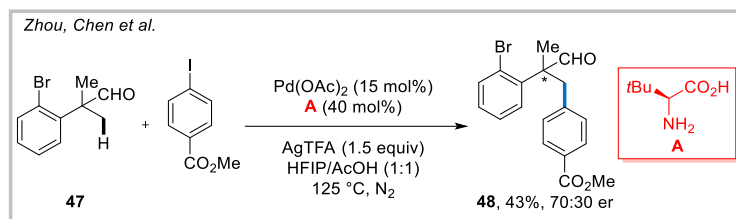
Scheme 18. Pd(II)-catalyzed enantioselective benzylic C(sp³)–H arylation of benzaldehyde derivatives using the *L*-*tert*-leucine as the chiral transient directing group precursor.



^a Reaction performed at 110 °C. ^b 5 mol% Pd(OAc)₂, 10 mol% **A**.

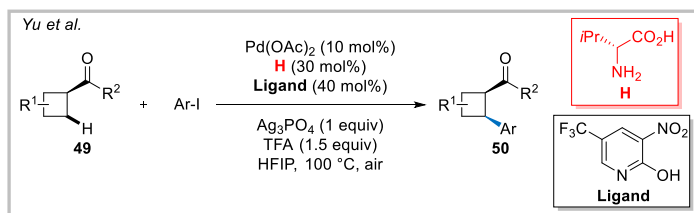
In 2019, during their investigations towards the arylation of phenylacetaldehyde derivatives with aryl iodides under Palladium catalysis, the group of Chen and Zhou applied a similar methodology than the one depicted by the Yu group.⁵² A single example of Pd(II)-catalyzed enantioselective arylation of the 2-bromo- α,α -dimethylbenzaldehyde 47 using the imine derived from L-*tert*-leucine as the transient directing group was achieved leading to the corresponding product 48 in 43% yield and an enantiomeric ratio of 70:30 (Scheme 19).

Scheme 19. Pd(II)-catalyzed C(sp³)-H asymmetric arylation of the phenylacetaldehyde derivative 47.

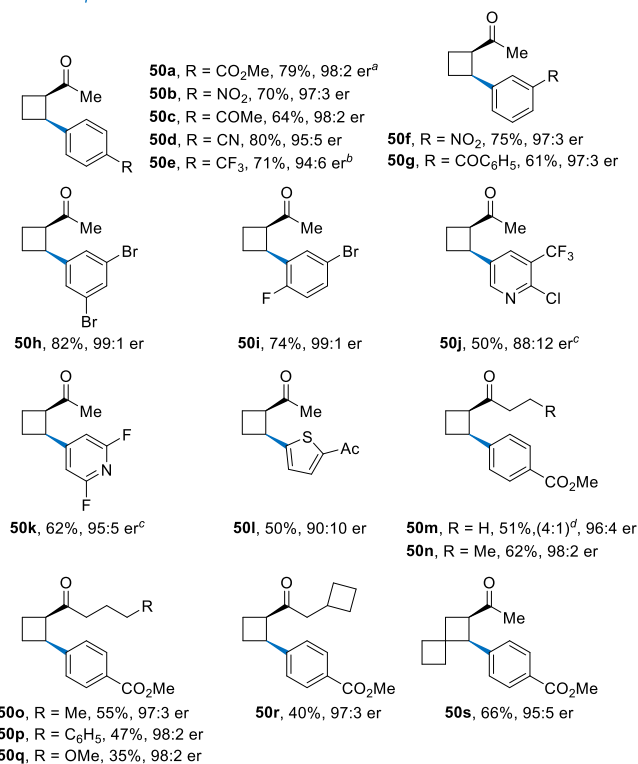


In 2020, Yu and co-workers provided a key contribution to the field by developing the Pd-catalyzed enantioselective arylation of nonactivated secondary C(sp³) centers. By employing a combination of Pd(OAc)₂, D-valine (H), pyridone and Ag₂PO₃, the authors were able to perform the arylation of cyclobutyl ketones 49, providing the corresponding products 50a-s with yields up to 82% and enantiomeric ratios up to 99:1 (Scheme 20).⁵³ Remarkably, by replacing Ag₂PO₃ by AgTFA, the products were obtained with a reversed enantioselectivity. Moreover, in this transformation, pyridone ligand, usually known for fastening the cleavage of C-H bonds,^{4k,7f,11k,54} was crucial to achieve the reaction with high enantioselectivities. The arylation proved to be efficient with several *para*- and *meta*-substituted aryl iodides bearing electron-withdrawing groups such as CO₂Me, NO₂, Ac, CN, CF₃ and COC₆H₅ (50a-g). Disubstituted electron-poor aryl iodides were also suitable coupling partners (50h-i). Although the functionalization was not efficient with electron-neutral or electron-rich iodoarenes, it went smoothly with heteroaromatic iodides (50k-l). Moreover, different cyclobutyl alkyl ketones were arylated at the α -position (50m-r) and only in the case of the ketone 49m, a competitive arylation of the methyl group of the alkyl chain was also observed. Note that even the spiro-derivative 50s was successfully functionalized. After mechanistic studies, a plausible pathway was suggested. First, coordination of the imine I derived from 49a to the palladium catalyst in the presence of the pyridone would afford the intermediate II, followed by the formation of the palladacycle III. This latter would undergo an oxidative addition with the aryl iodide (intermediate IV) and subsequently the iodine abstraction by the silver salt would take place (intermediate V). After reductive elimination, the catalyst would be regenerated and the ketimine VI would be obtained. A final hydrolysis of V would furnish the product 50a (or *ent*-50a) and H. Worth to mention that depending on the nature of the silver salt (AgTFA or Ag₂PO₃), either the C-H activation event or the iodine abstraction was suggested to be the rate determining step.

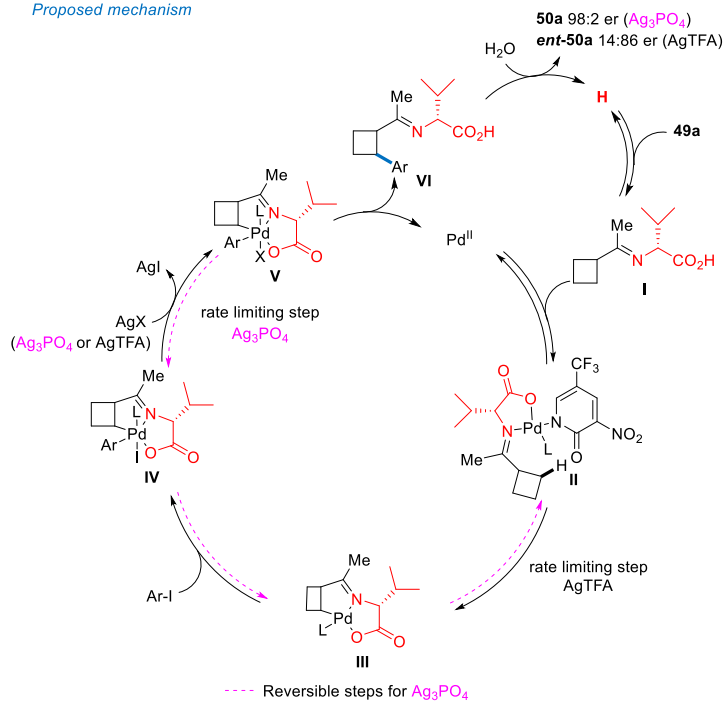
Scheme 20. Pd(II)-catalyzed enantioselective C(sp³)-H arylation of cyclobutyl ketones.



Selected examples



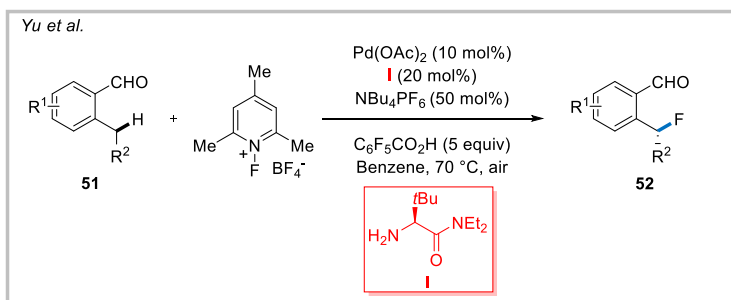
Proposed mechanism



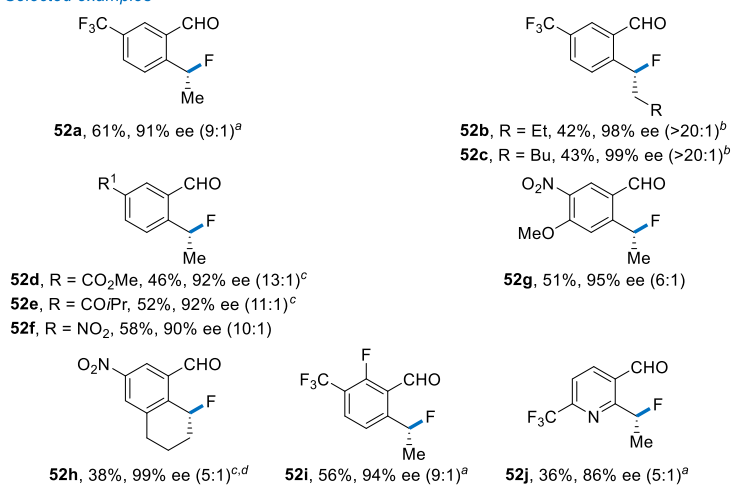
^a Using AgTFA instead of Ag₃PO₄, *ent*-50a was obtained in 34% yield (14:86 er) along with the corresponding diarylated product (50% yield). ^b D-*tert*-leucine was used as TDG precursor. ^c 1 equivalent of H was used. ^d Ratio of the products resulting from the arylation of the cyclobutane ring and the terminal methyl group.

The asymmetric formation of C(sp³)-F bonds has been achieved in the last two decades through different strategies.⁵⁵ In sharp contrast, the transition metal-catalyzed enantioselective direct fluorination of a C(sp³)-H bond is a highly difficult and appealing task and needs to be further investigated. To tackle this synthetic challenge, Yu and co-workers developed a new methodology based on the Pd(II)-catalyzed enantioselective fluorination of C(sp³) centers using a chiral transient directing group.⁵⁶ They anticipated that the design and use of a suitable ligand in this Pd(II)/Pd(IV) process would be crucial to successfully promote the C(sp³)-F bond formation in an enantioselective fashion over the side-competitive reductive eliminations (C-C or C-X bond formation) from Pd(IV) species,⁵⁷ and the undesirable S_N2-type reactions over C(sp³)-Pd(IV)-F intermediates.⁵⁸ Instead of using a traditional amino acid, it was discovered that the combination of the amide **1** (derived from L-*tert*-leucine) along with 2,3,4,5,6-pentafluorobenzoic allowed the fluorination of the trifluoromethylated benzaldehyde derivative **51a** on a secondary C(sp³) center in the presence of *N*-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate as the fluorinating reagent (Scheme 21). A panel of aromatic aldehydes was functionalized leading to the expected products **52b-j** in yields up to 61% and enantiomeric excesses ranging between 86-99%. Even though the competitive pathway that led to the formation of the undesired C(sp³)-O bond formation by an S_N2-type process could not be completely circumvented, moderate to excellent ratios in favor to the fluorinated products were obtained (5:1 to >20:1). Benzaldehydes bearing longer alkyl chains than an ethyl group at the *ortho* position were also suitable and furnished the best enantiomeric excesses and the best C(sp³)-F/C(sp³)-O ratio (>20:1), albeit with lower yields (**52b-c**). Moreover, benzaldehydes substituted with electron-withdrawing groups (CO₂Me, CO₂iPr, NO₂, **51d-f**) at the *meta* position were successfully functionalized. Although electron-rich substrates turned out to be inefficient in this transformation, the fluorination was achieved when the disubstituted benzaldehyde **51g** was used. Note that the tetraline derivative **51h**, the *ortho*-fluorinated aldehyde **51i** and the pyridine **51j** were also suitable substrates in this transformation. On the basis of mechanistic investigations and literature data,⁵⁹ the authors suggested that a cationic Pd(IV) intermediate would be the key intermediate in this transformation and would favor the fluorination reaction over the C(sp³)-O bond formation.

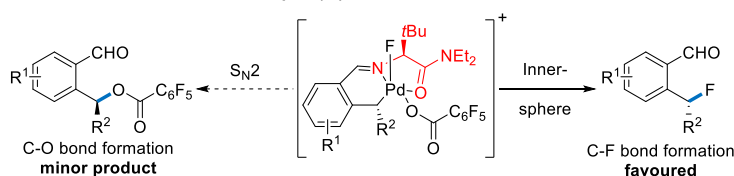
Scheme 21. Pd(II)-catalyzed enantioselective fluorination secondary C(sp³)-H bonds.



Selected examples



Key Pd(IV) cationic intermediate



Isolated yields were reported as a mixture of the product **52** with the starting material **51**. The numbers in parenthesis indicated the ratio of products resulting from either a C(sp³)-F or C(sp³)-O bond formation and were determined by ¹H NMR analysis. ^a ¹H NMR yields were given due to the volatility of the products. ^b 1-Fluoro-2,4,6-trimethylpyridinium hexafluorophosphate (1.5 equiv) was used as the fluorine source. ^c CH₂Cl₂ was used instead of benzene. ^d 25 mol% of **1** were used.

6. SUMMARY

Over the past few years, transition metal-catalyzed enantioselective transformations by C-H bond activation have been developed as a powerful tool for the construction of interesting chiral molecules. In particular, the use of the chiral transient directing group strategy was appealing, offering potent synthetic solutions to the challenging asymmetric transformations. In this review, a general overview of the recent groundbreaking advances made in this field was given. Original methodologies based on the astute use of chiral transient directing groups for the enantioselective synthesis of biaryls, as well as chiral heterocycles and carbocycles were developed. In addition, this strategy was successfully applied to the challenging enantioselective C(sp³)-H bond functionalization. Even though major breakthroughs were achieved, this modern and sustainable strategy is still in its infancy. Indeed, so far only aldehyde and ketone derivatives were used as substrates to provide the chiral transient directing group by the reversible formation of an imine and in most cases, acidic reaction conditions were necessary; which hampered the general use of this strategy. To widen the scope of these transformations, the use of amine derivatives as substrates and more generally, the reversible formation of other functional groups playing the role of chiral transient directing groups are expected to be explored. Moreover, most of the transformations were limited to the formation of C-C or C-F bonds, although in the last case, only a single example was reported. Therefore, there is an urgent need to further explore other transformations. Finally, the enantioselective

functionalization of unactivated aliphatic derivatives and the use of earth-abundant 3d transition metals were not achieved yet, and any advances using the chiral transient directing group strategy will bring significant breakthroughs. We do believe that this novel tool will be inspiring for the scientific community and milestones will be reached in the forthcoming years, expanding the chemical space for asymmetric transformations.

Acknowledgements

This work was partially supported by Normandie Université (NU), the Région Normandie, the Centre National de la Recherche Scientifique (CNRS), Université de Rouen Normandie (URN), INSA Rouen Normandie, Labex SynOrg (ANR-11-LABX-0029) and Innovation Chimie Carnot (I2C). M.I.L., S.M. and T.B. thank the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation program (grant agreement no. 758710).

Keywords: Transition Metal, Chiral Transient Directing Group, Asymmetric Transformations, Dual Catalysis, Synthetic Methodology, C–H Bond Functionalization

- (1) For selected reviews and accounts, see: (a) Giri, R.; Shi, B.-F.; Engle, K. M.; Maugel, N.; Yu, J.-Q. Transition metal-catalyzed C–H activation reactions: diastereoselectivity and enantioselectivity. *Chem. Soc. Rev.* **2009**, *38*, 3242–3272. (b) Lyons, T. M.; Sanford, M. S. Palladium-Catalyzed Ligand-Directed C–H Functionalization Reactions. *Chem. Rev.* **2010**, *110*, 1147–1169. (c) Jazzar, V.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. Functionalization of Organic Molecules by Transition-Metal-Catalyzed C(sp³)–H Activation. *Chem. Eur. J.* **2010**, *16*, 2654–2672. (d) Baudoin, O. Transition metal-catalyzed arylation of unactivated C(sp³)–H bonds. *Chem. Soc. Rev.* **2011**, *40*, 4902–4911. (e) Li, H.; Lia, B. J.; Shi, Z.-J. Challenge and progress: palladium-catalyzed sp³ C–H activation. *Catal. Sci. Technol.* **2011**, *1*, 191–206. (f) Ackermann, L. Carboxylate-Assisted Transition-Metal-Catalyzed C–H Bond Functionalizations: Mechanism and Scope. *Chem. Rev.* **2011**, *111*, 1315–1345. (g) Zhao, D.; You, J.; Hu, C. Recent Progress in Coupling of Two Heteroarenes. *Chem. Eur. J.* **2011**, *17*, 5466–5492. (h) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. Weak Coordination as a Powerful Means for Developing Broadly Useful C–H Functionalization Reactions. *Acc. Chem. Res.* **2012**, *45*, 788–802. (i) Kuhl, N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. Beyond Directing Groups: Transition-Metal-Catalyzed C–H Activation of Simple Arenes. *Angew. Chem. Int. Ed.* **2012**, *51*, 10236–10254. (j) Neufeldt, S. R.; Sanford, M. S. Controlling Site Selectivity in Palladium-Catalyzed C–H Bond Functionalization. *Acc. Chem. Res.* **2012**, *45*, 936–946. (k) Ackermann, L. Carboxylate-Assisted Ruthenium-Catalyzed Alkyne Annulations by C–H/Het–H Bond Functionalizations. *Acc. Chem. Res.* **2014**, *47*, 281–295. (l) Zhang, X.-S.; Chen, K.; Shi, Z.-J. Transition metal-catalyzed direct nucleophilic addition of C–H bonds to carbon–heteroatom double bonds. *Chem. Sci.* **2014**, *5*, 2146–2159. (m) Dastbaravardeh, N.; Christakakou, M.; Haider, M.; Schnürch, M. Recent Advances in Palladium-Catalyzed C(sp³)–H Activation for the Formation of Carbon–Carbon and Carbon–Heteroatom Bonds. *Synthesis* **2014**, *46*, 1421–1439. (n) Huang, Z.; Dong, G. Catalytic C–C bond forming transformations via direct β–C–H functionalization of carbonyl compounds. *Tetrahedron Lett.* **2014**, *55*, 5869–5889. (o) Huang, Z.; Lim, H. N.; Mo, F.; Young, M. C.; Dong, G. Transition metal-catalyzed ketone-directed or mediated C–H functionalization. *Chem. Soc. Rev.* **2015**, *44*, 7764–7786. (p) Song, G.; Li, X. Substrate Activation Strategies in Rhodium(III)-Catalyzed Selective Functionalization of Arenes. *Acc. Chem. Res.* **2015**, *48*, 1007–1020. (q) Hartwig, J. F. Evolution of C–H Bond Functionalization from Methane to Methodology. *J. Am. Chem. Soc.* **2016**, *138*, 2–24. (r) *C–H Bond Activation and Catalytic Functionalization I*. In *Topics in Organometallic Chemistry*, Dixneuf, P. H.; Doucet, H.; Eds.; Springer International: Switzerland, 2016; vol 55, 1–264. (s) Pototschnig, G.; Maulide, N.; Schnürch, M. Direct Functionalization of C–H Bonds by Iron, Nickel, and Cobalt Catalysis. *Chem. Eur. J.* **2017**, *23*, 9206–9232. (t) Dong, Z.; Ren, Z.; Thompson, S. J.; Xu, Y.; Dong, G. Transition-Metal-Catalyzed C–H Alkylation Using Alkenes. *Chem. Rev.* **2017**, *117*, 9333–9403. (u) He, J.; Wasa, M.; Chan, K. S. L.; Shao, Q.; Yu, J.-Q. Palladium-Catalyzed Transformations of Alkyl C–H Bonds. *Chem. Rev.* **2017**, *117*, 8754–8786. (v) Park, Y.; Kim, Y.; Chang, S. Transition Metal-Catalyzed C–H Amination: Scope, Mechanism, and Applications. *Chem. Rev.* **2017**, *117*, 9247–9301. (w) Ma, C.; Fang, P.; Mei, T.-S. Recent Advances in C–H Functionalization Using Electrochemical Transition Metal Catalysis. *ACS Catal.* **2018**, *8*, 7179–7189. (x) Gandeepan, P.; Muller, T.; Zell, D.; Cera, G.; Warratz, S.; Ackermann, L. 3d Transition Metals for C–H Activation. *Chem. Rev.* **2019**, *119*, 2192–2452.
- (2) For selected reviews, see: (a) McMurray, L.; O'Hara, F.; Gaunt, M. J. Recent developments in natural product synthesis using metal-catalysed C–H bond functionalisation. *Chem. Soc. Rev.* **2011**, *40*, 1885–1898. (b) Newhouse, T.; Baran, P. S. If C–H Bonds Could Talk: Selective C–H Bond Oxidation. *Angew. Chem. Int. Ed.* **2011**, *50*, 3362–3374. (c) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. C–H Bond Functionalization: Emerging Synthetic Tools for Natural Products and Pharmaceuticals. *Angew. Chem. Int. Ed.* **2012**, *51*, 8960–9009. (d) Chen, D. Y.-K.; Youn, S. W. C–H Activation: A Complementary Tool in the Total Synthesis of Complex Natural Products. *Chem. Eur. J.* **2012**, *18*, 9452–9474. (e) Wencel-Delord, J.; Glorius, F. C–H bond activation enables the rapid construction and late-stage diversification of functional molecules. *Nat. Chem.* **2013**, *5*, 369–375. (f) Segawa, Y.; Maekawa, T.; Itami, K. Synthesis of Extended π-Systems through C–H Activation. *Angew. Chem. Int. Ed.* **2015**, *54*, 66–81. (g) Qiu, Y.; Gao, S. Trends in applying C–H oxidation to the total synthesis of natural products. *Nat. Prod. Rep.* **2016**, *33*, 562–581. (h) Cernak, T.; Dykstra, K. D.; Tyagarajan, S.; Vachal, P. S.; Krska, W. The medicinal chemist's toolbox for late stage functionalization of drug-like molecules. *Chem. Soc. Rev.* **2016**, *45*, 546–576. (i) Bedell, T. A.; Hone, G. A. B.; Valette, D.; Yu, J.-Q.; Davies, H. M. L.; Sorensen, E. J. Rapid Construction of a Benzo-Fused Indoxamycin Core Enabled by Site-Selective C–H Functionalizations. *Angew. Chem. Int. Ed.* **2016**, *55*, 8270–8274. (j) Karimov, R. R.; Hartwig, J. F. Transition-Metal-Catalyzed Selective Functionalization of C(sp³)–H Bonds in Natural Products. *Angew. Chem. Int. Ed.* **2018**, *57*, 4234–4241. (k) Baudoin, O. Multiple Catalytic C–H Bond Functionalization for Natural Product Synthesis. *Angew. Chem. Int. Ed.* **2020**, [10.1002/anie.202001224](https://doi.org/10.1002/anie.202001224).
- (3) For selected reviews, see: (a) Rouquet, G.; Chatani, N. Catalytic Functionalization of C(sp²)–H and C(sp³)–H Bonds by Using Bidentate Directing Groups. *Angew. Chem. Int. Ed.* **2013**, *52*, 11726–11743. (b) Zhu, R.-Y.; Farmer, M. E.; Chen, Y.-Q.; Yu, J.-Q. A Simple and Versatile Amide Directing Group for C–H Functionalizations. *Angew. Chem. Int. Ed.* **2016**, *55*, 10578–10599. (c) Chen, Z.; Wang, B.; Zhang, J.; Yu, W.; Liu, Z.; Zhang, Y. Transition metal-catalyzed C–H bond functionalizations by the use of diverse directing groups. *Org. Chem. Front.* **2015**, *2*, 1107–12095. (d) Zhang, M.; Zhang, Y.; Jie, X.; Zhao, H.; Li, G.; Su, W. Recent advances in directed C–H functionalizations using monodentate nitrogen-based directing groups. *Org. Chem. Front.* **2014**, *1*, 843–895. (e) Rousseau, G.; Breit, B. Removable Directing Groups in Organic Synthesis and Catalysis. *Angew. Chem. Int. Ed.* **2011**, *50*, 2450–2494. (f) Zhang, L.; Fang, D. Explicit roles of diverse directing

- groups in determining transition state energy and reaction exothermicity of C–H activation pathways. *Org. Chem. Front.* **2017**, *4*, 1250–1260.
- (g) Castro, L. C. M.; Chatani, N. Nickel Catalysts/N,N'-Bidentate Directing Groups: An Excellent Partnership in Directed C–H Activation Reactions. *Chem. Lett.* **2015**, *44*, 410–421. (h) Corbet, M.; De Campo, F. 8-Aminoquinoline: A Powerful Directing Group in Metal-Catalyzed Direct Functionalization of C–H Bonds. *Angew. Chem. Int. Ed.* **2013**, *52*, 9896–9898. (i) Sambaglio, C.; Schönbauer, D.; Blicke, R.; Dao-Huy, T.; Pototschnig, G.; Schaaf, P.; Wiesinger, T.; Zia, M. F.; Wencel-Delord, J.; Besset, T.; Maes, B. U. W.; Schnürch, M. A comprehensive overview of directing groups applied in metal-catalysed C–H functionalisation chemistry. *Chem. Soc. Rev.* **2018**, *47*, 6603–6743. (j) Rej, S.; Ano, Y.; Chatani, N. Bidentate Directing Groups: An Efficient Tool in C–H Bond Functionalization Chemistry for the Expedient Construction of C–C Bonds. *Chem. Rev.* **2020**, *120*, 1788–1887.
- (4) For selected reviews regarding *meta* and *para* functionalization, see: (a) Yu, D.-G.; de Azambuja, F.; Glorius, F. Direct Functionalization with Complete and Switchable Positional Control: Free Phenol as a Role Model. *Angew. Chem. Int. Ed.* **2014**, *53*, 7710–7712. (b) Juliá-Hernández, F.; Simonetti, M.; Larrosa, I. Metalation Dictates Remote Regioselectivity: Ruthenium-Catalyzed Functionalization of *meta* C_{Ar}–H Bonds. *Angew. Chem. Int. Ed.* **2013**, *52*, 11458–11460 and references cited therein. (c) Yang, J. Transition metal catalyzed *meta*-C–H functionalization of aromatic compounds. *Org. Biomol. Chem.* **2015**, *13*, 1930–1941. (d) Dey, A.; Maity, S.; Maiti, D. Reaching the south: metal-catalyzed transformation of the aromatic *para*-position. *Chem. Commun.* **2016**, *52*, 12398–12414. (e) Dey, A.; Agasti, S.; Maiti, D. Palladium catalysed *meta*-C–H functionalization reactions. *Org. Biomol. Chem.* **2016**, *14*, 5440–5453. (f) Li J.; De Sarkar S.; Ackermann L. *meta*- and *para*-Selective C–H Functionalization by C–H Activation. In *C-H Bond Activation and Catalytic Functionalization I. Topics in Organometallic Chemistry*, Dixneuf, P. H., Doucet H., Eds. Springer International: Switzerland, 2016, vol 55, 217–257. (g) Mihai, M. T.; Genov, G. R.; Phipps, R. J. Access to the *meta* position of arenes through transition metal catalysed C–H bond functionalisation: a focus on metals other than Palladium. *Chem. Soc. Rev.* **2018**, *47*, 149–171. (h) Dey, A.; Sinha, S. K.; Achar, T. K.; Maiti, D. Accessing Remote *meta* - and *para*-C(sp²)-H Bonds with Covalently Attached Directing Groups. *Angew. Chem. Int. Ed.* **2019**, *58*, 10820–10843. (i) Meng, G.; Lam, N. Y. S.; Lucas, E. L.; Saint-Denis, T. G.; Verma, P.; Chekshin, N.; Yu, J.-Q. Achieving Site-Selectivity for C–H Activation Processes Based on Distance and Geometry: A Carpenter's Approach. *J. Am. Chem. Soc.* **2020**, *142*, 10571–10591. For selected examples of functionalization at the *meta* or *para* positions by C–H bond activation, see: (j) Gholap, A.; Bag, S.; Pradhan, S.; Kapdi, A. R.; Maiti, M. Diverse *meta*-C–H Functionalization of Amides. *ACS Catal.* **2020**, *10*, 5347–5352. (k) Fan, Z.; Bay, K. L.; Chen, X.; Zhuang, Z.; Park, H. S.; Yeung, K.-S.; Houk, K. N.; Yu, J.-Q. Rational Development of Remote C–H Functionalization of Biphenyl: Experimental and Computational Studies. *Angew. Chem. Int. Ed.* **2020**, *59*, 4770–4777. (l) Brochetta, M.; Borsari, T.; Bag, S.; Jana, S.; Maiti, S.; Porta, A.; Werz, D. B.; Zaroni, G.; Maiti, D. Direct *meta*-C–H Perfluoroalkenylation of Arenes Enabled by a Cleavable Pyrimidine-Based Template. *Chem. Eur. J.* **2019**, *25*, 10323–10327. (m) Dutta, U.; Maiti, S.; Pimparkar, S.; Maiti, S.; Gahan, L. R.; Krenske, E. H.; Lupton, D. W.; Maiti, D. Rhodium catalyzed template-assisted distal *para*-C–H olefination. *Chem. Sci.* **2019**, *10*, 7426–7432. (n) Pimparkar, S.; Bhattacharya, T.; Maji, A.; Saha, A.; Jayarajan, R.; Dutta, U.; Lu, G.; Lupton, D. W.; Maiti, D. *Para*-Selective Cyanation of Arenes by H-Bonded Template. *Chem. Eur. J.* **2020**, *26*, 11558–11564. (o) Jin, Z.; Chu, L.; Chen, Y.-Q.; Yu, J.-Q. Pd-Catalyzed Remote *Meta*-C–H Functionalization of Phenylacetic Acids Using a Pyridine Template. *Org. Lett.* **2018**, *20*, 425–428. (p) Liang, S.; Bolte, M.; Manolikakes, G. Copper-Catalyzed Remote *para*-C–H Functionalization of Anilines with Sodium and Lithium Sulfonates. *Chem. Eur. J.* **2017**, *23*, 96–100. (q) Bera, M.; Agasti, S.; Chowdhury, R.; Mondal, R.; Pal, D.; Maiti, D. Rhodium-Catalyzed *meta*-C–H Functionalization of Arenes. *Angew. Chem. Int. Ed.* **2017**, *56*, 5272–5276. (r) Dutta, U.; Modak, A.; Bhaskararao, B.; Bera, M.; Bag, S.; Mondal, A.; Lupton, D. W.; Sunoj, R. B.; Maiti, D. Catalytic Arene *meta*-C–H Functionalization Exploiting a Quinoline-Based Template. *ACS Catal.* **2017**, *7*, 3162–3168. (s) Li, J.; Korvorapun, K.; De Sarkar, S.; Rogge, T.; Burns, D. J.; Warratz, S.; Ackermann, L. Ruthenium(II)-catalysed remote C–H alkylations as a versatile platform to *meta*-decorated arenes. *Nat. Commun.* **2017**, *8*, 15430–15438. (t) Bag, S.; Patra, T.; Modak, A.; Deb, A.; Maity, S.; Dutta, U.; Dey, A.; Kancherla, R.; Maji, A.; Hazra, A.; Bera, M.; Maiti, D. Remote *para*-C–H Functionalization of Arenes by a D-Shaped Biphenyl Template-Based Assembly. *J. Am. Chem. Soc.* **2015**, *137*, 11888–11891 and references cited therein. (u) Tang, R.-Y.; Li, G.; Yu, J.-Q. Conformation-induced remote *meta*-C–H activation of amines. *Nature* **2014**, *507*, 215–220. (v) Cheng, G.-J.; Yang, Y.-F.; Liu, P.; Chen, P.; Sun, T.-Y.; Li, G.; Zhang, X.; Houk, K. N.; Yu, J.-Q.; Wu, Y.-D. Role of *N*-Acyl Amino Acid Ligands in Pd(II)-Catalyzed Remote C–H Activation of Tethered Arenes. *J. Am. Chem. Soc.* **2014**, *136*, 894–897. (w) Yang, Y.-F.; Cheng, G.-J.; Liu, P.; Leow, D.; Sun, T.-Y.; Chen, P.; Zhang, X.; Yu, J.-Q.; Wu, Y.-D.; Houk, K. N. Palladium-Catalyzed *Meta*-Selective C–H Bond Activation with a Nitrile-Containing Template: Computational Study on Mechanism and Origins of Selectivity. *J. Am. Chem. Soc.* **2014**, *136*, 344–355. (x) Lee, S.; Lee, H.; Tan, K. L. *Meta*-Selective C–H Functionalization Using a Nitrile-Based Directing Group and Cleavable Si-Tether. *J. Am. Chem. Soc.* **2013**, *135*, 18778–18781. (y) Chen, B.; Leow, D.; Li, G.; Mei, T.-S.; Yu, J.-Q. Activation of remote *meta*-C–H bonds assisted by an end-on template. *Nature* **2012**, *486*, 518–522. (z) Phipps, R. J.; Gaunt, M. J. A *Meta*-Selective Copper-Catalyzed C–H Bond Arylation. *Science* **2009**, *323*, 1593–1597. (aa) Porey, S.; Zhang, X.; Bhowmick, S.; Singh, V. K.; Guin, S.; Paton, R. S.; Maiti, D. Alkyne Linchpin Strategy for Drug: Pharmacophore Conjugation: Experimental and Computational Realization of a *Meta*-Selective Inverse Sonogashira Coupling. *J. Am. Chem. Soc.* **2020**, *142*, 3762–3774. (ab) Bag, S.; K, S.; Mondal, A.; Jayarajan, R.; Dutta, U.; Porey, S.; Sunoj, R. B.; Maiti, D. Palladium-catalyzed *meta*-C–H allylation of arenes: A unique combination of pyrimidine-based template and hexafluoroisopropanol. *J. Am. Chem. Soc.* **2020**, *142*, 12453–12466.
- (5) For selected reviews for remote C(sp³)-H activation, see: (a) Schranck, J.; Tlili, A.; Beller, M. Functionalization of Remote C–H Bonds: Expanding the Frontier. *Angew. Chem. Int. Ed.* **2014**, *53*, 9426–9428. (b) Qiu, G.; Wu, J. Transition metal-catalyzed direct remote C–H functionalization of alkyl groups via C(sp³)-H bond activation. *Org. Chem. Front.* **2015**, *2*, 169–178. For selected examples see: (c) Desai, L. V.; Hull, K. L.; Sanford, M. S. Palladium-Catalyzed Oxygenation of Unactivated sp³ C–H Bonds. *J. Am. Chem. Soc.* **2004**, *126*, 9542–9543. (d) Thu, H.-Y.; Yu, W.-Y.; Che, C. -M. Intermolecular Amidation of Unactivated sp² and sp³ C–H Bonds via Palladium-Catalyzed Cascade C–H Activation/Nitrene Insertion. *J. Am. Chem. Soc.* **2006**, *128*, 9048–9049. (e) Das, S.; Incarvito, C. D.; Crabtree, R. H.; Brudvig, G. W. Molecular Recognition in the Selective Oxygenation of Saturated C–H Bonds by a Dimanganese Catalyst. *Science* **2006**, *312*, 1941–1943. (f) Aspin, S.; Goutierre, A.-S.; Larini, P.; Jazsar, R.; Baudoin, O. Synthesis of Aromatic α -Aminoesters: Palladium-Catalyzed Long-Range Arylation of Primary C_{sp3}-H Bonds. *Angew. Chem. Int. Ed.* **2012**, *51*, 10808–10811. (g) Mu, Y.; Tan, X.; Zhang, Y.; Jing, X.; Shi, Z. Pd(II)-catalyzed β -C–H arylation of O-methyl ketoximes with iodoarenes. *Org. Chem. Front.* **2016**, *3*, 380–384. (h) Xu, J.-W.; Zhang, Z.-Z.; Rao, W.-H.; Shi, B.-F. Site-Selective Alkenylation of δ -C(sp³)-H Bonds with Alkynes via a Six-Membered Palladacycle. *J. Am. Chem. Soc.* **2016**, *138*, 10750–10753. (i) Deb, A.; Singh, S.; Seth, K.; Pimparkar, S.; Bhaskararao, B.; Guin, S.; Sunoj, R. B.; Maiti, D. Experimental and Computational Studies on Remote γ -C(sp³)-H Silylation and Germanylation of Aliphatic Carboxamides. *ACS Catal.* **2017**, *7*, 8171–8175. (j) Parella, R.; Babu, S. A. Pd(II)-Catalyzed Arylation and Intramolecular Amidation of γ -C(sp³)-H Bonds: En Route to Arylheteroarylmethane and Pyrrolidone Ring Annulated Furan/Thiophene Scaffolds. *J. Org. Chem.* **2017**, *82*, 7123–7150. (k) Guin, S.; Deb, A.; Dolui, P.; Chakraborty, S.; Singh, V. K.; Maiti, D. Promoting Highly Diastereoselective γ -C–H Chalcogenation of α -Amino Acids and Aliphatic Carboxylic Acids. *ACS Catal.* **2018**, *8*, 2664–2669.

- (6) For selected examples, see: Bhadra, S.; Dzik, W.; Gooßen, L. J. Synthesis of Aryl Ethers from Benzoates through Carboxylate-Directed C–H-Activating Alkoxylation with Concomitant Protodecarboxylation. *Angew. Chem. Int. Ed.* **2013**, *52*, 2959–2962. (b) Luo, J.; Preciado, S.; Larrosa, I. Overriding *Ortho*–*Para* Selectivity via a Traceless Directing Group Relay Strategy: The *Meta*-Selective Arylation of Phenols. *J. Am. Chem. Soc.* **2014**, *136*, 4109–4112. (c) Qin, X.; Sun, D.; You, Q.; Cheng, Y.; Lan, J.; You, J. Rh(III)-Catalyzed Decarboxylative *ortho*-Heteroarylation of Aromatic Carboxylic Acids by Using the Carboxylic Acid as a Traceless Directing Group. *Org. Lett.* **2015**, *17*, 1762–1765. (d) Maiti, D.; Agasti, S.; Dey, A. Traceless directing group mediated branched selective alkenylation of unbiased arenes. *Chem. Commun.* **2016**, *52*, 12191–12194. (e) Kumar, N. Y. P.; Bechtoldt, A.; Raghuvanshi, K.; Ackermann, L. Ruthenium(II)-Catalyzed Decarboxylative C–H Activation: Versatile Routes to *meta*-Alkenylated Arenes. *Angew. Chem. Int. Ed.* **2016**, *55*, 6929–6932. (f) Biafora, A.; Khan, B. A.; Bahri, J.; Hewer, J. M.; Goossen, L. J. Doubly Regioselective C–H Hydroarylation of Unsymmetrical Alkynes Using Carboxylates as Deciduous Directing Groups. *Org. Lett.* **2017**, *19*, 1232–1235. (g) Lu, Q.; Greßies, S.; Cembellin, S.; Klauk, F. J. R.; Daniliuc, C. G.; Glorius, F. Redox-Neutral Manganese(I)-Catalyzed C–H Activation: Traceless Directing Group Enabled Regioselective Annulation. *Angew. Chem. Int. Ed.* **2017**, *56*, 12778–12782. (h) Mandal, A.; Sahoo, H.; Dana, S.; Baidya, M. Ruthenium(II)-Catalyzed Hydroarylation of Maleimides Using Carboxylic Acids as a Traceless Directing Group. *Org. Lett.* **2017**, *19*, 4138–4141. (i) Font, M.; Spencera, A. R. A.; Larrosa, I. *meta*-C–H arylation of fluoroarenes via traceless directing group relay strategy. *Chem. Sci.* **2018**, *9*, 7133–7137. (j) Spencer, A. R. A.; Korde, R.; Fonta, M.; Larrosa, I. *meta*-Selective olefination of fluoroarenes with alkynes using CO₂ as a traceless directing group. *Chem. Sci.* **2020**, *11*, 4204–4208. (k) Dolui, P.; Das, J.; Chandrashekar, H. B.; Anjana, S. S.; Maiti, D. Ligand-Enabled Pd(II)-Catalyzed Iterative γ -C(sp³)-H Arylation of Free Aliphatic Acid. *Angew. Chem. Int. Ed.* **2019**, *58*, 13773–13777.
- (7) For selected reviews, see: (a) Della Ca', N.; Fontana, M.; Motti, E.; Catellani, M. Pd/Norbornene: A Winning Combination for Selective Aromatic Functionalization via C–H Bond Activation. *Acc. Chem. Res.* **2016**, *49*, 1389–1400. (b) Cheng, H.-G.; Chen, S.; Chen, R.; Zhou, Q. Palladium(II)-Initiated Catellani-Type Reactions. *Angew. Chem. Int. Ed.* **2019**, *58*, 5832–5844. (c) Wang, J.; Dong, G. Palladium/Norbornene Cooperative Catalysis. *Chem. Rev.* **2019**, *119*, 7478–7528. For selected examples, see: (d) Dong, Z.; Dong, G. *Ortho* vs *Ips*o: Site-Selective Pd and Norbornene-Catalyzed Arene C–H Amination Using Aryl Halides. *J. Am. Chem. Soc.* **2013**, *135*, 18350–18353. (e) Wang, X.-C.; Gong, W.; Fang, L.-Z.; Zhu, R.-Y.; Li, S.; Engle, K. M.; Yu, J.-Q. Ligand-enabled *meta*-C–H activation using a transient mediator. *Nature* **2015**, *519*, 334–338. (f) Wang, P.; Farmer, M. E.; Huo, X.; Jain, P.; Shen, P.-X.; Ishoe, M.; Bradner, J. E.; Wisniewski, S. R.; Eastgate, M. D.; Yu, J.-Q. Ligand-Promoted *Meta*-C–H Arylation of Anilines, Phenols, and Heterocycles. *J. Am. Chem. Soc.* **2016**, *138*, 9269–9276 and references cited therein. (g) Shen, P.-X.; Wang, X.-C.; Wang, P.; Zhu, R.-Y.; Yu, J.-Q. Ligand-Enabled *Meta*-C–H Alkylation and Arylation Using a Modified Norbornene. *J. Am. Chem. Soc.* **2015**, *137*, 36, 11574–11577. (h) Liu, L.; Qiao, J. X.; Yeung, K.; Ewing, W. R.; Yu, J.-Q. *meta*-Selective C–H Arylation of Fluoroarenes and Simple Arenes. *Angew. Chem. Int. Ed.* **2020**, *59*, 13831–13835.
- (8) For selected examples, see: (a) Wang, Z.; Reinus, B. J.; Dong, G. Catalytic Intermolecular C-Alkylation of 1,2-Diketones with Simple Olefins: A Recyclable Directing Group Strategy. *J. Am. Chem. Soc.* **2012**, *134*, 13954–13957. (b) Chen, S.; Yu, J.; Jiang, Y.; Chen, F.; Cheng, J. Rhodium-Catalyzed Direct Annulation of Aldehydes with Alkynes Leading to Indenones: Proceeding through *in Situ* Directing Group Formation and Removal. *Org. Lett.* **2013**, *15*, 4754–4757. (c) Li, Q.; Knight, B. J.; Ferreira, E. M. Palladium(II)-Catalyzed *ortho*-Arylation of Aromatic Alcohols with a Readily Attachable and Cleavable Molecular Scaffold. *Chem. Eur. J.* **2016**, *22*, 13054–13058. (d) Bisht, R.; Chattopadhyay, B. Formal Ir-Catalyzed Ligand-Enabled *Ortho* and *Meta* Borylation of Aromatic Aldehydes via *in Situ*-Generated Imines. *J. Am. Chem. Soc.* **2016**, *138*, 84–87.
- (9) For selected reviews, see: (a) Meeuwissen, J.; Reek, J. N. H. Supramolecular catalysis beyond enzyme mimics. *Nat. Chem.* **2010**, *2*, 615–621. (b) Raynal, M.; Ballester, P.; Vidal-Ferran, A.; van Leeuwen, P. W. N. M. Supramolecular catalysis. Part 1: non-covalent interactions as a tool for building and modifying homogeneous catalysts. *Chem. Soc. Rev.* **2014**, *43*, 1660–1733. (c) Dydio, P.; Reek, J. N. H. Supramolecular control of selectivity in transition-metal catalysis through substrate preorganization. *Chem. Sci.* **2014**, *5*, 2135–2145. (d) Davis, H. J.; Phipps, R. J. Harnessing non-covalent interactions to exert control over regioselectivity and site-selectivity in catalytic reactions. *Chem. Sci.* **2017**, *8*, 864–877. (e) Toste, F. D.; Sigman, M. S.; Miller, S. J. Pursuit of Noncovalent Interactions for Strategic Site-Selective Catalysis. *Acc. Chem. Res.* **2017**, *50*, 609–615. (f) Neel, A. J.; Hilton, M. J.; Sigman, M. S.; Toste, F. D. Exploiting non-covalent π interactions for catalyst design. *Nature* **2017**, *543*, 637–646. (g) Haldar, C.; Hoque, M. E.; Bisht, R.; Chattopadhyay, B. Concept of Ir-catalyzed C–H bond activation/borylation by noncovalent interaction. *Tetrahedron Lett.* **2018**, *59*, 1269–1277. (h) Kuninobu, Y.; Torigoe, T. Recent progress of transition metal-catalyzed regioselective C–H transformations based on noncovalent interactions. *Org. Biomol. Chem.* **2020**, *18*, 4126–4134. For selected examples, see: (i) Kuninobu, Y.; Ida, H.; Nishi, M.; Kanai, M. A *Meta*-Selective C–H Borylation Directed by a Secondary Interaction Between Ligand and Substrate. *Nat. Chem.* **2015**, *7*, 712–717. (j) Davis, H. J.; Mihai, M. T.; Phipps, R. J. Ion Pair-Directed Regiocontrol in Transition-Metal Catalysis: A *Meta*-Selective C–H Borylation of Aromatic Quaternary Ammonium Salts. *J. Am. Chem. Soc.* **2016**, *138*, 12759–12762. (k) Davis, H. J.; Genov, G. R.; Phipps, R. J. *meta*-Selective C–H Borylation of Benzylamine-, Phenethylamine-, and Phenylpropylamine-Derived Amides Enabled by a Single Anionic Ligand. *Angew. Chem. Int. Ed.* **2017**, *56*, 13351–13355. (l) Hoque, M. E.; Bisht, R.; Haldar, C.; Chattopadhyay, B. Noncovalent Interactions in Ir-Catalyzed C–H Activation: L-Shaped Ligand for *Para*-Selective Borylation of Aromatic Esters. *J. Am. Chem. Soc.* **2017**, *139*, 7745–7748. (m) Zhang, Z.; Tanaka, K.; Yu, J.-Q. Remote site-selective C–H activation directed by a catalytic bifunctional template. *Nature* **2017**, *543*, 538–542. (n) Mihai, M. T.; Davis, H. J.; Genov, G. R.; Phipps, R. J. Ion Pair-Directed C–H Activation on Flexible Ammonium Salts: *meta*-Selective Borylation of Quaternized Phenethylamines and Phenylpropylamines. *ACS Catal.* **2018**, *8*, 3764–3769. (o) Bisht, R.; Hoque, M. E.; Chattopadhyay, B. Amide Effects in C–H Activation: Noncovalent Interactions with L-Shaped Ligand for *meta* Borylation of Aromatic Amides. *Angew. Chem. Int. Ed.* **2018**, *57*, 15762–15766. (p) Lu, X.; Yoshigoe, Y.; Ida, H.; Nishi, M.; Kanai, M.; Kuninobu, Y. Hydrogen Bond-Accelerated *meta*-Selective C–H Borylation of Aromatic Compounds and Expression of Functional Group and Substrate Specificities. *ACS Catal.* **2019**, *9*, 1705–1709. (q) Bai, S. T.; Bheeter, C. B.; Reek, J. N. H. Hydrogen Bond Directed *ortho*-Selective C–H Borylation of Secondary Aromatic Amides. *Angew. Chem. Int. Ed.* **2019**, *58*, 13039–13043. (r) Lee, B.; Mihai, M. T.; Stojanikova, V.; Phipps, R. J. Ion-Pair-Directed Borylation of Aromatic Phosphonium Salts. *J. Org. Chem.*, **2019**, *84*, 13124–13134. (s) Mihai, M. T.; Williams, B. D.; Phipps, R. J. *Para*-Selective C–H Borylation of Common Arene Building Blocks Enabled by Ion-Pairing with a Bulky Counteranion. *J. Am. Chem. Soc.* **2019**, *141*, 15477–15482. (t) Montero Bastidas, J. R.; Oleskey, T. J.; Miller, S. L.; Smith, M. R.; Maleczka, R. E. *Para*-Selective, Iridium-Catalyzed C–H Borylations of Sulfated Phenols, Benzyl Alcohols, and Anilines Directed by Ion-Pair Electrostatic Interactions. *J. Am. Chem. Soc.* **2019**, *141*, 15483–15487. (u) Golding, W. A.; Phipps, R. J. Electrostatically-directed Pd-catalysis in combination with C–H activation: site-selective coupling of remote chlorides with fluoroarenes and fluoroheteroarenes. *Chem. Sci.* **2020**, *11*, 3022–3027.
- (10) For selected reviews, see: (a) Sun, H.; Guimond, N.; Huang, Y. Advances in the development of catalytic tethering directing groups for C–H functionalization reactions. *Org. Biomol. Chem.* **2016**, *14*, 8389–8397. (b) Afewerki, S.; Córdova, A. Combinations of Aminocatalysts and Metal Catalysts: A Powerful Cooperative Approach in Selective Organic Synthesis. *Chem. Rev.* **2016**, *116*, 13512–13570. (c) Zhao, Q.; Poisson, T.; Pannecoucke, X.; Besset, T. The Transient Directing Group Strategy: A New Trend in Transition-Metal-Catalyzed C–H Bond

- Functionalization. *Synthesis* **2017**, *49*, 4808–4826. (d) Kim, D.-S.; Park, W.-J.; Jun, C.-H. Metal–Organic Cooperative Catalysis in C–H and C–C Bond Activation. *Chem. Rev.* **2017**, *117*, 8977–9015. (e) Gandeeppan, V.; Ackermann, L. Transient Directing Groups for Transformative C–H Activation by Synergistic Metal Catalysis. *Chem* **2018**, *4*, 199–222. (f) Bhattacharya, T.; Pimparkar, S.; Maiti, D. Combining transition metals and transient directing groups for C–H functionalizations. *RSC Adv.* **2018**, *8*, 19456–19464. (g) St John-Campbell, S.; Campbell, J.; Bull, J. A. Transient imines as ‘next generation’ directing groups for the catalytic functionalisation of C–H bonds in a single operation. *Org. Biomol. Chem.* **2018**, *16*, 4582–4595. (h) Rasheed, O. K.; Sun, B. Advances in Development of C–H Activation/Functionalization Using a Catalytic Directing Group. *ChemistrySelect* **2018**, *3*, 5689–5708. (i) Niu, B.; Yang, K.; Lawrence, B.; Ge, H. Transient Ligand-Enabled Transition Metal-Catalyzed C–H Functionalization. *ChemSusChem* **2019**, *12*, 2955–2969 and references cited therein. (j) Wu, Y.-J.; Shi, B.-F. Transition Metal-Catalyzed C–H Activation via Imine-Based Transient Directing Group Strategy. *Chin. J. Org. Chem.* **2020**, *10.6023/cjoc202003057*.
- (11) For selected examples, see: (a) Wu, Y.; Chen, Y.-Q.; Liu, T.; Eastgate, M. D.; Yu, J.-Q. Pd-Catalyzed γ -C(sp³)–H Arylation of Free Amines Using a Transient Directing Group. *J. Am. Chem. Soc.* **2016**, *138*, 14554–14557. (b) Ma, F.; Lei, M.; Hu, L. Acetohydrazone: A Transient Directing Group for Arylation of Unactivated C(sp³)–H Bonds. *Org. Lett.* **2016**, *18*, 2708–2711. (c) Yang, K.; Li, Q.; Liu, Y.; Li, G.; Ge, H. Catalytic C–H Arylation of Aliphatic Aldehydes Enabled by a Transient Ligand. *J. Am. Chem. Soc.* **2016**, *138*, 12775–12778. (d) Xu, Y.; Young, M. C.; Wang, C.; Magness, D. M.; Dong, G. Catalytic C(sp³)–H Arylation of Free Primary Amines with an *exo* Directing Group Generated In Situ. *Angew. Chem. Int. Ed.* **2016**, *55*, 9084–9087. (e) Hong, K.; Park, H.; Yu, J.-Q. Methylene C(sp³)–H Arylation of Aliphatic Ketones Using a Transient Directing Group. *ACS Catal.* **2017**, *7*, 6938–6941. (f) Liu, Y.; Ge, H. Site-selective C–H arylation of primary aliphatic amines enabled by a catalytic transient directing group. *Nat. Chem.* **2017**, *9*, 26–32. (g) Yada, A.; Liao, W.; Sato, Y.; Murakami, M. Butressing Salicylaldehydes: A Multipurpose Directing Group for C(sp³)–H Bond Activation. *Angew. Chem. Int. Ed.* **2017**, *56*, 1073–1076. (h) St John-Campbell, S.; White, A. J. P.; Bull, J. A. Single operation palladium catalysed C(sp³)–H functionalisation of tertiary aldehydes: investigations into transient imine directing groups. *Chem. Sci.* **2017**, *8*, 4840–4847. (i) Pan, L.; Yang, K.; Li, G.; Ge, H. Palladium-catalyzed site-selective arylation of aliphatic ketones enabled by a transient ligand. *Chem. Commun.* **2018**, *54*, 2759–2762. (j) Wang, J.; Dong, C.; Wu, L.; Xu, M.; Lin, J.; Wei, K. Palladium-Catalyzed β -C–H Arylation of Ketones Using Amino Amide as a Transient Directing Group: Applications to Synthesis of Phenanthridinone Alkaloids. *Adv. Synth. Catal.* **2018**, *360*, 3709–3715. (k) Chen, Y.-Q.; Wang, Z.; Wu, Y.; Wisniewski, S. R.; Qiao, J. X.; Ewing, W. R.; Eastgate, M. D.; Yu, J.-Q. Overcoming the Limitations of γ - and δ -C–H Arylation of Amines through Ligand Development. *J. Am. Chem. Soc.* **2018**, *140*, 17884–17894. (l) Yong, Q.; Sun, B.; Zhang, F.-L. Palladium-catalyzed *ortho*-C(sp²)–H bromination of benzaldehydes via a monodentate transient directing group strategy. *Tetrahedron Lett.* **2019**, *60*, 151263–151266. (m) Wang, Y.-F.; Xu, W.-G.; Sun, B.; Yu, Q.-Q.; Li, T.-J.; Zhang, F.-L. Monodentate Transient Directing Group Assisted Pd-Catalyzed Direct Dehydrogenative Cross-Coupling of Benzaldehydes with Arenes toward 9-Fluorenones. *J. Org. Chem.* **2019**, *84*, 13104–13111. (n) Cheng, Y.; Zheng, J.; Tian, C.; He, Y.; Zhang, C.; Tan, Q.; An, G.; Li, G. Palladium-Catalyzed C–H Arylation of Aliphatic and Aromatic Ketones using Dipeptide Transient Directing Groups. *Asian J. Org. Chem.* **2019**, *8*, 526–531. (o) St John-Campbell, S.; Bull, J. A. Intramolecular palladium(II)/(IV) catalysed C(sp³)–H arylation of tertiary aldehydes using a transient imine directing group. *Chem. Commun.* **2019**, *55*, 9172–9175. (p) Zhang, X.-L.; Pan, G.-F.; Zhu, X.-Q.; Guo, R.-L.; Gao, Y.-R.; Wang, Y.-Q. Dehydrogenative β -Arylation of Saturated Aldehydes Using Transient Directing Groups. *Org. Lett.* **2019**, *21*, 2731–2735. (q) Li, F.; Zhou, Y.; Yang, H.; Wang, Z.; Yu, Q.; Zhang, F.-L. Monodentate Transient Directing Group Enabled Pd-Catalyzed *Ortho*-C–H Methoxylation and Chlorination of Benzaldehydes. *Org. Lett.* **2019**, *21*, 3692–3695. (r) Wang, Z.; Dong, W.; Sun, B.; Yu, Q.; Zhang, F.-L. Cascade reaction for the synthesis of polycyclic aromatic hydrocarbons via transient directing group strategy. *Tetrahedron* **2019**, *75*, 4031–4041. (s) Huang, J.; Ding, J.; Ding, T.-M.; Zhang, S.; Wang, Y.; Sha, F.; Zhang, S.-Y.; Wu, X.-Y.; Li, Q. Cobalt-Catalyzed *Ortho*-C(sp²)–H Amidation of Benzaldehydes with Dioxazolones Using Transient Directing Groups. *Org. Lett.* **2019**, *21*, 7342–7345. (t) Qiao, H.; Sun, B.; Yu, Q.; Huang, Y.-Y.; Zhou, Y.; Zhang, F.-L. Palladium-Catalyzed Direct *Ortho*-C–H Selenylation of Benzaldehydes Using Benzidine as a Transient Directing Group. *Org. Lett.* **2019**, *21*, 6914–6918. (u) Dong, C.; Wu, L.; Yao, J.; Wei, K. Palladium-Catalyzed β -C–H Arylation of Aliphatic Aldehydes and Ketones Using Amino Amide as a Transient Directing Group. *Org. Lett.* **2019**, *21*, 2085–2089. (v) St John-Campbell, S.; White, A. J. P.; Bull, J. A. Methylene C(sp³)–H β,β' -Diarylation of Cyclohexanecarbaldehydes Promoted by a Transient Directing Group and Pyridone Ligand. *Org. Lett.* **2020**, *22*, 1807–1812. (w) Chen, Y.-Q.; Wu, Y.; Wang, Z.; Qiao, J. X.; Yu, J.-Q. Transient Directing Group Enabled Pd-Catalyzed γ -C(sp³)–H Oxygenation of Alkyl Amines. *ACS Catal.* **2020**, *10*, 5657–5662. (x) Chen, Y.-Q.; Singh, S.; Wu, Y.; Wang, Z.; Hao, W.; Verma, P.; Qiao, J. X.; Sunoj, R. B.; Yu, J.-Q. Pd-Catalyzed γ -C(sp³)–H Fluorination of Free Amines. *J. Am. Chem. Soc.* **2020**, *142*, 9966–9974. (y) Reddy, C.; Shaikh, J. Y.; Bhat, R. G. Access to Hetero-Benzyl Scaffolds via Transient-Ligand-Enabled Direct γ -C(sp³)–H Arylation of 3-Methylheteroarene-2-Carbaldehydes. *J. Org. Chem.* **2020**, *85*, 6924–6934.
- (12) Jun, C.-H.; Lee, H.; Hong, J.-B. Chelation-Assisted Intermolecular Hydroacylation: Direct Synthesis of Ketone from Aldehyde and 1-Alkene. *J. Org. Chem.* **1997**, *62*, 1200–1201.
- (13) For selected reviews, see: (a) Yang, L.; Huang, H. Asymmetric catalytic carbon–carbon coupling reactions via C–H bond activation. *Catal. Sci. Technol.* **2012**, *2*, 1099–1112. (b) Engle, K. M.; Yu, J.-Q. Developing Ligands for Palladium(II)-Catalyzed C–H Functionalization: Intimate Dialogue between Ligand and Substrate. *J. Org. Chem.* **2013**, *78*, 8927–8955. (c) Wencel-Delord, J.; Colobert, F. Asymmetric C(sp²)–H Activation. *Chem. Eur. J.* **2013**, *19*, 14010–14017. (d) Zheng, C.; You, S.-L. Recent development of direct asymmetric functionalization of inert C–H bonds. *RSC Adv.* **2014**, *4*, 6173–6214. (e) Pedroni, J.; Cramer, N. TADDOL-based phosphorus(III)-ligands in enantioselective Pd(0)-catalysed C–H functionalisations. *Chem. Commun.* **2015**, *51*, 17647–17657. (f) Gao, D.-W.; Gu, Q.; Zheng, C.; You, S.-L. Synthesis of Planar Chiral Ferrocenes via Transition-Metal-Catalyzed Direct C–H Bond Functionalization. *Acc. Chem. Res.* **2017**, *50*, 351–365. (g) Newton, C. G.; Wang, S.-G.; Oliveira, C. C.; Cramer, N. Catalytic Enantioselective Transformations Involving C–H Bond Cleavage by Transition-Metal Complexes. *Chem. Rev.* **2017**, *117*, 8908–8976. (h) Saint-Denis, T. G.; Zhu, R.-Y.; Chen, G.; Wu, Q.-F.; Yu, J.-Q. Enantioselective C(sp³)–H bond activation by chiral transition metal catalysts. *Science* **2018**, *359*, 759. (i) Woźniak, Ł.; Cramer, N. Enantioselective C–H Bond Functionalizations by 3d Transition-Metal Catalysts. *Trends Chem.* **2019**, *1*, 471–484. (j) Loup, J.; Dhawa, U.; Pescioli, F.; Wencel-Delord, J.; Ackermann, L. Enantioselective C–H Activation with Earth-Abundant 3d Transition Metals. *Angew. Chem. Int. Ed.* **2019**, *58*, 12803–12818. (k) Shao, Q.; Wu, K.; Zhuang, Z.; Qian, S.; Yu, J.-Q. From Pd(OAc)₂ to Chiral Catalysts: The Discovery and Development of Bifunctional Mono-N-Protected Amino Acid Ligands for Diverse C–H Functionalization Reactions. *Acc. Chem. Res.* **2020**, *53*, 4, 833–851. Note that very recently two interesting reviews on a similar topic were reported: (l) Liao, G.; Zhang, T.; Lin, Z.-K.; Shi, B.-F. Transition Metal-Catalyzed Enantioselective C–H Functionalization via Transient Directing Group Strategies. *Angew. Chem. Int. Ed.* **2020**, *59*, 10.1002/anie.202008437. (m) Bag, D.; Verma, P. K.; Sawant, S. D. Chiral Transient Directing Group Strategies in Asymmetric Synthesis. *Chem Asian J.* **2020**, *15*, 10.1002/asia.202000657.
- (14) For selected examples, see: (a) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley, New York, 1994. (b) Bringmann, G.; Hinrichs, J.; Pabst, T.; Henschel, P.; Peters, K.; Peters, E.-M. From Dynamic to Non-Dynamic Kinetic Resolution of Lactone-Bridged Biaryls: Synthesis of Mastigophorene B. *Synthesis* **2001**, 155–167. (c) Bringmann, G.; Price Mortimer, A. J.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning,

- M. Atroposelective Synthesis of Axially Chiral Biaryl Compounds. *Angew. Chem. Int. Ed.* **2005**, *44*, 5384–5427. (d) Kozłowski, M. C.; Morgan, B. J.; Linton, E. C. Total Synthesis of Chiral Biaryl Natural Products by Asymmetric Biaryl Coupling. *Chem. Soc. Rev.* **2009**, *38*, 3193–3207. (e) Bringmann, G.; Gulder, T.; Gulder, T. A. M.; Breuning, M. Atroposelective Total Synthesis of Axially Chiral Biaryl Natural Products. *Chem. Rev.* **2011**, *111*, 563–639. (f) Smyth, J. E.; Butler, N. M.; Keller, P. A. A Twist of Nature – the Significance of Atropisomers in Biological Systems. *Nat. Prod. Rep.* **2015**, *32*, 1562–1583. (g) Clayden, J.; Moran, W. J.; Edwards, P. J.; LaPlante, S. R. The Challenge of Atropisomerism in Drug Discovery. *Angew. Chem. Int. Ed.* **2009**, *48*, 6398–6401. (h) Bringmann, G.; Menche, D. Stereoselective Total Synthesis of Axially Chiral Natural Products via Biaryl Lactones. *Acc. Chem. Res.* **2001**, *34*, 615–624.
- (15) Wu, Y.-L.; Ferroni, F.; Pieraccini, S.; Bernd Schweizer, W.; Frank, B. B.; Piero Spada, G.; Diederich, F. 1,2-Di(phenylethynyl)ethenes with Axially Chiral, 2,2'-bridged 1,1'-dinaphthyl Substituents: Potent Cholesteric Liquid-Crystal Inducers. *Org. Biomol. Chem.* **2012**, *10*, 8016–8026.
- (16) For selected examples, see: (a) Noyori, R.; Takaya, H. BINAP: an efficient chiral element for asymmetric catalysis. *Acc. Chem. Res.* **1990**, *23*, 345–350. (b) Chen, Y.; Yekta, S.; Yudin, A. K. Modified BINOL Ligands in Asymmetric Catalysis. *Chem. Rev.* **2003**, *103*, 3155–3212. (c) Teichert, J. F.; Feringa, B. L. Phosphoramidites: Privileged Ligands in Asymmetric Catalysis. *Angew. Chem. Int. Ed.* **2010**, *49*, 2486–2528. (d) Tang, W.; Zhang, X. New Chiral Phosphorous Ligands for Enantioselective Hydrogenation. *Chem. Rev.* **2003**, *103*, 3029–3070. (e) Canac, Y.; Chauvin, R. Atropochiral C,X- and C,C-Chelating Carbon Ligands. *Eur. J. Inorg. Chem.* **2010**, *2010*, 2325–2335. (f) Zhang, D.; Wang, Q. Palladium Catalyzed Asymmetric Suzuki-Miyaura Coupling Reactions to Axially Chiral Biaryl Compounds: Chiral Ligands and Recent Advances. *Coord. Chem. Rev.* **2015**, *286*, 1–16.
- (17) For selected examples, see: (a) Akiyama, T.; Itoh, J.; Fuchibe, K. Recent Progress in Chiral Brønsted Acid Catalysis. *Adv. Synth. Catal.* **2006**, *348*, 999–1010. (b) Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. Complete Field Guide to Asymmetric BINOL-Phosphate Derived Brønsted Acid and Metal Catalysis: History and Classification by Mode of Activation; Brønsted Acidity, Hydrogen Bonding, Ion Pairing, and Metal Phosphates. *Chem. Rev.* **2014**, *114*, 9047–9153. (c) Min, C.; Seidel, D. Asymmetric Brønsted Acid Catalysis with Chiral Carboxylic Acids. *Chem. Soc. Rev.* **2017**, *46*, 5889–5902. (d) Wang, Q.; Gu, Q.; You, S.-L. Enantioselective Carbonyl Catalysis Enabled by Chiral Aldehydes. *Angew. Chem. Int. Ed.* **2019**, *58*, 6818–6825.
- (18) For selected examples, see: (a) Baudoin, O. The Asymmetric Suzuki Coupling Route to Axially Chiral Biaryls. *Eur. J. Org. Chem.* **2005**, *2005*, 4223–4229. (b) Wallace, T. W. Biaryl synthesis with control of axial chirality. *Org. Biomol. Chem.* **2006**, *4*, 3197–3210. (c) Wencel-Delord, J.; Panossian, A.; Leroux, F. R.; Colobert, F. Recent advances and new concepts for the synthesis of axially stereoenriched biaryls. *Chem. Soc. Rev.* **2015**, *44*, 3418–3430. (d) Ma, G.; Sibi, M. P. Catalytic Kinetic Resolution of Biaryl Compounds. *Chem. Eur. J.* **2015**, *21*, 11644–11657. (e) Loxq, P.; Manoury, E.; Poli, R.; Deydier, E.; Labande, A. Synthesis of axially chiral biaryl compounds by asymmetric catalytic reactions with transition metals. *Coord. Chem. Rev.* **2016**, *308*, 131–190. (f) Zilte, B.; Castrogiovanni, A.; Sparr, C. Catalyst-Controlled Stereoselective Synthesis of Atropisomers. *ACS Catal.* **2018**, *8*, 2981–2988. (g) Link, A.; Sparr, C. Stereoselective arene formation. *Chem. Soc. Rev.* **2018**, *47*, 3804–3815. (h) Wang, Y.-B.; Tan, B. Construction of Axially Chiral Compounds via Asymmetric Organocatalysis. *Acc. Chem. Res.* **2018**, *51*, 534–547.
- (19) For selected examples, see: (a) Luo, Z.; Liu, Q.; Gong, L.; Cui, X.; Mi, A.; Jiang, Y. Novel Achiral Biphenol-Derived Diastereomeric Oxovanadium(IV) Complexes for Highly Enantioselective Oxidative Coupling of 2-Naphthols. *Angew. Chem. Int. Ed.* **2002**, *41*, 4532–4535. (b) Mulrooney, C. A.; Li, X.; DiVirgilio, E. S.; Kozłowski, M. C. General Approach for the Synthesis of Chiral Perylenequinones via Catalytic Enantioselective Oxidative Biaryl Coupling. *J. Am. Chem. Soc.* **2003**, *125*, 6856–6857. (c) Guo, Q.-X.; Wu, Z.-J.; Luo, Z.-B.; Liu, Q.-Z.; Ye, J.-L.; Luo, S.-W.; Cun, L.-F.; Gong, L.-Z. Highly Enantioselective Oxidative Couplings of 2-Naphthols Catalyzed by Chiral Bimetallic Oxovanadium Complexes with Either Oxygen or Air as Oxidant. *J. Am. Chem. Soc.* **2007**, *129*, 13927–13938. (d) Shen, X.; Jones, G. O.; Watson, D. A.; Bhaana, B.; Buchwald, S. L. Enantioselective Synthesis of Axially Chiral Biaryls by the Pd-Catalyzed Suzuki-Miyaura Reaction: Substrate Scope and Quantum Mechanical Investigations. *J. Am. Chem. Soc.* **2010**, *132*, 11278–11287. (e) Yamaguchi, K.; Yamaguchi, J.; Studer, A.; Itami, K. Hindered biaryls by C–H coupling: bisoxazoline-Pd catalysis leading to enantioselective C–H coupling. *Chem. Sci.* **2012**, *3*, 2165–2169. (f) Yamaguchi, K.; Kondo, H.; Yamaguchi, J.; Itami, K. Aromatic C–H coupling with hindered arylboronic acids by Pd/Fe dual catalysts. *Chem. Sci.* **2013**, *4*, 3753–3757. (g) Xu, G.; Fu, W.; Liu, G.; Senanayake, C. H.; Tang, W. Efficient Syntheses of Korupensamines A, B and Michellamine B by Asymmetric Suzuki-Miyaura Coupling Reactions. *J. Am. Chem. Soc.* **2014**, *136*, 570–573. (h) Chen, Y.-H.; Cheng, D.-J.; Zhang, J.; Wang, Y.; Liu, X.-Y.; Tan, B. Atroposelective Synthesis of Axially Chiral Biaryldiols via Organocatalytic Arylation of 2-Naphthols. *J. Am. Chem. Soc.* **2015**, *137*, 15062–15065. (i) Feng, J.; Li, B.; He, Y.; Gu, Z. Enantioselective Synthesis of Atropisomeric Vinyl Arene Compounds by Palladium Catalysis: A Carbene Strategy. *Angew. Chem. Int. Ed.* **2016**, *55*, 2186–2190. (j) Yang, H.; Yang, X.; Tang, W. Transition-metal catalyzed asymmetric carbon–carbon cross-coupling with chiral ligands. *Tetrahedron* **2016**, *72*, 6143–6174.
- (20) (a) Gutnov, A.; Heller, B.; Fischer, C.; Drexler, H.-J.; Spannenberg, A.; Sundermann, B.; Sundermann, C. Cobalt(II)-catalyzed Asymmetric [2+2+2] Cycloaddition of Alkynes and Nitriles: Synthesis of Enantiomerically Enriched Atropisomers of 2-arylpyridines. *Angew. Chem. Int. Ed.* **2004**, *43*, 3795–3797. (b) Tanaka, K. Transition-Metal-Catalyzed Enantioselective [2+2+2] Cycloadditions for the Synthesis of Axially Chiral Biaryls. *Chem. Asian J.* **2009**, *4*, 508–518. (c) Amatore, M.; Auber, C. Recent Advances in Stereoselective [2+2+2] Cycloadditions. *Eur. J. Org. Chem.* **2015**, *2015*, 265–286.
- (21) For selected examples, see: (a) Hayashi, T.; Niizuma, S.; Kamikawa, T.; Suzuki, N.; Uozumi, Y. Catalytic asymmetric synthesis of axially chiral biaryls by palladium-catalyzed enantioselective cross-coupling. *J. Am. Chem. Soc.* **1995**, *117*, 9101–9102. (b) Kakiuchi, F.; Gendre, P. L.; Yamada, A.; Ohtaki, H.; Murai, S. Atroposelective alkylation of biaryl compounds by means of transition metal-catalyzed C–H/olefin coupling. *Tetrahedron: Asymmetry* **2000**, *11*, 2647–2651. (c) Gustafson, J.; Lim, D.; Miller, S. J. Dynamic Kinetic Resolution of Biaryl Atropisomers via Peptide-Catalyzed Asymmetric Bromination. *Science* **2010**, *328*, 1251–1255. (d) Ros, A.; Estepa, B.; Ramírez-López, P.; Álvarez, E.; Fernández, R.; Lassaletta, J. M. Dynamic Kinetic Cross-Coupling Strategy for the Asymmetric Synthesis of Axially Chiral Heterobiaryls. *J. Am. Chem. Soc.* **2013**, *135*, 15730–15733. (e) Bhat, V.; Wang, S.; Stoltz, B. M.; Virgil, S. C. Asymmetric Synthesis of QUINAP via Dynamic Kinetic Resolution. *J. Am. Chem. Soc.* **2013**, *135*, 16829–16832. (f) Zheng, J.; You, S.-L. Construction of Axial Chirality by Rhodium-Catalyzed Asymmetric Dehydrogenative Heck Coupling of Biaryl Compounds with Alkenes. *Angew. Chem. Int. Ed.* **2014**, *53*, 13244–13247. (g) Gao, D.-W.; Gu, Q.; You, S.-L. Pd(II)-Catalyzed Intermolecular Direct C–H Bond Iodination: An Efficient Approach toward the Synthesis of Axially Chiral Compounds via Kinetic Resolution. *ACS Catal.* **2014**, *4*, 2741–2745. (h) Ramírez-López, P.; Ros, A.; Estepa, B.; Fernández, R.; Fiser, B.; Gómez-Bengoa, E.; Lassaletta, J. M. A Dynamic Kinetic C–P Cross-Coupling for the Asymmetric Synthesis of Axially Chiral P,N Ligands. *ACS Catal.* **2016**, *6*, 3955–3964. (i) Ramírez-López, P.; Ros, A.; Romero-Arenas, A.; Iglesias-Sigüenza, J.; Fernández, R.; Lassaletta, J. M. Synthesis of IAN-type N,N-Ligands via Dynamic Kinetic Asymmetric Buchwald–Hartwig Amination. *J. Am. Chem. Soc.* **2016**, *138*, 12053–12056. (j) Hornillos, V.; Ros, A.; Ramírez-López, P.; Iglesias-Sigüenza, J.; Fernández, R.; Lassaletta, J. M. Synthesis of axially chiral heterobiaryl alkynes via dynamic kinetic asymmetric alkynylation. *Chem. Commun.* **2016**, *52*, 14121–14124. (k) Wang, Q.; Cai, Z.-J.; Liu, C.-X.; Gu, Q.; You, S.-L. Rhodium-Catalyzed Atroposelective C–H Arylation: Efficient Synthesis of Axially Chiral

- Heterobiaryls. *J. Am. Chem. Soc.* **2019**, *141*, 9504–9510. (l) Zheng, J.; Cui, W.-J.; Zheng, C.; You, S.-L. Synthesis and Application of Chiral Spiro Cp Ligands in Rhodium-Catalyzed Asymmetric Oxidative Coupling of Biaryl Compounds with Alkenes. *J. Am. Chem. Soc.* **2016**, *138*, 5242–5245. (m) Liao, G.; Zhou, T.; Yao, Q.-J.; Shi, B.-F. Recent advances in the synthesis of axially chiral biaryls via transition metal-catalysed asymmetric C–H functionalization. *Chem. Commun.* **2019**, 55, 8514–8523. (n) Jin, L.; Yao, Q.-J.; Xie, P.-P.; Li, Y.; Zhan, B.-B.; Han, Y.Q.; Hong, X.; Shi, B.-F. Atroposelective Synthesis of Axially Chiral Styrenes via an Asymmetric C–H Functionalization Strategy. *Chem* **2020**, *6*, 497–511. (o) Hazra, C. K.; Dherbassy, Q.; Wencel-Delord, J.; Colobert, F. Synthesis of Axially Chiral Biaryls Through Sulfoxide-Directed Asymmetric Mild C–H Activation and Dynamic Kinetic Resolution. *Angew. Chem. Int. Ed.* **2014**, *53*, 13871–13875. (p) Ma, Y.-N.; Zhang, H.-Y.; Yang, S.-D. Pd(II)-Catalyzed P(O)R¹R²-Directed Asymmetric C–H Activation and Dynamic Kinetic Resolution for the Synthesis of Chiral Biaryl Phosphates. *Org. Lett.* **2015**, *17*, 2034–2037.
- (22) For selected examples, see: (a) Guo, F.; Konkol, L. C.; Thomson, R. J. Enantioselective Synthesis of Biphenols from 1,4-Diketones by Traceless Central-to-Axial Chirality Exchange. *J. Am. Chem. Soc.* **2011**, *133*, 18–20. (b) Bringmann, G.; Menche, D. Stereoselective Total Synthesis of Axially Chiral Natural Products via Biaryl Lactones. *Acc. Chem. Res.* **2011**, *34*, 615–624. (c) Shirakawa, S.; Wu, X.; Maruoka, K. Kinetic Resolution of Axially Chiral 2-amino-1,1'-biaryls by Phase-Transfer-Catalyzed N-allylation. *Angew. Chem. Int. Ed.* **2013**, *52*, 14200–14203. (d) Mori, K.; Itakura, T.; Akiyama, T. Enantiodivergent Atroposelective Synthesis of Chiral Biaryls by Asymmetric Transfer Hydrogenation: Chiral Phosphoric Acid Catalyzed Dynamic Kinetic Resolution. *Angew. Chem. Int. Ed.* **2016**, *55*, 11642–11646.
- (23) Yao, Q.-J.; Zhang, S.; Zhan, B.-B.; Shi, B.-F. Atroposelective Synthesis of Axially Chiral Biaryls by Palladium-Catalyzed Asymmetric C–H Olefination Enabled by a Transient Chiral Auxiliary. *Angew. Chem. Int. Ed.* **2017**, *56*, 6617–6621.
- (24) Liao, G.; Li, B.; Chen, H.-M.; Yao, Q.-J.; Xia, Y.-N.; Luo, J.; Shi, B.-F. Pd-Catalyzed Atroposelective C–H Allylation through β -O Elimination: Diverse Synthesis of Axially Chiral Biaryls. *Angew. Chem. Int. Ed.* **2018**, *57*, 17151–17155.
- (25) (a) Gutekunst, W. R.; Baran, P. S. C–H functionalization logic in total synthesis. *Chem. Soc. Rev.* **2011**, *40*, 1976–1991. (b) Abrams, D. J.; Provencher, P. A.; Sorensen, E. J. Recent applications of C–H functionalization in complex natural product synthesis. *Chem. Soc. Rev.* **2018**, *47*, 8925–8967.
- (26) Fan, J.; Yao, Q.-J.; Liu, Y.-H.; Liao, G.; Zhang, S.; Shi, B.-F. Asymmetric Total Synthesis of TAN-1085 Facilitated by Pd-Catalyzed Atroposelective C–H Olefination. *Org. Lett.* **2019**, *21*, 3352–3356.
- (27) Kanamaru, T.; Nozaki, Y.; Muroi, M. (Kokai Tokyo Koho). JP 02- 289-532/1990, 1991. *Chem. Abstr.* **1991**, *115*, 47759n.
- (28) Zhang, J.; Xu, Q.; Wu, J.; Fan, J.; Xie, M. Construction of N–C Axial Chirality through Atroposelective C–H Olefination of N-Arylindoles by Palladium/Amino Acid Cooperative Catalysis. *Org. Lett.* **2019**, *21*, 6361–6365.
- (29) Chen, H.-M.; Zhang, S.; Liao, G.; Yao, Q.-J.; Xu, X.-T.; Zhang, K.; Shi, B.-F. Pd-Catalyzed Atroposelective C–H Allylation and Alkenylation: Access to Enantioenriched Atropisomers Featuring Pentatomic Heteroaromatics. *Organometallics*, **2019**, *38*, 4022–4028.
- (30) Dhawa, U.; Tian, C.; Wdowik, T.; Oliveira, J. C. A.; Hao, J.; Ackermann, L. Enantioselective Palladacyclo-Catalyzed C–H Activations by Transient Directing Groups: Expedient Access to Helicenes. *Angew. Chem. Int. Ed.* **2020**, *59*, 13451–13457.
- (31) Liao, G.; Chen, H.-M.; Xia, Y.-N.; Li, B.; Yao, Q.-J.; Shi, B.-F. Synthesis of Chiral Aldehyde Catalysts by Pd-Catalyzed Atroposelective C–H Naphthylation. *Angew. Chem. Int. Ed.* **2019**, *58*, 11464–11468.
- (32) For selected examples, see: (a) Chen, J.; Liu, Y. E.; Gong, X.; Shi, L.; Zhao, B. Biomimetic Chiral Pyridoxal and Pyridoxamine Catalysts. *Chin. J. Chem.* **2019**, *37*, 103–112. (b) Gong, L.-Z. Chiral aldehyde catalysis: a highly promising concept in asymmetric catalysis. *Sci. China Chem.* **2019**, *62*, 3–4. (c) Li, S.; Chen, X.-Y.; Enders, D. Aldehyde Catalysis: New Options for Asymmetric Organocatalytic Reactions. *Chem.* **2018**, *4*, 2026–2028. (d) Li, B.-J.; El-Nachef, C.; Beauchemin, A. M. Organocatalysis using aldehydes: the development and improvement of catalytic hydroaminations, hydrations and hydrolyses. *Chem. Commun.* **2017**, 53, 13192–13204. (e) Wen, W.; Chen, L.; Luo, M.-J.; Zhang, Y.; Chen, Y.-C.; Ouyang, Q.; Guo, Q.-X. Chiral Aldehyde Catalysis for the Catalytic Asymmetric Activation of Glycine Esters. *J. Am. Chem. Soc.* **2018**, *140*, 9774–9780.
- (33) Chang, J.; Reiner, J.; Xie, J. Progress on the Chemistry of Dibenzocyclooctadiene Lignans. *Chem. Rev.* **2005**, *105*, 4581–4608 and references cited therein.
- (34) Liao, G.; Yao, Q.-J.; Zhang, Z.-Z.; Wu, Y.-J.; Huang, D.-Y.; Shi, B.-F. Scalable, Stereocontrolled Formal Syntheses of (+)-Isoschizandrin and (+)-Steganone: Development and Applications of Palladium(II)-Catalyzed Atroposelective C–H Alkynylation. *Angew. Chem. Int. Ed.* **2018**, *57*, 3661–3665.
- (35) Zhang, S.; Yao, Q.-J.; Liao, G.; Li, X.; Li, H.; Chen, H.-M.; Hong, X.; Shi, B.-F. Enantioselective Synthesis of Atropisomers Featuring Pentatomic Heteroaromatics by Pd-Catalyzed C–H Alkynylation. *ACS Catal.* **2019**, *9*, 1956–1961.
- (36) Song, H.; Li, Y.; Yao, Q.-J.; Jin, L.; Liu, L.; Liu, Y.-H.; Shi, B.-F. Synthesis of Axially Chiral Styrenes through Pd-Catalyzed Asymmetric C–H Olefination Enabled by an Amino Amide Transient Directing Group. *Angew. Chem. Int. Ed.* **2020**, *59*, 6576–6580.
- (37) For selected examples, see: (a) Hyster, T. K.; Knörr, L.; Ward, T.R.; Rovis, T. Biotinylated Rh(III) Complexes in Engineered Streptavidin for Accelerated Asymmetric C–H Activation. *Science* **2012**, *338*, 500–503. (b) Ye, B.; Cramer, N. Chiral Cyclopentadienyl Ligands as Stereocontrolling Element in Asymmetric C–H Functionalization. *Science* **2012**, *338*, 504–506. (c) Chidipudi, S. R.; Burns, D. J.; Khan, I.; Lam, H. W. Enantioselective Synthesis of Spiroindenes by Enol-Directed Rhodium(III)-Catalyzed C–H Functionalization and Spiroannulation. *Angew. Chem. Int. Ed.* **2015**, *54*, 13975–13979. (d) Ye, B.; Cramer, N. Chiral Cyclopentadienyls: Enabling Ligands for Asymmetric Rh(III)-Catalyzed C–H Functionalizations. *Acc. Chem. Res.* **2015**, *48*, 1308–1318. (e) Zheng, J.; Wang, S.-B.; Zheng, C.; You, S.-L. Asymmetric Dearomatization of Naphthols via a Rh-Catalyzed C(sp²)–H Functionalization/Annulation Reaction. *J. Am. Chem. Soc.* **2015**, *137*, 4880–4883. (f) Pham, M.V.; Cramer, N. Enantioselective Access to Spirocyclic Sultams by ChiralCp^x–Rhodium(III)-Catalyzed Annulations. *Chem. Eur. J.* **2016**, *22*, 2270–2273. (g) Jia, Z.-J.; Merten, C.; Gontla, R.; Daniliuc, C. G.; Antonchick, A. P.; Waldmann, H. General Enantioselective C–H Activation with Efficiently Tunable Cyclopentadienyl Ligands. *Angew. Chem. Int. Ed.* **2017**, *56*, 2429–2434. (h) Sun, Y.; Cramer, N. Rhodium(III)-Catalyzed Enantiotopic C–H Activation Enables Access to P-Chiral Cyclic Phosphinamides. *Angew. Chem. Int. Ed.* **2017**, *56*, 364–367. (i) Zheng, J.; Wang, S.-B.; Zheng, C.; You, S.-L. Asymmetric Synthesis of Spiropyrazolones by Rhodium-Catalyzed C(sp²)–H Functionalization/Annulation Reactions. *Angew. Chem. Int. Ed.* **2017**, *56*, 4540–4544. (j) Shan, G.; Flegel, J.; Li, H.; Merten, C.; Ziegler, S.; Antonchick, A. P.; Waldmann, H. C–H Bond Activation for the Synthesis of Heterocyclic Atropisomers Yields Hedgehog Pathway Inhibitors. *Angew. Chem. Int. Ed.* **2018**, *57*, 14250–14254. (k) Shen, B.; Wan, B.; Li, X. Enantiodivergent Desymmetrization in the Rhodium(III)-Catalyzed Annulation of Sulfoximines with Diazo Compounds. *Angew. Chem. Int. Ed.* **2018**, *57*, 15534–15538. (l) Sun, Y.; Cramer, N. Enantioselective Synthesis of Chiral-at-Sulfur 1,2-Benzothiazines by Cp^xRh(III)-Catalyzed C–H Functionalization of Sulfoximines. *Angew. Chem. Int. Ed.* **2018**, *57*, 15539–15543. (m) Li, T.; Zhou, C.; Yan, X.; Wang, J. Solvent-Dependent Asymmetric Synthesis of Alkynyl and Monofluoroalkenyl Isoindolinones by CpRh^{III}-Catalyzed C–H Activation. *Angew. Chem. Int. Ed.* **2018**, *57*, 4048–4052. (n) Trifonova, E. A.; Ankudinov, N. M.; Mikhaylov, A. A.; Chusov, D. A.; Nelyubina, Y. V.; Perekalin, D. S. A Planar-Chiral Rhodium(III) Catalyst with a Sterically Demanding Cyclopentadienyl Ligand and Its Application in the Enantioselective Synthesis of Dihydroisoquinolones. *Angew. Chem. Int. Ed.* **2018**, *57*,

- 7714–7718. (o) Audic, B.; Wodrich, M. D.; Cramer, N. Mild complexation protocol for chiral Cp^{*}Rh and Ir complexes suitable for in situ catalysis. *Chem. Sci.* **2019**, *10*, 781–787. (p) Li, H.; Gontla, R.; Flegel, J.; Merten, C.; Ziegler, S.; Antonchick, A. P.; Waldmann, H. Enantioselective Formal C(sp³)–H Bond Activation in the Synthesis of Bioactive Spiropyrrolone Derivatives. *Angew. Chem. Int. Ed.* **2019**, *58*, 307–311 (q) Lin, L.; Fukagawa, S.; Sekine, D.; Tomita, E.; Yoshino, T.; Matsunaga, S. Chiral Carboxylic Acid Enabled Achiral Rhodium(III)-Catalyzed Enantioselective C–H Functionalization. *Angew. Chem. Int. Ed.* **2018**, *57*, 12048–12052.
- (38) Beletskiy, E. V.; Sudheer, C.; Douglas, C. J. Cooperative Catalysis Approach to Intramolecular Hydroacylation. *J. Org. Chem.*, **2012**, *77*, 5884–5893.
- (39) Wang, M.; Zhang, X.; Chen, Z.; Tang, Y.; Lei, M. A theoretical study on the mechanisms of intermolecular hydroacylation of aldehyde catalyzed by neutral and cationic rhodium complexes. *Sci. China Chem.* **2014**, *57*, 1264–1275.
- (40) Li, G.; Jiang, J.; Xie, H.; Wang, J. Introducing the Chiral Transient Directing Group Strategy to Rhodium(III)-Catalyzed Asymmetric C–H Activation. *Chem. -Eur. J.* **2019**, *25*, 4688–4694.
- (41) The racemic preparation of phthalides was reported in 2013: Tan, P. W.; Juwaini, N. A. B.; Seayad, J. Rhodium(III)-Amine Dual Catalysis for the Oxidative Coupling of Aldehydes by Directed C–H Activation: Synthesis of Phthalides. *Org. Lett.* **2013**, *15*, 5166–5169.
- (42) For selected examples, see: (a) Milczek, E.; Boudet, N.; Blakey, S. Enantioselective C–H Amination Using Cationic Ruthenium(II)–pybox Catalysts. *Angew. Chem. Int. Ed.* **2008**, *47*, 6825–6828. (b) Nishioka, Y.; Uchida, T.; Katsuki, T. Enantio- and Regioselective Intermolecular Benzylic and Allylic C–H Bond Amination. *Angew. Chem. Int. Ed.* **2013**, *52*, 1739–1742. (c) Xing, Q.; Chan, C.-M.; Yeung, Y.-W.; Yu, W.-Y. Ruthenium(II)-Catalyzed Enantioselective γ -Lactams Formation by Intramolecular C–H Amidation of 1,4,2-Dioxazol-5-ones. *J. Am. Chem. Soc.* **2019**, *141*, 3849–3853. (d) Zhou, Z.; Chen, S.; Qin, J.; Nie, X.; Zheng, X.; Harms, K.; Riedel, R.; Houk, K. N.; Meggers, E. Catalytic Enantioselective Intramolecular C(sp³)–H Amination of 2-Azidoacetamides. *Angew. Chem. Int. Ed.* **2019**, *58*, 1088–1093.
- (43) Li, Z.-Y.; Lakmal, H. H. C.; Quian, X.; Zhu, Z.; Donnadiou, B.; McClain, S. J.; Xu, X.; Cui, X. Ruthenium-Catalyzed Enantioselective C–H Functionalization: A Practical Access to Optically Active Indoline Derivatives. *J. Am. Chem. Soc.* **2019**, *141*, 15730–15736.
- (44) Li, G.; Liu, Q.; Vasamsetty, L.; Guo, W.; Wang, J. Ruthenium(II)-Catalyzed Asymmetric Inert C–H Bond Activation Assisted by a Chiral Transient Directing Group. *Angew. Chem. Int. Ed.* **2020**, *59*, 3475–3479.
- (45) Xu, J.; Liu, Y.; Zhang, J.; Xu, X.; Jin, Z. Palladium-catalyzed enantioselective C(sp²)–H arylation of ferrocenyl ketones enabled by a chiral transient directing group. *Chem. Comm.* **2018**, *54*, 689–692.
- (46) Oxtoby, L. J.; Li, Z.-Q.; Tran, V. T.; Erbay, T. G.; Deng, R.; Liu, P.; Engle, K. M. A. Transient Directing Group Strategy Enables Enantioselective Reductive Heck Hydroarylation of Alkenes. *Angew. Chem. Int. Ed.* **2020**, *59*, 8885–8890.
- (47) For selected examples, see: (a) Saxena, A.; Lam, H. W. Enantioselective rhodium-catalyzed arylation of electron-deficient alkenylarenes. *Chem. Sci.* **2011**, *2*, 2326–2331. (b) Roy, I. D.; Burns, A. R.; Pattison, G.; Michel, B.; Parker, A. J.; Lam, H. W. A second-generation ligand for the enantioselective rhodium-catalyzed addition of arylboronic acids to alkenylazaarenes. *Chem. Commun.* **2014**, *50*, 2865–2868. (c) Chen, Z.-M.; Hilton, M. J.; Sigman, M. S. Palladium-Catalyzed Enantioselective Redox-Relay Heck Arylation of 1,1-Disubstituted Homoallylic Alcohols. *J. Am. Chem. Soc.* **2016**, *138*, 11461–11464. (d) Yang, Q.; Wang, Y.; Luo, S.; Wang, J. J. Kinetic Resolution and Dynamic Kinetic Resolution of Chromene by Rhodium-Catalyzed Asymmetric Hydroarylation. *Angew. Chem. Int. Ed.* **2019**, *58*, 5343–5347.
- (48) For selected examples, see: (a) Podhajsky, S. M.; Iwai, Y.; Cook-Sneathen, A.; Sigman, M. S. Asymmetric palladium-catalyzed hydroarylation of styrenes and dienes. *Tetrahedron* **2011**, *67*, 4435–4441. (b) Friis, S. D.; Pirmot, M. T.; Buchwald, S. L. Asymmetric Hydroarylation of Vinylarenes Using a Synergistic Combination of CuH and Pd Catalysis. *J. Am. Chem. Soc.* **2016**, *138*, 8372–8375. (c) Grélaud, S.; Cooper, P.; Feron, L. J.; Bower, J. F. Branch-Selective and Enantioselective Iridium-Catalyzed Alkene Hydroarylation via Anilide-Directed C–H Oxidative Addition. *J. Am. Chem. Soc.* **2018**, *140*, 9351–9356. (d) Chen, Y.-G.; Shuai, B.; Xu, X.-T.; Li, Y.-Q.; Yang, Q.-L.; Qiu, H.; Zhang, K.; Fang, P.; Mei, T.-S. Nickel-catalyzed Enantioselective Hydroarylation and Hydroalkenylation of Styrenes. *J. Am. Chem. Soc.* **2019**, *141*, 3395–3399.
- (49) For selected examples, see: (a) Shi, B.-F.; Mangel, N.; Zhang, Y.-H.; Yu, J.-Q. Pd^{II}-Catalyzed Enantioselective Activation of C(sp²)–H and C(sp³)–H Bonds Using Monoprotected Amino Acids as Chiral Ligands. *Angew. Chem. Int. Ed.* **2008**, *47*, 4882–4886. (b) Nakanishi, M.; Katayev, D.; Besnard, C.; Kündig, E. P. Fused Indolines by Palladium-Catalyzed Asymmetric C–C Coupling Involving an Unactivated Methylene Group. *Angew. Chem. Int. Ed.* **2011**, *50*, 7438–7441. (c) Anas, S.; Cordi, A.; Kagan, H. B. Enantioselective synthesis of 2-methyl indolines by palladium catalyzed asymmetric C(sp³)–H activation/cyclisation. *Chem. Commun.* **2011**, *47*, 11483–11485. (d) Martin, N.; Pierre, C.; Davi, M.; Jazzar, R.; Baudoin, O. Diastereo- and Enantioselective Intramolecular C(sp³)–H Arylation for the Synthesis of Fused Cyclopentanes. *Chem. Eur. J.* **2012**, *18*, 4480–4484. (e) Chan, K. S. L.; Fu, H.-Y.; Yu, J.-Q. Palladium(II)-Catalyzed Highly Enantioselective C–H Arylation of Cyclopropylmethylamines. *J. Am. Chem. Soc.* **2015**, *137*, 2042–2046. (f) Yan, S.-B.; Zhang, S.; Duan, W.-L. Palladium-Catalyzed Asymmetric Arylation of C(sp³)–H Bonds of Aliphatic Amides: Controlling Enantioselectivity Using Chiral Phosphoric Amides/Acids. *Org. Lett.* **2015**, *17*, 2458–2461. (g) Wang, H.; Tong, H.-R.; He, G.; Chen, G. An Enantioselective Bidentate Auxiliary Directed Palladium-Catalyzed Benzylic C–H Arylation of Amines Using a BINOL Phosphate Ligand. *Angew. Chem. Int. Ed.* **2016**, *55*, 15387–15391. (h) Chen, G.; Gong, W.; Zhuang, Z.; Andra, M. S.; Chen, Y.-Q.; Hong, X.; Yang, Y.-F.; Liu, T.; Houk, K. N.; Yu, J.-Q. Ligand-accelerated enantioselective methylene C(sp³)–H bond activation. *Science* **2016**, *353*, 1023–1027. (i) Jain, P.; Verma, P.; Xia, G.; Yu, J.-Q. Enantioselective amine α -functionalization via palladium-catalyzed C–H arylation of thioamides. *Nat. Chem.* **2017**, *9*, 140–144. (j) Wu, Q.-F.; Shen, P.-X.; He, J.; Wang, X.-B.; Zhang, F.; Shao, Q.; Zhu, R.-Y.; Mapelli, C.; Qiao, J. X.; Poss, M. A.; Yu, J.-Q. Formation of α -chiral centers by asymmetric β -C(sp³)–H arylation, alkenylation, and alkynylation. *Science* **2017**, *355*, 499–503. (k) Zhu, C.; Wang, D.; Zhao, Y.; Sun, W.-Y.; Shi, Z. Enantioselective Palladium-Catalyzed Intramolecular α -Arylative Desymmetrization of 1,3-Diketones. *J. Am. Chem. Soc.* **2017**, *139*, 16486–16489. (l) Hu, L.; Shen, P.-X.; Shao, Q.; Hong, K.; Qiao, J. X.; Yu, J.-Q. Pd^{II}-Catalyzed Enantioselective C(sp³)–H Activation/Cross-Coupling Reactions of Free Carboxylic Acids. *Angew. Chem. Int. Ed.* **2019**, *58*, 2134–2138.
- (50) Zhang, F.-L.; Hong, K.; Li, T.-J.; Park, H.; Yu, J.-Q. Functionalization of C(sp³)–H bonds using a transient directing group. *Science* **2016**, *351*, 252–256.
- (51) Liu, W.; Zheng, J.; Liu, Z.; Hu, W.; Wang, X.; Dang, Y. How Does Palladium–Amino Acid Cooperative Catalysis Enable Regio- and Stereoselective C(sp³)–H Functionalization in Aldehydes and Ketones? A DFT Mechanistic Study. *ACS Catal.* **2018**, *8*, 7698–7709.
- (52) Gou, B.-B.; Liu, H.-F.; Chen, J.; Zhou, L. Palladium-Catalyzed Site-Selective C(sp³)–H Arylation of Phenylacetaldehydes. *Org. Lett.* **2019**, *21*, 7084–7088.
- (53) Xiao, L.-J.; Hong, K.; Luo, F.; Hu, L.; Ewing, W. R.; Yeung, K.-S.; Yu, J.-Q. Pd^{II}-Catalyzed Enantioselective C(sp³)–H Arylation of Cyclobutyl Ketones Using a Chiral Transient Directing Group. *Angew. Chem. Int. Ed.* **2020**, *59*, 9594–9600.
- (54) For selected examples, see: (a) Wang, P.; Verma, P.; Xia, G.; Shi, J.; Qiao, J. X.; Tao, S.; Cheng, P. T. W.; Poss, M. A.; Farmer, M. E.; Yeung, K. S.; Yu, J.-Q. Ligand-accelerated non-directed C–H functionalization of arenes. *Nature* **2017**, *551*, 489–493. (b) Li, G. C.; Wang, P.; Farmer, M. E.; Yu, J.-Q. Ligand-Enabled Auxiliary-Free meta-C–H Arylation of Phenylacetic Acids. *Angew. Chem. Int. Ed.* **2017**, *56*, 6874–

6877. (c) Farmer, M. E.; Wang, P.; Shi, H.; Yu, J.-Q. Palladium-Catalyzed meta-C–H Functionalization of Masked Aromatic Aldehydes. *ACS Catal.* **2018**, *8*, 7362–7367. (d) Zhu, R.-Y.; Li, Z.-Q.; Park, H. S.; Senanayake, C. H.; Yu, J.-Q. Ligand-Enabled γ -C(sp³)–H Activation of Ketones. *J. Am. Chem. Soc.* **2018**, *140*, 3564–3568.
- (55) For selected reviews, see: (a) Yang, X.; Wu, T.; Phipps, R. J.; Toste, F. D. Advances in catalytic enantioselective fluorination, mono-, di-, and trifluoromethylation, and trifluoromethylthiolation reactions. *Chem. Rev.* **2015**, *115*, 826–870 and references cited therein. (b) Thornbury, R.; Schäfer, G.; Toste, F. D. Catalytic Enantioselective Fluorination. In *Modern Synthesis Processes and Reactivity of Fluorinated Compounds. Progress in Fluorine Science*. Groult, H.; Leroux, F. R.; Tressaud, A.; Eds. Elsevier, 2017, 223–263. (c) Zhu, Y.; Han, J.; Wang, J.; Shibata, N.; Sodeoka, M.; Soloshonok, V. A.; Coelho, J. A. S.; Toste, F. D. Modern Approaches for Asymmetric Construction of Carbon–Fluorine Quaternary Stereogenic Centers: Synthetic Challenges and Pharmaceutical Needs. *Chem. Rev.* **2018**, *118*, 3887–3964.
- (56) Park, H.; Verma, P.; Hong, K.; Yu, J.-Q. Controlling Pd(IV) reductive elimination pathways enables Pd(II)-catalysed enantioselective C(sp³)–H fluorination. *Nature Chem.* **2018**, *10*, 755–762.
- (57) (a) Engle, K. M.; Mei, T.-S.; Wang, X.; Yu, J.-Q. Bystanding F⁺ oxidants enable selective reductive elimination from high-valent metal centers in catalysis. *Angew. Chem. Int. Ed.* **2011**, *50*, 1478–1491. (b) Yahav, A.; Goldberg, I.; Vigalok, A. Synthesis of the elusive (R₃P)₂MF₂ (M = Pd, Pt) complexes. *J. Am. Chem. Soc.* **2003**, *125*, 13634–13635. (c) Rosewall, C. F.; Sibbald, P. A.; Liskin, D. V.; Michael, F. E. Palladium-catalyzed carboamination of alkenes promoted by N-fluorobenzenesulfonimide via C–H activation of arenes. *J. Am. Chem. Soc.* **2009**, *131*, 9488–9489.
- (58) (a) Pérez-Temprano, M. H.; Racowski, J. M.; Kampf, J. W.; Sanford, M. S. Competition between sp³-C–N vs. sp³-C–F reductive elimination from Pd^{IV} complexes. *J. Am. Chem. Soc.* **2014**, *136*, 4097–4100. (b) Camasso, N. M.; Pérez-Temprano, M. H.; Sanford, M. S. C(sp³)–O bond-forming reductive elimination from Pd^{IV} with diverse oxygen nucleophiles. *J. Am. Chem. Soc.* **2014**, *136*, 12771–12775. (c) Sibbald, P. A.; Rosewall, C. F.; Swartz, R. D.; Michael, F. E. Mechanism of N-fluorobenzenesulfonimide promoted diamination and carboamination reactions: divergent reactivity of a Pd(IV) species. *J. Am. Chem. Soc.* **2009**, *131*, 15945–15951.
- (59) (a) Furuya, T.; Benitez, D.; Tkatchouk, E.; Strom, A. E.; Tang, P.; Goddard, W. A.; Ritter, T. Mechanism of C–F reductive elimination from palladium(IV) fluorides. *J. Am. Chem. Soc.* **2010**, *132*, 3793–3807. (b) Racowski, J. M.; Gary, J. B.; Sanford, M. S. Carbon(sp³)–fluorine bond-forming reductive elimination from palladium (IV) complexes. *Angew. Chem. Int. Ed.* **2012**, *51*, 3414–3417. (c) Kaspi, A. W.; Yahav-Levi, A.; Goldberg, I.; Vigalok, A. Xenon difluoride induced aryl iodide reductive elimination: a simple access to difluoropalladium(II) complexes. *Inorg. Chem.* **2008**, *47*, 5–7. (d) Zhao, S.-B.; Becker, J. J.; Gagné, M. R. Steric crowding makes challenging C_{sp3}–F reductive eliminations feasible. *Orga* or selected examples, see: a) S. S. Roy, P. Ghosh, U. H. Sk, P. Chakraborty, J. Biswas, S. Mandal, A. Bhattacharjee, S. Bhattacharya, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6951–6955; b) W. Ali, M. Álvarez-Pérez, M. A. Maré, N. Salardón-Jiménez, J. Handzlik, E. Domínguez-Álvarez, *Curr. Pharmacol. Rep.* **2018**, *4*, 468–481; c) D. Plano, D. N. Karelía, M. K. Pandey, J. E. Spallholz, S. Amin, A. K. Sharma, *J. Med. Chem.* **2016**, *59*, 1946–1959.