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

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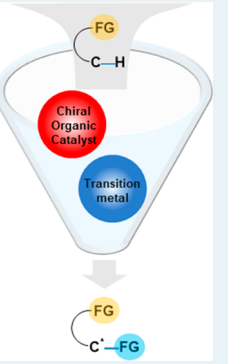
ABSTRACT: Transition-metal-catalyzed C−H bond functionalization has known a rapid evolution in the last years, offering modern strategies for reaching high molecular complexity in a step- and atom-economical way. Despite the indisputable advances, selectivity issues still remain, given the ubiquity of 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 for 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(sp^2)−H and C(sp^3)−H bonds by transition-metal catalysis.



KEYWORDS: *transition metal, chiral transient directing group, asymmetric transformations, dual catalysis, synthetic methodology, C−H bond functionalization*

1. INTRODUCTION

In the last few decades, 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 unarguable 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 aromatic[4] 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 groups[6] and transient mediators.[7,8] More recently, other promising alternatives have emerged, based on the use of noncovalent 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 toward the design and 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. Due to 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 species 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).

The aim of this review is to showcase and discuss the recent advances made in the cutting-edge C−H activation field based

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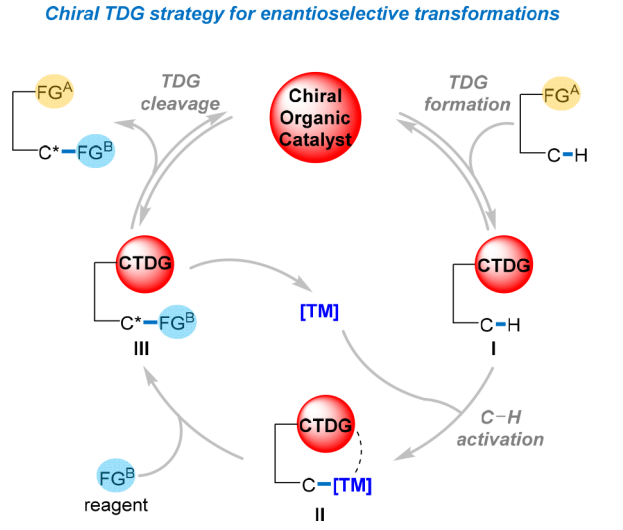
Scheme 1. Chiral Transient Directing Group Strategy in Transition-Metal-Catalyzed C−H Bond Activation Reactions



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(sp^2)−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 carbocyles along with miscellaneous reactions will be highlighted. Finally, the last part of the review will be dedicated to the recent developments in transition-metal-catalyzed enantioselective C(sp^3)−H bond functionalization.

2. ASYMMETRIC C(sp^2)−H BOND ACTIVATION FOR ATROPISOMER SYNTHESIS

2.1. From Biaryl Derivatives. Given the significance and abundance of axially chiral biaryls in bioactive natural products,[14] advanced material sciences,[15] chiral ligands,[16] and catalysts,[17] groundbreaking advances have been made toward a straightforward access to these scaffolds.[14c,18] Existing methods to synthesize such derivatives have generally relied on stereoselective cross-coupling reactions,[19] asymmetric cycloadditions,[20] and 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.

2.1.1. 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 hypothesis.[23] First, the 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 aldehdyes (***rac*-1**) were olefinated through a dynamic kinetic resolution pathway (Scheme 2). When substrates bearing electron-donating groups were used, the expected alkenylated products (**2a−d**) were obtained in yields up to 94% with 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 shown by the synthesis of 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 mentioning that in this case the reaction also went smoothly with other acrylate and electron-poor styrene derivatives, as demonstrated by the synthesis of compounds **2l−n**.

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 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 with 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 effect on the outcome of the reaction (**4a,b,g**). It is 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-C_2-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).

Applying the enantioselective C−H functionalization strategy to natural products synthesis,[2a,c,d,k,25] the Shi group reported a concise and highly enantioselective total synthesis of TAN-1085,[26] an angucycline antibiotic isolated from *Streptomyces* species (Scheme 4).[27] 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).

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

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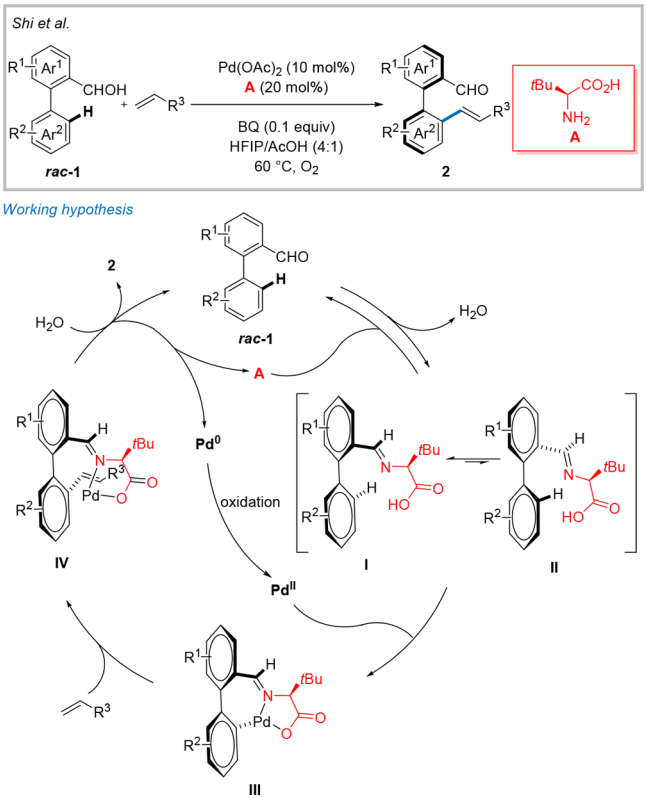
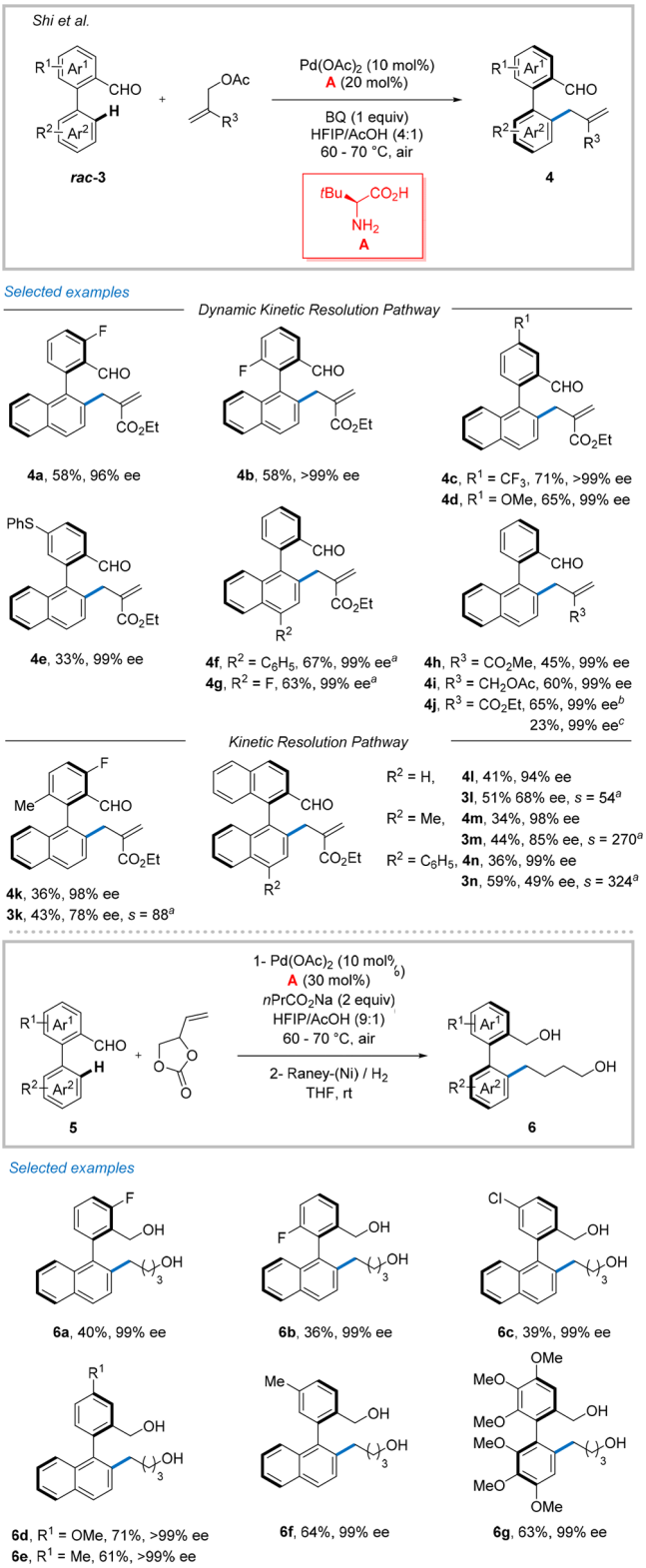
Scheme 2. Pd(II)-Catalyzed Atroposelective C−H Olefination Reaction by Using a Chiral Transient Directing Group



Scheme 3. Synthesis of Axially Chiral Biaryls via a Pd(II)-Catalyzed Asymmetric Allylation Reaction



[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.

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 *n*-butyl acrylate was achieved with high regio- and stereocontrol, leading to the corresponding alkenylated products **10a−g**. Various *N*-

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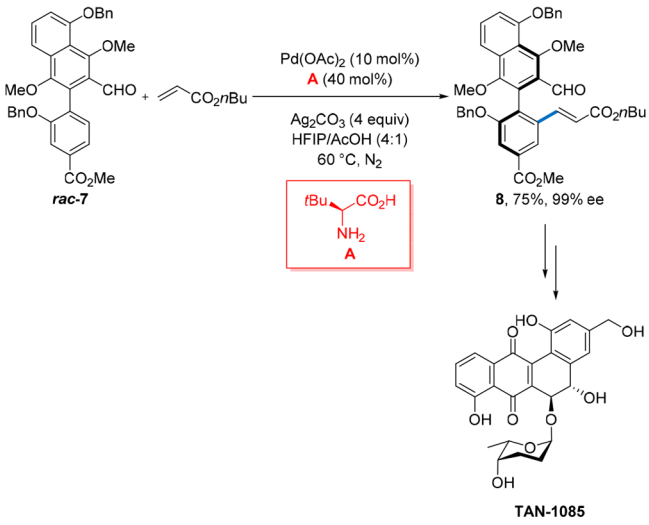
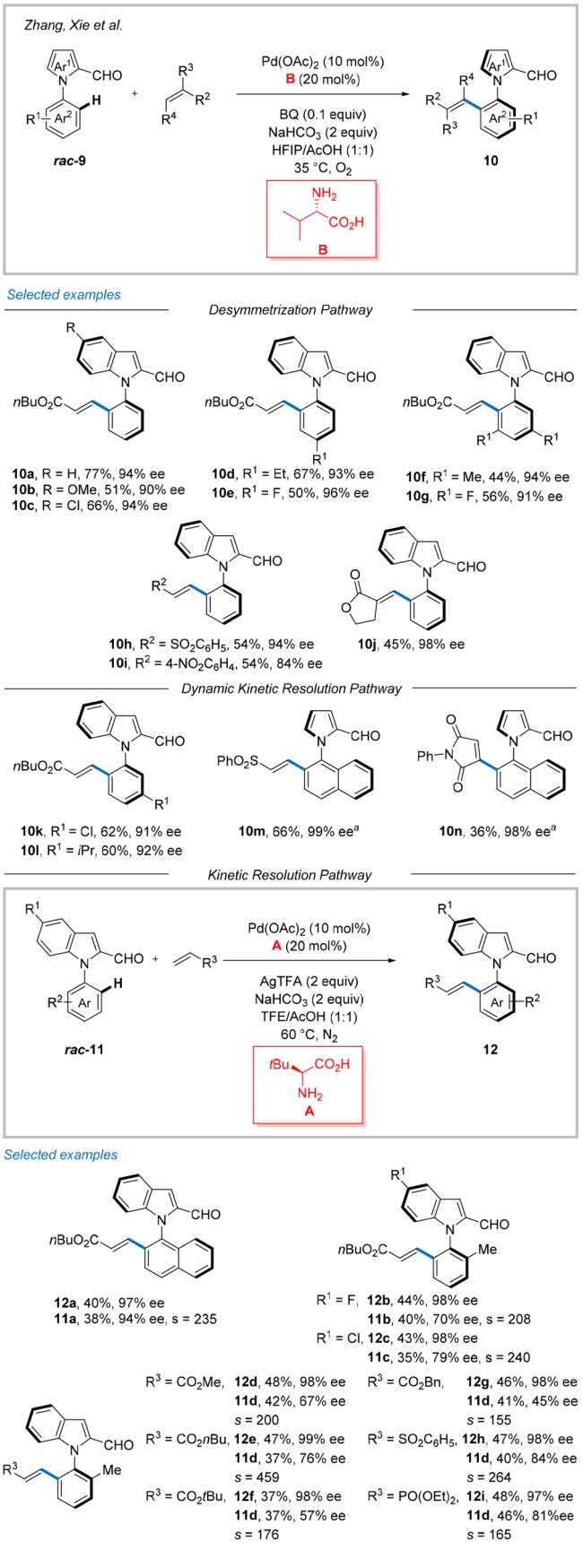
Scheme 4. Application of the Transient Directing Group Strategy to Access the Key Intermediate 8 for the Total Synthesis of TAN-1085



Scheme 5. Atroposelective Pd(II)-Catalyzed Olefination of *N*-Arylindoles



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 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**).

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 mentioning 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. However, 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

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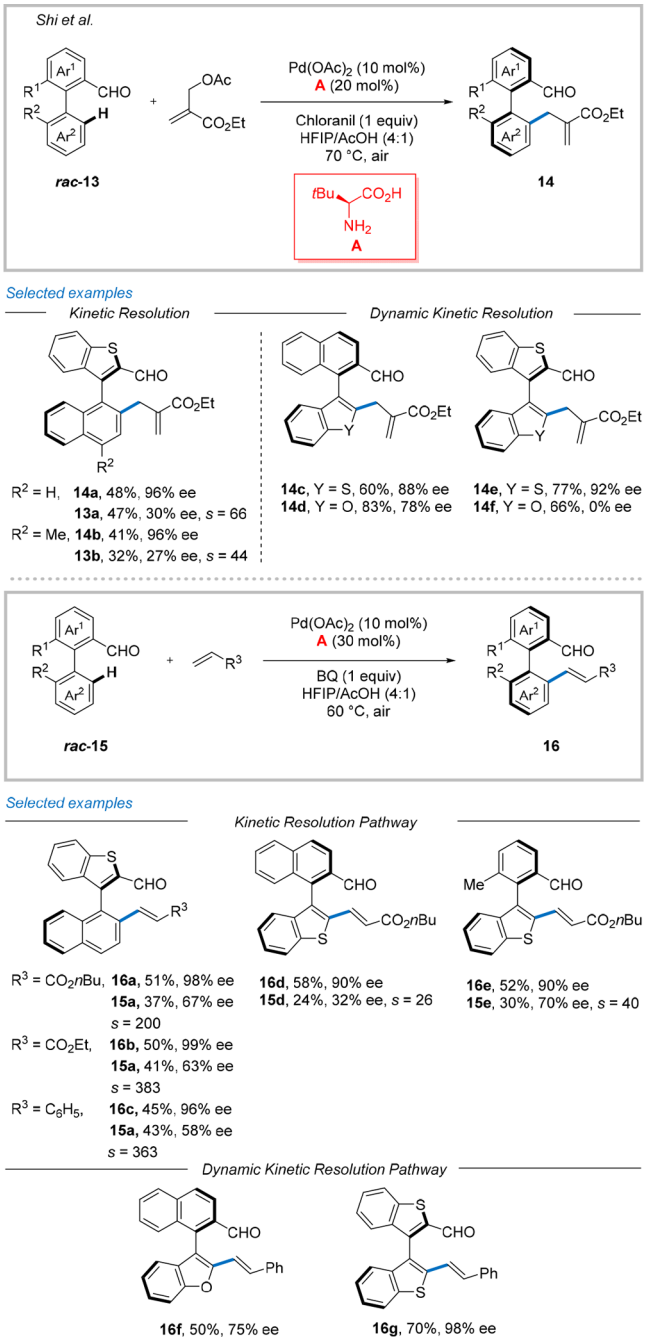
Scheme 5. continued

[a]$Pd(OAc)_2$ (10 mol %), **A** (20 mol %), AgTFA (2 equiv), $NaHCO_3$ (2 equiv), TFE/AcOH (1:1), 60 °C, N_2.

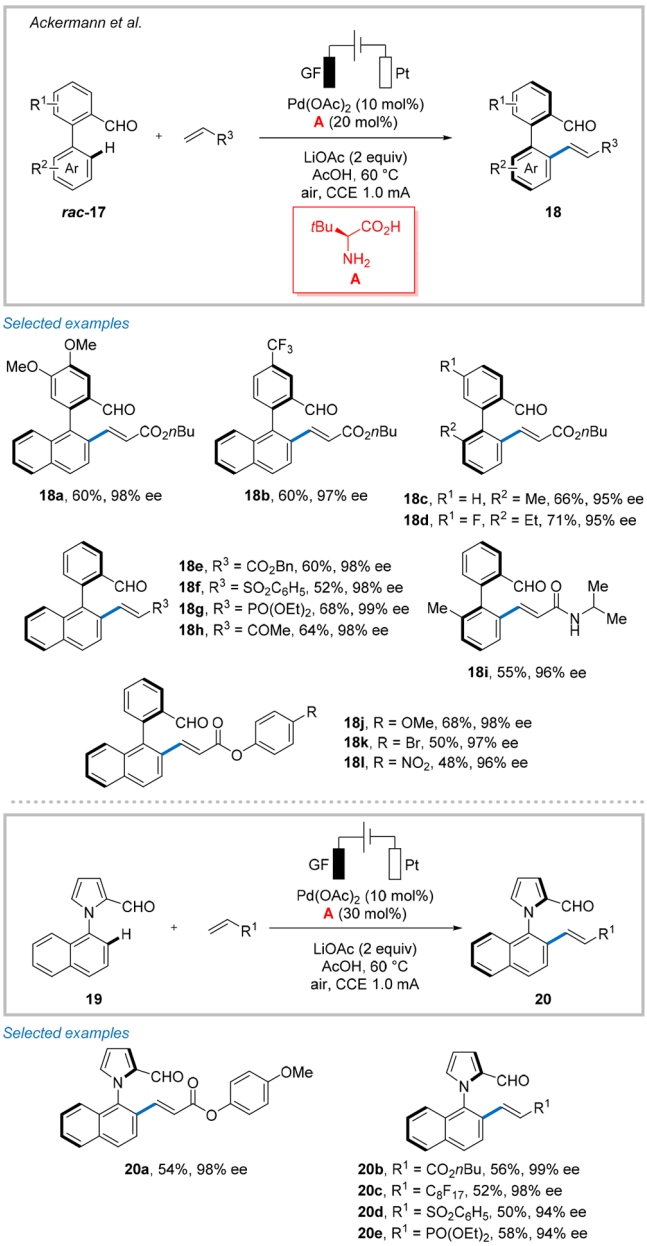
Scheme 6. Synthesis of Enantioenriched Atropoisomers Featuring a Heteroaryl Part by Pd(II) Catalysis



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.

This year, the Ackermann group described the first atroposelective palladaelectro-catalyzed olefination of biaryl aldehydes by C−H bond activation under mild reaction conditions (Scheme 7).[30] A panel of biaryl derivatives ***rac*-17**

Scheme 7. Electrochemical Enantioselective Olefination of Biaryl Aldehydes by Pd(II)-Catalyzed C−H Bond Activation Using the Chiral Transient Directing Group Strategy



was olefinated using L-*tert*-leucine as the 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. In addition, 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 also be efficient with *N*-

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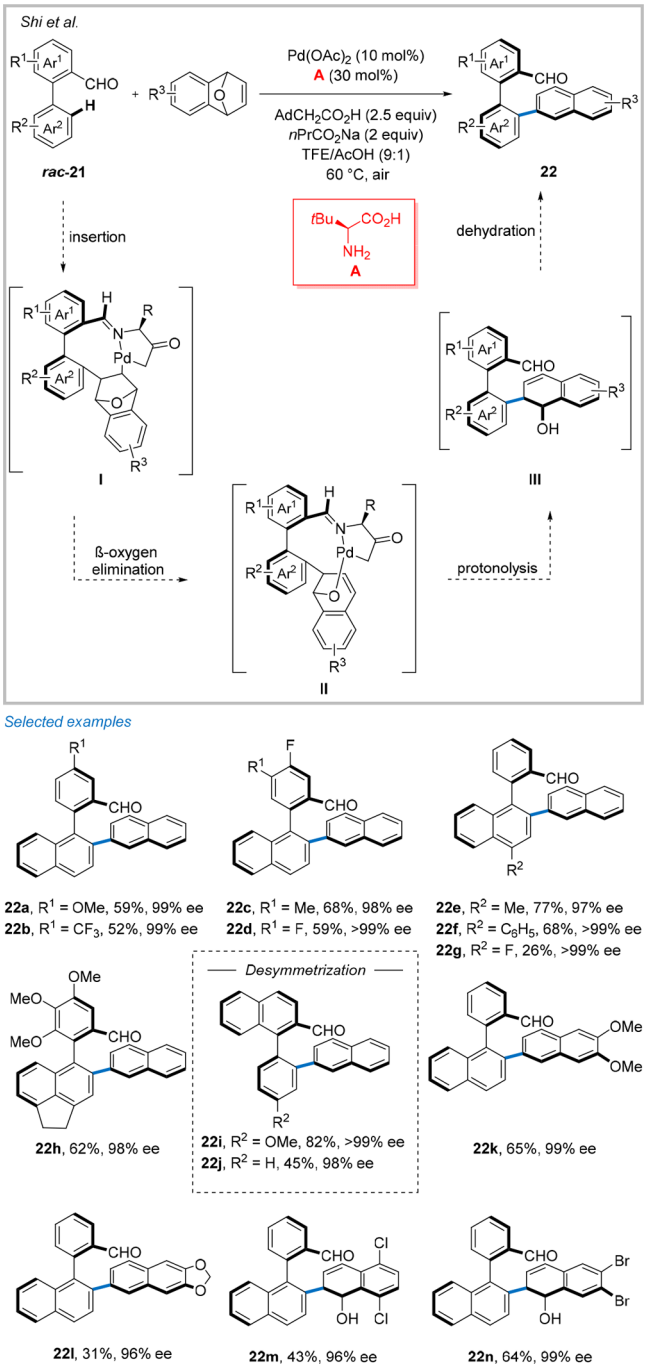
arylpyrrole derivatives. Hence, an access to N−C axially chiral heteroaryls **20a−e** was achieved in a complete regio- and stereoselective manner. Finally, the strategy was further applied to access key compounds such as chiral BINOLs, dicarboxylic acids, and helicenes.

2.1.2. 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 the use of 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 (**21a**) or an electron-withdrawing group (**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 was functionalized with an electron-withdrawing group (**22g**). In addition, an access to the chiral polysubstituted 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 7-oxabenzonorboranadiene were used, the desired products (**22k,l**) were successfully synthesized with electron-rich partners, in contrast to electron-poor partners, which only afforded the dihydronaphthol products (**22m,n**).

Scheme 8. Atroposelective Pd(II)-Catalyzed *ortho* C−H Naphthylation of Biaryl Aldehydes



2.1.3. Alkynylation Reaction. Aiming at having an efficient access toward 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. Polysubstituted biaryl aldehydes **23f−h** also underwent this reaction successfully. Moreover, different silyl-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).

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**), although *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 effect on the outcome of the reaction (**28n−q**). Interestingly, with this approach, the alkynylation of substrates having two five-membered hetero-

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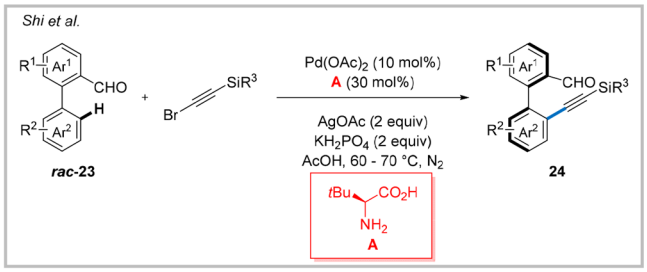
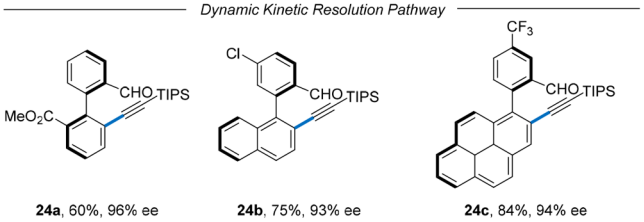
Scheme 9. Atroposelective Synthesis of Alkynylated Biaryl Scaffolds

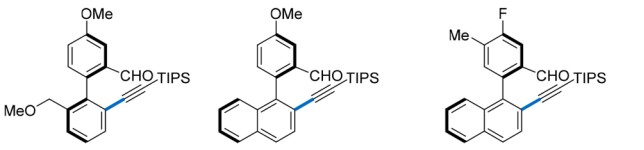


Selected examples

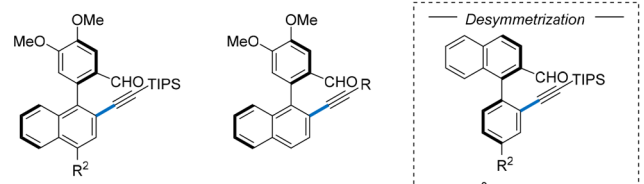
Dynamic Kinetic Resolution Pathway



24a, 60%, 96% ee; **24b**, 75%, 93% ee; **24c**, 84%, 94% ee



24d, 63%, 91% ee; **24e**, 88%, 91% ee; **24f**, 65%, 94% ee



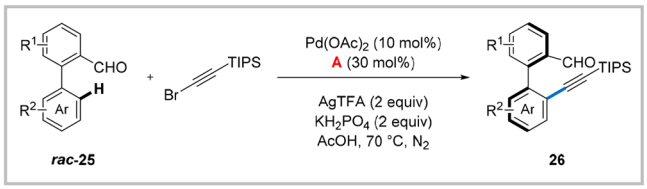
24g, R = H, 91%, 91% ee
24h, R = F, 62%, 90% ee

24i, R = TES, 45%, 99% ee
24j, R = TBS, 74%, 99% ee

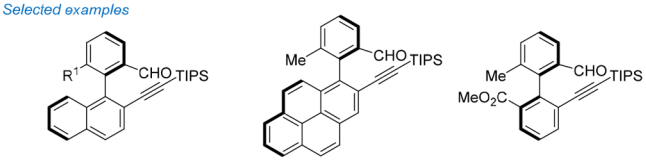
Desymmetrization

24k, R^2 = H, 61%, 90% ee
24l, R^2 = Cl, 54%, 92% ee
24m, R^2 = Me, 61%, 94% ee

Kinetic Resolution Pathway



Selected examples



R^1 = Me, **26a**, 42%, 96% ee
25a, 49%, 90% ee, *s* = 152
R^1 = Cl, **26b**, 46%, 99% ee
25b, 46%, 89% ee, *s* = 600

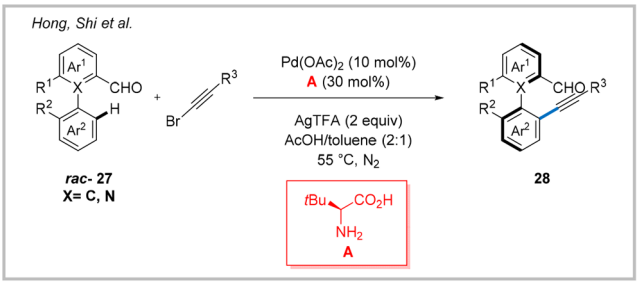
26c, 35%, 98% ee
25c, 53%, 75% ee, *s* = 224

26d, 31%, 98% ee
25d, 61%, 63% ee, *s* = 190

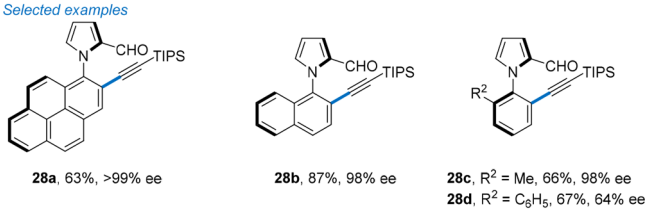
arenes was possible and it turned out that the enantioselectivity of the reaction was dependent on the nature of the heteroarene in the lower part (**28r** vs **28s**).

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, the 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 the replacement of the aryl part by a naphthyl part, 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 C(sp^3)−H amidation of a thioamide in comparison to their biaryl counterparts.

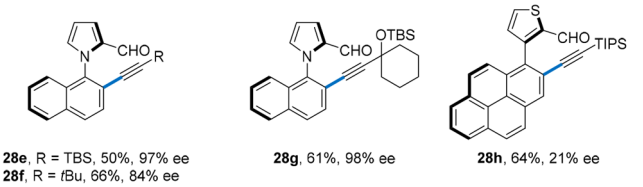
Scheme 10. Pd(II)-Catalyzed Alkynylation of Biaryls Containing a Five-Membered Ring by C−H Bond Activation



Selected examples

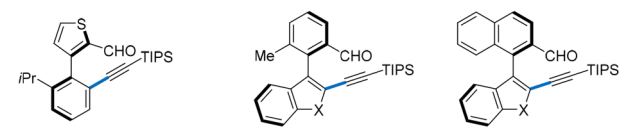


28a, 63%, >99% ee; **28b**, 87%, 98% ee; **28c**, R^2 = Me, 66%, 98% ee
28d, R^2 = C_6H_5, 67%, 64% ee



28e, R = TBS, 50%, 97% ee
28f, R = *t*Bu, 66%, 84% ee

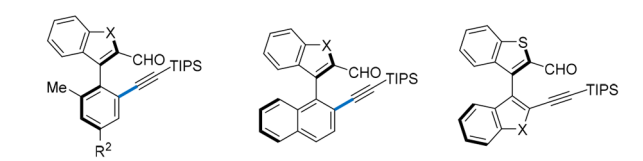
28g, 61%, 98% ee; **28h**, 64%, 21% ee



28i, 30%, 76% ee

28j, X = S, 84%, 92% ee
28k, X = O, 82%, 71% ee

28l, X = S, 47%, 99% ee
28m, X = O, 70%, 0% ee



28n, X = S, R^2 = OMe, 38%, 98% ee
28o, X = O, R^2 = H, 55%, 97% ee

28p, X = S, 47%, 99% ee
28q, X = O, 77%, 90% ee

28r, X = S, 98%, 93% ee
28s, X = O, 98%, 5% ee

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

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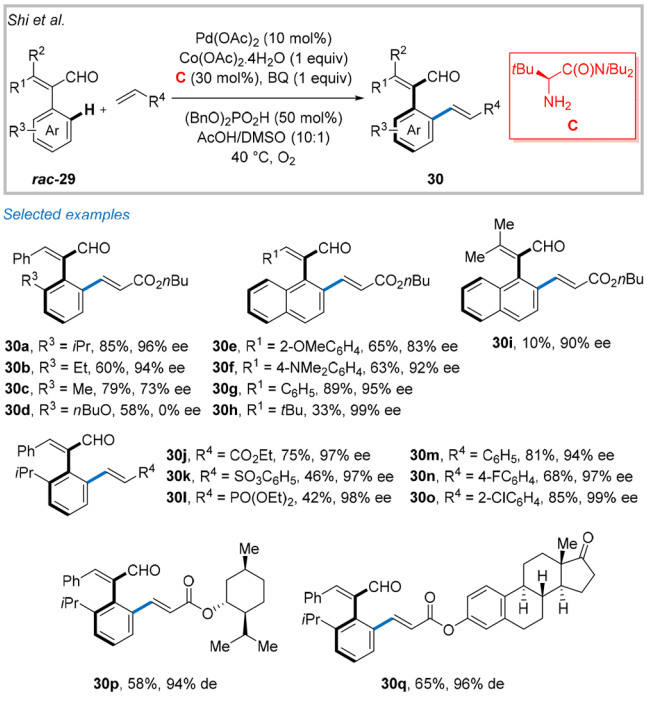
Scheme 11. Synthesis of Axially Chiral Styrenes *via* the Transient Directing Group Strategy

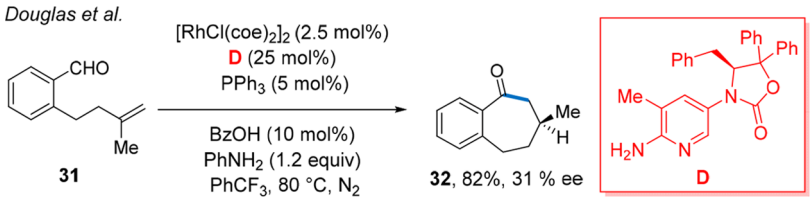


been considerably studied in the last decades. Indeed, the use of rhodium complexes, especially those containing cyclopentadienyl (Cp)-derived ligands, allowed many successful enantioselective transformations employing different strategies to induce asymmetry.[13g,37] In contrast, the utilization of chiral transient directing groups to this end is still in its infancy, despite the indisputable advances made in 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]

In 2019, Wang and co-workers took benefit from the use of cyclopentadienyl-containing Rh(III) catalysts for the asymmetric synthesis of phthalides.[40] Using a combination of the $[Cp^{*ipr}RhCl_2]_2$ catalyst and the chiral amine **E**, a methodology was developed for the enantioselective homo- and heterocoupling of benzaldehyde derivatives, offering 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,c**) as well as benzaldehyde (**33e**). In contrast, the presence of a CF_3 group (**33b**) or halogens (**33d,f**) 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 heterocouplings. First, the precatalyst $[Cp^{*ipr}RhCl_2]_2$ would react with the silver tetrafluoroborate to afford the active species $[Cp^{*ipr}Rh^{III}]$. Then, the formation of rhodacycle **II** 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 species would be easily hydrolyzed to provide the desired chiral phthalide **35** or **36** and the organo-catalyst.

In contrast to rhodium based-catalysts, ruthenium catalysts 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 $[Ru(p\text{-cymene})Cl_2]_2$ 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 group (OMe; **37a,c,g**) or an electron-withdrawing group (CF_3; **37e,h**) were functionalized with moderate to high yields. The substitution pattern on the aromatic aldehydes did not have a strong effect on the outcome of the reaction, except in the presence of a methoxy

Scheme 12. Rh(I)-Catalyzed Enantioselective Hydroacylation Using a Chiral TDG



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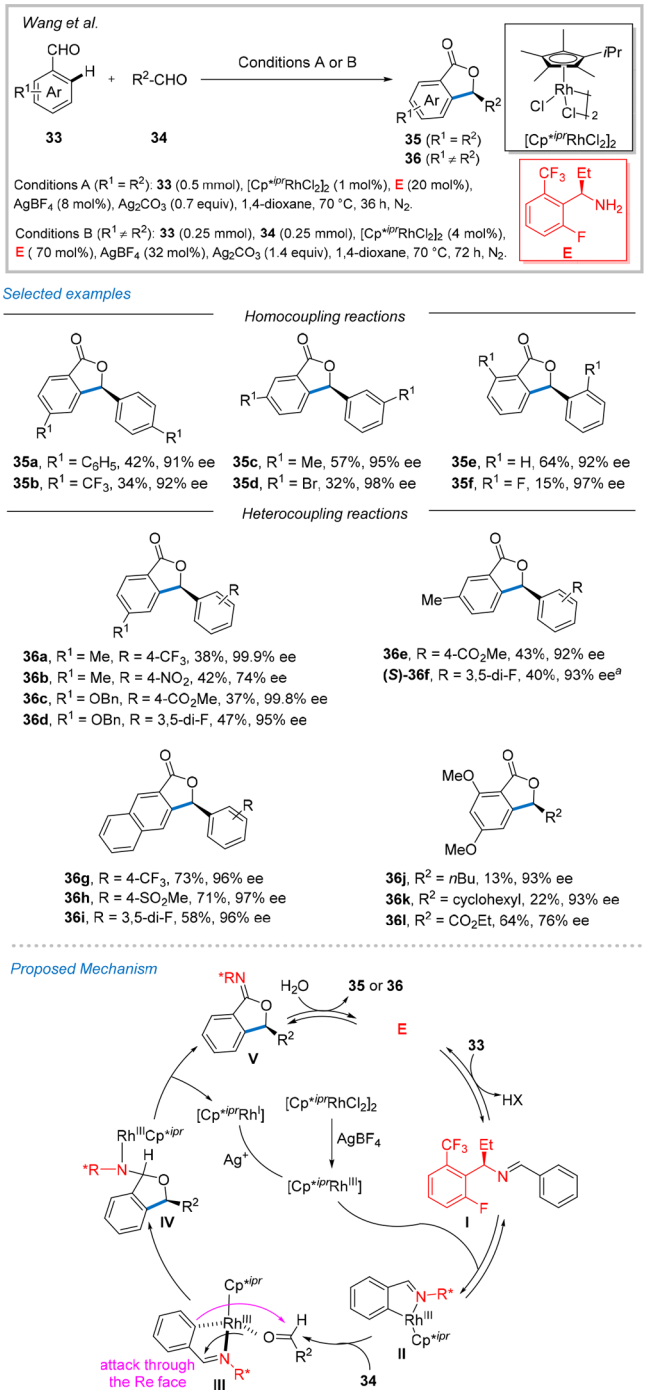
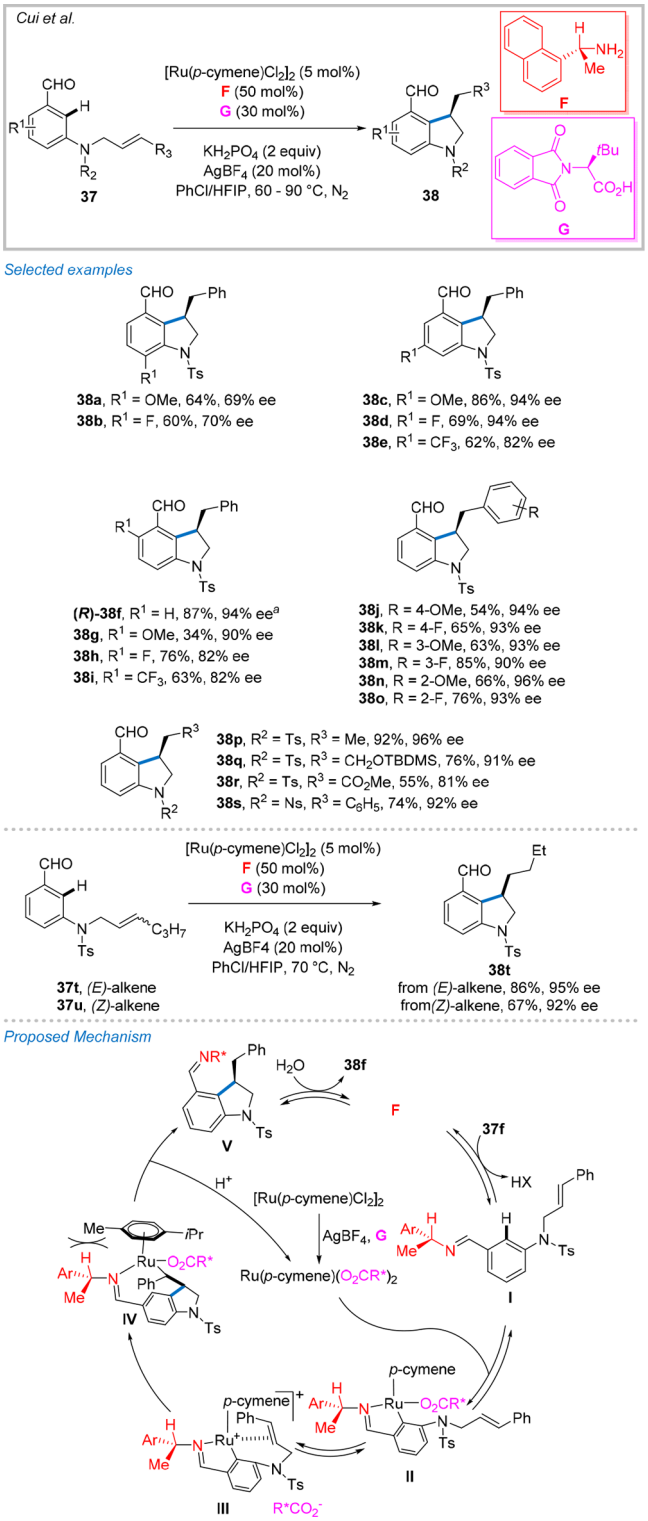
Scheme 13. Rh(III)-Catalyzed Preparation of Chiral Phthalides from Aldehydes Using a Chiral TDG



[a]Absolute configuration determined by X-ray diffraction.

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**

Scheme 14. Preparation of Chiral Indolines through an Enantioselective Ru(II)-Catalyzed Intramolecular Hydroarylation



[a]Absolute configuration determined by X-ray diffraction.

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

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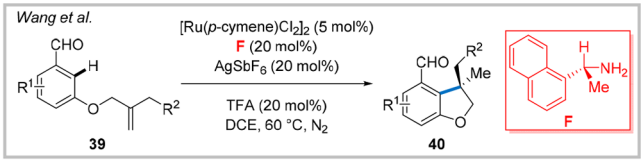
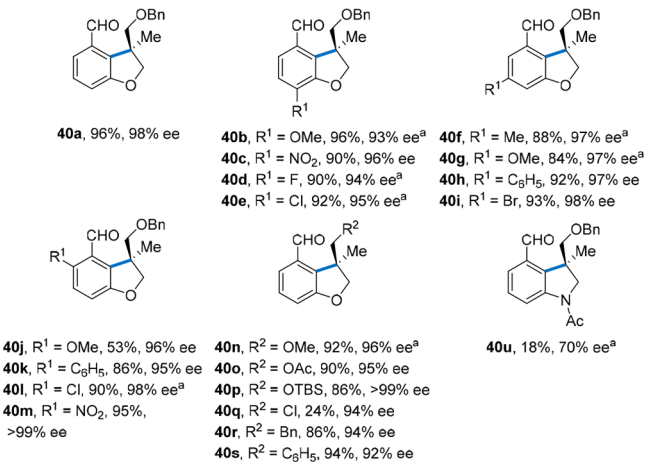
the transformation. A plausible mechanism was suggested for the enantioselective synthesis of indoline scaffolds and is shown in Scheme 14. First, the active catalyst species Ru(*p*-cymene)$(O_2CR^*)_2$ would be generated from Ru(*p*-cymene)-$(Cl_2)_2$ followed by the formation of the ruthenacycle **II** 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.

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 the [Ru(*p*-cymene)Cl_2]$_2$ 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 the

Scheme 15. Synthesis of Chiral 2,3-Dibenzofurans through a Ru(II)-Catalyzed Enantioselective Intramolecular Hydroarylation



Selected examples



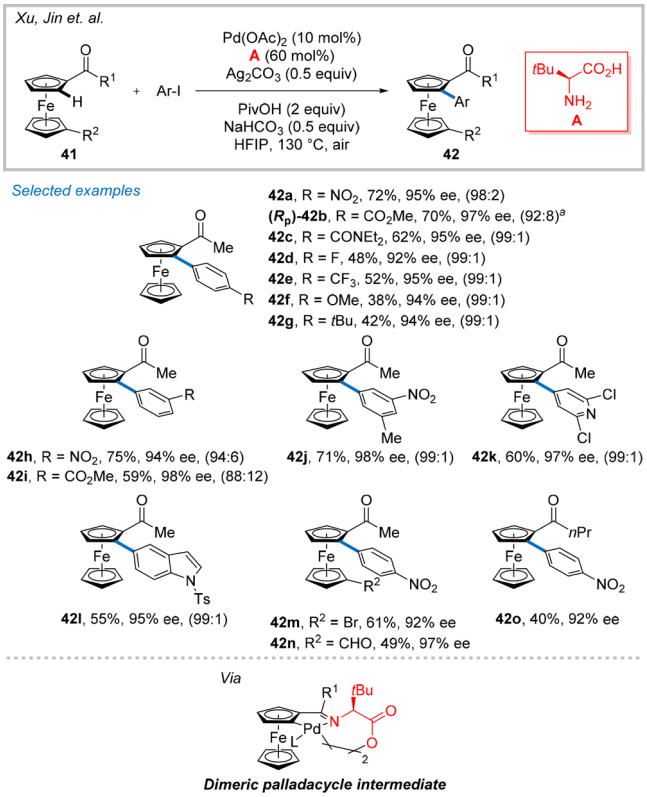
[a]**F** (40 mol %), TFA (40 mol %).

unsubstituted aldehyde **39a** as well as with aromatic aldehydes bearing halogens and electron-donating (e.g. OMe, Me) and electron-withdrawing groups (NO_2), 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**. An 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 mechanism similar to that depicted in Scheme 14 was suggested for this transformation, although the use of a chiral acid was not required to improve yields and enantioselectivities.

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(sp^2)−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 ratios of mono- vs difunctionalized products between 88:12 and 99:1 (Scheme 16).[45] It was found that the reaction

Scheme 16. Enantioselective Pd(II)-Catalyzed C(sp^2)−H Arylation of Ferrocenyl Ketones[b]



[a]The absolute configuration was assigned to R_p on the basis of X-ray diffraction. [b]Ratios of mono- to diarylated products are indicated in parentheses.

of acetylferrocene with 1-iodo-4-nitrobenzene was successfully achieved using L-*tert*-leucine as the transient directing group precursor, leading to the corresponding product **42a**. Both pivalic acid and 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

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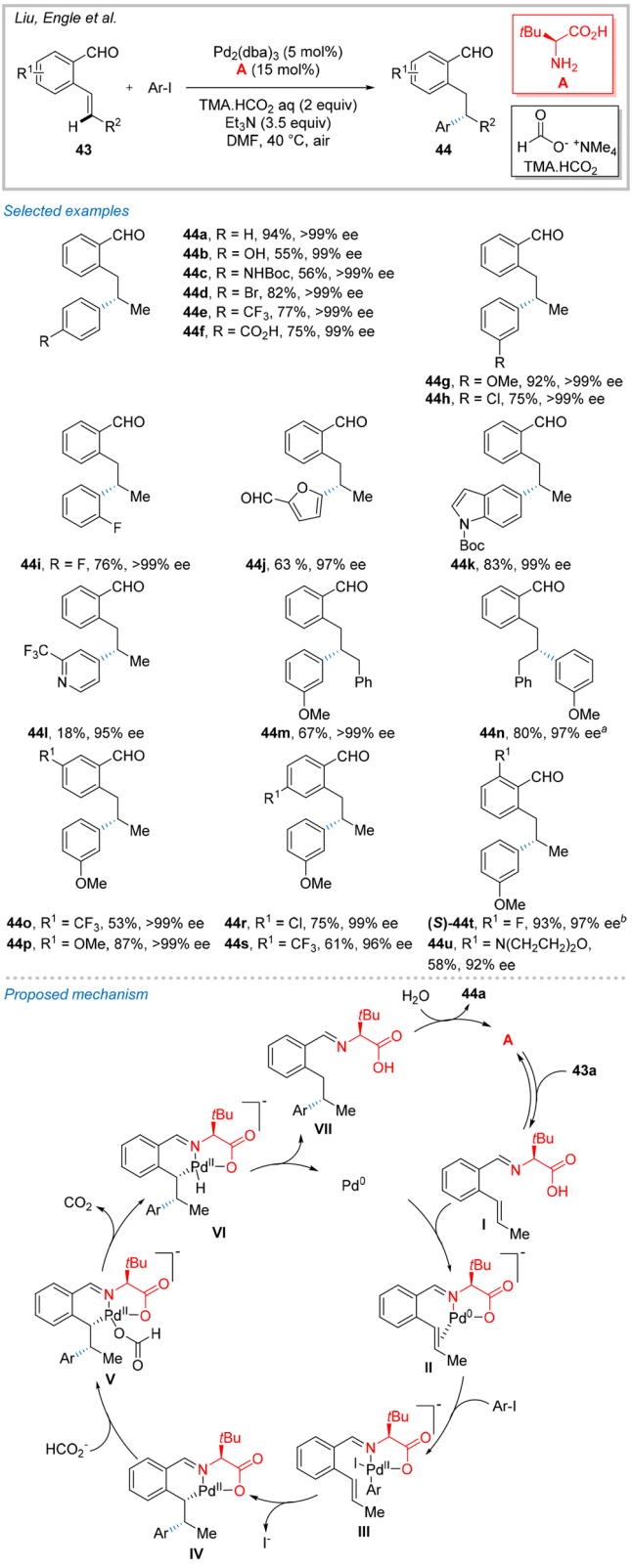
iodides (**42b−i**), electron-deficient species being more efficient coupling partners (**42b−e,h,i**). Aryl iodides bearing electron-donating substituents (OMe, *t*Bu) led to the expected products **42f,g** in lower yields. Note that the reaction went smoothly with disubstituted aryl iodides containing one electron-withdrawing group, as demonstrated with 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 of the cases, an excellent selectivity toward 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.

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 mentioning that the enantioselective β-hydroarylation of substituted alkenyl arenes[47] is still underdeveloped in comparison to the asymmetric α-hydroarylation reaction.[48] Using L-*tert*-leucine and in the presence of a hydride donor (TMA·HCO_2), 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 (*E*)-2-(prop-1-en-1-yl)benzaldehyde with several aryl iodides bearing electron-donating groups, electron-withdrawing groups, 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. With regard to 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 Pd(0) would lead to the species **II**, which would undergo an oxidative addition with the aryl iodide to afford the intermediate **III**. Then an 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, the 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



[a]From (*Z*)-alkene. [b]The absolute configuration was assigned through X-ray diffraction.

5. ENANTIOSELECTIVE FUNCTIONALIZATION OF C(sp^3)−H BONDS

Despite their lower reactivity in comparison with C(sp^2)−H bonds, groundbreaking advances have been made in the enantioselective functionalization of C(sp^3)−H bonds by transition-metal catalysis in the last few decades.[1a,13g,h,k]

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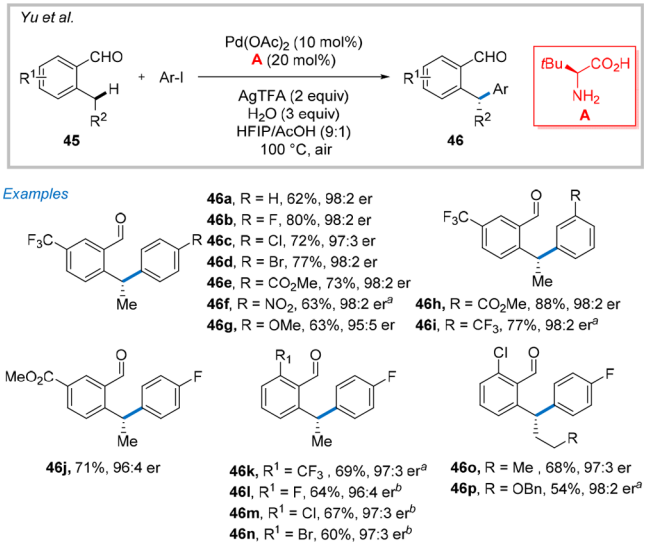
Among the existing approaches employed, the use of chiral ligands in Pd-catalyzed directed C−H bond functionalization reactions has been broadly exploited.[49] Therefore, the quest for new approaches to reach highly challenging asymmetric transformations was particularly attractive. In this context, although it is restricted so far to a 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 to achieve the Pd-catalyzed enantioselective arylation of benzylic C(sp^3)−H bonds.[50] In the course of their study related to the arylation of C(sp^3) 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). Due to the steric interactions between the bulky *tert*-butyl

Scheme 18. Pd(II)-Catalyzed Enantioselective Benzylic C(sp^3)−H Arylation of Benzaldehyde Derivatives Using L-*tert*-Leucine as the Chiral Transient Directing Group Precursor



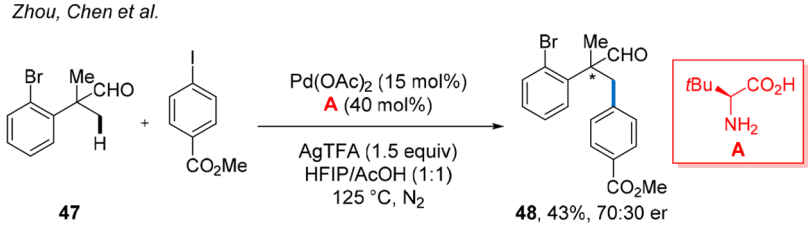
[a]Reaction performed at 110 °C. [b]5 mol % $Pd(OAc)_2$, 10 mol % **A**.

group of L-*tert*-leucine and the benzylic R^2 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 2-ethyl-5-(trifluoromethyl)benzaldehyde. Halogens as well as different electron-withdrawing (CO_2Me, NO_2, CF_3) 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 (R^2) 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 into the regio- and stereoselectivity observed for the Pd-catalyzed arylation of aldehydes and ketones by C(sp^3)−H activation using the chiral transient directing group strategy.[51]

In 2019, during their investigations toward the arylation of phenylacetaldehyde derivatives with aryl iodides under palladium catalysis, the Chen and Zhou group applied a methodology similar to that 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).

In 2020, Yu and co-workers provided a key contribution to the field by developing the Pd-catalyzed enantioselective arylation of nonactivated secondary C(sp^3) centers. By employing a combination of $Pd(OAc)_2$, D-valine (**H**), pyridone, and Ag_2PO_3, 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 Ag_2PO_3 by AgTFA, the products were obtained with a reversed enantioselectivity. Moreover, in this transformation, the 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 CO_2Me, NO_2, Ac, CN, CF_3, and COC_6H_5 (**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** was a competitive arylation of the methyl group of the alkyl chain 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 species would undergo an oxidative addition

Scheme 19. Pd(II)-Catalyzed C(sp^3)−H Asymmetric Arylation of the Phenylacetaldehyde Derivative 47



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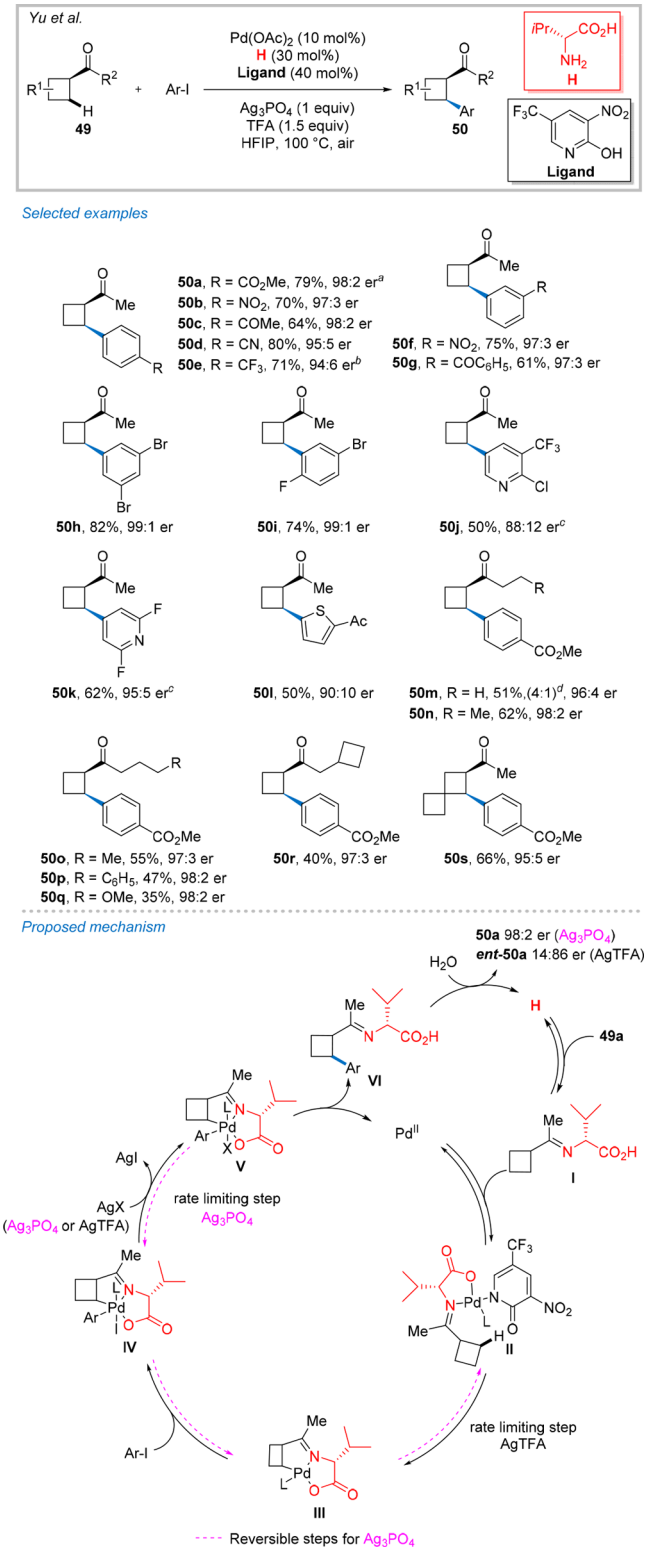
Scheme 20. Pd(II)-Catalyzed Enantioselective C(sp^3)−H Arylation of Cyclobutyl Ketones



[a]Using AgTFA instead of Ag_3PO_4, ***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 equiv of **H** was used. [d]Ratio of the products resulting from the arylation of the cyclobutane ring and the terminal methyl group.

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**. It is worth mentioning that, depending on the nature of the silver salt (AgTFA or Ag_2PO_3), either the C−H activation event or iodine abstraction was suggested to be the rate-determining step.

The asymmetric formation of C(sp^3)−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(sp^3)−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(sp^3) 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(sp^3)−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(sp^3)−Pd(IV)−F intermediates.[58] Instead of using an amino acid, it was discovered that the combination of the amide **I** (derived from L-*tert*-leucine) along with 2,3,4,5,6-pentafluorobenzoic acid allowed the fluorination of the trifluoromethylated benzaldehyde derivative **51a** on a secondary C(sp^3) 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 and 99%. Even though the competitive pathway that led to the formation of the undesired C(sp^3)−O bond formation by an S_N2-type process could not be completely circumvented, moderate to excellent ratios in favor of the fluorinated products were obtained (5:1 to >20:1). Benzaldehydes bearing alkyl chains longer than an ethyl group at the *ortho* position were also suitable and furnished the best enantiomeric excesses and the best C(sp^3)−F:C(sp^3)−O ratio (>20:1), albeit with lower yields (**52b,c**). Moreover, benzaldehydes substituted with electron-withdrawing groups (CO_2Me, CO*i*Pr, NO_2; **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(sp^3)−O bond formation.

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 challenging asymmetric transformations. In this review, a general overview of the recent groundbreaking advances made in this field was given. Original methodologies

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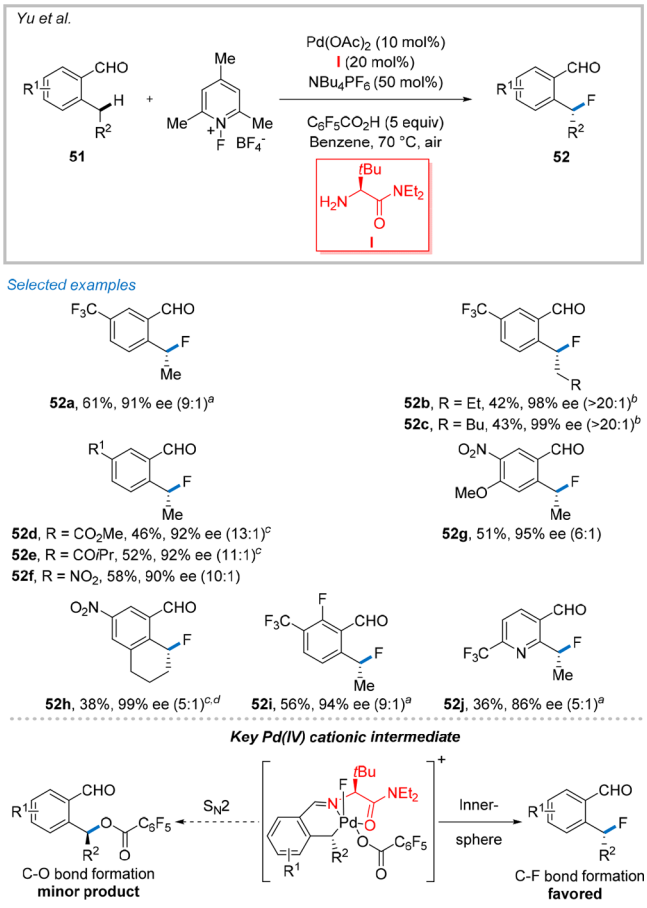
Scheme 21. Pd(II)-Catalyzed Enantioselective Fluorination of Secondary C(sp^3)−H Bonds[e]



[a]^{1}H NMR yields are 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]CH_2Cl_2 was used instead of benzene. [d]25 mol % of **I** was used. [e]Isolated yields were reported as a mixture of the product **52** with the starting material **51**. The values in parentheses indicated the ratio of products resulting from either C(sp^3)−F or C(sp^3)−O bond formation and were determined by ^{1}H NMR analysis.

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(sp^3)−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 have been 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 have been 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 have not yet been achieved, 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.

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ABBREVIATIONS

BQ, benzoquinone; CCE, constant-current electrolysis; *s*, selectivity factor

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