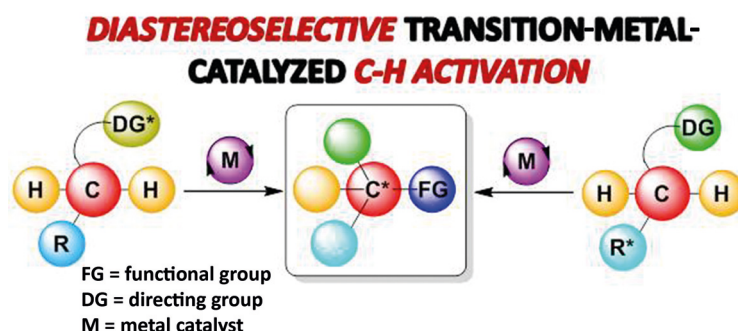


Diastereoselective Substrate-Controlled Transition-Metal-Catalyzed C–H Activation: An Old Solution to a Modern Synthetic Challenge

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Abstract The synthesis of chiral compounds by means of asymmetric C–H activation is an appealing modern strategy for the straightforward conversion of simple and nonfunctionalized substrates into high-value-added stereogenic molecules. For several years, considerable attention has been focused on the design of enantioselective transformations involving the use of chiral ligands as sources of chirality. In addition, a complementary strategy based on direct functionalization of substrates bearing a chiral element has recently demonstrated its potential. Such diastereoselective transformations can be achieved by incorporating a chiral auxiliary into a directing group (DG). Alternatively, direct functionalization of chiral-pool molecules, such as α -amino acids, provides a valuable synthetic route to novel non-natural amino acid derivatives. The aim of this account is to highlight major achievements in diastereoselective C–H activation. Particular attention will be paid to the contributions of our group in this emerging field.

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- 2 Directing Group Controlled Diastereoselective C–H Activation
- 3 Substrate-Controlled Diastereoselective C–H Activation
- 4 Conclusions

Key words direct functionalization, asymmetric synthesis, bond activation, diastereoselectivity, chiral auxiliary, directing group

1 Introduction

The growing level of environmental awareness has a direct impact on scientific research. Consequently, organic chemists face critical challenges, such as the design of more-ecoreliable transformations that permit the rapid construction of complex molecular scaffolds from available feedstocks. To meet these challenges, the scientific community has, since the beginning of this century, made significant efforts to develop reactions that allow the direct functionalization of ubiquitous C–H bonds to form desirable functional groups. Consequently, numerous innovative cat-

alytic systems have been designed for the conversion of latent C–H bonds into a wide variety of carbon–carbon and carbon–heteroatom linkages.¹ Moreover, advancements in the field of C–H activation continue to stimulate chemists to reconsider standard retrosynthetic disconnections, thereby allowing more-straightforward syntheses of high-value-added complex organic molecules in fewer steps.²

Chirality is an intriguing feature of numerous natural products, and its importance is universally recognized. In particular, the use of small three-dimensional molecules as biologically active moieties has recently emerged as a promising solution in medicinal chemistry.^{3–4} Furthermore, axial chirality is a key feature of several natural products and chiral ligands essential for homogeneous catalysis.⁵ For these reasons, the stereoselective synthesis of optically active skeletons is a challenging and appealing research target.

Despite the growing importance of the field of C–H bond activation, its applications in building up chiral molecules have been underestimated for quite a long time.⁶ Indeed, because studies have concentrated primarily on direct functionalizations of aromatic C–H bonds, opportunities for accessing stereogenic scaffolds have been limited. Also, the high reaction temperatures and the widespread use of strongly acidic and/or oxidative conditions appear to be incompatible with a use of chiral ligands and with efficient stereinduction. In 2005, however, Yu and co-workers demonstrated that chiral compounds can be generated by direct functionalization of C–H bonds, provided that a chiral directing group is embedded within a substrate and coordinates the metal catalyst to permit the formation of a stereogenic metallacyclic intermediate in the key C–H bond-cleavage step.⁷ Despite the importance of this seminal work, stereoselective C–H activation remained a niche topic until about 2010, when interest in asymmetric direct functionalization was revived. At this time, the development of

enantioselective transformations became clearly favored. Consequently, several classes of stereogenic ligands compatible with C–H activation reactions have been designed; among these ligands, chiral monoprotected amino acid derivatives are arguably the most prominent. The superiority of enantioselective transformations, which involve the use of a chiral ligand, over diastereoselective reactions, for which a stereogenic auxiliary is installed directly on a substrate, is widely recognized, because only a catalytic amount of the chiral source is required in the former case.⁸ If, however, the preparation of the chiral ligand requires a multistep, laborious, and difficult synthesis, this argument is no longer valid. This is even more true since a chiral auxiliary installed on a substrate can be readily obtained from a cheap and abundant chiral pool. In the context of asymmetric transition-metal-catalyzed C–H activation, there are several additional key points that favor the diastereoselective approach. Because of problems associated with regioselectivity and reactivity, C–H activation reactions frequently involve the use of substrates that bear a preinstalled coordinating DG. Consequently, if a chiral DG (DG*) can be embedded straightforwardly and can be easily removed after the C–H activation event, no additional step is required in comparison to analogous nonasymmetric C–H transformations. Moreover, the installation of a stereogenic element directly on a substrate ensures that the chiral source is near the metal atom in the key metallacyclic intermediate, thereby maximizing the chances of efficient chiral induction. Moreover, in such cases, only two coordination sites of the metal catalyst (M) are occupied (one DG*–M

bond and one C–M bond), thereby preserving the additional free coordination sites required to coordinate a coupling partner. In contrast, in enantioselective transformations, a metal catalyst is significantly more encumbered as a result of coordination to a nonchiral DG of the substrate, formation of a C–M bond, and complexation of an external monodentate or bidentate ligand. Consequently, the coordination of a second coupling partner might be compromised. Finally, the use of a DG* opens the possibility of accessing rather general catalytic systems, compatible with several different coupling reactions, because a single stereogenic metallacyclic intermediate can react smoothly with various coupling partners.

Accordingly, following the pioneering work of Yu, several research efforts have recently focused on the development of substrate-controlled stereoselective C–H activation reactions. Not only have novel monocoordinating chiral auxiliaries been successfully employed as stereogenic DGs, but also innovative bidentate asymmetric DGs have been devised. Furthermore, significant efforts have been devoted to the construction of non-natural α -amino acids through diastereoselective C–H activation. Since 2013, we too have been actively involved in this expanding field, and our research interest is concerned mainly with the synthesis of axially chiral compounds. In this account, therefore, we will discuss the use of diastereoselective C–H activation reactions as a complementary approach to enantioselective C–H functionalizations. Two distinct strategies are discussed: DG-controlled diastereoselective C–H activation, and substrate-controlled transformations. In addition, we would

Biographical Sketches



Joanna Wencel-Delord was educated in chemistry at the École Nationale Supérieure de Chimie de Rennes, France, and gained her Ph.D. in 2010 from the University of Rennes 1, France (Dr. C. Crévisy and Dr. M. Mauduit). After postdoctoral

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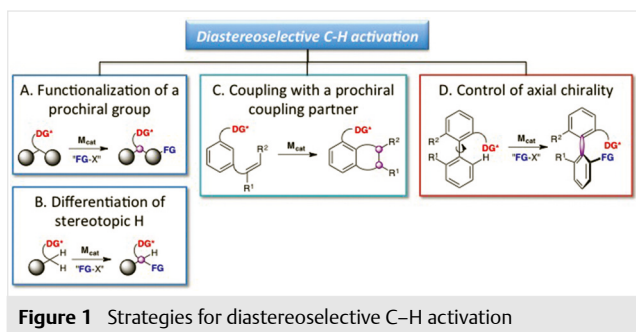


Françoise Colobert received a Ph.D. in organic chemistry in 1985 from the University Pierre et Marie Curie (Paris), working with Professor Jean-Pierre Genêt in the field of asymmetric catalysis. After a postdoctoral position in molecular biology in the

group of Professor Jules Hoffman (Nobel Prize, Strasbourg), she became an assistant professor in the group of Professor Guy Solladié, and was appointed full professor of organic chemistry in 2001. Currently, she is director of the molecular

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like to draw the reader's attention to various mechanistic strategies pertaining to these asymmetric transformations. Indeed, a stereogenic center can be generated either by a desymmetrization reaction, in which a prochiral substituent (such as a methyl or phenyl group) is functionalized [Figure 1(A)] or by selective C–H cleavage of a stereotopic hydrogen atom [Figure 1(B)]. Alternatively, a chiral carbon center can be constructed through the use of a prochiral coupling partner [Figure 1(C)]. Finally, diastereoselective direct functionalization is also an appealing route to axially chiral compounds [Figure 1(D)].

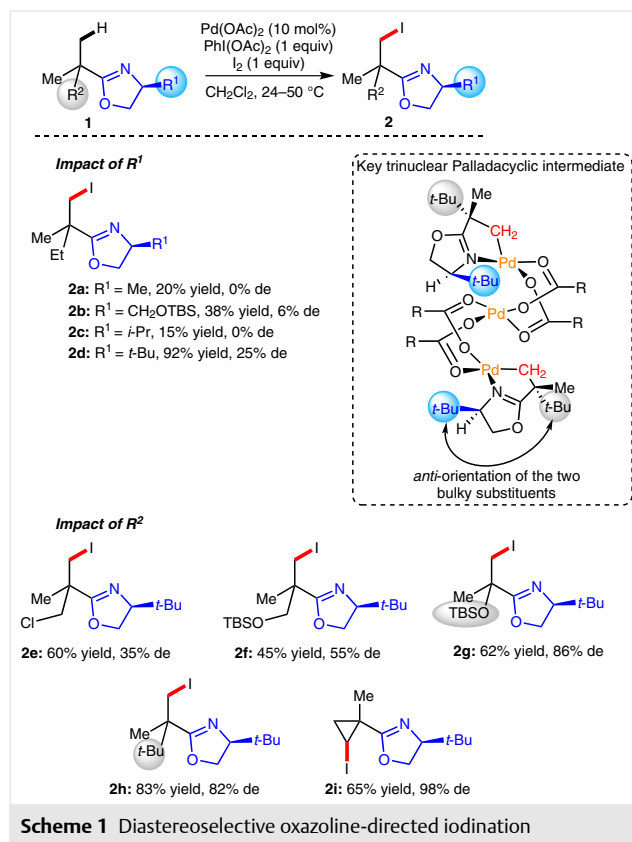


2 Directing Group-Controlled Diastereoselective C–H Activation

At the beginning of this century, although the stoichiometric activation of inert C–H bonds by metals such as palladium, iridium, rhodium, or ruthenium to give isolable metallacyclic intermediates was well established, the field of transition-metal-catalyzed C–H activation was in its infancy. At that time, most direct functionalization reactions involved aromatic substrates and, generally, high reaction temperatures were required to ensure acceptable efficiencies. In this context, the seminal work of Yu on asymmetric C–H activation represented a real breakthrough.⁷ Yu and co-workers surmised that the oxazoline moiety might be used as an efficient σ -chelating DG that would facilitate the assembly of a pretransition state for cyclometallation through a square-planar complex. This assumption was initially confirmed by conducting a palladium-mediated stoichiometric iodination of an aliphatic pivalic acid substrate to give a monoiodinated product in a high (80%) yield. In parallel, a trinuclear palladacyclic intermediate was isolated, unambiguously demonstrating the favored formation of a geometrically well-defined metallacyclic intermediate.

Subsequently, a related catalytic transformation was successfully achieved by using a (diacetoxyiodo)benzene–diiodine mixture as an iodine source and a precursor for the generation in situ of iodine monoacetate, required to regenerate the palladium(II) acetate catalyst at the end of the catalytic cycle. Accordingly, catalytic and diastereoselective direct C(sp³)–H functionalization could be performed under surprisingly mild conditions (Scheme 1). The substitution

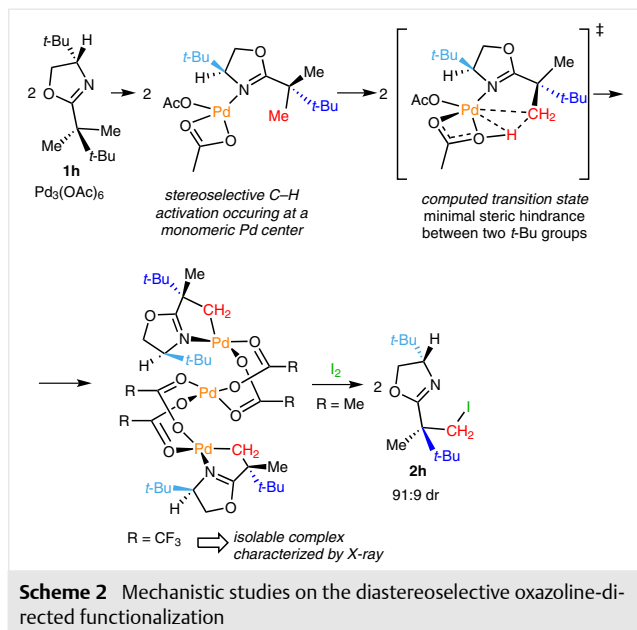
pattern of the oxazoline DG was found to have a marked effect on both the reactivity and stereoselectivity of the target transformation.⁹ When small substituents were introduced at the 4-position of oxazoline **1a**, direct iodination was sluggish and no stereoselection was observed. Intriguingly, high reactivity and an improved level of diastereoselectivity were achieved when a bulky *tert*-butyl group was present at the 4-position of the oxazoline DG in **1d**. The substitution pattern of the substrate also had a major impact on the diastereoselectivity of this transformation, as a bulky group at the α -position was required to reach high chiral induction in products **2g** and **2h**. Accordingly, the desired halogenated products could be obtained with diastereoselectivities of up to 86% when a noncyclic substrate was used. Furthermore, the asymmetric functionalization of the cyclopropane scaffold **1i** could also be performed with complete diastereoselectivity.



Interestingly, direct functionalization of cyclopropanes by means of enantioselective C–H activation remained unexplored until the beginning of this decade. In 2011, Yu used monoprotected amino acid ligands to achieve a palladium-catalyzed alkylation and arylation of cyclopropanes bearing a weakly coordinating amide DG. In this case, organoboron coupling partners were used as the arylating agents.¹⁰ Recently, the same research group discovered that (cyclopropylmethyl)amines are also attractive substrates

for palladium/chiral amino acid catalyzed direct arylations with iodoarenes.¹¹ An intramolecular palladium(0)-catalyzed enantioselective direct functionalization of cyclopropane skeletons has been investigated by Cramer and co-workers.¹²

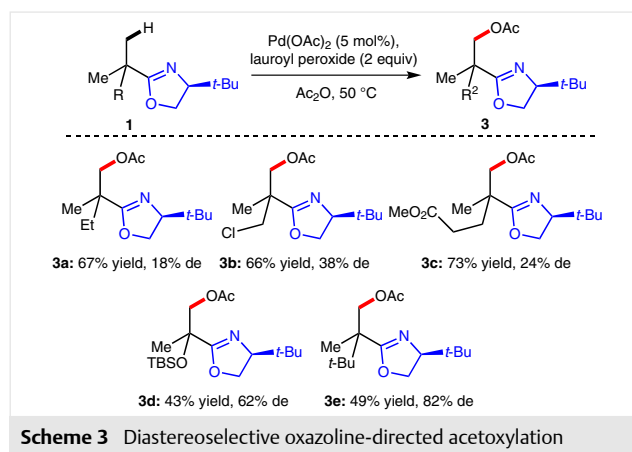
In-depth mechanistic investigations, involving the characterization of key intermediates and computational studies, provided a rationale for the stereoselectivity of the transformation (Scheme 2).¹³ When the prochiral substrate **1h**, bearing *tert*-butyl groups on the oxazoline DG and in the α -position, is treated with palladium(II) acetate, stereoselective C–H activation occurs at a monomeric palladium center, affording one isomer of the trinuclear palladium(II) complex (isomeric ratio 91:9) almost exclusively. Indeed, because of steric repulsion between the two bulky substituents, the palladacyclic intermediate in which these two groups are orientated in *anti*-positions at both termini of the trinuclear complex is favored, producing a highly diastereoselective outcome for the catalytic transformation. Importantly, the lack of reactivity of substrates bearing a less sterically demanding oxazoline DG (for example, one bearing an isopropyl substituent) can be attributed to the high stability of the bis(oxazoline)palladium(II) acetate complex and to a concomitant increase in the overall activation barrier. In contrast, a larger steric hindrance on the oxazoline DG results in destabilization of the corresponding bis(oxazoline)palladium(II) acetate, thereby enhancing its conversion into the catalytically active monomeric (oxazoline)palladium(II) acetate intermediate.



Another key aspect of this seminal work is the recyclable character of the catalytic system; palladium(II) iodide, generated through reductive elimination of the iodinated

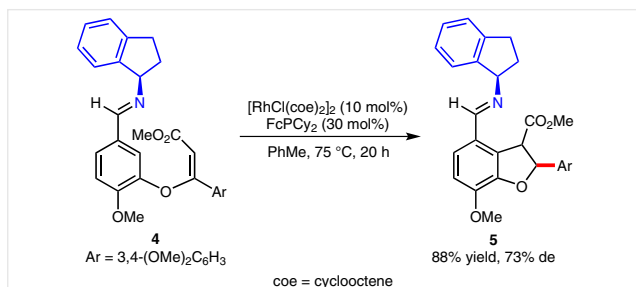
compound, precipitates from the solvent, and can be recovered by centrifugation and reused directly in a new catalytic system without any significant change in the efficiency of the reaction.

A few months later, the same research group expanded the potential of the chiral oxazoline-directed stereoselective C–H activation by performing an acetoxylation reaction (Scheme 3).¹⁴ The catalytic system based on palladium(II) acetate catalyst in combination with lauroyl peroxide as a stoichiometric oxidant and acetic anhydride (used as a crucial promoter of the oxidative addition of the peroxide to the palladacyclic intermediate), enabled mild and diastereoselective oxidation of prochiral aliphatic substrates bearing the same, highly sterically demanding, chiral oxazoline DG. The functionalization occurs selectively and the stereoinduction is strongly influenced by the steric environment around the two prochiral methyl groups of a starting material. Consequently, the enantioenriched acetoxyated products **3** could be isolated in yields of 38–73% and diastereomeric excesses of 18–82%.



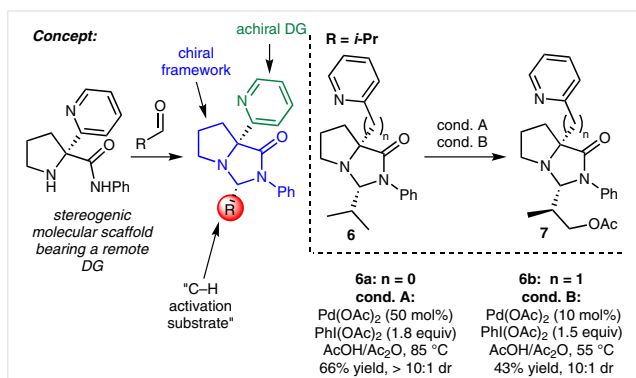
At the same time as Yu and co-workers were examining palladium-catalyzed oxazoline-directed iodination and acetoxylation, the group of Bergman and Ellman astutely used a chiral imine as a potent DG* (Scheme 4).¹⁵ When designing a new synthetic route to (+)-lithospermic acid, the researchers surmised that chiral 2,3-dihydrobenzofuran cores might be accessible by means of an intramolecular asymmetric Fujiwara–Moritani reaction. Although initial attempts at enantioselective transformations using a rhodium(I) catalyst in combination with chiral ligands failed, synthetically useful levels of diastereoselectivity were observed when a chiral imine was used as both the DG and the chiral auxiliary. The stereogenic benzylic amines turned out to be appealing precursors for imine DGs*, but the most selective transformation was achieved by using an (–)-aminoindane-derived substrate. Under the optimized reaction conditions, benzofuran **5**, a key precursor of (+)-lithosper-

mic acid, could be obtained in 88% yield and 73% de by means of diastereoselective rhodium(I)-catalyzed C–H functionalization.



Scheme 4 Rhodium(I)-catalyzed diastereoselective oxidative Heck reaction

Intriguingly, after the appearance of these seminal publications on diastereoselective C–H activation in the middle of the last decade, this research field remained overlooked for several years. In 2012, Ferreira proposed a complementary strategy to achieve regio- and stereoselective C–H activation.¹⁶ Contrary to the standard directing-group strategy, in which a DG is directly embedded within the substrate, this approach involved the use of a specific chiral molecular framework bearing an additional nonstereogenic coordinating moiety. This molecular framework should be easy to install on a C–H activation substrate and might be readily removable after the functionalization step. In pursuit of this idea, the researchers selected aldehydes as the C–H activation substrates and a chiral proline derivative as a molecular platform (Scheme 5). The acetalization reaction delivered amination products containing a pyridine DG. Such finely designed substrates were tested in a direct acetoxylation reaction. The isopropyl-derived substrate **6a** underwent the expected C–O coupling reaction, although a large loading of palladium(II) diacetate catalyst (50 mol%) was required. Importantly, chirality transfer occurred correctly during this transformation, as the acetoxylation product was formed with nearly complete selectivity. It is noteworthy that the



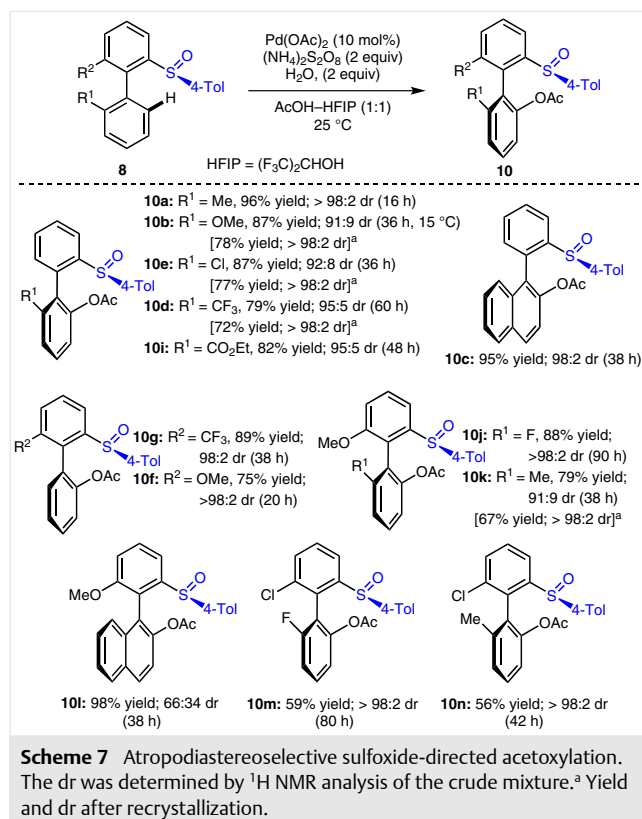
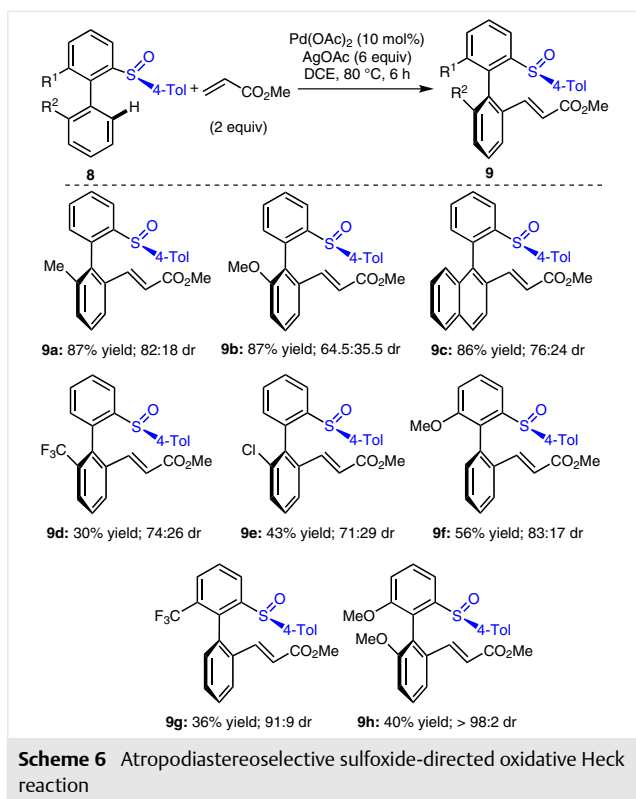
Scheme 5 Diastereoselective acetoxylation by an approach involving a chiral molecular scaffold and a remote DG

efficiency of this transformation was improved by the incorporation of conformational flexibility, for example, by introducing a CH₂ linker between the pyridine DG and the amination moiety in **6b**. Consequently, both the catalyst loading and the reaction temperature could be decreased.

In 2013, our research group initiated a new research project on diastereoselective C–H activation, with particular attention to the design of novel chiral DGs. Our laboratory has a longstanding experience in sulfoxide chemistry.^{17,18} In particular, in the first decade of the 21st century, we discovered that the atropodiastereoselective Suzuki–Miyaura coupling can be performed by using iodoarenes bearing a chiral sulfoxide substituent in the *ortho*-position as coupling partners.¹⁹ We speculated that a stereogenic sulfoxide-coordinated palladacyclic intermediate might be generated through oxidative addition and, consequently, chiral information might be efficiently transferred either through stereoselective transmetalation or reductive elimination. The possible generation of such chiral sulfoxide-coordinated palladacyclic species encouraged us to investigate the potential of our chiral auxiliary in the context of palladium-catalyzed C–H activation. Additionally, as enantiopure sulfoxides are readily available on a large scale from inexpensive starting materials, and because they can be straightforwardly removed through sulfoxide–lithium exchange followed by electrophilic trapping, these chiral auxiliaries appear to be particularly appealing.

Our initial efforts involved an atroposelective functionalization of biaryl scaffolds bearing the chiral sulfoxide DG.²⁰ We were soon able to devise a catalytic system that permitted direct olefination of the sulfoxides **8** (Scheme 6). The use of palladium(II) acetate as a catalyst in combination with a large excess of silver acetate as an oxidant (6 equiv) in dichloroethane at 80 °C gave the functionalized atropisomeric products **9** (Scheme 6). Unfortunately, rather moderate results were obtained in terms of both stereoselectivity and efficiency (dr 64.5:35.5 to 91:9). Importantly, total atroposelection could be achieved by using the trisubstituted biaryl substrate **8h**, but the desired product was isolated in only a modest 40% yield.

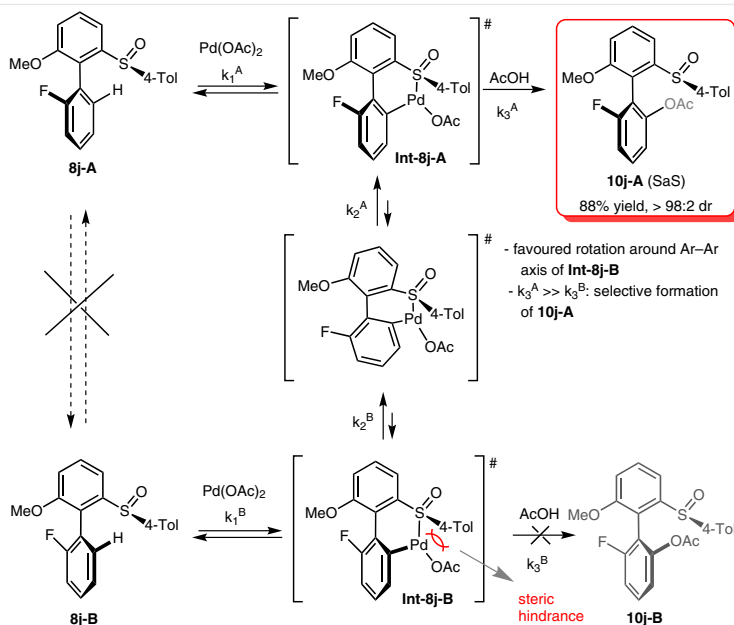
Although both the efficiency and stereoselectivity of this transformation were moderate, this pioneering work demonstrated that the sulfoxide moiety could be used as both a chiral auxiliary and a DG. In a continuation of our studies, we discovered a related acetoxylation reaction (Scheme 7).²¹ The use of acetic acid as a cosolvent in a presence of a catalytic amount of palladium(II) acetate as a catalyst and ammonium persulfate as an oxidant permitted selective oxidation to give the corresponding atropo-enriched acetate-substituted biaryls **10**. Surprisingly, 1,1,1,3,3,3-hexafluoropropan-2-ol turned out to be the optimal medium for this reaction, allowing direct functionalization to occur at room temperature. This acetoxylation reaction is also extremely robust; no precautions to avoid air or mois-



ture are required, and the addition of a small amount of water is even beneficial. Under the optimized reaction conditions, a large panel of variously substituted biaryl sulfoxides **8** underwent the atroposelective acetoxylation with remarkable efficiency and stereoselectivity. Both electron-donating and electron-withdrawing substituents could be installed at either the 2'-position or the 6-position, and the corresponding C–O coupling products **10** were isolated in 75–95% yield and 91:9 to > 98:2 diastereoselectivity. The trisubstituted biaryl sulfoxides **8j–n** could also be successfully used in this coupling reaction; the acetoxylation of substrate **8j** bearing two unbulky substituents (fluoro and methoxy, respectively), in addition to the sulfoxide DG, around the biaryl axis delivered the corresponding atropo-pure product **10j** in 88% yield. In contrast, increasing the steric demand around the biaryl axis turned out to be detrimental either to efficiency (**10m–n**) or diastereoselectivity (**10k–l**) of the transformation.

The majority of our biaryl sulfoxide substrates (R¹ ≠ H) are axially chiral molecules, atropisomerically stable at room temperature, that were used as mixtures of two atropisomers (typically, the NMR spectra of these substrates clearly indicated the presence of a mixture of two atropodiastereomers in 1:1.1 to 1:1.6 ratio). Our direct functional-

ization reaction allows their conversion at room temperature into highly atropo-enriched compounds, generally isolated in excellent yields. These results clearly suggest that this transformation might occur either through a dynamic kinetic asymmetric transformation or through dynamic kinetic resolution.²² Indeed, if the steric hindrance around the biaryl axis is high enough to prevent atropo-epimerization (rotation around the biaryl axis) of the substrate (rotation barrier > 22 kcal·mol⁻¹), the two atropisomers should react with palladium(II) acetate to generate the corresponding atropostereogenic palladacyclic intermediates. As the steric hindrance of such an intermediate is reduced when palladation occurs on the opposite side to the 4-tolyl substituent of the sulfoxide moiety, the disfavored palladacycle undergoes rapid atropo-epimerization. We surmise that this rotation around the Ar–Ar bond is possible as a result of the formation of a pallada-bridged cyclic species that might increase the angle between the two aromatic units, thereby lowering the rotation barrier in this intermediate compared with that in the corresponding substrate.²³ The rate of this atropo-epimerization is expected to be significantly faster than the reductive elimination from the disfavored metallacyclic intermediate, thereby permitting excellent stereocontrol throughout the reaction (Scheme 8).



Scheme 8 Dynamic kinetic asymmetric transformation mechanism of the sulfoxide-directed atroposelective acetoxylation

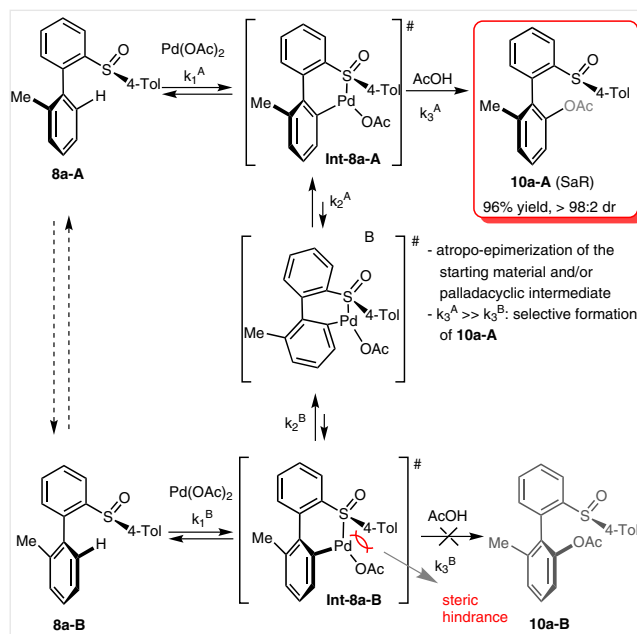
Alternatively, if the substituents around the biaryl axis are less sterically demanding (small R^1 and $R^2 = H$, as, for example, in **8a**), slow atropo-epimerization of the starting material over a prolonged time cannot be excluded. Consequently, the excellent atroposelection of this acetoxylation reaction might result from both dynamic kinetic resolution (epimerization of the starting material) and dynamic kinetic asymmetric transformation (epimerization of the palladacyclic intermediate) (Scheme 9).

Finally, if a bulky substituent is introduced in the *ortho* position of the aromatic ring bearing the DG [as, for example, in **8m** or **8n** ($R^2 = Cl$)], the acetoxyated product is isolated in an atropopure form, but in moderate yield. In addition, the unreacted starting material could be recovered from the reaction mixture, also as a single diastereomer. Accordingly, a simple kinetic resolution occurs in this case. The increase in steric hindrance either disfavors metallation of one atropisomer or it prevents the epimerization of the metallacyclic intermediate. Consequently, the sterically less-congested metallacyclic intermediate is functionalized in a stereoretentive manner, yielding a single diastereomer of the coupling product (Scheme 10).

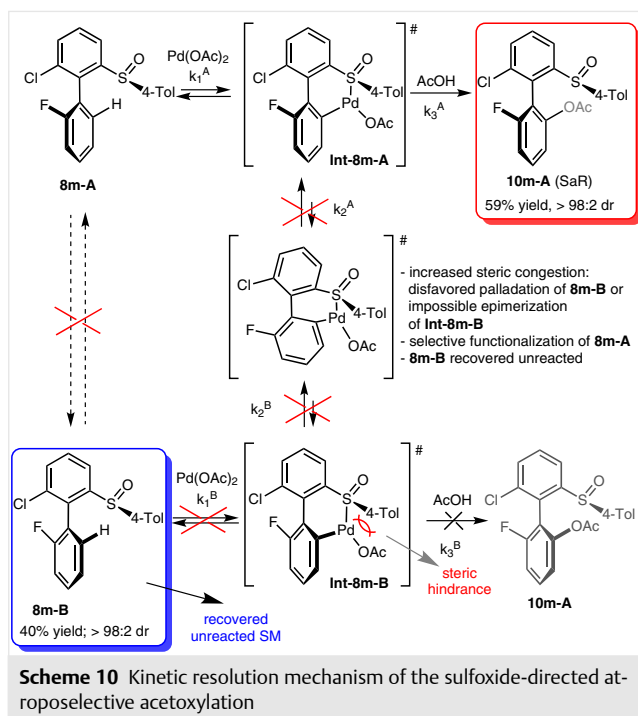
In pursuing our study, we were delighted to discover that this original diastereoselective sulfoxide-directed C–H protocol can also be efficiently used to construct halogenated atropopure products **11** (Scheme 11). A slight modification of the reaction conditions, i.e., by replacement of the ammonium persulfate oxidant with *N*-iodosuccinimide permitted extremely mild and selective iodination of biaryl sulfoxide substrates. This reaction is highly efficient and atroposelective for a large panel of substrates. As with the

acetoxylation reaction, this direct halogenation is believed to involve a comparable dynamic kinetic asymmetric transformation /dynamic kinetic resolution mechanism.

Finally, the truly synthetically useful character of this diastereoselective C–H functionalization was evidenced by a post-modification of the atropo-pure acetoxyated product. The sulfoxide auxiliary could be straightforwardly re-



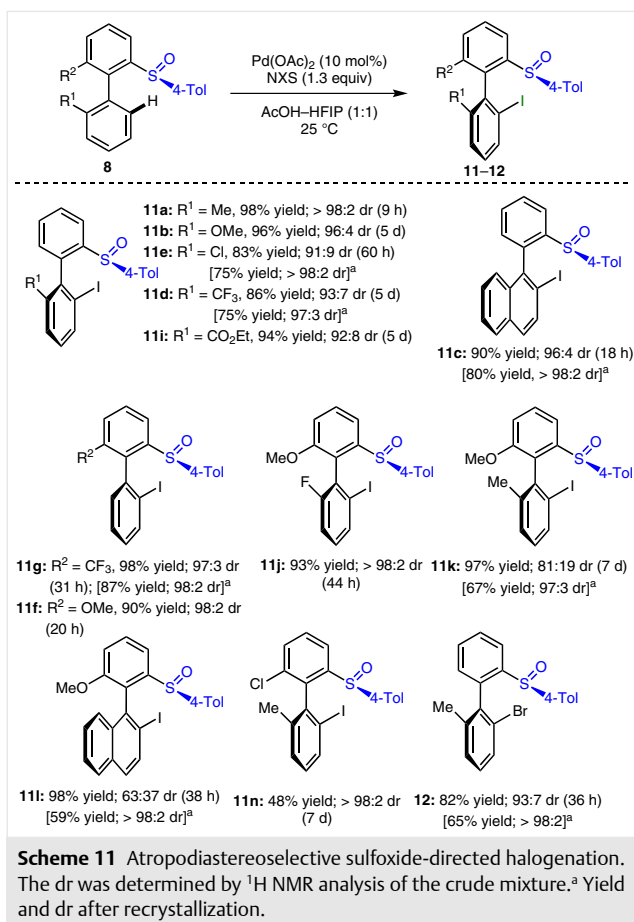
Scheme 9 Dynamic kinetic asymmetric transformation/dynamic kinetic resolution mechanism of the sulfoxide-directed atroposelective acetoxylation



moved in the presence of a lithium base to give an aryllithium intermediate that is configurationally stable at low temperature and can subsequently undergo electrophilic trapping without any loss of axial purity.

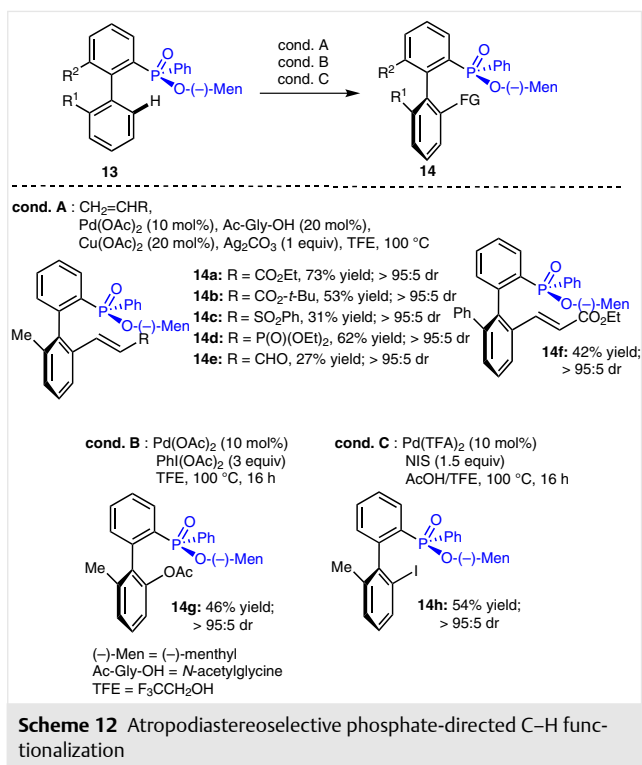
In 2015, Yang et al. reported a closely related diastereoselective C–H activation/dynamic kinetic resolution protocol for the synthesis of the axially chiral phosphates **14** (Scheme 12).²⁴ The researchers used a chiral menthyl-substituted P(O)R¹R²-DG to control the atroposelective outcome of the C–H activation event. (Notably, in the case of the olefination reaction, amino acid ligands were added to the reaction mixture). Accordingly, an oxidative Heck reaction, acetoxylation, and iodination of the biaryl precursors **13** were achieved with excellent stereoinduction. However, the efficiency of this transformation was rather moderate (yields 31–73%), and harsh reaction conditions (100 °C) were required. These results suggest that epimerization of the starting material and/or palladacyclic intermediates is less efficient compared with the related sulfoxide-directed protocol.

Concurrently with our work on atropodiastereoselective C–H functionalization, You described a related enantioselective transformation.²⁵ In this protocol, 1-(1-naphthyl)benzo[*h*]isoquinoline (**15**) was used as a biaryl substrate, and asymmetric oxidative olefination was achieved by using a chiral (η^5 -cyclopentadienyl)rhodium-derived catalyst (Scheme 13). Although the axially chiral compound **16** was delivered with good enantioselectivity (up to 86%) by using only a catalytic amount of the chiral inductor, this transfor-



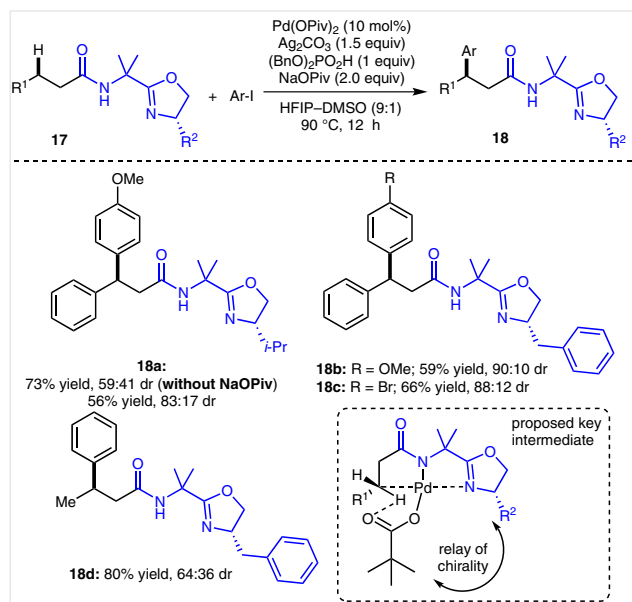
mation is limited to rather specific isoquinoline derivatives; consequently, it cannot be used as a general strategy to build up highly substituted atropo-pure skeletons.

Asymmetric transformations involving activation of C(sp²)–H bonds are relatively rare, as only specific skeletons containing either axial or planar chirality can be targeted. In contrast, the stereoselective functionalization of C(sp³)–H bonds is clearly more appealing, as an almost unlimited panel of stereogenic carbon moieties can be prepared in this manner from simple, nonfunctionalized substrates. However, the activation of aliphatic C–H bonds is generally much more challenging. A major advance in C(sp³)–H activation was achieved when Daugulis and co-workers discovered that bidentate DGs are particularly suitable for enhancing the direct insertion of a metal catalyst into such latent bonds.²⁶ Inspired by this seminal work, several research groups have devised catalytic systems that benefit from bicoordinating N,N- and N,S-DGs to permit activation of both primary and secondary C(sp³)–H bonds.²⁷ Surprisingly, no design of stereogenic bidentate DGs was reported until 2015. The first example of a diastereoselective C(sp³)–H activation by such an approach was reported by Shi and co-workers,²⁸ who speculated that the oxazoline group

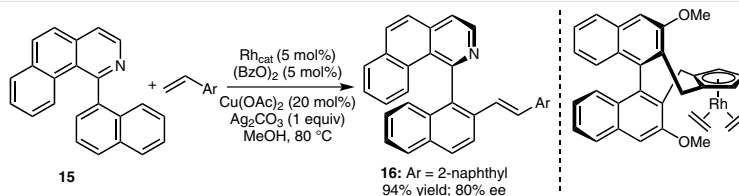


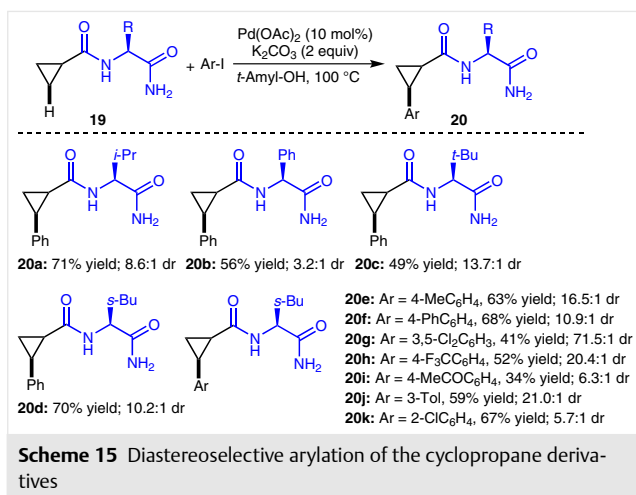
might be applied as a surrogate for the pyridine or quinoline moieties generally used as key coordinating functionalities of bidentate DGs. The choice of an oxazoline core presents some additional advantages, such as the opportunity to include chiral elements in the DG, straightforward synthesis of the DG from the corresponding amino alcohols, and possible cleavage of the DG after the C–H activation event. Initial efforts provided evidence that the α -amino-oxazoline moiety can indeed be used as a potent DG for palladium-catalyzed arylations of aliphatic substrates. Subsequently, an asymmetric version of this transformation was studied by using enantiopure oxazolines as a source of chirality (Scheme 14). Disappointingly, under the previously optimized reaction conditions, mediocre diastereoselectivity was observed when the isopropyl-substituted oxazoline **17a** was used as a chiral auxiliary (59:41 dr). This inefficient chirality transfer was attributed to the large distance between the stereogenic element and the reactive site. Elegant chirality enhancement was achieved in the presence of a sterically demanding sodium pivalate additive. It is be-

lieved that the pivalate anion participates in C–H activation event through a concerted metalation-deprotonation pathway, and subsequently influences the chirality of the oxazoline ring, thereby forming a chirality relay. Under such modified reaction conditions, arylation occurred with significantly better diastereoselectivity (83:17 dr). Further improvement was achieved by installing a benzylic substituent on the oxazoline ring **17b**, thereby affording the functionalized product **18b** in 90:10 dr and 59% yield. Unfortunately, such encouraging chirality transfer could only be observed when C–H activation occurred at a benzylic position.



Only few weeks later, Hong and co-workers reported another example of a stereogenic bidentate DG, in which they astutely employed an amino acid motif as a remote coordination site (Scheme 15).²⁹ Currently, monoprotected amino acids are arguably the most potent and general chiral ligands for use in the context of the Pd-catalyzed asymmetric C–H activation.^{1c} The initially designed valine-derived DG embedded in the cyclopropane substrate turned out to be an inefficient promoter of the palladium-catalyzed arylation. Intriguingly, the introduction of the aminomethyl motif on the valine core enhanced the desired transformation, and the arylated product was isolated in moderate 26%



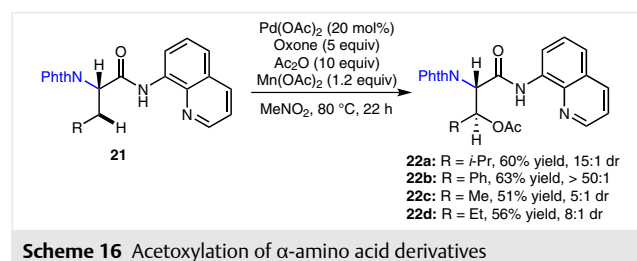


yield, but with encouraging diastereoselectivity (8.5:1 dr). Further investigations revealed that an NH₂-terminal motif on the DG was crucial to ensure acceptable reactivity and that the increased steric bulk enhanced the selectivity of the overall transformation. Under the optimized reaction conditions, diastereoselective arylation of the cyclopropane derivatives **19** occurred smoothly at 100 °C with a range of both electron-rich and electron-deficient aromatics, yielding the desired products **20** in 28–78% yield and a diastereomeric ratio of 5.7:1 to 71.5:1. It is noteworthy that the chiral induction during this transformation is rate dependent and is generally improved when higher conversions are achieved. Indeed, a second arylation of the functionalized products follows the kinetic resolution scenario; and the second arylation of the minor isomer of the monoarylated product is favored. As far as the mechanism is concerned, this arylation is believed to occur through an initial DG-assisted palladation to give two diastereomeric metallacyclic intermediates in equilibrium; this is followed by an oxidative addition of aryl iodides to generate palladium(IV) species, and a final reductive elimination. Because C–H cleavage of the two diastereotopic protons of the cyclopropane core appears to be relatively fast, the oxidative addition is assumed to be the stereoselective step.

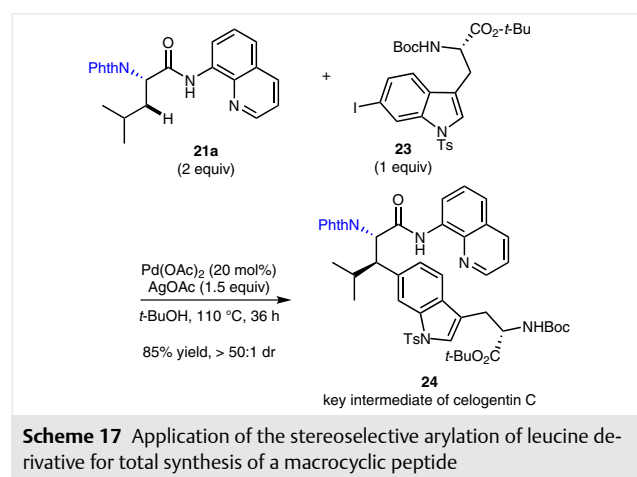
3 Substrate-Controlled Diastereoselective C–H Activation

A complementary approach to diastereoselective C–H activation involves the use of chiral pool-derived starting materials bearing nonstereogenic DGs. In this context, direct functionalization of α -amino acids is particularly appealing, as it paves the way to synthesis of structurally diverse nonnatural amino acids that might be difficult to prepare by other synthetic routes. A pioneering effort in this field was reported in 2006 by Corey and co-workers,³⁰ who

installed a bicoordinating DG on the carboxylate function of leucine and protected the amino moiety with a phthaloyl group (Scheme 16). The initial studies revealed that 8-aminoquinoline was the most potent DG and that under the optimized reaction conditions, β -acetoxylation of **21** occurred smoothly at 80 °C, delivering the desired compound in 60% yield and with excellent *trans*-stereoselectivity (20:1). It is noteworthy that chiral induction is believed to result from the preferential formation of a *trans*-palladacycle as a key intermediate. Accordingly, the diastereoselectivity of this transformation is strongly influenced by steric hindrance at the α -position. In addition, related *N*²-phthaloyl-*N*¹-quinolin-8-ylleucinamides (**21**) can also be used as substrates for this direct arylation, thereby providing a series of β -arylated leucine skeletons.

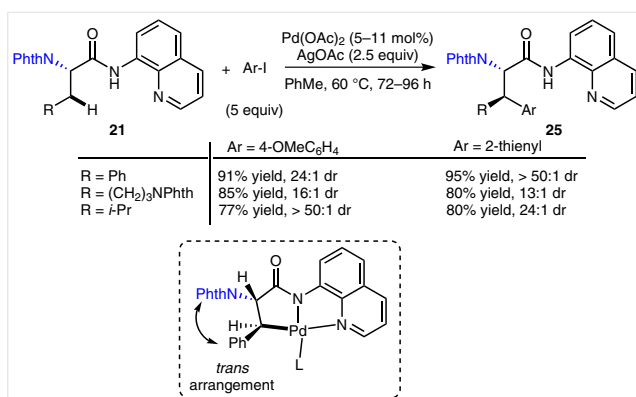


In 2010, this seminal work inspired Chen to utilize a similar stereoselective direct arylation as a key step in a total synthesis of celogentin C.³¹ They hypothesized that the strategy developed by Corey might provide a suitable approach for constructing a Leu–Trp linkage. In an attempt to reach this goal, they initially studied the stereoselective C–H coupling of *N*²-phthaloyl-*N*¹-quinolin-8-ylleucinamide (**21a**) and 6-iodo-1-tosyl-1*H*-indole, which gave the desired product in 80% yield when palladium(II) acetate was used as a catalyst with silver acetate as an additive in *tert*-butyl alcohol at 110 °C. Importantly, the functionalized iodotryptophan **23** is also a potent coupling partner in this reaction, allowing generation of the key intermediate **24** as sole di-



astereomer in an excellent 85% yield on a four-gram scale, unlocking the door to an original synthesis of the targeted macrocyclic peptide (Scheme 17).

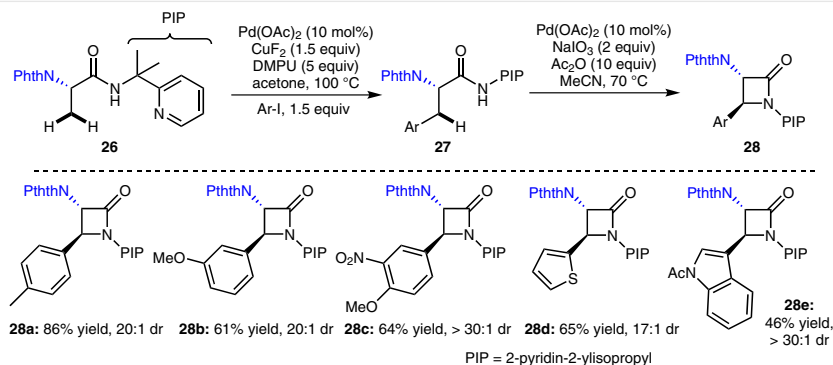
Since these initial reports, the scientific community has focused significant efforts on developing other diastereoselective functionalizations of α -amino acids. A general arylation protocol was reported by Tran and Daugulis in 2012.³² An 8-aminoquinoline DG and a phthalimide protecting group on the amino moiety were once again selected as the favored activating moieties for the aliphatic substrates (Scheme 18). When an aryl iodide was used as the coupling partner in combination with palladium(II) acetate as catalyst, silver acetate as base, and toluene as solvent, the desired asymmetric functionalization took place at 60 °C, permitting isolation of the corresponding nonnatural amino acids **25** in excellent yields (77–95%) and good diastereoselectivities (13:1 to >50:1). As previously, *anti*-diastereomers were generated. Deuteration experiments suggested that the key palladacyclic intermediate has a *trans*-arrangement of the phthaloyl moiety and the R group of the amino acid precursor; consequently, C–H activation is the stereo-determining step.



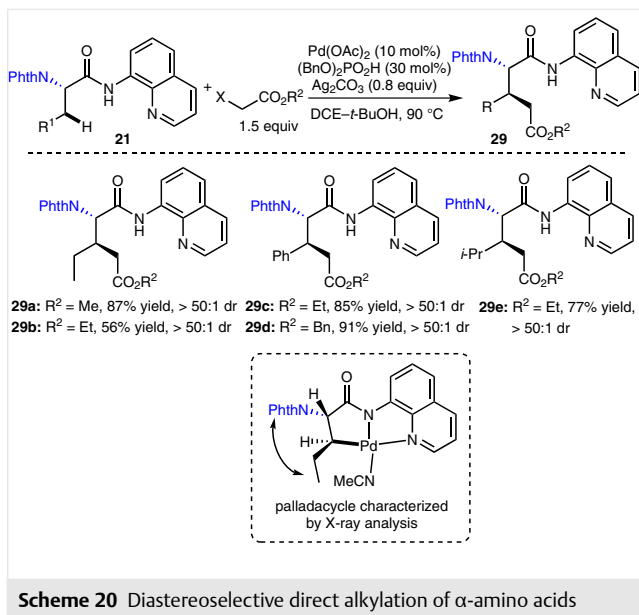
Scheme 18 Stereoselective arylation of α -amino acids

An interesting synthetic application of this stereoselective C(sp³)-H functionalization in preparing α -amino- β -lactams was reported by Shi and co-workers.³³ They hypothesized that by using the alanine derivative **26** as a starting material, β -arylation of the methyl group and subsequent intramolecular C–N coupling should deliver the common α -amino- β -lactam structural motifs. However, the development of this two-step reaction presents two major difficulties. First, in the initial C(sp³)-H arylation step, selective monofunctionalization rather than diarylation is required. Secondly, the catalytic system needs to be sufficiently reactive to enhance palladation of the methylene C(sp³)-H bond and the subsequent intramolecular amidation. The choice of the DG installed on the alanine precursor was therefore crucial, and a 2-pyridin-2-ylisopropyl (PIP) moiety turned out to be the optimal choice (Scheme 19). Rewardingly, arylation of **26** occurred in good yields and excellent monoselectivity. Furthermore, when the newly generated chiral substrates reacted with the palladium(II) acetate catalyst, a stereodiscriminating palladation of the benzylic methylene C(sp³)-H bond occurred. The final C–N coupling was promoted by a carefully selected oxidant (a mixture of sodium periodate and acetic anhydride) that facilitated palladium(II)/palladium(IV) oxidation, thereby expediting stereoretentive reductive elimination. Under optimized conditions, this sequential methyl arylation/diastereoselective CH₂ amidation permitted a straightforward and highly efficient synthesis of a large panel of α -amino β -lactams **28** from a simple chiral pool.

In attempts to expand the synthetic utility of this direct and diastereoselective functionalization of amino acid scaffolds, several research groups endeavored to design a catalytic system that would permit related C(sp³)-C(sp³) couplings. The challenging character of the stereoselective alkylation reactions stems from the difficulty in performing oxidative addition of alkyl halides, which are rather electron rich, and the sluggish alkyl-alkyl reductive elimination, which can be outcompeted by undesired side-reactions. The research groups of Shi³⁴ and Chen³⁵ simultane-



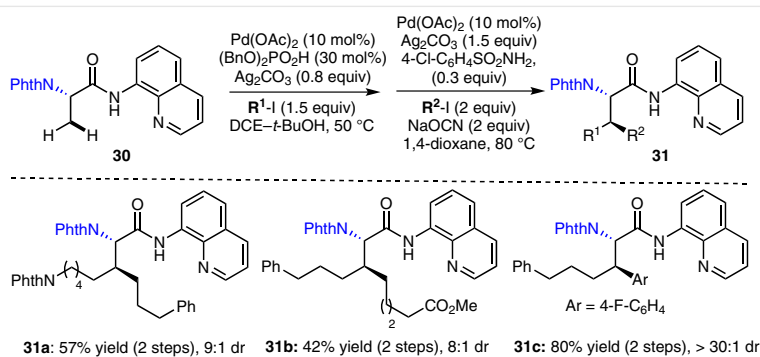
Scheme 19 α -Amino- β -lactam synthesis by a sequential arylation/stereoselective intramolecular amidation



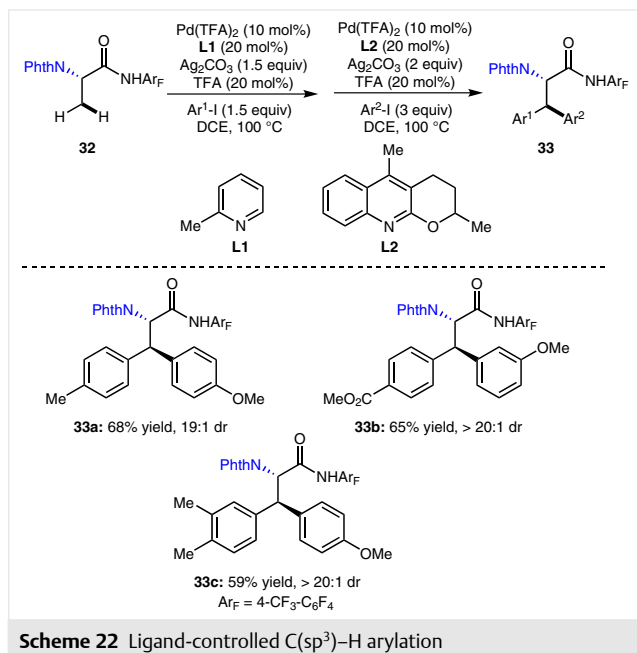
ously and independently discovered that the key to success in this ambitious transformation involved the use of a dibenzyl hydrogen phosphate ligand. Dibenzyl hydrogen phosphate is believed to enhance the solubility of the silver carbonate base, thereby increasing concentration of silver cations in the medium. In addition, dibenzyl hydrogen phosphate also facilitated both oxidative addition and reductive elimination events (by coordination to the palladium species), as well as subsequent protonolysis (release of the alkylated product), thereby ensuring optimal turnover of the catalytic system. Accordingly, stereoselective alkylation of the secondary $C(sp^3)$ -H bonds at β - or γ -positions with activated alkyl halides (iodo- or bromoacetate esters) delivered the aliphatic nonnatural α -amino acids with excellent control of the *trans*-configuration (Scheme 20). It is noteworthy that the key *trans*-palladacyclic intermediate has been isolated and characterized by X-ray analysis, corroborating the stereodiscriminant nature of the C-H activation step.³²

A further major advance in such diastereoselective alkylation was disclosed by Chen and Shi in 2014.³⁶ An intensive optimization study revealed that nonactivated alkyl halides could also be efficiently coupled with the amino acid derivatives when a sulfonamide ligand (4-chlorobenzenesulfonamide) and sodium cyanate base were added to the reaction mixture. The particular efficiency of this sulfonamide ligand can be attributed to its labile character. This permits its decoordination from the key palladacycle to provide a vacant coordination site (essential for oxidative addition of the alkyl iodide to generate a palladium(IV) species) and its subsequent recoordination with the palladium(IV) species to facilitate C(alkyl)-C(alkyl) reductive elimination. This optimized protocol is highly tolerant to a broad range of simple alkyl iodides, permitting expedient synthesis of β,β -heterodialkyl- and β -alkyl- β -aryl- α -amino acids by sequential methyl $C(sp^3)$ -H and stereoselective methylene $C(sp^3)$ -H functionalizations (Scheme 21).

A complementary approach to diastereoselective functionalization of α -amino acid scaffolds was reported by Yu and co-workers.³⁷ They surmised that a monoprotected DG installed on an aliphatic scaffold might efficiently promote a C-H activation event if an additional ligand was present in the reaction mixture. Notably, such ligand-controlled functionalizations might permit sequential one-pot difunctionalizations of alanine scaffolds. The polyfluorinated aromatic secondary amide **32** was selected as a weakly coordinating, powerful and general DG. An initial study identified 2-picoline as the best ligand for the arylation of primary $C(sp^3)$ -H bonds, and under such conditions various beta-arylamino acids could be prepared in high yields. Further investigations revealed that for activation of the secondary $C(sp^3)$ -H bonds, 2-substituted quinoline ligands stood out as promising promoters, and the most efficient catalytic system was obtained by using tricyclic 2,5-dimethyl-3,4-dihydro-2H-pyrano[2,3-*b*]quinoline (Scheme 22). Under the optimized reaction conditions, the required methylene C-H activation proceeded smoothly and with total stereoselectivity. Both electron-rich and electron-deficient aromatic iodides could be used as coupling partners. Finally, the feasibility of the targeted ligand-controlled $C(sp^3)$ -H arylation was demon-

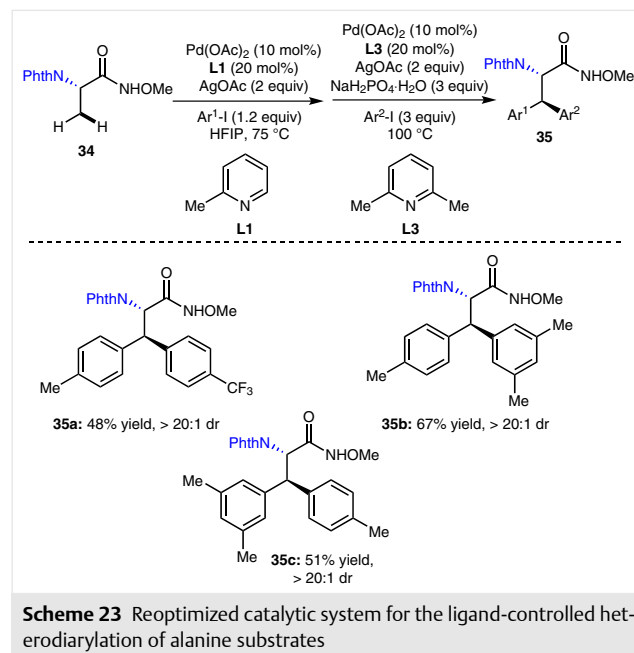


strated by performing sequential one-pot arylations. It is noteworthy that the configuration of the newly generated stereogenic center can be altered simply by switching the order of the two arylation events. In addition, in-depth theoretical studies were undertaken to elucidate the mechanism of this transformation and to determine the key factors that govern the stereoselectivity of the overall transformation.³⁸



One year later, the same research group reported an improved catalytic system.³⁹ Although the previously used polyfluorinated secondary amide DG is very efficient for various C-H activation reactions, its simpler congener, the *N*-methoxyamide (CONHOMe) motif, has appealing advantages in terms of its installation and removal. Moreover, it appears to be more appropriate for large-scale applications. Consequently, Yu and co-workers reinvestigated both primary and secondary arylations of the amino acid scaffolds by using the new *N*-methoxyamide as a simplified DG. The desired reactivity was achieved by using the same 2-picoline ligand, but with modifications to the reaction medium. 1,1,1,3,3,3-Hexafluoropropan-2-ol proved to be the solvent of choice, as it prevented decomposition of the starting material. Importantly, the scope of this arylation reaction could be enlarged to include the use of heteroaromatic iodides as coupling partners. With respect to the second arylation of the methylene moiety, an extensive optimization study identified 2,6-lutidine as the optimal ligand and showed that addition of sodium dihydrogen phosphate monohydrate was crucial to achieving maximal reactivity. Consequently, one-pot heterodiarlylation of the alanine derivative **34** gave structurally diverse diastereomerically pure β,β -heterodialkyl amino acids **35** in synthetically use-

ful yields (Scheme 23). The synthetic potential of this protocol was illustrated by applying this sequential asymmetric C(sp³)-H functionalization to construct BOX and PyBOX ligands.



Recently, the ligand-promoted *N*-(trifluorophenyl)amide-directed C(sp³)-H activation of α -amino acids was also applied to prepare nonnatural fluorinated scaffolds.⁴⁰ Selectfluor was selected as the fluorine source. The addition of an *N*-heterocyclic ligand was essential to promote this transformation, and an optimization study revealed that 5,7-dimethylquinoline clearly outperformed other pyridine- and quinoline-derived additives. Consequently, the targeted C-F coupling could be performed efficiently and in a totally diastereocontrolled manner. Importantly, a related asymmetric fluorination using Selectfluor as fluorine source was also achieved by using a bicoordinating 2-(pyridin-2-yl)isopropyl-derived DG.⁴¹

4 Conclusions

Despite significant advances achieved over the last 5 years, a chirality transfer in the C-H activation field still remains a great scientific challenge. Apart from enantioselective transformations involving the use of finely adjusted enantiopure ligands, a complementary approach based on diastereoselective transformations has gathered the interest of the scientific community. Indeed, as the chiral source is directly embedded within a substrate, a highly efficient control of the chiral environment of a metallacyclic intermediate may be reasonably expected. However, to be synthetically useful, the use of an inexpensive chiral auxiliary

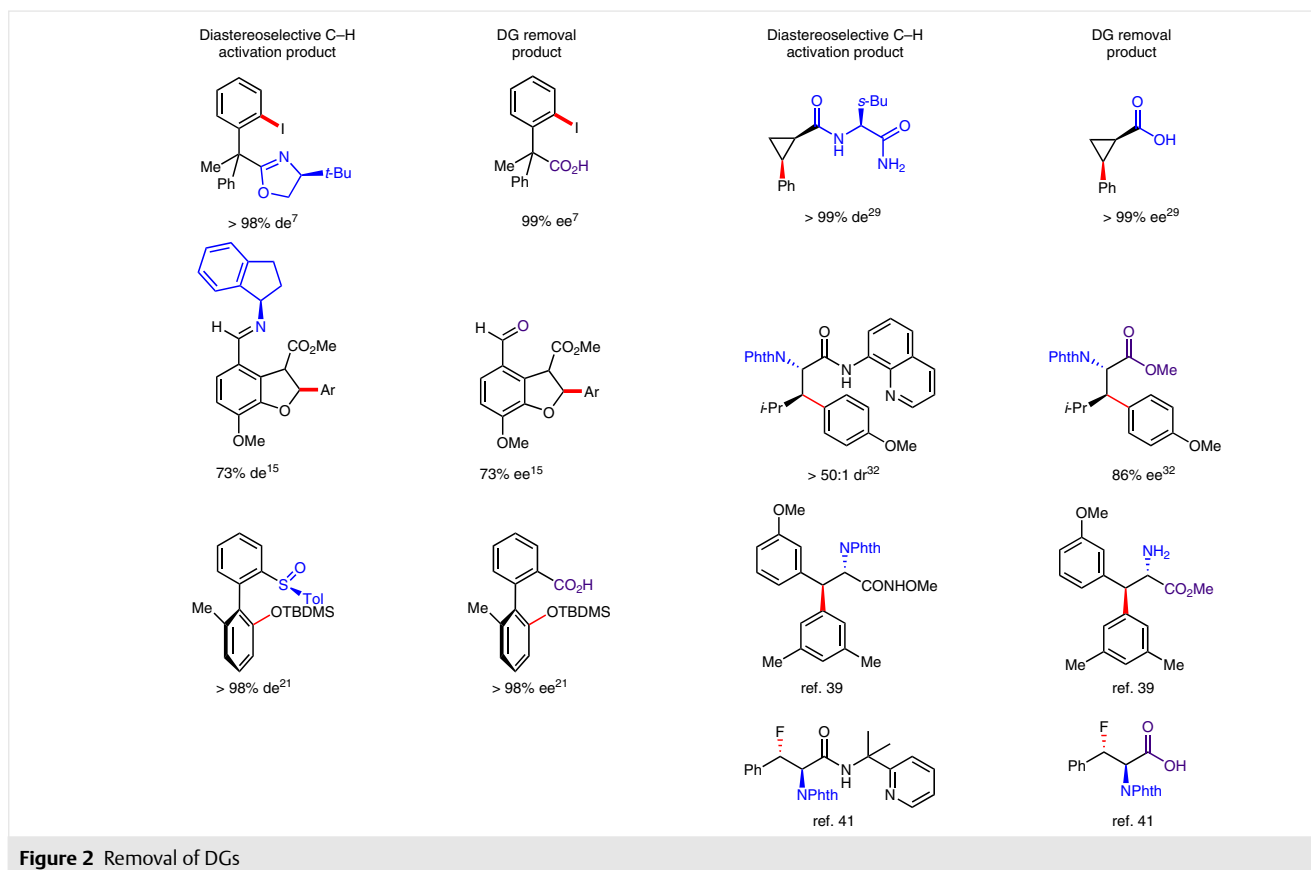


Figure 2 Removal of DGs

that is easy to install and remove after the functionalization event is crucial. Accordingly, in a majority of the herein discussed examples an efficient removal of a DG could indeed be achieved without loss of the optical purity (Figure 2). As an illustration, Yu's oxazoline DG can be hydrolyzed to give the corresponding carboxylic acid, the imine chiral DG* can be converted into the corresponding aldehyde. The sulfoxide is a truly traceless DG as it can be removed via lithium exchange followed by an electrophilic trapping thus enabling synthesis of the optically pure axially chiral compounds. Also any epimerization is observed when the bicoordinating, amide-based DGs* are cleaved. In addition, DG installed on amino acid scaffolds can also be hydrolyzed to give the corresponding carboxylic acid derivatives.

Besides, the C–H activation established itself as a reliable tool to build up chiral, unnatural α -amino acids. Presence of a stereogenic element on such scaffolds accounts for the stereocontrolled metallation event allowing formation of the sterically less hindered trans-palladacyclic intermediate and subsequent stereoretentive functionalization.

Accordingly, the diastereoselective C–H activation can be reasonably considered as a complementary strategy to the enantioselective transformations and in the near future

significant advances in this field may be expected. In particular design of original stereogenic DG could catch the increasing attention of the scientific community.

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