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.

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 catalytic 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 stereoinduction. 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. 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

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**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 studies with Professor F. Glorius at the Westfälische Wilhelms-Universität Münster (Germany) and a position as a temporary assistant professor (ATER) at the University of Strasbourg (Professor P. Compain), in 2013 she joined CNRS as an associate researcher in the group of Professor F. Colobert (University of Strasbourg, France). Her research focuses on transition-metal-catalyzed asymmetric C–H activation.

**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 chemistry department of the Chemistry Engineering High School of the University of Strasbourg. Her current research concerns asymmetric C–H functionalization and the synthesis of biologically active molecules.
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 iodoamination of an aliphatic pivalic acid substrate to give a monoiiodinated 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 (diazetoxoyiodo)benzenediiodine 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.8 When small substituents were introduced at the 4-position of oxazoline 1a, direct iodoamination was sluggish and no stereoinduction 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 arylation with iodoarenes.\textsuperscript{11} An intramolecular palladium(0)-catalyzed enantioselective direct functionalization of cyclopropane skeletons has been investigated by Cramer and co-workers.\textsuperscript{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).\textsuperscript{13} When the prochiral substrate \(1h\), bearing tert-butyl groups on the oxazoline DG and in the \(\alpha\)-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 \textit{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).\textsuperscript{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 acetoxylated 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).\textsuperscript{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 benzylc 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-
Ar/imentary strategy to achieve regio- and stereoselective C–H activation for several years. In 2012, Ferreira proposed a complementary platform (Scheme 5). The acetalization reaction delivered aminal products containing a pyridine DG. Such finely designed substrates were tested in a direct acetoxylation reaction in which a DG is directly embedded within the substrate, permitting direct olefination of the sulfoxides (Scheme 6). 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. 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. 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 transmetallation 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. We were soon able to devise a catalytic system that permitted direct olefination of the sulfoxides (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 (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, 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). 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. Surprisingly, 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 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 were isolated in 75–95% yield and 91:9 to >98:2 diastereoselectivity. The atroposelective acetoxylation of these substrates is even beneficial. Under the optimized reaction conditions, a large panel of variously substituted biaryl sulfoxides were fully used in this coupling reaction; the acetoxylation of 75–95% yield and 91:9 to >98:2 diastereoselectivity. The disfavored palladacycle undergoes atroposelective acetoxylation with 10 mol% Pd(OAc)2, (NH4)2S2O8 (2 equiv) H2O, (2 equiv) AcOH–HFIP (1:1) 25 °C.

The dr was determined by 1H NMR analysis of the crude mixture. Yield and dr after recrystallization.

Scheme 6 Atropodiastereoselective sulfoxide-directed oxidative Heck reaction

Scheme 7 Atropodiastereoselective sulfoxide-directed acetoxylation. The dr was determined by 1H NMR analysis of the crude mixture. Yield and dr after recrystallization.

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Alternatively, if the substituents around the biaryl axis are less sterically demanding (small \( R_1 \) and \( R_2 = \text{H} \), 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 \( 8n \) (\( R^2 = \text{Cl} \)], the acetoxylated 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 \( \text{N}-\text{iodosuccinimide} \) permitted extremely mild and selective iodonation 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 acetoxylated product. The sulfoxide auxiliary could be straightforwardly re-
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 (Scheme 12). The researchers used a chiral menthyl-substituted P(O)R1R2-DG to control the atroposelective outcome. (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 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 impossible epimerization of Int-8m-B or increased steric congestion; distavlor palladation of 8m-B or impossible epimerization of Int-8m-B.

Concurrently with our work on atropodiastereoselective C–H functionalization, You described a related enantioselective transformation. In this protocol, 1-(1-naphthyl)benzol[8]isoquinoline (15) was used as a biaryl substrate, and asymmetric oxidative olefination was achieved by using a chiral (η5-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 transformation 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(sp3)–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. 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. 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, who speculated that the oxazoline group

![Scheme 10 Kinetic resolution mechanism of the sulfoxide-directed atroposelective acetoxylation](image-url)

![Scheme 11 Atropodiastereoselective sulfoxide-directed halogenation](image-url)
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 alylations 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 believed that the pivalate anion participates in C–H activation event through a concerted metalation-deprotonation pathway, and consequently 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 coordinating functional group. 

**Scheme 12** Atropodiastereoselective phosphate-directed C–H functionalization

<table>
<thead>
<tr>
<th>Condition</th>
<th>Reaction Products</th>
<th>Yield</th>
<th>Diastereomeric Ratio</th>
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**Scheme 13** Atropo-enantiostereoselective C–H activation

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rect functionalization of materials bearing nonstereogenic DGs. In this context, di-
activation involves the use of chiral pool-derived starting

Further investigations revealed that an NH2-terminal motif
yield, but with encouraging diastereoselectivity (8.5:1 dr).
that the increased steric bulk enhanced the selectivity of
the overall transformation. Under the optimized reaction
conditions, diastereoselective arylation of the cyclopropane
derivatives occurred smoothly at 100 °C with a range of
both electron-rich and electron-deficient aromatics, yielding
the desired products in 28–78% yield and a diaste-
reomeric ratio of 5.7:1 to 71.5:1. It is noteworthy that the
chiral induction during this transformation is rate depen-
dent and is generally improved when higher conversions
are achieved. Indeed, a second arylation of the functional-
ized products follows the kinetic resolution scenario; and
the second arylation of the minor isomer of the monoary-
lated product is favored. As far as the mechanism is con-
cerned, this arylation is believed to occur through an initial
DG-assisted palladation to give two diastereomeric metalla-
cyclic 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 cyclopro-
pane core appears to be relatively fast, the oxidative addi-
tion 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, di-
rect functionalization of α-amino acids is particularly ap-
pealing, as it paves the way to synthesis of structurally di-
verse nonnatural amino acids that might be difficult to pre-
pare by other synthetic routes. A pioneering effort in
this field was reported in 2006 by Corey and co-workers, 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-ami-
noquinoline was the most potent DG and that under the
optimized reaction conditions, β-acetoxylation of 21 oc-
curred 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-palladacy-
cle as a key intermediate. Accordingly, the diastereoselec-
tivity of this transformation is strongly influenced by steric
hindrance at the α-position. In addition, related N2-phtha-
loyl-N1-quinolin-8-ylleucinamides (21) can also be used as
substrates for this direct arylation, thereby providing a se-
ries 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 to-
tal synthesis of celogentin C.31 They hypothesized that the
strategy developed by Corey might provide a suitable ap-
proach for constructing a Leu–Trp linkage. In an attempt to
reach this goal, they initially studied the stereoselective
C–H coupling of N2-phthaloyl-N1-quinolin-8-ylleucinamide
(21a) and 6-iodo-1-tosyl-1H-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 ido-
tryptophan 23 is also a potent coupling partner in this reaction,
allowing generation of the key intermediate 24 as sole di-

**Scheme 15 Diastereoselective arylation of the cyclopropane deri-
vatives**

**Scheme 16 Acetoxylation of α-amino acid derivatives**

**Scheme 17 Application of the stereoselective arylation of leucine de-
rivative for total synthesis of a macrocyclic peptide**
astereomer an in 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. Deuterium 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 stereodetermining step.

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 derivates 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 condition, 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 simulat-
A further major advance in such diastereoselective alkylation was disclosed by Chen and Shi in 2014. An intensive optimization study revealed that nonactivated alkyl halides could also be efficiently coupled with the amino acid derivatives when a sulfonamide ligand (4-chlorobenzenesulfonylamide) 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(sp³)–H and stereoselective methylene C(sp³)–H functionalizations (Scheme 21).

A complementary approach to diastereoselective functionalization of α-amino acid scaffolds was reported by Yu and co-workers. 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(sp³)–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(sp³)–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-pyran[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(sp³)–H arylation was demon-

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**Scheme 20** Diastereoselective direct alkylation of α-amino acids

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**Scheme 21** Sequential C(sp³)–H functionalizations of α-amino acids
Ar2
CF3
OMe
O
Ar2
Consequently, one-pot heterodiarylation of the alanine de-
monohydrate was crucial to achieving maximal reactivity.
showed that addition of sodium dihydrogen phosphate
study identified 2,6-lutidine as the optimal ligand and
lation of the methylene moiety, an extensive optimization
dides as coupling partners. With respect to the second ary-
could be enlarged to include the use of heteroaromatic io-
various C–H activation reactions, its simpler congener, the
proved catalytic system. 39 Although the previously used
mediator may be reasonably expected. However, to be syn-
control of the chiral environment of a metallacyclic inter-
mains a great scientific challenge. Apart from enantioselec-
tive transformations involving the use of finely adjusted
years, a chirality transfer in the C–H activation field still re-
iments a great scientific challenge. Apart from enantioselec-
tive transformations involving the use of finely adjusted

One year later, the same research group reported an im-
proved 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 advan-
tages 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 pri-
mary 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-pico-
line ligand, but with modifications to the reaction medium.

Recently, the ligand-promoted N-((trifluorophenyl)am-
ide-directed C(sp3)–H activation of α-amino acids was also
applied to prepare nonnatural fluorinated scaffolds.40 Se-
lectfluor 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 pyri-
dine- 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-(pyri-
din-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 re-
manns a great scientific challenge. Apart from enantioselec-
tive transformations involving the use of finely adjusted
enantiopure ligands, a complementary approach based on
diastereoselective transformations has gathered the inter-
est 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 inter-
mediate may be reasonably expected. However, to be syn-
thetically useful, the use of an inexpensive chiral auxiliary

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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 \( \alpha \)-amino acids. Presence of a stereogenic element on such scaffolds accounts for the stereocontrolled metallaion 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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