Chemical Science

ARTICLE TYPE

Asymmetric C–H Functionalization of Cyclopropanes Using Isoleucine-NH₂ Bidentate Directing Group

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Systematic investigation of substrate-bound α-amino acid auxiliaries has resulted in catalytic asymmetric C–H functionalization of cyclopropanes enabled by amino acid amide as chiral bidentate directing groups. The use of an Ile-NH₂
10 auxiliary embedded in the substrate could provide excellent levels of asymmetric induction (diastereomeric ratio of up to 72:1) in the Pd(II)-catalyzed β-methylene C(sp³)–H bond activation of cyclopropanes and cross-coupling with aryl iodides.

Introduction

15 Transition-metal-catalyzed direct and regioselective C–H bond activation/functionalization is a highly efficient and straightforward tool that is useful in the field of organic synthesis and total synthesis.[1] To achieve highly selective C–H activation, the directing group embedded in the substrate must coordinate to
20 a transition-metal center in a configuration that allows for the cleavage of a specific C–H bond, generally via the efficient formation of 5- or 6-membered metallacyclic intermediates.[2] Since the novel discovery by Daugulis' group, powerful bidentate directing groups, such as 8-aminoquinoline and picolinamide
25 auxiliaries have been widely used in the activation of both C(sp²)–H and C(sp³)–H bonds.[3] Bidentate directing groups have received considerable attention by granting favorable properties to the metalated complex, thus enabling new types of catalytic transformations that are known to be difficult with conventional
30 monodentate systems.[4] For improving convenience and efficiency, the development of new types of bidentate directing groups has been the subject of intensive research in many groups.[5] Recently, Chatani's group accomplished *ortho*-C(sp²)–H activation using α–amino ester moieties as bidentate directing groups.[6] Moreover,
35 Yu and coworkers demonstrated that the amino acid moiety of peptides can promote the functionalization of C(sp³)–H bonds in a number of peptides.[7]

Elegant examples of the diastereoselective functionalization of unactivated C(sp³)–H in chiral substrates were revealed by
40 Corey,[3b] Daugulis[3q] and Chen' groups.[3d,3m] Moreover, the remarkable achievements in catalytic asymmetric C–H activation have been demonstrated using chiral auxiliary[8] and chiral ligand.[9] We hypothesized that an appropriate chiral bidentate directing group embedded in the substrate could induce high levels of
45 stereocontrol during C–H functionalization via a steric repulsion model. As an outgrowth of these studies, we selected α–amino acid moieties as chiral bidentate directing groups in the context of

the diastereotopic β-methylene C(sp³)–H bonds functionalization/arylation of cyclopropanes, enabling
50 stereoselective installation of an aryl group and construction of new stereogenic centers (Scheme 1). Cyclopropane is a privileged class of structures found in many biologically active molecules.[10] In this regards, transition-metal-catalyzed asymmetric C–H arylation of cyclopropanes has been the focus of great research
55 interest.[9,11] Moreover, functionalized cyclopropanes bearing amino acid moiety are widely used as a conformational restricting linker in medicinal chemistry.[10d,e] Herein, we report the first example of chiral bidentate auxiliary-controlled diastereoselective C(sp³)–H bond activation/cross-coupling of cyclopropanes. From
60 a conceptual viewpoint, the ability of a substrate-bound α-amino acid auxiliary to promote diastereoselective C–H functionalization is intriguing because the amino acid moiety derived from readily available chiral pools plays not only the role as a bidentate directing group, but also as a chiral auxiliary to
65 provide efficient stereocontrol during C(sp³)–H bond functionalization. As a consequence, high levels of asymmetric induction could be expected in the C(sp³)–H functionalization of cyclopropanes controlled by a chiral bidentate directing group.
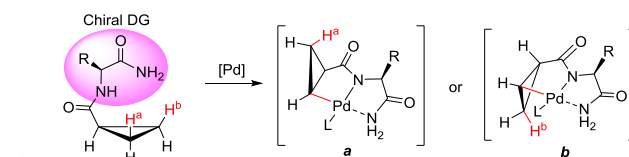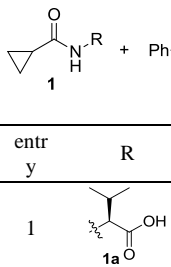

70 **Scheme 1** Amino acid auxiliary-controlled asymmetric C–H functionalization of cyclopropanes.
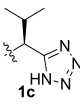
Results and discussion

To test these hypotheses, we began our studies by investigating
75 the direct β-methylene C(sp³)–H functionalization of a cyclopropane framework bearing a valine moiety as a potential directing group. Initially, we performed on a diastereoselective C–H arylation with iodobenzene using Pd(OAc)₂ (10 mol%) and K₂CO₃ as a base in *t*-Amyl-OH at 100 °C for 24 h (Table 1). Our
80 early investigations were discouraging because of the lack of reactivity of the L-valine directing group (**1a**) (entry 1). Subsequently, several other auxiliaries, such as ester (**1b**), tetrazole (**1c**), and amino acid amide groups (**1d**, **1e**, **1f**), were investigated for feasibility as directing groups on C(sp³)–H
85 arylation. Usage of ester or tetrazole moieties as directing groups

was unsuccessful on C–H activation/C–C bond formation (entries 2, 3). Intriguingly, the C(sp^3)–H bond activation of a substrate containing a Val–NHMe auxiliary (**1d**) occurred effectively to afford the desired cis-substituted phenylcyclopropane product with a 26% yield and high diastereoselectivity (entry 4, d.r = 8.1:1). This preliminary work prompted us to scrutinize additional types of amino acid amides as stereogenic directing groups. Further investigations revealed that having the Val–NH$_2$ group (**1f**) was crucial for obtaining higher reactivity and diastereoselectivity (entry 6, 60%, d.r = 8.5:1). The Val–NMe$_2$ group (**1e**) attached to the substrate led to a complete loss of reactivity (entry 5), indicating the favorable property of an NH$_2$ motif on coordination in the active complex. We therefore decided to employ Val–NH$_2$ (**1f**) as a directing group for further optimization; representative catalytic systems for the cross-coupling are listed in Table 1 (entries 6-11).[12] In general, an approximate 4.3:1 mixture of mono- and diarylated products were obtained with the substrate **1f** containing Val–NH$_2$ at 100 ℃. Attempts to improve the conversion in a higher temperature (120 ℃, entry 7) resulted in an increased proportion of the diarylated product (81%, *mono/di* = 2.5:1, d.r = 6.3:1) with mixtures of poly arylated by-products[13] (~10%). Several solvents were also evaluated and the use of *t*-Amyl-OH as the solvent was necessary to achieve a higher conversion. The use of AgOAc (entry 9) which was employed previously in arylation reactions,[10d-e] provided lower product yield (20%) along with recovery of the remaining starting material (58%). Alternative arylating coupling partners, such as diphenyliodonium salt[3o] failed to improve reaction efficiency (entry 10). With the use of 1.5 equiv of iodobenzene, the reaction could reach full conversion to provide mono- and diarylated products in yields of 71 and 16%, respectively with only negligible amount of the undesired by-products. Thus, the best results were obtained with a substrate (1 equiv) with iodobenzene (1.5 equiv), Pd(OAc)$_2$ (10 mol%), and K$_2$CO$_3$ (2 equiv) in *t*-Amyl-OH (0.5 M) at 100 ℃ to give the monoarylation product (71%) with high diastereoselectivity (d.r = 8.6:1) (entry 11). The structure of major diastereomer **2a** (Val–NH$_2$ derivative) was unambiguously verified by H NMR and X-ray crystallographic analyses (Figure 1).

Table 1 Screening of potential bidentate chiral auxiliary for C–H arylation with iodobenzene.[a]

entry	R	PhX (equiv)	Base (equiv)	Temp	Yield[b] (d.r)[c]
1	**1a**	PhI (3)	K$_2$CO$_3$ (2.5)	100	trace
2	**1b**	PhI (3)	K$_2$CO$_3$ (2.5)	100	NR
3	**1c**	PhI (3)	K$_2$CO$_3$ (2.5)	100	NR
4	**1d**	PhI (3)	K$_2$CO$_3$ (2.5)	100	26% (8.1:1)
5	**1e**	PhI (3)	K$_2$CO$_3$ (2.5)	100	NR
6		PhI (3)	K$_2$CO$_3$ (2.5)	100	60% (8.5:1)
7		PhI (3)	K$_2$CO$_3$ (2.5)	120	58% (6.3:1)
8	**1f**	PhI (3)	K$_2$CO$_3$ (2.5)	80	12%
9		PhI (4)	AgOAc (2.5)	100	20%
10		Ph$_2$IOTf (2)	K$_2$CO$_3$ (3)	100	33%
11[d]		PhI (1.5)	K$_2$CO$_3$ (2)	100	71% (8.6:1)

[a]Substrate (1.0 equiv), Pd(OAc)$_2$ (10 mol%), K$_2$CO$_3$ (2.5 equiv), ArX in *t*-Amyl-OH (0.5 M). [b]Isolated yields of monoarylation products. [c]The d.r was determined by HPLC analysis. [d]Mono- and diarylation products (4.5:1) were observed by NMR analysis.
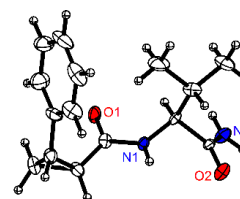

Figure 1 X-ray crystal structure for compound **2a** (Val–NH$_2$ derivative).

Having identified that the *N*-nonsubstituted –CONH$_2$ moiety was crucial for achieving both high reactivity and diastereoselectivity, we further explored the effect of steric bulk at the α-position of amino acid amides on the selectivity. For this purpose, substrates bearing a range of R substituents were examined and chiral auxiliaries featuring sterically bulky side chains appear to be essential for achieving high levels of stereoselectivity (Scheme 2). Importantly, the replacement of an isopropyl group (d.r = 8.6:1) at the α-position of the amino acid amide with sterically demanding isobutyl and *t*-butyl groups produced the corresponding products **3a** and **3b** with higher diastereoselectivity (d.r = 10.2:1 for **3a**, d.r = 13.7:1 for **3b**). Further studies revealed that the isobutyl and *t*-butyl groups present on the substrates gave superior results to those with benzyloxy ethyl (**3c**), phenyl (**3d**), cyclohexyl (**3e**), or benzyl (**3f**) groups. Of the various chiral auxiliaries that were tested, the Ile-NH$_2$ moiety (**3a**) was selected as a bidentate directing group considering both yield and diastereoselectivity. In order to gain insight of the influence of diarylation process on diastereoselectivity, a reaction profile was performed by monitoring the conversion to **3a** under standard conditions (See Table S4 in the Supporting Information for more details). The increase of d.r from 7.2:1 (after 1 h) to 10.2:1 (after 24 h) was observed, which suggests that favorable second arylation of the minor stereoisomer may contribute, in part, to the overall diastereoselectivity observed.
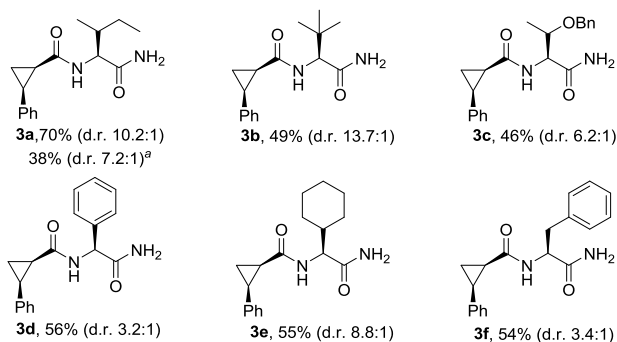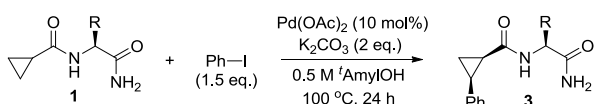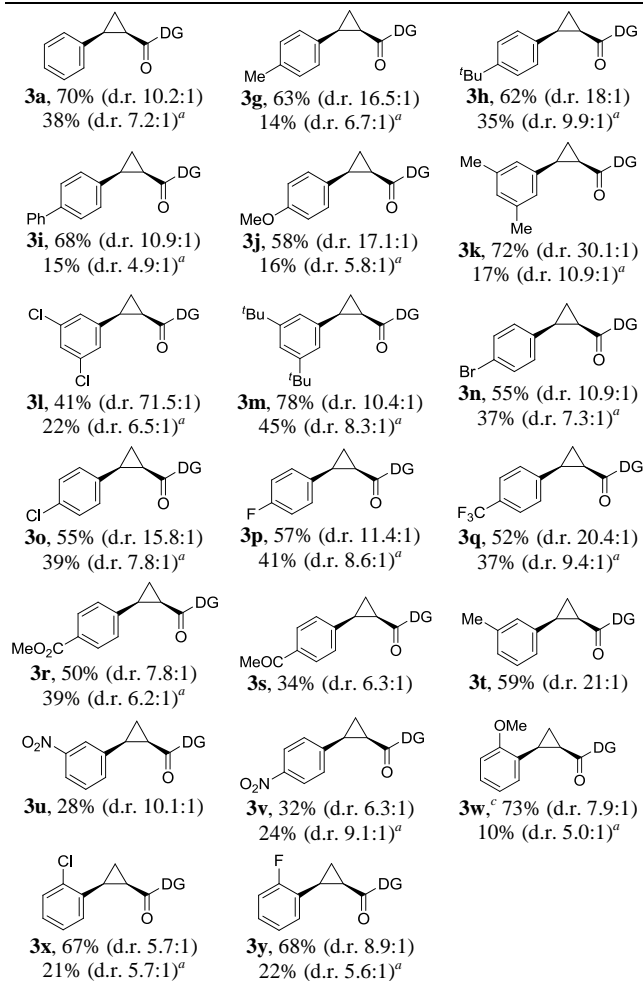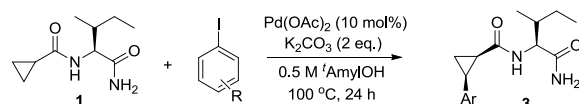
Scheme 2 Influence of side chain on C–H arylation. Substrate (1.0 equiv), Pd(OAc)$_2$ (10 mol%), K$_2$CO$_3$ (2.0 equiv), PhI (1.5 equiv) in t-Amyl-OH (0.5 M) at 100 °C for 24 h: isolated yields of monoarylation products after purification by silica gel chromatography. The d.r was determined by HPLC analysis. In general, mixtures of mono- and diarylation products (4.0–4.5:1) were observed by NMR analysis. ^{a}After 1 h: NMR yield of monoarylation products (See Table S4 in the Supporting Information for more details).

The directing group is removable and the hydrolysis of the amino acid amide group of **3a** occurred smoothly under the acidic conditions to afford arylated cyclopropanecarboxlic acid (81%) with conservation of the stereogenic centers (**eq 1**).[14,15]


(1)
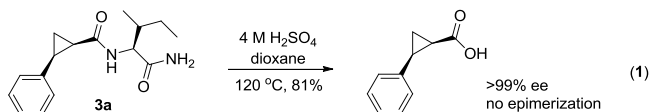
Having established that the Pd(II)-catalyzed highly diastereoselective C–H arylation of cyclopropanes was enabled by the Ile-NH$_2$ directing group, the scope of aryl iodides was studied with a range of functional groups such as phenyl, methoxy, ketone, ester, alkyl, halides, and trifluoromethyl that could be used as a useful synthetic handle for the further transformations. We were delighted to observe that substitution with both electron-donating- (Me–, ^{t}Bu–, and OMe–) and electron-withdrawing groups (F–, Cl–, Br–, CF$_3$–, CO$_2$Me–, and COMe–) on the aryl iodides were viable under the reaction conditions to afford the corresponding products with high levels of diastereoselectivity summarized in Scheme 3. In addition, the major isomer could be easily isolated by silica gel chromatography. Outstanding diastereoselectivities could be achieved in the reactions of 3,5-disubstituted iodobenzenes (d.r = 30.1:1 for **3k**, d.r = 71.5:1 for **3l**). The chemoselective coupling with bromo iodobenzene afforded the synthetically important **3n** for further synthetic elaboration. The position of substituents in iodobenzene did not show much change in the reactivity. Notably, aryl iodides with *ortho*-substituents, such as OMe, Cl, and F were also compatible with the reaction conditions to afford the corresponding products (**3w–y**) with good yields (67–73%). Expanding the scope to the nitro-substituted iodobenzenes was

also possible, but the products were obtained in only around 30% yields (**3u** and **3v**).

Scheme 3 Substrate scope. Substrate (1.0 equiv), Pd(OAc)$_2$ (10 mol%), K$_2$CO$_3$ (2.0-2.5 equiv), Ar-I (1.5-3.0 equiv) in t-Amyl-OH (0.5 M) at 100 °C for 24 h: isolated yields of monoarylation products. The d.r was determined by HPLC analysis. In general, mixtures of mono- and diarylation products (4.0–4.6:1) were observed by NMR analysis. ^{b}After 1 h: NMR yield of monoarylation products. ^{c}120 °C.

Although severe peak overlap occurs in the NMR spectra of two diastereotopic hydrogens, significant level of di-deuterated product (>40%) was observed when the reaction mixture was treated with D$_2$O under the optimized conditions and in the absence of aryl iodide (Scheme 4).[12] This controlled H/D exchange study implies a facile C–H activation process for both diastereotopic hydrogens of cyclopropanes.
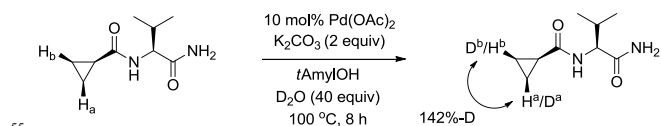
Scheme 4 H/D exchange studies.

We proposed one of the possible reaction mechanisms involving Ile-NH$_2$ auxiliary-controlled asymmetric C–H functionalization in which a Pd(II)/Pd(IV)[16] catalytic cycle is invoked (Scheme 5). The coordination of two nitrogen atoms to the Pd catalyst generates a palladium amide **I**. Subsequently, the cleavage of C(sp^3)–H bond on cyclopropane through concerted metalation deprotonation (CMD) process produces the palladacycle complex **II** and **III**, which may exist in equilibrium.[17] The diastereoselectivity of arylation could occur either at the C–H activation step or at the oxidative addition step. At this stage, the diastereoselectivity can be assumed to be established at the oxidative addition step under Curtin–Hammett control[18] because the C–H activation process of both diastereotopic hydrogens is relatively facile (Scheme 4). The oxidative addition of aryl iodide to **II** affords Pd(IV) intermediate **IV**,[19] which then undergoes reductive elimination followed by protonation leading to the formation of the arylated product. On the other hand, the oxidative addition process for insertion of aryl iodide into Pd complex **III** appears to be less feasible because the R substituent and the methylene group of cyclopropane cause blocking of the top and bottom faces.
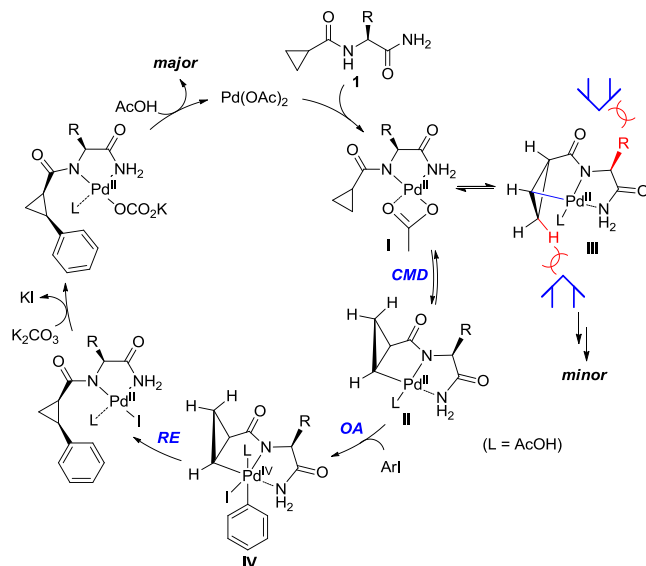
Scheme 5 Mechanistic considerations for Pd-catalyzed diastereoselective C–H activation of cyclopropanes.

Furthermore, we preliminarily investigated the diastereoselective C–H alkynylation and observed that **1f** reacted with bromoalkyne under the same reaction conditions,[20] resulting in the single diastereomer **4** in 53% yield along with 44% of unreacted starting material (Scheme 6).
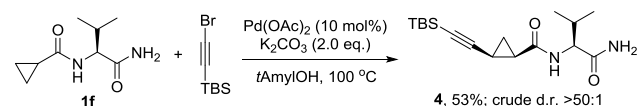
Scheme 6 C–H alkynylation.

Conclusions

In summary, we have developed Pd(II)-catalyzed highly diastereoselective β-methylene C(sp^3)–H bond activation/C–H arylation of cyclopropanes enabled by the Ile-NH$_2$ directing group. This study represents the first systematic investigation of substrate-bound α-amino acid amides as chiral bidentate directing groups in the asymmetric C(sp^3)–H functionalization of cyclopropanes. The present reactions demonstrated a broad range of substrate scope and permitted for selective installation of a variety of substituted on cyclopropanes. Further developments to extend this methodology to other substrates and detailed mechanistic studies are underway.

Acknowledgements

Notes and references

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† Electronic Supplementary Information (ESI) available: See DOI: 10.1039/b000000x/

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12. See the Supporting Information for more details.

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