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Pd(II)-Catalyzed Enantioselective C(sp³)–H Activation/Cross-Coupling Reactions of Free Carboxylic Acids

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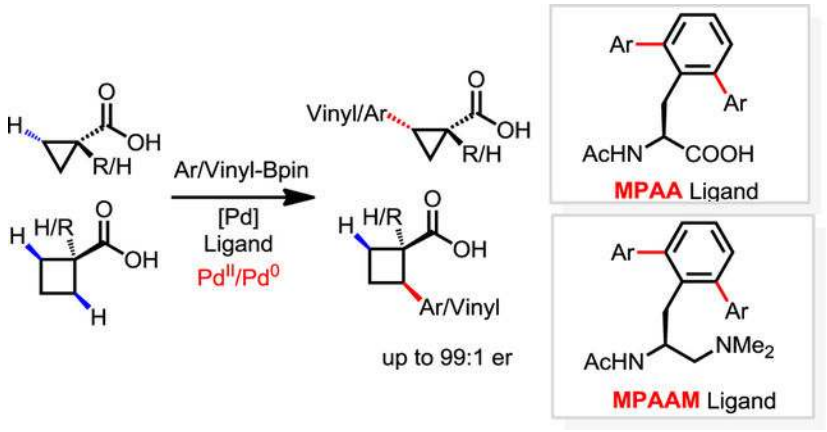
Abstract

Pd(II)-catalyzed enantioselective C(sp^3)–H cross-coupling of free carboxylic acids with organoborons has been realized using either mono-protected amino acid (MPAA) ligands or mono-protected aminoethyl amine (MPAAM) ligands. A diverse range of aryl- and vinyl-boron reagents can be used as coupling partners to provide chiral carboxylic acids. This reaction provides an alternative approach to the enantioselective synthesis of cyclopropanecarboxylic acids and cyclobutanecarboxylic acids containing α-chiral tertiary and quaternary stereocenters. The utility of this reaction was further demonstrated by converting the carboxylic acid into cyclopropyl amine without loss of optical activity.

Graphical Abstract



Keywords

arylation; vinylation; C–H activation; palladium

Enantioselective alkyl C(sp^3)–H bond activation is a longstanding goal in organic synthesis.[1] Recently, Pd-catalyzed asymmetric C–H activation reactions using chiral ligands have been

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Conflict of interest

The authors declare no conflict of interest.

demonstrated. The combination of monodentate coordinating substrates with chiral bidentate mono-N-protected amino acid ligand (MPAA) has led to the development of a wide range of Pd(II)-catalyzed enantioselective intermolecular C−H activation reactions.[2–5] Recently, chiral bidentate quinoline ligands and oxazoline ligands were developed to realize the enantioselective functionalization of methylene C−H bonds and methyl C−H bonds in carboxylic acid derivatives, respectively.[3c–3d] However, substrates in these reactions require preinstalled directing groups that need to be removed after C−H functionalization.[3] Therefore, the direct C−H functionalization of free carboxylic acids would afford superior atom and step economies in the context of protecting free synthesis.[6] To date, there exists a single example of enantioselective intermolecular C(sp^3)–H activation of carboxylic acids without using exogenous directing groups (Scheme 1).[7] Key to the development of this method was the design of a novel mono-protected aminoethyl amine (MPAAM) chiral ligand to match the weakly coordinating carboxylic acid for stereocontrol. However, only arylation via a Pd(II)/Pd(IV) catalytic cycle is compatible with this chiral catalyst. In addition, this method was not compatible with cyclobutane substrates, an important class of cycloalkane in synthesis. Herein, we report the first chiral catalyst for the enantioselective C(sp^3)–H cross-coupling of both cyclopropanecarboxylic acids and cyclobutanecarboxylic acids with both aryl and vinyl boron reagents. Both chiral ligands (**L25**, **L36**) were conveniently synthesized by C−H activation reactions developed in our laboratory. Enantioselective C−H coupling of free carboxylic acids via Pd(II)/Pd(0) catalytic cycle offers a new avenue to broaden the diversity of transformations.

With our previously developed β-C−H arylation of free cyclopropyl carboxylic acid with aryl iodides in mind,[7] we began our study by investigating the reactivity of cyclopropanecarboxylic acid under Pd(II)/Pd(0) catalysis.[8–9] Initially we focused on the C−H cross-coupling reactions with phenylboronic acid pinacol ester using various types of bidentate chiral ligands (Table 1**)**. While 11% yield was obtained in the absence of ligand, we were pleased to observe that mono-protected aminoethyl amine (MPAAM) ligand (**L1**) provided the desired arylated product in 38% yield with 96:4 er. Other ligand screening showed that our previous two classes of chiral ligands (**L2** and **L3**) gave poor yields or enantioselectivities. Further optimization using other ligands did not afford significant improvement (see supporting information). We then turned our attention to mono-protected amino acid (MPAA) ligands. Pleasingly, N-acetyl-L-phenylalanine (**L4**) afforded a 58% yield with 97:3 er. Notably, replacing acetyl with other protecting groups (**L5**–**L9**) led to either low yields or no reaction. Ligands with different side chains were also examined. The yield decreased when the benzyl group was replaced with other alkyl groups (**L10**–**L14**). On the other hand, only 13% yield and 88:12 er was obtained when we replaced benzyl side chain with phenyl substituent (**L15**) in this reaction, suggesting the importance of the benzyl group. We then focused on the modification of the benzyl group. Though *para*-OMe substituted N-acetyl-L-phenylalanine (**L17**) slightly improved the yield to 60%, other groups, such as *tert*-butyl, naphthalenyl and fluoro (**L16**, **L18**–**L19**), introduced to the *para* or *ortho* positions gave lower yields. Gratifyingly, N-acetyl-L-(2,6-di-phenyl)phenylalanine (**L20**) gave a better yield and high enantioselectivity (64% yield. 94:6 er). Since this type of ligand can be synthesized by our sulfonamide-directed C−H cross-coupling reaction[10], we prepared a series of 2,6-di-substituted phenylalanine-derived ligands (**L20**–**L28**) for

optimization. Among those 2,6-di-substituted ligands, the [2,6-di-(4-*tert*-butylphenyl)] phenylalanine ligand (**L25**) gave the best yield and enantioselectivity (70% yield, 97:3 er).

With the optimized reaction conditions in hand, we next explored the substrate scope of this method. The reaction was compatible with a wide range of aryl-boronic acid pinacol esters (Table 2). The coupling of **1a** with electron-withdrawing arylboronic acid pinacol esters afforded the arylated products in good yields with excellent enantioselectivities (**3a**–**3g**). On the other hand, arylboronic acid pinacol esters containing electron-rich groups tended to give the desired arylated products in slightly lower yields with similar enantioselectivities (**3h**–**3i**). In addition, both meta-substituted and *ortho*-substituted arylboron reagents were also viable coupling partners (**3j**–**3l**). We were also pleased to find that heteroaryl boronic ester can also participate in the reaction, albeit in a lower yield (**3o**). Furthermore, the reaction worked well with various 1-substituted 1-cyclopropanecarboxylic acids (**3p**–**3u**) to give similar enantioselectivity despite the drastic change of sterics. 1-Aryl-1-cyclopropanecarboxylic acids (**3p**–**3q**) were arylated to give the desired products in good yields with good enantioselectivities. 1-Butyl (**3r**), phenylpropyl (**3s**), chloropentyl (**3t**) and benzyl-protected 1-hydroxymethyl (**3u**) cyclopropanecarboxylic acids were also smoothly arylated in moderate to good yields with good enantioselectivities.

We next investigated the hitherto unreported coupling of cyclobutanecarboxylic acids with arylboronic acid pinacol esters. Asymmetric synthesis of diverse chiral cyclobutanes remains a significant challenge.[11] Previous attempts to enantioselectively functionalize cyclobutyl C−H bonds require the installation of a directing group.[12] Through ligand screening, we found that the mono-protected aminoethyl amine (MPAAM) ligand (**L1**) was promising for enantioselective C−H activation of cyclobutane carboxylic acid, affording a moderate yield and enantioselectivity. Though MPAA ligands worked well for cyclopropanecarboxylic acids, poor enantioselectivity was obtained with cyclobutanecarboxylic acid (**L4** and **L25**) in this reaction. We thus decided to focus on the modification of MPAAM ligands to further optimize this transformation (**L29**–**L39**). Changing the benzyl group to other alkyl groups (**L30**–**L33**) led to lower yields and moderate er. Remarkably, 2,6-di-aryl substituents on the phenyl ring (**L36**–**L39**) dramatically improved both the yield and er. Of the ligands prepared, the 2,6-phenyl substituted MPAAM ligand (**L36**) gave the best yield and enantioselectivity of 62% and 94:6 er, respectively.

With the optimized reaction conditions in hand, the scope of substrates and coupling partners was evaluated (Table 4). Electron-withdrawing groups (**5a**–**5g**), such as methoxycarbonyl, acetyl, nitro, cyano and phenyl groups provided the arylated products in moderate yields and with good enantioselectivities. On the other hand, the coupling of **4a** with electron-rich arylboronic acid pinacol esters (**5h** and **5i**) afforded the desired products in slightly lower yields and with similar enantioselectivities. Pleasingly, 1- and 2-naphthylboronic acid pinacol esters (**5l** and **5m**) were also successful coupling partners, albeit in moderate yield and with good enantioselectivities. The reaction also worked well with other 1-substituted 1-cyclobutanecarboxylic acids (**5p**–**5t**). 1-Aryl-1-cyclobutanecarboxylic acid and 1-alkyl cyclobutanecarboxylic acid (**5p**–**5r**) were arylated to give the desired products in moderate yields and enantioselectivities. Substrates containing

either an ether (**5s**) or a protected amine group (**5t**) were also compatible with this reaction conditions. Surprisingly, α-hydrogen cyclobutanecarboxylic acid (**5u**) gave poor enantioselectivity with this MPAAM ligand (57% yield, 64:36 er). Interestingly, the use of MPAA ligand **L25** afforded the desired product **5u** in 61% yield with 92:8 er. The absolute configuration of the product **5u** was confirmed by X-ray crystallographic analysis (see Supporting Information).

Subsequently, we explored the Pd(II)-catalyzed enantioselective C(sp^3)–H vinylation of free carboxylic acids **(**Table 5**)** as this transformation will provide access to a broader range of chiral carboxylic acids. Through extensive experimentation, we established the optimal reaction conditions that consisted of 2 equiv. of vinyl boronic ester with 20% ligand **L28** as the chiral ligand (**8a**). A number of disubstituted and trisubstituted (Z)-vinylboron reagents (**8a**–**8e**) were effective coupling partners for this reaction. Moreover, 1-cyclohexenyl-Bpin (**8f**) was compatible with this reaction, affording a lower yield with good er. We were also pleased to see that the heterocyclohexenyl boronic ester (**8g**) could also be subjected in the vinylation, giving the desired product in moderate yield with excellent enantioselectivity. Furthermore, this protocol was also successfully extended to the vinylation of cyclobutanecarboxylic acid, affording the desired product in 61% yield with 88:12 er (**8h**). Such olefin-containing chiral acids could provide valuable scaffold for organic synthesis and medicinal chemistry.

To demonstrate the synthetic utility of these C(sp^3)–H arylation products, the cross-coupling product **3f** was further transformed into chiral amine **9** without loss of optical activity (Scheme 2).[13] It should be noted that 2-substituted cyclopropanamines and 2-substituted cyclopropanecarboxylic acids are important structural motifs in biologically active molecules and natural products.

In summary, we have developed an efficient Pd(II)-catalyzed enantioselective C(sp^3)–H cross-coupling reaction of free carboxylic acids. The key to the success of this method was the use of the bidentate MPAA ligands or MPAAM ligands. This reaction is also compatible with aryl and vinyl coupling partners and affords aryl and olefin-containing chiral acids in high enantioselectivities. The synthetic utility of this reaction was also demonstrated by converting the chiral carboxylic acid into the chiral cyclopropyl amine without loss of optical activity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement

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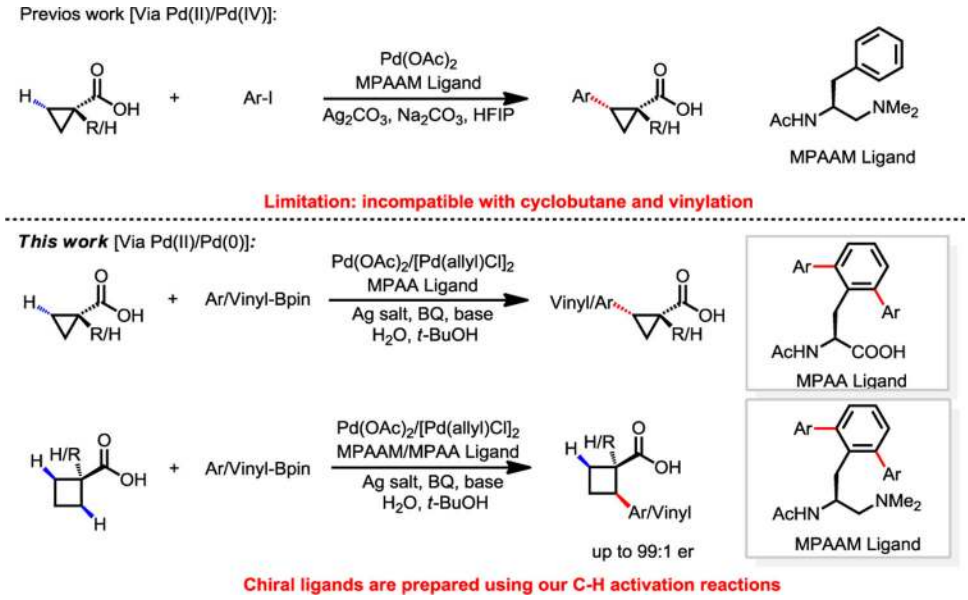
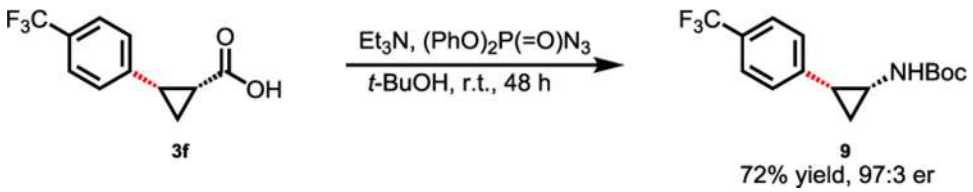


Scheme 1.

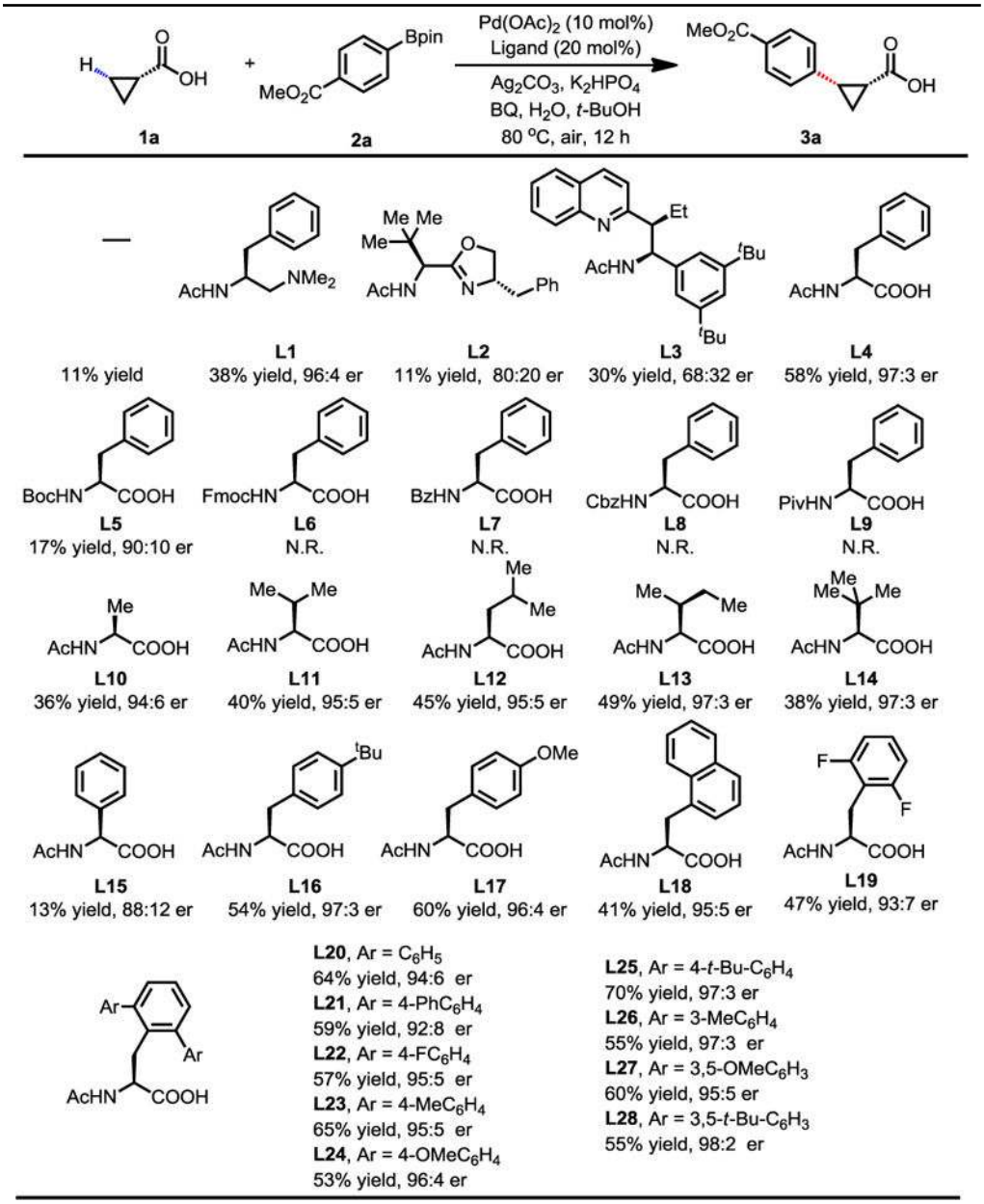
Pd-Catalyzed Enantioselective C–H Functionalization of Free Carboxylic Acids.



Scheme 2.
Synthesis of Cis-Chiral Amine from Carboxylic Acid

Table1.

Ligand Screening for Enantioselective Arylation of Cyclopropanecarboxylic Acid[a,b]

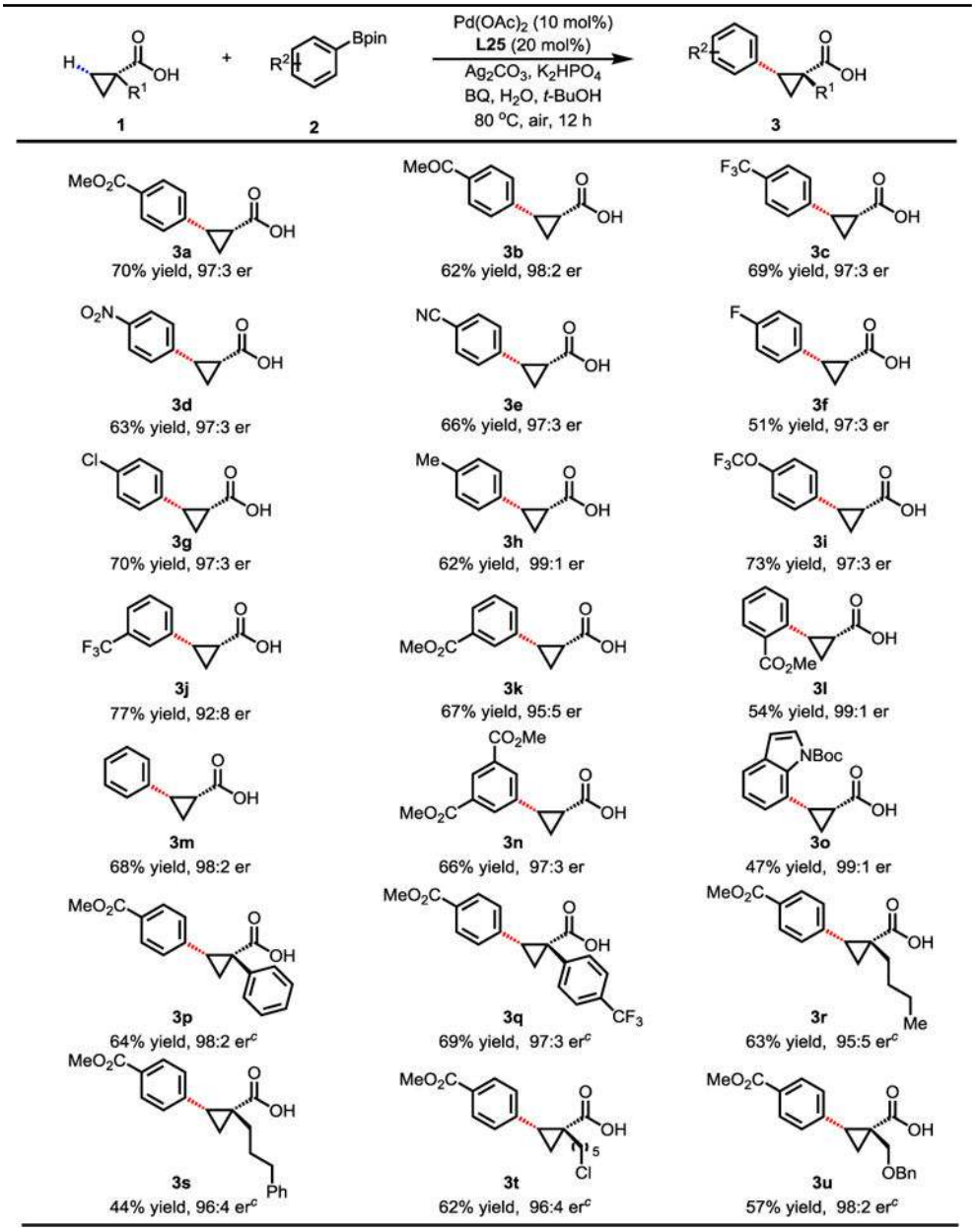


[a]Conditions: **1a** (0.1 mmol), **2a** (1.5 equiv), $Pd(OAc)_2$ (10 mol%), ligand (20 mol%), Ag_2CO_3 (1.5 equiv), K_2HPO_4 (1.5 equiv), BQ (0.5 equiv), H_2O (10.0 equiv), *t*-BuOH (1.0 mL), 80 °C, air, 12 h.

[b]^1H NMR yields, using CH_2Br_2 as an internal standard. BQ = benzoquinone.

Table 2.

The Scope of Enantioselective Arylation of Cyclopropanecarboxylic Acids[a,b]



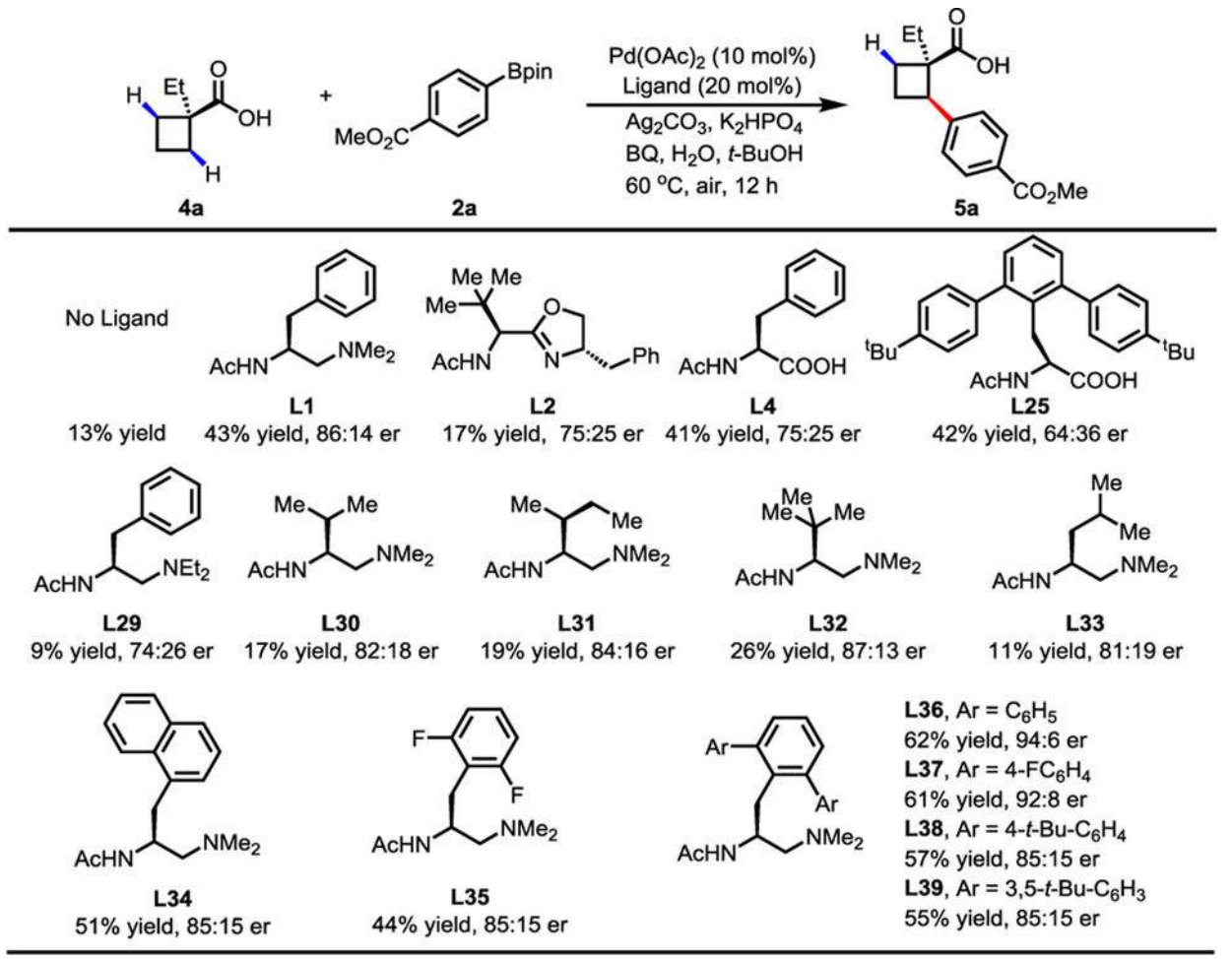
[a]Conditions: **1** (0.1 mmol), **2** (1.5 equiv), $Pd(OAc)_2$ (10 mol%), **L25** (20 mol%), Ag_2CO_3 (1.5 equiv), K_2HPO_4 (1.5 equiv), BQ (0.5 equiv), H_2O (10.0 equiv), *t*-BuOH (1.0 mL), 80 °C, air, 12 h.

[b]Isolated yields.

[c]Using **L36** instead of **L25**.

Table 3.

Ligand Screening for Enantioselective Arylation of Cyclobutanecarboxylic Acid[a,b]

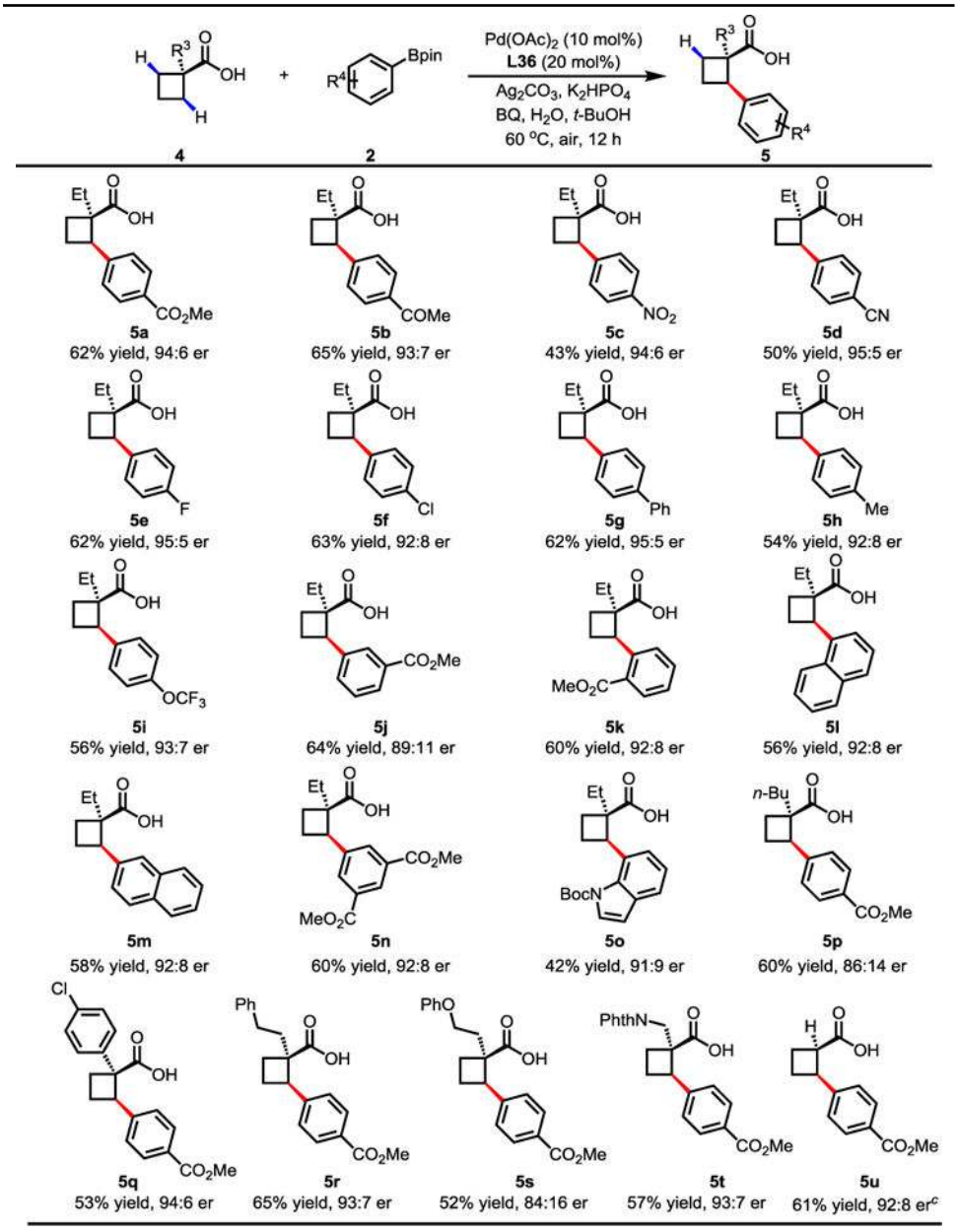


[a]Conditions: **4a** (0.1 mmol), **2a** (1.5 equiv), $Pd(OAc)_2$ (10 mol%), ligand (20 mol%), Ag_2CO_3 (2.0 equiv), K_2HPO_4 (1.5 equiv), BQ (0.5 equiv), H_2O (5.0 equiv), *t*-BuOH (1.0 mL), 60 °C, air, 12 h.

[b]^1H NMR yields, using CH_2Br_2 as an internal standard.

Table 4.

The Scope of Enantioselective Arylation of Cyclobutanecarboxylic Acids[a,b]



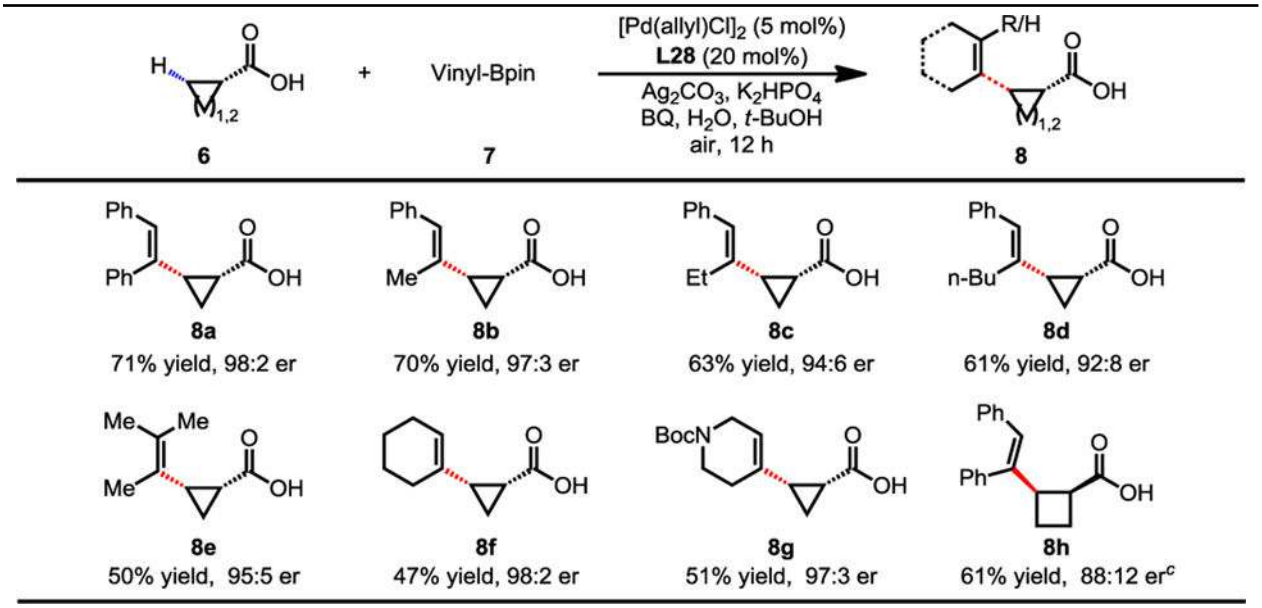
[a]Conditions: **4** (0.1 mmol), **2** (1.5 equiv), $Pd(OAc)_2$ (10 mol%), **L36** (20 mol%), Ag_2CO_3 (2.0 equiv), K_2HPO_4 (1.5 equiv), BQ (0.5 equiv), H_2O (5.0 equiv), *t*-BuOH (1.0 mL), 60 °C, air, 12 h.

[b]Isolated yields.

[c]Using **L25** instead of **L36**.

Table 5.

The Scope of Enantioselective Vinylation of free carboxylic Acids[a,b]



[a]Conditions: **6** (0.1 mmol), **7** (2.0 equiv), $[Pd(allyl)Cl]_2$ (5 mol%), **L28** (20 mol%), Ag_2CO_3 (1.5 equiv), K_2HPO_4 (1.5 equiv), BQ (0.5 equiv), H_2O (2.0 equiv), *t*-BuOH (1.0 mL), 80 °C, air, 12 h.

[b]Isolated yields.

[c]60 °C.