Published in final edited form as:

ACS Catal. 2018 March 2; 8(3): 2577–2584. doi:10.1021/acscatal.8b00069.

Enantioselective C–H Arylation and Vinylation of Cyclobutyl Carboxylic Amides

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Abstract

Chiral mono-*N*-protected aminomethyl oxazoline (MPAO) ligands are found to promote enantioselective C–H arylation and vinylation of the cyclobutyl carboxylic acid derivatives *via* Pd(II)/Pd(IV) redox catalysis. This ligand scaffold overcame two important limitations of the previous MPAHA (mono-*N*-protected α -amino-*O*-methylhydroxamic acid) ligands-enabled asymmetric C–H activation/C–C coupling reactions of cyclic carboxylic amides through Pd(II)/Pd(0) catalysis: substrates containing α -hydrogen atoms are not compatible; vinylation has not been developed. Sequential C–H arylation and vinylation of cyclobutanes are also accomplished to construct three consecutive chiral centers on the crowded cyclobutane rings, rendering this reaction highly versatile for the preparation of chiral cyclobutanes.

Graphical Abstract

Keywords

C–H activation; MPAO ligands; cyclobutanes; α -hydrogen atom; vinylation

1. Introduction

Cyclobutanes are prevalent motifs embedded in a diverse family of alkaloids, and important synthetic intermediates with unique bioactivity owing to their structural rigidity—a feature

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Notes. The authors declare no competing financial interest.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.XXXX.

Experimental details on experimental procedures for the catalytic reactions and spectroscopic data for the products (PDF).

that is often desirable in drug design (Figure 1).¹ Pipericyclobutanamide A demonstrate a selective inhibition of cytochrome P450 2D6 (CYP2D6) and Piperarborenine B was found to exhibit activity against P-388, A-549, and HT-29 cancer cell lines.² Other natural products such as Incarvilleine as well as the synthetic SB-FI-26 containing the cyclobutane core have also exhibited promising biological activities.³ However, cyclobutanes are not widely present in marketed drugs, partially due to the lacking of concise, general, and especially enantioselective strategies for the synthesis of cyclobutanes.

Enormous efforts have been devoted to the development of efficient synthetic protocols for the enantioselective construction of cyclobutane skeletons.⁴ Despite the remarkable progress on the asymmetric cyclobutanations and enantioselective functionalizations of cyclobutanes, constructing chiral cyclobutanes using exiting methods are not always successful depending on the substitution pattern on the cyclobutyl rings. For example, current methods for constructing three or four consecutive chiral centers on the cyclobutyl ring have extremely limited substrate scope.⁴ Thus, development of new strategies for the synthesis of enantiopure cyclobutanes remains an important task. Considering the challenges associated with the asymmetric ring forming reactions, rapid generation of chiral cyclobutanes through diversification of readily available cyclobutanes *via* enantioselective C–H activation offers an attractively alternative approach.^{5–8}

The combination of mono-dentate coordinating substrates with three classes of bi-dentate chiral ligands has led to the development of a wide range of Pd(II)-catalyzed enantioselective C–H activation reactions.^{9–12} In 2014, our group disclosed the first example of Pd(II)-catalyzed enantioselective cross-coupling of methylene β -C–H bonds in cyclobutyl carboxylic acid derivatives with arylboron reagents using the mono-*N*-protected α -amino-*O*-methylhydroxamic acid (MPAHA) ligands (Scheme 1).⁷ However, cyclobutane substrates containing α -hydrogen atoms gave poor yields and enantioselectivities (25% yield, 77:23 er). Recently, we reported the first example of Pd(II)-catalyzed enantioselective β -C–H borylation of carboxylic acid derivatives.⁸ Using MPAO ligands, a range of cyclic carboxylic acid derivatives were borylated with bis(pinacolato)diboron in high yields and enantioselectivities. While this C–H borylation can tolerate α -hydrogen atoms, subsequent synthetic elaborations of the congested chiral cyclobutyl borons are limited in scope and efficiency. Despite these preliminary advances through Pd(II)/Pd(0) catalysis, enantioselective C–H functionalizations of cyclobutyl carboxylic amides suffers from severe limitations: arylation with Ar-Bpin is not compatible with α -hydrogen atoms;⁷ transformations are limited to arylation⁷ and borylation.⁸ The development of broadly useful enantioselective C–H activation/C–C coupling reactions of cyclobutane substrates containing α -hydrogen atoms has two-fold challenges: substrates bearing α -hydrogen atom are significantly less reactive than that bearing quaternary centers due to Thorpe-Ingold effect; the presence of the small α -hydrogen atom instead of an α -alkyl group renders the chiral differentiation more challenging as the latter has a bulkier steric influence. These obstacles are reflected by a significant decrease in both yield and enantioselectivity when α -hydrogen atom-containing substrate is employed in our previous enantioselective arylation reaction.⁷

Herein, we report a Pd(II)-catalyzed enantioselective arylation of the cyclobutyl carboxylic amide bearing α -hydrogen atoms using chiral mono-*N*-protected aminomethyl oxazoline (MPAO) ligands. Enantioselective C(sp³)-H vinylation of cyclobutyl carboxylic amide is developed for the first time. Compared to our previous enantioselective C-H arylation of cyclobutyl amides *via* Pd(II)/Pd(0) catalysis, the MPAO ligand enabled Pd(II)/Pd(IV) catalysis entails significantly broader substrate scope. The sequential C-H arylation and vinylation also successfully construct three consecutive chiral centers on crowded cyclobutane rings, which are still challenging for previous ring forming methods.⁴

2. Results and Discussion

2.1 Arylation of Cyclobutyl Carboxylic Amide

The presence of multiple β -C-H bonds in simple mono-substituted cyclobutanes offers possibility for sequential di-C-H functionalizations. If both mono/di- selectivity and stereoselectivity can be controlled, such diversification processes using various coupling partners could provide a large number of chiral cyclobutane compounds that are difficult to access using existing methods. Our experimental efforts began with establishing conditions for the enantioselective C(sp³)-H arylation of the readily available cyclobutyl carboxylic amide **1** (Table 1). Brief survey of reaction conditions led to the initial finding of encouraging reactivity. Substrate **1** was stirred with 2.0 equiv. of 4-iodotoluene in the presence of 10 mol% of Pd(MeCN)₂Cl₂, 10 mol% of the chiral bi-dentate ligand **L1**, and 2.0 equiv. of Ag₂CO₃ (in CHCl₃ at 80 °C for 24 h). The arylated product **2a** was obtained in 20% yield, albeit in racemic form (entry 1, Table 1). Switch to ligand **L2** containing a chiral side chain and achiral oxazoline moiety gave a slightly improved yield, and most importantly, moderate enantioselectivity (50% yield, 75:25 er, entry 2). While **L3** containing both chiral centers gave poor yield and enantioselectivity (26% yield, 68:32 er, entry 3), the diastereomer **L4** significantly improved both the yield and enantioselectivity (63% yield, 95.5:4.5 er, entry 4). Increasing the steric hindrance on the oxazoline ring (**L5**) only improved the yield and enantioselectivity slightly (65% yield, 96:4 er, entry 5). Ligand containing bulky *tert*-butyl group on the oxazoline ring (**L6**) gave lower yield and enantioselectivity (50% yield, 94:6 er, entry 6), presumably due to its less effective coordination with Pd(II) species. Increasing the loading of **L5** from 10 mol% to 15 mol% slightly improved the yield and enantioselectivity (68% yield, 96.5:3.5 er, entry 7). Further increase the loading of **L5** to 20 mol% led to the drop of the yield with similar enantioselectivity (58% yield, 96:4 er, entry 8). Extending the reaction time to 48 hours (entry 9) and increase the loading of 4-iodotoluene to 3.0 equiv. (entry 10) impacted the results drastically, affording the product in excellent yield and enantioselectivity (81% yield, 97:3 er). (see Supporting Information for extensive optimizations of Pd sources, solvents, and additives). Interestingly, while this new protocol provides a solution for the challenging cyclobutane substrates containing α -hydrogen, it is not compatible with cyclobutanes containing α -substituents which indicates the importance of ligand design for substrates possessing different steric environment.

The scope of aryl iodides was surveyed under the optimized conditions (Table 2). Arylation by *para*-methyl phenyl iodide provided **2a** in 81% yield and 97:3 er. Arylation with simple

iodobenzene gave **2b** in 85% yield and 97:3 er. Methoxy group at the *para*-position is tolerated (67% yield and 96.5:3.5 er). Aryl iodides containing various halogen groups (**2d–2f**) and other electron-withdrawing groups (**2g–2k**) at *para*-position are also compatible, affording the corresponding products in moderate to good yields and excellent enantioselectivities (45%–72% yields, 95:5–97:3 er). The tolerance of acetyl, formyl, and nitro groups are particularly worth-noting (**2h–2j**). *Meta*-substituted aryl iodides bearing either electron-donating (Me, OMe) or electron-withdrawing (halides, CF₃, and acetyl) functional groups are reactive, providing the desired products in good yields and excellent enantioselectivities (58%–73% yields, 95:5–96.5:3.5 er, **2l–2q**). *Ortho*-fluoro, *ortho*-methylcarboxyl, 3,5-dimethyl, and 3,5-ditrifluoromethyl aryl iodides gave the corresponding products in high yields and enantioselectivities (63%–80% yields, 93:7–97:3 er, **2r–2u**). A number of heteroaryl iodides are also suitable coupling partners, affording products with high enantioselectivities, albeit in lower yields (50%–65% yields, 91:9–96:4 er, **2v–2y**).

2.2 Vinylation of Cyclobutyl Carboxylic Amide

To enable the access to more diverse chiral cyclobutanes *via* enantioselective C–H activation, we embarked on the development of enantioselective vinylation of **1**. We envision the combination of vinylation and arylation of cyclobutane will expand the diversity significantly. Despite recent advances of Pd(II)-catalyzed enantioselective C(sp³)–H activation reactions, vinyl-based coupling partners remains incompatible with these chiral catalysts. Such challenge is also reflected by the underdevelopment of C–H vinylation in general.^{1g,1h,13} Through modification of the reaction conditions, we were able to couple **1** with (*E*)-styrenyl iodide using ligand **L5** to give the vinylation product in moderate yield and excellent enantioselectivity (**3a**, Table 3). Either electron donating or electron withdrawing substitute groups on the *para*-, and *meta*-positions of the phenyl ring are all well tolerated, affording the desired products in moderate yields and excellent enantioselectivities (43–58% yields, 96:4–97:3 er, **3a–3h**). *Ortho* substituents, including methyl, methoxy, -(CH₃)₄-, fluoro, bromo, and trifluoromethyl groups, were compatible with this method (34–65% yields, **3i–3n**). The use of (*E*)-styrenyl iodide with 2,4-disubstituted on the phenyl ring or disubstituted on the olefin double bond also gave good enantioselectivities, albeit in lower yields (35–40% yields, 96:4–97:3 er, **3o**, **3p**). In general, vinylation is less efficient partly due to their instability under these conditions.

2.4 Absolute Stereochemistry and Proposed Catalytic Cycle

The absolute configuration of **2j** was unambiguously confirmed by using a HPLC standard of which the absolute configuration was established by X-ray crystallographic analysis in our previous study.⁸ This enantioselective C–H coupling reaction is likely to proceed through a Pd(II)/Pd(IV) catalysis (Scheme 2). Pre-coordination of the ligand to palladium to form the active Pd(II) species **I**. Coordination of substrate **1** to this species followed by a enantiodetermining C–H metalation step to form the chiral Pd(II) intermediate **II**. Oxidative addition of aryl or vinyl iodides to intermediate **II** generates the Pd(IV) species **III**. Reductive elimination provides the products and closes the catalytic cycle.

2.4 Diverse Chiral Cyclobutanes via Sequential C–H Arylation and Vinylation

To demonstrate the robustness of the reaction, a gram-scale reaction was carried out (Scheme 3). Arylation of **1** under the standard conditions with the iodobenzene as the coupling partner gave 1.6 g of enantioenriched product **2b** in 86% isolated yield and 97:3 er. Treatment of **2b** with 2.0 equiv. Sodium *tert*-butoxide in toluene successfully epimerized the C-1 stereocenter to give **4** in 92% yield without erosion in enantioselectivity.^{1f} To further broaden the diversity of the chiral cyclobutanes accessible through this method, **4** was subjected to the standard arylation conditions with methyl 4-iodobenzoate as the coupling partner, affording the enantiopure cyclobutanes bearing two distinct aryl rings **5** in 85% yield. In addition, the (*E*)-styrenyl group can also be installed efficiently to give **6** with excellent enantioselectivity and synthetically useful yield. These chiral cyclobutanes bearing three consecutive chiral centers are not readily accessible by previous ring forming approaches.⁴

2.5 Removal of Directing Auxiliary

To meet the needs for various synthetic applications, different protocols are also established to deprotect the amide auxiliary (Scheme 4). Treatment of **2b** with BF₃·Et₂O in methanol resulted in removal of the auxiliary to give the *cis*-disubstituted cyclobutane **7** in 92% yield without erosion in enantioselectivity (97:3 er).⁸ Deprotection can also be accomplished using our recently developed conditions using epoxide and KOAc.¹⁵ Auxiliary cleavage and the in situ epimerization of the C-1 stereocenter afforded the *trans*-disubstituted cyclobutane **8** in 90% yield and 97:3 er.

3. Conclusion

In conclusion, we have developed a Pd(II)-catalyzed enantioselective arylation and vinylation of cyclobutyl carboxylic amides using chiral MPAO ligands. Sequential C–H arylation and vinylation provides an efficient methodology for the construction of diverse chiral cyclobutanes from simple mono-substituted cyclobutane. The rapid preparation of chiral cyclobutanes bearing three consecutive chiral centers are especially valuable as previous ring forming approaches to access these compounds have highly limited substrate scope.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We gratefully acknowledge The Scripps Research Institute and the NIH (NIGMS, 2R01GM084019) for financial support.

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Figure 1.
Biologically Active Compounds Containing Cyclobutanes

Arylation with MPAHA ligand: *Incompatible with α -hydrogen substrates***Pd(II)/Pd(0) catalysis:** **Borylation with MPAO ligand:** *Poor efficiency in subsequent coupling with ArCl***Pd(II)/Pd(0) catalysis:** **This work:** *Compatible with α -hydrogen substrates; arylation and vinylation***Pd(II)/Pd(IV) catalysis:** **Scheme 1.**

Enantioselective C–H Functionalization of Cyclobutyl Carboxylic Amide

Scheme 2.
Proposed Catalytic Cycle

Scheme 3.
Diversification of the Chiral Cyclobutanes

Scheme 4.
Removal of the amide auxiliary

Table 1

Optimization for Arylation of Cyclobutyl Carboxylic Amide^{a,b}

entry	L	x	y	t (h)	yield (%)	er
1	L1	10	2.0	24	20	50:50
2	L2	10	2.0	24	50	75:25
3	L3	10	2.0	24	26	68:32
4	L4	10	2.0	24	63	95.5:4.5
5	L5	10	2.0	24	65	96:4
6	L6	10	2.0	24	50	94:6
7	L5	15	2.0	24	68	96.5:3.5
8	L5	20	2.0	24	58	96:4
9	L5	15	2.0	48	75	96.5:3.5
10	L5	15	3.0	48	87(81) ^c	97:3

^aReaction conditions: $\text{Pd}(\text{MeCN})_2\text{Cl}_2$ (0.01 mmol), **L** (x mol%), **1** (0.1 mmol), 4-iodotoluene (y equiv.), Ag_2CO_3 (0.2 mmol), CHCl_3 (0.5 mL), 80 °C.^bYields determined by ¹H NMR analysis of the crude reaction mixture using CH_2Br_2 as internal standard. Enantiomeric ratios (er) were determined by chiral high-performance liquid chromatography.^cIsolated yield.

Table 2

Scope of Arylation of Cyclobutyl Carboxylic Amide ^{a,b}

81%, 97:3 er	85%, 97:3 er	67%, 96.5:3.5 er	70%, 97:3 er	66%, 95:5 er
64%, 97:3 er	60%, 96.5:3.5 er	70%, 97:3 er	72%, 97:3 er	68%, 96:4 er
45%, 97:3 er	73%, 96.5:3.5 er	73%, 96:4 er	60%, 96:4 er	63%, 95:5 er
58%, 95:5 er	70%, 95:5 er	65%, 93:7 er	80%, 97:3 er	68%, 94:6 er
63%, 95:5 er	65%, 96:4 er	50%, 91:9 er	53%, 95:5 er	53%, 96:4 er

^a Conditions: **1** (0.1 mmol), Ar(Het)-I (0.3 mmol), Pd(MeCN)₂Cl₂ (0.01 mmol), **L5** (0.015 mmol), Ag₂CO₃ (0.2 mmol), CHCl₃ (0.5 mL), 80 °C, 48 h.

^b Isolated yields. Enantiomeric ratios (er) were determined by chiral high-performance liquid chromatography.

Table 3

Scope of Vinylation of Cyclobutyl Carboxylic Amide^{a,b}

^a Conditions: **1** (0.1 mmol), Vinyl-I (0.3 mmol), Pd(MeCN)₂Cl₂ (0.01 mmol), **L5** (0.015 mmol), Ag₂CO₃ (0.2 mmol), CHCl₃ (0.5 mL), 60 °C, 48 h.

^b Isolated yields. Enantiomeric ratios (er) were determined by chiral high-performance liquid chromatography.