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Enantioselective γ -C(sp³)-H Activation of Alkyl Amines via Pd(II)/Pd(0) Catalysis

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Abstract

Pd(II)-catalyzed enantioselective γ -C(sp³)-H cross-coupling of alkyl amines *via* desymmetrization and kinetic resolution has been realized for the first time using chiral acetyl-protected aminomethyl oxazoline ligands (APAO). A diverse range of aryl- and vinyl-boron reagents can be used as coupling partners. The chiral γ -arylated alkylamine products are further transformed into chiral 2-substituted 1,2,3,4-tetra-hydroquinolines and *spiro*-pyrrolidines as important structural motifs in natural products and biologically active molecules.

Graphical Abstract

While Pd(OAc)₂ has been long known to activate both sp² and sp³ C–H bonds,¹ such reactivity driven by strong coordination from substrates can also lead to persistent background reactions, which presents a fundamental challenge for rendering Pd(II)-catalyzed racemic C–H activation reactions² enantioselective. Despite recent development of chiral Pd(II) catalysts for enantioselective intermolecular C–H activation reactions through weak coordination and ligand acceleration,^{3–5} as well as Pd(0)-catalyzed intramolecular enantioselective C–H arylation,⁶ scope and efficiency remains limited. For example, protocols for enantioselective C–H activation reactions of carboxylic acids and amide substrates are not applicable to alkyl amine substrates. To date, there are only two examples of enantioselective intermolecular γ -C(sp³)-H activation of amine substrates involving cyclopropyl and benzylic C–H bonds (Scheme 1).^{7, 8} In addition, only arylation *via* a Pd(II)/Pd(IV) catalytic cycle is compatible with these chiral catalysts. Considering the broad utility of chiral amines in organic synthesis and drug discovery,⁹ it is of great importance to

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Supporting Information Available: Experimental procedures and spectral data for all new compounds (PDF). This material is available free of charge *via* the Internet at <http://pubs.acs.org>.

develop enantioselective C–H activation reactions of simple alkyl amines using other catalytic cycles. Herein, we report the first chiral catalyst for enantioselective γ -C(sp³)–H cross-coupling of aliphatic amines with both aryl and vinyl boron reagents through desymmetrization. Kinetic resolution¹⁰ of alkyl amines bearing various α -substituents *via* γ -C(sp³)–H cross-coupling is also made possible through catalyst modification, allowing the access to a broader range of chiral amines.

Based on our previously developed γ -C(sp³)–H arylation⁷ and cross coupling¹¹ of alkyl amines, we initiated our investigation to develop γ -C(sp³)–H cross-coupling of amine **1a** using various types of bidentate chiral ligands (Table 1). While no C(sp³)–H arylation occurred in the absence of ligand, we were delighted to observe that the acetyl-protected aminoethyl quinoline (APAQ) ligand (**L1**) provided the desired product in 30% yield with 97% ee, and Ac-L-Val-OH (**L2**) provided product in 38% yield with 26% ee. However, the efforts to further improve the yield and enantioselectivity failed after an extensive screening of APAQ and mono-*N*-protected amino acid (MPAA) ligands. Considering the fact that acetyl protected amino oxazoline (APAO) chiral ligands can facilitate carboxylic amide-directed enantioselective C(sp³)–H arylation (Pd(II)/Pd(IV)) and borylation (Pd(II)/Pd(0)),^{5e, 5f} we began to test this ligand for alkyl amine derived substrates **1a**. Encouragingly, the use of (*S,S*)-**L3** furnished the cross-coupling product in 54% yield with 98% ee. We then systematically modified APAO ligands at both the side chain and the oxazoline ring to further optimize this transformation (**L4–L13**). We found that the reactivity of this cross-coupling reaction is highly sensitive to the steric hindrance of the ligand side chain (**L4–L7**). Reaction with ligand bearing a bulky *t*-Bu group improved the yield from 54% to 65% (**L7**). Fine tuning of other substituents on the side chain did not provide better results. The use of (*S,R*)-**L7**, the other diastereomer of the optimal ligand, provided the enantiomer of product with 32% yield and 98% ee. *Para*-trifluoromethyl substitution on the phenyl ring gave slightly lower yield (**L8**). Increasing the steric hindrance on the oxazoline ring was detrimental to the reaction, presumably due to the ineffective binding of APAO ligand to Pd(II) species (**L9–L11**). The chiral oxazoline ligands lacking a stereocenter on either the side chain or the oxazoline moiety gave poor yields and enantioselectivities (**L12** and **L13**), which speaks to the importance of both chiral centers on the APAO ligand backbones for chiral induction. Finally, control experiments revealed that the Pd catalyst, silver source, BQ, base, and H₂O were all crucial for the C(sp³)–H cross-coupling reaction (see Supporting Information for the detail optimization of these parameters).

With the optimal reaction conditions established, we set out to explore this enantioselective γ -C(sp³)–H cross-coupling reaction of amine derivative **1a** with a wide range of arylboron reagents in the presence of (*S,S*)-**L7** as ligand (Table 2). Reaction with simple phenylboronic acid pinacol ester provided **3b** in good yield and excellent enantioselectivity (64%, 97% ee). Arylboron reagents with both electron-donating and electron-withdrawing substituents at the *para* and *meta* positions are well tolerated, affording the desired products in good yields with excellent enantioselectivities (>96% ee in all cases). Coupling partners bearing electron-withdrawing ester, acetyl, trifluoromethyl, and fluoro groups gave moderate to good yields (52%–65%) with excellent enantioselectivities (**3a**, **3c–3e**). Coupling partners bearing electron-donating substituents such as methyl and methoxyl groups at the *para* position also

performed well (**3f** and **3g**). Reactions with biphenyl, 1-naphthyl, and 2-naphthyl boronic acid pinacol ester furnished the desired products in good yields with excellent enantioselectivities (**3h–3j**). Furthermore, *meta*-substituted and disubstituted arylboron reagents were all well tolerated (**3k–3o**). Heteroaryl boronate ester was also compatible with this reaction, albeit giving lower yield (**3p**). The Tf group of **3b** could be readily removed in a two-step procedure to yield free amine without loss of optical activity (see Supporting Information for the deprotected reaction). The free amine can also direct γ -C(sp³)-H arylation of the remaining ethyl group using our transient directing group to access a wider range of amines.¹²

Extending this enantioselective C–H activation method to γ -C(sp³)-H coupling with vinylboron reagents will allow the access to a broader range of chiral amines. Hence, we next investigated the coupling of Tf-protected amines with various vinylboron reagents, which has not been reported to date. γ -Styrenylation of amine **1a** using chiral ligand (*S,S*)-**L7** afforded the product in 50% yield and 96% ee. The use of (*S,S,S*)-**L14**, containing an additional chiral center at C-5, improved the yield to 56% and enantioselectivity to 99% ee (Table 3). A number of disubstituted (*Z*)-vinylboron reagents (**5a–5e**), as well as trisubstituted vinylboron reagent (**5f**) were compatible with this reaction. Coupling partners bearing 1-aryl-2-alkyl, diaryl, dialkyl, and trialkyl groups gave moderate yields and excellent enantioselectivities. 1-Cyclohexenyl-Bpin and 1-cyclopentyl-Bpin were both well tolerated as coupling partners in this reaction (**5g**, **5h**). Hetero-cyclohexenyl boronate esters also afforded desired products in good enantioselectivities, albeit in lower yields (**5i**, **5j**). These heterocycle-containing chiral amines are useful intermediates in drug discovery.

Next, we began to develop chiral ligands for enantioselective γ -C(sp³)-H coupling of unsymmetric amines through kinetic resolution (Table 4). Guided by the established enantioselective desymmetrization C–H coupling (Table 1), the reaction of racemic **1b** with *para*-methoxycarbonyl-phenylboronic acid pinacol ester was carried out in the presence of 10 mol% Pd(OAc)₂, 15 mol% (*S,S*)-**L7**, 2.0 equiv. of Ag₂CO₃, 2.0 equiv. of Na₂CO₃, 0.5 equiv. of BQ, and 5.5 equiv. of H₂O in *t*-AmylOH at 80 °C. We were pleased to find that the desired cross-coupling product **6a** was obtained with 40% yield and 84% ee.

Encouraged by this result, a variety of APAO ligands with different side chains were screened and (*S,S*)-**L15** was found to give the best *s*-factor of 167 (**6a**, 34% yield, 98% ee) (see Supporting Information for detail optimization of the reaction). With the optimized reaction conditions in hand, we next investigated different amines and arylboron coupling partners. Notably, differentiation of a hydrogen atom and a relatively small methyl group in 2-butylamine is highly challenging. We were pleased to find that cross-coupling of 2-butylamine derived substrate gave the arylated product in 32% yield and 96% ee (**6b**). This enantioselective C–H activation method is also compatible with amino alcohol derived substrate (**6c**, *s* = 67).

To showcase the synthetic utility of this enantioselective C–H activation reaction, the cross-coupling products were further transformed into chiral 2-substituted 1,2,3,4-tetrahydroquinolines without loss of optical activity (Table 5).¹³ Various substituents such as 2-naphthyl, *para*- and *meta*-substituted arylated products were well tolerated in the condition.

Treatment of the vinylated product **5j** with concentrated sulfuric acid in DCM gave the *spiro*-pyrrolidine derivative **7g** in 79% yield.¹⁴ Deprotection was readily accomplished by treating the cyclization product with Red-Al in toluene at 50 °C, affording chiral 2-methyl-1,2,3,4-tetra-hydroquinoline in 99% yield and 96% ee (Scheme 2). It should be noted that 2-substituted 1,2,3,4-tetra-hydroquinolines and *spiro*-pyrrolidines are important structural motifs in biologically active molecules and natural products.

In summary, we have developed Pd(II)-catalyzed enantioselective γ -C(sp³)-H cross-coupling of alkyl amines protected by a removable Tf group. C-H arylation and vinylation *via* desymmetrization or kinetic resolution provide an access to a broad range of chiral alkyl amines.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Limited to the highly active cyclopropyl and benzylic C–H bonds.

Enantioselective γ -C–H arylation and vinylation

Scheme 1.

Enantioselective γ -C(sp³)-H Activation of Alkyl Amines

Scheme 2. The Removal of Auxiliary ^{a, b}

^a Reaction conditions: **7a** (0.1 mmol), Red-Al (10.0 equiv.), toluene (1.0 mL), 50 °C, N₂, 10 h. ^b Isolated yield.

Table 1

Ligand Development^{a, b}

—	 L1 30%, 97% ee	 L2 38%, 26% ee
n.d.		
 (S,S)-L3 54%, 98% ee	 (S,S)-L4 29%, 80% ee	 (S,S)-L5 52%, 95% ee
 (S,S)-L6 56%, 98% ee	 (S,S)-L7 65%, 98% ee	 (S,R)-L7 32%, -98% ee
 (S,S)-L8 61%, 97% ee	 (S,S)-L9 58%, 99% ee	 (S,S)-L10 30%, 98% ee
 (S,S,S)-L11 56%, 99% ee	 (S,S)-L12 28%, 19% ee	 (S)-L13 13%, 22% ee

^aReaction conditions: substrate **1a** (0.1 mmol), **2a** (2.0 equiv.), Pd(OAc)₂ (10 mol%), ligand (15 mol%), Ag₂CO₃ (2.0 equiv.), Na₂CO₃ (2.0 equiv.), 1,4-benzoquinone (BQ) (0.5 equiv.), H₂O (5.5 equiv.), *t*-AmylOH (1.0 mL), 80 °C, 12 h, N₂.

^bThe yields were determined by ¹H NMR analysis of the crude product using CH₂Br₂ as the internal standard. The ee values were determined by HPLC analysis on a chiral stationary phase.

Table 2

Enantioselective Cross-Coupling with Arylboron Reagents^{a, b}

^aReaction conditions: substrate **1a** (0.1 mmol), **2** (2.0 equiv.), Pd(OAc)₂ (10 mol%), (S,S)-**L7** (15 mol%), Ag₂CO₃ (2.0 equiv.), Na₂CO₃ (2.0 equiv.), 1,4-benzoquinone (BQ) (0.5 equiv.), H₂O (5.5 equiv.), *t*-AmylOH (1.0 mL), 80 °C, 12 h, N₂.

^bIsolated yields. The ee values were determined by HPLC analysis on a chiral stationary phase.

Table 3

Enantioselective Cross-Coupling with Vinylboron Reagents^{a, b}

^aReaction conditions: substrate **1a** (0.1 mmol), **4** (3.0 equiv.), Pd(OAc)₂ (10 mol%), ligand (15 mol%), Ag₂CO₃ (2.0 equiv.), Na₂CO₃ (2.0 equiv.), 1,4-benzoquinone (BQ) (0.5 equiv.), H₂O (5.5 equiv.), THF (1.0 mL), 70 °C, 24 h, N₂.

^bIsolated yields. The ee values were determined by HPLC analysis on a chiral stationary phase.

Table 4Kinetic Resolution of Cross-Coupling with Arylboron Reagents^{a, b}

^a Reaction conditions: substrate **1** (0.1 mmol), **2** (2.0 equiv.), Pd(OAc)₂ (10 mol%), ligand (15 mol%), Ag₂CO₃ (2.0 equiv.), Na₂CO₃ (2.0 equiv.), 1,4-benzoquinone (BQ) (0.5 equiv.), H₂O (5.5 equiv.), *t*-AmylOH (1.0 mL), 80 °C, 24 h, N₂.

^b Isolated yields. The ee values were determined by HPLC analysis on a chiral stationary phase.

Table 5Cyclization of Cross-Coupling Products^{a, b}

^a Reaction conditions: substrate **3** or **6** (0.1 mmol), 1,3-diiodo-5,5-dimethylhydantoin (DIH) (2.0 equiv.), DCE (5.0 mL), *hν*, 60 °C, 6 h, N₂.

^b Isolated yields. The ee values were determined by HPLC analysis on a chiral stationary phase.