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Ligand-Enabled Methylene C(sp³)–H Bond Activation with A Pd(II) Catalyst

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Abstract

Pd(II)-Insertion into β -methylene C(sp³)–H bonds was enabled by a mutually-repulsive and electron-rich quinoline ligand. Ligand tuning has led to the development of a method that allows for installation of an aryl group on a range of acyclic and cyclic amides containing β -methylene C(sp³)–H bonds.

Development of synthetic transformations based on transition metal-catalyzed functionalization of C(sp³)–H bonds continues to attract intensive efforts.^{1,2} Recently, our laboratory has demonstrated that a weakly-coordinating *N*-arylamide (CONHAr) moiety serves as a powerful auxiliary to effect a diverse array of Pd-catalyzed C(sp³)–H functionalization reactions of aliphatic acids.³ However, this auxiliary and others¹ developed in our laboratory are not capable of activating methylene C(sp³)–H bonds. Previous studies showed that Pd-insertion into inert methylene C–H bonds requires strongly coordinating phosphine or pyridine auxiliaries (Scheme 1).^{4–7} Encouraged by the observed ligand acceleration in a number of Pd(II)-catalyzed C(sp²)–H activation reactions,⁸ we focused our efforts on developing ligands that can promote β -methylene C(sp³)–H activation using the weakly coordinating *N*-arylamide auxiliary. Herein, we report the first example of ligand-enabled *N*-arylamide-directed Pd(II)-catalyzed arylation of acyclic and cyclic β -methylene C(sp³)–H bonds (Scheme 1).

While ligand-promoted aryl C(sp²)–H activation reactions with Pd(II) catalyst have been developed in recent years,^{8,9} ligand scaffolds that facilitate C(sp³)–H activation are rare.^{3a,3e,7} Methylene C–H bonds are significantly more resistant to Pd insertion than primary C–H bonds due to being more sterically hindered.¹ Furthermore, following the methylene C(sp³)–H cleavage step to form the cyclopalladation complex, undesired β -hydride elimination could occur due to the presence of γ -C–H bonds adjacent to the Pd center, outcompeting the sluggish reductive elimination pathway leading to the formation of desired C(sp³)–C bond. Therefore, we decided to develop a ligand to provide a solution to this significant challenge.

Since the acidic *N*-arylamide has been demonstrated to be a versatile auxiliary for alkyl C(sp³)–H activation, a ligand that strongly coordinates with Pd(II) center and yet allows the weakly coordinating amide moiety to bind to the same Pd center is needed. Guided by our previous development of a “mutually-repulsive” pyridine ligand that coordinates with Pd-catalyst in a singly-bound fashion and also allows the coordination of electron-deficient

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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>.

arenes,^{9b} we focused on a pyridine-based ligand scaffold. Systematic screening of the ligands using Pd(II)-catalyzed arylation with p-Tol-I (Table 1) as a platform was carried out. In the absence of ligand, substrate **1** was treated with 15 mol% of Pd(TFA)₂, 4.0 equiv of p-Tol-I, 2.5 equiv of Ag₂CO₃, 1.2 equiv of K₂HPO₄ in DCE at 120 °C for 24 hours to give less than 2% of the mono-arylated product **1a** based on ¹H NMR and GC/MS spectroscopic analyses. Interestingly, a slight increase in the product yield was observed (7%) when 0.3 equiv of pyridine **L2** was added to the reactions mixture. To increase the sterics of the ligand, we screened 2,6-disubstituted pyridines for the methylene C(sp³)-H arylation reaction. The 2,6-dimethylpyridine **L3** gave 9% of mono-arylated product, while more sterically hindered **L4** yielded no product. However, we were delighted to find that 2,6-dimethoxypyridine **L5** gave mono- and di-arylated products in 60% and 16%, respectively, suggesting that the electronic properties of the pyridine are crucial. The diastereotopic ratio values of products **1a mono** and **1a di** were determined to be 4:1 and 1:1, respectively, based on the ¹H NMR and GC/MS spectroscopic analyses. The d. r. values were not affected in an appreciable extent by varying the ligands. To verify the importance of using monodentate ligands, bidentate ligands such as *N*-protected amino acids and phenanthroline **L1** were also tested and shown to give no arylation products.

Further optimization of the 2,6-disubstituted pyridines suggests that both the steric bulk and electron-donating ability of the ligand are crucial for the desired reactivity. For example, 2,6-dichloropyridine **L6**, 2-methoxypyridine **L7** and 2-isopropyl-6-methoxypyridine **L8** gave drastically diminished yields. Highly electron-rich 2,4,6-triethoxypyridine **L9** gave 96% combined yield of the products (mono:di = 1.3:1). We also found that 2-methoxyquinoline **L10** is effective, affording 74% yield (mono:di = 5.2:1). Considering that 2-alkoxyquinoline scaffolds are easy to prepare, we focused on tuning this structure. Hence, we synthesized 2-isopropoxyquinoline **L11** and 2-isobutoxyquinoline **L12**, both of which gave full conversion.

With the optimized ligand **L12** in hand, we converted a variety of commercially available carboxylic acids into the corresponding *N*-arylamides to examine the scope of the arylation protocol. In addition, further optimization of reaction conditions was carried out; hexane served as the optimal solvent as it suppressed the homocoupling of p-Tol-I. As a result, Pd loading and reaction temperature could be lowered to 10 mol% and 110 °C, respectively (see Supporting Information). Product **1a** was obtained as a mixture of mono- and di-arylation products in 3:1 ratio; the mono-substituted product was isolated as a mixture of diastereomers (d.r. = 4:1). Amide substrates **2** and **3** derived from butanoic and pentanoic acids were arylated to give the products in 77% and 55% yields, respectively. Substrate **2** could also be arylated using 1-iodo-4-methoxybenzene and 1-fluoro-4-iodobenzene to give **2b** and **2c** in 71% and 68%, respectively. Arylation of α -isopropyl-substituted substrate **4** gave the desired product **4a** in 82% yield as a single diastereomer, with the methine C(sp³)-H bond remaining intact. Substrate **5** possesses benzylic and aliphatic methylene C(sp³)-H bonds that could both be arylated. We found that arylation of the benzylic C(sp³)-H bond took place predominantly, giving **5a** as the major product in 71% yield (d.r. = 7:1). The di-arylated product **5b** was also isolated in 20% yield.

This method was also found to be effective in activating cyclic methylene C-H bonds (**6-11**). Arylation of *N*-arylcyclopropanecarboxamide **6** gave the mono-arylated product **6a** in 86% isolated yield as a single *cis*-substituted diastereomer. Although cyclopropyl C-H bonds have been shown to be more reactive,³ only 18% of **6a** was obtained in absence of **L12**. Cyclobutyl substrate **7** was di-arylated to give **7a** as the major product is a single diastereomer. For cyclopentyl, cyclohexyl and pyran substrates (**8-11**), the corresponding mono-arylation products were isolated as major products. **9a** was obtained as a mixture of *cis*- and *trans*-substituted products in a 4:1 ratio; a trace amount of di-arylated product was

observed by ^1H NMR. For substrate **10**, δ -lactam **10b** as a side product was also formed in 12% yield via Pd-mediated *ortho*-C–H amidation of the *trans*-arylation product. Arylation of tetrahydro-2H-pyran-4-carboxamide **11** gave a mixture of *cis* and *trans*-arylated products (**11a**) in a 6:1 ratio.

In summary, ligand-enabled methylene $\text{C}(\text{sp}^3)\text{--H}$ activation was achieved through systematic design of the mutually-repulsive 2,6-dialkoxypyridine and 2-alkoxyquinoline ligands. Development of cross-coupling reactions of methylene $\text{C}(\text{sp}^3)\text{--H}$ bonds with organo-boron reagents and enantioselective methylene $\text{C}(\text{sp}^3)\text{--H}$ activation reactions are currently underway in our laboratory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Ligand-enabled methylene C(sp³)-H activation:

Scheme 1.
Methylene C(sp³)-H Bond Activation

Table 1

Ligand Screening^{a,b}

no ligand				
2% mono	L1 SM recovered	7% mono	9% mono	SM recovered
60% mono 16% di	9% mono	3% mono	28% mono 4% di	54% mono 42% di
L10 62% mono 12% di	L11 53% mono 47% di	L12 25% mono 75% di	L13 41% mono 59% di	

^aConditions: 0.2 mmol of substrate, 15 mol% Pd(TFA)₂, 30 mol% ligand, 4.0 equiv of p-Tol-I, 3.0 equiv of Ag₂CO₃, 1.2 equiv of K₂HPO₄, 0.5 mL of DCE, 120 °C, 24 h.

^bThe yield was determined by ¹H NMR analysis of the crude product using CH₂Br₂ as an internal standard, and GC/MS spectroscopic analysis for mono:di ratio.

Table 2

Arylation of Methylene C(sp³)-H Bond^{a, b, c}

^aConditions: 0.2 mmol of substrate, 10 mol% Pd(TFA)₂, 20 mol% ligand, 3.0 equiv of Ar-I, 2.0 equiv of Ag₂CO₃, 1.2 equiv of K₂HPO₄, 1.0 mL of hexane, 110 °C, 24 h.

^bIsolated yields.

^cDiastereomeric ratio was determined by the ¹H NMR analysis of the crude NMR and verified by GC/MS spectroscopic analysis.