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Ligand-Enabled Methylene C(sp^3)−H Bond Activation with a Pd(II) Catalyst

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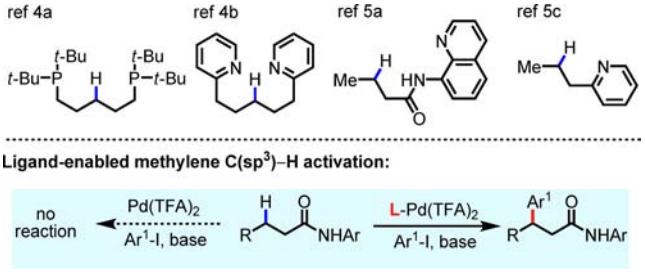
Supporting Information

ABSTRACT: Pd(II) insertion into β-methylene C(sp^3)−H bonds was enabled by a mutually repulsive and electron-rich quinoline ligand. Ligand tuning 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(sp^3)−H bonds.

Development of synthetic transformations based on transition-metal-catalyzed functionalization of C(sp^3)−H bonds continues to attract intensive efforts.[1,2] Our laboratory recently demonstrated that a weakly coordinating *N*-arylamide (CONHAr) moiety serves as a powerful auxiliary to effect a diverse array of Pd-catalyzed C(sp^3)−H functionalization reactions of aliphatic acids.[3] However, this auxiliary and others[1] developed in our laboratory are not capable of activating methylene C(sp^3)−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]

Scheme 1. Methylene C(sp^3)−H Bond Activation

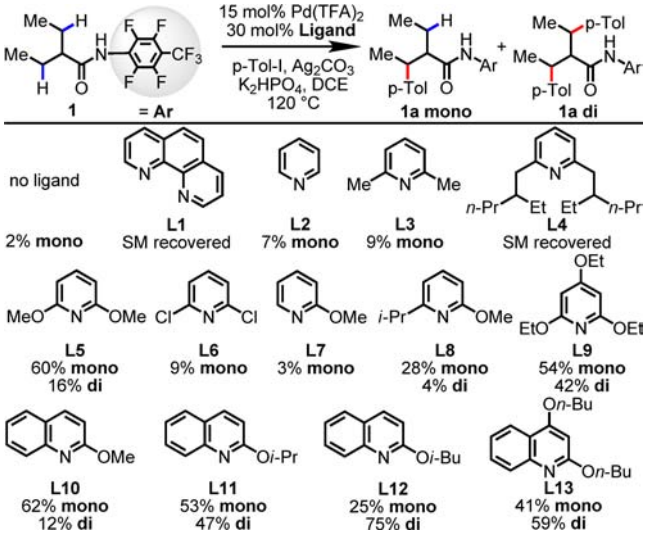


Encouraged by the observed ligand acceleration in a number of Pd(II)-catalyzed C(sp^2)−H activation reactions,[8] we focused our efforts on developing ligands that can promote β-methylene C(sp^3)−H activation using the weakly coordinating *N*-arylamide auxiliary. Herein we report the first example of ligand-enabled *N*-arylamide-directed Pd(II)-catalyzed arylation of acyclic and cyclic β-methylene C(sp^3)−H bonds (Scheme 1).

While ligand-promoted aryl C(sp^2)−H activation reactions with Pd(II) catalysts have been developed in recent years,[8,9] ligand scaffolds that facilitate C(sp^3)−H activation are rare.[3a,e,7] Methylene C−H bonds are significantly more resistant to Pd insertion than primary C−H bonds because they are more sterically hindered.[1] Furthermore, following the methylene C(sp^3)−H cleavage step to form the cyclopalladation complex, undesired β-hydride elimination could occur as a result of the presence of γ-C−H bonds adjacent to the Pd center, which could outcompete the sluggish reductive elimination pathway leading to the formation of the desired C(sp^3)−C bond. Therefore, we decided to develop a ligand to provide a solution to this significant challenge.

Since acidic *N*-arylamides has been demonstrated to be versatile auxiliaries for alkyl C(sp^3)−H activation, a ligand that strongly coordinates with the 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 catalysts in a singly bound fashion and also allows the coordination of electron-deficient arenes,[9b] we focused on a pyridine-based ligand scaffold. Systematic ligand screening using Pd(II)-catalyzed arylation with *p*-iodotoluene (*p*-Tol−I) as a platform was carried out (Table 1). In the absence of ligand, substrate **1** was treated with 15 mol % Pd(TFA)$_2$, 4.0 equiv of *p*-Tol−I, 2.5 equiv of Ag_2CO_3, and 1.2 equiv of

Table 1. Ligand Screening[a,b]



[a]Conditions: 0.2 mmol of substrate, 15 mol % Pd(TFA)$_2$, 30 mol % ligand, 4.0 equiv of *p*-Tol−I, 3.0 equiv of Ag_2CO_3, 1.2 equiv of K_2HPO_4, 0.5 mL of DCE, 120 °C, 24 h. [b]The yield was determined by ^{1}H NMR analysis of the crude product using CH_2Br_2 as an internal standard, and GC/MS analysis was used to determine the mono:di ratio.

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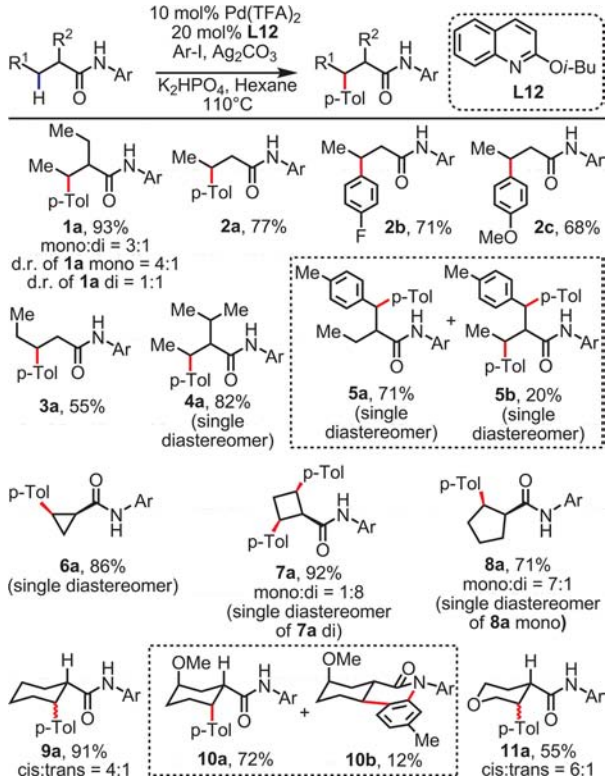
K_2HPO_4 in 1,2-dichloroethane (DCE) at 120 °C for 24 h and gave a <2% yield of the monoarylated product **1a** based on ^{1}H NMR and GC/MS analyses. Interestingly, a slight increase in the product yield to 7% was observed when 0.3 equiv of pyridine (**L2**) was added to the reaction mixture. To increase the sterics of the ligand, we screened 2,6-disubstituted pyridines for the methylene C(sp^3)−H arylation reaction. 2,6-Dimethylpyridine (**L3**) gave a 9% yield of the monoarylated product, while more sterically hindered **L4** yielded no product. However, we were delighted to find that 2,6-dimethoxypyridine (**L5**) gave mono- and diarylated products in yields of 60 and 16%, respectively, suggesting that the electronic properties of the pyridine are crucial. The diastereotopic ratio (dr) values of products **1a mono** and **1a di** were determined to be 4:1 and 1:1, respectively, based on ^{1}H NMR and GC/MS analyses. The dr values were not affected to an appreciable extent by varying the ligand. 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 suggested 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 a 96% combined yield of the products (mono:di = 1.3:1). We also found 2-methoxyquinoline (**L10**) to be effective, affording a 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 (Table 2). In addition, further optimization of the reaction conditions was carried out, and hexane was found to be the optimal solvent, as it suppressed the homocoupling of *p*-Tol−I. As a result, the Pd loading and reaction temperature could be lowered to 10 mol % and 110 °C, respectively (see the Supporting Information). Product **1a** was obtained as a mixture of mono- and diarylation products in 3:1 ratio; the monosubstituted product was isolated as a mixture of diastereomers (dr = 4:1). Amide substrates **2** and **3** derived from butanoic and pentanoic acids were arylated to give the products in yields of 77 and 55%, respectively. Substrate **2** could also be arylated using 1-iodo-4-methoxybenzene and 1-fluoro-4-iodobenzene to give **2b** and **2c** in yields of 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(sp^3)−H bond remaining intact. Substrate **5** possesses benzylic and aliphatic methylene C(sp^3)−H bonds that could both be arylated. We found that arylation of the benzylic C(sp^3)−H bond took place predominantly, giving **5a** as the major product in 71% yield (dr = 7:1). The diarylated 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 monoarylated 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 an 18% yield of **6a** was obtained in the absence of **L12**. Cyclobutyl substrate **7** was diarylated to give **7a** as the major product as a single diastereomer. For cyclopentyl, cyclohexyl, and pyran substrates (**8**−**11**), the corresponding monoarylation products were isolated as the major products. **9a** was obtained as a mixture of cis- and trans-substituted products in a 4:1 ratio; a trace amount of diarylated product was observed by ^{1}H NMR analysis. For substrate **10**, δ-lactam **10b** as a side product was also formed in 12% yield via Pd-mediated *o*-C−H amidation of the trans-arylated product. Arylation of tetrahydro-2*H*-pyran-4-carboxamide **11** gave a mixture of cis- and trans-arylated products **11a** in a 6:1 ratio.

Table 2. Arylation of Methylene C(sp^3)−H Bonds[a,b,c]



[a]Conditions: 0.2 mmol of substrate, 10 mol % Pd(TFA)$_2$, 20 mol % ligand, 3.0 equiv of Ar−I, 2.0 equiv of Ag_2CO_3, 1.2 equiv of K_2HPO_4, 1.0 mL of hexane, 110 °C, 24 h. [b]Isolated yields are shown. [c]Diastereomeric ratios were determined by ^{1}H NMR analysis of the crude product and verified by GC/MS analysis.

In summary, ligand-enabled methylene C(sp^3)−H activation has been achieved through systematic design of the mutually repulsive 2,6-dialkoxypyridine and 2-alkoxyquinoline ligands. The development of cross-coupling reactions of methylene C(sp^3)−H bonds with organoboron reagents and enantioselective methylene C(sp^3)−H activation reactions are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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