C–H Amination

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Ligand-Promoted *ortho*-C–H Amination with Pd Catalysts**

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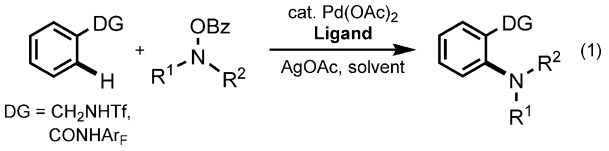
Abstract: *2,4,6-Trimethoxypyridine is identified as an efficient ligand for promoting a Pd-catalyzed ortho-C–H amination of both benzamides and triflyl-protected benzylamines. This finding provides guidance for the development of ligands that can improve or enable Pd^{II}-catalyzed C_{sp^2}–H activation reactions directed by weakly coordinating functional groups.*

Catalytic C–H amination has the potential to become a complementary tool for C–N bond forming reaction when the aryl halides are not readily available in a synthetic sequence.[1] Several catalytic systems have been reported.[2–16] However, the limited substrate scope and poor efficiency of these reactions have prevented their synthetic applications.[1] Based on the impact of ligand development on the Buchwald–Hartwig amination reaction,[17] it is reasonable to assume that identification of a ligand scaffold for promoting catalytic C–H amination could partially overcome the current limitations. Herein we report the development of a ligand that significantly promotes Pd^{II}-catalyzed C–H amination reactions of two distinct classes of substrates: triflyl-protected benzylamines and benzamides, thus demonstrating the feasibility of using a ligand to promote or enable directed C_{sp^2}–H amination [Eq. (1)].



(1)

To establish a platform for ligand development, we selected triflyl-protected benzylamine **1a** as the substrate. Pd-catalyzed C–H amination of **1a** under our previously reported conditions[6a] gave the amination product **2a** in less than 10% yield. We further optimized reaction parameters for this particular substrate by carrying out extensive screening of Pd sources, solvents, and bases to obtain the optimum yield (see the Supporting Information (SI), Tables S1–S3). Thus, stirring **1a** with *O*-benzoyl hydroxylmorpholine (2 equiv) in the presence of $Pd(OAc)_2$ (10 mol%), AgOAc (2 equiv), K_3PO_4 (1 equiv), and 4 Å molecular sieves (40 mg) in C_6F_6 at 130°C for 24 h afforded the product **2a** in 24% yield.

With this initial result in hand, we set out to search for ligands that can significantly improve this reaction. Mono-protected amino acid ligands (MPAA) have been shown to accelerate C_{sp^2}–H activation,[18] whereas pyridine and quinoline ligands have been shown to promote C_{sp^3}–H activation.[19] These observations prompted us to test whether these types of ligands can be modified to improve this C_{sp^2}–H amination reaction. Whereas MPAA ligands are found to have negligible effects, pyridine and quinoline-based ligands significantly improve this reaction (Table 1). The use of 2,4,6-trimethoxypyridine **L12** increased the yield to 58%.

With the optimal ligand **L12** identified, we performed the second round of optimizations of the reaction parameters (see SI, Tables S4–S6) and found that the use of binary bases (2 equiv Na_2CO_3, 1 equiv K_3PO_4) improved the yield to 85%.

Although the use of binary bases afforded significant improvement, the removal of **L12** from these reaction conditions reduced the yield to 31%, confirming the predominant effect of the ligand. Notably, this ligand-promoted amination reaction also proceeds without AgOAc to give **2a** in 69% yield (see Table S6 in SI).

A wide range of benzylamine substrates is compatible with this amination protocol (Table 2). Electron-donating groups at the *ortho*, *meta* and *para* positions are all well tolerated (**2a**–**2f**). Excellent monoselectivity is achieved with all substrates including the nonsubstituted arene **2g**. Electron-withdrawing fluoro, chloro, bromo and trifluoromethyl groups are all compatible with this reaction. We also examined the scope of the amine donors using substrate **1a** (Table 3). Both piperidine and piperazine donors coupled well to give the desired amination product in good yields (**2p**–**2r**). A dialkylamine unit can also be installed through this amination reaction (**2s**, **2t**). Based on the reaction conditions, a tentative catalytic cycle for this reaction can be proposed (Figure 1). Although the triflyl-protected amine could be potentially deprotonated and coordinate with the Pd^{II} center as a neutral sulfonimidate,[20] a precursor **I** coordinated to the anionic triflamide and the pyridine ligand is proposed. Subsequent C–H activation occurs to give intermediate **II** which is then oxidized to the Pd^{IV} species **III** by the aminating reagent R^1R^2NOBz. C–N reductive elimination from **III** affords the amination product as well as regenerates the Pd^{II}

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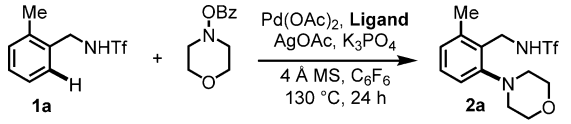
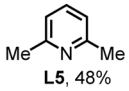
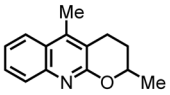
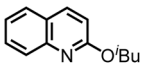
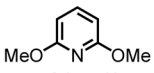
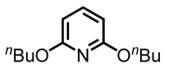
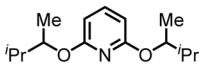
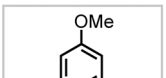
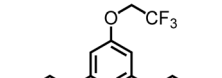
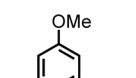
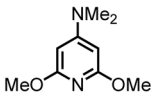
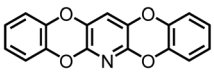
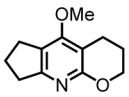
Table 1: Ligand optimization.[a,b]



no ligand 24%	Boc-Phe-OH **L1**, 27%	Boc-Ile-OH **L2**, 20%
Ac-Val-OH **L3**, 24%	 **L4**, 40%	 **L5**, 48%
 **L6**, 21%	 **L7**, 36%	 **L8**, 37%
 **L9**, 52%	 **L10**, 48%	 **L11**, 52%
 **L12**, 58%	 **L13**, 54%	 **L14**, 51%
 **L15**, 41%	 **L16**, 47%	 **L17**, 39%

[a] Reaction conditions: **1a** (0.1 mmol), *O*-benzoyl hydroxylmorpholine (2 equiv), $Pd(OAc)_2$ (10 mol%), ligand (20 mol%), AgOAc (2 equiv), K_3PO_4 (1 equiv), 4 Å MS (40 mg), C_6F_6 (1 mL), 130°C, 24 h. [b] The yield was determined by ^1H NMR analysis of the crude product using dibromomethane as the internal standard.

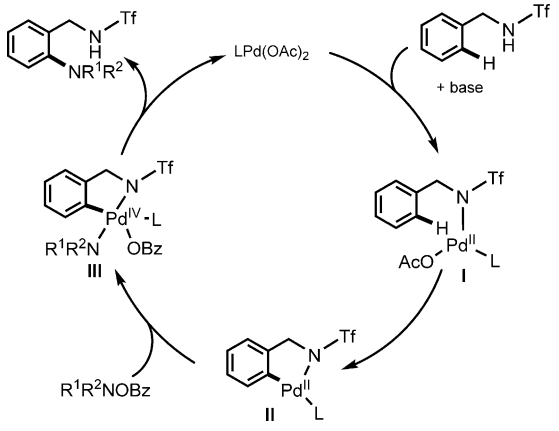
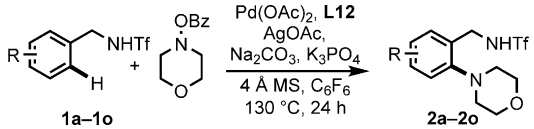
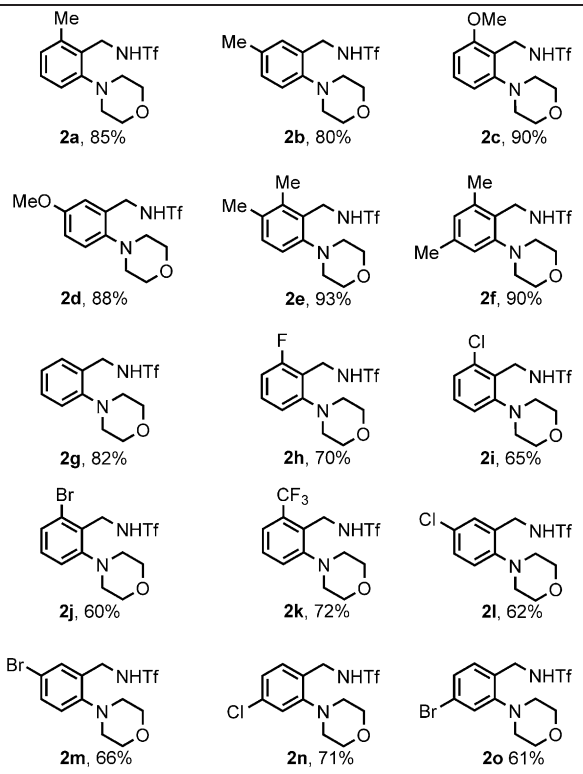


Figure 1. Catalytic cycle for ligand-promoted C–H amination.

catalyst. It is conceivable that the coordinated trimethoxypyridine ligand promotes both the oxidation step (from **II** to **III**) and the reductive elimination step. Based on this catalytic cycle, the observed enhancing effect of AgOAc (typically increases the yield of the amination by about 15%) can be attributed to the reoxidation of Pd^0 generated by off-cycle pathways.

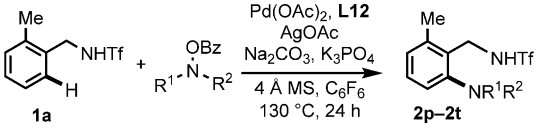
Table 2: Scope of triflyl-protected benzylamines.[a,b]

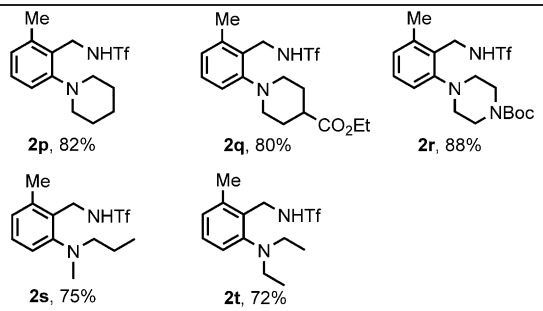




[a] Reaction conditions: **1a-1o** (0.1 mmol), *O*-benzoyl hydroxylmorpholine (2 equiv), $Pd(OAc)_2$ (10 mol%), **L12** (20 mol%), AgOAc (2 equiv), Na_2CO_3 (2 equiv), K_3PO_4 (1 equiv), 4 Å MS (40 mg), C_6F_6 (1 mL), 130°C, 24 h. [b] Yields of isolated products.

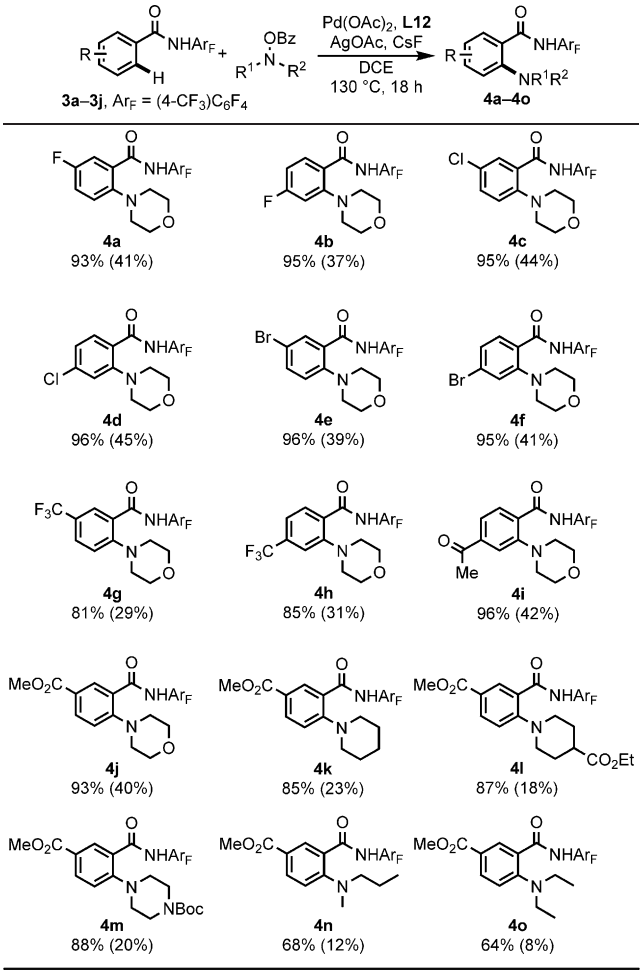
Table 3: Scope of amine donors for substrate **1a**.[a,b]



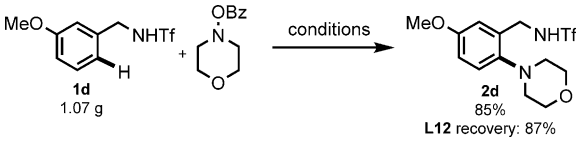


[a] Reaction conditions: **1a** (0.1 mmol), *O*-benzoyl hydroxylmorpholine (2 equiv), $Pd(OAc)_2$ (10 mol%), **L12** (20 mol%), AgOAc (2 equiv), Na_2CO_3 (2 equiv), K_3PO_4 (1 equiv), 4 Å MS (40 mg), C_6F_6 (1 mL), 130°C, 24 h. [b] Yields of isolated products.

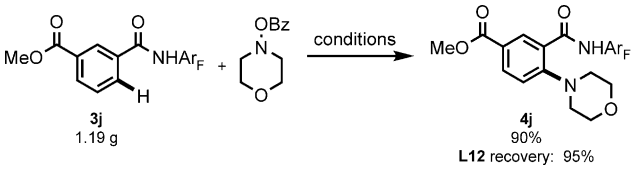
Table 4: Ligand-promoted amination of benzamides.[a,b,c]



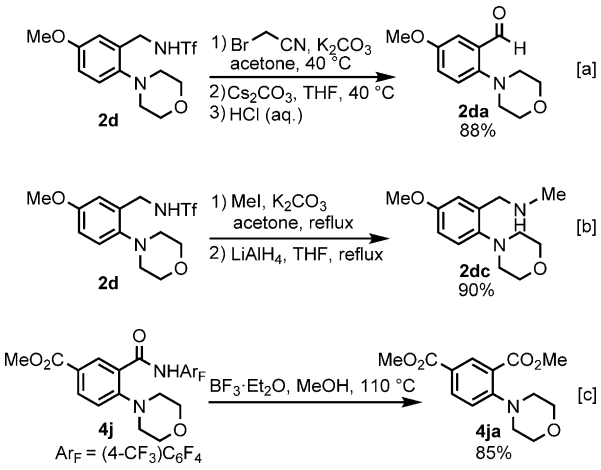
[a] Reaction conditions: **3a**–**3j** (0.1 mmol), *O*-benzoyl hydroxylamine (2 equiv), $Pd(OAc)_2$ (10 mol%), **L12** (20 mol%), AgOAc (1 equiv), CsF (2 equiv), DCE (1 mL), 130°C, 18 h. [b] Yields of isolated products. [c] Yield without ligand in parentheses.



Scheme 1. Amination of triflyl-protected benzylamine on a gram scale. Reaction conditions: **1d** (4 mmol), *O*-benzoyl hydroxylmorpholine (2 equiv), $Pd(OAc)_2$ (10 mol%), **L12** (20 mol%), AgOAc (2 equiv), Na_2CO_3 (2 equiv), K_3PO_4 (1 equiv), 4 Å MS (1.60 g), C_6F_6 (40 mL), 130°C, 24 h.



Scheme 2. Amination of benzamide on a gram scale. Reaction conditions: **3j** (3 mmol), *O*-benzoyl hydroxylmorpholine (2 equiv), $Pd(OAc)_2$ (10 mol%), **L12** (20 mol%), AgOAc (1 equiv), CsF (2 equiv), DCE (30 mL), 130°C, 18 h. DCE = dichloroethane, $Ar_F = (4\text{-}CF_3)C_6F_4$.



Scheme 3. Removal of the auxiliaries. [a] 1) **2d** (0.5 mmol), $BrCH_2CN$ (2.4 equiv), K_2CO_3 (2.4 equiv), acetone (5 mL), 40°C, 24 h; 2) Cs_2CO_3 (2.4 equiv), THF (5 mL), 40°C, 24 h; 3) 1 M HCl (aq) (5 mL), reflux, 2 h. [b] 1) **2d** (0.2 mmol), MeI (3 equiv), K_2CO_3 (1.5 equiv), acetone (5 mL), reflux, 12 h; 2) $LiAlH_4$ (2 equiv), THF (5 mL), reflux, 20 h. [c] **4j** (0.2 mmol), $BF_3{\cdot}Et_2O$ (10 equiv), MeOH (5 mL), 110°C, 48 h.

The ligand effect is further demonstrated in the *ortho*-amination of benzamides (Table 4). Since benzamides containing electron-donating substituents worked well under previously reported ligandless conditions,[6a] we focused on the less effective electron-deficient arenes and compared the reactions with and without ligand in each case. The use of ligand **L12** significantly improved the reaction to give the *ortho*-aminated products in excellent yields (**4a**–**4i**). In light of the abundance of the 1,3-diacid and the potential utility of the *ortho*-aminated products for preparing polyfunctionalized arenes, we coupled **3j** (derived from 1,3-diacid) with various alkylamine donors. Ligand **L12** is shown to be crucial in all cases for obtaining good yields (**4j**–**4o**). Considering the distinct structures of triflyl-protected benzylamines and benzamides, these results demonstrate the versatility of ligand **L12**.

The amination of both the triflyl-protected benzylamine and benzamide substrates can be easily run on gram scales to give the desired products and the recovered ligands in excellent yields (Schemes 1 and 2). The auxiliaries can also be removed under various conditions to give different synthetically useful products (Scheme 3).

In conclusion, we have identified the first ligand to promote the C_{sp^2}–H amination reaction of two distinct classes of substrates derived from benzylamines and benzoic acids. Mechanistic investigations of the precise role of this ligand and further optimizations of the ligand structure to improve the scope and efficiency of C–H amination reactions are under way in our laboratory.

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