C–H Activation

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Enantioselective *ortho*-C–H Cross-Coupling of Diarylmethylamines with Organoborons

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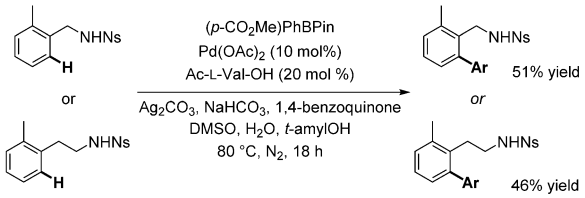
Abstract: *The commonly used para-nitrobenzenesulfonyl (nosyl) protecting group is employed to direct the C–H activation of amines for the first time. An enantioselective ortho-C–H cross-coupling between nosyl-protected diarylmethylamines and arylboronic acid pinacol esters has been achieved utilizing chiral mono-N-protected amino acid (MPAA) ligands as a promoter.*

Despite extensive efforts to develop C–H activation reactions of broadly useful substrates using weak coordination,[1] design of practical directing groups for amines has been met with limited success. While triflyl-protected amines have demonstrated a relatively broad scope of both substrates (benzylamines, phenylethylamines, and propyl amines) and transformations (iodination, olefination, fluorination, and amination),[2] the use of expensive and corrosive triflic anhydride for installation of the triflyl moiety, as well as the relatively harsh procedures required for removal,[2a,c] limits its appeal as a synthetically useful directing group. Alternative two-step deprotection conditions have been developed, but have proven incompatible with compounds bearing acidic α-hydrogens due to the potential for deprotonation, which could lead to a variety of decomposition pathways.[2e–g] The recent success in the development of enantioselective iodinations of triflyl-protected amines by desymmetrization and kinetic resolution[2e,f] has provided us incentive to seek a practical directing group for amine substrates to allow for a rapid synthesis of valuable chiral amine scaffolds.[3] Although there have been a few reports of Pd^{II}-catalyzed C–H arylation reactions directed by free[4] and tertiary amines,[5] the scope of these transformations is limited due to the strongly acidic conditions required,[4a,b] and the use of directing groups that cannot be easily removed.[5] The development of C–H activation reactions of amines employing commonly used synthetic protecting groups is a prerequisite for broad applications of C–H activation in amine synthesis. To the best of our knowledge there are no known protocols for the directed C–H functionalization of the commonly employed nosyl-protected amine (nosyl = *para*-nitrobenzenesulfonyl), due to a lack of reactivity of the nosylamide under a variety of previously developed C–H activation conditions.[6] Herein, we report a ligand-promoted enantioselective *ortho*-C–H coupling of nosyl-protected diarylmethylamines with arylboronic acid pinacol esters, adding a valuable example to the intensively pursued development of enantioselective C–H activation reactions.[7,8] The newly established reactivity of nosylamides also paves the way for the further development of practical C–H activation transformations of amines.

As illustrated in Scheme 1, we initiated our studies by attempting the nosylamide-directed C_{sp^2}–H arylation of



Scheme 1. Nosyl-directed C_{sp^2}–H activation.

simple benzyl- and phenethylamines. From these preliminary experiments, we were delighted to find that nosyl-protected amines indeed proved to be viable directing groups for C–H activation. Similar to the triflamide-directed C–H coupling,[2g] the use of $NaHCO_3$ is required to deprotonate the sulfonamide for coordination. Ag_2CO_3 acts both as oxidant for the reoxidation of Pd^0 and as promoter for the coupling step. DMSO prevents Pd^0 species from aggregation. Since chiral diarylmethylamines are known to be medicinally important scaffolds, with *ortho*-substituted diarylamines in particular having been known to display a range of bioactivity including γ-secretase modulation and HPV inhibition (Figure 1),[9,10] we

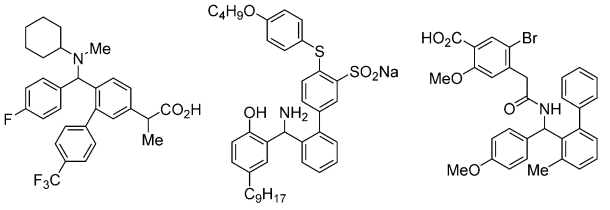


Figure 1. Bioactive *ortho*-aryl diarylmethylamines.

redirected our focus toward the enantioselective cross-coupling of prochiral diarylmethylamine **1** with *para*-methoxycarbonylphenylboronic acid pinacol ester.

We were pleased to find that inclusion of the MPAA ligand Ac-Ala-OH afforded the desired arylated product **2** in 62% yield and 76% *ee*. After an extensive survey of readily

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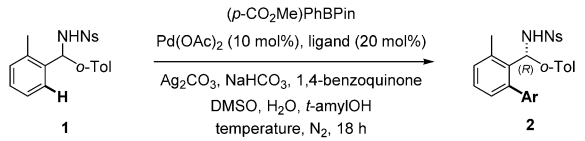
Table 1: Ligand evaluation.[a]



Entry	Ligand	*T* [°C]	Yield [%][b]	*ee* [%][c]
1	Ac-L-Val-OH	100	62	76
2	Boc-L-Val-OH	100	66	84
3	Fmoc-L-Val-OH	100	65	89
4	Troc-L-Val-OH	100	43	88
5	Boc-L-Leu-OH	100	71	90
6	Boc-L-Phe-OH	100	67	87
7	Fmoc-L-Ala-OH	100	63	89
8	Fmoc-L-Val-OH	80	63	91
9	Fmoc-L-Val-NHOMe	80	83	96
10[d]	Fmoc-L-Leu-NHOMe	80	90	96

[a] Reaction conditions: 0.1 mmol of substrate, 2 equiv ArBPin, 0.1 equiv $Pd(OAc)_2$, 0.2 equiv ligand, 2.5 equiv Ag_2CO_3, 6 equiv $NaHCO_3$, 0.5 equiv 1,4-benzoquinone, 10 μL H_2O, 2.8 μL DMSO, 1 mL *t*-amylOH. [b] Yield determined by ^1H NMR analysis using 1,3-benzodioxole as an internal standard. [c] Enantioselectivity determined by HPLC analysis on a chiral stationary phase. [d] 0.15 equiv ligand.

available MPAA ligands (see the Supporting Information), we quickly narrowed down our options to carbamate-protected, aliphatic amino acids. As shown in Table 1, Fmoc-Val-OH provided **2** in 65% yield and 89% *ee* (entry 3). Lower temperatures (80 °C) could also be employed without sacrificing reaction efficiency (entry 8, 63% yield, 91% *ee*). In addition, by substituting the acid moiety of the ligand with an *N*-methoxyamide, a noticeable boost in both yield and enantioselectivity was observed (entry 9, 83% yield, 96% *ee*). It was quickly found that Fmoc-Leu-NHOMe proved to be the optimal ligand for this enantioselective cross-coupling protocol (entry 10, 90% yield, 96% *ee*).

The absolute configuration of arylated product **2** was determined by X-ray crystallography (Figure 2). The

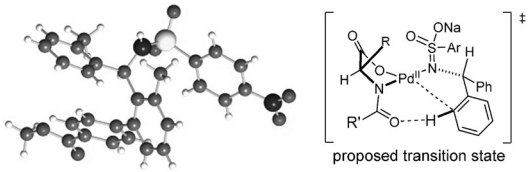
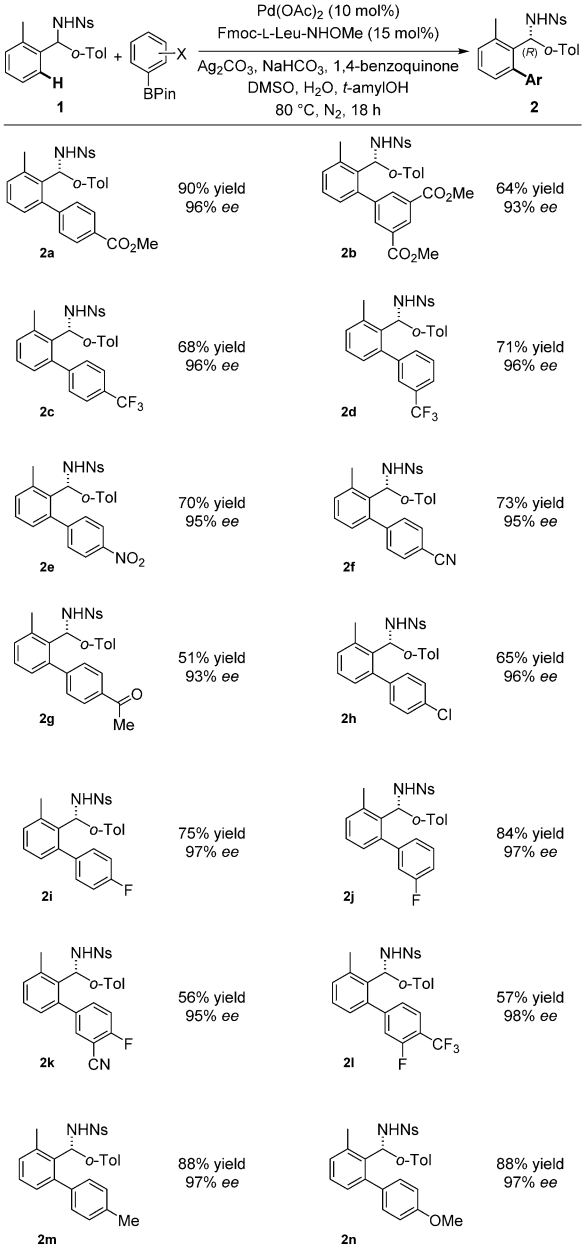


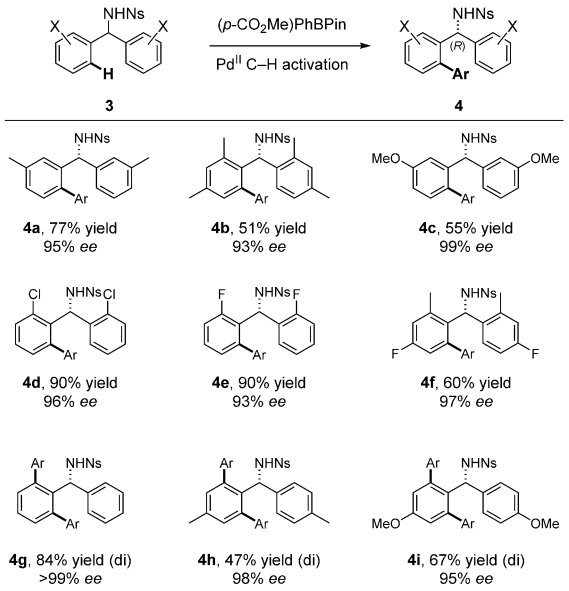
Figure 2. X-ray crystal structure of (*R*)-**2a**.



Scheme 2. Arylboronic acid pinacol ester scope. [a] Reaction conditions: 0.1 mmol of substrate, 2 equiv ArBPin, 0.1 equiv $Pd(OAc)_2$, 0.15 equiv ligand, 2.5 equiv Ag_2CO_3, 6 equiv $NaHCO_3$, 0.5 equiv 1,4-benzoquinone, 10 μL H_2O, 2.8 μL DMSO, 1 mL *t*-amylOH. [b] Yield of isolated product. [c] Enantioselectivity determined by HPLC analysis on a chiral stationary phase.

observed enantioselectivity is rationalized with a stereochemical model analogous to one previously proposed,[2e,11] wherein the deprotonated anionic sulfonamide coordinates to the palladium(II) center through the imine moiety, facilitating selective C–H cleavage.

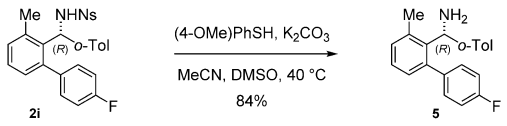
After elucidation of the optimized reaction conditions, we next investigated the scope of the arylboronic acid coupling partner. As demonstrated in Scheme 2, a variety of arylboron reagents coupled smoothly to provide arylated products with excellent levels of enantioselectivity. Trifluoromethyl-, nitro-, and nitrile-substituted arylboron compounds afforded the desired products in good yield (**2c–f**; 68–73% yield, 95–96% *ee*), and both esters and ketones proved stable under the reaction conditions (**2a, 2b, 2g**; 64–90% yield, 93–96% *ee*). Furthermore, halogen substitution was also well tolerated, as evidenced by arylated products **2h–j** bearing chlorine and fluorine atoms (65–84% yield, 96–97% *ee*). Electron-rich arylboronic acid pinacol esters also performed well in this reaction (**2m, 2n**; both 88% yield, 97% *ee*), as did disubstituted electron-deficient arylboron reagents (**2b, 2k, 2l**).



Scheme 3. Diarylmethylamine substrate scope. [a] Reaction conditions: 0.1 mmol of substrate, 2 equiv ArBPin, 0.1 equiv $Pd(OAc)_2$, 0.15 equiv Fmoc-L-Leu-NHOMe, 2.5 equiv Ag_2CO_3, 6 equiv $NaHCO_3$, 0.5 equiv 1,4-benzoquinone, 10 μL H_2O, 2.8 μL DMSO, 1 mL *t*-amylOH. [b] Yield of isolated product. [c] Enantioselectivity determined by HPLC analysis on a chiral stationary phase.

We also examined the scope of the diarylmethylamines (Scheme 3). Substitution on the diarylmethylamine was well tolerated, allowing for both electron-rich and electron-deficient substrates to readily undergo cross-coupling with high levels of enantioselectivity. Halogenated diarylmethylamines also underwent coupling smoothly (entries **4d**–**4f**, 60–90% yield, 93–97% *ee*). Both *ortho*- and *meta*-substituted substrates provided monoarylated products; however, unsubstituted or *para*-substituted substrates led predominantly to diarylation (entries **4g**–**4i**, 47–84% yield of diarylated products).

To demonstrate the synthetic utility of the *para*-nitrobenzenesulfonamide directing group, we next sought to remove the nosyl moiety from the arylated product under mildly basic conditions with gentle heating.[12] As illustrated in Scheme 4, deprotection proceeded smoothly in the presence of *para*-methoxythiophenol and potassium carbonate at 40 °C to afford the corresponding free amine **5** in 84% yield.



Scheme 4. Deprotection of nitrobenzenesulfonyl protecting group.

In conclusion, we have developed an enantioselective cross-coupling of diarylmethylamine C_{sp^2}–H bonds and arylboronic acid pinacol esters, using chiral amino acids and *N*-methoxyamides to induce asymmetry. Notably, this protocol exploits the synthetically practical and easily deprotected *para*-nitrobenzenesulfonamide as a directing group. Further development of C–H functionalizations directed by nosyl-protected amines and other widely used protecting groups is currently underway in our laboratory.

Experimental Section

General procedure for the enantioselective arylation of nosyl-protected diarylmethylamines: nosylamide substrate (0.1 mmol), aryl boronic acid pinacol ester (2 equiv), $Pd(OAc)_2$ (0.1 equiv), amino acid ligand (0.15 equiv), $NaHCO_3$ (6 equiv), Ag_2CO_3 (2 equiv), and 1,4-benzoquinone (0.5 equiv) were added to a sealable Schlenk tube, and a solution of H_2O (10 μL) and DMSO (2.8 μL) in *t*-AmOH (1 mL), and the reaction vessel was evacuated and backfilled with N_2 (3×). The Schlenk tube was sealed, and the mixture was stirred vigorously at 80 °C. After 18 h, the reaction was cooled to room temperature, EtOAc was added (5 mL), and the reaction was filtered through a pad of Celite over a plug of silica gel, and eluted with EtOAc (30 mL). The crude solution was concentrated in vacuo, and the residue purified by preparative thin layer chromatography to produce the corresponding chiral amines as white or pale yellow solids.

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