

Palladium-Catalyzed Benzylic Addition of 2-Methyl Azaarenes to *N*-Sulfonyl Aldimines via C–H Bond Activation

Bo Qian, Shengmei Guo, Jianping Shao, Qiming Zhu, Lei Yang, Chungu Xia,* and Hanmin Huang*
State Key Laboratory for Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, 18 Tianshui Middle Road, Lanzhou 730000, China

Received November 30, 2009; E-mail: hmhuang@licp.cas.cn

Transition-metal-catalyzed addition of organometallic compounds to imines is an attractive carbon–carbon bond-forming process for the synthesis of amines in which transmetalation is involved for the generation of the R–M (M = Rh, Pd) intermediate as the key species in furnishing the subsequent nucleophilic addition.¹ Recent studies have demonstrated that direct C–H activation by transition metals is an alternative method for generating R–M intermediates, which have been applied under versatile reaction conditions to achieve new C–X (X = C, N, O, etc.) bond formation.² We reasoned that if this R–M species produced by C–H activation could react with imines, then transition-metal-catalyzed nucleophilic addition of simple substrates to imines would be realized.³

As a reactive intermediate, **2** is known to undergo synthetically useful transformations and has previously been generated by oxidative addition of corresponding benzyl halides to Pd(0) or by Pd-catalyzed C–C bond cleavage.⁴ For example, Oshima and co-workers recently described an ingenious method for generating such a moiety via Pd-catalyzed C–C bond cleavage of pyridyl alcohol and its subsequent use in coupling reactions (Scheme 1).^{4c} Recent elegant studies⁵ of the direct C–H functionalization of azaarenes reported by Fagnou, Hiyama, Yu, Chang, Sames, Sanford, and others have prompted us to envision that this kind of moiety **2** might also be produced from **1** by transition-metal-catalyzed C–H bond cleavage. Herein, we report an efficient and atom-economical protocol for the direct benzylic addition of 2-methyl azaarenes to imines via sp³ C–H activation by palladium catalysis under neutral conditions.

To test the viability of our hypothesis, 2,6-lutidine (**1a**) was chosen as a model substrate to react with tosylimine **4a** derived from benzaldehyde, and the reaction was performed under an Ar atmosphere at 120 °C for 24 h. To our delight, the desired nucleophilic addition reaction proceeded smoothly in the presence of palladium catalyst (Table 1, entry 1).⁶ Screening of palladium sources revealed Pd(OAc)₂ as the most efficient catalyst, while other palladium precursors gave lower yields (Table 1, entries 2–7). A control experiment showed that no reaction occurred in the absence of Pd catalyst. With Pd(OAc)₂ as the catalyst, we went on to screen other reaction parameters. The reaction was found to proceed more efficiently in polar solvents than in nonpolar ones, and tetrahydrofuran (THF) was found to be the best solvent. Ligand screening showed that nitrogen-containing ligands were promising, and 1,10-phenanthroline (Phen) proved to be the best one, affording the highest yield (82%).

With the optimized reaction conditions, the scope of this reaction with various *N*-sulfonyl aldimines was explored (Table 2). The data in Table 2 show that the reactions of *N*-tosyl aldimines **4** bearing an electron-withdrawing or electron-neutral group at the ortho, meta, or para position of the phenyl ring proceeded smoothly to provide corresponding adducts **5aa–5ak** in 67–92% yield (Table 2, entries 1–11). It is noteworthy that halide substituents were tolerated, as this is advantageous for further transformations with transition-metal catalysis. However, difficulties were encountered when substrates containing an electron-donating group were employed (Table 2, entries 12–14); in contrast to the imines with electron-withdrawing substituents,

Scheme 1. Strategy for Transition-Metal-Catalyzed Addition of Nucleophiles to Imines

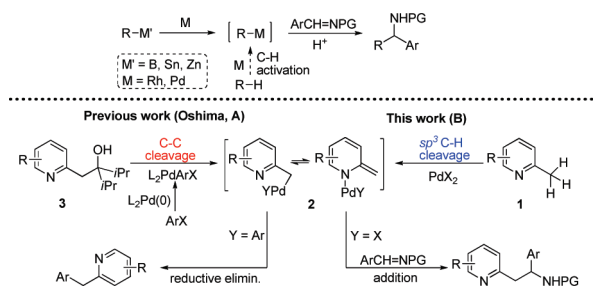


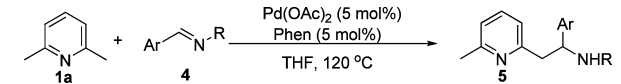
Table 1. Screening of Reaction Conditions^a

entry	[Pd]	ligand	solvent	yield (%) ^b
1	Pd(OAc) ₂	none	THF	70
2	PdCl ₂	none	THF	34
3	Pd(OCOCF ₃) ₂	none	THF	60
4	Pd(CH ₃ CN) ₂ Cl ₂	none	THF	24
5	Pd(PhCN) ₂ Cl ₂	none	THF	55
6	Pd(PPh ₃) ₂ Cl ₂	none	THF	11
7	Pd(DPPE)Cl ₂	none	THF	32
8	Pd(OAc) ₂	none	MTBE	68
9	Pd(OAc) ₂	none	CH ₂ Cl ₂	55
10	Pd(OAc) ₂	none	CH ₃ CN	48
11	Pd(OAc) ₂	none	toluene	41
12	Pd(OAc) ₂	none	dioxane	47
13	Pd(OAc) ₂	none	2-PrOH	60
14	Pd(OAc) ₂	bathocuprine	THF	62
15	Pd(OAc) ₂	1,10-phenanthroline	THF	82
16	Pd(OAc) ₂	2,2-bipyridine	THF	75

^a Reaction conditions: **1a** (0.75 mmol), **4a** (0.3 mmol), [Pd] (5 mol %), ligand (5 mol %), solvent (1.5 mL), 120 °C, 24 h. ^b Isolated yield.

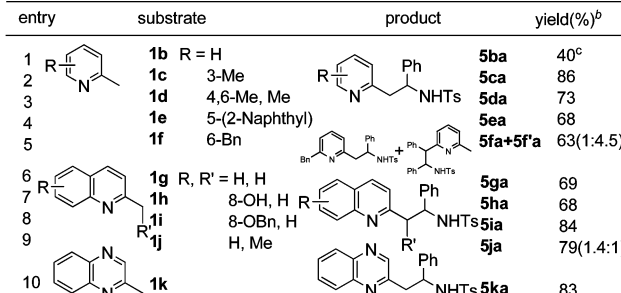
tutents, the desired amines were obtained in less than 50% yield under the same conditions; the relatively low yields probably reflect the lower electrophilicity of the imines. The lower reactivity of these substrates can be addressed by the introduction of electron-withdrawing groups on the *N*-protecting group. Thus, when a *p*-nitrobenzenesulfonyl (Ns) group instead of a tosyl group was used as the *N*-protecting group, **1a** was smoothly added to the corresponding imines to afford **5** in high yield (Table 2, entries 15 and 16). Alkenyl aldimines were compatible, but aliphatic tosyl imines were unreactive here.

The scope of 2-methyl azaarenes was also examined. Relative to 2,6-lutidine, the reaction of 2-picoline gave **5ba** in lower yield, but in the reactions of other substituted picolines, good to excellent yields were obtained. The quinolines **1g–j** were also compatible with the reaction, providing the corresponding adducts in 68–84% yield (Table 3, entries 6–9). Finally, the 2-methylquinoxaline **1k** proved to be a good substrate for this transformation, generating the adduct **5ka** in 83% yield.

Table 2. Substrate Scope of *N*-Sulfonyl Aldimines^a


entry	Ar	R	product	yield (%) ^b
1	C ₆ H ₅	Ts	5aa	82
2	4-ClC ₆ H ₄	Ts	5ab	92
3	2-ClC ₆ H ₄	Ts	5ac	91
4	3-ClC ₆ H ₄	Ts	5ad	67
5	4-BrC ₆ H ₄	Ts	5ae	85
6	2-BrC ₆ H ₄	Ts	5af	86
7	3-BrC ₆ H ₄	Ts	5ag	82
8	4-CF ₃ C ₆ H ₄	Ts	5ah	91
9	2,4-Cl ₂ C ₆ H ₃	Ts	5ai	81
10	2,6-Cl ₂ C ₆ H ₃	Ts	5aj	78
11	1-naphthyl	Ts	5ak	68
12	4-MeC ₆ H ₄	Ts	5al	47
13	4-MeOC ₆ H ₄	Ts	5am	41
14	2-MeOC ₆ H ₄	Ts	5an	42
15	4-MeC ₆ H ₄	Ns	5ao	73
16	2-BrC ₆ H ₄	Ns	5ap	77
17	(<i>E</i>)-PhCH=CH	Ts	5aq	57

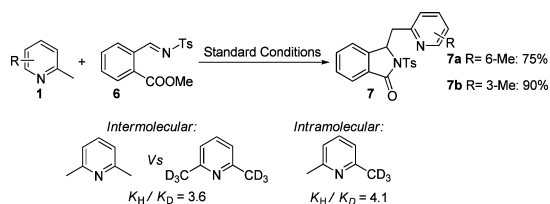
^a Reaction conditions: **1a** (0.75 mmol), **4** (0.3 mmol), Pd(OAc)₂ (5 mol %), Phen (5 mol %), THF (1.5 mL), 120 °C, 24–30 h. ^b Isolated yield.

Table 3. Substrate Scope of Heterocycles^a


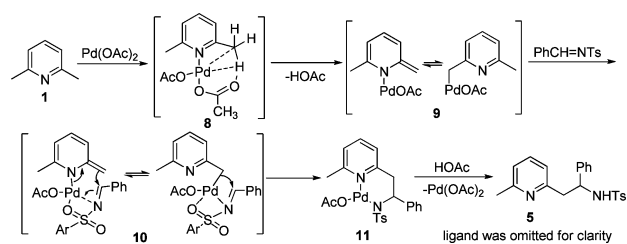
entry	substrate	product	yield(%) ^b
1	1b R = H	5ba	40 ^c
2	1c 3-Me	5ca	86
3	1d 4,6-Me, Me	5da	73
4	1e 5-(2-Naphthyl)	5ea	68
5	1f 6-Bn	5fa+5f'a	63(1:4.5) ^d
6	1g R, R' = H, H	5ga	69
7	1h 8-OH, H	5ha	68
8	1i 8-OBn, H	5ia	84
9	1j H, Me	5ja	79(1.4:1) ^e
10	1k	5ka	83

^a Reaction conditions: **1** (0.75 mmol), **4a** (0.3 mmol), Pd(OAc)₂ (5 mol %), Phen (5 mol %), THF (1.5 mL), 120 °C, 24 h. ^b Isolated yield. ^c Reaction time 36 h. ^d The **5fa/5f'a** ratio. ^e dr ratio.

As an interesting application of the present reaction, methyl 2-[(tosylimino)methyl]benzoate (**6**) was treated with 2-methyl-substituted pyridines under the standard conditions. The tandem benzylic addition and amidation occurred, giving the desired isoindolinones **7** in high yield; these were characterized by X-ray structural analysis. Isoindolinones are interesting structures found in many useful biologically active compounds.⁷



The kinetic isotope effects observed in both intermolecular ($k_H/k_D = 3.6$) and intramolecular ($k_H/k_D = 4.1$) competition experiments (see Supporting Information) are consistent with C–H cleavage being the rate-limiting step. On the basis of the experimental results, a plausible reaction pathway is outlined in Scheme 2. **1** is coordinated to Pd(OAc)₂ to form complex **8**, after which C–H bond cleavage might proceed via agostic three-center–two-electron interactions⁸ to form the intermediate **9**⁴ at elevated temperature, in which the acetate (OAc[−]) serves as an internal base. Intermediate **9** might be coordinated with imine **4**,

Scheme 2. Proposed Reaction Pathway

giving intermediate **10**,⁹ which would undergo nucleophilic addition to produce addition product **11**. Subsequent protolysis would form the desired product **5** and regenerate the Pd catalyst to complete the catalytic cycle.

In conclusion, we have developed a novel palladium-catalyzed addition of 2-methyl azaarenes to imines through C–H bond functionalization. This transformation represents a very efficient methodology for the synthesis of amines and thus opens a new way to access amines through C–H bond activation. Further studies to clearly understand the detailed mechanism as well as extrapolation of the reaction to the stereoselective synthesis of heterocycle-containing chiral amines are currently underway.

Acknowledgment. This work was supported by the Chinese Academy of Sciences and the NSFC (20802085, 20625308).

Supporting Information Available: Detailed experimental procedures, analytical data for all new compounds, and crystallographic data (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- (1) For reviews, see: (a) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169. (b) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829. (c) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069.
- (2) For reviews, see: (a) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. (b) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077. (c) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439. (d) Yu, J.-Q.; Giri, R.; Chen, X. *Org. Biomol. Chem.* **2006**, *4*, 4041. (e) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (f) Li, B.; Yang, S.; Shi, Z. *Synlett* **2008**, 949. (g) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094.
- (3) For Pd-catalyzed allylation of imines via allylic C–H activation, see: Aydin, J.; Szabó, K. J. *Org. Lett.* **2008**, *10*, 2881.
- (4) (a) Onishi, M.; Hiraki, K.; Maeda, K.; Itoh, T. *J. Organomet. Chem.* **1980**, *188*, 245. (b) Isobe, K.; Nakamura, Y.; Kawaguchi, S. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1802. (c) Niwa, T.; Yorimitsu, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 2643.
- (5) For selected examples, see: (a) Schipper, D. J.; Campeau, L.-C.; Fagnou, K. *Tetrahedron* **2009**, *65*, 3155. (b) Campeau, L.-C.; Shipper, D. J.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3266. (c) Nakao, Y.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2008**, *130*, 2448. (d) Kanyiva, K. S.; Nakao, Y.; Hiyama, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 8872. (e) Cho, S. H.; Hwang, S. J.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 9254. (f) Chen, X.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 12634. (g) Godula, K.; Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 3648. (h) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330. (i) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 5332. (j) Wu, J.; Cui, X.; Chen, L.; Jiang, G.; Wu, Y. *J. Am. Chem. Soc.* **2009**, *131*, 13888. (k) Larivée, A.; Mousseau, J. J.; Charette, A. B. *J. Am. Chem. Soc.* **2008**, *130*, 52. (l) Mousseau, J. J.; Larivée, A.; Charette, A. B. *Org. Lett.* **2008**, *10*, 1641. (m) Kakiuchi, F.; Tsuchiya, K.; Matsumoto, M.; Mizushima, E.; Chatani, N. *J. Am. Chem. Soc.* **2004**, *126*, 12792. (n) Murakami, M.; Hori, S. *J. Am. Chem. Soc.* **2003**, *125*, 4720.
- (6) The *N*-oxide of 2,6-lutidine was unreactive under these conditions.
- (7) Zhu, Q.; Huang, H.; Shi, D.; Shen, Z.; Xia, C. *Org. Lett.* **2009**, *11*, 4536, and references therein.
- (8) (a) Brookhart, M.; Green, M. L. H.; Parkin, G. *Proc. Natl. Acad. Sci. U.S.A.* **2007**, *104*, 6908. (b) Lafrance, M.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 14570. (c) Li, J.-J.; Giri, R.; Yu, J.-Q. *Tetrahedron* **2008**, *64*, 6979. The shortest Pd–H(CH₃) distances in the crystals of Pd(**1a**)Cl₂ and Pd(**1a**)₂(OAc)₂ are 2.841 and 2.907 Å, respectively, and the shortest (CH₃COO)O–H(CH₃) distance is 2.392 Å (see the Supporting Information for details).
- (9) The fact that ArCH=N^tBoc, ArCH=N^tCbz, ArCH=NP(O)Ph₂, and ArCH=NCH₂Ph are unreactive and additives such as *t*-BuCO₂H, AcOH, and *i*-PrCO₂H erode the activity supports our hypothesis that the *N*-sulfonyl imine is likely to be activated via coordination to the metal. See: (a) Dai, H.; Yang, M.; Lu, X. *Adv. Synth. Catal.* **2008**, *350*, 249. (b) Jia, Y.; Xie, J.; Duan, L.; Wang, L.; Zhou, Q. *Org. Lett.* **2006**, *8*, 1621.

JA910104N