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Synthesis of Indolines via Pd(II)-Catalyzed Amination of C−H Bonds Using $PhI(OAc)_2$ as the Bystanding Oxidant

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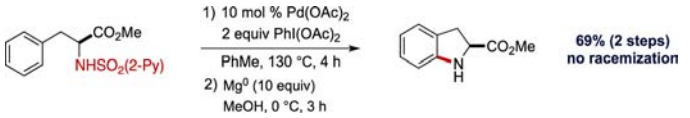
ABSTRACT



The Pd(II)-catalyzed intramolecular C−H amination of 2-pyridinesulfonyl-protected phenethylamine derivatives has been achieved using $PhI(OAc)_2$ as a bystanding oxidant, providing access to a variety of substituted indoline derivatives in good yields. The use of the 2-pyridinesulfonyl protecting group allows for facile deprotection following C−H functionalization.

Because of their prevalence in agrochemicals, pharmaceuticals, and other biologically active molecular scaffolds, the design of novel protocols to efficiently synthesize heterocycles remains a major area of focus in synthetic organic chemistry.[1] Over the past few years, transition-metal-catalyzed C−H activation/C−heteroatom bond-forming reactions have received substantial attention because of their ability to construct these motifs in an extremely rapid manner.[2] In particular, palladium-catalyzed C−H aminations have emerged as powerful tools for the synthesis of a number of unique heterocycles.[3] For example, in 2005, Buchwald and co-workers disclosed an early report detailing the expedient synthesis of carbazoles via the tandem directed C−H activation/amide arylation of 2-acetaminobiphenyl derivatives.[4] Moreover, in 2007, Inamoto and Hiroya developed a protocol for the formation of indazole rings from conjugated hydrazones via Pd-catalyzed C−H amination.[5] Since these seminal publications, the direct Pd-catalyzed intramolecular amination of arenes has proven to be an attractive approach toward the generation of nitrogen-containing polycycles, and a number of new methods have been introduced to affect these transformations.[6,7]

Because of their synthetic value, we sought to develop a C−H activation/amination protocol directed toward the preparation of indolines from simple phenethylamine derivatives. Synthesis of these types of heterocycles through directed C−H functionalizations via six-membered

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(4) Tsang, W. C. P.; Zheng, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 14560.

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(7) (a) Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 14058. (b) Miura, T.; Ito, Y.; Murakami, M. *Chem. Lett.* **2009**, *38*, 328.

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palladacycles have remained largely underdeveloped thus far, with the notable exception being the synthesis of carbazoles utilizing highly conjugated biphenyl systems.[6] Recently, our laboratory has developed the cyclization of *N*-protected arylethylamines to yield a variety substituted indolines in good yield via a one-pot C−H iodination/amination sequence, as well as the direct intramolecular C−H amination of phenethylamines with the aide of single- or two-electron bystanding oxidants.[8−10] While these two methods provide powerful means to synthesize a variety of indolines in an extremely rapid manner, both of these protocols require the use of a trifluoromethylsulfonyl-protected amine as the requisite directing group, which has proven crucial to allow efficient C−H cleavage for amine-directed C−H functionalization. Unfortunately, this necessity potentially complicates further synthetic manipulations due to the traditionally harsh conditions employed for the deprotection of trifluoromethylsulfonamides, thus severely limiting functional group tolerance.[11] Additionally, long reaction times and expensive reagents are typically employed under these reaction conditions.

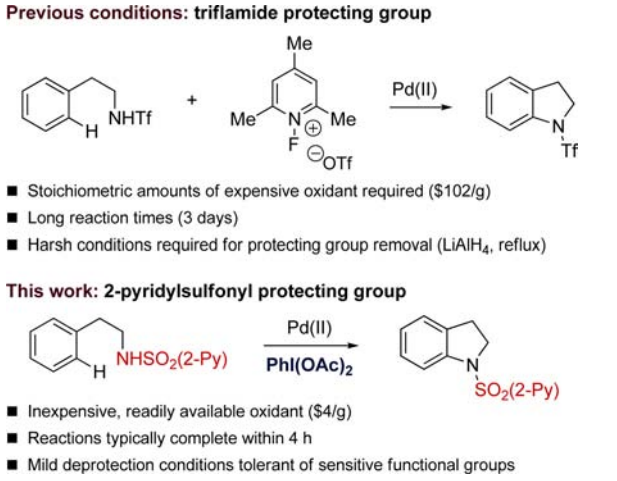
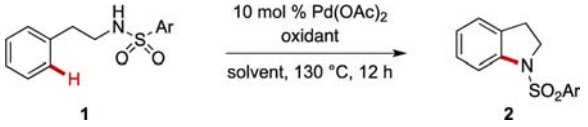


Figure 1. New conditions for the synthesis of indolines via Pd(II)-catalyzed C−H activation.

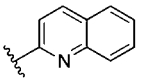
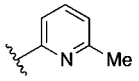
In an effort to address these challenges, we investigated the use of alternative protecting groups that would not only allow efficient C−H activation, but also be easily removed under relatively mild conditions (Figure 1). Recently, Carretero and co-workers introduced the use of the 2-pyridylsulfonyl moeity as a capable directing group for a variety of C−H functionalization reactions.[12] In light of recent developments using pyridine[13] and pyridine-containing auxiliaries[14,15] as directing groups for C−H functionalization, we envisioned that the 2-pyridylsulfonyl protecting group could potentially address difficulties in its subsequent removal while still maintaining high levels of reactivity for the cyclization of phenethylamines.

We began our investigations by preparing several *N*-protected phenethylamine derivatives and submitting them to our previously developed intramolecular C−H amination conditions (Table 1).[9] We were delighted to observe formation of the desired indoline in 20% yield with use of the 2-pyridylsulfonyl protecting group and

Table 1. Optimization of Reaction Conditions



1 2

entry	Ar	oxidant	solvent (0.05 M)	yield (%)[a, b]
1[c]		F^+	$ClCH_2CH_2Cl$	5
2[c]		F^+	$ClCH_2CH_2Cl$	10
3[c]		F^+	$ClCH_2CH_2Cl$	20
4		$PhI(OAc)_2$	$ClCH_2CH_2Cl$	34
5		$PhI(OAc)_2$	PhH	54
6		$PhI(OAc)_2$	PhMe	69
7		$PhI(OAc)_2$	PhMe (0.02 M)	88 (82)

[a] Yield determined by ^1H NMR analysis of crude reaction mixture using CH_2Br_2 as an internal standard. [b] Isolated yield in parentheses. [c] *N*-Fluoro-2,4,6-trimethylpyridinium triflate used as oxidant.

(8) (a) Li, J.-J.; Mei, T.-S.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 6452. (b) Mei, T.-S.; Wang, X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 10806. (c) Vickers, C. J.; Mei, T.-S.; Yu, J.-Q. *Org. Lett.* **2010**, *12*, 2511.

(9) Indolines have also recently been prepared via an alternative C(sp^3)−H activation/amination protocol using anilines as starting materials: Neumann, J. L.; Rakshit, S.; Dröge, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2009**, *48*, 6892.

(10) For a review on bystanding oxidants, see: Engle, K. M.; Mei, T.-S.; Wang, X.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2011**, *50*, 1478.

(11) Hendrickson, J. B.; Bergeron, R. *Tetrahedron Lett.* **1973**, *14*, 3839.

(12) (a) García-Rubia, A.; Arrayás, R. G.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 6511. (b) García-Rubia, A.; Urones, B.; Arrayás, R. G.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2011**, *50*, 10927. (c) García-Rubia, A.; Fernández-Ibáñez, M. Á.; Arrayás, R. G.; Carretero, J. C. *Chem.−Eur. J.* **2011**, *17*, 3567. (d) Rodríguez, N.; Romero-Revilla, J. A.; Fernández-Ibáñez, M. Á.; Carretero, J. C. *Chem. Sci.* **2013**, *4*, 175.

(13) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147.

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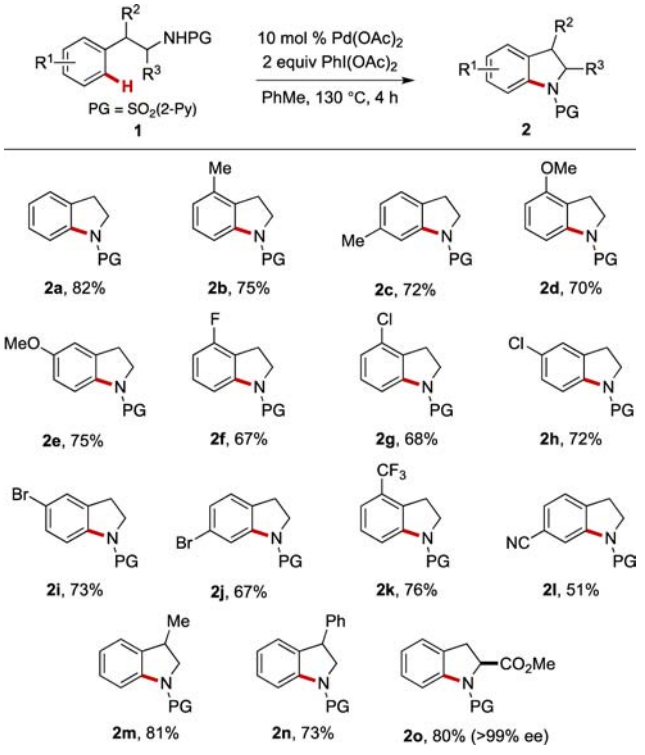
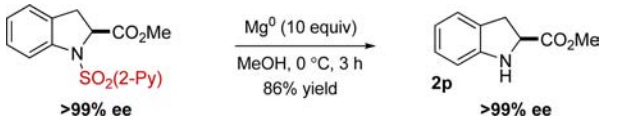
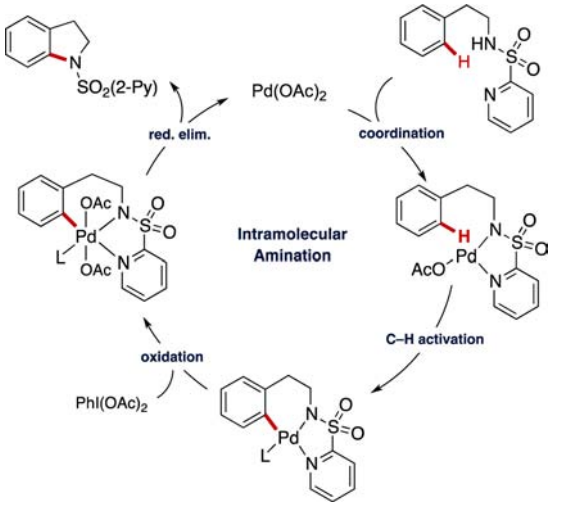
Scheme 1. Pd-Catalyzed C−H Activation/Amination Scope



Scheme 2. Removal of 2-Pyridylsulfonyl Protecting Group



Scheme 3. Plausible Catalytic Cycle



N-fluoro-2,4,6-trimethylpyridinium triflate (F^+) as the oxidant (entry 3); however, attempts to modify the pyridine ring proved detrimental and resulted in a significant drop in reactivity (entries 1 and 2). Gratifyingly, by substituting F^+ with $PhI(OAc)_2$ as the requisite oxidant, we were able to discern a noticeable increase in reaction efficiency (34% yield, entry 4). Interestingly, use of $PhI(OAc)_2$ as the oxidant resulted in exclusive formation of the cyclized product. This lies in stark contrast to when the trifluorosulfonyl protecting group is employed, which results in acetoxylation of the aromatic ring under otherwise similar conditions.[8c,16] Although the origin of this phenomenon is still currently being investigated, these observations highlight the importance of controlling the selectivity of multiple competitive reductive elimination pathways from Pd(IV) centers.[17] Choice of reaction medium had the most significant impact on cyclization, with aromatic solvents proving to be most efficient for the desired transformation (entries 5−7, 54−88% yield). It should be noted that when either the quinolyl or 2-methylpyridyl directing group is utilized under these optimal conditions, < 50% desired product is observed.

Having thus identified optimal conditions for the intramolecular amination of phenethylamine, we next examined the scope of the cyclization reaction. As illustrated in Scheme 1, a variety of substituted indolines are readily prepared in good yield through this C−H functionalization protocol. Both electron-donating (**2b**−**e**) and electron-withdrawing (**2f**−**l**) groups are tolerated at a variety of positions on the aromatic ring. Substrates incorporating Br and Cl at the *ortho*- and *meta*-positions allowed access to indolines well suited for future synthetic manipulations (in particular, metal-catalyzed cross-coupling reactions).[18] Moreover, substitution on the alkyl tether provided 2- and 3-substituted cyclized products in good yield (**2m**−**o**), highlighting the versatility of this C−H activation protocol. It is worth noting that the reaction described above typically reached completion within 4 h, which is a substantial improvement over previous protocols, which required up to 72 h to achieve satisfactory yields.[9b]

As mentioned previously, a major concern regarding *N*-protected directed C−H activation reactions is removal of the protecting group following successful functionalization. To demonstrate the advantages of utilizing the 2-pyridylsulfonyl directing group, we sought to deprotect phenylalanine-derived indoline **2o**, which contain both a readily reduced ester moeity and an easily racemizable α-stereocenter. To our delight, by treating the cyclized product with excess magnesium in methanol at 0 °C,[19] we were able to isolate the free indoline in 86% yield with no

(16) No acetoxylation from $Pd(OAc)_2$ is observed when *N*-fluoro-2,4,6-trimethylpyridinium triflate is utilized as the oxidant (Table 1, entry 3).

(17) Racowski, J. M.; Sanford, M. S. *Top. Organomet. Chem.* **2011**, *35*, 61.

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observed racemization of the sensitive stereocenter (Scheme 2).

A plausible mechanism for this Pd-catalyzed intramolecular amination protocol is depicted in Scheme 3. Coordination of Pd by the amine and pyridine functional units allows selective *o*-C−H cleavage resulting in an organopalladium(II) complex. At this stage, oxidation by $PhI(OAc)_2$ provides an intermediate Pd(IV) species, which could then undergo selective C−N reductive elimination to forge the new carbon−heteroatom bond, thus yielding the desired indoline and regenerating the active palladium catalyst.

In summary, we have developed a new protocol for the synthesis of indolines via a palladium-catalyzed C−H activation/cyclization sequence utilizing the 2-pyridylsulfonyl directing group and $PhI(OAc)_2$ as a bystanding oxidant. Use of this novel amine protecting group allows its facile removal postcyclization under relatively mild conditions.

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Supporting Information Available. Experimental procedure and characterization of all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org

The authors declare no competing financial interest.