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COMMUNICATIONS

Published on Web 06/22/2009

Palladium-Catalyzed Carboamination of Alkenes Promoted by *N*-Fluorobenzenesulfonimide via C−H Activation of Arenes

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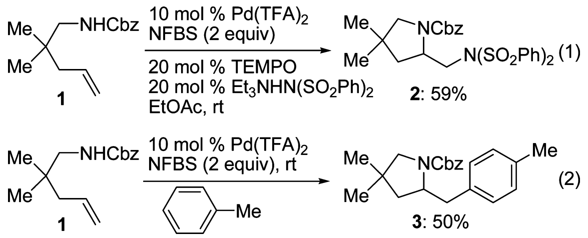
The intramolecular oxidative difunctionalization of alkenes is a powerful method for the introduction of diverse functional groups into organic molecules.[1] Simultaneous formation of C−N and C−C bonds from an olefin (carboamination) is particularly appealing, in part because of the rarity of this transformation.[2] Pd-catalyzed aminocarbonylation of alkenes using CO as the carbon source was extensively developed by Hegedus and Tamaru.[3] Wolfe has shown that aryl bromides can be used to form C−C bonds via Pd-catalyzed carboamination of aminoalkenes.[4] Chemler has reported a doubly intramolecular Cu-catalyzed bicyclization of arylsulfonamidoalkenes and arylamidoalkenes to give products resulting from carboamination of the olefin.[5] In the latter two reactions, the aryl group to be incorporated must be preactivated as its halide or present intramolecularly as a sulfonamide or amide. In this report, we describe a unique Pd-catalyzed oxidative carboamination of protected aminoalkenes in which inexpensive unactivated nucleophilic arenes are incorporated to give carboamination products.

We reported previously that treatment of a variety of protected aminoalkenes with *N*-fluorobenzenesulfonimide (NFBS) in the presence of a Pd catalyst in EtOAc affords the products of alkene diamination in good yields. In these reactions, NFBS acts as an intermolecular source of electrophilic nitrogen (eq 1 in Scheme 1).[6] During the course of that study, a remarkable solvent effect was discovered: treatment of Cbz-protected aminoalkene **1** under diamination conditions in toluene instead of EtOAc afforded poor yields of the expected diamination product **2**. Surprisingly, compound **3** was isolated as a significant byproduct resulting from incorporation of 1 equiv of toluene (eq 2 in Scheme 1).

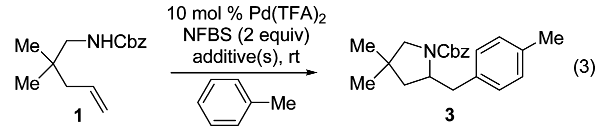
Scheme 1. Pd-Catalyzed Diamination Promoted by NFBS



Several avenues for optimizing the yield of this remarkable transformation were explored. The use of other Pd sources and basic additives uniformly failed to improve upon the initial conditions (Table 1). Radical scavengers had previously proved beneficial in the NFBS-promoted diamination reaction,[6] so a variety of these were investigated (entries 5−7) and once again found to improve the yield. The optimal conditions for substrate **1** proved to be use of Pd(TFA)$_2$ as the catalyst, 3 Å molecular sieves, and 1 equiv of BHT at room temperature, which gave a 75% yield of product **3**.[7]

A number of synthetically useful nitrogen protecting groups were found to be compatible with these conditions (Table 2). Good yields of carboamination products were observed with both carbamates (**5a**−**d**) and amides (**5e**, **5f**).

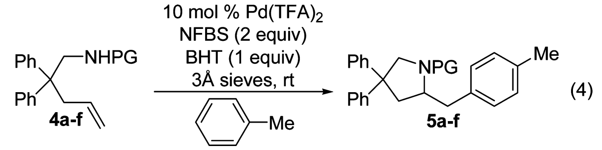
Table 1. Optimization of Reaction Conditions



entry	additive(s)[a]	% yield[b]
1	none	50
2	2,6-di-*tert*-butylpyridine	43
3	Cs$_2$CO$_3$	46
4	BHT	68
5	TEMPO (20 mol %)	51
6	dihydroanthracene	65
7	BHT/3 Å molecular sieves	**75**

[a] Unless otherwise specified, 1 equiv was used. [b] Determined by HPLC.

Table 2. Nitrogen Protecting Group Scope



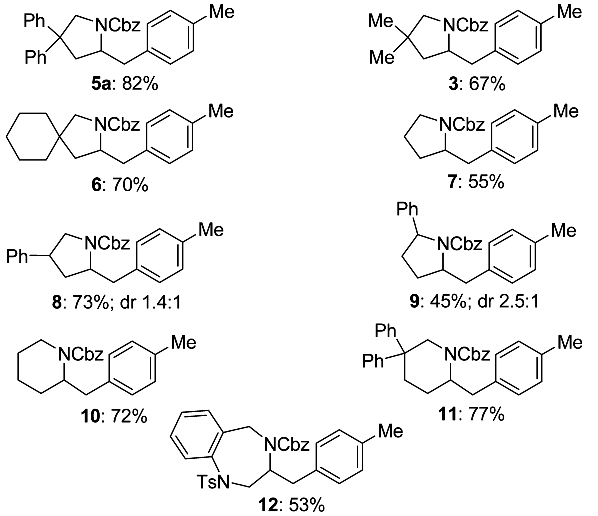
entry	PG	% yield (isolated)
1	Cbz (**5a**)	82
2	Boc (**5b**)	62
3	Troc (**5c**)	56
4	CO$_2$Et (**5d**)	73
5	Ac (**5e**)	84
6	*p*-toluoyl (**5f**)	81

A variety of aminoalkene substrates were able to participate in the carboamination with toluene in good yields (Scheme 2). In addition to the geminally disubstituted products (**3**, **5a**, **6**), mono- and unsubstituted carbon backbones could also be cyclized under these conditions (**7**−**9**), albeit with moderate diastereoselectivity. Additionally, six- and seven-membered rings with various substitution patterns (**10**−**12**) could also be formed.[8]

Several different arenes were suitable for use in the carboamination reaction (Scheme 3). Electron-rich aromatics, such as anisole and alkylbenzenes, were effectively incorporated.[8] Halobenzenes were also suitable reagents but gave somewhat lower yields. It is noteworthy that no participation of the Ar−Br bond was observed under these conditions. The regioselectivity was uniformly high: monosubstituted arenes exclusively gave para substitution products, and *o*- and *m*-xylene exclusively gave the regioisomers coupled para to one of the methyl groups.

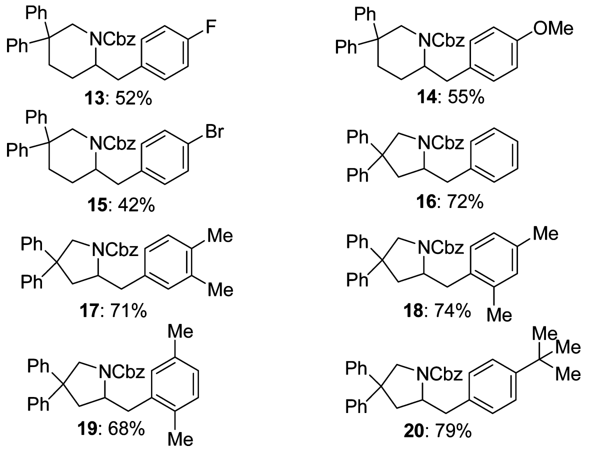
10.1021/ja9031659 CCC: $40.75 © 2009 American Chemical Society

Scheme 2. Aminoalkene Substrate Scope[a]



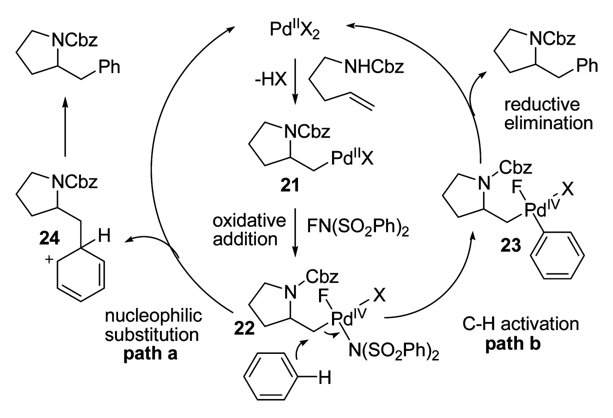
[a] Conditions: 10 mol % Pd(TFA)$_2$, 2 equiv of NFBS, 1 equiv of BHT, 3 Å molecular sieves, toluene, rt.

Scheme 3. Scope of Arene Incorporation[a]



[a] Conditions: 10 mol % Pd(TFA)$_2$, 2 equiv of NFBS, 1 equiv of BHT, 3 Å molecular sieves, arene, rt.

Scheme 4. Proposed Mechanistic Cycle



The proposed mechanism for carboamination is similar to that proposed for the Pd-catalyzed diamination reaction (Scheme 4). Initial aminopalladation of the alkene gives Pd(II)−alkyl complex **21**, and subsequent oxidative addition of NFBS generates key Pd(IV) complex **22**.[9] From this intermediate, reductive elimination of the benzenesulfonimide group had previously given the diamination product. In the presence of nucleophilic arenes, however, the Pd(IV) center is intercepted and displaced in an electrophilic aromatic substitution reaction, forming the final product and regenerating the Pd(II) catalyst (path a).[10] Alternatively, C−H activation of the arene by the Pd(IV) species followed by reductive elimination is also a plausible route to the observed product (path b).[11]

The relative arene reactivities are consistent with either of the two mechanisms in Scheme 4. More nucleophilic arenes react preferentially, and electron-poor arenes (nitrobenzene, methyl benzoate) fail to react at all. The very high regioselectivity observed in this reaction, despite the absence of any directing group, is difficult to explain given that Friedel−Crafts alkylations and C−H activations at both Pd(II) and Pd(IV) are generally poorly regioselective.[12] The fact that radical scavengers substantially increase the yield of carboamination argues strongly against a radical mechanism.

In summary, we have demonstrated a novel method for Pd-catalyzed carboamination of alkenes using NFBS as an oxidant to incorporate weakly nucleophilic arenes. A variety of synthetically useful five-, six- and seven-membered-ring nitrogen heterocycles can be formed under these conditions.

Acknowledgment. The University of Washington and the National Science Foundation are acknowledged for financial support.

Supporting Information Available: Reaction conditions and experimental data for the syntheses of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) In all cases, full consumption of the starting material was observed, and where a major byproduct could be identified, it was the diamination product.
(8) Under these conditions, internal alkenes do not cyclize and incorporation of furan, pyrrole, or thiophene does not occur because of oxidative decomposition of the heteroarene.
(9) A Pd(0)/Pd(II) cycle is unlikely, since no carboamination product was observed in the absence of NFBS (only Wacker oxidation and Pd black were observed).
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JA9031659