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Palladium-Catalyzed Diamination of Unactivated Alkenes Using *N*-Fluorobenzenesulfonimide as Source of Electrophilic Nitrogen

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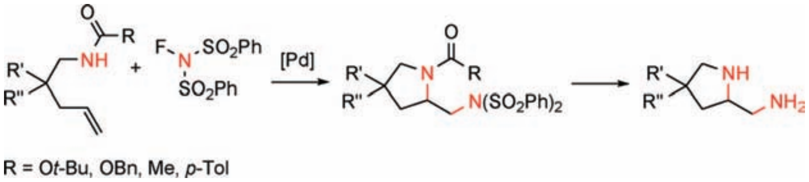
ABSTRACT



A remarkable Pd-catalyzed diamination of unactivated alkenes using *N*-fluorobenzenesulfonimide (NFBS) as an aminating reagent is described. The reaction occurs in an intra/intermolecular fashion, incorporating one nitrogen donor from the substrate and the other from the NFBS, thereby generating cyclic diamine derivatives in a single step. The products are differentially protected at both nitrogens, allowing for maximal synthetic flexibility. The intermediacy of the Pd(IV) species is proposed to be responsible for the unusual reactivity of NFBS.

Vicinal diamines are an important class of compounds as a result of their useful biological activities and their utility as chiral auxiliaries and ligands in asymmetric synthesis.[1] The direct diamination of alkenes is an especially efficient method for the synthesis of such compounds. However, in contrast to the ubiquity of the corresponding dihydroxylation of alkenes, methods for the direct diamination of alkenes are rare.[2] Recently, several new metal-catalyzed diamination reactions have been reported, including intramolecular diaminations of urea and sulfamide-tethered alkenes,[3] as well as intermolecular additions of ureas, sulfamides, and diaziridinones to alkenes.[4,5] Despite these recent successes, current diamination methods generally suffer from limited substrate scope and/or protecting group versatility or are limited to the reactions of activated alkenes. Herein, we report a novel palladium-catalyzed inter/intramolecular diamination of unactivated alkenes using *N*-fluorobenzenesulfonimide as an electrophilic aminating reagent.

We recently disclosed a palladium-catalyzed intramolecular haloamination of alkenes using *N*-halosuccinimides[6] as halide sources (eq 1). In an attempt to extend this chemistry

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(1) Vicinal diamine review: Lucet, D.; Gall, T. L.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580.

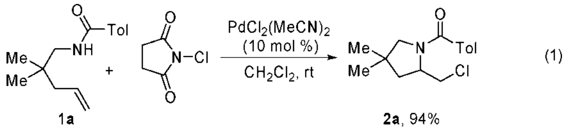
(2) For stoichiometric metal-promoted diaminations, see the following. (a) Pd: Backvall, J. E. *Tetrahedron Lett.* **1978**, 163–166. (b) Hg: Barluenga, J.; Alonsocires, L.; Asensio, G. *Synthesis* **1979**, 962–964. (c) Se: Sharpless, K. B.; Singer, S. P. *J. Org. Chem.* **1976**, *41*, 2504–2506. (d) Os: Chong, A. A. O.; Oshima, K.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 3420–3426. (e) Os: Muñiz, K.; Nieger, M.; Mansikkamaki, H. *Angew. Chem., Int. Ed.* **2003**, *42*, 5958–5961. (f) Co: Becker, P. N.; White, M. A.; Bergman, R. G. *J. Am. Chem. Soc.* **1980**, *102*, 5676–5677. (g) Cu: Zabawa, T. P.; Chemler, S. R. *Org. Lett.* **2007**, *9*, 2035–2038. (h) Cu Zabawa, T. P.; Kasi, D.; Chemler, S. R. *J. Am. Chem. Soc.* **2005**, *127*, 11250–11251.

(3) (a) Muñiz, K.; Hövelmann, C. H.; Streuff, J. *J. Am. Chem. Soc.* **2008**, *130*, 763–773. (b) Muñiz, K.; Hövelmann, C.; Streuff, J.; Campos-Gomez, E. *Pure Appl. Chem.* **2008**, *80*, 1089–1096.

(4) (a) Bar, G. L. J.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *J. Am. Chem. Soc.* **2005**, *127*, 7308–7309. (b) Zhao, B. G.; Yuan, W. C.; Du, H. F.; Shi, Y. A. *Org. Lett.* **2007**, *9*, 4943–4945. (c) Yuan, W. C.; Du, H. F.; Zhao, B. G.; Shi, Y. A. *Org. Lett.* **2007**, *9*, 2589–2591. (d) Du, H. F.; Zhao, B. G.; Shi, Y. A. *J. Am. Chem. Soc.* **2007**, *129*, 762–763.

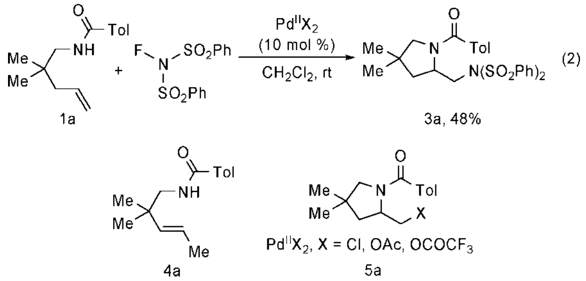
(5) Rh- and Fe-catalyzed Ritter-type diamination: (a) Wei, H. X.; Kim, S. H; Li, G. G. *J. Org. Chem.* **2002**, *67*, 4777–4781. (b) Li, G. G.; Wei, H. X.; Kim, S. H.; Carducci, M. D. *Angew. Chem., Int. Ed.* **2001**, *40*, 4277–4280.

10.1021/ol9000087 CCC: $40.75



to the fluoroamination of these substrates, *N*-fluorobenzenesulfonimide (NFBS) was used as a source of electrophilic fluorine. Surprisingly, no trace of the expected fluorination product was observed and diamination product **3a** was isolated as the major species in 48% yield (eq 2). Instead of acting as a source of "F^+", NFBS serves as an electrophilic aminating reagent, which is a nearly unprecedented mode of reactivity for this reagent.[7]

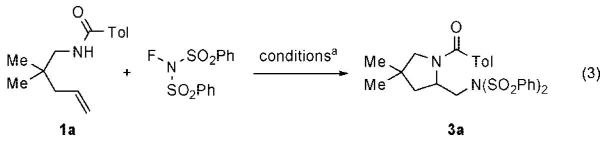
Scheme 1. Attempted Fluoroamination of Amidoalkene Substrate



In addition to the formation of diamination product **3a**, two main byproducts were identified: internal alkene **4a** and chloride **5a** (eq 2, X = Cl). The alkene product arose from isomerization of the alkene to the more stable internal position, possibly catalyzed by small amounts of a palladium hydride complex. Switching to catalytic $Pd(TFA)_2$ significantly reduced the amount of isomerization byproduct. More effectively, addition of radical traps such as 2,6-di-*tert*-butyl-4-methylphenol (BHT) and 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO) inhibited the isomerization reaction, resulting in improved yields of product **3a** (Table 1).[8]

Chloride byproduct **5a** presumably arose from incorporation of the chloride counterion of the palladium salt. Similar counterion incorporation products were observed with both $Pd(OAc)_2$ and $Pd(TFA)_2$. We reasoned that displacement of the counterions of the palladium source with the desired benzenesulfonimide anion would minimize formation of these byproducts. Indeed, treatment of the palladium precatalyst with triethylammonium benzenesulfonimide reduced the formation of byproduct **5a** and further improved the yield. The highest yields were obtained when both TEMPO and triethylammonium benzenesulfonimide additives were used. Commercial ("wet") ethyl acetate was found to be an excellent solvent for this reaction and was used as received without additional drying of purification, indicating that small amounts of water are well tolerated.

Table 1. Diamination of Protected Aminoalkenes **1a**[a]

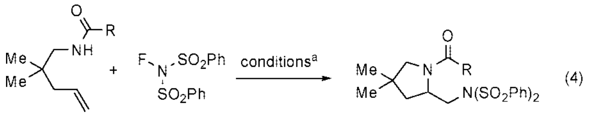


entry	solvent	additive	% yield
1	THF	none	55
2	EtOAc	none	62
3	EtOAc	BHT (1.0 equiv)	64
4	EtOAc	TEMPO (0.2 equiv)	68
5	EtOAc	$[Et_3NH][N(SO_2Ph)_2]$ (0.2 equiv)	67
6	EtOAc	$[Et_3NH][N(SO_2Ph)_2]$ (0.2 equiv) and TEMPO (0.2 equiv)	77

[a] NFBS (2.0 equiv), $Pd(TFA)_2$ (10 mol %), rt, 18 h.

Under these optimized conditions a number of different protecting groups on nitrogen were tolerated (Table 2). Both electron-rich and electron-poor amides successfully underwent diamination. Carbamates and ureas were also suitable substrates, albeit in somewhat lower yields.

Table 2. Effect of Nitrogen Protecting Group on Diamination[a]



entry	R	alkene	product	% yield
1	*p*-Tol	**1a**	**3a**	77
2	Ph	**1b**	**3b**	74
3	*p*-$MeOC_6H_4$	**1c**	**3c**	82
4	*p*-BrC_6H_4	**1d**	**3d**	73
5	OBn	**1e**	**3e**	59
6	O*t*-Bu	**1f**	**3f**	30
7	NHBn	**1g**	**3g**	57
8	NHPh	**1h**	**3h**	49

[a] NFBS (2.0 equiv), $Pd(TFA)_2$ (10 mol %), $[Et_3NH][N(SO_2Ph)_2]$ (0.2 equiv), TEMPO (0.2 equiv), EtOAc, rt, 18 h.

A number of additional substrates successfully underwent diamination under these conditions (Scheme 2). As expected, better yields were achieved with the *gem*-diphenyl substrates **6a,d,e** than with their *gem*-dimethyl counterparts due to their enhanced Thorpe–Ingold effect. Monosubstituted tethers could also be used, giving protected diamine products **11** and **13** with moderate levels of diastereoselectivity (eqs 8 and 9).

One advantage to the use of benzenesulfonimide as the nitrogen source in this reaction is that the resultant diamine products are obtained in differentially protected form. For

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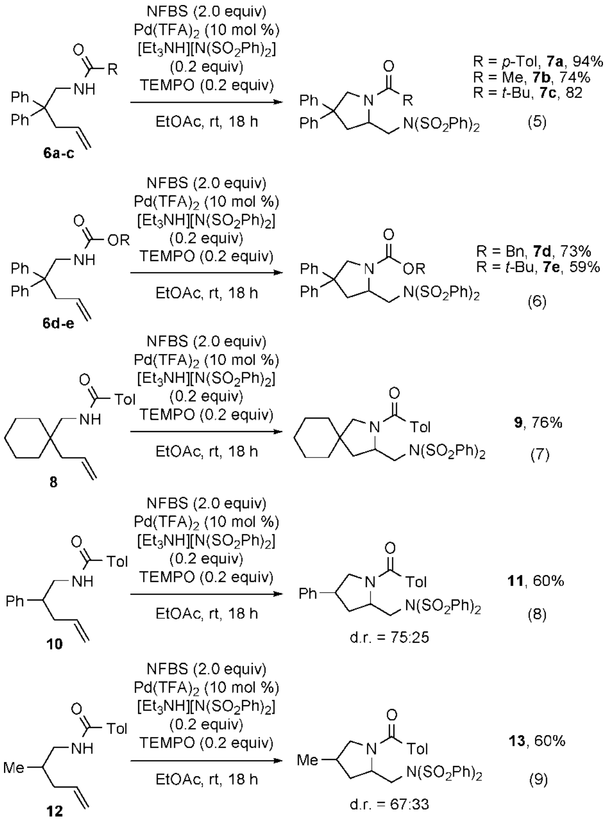
(6) Michael, F. E.; Sibbald, P. A.; Cochran, B. M. *Org. Lett.* **2008**, *10*, 793–796.

(7) We are aware of one exception involving amination of a pyrrole: De Rosa, M.; Marwaha, V. R. *Heterocycles* **1994**, *37*, 979–983.

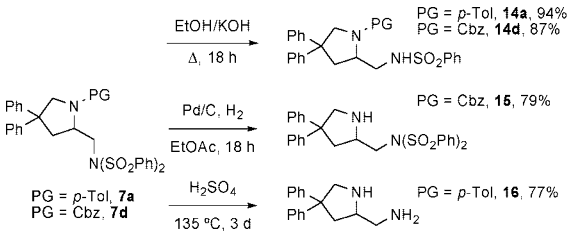
(8) TEMPO and other radical traps retard alkene isomerization by reacting with Pd-H complexes. Albéniz, A. C.; Espinet, P.; López-Fernández, R.; Sen, A. *J. Am. Chem. Soc.* **2002**, *124*, 11278–11279.

Scheme 2. Additional Diaminations of Aminoalkenes



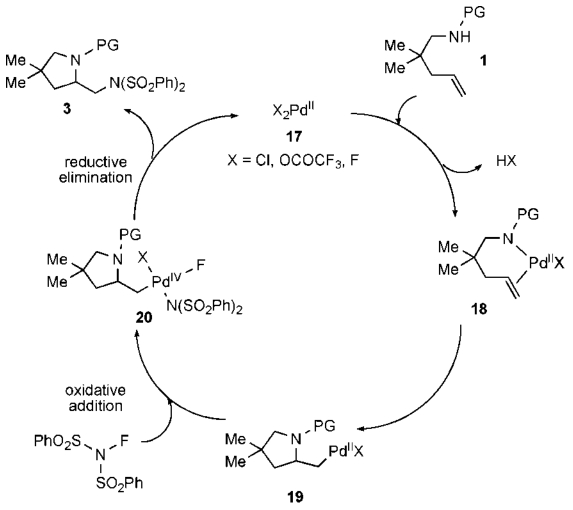
instance, when products **7a** and **7d** were subjected to basic ethanol, selective removal of one sulfonyl group could be effected in high yields. To free the endocyclic amine selectively, hydrogenolysis of the Cbz protecting group afforded **15** in 79% yield. Exhaustive deprotection of both amines was accomplished by heating compound **7a** at 135 °C in H_2SO_4/H_2O to yield the free diamine **16** in 77% yield (Scheme 3).

Scheme 3. Selective Deprotection of **7a** and **7d**



Although the exact reason for the unique reactivity of NFBS has yet to be fully elucidated, a possible catalytic cycle is illustrated in Scheme 4. In a fashion analogous to other palladium-catalyzed transformations of alkenes, the initial step is an aminopalladation of the C═C bond, generating palladium-alkyl intermediate **19**. Rather than acting as a direct fluorination agent, the strong oxidant NFBS can oxidatively add to this Pd(II) species to give a Pd(IV) complex.[9] Reductive elimination of the benzenesulfonimide group would generate the observed diamination product and regenerate the Pd(II) catalyst. The observed formation of the byproducts **5a** can be explained by competing reductive elimination of the Pd-derived counterion from the key Pd(IV) complex **20**. It is interesting to note that although reductive elimination of chloride, acetate, and trifluoroacetate groups appears to be competitive with that of the benzenesulfonimide group, reductive elimination of fluoride to form the fluoroamination product was never observed.

Scheme 4. Proposed Mechanistic Cycle



In conclusion, a mild and facile Pd-catalyzed diamination of unactivated alkenes using NFBS as a nitrogen source has been described. This reaction takes place at room temperature and is tolerant of synthetically useful protecting groups. The inter/intramolecular nature of this reaction allows for the production of differentially protected diamine derivatives by appropriate selection of the aminoalkene substrate, and both newly introduced amines can be fully deprotected, giving efficient access to the free diamine.

Acknowledgment. The University of Washington, ACS PRF, and the NSF CAREER Award are acknowledged for financial support.

Supporting Information Available: Reaction conditions and experimental data for synthesis of all starting materials, catalysts, and diamination products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Recent reports have illustrated the key role that Pd(IV) species can play in other oxidative transformations of Pd-C bonds. See: Dick, A. R.; Kampf, J. W.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 12790–12791. Furuya, T.; Ritter, T. *J. Am. Chem. Soc.* **2008**, *130*, 10060–10061.