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Palladium-Catalyzed Alkoxyamination of Alkenes with Use of *N*-Fluorobenzenesulfonimide as Oxidant

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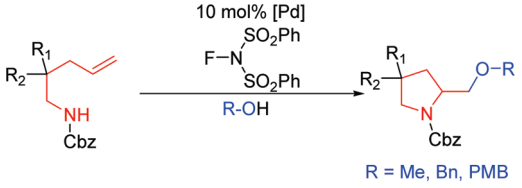


A Pd-catalyzed alkoxyamination of protected aminoalkenes promoted by *N*-fluorobenzenesulfonimide is described. This mild transformation allows the direct formation of ethers from carbon−carbon double bonds. An unusual switch from exo to endo selectivity in polar solvents was discovered, allowing the selective formation of either regioisomer by careful choice of reaction conditions.

The simultaneous addition of oxygen and nitrogen heteroatoms across a carbon−carbon double bond is a powerful tool for the synthesis of biologically active molecules. Several examples of these reactions have been previously reported, most commonly aminohydroxylation[1,2] and aminoacetoxylation reactions.[3,4] Direct introduction of an alkoxy group in such a process is quite rare,[5] but would greatly increase the potential utility of this type of transformation by allowing the direct formation of protected alcohols or ethers from alkenes. Herein, we report an intramolecular Pd-catalyzed alkoxyamination of unactivated alkenes under mild conditions to yield nitrogen heterocycles.

SCHEME 1. Palladium-Catalyzed Diamination and Alkoxyamination

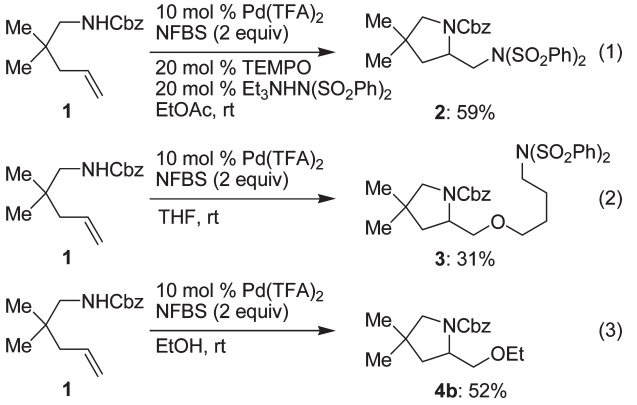
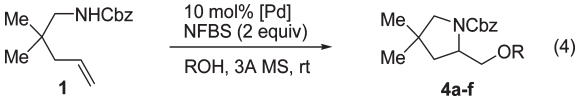


TABLE 1. Nucleophile Scope



entry	[Pd]	R	% yield
1	$Pd(TFA)_2$	Me	53 (**4a**)
2	$PdCl_2(MeCN)_2$	Et[a]	63 (**4b**)
3	$PdCl_2(MeCN)_2$	*n*-Pr	57 (**4c**)
4	$PdCl_2(MeCN)_2$	*n*-Bu	66 (**4d**)
5	$PdCl_2(MeCN)_2$	*i*-Pr	63 (**4e**)
6	$Pd(TFA)_2$	Ac	55 (**4f**)

[a] 9:1 EtOAc/EtOH.

We recently reported the diamination of protected aminoalkenes using *N*-fluorobenzenesulfonimide (NFBS) as an electrophilic nitrogen source (Scheme 1).[6] When this reaction was performed in THF, an unusual byproduct, **3**, was isolated from the reaction mixture. Compound **3** appears to arise from nucleophilic incorporation of the THF solvent. We reasoned that other oxygen nucleophiles might also be incorporated under similar conditions. Gratifyingly, treatment of substrate **1** under identical conditions in ethanol provided the alkoxyamination product **4b** in 52% yield (Scheme 1, eq 3).

The effects of various palladium catalysts and additives were evaluated (see the Supporting Information). The optimal conditions involved the use of either $Pd(TFA)_2$ or $PdCl_2(MeCN)_2$ as catalyst. Radical scavengers such as BHT and TEMPO have been shown to improve other NFBS-promoted reactions but in this case did not improve the yield.[6,7]

A range of primary and secondary alcohols was successfully incorporated under mild conditions (Table 1). Acetic acid could also be used to yield ester **4f** in 55% yield. For methanol and acetic acid incorporation, $Pd(TFA)_2$ gave better yields of the desired product, but for all other alcohols $PdCl_2(MeCN)_2$ was the optimal catalyst.

(1) For selected reviews, see: (a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547. (b) Nilov, D.; Reiser, O. *Adv. Synth. Catal.* **2002**, *344*, 1169–1173. (c) Bodkin, J. A.; McLeod, M. D. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2733–2746. (d) Muniz, K. *Chem. Soc. Rev.* **2004**, *33*, 166–174.

(2) Donohoe, T. J.; Lindsay-Scott, P. J.; Parker, J. S.; Callens, C. K. *Org. Lett.* **2010**, *12*, 1060–1063. Donohoe, T. J.; Callens, C. K.; Thompson, A. L. *Org. Lett.* **2009**, *11*, 2305–7.

(3) Stoichiometric: Backvall, J.-E. *Acc. Chem. Res.* **1983**, *16*, 335–342. Catalytic: Alexanian, E. J.; Lee, C.; Sorensen, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 7690–7691. Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2006**, *128*, 7179–7181.

(4) Aminotrifluoroacetoxylation of alkenes, see: Lovick, H. M.; Michael, F. E. *J. Am. Chem. Soc.* **2010**, *132*, 1249–1251.

(5) Intramolecular alkoxide (from alkenols): Szolcsanyi, P.; Gracza, T. *Chem. Commun.* **2005**, 3948. Desai, L. V.; Sanford, M. S. *Angew. Chem., Int. Ed.* **2007**, *46*, 5737. Using TEMPO as alkoxy group: Fuller, P. H.; Kim, J.-W.; Chemler, S. R. *J. Am. Chem. Soc.* **2008**, *130*, 17638–17639.

(6) Sibbald, P. A.; Michael, F. E. *Org. Lett.* **2009**, *11*, 1147–1149.

(7) Rosewall, C. F.; Sibbald, P. A.; Liskin, D. V.; Michael, F. E. *J. Am. Chem. Soc.* **2009**, *131*, 9488–9489.

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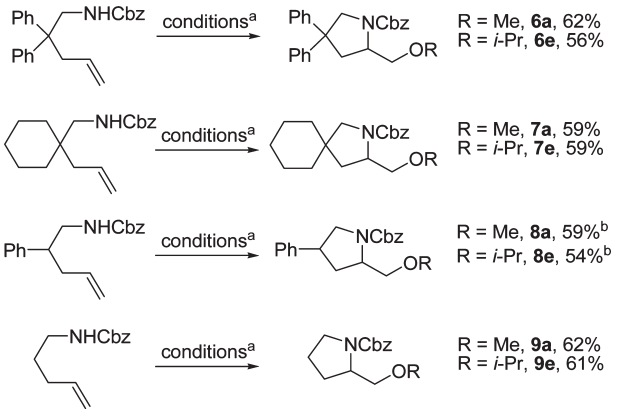
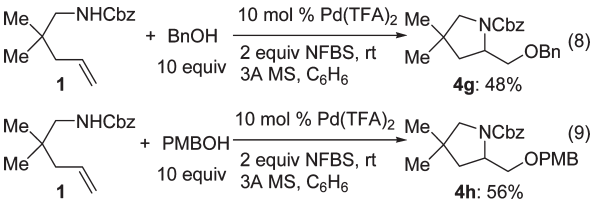
SCHEME 2. Direct Synthesis of Methyl and Isopropyl Ethers



[a]Conditions: 10 mol % [Pd] ($Pd(TFA)_2$ with MeOH; $PdCl_2(MeCN)_2$ with *i*-PrOH), 2 equiv of NFBS, ROH, 3 Å MS, rt. [b]1:2 mixture of diastereomers.

SCHEME 3. Direct Formation of Bn and PMB Ethers



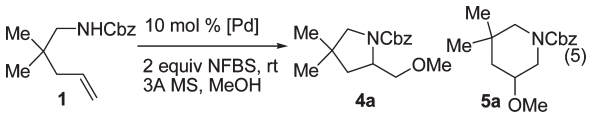
Other aminoalkenes were suitable substrates for the alkoxyamination reaction under standard conditions (Scheme 2). Though the yields are moderate, the ability to directly form an ether could save several synthetic steps over the corresponding aminohydroxylation or aminoacetoxylation reaction.

To allow the efficient use of expensive or high-boiling alcohols, reaction conditions to enable the use of smaller quantities of alcohol nucleophile were examined. A screen of cosolvents and conditions revealed that catalytic $Pd(TFA)_2$ in benzene afforded the synthetically useful Bn and PMB protected alcohols **4g** and **4h** in moderate yields with these conditions (Scheme 3).

The change in catalyst when using MeOH or AcOH as the nucleophile was due to a surprising change in regioselectivity.[8] The reaction of methanol with substrate **1** in the presence of catalytic $PdCl_2(MeCN)_2$ afforded a 1:1 mixture of exo and endo cyclization products **4a** and **5a**, respectively (eq 5). Under identical conditions, $Pd(TFA)_2$ gave exclusively exo product **4a**. To test if the presence of the halide counterion was responsible for the anomalous endo cyclization, a number of halide sources were added to the reaction catalyzed by $Pd(TFA)_2$ (Table 2). The addition of halides to the reaction mixture always increased the amount of endo cyclization product **5a**.

Since the endo product was only observed when using MeOH or AcOH as solvent, it appeared that the polarity of the reaction mixture might have an influence on the exo/endo selectivity. Addition of a less polar cosolvent favored formation of exo product **4a**, while addition of a more polar

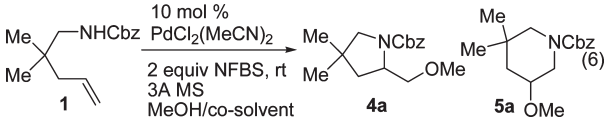
TABLE 2. Effect of Halide on Regioselectivity



entry	[Pd]	additive (20 mol %)	**4a**:**5a**[a]
1	$Pd(TFA)_2$	none	> 20:1
2	$PdCl_2(MeCN)_2$	none	1:2.5
3	$PdCl_2$	none	1:0.7
4	$Pd(TFA)_2$	LiCl	1:1.8
5	$Pd(TFA)_2$	LiBr	1:1.8
6	$Pd(TFA)_2$	$(n\text{-Bu})_4NBr$	1:2.2

[a]Determined by ^1H NMR spectroscopy

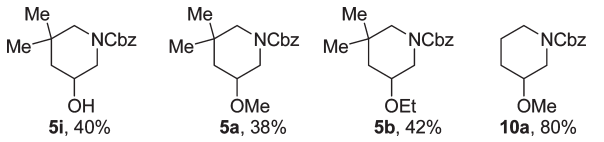
TABLE 3. Regioselectivity Changes with Solvent Polarity



entry	cosolvent	vol % MeOH	**4a**:**5a**[a]
1	none	100	1:2.5
2	1,4-dioxane	60	1:0.5
2	CCl_4	60	1:0.9
3	Et_2O	60	1:1.1
4	EtOAc	20	1:0.4
5	EtOAc	60	1:1.2
6	EtOAc	80	1:1.5
7	DMF	60	1:8

[a]Determined by ^1H NMR spectroscopy

SCHEME 4. Scope of 6-Endo Cyclization[a]



[a]Conditions: 10 mol % of $PdCl_2(MeCN)_2$, 2 equiv of NFBS, 9:1 DMF/ROH.

solvent such as DMF promoted endo cyclization to form **5a** (Table 3).

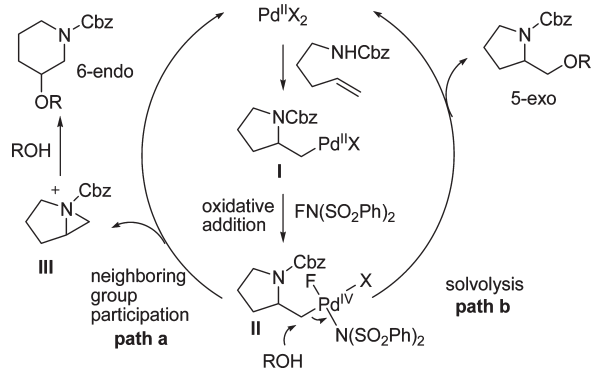
Conditions were optimized for the selective formation of the 6-endo cyclization products in DMF. Though the regioselectivity is uniformly high, yields were moderate (Scheme 4). The major byproduct of this reaction was diamination product **2**. The high yield of **10a** is explained by the fact that unsubstituted substrate **10** does not undergo diamination under these conditions.

A plausible mechanism appears in Scheme 5. By analogy to previous oxidative aminations,[9] initial exoselective aminopalladation occurs to generate complex **I**. Oxidative addition of NFBS generates a Pd(IV) species **II**, which can undergo nucleophilic substitution by the alcohol to generate the 5-exo cyclization product. The origin of the 6-endo product is

(8) A substrate directed change in regiochemistry has been reported: Sherman, E. S.; Chemler, S. R. *Adv. Synth. Catal.* **2009**, *351*, 467–471.

(9) Sibbald, P. A.; Rosewall, C. F.; Swartz, R. D.; Michael, F. E. *J. Am. Chem. Soc.* **2009**, *131*, 15945–15951.

SCHEME 5. Proposed Mechanistic Cycle



currently unclear. One possibility is that under highly polar reaction conditions, aziridinium species **III** could be generated upon departure of the Pd, and preferential internal attack would lead to selective formation of the 6-endo product.

In summary, we have successfully developed a Pd-catalyzed alkoxyamination of protected aminoalkenes using NFBS as oxidant. The regioselectivity could be controlled by careful choice of catalyst and solvent, leading to selective formation of either the 5-exo or 6-endo cyclization products. The direct formation of benzyl and PMB protected alcohols could also be achieved, potentially saving several synthetic steps.

Experimental Section

General Procedure for 5-Exo Alkoxyamination. [Pd][10] (10 mol %, 0.025 mmol) and *N*-fluorobenzenesulfonimide (0.158 g, 0.500 mmol, 2 equiv) were weighed into a 10 mL round-bottomed flask containing a magnetic stir bar and 3 Å molecular sieves (10−15 sieves), capped with a rubber septum, and placed under dry N_2 gas. The substrate (0.250 mmol) was dissolved in 5 mL of the corresponding alcohol and added to the flask. The reaction was allowed to stir overnight and then was diluted with ethyl acetate and separated from the sieves and magnetic stirbar by transferring into another flask. The mixture was concentrated under reduced pressure and chromatographed with 25:75 EtOAc/hexanes. The product was collected and further purified by chromatography with a less polar mixture of EtOAc/hexanes.

(10) See the Supporting Information for Pd source.

Benzyl 2-(methoxymethyl)-4,4-dimethylpyrrolidine-1-carboxylate (4a): clear oil, 52% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43−7.30 (m, 5H), 5.25−5.09 (m, 2H), 4.08−3.02 (m, 1H), 3.69−3.45 (m, 2H), 3.45−3.12 (m, 6H), 3.01 (d, J = 10 Hz, 1H), 1.87−1.78 (m, 1H), 1.78−1.71 (m, 1H), 1.09 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, observed as a mixture of rotamers, ~1.5:1) δ 155.3, 136.9, 128.4, 127.8, 127.6, 74.3, 73.1, 66.8 (minor), 66.6 (major), 59.64 (minor), 59.1 (major), 57.0 (major), 56.3 (minor), 43.6 (minor), 42.4 (major), 37.4 (major), 37.1 (minor), 26.5, 25.9; FTIR (neat, cm^{-1}) 2958, 2872, 1703, 1452, 1415, 1358, 1188, 1101; MS (EI) 277.2, (M^+, 0.3%), 232.2 ([M − CH_2OCH_3]$^+$, 27%), 188.2 ([M − $PhCH_2OCO$]$^+$, 37%), 91.1 (Bn^+, 100%); HRMS (FAB) calcd for $C_{16}H_{24}NO_3$ 278.1756, found 278.1761.

General Procedure for 6-Endo Alkoxyamination. $Pd(TFA)_2$ (10 mol %, 0.025 mmol) and *N*-fluorobenzenesulfonimide (0.158 g, 0.500 mmol, 2 equiv) were weighed into a 10 mL round-bottomed flask containing a magnetic stir bar, capped with a rubber septum, and placed under dry N_2 gas. The substrate (0.250 mmol) was dissolved in a mixture of 1 mL of the corresponding alcohol and 4 mL of dimethylformamide and added to the flask. The reaction was allowed to stir overnight and then was diluted with ethyl acetate and separated from the sieves and magnetic stirbar by transferring into another flask. The mixture was concentrated under reduced pressure (0.1 Torr) at 50 °C and chromatographed with 25:75 EtOAc/hexanes. The product was collected and further purified by chromatography with a less polar mixture of EtOAc/hexanes.

Benzyl 5-methoxy-3,3-dimethylpiperidine-1-carboxylate (5a): colorless oil (38% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41−7.29 (m, 5H), 5.20−5.10 (m, 2H), 4.36−4.34 (m, 0.5H), 4.23−4.16 (m, 0.5H), 3.68−3.58 (m, 1H), 3.36 (d, J = 18 Hz, 3H), 2.74−2.63 (m, 0.5H), 2.65 (d, J = 13.5 Hz), 1.80 (m, 1H), 1.21−1.16 (m, 1H), 0.98−0.89 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$, observed as a mixture of rotamers, ~1.5:1) δ 155.6, 155.5, 136.8, 128.4, 128.0, 127.9, 127.8, 73.2 (minor), 72.8 (major), 67.1, 56.4 (major), 56.3 (minor), 55.0 (major), 54.9 (minor), 47.7, 43.8 (major), 43.8 (minor), 32.2 (major), 32.1, 28.2, 24.9, 24.7; FTIR (neat, cm^{-1}) 2929, 1700, 1430, 1200, 1090; MS (ES) 300 [M + Na]$^+$; HRMS (FAB) calcd for $C_{16}H_{24}NO_3$ 278.1756, found 278.1747.

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Supporting Information Available: Reaction conditions and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.