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# Intramolecular Pd(II)-Catalyzed Aerobic Oxidative Amination of Alkenes: Synthesis of Six-Membered *N*-Heterocycles

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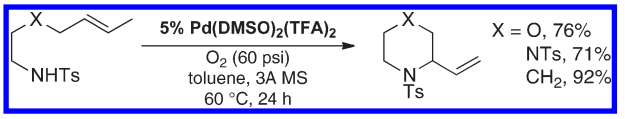
## ABSTRACT




**Use of a base-free $Pd(DMSO)_2(TFA)_2$ catalyst system enables the synthesis of six-membered nitrogen heterocycles via a Wacker-type aerobic oxidative cyclization of alkenes bearing tethered sulfonamides. Various heterocycles, including morpholines, piperidines, piperazines, and piperazinones, are accessible by this method.**

Nitrogen heterocycles, such as morpholines, piperazines, and piperidines, are ubiquitous in natural products and pharmaceuticals, and they have been the focus of extensive synthetic interest.[1] $Pd^{II}$-catalyzed oxidative cyclization of alkenes represents an efficient route to heterocycles,[2] and many "Wacker-type" reactions of this type are compatible with the use of $O_2$ as the stoichiometric oxidant.[3] Nevertheless, while many of these reactions are effective for the formation of five-membered rings,[2] few general methods have been reported for the synthesis of

(1) (a) Wijtmans, R.; Vink, M. K. S.; Schoemaker, H. E.; van Delft, F. L.; Blaauw, R. H.; Rutjes, F. P. J. T. *Synthesis-Stuttgart* **2004**, 641–662. (b) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127–2198. (c) Álvarez-Corral, M.; Muñoz-Dorado, M.; Rodríguez-García, I. *Chem. Rev.* **2008**, *108*, 3174–3198. (d) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395–3442. (e) Müller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795–3892. (f) Candeias, N. R.; Branco, L. C.; Gois, P. M. P.; Afonso, C. A. M.; Trindade, A. F. *Chem. Rev.* **2009**, *109*, 2703–2802. (g) Majumdar, K. C.; Chattopadhyay, B.; Maji, P. K.; Chattopadhyay, S. K.; Samanta, S. *Heterocycles* **2010**, *81*, 795–866.

(2) For representative reviews, see: (a) Hegedus, L. S. In *Comprehensive Organic Synthesis*; Semmelhack, M. F., Ed.; Pergamon Press, Inc.: Elmsford, NY, 1991; Vol. 4, pp 551–569. (b) Hosokawa, T.; Murahashi, S.-I. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., de Meijere, A., Eds.; John Wiley and Sons, Inc.: New York, 2002; Vol. 2, pp 2169–2192. (c) Hosokawa, T. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., de Meijere, A., Eds.; John Wiley and Sons, Inc.: New York, 2002; Vol. 2, pp 2211–2225. (d) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285–2309. (e) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644–4680. (f) Minatti, A.; Muñiz, K. *Chem. Soc. Rev.* **2007**, *36*, 1142–1152. (g) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318–5365. (h) Kotov, V.; Scarborough, C. C.; Stahl, S. S. *Inorg. Chem.* **2007**, *46*, 1910–1923. (i) Wolfe, J. P. *Synlett* **2008**, 2913–2937. (j) McDonald, R. I.; Liu, G.; Stahl, S. S. *Chem. Rev.* **2011**, *111*, 2981–3019.

(3) For reviews of Pd(II)-catalyzed aerobic oxidation reactions, including Wacker-type cyclizations, see: (a) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400–3420. (b) Sigman, M. S.; Jensen, D. R. *Acc. Chem. Res.* **2006**, *39*, 221–229.

(4) Studies of heterocyclization reactions often include six-membered rings in the substrate scope, but routes to these products tend to be less effective than those for five-membered rings. For representative examples of aminocyclization reactions (non-Wacker-type reactions) that include six-membered ring formation, see: (a) Tamaru, Y.; Hojo, M.; Kawamura, S.-i.; Yoshida, Z.-i. *J. Org. Chem.* **1986**, *51*, 4089–4090. (b) Takemiya, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 6042–6043. (c) Han, X.; Widenhoefer, R. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1747–1749. (d) Nakhla, J. S.; Wolfe, J. P. *Org. Lett.* **2007**, *9*, 3279–3282. (e) Stubbert, B. D.; Marks, T. J. *J. Am. Chem. Soc.* **2007**, *129*, 4253–4271. (f) Leathen, M. L.; Rosen, B. R.; Wolfe, J. P. *J. Org. Chem.* **2009**, *74*, 5107–5110. (g) Wu, L.; Qiu, S.; Liu, G. *Org. Lett.* **2009**, *11*, 2707–2710. (h) Rice, G. T.; White, M. C. *J. Am. Chem. Soc.* **2009**, *131*, 11707–11711. (i) Wu, T.; Yin, G.; Liu, G. *J. Am. Chem. Soc.* **2009**, *131*, 16354–16355. (j) Balázs, Á.; Hetényi, A.; Szakonyi, Z.; Sillanpää, R.; Fülöp, F. *Chem.—Eur. J.* **2009**, *15*, 7376–7381. (k) Julian, L. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 13813–13822. (l) Hoover, J. M.; DiPasquale, A.; Mayer, J. M.; Michael, F. E. *J. Am. Chem. Soc.* **2010**, *132*, 5043–5053. (m) Xu, H.-C.; Moeller, K. D. *J. Am. Chem. Soc.* **2010**, *132*, 2839–2844.

(5) For representative Wacker-type reactions compatible with six-membered ring formation, see ref 2 and the following: (a) Tamaru, Y.; Hojo, M.; Higashimura, H.; Yoshida, Z. *J. Am. Chem. Soc.* **1988**, *110*, 3994–4002. (b) Larock, R. C.; Hightower, T. R.; Hasvold, L. A.; Peterson, K. P. *J. Org. Chem.* **1996**, *61*, 3584–3585.

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six-membered and larger nitrogen heterocycles.[4−6] Here, we describe the application of a recently developed Pd(DMSO)$_2$(TFA)$_2$ catalyst system (DMSO = dimethylsulfoxide, TFA = trifluoroacetate)[7,8] for the synthesis of a variety of six-membered nitrogen heterocycles under aerobic conditions.

The challenge of preparing six-membered rings via Wacker-type oxidative cyclization is illustrated with substrate **1a**, a precursor to 3-vinylmorpholine derivative **2a** (Scheme 1). Cyclization of this substrate was attempted with two of the most versatile catalyst systems that have been reported previously: Pd(OAc)$_2$ in DMSO as the solvent, introduced by Larock and Hiemstra,[9] and Pd(OAc)$_2$/pyridine in toluene, which we reported in 2002.[10−12] These catalysts have been used to prepare diverse pyrrolidine derivatives, but they have exhibited limited success in the preparation of six-membered rings. Reactions of **1a** with these catalysts afforded only trace yields of product **2a** (Scheme 1).

We recently identified Pd(DMSO)$_2$(TFA)$_2$ as an effective catalyst for the oxidative cyclization of allylic sulfamides in THF.[7b] Use of DMSO as a stoichiometric ligand for the Pd catalyst in 2:1 stoichiometry, rather than the solvent, resulted in a significantly higher product yield, and optimal results were obtained with sodium benzoate (NaOBz) as a Brønsted base. We tested similar catalytic conditions for the cyclization of **1a**. A 15% yield of **2a** was obtained when 10 mol % Pd(DMSO)$_2$(TFA)$_2$ was used as the catalyst in THF with 1 equiv of NaOBz (Table 1, entry 1), an outcome slightly better than that observed with DMSO as the solvent (entry 2). Despite the modest yields from these reactions, the improvements relative to the results in Scheme 1 prompted us to explore additional conditions. Numerous other solvents were tested (acetonitrile, dichloroethane, dimethylacetamide, dimethoxyethane, dimethylformamide, dioxane, nitromethane, and toluene), and ~40% yields of **2a** were obtained in acetonitrile and toluene (entries 3 and 4). Replacement of NaOBz with other bases (e.g., NaOAc, NaHCO$_3$, and Na$_2$CO$_3$) did not have a significant impact on the outcome of the reaction, but the yield improved to ~60% in the absence of added base (entries 5 and 6). Replacing Pd(TFA)$_2$ with Pd(OAc)$_2$ as a catalyst precursor led to a lower yield of **2a** (32%, entry 7).

The yield of **2a** decreased significantly upon reducing the catalyst loading from 10 to 5 mol % (entry 8). The presence of Pd black at the end of the reaction suggested that the low conversion under these conditions could be explained, at least in part, by decomposition of the catalyst. The yield of **2a** increased to 71% when the reaction was performed under 60 psi of O$_2$. We have previously noted

**Scheme 1.** Illustration of the Difficulty of Wacker-Type Cyclization To Afford a Six-Membered Heterocycle

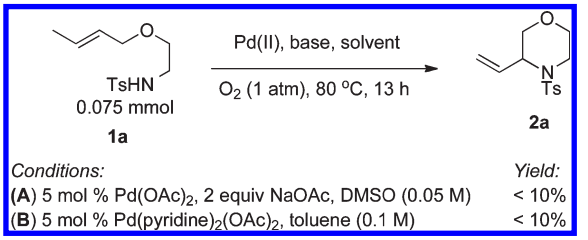
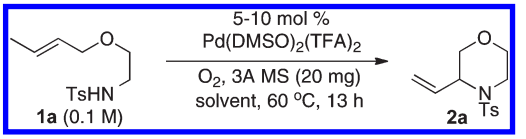



**Table 1.** Evaluation of Catalytic Conditions for Intermolecular Oxidative Amination of Alkenes[a]




| entry | mol % Pd$^{II}$ | solvent | comment | (conv) yield[b] |
|---|---|---|---|---|
| 1 | 10 | THF | 1 equiv NaOBz | (43) 15 |
| 2 | 10 | DMSO | 1 equiv NaOBz | (35) 10 |
| 3 | 10 | MeCN | 1 equiv NaOBz | (70) 41 |
| 4 | 10 | toluene | 1 equiv NaOBz | (68) 38 |
| 5 | 10 | MeCN | no base | (80) 57 |
| 6 | 10 | toluene | no base | (100) 62 |
| 7 | 10 | toluene | Pd(OAc)$_2$[c] | (50) 32 |
| 8 | 5 | toluene | no base | (51) 31 |
| 9 | 5 | toluene | no base, 60 psi O$_2$[d] | (100) 71 |

[a] Conditions: **1a** (0.075 mmol), Pd(TFA)$_2$ (5 or 10 mol %), DMSO (10 or 20 mol %), base, solvent (0.1 M), 3A MS (20 mg), O$_2$ (1 atm), 60 °C, 13 h. [b] Conversion of **1a** in parentheses; yield determined by $^1$H NMR spectroscopy with 1,3,5-trimethylbenzene as the int. std. [c] Pd(OAc)$_2$ used instead of Pd(TFA)$_2$. [d] Substrate concentration of 0.032 M.

(6) Pd-catalyzed carbopalladation of alkenes provides an alternate route to six-membered *N*-heterocycles. For representative examples, see the following: (a) Bowie, A. L., Jr.; Trauner, D. *J. Org. Chem.* **2009**, *74*, 1581–1586. (b) Yip, K.-T.; Li, J.-H.; Lee, O.-Y.; Yang, D. *Org. Lett.* **2005**, *7*, 5717–5719. (c) Baran, P. S.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 7904–7905.

(7) For applications of this catalyst system to other Pd-catalyzed aerobic oxidation reactions, see the following: (a) Brasche, G.; García-Fortanet, J.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 2207–2210. (b) McDonald, R. I.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2010**, *49*, 5529–5532. (c) Diao, T.; Stahl, S. S. *J. Am. Chem. Soc.* **2011**, *133*, 14566–14569.

(8) This catalyst system is typically prepared in situ from Pd(TFA)$_2$ and 2 equiv of DMSO. The "Pd(DMSO)$_2$(TFA)$_2$" notation is used to distinguish this catalyst composition from the common Pd(O$_2$CR)$_2$/DMSO catalysts that employ DMSO as the solvent. $^1$H NMR and IR spectroscopic studies demonstrate that Pd(DMSO)$_2$(TFA)$_2$ is the catalyst composition formed in situ (see ref 7b). For crystallographic characterization of *trans*-Pd(DMSO)$_2$(TFA)$_2$, see: Bancroft, D. P.; Cotton, F. A.; Verbruggen, M. *Acta Crystallogr., Sect. C* **1989**, *45*, 1289–1292.

(9) See ref 5b and the following: (a) Larock, R. C.; Hightower, T. R. *J. Org. Chem.* **1993**, *58*, 5298–5300. (b) van Benthem, R. A. T. M.; Hiemstra, H.; Michels, J. J.; Speckamp, W. N. *J. Chem. Soc., Chem. Commun.* **1994**, 357–359.

(10) Fix, S. R.; Brice, J. L.; Stahl., S. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 164–166.

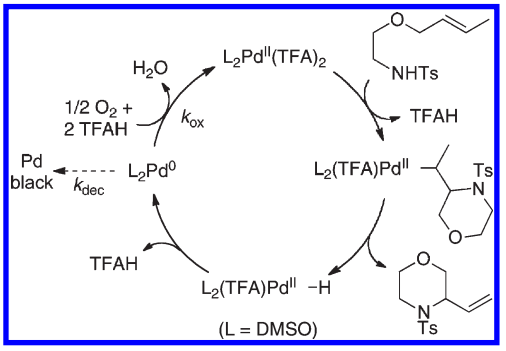
(11) The Pd(OAc)$_2$/pyridine catalyst system was first reported for aerobic alcohol oxidation: Nishimura, T.; Onoue, T.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1999**, *64*, 6750–6755.

(12) For other examples of oxidative cyclization reactions catalyzed by a PdX$_2$/pyridine catalyst systems (X = carboxylate), see: (a) Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 9578–9579. (b) Trend, R. M.; Ramtohul, Y. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 17778–17788. (c) Yip, K.-T.; Yang, M.; Law, K.-L.; Zhu, N.-Y.; Yang, D. *J. Am. Chem. Soc.* **2006**, *128*, 3130–3131.

(13) Rogers, M. M.; Kotov, V.; Chatwichien, J.; Stahl, S. S. *Org. Lett.* **2007**, *9*, 4331–4334.

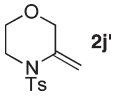
in intermolecular oxidative oxidative amination reactions that catalyst stability can be increased under elevated $O_2$ pressures.[13] The beneficial effect of the higher $O_2$ pressure is rationalized by the mechanism in Scheme 2, whereby productive oxidation of the catalyst ($k_{ox}$ step) can be enhanced relative to catalyst decomposition ($k_{dec}$ step).

**Scheme 2.** Proposed Mechanism of Palladium-Catalyzed Intramolecular Aerobic Oxidative Amination of Alkenes




The optimized oxidative amination conditions were examined with a number of different alkene substrates bearing tethered sulfonamides (Table 2). The reactions were performed at a 0.3 mmol scale under 60 psi of $O_2$ in a Parr pressure vessel. A higher yield of **2a** was obtained (76% isolated yield) relative to the smaller-scale screening reaction, and the *o*-nitrobenzenesulfonamide (Ns) derivative **1b** and the *cis*-alkene substrate *cis*-**1a** also reacted in good yields (86% in both cases). The trisubstituted alkene derivative **1c** reacted to afford a product with a quaternary carbon center adjacent to nitrogen (entry 4, 73% yield), and the reaction of the substrates with branching at the carbon centers on either side of the oxygen atom, **1d**–**1g**, afforded the desired products with good diastereoselectivities (entries 5–8). *N*-Tosyl benzomorpholine derivatives **2h** and **2i** formed in near-quantitative yield from **1h** and **1i**, respectively (entries 9 and 10).

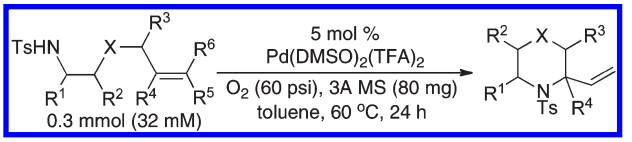
The reaction of **1j** with a terminal alkene led to product **2j**, which probably forms via isomerization of the double bond of an initial product **2j′** containing an exomethylene substituent. Alkene isomerization could be mediated by a $Pd^{II}$–H intermediate (cf. Scheme 2).[14] A five-membered cyclic aminal **3j**, isolated from this reaction in low yield, formally reflects an allylic amination product. However, in light of the alkene isomerization evident in the formation of **2j**, this product probably arises from $Pd^{II}$–H mediated migration of the double bond of **1j** to afford a vinyl ether derivative, followed by Wacker-type oxidative cyclization of the isomeric substrate (see below for further mechanistic analysis).

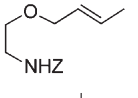
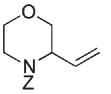
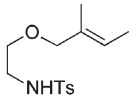
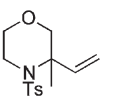
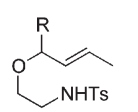
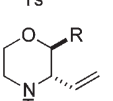
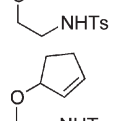
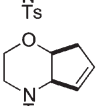
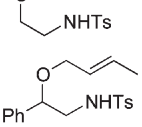
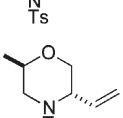
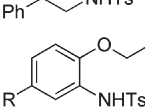
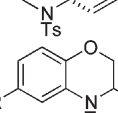
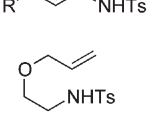
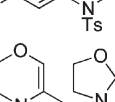
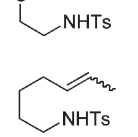
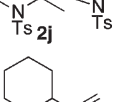
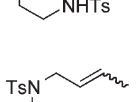
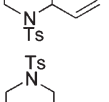
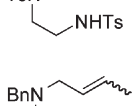
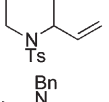
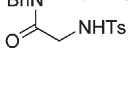
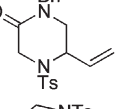
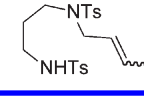
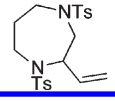


**2j′**

(14) Alkene isomerization in reactions that proceed via $Pd^{II}$–H intermediates is quite common. For a leading reference, see: Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2–7.

**Table 2.** Pd-Catalyzed Intramolecular Aerobic Oxidative Amination Reaction[a]



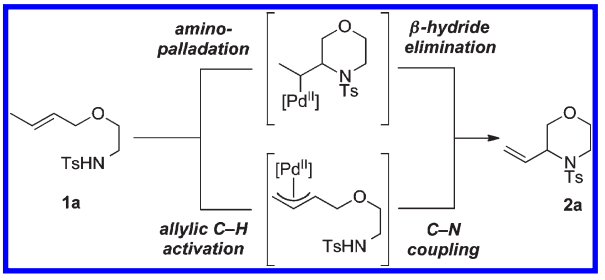

| entry | substrate | product | yield[b] (%) |
|---|---|---|---|
| 1 |  Z = Ts (**1a**) |  | **2a**: 76% |
| 2 | Z = 2-Ns (**1b**) | | **2b**: 86% |
| 3 |  *cis*-**1a** |  | **2a**: 86% |
| 4 |  **1c** |  | **2c**: 73% |
| 5 |  R = Me (**1d**) |  | **2d**: 72% (dr = 6:1) |
| 6 | R = *i*Pr (**1e**) | | **2e**: 59% (dr = >10:1) |
| 7 |  **1f** |  | **2f**: 66% |
| 8 |  **1g** |  | **2g**: 50% (dr = 7:1) |
| 9 |  **1h**[d]: R = H |  | **2h**: 96% |
| 10 | **1i**[d]: R = OMe | | **2i**: 96% |
| 11 |  **1j** |  **2j**  **3j** | **2j**: 60% **3j**: 9% |
| 12 |  **1k**[c] |  | **2k**: 92% |
| 13 |  **1l**[d] |  | **2l**: 71% |
| 14 |  **1m**[c] |  | **2m**: 92% |
| 15 |  **1n**[e] |  | **2n**: 85%[f] |

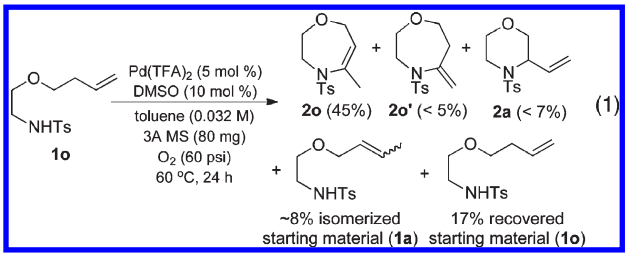
[a] Conditions: **1** (0.3 mmol), $Pd(TFA)_2$ (5 mol %), DMSO (10 mol %), toluene (0.032 M), 3A MS (80 mg), $O_2$ (60 psi), 60 °C, 24 h. [b] Isolated yield. [c] $E/Z$ = 2/1. [d] $E/Z$ = 6/1. [e] $E/Z$ = 4/1. [f] Reaction conditions: Pd(DMSO)-$(TFA)_2$ (15 mol %), [**1n**] = 0.01 M.

The same catalyst and reaction conditions were applied to the preparation of other heterocyclic rings, including piperidine, piperazine, piperazinone, and seven-membered heterocycles **2k**–**2n** (entries 12–15). These products were formed in good yield, although formation of the seven-membered heterocycle **2n** in good yield required the use of an elevated catalyst loading (15 mol %).

The predominant formation of allylic amide products, including the formation of **3j** from **1j**, raises the possibility that these reactions could proceed via an allylic C−H activation pathway, rather than via aminopalladation of the alkene (Scheme 3). The allylic amination reactions reported by White et al., which employ $Pd^{II}$ catalysts in DMSO, are of particular relevance in this context.[15] To distinguish between the two mechanisms, the homoallyl ether substrate **1o** was subjected to the oxidative cyclization conditions (eq 1), and the reaction mixture was analyzed by $^1H$ NMR spectroscopy. The seven-membered ring **2o**, expected from an aminopalladation pathway, was the major product of the reaction. Only a small amount of the allylic C−H activation product **2a** was detected; however, the formation of this product probably arises from aminopalladation of **1a**, which forms in situ via isomerization of **1o**. Collectively, these observations suggest that product formation arises predominantly from the aminopalladation pathway.

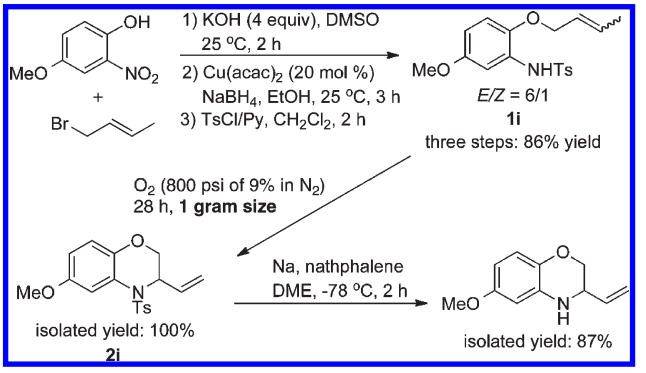
**Scheme 3.** Possible Mechanisms for the Formation of Allylic Sulfonamide Products




The use of high pressures of $O_2$ with an organic solvent is a potential safety hazard. This issue can be addressed by diluting the $O_2$ with an inert gas, such as $N_2$, to ensure the mixture remains outside of flammability limits for the solvent.[16] Such conditions were implemented in a 1 g scale oxidative cyclization of **1i**, which was featured in the five-step synthesis of the unprotected benzomorpholine product from commercially available starting materials (Scheme 4). The aerobic oxidative cyclization step proceeds in quantitative yield under these modified conditions.

**Scheme 4.** Gram-Scale Oxidative Cyclization Reaction Using Diluted $O_2$




Recent studies have shown that $Pd(DMSO)_2(TFA)_2$ is an important variant of previously known $Pd^{II}$ catalyst systems for aerobic oxidation reactions.[7] Its utility has been demonstrated for diverse methods, including directed oxidative arylation of C−H bonds,[7a] oxidative heterocyclization reactions of alkenes,[7b] and α,β-dehydrogenation of cyclic ketones.[7c] The results presented here show that Wacker-type aerobic oxidative cyclization reactions can provide efficient access to six-membered nitrogen heterocycles, and the $Pd(DMSO)_2(TFA)_2$ catalyst system is critical to the success of these reactions.

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**Supporting Information Available.** Experimental procedures and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.