

Stereoselective Synthesis of *cis*-2,5-Disubstituted Pyrrolidines via Wacker-Type Aerobic Oxidative Cyclization of Alkenes with *tert*-Butanesulfinamide Nucleophiles

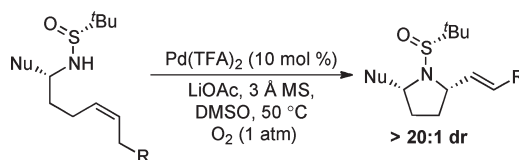
Joanne E. Redford, Richard I. McDonald, Matthew L. Rigsby, Joshua D. Wiensch, and Shannon S. Stahl*

University of Wisconsin–Madison, 1101 University Avenue, Madison, Wisconsin 53706, United States

stahl@chem.wisc.edu

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ABSTRACT



Palladium(II)-catalyzed aerobic oxidative cyclization of alkenes with tethered *tert*-butanesulfinamides furnishes enantiopure 2,5-disubstituted pyrrolidines, originating from readily available and easily diversified starting materials. These reactions are the first reported examples of metal-catalyzed addition of sulfinamide nucleophiles to alkenes.

2,5-Disubstituted pyrrolidines are an important class of heterocycles featured in numerous natural products, pharmaceuticals, ligands for transition metals, and

organocatalysts.¹ Pd^{II}-catalyzed aerobic oxidative cyclization reactions provide efficient routes to pyrrolidines (eq 1);^{2,3} however, few of these methods enable stereoselective C–N bond formation. The first examples of enantioselective oxidative cyclization have been reported only recently.^{4–6} Here, we show that chiral γ -amino-alkene substrates bearing a *t*Bu-sulfinyl auxiliary undergo efficient Pd^{II}-catalyzed aerobic oxidative cyclization to afford enantiopure 2,5-disubstituted pyrrolidines.⁷ *t*Bu-Sulfinamides have been widely used for the

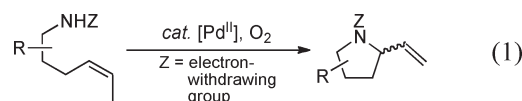
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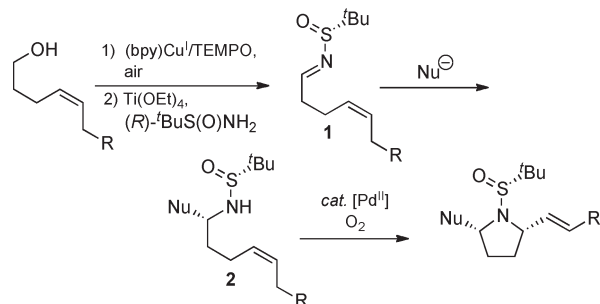
stereoselective synthesis of amines, as summarized in an extensive recent review by Ellman,⁸ however, the present reactions are the first use of sulfinamides in metal-catalyzed nucleophilic functionalization of alkenes.⁹



Our strategy to prepare 2,5-disubstituted pyrrolidines is illustrated in Scheme 1 and begins with readily available *cis*-4-hexen-1-ols.¹⁰ Aerobic oxidation of the alcohol¹¹ and condensation of the resulting aldehyde with ^tBu-sulfinamide^{8,12} furnish the sulfinyl imine derivative **1**. Methods for stereoselective addition of nucleophiles to chiral sulfinyl imines provide access to a variety of enantiopure α -substituted sulfinamides **2**.⁸ Pd^{II}-catalyzed aerobic oxidative cyclization of **2** affords the desired 2,5-disubstituted pyrrolidines.

The enantiopure α -Me-substituted sulfinamide **3** was used as the substrate in the development of a suitable heterocyclization catalyst (Table 1).¹³ Testing of catalyst systems that have been shown previously to promote aerobic oxidative cyclization of γ -aminoalkene derivatives led

Scheme 1. Stereoselective Synthesis of 2,5-Disubstituted Pyrrolidines

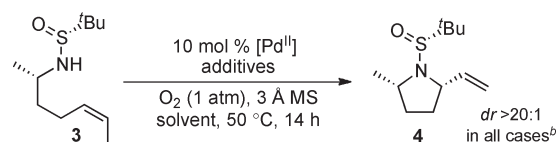


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Table 1. Optimization of a Catalyst System for Diastereoselective Oxidative Cyclization^a



entry	[Pd ^{II}]/additives	solvent	yield ^c
1	Pd(OAc) ₂ /2 equiv of NaOAc, no 3 Å MS	DMSO	87
2	Pd(OAc) ₂ /20 mol % pyridine	toluene	38
3	Pd(TFA) ₂ /40 mol % pyridine, 2 equiv of Na ₂ CO ₃ , no 3 Å MS	toluene	8
4	Pd(TFA) ₂ /20 mol % DMSO, 1 equiv of LiOAc	THF	83
5	Pd(TFA) ₂ /no base	DMSO	6
6	Pd(TFA) ₂ /1 equiv of NaOAc	DMSO	81
7	Pd(TFA) ₂ /1 equiv of NaOBz	DMSO	79
8	Pd(TFA)₂/1 equiv of LiOAc	DMSO	92
9	Pd(TFA) ₂ /1 equiv of Na ₂ CO ₃	DMSO	14
10	PdCl ₂ /1 equiv of LiOAc	DMSO	81
11	Pd(OPiv) ₂ /1 equiv of LiOAc	DMSO	13

^a Conditions: substrate (0.08 mmol), Pd^{II} (0.008 mmol), 3 Å MS (40 mg), O₂ (1 atm), solvent (0.8 mL), 50 °C, 14 h. ^b Diastereomeric ratio determined by ¹H NMR spectroscopy. ^c Yield determined by ¹H NMR spectroscopy, int. std. = PhSiMe₃.

to mixed results (Table 1, entries 1–4).^{3,14} Good product yields were obtained with Pd^{II} catalysts in which DMSO was used as a solvent and/or ligand (entries 1 and 4),^{3a,14} while Pd^{II}/pyridine-based catalyst systems (entries 2 and 3)^{3b,c} afforded low yields. Further screening of anionic base additives, the Pd^{II} source, and solvents (Table 1, entries 5–11; Table S1) revealed that optimal results were obtained with Pd(TFA)₂ (TFA = trifluoroacetate) as the Pd^{II} source, 1 equiv of LiOAc, and DMSO as the solvent. All conditions tested led to formation of a single diastereomeric product (>20:1 dr), affording the *cis* disubstituted pyrrolidine **4**. The sulfinamide group is readily removed upon treatment of **4** with 4 M HCl,¹⁵ affording the HCl salt of the unprotected pyrrolidine in 95% yield.¹⁶

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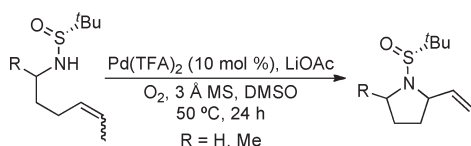
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Table 2. Substrate Effects on the Diastereoselectivity of Pd^{II}-Catalyzed Oxidative Cyclization^a

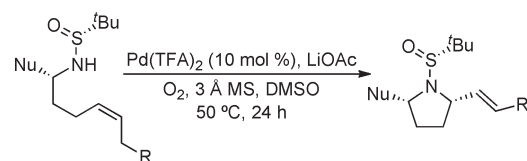


entry	substrate	product	yield ^b	dr ^c
1			68%	7:1
2			83%	6:1
3			98%	>20:1
4			78%	>20:1
5			41%	7:1

^a Conditions: substrate (0.07 mmol), Pd(TFA)₂ (0.007 mmol), 3 Å MS (35 mg), O₂ (1 atm), DMSO-*d*₆ (0.7 mL), 50 °C, 24 h. ^b Yield determined by ¹H NMR spectroscopy, int. std. = PhSiMe₃. ^c Diastereomeric ratio determined by ¹H NMR spectroscopy of crude reaction mixture.

The presence of two stereocenters in **3**, one associated with the sulfinyl group and the other α to the nitrogen atom, raises fundamental questions concerning the origin of stereocontrol in these reactions. The optimized catalyst system was used to probe these issues (Table 2). Substrate **5**, which lacks a stereocenter adjacent to nitrogen, underwent cyclization with 7:1 dr (68% yield, entry 1), demonstrating that the *t*-Bu-sulfinyl group could be used as an auxiliary to achieve stereocontrol when no other stereocenters are present in the substrate. The influence of the α-Me group on diastereoselectivity was evaluated by performing the cyclization of **6**, in which the *t*-Bu-sulfinyl group was replaced with an achiral toluenesulfonyl (Ts) group. This reaction afforded the *cis*-pyrrolidine product with moderate diastereoselectivity (6:1 dr, entry 2). The

Table 3. Stereoselective Oxidative Cyclization of Alkenes Bearing Tethered α-Substituted *t*-Bu-Sulfinamide Nucleophiles^a



entry	substrates	product	yield ^c	dr ^b
1			85%	>20:1
2			64%	>20:1
3			68%	>20:1
4			71%	>20:1
5			54%	>20:1
6			80%	>20:1
7			67%	>20:1
8			70% ^d	15:1

^a Conditions: substrate (0.5 mmol), Pd(TFA)₂ (0.05 mmol), 3 Å MS (250 mg), O₂ balloon, DMSO (5 mL), 50 °C, 24 h. ^c Isolated yield. ^b Diastereomeric ratio determined by ¹H NMR spectroscopy of crude reaction mixture. ^d Performed at 70 °C, 3 atm of O₂.

cooperative effect of the two stereocenters is evident from the improved yield and diastereoselectivity in the

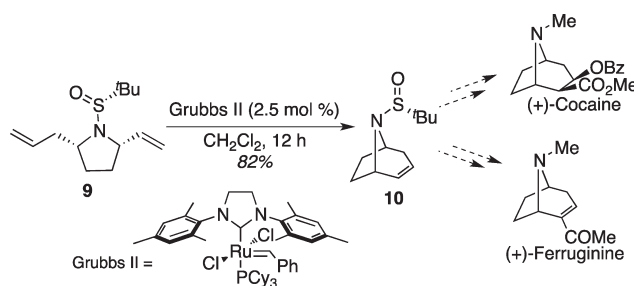
(16) See Supporting Information for further information.

cyclization of the parent substrate **3** (98% yield, > 20:1 dr; entry 3). The pairwise influence of the sulfur- and carbon-based stereocenters was analyzed further by testing the reaction of *epi-3*, in which the stereochemical configuration α to nitrogen is inverted (entry 4). This substrate afforded the corresponding *cis*-pyrrolidine¹⁶ as a single diastereomer, but with moderately reduced yield relative to the reaction of **3**. This observation suggests that rotation about the N–S bond enables the sulfinamide to act cooperatively with either epimeric form of the substrate to enforce highly diastereoselective C–N bond formation. Finally, analysis of the alkene stereochemistry revealed that a significantly lower yield and diastereoselectivity was observed with substrate **7**, bearing a *trans*-alkene (cf. entries 3 and 5).¹⁷

With these results in hand, we investigated the reactivity of a number of different substrates (Table 3). A benzyl-substituted alkene underwent cyclization in 85% yield to provide the stryrenyl product (entry 1). Each of the other substrates, bearing diverse functional groups in the α position, was readily obtained by stereoselective addition of the appropriate nucleophile to the sulfinylimine precursor (cf. Scheme 1).^{8,16} Oxidative cyclization of these substrates proceeded with excellent diastereoselectivity, in most cases affording a single detectable diastereomer (Table 3). All of the reactions proved to be operationally straightforward, with substrates and reagents weighed and combined in a flask open to the air and stirred under a balloon of O₂. Substrates with relatively large α substituents, including isopropyl and aryl groups, proceeded effectively, albeit with a somewhat lower yield relative to the α -Me derivative **3** (61–74% yield, entries 2–4). Substrates featuring an aryl chloride (entry 4), phosphonate (entry 5), carboxylic ester (entry 6), or acetal (entry 7) also underwent successful cyclization. The latter functional groups are appealing because they are readily amenable to further functional-group manipulations to prepare more complex molecules.

Substrate **8**, which contains an α -propenyl substituent, cyclized in good yield with increased temperature and O₂ pressure (Table 3, entry 8). Alkene metathesis of the diene product **9** using the Grubbs II catalyst yielded the

Scheme 2. Synthesis of a Common Precursor for the Synthesis of Tropane Alkaloids



azabicyclic tropene **10** in 82% yield (Scheme 2).¹⁶ Tropane alkaloids have received substantial attention in recent years due to the effect of these molecules on the central nervous system,¹⁸ and tropene derivatives directly analogous to **10** have been converted by straightforward methods to various alkaloid products.^{18d}

In summary, we have developed catalytic conditions that enable Wacker-type aerobic oxidative cyclization of alkenes bearing tethered ^tBu-sulfinamide nucleophiles. These reactions benefit from efficient access to the enantiopure substrates and highly diastereoselective cyclization, and they enable modular, stereocontrolled synthesis of a diverse collection of *cis*-2,5-disubstituted pyrrolidines. These results highlight the prospective utility of ^tBu-sulfinamides as chiral nitrogen nucleophiles in metal-catalyzed additions to alkenes and related electrophiles.

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Supporting Information Available. Experimental procedures, ¹H and ¹³C NMR spectra, and methods for determination of configuration. This material is available free of charge via the Internet at <http://pubs.acs.org>.

(17) Recent studies suggest that C–N bond formation could proceed via *cis* or *trans* aminopalladation of the alkene, and further work will be needed to resolve this issue for the present reactions. Nevertheless, the results in Tables 2 and 3 demonstrate that the diastereoselectivity of these reactions is predictable from the substrate structure. For consideration of the factors that influence *cis* vs *trans* aminopalladation of alkenes, see ref 5 and the following leading references: (a) Nakhla, J. S.; Kampf, J. W.; Wolfe, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 2893–2901. (b) Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 6328–6335. (c) Sibbald, P. A.; Rosewall, C. F.; Swartz, R. D.; Michael, F. E. *J. Am. Chem. Soc.* **2009**, *131*, 15945–15951.

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The authors declare no competing financial interest.