ORGANIC LETTERS

2012
Vol. 14, No. 5
1242–1245

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

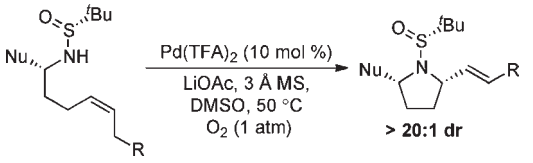
Joanne E. Redford, Richard I. McDonald, Matthew L. Rigsby, Joshua D. Wiensch, and Shannon S. Stahl*

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

stahl@chem.wisc.edu

Received January 10, 2012

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-aminoalkene 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

(1) (a) Ronzani, N.; Lajat, M. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1131–1132. (b) O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435–446. (c) Wright, S. W.; Ammirati, M. J.; Andrews, K. M.; Brodeur, A. M.; Danley, D. E.; Doran, S. D.; Lillquist, J. S.; McClure, L. D.; McPherson, R. K.; Orena, S. J.; Parker, J. C.; Polivkova, J.; Qiu, X.; Soeller, W. C.; Soglia, C. B.; Treadway, J. L.; VanVolkenburg, M. A.; Wang, H.; Wilder, D. C.; Olson, T. V. *J. Med. Chem.* **2006**, *49*, 3068–3076. (d) Sionini, V.; Benaglia, M.; Pignataro, L.; Guizzetti, S.; Celentano, G. *Synlett* **2008**, *7*, 1061–1065. (e) Grynkiewicz, G.; Gadzikowska, M. *Pharmacol. Rep.* **2008**, *60*, 439–463. (f) Chen, H.; Sweet, J. A.; Lam, K. C.; Rheingold, A. L.; McGrath, D. V. *Tetrahedron: Asymmetry* **2009**, *20*, 1672–1682.

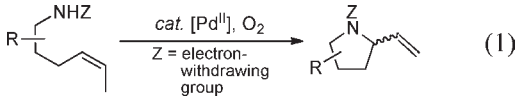
(2) For reviews, see: (a) Hegedus, L. S. In *Comprehensive Organic Synthesis*; Semmelhack, M. F., Ed.; Pergamon Press, Inc.: Elmsford, 1991; Vol. 4, pp 551−569. (b) Hosokawa, T.; Murahashi, S.-I. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., de Meijere, A., Eds.; John 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.: NewYork, 2002; Vol. 2, pp 2211−2225. (d) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285–2309. (e) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400–3420. (f) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318–5365. (g) Minatti, A.; Muñiz, K. *Chem. Soc. Rev.* **2007**, *36*, 1142–1152. (h) Kotov, V.; Scarborough, C. C.; Stahl, S. S. *Inorg. Chem.* **2007**, *46*, 1910–1923.

(3) For the development of aerobic catalyst systems for the synthesis of pyrrolidines, see: (a) Larock, R. C.; Hightower, T. R.; Hasvold, L. A.; Peterson, K. P. *J. Org. Chem.* **1996**, *61*, 3584–3584. (b) Fix, S. R.; Brice, J. L.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 164–166. (c) Trend, R. M.; Ramtohul, Y. K.; Ferreira, E. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2892–2895. (d) Rogers, M. M.; Wendlandt, J. E.; Guzei, I. A.; Stahl, S. S. *Org. Lett.* **2006**, *8*, 2257–2260.

(4) (a) Yip, K.-T.; Yang, M.; Law, K.-L.; Zhu, N.-Y.; Yang, D. *J. Am. Chem. Soc.* **2006**, *128*, 3130–3131. (b) He, W.; Yip, K.-T.; Zhu, N.-Y.; Yang, D. *Org. Lett.* **2009**, *11*, 5626–5628. (c) Scarborough, C. C.; Bergant, A.; Sazama, G. T.; Guzei, I. A.; Spencer, L. C.; Stahl, S. S. *Tetrahedron* **2009**, *65*, 5084–5092. (d) Jiang, F.; Wu, Z.; Zhang, W. *Tetrahedron Lett.* **2010**, *51*, 5124–5126. (e) McDonald, R. I.; White, P. B.; Weinstein, A. B.; Tam, C. P.; Stahl, S. S. *Org. Lett.* **2011**, *13*, 2830–2833.

10.1021/ol3000519
Published on Web 02/21/2012

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]



(1)

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 alcohol[11] and condensation of the resulting aldehyde with ^{t}Bu-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

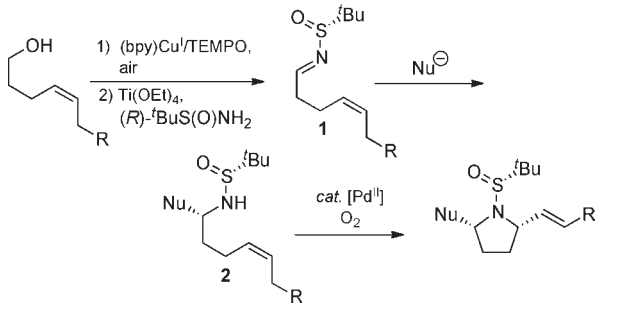
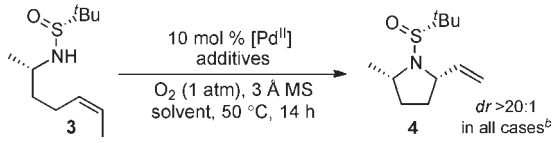


Table 1. Optimization of a Catalyst System for Diastereoselective Oxidative Cyclization[a]



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_2CO_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_2CO_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), O_2 (1 atm), solvent (0.8 mL), 50 °C, 14 h. [b] Diastereomeric ratio determined by ^{1}H NMR spectroscopy. [c] Yield determined by ^{1}H NMR spectroscopy, int. std. = $PhSiMe_3$.

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 = trifluoroactate) 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]

(5) For a review of stereoselective nucleopalladation reactions, including oxidative cyclizations, see: McDonald, R. I.; Liu, G.; Stahl, S. S. *Chem. Rev.* **2011**, *111*, 2981–3019.

(6) For leading references to other enantioselective metal-catalyzed aminocyclization reactions, see: (a) Hong, S.; Tian, S.; Metz, M. V.; Marks, T. J. *J. Am. Chem. Soc.* **2003**, *125*, 14768–14783. (b) Wood, M. C.; Leitch, D. C.; Yeung, C. S.; Kozak, J. A.; Schafer, L. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 354–358. (c) Chemler, S. R. *Org. Biomol. Chem.* **2009**, *7*, 3009–3019. (d) Fuller, P. H.; Kim, J.-W.; Chemler, S. R. *J. Am. Chem. Soc.* **2008**, *130*, 17638–17639. (e) Shen, X.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2010**, *49*, 564–567. (f) Mai, D. N.; Wolfe, J. P. *J. Am. Chem. Soc.* **2010**, *132*, 12157–12159.

(7) For leading references on the synthesis of 2,5-disubstituted pyrrolidines, see: (a) Pichon, M.; Figadere, B. *Tetrahedron: Asymmetry* **1996**, *7*, 927–964. (b) Rudolph, A. C.; Machauer, R.; Martin, S. F. *Tetrahedron Lett.* **2004**, *45*, 4895–4898. (c) Hussaini, S. R.; Moloney, M. G. *Org. Biomol. Chem.* **2006**, *4*, 2600–2615. (d) Llamas, T.; Arrayás, R. G.; Carretero, J. C. *Org. Lett.* **2006**, *8*, 1795–1798. (e) Wang, P.-A.; Xu, Z.-S.; Chen, C.-F.; Gao, X.-G.; Sun, X.-L.; Zhang, S.-Y. *Chirality* **2007**, *19*, 581–588. (f) Zhang, S.; Xu, L.; Miao, L.; Shu, H.; Trudell, M. L. *J. Org. Chem.* **2007**, *72*, 3133–3136. (g) Paderes, M. C.; Chemler, S. R. *Org. Lett.* **2009**, *11*, 1915–1918. (h) Lygo, B.; Beynon, C.; McLeod, M. C.; Roy, C.-E.; Wade, C. E. *Tetrahedron* **2010**, *66*, 8832–8836. (i) Lemen, G. S.; Wolfe, J. P. *Org. Lett.* **2010**, *12*, 2322–2325. (j) Lemen, G. S.; Wolfe, J. P. *Org. Lett.* **2011**, *13*, 3218–3221.

(8) Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600–3740.

(9) For alternative heterocyclization methods using ^{t}Bu-sulfinamides in the stereoselective formation of C−N bonds, see: (a) Brinner, K. M.; Ellman, J. A. *Org. Biomol. Chem.* **2005**, *3*, 2109–2113. (b) Li, Y.; Ni, C.; Liu, J.; Zhang, L.; Zheng, J.; Zhu, L.; Hu, J. *Org. Lett.* **2006**, *8*, 1693–1696. (c) Reddy, L. R.; Das, S. G.; Lui, Y.; Prashad, M. *J. Org. Chem.* **2010**, *75*, 2236–2246.

(10) Wenkert, E.; Micheloti, E. L.; Swindell, C. S.; Tingoli, M. *J. Org. Chem.* **1984**, *49*, 4894–4899.

(11) Hoover, J. M.; Stahl, S. S. *J. Am. Chem. Soc.* **2011**, *133*, 16901–16910.

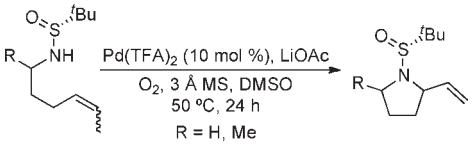
(12) Liu, G.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 1278–1284.

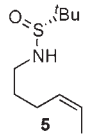
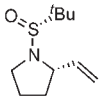
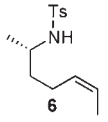
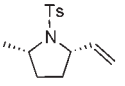
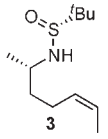
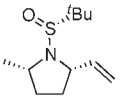
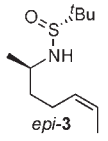
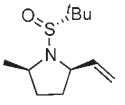
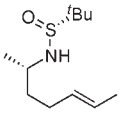
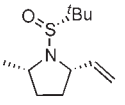
(13) Additional reaction optimization data are provided in the Supporting Information.

(14) McDonald, R. I.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2010**, *49*, 5529–5532.

(15) Cogan, D. A.; Liu, G.; Ellman, J. *Tetrahedron* **1999**, *55*, 8883–8904.

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



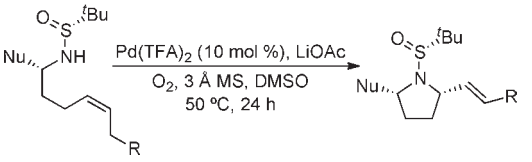
entry	substrate	product	yield[b]	dr[c]
1	 **5**		68%	7:1
2	 **6**		83%	6:1
3	 **3**		98%	>20:1
4	 *epi*-**3**		78%	>20:1
5	 **7**		41%	7:1

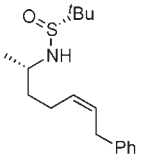
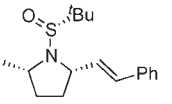
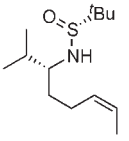
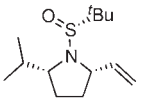
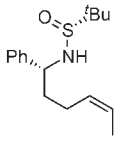
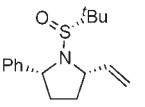
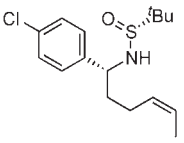
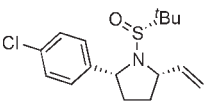
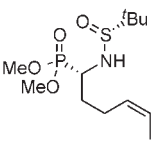
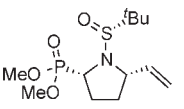
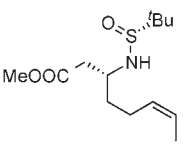
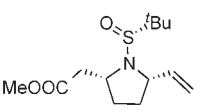
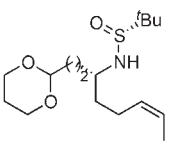
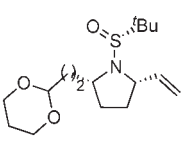
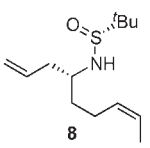
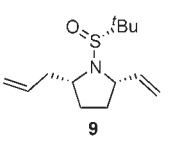
[a] Conditions: substrate (0.07 mmol), $Pd(TFA)_2$ (0.007 mmol), 3 Å MS (35 mg), O_2 (1 atm), DMSO-d_6 (0.7 mL), 50 °C, 24 h. [b] Yield determined by ^1H NMR spectroscopy, int. std. = $PhSiMe_3$. [c] Diastereomeric ratio determined by ^1H NMR spectroscopy of crude reaction mixture.

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

(16) See Supporting Information for further information.

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	 **8**	 **9**	70%[d]	15:1

[a] Conditions: substrate (0.5 mmol), $Pd(TFA)_2$ (0.05 mmol), 3 Å MS (250 mg), O_2 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 O_2.

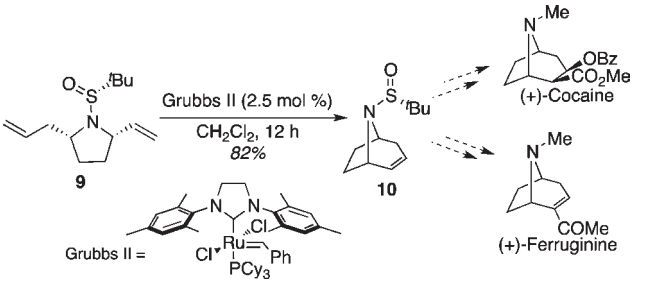
cooperative effect of the two stereocenters is evident from the improved yield and diastereoselectivity in the

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*-pyrrolidine[16] 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 stryenyl 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 O_2. 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). Subtrates 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 O_2 pressure (Table 3, entry 8). Alkene metathesis of the diene product **9** using the Grubbs II catalyst yielded the 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]

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



In summary, we have developed catalytic conditions that enable Wacker-type aerobic oxidative cyclization of alkenes bearing tethered ^{t}Bu-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 ^{t}Bu-sulfinamides as chiral nitrogen nucleophiles in metal-catalyzed additions to alkenes and related electrophiles.

Acknowledgment. We thank the NIH (R01 GM67163) and Abbott Laboratories (graduate fellowship for R.I.M.) for financial support. Spectroscopic instrumentation was partially funded by the NSF (CHE-9208463, CHE-0342998, CHE-9629688, CHE-9974839), and high-pressure instrumentation was funded by the NSF (CHE-0946901).

Supporting Information Available. Experimental procedures, ^{1}H and ^{13}C 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 consideriation 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.

(18) (a) Aggarwal, V. K.; Astle, C. J.; Rogers-Evans, M. *Org. Lett.* **2004**, *6*, 1469–1471. (b) Mans, D. M.; Pearson, W. H. *Org. Lett.* **2004**, *6*, 3305–3308. (c) Grynkiewicz, G.; Gadzikowska, M. *Pharmacol. Rep.* **2008**, *60*, 439–463. (d) Cheng, G.; Wang, X.; Zhu, R.; Shao, C.; Xu, J.; Hu, Y. *J. Org. Chem.* **2011**, *76*, 2694–2700. (e) Schultz, D. M.; Wolfe, J. P. *Org. Lett.* **2011**, *13*, 2962–2965.

The authors declare no competing financial interest.