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Transition-Metal-Free Synthesis of Tertiary Aminocyclopropanes

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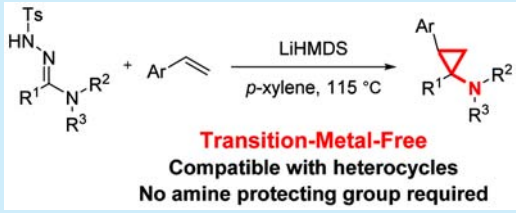
Supporting Information

ABSTRACT: A transition-metal-free methodology for the construction of pharmaceutically relevant tertiary aminocyclopropanes is reported. Hydrazonamides, safe and stable carbene precursors, undergo smooth cyclopropanation with vinyl arenes in the presence of a base. The reaction proceeds with stereoselectivity to favor the *Z* isomer and provides facile access to a variety of substitution patterns through variation of the coupling partners.



The aminocyclopropane motif is a key pharmacophore present in numerous natural products and a wide variety of biologically active pharmaceuticals.[1] Such compounds include the phytotoxin coronatine (**I**, Figure 1),[2] the FDA-approved dipeptidyl peptidase IV inhibitor saxagliptin (**II**) used in the treatment of type 2 diabetes,[3] the Hepatitis C Virus NS3/4A protease inhibitor danoprevir (**III**),[4] and the preclinical NPY1 antagonist **IV**.[5]

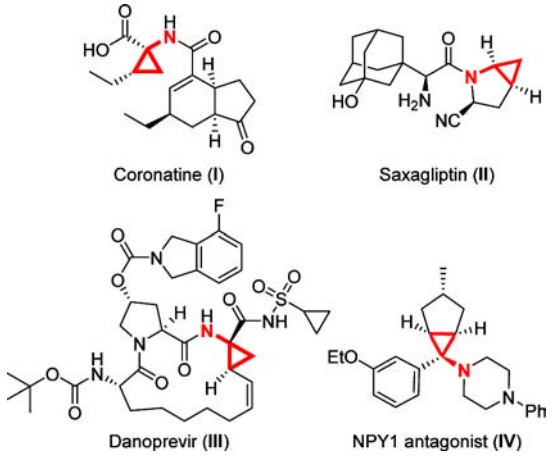


Figure 1. Bioactive pharmaceutical molecules bearing the substituted aminocyclopropane motif.

Because of the prevalence of the aminocyclopropane motif in biologically relevant compounds, its synthesis has been the subject of extensive research within the synthetic community. While classical methods to construct aminocyclopropanes such as the Curtius rearrangement of cyclopropylcarboxylic acids[6] and the Kulinkovich–de Meijere reaction[7] are very robust, the former requires prefunctionalization of a cyclopropane and the latter synthetic strategy suffers from limited functional group tolerance. Many alternative approaches have been developed to overcome these limitations,[8] with the rhodium-catalyzed cyclopropanation of diazo compounds being arguably the most efficient.[9]

Despite earlier successes of the aminocyclopropane motif in drug discovery, this functionality has recently been stigmatized as a toxicophore due to possible reactive metabolite formation.[10] This is certainly a concern with most basic primary and secondary cyclopropylamines. Hanzlik demonstrated that aminocyclopropanes bearing a fully substituted nitrogen are less prone to form reactive metabolites via P450-mediated reactions and, consequently, represent very attractive building blocks in medicinal chemistry.[11]

While gains in aminocyclopropane methodology have been made, construction of tertiary aminocyclopropanes remains especially challenging and generally requires lengthy synthetic sequences or utilizes intramolecular cyclizations, limiting the substrate scope to bicyclic compounds. The most direct approach to access tertiary aminocyclopropanes is via addition of an easily accessible aminocarbenoid or aminocarbene to an alkene. This transformation is known, but generally requires stoichiometric quantities of transition metals and suffers from limited functional group tolerance.[12] An elegant cyclopropanation methodology developed by Davies and co-workers is unique in that no transition metals are required.[13] While cyclopropanation proceeded with good diastereoselectivities across a wide range of alkene substrates, this methodology was limited to a single carbene precursor bearing a phthalimide protecting group; as a result, the phthalimide-protected product requires further manipulation to access tertiary aminocyclopropanes of interest.

Our strategy to access tertiary aminocyclopropanes focused on identification of a readily available carbene precursor that would allow for variation of substituents on either carbene or alkene starting material. Inspired by previous cyclopropanation methodologies using tosyl hydrazones as safe and stable diazo alternatives,[14] we envisioned utilizing hydrazonamides (**2**, Scheme 1), which are easily synthesized via tertiary amides (**1**).[15,16] One literature example exploits a strained hydrazonamide sodium salt to generate aminocyclopropanes via photolysis, supporting our strategy.[17]

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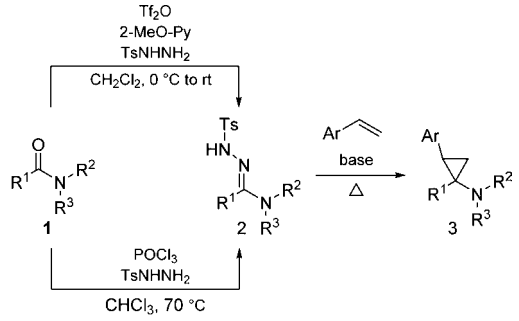
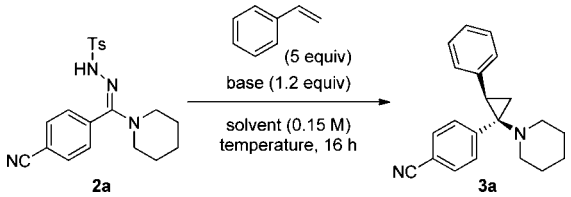
Scheme 1. Synthetic Strategy toward Tertiary Aminocyclopropanes



Initial optimization of the reaction was performed with hydrazonamide **2a** as a model substrate and styrene as the alkene partner. Compound **2a** was submitted to conditions developed by Barluenga and Cabal for the cyclopropanation of tosylhydrazones (Table 1, entry 1).[14b] After observing no formation of desired cyclopropane **3a**, it was rationalized that deprotonation of electron-rich hydrazonamide **2a** would require a stronger base. Indeed, selection of the base proved to be critical; a brief survey of bases identified LiHMDS as the optimal base, affording desired aminocyclopropane **3a** in 42% yield, as determined by NMR, relative to the internal standard (Table 1, entries 2−5). Importantly, only the *Z* stereoisomer was observed to form, in agreement with a report by Zhang and co-workers which disclosed a stereospecific aminocyclopropanation via thioamides.[12c] A solvent screen identified *p*-xylene as the optimal solvent for aminocyclopropanation (Table 1, entries 5−8). Increasing the reaction temperature to 115 °C further improved the yield, affording the desired aminocyclopropane **3a** in 64% yield (Table 1, entry 9).

To our surprise, performing the reaction with **2a** on a larger scale led to the isolation of both *Z* and *E* diastereoisomers, the *Z* isomer being the major product (Table 2, 63% yield, dr = 5:1). Throughout our study, both diastereoisomers displayed a striking difference in polarity; the *E* stereoisomer was systematically more difficult to isolate and in some cases seemed to be unstable during purification of the crude reaction mixture.

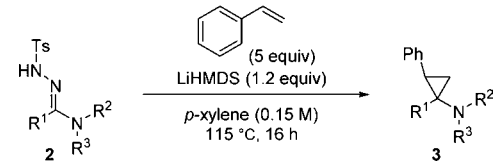
Table 1. Optimization of Reaction Conditions[a]

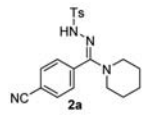
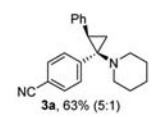
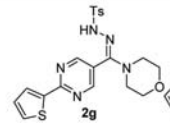
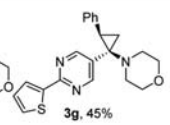
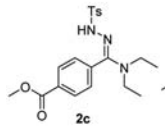
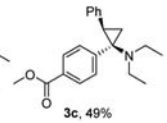
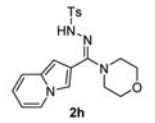
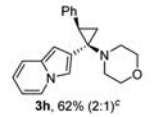
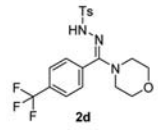
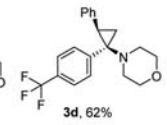
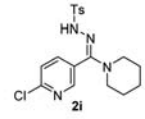
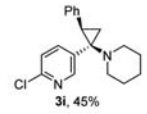
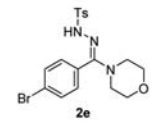
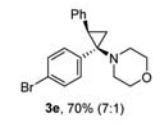
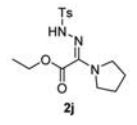
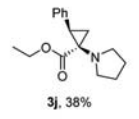
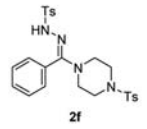
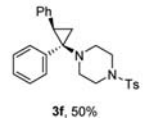
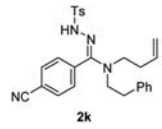
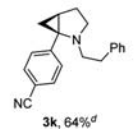


entry	base	solvent	temp (°C)	yield (%)[b]
1	K_2CO_3	dioxane	110	–
2	*t*-BuOLi	$PhCF_3$[c]	110	–
3	NaH	$PhCF_3$[c]	110	<5
4	*n*-BuLi	$PhCF_3$[c]	110	11
5	LiHMDS	$PhCF_3$	110	42
6	LiHMDS	toluene	110	20
7	LiHMDS	dioxane	110	40
8	LiHMDS	*p*-xylene	110	56
9	LiHMDS	*p*-xylene	115	64

[a]Reactions were run on a 0.065 mmol scale. [b]Yields determined from analysis of the ^{1}H NMR spectrum using triphenylmethane as an internal standard. [c]0.05 M concentration was used.

Table 2. Substrate Scope of Hydrazonamides[a]



hydrazonamide **2**	product **3** yield (*Z*/*E* dr)[b]	hydrazonamide **2**	product **3** yield (*Z*/*E* dr)[b]
 **2a**	 **3a**, 63% (5:1)	 **2g**	 **3g**, 45%
 **2c**	 **3c**, 49%	 **2h**	 **3h**, 62% (2:1)[c]
 **2d**	 **3d**, 62%	 **2i**	 **3i**, 45%
 **2e**	 **3e**, 70% (7:1)	 **2j**	 **3j**, 38%
 **2f**	 **3f**, 50%	 **2k**	 **3k**, 64%[d]

[a]Reactions were run on a 0.26 mmol scale; isolated yields. [b]Yields without dr are based on the *Z* isomer only. [c]135 °C was used. [d]Reaction was conducted in the absence of styrene at 0.05 M.

The substrate scope of the reaction was examined using the optimized conditions (Table 2). When electron-neutral hydrazonamide **2b**,[18] lacking the nitrile substituent, was treated under the reaction conditions, no desired aminocyclopropane was obtained. We reasoned that the reactive intermediate, potentially an *α*-aminocarbene, needed to be stabilized with an electron-withdrawing group to efficiently react with styrene. Tosylhydrazonamides bearing electron-withdrawing substituents on the aromatic group were readily converted to their corresponding aminocyclopropanes in moderate to good yields (Table 2, products **3a**, **3c**−**3e**). Cyclic and acyclic amines can both be incorporated on the cyclopropane as well as other medicinally privileged amines such as morpholine and piperazine (Table 2, products **3a**, **3d**−**3i**). We then turned our attention toward the incorporation of heteroaromatic groups. To our delight, many heterocyclic cores afforded the desired aminocyclopropanes in moderate yields (Table 2, products **3g**−**3i**), providing the first generally applicable procedure for the synthesis of such systems. The aromatic substituent could be replaced by an ester, although in lower yield (Table 2, product **3j**, 38% yield). The reaction was also suitable in an intramolecular cyclopropanation affording the desired product in 64% yield (Table 2, product **3k**).

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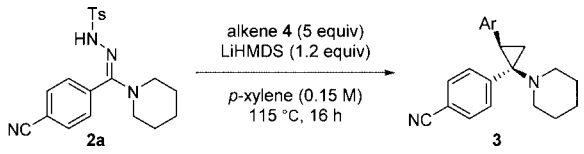
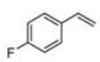
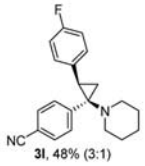
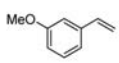
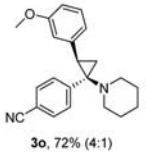
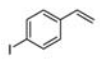
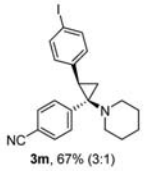
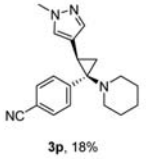
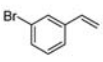
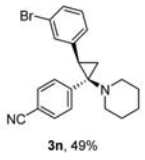
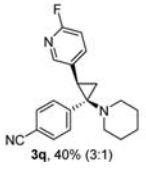
To further validate the utility of the method, the substrate scope was extended to different alkenes (Table 3). Electron-withdrawing substituents were well tolerated, leading to the desired aminocyclopropanes in moderate to good yields (Table 3, products **3l**–**3o**). Alkenes bearing heterocycles could also be used in the reaction, although in lower yields (Table 3, products **3p** and **3q**). However, the more electron-rich *p*-methoxystyrene **4r** did not afford any desired cyclopropane product, instead effecting dimerization of hydrazonamide **2a** (Scheme 2, product **5**).[19] This result can be rationalized by the relatively electron-rich nature of the potential carbene intermediate involved. When performing the transformation with the more basic 2-vinylpyridine **4s**, the corresponding ketone was obtained in 83% yield (Scheme 2, product **6**), likely resulting from ring opening of the desired aminocyclopropane **3s**.[12b] This result could provide a new strategy for the synthesis of aromatic ketones from amides.[20] Upon treatment of alkene source *N*-Boc-indole **4t** to the reaction conditions, the unanticipated product **7** was isolated in 35% yield (Scheme 2), presumably forming via C–O insertion into the carbamate. To the best of our knowledge, this represents the first example of a C–O carbamate insertion in the absence of metal.

In summary, we have developed a transition-metal-free protocol for the synthesis of valuable tertiary aminocyclopropanes. This privileged motif is rapidly assembled in only two steps from readily available tertiary amides. The optimized conditions for the aminocyclopropanation allow for the synthesis of synthetically difficult heterocyclic cyclopropane moieties. Moreover, a variety of different substitution patterns are tolerated, including functional group handles that facilitate further elaboration. We anticipate that this methodology will open new opportunities in medicinal chemistry, where prized aminocyclopropane scaffolds are often overlooked due to tedious syntheses.

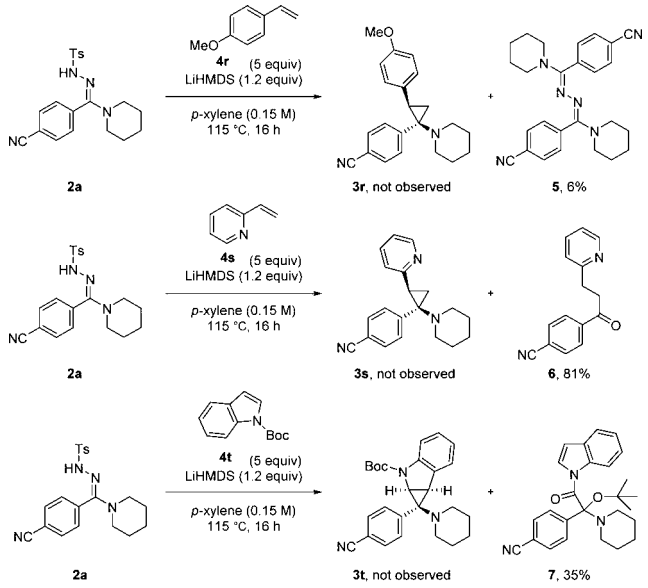
Table 3. Substrate Scope of Alkenes[a]



alkene 4	product 3 yield (Z/E dr)[b]	alkene 4	product 3 yield (Z/E dr)[b]
 4l	 3l, 48% (3:1)	 4o	 3o, 72% (4:1)
 4m	 3m, 67% (3:1)	 4p	 3p, 18%
 4n	 3n, 49%	 4q	 3q, 40% (3:1)

[a]Reactions were run on a 0.26 mmol scale, isolated yields. [b]Yields without dr are based on the *Z* isomer only.

Scheme 2. Alternative Reaction Pathways



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03345.

Optimization tables, experimental procedures, characterization data and copies of NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Talele, T. T. *J. Med. Chem.* **2016**, *59*, 8712–8756. (b) Brackmann, F.; de Meijere, A. *Chem. Rev.* **2007**, *107*, 4493–4537.

(2) Vaillancourt, F. H.; Yeh, E.; Vosburg, D. A.; O'Connor, S. E.; Walsh, C. T. *Nature* **2005**, *436*, 1191–1194.

(3) Augeri, D. J.; Robl, J. A.; Betebenner, D. A.; Magnin, D. R.; Khanna, A.; Robertson, J. G.; Wang, A.; Simpkins, L. M.; Taunk, P.; Huang, Q.; Han, S.-P.; Abboa-Offei, B.; Cap, M.; Xin, L.; Tao, L.; Tozzo, E.; Welzel, G. E.; Egan, D. M.; Marcinkeviciene, J.; Chang, S. Y.; Biller, S. A.; Kirby, M. S.; Parker, R. A.; Hamann, L. G. *J. Med. Chem.* **2005**, *48*, 5025–5037.

(4) (a) Array biopharma pipeline, http://www.arraybiopharma.com/product-pipeline/other-compounds/danoprevir (accessed 17 September 2016). (b) Jiang, Y.; Andrews, S. W.; Condroski, K. R.; Buckman,

DOI: 10.1021/acs.orglett.6b03345
Org. Lett. 2016, 18, 6448–6451

B.; Serebryany, V.; Wenglowsky, S.; Kennedy, A. L.; Madduru, M. R.; Wang, B.; Lyon, M.; Doherty, G. A.; Woodard, B. T.; Lemieux, C.; Geck Do, M.; Zhang, H.; Ballard, J.; Vigers, G.; Brandhuber, B. J.; Stengel, P.; Josey, J. A.; Beigelman, L.; Blatt, L.; Seiwert, S. D. *J. Med. Chem.* **2014**, *57*, 1753−1769.

(5) (a) Luo, G.; Chen, L.; Hu, S.; Huang, Y.; Mattson, G.; Iben, L. G.; Russell, J. W.; Clarke, W. J.; Hogan, J. B.; Antal-Zimanyi, I.; Poindexter, G. S. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 3814−3817. (b) Hu, S.; Huang, Y.; Deshpande, M.; Luo, G.; Bruce, M. A.; Chen, L.; Mattson, G.; Iben, L. G.; Zhang, J.; Russell, J. W.; Clarke, W. J.; Hogan, J. B.; Ortiz, A.; Flint, O.; Henwood, A.; Gao, Q.; Antal-Zimanyi, I.; Poindexter, G. S. *ACS Med. Chem. Lett.* **2012**, *3*, 222−226.

(6) (a) Gnad, F.; Reiser, O. *Chem. Rev.* **2003**, *103*, 1603−1623. (b) Davies, H. M. L.; Bruzinski, P. R.; Lake, D. H.; Kong, N.; Fall, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 6897−6907. (c) Charette, A. B.; Côté, B. *J. Am. Chem. Soc.* **1995**, *117*, 12721−12732.

(7) (a) Lin, K.-W.; Yan, S.; Hsieh, I.-L.; Yan, T.-H. *Org. Lett.* **2006**, *8*, 2265−2267. (b) de Meijere, A.; Kozhushkov, S. I.; Savchenko, A. I. *J. Organomet. Chem.* **2004**, *689*, 2033−2055. (c) de Meijere, A.; Williams, C. M.; Kourdioukov, A.; Sviridov, S. V.; Chaplinski, V.; Kordes, M.; Savchenko, A. I.; Stratmann, C.; Noltemeyer, M. *Chem. - Eur. J.* **2002**, *8*, 3789−3801. (d) Kulinkovich, O. G.; de Meijere, A. *Chem. Rev.* **2000**, *100*, 2789−2834.

(8) (a) Zhu, C.; Li, J.; Chen, P.; Wu, W.; Ren, Y.; Jiang, H. *Org. Lett.* **2016**, *18*, 1470−1473. (b) Gildner, P. G.; DeAngelis, A.; Colacot, T. J. *Org. Lett.* **2016**, *18*, 1442−1445. (c) Du, W.; Gu, Q.; Li, Z.; Yang, D. *J. Am. Chem. Soc.* **2015**, *137*, 1130−1135. (d) Sakae, R.; Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2014**, *16*, 1228−1231. (e) Valenta, P.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2010**, *132*, 14179−14190. (f) Prosser, A. R.; Banning, J. E.; Rubina, M.; Rubin, M. *Org. Lett.* **2010**, *12*, 3968−3971. (g) Gagnon, A.; St-Onge, M.; Little, K.; Duplessis, M.; Barabé, F. *J. Am. Chem. Soc.* **2007**, *129*, 44−45. (h) Tsai, C.-C.; Hsieh, I.-L.; Cheng, T.-T.; Tsai, P.-K.; Lin, K.-W.; Yan, T.-H. *Org. Lett.* **2006**, *8*, 2261−2263.

(9) (a) Chanthamath, S.; Nguyen, D. T.; Shibatomi, K.; Iwasa, S. *Org. Lett.* **2013**, *15*, 772−775. (b) Lindsay, V. N. G.; Nicolas, C.; Charette, A. B. *J. Am. Chem. Soc.* **2011**, *133*, 8972−8981. (c) Lindsay, V. N. G.; Lin, W.; Charette, A. B. *J. Am. Chem. Soc.* **2009**, *131*, 16383−16385. (d) Moreau, B.; Charette, A. B. *J. Am. Chem. Soc.* **2005**, *127*, 18014−18015. (e) Wurz, R. P.; Charette, A. B. *J. Org. Chem.* **2004**, *69*, 1262−1269. (f) Aggarwal, V. K.; de Vicente, J.; Bonnert, R. V. *Org. Lett.* **2001**, *3*, 2785−2788.

(10) (a) Stepan, A. F.; Walker, D. P.; Bauman, J.; Price, D. A.; Baillie, T. A.; Kalgutkar, A. S.; Aleo, M. D. *Chem. Res. Toxicol.* **2011**, *24*, 1345−1410. (b) Kalgutkar, A. S.; Gardner, I.; Obach, R. S.; Shaffer, C. L.; Callegari, E.; Henne, K. R.; Mutlib, A. E.; Dalvie, D. K.; Lee, J. S.; Nakai, Y.; O'Donnell, J. P.; Boer, J.; Harriman, S. P. *Curr. Drug Metab.* **2005**, *6*, 161−225. (c) Sun, Q.; Zhu, R.; Foss, F. W., Jr.; Macdonald, T. L. *Chem. Res. Toxicol.* **2008**, *21*, 711−719.

(11) (a) Cerny, M. A.; Hanzlik, R. P. *J. Am. Chem. Soc.* **2006**, *128*, 3346−3354. (b) Cerny, M. A.; Hanzlik, R. P. *Arch. Biochem. Biophys.* **2005**, *436*, 265−275. (c) Shaffer, C. L.; Harriman, S.; Koen, Y. M.; Hanzlik, R. P. *J. Am. Chem. Soc.* **2002**, *124*, 8268−8274.

(12) (a) Ishikawa, S.; Sheppard, T. D.; D'Oyley, J. M.; Kamimura, A.; Motherwell, W. B. *Angew. Chem., Int. Ed.* **2013**, *52*, 10060−10063. (b) Mitamura, T.; Nomoto, A.; Sonoda, M.; Ogawa, A. *Tetrahedron* **2008**, *64*, 9983−9988. (c) Zhu, W.; Qian, W.; Zhang, Y. *J. Chem. Res.* **2005**, *2005*, 164−166. (d) Bégis, G.; Cladingboel, D.; Motherwell, W. B. *Chem. Commun.* **2003**, 2656−2657. (e) Barluenga, J.; Aznar, F.; Gutiérrez, I.; García-Granda, S.; Llorca-Baragaño, M. A. *Org. Lett.* **2002**, *4*, 4273−4276. (f) Ogawa, A.; Takami, N.; Nanke, T.; Ohya, S.; Hirao, T.; Sonoda, N. *Tetrahedron* **1997**, *53*, 12895−12902. (g) Ogawa, A.; Takami, N.; Sekiguchi, M.; Ryu, I.; Kambe, N.; Sonoda, N. *J. Am. Chem. Soc.* **1992**, *114*, 8729−8730.

(13) Alford, J. S.; Davies, H. M. L. *Org. Lett.* **2012**, *14*, 6020−6023.

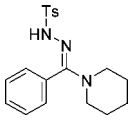
(14) (a) Jia, M.; Ma, S. *Angew. Chem., Int. Ed.* **2016**, *55*, 9134−9166. (b) Barluenga, J.; Quiñones, N.; Tomás-Gamasa, M.; Cabal, M.-P. *Eur. J. Org. Chem.* **2012**, *2012*, 2312−2317. (c) Barluenga, J.; Valdés, C. *Angew. Chem., Int. Ed.* **2011**, *50*, 7486−7500. (d) Taber, D. F.; Guo, P.; Guo, N. *J. Am. Chem. Soc.* **2010**, *132*, 11179−11182. (e) Taber, D. F.; Guo, P. *J. Org. Chem.* **2008**, *73*, 9479−9481. (f) Fulton, J. R.; Aggarwal, V. K.; de Vicente, J. *Eur. J. Org. Chem.* **2005**, *2005*, 1479−1492. (g) Adams, L. A.; Aggarwal, V. K.; Bonnert, R. V.; Bressel, B.; Cox, R. J.; Shepherd, J.; de Vicente, J.; Walter, M.; Whittingham, W. G.; Winn, C. L. *J. Org. Chem.* **2003**, *68*, 9433−9440.

(15) (a) Cyr, P.; Régnier, S.; Bechara, W. S.; Charette, A. B. *Org. Lett.* **2015**, *17*, 3386−3389. (b) Rapoport, H.; Bonner, R. M. *J. Am. Chem. Soc.* **1950**, *72*, 2783−2784.

(16) A first attempt at cyclopropanating styrene using a *N*-tosylhydrazonamide derived from *N*,*N*-diethylbenzamide was carried out at the Université de Montréal: Cyr, P.; Charette, A. B., unpublished results.

(17) Ye, Q.; Komarov, I. V.; Kirby, A. J.; Jones, M., Jr. *J. Org. Chem.* **2002**, *67*, 9288−9294.

(18) Hydrazonamide **2b**:



(19) Product **3s** appeared to be the major product as determined by HPLC-MS, but was only isolated in 6% yield.

(20) (a) Meng, G.; Shi, S.; Szostak, M. *Synlett* **2016**, *27*, 2530−2540. (b) Simmons, B. J.; Weires, N. A.; Dander, J. E.; Garg, N. K. *ACS Catal.* **2016**, *6*, 3176−3179. (c) Weires, N. A.; Baker, E. L.; Garg, N. K. *Nat. Chem.* **2015**, *8*, 75−79. (d) Li, X.; Zou, G. *Chem. Commun.* **2015**, *51*, 5089−5092. (e) Meng, G.; Szostak, M. *Org. Lett.* **2015**, *17*, 4364−4367. (f) Bechara, W. S.; Pelletier, G.; Charette, A. B. *Nat. Chem.* **2012**, *4*, 228−234.

DOI: 10.1021/acs.orglett.6b03345
Org. Lett. 2016, 18, 6448−6451