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Markovnikov-Selective Hydrothiolation of Styrenes: Application to the Synthesis of Stereodefined Trisubstituted Olefins

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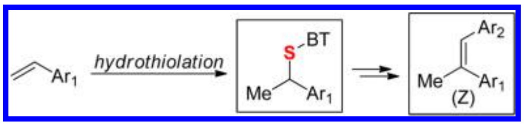
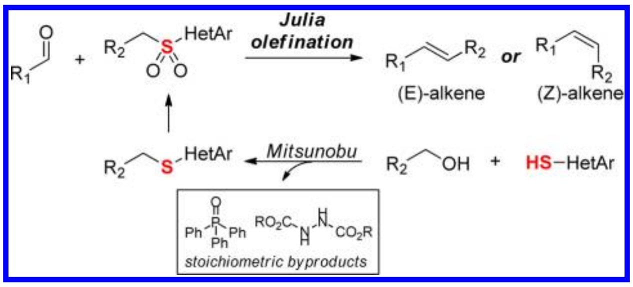
ABSTRACT



BT-sulfones react with aromatic aldehydes to furnish trisubstituted alkenes with excellent *Z* stereoselectivity. These sulfones are synthesized by hydrothiolation of styrene and styrenyl derivatives (followed by oxidation). This method provides a conceptually novel way to prepare these important sulfur compounds.

The Julia olefination reaction (and its numerous modifications) is a convenient tool for the synthesis of stereodefined (*E*)- and (*Z*)-1,2-disubstituted alkenes (Scheme 1).[1] As such, it is therefore an important transformation in the repertoire of synthetic chemists.

Scheme 1. Alkene Synthesis by Julia Olefination



One particular drawback of the Julia olefination reaction lies in the preparation of the requisite sulfone starting materials. These are accessed by oxidation of the corresponding thioether which, in turn, is typically obtained by the Mitsunobu reaction between an alcohol and the appropriate thiol. While the Mitsunobu reaction has been validated in numerous complex total syntheses, it is decidedly not atom economical since it produces stoichiometric amounts of phosphine oxides and hydrazine dicarboxylates. These side products often complicate the purification of the desired thioethers and render the reaction less desirable from an industrial point of view. Alternatively, these intermediates can also be prepared by alkylation with alkyl halides.[2]

Our group has been involved in developing new methods for the construction of carbon–sulfur bonds.[3] Recently, we reported an improved method for preparing the requisite thioethers for Julia olefination reactions through the $Ga(OTf)_3$-catalyzed direct displacement of alcohols.[4] The only byproduct is water.

In theory, the thioether precursors required for the Julia olefination may also be prepared by hydrothiolation[5] between an alkene and the appropriate thiol. *Anti*-Markovnikov additions of thiols across alkenes (thiol–ene reaction) have been known since 1905.[6] This is a radical-mediated reaction that satisfies many of the criteria of click

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[1] Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563.

[2] For lead references, see: (a) Williams, D. R.; Cortez, G. S.; Bogen, S. L.; Rojas, C. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4612. (b) Crimmins, M. T.; DeBaillie, A. C. *J. Am. Chem. Soc.* **2006**, *128*, 4936. (c) Frankowski, K. J.; Golden, J. E.; Zeng, Y.; Lei, Y.; Aubé, J. *J. Am. Chem. Soc.* **2008**, *130*, 6018. (d) Nielsen, M.; Jacobsen, C. B.; Paixão, M. W.; Holub, N.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2009**, *131*, 10581.

[3] (a) Han, X.; Zhang, Y.; Wu, J. *J. Am. Chem. Soc.* **2010**, *132*, 4104. (b) Robertson, F. J.; Wu, J. *J. Am. Chem. Soc.* **2012**, *134*, 2775. (c) Robertson, F. J.; Wu, J. *Org. Lett.* **2010**, *12*, 2668.

[4] Han, X.; Wu, J. *Org. Lett.* **2010**, *12*, 5780.

[5] Castarlenas, R.; Di Giuseppe, A.; Pérez-Torrente, J. J.; Oro, L. A. *Angew. Chem., Int. Ed.* **2013**, *52*, 211.

[6] Posner, T. *Ber. Deut. Chem. Ges.* **1905**, *38*, 646.

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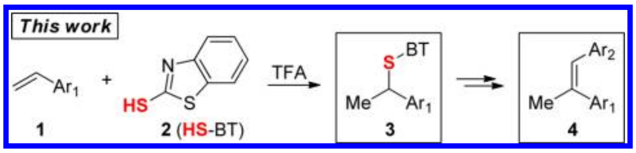
chemistry. It has recently emerged as a powerful tool for bioconjugation and in supramolecular chemistry.[7] In contrast, Markovnikov-selective hydrothiolation is unusual and is an active area of research.[8−11]

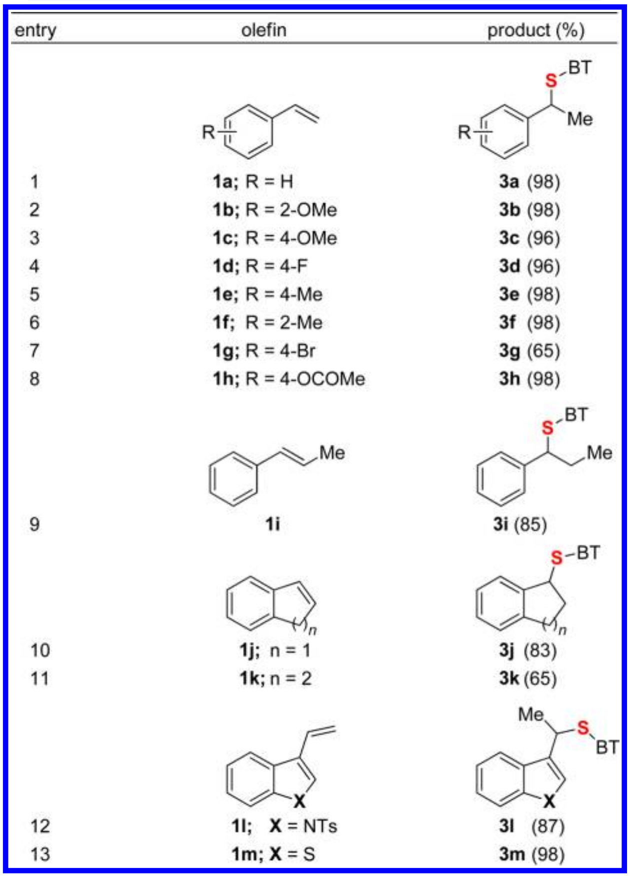


In this study, we report the synthesis of Julia-type thioethers by Brønsted acid catalyzed, Markovnikov-selective hydrothiolation of styrene and its derivatives **1** with 2-mercaptobenzothiazole (**2**) to furnish **3**. This is a conceptually novel and, in principle, perfectly atom economical approach for preparing these important intermediates.

We also demonstrate that the subsequently derived sulfones participate in stereoselective olefination reactions to generate trisubstituted *Z* alkenes **4**. This is significant in that there are exceedingly few examples of highly stereoselective syntheses of trisubstituted alkenes by way of Julia olefination. These compounds are most commonly prepared via transition metal-catalyzed cross-coupling reactions with alkenyl halides or vinylmetal species derived from the corresponding alkynes.[12,13]

In order to identify optimal conditions for the hydrothiolation, we surveyed the reaction between styrene (**1a**) and 2-mercaptobenzothiazole (**2**) catalyzed by various Lewis and Brønsted acids. After extensive optimization, we discovered that 10 equiv of trifluoroacetic acid (TFA) in dichloromethane at room temperature afforded the desired hydrothiolation product **3a** with the highest isolated yield and selectivity (98% yield and > 20:1 Markovnikov regioselectivity). Omission of TFA did not provide any of the desired hydrothiolation product. Instead, it generated a compound of which mass spectrometry and NMR data are consistent with hydroxythiolation across the alkene. The precise structural assignment remains to be confirmed.

Table 1. Scope of Markovnikov-Selective Hydrothiolation



entry	olefin	product (%)
1	**1a**; R = H	**3a** (98)
2	**1b**; R = 2-OMe	**3b** (98)
3	**1c**; R = 4-OMe	**3c** (96)
4	**1d**; R = 4-F	**3d** (96)
5	**1e**; R = 4-Me	**3e** (98)
6	**1f**; R = 2-Me	**3f** (98)
7	**1g**; R = 4-Br	**3g** (65)
8	**1h**; R = 4-OCOMe	**3h** (98)
9	**1i**	**3i** (85)
10	**1j**; n = 1	**3j** (83)
11	**1k**; n = 2	**3k** (65)
12	**1l**; X = NTs	**3l** (87)
13	**1m**; X = S	**3m** (98)

With these optimized conditions in hand, we proceeded to explore the scope of the hydrothiolation. As is evident in Table 1, this method is compatible with both electron-rich, electron-deficient, and cyclic styrenyl substrates. It should be noted that Brønsted acids often promote unwanted polymerization of styrene and its derivatives. These byproducts are not formed in any appreciable amounts. It is likely that attack of a putative benzylic carbocation intermediate by the highly nucleophilic **2** is faster than the rate of polymerization.

To explore the synthesis of configurationally enriched trisubstituted alkenes, we carried out olefination reactions between sulfone **5** (prepared by *m*cpba oxidation of **3e**) and several aldehydes (Table 2). The reactions were carried out in the presence of lithium diisopropyl amide (LDA) under Barbier-type conditions which was required to minimize homocoupling of the BT-sulfone.[1] The reaction is compatible with a wide array of functionalized aromatic and

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[7] Dondoni, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 8995.

[8] For examples of Brønsted acid catalyzed hydrothiolations of *alkyl*-substituted alkenes, see: (a) Ipatieff, V. N.; Pines, H.; Friedman, B. S. *J. Am. Chem. Soc.* **1938**, *60*, 2731. (b) Screttas, C. G.; Micha-Screttas, M. *J. Org. Chem.* **1979**, *44*, 713.

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[11] For lead references of metal-catalyzed hydrothiolation of *alkynes*, see: (a) Weiss, C. J.; Marks, T. J. *J. Am. Chem. Soc.* **2010**, *132*, 10533. (b) Weiss, C. J.; Wobser, S. D.; Marks, T. J. *J. Am. Chem. Soc.* **2009**, *131*, 2062. (c) Cao, C.; Fraser, L. R.; Love, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 17614. (d) Yang, J.; Sabarre, A.; Fraser, L. R.; Patrick, B. O.; Love, J. A. *J. Org. Chem.* **2009**, *74*, 182. (e) Ogawa, A.; Ikeda, T.; Kimura, K.; Hirao, T. *J. Am. Chem. Soc.* **1999**, *121*, 5108. (f) Kondoh, A.; Takami, K.; Yorimitsu, H.; Oshima, K. *J. Org. Chem.* **2005**, *70*, 6468. (g) Ananikov, V. P.; Malyshev, D. A.; Beletskaya, I. P.; Aleksandrov, G. G.; Eremenko, I. L. *Adv. Synth. Catal.* **2005**, *347*, 1993. (h) Sarma, R.; Rajesh, N.; Prajapati, D. *Chem. Commun.* **2012**, *48*, 4014.

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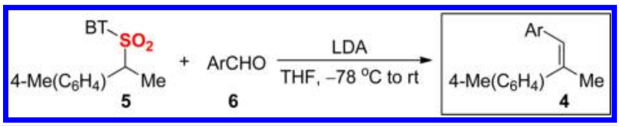
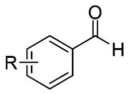
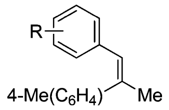
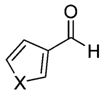
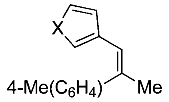
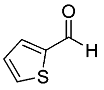
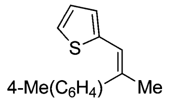
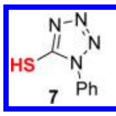
Table 2. Stereodefined Trisubstituted Olefin Synthesis



entry	aldehyde	product (%)	*Z*:*E*
			
1	**6a**; R = 4-CO2Me	**4a** (67)	>95:5
2	**6b**; R = 4-CF3	**4b** (64)	>95:5
3	**6c**; R = 4-Cl	**4c** (82)	>95:5
4	**6d**; R = 4-NO2	**4d** (50)	93:7
5	**6e**; R = 4-OMe	**4e** (90)	>95:5
6	**6f**; R = 4-CN	**4f** (38)	92:8
7	**6g**; R = 4-NMe2	**4g** (85)	90:10
8	**6h**; R = H	**4h** (75)	>95:5
			
9	**6i**; X = O	**4i** (97)	>95:5
10	**6j**; X = S	**4j** (68)	>95:5
			
11	**6k**	**4k** (81)	>95:5

heteroaromatic aldehydes. The desired alkenes **4a**−**k** could be isolated in good yields with high *Z*-selectivities. These are among the best selectivities obtained for the preparation of trisubstituted alkenes utilizing the Julia olefination reaction.[14]

Other Julia-type thiols were also explored for their utility in the Markovnikov-selective hydrothiolation of styrenes. However, these experiments yielded mixed results. In the case of 1-phenyl-1*H*-tetrazole-5-thiol (**7**), catalytic Ga(OTf)$_3$ was required to furnish the Markovnikov-selective hydrothiolation. The use of 2-mercaptopyridine (**8**) generated hydrothiolation products as 1:1 mixtures of regioisomers.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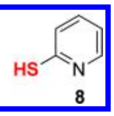
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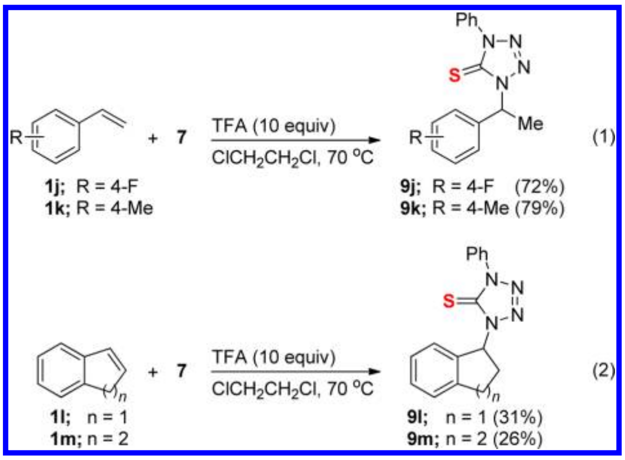

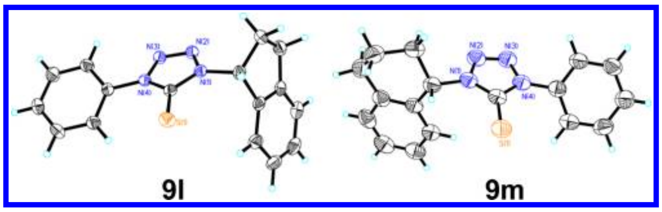

Figure 1. X-ray crystal structure of **9l** and **9m**.

At elevated temperatures, the reaction between **7** and **1j**−**m** unexpectedly yielded formal hydroamination products (eqs 1−2).[15] The X-ray crystal structures of two representative compounds are shown in Figure 1.[16] Interestingly, related tetrazole thiones have been converted to the carbodiimides by photochemical irradiation.[17] In that work, three chemical steps were needed to access the requisite tetrazone thione starting materials. In comparison, our method provides analogous structures in a single step via formal hydroamination. Finally, Vicario and co-workers showed that treatment of tetrazole thiones with H$_2$ and Raney-Ni generated the corresponding isoureas and formamidines.[15] Further work related to this unusual reaction (e.g., mechanistic studies and the conversion of **9j**−**m** to the corresponding amines) is ongoing in our laboratories.

In this communcation, we have described the Markovnikov-selective hydrothiolation of styrenyl derivatives with 2- mercaptobenzothiazole (**2**) to furnish thioethers **3**. This method represents a more atom economical alternative to a classical means for preparing these important intermediates (usually by the Mitsunobu reaction). Oxidation to the sulfone followed by reaction with various aldehydes using the modified Julia olefination protocol furnishes stereodefined trisubstituted alkenes. This method provides a high stereochemical bias for *Z*-olefins.

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Supporting Information Available. Experimental procedures and spectra for all previously unreported compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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(15) For another example in which phenyl-1*H*-tetrazole-5-thiol (**6**) is alkylated at nitrogen, see: Uria, U.; Reyes, E.; Vicario, J. L.; Badía, D.; Carrillo, L. *Org. Lett.* **2011**, *13*, 336.

(16) CCDC 940539, 940540.

(17) Alawode, O. E.; Robinson, C.; Rayat, S. *J. Org. Chem.* **2010**, *76*, 216.