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Diastereoselective Synthesis of CF_3-Substituted, Epoxide-Fused Heterocycles with β-(Trifluoromethyl)vinylsulfonium Salts

Sven P. Fritz,[†] Thomas H. West,[†] Eoghan M. McGarrigle,*[,†,‡] and Varinder K. Aggarwal*[,†]

School of Chemistry, University of Bristol, Cantock's Close, BS8 1TS Bristol, U.K., and Centre for Synthesis and Chemical Biology, UCD School of Chemistry and Chemical Biology, University College Dublin, Belfield, Dublin 4, Ireland

V.Aggarwal@bristol.ac.uk; Eoghan.McGarrigle@ucd.ie

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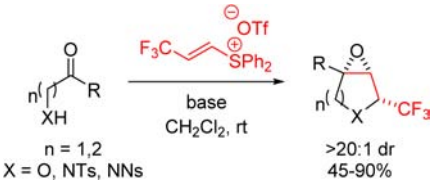
ABSTRACT



CF_3-substituted vinyl diphenylsulfonium triflate is an effective annulation reagent for the formation of α-CF_3 substituted, epoxide-fused heterocycles (pyrrolidines, piperidines, and tetrahydrofurans). This simple method affords a variety of valuable heterocyclic building blocks in a highly diastereoselective manner (dr >20:1).

Fluorinated and especially CF_3-substituted compounds are of considerable contemporary interest,[1] due to the development of biologically active compounds containing this functionality.[2] Combined into heterocyclic frameworks, this often leads to the creation of superior pharmacophores.[3] Despite this high interest, efficient methods, starting from simple materials, for the introduction of the trifluoromethyl group into saturated heterocycles are still scarce.[4,5] We recently reported the synthesis of epoxide- and aziridine-fused five-, six-, and seven-membered heterocycles from unsubstituted vinylsulfonium triflates[6,7] and explored alternative modes of reactivity with these reagents for the construction of other monocyclic four- to seven-membered heterocycles such as morpholines.[8,9] We envisioned that we could combine our advances on the Michael-type-addition/annulation sequence for fused ring systems with CF_3-substituted vinylsulfonium salts reported by others[10] to produce useful heterocyclic building blocks (Scheme 1).

[†] University of Bristol.
[‡] University College Dublin.

(1) (a) Yale, H. L. *J. Med. Pharmaceut. Chem.* **1959**, *1*, 121. (b) Dolbier, W. R. *J. Fluorine Chem.* **2005**, *126*, 157. (c) Muller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (d) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308.

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(5) For recent examples on the formation of sp^3 C–CF_3 bonds leading to building blocks for similar heterocycles, see: (a) Kieltsch, I.; Eisenberger, P.; Togni, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 754. (b) Pham, P. V.; Nagib, D. A.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2011**, *50*, 6119. (c) Yasu, Y.; Koike, T.; Akita, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 9567 and references therein.

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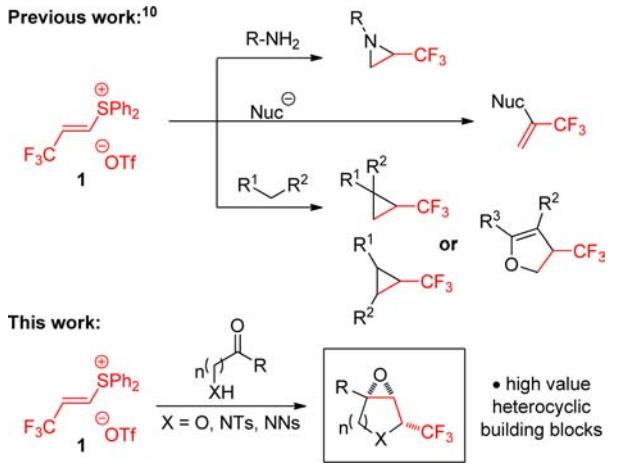
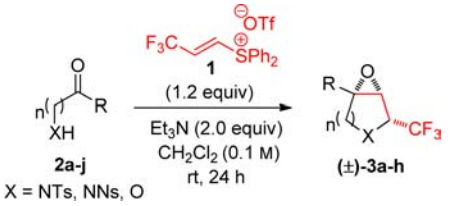
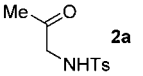
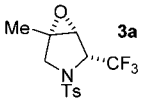
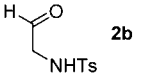
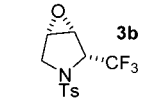
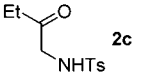
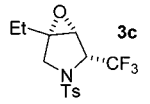
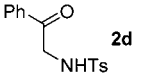
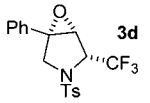
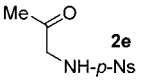
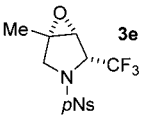
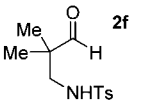
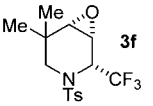
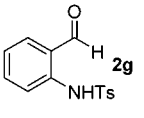
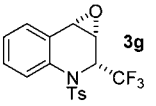
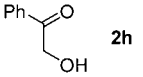
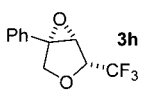
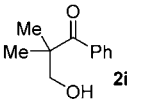
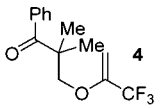
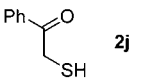
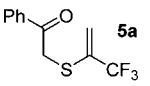
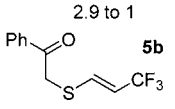
Scheme 1. Context of Presented Work



Screening of reaction conditions using aminoketone **2a** and β-trifluoromethylvinyl sulfonium salt **1** led to an optimized method that produced **3a** in 81% yield and in > 20:1 dr (please see Supporting Information for optimization details). The scope of the reaction (Table 1) was shown to extend to the synthesis of other *N*-tosyl pyrrolidines **3a**–**d**, giving good yields and excellent diastereoselectivity. Sulfonamide **3e** bearing the easier-to-cleave *p*-Ns[11] also worked well. Furthermore, the synthesis of fused piperidines **3f,g** was possible, as long as enolizable protons were not present, otherwise competing elimination occurred.[12]

Table 1. Substrate Scope of the Annulation Reaction



entry	reactant	product	yield[a] [%]	dr
1	 **2a**	 **3a**	81	> 20:1
2	 **2b**	 **3b**	49[b]	> 20:1
3	 **2c**	 **3c**	71	> 20:1
4	 **2d**	 **3d**	64	> 20:1
5	 **2e**	 **3e**	90	> 20:1
6	 **2f**	 **3f**	72[c]	> 20:1
7	 **2g**	 **3g**	45	> 20:1
8	 **2h**	 **3h**	88	> 20:1
9	 **2i**	 **4**	63[d]	-
10	 **2j**	 **5a**  **5b** 2.9 to 1	91[d,e]	-

[a] Isolated yield after purification. [b] From polymeric aldehyde **2b**. [c] 36 h reaction time. [d] A weaker (pyridine) or stronger (NaH) base did not change the outcome of the reaction, but led to much lower conversion. [e] Combined yield of **5a** and **5b**, **5a:5b** = 2.9:1.

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(7) For our work, see: (a) Unthank, M. G.; Hussain, N.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2006**, *45*, 7066. (b) Kokotos, C. G.; McGarrigle, E. M.; Aggarwal, V. K. *Synlett* **2008**, 219. (c) Unthank, M. G.; Tavassoli, B.; Aggarwal, V. K. *Org. Lett.* **2008**, *10*, 1501. (d) Yar, M.; Unthank, M. G.; McGarrigle, E. M.; Aggarwal, V. K. *Chem.—Asian. J.* **2011**, *6*, 372. (e) Fritz, S. P.; Ali, Z.; Unthank, M. G.; McGarrigle, E. M.; Aggarwal, V. K. *Helv. Chim. Acta* **2012**, in press, doi:10.1002/hlca.201200455.

(8) For further vinylsulfonium mediated annulation reactions, see: (a) Matsuo, J.; Yamanaka, H.; Kawana, A.; Mukaiyama, T. *Chem. Lett.* **2003**, *32*, 392. (b) Yamanaka, H.; Matsuo, J.; Kawana, A.; Mukaiyama, T. *Chem. Lett.* **2003**, *32*, 626. (c) Yamanaka, H.; Mukaiyama, T. *Chem. Lett.* **2003**, *32*, 1192. (d) Yamanaka, H.; Matsuo, J.; Kawana, A.; Mukaiyama, T. *ARKIVOC* **2004**, 42. (e) Yar, M.; McGarrigle, E. M.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2008**, *47*, 3784. (f) Hansch, M.; Illa, O.; McGarrigle, E. M.; Aggarwal, V. K. *Chem.—Asian. J.* **2008**, *3*, 1657. (g) Yar, M.; McGarrigle, E. M.; Aggarwal, V. K. *Org. Lett.* **2009**, *11*, 257. (h) Xie, C. S.; Han, D. Y.; Liu, J. H.; Xie, T. *Synlett* **2009**, 3155. (i) Bornholdt, J.; Felding, J.; Kristensen, J. L. *J. Org. Chem.* **2010**, *75*, 7454. (j) Catalan-Munoz, S.; Muller, C. A.; Ley, S. V. *Eur. J. Org. Chem.* **2010**, 183. (k) Xie, C. S.; Han, D. Y.; Hu, Y.; Liu, J. H.; Xie, T. A. *Tetrahedron Lett.* **2010**, *51*, 5238. (l) Chen, J. R.; An, J.; Chang, N. J.; Song, L. D.; Jin, Y. Q.; Ma, Y.; Xiao, W. J. *Chem. Commun.* **2011**, *47*, 1869. (m) Fritz, S. P.; Mumtaz, A.; Yar, M.; McGarrigle, E. M.; Aggarwal, V. K. *Eur. J. Org. Chem.* **2011**, 3156. (n) McGarrigle, E. M.; Fritz, S. P.; Favereau, L.; Yar, M.; Aggarwal, V. K. *Org. Lett.* **2011**, *13*, 3060. (o) Yar, M.; Fritz, S. P.; Gates, P. J.; McGarrigle, E. M.; Aggarwal, V. K. *Eur. J. Org. Chem.* **2012**, 160. (p) Fritz, S. P.; Moya, J. F.; Unthank, M. G.; McGarrigle, E. M.; Aggarwal, V. K. *Synthesis* **2012**, *44*, 1584. (q) Mao, Z.; Qu, H.; Zhao, Y.; Lin, X. *Chem. Commun.* **2012**, *48*, 9927.

(9) For reviews, see: (a) Fritz, S. P. *Synlett* **2012**, *23*, 480. (b) Yar, M.; McGarrigle, E. M.; Aggarwal, V. K. Sulfonium, Ethenyldiphenyl-, 1,1,1-Trifluoromethanesulfonate. In *Encyclopedia of Reagents for Organic Synthesis*, eEROS; Paquette, L. A., Crich, D., Fuchs, P. L., Molander, G. A., Eds.; John Wiley & Sons Ltd.: 2012; doi: 10.1002/047084289X.rn01409.

Epoxide-fused tetrahydrofuran **3h** was synthesized in good yield and excellent diastereoselectivity, but the attempted synthesis of six-membered oxygen heterocycles was dominated by competing elimination, forming enol ether **4**.[12] Thiol **2j**, with increased acidity adjacent to the CF_3 group, also resulted in elimination giving rise to products **5a/5b**. Evidently, in cases of slow cyclization or increased acidity of the C*H*CF_3, competing elimination dominates.[13] The *cis* relative stereochemistry of the product from **2a** was confirmed from a crystal structure of **3a** (Figure 1).

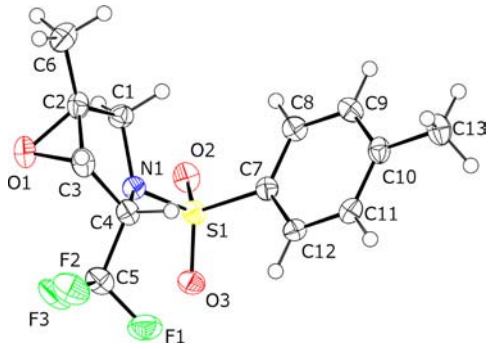
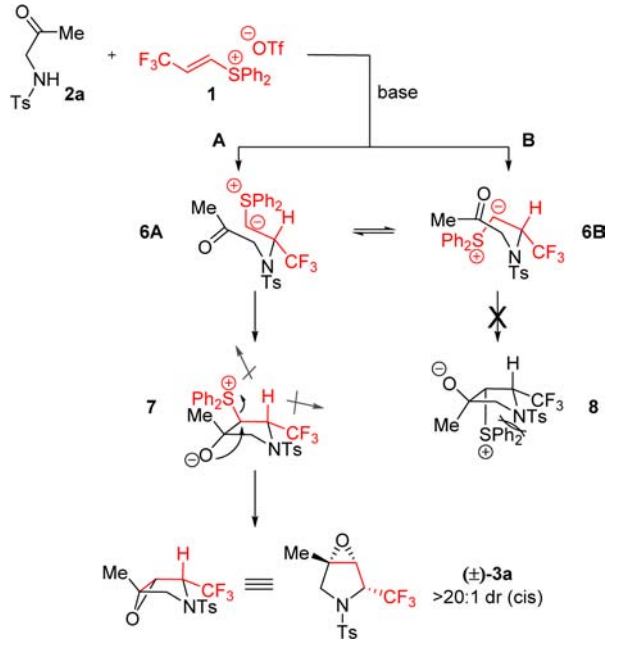


Figure 1. X-ray crystal structure of **3a**, showing *cis* configuration of epoxide to CF_3 (thermal ellipsoids are drawn at the 50% probability level).

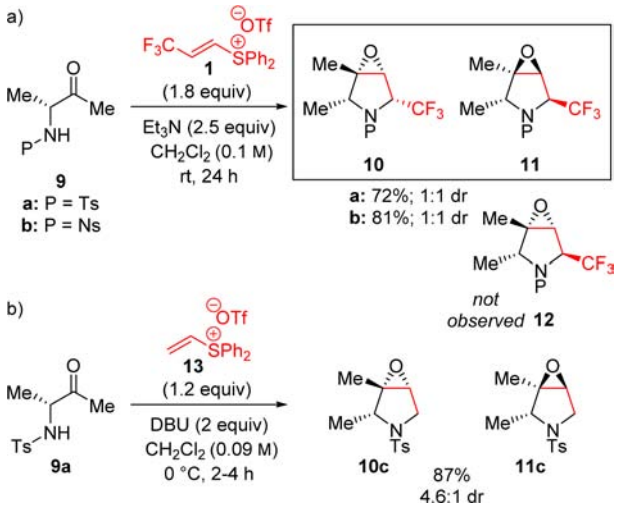
Scheme 2. Proposed Reaction Pathway for the Diastereoselective Formation of **3a**



Based on our experience with unsubstituted vinylsulfonium salts,[7] we propose that, after initial addition of the nucleophile **2a** to vinyl sulfonium salt **1** to form sulfur ylide **6**, two possible pathways (**A** and **B**) leading to *cis* and *trans* products should be considered (Scheme 2). Betaine **7** would suffer less from steric strain than **8** and has more favorable dipole interactions than **8**. Pathway **A** with a transition state leading from conformer **6A** to betaine **7** would be expected to be lower in energy than pathway **B** (with a transition state leading from conformer **6B** to betaine **8**) as the transition states will experience similar steric and dipole interactions as the betaines. This accounts for the preferred formation of the *cis*-epoxide **3a**.

The strength of the diastereocontrol provided by the CF_3 group (reagent control) was probed using the chiral substrates derived from alanine, **9a,b**. Out of four possible products, only two were obtained, **10** and **11**, in a 1:1 ratio (Scheme 3a). Unsurprisingly, the stereogenic center in **9** does not influence which face of the vinyl sulfonium salt is attacked. The chiral substrate **9a** shows an inherent preference for formation of the epoxide *cis* to the methyl group (Scheme 3b).[7c] Thus, product **10**, with the epoxide *cis* to both the Me and CF_3 groups, is "doubly matched" and expected to be easily formed. In contrast, compound **11** has the epoxide *cis* to the CF_3 group but *trans* to the Me group and so is mismatched. Despite the inherent bias of a 4.6:1 ratio against its formation imposed by the Me group, it was still formed with complete exclusion of the other mismatched isomer **12** [with the epoxide *cis* to the Me group (matched) but *trans* to the CF_3 group (mismatched)], showing that the CF_3 group appears to induce a selectivity of $>92{:}1$ ($>20{:}1 \times 4.6{:}1$).[14]

Scheme 3. Reactions of α-Substituted Aminoketones **9**

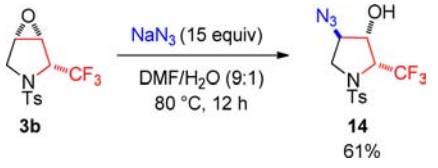


Finally, to give an example of how this method enables rapid access to functionalized building blocks with diverse options for elaboration, a regioselective opening[15] of

(10) (a) Maeda, R.; Ooyama, K.; Anno, R.; Shiosaki, M.; Azema, T.; Hanamoto, T. *Org. Lett.* **2010**, *12*, 2548. (b) Lin, H.; Shen, Q. L.; Lu, L. *J. Org. Chem.* **2011**, *76*, 7359. (c) Kasai, N.; Maeda, R.; Furuno, H.; Hanamoto, T. *Synthesis* **2012**, *44*, 3489. Sulfonium salt **1** can be synthesized in two steps from 2-bromo-3,3,3-trifluoroprop-1-ene (ref 10c).

(11) (a) Kocienski, P. J. *Protecting Groups*; Thieme: New York, 1994. (b) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley-Interscience: New York, 1999.

Scheme 4. Ring Opening of **3b** with NaN_3



epoxide **3b** with NaN_3 was carried out to give azido alcohol **14** in 61% yield (Scheme 4).

In conclusion, we have demonstrated an easy and efficient synthesis of CF_3-substituted heterocyclic building blocks in good yields and very high diastereoselectivities. Through probing matched and mismatched stereoisomers, it was found that the diastereoselectivities are >20:1 and could be higher than >90:1. The methodology has been extended to an array of different classes of CF_3 substituted, epoxide-fused heterocycles (N-, O-, five and six rings), which are useful intermediates in synthesis.

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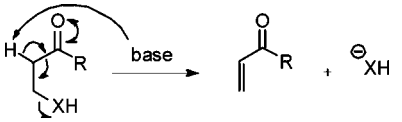
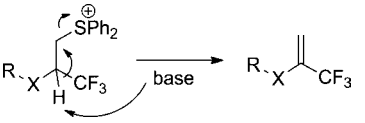
Supporting Information Available. Experimental procedures, compound characterization, spectra, and X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

(12) Substrates with an enolizable proton are prone to a competing elimination reaction. We note that with unsubstituted vinyldiphenylsulfonium salts the conjugate addition/annulation sequence was successful but it was a problem with hindered chiral vinylsulfonium salts; see ref 7a.



(13) If cyclization towards the betaine is slow, competing elimination dominates. Related competing eliminations were also observed by Hanamoto et al. (ref 10c).



(14) If, for example, the CF_3 group exerted a selectivity of 50:1, then in the mismatched case we would expect to see an 11:1 ratio of **11:12**, which would be observable by ^1H NMR. The absence of **12** shows that the CF_3 group exerts very high selectivity and probably >90:1.

(15) (a) Herdeis, C.; Aschenbrenner, A.; Kirfel, A.; Schwabenländer, F. *Tetrahedron: Asymmetry* **1997**, *8*, 2421. (b) Curtis, K. L.; Evinson, E. L.; Handa, S.; Singh, K. *Org. Biomol. Chem.* **2007**, *5*, 3544. (c) Rives, A.; Génisson, Y.; Faugeroux, V.; Zedde, C.; Lepetit, C.; Chauvin, R.; Saffon, N.; Andrieu-Abadie, N.; Colié, S.; Levade, T.; Baltas, M. *Eur. J. Org. Chem.* **2009**, 2474.

The authors declare no competing financial interest.