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Efficient Synthesis of Cyclopropane Fused Heterocycles with Bromoethylsulfonium Salt

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Dedication ((optional))

The 3-azabicyclo[3.1.0]hexane is a common motif in natural products.[1-6] Furthermore this rigid framework represents a privileged class of pharmacologically active compounds, often showing enhanced binding affinities with their targets (Figure 1).[7] These bicycles also represent conformationally restricted analogues of piperidines (*e.g.* trovafloxacin).[8] When substituted with a carboxylic acid moiety, they resemble conformationally restricted analogues of glutamate, gamma-amino butyric acid (GABA) or *α/β*-proline analogues (Figure 2).[9]

Numerous methods have been developed for the construction of azabicyclo[3.1.0]hexanes.[10] These include the Kulinkovich/de Meijere reaction[11,12], cyclisation of tethered amines with metals (Pd[13], Ru[14], Rh[15], Ag[16]), cyclisation of tethered cyclopropanes[17], and the Simmons-Smith[18]/Corey-Chaykovsky[19]/sulfur ylide-Au[20] cyclopropanations. These methods are usually only effective in the synthesis of one specific type of scaffold.

We were keen to develop a general strategy that could deliver 3-azabicyclo[3.1.0]hexanes with a range of functional groups in a range of positions. Our design plan for the synthesis of the scaffold was to effect a tandem process initiated by conjugate addition of an unsaturated amine **1** to vinyl sulfonium salt **2**, generated *in situ* from the stable and crystalline salt **3** (Scheme 1). The intermediate sulfur ylide **4** would undergo intramolecular addition to the Michael acceptor to give a sulfonium enolate **5** which would ring close to the cyclopropane **6**.

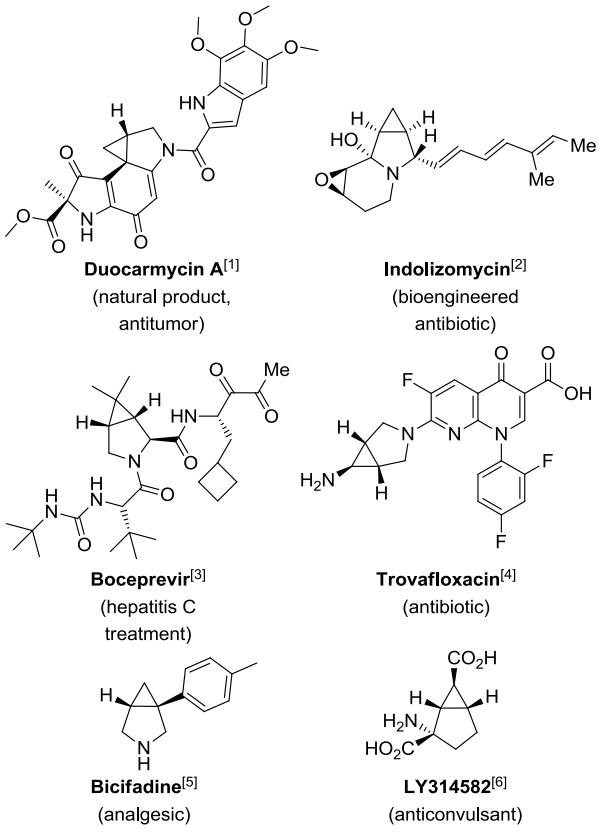

Figure 1. Selected examples of important bicyclo[3.1.0]hexanes.

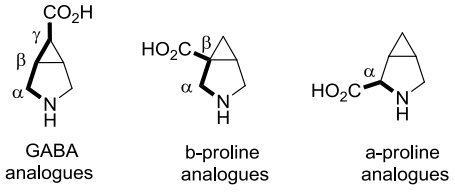

Figure 2. Conformationally restricted scaffolds discussed in this work.

This tandem process is related to the previously described reactions that bear aldehydes or imines in place of Michael acceptors, giving fused bicyclic epoxides and aziridines respectively.[21,22] However, the more complex reaction with

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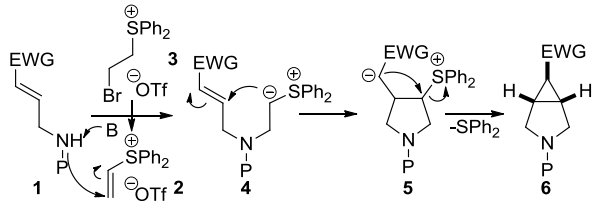
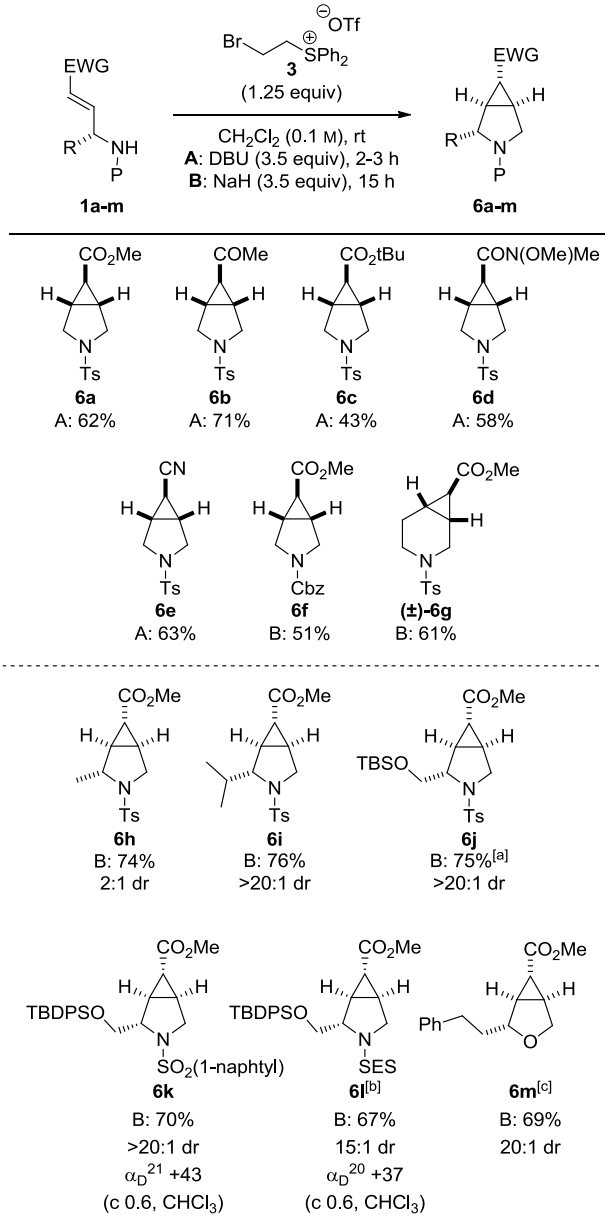


Scheme 1. Proposed mechanism of the reaction. (B = Base)

Table 1: Scope of the transformation.



All yields are isolated yields and dr is determined by ^{1}H NMR of the crude; [a] Yield of TBS deprotected product including an *in situ* deprotection with TBAF (5 equiv) added after 15 h; [b] reaction at 0 °C, if run at rt yield is 75% and d.r. is 7:1; [c] minor traces of other diastereomer visible in ^{1}H NMR.

Michael acceptors (leading to products with additional stereogenic centers) has not been previously reported.[23] The potential for a very rapid increase in molecular complexity from simple starting materials was an additional attractive feature of the chemistry. In this paper, we report the successful realisation of this strategy and the formation of azabicyclo[3.1.0]hexanes with surprisingly high diastereoselectivity.

Our studies began with the preparation of a diverse array of allylic amines. The allylic amines **1a-g** were prepared in one step using either cross-metathesis[24] or Wittig chemistry. Similarly, **1h-j** were synthesized in two steps from commerically available amino acid-derived methyl esters through a DIBAL-H reduction/Wittig reaction sequence. Allylic amines **1k**, and **1l** with the appropriate protecting groups required several steps[25] whilst **1m** was available in one step from reaction of dihydrocinnamaldehyde with a vinylchromium nucleophile[26] (see SI for details).

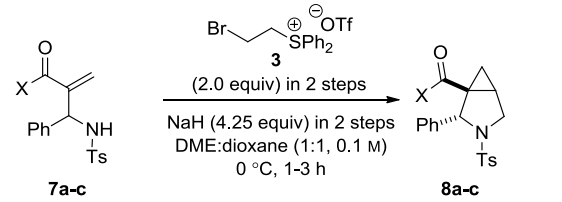
The reaction of unsaturated amide **1a** with the stable and crystalline salt **3** was initially tested. After optimisation of the process (see supporting information) a set of conditions were established (method A), that led to moderate-high yields of the [3.1.0] bicycles with complete diastereoselectivity (Table 1).[27] For example, unsaturated amide **1a** gave the cyclopropane **6a** in 62% yield as a single diastereomer. The Michael acceptors tested bore a range of electron-withdrawing groups, including Me and *t*Bu esters, ketones, amides and nitriles (**6a-6e**). Furthermore, in the case of the unsubstituted allylic amide, the *N*-Cbz carbamate **1f**[28] could also be employed in place of the tosyl protecting group leading to the pyrrolidine **6f**. The piperidine **6g** was also accessible using the same process and again was formed with complete diastereoselectivity.

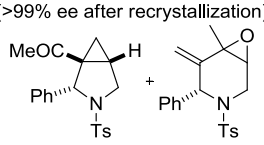
The method was further extended to a range of α-substituted allylic amines (**1h-1m**), although in this case NaH was found to be superior to DBU (method B). With a small substituent (Me, **1h**), the azabicyclo[3.1.0] hexane **6h** was formed with low diastereoselectivity but with larger substituents (**1i, 1j**) the adducts (**6i, 6j**) were formed with essentially complete diastereoselectivity. In terms of the *N*-protecting group, with α-substituted allylic amines, it was not possible to use the Cbz or Boc groups, but the more easily cleavable[28] 1-naphthyl or SES sulfonamides (**1k, 1l**) worked well giving similarly high yield and diastereoselectivity. Interestingly, allylic alcohol **1m** could also be used and gave the tetrahydrofuran **6m**, again with high selectivity. The methodology readily lent itself to the preparation of enantioenriched products, as illustrated with **6k**, **6l**, since the α-substituted allylic amines are easily obtained from chiral amino acids (serine in this case).

Expanding this methodology further, we were able to utilise easily accessible aza-Morita-Baylis-Hillman adducts **7a-7c**[29] (one step from the acrylate), as starting materials for the cyclisation. These reactions now lead to the formation of β-proline-derived fused cyclopropanes **8a-8c** (Table 2).[30]

Whilst unsaturated esters **7a** and **7b** worked well, giving the corresponding adducts **8a** and **8b**, respectively, in high yield and very high diastereoselectivity, unsaturated ketone (**7c**) behaved differently. In this case the major product was the epoxy-annulation adduct **9**. Evidently, after 1,4-addition of the amide **7c** to the vinyl sulfonium salt **1**, the ylide intermediate reacts in a more favoured 6-*exo*-*trig* mode with the ketone moiety, rather than the desired 6-*endo*-*trig* mode with the alkene. Nevertheless, the pyrrolidine **8c** was formed with high diastereoselectivity as before. The methodology readily lends itself to asymmetric synthesis, since the aza-Morita-Baylis-Hillman adducts **7a, 7b** are obtainable using asymmetric organocatalysis.[31] This was illustrated in the use of **(+)-7a** (82% ee), which gave the [3.1.0] bicycle **(+)-8a** without measurable racemization, which was increased to >99% ee after recrystallization.

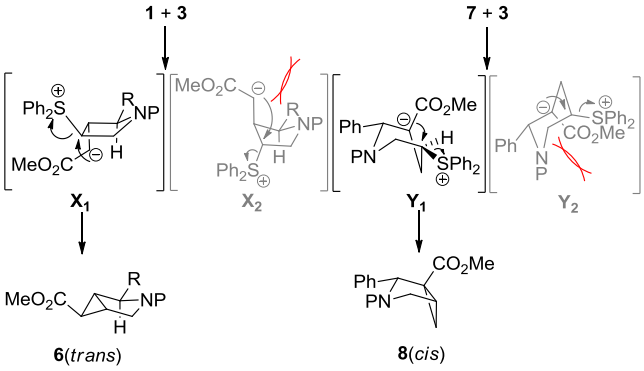
Table 2: Reactivity of (aza)-Morita-Baylis-Hillman adducts.



7a: X = OMe	**(±)-8a**, 64%, >20:1 dr
7b: X = OtBu	**(±)-8b**, 45%, >20:1 dr
7a: X = OMe (82% ee)	**(+)-8a**, 63%, >20:1 dr 82% ee (>99% ee after recrystallization)
7c: X = Me	
	(±)-8c (minor) 16% >20:1 dr
	9 (major) 76% 1:1 dr

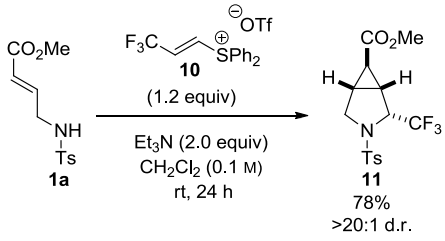
All yields are isolated yields and dr is determined by 1H NMR of the crude; [a] The ee was determined by chiral SFC, see SI for full details.

The relative stereochemistry of cyclopropanes **6g, 6i,** and **8a** were determined by X-ray analysis and related compounds were assigned by analogy (see Supporting information for details). It is believed that the steps prior to ring closure are reversible and that the selectivity is determined in the non-reversible ring closure step which forms the cyclopropane. The origin of selectivity of the two classes of substrates **1** and **7** can be rationalised by considering the non-bonded steric interactions in the TSs where the less hindered **X1** and **Y1** are favoured over **X2** and **Y2**, which subsequently leads to the preferred formation of *trans* (**6h-6m**) and *cis* (**8a-8c**) isomers (Scheme 2).

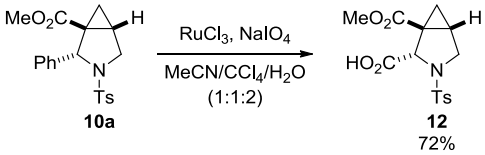


Scheme 2. Model for diastereoselectivity in the formation of **6** and **8**

The cyclopropyl-annulation reaction was further extended to include the medicinally important CF_3 group. Thus, reaction of **1a** with the CF_3-substituted vinyl sulfonium salt **10**[32] gave the CF_3-substitued [3.1.0] pyrrolidine **11**[33], again with essentially complete diastereoselectivity[21i] (Scheme 3).



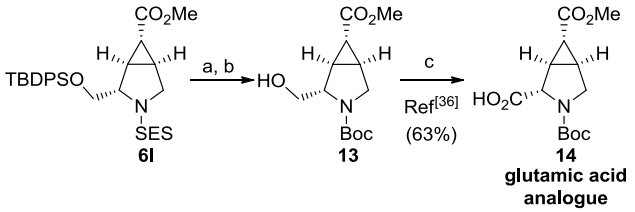
Scheme 3. Formation of **11** with β-CF_3 vinylsulfonium salt **10**.



Scheme 4. Oxidation to α,β-amino acid derivative **12**.

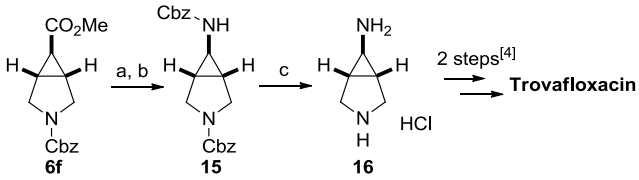
The synthetic utility of the methodology is illustrated through a range of functional group transformations of several of the [3.1.0] pyrrolidines. For example, oxidative cleavage of the Ph group[34] in **8a** gave pyrrolidine **13** which is both an α- and a β-amino acid derivative (Scheme 4).[35]

Deprotection and oxidation of **6l** gave the conformationally locked glutamic acid analogue (Scheme 5).[36]



Scheme 5. Deprotection and transformation of **6l**. a) CsF (5 equiv), DMF (0.1 M), 95 °C, 4 h then b) Boc_2O(1.2 equiv), NEt_3 (3 equiv), CH_2Cl_2, rt, 2 h, 62% over 2 steps; c) PDC (4 equiv), DMF (0.5 M), Ref[36] 63%.

Finally, pyrrolidine **6f** was converted into 6-amino-3-azabicyclo[3.1.0]hexan-3-ium chloride **16**, an intermediate used in the synthesis of trovafloxacin, a potent antibiotic.[4] Thus, saponification of the ester **6f**, followed by the Schmidt reaction with diphenyl phosphoryl azide (DPPA) gave pyrrolidine **15**. Finally, hydrogenolysis gave amino pyrrolidine **16** in just a few synthetic steps (Scheme 6).



Scheme 6. Formal synthesis of the trovafloxacin precursor **16**. a) aq. NaOH (1 M), THF, rt, 15 h then b) DPPA (1.1 equiv), NEt_3 (1.1 equiv), BnOH (5 equiv), PhMe (0.25 M), 90 C, 1.5 h, 62% (0.3 g scale) over 2 steps; c) H_2 (1 atm), Pd/C (cat.), HCl in Et_2O (2 M, 3 equiv), MeOH, rt, 3 h, 99%.

In conclusion we have developed a novel, efficient and versatile route for the formation of cyclopropane-fused heterocycles from easily available starting materials. In comparison to previous methods, this protocol enables the synthesis of a more diverse range of substituted and functionalized [3.1.0] scaffolds with very high diastereoselectivity. There is considerable interest in exploring this class of bioactive compounds, which should now be enabled by the methodology described herein.

Experimental Section

A stirred solution of amine or alcohol 1 (1.0 equiv.) and diphenyl bromoethyl sulfonium salt 3 (1.25 equiv.) in anhydrous solvent (0.1 M) at room temperature under inert atmosphere was treated with base (3.5 equiv.) and stirred for the indicated time (until complete consumption of starting material was detected by

HPLC or TLC). The reaction mixture was then quenched with 10% aqueous citric acid solution (15 mL/mmol) and the aqueous was extracted with CH_2Cl_2 (3 × 30 mL/mmol). The combined organic layers were washed with brine (30 mL/mmol), dried ($MgSO_4$) and concentrated *in vacuo*. The crude reaction mixture was purified by flash chromatography, eluting with either EtOAc/*n*-pentane or Et_2O/*n*-pentane to give the desired product.

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Keywords: heterocycles • cyclopropanes • sulfur ylides • amino acids • Baylis-Hillman

[1] a) I. Takahashi, K. Takahashi, M. Ichimura, M. Morimoto, K. Asano, I. Kawamoto, F. Tomita, H. Nakano, *J. Antibiot.* **1988**, *41*, 1915-1917; b) D. L. Boger, D. S. Johnson, *PNAS* **1995**, *92*, 3642-3649; c) T. Wirth, K. Schmuck, L. F. Tietze, S. A. Sieber, *Angew. Chem. Int. Ed.* **2012**, *51*, 2874-2877.

[2] a) S. Gomi, D. Ikeda, H. Nakamura, H. Naganawa, F. Yamashita, K. Hotta, S. Kondo, Y. Okami, H. Umezawa, Y. Iitaka, *J. Antibiot.* **1984**, *37*, 1491-1494. b) G. Kim, M. Y. Chumoyer, S. J. Danishefsky, G. K. Schulte, *J. Am. Chem. Soc.* **1993**, *115*, 30-39.

[3] F. G. Njoroge, K. X. Chen, N. Y. Shih, J. J. Piwinski, *Acc. Chem. Res*, **2008**, *41*, 50-59.

[4] T. Norris, T. F. Braish, M. Butters, K. M. DeVries, J. M. Hawkins, S. S. Massett, P. R. Rose, D. Santafianos, C. Sklavounos, *J. Chem. Soc. Perk. Trans. 1* **2000**, 1615-1622.

[5] a) F. Xu, J. A. Murry, B. Simmons, E. Corley, K. Fitch, S. Karady, D. Tschaen, *Org. Lett.* **2006**, *8*, 3885-3888; b) P. A. Krieter, M. Gohdes, T. J. Musick, F. P. Duncanson, W. E. Bridson, *Drug Metab. Dispos.* **2008**, *36*, 252-259.

[6] D. D. Schoepp, B. G. Johnson, R. A. Wright, C. R. Salhoff, N. G. Mayne, S. Wu, S. L. Cockerham, J. P. Burnett, R. Belegaje, D. Bleakman, J. A. Monn, *Neuropharmacology* **1997**, *36*, 1-11.

[7] For an example see S. J. Miller, R. H. Grubbs, *J. Am. Chem. Soc.* **1995**, *117*, 5855-5856.

[8] a) J. A. Sattigeri, M. M. S. Andappan, K. Kishore, S. Thangathirupathy, S. Sundaram, S. Singh, S. Sharma, J. A. Davis, A. Chugh, V. S. Bansal, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4087-4091.

[9] a) B. Meldrum, *Nature* **1995**, *376*, 122-123; b) R. Galeazzi, G. Mobbili, M. Orena, *Tetrahedron: Asymmetry* **1997**, *8*, 133-137.

[10] Krow, G. R. Cannon, K. C. *Org. Prep. Proc. Intl.* **2000**, *32*, 103-122.

[11] O. G. Kulinkovich, S. V. Sviridov, D. A. Vasilevskii, T. S. Prityts kaya, *Zh. Org. Khim.* **1989**, *25*, 2244-2245.

[12] a) V. Chaplinski, A. deMeijere, *Angew. Chem. Int. Ed.* **1996**, *35*, 413-414; b) M. Gensini, S. I. Kozhushkov, D. S. Yufit, J. A. K. Howard, M. Es-Sayed, A. de Meijere, *Eur. J. Org. Chem.* **2002**, 2499-2507.

[13] a) H. Ohno, Y. Takeoka, K. Miyamura, Y. Kadoh, T. Tanaka, *Org. Lett.* **2003**, *5*, 4763-4766; b) B. de Carne-Carnavalet, A. Archambeau, C. Meyer, J. Cossy, B. Folleas, J. L. Brayer, J. P. Demoute, *Chem. Eur. J.* **2012**, *18*, 16716-16727.

[14] M. Eckert, S. Moulin, F. Monnier, I. D. Titanyuk, S. N. Osipov, T. Roisnel, S. Derien, P. H. Dixneuf, *Chem. Eur. J.* **2011**, *17*, 9456-9462.

[15] J. J. Feng, J. L. Zhang, *J. Am. Chem. Soc.* **2011**, *133*, 7304-7307.

[16] A. Kamimura, A. Kadowaki, T. Yoshida, R. Takeuchi, H. Uno, *Chem. Eur. J.* **2009**, *15*, 10330-10334.

[17] V. V. Tverezovsky, M. S. Baird, I. G. Bolesov, *Tetrahedron* **1997**, *53*, 14773-14792.

[18] A. R. Renslo, P. Jaishankar, R. Venkatachalam, C. Hackbarth, S. Lopez, D. V. Patel, M. F. Gordeev, *J. Med. Chem.* **2005**, *48*, 5009-5024.

[19] F. M. Sabbatini, S. Melotto, G. Bernasconi, S. M. Bromidge, L. D'Adamo, M. Rinaldi, C. Savoia, C. Mundi, C. Di Francesco, L. Zonzini, V. J. A. Costantini, B. Perini, E. Valerio, A. Pozzan, E. Perdona, F. Visentini, M. Corsi, R. Di Fabio, *ChemMedChem*, **2011**, *6*, 1981-1985;

[20] X. Huang, S. Klimczyk, L. F. Veiros, N. Maulide, *Chem. Sci.* **2013**, *4*, 1105-1110.

[21] For epoxide and aziridine fused heterocycles see: a) K. H. Kim, L. S. Jimenez, *Tetrahedron: Asymmetry* **2001**, *12*, 999-1005 and references therein; b) H. Yamanaka, J. Matsuo, A. Kawana, T. Mukaiyama, *ARKIVOC* **2004**, 42-65 and references therein; c) M. G. Unthank, N. Hussain, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2006**, *45*, 7066-7069; d) C. G. Kokotos, E. M. McGarrigle, V. K. Aggarwal, *Synlett* **2008**, 2191-2195; e) M. G. Unthank, B. Tavassoli, V. K. Aggarwal, *Org. Lett.* **2008**, *10*, 1501-1504; f) S. Catalan-Munoz, C. A. Muller, S. V. Ley, *Eur. J. Org. Chem.* **2010**, 183-190 g) E. M. McGarrigle, M. Yar, M. G. Unthank, V. K. Aggarwal, *Chem. Asian. J.* **2011**, *6*, 372-375; h) S. P. Fritz, Z. Ali, M. G. Unthank, E. M. McGarrigle, V. K. Aggarwal, *Helv. Chim. Acta* **2012**, *95*, 2384-2398; i) S. P. Fritz, T. H. West, E. M. McGarrigle, V. K. Aggarwal, *Org. Lett.* **2012**, *14*, 6370-6373.

[22] For all other heterocycles see: a) M. Yar, E. M. McGarrigle, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2008**, *47*, 3784-3786; b) M. Hansch, O. Illa, E. M. McGarrigle, V. K. Aggarwal, *Chem. Asian. J.* **2008**, *3*, 1657-1663; c) M. Yar, E. M. McGarrigle, V. K. Aggarwal, *Org. Lett.* **2009**, *11*, 257-260; d) C. S. Xie, D. Y. Han, J. H. Liu, T. Xie, *Synlett* **2009**, 3155-3158; e) J. Bornholdt, J. Felding, J. L. Kristensen, *J. Org. Chem.* **2010**, *75*, 7454-7457; f) C. S. Xie, D. Y. Han, Y. Hu, J. H. Liu, T. A. Xie, *Tetrahedron Lett.* **2010**, *51*, 5238-5241; g) V. K. Aggarwal, S. P. Fritz, A. Mumtaz, M. Yar, E. M. McGarrigle, *Eur. J. Org. Chem.* **2011**, 3156-3164; h) E. M. McGarrigle, S. P. Fritz, L. Favereau, M. Yar, V. K. Aggarwal, *Org. Lett.* **2011**, *13*, 3060-3063; i) S. P. Fritz, J. F. Moya, M. G. Unthank, E. M. McGarrigle, V. K. Aggarwal, *Synthesis* **2012**, *44*, 1584-1590; j) M. Yar, S. P. Fritz, P. J. Gates, E. M. McGarrigle, V. K. Aggarwal, *Eur. J. Org. Chem.* **2012**, 160-166.

[23] For the synthesis of non-fused cyclopropanes with a vinylsulfonium salt see: a) J. Gosselck, G. Schmidt, *Tetrahedron Lett.* **1969**, 2615-2618; b) J. Gosselck, G. Schmidt, *Angew. Chem. Int. Ed.* **1968**, *7*, 456-458; c) Z. J. Mao, H. J. Qu, Y. Y. Zhao, X. F. Lin, *Chem. Commun.* **2012**, *48*, 9927-9929.

[24] a) T. J. Donohoe, J. F. Bower, J. A. Basutto, *Nat. Protoc.* **2010**, *5*, 2005. b) A. W. Van Zijl, A. J. Minnaard, B. L. Feringa, *J. Org. Chem.* **2008**, *73*, 5651.

[25] S. Hanessian, S. Ninkovic, U. Reinhold, *Tetrahedron Lett.* **1996**, *37*, 8971-8974.

[26] K. Namba, Y. Kishi, *Org. Lett.* **2004**, *6*, 5031-5033.

[27] During optimisation both a mild (DBU) and a strong (NaH) base were used for the synthesis of **6a**, giving a single diastereomer in both cases. Thus it is unlikely that the diastereoselectivity arises by epimerisation at the centre α to the electron withdrawing group.

[28] T. W. Greene, P. G. M. Wuts, *Protective Groups in Organic Synthesis, 3rd ed.*, Wiley-Interscience, New York, **1999**.

[29] D. Basavaiah, A. J. Rao, T. Satyanarayana, *Chem. Rev.* **2003**, *103*, 811-891.

[30] For examples of ring contractions from 6-membered ring to 5,3-fused bicycle see a) N. A. Nelson, G. Mortimer, *J. Org. Chem.* **1957**, 1146-1151; b) K. B. Wiberg, D. R. Artis, G. Bonneville, *J. Am. Chem. Soc.* **1991**, 113, 7969-7979. c) S. M. Jeffery, S. Niedoba, C. J. M. Stirling, *J. Chem. Soc., Chem. Commun.* **1992**, 650-652.

[31] For a review see Y. Wei, M. Shi, *Chem. Rev.* **2013**, 10.1021/cr300192h. a) Y. Iwabuchi, M. Nakatani, N. Yokoyama, S. Hatakeyama, *J. Am. Chem. Soc.* **1999**, *121*, 10219. b) M. Shi, Y.-M. Xu, Y.-L. Shi, *Chem. Eur. J.* **2005**, *11*, 1794-1802.

[32] a) Maeda, R. Ooyama, K. Anno, R. Shiosaki, M. Azema, T. Hanamoto, T. *Org. Lett.* **2010**, *12*, 2548-2550. 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.

[33] O. S. Artamonov, E. Y. Slobodyanyuk, O. V. Shishkin, I. V. Komarov, P. K. Mykhailiuk, *Synthesis* **2013**, *45*, 225-230.

[34] M. T. Nunez, V. S. Martin, *J. Org. Chem.* **1990**, *55*, 1928-1932.

[35] N. A. Sasaki, R. Pauly, C. Fontaine, A. Chiaroni, C. Riche, P. Potier, *Tetrahedron Lett.* **1994**, *35*, 241-244.

[36] R. Zhang, A. Mamai, J. S. Madalengoitia, *J. Org. Chem.* **1999**, *64*, 547-555.

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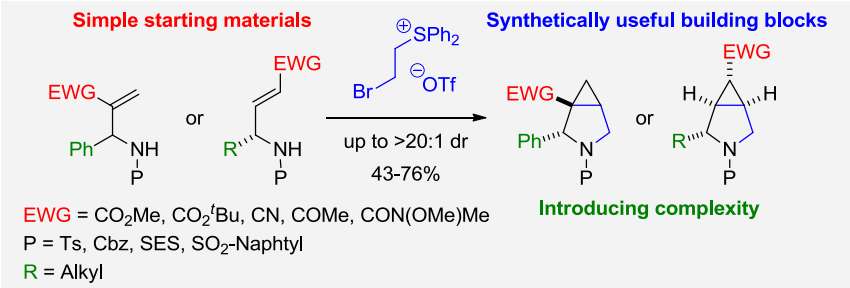
Layout 2:

Nitrogen Heterocycles

S. P. Fritz, J. V. Matlock, E. M. McGarrigle, V. K. Aggarwal** Page – Page

Efficient Synthesis of Cyclopropane Fused Heterocycles with Bromoethylsulfonium Salt



Lord of the Rings: [3.1.0] Bicyclic ring systems were synthesized using bromoethylsulfonium triflate and easily available, amino acid/aza-Morita-Baylis-Hillman derived allylic amines. The simple transformation displays a very high degree of diastereoselectivity and enables access to a diverse range of densely substituted pyrrolidine-based bicycles, a class of biologically important scaffolds.

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