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Asymmetric radical additions of trialkylboranes to 2*H*-azirine-3-carboxylates

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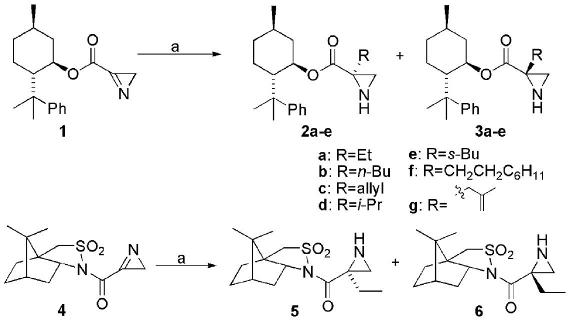
Received (in Cambridge, UK) 7th June 2004, Accepted 13th July 2004
First published as an Advance Article on the web 20th August 2004

Asymmetric additions of alkyl radicals, generated from R_3B, to chiral 2*H*-azirine-3-carboxylates offer a new entry to enantio-enriched aziridines, and proceed with high diastereoselectivity when using 8-phenylmenthol as chiral auxiliary.

2*H*-Azirines are highly reactive, nitrogen-containing, 3-membered heterocycles and represent interesting starting materials for the preparation of amino acids and alkaloids.[1] The pronounced reactivity of these compounds is due to their ring strain, the electron-rich nature of the C=N-bond and the nitrogen lone pair.[2] Asymmetric nucleophilic addition to azirines is a potentially attractive entry to enantio-enriched aziridines, a class of compounds that has received much recent interest.[3] In principle the stereochemical outcome of such additions can be controlled by employing a chiral auxiliary or, more efficiently, by the use of a chiral catalyst. In a previous study we showed that the asymmetric alkylation of 2*H*-azirines using organolithium reagents in the presence of various chiral ligands gave the corresponding aziridine in low to modest ee.[4] Consequently, an alternative stereoselective alkylation protocol was required and herein is detailed a stereoselective addition of alkyl radicals to azirines.[5] We have previously shown that enantiomerically pure 2*H*-azirine-3-carboxylates **1** and **4** are excellent dienophiles in Lewis acid-mediated hetero Diels–Alder reactions,[6] and consequently, these compounds were selected as substrates for the initial screening in the Et_3B–O_2 mediated addition of nucleophilic radicals (Scheme 1).[7]

For the 8-phenylmenthol derived azirine **1** CH_2Cl_2 and Et_2O gave the best results affording aziridine **2a** in good yield and excellent diastereoselectivity (Table 1, entries 1, 2). Other solvents, such as PhMe and THF, gave inferior results (entries 3, 4). Azirine **4**, incorporating Oppolzer's sultam as auxiliary, gave aziridine **5** in good yield, although with poor dr (entry 5); other solvents did not improve the outcome. Satisfied with these results we turned our attention towards the addition of other alkyl radicals to azirine **1**.

For the addition of radical fragments other than ethyl, a corresponding alkyl iodide (R–I) can be used together with the initiator (Et_3B–O_2) and the substrate.[8,9] Not surprisingly, mixtures derived from incorporation of both the R moiety and the ethyl radical are often obtained. When using this protocol for the addition of a cyclohexyl radical to azirine **1** only the formation of **2a** and **3a** could be detected (Table 2, entry 1), presumably due to a slow iodine atom transfer process from cyclohexyl iodide (c-$C_6H_{11}I$) to the ethyl radical under these reaction conditions.[5,9] Somewhat puzzlingly, the dr obtained in this reaction was higher than that achieved in the absence of c-$C_6H_{11}I$ (Table 1, entry 1). When repeating the reaction with freshly distilled c-$C_6H_{11}I$ the dr decreased (Table 2, entry 2), suggesting that the copper added to stabilize the commercial c-$C_6H_{11}I$ might play a pivotal role. Indeed, when the reaction was repeated in the presence of CuCl (cat.), and excluding c-$C_6H_{11}I$, **2a** : **3a** was obtained in excellent diastereoselectivity.† Other Lewis acids tested proved less efficient.[10]



Scheme 1 *Reaction conditions*: (a) RI, R_3B, O_2, CH_2Cl_2, −105 °C.

Table 1 Solvent optimisation in alkyl radical addition to **1** and **4**[a]

Entry	Azirine	Solvent	Yield[b] (%)	Dr[c]
1	**1**	CH_2Cl_2	77	91 : 9
2	**1**	Et_2O	73	91 : 9
3	**1**	PhMe	64	86 : 14
4	**1**	THF	58	68 : 32
5	**4**	CH_2Cl_2	95	79 : 21

[a] Reaction conditions: azirine (1 equiv.), solvent (2 mL), EtI (10 equiv.), Et_3B (5 equiv.) and O_2 (5 mL) at −105 °C, 5 minutes. [b] Isolated yield. [c] Ratio of **2** : **3** in entry 1–4 and of **5** : **6** in entry 5, determined by HPLC.

Since no radical transfer was observed in the presence of cyclohexyl iodide at low temperatures, an alternative approach would be to use other trialkylboranes to generate a reacting radical.[11] To test this several trialkylboranes were investigated and the results are summarized in Table 3. The addition of Et_3B went smoothly and gave **2a** in high yields and excellent ds (entry 1). Addition of butyl radical also proceeded in good yield with high ds (entry 3). With trialkylboranes forming more stable radicals, yields were moderate to good but ds dropped dramatically (entries 5, 7, 9). In addition, two trialkylboranes were prepared and used in the reaction giving aziridines **2f** and **2g** in moderate to good yield with moderate dr (entries 11, 13). In order to further investigate the importance of an additional Lewis acid in these reactions all alkyl radical additions were repeated in the presence of 0.1 equiv. CuCl (entries 2, 4, 6, 8, 10, 12, 14). Activation of azirine **1** with CuCl gave a low increase of the dr and varying effect on the yield. The simple preparation of R_3B, *via* transmetallation or hydroboration,[11,12] offers an attractive approach for the stereoselective addition of functionalized alkyl radicals to 2*H*-azirines.

In order to determine the stereochemical outcome of the radical

Table 2 Additions to azirine **1** activated by Lewis acids to give **2a** : **3a**[a]

Entry	Lewis acid[b]	Et_3B equiv.	c-$C_6H_{11}I$ equiv.	Yield (%)[e]	Dr[f]
1	—	5	10[c]	71	94 : 6
2	—	5	10[d]	82	89 : 11
3	CuCl	3	—	69	96 : 4

[a] Reaction run in CH_2Cl_2 at −105 °C under conditions given in Table 1above. [b] 0.1 equiv. [c] Stabilized with metallic copper. [d] Distilled prior to use. [e] Isolated yield. [f] Determined by HPLC.

DOI: 10.1039/b408532a

Table 3 Addition of various alkyl groups to **1**[a]

Entry	R_3B/equiv.	Lewis acid/equiv.	Product/yield (%)[b]	Ratio[c]
1	Et_3B/3	—	**2a** : **3a**/81	91 : 9
2	Et_3B/3	CuCl/0.1	**2a** : **3a**/69	96 : 4
3	*n*-Bu_3B/3	—	**2b** : **3b**/69	87 : 13
4	*n*-Bu_3B/3	CuCl/0.1	**2b** : **3b**/81	88 : 12
5	$(allyl)_3B$/ > 3[d]	—	**2c** : **3c**/72	59 : 41
6	$(allyl)_3B$/ > 3[d]	CuCl/0.1	**2c** : **3c**/85	66 : 34
7	*i*-Pr_3B/ > 3[d]	—	**2d** : **3d**/51	49 : 51
8	*i*-Pr_3B/ > 3[d]	CuCl/0.1	**2d** : **3d**/63	61 : 39
9	*s*-Bu_3B/3	—	**2e** : **3e**/43	50 : 50
10	*s*-Bu_3B/3	CuCl/0.1	**2e** : **3e**/63	55 : 45
11	$(C_6H_{11}CH_2CH_2)_3B$/ > 3[d]	—	**2f** : **3f**/56	72 : 28
12	$(C_6H_{11}CH_2CH_2)_3B$/ > 3[d]	CuCl/0.1	**2f** : **3f**/28	83 : 17
13	$(2\text{-methylallyl})_3B$/ > 3[d]	—	**2g** : **3g**/71	78 : 22
14	$(2\text{-methylallyl})_3B$/ > 3[d]	CuCl/0.1	**2g** : **3g**/71	83 : 17

[a] Azirine (1 equiv.) in CH_2Cl_2, R_3B, O_2 (5 mL), −105 °C, 5 min. [b] Isolated yield. [c] Determined by HPLC. [d] R_3B was not isolated and excess was used.

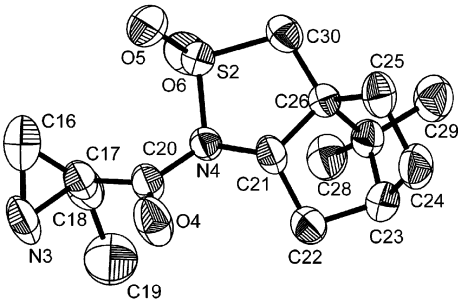
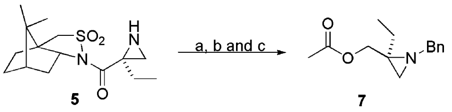


Fig. 1 One of the four molecules of **5** in the asymmetric unit. Thermal ellipsoids are drawn at a 50% probability level.



Scheme 2 *Reaction conditions*: (a) BnBr, K_2CO_3, MeCN, reflux, 67%; (b) LAH, Et_2O, −78 °C to rt; (c) Ac_2O, DMAP, CH_2Cl_2; combined yield over two steps 86%.

additions compound **5** was subjected to an X-ray crystallographic analysis (Fig. 1).‡

Using standard reaction conditions aziridine **5** was converted into aziridine **7** (Scheme 2). Applying the same reaction conditions, **2a** was transformed into *ent*-**7**.

We have shown that azirine **1** is an excellent radical acceptor in diastereoselective intermolecular alkyl radical additions, forming the corresponding aziridine carboxylates in good to excellent selectivity, substrates that are valuable intermediates in organic synthesis.[3b,13] Applying CuCl as a Lewis acid can further increase the diastereoselectivity in the addition reaction. By using various trialkylboranes to generate the reacting radical, the desired radical was added and chemoselectivity problems avoided. Further studies regarding the scope of this reaction are currently ongoing in our laboratory.

The authors thank the Swedish Foundation for Strategic Research (SELCHEM) and the Swedish Research Council for financial support.

Notes and references

† A typical procedure: to the azirine **1** (60 μmol) in CH_2Cl_2 was added CuCl (6 μmol) under argon at −105 °C. The reaction was stirred for 10 minutes before Et_3B (180 μl, 1 M in hexanes) was added, followed by addition of O_2 (5 mL, bubbled through the reaction mixture). After 5 minutes at −105 °C the reaction was quenched by addition of $NaHCO_3$ (1 mL), filtered through an Extrelut® NT3 tube eluting with CH_2Cl_2 (15 mL), EtOAc (15 mL) and CH_2Cl_2 (15 mL) and concentrated to give a yellow oil. Flash chromatography (pentane–EtOAc 1 : 0→4 : 1) gave **2a** : **3a** as a pale yellow oil.

‡ Crystal data: $C_{15}H_{23}N_2O_3S$, M = 311.43, monoclinic, a = 10.7254(6), b = 11.9768(9), c = 24.980(2) Å, β = 91.273(4)°, V = 3208.1(3) Å^3, T = 299 K, space group $P2_1$ (No. 4), Z = 8, μ(Mo–Kα) = 0.21 mm^{-1}, 26285 reflections measured, 8908 unique reflections (R_{int} = 0.0490) used in all calculations. Friedel pairs were not merged before refinement. Hydrogen atoms were placed at calculated positions and refined using a riding model. The final $wR(F^2)$ was 0.126 (all reflections). Flack parameter x = −0.05(8). One of the four molecules in the asymmetric unit exhibited severe disorder. A structure model with split positions for some of the atoms was applied. CCDC 241323. See http://www.rsc.org/suppdata/cc/b4/b408532a/ for crystallographic data in .cif format.

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