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Oxaziridine-Mediated Amination of Branched Allylic Sulfides: Stereospecific Formation of Allylic Amine Derivatives via [2,3]-Sigmatropic Rearrangement

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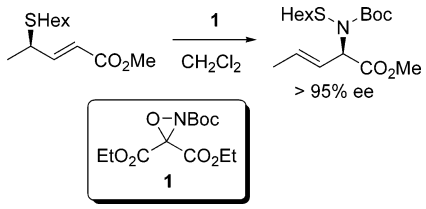
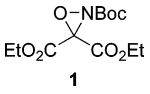
Received February 22, 2006



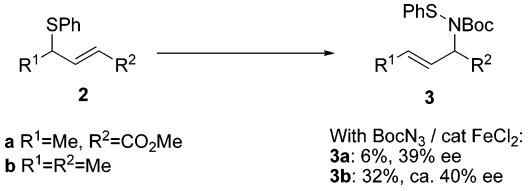
Reaction of branched allylic sulfides with the *N*-Boc-oxaziridine **1** results in [2,3]-sigmatropic rearrangement of the intermediate allylic *N*-Boc-sulfimides with a high level of chirality transfer. The first example of formation of a quaternary stereocenter using this transformation is reported.

We have recently developed the novel oxaziridine reagent **1** and demonstrated that it will effect efficient conversion of sulfides to *N*-Boc-sulfimides under metal-free conditions.[1,2]



Reagents which, like **1**, efficiently transfer electrophilic nitrogen with a carbamate protecting group are rare.[3] We have also shown that this reagent will effect amination of allylic sulfides, leading to allylic amine products via [2,3]-sigmatropic rearrangement of the intermediate allylic sulfimide (Scheme 1).[1a] These results extended the scope of the rearrangement since the only prior report of the *N*-carbamate variant of this chemistry, from Bach's group and using $BocN_3/FeCl_2$, gave poor yields with substrates

SCHEME 1



bearing radical-stabilizing groups (e.g., $R^2 = CO_2Me$) due to competing homolytic cleavage of the allylic C−S bond.[4] Pleasingly, these substrates gave good results with oxaziridine **1**.[1a] Bach also made interesting stereochemical observations when using branched allylic sulfides (**2**, $R^1 \neq H$). While the [2,3]-sigmatropic rearrangement would be expected to proceed with a high degree of chirality transfer,[5] as has been observed with *N*-sulfonylallylic sulfimides,[6] Bach obtained products of eroded ee when enantiomerically pure branched allylic sulfides were used in his $BocN_3/FeCl_2$ system (Scheme 1). While the poor ee of **3a** could be rationalized by possible product epimerization, this explanation is unlikely for **3b**; furthermore, it was discovered that recovered starting material **2b** had a deteriorated enantiopurity (75% ee). In addition to partial substrate racemization, Bach postulated that the stereogenic center at sulfur in the intermediate *N*-Boc-allylic sulfimides may influence the stereochemical outcome of the reactions. As our oxaziridine system is mechanistically distinct to Bach's Fe-catalyzed chemistry, we were interested in testing these more demanding branched substrates in order to determine whether efficient and stereocontrolled rearrangement would be possible.

Our initial studies focused on reactions of racemic α-branched phenyl sulfides **2a** and **2b**. In view of the high chemoselectivity observed earlier with unbranched phenylsulfides **2** ($R^1 = H$) with **1**,[1a] we were initially surprised that attempted amination−rearrangement of ***rac*-2a** led not only to the expected allylic amine derivative ***rac*-3a** (30%), but also to large quantities of sulfoxide (60%, mixture of diastereomers). A relatively low yield (55%) was also obtained for amination/rearrangement of ***rac*-2b**. The low level of chemoselectivity is most likely due to steric factors: Collet has demonstrated that increasing the size of the oxaziridine N-substituent generally leads to higher levels of oxidation versus amination,[7] and it is reasonable to expect that steric hindrance in the substrate would have the same effect. In line with this idea, we found that while phenyl ethyl sulfide

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(2) For reviews of sulfimide chemistry, see: (a) Taylor, P. C. *Sulfur Rep.* **1999**, *21*, 241. (b) Gilchrist, T. L.; Moody, C. J. *Chem. Rev.* **1977**, *77*, 409. For some recent examples of sulfimidation, see: (c) Marzinzik, A. L.; Sharpless, *J. Org. Chem.* **2001**, *66*, 594 and references therein. (d) Takada, H.; Nishibashi, Y.; Ohe, K.; Uemura, S.; Baird, C. P.; Sparey, T. J.; Taylor, P. C. *J. Org. Chem.* **1997**, *62*, 6512.

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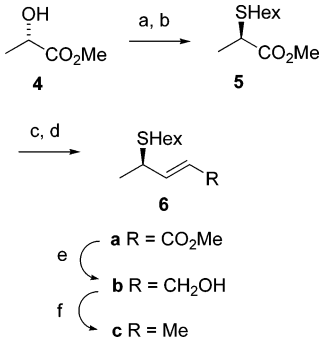
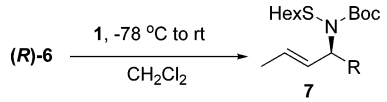
10.1021/jo060369s CCC: $33.50
Published on Web 03/28/2006

SCHEME 2 [a]



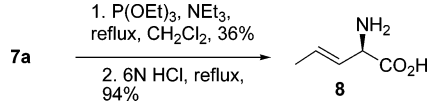
[a] Reagents and conditions: (a) TsCl, NEt_3, DMAP, CH_2Cl_2, 74%; (b) HexSH, K_2CO_3, MeCN, 86%; (c) Dibal-H, CH_2Cl_2; (d) $(EtO)_2P(O)$-CH_2CO_2Me, 83%; (e) Dibal-H, CH_2Cl_2, 81%; (f) (i) Py·SO_3, THF, 0 °C; (ii) $LiAlH_4$, THF, reflux, 71%.

SCHEME 3



a R = CO_2Me, 72%, > 95% ee
b R = CH_2OH, 76%, > 95% ee
c R = Me, 69%, > 95% ee

SCHEME 4

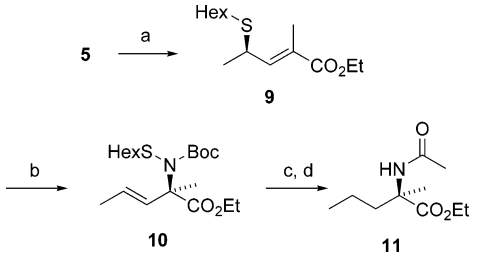


gave exclusively sulfimide on reaction with **1**, phenyl isopropyl sulfide afforded a 2.4:1 ratio of sulfimide/sulfoxide. We therefore reasoned that replacement of the sulfur phenyl substituent in **2** with an unbranched alkyl group may restore the required chemoselectivity. *n*-Hexyl was chosen because the thiol required to synthesize this substrate is relatively nonvolatile. After initial experiments with racemic material indicated that the desired chemoselectivity was indeed restored, we prepared the hexyl sulfides **6a**−**c** in enantiomerically pure form from *S*-methyl lactate (Scheme 2) by a route analogous to that developed by Bach for the phenylsulfide series.[4b] When these enantiopure substrates were reacted with **1**, we were able to establish that the amination/rearrangement proceeded with essentially complete transfer of chirality (Scheme 3). The product configuration is depicted based on the expectation of suprafacial rearrangement and was proven in the case of **7a** by conversion to the known[8] amino acid **8** and comparison of its optical rotation to literature values (Scheme 4). Unless amination of sulfides **6** proceeds with complete diastereoselectivity, the diastereomeric intermediate sulfimides must rearrange to give the same product enantiomer.

Our work with unbranched allylic sulfides[1a] indicated that quaternary centers could be formed efficiently by sulfimide rearrangement onto trisubstituted alkenes. However, there appear to be no examples in the literature to date of using chirality transfer from branched allylic sulfides to generate quaternary stereocenters. To test this possibility, we prepared sulfide **9** from *S*-lactate. After some experimentation, we were able to effect olefination to give **9** in good yield and *E*/*Z* ratio (9:1) while

(8) Mulzer, J.; Funk, G. *Synthesis* **1995**, 101.

SCHEME 5 [a]



[a] Reagents and conditions: (a) (i) DIBAL-H, CH_2Cl_2, −78 °C, (ii) $(EtO)_2P(O)CH(Me)CO_2Et$, BuLi, 80%; (b) **1**, −78 °C to rt, CH_2Cl_2, 77%; (c) Raney Ni (W-2), EtOH, reflux, 74%; (d) (i) 4.0 N HCl in dioxane, (ii) 2 equiv of NEt_3, AcCl, 100%.

minimizing racemization of the intermediate aldehyde. Column chromatography allowed separation of the alkene isomers giving ***E*-9** (Scheme 5). Treatment of ***E*-9** with oxaziridine **1** gave the rearrangement product **10** of 94% ee, again demonstrating a high level of chirality transfer. The product configuration was proved by conversion to the known *N*-acetyl aminoester **11** and comparison of optical rotation data.[9]

We have shown that ketomalonate-derived *N*-Boc-oxaziridine **1** effects efficient amination of branched allylic hexyl sulfides and that the rearrangement proceeds with a high level of chirality transfer. The reagent therefore expands the scope of the *N*-carbamate-protected allylic sulfimide rearrangement chemistry relative to the previously reported[4] $BocN_3/FeCl_2$ amination system.[10] Additionally, we have described the first example of formation of a quaternary stereocenter using the sulfimide rearrangement process. Overall, the simple and metal-free nature of the reaction conditions is an attractive feature, and allows for the synthesis of a range of sulfimide and allylic amine products for further synthetic applications.

Experimental Section

General Procedure for the [2,3] Rearrangement of Allylic Sulfides (Schemes 3 and 5). To a stirred solution of oxaziridine **1** (1.05 equiv) in CH_2Cl_2 (0.18 M) at −78 °C under N_2 was added allylic sulfide **6** (1.0 equiv) in CH_2Cl_2 (0.16 M) dropwise. The resulting solution was allowed to warm to room temperature over 30 min, after which time the solvent was removed under reduced pressure. Column chromatography on silica afforded the sulfenamide products. Data for products are given below.

(*R*)-*N*-*tert*-Butoxycarbonyl-*N*-[(*E*)-1-methoxycarbonyl-2-butenyl]hexylsulfenamide 7a. Rearrangement of **6a** (190 mg, 0.823 mmol) upon chromatography (petrol/EtOAc 20:1) yielded **7a** (205 mg, 72%) as a colorless oil: $[\alpha]^{23}_D$ +31 (*c* 0.2, $CHCl_3$); HPLC flow rate 1 mL/min; 100% hexane; 30 °C, chiral AD column; detection at 254 nm gave ee of 95.6%; t_R 19.4 min (major), 23.5 min (minor); ν_{max}(film)/cm^{-1} 1750 (C═O), 1162 (COC), 860 (SN), 752 (SC); ^{1}H NMR (250 MHz, $CDCl_3$, δ) 0.88 (t, J = 6.7, 3H), 1.46 (s, 9H), 1.21−1.63 (m, 8H), 1.77 (d, J = 4.9, 3H), 2.81 (t, J = 7.3, 2H), 3.72 (s, 3H), 4.87 (d, J = 6.1, 1H), 5.67−5.84 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 14.0, 18.0, 22.5, 27.2, 28.0, 28.5, 31.5, 39.2, 52.2, 67.6, 81.9, 125.1, 131.8, 156.4, 171.2; *m*/*z* (CI) 346 (MH^+ 41%); found MH^+ 346.2053, $C_{17}H_{32}NO_4S$ requires 346.2052.

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(*R*)-*N*-*tert*-Butoxycarbonyl-*N*-[(*E*)-1-hydroxymethyl-2-butenyl]-hexylsulfenamide 7b. Rearrangement of **6b** (17 mg, 0.080 mmol) upon chromatography (petroleum ether/EtOAc 20:1) yielded **7b** (20.2 mg, 76%) as a colorless oil: $[\alpha]^{20}_D$ −6.7 (*c* 0.3, $CHCl_3$); >95% ee according to ^{19}F NMR analysis of its Mosher's ester (see the Supporting Information); ν_{max}(film)/cm^{-1} 3463 (OH), 1752 (C═O), 1164 (COC); ^1H NMR (300 MHz, $CDCl_3$, δ) 0.89 (t, J = 6.6, 3H), 1.50 (s, 9H), 1.29−1.58 (m, 8H), 1.73 (d, J = 6.9, 3H), 1.93 (br s, 1H), 2.74−2.82 (m, 2H), 3.65−3.82 (m, 2H), 4.67 (dd, J = 13.2 and 7.6, 1H), 5.51−7.75 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 14.0, 18.0, 22.4, 27.0, 28.1, 28.5, 31.4, 39.5, 63.9, 64.0, 81.5, 127.1, 130.0, 157.7; *m*/*z* (CI) 318 (MH^+ 100); found MH^+ 318.2106, $C_{16}H_{32}NO_3S$ requires 318.2103.

(*S*)-*N*-*tert*-Butoxycarbonyl-*N*-[(*E*)-1-methyl-2-butenyl]hexyl-sulfenamide 7c. Rearrangement of **6c** (30 mg, 0.16 mmol) upon chromatography (petroleum ether/EtOAc 10:1) yielded **7c** (33.4 mg, 69%) as a colorless oil: $[\alpha]^{25}_D$ −25 (*c* 1.3, $CHCl_3$); >95% ee as determined by cleavage of the N−S bond with $P(OEt)_3$, acidic Boc deprotection, and ^{19}F NMR analysis of the Mosher's amide (see the Supporting Information); ν_{max}(film)/cm^{-1} 1696 (C═O), 1168 (COC), 752 (SC); ^1H NMR (250 MHz, $CDCl_3$, δ) 0.88 (t, J = 7.0, 3H), 1.48 (s, 9H), 1.24−1.69 (m, 14H), 2.71−2.78 (m, 2H), 4.71−4.81 (m, 1H), 5.46−5.64 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 13.0, 16.8, 18.1, 21.5, 26.1, 27.2, 27.6, 30.5, 39.1, 55.6, 79.9, 125.0, 131.2, 156.0; *m*/*z* (CI) 302 (MH^+, 20), 263 (MNH_4^+ − *t*-Bu, 100); found MH^+ 302.2146, $C_{16}H_{32}NO_2S$ requires 302.2154.

(*R*)-*N*-*tert*-Butoxycarbonyl-*N*-[(*E*)-2-ethoxycarbonyl-3-pentenyl]hexylsulfenamide 10. Rearrangement of **9** (37 mg, 0.14 mmol) followed by chromatography (petroleum ether/EtOAc 30:1) yielded the title compound (41 mg, 77%) as a colorless oil: $[\alpha]^{27}_D$ −28 (*c* 1.9, CH_2Cl_2); HPLC flow rate 1 mL/min; hexane/IPA 0.5%; 23 °C, chiral OD-H; detection at 215 nm gave ee of 94%; t_R 15.8 min (major), 21.6 min (minor); ν_{max}(film)/cm^{-1} 1744 (C═O), 1163 (COC), 772 (SC); ^1H NMR (500 MHz, $CDCl_3$, δ) 0.89 (t, J = 6.9, 3H), 1.23 (t, J = 7.1, 3H), 1.22−1.37 (m, 6H), 1.50 (s, 9H), 1.58 (m, 2H), 1.59 (s, 3H), 1.74 (dd, J = 6.5 and 0.1 3H), 2.78 (s, 1H), 4.13 (q, J = 7.1, 2H), 5.56 (m, 1H), 5.88 (d, J = 15.6, 1H); ^{13}C NMR (500 MHz, $CDCl_3$, δ) 14.0, 17.9, 22.5, 23.1, 27.0, 28.1, 28.6, 30.9, 31.5, 40.0, 61.0, 68.6, 81.8, 125.4, 131.7, 156.6, 173.0; *m*/*z* (CI) 374 (MH^+, 53), 335 (MNH_4^+ − *t*Bu, 100); found MH^+ 374.2365, $C_{19}H_{36}NO_4S$ requires 374.2365.

Acknowledgment. We thank the EPSRC (GR/M54668) and Organon (CASE award to L.C.) for their support of this work and Bristol-Myers Squibb, Pfizer, and Merck Sharpe and Dohme for generous unrestricted funding.

Supporting Information Available: Experimental procedures for the preparation of allylic sulfide substrates, for the conversion of **7a** to **8**, and for the conversion of **10** to **11**. Copies of ^1H and ^{13}C NMR spectra of all new compounds. Details of ee determination for **6a**−**c**, **7a**−**c**, and **10** (HPLC traces and copies of relevant spectra). This material is available free of charge via the Internet at http://pubs.acs.org.

JO060369S