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Studies in the stereoselective trapping of prochiral carbon radicals by optically active camphoxyl nitroxides

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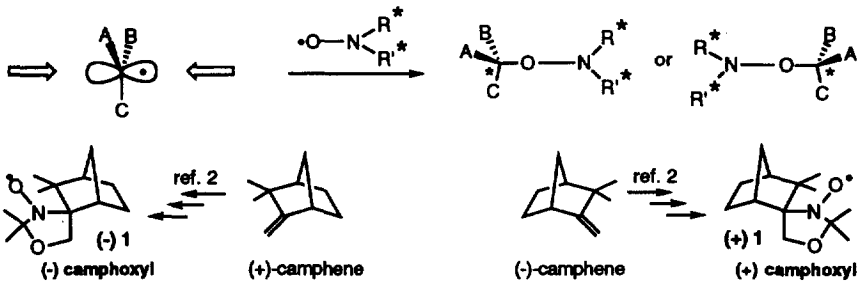
Abstract: Optically active camphoxyl nitroxides derived from camphene react with prochiral carbon radicals to give diastereomeric coupling products. The diastereomeric ratio can be conveniently measured by ^{1}H-NMR spectroscopy, in contrast to previous work employing steroidal nitroxides. The structure of the camphoxyl radical was modified; all couplings resulted in modest diastereoselectivity. © 1997 Elsevier Science Ltd

We have undertaken a research program to study the ability of non-bonded optically active reagents to discriminate between the two faces of a prochiral radical. Nitroxides are persistent species, and are highly effective traps for carbon radicals. In our previous work, steroidal nitroxides were investigated as the chiral coupling partner.[1] Whereas the facial selectivities observed in the steroidal systems were good, varying from 3:1 to 11:1, the analysis of the product ratios was challenging, due to extremely complex NMR spectra resulting from dynamic behavior on the NMR timescale. Herein, we investigate the stereoselectivity in the coupling of optically active camphoxyl nitroxides[2] **1** with transient prochiral carbon radicals.



The camphoxyl nitroxides were chosen due to their rigid structure, and the availability of either enantiomer derived from either (+) or (−)-camphene.[3] The initial coupling reactions utilized the alkyl hydrazine/lead dioxide protocol used in our earlier work for the generation of stoichiometric transient prochiral radicals at low temperature.[4] Thus phenethyl bromide was sonicated with neat hydrazine to form the corresponding alkyl hydrazine, which was subjected to oxidation by lead dioxide in the presence of the optically active nitroxide at −78°C (Scheme 1). The desired coupling product **2**[5] was isolated in excellent yield. Gratifyingly, the diastereomeric ratio of **2** was evaluated easily by NMR integration of the bridgehead methine hydrogen atoms adjacent to the spiro oxazolidine ring at δ 2.83 and 2.65 ppm. The observed diastereoselectivity was modest with the two products being formed in a ratio of 1.6:1. The 1-tetralinyl radical in our previous work gave very good selectivity, but coupling with camphoxyl radical gave a diastereomeric ratio for **3** of 1.5:1. Alternatively, the prochiral radical 2-tetrahydrofuranyl, obtained by photolysis of *t*-butyl peroxide[6] in THF, was completely non-selective: both diastereomers of **4** were formed in equal amounts. This is not surprising, as the

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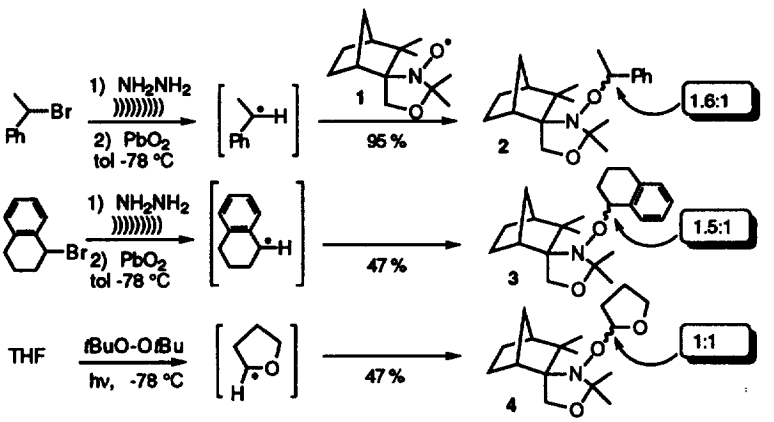
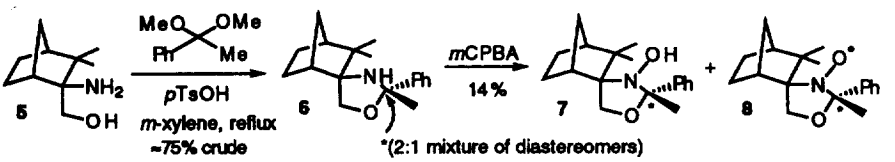
steric characteristics of the methylene-ring and oxy-ring substituents of the prochiral THF radical are expected to be similar.



Scheme 1.

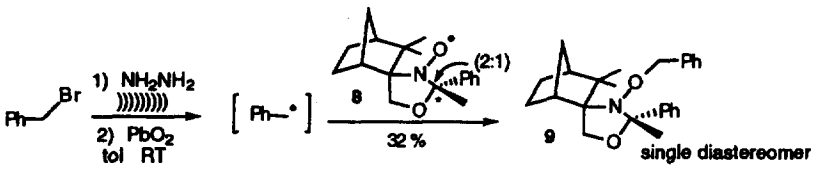
In order to improve the selectivity, a second generation of camphoxyl radicals was synthesized, in which the geminal dimethyl groups on the oxazolidine ring were replaced with other substituents. Trans-ketalization of amino alcohol **5** with (1,1-dimethoxyethyl)benzene provided the marginally stable oxazolidine **6** as a 2:1 mixture of diastereomers (Scheme 2). The crude oxazolidine was directly subjected to oxidation with purified *m*CPBA[7] to give 14% yield of a bright orange oil which surprisingly displayed sharp peaks in the ^{1}H-NMR in addition to showing the characteristic nitroxide triplet in the ESR. It is likely that the oxidation product consists primarily of hydroxylamine **7**, giving rise to sharp NMR signals, and a small amount of nitroxide **8**, giving rise to the ESR signal.[8] By NMR, the oxidation product was clearly formed in the same 2:1 diastereomeric ratio as the preceding oxazolidine **6**. NOE experiments indicate the major diastereomer is formed with the phenyl group back, proximal to the geminal dimethyl groups, and the oxazolidine methyl forward, remote from the geminal dimethyl groups. Irradiation of lower geminal methyl group at δ 1.01 resulted in enhancement of one diastereotopic oxazolidine methylene proton at δ 3.83. Irradiation of the upper geminal methyl group at δ 1.14 or the oxazolidine methyl group at δ 1.59 resulted in no significant methyl group enhancements.



Scheme 2.

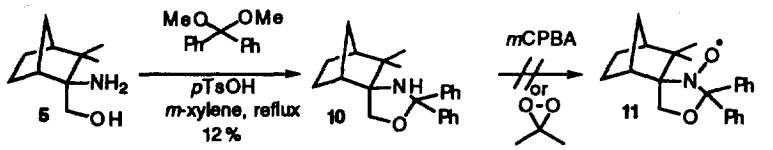
The identity of the oxidation product was confirmed by coupling with benzyl radical (Scheme 3). If hydroxylamine **7** constitutes a portion of the sample, it should be converted to the desired nitroxyl **8** upon exposure to lead dioxide. The coupling product **9** was indeed formed, in 32% yield, however only one of the two diastereomers of **8** reacted, as **9** was formed as a single diastereomer. NOE experiments again support the assignment of the phenyl group proximal, and the oxazolidine methyl group distal, to the geminal dimethyl groups.

To expand the series, the preparation of the geminal diphenyl camphoxyl derivative **11** was pursued (Scheme 4). The diphenyl substituted oxazolidine **10** was formed following the standard protocol, but proved completely resistant to oxidation. Even dioxirane was ineffective in producing nitroxide **11**.

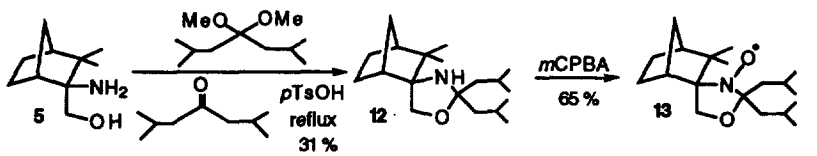


Scheme 3.

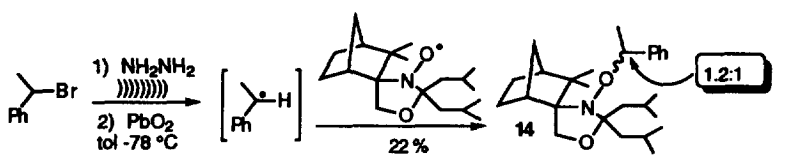
Not only is the nitrogen in **10** doubly neopentyl, but the flanking geminal phenyl groups apparently make the nitrogen atom inaccessible to even the small dioxirane molecule. To alleviate this problem, the geminal isobutyl camphoxyl derivative **13** was prepared (Scheme 5). In this case, oxidation with *m*CPBA proceeded in 65% yield to provide **13** as an orange crystalline solid. Despite the larger steric bulk of the isobutyl groups, coupling of **13** with the prochiral 1-phenethyl radical proceeded to give product **14** in a 1.2:1 ratio of diastereomers (Scheme 6). Thus it is clear that increasing the steric bulk of the geminal substituents at the 2-oxazolidine position is *not* effective in increasing the diastereoselectivity of the key coupling reaction.



Scheme 4.



Scheme 5.



Scheme 6.

Acknowledgements

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References

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2. Braslau, R.; Kuhn, H.; Burrill, L. C.; Lanham, K.; Stenland, C. J. *Tetrahedron Lett.* **1996**, *37*, 7933–7936.

3. Material derived from both (+) and (−)-camphene was utilized in this study, however all structures are drawn as coming from (−)-camphene for clarity.
4. Representative experimental procedure (**2**): Fuming hydrazine (1.17 mL, 37.3 mmol) and (1-bromoethyl)benzene (0.3450 g, 1.86 mmol) was sonicated for 30 min. Aqueous work-up with KOH and brine gave 210.0 mg of a slightly yellow oil which was diluted with degassed toluene (0.6 mL); 0.3 mL of this solution was cooled to −78°C. In a separate flask, lead dioxide (0.078 g, 0.325 mmol), camphoxyl (0.0365 g, 0.163 mmol) and degassed toluene (0.5 mL) were sonicated for 3 min, then cooled to −78°C. The cooled benzylic hydrazine solution was added by cannula and residues washed in with 0.3 mL of toluene. After warming to RT overnight, filtration through Celite with hexanes, and evaporation gave 0.0989 g of a cloudy oil. Chromatography (98:2 hexane:ethyl acetate) afforded 62.9 mg of clear oil which consisted of the desired coupling product **2** in addition to 1,1′-azobis(1-phenylethane) in a 3:1 ratio (50.7 mg coupling product, 95% yield). The coupling product was determined to be a 1.6:1 mixture of diastereomers by integration of the methine hydrogen atoms at δ 2.83 and 2.65 ppm. TLC: 6:1 hexane: ethyl acetate, UV, *p*-anisaldehyde stain, R_f=0.70; IR($CDCl_3$) 2976, 1454, 1366, 1056 cm^{-1}; MS (FAB) *m/z* 330 ($[M+1]^+$, 5), 225 (23), 224 (24), 208 (15), 105 (100); HRMS exact mass calcd for $[M+1]^+$ $C_{21}H_{32}NO_2$ 330.2433, found 330.2433. Major diastereomer: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.42–7.27 (m, 5H), 4.75 (q, 1H, J=6.6 Hz), 3.87 (d, 1H, J=10 Hz), 3.49 (d, 1H, J=10 Hz), 2.83 (m, 1H), 2.04 (m, 1H), 1.87 (m, 1H), 1.7–1.6 (m, 1H), 1.55–1.40 (m, 2H), 1.49 (d, 3H, J=6.6 Hz), 1.40–1.35 (m, 1H), 1.19 (s, 3H), 1.18–1.12 (m, 1H), 1.11 (s, 3H), 1.01 (s, 3H), 0.57 (s, 3H); ^{13}C-NMR (APT) (125 MHz, $CDCl_3$) δ 144.0 (s), three of the following: [128.3 (d), 128.2 (d), 128.2 (d), 127.9 (d), 127.4 (d), 126.9 (d)], 99.5 (s), 81.7 (d), 78.3 (s), 68.2 (t), 50.4 (d), 45.9 (s), 42.9 (d), 36.7 (t), 30.4 (q), 27.1 (q), 24.5 (t), 23.4 (t), 22.6 (q), 22.2 (q), 20.7 (q). Minor diastereomer: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.42–7.27 (m, 5H), 4.79 (q, 1H, J=6.6 Hz), 3.87 (d, 1H, J=10 Hz), 3.51 (d, 1H, J=10 Hz), 2.65 (m, 1H), 1.73 (m, 1H), 1.71–1.63 (m, 1H), 1.52 (d, 3H, J=6.6 Hz), 1.50 (s, 3H), 1.45 (s, 3H), 1.40–1.23 (m, 3H), 1.24–1.20 (m, 1H), 1.04 (s, 3H), 1.02 (s, 3H), 0.94–0.90 (m, 1H); ^{13}C-NMR (APT) (125 MHz, $CDCl_3$) δ 143.3 (s), three of the following: [128.3 (d), 128.2 (d), 128.2 (d), 127.9 (d), 127.4 (d), 126.9 (d)], 100.6 (s), 80.9 (d), 78.7 (s), 68.4 (t), 51.0 (d), 45.8 (s), 42.8 (d), 36.7 (t), 29.6 (q), 28.2 (q), 24.9 (t), 23.5 (q), 23.1 (t), 22.5 (q), 21.6 (q).
5. Compounds **1**, **2**, **3**, **4**, **5**, **10**, **12**, **13** and **14** have been fully characterized, including satisfactory HRMS or elemental analysis. Nitroxides **1**, **8**, and **13** show triplets in the ESR: g=2.006, a_n=15.0, 14.0 and 14.9 G respectively.
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7. Fieser, L. F. and Fieser, M. *Reagents for Organic Synthesis*, Vol. 1, Wiley: New York, 1967; p. 135.
8. The typical broadening of NMR spectra by paramagnetic nitroxides is concentration dependent. It is possible that the sharp peaks seen here are due to a concentration effect, although as 9 mg of the sample were used in a 5 mm NMR tube, this is unlikely.

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