A Totally Radical Approach to the Control of Stereochemistry: Coupling of Prochiral Radicals with Chiral Nitroxyl Radicals**

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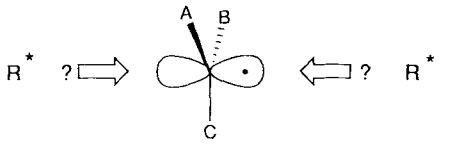
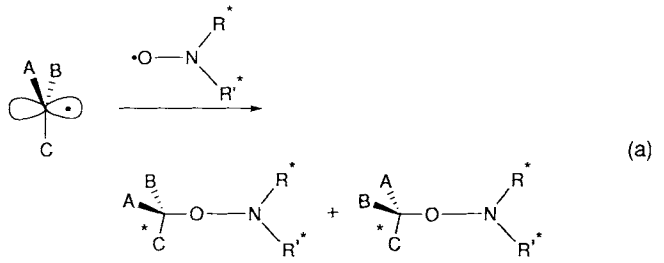
The development of new, selective methods for preparing optically pure compounds is a major challenge facing organic chemists. The control of stereochemistry in reactions with free radical intermediates has been successfully approached by using relative diastereoselectivity. Extension to the control of absolute stereochemistry has been effected with temporarily appended chiral auxiliaries.[1] A more elegant approach is that of enantioselectivity,[2] in which a prochiral radical[3,4] containing no preexisting stereogenic centers reacts with a noncovalently bonded optically active reagent to form a new stereogenic center selectively. We have initiated a research program to study the ability of nonbonded optically active reagents to discriminate between the two faces of a prochiral radical (Scheme 1). Nitroxyl radicals



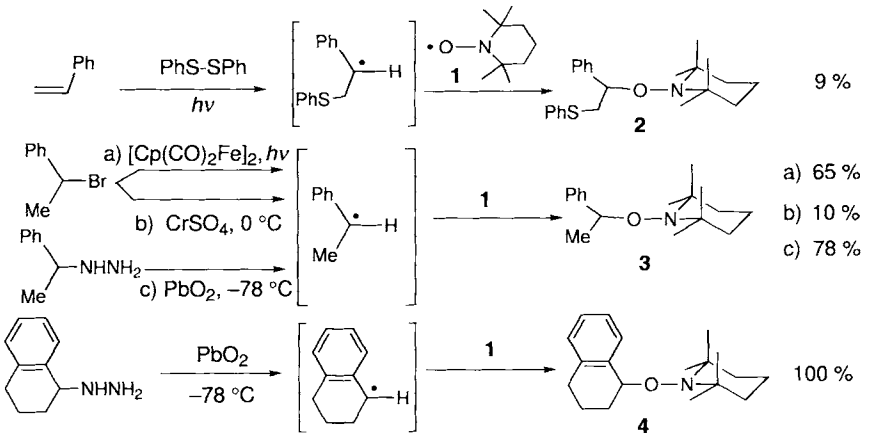
Scheme 1. Optically active reagent R* approaching the two enantiotopic faces of a prochiral carbon radical.

are persistent species[5] and are highly effective traps for carbon radicals.[6] Herein, we demonstrate stereoselectivity in the coupling of optically active nitroxyl radicals with transient prochiral carbon radicals [Eq. (a)].[7]



(a)

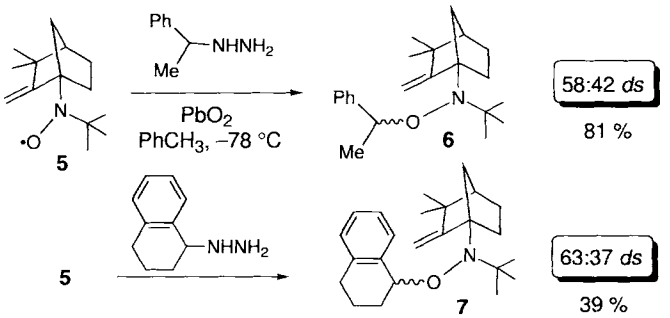
Strategies for radical coupling required stoichiometric carbon radical generation in the presence of the nitroxyl functionality. We first used achiral 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO, **1**) as a model. In Scheme 2, addition of thiol radicals



Scheme 2. Generation of prochiral radicals and trapping with TEMPO (**1**).

to styrene, photolysis of an organohalide with dicarbonyl(η^5-cyclopentadienyl)iron dimer,[8] and treatment of alkyl halides with chromium(II)[9] produced the TEMPO trapping products in poor to acceptable yields. Much cleaner results were obtained under mild oxidative conditions with lead dioxide and alkyl hydrazines[10] in toluene at $-78\,^{\circ}C$.

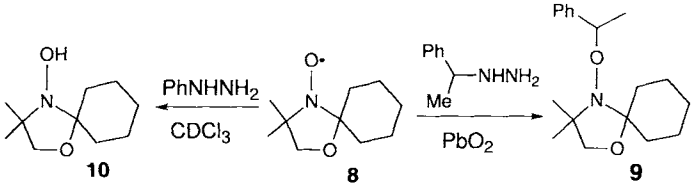
The first chiral nitroxyl radical examined was Rassat's camphor-derived **5** (Scheme 3),[11] which coupled with 1-phenethyl



Scheme 3. Stereoselectivity in the coupling of prochiral carbon radicals with nitroxyl radical **5**.

radical at $-78\,^{\circ}C$ with a diastereoselectivity of 58:42. The tetralinyl radical proved somewhat more discriminating, providing a 63:37 ratio of diastereomers.[12] An inherent drawback of radical **5** for this study is its conformational mobility. Much more advantageous would be a conformationally restrained nitroxyl radical in a stereochemically rigid environment.

We thus turned to the steroidal doxyl radical **11**.[13] First 1-phenethyl radical was coupled to a model compound, the doxyl radical **8** derived from cyclohexanone (Scheme 4). The chromatographically pure coupling product **9** was obtained; however, the ^1H and ^{13}C NMR spectra showed duplicate resonances. In contrast, the ^1H and ^{13}C NMR spectra of the re-



Scheme 4. Reduction and radical coupling of the model compound **8**.

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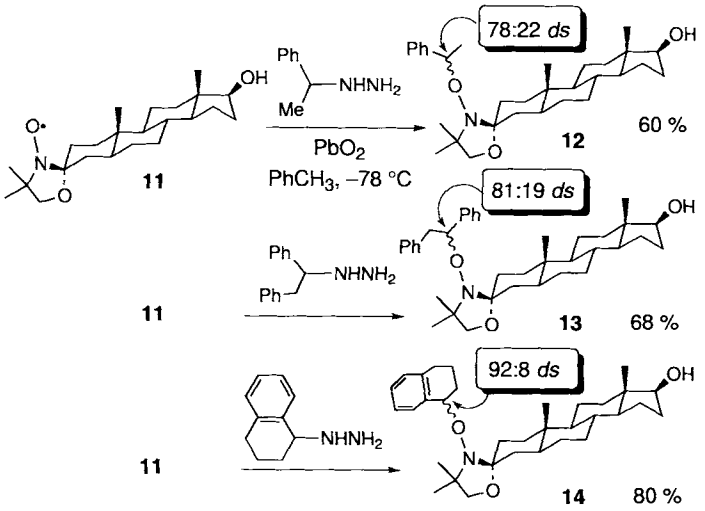
duced hydroxyl amine **10** were single sets of peaks. This implies that the nitrogen atom in compound **9** behaves as a stereogenic center on the NMR timescale, resulting in transient diastereomers.[14]

The key coupling reaction with chiral doxyl radical **11** proceeded smoothly (Scheme 5). The NMR spectra of the isolated



Scheme 5. Stereoselectivity in the coupling of prochiral carbon radicals with nitroxyl radical **11**.

products were extremely complex due to nitrogen inversion, as observed in the doxyl **8** model system. The product ratios were ultimately evaluated by HPLC and ranged from 78:22 to 92:8.[15]

Secondary benzylic radicals react with TEMPO approximately ten times slower than nonstabilized alkyl radicals.[16] The diastereomer ratios could result from reversible cleavage in a thermodynamic equilibration.[17] A few stabilized tertiary radicals have been shown to couple with nitroxyl radicals reversibly;[18] prolonged heating results in disproportionation to give olefin and hydroxyl amine. To test the thermal stability of our products, model coupling adduct **9** was heated in deoxygenated $CDCl_3$ at 50 °C for several days: no evidence of styrene formation could be detected, and the sample remained completely intact. Furthermore, addition of thiophenol did not result in the formation of 1-phenylethane. This suggests that these nitroxyl coupling products are formed under kinetic control.

In summary, we have demonstrated several examples of a chiral nonbonded reagent distinguishing between the two prochiral faces of a carbon radical.

Experimental Section

6: Hydrazine (935 mg, 29 mmol) was added to (1-bromoethyl)benzene (270 mg, 1.45 mmol) and sonnicated for 30 min. The reaction mixture was diluted with 15 mL diethyl ether, the layers separated, and the hydrazine layer washed with diethyl ether (5 mL). The combined organic layer was washed with 10% aqueous KOH (5 mL) followed by aqueous saturated sodium chloride solution (5 mL) and dried over magnesium sulfate. The solvent was removed in vacuo yielding 180.4 mg of 1-phenylethyl hydrazine as a viscous oil. In a separate flask, lead dioxide (211.3 mg, 0.883 mmol) and D,L-camphenyl-1-*t*-butylnitroxide (98.1 mg, 0.441 mmol) were suspended in 0.75 mL toluene and sonnicated for 30 min. The nitroxyl mixture was cooled to –78 °C, and the 1-phenylethyl hydrazine suspended in toluene (0.5 mL) was added by cannula in portions. An additional 0.75 mL of toluene was added to the hydrazine flask and again cannulated into the suspension at –78 °C. The reaction mixture was allowed to stir overnight while slowly warming to room temperature. The mixture was diluted with diethyl ether (10 mL) and filtered through celite, and the celite washed with diethyl ether (20 mL). The solvent was removed in vacuo to give 196.1 mg of a yellow oil. Purification by flash chromatography (95:5 hexane:ethyl acetate) afforded 125.5 mg (81% yield) of the major and minor diastereomers as an inseparable mixture in a 1.4:1 ratio (by 500 MHz ^{1}H NMR spectroscopy, C_6D_6). An additional 9.5 mg of impure product of the same diastereomeric ratio was obtained (approximately 6%). IR($CDCl_3$) $\tilde{\nu}$ = 3070, 2949 (br), 1458, 1365, 1066 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6, 25 °C, TMS, major (**a**) and minor (**b**) diastereomers): δ = 7.24-7.42 (m, 10H), 5.31 (**a**, s, 1H), 5.23 (**b**, q, 1H, ^3J(H,H) = 6.5 Hz), 4.76 (**b**, q, 1H, ^3J(H,H) = 6.5 Hz), 4.75 (**a**, s, 1H), 4.76 (**b**, q, 1H, ^3J(H,H) = 6.5 Hz), 4.75 (**a**, s, 1H), 4.68 (**b**, s, 1H), 2.54–2.60 (m, 1H), 2.02–2.12 (m, 3H), 1.86 (**a**, br s, 1H), 1.76 (**b**, br s, 1H), 1.69 (**a**, br s, 1H), 1.67 (**b**, br s, 1H), 1.59 (**b**, d, 3H, ^3J(H,H) = 6.5 Hz), 1.51 (**a**, d, 3H, ^3J(H,H) = 6.5 Hz), 1.30–1.62 (m, 5H), 1.34–1.35 (m, 1H), 1.28 (**b**, s, 9H), 1.15 (**a**, s, 3H), 1.07 (**b**, s, 3H), 1.05 (**b**, s, 3H), 1.04 (**a**, s, 12H); ^{13}C NMR (APT; 63 MHz, $CDCl_3$, 25 °C) major diastereomer: δ = 167.5 (s), 143.7 (s), 128.1 (d), 127.6 (d), 127.3 (d), 101.5 (t), 81.8 (d), 78.5 (s), 62.1 (s), 45.3 (d), 42.0 (s), 39.8 (t), 36.1 (t), 29.5 (q), 26.6(q), 23.5 (t), 21.5 (q); minor diastereomer: δ = 167.5 (s), 143.7 (s), 128.1 (d), 127.6 (d), 127.2 (d), 101.5 (t), 80.9 (d), 78.6 (s), 61.8 (s), 45.2 (d), 42.0 (s), 39.6 (t), 35.5 (t), 29.3 (q), 26.6 (q), 23.2 (t), 21.9 (q); Analysis calcd for $C_{22}H_{33}NO$: C 80.68, H 10.16, N 4.28; found: C 80.59, H 10.14, N 4.12.

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