TEMPO-Induced Generation of Alkyl Radicals from *B*-Alkylcatecholboranes

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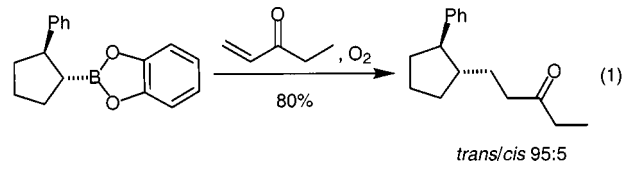
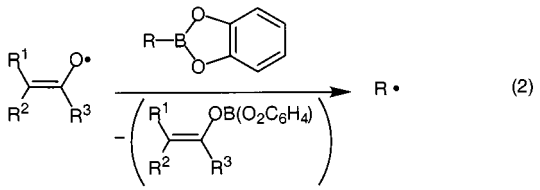
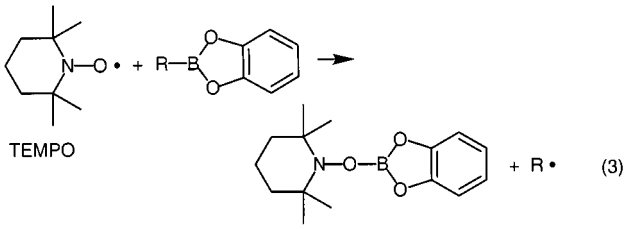
Abstract: *B*-alkylcatecholboranes react efficiently with 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) to give alkyl radicals. In the presence of an excess of TEMPO, the generated radicals are efficiently converted to alkoxyamine derivatives.

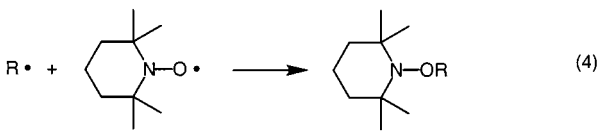
Key words: alkyl radical, alkoxyamine, alkyl-catecholborane

Boron chemistry represents a unique and highly versatile tool for transformations of organic molecules.[1] The use of organoboranes as radical precursors has been reported in the early seventies by Brown.[2-3] However, this work has not found many synthetic applications except for the system Et_3B/O_2 that is routinely used for the initiation of radical reactions.[4-6] Recently, we have reported that *B*-alkylcatecholboranes are efficient radical precursors which can be applied for radical mediated conjugate addition with various α,β-unsaturated ketones and aldehydes (equation 1).[7] The key step in the propagation of the chain reaction was the reaction between the enolate radical and the *B*-alkylcatecholborane (equation 2). Other types of oxy radicals should offer similar opportunities to perform radical substitution at boron with formation of alkyl radicals.[8] In this communication, we report that 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) reacts cleanly with *B*-alkylcatecholboranes to afford alkyl radicals (equation 3) which can be trapped by a second equivalent of TEMPO to give alkoxyamines (equation 4).[9]

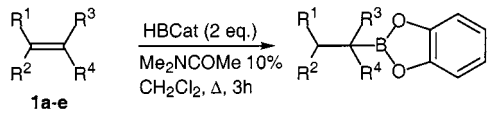


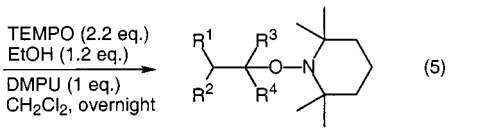






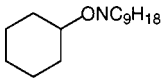
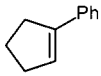
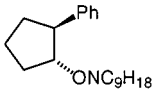
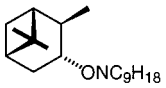
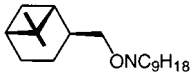
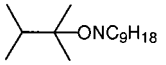
B-alkylcatecholboranes were prepared by hydroboration of the corresponding alkenes **1a-e** with catecholborane (2 equivalents) in the presence of a catalytic amount of *N*,*N*-dimethylacetamide in dichloromethane.[10] The excess of catecholborane was solvolyzed with 1.2 equivalent of ethanol. DMPU (1 equivalent) was then added followed by 2.2 equivalents of TEMPO. This one-pot procedure furnished the alkoxyamines **2a-e** in good yields (equation 5). The role of DMPU is not yet understood, but in the absence of DMPU, a decrease of the yields was observed; for instance, **1a** was converted to **2a** in only 63% yield. A similar but more pronounced effect was already observed in the oxygen initiated reaction depicted in equation 1.[7] It is also important to note that this reaction works efficiently with *B*-alkylcatecholboranes but not with trialkylboranes. For instance, under similar reaction conditions (with and without DMPU), triethylborane gave no trace of 1-ethoxy-2,2,6,6-tetramethylpiperidine. The exact reason for this considerable difference of reactivity is not understood at the moment.





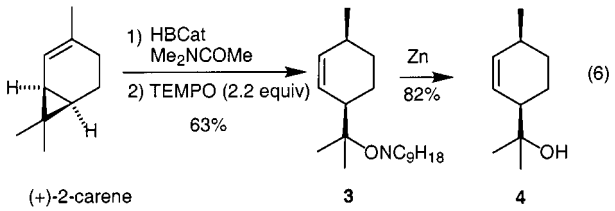
HBcat = catecholborane
DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone (= *N*,*N*'-dimethylpropyleneurea)

Table 1. Hydroboration of alkenes **1a-e** followed by reaction with TEMPO according to equation 5 (NC_9H_{18} = 2,2,6,6-tetramethylpiperidin-1-yl).

Entry	Alkene		Alkoxyamine		Yield [%]
1		**1a**		**2a**	87
2		**1b**		**2b**	71 (dr 89:11)
3		**1c**		**2c**	82 (dr >98:2)
4		**1d**		**2d**	57
5		**1e**		**2e**	64

Moderate to good yields were obtained depending on the nature of the radical. The best yields have been obtained with secondary alkyl radicals generated from cyclohexene, 1-phenylcyclopentene and α-pinene (entries 1-3). Primary and tertiary alkylcatecholboranes generated from β-pinene and 2,3-dimethyl-2-butene afforded the corresponding alkoxyamines with slightly lower yields (entries 4 and 5). The stereochemical outcome fits the expectation for radical reactions: radicals react from the less hindered face leading to *trans* compounds (table 1, entries 2 and 3).[11]

The radical nature of the reaction was demonstrated by the reaction of (+)-2-carene (equation 6). The intermediate cyclopropylmethyl radical undergoes a ring opening to a homoallyl radical. The resulting alkoxyamine was reduced with Zn/AcOH to afford the corresponding alcohol in excellent yield.[12,13]



In summary, we reported an alternative method to generate alkyl radicals from *B*-alkylcatecholboranes. Further investigations to demonstrate the utility of this approach to run inter- and intramolecular carbon-carbon bond forming reactions is underway in our laboratory. Moreover, this procedure constitutes an alternative way to oxidize organoboranes to alcohols under weakly acidic and reductive conditions. Finally, the use of optically active nitroxides[14] should broaden the scope of the radical asymmetric hydroxylation procedure developed by Braslau.[9]

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(13) Typical experimental procedures:
2,2,6,6-Tetramethyl-1-{1-methyl-1-[(1*R*,4*S*)-4-methyl-2-cyclohexen1-yl]ethoxy}piperidine (**3**). Catecholborane (0.64 ml, 6.0 mmol) was added dropwise at 0 °C under N_2 to a soln. of (+)-2-carene (409 mg, 3.0 mmol) and *N*,*N*-dimethylacetamide (28.0 µl, 0.3 mmol) in CH_2Cl_2 (2.0 ml), and the reaction mixture was heated under reflux for 3 h. EtOH (0.21 ml, 3.6 mmol) was added at 0 °C and the soln. was stirred for 15 min at rt. To this solution, TEMPO (1.03 g, 6.6 mmol) in CH_2Cl_2 (4 ml) and DMPU (0.36 ml, 3.0 mmol), were successively added. The reaction was stirred overnight at rt. The resulting mixture was treated with sat. $NaHCO_3$ (10 ml) and extracted with Et_2O (3 x 20 ml). The organic layer was dried ($MgSO_4$), filtered and concentrated. The crude product was purified by flash chromatography (hexane, hexane/Et_2O 95:5) to afford **3** (552 mg, 63%) as a colorless oil. $[\alpha]_D^{21} = -49.8°$ (c = 0.54, C_6H_6). ^{1}H-NMR (360 MHz, $CDCl_3$): 0.98 (d, J = 7, C*H*$_3$CH); 1.09, 1.10 (2s, 2 CH_3); 1.12 (s, 2 CH_3); 1.19, 1.21 (2s, 2 CH_3); 1.31-1.25 (m, 2 H); 1.59-1.43 (m, 6 H); 1.75-1.61 (m, 2 H); 2.20-2.14 (m, 1 H); 2.56-2.51 (m, 1 H); 5.70-5.65 (m, 1 H, C=CH); 5.79-5.75 (m, 1 H, C=CH). ^{13}C-NMR (50 MHz, $CDCl_3$): 17.2, 20.5, 20.9 (2 CH_3), 21.1, 23.6, 23.8, 28.8, 29.2, 34.9, 35.2, 41.0 (2 CH_2), 47.0, 59.3 (2 C), 80.9, 128.6, 133.8. Anal. $C_{19}H_{35}NO$ (293.49): calcd: C 77.76, H 12.02, N 4.77; found: C 77.95, H 12.12, N 4.66.
2-[(1*R*,4*S*)-4-methyl-2-cyclohexen-1-yl]-2-propanol (**4**). Reduction of the alkoxyamine **3** (147 mg, 0.50 mmol) with Zn/AcOH according to the procedure of Kibayashi[12] afforded the alcohol **4** (63 mg, 82%) as a colorless liquid. $[\alpha]_D^{21} = -74°$ (c = 0.75, C_6H_6), ref 15: $[\alpha]_D^{21} = -47.3$ (c = 0.54, C_6H_6). ^{1}H-NMR (360 MHz, $CDCl_3$): 0.98 (d, J = 7.3, 3 H); 1.18 (s, 3 H); 1.22 (s, 3 H); 1.53-1.43 (m, 2 H); 1.75-1.60 (m, 2 H); 2.13-2.08 (m, 1 H); 2.21-2.16 (m, 1 H); 5.71-5.67 (m, 1 H); 5.79-5.74 (m, 1 H). Anal. $C_{10}H_{18}O$ (154.25): calcd: C 77.87, H 11.76; found: C 77.39, H 11.60.
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