Synthetic Methods

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Oxidation of Catecholboron Enolates with TEMPO**

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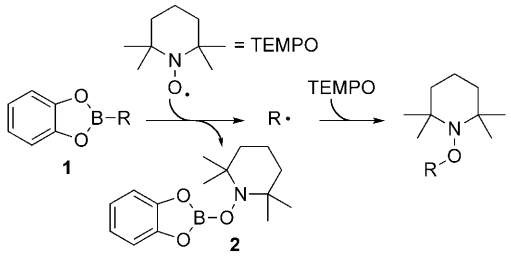
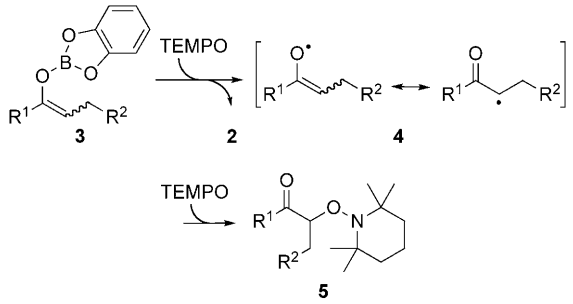
The persistent nitroxide radical 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) has found widespread application in organic synthesis. Along with its use as a catalyst for the oxidation of alcohols, TEMPO has been shown to oxidize various organometallic compounds leading to efficient C–H arylation and homocoupling reactions.[1–4] However, alkyl organometallic species of Li, Mg, Zn, Cu, Sm, and Ti do not provide the corresponding homocoupling products upon exposure to TEMPO.[5] In these processes, one equivalent of the nitroxide is used to oxidize the organometallic species to the corresponding C-centered radical, which is then trapped by a second equivalent of TEMPO to give the alkoxyamine. Along these lines, we have shown that *B*-alkylcatecholboranes **1** react similarly: formal homolytic substitution at boron in **1** with TEMPO leads to the boric ester **2** and the corresponding C-centered radical, which is irreversibly trapped by TEMPO (Scheme 1).[6]



Scheme 1. Reaction of *B*-alkylcatecholboranes with TEMPO.

B-alkylcatecholboranes, easily prepared by hydroboration of alkenes with catecholborane, constitute a highly effective source of alkyl radicals. Based on this property, a wide range of synthetic applications including conjugate addition, allylation, and chalcogenation have been recently developed.[7] However, so far all reactions involving *B*-alkylcatecholboranes concern exclusively the generation of non-functionalized alkyl and benzyl radicals. Herein we report the first examples of the generation of resonance-stabilized α-carbonyl radicals (enolyl radicals) from ketone-derived catecholboron enolates by reaction with TEMPO and their further trapping with TEMPO to form the corresponding α-aminoxylated ketones.[8,9] In addition, we introduce two simple and general methods for the formation of catecholboron enolates and report on regio- and stereoselective transformations.

We envisaged that a formal homolytic substitution at boron in catecholboron ketone enolate **3** with TEMPO should liberate the stabilized enolyl radical **4**, which upon trapping with TEMPO should give the corresponding α-aminoxylated ketone **5** (Scheme 2).



Scheme 2. Generation of α-carbonyl radicals from catecholboron enolates.

We were surprised to find that catecholboron ketone enolates have not been well investigated to date. These enolates have been generated either by reduction of α-halo ketones with catecholborane[10] or from the corresponding enones by conjugate reduction with catecholborane.[11] Our initial studies were performed on a boron enolate readily generated in situ from chlorochalcone **6**. Enolate formation and TEMPO trapping could be conducted under mild conditions as a one-pot process. The best result was achieved in CH_2Cl_2 by using a slight excess of borane (1.1 equiv) and TEMPO (2.5 equiv) to afford **7** in 87% yield and **8** in 11% yield (Scheme 3). In THF as a solvent under otherwise identical conditions **7** was isolated in 81% yield along with **8** in 10% yield.[12] Our attempts to convert the corresponding pinacol- or dibutylboron enolate to the α-aminoxylated ketone **7** were not successful. We attribute this to unproductive homolytic bond cleavage of these enolates.

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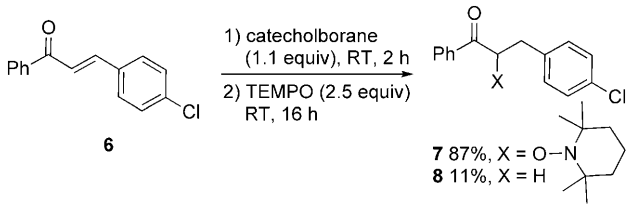
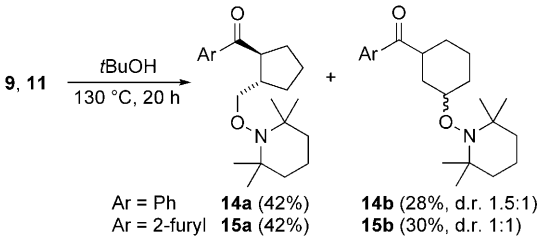


Scheme 3. Generation of catecholboron enolate and subsequent TEMPO oxidation.



Scheme 4. Thermal isomerization of alkoxyamines.

Under optimized conditions a series of readily available enones (see the Supporting Information) were transformed to the corresponding alkoxyamines **9**–**13** (Figure 1). Aryl alkenyl ketones gave the desired oxidation products **9** and **10** in high

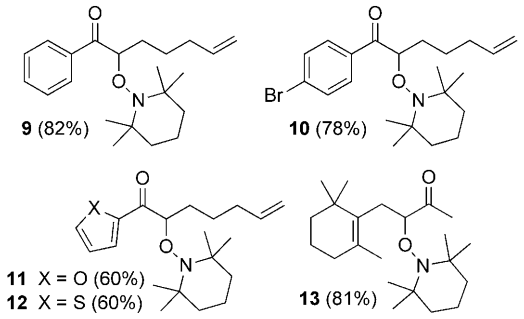


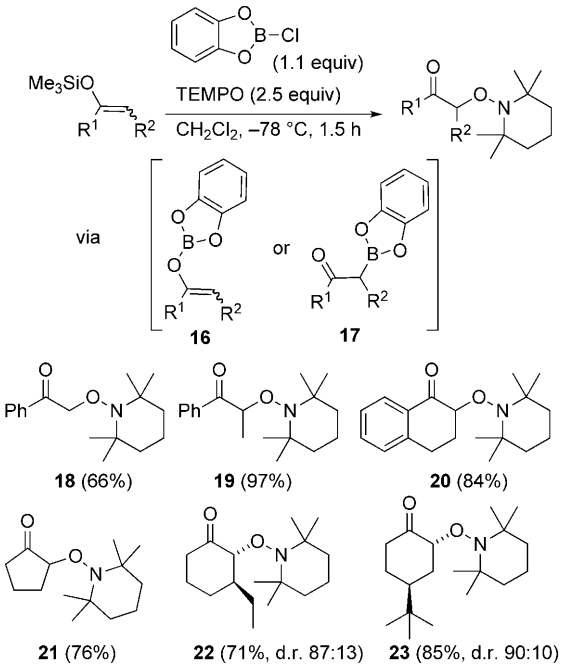
Figure 1. Preparation of TEMPO-derived alkoxyamines **9**–**13**.

yields. Alkoxyamines **11** and **12** derived from heteroaryl-substituted enones were obtained in slightly lower yields. It is important to note that hydroboration and hence oxidation occurred with excellent regioselectivity. Products arising from oxidation of the terminal double bond were not identified. Furthermore, no cyclization products were observed in these reactions because of the highly efficient TEMPO trapping of the α-carbonyl radicals generated in situ. Pleasingly, this strategy also worked for alkyl alkenyl ketones as shown for regioselective transformation of β-ionone to give alkoxyamine **13** (81%).

TEMPO-derived alkoxyamines bearing a double bond at an appropriate position can serve as substrates for tin-free radical isomerization reactions, as we have previously shown.[13] Heating of alkoxyamine **9** in *t*BuOH at 130°C in a sealed tube for 20 h provided products **14a** (42%) and **14b** (28%) by radical 5-*exo* and 6-*endo* cyclizations, respectively. By analogy, alkoxyamine **12** was readily isomerized to give **15a** and **15b**. The 5-*exo* cyclizations afforded *trans* products, whereas the 6-*endo* products were obtained as mixtures of diastereomers (Scheme 4).[14]

Unfortunately, enolate formation followed by TEMPO oxidation could not be used for α-aminoxylation of cyclic α,β-unsaturated ketones. The desired boron enolates cannot be formed by application of the established conjugate reduction protocol, as presented above, since these undergo slow 1,2-reduction.[11a] Moreover, this procedure inherently precludes the α-aminoxylation of the methyl residue of methyl ketones such as acetophenone. Therefore, we tried to access catecholboron enolates by transmetalation of the corresponding ketone enolates. Unfortunately, all attempts to obtain these by ketone deprotonation with Li amide bases (several tested) or amines followed by treatment with bromo- or chlorocatecholborane failed.

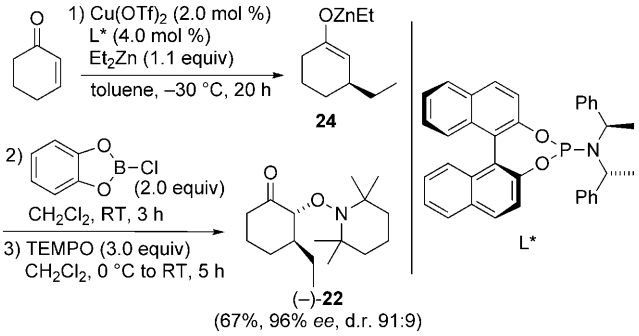
However, we succeeded in generating these boron enolates in situ from readily available trimethylsilyl enol ethers (see the Supporting Information) upon treatment with chlorocatecholborane. To the best of our knowledge, this approach to catecholboron enolates is unprecedented.[15] Importantly, boron enolate formation and TEMPO trapping could be performed as a one-pot process. Hence, treatment of a trimethylsilyl enol ether with chlorocatecholborane and TEMPO in CH_2Cl_2 at low temperature afforded the corresponding α-oxidation products **18**–**23** in good to excellent yields (66–97%, Scheme 5). Although we currently favor the boron enolate **16** as an intermediate, the reaction might also proceed via the B–C-bound species **17.** This novel method allowed α-aminoxylation of cyclic ketones as shown for alkoxyamines **20**–**23**, which were not accessible via the corresponding cyclic α,β-unsaturated ketones. As expected for a radical reaction, *trans*-**22** and *trans*-**23** were obtained as



Scheme 5. Aminoxylation of silyl enol ethers.

the major diastereomers from the kinetically favored trapping of the corresponding cyclohexyl radicals.[16] The relative configuration of **22** and **23** was secured by X-ray crystallography (see the Supporting Information).[17]

Finally, we tried to combine our novel α-aminoxylation with a stereoselective C–C bond-forming reaction. The asymmetric reaction should deliver an intermediate that can be readily transformed to the corresponding catecholboron enolate. The intensively investigated copper-catalyzed 1,4-addition of diethyl zinc to cyclohexenone was chosen as the test reaction.[18] Initially, we tried to convert the zinc enolate formed in situ to the corresponding silyl enol ether (by addition of TMSOTf)[19] followed by α-aminoxylation. This route provided the desired alkoxyamine (−)-**22** in only 20% yield. However, we found that direct treatment of the zinc enolate intermediate **24** with chlorocatecholborane and subsequent TEMPO trapping gave alkoxyamine (−)-**22** in 61% overall yield (Scheme 6). TEMPO trapping occurred



Scheme 6. One-pot enantioselective 1,4-addition/α-aminoxylation.

with very good *trans* diastereoselectivity (91:9). This cascade reaction clearly showed that the zinc enolate was efficiently converted to the corresponding catecholboron enolate upon treatment with chlorocatecholborane. Ketone **22** was obtained with excellent enantioselectivity (96% *ee*).[20]

In summary, we have developed a novel method for the generation of α-carbonyl radicals from catecholboron ketone enolates by reaction with TEMPO. The boron enolates were readily obtained by reduction of linear enones with catecholborane or by transmetalation of silyl enol ethers and zinc enolates with chlorocatecholborane. In situ trapping of the α-carbonyl radicals with TEMPO provided the corresponding alkoxyamines in high yields. An enantiomerically enriched chiral boron enolate generated in situ reacted with TEMPO with very good diastereoselectivity.

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