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# α-Aminoxylation of Ketones and β-Chloro-α-aminoxylation of Enones with TEMPO and Chlorocatecholborane

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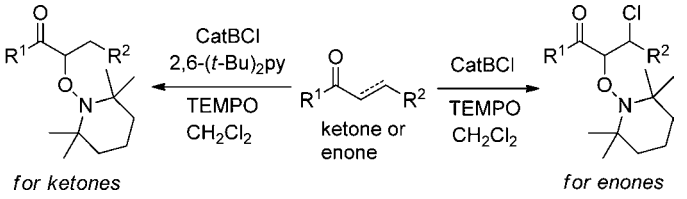
## ABSTRACT




**Oxidation of various cyclic and acyclic ketones under mild conditions with chlorocatecholborane, a bulky pyridine base, and TEMPO to the corresponding α-aminoxylated products in good to excellent yields (52−99%) is described. For enones as substrates, products of a β-chloro-α-aminoxylation are obtained (70−89%).**

The 2,2,6,6-tetramethylpiperidine-*N*-oxyl radical (TEMPO) has become a highly valuable reagent for organic synthesis.[1] It is well-known that ester and amide enolates are not oxidized by TEMPO to the corresponding α-aminoxylation products.[2] However, *N*-oxoammonium salts ($TEMPO^+X^-$), which can be generated *in situ* by oxidation of TEMPO or be used as stoichiometric reagents, show far higher reactivity and various metal enolates are readily transformed to the corresponding alkoxyamines upon reaction with $TEMPO^+X^-$.[3] Readily enolizable ketones also react with TEMPO-derived oxoammonium salts to provide α-diketones.[4] α-Aminoxylation of enolates with TEMPO can be achieved in the presence of an external oxidant,[5] and aldehydes are α-aminoxylated by TEMPO using secondary amines in combination with an external oxidant.[6] Enolate oxidations have been intensively studied in the past with various oxidants.[7]

We recently showed that catecholboronenolates are readily oxidized with 2.5 equiv of TEMPO.[8,9] In these transformations, the first *N*-oxyl radical reacts at the boron atom of the *B*-enolate thereby generating an α-enoyl radical which in turn gets trapped by TEMPO to form the corresponding α-aminoxylation product (Scheme 1). The intermediate CatB-enolates can be generated either by

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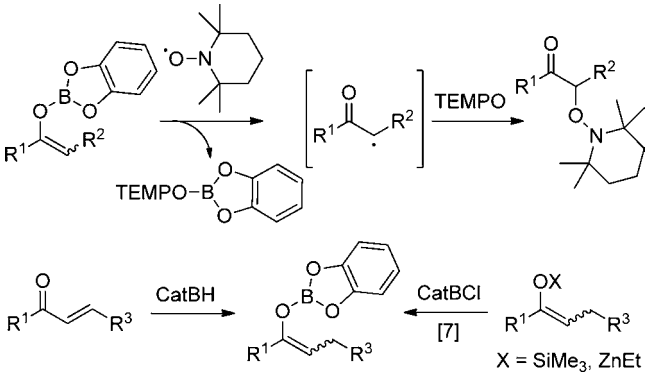
reduction of enones with catecholborane (CatBH) or by transmetalation of silyl enol ethers or zinc enolates with chlorocatecholborane (CatBCl).[8] We report herein that α-aminoxylation can be achieved directly from ketones upon reaction with a bulky amine base, TEMPO, and CatBCl. Moreover, we disclose the first results on an unprecedented *β*-chloro-α-aminoxylation of enones by using CatBCl and TEMPO and provide some mechanistic studies.

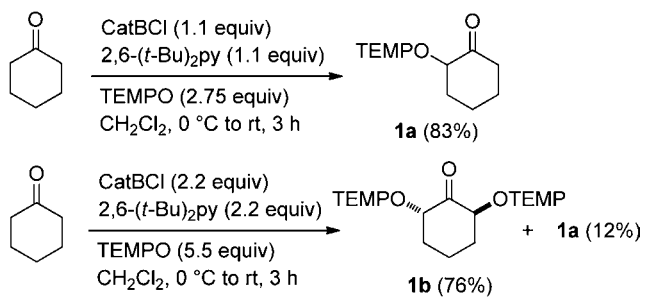
**Scheme 1.** Generation of Catecholboronenolates and TEMPO-Mediated α-Oxidation




We first studied the α-aminoxylation of cyclohexanone and found that the reaction is best conducted in dichloromethane with 1.1 equiv of CatBCl and 2,6-di-*tert*-butylpyridine (1.1 equiv) as the base in the presence of TEMPO (2.8 equiv). TEMPO, the base, and then CatBCl were added at 0 °C, and the reaction mixture was allowed to warm to room temperature over 3 h, resulting in alkoxyamine **1a** being isolated in 83% yield (Scheme 2). It is important to note that B-enolization in the presence of TEMPO afforded the optimal results. If TEMPO is added after enolization, the yield dropped to 20%. The yield also decreased in the absence of the pyridine base (67%). Double oxidation was achieved upon increasing the amount of base (2.2 equiv), CatBCl (2.2 equiv), and TEMPO (5.5 equiv), and bisalkoxyamine **1b** was obtained in 76% yield with complete *trans*-selectivity along with 12% of the monooxidation product **1a**.

The scope of the monoaminoxylation was studied next under optimized reaction conditions. The products and yields are presented in Figure 1. The ring size of cyclic ketones heavily influences the reaction outcome. Whereas transformation of cyclopentanone delivered a complex mixture in which the targeted product was not identified, cycloheptanone provided alkoxyamine **1c** in quantitative yield. Open chain aliphatic ketones, as shown for acetone used in large excess, can also be oxidized with this method (see **1d**). Alkyl aryl ketones are good substrates for this reaction. α-Aminoxylation of acetophenone provided **1e** in 56% isolated yield. In this transformation, overoxidation to the corresponding gem-diaminoxylated compound was also observed (5% yield, see Supporting Information (SI)). Overoxidation is fully suppressed when an alkyl group is present at the α-position.

**Scheme 2.** α-Aminoxylation of Cyclohexanone



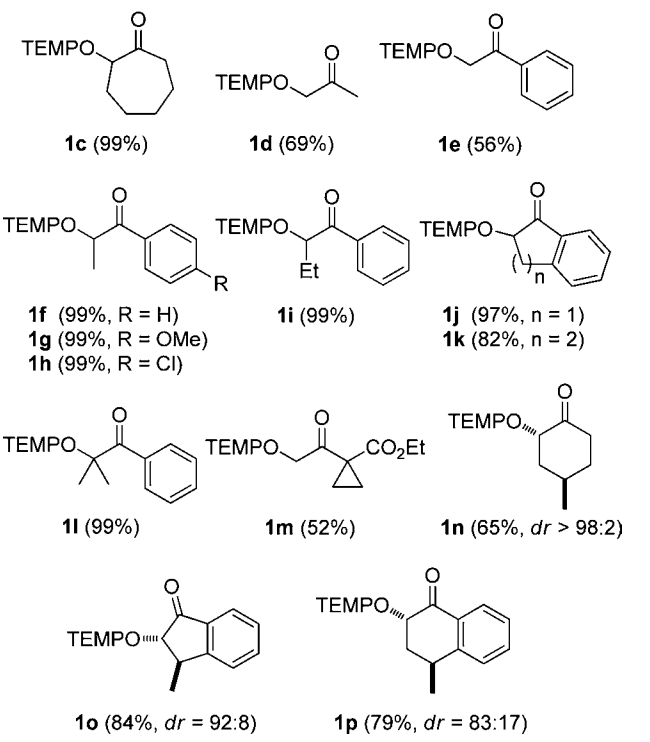




**Figure 1.** Various alkoxyamines prepared via mild α-aminoxylation of ketones.

Hence, ethyl phenyl ketone and propyl phenyl ketone were quantitatively oxidized to **1f** and **1i**, respectively. *p*-Methoxy and *p*-chloro substituents on the aryl group are well tolerated, and the corresponding α-aminoxylation products **1g** and **1h** formed in quantitative yields. Cyclic alkyl aryl ketones also worked well (see **1j** and **1k**), and even formation of a quaternary C-center by oxidation of phenyl propyl ketone was possible (see **1l**). *β*-Ketoesters lacking acidic α-protons are also substrates for the

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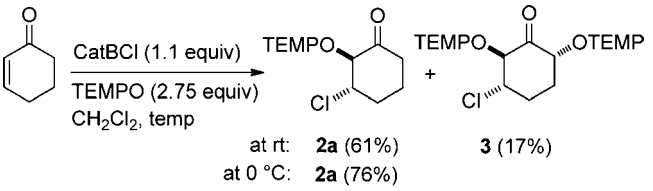
aminoxylation, and **1m** was isolated in 52% yield. α-Aminoxylation of 4-methylcyclohexanone occurred with complete diastereoselectivity (see **1n**, >98:2, 1,3-stereoinduction).[10] The preparation of **1o** and **1p** proceeded also with good stereoselectivities.

During investigations on the α-aminoxylation of 2-cyclohexenone we observed stereoselective formation of *trans*-3-chloro-2-TEMPO-cyclohexan-1-one **2a** as a major product. Upon treatment of 2-cyclohexenone with CatBCl and TEMPO at room temperature in $CH_2Cl_2$ in the absence of base, **2a** was formed in 79% yield. However, we faced difficulties in reproducing that result. Yields of **2a** varied from 50 to 70%, and the alkoxyamine derived from α-aminoxylation of 2-cyclohexenone (not shown) was obtained in 15−20% yield as a side product.

**Scheme 3.** Oxidation of 2-Cyclohexenone




The lack of reproducibility of the reaction was attributed to small variations of the mixing time of CatBCl and TEMPO. In order to obtain reproducible results, CatBCl was added to a solution of TEMPO and 2-cyclohexenone at rt. While this procedure allowed the formation of **2a** with a reproducible yield (61%), the overoxidized bisalkoxyamine **3** was also obtained in 17% yield (Scheme 3). Formation of **3** could be suppressed by running the reaction at 0 °C (reaction worked even at −78 °C), and **2a** was obtained with complete regio- and diastereoselectivity in 76% isolated yield. Under optimized conditions, various enones were tested in the β-chloro-α-aminoxylation reaction (Figure 2). 2-Cycloheptenone provided alkoxyamine **2b** with complete stereoselectivity in 84% isolated yield. Similar results were achieved with methyl vinyl ketone and phenyl vinyl ketone (see products **2c** and **2d**). However, β,β-doubly substituted enones such as 4-methylpent-3-en-2-one and isophorone were unreactive and the targeted products were not detected. Chiral 2-cyclohexenones bearing additional substituents at position 4 or 5 reacted with complete stereoselectivity, and products **2f** and **2g** were isolated in good yields. The relative configuration was assigned by NMR spectroscopy (see SI).

In order to elucidate the mechanism of these transformations we performed additional control experiments. We noted a fast reaction of TEMPO upon addition of CatBCl in $CH_2Cl_2$ in the absence of ketone as judged by the immediate color change. Based on this observation, we assumed that TEMPO dismutates in the presence of CatBCl to produce $TEMPO^+Cl^-$ and TEMPOBCat (Scheme 4).

(10) In the $^1$H NMR spectrum the other isomer was not identified. The relative configuration was assigned by NMR analysis.

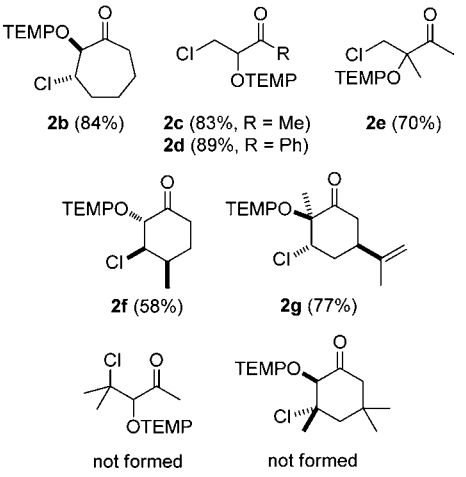
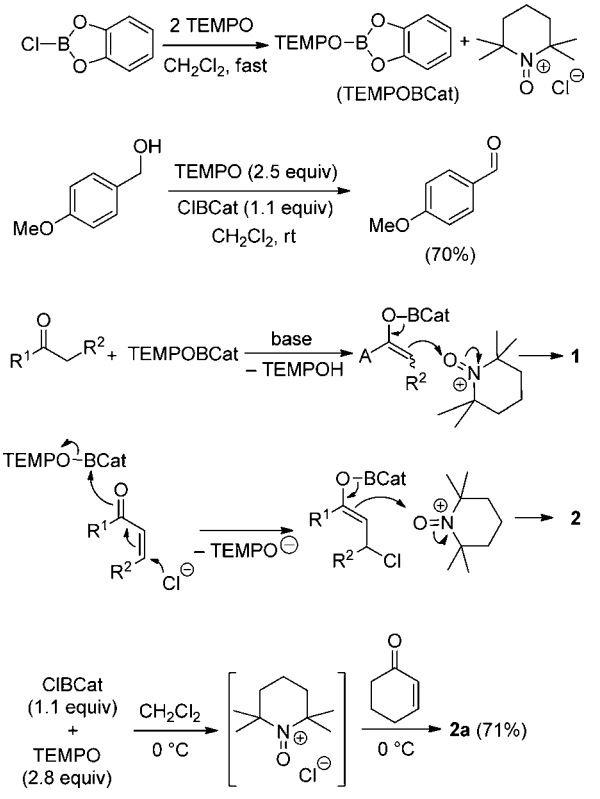



**Figure 2.** β-Chloro-α-aminoxylation of various enones.

$TEMPO^+Cl^-$ is known to act as an oxidant for alcohol oxidations. To prove its formation, we reacted *p*-methoxybenzylalcohol with TEMPO and CatBCl in $CH_2Cl_2$ and indeed obtained *p*-methoxybenzaldehyde in 70% isolated yield. This experiment gives strong support to the fact that $TEMPO^+Cl^-$ can be generated from TEMPO and CatBCl. Moreover, since that reaction is very fast, we currently assume that all α-aminoxylations occur with $TEMPO^+Cl^-$ as the oxidant.

**Scheme 4.** Control Experiments and Suggested Mechanisms



Hence, deprotonation of the ketone, which is probably activated by interaction with the Lewis acidic TEMPOBCat formed as a byproduct during oxoammonium salt formation, provides a *B*-enolate that undergoes ionic reaction with $TEMPO^+Cl^-$ to afford the α-aminoxylated ketone **1**. *β*-Chlorination likely occurs via activation of the enone with a B-Lewis acid and subsequent conjugate ionic chloride addition. The *B*-enolate is subsequently trapped with TEMPO to eventually give the *β*-chloro-α-aminoxylation product **2**. We ran an additional control experiment to support that mechanism. TEMPO was first reacted with CatBCl at 0 °C (formation of $TEMPO^+Cl^-$ and TEMPOBCat). Then 2-cyclohexenone was added to the reaction mixture at that temperature, and after workup and purification, **2a** was isolated in 71% yield. This yield compares well with the yield obtained using the standard protocol (76%; see Scheme 3).

In conclusion, we presented the high yielding α-aminoxylation of various ketones with chlorocatecholborane, TEMPO, and 2,6-di-*tert*-butylpyridine under mild conditions. The substrate scope is broad, and products are obtained with good to excellent yields. For enones as substrates in the absence of the pyridine base, an unprecedented *β*-chloro-α-aminoxylation reaction is obtained. For cyclic enones, this vicinal difunctionalization occurs with complete *trans*-diastereoselectivity. Reactions are easy to conduct, and all reagents used are commercially available.

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**Supporting Information Available.** Experimental details, characterization data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.