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A General Method for the α-Acyloxylation of Carbonyl Compounds

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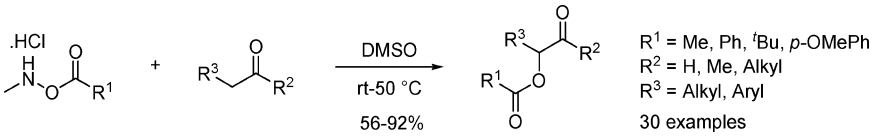
ABSTRACT



A simple, one-pot method for the α-acyloxylation of carbonyl compounds that proceeds at room temperature in the presence of both moisture and air has been developed. Treatment of a variety of aldehydes and both cyclic and acyclic ketones with *N*-methyl-*O*-benzoylhydroxylamine hydrochloride provides the α-functionalized product in 69–92% isolated yield. The transformation is tolerant of a wide range of functional groups and, significantly, is regiospecific in the discrimination of secondary over primary centers in the case of nonsymmetrical substrates.

At the heart of synthetic chemistry is the drive to develop novel, cleaner, more efficient, and selective transformations. To this end, there has been a recent explosion of interest in the use of metal-free processes to carry out functional group manipulations and transformations due to the potential for academic, industrial, economic, and environmental benefit.[1] Herein, we report a simple and practical method for the α-functionalization of carbonyl compounds that proceeds via a proposed concerted pericyclic rearrangement.

The α-hydroxy carbonyl functionality represents a significant building block in organic synthesis and is present in a substantial number of both naturally occurring and synthetic biologically significant molecules. This importance is reflected in the extensive synthetic research directed toward introducing this group in a chemo- regio-, stereo-, and enantioselective manner. Particularly noteworthy among these contributions are the α-oxygenation of enolates with electrophilic oxidizing agents, and the dihydroxylation or epoxidation of preformed enol ethers.[2] More recently, there have been major advances in the area which allow the aminooxylation of aldehydes[3] and ketones.[4] Treatment of an excess of the substrate carbonyl species with nitrosobenzene in the presence of a catalytic amount of proline delivers the α-aminooxylated species in excellent yield and ee. Unmasking of the hydroxyl functionality is then accomplished under reductive conditions. Advances continue to be made in this area[5] toward the ultimate goal of using just 1 equiv of substrate carbonyl and oxidant to make a truly practical procedure.[6]

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(1) (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. (b) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726. (c) Groger, H.; Wilken, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 529.

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(4) (a) Bøgevig, A.; Sundén, H.; Córdova, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1109. (b) Hayashi, Y.; Yamaguchi, J.; Sumiya, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 1112. (c) Córdova, A.; Sundén, H.; Bøgevig, A.; Johannson, M.; Himo, F. *Chem. Eur. J.* **2004**, *10*, 3673.

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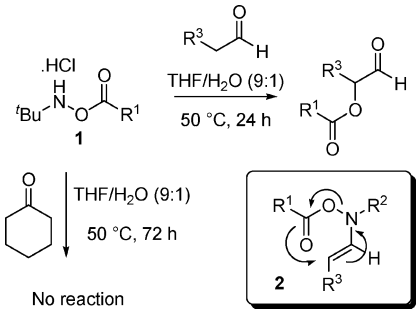
Scheme 1

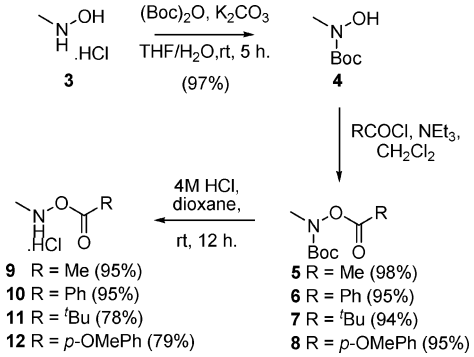


We have recently described a direct method for the chemospecific α-functionalization of aldehydes using *N*-*tert*-butyl-*O*-benzoylhydroxylamine hydrochloride (**1**) (Scheme 1).[7] However, we found **1** to be ineffective for the analogous transformation with ketones. Although this permits useful chemoselectivity, we sought to develop a more general reagent that would permit the transformation of both aldehydes and ketones. We rationalized that the hindered nature of the nitrogen lone pair in **1** rendered the reagent too sterically encumbered to form the proposed iminium ion and subsequent enamine (**2**) intermediates. Therefore, we reasoned that reduction in the size of the nitrogen substituent would provide a system that avoided this deficiency. Herein, we report that a series of *N*-methyl-*O*-acylhydroxylamines (**9**−**12**) can be used for the effective α-acyloxylation of both aldehydes and ketones.

The origin of our investigation lay in a report by House, who showed that cyclohexanone could be converted to 2-acetoxycyclohexanone via a five-step protocol.[8] This sequence was shortened to three steps by Coates in 1982[9] and was elegantly used in the preparation of fumagillol by Sorensen and co-workers.[10] Both of these sequences proposed a [3,3] sigmatropic rearrangement in the key bond-forming sequence under basic reaction conditions. More recently, Lobo has described the α-oxyacylation of enehydroxylamines by a proposed sigmatropic rearrangement, once again under basic reaction conditions.[11]

Preparation of the reagent commenced with protection of commercially available *N*-methylhydroxylamine hydrochloride (**3**) as its *N*-*tert*-butylcarbamate **4** (97%), followed by acylation of the product with benzoyl chloride under standard conditions to give **6**. Removal of the protecting group with hydrochloric acid in dioxane gave the desired reagent **10** in 88% overall yield for the three steps (Scheme 2). It is particularly noteworthy that both of the synthetic intermediates **4** and **6** were purified by distillation, and the *N*-methyl-

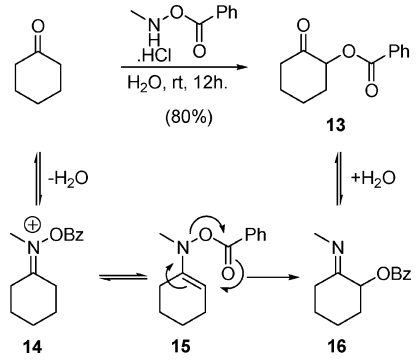
Scheme 2



O-benzoylhydroxylamine hydrochloride **10** crystallized directly from the reaction mixture and could therefore be isolated by a simple filtration, providing a practical and accessible route to significant quantities of the reagent.[12] Acetyl **9**, pivaloyl **11**, and 4-methoxyphenyl **12** systems were also prepared in an analogous manner providing a series of compounds with which to investigate the α-oxygenation reaction.

We initially examined the reaction between cyclohexanone and *N*-methyl-*O*-benzoylhydroxylamine hydrochloride (**10**) at room temperature using water as the solvent and were delighted to discover that the desired product **13** could be isolated from the reaction mixture in 80% yield after purification by column chromatography.

Scheme 3



We believe this reaction proceeds via condensation of the reagents to give the iminium ion **14**, which is then converted into the enamine **15** under aqueous acidic reaction conditions. Concerted pericyclic rearrangement provides the α-benzoyloxy imine **16**, which is hydrolyzed in situ to give the observed product **13** (Scheme 3).[13] Having established that

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(8) House, H. O.; Forrest, A. R. *J. Org. Chem.* **1969**, *34*, 1340.

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(10) Vosburg, D. A.; Weiler, S.; Sorensen, E. *Chirality* **2003**, *15*, 156.

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(12) This reaction sequence has been carried out successfully on a 25 g scale and the resulting salts **9**−**12** were all bench stable throughout the course of this investigation.

(13) Clark and co-workers have reported a base catalyzed rearrangement of *N*-alkyl-*O*-acylhydroxamic acids to deliver 2-acyloxyamides, see: (a) Clark, A. J.; Al-Faiyz, Y. S. S.; Broadhurst, M. J.; Patel, D.; Peacock, J. L. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1117. (b) Al-Faiyz, Y. S. S.; Clark, A. J.; Filik, R. P.; Peacock, J. L.; Thomas, G. H. *Tetrahedron Lett.* **1998**, *39*, 1269.

Table 1. Scope of Transformation

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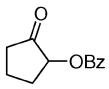
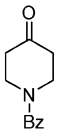
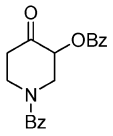
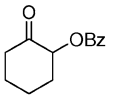
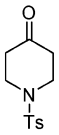
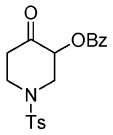
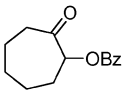
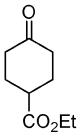
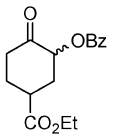
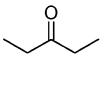
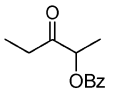
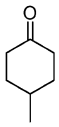
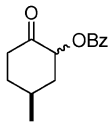
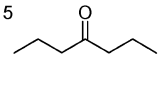
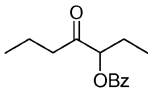
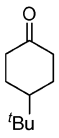
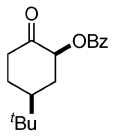
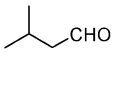
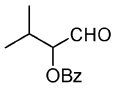
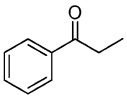
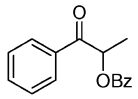
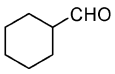
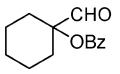
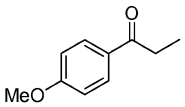
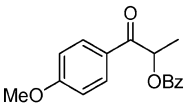
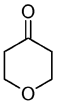
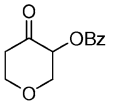
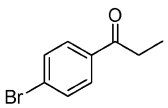
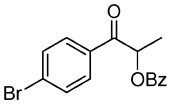
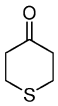
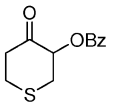
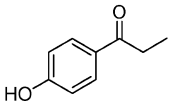
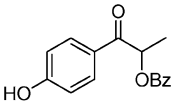
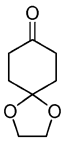
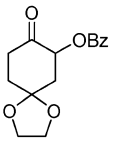
1			73[a]	11			69[a]
2			80[a]	12			74[a]
3			69[a]	13			75[a]
4			74[b]	14			72[a]
5			90[b]	15			76[a]
6			92[a]	16			69[c]
7			74[c]	17			92[d]
8			79[a]	18			82[d]
9			75[a]	19			85[d]
10			70[a]				

[a] DMSO, rt, 4−24 h, 1 equiv of **10**. [b] DMSO, 50 °C, 24 h, 1 equiv of **10**. [c] DMSO, 50 °C, 48 h, 1.5 equiv of **10**. [d] DMSO, 50 °C, 48 h, 2 equiv of **10**.

it was indeed possible to carry out the proposed rearrangement on ketone substrates, we went on to explore the scope of this novel transformation.

Although the reaction was effective when water was used as the solvent, consistently higher yields and cleaner transformations were observed using dimethyl sulfoxide which we adopted in our standard protocol.[14] The results obtained are outlined in Table 1. The reaction was effective for the functionalization of five- (73%, entry 1), six- (80%) and seven-membered rings (69%, entry 3). It was also possible to functionalize acyclic systems, although the reaction was sluggish at room temperature with this class of ketone. Convenient rates were achieved by warming the reaction mixture to 50 °C. For example, pentan-3-one (entry 4) and heptan-4-one (entry 5) gave α-benzoylated products in 74% and 90% isolated yields, respectively. Aldehydes were also efficient substrates for rearrangement into both secondary (entry 6) and tertiary (entry 7) centers, which suggested that this reaction should be effective for a wide variety of carbonyl-containing compounds.

We next went on to examine the functional group tolerance of the transformation. The reaction was tolerant of ethers, tetrahydropyran-4-one giving the expected product in 79% yield (entry 8) as well as hydrolytically sensitive functionalities including cyclic acetals (70%, entry 10) and esters (75%, entry 13). The nonoxidizing nature of the reagent

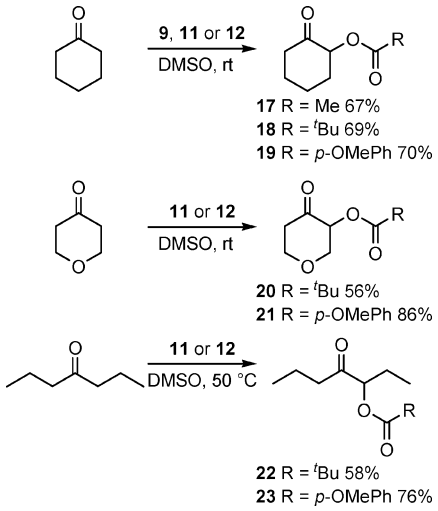
(14) The reaction is effective in both polar and nonpolar solvents with the α-functionalised product being isolated as the major product in each case, however, reactions are cleaner and faster in DMSO. Representative yields for the reaction of cyclohexanone with **10** at room temperature for 24 h: $CHCl_3$ (76%), THF (80%), THF/H_2O (9/1) (62%), DMSO (80%). ^1H NMR spectra of crude reaction mixtures in these solvents are contained in the Supporting Information.

means that sulfides can also be used effectively within this transformation (75%, entry 9). Amides (entry 11) and sulfonamides (entry 12) also remain unaffected under the reaction conditions. Interestingly, the reaction tended to give the thermodynamically more stable product, for example, treatment of 4-*tert*butyl cyclohexanone with 1 equiv of **10** gave the *cis*-substituted product in 76% isolated yield (entry 15), with no indication of the *trans*-diastereoisomer detected in the ^{1}H NMR of the crude reaction mixture. Use of the less sterically encumbered 4-methyl cyclohexanone, however, led to a 1:1 mixture of diastereoisomers being observed for the product (entry 14).

The reaction was also effective in the presence of a variety of aromatic systems. Although these reactions were slow under our standard reaction conditions for acyclic ketones, addition of 1.5 equiv of the reagent **10** led to good yields with propiophenone (69%, entry 16), electron-rich aromatics (92%, entry 17), and electron-deficient aromatics (82%, entry 18). Of particular note is the fact that this transformation is also tolerant of the presence of a free hydroxyl group with 4-hydroxypropiophenone giving the expected product in 85% isolated yield (entry 19), greatly adding to the potential of this intriguing transformation.

Having shown that the procedure was effective for a variety of carbonyl compounds and established the range of the reaction profile, we then went on to investigate if the rearrangement was also tolerant of alternative acyl substituents (Scheme 4).

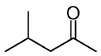
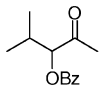
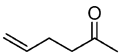
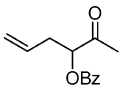
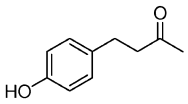
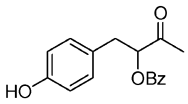
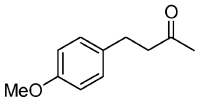
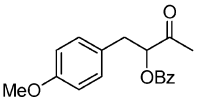
Scheme 4



The reactivity profile of the alternative reagents **9**, **11**, and **12** turned out to be similar to the standard benzoyl reagent **10**, with the compounds working effectively with both cyclic and acyclic carbonyl compounds (Scheme 4). These results suggest that the reaction is not only effective for the reaction of a broad spectrum of carbonyl compounds, but is also capable of delivering the acyl group of choice.

Finally, we examined the reaction of a series of nonsymmetrical substrates with the reagent **10** (Table 2). In each case, when distinguishing primary from secondary centers,

Table 2. Reaction of Nonsymmetrical Substrates

Entry[a]	Substrate	Product	% Yield
1			73
2			81
3			83
4			83

[a] DMSO, 50 °C, 24 h, 1 equiv of **10**.

complete regiospecificity was observed for the secondary center, highlighting the utility of this transformation. With the aliphatic substrates 4-methylpentan-2-one (entry 1) and 5-hexen-2-one (entry 2) the products were isolated in 73% and 81% yield, respectively. This specificity was also the case for the aromatic substrates (entry 3 83% and entry 4 83%). A limitation to the procedure was that we were unable to bring about reaction at primary centers; for example, both acetone and acetophenone gave no indication of the desired α-functionalized product after prolonged reaction times (50 °C, up to 72 h). We are unable to explain this lack of reactivity at present, but such regiospecificity may be exploited to great effect with nonsymmetrical substrates.

In summary, we have described the synthesis of a new family of reagents for the α-functionalization of aldehyde and ketone substrates. The reagents are simple to prepare, with intermediates being purified by distillation and the final compound crystallizing directly from the reaction mixture. The reactions are operationally simple and can be conducted at either room temperature or warming to 50 °C in the presence of both moisture and air without the need for any specialized reaction techniques and equipment or purification of solvents. Particularly useful is the fact that the reaction is tolerant of a wide variety of functional groups and that the reaction does not work for primary centers, providing a regiospecific method for the functionalization of nonsymmetrical substrates. We are currently investigating the development of a catalytic asymmetric variant of this procedure and will report our findings shortly.

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Supporting Information Available: Analytical data and experimental details for preparation of the reagents **9**−**12** and α-functionalized products. This material is available free of charge via the Internet at http://pubs.acs.org.

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