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EDGE ARTICLE

A general approach to the enantioselective α-oxidation of aldehydes *via* synergistic catalysis†

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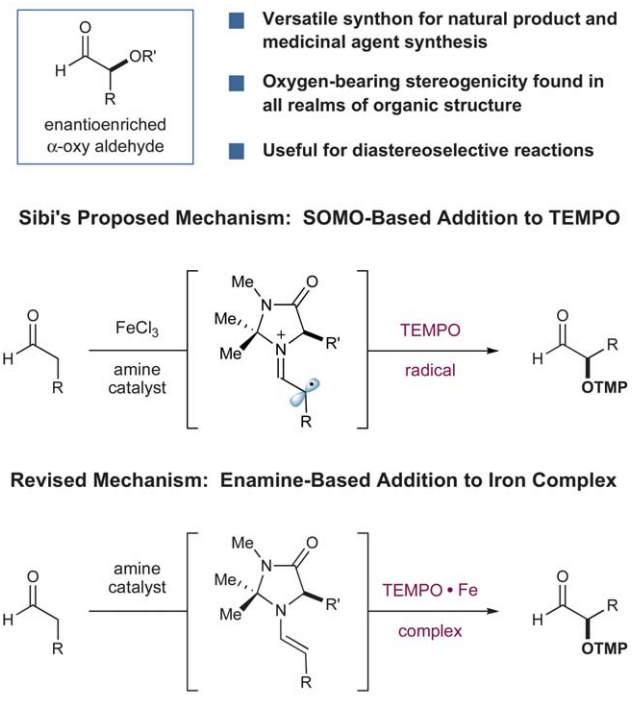
A new enantioselective α-oxidation of aldehydes has been accomplished using TEMPO and a synergistic combination of copper and organic catalysis. Expanding upon recently reported mechanistic studies, these mild catalytic conditions provide stable aldehyde products bearing a wide array of electronically and sterically diverse substructures. The utility of these oxidized products is highlighted by subsequent derivatization to a variety of common chiral synthons, without loss in enantiopurity.

Introduction

Found among many natural and non-natural medicinal agents, oxygen-bearing stereocenters are a fundamental structural motif that is broadly represented throughout the realm of organic architecture.[1–3] While traditional synthetic approaches to enantioselective C–O bond formation are strikingly powerful (olefin epoxidation/dihydroxylation, ketone reduction), new strategies continue to expand the range of starting materials or functional groups from which this important stereogenicity can be created. Recently, the enantioselective α-oxidation of aldehydes has garnered substantial attention as a novel catalytic approach to asymmetric oxygen-bearing stereocenters. In particular, the capacity to selectively install C–O bonds in direct proximity to high value carbonyl systems allows for a diverse range of post synthetic elaboration steps (*e.g.* oxidation, reduction, Wittig olefination, alkyl or aryl nucleophilic addition *etc.*).[4] A number of enantioselective aldehyde α-oxidation reactions have recently been reported; however, there are no direct methods that demonstrate high reaction efficiency and enantioselectivity, while generating stable aldehyde products with an expansive substrate scope. Given the demonstrated value of α-oxy carbonyl synthons, we recently sought to address this need for a broadly applicable and highly selective protocol. Herein we report the successful execution of these ideals *via* the exploitation of mechanistic insight gained in studies of the organocatalytic Sibi oxyamination reaction.



Can this new insight lead to a highly enantioselective oxidation?

In 2003, along with Zhong, we reported the first catalytic enantioselective α-oxidation of aldehydes, utilizing nitrosobenzene as an electrophilic source of oxygen.[5,6] While the aldehyde products of this protocol were formed in high yield and with excellent enantioselectivity, their structural ground state was that of oligomers, rendering their isolation and derivatization troublesome. Later, Sibi disclosed an alternative method for preparing a number of stable α-oxy aldehydes using the commercially available 2,2,6,6-tetramethylpiperidine-1-oxyl radical (TEMPO) with an amine catalyst and $FeCl_3$.[7] In this

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report, it was proposed that an outer-sphere single electron oxidation of a transiently generated enamine (using $FeCl_3$) produced a radical cation, which trapped the oxygen radical at the α-position. While on first inspection this mechanism seemed quite reasonable, we have recently demonstrated that this protocol does not involve SOMO-activation[8] but instead an enamine addition pathway.[9] More specifically, we found that the metal catalyst employed in the Sibi studies does not participate as an oxidant, but as a coordinating metal for the nitroxyl radical of TEMPO, generating a well-precedented η_2 complex that is electrophilic at oxygen.[10] As a result, enantioselective C–O bond formation in the Sibi oxyamination reaction occurs *via* addition of the transient enamine to an electrophilic iron-TEMPO complex.

Design plan

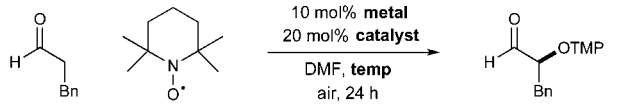
Inspired by these new mechanistic insights, we hypothesized that the use of alternative metal salts, which are known to form stable complexes with TEMPO,[10] could lead to a more general and highly enantioselective method for the α-oxidation of aldehydes. To provide an electrophile optimally suited for coupling with an enamine, the electronic nature of the η_2 complex could easily be tested by the choice of TEMPO framework[11] and metal, while selection of a refined organocatalyst should increase the inherent enantioselectivity of the process. Since products of this nature are stable to racemization, the incorporation of an OTMP group offers a valuable handle for further structural elaboration, while the resulting N–O bond is readily cleaved to the free hydroxyl using mild yet chemically orthogonal conditions to that of carbonyl functionalization.[7,12]

Results and discussion

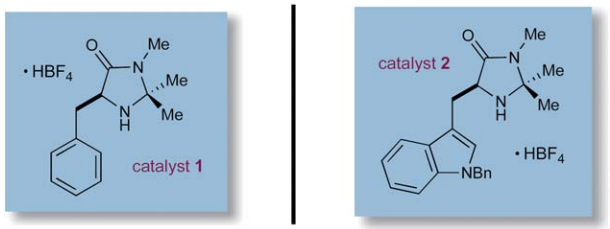
To evaluate the efficiency of this synergistic metal and amine catalyzed process, we began our investigations with TEMPO, 3-phenylpropanal, imidazolidinone catalyst **1**, and $[Fe(DMF)_3Cl_2][FeCl_4]$ under ambient atmosphere in DMF (Table 1). We were delighted to find that the desired product[13] was isolated in 70% yield, albeit with modest enantioselectivity in accord with Sibi's studies (73% ee). Moreover, we observed that ambient air served as a stoichiometric oxidant, avoiding the need for additional equivalents of TEMPO as required in the original method (entry 1).[14] In contrast to the use of iron-based catalysts,[7] switching to $CuCl_2$ provided the desired product with excellent yield and good selectivity at room temperature (entry 2). The pendant phenyl group of catalyst **1** was then replaced with a larger benzyl indole moiety (entry 3), leading to a further increase in enantiocontrol (93% yield, 87% ee). Moreover, lowering the reaction temperature to 0 °C afforded a useful increase in asymmetric induction (entry 4), while subsequent replacement of DMF with ethyl acetate or acetone (entries 5–6) promoted facile oxidation at −30 °C, (74–89% yield, 91–92% ee). Conveniently, ethyl acetate and acetone were taken from benchtop solvent bottles and simply stored for 1 h over oven-dried 4 Å molecular sieves prior to use.

We next performed a series of experiments to define the scope of functional groups and steric constraints that are readily tolerated on the aldehydic component. As revealed in Table 2,

Table 1 Development of general enamine oxidation protocol



Entry	Catalyst	Metal	*T*/°C	%yield[a]	%ee[b]
1[c]	**1**	Fe^{3+}	23	70	73
2	**1**	$CuCl_2$	23	95	85
3	**2**	$CuCl_2$	23	93	87
4	**2**	$CuCl_2$	0	78	90
5[d]	**2**	$CuCl_2$	−30	74	91
6[e]	**2**	$CuCl_2$	−30	89	92

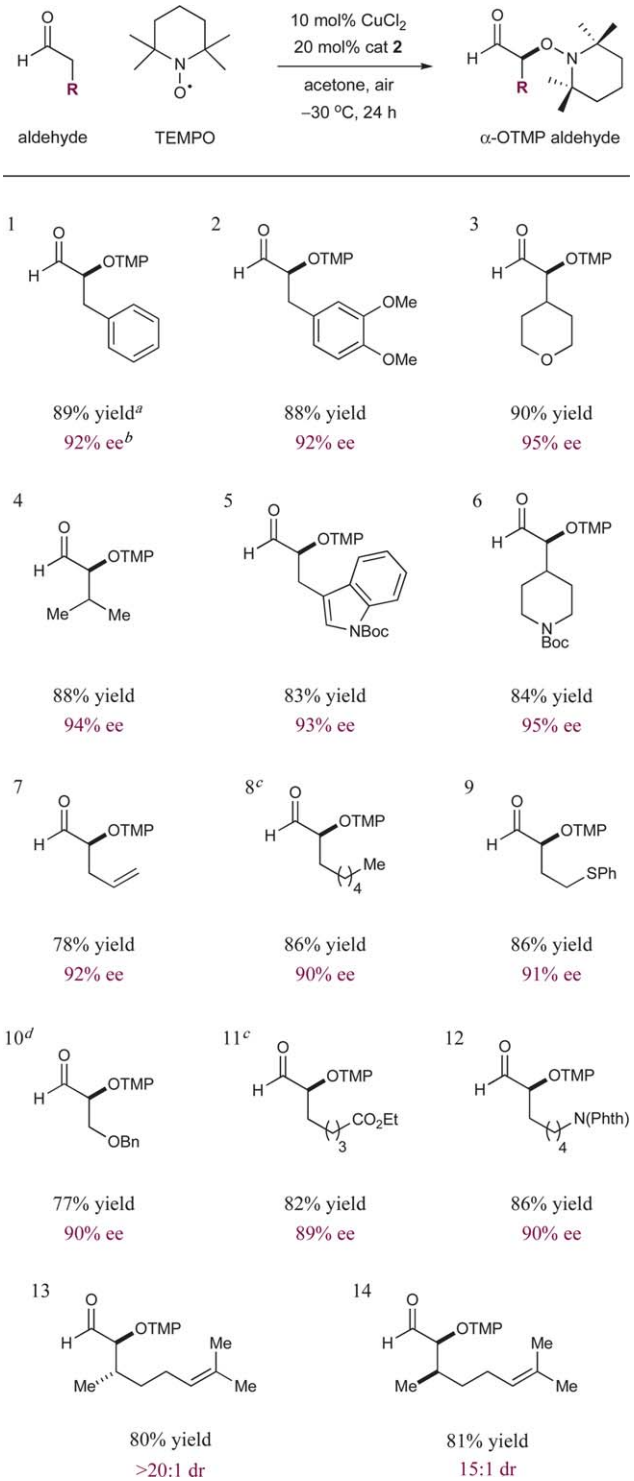


[a] Determined by ^1H NMR. [b] Determined by chiral HPLC of the corresponding alcohol; absolute configuration determined by correlation. [c] $[Fe(DMF)_3Cl_2][FeCl_4]$. [d] Ethyl acetate as solvent. [e] Acetone as solvent.

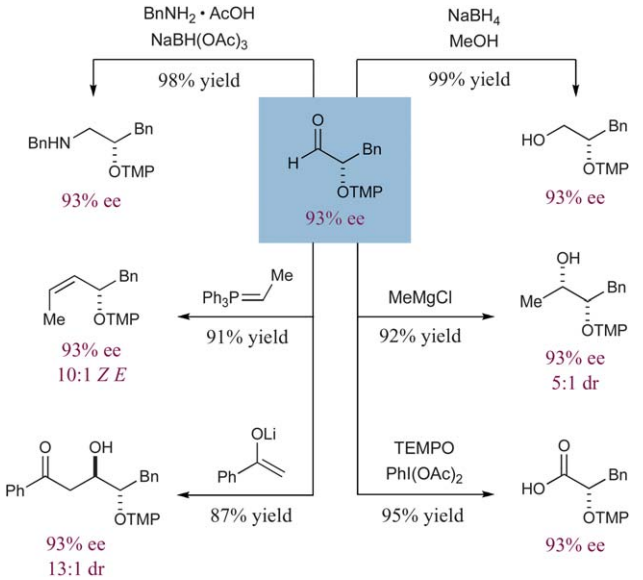
ethers, esters, carbamates, and phthalimides can be incorporated without significant impact on yield or selectivity (entries 3, 6, and 10–12). Surprisingly, aldehydes bearing phenyl sulfides do not undergo oxidation at sulfur under these mild conditions or interfere with the inorganic catalyst, allowing the desired α-formyl oxidation product to be formed in 86% yield and 91% ee (entry 9). Aliphatic aldehydes are functionalized effectively (entries 4 and 8), while the incorporation of unsaturation in the form of olefins and aromatic rings is not detrimental to the process (entries 1–2, 5, 7, and 13–14). Notably, significant variation in steric environment on the aldehyde component is readily accommodated, with the more demanding frameworks furnishing the highest levels of asymmetric induction (entries 3–4, 6, and 13–14). Finally, subjection of (*S*)- and (*R*)-citronellal to oxidation yields the desired *anti* and *syn* products, respectively (entries 13–14). These experiments clearly demonstrate the value of catalyst-induced stereocontrol in preference to substrate-directed induction.

As shown in Scheme 1, numerous carbonyl transformations can be readily employed with these α-oxyamination products without any detectable loss in enantiopurity.[15] For example, oxidation or reduction of the formyl group leads to α-oxygenated carboxylic acids or terminal alcohols, respectively. Reductive amination leads to 1,2-aminoalcohols, while Wittig olefination provides allylic alcohols with good *cis*-olefin selectivity (10 : 1 *Z* : *E*). Carbonyl addition using lithium enolates or Grignard reagents furnishes the corresponding ketones or substituted diols with good to excellent diastereomeric induction (13 : 1 and 5 : 1 dr respectively). As noted above, there is no loss in enantiopurity observed during any of these transformations, further highlighting the versatility and value of this enantioselective oxidation protocol and the resulting α-oxygenated formyl products.

Table 2 Enantioselective formyl α-oxidation: aldehyde scope



[a] Isolated yields of aldehyde product (1.0 mmol scale). [b] Enantiomeric excess determined by chiral HPLC on corresponding alcohol or *m*-nitrobenzoyl ester. [c] Performed at −40 °C. [d] Ethyl acetate as solvent.



Scheme 1 Elaboration to common enantioenriched synthons.

Conclusions

On the basis of mechanistic insight into the Sibi oxyamination reaction, we have developed a widely applicable, highly enantioselective oxidation protocol that combines imidazolidinones and $CuCl_2$ in a synergistic catalysis transform. The robust nature of this oxidation is highlighted by the use of ambient air and benchtop solvents. In contrast to existing methods, a broad range of heteroatoms, olefins, arenes, and steric environments are tolerated to provide stable aldehyde products in high yield and with excellent enantioselectivity. This protocol allows access to α-oxygenated systems in a broad sense that can be readily translated to many well-known synthons without loss in enantiopurity.

Acknowledgements

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