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KetoABNO/NO_x Cocatalytic Aerobic Oxidation of Aldehydes to Carboxylic Acids and Access to α-Chiral Carboxylic Acids via Sequential Asymmetric Hydroformylation/Oxidation

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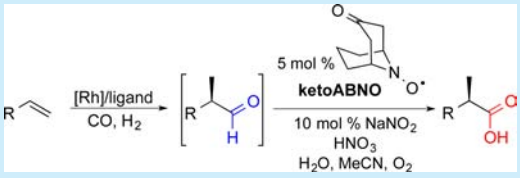
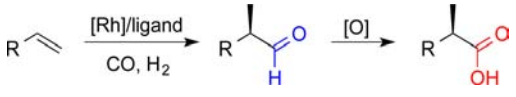
Supporting Information

ABSTRACT: A method for aerobic oxidation of aldehydes to carboxylic acids has been developed using organic nitroxyl and NO_x cocatalysts. KetoABNO (9-azabicyclo[3.3.1]nonan-3-one *N*-oxyl) and $NaNO_2$ were identified as the optimal nitroxyl and NO_x sources, respectively. The mildness of the reaction conditions enables sequential asymmetric hydroformylation of alkenes/aerobic aldehyde oxidation to access α-chiral carboxylic acids without racemization. The scope, utility, and limitations of the oxidation method are further evaluated with a series of achiral aldehydes bearing diverse functional groups.



Carboxylic acids are prevalent functional groups in agrochemicals, pharmaceuticals, and other industrial chemicals. Carboxylic acids are readily obtained in the laboratory via oxidation of the corresponding alcohol or aldehyde using various stoichiometric oxidants.[1−3] Classical oxidants include chromium or manganese oxides, but stoichiometric and catalytic methods employing $NaClO_2$ as the terminal oxidant are quite common in both laboratory and large-scale applications.[4] Aerobic oxidation methods have intrinsic appeal that could find utility on small and large scale,[5] and recent progress has led to homogeneous[6] and heterogeneous[7] catalysts for these applications. The majority of examples, however, employ stoichiometric or larger quantities of a Brønsted base that will result in epimerization of aldehydes bearing adjacent stereocenters. Asymmetric hydroformylation (AHF) of olefins provides a highly appealing, atom-economical route to α-chiral aldehydes,[8,9] and recent efforts in one of our laboratories has focused on synthesis of pharmaceutically important α-chiral carboxylic acids (Scheme 1) via sequential

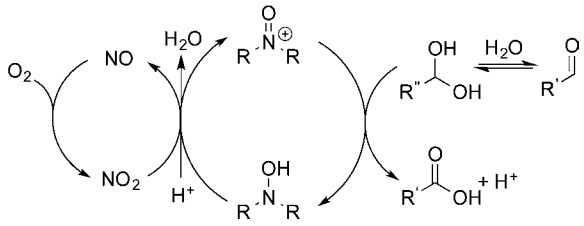
Scheme 1. Preparation of α-Chiral Carboxylic Acids via Sequential Asymmetric Hydroformylation/Oxidation



AHF of olefins followed by oxidation of the aldehyde.[10] In this context, we sought a mild, aerobic oxidation method that could avoid epimerization of sensitive α-chiral aldehyde intermediates.

Aerobic oxidation methods that utilize nitroxyl (co)catalysts for aerobic alcohol oxidation have emerged as appealing alternatives to conventional alcohol oxidation methods.[5b,c,11] Cu/nitroxyl cocatalyst systems, in particular, are highly effective for the oxidation of alcohols to aldehydes and ketones,[5b,12] but these catalysts are poisoned by acidic functional groups, such as phenols and carboxylic acids.[13] Therefore, they are not well suited for oxidation of 1° alcohols or aldehydes to carboxylic acids. On the other hand, nitroxyl/NO_x cocatalyst systems (Scheme 2)[14,15] should be compatible with this transformation,

Scheme 2. Nitroxyl/NO_x-Catalyzed Aerobic Oxidation Aldehydes



as the reactions are typically performed under acidic conditions. Moreover, these conditions might enable oxidation of α-chiral aldehydes without promoting epimerization of the sensitive stereocenter. Diverse nitroxyl/NO_x catalyst systems have been employed for the oxidation of alcohols to aldehydes and ketones,[14,15] but they have not yet been investigated for the oxidation of 1° alcohols or aldehydes to carboxylic acids. Here, we report nitroxyl/NO_x-catalyzed oxidation of aldehydes, initially focusing on substrates derived from AHF of olefins and subsequently on other aromatic and aliphatic aldehydes. The scope and limitations of these methods are presented.

Efforts to develop a suitable oxidation method were initiated by evaluating the oxidation of (*R*)-2-phenylpropanal (**1**, 73% ee) (Table 1). Aldehyde **1** was synthesized in quantitative yield via AHF of styrene according to the previously reported

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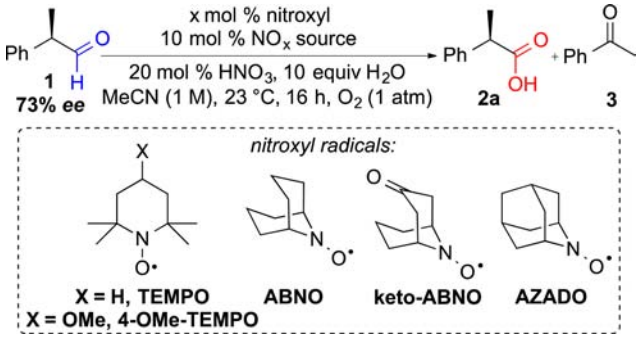
Table 1. Optimization of Aerobic Oxidation of (*R*)-2-Phenylpropanal[a]



entry	nitroxyl (mol %)	oxidant	conv	2a[b] (ee)	3[b]
1[c]	4-OMe-TEMPO (5)	KBr/NaOCl	98	50 (71)	12
2	TEMPO (5)	$NaNO_2/O_2$	44	14 (71)	26
3	AZADO (5)	$NaNO_2/O_2$	82	45 (72)	30
4	ABNO (5)	$NaNO_2/O_2$	82	47 (72)	30
5	**ketoABNO (5)**	$NaNO_2/O_2$	**97**	**85 (72)**	**8**
6[d]	ketoABNO (5)	$NaNO_2/O_2$	87	51 (69)	30
7[e]	ketoABNO (5)	$NaNO_2/O_2$	88	76 (71)	5
8	ketoABNO (2.5)	$NaNO_2/O_2$	75	30 (70)	38
9	ketoABNO (2.5)	$^tBuONO/O_2$	86	44 (70)	37
10[f]	ketoABNO (2.5)	$^tBuONO/O_2$	100	13 (66)	69

[a]Reactions performed on 0.5 mmol scale. [b]Yield determined by ^1H NMR spectroscopy using PhTMS as an internal standard, ee determined by HPLC. [c]See ref 16. [d]No H_2O added. [e]20 equiv H_2O added. [f]Reaction performed at 50 °C.

protocol.[9b] To minimize handling and possible epimerization of the sensitive chiral aldehyde, the crude aldehyde was used without purification, following evaporation of the (THF) solvent from the AHF reaction. As a benchmark, traditional Anelli-type conditions led to carboxylic acid with full retention of enantioselectivity, but only moderate yield (entry 1).[16,17] Use of TEMPO in the aerobic NO_x-based conditions resulted in poor conversion and only 14% yield of **2a** (entry 2). The bicyclic nitroxyls AZADO and ABNO improved the yield of **2a** (entries 3 and 4), but acetophenone was obtained as a major byproduct (30% yield). Significant improvement was observed with ketoABNO, which afforded **2a** in 85% yield (entry 5) without any erosion of the ee, relative to the starting aldehyde. Small amounts of water (10 equiv) were essential to obtain **2a** in good yield (cf. entry 6), presumably to ensure formation of the aldehyde hydrate as the substrate for oxidation. Increasing the amount of water to 20 equiv, however, lowered the yield of **2a** (entry 7). Reducing the catalyst loading to 2.5 mol % increased the formation of acetophenone (entry 8). Changing the NO_x source to *tert*-butyl nitrite led to decreased selectivity and yields (entry 9), and heating the reaction to 50 °C resulted in a significant amount of acetophenone (69%) with a low yield of the carboxylic acid (13%) and partial erosion of the ee (66% ee, entry 10).

The higher reactivity of the bicyclic nitroxyls (AZADO, ABNO, ketoABNO) relative to TEMPO is attributed to their smaller steric profile, which facilitates oxidation of the more-sterically encumbered aldehyde hydrate. This hypothesis aligns with the improved reactivity of bicyclic nitroxyls in the oxidation of secondary alcohols, which sterically resemble the aldehyde hydrate.[15] Plots of the reaction time courses for oxidation of (*R*)-2-phenylpropanal with ketoABNO and ABNO

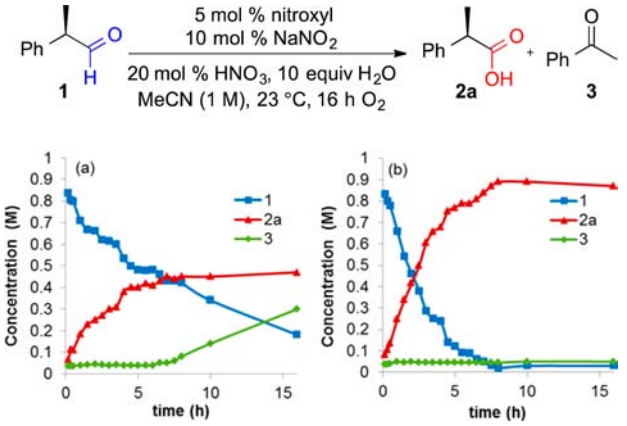
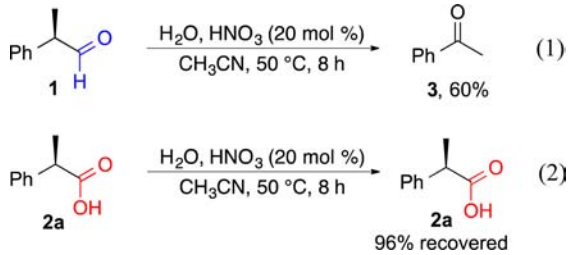


Figure 1. Reaction time course of the nitroxyl/NO_x-catalyzed oxidation of (*R*)-2-phenylpropanal with ABNO (chart a) and ketoABNO (chart b) monitored by ^1H NMR spectroscopy.

show that ketoABNO reacts more rapidly with the substrate, presumably via the intermediate hydrate (Figure 1). The slower oxidation with ABNO resulted in significant formation of acetophenone. Control experiments suggest this product arises from autoxidation of the starting aldehyde under acidic conditions.[18] For example, aldehyde **1** was subjected to the standard reaction conditions in the absence of a nitroxyl cocatalyst at slightly elevated temperatures (50 °C), and acetophenone was obtained as the sole product in 60% yield (eq 1). In contrast, no acetophenone was formed when



carboxylic acid **2a** was subjected to the same conditions (eq 2). The improved reactivity of ketoABNO relative to ABNO is attributed to the higher redox potential of ketoABNO.[19]

The optimized oxidation conditions were then investigated in a two-step AHF/oxidation sequence with alkenes that are particularly effective in the AHF reaction (Scheme 3). The hydroformylation reaction was carried out under previously reported conditions with 0.1 mol % Rh(acac) $(CO)_2$ and 0.12 mol % (*R*,*R*,*R*)-BisDiazaphos ligand **L** (1 mmol alkene, 140 psig 1:1 CO/H_2, 60 °C, glass pressure bottle). In each case, AHF proceeded with quantitative conversion of the olefins to the corresponding chiral aldehyde. When the AHF reaction was complete, the THF solvent was removed under vacuum, and the crude aldehyde was subjected to the ketoABNO-catalyzed oxidation conditions. Styrene was converted to (*S*)-2-phenylpropanoic acid in 89% overall yield without loss of enantiopurity (72−73% ee, (*S*)-**2a**). In most cases, the enantiomeric purity of the intermediate aldehyde was not determined, owing to the sensitivity of the aldehydes toward erosion of the ee. Electron-rich and electron-deficient substituted styrenes were converted to the corresponding carboxylic acids in high yields and good enantioselectivity (**2b**−**2d**). Vinyl benzoate and vinyl acetate underwent successful hydroformylation/oxidation to the lactic acid derivatives **2e** and

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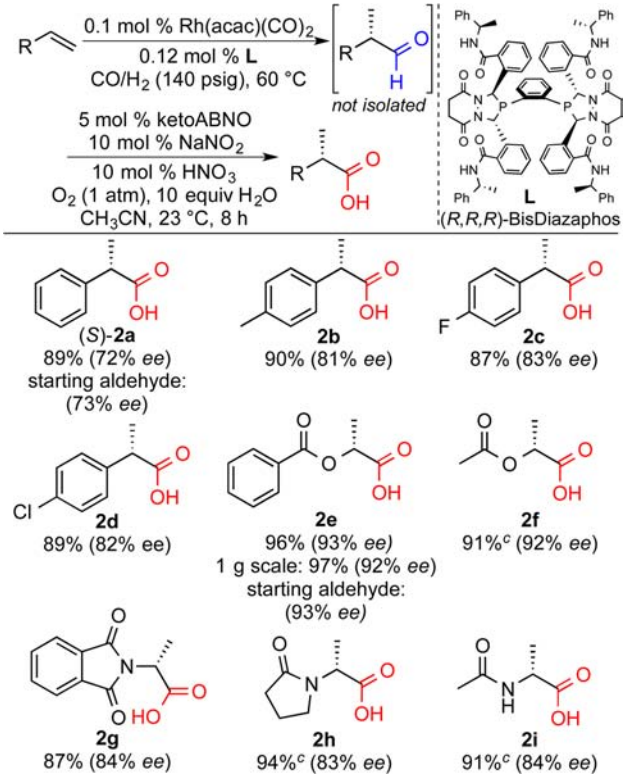
Scheme 3. Alkene AHF/Aldehyde Aerobic Oxidation Sequence to Access α-Chiral Carboxylic Acids[a,b]

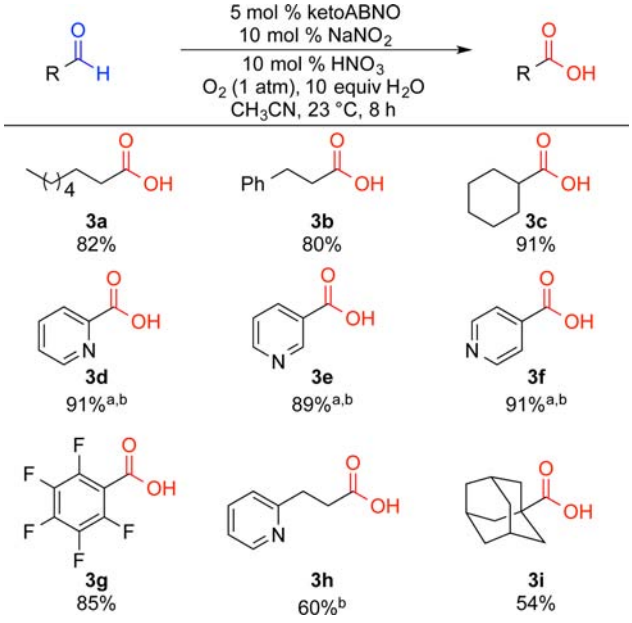


[a]Asymmetric hydroformylation conditions: olefin (1 mmol), CO/H_2 = 1:1, THF (1 M). Oxidation conditions: aldehyde (1 mmol), CH_3CN (1 M), O_2 balloon. [b]Isolated yields over two steps. [c]Yield determined by ^1H NMR spectroscopy using dioxane as an internal standard. ee determined by chiral HPLC or GC.

2f in 96% and 91% yields, respectively. The high enantioselectivities (>90% ee) for AHF obtained with these olefins are retained through the oxidation (verified by analysis of the benzoate-substituted aldehyde precursor to **2e**). A 1 g scale reaction with vinyl benzoate afforded the corresponding chiral acid in 97% yield and 92% ee. Vinyl phthalimide was similarly successful in the hydroformylation/oxidation sequence to **2g** (87% yield, 84% ee) and analogous excellent results were obtained with vinyl amides (cf. **2h** and **2i**).

This method for conversion of aldehydes to carboxylic acids could find utility beyond the oxidation of aldehydes derived from the AHF of alkenes. Therefore, the nitroxyl/NO_x cocatalytic conditions were investigated with a small set of additional aldehydes (Scheme 4). Simple aliphatic aldehydes **3a**–**3c** were cleanly oxidized under the reaction conditions to provide the carboxylic acids in good yields. Electron-deficient aromatic aldehydes, including the *ortho*, *meta*, and *para* isomers of pyridine carboxaldehyde and pentafluorobenzaldehyde, underwent effective oxidation in yields of 85–91% (**3d**–**3g**). Oxidation of 3-(pyridin-2-yl)-propanal afforded the corresponding carboxylic acid **3h** in 60% yield, and a moderate yield of 55% was obtained for the oxidation of the sterically hindered 1-adamantane carboxaldehyde to the acid **3i**. A substantial amount of adamantane was observed as a byproduct, possibly arising from steric inhibition of the ketoABNO-mediated reaction, which allows competition from an autoxidation-based side reaction.

Scheme 4. ABNO/NO_x- and ketoABNO/NO_x-Catalyzed Aerobic Aldehyde Oxidation[c]



[a]Isolated as the HCl salt. [b]1.1 equiv HNO_3 used. [c]Oxidation conditions: aldehyde (1 mmol), CH_3CN (1 M), O_2 balloon.

The reactivity of aromatic aldehydes with this catalyst system appears to be limited to electron-deficient substrates that can undergo reasonably favorable addition of water to the aldehyde hydrate.[20] For example, the parent benzaldehyde was found to undergo neglible conversion to benzoic acid. Meanwhile, limitations with aliphatic aldehydes appear to be associated with substrates that feature alkenes and electron rich aromatic substituents, which could interfere with the cocatalytic redox cycle involving NO_x-based radical intermediates. Representative unsuccessful substrates are depicted in Figure 2. The 2-(6-methoxynaphthalen-2-yl)propanal substrate was of particular interest because it is a direct precursor to (*S*)-Naproxen. The ineffectiveness of the present oxidation method required us to defer to Pinnick oxidation conditions,[4a] which afforded the desired product in 83% yield and minimal erosion of the enantioselectivity established in the AHF step (94.3 → 92.4% ee).[10] For compatible substrates, the catalytic ketoABNO/NO_x oxidation conditions would provide a compelling alternative.

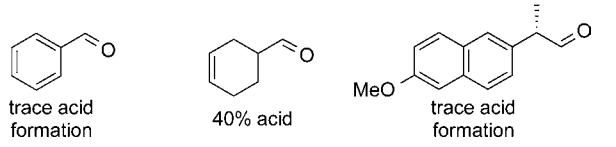


Figure 2. Representative examples of ineffective substrates.

In summary, we have identified a ketoABNO/NO_x-catalyzed method for the aerobic oxidation of aldehydes to carboxylic acids. The mildness of the reaction conditions enable near-perfect preservation of the enantioselectivity of α-chiral aldehydes. To our knowledge, this is the first aerobic oxidation method capable of achieving this goal. Sequential asymmetric hydroformylation of alkenes, followed by ketoABNO/NO_x-catalyzed aerobic oxidation of the aldehyde provides a powerful strategy for the formation of α-chiral carboxylic acids. Overall,

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the ease of the reaction setup, the mildness of the reaction conditions, and the commercial availability of all reagents suggest that this method could find valuable application with compatible substrates.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01598.

Experimental procedures and characterization data for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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