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Aerobic Amide Bond Formation with *N*-hydroxysuccinimide

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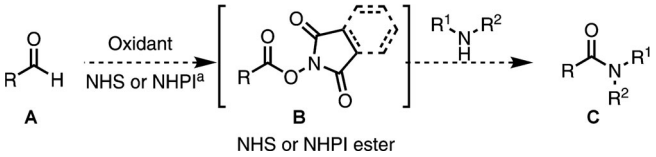
The amide functionality is a ubiquitous motif seen in pharmaceuticals, agrochemicals, and natural products.[1] The synthesis of amides has been the subject of intense research, and numerous methods have been developed. However, cost-effective, high-yielding, and atom-efficient procedures with a broad substrate scope have yet to be realized. The most prevalent synthetic methods for amides rely on condensation of carboxylic acids and amines through stoichiometric activation, harsh conditions, or both.[2] A milder alternative approach is oxidative condensation of aldehydes or alcohols with amines.[3] Recent examples of this strategy include: From aldehydes: hypervalent iodine (III) reagents;[4a] sodium hydride with molecular oxygen;[4b] copper(II) catalysis with *tert*-butylhydroperoxide (TBHP);[4c] metal-free conditions with TBHP;[4d,e] palladium catalysis with hydrogen peroxide;[4f] lanthanide-mediated conversions;[4g] and biomimetic *N*-heterocyclic carbene catalyzed procedures.[5] From alcohols: iridium(II)[6] and ruthenium(II)[7] mediated dehydrogenative amide bond formations.

Most of these oxidative methods were studied with aromatic or unsaturated aldehydes and were only marginally effective when applied to aliphatic aldehydes. Some of them required an excess of either of the coupling partners. We have developed a new amide formation reaction that circumvents some of these limitations and is complementally to the existing methods.

Apart from a few examples, the reported oxidative amide formations rely on formation of hemiaminals or imines that are subsequently oxidized to amide. This direct coupling is dictated by the inherent reactivity of both components. In order to alleviate such structural dependence, we opted for oxidative formation of an activated acid intermediate (Scheme 1, **A**→**B**), which would be displaced in situ by an amine.[8]

The *N*-hydroxysuccinimide (NHS) esters are valuable intermediates in amide (peptide) bond formation.[9] Because the structurally related *N*-hydroxyphthalimide (NHPI) mediates various autoxidation reactions with molecular oxygen,[10] we speculated that the NHS ester would form



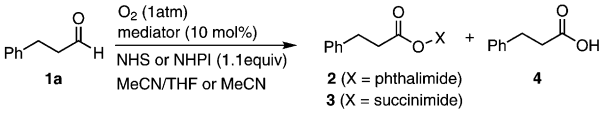
Scheme 1. Two-step oxidative amide bond formation. Nitroxides, formed in situ from NHS or NHPI, are the active species.

self-catalytically when treated with an aldehyde under similar oxidation conditions. We expected that subsequent displacement with an amine would deliver an amide in a single step (**B**→**C**). Alternatively, the NHPI ester might serve as an equally efficient acylation reagent for amide formation. Herein, we present realization of the concept.

The study was initiated by screening for suitable electron-transfer mediators necessary for aerobic oxidation with NHPI as a catalyst (Table 1). We have identified competing formation of the corresponding acid, **4**. Nevertheless, we found that cobalt diacetate gave the desired NHPI ester **2** as a major product (Table 1, entry 2). Further, replacing NHPI with NHS under identical conditions provided the corresponding NHS ester **3** in a comparable yield and selectivity (Table 1, entry 5). Both reactions provided a mixture of the ester and the acid in a ratio of approximately 3:1. We found that ester **3** is slightly moisture sensitive,[11,12] yet reasoned it could serve as an intermediate. Finally, the loading of cobalt diacetate could be decreased to 0.5–1 mol% without affecting the reaction outcome.

Next, we examined the feasibility of the second step, the amine displacement [Scheme 2, Eq. (1)]. As expected, treat-

Table 1. Screening of electron-transfer mediators for aerobic oxidative esterification of an aldehyde with NHPI.[a]



Entry	Imide	Mediator	*t* [h]	Product
1	NHPI	–	22	N.R.
2	NHPI	$Co(OAc)_2{\cdot}4H_2O$[b]	25	**2** (40%)[d] + **4**
3	NHPI	$FeCl_3$	18	**4**
4	NHPI	$MnCl_2$	2.5	**4**
5[c]	NHS	$Co(OAc)_2{\cdot}4H_2O$[b]	25	**3** (38%)[d] + **4**

[a] Conditions: 3-phenylpropionaldehyde (1.0 equiv), NHPI (1.1 equiv), mediator, THF/MeCN (1.25:1 vol/vol), O_2 (1 atm), room temperature. [b] Loading of 0.5 mol% instead of 10 mol%. [c] MeCN alone was used. [d] Un-optimized yield.

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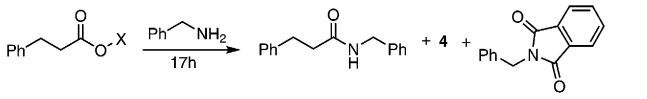


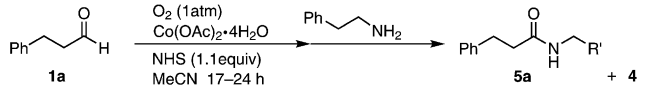
Scheme 2. Examination of the amine displacement.

ment of the isolated ester **2** with benzylamine gave the expected amide **5b** as the major product. However, the reaction was accompanied by a small amount of acid **4** as well as benzylphthalimide **2a**, which presumably formed as a result of attack of the amine at the phthalimide ester. In contrast, NHS ester **3** underwent smooth conversion to provide the desired amide **5b** [Eq. (2)]. Subsequent optimization studies were therefore performed using NHS.

The two steps were then combined for the development of a one-pot oxidative amide synthesis. Aldehyde **1a** was subjected to the same reaction conditions as used for NHS ester synthesis, except in the presence of benzyl amine (conditions: 3-phenylpropionaldehyde (1.0 equiv), NHS (1.1 equiv), $Co(OAc)_2{\cdot}4H_2O$ (1 mol%), benzylamine (1.1 equiv), O_2 (1 atm) in MeCN (0.67 M)). However, the reaction resulted in numerous products, the majority of which derived from self- and cross-aldol condensation with the substrate and benzaldehyde, which was formed by oxidation of the amine.

One way to circumvent the formation of these products was to add the amine to the reaction mixture after NHS ester formation and purging the remaining oxidant. This procedure can be done conveniently by displacing oxygen gas with nitrogen. Addition of phenylethylamine after the formation of the NHS ester gave the desired amide **5a** and acid **4** (Table 2, entry 1). Acid formation was, to some

Table 2. Two-step oxidative amide bond formation.[a]



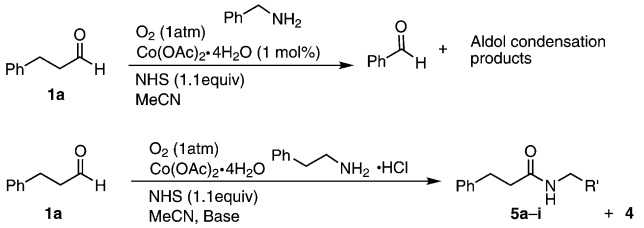
Entry	Catalyst	Molecular sieves [g]	**5a**/**4**[b]
1	$Co(OAc)_2{\cdot}4H_2O$	–[c]	1
2	$Co(OAc)_2{\cdot}4H_2O$	0.1[d]	3.9

[a] Conditions: 3-phenylpropionaldehyde (1.0 equiv), NHS (1.1 equiv), $Co(OAc)_2{\cdot}4H_2O$ (1 mol%), phenylethylamine (1.1 equiv) in MeCN (0.67 M), 22 h. [b] The ratio was determined from the yields of isolated products. [c] Without molecular sieves. [d] With 100 mg of molecular sieves (5 Å).

extent, avoided by addition of molecular sieves (Table 2, entry 2). This result suggested that the formation of **4**, at least partially, is due to water attack on the presumed intermediate, NHS ester.

Alternatively, competitive oxidation of the amine was avoided by replacing it with the corresponding amine hydrochloride salt. In the presence of a mild base, amine displacement occurred as the amine was converted to the free base.

Table 3. Screening of bases for one-step method.[a]



Entry	Base	Product	Yield [%][b]
1	$NaHCO_3$	**5a**	80
2	$CaCO_3$	–	N.R.
3		–	N.R.
4[c]	$NaHCO_3$	**5a**+**4**	14[d]

[a] Conditions: 3-phenylpropionaldehyde (1.0 equiv), NHS (1.1 equiv), $Co(OAc)_2{\cdot}4H_2O$ (1 mol%), base (1.1 equiv), amine HCl (1.5 equiv), molecular sieves (5 Å, 100 mg) in solvent (C = 0.67 M), 23 h. [b] Yields of isolated product were based on 3-phenylpropionaldehyde. [c] 0.1 equiv of NHS used. [d] 86% of **4** was also isolated.

A brief survey of bases revealed that $NaHCO_3$ was the best reaction promoter (Table 3). No amine oxidation was seen under these reaction conditions. Interestingly, we found premixing of all components prior to amine addition to be essential for successful reaction progress.

With improved procedures for successful amide formation in hand, we then focused on evaluation of the substrate scope. First, a set of structurally diverse amines was coupled with aldehyde **1a** using two methods (Table 4). A broad range of amides were successfully formed with moderate to good yield using these protocols (Table 4, entries 1–8). The secondary amines gave modest to good yields (Table 4, entries 3–4, 9–10, 12–15), even with the less reactive Weinreb amine. The glycine methyl ester (Table 4, entry 11) resulted in lower conversion after the typical reaction time. The methyl ester functionality was retained intact in this reaction.

Primary and secondary alcohols were also resistant to oxidation.[13,14] Thus, *trans*-4-aminocyclohexanol and 2-amino-3-phenylpropanol bearing hydroxy groups were chemoselectively oxidized to form the corresponding amides (Table 4, entries 6–8). In cases with amines with stereocenters at the α-position (Table 4, entries 5, 7, 8, 12–15), we found that their optical purity was retained.

Subsequently, the reaction scope of aldehydes was assessed (Table 5). In general, the reaction proceeded well with a wide range of aldehydes. The reaction was tolerant to steric hindrance, giving good yields with secondary or tertiary aldehydes (Table 5, entries 2, 3). In contrast, the reaction appeared to be sensitive to electronic factors. The aryl aldehydes with electron-donating substituents provided increased acid formation, contributing to a decreased yield (Table 5, entry 4). We observed that electron-withdrawing substituents also retarded the reaction (Table 5, entry 5). It is of note that the reaction proceeds well with saturated aldehydes and is thus complementary to known oxidative amide bond formation methods, most of which proceed well

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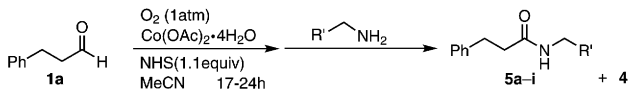
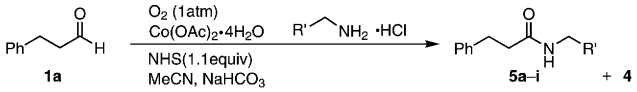
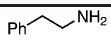
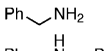
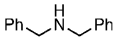
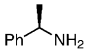
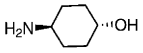
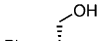
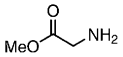
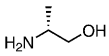
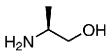
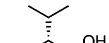
Table 4. Scope of amine substrates for one- or two-step method.[a]

Two-step Mehod (A)



One-step Method (B)



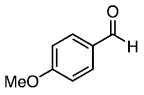
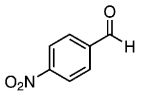
Entry	Amine	Method[c]	Product	Yield [%]
1		A/B	**5a**	78/80
2		A/B	**5b**	76/57
3		A	**5c**	80
4		A/B	**5d**	56/48
5		A	**5e**	67[d]/48[d]
6		A	**5f**	49
7		A	**5g**	28[d]
8		A/B	**5h**	33[d]/36[d]
9		B	**5i**	33
10		B	**5j**	52
11		B	**5k**	28
12		A	**5l**	44[d,e]
13		A	**5m**	36[d,e]
14		A	**5n**	29[d–f]
15		A	**5o**	36[d–f]

[a] Conditions: 3-phenylpropionaldehyde (1.0 equiv), NHS (1.1 equiv), $Co(OAc)_2{\cdot}4H_2O$ (1 mol%), amine (1.1equiv), molecular sieves (5 Å, 100 mg) in solvent ($C = 0.67$ M), 18–24 h. [b] Yields of isolated products were based on 3-phenylpropionaldehyde. [c] Method A: one-step method. Method B: two-step method. [d] Optical purity of the isolated amides was retained (>99% *ee*, see the Supporting Information). [e] Acids were also isolated. [f] Esters were also isolated (12–24%).

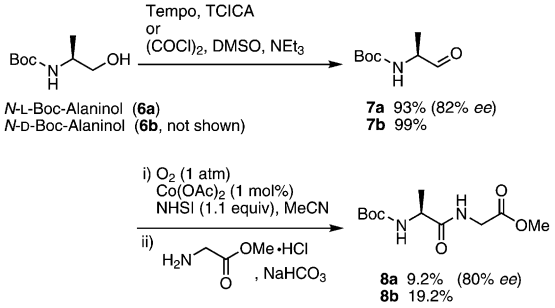
with unsaturated or aromatic aldehydes but less efficiently with saturated aldehydes.

Finally, we examined the applicability of the reaction to the amide formation with a chiral aldehyde. Thus, *N*-Boc-L-alaninol **6** was oxidized to aldehyde **7** under either Swern or Tempo[15] oxidation conditions (Scheme 3). The amide formation with glycine methyl ester underwent with complete retention of optical purity to smoothly provide the corresponding dipeptides **8**. Their optical purity was confirmed by comparison of the optical rotation of the product with the reported value (see the Supporting information).

Table 5. Scope of aldehyde substrates with one-step method.[a]

Entry	Aldehyde		Product	Yield [%]
1		**1b**	**5p**	80
2		**1c**	**5q**	76
3		**12**	**5r**	58
4		**1e**	**5s**	49
5		**1f**	**5t**	<10[b]

[a] One-step method (method A of Table 5). [b] The starting material was recovered (75%).



Scheme 3.
Amide formation with chiral aldehydes. Boc = *tert*-butoxycarbonyl; Tempo = 2,2,6,6-tetramethylpiperidine-1-oxy radical, TCICA = trichloroisocyanuric acid.

A mild aerobic oxidative method of amide formation for aliphatic and aromatic aldehydes was developed. The procedure represents the first example that utilizes NHS as a dual promoter of aldehyde oxidation and amine displacement. The reaction was shown to tolerate a variety of functional groups, such as unprotected primary and secondary alcohols, esters, amides, as well as optically active amines and aldehydes with stereocenters at α-positions. Investigations of the reaction mechanism, as well as extension of the chemistry to other transformations, are currently underway in our group.

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Keywords: amides · oxidation · oxygen · peptide coupling · synthetic methods

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[11] The rate of hydrolysis of **3** was examined by the addition of 2 equiv water to **4** in $CDCl_3$ for 23 h. Acid **4** (5%) was generated under these conditions.

[12] To minimize the hydrolysis, catalysts were premixed with molecular sieves to exclude any water from metal hydrates.

[13] Related NHPI is known to oxidize secondary alcohols under similar reaction conditions. The reaction requires additional additives for high conversion.

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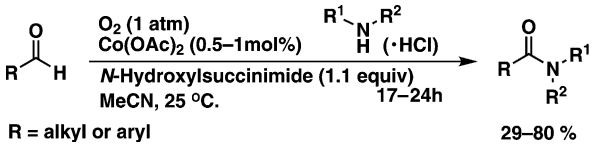

Breathe easy: Molecular oxygen is one of the most abundant, atom-efficient, and economical oxidants. An aerobic oxidative amide formation from aldehydes and amines is reported. The method uses a catalytic amount of $Co(OAc)_2$ and *N*-hydroxysuccinimide as reaction promoters. It is applicable to chiral substrates without loss of their optical purity.

Amide Formation

Haoyi Yao,
*Kana Yamamoto** ——— ▮▮▮▮–▮▮▮▮

Aerobic Amide Bond Formation with *N*-hydroxysuccinimide

