VIP α-Amination Very Important Paper

DOI: 10.1002/anie.201400776

Merging Aerobic Oxidation and Enamine Catalysis in the Asymmetric α-Amination of β-Ketocarbonyls Using *N*-Hydroxycarbamates as Nitrogen Sources**

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Abstract: *We describe herein an unprecedented asymmetric α-amination of β-ketocarbonyls under aerobic conditions. The process is enabled by a simple chiral primary amine through the coupling of a catalytic enamine ester intermediate and a nitrosocarbonyl (generated in situ) derived from N-hydroxycarbamate. The reaction features high chemoselectivity and excellent enantioselectivity for a broad range of substrates.*

Asymmetric direct α-amination of carbonyl compounds are fundamental C–N bond forming reactions that are of significant relevance in the synthesis of chiral materials and pharmaceuticals.[1] Typically, the reactions are conducted with electrophilic nitrogen sources coupled with nucleophilic enols or enamines.[2–4] Provided with the vast number of readily accessible amines, the direct coupling of carbonyls and nucleophilic amines is an appealing and more straightforward strategy for the synthesis of α-aminocarbonyls. Mechanistically, such a coupling of two nucleophiles would require judicious selection of oxidative conditions, and in this regard oxygen/air is the most economical and an ideal choice of terminal oxidant.[5] Recently, MacMillan et al. reported an elegant direct α-amination reaction with simple amines under aerobic conditions in which an electrophilic α-bromocarbonyl was generated in situ through an aerobic-oxidation-coupled process.[6] In this context, a catalytic asymmetric version remains to be realized.

Very recently, the groups of Yamamoto[7] and Read de Alaniz[8] have independently reported nitroso-carbonyls oxidized in situ for aminoxylation (i.e. nitroso-aldol) and hydroxyamination reactions of β-ketoesters, respectively. In the latter case, aerobic conditions can be successfully used in the presence of $CuCl/Cu(OTf)_2$ and the overall method represents a complementary strategy for oxidative α-amination wherein electrophilic nitrogen sources are generated in situ by aerobic oxidation. Unfortunately, efforts to render this process enantioselective have not been successful thus far, and O-selective aminoxylation products, instead of the hydroxyamination products, were predominantly formed when chiral ligands were applied.[9] During the preparation of this work, Maruoka et al. reported an asymmetric N-selective coupling with aldehydes using oxidative nitrosocarbonyl chemistry. However, the use of aerobic conditions was ineffective to deliver the desired products, and the reactions required stoichiometric TEMPO and BPO as the oxidants.[10] Achieving asymmetric oxidative amination under aerobic conditions remains elusive in this regard. Herein, we report an unprecedented asymmetric α-amination of β-ketoesters under aerobic conditions catalyzed by chiral primary amines. In this process the enamine catalysis of β-ketoesters was successfully coupled with aerobic oxidation of *N*-hydroxycarbamates to afford the desired amination products in high yields and with excellent enantioselectivities.

β-Ketocarbonyls (e.g. ketoesters and 1,3-diketones) remain a challenging type of substrates in enamine catalysis, as it is known that amines (mostly primary amines) tend to form stabilized enamines with β-ketocarbonyls owing to intramolecular H bonding (Figure 1), and catalytic turnover with enamine carbonyls has thus far not been achieved.[11] In fact, the resulting enamine carbonyls have been reported to be versatile synthons in asymmetric synthesis,[12] or can act as haptens to induce antibody aldolases.[13] In addition, the oxidative stability of enamines is also of serious concern in

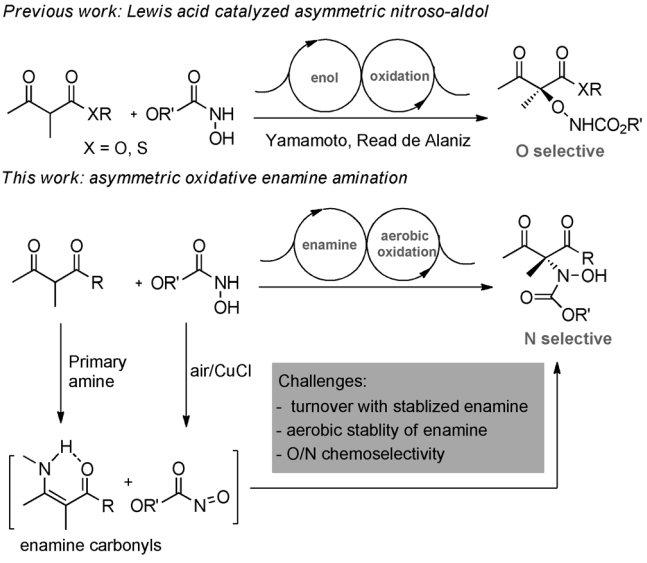

Figure 1. α-Amination of β-ketocarbonyls.

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[**] We thank the Natural Science Foundation of China (21390400, 21025208, and 21202171) and the National Basic Research Program of China (2011CB808600) for financial support.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201400776.

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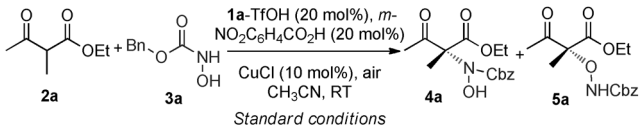
pursuing oxidative amination, as enamines can be easily degraded or cleaved under aerobic conditions.[14] Bearing these points in mind, we were quite delighted to find that our previously developed chiral primary amines **1** were viable catalysts for the oxidative coupling of acetoacetate **2a** and *N*-hydroxycarbamate **3a** under air.[15] Amination product **4a** can be exclusively formed (**4a**/**5a** > 20:1) in 97% yield and 96% *ee* under the optimized conditions (Table 1, entry 1). Chiral primary amine **1a**, derived from *tert*-leucine, in concert with triflic acid (TfOH) and *m*-nitrobenzoic acid, was identified as the optimal catalyst (Table 1, entry 1 vs. 2 and 3). In this case, the addition of weak acid *m*-nitrobenzoic acid has been found to significantly improve both the product yield (from 62% in 68 h to 97% in 30 h) and the **4a**/**5a** ratio (from 6:1 to > 20:1; Table 1, entry 4 vs. 1). This result is consistent with the known acidic additive effect in promoting enamine turnover, as we previously observed in similar catalysis.[15] Both CuCl and air have been found to be essential for catalysis, and reactions in the absence of either CuCl or air showed no activity at all (Table 1, entries 5 and 6). The use of other chemical oxidants such as MnO_2 led to much poorer results (Table 1, entry 7). The screening of other copper salts was also conducted, but none of them showed activity under the aerobic conditions, except for CuO (Table 1, entries 8–11). The reaction has also been optimized in terms of solvents, and acetonitrile was identified as the optimal solvent (Table 1, entries 1 and 12–16).

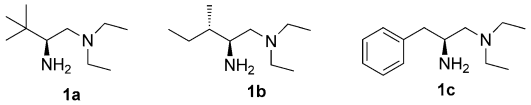
Table 1: Screening and optimization.[a]



2a **3a** **4a** **5a**

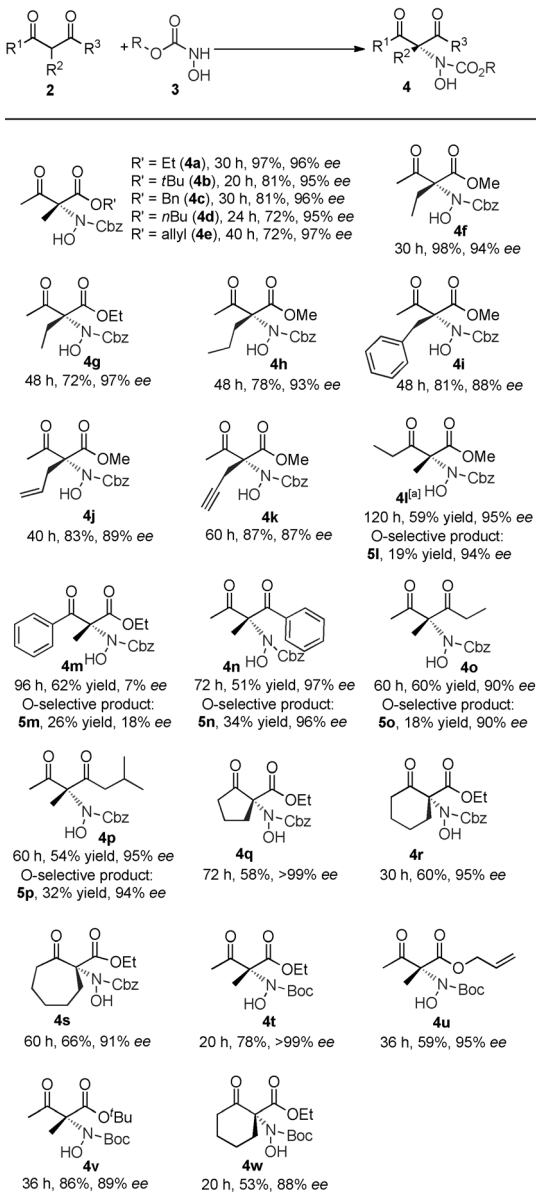
Entry	Variation from standard conditions	*t* [h]	Yield [%][b]	**4a**/**5a**	*ee* [%][c]
1	none	30	97	> 20:1	96
2	**1b**	60	61	5:1	65
3	**1c**	120	52	3:1	83
4	without *m*-NO_2PhCO_2H	68	62	6:1	94
5	without CuCl	30	n.r.		
6	under Ar	30	trace		
7	MnO_2 as oxidant[d]	24	26	n.d.	60
8	$CuCl_2$	30	n.r.		
9	CuO	36	40	3:1	58
10	CuCN	30	n.r.		
11	CuI	30	n.r.		
12	CH_2Cl_2	40	78	5:1	95
13	THF	30	52	4:1	55
14	Et_2O	36	65	8:1	86
15	toluene	30	69	3:1	65
16	MeOH	30	85	n.d.	35

[a] Reactions were performed at room temperature in 0.3 mL solvent with **2a** (0.12 mmol), **3a** (0.10 mmol), **1**-TfOH (20 mol%), *m*-nitrobenzoic acid (20 mol%), and copper salts (10 mol%) under air at room temperature. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase. [d] 5 equiv of MnO_2. n.d. = not determined, n.r. = no reaction.



1a **1b** **1c**

Under the optimized conditions, we then examined the substrate scope of this aerobically oxidative amination reaction. As shown in Scheme 1, acetoacetates with variations on the ester moiety (R^3 position), including those with sterically bulky *tert*-butyl ester, benzyl, and allyl ester groups, afford the desired amination adducts in high yields with excellent enantioselectivities (**4a**–**e**). The reactions also tolerate a range of α-substituents on acetoacetates (R^2 position; **4f**–**k**). In particular, the reaction with acetoacetates bearing α-allyl and propargyl substituents proceeded smoothly to deliver the desired amination adducts with high



Scheme 1. Substrate scope. All reactions were performed at room temperature in MeCN (0.3 mL) with **2** (0.12 mmol), **3** (0.10 mmol), **1a**-TfOH (20 mol%), *m*-nitrobenzoic acid (20 mol%), and CuCl (10 mol%) under air at room temperature. Yields shown are of isolated products. [a] CuCl (5 mol%).

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yields and enantioselectivities (**4j** and **4k**), and no oxidation of unsaturated bonds was observed. High N/O regioselectivities were maintained in all cases, with only trace aminoxylation products detected by TLC analysis.

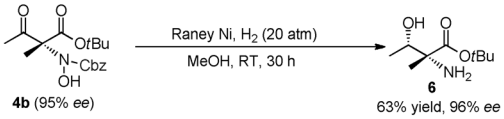
Variations on the ketone substituent R^1 were next examined. With ethyl ketone ($R^1 = Et$), the reaction furnished the major N adduct, **4l** (59% yield), along with a minor O adduct, **5l** (19% yield); both products were obtained with excellent enantioselectivities (95% and 94% *ee*, respectively; Scheme 1). The sluggish reaction rate observed in this case indicates the inhibition of enamine catalysis with large aliphatic ketones, which are known as difficult substrates for aminocatalysis.[11] To test the limits of the reaction, a phenyl ketone ($R^1 = Ph$) was attempted. Although the desired amination adduct **4m** could be obtained in a reasonable 62% yield, along with a minor O-selective adduct, **5m**, both products showed rather poor enantioselectivities (< 20% *ee*; Scheme 1), which suggests that enamine catalysis is likely not involved and the reaction may proceed instead through an unselective enol-based process.

Notably, acyclic 1,3-diketones are also workable substrates under oxidative enamine conditions. Accordingly, phenylbuta-1,3-dione reacted smoothly to give the major amination product in 51% yield and 97% *ee* (**4n**; Scheme 1). Most delightfully, aliphatic 1,3-diketones, such as hexane-2,4-dione and heptane-2,4-dione, can also be applied to give the desired amination products with excellent enantioselectivities (**4o** and **4p**). In these cases, minor aminoxyl adducts were also isolated with high enantioselectivities (**4n–p**). Taken together, these results highlight the power of enamine catalysis with primary amines to differentiate the two ketone moieties; the successes along these lines nicely bypass the difficulties associated with ketoesters bearing larger ketone moieties (**4m** vs. **4n**).[16]

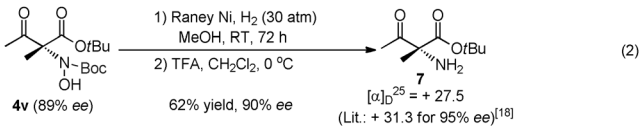
The reactions worked equally well with cyclic β-ketoesters to give exclusively N-selective adducts with excellent enantioselectivities (**4q–s**; Scheme 1). Finally, the reaction was also found to be compatible with *tert*-butyl *N*-hydroxycarbamate **3b** as the nitrogen source (**4t–w**), furnishing the desired amination adducts in slightly reduced yields but with comparable enantioselectivities.

The obtained amination adducts can be selectively reduced to reveal the free amino group in the presence of Raney Ni under H_2. Accordingly, the hydrogenation of Cbz-protected adduct **4b** produced the *syn* amino alcohol **6** with high stereoselectivity; both the N–OH and ketone carbonyl groups were reduced under these conditions [Eq. (1)]. On the other hand, the hydrogenation of the Boc-protected **4v** occurred selectively on the N-OH moiety to give the aminoketone product **7** [Eq. (2)]. A free amino group, generated in situ through hydrogenative Cbz deprotection, seems essential for directing the further reduction of the ketone moiety.

Preliminary studies have been carried out to understand the mechanistic details of this reaction. Taking advantage of

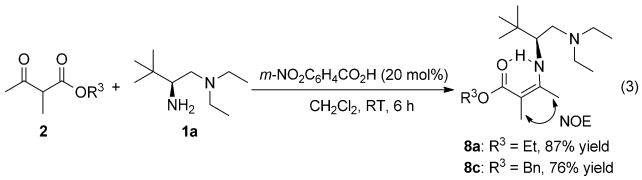


(1)



(2)

the stabilizing nature of enamine carbonyls, a stoichiometric reaction of acetoacetate **2a** (or **2c**) and chiral primary amine **1a** was carried out. In this regard, a catalytic amount of *m*-nitrobenzoic acid, the weak acid used in our catalysis, was found to promote the formation of the expected enamines **8a** and **8c**, which can be isolated and purified on a basic alumina column in 87% and 76% yield, respectively [Eq. (3)]. This result indicates that the enamine formation should be quite facile under the catalytic conditions. NMR analysis of compound **8** clearly showed a NOE between the two methyl groups, characteristics of the *Z* enamine configuration, and no other conformers were detected in the solution phase at room temperature [Eq. (3)]. We were able to crystalize enamine **8a** in the presence of TfOH (1.0 equiv). The crystal structure of **8a**-TfOH, clearly indicates the *Z* enamine geometry as well as the H bonding between the enamine N–H and the ester moiety (Figure 2a). To the best of our knowledge, this represents the first crystal structure of a catalytically active enamine intermediate derived from a primary amine.[17]



(3)

The stability and reactivity of enamine **8a** was next examined. Though pure compound **8a** is quite stable in stock, it quickly equilibrates with its parent ketoester **2a** in the presence of one equivalent of H_2O, when treated with the identified optimal acidic additives TfOH/*m*-nitrobenzoic acid [Eq. (4)]. These results suggest catalytic turnover with enamine esters turns out to be a quite facile process by the aid of the acidic additive under our conditions. Stoichiometric

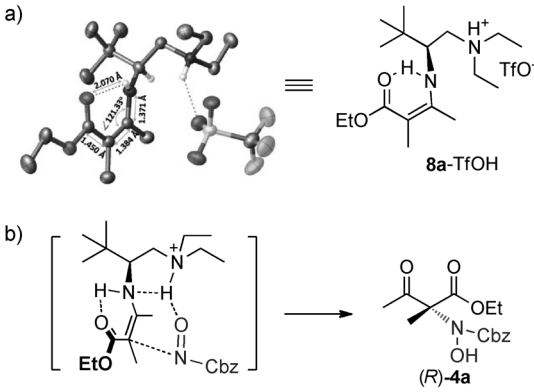


Figure 2. a) X-ray crystal structure of **8a**-TfOH. H atoms are omitted for clarity. Thermal ellipsoids set at 30%. b) Proposed transition state.

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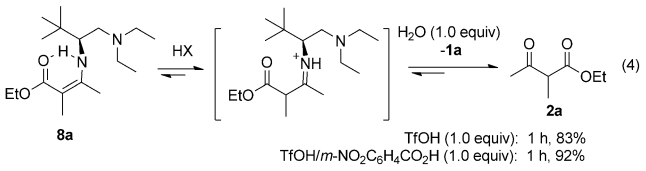
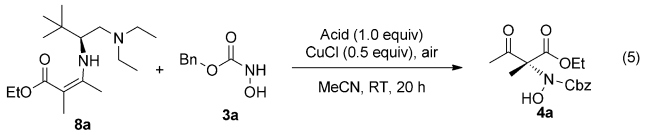
reactions of enamine **8a** with *N*-hydroxycarbamate **3a** have also been conducted. Under the aerobic conditions, the reaction smoothly gave the amination adduct **4a** in 85% yield and 97% *ee*, with the same configuration obtained under catalytic conditions, thus unequivocally verifying the enamine catalytic nature of this reaction. The critical role of acids in tuning reactivity and selectivity is also quite evident, as the reactions led to poor outcome in the absence of either of the acids, and was completely shut down when no acids were added [Eq. (5)].



(4)



(5)

Acid	4a	4a/5a
none	0	-
TfOH only	30%, 91% *ee*	4:1
m-$NO_2C_6H_4CO_2H$ only	46%, 95% *ee*	5:1
TfOH/*m*-$NO_2C_6H_4CO_2H$	85%, 97% *ee*	14:1

The absolute configuration of the amination adduct **4v** was determined to be *R* by comparison with the known compound **7** after simple derivatization [Eq. (2)].[18] Based on the solid and solution phase structures of the enamine intermediate, we proposed the transition state (TS) in Figure 2b to account for the observed stereoselectivity. In this TS, the H-bonding network involved protonated tertiary amine and the N–H group of the enamine helps to stabilize the conformation of the catalyst and the configuration of the enamine. The H bonding between the protonated tertiary amine and nitroso O atom facilitates the *Re*-face attack of the enamine to give the desired adduct. Likely, the origin of the chemoselectivity may be also closely related to the H bonding with the N or O atom of the nitroso moiety, a similar H-bonding effect is known in enamine-based nitroso chemistry.[3]

In summary, we have developed a highly enantioselective α-amination of β-ketocarbonyls under aerobic conditions enabled by a simple chiral primary amine. The reaction features unprecedented enamine catalysis with β-ketocarbonyls, including β-ketoesters and 1,3-diketones, as well as its successful coupling with aerobic oxidation. Further studies are currently underway to disclose the mechanistic details and to extend the aerobically oxidative enamine catalysis of β-ketoesters to other reactions.

Received: January 24, 2014
Published online: March 12, 2014

Keywords: aerobic oxidation · α-amination · β-ketocarbonyls · enamine catalysis · organocatalysis

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