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Catalytic Asymmetric Oxidative α-C−H N,O-Ketalization of Ketones by Chiral Primary Amine

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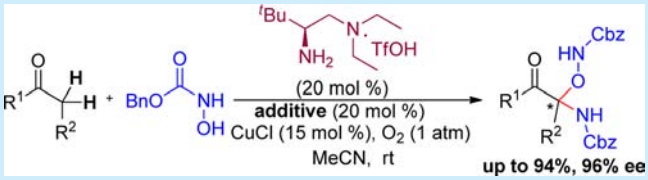
Supporting Information

ABSTRACT: A highly enantioselective primary amine catalyzed α,α-bis-functionalization of β-ketocarbonyls and cyclohexanones is described. This transformation employs *N*-hydroxycarbamates as both nitrogen and oxygen sources under aerobic oxidative conditions to furnish chiral N,O-ketals with high yields and enantioselectivities.



Enamine catalysis has been proven to be a powerful approach for asymmetric α-functionalization of aldehydes and ketones over the past decade.[1] One of the next targets in this field lies in the development of novel catalytic strategies aimed at more complex chemical transformations. One-pot stereoselective α,α-bis-functionalization of carbonyl compounds is a highly efficient process to construct multifunctional chiral building blocks. In 2009, the List group reported the first highly diastereo- and enantioselective double Mannich reaction of acetaldehyde with N-Boc imines catalyzed by proline.[2] Following this work, Maruoka et al. accomplished a one-pot cross double-Mannich reaction of acetaldehyde with two different imines.[3] The Greck group also reported a stereoselective one-pot Mannich reaction−amination of acetaldehyde through double enamine catalysis.[4] All of these examples couple enamines with two electrophiles and are limited to the simplest enolizable nucleophile acetaldehyde. Herein, we reported a conceptually distinctive oxidative α-C−H bis-functionalization of ketone to form chiral ketals by chiral primary amine catalysis. In this oxidative ketalization reaction, the enamine−amination adduct undergoes a facile dehydration prior to catalyst release to generate a unprecedented diimine intermediate, which reacts with an oxygen-nucleophile to give an α-N,O-ketal product (Scheme 1).

Chiral N,O-aminals/ketals are structural motifs found in a number of natural products and pharmaceuticals.[5,6] In 2008, Antilla reported the first catalytic asymmetric method for the synthesis of chiral *N,O*-aminals by the BINOL phosphoric acid catalyzed enantioselective addition of alcohols to imines.[7] Two years later, List achieved a *N*-phosphinyl phosphoramide catalyzed strategy for the synthesis of chiral cyclic N,O-acetals from aldehydes and hydroxyl amides.[8] Most current acetalization/ketalization processes are based on preformed carbonyl compounds; direct C−H acetalization/ketalization with sp^3 carbon center has not been reported. Recently, we reported a highly enantioselective α-amination of β-ketocarbonyls under aerobic conditions enabled by chiral primary amine using *N*-hydroxycarbamates as nitrogen sources.[9] As a part of ongoing work, the α-unsubstituted β-ketoester **1a** was tested under standard conditions. To our surprise, a single *N,O*-ketal product **4a**, instead of the expected α-amination product **5**, was obtained in high yield with moderate enantioselectivity (Table 1, entry 1). Given the scarcity of reports concerning synthesis of chiral *N,O*-ketals, the development of a catalytic asymmetric ketalization was hence pursued. Herein we report the direct enantioselective synthesis of α-*N,O*-ketals from ketones by primary amine catalysis, wherein *N*-hydroxycarbamates are employed as both nitrogen and oxygen sources under aerobically oxidative conditions (Scheme 1).

We started to optimize the oxidative ketalization reaction using β-ketoester **1a** as a model substrate. Screening of primary amine catalysts did not give better outcomes, and the primary amine **3** derived from *tert*-leucine remained the optimal catalyst.

Scheme 1. Aminocatalytic Asymmetric α,α-Bifunctionalization of Carbonyls

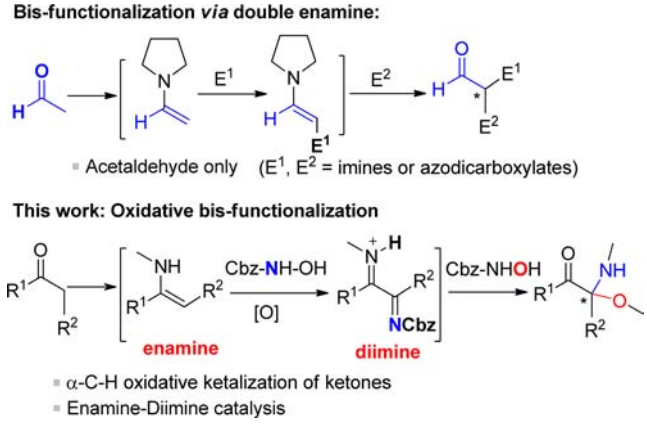


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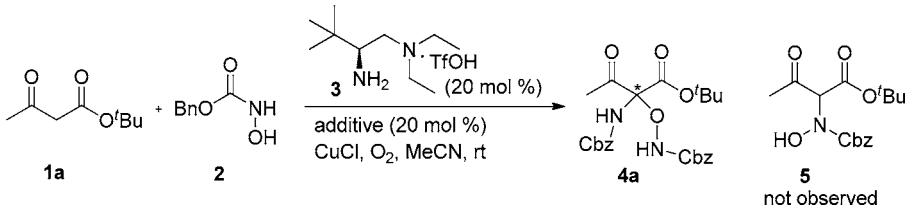
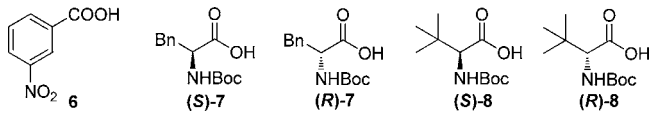
Table 1. Screening and Optimization[a]



entry	n(**1a**):n(**2**)	concn (**1a**) (mol/L)	additive	CuCl (mol %)	O_2 (1 atm)	time (h)	yield (%)[b]	ee (%)[c]
1	1:2	0.5	**6**	10	air	24	90	76
2	1:2	0.5	(*S*)-**7**	10	air	18	91	83
3	1:2	0.5	(*R*)-**7**	10	air	18	90	83
4	1:2	0.5	(*S*)-**8**	10	air	26	93	82
5	1:2	0.5	(*R*)-**8**	10	air	20	80	85
6	1:2	0.2	(*R*)-**8**	10	air	30	91	86
7	1:2	0.1	(*R*)-**8**	10	air	60	90	91
8	1:2	0.05	(*R*)-**8**	10	air	120	88	92
9	1:2	0.1	(*R*)-**8**	15	air	42	91	91
10	1:2	0.1	(*R*)-**8**	20	air	36	91	89
11	1:2	0.1	(*R*)-**8**	15	O_2	36	98	94
12	1:3	0.1	(*R*)-**8**	15	O_2	32	94	96
13[d]	1:3	0.1	(*R*)-**8**	15	O_2	16	85	95
14[e]	1:3	0.1	(*R*)-**8**	15	O_2	24	NR	–

[a]The reactions were performed at room temperature in MeCN (0.2−2.0 mL) with **1a** (0.1 mmol), **2** (0.1−0.3 mmol), **3** (20 mol %), additive (20 mol %), and CuCl (10−20 mol %). [b]Isolated yields. [c]Determined by chiral HPLC. [d]O_2 (10 atm). [e]In the absence of **3**. NR: No Reaction.



Consequently, we turned our attention to chiral additives. Initially *N*-Boc-phenylalanine **7** was examined; both the *S*- and *R*-isomer furnished desired adduct **4a** with high yields and promising levels of enantioselectivities (83% ee) (Table 1, entries 2−3). With *N*-Boc-*tert*-leucine, a considerable match−mismatch effect was noted. The *S*-isomer delivered product **4a** with a 93% yield and 82% ee (entry 4), while the *R*-isomer led to higher enantioselectivity (85% ee), albeit with a slightly reduced yield (entry 5). (*R*)-*N*-Boc-*tert*-leucine ((*R*)-**8**) was employed as the additive in the succeeding experiments. When the concentration of *β*-ketoester **1a** was reduced, the enantioselectivity of **4a** could be further improved, but was accompanied by lower reaction rates (entries 5−8). With a balance of reaction rate and enantioselectivity, 0.1 mol/L of **1a** was deemed the appropriate concentration (entry 7). Subsequently, increasing the amount of CuCl to 15 mol % led to an elevated reaction rate without erosion of ee (entry 9), and further increasing the loading to 20 mol % resulted in decline in enantioselectivity of **4a** (entry 10). In order to further enhance the reaction rate, changing the oxidant from air to pure oxygen gave a higher yield and ee (entry 11). Further increasing the amount of hydroxyl amine **2** to 3 equiv led to product **4a** with a 94% yield and 96% ee (entry 12). The reaction rate could be further enhanced when the reaction is conducted under a higher pressure of oxygen (entry 12 vs 13). For the convenience of operation, most of the following experiments were conducted under 1 atm of oxygen (entry 12). The control experiment indicated that no reaction occurred in the absence of primary amine catalyst **3** (entry 14), highlighting the aminocatalytic nature of the present reactions.

Having established the optimal conditions for the synthesis of chiral *N*,*O*-ketals, we next examined the scope of the *β*-ketoester component in this reaction. As shown in Scheme 2, ethyl acetoacetate afforded the desired *N*,*O*-ketal adduct in high yield and enantioselectivity (**4b**). Phenyl acetoacetate showed low activity under standard conditions, but the desired product **4c** could be obtained in high yield with excellent enantioselectivity under 10 atm of oxygen. An allyl acetoacetate could react smoothly to deliver *N*,*O*-ketal **4d** with an 80% yield and 89% ee, and no oxidation of unsaturated bonds was observed. Acetoacetates bearing a sterically bulky ester group, including diphenylmethyl and adamantanyl groups, were tolerated and afforded corresponding *N*,*O*-ketal **4e**−**4f** with high yields and enantioselectivities. Variations on the ketone substituent R^1 were next examined. With methyl propionylacetate or methyl butyrylacetate, the reaction furnished the desired product **4g** or **4h** with a high yield and enantioselectivity. Unsurprisingly, the reactions with *β*-ketoesters that bear a sterically demanding keto moiety at R^1, e.g. methyl isobutyrylacetate and ethyl benzoylacetate, proceeded with rather poor enantioselectivities (**4i** and **4j**), suggesting that these bulky ketones likely followed an enol type cycle that escaped the enamine catalytic cycle as known previously.[10−12] The reaction with *β*-ketoamides worked smoothly and delivered *N*,*O*-ketals **4k**−**4l** in high yields but with low enantioselectivities. 1,3-Diketone also afforded the target product **4m** with a moderate yield and enantioselectivity.

Aside from *β*-ketocarbonyls, simple carbonyl compounds were also tested in the *α*,*α*-bis-functionalization reactions (Scheme 3). Cyclohexanone was able to smoothly undergo the reaction to deliver the adduct **10a** with a moderate yield and enantioselectivity. 4-Oxacyclohexanone was also tolerated to give *N*,*O*-ketal **10b** with comparable outcomes. As for 4-thiacyclohexanone, the reaction furnished the target product

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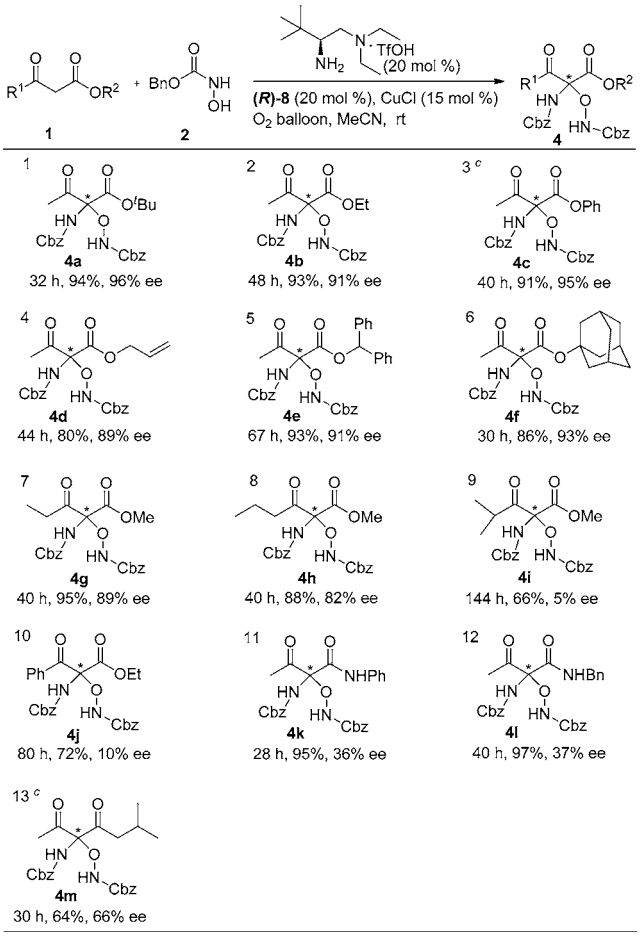
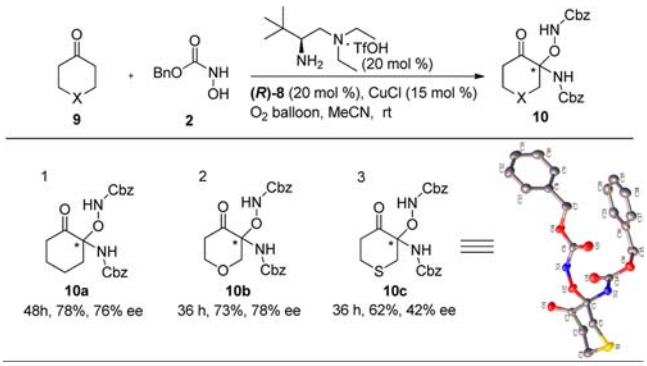
Scheme 2. Substrate Scope of β-Ketocarbonyls[a,b]



[a]The reactions were performed at room temperature in MeCN (1.0 mL) with **1** (0.1 mmol), **2** (0.3 mmol), **3** (20 mol %), (*R*)-**8** (20 mol %), and CuCl (15 mol %) under O_2 (1 atm). [b]Isolated yields. [c]O_2 (10 atm).

Scheme 3. Substrate Scope of Cyclic Ketones[a,b]

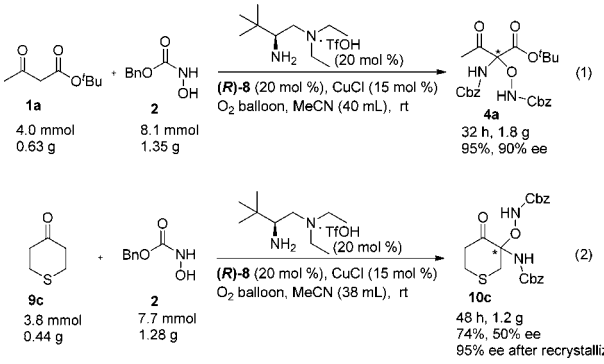


[a]The reactions were performed at room temperature in MeCN (1.0 mL) with **9** (0.1 mmol), **2** (0.3 mmol), **3** (20 mol %), (*R*)-**8** (20 mol %), and CuCl (15 mol %) under O_2 (1 atm). [b]Isolated yields.

10c in moderate yield and moderate enantioselectivity. X-ray crystal structure analysis of **10c** confirmed the structure of ketalization products.[13] In contrast to six-membered cyclic ketones, other cyclic ketones, such as cyclopentanone and cycloheptanone, and linear ketones such as 3-pentanone showed no activity. Simple aldehydes such as 1-pentanal and 3-phenylpropanal failed to participate in the reaction due to their oxidative instability.

To further demonstrate the applicability of the α,α-bis-functionalization process, gram-scale reactions were attempted. Under standard conditions, the reaction of **1a** proceeded to completion in 32 h to afford the desired *N,O*-ketal **4a** in 95% yield with 90% ee (Scheme 4, eq 1). With 4-thiacyclohexanone,

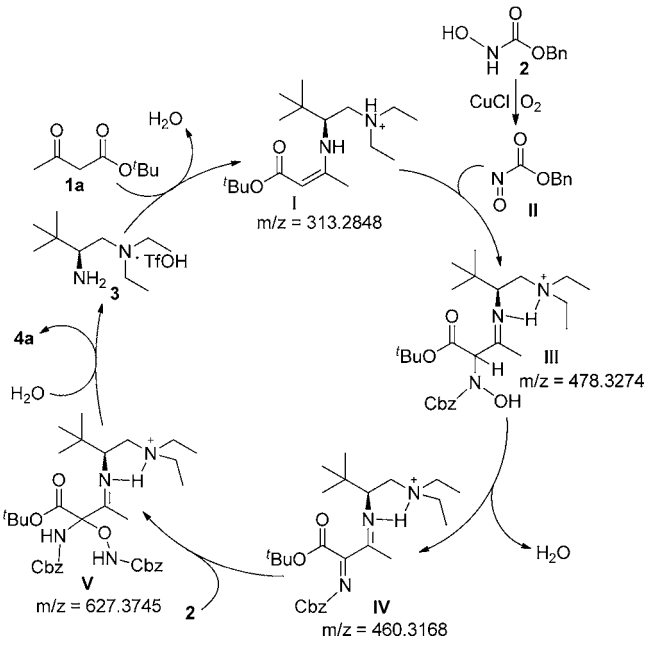
Scheme 4. Gram Scale Reaction



the reaction also delivered target product **10c** in 74% isolated yield with 50% ee (eq 2). It was noted that the enantiomeric excess of *N,O*-ketal **10c** can be easily enriched to 95% from a single recrystallization from hexane/ethyl acetate (50% recovered yield). To our disappointment, further derivations of the products have been found to be very difficult due to the instabilities of *N,O*-ketals. Nevertheless, the current protocol is amenable to scale up, providing ready access to chiral *N,O*-ketals that are not possible with other approaches.

Based on the above-mentioned results, a plausible catalytic cycle was proposed to understand the transformation (Scheme 5). The β-ketoester **1a** was first activated to generate enamine intermediate **I**, which reacted with in situ generated nitroso compound **II** to yield intermediate **III**. Owing to the strong acidity of α-H present in intermediate **III**, one molecule of

Scheme 5. Plausible Reaction Mechanism



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water was released to result in a highly active diamine intermediate **IV**.[14] Another molecule of *N*-hydroxycarbamate **2** reacted with intermediate **IV** to produce intermediate **V**, which was hydrolyzed to deliver product **4a** and regenerate primary amine catalyst **3**. The intermediates **I**, **III**, **IV**, and **V** could be observed by HRMS when a reaction system was analyzed. In this procedure, the stereoselectivity of *N*,*O*-ketal **4a** was induced by key intermediate di-imine **IV** and the chiral acidic additive (*R*)-**8** may play dual roles in enhancing the chiral induction as a counteranion and in facilitating the enamine−iminium−diiminium cycle as normally observed in primary amine catalysis.[10]

In conclusion, we have established a highly enantioselective α,α-bis-functionalization of ketones with *N*-hydroxycarbamates under aerobically oxidative conditions and developed the first asymmetric catalytic protocol for the synthesis of chiral *N*,*O*-ketals by a chiral primary amine. This methodology opens up new opportunities for one-pot enantioselective α,α-bis-functionalization of ketones, and further investigations are underway to extend this process to three-component reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02322.

Experimental procedures, characterization data, and copies of ^{1}H NMR and ^{13}C NMR spectra and HPLC traces (PDF)

Crystallographic data for **10c** (CIF)

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Notes

The authors declare no competing financial interest.

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