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COMMUNICATION

Bench-stable Imine Surrogates for the One-pot and Catalytic Asymmetric Synthesis of α-Amino Esters/Ketones

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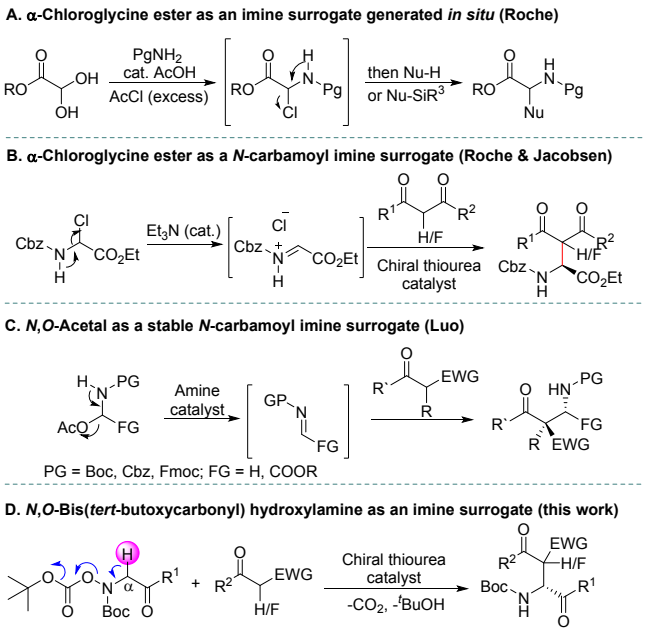
***N*,*O*-Bis(*tert*-butoxycarbonyl) hydroxylamines are readily accessible as imine surrogates, which are bench stable and could quantitatively generate the corresponding imines for *in situ* applications. An unpresented catalytic asymmetric method for the synthesis of α-amino esters and ketones from novel imine surrogates, *N*,*O*-bis(*tert*-butoxycarbonyl) hydroxylamines, as well as its preliminary mechanistic studies are reported. A variety of optically enriched products were obtained in excellent yields and enantioselectivities (up to 99% yield and >99% ee).**

As one class of the most active organic intermediates, imines have found numerous synthetic applications in the past hundred years.[1] In particular, the development of different imines or iminiums for Mannich reactions has attracted significant attention of organic chemists. Owing to their versatile utility and adaptability, *N*-carbamoyl imines are a class of highly desirable reagents for the synthesis of various types of unnatural α-substituted amino acids or esters.[2] However, *N*-carbamoyl imines generally require cumbersome preparations and strictly controlled conditions for catalytic reactions. Although *N*-carbamoyl imine surrogates such as α-haloamines, α-oxygenicamines or α-sulfonylamines have been reported, their syntheses are still nontrivial, requiring multiple steps and excess bases for the imine preparation.[3] Noteworthy, α-haloamines are generally unstable even in refrigerator.[4]

In the past decade, Roche group developed an efficient one-pot, three components method for the synthesis of α-substituted amino esters with α-chloroglycine ester as a practical imine surrogate generated from benzyl carbamate and ethyl glyoxylate (Scheme 1, A).[4] Roche, Jacobsen, and coworkers reported a scalable, one-pot Mannich route to access enantioenriched α-amino esters and α-allyl amino esters with α-chloroglycine ester as direct imine surrogate in 2014 and 2019 (Scheme 1, B).[5] And Luo group developed a catalytic asymmetric Mannich reaction with stable *N*,*O*-acetals as the *N*-carbamoyl imine surrogates in 2017 (Scheme 1, C).[6] Although these imine surrogates facilitated the development of imine chemistry in organic synthesis, their applications are still handicapped by their instability and cumbersome preparation. Thus, developing stable imine surrogates in a convenient and simple way would significantly facilitate and expand imine's applications in asymmetric synthesis.

All reported imine generations were based on the traditional *N*-*H*-elimination of imine surrogates with a leaving group at the vicinal position of nitrogen. During our total synthetic studies of



Scheme 1 Catalytic asymmetric reactions with different *N*-carbamoyl imine surrogates

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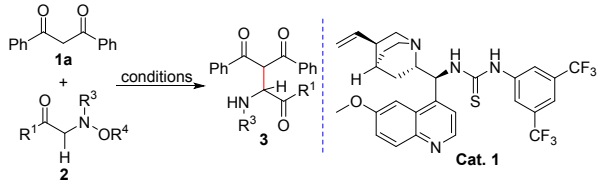
† Electronic Supplementary Information (ESI) available: Experimental procedures, spectroscopic data, copies of ^{1}H and ^{13}C NMR spectra, CCDC 2007033 (**3e**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/x0xx00000x.

natural products, we occasionally observed that the readily accessible intermediate *N*,*O*-bis(*tert*-butoxycarbonyl) hydroxylamine methyl glycinate could generate the corresponding imine *via* *N*-α*H*-elimination with a leaving group on the nitrogen atom under mild conditions. Continuing our efforts in developing novel asymmetric synthesis methodologies,[7] we envisioned that *N*,*O*-bis(*tert*-butoxycarbonyl) hydroxylamines could serve as novel, efficient and direct *N*-carbamoyl imine surrogates for the synthesis of α-substituted amino esters or ketones (Scheme 1, D).

To validate our hypothesis, we optimized the reaction conditions (Table 1). The initial exploration utilized diketone **1a** and α-*N*-OBoc-benzyl ester **2** with varying R^1, R^3 and R^4, and chiral thiourea as the catalyst.[5a,8] To our delight, the reaction proceeded as expected, leading to the corresponding amino ester **3** in 95% yield and 92% ee at room temperature using toluene as the solvent (Table 1. Entry 1). Encouraged by this exhilarating result, we investigated the effects of R^3 group on the nitrogen atom. Replacing Boc with Bz resulted in dramatically decrease in yield and enantioselectivity (Table 1, Entry 2), suggesting that Boc at this position was critical for the smooth reaction. Varying temperatures and solvents did not benefit the reaction (Table 1. Entries 3-6). We then evaluated whether the ester moiety of α-amino esters might have a steric effect on the performance of the catalyst (Table 1. Entries 7-9), and found that the small OMe ester gave the highest yield as well as enantioselectivity (Table 1. Entry 9). Other leaving groups such as OPiv, OCO_2Et and OFmoc were also examined under the same condition, but the yields and enantioselectivities could not be retained simultaneously (Table1. Entries 10-12). Besides, when the α-proton of **2** was replaced with aryl and alkynyl, or modification of α-carbonyl moieties on **2** with different electronic effect substituents, no reaction happened under this condition. Several bifunctional thiourea catalysts were also evaluated for their promoting effects, but did not improve the enantioselectivity. (See ESI for details)

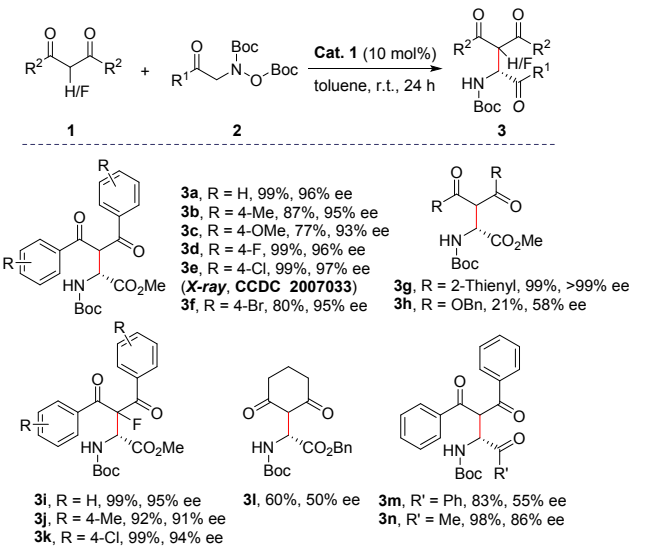
With the optimized condition in hand, we explored the scope of this reaction. A variety of symmetrical 1,3-diketones were found to react effectively under the optimized condition, and the results are summarized in Scheme 2. Introduction of electron-donating groups *p*-Me and *p*-OMe on the phenyl group resulted in products **3b-c** with excellent enantioselectivities (93%-95%) and good yields (77%-87%). Similarly, substrates with electron-withdrawing groups *p*-F/Cl/Br on the phenyl ring, or with 2-thiophenyl as R^2 led to the corresponding products (**3d**-**g**) in almost quantitative yields (only a slight loss for **3f**) and uniformly excellent enantioselectivities (95%-99%). Unfortunately, the common nucleophile dibenzyl malonate only gave the corresponding product in 21% yield and moderate enantioselectivity with substrate recovery (**3h**), due to the low reactivity, the dimer of imine surrogate and the cycloaddition product of imine with catalyst could be observed (See Scheme 6). Although the steric hindrance and electronic effect were changed with introduction of a fluorine atom at the α position of diketone, there was no significant influence on yields and enantioselectivities of the reactions (**3i**-**k**). Interestingly, replacement of the phenyl group in the substrate diketone with 1,3-cyclohexanediones led to the corresponding product **3l** with moderate yield (60%) and enantioselectivity (50%). The poor result was likely due to the structure of the diketone, making it a less efficient H-bond donor for the thiourea catalysts.[9] Furthermore, to examine the diversity of ester motif on **2**, two additional *N*,*O*-bis(*tert*-butoxycarbonyl) hydroxylamines were subjected to the optimized condition, affording the products (**3m**-**n**) in good to excellent yields (83%-98%). Product **3m** had

Table 1 Optimization of reaction conditions.[a]



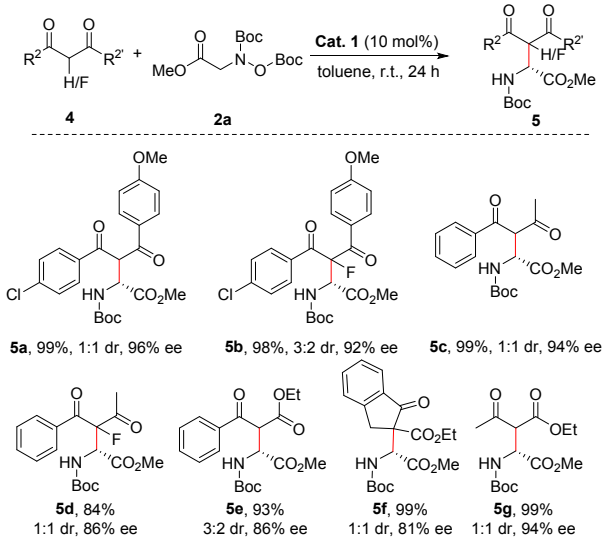
Entry	R^1	R^3	R^4	Solvent	Temp. (℃)	Yield[b] (%)	ee[c] (%)
1	OBn	Boc	Boc	toluene	r.t.	95	92
2	OBn	Bz	Boc	toluene	r.t.	15	10
3	OBn	Boc	Boc	toluene	0	95	92
4	OBn	Boc	Boc	Et_2O	r.t.	87	92
5	OBn	Boc	Boc	THF	r.t.	50	77
6	OBn	Boc	Boc	$CHCl_3$	r.t.	46	69
7	O^{t}Bu	Boc	Boc	toluene	r.t.	90	90
8	OEt	Boc	Boc	toluene	r.t.	93	94
9	OMe	Boc	Boc	toluene	r.t.	99	96
10	OMe	Boc	Piv	toluene	r.t.	44	96
11	OMe	Boc	-CO_2Et	toluene	r.t.	88	96
12	OMe	Boc	Fmoc	toluene	r.t.	99	87

[a]Conditions: diketone **1a** (0.2 mmol), imine surrogates **2** (0.3 mmol), **Cat. 1** (10 mol%), solvent (2.0 mL), 24 h. [b]Isolated yields. [c]ee of the product was determined by HPLC analysis using a chiral stationary phase.



Scheme 2 Substrate scope with symmetrical 1,3-diketones.[a-c]

[a]Condition: diketone **1** (0.2 mmol), imine surrogate **2** (0.3 mmol), **Cat. 1** (10 mol%), toluene (2.0 mL), rt, 24 h. [b]Isolated yields. [c]ee of the product was determined by HPLC analysis using a chiral stationary phase.



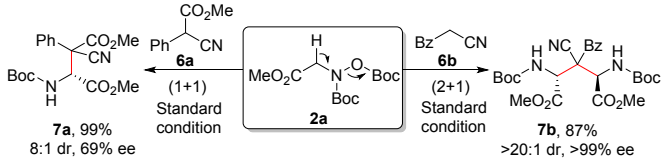
Scheme 3 Substrate scope with unsymmetrical 1,3-diketones.[a-c] [a]Condition: diketone **4** (0.2 mmol), imine surrogate **2a** (0.3 mmol), **Cat. 1** (10 mol%), toluene (2.0 mL), rt, 24 h. [b]Isolated yields. [c]ee of the product was determined by HPLC analysis using a chiral stationary phase.

reduced enantioselectivity, presumably due to the different electronic effects from the phenyl and methyl group. The relative and absolute configuration of **3e** were established by single crystal X-ray analysis, and those of other products were assigned by analogy (See ESI for details).[10]

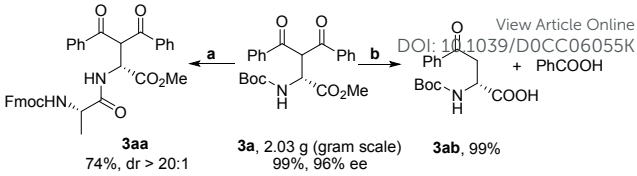
Subsequently, unsymmetrical 1,3-diketones and β-ketoesters were subjected to the reaction condition (Scheme 3). The diketones with aryl groups (**5a**-**b**) or alkyl groups (**5c**-**g**) could all proceed smoothly to furnish products in good to excellent yields (84%-99%) and enantioselectivities (81%-96%), but a nearly statistical mixture of diastereomers was obtained in all cases, which bear a non-epimerizable β-dicarbonyl stereocenter.

As at least two H-bond receptors exist in diketones, they could potentially influence the interactions of substrates with the thiourea catalyst. To reduce the effect, β-monocarbonyl compounds were used as nucleophiles following the catalytic protocol (Scheme 4).[11] To our delight, the reaction of **6a** with **2a** could clearly improve the diastereoselectivity (8:1), albeit the enantioselectivity was reduced (69% ee). Interestingly, when β-carbonylnitrile **6b** was employed as the nucleophile, the reaction could proceed twice, giving rise to the double-addition product **7b** in good yield and excellent stereoselectivity (>20:1 dr, >99% ee).

We further performed a preparative scale experiment to evaluate the practicability of this protocol (Scheme 5). The desired product **3a** was obtained smoothly under standard condition without loss of reactivity and enantioselectivity (99%



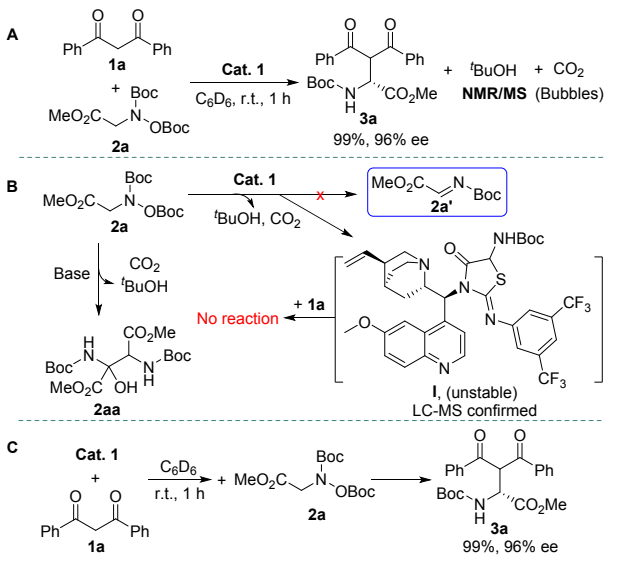
Scheme 4 Reaction of **2a** with β-monocarbonyl nucleophiles.



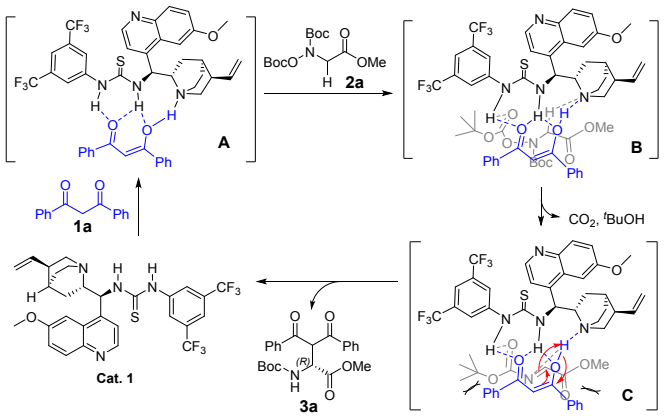
Scheme 5 Gram scale synthesis and further modifications of **3a**.[a] [a]Conditions: **a**) DCM:TFA = 3:1, rt; Fomoc-Ala-OH, EDCI, HOBt, DIPEA, DMF, 0 °C, rt; **b**) LiOH, sillica gel, MeOH:H_2O = 3:1, rt.

yield, and 96% ee). To highlight the utility of the products in organic synthesis, we explored the transferability of **3a**. Deprotection of Boc group followed by condensation with Fomoc-Ala-OH gave the desired product **3aa** in good yield and diastereoselectivity. However, hydrolysis of the methyl ester could not produce the corresponding acid or lactone, instead, a de-benzoyl product **3ab** was obtained in quantitative yield *via* the reverse Claisen condensation pathway.[12]

In an effort to better understand the reaction, mechanism verification experiments were carried out (Scheme 6). For the convenience of monitoring, the reaction was conducted in C_6D_6. After addition of the reactants, lot of bubbles (CO_2) were released immediately, ^{t}BuOH could be observed *via* both NMR and GC-MS (See ESI for details), while the imine intermediate **2a'** cannot be detected (Scheme 6, A). In order to obtain imine **2a'**, **2a** was treated with **Cat. 1**, unfortunately, no desired product was observed even by increasing the catalyst loading to 1 equivalent. In contrast, an unstable cycloaddition product **I**, detected by LC-MS (See ESI for details), was formed as Drach reported manner (Scheme 6, B),[13] and addition of **1a** to the resulting reaction mixture could not promote the reaction anymore. Other reactions including using organic bases (TEA, DBU) or inorganic bases (K_2CO_3, NaOH) for the imine generation were also performed, however, there was no product formed, instead, a hydroxyl substituted dimer adduct **2aa** was obtained (Scheme 6, B). To further explore the catalytic process, control experiment was performed by adding **2a** to a solution of diketone **1a** and catalyst **Cat. 1**, to our delight, product **3a** was



Scheme 6 Mechanism studies.



Scheme 7 Possible mechanistic pathway.

obtained in 99% yield without loss of enantioselectivity (Scheme 6, C). These results indicated that *N*-carbamoyl imine **2a'** is very unstable and would be immediately trapped by the nucleophiles once generated, the catalyst **Cat. 1** couldn't chelate with imine to form a stable intermediate.

Although the detailed mechanism of this reaction requires in-depth studies, a plausible mechanistic pathway is depicted based on our studies and previous reports (Scheme 7).[9] In this process, as a strong H-bond accepter, dicarbonyl compound **1a** could be easily deprotonated and chelate to **Cat. 1** *via* hydrogen-bonding to form complex **A**. Next, the α-proton of **2a** would be abstracted by the tertiary amine of the catalyst, and after releasing CO_2 and ^{t}BuOH, the resulting imine would be hydrogen-bonded to the catalyst with nitrogen and oxygen on the ester motif. Owing to the steric hindrance, the imine motif is situated below the phenyl group. Subsequently, the imine would be attacked by enol from the upside to form product **3a** with newly generated stereocenters and release of the catalyst.

In summary, we have successfully developed novel imine surrogates, *N*,*O*-bis(*tert*-butoxycarbonyl) hydroxylamines, which are simple to prepare, air stable at room temperature and easy to use. The utility of such imine surrogates has been demonstrated for the first one-pot catalytic asymmetric synthesis of both α-amino esters and ketones with excellent yield (up to 99%) and enantioselectivity (up to >99% ee). Further applications of such imine surrogates in catalytic transformations, medicinal chemistry as well as natural product synthesis are ongoing, and shall be reported in due course.

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Conflicts of interest

There are no conflicts to declare.

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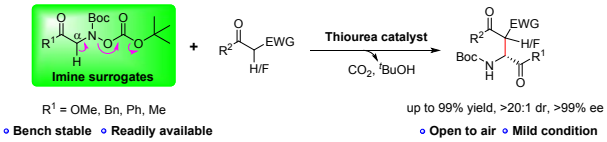

An unpresented catalytic asymmetric method for the synthesis of α-amino esters and ketones from novel imine surrogates is reported.