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Catalytic Asymmetric Mannich Reaction with *N*-Carbamoyl Imine Surrogates of Formaldehyde and Glyoxylate

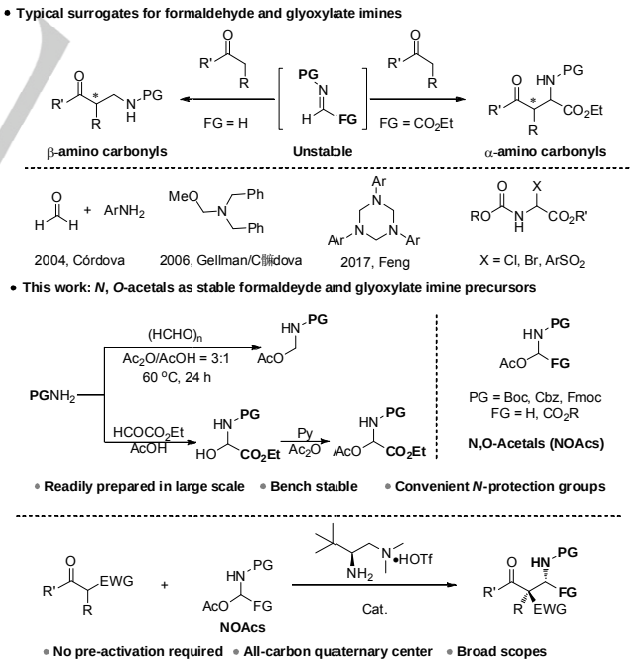
Yang'en You, Long Zhang, Linfeng Cui, Xueling Mi, Sanzhong Luo*

Dedicated to Prof. Jin-Pei Cheng on the occasion of his 70th birthday

Abstract: *N, O-acetal*s (NOAcs) have been developed as bench stable surrogates for *N*-carbamoyl (Boc, Cbz and Fmoc) formaldehyde and glyoxylate imines in asymmetric Mannich reactions. The NOAcs can be directly utilized in the chiral primary amine catalyzed Mannich reactions of both acyclic and cyclic β-ketocarbonyls with high yields and excellent stereoselectivity. The current reaction offers a straightforward approach in the asymmetric synthesis of α- or β-amino carbonyls bearing chiral quaternary centers in a practical and highly stereocontrolled manner.

The Mannich reaction with imines or iminiums is a classical and fundamental C-C bond formation reactions in organic synthesis.[1] Advances in asymmetric catalysis with either metal or organic catalysts have made enantioselective Mannich reactions the most attractive and atom-economic approaches for the synthesis of chiral β-amino carbonyl compounds.[2,3] From the synthetic point of view, *N*-carbamoyl (e.g. Boc-, Cbz- or Fmoc-) imines are highly desirable due to their versatile synthetic utility and readily adaptability in established synthetic procedures. However, *N*-carbamoyl imines are generally unstable and their preparation remains a major drawback in Mannich chemistry. *N*-Carbamoyl imine surrogates such as α-haloamines[4] or α-sulfonylamines[5] have been developed, however, their syntheses are still nontrivial requiring multiple steps and excess bases for imine generation. In particular, simple yet synthetically important *N*-carbamoyl imines from formaldehyde[6a] and glyoxylate ester[4b,6b] are difficult to access and their enantioselective Mannich catalysis remains to be further developed. *N*,*O*-acetals are very useful reagents and intermediates in organic synthesis.[6, 7] However, the exploration of *N*,*O*-acetals as *N*-carbamoyl imine surrogates remained surprisingly underdeveloped in asymmetric Mannich reactions. In one single example, *N*-Cbz amiomethylacetate has been examined in Mannich reaction of silyl enol ether with low enantioselecitvity.[6d] Herein, we reported *N*, *O*-acetals (NOAcs) as *N*-carbamoyl imine surrogates for both formaldehyde and gyloxylate ester (Scheme 1). Typical carbamoyl groups including Boc, Cbz and Fmoc can all be incorporated and the resulting NOAcs can be directly used in enantioselective Mannich reactions.

Enamine-Mannich reaction has also gained prominent progresses echoing the renaissance of organocatalysis.[3a,b] Most of reactions have been reported with α-unsubstituted aldehydes and ketones. In one single case, enantioselective enamine Mannich reactions of α-branched aldehydes was reported by Barbas and coworkers with good enantioselectivity but moderate diastereoselectivity.[8] Catalytic asymmetric Mannich reaction with α-branched ketones have not been achieved to date in enamine catalysis. In general, the access to α-quaternary carbonyls by catalytic asymmetric Mannich reactions have been mainly achieved with cyclic ketones or lactones *via* enolate processes.[9] Based on our developed chiral primary amine catalysts,[10] we herein reported an asymmetric Mannich reactions of both cyclic and acyclic α-branched ketones particularly β-ketocarbonyls with NOAc imine precursors.



Scheme 1. *N*, *O*-Acetals as *N*-Carbamoyl Imine Precursors.

The NOAcs were readily synthesized starting from aldehyde and carbamates in the presence of Ac_2O/AcOH.[6a] The resulted *N*, *O*-acetals can be distilled (Boc-, Cbz-) or recrystallized

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(Fmoc-) and are bench-stable for months. We first tested NOAcs in the aminomethylation reactions. There are a few examples on catalytic asymmetric aminomethylation. Seminal works by Córdova, Gellman and Feng have mainly been achieved with in-situ generated *N*-aryl imines from anilines, 1,3,5-trazines or α-dibenzyl amino methyl ether.[11] Multi-steps are generally required to reach the useful *N*-carbamoyl amino products in these cases. Very recently, Stoltz reported an aminomethylation with *N*-carbamoyl imines using sulfonylmethyl carbamates precursors,[12] but the stereoselectivity was generated in the late decarboxylative alkylations stage, not in the Mannich step.

We tested the NOAc reagents in the aminomethylation of β-ketoester **1a**, for which a highly enantioselective process has not been achieved. Our benchmark chiral primary amine catalysts turned out to be highly effective for the reaction in terms of both activity and enantioselectivity (Figure 1).[9] The NOAc reagent **2a** could be directly applied without separate activation, and the addition of a weak acid m-nitrobenzoic acid was critical for attaining good conversion and high stereocontrol, likely via in-situ activating the NOAc reagent. A less bulky primary amine catalyst (**B**) gave slightly better activity and enantioselectivity and under this condition the desired adduct **3a** could be obtained in 92% isolated yield as an optically pure product (>99% *ee*) (Figure 1).

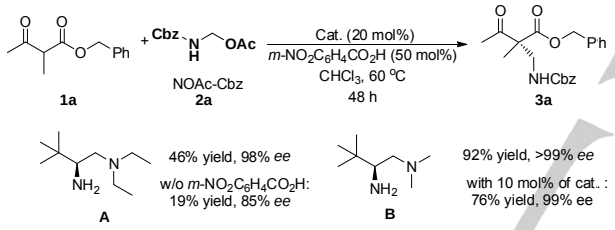
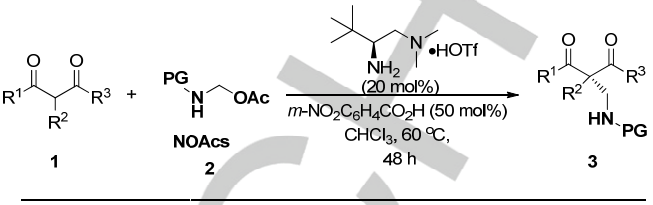


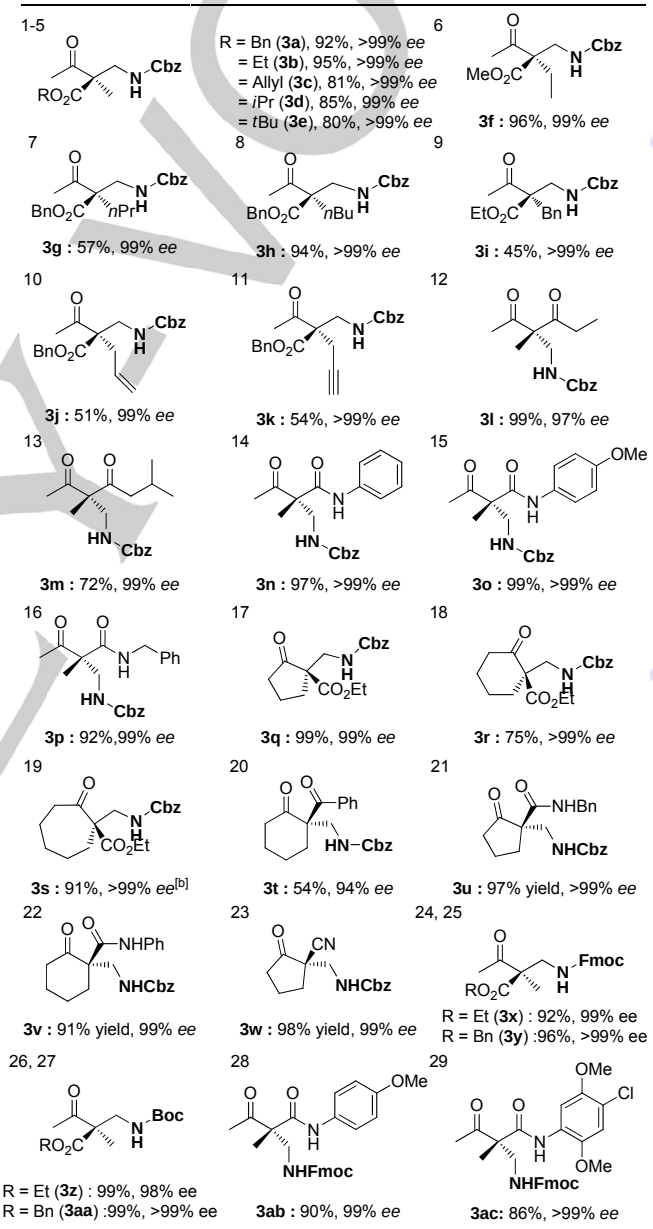
Figure 1. Optimized Conditions for Aminomethylation.

The scope of our primary amine catalysis in the asymmetric aminomethylation was then examined (Table 1). Different ester moieties in β-keto esters, including benzyl, ethyl, allyl, isopropyl, tert-butyl ester all gave the desired products **3a**-**3e** with ⩾99% *ee* and good yields (up to 95%) (Table 1, entries 1-5). The reactions tolerated a number of α-substituents including liner alkyl C1-C4, benzyl, allyl and propargyl to give the desired aminomethylation adducts **3f**-**3k** with excellent enantioselectivity in all cases (Table 1, entries 6-11). Desymmetric 1,3-diketones can be applied to give the desired β-aminocarbonyls **3l** and **3m** with good reactivity and high enantioselectivity (Table 1, entries 12 and 13). The substrate scope could be further extended to β-ketoamides. Both *N*-aryl (**3n** and **3o**) and *N*-aliphatic (**3p**) amides worked well in the reactions to afford the desired aminomethylation adducts in good yields and high enantioselectivities (Table 1, entries 14-16).

Furthermore, the reaction also worked well with cyclic ketocarbonyls. For instance, cyclic ketoesters (**3q**-**3s**), 1,3-diketone (**3t**) or ketoamides (**3u** and **3v**) all could be transformed to the corresponding products with high enantioselectivities (Table 1, entries 17-22). Notably, 2-cyanocyclopentanone also reacted well in this system to give the corresponding product **3w** in 98% yield and with 99% *ee* (Table 1, entry 23). Other NOAcs reagents worked equally well in the reactions.

Table 1. Substrate Sccpe with NOAcs[a].





[a] All reactions were performed at 60 °C in 0.5 mL $CHCl_3$, with **1** (0.1 mmol), **2** (0.15 mmol), **B**/TfOH (20 mol%), m-nitrobenzoicacid (50 mol%), 24-48 h. Yield of isolated product. *Ee* was determined by HPLC analysis. [b] Reaction was performed at rt for 72 h.

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The corresponding *N*-Fmoc (**3x**, **3y**, **3ab** and **3ac**) (Table 1, entries 24, 25, 28 and 29)) and *N*-Boc (**3z** and **3aa**) (Table 1, entries 26 and 27) aminomethylation adducts could be obtained in high yields and with superb enantioselectivity under otherwise identical conditions.

Asymmetric Mannich reaction with imino esters is one of the important approaches for the synthesis of α-amino esters. *N*-carbamoyl imino esters have been frequently explored for this purpose.[4,5,13] However, *N*-carbamoyl imino esters are rather unstable, requiring tedious procedure for their synthesis and must be freshly prepared and handled with great care. Direct use of imino esters surrogates in a one-pot manner is hence highly desirable. Recently, Jacobsen reported the only examples on asymmetric Mannich synthesis of α-amino esters with α-chloroglycine ester as imino ester surrogate in a one-pot operation.[4b]

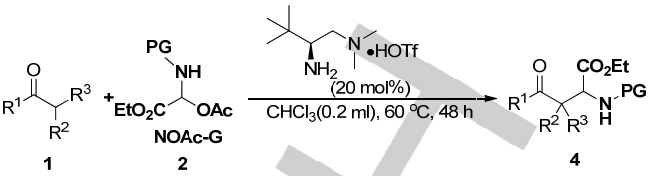
In this context, we explored the direct use of *N,O*-acetal of glyoxylate ester (NOAc-G) as imino ester precursor in asymmetric Mannich reactions. Delightfully, previous conditions for aminomethylation process worked equally well with imino esters. Further experiment indicated that acid additive was not necessary in this case. Simple mixing NOAc-G reagent with β-ketoester **1a** led smoothly to the desired Mannch adduct **4a** in 75% yield and with >19:1 *dr* and >99% *ee* in the presence of chiral primary catalyst (Table 2, entry 1). Different ester moieties on the donor part were tolerated (**4b** and **4c**) (Table 2, entries 1-3). Cyclic ketoesters also worked very well to give the desired Mannich adducts as single diastereoisomers with >99% *ee* (**4d** and **4e**) (Table 2, entries 4 and 5). The reactions with larger α-alkyl substituents beyond methyl group did not work, indicating the reaction was quite sensitive to steric effect. Delightfully, α-fluoro ketoester worked very well to give the amino ester **4f** in quantitative yield with 19:1 *dr* and 92% *ee* (Table 2, entry 6).

Different β-ketocarbonyls could be applied in the current reactions (**4g**-**4p**) (Table 2, entries 7-16). α-Unsubstituted and unsymmetric β-ketocarbonyls gave the Mannich product in 1:1 *dr* due to readily enolizable α-carbon, and both diastereoisomers were obtained with excellent enantioselectivity (entries 7-11). 1,3-Diketones worked particularly well in the reactions (entries 10-16). In particular, phenyl ketones can also be incorporated with good enantioselectivity, though the yields are low as enamine formation with phenyl ketone is sluggish (Table 2, entries 9 and 14). Notably, *N*-Fmoc (**4q** and **4s**) and *N*-Boc (**4r** and **4t**) imino ester precursors could be equally applied in the current protocol to give the desired products with good activity and high enantioselectivity (Table 2, entries 17-20).

The imino ester Mannich reaction is not limited to β-ketocarbonys. Simple ketone and aldehyde donors such as acetone (**4u**), cyclopentanone (**4v**), cyclohexanone (**4w**) and aliphatic aldehydes(**4x**) could be applied with good yields and high enantioselectivity (Table 2, entries 21-24).

Gram-scale reactions for both formaldehyde imine and α-imino esters have been conducted in the presence of 10 mol% of chiral primary amine catalyst **B**/TfOH (Scheme 2). In both cases, the reaction worked well with comparable yield and enantioselectivity and the chiral primary amine catalyst could be quantitatively recycled by simple aqueous workup, verifying the practicability of the current protocol in the synthesis α-amino esters and β- amino carbonyls.[4,12,13]

Table 2. Substrate Sccpe with NOAc-Gs[a].



1-3 — R = Bn (**4a**), 75%; >19:1 *dr*, >99% *ee*
R = *t*- Bu (**4b**), 74%; >19:1 *dr*, >99% *ee*
R = allyl (**4c**), 63%; >19:1 *dr*, >99% *ee*

4 — **4d**, 88%, >19:1 *dr*, >99% *ee*

5 — **4e**, 81%, >19:1 *dr*, >99% *ee*

6 — **4f**, 99%, 19:1 *dr*, 92% *ee*

7 — **4g**, 76%, 51:49 *dr*, >99%/ >99% *ee*

8 — **4h**,75%, 52:48 *dr*, >99%/ >99% *ee*

9 — **4i**,18%, 52:48 *dr*, 96%/ 95% *ee*

10 — **4j**, 99%, 72:28 *dr*, >99%/ >99% *ee*

11 — **4k**. 99%, 52:48 *dr*, >99% />99% *ee*

12 — **4l**, 67%, >19:1 *dr*, >99% *ee*[b]

13 — **4m**, 67%, >99% *ee*

14 — **4n**, 20%, 90% *ee*

15 — **4o**, 85%, >99% *ee*

16 — **4p**, 84%, >99% *ee*

17 — **4q**, 88%, >99% *ee*

18 — **4r**, 87%, >99% *ee*

19 — **4s**, 73%, >19:1 *dr*, >99%*ee*

20 — **4t**, 97%, >19:1 *dr*, >99%*ee*

21 — **4u**, 65%, 94% *ee*[c]

22 — **4v**, 99%, 59:41 *dr*, 98%/ 70% *ee*

23 — **4w**, 78%, 84:16 *dr*, 95%/ 98% *ee*

24 — **4x**, 68%, 91% *ee*[b]

[a] All reactions were performed at 60 °C in 0.2 mL $CHCl_3$, with **1** (0.12 mmol), **2** (0.10 mmol), **B**/TfOH (20 mol%), 24-48 h. Yield of isolated product. *Dr* was determined by NMR and *ee* was determined by HPLC analysis. [b] At room temperature. [c] Acetone as solvent.

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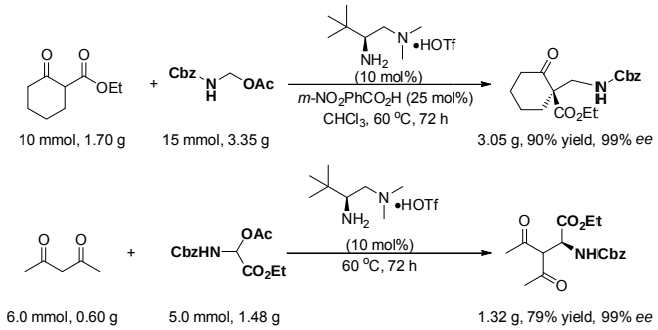

Scheme 2. Gram-Scale Synthesis.

Plausible transition states were proposed based on previous studies[10] as well as the determined configurations (SI for details). ESI-MS analysis revealed imine generation is quite facile under the aminocatalytic conditions. The enamine addition with imine occurs from the *Re*-face of enamine, and the H-bonding between the protonated N-H and imine (**TS I**) or imine esters (**TS II**) is critical in dictating the facial selection as well as the diastereoselectivity (**Figure 2**).[10]

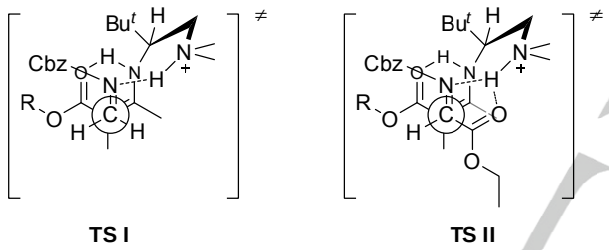

Figure 2. Proposed Transition States.

In conclusion, we have developed a catalytic asymmetric Mannich reaction of ketones with high enantioselectivity using six bench stable *N*,*O*-acetals as the reagents by a simple chiral primary amine catalysis. This protocol provides a highly efficient and stereoselective approach to synthesis α-amino esters and β-amino carbonyls. Ongoing studies are aimed at expanding the scope of *N*,*O*-acetals as imine surrogates and their catalytic applications.

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Keywords: *N*,*O*-acetals • enamine catalysis • Mannich reaction •imine surrogate •amino carbonyls

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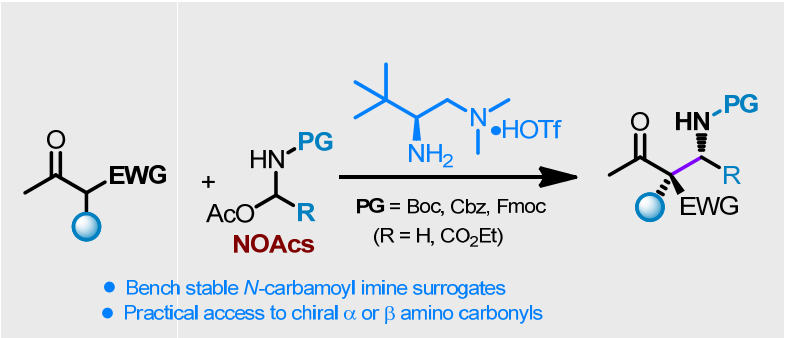

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Bench stable imine surrogates: *N*, *O*-acetals (NOAcs) have been developed as bench stable surrogates for *N*-carbamoyl (Boc, Cbz and Fmoc) formaldehyde and glyoxylate imines in asymmetric Mannich reactions. This reaction offers a straightforward approach in the asymmetric synthesis of α- or β-amino carbonyls bearing chiral quaternary centers in a practical and highly stereocontrolled manner.