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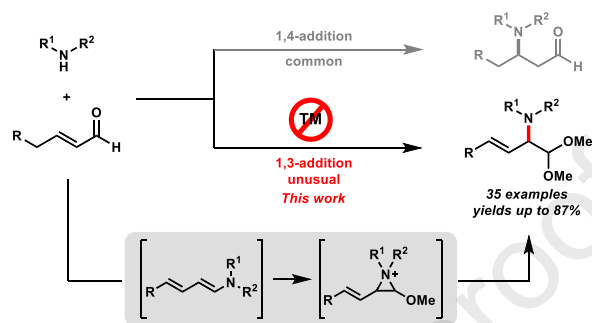
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Communication

Carbonyl group-assisted 1,3-amine addition to α,β -unsaturated aldehydesZhenguo Zhang ^{a,b,§}, Mi Ren ^{c,§}, Ming-Zhu Lu ^a, Zhenhua Jia ^a, Teck-Peng Loh ^{a,b,c,*}^a College of Advanced Interdisciplinary Science and Technology, Henan University of Technology, Zhengzhou, 450001, China^b Division of Chemistry and Biological Chemistry, School of Chemistry Chemical Engineering & Biotechnology, Nanyang Technological University, 21 Nanyang Link, 637371, Singapore^c School of Chemistry and Molecular Engineering, Nanjing Tech University, Nanjing, 211816, China

Loh *et al.* report a metal-free protocol of 1,3-amine addition products are obtained when amines are reacted with α,β -unsaturated carbonyl compounds. Various control experiments have indicated that the reaction proceeded *via* a mechanism involving the formation of imine/enamine intermediates followed by a 1,2-amine group migration reaction.

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ABSTRACT

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An unusual 1,3-addition products were obtained when amines were reacted with α,β -unsaturated aldehydes compounds in the presence of iodine and an oxidant. The versatile unsaturated α -amino acetals are highly useful amino acid derivatives and can be converted to a wide variety of synthetically useful building blocks. Various control experiments have shown that the reaction proceeded via a mechanism involving the formation of imine/enamine intermediates followed by a 1,2-amine group migration reaction.

Developing efficient methods for the unconventional 1,3-addition of nucleophiles like amines to α,β -unsaturated carbonyl compounds is vital in organic synthesis, as it produces valuable α -amino acid derivatives. [1,2] However, developing this type of process has been challenging because amines typically preferentially react with the electrophilic β -carbon of the α,β -unsaturated carbonyl compound, resulting in 1,4-addition reactions that form β -amino compounds or undergo 1,2-addition to create imines (Fig. 1). [3-12] Consequently, substantial efforts have been dedicated to developing new methods for the 1,3-addition of amines to α,β -unsaturated systems to obtain the α -substituted carbonyl compounds. Recently, organic chemists have demonstrated the feasibility of performing 1,3-addition (anti-Michael) reactions to α,β -unsaturated ester products by utilizing a directing group in the presence of a transition metal catalyst. [13-18] Last year, Meggers reported an elegant work on the stereocontrolled 1,3-nitrogen migration to access chiral α -amino acid. [19] However, to the best of our knowledge, metal-free 1,3-addition reactions of α,β -unsaturated aldehydes with amines in the absence of a directing group have not been reported.

In this study, we introduce a simple and effective method for the 1,3-addition of amines to β -substituted unsaturated carbonyl compounds using iodine and an oxidant in methanol. Initial

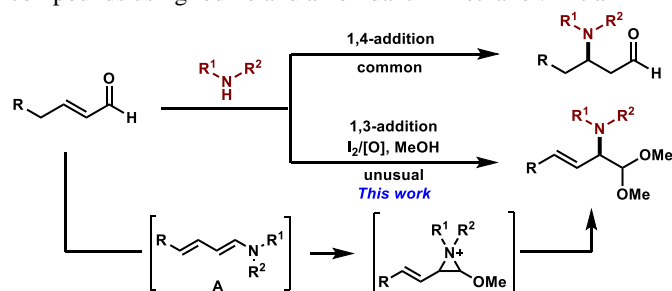


Fig. 1. Design of 1,3-Amine Addition to α,β -Unsaturated Carbonyl Compounds.

studies with various α,β -unsaturated aldehydes have resulted in the commonly observed 1,4-addition products. However, when with β -aromatic and heterocyclic substituted α,β -unsaturated aldehydes as substrates, the unexpected 1,3-addition products were observed. Mechanistic studies indicate that the reactions most likely proceeded through a carbonyl group-assisted 1,2-

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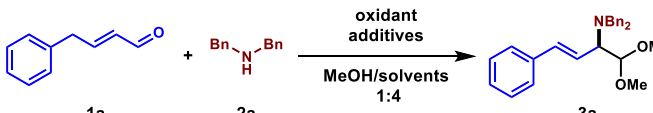
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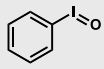
§ These authors contributed equally to this work.

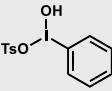
amino group migration *via* a vinylic aziridine intermediate (Fig. 1).

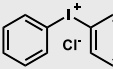
Table 1

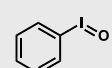
Optimization of the reaction conditions.^a




 Iodosobenzene


 Koser's Reagent


 Diphenyliodonium


 Tognis Reagent

Entry	Oxidant (equiv.)	Additive	Yield ^b
1	O ₂	CuBr ₂ , TMEDA	0 ^{c,d}
2	O ₂	I ₂	trace
3	30% H ₂ O ₂ (1.5)	I ₂	28
4	Na ₂ CO ₃ •1.5H ₂ O ₂ (2.0)	I ₂	82
5	Na ₂ CO ₃ •1.5H ₂ O ₂ (2.0)	I ₂	69 ^c
6	Na ₂ CO ₃ •1.5H ₂ O ₂ (1.0)	I ₂	44
7	Na ₂ CO ₃ •1.5H ₂ O ₂ (2.0)	I ₂	0 ^e
8	Na ₂ CO ₃ •1.5H ₂ O ₂ (2.0)	Iodosobenzene	0
9	Na ₂ CO ₃ •1.5H ₂ O ₂ (2.0)	Koser's reagent	0
10	Na ₂ CO ₃ •1.5H ₂ O ₂ (2.0)	Diphenyliodonium	0
11	Na ₂ CO ₃ •1.5H ₂ O ₂ (2.0)	Tognis reagent	0
12	Na ₂ CO ₃ •1.5H ₂ O ₂ (2.0)	--	0
13	--	I ₂	trace

^aReaction conditions: α,β -unsaturated aldehydes **1a** (0.6 mmol, 3.0 equiv.), secondary amines **2a** (0.2 mmol, 1.0 equiv.), additives (0.04 mmol, 0.2 equiv.), oxidant (0.4 mmol, 2.0 equiv.), MeOH (0.5 ml), DCE (2.0 ml), in air, 60 °C, 16 h.

^bIsolated yields based on secondary amines **2a**.

^c40 °C.

^dMeCN as solvent.

^eH₂O as solvent.

Reaction condition optimization. With our continuing interest in the development of new synthetic methodologies, we investigated the reaction of α,β -unsaturated aldehydes **1a** with dibenzylamine **2a** under metal-free oxidative conditions. We first screened the reaction of dibenzylamine with β -benzyl substituted α,β -unsaturated aldehyde under a wide variety of conditions. Indeed, in most cases, the 1,4-conjugated product was obtained as the major products. We were surprised when the reaction was carried out in I₂/30% H₂O₂ aq. at 60 °C, the unusual 1,3-addition product was obtained, albeit in a low 28% yield (entry 3). Further optimization revealed that the reactions proceeded best in Na₂CO₃•1.5 H₂O₂/I₂ at 60 °C with 82% yield (entry 4). The reaction also worked at 40 °C, albeit in a lower 69% yield (entry 5). When attempting to reduce the dosage of the oxidant, unfortunately, there is a significant decrease in yield, 44% (entry 6). The reaction carried out in aqueous media did not afford any of the desired products (entry 7). Also, other hypervalent iodine reagents were screened to further optimize the reaction conditions,

but none of them yielded the target product (entries 8-11). Control experiments indicate that sodium percarbonate and elemental iodine were crucial for the synthesis of unsaturated α -amino acetals (entries 12, 13). Eventually, the optimized reaction conditions for the synthesis of unsaturated α -amino acetals

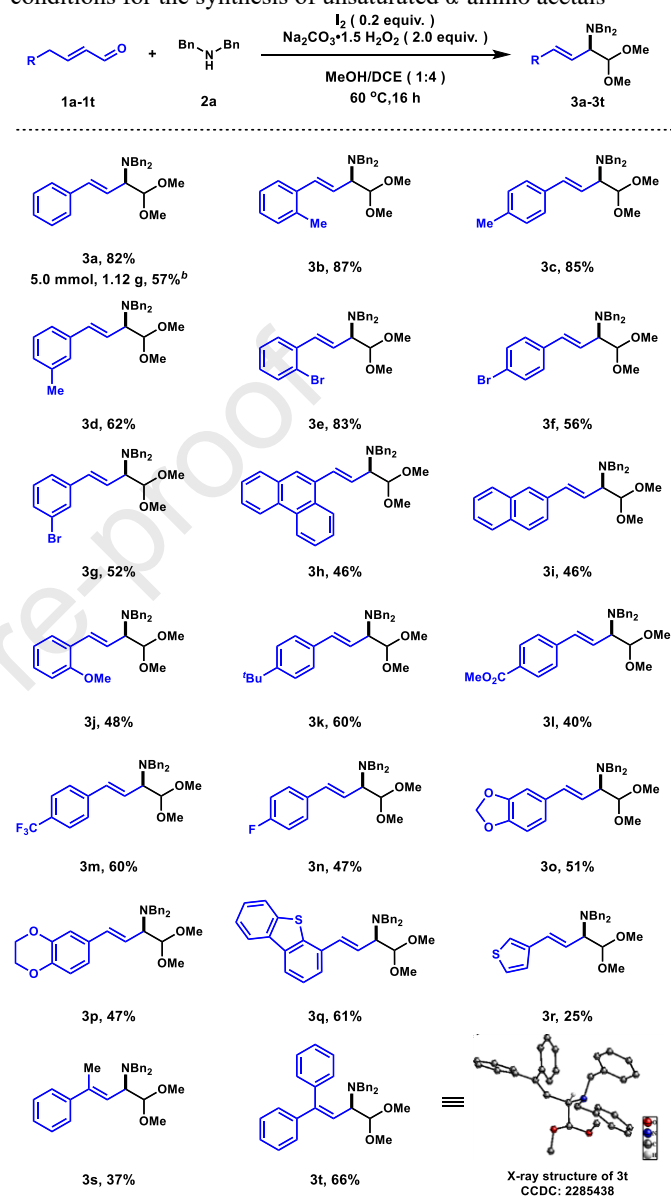


Fig. 2. Scope of α,β -Unsaturated Aldehydes. ^aReaction conditions: α,β -unsaturated aldehydes **1a** (0.6 mmol, 3.0 equiv.), secondary amines **2a** (0.2 mmol, 1.0 equiv.), additives (0.04 mmol, 0.2 equiv.), oxidant (0.4 mmol, 2.0 equiv.), MeOH (0.5 ml), DCE (2.0 ml), in air, 60 °C, 16 h. All yields are isolated yields based on secondary amines **2a**. ^bGram-scale reaction.

employing our method include: the use of sodium percarbonate as the co-oxidant, conducting of the reaction at 60 °C, use of DCE as the solvent, use of secondary amine and conjugated aldehyde in a ratio of 1:3, adjustment of the solvent ratio of MeOH/DCE to 1:4 (v/v), and use of 0.2 equivalents of molecular iodine as the precatalyst. Other parameters were systematically screened and the results were summarized in the supporting information (Table S1-S4 in Supporting information for details).

Scope of substrates. Subsequently, the scope of α,β -unsaturated aldehydes and secondary amine was investigated under the optimized reaction conditions as shown in Figures 2 and 3. The desired unsaturated α -amino acetals **3b-3g** were obtained in 52%–87% yield by altering the position of the **-Me** and **-Br** on the benzene ring, and it can be found that the ortho yield was the highest. An aldehyde with a large aromatic group, such as phenanthrene and naphthyl, were also suitable for this reaction and the desired product **3h-3i** were obtained in moderate yields of 46%. A variety of α,β -unsaturated aldehydes containing functional groups, such as **-OMe**, **-tBu**, **-CO₂Me**, **-CF₃**, and **-F**, were compatible with this transformation, providing the desired unsaturated α -amino acetals **3j-3n** in 40%–60% yields. An aldehyde with acetal such as **3o-3p** were obtained in moderate yields of 47%–51%. Notably, the model reaction was suitable for this protocol to produce unsaturated α -amino acetals **3a** in gram scale with a yield of 57%.

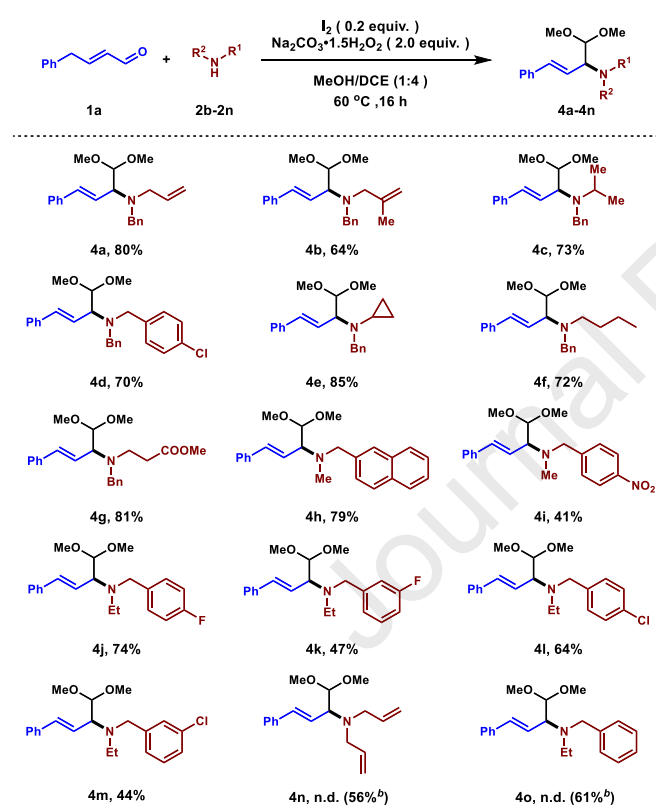


Fig. 3. Scope of secondary amines. ^aReaction conditions: α,β -unsaturated aldehydes **1a** (0.6 mmol, 3.0 equiv.), secondary amines **2** (0.2 mmol, 1.0 equiv.), additives (0.04 mmol, 0.2 equiv.), oxidant (0.4 mmol, 2.0 equiv.), MeOH (0.5 ml), DCE (2.0 ml), in air, 60 °C, 16 h. ^b Stepwise reactions were shown in the supporting information. All yields are isolated yields based on secondary amines **2**.

It is worth noting that, as a result of the mild reaction conditions, the reaction showed good tolerance for heteroaromatic substituents. For example, (E)-4-(dibenzo[b,d]thiophen-4-yl)but-2-enal offered α -amino **3q** in a moderate yield of 61%. (E)-4-(thiophen-3-yl)but-2-enal offered α -amino **3r** in a moderate yield of 25%. When there is an additional substituent such as (**-Me**, **-Ph**) on the carbon connected to the γ -position **3s-3t**, the yield increased correspondingly with the increase of the relative molecular weight

of the substituent. Fortunately, the X-ray structure of the compound **3t** (CCDC:2285438) further confined the structure.

During the experiment, our group did not obtain the target product when aniline was used. Therefore, our group used secondary amines as the only nitrogen source in the reaction. The desired unsaturated α -amino acetals **4a-4g** were obtained in 64%–81% excellent yields. When the secondary amine was dibenzylamine, the yield of the target product was 82%.

A secondary amine with a large aromatic group, such as naphthyl, was also suitable for this reaction and the desired product **4h** was obtained with a good yield of 79%. The desired unsaturated α -amino acetals **4i-4m** were obtained in 41%–74% yield by altering the position of the strong electron-withdrawing group (**-NO₂**, **-F**, **-Br** and **-Cl**) on the benzyl benzene ring. When substrates with weakly electron-donating alkyl groups as substituents were used in one-pot, this method failed to produce the unsaturated α -amino acetals.

Mechanistic studies. Based on various controlled experiments and reported work, [20–23] we proposed the mechanism for the formation of unsaturated α -amino acetals involving 1,3-amine addition (Fig. 4). Firstly, the active cationic iodine species, hypoiodite acid, which is thought to function as a one-electron oxidizing reagent or electrophilic reagent, is formed by oxidation of iodine (**I₂**) or (**I**) with hydrogen peroxide. [20–22,24] Secondly, the hypoiodite reacts with enamine **A** to provide iminium ion **B**. Subsequently, methanol attacks iminium ion **B** to generate the iodo-substituted intermediate **C**, which undergoes intramolecular cyclization to afford aziridinium ion **D**. Finally, an additional methanol molecule captures the ring-opened intermediate **E** to afford the desired product.

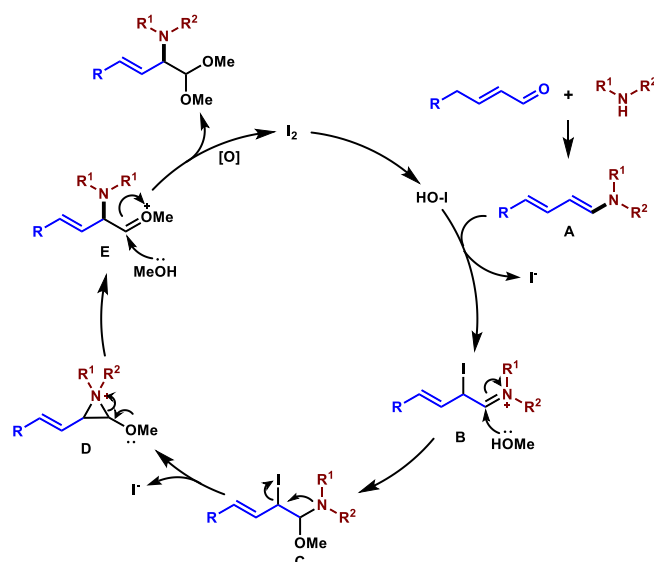


Fig. 4. Proposed mechanism.

To propose a potential mechanism for the 1,3-addition reaction, we sought to detect the intermediate involved (Fig. 5). Through NMR studies, we detected the formation of the diene enamine (compound **A**). When this intermediate was subjected to the reaction conditions, the product was obtained in a good yield of 80%.

Introducing a different amine to the reaction mixture containing the intermediate did not yield a crossover product, suggesting an intramolecular process. Furthermore, when utilizing the allylic amine (compound **F**) as a starting material, the desired product was also obtained, albeit with a lower yield due to competing imine formation pathways. Based on these observations, we propose that the reaction proceeds through an intramolecular 1,2-amino migration pathway, assisted by the carbonyl group.

In employing a combination of molecular iodine and two equivalents of potassium hydroxide in this reaction, we achieved a yield of 36% for the desired product. This success leads us to propose the involvement of an *in situ* generated hypoiodite (IO^-) or iodite (IO_2^-) as the active intermediate[20] (Fig. S6 in Supporting information for details).

To investigate why certain amines failed to yield the desired products, we began by examining the reactions involving the preformed iminium intermediate of diallylamine and N-benzylethanamine under the specified reaction conditions, as shown in supporting information. To our surprise, we successfully obtained the desired unsaturated α -amino acetals (**4n**, **4o**) with moderate yields of 56% and 61% respectively (Fig. 3), which suggested that the iminium intermediate was not formed when methanol was used as the solvent in the reaction.

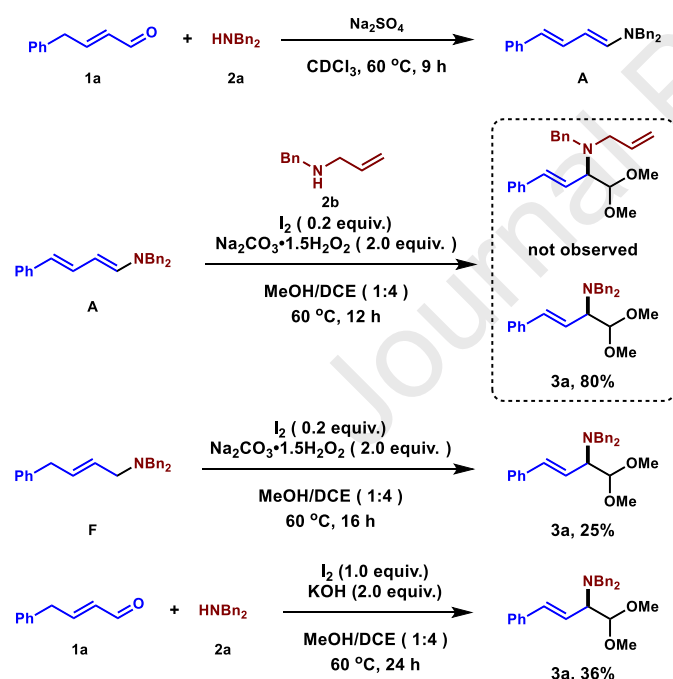


Fig. 5. Mechanistic supplement.

In summary, we have developed a new 1,3-addition reaction between secondary amines and α,β -unsaturated aldehydes that does not require metal catalysts. The resulting amino acetals derivatives have proven to be versatile intermediates for synthesizing alkaloids. This reaction offers several benefits, including mild reaction conditions, non-toxicity, and ease of handling, and employs sodium percarbonate as an environmentally friendly co-oxidant. Furthermore, the reaction tolerates a wide range of functional groups, including bulky aldehydes. Mechanistic studies, such as intermediate trapping and

cross-over experiments, have demonstrated that the 1,3-amine addition to α,β -unsaturated aldehydes proceeds via a 1,2-amino group migration assisted by the carbonyl group. This discovery could serve as inspiration for developing other 1,n-nucleophilic additions to various conjugated systems that were previously unknown. Furthermore, another challenge for future research lies in controlling the stereo-selectivity generated during the reaction process.

Declaration of competing interest

Zhenhua Jia and Teck-Peng Loh is an editorial board member/editor-in-chief for Green Synthesis and Catalysis and was not involved in the editorial review or the decision to publish this article. All authors declare that there are no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: