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Iodine-promoted Intermolecular Dehydrogenation Diamination : Synthesis of Unsymmetrical α , β -diamido Ketones

YongJian Zhang, Junyi Su, Wenjie Niu, and Yujin Li*

Abstract: Iodine-promoted direct diamination of α , β -unsaturated ketone to form two C-N bonds has been developed starting from chalcone and secondary amine. This reaction was performed in THF at 50 °C in the presence of I₂ and K₂CO₃. The protocol is metal-free and it only needs to be carried out under mild conditions, simple operation, accessible raw materials, good atomic and so on, which provides an effective new way for directing diamination reaction.

Introduction

Vicinal diamines as a key motif widespread exist in natural products (e.g., Biotin),^[1] bio-medicinal and pharmaceutical sciences (e.g., Tamiflu, an antiviral drug; and Eloxatin, an anticancer drug)^[1,2] and in ligands for asymmetric metal catalysis (e.g., Maruoka organocatalyst),^[1,3] and have attracted continuous interest by scientists (Figure 1).^[1b,4] Undoubtedly, direct diamination of olefin to achieve the construction of the two C-N bonds represents one of the most straightforward and efficient approaches for obtaining vicinal diamines due to its high atom and step economy.^[4d,5]

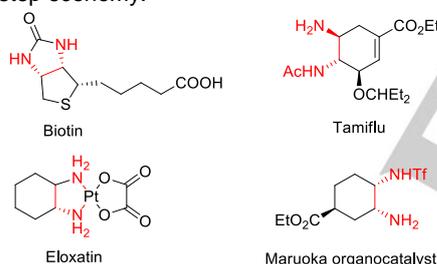


Figure 1. Selected bioactive and catalytic compounds.

Nevertheless, unlike the Sharpless dihydroxylation, epoxidation and aminohydroxylation have been employed in a variety of chemistry reactions, developing a simple direct diamination reaction is a long way to go. In past decades, although a number of elegant methods for the preparation of vicinal diamines compounds by using transition-metal-catalyzed and iodine(I/III)-catalyzed 1,2-diamination of alkenes have been reported, which mainly include Pd,^[6] Cu,^[7] Ti,^[8] Ni,^[9] Ir^[10]

etc. and like the hypervalent iodine reagents type of ArI[R]₂ or ArI[N]₂, such as PhI(O₂CCF₃)₂ (PIFA)^[11], PhI(OAc)₂/HNtS₂^[12] and PhI(OAc)₂/HNMs₂^[13] etc. From a synthetic point of view, most of the above methods need toxic metal compounds or special, expensive reagents, specific substrates, and harsh reaction conditions prepared in lengthy reaction. Therefore, a mild and simple catalytic methodology to yield vicinal diamines from material easily available in any would be desirable.

Nowadays, iodine-promoted direct oxidative C-H dehydrogenation or functionalization has been a typical means for constructing C-C and C-heteroatom bonds.^[14] Inspired by a few examples of iodine-catalyzed (iodic compound) diamination reaction^[15] to prepare vicinal diamines from olefin, herein we report a feasible molecular iodine-promoted intermolecular reaction synthetic method carrying out under mild conditions, simple operation and accessible raw materials. To the best of our knowledge, this tactics hasn't been reported thorough investigation of the diamination reaction from α , β -unsaturated ketones and amines for the direct construction of 1,2-diamines.

Results and Discussion

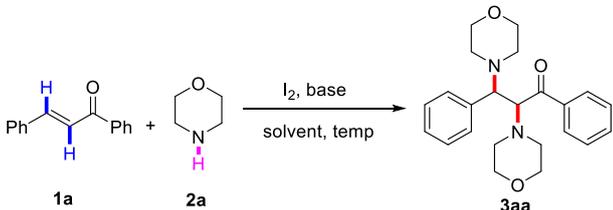
In order to explore the feasibility of iodine-promoted diamination of α , β -unsaturated ketone, chalcone (**1aa**, 0.4 mmol) and morpholine (**2aa**, 1.2 mmol) were selected as a model substrates to investigate the reaction. To our delight, the desired diamination product 2,3-dimorpholino-1,3-diphenylpropan-1-one (**3aa**) was formed in 59%, in the presence of 1.0 equiv. of iodine and 1.5 equiv. of K₂CO₃ with CH₃CN as solvent at 80 °C for 4 h (Table 1, entry 1). Encouraged by this preliminary result, we intended to explore and optimize this reaction conditions for this transformation. The aim is to develop a rapid and straightforward method to receive 1,2-diamines compounds in a simple and economical way rather than multi-steps.^[16] After screening the various common solvents like THF, EtOH, 1,4-dioxane, Et₂O, toluene, DMF and DMSO (Table 1, entries 2–8), we found that the yield of **3aa** was an apparently increasing to 84% in THF and so we chose THF as the reaction solvent. Then, some familiar bases including inorganic bases like Na₂CO₃, Cs₂CO₃ (Table 1, entries 9–10), and organic bases like Et₃N, DBU, DIPEA (Table 1, entries 11–13) were employed to this reaction, the diamination products were formed in all of cases, however, we discovered that inorganic bases were more beneficial to this reaction than organic bases, while none were further effective for the formation of the product **3aa**. Accordingly, we chose K₂CO₃ as the reaction base. Further experiments revealed that molecular iodine was a crucial promoter in this reaction since no target product was observed in the absence of molecular iodine (Table 1, entry 19).

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Then, we discussed the effect of temperature on the reaction and discovered when the temperature of reaction was decreased to 50 °C, the effect of the reaction is basically the same as 80 °C (Table 1, entry 14), however, when we brought the temperature down to room temperature, the reaction needed 5 h, produced a small amount of by-products and obtained **3aa** in 58% yield (Table 1, entry 15). Next examination of the amount of I₂ and K₂CO₃ showed that 0.5 equiv. of I₂ and 1.0 equiv. of K₂CO₃ gave **3aa** in 52% and 70% yield correspondingly (Table 1, entries 16-17). Moreover, when the reaction was performed in a 1.2 equiv of DTBP or TBHP as an additional oxidant, **3aa** was decreased slightly gave in 80% yield (Table 1, entry 18). Therefore, the optimum reaction conditions were obtained by using 1.0 equiv. of molecular iodine, 1.5 equiv. of K₂CO₃ in THF as reaction solvent at 50 °C (Table 1, entry 14).

Table 1. Screening of optimal reaction conditions.^[a]



Entry	Additive	Base	Solvent	Yield(%) ^[b]
1	I ₂	K ₂ CO ₃	CH ₃ CN	59
2	I ₂	K ₂ CO ₃	THF	84
3	I ₂	K ₂ CO ₃	EtOH	63
4	I ₂	K ₂ CO ₃	1,4-dioxane	51
5	I ₂	K ₂ CO ₃	Et ₂ O	58
6	I ₂	K ₂ CO ₃	DMF	62
7	I ₂	K ₂ CO ₃	Toluene	72
8	I ₂	K ₂ CO ₃	DMSO	33
9	I ₂	Na ₂ CO ₃	THF	71
10	I ₂	Cs ₂ CO ₃	THF	64
11	I ₂	Et ₃ N	THF	47
12	I ₂	DBU	THF	18
13	I ₂	DIPEA	THF	23
14 ^[c]	I ₂	K ₂ CO ₃	THF	84
15 ^[d]	I ₂	K ₂ CO ₃	THF	58
16 ^[e]	I ₂	K ₂ CO ₃	THF	52
17 ^[f]	I ₂	K ₂ CO ₃	THF	70
18 ^[g]	I ₂	K ₂ CO ₃	THF	80
19	-	K ₂ CO ₃	THF	NR

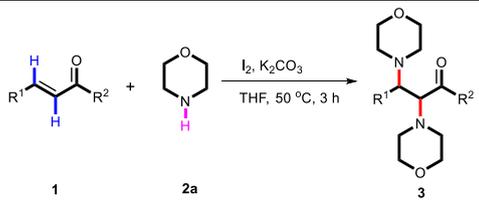
^[a] Reaction conditions: **1a** (0.4 mmol), **2a** (1.2 mmol), additive (I₂ 1.0 equiv.), base (1.5 equiv.), solvent (2.0 mL), 80 °C, 4 h. ^[b] Isolated yield based on **1a**. ^[c] 50 °C, 3 h. ^[d] At room temperature, 5 h. ^[e] I₂ (0.5 equiv.). ^[f] K₂CO₃ (1.0 equiv.). ^[g] I₂ (1.0 equiv.), DTBP (1.2 equiv.) or TBHP (1.2 equiv.).

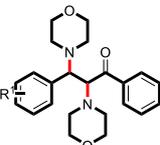
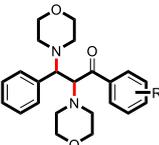
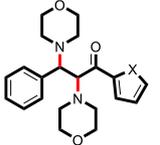
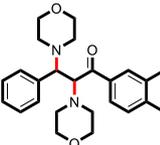
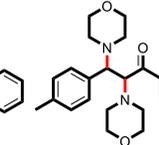
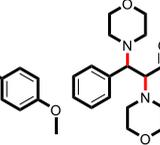
With the optimization conditions in hand to prepare the diamination compounds **3aa** in a good yield, attention turned to estimating the different substitute scope of the reaction under the optimized conditions and the results are illustrated in Table 2 and 3.

To explore the scope of this reaction we started with the screening of various chalcones and the results are show in Table 2. Gratifyingly, diversiform chalcones with distinguishing substituents 1 bearing either electron donating or withdrawing groups on the aryl rings were all smoothly converted to furnish the corresponding derivatives **3ba–3qa** in moderate to good yields in all cases. In general, both aryl ring with para-substitutions link to C-C double bond and connect to carbonyl group were obtained in good yields.

In contrast, the yields of products **3** were reduced further when aryl ring substituents of the chalcones were strong electron withdrawing groups (e.g. –NO₂, **3ea**, **3ka**) than halogen atoms (e.g., –F, –Cl, –Br, **3ba–3da**, **3ha–3ja**) or electron donating groups (e.g., –CH₃, –OCH₃, **3fa–3ga**, **3la–3ma**), that is because the chalcone of –NO₂ substituted produced other unknown by-products during the reaction. In addition, heteroaromatic groups at the olefin terminus, i.e. R², such as furanyl and thiophenyl (**3na**, **3oa**) and fused aromatic group, i.e. naphthyl (**3pa**) are well accommodated. Meanwhile, double *para*-substitutions of chalcone **1q** was also applicable to this experimental protocol to achieve **3qa** in a good yield (80%).

Table 2. Scope of chalcones in diamination reaction. ^[a,b]



 R ₁ =H, 3aa , 84% R ₁ = <i>p</i> -F, 3ba , 70% R ₁ = <i>p</i> -Cl, 3ca , 79% R ₁ = <i>p</i> -Br, 3da , 72% R ₁ = <i>p</i> -NO ₂ , 3ea , 64% R ₁ = <i>p</i> -CH ₃ , 3fa , 70% R ₁ = <i>p</i> -OCH ₃ , 3ga , 73%	 R ₂ = <i>p</i> -F, 3ha , 81% R ₂ = <i>p</i> -Cl, 3ia , 83% R ₂ = <i>p</i> -Br, 3ja , 80% R ₂ = <i>p</i> -NO ₂ , 3ka , 60% R ₂ = <i>p</i> -CH ₃ , 3la , 71% R ₂ = <i>p</i> -OCH ₃ , 3ma , 76%		
 X=S, 3na , 65% X=O, 3oa , 63%	 3pa , 75%	 3qa , 80%	 3ra , 55%

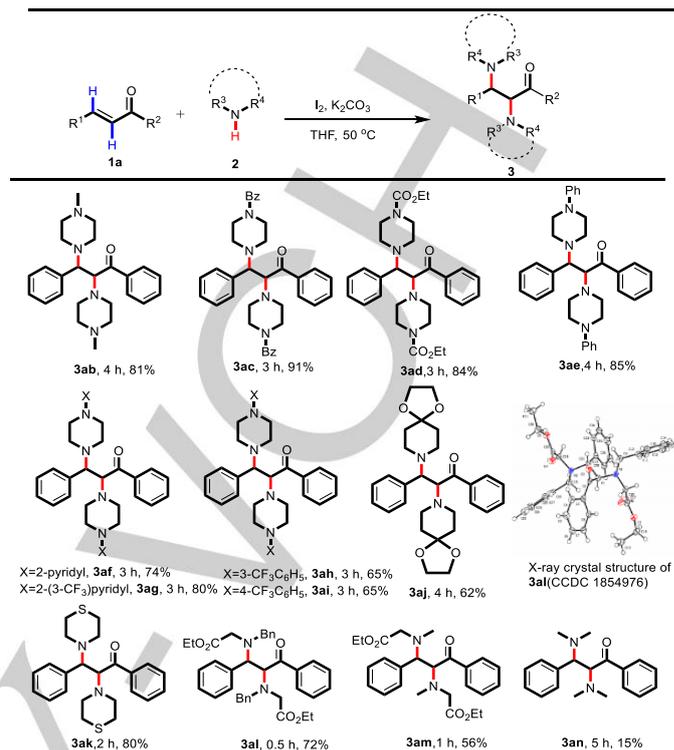
^[a] General conditions: **1a** (0.4 mmol), **2a** (1.2 mmol), additive (I₂ 1.0 equiv.), base (1.5 equiv.), solvent (2.0 mL), 50 °C, 3 h. ^[b] Isolated yield based on **1a**.

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Under the standard reaction conditions, the hybrid (one aromatic and the other aliphatic) substituted α,β -unsaturated ketones like 4-phenyl but-3-en-2-one were also well tolerated and the target product **3a** was afforded in 55% yield. Unfortunately, we failed we tried this reaction apply to the aliphatic substituted α,β -unsaturated ketones like pent-3-en-2-one, cyclohex-2-en-1-one and methyl acrylate or the unactivated olefins like styrene.

Next, the substrate scope of the intermolecular diamination reaction with respect to the amine was then investigated and we found this reaction is tolerant of a various scope of secondary amines (Table 3). Under the optimized conditions, various N-protected piperazines such as N-methyl, N-Bz, N-CO₂Et, N-Ph were employed to the reaction and led to diamination products in good (74%–91%) yields (Table 3, **3ab–3ag**). N-(3-(trifluoromethyl) phenyl) piperazine and N-(4-(trifluoromethyl) phenyl) piperazine, nevertheless, engaged in diamination in moderate 65% yields (Table 3, **3ah–3ai**). We also obtained product **3aj** in 62% yield. Then, thiomorphine was also used in this reaction and the expected products **3ak** was afforded in 80% yield. With the exciting results of cyclic amines above, we tried to employ secondary aliphatic chains amine to this diamination reaction. N-benzylglycine ethyl ester and sarcosine ethyl ester were all compatible with the reaction to give the desired products **3al–3am** in moderate yields. The product **3an** received in a depressed yield when we used dimethylamine (in 40% aqueous), only 15%, along with a lot of chalcone left over. In particular, due to own perfect crystal, the structure of **3al** was unequivocally determined by single crystal X-ray crystallographic analysis^[17] at the same time, and the configuration of the product is *trans*. Nevertheless, the trace of desired product was obtained when arylamines such as aniline and N-methylaniline were engaged in standard conditions and the reaction mixture was complicated.

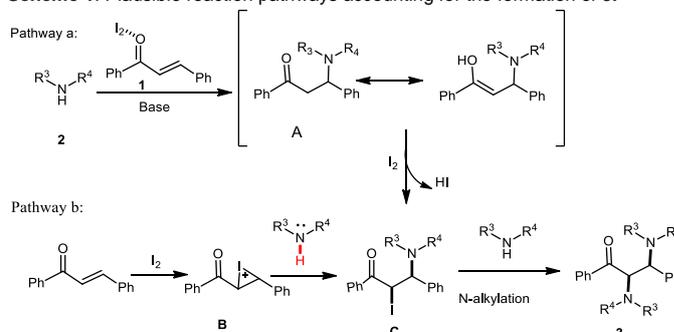
Table 3. Scope of amines in diamination reaction. ^[a, b]



^[a] General conditions: **1a** (0.4 mmol), **2a** (1.2 mmol), additive (I₂ 1.0 equiv.), base (1.5 equiv.), solvent (2.0 mL), 50 °C. ^[b] Isolated yield based on **1a**.

On the basis of the above experimental results and relevant literature report,^[18] two plausible diamination mechanisms were proposed (Scheme 1). For pathway a, initially, chalcone **1** reacted Michael addition with secondary amine **2** under the activation of iodine and obtained intermediate **A**, consider as a common pathway. Next, the **A** was α -iodized to obtain compound **C** (the fragment of [M-I]⁺ was detected). Finally, the compound **C** alkylated with the amine and afforded the desired product **3**. For pathway b, the activated olefin **1** bearing benzoyl group formed iodonium ion in the presence of iodine, which was then electrophilic added with the amine to form compound **C** and the intermediate **C** was immediately substituted with the amine. Since the addition reaction of olefin and iodine often obtains *trans* product, this was once again proved by the single crystal structure of **3al**.

Scheme 1. Plausible reaction pathways accounting for the formation of **3**.



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Conclusions

In summary, a novel single step method to obtain vicinal amines by direct diamination reaction from accessible amines and α , β -unsaturated ketones we have achieved. Chalcones and secondary amines provided anticipated products in good to excellent yields. The method obviated the need of metal catalyst or hypervalent iodine reagents and proceeded well under mild conditions, ready accessibility of the starting materials, simple operation and good to high yields characterize the present transformation. The investigation of diamination of alkene is still ongoing.

Experimental Section

General Information Unless otherwise noted, all commercial reagents and solvents were obtained from the commercial provider and used without further purification. ^1H NMR spectra were recorded on an NMR instrument operated at 500 MHz. Chemical shifts are reported in parts per million with the solvent resonance as the internal standard (CDCl_3 , δ 7.26). ^{13}C NMR spectra were recorded on an NMR instrument operated at 125 MHz with complete proton decoupling. Chemical shifts are reported in parts per million with the solvent resonance as the internal standard (CDCl_3 , δ 77.1). HRMS were recorded on a Bruker MicroTOF-QII mass instrument (ESI). Thin-layer chromatography was performed on precoated glass-back plates and visualized with UV light at 254 nm. Flash column chromatography was performed on 200–300 mesh silica.

General Procedure for the Synthesis of 1. To a solution of benzaldehyde (1.06 g, 10 mmol) and acetophenone (1.20 g, 10 mmol) in ethanol (30 mL) was added 30 mL 2.5 M aqueous sodium hydroxide (0.8 g, 20 mmol) dropwise via addition funnel at 0 °C. After completion of the reaction (detected by TLC), the reaction mixture was filtered, wash with ethanol-water solution (1/1) and dried. The desired chalcone **1a** was obtained in 85% isolated yield.

General Procedure for the Synthesis of 3. A mixture of chalcone (**1a**, 83.2 mg, 0.4 mmol), morpholine (**2a**, 105.0 mg, 1.2 mmol), K_2CO_3 (64.8 mg, 0.6 mmol), and iodine (101.6 mg, 0.4 mmol) in THF (3.0 mL) was stirred at 50 °C for 3 h. The reaction was detected by TLC. After the reaction finished, the reaction mixture was extracted with ethyl acetate (10 mL x 3), washed with water and the combined organic layers were washed with brine and aqueous $\text{Na}_2\text{S}_2\text{O}_3$, dried over anhydrous Na_2SO_4 , and concentrated in vacuo. Purification of the crude product by flash chromatography on silica gel (eluent ethyl acetate/petroleum ether = 1/4) provided desired product **3aa** as a white solid (127.8 mg, 84% yield).

Acknowledgements ((optional))

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Keywords: iodine • diamination • α , β - diamido ketone • C-N bond • metal-free

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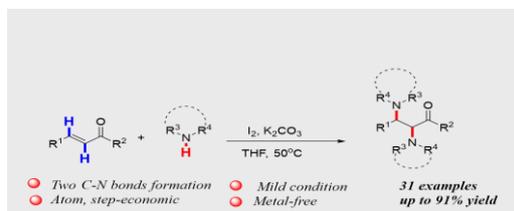
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FULL PAPER



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