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COMMUNICATION

Deaminative Carbonylative Coupling of Alkylamines with Styrenes under Transition-Metal-Free Conditions

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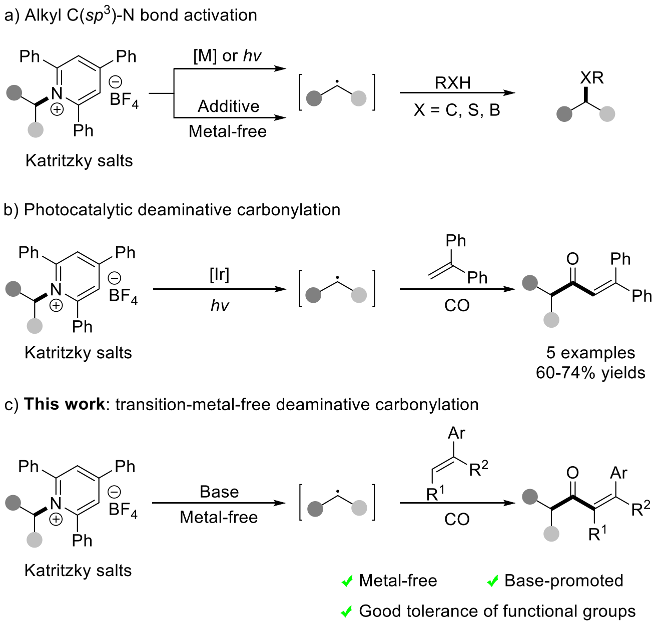
A transition-metal-free deaminative carbonylation of alkylamines with styrenes has been developed. The reaction shows good functional group compatibility and various *α*, *β*-unsaturated ketones were obtained in moderate to good yields. The alkyl radical generated from Katritzky salts via base-promoted C-N bond cleavage is one of the key intermediates in this reaction.

Transition-metal-catalyzed cross-coupling reactions are among the most powerful methods in organic synthesis and have been achieved in the construction of various C-C, C-N, C-O, and C-S bonds in the past few decades.[1] Given that some transition-metal catalysts are expensive, sensitive to air and moisture, and special attention should be given to the metal residues in the produced fine chemicals, the development of transition-metal-free strategies would offer economical friendly and environmental benignly alternates in organic synthesis.

Alkylamines are widely present in natural products, pharmaceuticals and materials.[2] Derivatization of amino groups is one of the most important transformations, and it is also an attractive direction to modify the structure of related biomolecules.[3] Compared to the benzylic and allylic amines, which are used as an alkylating agent via the cleavage of C(sp^3)-N bonds,[4] alkylamines are rarely used due to the stronger C-N bonds. Recently, an attractive strategy, by converting the alkylamines into Katritzky salts to activate the C-N bonds, have been developed. The synthetic value of the Katritzky salts have been demonstrated by the achievements in cross-coupling reactions (Scheme 1a).[5] Metal- or photo-catalysts were applied to initiate the single electron transfer (SET) process.[6-7] Remarkably, in 2019, Shi, Li and co-workers reported a metal/light-free deaminative borylation of alkylamines under mild conditions with catalytic amount of Lewis base as the promoter.[8] Hong's group developed a *N*-heterocyclic carbene-catalyzed deaminative radical-radical coupling strategy of Katritzky salts with aldehydes.[9] More recently, the research group of Loh and Hu described a base-promoted deaminative vinylation of alkylamines with alkenyl boronic acids via Katritzky salts.[10a] Interestingly, these transformations provided novel approaches to transform the C-N bonds under metal- and photocatalyst-free conditions.



Scheme 1. Deaminative transformations of alkylamines through Katritzky salts.

On the other hand, as a convenient and cheap C1 resource, CO is an indispensable reagent for carbonylation reactions.[11] Numerous procedures have been developed and applied based on academic or industrial interests. In 2019, Xiao, Lu and co-workers report their achievement on deaminative alkyl-Heck-type reactions by photo-induced C-N bonds scission of Katritzky salts. By performing the reaction under CO pressure, the carbonylative transformation version can be realized as well and five examples of *α*, *β*-unsaturated ketones were

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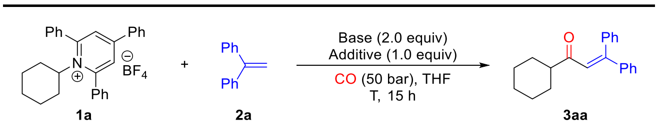
Electronic Supplementary Information (ESI) available: [general information, analytic data, NMR spectra]. See DOI: 10.1039/x0xx00000x obtained in good yields (Scheme 1b).[12] However, transition-metal- and/or photo-catalyst free deaminative carbonylation reactions of Katritzky salts have not been reported yet. Considering our continual interests in the field of carbonylative transformations, and to develop methodologies to overcome the challenges discussed, we herein report a transition metal-free deaminative carbonylation reaction of alkylamines with styrenes toward the synthesize of α, β-unsaturated ketones.

Table 1. Optimization of the reaction conditions.[a]

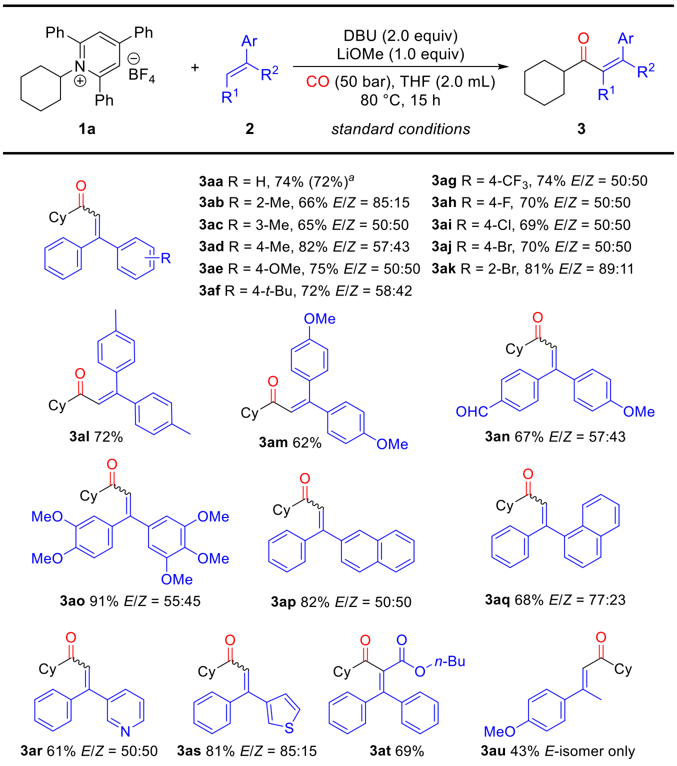


Entry	Base	Additive	T [°C]	Yield [%][b]
1	DBU	/	100	54
2	DBN	/	100	53
3	TBD	/	100	54
4	DABCO	/	100	1
5	DBU	Cs_2CO_3	100	58
6	DBU	KOH	100	55
7	DBU	K_2HPO_4	100	41
8	DBU	*t*-BuOK	100	64
9	DBU	*t*-BuONa	100	50
10	DBU	*t*-BuOLi	100	66
11	DBN	LiOMe	100	68
12	DBU	LiOH	100	59
13	DBU	Li_2CO_3	100	40
14	/	LiOMe	100	2
15	DBU	LiOMe	80	70
16[c]	DBU	LiOMe	80	76 (74)[d]

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), base (0.2 mmol), additive (0.1 mmol), THF (1.0 mL), CO (50 bar), 15 h. [b]Determined by GC using hexadecane as the internal standard. [c]THF (2.0 mL). [d]Isolated yield. DBU = 1,8-Diazabicyclo [5.4.0]undec-7-ene. DBN = 1,5-Diazabicyclo[4.3.0]non-5-ene. TBD = 1,3,4,6,7,8-Hexahydro-2H-pyrimido[1,2-a]pyrimidine. DABCO = Triethylenediamine.

Our optimization studies started with the cross-coupling of cyclohexyl-substituted pyridinium salt **1a** with 1,1-diphenylethylene **2a** (Table 1). The desired product **3aa** was detected in 54% yield by GC with DBU as the base and THF as the solvent (Table 1, entry 1). Other bases, such as DBN and TBD, gave similar results whereas DABCO resulted poor yield (Table 1, entries 2-4). The amount of DBU was examined as well and no increase in the yield even with 4.0 equivalents of DBU were used (see the Supporting Information for more details). Subsequently, some additives were added to the reaction system. It was found that LiOMe was best for this transformation and given a significant increase in the yield of the target product (Table 1, entries 5-13). However, only trace amount of the desired product was detected in the absence of DBU (Table 1, entry 14). A slight decrease in temperature was beneficial for this conversion (Table 1, entry 15). In addition, by reducing the concentration of **1a** to 0.05 M, the yield was increased slightly as well (Table 1, entry 16). Finally, the desired product **3aa** can be obtained in 76% yield by reacting 1.0 equivalent of Katritzky salt **1a** with 2.0 equivalents of 1,1-diphenylethylene **2a** in the presence of 2.0 equivalents of DBU and 1.0 equivalent of LiOMe in THF (2.0 mL) under the CO (50 bar) at 80 °C for 15 h.

Table 2. Scope of styrenes for the deaminative carbonylation.



Reaction conditions: **1a** (0.1 mmol), **2** (0.2 mmol, 2.0 equiv), DBU (0.2 mmol, 2.0 equiv), LiOMe (0.1 mmol, 1.0 equiv), THF (2.0 mL), CO (50 bar), 80 °C, 15 h, isolated yield. [a] 1 mmol scale.

Under the optimized conditions, the substrate scope of this transformation were carried out. A variety of styrenes were tested firstly and led to the corresponding α, β-unsaturated ketones in moderate to good yields in general (Table 2). 2, 3 or 4-Alkyl and alkoxyl-substituted diaryl alkenes can all be effectively transformed in this reaction and gave the desired products in good to excellent yields (**3aa**-**3af**). When substrates with strong electron-deficient functional groups or halogen were used, the desired products can be obtained in good yields as well (**3ag**-**3ak**). Disubstituted and polysubstituted diaryl alkenes were also well-tolerated (**3al**-

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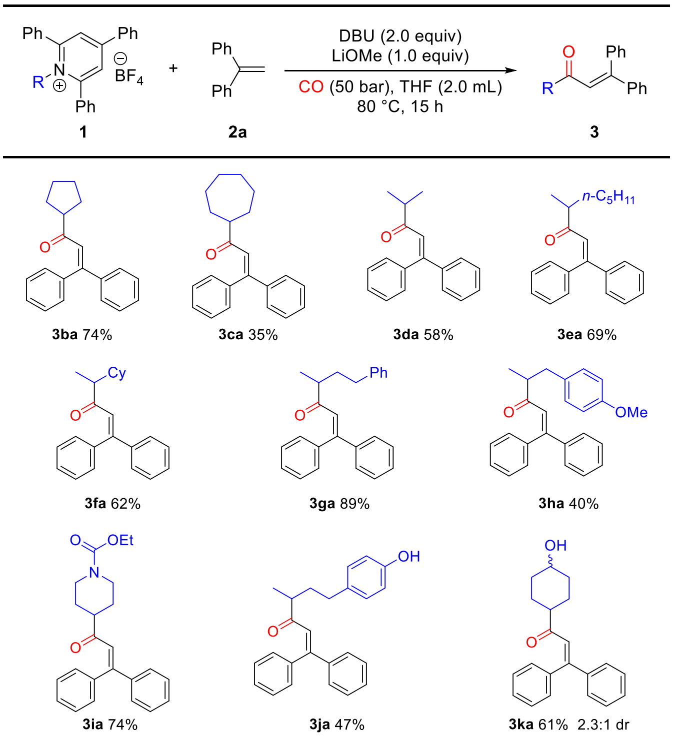
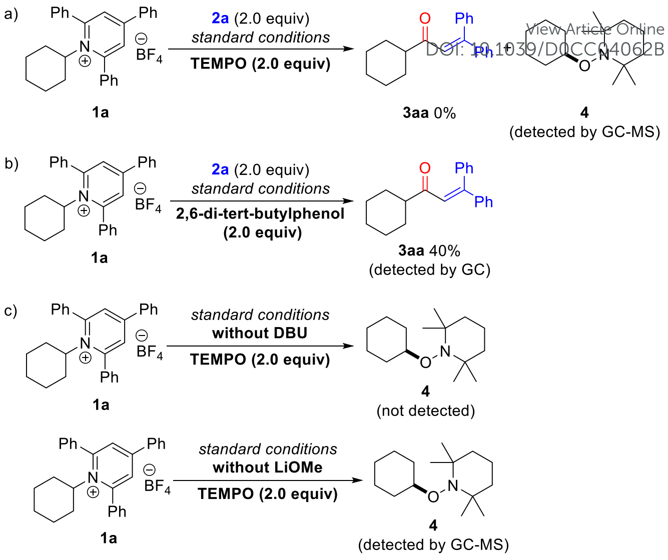
3ao). Styrene with 1-naphthyl, 2-naphthyl, thienyl and pyridyl substitutions at *α*-positions gave the corresponding products smoothly as well (**3ap**-**3as**). This novel strategy can also be extended to internal diaryl alkenes, 69% yield of the desired product was provided when *β*-ester substituted diaryl alkene was used (**3at**). Furthermore, *α*-methyl substituted arylalkene can also be used as the substrate and gave the targeted **3au** in 43% yield. However, poor yield (<30%) was obtained when styrene or trans-1,2-diphenylethene was tested in this reaction. It is important to mention that, for the unsymmetrical diaryl alkenes, (*Z*) and (*E*)-stereoisomers were obtained as a mixture in almost equal amount (except **3ab**, **3ak**, **3aq**, **3as** and **3au**). 2-Phenyl-substituted alkenes afford the (*E*)-isomer as the major product (**3ab** : *E*/*Z* = 85:15; **3ak** : *E*/*Z* = 96:4) due to the steric hindrance. However, 1-(1-phenylvinyl)naphthalene **2q** gave even worse result on the stereoselectivity (*E*/*Z* = 77:23).

Table 3. Scope of Katritzky salts for the deaminative carbonylation.



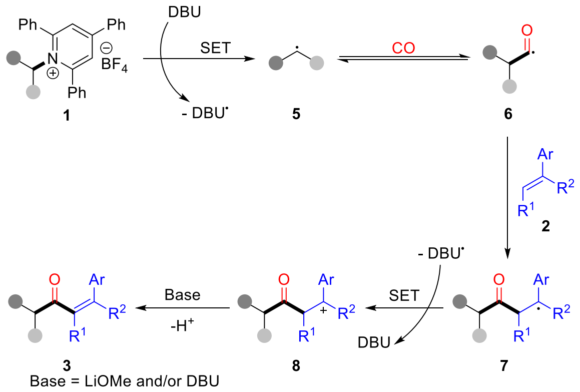
Reaction conditions: **1** (0.1 mmol), **2** (0.2 mmol, 2.0 equiv), DBU (0.2 mmol, 2.0 equiv), LiOMe (0.1 mmol, 1.0 equiv), THF (2.0 mL), CO (50 bar), 80 °C, 15 h, isolated yield.

Then various Katritzky salts derived from alkyl amines were explored (Table 3). Cyclic, chain and phenyl-containing amine derivatives were transformed into the desired products in moderate to good yields (**3ba**-**3ha**). It is worth noting that pharmaceutically relevant saturated heterocyclic amine was also tolerated, the desired product was obtained in good yield (**3ia**). And free alcohol could undergo the transformation as well, given the corresponding products smoothly (**3ja**-**3ka**).



Scheme 2. Mechanistic experiments.

To gain some insight into the reaction mechanism, several control experiments were performed (Scheme 2). The reaction was inhibited in the presence of TEMPO under the standard conditions, the adduct **4** of radical trapped by TEMPO was detected by GC-MS while no desired product could be obtained (Scheme 2a). And when 2,6-di-*tert*-butylphenol was added to this reaction, the product was only obtained in 40% yield (Scheme 2b). These results suggest that a radical was generated in the reaction. In addition, lack of DBU lead to no adduct **4** observed whereas it was detected in the absence of LiOMe (Scheme 2c). These results indicate that DBU is the key to promote the cleavage of C-N bond.



Scheme 3. Proposed mechanism.

On the basis of the mechanistic studies and literature,[7,8,11,12] a possible mechanism is proposed (Scheme 3). Under the assistant of DBU, an alkyl radical **5** was formed from Katritzky salts **1** by the cleavage of C-N bonds firstly and meanwhile produce a DBU˙ radical. Then, the alkyl radical **5** was captured by CO to give the acyl radical **6**. Subsequently, the addition of acyl radical **6** to alkenes **2** form a more stable radical species **7**, which was transformed into a cationic

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intermediate **8** by the previously produced $DBU^{\cdot}$ radical via a SET pathway. Finally, the deprotonation of **8** afforded the corresponding product **3**.

Conclusions

In summary, a transition-metal-free deaminative carbonylation of activated alkylamines with styrenes via cleavage of C-N bonds of Katritzky salts has been developed. In the absence of transition metal catalyst or light irradiation, various *α*, *β*-unsaturated ketones were obtained in moderate to good yields. Versatile functional groups, such as aldehyde, halogen, alkoxy, thienyl, pyridyl, ester, hydroxyl, were tolerated in this reaction.

Conflicts of interest

There are no conflicts to declare.

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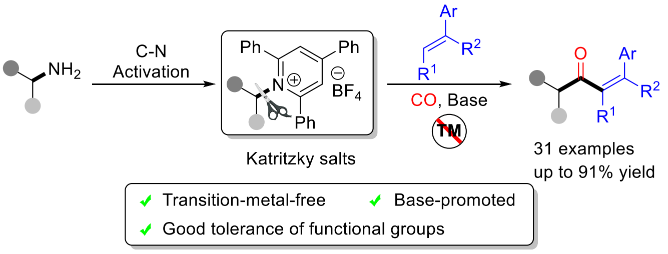
Graphic abstract:



Transition-metal-free deaminative carbonylation through C-N bonds activation via Katritzky salts has been successful developed. Various α, β-unsaturated ketones were obtained in moderate to good yields with alkylamines and styrenes as the substrates.