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Carbene-catalyzed LUMO activation of alkyne esters for access to functional pyridines†

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A carbene-catalyzed LUMO activation of α,β -unsaturated alkyne esters is reported. This catalytic process allows for effective reactions of alkyne esters with enamides to synthesize functional pyridines *via* simple protocols. A previously unexplored unsaturated alkyne acyl azolium intermediate is involved in the key step of the reaction.

Pyridines are common scaffolds in both natural and synthetic molecules with broad utilities.¹ For example, various pyridine and bipyridine derivatives have been extensively studied as ligands for transition metal catalysis (Fig. 1a).² Numerous methods, typically complementary to each other, have been developed for the synthesis of pyridine derivatives.³ We are interested in exploring metal-free N-heterocyclic carbene (abbreviated as NHC or carbene) catalysis for new activations and/or effective organic synthesis. Carbene organic catalysis has a long history of studies⁴ and regenerated great interest in recent years.⁵ The most widely studied key intermediates involved in NHC catalysis include Breslow intermediates⁶ derived from aldehydes and acyl azolium ester intermediates⁷ derived from carboxylic esters (Fig. 1b). The NHC-bound intermediates derived from the related α,β -unsaturated aldehydes⁸ and esters⁹ bearing a carbon–carbon double bond next to the carbonyl group have also been studied.

Here we disclose a catalytic generation and reaction of an unsaturated alkyne ester-derived azolium ester intermediate bearing a carbon–carbon triple bond (Fig. 1b). This previously unexplored intermediate could likely lead to a unique reaction and a reaction cascade due to the presence of a carbon–carbon triple bond. For example, carbene-catalyzed reactions between

a) Examples of pyridine ligands in transition metal catalysis.

b) Key intermediates in NHC-catalyzed reactions.

c) **This work:** NHC-catalyzed alkyne ester activation and pyridine synthesis. (see SI for a complete pathway)

Fig. 1 Functional pyridines and our carbene-catalyzed synthetic method.

alkyne esters and enamides can be realized for quick access to hydroxyl pyridines (Fig. 1c). Specifically, the addition of an NHC catalyst to the ester moiety of unsaturated alkyne ester 1 leads to the corresponding acyl azolium intermediate I. The nucleophilic conjugated addition¹⁰ or 1,2-addition/Claisen

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rearrangement¹¹ of enamide **2** with intermediate **I** affords intermediate **II** that undergoes further reactions to eventually form unsaturated lactam adduct **3**⁰ (see the ESI† for the complete pathway) with the generation of the NHC catalyst. At a slightly elevated temperature in the same reaction mixture, adduct **3**⁰ undergoes isomerization to form hydroxyl pyridine **3** as the product.¹² The hydroxyl pyridine products (**3**) formed from our reactions can be readily transformed to useful bipyridines¹³ and other pyridine-derived amine functional molecules.¹⁴

3-Phenylpropynoic acid ester **1a** was chosen as the model substrate to react with the enamide precursor **2a** for the synthesis of multi-substituted hydroxyl pyridine **3a**. Various NHC pre-catalysts could mediate this transformation (Table 1, entries 1–3). The triazolium-type NHC pre-catalyst **B** bearing one mesityl group gave the desired product with the best yield (entry 2). We then decided to use catalyst **B** for further optimizations. Switching the base additive from NaHCO₃ to K₃PO₃ led to an increase in the product yield (entry 5). After screening different solvents we found that solvents with higher polarities could give the desired products in better yields, while solvents with lower polarities such as toluene and CH₂Cl₂ could hardly afford the pyridine product (entries 7–10). At last, we could get the product of **3a** in 83% isolated yield when carrying out the reaction in DMF using NHC **B** as the catalyst and K₃PO₄ as the base (entry 9).

With the optimized reaction conditions at hand, we then examined the reaction scope using different substituted substrates **1** and **2** (Table 2). Both electron-donating and electron-withdrawing groups were well tolerated on the benzene rings of substrate **1** (**3b** to **3f**). Substituents on the 4- and 3-positions of the benzene rings generally gave the corresponding products in good yields (*e.g.* **3b** to **3e**). Lower product yields were observed

with substrates **1** bearing 2-substituted benzene groups (*e.g.* **3f**). The aromatic phenyl group on substrate **1** could be switched to an aliphatic methyl group with the substituted pyridine product afforded in 67% yield (**3g**). Various substituents with different electronic properties could be installed on the benzene rings of the imide substrate **2** with the corresponding products afforded in moderate to good yields (**3h** to **3m**). The substituted benzene rings on substrate **2** could also be replaced with both hetero aromatic groups (**3n** to **3o**) and even simple aliphatic groups (**3p**), and the tri-substituted pyridine products could be afforded in moderate to good yields. To our delight, the 2-substituted imide substrate (**2q**) and the cyclic imide substrate (**2r**) could be also reacted smoothly with 3-phenylpropynoic acid ester **1a** through this process. Both of the tetra-substituted pyridine product (**3q**) and the dihydrobenzoquinoline product (**3r**) could be afforded in moderate yields under our current catalytic conditions. Switching the Ts protecting group on imine substrate **2** to an Ms (methanesulfonyl) group did not afford the desired product. Our attempt to prepare imine substrates with a Tf (Triflate) unit as the protecting group was unsuccessful.

The *O*-tosyl group on product **3a** could be switched to a good leaving group to afford **5** in excellent yield over 2 steps.¹⁵ Product **5** could be coupled with another 2-substituted pyridine compound **6** to produce the bi-pyridine molecule **7** (Fig. 2).¹⁶ Molecules containing the bi-pyridine structures have been frequently used as ligands in various transition metal catalyzed reactions (Fig. 1a, A).¹³

The dihydrobenzoquinoline product (**3r**) that was obtained from the cyclic imide substrate (**2r**) through our developed methodology could be converted to the benzoquinolin-2(1*H*)-one derivative **8** through a one-pot oxidation/deprotection reaction relay in 40% isolated yield (Fig. 3).¹⁷ Benzoquinolin-2(1*H*)-one **8** could be transformed to the quinoline-amine bi-dentate functional molecule **9** through reported procedures.¹³ Compound **9** has been proven to be an efficient ligand in transition metal catalysis (Fig. 1a, B).¹⁴

In summary, we have developed an NHC-catalyzed activation of α,β -unsaturated alkyne esters. This catalytic activation generates a previously unexplored unsaturated azolium ester intermediate bearing a reactive carbon–carbon triple bond. Under mild conditions, the catalytic reactions of alkyne esters and enamides effectively afford pyridine derivatives with important utilities. For example, our products can be transformed to bi-pyridines and related functional molecules that can be used as ligands in transition metal catalysis. The alkyne ester-derived azolium ester intermediate contains a carbon–carbon triple bond and shall exhibit rich chemical reactivities. We therefore expect that further study of this intermediate shall lead to a valuable set of reactions such as cascade reactions for quick access to sophisticated functional molecules.

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Table 1 Condition optimization^a

Entry	NHC	Base	Solvent	Yield ^b [%]
1	A	NaHCO ₃	THF	25
2	B	NaHCO ₃	THF	30
3	C	NaHCO ₃	THF	20
4	B	Na ₂ CO ₃	THF	37
5	B	K ₃ PO ₃	THF	40
6	B	TEA	THF	19
7	B	K ₃ PO ₃	Toluene	Trace
8	B	K ₃ PO ₃	CH ₂ Cl ₂	Trace
9	B	K ₃ PO ₃	DMF	83
10	B	K ₃ PO ₃	CH ₃ CN	39

^a Reaction conditions: **1a** (0.05 mmol), **2a** (0.10 mmol), NHC (0.01 mmol), base (0.05 mmol), solvent (0.5 mL), RT, 24 h. ^b Yields were isolated yields after column chromatography.

Table 2 Substrate scope^a

^a Reaction conditions as stated in Table 1, entry 9. Yields are isolated yields after purification using column chromatography.

Fig. 2 Construction of a bipyridine ligand from product 3a.

Fig. 3 Construction of a bipyridine ligand from product 3r.

Conflicts of interest

There are no conflicts to declare.

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