ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2017, 53, 13359

Received 18th October 2017,
Accepted 20th November 2017

DOI: 10.1039/c7cc08039e

rsc.li/chemcomm

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 studies[4] and regenerated great interest in recent years.[5] The most widely studied key intermediates involved in NHC catalysis include Breslow intermediates[6] derived from aldehydes and acyl azolium ester intermediates[7] derived from carboxylic esters (Fig. 1b). The NHC-bound intermediates derived from the related α,β-unsaturated aldehydes[8] and esters[9] 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 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 addition[10] or 1,2-addition/Claisen

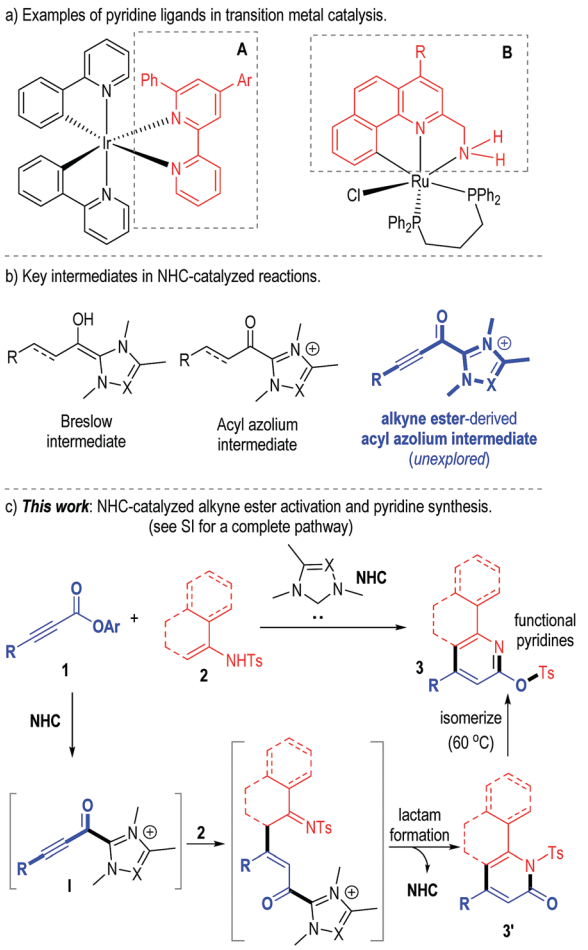

Fig. 1 Functional pyridines and our carbene-catalyzed synthetic method.

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† Electronic supplementary information (ESI) available. See DOI: 10.1039/c7cc08039e

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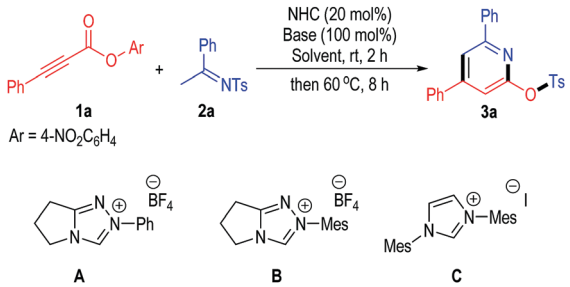
rearrangement[11] of enamide **2** with intermediate **I** affords intermediate **II** that undergoes further reactions to eventually form unsaturated lactam adduct **3′** (see the ESI† for the complete pathway) with the generation of the NHC catalyst. At a slightly elevated temperature in the same reaction mixture, adduct **3′** 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 bypyridines[13] 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 $NaHCO_3$ to K_3PO_3 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 CH_2Cl_2 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 K_3PO_4 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

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_2CO_3	THF	37
5	B	K_3PO_3	THF	40
6	B	TEA	THF	19
7	B	K_3PO_3	Toluene	Trace
8	B	K_3PO_3	CH_2Cl_2	Trace
9	**B**	**K_3PO_3**	**DMF**	**83**
10	B	K_3PO_3	CH_3CN	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.

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.

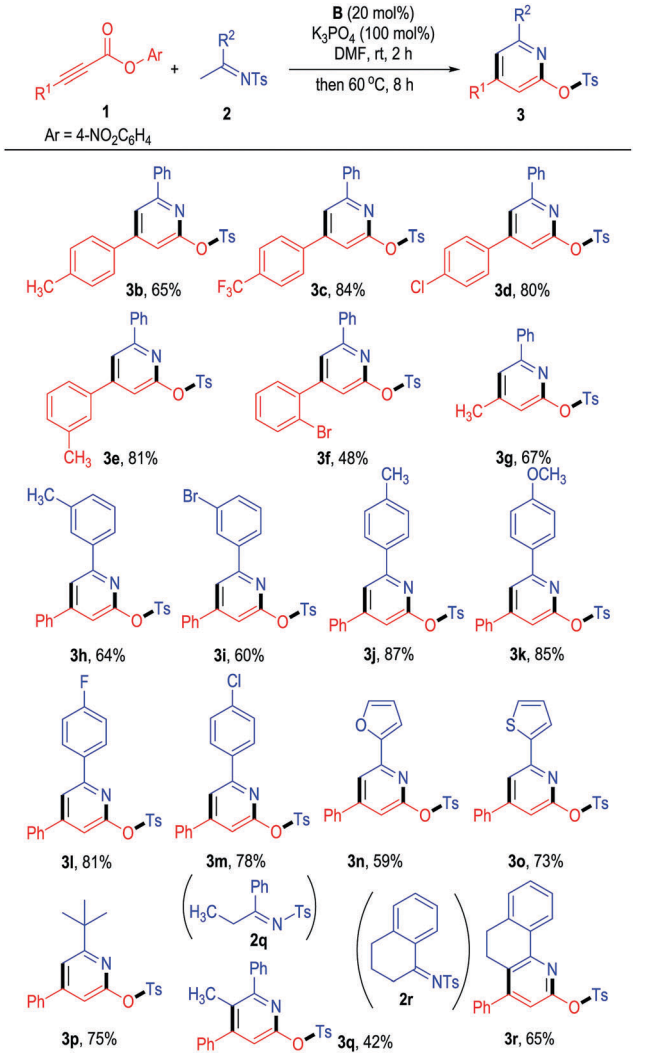
The *O*-tosyl group on product **3a** could be switched to a good leaving group to afford **5** in excellent yield over 2 steps.[15] Product **5** could be coupled with another 2-substituted pyridine compound **6** to produce the bi-pyridine molecule **7** (Fig. 2).[16] Molecules containing the bi-pyridine 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.

We acknowledge financial support by the National Natural Science Foundation of China (No. 21472028), the National Key Technologies R&D Program (No. 2014BAD23B01), the "Thousand Talent Plan", the 10 Talent Plan (Shicengci) of Guizhou Province, the Guizhou Province Returned Oversea Student Science and Technology Activity Program, Guizhou University (China) and

Table 2 Substrate scope[a]



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

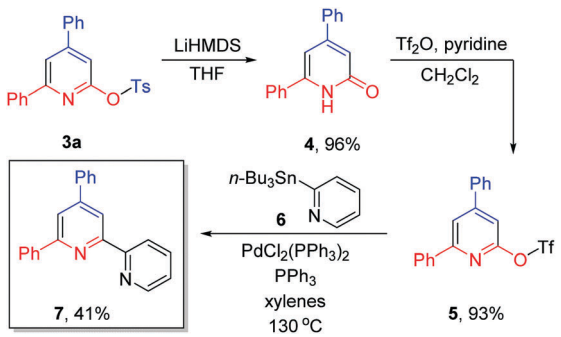


Fig. 2 Construction of a bipyridine ligand from product **3a**.

Singapore National Research Foundation (NRF-NRFI2016- 06), the Ministry of Education of Singapore (MOE2013-T2-2-003; MOE2016-T2-1-032; and RG108/16), A*STAR Individual Research Grant (A1783c0008), and Nanyang Technological University.

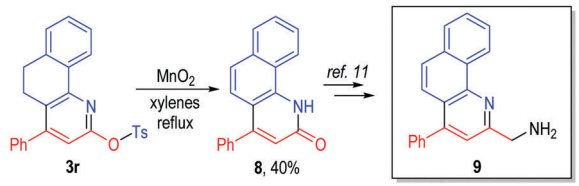


Fig. 3 Construction of a bipyridine ligand from product **3r**.

Conflicts of interest

There are no conflicts to declare.

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