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Umpolung coupling of pyridine-2-carboxaldehydes and propargylic carbonates *via* N-heterocyclic carbene/palladium synergetic catalysis†

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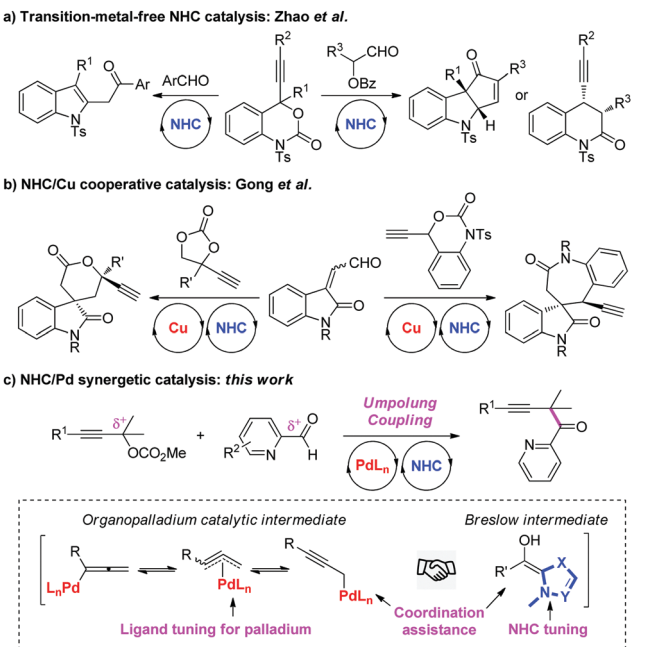
The umpolung cross-coupling reaction of pyridine-2-carboxaldehydes and propargylic carbonates has been developed for the first time through N-heterocyclic carbene/palladium cooperative catalysis with the judicious selection of the palladium catalyst, ligand and N-heterocyclic carbene, giving the propargylic ketones regioselectively.

Synergetic catalysis is a powerful synthetic strategy wherein diverse catalysts activate different substrates simultaneously in a single chemical transformation.[1] Recent progress on combining transition metal catalysis and organocatalysis has attracted considerable attention as it could enable unprecedented transformations not achieved by the use of transition metal catalysis or organocatalysis alone.[2] Nevertheless, the combination of N-heterocyclic carbene (NHC) catalysis with transition metal catalysis remains continuously challenging, possibly due to the reactivity mismatch of key organic and metallic intermediates, incompatibility of reaction conditions, and the fact that NHC is an important type of ligand that can bind to transition metals thus causing difficulties for their individual catalytic cycles, among others.[3] A number of groups have recently addressed these problems by judicious choices of transition metals, reaction conditions, competitive ligands and so on to achieve the synergetic catalysis of NHC and transition metal catalysts such as palladium,[4] ruthenium,[5] copper,[6] gold,[7] silver[8] and iridium.[9]

In comparison with the widely studied allylic electrophiles,[4,6,9] the propargylic electrophiles have been less explored in the cross-coupling reactions through NHC catalysis.[10] In 2018, Zhao and co-workers disclosed a transition-metal-free NHC-catalyzed asymmetric decarboxylative propargylic substitution/cyclization of aldehydes (Scheme 1a).[11] A series of skeletally diverse polycyclic products were approached selectively depending upon the categories of aldehydes and reaction conditions. In 2019, Gong *et al.* demonstrated an NHC/Cu cooperative catalysis enabling [3+3] and [3+4] cyclizations of isatin-derived aldehydes with propargylic electrophiles to access spirooxindoles selectively (Scheme 1b).[6b]

On the other hand, palladium-catalyzed cross-coupling reactions of propargylic electrophiles with varied nucleophiles are among the most successful tools for chemical bond formation in organic synthesis.[12] To the best of our knowledge, the combinative catalysis of palladium and NHC for the reaction



Scheme 1 NHC-catalyzed reactions of aldehydes with propargylic electrophiles.

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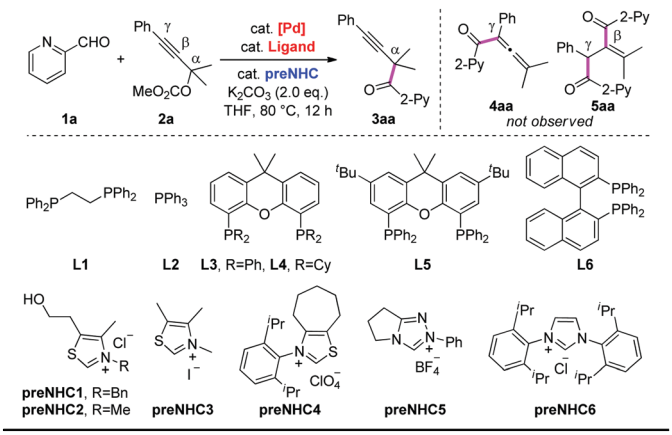
of propargylic electrophiles with aldehydes remains surprisingly unknown so far. We surmised that the reactivity match between organopalladium catalytic intermediates derived from the propargylic electrophile and Breslow intermediate from the aldehyde would be the key issue in view of the tetrasubstituted olefin characteristics of the Breslow intermediate, which will be challenging to react with the palladium species *via* inner- or outer-sphere mechanisms. The judicious tuning of the ligands for palladium and NHC for the Breslow intermediate and, importantly, rendering these two species close *via* coordination assistance[4f] might be essential to meet the above challenge. Herein, we report our efforts on the umpolung cross coupling of *o*-azaaryl aldehydes and propargylic carbonates by resorting to NHC/palladium synergetic catalysis, which represents the first example of the Breslow intermediate reacting with organopalladium derived from propargylic electrophiles.

We commenced our study from the model reaction of pyridine-2-carboxaldehyde **1a** with propargylic carbonate **2a** under the co-catalysis of NHC and palladium (Table 1). After the initial screening of the reaction conditions, it was found that the reaction gave the propargylic ketone product **3aa** in a 6% NMR yield in the presence of catalytic $Pd(OAc)_2$ with bidentate dppe **L1** as the ligand and a thiazolium precatalyst **preNHC1** (Table 1, entry 1). Encouraged by this result, the influence of the critical reaction parameters was investigated. First, commonly used palladium catalysts were examined and it was shown that $Pd(dba)_2$ was the most effective one (entries 2–4). Next, a series of ligands for palladium were tested. It revealed that monodentate triphenylphosphine (PPh_3, **L2**) failed to give the expected product (entry 5). In contrast, bisphosphorus ligands (**L3–L6**) mostly worked better for this reaction (entries 6–9) and xantphos (**L3**) could provide the product **3aa** in a 47% yield (entry 6). Finally, a survey of NHC precatalysts (**preNHC2–6**) indicated that only the thiazolium NHC precatalysts were compatible with the palladium catalysts affording the corresponding product **3aa** successfully (entries 10–14) and the combination of **preNHC2**, $Pd(dba)_2$ and xantphos **L3** was the optimal catalyst system (entry 10). After further evaluation of the reaction temperature, solvents, bases and reaction times, a 74% isolated yield of product **3aa** could be obtained when the reaction was performed at 65 °C for 24 h with $NaHCO_3$ as the base (entry 15). It should be noted that Pd-catalyzed reactions of propargylic electrophiles with hard nucleophiles typically afford allene products *via* the allenyl palladium intermediate (Scheme 1c), while reactions with soft nucleophiles may deliver alkene products through nucleophilic attack twice.[12] Meanwhile, regioselective formation of α-propargylic products has been reported in rare cases.[13] Remarkably, no γ-attack allene product **4aa** or β,γ-attack alkene product **5aa** was detected during the whole optimization process of the current NHC/Pd-catalyzed cross coupling of propargylic carbonate with the umpolung Brewslow intermediate, which demonstrated excellent regioselectivity in the reaction.

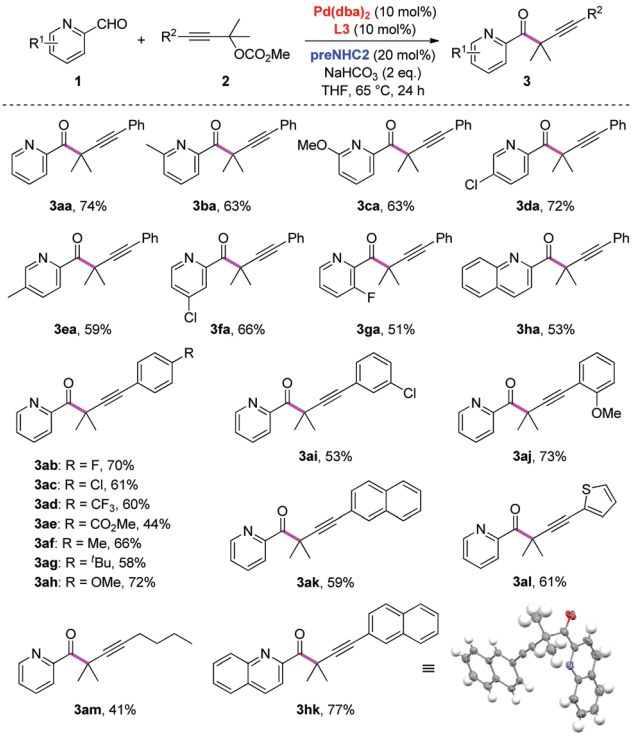
Table 1 Optimization of key reaction parameters[a]



Entry	[Pd]	Ligand	preNHC	Yield[b] (%)
1	$Pd(OAc)_2$	**L1**	**preNHC1**	6
2	$PdCl_2$	**L1**	**preNHC1**	21
3	$Pd(dba)_2$	**L1**	**preNHC1**	34
4	$Pd(PPh_3)_4$	**L1**	**preNHC1**	29
5	$Pd(dba)_2$	**L2**	**preNHC1**	n.d.
6	$Pd(dba)_2$	**L3**	**preNHC1**	47
7	$Pd(dba)_2$	**L4**	**preNHC1**	4
8	$Pd(dba)_2$	**L5**	**preNHC1**	42
9	$Pd(dba)_2$	**L6**	**preNHC1**	32
10	$Pd(dba)_2$	**L3**	**preNHC2**	56
11	$Pd(dba)_2$	**L3**	**preNHC3**	28
12	$Pd(dba)_2$	**L3**	**preNHC4**	39
13	$Pd(dba)_2$	**L3**	**preNHC5**	n.d.
14	$Pd(dba)_2$	**L3**	**preNHC6**	n.d.
15[c]	$Pd(dba)_2$	**L3**	**preNHC2**	74[d]

[a] Reaction conditions unless otherwise noted: **1a** (0.4 mmol), **2a** (0.2 mmol), [Pd] catalyst (10 mol%), ligand (10 mol%), preNHC (20 mol%), K_2CO_3 (0.4 mmol), THF (3.0 mL) and under a nitrogen atmosphere. [b] Yields determined by ^1H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. [c] $NaHCO_3$ was used instead of K_2CO_3 at 65 °C for 24 h. [d] Isolated yield on 0.5 mmol scale.

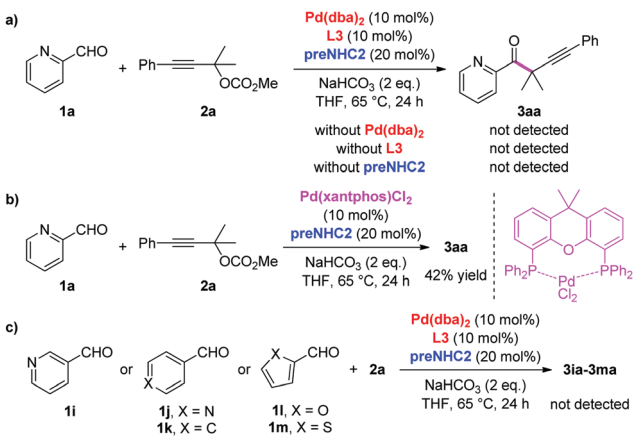
With the optimized conditions in hand, we first examined the reactivity of various substituted pyridine-2-carboxaldehydes using propargylic carbonate **2a** as a model reaction partner (Scheme 2). Aldehydes **1** bearing different substituents at the 2-, 3-, 4- or 5-positions of the pyridine ring all gave the desired products **3aa–ga** in good yields with sole regioselectivity. In addition, quinoline-2-carbaldehyde (**1h**) was also suitable for the reaction to afford the corresponding product **3ha** in a synthetically useful yield. Then, the scope of propargylic carbonates **2** to react with pyridine-2-carboxaldehyde **1a** was examined. Substrates bearing either electron-deficient or electron-rich groups on the benzene ring could participate in the umpolung coupling, affording the corresponding ketones smoothly (**3ab–aj**). Functional groups such as fluoro, chloro, trifluoromethyl, alkyl, methoxy and ester were all tolerated at the *para*-, *meta*- or *ortho*-positions of aryl propargylic carbonates. Moreover, propargylic carbonates with naphthyl, thienyl or *n*-butyl groups also reacted with **1a** successfully to give the desired products in decent yields (**3ak–am**). Unfortunately, variations in the dimethyl groups of the propargylic carbonates have been unsuccessful so far, which reflects the steric importance at this position for the reaction (see Scheme S1 in ESI†). In addition, the structure of product **3hk** was confirmed



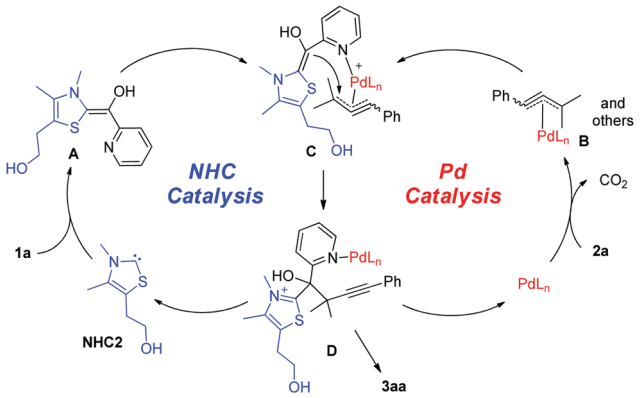
Scheme 2 Scope of *o*-azaaryl aldehydes and propargylic carbonates.[a]
[a] Reaction conditions: **1** (1.0 mmol), **2** (0.5 mmol), $Pd(dba)_2$ (10 mol%), **L3** (10 mol%), **preNHC2** (20 mol%), $NaHCO_3$ (1.0 mmol), and THF (6.0 mL) under a nitrogen atmosphere. Isolated yields are shown.

unambiguously by single-crystal X-ray diffraction analysis (CCDC†: 2068444).

To gain insights into the possible reaction pathways operating in the NHC/Pd synergetic catalysis, control experiments were first conducted. It was shown that no product **3aa** was detected in the absence of either $Pd(dba)_2$, the ligand of **L3** or **preNHC2** under otherwise identical conditions (Scheme 3a), which highlights the essential roles of these key components for the umpolung coupling. Next, the preformed palladium/xantphos complex, [Pd(xantphos)Cl_2], was subjected to the reaction and the propargylic ketone product **3aa** could be obtained in 42% yield



Scheme 3 Mechanistic experiments.



Scheme 4 Proposed reaction mechanism.

(Scheme 3b). Finally, in order to verify the importance of *ortho*-pyridine coordination assistance, pyridinecarboxaldehydes **1i** and **1j** with N-atoms at other positions, benzaldehyde **1k**, 2-furaldehyde **1l** and 2-thiophenecarboxaldehyde **1m** were tested in the reactions (Scheme 3c) and only benzoin by-products were found after the reactions, which indicated the indispensible role of the *ortho* N-coordination of pyridine towards the palladium center for the reaction.

A plausible reaction mechanism comprising two fused catalytic cycles, namely NHC and palladium catalysis, is depicted in Scheme 4. The Breslow intermediate **A** is first formed by the reaction of **preNHC2** and the aldehyde **1a** in the NHC catalytic cycle. Meanwhile, the reaction of the palladium catalyst with propargylic carbonate **2a** generates the η^1-, η^3-propargylic palladium or allenyl palladium complexes **B** in the Pd catalytic cycle. Then, the above two intermediates approach each other through coordination assistance of the N-atom in the pyridine towards Pd and form the key palladium complex **C**. Thereafter, intermediate **D** is generated *via* an intramolecular nucleophilic attack of the Breslow intermediate at the α-position of η^3-propargylic palladium. Finally, the intermediate **D** releases the desired product **3aa** and regenerates free **NHC2** and the palladium catalyst for the next catalytic cycles. Currently, the reaction pathways through the allenyl palladium complex cannot be ruled out in the reaction.

In summary, the umpolung cross-coupling reaction of *o*-azaaryl carboxaldehydes and propargylic carbonates has been developed for the first time through NHC/palladium synergetic catalysis. Thus, the propargylic ketones were accessed directly and regioselectively without the formation of allenyl or alkenyl ketone by-products. The judicious choices of the palladium catalyst bearing a xantphos ligand and the thiazolium-derived NHC catalyst are crucial for the successful merging of the two NHC and palladium catalytic cycles. Further studies on NHC/palladium synergetic catalysis are ongoing in our laboratories.

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Conflicts of interest

There are no conflicts to declare.

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