Chinese Chemical Letters 36 (2025) 110334

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

2,3-Arylacylation of allenes through synergetic catalysis of palladium and *N*-heterocyclic carbene

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ARTICLE INFO

Article history:
Received 3 March 2024
Revised 20 July 2024
Accepted 10 August 2024
Available online 12 August 2024

Keywords:
Allenes
Arylacylation
Palladium
N-Heterocyclic carbene
Synergetic catalysis

ABSTRACT

An unprecedented 2,3-arylacylation reaction of allenes with aryl iodides and aldehydes was developed by resorting to Pd/NHC synergetic catalysis. It is the first time that allene was introduced into transition metal and NHC synergetic catalysis, which demonstrated a versatile three-component reaction pattern, thus enabling two C-C bonds forged regioselectively in the reaction. The important reaction intermediates were successfully captured and characterized by HRMS analysis, and the migrative insertion of allene to the Ph-Pd species was identified as the reaction rate-limiting step by kinetic experiments.

Allenes, bearing two adjacent perpendicular π-bonds in their core structure, have stood out as privileged 3-carbon building blocks in organic synthesis, which are different from traditional 2-carbon units of olefins and alkynes in term of reactivity, regioselectivity and stereoselectivity [1–7]. Among versatile reactions of allenes with varied organic substrates, the transformations of allenes with aldehydes are of particular interest due to their straightforward access to important allylic and homoallylic alcohols with the power of transition metal catalysis. In general, a nucleophilic transition metal species (Nu-TM, Nu = H, B, C, *etc.*) was formed *in situ*, which promoted the coupling of allene and aldehyde *via* mechanism of either allylic metal addition to aldehyde or oxidative cyclization of C=C and C=O on the metal center, affording 1-, 2-, and/or 3-position bonded allylic and/or homoallylic alcohols (Fig. 1a). On the other hand, *N*-heterocyclic carbenes (NHCs) are well established organocatalysts which can activate aldehyde in an "umpolung" manner as a nucleophile *via* Breslow intermediate [8–11]. Ma and coworkers reported a NHC-catalyzed 1,2-hydroacylation of allenones with aldehydes followed by intramolecular cyclization leading to cyclopent-2-enone-4-ols eventually (Fig. 1b) [12]. The "umpolung" Stetter-type reaction of Breslow intermediate from aldehyde to electron-deficient allenone was key to this transformation. Of note, NHC-organocatalyzed reactions of unbiased allenes with aldehydes haven't been reported yet.

Synergetic catalysis is one of the most widely used strategies in current organic synthesis where two or more catalytic systems cooperate to achieve unexplored reaction routes, not accessible by the single system [13,14]. The past decade has seen creative combinations of transition metals (TM) and *N*-heterocyclic carbenes in synergetic catalysis where versatile TM catalytic species merged with varied NHC catalytic intermediates [15,16]. For instance, The TM/NHC-enolate based synergetic catalysis enabling functionalization at α-C of aldehydes were reported by Scheidt, Glorius, Du, Deng and others [17–21]. The TM/NHC-homoenolate synergetic systems with functionalization at β-C of α,β-unsaturated aldehydes were reported by Glorius, Deng, Ohmiya and Gong [22–35]. The TM/NHC-Breslow intermediate combined synergetic systems forming C-C bonds at the carbonyl position of an aldehyde were achieved by Liu, Ohmiya, Wang and Ye, among others [36–42]. Though successful, challenges still remain in this field, such as exploring new applicable substrates, incorporation of the third reaction component forming two C-C bonds and regioselectivity control in complex reactions. Herein, we described the unprecedented 2,3-arylacylation of allenes with aldehydes and aryl iodides (ArI) through Pd/NHC synergetic catalysis (Fig. 1c). Significantly, allenes were used as effective substrates for the first time in TM/NHC synergetic catalysis and two C-C bonds were forged regioselectively.

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https://doi.org/10.1016/j.cclet.2024.110334
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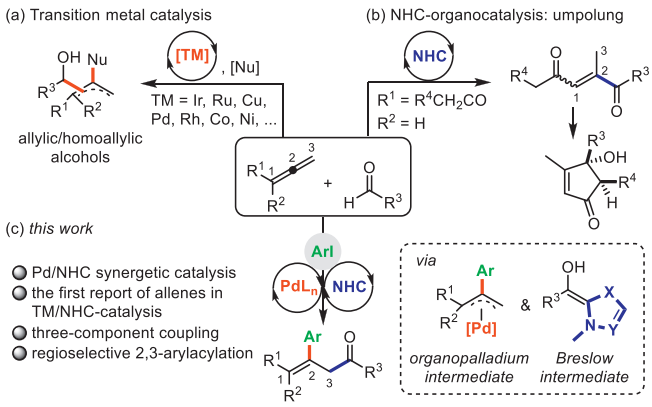


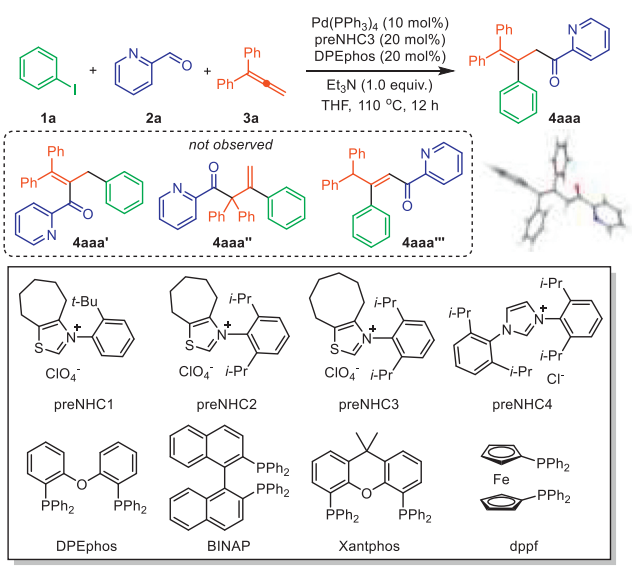
Fig. 1. Transition metal and NHC catalysis with allenes and aldehydes.

We set out our study with iodobenzene **1a**, picolinaldehyde **2a** and 1,1-diphenylallene **3a** as model substrates to test our hypothesis (Table 1). After a range of optimizations, it was proved that the 2,3-arylacylation product **4aaa** was successfully separated from the reaction mixture (entry 1) and the product structure was confirmed by single-crystal X-ray diffraction analysis (CCDC: 2336712 for **4aaa**). It is worth noting that other regioisomers such as 2,3-acylarylation product **4aaa'** and 1,2-acylarylation product **4aaa"** weren't observed in the reaction. Another possible product **4aaa"'** which might result from C-C double bond migration of **4aaa** was not found either. The absence of these side products demonstrated an excellent regioselectivity in this three-component reaction. Such delightful results encouraged us to explore the influence of varied reaction conditions for further optimizations of product yield. The screening of preNHCs showed the importance of perchlorate thiazolium preNHCs as other types of NHCs such as those derived from imidazolium and triazolium salts were not effective towards this reaction (entries 2–4). The product yields benefited from greater steric hindrance of aryl substituents of preNHCs with 2,6-diisopropylphenyl group being the best. The size of fused rings on preNHCs seemed to influence the reaction outcome where preNHCs of six- and eight-membered fused rings gave better results than that of six-membered ring. Lower yields of product were found when changing bases and solvents (entries 5–8). Varied phosphine ligands in particular bisphosphorous ones were tested and DPEphos was shown as the best among these ligands (entries 9–10). The palladium catalysts were further screened and Pd(0) catalysts could provide better product yields than that of the Pd(II) catalyst (entries 11 and 12). The reaction conditions were finalized as $Pd_2(dba)_3$, DPEphos, preNHC3, 110 °C, 18 h with Et_3N as the base and gave product **4aaa** in a decent isolated yield of 73%.

With the optimal reaction conditions in hand, we started to explore the scopes of this reaction (Fig. 2). Aryl iodide was first examined in the aspects of electronic and steric effects with aldehyde **2a** and allene **3a** as its standard reaction partners. It turned out that aryl iodides bearing electronically-varied substituents such as halogen, methoxy, cyano, trifluoromethyl, carbonyl, and nitro groups at the *para*-position delivered the corresponding 2,3-arylacylation products in moderate to good yields (**4baa-iaa**). Of note, small amounts of **4aaa** were isolated from the reactions of **4baa**, **4caa** and **4iaa**. It was supposed that aryl iodides bearing strong electronic-effect groups were susceptible to undergo aryl-exchange between aryl iodide and the DPEphos ligand, which is similar to the phenomenon reported by Morandi's group in 2017 [43]. Such aryl-exchange reactions could be avoided by utilizing alkyl phosphine ligands like tricyclohexylphosphine in cost of the product yield. While bromobenzene usually undergoes oxidation addition with Pd(0), the C-Br functionality could be tolerated in this reaction (**4eaa**). Substituents at *meta*-positions of aryl iodides had no obvious effects on the reaction outcome (**4jaa-maa**). However, *ortho*-substituted iodobenzenes showed low reactivity in this protocol (**4naa**), which indicated sensitiveness toward steric hindrance in the arylation step. Heteroaryl iodides were also found suitable for this reaction giving the expected products in synthetically useful yields (**4oaa-qaa**). It is noteworthy that alkenyl iodide was applicable in the reaction affording the desired products (**4raa**) as *Z*- and *E*-isomers.

Then the scope of aldehydes **2** was examined with phenyl iodide **1a** and allene **3a** as model substrates (Fig. 3). It turned out that a series of substituted 2-pyridinecarboxaldehydes at varied positions were suitable for the reaction (**4aba-ga**), while 6-methyl-2-pyridinecarboxaldehyde gave the best yield of 90%. Other heteroaryl aldehydes like 2-quinolinecarboxaldehyde, thiazole-4-carboxaldehyde and 1*H*-benzimidazole-2-carboxaldehyde could also produce the corresponding products smoothly (**4aha-ka**). Aliphatic aldehydes were applied into this reaction and the expected products could be isolated in relatively low yields (**4ala-ma**). Of note, aromatic aldehydes bearing strong electron-withdrawing groups could generate trace amount of products,

Table 1
Optimization of reaction conditions.[a]



Entry	Variation of standard conditions	Yield (%)[b]
1	None	78
2[c,d]	preNHC1 instead of preNHC3	46
3[c,d]	preNHC2 instead of preNHC3	53
4[c,d]	preNHC4 instead of preNHC3	n.d.
5	Cs_2CO_3 instead of Et_3N	12
6	Toluene instead of THF	70
7	MeCN instead of THF	46
8	Xantphos instead of DPEphos	70
9	dppf instead of DPEphos	67
10[d]	BINAP instead of DPEphos	70
11	$Pd(OAc)_2$ instead of $Pd(PPh_3)_4$	45
12[e]	$Pd_2(dba)_3$ instead of $Pd(PPh_3)_4$	75 (73)[f]

[a] Standard conditions: $Pd(PPh_3)_4$ (10 mol%), preNHC3 (20 mol%), DPEphos (20 mol%), Et_3N (1.0 equiv.), THF (2 mL), iodobenzene **1a** (0.2 mmol), 2-pyridinecarboxaldehyde **2a** (0.3 mmol), 1,1-diphenylallene **3a** (0.2 mmol), 110 °C, 18 h.
[b] ^1H NMR yield was determined with methyldiphenylsilane as an internal standard.
[c] BINAP (20 mol%) as ligand.
[d] Toluene (2 mL) as solvent.
[e] 5 mol% $Pd_2(dba)_3$ was added.
[f] Isolated yield.

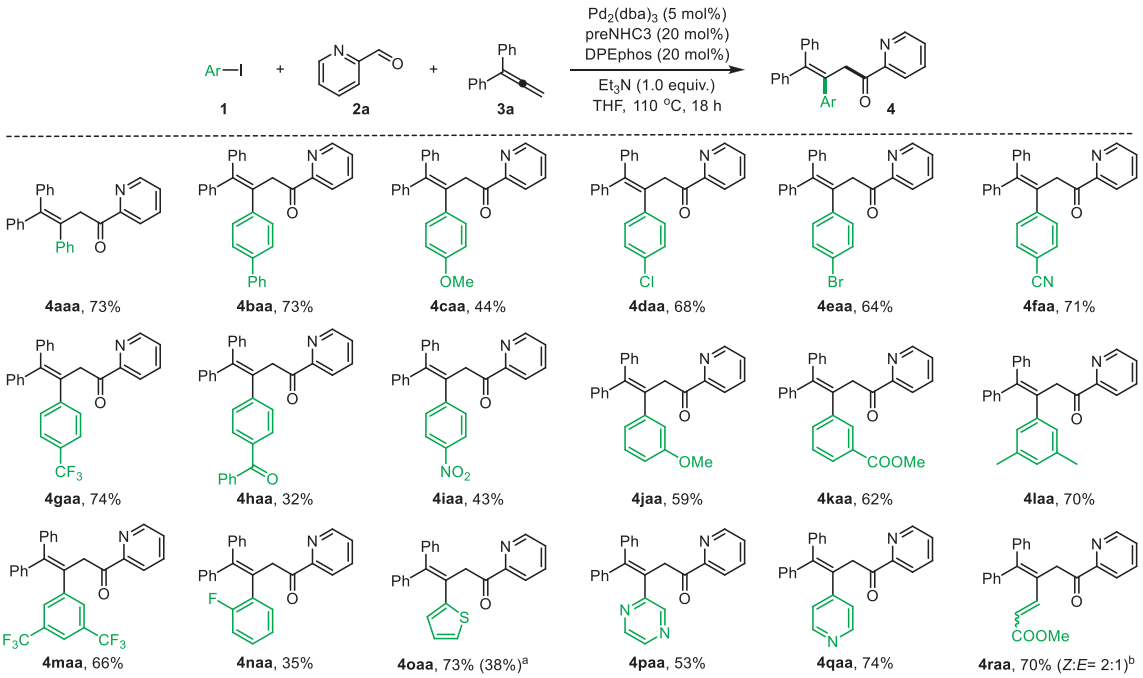


Fig. 2. Scope of aryliodides. Reaction conditions: **1** (0.3 mmol), **2a** (0.45 mmol), **3a** (0.3 mmol), $Pd_2(dba)_3$ (0.015 mmol), preNHC3 (0.06 mmol), DPEphos (0.06 mmol), Et_3N (0.3 mmol), THF (3 mL) under nitrogen atmosphere, isolated yields are shown. [a] Using PCy_3 as ligand, isolated yield is shown. [b] *Z*/*E* ratio was determined by ^1H NMR.

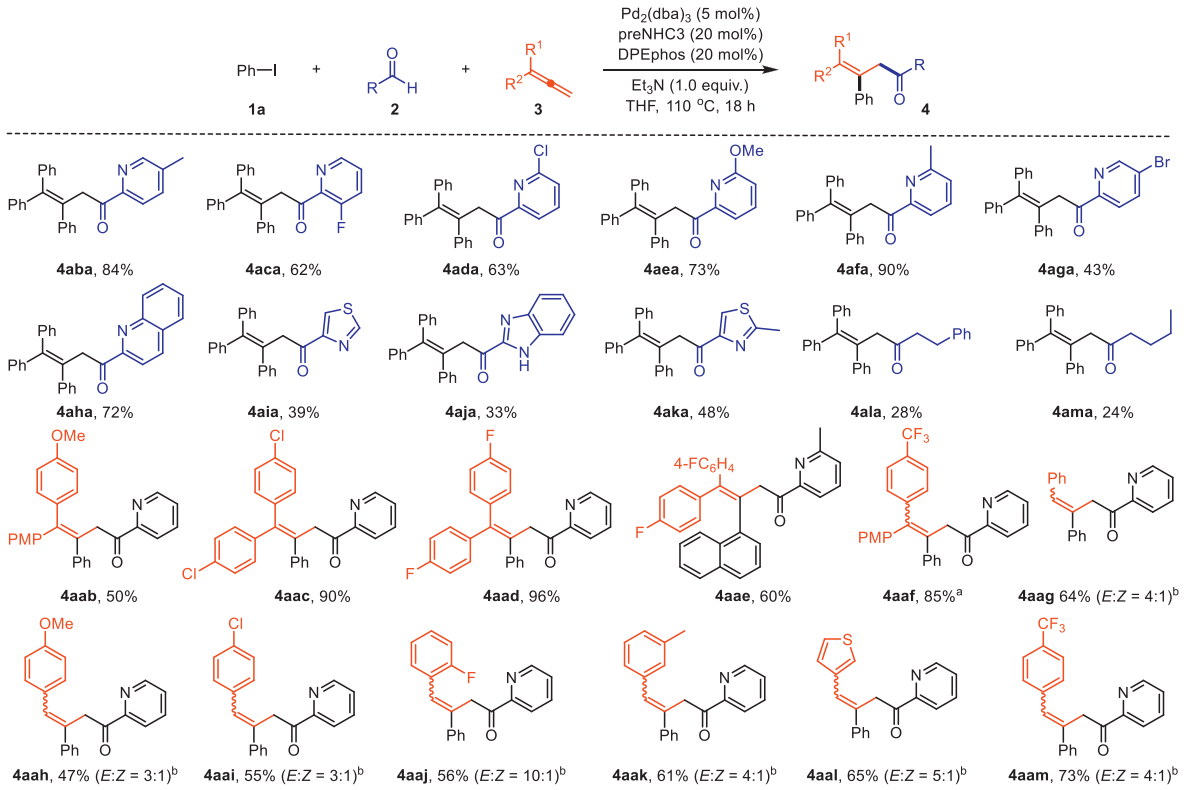


Fig. 3. Scope of aldehydes and allenes. Reaction conditions: **1a** (0.3 mmol), **2** (0.45 mmol), **3** (0.3 mmol), $Pd_2(dba)_3$ (0.015 mmol), preNHC3 (0.06 mmol), DPEphos (0.06 mmol), Et_3N (0.3 mmol), THF (3 mL) under nitrogen atmosphere, isolated yields are shown. [a] Mixed products with 1:1 *Z*/*E* ratio. [b] The *E*/*Z* ratio was determined by ^1H NMR. PMP = *para*-methoxyphenyl.

which could be detected by GC–MS. Unfortunately, benzaldehyde was reluctant to react with aryl iodide and allene in this protocol.

Finally, the scope of allenes was interrogated (Fig. 3). While 1,1-di(4-methoxyphenyl)−1,2-diene led to a slight decrease in product yield, allenes like 1,1-di(4-halophenyl)−1,2-diene and 1-(4-methoxyphenyl)−1-((trifluoromethyl)phenyl)−1,2-diene gave dramatically increased yields of products as high as 96% (**4aab-f**) (CCDC 2336713 for **4aae**). When mono-substituted allenes were applied to this reaction, both *Z*- and *E*-configured isomers were formed in the reaction (**4aag-m**). The substituents on the phenyl group of allenes would affect the outcome of the reaction. For instance, (2-fluorobenzyl)−1,2-diene gave a good *E*/*Z* ratio of 10:1 in the product (**4aaj**), while other 4-substituted phenyl-1,2-dienes delivered mediocre *E*/*Z* ratios of around 4:1 of products.

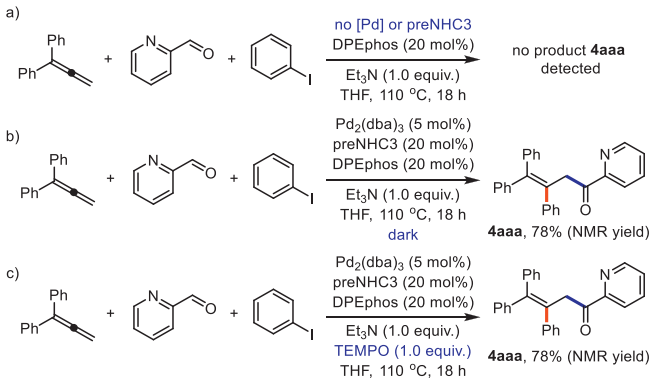


Fig. 4. Control experiments. (a) Reactions without catalysts. (b) Reaction without light. (c) Reaction with a radical scavenger.

To probe the possible reaction mechanism, several control experiments were carried out. The reactions without addition of the palladium catalyst or preNHC3 showed that no desired product was obtained after reaction (Fig. 4a), which indicated the critical synergistic effect of Pd/NHC catalysts. The reaction was also conducted in the absence of light and the product yield of **4aaa** was unaffected (Fig. 4b). Furthermore, a radical scavenger TEMPO was added to the reaction and it had no influence on the product yield (Fig. 4c). These experiments suggested that the reaction was unlikely to occur through a radical pathway.

To capture the key reaction intermediates, ESI-HRMS analysis of the crude reaction mixture was done when the reaction was stopped after 1.5 h under otherwise the same reaction conditions (Fig. 5). The 2-phenylated allylic palladium intermediate **Int-1** was detected at *m/z* 913.19904 with DPEphos ligating to the palladium center. The characteristic isotope peaks could match the calculation simulation of its formula. There was also a group of peaks around *m/z* 929.19507, which was in agreement with characteristics of **Int-1O**, the possible oxidation species of **Int-1**. It might be generated during post processing of the reaction mixture. The possible NHC-ligating allylic-Pd intermediate was not found in HRMS,

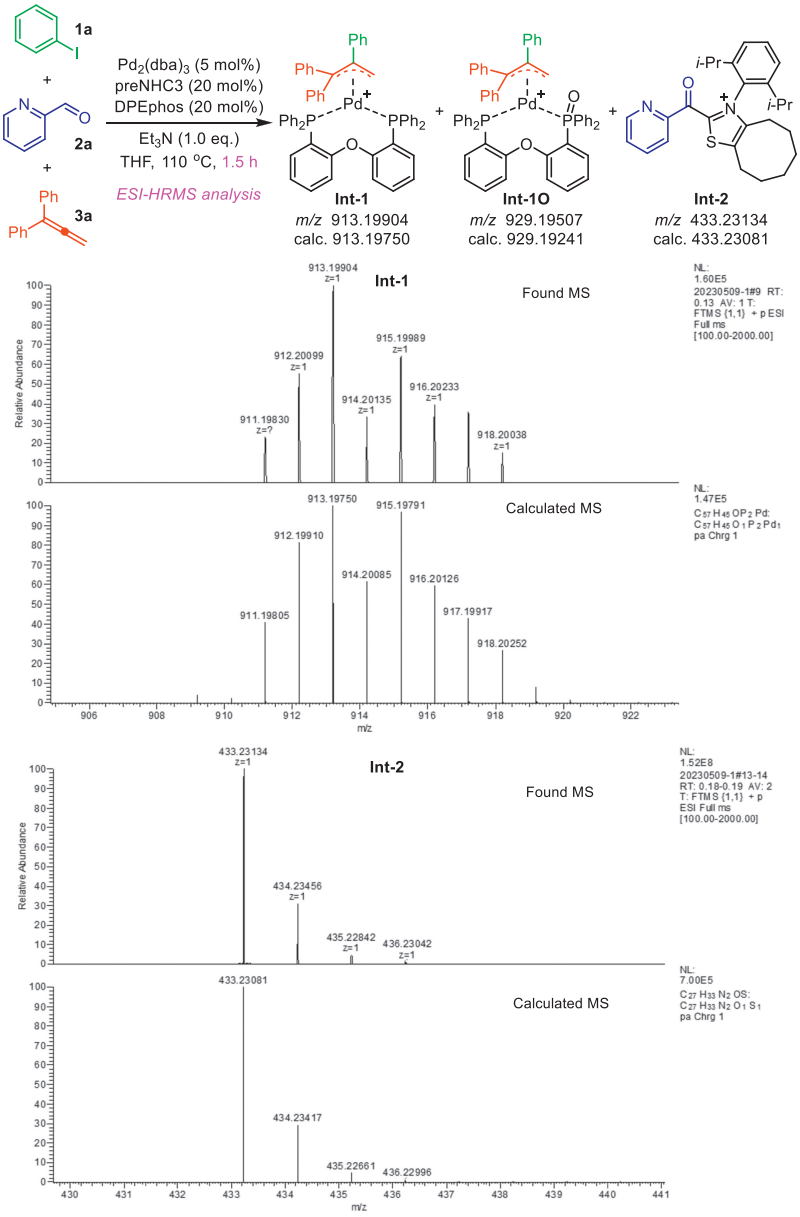


Fig. 5. ESI-HRMS analysis to capture Pd- and NHC-intermediates.

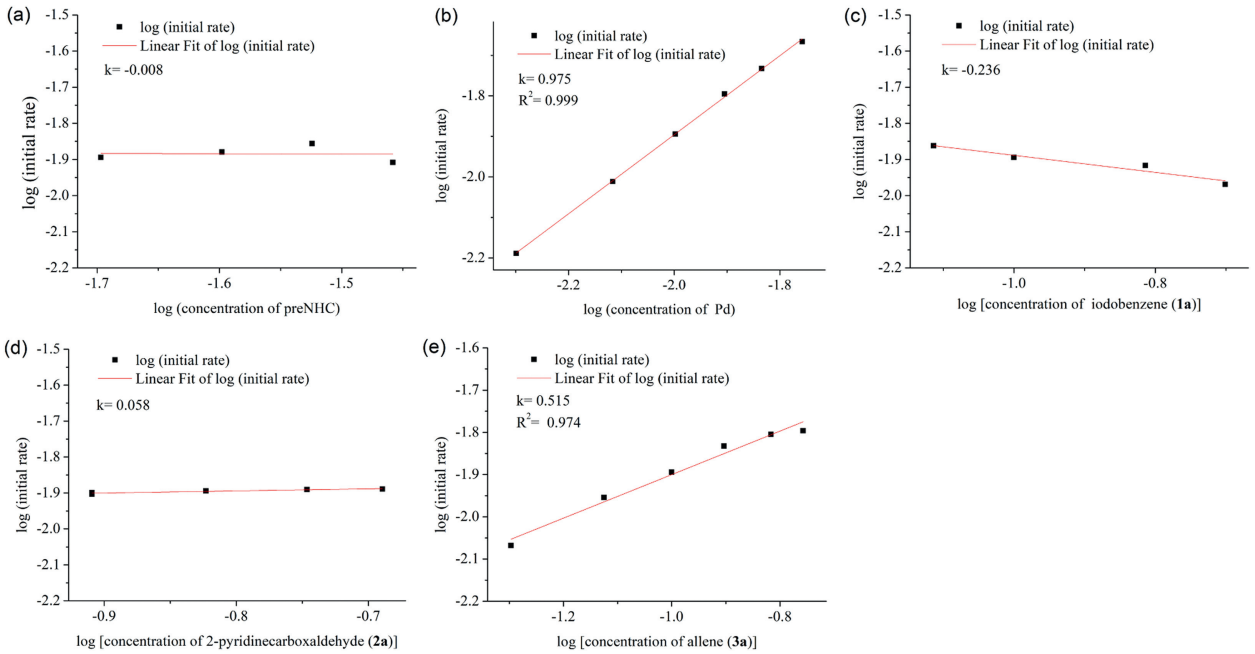


Fig. 6. Measurement of reaction orders of catalysts and reactants. (a) Plot of initial rates *vs.* preNHC concentration. (b) Plot of initial rates *vs.* the Pd-catalyst concentration. (c) Plot of initial rates *vs.* iodobenzene **1a** concentration. (d) Plot of initial rates *vs.* aldehyde **2a** concentration. (e) Plot of initial rates *vs.* allene **3a** concentration.

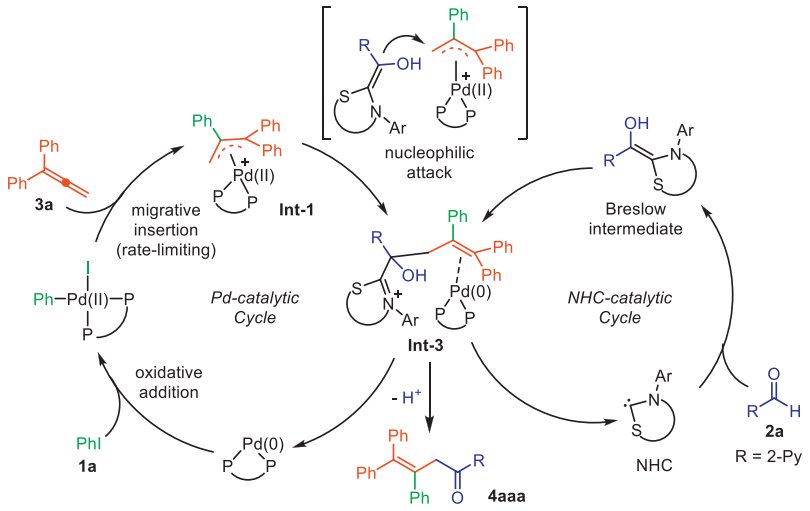


Fig. 7. Proposed mechanism for the reaction.

which might indicate NHC as an organocatalyst, rather than a ligand for palladium [29,44]. Meanwhile, the acylazolium intermediate **Int-2** that derived from the oxidation of Breslow intermediate could be found at *m/z* 433.23134. Because the Breslow intermediate was uncharged, susceptible to oxidation and low in concentration, it's possible that the Breslow intermediate was transformed into acylazolium species **Int-2** during the processes after reaction. Besides, we didn't find intermediates in which both the 2-phenylated allyl group and the Breslow intermediate ligated to the palladium center. It hinted that the reaction between 2-phenylated allylic palladium and the Breslow intermediate occurred possibly through an outer-sphere mechanism.

Finally, the reaction orders of both catalysts and reactants were measured through a series of *in situ* ^{1}H NMR experiments in order to find out the rate-determining step of this synergetic catalytic reaction and gain a deeper insight into the reaction mechanism (Fig. 6). As a result, the reaction showed first-order dependence on the Pd catalyst whilst zero-order dependence on the NHC catalyst, which suggested that the rate-limiting step lied in the Pd-catalytic cycle rather than the NHC-catalytic cycle. The zero-order dependence on phenyl iodide **1a** indicated the oxidative addition of aryl iodide to palladium should not be the rate-limiting step. The zero-order dependence on aldehyde **2a** suggested the formation of Breslow intermediate should also not be rate-limiting. The 1/2-order dependence on allene **3a** indicated that the insertion of allene to the Ph-Pd bond was the possible rate-limiting step. The kinetics and key reaction intermediates of the current reaction were in contrast to those of the well-studied Pd/NHC synergetic system reported by Glorius where the rate-limiting step lied in both Pd- and NHC-catalytic cycles with NHC being as both a ligand and an organocatalyst [44].

Based on the mechanistic study and literature clues, we speculated a Pd/NHC synergetic catalysis profile as shown in Fig. 7. In the Pd-catalytic cycle, the oxidative addition occurred first between the Pd(0) species and iodobenzene **1a** to form an aryl Pd(II) species, which then reacted with allene **3a** to afford 2-phenylated

allylic palladium intermediate **Int-1** *via* migrative insertion of allene into the Pd-C bond. Meanwhile in the NHC-catalytic cycle, the Breslow intermediate was produced from aldehyde **2a** and NHC. It further underwent nucleophilic attack at the 3-position of **Int-1** giving **Int-3**, which eventually released product **4aaa** and regenerated free NHC and the Pd(0) catalyst for the next catalytic cycles.

In conclusion, an unprecedented 2,3-arylacylation reaction of allenes with aryl iodides and aldehydes was developed by resorting to Pd/NHC synergetic catalysis. It's the first time that allene was introduced into transition metal and NHC synergetic catalysis, which demonstrated a versatile three-component reaction pattern of this synergetic catalysis, thus enabling two C–C bonds forged regioselectively in the reaction. The important reaction intermediates were successfully captured and characterized by HRMS analysis, and the migrative insertion of allene to the Ph-Pd species was identified as the reaction rate-limiting step by kinetic experiments. Further studies of novel reactions through transition metal and NHC synergetic catalysis is underway in our group.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Zhao Gu: Writing – original draft, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Yunhui Yang:** Writing – review & editing, Project administration, Methodology, Investigation. **Song Ye:** Project administration. **Congyang Wang:** Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Funding acquisition, Conceptualization.

Acknowledgments

Financial support from the National Natural Science Foundation of China (Nos. 21831008, 22025109, 22101286), CAS Project for Young Scientists in Basic Research (No. YSBR-050), Beijing National Laboratory for Molecular Sciences (No. BNLMS-CXXM-201901) and the State Key Laboratory of Fine Chemicals, Dalian University of Technology (No. KF2102) are gratefully acknowledged.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2024.110334.

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