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A cooperative *N*-heterocyclic carbene/palladium catalysis system†

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N-heterocyclic carbenes (NHC) have been extensively studied as organocatalysts and ligands for transition metals, but the successful integration of NHCs and late transition metals in cooperative catalysis remains an underexplored area. We have developed a cooperative palladium-catalyzed allylation of NHC-activated aldehydes to access a variety of 3-allyl dihydrocoumarin derivatives. Kinetic experiments support a cooperative pathway for this transformation.

Introduction

The integration of two distinct catalytic pathways in a single flask is a powerful strategy in chemical synthesis.[1] Through independent activation of separate nucleophilic and electrophilic species, this synergistic approach makes possible previously inaccessible transformations and can improve existing chemical reactions. In particular, the fusion of transition metal and organocatalysis concepts has become a major research endeavor over the last decade.[1] Although there has been remarkable progress in this area, the combination of *N*-heterocyclic carbenes (NHCs)[2] with late transition metals remains underexplored, and more importantly, quite counter-intuitive given the strong propensity for NHCs to bind to transition metals with high affinity. While cooperative catalysis with NHCs and Lewis or Brønsted acids has been shown to increase reactivity and afford products with unprecedented levels of selectivity,[3] the incorporation of NHCs with late transition metals (TMs) presents a considerable challenge due to the potential for the formation of stable NHC–TM complexes (Fig. 1),[4] which do not possess the desired catalytic activity.

Plan

Given the background above, we were motivated by the opportunity to harness the unconventional reactivity of NHCs with the assistance of transition metals to effect new chemical transformations. A highly desired objective is the addition of NHC-bound nucleophiles to TM-activated electrophiles. As proof of a concept to this general approach, the combination of Pd-catalyzed allylations[5] with α,β-unsaturated aldehydes under carbene catalysis conditions could facilitate rapid access to synthetically valuable products, specifically dihydrocoumarin derivatives. A number of methods for accessing dihydrocoumarins have been developed[6] as this structural motif is prevalent in natural products and biologically relevant small molecules.[7] However, few methods exist to prepare 3-allylated dihydrocoumarins,[8] and surprisingly the direct allylation of dihydrocoumarins is un-explored.[9] It is clear that new catalytic methods to directly access this important molecular scaffold are necessary to facilitate structural diversification and efficient assembly of bioactive compounds. Herein we report the development of the novel cooperative NHC/TM strategy for the synthesis of allylated dihydrocoumarin derivatives through allylation and subsequent acylation of aldehyde **1a**. The activation of the α,β-unsaturated aldehyde moiety within **1a** through NHC catalysis and capture of a cationic Pd[π-allyl]L_n

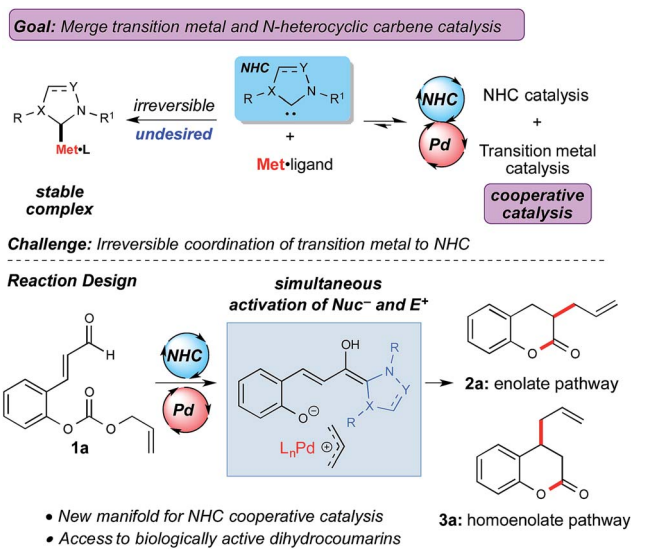

Fig. 1 NHC/transition metal cooperative catalysis.

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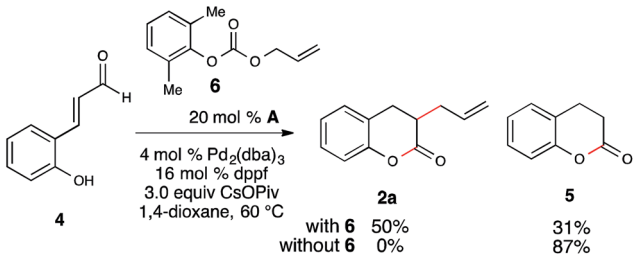
complex in a cooperative fashion facilitates access to dihydrocoumarins **2a** or **3a** through an enolate or homoenolate pathway, respectively.

Results and discussion

Initially, we investigated the intermolecular reaction of **4** with allyl carbonate **6** using our proposed cooperative NHC–Pd catalysis system (eqn (1)). After extensive optimization, allylated dihydrocoumarin **2a** could be obtained in 50% yield, but with dihydrocoumarin **5** as a competing side product in 31% yield. Further investigation showed that omitting **6** from the reaction mixture yielded the undesired dihydrocoumarin **5** in 87% yield. With the robustness of this competing pathway uncovered,[6e] an alternative strategy was deemed necessary to move forward with our reaction development.

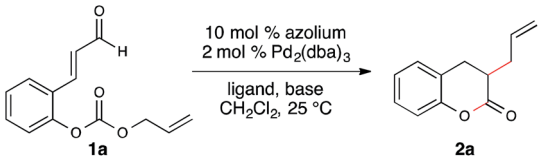


(1)

We hypothesized that the phenolic proton promotes the tautomerization of the NHC-enolate to the NHC-acyl adduct, which leads to the undesired dihydrocoumarin **5**. To overcome this limitation, we envisioned using *O*-alloc aldehyde **1a** to inhibit the formation of dihydrocoumarin **5**. By masking the phenol with the allyl source, allylation of NHC-enolate intermediate would be the preferred pathway. With this hypothesis, we turned our focus toward utilizing aldehyde **1a** in our cooperative catalysis system. Initial investigation with **A** (IMesCl) and DBU, followed by addition of a solution of $Pd_2(dba)_3$ and PPh_3, provided enolate product **2a** (14% yield by ^{1}H NMR integration, Table 1, entry 1). The homoenolate adduct **3a** (7% yield by ^{1}H NMR integration, not shown) was also detected. In an effort to suppress formation of the homoenolate product (**3a**), a variety of bases were screened. Both Hünig's base and potassium carbonate gave solely the enolate product, with the latter resulting in a slightly higher yield (entry 2 and 3). Different NHC precatalysts were also evaluated, but only the NHC derived from **A** was found to be competent in this transformation (entry 4–6). Gratifyingly, the use of a large cone angle ligand, JohnPhos, (246°) led to an improved yield of 49% (entry 7).[10]

We hypothesized that a bidentate ligand would coordinate strongly with palladium, thus minimizing Pd–NHC ligation. We initially explored the use of BINAP (natural bite angle (ref. 11) = 92°), but were disappointed to obtain dihydrocoumarin **2a** in a diminished 19% yield (entry 8). However, with dppf (natural bite angle = 99°) as the ligand, enolate product **2a** was generated in 56% yield (entry 9). This result is consistent with observations that support the role of a larger natural bite angle

Table 1 Optimization of reaction conditions[a]

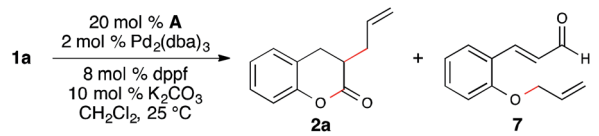


Entry	Azolium	Ligand (mol %)	Base (mol %)	Yield[b] (%)
1	**A**	PPh_3 (16)	DBU (20)	14
2	**A**	PPh_3 (16)	*i*-Pr_2NEt (20)	24
3	**A**	PPh_3 (16)	K_2CO_3 (20)	31
4	**B**	PPh_3 (16)	K_2CO_3 (20)	5
5	**C**	PPh_3 (16)	K_2CO_3 (20)	4
6	**D**	PPh_3 (16)	K_2CO_3 (20)	—
7	**A**	JohnPhos (16)	K_2CO_3 (20)	49
8	**A**	BINAP (8)	K_2CO_3 (20)	19
9	**A**	dppf (8)	K_2CO_3 (20)	56
10[c]	**A**	dppf (8)	K_2CO_3 (10)	**61**

[a] See ESI. [b] Determined by ^{1}H NMR integration (500 MHz, $PhSiMe_3$ as an internal standard). [c] 20 mol % azolium **A**.

in the heightened reactivity of the allyl moiety towards the enolate.[12] There is a balance between angle and yield since DPE-Phos (natural bite angle = 131°) afford decreased yields (see ESI† for details). Other Pd sources have been evaluated (such as $[Pd(allyl)Cl]_2$ or $Pd(OAc)_2$) with dppf as ligand, however reactions evaluated with these sources of Pd(0) afforded decreased yields of the desired product. Further evaluation of reaction solvents did not improve the yield of **2a**, with polar solvents observed to depress reaction efficiency significantly (see ESI† for details). Finally, upon modification of the stoichiometry of the azolium and base, the yield could be further improved to 61% (entry 10).

Table 2 Evaluation of the role of the reaction components



Entry	Variation of the standard conditions	Results[a]
1	None	61% yield **2a**
2	No IMes (**A**)	76% yield **7**
3	No $Pd_2(dba)_3$	69% recovered **1a**
4	No ligand (dppf)	62% recovered **1a**
5	No base (k_2CO_3)	56% yield **2a**

[a] Yield determined by ^{1}H NMR integration of the unpurified reaction.

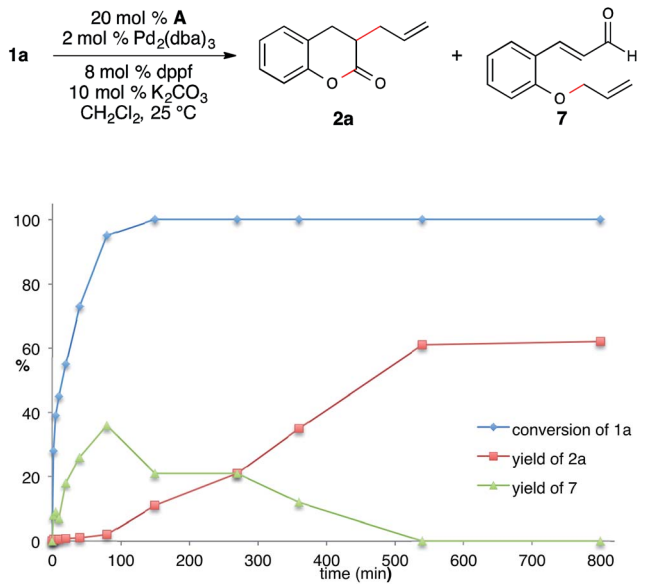


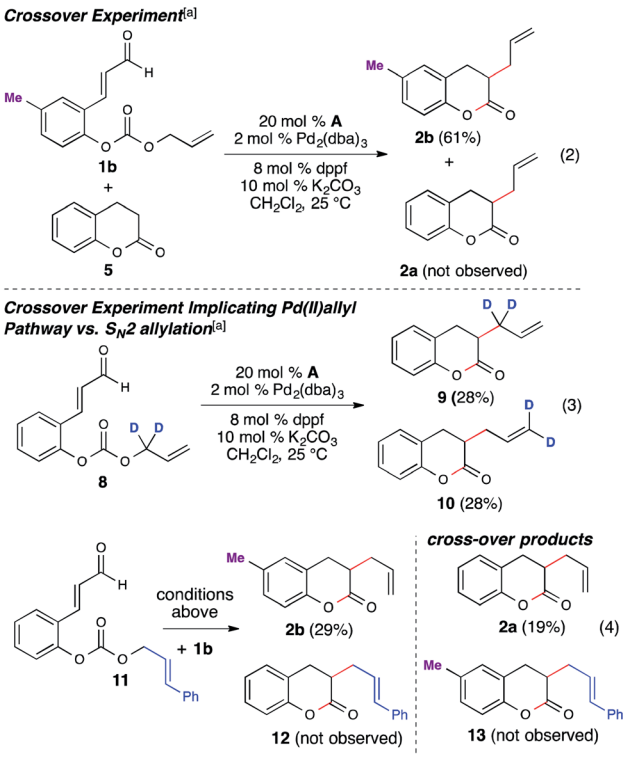
Fig. 2 Fate of aldehyde 7 during the reaction.

In control experiments, we observed that in the absence of NHC (**A**), aldehyde 7 was formed exclusively (Table 2, entry 2), while the omission of either dppf or $Pd_2(dba)_3$ from the reaction resulted in the recovery of the aldehyde starting material (Table 2, entry 3 and 4). Surprisingly, when the reaction was conducted without an exogenous base, *only a slight decrease in the yield of allylation product **2a** was observed*. Typically a base is required in NHC-catalyzed transformations to generate the active carbene, however, we hypothesize that in this case, the *in situ* generated phenoxide can serve this role competently (Table 2, entry 5).[13]

The rapid production of aldehyde 7 under palladium catalysis conditions prompted us to investigate if 7 is a competent intermediate in the cooperative pathway. Thus, the exposure of 7 to the standard reaction conditions resulted in formation of dihydrocoumarin **2a**, but in a significantly lower yield (31%). To further clarify if aldehyde 7 is a productive intermediate, the reaction was carried out under the standard conditions using GC-MS to monitor the presence of **1a**, 7 and allylated adduct **2a** (Fig. 2).[14] This experiment indicated that the starting aldehyde was almost completely consumed after 1 hour, during which time aldehyde 7 accumulated and then was consumed. At prolonged reaction times (>100 min), the disappearance of aldehyde 7 corresponds approximately with the formation of desired product **2a**, demonstrating that the allylation of the *in situ* generated phenoxide is faster than allylation of NHC-bound enolate.

During our study, the formation of the undesired parent dihydrocoumarin **5** was detected in approximately 10% yield. This product could also serve as an intermediate en route to the desired product **2a** through a serial process in which the NHC catalyzed unsubstituted coumarin formed first, followed by Pd-catalyzed allylation. Thus, dihydrocoumarin **5** was combined with aldehyde **1b** under the standard reaction conditions (eqn (2)). The exclusive formation of **2b** and quantitative recovery of **5** *discounts the serial pathway and fully supports a cooperative catalysis mechanism (vide infra)*.

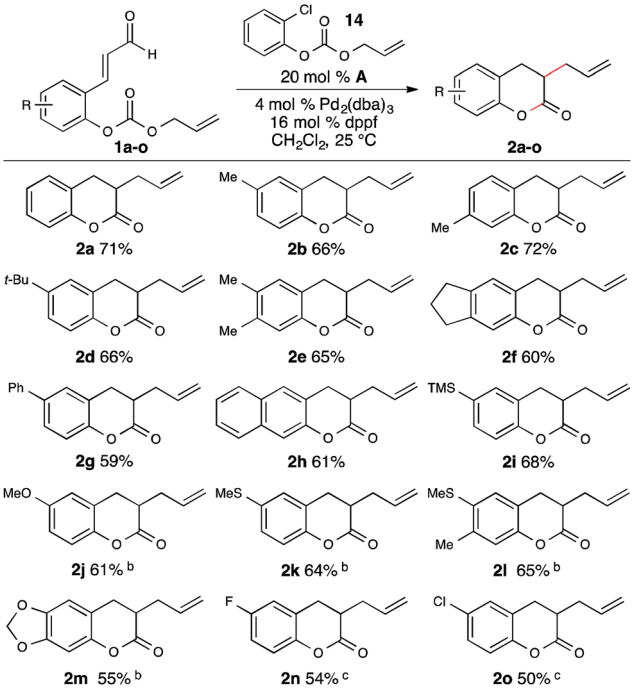
To support formation of the Pd[π-allyl]L_n complex, deuterated aldehyde **8** was subjected to the optimized reaction conditions. The resultant allylated products were obtained as a 1 : 1 mixture of regioisomers **9** and **10** (eqn (3)). Moreover, when an equimolar amount of aldehyde **8** was mixed with **1b** under the standard reaction conditions, cross-over products were observed (see ESI† for details).[15] These results, together with the information gained from the control experiments, support the initial formation of a Pd[π-allyl]L_n complex. In an effort to understand the kinetics of ion exchange within the reaction, aldehyde **11** was prepared and combined with **1b** in a 1 : 1 ratio under the standard conditions (eqn (4)). Only two products were obtained from this experiment: the non-cross-over product (**2b**) derived from aldehyde **1b** in 29% yield and the cross-over product (**2a**) from starting aldehyde **11** in 19% yield. The results from the cross-over experiment indicate that although ion exchange is rapid, the interaction between the phenoxide ion and Pd[π-allyl]L_n complex is important as the non-cross-over product is favored in the reaction.



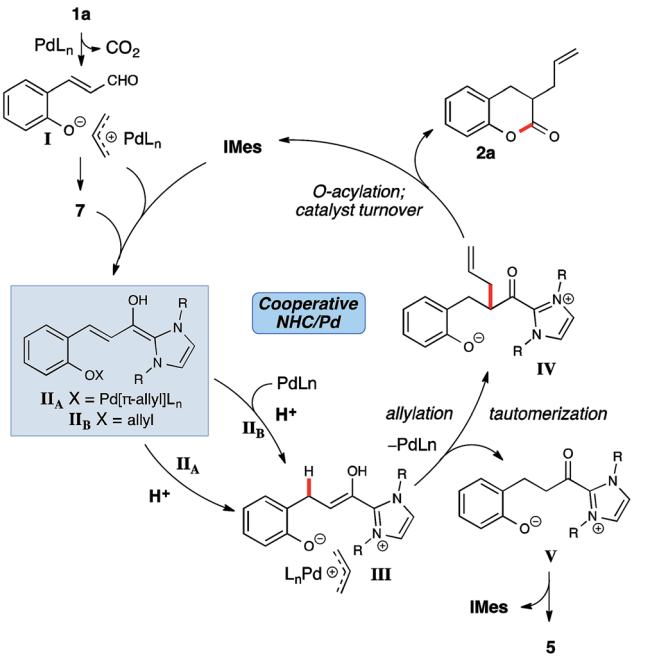
[a]Yield determined by ^{1}H NMR integration (500 MHz), $PhSiMe_3$ as an internal standard.

Based on the mechanistic investigations, we hypothesized that increasing the concentration of the allyl electrophile could improve the yield of the desired product (Table 3). Starting from carbonate **6**, we systematically screened phenolic allyl carbonates arriving at carbonate **14** as the best allyl source additive. We hypothesize that the subtle electronic effect of the *ortho*-chloro substituent on the acidity of the phenol moiety plays a crucial role in this result, but all experiments to probe this empirical observation have proven inconclusive to date. This

Table 3 Substrate scope[a]



[a] See ESI for details. Reactions were carried out on 0.4 mmol scale (0.2 M in degassed CH_2Cl_2). [b] 0.1 M in degassed CH_2Cl_2. [c] 20 mol% 1,3-bis(2,6-diethylphenyl)imidazolium chloride used instead of **A**.



Scheme 1 Proposed reaction pathway.

modification, in combination with increasing the amount of palladium, afforded enolate allylation product **2a** in an improved 71% isolated yield. With these optimized conditions, we explored the scope of this cooperative NHC/transition metal-catalyzed transformation. We found that the electronic character of the allylation precursor greatly affected the reaction outcome. We discovered that aldehydes with electron-donating groups provided the corresponding products in good yield (**2a–2m**). In certain cases, the yield of the allylated dihydrocoumarin could be increased by conducting the reaction at reduced concentration (**2j–2m**). We observed that aldehydes with electron-withdrawing groups on the phenol moiety provided lower yields with precatalyst **A**. One possible explanation is that weaker binding of the electron-deficient phenoxides to the Pd [π-allyl]L_n species leads to lower reactivity. For substrate aldehyde **1n**, replacing the *N*-mesityl moieties of the imidazolium precatalyst with 2,6-diethylphenyl increased the yield of **2n** slightly. This effect was also observed for chloro-substituted aldehyde **1o** and was necessary to obtain **2o** in moderate yield. This precatalyst effect was not observed for electron neutral aldehyde **1a**. The substitution of the allyl moiety was also explored and found to be detrimental to reactivity. This limitation is similar to many reported transition metal-catalyzed allylation methods[16] and is likely a result of unfavorable steric interactions. Investigations to understand this current restriction with our NHC/Pd platform are ongoing.

Based on the mechanistic studies above, the current understanding of this allylation process is shown in Scheme 1. Since aldehyde **1a** is rapidly consumed, we hypothesize that rate of palladium insertion is more facile than addition of the NHC to aldehyde **1a**, resulting in formation of intermediate **I** or aldehyde 7 (formed Pd-allyl formation/allylation). Fortuitously, either aldehyde **I** or 7 can enter into the catalytic cycle. The NHC undergoes addition to either aldehyde **I** or 7 to generate extended Breslow intermediate $\mathbf{II_A}$ or $\mathbf{II_B}$, respectively. At this point, NHC-bound homoenolate $\mathbf{II_A}$ can undergo either β-protonation to generate catalytic enol intermediate **III**, or allylation to arrive at an alternate catalytic enol to ultimately yield the undesired homoenolate product **3a**. Alternatively, β-protonation and palladium insertion of $\mathbf{II_B}$ can occur to afford the common enol intermediate **III**. The ionic interaction between the *in situ* generated phenoxide anion and cationic Pd [π-allyl]L_n species allows for pseudo-intramolecular allylation[17] of the NHC-enol to generate acyl azolium **IV**, with concomitant regeneration of the Pd catalyst. Current data suggests that this ionic interaction is critical to achieve C–C bond formation over acylation of phenoxide **V**, which would instead furnish undesired dihydrocoumarin **5**. Finally, intramolecular acylation of allylated acyl azolium **IV** affords the desired product **2a** and regenerates the NHC catalyst.

Conclusions

In conclusion, a new cooperative NHC/TM catalysis approach has been developed. This proof of concept process involves the combination of an NHC-generated nucleophile with a TM-activated electrophile. Successful realization of this strategy required judicious choice of the reaction components to maintain the operability of the NHC and TM·ligand complex as *separate, operative catalytic entities*. Multiple control

experiments provide strong evidence for the proposed cooperative catalysis pathway. These investigations also provided insight into the role of ion exchange in this transformation, prompting an increase in the concentration of the allyl electrophile and resulting in an improvement in efficiency. This system documents the feasibility of using NHCs and late TMs in a cooperative fashion and further exploration of this catalysis strategy involving *N*-heterocyclic carbenes and transition metals is underway.

Acknowledgements

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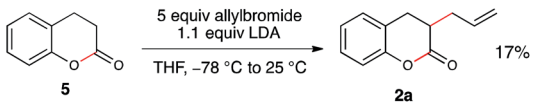

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17 This process can be described as a pseudo-intramolecular allylation due to the presence of proposed intermediate **III**, which involves an ion pair. However, since ion exchange can occur, this is not a classic intramolecular allylation reaction. However, an alternative mechanism would be more inner-sphere with coordination of the NHC enolate to the pi-allyl Pd species. This assembly would provide a more intramolecular pathway. For a relevant detailed study of enolate/pi allyl Pd coordination, see: J. A. Keith, D. C. Behenna, N. Sherden, J. T. Mohr, S. Ma, S. C. Marinescu, R. J. Nielsen, J. Oxgaard, B. M. Stoltz and W. A. Goddard, *J. Am. Chem. Soc.*, 2012, **134**, 19050–19060 and references cited therein.