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Cooperative N-Heterocyclic Carbene/Palladium-Catalyzed Enantioselective Umpolung Annulations

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Supporting Information

ABSTRACT: A combination of NHC organocatalysis and transition-metal catalysis gives rise to fundamentally new cooperative reactivity and enables the regio- and enantioselective annulation reaction between enals and vinyl benzoxazinanones. The cooperative umpolung annulation eliminates mutual deactivation and leads to a diverse set of benzazepine derivatives in good yields with excellent enantioselectivities (up to 99% ee). The development of such a cooperative catalytic system dramatically expands the scope of NHC organocatalysis by opening up new metal-catalyzed reaction pathways for homoenolate intermediates.

The N-heterocyclic carbenes (NHCs)[1] are recognized as the most powerful organocatalysts for accessing umpolung reactivity,[2] as a platform for the discovery of novel asymmetric synthetic transformations, allowing access to a wide array of heterocycles and bioactive compounds. The use of NHCs as umpolung catalysts has introduced a set of elementary steps that operate via discrete reactive species, wherein the natural polarity-based reactivity is inverted from electrophilic to nucleophilic through catalysis. One particularly versatile and reactive species is the NHC-homoenolate generated upon addition of the carbene to an enal substrate.[3] This species is nucleophilic at the β-position and thus provides an umpolung approach for accessing β-anionic carbonyl equivalent. However, despite the potential progress of this NHC-homoenolate intermediate, highly activated electrophilic substrates are required, while less activated partners fail to engage the NHC-homoenolate efficiently.

In recent years, cooperative catalysis by combining transition metal and organocatalysis has enabled a series of new enantioselective transformations.[4] Importantly, the combined use of transition-metal catalyst with organocatalytic activation modes, such as chiral phase-transfer catalyst,[5] chiral amine,[6] or phosphoric acid catalyst,[7] has emerged as a new and powerful strategy. In addition, cooperative activation of both substrates could allow using less reactive starting materials and consequently enable milder reaction conditions. We envisaged that the cooperative combination of transition-metal catalysis and NHC organocatalysis could give rise to fundamentally new cooperative umpolung reactivity capable of expanding the fields of both strategies and providing access to currently inaccessible reaction pathways, especially via the umpolung of "natural" reactivity.[8] However, to date, an asymmetric cooperative system for the intermolecular reaction that combines transition-metal/NHC organocatalysis has not been realized. Limited research has been reported in this field, presumably due to the assumption that NHCs would act as ligands for the late transition metal involved,[9] thus diminishing or even preventing the individual reactivity of each component. The major unsolved challenge in the design of cooperative transition-metal/NHC organocatalysis has been the difficulty of controlling compatibility problems.

Indeed, several research groups have demonstrated that NHCs can be combined with a second mode of activation, such as Lewis acid catalysis[10] or Brønsted acid,[11] to enable new transformations. Furthermore, racemic intramolecular transformations were also achieved recently in the combination of transition-metal catalysis and NHC organocatalysis (Scheme 1A).[12] We speculated, however, that a successful system could be developed, if careful consideration is taken to avoid mutual deactivation.[13]

Our reaction design involves an allylic alkylation process where an electrophilic allyl-palladium intermediate (**I**, Scheme 1B) is generated upon Pd-mediated decarboxylation of an electrophilic allylic substrate (**1a**).[14] Meanwhile, the combination of an α,β-unsaturated aldehyde **2** and an NHC would lead to the nucleophilic homoenolate equivalent (**II**). Subsequent nucleophilic addition of the NHC-coordinated homoenolate (**II**) in an umpolung process onto the allyl-palladium species[15] followed by cyclization would provide a powerful route to access enantioenriched benzazepines. Herein, we describe the development of such a cooperative catalytic system which combines NHC-mediated umpolung of an enal substrate with palladium-catalyzed allylic substitution onto benzoxazinanones. This asymmetric process demonstrates the compatibility of these two important catalytic modes for the first time and efficiently delivers annulated 1-benzazepine products with excellent regio- and enantioselectivities. These compounds are key structural motifs in a range of biologically active natural products and pharmaceuticals, such as Tolvaptan, Zilpaterol, and Benazepril.[16] The asymmetric synthesis of 1-benzazepine derivatives is also relatively unexplored despite their importance.[17]

On the basis of this synergistic catalysis design plan, we began our investigations into the proposed NHC/Pd-catalyzed umpolung annulation using vinyl benzoxazinanone **1a** and enal **2a** (Table 1). However, the precatalyst **4a** did not catalyze this transformation (entry 1). Gratifyingly, the use of chiral triazolium **4b** as an NHC precatalyst could lead to the desired

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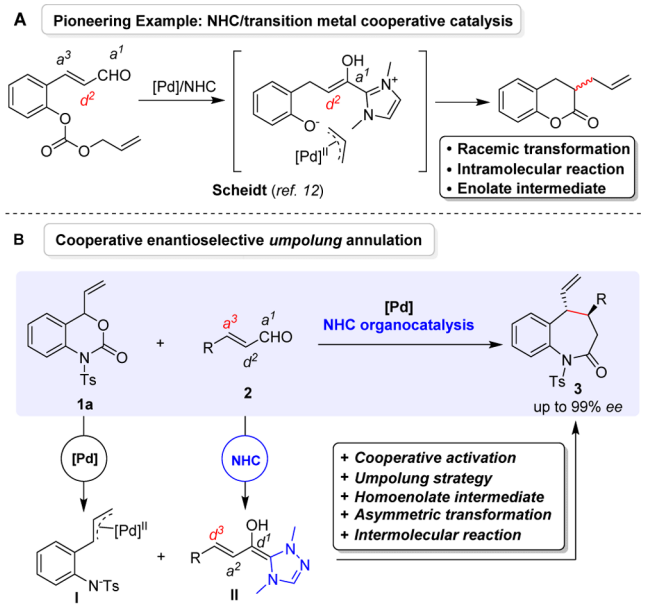
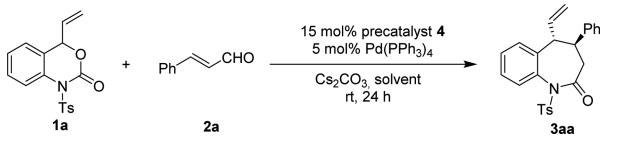
Scheme 1. Design of Enantioselective Catalytic Umpolung Annulation



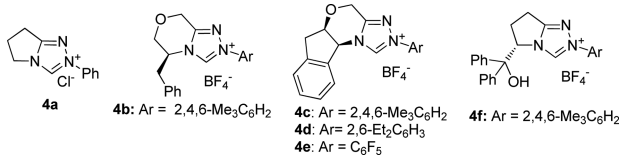
i) Utilizing compatibility between the transition metal and NHC organocatalyst
ii) Demonstration of cooperative activation via umpolung strategy
iii) Mild and general C-C bond formation with excellent enantiocontrol (up to 99% ee)
iv) High-value chiral heterocycles with various substitution patterns

Table 1. Optimization of the Reaction Conditions[a]



entry	precat.	solvent	yield (%)[b]	dr of **3aa**[c]	ee (%)[d]
1	**4a**	THF	nr	–	–
2	**4b**	THF	38	5:1	63
3	**4c**	THF	86	12:1	99
4	**4d**	THF	58	14:1	98
5	**4e**	THF	nr	–	–
6	**4f**	THF	28	7:1	90
7	**4c**	toluene	56	12:1	96
8	**4c**	$CHCl_3$	29	15:1	94
9	**4c**	DME	85	12:1	98
10	–	THF	nr	–	–
11[e]	**4c**	THF	nr	–	–
12[f]	**4c**	THF	nr	–	–

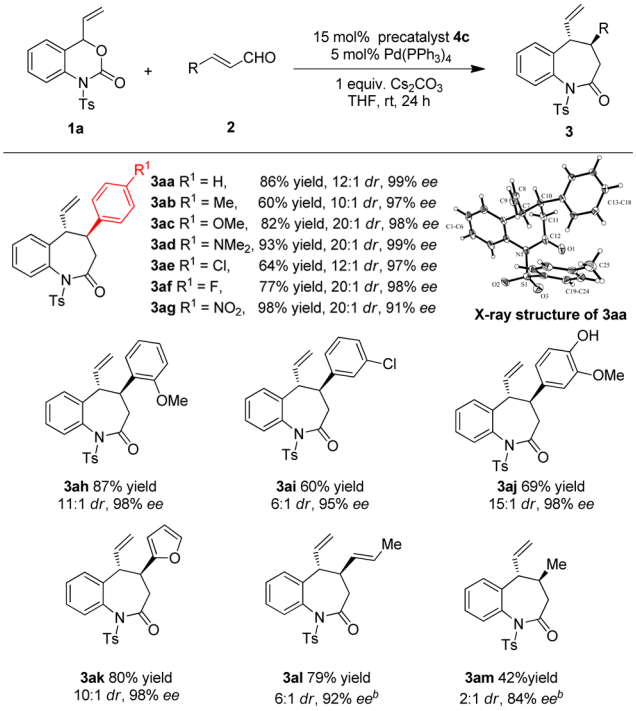
[a]Reactions were conducted with 1.0 equiv of **1a** and 2.0 equiv of **2a**, 24 h. [b]Isolated yields after chromatography are shown. [c]Determined by ^{1}H NMR spectroscopy. [d]Determined by HPLC analysis. [e]In the absence of $Pd(PPh_3)_4$. [f]In the absence of Cs_2CO_3; nr = no reaction; rt = room temperature.



product **3aa** in moderate yield with 63% ee (entry 2). Encouraged by this result, we next evaluated chiral triazolium NHC precatalysts, which displayed remarkable effects on the outcome of the reaction (entries 2–6). To great delight, using the newly designed cooperative NHC/Pd system, we found that the desired annulation product could be forged in excellent yield and excellent enantioselectivity (99% ee) at room temperature using 15 mol % of NHC (**4c**) as an organocatalyst along with 5 mol % of $Pd(PPh_3)_4$ as allylation catalyst. However, no improvement in yield was observed for the reaction by screening different bases and solvents (entries 7–9, see Supporting Information). A series of control experiments verified the necessity of each reaction component (entries 10–12). In the absence of any one of the reaction components (palladium, NHC precatalyst, or base), no product was formed.

With the optimal conditions in hand, we next sought to explore the scope of the enal component in this new NHC/Pd-catalyzed asymmetric annulation reaction. As shown in Table 2,

Table 2. Functionalization of Substituents on the Enals[a]



[a]Reaction conditions: **1a** (0.2 mmol), 2 (0.4 mmol), $Pd(PPh_3)_4$ (5 mol %), precatalyst **4c** (15 mol %), Cs_2CO_3 (0.2 mmol), and THF (3 mL) in a sealed Schlenk tube at rt for 24 h. [b]Enal (4 equiv).

a diverse array of electron-donating and -withdrawing enals with a variety of functional groups (methyl, chloro, nitro, furanyl) performed well in this synergistic reaction. The corresponding products were isolated in good yields with excellent ee's (**3aa**–**3ak**). The absolute configuration of the resulting molecule **3aa** was assigned by single-crystal X-ray diffraction analysis. To test the synthetic utility of this method, the enantioselective annulation was conducted on a gram scale, and **3aa** was produced in comparable yield and selectivity (0.93 g of product, 74% yield, 12:1 dr, 98% ee). Moreover, 4-hydroxycinnamaldehyde was found to be a competent substrate in this transformation, demonstrating the diversity of substituents that are tolerated in this transformation (**3aj**, 69% yield, 15:1 dr, 98% ee). Notably, this method was compatible with β-alkyl enals, giving the desired products in moderate yields and good enantioselectivities (**3al** and **3am**).

The generality of the reaction with respect to the substituents on the benzoxazinanone coupling partners was also investigated

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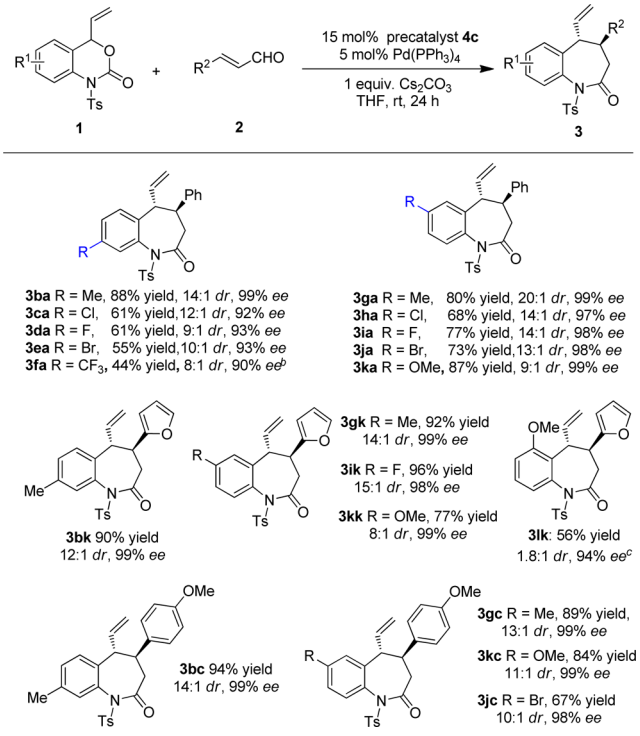
(Table 3). Both electron-donating and -withdrawing substituents were accommodated on the benzoxazinanone ring

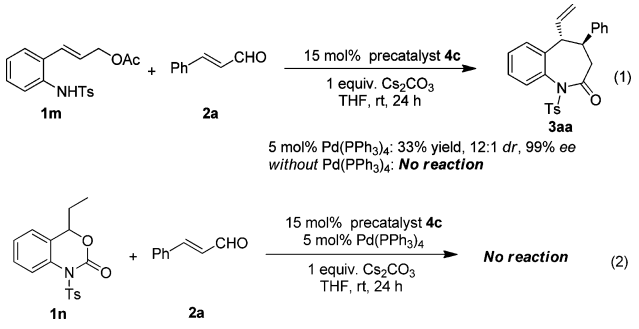
Table 3. Scope of Vinyl Benzoxazinanones[a]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), $Pd(PPh_3)_4$ (5 mol %), precatalyst **4c** (15 mol %), Cs_2CO_3 (0.2 mmol), and THF (3 mL) in a sealed Schlenk tube at rt for 24 h. [b]Enal (4 equiv). [c]Phosphine ligand dppf (10 mol %) and $Pd(dba)_2$ (5 mol %) were used.

with excellent levels of enantioselectivity (**3ba**–**3ka**). A variety of vinyl benzoxazinanones proved to be excellent electrophiles with 2-furanacrolein (**2k**) or 4-methoxycinnamaldehyde (**2c**) as umpolung coupling partners in this annulation and afforded the desired 1-benzazepines in high yields and excellent enantioselectivities (**3bk**–**3jc**).

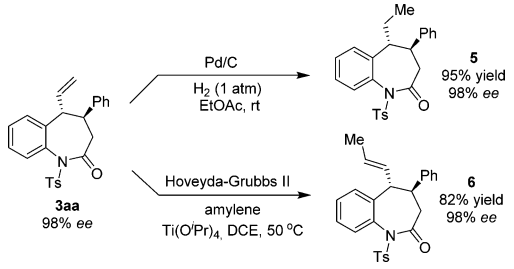
To further demonstrate the utility of this cooperative catalysis strategy, we investigated the direct annulation of acyclic substrates with enals. 3-(2-Aminophenyl)allyl acetate **1m** was also accommodated in this cooperative umpolung strategy,[18] giving the corresponding products **3aa** in moderate yields and excellent enantioselectivity (eq 1, 99% ee). In



contrast, the reaction failed in the absence of $Pd(PPh_3)_4$, also suggesting that a cooperative activation mode in the annulation is operative. Next, the importance of the olefin on the benzoxazinanone was demonstrated by the inability of ethyl benzoxazinaone **1n** to form π-allyl-palladium species (eq 2).

The optically active benzazepine **3aa** could be easily elaborated in different ways, as shown in Scheme 2, highlighting

Scheme 2. Derivatization of Benzazepine 3aa



the synthetic potential of the present method. Hydrogenation of **3aa** in the presence of a catalytic amount of Pd/C led to the reduction of the olefin, providing compound **5** in good yield with no loss of enantiopurity. In addition, the vinyl moiety of **3aa** underwent cross-metathesis with amylene in the presence of the Grubbs–Hoveyda II catalyst to generate **6** in 82% yield.

A plausible mechanistic cycle, in which palladium catalysis intertwines with asymmetric NHC organocatalysis, is outlined in Figure 1. This challenging "cooperative activation" concept

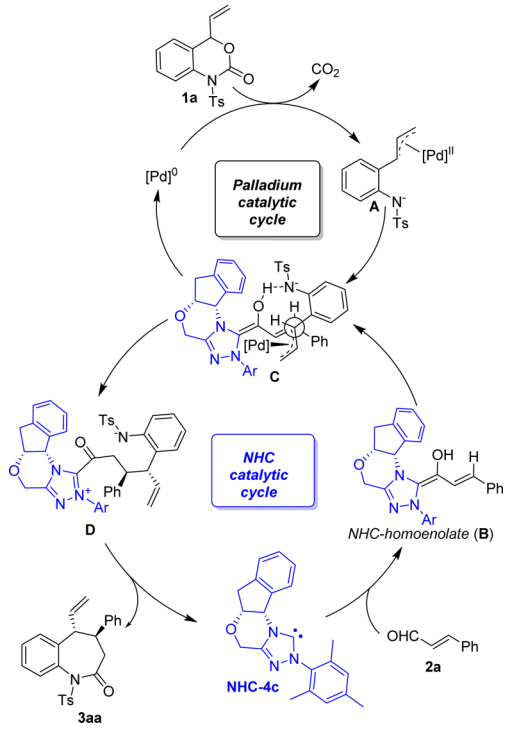


Figure 1. Proposed cooperative catalytic cycle.

was successfully realized through concomitant catalytic generation of two reactive species: a nucleophilic NHC-homonenolate (**B**) and a highly electrophilic allyl-palladium cation (**A**). Herein, the catalysis is initiated by the coordination of vinyl benzoxazinanone **1a** to the palladium catalyst, followed by the formation of an electrophilic allyl-palladium(II) complex (**A**) upon decarboxylation. In a parallel organocatalytic cycle, the addition of NHC organocatalyst **4c** to the enal **2a** gives rise to the NHC-homoenolate (**B**). At this point, the NHC-

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homoenolate (**B**) can undergo conjugate addition to the *in situ* formed allyl-palladium(II) complex **A**, presumably promoted by a hydrogen-bonding interaction. Notably, the stereochemical outcome can be best explained by the proposed transition state **C**. Following carbon−carbon bond formation, release of the palladium catalyst and tautomerization give rise to acyl azolium **D**. This species then undergoes N-acylation cyclization to furnish the final product **3aa** and regenerate the NHC organocatalyst **4c**.

In this study, we have demonstrated that transition-metal catalysis can be combined with NHC organocatalysis in a cooperative process. Asymmetric induction can be realized through the cooperative activation of a chiral NHC organocatalyst with a palladium co-catalyst. The combination of the palladium catalysis with the unique umpolung reactivity of catalytic chiral NHC intermediates has the potential to be a valuable platform for the development of a wide range of broadly useful stereocontrolled reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b04364.

Crystallographic data (CIF)
Experimental procedures and spectroscopic data (PDF)

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Notes

The authors declare no competing financial interest.

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