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Sulfinate and Carbene Co-catalyzed Rauhut-Currier Reaction for Enantioselective Access to Azepino[1,2-*a*]indole

Xingxing Wu,† Liejin Zhou,† Rakesh Maiti, Chengli Mou, Lutai Pan,* and Yonggui Robin Chi*

Abstract: A carbene and sulfinate co-catalyzed intermolecular Rauhut-Currier reaction between enals and nitrovinyl indoles is disclosed. The carbene catalyst activates the enal and the sulfinate co-catalyst activates the nitrovinyl indole. Both activation processes are realized via the formation of covalent bonds between catalysts and substrates to generate the catalyst-bound intermediates. The dual catalytic reaction affords azepino[1,2-*a*]indole products with excellent stereo-selectivities. Our study demonstrates the unique involvement of sulfinate as effective nucleophilic catalyst in activating electron-deficient alkenes for asymmetric reactions. The dual catalytic approach shall also encourage future explorations of both sulfinate and carbene catalysts for new reactions.

The dimerization of two electron-deficient alkenes, known as Rauhut-Currier reaction, is an important method to prepare functional molecules bearing an unsaturated carbon-carbon bond.[1] This reaction is typically realized through the use of a nucleophilic organocatalyst to activate one of the alkenes (**1**) to form a nucleophilic zwitterionic species that subsequently reacts with a second electron-deficient alkene (**2**) (Figure 1a). Phosphines and amines are two types of mostly-studied catalysts for the Rauhut-Currier reactions.[2] Thiols (from cysteine) and thiolates have also been demonstrated by Miller, Murphy and Moore as nucleophilic catalysts.[3] These catalysts are found effective for enantioselective processes mostly in intramolecular reactions, as reported by Miller, Xiao, Enders and Sasai, Zhang and others.[4] When moving from intramolecular reactions to intermolecular versions, both chemical reactivities and enantioselectivities become much more challenging.[5] The incorporation of a second catalyst to simultaneously activate the electrophile **2** therefore provides a promising strategy to achieve efficient Rauhut-Currier reactions. For example, the groups of Shi and Feng have used amines as co-catalysts to activate unsaturated ketones or aldehydes (via iminium formation) as electrophiles in enantioselective Rauhut-Currier reactions.[6]

Our laboratory is interested in using N-heterocyclic carbene (NHC) to activate aldehydes and carboxylic esters for efficient asymmetric synthesis of functional molecules.[7,8] Here we demonstrate that the merge of a sulfinate and an NHC catalyst readily allows for catalytic intermolecular Rauhut-Currier reactions to generate azepino[1,2-*a*]indole scaffold with high enantioselectivities (Figure 1b). Briefly, the addition of a sulfinate catalyst to a nitroalkene substrate (**1a**) generates intermediate **I** bearing a nucleophilic carbon.[9] Simultaneously in the same system, the reaction of an NHC catalyst with α-bromoenal (**2a**) generates the α,β-unsaturated acyl azolium intermediate **II**.[10,11] Michael-type addition of intermediate **I** to **II** followed by a few processes (see Supporting Information for a complete pathway) eventually leads to product **3a** with both sulfinate and NHC catalysts regenerated. The optically enriched products from our catalytic reactions contain an azepino[1,2-*a*]indole moiety that is widely found as a core scaffold in natural products and bioactive functional molecules (Figure 1c).[12] In our approach, the chemical reactivity is enabled by both catalysts cooperatively, and the enantioselectivity is controlled by the chiral NHC catalyst. Notably, in previous cooperative NHC catalysis,[13] the other catalyst is typically non-covalent catalyst such as Lewis/Brønsted acid,[14a-f] hydrogen-bond donor.[14g-h] In our dual catalytic approach, both NHC and the sulfinate catalysts activate the substrates via covalent bond formations.[15] Our study constitutes the first

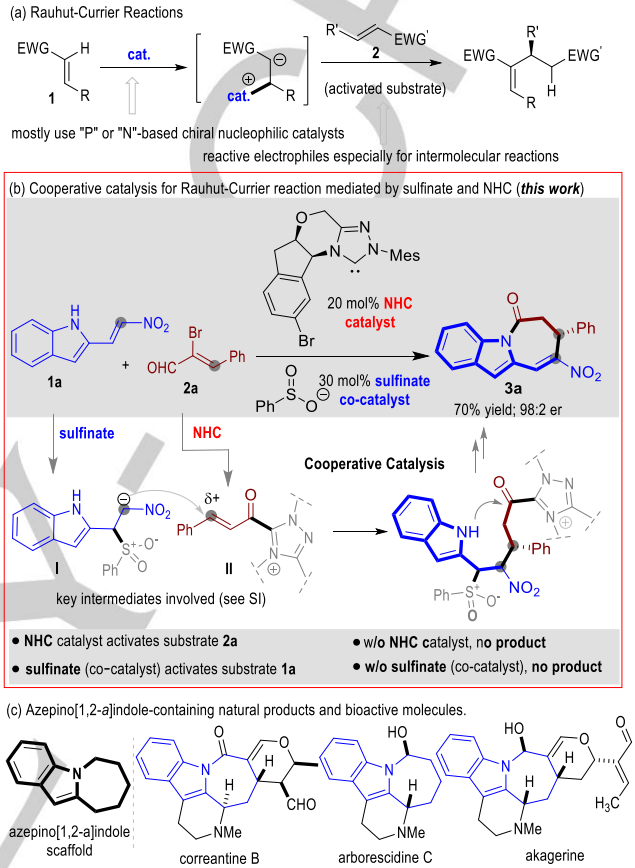

Figure 1. Rauhut-Currier reaction and bioactive molecules containing azepino[1,2-*a*]indoles. SI = Supporting Information.

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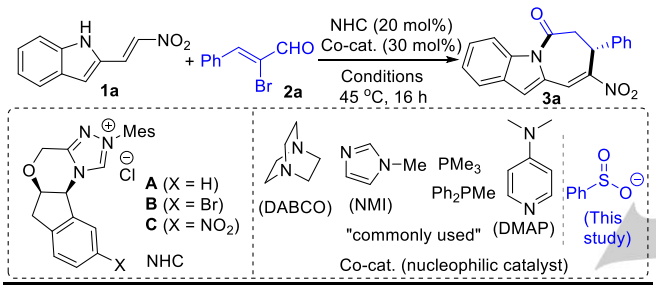
success in using NHC to activate the electrophilic partner for enantioselective Rauhut-Currier reactions. Additionally, our work shall encourage further explorations of sulfinates (including the chiral variants) as potentially versatile nucleophilic catalysts for other asymmetric reactions.

Based on our dual activation design, we began the investigation by using nitrovinylindole **1a** and bromoenal **2a** as the model substrates (Table 1). It is known that NHC catalyst can react with bromoenal **2a** to generate the α,β-unsaturated acyl azolium intermediate that can behave as an electrophilic component.[10] To generate a nucleophilic partner for the Rauhut-Currier reaction, we first studied several commonly used amine and phosphine catalysts to activate nitrovinylindole **1a**. The model reaction was performed at 45 °C with **A**[16a] as an NHC pre-catalyst, Cs_2CO_3 as a base, and DCM as the solvent. No product (**3a**) was observed while the nitroalkene **1a** was fully consumed when DABCO, NMI, PMe_3, or Ph_2PMe was used as the co-catalyst to activate **1a** (entry 1). We next found the use of DMAP as the co-catalyst could afford product **3a** with around 8% yield (entry 2). Further optimizations with DMAP as the co-catalyst did not lead to significant improvement.

Table 1. Optimization of the Reaction Conditions.[a]



Entry	NHC	Base	Co-Cat.	**3a** Yield [%][b]	e.r.
1	**A**	Cs_2CO_3	DABCO, NMI, PMe_3, or Ph_2PMe as co-cat., no product **3a** was observed		
2	**A**	Cs_2CO_3	DMAP	8	90:10
3	**A**	Cs_2CO_3	PhSH or ^{n}PrSH (See SI), no product		
4	**A**	Cs_2CO_3	$PhSO_2Na$	49	70:30
5	**A**	Cs_2CO_3	$PhSO_2H$	54	70:30
6	**B**	Cs_2CO_3	$PhSO_2H$	63	96:4
7	**C**	Cs_2CO_3	$PhSO_2H$	61	88:12
8	**B**	Cs_2CO_3	$PhSO_2Na$	55	96:4
9	**B**	K_2CO_3	$PhSO_2H$	45	93:7
10	**B**	Et_3N	$PhSO_2H$	–	–
11	–	Cs_2CO_3	$PhSO_2H$	–	–
12	**B**	Cs_2CO_3	–	–	–
13[c]	**B**	Cs_2CO_3	$PhSO_2H$	71 (70)[d]	98:2

[a] Reaction conditions: **1a** (0.07 mmol, 1.4 equiv), **2a** (0.05 mmol, 1.0 equiv), NHC (20 mol%), co-cat. (30 mol%), base (2.0 equiv), 4 Å MS (50 mg), CH_2Cl_2 (0.04 M) at 45 °C, 16 h. [b] Yield estimated via ^{1}H NMR analysis of crude reaction mixture, based on **2a**, by using 1,3,5-trimethoxybenzene as an internal standard. [c] 15 mol% of Pivalic acid was added, and reaction completed within 3 h. [d] Isolated yield within parentheses.

Inspired by pioneering studies from Murphy, Moore and Miller,[3] we then turned to evaluate thiol-based nucleophilic catalysts (entry 3). Unfortunately, the use of thiol or thiophenol as the co-catalyst failed to afford product **3a** (entry 3). Analysis of the reaction (entry 3) indicated that these co-catalysts reacted with acyl azolium intermediate (**II**, Figure 1b) to form the corresponding thioester adduct. We hypothesized that the sulfinate as the co-catalyst should prevent the undesired pathway for thioester formation. To our great delight, the use of $PhSO_2Na$ as a co-catalyst resulted in **3a** with a very encouraging 49% yield (entry 4). We next found that the use of benzenesulfinic acid as the precursor provided a slight increase in the product yield (54%, entry 5), probably due to a better solubility of the *in situ* generated sulfinate salt in the reaction. To achieve an optimal enantioselectivity, several amino-indanol-derived NHCs were examined. We found the bromo-substituted pre-catalyst **B**[16b,c] afforded **3a** in 63% yield and 96:4 er (entry 6). The pre-catalyst **C**[16b,c] substituted with nitro group did not perform as well as **B** (entry 7). K_2CO_3 could be used as a base, while organic base Et_3N was not effective (entries 9-10). Control experiments without either NHC pre-catalyst (**B**) or sulfinate pre-co-catalyst ($PhSO_2H$) did not provide any desired product, with the starting materials (**1a** and **2a**) remained mostly unconsumed in both reactions (entries 11 and 12). These results (entries 11-12) strongly supported that simultaneous dual activations were critical for the transformation. Finally, we were pleased to find that with 15 mol% of pivalic acid ($tBuCO_2H$) as an additive,[14e] **3a** was obtained in an acceptable yield (70%) and 98:2 er (entry 13).

With optimized reaction conditions in hand (Table 1, entry 13), we next explored the generality of the reaction. Initially, we studied the scope of bromoenal **2** (Table 2). A diverse set of substituents (OCH_3, CH_3, halogens *etc*) at the *para*-, *meta*- or *ortho*-position of the β-phenyl group of enals were well tolerated and the corresponding annulation products (**3a**-**k**) were obtained with good yields and excellent er values. The β-phenyl group of **2a** could be replaced with heteroaryl units, such as furyl (**3m**) and thienyl (**3n**) substituents. Moreover, the enal bearing further transferable alkenyl group was also compatible in this reaction, giving product **3o** in 63% yield and 96:4 er. Notably, substrates possessing electron-withdrawing group (F, Cl, Br, NO_2 and CO_2Me) at the *para*-position of the β-phenyl group delivered the corresponding products in low yields, probably due to the relatively strong reactivity of the enals. In these cases, removal of the pivalic acid additive from the optimal conditions gave better results (**3d**-**h**). Unfortunately, this protocol was not applicable for β-alkyl bromoenal substrates (please see SI for more details).

The scope of nitrovinylindole **1** by using enal **2a** as the model substrate was also investigated (Table 3). Various substituents (e.g. methyl, chloro, bromo) and substitution patterns on the indole aromatic ring were compatible in the catalytic reactions. As a technique note, when electron-withdrawing substituents (Cl, Br) were placed on the vinylindoles (**1**), the reactions were performed in $CHCl_3$ as the solvent with the absence of pivalic acid additive in order to achieve good yields and high er values (**3s**-**t**, **3v**-**w**). Additionally, nitrovinylpyrrole was also screened in our reaction to

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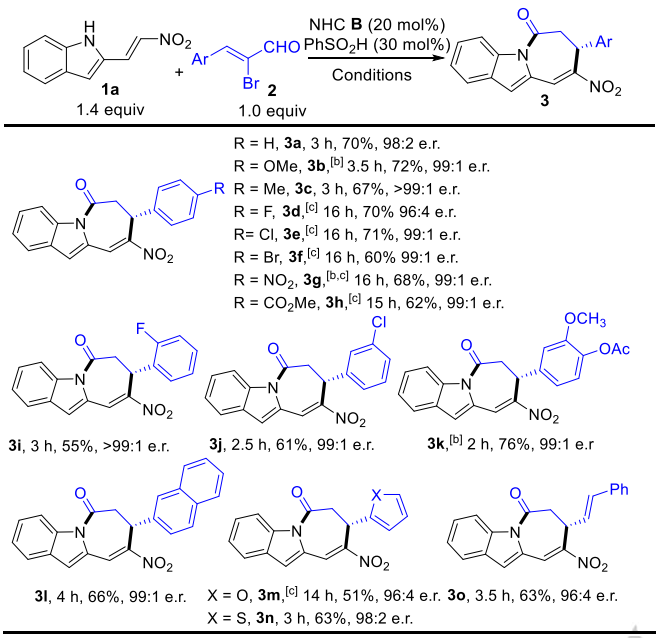
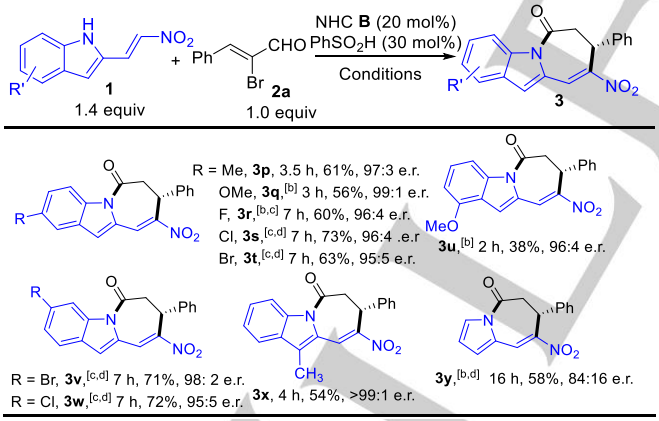
deliver the corresponding product **3y** in 58% yield and a moderate er (84:16 er), probably because of the weak steric interaction with NHC catalyst owing to the inherent smaller size of pyrrole.

Table 2. Substrate scope of bromoenals **2**.[a]



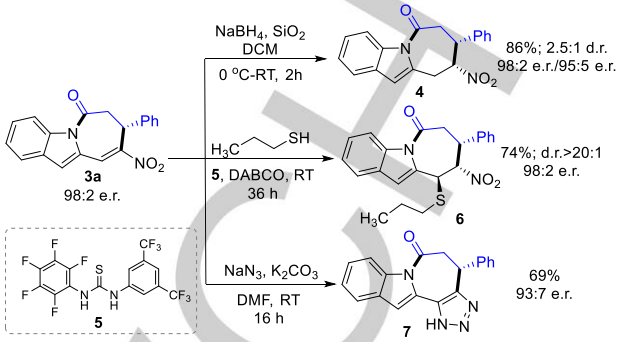
[a] Reaction conditions were as in Table 1, entry 13, unless otherwise specified. Isolated yields (after SiO_2 chromatography purification) based on the enal **2**. [b] Reactions performed at 50 °C. [c] No pivalic acid was added.

Table 3. Substrate scope of vinylindoles **1**.[a]



[a] Unless otherwise noted, reaction conditions were as in Table 1, entry 13. Isolated yields based on enal **2a**. [b] Reactions performed at 50 °C. [c] $CHCl_3$ was used instead of CH_2Cl_2. [d] No pivalic acid was added.

The optically enriched products obtained in our approach can readily undergo further transformations (Scheme 1). For example, selective reduction of C=C double bond of **3a** with $NaBH_4$ afforded the saturated nitro compound **4**. Michael addition of *n*-propylthiol to product **3a** under mild conditions provided adduct **6** in 74% yield without loss in the er values. In addition, reaction of **3a** with sodium azide under basic condition gave triazole product **7** via an aza-Michael addition, annulation, and elimination process. The triazole structure is widely found as a core moiety of biological agents and can be employed as ligands in synthetic chemistry.[17]



Scheme 1. Synthetic transformations of product **3a**

In summary, we have developed a new dual catalytic activation approach that employ NHC and benzenesulfinate as the catalysts. For the first time we demonstrate the unique involvement of benzenesulfinate as an effective catalyst for enantioselective Rauhut-Currier reactions. Both catalysts activate the corresponding substrates via covalent bond formations. The key reaction step involves two *in situ* generated catalyst-bound intermediates (a $PhSO_2$-bound and an NHC-bound intermediate). Our dual catalytic reaction allows for access to azepino[1,2-*a*]indoles in excellent enantioselectivities. Ongoing studies include asymmetric reaction development by designing new chiral sulfinate catalysts, and rapid synthesis and activity evaluation of medicinally relevant molecules.

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Keywords: azepino[1,2-*a*]indole • N-heterocyclic carbene • Rauhut-Currier reaction • cooperative catalysis • organocatalysis

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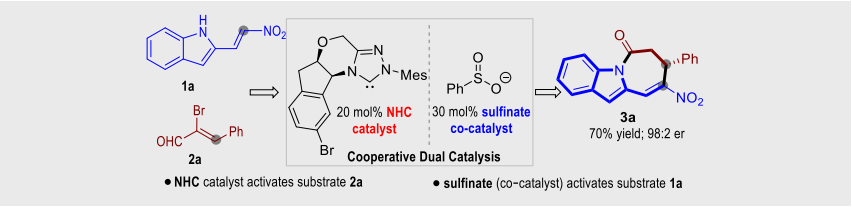

Cooperative: A carbene and sulfinate co-catalyzed intermolecular Rauhut-Currier reaction provides an efficient method for access to azepino[1,2-*a*]indoles with excellent stereo-selectivities. The sulfinate was found to be a unique and effective nucleophilic catalyst in activating nitrovinyl indoles for the Rauhut-Currier reaction.

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Sulfinate and Carbene Co-catalyzed Rauhut-Currier Reaction for Enantioselective Access to Azepino[1,2-*a*]indole