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

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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 the catalysts and substrates to generate catalyst-bound intermediates. The dual catalytic reaction affords azepino[1,2-a]indole products with excellent stereoselectivity. Our study demonstrates the unique involvement of sulfinate as an effective nucleophilic catalyst in activating electron-deficient alkenes for asymmetric reactions. This dual catalytic approach should also encourage future explorations of both sulfinate and carbene catalysts for new reactions.*

The dimerization of electron-deficient alkenes, known as the 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 1 a). Phosphines and amines are two of the most-studied types of catalyst 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 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 reactivity and enantioselectivity becomes much more challenging.[5] 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]

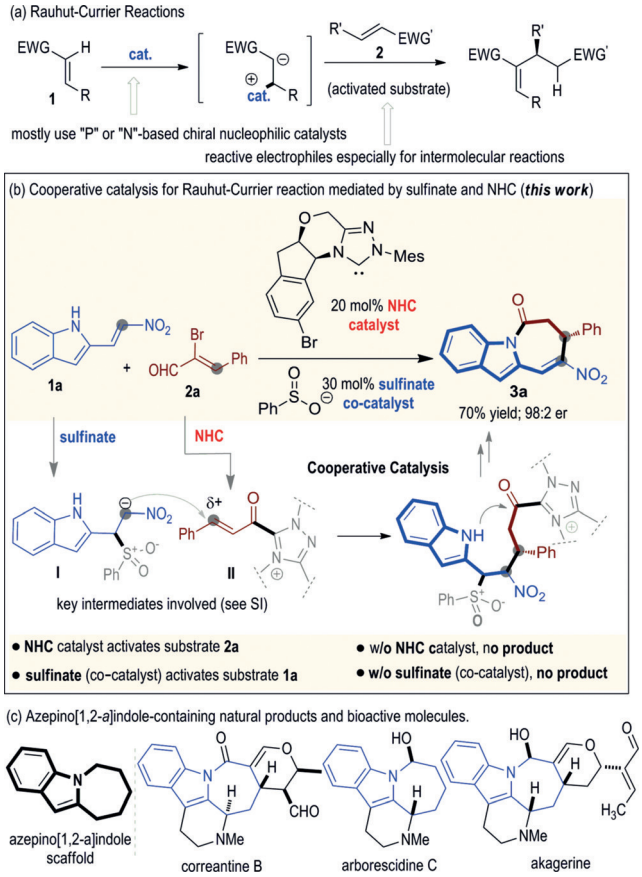

Figure 1. The Rauhut–Currier reaction and bioactive molecules containing azepino[1,2-*a*]indoles.

Our laboratory is interested in using N-heterocyclic carbenes (NHCs) to activate aldehydes and carboxylic esters for the efficient asymmetric synthesis of functional molecules.[7,8] Here, we demonstrate that the merging of a sulfinate and an NHC catalyst readily enables catalytic intermolecular Rauhut–Currier reactions to generate azepino[1,2-*a*]indole scaffolds with high enantioselectivity (Figure 1 b). Briefly, the addition of a sulfinate catalyst to a nitroalkene substrate (**1a**) generates intermediate **I**, which bears 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 regeneration of both the sulfinate and NHC catalyst. The optically enriched products from our catalytic reactions contain an azepino[1,2-

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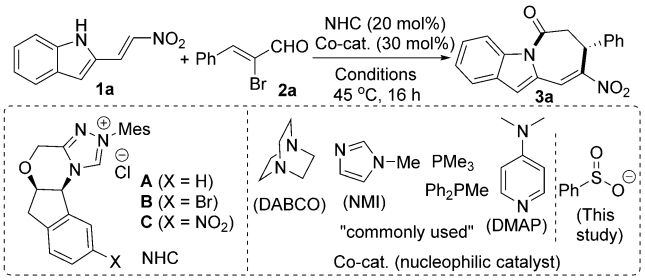
a]indole moiety that is widely found as a core scaffold in natural products and bioactive functional molecules (Figure 1c).[12] In our approach, the chemical reactivity is enabled by both catalysts cooperatively, and the enantioselectivity is controlled by the chiral NHC catalyst. Notably, in previous cooperative NHC catalysis,[13] the other catalyst has typically been a non-covalent catalyst such as a Lewis/Brønsted acid[14a–f] or hydrogen-bond donor.[14g–h] In our dual catalytic approach, both NHC and the sulfinate catalysts activate the substrates through covalent bond formations.[15] Our study constitutes the first success in using NHCs to activate the electrophilic partner for enantioselective Rauhut–Currier reactions. Additionally, our work should 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 catalysts can react with bromoenal **2a** to generate an 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 dichloromethane as the solvent. No product (**3a**) was observed although 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.

Inspired by pioneering studies by Murphy, Moore, and Miller,[3] we then evaluated 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 the acyl azolium intermediate (**II**, Figure 1b) to form the corresponding thioester adduct. We hypothesized that a 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 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 that 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 a nitro group, did not perform as well as **B** (entry 7). K_2CO_3 could be used as a base, while the organic base Et_3N was not effective (entries 9–10). Control experiments without either the NHC pre-catalyst (**B**) or the sulfinate pre-co-catalyst ($PhSO_2H$) did not provide any desired product, with the starting materials (**1a** and **2a**) remaining mostly unconsumed in both reactions (entries 11 and 12). These results (entries 11–12) strongly support the idea that simultaneous dual activations are 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 with respect to bromoenal **2** (Table 2). A diverse set of substituents (OCH_3, CH_3, halogens *etc*) at the *para*, *meta*, or *ortho* positions 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, an enal bearing a 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 groups (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 the Supporting Information for more details).

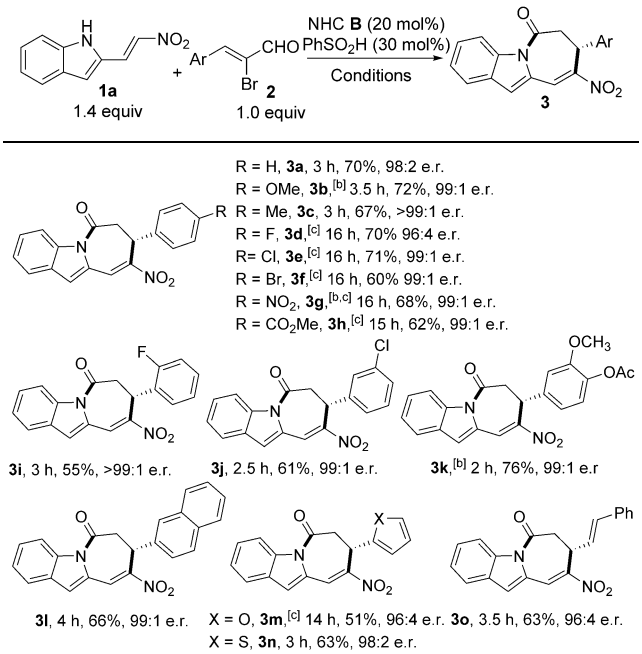
Table 1: Optimization of the Reaction Conditions.[a]



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 by ^{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] Yield of isolated product within parentheses.

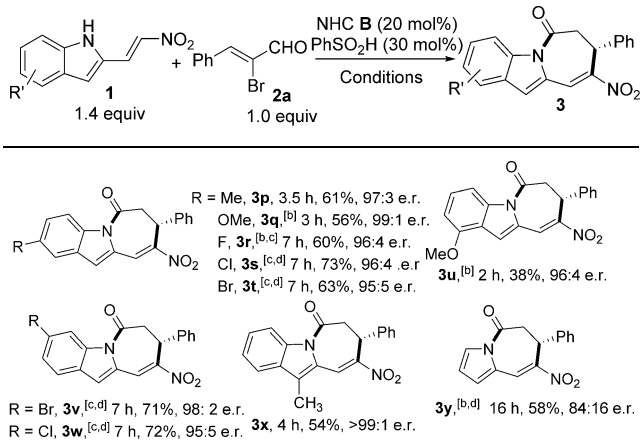
Table 2: Substrate scope with respect to bromoenals **2**.[a]



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

The scope with respect to nitrovinylindole **1** when 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 technical note, when electron-withdrawing substituents (Cl, Br) were placed on the vinylindoles (**1**), the reactions were performed in $CHCl_3$ as the solvent without the pivalic acid additive in order to achieve

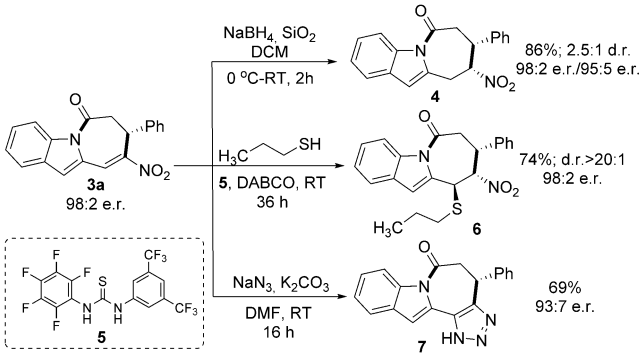
Table 3: Substrate scope with respect to vinylindoles **1**.[a]



[a] Unless otherwise noted, reaction conditions were as in Table 1, entry 13. Yields of isolated product 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.

good yields and high er values (**3s–t**, **3v–w**). Nitrovinylpyrrole was also screened in our reaction to 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 inherently smaller size of pyrrole.

The optically enriched products obtained in our approach can readily undergo further transformations (Scheme 1). For example, selective reduction of the C=C double bond of **3a** with $NaBH_4$ afforded the saturated nitro compound **4**.



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

Michael addition of *n*-propylthiol to product **3a** under mild conditions provided adduct **6** in 74% yield without loss in the er value. In addition, reaction of **3a** with sodium azide under basic condition gave triazole product **7** through 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 a ligand in synthetic chemistry.[17]

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 through covalent bond formation. 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 provides access to azepino[1,2-*a*]indoles with excellent enantioselectivity. Ongoing studies include asymmetric reaction development by designing new chiral sulfinate catalysts, and the rapid synthesis and activity evaluation of medicinally relevant molecules.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: cooperative catalysis · indoles · N-heterocyclic carbenes · organocatalysis · Rauhut–Currier reactions

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