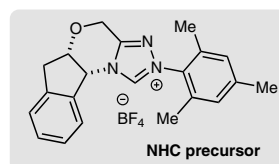
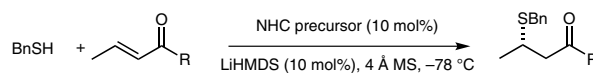


Asymmetric Sulfa-Michael Addition of α,β -Unsaturated Esters/Amides Using a Chiral N-Heterocyclic Carbene as a Noncovalent Organocatalyst

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R = OAr, pyrrolidinone, oxazolidinone
NHC as a noncovalent organocatalyst
less reactive esters and amides
no proton shuttle required
26 examples, up to 98% yield, 87% ee

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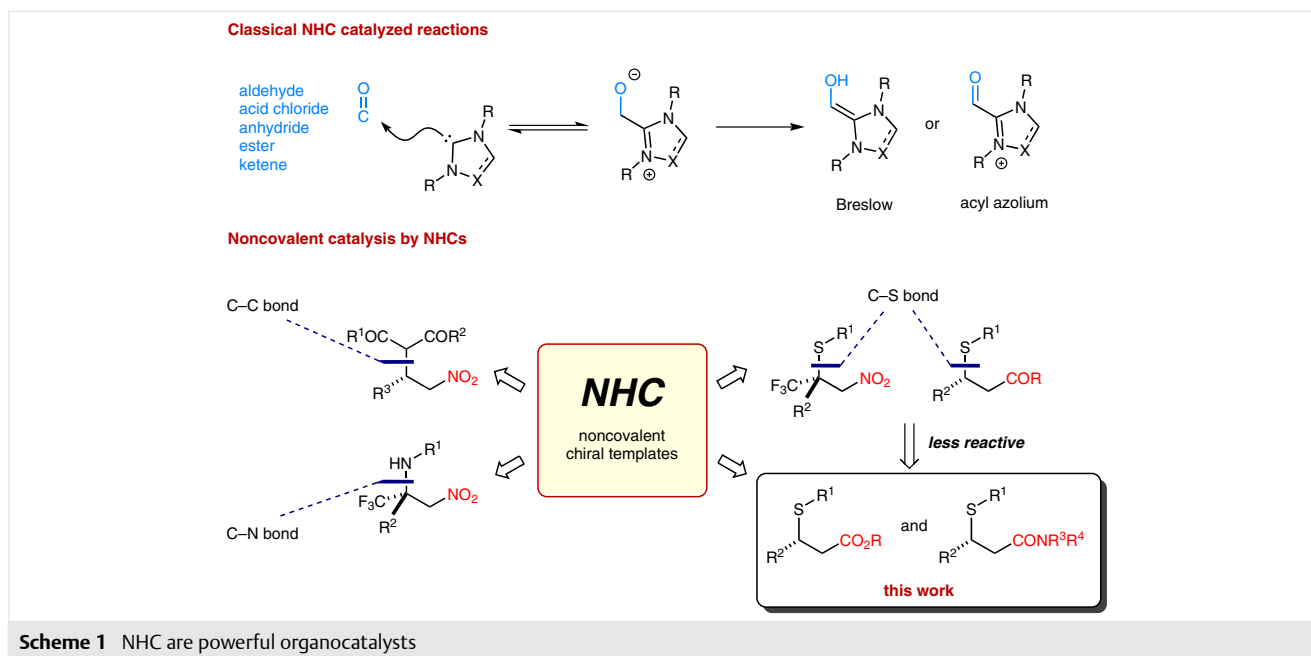
Abstract We report an asymmetric sulfa-Michael reaction of α,β -unsaturated amides and esters using a chiral N-heterocyclic carbene as the HOMO-raising organocatalyst. We discovered an interesting correlation between ^{13}C NMR shifts of substrates and ee of their products. More electron-deficient Michael acceptors afforded higher enantioselectivity.

Key words N-heterocyclic carbenes, noncovalent catalysis, sulfa-Michael, organocatalysis, asymmetric synthesis

Unlike other organocatalysts, N-heterocyclic carbenes (NHC) possess several unique chemical properties that enable them to unlock multiple generic modes of substrate activation for catalysis.¹ More recently, focus in the field of NHC catalysis has diverted away from the classical aldehyde umpolung chemistry.² Many acyl anion free reactions, especially those involving less reactive substrates, were reported that have substantially increased the ‘market share’ of NHC among other organocatalysts. Nevertheless, nearly all NHC-mediated transformations start from a nucleophilic attack of NHC to a carbonyl functionality. The newly formed carbon-carbon bond secures a robust relay of chiral information from the catalyst to the substrate. On the other hand, the well-known Brønsted basicity of NHC received little success as a potential HOMO-raising activation strategy.³ Recently, we reported the first enantioselective C-C, C-S, and C-N bond synthesis using NHC as a noncovalent chiral template.⁴ One key to high asymmetric induction in these reactions is the use of very reactive Michael acceptors, such CF_3 -containing nitroolefins. The more challenging α,β -unsaturated esters and amides were not studied. Enantioselective sulfa-Michael addition reactions of α,β -unsaturated

esters are not very common and only thiophenols and thioacids were used as the nucleophile.⁵ Reactions involving simple alkyl mercaptans are rare.^{5b} As for α,β -unsaturated amides, only oxazolidinone-derived imides were successful substrates.⁶ Herein, we disclose our recent finding of asymmetric sulfa-Michael reactions involving these less reactive, yet underexplored α,β -unsaturated esters and amides (Scheme 1).

We initially evaluated the reactivity of benzyl mercaptan against various crotonic esters. Simple methyl crotonate failed to react with BnSH at -78°C . The more reactive hexafluoroisopropyl ester reacted in high yield (89%) with poor selectivity (23% ee). In sharp contrast, the corresponding phenyl ester afforded the sulfa-Michael adduct in good yield and decent ee. Our previous reports showed that an acidic proton shuttle (hexafluoroisopropanol) is often required for noncovalent catalysis by NHC. However, we found the reaction performed better in the absence of such a proton shuttle. We reason that ester enolates are quite basic and BnSH serves as an effective additive by itself. We next optimized the structure of the catalyst (Table 1). The Ar group of the aminoindanol-derived triazolium scaffold was modified. It was very interesting that only those containing a bulky 2,6-disubstituted aryl (**4a,b**, Table 1, entries 1 and 2) yielded both good reactivity and selectivity. Simple phenyl or pentafluorophenyl analogues (**4c,d**, Table 1, entries 3 and 4) failed to promote this reaction. When *N*-aryl was changed to *N*-benzyl (**4f**, Table 1, entry 6), the product was obtained with the opposite enantiomer enriched. Other chiral triazolium and imidazolium NHC precursors were examined as well. Several commonly used chiral scaffolds (**4g-i**, Table 1, entries 7–9) for covalent catalysis returned very poor selectivity. Solvent was briefly examined. Nonpolar solvents, toluene and diethyl ether in particular, gave the



Scheme 1 NHC are powerful organocatalysts

highest selectivity, 67% ee and 72% ee, respectively. Due to the noticeably fast reaction in toluene, it was chosen for subsequent substrate-scope survey (Scheme 2).

Various aryl esters of crotonic acid were examined for the sulfa-Michael addition with BnSH. *ortho* Substitution has a negative impact on the selectivity, regardless of the electronic property of the substituent (**3aj,al,an,aq**). The *meta* and *para* substituents, on the other hand, have little effect. However, the electronic nature of the *para* substituent does influence the ee of its product. For example, a substrate bearing a strong electron-donating *p*-methoxy reacted with 56% ee, while the corresponding *p*-nitro analogue gave 77% ee (**3ak** vs. **3ac**). Interestingly, although Chi and co-workers reported the activation of *p*-nitrophenyl esters (**3ac**, to the corresponding acyl azolium intermediate) using similar NHC,²¹⁻¹ no such reaction was observed due to the low reaction temperature. No methyl ester was formed when methanol, a well-known acyl azolium scavenger, was introduced to the reaction. It is noteworthy that heteroaryls are well tolerated for this reaction. Those containing a basic nitrogen – pyridine, and quinoline, for example – did not interfere with the catalyst (**3ao-aq**). Decreased selectivity was observed for large β -alkyl groups (**3ar**). Due to diminished reactivity, no sulfa-Michael addition occurred for cinnamates even at room temperature. Benzyl mercaptan is the best sulfur source for this reaction. Aromatic substitution is well tolerated for the benzyl group (**3da-ga**).

Our previous studies using β -aryl- β -trifluoromethylnitroolefins showed that the electronic density of the β -aryl group directly correlates to the ee of the product. We wondered whether we could affect the electronic density of the

β -carbon similarly by tuning the electronics of the aryloxy group. We plotted the ^{13}C NMR shift of the β -carbon against the $\log(\text{er})$ of the product (Figure 1). Interestingly, for β -carbons with ^{13}C NMR ranging from $\delta = 146.80$ – 148.87 ppm, the selectivity of the sulfa-Michael reaction steadily increased and plateaued (Table 2). These data clearly show that more reactive substrates give higher ee, which is in sharp contrast to nitroolefins. Linear free-energy relationship (LFER) study using substrates in Table 2 revealed a similar correlation between Hammett σ and σ^+ values of R and the ee of the product.⁷ Although we cannot provide an unambiguous answer for this behavior, a weak interaction between the catalyst and the conjugate system of the Michael acceptor might be operative.

Amides were examined as well. Although simple alkyl amides did not react with thiols under the standard reaction conditions, more reactive imides were good substrates. Both pyrrolidinone- and oxazolidinone-derived imides were good substrates for asymmetric sulfa-Michael reac-

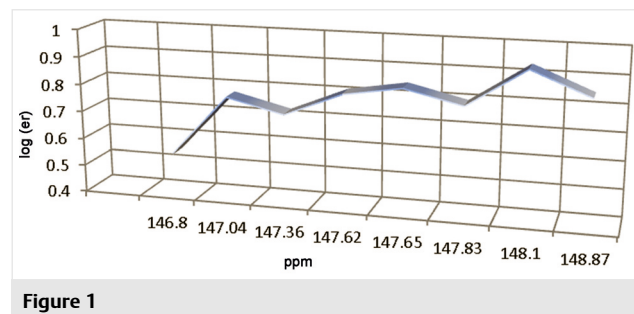
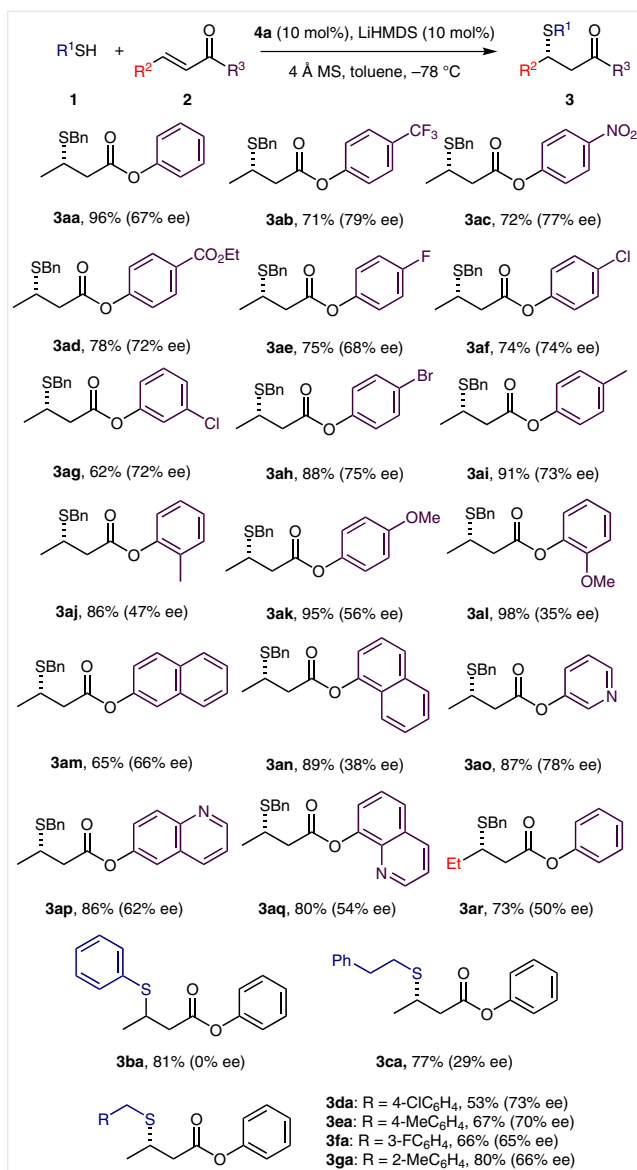


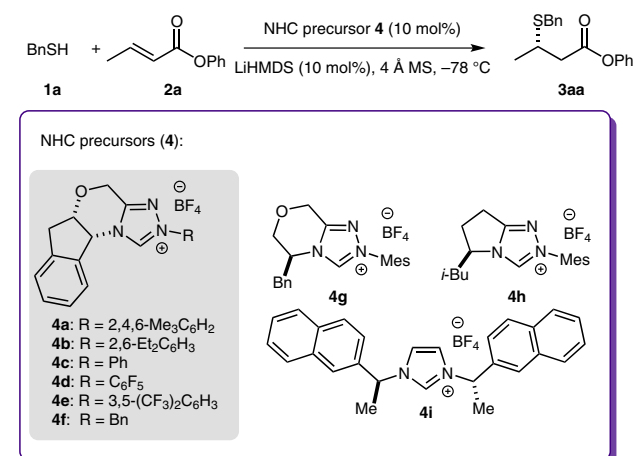
Figure 1



tion with benzyl mercaptan. For the reaction using **4a**, 89% yield and 87% ee were obtained. Slightly lower ee was obtained for substrate **4b**. Again, more reactive substrate afforded higher enantioselectivity (Scheme 3).

We propose the following transition state that explains the observed absolute stereochemistry (Scheme 4). Up on hydrogen bonding to the NHC catalyst, the thiol is pushed above the flat NHC heterocycle due to severe crowding in the lower space. The Michael acceptor approaches from the top, with the large aryl ester oriented away from the bulky mesyl group. The α -carbon of the ester is in close proximity to the thiol hydrogen for intramolecular proton transfer.^{4b,c} The newly formed chiral center was determined to be S

Table 1 Optimization of Conditions^a



Entry	NHC precursor 4	Solvent	Yield (%) ^b	ee (%) ^c
1	4a	toluene	96	67
2	4b	toluene	78	65
3	4c	toluene	<5	– ^d
4	4d	toluene	<5	– ^d
5	4e	toluene	<5	– ^d
6	4f	toluene	56	–20
7	4g	toluene	84	–36
8	4h	toluene	63	–4
9	4i	toluene	92	–11
10	4a	CH ₂ Cl ₂	42	54
11	4a	MeCN	65	23
12	4a	THF	50	42
13	4a	Et ₂ O	48	72

^a Reaction conditions: **1a** (0.2 mmol), **2c** (0.1 mmol), NHC precursor (10 mol%), LiHMDS (10 mol%), 4 Å MS (100 mg), solvent (1.2 mL), -78 °C, 36 h.
^b Isolated yield.
^c Determined by chiral HPLC.
^d Not determined.

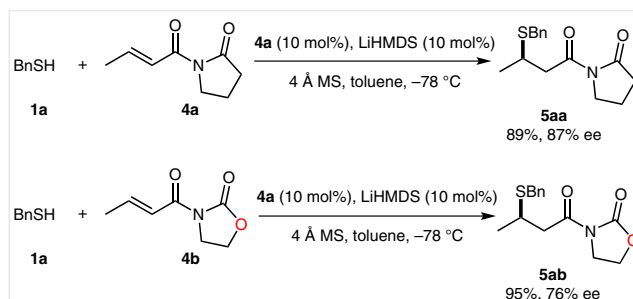
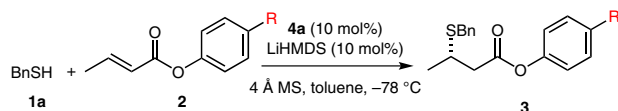
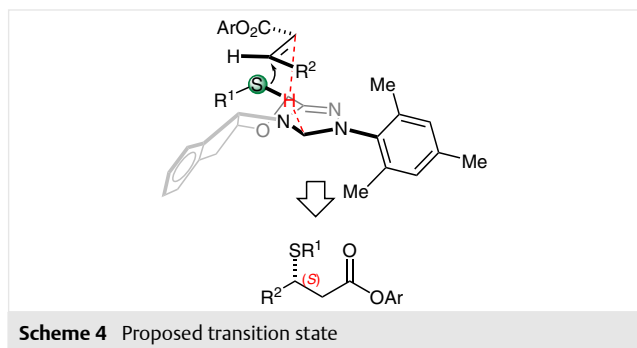


Table 2 Correlation of Electron Density of the β -Carbon with the Selectivity

Entry	R	^{13}C NMR δ of the β -carbon (ppm)	er	log (er)
1	2k OMe	146.80	78:22	0.550
2	2a H	147.04	85.5:14.5	0.771
3	2e F	147.36	84:16	0.720
4	2f Cl	147.62	86.5:13.5	0.807
5	2h Br	147.65	87.5:12.5	0.841
6	2d CO ₂ Et	147.83	86:14	0.792
7	2b CF ₃	148.10	89.5:10.5	0.931
8	2c NO ₂	148.87	88.5:11.5	0.886

**Scheme 4** Proposed transition state

configuration by comparing to literature reported optical rotation values.^{6b,d}

In summary, the recently unlocked noncovalent catalysis mode for chiral NHC was investigated in asymmetric sulfa-Michael addition reactions using less reactive α,β -unsaturated esters and amides.⁸ β -Benzylthio esters were synthesized in good yield and moderate to good enantioselectivity. In contrast to nitroolefins, more reactive ester/amide substrates yielded higher selectivity and no external proton shuttle is required for catalyst turnover. We expect NHC will be more intensively studied as a powerful noncovalent organocatalysts in the near future.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at <http://dx.doi.org/10.1055/s-0035-1561843>.

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(8) **General Procedure for the NHC-Catalyzed Sulfa-Michael Addition Reaction**

NHC precursor **4a** (4.2 mg, 0.01 mmol) and oven-dried 4 Å MS (100 mg) were mixed in dry toluene (0.6 mL) in a 10 mL test tube. The reaction vessel was degassed and back-filled with argon three times before LiHMDS (1 M in THF-ethylbenzene, 10 µL, 0.01 mmol) was slowly added. The mixture was stirred at r.t. for 30 min and another 30 min at -78 °C. Thiol **1** (0.2 mmol) was slowly added, and the mixture was stirred for 30 min at

-78 °C. A solution of substrate **2** (0.1 mmol) in toluene (0.6 mL) was slowly added over 30 min. The reaction was stirred at -78 °C for 48 h. The reaction was quickly filtered through a plug of silica gel and concentrated. The residue was purified by silica gel flash column chromatography (eluent: hexane-EtOAc = 50:1) to give product **3**.

Compound **3aa**: 27 mg; 96% yield; colorless oil. ¹H NMR (400 MHz, CDCl₃): δ = 7.51–7.19 (m, 8 H), 7.10 (d, *J* = 7.7 Hz, 2 H), 3.97–3.77 (m, 2 H), 3.36–3.18 (m, 1 H), 2.87 (dd, *J* = 15.4, 6.5 Hz, 1 H), 2.73 (dd, *J* = 15.4, 7.9 Hz, 1 H), 1.43 (d, *J* = 6.8 Hz, 3 H). ¹³C NMR (100 MHz, CDCl₃): δ = 169.87 (s), 150.58 (s), 138.08 (s), 129.43 (s), 128.87 (s), 128.58 (s), 127.10 (s), 125.90 (s), 121.54 (s), 42.09 (s), 36.05 (s), 35.38 (s), 21.34 (s). Chiral HPLC (AD-H, 5% EtOH in hexanes, 1.0 mL/min, 210 nm): *t*_R (major) = 7.4 min, *t*_R (minor) = 6.4 min, 67% ee. HRMS (ESI⁺): *m/z* calcd for C₁₇H₁₈O₂NaS⁺ [M + Na]⁺: 309.0925; found: 309.0920.