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Organocatalytic Asymmetric Sulfa-Michael Addition to α,β-Unsaturated Ketones

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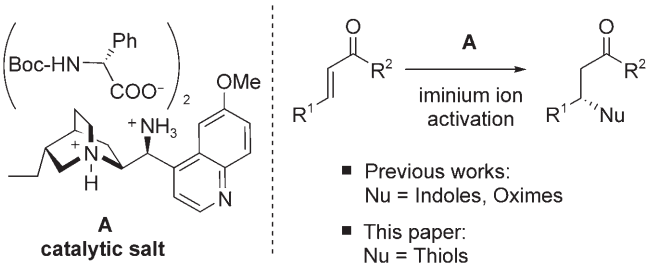
Abstract: The highly enantioselective organocatalytic sulfa-Michael addition to α,β-unsaturated ketones has been accomplished using benzyl and *tert*-butyl mercaptans as the sulfur-centered nucleophiles. Optically active products are obtained in high yields and good to excellent stereocontrol (up to 96% *ee*) from a large variety of enones. Central to these studies has been the use of the catalytic primary amine salt **A**, derived from 9-amino-(9-deoxy)-*epi*-hydroquinine and D-*N*-Boc-phenylglycine, in which both the cation and the anion are chiral, that exhibits high reactivity and selectivity for iminium ion catalysis with enones.

Keywords: asymmetric catalysis; conjugate addition; ketones; organocatalysis; sulfur

The enantioselective construction of carbon-sulfur stereogenicity represents an important objective in organic and pharmaceutical synthesis.[1] Among the existing methods for the preparation of chiral sulfur-containing molecules, the asymmetric sulfa-Michael addition (SMA), the reaction of sulfur-centered nucleophiles with electron-deficient olefins, is of prime importance.[2] While the use of stoichiometric chiral auxiliaries and reagents has been established as an effective strategy for C–S bond construction,[3] the corresponding catalytic variants have been far less developed.[4]

Highly enantioselective sulfa-Michael additions promoted by both metal and organic catalysts have been limited to unsaturated imides,[5] cyclic enones[6] and, more recently, unsaturated aldehydes.[7] On the contrary, just two organocatalytic asymmetric SMA to simple enones have been reported recently, affording the β-functionalized carbonyl derivatives in moderate optical purity and with important restrictions in substrate scope.[8] Thus, the use of simple α,β-unsaturated ketones still remains an important challenge for the asymmetric SMA strategy. Additionally, the range of sulfur-centered nucleophiles well suited for both catalytic and stoichiometric methodologies is generally restricted to aromatic thiols.[9]

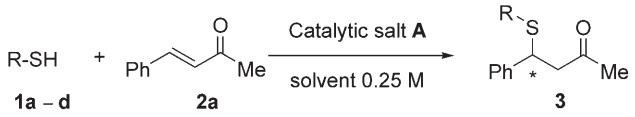
Recently, we have developed a new primary amine salt catalyst, in which both the cation and the anion are chiral, that exhibits high reactivity and selectivity for iminium ion catalysis with α,β-unsaturated ketones.[10] In particular we have shown that salt **A**,



made by combining the easily available 9-amino-(9-deoxy)-*epi*-hydroquinine[11] with D-*N*-Boc-phenylglycine as the chiral counteranion, can function as highly efficient catalyst for the asymmetric conjugated addition of indoles[10a] and oximes[10b] to simple enones; the efficient activation relies on the proven ability of primary amines to form iminium ion intermediates from ketones, owing to reduced steric constraints,[12] combined synergistically with the benefits of asymmetric counteranion-directed catalysis (ACDC), an efficient strategy for enantioselective transformations that proceed *via* cationic species.[13]

Herein, we further advance this organocatalytic activation strategy to document an operationally trivial procedure for the highly chemo- and enantioselective

Table 1. Screening results for the organocatalytic addition of different thiols (**1**) to enone (**2a**).[a]



1a – d 2a 3

Entry	R	**A** [mol%]	Solvent	*T* [°C]	Time [h]	Conversion [%][b]	*ee* [%][c]
1	Ph, **1a**	20	toluene	r.t.	18	>95	45
2	Ph, **1a**	20	toluene	−10	30	75	55
3	Naphthyl, **1b**	20	toluene	r.t.	3	>95	0
4	Bn, **1c**	20	toluene	r.t.	18	>95	56
5	Bn, **1c**	10	toluene	r.t.	18	>95	40
6	Bn, **1c**	10	toluene	−30	24	40	86
7[d]	Bn, **1c**	20	toluene	r.t.	18	30	- 8
8[e]	Bn, **1c**	20	toluene	−30	24	26	76
9	Bn, **1c**	10	CH_2Cl_2	−30	24	37	70
10	Bn, **1c**	10	Et_2O	−30	24	70	79
11[f]	Bn, **1c**	10	toluene	−30	24	60	83
12	Bn, **1c**	5	toluene	−30	24	20	85
13	Bn, **1c**	15	toluene	−20	66	90 (81)	85
14	*t*-Bu, **1d**	20	toluene	r.t.	116	72 (59)	95

[a] Reactions were carried out in undistilled solvents without any precaution to exclude air, using 1.2 equivs. of thiols **1** on a 0.2-mmol scale.
[b] Determined by ^{1}H NMR of the crude mixture; isolated yield is indicated between brackets.
[c] The *ee* of **3** was determined by HPLC analysis on chiral support.
[d] 9-Amino(9-deoxy)-*epi*-hydroquinine without any acidic counterion was used as the catalysts.
[e] L-*N*-Boc-phenylglycine was used as the counterion.
[f] $[\mathbf{2a}]_0 = 0.5$ M.

sulfa-Michael addition of benzyl and *tert*-butyl mercaptans to α,β-unsaturated ketones catalyzed by the chiral salt **A**. The high efficiency obtained in terms of both yield and enantioselectivity (up to 96% *ee*) for a large variety of Michael acceptors highlights the applicability and utility of this catalytic system as an iminium ion activator of simple enones.

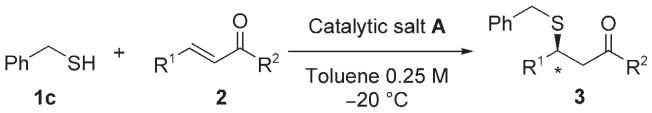
To assess the feasibility of such an asymmetric organocatalytic sulfa-Michael addition to α,β-unsaturated ketones, we screened various *S*-centered nucleophiles in the addition to *trans*-4-phenyl-3-buten-2-one **2a** in the presence of catalytic salt **A**;[14] the results of this survey are reported in Table 1. Aromatic thiols did not furnish the desired product in good enantioselectivity. Thiophenol **1a** provided the Michael adduct in 45% *ee* after 18 h at room temperature (entry 1) and lowering the reaction temperature to −10 °C did not improve the enantioselectivity to a satisfactory level (55% *ee*, entry 2).[15] The employment of a more encumbered aromatic thiol brought about a dramatic loss in stereocontrol (entry 3).

Interestingly, the use of benzyl mercaptan **1c** provided the desired product with improved steroselectivity (56% *ee*, entry 4) and this prompted us to further screen such a nucleophile. Lowering the catalyst loading showed the occurrence of a decrease in enantioselectivity (40% *ee*, entry 5); nevertheless on carrying out the reaction at lower temperature in the presence of 10 mol% of **A**, the stereoselectivity reached satisfactory levels, albeit at the expenses of reactivity (40% conversion and 86% *ee*, entry 6).

Noteworthy, in the absence of an acidic counteranion (entry 7), the diamine 9-amino-(9-deoxy)-*epi*-hydroquinine is still able to promote the sulfa-Michael addition, albeit with lower reactivity, by activating the nucleophilic component **1c** through Brønsted base catalysis.[16] However, the observed low optical purity (8% *ee*) together with reversal in the stereochemistry supports an iminium ion activation mode of catalysis when the chiral salt **A** is employed. Remarkably, consistently with previous observations,[10] using the opposite enantiomeric counteranion (L-*N*-Boc-phenylglycine) afforded the same enantiomeric product **3** with lower reactivity and selectivity (entry 8), illustrating a marked case of a matched/mismatched catalyst-ion pair combination.[17]

Evaluation of usual reaction media led to the identification of toluene as the best solvent (entries 6 and 9–10). Further optimization of standard parameters revealed that carrying out the reaction at −20 °C in the presence of 15 mol% of the catalytic salt **A** represents the best compromise between reactivity and enantioselectivity (81% isolated yield and 85% *ee* after 66 h, entry 13). Finally *tert*-butyl mercaptan **1d**, albeit less reactive, proved to be a promising alternative *S*-nucleophile for the present SMA strategy, as

Table 2. Organocatalytic asymmetric sulfa-Michael addition of benzyl mercaptan (**1c**) to enones (**2**).[a]



Entry	R^1	R^2	**A** [mol%]	Time [h]	Product and Yield [%][b]	*ee* [%][c]
1	Ph	Me, **2a**	15	66	**3a** 81	85
2	*p*-ClC_6H_4	Me, **2b**	15	46	**3b** 78	84
3	2-thienyl	Me, **2c**	15	66	**3c** 84	84
4	Pent	Me, **2d**	20	96	**3d** 81	89
5	Pent	Et, **2e**	20	96	**3e** 75	96
6	Me	Et, **2f**	20	96	**3f** 55	94
7[d]	Ph	Ph, **2g**	20	40	**3g** 75	54[e]

[a] Reactions carried out using 1.2 equivs. of **1c** on a 0.2 mmol scale.
[b] Isolated yield.
[c] Determined by HPLC analysis on chiral support.
[d] Reaction carried out at room temperature.
[e] The absolute configuration of the product **3g** was assigned to be (*S*) by comparison of the measured optical rotation with the value reported in the literature.[8a]

the corresponding product was isolated in satisfactory yield and very high enantiomeric excess (59% yield and 95% *ee*, entry 14). Besides these interesting results, the use of benzyl and *tert*-butyl mercaptan represents an important feature from a synthetic standpoint, providing orthogonal sets of removable *S*-protecting groups.[18]

Having identified **1c** and **1d** as two suitable nucleophiles, we set out to investigate the scope of the organocatalyzed SMA reaction with respect to various α,β-unsaturated ketones. The addition of benzyl mercaptan **1c** proved to be efficiently activated by the catalytic salt **A**, providing the desired adduct in good yields and high *ee* (Table 2). There appears to be significant tolerance towards steric and electronic demands of the β-olefin substituent as highly enantioenriched adducts could be obtained using aromatic, heteroaromatic and alkyl groups.

Variation in the steric contribution of R^2 ketone substituents (compare entries 4 and 5) revealed that the more encumbered ethyl group engenders higher selectivity, albeit at the expenses of the reactivity; the sulfa-Michael adducts could be isolated in good yields and very high optical purity (*ee* values ranging from 94% to 96%) by adjusting the catalyst loading and the reaction time (entries 5–6).[19]

In our previous studies[10a] we observed that the chiral salt **A** was an effective catalyst also for aromatic ketones (R^2 = Ph), a class of substrates which is not generally suitable for iminium ion activation. Notably, our organocatalytic protocol confirms its efficiency in activating aromatic ketones such as *trans*-chalcone **2g** providing the desired product **3g**, albeit with moderate stereocontrol (entry 7). The absolute configuration of the product **3g** was assigned to be (*S*) by comparison of the measured optical rotation with the value reported in the literature.[8a] The sense of the stereochemical induction is in agreement with the observation made in the previously reported Michael additions catalyzed by the catalytic salt **A**.[10] Theoretical studies based on DFT calculations on the iminium ion intermediate to understand the origin of the enantioselectivity are ongoing and will be reported in due course.

We next examined whether the presented organocatalytic SMA protocol could be extended to an alternative thiol having a different removable protecting group. Indeed, the catalytic salt **A** efficiently catalyzed the sulfa-Michael addition of *tert*-butyl mercaptan **1d** to a large variety of simple enones. Albeit the low reactivity of **1d** required the use of 20 mol% of the catalyst and prolonged reaction time, impressive levels of stereocontrol was achieved even at room temperature (Table 3).

In the presence of aromatic substituents at the β-position of the Michael acceptor, enantioselectivities ranging from 91% to 95% were obtained with great tolerance for heteroaromatic and variously substituted functional groups (entries 1–5). The protocol was also efficient for aliphatic enones providing the expected products in high optical purity and good yields (entries 6–9).

Interestingly, the presented organocatalytic SMA proceeds efficiently also with cyclic enones, the product derived from 2-cycloexen-1-one being isolated in high yield and enantioselectivity (96% yield, 87% *ee*, entry 10). This result, in conjunction with the observation that reaction with *trans*-chalcone provided product **4k** with excellent enantiomeric excess (95% *ee*, entry 11), adds significant importance to the present organocatalytic SMA protocol demonstrating that **A** is able to activate efficiently and in a high stereoselec-

Table 3. Organocatalytic asymmetric sulfa-Michael addition of *tert*-butyl mercaptan (**1d**) to enones (**2**).[a]

Entry	R^1	R^2	Product and Yield [%][b]	*ee* [%][c]
1	Ph	Me, **2a**	**4a** 59	95
2	*p*-ClC_6H_4	Me, **2b**	**4b** 70	94
3	*p*-$NO_2C_6H_4$	Me, **2i**	**4c** 98	91
4	*p*-CNC_6H_4	Me, **2j**	**4d** 96	94
5	2-thienyl	Me, **2c**	**4e** 65	92
6	Pent	Me, **2d**	**4f** 76	91
7	Me	Me, **2k**	**4g** 71	82
8	*i*Pr	Me, **2l**	**4h** 46	88
9	$PhCH_2CH_2$	Me, **2m**	**4i** 49	87
10[d]	$(CH_2)_3$, **2n**		**4j** 96	87
11	Ph	Ph, **2h**	**4k** 44	95

[a] Reactions carried out using 1.2 equivs. of **1d** on a 0.2-mmol scale.
[b] Isolated yield.
[c] Determined by HPLC analysis on chiral support.
[d] Reaction carried out over 5 h.

tive fashion different classes of α,β-unsaturated ketones.[20]

In summary, we have disclosed an organocatalytic asymmetric protocol for the highly enantioselective sulfa-Michael addition that is effective for a large variety of α,β-unsaturated ketones. The high chemical yields and enantioselectivities obtained consolidate the catalytic salt **A** as a general iminium ion activator of simple enones. From a synthetic perspective, the simplicity of the procedure that employs easily available starting materials and catalyst in combination with the use of *S*-centered nucleophiles having different removable protecting groups, renders the method potentially useful to the chemical community.

Experimental Section

General Procedure for the Organocatalytic Sulfa-Michael Addition to α,β-Unsaturated Ketones

All the reactions were carried out in undistilled toluene without any precautions to exclude water. In an ordinary test tube equipped with a magnetic stirring bar, 9-amino-(9-deoxy)-*epi*-hydroquinine (10–20 mol%) and D-*N*-Boc-phenylglycine (20–40 mol%) as the chiral counteranion were dissolved in 0.8 mL of toluene. The solution was stirred for 20 min at room temperature to allow the formation of the catalytic salt **A**. After addition of α,β-unsaturated ketones **2** (0.2 mmol), the mixture was stirred at the appropriate temperature for 10 min. Then thiol **1** (0.24 mmol, 1.2 equivs.) was added in one portion, the tube was closed with a rubber stopper and stirring was continued for the indicated time. Then the crude reaction mixture was diluted with hexane (2 mL) and flushed through a short plug of silica, using hexane/Et_2O (1/1) as the eluent. Solvent was removed under vacuum, and the residue was purified by flash chromatography to yield the desired product.

Supporting Information

Complete experimental procedures and full characterization of compounds **3a–g** and **4a–k** are given in the Supporting Information.

Acknowledgements

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[14] The results obtained by using 9-amino-(9-deoxy)-*epi*-hydroquinine in combination with different counterions (TFA, *p*-TSA, L-*N*-Boc-phenylalanine) in the organocatalyzed SMA did not bring any appreciable improvement in terms of enantioselectivity, confirming the superior efficiency of the catalytic salt **A**.

[15] Considering the relative high acidity of phenyl thiol **1a**, its Michael addition to **2a** could be easily promoted by weak bases, see Ref.[16] Since the catalyst amine component 9-amino-(9-deoxy)-*epi*-hydroquinine has three basic nitrogen atoms, a Brønsted base-catalyzed background reaction, affecting the stereoselectivity of the process, could be envisaged. As interestingly suggested by one reviewer, the use of 3 equivs. of D-*N*-Boc-phenylalanine as the acidic additive to avoid this parasitic reaction has been investigated, resulting in only a slight enhancement of enantioselectivity: $T = -10\,^{\circ}C$, 30 h reaction time, 80% conversion, 62% *ee* (compare to entry 2, Table 1).

[16] The potentiality of *Cinchona* alkaloids to act as bases to deprotonate substrates with relatively acidic protons such as thiols, thus forming a contact ion-pair between the resulting anion and the protonated quinuclidine moiety, is well established, see Refs.[4b,6b]

[17] For a similar behavior in ACDC activation strategy, see Ref.[13b]

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[19] α,β-Unsaturated ketone with $R^1 = Ph$ and $R^2 = Et$ gave a sluggish reaction rate (27% conversion after 42 h), although the product was formed in 90% *ee* at $-30\,^{\circ}C$ in the presence of 20 mol% of catalytic salt **A**.

[20] Achieving high levels of generality and selectivity in asymmetric SMA under catalytic conditions is rather challenging, as methods that provide regularly high enantioselectivity (*ee*s above 90%) are scarce; see Refs.[6b,7a–c]

