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The highly enantioselective sulfa-Michael addition of alkyl thiols to unactivated β -substituted- α,β -unsaturated esters catalyzed by a bifunctional iminophosphorane (BIMP) organocatalyst is described. The low acidity of the alkyl thiol pro-nucleophiles is overcome by the high Brønsted basicity of the catalyst and the chiral scaffold/thiourea hydrogen-bond donor moiety provides the required enantiofacial discrimination in the addition step. The reaction is broad in scope with respect to the alkyl thiol and β -substituent of the α,β -unsaturated ester, affords sulfa-Michael adducts in excellent yields (up to >99%) and enantioselectivity (up to 97 : 3 er) and can operate down to 1 mol% catalyst loading.

electrophiles for new enantioselective organocatalytic reaction development (Fig. 1).

A proven strategy to overcome low substrate electrophilicity in base-catalyzed polar addition reactions is to increase the concentration of the nucleophilic conjugate base in the pot – and therefore the rate of the nucleophilic addition reaction – by enhancing the Brønsted basicity of the catalyst relative to tertiary amine catalysts.^{11–13} To this end, we disclosed that bifunctional iminophosphorane (BIMP) catalysts, containing a novel organosuperbase were highly efficacious in the first general enantioselective organocatalytic ketimine nitro-Mannich reaction.^{12*b,d*} Likewise, very recently, high catalyst performance (in terms of

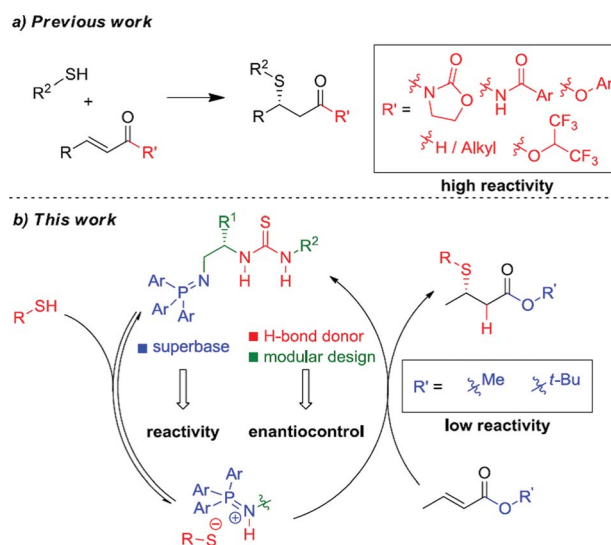


Fig. 1 Bifunctional Brønsted base/H-bond donor organocatalytic SMA to α,β -unsaturated ester derivatives.

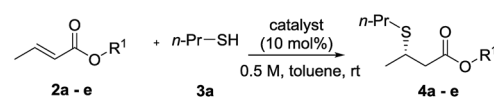
† Electronic supplementary information (ESI) available: Experimental procedures, spectroscopic data, copies of ^1H and ^{13}C NMR spectra and HPLC and GC chromatograms. See DOI: 10.1039/c6sc02878k

reactivity and enantioselectivity) with a second generation BIMP catalyst was also witnessed in the first organocatalytic conjugate addition of alkyl thiols to unactivated α -substituted acrylate esters (such as methyl methacrylate).^{12e} In both of these transformations an organosuperbase was demonstrated to be essential for reactivity.

We speculated that the reluctance of unactivated β -substituted- α,β -unsaturated esters to undergo organocatalytic Michael addition reactions could be overcome using our BIMP catalyst family. To exemplify this we chose the sulfa-Michael addition (SMA) of alkyl thiols as this is a reaction of central importance for the asymmetric construction of chiral sulfides possessing a stereogenic centre at the β -carbon and no organocatalytic enantioselective version has previously been reported.^{14,15} We reasoned that the high Brønsted basicity of our BIMP catalysts could activate the high pK_a alkyl thiol pro-nucleophile ($pK_{a(\text{DMSO})} = 17$ for $n\text{-BuSH}$)^{16,17} and the modular design of the catalyst family, through its variable backbone scaffold, hydrogen-bond donor group and iminophosphorane superbase would expedite optimal catalyst identification. Herein, and as part of our research program towards the development of novel asymmetric reactions with challenging electrophile/pro-nucleophile combinations, we wish to report our investigations leading to the highly enantioselective SMA reaction of alkyl thiols to unactivated β -substituted- α,β -unsaturated esters.

We chose commercially available methyl crotonate (**2a**) and 1-propanethiol (**3a**) as our model system and investigated reactivity using first generation BIMP catalyst **1a** (Table 1, entry 1). In toluene, at room temperature using 10 mol% catalyst we were delighted to observe an exceptional reactivity profile; β -mercaptoester product **4a** was afforded in near quantitative yield after only 2 hours with low but significant enantiocontrol (55 : 45 er).¹⁸ With good reactivity established we next investigated the performance of a small library of second generation BIMP catalysts featuring variations around the amide-thiourea motif that we recently reported^{12e} (Table 1, entries 2–6). The modular design of our BIMP catalysts allowed rapid library

Table 1 Catalyst screening studies and reaction optimization^a

						
Entry	Cat.	R ¹	Product	Time (h)	Yield ^b (%)	er ^c
1	1a	Me	4a	2	94	55 : 45
2	1b	Me	4a	2	98	55 : 45
3	1c	Me	4a	2	94	52 : 48
4	1d	Me	4a	2	93	59 : 41
5	1e	Me	4a	2	>99	75 : 25
6	1f	Me	4a	2	97	62 : 38
7 ^d	1g	Me	4a	3	>99	81 : 19
8	1g	Et	4b	3	95	84 : 16
9	1g	i-Pr	4c	3	>99	85 : 15
10	1g	Bn	4d	3	>99	81 : 19
11 ^d	1g	<i>t</i> -Bu	4e	8	94	92 : 8
12 ^{d,e}	1g	<i>t</i> -Bu	4e	8	95	94 : 6
13 ^f	1g	<i>t</i> -Bu	4e	24	94	96 : 4
14 ^g	1g	<i>t</i> -Bu	4e	72	94	97 : 3

^a Reactions were carried out with 0.20 mmol of **2** and 0.60 mmol of **3a**.

^b Isolated yield. ^c Determined by HPLC analysis on a chiral stationary phase. ^d Reaction performed on 0.10 mmol scale of **2a**. ^e Reaction performed at 0 °C. ^f Reaction performed at 0 °C in Et₂O. ^g Reaction performed at –15 °C in Et₂O.

generation and our attention focussed on the amide-thiourea moiety as the H-bond donor group and the tris-(4-methoxyphenylphosphine) derived iminophosphorane as the Brønsted basic group (Fig. 2).

Catalysts **1b–d** possessing a thiourea constructed from two (*S*)-configured *tert*-leucine derived residues, the tris-(4-methoxyphenylphosphine)-derived iminophosphorane and a variable terminal amide group gave poor enantioselectivity in all cases (Table 1, entries 2, 3, and 4). When catalyst **1e** – the diastereomer of **1d** – was trialled however, a significant boost to the enantioselectivity was witnessed (Table 1, entry 5, 75 : 25 er).¹⁹

A comparison with an analogous catalyst possessing a phenylglycine and a *tert*-leucine residue (**1g**) resulted in a slight improvement to the enantioselectivity (Table 1, entry 7, 81 : 19 er). At this stage, the effect of varying the ester group of the crotonate on the enantioselectivity in the SMA was investigated. A range of simple, commercial or readily synthesized alkyl crotonate esters were trialled and a correlation between the size of the ester group and the enantioselectivity was observed – pleasingly *tert*-butyl crotonate (**2e**) afforded the product **4e** in 92 : 8 er albeit in a slightly increased reaction time of 8 h (Table 1, entry 11). A reoptimization of the reaction conditions to 0.5 M in Et₂O at 0 °C (Table 1, entries 12 & 13 and ESI†) resulted in a significant boost to the enantioselectivity (96 : 4 er) and cooling the reaction temperature further to –15 °C afforded β -mercaptoester **4e** in 94% yield and 97 : 3 er (Table 1, entry 14).

With optimized reaction conditions established, the scope of the transformation with respect to the thiol pro-nucleophile and the α,β -unsaturated ester was investigated (Fig. 3). Minimal variation to the enantioselectivity was observed across a good range of linear (propyl to decyl) or branched (cyclic and acyclic)

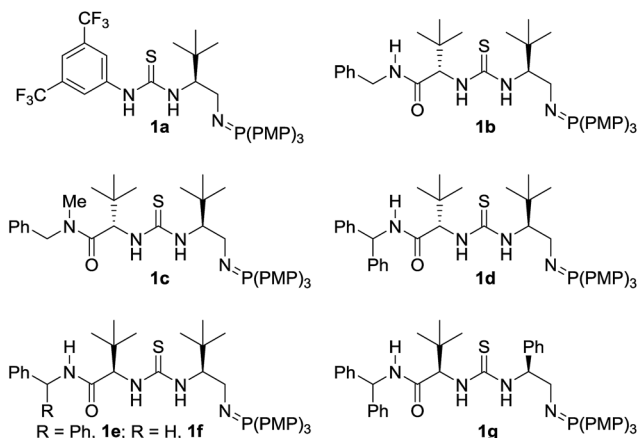
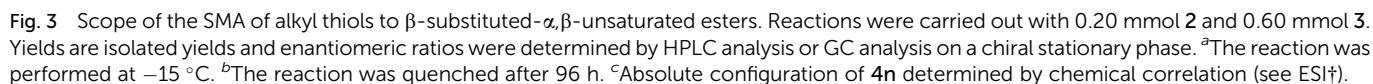


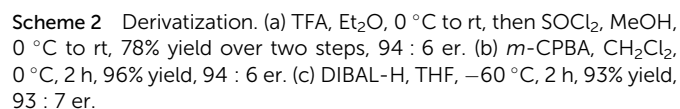
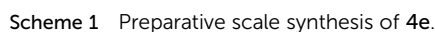
Fig. 2 Bifunctional iminophosphorane (BIMP) organocatalysts used in the optimization of the SMA reaction. PMP = *p*-methoxyphenyl.





Similarly, excellent yields of the β -mercaptoesters **4o–r** were obtained from the corresponding primary alkyl β -substituted- α,β -unsaturated esters with very good levels of enantiocontrol. β -Mercaptoesters **4s** and **4t** containing a terminal *N*-Boc protected amine and TBS protected hydroxyl group respectively

To demonstrate synthetic utility of the β -mercaptoester products a selection of standard chemical transformations were carried out (Scheme 2). Thus β -mercaptoester **4e** (95 : 5 er) was transesterified to the methyl ester **4a** in a two step process;



initial acidic cleavage of the *tert*-butyl ester and subsequent methyl ester formation under acidic conditions afforded **4a** in 78% yield without compromising stereochemical integrity. Oxidation of **4e** afforded sulfone **5a** without any observable racemization in near quantitative yield. Finally, β -mercaptoester **4m** was reduced to the alcohol in excellent yield, without appreciable loss of enantiopurity.²⁰

In summary, we have developed the first organocatalytic enantioselective SMA of alkyl thiols to unactivated β -substituted- α,β -unsaturated esters. Impressive reactivity and excellent levels of enantioselectivities were achieved across a range of linear, branched, cyclic alkyl and benzylic thiols, in SMA reactions to various β -substituted- α,β -unsaturated esters using a novel bifunctional iminophosphorane catalyst. This work demonstrates that the high reactivity of the BIMP catalysts enables low reactivity electrophiles such as β -substituted- α,β -unsaturated esters to undergo highly enantioselective conjugate addition reactions for the first time and thus represents a significant advance in the field. Work to uncover further capabilities of the BIMP catalyst family is ongoing in our laboratories and the results will be disclosed in due course.

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- 20 The PMB thiol can be readily cleaved to afford the free mercaptan, see for example ref. 15g.

