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# Enantioselective bifunctional iminophosphorane catalyzed sulfa-Michael addition of alkyl thiols to unactivated $\beta$ -substituted- $\alpha,\beta$ -unsaturated esters†

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The highly enantioselective sulfa-Michael addition of alkyl thiols to unactivated  $\beta$ -substituted- $\alpha,\beta$ -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  $\beta$ -substituent of the  $\alpha,\beta$ -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.

Unactivated  $\beta$ -substituted- $\alpha,\beta$ -unsaturated esters, such as methyl crotonate, methyl cinnamate and their homologues, are a class of low reactivity electrophiles that offer a wealth of untapped potential in the field of enantioselective organocatalysis.<sup>1</sup> To date, these esters have remained a persistent challenge as Michael acceptors in asymmetric catalysis using both metal-rich and metal-free catalyst systems, largely due to their low inherent electrophilicity<sup>2</sup> and low propensity for catalyst activation and enantioface discrimination.<sup>3,4</sup> They are commercial and cheap, or are readily prepared by a variety of standard methods and are stable. In contrast to commonly used (reactive) Michael acceptors such as nitroolefins, they lie at the bottom of the Mayr electrophile reactivity ( $E$ ) scale,<sup>5,6</sup> and unlike enal and enone Michael acceptors they cannot be activated through iminium ion formation with chiral amine catalysts.<sup>7</sup> Related literature examples employ activated carboxylic derivatives<sup>8</sup> such as *N*-enoyl imides, *N*-enoyl oxazolidinones, perfluorinated alkyl esters, thioamides, *N*-enoyl pyrroles and, most recently, aryl esters.<sup>9</sup> Alternatively, activating substituents at the  $\alpha$ - or  $\beta$ -positions can also be used to gain reactivity and/or stereoselectivity. To illustrate the case in point, to date there has not been a single report of a highly enantioselective addition of a pro-nucleophilic reagent [a carbon-centered (C–H) or heteroatom-centered (X–H) acid] to unactivated alkyl cinnamate or crotonate esters under organocatalytic conditions.<sup>10</sup> Effectively, these cheap chemical feedstocks are out of reach of existing chiral organocatalysts and accordingly are a very attractive ‘simple’ target class of

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.<sup>11–13</sup> To this end, we disclosed that bifunctional iminophosphorane (BIMP) catalysts, containing a novel organo-superbase were highly efficacious in the first general enantioselective organocatalytic ketimine nitro-Mannich reaction.<sup>12b,d</sup> Likewise, very recently, high catalyst performance (in terms of

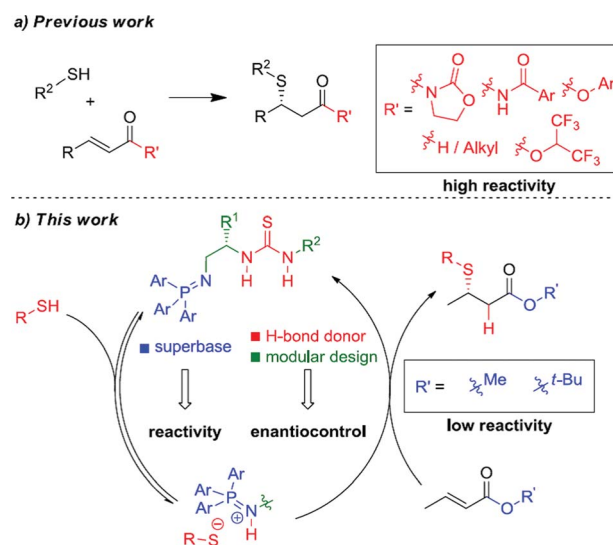


Fig. 1 Bifunctional Brønsted base/H-bond donor organocatalytic SMA to  $\alpha,\beta$ -unsaturated ester derivatives.

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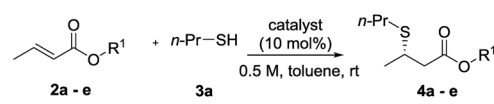
† Electronic supplementary information (ESI) available: Experimental procedures, spectroscopic data, copies of  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra and HPLC and GC chromatograms. See DOI: 10.1039/c6sc02878k

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

We speculated that the reluctance of unactivated  $\beta$ -substituted- $\alpha,\beta$ -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  $\beta$ -carbon and no organocatalytic enantioselective version has previously been reported.<sup>14,15</sup> 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  $n\text{-BuSH}$ )<sup>16,17</sup> 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  $\beta$ -substituted- $\alpha,\beta$ -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;  $\beta$ -mercaptoester product **4a** was afforded in near quantitative yield after only 2 hours with low but significant enantiocontrol (55 : 45 er).<sup>18</sup> 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<sup>12e</sup> (Table 1, entries 2–6). The modular design of our BIMP catalysts allowed rapid library

Table 1 Catalyst screening studies and reaction optimization<sup>a</sup>

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

<sup>a</sup> Reactions were carried out with 0.20 mmol of **2** and 0.60 mmol of **3a**.

<sup>b</sup> Isolated yield. <sup>c</sup> Determined by HPLC analysis on a chiral stationary phase. <sup>d</sup> Reaction performed on 0.10 mmol scale of **2a**. <sup>e</sup> Reaction performed at 0 °C. <sup>f</sup> Reaction performed at 0 °C in Et<sub>2</sub>O. <sup>g</sup> Reaction performed at –15 °C in Et<sub>2</sub>O.

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).<sup>19</sup>

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 Et<sub>2</sub>O 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  $\beta$ -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  $\alpha,\beta$ -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)

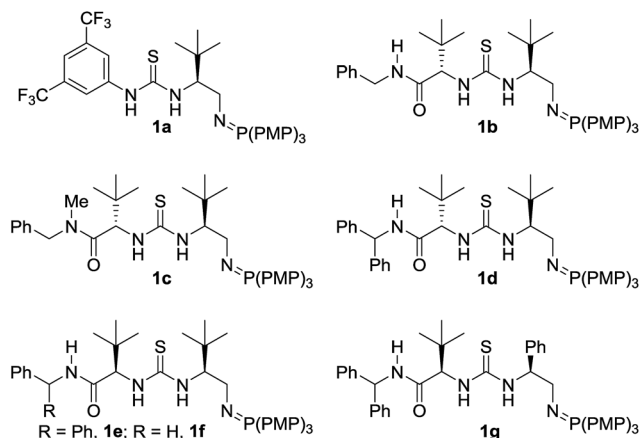
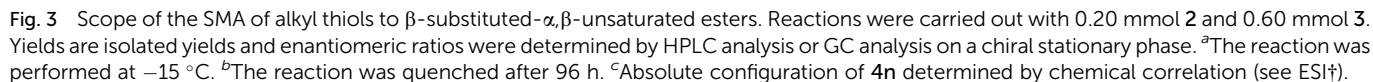


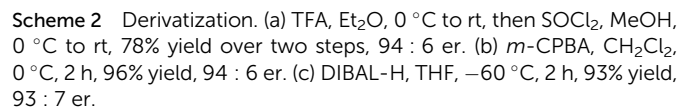
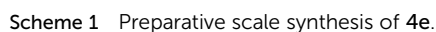
Fig. 2 Bifunctional iminophosphorane (BIMP) organocatalysts used in the optimization of the SMA reaction. PMP = *p*-methoxyphenyl.





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

To demonstrate synthetic utility of the  $\beta$ -mercaptoester products a selection of standard chemical transformations were carried out (Scheme 2). Thus  $\beta$ -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,  $\beta$ -mercaptoester **4m** was reduced to the alcohol in excellent yield, without appreciable loss of enantiopurity.<sup>20</sup>

In summary, we have developed the first organocatalytic enantioselective SMA of alkyl thiols to unactivated  $\beta$ -substituted- $\alpha,\beta$ -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  $\beta$ -substituted- $\alpha,\beta$ -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  $\beta$ -substituted- $\alpha,\beta$ -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.

