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Bifunctional Iminophosphorane Catalyzed Enantioselective Sulfa-Michael Addition to Unactivated α-Substituted Acrylate Esters

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Supporting Information

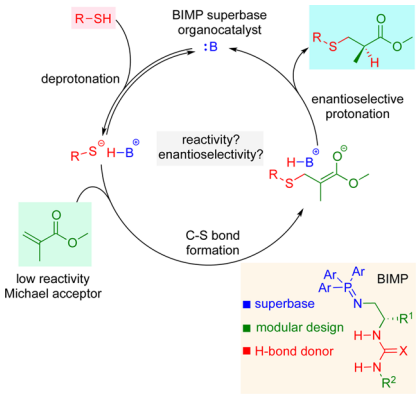
ABSTRACT: The highly enantioselective sulfa-Michael addition of alkyl thiols to unactivated α-substituted acrylate esters catalyzed by a bifunctional iminophosphorane organocatalyst under mild conditions is described. The strong Brønsted basicity of the iminophosphorane moiety of the catalyst provides the necessary activation of the alkyl thiol pro-nucleophile, while the two *tert*-leucine residues flanking a central thiourea hydrogen-bond donor facilitate high enantiofacial selectivity in the protonation of the transient enolate intermediate. The reaction is broad in scope with respect to the alkyl thiol, the ester moiety, and the α-substituent of the α,β-unsaturated ester, affords sulfa-Michael adducts in excellent yields (up to >99%) and enantioselectivities (up to 96% ee), and is amenable to decagram scale-up using catalyst loadings as low as 0.05 mol %.

The Michael addition of a carbon-centered (C−H) or heteroatom-centered (X−H) acid to a conjugated electron-deficient alkene is a fundamental reaction in organic chemistry that allows the direct and efficient construction of C−C or C−X bonds with perfect atom economy.[1] In this union, the creation of stereogenic centers, either directly at the β-carbon or indirectly through protonation at the α-carbon, is common and controlling the enantioselectivity with both metal-rich and metal-free catalysts has been the subject of intense research activity over the decades.[2] Recently, much activity has focused on organocatalytic methods,[3] and enantioselective additions of a wide range of pro-nucleophiles under iminium, enamine, or tertiary amine Brønsted base/H-bond donor catalysis to various conjugated electron deficient acceptors including enals, enones, nitroolefins, and other reactive Michael acceptors have been successfully achieved.[3g,h]

To date, however, one class of Michael acceptor, α,β-unsaturated esters substituted with alkyl or aryl groups at either the α- or β-position, has remained a persistent challenge in enantioselective organocatalysis due to their low inherent electrophilicity[4] and low propensity for catalyst activation. Both subclasses are problematic in their own way, and each one requires a solution. In this paper, we chose to tackle α-substituted acrylate esters.[5] Our primary aim was to realize reactivity and enantiocontrol with substrates possessing simple alkyl groups at the α-position. To the best of our knowledge, organocatalytic enantioselective Michael additions to methacrylate esters has been limited to NHC catalysis of aldehydes in the Stetter reaction, and examples under Brønsted base catalysis have yet to be reported.[6]

An effective approach to overcoming low inherent reagent electrophilicity in Brønsted base catalyzed addition reactions of pronucleophiles is to raise the Brønsted basicity of the catalyst.[7] Under a fast acid/base proton transfer regime, augmented Brønsted basicity in the catalyst increases the concentration of the nucleophilic conjugate base and, as a consequence, the rate of the bimolecular addition step. To this end, we recently developed a new family of modular bifunctional iminophosphorane (BIMP) superbase organocatalysts for the first general enantioselective organocatalytic nitro-Mannich reaction to unactivated ketimines;[8] a reaction where an organosuperbase was *essential* for reactivity.[9] In the same vein, we postulated that the poor reactivity of unactivated methacrylate esters toward nucleophilic addition may be overcome using our BIMP organosuperbase family (Scheme 1). We chose the SMA addition of alkyl thiols as this is an important reaction for the asymmetric construction of chiral sulfides,[10,11] and no catalytic enantioselective version to unactivated α-substituted acrylate esters under metal-free catalysis has previously been reported.[6b] Related literature examples have employed activated derivatives including imides[11f,o] and oxazolidinones[10h,11m,q,r] as the Michael acceptor or possess activating α-substituents.[11b,d,g,q] Additionally the use of simple aliphatic thiols[11h,k,n,o,q,u] ($pK_{a(DMSO)}$ = 17)[12] in organocatalytic asymmetric sulfa-Michael additions is much more challenging than the use of more acidic thiol pro-

Scheme 1. Proposed BIMP Catalyzed Enantioselective Sulfa-Michael Addition to Methyl Methacrylate



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nucleophiles such as aryl thiols or thiocarboxylic acids.[11] Our hope was that the strong Brønsted basicity of the BIMP would surmount the low inherent electrophilicity of the Michael acceptor by increasing the concentration of the thiol conjugate base. Following C−S bond formation, selective enantiofacial protonation of the transient enolate intermediate would deliver the enantioenriched Michael adduct and release the catalyst back into the cycle (Scheme 1).

1-Propanethiol was chosen to test reactivity in a model reaction using the inexpensive feedstock chemical methyl methacrylate (**2a**) as the Michael acceptor. A promising reactivity profile was initially established using 10 mol % of our previously reported first generation *tert*-leucine derived BIMP catalyst **1a** derived from triphenylphosphine (Figure 1 and Table 1, entry 1).[13] After just 3 h at rt, 49% yield of product **4a** was afforded with an encouraging ee of 66%. However, switching to the analogous but more basic catalyst **1b** derived from tris(*p*-methoxyphenyl)phosphine gave rise to a significant boost in reactivity, and good levels of enantiocontrol were also witnessed; adduct **4a** was afforded in quantitative yield and with 72% ee (Table 1, entry 2). Poor reactivity was observed with less basic BIMP catalyst **1c** (Table 1, entry 3), and a drop in enantioselectivity was witnessed using tributylphosphine derived BIMP **1d** (Table 1, entry 4).

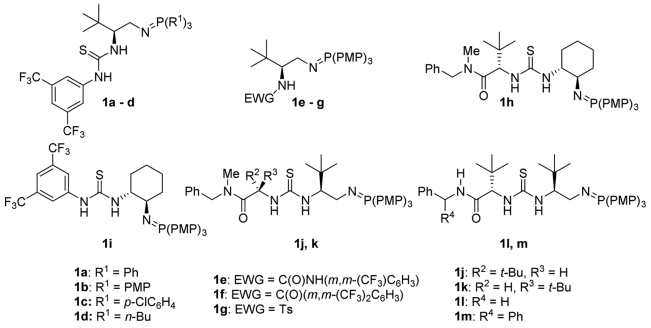
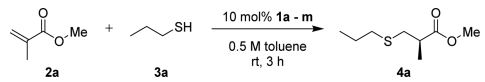


Figure 1. Bifunctional iminophosphorane (BIMP) organocatalysts screened for performance in the sulfa-Michael addition reaction. PMP = *p*-methoxyphenyl.

Table 1. Catalyst Screen in the Sulfa-Michael Addition of 1-Propanethiol to Methyl Methacrylate[a]



entry	catalyst	yield[b] (%)	ee[c] (%)
1	**1a**	49	66
2	**1b**	>99	72
3	**1c**	9	68
4	**1d**	91	35
5	**1e**	>99	57
6[d]	**1f**	57	37
7	**1g**	40	4
8	**1h**	91	9
9	**1i**	40	6
10	**1j**	97	76
11	**1k**	91	29
12	**1l**	>99	84
13	**1m**	>99	87
14[e]	**1m**	86	89
15[f]	**1m**	97	94

[a]Reactions were carried out with 0.20 mmol of **3a** and 1.0 mmol of **2a**. [b]Isolated yield. [c]Enantiomeric excess (ee) determined by HPLC analysis on a chiral stationary phase. [d]Catalyst **1f** used at 5 mol %. [e]Reaction performed in 0.5 M Et_2O. [f]Reaction conducted in 4.0 mL of Et_2O at rt using 5 mol % **1m** and quenched after 24 h.

Simple modification of the thiourea hydrogen-bond donor group of the first generation BIMP organocatalysts led to no improvement in the level of enantiocontrol (Table 1, entries 5−7, and Supporting Information), and accordingly alternative second generation BIMP organocatalyst designs were considered. Drawing inspiration from the cyclohexanediamine-derived H-bond donor organocatalysts pioneered by Jacobsen[14] and Takemoto[15] and their co-workers, we synthesized the corresponding BIMPs **1h** and **1i** and assessed them in the model reaction (Table 1, entries 8 and 9). Although catalytically active, both afforded **4a** with low levels of enantiocontrol, and we postulated that the *trans*-1,2-diaminocyclohexane motif was having a detrimental effect on the enantioselectivity. This was confirmed when hybrid catalyst **1j**, arising from a fusion of the amide/thiourea unit of **1h** with the *tert*-leucine residue of our original BIMP catalysts **1a−g**, was synthesized; we were delighted to observe enhanced enantioselectivity (76% ee, entry 10), while maintaining the excellent reactivity.

Further elaboration of this second generation BIMP catalyst design revealed that both stereocenters were contributing to enantiocontrol in the formation of **4a**. When the diastereomeric catalyst **1k** was tried, the enantioselectivity was reduced to 29% ee (Table 1, entry 11), while maintaining the same absolute configuration, indicating that the stereogenic center of the amide/thiourea unit was less influential on enantiofacial control than the stereogenic center proximal to the iminophosphorane. Fine-tuning of the amide moiety of the catalyst[16] revealed **1m**, which afforded **4a** in 87% ee (Table 1, entry 13). A reoptimization of the reaction conditions to 0.05 M in diethyl ether resulted in a marked improvement in the enantioselectivity to 94% ee while maintaining near quantitative yields (Table 1, entries 14 and 15 and Supporting Information).

With optimized reaction conditions established, we investigated the scope of the transformation (Table 2). An initial screen using 1-propanethiol showed good performance across a range of small, medium, and large ester types (89−96% ee, entries 1−6), although the more sterically bulky esters (e.g., R^1 = *t*-Bu, entry 6) substantially retarded the reaction rate. Subsequent scope with respect to the thiol was investigated using methyl methacrylate and minimal variation to the high enantioselectivity was observed irrespective of alkyl chain length, branching in the α- or β-positions, or cyclic substituents (Table 2, entries 7−12).[17]

Next, variation of the α-substituent of α-substituted α,β-unsaturated methyl or phenyl esters (**2g−r**) was studied using 1-propanethiol as the *S*-centered nucleophile (Table 3). Using methyl ester Michael acceptors, the reaction performed well with substituted α-methyl substituents possessing electron withdrawing groups such as vinyl, ester, or phenyl moieties or with an α-phenyl substituent (83−93% ee, Table 3, entries 1−4). With alkyl substituted methyl substituents or branched substituents at the α-position, it was advantageous to use the slightly more active phenyl ester to compensate for the reduction in reaction rate while maintaining high levels of enantiocontrol (85−92% ee, Table 3, entries 6−9). Pleasingly, in addition to the phenyl substituted substrate **2j**, the reaction was also applicable

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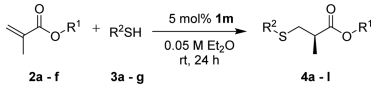
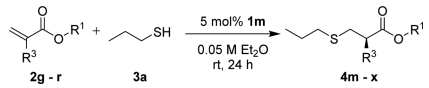
Table 2. Scope with Respect to the Ester Group and Thiol Pro-nucleophiles[a]



entry	R^1	R^2	product	yield[b] (%)	ee[c] (%)
1	Me (**2a**)	*n*-Pr (**3a**)	**4a**	97	94
2[d]	Ph (**2b**)	*n*-Pr (**3a**)	**4b**	>99	95
3	Et (**2c**)	*n*-Pr (**3a**)	**4c**	87	92
4[d]	Bn (**2d**)	*n*-Pr (**3a**)	**4d**	78	89
5	*i*-Pr (**2e**)	*n*-Pr (**3a**)	**4e**	71	93
6[e]	*t*-Bu (**2f**)	*n*-Pr (**3a**)	**4f**	36	96
7	Me (**2a**)	*n*-Pent (**3b**)	**4g**	>99	93
8	Me (**2a**)	*i*-Pent (**3c**)	**4h**	86	92
9	Me (**2a**)	*i*-Pr (**3d**)	**4i**	>99	92
10	Me (**2a**)	*c*-Hex (**3e**)	**4j**	81	90
11	Me (**2a**)	Bn (**3f**)	**4k**	85	90
12	Me (**2a**)	PMB (**3g**)	**4l**	89	89

[a]Reactions were carried out with 0.20 mmol of thiol (**3**) and 1.0 mmol of methacrylate ester (**2**). [b]Isolated yield. [c]Determined by HPLC or GC analysis on a chiral stationary phase. [d]Reaction performed with 0.40 mmol of **2**. [e]Reaction quenched after 48 h.

Table 3. Scope with Respect to the α-Substituent on the Michael Acceptor[a]



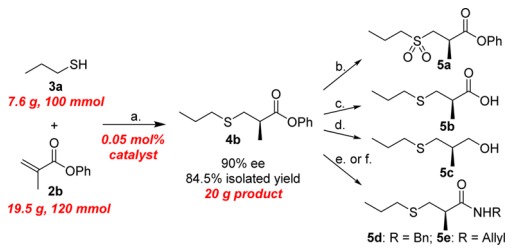
entry	R^1	R^3	product	yield[b] (%)	ee[c] (%)
1	Me	allyl (**2g**)	**4m**	94	93
2	Me	CH_2CO_2Me (**2h**)	**4n**	85	90
3[d]	Me	Bn (**2i**)	**4o**[e]	99	86
4	Me	Ph (**2j**)	**4p**	84	83
5[d]	Me	Et (**2k**)	**4q**	47	92
6	Ph	Et (**2l**)	**4r**	85	92
7	Ph	*i*-Pr (**2m**)	**4s**	98	88
8	Ph	*c*-Hex (**2n**)	**4t**	93	85
9	Ph	*c*-Pent (**2o**)	**4u**	96	90
10[f]	Me	4-OMe(C_6H_4) (**2p**)	**4v**	94	86
11	Me	2-OMe(C_6H_4) (**2q**)	**4w**	89	94
12	Me	2-NO_2(C_6H_4) (**2r**)	**4x**	98	84

[a]Reactions were carried out with 0.20 mmol of **3a** and 0.40 mmol of **2**. [b]Isolated yield. [c]Determined by HPLC analysis on a chiral stationary phase. [d]Reaction quenched after 48 h. [e]Absolute configuration of **4o** determined by chemical correlation (see Supporting Information). [f]Compound **2p** (0.20 mmol) was used.

to electron rich and deficient aryl substituents (84−94% ee, entries 10−12).

Although our methodological study was routinely carried out at 5 mol % catalyst loading, all indications suggested that our optimal BIMP catalyst **1m** was highly active in the SMA and that the loadings could be significantly reduced.[18] Indeed, in the reaction of **2b** with **3a**, after re-optimization of the reaction parameters, we were delighted to find the catalyst loading of **1m** could be readily reduced down to 0.05 mol % while performing the reaction on a 100 mmol scale (Scheme 2). Near full conversion was achieved after 24 h using only ∼40 mg of *in situ* generated **1m** whereupon the reaction was quenched, a crude ee of 90% was measured, and the product was purified by distillation to afford **4b** in 84.5% isolated yield with no loss in ee. To

Scheme 2. Decagram Scale Sulfa-Michael Addition and Subsequent Derivatization[a]



[a]Reagents and conditions: (a) catalyst **1m** (0.05 mol %), MTBE, 55 °C, 24 h; (b) H_2O_2/TFA, rt, 4 h, >99% yield, 89% ee; (c) LiOH, THF/H_2O, rt, 2 h, 82% yield, 86% ee; (d) DIBAL-H, THF, −78 °C, 1 h, 64% yield, 90% ee; (e) benzylamine (3 equiv), neat, 0 °C, 12 h, 99% yield, 89% ee; (f) allylamine (3 equiv), neat, 0 °C, 2 h, 99% yield, 91% ee.

demonstrate the synthetic utility of the β-mercapto ester products **4** resulting from the reaction, **4b** was subsequently oxidized to the sulfone **5a**, hydrolyzed to the acid **5b**, reduced to the alcohol **5c**, and converted quantitatively to amides **5d** and **5e** by direct aminolysis with benzylamine and allylamine, respectively.

In summary, the first highly enantioselective organocatalytic SMA of alkyl thiol pro-nucleophiles to unactivated α-substituted acrylate esters has been developed. Good levels of reactivity, and excellent enantioselectivities were achieved across a diverse range of alkyl thiols and unactivated α-substituted acrylate esters using a new second generation bifunctional iminophosphorane (BIMP) superbase organocatalyst. The ability of BIMP organocatalysts to enable unactivated α-substituted acrylate esters to undergo asymmetric conjugate additions is, we believe, a significant advancement in the field, and further work to uncover the breadth of their use is ongoing in our laboratories and will be disclosed in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b10226.

Experimental details and characterization data (PDF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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