Bifunctional Iminophosphorane Catalyzed Enantioselective Sulfa-Michael Addition to Unactivated α,β-Unsaturated Amides

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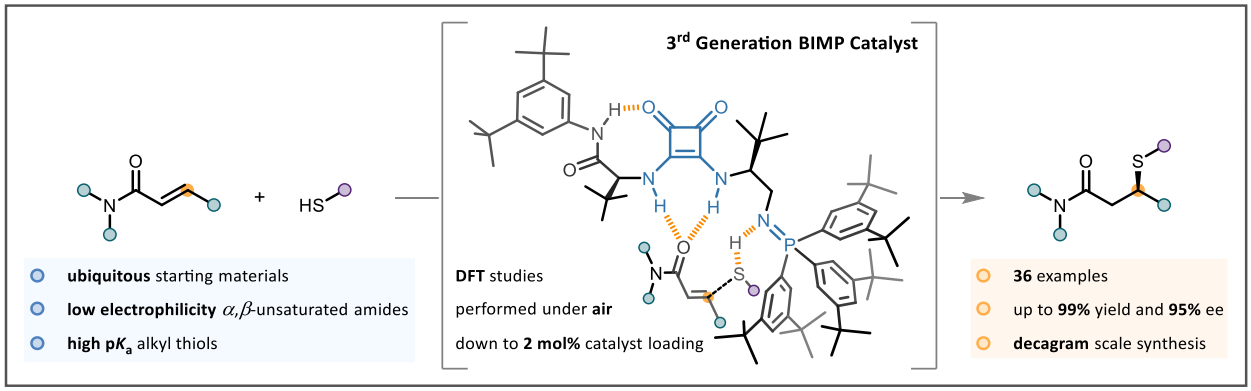
ABSTRACT: The first metal-free catalytic intermolecular enantioselective sulfa-Michael addition to unactivated α,β-unsaturated amides is described. Consistently high enantiomeric excesses, and yields were obtained over a wide range of alkyl thiol pronucleophiles and electrophiles under mild reaction conditions, enabled by a novel squaramide-based bifunctional iminophosphorane (BIMP) catalyst. Low catalyst loadings (2 mol%) were achieved on a decagram scale, demonstrating the scalability of the reaction. Computational analysis revealed the origin of the high enantiofacial selectivity, corresponding transition states, and provided substantial evidence for specific non-covalent activation of the carbonyl group of the α,β-unsaturated amide by the catalyst.



INTRODUCTION

Conjugate additions are amongst the most prevalent transformations in organic chemistry due to their ability to quickly generate complexity from simple starting materials with perfect atom economy.[1a] Since the discovery of the reaction in the late 19th century,[1b,c] it has garnered wide attention from the chemical community and, over the course of more than 130 years, the transformation has become one of the most well understood and well documented reactions. Despite the maturity of the field, examples of enantioselective conjugate additions to α,β-unsaturated amides remain scarce. Contrary to other carboxylic acid derivatives, the electron withdrawing property of the carboxamide functionality is greatly diminished, rendering amides, and alkenes conjugated to them, exceptionally unreactive.[2-5]

Over the past two decades, multiple strategies relying on structural and electronic modification of α,β-unsaturated amides have been disclosed, enabling enantioselective conjugate additions. These, however, are reliant on tailored activating groups, such as imides, *N*-acyl pyrroles, and thioamides amongst others, curtailing the synthetic efficiency and potential late-stage utility of these procedures.[6] To date, only a handful of catalytic enantioselective methods have been described featuring 1,4-additions to non-activated α,β-unsaturated amides. Pioneering studies by Kobayashi employed chiral crown ethers in the presence of KHMDS to gain reactivity and enantiofacial control in the conjugate addition between α,β-unsaturated amides and carbon centered pronucleophiles,[7] while Harutyunyan,[8] and most recently Yin,[9] employed chiral bisphosphine ligated copper(I) catalysis for the conjugate addition of alkyl Grignard reagents and diarylphosphines, respectively, to α,β-unsaturated amides. Whilst elegant and synthetically useful, these methods required the use of bespoke ligated metal systems for enabling reactivity and imparting control, as well as the rigorous exclusion of air and moisture and cryogenic temperatures or super stoichiometric activators for optimal performance.

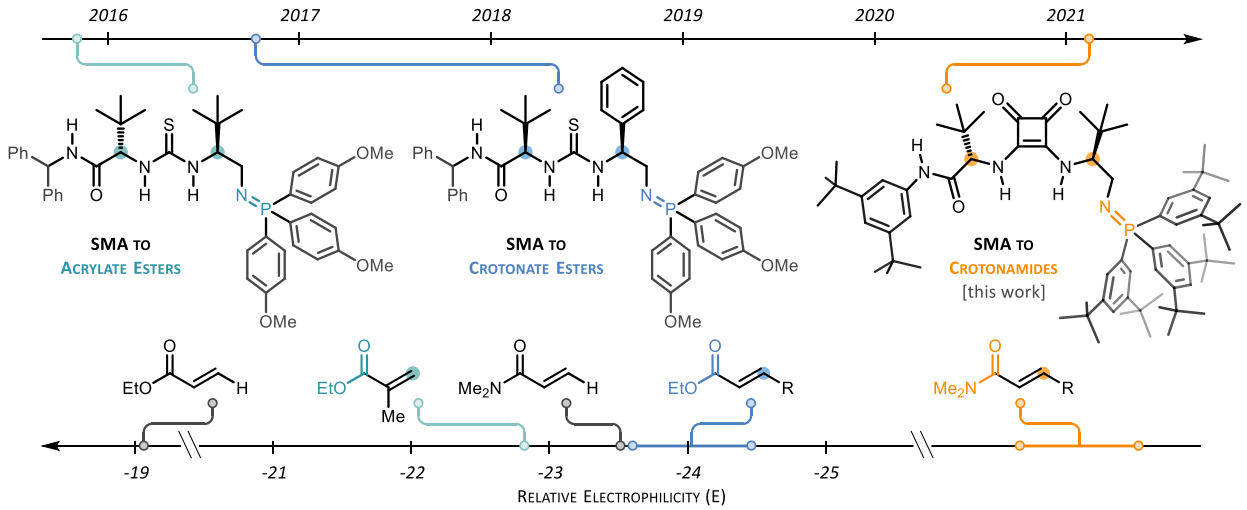


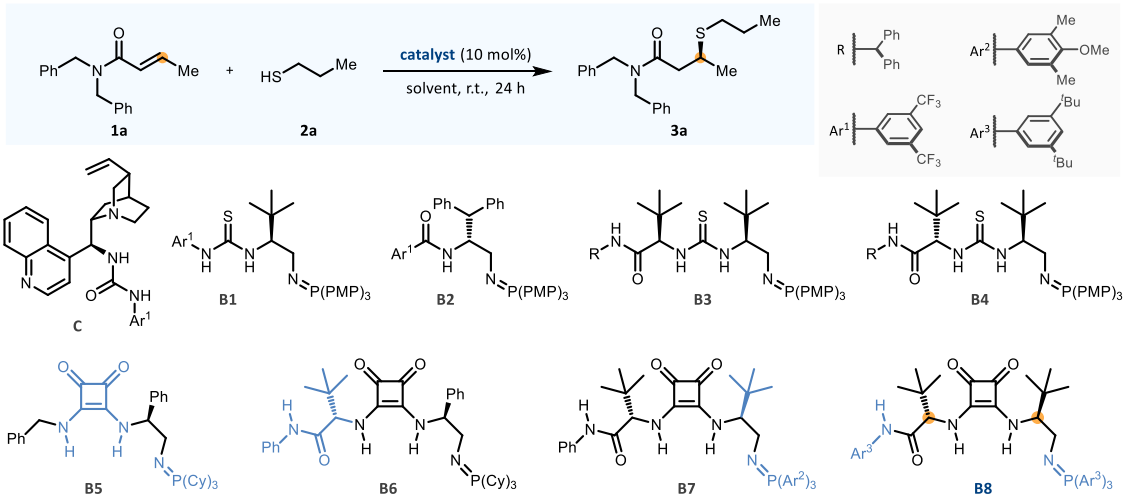
Figure 1. Mayr's electrophilicity scale (bottom). Previous BIMP catalysts for sulfa-Michael additions to unsaturated carboxylic acid derivatives, and this work (top).

Although metal free catalytic approaches have been successfully deployed on reactive *α,β*-unsaturated imide derivatives, to date the successful addition of (pro)nucleophiles to unactivated *α,β*-unsaturated amides under metal free catalysis remains an unsolved problem awaiting a general catalytic solution. To this end, in 2013 our group disclosed a new class of superbasic catalysts, the bifunctional iminophosphorane (BIMP), which has proven to be exceptionally active in catalyzing challenging enantioselective conjugate additions, for example with *α*-substituted acrylate esters,[14a] crotonate esters,[14b] and alkenyl benzimidazoles[14c] as electrophiles.[10-14] Recognizing the limitations in state-of-the-art enantioselective conjugate additions to *α,β*-unsaturated amides and seeking the opportunity to test the capabilities of new BIMP catalyst systems on conjugate acceptors at the bottom end of Mayr's electrophilicity scale (**Figure 1**),[5c] we sought to realize the first non-metal catalyzed enantioselective conjugate addition reaction to *α,β*-unsaturated amides. We chose to exemplify this with the sulfa-Michael addition (SMA) and our hope was to identify a suitable BIMP superbase catalyst capable of significant non-covalent activation of the electrophile and simultaneous deprotonation of high pK_a pronucleophile, and here we wish to report our findings.

RESULTS AND DISCUSSION

Readily available (*E*)-*N*,*N*-dibenzyl crotonamide **1a**, being sterically and electronically unbiased, was selected as the model substrate for the enantioselective sulfa-Michael addition.[5d,8b] A preliminary performance investigation of catalysts (at 10 mol%) was carried out in THF at room temperature in the presence 3.0 equivalents of 1-propanethiol **2a** (**Table 1**). Initial experiments revealed that cinchona derived catalyst **C** was essentially inactive in the transformation, resulting in less than 3% product **3a** formation after more than one week reaction time (Entry 1; see SI for details). First generation thiourea and amide-containing BIMP catalysts **B1** and **B2** bearing a single stereocenter, provided **3a** in high yield, albeit with 37% and 55% ee, respectively (Entries 2 and 3). Diastereomeric second generation catalysts **B3** and **B4** bearing an additional stereocenter flanking the hydrogen bond donor group efficiently furnished the product **3a** in 25% and 51% ee, respectively (Entries 4 and 5), demonstrating enantiocontrol was arising from both stereogenic centers.

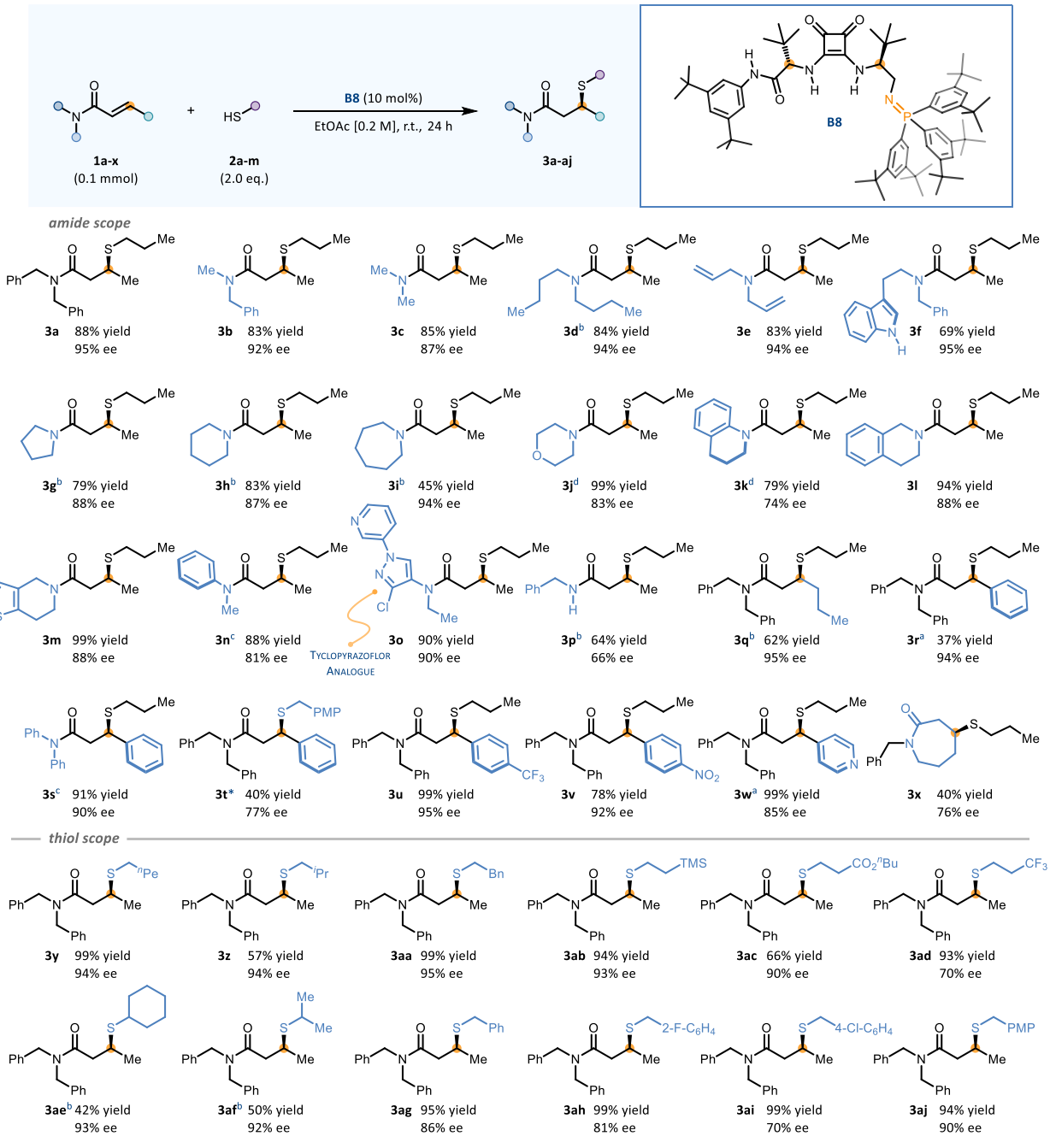
Further architectural fine-tuning of catalyst **B4** did not allow for significantly higher enantiocontrol (see SI for details), thus we turned our attention to the nature of the hydrogen bond donor moiety of the catalyst. Due to the inherently high Lewis basicity of carboxamides, we speculated that a hydrogen bond donor with an increased Brønsted acidity could offer enhanced non-covalent binding and thus better stabilization of the transition structure. Based on this reasoning, and inspired by the pioneering work of Rawal, and Jacobsen, a squaramide-containing catalyst appeared to be a rational choice, due to its enhanced hydrogen bonding properties.[15,16] To our delight, switching to squaramide-based catalyst **B5** and the solvent to toluene, resulted in the isolation of **3a** in 90% yield and 66% ee (Entry 6). In a bid to boost enantiocontrol, we introduced an additional stereocenter on the distil side of the squaramide motif, to give 3rd generation BIMP catalyst, **B6**. We were pleased to find this structural modification provided 70% ee and 82% yield (Entry 7). Changing the catalyst to one bearing two *anti*-configured *tert*-butyl groups, and switching the solvent to EtOAc, boosted the ee to 85% (Entry 8). The convenient late stage formation of the iminophosphorane moiety then allowed for both coarse and precision tuning of the BIMP catalyst system by simply varying the phosphine component of the Staudinger reaction with the optimal organoazide unit (see SI for details). This systematic structural variation revealed the importance of peripheral, bulky *and* electron-donating groups, leading to catalyst **B8**, which provided **3a** in 95% ee and 88% isolated yield after



entry	catalyst	solvent	c [M]	thiol eq.	yield (%)[a]	ee (%)
1	C	THF	0.5	3.0	<3[b]	n.d.
2	B1	THF	0.5	3.0	91	37
3	B2	THF	0.5	3.0	74	55
4	B3	THF	0.5	3.0	83	25
5	B4	THF	0.5	3.0	81	51
6	B5	toluene	0.5	3.0	90	66
7	B6	toluene	0.5	3.0	82	70
8	B7	EtOAc	0.5	3.0	88	85
9	**B8**	**EtOAc**	**0.2**	**2.0**	**88**	**95**

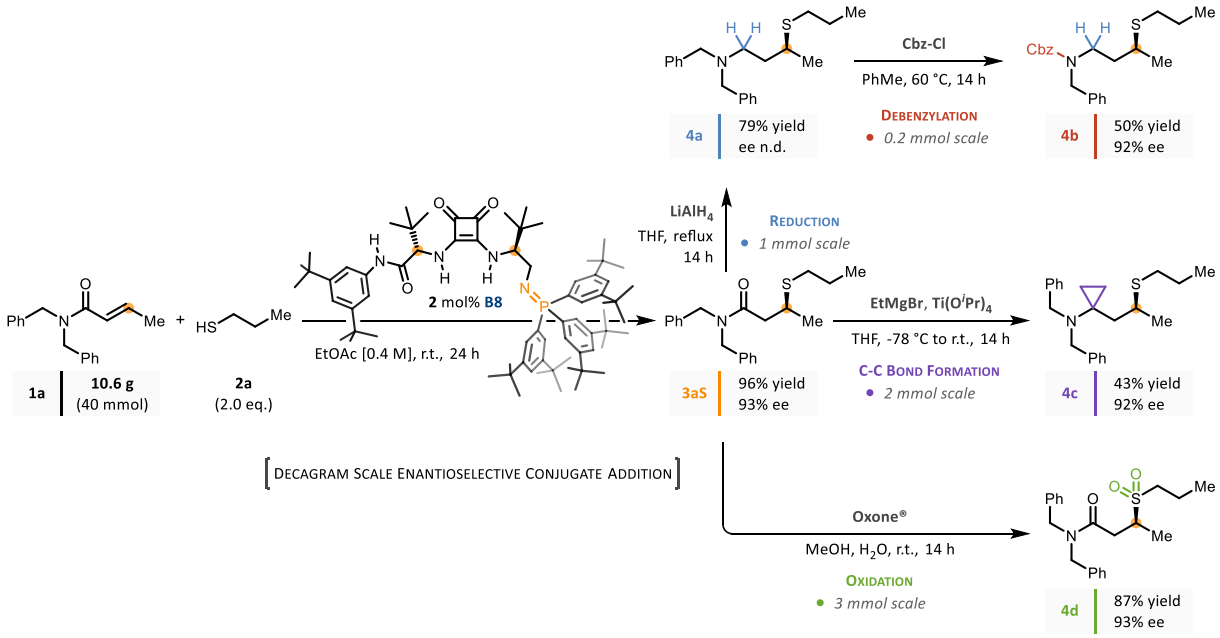
Table 1. Selected reaction optimization (0.1 mmol scale). [a]Isolated yield. [b]NMR yield after 7 days (see SI for details). Ee determined by HPLC on a chiral stationary phase. PMP: 4-methoxyphenyl.

decreasing the concentration to 0.2 M and amount of thiol to 2.0 equivalents (Entry 9). Additionally, the inclusion of air in the reaction vessel did not change the outcome of the reaction. With the optimized conditions in hand, we explored the scope of our protocol with respect to the conjugated amide electrophiles and thiol pronucleophiles (**Scheme 1**). Initially we evaluated the effects of substituents on the amide nitrogen (**3a-3x**). Pleasingly, switching one benzyl group on **1a** to a methyl group was well tolerated, and corresponding product **3b** was formed with 83% yield and 92% ee. Additionally, even significantly less bulky dimethylamine derivative **1c** afforded product **3c** in 87% ee and no major change in reactivity was observed. Dibutylamine derivative **1d** exhibited diminished reactivity and necessitated the use of an increased amount of thiol to drive the reaction to completion whilst maintaining high levels of enantiocontrol. Product **3e** and unprotected indole derivative **3f** were formed smoothly under the optimized conditions in 94% ee and 95% ee respectively. Substrates bearing cyclic *N*-substituents afforded products **3g-i** with excellent levels of enantioselectivity and moderate to high yield. Amides **1j** and **1k** proved to be exceptionally reactive under the optimized reaction conditions, and consequently cooling to –20 °C was required to enhance enantioselectivity and control, and products **3j** and **3k** were yielded with 83% ee and 74% ee, respectively. Pharmaceutically relevant[17] isoquinoline derivative **3l** and isothienopyridine derivative **3m** were both compatible with our method providing nearly quantitative yield and high ee. Even *N*-methylaniline derived substrate **1n** was well tolerated furnishing **3n** with 88% yield and 81% ee. Encouraged by the high degree of tolerance of heterocyclic moieties, we explored the enantioselective sulfa-Michael addition to *α,β*-unsaturated amide **1o**. The reaction proceeded smoothly under the optimized conditions, furnishing **3o**, an analogue of Tyclopyrazoflor (a potent insecticide)[18a-e] with 90% ee and 90% isolated yield. Secondary amide **1p** was also a competent substrate in this reaction albeit with diminished levels of enantiocontrol. We then turned our attention to the *β*-substituents on the enoyl backbone. The introduction of a longer alkyl chain in substrate **1q** was well tolerated, albeit with a slight decrease in reactivity. Particularly unreactive[5c] cinnamide derivative **3r** was obtained with excellent



Scheme 1. Reaction scope for the BIMP **B8** catalyzed enantioselective sulfa-Michael addition to *α,β*-unsaturated amides (0.1 mmol scale). Reactions were conducted under air. Reaction carried out using [a]10.0 eq., [b]4.0 eq., [c]3.0 eq. thiol. [d]Reaction carried out at −20 °C. *Absolute stereochemical configuration of product **3t** was determined by chemical correlation (see SI for details).

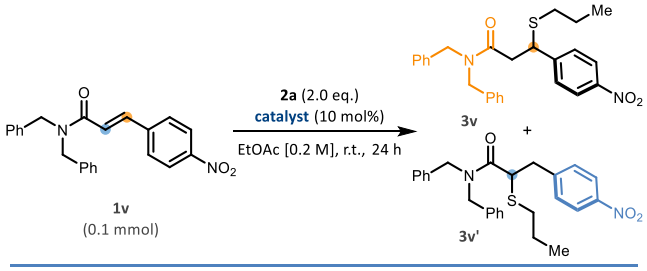
enantioselectivity (95% ee) but moderate yield. Product **3s**, on the contrary, was easily obtained, likely due to the phenyl groups present on the amide moiety, twisting the *N* atom out of conjugation.[5d] Product **3t** was obtained with moderate yield and ee, and was used to determine absolute stereochemical configuration (see SI for details). Cinnamides **1u** and **1v** bearing electron withdrawing groups were smoothly converted to the corresponding thioethers with high levels of selectivity and reactivity. Pyridine containing derivative **1w** was well tolerated furnishing **3w** in near quantitative yield and 85% ee. When *α,β*-unsaturated lactam **1x** was used as substrate, product **3x** was obtained in 40% yield and 76% ee. Finally, a thorough assessment of the nucleophile scope was performed using primary, secondary alkyl, and benzyl substituted thiols. Primary alkyl thiol nucleophiles were broadly

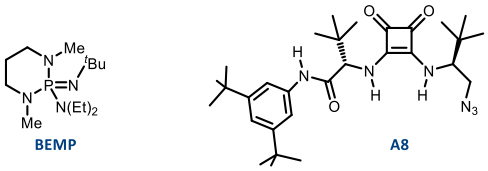


Scheme 2. Decagram scale enantioselective sulfa-Michael addition (left) and product derivatization (right).

tolerated, affording the corresponding thioethers with high enantioselectivity and reactivity (**3y**-**3ac**). Notably, a thiol bearing a Lewis basic ester functionality afforded product **3ac** in 66% yield and 90% ee. A decrease in ee was observed in the case of **3ad** which contained a proximal CF_3 group. Secondary alkyl thiols provided products with high enantioselectivities albeit with slightly diminished reactivity (**3ae**-**3af**), whilst benzylic thiols underwent the transformation with high levels of reactivity at a modest expense of ee (**3ag**-**3aj**). Interestingly thiophenol, furnished no product, presumably due to its low inherent nucleophilicity, whereas tertiary alkyl thiols similarly provided no product formation, most certainly due to increased steric hindrance in the transition structure.[18f]

After establishing the scope and limitations of this new methodology, we wanted to demonstrate its scalability using model substrate **1a** and 1-propanethiol **2a**. Increasing the reaction concentration two-fold allowed us to reduce catalyst loading to 2 mol% and scale-up our model reaction 400 times (40.0 mmol). Desired product **3aS** was obtained in 96% isolated yield (13.2 g) and 93% ee (**Scheme 2**). Next, a series of transformations were performed using **3aS** to showcase the synthetic utility of this product. When treated with lithium aluminum hydride, aminosulfide **4a** was obtained in 79% isolated yield and was subsequently de-benzylated in the presence of CbzCl in PhMe at 60 °C to afford protected secondary amine **4b** in 50% yield and 92% ee. A cyclopropane motif could be installed *via* the Kulinkovich-de Meijere reaction[19] using ethylmagnesium bromide and titanium(IV) isopropoxide. Aminocyclopropane **4c** was obtained in 43% yield and 92% ee. Finally, oxidation in the presence of Oxone® provided sulfone **4d** in 87% yield with no loss of optical purity. Unintentionally, substrate binding / activation of the new catalyst system was effectively revealed using *N*,*N*-dibenzyl 4-nitrocinnamide **1v** and thiol **2a**. Substrate **1v** can undergo nucleophilic addition reactions to the conjugated alkene at either the α or β position with respect to the amide functionality and thus regioselectivity of the addition to this dual Michael acceptor can be used to probe catalyst function (**Table 2**).





entry	catalyst	ratio 3v	ratio 3v'	ee 3v
1	BEMP	1	10	N/A
2	B8	4	1	92%
3	A8 + BEMP	1	1.6	22%

Table 2. Mechanistic investigation employing a dual Michael acceptor. Product ratios were determined by quantitative ^{1}H NMR.

Performing the reaction under the optimized conditions using an achiral organic superbase bearing no hydrogen bond donor (BEMP) revealed that the inherent reactivity of **1v** is governed by the 4-nitrostyrene moiety, providing a 1:10 mixture of **3v**:**3v'**, implying that this functionality is indeed more electron withdrawing than the amide moiety (Entry 1). However, running the reaction using catalyst **B8** under the same conditions reversed the regioselectivity, furnishing products **3v** and **3v'** in a 4:1 ratio, thus providing convincing evidence for the activation of the amide moiety by the BIMP catalyst (Entry 2). Subjecting the 1:1 mixture of **B8** catalyst's azide precursor **A8** and BEMP to the optimal reaction conditions afforded a 1:1.6 ratio of **3v**:**3v'**, and a significantly lower ee of **3v** compared to **B8** catalyzed reaction, accentuating the importance of the chiral tether between the iminophosphorane superbase and hydrogen bond donor in **B8** (Entry 3).

To elucidate the origin of stereocontrol in the BIMP catalyzed sulfa-Michael addition to *α*,*β*-unsaturated amides, a DFT study was performed (**Figure 2**).[20] Due to the conformational freedom and the existence of two potential activation modes of the BIMP catalyst, we computed and compared all the possible transition structures (TSs) on the enantio-determining Michael-reaction step, involving the amide substrate **1c** and methyl thiol as the model nucleophile (see SI for details).[11k,12c,14f,14h] The lowest-energy TS was **TS–ModeA–LA2–RA1–*S*** that forms the (*S*)-product, which is in agreement with the experimentally confirmed absolute stereochemical outcome of the reaction. This reaction has a high enantioselectivity as the lowest-energy TS that forms the (*R*)-product has a much higher barrier ($\Delta\Delta G^{\ddagger}$ = 4.1 kcal mol^{-1}). The selectivity originates from the TS geometry that benefits from multiple inter– and intramolecular stabilizing interactions, including hydrogen bonding, CH–*π* and *π*–*π* interactions. The intramolecular hydrogen bonding between the O(squaramide)–H(amide) fixes the conformational freedom of the "*left arm*" of the BIMP catalyst, creating a 3-dimensionally defined pocket within which the *α*,*β*-unsaturated amide can fit without considerable steric repulsion during the C–S bond forming event. The thiolate anion can also interact with the aromatic ring of the iminophosphorane moiety for an additional stabilizing interaction. Analysis of non-covalent interaction (NCI) plots allows one to qualitatively visualize these weak interactions between the catalyst and the substrate (see SI for details).[21]

CONCLUSION

Exemplified by the alkyl thiol sulfa-Michael addition, the first metal-free catalytic enantioselective intermolecular conjugate addition to unactivated *α*,*β*-unsaturated amides has been developed. A thorough investigation of substrate types revealed a general methodology that furnishes a wide range of sulfa-Michael addition products, including heterocyclic derivatives, in high yields and ee. Computational and mechanistic studies revealed the origins of selectivity and the important substrate / catalyst binding modes. Efforts continue in our laboratories to uncover new BIMP designs and to expand the range of BIMP-enabled transformations.

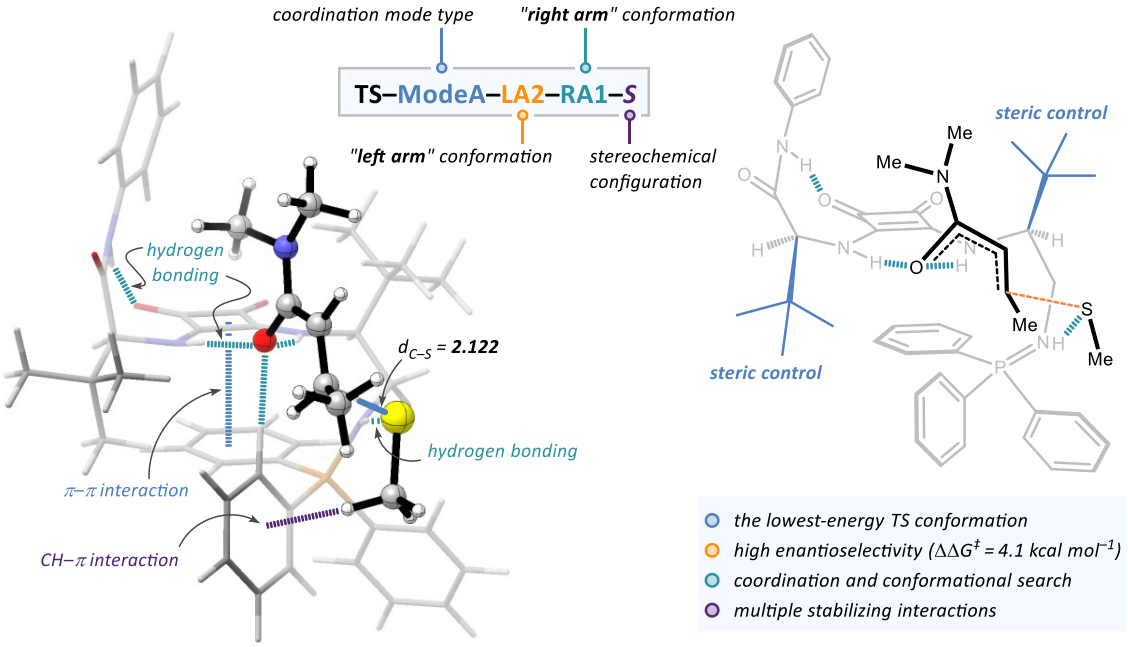


Figure 2. The lowest-energy transition structure of the BIMP squaramide-catalyzed enantioselective sulfa-Michael addition computed at COSMO(EtOAc)-ZORA-M06-2X/TZ2P//COSMO(EtOAc)-ZORA-BLYP-D3(BJ)/DZP. A forming bond length (Å) of the TS geometry is provided in the insert.

ASSOCIATED CONTENT

Supporting Information.

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Notes

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