

Bifunctional Iminophosphorane-Catalyzed Enantioselective Sulfa-Michael Addition to Unactivated α,β -Unsaturated AmidesDaniel Rozsar, Michele Formica,[§] Ken Yamazaki,[§] Trevor A. Hamlin,^{*} and Darren J. Dixon^{*}Cite This: *J. Am. Chem. Soc.* 2022, 144, 1006–1015

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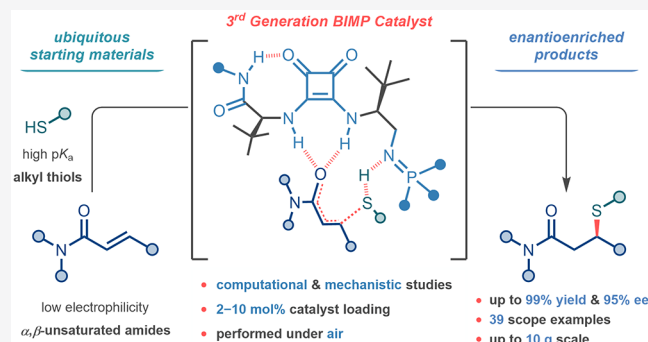


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ABSTRACT: The first metal-free catalytic intermolecular enantioselective Michael addition to unactivated α,β -unsaturated amides is described. Consistently high enantiomeric excesses and yields were obtained over a wide range of alkyl thiol pronucleophiles and electrophiles under mild reaction conditions, enabled by a novel squaramide-based bifunctional iminophosphorane catalyst. Low catalyst loadings (2.0 mol %) were achieved on a decagram scale, demonstrating the scalability of the reaction. Computational analysis revealed the origin of the high enantiofacial selectivity via analysis of relevant transition structures and provided substantial support for specific noncovalent activation of the carbonyl group of the α,β -unsaturated amide by the catalyst.



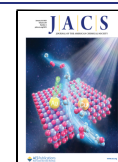
INTRODUCTION

Conjugate additions are among the most prevalent transformations in organic chemistry due to their ability to quickly generate complexity from simple starting materials with perfect atom economy.¹ 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.^{2–5} Over the past two decades, multiple strategies relying on structural 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 among others, curtailing the synthetic efficiency of these procedures.⁶ To date, only a handful of catalytic enantioselective methods have been described featuring 1,4-additions to nonactivated 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 employed chiral bisphosphine ligated copper(I) catalysis for the conjugate addition of alkyl Grignard reagents to α,β -unsaturated amides. Most recently the enantioselective copper(I)-catalyzed hydrophosphination and rhodium(I)-catalyzed hydroboration of α,β -unsaturated amides in the presence of chiral bisphosphine ligands were reported by Yin and Li, respectively.⁹ While elegant, these methods required the use of bespoke and sensitive ligated metal systems sometimes combined with super stoichiometric activators. However, the enantioselective addition of (pro)nucleophiles to unactivated α,β -unsaturated amides under metal-free catalysis

remains an unsolved problem. 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.^{10–14} Recognizing the limitations in 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 nonmetal-catalyzed enantioselective conjugate addition reaction to α,β -unsaturated amides. We chose to exemplify this with the sulfa-Michael addition (SMA). Enantioselective carbon–sulfur bond-forming reactions are prevalent transformations in organic chemistry due to the abundance of sulfur atoms in biomolecules and pharmaceutical compounds.^{15a} Recently developed β -thioamide Tyclopyrazflor, for example, is a powerful pesticide.^{15b–f} If successful, our new methodology could be applied to the rapid assembly of libraries of novel, otherwise difficult-to-obtain enantiomerically enriched β -thioamides. Our hope was to identify a suitable BIMP superbase catalyst capable of significant activation of the α,β -unsaturated amide electrophile and simultaneous deprotonation of high pK_a alkyl thiol pronucleophile, and here we wish to report our findings.

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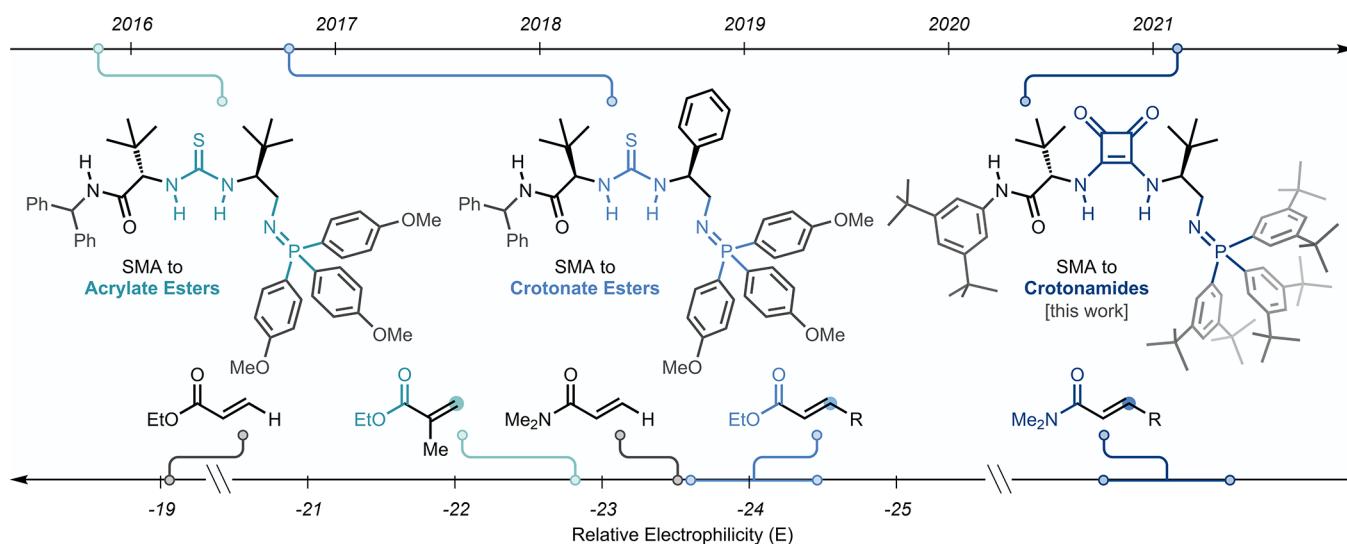


Figure 1. Mayr's electrophilicity scale (bottom). Previous BIMP catalysts for SMAs to unsaturated carboxylic acid derivatives and this work (top).

Table 1. Selected Reaction Optimization (0.1 mmol Scale)

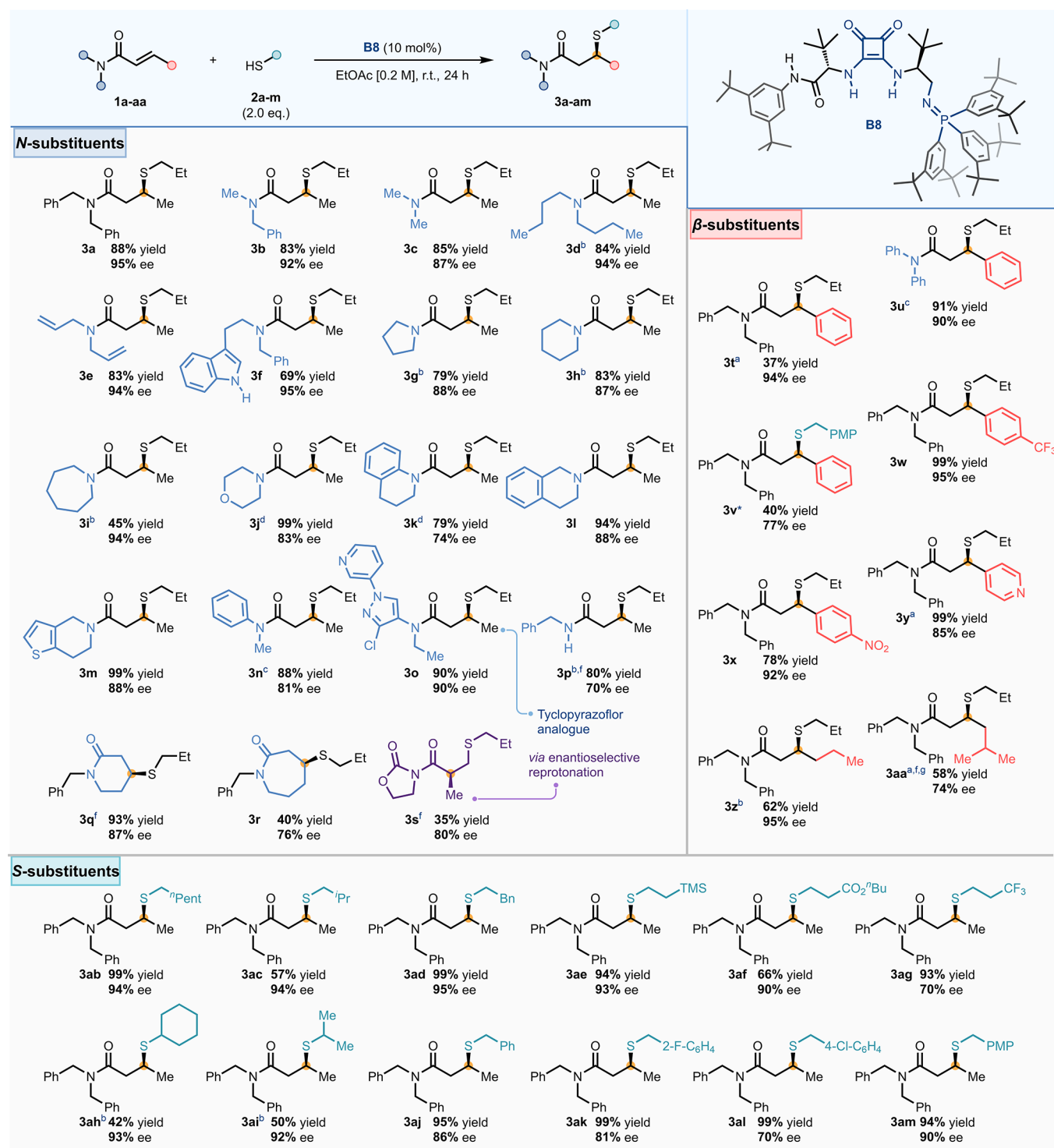
entry	catalyst	solvent	c [M]	thiol eq.	yield (%) ^a	ee (%)
1	C	THF	0.5	3.0	<3 ^b	n.d.
2	B1	THF	0.5	3.0	91	37
3	B2	THF	0.5	3.0	74	55
4	B3	THF	0.5	3.0	83	25
5	B4	THF	0.5	3.0	81	51
6	B5	toluene	0.5	3.0	90	66
7	B6	toluene	0.5	3.0	82	70
8	B7	EtOAc	0.5	3.0	88	85
9	B8	EtOAc	0.2	2.0	88	95

^aIsolated yield. ^bNMR yield after 7 days. Ee determined by HPLC on a chiral stationary phase. PMP: *p*-methoxyphenyl.

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 SMA.^{5e} A preliminary performance investigation of catalysts (at 10 mol %) was carried

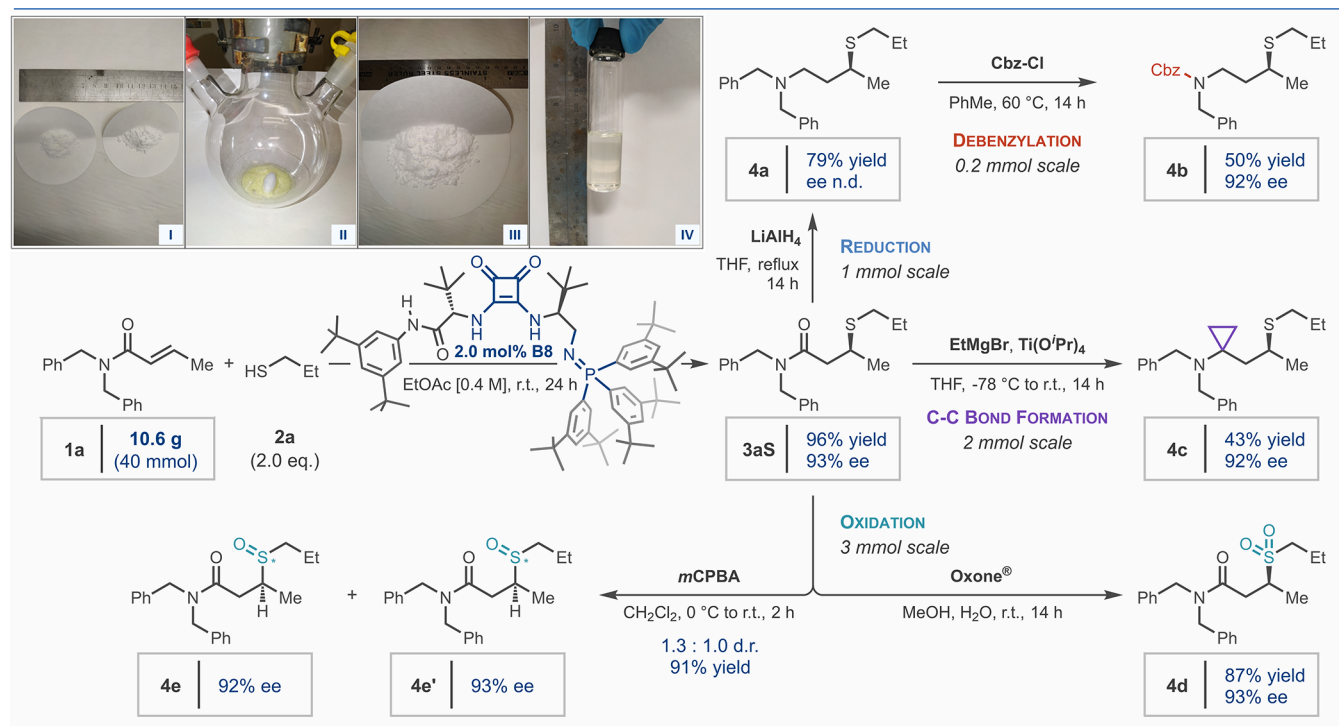
out in THF at room temperature in the presence of 3.0 equiv of 1-propanethiol **2a** (Table 1). Initial experiments revealed that cinchona-derived catalyst **C** was essentially inactive in the transformation, resulting in <3% product **3a** formation after more than 1 week reaction time (entry 1). First-generation thiourea and amide-containing BIMP catalysts **B1** and **B2**

Scheme 1. Reaction Scope for the BIMP B8-Catalyzed Enantioselective SMA to α,β -Unsaturated Amides (0.1 mmol Scale)[#]

[#]Reactions were conducted under air. Reaction carried out using: ^a10.0 equiv, ^b4.0 equiv, ^c3.0 equiv thiol. Reaction carried out at: ^d−20 °C and ^e40 °C. ^fReaction carried out in toluene. ^g0.5 M concentration. ^{*}Absolute stereochemical configuration of product 3v was determined by chemical correlation.¹⁸

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 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, 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

Scheme 2. Decagram-Scale Enantioselective SMA[#]

[#](I) Azide **A8** on the left, phosphine **P19** on the right; (II) crude catalyst **B8** after removal of THF; (III) substrate **1a**; (IV) product **3aS** (left) and product derivatization (right).

could offer enhanced binding and thus better stabilization of the transition structure (TS). 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.^{16,17} To our delight, switching to squaramide-based catalyst **B5** and the solvent to toluene afforded **3a** in 90% yield and 66% ee (entry 6). In a bid to boost enantiocontrol, we introduced an additional stereocenter on the distal side of the squaramide motif to give third-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 facile tuning of the BIMP catalyst by simply varying the phosphine component of the Staudinger reaction. 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 (entry 9).¹⁸ Additionally, the inclusion of air in the reaction vessel did not change the outcome of the transformation, and with the optimized conditions in hand, the scope of the protocol was then explored (Scheme 1). Initially the effects of substituents on the amide nitrogen were evaluated (**3a–3s**). 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. Dimethylamine derivative **1c** afforded product **3c** in 87% ee, and no major change in reactivity was observed. Dibutylamine derivative product **3d** was obtained in 84% yield and 94% ee. 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

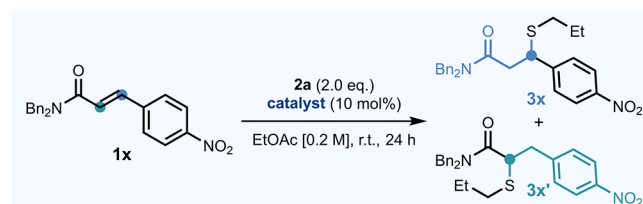
products **3g–3i** with excellent enantioselectivities and moderate to high yields. Amides **1j** and **1k** proved to be exceptionally reactive, and consequently cooling to −20 °C was exploited to enhance enantioselectivity and control, and products **3j** and **3k** were yielded with 83% ee and 74% ee, respectively. Pharmaceutically relevant¹⁹ isoquinoline derivative **3l** and thienopyridine 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 SMA to α,β -unsaturated amide **1o**. The reaction proceeded smoothly under the optimized conditions, furnishing **3o**, an analogue of Tylopyrazoflor^{15b–e} with 90% ee and 90% isolated yield. Secondary amide **1p** was also a competent substrate in this reaction, albeit a solvent switch to toluene was required to better solubilize the starting material. When six- and seven-membered α,β -unsaturated lactams **1q** and **1r** were used as substrates, products **3q** and **3r** were obtained in 93% yield and 87% ee and 40% yield and 76% ee, respectively. Product **3s**, bearing an α -stereogenic center, could also be obtained (via enantioselective reprotonation) employing the same catalyst in 35% yield and 80% ee. We then turned our attention to the β -substituents on the enoyl backbone. Particularly unreactive^{5c} cinnamide derivative **3t** was obtained with excellent enantioselectivity (95% ee) but moderate yield. Product **3u**, on the contrary, was easily obtained, likely due to the phenyl groups present on the amide moiety, twisting the N atom out of conjugation.^{5e} Product **3v** was obtained with moderate yield and ee and was used to determine absolute stereochemical configuration.¹⁸ Cinnamides **1w** and **1x** bearing electron-withdrawing groups were smoothly converted to the corresponding thioethers with high levels of selectivity and reactivity. Pyridine-containing derivative **1y** was

well tolerated, furnishing **3w** in near quantitative yield and 85% ee. The introduction of a longer alkyl chain in substrate **1z** was well tolerated, albeit with a slight decrease in reactivity. Substrate **1aa** bearing an additional methyl group compared to **1z** exhibited decreased reactivity (most probably due to additional steric encumbrance), and therefore more forcing conditions had to be applied to afford product **3aa** in 58% yield and 74% ee. Finally, a thorough assessment of the nucleophile scope was performed using primary, secondary alkyl, and benzyl-substituted thiols. Primary alkyl thiols were broadly tolerated, affording the corresponding thioethers with high enantioselectivity and reactivity (**3ab–3af**). Notably, a thiol bearing an ester functionality afforded product **3af** in 66% yield and 90% ee. A decrease in ee was observed in the case of **3ag** which contained a proximal CF₃ group. Secondary alkyl thiols provided products with high enantioselectivities albeit with slightly diminished reactivity (**3ah–3ai**), while benzylic thiols underwent the transformation with high levels of reactivity at a modest expense of ee (**3aj–3am**).²⁰

After establishing the scope and limitations of this new methodology, we wanted to demonstrate its scalability using model substrate **1a** and 1-propanethiol **2a**. Doubling the reaction concentration and reducing catalyst loading to 2.0 mol % allowed a 400-fold (40.0 mmol) scale-up of the model reaction, and 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 debenzylated 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 reaction²¹ using ethylmagnesium bromide and titanium(IV) isopropoxide. Aminocyclopropane **4c** was obtained in 43% yield and 92% ee. Oxidation in the presence of oxone provided sulfone **4d** in 87% yield with no loss of optical purity. Oxidation with *m*CPBA furnished sulfoxides **4e** and **4e'** in 91% yield but low diastereoselectivity; however, the two diastereoisomers could be separated, providing single diastereoisomers with practically no erosion in ee.

Unintentionally, substrate binding/activation of the new catalyst system was effectively revealed using *N,N*-dibenzyl 4-nitrocinnamide **1x** and thiol **2a**. Substrate **1x** 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-mode Michael acceptor can be used to probe catalyst function (Table 2). 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 **3x**:**3x'**, 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 **3x** and **3x'** 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 1.0:1.6 ratio of **3x**:**3x'** and a significantly lower ee of **3x** compared to **B8**-catalyzed reaction, accentuating

Table 2. Mechanistic Investigation Employing a Dual-mode Michael Acceptor[#]



entry	catalyst	yield (% 3x)	yield (% 3x')	ee (% 3x)
1	BEMP	9	91	N/A
2	B8	81	19	92
3	A8 & BEMP	38	62	22

[#]Yields were determined by quantitative ¹H NMR (0.1 mmol scale).

the importance of the chiral tether between the iminophosphorane superbase and hydrogen-bond donor in **B8** (entry 3).

COMPUTATIONAL STUDY

A DFT study using the ADF program²² was performed to elucidate the origins of stereocontrol in the BIMP-catalyzed SMA to α,β -unsaturated amides (Figure 2).²³ The reaction

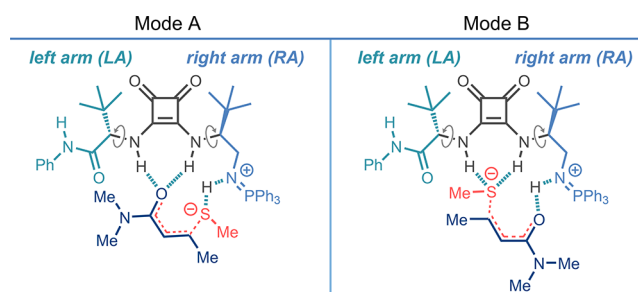


Figure 2. Possible binding modes and terminology used for computational studies.

proceeds *via* the sequential complexation between the catalyst and substrates, leading to a TS, a subsequent conjugate addition, and finally an irreversible protonation of the enolate. In this study, we have focused on the stereoselectivity-determining conjugate addition step, as no kinetic isotope effect (KIE = 1.0) or a change in ee was observed when performing the reaction with propanethiol-*d*₁, suggesting that the protonation step is neither rate- nor enantio-determining.¹⁸ Initially, the iminophosphorane moiety of the BIMP catalyst deprotonates the thiol and forms zwitterionic intermediate **RC1**, stabilized by the two hydrogen-bond donors of the squaramide, and the protonated iminophosphorane. Prior to the conjugate addition step, the amide electrophile coordinates to **RC1** and generates intermediate **RC2**. Due to the conformational freedom and the existence of two potential activation modes of the BIMP catalyst, we computed and compared all the possible TSs during the enantio-determining conjugate addition step, involving amide **1c** and methyl thiol as the model nucleophile (Figure

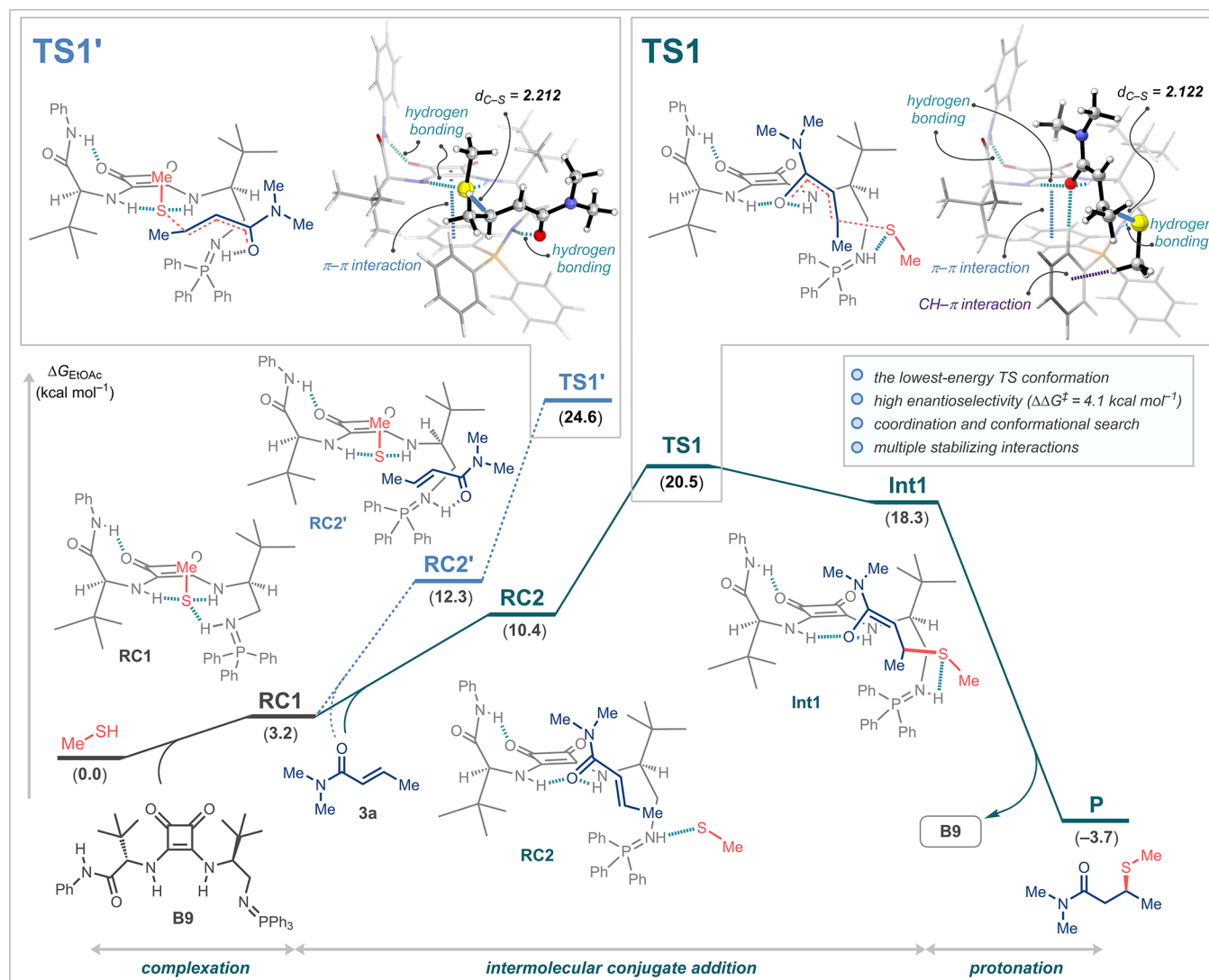


Figure 3. Computed potential energy surface (ΔG [kcal mol⁻¹]) of the BIMP squaramide-catalyzed sulfa-Michael addition computed at COSMO(EtOAc)-ZORA-M06-2X/TZ2P//COSMO(EtOAc)-ZORA-BLYP-D3(BJ)/DZP. Energies (kcal mol⁻¹) and forming bond lengths (Å) of the TS geometries are provided in the inset.

S9).^{11k,12c,14f,h} Both side chains of the BIMP squaramide catalyst can freely rotate and the two most stable conformations for its “left arm” (LA) and “right arm” (RA) were explored.¹⁸ As originally hypothesized by Pápai, there are two modes (mode A and B) in which the catalyst may bind to the substrate in the TSs.^{18,24} In the case of mode A, the electrophile is activated by the hydrogen-bond-donor moiety, while the nucleophile is bound to the protonated iminophosphorane. In the case of mode B, the nucleophile is coordinated to the hydrogen-bond donor and the electrophile is activated by the protonated iminophosphorane. Our computational analysis utilizes the terminology discussed above (Figure 2).¹⁸

All 16 possible TSs for the stereoselectivity-determining conjugate addition step were located (Figure S9). The lowest-energy conjugate addition TS was **TS1** that forms the (S)-product, which is in agreement with the experimentally confirmed absolute stereochemical outcome of the reaction (Figure 3). The relatively low-energy barrier of 20.5 kcal mol⁻¹ is furthermore consistent with the mild reaction conditions required to perform the transformation. The lowest-energy TS, responsible for the formation of the minor (R)-product, is

TS1', which proceeds through a higher energy barrier than **TS1** ($\Delta\Delta G^\ddagger = 4.1$ kcal mol⁻¹). The stereoselectivity for this transformation originates from the TS geometry that benefits from multiple inter- and intramolecular stabilizing interactions, including hydrogen bonding, CH- π , and π - π interactions. These stabilizing features are enhanced in **TS1** compared to **TS1'**. The intramolecular hydrogen bonding between the O(squaramide)-H(amide) fixes the conformational freedom of the “LA” of the BIMP catalyst, creating a three-dimensionally defined pocket within which the α,β -unsaturated amide can fit without considerable steric repulsion during the C-S bond forming event. Furthermore, the thiolate anion interacts with the aromatic ring of the iminophosphorane moiety for additional stabilization. Analysis of noncovalent interaction (NCI) plots allows one to qualitatively visualize these weak interactions between the catalyst and substrates (Figure S12).²⁵ The observed NCIs were then quantified using energy decomposition analysis (EDA) for the comparison of the stabilization effects between **TS1** and **TS1'** (Figures S13 and S14).^{18,26} In addition, to understand why both the reactivity and enantioselectivity were improved by the exchange of a thiourea

with a squaramide in the catalyst structure, a computational comparison between these motifs was performed. Our findings indicate that the squaramide BIMP catalyst can facilitate a faster conjugate addition (lower ΔG^\ddagger) with a greater degree of enantioselectivity (larger $\Delta\Delta G^\ddagger$ relative to the next most favorable TS) compared to the thiourea BIMP catalyst. These findings were supported by experimental studies comparing analogous squaramide and thiourea-based BIMPs (Figure S11).¹⁸ Overall, our state-of-the-art computations have enabled us to understand the origin of the enantioselectivity for this transformation and open up new avenues toward the rational design of novel catalysts.

CONCLUSION

Exemplified by the alkyl thiol SMA, 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 SMA 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.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacs.1c11898>.

Experimental details, analytical data, computational data, additional experiments (PDF)

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Notes

The authors declare no competing financial interest.

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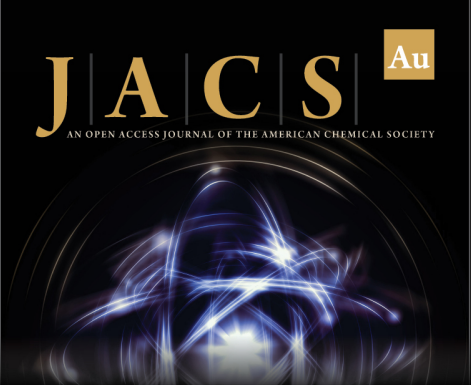
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