JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
pubs.acs.org/JACS
Article

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

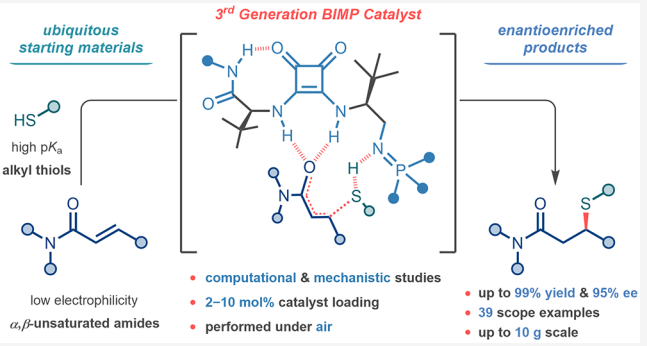
Daniel Rozsar, Michele Formica,[§] Ken Yamazaki,[§] Trevor A. Hamlin,* and Darren J. Dixon*

Cite This: J. Am. Chem. Soc. 2022, 144, 1006−1015

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

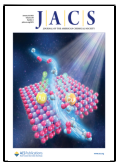
ABSTRACT: The first metal-free catalytic intermolecular enantioselective Michael addition to unactivated α,β-unsaturated amides is described. Consistently high enantiomeric excesses and yields were obtained over a wide range of alkyl thiol pronucleophiles and electrophiles under mild reaction conditions, 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.

Received: November 10, 2021
Published: January 6, 2022



https://doi.org/10.1021/jacs.1c11898
J. Am. Chem. Soc. 2022, 144, 1006−1015

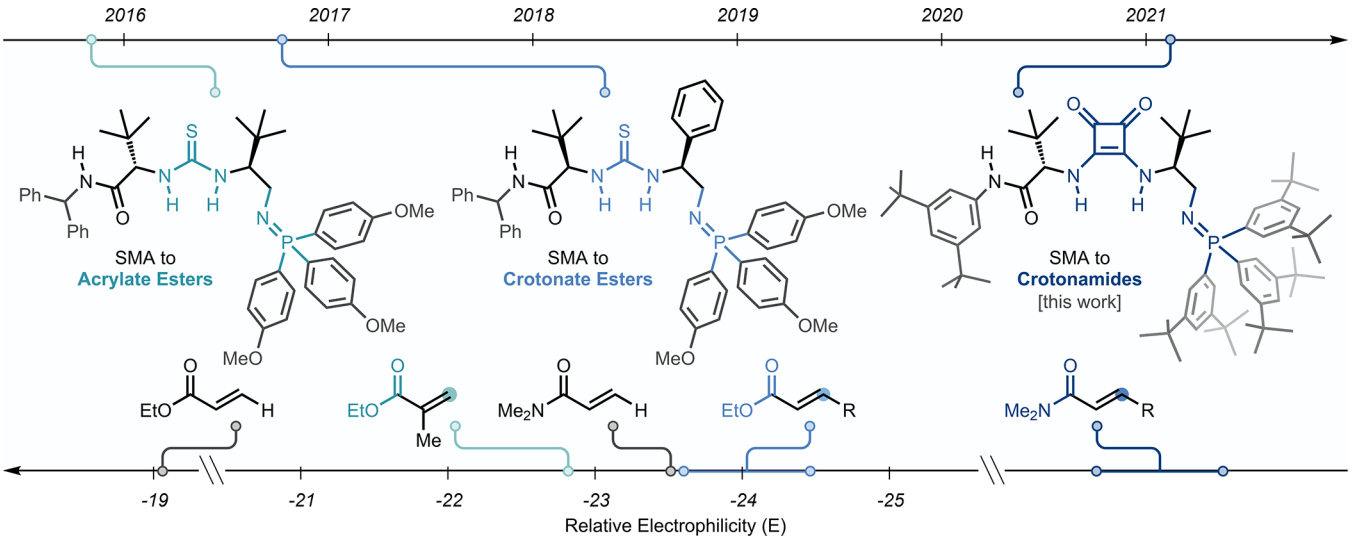
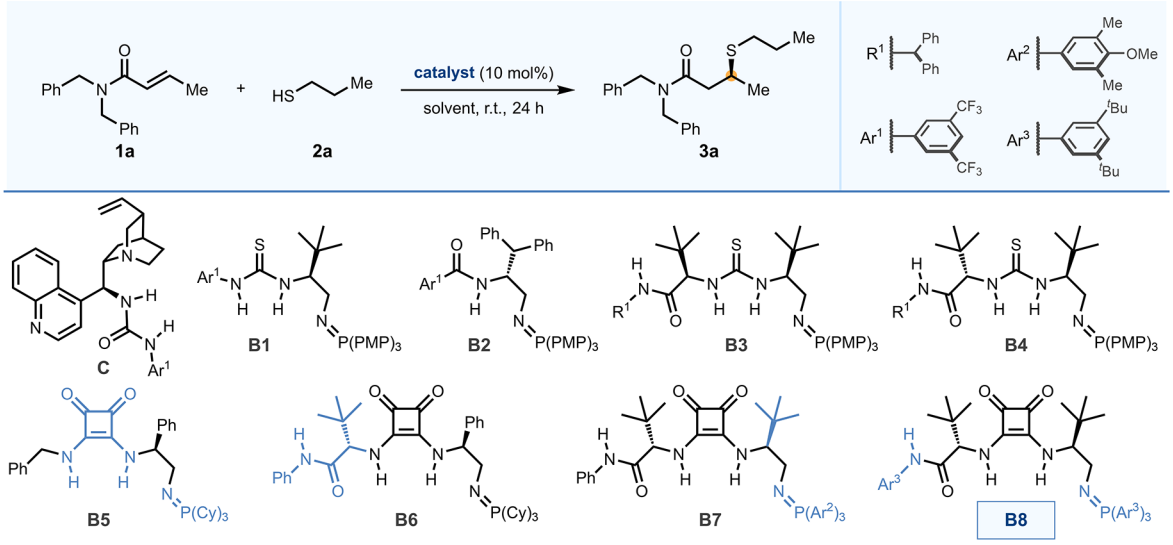


Figure 1. Mayr's electrophilicity scale (bottom). Previous BIMP catalysts for SMAs to unsaturated carboxylic acid derivatives and this work (top).

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**

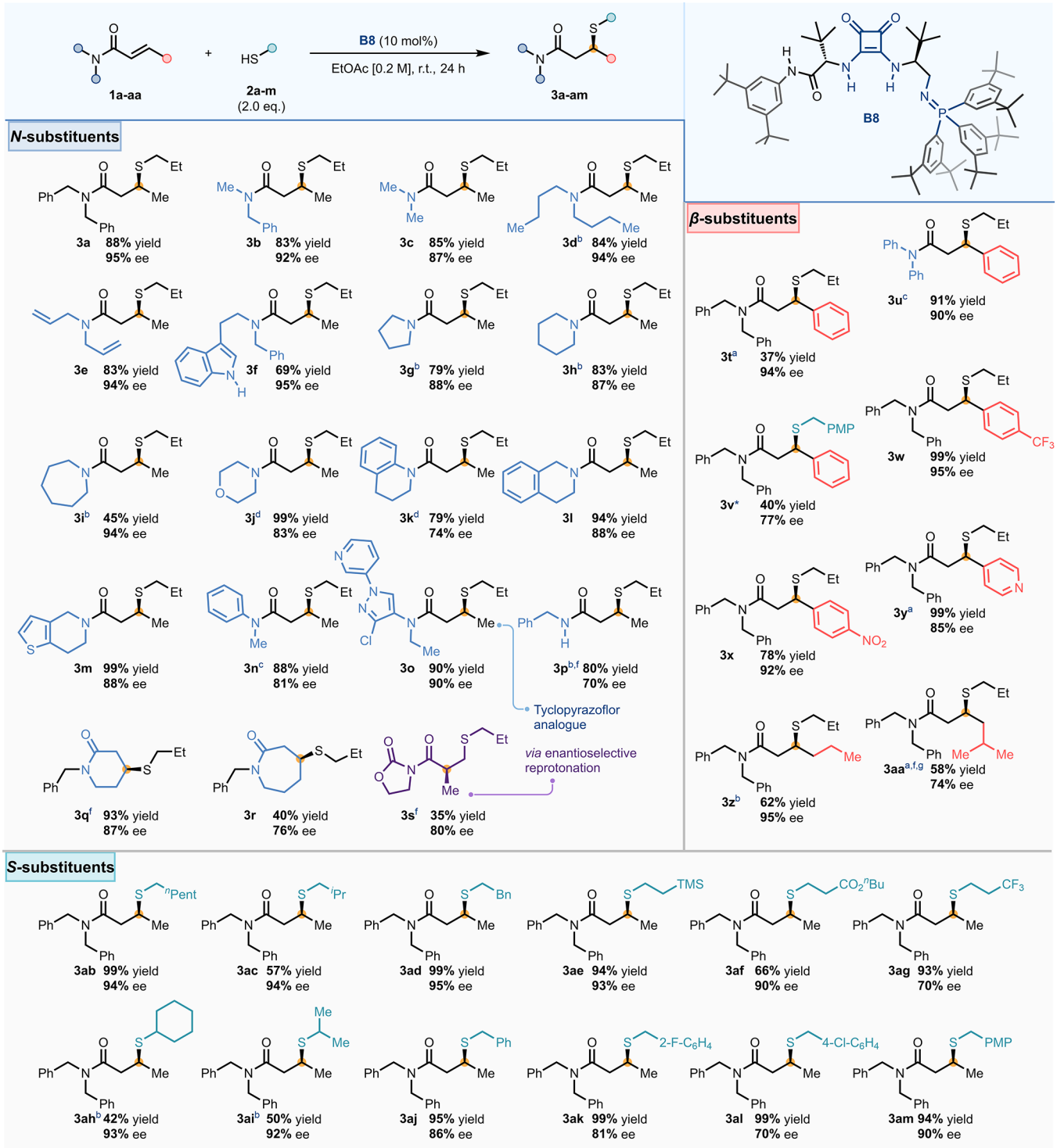
[a]Isolated yield. [b]NMR yield after 7 days. Ee determined by HPLC on a chiral stationary phase. PMP: *p*-methoxyphenyl.

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**

https://doi.org/10.1021/jacs.1c11898
J. Am. Chem. Soc. 2022, 144, 1006−1015

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

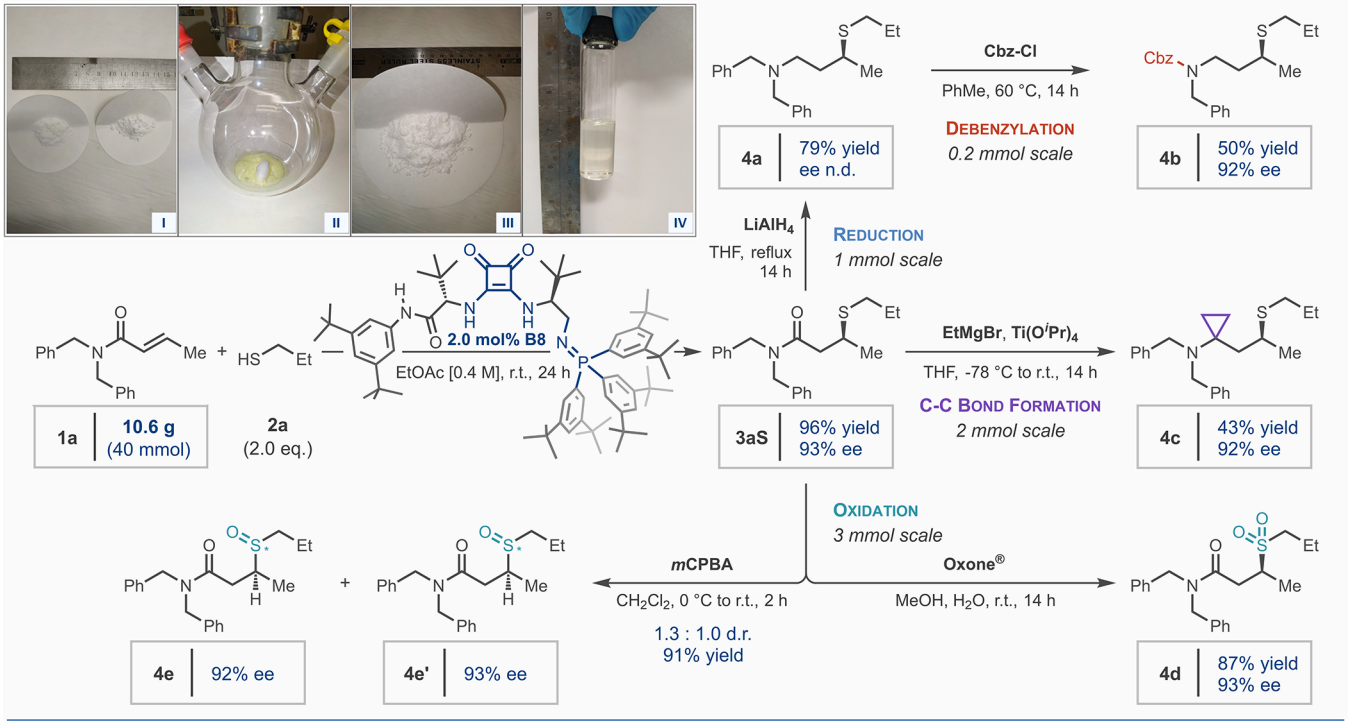


[#]Reactions were conducted under air. Reaction carried out using: [a]10.0 equiv, [b]4.0 equiv, [c]3.0 equiv thiol. Reaction carried out at: [d]−20 °C and [e]40 °C. [f]Reaction carried out in toluene. [g]0.5 M concentration. *Absolute stereochemical configuration of product **3v** was determined by chemical 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

https://doi.org/10.1021/jacs.1c11898
J. Am. Chem. Soc. 2022, 144, 1006−1015

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 relevant[19] 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 Tyclopyrazoflor[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

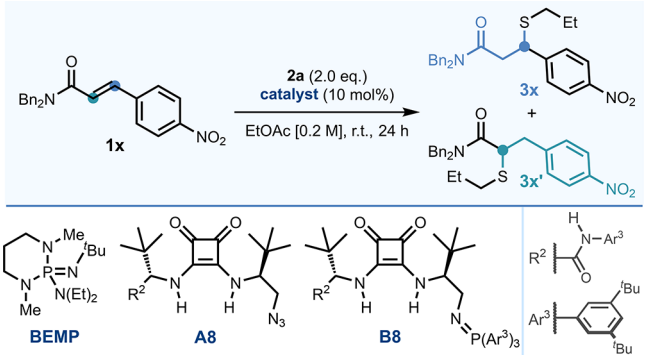
https://doi.org/10.1021/jacs.1c11898
J. Am. Chem. Soc. 2022, 144, 1006−1015

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 CF_3 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 reaction[21] 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 ^{1}H 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 program[22] was performed to elucidate the origins of stereocontrol in the BIMP-catalyzed SMA to α,β-unsaturated amides (Figure 2).[23] The reaction

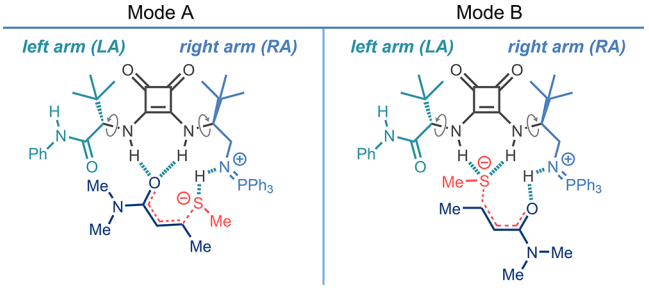


Figure 2. Possible binding modes and terminology used for computational studies.

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

https://doi.org/10.1021/jacs.1c11898
J. Am. Chem. Soc. 2022, 144, 1006−1015

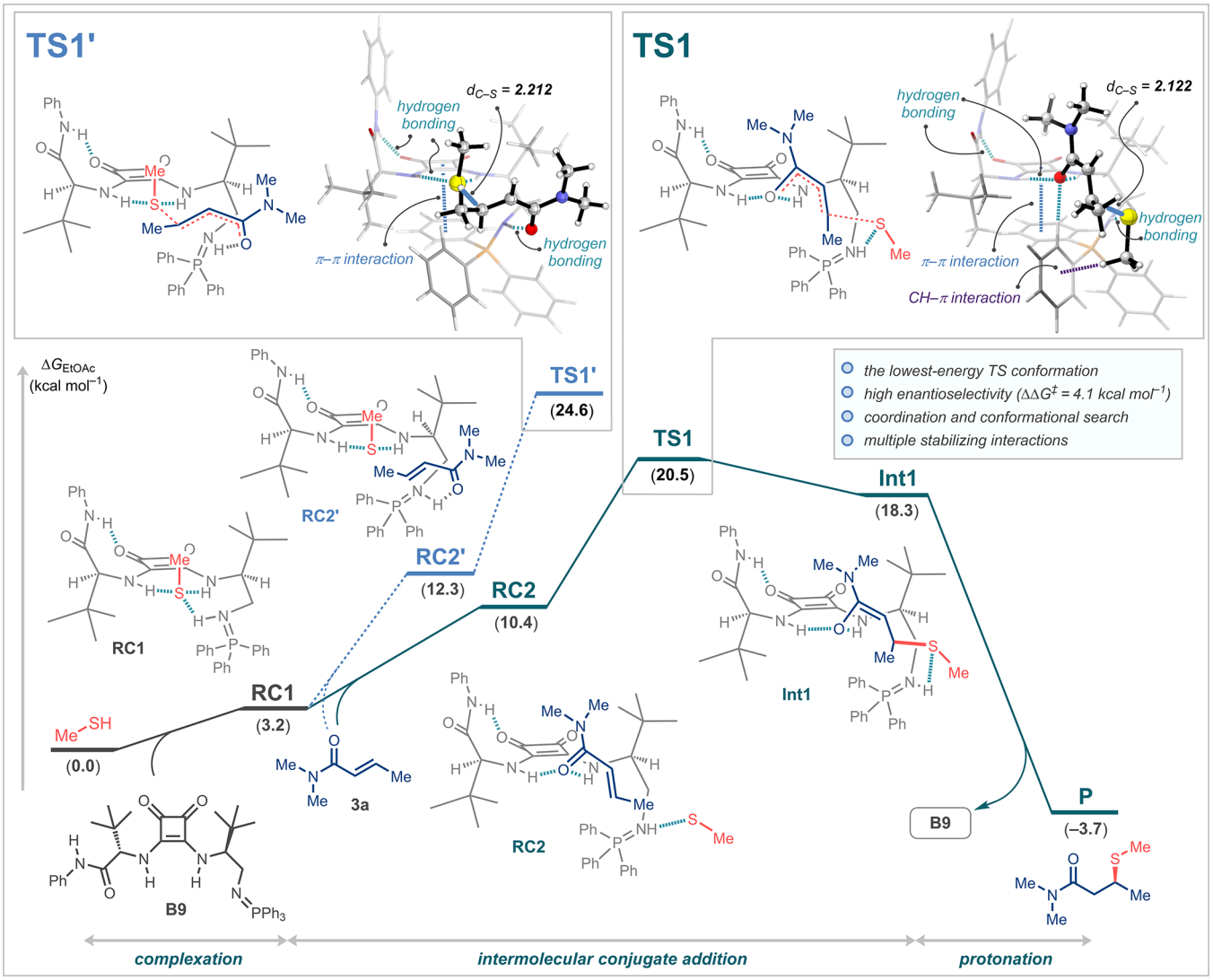


Figure 3. Computed potential energy surface (ΔG [kcal mol^{-1}]) of the BIMP squaramide-catalyzed sulfa-Michael addition computed at COSMO(EtOAc)-ZORA-M06-2X/TZ2P//COSMO(EtOAc)-ZORA-BLYP-D3(BJ)/DZP. Energies (kcal mol^{-1}) and forming bond lengths (Å) of the TS geometries are provided in the inset.

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** (ΔΔ$G^{‡}$ = 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 satbilization. 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

https://doi.org/10.1021/jacs.1c11898
J. Am. Chem. Soc. 2022, 144, 1006−1015

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 conguate addition (lower $\Delta G^{\ddagger}$) 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)

AUTHOR INFORMATION

Corresponding Authors

Trevor A. Hamlin − *Department of Theoretical Chemistry, Amsterdam Institute of Molecular and Life Sciences (AIMMS), Amsterdam Center for Multiscale Modeling (ACMM), Vrije Universiteit Amsterdam, 1081 HV Amsterdam, The Netherlands;* orcid.org/0000-0002-5128-1004; Email: t.a.hamlin@vu.nl

Darren J. Dixon − *Department of Chemistry, Chemistry Research Laboratory, University of Oxford, OX1 3TA Oxford, United Kingdom;* orcid.org/0000-0003-2456-5236; Email: darren.dixon@chem.ox.ac.uk

Authors

Daniel Rozsar − *Department of Chemistry, Chemistry Research Laboratory, University of Oxford, OX1 3TA Oxford, United Kingdom;* orcid.org/0000-0002-0516-1722

Michele Formica − *Department of Chemistry, Chemistry Research Laboratory, University of Oxford, OX1 3TA Oxford, United Kingdom;* orcid.org/0000-0003-3641-7281

Ken Yamazaki − *Department of Chemistry, Chemistry Research Laboratory, University of Oxford, OX1 3TA Oxford, United Kingdom; Department of Theoretical Chemistry, Amsterdam Institute of Molecular and Life Sciences (AIMMS), Amsterdam Center for Multiscale Modeling (ACMM), Vrije Universiteit Amsterdam, 1081 HV Amsterdam, The Netherlands;* orcid.org/0000-0002-2039-4321

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.1c11898

Author Contributions

[§]These authors contributed equally to this paper.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

D.R. and M.F. are grateful to the EPSRC Centre for Doctoral Training in Synthesis for Biology and Medicine (EP/L015838/1) for studentships, generously supported by AstraZeneca, Diamond Light Source, Defence Science and Technology Laboratory, Evotec, GlaxoSmithKline, Janssen, Novartis, Pfizer, Syngenta, Takeda, UCB, and Vertex. K.Y. thanks the Honjo International Scholarship Foundation for a postgraduate scholarship. T.A.H. thanks The Netherlands Organization for Scientific Research (NWO) for financial support. All DFT calculations were carried out on the Dutch national e-infrastructure with the support of SURF Cooperative. Yaseen A. Almehmadi (for the synthesis of substrates **1f** and **1q**) and F. Wieland Goetzke (for determining the ee of **4c** by supercritical fluid chromatography) are gratefully acknowledged. Roman Kučera, J. Andrew P. Maitland, and Daniel Matheau-Raven are thanked for useful discussions and proofreading.

REFERENCES

(1) (a) Trost, B. M. The atom economy–a search for synthetic efficiency. *Science* **1991**, *254*, 1471−1477. (b) Michael, A. Ueber die Addition von Natriumacetessig- und Natriummalonsäureäthern zu den Aethern ungesättigter Säuren. *J. Prakt. Chem.* **1887**, *35*, 349−356. (c) Michael, A. On the addition of sodium acetoacetate- and sodium malonic acid esters to the esters of unsaturated acids. *Am. Chem. J.* **1887**, *9*, 112−124.

(2) For general information about enantio- and diastereoselective Michael-additions and reactivities, see: (a) Little, R. D.; Masjedizadeh, M. R.; Wallquist, O.; McLoughlin, J. I. The Intramolecular Michael Reaction. *Org. React.* **1995**, *47*, 315−552. (b) Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, 2001; pp 70−125. (c) Nising, C. F.; Bräse, S. The oxa-Michael reaction: from recent developments to applications in natural product synthesis. *Chem. Soc. Rev.* **2008**, *37*, 1218−1228. (d) Phelan, J. P.; Ellman, J. A. Conjugate addition−enantioselective protonation reactions. *Beilstein J. Org. Chem.* **2016**, *12*, 1203−1228. (e) Reyes, E.; Uria, U.; Vicario, J. L.; Carrillo, L. The Catalytic, Enantioselective Michael Reaction. *Org. React.* **2016**, *90*, 1−898.

(3) For selected reviews on metal-catalyzed enantioselective conjugate additions, see: (a) López, F.; Minnaard, A. J.; Feringa, B. L. Catalytic Enantioselective Conjugate Addition with Grignard Reagents. *Acc. Chem. Res.* **2007**, *40*, 179−188. (b) Alexakis, A.; Bäckvall, J. E.; Krause, N.; Pàmies, O.; Diéguez, M. Enantioselective Copper-Catalyzed Conjugate Addition and Allylic Substitution. *Chem. Rev.* **2008**, *108*, 2796−2823. (c) Best, D.; Lam, H. W. C═N-Containing Azaarenes as Activating Groups in Enantioselective Catalysis. *J. Org. Chem.* **2014**, *79*, 831−845. (d) Burns, A. R.; Lam, H. W.; Roy, I. D. Enantioselective, Rhodium-Catalyzed 1,4-Addition of Organoboron Reagents to Electron-Deficient Alkenes. *Org. React.* **2017**, *93*, 1−686. (e) Zheng, K.; Liu, X.; Feng, X. Recent Advances in Metal-Catalyzed Asymmetric 1,4-Conjugate Addition (ACA) of Nonorganometallic Nucleophiles. *Chem. Rev.* **2018**, *118*, 7586−7656.

(4) For nonmetal-catalyzed enantio- and diastereoselective conjugate additions, see: (a) Chauhan, P.; Chimni, S. S. Recent advances in asymmetric organocatalytic conjugate addition of arenes and heteroarenes. *RSC Adv.* **2012**, *2*, 6117. (b) Zhang, Y.; Wang, W. Recent advances in organocatalytic asymmetric Michael reactions. *Catal. Sci. Technol.* **2012**, *2*, 42−53. (c) Ferko, B.; Zeman, M.; Formica, M.; Veselý, S.; Doháňošová, J.; Moncol, J.; Olejníková, P.; Berkeš, D.; Jakubec, P.; Dixon, D. J.; Caletková, O. Total Synthesis of Berkeleylactone A. *J. Org. Chem.* **2019**, *84*, 7159−7165.

(5) For general information about amides and their reactivity, see: (a) Pattabiraman, V. R.; Bode, J. W. Rethinking amide bond synthesis. *Nature* **2011**, *480*, 471−479. (b) Ruider, S. A.; Maulide, N. Strong Bonds Made Weak: Towards the General Utility of Amides as Synthetic Modules. *Angew. Chem., Int. Ed.* **2015**, *54*, 13856−13858. (c) Allgäuer, D. S.; Jangra, H.; Asahara, H.; Li, Z.; Chen, Q.; Zipse, H.; Ofial, A. R.; Mayr, H. Quantification and Theoretical Analysis of the Electrophilicities of Michael Acceptors. *J. Am. Chem. Soc.* **2017**, *139*, 13318−13329. (d) Kaiser, D.; Bauer, A.; Lemmerer, M.; Maulide, N. Amide activation: an emerging tool for chemoselective synthesis. *Chem. Soc. Rev.* **2018**, *47*, 7899−7925. (e) Ielo, L.; Pace, V.; Holzer, W.; Rahman, M.; Meng, G.; Szostak, R.; Szostak, M. Electrophilicity Scale of Activated Amides: ^{17}O NMR and ^{15}N NMR Chemical Shifts of Acyclic Twisted Amides in N−C(O) Cross-Coupling. *Chem. - Eur. J.* **2020**, *26*, 16246−16250.

(6) For selected conjugate additions of activated amides, see: (a) Hird, A. W.; Hoveyda, A. H. Cu-Catalyzed Enantioselective Conjugate Additions of Alkyl Zinc Reagents to Unsaturated *N*-Acyloxazolidinones Promoted by a Chiral Triamide Phosphane. *Angew. Chem., Int. Ed.* **2003**, *42*, 1276−1279. (b) Shintani, R.; Kimura, T.; Hayashi, T. Rhodium/diene-catalyzed asymmetric 1,4-addition of arylboronic acids to α,β-unsaturated Weinreb amides. *Chem. Commun.* **2005**, 3213−3214. (c) Pineschi, M.; Del Moro, F.; Di Bussolo, V.; Macchia, F. Highly Enantioselective Copper-Phosphoramidite-Catalyzed Conjugate Addition of Dialkylzinc Reagents to Acyclic α,β-Unsaturated Imides. *Adv. Synth. Catal.* **2006**, *348*, 301−304. (d) Mazet, C.; Jacobsen, E. N. Dinuclear {(salen)Al} Complexes Display Expanded Scope in the Conjugate Cyanation of α,β-Unsaturated Imides. *Angew. Chem., Int. Ed.* **2008**, *47*, 1762−1765. (e) Inokuma, T.; Nagamoto, Y.; Sakamoto, S.; Miyabe, H.; Takasu, K.; Takemoto, Y. Asymmetric synthesis of 4-substituted 2,6-dioxopiperidine-3-carbonitrile by using thiourea-catalyzed asymmetric Michael addition. *Heterocycles* **2009**, *79*, 573−582. (f) Sheshenev, A. E.; Boltukhina, E. V.; Hii, K. K. Levonantradol: asymmetric synthesis and structural analysis. *Chem. Commun.* **2013**, *49*, 3685−3687. (g) Byrd, K. M. Diastereoselective and enantioselective conjugate addition reactions utilizing activated α,β-unsaturated amides and lactams. *Beilstein J. Org. Chem.* **2015**, *11*, 530−562. (h) Barron, B. J.; Wong, W.-T.; Chiu, P.; Hii, K. K. Goldilocks Effect" of Water in Lewis-Brønsted Acid and Base Catalysis. *ACS Catal.* **2016**, *6*, 4189−4194. (i) Chen, D.-F.; Chu, J. C. K.; Rovis, T. Directed γ-C(sp^3)−H Alkylation of Carboxylic Acid Derivatives through Visible Light Photoredox Catalysis. *J. Am. Chem. Soc.* **2017**, *139*, 14897−14900. (j) Zhu, C.; Dong, J.; Liu, X.; Gao, L.; Zhao, Y.; Xie, J.; Li, S.; Zhu, C. Photoredox-Controlled β-Regioselective Radical Hydroboration of Activated Alkenes with NHC-Boranes. *Angew. Chem., Int. Ed.* **2020**, *59*, 12817−12821. (k) Wang, D.; Dong, J.; Fan, W.; Yuan, X.-A.; Han, J.; Xie, J. Dimeric Manganese-Catalyzed Hydroarylation and Hydroalkenylation of Unsaturated Amides. *Angew. Chem., Int. Ed.* **2020**, *59*, 8430−8434.

(7) (a) Suzuki, H.; Sato, I.; Yamashita, Y.; Kobayashi, S. Catalytic Asymmetric Direct-Type 1,4-Addition Reactions of Simple Amides. *J. Am. Chem. Soc.* **2015**, *137*, 4336−4339. (b) Yamashita, Y.; Sato, I.; Suzuki, H.; Kobayashi, S. Catalytic Asymmetric 1,4-Addition Reactions of Simple Alkylnitriles. *Chem. - Asian J.* **2015**, *10*, 2143−2146. (c) Sato, I.; Suzuki, H.; Yamashita, Y.; Kobayashi, S. Catalytic asymmetric direct-type 1,4-addition reactions of simple esters. *Org. Chem. Front.* **2016**, *3*, 1241−1245. (d) Suzuki, H.; Igarashi, R.; Yamashita, Y.; Kobayashi, S. Catalytic Direct-type 1,4-Addition Reactions of Alkylazaarenes. *Angew. Chem., Int. Ed.* **2017**, *56*, 4520−4524. (e) Yamashita, Y.; Igarashi, R.; Suzuki, H.; Kobayashi, S. Catalytic Asymmetric Direct-Type 1,4-Addition Reactions of Alkanesulfonamides. *Synlett* **2017**, *28*, 1287−1290.

(8) Rodríguez-Fernández, M.; Yan, X.; Collados, J. F.; White, P. B.; Harutyunyan, S. R. Lewis Acid Enabled Copper-Catalyzed Asymmetric Synthesis of Chiral β-Substituted Amides. *J. Am. Chem. Soc.* **2017**, *139*, 14224−14231.

(9) (a) Gao, T.-T.; Zhang, W.-W.; Sun, X.; Lu, H.-X.; Li, B. J. Stereodivergent Synthesis through Catalytic Asymmetric Reversed Hydroboration. *J. Am. Chem. Soc.* **2019**, *141*, 4670−4677. (b) Li, Y.-B.; Tian, H.; Yin, L. Copper(I)-Catalyzed Asymmetric 1,4-Conjugate Hydrophosphination of α,β-Unsaturated Amides. *J. Am. Chem. Soc.* **2020**, *142*, 20098−20106. (c) Gao, T.-T.; Lu, H.-X.; Gao, P.-C.; Li, B.-J. Enantioselective synthesis of tertiary boronic esters through catalytic asymmetric reversed hydroboration. *Nat. Commun.* **2021**, *12*, 3776.

(10) For information about superbases, see: (a) Palomo, C.; Oiarbide, M.; López, R. Asymmetric organocatalysis by chiral Brønsted bases: implications and applications. *Chem. Soc. Rev.* **2009**, *38*, 632−653. (b) Ishikawa, T. *Superbases for Organic Synthesis: Guanidines, Amidines, Phosphazenes and Related Organocatalysts*; John Wiley & Sons, Ltd: Chichester, 2009. (c) Krawczyk, H.; Dzięgielewski, M.; Deredas, D.; Albrecht, A.; Albrecht, Ł. Chiral Iminophosphoranes - An Emerging Class of Superbase Organocatalysts. *Chem. - Eur. J.* **2015**, *21*, 10268−10277. (d) Teng, B.; Lim, W. C.; Tan, C. H. Recent Advances in Enantioselective Bronsted Base Organocatalytic Reactions. *Synlett* **2017**, *28*, 1272−1277. (e) Dong, S.; Feng, X.; Liu, X. Chiral guanidines and their derivatives in asymmetric synthesis. *Chem. Soc. Rev.* **2018**, *47*, 8525−8540. (f) Wang, Y.-H.; Cao, Z.-Y.; Li, Q.-H.; Lin, G.-Q.; Zhou, J.; Tian, P. Activating Pronucleophiles with High pK_a Values: Chiral Organo-Superbases. *Angew. Chem., Int. Ed.* **2020**, *59*, 8004−8014. (g) Kondoh, A.; Terada, M. Development of Molecular Transformations on the Basis of Catalytic Generation of Anionic Species by Organosuperbase. *Bull. Chem. Soc. Jpn.* **2021**, *94*, 339−356.

(11) For representative papers in organic superbase catalysis, see: (a) Corey, E. J.; Grogan, M. J. Enantioselective Synthesis of α-Amino Nitriles from *N*-Benzhydryl Imines and HCN with a Chiral Bicyclic Guanidine as Catalyst. *Org. Lett.* **1999**, *1*, 157−160. (b) Terada, M.; Ube, H.; Yaguchi, Y. Axially Chiral Guanidine as Enantioselective Base Catalyst for 1,4-Addition Reaction of 1,3-Dicarbonyl Compounds with Conjugated Nitroalkenes. *J. Am. Chem. Soc.* **2006**, *128*, 1454−1455. (c) Leow, D.; Lin, S.; Chittimalla, S. K.; Fu, X.; Tan, C.-H. Enantioselective Protonation Catalyzed by a Chiral Bicyclic Guanidine Derivative. *Angew. Chem., Int. Ed.* **2008**, *47*, 5641−5645. (d) Uraguchi, D.; Ooi, T. Development of P-Spiro Chiral Aminophosphonium Salts as a New Class of Versatile Organic Molecular Catalyst. *Yuki Gosei Kagaku Kyokaishi* **2010**, *68*, 1185−1194. (e) Dong, S.; Liu, X.; Chen, X.; Mei, F.; Zhang, Y.; Gao, B.; Lin, L.; Feng, X. Chiral Bisguanidine-Catalyzed Inverse-Electron-Demand Hetero-Diels−Alder Reaction of Chalcones with Azlactones. *J. Am. Chem. Soc.* **2010**, *132*, 10650−10651. (f) Yang, Y.; Dong, S.; Liu, X.; Lin, L.; Feng, X. Chiral guanidine-catalyzed asymmetric direct vinylogous Michael reaction of α,β-unsaturated γ-butyrolactams with alkylidene malonates. *Chem. Commun.* **2012**, *48*, 5040−5042. (g) Cho, B.; Tan, C. H.; Wong, M. W. Origin of Asymmetric Induction in Bicyclic Guanidine-Catalyzed Thio-Michael Reaction: A Bifunctional Mode of Lewis Acid-Brønsted Acid Activation. *J. Org. Chem.* **2012**, *77*, 6553−6562. (h) Bandar, J. S.; Lambert, T. H. Enantioselective Brønsted Base Catalysis with Chiral Cyclopropenimines. *J. Am. Chem. Soc.* **2012**, *134*, 5552−5555. (i) Takeda, T.; Terada, M. Development of a Chiral Bis(guanidino)-iminophosphorane as an Uncharged Organosuperbase for the Enantioselective Amination of Ketones. *J. Am. Chem. Soc.* **2013**, *135*, 15306−15309. (j) Uraguchi, D.; Yoshioka, K.; Ooi, T. Complete diastereodivergence in asymmetric 1,6-addition reactions enabled by minimal modification of a chiral catalyst. *Nat. Commun.* **2017**, *8*, 14793. (k) Shi, H.; Michaelides, I. N.; Darses, B.; Jakubec, P.; Nguyen, Q. N. N.; Paton, R. S.; Dixon, D. J. Total Synthesis of (−)-Himalensine A. *J. Am. Chem. Soc.* **2017**, *139*, 17755−17758. (l) Kondoh, A.; Oishi, M.; Tezuka, H.; Terada, M. Development of Chiral Organosuperbase Catalysts Consisting of Two Different Organobase Functionalities. *Angew. Chem., Int. Ed.* **2020**, *59*, 7472−7477. (m) Kondoh, A.; Ishikawa, S.; Terada, M. Development of Chiral Ureates as Chiral Strong Brønsted Base Catalysts. *J. Am. Chem. Soc.* **2020**, *142*, 3724−3728.

(12) For representative examples of BIMP catalysis, see: (a) Núñez, M. G.; Farley, A. J. M.; Dixon, D. J. Bifunctional Iminophosphorane Organocatalysts for Enantioselective Synthesis: Application to the Ketimine Nitro-Mannich Reaction. *J. Am. Chem. Soc.* **2013**, *135*, 16348−16357. (b) Thomson, C. J.; Barber, D. M.; Dixon, D. J. Catalytic Enantioselective Direct Aldol Addition of Aryl Ketones to α-

https://doi.org/10.1021/jacs.1c11898
J. Am. Chem. Soc. 2022, 144, 1006−1015

Fluorinated Ketones. *Angew. Chem., Int. Ed.* **2020**, *59*, 5359−5364. (c) Golec, J. C.; Carter, E. M.; Ward, J. W.; Whittingham, W. G.; Simón, L.; Paton, R. S.; Dixon, D. J. BIMP-Catalyzed 1,3-Prototropic Shift for the Highly Enantioselective Synthesis of Conjugated Cyclohexenones. *Angew. Chem., Int. Ed.* **2020**, *59*, 17417−17422.

(13) For a review on BIMP catalysis, see: Formica, M.; Rozsar, D.; Su, G.; Farley, A. J. M.; Dixon, D. J. Bifunctional Iminophosphorane Superbase Catalysis: Applications in Organic Synthesis. *Acc. Chem. Res.* **2020**, *53*, 2235−2247.

(14) For BIMP-catalyzed Michael-additions, see: (a) Goldys, A. M.; Nuñez, M. G.; Dixon, D. J. Creation through Immobilization: A New Family of High Performance Heterogeneous Bifunctional Iminophosphorane (BIMP) Superbase Organocatalysts. *Org. Lett.* **2014**, *16*, 6294−6297. (b) Farley, A. J. M; Sandford, C.; Dixon, D. J. Bifunctional Iminophosphorane Catalyzed Enantioselective Sulfa-Michael Addition to Unactivated α-Substituted Acrylate Esters. *J. Am. Chem. Soc.* **2015**, *137*, 15992−15995. (c) Yang, J.; Farley, A. J. M.; Dixon, D. J. Enantioselective bifunctional iminophosphorane catalyzed sulfa-Michael addition of alkyl thiols to unactivated β-substituted-α,β-unsaturated esters. *Chem. Sci.* **2017**, *8*, 606−210. (d) Horwitz, M. A.; Fulton, J. L.; Johnson, J. S. Enantio- and Diastereoselective Organocatalytic Conjugate Additions of Nitroalkanes to Enone Diesters. *Org. Lett.* **2017**, *19*, 5783−5785. (e) Fulton, J. L.; Horwitz, M. A.; Bruske, E. L.; Johnson, J. S. Asymmetric Organocatalytic Sulfa-Michael Addition to Enone Diesters. *J. Org. Chem.* **2018**, *83*, 3385−3391. (f) Formica, M.; Sorin, G.; Farley, A. J. M.; Díaz, J.; Paton, R. S.; Dixon, D. J. Bifunctional iminophosphorane catalysed enantioselective sulfa-Michael addition of alkyl thiols to alkenyl benzimidazoles. *Chem. Sci.* **2018**, *9*, 6969−6974. (g) Farley, A. J. M.; Jakubec, P.; Goldys, A. M.; Dixon, D. J. Bifunctional iminophosphorane superbases: Potent organocatalysts for enantio- and diastereoselective Michael addition reactions. *Tetrahedron* **2018**, *74*, 5206−5212. (h) Su, G.; Thomson, C. J.; Yamazaki, K.; Rozsar, D.; Christensen, K. E.; Hamlin, T. A.; Dixon, D. J. A Bifunctional Iminophosphorane Squaramide Catalyzed Enantioselective Synthesis of Hydroquinazolines via Intramolecular Aza-Michael Addition to α,β-Unsaturated Esters. *Chem. Sci.* **2021**, *12*, 6064−6072.

(15) For biologically active sulfur-containing molecules see: (a) Chauhan, P.; Mahajan, S.; Enders, D. Organocatalytic Carbon−Sulfur Bond-Forming Reactions. *Chem. Rev.* **2014**, *114*, 8807−8864. (b) Niyaz, N. M.; Garizi, N.; Zhang, Y.; Trullinger, T. K.; Hunter, R.; Buysse, A. M.; Kubota, A.; LePlae, P. R., Jr.; Knueppel, D.; Lowe, C. T.; Pernich, D.; Demeter, D. A.; Johnson, T. C. Pesticidal Compositions and Processes Related Thereto. US Patent US 20150072859 A1, 2015. (c) Yang, Q.; Zhang, Y.; Lorsbach, B.; Li, X.; Roth, G. Processes for the preparation of pesticidal compounds. US Patent US 2018186765 A1, 2018. (d) Yang, Q.; Li, X.; Lorsbach, B. A.; Roth, G. A.; Podhorez, D. E.; Ross, R.; Niyaz, N.; Buysse, A.; Knueppel, D.; Nissen, J. Development of a Scalable Process for the Insecticidal Candidate Tyclopyrazoflor. Part 1. Evaluation of [3 + 2] Cyclization Strategies to 3-(3-Chloro-1H-pyrazol-1-yl)pyridine. *Org. Process Res. Dev.* **2019**, *23*, 2122−2132. (e) Yang, Q.; Li, X.; Lorsbach, B. A.; Muhuhi, J. M.; Roth, G. A.; Gray, K. C.; Podhorez, D. E. Development of a Scalable Process for the Insecticidal Candidate Tyclopyrazoflor. Part 2. Fit-for-Purpose Optimization of the Route to Tyclopyrazoflor Featuring [3 + 2] Cyclization of 3-Hydrazinopyridine·2HCl and Methyl Acrylate. *Org. Process Res. Dev.* **2019**, *23*, 2133−2141. (f) Gray, K. C.; Heider, P.; McGough, P.; Ondari, M.; Devaraj, J.; Yang, Q.; Frycek, G.; Graham, B.; Neuman, J.; Lorsbach, B. A.; Zhang, Y. Development of a Scalable Process for the Insecticidal Candidate Tyclopyrazoflor. Part 3. A Scalable Synthesis of Methyl 3-((3,3,3-Trifluoropropyl)thio)-propanoate via Thiol−Ene Chemistry. *Org. Process Res. Dev.* **2019**, *23*, 2142−2147.

(16) For representative papers using chiral squaramide derivatives as hydrogen-bond-donor catalysts, see: (a) Malerich, J. P.; Hagihara, K.; Rawal, V. H. Chiral Squaramide Derivatives are Excellent Hydrogen Bond Donor Catalysts. H. *J. Am. Chem. Soc.* **2008**, *130*, 14416−14417. (b) Zhu, Y.; Malerich, J. P.; Rawal, V. H. Squaramide-catalyzed enantioselective Michael addition of diphenyl phosphite to nitroalkenes. *Angew. Chem., Int. Ed.* **2010**, *49*, 153−156. (c) Konishi, H.; Lam, T. Y.; Malerich, J. P.; Rawal, V. H. Enantioselective α-Amination of 1,3-Dicarbonyl Compounds Using Squaramide Derivatives as Hydrogen Bonding Catalysts. *Org. Lett.* **2010**, *12*, 2028−2031. (d) Yang, K. S.; Nibbs, A. E.; Türkmen, Y. E.; Rawal, V. H. Squaramide-Catalyzed Enantioselective Michael Addition of Masked Acyl Cyanides to Substituted Enones. *J. Am. Chem. Soc.* **2013**, *135*, 16050−16053. (e) Banik, S. M.; Levina, A.; Hyde, A. M.; Jacobsen, E. N. Lewis acid enhancement by hydrogen-bond donors for asymmetric catalysis. *Science* **2017**, *358*, 761−764. (f) Wendlandt, A. E.; Vangal, P.; Jacobsen, E. N. Quaternary stereocentres via an enantioconvergent catalytic S_N1 reaction. *Nature* **2018**, *556*, 447−451.

(17) For properties of squaramides, see: (a) Storer, R. I.; Aciro, C.; Jones, L. H. Squaramides: physical properties, synthesis and applications. *Chem. Soc. Rev.* **2011**, *40*, 2330−2346. (b) Ni, X.; Li, X.; Wang, Z.; Cheng, J.-P. Squaramide Equilibrium Acidities in DMSO. *Org. Lett.* **2014**, *16*, 1786−1789.

(18) See Supporting Information for further details.

(19) (a) Khan, A. Y.; Kumar, G. S. Natural isoquinoline alkaloids: binding aspects to functional proteins, serum albumins, hemoglobin, and lysozyme. *Biophys. Rev.* **2015**, *7*, 407−420. (b) Shang, X.-F.; Yang, C.-J.; Morris-Natschke, S. L.; Li, J.-C.; Yin, X.-D.; Liu, Y.-Q.; Guo, X.; Peng, J.-W.; Goto, M.; Zhang, J.-Y.; Lee, K.-H. Biologically active isoquinoline alkaloids covering 2014−2018. *Med. Res. Rev.* **2020**, *40*, 2212−2289.

(20) Interestingly, both thiophenol and *tert*-butyl thiol furnished no SMA products under the optimized reaction conditions. In the former case, low reactivity was presumably due to the reduced nucleophilicity of thiophenolate ion, whereas in the latter case, it was likely due to increased steric hindrance in the transition structure.

(21) Chaplinski, V.; de Meijere, A. A Versatile New Preparation of Cyclopropylamines from Acid Dialkylamides. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 413−414.

(22) (a) te Velde, G.; Bickelhaupt, F. M.; Baerends, E. J.; Fonseca Guerra, C.; van Gisbergen, S. J. A.; Snijders, J. G.; Ziegler, T. Chemistry with ADF. *J. Comput. Chem.* **2001**, *22*, 931−967. (b) Fonseca Guerra, C.; Snijders, J. G.; te Velde, G.; Baerends, E. J. Towards an Order-N DFT Method. *Theor. Chem. Acc.* **1998**, *99*, 391−403. (c) *ADF2018.105, SCM Theoretical Chemistry*; Vrije Universiteit: Amsterdam, The Netherlands. https://www.scm.com (accessed 2021-12-08).

(23) For representative references on theoretical studies of Michael-addition reactions catalyzed by bifunctional organocatalysts, see: (a) Hamza, A.; Schubert, G.; Soós, T.; Pápai, I. Theoretical Studies on the Bifunctionality of Chiral Thiourea-Based Organocatalysts: Competing Routes to C−C Bond Formation. *J. Am. Chem. Soc.* **2006**, *128*, 13151−13160. (b) Hammar, P.; Marcelli, T.; Hiemstra, H.; Himo, F. Density Functional Theory Study of the Cinchona Thiourea-Catalyzed Henry Reaction: Mechanism and Enantioselectivity. *Adv. Synth. Catal.* **2007**, *349*, 2537−2548. (c) Fu, A.; Li, H.; Si, H.; Yuan, S.; Duan, Y. Theoretical studies of stereoselectivities in the direct syn- and anti-Mannich reactions catalyzed by different amino acids. *Tetrahedron: Asymmetry* **2008**, *19*, 2285−2292. (d) Cucinotta, C. S.; Kosa, M.; Melchiorre, P.; Cavalli, A.; Gervasio, F. L. Bifunctional Catalysis by Natural Cinchona Alkaloids: A Mechanism Explained. *Chem. - Eur. J.* **2009**, *15*, 7913−7921. (e) Manzano, R.; Andrés, J. M.; Álvarez, R.; Muruzábal, M. D.; de Lera, Á. R.; Pedrosa, R. Enantioselective Conjugate Addition of Nitro Compounds to α,β-Unsaturated Ketones: An Experimental and Computational Study. *Chem. - Eur. J.* **2011**, *17*, 5931−5938. (f) Shubina, T. E.; Freund, M.; Schenker, S.; Clark, T.; Tsogoeva, S. B. Synthesis and evaluation of new guanidine-thiourea organocatalyst for the nitro-Michael reaction: Theoretical studies on mechanism and enantioselectivity. *Beilstein J. Org. Chem.* **2012**, *8*, 1485−1498. (g) Yang, H.; Wong, M. W. (S)-Proline-catalyzed nitro-Michael reactions: towards a better understanding of the catalytic mechanism and enantioselectivity. *Org. Biomol. Chem.* **2012**, *10*, 3229−3235. (h) Kótai, B.; Kardos, G.; Hamza, A.; Farkas, V.; Pápai, I.; Soós, T. On the Mechanism of Bifunctional Squaramide-Catalyzed Organocatalytic Michael Addition: A Protonated Catalyst as an Oxyanion Hole. *Chem. - Eur. J.* **2014**, *20*, 5631−5639. (i) Reiter, C.; López-Molina, S.; Schmid, B.; Neiss, C.; Görling, A.; Tsogoeva, S. B. Michael

https://doi.org/10.1021/jacs.1c11898
J. Am. Chem. Soc. 2022, 144, 1006−1015

Addition of N-Unprotected 2-Oxindoles to Nitrostyrene Catalyzed by Bifunctional Tertiary Amines: Crucial Role of Dispersion Interactions. *ChemCatChem.* **2014**, *74*, 1324−1332. (j) Varga, E.; Mika, L. T.; Csámpai, A.; Holczbauer, T.; Kardos, G.; Soós, T. Mechanistic investigations of a bifunctional squaramide organocatalyst in asymmetric Michael reaction and observation of stereoselective retro-Michael reaction. *RSC Adv.* **2015**, *5*, 95079−95086. (k) Quintard, A.; Cheshmedzhieva, D.; Maria del Mar Sanchez Duque; Gaudel-Siri, A.; Naubron, J.-V.; Génisson, Y.; Plaquevent, J.-C.; Bugaut, X.; Rodriguez, J.; Constantieux, T. Origin of the Enantioselectivity in Organocatalytic Michael Additions of β-Ketoamides to α,β-Unsaturated Carbonyls: A Combined Experimental, Spectroscopic and Theoretical Study. *Chem.—Eur. J.* **2015**, *21*, 778−790. (l) Xue, Y.; Wang, Y.; Cao, Z.; Zhou, J.; Chen, Z.-X. Computational insight into the cooperative role of non-covalent interactions in the aza-Henry reaction catalyzed by quinine derivatives: mechanism and enantioselectivity. *Org. Biomol. Chem.* **2016**, *14*, 9588−9597. (m) Grayson, M. N.; Houk, K. N. Cinchona Urea-Catalyzed Asymmetric Sulfa-Michael Reactions: The Brønsted Acid−Hydrogen Bonding Model. *J. Am. Chem. Soc.* **2016**, *138*, 9041−9044. (n) Grayson, M. N.; Houk, K. N. Cinchona Alkaloid-Catalyzed Asymmetric Conjugate Additions: The Bifunctional Brønsted Acid−Hydrogen Bonding Model. *J. Am. Chem. Soc.* **2016**, *138*, 1170−1173. (o) Grayson, M. N. Mechanism and Origins of Stereoselectivity in the Cinchona Thiourea- and Squaramide-Catalyzed Asymmetric Michael Addition of Nitroalkanes to Enones. *J. Org. Chem.* **2017**, *82*, 4396−4401. (p) Bhaskararao, B.; Sunoj, R. B. Two chiral catalysts in action: insights into cooperativity and stereoselectivity in proline and cinchona-thiourea dual organocatalysis. *Chem. Sci.* **2018**, *9*, 8738−8747.

(24) (a) Okino, T.; Hoashi, Y.; Takemoto, Y. Enantioselective Michael Reaction of Malonates to Nitroolefins Catalyzed by Bifunctional Organocatalysts. *J. Am. Chem. Soc.* **2003**, *125*, 12672−12673. (b) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. Enantio- and Diastereoselective Michael Reaction of 1,3-Dicarbonyl Compounds to Nitroolefins Catalyzed by a Bifunctional Thiourea. *J. Am. Chem. Soc.* **2005**, *127*, 119−125. (c) Hamza, A.; Schubert, G.; Soós, T.; Pápai, I. Theoretical Studies on the Bifunctionality of Chiral Thiourea-Based Organocatalysts: Competing Routes to C−C Bond Formation. *J. Am. Chem. Soc.* **2006**, *128*, 13151−13160.

(25) (a) Johnson, E. R.; Keinan, S.; Mori-Sánchez, P.; Contreras-García, J.; Cohen, A. J.; Yang, W. Revealing Non-covalent Interactions. *J. Am. Chem. Soc.* **2010**, *132*, 6498−6506. (b) Contreras-García, J.; Johnson, E. R.; Keinan, S.; Chaudret, R.; Piquemal, J.-P.; Beratan, D. N.; Yang, W. NCIPLOT: A Program for Plotting Non-covalent Interaction Regions. *J. Chem. Theory Comput.* **2011**, *7*, 625−632.

(26) For an overview of the EDA method, see: (a) Hamlin, T. A.; Vermeeren, P.; Fonseca Guerra, C.; Bickelhaupt, F. M. Energy Decomposition Analysis in the Context of Quantitative Molecular Orbital Theory. In *Complementary Bonding Analyses*; Grabowsky, S., Ed.; De Gruyter: Berlin, 2021; pp 199−212. For a complete analysis of the EDA method, see: (b) Bickelhaupt, F. M.; Baerends, E. J. Kohn-Sham Density Functional Theory: Predicting and Understanding Chemistry. In *Reviews in Computational Chemistry*; Lipkowitz, K. B., Boyd, D. B., Eds.; Wiley-VCH: New York, 2000; Vol. *15*, pp 1−86.

https://doi.org/10.1021/jacs.1c11898
J. Am. Chem. Soc. 2022, 144, 1006−1015