

Sulfoxonium Ylides in Aminocatalysis: An Enantioselective Entry to Cyclopropane-Fused Chromanol Structures

Giorgiana Denisa Bisag, Pietro Pecchini, Michele Mancinelli, Mariafrancesca Fochi,* and Luca Bernardi*



Cite This: *Org. Lett.* 2022, 24, 5468–5473



Read Online

ACCESS |



Metrics & More

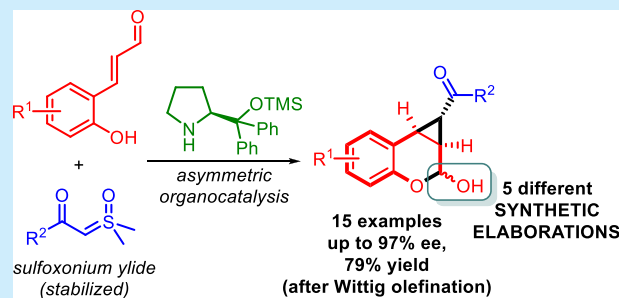


Article Recommendations



Supporting Information

ABSTRACT: The 1,1a,2,7b-tetrahydrocyclopropa[*c*]chromene, arising from fusion of chromane and cyclopropane rings is the core of medicinally relevant compounds. Engaging sulfoxonium ylides in enantioselective aminocatalytic reactions for the first time, a convenient entry to this scaffold is presented. Several ring-fused derivatives were obtained in moderate-to-good yields and enantioselectivities and with perfect diastereoselectivity at the cyclopropane, using an α,α -diphenylprolinol aminocatalyst. The versatility of the hemiacetal moiety in the products was leveraged to effect various synthetic manipulations.



The cyclopropane ring is present in numerous pharmacologically active compounds. The fame of this ring in medicinal chemistry is not only due to the strain of the cycle, which reserves a reactivity somewhat similar to an olefin, but also to the presence of C–H bonds shorter and stronger than those of common alkanes. Furthermore, the coplanarity of the three carbon atoms makes the reactivity displayed by cyclopropane truly unique.¹ In this context, the specific tricyclic 1,1a,2,7b-tetrahydrocyclopropa[*c*]chromene framework, arising from fusion of chromane and cyclopropane rings, is the core of several medicinally relevant compounds (Scheme 1a). Examples include 8-carboxy-7-sulfonamido derivatives **I**, whose activity against methionyl aminopeptidase 2 suggests their use in the treatment of liver disorders and obesity,² urea **II** (MIV-160), a reverse transcriptase inhibitor studied for anti-HIV therapy,³ and carboxylic acid **III**, a member of a series of fused cyclopropane derivatives agonists of G-protein coupled receptor 40 (GP40) and potentially useful in the treatment of type 2 diabetes.⁴ Furthermore, “cyclopropanochroman” natural products, such as radulanins I–K (**IV–VI**), have been isolated from liverwort extracts in racemic or enantiopure form.⁵ Radulanin K from *Radula javanica* has shown to inhibit the release of superoxide anion radical from guinea pig macrophage.⁶

In the frame of our interest in asymmetric aminocatalysis⁷ and sulfoxonium ylide chemistry,⁸ we herein report an enantioselective access to cyclopropane-fused chromanol derivatives **3** via aminocatalytic Corey–Chaykovsky-type cyclopropanation⁹ of 2'-hydroxycinnamaldehydes **1** with stabilized sulfoxonium ylides **2** (Scheme 1b). Aminocatalytic cyclopropanation reactions of other α,β -unsaturated aldehydes have been reported. In this context, examples of Corey–Chaykovsky-type reactions are relatively rare and restricted to α -keto sulfonium ylides,^{9c–f} while cyclopropanations with α -

halo(di)carbonyl compounds, 1-bromonitroalkanes, and activated benzyl halides (e.g., 2,4-dinitrobenzyl chloride) are more abundant.¹⁰ The latter group of reactions is generally performed with Jørgensen–Hayashi type catalysts,¹¹ whose simplest congener proved to be effective in our case too (Scheme 1b). This reaction represents the first example of utilization of sulfoxonium ylides in asymmetric aminocatalysis¹² and affords the tricyclic ring-fused derivatives **3** with very good stereocontrol. Importantly, the connectivity and relative stereochemistry of these compounds match the core of GP40 agonist **III** (Scheme 1a). Lastly, besides providing an alternative, and enantioselective, approach to this scaffold,^{13,14} this methodology affords adducts (**3**) carrying a hemiacetal functionality, which can be leveraged as a synthetic handle enabling access to a variety of compounds.

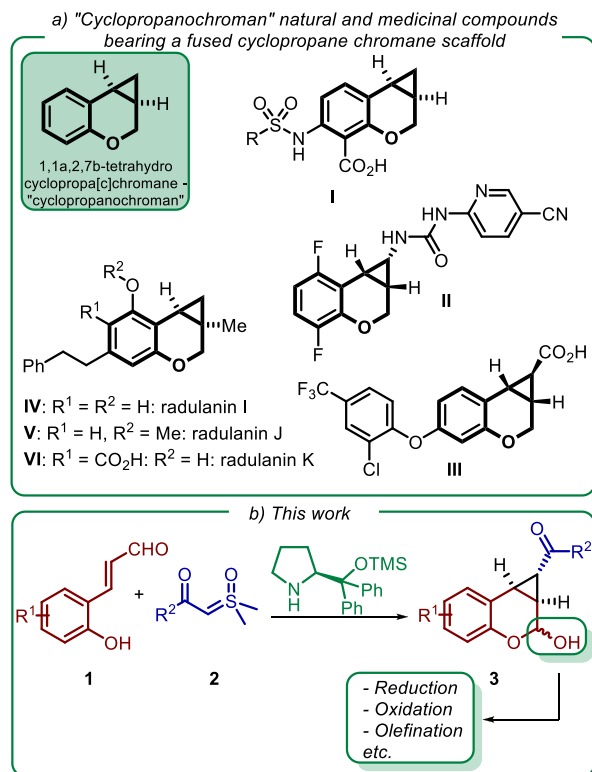
During our initial studies on the reaction between 2'-hydroxycinnamaldehyde **1a** and sulfoxonium ylide **2a** under the promotion of a common Jørgensen–Hayashi catalyst¹¹ (Table 1), we noticed an immediate color change by mixing aldehyde **1a** with the secondary amine catalyst in CDCl₃. Such a color change can be attributed to the formation of a stable and nucleophilic hemiaminal adduct.¹⁵ In order to revert this hemiaminal to an electrophilic iminium ion species, presumably *E*-configured,¹⁶ 20 mol% of benzoic acid co-catalyst was added followed by the nucleophilic sulfoxonium ylide **2a**. To our delight, we observed the formation of the desired

Received: June 29, 2022

Published: July 20, 2022

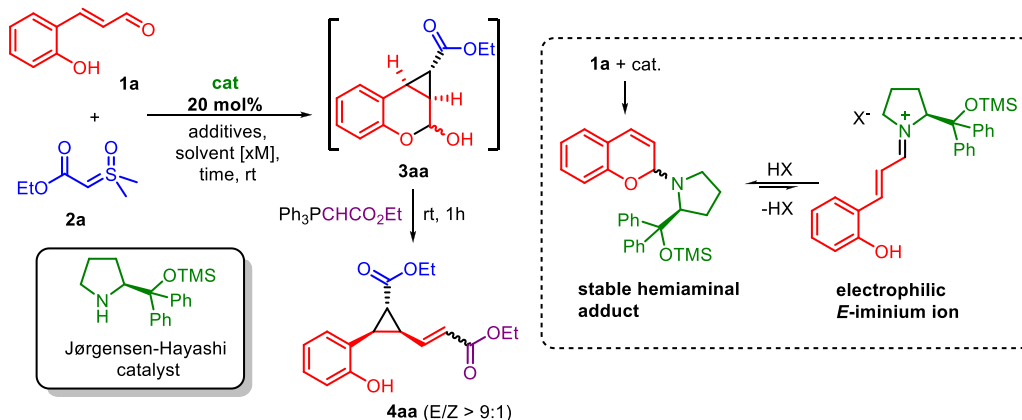


Scheme 1. (a) Natural and Medicinally Relevant Compounds Embedding the 1,1a,2,7b-Tetrahydrocyclopropa[*c*]chromene Framework; (b) This Work: enantioselective Access to This Scaffold via Aminocatalytic Cyclopropanation of Enals **1 with Sulfoxonium Ylides **2****



chromanol derivative **3aa**,¹⁷ which was derivatized by Wittig olefination into the corresponding **4aa**, obtained as a highly prevalent *E*-isomer for isolation and determination of the enantiomeric excess. Immediately, we understood that the reaction was characterized by promising results in terms of yield and enantioselectivity. Indeed, when the reaction was performed under these standard conditions, 50% yield and 88% enantioselectivity were achieved (entry 1). Furthermore, regarding the chirality centers of the cyclopropane ring, the diastereoselectivity of the reaction appeared to be complete. Because of the short reaction time, we decided to decrease the concentration of the reaction medium, which resulted in a cleaner reaction profile and increased values of yield and enantiomeric excess of product **4aa** (entry 2). Next, we continued the optimization reaction using different co-catalysts and, among all the results (see also the SI), the reaction with acetic acid gave product **4aa** with slightly better enantioselectivity, albeit longer reaction time (entry 3). At this stage, we decided to explore the buffer system AcONa/AcOH. When the reaction was performed with equal amounts of acetic acid and sodium acetate, an increment of the yield was achieved, while the enantioselectivity decreased (entry 4). Then, when the reaction was performed with different relative amounts of the acid and its conjugate base, two different behaviors were observed. With an excess of sodium acetate, the yield of product **4aa** decreased again while its enantiomeric excess increased slightly (entry 5). Running the reaction with more acetic acid than sodium acetate improved the yield, but the enantioselectivity dropped (entry 6). Surprisingly, we found that when the reaction was performed with sodium acetate as the only co-catalyst both the yield and enantioselectivity of product **4aa** increased (entry 7). Our current understanding is that the acidity of 2'-hydroxycinnamaldehyde **1a** is enough to

Table 1. Representative Optimization Results^a



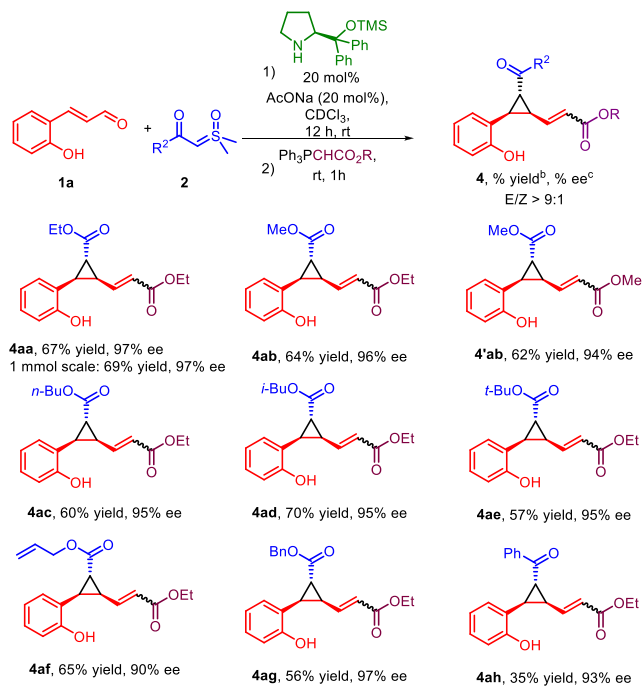
entry	solvent (M)	time (h)	co-catalysts (mol%)	yield of 4aa ^b (%)	ee of 4aa ^c (%)
1	CDCl ₃ (0.5)	1	PhCOOH (20)	50	88
2	CDCl ₃ (0.1)	2	PhCOOH (20)	57	95
3	CDCl ₃ (0.1)	12	AcOH (20)	52	96
4	CDCl ₃ (0.1)	12	AcONa (20) + AcOH (20)	74	79
5	CDCl ₃ (0.1)	12	AcONa (20) + AcOH (10)	65	82
6	CDCl ₃ (0.1)	12	AcONa (10) + AcOH (20)	75	74
7	CDCl ₃ (0.1)	12	AcONa (20)	67	97
8	CDCl ₃ (0.1)	12		41	96
9	CHCl ₃ (0.1)	12	AcONa (20)	65	97

^aReaction conditions: **1a** (0.1 mmol), **2a** (0.15 mmol), catalyst (0.02 mmol), additive, solvent, rt. Then phosphorus ylide, rt, 1 h. ^bIsolated yield after column chromatography. ^cDetermined by CSP (chiral stationary phase) HPLC analysis after column chromatography.

form sufficient amounts of the reactive iminium ion for the reaction to proceed. Meanwhile, sodium acetate might be helpful for scavenging more acidic species which could be harmful to the acid-sensitive sulfoxonium ylide. Indeed, a reaction performed without additives afforded product **4aa** in comparably high enantiomeric excess but lower yield (entry 8). Having chosen sodium acetate as the best additive, we ascertained that the results in chloroform (entry 9) are in line with results obtained so far in the corresponding deuterated solvent. Interestingly, a reaction performed using a sulfonium, instead of sulfoxonium, ylide did not afford product **3aa** under these reaction conditions. Furthermore, cinnamaldehyde was found to be unreactive toward sulfoxonium ylide **2a**, even when the Jørgensen–Hayashi catalyst was combined with acid co-catalysts. Thus, 2'-hydroxycinnamaldehydes showcase a distinct reactivity compared to their simpler nonhydroxylated counterparts,¹⁶ at least for this reaction.

We then moved to evaluate the generality of the reaction after having verified that the reaction can be carried out with similar results on a 1 mmol scale (Scheme 2). The variation of

Scheme 2. Sulfoxonium Ylide 2 Substrate Scope^a

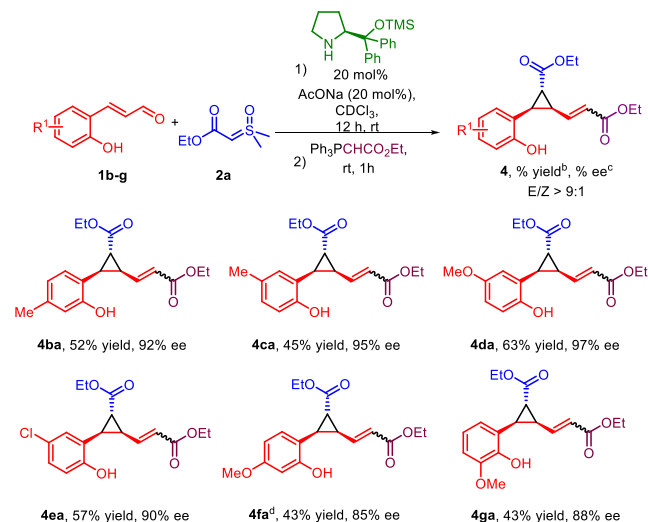


the sulfoxonium ylide **2** reported in Scheme 2 showed that both short-chain and long-chain ester substituents are very well tolerated, giving products **4ab** and **4ac** with comparable results in terms of yield and very good enantioselectivity. In addition, bulky substituents such as the isobutyl or the *tert*-butyl group on the ester moiety give products **4ad** and **4ae**, respectively, in good yields and with high enantiomeric excesses. Similarly, the use of an allylic or a benzylic ester did not significantly affect either the yield or the enantioenrichment of products **4af** and **4ag**. Next, the sulfoxonium ylide **2h** with a ketone instead of an ester substituent was tested. Product **4ah** was obtained in a

lower yield, possibly due to the less nucleophilic nature of this ylide, but with high enantiomeric excess. Finally, using a different phosphorus ylide, compound **4'ab** with two methyl esters was prepared, and its relative and absolute configurations were determined as 1*R*,2*R*,3*S* by means of NOESY-1D NMR and the electronic circular dichroism (ECD) method (see the SI). This assignment, fully in line with the proposed pathway,¹⁷ was extended by analogy to all products **4**.

We then explored the reactivity of sulfoxonium ylide **2a** with different 2'-hydroxycinnamaldehydes **1b–g**, and the results are reported in Scheme 3. A 4'-methyl substituent gave product

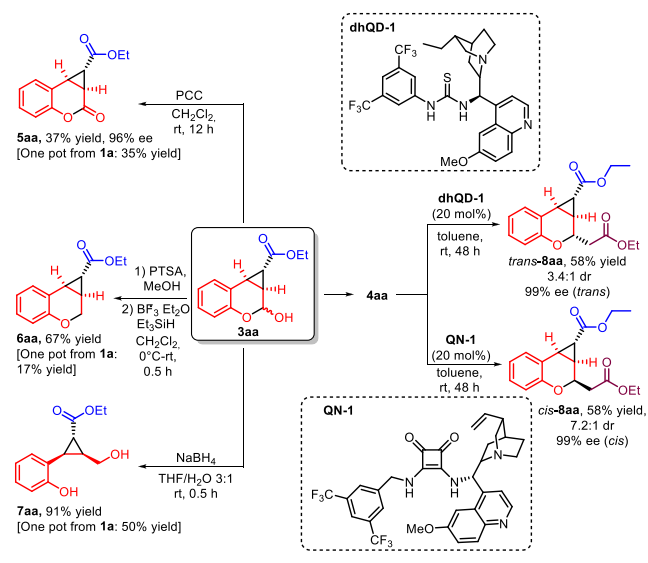
Scheme 3. 2'-Hydroxycinnamaldehyde 1 Substrate Scope^a



4ba in good yield and high enantiomeric excess, while the same group at the 5' position led to product **4ca** in a lower yield but still high enantioselectivity. A more electron-donating substituent like a methoxy group at different positions was also tolerated, delivering products **4da**, **4fa**, and **4ga** in moderate to good yields and good enantiomeric excesses. Interestingly, product **4fa** bears an oxygenated substituent at the same position of the aryloxy group of GP40 agonist **III** (Scheme 1). Finally, using an electron-withdrawing substituent like a chlorine atom led to the corresponding product **4ea** with good results.

As mentioned in the introduction, the backbone of the catalytic products is present in numerous natural and medicinal compounds. For this reason, we moved to explore their synthetic versatility (Scheme 4). When **3aa** was treated with PCC, the hemiacetal group could be oxidized to deliver coumarin **5aa** in moderate yield. The readily obtained methyl acetal of **3aa** could be smoothly reduced to the corresponding chromane **6aa** using triethylsilane in the presence of BF₃·OEt. Using sodium borohydride, the fleeting aldehydic function could instead be converted into a primary alcohol, obtaining product **7aa** in very good yield. Protocols combining the catalytic reaction and these reductions or oxidations in one-pot¹⁸ fashion were also implemented (see the Supporting Information). Using these streamlined and convenient

Scheme 4. Synthetic Elaborations



methods, product **5aa** was obtained with comparable yield, while **6aa** and **7aa** were afforded with lower yield values. Product **4aa** resulting from Wittig olefination of **3aa** was subjected to an intramolecular diastereodivergent oxa-Michael reaction.¹⁹ When the reaction was performed with bifunctional catalysts derived from pseudoenantiomeric *Cinchona* alkaloids, it was possible to direct the diastereoselectivity of the reaction either toward the *cis-8aa* or the *trans-8aa* derivative. The intrinsic diastereomeric relationship between the transition states leading to the *cis-8aa* and to the *trans-8aa* isomer justifies the requirement of different (i.e., not enantiomeric) catalytic structures for the two reactions (see the Supporting Information).²⁰

In conclusion, we have developed a catalytic enantioselective reaction between 2'-hydroxycinnamaldehydes **1** and stabilized sulfoxonium ylides **2**, affording cyclopropane-fused chromane derivatives **3** in moderate yields and excellent enantioselectivities. Besides the evident relevance of the scaffold of these products in medicinal compounds, the presence of a versatile hemiacetal moiety allowed us to perform various synthetic elaborations. Disclosing the first utilization of sulfoxonium ylides under aminocatalytic conditions, these results add an important piece to the still poorly disclosed puzzle of asymmetric organocatalysis with sulfoxonium ylide substrates.^{8b,12}

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.orglett.2c02204>.

Additional optimization studies, catalytic cycle, determination of the relative and absolute configuration of products **4'ab** and **8aa**, experimental section, copies of NMR and IR spectra and HPLC traces (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Mariafrancesca Fochi – Department of Industrial Chemistry “Toso Montanari”, Center for Chemical Catalysis - C³, and INSTM RU Bologna, Alma Mater Studiorum - University of

Bologna, 40136 Bologna, Italy; orcid.org/0000-0001-9124-3304; Email: mariafrancesca.fochi@unibo.it

Luca Bernardi – Department of Industrial Chemistry “Toso Montanari”, Center for Chemical Catalysis - C³, and INSTM RU Bologna, Alma Mater Studiorum - University of Bologna, 40136 Bologna, Italy; orcid.org/0000-0002-7840-3200; Email: luca.bernardi2@unibo.it

Authors

Giorgiana Denisa Bisag – Department of Industrial Chemistry “Toso Montanari”, Center for Chemical Catalysis - C³, and INSTM RU Bologna, Alma Mater Studiorum - University of Bologna, 40136 Bologna, Italy

Pietro Pecchini – Department of Industrial Chemistry “Toso Montanari”, Center for Chemical Catalysis - C³, and INSTM RU Bologna, Alma Mater Studiorum - University of Bologna, 40136 Bologna, Italy

Michele Mancinelli – Department of Industrial Chemistry “Toso Montanari”, Center for Chemical Catalysis - C³, and INSTM RU Bologna, Alma Mater Studiorum - University of Bologna, 40136 Bologna, Italy; orcid.org/0000-0002-8499-5265

Complete contact information is available at: <https://pubs.acs.org/10.1021/acs.orglett.2c02204>

Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Italian Ministry for University and Research (MUR, PRIN 2020, 2020AEX4TA project). We acknowledge further financial support from the University of Bologna (RFO program) and F.I.S. (Fabbrica Italiana Sintetici). Open Access Funding provided by Università di Bologna within a CRUI-CARE agreement.

■ REFERENCES

- (1) Talele, T. T. The “Cyclopropyl Fragment” is a Versatile Player that Frequently Appears in Preclinical/Clinical Drug Molecules. *J. Med. Chem.* **2016**, *59*, 8712–8756.
- (2) (a) Pallin, T. D.; Cramp, S. M.; Dyke, H. J.; Zahler, R. (Zafgen Inc.) Tricyclic compounds for use in the treatment and/or control of obesity. WO2014071369. (b) Hughes, T. E.; Vath, J. E. (Zafgen Inc.) Methods of treating liver diseases. WO2014071368.
- (3) Sahlberg, C.; Zhou, X.-X. Development of Non-Nucleoside Reverse Transcriptase Inhibitors for Anti-HIV Therapy. *Antimicrob. Agents in Med. Chem.* **2008**, *7*, 101–117.
- (4) Ge, M.; He, J.; Lau, F. W. Y.; Liang, G.-B.; Lin, S.; Liu, W.; Walsh, S. P.; Yang, L. (Merck & Co. Inc.) Antidiabetic bicyclic compounds. US20070265332.
- (5) (a) Asakawa, Y.; Kondo, K.; Tori, M. Cyclopropanochroman derivatives from the liverwort *Radula javanica*. *Phytochem.* **1991**, *30*, 325–328. (b) Wang, X.; Li, L.; Zhu, R.; Zhang, J.; Zhou, J.; Lou, H. Bibenzyl-Based Meroterpenoid Enantiomers from the Chinese Liverwort *Radula sumatrana*. *J. Nat. Prod.* **2017**, *80*, 3143–3150.
- (6) Asakawa, Y. Liverworts-Potential Source of Medicinal Compounds. *Curr. Pharm. Design* **2008**, *14*, 3067–3088.
- (7) See, for example: (a) Bertuzzi, G.; Sinisi, A.; Pecorari, D.; Caruana, L.; Mazzanti, A.; Bernardi, L.; Fochi, M. Nucleophilic Dearomatization of Pyridines under Enamine Catalysis: Regio-, Diastereo-, and Enantioselective Addition of Aldehydes to Activated

- N-Alkylpyridinium Salts. *Org. Lett.* **2017**, *19*, 834–837. (b) Bertuzzi, G.; Pecorari, D.; Bernardi, L.; Fochi, M. An organocatalytic enantioselective direct α -heteroarylation of aldehydes with isoquinoline N-oxides. *Chem. Commun.* **2018**, *54*, 3977–3980.
- (8) (a) Bisag, G. D.; Ruggieri, S.; Fochi, M.; Bernardi, L. Catalyst- and Substrate-Dependent Chemodivergent Reactivity of Stabilised Sulfur Ylides with Salicylaldehydes. *Adv. Synth. Catal.* **2021**, *363*, 3053–3059. (b) Bisag, G. D.; Ruggieri, S.; Fochi, M.; Bernardi, L. Sulfoxonium ylides: simple compounds with chameleonic reactivity. *Org. Biomol. Chem.* **2020**, *18*, 8793–8809.
- (9) For enantioselective cyclopropanations of sulfur ylides with Lewis acid catalysts, see: (a) Mamai, A.; Madalengoitia, J. S. Lewis acid mediated diastereoselective and enantioselective cyclopropanation of Michael acceptors with sulfur ylides. *Tetrahedron* **2000**, *41*, 9009–9014. (b) Pagire, S. K.; Kumagai, N.; Shibasaki, M. Highly Enantio- and Diastereoselective Synthesis of 1,2,3-Trisubstituted Cyclopropanes from α,β -Unsaturated Amides and Stabilized Sulfur Ylides Catalyzed by a Chiral Copper(I) Complex. *ACS Catal.* **2021**, *11*, 11597–11606. See also references cited therein. For aminocatalytic enantioselective cyclopropanations with sulfonium ylides, see: (c) Kunz, R. K.; MacMillan, D. W. C. Enantioselective Organocatalytic Cyclopropanations. The Identification of a New Class of Iminium Catalyst Based upon Directed Electrostatic Activation. *J. Am. Chem. Soc.* **2005**, *127*, 3240–3241. (d) Hartikka, A.; Arvidsson, P. I. Tetrazolic Acid Functionalized Dihydroindol: Rational Design of a Highly Selective Cyclopropanation Organocatalyst. *J. Org. Chem.* **2007**, *72*, 5874–5877. (e) Akagawa, K.; Takigawa, S.; Nagamine, I. S.; Umezawa, R.; Kudo, K. Peptide-Catalyzed Diastereo- and Enantioselective Cyclopropanation of Aromatic α,β -Unsaturated Aldehydes. *Org. Lett.* **2013**, *15*, 4964–4967. (f) Wang, J.; Liu, X.; Dong, S.; Lin, L.; Feng, X. Asymmetric Organocatalytic Cyclopropanation of Cinnamone Derivatives with Stabilized Sulfonium Ylides. *J. Org. Chem.* **2013**, *78*, 6322–6327.
- (10) For representative examples, see: (a) Xie, H.; Zu, L.; Li, H.; Wang, J.; Wang, W. Organocatalytic Enantioselective Cascade Michael-Alkylation Reactions: Synthesis of Chiral Cyclopropanes and Investigation of Unexpected Organocatalyzed Stereoselective Ring Opening of Cyclopropanes. *J. Am. Chem. Soc.* **2007**, *129*, 10886–10894. (b) Vesely, J.; Zhao, G.-L.; Bartoszewicz, A.; Córdova, A. Organocatalytic asymmetric nitrocyclopropanation of α,β -unsaturated aldehydes. *Tetrahedron Lett.* **2008**, *49*, 4209–4212. (c) Zhang, J.-m.; Hu, Z.-p.; Dong, L.-t.; Xuan, Y.-n.; Lou, C.-L.; Yan, M. Enantioselective conjugate addition of 1-bromonitroalkanes to α,β -unsaturated aldehydes catalyzed by chiral secondary amines. *Tetrahedron: Asymm.* **2009**, *20*, 355–361. (d) Li, W.; Li, X.; Ye, T.; Wu, W.; Liang, X.; Ye, J. Asymmetric organocatalytic Michael/ α -alkylation reaction of α,β -unsaturated aldehyde with chloroacetophenone. *Tetrahedron Lett.* **2011**, *52*, 2715–2718. (e) Meazza, M.; Ashe, M.; Shin, H. Y.; Yang, H. S.; Mazzanti, A.; Yang, J. W.; Rios, R. Enantioselective Organocatalytic Cyclopropanation of Enals Using Benzyl Chlorides. *J. Org. Chem.* **2016**, *81*, 3488–3500. (f) Terrason, V.; van der Lee, A.; Marcia de Figueiredo, R.; Campagne, J. M. Organocatalyzed Cyclopropanation of α -Substituted α,β -Unsaturated Aldehydes: Enantioselective Synthesis of Cyclopropanes Bearing a Chiral Quaternary Center. *Chem.—Eur. J.* **2010**, *16*, 7875–7880. (g) Rueping, M.; Sundén, H.; Hubener, L.; Sugiono, E. Asymmetric oxidative Lewis base catalysis—unifying iminium and enamine organocatalysis with oxidations. *Chem. Commun.* **2012**, *48*, 2201–2203. (h) Džambaski, Z.; Bondžić, A. M.; Triandafillidi, I.; Kokotos, C. G.; Bondžić, B. P. Organocatalytic, Organic Oxidant Promoted, Enamine C-H Oxidation/Cyclopropanation Reaction. *Adv. Synth. Catal.* **2021**, *363*, 4002–4008. (i) Uria, U.; Vicario, J. L.; Badía, D.; Carrillo, L.; Reyes, E.; Pesquera, A. 'On Water' Iminium/Enamine Catalysis: Organocatalytic Enantioselective Cyclopropanation of α,β -Unsaturated Aldehydes. *Synthesis* **2010**, 701–713. (j) Byeon, H.; Ryu, S.; Yoo, E. J.; Yang, J. W. Substrate-Controlled Chemo-/Enantioselective Synthesis of α -Benzylated Enals and Chiral Cyclopropane-Fused 2-Chromanone Derivatives. *Adv. Synth. Catal.* **2021**, *363*, 5085–5091.
- (11) (a) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. Diphenylprolinol Silyl Ethers as Efficient Organocatalysts for the Asymmetric Michael Reaction of Aldehydes and Nitroalkenes. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212–4215. (b) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. Enantioselective organocatalyzed α -sulfenylation of aldehydes. *Angew. Chem., Int. Ed.* **2005**, *44*, 794–797.
- (12) For a review on asymmetric reactions with sulfoxonium ylides, see: (a) Caiuby, C. A. D.; Furniel, L. G.; Burtoloso, A. C. B. Asymmetric transformations from sulfoxonium ylides. *Chem. Sci.* **2022**, *13*, 1192–1209. Recent organocatalytic approaches: (b) Momo, P. B.; Leveille, A. N.; Farrar, E. H. E.; Grayson, M. N.; Mattson, A. E.; Burtoloso, A. C. B. Enantioselective S–H Insertion Reactions of α -Carbonyl Sulfoxonium Ylides. *Angew. Chem., Int. Ed.* **2020**, *59*, 15554–15559. (c) Guo, W.; Wang, M.; Han, Z.; Huang, H.; Sun, J. Organocatalytic asymmetric synthesis of α -amino esters from sulfoxonium ylides. *Chem. Sci.* **2021**, *12*, 11191–11196. (d) Leveille, A. N.; Echেমendía, R.; Mattson, A. E.; Burtoloso, A. C. B. Enantioselective Indole Insertion Reactions of α -Carbonyl Sulfoxonium Ylides. *Org. Lett.* **2021**, *23*, 9446–9450.
- (13) Compound **III** was prepared in racemic form then resolved by chiral stationary phase chromatography; see ref 4. A related *all-cis* derivative was accessed in enantioenriched form via an elegant enantioselective cyclopropanation–ring-opening–cyclization sequence in the context of the disclosure of **II**; see: Sund, C.; Roue, N.; Lindström, S.; Antonov, D.; Sahlberg, C.; Jansson, K. (Medivir AB) Non nucleotide reverse transcriptase inhibitors. WO2005066131, 2005.
- (14) For a very recent report on the cyclopropanation reaction of enals **1** with 2,4-dinitrobenzyl chloride, which affords chromane-fused, aryl-substituted cyclopropanes, see ref 10j.
- (15) (a) Zu, L.; Zhang, S.; Xie, H.; Wang, W. Catalytic Asymmetric oxa-Michael-Michael Cascade for Facile Construction of Chiral Chromans via an Aminal Intermediate. *Org. Lett.* **2009**, *11*, 1627–1630. (b) Ramachary, D. B.; Prasad, M. S.; Laxmi, S. V.; Madhavachary, R. Asymmetric synthesis of drug-like spiro[chroman-3,3'-indolin]-2'-ones through aminal-catalysis. *Org. Biomol. Chem.* **2014**, *12*, 574–580.
- (16) 2'-Hydroxycinnamaldehydes have been explored as electrophiles under aminocatalytic conditions; see, for example: (a) Lee, Y.; Seo, S. W.; Kim, S.-G. Highly Enantioselective Conjugate Addition–Cyclization Cascade Reaction of Malonates with o-Hydroxycinnamaldehydes: Asymmetric Synthesis of 4-Substituted Chromanols. *Adv. Synth. Catal.* **2011**, *353*, 2671–2675. (b) Kim, Y. S.; Kim, S. M.; Wang, B.; Companyó, X.; Li, J.; Moyano, A.; Im, S.; Tošner, Z.; Yang, J. W.; Rios, R. Expanding the Scope of the Organocatalytic Addition of Fluorobis(phenylsulfonyl)methane to Enals: Enantioselective Cascade Synthesis of Fluoroindane and Fluorochromanol Derivatives. *Adv. Synth. Catal.* **2014**, *356*, 437–446. (c) You, Z.-H.; Chen, Y.-H.; Tang, Y.; Liu, Y.-K. Organocatalytic Asymmetric Synthesis of Spiro-Bridged and Spiro-Fused Heterocyclic Compounds Containing Chromane, Indole, and Oxindole Moieties. *Org. Lett.* **2018**, *20*, 6682–6686. (d) Wu, H.-C.; Wang, C.; Chen, Y.-H.; Liu, Y.-K. Asymmetric organocatalytic vinylogous Michael addition triggered triple-cascade reactions of 2-hydroxycinnamaldehydes and vinylogous nucleophiles: construction of benzofused oxabicyclo[3.3.1]nonane scaffolds. *Chem. Commun.* **2021**, *57*, 1762–1765. See also references cited therein.
- (17) For a discussion on the full catalytic cycle, see the [Supporting Information](#).
- (18) Hayashi, Y. Pot economy and one-pot synthesis. *Chem. Sci.* **2016**, *7*, 866–880.
- (19) Zhu, D.-X.; Liu, J.-G.; Xu, M.-H. Stereodivergent Synthesis of Enantioenriched 2,3-Disubstituted Dihydrobenzofurans via a One-Pot C–H Functionalization/Oxa-Michael Addition Cascade. *J. Am. Chem. Soc.* **2021**, *143*, 8583–8589.
- (20) For a discussion, see: Corti, V.; Riccioli, R.; Martinelli, A.; Sandri, S.; Fochi, M.; Bernardi, L. Stereodivergent entry to β -

branched β -trifluoromethyl α -amino acid derivatives by sequential catalytic asymmetric reactions. *Chem. Sci.* **2021**, *12*, 10233–10241.

Recommended by ACS

Squaramide-Catalyzed Asymmetric Intramolecular Oxa-Michael Reaction of α,β -Unsaturated Carbonyls Containing Benzyl Alcohol: Construction of Chiral 1...

Eun Chae Son, Sung-Gon Kim, *et al.*

APRIL 27, 2021
THE JOURNAL OF ORGANIC CHEMISTRY

READ 

Construction of Acyclic Quaternary Stereocenters via Mannich-Type Addition of α,α -Disubstituted *N*-*tert*-Butanesulfinyl Ketimines to Isatin-Derived Ketimines

Zheng-Fei Li, Chong-Dao Lu, *et al.*

APRIL 14, 2022
ORGANIC LETTERS

READ 

Highly Enantioselective, Hydrogen-Bond-Donor Catalyzed Additions to Oxetanes

Daniel A. Strassfeld, Eric N. Jacobsen, *et al.*

MAY 04, 2020
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

READ 

Enantioselective Syntheses of 4*H*-3,1-Benzoxazines via Catalytic Asymmetric Chlorocyclization of *o*-Vinylanilides

Qinxia Xie, Jun Deng, *et al.*

DECEMBER 27, 2019
THE JOURNAL OF ORGANIC CHEMISTRY

READ 

Get More Suggestions >