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Organocatalytic Strategy for a Formal 1,6-Conjugate Hydroxylation

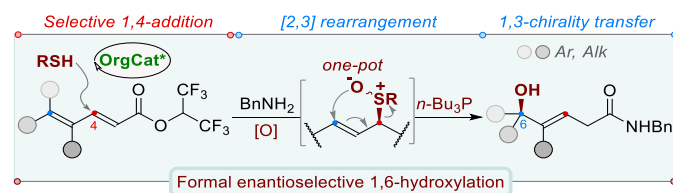
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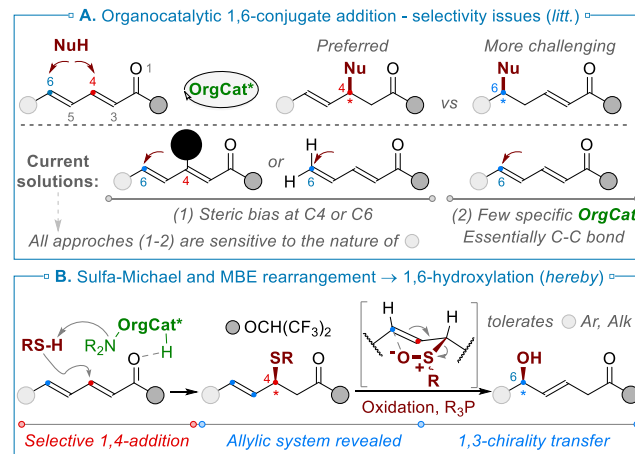


ABSTRACT: Thanks to the versatile vinylogous hexafluoro *iso*-propyl acrylate molecular platforms, a regio- and enantioselective sulfa-Michael reaction was achieved upon organocatalytic conditions, allowing the subsequent amidation, one-pot oxidation and Mislow-Braverman-Evans [2,3]-sigmatropic rearrangement along with a 1,3-chirality transfer, leading eventually to a formal asymmetric 1,6-hydroxylation sequence.

The organocatalytic enantioselective conjugate 1,6-addition reaction on electron-poor 1,3-dienes is a fascinating exercise in asymmetric catalysis involving a remote control and creation of a stereocenter.¹ However, the competing 1,4-addition is usually favored due to an inefficient vinylogous event (Scheme 1A).^{1a-e} In order to overcome this hurdle, most of the initial investigations made use of a steric bias at C4 (bulky R⁴ shielding C4), or at C6 position (R⁶ = H favoring C6 addition) to secure the vinylogous C⁶-C or C⁶-X bonds formation.^{1a-e,2} The more challenging organocatalyzed 1,6-enantioselective functionalization onto dienes only substituted at C6 was achieved by few specific organocatalytic strategies and organocatalysts.³ In 2013, Jørgensen and collaborators initiated the development of several 1,6-C-C bond forming processes upon iminium activation of vinylogous enals,^{3b, 3c} while Ooi made use of *P*-spiro-tri-aminophosphorane catalysts on dienyl *N*-acylpyrroles.^{3a, 3d} To date, few organocatalytic enantioselective C-X (X = N, O) bonds construction at C6 exist. They require an annulation strategy,^{4,5} by means of *para*-quinones flanked by a phenol moiety or an hydroxylamine derivatives as nucleophiles,^{4a, 4c, 4d} likewise a nitron involves in a 1,3-dipolar cycloaddition process.^{4b} Alternatively, the group of Lam proposed one of the rare example of formal asymmetric 1,6-hydroxylation *via* a C6-selective borylation of vinylogous acrylates unsubstituted at C3-5 catalyzed by a chiral copper complex.⁶ The obtained products were oxidized into the corresponding alcohols with retention of configuration. The authors highlighted the usefulness of these versatile allylic alcohol building blocks for the total synthesis an HMG-CoA reductase inhibitor useful to treat hypercholesterolemia. Nevertheless, in all these elegant methodologies, the 1,4-*versus* 1,6-regioselectivity outcome markedly depends on the nature of the functional group at C6 whereby alkyl substituents

were mostly preferred over aryl pendants for 1,6-addition. Owing to the lack of straightforward tactic to perform a catalytic 1,6-hydration of electron-poor 1,3-dienes without a steric bias, we tackled an alternative sequence.

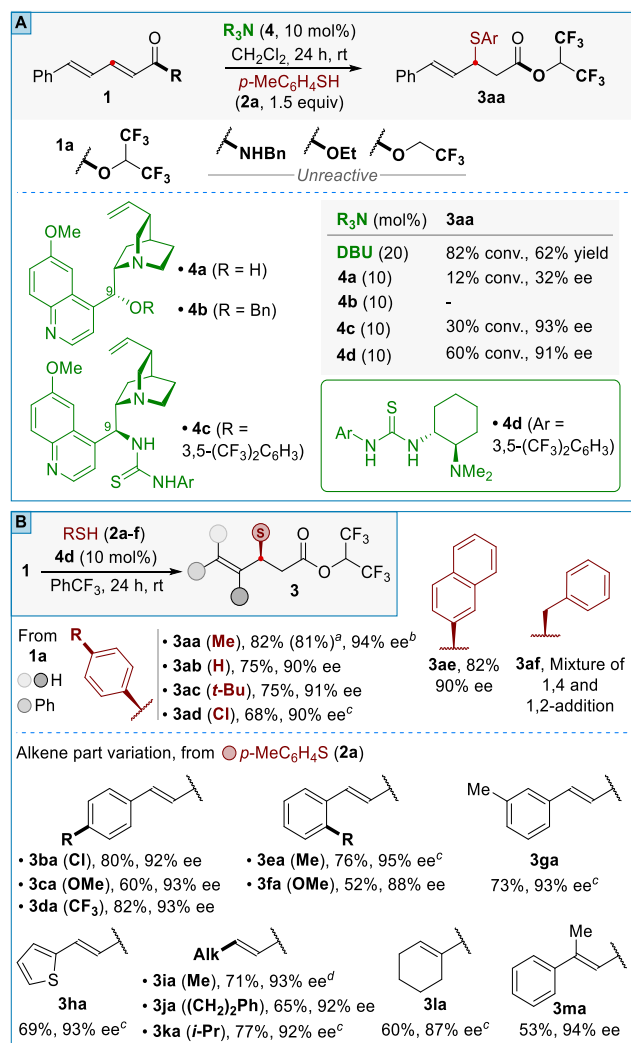
Scheme 1. Organocatalytic Enantioselective 1,6-Conjugate Addition



At first, we envisaged a regio- and enantioselective 1,4-sulfa-Michael on C^{3,4,5}-unsubstituted dienes by means of a suited bifunctional organocatalyst (Scheme 1B). Then, oxidation into sulfoxide of the revealed allylic sulfide motif would allow the so-called Mislow-Braverman-Evans (MBE) rearrangement to deliver in an asymmetric manner a hydroxyl group at the C6-position.⁷ Although a diastereoisomeric mixture of sulfinyl

intermediate could be obtained, the stereospecific [2,3]-sigmatropic rearrangement usually occurred in a suprafacial fashion, allowing a 1,3-chirality transfer. In that context, Kowalczyk *et al.* previously observed the preferred 1,4-sulfa-Michael on vinylogous chalcones (R = Ph).^{8,9,10} However, in our hands, every attempt to perform a MBE rearrangement on this type of substrate, inevitably led to a 1,2-elimination reaction of sulfenic acid (RSOH), reversing back to the diene precursor. We are pleased to report the achievement of this asymmetric hydroxylation strategy, which highlights the use of original hexafluoro *iso*-propyl ester derived dienes, and the fine tuning of organocatalytic and MBE-rearrangement conditions in order to overcome all the selectivity issues (1,4 vs 1,6-addition and preventing the 1,2-elimination of sulfenic acid), to eventually affords a straightforward sequence tolerating various dienes.

Scheme 2. Organocatalytic 1,4-Conjugate Addition



Sulfa-Michael reaction conditions: HFIP-ester **1** (0.15-0.45 mmol, 0.6 M), thiol **2** (1.5 equiv), organocatalyst **4d** (10 mol%) in PhCF₃ at 20 °C for 24 hours. ^aOn 1 mmol scale. ^bAbsolute configuration determined by chemical correlation and electronic and vibrational circular dichroism (ECD and VCD). ^cSee determined by HPLC after formation of the NHBn-amide product **10**. ^dA mixture of *E*:*Z* = >90:10 is likely obtained due to a mixture of stereoisomers of the starting material **11**.

At the onset, the preliminary investigations of several type of vinylogous cinnamic acid derivatives as dienes **1** (R⁶ = Ph, see Supplementary Information, SI), revealed that acrylamide or acrylate derivatives were unreactive under the organocatalytic sulfa-Michael reaction conditions tested, while the

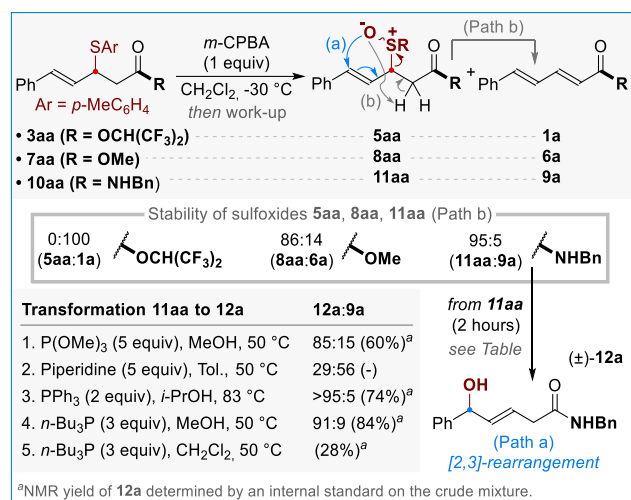
unprecedented hexafluoro *iso*-propyl ester derivative **1a** (HFIP-ester) afforded promising results (Scheme 2A).¹¹ In the presence of the DBU (20 mol%) and *p*-MeC₆H₄SH **2a** (1.5 equiv), an exclusive formation of the sulfa-Michael addition product **3aa** was observed, in a 62% yield (82% conversion).¹² After a screening of various chiral organocatalysts (10 mol%, see SI), it was found that quinine **4a** afforded product **3aa** in a 32% enantiomeric excess (ee) with a conversion of 12% after 24 hours. In contrast, the C⁹-OBn analogue **4b** failed to catalyze the reaction. The C⁹-*epi*-amino thiourea catalyst **4c** furnished the sulfa-Michael adduct in an excellent 93% ee albeit in 30% of conversion, thus showing the importance of the hydrogen-bonding donor capabilities of the function at C9 for reactivity issues. These hindered chiral organocatalysts led however to sluggish reaction rates of this moderately reactive substrate **1a** and a competitive dimerization of the mercaptan into the corresponding disulfide. To our delight, the commercially available Takemoto catalyst **4d** gave the adduct **3aa** in a good 91% ee and an improved conversion of 60%. Interestingly, Wang reported efficient sulfa-Michael reactions to the HFIP-derived cinnamate esters with specific organocatalyst,¹¹ but only a 65% ee was observed with catalyst **4d**. These aspects show the uniqueness of the vinylogous HFIP-derived cinnamate ester **1a**, and we thus explored the possibility to improve the sequence and vary the structure of the terminal alkene moiety.

The optimization endeavor revealed that the 1,4-conjugate addition reaction affording product **3aa** in an improved 82% yield (81% on 1 mmol scale) and an excellent 94% ee in PhCF₃ as solvent at room temperature (Scheme 2B, see also SI). Various substituted thiophenols **2b-d** and the 2-naphthyl derivative **2e** allowed the formation of the sulfanyl products **3ab-3ae** in 90-91% ees and yields ranging from 68% to 82%. However, it was found that aliphatic thiols, like BnSH **2f**, led to a competitive 1,2-addition to the HFIP-ester moiety beside the formation of **3af**. By means of MeC₆H₄SH **2a** as a model sulfur nucleophile a series of vinylogous HFIP-derived cinnamate esters **1b-g** were investigated. The transformation into the corresponding sulfa-Michael adducts **3ba-3ga** took place in goods 88-95% ees, regardless the nature of the styryl moiety having substituents at the *para*- (**3ba-3da**, 60-82%, 92-93% ee), *ortho*- (**3ea-3fa**, 52-75%, 88-95% ee) and *meta*-position (**3ga**, 73%, 93% ee) of the C6-phenyl. Importantly, the *ortho*-methoxy product **3fa**, the only one in this series obtained in lower than 90% ee, proved to be unstable during storage and had to be engaged in the subsequent step rapidly (*vide infra*). The 2-thiophene heterocycle was also tolerated to give product **3ha** in a 69% yield and a 93% ee. Interestingly, vinylogous acrylates with a linear (R = Me, (CH₂)₂Ph, **1i-j**) or branched (R = *i*-Pr, **1k**) alkyl substituent at C6 also underwent the regio- and enantioselective sulfa-Michael process to give **3ia-3ka** with high 92-93% ees and yields of 65-77%. Unlike to the other substrates, the methyl-substituted adduct **3ia** was obtained as a likely mixture of *E* and *Z*-alkenes (>90:10) due to the lack of configurational purity of the starting material. For structural diversity purposes, the organocatalytic asymmetric sulfa-conjugate addition reaction was applied to C5,6 and C6,6-disubstituted dienes **1l** and **1m**, and led to the formation of the disulfides **3la** (60%, 87% ee) and **3ma** (53%, 94% ee) in very good selectivities. The capability of the bifunctional Takemoto catalyst **4d** to secure both a general enantioselective (88-94% ee) and a C4-regioselective C-S bond formation on a large series of vinylogous HFIP-derived cinnamate esters **1** is noteworthy, especially with the diene-platforms **1i-l** having an alkyl substituent at C6. Indeed,

the achiral DBU catalyst furnished a mixture of 1,4 and 1,6-products from **11-I** (1,6-adduct being favored as estimated on the crude product by ^1H NMR, see SI).

With the original allylic sulfides **3** with a HFIP-ester moiety in hands, we probed the stability/reactivity of the corresponding sulfoxide **5aa** (obtained after a *m*-CPBA oxidation **3aa**), as precursor of the envisaged MBE rearrangement (Scheme 3). Unfortunately, a 1,2-elimination reaction took place rapidly during the work-up of **5aa** giving rise to the competitive formation of diene **1a**, *i.e.* the initial starting material. Nevertheless, by decreasing the electron-withdrawing properties of the carbonyl moiety, going from an ester to an amide, significantly increase the stability of the corresponding sulfoxides **8aa** (R = OMe obtained from sulfide **7aa**) and **11aa** (R = NHBn from sulfide **10aa**), the latter being isolated with only traces of the elimination product **9a**. Then, the [2,3]-sigmatropic rearrangement was studied with the amide compound **11aa** in the presence of various thiophilic reagents, in order to cleave S-O bond of the transient sulfenic ester (Table in Scheme 3).^{7,13} The phosphorous thiophilic agents,¹³ like triethylphosphite and Ph_3P (entries 1-3), afforded the best results in alcoholic solvents, albeit a major co-elution issue of the generated phosphine oxide side products proved to be problematic during purification by column chromatography. Eventually, we found that tri-*n*-butylphosphine in methanol at 50 °C (entry 4), barely used for the MBE rearrangement, furnished the corresponding alcohol **12a** in an 84% NMR yield and traces of the elimination side product **1a**. Advantageously, the liberated and water-soluble tri-*n*-butylphosphine oxide side product was easily eliminated by a simple work-up.

Scheme 3. [2,3]-Sigmatropic Rearrangement vs 1,2-Elimination

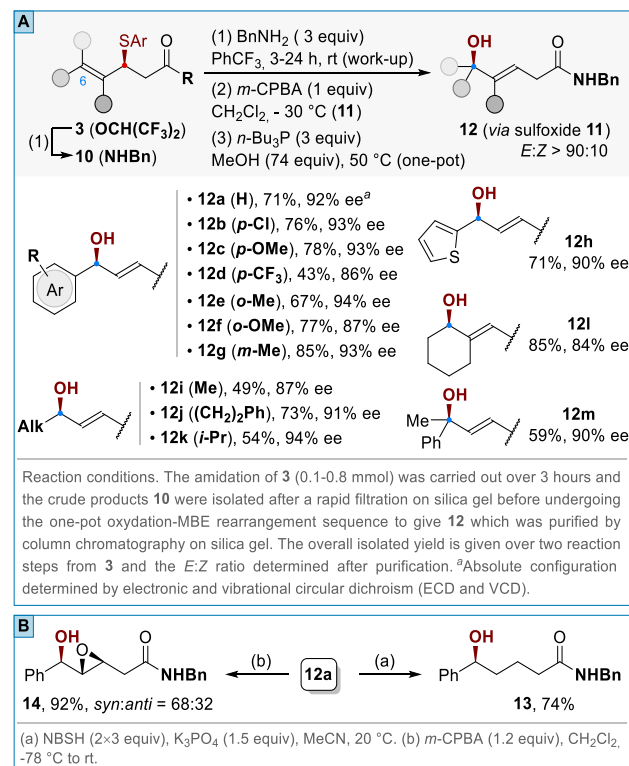


With this valuable information in hands, we tackled a convenient protocol encompasses the amide formation followed by a MBE rearrangement (Scheme 4A). Taking advantage of the versatility of HFIP-derived esters,^{11,14} a facile synthesis of the amide **10aa** (88% yield, 93% ee) was carried out in 3 hours from benzylamine and acrylate **3aa** (94% ee) without significant racemization. After a rapid filtration on silica gel, the amido sulfide product **10aa** was immediately oxidized into the sulfoxide **11aa** by *m*-CPBA at low temperature (-30 °C) in CH_2Cl_2 . The subsequent [2,3]-sigmatropic rearrangement was undertaken with heating at 50 °C in a one-pot fashion after the addition of *n*-Bu₃P. This convenient sequence eventually led to the corresponding alcohol **12a** in excellent an 92% ee and a 71% overall

isolated yield. Importantly, it turned out that the addition of methanol (74 equiv) as protic solvent after the oxidation step minimized the formation of the competitive elimination product **9a** (**12a:9a** = 87:13 without MeOH), and overcome the poor yield obtained for the [2,3]-sigmatropic rearrangement previously carried out in dichloromethane (see Scheme 3, Table, entry 5). At that stage, we believe that the *in situ* liberated *meta*-chlorobenzoic acid from *m*-CPBA is the main component which facilitates protonation of the liberated alcoholate after the ArS-O bond cleavage by *n*-Bu₃P, and secured a markedly improved overall yield of this convenient one-pot protocol in CH_2Cl_2 .

We were delighted to observe that the amidation-MBE rearrangement sequence was successfully applied to C6-arylated precursors **3ba-3ca** and **3ea-3ga** to provide the corresponding products with an (*E*)-C-C double bond and *para*- (**12b-12c**, *p*-Cl and *p*-OMe 76-78%, 93% ee), *ortho*- (**12e-12f**, *o*-Me and *o*-OMe 67-77%, 87-94% ee) and *meta*-substituents (**12g**, *m*-Me, 85%, 93% ee) and an excellent 1,3-chirality transfer allowing to preserve the ees of the sulfanylated starting materials **3** (Scheme 4A). Precursor **3da** (93% ee) with a *p*-CF₃ aryl moiety, was more challenging since this compound led to the alcohol **12d** in 43% yield and a slight decreased in ee to 86%. It is believed that the positive charge development at C6 during the [2,3]-sigmatropic rearrangement might be destabilized due to the electron-withdrawing nature of the *p*-CF₃ aryl moiety, leading to a more equilibrated rearrangement process (before the ArS-O cleavage) and a slight racemization event. The allylic substrate with a thienyl part **3ha**, while being sensitive to oxidation, afforded the alcohol **12h** in a 90% ee and 71% yield.

Scheme 4. Formal 1,6-Functionalization



The precursors flanked by a linear (**3ja**, R = (CH_2)₂Ph) and branched (**3ka**, R = *i*-Pr) alkyl moieties at C6 underwent the transformation into the corresponding allylic alcohols **12j** and **12k** in 91% and 94% ee respectively (73% and 54% yields). However, the rather challenging methyl-substituted precursor

3ia led to the hydroxy compound **12i** in a 49% and a descent ee of 87%. The drop of 6% in selectivity, with respect to the starting material **6ib** (93% ee), is likely due to the *E:Z* mixture of starting material **1i**, whose traces of minor *Z*-isomer is difficult to separate even after the sulfanylation reaction (**3ia**). Thus, a stereodivergent [2,3]-sigmatropic rearrangement can take place giving the minor enantiomer from the *Z*-alkene. This formal hydroxylation procedure proved to be also efficient on the substrate with a cyclohexyl architecture providing **12i** in an 84% ee and an 85% yield. Interestingly, the more hindered precursor **3ma**, with a disubstituted terminal alkene, afforded the corresponding compound with the challenging creation of a tertiary allylic alcohol with a good 90% ee and a 59% yield. Note of worthy, the determination of the absolute configuration of the allylic alcohol **12a** turned out to be not a trivial task. Eventually, the (*S*)-configuration of sulfide **3aa** and alcohol **12a** was ascertain by both chemical correlations and electronic and vibrational circular dichroism (ECD and VCD, see SI for details), in agreement to the expective outcome of the suprafacial and stereospecific [2,3]-sigmatropic rearrangement.

Finally, we tackle some chemical transformation of these new substrates. At first, it was demonstrated the selective C-C double bond reduction of **12a**, by means of the *in situ* generating diimide reagent, furnished the saturated alcohol **13** in 74% yield (Scheme 4B). Next, thanks to the allylic alcohol structure of **12a**, an epoxidation reaction can be easily performed to give the corresponding epoxide **14** in good 92% yield albeit in moderate *syn:anti* ratio of 68:32.

In summary, we demonstrated that original vinylogous hexafluoro *iso*-propyl acrylates are versatile molecular platforms allowing a formal asymmetric 1,6-hydroxylation reaction. Thanks to the commercially available Takemoto organocatalyst, a straightforward sequence involved an enantioselective organocatalyzed sulfa-Michael reaction, followed by a convenient amidation and a one-pot MBE [2,3]-sigmatropic rearrangement of an intermediate allylic sulfoxide. An excellent 1,3-chirality transfer was observed and several types of dienes were tolerated. One can anticipate to apply this formal remote functionalization strategy to more complex molecules, together with the exploitation of the easily obtained enantioenriched allylic sulfides into a larger array of sigmatropic processes for C-C and C-N bond formations. Investigations in that direction are currently in progress in our laboratory.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures, characterization data, NMR spectra, and electronic and vibrational circular dichroism (ECD and VCD) (PDF).

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Authors Contributions

All authors have given approval to the final version of the manuscript. [†]These authors were involved in the determination of the absolute configuration of chiral key molecules by means of by chemical correlation and electronic and vibrational circular dichroism (ECD and VCD).

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REFERENCES

- (1) (a) Biju, A. T., Organocatalytic Asymmetric 1,6-Addition Reactions. *ChemCatChem* **2011**, *3*, 1847-1849; (b) Silva, E. M. P.; Silva, A. M. S., 1,6-Conjugate Addition of Nucleophiles to $\alpha,\beta,\gamma,\delta$ -Diunsaturated Systems. *Synthesis* **2012**, *44*, 3109-3128; (c) Lear, M. J.; Hayashi, Y., Remote 1,6-Stereocontrol by Iminium-mediated Organocatalytic Events. *ChemCatChem* **2013**, *5*, 3499-3501; (d) Chauhan, P.; Kaya, U.; Enders, D., Advances in Organocatalytic 1,6-Addition Reactions: Enantioselective Construction of Remote Stereogenic Centers. *Adv. Synth. Catal.* **2017**, *359*, 888-912; (e) Hussain, Y.; Tamanna; Sharma, M.; Kumar, A.; Chauhan, P., Recent development in asymmetric organocatalytic domino reactions involving 1,6-addition as a key step. *Org. Chem. Front.* **2022**, *9*, 572-592; (f) Yue, Z.; Fang, F.; Xia, Y.; Li, P.; Li, W., Organocatalytic Remote Stereocontrolled Additions of In Situ Formed Electron-Deficient Conjugate Systems. *Adv. Synth. Catal.* **2023**, *365*, 1926-1933; (g) Xia, Y.; Liu, M.; Li, W.; Li, P., Recent Advances in Organocatalytic Enantioselective Reactions of α -Functionalized Propargylic Alcohols. *Asian J. Org. Chem.* **2024**, e202400377.
- (2) For selected pioneering contributions, see: (a) Bernardi, L.; López-Cantarero, J.; Niess, B.; Jørgensen, K. A., Organocatalytic Asymmetric 1,6-Additions of β -Ketoesters and Glycine Imine. *J. Am. Chem. Soc.* **2007**, *129*, 5772-5778; (b) Murphy, J. J.; Quintard, A.; McArdle, P.; Alexakis, A.; Stephens, J. C., Asymmetric Organocatalytic 1,6-Conjugate Addition of Aldehydes to Dienic Sulfones. *Angew. Chem. Int. Ed.* **2011**, *50*, 5095-5098; (c) Zhou, Z.; Feng, X.; Yin, X.; Chen, Y.-C., Direct Remote Asymmetric Bisvinylogous 1,4-Additions of Cyclic 2,5-Dienones to Nitroalkenes. *Org. Lett.* **2014**, *16*, 2370-2373; (d) Gu, X.; Guo, T.; Dai, Y.; Franchino, A.; Fei, J.; Zou, C.; Dixon, D. J.; Ye, J., Direct Catalytic

- Asymmetric Doubly Vinylogous Michael Addition of α,β -Unsaturated γ -Butyrolactams to Dienones. *Angew. Chem.* **2015**, *127*, 10387-10391;
- (e) Wei, Y.; Liu, Z.; Wu, X.; Fei, J.; Gu, X.; Yuan, X.; Ye, J., Remote Construction of Chiral Vicinal Tertiary and Quaternary Centers by Catalytic Asymmetric 1,6-Conjugate Addition of Prochiral Carbon Nucleophiles to Cyclic Dienones. *Chem. Eur. J.* **2015**, *21*, 18921-18924; (f) Kowalczyk, R.; Boratyński, P. J.; Wierzba, A. J.; Bąkiewicz, J., Site and stereoselectivity in sulfa-Michael addition to equivocally activated conjugated dienes. *RSC Adv.* **2015**, *5*, 66681-66686.
- (3) (a) Uraguchi, D.; Yoshioka, K.; Ueki, Y.; Ooi, T., Highly Regio-, Diastereo-, and Enantioselective 1,6- and 1,8-Additions of Azlactones to Di- and Trienyl N-Acylpyrroles. *J. Am. Chem. Soc.* **2012**, *134*, 19370-19373; (b) Dell'Amico, L.; Albrecht, L.; Naicker, T.; Poulsen, P. H.; Jørgensen, K. A., Beyond Classical Reactivity Patterns: Shifting from 1,4- to 1,6-Additions in Regio- and Enantioselective Organocatalyzed Vinylogous Reactions of Olefinic Lactones with Enals and 2,4-Dienals. *J. Am. Chem. Soc.* **2013**, *135*, 8063-8070; (c) Poulsen, P. H.; Feu, K. S.; Paz, B. M.; Jensen, F.; Jørgensen, K. A., Organocatalytic Asymmetric 1,6-Addition/1,4-Addition Sequence to 2,4-Dienals for the Synthesis of Chiral Chromans. *Angew. Chem. Int. Ed.* **2015**, *54*, 8203-8207; (d) Yoshioka, K.; Yamada, K.; Uraguchi, D.; Ooi, T., Unique site-selectivity control in asymmetric Michael addition of azlactone to alkenyl dienyl ketones enabled by P-spiro chiral iminophosphorane catalysis. *Chem. Commun.* **2017**, *53*, 5495-5498.
- (4) (a) Dou, Q.-Y.; Tu, Y.-Q.; Zhang, Y.; Tian, J.-M.; Zhang, F.-M.; Wang, S.-H., Spiro-Pyrrolidine-Catalyzed Asymmetric Conjugate Addition of Hydroxylamine to Enals and 2,4-Dienals. *Adv. Synth. Catal.* **2016**, *358*, 874-879; (b) Poulsen, P. H.; Vergura, S.; Monleón, A.; Jørgensen, D. K. B.; Jørgensen, K. A., Controlling Asymmetric Remote and Cascade 1,3-Dipolar Cycloaddition Reactions by Organocatalysis. *J. Am. Chem. Soc.* **2016**, *138*, 6412-6415; (c) Torán, R.; Vila, C.; Sanz-Marco, A.; Muñoz, M. C.; Pedro, J. R.; Blay, G., Organocatalytic Enantioselective 1,6-aza-Michael Addition of Isoxazolin-5-ones to p-Quinone Methides. *Eur. J. Org. Chem.* **2020**, *2020*, 627-630; (d) Roy, S.; Pradhan, S.; Kumar, K.; Chatterjee, I., Asymmetric organocatalytic double 1,6-addition: rapid access to chiral chromans with molecular complexity. *Org. Chem. Front.* **2020**, *7*, 1388-1394.
- (5) Jiang, H.; Zhou, L.; Mao, B.; Yuan, C.; Wang, W.; Wu, Y.; Zhang, C.; Guo, H., Organocatalytic Enantioselective [3+2] Cycloaddition of Azomethine Ylides with 2,4-Dienals: Construction of Remote Stereogenic Centers via 1,6-Addition Reaction. *Adv. Synth. Catal.* **2020**, *362*, 5716-5720.
- (6) (a) Luo, Y.; Roy, I. D.; Madec, A. G. E.; Lam, H. W., Enantioselective Synthesis of Allylboronates and Allylic Alcohols by Copper-Catalyzed 1,6-Boration. *Angew. Chem. Int. Ed.* **2014**, *53*, 4186-4190; (b) Luo, Y.; Wales, S. M.; Korkis, S. E.; Roy, I. D.; Lewis, W.; Lam, H. W., Switchable Synthesis of Z-Homoallylic Boronates and E-Allylic Boronates by Enantioselective Copper-Catalyzed 1,6-Boration. *Chem. Eur. J.* **2018**, *24*, 8315-8319.
- (7) (a) Evans, D. A.; Andrews, G. C., Allylic sulfoxides. Useful intermediates in organic synthesis. *Acc. Chem. Res.* **1974**, *7*, 147-155; (b) Colomer, I.; Velado, M.; Fernández de la Pradilla, R.; Viso, A., From Allylic Sulfoxides to Allylic Sulfenates: Fifty Years of a Never-Ending [2,3]-Sigmatropic Rearrangement. *Chem. Rev.* **2017**, *117*, 14201-14243; (c) Kaiser, D.; Klose, I.; Oost, R.; Neuhaus, J.; Maulide, N., Bond-Forming and -Breaking Reactions at Sulfur(IV): Sulfoxides, Sulfonium Salts, Sulfur Ylides, and Sulfinate Salts. *Chem. Rev.* **2019**, *119*, 8701-8780.
- (8) (a) Kowalczyk, R.; Nowak, A. E.; Skarzewski, J., Organocatalytic asymmetric addition of aliphatic thiols to nitro olefins and nitro dienes. *Tetrahedron: Asymmetry* **2013**, *24*, 505-514; (b) Kowalczyk, R.; Boratyński, P. J., Stereoselective thia-Michael 1,4-Addition to Acyclic 2,4-Dienones and 2-En-4-ynones. *Adv. Synth. Catal.* **2016**, *358*, 1289-1295; (c) Mała, Ż. A.; Janicki, M. J.; Niedźwiecka, N. H.; Góra, R. W.; Konieczny, K. A.; Kowalczyk, R., Stereoselectivity Enhancement During the Generation of Three Contiguous Stereocenters in Tetrahydrothiophenes. *ChemCatChem* **2021**, *13*, 574-580.
- (9) For a rare example of enantioselective 1,6-conjugate sulfa-Michael upon organometallic catalysis, see: Shaw, S.; White, J. D., Regioselective and Enantioselective Addition of Sulfur Nucleophiles to Acyclic $\alpha,\beta,\gamma,\delta$ -Unsaturated Dienones Catalyzed by an Iron(III)-Salen Complex. *Org. Lett.* **2015**, *17*, 4564-4567.
- (10) (a) Chauhan, P.; Mahajan, S.; Enders, D., Organocatalytic Carbon-Sulfur Bond-Forming Reactions. *Chem. Rev.* **2014**, *114*, 8807-8864; (b) Chen, H.; Jiang, W.; Zeng, Q., Recent Advances in Synthesis of Chiral Thioethers. *Chem. Rec.* **2020**, *20*, 1269-1296; (c) Sunny, S.; Maingle, M.; Seth, K., Advances in Bifunctional Squaramide-Catalyzed Asymmetric Sulfa-Michael Addition: A Decade Update. *Synlett* **2022**, *34*, 572-600.
- (11) Fang, X.; Li, J.; Wang, C.-J., Organocatalytic Asymmetric Sulfa-Michael Addition of Thiols to α,β -Unsaturated Hexafluoroisopropyl Esters: Expedient Access to (R)-Thiazesim. *Org. Lett.* **2013**, *15*, 3448-3451.
- (12) It was observed a competitive 1,4- versus 1,6-conjugate addition upon the use of DABCO instead of DBU (see SI).
- (13) (a) Debien, L.; Zard, S. Z., A Two-Step Synthesis of α -Keto Vinyl Carbinols from Ketones. *Org. Lett.* **2013**, *15*, 6066-6069; (b) Colomer, I.; Ureña, M.; Viso, A.; Fernández de la Pradilla, R., Sulfinyl-Mediated Stereoselective Functionalization of Acyclic Conjugated Dienes. *Chem. Eur. J.* **2020**, *26*, 4620-4632.
- (14) Vatele, J.-M., TEMPO-Catalyzed Oxidative Amidation of Alcohols via Hexa-fluoroisopropyl Esters. *Synlett* **2015**, *26*, 2280-2284.