RESEARCH ARTICLE doi.org/10.1002/adsc.70153

ADVANCED SYNTHESIS & CATALYSIS

Installation of Trifluoromethylated Quaternary Carbon Stereocenters via Asymmetric Epoxidation of Tetrasubstituted Alkenes

Vincenzo Battaglia,[a] Isaac G. Sonsona,[a] Andrea Pellegrini,[b] Andrea Mazzanti,[b] and Alessandra Lattanzi[a,*]

[a] Dipartimento di Chimica e Biologia "A. Zambelli", Università di Salerno, 84084 Fisciano, Italy
E-mail: lattanzi@unisa.it
[b] Dipartimento di Chimica Industriale "Toso Montanari", Università di Bologna, 40136 Bologna, Italy

Manuscript received: June 5, 2025; Revised manuscript received: September 17, 2025;
Version of record online: October 8, 2025

Supporting information for this article is available on the WWW under https://doi.org/10.1002/adsc.70153

Abstract: The construction of vicinal quaternary carbon centers via epoxidation of tetrasubstituted alkenes remains a formidable challenge in asymmetric synthesis. Herein, a first catalytic enantioselective epoxidation of acyclic tetrasubstituted alkenes is reported, prepared through the Knoevenagel condensation of trifluoromethyl ketones with malononitrile. (*S*)- and (*R*)-configured epoxides are obtained in generally excellent yields (up to 98%) and with good to high enantioselectivities (up to 89% ee), employing a commercially available system, comprising Takemoto's catalysts and tert-butyl hydroperoxide (TBHP). Highly reactive new tetrasubtituted alkenes allow the first successful use of Takemoto's catalyst under oxidative conditions. Interestingly, density functional theory studies show that TBHP is exclusively activated by the amino thiourea, with halogen-bonding interactions playing a critical role in affecting the stereochemical outcome of the epoxidation. Derivatizations provide access to densely functionalized trifluoromethylated compounds, featuring one or two vicinal carbon quaternary stereocenters, with the second center being introduced in a highly stereoselective manner.

Keywords: asymmetric epoxidation, epoxides, organocatalysis, quaternary stereocenters, tetrasubstituted alkenes

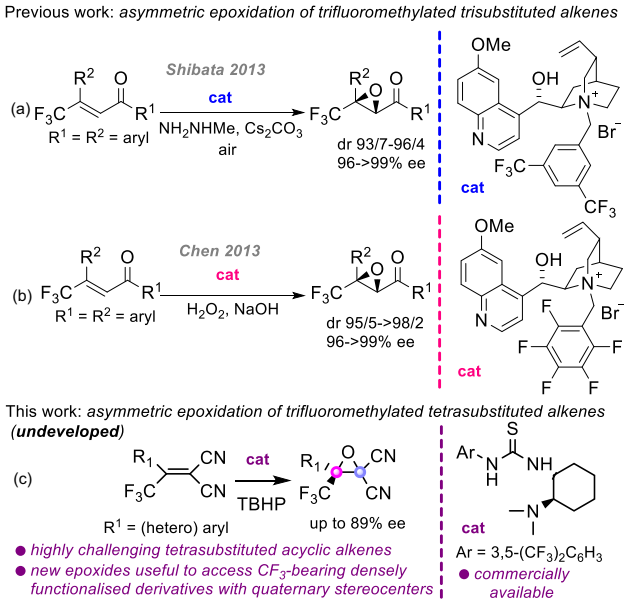
1. Introduction

Natural, non-natural compounds and drugs often embed in their structure, one or more quaternary carbon stereocenters, which impart molecular complexity.[1,2] Moreover, the presence of sp^3 carbon centers and their chirality affect metabolic stability of bioactive compounds, being among others, an important parameter to assess in clinical trials.[3] From a synthetic point of view, the stereoselective installation of quaternary carbon centers is arguably a challenging goal.[4–6] Over the last decades, significant progress has been achieved, by designing a great variety of catalytic asymmetric processes, although in this context there is great urgency of suitable ones to construct vicinal carbon quaternary stereocenters.[7,8]

Chiral nonracemic epoxides are amongst the most valuable intermediates in organic synthesis[9–12] and the epoxidation of alkenes is considered a venerable reaction in asymmetric catalysis. Remarkable developments over the past decades have broadened the epoxide scope, as exemplified by the efficient protocols reported by Sharpless,[13] Katsuki,[14] Jacobsen,[15] Shi,[16] and Juliá-Colonna.[17,18] A considerable number of acyclic and cyclic simple or functionalized 1,2-disubstituted alkenes can be transformed to synthetically useful epoxides with high level of stereocontrol.[19–26] When moving to acyclic trisubstituted electron-poor alkenes such as β,β-disubstituted α,β-unsaturated carboxylic acid derivatives only a few systems provide epoxides, with vicinal quaternary and tertiary centers, in highly stereoselective

fashion.[27–29] In this context, literature search for methods suitable to forge quaternary stereocenters, bearing a trifluoromethyl group, revealed only two examples. The groups of Shibata[30] and Chen[31] successfully developed the asymmetric epoxidation of β-trifluoromethyl β,β-disubstituted α,β-unsaturated ketones under phase transfer catalysis (**Scheme1**a,b).

The transformation appears of particular significance, being a useful tool for the introduction of the trifluoromethyl group, alternative to the widespread usage of trifluoromethylating agents to pursue this goal.[32] The installation of a trifluoromethyl group is of notable synthetic importance among all the fluorine-based fragments, serving to improve lipophilicity and modulate metabolic stability of pharmaceuticals and bioactive compounds.[33–38] The asymmetric epoxidation reactions of highly challenging tetrasubstituted alkenes showed marked substrate control dependance of the enantioselectivity,[39,40] as demonstrated by the results achieved on acyclic and unfunctionalised tetrasubstituted olefins, where the stereocontrol achieved was scarce or modest.[39] To the best of our knowledge, examples on asymmetric epoxidation reactions of trifluoromethylated tetrasubstituted olefins have not yet been developed. This prompted us to tackle the ambitious goal to investigate acyclic alkenes, obtainable by Knoevenagel condensation of trifluoromethyl ketones and malononitrile. We envisioned that this unprecedented class of highly electron-poor alkenes might undergo nucleophilic epoxidation[41] to give epoxides bearing two vicinal quaternary carbon centers, one being chiral, under organocatalytic conditions (Scheme 1c).[42–45] Herein, we illustrate the first asymmetric epoxidation of trifluoromethylated alkylidene malononitriles, mediated by commercially available Takemoto's amino thiourea catalyst and TBHP as the oxidant. The epoxides, obtained with good to high enantioselectivity, are attractive novel intermediates, useful to prepare trifluoromethylated products, bearing quaternary carbon stereocenters, via postfunctionalizations.



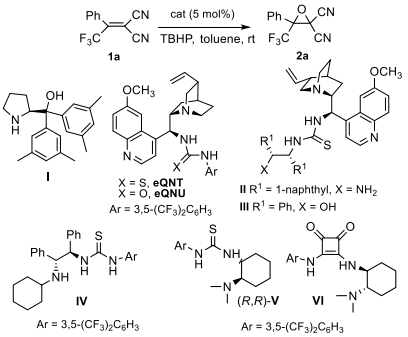
Scheme 1. State-of-art in the asymmetric epoxidations to construct quaternary carbon stereocenters bearing a trifluoromethyl group.

2. Results and Discussion

After having developed a protocol for the Knoevenagel condensation of trifluoromethyl aryl ketones and malononitrile,[46] the asymmetric epoxidation of dicyano alkylidenes was studied on model compound **1a** using bifunctional organocatalysts and TBHP in toluene at room temperature (**Table 1**).

When 5 mol% of quinine was used, a good conversion to almost racemic epoxide **2a** was observed (entry 1), as well as when using diaryl prolinol **I**, which provided a higher yield in shorter reaction time (entry 2). Importantly, these data attested the feasibility of a nucleophilic epoxidation for the tetrasubstituted alkenes **1**. Delightfully, 9-amino-9-deoxy-*epi*-quinine-derived thiourea

Table 1. Catalyst optimization in the enantioselective epoxidation of alkene **1a**.



Entry	Cat	t [h][a)]	Yield [%][b)]	ee [%][c)]
1	quinine	9	63	4 [+]
2	**I**	5	73	5 [−]
3	**eQNT**	6	53	75 [+]
4	**eQNU**	6	46	29 [+]
5	**II**	3	79	20 [+]
6	**III**	3.5	80	10 [+]
7	**IV**	1.5	59	56 [+]
8	(*R*,*R*)-**V**	2	85	74 [+]
9	**VI**	4.5	67	16 [+]

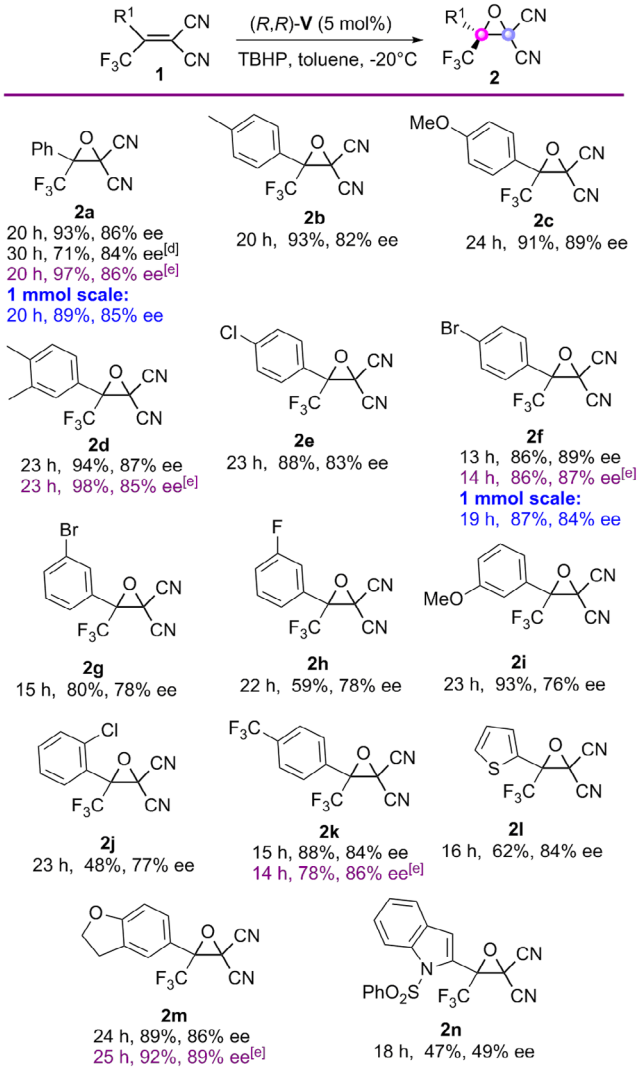
[a)]Reaction conditions: alkene **1a** (0.1 mmol), cat (0.005 mmol), TBHP (0.12 mmol) in anhydrous toluene (500 mL);
[b)]Yield determined by fluorine-19 nuclear magnetic resonance (^{19}F NMR) analysis of crude reaction mixture using $CF_3C_6H_5$ as an internal standard;
[c)]High-performance liquid chromatography (HPLC) analysis on a chiral stationary phase. Sign in parenthesis indicates the opposite enantiomer was prevalently obtained.

(**eQNT**) afforded epoxide **2a** in 54% yield and 75% ee (entry 3), whereas the corresponding urea 9-amino-9-deoxy-epi-quinine-derived urea (**eQNU**) proved to be markedly less effective (entry 4), as an indication that the nature of the H-bonding group played a critical role in the control of the enantioselectivity. The multifunctionalised quinidine derived thioureas **II** and **III**, although being more active than previous ones, were scarcely enantioselective (entries 5 and 6). Thiourea amine **IV** derived from readily available (*R*,*R*)−1,2-diphenylethylenediamine, provided compound **2a** in satisfactory yield and 56% ee (entry 7). Interestingly, commercially available Takemoto's amino thiourea **V** proved to be the most efficient, affording the epoxide with 85% yield and 74% ee in the shortest reaction time (entry 8). The corresponding amino squaramide **VI** led to product **2a** with reduced yield and dramatically lower enantioselectivity (entry 9), confirming thiourea amines as the most efficient bifunctional catalysts and in particular Takemoto's catalyst **V** (entry 8). This amino thiourea, originally developed in 2003,[47,48] demonstrated to be a powerful catalyst in countless asymmetric reactions, with the exception of oxidations.[49]

Under optimized reaction conditions[46] the scope and limitations of the enantioselective epoxidation of alkenes **1** was investigated using 5 mol% of catalyst **V** with TBHP in toluene at –20 °C (**Scheme 2**).

Irrespective of the (hetero) aromatic substitution pattern, epoxides were generally obtained in high yield, after relatively short reaction times. Specifically, model epoxide **2a** was recovered in 93% yield and 86% ee. Unfortunately, when working at –40 °C both conversion and enantioselectivity decreased. Commercial availability of both enantiomeric Takemoto's amino thioureas enables an easy preparation of *ent*-**2a** in 97% yield and 86% ee when using (*S*,*S*)-**V**. Gratifyingly, the protocol demonstrated to be robust, with the one mmol scale up reaction proceeding similarly in terms of efficiency and enantiocontrol.[50] Epoxides, bearing electron-donating groups at *para* position in the phenyl ring, were well tolerated leading to the corresponding epoxides **2b–d** with excellent yields and fairly good to high ee values. In the case of alkenes phenyl substituted with halogen atoms, a similar trend has been observed for epoxides **2e**,**f**, with the *p*-Br substituted epoxide **2f** obtained with up to 89% ee in both absolute configurations. For this substrate, the one mmol scale up reaction also proceeded with a comparable outcome. Slightly lower enantioselectivity was observed with *meta*-halogenated or *meta*-methoxy-phenyl substituted epoxides **2g–i** and a comparable result was achieved for the *ortho*-chloro phenyl derivative **2j**. Electron-withdrawing groups in the phenyl ring appear to be well tolerated, exemplified by the *para*-trifluoromethyl-phenyl epoxide **2k**, isolated in up to 88% yield and 86% ee in both absolute configurations.

Unfortunately, the highly reactive nature and instability toward isolation displayed by alkenes bearing other



Scheme 2. Substrate scope. [a]Reaction conditions: alkene **1** (0.1 mmol), (*R*,*R*)-**V** (0.005 mmol), TBHP (0.12 mmol) in anhydrous toluene (5 mL). [b]Yield of isolated product. [c]HPLC analysis on a chiral stationary phase. [d]Reaction run at −40 °C. [e]Reaction run with (*S*,*S*)-**V**.

electron-withdrawing groups, prevented their investigation in the epoxidation.[51]

Pleasingly, heteroaromatic groups, such as thiophene and dihydrobenzofuran could be incorporated onto the alkene, giving epoxides **2l**,**m** in good to high yields and up to 89% ee. However, when a sterically congested *N*-protected indole group was installed, the corresponding epoxide **2n** was recovered in moderate yield and 49% ee value.

The absolute configuration of epoxides **2**, has been indirectly determined by TD-density functional theory (DFT) simulation of the electronic circular dichroism (ECD) spectra, supported by DFT conformational analysis and TD-DFT calculation of ECD spectrum of the bis methyl ester epoxide **3b**, readily obtained from epoxide **2f** through a one-pot sequence.[52–55] The ECD spectrum was successfully simulated considering the 3*S* absolute

configuration for epoxide **3b** (**Figure 1**).[46] The absolute configuration of other epoxides **2** was assigned by analogy.

The synthetic versatility of new trifluoromethylated epoxides **2** was showcased, after having transformed model enantioenriched **2a** to the corresponding bis methyl ester **3a** (**Scheme 3**).

Treatment of compound **3a** under reductive conditions was investigated to achieve two synthetic goals: i) selective ester group manipulation and ii) epoxide ring-opening. The feasibility of esters reduction by methanolic $NaBH_4$ has been attained under different reaction conditions.[54,55] More specifically, according to the literature,[56] trisubstituted bis ester epoxides of

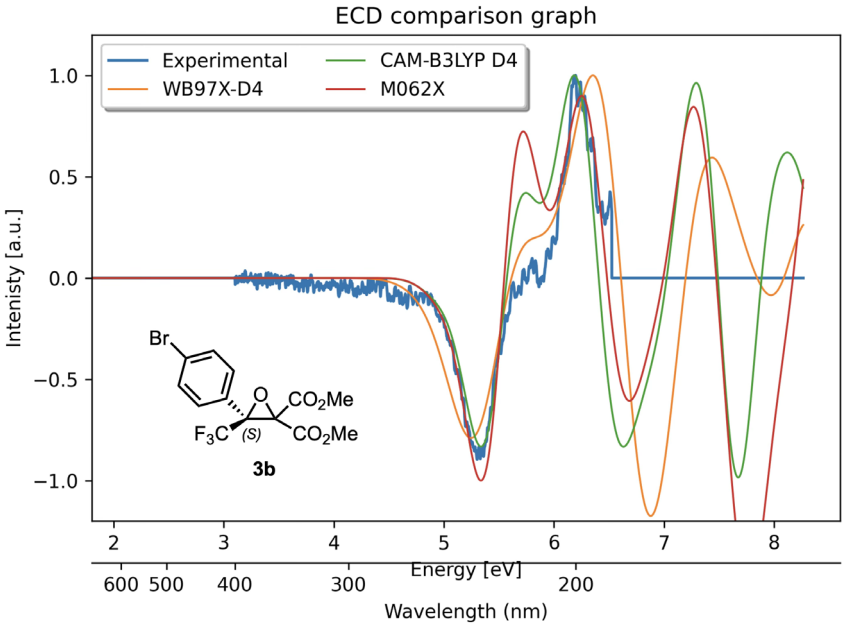
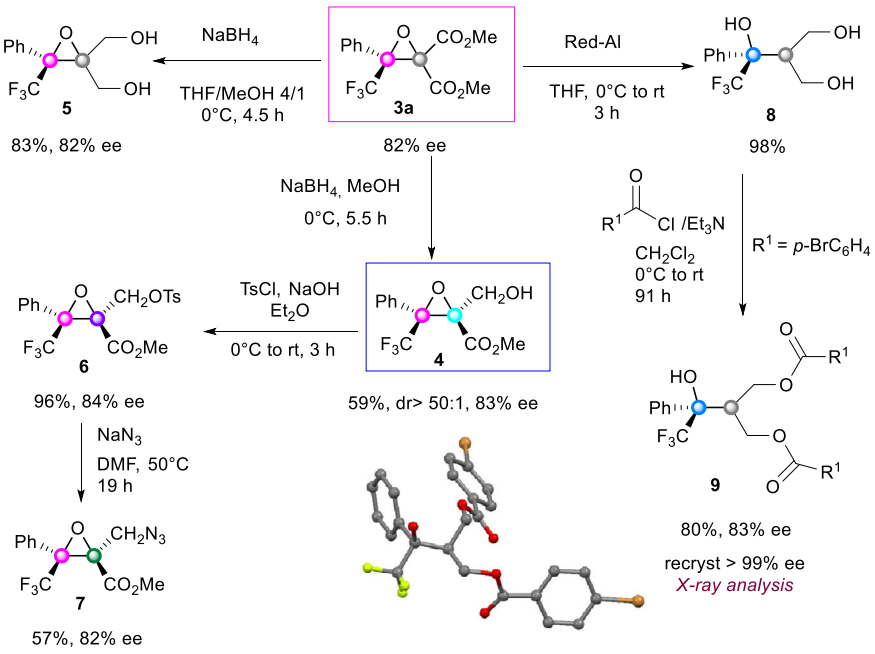


Figure 1. TD-DFT simulations of the ECD spectrum of compound **3b**. The vertical scales of experimental and simulated spectra have been normalized to +1.



Scheme 3. Synthetic derivatizations of epoxide **3a**.

type **3**, lacking the CF_3 group, were found to be unreactive when treated with readily available $NaBH_4$. However, we surmised that the presence of the electron-withdrawing CF_3 moiety would have enhanced ester electrophilicity, facilitating the reduction.

After optimization,[46] mono alcohol **4** was successfully isolated as single diastereoisomer in 59% yield, maintaining the ee value. The complete control of the diastereoselectivity might be ascribed to the CF_3 group steric[57] and electronic features,[58] which concurrently favored the reduction of the methyl ester group anti to the trifluoromethyl group, as confirmed by NOESY analysis. Notably, this process enables the highly challenging synthesis of acyclic and densely functionalized epoxides, bearing vicinal chiral quaternary centers in an asymmetric fashion. The reduction of epoxide **3a**, carried out in THF/MeOH mixture, furnished epoxy diol **5** in 83% yield and 82% ee. Multifunctionalised epoxide **4** served as a versatile intermediate, amenable of other classical functional group transformations.

First, it was converted into the corresponding tosylated epoxide **6** in 96% yield and 84% ee. In addition, compound **6** was reacted with NaN_3 to prepare azide **7** in 57% yield and 82% ee. Epoxy azides **7**, beside application in click chemistry, can be precursors of challenging α-epoxy-β-amino acids, useful building-blocks for the design of new peptidomimetics with enhanced properties, thanks to the presence of two vicinal quaternary stereocenters.[59,60] Interestingly, the reaction of epoxide **3a** with Red-Al smoothly proceeded with both ester groups reduction and a highly regioselective hydride ring-opening reaction to triol **8**, which was isolated in 98% yield. This exhaustive reductive transformation of epoxides **3** enables an efficient synthesis of uncommon fluorine based chiral ligands of potential applications in metal catalysis[61–64] and anion recognition.[65,66] *p*-Bromo benzoylation of the primary alcohol groups furnished the tertiary trifluoromethylated alcohol **9** in 80% yield and 83% ee, which confirmed that no racemization occurred in the previous step. Single crystal X-ray analysis of recrystallized compound **9** enabled to determine the absolute configuration as *R*, thus confirming the *S* absolute configuration of the starting epoxide **3a**.[67]

Mechanistic investigations were then carried out in order to gain more insight into the stereochemical outcome of the epoxidation provided by Takemoto's amino thiourea. As a first experimental evidence for further computational investigation, nonlinear effects were studied under optimized reaction conditions (**Figure 2**).

A linear relationship between enantiopurity of model epoxide **2a** and catalyst (*R*,*R*)-**V** was observed. This suggests the involvement of a single molecule of the catalyst in the enantiodetermining transition state.[68]

DFT calculations were conducted using model compound **2f** to elucidate the complete reaction pathway and

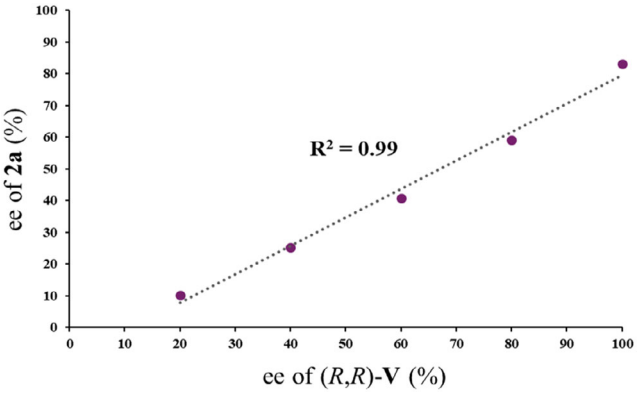


Figure 2. Nonlinear effects study in the asymmetric epoxidation of **1a** under conditions reported in Scheme 2.

investigate the key factors governing the observed enantioselectivity.[46] The transformation was modeled as a two-step nucleophilic epoxidation sequence, in which the stereocenter is established during the initial addition of the TBHP–catalyst complex to the alkene, followed by ring-closure to the epoxide accompanied by elimination of tert-butanol (**Figure 3**).

Computations were performed at the r^{2}SCAN-3c D4/def2-mTZVPP level of theory,[69,70] incorporating solvent effects via the CPCM model. The calculated energy profiles for both reactions toward the *S*- or the *R*-epoxide suggest that the rate-determining step corresponds to the oxa-Michael addition (**TS1**), while the subsequent ring-closure (**TS2**) proceeds with a lower barrier. A computed $\Delta\Delta G^{\neq}$ of 1.2 kcal mol^{-1} between the transition states for *Re* and *Si* face addition at 253 K predicts an enantiomeric excess of 83% in favor of the *S* enantiomer (*Si* face attack), in excellent agreement with the experimental value of 89%. In **TS1-*R***, the two hydrogen bonds between the thiourea and TBHP are 1.89 and 2.11 Å, while the same distances are 1.93 and 2.07 Å in **TS1-*S***. The angle resembling the Bürgi-Dunitz trajectory is 113° in **TS1-*R*** and 95° for **TS1-*S*** geometry, respectively. The C─O distances of the forming bond are 2.41 and 2.69 Å for **TS1-*R*** and **TS1-*S***, respectively. It thus appears that the TS geometry for the *R* enantiomer is more shifted toward the product, at difference with an earlier transition state in the pathway for the *S* enantiomer.

Although the hydrogen-bonding network stabilizing the TBHP/catalyst complex remains consistent in the two transition states, noncovalent interaction (NCI) analysis[71] revealed that an additional halogen bonding interaction, between the trifluoromethyl group of the alkene and one aromatic hydrogen of the catalyst, is accessible only in the **TS1-*S*** transition state involving *Si* face attack (**Figure 4**).

This interaction provides enhanced stabilization and is proposed to be a key factor in determining the

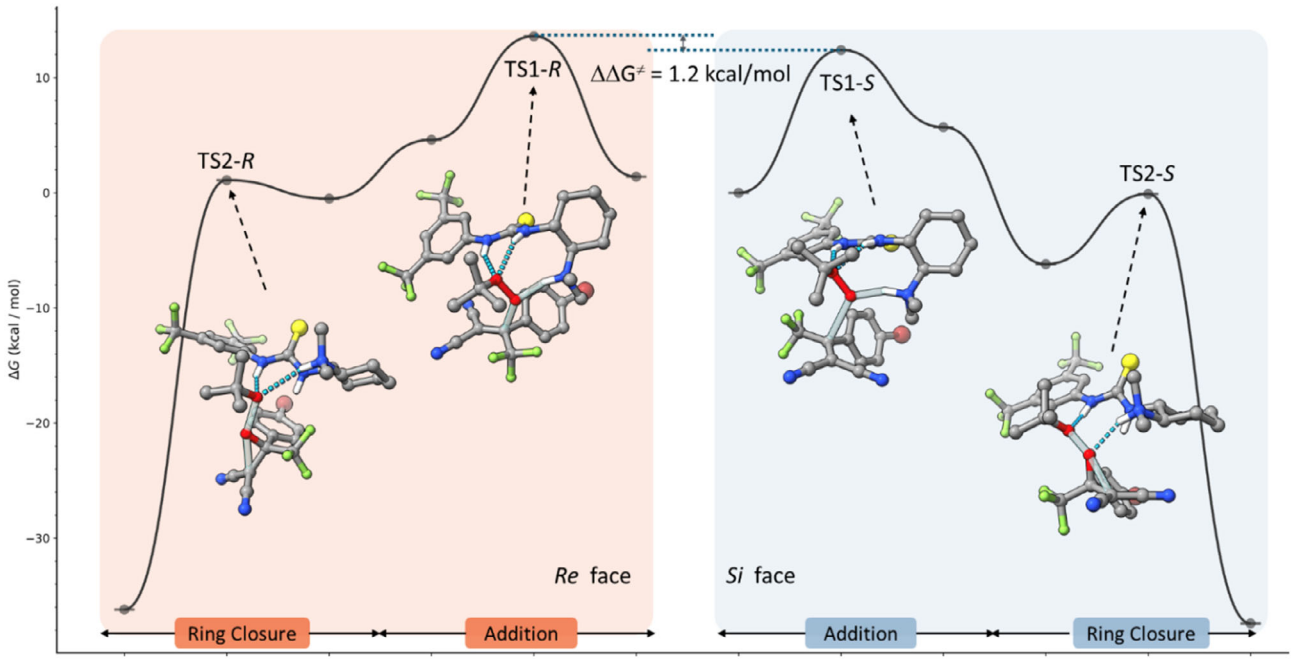


Figure 3. Calculated reaction pathways to epoxide **2f** by oxa-Michael addition followed by ring closure. Calculations at the CPCM-r^{2}SCAN-3c D4/def2-mTZVPP level of theory. Starting from the center, the reaction pathway on the left yields the (*R*)-epoxide, the pathway on the right yields the (*S*)-epoxide. The reference energy is set at the prereaction complex of the *S*-pathway.

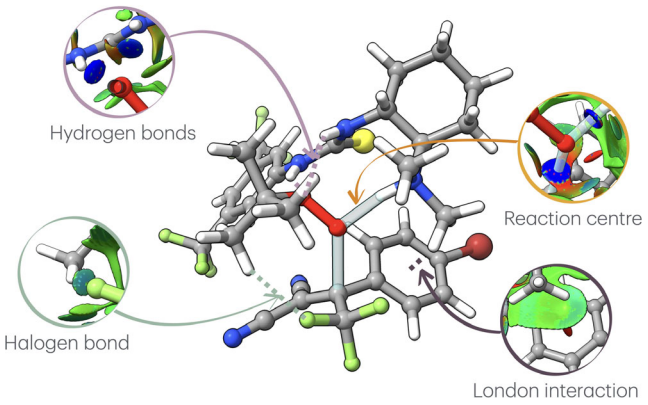


Figure 4. 3D-representation of TS1-*S*, related to nucleophilic addition of TBHP to the *Si* face of the alkene with NCI analysis. Color scheme for the NCI surfaces: red: repulsive, green: mild interaction, blue: strong interaction (e.g. H-bonds).

enantioselectivity of the reaction. It is noteworthy that widely used bifunctional amino ureas and thioureas exhibit distinct behaviors in the activation of electron-poor alkenes and alkyl hydroperoxides, as revealed by DFT studies. In a previous investigation,[44] replacing a cyano group on the alkene with a phenylsulfonyl moiety led to a more intuitive activation of the alkyl hydroperoxide. In that case, the basic site of a quinine-derived urea, together with a key hydrogen–bond interaction between the urea and the strong hydrogen-bonding acceptor phenylsulfonyl group on the alkene, played a crucial role in the catalysis. By contrast, in the present study, the hydrogen-bonding network, established by Takemoto's amino thiourea, appears to be restricted to the activation of TBHP. All these findings provide valuable insights that enhance our understanding and predictive ability to develop new organocatalytic asymmetric epoxidation reactions.

3. Conclusion

In summary, a first example of asymmetric catalytic epoxidation of unprecedented tetrasubstituted CF_3-bearing acyclic electron-poor alkenes has been developed by using a commercially available organocatalytic system. Notable features of the process are: i) preparation of hitherto inaccessible trifluoromethylated epoxides with two vicinal quaternary centers, being one chiral, achieving generally high yield and good to high enantioselectivity; ii) first successful example of Takemoto's amino thiourea catalyzed process in the area of asymmetric oxidations; iii) stereoselective access to densely functionalized trifluoromethylated derivatives of synthetic interest, bearing one or two vicinal quaternary stereocenters; and iv) theoretical insight on the catalytic activity of Takemoto's amino thiourea. This work unlocks opportunities to explore new classes of acyclic trifluoromethylated tetrasubstituted alkenes in asymmetric epoxidation and catalysis. Along this line, further studies to expand the access

to fluorinated molecular motifs, bearing quaternary carbon stereocenters, are ongoing in our laboratory.

4. Experimental Section

General Procedure for the Asymmetric Epoxidation of Alkenes 1: In a sample vial containing a solution of alkene **1** (0.1 mmol) and (*R*,*R*)-**V** catalyst or (*S*,*S*)-**V** catalyst (2.1 mg, 0.005 mmol) in anhydrous toluene (5 mL) at –20 °C, TBHP (≈5.5 M in decane, 23 μL, 0.12 mmol) was added. The reaction was stirred at –20 °C for 7–43 h, monitored by TLC (eluent PE/ethyl acetate 90/10). Purification of the crude reaction mixture by flash chromatography (eluting with PE/ethyl acetate 100/0 to 95/5) gives enantioenriched epoxides **2**.

Acknowledgements

V.B. and I.G.S. contributed equally to this work. The authors acknowledge financial support from the European Union—NextGeneration EU under the Italian Ministry of University and Research (MUR) in the context of PRIN2022—CUP D53D23010060006, project code: 20222Z8CKP (TECHNO) and from the University of Bologna (RFO funds 2023). The authors thank Dr. P. Iannece for assistance with elemental and MS analyses.

Open access publishing facilitated by Universita degli Studi di Salerno, as part of the Wiley - CRUI-CARE agreement.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that supports the findings of this study are available in the supplementary material of this article.

References

[1] E. J. Corey, A. Guzman-Perez, *Angew. Chem. Int. Ed.* **1998**, *37*, 388.
[2] K. W. Quasdorf, L. E. Overman, *Nature* **2014**, *516*, 181.
[3] J. Lovering, C. Bikker, J. Humblet, *J. Med. Chem.* **2009**, *52*, 6752.
[4] J. P. Das, I. Marek, *Chem. Commun.* **2011**, *47*, 4593.
[5] M. Buschleb, S. Dorich, S. Hanessian, D. Tao, K. B. Schenthal, L. E. Overman, *Angew. Chem. Int. Ed.* **2016**, *55*, 4156.
[6] J. Feng, M. Holmes, M. J. Krische, *Chem. Rev.* **2017**, *117*, 12564.
[7] R. Long, J. Huang, J. Gong, Z. Yang, *Nat. Prod. Rep.* **2015**, *32*, 1584.
[8] F. Zhou, L. Zhu, B. W. Pan, Y. Shi, Y. L. Liu, J. Zhou, *Chem. Sci.* **2020**, *11*, 9341.
[9] J. Marco-Contelles, M. T. Molina, S. Anjum, *Chem. Rev.* **2004**, *104*, 2857.
[10] L. P. C. Nielsen, E. N. Jacobsen,*Aziridines and Epoxides in Organic Synthesis*, (Ed. A. K. Yudin), Wiley-VCH, Weinheim, Germany, **2006**, 7–9.
[11] M. M. Heravi, T. B. Lashaki, N. Poorahmad, *Tetrahedron: Asymmetry* **2015**, *26*, 405.
[12] H. Yang, H. Yu, I. A. Stolarzewicz, W. Tang, *Chem. Rev.* **2023**, *123*, 9397.
[13] T. Katsuki, K. B. Sharpless, *J. Am. Chem. Soc.* **1980**, *102*, 5974.
[14] R. Irie, K. Noda, Y. Ito, N. Matsumoto, T. Katsuki, *Tetrahedron Lett.* **1990**, *31*, 7345.
[15] W. Zhang, J. L. Loebach, S. R. Wilson, E. N. Jacobsen, *J. Am. Chem. Soc.* **1990**, *112*, 2801.
[16] Y. Tu, Z.-X. Wang, Y. Shi, *J. Am. Chem. Soc.* **1996**, *118*, 9806.
[17] S. Juliá, J. Masana, J. C. Vega, *Angew. Chem. Int. Ed.* **1980**, *19*, 929.
[18] S. Juliá, J. Guixer, J. Masana, J. Rocas, S. Colonna, R. Annunziata, H. Molinari, *J. Chem. Soc. Perkin Trans. 1* **1982**, 1317.
[19] Z.-X. Wang, Y. Tu, M. Frohn, J.-R. Zhang, Y. Shi, *J. Am. Chem. Soc.* **1997**, *119*, 11224.
[20] Y.-M. Shen, B. Wang, Y. Shi, *Angew. Chem. Int. Ed.* **2006**, *45*, 1429.
[21] B.-F. Sun, R. Hong, Y.-B. Kang, L. Deng, *J. Am. Chem. Soc.* **2009**, *131*, 10384.
[22] Y. Nishikawa, H. Yamamoto, *J. Am. Chem. Soc.* **2011**, *133*, 8432.
[23] O. Cussó, I. Garcia-Bosch, D. Font, X. Ribas, J. Lloret-Fillol, M. Costas, *Org. Lett.* **2013**, *15*, 6158.
[24] O. Cussó, M. Cianfanelli, X. Ribas, R. J. K. Gebbink, M. Costas, *J. Am. Chem. Soc.* **2016**, *138*, 2732.
[25] Q. He, M.-P. Pu, Z. Jiang, H. Wang, X. Feng, X. Liu, *J. Am. Chem. Soc.* **2023**, *145*, 15611.
[26] Y. Tang, Z. Li, M. Q. Zeng, R. Li, H. Song, D. Zhang, F. Xue, Y. Qin, *J. Org. Chem.* **2024**, *89*, 4971.
[27] X.-Y. Wu, X. She, Y. Shi, *J. Am. Chem. Soc.* **2002**, *124*, 8792.
[28] L. Luo, H. Yamamoto, *Eur. J. Org. Chem.* **2014**, *2014*, 7803.
[29] C. Clarasó, L. Vicens, A. Polo, M. Costas, *Org. Lett.* **2019**, *21*, 2430.
[30] H. Kawai, S. Okusu, Z. Yuan, E. Tokunaga, A. Yamano, M. Shiro, N. Shibata, *Angew. Chem. Int. Ed.* **2013**, *52*, 2221.
[31] S. Wu, D. Pan, C. Cao, Q. Wang, F.-X. Chen, *Adv. Synth. Catal.* **2013**, *355*, 1917.
[32] J. Nie, H.-C. Guo, D. Cahard, J.-A. Ma, *Chem. Rev.* **2011**, *111*, 455.
[33] S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320.
[34] J.-C. Zhang, S.-X. Li, K. Hashimoto, *Pharmacol. Biochem. Behav.* **2014**, *116*, 137.
[35] Y. Liu, S. J. Han, W.-B. Liu, B. M. Stoltz, *Acc. Chem. Res.* **2015**, *48*, 740.
[36] S. Okusu, K. Hirano, Y. Yasuda, J. Tanaka, E. Tokunaga, H. Fukaya, N. Shibata, *Org. Lett.* **2016**, *18*, 5568.
[37] N. Gaggero, *Eur. J. Org. Chem.* **2019**, *2019*, 7615.

[38] M. Inoue, Y. Sumii, N. Shibata, *ACS Omega* **2020**, *5*, 10633.
[39] B. D. Brandes, E. N. Jacobsen, *Tetrahedron Lett.* **1995**, *36*, 5123.
[40] E. Ogino, A. Nakamura, S. Kuwano, T. Arai, *Org. Lett.* **2021**, *23*, 1980.
[41] E. Weitz, A. Scheffer, *Chem. Ber.* **1921**, *54*, 2327.
[42] A. Russo, G. Galdi, G. Croce, A. Lattanzi, *Chem. Eur. J.* **2012**, *18*, 6152.
[43] S. Meninno, A. Roselli, A. Capobianco, J. Overgaard, A. Lattanzi, *Org. Lett.* **2017**, *19*, 5030.
[44] C. Volpe, S. Meninno, C. Crescenzi, M. Mancinelli, A. Mazzanti, A. Lattanzi, *Angew. Chem. Int. Ed.* **2021**, *60*, 23819.
[45] A. Lattanzi, *Chem Rec.* **2023**, *23*, e202300066.
[46] See the Supporting Information.
[47] T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672.
[48] Y. Takemoto, *Org. Biomol. Chem.* **2005**, *3*, 4299.
[49] Y. Kobayashi, S. Li, Y. Takemoto, *Asian J. Org. Chem.* **2014**, *3*, 403.
[50] Unfortunately at the end of the epoxidation, catalyst V could not be recovered after column chromatography as only unidentified by-products were present.
[51] The phenyl rings, bearing electron-withdrawing groups in the trifluoromethyl ketone used, were the following: 4-nitro phenyl, 3-nitro phenyl and 3,5-dichloro phenyl.
[52] K. Nanjo, K. Suzuki, M. Sekiya, *Chem. Pharm. Bull.* **1981**, *29*, 336.
[53] D. Hurtaud, M. Baudy-Floc'h, P. L. Grel, *Tetrahedron Lett.* **1999**, *40*, 5001.
[54] M. S. Brown, H. Rapoport, *J. Org. Chem.* **1963**, *28*, 3261.
[55] C. P. Prasanth, E. Joseph, A. Abhijith, D. S. Nair, I. Ibnusaud, J. Raskatov, B. Singaram, *J. Org. Chem.* **2018**, *83*, 1431.
[56] J. Mauger, A. Robert, *Tetrahedron* **1988**, *44*, 2493.
[57] R. Ruzziconi, S. Spizzichino, A. Mazzanti, L. Lunazzi, M. Schlosser, *Org. Biomol. Chem.* **2010**, *8*, 4463.
[58] A slight increase in the condensed Fukui function and a higher positive charge on the carbomethoxy group anti to the CF_3 group have been calculated. See the Supporting Information for details.
[59] J. B. Schwarz, S. E. Gibbons, S. R. Graham, N. L. Colbry, P. R. Guzzo, V. D. Le, M. G. Vartanian, J. J. Kinsora, S. M. Lotarski, Z. Li, M. R. Dickerson, T.-Z. Su, M. L. Weber, A. El-Kattan, A. J. Thorpe, S. D. Donevan, C. P. Taylor, D. J. Wustrow, *J. Med. Chem.* **2005**, *48*, 3026.
[60] E. Semina, A. Žukauskaitė, A. Šačkus, N. De Kimpe, S. Mangelinckx, *Eur. J. Org. Chem.* **2016**, *2016*, 1720.
[61] D. Callant, D. Stanssens, J. G. de Vries, *Tetrahedron: Asymmetry* **1993**, *4*, 185.
[62] H. Lütjens, G. Wahl, F. Möller, P. Knochel, J. Sundermeyer, *Organometallics* **1997**, *16*, 5869.
[63] F. Fabris, L. Pellizzaro, C. Zonta, O. De Lucchi, *Eur. J. Org. Chem.* **2007**, *2007*, 283.
[64] T. M. Le, T. Huynh, G. Endre, A. Szekeres, F. Fülöp, Z. Szakonyi, *RSC Adv.* **2020**, *10*, 38468.
[65] C. Sperandio, J. Rodriguez, A. Quintard, *Chem. Sci.* **2020**, *11*, 1629.
[66] C. Sperandio, J. Rodriguez, A. Quintard, *Org. Biomol. Chem.* **2020**, *18*, 2637.
[67] CCDC 2448374 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.
[68] T. Satyanarayana, S. Abraham, H. B. Kagan, *Angew. Chem. Int. Ed.* **2009**, *48*, 456.
[69] S. Grimme, A. Hansen, S. Ehlert, J.-M. Mewes, *J. Chem. Phys.* **2021**, *154*, 064103.
[70] E. Caldeweyher, J.-M. Mewes, S. Ehlert, S. Grimme, *Phys. Chem. Chem. Phys.* **2020**, *22*, 8499.
[71] R. Laplaza, F. A. Peccati, R. Boto, C. Quan, A. Carbone, J.-P. Piquemal, Y. Maday, J. Contreras-Garcia, *WIREs Comput. Mol. Sci.* **2021**, *11*, e1497.