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Chemoenzymatic synthesis of optically active α-cyclopropyl-pyruvates and cyclobutenoates *via* enzyme-catalyzed carbene transfer with diazopyruvate†

Raphaël Dollet,‡[a] Juan D. Villada,‡[b] Thomas Poisson,[a] Rudi Fasan *[b] and Philippe Jubault *[a]

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Cyclopropanes are recurrent structural motifs in natural products and bioactive molecules. Recently, biocatalytic cyclopropanations have emerged as a powerful approach to access enantioenriched cyclopropanes, complementing chemocatalytic approaches developed over the last several decades. Here, we report the development of a first biocatalytic strategy for cyclopropanation using ethyl α-diazopyruvate as a novel enzyme-compatible carbene precursor. Using myoglobin variant Mb(H64V,V68G) as the biocatalyst, this method afforded the efficient synthesis of α-cyclopropylpyruvates in high diastereomeric ratios and enantiomeric excess (up to 99% ee). The ketoester moiety in the cyclopropane products can be used to synthesize diverse optically pure cyclopropane derivatives. Furthermore, the enzymatically obtained α-cyclopropylpyruvate products could be converted into enantiopure cyclobutenoates *via* a metal-free photochemical ring expansion without loss of optical activity.

Introduction

Cyclopropane is a recurrent structure in natural products[1–3] and bioactive molecules,[4–6] and the third most represented carbocycle, after benzene and cyclohexane, within the structure of FDA-approved drugs.[7] In recent years, motivated by their high prevalence in drug molecules and drug candidates, a variety of powerful and selective approaches have been developed to synthesize optically pure cyclopropanes.[8–11] Complementing chemocatalytic cyclopropanation protocols, significant progress has been made over the past decade in the development of biocatalytic strategies for the stereoselective cyclopropanation using engineered hemoproteins such as myoglobin and cytochrome P450s.[12–18] These strategies have also proven to be synthetically relevant for the preparation of cyclopropane containing drugs and drug precursors.[14–17]

In this context, there is an ongoing interest in broadening the accessible chemical space of optically active cyclopropanes through biocatalysis. Efforts in this direction have included the use of readily available diazo carbene precursors, which have resulted in different examples of acceptor only diazo compounds for biocatalytic cyclopropanation[13,19,20] as well as the use of new carbene precursors like diaziridines.[21] This progress has resulted in newly functionalized enantiopure cyclopropanes, which can be readily manipulated through further chemical modifications to achieve greater diversification of the cyclopropane scaffolds.

Recently, some of us reported biocatalytic methods for olefin cyclopropanation in the presence of α-diazoacetonitrile and α-cyclopropylketones,[22,23] leading to enantioenriched cyclopropanes in up to >99% ee (Scheme 1). Both the cyano and the keto-groups in these products can be converted into various new moieties, with a complete stereoretention of the cyclopropane chiral centers. This work showcased the importance of introducing new densely functionalized biocatalyst-compatible diazo compounds that ultimately allow further manipulations to increase the molecular complexity of the cyclopropane. On the other hand, the Arnold group demonstrated the diasterodivergent cyclopropanation of vinyl boronic acid pinacol ester with ethyldiazoacetate and diversification of the resulting cyclopropanes by Suzuki coupling (Scheme 1).[24]

As part of our ongoing program dedicated to the development of straightforward access to functionalized cyclopro-

[a]INSA Rouen Normandie, Univ Rouen Normandie, CNRS, Normandie Univ, COBRA UMR 6014, INC3M FR 3038, F-76000 Rouen, France. E-mail: philippe.jubault@insa-rouen.fr
[b]Department of Chemistry and Biochemistry, University of Texas at Dallas, 800 W. Campbell Road, Richardson, TX 75080, USA. E-mail: rudi.fasan@utdallas.edu
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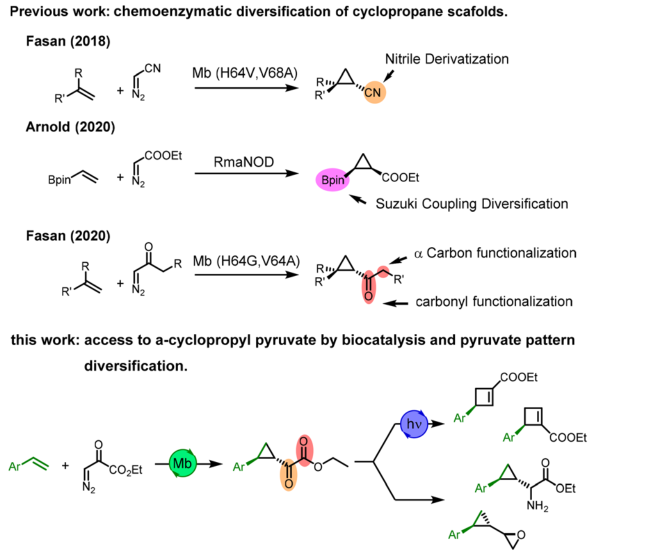
‡ These authors have contributed equally to this work.



Scheme 1 Biocatalytic synthesis of functionalized cyclopropanes and library extension.

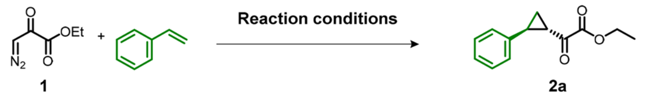
panes,[25] here we report the first example of biocatalytic enantioselective cyclopropanation using ethyl diazopyruvate (EDPv) as a new biocatalyst-compatible carbene source. The resulting α-cyclopropylpyruvates can be produced with high enantioselectivity (up to >99% ee). To date, the catalytic asymmetric synthesis of α-cyclopropylpyruvates remained elusive, and only racemic chiral derivatives have been reported.[26,27] We also showcased the α-cyclopropylpyruvate motif as a privilege precursor of enantiopure cyclobutenoates and other enantioenriched compounds.

Results and discussion

To initiate our investigations dealing with the biocatalytic synthesis of chiral α-cyclopropylpyruvates, different myoglobin variants were tested on the model reaction between EDPv **1** and styrene in whole cell transformation. Variant Mb(H64V, V68A), which previously showed activity for different carbene transfer reactions with ethyl diazoacetate (EDA),[12] afforded only traces of the desired product (Table 1, entry 4), whereas no activity was shown by wild-type Mb or hemin alone (Table 1, entries 2 and 3).

Decreasing the size of the amino acid at the level of the distal histidine 64 by switching from valine to glycine, Mb (H64G,V68A), increased the yield of the cyclopropane **2a** to 8% as shown in entry 4 of Table 1. A similar modification of the amino acid residue at the position 68 (from valine to glycine) resulted in the improved biocatalyst Mb(H64V,V68G), which provides **2a** in 34% yield (Table 1, entry 5). Other modifications in position 64 did not further improve the yield (Table 1, entries 7 and 8). Similarly, additional mutations at positions 111, 28, and 43 were also tested but none of them resulted in improved reactivity (Table S3†). Finally the use of

Table 1 Catalyst screening for cyclopropanation of styrene with the EDPv



Entry	Catalyst	Yield[c]
1	Hemin[a]	0%
2	Mb(WT)	0%
3	Mb(H64V,V68A)	<2%
4	Mb(H64G,V68A)	8%
5	Mb(H64V,V68G)	34%
6	Mb(H64A,V68G)	<2%
7	Mb(H64G,V68G)	4%
8	Mb(H64V,V68G)[b]	5%

Reaction conditions: 20 mM olefin, 10 mM of EDPv **1**, OD_{600} = 20; in 50 mM potassium phosphate (pH 7) buffer (Kpi 50 mM) with 10% ethanol, room temperature under anaerobic conditions. [a] 60 μM of hemin, 10 mM sodium dithionite in 50 mM potassium phosphate buffer (pH 7) containing 10% DMF, room temp. [b] 20 μM of purified Mb(H64V,V68G), 10 mM sodium dithionite in 50 mM potassium phosphate buffer (pH 7) containing 10% Ethanol. [c] Yield is determined by GC compared with authentic standards.

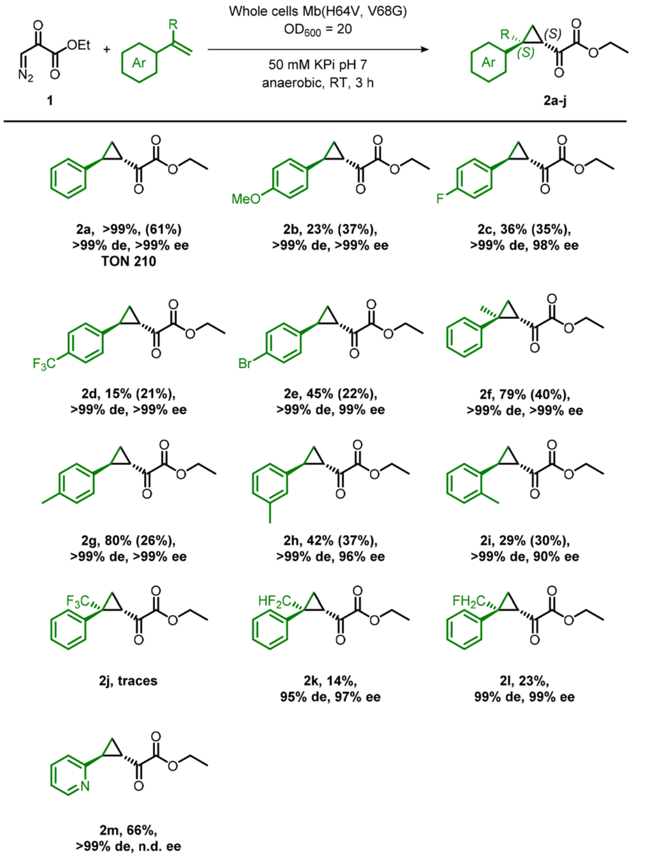
Mb(H64V,V68G) as purified enzyme led to an important decrease of the yield of **2a** from 34% to 5% (Table 1, entry 8), demonstrating a beneficial effect of conducting the reaction in whole cells compared to the isolated enzyme.

Reaction optimization studies showed that an excess of styrene (5-fold) over the diazo reagent was beneficial to obtain quantitative yields of **2a** in the Mb(H64V,V68G)-catalyzed reaction (Table 2, entries 3 and 5) with up to 210 TON (Scheme 2 product **2a**). A similar trend was previously observed in Mb-catalyzed cyclopropanation with the α-diazo ketone reagent as the carbene precursor.[23] More recent studies indicated that once the metal carbene is formed, it can either react with the olefin to produce the desired cyclopropane product or inserts into the heme cofactor in a non-productive pathway to produce a green colored adduct.[28] A similar non-productive reactivity can occur in the case of the diazopyruvate **1**, as supported by the observation of a green coloration of the reaction

Table 2 Concentrations screening for cyclopropanation of styrene with the EDPv

Entry	Mb(H64V,V68G) (OD_{600})	Styrene (mM)	EDPv (mM)	Yield[a] (%)	de (%)
1	20	10	5	43	>99
2	10	50	10	39	>99
3	20	50	10	>99	>99
4	20	25	5	85	>99
5	20	50	5	>99	>99
6[b]	20	50	10	61%	>99

Reaction conditions: 50 mM potassium phosphate (pH 7) buffer (kpi 50 mM) with 10% ethanol, room temperature under anaerobic conditions. [a] Yield is determined by GC compared with authentic standards. [b] Reaction performed on 50 mL scale (volume of the enzymatic scale-up reaction).

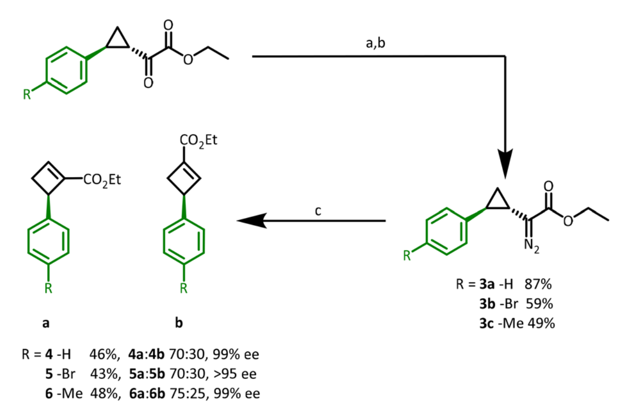


Scheme 2 Substrate scope of Mb(H64V,V68G)-catalyzed olefin cyclopropanation with EDPv. Reaction conditions: reaction performed in 400 µL KPi buffer 50 mM (pH 7) with 10 mM of EDPv **1** and 50 mM of olefin during 3 h. Yield is determined by GC compared with authentic standards. (In parenthesis, isolated yield obtained using slow addition (see ESI,† general procedure A) of the diazo compound **1**.)

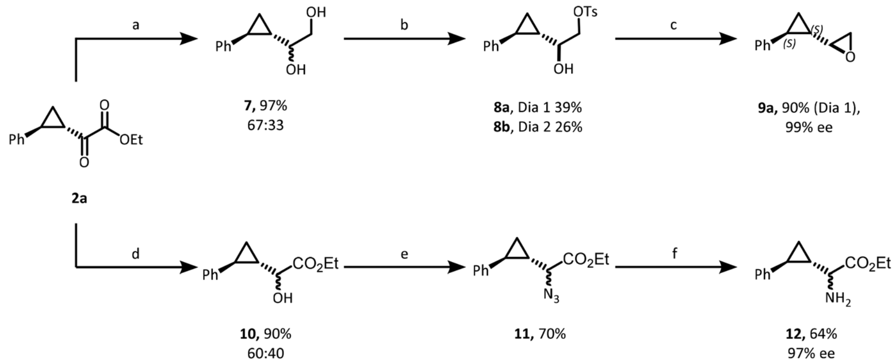
mixture after the addition of the diazo compound in the absence of the olefin (Fig. S3†). For synthetic purposes, a scaled-up reaction was performed and product **2a** was obtained in 61% isolated yield and an excellent enantiomeric excess (99% ee) (Table 2, entry 6). Interestingly, we observed that extended reaction times (>12–18 h) led to only traces of the cyclopropane product. Time course experiments revealed that optimal yields were achieved after 3 hours of reaction (see ESI for details, Fig. S1†), whereas a rapid decrease in yield was noted at longer reaction times, likely due to degradation of **2a** in the reaction mixture or the intracellular milieu.

Having defined optimal conditions for this reaction, its scope was further examined. As summarized in Scheme 2, several styrene derivatives could be transformed through this biocatalytic process with excellent enantioselectivity (>99% ee) being obtained in all cases. Different functionalities are tolerated at the *para* position of the aryl moiety, as exemplified by the *para*-methyl- and *para*-bromostyrenes affording the desired cyclopropane **2g** and **2e** [29] in good to high yields (45–80%) and with excellent ee. Electron-withdrawing CF_3 group significantly decreased the yield of cyclopropane (**2d:** 15% yield). Interestingly, *para*-methoxy cyclopropane **2b** was obtained in low yield, which can result from a combination of the steric effects and the formation of a side product deriving from the undesired Clock-Wilson rearrangement,[30] which was detected by GC-MS. A similar phenomenon was observed during the cyclopropanation of electron rich olefins such as 2-vinyl furan and 2-vinyl thiophene, whose transformation primarily led to the corresponding Clock-Wilson rearrangement products. Methyl substitution at the *meta*-, *ortho*- or α-position were all tolerated, yielding the desired cyclopropanes in 42%, 28% and 79% yield and 98%, 90% and 99% ee. As fluorinated compounds are of high interest in medicinal chemistry,[31] this biocatalytic approach was tested also with styrene derivatives bearing a fluorinated group (CF_3, CHF_2, CH_2F) at the α-position. Using the optimized conditions, the corresponding cyclopropanes **2j–l** were obtained in excellent de and ee, albeit in modest yields (5–23%). The 2-pyridyl cyclopropane **2m**, which is not accessible *via* known alternative methods using transition metal chiral catalyst, was also synthesized in good yield (66%) and excellent diastereoselectivity.[32] Non-styrenyl substrates such as vinylbenzoate, *N*-vinyl phtalimide, 3-phenylpropene and 4-phenylpropene were tested but no activity was observed.

With these enantiopure cyclopropanes in hand, we investigated their transformations into cyclobutenoates. Indeed, four-membered rings are present in the structure of multiple natural products[33–35] and biologically active compounds.[36–40] Cyclobutenes, in particular have been prepared *via* photochemical[41–43] or metal-catalyzed[44–46] [2 + 2]-cycloaddition, as well as from ring expansion reactions, starting from a large variety of cyclopropanes.[47–50] After establishing an efficient route to optically active α-cyclopropylpyruvates, we aimed at developing a sustainable metal-free approach to cyclobutenoates *via* a photochemical ring expansion of α-cyclopropyl diazo derivatives of these enzymatic products. Indeed, in analogy to the work reported by Tang[47] using transition metal carbene, the photoinduced formation of the free



Scheme 3 Stereoselectivity retention through photochemical ring expansion reaction. Reaction conditions: (a) $TsNHNH_2$, PhMe, reflux, 5 h; (b) DBU, DCM, 16 h; (c) MeCN, blue light 425 nm (Hepatochem), 3 h 30 min. Regioisomeric ratios were determined on ^1H NMR crude.



Scheme 4 Synthetic pathway for enantiopure alpha-cyclopropyl epoxide and non-natural amino-ester. Reaction conditions: (a) $LiAlH_4$, THF; 0 °C, 3 h; (b) TsCl, Bu_2SnO (2 eq.), DCM, r.t., 16 h; (c) nBuLi (1 eq.), −78 °C, 1 h; (d) $NaBH_4$, EtOH, −10 °C, 30 min; (e) PPH_3, DIAD, DPPA, pyridine, 0 °C to r.t., 16 h; (f) PPh_3, PhMe, 60 °C then H_2O, 6 h.

carbene might allow its rearrangement into the corresponding cyclobutene.

To this end, we chose racemic cyclopropane (±)-**2a** as model substrate for this transformation. Ketone **2a** was efficiently converted into the corresponding diazo derivative **3a** in 87% yield over two steps. Thanks to the UV spectra analysis (see ESI for details, Fig. S2†) of this diazo compound (λ_{abs} = 423 nm), we selected a 425 nm irradiation to perform a photoinduced ring-expansion reaction. The reaction parameters were evaluated and among the various solvents tested (see ESI for details, Table S2†), and optimal yield for **4** (64%) was obtained using diethyl ether as solvent. Note that **4** was isolated as a 50 : 50 mixture of regioisomers. Performing the photochemical rearrangement in acetonitrile led to an improved regioselectivity of 70 : 30 in favour of product **4a** (Scheme 3).[51] Using these optimized conditions, the reaction was then carried out the rearrangement with enantiopure cyclopropane **2a**. To our delight the expected cyclobutenoates **4a** and **4b** were obtained in identical global yield (46%) and regioisomeric ratio, along with a complete stereoretention of the absolute configuration for each regioisomer. Similarly, the sequence was then applied to the enantiopure cyclopropanes **2b** and **2c**, which were converted into cyclobutenoates **5** and **6** with identical efficiency (Scheme 3).

In addition to this unprecedented photochemical rearrangement of α-diazocyclopropanes, we examined further functionalization of the pyruvate unit to gain access to other functionalized cyclopropanes. First, the ketoester residue of **2a** was reduced in the presence of $LiAlH_4$ in high yield (97%), giving the diol **7** as a 2 : 1 mixture of diasteroisomers without any degradation of the cyclopropane ring. Then, **7** was converted into the α-cyclopropyl epoxide **9a**, *via* the selective activation of the primary hydroxyl group into a tosyl one, followed by epoxide ring formation under basic conditions. The product was obtained in 90% yield, without erosion of the optical purity (Scheme 4). On the other hand, the α-keto group of **2a** could be reduced selectively in the presence of $NaBH_4$ to give the α-hydroxyester **10** as a 60 : 40 mixture of diastereoisomers. This product was successfully used in a Mitsunobu and Staudinger reactions sequence to afford the corresponding amino-ester **12** as a nearly 1 : 1 mixture of diastereoisomers, both in an enantiopure form.

Conclusions

In summary, we have developed an efficient and stereoselective biocatalytic strategy for the synthesis of pyruvate containing cyclopropanes, using engineered myoglobin as the catalyst and ethyl α-diazopyruvate as carbene precursor. This method provides a scalable access to these enantioenriched cyclopropanes, which can be used as valuable building blocks to access different cyclopropane derivatives. Interestingly, the enzymatic cyclopropanation sequence was coupled to the photoinduced ring expansion to access optically active cyclobutenes in high enantiomeric excess and good yields.

Conflicts of interest

There are no conflicts to declare.

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References

1 R. Faust, Fascinating Natural and Artificial Cyclopropane Architectures, *Angew. Chem., Int. Ed.*, 2001, **40**, 2251–2253.

2 A. M. Adelekan, E. A. Prozesky, A. A. Hussein, L. D. Ureña, P. H. Van Rooyen, D. C. Liles, J. J. M. Meyer and B. Rodríguez, Bioactive Diterpenes and Other Constituents of Croton steenkampianus, *J. Nat. Prod.*, 2008, **71**, 1919–1922.

3 M.-L. Liu, Y.-H. Duan, Y.-L. Hou, C. Li, H. Gao, Y. Dai and X.-S. Yao, Nardoaristolones A and B, Two Terpenoids with Unusual Skeletons from Nardostachys chinensis Batal, *Org. Lett.*, 2013, **15**, 1000–1003.

4 E. D. Deeks, Olaparib: First Global Approval, *Drugs*, 2015, **75**, 231–240.

5 M. Cazzola, L. Calzetta, P. Rogliani and M. G. Matera, The discovery of roflumilast for the treatment of chronic obstructive pulmonary disease, *Expert Opin. Drug Discovery*, 2016, **11**, 733–744.

6 J. Gu, K. Rodriguez, Y. Kanda, S. Yang, M. Ociepa, H. Wilke, A. Abrishami, L. Joergensen, T. Skak-Nielsen, J. Chen and P. Baran, Convergent Total Synthesis of (+)-Calcipotriol: A Scalable, Modular Approach to Vitamin D Analogs, *Chemistry*, 2022, **119**, e2200814119.

7 R. D. Taylor, M. MacCoss and A. D. G. Lawson, Rings in Drugs, *J. Med. Chem.*, 2014, **57**, 5845–5859.

8 H. Wang, D. M. Guptill, A. Varela-Alvarez, D. G. Musaev and H. M. L. Davies, Rhodium-catalyzed Enantioselective Cyclopropanation of Electron-deficient Alkenes, *Chem. Sci.*, 2013, **4**, 2844–2850.

9 M. Bos, W. S. Huang, W. T. Poisson, X. Pannecoucke, A. B. Charette and P. Jubault, Catalytic Enantioselective Synthesis of Highly Functionalized Difluoromethylated Cyclopropanes, *Angew. Chem., Int. Ed.*, 2017, **56**, 13319–13323.

10 H. Inoue, N. Phan Thi Thanh, I. Fujisawa and S. Iwasa, Synthesis of Forms of a Chiral Ruthenium Complex Containing a Ru–Colefin(sp2) Bond and Their Application to Catalytic Asymmetric Cyclopropanation Reactions, *Org. Lett.*, 2020, **22**, 1475–1479.

11 J. Shearer, J. L. Castro, A. D. G. Lawson, M. MacCoss and R. D. Taylor, Rings in Clinical Trials and Drugs: Present and Future, *J. Med. Chem.*, 2022, **65**, 8699–8712.

12 M. Bordeaux, V. Tyagi and R. Fasan, Highly Diastereoselective and Enantioselective Olefin Cyclopropanation Using Engineered Myoglobin-Based Catalysts, *Angew. Chem., Int. Ed.*, 2015, **54**, 1744–1748.

13 X. Ren, A. L. Chandgude, D. M. Carminati, Z. Shen, S. Khare and R. Fasan, Highly Stereoselective and Enantiodivergent Synthesis of Cyclopropylphosphonates with Engineered Carbene Transferases, *Chem. Sci.*, 2022, **13**, 8550–8556.

14 D. M. Carminati, J. Decaens, S. Couve-Bonnaire, P. Jubault and R. Fasan, Biocatalytic Strategy for the Highly Stereoselective Synthesis of CHF_2-Containing Trisubstituted Cyclopropanes, *Angew. Chem., Int. Ed.*, 2021, **60**, 7072–7076.

15 R. Mao, D. J. Wackelin, C. S. Jamieson, T. Rogge, S. Gao, A. Das, D. M. Taylor, K. N. Houk and F. H. Arnold, Enantio- and Diastereoenriched Enzymatic Synthesis of 1,2,3-Polysubstituted Cyclopropanes from (Z/E)-Trisubstituted Enol Acetates, *J. Am. Chem. Soc.*, 2023, **145**, 16176–16185.

16 P. Bajaj, G. Sreenilayam, V. Tyagi and R. Fasan, Gram-Scale Synthesis of Chiral Cyclopropane-Containing Drugs and Drug Precursors with Engineered Myoglobin Catalysts Featuring Complementary Stereoselectivity, *Angew. Chem., Int. Ed.*, 2016, **55**, 16110–16114.

17 K. E. Hernandez, H. Renata, R. D. Lewis, S. B. J. Kan, C. Zhang, J. Forte, D. Rozzell, J. A. McIntosh and F. H. Arnold, Highly Stereoselective Biocatalytic Synthesis of Key Cyclopropane Intermediate to Ticagrelor, *ACS Catal.*, 2016, **6**, 7810–7813.

18 H. M. Key, P. Dydio, Z. Liu, J. Y.-E. Rha, A. Nazarenko, V. Seyedkazemi, D. S. Clark and J. F. Hartwig, Beyond Iron: Iridium-Containing P450 Enzymes for Selective Cyclopropanations of Structurally Diverse Alkenes, *ACS Cent. Sci.*, 2017, **3**, 302–308.

19 L. Schaus, A. Das, A. M. Knight, G. Jimenez-Osés, K. N. Houk, M. Garcia-Borràs, F. H. Arnold and X. Huang, Protoglobin-Catalyzed Formation of cis-Trifluoromethyl-Substituted Cyclopropanes by Carbene Transfer, *Angew. Chem., Int. Ed.*, 2023, **62**, e202208936.

20 A. Tinoco, V. Steck, V. Tyagi and R. Fasan, Highly Diastereo- and Enantioselective Synthesis of Trifluoromethyl-Substituted Cyclopropanes via Myoglobin-Catalyzed Transfer of Trifluoromethylcarbene, *J. Am. Chem. Soc.*, 2017, **139**, 5293–5296.

21 N. J. Porter, E. Danelius, T. Gonen and F. H. Arnold, Biocatalytic Carbene Transfer Using Diazirines, *J. Am. Chem. Soc.*, 2022, **144**, 8892–8896.

22 A. L. Chandgude and R. Fasan, Highly Diastereo- and Enantioselective Synthesis of Nitrile-Substituted Cyclopropanes by Myoglobin-Mediated Carbene Transfer Catalysis, *Angew. Chem., Int. Ed.*, 2018, **57**, 15852–15856.

23 D. Nam, V. Steck, R. J. Potenzino and R. Fasan, A Diverse Library of Chiral Cyclopropane Scaffolds via Chemoenzymatic Assembly and Diversification of Cyclopropyl Ketones, *J. Am. Chem. Soc.*, 2021, **143**, 2221–2231.

24 B. J. Wittmann, A. M. Knight, J. L. Hofstra, S. E. Reisman, S. B. Jennifer Kan and F. H. Arnold, Diversity-Oriented Enzymatic Synthesis of Cyclopropane Building Blocks, *ACS Catal.*, 2020, **10**, 7112–7116.

25 A. Pons, L. Delion, T. Poisson, A. B. Charette and P. Jubault, Asymmetric Synthesis of Fluoro, Fluoromethyl, Difluoro-methyl, and Trifluoromethylcyclopropanes, *Acc. Chem. Res.*, 2021, **54**, 2969–2990; W.-S. Huang, C. Schlinquer, T. Poisson, X. Pannecoucke, A. B. Charette and P. Jubault, General Catalytic Enantioselective Access to Monohalomethyl and Trifluoromethyl Cyclopropanes, *Chem. – Eur. J.*, 2018, **24**, 10339–10343; C. Schlinquer, W.-S. Huang, L. Chen, X. Pannecoucke, A. B. Charette and P. Jubault, Rhodium Catalysed Enantioselective Synthesis of Mono-(halo)-methyl-cyclopropanes, *Org. Biomol. Chem.*, 2019, **17**, 472–476; Y. Hasegawa, T. Cantin, J. Decaens, S. Couve-Bonnaire, A. B. Charette, T. Poisson and P. Jubault, Catalytic Asymmetric Syntheses of Alkylidenecyclopropanes from Allenoates with Donor-Acceptor and Diacceptor Diazo Reagents, *Chem. – Eur. J.*, 2022, **28**, e202201438; L. Chen, T. M. Le, J.-P. Bouillon, T. Poisson and P. Jubault, Catalytic Enantioselective Synthesis of Functionalized Cyclopropanes from α-Substituted Allyl Sulfones with Donor-Acceptor or Diacceptor Diazo Reagents, *Chem. – Eur. J.*, 2022, **28**, e202201254.

26 L.-J. Liu, M. Dai, L. Song, H. Y. Chen, M. Bian, Y.-N. Gao and Z.-J. Liu, Water-assisted, Highly-selective and Rapid Synthesis of Cyclopropane Derivatives by a [2 + 1] Annulation Reaction, *ChemistrySelect*, 2022, **7**, e202203870.

27 A. de Meijere, V. Bagutski, F. Zeuner, U. K. Fischer, V. Rheinberger and N. Moszner, Synthesis and Radical Polymerization of Various 2-Cyclopropylacrylates, *Eur. J. Org. Chem.*, 2004, 3669–3678.

28 D. Nam, J.-P. Bacik, R. Khade, M. C. Aguileraa, Y. Wei, M. Neidig, Y. Zhang, N. Ando and R. Fasan, Mechanistic Manifold in a Hemoprotein-Catalyzed Cyclopropanation Reaction with Diazoketone, *Nat. Commun.*, 2023, **14**, 7985.

29 Deposition Number 2305160 (for **2e**) contain the supplementary crystallographic data for this paper.†

30 A. Ortega, R. Manzano, U. Uria, L. Carrillo, E. Reyes, T. Tejero, P. Merino and J. L. Vicario, Catalytic Enantioselective Cloke–Wilson Rearrangement, *Angew. Chem., Int. Ed.*, 2018, **57**, 8225–8229.

31 See these reviews for more information: (*a*) M. Inoue, Y. Sumii and N. Shibata, Contribution of Organofluorine Compounds to Pharmaceuticals, *ACS Omega*, 2020, **5**, 10633–10640; (*b*) B. M. Johnson, Y.-Z. Shu, X. Zhuo and N. A. Meanwell, Metabolic and Pharmaceutical Aspects of Fluorinated Compounds, *J. Med. Chem.*, 2020, **63**, 6315–6386.

32 We were unable to synthesize racemic **2m**, as a consequence ee was not measured.

33 M. W. Bernart, Y. Kashman, M. Tischler, J. H. Cardellina II and M. R. Boyd, Bershacolone, an Unprecedented Diterpene Cyclobutene from Maprounea africana, *Tetrahedron Lett.*, 1993, **34**, 4461–4464.

34 P. Fokialakis, P. Magiatis, A. Terzis, F. Tillequin and A.-L. Skaltsounis, Cyclomegistine, The First Alkaloid with the New Cyclobuta[b]quinoline Ring System from Sarcomelicope Megistophylla, *Tetrahedron Lett.*, 2001, **42**, 5323–5325; T. Misonou, J. Saitoh, S. Oshiba, Y. Tokitomo, M. Maegawa, Y. Inoue, H. Hori and T. Sakurai, UV-Absorbing Substance in the Red Alga Porphyra yezoensis (Bangiales, Rhodophyta) Block Thymine Photodimer Production, *Mar. Biotechnol.*, 2003, **5**, 194–200.

35 Y. Endo, T. Ohta and S. Nozoe, Neofavelanone, A Novel Tetracyclic Cyclobutene Derivative from the Brazilian Plant, Cnidoscolus Phyllacanthus, *Tetrahedron Lett.*, 1992, **33**, 353–356.

36 J. Yang, C. Yuwu, F. Xiaozhang, Y. Dequan and L. Xiaotian, Chemical Constituents of Armillaria mellea Mycelium I. Isolation and Characterization of Armillarin and Armillaridin, *Planta Med.*, 1984, **50**, 288–290.

37 M. T. Hovey, D. T. Cohen, D. M. Walden, P. H.-Y. Cheong and K. A. Scheidt, A Carbene Catalysis Strategy for the Synthesis of Protoilludane Natural Products, *Angew. Chem., Int. Ed.*, 2017, **56**, 9864–9867.

38 J. Li, K. Gao, M. Bian and H. Ding, Recent Advances in the Total Synthesis of Cyclobutane-containing Natural Products, *Org. Chem. Front.*, 2020, **7**, 136–154.

39 M. R. Kolk, M. A. C. H. Janssen, F. P. J. T. Rutjes and D. Blanco-Ania, Cyclobutanes in Small–Molecule Drug Candidates, *ChemMedChem*, 2022, **17**, e202200020.

40 T. Bieber, E. L. Simpson, J. I. Silverberg, D. Thaçi, C. Paul, A. E. Pink, Y. Kataoka, C.-Y. Chu, M. DiBonaventura, R. Rojo, J. Antinew, I. Ionita, R. Sinclair, S. Forman, J. Zdybski, P. Biswas, B. Malhotra, F. Zhang and H. Valdez, Abrocitinib versus Placebo or Dupilumab for Atopic Dermatitis, *Engl. J. Med.*, 2021, **384**, 1101–1112.

41 J. D. White, M. A. Avery and J. P. Carter, Synthesis of (+-)-Lineatin, an Aggregation Pheromone of Trypodendron Lineatum, *J. Am. Chem. Soc.*, 1982, **104**, 5486–5489.

42 Y. Ha, Y. Lee, Y. Kwak, A. Mishra, E. Yu, B. Ryou and C.-M. Park, Alkyne-Alkene [2 + 2] Cycloaddition based on Visible Light Photocatalysis, *Nat. Commun.*, 2020, **11**, 2509.

43 M. M. Maturi and T. Bach, Alkyne–Alkene [2 + 2] Cycloaddition based on Visible Light Photocatalysis, *Angew. Chem., Int. Ed.*, 2014, **53**, 7661–7664.

44 M. M. Parsutkar, V. V. Pagar and T. V. RajanBabu, Catalytic Enantioselective Synthesis of Cyclobutenes from Alkynes and Alkenyl Derivatives, *J. Am. Chem. Soc.*, 2019, **141**, 15367–15377.

45 K. Sakai, T. Kochi and F. Kakiuchi, Rhodium-Catalyzed Intermolecular [2 + 2] Cycloaddition of Terminal Alkynes with Electron-Deficient Alkenes, *Org. Lett.*, 2013, **15**, 1024–1027.

46 M. E. Farmer, L. E. Ehehalt, T. P. Pabst, M. T. Tudge and P. J. Chirik, Well-Defined Cationic Cobalt(I) Precatalyst for Olefin-Alkyne [2 + 2] Cycloaddition and Olefin-Diene Hydrovinylation Reactions: Experimental Evidence for Metallacycle Intermediates, *Organometallics*, 2021, **40**, 3599–3607.

47 H. Xu, W. Zhang, D. Shu, J. B. Werness and W. Tang, Synthesis of Cyclobutenes by Highly Selective Transition-Metal-Catalyzed Ring Expansion of Cyclopropanes, *Angew. Chem., Int. Ed.*, 2008, **47**, 8933–8936.

48 A. Fürstner and C. Aïssa, PtCl2-Catalyzed Rearrangement of Methylenecyclopropanes, *J. Am. Chem. Soc.*, 2006, **128**, 6306–6307.

49 G.-Q. Tian, Z.-L. Yuan, Z.-B. Zhu and M. Shi, Palladium(II)-Catalyzed Ring Enlargement of 2-(Arylmethylene) cyclopropylcarbinols: Strong Effect of Substituent Electronic Nature on the Reaction Pathway, *Chem. Commun.*, 2008, **23**, 2668–2670.

50 F.-G. Zhang and I. Marek, Brook Rearrangement as Trigger for Carbene Generation: Synthesis of Stereodefined and Fully Substituted Cyclobutenes, *J. Am. Chem. Soc.*, 2017, **139**, 8364–8370.

51 Following the procedure reported by Tang (ref. 47) with substrate **2a**, we observed using Rh2(OAc)4 a 12/88 mixture of regioisomers (**4a**/**4b**) and 74% NMR yield.