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Biocatalytic strategy for the highly stereoselective synthesis of CHF_2-containing trisubstituted cyclopropanes

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Abstract: *The difluoromethyl (CHF_2) group has attracted significant attention in drug discovery and development efforts, owing to its ability to serve as fluorinated bioisostere of methyl, hydroxyl, and thiol groups. Herein, we report an efficient biocatalytic method for the highly diastereo- and enantioselective synthesis of CHF_2-containing trisubstituted cyclopropanes. Using engineered myoglobin catalysts, a broad range of α-difluoromethyl alkenes are cyclopropanated in the presence of ethyl diazoacetate to give CHF_2-containing cyclopropanes in high yield (up to >99%, up to 3,000 TON) and with excellent stereoselectivity (up to >99% de and ee). By means of an enantiodivergent myoglobin variant, the opposite enantiomer of the cyclopropane product was also obtained. This methodology represents a powerful strategy for the stereoselective synthesis of high-value fluorinated building blocks for medicinal chemistry, as exemplified through the formal total synthesis of a CHF_2 isostere of a TRPV1 inhibitor drug.*

Due to their peculiar conformational properties, cyclopropane rings contribute key structural motifs and pharmacophores in many natural and synthetic bioactive molecules.[1] Accordingly, there has been a significant interest in developing methodologies for the synthesis of functionalized cyclopropanes.[2] Along with cyclopropanes, fluorinated substituents have been extensively exploited in medicinal chemistry toward the discovery and development of new drugs.[3] It is indeed well recognized that the introduction of fluorinated substituents can significantly affect the pKa, lipophilicity, cell permeability, and/or metabolic stability of a bioactive molecule, often leading to significant improvements in its pharmacological and/or pharmacokinetic properties.[3]

Among fluorinated substituents, the CHF_2 group has recently attracted considerable attention due to its value in serving as bioisostere for the methyl group,[4] which is widely exploited for tuning the pharmacological properties of bioactive molecules.[5] In addition, owing to its electronic and hydrogen bond donor properties, the CHF_2 group has also been exploited as a functional mimic of hydroxyl or thiol groups.[6] For example, a CHF_2 moiety was employed to mimic a cysteine thiol group in inhibitors of the hepatitis C virus NS3 protease, resulting in analogs with enhanced potency.[7]

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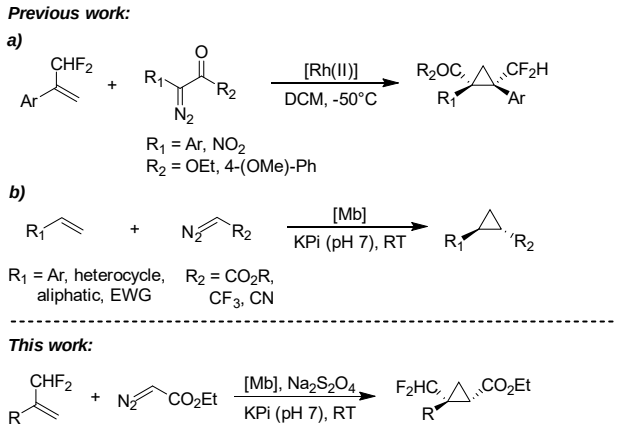
Despite the well recognized utility of cyclopropanes and CHF_2 groups in medicinal chemistry, the asymmetric synthesis of difluoromethyl-containing cyclopropanes has remained largely underdeveloped.[8] To the best of our knowledge, the only example of an asymmetric synthesis of CHF_2-containing cyclopropanes with broad substrate scope involves rhodium-catalyzed cyclopropanations in the presence of donor-acceptor or acceptor-acceptor diazo reagents (**Scheme 1a**).[9a] Notably, no chemo- or biocatalytic methods have been reported for the asymmetric cyclopropanation of CHF_2-containing olefins with readily available acceptor-only diazo reagents.

Over the past few years, heme-containing proteins[10] and artificial metalloenzymes[11] have emerged as promising systems for catalyzing 'abiological' cyclopropanation reactions.[12] In particular, our group has previously reported the high activity and stereoselectivity of engineered myoglobins (Mb) toward promoting the cyclopropanation of aryl-substituted olefins with ethyl diazoacetate.[10b, 10c] More recently, the scope of these biocatalysts and myoglobin-catalyzed reactions was expanded to include other diazo reagents carrying α-electron withdrawing groups (**Scheme 1b**) as well as other olefins, producing enantioenriched cyclopropanes amenable to further diversification.[13] Despite this progress, fluorinated olefins have remained elusive substrates for biocatalytic cyclopropanations. Herein, we report the first example of a (bio)catalytic method for the stereoselective synthesis of difluoromethyl-functionalized cyclopropanes, which was made possible through the cyclopropanation of electron poor α-difluoromethyl alkenes by means of engineered myoglobin catalysts (**Scheme 1**).



Scheme 1. Biocatalytic cyclopropanation of α-difluoromethylated alkenes.

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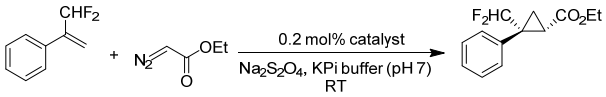
Table 1. Myoglobin-catalyzed cyclopropanation of α-difluoromethyl-styrene (**2a**) in the presence of ethyl 2-diazoacetate (EDA, **1**).[a]



2a **1** **3a**

Entry	Protein	Yield (GC)	TON	*d.e.*	*e.e.*
1	Mb	37%	185	79%	5%
2	Mb(H64V)	20%	100	75%	4%
3	Mb(V68A)	33%	165	97%	91%
4	Mb(H64G,V68A)	38%	190	99%	90%
5	Mb(H64A,V68A)	26%	130	99%	98%
6	Mb(H64V,V68A)	97%	485	97%	>99%
7	Mb(H64V,V68G)	44%	220	71%	92%
8	Mb(H64V,V68F)	21%	105	76%	-4%
9	Mb(H64V,V68A)[b]	30%	3,000	96%	98%
10	Mb(H64V,V68A)[c]	87%[d]	435	>99%	>99%
11	Mb(H64V,V68A)[e]	67%	335	96%	>99%
12	Mb(L29T,H64V,V68F)	58%	290	90%	-87%

[a] Reaction conditions: 20 μM purified Mb variant, 10 mM styrene (**2a**), 20 mM EDA (**1**), 10 mM $Na_2S_2O_4$, in phosphate buffer (KPi 50 mM, pH 7), r.t., 16 hours. Product yield, diastereomeric and enantiomeric excess were determined by chiral GC-FID analysis. [b] Using 1 μM Mb(H64V,V68A). [c] 70 mg of **2a** in 45-mL scale. [d] Isolated yield. [e] Using whole cells (OD_{600} = 10).

We started this work by testing the catalytic activity of wild-type sperm whale myoglobin (Mb) toward catalyzing the formation of cyclopropane **3a** starting from α-difluoromethyl styrene (**2a**) in the presence of ethyl diazoacetate (EDA, **1**) as carbene source (**Table 1**, entry 1). While showing promising activity (37% yield), wild-type Mb produced **3a** with only moderate diastereoselectivity (79% *de*) and very poor enantioselectivity (5% *ee*). Given the previously established influence of these residues on the activity and stereoselectivity of myoglobin-catalyzed cyclopropanation reactions,[10b, 10c, 10h, 10i] we decided to screen a panel of Mb variants with varying steric demands at the level of the distal His64 residue (→Gly/Ala/Val) and Val68 (→Gly/Ala/Phe) (**Table 1**), which is located in close proximity to the heme center (**SI Figure S1**). Among these variants, Mb(H64V,V68A) and Mb(H64A,V68A) were found to exhibit significantly improved diastereo- and enantioselectivity (97 to >99% *de* and *ee*) compared to the wild-type protein (**Table 1**, entries 5-6). In addition, Mb(H64V,V68A) offered also improved activity, resulting in the nearly quantitative conversion (97%) of the fluorinated olefin to the desired cyclopropanation product **3a**. Comparison of the results for the single variants Mb(H64V) and Mb(V68A) (**Table 1**, entries 2-3) and other double mutant variants, the two mutations in Mb(H64V,V68A) appear to have a clear synergistic effect in improving the performance of the biocatalyst, with the Val68Ala mutation mainly driving the improvement in stereoinduction and the His64Val mutation being crucial for improving activity and further refining its stereoselectivity (e.g., 91 → >99% *ee*). At position 68, a further reduction in steric bulk (e.g., Ala→Gly) reduces both diastereo- and enantioselectivity (entry 7 *vs.* 6), while the introduction of a bulkier residue (Phe) produces a variant with parent-like properties and a slight preference for the opposite enantiomer (-4% *ee*; entry 8).

On the basis of these results, Mb(H64V,V68A) was selected as the most promising biocatalyst for the target cyclopropanation reaction. Further investigations showed that Mb(H64V,V68A) catalyzes the formation of **3a** with an initial rate of 520 TON/min and the reaction reaches >75% completion in less than 5 min (**SI Figure S2**). While fast, this rate is 2-fold lower than the Mb(H64V,V68A)-catalyzed cyclopropanation of styrene with EDA (initial rate of 1000 TON/min),[10b] possibly reflecting the lower reactivity of the CHF_2-containing substrate due to both electronic and steric effects. Under catalyst-limited condition, Mb(H64V,V68A) was determined to support up to 3,000 turnovers (TON) (**Table 1**, entry 9). Furthermore, the reaction could be readily scaled up to afford 95 mg of enantiopure **3a** (>99% *de* and *ee*) in high isolated yield (87%) (**Table 1**, entry 10).

We also tested the possibility to carry out this transformation in whole cells, which is of practical relevance for industrial processes.[14] Under these conditions, the Mb(H64V,V68A)-catalyzed reaction *in cellulo* successfully produced the desired cyclopropane **3a** while maintaining high diastereoselectivity and excellent enantioselectivity (96% *de* and >99% *ee*; **Table 1**, entry 11), albeit with reduced yield compared to the reaction with purified protein (67% *vs.* 97%). Interestingly, these experiments showed a bell-shape dependence of yield on cell density, with an optimum at relatively low cell density (OD_{600} = 10) (**SI Table S1**). Counterintuitively, a reduction in yield was observed at higher cell densities (67%→45-48%), which may arise from partial sequestration of the fluorinated substrate by the cell membrane or other cellular components.

To explore the generality of this biocatalytic method, several α-difluoromethylated styrenes bearing different electron-donating and withdrawing substituents at the *ortho*-, *meta*- and *para*-position of the phenyl ring were tested in the Mb(H64V,V68A)-catalyzed cyclopropanation with EDA (**Scheme 2**). Despite a general reduction in yield (35-82% *vs.* 98%), substituents in *meta*- and *ortho*- positions were well tolerated by the Mb(H64V,V68A) catalyst, as evinced from the synthesis of **3b**-**3d** with high to excellent diastereo- and enantioselectivity (95-96% *de* and 89-99% *ee*). A similar trend applies to *para*-substituted styrenes with small to medium-sized substituents at the *para* position such as fluoro (**3i**), methyl (**3e**), chloro (**3j**), and bromo (**3k**) groups, all of which underwent Mb(H64V,V68A)-catalyzed transformation to give the corresponding CHF_2-substituted cyclopropanes with high stereoselectivity (93-96% *de*, 82-94% *ee*) along with high yields (93-96%; **Scheme 2**). In contrast, the presence of bulkier substituents at the *para* position such as methoxy (**3g**), isopropyl (**3f**) and dimethylamino (**3h**) groups were accompanied by a noticeable reduction in yield and, for the latter two, also in enantioselectivity (21-25% *ee*). Interestingly, this structure-reactivity trend diverges significantly from that observed for the Mb(H64V,V68A)-catalyzed cyclopropanation of styrenes with EDA and other acceptor-only diazo reagents,[10c] thus indicating an important effect of the CHF_2 group on the substrate interaction with the biocatalyst. Nevertheless, structural characterization of **3k** by X-ray crystallography (**Scheme 2**; **SI Figure S4**) revealed a (1*R*,2*S*) absolute configuration of the cyclopropane product, which mirrors the (1*S*,2*S*)-stereoselectivity of Mb(H64V,V68A) with styrene and EDA.[10b, 10c] Based on this information and the previously reported stereochemical model for this reaction, we posited that enlargement of the active site cavity at the level of

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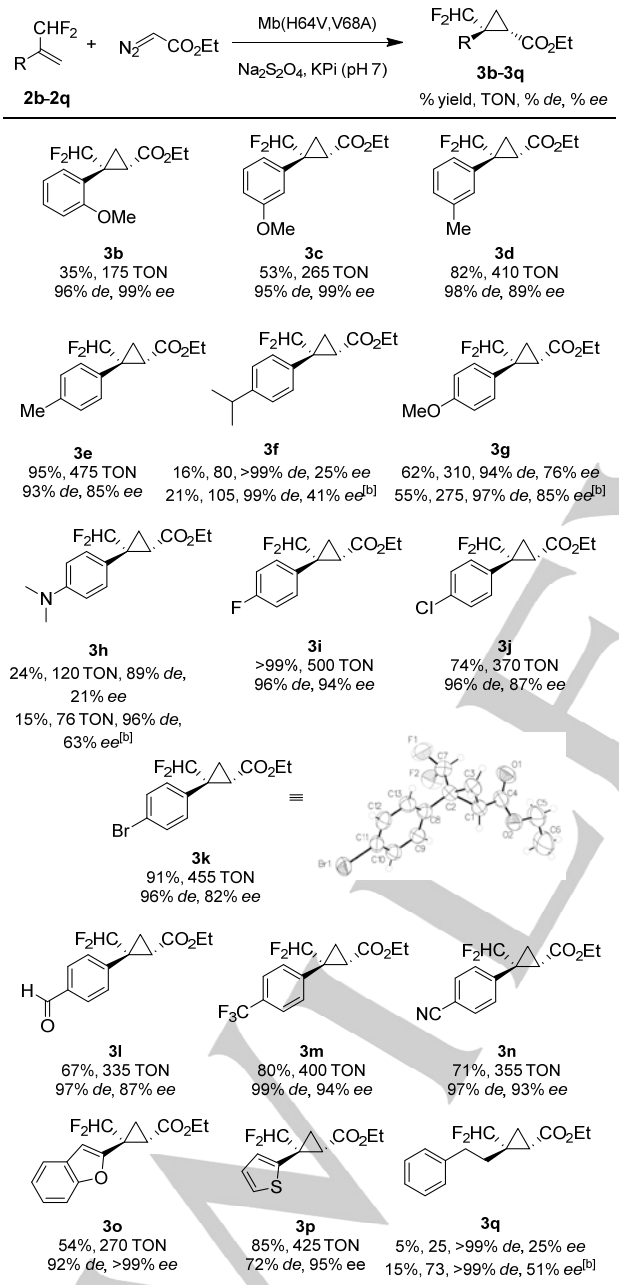
His64, such as in Mb(H64G,V68A), should better accommodate the bulkier *para*-substituted styrenes. Gratifyingly, the Mb(H64G,V68A) variant proved indeed to be a superior catalyst for the synthesis of **3f-3h**, offering higher diastereo- and enantioselectivity for these transformations (96-99% *de*, 41-85% *ee*).

Scheme 2. Substrate scope of Mb(H64V,V68A)-catalyzed cyclopropanation of α-difluoromethyl-olefins. [a]



[a] Reaction conditions: 20 μM Mb(H64V,V68A), 10 mM alkene, 20 mM EDA (**1**), 10 mM $Na_2S_2O_4$ in KPi 50 mM (pH 7), r.t., 16 hours. Yield, diastereomeric and enantiomeric excess determined by chiral GC-FID analysis using 1,3-benzodioxole as internal standard. [b] Using Mb(H64G,V68A) as catalyst. CCDC entry for **3k**: 1893087

The high activity of Mb(H64V,V68A) in the cyclopropanation of p-(fluoro)-α-CHF_2-fluorostyrene (**2i**) encouraged us to test additional electron-deficient alkenes, which are challenging substrates for carbene transfer catalysts due to the typically electrophilic character of their metallo-carbene intermediate.[11h, 15] Notably, electrondeficient α-difluoromethyl-styrenes carrying CF_3-, formyl-, or a cyano substituent in the ring could efficiently converted into the corresponding cyclopropanation products **3l**, **3m**, and **3n**, respectively, in good yields (up to 80%) and excellent stereoselectivity (up to 99% *de* and 96% *ee*). Moreover, the absence of side reactions with 4-(formyl)–α-CHF_2-styrene demonstrated the chemoselectivity and compatibility of the biocatalytic method with a substrate containing a reactive aldehyde group.

Substrate scope was then extended to aromatic O- and S-containing heterocycles which are widely used in medicinal chemistry.[3e] Specifically, benzofuran- and thiophene-containing substrates were converted into product **3o** and **3p**, respectively, with high diastereo- and enantioselectivity (72-92% *de,* 95 to >99% *ee*). Of note, Mb(H64V,V68A) also retained high activity toward **2o** (54% yield) despite the relatively large size of this substrate. An unactivated alkene such as 4-phenyl-2-(difluoromethyl) butene (**2q**) was also tested. While Mb(H64V,V68A) was able to afford the desired cyclopropane product **3q** in low yield (**Scheme 2**), the Mb(H64G,V68A) variant proved to be a superior biocatalyst for this transformation, offering higher yield (15% *vs.* 5%) along with higher enantioselectivity (51% *vs.* 25% *ee*) and excellent diastereoselectivity (>99% *de*), thus demonstrating the utility of these biocatalysts also in the context of unactivated olefins.

Having established the generality of Mb(H64V,V68A) for the synthesis of *cis*-(*1R*,*2S*)-difluoromethylated cyclopropanes, we investigated the possibility to obtain an enantiodivergent biocatalyst for this reaction. As shown for Mb(H64V,V68F) in **Table 1**, the substitution of Val68 with Phe resulted in a modest but detectable inversion of enantioselectivity toward formation of the (*1S*,*2R*)-configured cyclopropane (**Table 1**, entry 8). Based on this result, a panel of V68F-containing engineered myoglobins were tested and found to exhibit enhanced (*1S*,*2R*)-enantioselectivity (**SI Table S2**). Among them, Mb(L29T,H64V,V68F) was able to produce the desired (*1S*,*2R*)-enantiomer of **3a** in good yield (58%) and high enantiomeric excess (90% *de* and -87% *ee*) (**Table 1**, entry 12), thereby demonstrating the feasibility of achieving enantiodivergent selectivity in this myoglobin-catalyzed reaction.

To further explore the scope of this methodology in the context of fluoromethylated olefins, Mb(H64V,V68A) was challenged with α-fluoromethyl-styrene (**4**) and α-(trifluoromethyl)-styrene (**6**). Notably, both substrates were efficiently converted into the desired CH_2F- and CF_3-substituted cyclopropanes **5** and **7**, respectively, in high yield and excellent diastereo- and enantioselectivity (96-99% *de* and 98 to >99% *ee*; **Scheme 3a-b**), which further highlighted the broad substrate profile of this enzyme.

Finally, we tested the utility of the present biocatalytic approach toward the generation of a difluoromethyl bioisostere of

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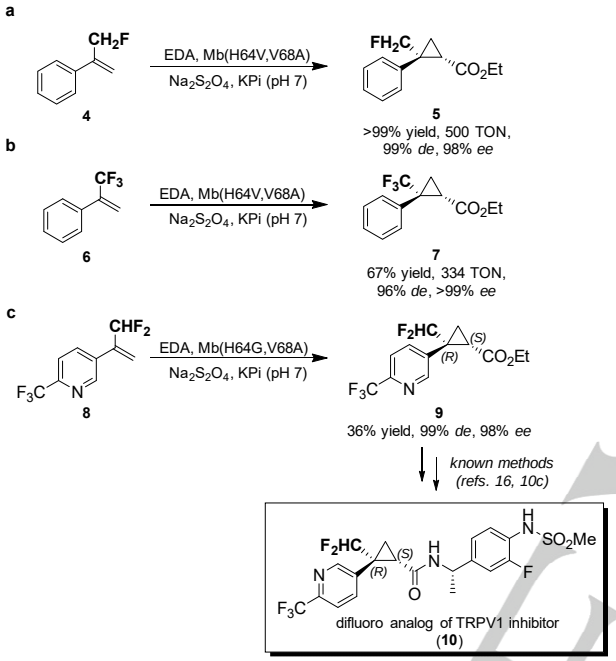
a drug molecule. To this end, we targeted the synthesis of **10** (**Scheme 3c**), which corresponds to an analog of a TRPV1 inhibitor drug candidate developed by Pfizer[16] in which the methyl group is replaced by a CHF_2 group. Using Mb(H64G,V68A) as the catalyst, α-difluoromethyl-substituted olefin **8** could be successfully cyclopropanated in a semi-preparative scale reaction to afford **9** (50 mg, 36%) with high stereoselectivity (99% *de,* 98% *ee*). This key intermediate can be then converted into the final product **10** in only two steps using established routes.[10c, 16]



Scheme 3. Biocatalytic cyclopropanation of α-CH_2F- and α-CF_3-styrene and formal synthesis of a CHF_2 isostere of a TRPV1 inhibitor drug candidate.

In summary, we reported the first example of a biocatalytic system for the asymmetric cyclopropanation of difluoromethylated alkenes. Using two engineered myoglobins, Mb(H64V,V68A) and Mb(H64G,V68A), a broad panel of trisubstituted difluoromethylcyclopropanes were synthesized with good efficiency (up to 99% yield) and high to excellent stereoselectivity (up to >99% *de* and *ee*) using ethyl 2-diazoacetate as carbene donor. The scope of these biocatalysts extends to include the stereoselective cyclopropanation of unactivated olefins as well as mono- and trifluoro-methylated olefins, as exemplified through the successful synthesis of enantioenriched **3q**, **5** and **7**, respectively. The possibility of achieving enantiodivergent selectivity in this transformation was also demonstrated, with a stereocomplementary myoglobin variant showing up to -87% *ee* for this transformation. Finally, this strategy could be readily applied to enable the highly stereoselective synthesis of a key synthon for the chemoenzymatic synthesis of a difluoromethyl isostere of a drug candidate. This methodology is expected to create new opportunities for the biocatalytic asymmetric synthesis of high-value fluorinated building blocks for organic and medicinal chemistry.

Acknowledgements

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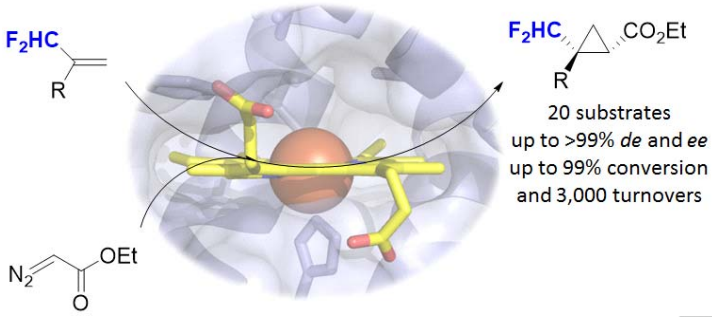

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Biocatalytic strategy for the highly stereoselective synthesis of CHF_2-containing trisubstituted cyclopropanes

CHieF$_2$ cyclopropanes: A biocatalytic method was developed for the highly diastereo- and enantioselective synthesis of CHF_2-substituted cyclopropanes via myoglobin-catalyzed carbene transfer. These biocatalysts offer broad substrate scope, enantiodivergent selectivity and could be applied to produce a difluoromethyl bioisostere of a drug candidate.