

Highly Diastereo- and Enantioselective Synthesis of Trifluoromethyl-Substituted Cyclopropanes via Myoglobin-Catalyzed Transfer of Trifluoromethylcarbene

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S Supporting Information

ABSTRACT: We report an efficient strategy for the asymmetric synthesis of trifluoromethyl-substituted cyclopropanes by means of myoglobin-catalyzed olefin cyclopropanation reactions in the presence of 2-diazo-1,1,1-trifluoroethane (CF₃CHN₂) as the carbene donor. These transformations were realized using a two-compartment setup in which *ex situ* generated gaseous CF₃CHN₂ is processed by engineered myoglobin catalysts expressed in bacterial cells. This approach was successfully applied to afford a variety of *trans*-1-trifluoromethyl-2-arylcyclopropanes in high yields (61–99%) and excellent diastereo- and enantioselectivity (97–99% *de* and *ee*). Furthermore, mirror-image forms of these products could be obtained using myoglobin variants featuring stereodivergent selectivity. These reactions provide a convenient and effective biocatalytic route to the stereoselective synthesis of key fluorinated building blocks of high value for medicinal chemistry and drug discovery. This work expands the range of carbene-mediated transformations accessible via metalloprotein catalysts and introduces a potentially general strategy for exploiting gaseous and/or hard-to-handle carbene donor reagents in biocatalytic carbene transfer reactions.

Trifluoromethyl-substituted cyclopropanes constitute attractive synthons in medicinal chemistry as they combine the conformational rigidity of three-membered rings with the unique and often highly beneficial features of fluorinated substituents.¹ Reflecting this notion, these structural motifs have represented key building blocks for the design and development of several bioactive molecules and investigational drugs.^{1a} Various methods have been investigated to afford these structures, most of which involve starting materials that already incorporate the trifluoromethyl group.² A convenient and most direct strategy to access this class of compounds is through the addition of trifluoromethylcarbene to an olefin. Early studies in this area have entailed the use of trifluoromethylcarbene generated by photolytic decomposition of 2-diazo-1,1,1-trifluoroethane (CF₃CHN₂), resulting in a mixture of products.³ More synthetically useful strategies for olefin trifluoromethylcyclopropanation with this reagent were made available only recently using transition metal catalysis.⁴ To date, however, only a few studies have addressed the problem of developing enantioselective variants of these transformations.^{4a,5} In a first report, Simmoneaux and co-workers described the use of chiral metalloporphyrins for the asymmetric cyclopropanation of

styrenes in the presence of 2-diazo-1,1,1-trifluoroethane, but only moderate enantioselectivity (30–79% *ee*) was observed using this system.^{4a} Higher selectivity was more recently achieved in similar reactions using Co(III)-salen complexes by Carreira and co-workers.⁵ Despite these advances, the development of highly stereoselective strategies for olefin cyclopropanation with 2-diazo-1,1,1-trifluoroethane as the carbene donor remains an outstanding challenge. Here, we report a simple and efficient biocatalytic approach for promoting these transformations that hinges upon the use of engineered myoglobin variants in combination with a compartmentalized reaction setup. This strategy could be applied to the conversion of a broad range of vinylarene substrates, providing access to trifluoromethyl-substituted cyclopropanes with high diastereo- and enantioselectivity as well as stereo-complementary selectivity.

Our group has recently reported the development of engineered myoglobin catalysts for promoting a variety of carbene transfer reactions,⁶ including olefin cyclopropanation.⁷ These transformations are believed to be mediated by an electrophilic heme-bound carbenoid species generated upon reaction of a diazo compound with the heme cofactor embedded in the protein.^{7a} This species can react with a number of nucleophiles (olefins, amines, thiols, phosphines) to form new C–C and C–heteroatom bonds, with the protein active site providing an asymmetric environment to affect the stereoselectivity of the carbene transfer process.^{6,7} In addition to myoglobin (Mb), other biocatalysts⁸ have been investigated for promoting carbene transfer reactions, but the scope of biocatalytic carbene transfer reactions has so far been restricted to α -diazoacetates as carbene donor reagents. Given the high reactivity of myoglobin variants toward the acceptor-only carbene donor reagent ethyl diazoacetate (EDA, **1**), we envisioned that 2-diazo-1,1,1-trifluoroethane (DTE, **2**) could provide a potentially viable carbene precursor for myoglobin-catalyzed cyclopropanations. A well-known challenge associated with the use of DTE in carbene transfer reactions, however, is the difficulty in handling this reagent due to its high toxicity and volatility. *In situ* generation of DTE via diazotization of 2,2,2-trifluoroethylamine has provided an attractive approach for utilizing this reagent in various reaction manifolds,^{4c,9} but these conditions are too harsh for protein-based catalysts. To overcome this problem, we envisioned the possibility to utilize a two-compartment reaction setup, in which *ex situ* produced DTE from a 'reagent generation chamber' is carried through a solution

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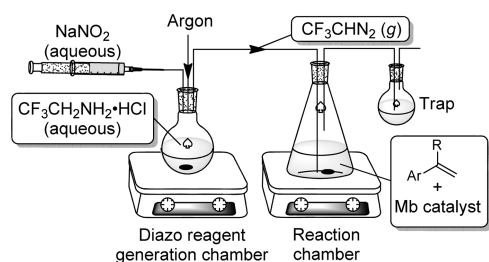
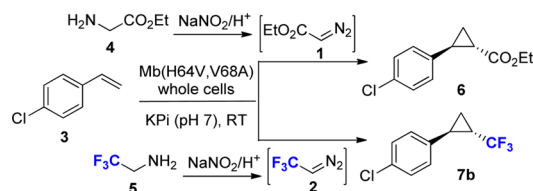


Figure 1. Compartmentalized reaction setup for coupling myoglobin-catalyzed cyclopropanation with *ex situ* generation of 2-diazo-1,1,1-trifluoroethane (DTE).

containing the myoglobin catalyst by inert gas (Figure 1). This system would effectively segregate the two incompatible reactions, thereby preserving the stability of the biocatalyst while eliminating the need for isolating and handling DTE.

To implement this approach, we initially tested the possibility to carry out the myoglobin-catalyzed cyclopropanation of *p*-chlorostyrene (**3**) in the presence of *ex situ* generated EDA. The latter was produced by diazotization of glycine ethyl ester (**4**) in the presence of sodium nitrite and acid (Table 1).¹⁰ For these experiments, the

Table 1. Mb(H64V,V68A)-Catalyzed Cyclopropanation of *p*-Chlorostyrene in the Presence of *ex Situ* Generated EDA and DTE^a



entry	catal.	prod.	equiv 4 or 5 ^b	yield ^c	TON	% <i>de</i>	% <i>ee</i>
1	protein	6	2	4%	180	99.9	99.8
2	cells ^d	6	2	47%	560	97.2	99.9
3	cells	6	5	80%	365	99.9	99.8
4	cells	6	10	75%	340	98.5	99.9
5	cells	6	10	>99% ^e	500	99.9	99.9
6	protein	7b	5	22%	1110	98.5	99.9
7	cells	7b	5	92%	520	99.9	99.9

(67%)

^aReactions were carried out at a 20 mL scale with 30 mM 4-chlorostyrene (**3**), purified Mb variant (20 μM) or Mb(H64V,V68A)-expressing *E. coli* (BL21(DE3)) cells (OD₆₀₀ = 40) in KPi 50 mM (pH 7), rt, 5 h. Diazo reagent was supplied using indicated equivalents of **4** or **5** (slow addition over 4 h). ^bRelative to olefin. ^cAs determined by GC using calibration curves generated with isolated product as reference. Isolated yields are reported in parentheses. ^dOD₆₀₀ = 20. ^eReaction time: 12 h.

Mb(H64V,V64A) variant was chosen as the catalyst based on its high activity and selectivity toward cyclopropanation of aryl-substituted olefins with EDA.^{7a} Initial tests involving purified Mb(H64V,V64A) in the reaction chamber produced only small amounts of the cyclopropanation product **6** (Table 1, entry 1), a result we attributed to protein inactivation by the gas stream flowing through the reaction mixture. Given our recent finding that Mb-catalyzed cyclopropanation reactions can be realized using whole cell systems,^{7b} a suspension of *E. coli* cells expressing the Mb(H64V,V64A) variant was used as the biocatalytic system in the reaction chamber. Gratifyingly, this modified setup resulted in the accumulation of larger amounts of **6** (Table 1, entry 2). Further

improvement of the reaction was possible by varying the cell density of the whole cell transformation and the molar ratio between the olefin substrate and the EDA precursor (Table 1, entries 3–4). Under optimized conditions (OD₆₀₀ = 40, corresponding to a cell density of ~3.5 g cdw L⁻¹, 10 equiv of glycine ethyl ester relative to the olefin), nearly quantitative conversion of the *p*-chloro-styrene substrate to **6** was observed within 12 h (Table 1, entry 5). Importantly, neither the reaction setup nor the whole cell setting was found to have a noticeable impact on the stereoselectivity of the Mb(H64V,V64A)-catalyzed reaction, leading to the formation of the *trans*-(1*S*,2*S*)-configured cyclopropanation product in excellent diastereo- and enantiomeric excess (98.5–99.9% *de*, 99.8–99.9% *ee*).

Based on these promising results, we next investigated the possibility to supply the Mb catalyst in the whole cell system with gaseous DTE as the carbene donor. In this case, 2,2,2-trifluoroethylamine (**5**) was subjected to the diazotization reaction in the reagent generation chamber (Table 1). To our delight, excellent conversion of *p*-chloro-styrene to the desired trifluoromethyl-substituted cyclopropane **7b** (92%) was observed in less than 5 h (entry 7, Table 1) and using only 5 equiv of the diazo reagent precursor **5**. Because of the higher volatility of **7b** compared to **6**, product recovery in this case was improved by addition of a water trap downstream of the reaction vessel. No product was detected using cells not expressing the Mb variant, thus demonstrating the direct role of the hemoprotein in mediating the carbene transfer reaction. Under the applied conditions, the Mb variant was estimated to support about 520 catalytic turnovers (TON), as determined based on the hemoprotein concentration in the reaction mixture measured via a CO-binding assay. This TON value is higher than that observed in the presence of *ex situ* generated EDA under identical operational conditions (entry 7 vs 3, Table 1). Higher yields (GC) and TON were also observed in the presence of DTE vs EDA when purified Mb(H64V,V64A) was applied as the catalyst (entry 6 vs 1). These differences are likely to reflect the inherent reactivity of the diazo reagents as well as differences in the rate and efficiency with which the *ex situ* generated reagents are transferred from the generation chamber to the reaction vessel (Figure 1). Importantly, Mb(H64V,V68A)-catalyzed synthesis of **7b** occurred with excellent diastereo- and enantioselectivity (99.9% *de* and *ee*).

To explore the scope of this reaction, a series of styrene derivatives and aryl-substituted olefins were investigated. As shown by the data in Table 2, all of these substrates could be efficiently converted to the corresponding trifluoromethyl-containing cyclopropanes (54–99%) using Mb(H64,V68A)-expressing cells in the two-compartment setup described in Figure 1. These included *meta*- and *para*-substituted styrene derivatives containing both electron-donating and -withdrawing groups. 4-Nitrostyrene displayed lower reactivity toward Mb-catalyzed cyclopropanation than electron-rich styrene derivatives (e.g., products **9b**, **11b**, **12b**), a result consistent with the electrophilic character of the putative heme-carbenoid intermediate expected to mediate these reactions.^{7a} As demonstrated by the results with **13b** and **14b**, the Mb-catalyzed transformation could be readily extended to other aryl-substituted olefins such as 2-vinyl-naphthalene and 3-(propen-2-yl)thiophene, supporting the broad substrate scope of the Mb(H64,V64A) variant. In contrast to protocols involving chiral metalloporphyrins,^{4a} the biocatalytic reactions proceed efficiently using the olefin as the limiting reagent, which increases their attractiveness for the transformation of valuable starting materials. Importantly, using Mb(H64V,V68A)-expressing cells, the cyclopropanation product

Table 2. Substrate Scope of Myoglobin-Catalyzed Olefin Cyclopropanation with *ex Situ* Generated DTE^a

Entry	Product	OD ₆₀₀	Yield ^b	% <i>de</i>	% <i>ee</i>
1		80	69% (68%)	99.9	99.9
2		80	92% (76%)	99.9	99.9
3		80	54% (43%)	99.9	99.9
4		40	85% 88%	96	31
5		80	76% (82%)	99.8	28
6		80	70% (58%)	99.9	92
7		40	>99% (71%)	99.9	99.9

^aReactions were carried out at 20 mL scale with Mb(H64V,V68A)-expressing *E. coli* at indicated cell density, 8–30 mM olefin in KPi 50 mM (pH 7), rt, 5 h. DTE was supplied using 5 equiv of **5** (slow addition over 4 h). ^bAs determined by GC using calibration curves generated with isolated product as reference. Isolated yields are reported in parentheses. ^cUsing cells expressing Mb(H64V,V68G).

was afforded in most cases with high diastereoselectivity (99.9% *de*) and enantioselectivity (92–99.9% *ee*). As an exception, moderate enantioselectivity (28–31% *ee*) was observed with the toluene derivatives **11a** and **12a** (Table 2, entries 4–5). For these compounds, however, excellent diastereo- and enantioselectivity (97–99.9% *de* and *ee*) could be achieved using cells expressing Mb(H64V,V68G), a Mb variant previously identified as having similar selectivity properties to Mb(H64V,V68A) in cyclopropanation reactions with EDA.^{7b} Altogether, the stereoselectivity offered by these Mb-based catalysts exceeds those provided by the most selective synthetic catalysts reported to date for the asymmetric synthesis of related CF₃-containing cyclopropanes (84–91% *ee*).⁵ Compared to the latter, the Mb-catalyzed transformations also involve shorter reaction times (5 vs 14 h) and higher catalytic efficiency (e.g., 520 vs ~10 TON for **7b**). Of note, the use of whole cells bypasses the need for purification and isolation of the myoglobin catalyst, which further simplifies the overall procedure from a technical standpoint. From these reactions, the CF₃-substituted cyclopropane products could be isolated in good yields (43–82%, Table 2). The synthetic utility of

these transformations was further evidenced by a larger scale reaction with *p*-methoxy-styrene, from which 0.1 g of **9b** was obtained in 76% isolated yield and excellent diastereo- and enantiomeric excess (99.9% *de*, 99.9% *ee*).

To elucidate the stereoselectivity of the Mb(H64V,V68A) catalyst in these reactions, product **10b** was crystallized and determined to have a *trans*-(1*S*,2*S*) configuration by X-ray diffraction analysis (Figure 2A). The same configuration was indirectly assigned to **7b** and the other cyclopropanation products of Table 2 based on the similar order of elution for the corresponding enantiomers upon resolution via chiral GC or SFC (see Figure S2). The stereoselectivity of Mb(H64V,V68A) in the cyclopropanation reactions with DTE thus mirrors that observed in the reactions with EDA.^{7a} Leveraging this insight and in consideration of the structural and electronic similarities between EDA and DTE, we propose a stereochemical scenario analogous to that proposed for Mb(H64V,V68A)-catalyzed cyclopropanation of aryl-substituted olefins with EDA.^{7a} Specifically, the “cavity” created by the Val68 → Ala substitution (Figure S1) is expected to facilitate orientation of the bulkier –CF₃ group (cp. to –H) in the heme-bound carbene intermediate in proximity to the N2 atom of the heme cofactor (Figure 2B). This active site configuration enforces high facial selectivity during end-on attack of the olefin to this reactive species, giving rise to the observed *trans*-(1*S*,2*S*)-configured product. Consistent with this scenario, the Mb(H64V,V68G) variant, which features a similar “large-to-small” mutation at position 68 (Figure S1), is also *trans*-(1*S*,2*S*) selective (Table 2, entries 4–5). An implication of the proposed model is that the aryl ring of the olefin projects toward the solvent-exposed side of the active site, a molecular arrangement that is consistent with the ability of Mb(H64V,V68A) to process structurally diverse vinylarene substrates with consistently high *trans*-(1*S*,2*S*) selectivity (Table 2).

Given the parallelism between the stereoselectivity exhibited by Mb(H64V,V68A) with EDA and DTE, we surmised that the stereoselectivity of Mb variants in cyclopropanation reactions with EDA could serve as a general predictor for their stereoselectivity in the cyclopropanation of related substrates with DTE. Supporting this notion, a very good correlation ($R^2 = 0.911$) was found between the enantiomeric excess exhibited by a series of active site Mb variants in the cyclopropanation of *p*-methoxy-styrene with EDA vs that of parallel reactions with DTE as the carbene donor (Figure 3A). In addition to Mb(H64V,V68A), this panel comprised other Mb variants with high *trans*-(1*S*,2*S*)-selectivity (Mb(H64V,V68G), Mb(H64V,V68S)) as well as a series of recently developed Mb catalysts with high *trans*-(1*R*,2*R*)-selectivity in olefin cyclopropanation with EDA (variants RR1 through RR5).^{7b} Mb variants that span a range of enantioselectivity values from 13% *ee* (wild-type Mb) to 86% *ee* (Mb(V68A)) in the latter reaction were included as additional references (Table S1). As illustrated by the data of Figure 3A and Table S1, the diastereo- and enantioselectivity of the trifluoromethylcarbene transfer reaction was found to closely mirror the diastereo- and enantioselectivity of these Mb variants in the α -diazoester carbene transfer reaction (average $|\Delta(de)| = 3.3\%$; average $|\Delta(ee)| = 14.4\%$; Table S1). Based on these analyses, RR2 (= Mb(H64 V,V68L,L29T)) was selected as a promising candidate for gaining access to the mirror-image forms of products **7b**–**14b**. Gratifyingly, reactions with RR2-expressing *E. coli* cells produced the desired *trans*-(1*R*,2*R*) trifluoromethyl-substituted cyclopropanes **7c**–**14c** with excellent diastereoselectivity (98% *de* for **9c**, >99.5% *de* for the others) and high enantioselectivity (80–92% *ee*; Figure 3B; Figure S2). As an exception, **13c** was obtained

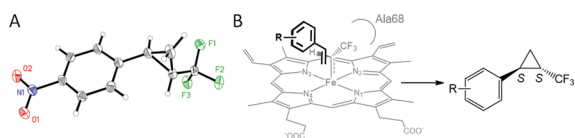


Figure 2. (A) Crystal structure of (1*S*,2*S*)-2-(trifluoromethyl)-cyclopropyl-4-nitro-benzene product (**10b**). (B) Plausible geometry for vinylarene attack to heme-bound trifluoromethylcarbene intermediate leading to the (1*S*,2*S*)-configured cyclopropane product.

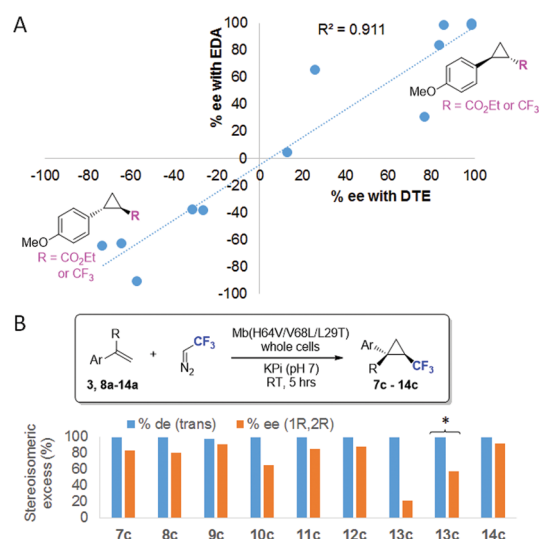


Figure 3. Stereocomplementary selectivity. (A) Correlation between enantioselectivity of Mb variants ($n = 12$) in cyclopropanation of *p*-methoxy-styrene with EDA vs DTE. See Table S1 for additional data. (B) Diastereo- and enantioselectivity of *trans*-(1*R*,2*R*)-selective Mb variant RR2 in cyclopropanation of aryl-substituted olefins in the presence of DTE. See Table S2 for details. * = with RR4-expressing cells.

only in 21% *ee*. However, this compound could be synthesized in higher enantiomeric excess (58% *ee*) using RR4, as anticipated by the high *trans*-(1*R*,2*R*)-selectivity of this Mb variant in olefin cyclopropanation with EDA (Figure 3A). Altogether, these experiments demonstrate the versatility of the Mb scaffold toward providing access to both enantiomeric forms of the target trifluoromethyl-containing cyclopropanes. They also support the predictable reactivity of these biocatalysts in the presence of structurally and electronically related carbene donors.

In summary, we have developed a biocatalytic strategy for the asymmetric synthesis of trifluoromethyl-substituted cyclopropanes via myoglobin-catalyzed addition of trifluoromethylcarbene to olefins. These transformations could be applied to a variety of vinylarene substrates, offering unprecedented levels of diastereo- and enantioselectivity. Furthermore, both enantiomers of the target CF_3 -containing products could be accessed using Mb catalysts with complementary stereoselectivity, whose choice was guided by their reactivity with EDA. The reactions presented here provide access to enantioenriched fluorinated building blocks of high value for medicinal chemistry. This study provides a first-time demonstration that carbene donor reagents other than α -diazoesters can be engaged in biocatalytic carbene transfer reactions. This finding, combined with the demonstrated feasibility of coupling these reactions with *ex situ* generated diazo compounds, is anticipated to enable extension of the present approach to a variety of other carbene precursors in order to expand the scope of carbene-mediated transformations accessible with myoglobins and other metalloprotein catalysts.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b00768.

Supplementary tables and figures, experimental procedures, characterization data, and X-ray data (PDF)
Crystallographic data (CIF)

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Notes

The authors declare the following competing financial interest(s): A PCT application was filed by the University of Rochester on 25 Nov, 2015 that covers the biocatalysts and transformations described in this paper.

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