Cyclopropanation

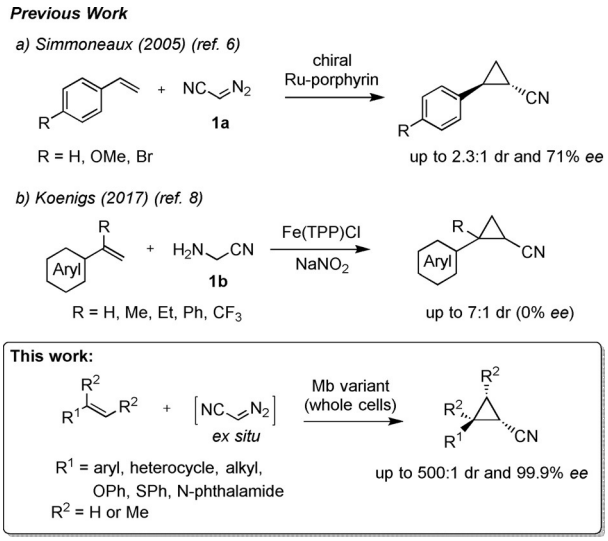
International Edition: DOI: 10.1002/anie.201810059
German Edition: DOI: 10.1002/ange.201810059

# Highly Diastereo- and Enantioselective Synthesis of Nitrile-Substituted Cyclopropanes by Myoglobin-Mediated Carbene Transfer Catalysis

*Ajay L. Chandgude and Rudi Fasan**

***Abstract:*** *A chemobiocatalytic strategy for the highly stereoselective synthesis of nitrile-substituted cyclopropanes is reported. The present approach relies on an asymmetric olefin cyclopropanation reaction catalyzed by an engineered myoglobin in the presence of ex situ generated diazoacetonitrile within a compartmentalized reaction system. This method enabled the efficient transformation of a broad range of olefin substrates at a preparative scale with up to 99.9% de and ee and up to 5600 turnovers. The enzymatic product could be further elaborated to afford a variety of functionalized chiral cyclopropanes. This work expands the range of synthetically valuable, abiotic transformations accessible through biocatalysis and paves the way to the practical and safe exploitation of diazoacetonitrile in biocatalytic carbene transfer reactions.*

The catalytic asymmetric cyclopropanation of alkenes with diazo compounds constitutes a convenient and direct strategy for the construction of optically active cyclopropanes,[1] which are key structural motifs in numerous natural products and pharmaceuticals.[2] Within this structural class, cyano-substituted cyclopropanes represent particularly attractive building blocks owing to the versatility of the cyano group toward its interconversion to a variety of functional groups.[3] Moreover, cyano-functionalized cyclopropanes have been incorporated into pharmacologically active molecules, including the potent cathepsin K inhibitor Odanacatib.[4] Notable contributions from the Davies, Charette, and Zhang groups have recently introduced chemocatalytic protocols for the asymmetric synthesis of cyano-substituted cyclopropanes starting from donor–acceptor or acceptor–acceptor diazo compounds.[5] In stark contrast, methods for the asymmetric synthesis of cyano-substituted cyclopropanes using the acceptor-only diazo reagent diazoacetonitrile ($N_2CHCN$) have remained elusive. As an isolated effort in this direction, chiral Ru-porphyrins were reported to catalyze the cyclopropanation of styrene derivatives in the presence of pre-formed diazoacetonitrile (**1a**), but only with moderate diastereoselectivity (20–50% *de*) and enantioselectivity (41–71% *ee*) (Scheme 1).[6] More recently, the Koenigs group has reported the iron-catalyzed cyclopropanation of vinylarenes in the presence of in situ generated[7] diazoacetonitrile.[8] While offering good yields and scalability, this method provides only moderate diastereoselectivity (2:1 to 7:1 d.r.) and no enantioselectivity in the cyclopropanation reaction (Scheme 1).[8] Motivated by the shortcomings of current methodologies for this transformation, we have pursued and report herein the development of a biocatalytic strategy for the highly stereoselective synthesis of nitrile-substituted cyclopropanes by myoglobin-catalyzed olefin functionalization with diazoacetonitrile. This method provides a rather general, efficient, and scalable route to enantiopure cyclopropanes incorporating a cyano group, which can be readily elaborated to afford variously functionalized chiral cyclopropanes.




***Scheme 1.*** Methods for synthesis of nitrile-substituted cyclopropanes using diazoacetonitrile.

Heme-containing proteins[9] as well as engineered/artificial metalloenzymes[10] have been recently identified as viable biocatalysts for promoting olefin cyclopropanations in the presence of diazo reagents. In particular, we previously reported the ability of engineered variants of myoglobin (Mb) to catalyze the cyclopropanation of vinylstyrenes with ethyl α-diazoacetate (EDA) with a high degree of diastereo- and enantioselectivity.[9c,d] Despite this progress, the scope of biocatalytic cyclopropanations has been largely restricted to α-diazoacetates, limiting the types of functionalized cyclopropanes accessible using these systems. To overcome these limitations, our attention was drawn to diazoacetonitrile, a largely underutilized reagent in organic chemistry.[11] The application of pre-formed diazoacetonitrile in carbene transfer manifolds presents important challenges since this reagent cannot be handled easily due to its high volatility, toxicity, and explosive nature.[12] On the other hand, protocols for in situ

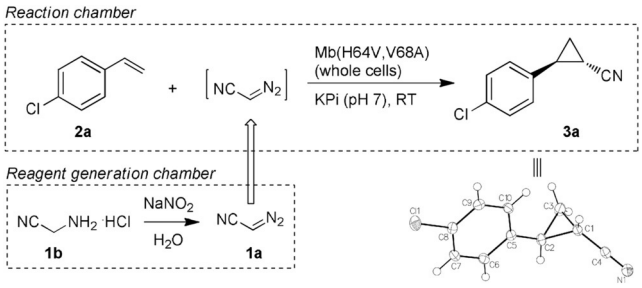
[*] Dr. A. L. Chandgude, Prof. Dr. R. Fasan
Department of Chemistry, University of Rochester
120 Trustee Road, Rochester, NY 14627 (USA)
E-mail: rfasan@ur.rochester.edu

Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/anie.201810059.

generation of diazoacetonitrile through diazotization of 2-amino-acetonitrile,[11,13] a shelf-stable, readily available, and inexpensive reagent, are incompatible with protein stability and function. Our recent success in engaging gaseous 2-diazotrifluoroethane (DTE) in myoglobin catalysis[9g] prompted us to apply an analogous compartmentalized reaction system for testing the ability of myoglobin to accept diazoacetonitrile as a carbene donor for olefin cyclopropanation. Accordingly, we tested a reaction system in which diazoacetonitrile (**1a**), generated in situ by diazotization of 2-amino-acetonitrile (**1b**) in a "reagent generation chamber", is carried through a "reaction chamber" containing the biocatalyst and a model olefin substrate (*p*-chloro-styrene, **2a**) by a continuous flow of inert gas (Ar) (Table 1 and Figure S1 in the Supporting Information). The myoglobin variant Mb(H64V,V68A) was selected as the catalyst because of its high stereoselectivity in olefin cyclopropanations with EDA.[9c,d] Gratifyingly, a reaction system involving Mb(H64V,V68A)-containing whole cells ($OD_{600}$: 80) and ex situ generated diazoacetonitrile resulted in the accumulation of the desired nitrile-substituted cyclopropane product **3a** in good conversion (44%; Table 1, Entry 2). A similar reaction with purified protein did not yield any product (Table 1, Entry 1), indicating that the whole cell system protects the biocatalyst from inactivation by the gas flow. Importantly, the Mb(H64V,V68A)-catalyzed reaction was found to proceed also with excellent diastereo- and enantioselectivity (99.9% *de* and *ee*), producing a single stereoisomer with *trans*-(1*S*,2*S*) absolute configuration as established by X-ray crystallography (Table 1; Figure S3 in the Supporting Information). These results thus showed that diazoacetonitrile can be effectively utilized as carbene donor by the Mb-based carbene transferase. Additionally, the chiral induction imposed by Mb(H64V,V68A) in the cyclopropanation reaction with diazoacetonitrile mirrors, which is observed in styrene cyclopropanation with EDA[9c] and DTE,[9g] highlighting the conserved stereoselectivity of this biocatalyst across these acceptor-only carbene donors. Further experiments showed that other hemoproteins can catalyze this reaction, but only with lower activity and/or stereoselectivity compared to Mb(H64V,V68A) (Table S1 in the Supporting Information).

***Table 1:*** Mb(H64V,V68A)-catalyzed cyclopropanation of *p*-chlorostyrene with ex situ generated diazoacetonitrile.[a]




| Entry | Cat. | $OD_{600}$ | equiv 1[b] | Conv. (Yield)[c] | TON | % *de* | % *ee* |
|---|---|---|---|---|---|---|---|
| 1 | protein | – | 5 | 0 | – | – | – |
| 2 | cells | 80 | 5 | 44% | 230 | 99.9 | 99.9 |
| 3 | cells | 40 | 5 | 43% | 465 | 99.9 | 99.9 |
| 4 | cells | 20 | 5 | 55% | 930 | 99.9 | 99.9 |
| 5 | cells | 10 | 5 | 50% | 1,700 | 99.9 | 99.9 |
| 6 | cells | 5 | 5 | 46% | 3,110 | 99.9 | 99.9 |
| 7[d] | cells | 20 | 10 | 40% | 675 | 99.9 | 99.9 |
| 8[e] | cells | 20 | 5 | 72% (87%[f]) | 1,500 | 99.9 | 99.9 |
| 9[e,g] | cells | 20 | 5 | 86% (81%)[f] | 5,600 | 99.9 | 99.9 |

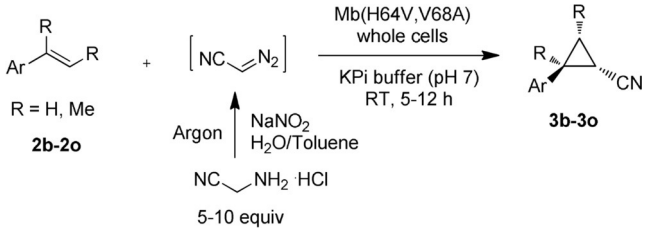
[a] Reaction conditions: 10 mM 4-chloro-styrene (**2a**), purified Mb variant (20 μM) or Mb(H64V,V68A)-expressing *E. coli* (BL21(DE3)) cells in KPi 50 mM (pH 7), at 20 mL-scale, RT, 5 hours. $NaNO_2$ was slowly added over 30 min.[22] [b] Relative to olefin. [c] Product conversion as determined by SFC. Yields of isolated products are reported in brackets. Errors are within 10%. [d] Slow addition of $NaNO_2$ over 4 h. [e] 2-Aminoacetonitrile in 2 mL of 1:1 $H_2O$:toluene mixture. [f] Reaction time: 15 hours. [g] **2a** at 30 mM.

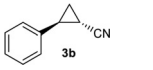
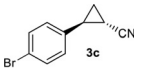
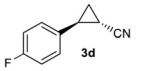
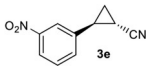
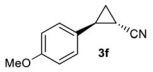
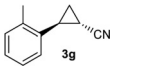
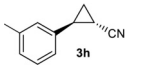
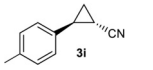
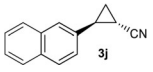
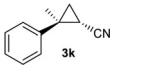
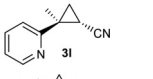
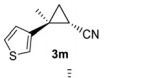
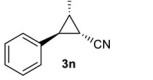
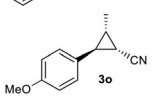
Based on the promise of these initial results, the Mb(H64V,V68A)-catalyzed reaction was further optimized. A decrease in catalyst loading (that is, cell density ($OD_{600}$) from 80 to 5) showed a progressive increase in the catalytic turnovers (TON) supported by the hemoprotein (230→3110), while providing similar or higher product conversions (44–55%) and maintaining excellent stereoselectivity (Table 1, Entries 3–6). Because of its superior efficiency, a cell density ($OD_{600}$) of 20 was thus chosen for the subsequent studies. Upon observing that a larger excess of carbene precursor (10 vs. 5 equiv of **1b**), generated over a longer time period (4 vs. 0.5 hours), did not lead to noticeable improvement in product conversion (Entry 7), we surmised that only part of the diazo compound produced in the reagent generation chamber is made available to the biocatalyst. We attributed this phenomenon to the high solubility of diazoacetonitrile in water, which would hamper its effective transfer to the reaction chamber. Upon optimization of the reagent generation reaction using different solvent systems (Table S2 in the Supporting information), we found that a water:toluene (1:1) mixture was optimal for maximizing both formation of the diazo reagent and its mass transfer to the reaction chamber, leading to improved product conversions of 72% and 87% over 5 and 15 hours, respectively, with no impact on diastereo- and enantioselectivity (Table 1, entry 8). Moreover, the reaction could be readily scaled up (from 10 to 30 mM *p*-chlorostyrene, **2a**), enabling the isolation of 86 mg of enantiopure **3a** (99.9% *de* and *ee*) in 81% yield (Table 1, entry 9). Under these conditions, Mb(H64V,V68A) catalyzes 5600 turnovers, which corresponds to an approximately 50 to 100-fold higher catalytic activity than reported with chemocatalytic systems (ca. 50–100 TON).[6,8]

To explore the scope of this reaction, a diverse panel of styrene derivatives and vinylarenes was subjected to Mb(H64V,V68A)-catalyzed cyclopropanation with α-diazoacetonitrile under the optimized conditions described above and at a preparative scale (0.6 mmol olefin) (Table 2). These experiments showed that styrene (**2b**) as well as various styrene derivatives carrying *para*, *meta*, and *ortho* substituents (**2c**–**2i**) are efficiently processed by the Mb(H64V,V68A) variant, leading to the corresponding cyclopropanation products **3b**–**3i** in good to excellent conversion (50–99%) and isolated yields (44–84%) (Table 2; Entries 1–2;4–8). Both electron-donating (**3f**–**i**) and electron-withdrawing substituents (**3c**, **3e**) on the benzene ring of the olefin were equally

***Table 2:*** Substrate scope of Mb(H64V,V68A)-mediated olefin cyclopropanation with diazoacetonitrile.[a]




| Entry | Product | Conv. (Yield)[b] | TON | % *de* | % *ee* |
|---|---|---|---|---|---|
| 1 |  | 50% (44%) | 2080 | >99 | 96 |
| 2 |  | 99% (74%) | 4960 | 97 | 96 |
| 3 |  | 32% (31%) | 2420 | >99 | >99 |
| 4 |  | 77% (50%) | 3820 | >99 | >99 |
| 5 |  | 77% (66%) | 3820 | 98 | 97 |
| 6 |  | 98% (84%) | 4880 | >99 | 99 |
| 7 |  | 75% (66%) | 3730 | >99 | >99 |
| 8 |  | 65% (61%) | 2760 | 99 | 97 |
| 9 |  | 63% (61%) | 2550 | 84 | 85 |
| 10 |  | 87% (73%) | 3540 | >99 | 99 |
| 11 |  | 96% (61%) | 3810 | >99 | 76 |
| 12 |  | 90% (71%) | 3590 | >99 | 85 |
| 13 |  | 2% (nd) | 110 | 69 | >99 |
| 14 |  | 5% (nd) | 380 | 17 | 46 |

[a] Reaction conditions: 30 mM olefin, Mb(H64V,V68A)-expressing *E. coli* ($OD_{600}$ = 20) in KPi buffer (50 mM, pH 7), 20 mL-scale, RT, 5–12 hours. $NaNO_2$ was slowly added over 30 min. [b] Product conversion as determined by SFC. Yields of isolated products are reported in brackets. Errors are within 15%.

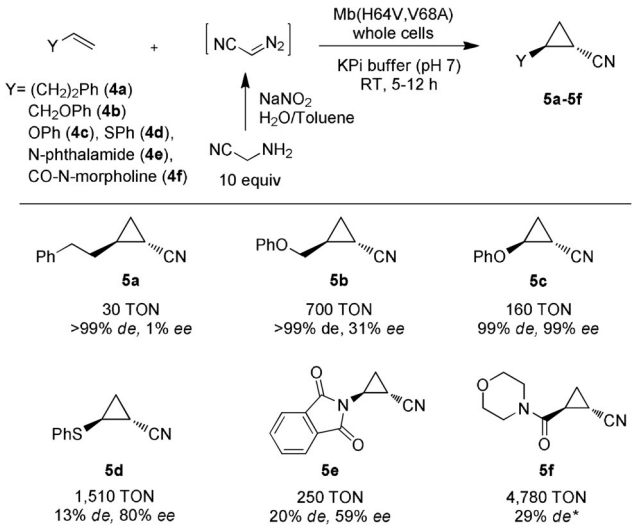
well tolerated, although lower yields were obtained for **3d** due to its volatility. Importantly, excellent levels of diastereo- and enantioselectivity (96–>99% *de* and *ee*) were maintained for these styrenyl substrates. Additionally, different vinylarenes such as naphthyl-, pyridyl-, and thiophenyl-substituted olefins could be efficiently transformed by the Mb(H64V,V68A) biocatalyst to give the corresponding cyclopropane products **3j**, **3l**, and **3m** in good yields (61–71%) and with high stereoselectivity (84–99% *de* and *ee*) (Table 2; Entries 9, 11–12). Along with **3l** and **3m**, the efficient synthesis of **3k** in high enantiopurity further demonstrated the utility of Mb(H64V,V68A) for the cyclopropanation of α,α-disubstituted olefins (Entry 10), as well as olefins incorporating N- and S-containing heterocycles, which find widespread use in medicinal chemistry.

The high catalytic activity of Mb(H64V,V68A) across these substrates (2080–4960 TON; Table 2) prompted us to investigate challenging substrates such as β-methyl-styrene, which has previously eluded Mb-catalyzed cyclopropanation with EDA.[9c] Albeit in low yields, **3n** and **3o** could be obtained in enantioenriched form (4699% *ee*), demonstrating the feasibility of the present methodology to access trisubstituted cyclopropanes (Table 2; Entries 13 and 14). Notably, the catalytic activity of the iron-based Mb(H64V,V68A) in this reaction (110–380 TON) compares well with that reported for the cyclopropanation of β-methyl-styrene with EDA, using an artificial enzyme containing a highly reactive[14] iridium-porphyrin (20–310 TON).[10d] Altogether, the results summarized in Table 2 denote the broad substrate scope of Mb(H64V,V68A)-mediated olefin cyclopropanation with diazoacetonitrile. Remarkably, this biocatalyst maintains high *trans*-(1*S*,2*S*) stereoselectivity across the diverse arylarenes, as judged based on crystallographic analysis of **3c**, **3d**, and **3i** (Figure S4–S6 in the Supporting Information), and the similar chromatographic behavior of the other products in chiral SFC or GC compared to that of the structurally characterized enantiopure products (Table S5–S8 in the Supporting Information).

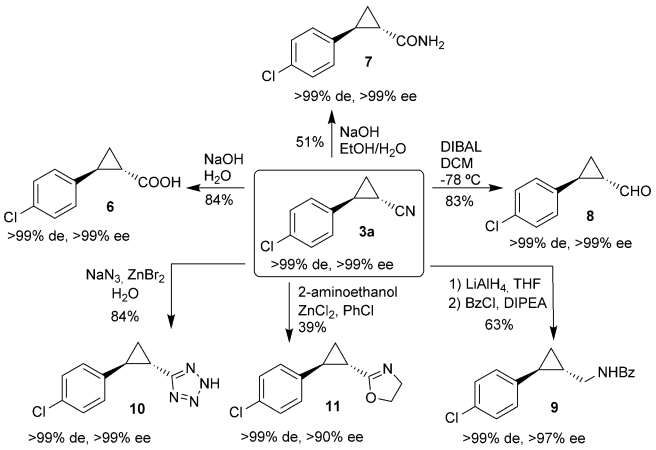
Motivated by the positive results with α,β-disubstituted alkenes, we further probed the capability of the method to enable the transformation of alkenes other than aryl-substituted olefins, whose successful cyclopropanation with diazoacetonitrile was not previously reported.[6,8] This group included unactivated substrates such as alkyl-substituted (**5a**,**b**) and electron-deficient olefins (**5e**,**f**). To our delight, all the reactions afforded the desired nitrile-substituted cyclopropane products **5a–f** with modest to excellent diastereo- and enantioselectivity (Scheme 2).Notably, the biocatalyst displayed over 4700 TON in the conversion of the acrylamide substrate **4f** to **5f**. These results further highlighted the generality of Mb(H64V,V68A)-catalyzed cyclopropanation reaction with diazoacetonitrile as well as its expanded scope compared to Mb-catalyzed cyclopropanation with α-diazoesters.[9c,d]

While biocatalytic cyclopropanation reactions have so far remained largely confined to α-diazo esters,[9a–f,h,i,10,15] we envisioned that a key advantage of the present strategy would lie in the possibility to access diverse cyclopropane structures by leveraging the versatile reactivity of the cyano group.[3] Illustrating this point, the enzymatically produced compound **3a** could be further processed to access a variety of functionally diversified cyclopropanes (Scheme 3). Specifically, alkaline hydrolysis of **3a** readily produced the carboxy- and the carboxyamide-functionalized cyclopropanes **6** and **7**, respectively, in 51–84% yield in a single step. On the other hand, reduction of **3a** with DIBAL furnished the formyl-substituted




***Scheme 2.*** Expanded scope of biocatalytic olefin cyclopropanation with diazoacetonitrile. *Enantiomers could not be resolved using chiral SFC or GC.




***Scheme 3.*** Diversification of biocatalytically produced nitrile-substituted cyclopropane.

cyclopropane **8** in 83% yield, whereas its reduction with LAH followed by N-benzoylation afforded the methylamino derivative **9** in 63% yield over two steps. Of note, methylaminocyclopropanes constitute the core structure of marketed drugs such as Tasimelteon[16] and Levomilnacipran.[17] Finally, a zinc-catalyzed [2+3] cycloaddition reaction of **3a** with $NaN_3$[18] gave the tetrazole-substituted cyclopropane **10**, whereas a reaction with aminoethanol and zinc chloride[19] afforded the oxazoline-functionalized cyclopropane **11** in good yields (39–84%). In most cases, the transformation of the nitrile group occurred with no erosion of enantiopurity (>99% *ee*, Scheme 3).

In summary, we have developed an efficient biocatalytic method for the highly diastereo- and enantioselective synthesis of nitrile-substituted cyclopropanes through the activation of diazoacetonitrile. The present strategy offers unprecedented degrees of stereocontrol compared to previously reported chemocatalytic strategies (Scheme 1), along with high TON, scalability, and a broad substrate scope that extends beyond that of Mb-catalyzed cyclopropanations with α-diazoesters.[9c,d] The latter feature may stem from a higher reactivity of the heme-carbene intermediate[20] generated from acetonitrile, an aspect that will be addressed in future studies. Describing the first example of a biocatalytic reaction involving diazoacetonitrile, this study paves the way to the application of this reagent in the context of other metalloprotein-catalyzed carbene transfer reactions. This capability combined with the versatility of the cyano functional group, as exemplified by the transformations of Scheme 2, is expected to expand opportunities toward the exploitation of biocatalysis for asymmetric synthesis of pharmaceuticals and other high-value compounds.[21]

## Acknowledgements

This work was supported by the U.S. National Institute of Health grant GM098628. The authors are grateful to Dr. William Brennessel for assistance with crystallographic analyses. MS and X-ray instrumentation are supported by U.S. National Science Foundation grants CHE-0946653 and CHE-1725028.

## Conflict of interest

The authors declare no conflict of interest.

**Keywords:** carbene transfer · cyclopropanation · myoglobin · nitrile-substituted cyclopropanes · protein engineering

**How to cite:** *Angew. Chem. Int. Ed.* **2018**, *57*, 15852–15856
*Angew. Chem.* **2018**, *130*, 16078–16082

[1] a) M. P. Doyle, D. C. Forbes, *Chem. Rev.* **1998**, *98*, 911–936; b) H. Lebel, J. F. Marcoux, C. Molinaro, A. B. Charette, *Chem. Rev.* **2003**, *103*, 977–1050; c) H. M. L. Davies, S. J. Hedley, *Chem. Soc. Rev.* **2007**, *36*, 1109–1119; d) H. Pellissier, *Tetrahedron* **2008**, *64*, 7041–7095.
[2] T. T. Talele, *J. Med. Chem.* **2016**, *59*, 8712–8756.
[3] a) A. J. Fatiadi, *Preparation and Synthetic Applications of Cyano Compounds*, Wiley-VCH, New York, **1983**; b) F. C. Schaefer, *The Chemistry of the Cyano Group: Nitrile Reactivity*, Wiley Interscience, New York, **1970**.
[4] a) J. Y. Gauthier, N. Chauret, W. Cromlish, S. Desmarais, L. T. Duong, J. P. Falgueyret, D. B. Kimmel, S. Lamontagne, S. Leger, T. LeRiche, C. S. Li, F. Masse, et al., *Bioorg. Med. Chem. Lett.* **2008**, *18*, 923–928; b) J. Pedersen, C. Lauritzen, **2012**.
[5] a) J. R. Denton, K. Cheng, H. M. L. Davies, *Chem. Commun.* **2008**, 1238–1240; b) W. Lin, A. B. Charette, *Adv. Synth. Catal.* **2005**, *347*, 1547–1552; c) D. Marcoux, S. Azzi, A. B. Charette, *J. Am. Chem. Soc.* **2009**, *131*, 6970–6972; d) S. F. Zhu, X. Xu, J. A. Perman, X. P. Zhang, *J. Am. Chem. Soc.* **2010**, *132*, 12796–12799.
[6] Y. Ferrand, P. Le Maux, G. Simonneaux, *Tetrahedron: Asymmetry* **2005**, *16*, 3829–3836.
[7] a) R. P. Wurz, A. B. Charette, *Org. Lett.* **2002**, *4*, 4531–4533; b) B. Morandi, E. M. Carreira, *Angew. Chem. Int. Ed.* **2010**, *49*, 938–941; *Angew. Chem.* **2010**, *122*, 950–953; c) B. Morandi, B. Mariampillai, E. M. Carreira, *Angew. Chem. Int. Ed.* **2011**, *50*, 1101–1104; *Angew. Chem.* **2011**, *123*, 1133–1136.

[8] K. J. Hock, R. Spitzner, R. M. Koenigs, *Green Chem.* **2017**, *19*, 2118 – 2122.
[9] a) P. S. Coelho, E. M. Brustad, A. Kannan, F. H. Arnold, *Science* **2013**, *339*, 307 – 310; b) P. S. Coelho, Z. J. Wang, M. E. Ener, S. A. Baril, A. Kannan, F. H. Arnold, E. M. Brustad, *Nat. Chem. Biol.* **2013**, *9*, 485 – 487; c) M. Bordeaux, V. Tyagi, R. Fasan, *Angew. Chem. Int. Ed.* **2015**, *54*, 1744 – 1748; *Angew. Chem.* **2015**, *127*, 1764 – 1768; d) P. Bajaj, G. Sreenilayam, V. Tyagi, R. Fasan, *Angew. Chem. Int. Ed.* **2016**, *55*, 16110 – 16114; *Angew. Chem.* **2016**, *128*, 16344 – 16348; e) J. G. Gober, A. E. Rydeen, E. J. Gibson-O'Grady, J. B. Leuthaeuser, J. S. Fetrow, E. M. Brustad, *ChemBioChem* **2016**, *17*, 394 – 397; f) J. G. Gober, S. V. Ghodge, J. W. Bogart, W. J. Wever, R. R. Watkins, E. M. Brustad, A. A. Bowers, *ACS Chem. Biol.* **2017**, *12*, 1726 – 1731; g) A. Tinoco, V. Steck, V. Tyagi, R. Fasan, *J. Am. Chem. Soc.* **2017**, *139*, 5293 – 5296; h) A. M. Knight, S. B. J. Kan, R. D. Lewis, O. F. Brandenberg, K. Chen, F. H. Arnold, *ACS Cent. Sci.* **2018**, *4*, 372 – 377; i) O. F. Brandenberg, C. K. Prier, K. Chen, A. M. Knight, Z. Wu, F. H. Arnold, *ACS Catal.* **2018**, *8*, 2629 – 2634.
[10] a) P. Srivastava, H. Yang, K. Ellis-Guardiola, J. C. Lewis, *Nat. Commun.* **2015**, *6*, 7789; b) G. Sreenilayam, E. J. Moore, V. Steck, R. Fasan, *Adv. Synth. Catal.* **2017**, *359*, 2076 – 2089; c) G. Sreenilayam, E. J. Moore, V. Steck, R. Fasan, *ACS Catal.* **2017**, *7*, 7629 – 7633; d) H. M. Key, P. Dydio, D. S. Clark, J. F. Hartwig, *Nature* **2016**, *534*, 534 – 537; e) H. M. Key, P. Dydio, Z. N. Liu, J. Y. E. Rha, A. Nazarenko, V. Seyedkazemi, D. S. Cark, J. F. Hartwig, *ACS Cent. Sci.* **2017**, *3*, 302 – 308; f) M. W. Wolf, D. A. Vargas, N. Lehnert, *Inorg. Chem.* **2017**, *56*, 5623 – 5635; g) K. Oohora, H. Meichin, L. M. Zhao, M. W. Wolf, A. Nakayama, J. Hasegawa, N. Lehnert, T. Hayashi, *J. Am. Chem. Soc.* **2017**, *139*, 17265 – 17268; h) H. Yang, A. M. Swartz, H. J. Park, P. Srivastava, K. Ellis-Guardiola, D. M. Upp, G. Lee, K. Belsare, Y. F. Gu, C. Zhang, R. E. Moellering, J. C. Lewis, *Nat. Chem.* **2018**, *10*, 318 – 324; i) L. Villarino, K. E. Splan, E. Reddem, L. Alonso-Cotchico, C. Gutiérrez de Souza, A. Lledós, J.-D. Maréchal, A.-M. W. H. Thunnissen, G. Roelfes, *Angew. Chem. Int. Ed.* **2018**, *57*, 7785 – 7789; *Angew. Chem.* **2018**, *130*, 7911 – 7915.
[11] P. K. Mykhailiuk, *Eur. J. Org. Chem.* **2015**, 7235 – 7239.
[12] a) D. D. Phillips, W. C. Champion, *J. Am. Chem. Soc.* **1956**, *78*, 5452; b) M. J. S. Dewar, R. Pettit, *J. Chem. Soc.* **1956**, 2026 – 2029.
[13] K. J. Hock, L. Mertens, R. Hommelsheim, R. Spitzner, R. M. Koenigs, *Chem. Commun.* **2017**, *53*, 6577 – 6580.
[14] B. J. Anding, A. Ellern, L. K. Woo, *Organometallics* **2012**, *31*, 3628 – 3635.
[15] E. W. Reynolds, T. D. Schwochert, M. W. McHenry, J. W. Watters, E. M. Brustad, *ChemBioChem* **2017**, *18*, 2380 – 2384.
[16] J. Catt, G. Johnson, D. Keavy, R. Mattson, M. Parker, K. Takaki, J. Yevich, U.S. Pat. 5,981,571 Bristol Myers Squibb, **1999**.
[17] R. Mago, R. Mahajan, M. E. Thase, *Expert Rev. Clin. Pharmacol.* **2014**, *7*, 137 – 145.
[18] Z. P. Demko, K. B. Sharpless, *J. Org. Chem.* **2001**, *66*, 7945 – 7950.
[19] K. Qiao, X. Yuan, L. Wan, M. W. Zheng, D. Zhang, B. B. Fan, Z. C. Di, Z. Fang, K. Guo, *Green Chem.* **2017**, *19*, 5789 – 5793.
[20] Y. Wei, A. Tinoco, V. Steck, R. Fasan, Y. Zhang, *J. Am. Chem. Soc.* **2018**, *140*, 1649 – 1662.
[21] a) U. T. Bornscheuer, G. W. Huisman, R. J. Kazlauskas, S. Lutz, J. C. Moore, K. Robins, *Nature* **2012**, *485*, 185 – 194; b) M. Hönig, P. Sondermann, N. J. Turner, E. M. Carreira, *Angew. Chem. Int. Ed.* **2017**, *56*, 8942 – 8973; *Angew. Chem.* **2017**, *129*, 9068 – 9100; c) M. T. Reetz, *J. Am. Chem. Soc.* **2013**, *135*, 12480 – 12496; d) M. Hönig, P. Sondermann, N. J. Turner, E. M. Carreira, *Angew. Chem. Int. Ed.* **2017**, *56*, 8942 – 8973; *Angew. Chem.* **2017**, *129*, 9068 – 9100.
[22] CCDC 1872015 (**3a**), 1872017 (**3c**), 1872014 (**3d**), and 1872016 (**3i**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

Manuscript received: September 1, 2018
Accepted manuscript online: October 9, 2018
Version of record online: November 5, 2018