Biocatalytic Synthesis of Allylic and Allenyl Sulfides through a Myoglobin-Catalyzed Doyle–Kirmse Reaction

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Dedicated to Prof. Frances H. Arnold on the occasion of her 60th birthday.

Abstract: *The first example of a biocatalytic [2,3]-sigmatropic rearrangement reaction involving allylic sulfides and diazo reagents (Doyle–Kirmse reaction) is reported. Engineered variants of sperm whale myoglobin catalyze this synthetically valuable C−C bond-forming transformation with high efficiency and product conversions across a variety of sulfide substrates (e.g., aryl-, benzyl-, and alkyl-substituted allylic sulfides) and α-diazo esters. Moreover, the scope of this myoglobin-mediated transformation could be extended to the conversion of propargylic sulfides to give substituted allenes. Active-site mutations proved effective in enhancing the catalytic efficiency of the hemoprotein in these reactions as well as modulating the enantioselectivity, resulting in the identification of the myoglobin variant Mb(L29S,H64V,V68F), which is capable of mediating asymmetric Doyle–Kirmse reactions with an enantiomeric excess up to 71%. This work extends the toolbox of currently available biocatalytic strategies for the asymmetric formation of carbon–carbon bonds.*
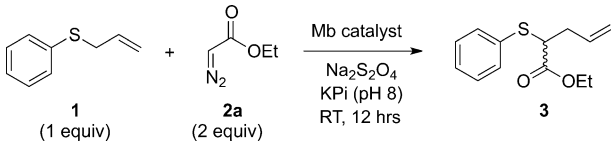
Biocatalytic transformations can provide key opportunities for the development of economical and sustainable processes for the synthesis and manufacturing of fine chemicals and pharmaceuticals.[1] Enzyme-catalyzed carbon–carbon bond-forming reactions have traditionally involved the use of aldolases, thiamine diphosphate-dependent enzymes, hydroxynitrile lyases, and terpene cyclases, with protein engineering providing a means to expand the scope of these enzymes to non-native substrates.[2] More recently, engineered and artificial metalloenzymes have made possible other valuable C−C bond-forming transformations, including olefin cyclopropanation,[3] Suzuki coupling,[4] Diels–Alder reactions,[5] Friedel–Crafts indole alkylation,[6] Wittig olefination,[7] and olefin metathesis.[8] Despite this progress, the toolbox of biocatalytic systems useful for the construction of C−C bonds remains limited when compared to synthetic methods.

Our laboratory and the Arnold group have recently reported the ability of heme-containing proteins such as myoglobin[3d,7,9] and P450,[3a–c] respectively, to engage α-diazo ester reagents in carbene-transfer reactions. In particular, we found that engineered variants of sperm whale myoglobin can provide highly active and selective biocatalysts for carbene-mediated transformations such as olefin cyclopropanation,[3d] Y−H carbene insertion (Y = N, S),[9] and aldehyde olefination.[7] The transition-metal-catalyzed reaction between allyl sulfides and a diazo reagent (the Doyle–Kirmse reaction)[10] represents a powerful method for the creation of new C−C bonds, which has found application in the synthesis of various biologically active molecules.[11] This process involves a reaction between the allyl sulfide and a metallo-carbenoid species, leading to the formation of a sulfur ylide, which undergoes a [2,3]-sigmatropic rearrangement.[10c,11] While several organometallic catalysts, including rhodium,[10b,12] copper,[12a–c,13] and cobalt[14] complexes, have proven useful for promoting this transformation,[15] the development of catalytically efficient and enantioselective variants of this reaction has proven very challenging.[11b] Herein, we report the development of myoglobin-based biocatalysts capable of promoting asymmetric Doyle–Kirmse reactions with high catalytic efficiency across a broad panel of allylic and propargylic sulfide substrates and different α-diazoesters.

Initially, we investigated the activity of sperm whale myoglobin (Mb) in catalyzing the [2,3]-sigmatropic rearrangement of allyl phenyl sulfide **1** in the presence of ethyl α-

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Table 1: Myoglobin-catalyzed tandem sulfur ylide formation and [2,3]-sigmatropic rearrangement of phenyl allyl sulfide with EDA.[a]

Entry	Catalyst	Deviation from s.r.c.	% conv.[b]	TON[c]
1	WT Mb	–	44%	445
2	WT Mb	aerobic	0%	0
3	WT Mb	no Na$_2$S$_2$O$_4$	19%	195
4	WT Mb	1 equiv **2a**	19%	185
5	WT Mb	0.5 equiv **2a**	11%	115
6	Mb(L29S,H64V,V68F)	–	>99%	>995
7	Mb(L29S,H64V,V68F)	0.025 mol%	87%	3500
8	Mb(L29S,H64V,V68F)	0.01 mol%	63%	6270
9	Mb(L29S,H64V,V68F)	30 min	>99%	>995

[a] Standard reaction conditions (s.r.c.) = 10 mM **1**, 20 mM **2a**, 10 μM Mb catalyst (0.1 mol%), 10 mM Na$_2$S$_2$O$_4$ in oxygen-free potassium phosphate buffer (50 mM, pH 8) at room temperature. [b] As determined by gas chromatography. [c] TON = number of turnovers (nmol product/nmol catalyst). Errors are within ±10%.

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diazo acetate (EDA, **2a**). Gratifyingly, this reaction resulted in the formation of the desired [2,3]-sigmatropic rearrangement product **3** with 44% conversion (445 TON) under optimized conditions (Table 1, Entry 1). No product formation was observed under aerobic conditions (Table 1, Entry 2), thus indicating that oxygen, that is, the native ligand of Mb, inhibits this reactivity. Reactions performed in the presence and absence of reductant ($Na_2S_2O_4$) showed that ferrous Mb is catalytically more efficient than the ferric counterpart (445 vs. 195 TON, Table 1), although the latter remains a viable catalyst for this reaction, as supported by these results and additional experiments (Table S1 and Figure S2 in the Supporting Information). Varying the pH between 6 and 9 had a negligible effect on Mb-dependent catalytic activity, whereas improved conversion was obtained with a two-fold excess of EDA (55% vs. 19% with one equiv EDA). As observed for hemin, the Mb-catalyzed formation of **3** show no enantiomeric excess (< 1% *ee*), thus indicating that the native Mb scaffold is unable to exert any asymmetric induction during the reaction.

In order to identify more-efficient and selective Mb-based biocatalysts for this reaction, we evaluated a panel of engineered Mb variants containing one to three amino acid substitutions at the level of the five residues defining the distal cavity of the hemoprotein (Leu29, Phe43, His64, Val68, Ile107; Figure S1). Previously, we found that mutations at these positions can dramatically alter the activity and selectivity of Mb variants as carbene-[3d,7,9,16] and nitrene-[17] transfer catalysts. Upon testing in the reaction with **1** and EDA, a number of Mb variants with significantly improved catalytic activity compared to the wild-type protein were identified (Figure S3). Among them, Mb(L29S,H64V,V68F) emerged as the most active biocatalyst for this reaction, giving quantitative conversion of **1** into **3** at a catalyst loading of only 0.1 mol%. Notably, product conversion values of 87% (3500 TON) and 63% (6270 TON) were obtained with even lower catalyst loadings of 0.025 and 0.01 mol%, respectively (Table 1, Entries 7,8). These results are notable considering that similar yields in related Doyle–Kirmse reactions have been achieved with catalyst loadings of 1–5 mol% for Rh-based complexes[12a,d,f] and 5–20 mol% for synthetic catalysts based on non-precious metals.[12c,13c,14] In addition, in contrast to the need for slow addition of the diazo reagent in Rh-[12a,d] and Cu-catalyzed[13a] reactions, the Mb(L29S,H64V,V68F)-catalyzed reaction proceeds with excellent chemoselectivity, that is, without carbene dimerization, even upon direct mixing of the sulfide and diazo reactants. Time-course experiments further showed that the biocatalytic formation of **3** occurs with an initial rate of 167 turnovers per minute (Table S2) and reaches completion within 30 min (Table 1, Entry 9). These kinetics also compare very favorably with those of organometallic catalysts, and in particular those involving Cu and Co complexes, for which reaction times of 10–36 hours have been reported.[13b,c,14]

Controlling the enantioselectivity of Doyle–Kirmse reactions has proven challenging (typically, < 10–50% *ee*), a phenomenon that has been attributed to the difficulty of discriminating, using chiral catalysts, between the heterotopic lone pairs of the sulfide during attack on the metallo-

carbenoid species to yield a chiral sulfur ylide,[12a,13a,c,14b] the stereochemical information of which is then readily transferred to the carbon atom during the bond-rearrangement process.[18] While the native Mb scaffold produces **3** in racemic form, moderate to good levels of enantioselectivity were obtained with some of the engineered Mb variants (Figure S3). Importantly, the highly active Mb(L29S,H64V,V68F) variant also showed the highest degree of stereocontrol, yielding **3** with an enantiomeric excess (*ee*) of 71% (Figure S3). Notably, Mb(H64V,V68A) favors formation of the opposite enantiomeric product with 46% *ee* (49% conv., 490 TON).

To examine the substrate scope of Mb(L29S,H64V,V68F), variously substituted α-diazo esters and allyl sulfides were tested. As shown in Table 2, quantitative or nearly quantitative conversions to the desired products **13**–**15** (94–99%) were achieved when starting from **1** and diazo reagents such as *tert*-butyl (**2b**), cyclohexyl (**2c**), or benzyl (**2d**) α-diazoacetate. Good to excellent conversions (57–99%) were also obtained for reactions involving allyl phenyl sulfides with substituted phenyl rings (**4**–**6**) to give products **16**–**18**. Next, the Mb(L29S,H64V,V68F)-catalyzed transformation of benzyl- (**8**–**9**) and alkyl-substituted allyl sulfides (**10**–**12**) in the presence of EDA was examined. The high yields measured for **20** and **21** (78–93%) indicate that benzyl-substituted allyl sulfides are also efficiently processed by the biocatalyst. Except for the poorly water-soluble octyl allyl sulfide (**11**), moderate to high product conversions (35–86%) were achieved for the reactions with other alkyl-substituted allyl sulfides (**22**, **24**), which further supports the broad substrate scope of Mb(L29S,H64V,V68F). Finally, the successful synthesis of **19** from phenyl but-2-enyl sulfide (**7**) and EDA (> 99% conv.) showed that substitutions at the level of the allyl group are also tolerated by the Mb variant. Under catalyst-limited conditions (i.e., using 0.01 mol%), Mb(L29S,H64V,V68F) was found to support thousands of catalytic turnovers (1000–8800) for all of the tested substrates except **11** (Table 2).

The [2,3]-sigmatropic rearrangement of propargylic sulfides offers a convenient route to generate allenes, which are valuable intermediates for a host of synthetic transformations.[19] To assess the scope of the Mb(L29S,H64V,V68F)
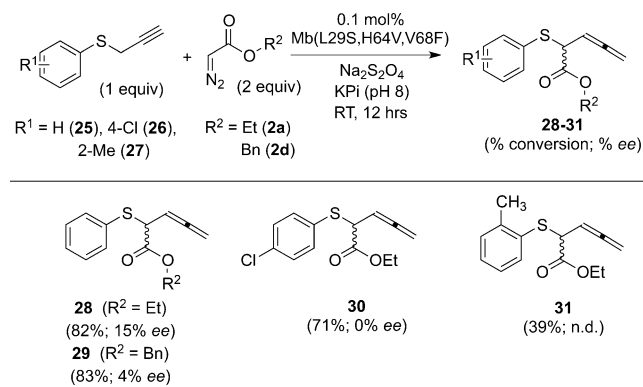
Scheme 1. Mb(L29S,H64V,V68F)-catalyzed [2,3]-sigmatropic rearrangement of propargylic sulfides.

Table 2: Substrate scope of Mb(L29S,H64V,V68F).[a]

| Sulfide	Diazo reag.	Product	% conv. (TON)	TTN[b]	ee [%][c]
1	2b	13	>99% (>1000)	8170	6%
1	2c	14	>99% (>1000)	8820	9%
1	2d	15	94% (940)	3570	47%
4	2a	16	>99% (>1000)	5050	20% −60%[d]
5	2a	17	>99% (>1000)	5960	40%
6	2a	18	57% (570)	1000	18% 58%[d]
7	2a	19	>99% (>1000)	8120	57/59% 1:1 d.r.
8	2a	20	78% (780)	7040	10%
9	2a	21	93% (930)	5470	43%
10	2a	22	35% (350)	3570	38%
11	2a	23	8% (80)	125	n.d.[e]
12	2a	24	86% (860)	4190	19%

[a] Under standard reactions conditions as described in Table 1.
[b] TTN = total turnover number. Measured using 1 μM Mb catalyst instead of 10 μM. [c] As determined by chiral GC or Supercritical Fluid Chromatography (SFC). [d] Using Mb(H64V,V68A). [e] Enantiomers could not be resolved.

catalyst in the context of this reaction, variously substituted phenyl propargylic sulfides in combination with ethyl or benzyl α-diazo-acetate as carbene precursors were tested (Scheme 1). Notably, the corresponding allenyl-substituted sulfide products (**28–31**) were obtained in high yields (71–83%) in most cases, thereby demonstrating the functionality of the Mb-based catalyst in promoting the [2,3]-sigmatropic rearrangement of propargylic sulfide substrates.

Chiral GC/SFC analyses showed that Mb(L29S,H64V,V68F) exhibits moderate to good enantiose-lectivity (20–60% *ee*) in the transformation of several of the allylic sulfide substrates of Table 2. In comparison, biocatalytic transformation of the propargylic sulfides occurred with significantly reduced enantiocontrol (<15% *ee*; Scheme 1). These experiments also revealed that the degree of asymmetric induction can be influenced by the structure of the diazo reagent (e.g., 47–71% *ee* for **3** and **15** vs. 6–9% *ee* for **13** and **14**). Finally, a larger-scale reaction with 15 mg of phenyl allyl sulfide (**1**), 2 equiv of EDA (**2a**), and 0.1 mol% Mb(L29S,H64V,V68F) enabled the isolation of 19.4 mg of **3** in 84% yield, thus demonstrating the scalability of the biocatalytic process.

Scheme 2 depicts a plausible mechanism for the Mb-catalyzed reaction reported herein. We envisage the initial
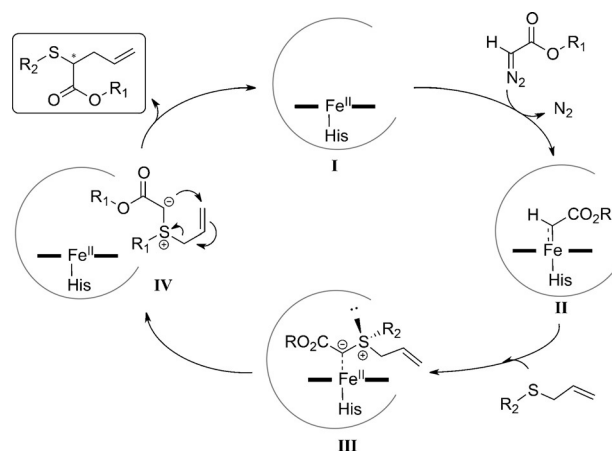
Scheme 2. Proposed mechanism and catalytic steps for the myoglobin-catalyzed Doyle–Kirmse reaction.

formation of an iron-porphyrin-bound carbenoid species (**II**), which has electrophilic character[3d,20] and can react with nucleophiles.[7,9] Accordingly, nucleophilic attack through the action of the allylic sulfide on this intermediate is envisioned to give rise to a sulfonium ylide (**III**), followed by a rapid [2,3]-sigmatropic rearrangement to yield the final product. The proposed role of the sulfide substrate as a nucleophile is consistent with the experimentally observed higher reactivity of electron-rich allyl sulfides versus isosteric, electrodeficient counterparts (**17** vs. **18**; Table 2). This trend was reproduced with other Mb variants [e.g., 83–95% conversion for **17** vs. 13–30% for **18** with Mb(H64V,V68A) and Mb(F43V,V68F)], thus suggesting that the differential reactivity is largely driven by the electronic properties of the substrate rather than by the biocatalyst. The enantioselectivity-determining step in asymmetric Doyle–Kirmse reactions is generally assumed to be associated with formation of the (chiral) sulfonium ylide,[12a,13a,c,14b] an assumption based on the high degree of stereoretention observed during the rearrangement of in situ prepared optically active sulfonium ylides.[18,21] Within this mechanistic framework, we envision two alternative, although not mutually exclusive, scenarios by which enantiocontrol could be exerted by the engineered Mb catalysts: 1) by

influencing the pre-attack orientation of the sulfide so that approach to the heme–carbene intermediate through one of the lone pairs on the sulfur atom is preferred, and/or 2) by dictating which face of the heme-bound carbenoid group is exposed to attack by the sulfide nucleophile, in analogy to our proposed stereochemical model for Mb-catalyzed olefin cyclopropanation.[3d]

While further studies are warranted to discriminate between these scenarios, experiments were performed to clarify the beneficial role of the active-site mutations in Mb(L29S,H64V,V68F). To this end, we characterized and compared the catalytic activity and selectivity of a set of single and double reversion mutants in the reaction with phenyl allyl sulfide (**1**) and EDA (Table S2). In line with our previous observations,[3d,9a,16] mutation of the distal His residue (H64V) increases both the TTN (2230 vs. 1615 for Mb) and product formation rate (121 vs. 79 min^{-1}), possibly through facilitating access of the substrate to the heme cavity (Figure S1). The L29S mutation further enhances the catalytic competency of the hemoprotein, as suggested by the increased total turn-overs (3085 TTN) supported by Mb(L29S,H64V). The V68F mutation has no beneficial effect when used alone or in combination with H64V, but it contributes synergistically with L29S to improving both TTN [6280 for Mb(L29S,H64V,V68F) vs. 3085 for Mb(L29S,H64V)] and rate (167 vs. 118 min^{-1}, respectively). Interestingly, none of the single-site or double-site variants showed significantly improved enantioselectivity compared to wild-type Mb (< 5% *ee*; Table S2). These results indicate that the enhanced enantioselectivity of Mb(L29S,H64V,V68F) stems from a synergistic contribution from the three active-site mutations. This effect is likely facilitated by the close proximity of these residues within the heme pocket (ca. 7 Å for C(β)···C(β) distance; Figure S1).

In summary, this study demonstrates that engineered Mb variants can serve as efficient biocatalysts for asymmetric Doyle–Kirmse reactions. When using the optimized variant Mb(L29S,H64V,V68F), good to excellent product conversions as well as high numbers of catalytic turnovers (up to 8820) were achieved across a variety of allylic and propargylic sulfides in the presence of α-diazo ester-based carbene precursors. Importantly, the enantioselectivity of the Mb catalyst could be tuned and optimized through mutations within the distal pocket of the protein. This work expands the toolbox of biocatalytic strategies for mediating sigmatropic rearrangements[22] and the asymmetric formation of carbon–carbon bonds.[2a]

Acknowledgements

[1] a) U. T. Bornscheuer, G. W. Huisman, R. J. Kazlauskas, S. Lutz, J. C. Moore, K. Robins, *Nature* **2012**, *485*, 185–194; b) N. J. Turner, *Nat. Chem. Biol.* **2009**, *5*, 568–574; c) A. S. Bommarius, J. K. Blum, M. J. Abrahamson, *Curr. Opin. Chem. Biol.* **2011**, *15*, 194–200; d) M. T. Reetz, *J. Am. Chem. Soc.* **2013**, *135*, 12480–12496.

[2] a) N. G. Schmidt, E. Eger, W. Kroutil, *ACS Catal.* **2016**, *6*, 4286–4311; b) K. Faber, W. D. Fessner, N. J. Turner, *Biocatalysis in Organic Synthesis. Science of Synthesis*, Vol. 1–3, Georg Thieme, Stuttgart, **2015**; c) K. Fesko, M. Gruber-Khadjawi, *ChemCatChem* **2013**, *5*, 1248–1272; d) S. C. Hammer, P. O. Syren, M. Seitz, B. M. Nestl, B. Hauer, *Curr. Opin. Chem. Biol.* **2013**, *17*, 293–300.

[3] 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) Z. J. Wang, H. Renata, N. E. Peck, C. C. Farwell, P. S. Coelho, F. H. Arnold, *Angew. Chem. Int. Ed.* **2014**, *53*, 6810–6813; *Angew. Chem.* **2014**, *126*, 6928–6931; d) M. Bordeaux, V. Tyagi, R. Fasan, *Angew. Chem. Int. Ed.* **2015**, *54*, 1744–1748; *Angew. Chem.* **2015**, *127*, 1764–1768; e) P. Srivastava, H. Yang, K. Ellis-Guardiola, J. C. Lewis, *Nat. Commun.* **2015**, *6*, 7789; f) 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.

[4] a) S. Abe, J. Niemeyer, M. Abe, Y. Takezawa, T. Ueno, T. Hikage, G. Erker, Y. Watanabe, *J. Am. Chem. Soc.* **2008**, *130*, 10512–10514; b) A. Chatterjee, H. Mallin, J. Klehr, J. Vallapurackal, A. D. Finke, L. Vera, M. Marsh, T. R. Ward, *Chem. Sci.* **2016**, *7*, 673–677.

[5] a) D. Coquière, J. Bos, J. Beld, G. Roelfes, *Angew. Chem. Int. Ed.* **2009**, *48*, 5159–5162; *Angew. Chem.* **2009**, *121*, 5261–5264; b) J. Podtetenieff, A. Taglieber, E. Bill, E. J. Reijerse, M. T. Reetz, *Angew. Chem. Int. Ed.* **2010**, *49*, 5151–5155; *Angew. Chem.* **2010**, *122*, 5277–5281.

[6] J. Bos, W. R. Browne, A. J. Driessen, G. Roelfes, *J. Am. Chem. Soc.* **2015**, *137*, 9796–9799.

[7] V. Tyagi, R. Fasan, *Angew. Chem. Int. Ed.* **2016**, *55*, 2512–2516; *Angew. Chem.* **2016**, *128*, 2558–2562.

[8] a) C. Mayer, D. G. Gillingham, T. R. Ward, D. Hilvert, *Chem. Commun.* **2011**, *47*, 12068–12070; b) F. Philippart, M. Arlt, S. Gotzen, S. J. Tenne, M. Bocola, H. H. Chen, L. Zhu, U. Schwaneberg, J. Okuda, *Chem. Eur. J.* **2013**, *19*, 13865–13871; c) M. Basauri-Molina, D. G. A. Verhoeven, A. J. van Schaik, H. Kleijn, R. J. M. K. Gebbink, *Chem. Eur. J.* **2015**, *21*, 15676–15685.

[9] a) G. Sreenilayam, R. Fasan, *Chem. Commun.* **2015**, *51*, 1532–1534; b) V. Tyagi, R. B. Bonn, R. Fasan, *Chem. Sci.* **2015**, *6*, 2488–2494.

[10] a) W. Kirmse, M. Kapps, *Chem. Ber.* **1968**, *101*, 994–996; b) M. P. Doyle, J. H. Griffin, M. S. Chinn, D. Vanleusen, *J. Org. Chem.* **1984**, *49*, 1917–1925; c) M. P. Doyle, D. C. Forbes, *Chem. Rev.* **1998**, *98*, 911–936.

[11] a) J. B. Sweeney, *Chem. Soc. Rev.* **2009**, *38*, 1027–1038; b) T. H. West, S. S. M. Spoehrle, K. Kasten, J. E. Taylor, A. D. Smith, *ACS Catal.* **2015**, *5*, 7446–7479.

[12] a) Y. Nishibayashi, K. Ohe, S. Uemura, *J. Chem. Soc. Chem. Commun.* **1995**, 1245–1246; b) V. K. Aggarwal, M. Ferrara, R. Hainz, S. E. Spey, *Tetrahedron Lett.* **1999**, *40*, 8923–8927; c) X. M. Zhang, M. Ma, J. B. Wang, *Tetrahedron: Asymmetry* **2003**, *14*, 891–895; d) A. G. H. Wee, Q. Shi, Z. Y. Wang, K. Hatton, *Tetrahedron: Asymmetry* **2003**, *14*, 897–909; e) P.

Müller, S. Grass, S. P. Shahi, G. Bernardinelli, *Tetrahedron* **2004**, *60*, 4755–4763; f) M. Liao, B. Wang, *Green Chem.* **2007**, *9*, 184–188; g) H. Zhang, B. Wang, H. Yi, Y. Zhang, J. B. Wang, *Org. Lett.* **2015**, *17*, 3322–3325.

[13] a) D. W. McMillen, N. Varga, B. A. Reed, C. King, *J. Org. Chem.* **2000**, *65*, 2532–2536; b) X. M. Zhang, Z. H. Qu, Z. H. Ma, W. F. Shi, X. L. Jin, J. B. Wang, *J. Org. Chem.* **2002**, *67*, 5621–5625; c) M. Ma, L. L. Peng, C. K. Li, X. Zhang, J. B. Wang, *J. Am. Chem. Soc.* **2005**, *127*, 15016–15017.

[14] a) T. Fukuda, T. Katsuki, *Tetrahedron Lett.* **1997**, *38*, 3435–3438; b) T. Fukuda, R. Irie, T. Katsuki, *Tetrahedron* **1999**, *55*, 649–664.

[15] a) C. Y. Zhou, W. Y. Yu, P. W. H. Chan, C. M. Che, *J. Org. Chem.* **2004**, *69*, 7072–7082; b) P. W. Davies, S. J. C. Albrecht, G. Assanelli, *Org. Biomol. Chem.* **2009**, *7*, 1276–1279; c) D. S. Carter, D. L. Van Vranken, *Org. Lett.* **2000**, *2*, 1303–1305; d) M. S. Holzwarth, I. Alt, B. Plietker, *Angew. Chem. Int. Ed.* **2012**, *51*, 5351–5354; *Angew. Chem.* **2012**, *124*, 5447–5450.

[16] S. Giovani, R. Singh, R. Fasan, *Chem. Sci.* **2016**, *7*, 234–239.

[17] M. Bordeaux, R. Singh, R. Fasan, *Bioorg. Med. Chem.* **2014**, *22*, 5697–5704.

[18] B. M. Trost, R. F. Hammen, *J. Am. Chem. Soc.* **1973**, *95*, 962–964.

[19] *Modern Allene Chemistry* (Eds.: N. Krause, A. S. K. Hashmi), Wiley-VCH, Weinheim, **2004**.

[20] a) R. L. Khade, W. C. Fan, Y. Ling, L. Yang, E. Oldfield, Y. Zhang, *Angew. Chem. Int. Ed.* **2014**, *53*, 7574–7578; *Angew. Chem.* **2014**, *126*, 7704–7708; b) J. R. Wolf, C. G. Hamaker, J. P. Djukic, T. Kodadek, L. K. Woo, *J. Am. Chem. Soc.* **1995**, *117*, 9194–9199.

[21] B. M. Trost, W. G. Biddlecom, *J. Org. Chem.* **1973**, *38*, 3438–3439.

[22] a) D. Hilvert, S. H. Carpenter, K. D. Nared, M. T. M. Auditor, *Proc. Natl. Acad. Sci. USA* **1988**, *85*, 4953–4955; b) D. Y. Jackson, J. W. Jacobs, R. Sugasawara, S. H. Reich, P. A. Bartlett, P. G. Schultz, *J. Am. Chem. Soc.* **1988**, *110*, 4841–4842; c) M. R. Haynes, E. A. Stura, D. Hilvert, I. A. Wilson, *Science* **1994**, *263*, 646–652; d) S. S. Yoon, Y. Oei, E. Sweet, P. G. Schultz, *J. Am. Chem. Soc.* **1996**, *118*, 11686–11687; e) H. D. Ulrich, E. Mundroff, B. D. Santarsiero, E. M. Driggers, R. C. Stevens, P. G. Schultz, *Nature* **1997**, *389*, 271–275; f) Z. H. S. Zhou, A. Flohr, D. Hilvert, *J. Org. Chem.* **1999**, *64*, 8334–8341; g) C. K. Prier, T. K. Hyster, C. C. Farwell, A. Huang, F. H. Arnold, *Angew. Chem. Int. Ed.* **2016**, *55*, 4711–4715; *Angew. Chem.* **2016**, *128*, 4789–4793.