ChemPubSoc Europe

DOI: 10.1002/cctc.201600317

CHEMCATCHEM Full Papers

Modular Combination of Enzymatic Halogenation of Tryptophan with Suzuki–Miyaura Cross-Coupling Reactions

Marcel Frese, Christian Schnepel, Hannah Minges, Hauke Voß, Rebecca Feiner, and Norbert Sewald*[a]

The combination of the biocatalytic halogenation of L-tryptophan with subsequent chemocatalytic Suzuki–Miyaura cross-coupling reactions leads to the modular synthesis of an array of C5, C6, or C7 aryl-substituted tryptophan derivatives. In a three-step one-pot reaction, the bromo substituent is initially incorporated regioselectively by immobilized tryptophan 5-, 6-, or 7-halogenases, respectively, with concomitant cofactor regeneration. The halogenation proceeds in aqueous media at room temperature in the presence of NaBr and O_2. After the separation of the biocatalyst by filtration, a Pd catalyst, base, and boronic acid are added to the aryl halide formed in situ to effect direct Suzuki–Miyaura cross-coupling reactions followed by *tert*-butoxycarbonyl (Boc) protection. After a single purification step, different Boc-protected aryl tryptophan derivatives are obtained that can, for example, be used for peptide or peptidomimetic synthesis.

Introduction

Biocatalysis has emerged as an important research area in organic synthesis both in academia and industry.[1] The high stereo- and regioselectivity of enzyme-catalyzed reactions and their compatibility with many unprotected functional groups are major advantages. However, there are several important chemical transformations, such as cross-coupling reactions, for which no enzymatic processes are known, so the use of biocatalysis together with chemocatalysis combines the advantages of both areas.[2] In particular, multistep one-pot reactions offer the unique opportunity to circumvent time-consuming, waste-producing, and solvent-intensive work-up and purification steps of intermediates, which leads to more sustainable and economic synthetic routes.[3] A handful of combined chemo-biocatalytic reactions has been described since the 1980s. The major bottleneck of these processes is the mandatory compatibility of the chemo- and biocatalyst to solvent and reaction conditions. As few enzymes are stable and active in organic solvents, the combination of biocatalysis and chemocatalysis in a multistep one-pot reaction should proceed in aqueous media, as water provides the potential to combine a huge toolbox of different enzymes with several chemocatalysts. In addition, water shows outstanding benefits as a nonflammable, environmentally friendly, non-toxic, low-cost solvent.

Gröger and co-workers, pioneers in the field of chemoenzymatic catalysis, published several reactions that combine both types of catalysis in an aqueous medium. This includes the combination of an asymmetric organocatalytic aldol reaction with the subsequent enzymatic reduction of the ketone to chiral 1,3-diols.[4,5] The Wacker–Tsuji oxidation of styrene followed by enzymatic ketone reduction gives enantiomerically pure secondary alcohols,[6] and olefin metathesis together with pig liver esterase hydrolysis provides access to cyclic malonic acid monoesters in aqueous media.[7]

In this context, the regioselective introduction of halogen substituents into organic scaffolds using enzymatic approaches would be a highly beneficial approach to be combined with further metal-catalyzed modification. Halogenated products form important intermediates in the synthesis of fine chemicals as they can be modified easily in established procedures. In recent years, Pd-catalyzed cross-coupling reactions have emerged as an outstanding methodology for the formation of C–C bonds, especially for large scaffolds. Gröger and co-workers have already shown the combination of Pd-catalyzed cross-coupling reactions with the enzymatic asymmetric reduction of ketones.[8,9]

The chemical incorporation of the halide substituent requires corrosive and hazardous chemicals such as Cl_2 or Br_2 under harsh conditions and often results in product mixtures because of ambiguous regioselectivity. In contrast to chemical methods, biocatalytic halogenation using flavin adenine dinucleotide (FAD) dependent halogenases emerged as a promising and sustainable approach to obtain aryl halides.[10,11] These enzymes introduce halogen substituents even at electronically unfavored positions of the indole ring and only require benign halide salts such as NaCl or NaBr and oxygen for the regioselective halogenation.[12–16] The first members of this class of enzymes that have been characterized in detail are the trypto-

[a] Dr. M. Frese, C. Schnepel, H. Minges, H. Voß, R. Feiner, Prof. Dr. N. Sewald
Organische und Bioorganische Chemie, Fakultät für Chemie
Universität Bielefeld
Universitätsstr. 25
33615 Bielefeld (Germany)
E-mail: norbert.sewald@uni-bielefeld.de
Homepage: http://www.uni-bielefeld.de/chemie/oc3sewald/

Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under http://dx.doi.org/10.1002/cctc.201600317.

phan 7-halogenase PrnA, which originates from the pyrrolnitrin biosynthesis in *Pseudomonas fluorescens*,[10] and RebH from the bacterium *Lechevalieria aerocolonigenes*, involved in rebeccamycin biosynthesis.[11] By introducing the *prnA* gene into the biosynthesis pathway of the uridyl peptide antibiotic pacidamycin, the resulting chlorinated indole moiety serves as a chemical handle for the post-biosynthetic modification towards several new analogs.[17] Likewise, *rebH* was integrated into the medicinal plant *Catharanthus roseus* in the biosynthesis of monoterpene indole alkaloids followed by chemical derivatization of the extracted chlorinated compounds using Pd-catalyzed Suzuki–Miyaura cross-coupling reactions.[18] As these secondary metabolites were only formed in minor amounts, the reactions could not be performed on a preparative scale. Only recently, Suzuki–Miyaura cross-couplings performed subsequently to the enzymatic halogenation of tryptoline derivatives were communicated.[19]

Results and Discussion

We established an efficient methodology for the regioselective enzymatic bromination of L-tryptophan and its derivatives even on a multigram scale using the immobilized Trp 7-halogenase RebH.[20] Precipitation and cross-linking of RebH in the presence of all auxiliary enzymes necessary for concomitant cofactor regeneration gives so-called combiCLEAs that brominate L-tryptophan with full conversion at substrate concentrations of 200 mg L^{-1}. As this biocatalytic halogenation is highly regioselective without the formation of any side products, the crude product is sufficiently pure for further modification (Figure S1).

Consequently, we embarked on the subsequent modification of the biocatalytically introduced halogen by in situ Suzuki–Miyaura cross-coupling reactions without any purification steps of intermediates in a sequential two-step one-pot process (Figure 1).

To derivatize different positions of the indole moiety independently and selectively, the tryptophan 5-halogenase PyrH and the 6-halogenase Thal were tested for their ability to brominate tryptophan regioselectively on a preparative scale using the CLEA methodology as described previously for RebH.[20] *E. coli* lysate that contained the overexpressed halogenase supplemented with flavin reductase PrnF and alcohol dehydrogenase ADH from *Rhodococcus sp.* was precipitated by the addition of ammonium sulfate. After subsequent cross-linking with glutaraldehyde, an active and solid biocatalyst was obtained for halogenation.

With the optimized cross-linking conditions for combiCLEA generation, the quantitative halogenation of 150 mg L-tryptophan (1 mM, 750 mL) could be obtained in both cases for PyrH and Thal (Figure S1), which showed conversions similar to RebH. By using these three Trp-halogenases, the C5-, C6-, or C7-position can be addressed regioselectively for bromination.

For the subsequent Suzuki–Miyaura cross-coupling, we started the optimization using purified L-7-bromotryptophan and phenylboronic acid starting materials. Inspired by the approach of the Goss group who cross-coupled halotryptophans synthesized from halogenated indoles using tryptophan synthase,[21] we chose Na_2PdCl_4 as a Pd source in combination with the Buchwald ligand SPhos. This system is known to catalyze challenging substrate combinations with excellent results even at low temperatures.[18b,19,22,23] Reactions that contained 5 mol% of Pd and 1.1 equivalents of phenylboronic acid in the presence of 5 equivalents of K_2CO_3 resulted in a conversion of only 50% within 3 h at 95 °C (Table 1, Entry 1). By increasing the amount of boronic acid to 3 equivalents, the conversion increased to 80% (Table 1, Entry 2). As SPhos is barely soluble in water, a mixture of water and *n*-butanol was used.[18b] By replacing the solvent system with water/dioxane/toluene, the aryl halide could be converted completely into the cross-coupling product (Table 1, Entry 3). For the adaptation of these conditions to the one-pot cross-coupling of in situ formed L-7-bromotryptophan, the biocatalytic bromination was conducted as described previously using RebH combiCLEAs.[20] Once halogenation had reached quantitative substrate conversion, the immobilized biocatalyst was removed by filtration. Phenylboronic acid, base, and Pd catalyst were added to the solution, which was then heated to 95 °C for direct Suzuki–Miyaura cross-coupling without any further purification of intermediates. As the enzymatic halogenation was performed in a phosphate-buffered system, the amount of base needed to be increased to 25 equivalents to obtain a pH value of nearly 11. Unfortunately, if we used the conditions optimized for the purified aryl halide, the conversion decreased to 51% for the

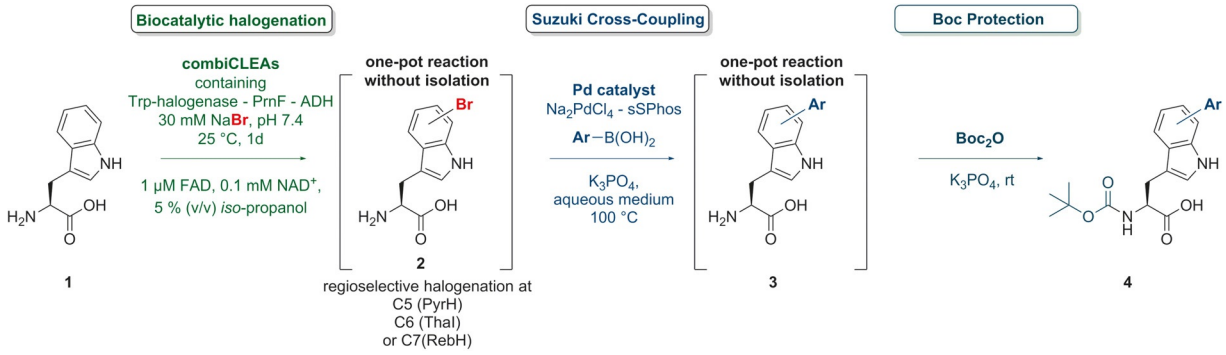
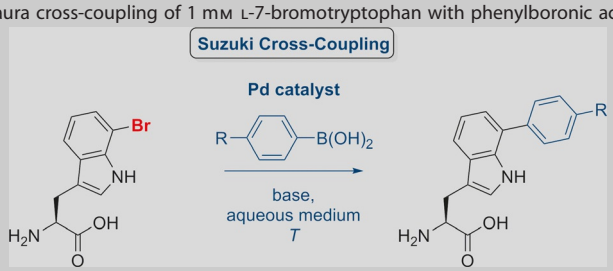


Figure 1. Chemoenzymatic synthesis of Boc-protected aryl tryptophan derivatives.

Table 1. Optimization of the Suzuki–Miyaura cross-coupling of 1 mM L-7-bromotryptophan with phenylboronic acid.



Entry	Pd catalyst [5 mol %]	Ligand [15 mol %]	Solvent	Boronic acid [equiv.]	Base [equiv.]	T [°C]	Conversion[d] [%]	t [h]
1[a]	Na_2PdCl_4	SPhos	water/*n*BuOH 3:1	R = H (1.1)	K_2CO_3 (5)	95	50	3
2[a]	Na_2PdCl_4	SPhos	water/*n*BuOH 3:1	R = H (3)	K_2CO_3 (5)	95	80	3
3[a]	Na_2PdCl_4	SPhos	water/dioxane/toluene 10:2:1	R = H (3)	K_2CO_3 (5)	95	99	1
4[b]	Na_2PdCl_4	SPhos	water/dioxane/toluene 10:2:1	R = H (3)	K_2CO_3 (25)	95	51	3
5[b]	Na_2PdCl_4	SPhos	water/dioxane/toluene 10:2:1	R = H (5)	K_3PO_4 (25)	95	53	3
6[b]	Na_2PdCl_4	sSPhos	water	R = H (5)	K_3PO_4 (25)	95	85	3
7[b,c]	Na_2PdCl_4	sSPhos	water	R = H (5)	K_3PO_4 (25)	95	99 (94)[e]	3
8[b,c]	Na_2PdCl_4	sSPhos	water	R = OCH_3 (5)	K_3PO_4 (25)	95	99 (78)[e]	3

General conditions: 5 μmol scale in Eppendorf tubes by using a thermoshaker. [a] Purified product was used. [b] 1 mM L-7-Bromotryptophan that originated from the CLEA halogenation was used. [c] 0.1 mmol scale, performed under Ar atmosphere. All solutions were degassed using ultrasound with Ar sparging. The Na_2PdCl_4 was preactivated together with sSPhos for 10 min at 42 °C and added to the hot reaction solution. [d] Calculation based on RP-HPLC. [e] Isolated yield after preparative HPLC.

crude aryl halide that originates from the CLEA halogenation (Table 1, Entry 4). Variation of the base (K_2CO_3 vs. K_3PO_4) in accordance with the phosphate buffer used for RebH halogenation only resulted in a slight increase to 53% conversion (Table 1, Entry 5). The low water solubility of the SPhos ligand clearly impeded conversion, which led to lower yields in the crude CLEA filtrate. Consequently, we changed the ligand to the sulfonated water-soluble variant sSPhos, and a significantly higher conversion of 85% could be observed (Table 1, Entry 6). Further optimization under Ar atmosphere led to a quantitative conversion of L-7-bromotryptophan with 5 equivalents of phenylboronic acid or 4-methoxyphenylboronic acid, respectively, on a 0.1 mmol scale in good yields (Table 1, Entries 7–8).

Remarkably, the unprotected zwitterionic cross-coupling products can be extracted into the organic phase to facilitate purification. These findings clearly emphasize the benefits of the presented one-pot reaction cascade to a prevalent sequential stepwise reaction in which the bromotryptophans need to be isolated from the aqueous phase, which contains large amounts of salts such as NaBr and Na_2HPO_4 from the biocatalytic halogenation.[20] As a result of this modular approach, each of the C5, C6, or C7 L-bromotryptophan derivatives could be coupled successfully to six different boronic acids, followed by N^{α}-*tert*-butoxycarbonyl (Boc) protection as a third step in the one-pot reaction (Figure 1). This offers the direct application of each synthesized amino acid for further reactions, for example, in peptide synthesis. For this protection step, the pH value of the reaction solution after the cross-coupling was readjusted to pH 11, Boc-anhydride (4 equivalents) was added portionwise, and the mixture was stirred overnight at room temperature. After acidification, the product was extracted and purified by using preparative reversed-phase (RP) HPLC. With L-7-bromotryptophan as the aryl halide, isolated yields up to 94% over three steps could be obtained (Table 2, Entry 1). Even electron-deficient boronic acids such as 4-carboxyphenylboronic acid or 4-trifluoromethylphenylboronic acid led to satisfactory results (87 and 66% isolated yields, respectively, Table 2, Entries 13 and 7). Surprisingly, in all cases the C7-brominated aryl halide resulted in the highest yields, even slightly higher than that of the virtually most reactive, electron-defi-

Table 2. Substrate scope of the three-step one-pot synthesis.

Entry	Aryl halide[a]	Boronic acid[b]	Product[a]	Yield[c] [%]
1	7-Br–W		Boc–7-Ph–W	94
2	6-Br–W	Ph–R	Boc–6-Ph–W	75
3	5-Br–W		Boc–5-Ph–W	32
4	7-Br–W		Boc–7-(4-CH_3O–Ph)–W	74
5	6-Br–W	4-CH_3O–Ph–R	Boc–6-(4-CH_3O–Ph)–W	57
6	5-Br–W		Boc–5-(4-CH_3O–Ph)–W	54
7	7-Br–W		Boc–7-(4-CF_3–Ph)–W	66
8	6-Br–W	4-CF_3–Ph–R	Boc–6-(4-CF_3–Ph)–W	44
9	5-Br–W		Boc–5-(4-CF_3–Ph)–W	23
10	7-Br–W		Boc–7-(2′-Furyl)–W	69
11	6-Br–W	2-Furyl–R	Boc–6-(2′-Furyl)–W	63
12	5-Br–W		Boc–5-(2′-Furyl)–W	46
13	7-Br–W		Boc–7-(4-CO_2H–Ph)–W	87
14	6-Br–W	4-CO_2H–Ph–R	Boc–6-(4-CO_2H–Ph)–W	28
15	5-Br–W		Boc–5-(4-CO_2H–Ph)–W	18
16	7-Br–W		Boc–7-(3-CH_3–Ph)–W	67
17	6-Br–W	3-CH_3–Ph–R	Boc–6-(3-CH_3–Ph)–W	56
18	5-Br–W		Boc–5-(3-CH_3–Ph)–W	32

[a] W = L-tryptophan [b] R = $B(OH)_2$ [c] Isolated yields over three steps.

cient L-6-bromotryptophan. As expected, L-5-bromotryptophan showed the lowest conversions and yields, probably because of the relatively high electron density at the carbon–halide bond.

Conclusions

Although the biocatalytic reductions of ketones and hydrolysis of racemic mixtures are established nowadays as an inherent part of organic synthesis, halogenation reactions are performed predominantly using chemical approaches. To the best of our knowledge, our findings represent the first example of a consecutive biocatalytic halogenation–chemocatalytic Suzuki–Miyaura cross-coupling combination in a one-pot approach on a preparative scale. With the modular reaction cascade presented here, a bromine substituent is introduced biocatalytically at the C5-, C6-, or C7-position of tryptophan, which depends on the FAD-dependent halogenase employed. The CLEA methodology is suitable not only for the Trp-7 halogenase RebH but also for the Trp-5 halogenase PyrH and the Trp-6 halogenase Thal on a preparative scale with comparable yields. After the separation of the immobilized biocatalyst by filtration, the bromine substituent can be displaced subsequently in Suzuki–Miyaura cross-coupling reactions by the addition of base, boronic acid, and Pd catalyst to the reaction solution. The resulting cross-coupling product can either be isolated after neutralization in the zwitterionic form or transformed in a third one-pot step to an N^{α}-Boc-protected amino acid that may be used directly for further (peptide) synthesis. Depending on the electronic properties of the boronic acid, this easily scalable reaction gives rise to 18 different tryptophan derivatives in good yields over three steps with only one final purification step. These amino acids form interesting building blocks for the synthesis of peptides and peptidomimetics that are otherwise chemically accessible only through laborious multistep reactions. The cross-coupling product can be extracted from the aqueous phase. As a result, only NaBr, 2-propanol, and Boc-anhydride are required in excess, and the boronic acid can be used in stoichiometric amounts; cofactors and the Pd catalyst are only used catalytically. In addition, solvent- and time-consuming purification steps are minimized because of the one-pot approach, which underlines the sustainability of the presented process towards arylated tryptophan derivatives. As much effort has been put into the expansion of the substrate scope of tryptophan halogenases by means of directed evolution with promising results,[24–26] the one-pot enzymatic halogenation–Suzuki–Miyaura cross-coupling methodology could also be applied to other non-tryptophan aryl halides.[19]

Experimental Section

Unless otherwise noted, all chemicals were obtained from commercial suppliers as specified for analytical applications (p.a.).

Molecular cloning of *pyrH* and *thal*

PyrH (Uniprot ID: A4D0H5) and *thal* (Uniprot ID: A1E280) genes were synthesized codon-optimized for *E. coli* from GeneArt Technologies (Invitrogen) and subcloned into the pET28a vector using *Nde*I and *Bam*HI restriction sites with standard molecular cloning procedures.

RP-HPLC

Reactions were monitored by using RP-HPLC by using a Thermo Scientific Accela 600 equipped with a Thermo Scientific Hypersil GOLD 3 μm column (C_{18}, 150×2.1 mm, eluent A H_2O/CH_3CN/trifluoroacetic acid (TFA) = 95:5:0.1, eluent B H_2O/CH_3CN/TFA = 5:95:0.1, flow rate 0.7 mL min^{-1} using a linear gradient from 0–100% B over 5 min).

For preparative HPLC purification, a LaChrom System (Merck Hitachi) equipped with a Phenomenex Jupiter column (10 μm, C18, 300 Å, 250×21.1 mm, eluent A H_2O/CH_3CN/TFA = 95:5:0.1, eluent B H_2O/CH_3CN/TFA = 5:95:0.1, flow rate 10 mL min^{-1}) was used. For N_{α}-unprotected amino acids, the eluents without TFA were used to obtain the zwitterionic form after purification.

ESI-MS

ESI/atmospheric-pressure chemical ionization (APCI) mass spectra were recorded by using an Esquire 3000 ion trap mass spectrometer (Bruker Daltonik GmbH, Bremen, Germany) equipped with a standard ESI/APCI source. Samples were introduced directly by using a syringe pump. Nitrogen served both as the nebulizer gas and the dry gas. Nitrogen was generated by using a Bruker nitrogen generator NGM 11. Helium served as cooling gas for the ion trap and collision gas for MS^n experiments.

HRMS was recorded by using a MicroToF mass spectrometer (Bruker Daltonics, Bremen) with sample-loop injection. Mass calibration was performed immediately before measurement with sodium formate cluster and quasi-internal calibration.

NMR spectroscopy

NMR spectra were recorded by using a Bruker DRX-500 (^{1}H: 500 MHz, ^{13}C: 126 MHz) spectrometer at 298 K, and chemical shifts are reported relative to residual solvent peaks ([D_6]DMSO: ^{1}H: 2.50 ppm, ^{13}C: 39.52 ppm).

General procedure of the three-step one-pot reaction (enzymatic halogenation–Suzuki cross coupling–Boc protection)

The biocatalytic halogenation using combiCLEAs was described in detail previously.[20] *E. coli* lysate (30 mL) from 1.5 L of culture that contained the overexpressed halogenase supplemented with 75 U flavin reductase PrnF and 50 U alcohol dehydrogenase (ADH) from *Rhodococcus* sp. was precipitated by the addition of ammonium sulfate (95% saturation) for 1 h at 4 °C. Glutaraldehyde was added as a cross-linker (final concentration for RebH 0.5%, Thal 1%, PyrH 1.25%) to the solution and incubated for 2 h at 4 °C. The resulting combiCLEAs were washed three times with Na_2HPO_4 (50 mL, 100 mM), stored overnight at 4 °C, and resuspended the next day in the reaction solution that contained L-tryptophan (1 mM), NaBr (30 mM), NAD^+ (0.1 mM), FAD (1 μM), 2-propanol (5% v/v), and Na_2HPO_4 (15 mM) at pH 7.4 adjusted with H_3PO_4. The reaction pro-

cess was monitored by RP-HPLC. After full conversion, typically after 4–6 days, the immobilized biocatalyst was removed by filtration, and the reaction solution that contained 1 mM brominated tryptophan was aliquoted and stored at −20 °C. For the following Suzuki–Miyaura coupling, 100 mL solution (0.1 mmol scale) was thawed, boronic acid (5 equiv.) was added, and the solution was degassed using ultrasound and Ar sparging for 1 h at 60 °C. The solution was then heated to reflux under Ar, and K_3PO_4 (25 equiv.) and preactivated Pd catalyst (5 mol%) were added. The preactivation was performed immediately before addition by heating a 1 mL solution of 5 mM Na_2PdCl_4 (5 mol%) and 15 mM sSPhos (15 mol%) for 10 min at 42 °C by using a thermal shaker. After the addition of the Pd catalyst, the reaction solution was heated for additional 4 h at 100 °C. After cooling to RT, the cross-coupling product can either be extracted into ethyl acetate (6×50 mL) at a pH of 2–4 to obtain the unprotected amino acid after preparative HPLC, or a Boc protection of the N^{α}-amino functionality can be performed: The pH was checked and adjusted to ~11 again using K_3PO_4. Boc_2O (4 equiv.) was added portionwise, and the pH value was kept constant at ~11. After stirring overnight at RT, the solution was acidified to pH 2.5, and the cross-coupling product as well as the boronic acid were extracted into ethyl acetate (6× 50 mL). The solvent was removed under reduced pressure, and both compounds were separated by using preparative RP-HPLC.

For detailed analytical data of the synthesized compounds, please refer to the Supporting Information.

Acknowledgements

We thank Prof. Dr. Karl-Heinz van Pée for donating the plasmid encoding for the flavin reductase PrnF and Prof. Dr. Werner Hummel for donating the plasmid encoding for the alcohol dehydrogenase.

Keywords: biocatalysis · enzyme catalysis · cross-coupling · multicomponent reactions · palladium

[1] A. Schmid, F. Hollmann, J. B. Park, B. Bühler, *Curr. Opin. Biotechnol.* **2002**, *13*, 359 – 366.
[2] H. Gröger, W. Hummel, *Curr. Opin. Chem. Biol.* **2014**, *19*, 171 – 179.
[3] J. Muschiol, C. Peters, N. Oberleitner, M. D. Mihovilovic, U. T. Bornscheuer, F. Rudroff, *Chem. Commun.* **2015**, *51*, 5798 – 5811.
[4] K. Baer, M. Kraußer, E. Burda, W. Hummel, A. Berkessel, H. Gröger, *Angew. Chem. Int. Ed.* **2009**, *48*, 9355 – 9358; *Angew. Chem.* **2009**, *121*, 9519 – 9522.
[5] M. Heidlindemann, G. Rulli, A. Berkessel, W. Hummel, H. Gröger, *ACS Catal.* **2014**, *4*, 1099 – 1103.
[6] I. Schnapperelle, W. Hummel, H. Gröger, *Chem. Eur. J.* **2012**, *18*, 1073 – 1076.
[7] K. Tenbrink, M. Seßler, J. Schatz, H. Gröger, *Adv. Synth. Catal.* **2011**, *353*, 2363 – 2367.
[8] E. Burda, W. Hummel, H. Gröger, *Angew. Chem. Int. Ed.* **2008**, *47*, 9551 – 9554; *Angew. Chem.* **2008**, *120*, 9693 – 9696.
[9] S. Borchert, E. Burda, J. Schatz, W. Hummel, H. Gröger, *J. Mol. Catal. B* **2012**, *84*, 89 – 93.
[10] S. Keller, T. Wage, K. Hohaus, M. Hölzer, E. Eichhorn, K.-H. van Pée, *Angew. Chem. Int. Ed.* **2000**, *39*, 2300 – 2302; *Angew. Chem.* **2000**, *112*, 2380 – 2382.
[11] E. Yeh, S. Garneau, C. T. Walsh, *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 3960 – 3965.
[12] J. T. Payne, M. C. Andorfer, J. C. Lewis, *Angew. Chem. Int. Ed.* **2013**, *52*, 5271 – 5274; *Angew. Chem.* **2013**, *125*, 5379 – 5382.
[13] M. Frese, P. H. Guzowska, H. Voß, N. Sewald, *ChemCatChem* **2014**, *6*, 1270 – 1276.
[14] S. Flecks, E. P. Patallo, X. Zhu, A. J. Ernyei, G. Seifert, A. Schneider, C. Dong, J. H. Naismith, K. van Pée, *Angew. Chem. Int. Ed.* **2008**, *47*, 9533 – 9536; *Angew. Chem.* **2008**, *120*, 9676 – 9679.
[15] C. Dong, S. Flecks, S. Unversucht, C. Haupt, K.-H. van Pée, J. H. Naismith, *Science* **2005**, *309*, 2216 – 2219.
[16] E. Yeh, L. C. Blasiak, A. Koglin, C. L. Drennan, C. T. Walsh, *Biochemistry* **2007**, *46*, 1284 – 1292.
[17] A. D. Roy, S. Grüschow, N. Cairns, R. J. M. Goss, *J. Am. Chem. Soc.* **2010**, *132*, 12243 – 12245.
[18] a) W. Runguphan, X. Qu, S. E. O'Connor, *Nature* **2010**, *468*, 461 – 464; b) W. Runguphan, S. E. O'Connor, *Org. Lett.* **2013**, *15*, 2850 – 2853.
[19] L. J. Durak, J. T. Payne, J. C. Lewis, *ACS Catal.* **2016**, *6*, 1451 – 1454.
[20] M. Frese, N. Sewald, *Angew. Chem. Int. Ed.* **2015**, *54*, 298 – 301; *Angew. Chem.* **2015**, *127*, 302 – 305.
[21] A. D. Roy, R. J. M. Goss, G. K. Wagner, M. Winn, *Chem. Commun.* **2008**, 4831.
[22] S. D. Walker, T. E. Barder, J. R. Martinelli, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2004**, *43*, 1871 – 1876; *Angew. Chem.* **2004**, *116*, 1907 – 1912.
[23] T. E. Barder, S. D. Walker, J. R. Martinelli, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 4685 – 4696.
[24] J. T. Payne, C. B. Poor, J. C. Lewis, *Angew. Chem. Int. Ed.* **2015**, *54*, 4226 – 4230; *Angew. Chem.* **2015**, *127*, 4300 – 4304.
[25] C. B. Poor, M. C. Andorfer, J. C. Lewis, *ChemBioChem* **2014**, *15*, 1286 – 1289.
[26] S. A. Shepherd, C. Karthikeyan, J. Latham, A.-W. Struck, M. L. Thompson, B. R. K. Menon, M. Q. Styles, C. Levy, D. Leys, J. Micklefield, *Chem. Sci.* **2015**, *6*, 3454 – 3460.

Received: March 18, 2016
Published online on May 6, 2016