Reaction Cascades

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A Bioinspired Catalytic Oxygenase Cascade to Generate Complex Oxindoles**

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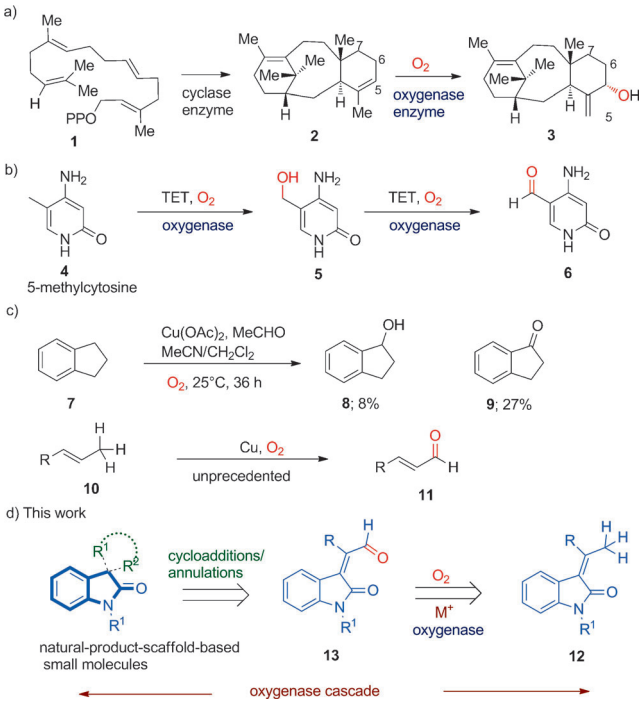
Dedicated to Professor Matthias Beller

Abstract: *Catalytic, selective, and controlled oxidative functionalization of C–H bonds using molecular oxygen as an oxidant remains highly desirable and equally challenging in the development of synthetic methodologies. Presented herein is a one-pot oxygenase cascade reaction wherein a copper(I)-catalyzed oxygenase reaction transforms the allylic methyl group in 3-methylidene oxindoles into an aldehyde, which then undergoes an aldol–oxa-Michael addition sequence with β-ketoesters to yield dihydrofuran-bearing oxindoles.*

Nature remains a source of inspiration for organic chemists to develop efficient and cleaner synthetic methods directed towards greater molecular complexity.[1] Amongst the most challenging transformations that remain underdeveloped in a synthesis laboratory, are selective oxidative functionalizations of C–H bonds, despite the fact that such reactions are beautifully exploited by nature in the biogenesis of natural products.[2] For its abundance, low cost, and lack of toxic byproducts, molecular oxygen is an ideal oxidant for these transformations. In the biosynthesis of natural products, generally two types of metalloenzymes catalyze the oxidations:[3] 1) oxidases that couple the reduction of O_2 to H_2O or H_2O_2 during the oxidation of a diversity of substrates, and 2) oxygenases that catalyze the transfer of an oxygen atom from molecular dioxygen to organic substrates.[4] For instance, generation of the polycyclic taxane precursor **2** from acyclic tetraene **1** is followed by introduction of a 5-α-hydroxy group (**3**) by a cytochrome-P450-dependent hydroxylase-mediated oxygenase reaction (Scheme 1 a).[5] TET (ten eleven translocation) proteins induce oxidation of 5-methylcytosine (**4**) into 5-hydroxymethylcytosine (**5**) and 5-formylcytosine (**6**, Scheme 1 b)[6] which undergoes decarboxylation and thereby induces DNA demethylation as an epigenetic control.[7] A large class of oxidase and oxygenase enzymes contains copper metal in their active sites to bind and activate O_2.[4] This reactivity has inspired the development of biomimetic copper-catalyzed oxidative reactions, for instance, oxidation of an alcohol to an aldehyde and/or acid. However, oxygenative C–H functionalizations remain exceptional[8] and are often challenged by selectivity and efficiency problems (for instance, **7**→**8**+**9**, Scheme 1 c).[9] In particular, oxygenative transformation of the allylic methyl group into an aldehyde, in general, remains unprecedented (**10**→**11**, Scheme 1 c). However, rationally designed activated substrates which could bind to metal centers might provide desired oxygenase reactions and α,β-unsaturated aldehydes for further applications in organic synthesis (Scheme 1 d).[10]



Scheme 1. a–c) Different bio- and synthetic oxygenase transformations. d) A retrosynthetic design based on oxygenase cascade sequence leading to complex oxindoles.

In a research program aimed to build natural-product-inspired compound collections,[11] we seek highly concise

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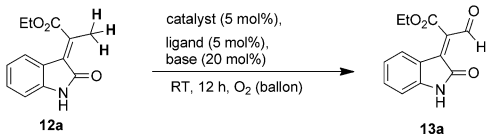
complexity-generating transformations such as cascade- or domino-reaction-based synthetic strategies.[12] A significant and unaddressed challenge in this field is to develop catalytic transformations which employ nontoxic and inexpensive O_2 to generate, in situ, a functionality which could be explored in a cascade reaction to build molecular complexity. Herein we describe the first oxygenase cascade involving two sequential catalytic cycles occurring in a one-pot method. The first copper-catalyzed oxygenase reaction converts the allylic methyl group in 3-methylidine oxindoles into the corresponding aldehyde, which undergo the base-catalyzed aldol/oxa-Michael addition sequence with β-ketoesters to yield sp^3-rich dihydrofuran-bearing oxindoles.

The oxindole scaffold represents a biologically relevant molecular framework embodied by numerous bioactive natural products.[13] To develop an oxygenative cascade route to complex oxindoles, we envisioned that a direct allylic oxidation of the methyl group in **12** into the aldehyde **13** would provide a substrate amenable to various cycloaddition and annulation reactions (Scheme 1 d). To first establish the oxygenase reaction, we explored ethyl (*E*)-2-(2-oxoindolin-3-ylidene)propanoate (**12a**) as a substrate for oxidation to the aldehyde (*E*)-**13a**. Various metal salts in the presence of molecular oxygen and a base were explored before discovering the optimal combination to provide the desired aldehyde (*E*)-**13a** (Table 1).

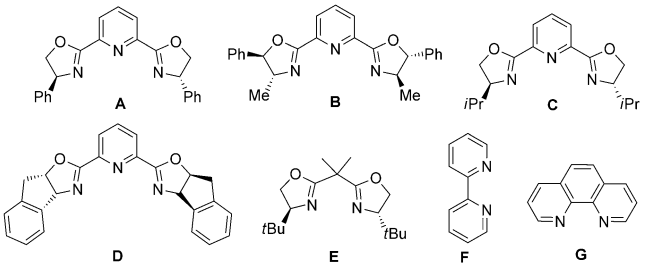
Copper(II) and magnesium(II) salts did not show the desired oxidation of **12a** in the presence of pybox (**A**) and (dimethyl)Box (**E**) along with DIPEA as the base (entries 1–4, Table 1). The biological relevance of ligated copper(I) complexes, which many oxygenase enzymes smartly exploit to activate oxygen, motivated us to turn to copper(I) salts. Very encouragingly, copper cyanide and the ligand **B** (5-Ph-4-Me-Pybox) led to the desired aldehyde **13a** in high yield and moderate selectivity for (*E*)-**13a** (entry 5, Table 1).[14] Screening of more copper(I) salts with **A** and **B** (entries 5–10) revealed $[Cu(CH_3CN)_4]PF_6$ as the best metal salt for this reaction, thus yielding (*E*)-**13a** in good yield and high stereoselectivity (entry 10). Racemic pybox was as good as enantiopure for this oxygenase catalysis (entry 11). Reducing the amount of DIPEA to 5 mol% reduced the yield for (*E*)-**13a** by more than 35% (entry 12). Other bases exhibited lower efficiencies (entries 13 and 14). In the absence of any base, only a small amount of aldehyde was obtained (entry 15). Some other pyridine-based ligands, for instance, pyridine, bipyridine (**F**), and phenanthroline (**G**) provided only moderate yields and stereoselectivities (entries 16–18). Among the pybox-based ligands, *i*Pr-Pybox (**C**) as well as indeno-Pybox (**D**) proved to be less stereoselective and efficient than **A** (entries 19 and 20). Dimethyl-Box (**E**) did not provide any oxidation reaction (entry 21), thus indicating the significance of pyridine ligation in the copper complex. CH_2Cl_2 was the best solvent among those tested (entries 22–24). For its commercial availability, we preferred enantiopure **A** over the equally effective (*rac*)-**A** for synthesis of **13** and further optimization of the oxygenase cascade. A couple of aldehydes (**13a–c**) were synthesized separately in very high yields (62–78%, *E*/*Z* 7:1 to 11:1; see the Supporting Information) before optimizing the complete oxygenase cascade, that is, copper-catalyzed allylic oxidation to form aldehydes and an annulation reaction with the newly generated aldehyde moiety to form sp^3-rich oxindoles.[15]

Table 1: Copper-catalyzed oxygenase synthesis of ethyl (*E*)-3-oxo-2-(2-oxoindolin-3-ylidene)propanoate.[a]



Entry	Metal	Ligand	Solvent	Base	Yield [%][b]	*E*/*Z*[c]
1	$Cu(OTf)_2$	**A**	CH_2Cl_2	DIPEA	n.r.	–
2	$Cu(OTf)_2$	**E**	CH_2Cl_2	DIPEA	n.r.	
3	$Mg(OtBu)_2$	**A**	CH_2Cl_2	DIPEA	n.r.	–
4	$Mg(OtBu)_2$	**E**	CH_2Cl_2	DIPEA	n.r.	–
5	CuCN	**B**	CH_2Cl_2	DIPEA	65	5:1
6	$[Cu(CH_3CN)_4]PF_6$	**B**	CH_2Cl_2	DIPEA	78	8:1
7	$CuBr{\cdot}SMe_2$	**B**	CH_2Cl_2	DIPEA	71	9:1
8	$[Cu(CH_3CN)_4]BF_4$	**B**	CH_2Cl_2	DIPEA	75	5:1
9	$[Cu(CH_3CN)_4]OTf$	**B**	CH_2Cl_2	DIPEA	75	4:1
10	$[Cu(CH_3CN)_4]PF_6$	**A**	CH_2Cl_2	DIPEA	83	11:1
11	$[Cu(CH_3CN)_4]PF_6$	±**A**	CH_2Cl_2	DIPEA	81	12:1
12	$[Cu(CH_3CN)_4]PF_6$	**A**	CH_2Cl_2	DIPEA[d]	53	11:1
13	$[Cu(CH_3CN)_4]PF_6$	**A**	CH_2Cl_2	DABCO	18	9:1
14	$[Cu(CH_3CN)_4]PF_6$	**A**	CH_2Cl_2	Et_3N	71	7:1
15	$[Cu(CH_3CN)_4]PF_6$	**A**	CH_2Cl_2	–	< 10	–
16	$[Cu(CH_3CN)_4]PF_6$	**F**	CH_2Cl_2	DIPEA	45	4:1
17	$[Cu(CH_3CN)_4]PF_6$	**G**	CH_2Cl_2	DIPEA	49	4:1
18	$[Cu(CH_3CN)_4]PF_6$	**Py**[e]	CH_2Cl_2	DIPEA	47	2:1
19	$[Cu(CH_3CN)_4]PF_6$	**C**	CH_2Cl_2	DIPEA	73	5:1
20	$[Cu(CH_3CN)_4]PF_6$	**D**	CH_2Cl_2	DIPEA	77	5:1
21	$[Cu(CH_3CN)_4]PF_6$	**E**	CH_2Cl_2	DIPEA	trace	–
22	$[Cu(CH_3CN)_4]PF_6$	**A**	MeCN	DIPEA	50	9:1
23	$[Cu(CH_3CN)_4]PF_6$	**A**	THF	DIPEA	27	11:1
24	$[Cu(CH_3CN)_4]PF_6$	**A**	toluene	DIPEA	53	13:1

[a] For details, see the Supporting Information. [b] Yield of isolated product. [c] Based on ^{1}H NMR analysis of the crude reaction mixture. [d] 5 mol%. [e] 30 mol%. DIPEA = diisopropylethylamine, DABCO = 1,4-diazabicyclo[2.2.2]octane, n.r. = no reaction, THF = tetrahydrofuran.



To make the best use of the optimized reaction conditions for allylic oxidation of **12** into **13**, thus providing complex oxindoles, we resorted to a base-catalyzed annulation of the aldehydes **13** with β-ketoesters (**15**). The reaction optimization (see the Supporting Information) revealed that 50 mol% of DABCO along with **A** provided the best yield for the adduct **14a** (Scheme 2). With optimized reaction conditions for the oxygenase cascade, differently substituted oxindoles (**12**) and β-ketoesters (**15**) were employed to provide novel dihydrofuran-appended oxindoles (Scheme 2). Both electron-

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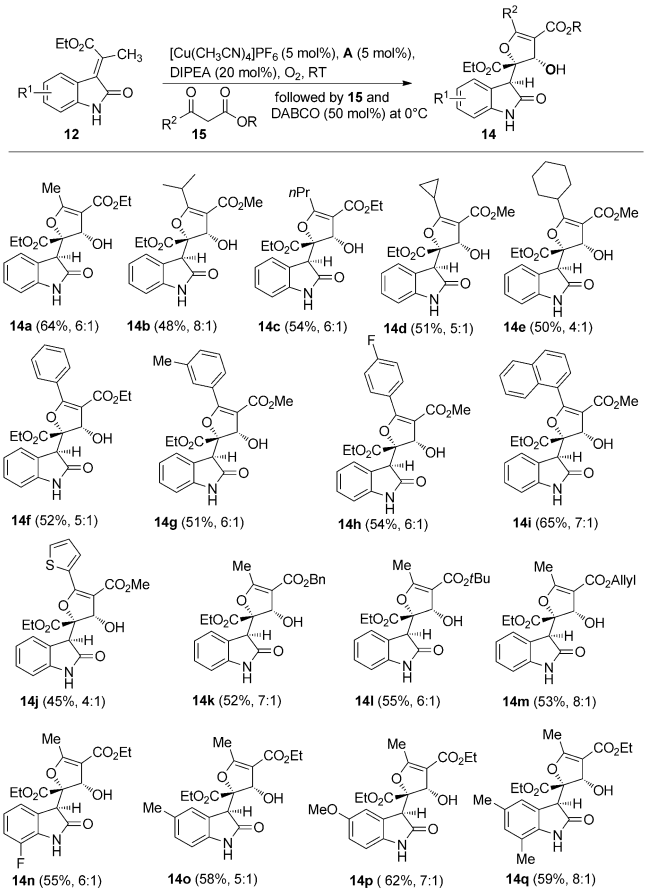
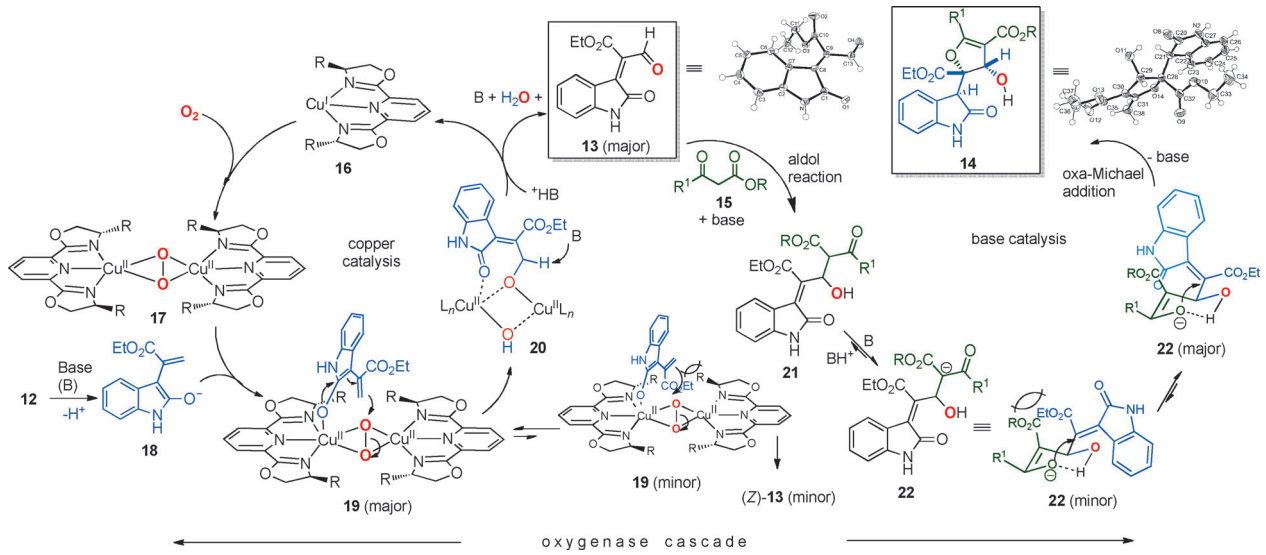


Scheme 2. Oxygenase cascade synthesis of dihydrofuran-appended oxidnoles (**14**).

rich and electron-poor oxindole substrates worked nicely in the cascade reaction, thus providing the adducts **14** in good yields and diastereoselectivities. Differently substituted ketoesters yielded adducts decorated with alkyl, aryl, and heterocyclic moieties with good stereoselectivities and appreciable yields, thus demonstrating the scope and generality of the catalytic oxygenase cascade reaction (Scheme 2). Cascade synthesis also tolerated different ester functions on the ketoesters (**14k–m**) and could thus provide a good handle in building a larger compound collection. In a separate reaction of the pure aldehyde (*E*)-**13a** and the ketoester **15a** (R = Et, R^2 = Me), the adduct **14a** was obtained in similar yields and diastereoselectivities.[16]

Highly enlightening results from the groups of Karlin[4a,-b,e,9d,17] and Ito[18] on Cu-O_2 chemistry, along with support from crystallographic[19] and spectroscopic[20] evidence, strongly suggest an electrophilic reactivity of a side-on-type peroxo intermediate for aromatic *o*-hydroxylation of monophenols by tyrosinase.[21] The oxygenase transformation of the oxindole **12** into **13** seems to follow a similar reaction mechanism. Thus, insertion of molecular oxygen into the copper(I) complex **16** generates a side-on μ-η^2:η^2-peroxo complex (**17**; Scheme 3).[4d,e,22] Coordination of the enolate **18** to one of the metal centers in **19** avoids the steric repulsions between the allylic ester moiety and oxazoline ligand, and thereby determines the stereoselectivity in the reaction. Enol addition facilitates the oxo-bridge opening and proton transfer, thus leading to the intermediate **20**. Finally, base-mediated allylic deprotonation and release of the aldehyde **13** regenerates copper(I) for further catalysis. Interestingly, another oxygenase enzyme, NspF, was recently reported to follow similar final steps in oxygenation of *o*-aminophenol to nitrosophenol.[23] Aldol addition of the enolate of ketoester **15** to the newly generated aldehyde forms the intermediate **21**. A six-membered transition state, stabilized by hydrogen-bonding between the newly formed hydroxy group and the enolate, avoids the steric hinderance between two ester moeities. A *re*-face oxa-Michael addition[24] of **21** is therefore preferred, thus generating another stabilized oxindole enolate. While the *si* face is now shielded by an ester moiety, the oxindole/enolate receives a proton from the *re*-face to yield the adduct **14**.[16]



Scheme 3. A mechanistic proposal for individual catalytic steps in oxygenase cascade synthesis of the oxindoles **14**.

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In summary, we have disclosed the first copper(I) catalyzed oxygenase reaction which transforms the allylic methyl group of 3-methylidene oxindoles into the corresponding aldehyde stereoselectively and with great efficiency. A base-catalyzed cascade reaction (aldo/oxa-Michael addition) of the newly generated aldehyde in a one-pot synthesis provided stereoselective entry to complex oxindoles which contain a dihydrofuran ring supporting three consecutive chiral centers. We believe that with rising demands for sustainable and environmentally benign synthetic routes to complex molecules, catalytic oxygenase cascades, where O_2 is the driving force of the reaction sequence, will draw the attention of the chemistry community and find more applications in green and clean bioinspired organic syntheses.

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[1] a) A. M. Boldi, *Curr. Opin. Chem. Biol.* **2004**, *8*, 281 – 286; b) G. L. Thomas, C. W. Johannes, *Curr. Opin. Chem. Biol.* **2011**, *15*, 516 – 522; c) A. M. Szpilman, E. M. Carreira, *Angew. Chem.* **2010**, *122*, 9786 – 9823; *Angew. Chem. Int. Ed.* **2010**, *49*, 9592 – 9628; d) R. W. Huigens III, K. C. Morrison, R. W. Hicklin, T. A. Flood, M. F. Richter, P. J. Hergenrother, *Nat. Chem.* **2013**, *5*, 195 – 202; e) F. Lovering, J. Bikker, C. Humblet, *J. Med. Chem.* **2009**, *52*, 6752 – 6756.

[2] a) J. A. Labinger, J. E. Bercaw, *Nature* **2002**, *417*, 507 – 514; b) A. R. Dick, M. S. Sanford, *Tetrahedron* **2006**, *62*, 2439 – 2463; c) A. E. Wendlandt, A. M. Suess, S. S. Stahl, *Angew. Chem.* **2011**, *123*, 11256 – 11283; *Angew. Chem. Int. Ed.* **2011**, *50*, 11062 – 11087; d) H. M. L. Davies, J. R. Manning, *Nature* **2008**, *451*, 417 – 424.

[3] a) E. M. Davis, R. Croteau, *Biosynth.: Aromat. Polyketides Isoprenoids Alkaloids* **2000**, *209*, 53 – 95; b) M. Razzak, J. K. De Brabander, *Nat. Chem. Biol.* **2011**, *7*, 865 – 875; c) Y. J. Hong, D. J. Tantillo, *J. Am. Chem. Soc.* **2014**, *136*, 2450 – 2463.

[4] a) E. E. Chufán, S. C. Puiu, K. D. Karlin, *Acc. Chem. Res.* **2007**, *40*, 563 – 572; b) R. A. Himes, K. D. Karlin, *Curr. Opin. Chem. Biol.* **2009**, *13*, 119 – 131; c) L. Que, W. B. Tolman, *Nature* **2008**, *455*, 333 – 340; d) L. M. Mirica, O. X, T. D. P. Stack, *Chem. Rev.* **2004**, *104*, 1013 – 1045; e) E. Kim, E. E. Chufan, K. Kamaraj, K. D. Karlin, *Chem. Rev.* **2004**, *104*, 1077 – 1133.

[5] a) J. Hefner, S. M. Rubenstein, R. E. B. Ketchum, D. M. Gibson, R. M. Williams, R. Croteau, *Chem. Biol.* **1996**, *3*, 479 – 489; b) R. Croteau, M. Hezari, J. Hefner, A. Koepp, N. G. Lewis, *ACS Symp. Ser.* **1995**, *583*, 72 – 80; c) W. Eisenreich, B. Menhard, M. S. Lee, M. H. Zenk, A. Bacher, *J. Am. Chem. Soc.* **1998**, *120*, 9694 – 9695.

[6] a) T. Pfaffeneder, B. Hackner, M. Truss, M. Munzel, M. Muller, C. A. Deiml, C. Hagemeier, T. Carell, *Angew. Chem.* **2011**, *123*, 7146 – 7150; *Angew. Chem. Int. Ed.* **2011**, *50*, 7008 – 7012; b) S. Ito, L. Shen, Q. Dai, S. C. Wu, L. B. Collins, J. A. Swenberg, C. He, Y. Zhang, *Science* **2011**, *333*, 1300 – 1303.

[7] a) C. Loenarz, C. J. Schofield, *Chem. Biol.* **2009**, *16*, 580 – 583; b) M. Tahiliani, K. P. Koh, Y. H. Shen, W. A. Pastor, H. Bandukwala, Y. Brudno, S. Agarwal, L. M. Iyer, D. R. Liu, L. Aravind, A. Rao, *Science* **2009**, *324*, 930 – 935.

[8] a) Q. Liu, P. Wu, Y. H. Yang, Z. Q. Zeng, J. Liu, H. Yi, A. W. Lei, *Angew. Chem.* **2012**, *124*, 4744 – 4748; *Angew. Chem. Int. Ed.* **2012**, *51*, 4666 – 4670; b) T. Punniyamurthy, L. Rout, *Coord. Chem. Rev.* **2008**, *252*, 134 – 154; c) C. Zhang, C. H. Tang, N. Jiao, *Chem. Soc. Rev.* **2012**, *41*, 3464 – 3484.

[9] a) F. Wang, G. Y. Yang, W. Zhang, W. H. Wu, J. Xu, *Chem. Commun.* **2003**, 1172 – 1173; b) C. Würtele, O. Sander, V. Lutz, T. Waitz, F. Tuczek, S. Schindler, *J. Am. Chem. Soc.* **2009**, *131*, 7544 – 7545; c) J. De Houwer, K. A. Tehrani, B. U. W. Maes, *Angew. Chem.* **2012**, *124*, 2799 – 2802; *Angew. Chem. Int. Ed.* **2012**, *51*, 2745 – 2748; d) H. R. Lucas, L. Li, A. A. N. Sarjeant, M. A. Vance, E. I. Solomon, K. D. Karlin, *J. Am. Chem. Soc.* **2009**, *131*, 3230 – 3245; e) S.-I. Murahashi, N. Komiya, Y. Hayashi, Eur. Pat. Appl. **2002**, EP1174410, **2002**, p. 7.

[10] a) M. B. Andrus in *Science of Synthesis Stereoselective Synthesis*, *Vol. 3* (Ed.: J. G. M. De Vries, G. A. Evans, P. Andrew), Georg Thieme, Stuttgart, **2011**, pp. 469 – 482; b) R. M. Patel, V. G. Puranik, N. P. Argade, *Org. Biomol. Chem.* **2011**, *9*, 6312 – 6322; c) C. S. Ra, E. M. Park, G. Park, *Bull. Korean Chem. Soc.* **2008**, *29*, 2513 – 2516.

[11] K. Kumar, H. Waldmann, *Angew. Chem.* **2009**, *121*, 3272 – 3290; *Angew. Chem. Int. Ed.* **2009**, *48*, 3224 – 3242.

[12] a) B. Baskar, P. Y. Dakas, K. Kumar, *Org. Lett.* **2011**, *13*, 1988 – 1991; b) W. Liu, V. Khedkar, B. Baskar, M. Schurmann, K. Kumar, *Angew. Chem.* **2011**, *123*, 7032 – 7037; *Angew. Chem. Int. Ed.* **2011**, *50*, 6900 – 6905; c) H. Dückert, V. Pries, V. Khedkar, S. Menninger, H. Bruss, A. W. Bird, Z. Maliga, A. Brockmeyer, P. Janning, A. Hyman, S. Grimme, M. Schurmann, H. Preut, K. Hubel, S. Ziegler, K. Kumar, H. Waldmann, *Nat. Chem. Biol.* **2012**, *8*, 179 – 184; d) P. Y. Dakas, J. A. Parga, S. Hoing, H. R. Scholer, J. Sterneckert, K. Kumar, H. Waldmann, *Angew. Chem.* **2013**, *125*, 9755 – 9760; *Angew. Chem. Int. Ed.* **2013**, *52*, 9576 – 9581.

[13] a) C. V. Galliford, K. A. Scheidt, *Angew. Chem.* **2007**, *119*, 8902 – 8912; *Angew. Chem. Int. Ed.* **2007**, *46*, 8748 – 8758; b) B. M. Trost, M. K. Brennan, *Synthesis* **2009**, 3003 – 3025; c) C. Marti, E. M. Carreira, *Eur. J. Org. Chem.* **2003**, 2209 – 2219; d) S. Peddibhotla, *Curr. Bioact. Compd.* **2009**, *5*, 20 – 38.

[14] CCDC 990261 (**13a**) and 990260 (**14a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[15] Our initial attempts towards similar oxygenase reactions of unactivated methyl groups in β-styrene under the optimized reaction conditions (Table 1, entry 10) failed and thus calls for further developments in this direction.

[16] Attempts were made for an asymmetric cascade reaction sequence of aldol–oxa-Michael addition of the β-ketoester **15a** with the aldehyde **13a** using different bifunctional thioureas and amine catalysts. However, only low reaction yields (incomplete conversions) and low to moderate enantioselectivities were observed (see the Supporting Information).

[17] a) K. D. Karlin, J. C. Hayes, Y. Gultneh, R. W. Cruse, J. W. Mckown, J. P. Hutchinson, J. Zubieta, *J. Am. Chem. Soc.* **1984**, *106*, 2121 – 2128; b) K. D. Karlin, M. S. Nasir, B. I. Cohen, R. W. Cruse, S. Kaderli, A. D. Zuberbuhler, *J. Am. Chem. Soc.* **1994**, *116*, 1324 – 1336; c) E. Pidcock, H. V. Obias, C. X. Zhang, K. D. Karlin, E. I. Solomon, *J. Am. Chem. Soc.* **1998**, *120*, 7841 – 7847; d) K. Kamaraj, E. Kim, B. Galliker, L. N. Zakharov, A. L. Rheingold, A. D. Zuberbuhler, K. D. Karlin, *J. Am. Chem. Soc.* **2003**, *125*, 6028 – 6029; e) J. Shearer, C. X. Zhang, L. Q. Hatcher, K. D. Karlin, *J. Am. Chem. Soc.* **2003**, *125*, 12670 – 12671; f) J. Shearer, C. X. Zhang, L. N. Zakharov, A. L. Rheingold, K. D. Karlin, *J. Am. Chem. Soc.* **2005**, *127*, 5469 – 5483.

[18] a) S. Itoh, H. Nakao, L. M. Berreau, T. Kondo, M. Komatsu, S. Fukuzumi, *J. Am. Chem. Soc.* **1998**, *120*, 2890 – 2899; b) S. Itoh, M. Taki, P. Holland, W. B. Tolman, L. Que, S. Fukuzumi, *J. Inorg. Biochem.* **1999**, *74*, 33 – 33; c) S. Itoh, M. Taki, H. Nakao, P. L. Holland, W. B. Tolman, L. Que, S. Fukuzumi, *Angew. Chem.*

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2000, *112*, 409 – 411; *Angew. Chem. Int. Ed.* **2000**, *39*, 398 – 400; d) S. Itoh, H. Kumei, M. Taki, S. Nagatomo, T. Kitagawa, S. Fukuzumi, *J. Am. Chem. Soc.* **2001**, *123*, 6708 – 6709.

[19] Y. Matoba, T. Kumagai, A. Yamamoto, H. Yoshitsu, M. Sugiyama, *J. Biol. Chem.* **2006**, *281*, 8981 – 8990.

[20] E. I. Solomon, U. M. Sundaram, T. E. Machonkin, *Chem. Rev.* **1996**, *96*, 2563 – 2605.

[21] a) A. Hoffmann, C. Citek, S. Binder, A. Goos, M. Rubhausen, O. Troeppner, I. Ivanovic-Burmazovic, E. C. Wasinger, T. D. P. Stack, S. Herres-Pawlis, *Angew. Chem.* **2013**, *125*, 5508 – 5512; *Angew. Chem. Int. Ed.* **2013**, *52*, 5398 – 5401; b) C. Citek, C. T. Lyons, E. C. Wasinger, T. D. P. Stack, *Nat. Chem.* **2012**, *4*, 317 – 322.

[22] a) P. Haack, C. Limberg, *Angew. Chem.* **2014**, *126*, 4368 – 4380; *Angew. Chem. Int. Ed.* **2014**, *53*, 4282 – 4293; b) E. A. Lewis, W. B. Tolman, *Chem. Rev.* **2004**, *104*, 1047 – 1076; c) M. Panera, J. Diez, I. Merino, E. Rubio, M. P. Gamasa, *Eur. J. Inorg. Chem.* **2011**, 393 – 404.

[23] J. W. Ginsbach, M. T. Kieber-Emmons, R. Nomoto, A. Noguchi, Y. Ohnishi, E. I. Solomon, *Proc. Natl. Acad. Sci. USA* **2012**, *109*, 10793 – 10797.

[24] C. F. Nising, S. Bräse, *Chem. Soc. Rev.* **2012**, *41*, 988 – 999, and references therein.

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