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Asymmetric Catalysis |*Hot Paper*|

Synergistic Stereocontrol in the Enantioselective Ruthenium-Catalyzed Sulfoxidation of Spirodithiolane-Indolones

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Abstract: A chiral ruthenium catalyst was developed for the enantioselective sulfoxidation of the title compounds. The catalyst combines two elements of chirality, a chiral pybox ligand and a chiral bicylic lactam unit, to which the ligand is attached. The latter unit was shown to improve significantly the performance of the catalyst by exposing one of the two enantiotopic sulfur atoms to the active site via hydrogen-bond mediated coordination. Ten differently substituted substrates were converted into the respective sulfoxides in yields of 52–71% and with ≥90% *ee*.

There is a variety of synergistic effects, which have been described in the design of chiral catalysts.[1] Generally speaking, any two or more parameters, the modification of which provides an improved enantioselectivity in a given catalytic reaction "work favorably together" (συνεργός) and are by definition synergistic. In more specific terms, changing the chirality of the individual construction elements of a catalyst can lead to an enhancement or decrease of enantioselectivity. This effect is notable for example in the design of peptide-based organocatalysts, with a defined set of amino acids providing the highest enantioselectivities as compared to other epimeric sets of amino acids.[2] Similarly, synergistic effects can be observed in enzymatic catalysis with a specific set of mutants being highly superior to others.[3]

In previous work, we explored the catalytic effect of certain substrate-specific[4] ruthenium–porphyrin complexes, which display lactam-based hydrogen-bonding ligands.[5] We have stressed the enzyme-like character of their supramolecular arrangement,[6] in which the lactam acts as a binding pocket and the transition metal as a prosthetic group. In the present work we sought to explore a possible synergy of the chiral ligand environment at the metal center and the chirality of the lactam backbone. To this end, we selected spiro[1,3-dithiolane-2,3′-indol]-2′(1′*H*)-ones (spirodithiolane-indolones) as substrates[7,8] and we have now studied their enantioselective oxidation employing chiral ruthenium catalysts with *N*,*N*,*N*-pyridine-2,6-bisoxazoline (pybox) ligands.[9]

Multifunctional ruthenium complexes **4** were readily prepared from commercially available starting materials (Figure 1). Optically pure 4-bromo-substituted pybox ligands **2** were generated from chelidamic acid (**1**) in high yields using known methods,[10] and were accordingly attached to chiral lactam **3**[5a] via a C–C triple bond linker employing a Sonogashira cross-coupling protocol (72–93% yield). Ligands **3** were further treated with commercially available [{Ru(*p*-cymene)Cl_2}$_2$] in the presence of dipicolinic acid under established conditions[9a] to furnish the desired ruthenium pybox complexes **4a**–**4b**′ in 60–81% chemical yield. For comparison, the known complexes **5a**–**5d** were prepared according to previously described procedures.[9]

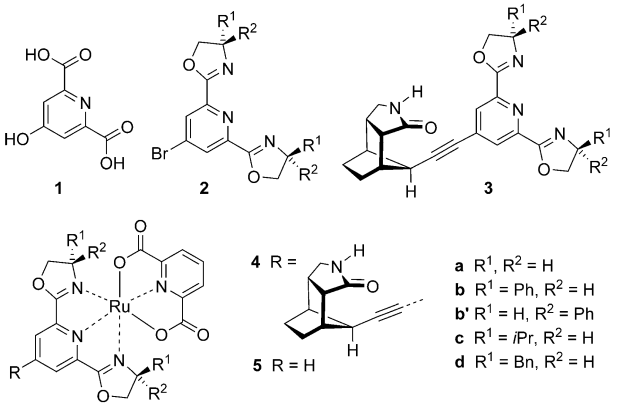

Figure 1. Starting materials and intermediates required for the synthesis of bifunctional ruthenium complexes **4a**–**4b**′ and structure of the known ruthenium complexes **5a**–**5d**.

While the enantioselective oxidation of sulfides has been extensively investigated in the past,[11] there are comparably few reports on the enantioselective oxidation of 1,3-dithiolanes.[12] An interesting feature of their oxidation is the fact that two stereogenic centers are created in one step if the 1,3-dithiolane is derived from a non-symmetric carbonyl compound. Initial experiments were performed in the present work with dithiolane **6a** which in turn was readily obtained by thioacetal formation from isatin.[8a,13] Applying dipivaloyloxyiodobenzene [PhI(OPiv)$_2$] as the oxidant in benzene as the solvent,[14] we found the achiral ruthenium compound **5a** to be a competent catalyst for the desired oxidation although the diastereoselec-

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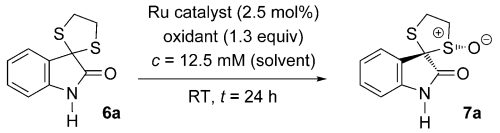
tivity was relatively low (Table 1, entry 1). Upon replacing the achiral pybox ligand with chiral analogues (catalysts **5b**–**5d**) an enantioselective reaction course was observed (entries 2–4) with ligand **5b** providing the best result (entry 2). Ruthenium pybox complex **4a**, in which the octahydro-1*H*-4,7-methanoisoindol-1-one backbone is the only source of chirality, provided product **7a** in a low *ee* but with improved diastereoselectivity as compared to catalysts **5a**–**5d** (entry 5). Remarkably, the major product stereoisomer was the same as for catalyst **5b**. Consequently, a synergistic effect was expected and indeed found for catalyst **4b** (entry 6), with which an enantioselectivity of 70% *ee* was achieved. If the two chiral entities were combined in a mismatched fashion, the enantioselectivity was low in favor of *ent*-**7a**, the enantiomer of **7a** (entry 7). Further optimization work was performed regarding the solvent (entry 8), the oxidant (entry 9), the substrate concentration (entry 10) and the stoichiometry (entry 11). Details of the optimization experiments can be found in the Supporting Information. Optimization eventually culminated in a reaction, which proceeded with good yield (71%) to a major diastereoisomer (d.r. 84:16) in significant enantioselectivity (90% *ee*).

Table 1. Influence of the ligand configuration on the enantioselective Ru-catalyzed sulfoxidation of spirodithiolane-indolone **6a**.

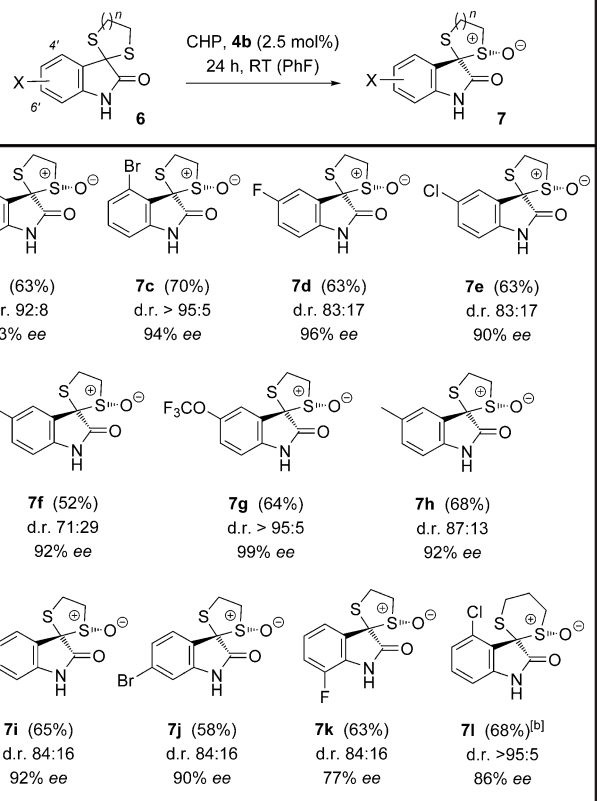


Entry	Ru cat.	Oxidant	Solvent	Yield[a] [%]	d.r.[b]	*ee*[c] [%]
1	**5a**	$PhI(OPiv)_2$	PhH	51	66:34	–
2	**5b**	$PhI(OPiv)_2$	PhH	57	68:32	53
3	**5c**	$PhI(OPiv)_2$	PhH	45	69:31	14
4	**5d**	$PhI(OPiv)_2$	PhH	52	67:33	22
5	**4a**	$PhI(OPiv)_2$	PhH	51	80:20	21
6	**4b**	$PhI(OPiv)_2$	PhH	55	84:16	70
7	**4b′**	$PhI(OPiv)_2$	PhH	53	75:25	−21[e]
8	**4b**	$PhI(OPiv)_2$	PhF	73	87:13	73
9	**4b**	CHP[d]	PhF	69	87:13	82
10[f]	**4b**	CHP	PhF	62	87:13	84
11[f,g]	**4b**	CHP	PhF	71	84:16	90

[a] Yield of isolated product after chromatographic purification. [b] Diasteromeric ratio (d.r.) as determined by ^{1}H NMR analysis of the crude product mixture. [c] Enantiomeric excess (*ee*) calculated from the enantiomeric ratio as determined by HPLC analysis on a chiral stationary phase. [d] Cumene hydroperoxide. [e] The major enantiomer was not **7a** but its enantiomer *ent*-**7a**. [f] $c = 10$ mM. [g] 1.5 equiv of oxidant.

The optimized conditions were subsequently applied to different substrates (Table 2). It turned out that the enantioselectivity remained high for the sulfoxidation of various spirodithiolane-indolones with substituents in positions C4′ to C6′ of the indolone core (products **7b**–**7j**). For one substrate (**6f**) the diastereoselectivity of the sulfoxidation decreased significantly while for the 7′-fluoroindolone **6k** there was a significant drop in enantioselectivity (77% *ee*). Spirodithiane-indolone **6l** delivered the sulfoxide with perfect diastereoselectivity (d.r. > 95:5)

Table 2. Products **7** obtained by enantioselective ruthenium-catalyzed sulfoxidation.[a]



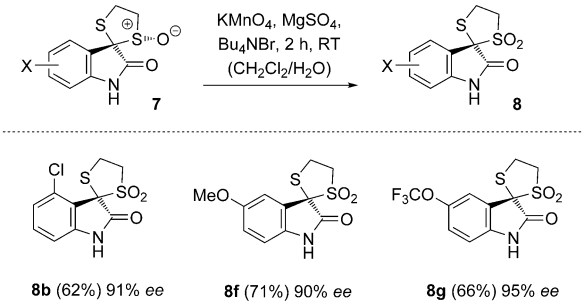
[a] Yields are given as combined yields for the separated diastereoisomers. The d.r. was determined by ^{1}H NMR analysis of the crude product mixture but remained unchanged upon work-up. [b] In this single instance, a Ru complex with an (1*S*,2*R*)-(−)-*cis*-1-amino-2-indanol-derived pybox ligand turned out to be a superior catalyst (see Supporting Information for further details).

but with diminished enantioselectivity (86% *ee*) compared to the spirodithiolanes.

The *ee* of the minor diastereoisomers, which could be separated from the major diastereoisomers by chromatography, was not determined in all cases. It was determined, however, for the epimer of **7a** to be 45% *ee* and for the epimer of product **7f**, *epi*-**7f** (see below), to be 41% *ee*.

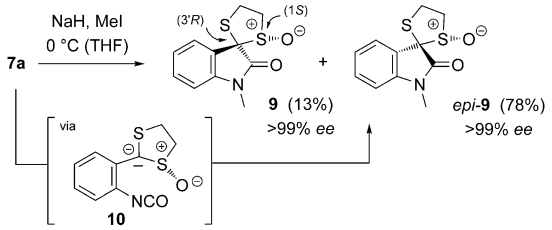
Diastereomerically pure sulfoxides **7** could be converted to the respective sulfones **8** by oxidation (Scheme 1). Initial attempts under aqueous conditions[15] led to partial racemization and in a side reaction to thioketones by elimination.[16] The reaction could be successfully performed, however, with tetrabutylammonium bromide as a phase-transfer catalyst in a biphasic solvent mixture.[17]

The limited stability of products **7** prohibited attempts to obtain crystals suitable for single crystal X-ray crystallography by solvent evaporation and diffusion methods. Eventually, the *N*-methylated derivatives of product **7a** were obtained, which turned out to be more stable. Compound **7a** was purified to > 99% *ee* by chiral semipreparative HPLC (Daicel Chiralpak, AD-H, *n*-hexane/*i*PrOH 70:30) and was subjected to methylation conditions (Scheme 2). Surprisingly, two diastereoisomers



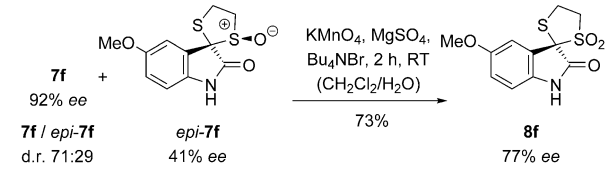
Scheme 1. Conversion of enantiomerically and diastereomerically pure sulfoxides **7** into sulfones **8**.

9 and *epi*-**9** were produced, both of which were still enantiopure. Based on NMR data, it could be unambiguously shown that the relative configuration of **9** and **7 a** were identical. The absolute configuration of **9** was subsequently proven by anomalous X-ray diffraction techniques thus also establishing the absolute configuration of product **7 a**. We assume that the epimerization is due to the intermediacy of isocyanate **10**[18] during the methylation protocol. The absolute configuration at the sulfoxide sulfur atom is retained as proven by the enantiopurity of both products.



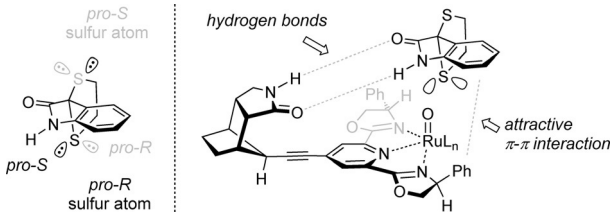
Scheme 2. Conversion of enantiomerically and diastereomerically pure indolone **7 a** into its *N*-methyl derivatives **9** and *epi*-**9**.

While the latter experiments established the absolute configuration of the major stereoisomer in the sulfoxidation to be (1*S*,3′*R*) and the configuration of its enantiomer to be (1*R*,3′*S*), the absolute configuration of the minor diastereoisomers remained unclear. In other words, it was not clear whether the catalyst selectively attacks one of the two enantiotopic sulfur atoms [leading preferentially to the (1*R*,3′*R*)-stereoisomer] or whether it has a preference for one of the two enantiotopic electron pairs at sulfur [leading preferentially to the (1*S*,3′*S*)-stereoisomer]. Since further oxidation to the sulfone (cf. Scheme 1) leads to a deletion of the stereogenic center at sulfur, we were able to clarify this issue by oxidation of the product mixture obtained from enantioselective sulfoxidation of substrate **6 f**. In this specific example the formation of the other diastereomer *epi*-**7 f** was particularly high. Upon oxidation, product **8 f** with *R*-configuration at carbon C3′ was obtained in 77% *ee* (Scheme 3), which is only possible if the major enantiomer of *epi*-**7 f** was also *R*-configured at this stereogenic center. Had it been *S*-configured the product *ee* should have been significantly lower.



Scheme 3. Further oxidation of the product mixture **7 f**/*epi*-**7 f** from sulfoxidation of substrate **6 f** supports the configuration assignment for *epi*-**7 f**.

Although we have not yet done any further mechanistic work, the product composition and previous work on the enantioselective olefin epoxidation by related ruthenium pybox complexes[9d] can serve as basis for a preliminary mechanistic model. Accordingly, a ruthenium oxo complex with a distorted octahedral conformation is assumed to be the active catalyst.[9d] Product analysis indicates that it is the *pro-S* electron pair of the *pro-R* sulfur atom, which is preferentially attacked by the oxidant (Scheme 4). This preference is suggested to be the result of two synergestic effects. Attractive π–π interactions[19] between the phenyl group of the ligand and the aromatic ring of the substrate guide the *pro-R* sulfur atom to the active center. Without any further assistance the enantioselectivity is only moderate, however, and, in addition, the sulfur atom is not sufficiently fixed so that attack at the two electron pairs is not selective (low d.r., see Table 1, entry 2). This fixation is significantly improved by hydrogen bonding to catalyst **4 b** resulting in a higher diastereoselectivity and a further increase in enantioselectivity (Table 1, entries 6, 8–10).



Scheme 4. Topicity of the prostereogenic elements in spirodithiolane-indolones and a model for the enantioselective attack of the putative oxidant.

From the data of Table 1 it is evident that an excess of the stoichiometric oxidant improves the enantioselectivity at the expense of diastereoselectivity (Table 1, entries 10, 11). Indeed, based on the mechanistic model, further oxidation will occur preferentially at the *pro-S* electron pair of the *pro-R* sulfur atom. The enantiomers of products **7** will thus be more rapidly transformed to the respective disulfoxides than any other stereoisomer. If the amount of this specific stereoisomer decreases, the *ee* increases but the d.r. decreases, which is in line with the data. Still, it should be stressed, that the major mode of action in the present case is not a kinetic resolution but an enantioselective sulfoxidation.

Hydrogen bonding strongly facilitates the enantioselective sulfoxidation as evident when employing a substrate, which is not capable of two-point hydrogen bonding. The *N*-methyl derivative of substrate **6 a** was converted into the corresponding

sulfoxides **7** and *epi*-**7** under standard conditions (catalyst **4b**) in 70% yield but with significantly diminished stereoselectivity (d.r. 70:30, 5% *ee*). The *N*-methyl derivative of catalyst **4b** was a competent catalyst for the sulfoxidation but delivered for the conversion **6a**→**7a** similar results as the monofunctional catalyst **5b** (65%, d.r. 76:24, 59% *ee*).

In summary, we have shown that non-covalent hydrogen-bonding interactions between a substrate and a transition metal catalyst can be favorably used to increase the given asymmetric induction of a chiral ligand at the metal center and vice versa. If, like in the chosen catalytic system, the two chiral entities (the chiral ligand and the substrate-binding site) are linked in a modular fashion substrate-specific catalysts can be easily assembled and they can be tailored to a given reaction. Although we have in the present contribution put emphasis on stereoselectivity issues, the concept should be equally applicable to other selectivity parameters, such as chemo- and regioselectivity.

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Keywords: asymmetric catalysis · hydrogen bond · oxidation · ruthenium · sulfur heterocycles

[1] Selected examples: a) K. Ding, *Chem. Commun.* **2008**, 909 – 921; b) K. Aikawa, M. Kojima, K. Mikami, *Adv. Synth. Catal.* **2010**, *352*, 3131 – 3135; c) H. Ren, W. D. Wulff, *J. Am. Chem. Soc.* **2011**, *133*, 5656 – 5659; d) M. Yoshida, E. Masaki, T. Terumine, S. Hara, *Synthesis* **2014**, 1367 – 1373; e) W. Chen, M. Chen, J. F. Hartwig, *J. Am. Chem. Soc.* **2014**, *136*, 15825 – 15828; f) O. Cussó, X. Ribas, J. Lloret-Fillol, M. Costas, *Angew. Chem. Int. Ed.* **2015**, *54*, 2729 – 2733; *Angew. Chem.* **2015**, *127*, 2767 – 2771.

[2] Reviews: a) J. Duschmalé, Y. Arakawa, H. Wennemers in *Science of Synthesis: Asymmetric Organocatalysis* (Eds.: B. List, K. Maruoka), Thieme, Stuttgart, **2012**, pp. 741 – 786; b) E. A. C. Davie, S. M. Mennen, Y. Xu, S. J. Miller, *Chem. Rev.* **2007**, *107*, 5759 – 5812.

[3] Z.-G. Zhang, R. Lonsdale, J. Sanchis, M. T. Reetz, *J. Am. Chem. Soc.* **2014**, *136*, 17262 – 17272 and refs. cited therein.

[4] Review: E. Lindbäck, S. Dawaigher, K. Wärnmark, *Chem. Eur. J.* **2014**, *20*, 13432 – 13481.

[5] a) P. Fackler, C. Berthold, F. Voss, T. Bach, *J. Am. Chem. Soc.* **2010**, *132*, 15911 – 15913; b) P. Fackler, S. M. Huber, T. Bach, *J. Am. Chem. Soc.* **2012**, *134*, 12869 – 12878; c) J. R. Frost, S. M. Huber, S. Breitenlechner, C. Bannwarth, T. Bach, *Angew. Chem. Int. Ed.* **2015**, *54*, 691 – 695; *Angew. Chem.* **2015**, *127*, 701 – 705; d) F. Zhong, T. Bach, *Chem. Eur. J.* **2014**, *20*, 13522 – 13526.

[6] For recent reviews on supramolecular catalysis, see: a) P. Dydio, J. N. H. Reek, *Chem. Sci.* **2014**, *5*, 2135 – 2145; b) M. Raynal, P. Ballester, A. Vidal-Ferran, P. W. N. M. van Leeuwen, *Chem. Soc. Rev.* **2014**, *43*, 1660 – 1733; c) S. Carboni, C. Gennari, L. Pignatoro, U. Piarulli, *Dalton Trans.* **2011**, *40*, 4355 – 4373.

[7] For a general review on the synthesis of biologically active spiroindolones, see: M. M. M. Santos, *Tetrahedron* **2014**, *70*, 9735 – 9757.

[8] For the biological activity of spiro[1,3-dithiolane-2,3′-indol]-2′(1′*H*)-ones, see: a) M. Rajopadhye, F. D. Popp, *J. Med. Chem.* **1988**, *31*, 1001 – 1005; b) M.-C. Forest, P. Lahouratate, M. Martin, G. Nadler, M. J. Quiniou, R. G. Zimmermann, *J. Med. Chem.* **1992**, *35*, 163 – 172; c) A.-H. Li, H. Dong, T. Zhang, Patent US 2006/63791A1.

[9] a) H. Nishiyama, T. Shimada, H. Itoh, H. Sugiyama, Y. Motoyama, *Chem. Commun.* **1997**, 1863 – 1864; b) M. K. Tse, C. Döbler, S. Bhor, M. Klawonn, W. Mägerlein, H. Hugl, M. Beller, *Angew. Chem. Int. Ed.* **2004**, *43*, 5255 – 5260; *Angew. Chem.* **2004**, *116*, 5367 – 5372; c) M. K. Tse, S. Bhor, M. Klawonn, G. Anilkumar, H. Jiao, C. Döbler, A. Spannenberg, W. Mägerlein, H. Hugl, M. Beller, *Chem. Eur. J.* **2006**, *12*, 1855 – 1874; d) M. K. Tse, S. Bhor, M. Klawonn, G. Anilkumar, H. Jiao, A. Spannenberg, C. Döbler, W. Mägerlein, H. Hugl, M. Beller, *Chem. Eur. J.* **2006**, *12*, 1875 – 1888.

[10] T. Zeng, L. Yang, R. Hudson, G. Song, A. R. Moores, C.-J. Li, *Org. Lett.* **2011**, *13*, 442 – 445.

[11] Reviews: a) H. Ishitani, M. Iwamoto in *Comprehensive Chiralitiy* (Eds.: E. M. Carreira, H. Yamamoto), *Vol. 5*, Elsevier, Amsterdam, **2012**, 198 – 217; b) E. Wojaczyńska, J. Wojaczyński, *Chem. Rev.* **2010**, *110*, 4303 – 4356; c) H. B. Kagan in *Organosulfur Chemistry in Asymmetric Synthesis* (Eds.: T. Toru, C. Bolm), Wiley-VCH, Weinheim **2009**, 1 – 29; d) J. Legros, J. R. Dehli, C. Bolm, *Adv. Synth. Catal.* **2005**, *347*, 19 – 31.

[12] For key references, see: a) O. Bortolini, F. DiFuria, G. Licini, G. Modena, M. Rossi, *Tetrahedron Lett.* **1986**, *27*, 6257 – 6260; b) M. T. Barros, A. J. Leitão, C. D. Maycock, *Tetrahedron Lett.* **1995**, *36*, 6537 – 6540; c) C. Bolm, F. Bienewald, *Synlett* **1998**, 1327 – 1328; d) T. Tanaka, B. Saito, T. Katsuki, *Tetrahedron Lett.* **2002**, *43*, 3259 – 3262; e) A. Lattanzi, S. Piccirillo, A. Scettri, *Eur. J. Org. Chem.* **2006**, 713 – 718; f) J. Fujisaki, K. Matsumoto, K. Matsumoto, T. Katsuki, *J. Am. Chem. Soc.* **2011**, *133*, 56 – 61.

[13] A. Frycia, J.-P. Starck, S. Jadot, B. Lallemand, K. Leclercq, P. L. Brutto, A. Matagne, V. Verbois, J. Mercier, B. Kenda, *ChemMedChem* **2010**, *5*, 200 – 205.

[14] F. Voss, E. Herdtweck, T. Bach, *Chem. Commun.* **2011**, *47*, 2137 – 2139.

[15] a) F. D. Chattaway, E. G. Kellett, *J. Chem. Soc.* **1930**, 1352 – 1356; b) H. B. Henbest, S. A. Khan, *Chem. Commun.* **1968**, 1036; c) F. A. Carey, O. D. Dailey, Jr., *Phosphorus and Sulfur* **1981**, *10*, 169 – 174.

[16] a) E. Schaumann, U. Wried, G. Rühter, *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 63 – 69; *Angew. Chem.* **1983**, *95*, 52 – 53; b) E. Schaumann, G. Rühter, *Chem. Ber.* **1988**, *121*, 1159 – 1163.

[17] a) G. W. Gokel, H. M. Gerdes, D. M. Dishong, *J. Org. Chem.* **1980**, *45*, 3634 – 3639; b) S. E. Denmark, L. R. Cullen, *Org. Lett.* **2014**, *16*, 70 – 73.

[18] J. Bergman, S. Bergman, T. Brimert, *Tetrahedron* **1999**, *55*, 10447 – 10466.

[19] E. H. Krenske, K. N. Houk, *Acc. Chem. Res.* **2013**, *46*, 979 – 989 and references therein.

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