Asymmetric Sulfoxidation

Deutsche Ausgabe: DOI: 10.1002/ange.201601574
Internationale Ausgabe: DOI: 10.1002/anie.201601574

Enantioselective Sulfoxidation Catalyzed by a Bisguanidinium Diphosphatobisperoxotungstate Ion Pair

*Xinyi Ye, Adhitya Mangala Putra Moeljadi, Kek Foo Chin, Hajime Hirao, Lili Zong, and Choon-Hong Tan**

Abstract: *The first enantioselective tungstate-catalyzed oxidation reaction is presented. High enantioselectivities were achieved for a variety of drug-like phenyl and heterocyclic sulfides under mild conditions with H_2O_2, a cheap and environmentally friendly oxidant. Synthetic utility was demonstrated through the preparation of (S)-Lansoprazole, a commercial proton-pump inhibitor. The active ion-pair catalyst was identified to be bisguanidinium diphosphatobisperoxotungstate using Raman spectroscopy and computational studies.*

Sodium tungstate-catalyzed epoxidation of α,β-unsaturated acids using H_2O_2 in water was first demonstrated by Payne in 1959 and was followed up by Sharpless in 1985.[1] Tungstates are known to be polymeric in aqueous solutions, and the distribution of the polyoxotungstate species is dependent on pH and concentration.[2] Peroxotungstate complexes are known to be the catalytic species in these reactions.[3] Investigation by Venturello into the role of phosphate in phase transfer tungstate oxidation reactions, resulted in the isolation and identification of the heteropolyperoxotungstate, $[PO_4\{WO(O_2)_2\}_4]^{3-}$.[4] This peroxotungstate species was also postulated to be the catalytically active species for the $H_3PW_{12}O_{40}/H_2O_2$ (Keggin's reagent) oxidation system developed by Ishii.[5] Subsequently, Noyori developed an efficient catalyst suitable on a practical scale with high turnover number.[6] It was found that (aminomethyl)phosphonic acid or phenylphosphonic acid was effective in accelerating the reaction. It was proposed that a 1:1 complex between phosphonic acid and monoperoxotungstate is the active catalyst.[6c] Using this method, they furnished olefin epoxidation[6a] and sulfoxidation[6d] in high chemoselectivities.

We are interested in the practical preparation of enantiopure chiral sulfoxides.[7] While Kagan oxidation is widely adopted for asymmetric sulfoxidation,[8] there are emerging methods[9a–d] to prepare chiral sulfoxides, including some recent breakthroughs utilizing imidodiphosphoric acid,[9e] binuclear titanium chiral complex,[9f] or pentanidium.[10c] Pentanidiums belong to a new class of efficient phase-transfer catalysts that we have developed and have shown to be useful for a growing number of reactions.[10] We have also recently described how chiral cations including pentanidiums and other cationic phase transfer catalysts can be used as ion-pairing catalysts to activate inorganic anionic metal salts.[11] We demonstrated that by using potassium permanganate salt in the presence of a chiral dicationic bisguanidinium, highly enantioselective dihydroxylation and oxohydroxylation of α,β-unsaturated esters can be achieved (reaction 3 in Figure 1).[11] This strategy is highly complementary to the chiral anion ion-pairing catalysis that was demonstrated to be compatible with a variety of cationic metal species.[12]

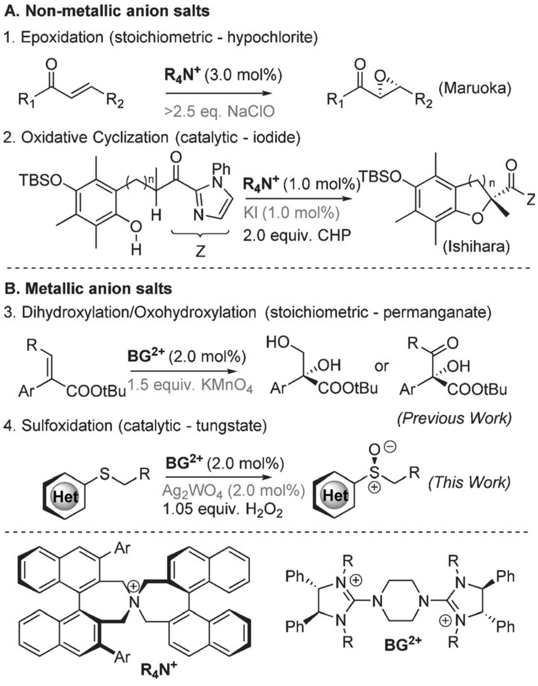


Figure 1. Enantioselective chiral cation ion-pairing oxidations.

Chiral cationic ion-pairing catalysis using inorganic salts is well-known. The oxidizing anionic salts can be stoichiometric as in the epoxidation of chalcone with sodium hypochlorite using Maruoka catalyst (reaction 1 in Figure 1).[13] Alternatively, the actual oxidant, (hypo)iodite, can be generated in situ through the use of iodide and stoichiometric oxidant such as cumene hydroperoxide (CHP) (reaction 2 in Figure 1). Ishihara demonstrated that enantioselective oxidative cycloetherification can be accomplished with this approach.[14] Herein, we wish to report the enantioselective sulfoxidation using catalytic amount of silver tungstate in the

---

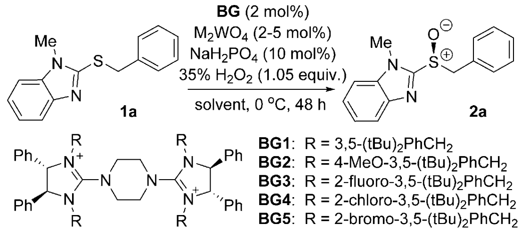
[*] X. Ye, A. M. P. Moeljadi, K. F. Chin, Prof. Dr. H. Hirao, Dr. L. Zong, Prof. Dr. C.-H. Tan
Division of Chemistry and Biological Chemistry
Nanyang Technological University
21 Nanyang Link, 637371 Singapore (Singapore)
E-mail: choonhong@ntu.edu.sg

Supporting information for this article can be found under: http://dx.doi.org/10.1002/anie.201601574.

presence of chiral dicationic bisguanidinium (reaction 4 in Figure 1).

At the outset, benzimidazole-derived benzyl sulfide **1a** was chosen as the model substrate to investigate the reaction conditions (Table 1). In the presence of 2.0 mol % of bisguanidinium **BG1** with Et_2O as solvent, no reaction was found when only H_2O_2 was used; indicating that **BG1** alone cannot catalyze the reaction. When 5.0 mol % of Na_2WO_4 was added, the reaction gave sulfoxide **2a** in poor yield and low enantioselectivity. It is only when 10 mol % NaH_2PO_4 was added, the yield of sulfoxide **2a** improved significantly to 36 % and its *ee* value improved to 20 % (Table 1, entry 1). When Na_2HPO_4 and Na_3PO_4 were used instead, the reactions were inhibited. Next, a range of commercially available tungstate salts, such as K_2WO_4, $(NH_4)_2WO_4$, and Ag_2WO_4, were evaluated (entries 2–4). Sulfoxide **2a** was obtained in 83 % yield with 88 % *ee* value when Ag_2WO_4 was used (entry 4). When the catalyst loading of Ag_2WO_4 was decreased to 2.0 mol %, it is necessary to change the solvent to diisopropyl ether to provide the best results (entry 6). Other bisguanidiniums **BG2–5** featuring different benzyl groups was unable to improve the results obtained with **BG1** (entries 7–10). We also confirm that NaH_2PO_4 in the absence of Ag_2WO_4 did not promote the sulfoxidation reaction.

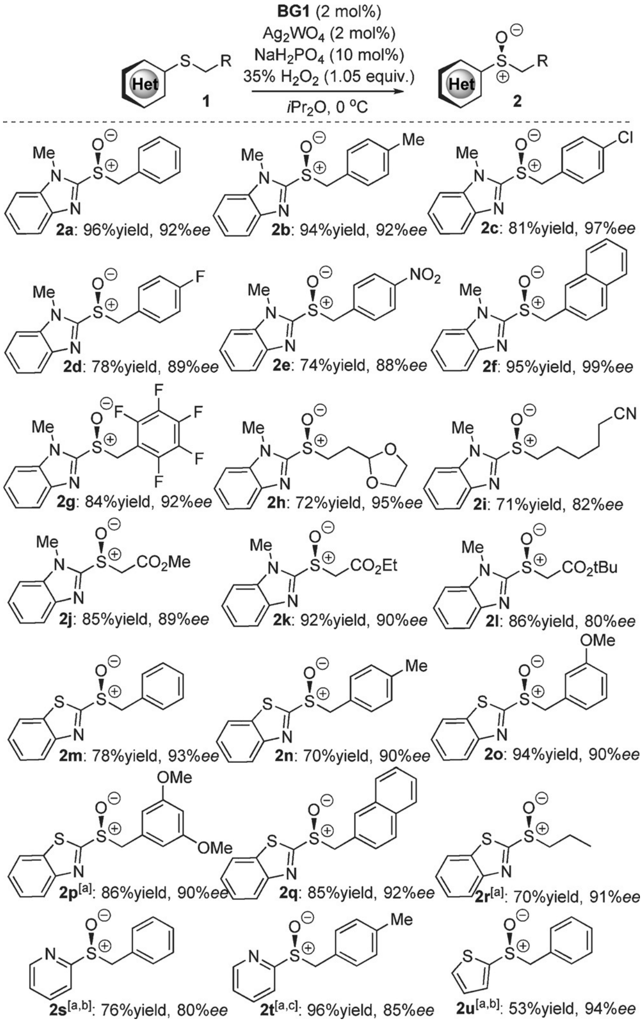
Table 1: Optimization of the reaction conditions.



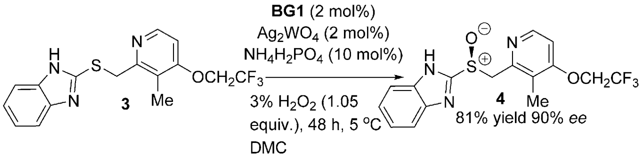
Entry	BG	M_2WO_4 [mol %]	Solvent	Yield [%][a]	*ee* [%][b]
1	**BG1**	Na_2WO_4 (5)	Et_2O	36	20
2	**BG1**	K_2WO_4 (5)	Et_2O	18	−2
3	**BG1**	$(NH_4)_2WO_4$ (5)	Et_2O	48	42
4	**BG1**	Ag_2WO_4 (5)	Et_2O	83	88
5	***ent*-BG1**	Ag_2WO_4 (5)	Et_2O	90	−89
6	**BG1**	Ag_2WO_4 (2)	*i*Pr_2O	96	92
7	**BG2**	Ag_2WO_4 (2)	*i*Pr_2O	65	63
8	**BG3**	Ag_2WO_4 (2)	*i*Pr_2O	63	50
9	**BG4**	Ag_2WO_4 (2)	*i*Pr_2O	52	32
10	**BG5**	Ag_2WO_4 (2)	*i*Pr_2O	84	8

[a] Yield of isolated product. [b] Determined by HPLC analysis on a chiral stationary phase.

With the optimized reaction conditions in hand, the substrate scope of benzimidazole-derived sulfides was examined (Scheme 1, **2a**–**2i**). The benzimidazole group does not seem to act as a ligand and inhibit the reaction. Both electron-donating and electron-withdrawing substitutions on the benzyl group worked well, affording the corresponding sulfoxidation products in good to excellent yields with good levels of enantioselectivities. The oxidation ability of the catalyst is able to override even a highly electron-withdrawing group such as pentafluorobenzyl (Scheme 1, **2g**). Besides benzyl groups, simple alkyl groups or esters are also tolerated in this reaction (**2h**-**l**). Other heterocyclic systems, such as benzothiazole (**2m**–**r**), pyridine (**2s**-**t**), and thiophene (**2u**), also worked well, providing products with excellent *ee* values. However, thiophene heterocyclic sulfides gave lower yields with significant amount of sulfone detected. We were also able to scale the reaction to gram scale (3.5 mmol) to give **2q** in 91 % yield and 92 % *ee*. The established strategy was also successfully applied to the preparation of (*S*)-Lansoprazole, a commercial proton-pump inhibitor (Scheme 2).

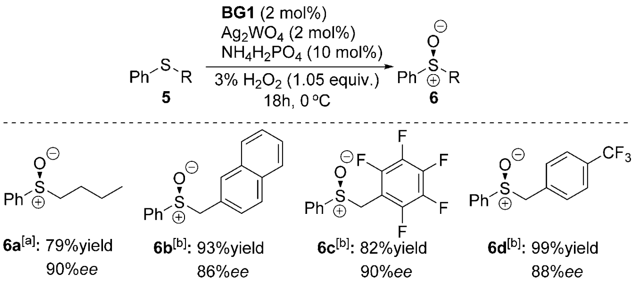


Scheme 1. Enantioselective sulfoxidation of heterocyclic sulfides. Reactions were carried out on a 0.2 mmol scale in 4.0 mL solvent for 36 hours unless otherwise noted; yield values refer to isolated yields after purification; *ee* was determined by chiral-phase HPLC. [a] 5.0 mol % of Ag_2WO_4 was used. [b] Et_2O as the solvent. [c] 8.0 mL *i*Pr_2O was used.



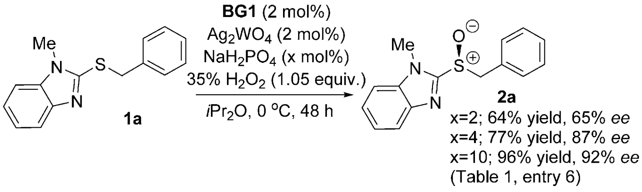
Scheme 2. Enantioselective synthesis of (*S*)-lansoprazole.

To further demonstrate the substrate scope of this new method, several conventional substrates containing phenyl sulfide moiety were also tested (Scheme 3). For such substrates, a balance between reaction yields and enantioselectivities was achieved by employing a solvent mixture between dimethyl carbonate (DMC) and ethers. The substrates that could be tolerated included those with simple alkyl chains to electron-withdrawing aromatic rings.



Scheme 3. Enantioselective sulfoxidation of phenyl sulfides. [a] Reactions were carried out on 0.2 mmol scale in a solvent mixture of DMC (4.0 mL)/ *i*Pr_2O (4.0 mL). (DMC = dimethyl carbonate) [b] Reactions were carried out in a solvent mixture of DMC (4.0 mL)/Et_2O (4.0 mL).

During optimization of the reaction conditions, we realized that the ratio between Ag_2WO_4 to NaH_2PO_4 is crucial to obtaining good yields and enantioselectivities (Scheme 4). The most significant improvement was achieved when the ratio of phosphate to tungstate reached 1:2. As the amount of phosphate in this current method is in excess over tungstate, we speculated that the Ishii–Venturello catalyst, $[PO_4\{WO(O_2)_2\}_4]^{3-}$, is not the active catalyst in this method. When we replaced the Ag_2WO_4/NaH_2PO_4 with $H_3PW_{12}O_{40}$ (Keggin's reagent) as in Ishii's procedure, the reaction provided sulfoxides in 40% yield and 30% *ee*.



Scheme 4. Influence of phosphate loading.

Ligand coordination or substitution has been previously shown to be an important factor that can influence the catalytic activities of peroxotungstates. Under the current experimental conditions, monomeric and oligomeric dihydroxide species **i** (Figure 2) should exist and in the presence of phosphate additive, form substituted phosphate species **ii**–**iv**.[15] These complexes assume distorted pentagonal bipyramid geometry and obey the 18-electron rule. As a result, coordination of three or more phosphates to the tungstate center can be considered to be unlikely. It is also important to note that owing to the short O–O bond distances (1.45 to 1.47 Å)[16] in the peroxo group, the oxygen atoms will most likely lie in the equatorial plane, instead of occupying both axial and equatorial positions in the complex. Based on these premises, the four possible configurations of substituted peroxotungstate species are presented (Figure 2).

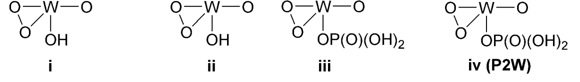


Figure 2. Four possible peroxotungstate species.

Raman spectra of the active species were obtained and compared with predicted Raman spectra of the four possible intermediates. Computed Raman spectra were obtained by performing vibrational frequency analysis on stationary points optimized at the B3LYP/B1 level of theory in gas phase, where B1 is a combination of LANL2DZ effective core potential basis set for W and the 6-31g* basis set for remaining atoms. A peak was observed experimentally at 711 cm^{-1}, which corresponds to the twisting of P-O-H group in the phosphate ligand (Figure 3 and Table 2; see the Supporting Information, Figures S18–S23, for details). This same peak was found only in the computed spectra of **P2W** (713 cm^{-1}). A more thorough analysis of the **P2W** structures revealed that intramolecular hydrogen bond interaction between the two phosphate ligands is important for this peak; absence of such interaction will shift the vibrational frequency towards 800 cm^{-1}. We thus proposed that the active anion of this enantioselective sulfoxidation is diphosphatobisperoxotungstate, $[\{PO_2(OH)_2\}_2\{WO(O_2)_2\}]^{2-}$.

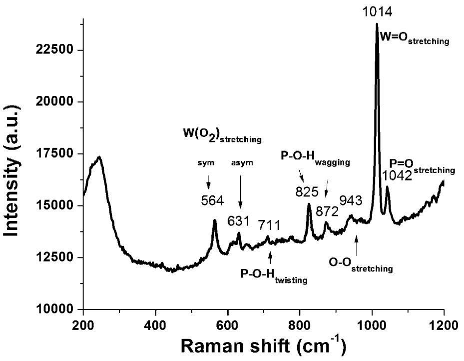


Figure 3. Experimental Raman spectrum of P2W, $[\{PO_2(OH)_2\}_2\{WO(O_2)_2\}]^{2-}$. For the vibration diagram, see Table 2.

Table 2: Vibrations of the Raman spectrum of P2W, $[\{PO_2(OH)_2\}_2\{WO(O_2)_2\}]^{2-}$.

	P=O	W=O	O–O	P–O–H	P–O–H	$W(O_2)$
calcd.	1014	1001	940	840, 802	713	643_{asym}, 564_{sym}
expt.	1042	1014	943	872, 825	711	631_{asym}, 564_{sym}

Preliminary computational studies of the complete **BG1-P2W** structure using ONIOM method (Supporting Information, Figures S24–S31) revealed a stable ion-pair interaction, where **P2W** is buried in the chiral cavity of **BG1** (Figure 4). This configuration results in only one of the peroxo-oxygen

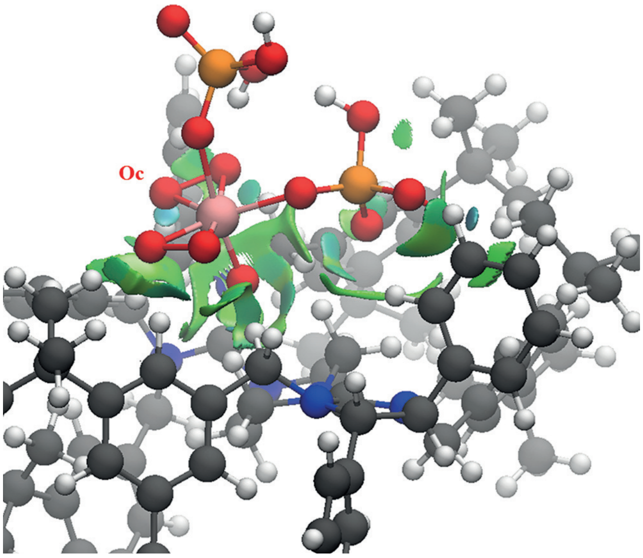


Figure 4. Representation of BG1-P2W ion-pair from ONIOM optimization result. C gray, N blue, H white, P orange, O red, W pink. NCI surface of BG1 structure is displayed: green indicates attractive non-covalent interactions.

(marked as **Oc** in Figure 4) being exposed, leaving it as the only possible reaction site. This will restrict the direction of approach of the sulfide, thereby providing fertile condition for an enantioselective reaction. We thus propose a simple working model, which includes the initial formation of **P2W** in the aqueous phase through the interactions of silver tungstate, phosphate, and hydrogen peroxide (Figure 5). The formation of the ion-pair **BG1-P2W** in the organic phase is facilitated by **BG1**. After oxidation, **P2W** is regenerated in the aqueous phase by H_2O_2.

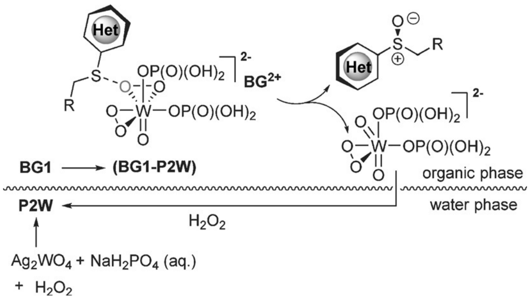


Figure 5. Working model.

In summary, we report the first enantioselective tungstate-catalyzed oxidation reaction. High enantioselectivities were achieved for a variety of drug-like heterocyclic sulfides under mild conditions with H_2O_2, a cheap and environmentally friendly oxidant. Synthetic utility was demonstrated through the preparation of (*S*)-Lansoprazole, a commercial proton-pump inhibitor. The active ion-pair catalyst was identified to be bisguanidinium diphosphatobisperoxotungstate using Raman spectroscopy and computational studies.

Acknowledgements

We gratefully acknowledge the financial support by grants from NTU (M4080946.110 and M4011372.110) and a scholarship (to X.Y.). A.M.P.M. and H.H. accomplished the computational work.

Keywords: asymmetric sulfoxidation · bisguanidinium · ion-pair catalysis · lansoprazole · Raman spectroscopy

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 7101–7105
Angew. Chem. **2016**, *128*, 7217–7221

---

[1] a) G. B. Payne, P. H. Williams, *J. Org. Chem.* **1959**, *24*, 54; b) K. S. Kirshenbaum, K. B. Sharpless, *J. Org. Chem.* **1985**, *50*, 1979.
[2] F. A. Cotton, G. Wilkinson, *Advanced Inorganic Chemistry*, 5th ed., Wiley, New York, **1999**, p. 812, Chap. 18.
[3] a) K. A. Joergensen, *Chem. Rev.* **1989**, *89*, 431; b) M. H. Dickman, M. T. Pope, *Chem. Rev.* **1994**, *94*, 569; c) N. Mizuno, K. Yamaguchi, K. Kamata, *Coord. Chem. Rev.* **2005**, *249*, 1944.
[4] a) C. Venturello, E. Alneri, M. Ricci, *J. Org. Chem.* **1983**, *48*, 3831; b) C. Venturello, R. D'Aloisio, J. C. J. Bart, M. Ricci, *J. Mol. Catal.* **1985**, *32*, 107.
[5] a) Y. Ishii, K. Yamawaki, T. Ura, H. Yamada, T. Yoshida, M. Ogawa, *J. Org. Chem.* **1988**, *53*, 3587; b) A. J. Bailey, W. P. Griffith, B. C. Parkin, *J. Chem. Soc. Dalton Trans.* **1995**, 1833; c) D. C. Duncan, R. C. Chambers, E. Hecht, C. L. Hill, *J. Am. Chem. Soc.* **1995**, *117*, 681.
[6] a) K. Sato, M. Aoki, M. Ogawa, T. Hashimoto, R. Noyori, *J. Org. Chem.* **1996**, *61*, 8310; b) K. Sato, M. Aoki, J. Takagi, K. Zimmermann, R. Noyori, *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2287; c) R. Noyori, M. Aoki, K. Sato, *Chem. Commun.* **2003**, 1977; d) K. Sato, M. Hyodo, M. Aoki, X. Q. Zheng, R. Noyori, *Tetrahedron* **2001**, *57*, 2469.
[7] For selected reviews, see: a) I. Fernández, N. Khiar, *Chem. Rev.* **2003**, *103*, 3651; b) H. B. Kagan, T. O. Luukas in *Transition Metals for Organic Synthesis: Building Blocks and Fine Chemicals*, 2nd ed. (Ed. H. B. Kagan), Wiley-VCH: Weinheim, **2008**, p. 479; c) G. E. O'Mahony, A. Ford, A. R. Maguire, *J. Sulfur Chem.* **2013**, *34*, 301.
[8] H. B. Kagan, F. Rebiere, *Synlett* **1990**, 643.
[9] a) F. A. Davis, R. T. Reddy, W. Han, P. J. Carroll, *J. Am. Chem. Soc.* **1992**, *114*, 1428; b) J. Legros, C. Bolm, *Angew. Chem. Int. Ed.* **2004**, *43*, 4225; *Angew. Chem.* **2004**, *116*, 4321; c) C. Drago, L. Caggiano, R. F. W. Jackson, *Angew. Chem. Int. Ed.* **2005**, *44*, 7221; *Angew. Chem.* **2005**, *117*, 7387; d) J. Fujisaki, K. Matsumoto, K. Matsumoto, T. Katsuki, *J. Am. Chem. Soc.* **2011**, *133*, 56; e) S. Liao, I. Čorić, Q. Wang, B. List, *J. Am. Chem. Soc.* **2012**, *134*, 10765; f) S. Bhadra, M. Akakura, H. Yamamoto, *J. Am. Chem. Soc.* **2015**, *137*, 15612.
[10] a) T. Ma, X. Fu, C. W. Kee, L. Zong, Y. Pan, K. W. Huang, C.-H. Tan, *J. Am. Chem. Soc.* **2011**, *133*, 2828; b) Y. Yang, F. Moinodeen, W. Chin, T. Ma, Z. Jiang, C.-H. Tan, *Org. Lett.* **2012**, *14*, 4762; c) L. Zong, X. Ban, C. W. Kee, C.-H. Tan, *Angew. Chem. Int. Ed.* **2014**, *53*, 11849; *Angew. Chem.* **2014**, *126*, 12043; d) L. Zong, S. Du, K. F. Chin, C. Wang, C.-H. Tan, *Angew. Chem. Int. Ed.* **2015**, *54*, 9390; *Angew. Chem.* **2015**, *127*, 9522.
[11] C. Wang, L. Zong, C.-H. Tan, *J. Am. Chem. Soc.* **2015**, *137*, 10677.
[12] a) K. Brak, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2013**, *52*, 534; *Angew. Chem.* **2013**, *125*, 558; b) M. Mahlau, B. List, *Angew. Chem. Int. Ed.* **2013**, *52*, 518; *Angew. Chem.* **2013**, *125*, 540; c) R. J. Phipps, G. L. Hamilton, F. D. Toste, *Nat. Chem.* **2012**, *4*, 603.
[13] a) T. Ooi, D. Ohara, M. Tamura, K. Maruoka, *J. Am. Chem. Soc.* **2004**, *126*, 6844; b) S. Shirakawa, K. Maruoka, *Angew. Chem. Int.

Ed. **2013**, *52*, 4312; *Angew. Chem.* **2013**, *125*, 4408; c) T. Ooi, K. Maruoka, *Angew. Chem. Int. Ed.* **2007**, *46*, 4222; *Angew. Chem.* **2007**, *119*, 4300.
[14] a) M. Uyanik, H. Okamoto, T. Yasui, K. Ishihara, *Science* **2010**, *328*, 1376; b) M. Uyanik, H. Hayashi, K. Ishihara, *Science* **2014**, *345*, 291.
[15] a) S. Campestrini, V. Conte, F. Di Furia, G. Modena, O. Bortolini, *J. Org. Chem.* **1988**, *53*, 5721; b) C. H. Yang, S. J. Dzugan, V. L. Goedken, *J. Chem. Soc. Chem. Commun.* **1985**, 1425; c) G. Amato, A. Arcoria, F. P. Ballistreri, G. A. Tomaselli, O. Bortolini, V. Conte, G. Valle, *J. Mol. Catal.* **1986**, *37*, 165.
[16] S. E. Jacobson, R. Tang, F. Mares, *Inorg. Chem.* **1978**, *17*, 3055.

Received: February 14, 2016
Revised: March 24, 2016