ARTICLE

Enantioselective oxidative coupling reaction of 2-naphthol derivatives catalyzed by chiral diphosphine oxide–iron(II) complexes

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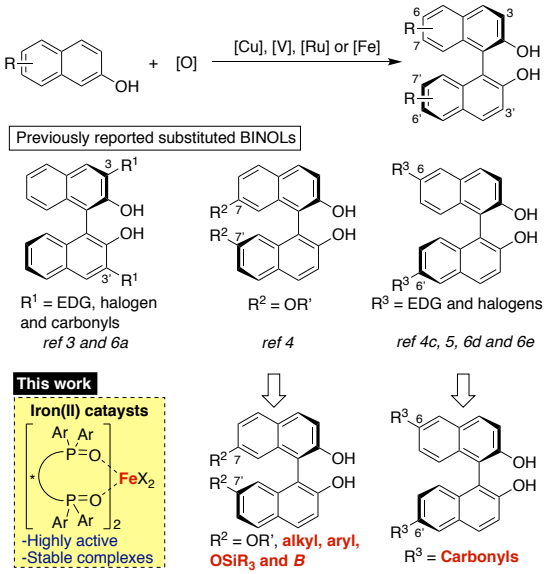
An enantioselective oxidative coupling of 2-naphthol derivatives is developed with the use of chiral Fe(II)-diphosphine oxide complexes. Optically active 1,1-bi-2-naphthol derivatives can be synthesized in high yields when a 2:1 complex of (*S*)-xylyl-*i*PrO-BIPHEP-oxide and $Fe(OTf)_2$ is used in the presence of *t*-butyl hydroperoxide as an oxidant. Non-linear effect, X-ray crystal structure and ESI-MS suggest that a 2:1 complex of (*S*)-xylyl-*i*PrO-BIPHEP-oxide and $Fe(OTf)_2$ is a pre-catalyst for a Fe(III)/Fe(IV) redox cycle.

Optically pure C_2-symmetric 1,1-bi-2-naphthols (BINOLs) have been widely used as chiral ligands or chiral auxiliaries.[1] Because of their importance in asymmetric synthesis, various methods for constructing chiral BINOLs have been developed. Among them, an oxidative coupling reaction of 2-naphthol derivatives is one of the most straightforward methods for constructing chiral BINOLs.[2] Because various 2-naphthols can directly provide optically pure BINOLs, great progress has been made in using metal catalysts for enantioselective oxidative coupling reactions. To date, chiral BINOL derivatives have been synthesized by leveraging asymmetric catalysis by transition metals such as copper,[3] vanadium,[4] ruthenium[5] and iron.[6] Nevertheless, the synthesis of 7,7'- and 6,6'-substituted BINOLs have been less studied in comparison with that of 3,3'-substituted BINOL. Although chiral vanadium catalysis provides optically active 7,7'-substituted BINOLs,[4] the scope of substrate has been still limited to 7-alkoxyl substituted naphthols. Regarding to 6,6'-substituted BINOL, less is known about using highly electron-deficient 2-naphthols, such as 6-carbonyl substituted 2-naphthols. Because such electron-deficient 2-naphthol is less-reducing substrate, it has been recognized that oxidative coupling is less likely in the conventional catalysis.[6b]

To address these issues, redox property of iron catalysis attracted us.[7–10] Chiral iron complexes (iron-salan, iron-phosphate and iron-aminopyridine) have been known as efficient catalysts for the synthesis of optically active 3,3'- and 6,6'-substituted BINOLs developed by Katsuki, Pappo and Bryliakov, respectively. Therefore, we anticipated that even electron-deficient 2-naphthol can be oxidized if a reactive, yet stable iron-complex is used. Among them, chiral diphosphine oxides–Fe(II) complex is of particular interest.[11] Phosphine oxide has been known as a suitable ligand to afford an isolable phosphine oxides–Fe(II) complexes.[12,13] Despite its stability, the phosphine oxide–Fe(II) complex is rapidly oxidized by *t*-butyl hydroperoxide (*t*BuOOH).[13] The resulting complex can smoothly oxidize reductive organic molecules at room temperature. These properties suggest that diphosphine oxide–Fe(II) complexes might act as highly active oxidation catalysts. In addition, the bidentate coordination of chiral diphosphine oxides[14] might stabilize chiral Fe(II) complex,



Scheme 1 Chiral metal-catalyzed oxidative coupling of 2-naphthols and the products.

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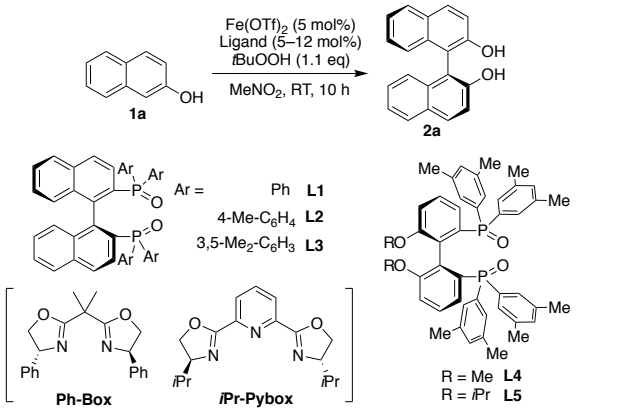
which provide sufficiently chiral environment for 6- and 7-substituted naphthols during the oxidative coupling reaction.

Our initial investigations focused on the oxidative coupling reaction of 2-naphthol **1a** catalyzed by chiral diphosphine oxide ligands (**L1–L3**), which were prepared from BINAP derivatives (Table 1). In the presence of 5 mol% each of $Fe(OTf)_2$ and ligands (**L1** and **L2**), no enantioselectivity was induced. (entries 1 and 2). When **L3** was used as a chiral ligand, enantioselectivity was observed, although it was low (entry 3). Considering the four coordination sites of $Fe(OTf)_2$, we optimized the amount of **L3**. To our delight, the enantioselectivity dramatically improved in the presence of 10 mol% of **L3** (entry 4). A higher enantioselectivity was observed when 12 mol% of **L3** with 5 mol% of $Fe(OTf)_2$ was used (entry 5). Further screening of the ligand revealed that 12 mol% of (*S*)-xylyl-BIPHEP oxide (**L4** and **L5**) gave **2a** in slightly improved enantioselectivity (entries 7 and 8). In conventional Fe(II)-catalysis, **Ph-Box** and ***i*Pr-Pybox** have been recognized as suitable chiral ligands.[15] However, slightly decreases in the yields of **2a** with low enantioselectivities were observed when **Ph-Box** and ***i*Pr-Pybox** were used (entries 9 and 10). These results suggest that chiral diphosphine oxide–iron(II) may be useful for the oxidative coupling reaction.

The scope of 2-naphthols **1**, with a substituent at the 3- and 7-position, was examined (Table 2). Unfortunately, 3-substituted 2-naphthol **1b** provided the corresponding product **2b** in low yield. In

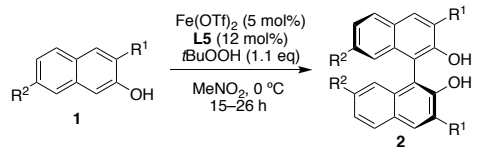
Table 1 Screening of Ligands.[a]



entry	Ligand [mol %]	Yield[b] [%]	Ee [%]
1	**L1**, 5	86	0
2	**L2**, 5	84	0
3	**L3**, 5	81	6
4	**L3**, 10	98	40
5	**L3**, 12	98	62
6	**L3**, 12	96[c]	66
7	**L4**, 12	98[c]	68
8	**L5**, 12	95[c]	70
9	**Ph-Box**, 10	80[c]	4
10	***i*Pr-Pybox**, 10	77[c]	23

[a] The reaction was carried out with $Fe(OTf)_2$ (5.0 mol %), ligand (5.0–12.0 mol %), **1a** (2 equiv) and *t*BuOOH (1.1 equiv) in $MeNO_2$ at room temperature. [b] Isolated yield. [c] 0 ºC.

Table 2 Scope of Substrates.[a]



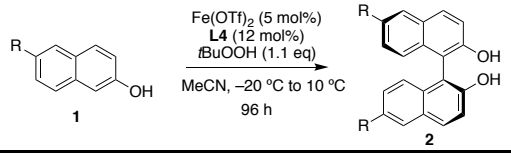
entry	R^1	R^2		Yield [%]	Ee [%]
1	Me	H	**2b**	15	10
2	H	Me	**2c**	98	87
3	H	MeO	**2d**	93	84
4	H	*i*PrO	**2e**	91	82
5	H	AllylO	**2f**	97	81
6	H	Br	**2g**	90	83
7	H	I	**2h**	80[b]	87
8	H	*i*Pr	**2i**	98	90
9	H	nOctyl	**2j**	91	85
10	H	*c*Pent	**2k**	98	86
11	H	*c*Hex	**2l**	92[c,d]	88
12	H	*c*Hep	**2m**	94	84
13	H	Ph	**2n**	98[d]	87
14	H	4-Cl-C_6H_4	**2o**	98[b]	88
15	H	4-Me-C_6H_4	**2p**	98[b]	88
16	H	3,5-Me_2-C_6H_3	**2q**	97[d]	89
17	H	TESO	**2r**	82[e]	90
18	H	TBSO	**2s**	95[d]	92
19	H	pinB	**2t**	94[d,f,g]	81

[a]The reaction was carried out with $Fe(OTf)_2$ (5 mol %), **L5** (12 mol %), **1** (2 equiv) and *t*BuOOH (1.1 equiv) in $MeNO_2$ at 0 ºC. [b]60 h. [c]$Fe(OTf)_2$ (2.5 mol %), **L5** (6 mol %) was used. [d]45 h. [e]48 h. [f]**L4** was used instead of **L5**. [g] –10 ºC.

contrast, 7-substituted 2-naphthols **1c–1t** were found to be suitable substrates for our reaction conditions. Both electron-donating group and -withdrawing group at the 7-position of naphthols **1c–1m** were well-tolerated (entries 2-12). In the coupling of **1l**, the amount of catalyst could be reduced to 2.5 mol% without a decrease in enantioselectivity. Aromatic substituents at the 7-position did not decrease the enantioselectivity (entries 13–16). Notably, labile functional groups of **1r–1t**, such as siloxy groups and boronic acid ester, were well-tolerated. The highest enantioselectivity was observed with the use of 7-siloxy-2-naphthol **1s** [95% yield, 92% ee]. These 7,7′-substituted BINOLs are of particular interest because of their modulated dihedral angles and electronic properties. Despite their unique physical properties, there have been few studies on the synthesis of optically active 7,7′-substituted BINOLs, except for chiral vanadium catalysis.[4] Besides, the scope of substrate in these chiral vanadium catalyses has been limited to 7-alkoxyl substituted naphthols. In sharp contrast, chiral Fe(II) diphosphine oxides provided a variety of 7,7′-substituted BINOLs **2**, including those with labile functional groups. Moreover, our reaction conditions do not require either a long reaction time (2–6 days) or a less-practical solvent (CCl_4), which are required for chiral vanadium catalysis.[4] Therefore, this is one of the most practical methods for the synthesis of optically active 7,7′-substituted BINOLs.

The scope of 6-substituted 2-naphthols was also examined in MeCN (Table 3). In these cases, **L4** was more efficient than **L5** in terms of

Table 3 Scope of 6-Substituted 2-Naphthols.[a]



entry	R		Yield [%]	Ee [%]
1	Me	**2u**	98	60
2	Br	**2v**	72	74
3	MeO_2C	**2w**	93 (87)[b]	85 (92)[b]
4	EtO_2C	**2x**	75	81
5	(EtS)OC	**2y**	71 (56)[b]	80 (95)[b]
6	MsO	**2z**	98	81

[a]The reaction was carried out with $Fe(OTf)_2$ (5 mol %), **L4** (12 mol %), **1** (2 equiv) and *t*BuOOH (1.1 equiv) in MeCN. [b]The yield and ee value of **2w** and **2y** after a single recrystallization.

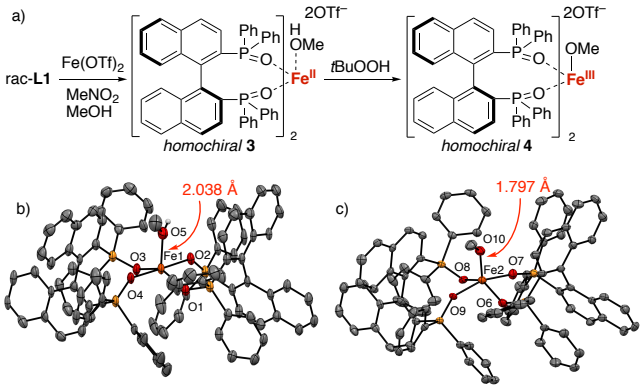
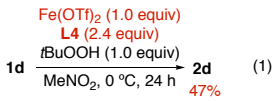


Fig. 1 (a) The generation of **3** and subsequent oxidation of **3**. (b and c) Thermal ellipsoids of **3** and **4** respectively. TfO^-, solvent molecules and hydrogens have been omitted for clarity, except for the hydroxy proton of MeOH.

enantioselectivity (see, Table S4). Whereas electron-rich **1u** decreased the enantioselectivity, electron-deficient **1v–1z** improved enantioselectivity of the product. For examples, ester, thioester and methanesulfonate (MsO) were suitable functional groups under these reaction conditions. In the conventional oxidative coupling of 6-substituted 2-naphthols, the scope of substrate has been limited to **1** having electron-donating substituent because electron-deficient **1** is less oxidizable than electron-rich **1**.[6b] Therefore, enantioselective oxidative coupling of **1w–1y** having carbonyl groups has been scarcely studied. These results in Table 3 imply the higher catalytic activity of the iron(II)–diphosphine oxide complexes than that of the conventional catalysis.

Next we sought to elucidate the active species. Regarding the relationship between the ee of **L5** and that of **2d**, a positive non-linear effect was observed in the oxidative coupling reaction of **1d** (Figure S1). To check the solution state of the Fe(II) complexes, ESI-MS analysis was conducted for a 2.4:1 molar ratio of **L5** and $Fe(OTf)_2$ in MeCN. Indeed, a 2:1 complex of **L5** and $Fe(OTf)_2$ was identified (Figure S2). These results suggest that the active species under these reaction conditions could be a 2:1 complex. Based on these findings, the chiral diphosphine oxide–Fe(II) complexes were isolated. The combination of **L5** and $Fe(OTf)_2$ in various solvents did not give an isolable complex. However, when *rac*-**L1** with $Fe(OTf)_2$ was used in MeOH, Fe**L1**$_2$(MeOH)$(OTf)_2$ (**3**) was obtained (Figure 1a). Complex **3** has two homochiral **L1** coordinating to $Fe(OTf)_2$, in which the coordination of MeOH is observed (Figure 1b). The X-ray crystal structure of **3** reveals a five-coordinate distorted trigonal bipyramidal geometry at the Fe(II) center. The average value for the four Fe(1)–O(1 to 4) bond lengths (2.051 Å) and the Fe(1)–O(5) bond length (2.038 Å) indicate that the cationic Fe(II) center of **3** is oxophilic. The oxidation of **3** by 0.5 equiv of *t*BuOOH afforded Fe**L1**$_2$(OMe)$(OTf)_2$ (**4**) (Figure 1a). In the solid state of **4**, the coordinated MeOH of **3** was oxidized to form an ionic Fe(2)–O(10) bond. The resulting Fe(III) center is a five-coordinate distorted square pyramidal geometry (Figure 1c). The bond length for Fe(2)–O(10) in **4** is 1.797 Å, which is much less than 2.038 Å for Fe(1)–O(5) in **3**. Such a short distance has only been observed in a pair of previously reported redox active Fe(III)(OMe) complexes.[16] These results suggest that a 2:1 complex of **L5**:$Fe(OTf)_2$ is likely to form under these reaction conditions in the presence of *t*BuOOH.

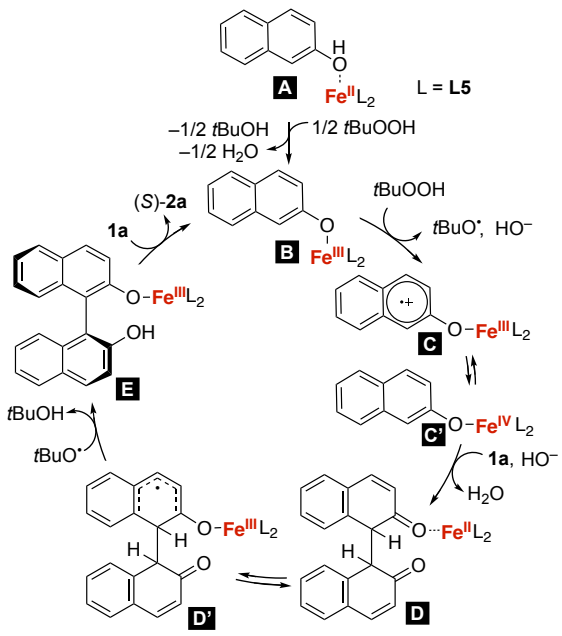
With regard to the catalytic cycle, there are two possible redox cycles: either Fe(II)/Fe(III) or Fe(III)/Fe(IV). To reveal the actual redox cycle, a control experiment using a stoichiometric amount of **L4**$_2$–$Fe(OTf)_2$ complex was examined for the oxidative coupling reaction of **1d** (Eq 1). If the redox cycle involves Fe(II)/Fe(III), **2d** is obtained in 100% yield from 1.0 equiv of *t*BuOOH. In contrast, the Fe(III)/Fe(IV) redox cycle gives **2d** in only 50% yield because 0.5 equiv of *t*BuOOH is required for the generation of an active Fe(III) complex from an Fe(II) complex. Indeed, the corresponding **2d** was obtained in only 47% yield when 1.0 equiv of *t*BuOOH was used. The consumption of 0.5 equiv of *t*BuOOH before product formation implies the generation of active Fe(III) from catalytically inactive Fe(II). Therefore, Fe(III)/Fe(IV) is more likely the active redox cycle under our reaction conditions.



(1)

Based on the conventional Fe(III)/Fe(IV) redox mechanism reported by Katsuki and Pappo,[6a–d] we propose the catalytic cycle shown in Scheme 3. A pre-catalyst **A** is oxidized by 0.5 equiv of *t*BuOOH to give Fe(III) complex **B**. Subsequent oxidation of **B** by another *t*BuOOH affords radical cation **C**, which tautomerizes to high-valent Fe(IV) complex **C'**. A nucleophilic attack of **1a** for electrophilic **C'** affords Fe(II) complex **D**. An Fe(III) tautomer **D'** undergoes hydrogen-atom transfer by $tBuO^{\bullet}$. The corresponding (*S*)-**2a** is obtained upon a ligand exchange of **E** with **1a**, which regenerates **B**.

In summary, a chiral diphosphine oxide-Fe(II) complex has been developed for the enantioselective oxidative coupling reaction of 2-naphthols . A stable diphosphine oxide–Fe(II) complex acts as an active oxidation catalyst in the presence of *t*-butyl hydroperoxide as a readily available oxidant. This practical method facilitates the construction of enantio-enriched 7,7'- and 6,6'-substituted BINOLs. Moreover, the reaction likely proceeds *via* an Fe(III)/Fe(IV) redox cycle, which is supported by mechanistic studies. We believe that this study not only provides a method for the synthesis of BINOLs, but also provides insight into the mechanism of the oxidation property of Fe(II) complex for other relevant Fe-catalyzed oxidation reactions.



Scheme 3 Proposed catalytic cycle.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

1 For selected reviews of the application of chiral BINOLs and BINAPs, see; a) Y. Chen, S. Yekta and A. K. Yudin, *Chem. Rev.* 2003, **103**, 3155; b) M. Berthod, G. Mignani, G. Woodward and M. Lemaire, *Chem. Rev.* 2005, **105**, 1801; c) J. M. Brunel, *Chem. Rev.* 2005, **105**, 857.

2 (a) B. Feringa and H. Wynberg, *J. Org. Chem.* 1981, **46**, 2547; (b) K. Yamamoto, H. Fukushima, Y. Okamoto, K. Hatada and M. Nakazaki, *J. Chem. Soc., Chem. Commun.* 1984, 1111; (c) M. Noji, M. Nakajima and K. Koga, *Tetrahedron Lett.* 1994, **35**, 7983.

3 For selected examples of copper-catalyzed enantioselective coupling, see; (a) M. Nakajima, K. Kanayama, I. Miyoshi and S. Hashimoto, *Tetrahedron Lett.* 1995, **36**, 9519; (b) C. A. Mulrooney, X. Li, E. S. DiVirgilio and M. C. Kozlowski, *J. Am. Chem. Soc.* 2003, **125**, 6856; (c) T. Temma and S. Habaue, *Tetrahedron Lett.* 2005, **46**, 5655; (d) T. Temma, B. Hatano and S. Habaue, *Tetrahedron* 2006, **62**, 8559; (e) J. B. Hewgley, S. S. Stahl and M. C. Kozlowski, *J. Am. Chem. Soc.* 2008, **130**, 12232.

4 For selected examples of vanadium-catalyzed enantioselective coupling, see; (a) Z. Luo, Q. Liu, L. Gong, X. Cui, A. Mi and Y. Jiang, *Angew. Chem., Int. Ed.* 2002, **41**, 4532; (b) Q.-X. Guo, Z.-J. Wu, Z.-B. Luo, Q.-Z. Liu, J.-L. Ye, S.-W. Luo, L.-F. Cun and L.-Z. Gong, *J. Am. Chem. Soc.* 2007, **129**, 13927; (c) S. Takizawa, T. Katayama and H. Sasai, *Chem. Commun.* 2008, 4113; d) M. Sako, S. Takizawa, Y. Yoshida and H. Sasai, *Tetrahedron: Asymmetry* 2015, **26**, 613.

5 R. Irie, K. Masutani and T. Katsuki, *Synlett*, 2000, 1433.

6 (a) H. Egami and T. Katsuki, *J. Am. Chem. Soc.* 2009, **131**, 6082; (b) H. Egami, K. Matsumoto, T. Oguma, T. Kunisu and T. Katsuki, *J. Am. Chem. Soc.* 2010, **132**, 13633; (c) K. Matsumoto, H. Egami, T. Oguma and T. Katsuki, *Chem. Commun.* 2012, **48**, 5823; (d) S. Narute, R. Parnes, F. D. Toste and D. Pappo, *J. Am. Chem. Soc.* 2016, **138**, 16553; (e) N. V. Tkachenko, O. Y. Lyakin, D. G. Samsonenko, E. P. Talsi and K. P. Bryliakov, *Catal. Commun.* 2018, **104**, 112.

7 For reviews of iron-mediated oxidative coupling, see: (a) A. A. O. Sarhan and C. Bolm, *Chem. Soc. Rev.* 2009, **38**, 2730; b) F. Jia and Z. Li, *Org. Chem. Front.* 2014, **1**, 194.

8 (a) A. Correa, O. G. Mancheño and C. Bolm, *Chem. Soc. Rev.* 2008, **37**, 1108; (b) S. Gaillard and J.-L. Renaud, *ChemSusChem* 2008, **1**, 505; (d) S. Enthaler, K. Junge and M. Beller, *Angew. Chem., Int. Ed.* 2008, **47**, 3317; (c) I. Bauer and H.-J. Knölker, *Chem. Rev.* 2015, **115**, 3170.

9 For selected reports of iron-catalyzed asymmetric oxidation, see; (a) C. Duboc-Toia, S. Ménage, C. Lambeaux and M. Fontecave, *Tetrahedron Lett.* 1997, **38,** 3727; (b) J. Legros and C. Bolm, *Angew. Chem., Int. Ed.* 2003, **42**, 5487; (c) Y. Nishikawa and H. Yamamoto, *J. Am. Chem. Soc.* 2011, **133**, 8432; (d) T. Oguma and T. Katsuki, *J. Am. Chem. Soc.* 2012, **134,** 20017; (e) T. Niwa and M. Nakada, *J. Am. Chem. Soc.* 2012, **134**, 13538; (f) O. Cussó, M. Cianfanelli, X. Ribas, R. J. M. K. Gebbink and M. Costas, *J. Am. Chem. Soc.* 2016, **138**, 2732.

10 For selected reports of iron-catalyzed oxidation, see; (a) M. C. White, A. G. Doyle and E. N. Jacobsen, *J. Am. Chem. Soc.* 2001, **123**, 7194; (b) M. S. Chen and M. C. White, *Science,* 2007, **318**, 783; (c) T. Tanaka, T. Tanaka, T. Tsuji, R. Yazaki and T. Ohshima, *Org. Lett.* 2018, **20**, 3541; (d) T. Horibe, S. Ohmura and K. Ishihara, *J. Am. Chem. Soc.* 2019, **141**, 1877.

11 Recently, phosphine oxides have been shown to be suitable ligands for Fe(II) in the oxidation reaction; T. Tanaka, K. Hashiguchi, T. Tanaka, R. Yazaki and T. Ohshima, *ACS Catal.* 2018, **8**, 8430.

12 (a) N. M. Karayannis, C. M. Mikulski, M. J. Strocko, L. L. Pytlewski and M. M. Labes, *J. Inorg. Nucl. Chem.* 1970, **32**, 2629; (b) T. S. Lobana, H. S. Cheema and S. S. Sandhu, *Polyhedron* 1985, **4**, 717; (c) J. E. Barclay, D. J. Evans, D. L. Hughes and G. J. Leigh, *J. Chem. Soc. Dalton Trans.* 1993, 69.

13 D. T. Sawyer, M. S. McDowell, L. Spencer and P. K. S. Tsang, *Inorg. Chem.* 1989, **28**, 1166.

14 For selected examples of diphosphine oxide-catalyzed reaction, see; (a) C. Ogawa, M. Sugiura and S. Kobayashi, *Angew. Chem., Int. Ed.* 2004, **43**, 6491; (b) M. Hatano, E. Takagi and K. Ishihara, *Org. Lett.* 2007, **9**, 4527; (c) Y. Shimoda, T. Kubo, M. Sugiura, S. Kotani and M. Nakajima, *Angew. Chem., Int. Ed.* 2013, **52**, 3461.

15 (a) G.-S. Liu, Y.-Q. Zhang, Y.-A. Yuan and H. Xu, *J. Am. Chem. Soc.* 2013, **135**, 3343; (b) D.-F. Lu, C.-L. Zhu, J.-D. Sears and H. Xu, *J. Am. Chem. Soc.* 2016, **138**, 11360.

16 (a) J. L. Hoard, M. J. Hamor, T. A. Hamor and W. S. Caughey, *J. Am. Chem. Soc.* 1965, **87**, 2312; (b) R. T. Jonas and T. D. P. Stack, *J. Am. Chem. Soc.* 1997, **119**, 8566.