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J. Am. Chem. Soc., **Just Accepted Manuscript** • Publication Date (Web): 01 Sep 2017

meso-Tetraphenylporphyrin Iron Chloride Catalyzed Selective Oxidative Cross-Coupling of Phenols

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Supporting Information Placeholder

ABSTRACT: A novel catalytic system for oxidative cross-coupling of readily oxidized phenols with poor nucleophilic phenolic partners based on an iron *meso*-tetraphenylporphyrin chloride (Fe[TPP]Cl) complex in 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP) was developed. The unique chemoselectivity of this reaction is attributed to the coupling between a liberated phenoxyl radical with an iron-ligated phenolic coupling partner. The conditions are scalable for preparing a long list of unsymmetrical biphenols assembled from a less reactive phenolic unit substituted with alkyl or halide groups.

INTRODUCTION

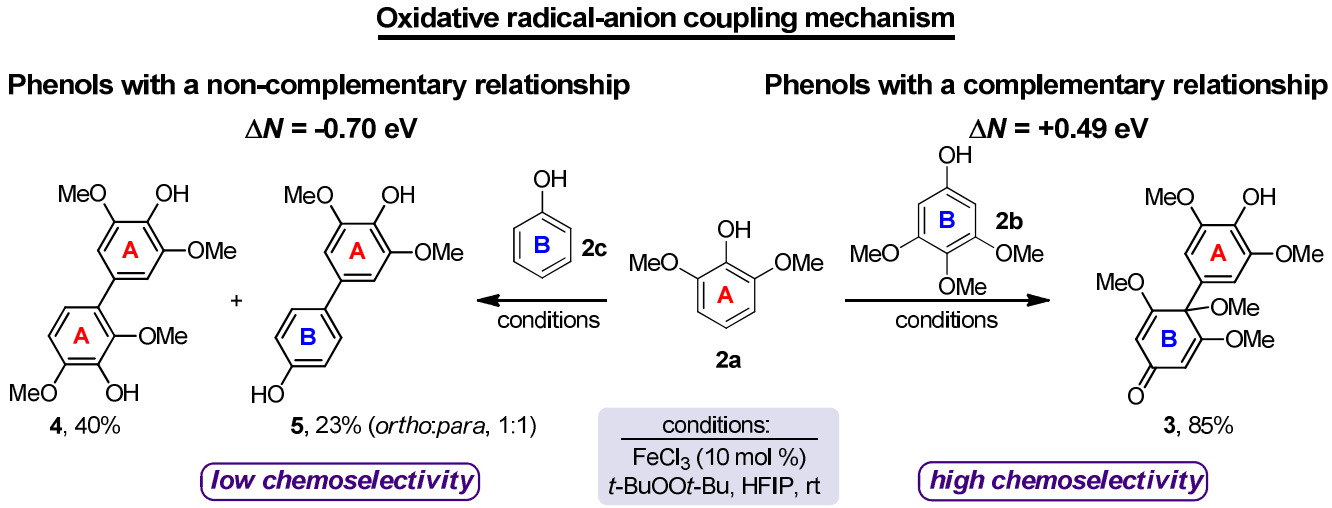
Unsymmetrical biaryls, an important class of structural motifs found in natural products and bioactive compounds, also serve as ligands in asymmetric catalysis and in various synthetic applications.[1] Current protocols for syntheses of biaryl compounds rely on transition-metal-catalyzed cross-coupling between two activated arenes (Ar–X and Ar–M).[2] In general, each coupling step is accompanied by number of selectivity-determining steps, which are essential to set the regioselectivity (site selection) and the chemoselectivity (cross-coupling vs. homocoupling) of the coupling reaction. These burdensome steps impinge on both the atom economy and step economy of the entire process.[3] In contrast, the biomimetic metal-catalyzed oxidative phenol coupling reaction offers a superior alternative for synthesizing biaryl bonds directly from two un-functionalized phenolic components. In such a reaction, the absence of activated centers enforces induction of the regio-, chemo- and stereoselectivity (axial chirality) during the C–C bond forming step.[4] Therefore, to enable precise control of the selectivity, it is necessary to develop variety of metal complexes that mediate oxidative coupling through different mechanisms.[5] To achieve this challenging goal, our group has initiated a project that aims to address the selectivity problems inherent in the metal-catalyzed oxidative coupling of phenols through mechanistically driven catalyst design. Here, we report a novel catalytic system based on a *meso*-tetraphenylporphyrin iron chloride (Fe[TPP]Cl) complex and *t*-BuOOH in 1,1,1,3,3,3-hexafluoropropano-2-ol (HFIP). The particular mechanism involved in this reaction makes it suitable for preparing unsymmetrical biphenols that are not accessible in an efficient manner by any other direct methods.

Oxidative homocoupling of phenols is an important reaction that produces symmetrical dimeric,[1b,6] oligomeric and polymeric phenolic materials[7] that are essential for a wide range of advanced applications.[8] The selectivity and efficiency problems inherent in these transformations have already been successfully addressed.[9] In contrast, suitable conditions for the cross-coupling of two phenols, which are much more challenging transformations that demand a high degree of chemoselectivity (cross-coupling vs. homocoupling), are limited in number.[4a-c,9c,10] Early work on these transformations focused on the stoichiometric Cu(II)/amine-mediated system for the cross-coupling of substituted 2-naphthols, first studied by Hovorka and Zavada[10i-k] and later by Kočovský.[10h] Other studies included the aerobic oxidative cross-coupling of dialkylphenols by a Cr[salen] complex, investigated by the Kozlowski group[10f], and our group's[4b] efficient synthesis of unsymmetrical biphenols with an $FeCl_3$ catalyst in HFIP. In addition, enantio-enriched C_1- and C_2-symmetric BINOLs have been synthesized with chiral iron[salan] (the Katsuki group[4c,9c]) and iron[phosphate]$_3$ complexes (the Pappo group[4a]). Finally, other methods for coupling phenols with nucleophilic arenes have also been developed for preparing biaryls[10c,11] and polyarenes.[12]

Recently,[4b] we postulated that the above oxidative cross-coupling reactions between two phenols (**A** and **B**) follow a radical-anion coupling mechanism. Such mechanism proceeds with the selective oxidation of phenol **A** (E_{ox}**A** < E_{ox}**B**, where E_{ox} is the oxidation potential) by a redox catalyst, which generates an electrophilic phenoxyl **A**• radical that reacts with a nucleophilic phenol(ate) **B**. The degree of chemoselectivity relies on the difference in nucleophilicity between the two phenols ($\Delta N = N_B - N_A$, N is the theoretical global nucleophilicity[13]). Pairs of phenols with a complementary relationship (positive ΔN values) will favor the formation of an unsymmetrical biphenol **A**–**B**, while negative ΔN values will be indicative of the low chemoselectivity that favors the homocoupling biphenol **A**–**A** product.[4b] Thus, when we initiated the current study, only powerful phenolic nucleophiles, such as 2-naphthol derivatives or phenols with at least a single methoxy group, could serve as efficient type **B** phenols in oxidative cross-coupling reactions.[4b] For example, the $FeCl_3$-catalyzed reaction of 2,6-dimethoxyphenol (**2a**, E_{ox}**2a** = 0.40 V, in HFIP vs. Ag/$AgNO_3$[4b,11a]) with 3,4,5-trimethoxyphenol

(**2b**, E_{ox}**2b** = 0.46 V), which is relatively a better nucleophile than its coupling partner **2a** (ΔN = +0.49 eV), favored oxidative cross-coupling (product **3**, Scheme 1).[4b] In contrast, under similar conditions, the coupling between 2,6-dimethoxyphenol **2a** and phenol [**2c** (3 equiv), E_{ox}**2c** = 0.63 V], which have a non-complementary relationship (ΔN = -0.70 eV), afforded the homocoupling product **4** in 40% yield, while the desired cross-coupling product **5** was obtained only in 23% yield (Scheme 1). The development of methods for coupling pairs of phenols with a non-complementary relationship thus became an urgent scientific goal that we sought to address. We envisioned that the solution to this selectivity problem would involve a redox catalyst that would mediate oxidative cross-coupling via a mechanism that does not depend on the relative nucleophilicities of the two coupling partners.

Scheme 1. Chemoselectivity in oxidative coupling of phenols with complementary and non-complementary relationships by a radical-anion coupling mechanism.[4b]



Mechanistic studies that involve kinetic investigations and electrochemical methods for the oxidative coupling of phenols have been carried out by both the Katsuki group[4c,9c] and our group.[4a,4b] Based on these experiments, a correlation between the number of coordination sites available for binding phenolic ligands and the coupling modes has been established. The oxidative coupling of phenols by the multicoordinated $FeCl_3$ catalyst showed zero-order kinetics for the phenols, suggesting that the coupling takes place between an associated phenoxyl radical and a phenol(ate) ligand (intramolecular radical-anion/nucleophile coupling, Figure 1A). In contrast, first-order kinetics was found for 2-naphthols when the oxidative homocoupling was catalyzed by Fe[salan][4c] or Fe[phosphate]$_3$ complexes.[4a] These catalysts have one or two coordination sites available in *cis*-orientation,[14] and therefore an intermolecular coupling between an associated naphthoxyl radical and a second liberated naphthol(ate) was proposed (intermolecular radical-anion coupling, Figure 1B).[4c] To further investigate the relationship between the catalyst structure and the mode of coupling, the commercially available Fe[TPP]Cl complex (**1a**), which has only a single axial position available for binding, was examined as a catalyst in oxidative cross-coupling reactions of phenols.

The current study relies on previous comprehensive studies by Groves and others on the relationship between the structural and electronic environment of iron porphyrins and their catalytic functions—studies that facilitated investigations of the mode of action of heme enzymes.[15] The added value of these studies lies in the new pathways that they offer for the design of biomimetic catalysts with improved synthetic capabilities and unique selectivity.[16,17] In heme enzymes, the iron porphyrin cofactor attaches to the protein backbone by coordination of an axial cysteine (for hydroxylases), histidine (for peroxidases) or tyrosine (for catalases),[18] leaving the other axial position available for binding and activation of dioxygen or peroxides.[19] Iron(IV) oxide bound to the porphyryl radical[20] is responsible for the homolytic cleavage of an R–H bond in the relevant substrate.[21] The oxidized short-lived R• species is not in direct contact with the metal center and can either recombine with the iron-bound hydroxyl radical to form an alcohol R–OH (oxygen rebound mechanism)[22] or react with a second radical species to afford the coupling product R–R through a free radical-radical coupling mechanism.[20b] It has been shown that by donating spin density to the redox iron center the axial ligand plays an essential role in controlling the function and reactivity of the catalyst ('push effect').[16f,23] Despite the promise of this catalytic pathway, attempts to develop biomimetic oxidative coupling reactions of phenols that involve iron porphyrin catalysts has met with only limited success,[24] probably as a result of the formation of the catalytically inactive μ-oxo-bis[(5,10,15,20-tetraphenylporphyrinato)iron(III)] [(Fe[TPP])$_2$O (**1d**)] and the destruction of the porphyrin ligand by highly reactive radical species.[25]

Here, we report a novel Fe[TPP]Cl/*t*-BuOOH/HFIP system for preparing unsymmetrical biphenols from two non-complementary phenolic units. The power of this scalable catalytic system lies in the access that it offers to a class of biphenol products that cannot be synthesized with adequate efficiency by any other direct methods.[9m,9n,11b,26] On the basis of our mechanistic studies, a unique catalytic cycle that includes selective oxidation of a readily oxidized phenol **A** to a phenoxyl radical **A**•, which couples with an iron ligated phenoxyl radical **B**•, was postulated (Figure 1C).

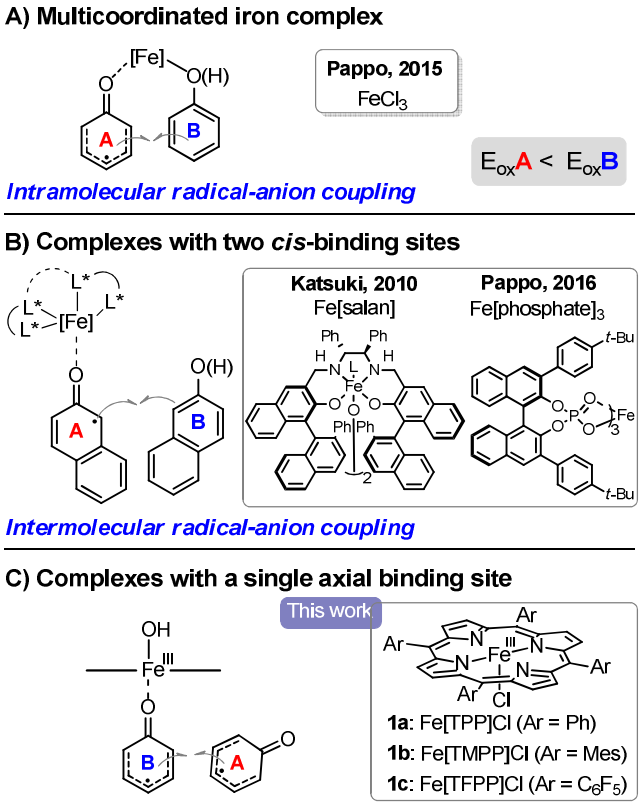


Figure 1. Different oxidative coupling mechanisms by various iron complexes.

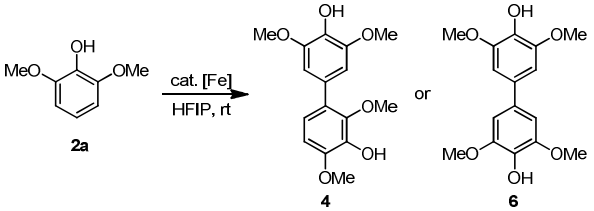
RESULTS AND DISCUSSION

Method development

The study commenced with the establishment of suitable conditions for oxidative homocoupling of 2,6-dimethoxyphenol (**2a**) with the commercially available Fe[TPP]Cl (**1a**) complex. At this point in the research, the true oxidation capability of the catalyst had to be explored; therefore, after the consumption of phenol **2a**, $NaBH_4$ was added to the reaction mixture to reduce any over-oxidation by-products. Our first attempt to catalyze the homocoupling of phenol **2a** by catalyst **1a** [1 mol %, *t*-BuOOH (2 equiv)] in HFIP was not successful; it afforded symmetrical biphenol **6** in poor 20% yield (Table 1, entry 1). A control experiment without the iron catalyst afforded product **6** in 12% yield (Table 1, entry 2), thereby indicating that iron porphyrin was not an efficient catalyst under those particular reaction conditions. The oxidative coupling of phenol **2a** in other solvents, such as chloroform or 2,2,2-trifluoroethanol (TFE), was also not successful, and the reaction under elevated temperatures furnished only oxygenation products.

We thus looked to previous studies showing that electron-deficient phenols have a strong axial ligand effect that significantly improves the catalytic activity of iron porphyrins in oxygenation reactions.[27] Indeed, addition of 4-nitrophenol (**2d**, 10 mol %, Table 1, entry 3) to the above reaction led to a significant improvement in the coupling efficiency; under these conditions, symmetrical biphenol **6** was obtained in 60% yield. It has been suggested that **2d** serves as a strong axial ligand that leaves zero coordination sites for substrate binding and, therefore, induces outer-sphere coupling between two liberated *para*-phenoxyl radicals of **2a**.[4b] In contrast, the oxidative homocoupling of **2a** by the $FeCl_3$ catalyst through a radical-anion coupling mechanism afforded unsymmetrical biphenol **4** as the sole product (Table 1, entry 4).[4b] The site specificity in this transformation may be explained in terms of the coupling between the *para*-phenoxyl radical of **2a** with the most nucleophilic *meta*-position of the second – phenol(ate) **2a** – molecule.[4b] The formation of the symmetrical biphenol **6** rather than biphenol **4** by catalyst **1a** implies that the two complexes mediate the homocoupling by different mechanisms. The observed regiospecificity emphasizes the power of oxidative coupling as a synthetic strategy for preparing constitutional biaryl isomers in a direct and efficient manner from (a) single un-functionalized phenolic unit(s).

Table 1. Oxidative homocoupling of phenol 2a by iron catalysts



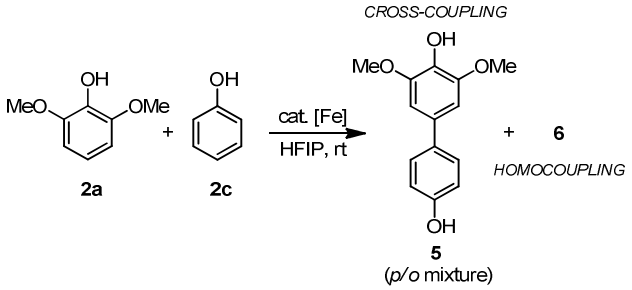
entry	conditions	yield of **4** [%][a]	yield of **6** [%][a]
1	Fe[TPP]Cl [1 mol %], *t*-BuOOH	--	20[b]
2	*t*-BuOOH	--	12[b]
3	Fe[TPP]Cl [1 mol %], 4-nitrophenol (**2d**, 10 mol %), *t*-BuOOH	--	60
4[c]	$FeCl_3$ [10 mol %], *t*-BuOO*t*-Bu	62	--

Conditions: phenol **2a** (0.5 mmol), [Fe] catalyst, *t*-BuOOH (2 equiv) in two portions every 24 h, HFIP, rt; then $NaBH_4$ (1 equiv) for 2 h [a]Isolated yields after complete consumption of phenol **2a**. [b]Low conversion after 48 h. [c]See reference [4b] for exact conditions.

Next, other electron-deficient phenols were examined as axial ligands for the oxidative homocoupling of phenol **2a** (1 equiv). The addition of phenol **2c**, first in catalytic amounts and later in excess (3 equiv, Table 2, entry 2), afforded the unsymmetrical biphenol **5** in 65% yield (mixture of *para* and *ortho* isomers, 2.5:1). Since phenol **2c** is less nucleophilic than 2,6-dimethoxyphenol **2a**, the formation of cross-coupling product **5** as a major product by the Fe[TPP]Cl/*t*-BuOOH/HFIP catalytic system implies that this reaction probably does not follow a radical-anion coupling mechanism (compare entries 1 and 2 in Table 2). The formation of a significant amount of homocoupling product **6** (29% yield, entry 2) may be explained in terms of a competitive free radical-radical coupling mechanism (*vide supra*). Other commercially available iron porphyrin catalysts, such as 5,10,15,20-tetrakis(2,4,6-trimethylphenyl)porphyrin (Fe[TMPP]Cl, **1b**) and 5,10,15,20-tetrakis(pentafluorophenyl)porphyrin (Fe[TFPP]Cl, **1c**), which differ from catalyst **1a** in their elec-

tronic and structural properties (Figure 1C), were found to be less effective (Table 2, entries 3 and 4).

Table 2. Oxidative cross-coupling of phenol 2a with phenol 2c by iron catalysts



entry	conditions	yield of **5** [%][a]	yield of **6** [%][a]	ratio (*p*:*o*)
1[b]	$FeCl_3$, *t*-BuOO*t*-Bu	23	40 (**4**)[c]	1:1
2	Fe[TPP]Cl, *t*-BuOOH	65	29	2.5:1
3	Fe[TMPP]Cl (**1b**), *t*-BuOOH	11	12	2.2:1
4	Fe[TFPP]Cl (**1c**), *t*-BuOOH	17	27	1.7:1

Conditions: 2,6-dimethoxyphenol (**2a**, 1 equiv), phenol (**2c**, 3 equiv), Fe porphyrin catalyst (1 mol%), *t*-BuOOH (2 equiv) in two portions every 24 h, HFIP, rt, then $NaBH_4$ (1 equiv) for 4 h. [a]Isolated yields after complete consumption of phenol **2a**. [b]10 mol % of catalyst and *t*-BuOO*t*-Bu (2 equiv), then $NaBH_4$. [c]Compound **4** was formed instead of compound **6**. TMPP = 5,10,15,20-tetrakis (2,4,6-trimethylphenyl)porphyrin, TFPP = 5,10,15,20-tetrakis(pentafluorophenyl)porphyrin.

Reaction scope

The power of the Fe[TPP]Cl/*t*-BuOOH/HFIP catalytic system in mediating oxidative cross-coupling reactions between readily oxidized phenols that have at least (a) single *ortho*- or *para*-methoxy group(s) with less nucleophilic phenols that possess either alkyl or *ortho*-halide(s) substituents is demonstrated in Figure 2. The reaction was found to be general, and a long list of unsymmetrical biphenols **7**–**30** that are not accessible in an efficient manner by other oxidative coupling methods were obtained in moderate to good yields. While *ortho*-halophenols with bond-dissociation energy (BDE) values[28] similar to those of phenol **2c** were found to be suitable coupling partners (biphenols **7**–**9**), the less activated *para*-halophenols failed to react under our novel conditions. Phenols with mono *ortho*-substituents afforded a mixture of two constitutional isomers in various ratios (**7**–**8**, **10**–**13**, **17**, **23** and **25**). The ability to perform the coupling on a gram scale was proven by reacting 1 g of 2-*t*-butyl-4-methoxyphenol (**2e**) with 2,4-dimethylphenol (**2f**, 3 equiv) to afford unsymmetrical biphenol **24** in 72% yield (1.22 g).

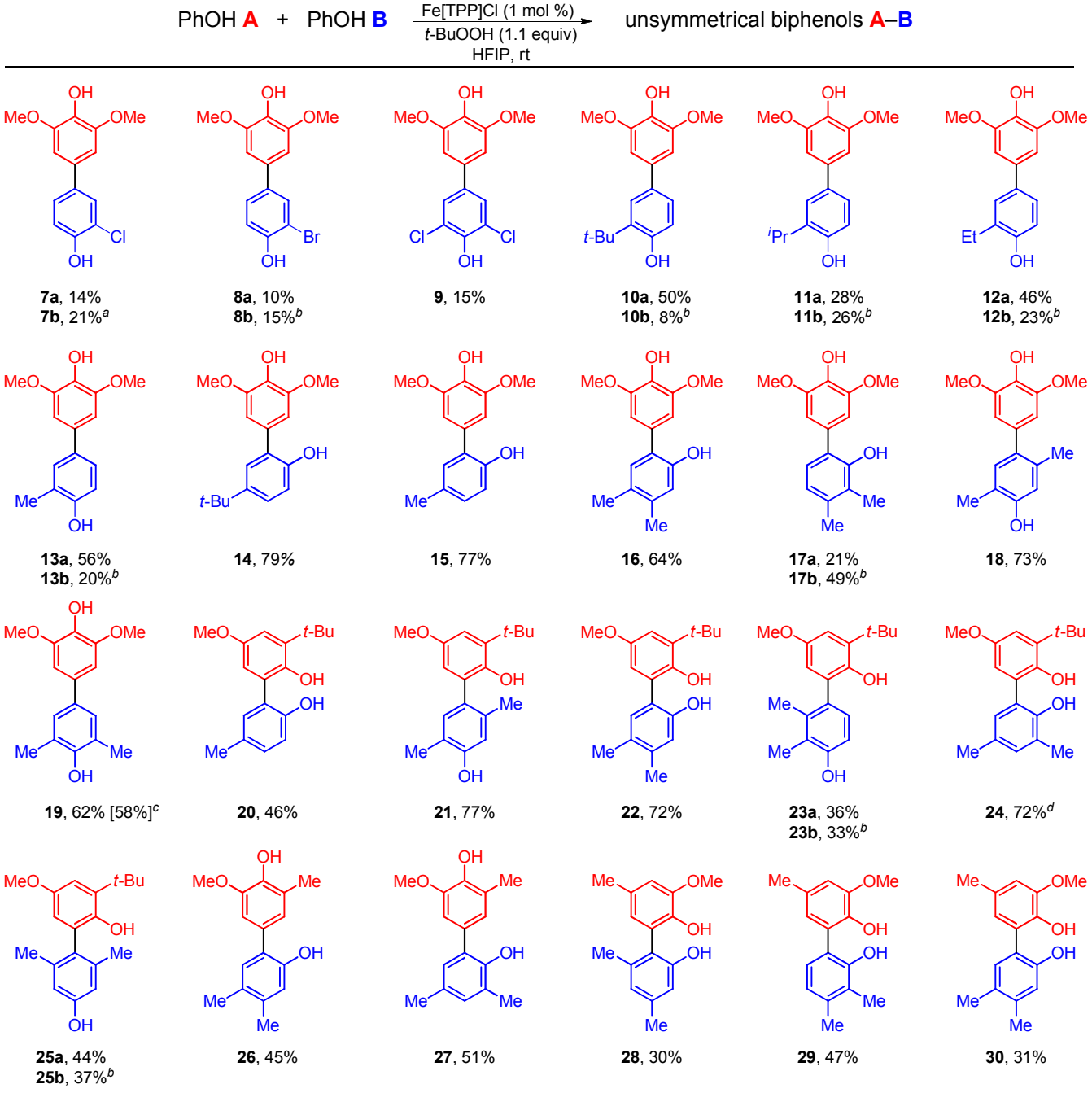


Figure 2. Scope and yields of oxidative coupling reactions of phenols by catalyst **1a** in HFIP. General conditions: phenol **A** (1 equiv), phenol **B** (2-3 equiv), Fe[TPP]Cl (**1a**, 1 mol %), *t*-BuOOH (1.1 equiv), HFIP, rt, 24 h. (a) Yields of isolated products. (b) *ortho*-isomer product. (c) $(Fe[TPP])_2O$ (0.5 mol %) was used instead of catalyst **1a**. (d) Isolated yield for reaction that was carried out on a gram scale.

Mechanistic studies

To probe the mechanism of the Fe[TPP]Cl/*t*-BuOOH/HFIP catalytic system and thereby to reveal some of the factors that control the chemoselectivity of the reaction, a comprehensive ^{1}H-NMR study of paramagnetic iron porphyrin complexes and iron-mediated BINOL racemization was undertaken.

^{1}H-NMR spectroscopy of iron porphyrin complexes

Isotropically shifted signals, sufficiently narrow to be observed in wide-range ^{1}H-NMR spectra (*ca* 250 ppm), constitute a powerful tool for determining the identity of the axial ligand in paramagnetic iron porphyrin complexes.[27b,29] In this work, a number of iron porphyrin complexes were prepared in an NMR tube by mixing Fe[TPP]Cl with different ligands and Ag_2CO_3 in $CDCl_3$. The Fe[TPP][phenolate] complexes were characterized by proton NMR (see SI-II file, sections 3-4) and the collected data was applied for studying ligand exchange processes with and without HFIP.

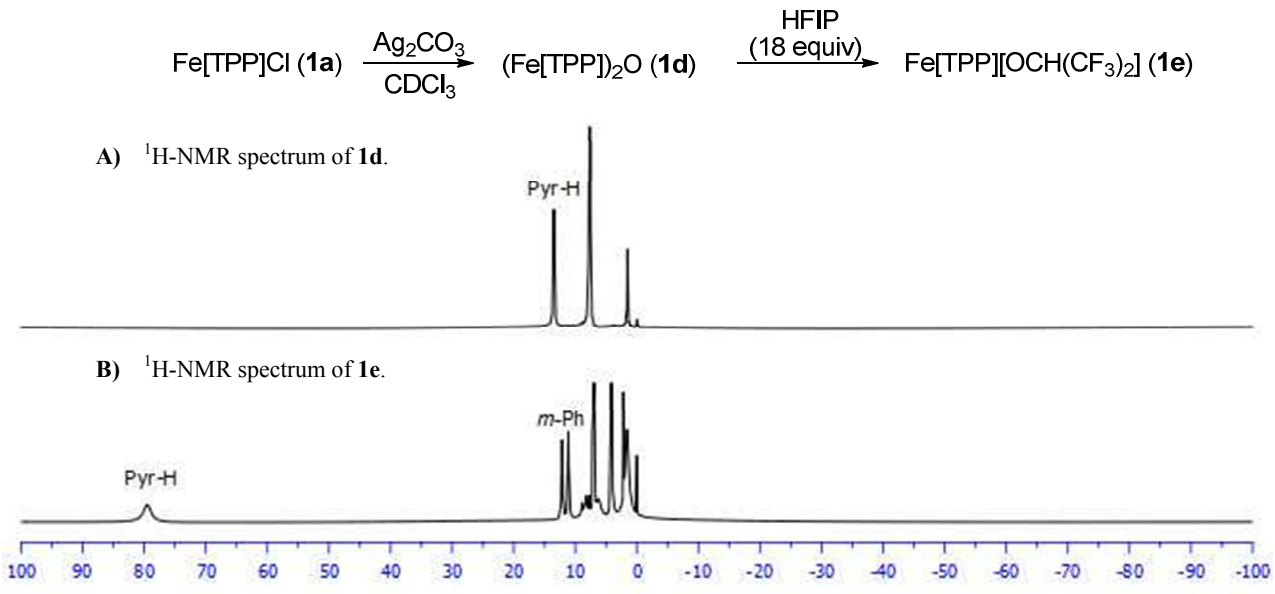


Figure 3. A) ^{1}H-NMR spectrum of $(Fe[TPP])_2O$ (1d) in $CDCl_3$ and B) ^{1}H-NMR spectrum of $Fe[TPP][OCH(CF_3)_2]$ (1e) after the addition of HFIP. Pyr = pyrrole hydrogen atoms of the TPP ligand, *m*-Ph = *meta*-hydrogen atoms of the phenyl groups in the TPP ligand.

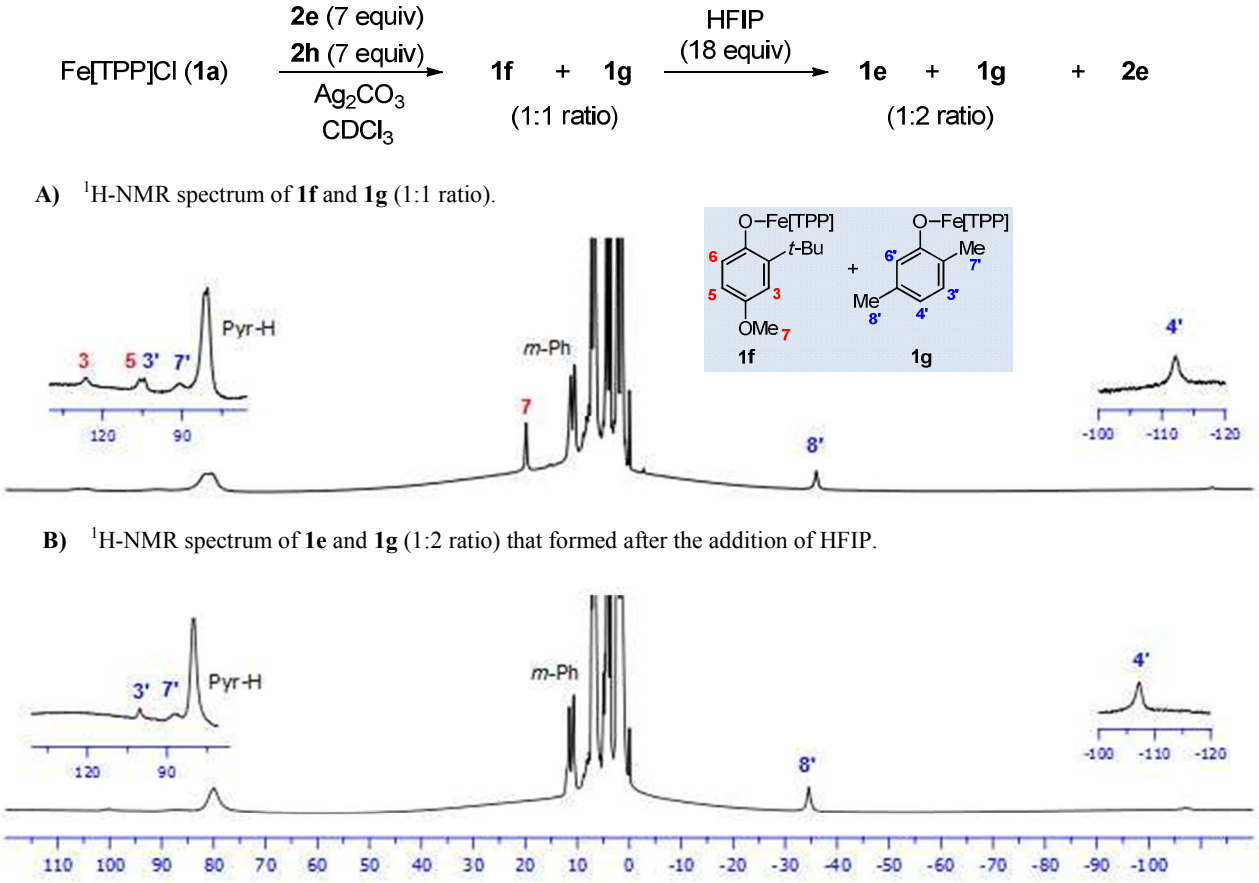


Figure 4. ^{1}H-NMR spectrum of (A) complexes **1f** and **1g** in $CDCl_3$ and (B) complexes **1e** and **1g** after the addition of HFIP. Pyr = pyrrole hydrogen atoms of the TPP ligand. *m*-Ph = meta-hydrogen atoms of the phenyl groups in the TPP ligand

As mentioned above, the oxidative coupling of phenol **2a** is highly efficient in HFIP. Indeed, in recent years, HFIP has become the solvent of choice in oxidative coupling reactions of phenols.[4a,4b,10c,10d,11a,11c,12,30] It is a mildly acidic (pKa = 9.3)

and highly polar solvent that forms strong hydrogen-bond pairs with hydrogen-bond acceptor groups, such as ethers, peroxides, and carbonyl compounds.[10d,30a,31] Furthermore, the fluorinated alcohol molecules seem to interact with charged and polar intermediates, such as phenoxyl radicals, leading to a significant enhancement in the rate and the selectivity of the radical process.[10d,11a,31a]

In this study, we reveal yet another role for HFIP—as an anionic ligand for iron complexes. When Fe[TPP]Cl and Ag_2CO_3 (9 equiv) were mixed in $CDCl_3$ for 8 h, a ligand-exchange process took place, affording the thermodynamically stable $(Fe[TPP])_2O$ (**1d**) complex (Figure 3A).[32] However, the use of HFIP (18 equiv) as an additive in the NMR tube, shifted the equilibrium away from complex **1d**, affording $Fe[TPP][OCH(CF_3)_2]$ (**1e**) as the sole detectable complex (Figure 3B, see SI-II, section 6, Figures S2 and S3). Under similar conditions, other less acidic fluorinated alcohols, such as TFE, 1,1,1-trifluoropropan-2-ol and 2,2,2-trifluoro-1-phenylethanol, were found to be inferior ligands, and complex **1d** was formed in various ratios (see SI-II, section 7, Figure S4). Furthermore, the oxidative cross-coupling between phenol **2a** and 2,6-dimethylphenol (**2g**) catalyzed by $Fe[TPP]_2O$ (0.5 mol %) afforded biphenol **19** in 58% yield. These experiments provide spectroscopic and experimental evidence that $(Fe[TPP])_2O$, which lacks catalytic activity, is not stable in HFIP, and therefore the catalytic activity of the iron porphyrin is retained throughout the reaction.

In general, the H_{ortho} and H_{para} protons of the phenolic axial ligand resonate at around -100 ppm (relative to TMS, Figure 4), while the H_{meta} signals are located in the low-field region, from 80 to 120 ppm. The chemical shifts of the phenol substituents vary according to their location on the ring [for example, the chemical shifts of 2-Me (7') and 5-Me (8') in complex Fe[TPP][**2h**] (**1g**) are 91 and -36 ppm, respectively, Figure 4A]. In light of this valuable observation [obtained via NMR studies of a long list of phenols (see SI-II file, section 4)], competitive binding experiments for determining the phenols' relative association strength to the axial vacant site of iron porphyrin were performed. For example, a mixture of complexes Fe[TPP][**2e**] (**1f**) and Fe[TPP][**2h**] was identified by ^{1}H-NMR when 2-*t*-butyl-4-methoxyphenol (**2e**, 7 equiv) and 2,5-dimethylphenol (**2h**, 7 equiv) were mixed with Fe[TPP]Cl (1 equiv) and Ag_2CO_3 in $CDCl_3$ (Figure 4A). A 1:1 molar ratio was determined for the two complexes based on the integration of the area of porphyrin's Ph-H_{meta} peaks (10–12 ppm). The addition of HFIP (18 equiv) to that solution initiated a ligand-exchange process that selectively dissociated phenol **2e** from the complex to afford complex **1g** and $Fe[TPP][OCH(CF_3)_2]$ (**1e**) in an approximately 2:1 ratio (Figure 4B). The weak binding strength of phenol **2e** to the iron in the presence of HFIP is associated with the strong hydrogen bonds between the fluorinated alcohol and its *para*-methoxy group as demonstrated by Lucarini, Pedulli and Guerra.[33] Indeed, the selective binding of phenol **2h** to the iron porphyrin in preference to the readily oxidized **2e** may explain the cross-coupling selectivity obtained when these two phenols were reacted by the Fe[TPP]Cl/*t*-BuOOH/HFIP catalytic system to afford unsymmetrical biphenol **21** in 77% yield (Figure 2).

The ligand-exchange process was further investigated using Fe[TPP]Cl as a probe to discriminate between phenols that associate to iron and phenols that generate weakly basic anionic ligands in HFIP (see SI-II file, section 5). The equilibrium constants (K, Figure 5) for the ligand-exchange process between HFIP and a number of phenols were evaluated by NMR spectroscopy. The results are displayed in a reactivity map (*N* vs. E_{ox}, Figure 5) of the type that was introduced by us in a previous study, in which the position of each phenol reflects its relative reactivity in cross-coupling reactions.[4b] On the basis of our NMR study, the phenols in the reactivity map were classified into two groups: a) phenols that dissociate from the iron porphyrin complex in the presence of HFIP (colored red, K < ~0.1), and b) phenols that do form detectable Fe[TPP][phenolate] complexes (colored blue, K > ~0.1). This part of the study revealed that, in general, electron-rich phenols with low oxidation potentials (phenols of type **A**) and at least one methoxy group at either the *ortho* or the *para* position belong to the first group.The second group is made up of phenols that have *meta*-methoxy, alkyl or halide substituents. These phenols have high oxidation potentials (phenols of type **B**) and are considered to be poor nucleophiles. It is therefore suggested that the origin of selectivity in this novel catalytic system is attributed to a selective oxidation of phenol **A** to a transient phenoxyl radical by Fe-ligated phenol **B** complex.

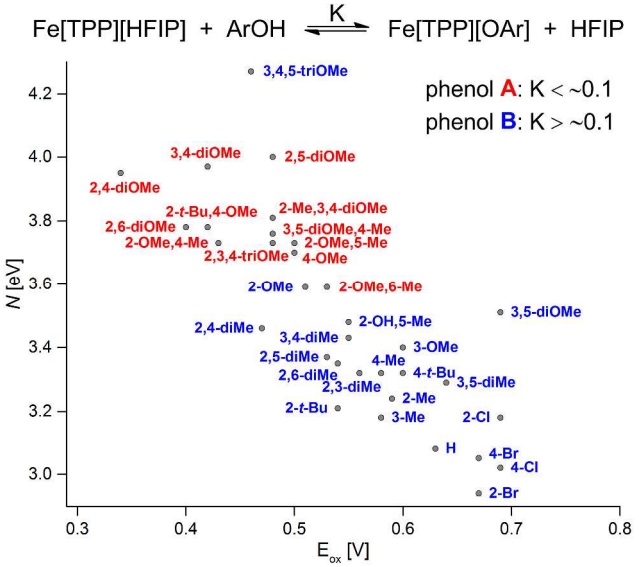


Figure 5. Modified reactivity map for phenols in HFIP based on their global nucleophilicity *N* values and their oxidation potentials (E_{ox}).[4b] The colors refer to the ability of each phenol to bind to complex **1a** in the presence of the competitive HFIP ligand, as determined by ^{1}H-NMR; red is used for phenols that do not form detectable Fe[TPP][phenolate] complexes and blue for phenols that do form detectable Fe[TPP][phenolate] complexes.

Consecutive oxidative coupling is a competitive side reaction that takes place when a biphenol product further reacts under oxidation conditions.[12] If the biphenol product has a low oxidation potential, it can act as a phenol **A** competitor. In contrast, if it binds strongly to the catalyst, it serves as a type **B** phenol. To investigate the ligand exchange process between phenols and their corresponding biphenol coupling products, ^{1}H-NMR spectra of 2,6-dimethylphenol (**2g**), biphenol **19** (Figure 2) and Fe[TPP]Cl (Ag_2CO_3, $CDCl_3$) with and without HFIP, were measured (See SI-II file, section 8,

Figure S5). In $CDCl_3$ both phenol **2g** and biphenol **19** were bound to the iron porphyrin complex, but the addition of HFIP led to complete liberation of biphenol **19**, which has methoxy groups at the remote phenolic unit. This finding supports our experimental results showing that consecutive reactions are less favorable under our reaction conditions that involve a limited amount of terminal oxidant and an excess of phenol **B**.

BINOL Racemization

The fact that the Fe[TPP]Cl complex efficiently catalyzes cross-coupling of phenolic pairs with non-complementary relationships (ΔN << 0, Figure 1) implies that the coupling does not follow a radical-anion coupling mechanism (between phenoxyl radical **A•** and ligated anionic phenolate **B**). We therefore posited a reaction between an associated phenoxyl radical **B•** and a liberated phenoxyl radical **A•**. To support this premise, it was necessary to confirm the existence of spin transfer from the axial phenolic ligand to the iron center ('push effect').[27b]

Recently, our group revealed that optically pure 1,1'-bi-2-naphthol (BINOL, **31**, Figure 6) undergoes rapid racemization in the presence of catalytic amounts of redox Fe(III) or Cu (II) complexes and that this process is accelerated in the presence of a terminal oxidant, such as *t*-BuOO*t*-Bu.[4a] It was postulated that a single electron transfer (SET) process between an associated binaphtholate ligand and the metal generates an optically unstable binaphthoxyl radical that yields racemic BINOL. This process (which is undesired in enantioselective oxidative coupling of 2-napthols) becomes a powerful tool for studying the structural and electronic properties of metal phenolate complexes.[4a] Indeed, when (*R*)-**31** was mixed with Fe[TPP]Cl (1 mol %) and Ag_2CO_3 (9 mol %) [HFIP:DCE (1:1), argon atmosphere, room temperature], complete racemization occurred within 3 h (green diamonds, Figure 6). The existence of the Fe[TPP][BINOL] (**1h**) complex was confirmed by ^{1}H-NMR; in contrast, BINOL failed to coordinate to Fe[TMPP]Cl (**1b**) and Fe[TFPP]Cl (**1c**) under identical conditions, probably as a result of steric hindrance or electronic considerations. Indeed, there was no loss in optical purity, when (*R*)-BINOL was mixed with complexes **1b** and **1c**. Next, the racemization of (*R*)-**31** by complex **1a** in the presence of competitive axial ligands (50 mol %) was studied. While phenol (**2c**, red circles) and 4-nitrophenol (**2d**, blue triangles, see SI-II file, sections 9-10, figure S6) decelerated the racemization rates, 4-nitrothiophenol **32**, which is a much stronger anionic ligand than **31** (see SI-II file, section 11, Figures S7) led to complete suspension of the racemization process (black squares). These experiments provide direct evidence for electron transfer between phenolic ligands and the iron porphyrin complex, which, in turn, supports the existence of two main isoelectronic structures, namely, **III** and **IV** (Scheme 2). On the basis of the above studies, it is most likely that a persistent iron–phenoxyl **B•** radical complex reacts with a transient liberated phenoxyl radical **A•**, according to the persistent radical effect (PRE) principle.[30b,34]

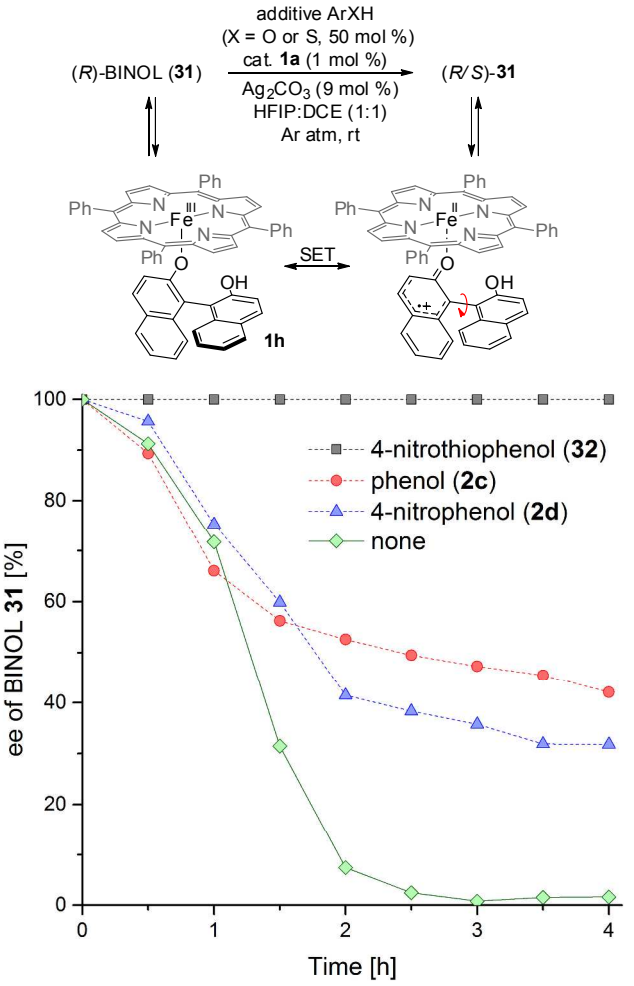


Figure 6. Racemization of (*R*)-BINOL by Fe[TPP]Cl in the presence of competitive ligands. Conditions: BINOL (0.25 mmol), additive ArXH (X = O or S, 0% or 50 mol %), Fe[TPP]Cl (**1a**, 1 mol%), Ag_2CO_3 (9 mol %), HFIP:DCE (1:1, 0.25 M), Ar atmosphere, room temperature, 4 h.

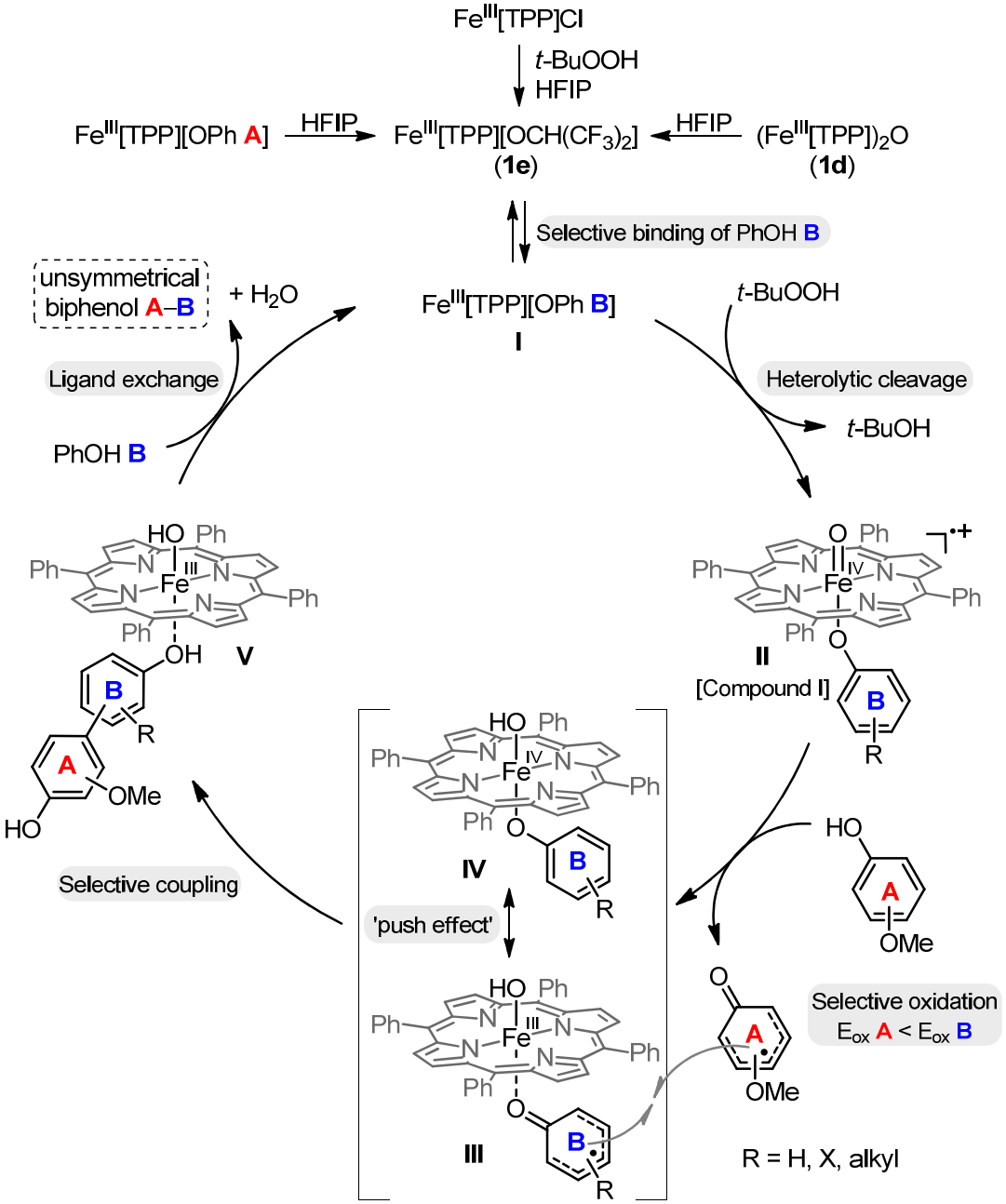
Based on the above findings and Groves' mechanistic studies of related bioinspired metal porphyrin based C–H functionalization reactions,[17] a mechanistic scheme for the selective oxidative cross-coupling of phenols by the Fe[TPP]Cl/*t*-BuOOH/HFIP catalytic system was postulated (Scheme 2). A reversible ligand-exchange process between HFIP and phenol **B** generates complex Fe[TPP][OCH(CF_3)$_2$] (**1e**). This complex lacks catalytic activity and its conversion to Fe[TPP][phenolate **B**] (**I**), which enters the catalytic cycle, is probably the selectivity-determining step of the process. The oxidation of complex **I** affords a high valance Fe(IV)=O porphyryl radical intermediate (**II**, 'Compound I')[23a,35] that selectively oxidizes phenol **A** to the phenoxyl **A•** radical (E_{ox}**A** < E_{ox}**B**). This transient radical species reacts with a persistent phenoxyl radical **B•** ligand (complex **III**) via an intermolecular radical-radical coupling mechanism[4b,4c,9c] to afford an unsymmetrical biphenol **A**–**B** ligand (complex **V**). The catalytic cycle is terminated by a second ligand-exchange process that releases the biphenol product (see SI-II file, section 8, Figure S5) while regenerating resting state complex **I**.

CONCLUSION

In summary, a novel catalytic system based on a biomimetic iron porphyrin catalyst in HFIP was developed for mediating the cross-coupling between pairs of phenols with a non-complementary relationship ($\Delta N < 0$). The efficient and scalable conditions offer a method to prepare unsymmetrical biphenols — assembled from an inactivated phenolic unit — that would otherwise not be accessible in an efficient manner. It is postulated that the mechanism involves an intermolecular radical-radical coupling between a transient phenoxyl radical **A**• with a ligated persistent phenoxyl radical **B**•. With the aid of ^{1}H-NMR spectroscopy of paramagnetic iron[TPP] complexes, the phenols were successfully classified according to their ability to serve as anionic phenolic **B** ligands in the presence of a competitive HFIP ligand. The existence of a 'push effect' between the phenolic ligands was proved by probing the racemization rates of (*R*)-BINOL in the presence of Fe[TPP]Cl and competitive axial ligands.

Finally, in addition to its well-known roles in oxidative coupling of phenols,[4b,10d,11a,30b] the importance of HFIP in the Fe[TPP]Cl/*t*-BuOOH/HFIP catalytic system lies in the facts that: 1) it efficiently distinguishes between phenols of the red group (**A**) that have low oxidation potentials and phenols of the blue group (**B**) that bind to the iron porphyrin complex; 2) it serves as a competitive axial ligand that prevents the formation of the undesired μ-(Fe[TPP])$_2$O complex and in so doing it preserves the catalytic activity of the iron porphyrin; and 3) it releases the biphenol **A**–**B** product from the iron complex, thereby reducing consecutive oxidation processes. This work thus demonstrates that selective formation of biaryl bonds is possible by mechanistically controlled oxidative cross-coupling reactions of phenols.

Scheme 2. Postulated mechanism for the oxidative cross-coupling of phenols by Fe[TPP]Cl in HFIP.



ASSOCIATED CONTENT

Supporting Information

Full experimental procedures, characterization data, and NMR spectra is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

This research was supported by the Israel Science Foundation (grant No. 164/16).

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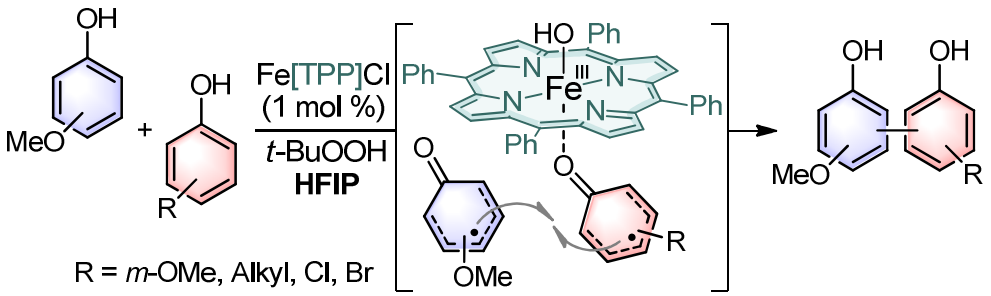

R = *m*-OMe, Alkyl, Cl, Br