

M[TPP]Cl (M = Fe or Mn)-Catalyzed Oxidative Amination of Phenols by Primary and Secondary Anilines

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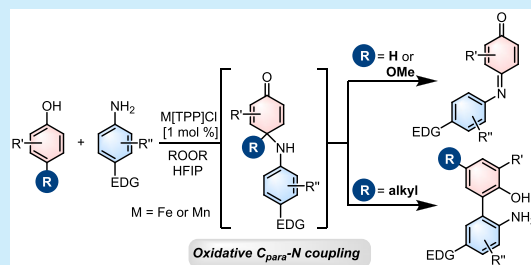


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ABSTRACT: Iron- and manganese-catalyzed *para*-selective oxidative amination of (4-*R*)phenols by primary and secondary anilines was developed. Depending on the identity of the *R* group, the products of this efficient reaction are either benzoquinone anils (C–N coupling) that are produced via a sequential oxidative amination/dehydrogenation (*R* = H), oxidative amination/elimination (*R* = OMe) steps, or *N,O*-biaryl compounds (C–C coupling) that are formed when *R* = alkyl through an oxidative amination/[3,3]-sigmatropic rearrangement (quinamine rearrangement) process.



Oxidative cross-coupling reactions¹ between phenols and anilines are powerful methods for assembling N-containing phenolic compounds that are applied in a variety of applications, such as natural product synthesis and asymmetric catalysis.² Phenols and anilines are both strong π -nucleophiles and have low oxidation potentials.³ Therefore, carrying out their oxidative coupling in a selective manner is a challenging synthetic task. The use of anilides, protected anilines,⁴ or masked phenols⁵ as coupling partners overcame part of the chemoselectivity challenges. However, these reactants do not necessarily react in the same fashion as their parent anilines and phenols.

Over the years, methods for mediating the oxidative coupling between tertiary or secondary aniline derivatives and phenols have been reported. Chandrasekharan⁶ and Knolker⁷ developed conditions for the iron-catalyzed oxidative cross-coupling between *N,N*-dialkylanilines and 2-naphthols, and Shindo reported that a heterogeneous Rh–C catalyst mediates the oxidative coupling between 1-(2-naphthalenyl)-piperidine and phenol derivatives (Scheme 1A).⁸ The accepted mechanism underlying these reactions, which affords the *N,O*-biaryl products, involves the coupling between the tertiary anilino radical and nucleophilic phenol(ate). On the other hand, Patureau,⁹ Xia,¹⁰ Lei,¹¹ and Antonchick¹² demonstrated that secondary diarylamines undergo oxidative amination of phenols under various metal-free oxidation conditions (Scheme 1B). However, primary anilines are considered to be more challenging coupling partners as they tend to form “aniline black” and azobenzenes under mild oxidation conditions.¹³ One of the very few examples is Kočovský’s synthesis of 2-amino-2’-hydroxy-1,1’-binaphthyl (BINOL), an axially chiral ligand, by coupling 2-naphthol and 2-aminonaphthalene using redox copper(II)amine complexes.¹⁴ Our study reveals that the chemical properties of 2-aminonaphthalenes and primary or secondary phenylamine deriva-

tives are different; therefore, they react by distinct mechanisms and selectivity.

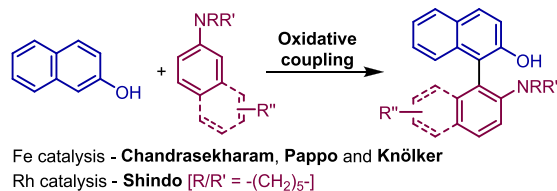
As part of our group’s ongoing research program, which focuses on the development of metal-catalyzed oxidative phenol coupling reactions, we have developed a highly efficient FeCl₃-catalyzed oxidative cross-coupling reaction between phenols and primary, secondary, and tertiary 2-aminonaphthalenes [FeCl₃ (10 mol %), TFA (1.25 equiv), *t*-BuOO*t*-Bu, and 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP) at rt].¹⁵ The mechanism underlying this reaction involves coupling between an iron-ligated phenoxyl radical and a neighboring nucleophilic 2-aminonaphthalene ligand (radical-anion/nucleophile coupling mechanism).¹⁵ 2-Aminonaphthalenes are much stronger nucleophiles and have oxidation potentials higher than those of their phenolic partners; therefore, a high level of cross-coupling selectivity is observed. However, the latter conditions were found to be limited to 2-aminonaphthalene derivatives. For example, no product was obtained when 2,6-dimethoxyphenol (**1a**) and 3,4-dimethoxyaniline (**2a**) coupled under the above conditions (Table 1, entries 1 and 2). Intrigued by these results, we examined alternative redox systems for mediating the oxidative cross-coupling between phenols and primary anilines.

Herein, an efficient M[TPP]Cl (M = Fe or Mn)-catalyzed *para*-selective oxidative amination of phenols by primary and secondary anilines is described. The products of this reaction are unstable quinamine intermediates (Scheme 1C) that, depending on the identity of the phenol’s *para*-substituent, are rapidly converted into either benzoquinone anils (via

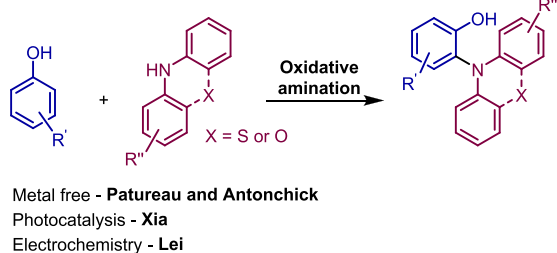
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Scheme 1. Oxidative Coupling between Phenols and Tertiary Anilines (A), Secondary Anilines (B), and Primary and Secondary Anilines (C, This Work)

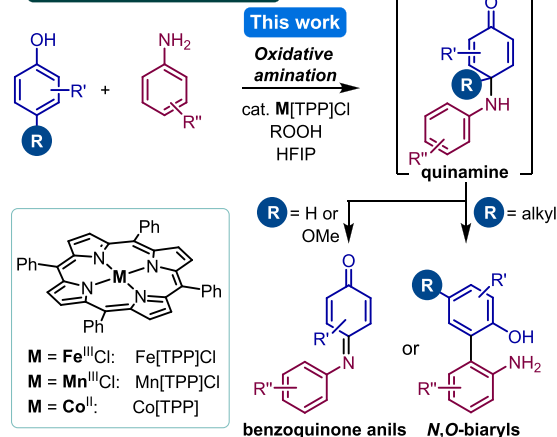
A] Tertiary anilines



B] Secondary anilines



C] Primary & secondary anilines



sequential dehydrogenation/elimination) or *N,O*-biaryl compounds (through quinamine rearrangement).

The coupling between 2,6-dimethoxyphenol (**1a**, 1.5 equiv) and 3,4-dimethoxyaniline (**2a**, 1 equiv) was chosen as a model reaction; we commenced by examining catalytic conditions based on *meso*-tetraphenylporphyrin iron(III) chloride complex [Fe[TPP]Cl (1 mol %), *t*-BuOOH (2 equiv), HFIP, rt] that were developed in our group for the oxidative cross-coupling of phenols.¹⁶ Under these conditions, benzoquinone anil **3** was obtained in 78% yield (entry 3). Other oxidants were examined; whereas urea hydrogen peroxide (UHP) afforded product **3** in a similar yield (79% yield, entry 4), *meta*-chloroperbenzoic acid (mCPBA) resulted in the complete decomposition of the aniline (entry 5), and dioxygen molecule (1 atm) afforded the product in poor yield (entry 6).

Formation of benzoquinone anil **3** from **1a** and **2a** is a process that involves two sequential dehydrogenation steps. Our attempts to isolate reaction intermediates (such as **I**, Table 1) by reducing the amount of the peroxide to 1 equiv or by using the less acidic 2,2,2-trifluoroethanol (TFE) solvent were not successful. Under these conditions, product **3** was obtained in reduced yields, as the sole detected product (57 and 44%, respectively, entries 7 and 8). Finally, monitoring the

Table 1. Optimization of the Reaction Conditions^a

entry	M catalyst	oxidant	yield (%) ^b
1 ^c	FeCl ₃	<i>t</i> -BuOO <i>t</i> -Bu	NR
2 ^{c,d}	FeCl ₃	<i>t</i> -BuOO <i>t</i> -Bu	0 ^e
3	Fe[TPP]Cl	<i>t</i> -BuOOH	78
4	Fe[TPP]Cl	urea·H ₂ O ₂	79
5	Fe[TPP]Cl	<i>m</i> CPBA	traces ^e
6	Fe[TPP]Cl	O ₂ (1 atm)	17
7 ^f	Fe[TPP]Cl	<i>t</i> -BuOOH	57
8 ^g	Fe[TPP]Cl	<i>t</i> -BuOOH	44
9 ^h	Fe[TPP]Cl	<i>t</i> -BuOOH	76
10	Co[TPP]	air	NR
11	Mn[TPP]Cl	urea·H ₂ O ₂	0 ^e
12	[Cu(OH)(TMEDA)] ₂ Cl ₂	O ₂ (1 atm)	49
13		<i>t</i> -BuOOH	NR

^aReaction conditions: phenol **1a** (0.375 mmol), aniline **2a** (0.25 mmol), M catalyst (1 mol %), oxidant (0.5 mmol), HFIP (0.5 M), overnight, rt. ^bIsolated yield. ^c10 mol % of catalyst. ^d0.3125 mmol of TFA was added. ^eDecomposition of aniline **2a** took place. ^f0.25 mmol of oxidant was used. ^gTFE was used as the solvent. ^hThe reaction was performed for 30 min. NR = no reaction.

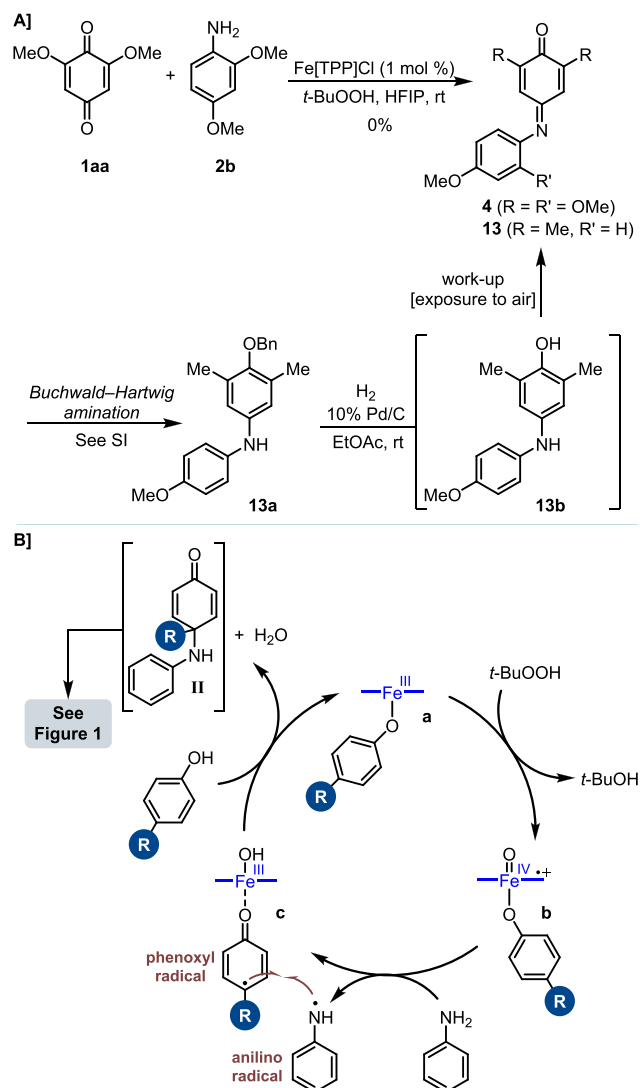
progress of the reaction by HPLC analysis revealed that the coupling is completed within 30 min (76% yield, entry 9).

Other redox catalysts were tested, as well; whereas Co[TPP] (1 mol %) failed to mediate the reaction under similar conditions [HFIP, air atmosphere, entry 10],¹⁷ Mn[TPP]Cl catalyst was found to be too reactive (entry 11) for the coupling between **1a** and **2a**, affording a mixture of undefined oxidation products. Interestingly, di- μ -hydroxo-bis(*N,N,N',N'*-tetramethylethylenediamine)copper(II) catalyst (1 mol %), under Nakajima and Koga modified conditions [HFIP, rt, O₂ (1 atm)],¹⁸ afforded compound **3** in 49% yield (entry 12). Finally, no reaction took place in the absence of a redox catalyst (entry 13).

Further insights into the oxidative amination of phenols by anilines were obtained from a set of control experiments. In order to dismiss a nucleophilic addition mechanism, 1,4-benzoquinone **1a** and 2,4-dimethoxyaniline (**2b**) were reacted under the coupling conditions (Scheme 2A). Indeed, HPLC analysis revealed that benzoquinone anil **4**, which is obtained in 96% yield from the reaction between phenol **1a** and aniline **2b** (Figure 1A), was not detected. Next, we examined the dehydrogenation reaction of anilinophenols. For that purpose, masked anilinophenol **13a** was prepared according to the Buchwald–Hartwig amination protocol (see the Supporting Information).¹⁹ The hydrogenolysis of the benzylic group from **13a** (H₂, Pd/C, EtOAc, rt) afforded air-sensitive anilinophenol **13b**, which rapidly developed the characteristic red color of benzoquinone anils. Unfortunately, our attempts to isolate **13b** in a pure form failed as it gradually oxidized into compound **13**, indicating that the dehydrogenation of the anilinophenol intermediates takes place spontaneously under air atmosphere, even in the absence of a redox metal catalyst.

Mechanistically, based on the work of Groves and others that studied the chemistry of iron porphyrins,²⁰ our group's

Scheme 2. Control Experiments (A) and Postulated Mechanism (B)



previous work,^{16b} and control experiments, a catalytic cycle that commences with the formation of Fe(III)[TPP]-[phenolate] complex **a** is offered (Scheme 2B). The oxidation of complex **a** by the peroxide affords a high valence Fe(IV)[phenolate]=O porphyrin radical intermediate (complex **b**)²¹ that selectively generates the anilino radical (by a HAT process) and the Fe(III)[TPP][phenoxyl radical]-OH complex (intermediate **c**). The latter two radical species, which are stabilized by HFIP,²² couple with a high degree of regioselectivity, via an outer-sphere radical-radical coupling mechanism.^{16b,17a,23} The C_{para}-N selectivity can be explained by the fact that the unpaired electron of the phenoxyl radical is highly conjugatively delocalized into the aromatic ring's para-position, whereas the primary anilino radical may be regarded as a nitrogen-centered radical.²⁴ On the basis of wide-range ¹H NMR spectroscopy experiments, the binding affinity of phenols and anilines to the axial position of the iron porphyrin catalyst was examined.^{16b,17a} This study showed that the primary anilines that serve as coupling partners in this work do not bind to Fe[TPP]Cl or Fe[TPP][OCH(CF₃)₂] in CDCl₃ (see the Supporting Information). In contrast, the phenols, as our group previously reported,^{16b} form Fe[TPP][phenolate]

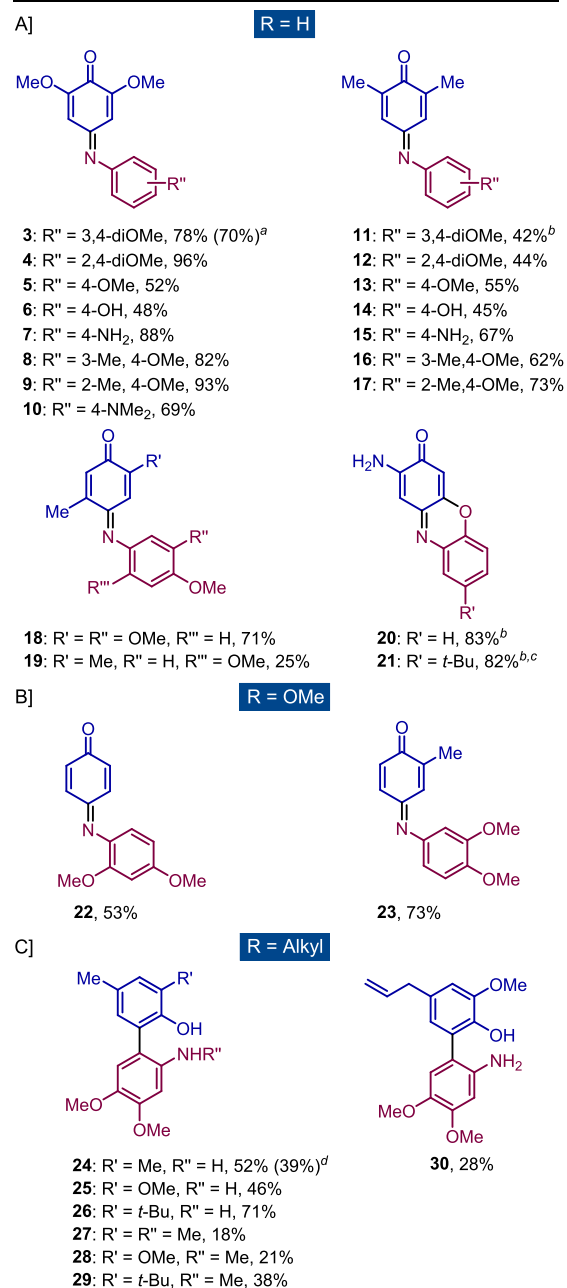
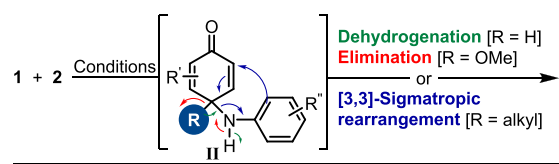


Figure 1. Reaction scope. Reaction conditions when R = H or OMe: phenol **1** (0.375 mmol), aniline **2** (0.25 mmol), Fe[TPP]Cl (1 mol %), *t*-BuOOH (0.5 mmol), HFIP (0.5 M), overnight, rt. Reaction conditions when R = Me: phenol **1** (0.375 mmol), aniline **2** (0.25 mmol), Mn[TPP]Cl (1 mol %), UHP (0.375 mmol), HFIP (0.5 M), overnight, rt. ^aThe reaction was performed on a 3 mmol scale. ^b0.75 mmol of *t*-BuOOH was used. ^cThe ratio between 2-aminophenol (**1e**) and 2-amino-(4-*t*-Bu)phenol (**1f**) is 1:3. ^dThe reaction was performed with Fe[TPP]Cl (1 mol %) and *t*-BuOOH (0.375 mmol).

complexes when phenol and Fe[TPP]Cl are mixed together in CDCl₃ in the presence of a base (Ag₂CO₃). With HFIP, which acts as a competitive axial ligand, a mixture of Fe[TPP]-[phenolate] and Fe[TPP][OCH(CF₃)₂] complexes is ob-

tained. These competitive binding experiments support our central hypothesis that the selective binding of the phenol to the axial ligand during the aniline dehydrogenation is the source of the cross-coupling selectivity.

The outcome of this catalytic cycle is unstable anilinoquinone intermediate **II** (Scheme 2B) that further reacts via pathways that are related to the identity of the phenolic R group. Yet, it is not necessarily catalyzed by the iron porphyrin catalyst. To study the courses that *para*-substituted phenols take during the oxidative amination reaction, various phenols (1.5 equiv) were reacted with anilines (1 equiv) under our general conditions [Fe[TPP]Cl (1 mol %), *t*-BuOOH (2 equiv), HFIP, rt, Figure 1]. First, 2,6-dimethoxyphenol (**1a**), 2,6-dimethylphenol (**1b**), 2-methoxy-5-methylphenol (**1c**), and 2,5-dimethylphenol (**1d**), which have an available *para*-position, reacted with a long list of aniline derivatives, affording, after a sequential dehydrogenation step, benzoquinone anils 3–19 in moderate to excellent yields (Figure 1A).²⁵ Only anilines with strong electron-donating groups at the *para*-position (such as methoxy, hydroxy, or amino) participate in the reaction. Aliphatic amines failed to react and seems to be beyond the scope of this reaction. To demonstrate the scalability of this reaction, benzoquinone anil **3** was prepared on a 3 mmol scale in 70% yield. The phenoxazinone is a common structural motif in natural products²⁶ and in pharmaceutically active compounds.²⁷ The homocoupling of 2-aminophenol (**1e**) and the cross-coupling with 2-amino-(4-*t*-Bu)phenol (**1f**) afforded 2-aminophenoxazinone **20** and **21** in 83 and 82% yields, respectively.

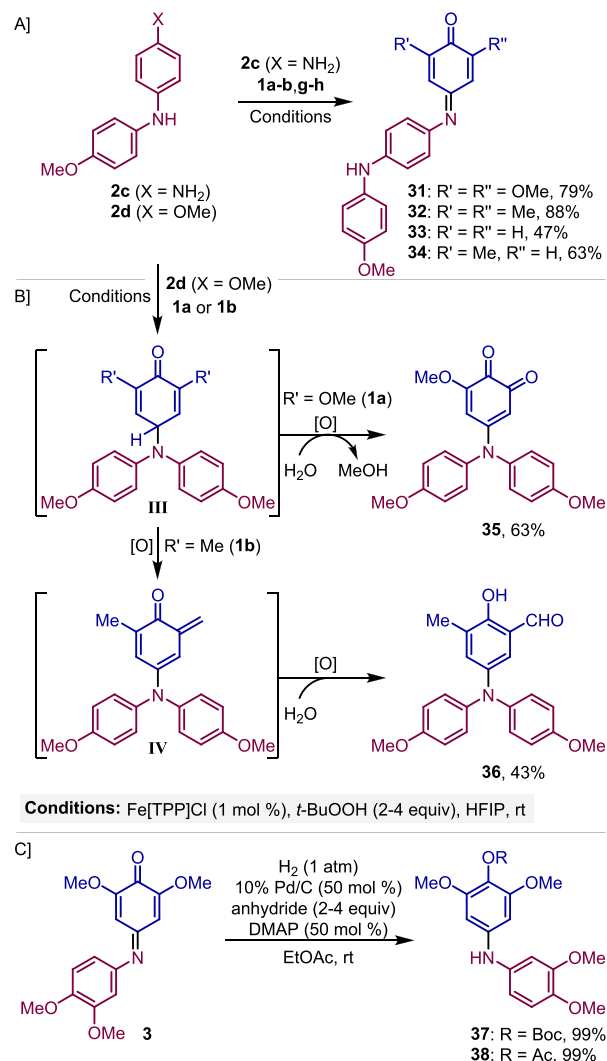
Recently, the Lei group demonstrated that the electrochemical oxidative amination of 4-methoxyphenol (**1g**) by phenothiazine is *ortho*-selective with regard to the phenolic group (Scheme 1B).¹¹ Interestingly, under our conditions, the coupling took place at the *ipso*-methoxy position, affording, after elimination of methanol, benzoquinone anil **22** [from 4-methoxyphenol (**1g**) and 2,4-dimethoxyaniline (**2b**)] in 53% yield and benzoquinone anil **23** [from 2-methyl-4-methoxyphenol (**1h**) and 3,4-dimethoxyaniline (**2a**)] as a mixture of *cis/trans* isomers in 73% yield (Figure 1B).

The oxidative amination of 4-alkylphenols led to a different class of compounds (Figure 1C). The reaction between 2,4-dimethylphenol (**1i**) and aniline **2a** with Fe[TPP]Cl as the catalyst afforded *N,O*-biaryl product **24** in 39% yield. However, Mn[TPP]Cl, which was too reactive for the oxidative amination of phenol **1a** by aniline **2a** (Table 1, entry 11), showed improved results in the case of less oxidizable *para*-alkylphenols. Indeed, with Mn[TPP]Cl (1 mol %, UHP (1.5 equiv), HFIP, rt) as the catalyst, we were able to isolate compound **24** in an improved (52%) yield. The alternative conditions provided entry to *N,O*-biaryl compounds **25**–**30** in moderate to good yields (Figure 1C). On the basis of the Miller studies,²⁸ it is postulated that the acid-sensitive quinamine intermediate **II** (R = alkyl) undergoes [3,3]-sigmatropic rearrangement.²⁹ Importantly, despite our efforts to react other aniline derivatives with *para*-alkylphenols, only aniline **2a** and its *N*-methyl **2a** derivative (products **27**–**29**) were found to be suitable coupling partners. This is probably because they have a suitable electronic structure for stabilizing the anilino radical in the first step and for facilitating the rearrangement in the second step.

Next, we studied the oxidative amination of phenols by secondary diarylamines. First, 4-(4-methoxyphenylamino)-aniline (**2c**), which has both primary and secondary amine

groups, was reacted with phenols **1a**, **1b**, **1g**, and **1h** (Scheme 3A). Although diarylamine **2c** can react with both amine

Scheme 3. Oxidative Amination of Diarylamines (A,B) and the Preparation of Protected Anilinophenols from Benzoquinone Anils (C)



groups, selective coupling at the primary amine took place, affording benzoquinone anils **31**–**34** in moderate to good yields. On the other hand, the reaction of 4,4'-dimethoxydiphenylamine (**2d**) with phenol **1a** led, after a sequential dehydrogenation steps, to the formation of catechol **35** (63% yield, Scheme 3B), presumably via intermediate **III**. In contrast, the reaction of **2d** and **1b** afforded benzaldehyde **36** in 43% yield, possibly through intermediates **III** and **IV**. These examples prove that secondary anilines are suitable coupling partners; however, they form highly unstable quinamine intermediates that further react under the reaction conditions.

Finally, in this work, we show that *para*-anilinophenols, such as **13b** (Scheme 2A), are highly air sensitive; therefore, their isolation in a pure form is a challenging task. To access *para*-anilinophenols from benzoquinone anils, the phenolic group needs to be blocked under reduction conditions. For example, the hydrogenation of benzoquinone anil **3** (H₂, Pd/C, EtOAc, rt) in the presence of di-*tert*-butyldicarbonate or acetic

anhydride and 4-dimethylaminopyridine affords O-protected anilinophenols **37** and **38** in quantitative yields (Scheme 3C).

In conclusion, a highly efficient *para*-selective oxidative amination of phenols by primary or secondary anilines catalyzed by M[TPP]Cl (M = Fe or Mn) complexes was developed. This reaction provides a direct entry to benzoquinone anils and *N,O*-biaryl compounds that are not readily accessible by any other sustainable method. The postulated mechanism involves the coupling of a liberated anilino radical and an iron-ligated (4-*R*)phenoxyl radical. The C–N coupling step affords unstable anilinoquinone intermediates that undergo either dehydrogenation (R = H), elimination (R = OMe), or [3,3]-sigmatropic rearrangement (R = alkyl), depending on the identity of the phenolic *para*-substituent. We intend to continue our group effort in developing novel catalytic systems for chemo-, regio-, and stereoselective oxidative aniline coupling reactions.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.orglett.0c00296>.

Experimental procedures and spectroscopic data of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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