Iron-Catalyzed Oxidative C–O and C–N Coupling Reactions Using Air as Sole Oxidant**

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In Memoriam Professor Siegfried Hünig (1921–2021)

Abstract: We describe the oxygenation of tertiary arylamines, and the amination of tertiary arylamines and phenols. The key step of these coupling reactions is an iron-catalyzed oxidative C–O or C–N bond formation which generally provides the corresponding products in high yields and with excellent regioselectivity. The transformations are accomplished using hexadecafluorophthalocyanine–iron(II) (FePcF$_{16}$) as catalyst in the presence of an acid or a base additive and require only ambient air as sole oxidant.

Introduction

The construction of carbon–heteroatom bonds is a crucial transformation for the synthesis of functionalized heterocyclic moieties present in natural products and pharmaceuticals. Transition metal catalysts have been widely applied for these coupling reactions.[1] The best known method to generate C–O bonds for diaryl ethers is the copper-catalyzed Ullmann-Goldberg reaction (Scheme 1a).[2] The palladium-catalyzed Buchwald-Hartwig amination of aryl halides represents a useful tool for C–N bond formation (Scheme 1b).[1c,3] These methods require pre-functionalized substrates, thus limiting their utility from an economic and environmental point of view.[4] Therefore, considerable efforts have been made to achieve a direct C–H bond functionalization by intermolecular oxidative C–O and C–N coupling reactions. A key challenge of the oxidative coupling is the fact that C–H bonds are relatively inert and thus, several groups have applied strong oxidants for this process.[5,6] However, these procedures often suffer from low atom-economy, poor selectivity, and harsh reaction conditions. Using green oxidants, the oxidative coupling becomes more attractive.[6] Thus, oxygen from ambient air represents the ideal oxidant due to its natural abundance and environmentally friendly features.[8]

Inspired by green and sustainable chemistry, transition metal-catalyzed oxidative coupling reactions have become a useful and versatile tool for the formation of carbon–heteroatom bonds with air as sole oxidant.[9] Especially copper

Scheme 1. Transition metal catalyzed C–O and C–N coupling reactions.
and noble metals\textsuperscript{[11]} have been applied successfully for this purpose.\textsuperscript{[20]} More recently, the search for inexpensive, less toxic, and thus environmentally benign and sustainable catalysts has come into the focus of interest.\textsuperscript{[12]} Iron compounds are in the center of this development.\textsuperscript{[13]} In this context, iron-based catalysts in combination with stoichiometric amounts of strong oxidants have been extensively studied for oxidative carbon–heteroatom coupling reactions.\textsuperscript{[14]} However, due to the hazard of the oxidant, these methods are not a fully sustainable alternative for such conversions. In contrast, iron-catalyzed oxidative carbon–heteroatom coupling reactions using oxygen from ambient air as oxidant represent green synthetic transformations.

Recently, we have developed an oxidative C–C homocoupling of anilines\textsuperscript{[15,16]} and hydroxycarbazoles\textsuperscript{[17]} as well as an oxidative C–C cross-coupling of tertiary anilines with hydroxyarenes\textsuperscript{[18]} using hexadecafluorophthalocyanine–iron(II) (FePcF\textsubscript{16}, Figure 1)\textsuperscript{[15,19]} as catalyst with air as sole oxidant.\textsuperscript{[20]} The iron-catalyzed reaction of 2-(dimethylamino)naphthalene with 2-naphthol afforded the oxidative C–C cross-coupling product (62\% yield) along with a diaryl ether (11\% yield) resulting from oxidative C–O coupling of 2-(dimethylamino)naphthalene with 2-naphthol as catalyst with air as sole oxidant.\textsuperscript{[21]} The reaction is assumed to proceed via a free-radical coupling mechanism (Scheme 1c).

### Results and Discussion

Based on our protocol for the iron-catalyzed oxidative C–C cross-coupling,\textsuperscript{[18]} we investigated the iron-catalyzed oxidative C–O coupling of 2-(dimethylamino)naphthalene (1a) and 4-methoxyphenol (2a) to the diaryl ether 3a in dichloromethane as model reaction (Table 1). No product was formed using catalytic amounts of FePcF\textsubscript{16} (4 mol\%) without additive at room temperature under ambient air (entry 1). Variation of the additives from acetic acid (entry 2) to methanesulfinic acid (entry 3) showed that the stronger Brønsted acid led to the diaryl ether 3a in 25\% yield along with the dioxygenated product 4a in 31\% yield (entry 3). Lewis acids proved to be superior providing selectively the diaryl ether 3a as major product (entries 4 and 5). An optimized protocol with 40 mol\% of BF\textsubscript{3}·OEt\textsubscript{2} as additive and air as oxidant afforded compound 3a in 66\% yield (entry 5). In contrast, the recently reported oxidative C–C coupling of 2-(dimethylamino)naphthalene (1a) with various phenols using a chromium–salen catalyst under aerobic conditions afforded mixtures of C–C and C–O coupling products.\textsuperscript{[21]} Variation of the reaction conditions given in entry 5 of Table 1 gave no further improvement. For example, the very slow reaction in ethanol as solvent afforded 3a in only 17\% yield after 24 h (entry 6) and the reaction at 0°C provided 3a in only 36\% yield (entry 7). Moreover, the reaction of entry 5 under an atmosphere of pure oxygen resulted in complete decomposition of the phenol 2a within 12 minutes. Whereas using Fe(acac)\textsubscript{3} as catalyst gave no turnover and allowed recovery of the starting materials 1a and 2a.

The iron-catalyzed oxidative C–O coupling of 2-(dimethylamino)naphthalene (1a) with a range of phenols 2a–e using the optimized reaction conditions provided selectively the corresponding diaryl ethers 3a–e (Table 2). Coupling of 1a with 1-methyl-2-naphthol (2d) led to the dinaphthyl ether 3d in 89\% yield. The structure of 3d was additionally confirmed by an X-ray analysis (Figure 2).\textsuperscript{[22]} The coupling of 1a with 1-bromo-2-naphthol (2e) required 40 mol\% of methanesulfinic acid as additive to afford the dinaphthyl ether 3e in 57\% yield. Coupling of N,N-dimethylaniline (1b) with 4-methoxyphenol (2a) provided compound 3f in 35\% yield. The reaction with primary and secondary arylamines did not lead to product formation.

The reaction is assumed to proceed via a free-radical coupling mechanism (Scheme 2). Single-electron transfer (SET) oxidation of the phenol by an iron(III) species and subsequent proton loss of the radical cation generate a phenoxy radical which attacks the Lewis acid–Lewis base complex of the tertiary arylamine and boron trifluoride. Cleavage of the boron trifluoride from the resulting cyclohexadienyl radical, oxidation by another SET to a cyclohexadienyl cation, and proton loss

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**Table 1. Optimization of the reaction conditions for the iron-catalyzed oxidative C–O coupling of 2-(dimethylamino)naphthalene (1a) with 4-methoxyphenol (2a).\textsuperscript{[a]}**

| Entry | Additive (mol%) | Time | Yield of 3a [%] | Yield of 4a [%] |
|-------|----------------|------|----------------|----------------|
| 1     | –              | 24 h | –              | –              |
| 2     | AcOH (200)     | 24 h | traces         | –              |
| 3     | MSOH (40)      | 2 h  | 25             | 31             |
| 4     | B(CF\textsubscript{3})\textsubscript{3} (40) | 50 min | 53 | traces |
| 5     | BF\textsubscript{3}·OEt\textsubscript{2} (40) | 40 min | 66 | traces |
| 6     | BF\textsubscript{3}·OEt\textsubscript{2} (40) | 24 h | 17 | – |
| 7     | BF\textsubscript{3}·OEt\textsubscript{2} (40) | 3.5 h | 36 | – |

\textsuperscript{[a]} Reaction conditions: 1a (0.30 mmol), 2a (0.38 mmol), FePcF\textsubscript{16} (4 mol\%), air (1 atm), CH\textsubscript{2}Cl\textsubscript{2} (3 mL), room temperature. \textsuperscript{[b]} Solvent: EtOH (3 mL). \textsuperscript{[c]} Reaction at 0°C, FePcF\textsubscript{16} = hexadecafluorophthalocyanine–iron(II).

**Figure 1.** Structure of hexadecafluorophthalocyanine–iron(II) (FePcF\textsubscript{16}).
afford the diaryl ether. The presence of boron trifluoride as additive appears to be crucial for the success of this oxidative C–O coupling since in the presence of Brønsted acid the C–C cross coupling generally is preferred.\(^{[13k,18]}\)

In contrast to the Buchwald-Hartwig amination, the oxidative C\(_2\)H/N\(_2\) coupling represents a more direct and atom-economical method.\(^{[23]}\)

Phenothiazines, compounds with useful biological\(^{[24]}\) and optoelectronic properties,\(^{[25]}\) have been applied recently for oxidative C–N coupling reactions by Patureau et al.\(^{[26]}\) and other groups.\(^{[27]}\) The resulting N-arylated phenothiazines exhibit interesting physical properties.\(^{[28]}\)

The iron-catalyzed oxidative C–N coupling reaction of 2-(dimethylamino)naphthalenes with the phenothiazines afforded the corresponding N-arylated products in good to excellent yields (Table 3). An X-ray crystal structure determination of 6a confirmed the N-(1-naphthyl)phenothiazine framework (Figure 3).\(^{[29]}\) The optimized reaction conditions for this reaction (4 mol% of FePcF\(_{16}\) and 60 mol% of methanesulfonic acid as additive in THF at room temperature under air) closely resemble those previously used for the iron-catalyzed oxidative C–C cross-coupling of tertiary anilines with hydroxyarenes.\(^{[16]}\)

The blank experiment, reaction of phenothiazine (5a) with 1a in the absence of the catalyst FePcF\(_{16}\), afforded compound 6a in only 11% yield after 3 h. The coupling of 2-(dimethylamino)naphthalene (1a) with phenoxazine or dibenzo[b,f]azepine provided the corresponding products 6f and 6g in high yields, whereas the reaction of \(N,N\)-dimethylaniline (1b) with phenothiazine (5a) using BF\(_3\)·OEt\(_2\) (40 mol%) as additive gave a moderate yield for 6h.

Following the excellent results achieved with phenothiazine (5a) as coupling substrate, we have extensively investigated the

| Table 2. Iron-catalyzed oxidative C–O coupling of tertiary arylamines 1 with phenols 2.\(^{[a]}\) |
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| \[
\begin{align*}
\text{R} & \quad \text{NMe}_2 \\
\text{MeO} & \quad \text{NMe}_2 \\
\text{MeO} & \quad \text{NMe}_2 \\
\text{MeO} & \quad \text{NMe}_2 \\
\text{MeO} & \quad \text{NMe}_2 \\
\text{MeO} & \quad \text{NMe}_2 \\
\end{align*}
\]
| \[
\begin{align*}
\text{1} & \quad \text{2} \\
\text{3} & \quad \text{MeO} \\
\text{3a} & \quad \text{MeO} \\
\text{3b} & \quad \text{MeO} \\
\text{3c} & \quad \text{MeO} \\
\text{3d} & \quad \text{MeO} \\
\text{3e} & \quad \text{MeO} \\
\end{align*}
\]
| \[
\begin{align*}
\text{4} & \quad \text{O} \\
\text{R} & \quad \text{R} \\
\text{5} & \quad \text{O} \\
\text{6} & \quad \text{O} \\
\text{7} & \quad \text{O} \\
\text{8} & \quad \text{O} \\
\end{align*}
\]
| \[
\begin{align*}
\text{a} & \quad \text{R} = \text{H}, 100\% \\
\text{b} & \quad \text{R} = \text{OMe}, 98\% \\
\text{c} & \quad \text{R} = \text{OMe}, 66\% \\
\text{d} & \quad \text{R} = \text{Cl}, 81\% \\
\text{e} & \quad \text{R} = \text{CF}_3, 91\% \\
\text{f} & \quad \text{R} = \text{H}, 77\% \\
\text{g} & \quad \text{R} = \text{OMe}, 45\% \\
\end{align*}
\]

[a] Reaction conditions: 1 (0.30 mmol), 2 (0.38 mmol), FePcF\(_{16}\) (4 mol%), BF\(_3\)·OEt\(_2\) (40 mol%), air (1 atm), CH\(_2\)Cl\(_2\) (3 mL), room temperature. [b] 1 (0.76 mmol), FePcF\(_{16}\) (4 mol%), MsOH (40 mol%).

| Figure 2. Molecular structure of the dinaphthyl ether 3d in the crystal (thermal ellipsoids are shown at the 50% probability level). |

| Scheme 2. Proposed mechanism for the iron-catalyzed oxidative C–O coupling of tertiary arylamines with phenols. |

| Table 3. Iron-catalyzed oxidative C–N coupling of tertiary arylamines 1 with compounds 5.\(^{[a]}\) |
| --- |
| \[
\begin{align*}
\text{R} & \quad \text{NMe}_2 \\
\text{MeO} & \quad \text{NMe}_2 \\
\text{MeO} & \quad \text{NMe}_2 \\
\text{MeO} & \quad \text{NMe}_2 \\
\text{MeO} & \quad \text{NMe}_2 \\
\text{MeO} & \quad \text{NMe}_2 \\
\end{align*}
\]
| \[
\begin{align*}
\text{1} & \quad \text{5} \\
\text{6} & \quad \text{6a} \\
\text{6b} & \quad \text{6c} \\
\text{6d} & \quad \text{6e} \\
\text{6f} & \quad \text{6g} \\
\text{6h} & \quad \text{6i} \\
\end{align*}
\]
| \[
\begin{align*}
\text{a} & \quad \text{R} = \text{H}, 100\% \\
\text{b} & \quad \text{R} = \text{OMe}, 98\% \\
\text{c} & \quad \text{R} = \text{OMe}, 66\% \\
\text{d} & \quad \text{R} = \text{Cl}, 81\% \\
\text{e} & \quad \text{R} = \text{CF}_3, 91\% \\
\text{f} & \quad \text{R} = \text{H}, 77\% \\
\text{g} & \quad \text{R} = \text{OMe}, 45\% \\
\end{align*}
\]

[a] Reaction conditions: 1 (0.30 mmol), 5 (0.51 mmol), FePcF\(_{16}\) (4 mol%), MsOH (60 mol%), air (1 atm), THF (3 mL), room temperature. [b] 1b (0.30 mmol), 5a (0.60 mmol), FePcF\(_{16}\) (4 mol%), BF\(_3\)·OEt\(_2\) (40 mol%), air (1 atm), CH\(_2\)Cl\(_2\) (3 mL), room temperature, 15 h.
iron-catalyzed oxidative amination of phenols using the reaction of 5a with 4-(tert-butyl)phenol (2f) as model system. Various iron compounds as catalysts (4 mol%) and several different additives have been tested for the reaction of 2f with two equivalents of 5a at room temperature under ambient air. Simple iron salts as catalysts gave no conversion and 5,10,15,20-tetrakis(pentafluorophenyl)porphyrin–iron(III) chloride led only to traces of the C–N coupling product 7a in 15–27% yield (entries 4–6). The high catalytic activity of FePcF3 for various oxidative transformations has been widely demonstrated by our group. Subsequently, we have screened a range of different additives for the oxidative C–N bond formation using 4 mol% of FePcF3 as catalyst (entries 7–13). With methanesulfonic acid as additive (entry 7), complete decomposition of the starting material was observed. Among the different bases tested as additives (entries 8–13), 40 mol% of Hünig’s base ([15–18,20,31,32] entries 8–13), 40 mol% of Hünig’s base ([15–18,20,31,32] entries 8–13) as additive for the iron-catalyzed oxidative N–N coupling could easily be applied to various oxidative C–N coupling reactions under air is the oxidation of the catalyst to μ-oxo(FePcF3)(μ-O(FePcF3)) (Table 4). Using μ-oxo(FePcF3)(μ-O(FePcF3)) as catalyst under otherwise identical conditions gave a similar yield of 7a (entry 15). In line with our mechanistic hypothesis of a catalytic [Fe(III)]/[Fe(II)] cycle, the reaction with FePcF3 under argon (entry 16) or in the absence of any iron catalyst (entry 17) gave no conversion of the starting materials. In other solvents (ethyl acetate, ethanol, or acetone) the reaction was less efficient than in dichloromethane (entries 18–20). Finally, using Fe(acac)3, as catalyst in the presence of 40 mol% Hünig’s base as additive gave no significant increase of the yield for the coupling product 7a (compare entries 4 and 21).

Using the optimized conditions (Table 4, entry 13), we investigated the scope of the oxidative C–N coupling reaction of various phenols 2 with phenothiazine (5a) (Table 5). While the reaction of anisole with phenothiazine (5a) gave no coupling product, simple phenols as substrates provided the ortho- or para-aminated products 7a–g in 69–99% yield. It is noteworthy that in the present case the coupling of thymol with phenothiazine (5a) led to product 7g as single regioisomer. The reaction of 4-(tert-butyl)phenol (2f) with substituted phenothiazines afforded selectively 7h–j in 73–91% yield. Shorter reaction times are sufficient for the coupling of 2f.
with the more reactive phenoxazine to compound 7k. Next, we studied the iron-catalyzed oxidative C–N coupling of phenothiazine (5a) with poly cyclic phenols (2-naphthol, 5-hydroxy-1-tosylindole, 2-hydroxydibenzofuran, 2-hydroxy-7-methoxy-3-methylcarbazole, and 4-hydroxycarbazole). These amination reactions provided the corresponding N-arylpheno thiazines 7l–p regioselectively and in high yields. The regiochemistry of 7p (amination at C-1 of the carbazole) was confirmed by 2D NMR spectroscopy (COSY, HSQC, HMBC, and NOESY) (see Supporting Information). The synthesis of 7o and 7p demonstrates that the present method enables late-stage functionalizations which are difficult to achieve by alternative procedures at the carbazole framework. Carbazoles are an important class of natural products with a broad range of pharmacological activities.

During the synthesis of compound 7p, we noted that prolonged reaction times lead to formation of a diaminated product. This observation prompted us to study the application of our iron-catalysis to a twofold oxidative C–N bond formation using appropriate substrates. Lei et al. prepared diaminated phenols by electrochemical oxidation. With an excess of four equivalents of phenothiazine (5a), we were able to transform 4-hydroxycarbazole into the corresponding product 8a by an iron-catalyzed oxidative dination (Table 6). Compound 8a was unequivocally confirmed by an X-ray crystal structure determination (Figure 4). Using phenol, o-cresol, or o-tert-butylphenol as substrates, the same set of reaction conditions led to the diaminated compounds 8b–d. However, the iron-catalyzed oxidative amination of the more electron-rich substrate guaiacol (2s) afforded the mono-aminated product 7q and the diaminated product 8e only in a 2:1 ratio even with an excess of 4 equivalents of 5a (Scheme 3). Prolonged reaction times led to no further conversion of 7q into 8e but resulted in partial decomposition. The amination at the position para to

| Table 5. Substrate scope for the iron-catalyzed oxidative C–N coupling of phenols 2 with compounds 5. |
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| ![Chemistry—A European Journal](https://i.imgur.com/1234567890.png) |

| Table 6. Substrate scope for the twofold iron-catalyzed oxidative C–N coupling of phenols 2 with phenothiazine (5a). |
|---|
| ![Chemistry—A European Journal](https://i.imgur.com/1234567890.png) |

Figure 4. Molecular structure of the carbazole 8a in the crystal (thermal ellipsoids are shown at the 50% probability level; the solvent molecule (CHCl₃) has been omitted for clarity).
the hydroxy group in compound 7q has been assigned based on 2D NMR spectroscopy (COSY, HSQC, HMBC, and NOESY) (see Supporting Information). Xia et al. described an ortho-selective coupling between guaiacol (2s) and phenothiazine (5a).\textsuperscript{[27a]} However, the $^1$H and $^{13}$C NMR data of our compound 7q are in excellent agreement with those reported by Xia et al. for their corresponding product.\textsuperscript{[27a]} We have additionally confirmed our structural assignment by an X-ray analysis (Figure 5).\textsuperscript{[39]} Therefore, the structure of the corresponding product described by Xia et al. has to be revised.

We postulate that the iron-catalyzed amination of phenols with phenothiazine (5a) proceeds via a phenothiazine radical intermediate formed by SET to the iron(III) species and subsequent proton loss (Scheme 4). Attack of the phenothiazine radical at the phenolate leads to a cyclohexadienyl radical which is oxidized in another SET to give the final coupling product.\textsuperscript{[40]} Alternatively, the coupling product may be formed by radical recombination of the phenothiazine radical with the phenoxy radical formed as described in Scheme 2.\textsuperscript{[40c,41]} Support for a mechanism via coupling of a phenothiazine free radical derives from a trapping experiment (Scheme 5) and ESR spectroscopy (Figure 6).

Previously, we trapped an aryl radical in the FePcF$_{16}^-$ catalyzed homocoupling of diarylamines with the free radical scavenger 2,6-di-(tert-butyl)-4-methylphenol (BHT).\textsuperscript{[15]} The iron-catalyzed oxidative C–N coupling of phenothiazine (5a) with phenols occurs exclusively in the positions para and ortho to the hydroxy group. Thus, the regiochemical course for this reaction using phenols with ortho- and para-positions blocked by substituents was in question. The iron-catalyzed oxidative coupling of the para-cresol derivatives 9a (BHT) and 9b with 5a under the standard reaction conditions provided the N-benzylphenothiazines 10a and 10b (Scheme 5). The formation of compounds 10 proceeds via addition of the phenothiazine radical to the corresponding p-quinone methides generated by initial oxidation of the p-cresols 9.\textsuperscript{[42]} Moreover, the synthesis of

Scheme 3. Iron-catalyzed oxidative amination of guaiacol (2s) with phenothiazine (5a). Reaction conditions: a) 2s (0.40 mmol), 5a (1.60 mmol), FePcF$_{16}$ (4 mol%), NiPr$_{2}$Et (40 mol%), air (1 atm), CH$_2$Cl$_2$, room temperature, 14 h.

Figure 5. Molecular structure of compound 7q in the crystal (thermal ellipsoids are shown at the 50% probability level.

Scheme 4. Proposed mechanism for the iron-catalyzed oxidative C–N coupling of phenols with phenothiazine.

Figure 6. Comparison of the experimental (exp; black) and simulated (sim; red) EPR spectra of the phenothiazine radical at room temperature.

Scheme 5. Iron-catalyzed oxidative C(sp$^3$)–H/N–H coupling of para-cresol derivatives 9 with phenothiazine (5a). Reaction conditions: a) 9 (0.40 mmol), 5a (0.80 mmol), FePcF$_{16}$ (4 mol%), NiPr$_{2}$Et (40 mol%), air (1 atm), CH$_2$Cl$_2$, room temperature, 15–24 h.
Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: air · C–H activation · homogeneous catalysis · iron · oxidative amination
Crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

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Crystallographic data for 6a: C$_{49}$H$_{60}$N$_{5}$S, M = 368.48 g mol$^{-1}$, crystal size: 0.180 × 0.226 × 0.485 mm$^{3}$, monoclinic, space group P2$_1$, a = 6.136(6), b = 12.7256(9), c = 11.2193(7) Å, β = 98.1618(1), V = 867.22(12) Å$^3$, Z = 2, ρ$_{calc}$ = 1.254 g cm$^{-3}$, μ = 0.076 mm$^{-1}$, λ = 0.7017 Å, T = 100(2) K, χ range: 3.39–28.15, reflections collected: 1691, independent: 4176 (R$_{int}$ = 0.0376); structure was solved by direct methods and refined by full-matrix least-squares on F$^2$; final R indices ($R_I$ = 0.0276); R = 0.0336 and wR = 0.0477; maximal residual electron density 0.444 e Å$^{-3}$. Deposition Number 2122918 contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.