Selective Oxidative Homo- and Cross-Coupling of Phenols with Aerobic Catalysts

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* Supporting Information

ABSTRACT: Simple catalysts that use atom-economical oxygen as the terminal oxidant to accomplish selective ortho−ortho, ortho−para, or para−para homo-couplings of phenols are described. In addition, chromium salen catalysts have been discovered as uniquely effective in the cross-coupling of different phenols with high chemoselectivity.

Since the groundbreaking work by Barton and Erdtmann that phenol oxidation is a key step in the biosynthesis of several natural product classes, chemists have been inspired to develop laboratory analogues of these important processes. Numerous natural products can be constructed via different oxidative phenol couplings including homo-coupling at the same site, homo-coupling at different sites, and cross-coupling of different phenols (Chart 1). Due to the vast array of useful biological activities associated with these compounds, especially their antibacterial and antifungal properties, these compounds remain the subject of intense interest. While many stoichiometric phenolic oxidations have been studied, the coupling selectivities are typically low when multiple coupling sites are available (see red arrows in Chart 1). Furthermore, the use of superstoichiometric reagents is undesirable. Herein, we disclose simple catalysts that use atom-economical oxygen as the terminal oxidant to accomplish selective ortho−ortho, ortho−para, or para−para homo-couplings of phenols. In addition, chromium salen catalysts have been found to be exceptional in cross-coupling two different phenols with high selectivity.

Few nonenzymatic catalytic systems have been reported for the oxidative coupling of the parent phenols, even though there are many for 2-naphthols. Due to the difference in oxidation potentials (naphthol = 1.87 eV, phenol = 2.10 eV), the oxidation of phenols is more difficult. In addition, diverse product mixtures are observed due to similar stabilities of the different radical resonance forms relative to naphthol (Scheme 1). In addition, direct oxygenation of the aromatic ring to quinones and further adducts becomes competitive.

Our strategy to explore this challenging transformation centered on metal catalysts that are reoxidized readily by O₂. Based on prior experience with 2-naphthol coupling, we elected to examine Cr, Cu, Fe, Mn, Ru, and V. An appropriate ligand framework that stabilizes the metal, is tuned easily and is oxidatively stable was crucial. For phenol coupling, the salen/salan scaffold proved superior. Due to the large number of variables (36 catalysts, Chart 2, R = H; solvent; additives; substrates), parallel microscale screening was used to rapidly identify trends (Figure 1). To test the premise that these catalysts are appropriate for phenol oxidation and that O₂ was being effectively introduced into the reaction microvials, a substrate (Table 1, entry 1) that readily undergoes phenolic coupling to a single ortho−ortho product was tested first. Gratifyingly, almost all the catalysts were effective to some degree with this substrate (Figure 1, entry 1). Further bench
scale optimization revealed a Ru catalyst as highly effective with oxygen for this substrate (Table 1, entry 1). With substrates that are not effectively coupled even with stoichiometric oxidants, the initial screen (Figure 1, bottom four entries) showed lower yields. However, the trends narrowed the focus for further optimization. By examining temperature, solvents, and additives, ortho−ortho coupling of a range of substrates was achieved (Table 1, entries 2−4, 7). To improve reactivity for reluctant substrates, we theorized that an electron-withdrawing substituent NO2 (R2, Chart 2) would improve the oxidizing power of the Ru-Salen-H. With this second generation catalyst, higher yields were seen for entries 9 and 11. Overall, Ru salens are the most general for ortho−ortho coupling, but some substrates respond better to V or Cu catalysts.

With entries 7 and 9 from Table 1, an additional major peak was seen in the HPLC spectra from the initial screening. Re-examination of the data rapidly identified catalysts selective for this compound (beige highlights in Figure 2). This material was ultimately determined to be the tricyclic Pummerer ketone1,2a, which forms via ortho−para coupling followed by a 1,4-addition (Scheme 2). Optimized conditions provided this PK with high efficiency (Table 1, entries 8, 10, 12). Notably, this

"Parenthetical yields are based on recovered substrate. Bracketed yields are unoptimized parallel screening results."
motif is found in several natural products such as the galanthamines and usnic acids. On the other hand, when the para-position is unsubstituted, ortho–para bisphenols are generated (entry 5). Notably, different catalysts permit control of ortho–ortho vs ortho–para coupling (Table 1, entries 4/5, 7/8, 9/10).

The next challenge was identifying catalysts for para–para coupling. When there is competition between ortho- and para-sites, selective catalysts were found (Table 1, entries 6, 13, 14), but yields were modest due to low reactivity, a challenge that...
remains to be addressed. When the ortho-positions are blocked, the expected para-product is obtained (Table 1, entries 15−
17). Most interestingly, selective catalysts for ortho−ortho, ortho−para, and para−para coupling of 2,3,5-trimethylphenol have been identified (Table 1, entries 4−6) showing the versatility of this catalytic aerobic coupling.

At this juncture, the question of cross-coupling different phenols arose, a very difficult venture since any catalyst must promote the cross-coupling much faster than either of the corresponding homo-couplings.\(^2,12,13\) Initially, phenols with only one open coupling site were used limiting the outcome to three coupling products (Table 2, entries 1−2). Remarkably, a Cr catalyst affected cross-coupling with high efficiency (75−85%) with only a 1:2:1 reactant stoichiometry.

Venturing to substrates where six products are possible led to the discovery that Cr-salen-Cy is broadly effective for the cross-coupling (entries 3−10). A 2:1 stoichiometry of the coupling partners was well tolerated. Notably, selective cross-coupling was seen for many substrates (yellow highlights, Table 2) where selective cross-coupling had been achieved in Table 1. Selective cross-coupling requires a 2,6-disubstituted partner (Type I), which is postulated to add at the para-site to a metal bound radical or radical cation of the complementary partner (Type II or III), which has a less hindered phenol for metal binding (Scheme 3). Site selectivity occurs at the sterically least hindered site of this metal bound phenol (Type II ortho, Type III para). To date, no other substitution patterns have been found effective for the Type I partner.

The degree of selectivity control in the catalysts described herein suggests significantly different mechanisms are operating. Further, preliminary studies with radical inhibitors reveal complex effects (see Supporting Information). For example, TEMPO inhibited reaction of the Cr catalyst with O2. Combined with the lack of reactivity of the Cr catalyst without O2 and the formation of product under N2 with a pregenerated Cr(IV) species,\(^14\) the data support the mechanism shown in Scheme 3 for the cross-coupling.

In summary, catalytic amounts of simple salen/salan complexes using O2 as the terminal oxidant provide access to phenolic dimers unattainable via conventional oxidants. The PK exemplifies oxidative coupling as a powerful strategy to rapidly build complexity without using leaving groups. The Cr salens, which have not been reported previously in oxidative phenolic coupling, exhibit unique cross-coupling activity enabling access to many unknown adducts. Further studies on the mechanisms to tailor catalysts for reactivity and selectivity are under way.

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