Visible-light Induced Oxidative Coupling of Phenols and Alkenylphenols with a Recyclable, Solid Photocatalyst

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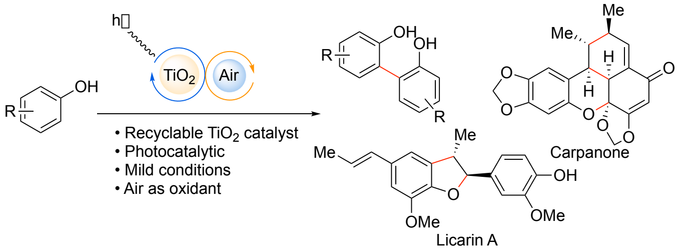
Supporting Information Placeholder

ABSTRACT: A photocatalytic method for phenol and alkenylphenol oxidative coupling is reported using an inexpensive heterogeneous titanium dioxide photocatalyst with air and visible light. During the coupling process, the Ti-substrate complex is activated under visible light through a ligand to metal charge transfer effect, and the diphenol adduct is proposed to form through a radical cation. The heterogeneous TiO_2 catalyst remains stable throughout the reaction and can be easily removed and reused multiple times.



The neolignan and biphenol structural classes comprise numerous natural products. Many of the compounds within these classes have antiviral, antibacterial, antifungal, antiparasitic, antioxidant or antimicrobial properties (Figure1).[1,2,3] Since the discovery that neolignan and biphenol natural products are likely to be formed through oxidative coupling reactions, much attention has been focused on the development of catalytic oxidative coupling methods that mimic such transformations.[4]

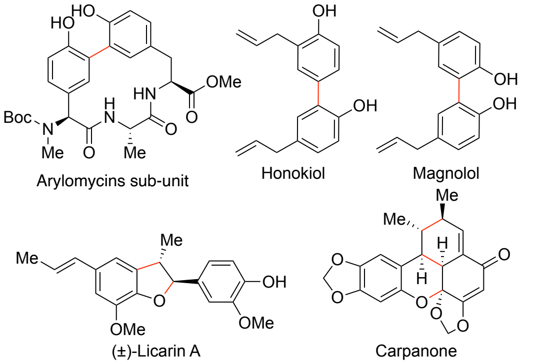
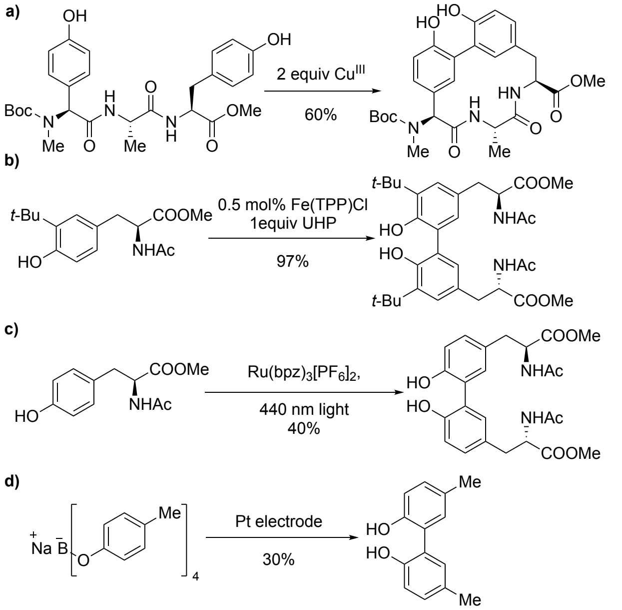


Figure 1. Coupled phenol natural products.

Unlike redox-neutral (such as Suzuki, Neigishi, Sonogashira, etc.) or reductive coupling methods (Ullmann) where the substrates are pre-functionalized with groups to control regio- and chemoselectivities, oxidative coupling methods often face challenges in controlling selectivity.[5] An excellent example can be found in the couplings of the phenols of tyrosine. As with virtually all mono-substituted phenols, yields are low in oxidative couplings as there are two equivalent *ortho*-positions that may give rise to polymerization and other undesired side-reactions. In one example, Baran and co-workers extensively screened condition to accomplish an intramolecular oxidative phenol-phenol coupling of tyrosine with nor-tyrosine and found that only a stoichiometric Cu^{II}-TMEDA complex was effective (Scheme 1 a).[6] In 2020 Pappo and co-workers utilized a removable *tert*-butyl group to block one of the reactive *ortho* -positions of tyrosine which allowed a Fe(TPP)Cl catalyst to affect oxidative coupling (Scheme1 b).[7] However, the installation and deinstallation of the *tert*-butyl group to tyrosine reduces the atom economy of such a reaction. Building on our prior studies in phenolic coupling,[8,9] we reported in 2021 the direct oxidative coupling of an unmodified tyrosine using a ruthenium photocatalyst (Scheme1 c).[10] In addition to transition metal catalyzed phenol-phenol coupling methods, phenols can also be coupled electrochemically. In 2006, Waldvogel and co-workers reported homo-coupling reactions using a boronate salt with a Pt electrode (Scheme 1d).[11]

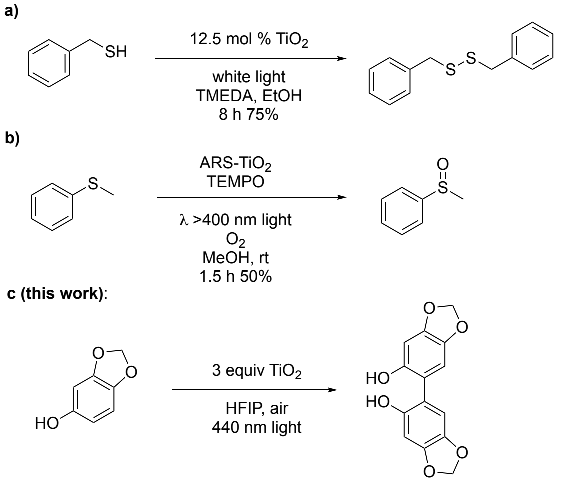
Scheme 1. Reported Phenol Couplings



The above-mentioned advances in oxidative phenol coupling allow utilization of a diverse array of phenolic substrates and synthesis of several natural products. However, improved methods for oxidative coupling of monosubstituted phenols are desirable as well as conditions that allow facile separation and reuse of the catalyst. Based on these considerations, we targeted use of a solid photocatalyst.

Titanium dioxide is such an example of an easily recyclable solid photocatalyst. Further advantages include low cost and low toxicity. Since the discovery of the photo-induced semi-conducting behavior of titanium dioxide under UV light, titanium dioxide has been widely used in water treatment industries for pollutant degradation and self-cleaning coating for various industrial devices such as solar panels and tunnel lights. [12] Despite the wide application of TiO_2 in water treatment industries, its application in organic synthesis remains limited. The wide band gap of TiO_2 requires a high energy light source for excitation, such that TiO_2 catalyzed organic reactions require use of high energy UV light.[13] The use of high energy UV light, however, poses health risks to researchers and many substrates may also be incompatible with such high energy UV light. Recent developments of TiO_2 catalyzed reactions reveal that the TiO_2 band gap may be shortened by means of surface interactions of a photosensitizer, permitting light absorption of the TiO_2-sensitizer complex in the visible light region.[13,14,15,16] Notably, in 2016, Noel and co-workers reported visible light induced photocatalytic synthesis of disulfide molecules using TMEDA as a photosensitizer (Scheme2 a).[17] In 2016, Chen and co-workers further reported dye sensitized TiO_2 catalyzed oxidation of sulfides (Scheme2 b).[18]

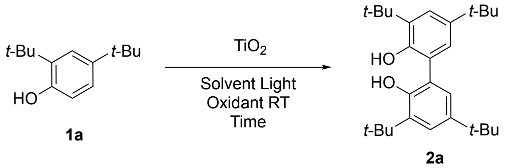
Scheme 2. TiO_2 Photocatalytic Reactions



To the best of our knowledge, no oxidative coupling of phenols has been reported using titanium derived catalysts. We envisioned that the high oxophilic nature of TiO_2 would cause the phenol hydroxyl group to interact via coordination or ligand exchange. Alternately, the phenol could hydrogen-bond to the oxygens of the TiO_2 structure. The resultant TiO_2-phenol adduct could potentially be activated with visible light giving rise to an excited state from which phenol coupling reactions could occur. Herein, we disclose the first heterogeneous TiO_2 catalyzed photocatalytic oxidative coupling of phenols using air and blue light (Scheme2 c).

Exploration of TiO_2 as a photocatalyst commenced with the readily oxidized substrate 2, 4-di-*tert*-butylphenol (see in Supporting Information for full optimization table). An excess of TiO_2 powder (3.0 equiv) was employed even though it is a catalyst, as reaction would only occur on the surface and the cost of TiO_2 is low. Screening different solvents (Table 1, entries 1-4) with UVA light (370 nm) light revealed that use of hexafluoroisopropanol was essential as has been noted previously in phenolic coupling.[7,10, 19] Exploration of other light sources revealed that white LEDs were ineffective (entry 5) whereas 440 nm light (blue LEDs) was almost as effective (entry 6). A longer reaction time (18 h vs 12 h) under these latter conditions gave a higher yield (entry 7). Use of air was equally effective (entry 8). On the other hand, lower yields were observed with lower amounts (1.0 equiv) of TiO_2 (entry 9). Control experiments without light (entry 10), air/oxygen (entries 11-12), or TiO_2 (entry 13) all failed to provide any product showing that each component was required.

Table 1. Reaction Optimization[a]

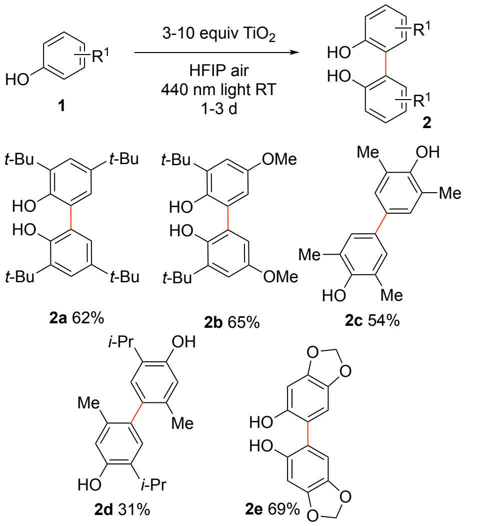


Entry	Solvent	Light	Atm	TiO_2 (equiv)	Yield **2a** (%)[b]
1	**MeOH**	370 nm	O_2	3.0	dec
2	**acetone**	370 nm	O_2	3.0	dec
3	**DCM**	370 nm	O_2	3.0	dec
4	**HFIP**	**370 nm**	O_2	3.0	31
5	HFIP	**white LED**	O_2	3.0	–
6	HFIP	**440 nm**	O_2	3.0	27
7	HFIP	440 nm	O_2	3.0	40[c]
8	HFIP	440 nm	**Air**	3.0	40[c]
9	HFIP	440 nm	Air	**1.0**	25[c]
10	HFIP	**no light**	O_2	3.0	–
11	HFIP	370 nm	**Ar**	3.0	–
12	HFIP	440 nm	**Ar**	3.0	–
13	HFIP	440 nm	O_2	**0.0**	–

[a]Reaction conditions: 2, 4-di-*tert*-butylphenol (0.48 mmol), 2.0 mL solvent, 12 h. [b] Isolated yield. Dec = decomposition, no recovered starting material and no **2a**. [c] 18 h, yield from ^1H NMR spectroscopy using dioxane as an internal standard.

A set of substituted phenols was examined for phenol-phenol C-C coupling using the optimized TiO_2 reaction conditions (Scheme 3). Ten biphenol adducts were synthesized in 31-69% isolated yields. The 2,4-disubstituted phenols (**2a**, **2b**) generally performed better than phenol substrates with different substitution patterns. Reaction of a phenol substrate with only an open *para*-position resulted in the *para-para* adduct with good efficiency (**2c**). For a substrate with both *ortho*- and *para*-positions available for reaction, the *para-para* coupling product **2d** was the major product. In the case of sesamol with two *ortho*-positions available, reaction occurred at the less hindered position to generate **2e** with high efficiency. Reaction using 4-amino-phenol substrate led formation of a purple mixture of unknown composition, most likely from competitive quinone immine formation[20] (see Supporting Information). Phenols with electron withdrawing nitro, formyl, or bromo groups were unreactive (see Supporting Information).

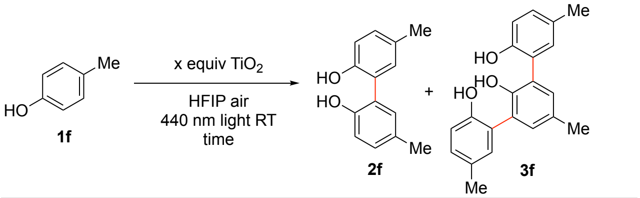
Scheme 3. Substrate Scope[a]



[a]Reaction conditions: **1** (100 mg), 3-10 equiv TiO_2, HFIP (0.25 M), 440 nm light, air, 1-3 d.

Challenging mono-substituted phenols with two open *ortho*-position were next examined. In particular, such substrates can undergo uncontrolled oxidative coupling to generate tri-phenols, and higher order oligomers. For a *para*-cresol, use of 3.0 equiv TiO_2 and a 48 h reaction time return 46% unreacted starting material and provided 31% of dimer **2f** along with 17% of trimer **3f** corresponding to 94% mass recovery (Table 2, entry 1). This result corresponds to 57% of dimer **2f** based on recovered starting material. With larger amounts (25 equiv) of TiO_2, greater conversion could be achieved (entry 2) but with poorer mass recovery and lower yield based on recovered starting material. Upon using longer reaction times, the yield of dimer **2f** also declined (entries 3-4). With even greater amounts of TiO_2 (50 equiv) and a shorter reaction time (entry 5), good mass recovery could be obtained, but the yield of dimer did not improve and far more trimer was obtained.

Table 2. Reaction Condition Screening for 1f [a]

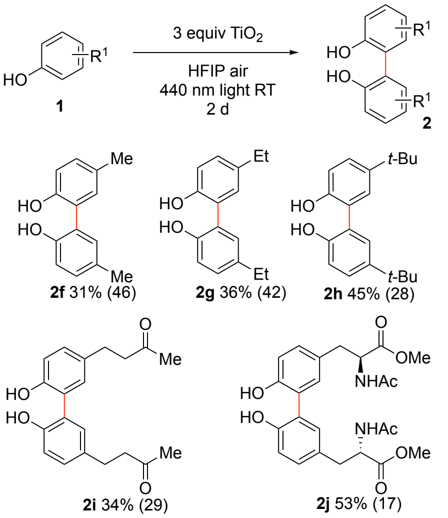


Entry	Time (h)	TiO_2 (equiv)	Recovered **1f** (%)	Yield **2f** (%)[b]	Yield **3f** (%)[b]
1	48	3.0	46	31	17
2[c]	26	25	30	35	8
3[c]	48	25	13	24	33
4[c]	60	25	5	11	42
5[c]	19	50	37	30	27

[a]Reaction conditions: **1f** (0.93 mmol), 2.0 mL HFIP [b] Isolated yield. [c] 5.0 mL HFIP.

Examination of addition mono-substituted phenols was thus undertaken use the best conditions (3 equiv TiO_2, 2 d) as shown in Scheme 4. Similar results were seen for the *para*-ethyl product **2g** but the *para-tert*-butyl compound **2h** formed in higher yield (45%). Raspberry ketone 1i coupled with similar efficiency as *para*-cresol. N-Acetyl-L-tyrosine methyl ester coupled in a notable 53%, the highest reported yield for this dimer via a nonenzymatic method to date (c.f. 40% in Scheme 1c).[10] It appears that sterically larger *para*-groups partially prevent further couplings of the dimers (e.g. **2h, 2j**).

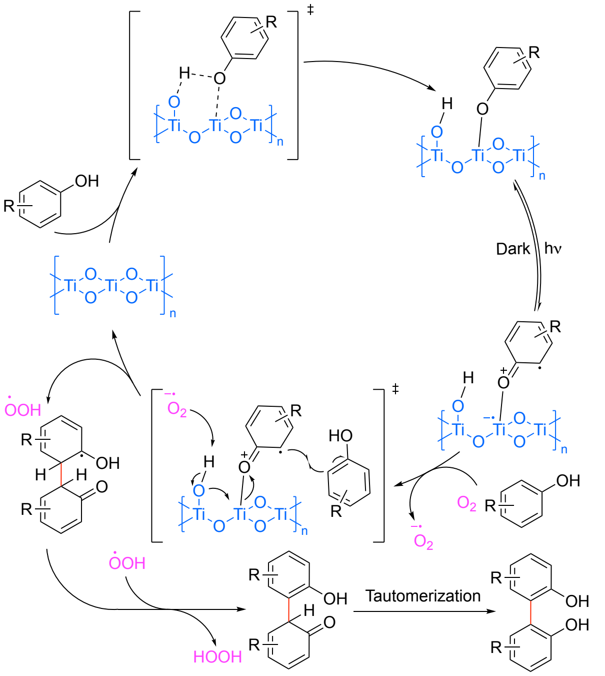
Scheme 4. Substrate Scope[a]



[a]Reaction conditions: **1** (100 mg), 3 equiv TiO_2, HFIP (0.25 M), 440 nm light, air, 2 d, numbers in parentheses are recovered **1**.

A mechanism for this TiO_2 catalyzed phenol-phenol coupling reaction was proposed (Scheme 5). The phenol first binds to Ti forming a Ti-phenol complex. A phenol cation radical then forms after photoexcitation of the Ti-phenol complex and ligand to metal charge transfer (LMCT).[21] The terminal oxidant, dioxygen subsequently removes one electron from the conducting band of Ti generating an electrophilic Ti-phenoxonium adduct that undergoes nucleophilic addition by a neutral phenol. Deprotonation of the titanium-hydroxo by superoxide regenerates TiO_2. The resultant peroxyl radical can abstract a hydrogen from the biphenol adduct which upon tautomerization forms the product.

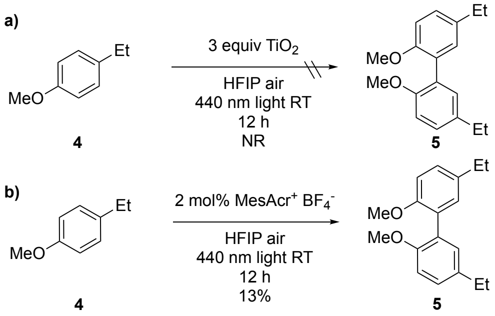
Scheme 5. Proposed Mechanism



To determine whether binding of the substrate to the TiO_2 was likely, a control reaction using anisole was performed (Scheme 6b).

When an acridinium photocatalyst was used in place of TiO_2, dimer **5** was observed indicating that anisole **4** is oxidizable under photocatalytic conditions. However, no reaction was observed using anisole **4** upon photoirradiation with the TiO_2 system (Scheme 6a). Thus, it appears that phenoxy coordination to the TiO_2 is necessary in this system. A positive KI test verified the generation of hydrogen peroxide during reaction (see Supporting Information). In addition, a color change from white to orange was observed when TiO_2 was mixed with *p*-cresol. No color change was observed when TiO_2 was mixed with the corresponding anisole (see Supporting-Information).

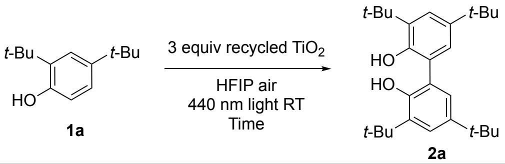
Scheme 6. Ti-Anisole Binding Test[a]



[a]Reaction conditions for Scheme 6a: **4** (0.73 mmol), 3.0 equiv TiO_2, HFIP (0.25 M), 440 nm light, air, 12 h. See Supporting Information for procedures; reaction condition for Scheme 6b **4** (0.73 mmol), $MesAcr^+BF_4^-$ (0.015 mmol), HFIP (0.25M).

To assess whether reuse the heterogeneous TiO_2 photocatalyst was simple and practical, the TiO_2 photocatalyst was recycled after reaction through centrifugal separation. No significant deactivation of TiO_2 photocatalyst was observed upon recycling three times (Table 3).

Table 3. TiO_2 Recyclability Test[a]

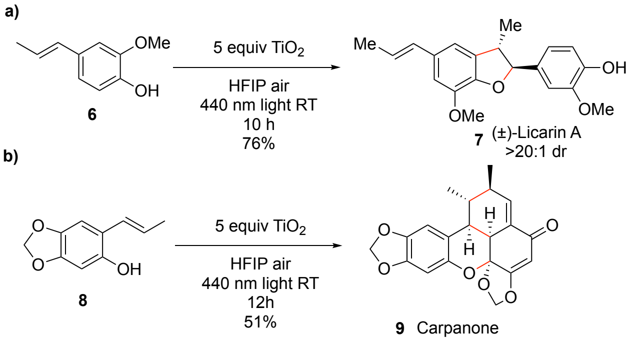


Entry[a]	yield **2a** (%)[b]
1	46
2	41
3	47
4	44

[a]Reaction conditions: 2, 4-di-*tert*-butylphenol (0.48 mmol), 3.0 equiv recycled TiO_2, HFIP (0.25 M), 440 nm light, air, 1 d. See Supporting Information for procedures. [b] isolated yield.

Alkenylphenols also underwent facile oxidative coupling using this system. For example, treatment of *para*-alkenylphenol **6** caused α-O and β-5 coupling to form neolignan natural product licarin A in 76% yield (Scheme 7a) as predominantly the trans diastereomer. This result compare favorably to a copper-catalyzed reaction using air as the oxidant (60% yield).[22] *ortho*-Alkenylphenol **8** underwent β-β coupling followed by Diels-Alder cyclization to form the natural product carpanone (Scheme 7b).[23,24]

Scheme 7. Neolignan Natural Product Synthesis[a]



[a] See Supporting Information for procedures and reaction conditions.

In conclusion, we have developed a selective oxidative phenol and alkenylphenol coupling protocol by means of light and a TiO_2 photo catalyst. This photocatalyst is inexpensive and environmentally benign. Further, the TiO_2 is readily removed by centrifugation and could be reused multiple times. During the coupling process, a TiO_2-phenol complex is hypothesized to be activated through a ligand to metal charge transfer effect (LMCT) Thus, the photocatalyst not only enables electron transfer, but also plays a key role by coordinating the phenol substrates which would allow greater modification of outcomes compared to outer sphere electron transfer catalysts.[10] This TiO_2 photocatalytic system has also proven effective in alkenyl phenol couplings to form neolignan natural products via both C-C and C-O bond formation.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. See FID for Publication for additional information.

Experimental procedures and NMR spectral copies (PDF)

FAIR data, including the primary NMR FID files, for compounds (ZIP)

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Notes

The authors declare no competing financial interest.

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