ORGANIC LETTERS

XXXX
Vol. XX, No. XX
000–000

Iron-Catalyzed Oxidative Cross-Coupling of Phenols and Alkenes

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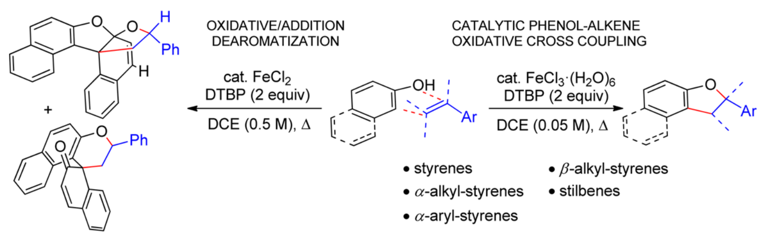
Received May 31, 2013

ABSTRACT



A novel bioinspired iron-catalyzed oxidative cross-coupling reaction between phenols and conjugated alkenes was developed. This method enables the direct coupling of phenols with styrene, α-alkyl- and α-arylstyrenes, β-alkyl styrenes, and stilbenes, thereby providing a new strategy for the preparation of the pharmacologically important 2,3-dihydrobenzofuran motif. In addition, this study revealed that under a different set of conditions an oxidative/addition dearomatization reaction of 1,1′-bi-2-naphthol (BINOL) with styrene can take place.

Oxidative coupling is one of Nature's most commonly used synthetic tools for the structural expression of complex oligo- and polyphenolic assemblies.[1] Of particular interest is the self-coupling of the phenol group of phenyl propanoids and natural stilbenes with the conjugated alkene unit of a second molecule. This phenol–alkene oxidative coupling reaction results in the formation of the 2,3-dihydrobenzofuran unit(s) found in many natural phenols (as in **1**, **2**, and **3**, in Scheme 1). Although many plants utilize this metalloenzymatic single-electron oxidative oligomerization for the production of specific metabolites that are essential for plant growth and protection,[1a,2] a comparable catalytic version of this oxidative cross-coupling method has not been developed.

Chemists have, however, applied the phenol–alkene oxidative coupling reaction for the self-merging of natural and natural-like phenylpropanoids and stilbenes.[3] Generally, stoichiometric single-electron metal oxidants, such as AgOAc,[4] Ag_2O,[5] MnO_2,[6] Ce(IV),[7] and $FeCl_3$,[6,8] were used, but in many cases the reactions were not efficient and suffered from poor regio- and chemoselectivity.[3,5,9] In the absence of a catalytic phenol–alkene oxidative cross-coupling reaction that can offer advanced synthetic opportunities, in terms of chemo- and stereoselectivity, other approaches, based on metalloenzymes, such as HRP/H_2O_2, P450, or laccases were studied, providing only partial solutions.[3,10] The anodic [3 + 2] cycloaddition reaction of phenols with alkenes[11] can offer access to a large number of dihydrobenzofuran derivatives via phenoxonium ion intermediates.

The dihydrobenzofuran structural motif is considered to be one of the most important heterocycles and is found in

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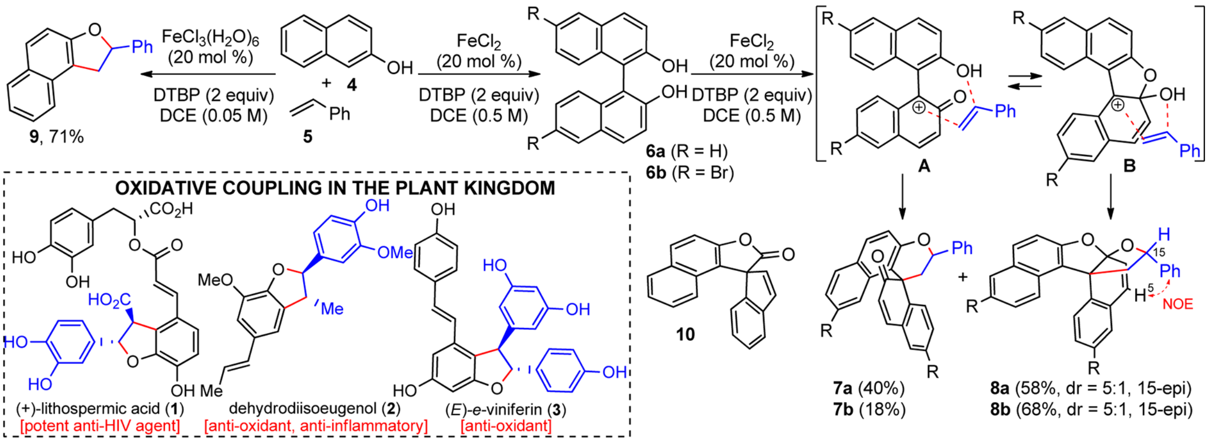
Scheme 1. Fe(II)-Oxidative/Addition Dearomatization and the Fe(III)-Catalyzed Oxidative Cross-Coupling Reactions



many biologically active natural products (as exemplified in Scheme 1).[12] Several synthetic strategies for the preparation of specific compounds have been developed, as well as complementary methods based on multistep syntheses to assemble active dihydrobenzofurans.[13,14]

Here we present an unpresented efficient catalytic iron-based phenol–alkene oxidative cross-coupling reaction, which provides direct entry to polysubstituted 2,3-dihydrobenzofurans. Our regio-, chemo-, and stereoselective method enables direct coupling of phenols with styrene derivatives in a formal [3 + 2] cycloaddition manner (Scheme 1) and thereby provides a new strategy for the preparation of the pharmacologically important 2,3-dihydrobenzofuran motif.[12,15]

Following strategies similar to those previously employed for the iron-based cross dehydrogenative coupling (CDC) reactions[16,17] of phenols with β-ketoesters and α-substituted-β-ketoesters,[18,19] we studied the oxidative coupling reaction of 2-naphthol (**4**, 0.5 mmol) and styrene (**5**, 1 mmol), with $FeCl_3$ (20 mol %) as the catalyst and tBuOOtBu (DTBP, 2 mmol) as the oxidant in DCE (0.5 M) at 80 °C (Table 1, entry 1). Unfortunately, under these conditions only BINOL **6a** was obtained. However, unexpectedly, with $FeCl_2$ (20 mol %) as the catalyst (entry 2), compound **6a**, after being formed, underwent a rapid oxidative/addition dearomatization[20] reaction with styrene to give a mixture of the constitutional isomers **7a** and **8a** (Scheme 1). Although compound **7a** was formed as a single stereoisomer (27% yield),[21] compound **8a** was isolated as a mixture of diastereoisomers (28%, 15-epi, dr = 5:1). The structures of **7a** and **8a**, as well as other key products in

Table 1. Optimization Study for the Oxidative Coupling Reaction between 2-Naphthol **4** and Styrene **5**[a,b]

entry	C (mol/L)	[Fe]	**7a** (%)	**8a** (%)	**9** (%)
1	0.5	$FeCl_3$	–[c]	–	–
2	0.5	$FeCl_2$	27	28	–
3	0.5	$FeCl_3\cdot(H_2O)_6$	[15][d]	[15][d]	[40][d]
4	0.05	$FeCl_2$	–	–	22
5	0.05	$FeCl_2\cdot(H_2O)_4$	–	–	[25][d]
6	0.05	$FeCl_3$	–	–	45
7	0.05	$FeCl_3\cdot(H_2O)_6$	–	–	71
8[e]	0.05	$FeCl_3\cdot(H_2O)_6$	–	–	65
9[f]	0.05	$FeCl_3\cdot(H_2O)_6$	–	–	60
10[g]	0.05	$FeCl_3\cdot(H_2O)_6$	–	–	42
11[h]	0.5	$FeCl_3$	–	–	[43][d]
12[i]	0.05	$FeCl_3$	–	–	[35][d]
13	0.05	no metal	–[j]	–	–

[a] Conditions: **4** (1 mmol), **5** (0.5 mmol), [Fe] (20 mol %), DTBP (2 mmol), DCE, 80 °C, 1 h. [b] Isolated yield. [c] Only BINOL was formed. [d] HPLC yield is given in square brackets. [e] Similar conditions except **4** (0.5 mmol), **5** (1 mmol). [f] $FeCl_3\cdot(H_2O)_6$ (10 mol %) was used. [g] The reaction was performed at 60 °C. [h] Solvent-free conditions; **4** (0.5 mmol), **5** (1 mL), $FeCl_3$ (20 mol %), DTBP (1 mmol), 80 °C. [i] 1,10-Phenanthroline (10 mol %) was used as an additive in the reaction mixture. [j] No reaction.

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(21) NOESY experiments failed to provide the data that will enable the determination of the relative configuration of compound **10a**.

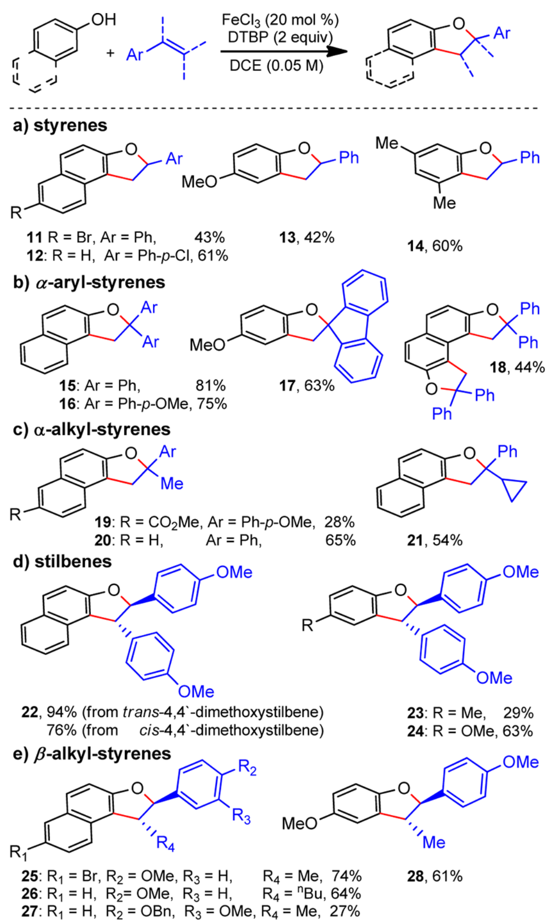
this work, were determined by 1D and 2D NMR. The relative configuration of the major diastereoisomer of **8a** was elucidated on the basis of NOE correlations between Ph-H and H-5. We assumed that, under the Fe(II)/DTBP conditions, BINOL underwent two single-electron oxidation steps, generating intermediates **A** and **B** (Scheme 1). The latter active intermediates reacted immediately with styrene in a formal [4 + 2]-cycloaddition or a [3 + 2]-cycloaddition fashion, affording isomers **7a** and **8a**, respectively (Scheme 1). Interestingly, when BINOL **6a** was subjected to the same reaction conditions in the absence of a nucleophile, spirolactone **10** was obtained via pinacol-type rearrangement of intermediate **B** (Scheme 1), a transformation that was recently reported by Tsubaki.[22] Moreover, when naphthol **4** and styrene **5** were reacted in the presence of the free radical scavenger BHT (3,5-ditert-butyl-4-hydroxytoluene, 2 equiv), the homocoupling product BINOL **6a** was obtained as a single product, with no evidence of **7a** and **8a**, suggesting that the oxidative/addition dearomatization coupling of BINOL does indeed involve a free radical process.

Better results were obtained when BINOL **6a** or **6b** was used instead of naphthol **4**. Under the same reaction conditions [**5** (2 equiv), $FeCl_2$ (20 mol %), DTBP (2 equiv), DCE (0.5 M), 80 °C] coupling products **7a** and **8a** were isolated in 40% and 58% (*dr* = 5:1) yields, respectively (98% overall yield), and **7b** and **8b** in 18% and 68% (*dr* = 5:1) yields, respectively.

Extensive optimization studies revealed that the reaction is sensitive to both the iron source and the reaction concentration. For example, when $FeCl_3 \cdot (H_2O)_6$ (20 mol %, Table 1, entry 3) was used as the catalyst instead of $FeCl_3$ or $FeCl_2$ (DCE, 0.5 M), the desired dihydronaphthofuran **9** was observed by HPLC together with **7a** and **8a**. When a diluted concentration was used (0.05 M), with $FeCl_2$, $FeCl_2 \cdot (H_2O)_4$, or $FeCl_3$ as the catalyst, dihydronaphthofuran **9** was obtained as a single product, albeit in low yield (entries 4–6). Fortunately, with $FeCl_3 \cdot (H_2O)_6$ (20 mol %) as the catalyst under diluted conditions [naphthol **4** (1 mmol) and styrene **5** (0.05 mmol), DTBP (2 mmol), DCE (10 mL), 80 °C, 1 h], the desired product **9** was isolated in 71% yield (entry 7). The evidence that **9** was isolated in low yield when anhydrous $FeCl_3$ (20 mol %) was used as the catalyst (entry 6) suggests that water might play a role in the proton transfer process of the reaction.[18a] Other reaction parameters were also examined, including inversion of the molar ratio of the coupling partners (entry 8, 65% yield), catalyst loading (entry 9, 60% yield), reducing the reaction temperature (entry 10, 42% yield), or using solvent-free conditions (entry 11). The introduction of 1,10-phenanthroline (10 mol %) as an additive, which was found to be a rewarding tactic for the coupling of phenols with β-ketoesters, was also examined (entry 12).[18b] Other metal salts, such as $Fe(ClO_4)_3$, $FeBr_3$, $Fe(acac)_3$, and CuBr, failed to promote the transformation, and in control experiments that were performed either in the absence of metal (entry 13) or DTBP (not shown), or when the coupling was performed in the presence of radical scavenger BHT (2 equiv), the desired coupling product was not observed.

Next, we investigated the scope of this simple yet highly effective catalytic phenol–alkene oxidative cross-coupling reaction. The results of our synthetic efforts are shown in Scheme 2. In general, naphthol derivatives (for example, as in products **11**, **18**, and **19**) and electron-rich phenols (as in products **13**, **14**, and **23**) were found to be suitable coupling partners. Under the oxidative conditions, 4-chlorostyrene reacted with naphthol **4** to afford 2-(4-chlorophenyl)-1,2-dihydronaphthofuran **12** in 61% yield (Scheme 2a). α-Arylstyrenes were found to be excellent coupling partners (Scheme 2b), and their reactions reached completion within several minutes, affording the corresponding 2,2-diaryl-2,3-dihydronaphtho- and benzofurans **15**–**18** in good yields (81%, 75%, 63%, and 44% respectively).

Scheme 2. Scope of the Phenol-Alkene Oxidative Cross-Coupling Reactions[a,b]



[a] For the exact conditions see the Supporting Information. [b] Isolated yields.

The tendency of α-alkylstyrenes to undergo cation-based reactions reduced the efficiency of these reactions. A partial solution lay in lowering the reaction temperature to 60 °C. Under these conditions, compounds **19**–**21**

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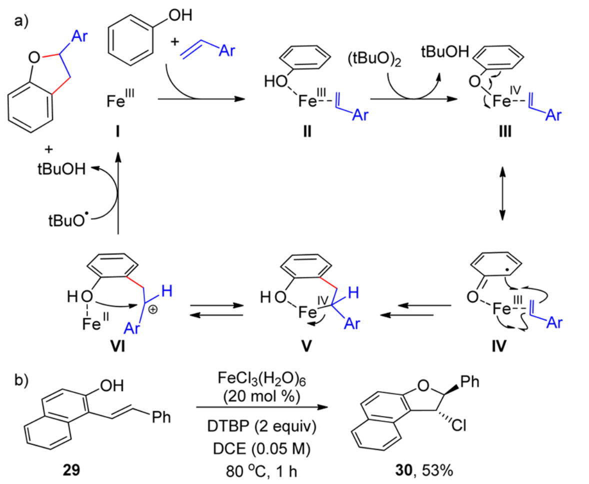
(Scheme 2c), which have methyl or cyclopropyl and aryl substituents at C-2 of the furan ring, were isolated in 28%, 65%, and 54% yields, respectively.

We then turned our efforts to evaluating stilbenes and β-alkyl styrenes as partners (Scheme 2d and 2e). Successful coupling of these partners should provide direct entry to stilbenoid and phenylpropanoid derivatives, two of the most important classes of natural phenolic products. Fortunately, while stilbene was inactive under our general conditions and 4-methoxystilbene underwent a cationic self-dimerization reaction and failed to participate in the oxidative coupling process, the more electron-rich stilbene, *trans*-4,4′-dimethoxystilbene, reacted smoothly with naphthol, *p*-cresol, and 4-methoxyphenol to afford the corresponding coupling products **22**–**24** in 94%, 29%, and 63% yields, respectively. Importantly, the *cis*-4,4′-dimethoxystilbene displayed reactivity similar to that of the *trans* isomer, affording **22** in 76% yield. In addition, we found that β-alkylstyrenes are suitable coupling partners, enabling entry to dehydrodiisoeugenol **2** analogues. For example, when *trans*-*p*-anethole (*p*-1-propenylanisole) was reacted with either 6-bromonaphthol or 4-methoxyphenol, the coupling products **25** and **28** were isolated in good yields (74% and 64%, respectively), and when naphthol **4** was coupled with *cis*-1-(1-hexenyl)-4-methoxybenzene, dihydronaphthofuran **26** was obtained in 61% yield. However, when the benzyl-protected isoeugenol was reacted with naphthol **9**, the corresponding dihydronaphthofuran **27** was obtained in a low yield of 27%, probably due to the deactivating property of the *m*-OMe group. In all cases, a single diastereoisomer was obtained, and based on the $^3J_{H\text{-}2/H\text{-}3}$ coupling constants the relative configuration was assigned as *anti*.

For this reaction, we postulated a chelated radical-coupling mechanism (Scheme 3a). Thus, in the course of the reaction, the Fe-chelated species **II** could be oxidized to give the electrophilic phenol species **IV**, which can then undergo a addition reaction with an alkene group to afford, after tautomerization, the intermediate **V**. The reductive elimination step (from **V** to **I**) might involve the formation of an iron-chelated benzylic carbocation species **VI**. Possible support for the existence of this species may be seen in the fact that the reaction of naphthol **4** with either *cis*- or *trans*-4,4′-dimethoxystilbene afforded only the more energetically stable *anti*-**22**. In addition, the observation that electron-donating groups, which can stabilize the positive charge generated in **VI**, are obligatory in the coupling of stilbenes (products **22**–**24**) and β-alkylstyrenes (products **25**–**28**) provides further support for the proposed mechanism.

An alternative mechanistic pathway for the reductive elimination step, which involves β-hydride elimination of intermediate **V** to afford Heck-type intermediates such as **29** (Scheme 3b), may also be suggested. According to this scenario, compound **29** would undergo Lewis acid catalyzed cyclization to afford compound **9**. Although such a cyclization is electronically unfavorable, it has been documented in the literature as taking place on similar compounds.[23] To examine this hypothesis, **29** was prepared and reacted under our general conditions. First, under Lewis acidic conditions, in the absence of an oxidant [$FeCl_3 \cdot (H_2O)_6$ (20 mol %), DCE (0.05 M), 80 °C, 5 h], **29** was stable and was fully recovered. In contrast, when the reaction was performed under oxidative conditions in the presence of DTBP (2 equiv), *anti*-3-chloro-2-phenyl-2,3-dihydronaphthofuran **30** was isolated in 53% yield (88% yield based on $FeCl_3$ as the limiting reagent). The fact that dihydronaphthofuran **9** was not observed in either experiment (by HPLC analysis) challenges a mechanistic pathway involving a β-hydride elimination step.

Scheme 3. Postulated Mechanism



In conclusion, a novel metal catalyzed oxidative cross-coupling reaction of phenols and conjugated alkenes based on iron chemistry was developed. The highly efficient and sustainable method enables direct entry to polysubstituted-2,3-dihydrobenzofurans in a regio-, chemo-, and stereoselective manner. This valuable synthetic tool, inspired by the biosynthetic phenol–alkene oxidative coupling reaction, can be applied for diverse syntheses of bioactive phenolic natural products and other materials containing the 2,3-dihydrobenzofuran structural motif. During this study an oxidative/addition dearomatization reaction of 1,1′-bi-2-naphthol (BINOL) with styrene was discovered, a chelated radical-coupling mechanism was proposed, and a possible mechanistic pathway that involves β-hydride elimination was ruled out. Further exploration of the chemistry's scope and limitations is currently underway in our laboratory.

Acknowledgment. We wish to thank Dr. Amira Rudi (BGU) for NMR spectroscopic assistance. This research was supported by the Israel Science Foundation (Grant No. 1406/11).

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

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The authors declare no competing financial interest.