Selective Iron-Mediated C- and O-Addition of Phenolic Nucleophiles to a Cyclohexadiene Scaffold Using Renewable Precursors

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ABSTRACT: Renewable phenols have been investigated as nucleophiles for the addition to a cationic cyclohexadienyl iron carbonyl scaffold. Benign conditions compatible with solvents such as ethanol and water were developed, and for the first time, selective C- or O-addition could be achieved. In addition, a novel atom-economic approach to forming the C-addition products directly from the neutral precursor complex in a single step using a catalytic acid is described. The formed C-addition product could then be selectively demetalated to form one of two different product classes, a functionalized arene or a cyclohexadiene.

KEYWORDS: Iron, Phenols, Cyclohexadiene, Metal carbonyl, Renewable resources, Green chemistry, Water

INTRODUCTION

Biomass is becoming increasingly important as a renewable feedstock to provide the chemicals needed for our society.1 A variety of platform chemicals can be obtained from feedstocks, such as lignin, which is rich in aromatic and phenolic compounds,2,3 and cellulose, abundant in mono- and polysaccharides.3 However, new chemical methods are needed to connect the often oxygen-rich building blocks obtained from biomass. Organometallic chemistry can provide tools for this purpose, in particular if inexpensive and abundant metals, such as iron, rather than rare transition metals, are used.5 Iron has the ability to coordinate dienes,6,7 a feature that can be exploited for synthetic purposes. Upon coordination, the carbon atoms adjacent to the diene are activated for hydride abstraction, resulting in the formation of a stable cationic iron carbonyl dienyl cation.8,9 The cationic iron carbonyl complex formed is bench stable, with a long shelf life, and can react with a wide range of nucleophiles to form carbon–carbon or carbon–heteroatom bonds.10–13 This nucleophilic coupling with iron complexes occurs in a highly regio- and stereo-selective manner. The regioselectivity of the initial cation formation is governed by the substitution pattern of the diene. Subsequent nucleophilic addition then takes place stereoselectively, to the opposite face of the coordinated iron carbonyl moiety.12,13 Other advantages of this methodology are the mild reaction conditions used, and the fact that the tailoring of reaction conditions for each class of nucleophile is generally not required. Applications of this method include the synthesis of natural products, such as siculinine14 and clausine K,15 antiviral compounds, such as oseltamivir phosphate (Tamiflu);16,17 probes for infrared spectroscopy,18 as well as parallel synthesis applications.19 While anilines have been widely shown to react as nucleophiles via selective C- or N-addition,20–23 the analogous reactivity of phenols has not been examined to the same extent.18,24 Considering also that phenols can potentially be sourced from lignin or other biomass sources, we have investigated their application as nucleophiles using the cationic iron carbonyl methodology. The reaction should ideally proceed under benign conditions using renewable and nontoxic solvents and should be selective for the C-addition or O-addition product. Our results from these studies are disclosed herein.

RESULTS AND DISCUSSION

Stable cationic iron carbonyl dienyl cations can be formed via hydride abstraction from a neutral iron carbonyl complex

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Supporting Information
leaving group, such as an alkoxy- or acetoxy group with an acid (Scheme 1, path b).\(^{25}\) We opted for the second of these strategies in the preparation of the initial cationic iron complex. Once formed, the complex can react with a wide range of nucleophiles, including alcohols,\(^{19}\) amines,\(^{26}\) amides,\(^{27}\) azide,\(^{16}\) hydride,\(^{16}\) carbanate,\(^{27}\) thiol,\(^{28}\) enolate,\(^{26}\) and malonate,\(^{29}\) allyl silanes,\(^{30}\) electron rich aromatics\(^{31}\) and heterocycles,\(^{30}\) organocuprates,\(^{26}\) organolithium reagents,\(^{20}\) organozinc reagents,\(^{30}\) Grignard reagents,\(^{26}\) phosphines,\(^{33}\) phosphites,\(^{34}\) and halides.\(^{35}\)

At the outset of our investigation, we aimed to perform the selective C- and O-addition of phenolic nucleophiles to cationic \(\eta^1\) iron carbonyl cyclohexadienyl complex 1 (Scheme 2). The development of green reaction conditions was also an important criterion. The precursor for complex 1, diene 2, could be synthesized via a cycloaddition reaction between an acrylate ester and furan,\(^{36}\) both available from biorenewable sources (Scheme 2).\(^{37−40}\) Alternatively, structurally similar dienes can also be made via biocatalytic cis-dihydroxylation of aromatic molecules, and these have been exploited using iron carbonyl chemistry.\(^{16,41}\)

Sesamol, a component of sesame oil,\(^{51}\) was selected as a model nucleophile for the optimization and preliminary experiments indicated that it could undergo selective C- or O-addition in good yields. Solvents were first evaluated, prioritizing the use of green and sustainable solvents\(^{32}\) and seeking to find alternatives to dichloromethane, acetonitrile, and tetrahydrofuran, commonly used for these reactions. 2-Methyltetrahydrofuran, accessible from the platform chemical levulinic acid,\(^{33,54}\) afforded disappointing results (Table 1, entry 1), while ethyl acetate performed slightly better but still afforded relatively low yields of the C-addition product 3a (entry 2). Using methyl ethyl ketone or methyl acetate saturated with water gave somewhat better results, with yields in the range of 59−67% (entries 3 and 4). However, we were happy to find that the reaction proceeded rapidly in 92% yield at room temperature using ethanol as an environmentally benign solvent (entry 5). Water could also be used as solvent, affording 3a in 75% yield (entry 6). The slightly lower yield in this case may to some extent be due to solubility issues.

### Table 1. Optimization of Reaction Conditions for the C-Addition of Sesamol to Cationic Iron Carbonyl Complex 1

| entry | solvent | time (h) | yield(%) |
|-------|---------|---------|----------|
| 1     | 2-MeTHF | 4.5     | 17       |
| 2     | EtOAc   | 4.5     | 41       |
| 3     | methyl ethyl ketone | 4.5 | 67 |
| 4     | wet MeOAc\(^{c}\) | 4.5 | 59 |
| 5     | EtOH (>99%) | 2 | 92 |
| 6     | H\(_2\)O | 2      | 75       |
| 7     | EtOH / H\(_2\)O (9:1) | 2 | 60 |

\(^{a}\)1.1 equiv sesamol. \(^{b}\)NMR yield. \(^{c}\)Saturated with water.

However, attempts to combine ethanol and water as the solvent system significantly reduced the yields (entry 7). Ethanol or water were therefore found to be the solvents of choice.

A practical feature of this reaction is that the cationic iron carbonyl cyclohexadienyl complex 1 has a low solubility in ethanol and initially forms a turbid light-yellow suspension. As the starting material is consumed, the solution becomes clearer as the product is soluble in the solvent (Figure 1). This feature was used to monitor the ensuing reactions, which were allowed to react for an additional 2 h after becoming transparent, before being terminated.

Crystals of 3a, obtained by slow diffusion of water into a solution of the compound in methanol, were subjected to X-ray structure determination (Figure 2).

With optimized conditions in hand, a number of phenolic molecules were used as nucleophiles (Scheme 3). Reactions with sesamol and 2-naphthol proceeded in excellent yields (Scheme 3, compounds 3a and 3b). Addition of dihydroumberilferone, prepared by hydrogenation of the natural product umbiliferone,\(^{53}\) effected a simultaneous ring opening, affording ethyl ester 3d as the product in good yield. 4-Hexylresorcinol, used as a local anesthetic,\(^{56}\) and topical antiseptic,\(^{57}\) was also a competent nucleophile, producing 3e in 80% yield. Reaction with resorcinol, as expected, gave rise to both monosubstitution, forming 3c, and disubstitution, forming diastereomers 3f/3f'. However, through variation of stoichiometry, the reaction could be tailored to selectively afford either 3c or 3f/3f' in good yields. In terms of scope and limitations, the reaction worked well for highly activated...
phenols, such as those possessing a 1,3-alkoxy or hydroxyl substitution pattern. However, no reaction occurred using less activated nucleophiles, such as 1-naphthol and the naturally occurring compounds vanillin, eugenol, and umbelliferone (Figure 3). Somewhat surprisingly, syringol, bearing a 1,2,3-oxygen substitution pattern also gave no reaction under these conditions.

The reaction with sesamol was also performed in water with more vigorous stirring (1500 rpm), whereupon a light yellow precipitate was formed as a suspension. The crude product could be easily isolated by filtration and after column chromatography, product 3a was obtained in 89% yield (Scheme 4).

In order to switch the selectivity of the phenolic nucleophiles from C- to O-addition, we reasoned that the addition of a base in an aprotic solvent would favor formation of the O-addition product, which would be reversible under acidic conditions. Indeed, it was found that if a homogeneous base, such as triethylamine, was added, the O-addition was favored, and this process was subjected to further optimization studies (Table 2). It was found that this reaction was significantly more rapid than the corresponding C-addition, and the initial turbid suspension converted to a clear solution in a matter of seconds. In order to suppress the formation of the C-addition product, rapid addition of the base was found to be important. Optimal conditions therefore involved adding the nucleophile and base as a premixed solution to the cationic complex in the indicated solvent with vigorous stirring.

Good yields, around 80%, were obtained for several polar solvents (Table 2, entries 1–4). The somewhat lower yield when using diethyl carbonate as the solvent (entry 5) could be attributed to reduced solubility of both the starting material and the triethylammonium hexafluorophosphate byproduct, which formed an adhesive precipitate along the walls of the

**Table 2. Optimization of Reaction Conditions for O-Addition to Complex 1**

| entry | solvent        | temp (°C) | time (min) | yield (%) |
|-------|----------------|-----------|------------|-----------|
| 1     | dimethyl carbonate | RT’       | 2          | 80        |
| 2     | EtOAc          | RT’       | 2          | 80        |
| 3     | MeOAc          | RT’       | 2          | 80        |
| 4     | acetone        | RT’       | 2          | 81        |
| 5     | diethyl carbonate | RT’       | 2          | 67        |
| 6     | tert-butyl methyl ether | RT’   | 2          | 5         |
| 7     | EtOAc          | 0         | 2          | 56        |
| 8     | EtOAc          | 0         | 10         | 89        |

*NMR yield.

Figure 3. Naturally occurring nucleophiles that did not afford the C-addition product.
The addition of sesamol and 2-naphthol proceeded with good isolated yields of 4a and 4b, respectively. The O-addition reaction also proved to have a broader scope than the C-addition reaction. Syringol and eugenol, both of which gave no desired product under the C-addition conditions (Figure 3), could be applied to form 4c and 4d in excellent yields. In the same manner as the corresponding C-addition reaction, the stoichiometry of resorcinol, which has two phenolic oxygenons, was controlled in an attempt to selectively achieve a single or double addition. As a result, the diastereomeric double addition products 4e/4e’ were obtained in 80% yield by using 0.5 equiv of resorcinol. However, when using an excess of resorcinol, no product from the single O-addition of the nucleophile could be isolated, instead a mixture of the C-addition products was obtained. During our work, it was found that the O-addition products could rearrange to the corresponding C-addition products in the presence of a strong acid. When the O-addition product 4a was treated with a catalytic amount of acetic acid in ethyl acetate, no rearrangement occurred. However, changing the acid to p-toluenesulfonic acid in acetonitrile afforded the C-addition product 3a in good yield (Scheme 6). We reasoned that this rearrangement occurred through protonation and elimination of the newly installed phenol, thus regenerating carbocation 1. Subsequent C-addition of sesamol and concurrent regeneration of the acid afforded the rearranged product. In an attempt to access a wider range of C-addition products, the O-addition products of eugenol and syringol were evaluated using this method also but decomposed under the reaction conditions, and no desired product could be isolated. This encouraged us to attempt a new approach to forming the C-addition products directly from the neutral n^6 complex 5, without preforming the cationic n^6 complex, using catalytic acid. This would provide a more atom economic and benign synthetic route to the C-addition products (Scheme 7). To our delight, allowing the neutral complex 5 to react with 3 equiv of sesamol in acetonitrile using 10 mol % hexafluorophosphoric acid as a catalyst afforded the C-addition product 3a in 76% yield. Reducing the amount of nucleophile to 1.1 equiv afforded nearly the same yield, 72% (Scheme 7b). This is comparable in yield to the two-step process normally employed (Scheme 7a). However, the main benefits of this novel method are that one reaction step is eliminated, which includes the isolation of cation 1, where a large amount of diethyl ether is used in the precipitation step. Furthermore, this catalytic protocol removes the need for acetic anhydride and greatly reduces the amount of hexafluorophosphoric acid used. As a result the atom economy of the reaction increases from 61% (Scheme 7a) to 93% (Scheme 7b) providing a greener and more efficient synthetic route. The catalytic reaction was also performed using tetrafluoroboric acid, using 3 equiv of the nucleophile, affording 3a in 76% yield, indicating a similar performance to HPF6.

While iron carbonyl complexes of dienes are of interest in their own right, for instance as bioprobes, the corresponding demetalated products are more likely to find a wider application scope. Our next goal was thus to demonstrate the demetalation of the addition products by oxidative removal of the iron carbonyl moiety. Several protocols for the oxidative removal of iron carbonyl from a diene exist, with the most commonly used reagents being hydrogen peroxide under basic conditions, ceric ammonium nitrate, or trimethylamine N-oxide. Attempted demetalation of the C-addition product 3a using basic hydrogen peroxide or ceric ammonium nitrate resulted in decomposition.
of the starting material, possibly caused by oxidation of the phenol group. Using the milder oxidant trimethylamine N-oxide yielded the aromatized demetalated product, as indicated by earlier studies in the group, producing product 6 in excellent yield (Scheme 8, reaction a). To investigate if the uncomplexed diene could also be obtained from the same precursor, compound 3a was protected as a tert-butyldimethylsilyl ether 7 to make it less sensitive to oxidation (Scheme 8, reaction b). Silyl protection was followed by oxidation using H$_2$O$_2$/NaOH or cerium ammonium nitrate, a reaction performed in ethyl acetate at 0 °C temperature. To attain selective addition of phenolic nucleophiles to a cationic complex have been developed. The addition of phenolic nucleophiles to complex 3a resulted in decomposition of the starting material. For the first time, reaction conditions for selective C- or O-addition of phenolic nucleophiles to a cationic $\eta^1$ iron carbonyl cyclohexadienyl complex have been achieved. The addition of phenolic nucleophiles to complex 1 has been achieved using green reaction conditions, and these conditions were used to add a variety of naturally occurring phenolic nucleophiles to the complex in a selective manner. For C-addition, the reaction afforded the best results in ethanol or water at ambient temperature. To attain selective O-addition, the reaction was performed in ethyl acetate at 0 °C in the presence of triethylamine. Decomplexation of a C-addition product was then demonstrated, allowing for the formation of either an aromatized product or a cyclohexadiene structure, depending on the conditions used. Furthermore, a new method to form the C-addition products directly from the neutral $\eta^1$ iron carbonyl cyclohexadienyl precursor complex, using a catalytic acid, is also described. The catalytic method affords similar yields to the overall yield of the classical two step reaction, resulting in significantly improved atom economy as well as reduction in the amount of solvent and reagents used.

### CONCLUSIONS

For the first time, reaction conditions for selective C- or O-addition of phenolic nucleophiles to a cationic $\eta^1$ iron carbonyl cyclohexadienyl complex have been developed. The addition of phenolic nucleophiles to complex 1 has been achieved using green reaction conditions, and these conditions were used to add a variety of naturally occurring phenolic nucleophiles to the complex in a selective manner. For C-addition, the reaction afforded the best results in ethanol or water at ambient temperature. To attain selective O-addition, the reaction was performed in ethyl acetate at 0 °C in the presence of triethylamine. Decomplexation of a C-addition product was then demonstrated, allowing for the formation of either an aromatized product or a cyclohexadiene structure, depending on the conditions used. Furthermore, a new method to form the C-addition products directly from the neutral $\eta^1$ iron carbonyl cyclohexadienyl precursor complex, using a catalytic acid, is also described. The catalytic method affords similar yields to the overall yield of the classical two step reaction, resulting in significantly improved atom economy as well as reduction in the amount of solvent and reagents used.

### EXPERIMENTAL SECTION

#### Materials

Methyl 5-hydroxycyclohexa-1,3-diene-1-carboxylate and dihydroumbelliferone were synthesized according to literature procedures. All other chemicals and solvents were purchased from commercial sources and used without further purification unless otherwise noted.

#### Analytical Methods

$^1$H and $^{13}$C NMR spectra were acquired on a Varian MR 400 MHz instrument. Chemical shifts are reported in parts per million (ppm), using the residual solvent peak for reference. The following abbreviations are used for reporting peak multiplicities, s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and app (apparent), and all coupling constants (J) are reported in hertz (Hz). For diastereomeric mixtures, peaks which can be attributed to a single diastereomer are labeled d$_{d}$/d$_{t}$. ATR-FTR spectra were recorded on a PerkinElmer Spectrum Frontier infrared spectrometer with pike-GladiaATR module and are reported as the wavenumber (cm$^{-1}$) at the maximum of the indicated peak. Flash column chromatography was performed using a Biotage Isolera One using the indicated solvent system and Biotage SNAP KP-Sil columns for normal phase chromatography or Biotage SNAP KP-C18-HS columns for reversed phase chromatography. HRMS was performed using an Agilent 1290 infinity LC system equipped with an autoSampler tandem to an Agilent 6520 Accurate Mass Q-TOF LC/MS. The samples were diluted to ca. 10 μg/mL in MeCN and analyzed without a column, with a 0.3 mL/min flow rate using an isotopic method (50% water + 0.04% formic acid/50% MeOH + 0.04% formic acid). Samples were analyzed using an ESI source in positive mode (scan range 100–1700 m/z).

#### X-ray Crystallography

Intensity data for the Fe-complex were collected at 150(2) K on a Rigaku Supernova Dual EosS2 single crystal diffractometer using monochromated Cu K$\alpha$ radiation ($\lambda = 1.54184$ Å). Unit cell determination, data collection, and data reduction were performed using the CrystAlisPro software. A numerical absorption correction based on Gaussian integration over a multifaceted crystal model was employed. The structure was solved with SHELXT and refined by a full-matrix least-squares procedure based on F2 (SHELXL-2018/3). All nonhydrogen atoms were refined anisotropically. Hydrogen atoms were placed onto calculated positions and refined using a riding model. The OH$^−$ hydrogen atoms were located in the difference Fourier map and freely refined.

#### General Procedure for the C-Addition of Phenolic Nucleophiles to Complex 1

A microwave vial was charged with 1 (0.1 mmol) and...
the nucleophile (0.05–0.5 mmol). The vial was sealed and put under an argon atmosphere. Ethanol (1 mL) was added, and the mixture was stirred at room temperature until the mixture was clear and then for an additional 2 h. The reaction mixture was diluted with 4 mL of diethyl ether and filtered through a plug of basic aluminum oxide. The solvent was evaporated in vacuo, and the residue was purified using reversed phase flash chromatography (silica gel-C18, water/methanol).

**General Procedure for O-Addition of Phenolic Nucleophiles to Complex 1.** A microwave vial containing 1 (0.1 mmol) was cooled in an ice bath. To the complex, a precooled mixture of nucleophile (0.11 mmol) and Et₃N (0.2 mmol) in 1 mL of EtOAc was added under vigorous stirring. The mixture was left to react for 10 min in an ice bath and then allowed to warm to room temperature before being diluted with 4 mL of diethyl ether and filtered through a plug of basic aluminum oxide. The solvent was evaporated in vacuo, and the residue was purified using flash chromatography (silica gel, 1% Et₃N in CH₂Cl₂).

**Synthesis of C-Addition Product 3a in Water.** A microwave vial was charged with 1 (42.0 mg, 0.1 mmol) and sesamol (15.6 mg, 0.11 mmol). The vial was sealed and put under an argon atmosphere. One milliliter of deionized water was added, and the mixture was stirred vigorously (1500 rpm) at room temperature for 4.5 h. The precipitate was collected by filtration through a plug of Celite and washed with water. The plug was then washed with diethyl ether, dissolving the product, and the collected filtrate was dried by filtration through a plug of anhydrous magnesium sulfate. The solvent was evaporated in vacuo. Purification with reversed phase flash chromatography (silica gel-C18, water/methanol) yielded 32.6 mg (89%) of the C-addition product 3a.

**Rearrangement of O-Addition Product 4a to C-Addition Product 3a.** Compound 4a (50.1 mg, 0.121 mmol) and 2.5 mg (0.013 mmol) of p-toluenesulfonic acid monohydrate were dissolved in 1 mL of acetonitrile in a microwave vial. The mixture was stirred at room temperature for 16 h before being diluted with 4 mL of diethyl ether and filtered through a plug of basic aluminum oxide. The solvent was evaporated under a stream of nitrogen. Purification with reversed phase flash chromatography (silica gel-C18, water/methanol) yielded 33.8 mg (67%) of C-addition product 3a. The same reaction using tetrafluoroboric acid as the catalyst afforded 3a in 53% yield.

**Addition of Sesamol to Neutral Complex 5 Using Catalytic Acid.** To a microwave vial containing iron complex 5 (30.5 mg, 0.104 mmol) and sesamol (15.5 mg, 0.114 mmol, 1.1 equiv or 43.0 mg, 0.311 mmol, 3.0 equiv), was added 1 mL of a 0.01 M solution of hexafluorophosphoric acid in acetonitrile (obtained from mixing 55% aqueous solution of HF₆PO₄ with acetonitrile), and the vial was put under an argon atmosphere. The mixture was allowed to react at room temperature for 24 h. The product was filtered through a plug of basic aluminum oxide, and the product 3a was isolated using reversed phase flash chromatography. Using 1.1 equiv of sesamol afforded 31.1 mg (72%) of 3a, while using 3.0 equiv gave 32.7 mg (76%). The same reaction using tetrafluoroboric acid and 3 equiv of sesamol also afforded 3a in 76% yield. A reaction using p-toluenesulfonic acid and 1.5 equiv of sesamol resulted in a lower yield (43% quantified by NMR).

**Demetalation of Compound 3a to Aromatized Product 6.** A microwave vial was charged with iron complex 3a (32.7 mg, 0.079 mmol) and trimethyleneamine N-oxide dihydrate (87.8 mg, 0.79 mmol). The vial was sealed and put under an argon atmosphere, 2 mL of acetone was added, and the mixture was heated at 50 °C for 6 h. The product was filtered through a plug of Celite, and the solvent was evaporated in vacuo. Purification by flash chromatography (silica gel, 30% EtOAc in petroleum ether) yielded the product 6 as a white solid (19.0 mg, 96% yield).

**Formation of TBDMS-ether 7.** To a microwave vial equipped with a magnetic stirrer were added iron complex 3a (41 mg, 0.1 mmol) and dichloromethane (2 mL). Then, TBDMSCl (30 mg, 0.2 mmol) was added portionwise, followed by TEA (27 µL, 0.2 mmol). The reaction mixture was capped and stirred at 60 °C for 15 h. The crude reaction mixture was then loaded directly onto silica and subjected to flash chromatography using 15% EtOAc in hexane as the eluent, affording compound 7 as a yellow oil (42 mg, 78% yield).

**Demetalation of Compound 7 to Free Diene 8.** To a microwave vial equipped with a magnetic stirrer was added iron complex 7 (52 mg, 0.1 mmol) and EtOH (1 mL). The vessel was sealed and placed under a nitrogen atmosphere before being cooled to 0 °C with an ice bath. H₂O₂ (0.72 mL) was then added in one portion, followed by the dropwise addition of 1 M NaOH (0.64 mL). The solution turned red, and some gas evolution was seen. After 10 min, the reaction was diluted with brine (10 mL) and extracted with dichloromethane (3 × 10 mL). Crude NMR analysis was employed to determine if full demetalation had taken place, and the procedure could be repeated if necessary. The reaction mixture was then purified by flash column chromatography (hexane) to afford compound 8 as a colorless oil (33 mg, 85% yield).

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**ASSOCIATED CONTENT**

**Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acssuschemeng.9b00127.

Experimental procedures for iron complexes 1 and 5, compound characterization data, crystal structure data and NMR spectra, and X-ray crystallographic data for compound 3a (CCDC #1880771) (PDF)

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**Notes**

The authors declare no competing financial interest.

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