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

Petter Dunäs, †‡ Andrew J. Paterson, †‡ Gabriele Kociok-Köhn, § Simon E. Lewis, †∥ Nina Kann †‡

†Chemistry and Biochemistry, Department of Chemistry and Chemical Engineering, Chalmers University of Technology, Kemivägen 10, SE-41296 Göteborg, Sweden
‡Centre for Sustainable Chemical Technologies, University of Bath, Convocation Avenue, Bath BA2 7AY, U.K.
§Centre for Materials and Chemical Characterization Facility, University of Bath, Convocation Avenue, Bath BA2 7AY, U.K.
∥Department of Chemistry, University of Bath, Convocation Avenue, Bath BA2 7AY, U.K.

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. 4 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 carbonyl—carbon or carbon—heteroatom bonds. 10,11 This nucleophilic coupling with iron complexes occurs in a highly regio- and stereoselective 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 siculine 14 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. 19,24 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.
This case may to some extent be due to solubility issues. Happy to
in the range of 59
(entry 2). Using methyl ethyl ketone or methyl acetate
benign solvent (entry 5). Water could also be used as solvent,
at room temperature using ethanol as an environmentally
acrylate ester and furan, both available from biorenewable
could be synthesized via a cycloaddition reaction between an
aromatic molecules, and these have been exploited using iron
dienes can also be made via biocatalytic
-addition in good yields. Solvents were
ord that the reaction proceeded rapidly in 92% yield
(Scheme 1, path a). The same type of cationic structure can
also be formed by treating an iron diene complex containing a
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 carbamate,27 thiol,28 enolates26 and malonates,29
allyl silanes,30 electron rich aromatics31 and heterocycles,30
organocuprates, organolithium reagents,32 organozinc re-
agents,32 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 η
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
caronyl cyclohexadienyl complex 1 (Scheme
2).

Scheme 1. Nucleophilic Addition to Cationic Iron Carbonyl 
 Dienyl Complexes

important criterion. The precursor for complex 1, diene 2,
could be synthesized via a cycloaddition reaction between an
acrylate ester and furan, 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
carboxyl 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 solvents52 and
seeking to find alternatives to dichloromethane, acetonitrile,
and tetrahydrofuran, commonly used for these reactions. 2-
Methyltetrahydrofuran, accessible from the platform chemical
levulinic acid,53,54 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

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>time (h)</th>
<th>yielda</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-MeTHF</td>
<td>4.5</td>
<td>17</td>
</tr>
<tr>
<td>2</td>
<td>EtOAc</td>
<td>4.5</td>
<td>41</td>
</tr>
<tr>
<td>3</td>
<td>methyl ethyl ketone</td>
<td>4.5</td>
<td>67</td>
</tr>
<tr>
<td>4</td>
<td>wet MeOAcc</td>
<td>4.5</td>
<td>59</td>
</tr>
<tr>
<td>5</td>
<td>EtOH (&gt;99%)</td>
<td>2</td>
<td>92</td>
</tr>
<tr>
<td>6</td>
<td>H2O</td>
<td>2</td>
<td>75</td>
</tr>
<tr>
<td>7</td>
<td>EtOH / H2O (9:1)</td>
<td>2</td>
<td>60</td>
</tr>
</tbody>
</table>

a1.1 equiv sesamol. NMR yield. 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
carboxyl 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 dihydroxy-
belliferone, prepared by hydrogenation of the natural product
umbelliferone,55 effected a simultaneous ring opening,
affording ethyl ester 3d as the product in good yield. 4-
Hexylresorcinol, used as a local anesthetic56 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

Figure 1. Visual monitoring of the reaction shown in Table 1; a clear
solution indicates a completed reaction.

Figure 2.
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.

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

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>temp (°C)</th>
<th>time (min)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>dimethyl carbonate</td>
<td>RT</td>
<td>2</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>EtOAc</td>
<td>RT</td>
<td>2</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>MeOAc</td>
<td>RT</td>
<td>2</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>acetone</td>
<td>RT</td>
<td>2</td>
<td>81</td>
</tr>
<tr>
<td>5</td>
<td>diethyl carbonate</td>
<td>RT</td>
<td>2</td>
<td>67</td>
</tr>
<tr>
<td>6</td>
<td>tert-butyl methyl ether</td>
<td>RT</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>7</td>
<td>EtOAc</td>
<td>0</td>
<td>2</td>
<td>56</td>
</tr>
<tr>
<td>8</td>
<td>EtOAc</td>
<td>0</td>
<td>10</td>
<td>89</td>
</tr>
</tbody>
</table>

"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 oxygen, 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-toluene sulfonic 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 η⁶ complex 5, without preforming the cationic η⁶ 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,\textsuperscript{31} 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 \( \text{H}_2\text{O}_2/\text{NaOH} \) or cerium ammonium nitrate, a similar procedure performed in ethyl acetate at 0 °C, yielding the aromatized demetalated product, as indicated in 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 \( \text{H}_2\text{O}_2/\text{NaOH} \) or cerium ammonium nitrate, a similar procedure performed in ethyl acetate at 0 °C, yielding the aromatized demetalated product, as indicated in Scheme 8, reaction a).

**Scheme 8. Selective Oxidative Demetallation of Iron Carbonyl Complex 3a To Form Aromatic Product 6 or Diene 8**

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 \( \text{H}_2\text{O}_2/\text{NaOH} \) or cerium ammonium nitrate, affording the free diene 8 in 85% yield. The \( O \)-addition products 4a–4e were found to be too sensitive to tolerate these conditions, and attempted oxidative demetalation, using all three methods, resulted in decomposition of the starting material.

**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 I 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\textsuperscript{36} and dihydrourambelliferone\textsuperscript{68} 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 \( d_{l} \)/\( d_{s} \). ATR-FTIR spectra were recorded on a PerkinElmer Spectrum Frontier infrared spectrometer with Pike-GladiATR 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 \( \mu \)g/mL in MeCN and analyzed without a column, with a 0.3 mL/min flow rate using an isotropic 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) °C 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– hydrogens 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 Et,N (0.2 mmol) in 1 mL of EtOAc was added under an ice bath. Then, a precooled mixture of nucleophile (0.11 mmol, 3.0 equiv) was added 1 mL of a 0.01 M solution of 5-fluoroboric acid as the catalyst. A microwave vial equipped with a magnetic stirrer was added iron complex 1 (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).

### 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)

### AUTHOR INFORMATION

**Corresponding Authors**

E-mail: S.E.Lewis@bath.ac.uk; Telephone: +44 1225 386568.
E-mail: kann@chalmers.se; Telephone: +46 31 7723070.

**ORCID**

Petter Dunäs: 0000-0002-3779-3265
Andrew J. Paterson: 0000-0001-7169-2524
Simon E. Lewis: 0000-0003-4555-4907
Nina Kann: 0000-0002-4457-5282

**Notes**

The authors declare no competing financial interest.

### ACKNOWLEDGMENTS

The Swedish Research Council (N.K., grant 2015-06350), the Swedish Research Council Formas (N.K., grant 942-2015-1106), the Engineering and Physical Sciences Research Council (S.E.L., grant EP/L016354/1), and the Carl Trygger Foundation (A.P., grant CTS 16:235) are gratefully acknowledged for funding. We also thank Dr. Carl Johan Wallentin and his group for discussions.

### REFERENCES


