Iron-catalyzed, Highly Regioselective, Synthesis of α-Aryl Carboxylic Acids from Styrene Derivatives and CO$_2$ **

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Supporting information: Full experimental procedures and analytical data are available. This material is available free of charge via the Internet at http://pubs.acs.org

Graphical abstract:
Abstract

The iron-catalyzed hydrocarboxylation of aryl alkenes has been developed using a highly active bench-stable iron(II) precatalyst to give α-aryl carboxylic acids in excellent yields and with near-perfect regioselectivity. Using just 1 mol % FeCl₂, bis(imino)pyridine 6 (1 mol %), CO₂ (atmospheric pressure), and a hydride source (EtMgBr, 1.2 equiv), a range of sterically and electronically differentiated aryl alkenes were transformed to the corresponding α-aryl carboxylic acids (up to 96% isolated yield). The catalyst was found to be equally active with a loading of 0.1 mol %. Preliminary mechanistic investigations show that an iron-catalyzed hydrometalation is followed by transmetalation and reaction with the electrophile (CO₂).

Main text

Iron-catalyzed processes have become increasingly important in the construction of complex molecular frameworks due to the environmental, health and cost benefits of using iron in place of traditionally used transition metals. Carbon dioxide is an attractive carbon source for organic synthesis due to its low cost, low toxicity and ease of handling. Despite the extensive use of carbon monoxide in homo- and heterogeneous catalysis as a C₁ feedstock, e.g. hydroformylation, methodology to utilize carbon dioxide under mild conditions remains underdeveloped. Iron-catalyzed processes offer an economical and environmentally benign alternative to the transition metals traditionally used in homogeneous catalysis. Herein we report the highly regioselective iron-catalyzed synthesis of carboxylic acids from alkenes and carbon dioxide; overall, an iron-catalysed hydrocarboxylation (Figure1).

Hoberg reported the reaction of carbon dioxide with stoichiometric low-valent nickel- and iron-alkene complexes to give carboxylic acids. Rovis developed Hoberg’s nickel-mediated carboxylation into a reductive carboxylation of electron-deficient and electron-neutral styrene derivatives using a sub-stoichiometric nickel(II) pre-catalyst (Figure 1). Hayashi and Shirakawa recently reported a cooperative iron-copper catalyzed hydromagnesiation of terminal alkenes by alkene-Grignard exchange (Figure 1). The process required an iron salt for the hydrometallation step and a copper salt to aid transmetallation to magnesium.

We sought to develop an iron-catalyzed hydrocarboxylation of alkenes starting from an inexpensive, commercially available, non-toxic and bench-stable iron(II) precatalyst. The reaction of iron(II) salts with Grignard reagents bearing β-hydrogens results in reduction of the iron centre to give a low-valent, highly reactive, ‘inorganic Grignard’ species. The proposed reduction pathway involves the formation of transient low valent iron-hydride species, which we aimed to exploit by trapping with a
suitable alkene in a hydrometallation process. The hydrometallated intermediate may then be able to react with carbon dioxide to produce the hydrocarboxylation product.

![Figure 1](image)

**Figure 1.** Proposed iron-catalyzed hydrocarboxylation of alkenes.

Initial studies focused on the hydrocarboxylation of styrene using 5 mol% of a simple iron salt with ethylmagnesium chloride as the hydride source. At room temperature very low yields of the carboxylic acid product 2 were observed (Table 1, entries 1-2), however upon heating the reaction at reflux, Fe(OTf)₂ was found to catalyze the reaction to an equal extent as that reported by Rovis (entry 3), however this yield could not be improved upon. At room temperature, 5 mol% N-methylpyrrolidone (NMP) 3 and FeCl₂ gave a reaction yield to 27% (entry 4). N,N',N″,N‴-Tetramethylethylenediamine (TMEDA) 4, tri(n-butyl)phosphine, and tetradentate amine ligand 5 all showed moderate reactivity and regioselectivity (entries 5-7). The most active catalyst was formed using bis(imino)pyridine ligand 6 which gave a yield of 85% and near-perfect regioselectivity for the α-carboxylic acid 2α (α:β >100:1) (entry 8). iso-Propylmagnesium chloride gave similar conversion, however with reduced regioselectivity (α:β 13:1) (entry 9). Ethylmagnesium bromide gave quantitative conversion to the carboxylic acids 2 (96% isolated yield 2α) with excellent regioselectivity (α:β 75:1) (entry 10), even when using just 0.1 mol% pre-catalyst or the hydrated iron salt (entries 12-14). Cyclopentylmagnesium bromide also gave good conversion; however the use of a secondary Grignard reagent, again, resulted in a lower regioselectivity (α:β 14:1) (entry 11). The hydrocarboxylation reaction showed reduced activity in other solvent systems and at lower temperatures.¹⁵,¹⁶

Importantly, in the absence of iron, no hydrocarboxylation was observed and the addition of trace levels of other transition metal salts to the standard reaction conditions did not increase the yield of the reaction. The use of these other transition metal salts in the absence of FeCl₂ showed no catalytic activity.¹⁵ High purity FeCl₂ (99.99%) also catalyzed the reaction with near quantitative yields.¹⁵,¹⁷
Table 1. Catalyst identification for the hydrocarboxylation of styrene.

<table>
<thead>
<tr>
<th>entry</th>
<th>Iron salt</th>
<th>Ligand</th>
<th>RMGX</th>
<th>Yield (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>FeCl₂</td>
<td>-</td>
<td>EtMgCl&lt;sup&gt;c&lt;/sup&gt;</td>
<td>&lt;1</td>
</tr>
<tr>
<td>2</td>
<td>FeCl₃</td>
<td>-</td>
<td>EtMgCl&lt;sup&gt;c&lt;/sup&gt;</td>
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<tr>
<td>3</td>
<td>Fe(OTf)&lt;sub&gt;2&lt;/sub&gt;&lt;sup&gt;d&lt;/sup&gt;</td>
<td>-</td>
<td>EtMgCl&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>NMP 3</td>
<td>EtMgCl&lt;sup&gt;c&lt;/sup&gt;</td>
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<tr>
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<td>TMEDA 4</td>
<td>EtMgCl&lt;sup&gt;c&lt;/sup&gt;</td>
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</tr>
<tr>
<td>6</td>
<td>FeCl₂</td>
<td>P(n-Bu)&lt;sub&gt;3&lt;/sub&gt;</td>
<td>EtMgBr&lt;sup&gt;e&lt;/sup&gt;</td>
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<td>Cyclopentyl-MgBr&lt;sup&gt;e&lt;/sup&gt;</td>
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</tr>
<tr>
<td>12&lt;sup&gt;i&lt;/sup&gt;</td>
<td>FeCl₂ (1 mol%)</td>
<td>6 (1 mol%)</td>
<td>EtMgBr&lt;sup&gt;e&lt;/sup&gt;</td>
<td>97</td>
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<tr>
<td>13</td>
<td>FeCl₂ (0.1 mol%)</td>
<td>6 (0.1 mol%)</td>
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<td>6&lt;sup)i&lt;/sup&gt;</td>
<td>EtMgBr&lt;sup&gt;e&lt;/sup&gt;</td>
<td>97</td>
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<sup>a</sup>Conditions: 0.7mmol 1, 5 mol% iron salt, 5 mol% ligand, THF (0.15M), 150 mol% RMGX, 1h, r.t (ii) CO₂, 30 min. <sup>b</sup>Yield determined by <sup>1</sup>H NMR using an internal standard. <sup>c</sup>2M in THF. <sup>d</sup>Heated at reflux. <sup>e</sup>3M in Et₂O. <sup>f</sup>1M in THF. <sup>g</sup>Isolated yield. <sup>i</sup>2M in Et₂O. <sup>j</sup>3h reaction time. <sup>k</sup>1 mol%.

The scope of the reaction was investigated using a 1 mol% catalyst loading, which was formed in situ from FeCl₂ and bis(imino)pyridine ligand 6 (Table 2). Pleasingly, it was found that the developed methodology worked most efficiently for styrene derivatives bearing electron-donating groups, demonstrating the complementary nature of this method to those of Rovis and Hayashi and Shirakawa (Figure 1).<sup>9,10,18</sup>

Alkyl substitution in all positions on the aromatic ring were well tolerated (Table 2, 8a-e), giving the α-carboxylic acids 8a-d in excellent yield, with only ortho-methyl styrene showing a slightly reduced
regioselectivity (α:β 10:1). The hydrocarboxylation of iso-butylstyrene gave directly the pharmaceutical ibuprofen in excellent yield and regioselectively (α:β 40:1). Benzyl protected phenol derivative 7f gave the α-carboxylic acid 8f with no benzyl deprotection observed under the reductive reaction conditions.

Table 2. Iron-catalyzed hydrocarboxylation of styrene derivatives: scope and limitations.  

The electron-rich ortho- and meta-methoxystyrene derivatives gave the α-carboxylic acids 8g and 8h in excellent yield and regioselectivity (α:β >100:1), however para-methoxystyrene gave α-carboxylic acid 8i in slightly reduced yield and regioselectivity (58%, α:β 18:1). 2,5-bismethoxystyrene gave α-carboxylic acid 8j in excellent yield and regioselectivity (92%, α:β >100:1), however 3,4-
bismethoxystyrene gave a reduced yield, possibly due to Grignard-mediated demethylation which was enhanced by coordination to the adjacent methoxy group (8k). Electron-deficient styrene derivatives showed reduced activity; 4-vinylbiphenyl and para-fluorostyrene gave moderate yields of α-carboxylic acids 8l and 8m, but with excellent regioselectivity (α:β >50:1). When 2,4-dimethyl- and 2,5-dimethyl styrene derivatives were tested significantly lower regioselectivity was observed (α:β ~1:1). Cyclopentylmagnesium bromide, in place of EtMgBr, gave much higher yields, albeit with a reverse in regioselectivity to the β-product 8nβ and 8oβ (74-78%, α:β 1:6). Presumably the change in regioselectivity arises due to the increased steric bulk around the iron catalyst, resulting in a kinetic preference for hydrometallation to give the linear β-product.

When the reaction was quenched with d⁵-methanol complete conversion to (1-deuteroethyl)benzene was observed implying the presence of an intermediate α-aryl organometallic species (Scheme 1A). To confirm that the incorporated hydride originated from the Grignard reagent, d⁵-ethylmagnesium bromide was used in the reaction (Scheme 1B). This gave a complex mixture of β-deuterated products, with zero, one, two and three deuterium atoms incorporated at the terminal position. This suggests that hydrometallation is both fast and reversible under the reaction conditions. It was calculated that 150 mol% deuterium incorporation had occurred, which is in support of a highly reversible process. No deuterium incorporation was observed at the alpha-position, suggesting that hydrometallation is highly regioselective in this case.

$$\text{Scheme 1. Mechanistic investigations into the iron-catalyzed hydrometallation of alkenes and isomerization of Grignard reagents.}$$

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a Percentage yields with respect to 10. b Percentage yields with respect to 4-t-Bu-styrene.
To investigate whether the α-selectivity originated from a regioselective hydrometallation or by isomerization of an intermediate Grignard reagent to the thermodynamically more stable α-Grignard, the β-Grignard reagent 10 was independently synthesized and exposed to the standard reaction conditions (Scheme 1C). Very little isomerization to the α-Grignard reagent was observed, suggesting the β-hydride elimination-hydrometallation process is faster than the conformational isomerization of the intermediate iron-hydride-styrene species needed to produce the α-product 2. However, the addition of an equivalent of tert-butylstyrene showed isomerization of the β-Grignard 10 to give a majority of the α-carboxylic acids arising from both the Grignard 10 (by β-hydride elimination, conformational isomerization and hydrometallation) and tert-butylstyrene (by direct hydrometallation) (Scheme 1D). Considering the rapid rate of β-hydride elimination-hydrometallation with respect to transmetallation or con conformational isomerization, and the decrease in regioselectivity (Table 2), it seems likely that tert-butylstyrene is co-ordinated to iron prior to β-hydride elimination of the Grignard reagent 10 or competitively coordinates to iron with the generated styrene.

Thus our suggested mechanism is based on the iron-catalyzed formation of a hydromagnesiated intermediate species capable of reaction with carbon dioxide (Scheme 2). Alkylation of the iron precatalyst and co-ordination of styrene gives an organoferrate complex B, which can undergo β-hydride elimination to give an active low-valent iron hydride complex C. Hydrometallation of styrene gives the organoferrate complex D, which could undergo transmetallation with another equivalent of ethylmagnesium bromide to release the hydromagnesiated product E, and reform the initial organoferrate complex A.

Scheme 2. Proposed mechanism for the iron-catalyzed hydrocarboxylation of alkenes.
In summary, an operationally simple, highly active, iron-catalyzed hydrocarboxylation of aryl alkenes has been developed for the synthesis of α-aryl carboxylic acids using CO\textsubscript{2} as the C\textsubscript{1}-feedstock. Excellent yields have been achieved for alkyl substituted styrene derivatives with excellent control of regioselectivity. Significantly, styrene derivatives bearing electron-donating groups, which have proved difficult previously, were successfully hydrocarboxylated with good yields and excellent regioselectivity. Mechanistic investigations showed the reaction proceeds by a highly regioselective and reversible iron-catalyzed hydrometallation, followed by transmetallation giving an α-aryl Grignard reagent which reacts with CO\textsubscript{2}. This methodology provides a significant advance in the iron-catalyzed functionalization of alkenes using mild and operationally simple conditions.
Notes and references


[12] FeCl₂ was chosen as the background reaction (without ligand) was minimal and due to its low cost and wide availability.


[14] This iron complex was first used by Gibson and Brookhart as a polymerisation catalyst, see: (a) Britovsek, G. J. P.; Gibson, V. C.; Kimberley, B. S.; Maddox, P. J.; McTavish, S. J.; Solan, G. A.; White A. J. P.; Williams, D. J. Chem. Commun. 1998, 849. (b) Small, B. L.; Brookhart M.; Bennett, A. M. A. J. Am. Chem. Soc. 1998, 120, 4049. It has since used by Chirik as a hydrogenation and hydrosilylation catalyst, see ref 6a,f.

[16] No other hydride sources (NaBH₄, LiAlH₄, NaHBET₃, LiHBEt₃, iBu₂AlH, LiHBEt₃, Li[Me₂NBH₃], tBuLi, Et₂Zn, Et₃Al) were found to mediate the hydrocarboxylation.


[19] (19) 4-F₃C-, 4-H₃CCO₂-, 4-O₂N- and 4-NC-styrene were not tolerated under the reaction conditions. Aryl bromides and chlorides underwent proto-dehalogenation, see: Czaplik, W. M.; Grupe, S.; Mayer M.; Jacobi von Wangelin, A. Chem. Commun. **2010**, *46*, 6350.

[20] In addition, methyl- and phenylmagnesium chloride failed to catalyze the reaction.

[21] The hydromagnesiation of styrene by alkylmagnesium halides has been previously reported to be catalyzed by TiCl₄ and NiCl₂, however in both cases only moderate yields were obtained under forcing conditions, see: (a) Cooper, G. D.; Finkbeiner, H. L. J. Org. Chem. **1962**, *27*, 1493. (b) Farády, L.; Bencze, L.; Markó, L. J. Organomet. Chem. **1967**, *10*, 505. FeCl₃ was also reported to catalyze the reaction albeit in low yield (15%).