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Citation for published version:

Digital Object Identifier (DOI):
10.1021/acscatal.6b03287

Link:
Link to publication record in Edinburgh Research Explorer

Document Version:
Peer reviewed version

Published In:
ACS Catalysis

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Iron-Catalyzed Heck-Type Alkenylation of Functionalized Alkyl Bromides

Kailong Zhu, Joanne Dunne, Michael P. Shaver* and Stephen P. Thomas*

EastCHEM, School of Chemistry, University of Edinburgh, Joseph Black Building, David Brewster Road, Edinburgh, EH9 3FJ, United Kingdom

**ABSTRACT:** The ability of iron to controllably generate alkyl radicals from alkyl halides as a key step in atom transfer radical polymerization (ATRP) has been adapted to facilitate a formal Heck cross-coupling between styrenes and functionalized alkyl bromides. A simple FeCl$_2$ catalyst in a coordinating solvent gave excellent activity without the need for expensive ligands. Tertiary, secondary and even primary alkyl bromides are tolerated to give the products in moderate to good yields (up to 94% yield). The easily accessible reagents and operational simplicity make this reaction a method of choice for the alkenylation of alkyl halides, especially for functionalized tertiary alkyl halides which are difficult to target by classic palladium-catalyzed Heck reactions because of the competing β-hydride elimination.

**KEYWORDS:** iron, catalysis, Heck-type reaction, radical, alkyl halides

The Heck reaction has become one of the most widely used methods for C-C bond formation since its discovery in 1972. Although tremendous effort has been devoted to the development of this synthetically useful reaction, the substrate scope is still largely limited to vinyl or aryl halides and few examples have been reported using alkyl halides. This can be attributed to the increased difficulty for oxidative addition of alkyl halides to the metal center, and the competing β-hydride elimination of the organopalladium insertion product (Scheme 1a).

To address this long-standing challenge, an alternative reaction pathway has been proposed which involves a radical intermediate. In this new mechanism, a transition metal donates an electron to the alkyl halide to generate an alkyl radical, a process akin to the initiation step in transition-metal mediated Atom Transfer Radical Polymerisation (ATRP) (upper equation, Scheme 1b). Radical addition to a styrene derivative generates the new carbon-carbon bond and a benzyl radical, which instead of propagating to give polymer ATRP can undergo an oxidation/elimination process to generate an alkenyl group in the presence of a base. The net outcome of this process is a formal Heck reaction between an alkyl halide and styrene (lower equation, Scheme 1b).

As the most abundant transition metal on earth, using iron catalysts in synthetic chemistry has clear advantages due to the inexpensive, non-toxic and environmentally benign nature of iron species. However, although iron is among the most widely used transition metals in the ATRP of styrene derivatives, the iron-catalyzed radical alkenylation of styrene is unprecedented. Herein, we extended our knowledge of iron-catalyzed ATRP to the synthesis of small molecules and report the first example of an iron-catalyzed radical alkenylation of functionalized alkyl halides. Tertiary, secondary and even primary alkyl halides as well as styrene derivatives with a wide electronic scope are well tolerated (Scheme 1c).

**Scheme 1.** a) The challenge of β-hydride elimination in palladium-catalyzed Heck reactions; b) Radical alkenylation for the construction of Heck-type products. c) Iron-catalyzed alkenylation of functionalized alkyl halides.

We first explored the reaction of $p$-methoxystyrene 1a and ethyl α-bromoisobutyrate 2a (Table 1). Hypothesizing...
that slower ATRP catalysts would favor this alternative reaction pathway, we tested α-diamine iron(II) complexes 4-6 in DMF. Indeed, catalyst 4, which promotes rapid ATRP, gave the lowest yield of the desired product (entry 1) while the sluggish ATRP catalyst 5 gave the highest yield (entry 3). The high rate of radical formation by catalyst 4 would facilitate the dimerization of the alkyl radical, circumventing the radical addition step. Further to this goal, a simple FeCl3 catalyst in this coordinating solvent – even a worse ATRP mediator – is even more active, producing the product in 65% yield (entry 4), increasing to 94% yield when using 3.0 equivalents of 2a (entry 5). Solvent is a key component in controlling the iron speciation, as shown by the low yield of 3a and concomitant formation of polystyrene in MeCN (10%, entry 6), THF (<1%, entry 7) and toluene (<1%, entry 8). Expectedly, an iron complex with a higher oxidation state was not active (entry 9) nor were weak radical traps like Fe(acac)3 (entry 10), Fe(Ott)3 or Fe(OAc)2. Finally, the nature of the base is also key. Alternative bases such as K2CO3 and K2PO4 gave much lower yields than Cs2CO3 (entries 11 and 12). Inexpensive Na2CO3 gave lower yields when 2.0 equivalents of 2a was used (entry 13), but gave almost identical result when 3.0 equivalent of 2a was used (entry 14). The different yields achieved by varying the bases used are presumably a result of the differing pKa, solubility and kinetic basicity leading to a different concentration of base in solution. Coordinating bases such as N,N,N′,N″,N‴-pentamethyldiethylenetriamine (PMDTA), which is also a commonly used ATRP ligand, favor polystyrene formation (entry 15).

Table 1. Optimizing the Heck-Type Alkenylation of Ethyl α-Bromoisobutyrate with p-Methoxystyrene

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>Solvent</th>
<th>base</th>
<th>yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cp[N,N]FeCl3</td>
<td>DMF</td>
<td>Cs2CO3</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>DippMet[N,N]FeCl3</td>
<td>DMF</td>
<td>Cs2CO3</td>
<td>36</td>
</tr>
<tr>
<td>3</td>
<td>DippMe[N,N]FeCl3</td>
<td>DMF</td>
<td>Cs2CO3</td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>FeCl3</td>
<td>DMF</td>
<td>Cs2CO3</td>
<td>65</td>
</tr>
<tr>
<td>5</td>
<td>FeCl2</td>
<td>DMF</td>
<td>Cs2CO3</td>
<td>94&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>FeCl2</td>
<td>MeCN</td>
<td>Cs2CO3</td>
<td>10</td>
</tr>
<tr>
<td>7</td>
<td>FeCl2</td>
<td>THF</td>
<td>Cs2CO3</td>
<td>Trace</td>
</tr>
<tr>
<td>8</td>
<td>FeCl2</td>
<td>Toluene</td>
<td>Cs2CO3</td>
<td>Trace</td>
</tr>
<tr>
<td>9</td>
<td>FeCl3</td>
<td>DMF</td>
<td>Cs2CO3</td>
<td>Trace</td>
</tr>
<tr>
<td>10</td>
<td>Fe(acac)3</td>
<td>DMF</td>
<td>Cs2CO3</td>
<td>Trace</td>
</tr>
<tr>
<td>11</td>
<td>FeCl2</td>
<td>DMF</td>
<td>K2CO3</td>
<td>35</td>
</tr>
<tr>
<td>12</td>
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<td>DMF</td>
<td>K2PO4</td>
<td>20</td>
</tr>
<tr>
<td>13</td>
<td>FeCl2</td>
<td>DMF</td>
<td>Na2CO3</td>
<td>55</td>
</tr>
</tbody>
</table>

<sup>4</sup> Reaction conducted at 80 °C for 16 h with 10 mol % catalyst, 1.1 equiv of base, 1a (0.25 mmol, 1.0 equiv) and 2a (2.0 equiv).<sup>5</sup> Determined by ‘H NMR using 1,3,5-trimethoxybenzene as internal standard.<sup>6</sup> 3.0 equiv of 2a was used.<sup>7</sup> Isolated yield. Yields are reported as the average of two parallel experiments.

The substrate scope of this iron-catalyzed radical alkyl halide alkenylation was investigated (Table 2). The reactions of various α-functionalized styrene derivatives with methyl α-bromoisobutyrate 2a were first explored (entries 3a-30). Styrene derivatives bearing electron-donating substituents all gave good yields of the formal Heck product, forming only the (E)-diastereomer (3a-j). Substitution in the para-, meta-, and ortho-positions were all tolerated, even for the styrene derivat-ives bearing potential metal coordinating groups (methoxy and dimethylamino). Only when an ortho disubstituted styrene 2f was used did the reaction fail to give a synthetically useful yield. The reactions of styrene derivatives bearing halide substituents gave the alkene products 3k and 3l in decreased yields as the reactions were dominated by styrene polymerization. This is in accordance with the conclusion of previous work where styrene monomers with less electron-donating substituents showed higher rates of polymerization.<sup>8</sup> In the reaction of α-methyl styrene, double bond migration was observed and the product 3m was isolated as a mixture of alkene regiosomers (9:1). The formation of the less substituted alkene can be attributed to the relative rates of β-hydride elimination from the intermediate species; elimination from the primary CH2 over the neopentyl CH2, favouring the production of the less substituted alkene product. Reaction of secondary styrene derivatives 1,1-diphenylethene 2n and indene 2o both proceeded in good yield to give the tertiary alkene products, 3n and 3o, respectively. We next explored the scope of the alkyl bromide coupling partner (entries 3p-3x). Using α-bromo aryl ester gave equal or better reactivity to that using ethyl α-bromoisobutyrate and products 3p and 3q were isolated in 91% and 86% yield respectively. Cyclic α-bromo ester was also found to be a suitable coupling partner to give product 3r in good yield however, an α-bromo amide was found to undergo beta-hydride elimination to give the corresponding α,β-unsaturated amide (3s). The use of secondary α-bromo esters also gave the formal Heck product in good yield and diastereoselectivity (3t-3w). The use of ethyl α-bromo phenylacetate gave the corresponding product 3v in higher yield<sup>9</sup> than equivalent reaction using methyl 2-bromopropionate, presumably due to the increased stability α-phenyl radical. Use of a nitride in place of the ester also resulted in good yield of 3w.<sup>10</sup> Finally, two primary halides could be used as coupling partners to give 3x, 3y and 3z albeit with a diminished yield.<sup>11</sup>

Table 2. Substrate Scope of the Iron-Catalyzed Heck-Type Reactions between Alkyl Halide and Styrene
Run at 80 °C for 16 h in DMF, 10 mol % FeCl₂, Na₂CO₃ (1.1 equiv), 1 (0.25 mmol, 1.0 equiv) and 2 (3.0 equiv). Isolated yields.

Isolated yields.

Yield determined by ¹H NMR using 1,3,5-trimethoxybenzene as internal standard.

Yield of the mixture of regioisomers. 20 mol % FeCl₂, 4.0 equiv of 2.

20 mol % FeCl₂, 4.0 equiv of 2, 100 °C.

Yields are reported as the average of two parallel experiments.

Radical capture experiments were used to support a radical mechanism. Adding TEMPO (2,2,6,6-tetramethylpiperidin-1-yl)oxyl) to the reaction mixture under standard conditions gave no alkenylation product or polystyrene while the direct reaction between α-bromoisobutyrate 2a and TEMPO with a stoichiometric amount of FeCl₂ produced the alkylated TEMPO product in 15% yield.⁶

While this iron-catalyzed formal Heck reaction is significant, we can further exploit radical reactivity by pairing reactive alkyl bromides with slow propagating styrene derivatives. In this case, the alkyl bromides would serve only as a radical source; the increased stability of the corresponding styrenyl radicals bypasses cross-coupling. Reaction of 4-methoxystyrene and 1-bromo-1-phenyl ethane promotes head-to-tail styrene dimerization to give 7a in 80% yield, avoiding the formal Heck cross-coupling product., likely through an iron hydride intermediate. 3,4-Dimethoxystyrene also selectively forms dimer 7b, albeit in slightly decreased yield (Eq 1).

In conclusion, the first example of iron catalyzed radical alkyl alkenylation is reported. Simple FeCl₂ catalyzed the reaction with high efficiency without an external ligand. The substrate scope is significantly broadened, covered tertiary, secondary and even primary functionalized alkyl bromides. Styrenes without electron-rich substituents were also well tolerated, expanding beyond the scope of other metals. We are currently exploring both a deeper mechanistic understanding of these radical addition reactions and an expansion to other unsaturated substrates to further explore the interface between radical polymerization and small molecule transformations.

ASSOCIATED CONTENT
Supporting Information
Experimental procedures, characterization and spectral data. are available free of charge at http://pubs.acs.org.

AUTHOR INFORMATION
Corresponding Author
*Email: michael.shaver@ed.ac.uk; stephen.thomas@ed.ac.uk

Notes
The authors declare no competing financial interests.

ACKNOWLEDGMENT
MPS and SPT thank the University of Edinburgh for Chancellor’s Fellowships. MPS thanks FP7 (MC-CIG) and EPSRC for research grants. SPT thanks the Royal Society for a University Research Fellowship and a Research Grant. KZ thanks the China Scholarship Council and the University of Edinburgh for a joint scholarship. JD thanks the EPSRC for a DTA studentship.

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(16) See Supporting Information for details.
(17) The final product was isolated as the hydrogenated product of 3v. See Supporting Information for details.
(18) For the Heck-type reaction between α-cyano alkyl halide and styrene, see: Tang, S.; Liu, C.; Lei, A. Chem. Commun. 2013, 49, 2442-2444.
(20) See Supporting Information for further details.
Diverting Fe-catalyzed polymerization mechanisms for organic synthesis

up to 93% yield
ligand-free
1st, 2nd, 3rd alkyl halides
operationally-simple