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# Iron-Catalyzed Heck-Type Alkenylation of Functionalized Alkyl Bromides

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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.[1] 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.[2] 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).[3]

To address this long-standing challenge, an alternative reaction pathway has been proposed which involves a radical intermediate.[4] 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).[5] 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).[6–9]

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.[10] However, although iron is among the most widely used transition metals in the ATRP of styrene derivatives,[11] the iron-catalyzed radical alkenylation of styrene is unprecedented. Herein, we extended our knowledge of iron-catalyzed ATRP[12] 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).
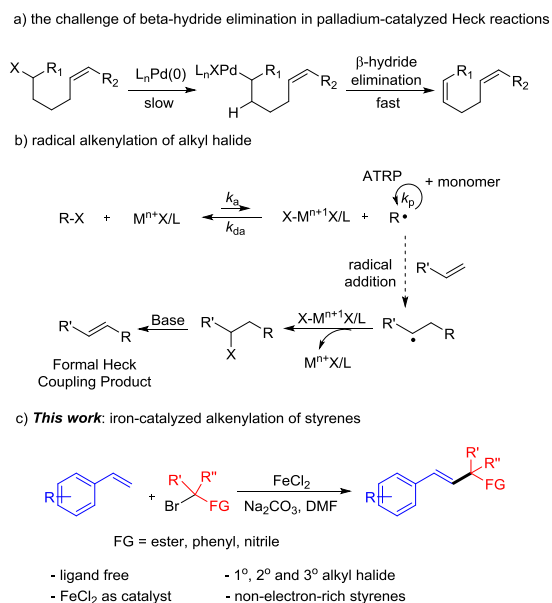


**Scheme 1**. a) The challenge of β-hydride elimination in palladium-catalyzed Heck reactions of alkyl halides; b) Radical alkenylation for the construction of Heck-type products. c) Iron-catalyzed alkenylation of functionalized alkyl halides.

We first explored the reaction of *p*-methoxystyrene **1a** and ethyl α-bromo*iso*butyrate **2a** (Table 1). Hypothesizing

that slower ATRP catalysts would favor this alternative reaction pathway, we tested α-diimine 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).[13] 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 FeCl$_2$ catalyst in this coordinating solvent – an even 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,[14] 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)$_2$ (entry 10), Fe(OTf)$_2$ or Fe(OAc)$_2$. Finally, the nature of the base is also key. Alternative bases such as K$_2$CO$_3$ and K$_3$PO$_4$ gave much lower yields than Cs$_2$CO$_3$ (entries 11 and 12). Inexpensive Na$_2$CO$_3$ 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[a]
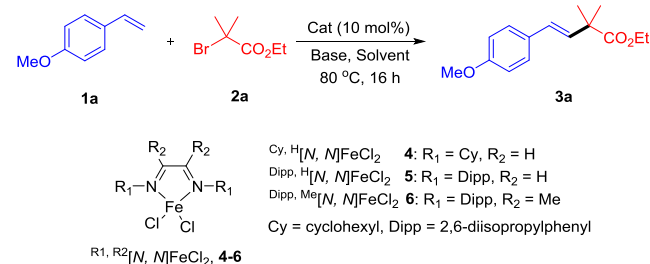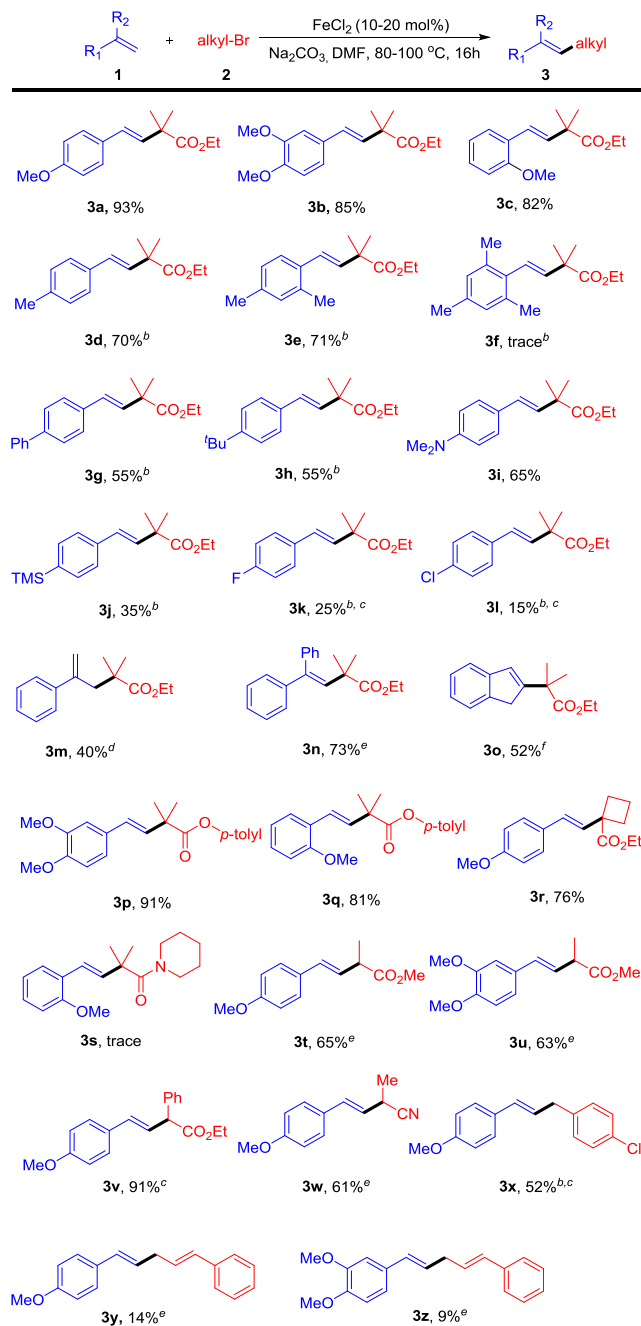


| entry | catalyst | Solvent | base | yield%[b] |
|---|---|---|---|---|
| 1 | $^{Cy,H}$[*N,N*]FeCl$_2$ | DMF | Cs$_2$CO$_3$ | 30 |
| 2 | $^{Dipp,Me}$[*N,N*]FeCl$_2$ | DMF | Cs$_2$CO$_3$ | 36 |
| 3 | $^{Dipp,H}$[*N,N*]FeCl$_2$ | DMF | Cs$_2$CO$_3$ | 50 |
| 4 | FeCl$_2$ | DMF | Cs$_2$CO$_3$ | 65 |
| 5[c] | FeCl$_2$ | DMF | Cs$_2$CO$_3$ | 94[d] |
| 6 | FeCl$_2$ | MeCN | Cs$_2$CO$_3$ | 10 |
| 7 | FeCl$_2$ | THF | Cs$_2$CO$_3$ | Trace |
| 8 | FeCl$_2$ | Toluene | Cs$_2$CO$_3$ | Trace |
| 9 | FeCl$_3$ | DMF | Cs$_2$CO$_3$ | Trace |
| 10 | Fe(acac)$_2$ | DMF | Cs$_2$CO$_3$ | Trace |
| 11 | FeCl$_2$ | DMF | K$_2$CO$_3$ | 35 |
| 12 | FeCl$_2$ | DMF | K$_3$PO$_4$ | 20 |
| 13 | FeCl$_2$ | DMF | Na$_2$CO$_3$ | 55 |
| 14[c] | FeCl$_2$ | DMF | Na$_2$CO$_3$ | 93[d] |
| 15 | FeCl$_2$ | DMF | PMDTA | trace |

[a] 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). [b] Determined by ¹H NMR using 1,3,5-trimethoxybenzene as internal standard. [c] 3.0 equiv of **2a** was used. [d] 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 **1** with ethyl α-bromo*iso*butyrate **2a** were first explored (entries **3a-3o**). 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 derivatives bearing potential metal coordinating groups (methoxy and dimethylamino). Only when an *ortho* disubstituted sytrene **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.[15] In the reaction of α-methyl styrene, double bond migration was observed and the product **3m** was isolated as a mixture of alkene regioisomers (9:1) .[16] 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 CH$_3$, over the neopentyl CH$_2$, 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-bromo*iso*butyrate and products **3p** and **3q** were isolated in 91% and 81% 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[17] than equivalent reaction using methyl 2-bromopropionate, presumably due to the increased stability α-phenyl radical. Use of a nitrile in place of the ester also resulted in good yield of **3w**.[18] Finally, two primary halides could be used as coupling partners to give **3x**, **3y** and **3z** albeit with a diminished yield.[19]
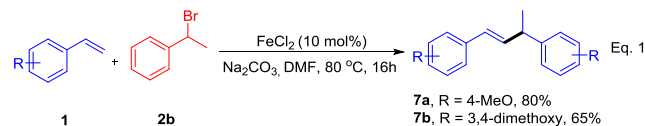
## Table 2. Substrate Scope of the Iron-Catalyzed Heck-Type Reactions between Alkyl Halide and Styrene[a]

Scheme conditions:

$R_2$ / $R_1$ (1) + alkyl-Br (2) → FeCl$_2$ (10-20 mol%), Na$_2$CO$_3$, DMF, 80-100 °C, 16h → product 3

**3a**, 93%  **3b**, 85%  **3c**, 82%

**3d**, 70%[b]  **3e**, 71%[b]  **3f**, trace[b]

**3g**, 55%[b]  **3h**, 55%[b]  **3i**, 65%

**3j**, 35%[b]  **3k**, 25%[b,c]  **3l**, 15%[b,c]

**3m**, 40%[d]  **3n**, 73%[e]  **3o**, 52%[f]

**3p**, 91%  **3q**, 81%  **3r**, 76%

**3s**, trace  **3t**, 65%[e]  **3u**, 63%[e]

**3v**, 91%[c]  **3w**, 61%[e]  **3x**, 52%[b,c]

**3y**, 14%[e]  **3z**, 9%[e]

[a] Run at 80 °C for 16 h in DMF, 10 mol % FeCl$_2$, Na$_2$CO$_3$ (1.1 equiv), **1** (0.25 mmol, 1.0 equiv) and **2** (3.0 equiv). Isolated yields. [b] 100 °C. [c] Yield determined by $^1$H NMR using 1,3,5-trimethoxybenzene as internal standard. [d] Yield of the mixture of regioisomers [e] 20 mol % FeCl$_2$, 4.0 equiv of **2**. [f] 20 mol % FeCl$_2$, 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-bromo*iso*butyrate **2a** and TEMPO with a stoichiometric amount of FeCl$_2$ produced the the alkylated TEMPO product in 15% yield.[20]

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,[21] likely through an iron hydride intermediate. 3,4-Dimethoxystyrene also selectively forms dimer **7b**, albeit in slightly decreased yield (Eq 1).

R (1) + Br-CH(CH$_3$)Ph (2b) → FeCl$_2$ (10 mol%), Na$_2$CO$_3$, DMF, 80 °C, 16h → **7a**, R = 4-MeO, 80%; **7b**, R = 3,4-dimethoxy, 65%   Eq. 1

In conclusion, the first example of iron catalyzed radical alkyl alkenylation is reported. Simple FeCl$_2$ 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.

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R
Ar (alkene) + alkyl-Br →[FeCl$_2$; Na$_2$CO$_3$, DMF, 80-100 °C] Ar, R, alkyl

*Diverting Fe-catalyzed polyimerization mechanisms for organic synthesis*

up to 93% yield
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