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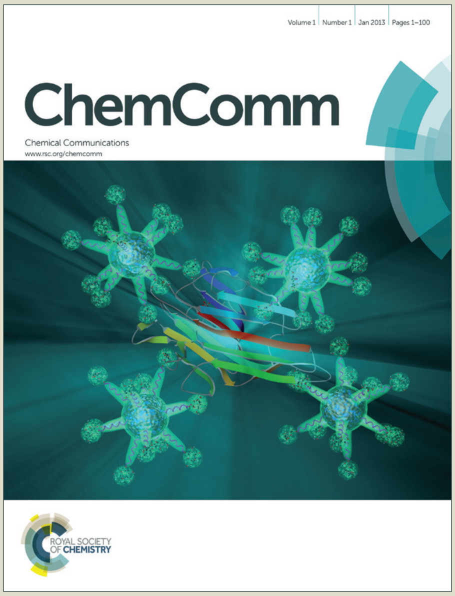

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Journal Name

COMMUNICATION

Iron-Mediated C-H Coupling of Arenes and Unactivated Terminal Alkenes Directed by Sulfur

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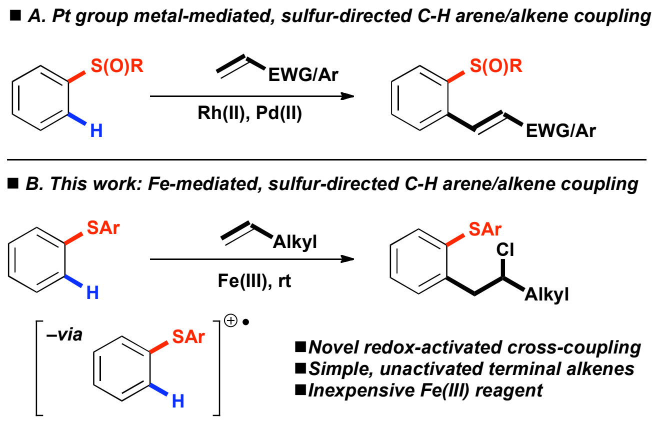
A sulfur-directed Fe(III)-mediated ortho C- H coupling of arenes with unactivated terminal alkenes gives products of regioselective alkene chloroarylation. The novel mechanism involves redox-activation of the arene partner and alkene addition to the resultant aryl radical cation.

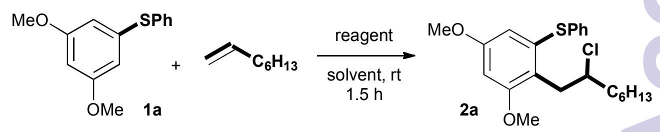
The use of metals to carry out C-H functionalisation in aromatic substrates is highly desirable due to favourable step and atom economy.[1] As regioselective C-H functionalisation can often prove difficult, directing groups are used to facilitate functionalisation with directed *ortho* C-H bond activation on an aromatic or heteroaromatic ring being a common approach.[2] In recent years, there has been great interest in the metal-catalysed *ortho* C-H coupling of arenes and heteroarenes with alkenes.



Scheme 1

This has been achieved using a range of directing groups (*e.g.* aldehydes, ketones, esters and amides), late transition metals (*e.g.* Pd, Ru, Rh) and reactive alkenes such as acrylates and styrenes.[3] Despite the plethora of directing groups studied, the use of a sulfur substituent on an aromatic ring to mediate C-H coupling with alkenes has only recently been developed (Scheme 1A).[4] The need to shift towards the use of inexpensive first row transition metals for cross-coupling processes, including those involving C-H functionalisation is well appreciated.[5] Due to the low cost and low toxicity of iron and its high natural abundance, iron-based reagents are ideal candidates for the development of such processes.

Table 1 Optimisation of Fe(III)-mediated C-H arene/alkene coupling[a]



Entry	Oxidant (equiv.)	Octene (equiv.)	Solvent	Atmosphere	Conversion (%)	Yield (%)[a]
1	$FeCl_3$ (2.2)	10	MeCN	N_2	55	10
2	$FeCl_3$ (2.2)	10	THF	N_2	0	0
3	$FeCl_3$ (2.2)	10	CH_2Cl_2	N_2	91	36
4	$FeCl_3$ (2.2)	10	$MeNO_2$	N_2	60	14
5	$FeCl_3.6H_2O$ (2.2)	10	CH_2Cl_2	N_2	13	4
6[b]	$FeBr_3$ (2.2)	10	CH_2Cl_2	N_2	63	22
7	Fe(acac)$_3$ (2.2)	10	CH_2Cl_2	N_2	0	0
8	$FeCl_3$ (2.2)	10	CH_2Cl_2	O_2	88	47
9	$FeCl_3$ (2.2)	10	CH_2Cl_2	air	88	49
10	$FeCl_3$ (2.2)	5	CH_2Cl_2	air	85	45
11	$FeCl_3$ (2.2)	2	CH_2Cl_2	air	81	3[illegible]
12	$FeCl_3$ (1)	10	CH_2Cl_2	air	48	25
13[c]	$FeCl_3$ (2.2)	5	$CH_2Cl_2/MeNO_2$	air	66	42
14[c]	$FeCl_3$ (4)	5	$CH_2Cl_2/MeNO_2$	air	98	70

Typical Conditions: Oxidant added to a mixture of **1a** (0.2 mmol) and octene and stirred for 1.5 h. [a] Yields by NMR spectroscopy. [b] The bromide analogue of **2a** was obtained. [c] $FeCl_3$ in $MeNO_2$ was added dropwise to the sulfide and alkene in CH_2Cl_2.

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† Additional experiments, full experimental details for the preparation of compounds, ^1H and ^{13}C NMR spectra for new compounds. See DOI: 10.1039/x0xx00000x

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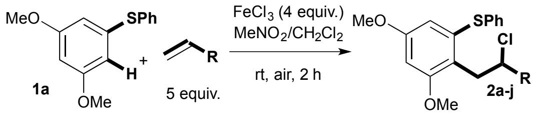
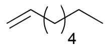
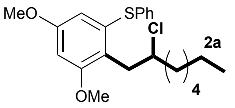
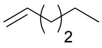
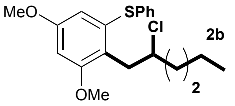
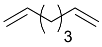
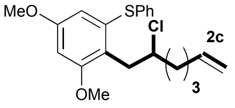
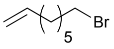
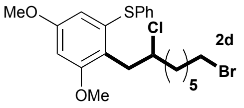
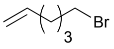
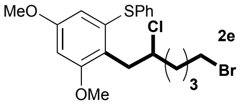
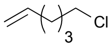
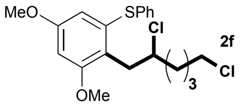
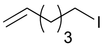
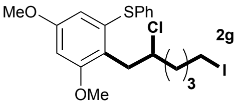
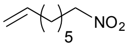
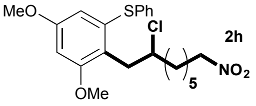
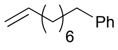
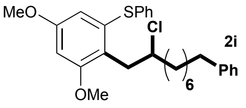
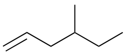
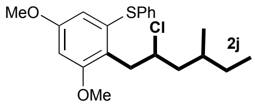
For example, in the context of the C-H coupling of aromatics and heteroaromatics with alkenes, Beller has reported the hydroarylation of styrenes catalysed by $FeCl_3$ to give the corresponding branched 1,1-diarylalkanes that likely proceeds by an S_EAr pathway.[6]

Herein we describe a Fe(III)-mediated C-H *ortho* coupling of arenes and unactivated alkenes directed by sulfur that gives the corresponding linear β-chloroarenes selectively (Scheme 1B). A likely mechanism for the coupling of the two nucleophilic components[7] involves the quenching of radical cations generated by Fe(III)-mediated electron-transfer activation of the arene partner with simple alkenes: a new strategy for arene C-H/alkene cross-coupling.[8]

Initial studies focussed on the reaction of aryl sulfide **1a** and 1-octene, using inexpensive $FeCl_3$ (Table 1). Entries 1-4 show that solvent plays an important role in the reaction.[9] In CH_2Cl_2, starting material was efficiently consumed using $FeCl_3$ (2.2 equiv.) as the oxidant at room temperature in 1.5 h and the coupling product **2a** was obtained in 36% yield (Entry 3). Use of the oxidants $FeCl_3.6H_2O$, $FeBr_3$, $Fe(acac)_3$ gave lower conversions and yields of product (Entries 5-7). The reaction was further improved by changing the atmosphere from N_2: the reaction was found to be as efficient when run in air as when under an O_2 atmosphere (Entries 8 and 9). Reducing the amount of alkene used in the coupling to 5 equiv. did not affect the yield greatly (Entry 10), however, the use of 2 equiv. of alkene lowered the yield of **2a** significantly (Entry 11). Similarly, the use of less $FeCl_3$ (1 equiv.) also resulted in a lower yield of **2a** (Entry 12). In all the reactions in Table 1, the only compounds observed in the product mixtures were **2a** and starting material **1a** and the poor mass balance in some reactions was ascribed to decomposition of a radical-cation intermediate (*vide infra*). To address this issue, slow addition of a solution of $FeCl_3$ in $MeNO_2$ to the sulfide and alkene was employed (Table 1, entries 13-14). Using 2.2 equiv. of $FeCl_3$ in the slow addition protocol gave a greatly improved mass balance (Entry 13). Finally, in the optimised conditions, the use of more $FeCl_3$ (4 equiv.) and the slow addition protocol gave a 70% yield of **2a** with little starting material remaining (Entry 14). With optimised reaction conditions in hand, we began to assess the scope of the process by varying the terminal alkene cross-coupling partner (Table 2). Bromide, chloride, iodide, nitro, alkyl, aryl and alkenyl groups were tolerated in the alkene partners and products were obtained in good yields (46-70%) (Entries 1-10). Interestingly 1,6-heptadiene underwent selective mono-coupling and no double addition product was observed (*vide infra*) (Entry 3). The scope of the process with regard to the aryl sulfide partner was next investigated (Table 3). Although the process is currently sensitive to substitution in the aryl ring undergoing coupling (*vide infra*), significant variation was tolerated in the non-reacting aryl group and methyl (**2k**), bromide (**2l**), fluoride (**2m** and **2r**), nitro (**2n**), trifluoromethyl (**2o**), and methoxy (**2p** and **2q**) substituents, in various positions on the ring, proved to be compatible with the cross-coupling. Finally, the methyl ether groups in **1a** could be changed to *iso*-propyl and allyl ethers with little reduction in the observed efficiency of the cross-coupling (**2s** and **2t**) (Table 3).

Table 2 Variation of alkene in the Fe(III)-mediated C-H coupling



Entry	Substrate	Product	Yield (%)[a]
1			64
2			65
3			56
4			60
5			53
6			46
7			49
8			48
9			63
10			46[b]

[a] Isolated yields. [b] 1:1 Mixture of diastereoisomers.

The products of the C-H arene/alkene cross-coupling are rich in synthetic potential (Figure 1). For example, directed metalation and electrophilic quenching (**3a-c**), sulfur oxidation (**3d**), reduction and elimination of chloride (**3e** and **3f**), and S_N2 displacement of

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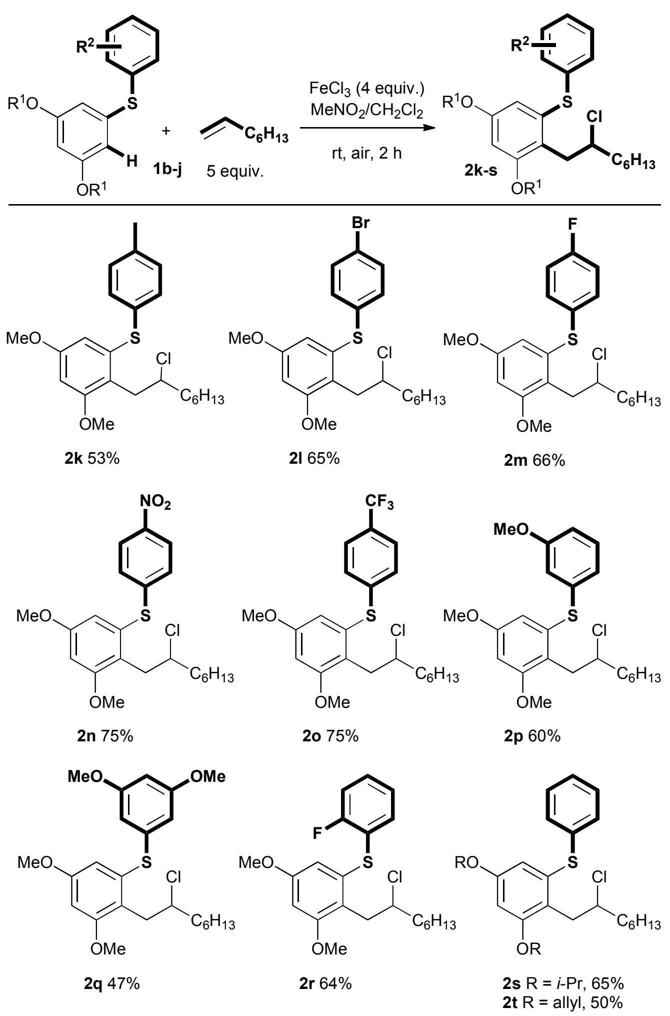
chloride (**3g**) can be carried out. Attractively, **3f** is formally the product of an oxidative Heck reaction involving **1a** and 1-octene.[10] Notably, the products of the cross-coupling resemble biologically important alkylresorcinols.[11] Finally, coupled products undergo deprotection to give important benzofuran motifs (**3h**).

Table 3 Variation of aryl sulfide in the Fe(III)-mediated C-H coupling



The formation of linear rather than branched coupling products suggests that an S_EAr process is not in operation.[6] Furthermore, the use of non-redox active Lewis acids (*e.g.* $BF_3{\bullet}OEt_2$, $Sc(OTf)_3$) resulted in no reaction.[12] A plausible mechanism for the Fe(III)-mediated C-H arene/alkene cross-coupling of aryl sulfides is illustrated in Scheme 2. Single electron oxidation by the strong anhydrous oxidant $FeCl_3$ (approx. +2.00 V (vs SHE) in MeCN)[9] gives radical cation **4** that undergoes coupling with the terminal alkene partner to give intermediate radical cation **5** that is deprotonated to give radical **6**. We have determined the oxidation potential of **1a** and found it to be compatible with the above mechanism (+1.71 V (vs SHE) in MeCN).[12] Oxidation of **6** with $FeCl_3$ then gives carbocation **7** that is quenched by chloride to give coupling products **2**. This mechanism is indirectly supported by the observation that the well-known oxidant CAN mediates the transformation: coupling of **1a** with 1-octene gave the nitrate analogous to **2a** in 47% yield.[12,14] Crucially, the terminal alkene partners have higher oxidation potentials than the aryl sulfides.[13] Preliminary attempts to intercept radical **6** using a 5-hexenyl radical cyclisation were unsuccessful (Table 2, entry 3: **2c** was the only coupled product) suggesting that radical oxidation under the experimental conditions is fast.[15]

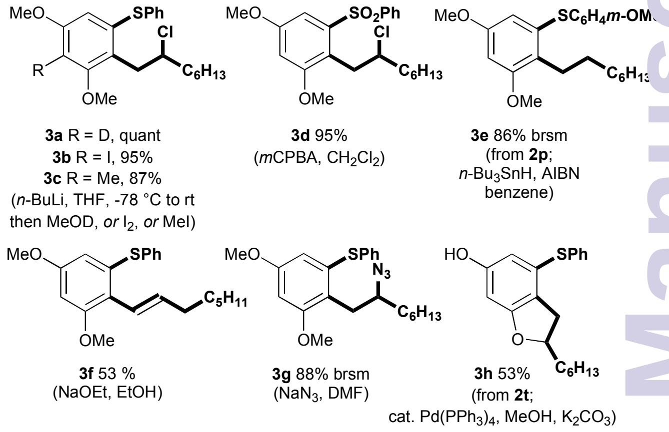
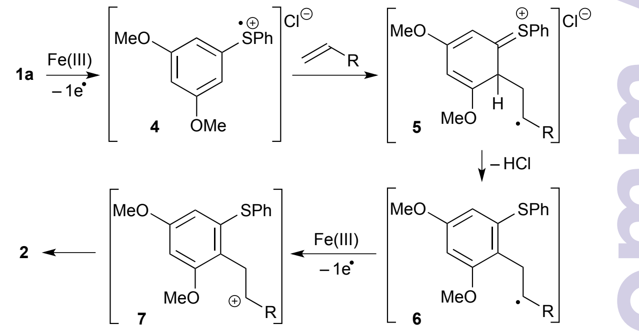


Figure 1 Synthetic manipulation of coupled product **2a**

Both the ease of oxidation of the aryl sulfide and the stability of the resultant radical cation **4** appear to be key to the success of the coupling process. For example, attempted coupling of 3-methoxyphenyl phenylsulfide with 1-octene led to complete consumption of starting material but only a trace of coupling product. As we have determined the oxidation potential of 3-methoxyphenyl phenylsulfide to be very similar to that of **1a** (+1.72 V (vs SHE) in MeCN),[12] we believe destructive side reactions of the aryl radical cation derived from 3-methoxyphenyl phenylsulfide results in inefficient cross-coupling. Thus, the stability of the radical cation **4** may be the most important role of substitution in the aryl sulfide.[16]



Scheme 2 Proposed mechanism of Fe(III)-mediated C-H arene/alkene coupling

Changing the electronic properties of the *para* substituent in the aryl group not involved in cross-coupling had an effect on the overall yield of the coupling process (Table 3). Somewhat surprisingly, coupling reactions to give sulfides **2n** and **2o** bearing electron-withdrawing nitro and trifluoromethyl groups, proceeded in higher yield compared to the coupling of analogous substrates lacking these substituents. A competition reaction between **1a** and **1n** (limiting $FeCl_3$) led to the selective formation of **2a** suggesting

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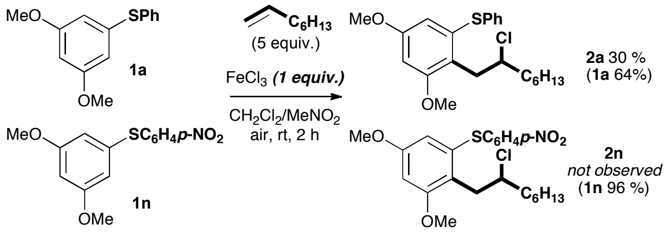
that the rate of coupling is highest for electron-rich substrates (Scheme 3). The higher yields obtained for the cross-coupling of sulfides to give **2n** and **2o** (Table 3) may therefore suggest that a slower rate of substrate oxidation prevents the build-up of large concentrations of radical cations which leads to their decomposition.[16]



Scheme 3 Competition experiment

In summary, Fe(III)-mediated C-H *ortho* coupling of arenes and unactivated terminal alkenes directed by sulfur delivers linear products of alkene chloroarylation in good yields and with high selectivity. A novel mechanism involving redox-activation of the arene partner and alkene addition to the resultant radical cations is proposed.

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14 An alternative process involving electrophilic metalation of the aryl sulfide followed by carbometalation of the alkene is less likely. For nucleophilic metalation, see: a) J. S. Bair, Y. Schramm, A. G. Sergeev, E. Clot, O. Eisenstein and J. F. Hartwig, *J. Am. Chem. Soc.*, 2014, **136**, 13098; b) Y. Hirata, A. Yada, E. Morita, Y. Nakao, T. Hiyama, M. Ohashi and S. Ogoshi, *J. Am . Chem. Soc.*, 2010, **132**, 10070; c) Y. Nakao, N. Kashihara, K. S. Kanyiva and T. Hiyama, *J. Am. Chem. Soc.*, 2008, **130**, 16170.

15 Rate of cyclisation ~1 × 10^5 s^{-1}. A. L. J. Beckwith, *Tetrahedron* 1981, **18**, 3073.

16 This is consistent with the observation that the slow addition of a solution of $FeCl_3$ in $MeNO_2$ to the aryl sulfide and alkene gave the highest yields of coupled product.

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