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Iron-mediated oxidative C–H coupling of arenes and alkenes directed by sulfur: an expedient route to dihydrobenzofurans†

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A novel route to medicinally-relevant dihydrobenzofurans utilises a sulfur-directed C–H *ortho*-coupling of arenes and unactivated terminal alkenes mediated by iron, and a palladium-catalysed deallylation/heterocyclisation sequence. The iron-mediated coupling affords linear products of alkene chloroarylation in good yield and with complete regioselectivity. The coupling likely proceeds by redox-activation of the arene partner by iron(III) and alkene addition to the resultant radical cation.

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Introduction

The search for more sustainable synthetic methods has led to increased interest in cross-couplings that unite two partners at the expense of a C–H bond in each, *i.e.* without the need for pre-functionalisation. Such processes would lead to lower costs, as fewer steps are required, and less waste results, when compared to standard metal-catalysed coupling reactions.¹ The ubiquity of C–H bonds means that achieving regioselectivity in C–H functionalisation can often prove difficult, and directing groups are often necessary to facilitate functionalisation with directed *ortho* C–H bond activation on an aromatic or heteroaromatic ring being a common strategy.² The oxidative *ortho* C–H coupling of arenes and heteroarenes with alkenes has been well investigated using various directing groups, reactive alkenes (*e.g.* acrylates and styrenes), and Pt group metals.³ In contrast, the use of a sulfur-based directing group to direct C–H coupling of an aromatic ring with alkenes is a recent advance and is largely unexplored (Scheme 1A).⁴ The replacement of Pt group metals with inexpensive first row transition metals for synthetic procedures, including those involving C–H functionalisation, has clear benefits.⁵ The low cost of iron, its high abundance, and its low toxicity, make iron-based reagents ideal for new transformations.

Here we describe the Fe(III)-mediated oxidative C–H *ortho* coupling of aryl sulfides with simple, terminal alkenes to give

linear β -chloroarenes.⁶ It is proposed that the two nucleophiles couple through oxidation of the arene partner by Fe(III), followed by addition of the alkene to quench the resulting radical cation.^{7,8} The sulfur-directed, iron-mediated coupling facilitates an expedient, novel route to decorated dihydrobenzofurans; a motif found in many natural products and drug molecules (Scheme 1B). The approach also features a Pd-catalysed deprotection/heterocyclisation and Ni-catalysed cross-couplings of sulfides (Scheme 1C).

Results and discussion

Scope and limitations

Previously reported optimisation studies found that FeCl₃ was the most effective oxidant for the C–H coupling of diaryl sulfides and alkenes and that the reaction proceeded at ambient temperature under air in CH₂Cl₂.⁶ As the coupling is thought to involve reactive radical cation intermediates that are prone to decomposition, slow addition of the Fe(III) oxidant to a mixture of arene and alkene was employed to maintain a low concentration of radical cation. Slow addition of FeCl₃ was found to give improved mass balance and yield. Regardless of how the oxidant was added, crude ¹H NMR spectra showed clean product and mass balance was the only issue.

We next assessed the scope of the process by varying the alkene partner in the coupling process (Scheme 2). Products were obtained in good isolated yields (37–65%) from couplings of alkene substrates bearing alkenyl (**2b**), iodide (**2c**), bromide (**2d** and **2e**), chloride (**2f**), aryl (**2g** and **2h**), and nitro (**2j**) functionality. Interestingly, 1,6-heptadiene underwent selective coupling to give the monoaddition product (formation of **2b**):

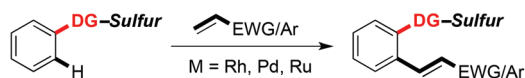
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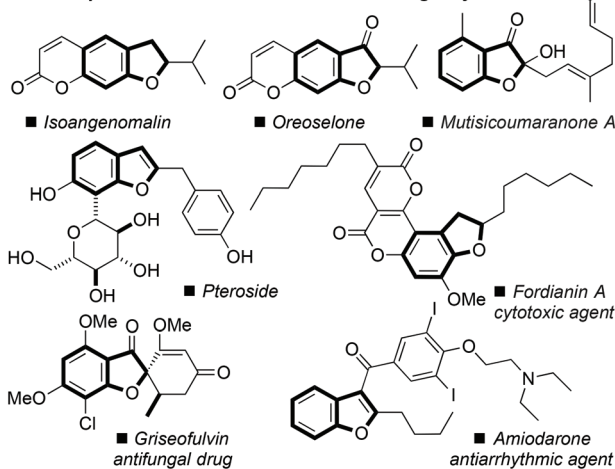
† Electronic supplementary information (ESI) available: Additional experiments, full experimental details for the preparation of compounds, ¹H and ¹³C NMR spectra for new compounds. See DOI: 10.1039/c6ob00883f



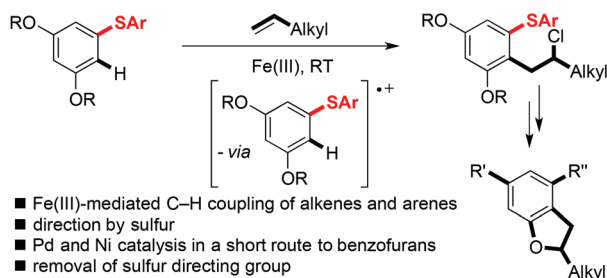
A. Pt-group metal-mediated, sulfur-directed C-H arene/alkene coupling



B. The importance of the benzofuran motif in target synthesis



C. This work: Fe-mediated, sulfur-directed C-H arene/alkene coupling in a novel route to dihydrobenzofurans



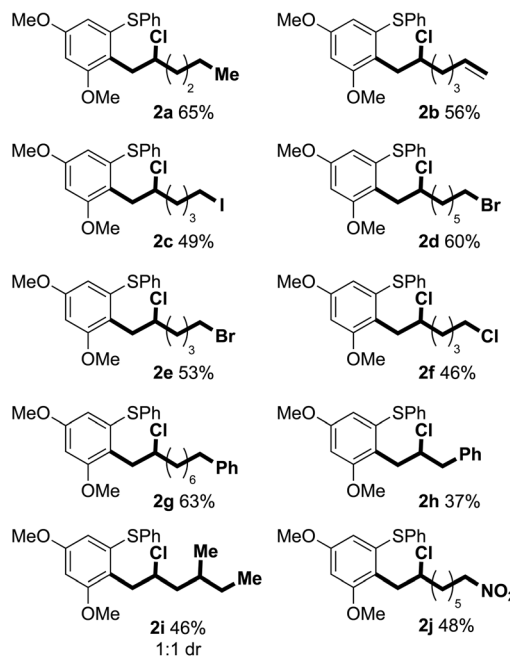
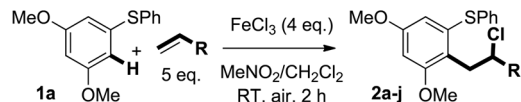
Scheme 1 A. Pt-group metal-mediated, sulfur-directed C-H alkenylation. B. Benzofuran motifs in important synthetic targets. C. This work: Fe(III)-mediated, sulfur directed C-H coupling of arenes and alkenes exploited in a novel approach to dihydrobenzofurans. DG-Sulfur = Sulfur-containing directing group.

the corresponding double addition product was not observed (*vide infra*).

The scope with regard to the aryl sulfide partner was next assessed (Scheme 3). Although the coupling is sensitive to substitution in the aryl ring undergoing carbon-carbon bond formation (*vide infra*), the non-reacting, right-hand aryl ring can be varied: methyl (**2k**), bromide (**2l**), fluoride (**2m** and **2n**), nitro (**2o**), trifluoromethyl (**2p**), and methoxy (**2q** and **2r**) groups were compatible with the coupling and products were isolated in good yield.

Whilst 3,5-dioxygenation in the left-hand aryl ring of the diaryl sulfides has to date proved indispensable, allyl- and isopropoxyethers can also be used in the C-H coupling and products were isolated in moderate yield. The use of an allyl ether-containing substrate allowed interesting avenues for product manipulation to be explored (*vide infra*, Scheme 4).

Fig. 1 shows a selection of substrate combinations that did not result in successful coupling. Styrene was an ineffective



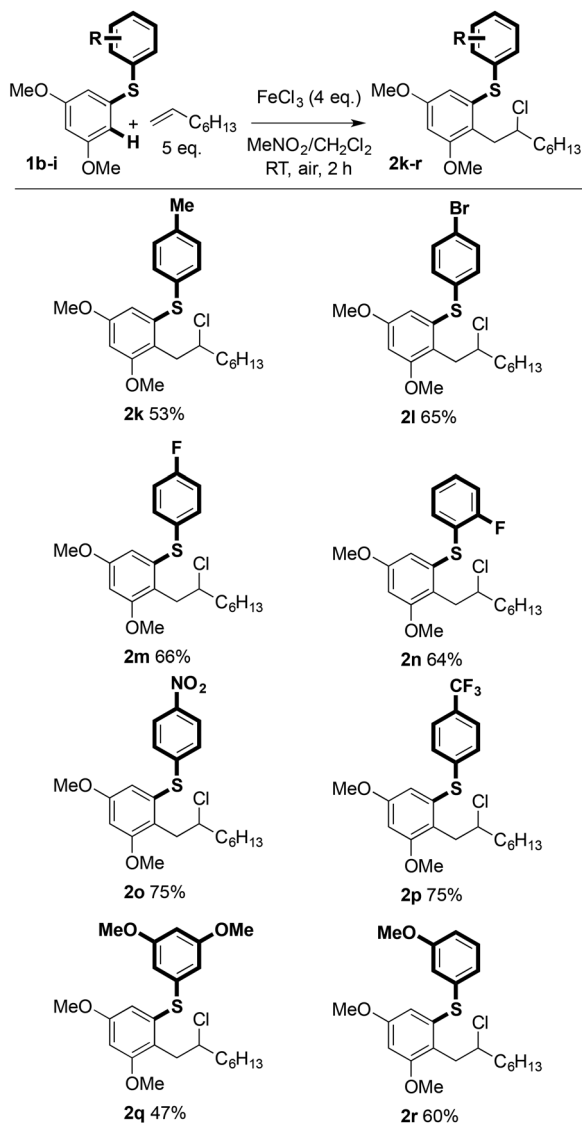
Scheme 2 Variation of alkene in the Fe(III)-mediated C-H coupling.

partner potentially due to it being easily oxidised and thus reacting with FeCl_3 . Alkenes bearing oxygen-containing functionality, such as ketones and alcohols, also proved ineffective coupling partners. This is likely due to competitive coordination of Fe(III) to the Lewis basic sites in the alkene partner. Finally, internal alkenes, such as cyclohexene, did not undergo coupling. In terms of the arene partner, 3-methoxyphenyl phenyl sulfide did not undergo coupling with 1-octene (*vide infra*). Also, in contrast to substrates bearing nitro and trifluoromethyl groups in the right-hand aryl ring, the presence of an electron-donating substituent in the *para*-position of that ring adversely affected coupling. This may be due to formation of a thioquinone-type species. To date, alkyl aryl sulfides have also proved to be incompatible with the coupling reaction. Additional substrates that failed to undergo coupling can be found in the ESI.†

Mechanistic insights

Carbon-carbon bond formation at the terminal position of the alkene, and the formation of linear products, rather than coupling at the internal position of the alkene, and the formation of branched products, suggests that an $\text{S}_{\text{E}}\text{Ar}$ process is not operational.⁹ In addition, control experiments using non-redox-active Lewis acids did not result in product formation (Scheme 5).

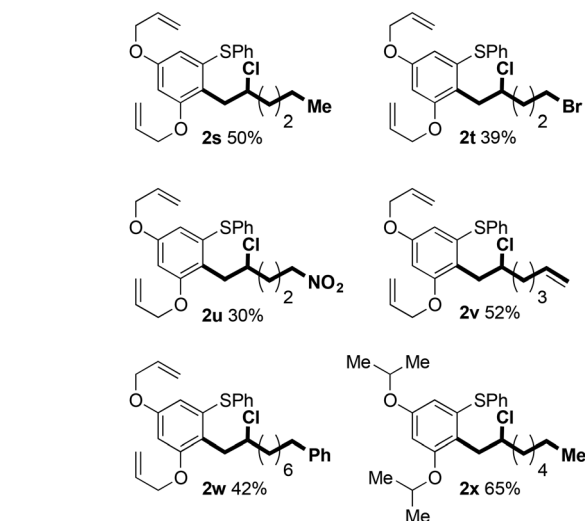




Scheme 3 Variation of aryl sulfide in the Fe(III)-mediated C–H coupling.

Scheme 6 shows a plausible mechanism for the Fe(III)-mediated arene/alkene coupling.¹⁰ Oxidation of the aryl sulfide **1** by the anhydrous oxidant FeCl₃ [approx. +2.00 V (vs. SHE) in MeCN]¹¹ gives radical cation **A**. Addition of the terminal alkene partner then gives intermediate radical cation **B**. The preference for bond formation *ortho* to sulfur may indicate that chelation with the metal centre in **D** directs reaction towards this position.¹² Substrates in which the arylsulfanyl substituent was replaced by an alkoxy or alkylamino substituent failed to undergo coupling, thus highlighting the important role played by sulfur (see the ESI†).

Our studies show that the oxidation potential of **1a** [+1.71 V (vs. SHE) in MeCN] is compatible with the initial step of the proposed mechanism (Fig. 2). A carbocation is then formed by the oxidation of radical cation **B** with FeCl₃ that is then quenched by chloride to deliver the products **2**. Indirect evidence for this mechanism comes from the observation that



Scheme 4 Variation of ether protection in the aryl sulfides undergoing Fe(III)-mediated C–H coupling.

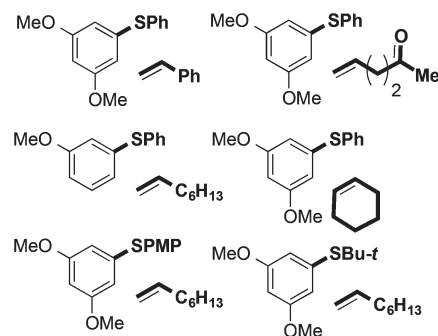
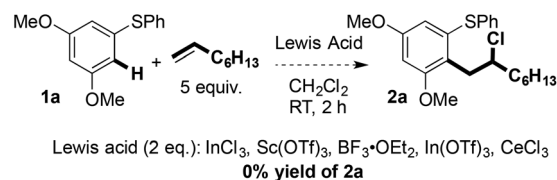


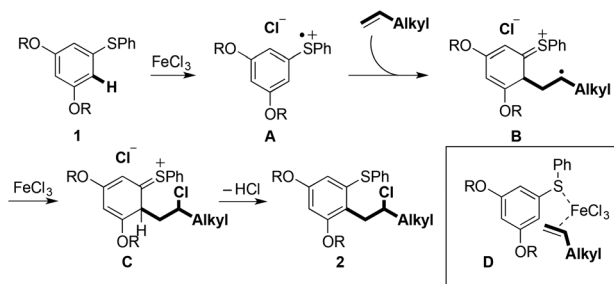
Fig. 1 Unsuccessful arene and alkene combinations for C–H coupling. PMP = 4-MeOC₆H₄.



Scheme 5 Control reactions employing a variety of Lewis acids.

well-known oxidant CAN mediates a similar transformation: coupling of **1a** with 1-octene gave the nitrate analogous to **2a** in 56% yield (Scheme 7).^{13,14} Furthermore, the oxidation of diaryl sulfides to the corresponding sulfoxides using CAN is





Scheme 6 Proposed mechanism of Fe(III)-mediated C–H arene/alkene coupling.

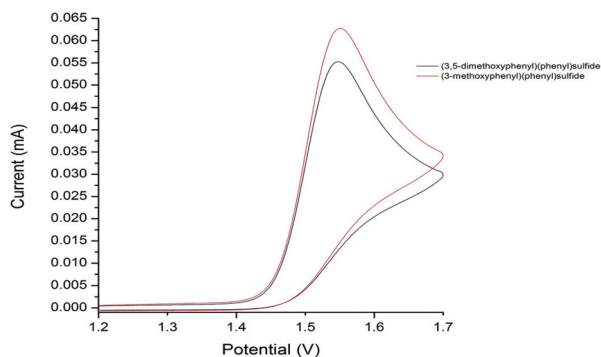
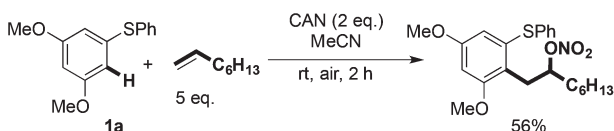


Fig. 2 Voltammograms for 3-methoxyphenyl phenyl sulfide and (3,5-dimethoxyphenyl)phenyl sulfide versus reference electrode.

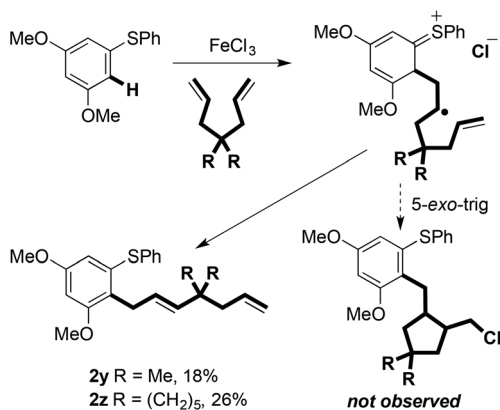


Scheme 7 CAN-mediated C–H coupling to give an analogous product.

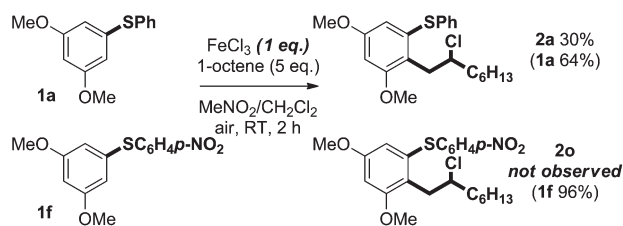
proposed to proceed through radical cations analogous to **A**.¹⁵ The terminal alkene partners are known to have higher oxidation potentials than the aryl sulfides.¹⁶

5-hexenyl ‘radical clock’ cyclisation was used in an unsuccessful attempt to intercept radical **B** (Scheme 2: **2b** was the only coupled product observed). Thus, under the experimental conditions, radical oxidation appears to be faster than cyclisation (*i.e.* $>1 \times 10^5 \text{ s}^{-1}$) (Scheme 8).^{17,18} Interestingly, attempts to promote cyclative radical trapping using dienes bearing geminal dialkyl substitution led to alternative coupling products **2y** and **2z** in low yield (Scheme 8). This may be due to the increased steric bulk impeding trapping of the carbocation intermediate with chloride.

Two factors appear crucial to the success of the cross-coupling process; (i) the ease of oxidation of the aryl sulfide, and (ii) the stability of the resultant radical cation **A**. For example, attempts to use 3-methoxyphenyl phenyl sulfide as a coupling partner with 1-octene led to only a trace of product even though the aryl sulfide starting material was consumed. We



Scheme 8 Attempts to trap radical intermediates formed during the Fe(III)-mediated C–H coupling.



Scheme 9 Competition experiment exploring the influence of the right-hand aryl ring.

have measured the oxidation potential of 3-methoxyphenyl phenyl sulfide and found it to be similar to that of **1a** [+1.72 V (*vs.* SHE) in MeCN] (Fig. 2), therefore, we propose that deleterious side reactions of the radical cation derived from 3-methoxyphenyl phenyl sulfide are likely responsible for inefficient carbon–carbon bond formation. Steric stabilisation of the radical cation **A** may therefore be the most important role played by substituents in the ring undergoing coupling in the aryl sulfide.

Switching the electronic properties of the *para* substituent in the non-coupling, right-hand aryl ring of substrates affected the yield of the process (Scheme 3). Coupling reactions of aryl sulfide substrates bearing nitro and trifluoromethyl electron-withdrawing groups, to give sulfides **2o** and **2p**, gave products in higher yield than processes involving comparable substrates lacking these substituents. As expected, the competition experiment shown in Scheme 9 using limiting FeCl₃ suggests that the rate of coupling is highest for electron-rich substrates: a mixture of 1-octene, **1a** and **1f** selectively delivered **2a** with no trace of **2o**. It appears likely that a decreased rate of aryl sulfide oxidation, thus avoiding large concentrations of radical cations that lead to decomposition,¹⁹ results in the improved yields obtained for the coupling of aryl sulfides to give **2o** and **2p** (Scheme 3).

Product manipulation

The products of C–H arene/alkene coupling possess a range of functional handles for further manipulation (Fig. 3). For



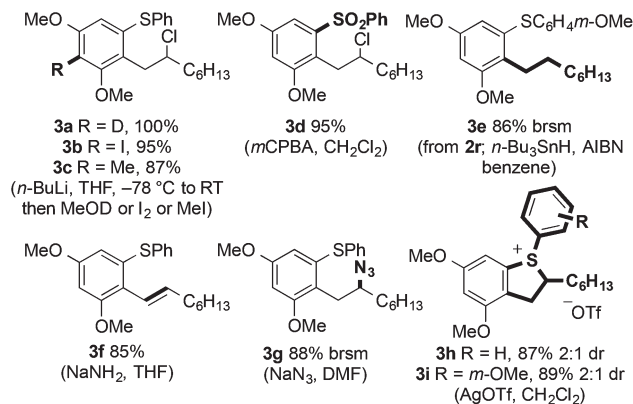


Fig. 3 Synthetic manipulation of coupled product **2a**.

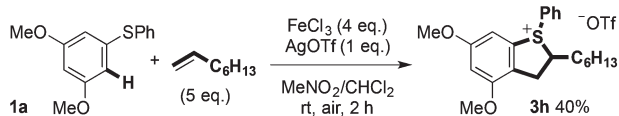
example, directed *ortho*-metalation of **2a** followed by reaction with various electrophiles (to form **3a–c**), oxidation of sulfur (to give sulfone **3d**), reduction and elimination of chloride (to form **3e** and **3f**, respectively), and S_N2 displacement of chloride (to give azide **3g**) can be efficiently performed.

Notably, styrene **3f** is formally the product of an oxidative Heck reaction involving aryl sulfide **1a** and 1-octene.²⁰ Coupling products can also undergo dehalogenation when treated with silver(I) salts to give the cyclic sulfonium salts (**3h** and **3i**) as a 2 : 1 mixture of diastereoisomers. Carrying out the Fe(III)-mediated C–H alkene/arene coupling in the presence of AgOTf allowed the sulfonium salt **3h** to be prepared directly in moderate isolated yield (Scheme 10).

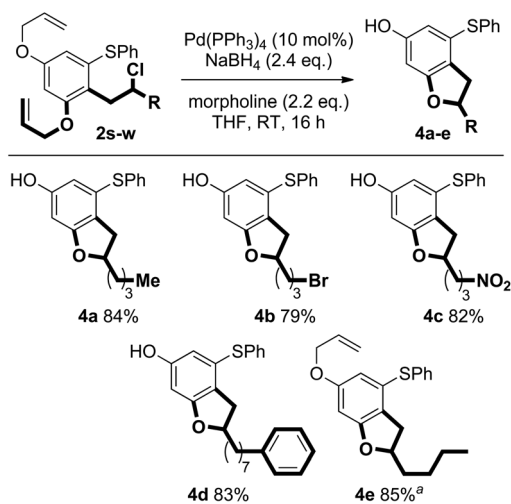
Pd-catalysed deprotection of the allyl ethers in the products of coupling **2s–w** triggered cyclisation to give important benzofuran scaffolds. The reaction proceeds efficiently under mild conditions employing NaBH₄ and the allyl scavenger, morpholine. Interestingly, when NaH was used in place of NaBH₄, only the mono-deprotected benzofuran product **4e** was observed (Scheme 11).

Conversion of dihydrobenzofuran **4a** to the corresponding triflate **5** (Tf₂NPh, *t*BuONa, THF, 2 h; 87%) paved the way for further decoration of the heterocyclic scaffold. Pd-catalysed Suzuki-Miyaura cross-coupling²¹ gave **6a–c** in high isolated yield. Alternatively, copper-free, Pd-catalysed Sonogashira cross-coupling gave **6d** in excellent isolated yield (Scheme 12).²²

The arylsulfanyl directing group can be removed using RANEY® nickel in excellent yield (RANEY® Ni, EtOH, 1 h) (Fig. 4). Notably, reductive removal of the arylsulfanyl from the products of Fe(III)-mediated C–H coupling completes a concise approach to biologically important alkylresorcinols (*e.g.* **7a**).²³

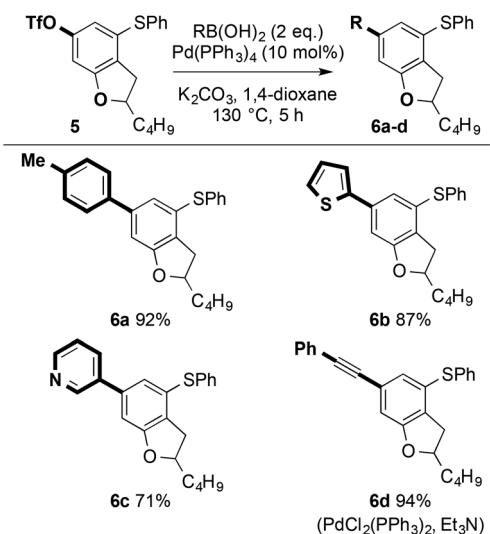


Scheme 10 Direct Fe(III)-mediated C–H coupling to form cyclic sulfonium salt.



^a NaH was used in place of NaBH₄

Scheme 11 Pd-catalysed deallylation/cyclisation.



Scheme 12 Pd-catalysed couplings for the decoration of dihydrobenzofurans.

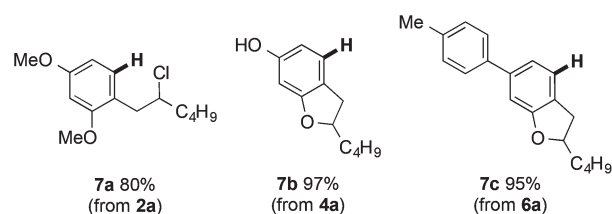
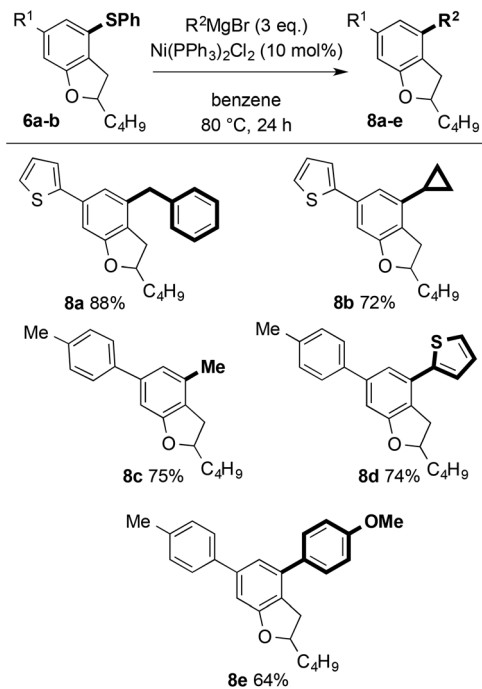


Fig. 4 Reductive removal of the arylsulfanyl directing group using RANEY® Ni.

More attractively, the arylsulfanyl directing group can also act as a synthetic handle for the introduction of further diversity. Nickel-catalysed Kumada couplings with aromatic, hetero-aromatic, and aliphatic Grignard reagents allow efficient





Scheme 13 Ni-catalysed couplings for the decoration of dihydrobenzofurans.

further decoration of the dihydrobenzofuran motifs (Scheme 13).²⁴ Notably, nickel-catalysed coupling to give **8a** and **8b**, proceeded smoothly with no nickel insertion into thiophene C–S bonds.²⁵

Conclusions

A novel route to medicinally-relevant dihydrobenzofurans has been developed that utilises a sulfur-directed C–H *ortho*-coupling of arenes and unactivated terminal alkenes mediated by iron, and a palladium-catalysed deallylation/heterocyclisation. The iron-mediated coupling affords linear products of alkene chloroarylation with complete regioselectivity. Redox-activation of the arene partner by iron(III) and coupling of the resultant radical-cation with the alkene partner is proposed. The dihydrobenzofuran scaffolds can be readily decorated using Pd and Ni-catalysed cross-couplings.

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