

Cite this: *Chem. Sci.*, 2022, 13, 10291

All publication charges for this article have been paid for by the Royal Society of Chemistry

Iron-catalysed alkene and heteroarene H/D exchange by reversible protonation of iron-hydride intermediates†

Luke Britton,^a Jamie H. Docherty,^a ^{*a} Jan Sklyaruk,^a Jessica Cooney,^a Gary S. Nichol,^a ^a Andrew P. Dominey^b and Stephen P. Thomas ^{*a}

C–H functionalisation reactions offer a sustainable method for molecular construction and diversification. These reactions however remain dominated by precious metal catalysis. While significant interest in iron-catalysed C–H activation reactions has emerged, the isolation, characterisation and mechanistic understanding of these processes remain lacking. Herein the iron-catalysed C(sp²)-H bond hydrogen/deuterium exchange reaction using CD₃OD is reported for both heterocycles and, for the first time, alkenes (38 examples). Isolation and characterisation, including by single-crystal X-ray diffraction, of the key iron-aryl and iron-alkenyl C–H metallation intermediates provided evidence for a reversible protonation of the active iron hydride catalyst. Good chemoselectivity was observed for both substrate classes. The developed procedure is orthogonal to previous iron-catalysed H/D exchange methods which used C₆D₆, D₂, or D₂O as the deuterium source, and uses only bench-stable reagents, including the iron(II) pre-catalyst. Further, a new mechanism of iron-hydride formation is reported in which β-hydride elimination from an alcohol generates the iron hydride. The ability to produce, isolate and characterise the organometallic products arising from C–H activation presents a basis for future discovery and development.

Received 7th July 2022

Accepted 8th August 2022

DOI: 10.1039/d2sc03802a

rsc.li/chemical-science

Introduction

Metal-catalysed C–H functionalisation has emerged as a powerful synthetic method for the direct derivatisation of typically inert C–H bonds and obviating the need for pre-functionalised substrates.¹ While the application of C–H functionalisation strategies has expanded, these methods generally rely on precious metal catalysts. Examples using Earth-abundant metal,² and even non-metal,³ catalysts have emerged as potential alternatives, however their use and development has been comparably limited.

A number of iron-catalysed C–H functionalisation methods have been developed,^{2a} but the isolation and characterisation of well-defined, catalytically relevant species has remained limited to only a few studies, particularly where C–H metallation, sometimes referred to as C–H activation, has been proposed.⁴ Holland reported the observation and isolation of an iron-aryl species arising from C–H metallation of benzene using a low oxidation-state iron β-diketimate complex (Scheme 1a).^{4a}

Similarly, Ackermann reported the C–H metallation of pivalophenone using a low oxidation-state iron complex [Fe(PMe₃)₄] that allowed for the isolation and characterisation of the key iron-aryl species responsible for allene hydroarylation (Scheme 1a).^{4b,c} Additional iron-aryl complexes have been isolated and characterised through independent synthesis, usually from organometallic aryl reagents.^{4d-g}

The iron bisdiphosphino complex, [dmpe₂FeH₂] 2 (dmpe = Me₂PCH₂CH₂PMe₂), has been shown to undergo stoichiometric C–H bond metallation of benzene in solution-phase studies.⁵ It was therefore questioned whether the metallation of C(sp²)-H bonds could be made general and harnessed to generate an iron-aryl species applicable to H/D exchange. In order to achieve H/D exchange, photoirradiation of [dmpe₂FeH₂] 2 would be used to trigger H₂ elimination to give [dmpe₂Fe⁰]. This would undergo C(sp²)-H bond oxidative addition (metallation) to give an aryl(hydrido) iron species, [dmpe₂Fe(H)Ar], from which exchange of the hydrido-ligand to the deuteride isotopologue, would give [dmpe₂Fe(D)Ar], and leave only a final reductive elimination to complete a potential catalytic cycle.

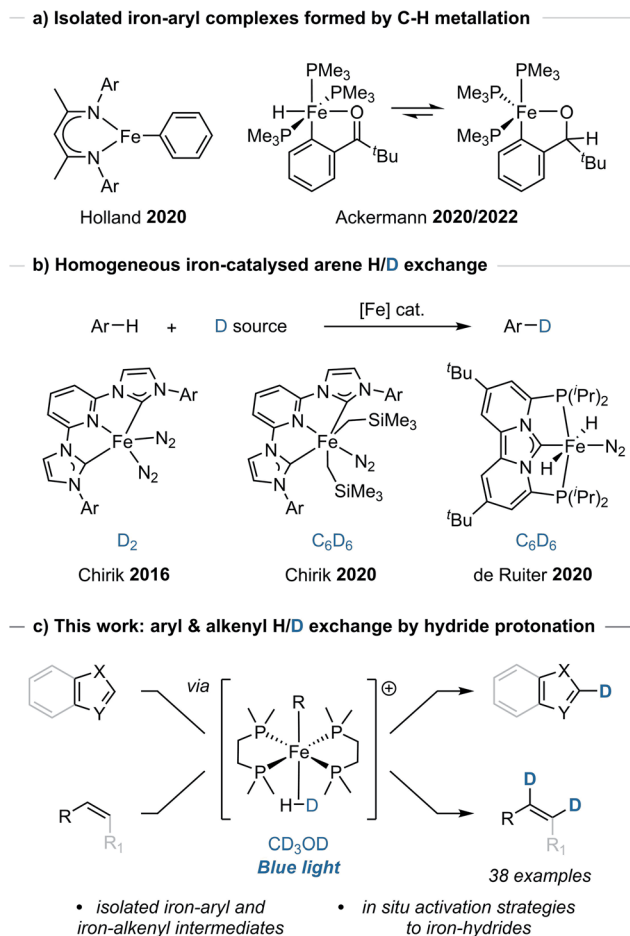
Commonly, direct H/D exchange reactions have involved the use of precious metal catalysts, with only a few Earth-abundant systems reported. Chirik reported the H/D exchange of arenes using iron-pincer complexes [(MesCNC)Fe(N₂)₂] and deuterium gas, as well as [(MesCNC)Fe(CH₂SiMe₃)₂(N₂)] and C₆D₆ (Scheme 1b).⁶ de Ruiter reported the C₆D₆-mediated H/D exchange

^aEaStCHEM School of Chemistry, University of Edinburgh, Edinburgh EH9 3FJ, UK. E-mail: jamie.docherty@ed.ac.uk; stephen.thomas@ed.ac.uk

^bGSK Medicines Research Centre, Stevenage SG1 2NY, UK

† Electronic supplementary information (ESI) available. CCDC 2073340, 2073339, 2159501. For ESI and crystallographic data in CIF or other electronic format see <https://doi.org/10.1039/d2sc03802a>





Scheme 1 a) Previous examples of isolated iron-aryl complexes by direct C–H metallation. (b) Previous homogeneous iron-catalysed H/D exchange catalysts. (c) This work: arene and alkene C–H metallation and H/D exchange using CD₃OD and a bench-stable iron(II) pre-catalyst.

reactions of (hetero)arenes using an alternative iron-complex [(PCNHCP)Fe(H)₂(N₂)] (Scheme 1b).⁷ Beller and Lei reported the H/D exchange reaction of arenes bearing electron-donating groups using D₂O and a heterogeneous iron catalyst.⁸ Additional examples of Earth-abundant metal-catalysed HIE reactions of arenes have been reported which rely on pre-installed directing groups.⁹ Of note to this manuscript, Hartwig used a Ag₂CO₃/JohnPhos catalyst and CH₃OD for the H/D exchange reaction of 5-membered heteroarenes.¹⁰

Results and discussion

Investigations began by exploring the viability of H/D exchange with a selection of related iron pre-catalysts, deuterium sources and catalyst activation methods (see ESI, Tables S1–S3†). Pre-catalyst activation with alkoxide salts has been shown to generate catalytically active metal-hydride species when combined with commercial silane or borane reagents such as pinacolborane (HBpin).¹¹ This removes the need to generate and handle the highly air- and moisture sensitive iron

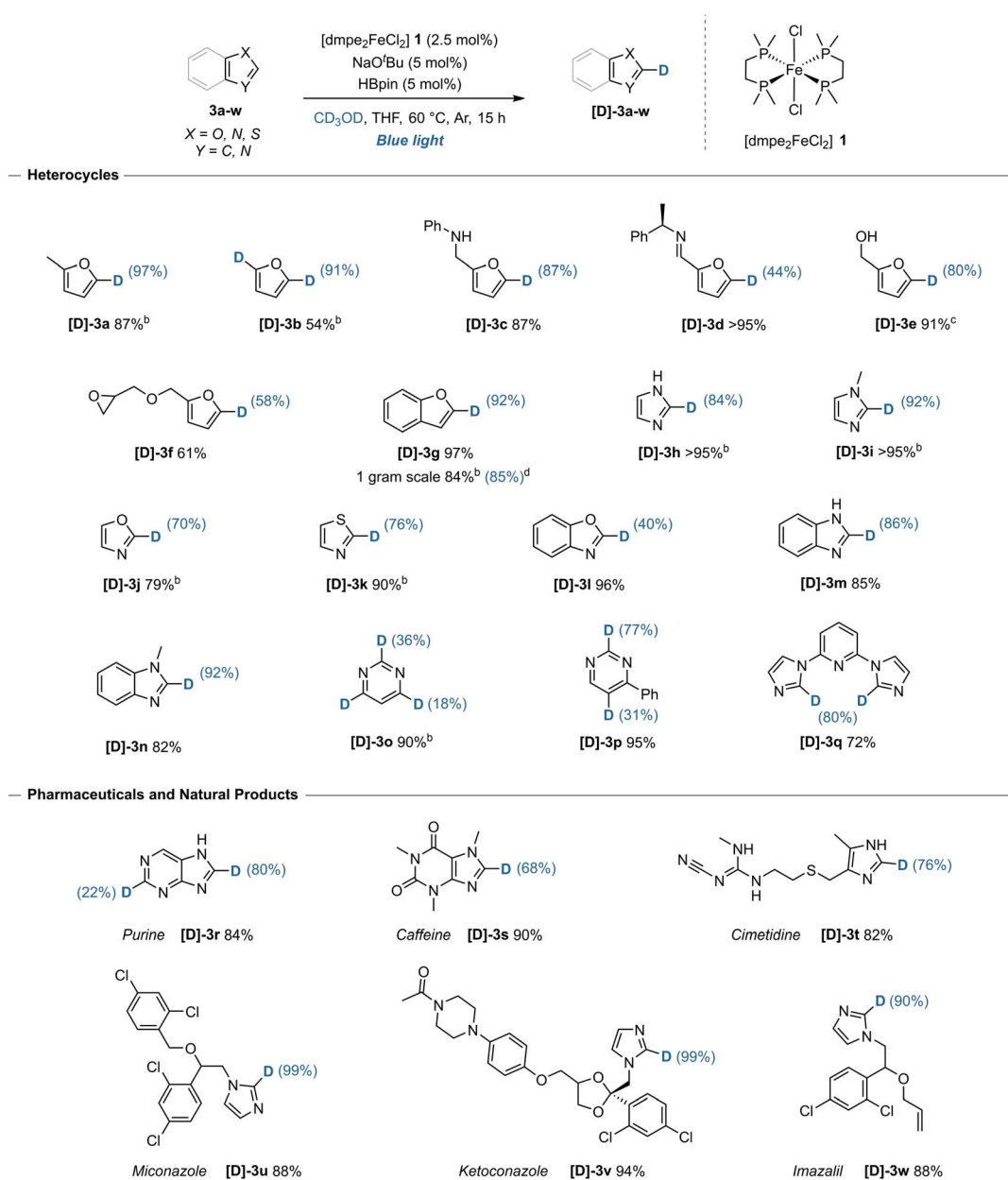
dihydride. To assess the catalytic feasibility of this strategy *in situ* generated [dmpe₂FeH₂] **2** (from [dmpe₂FeCl₂] **1** + NaO^tBu + HBpin) was used in combination with 2-methylfuran **3a**, blue light irradiation (450 nm) and a variety of deuterium sources. Deuterium incorporation was achieved using deuterated alcohols as the deuterium source, with CD₃OD giving the highest deuterium incorporation and exclusive C-5 regioselectivity. Control reactions showed the necessity for continuous light irradiation, iron complex, phosphine ligand, and the alkoxide activator (see ESI, Table S4†). Notably, good levels of deuterium incorporation were observed even in the absence of HBpin (*vide infra*). Optimisation of the light source using monochromatic LEDs in the range of 365–525 nm, showed the blue region (450 nm) of the spectrum to be optimal (see ESI, Table S5†). The substitution of CD₃OD for CD₃OH resulted in no deuterium incorporation, indicating that the most acidic, alcohol, hydrogen was responsible for deuterium-exchange. The state-of-the-art precious metal equivalent for non-directed H/D exchange of arenes using ROD-type deuterium sources resulted in global C–H deuteration and showed no chemoselectivity for alkene *versus* arene C–H bonds (reaction conditions: Pd(OAc)₂ (10 mol%), ligand (15–30 mol%), HFIP : D₂O = 3 : 7, 80–120 °C, 18–48 h).¹²

Catalytic H/D exchange of heteroarenes

The generality of the method with respect to substrate compatibility and scope was then assessed (Table 1). Furan **3b**, furan derivatives bearing a free secondary-amine **3c** and imine **3d** all underwent successful, chemoselective deuteration to give the monodeuterated furans [D]-**3b**, [D]-**3c** and [D]-**3d**, respectively, with good to excellent deuterium incorporation and complete control of regioselectivity (C-5) in all cases. Pinacol boronic ester protected alcohol **3e** reacted to give the deuterated isotopologue [D]-**3e**, albeit with alcohol deprotection upon work up. Benzofuran **3g** underwent site-selective deuteration at the C-2 position, with no detectable deuteration at any of the other five available C(sp²)–H bonds. Unprotected imidazole **3h** and methyl-protected imidazole **3i** underwent exclusive C-2 selective deuteration to give the deuterated imidazoles [D]-**3h** and [D]-**3i**, respectively. This is notable as both previously reported iron-catalysts gave unselective deuteration of *N*-methyl imidazole with exchange at all the C(sp²)–H bonds.^{6,7} Using this system, oxazole **3j**, 1,3-thiazole **3k** and benzoxazole **3l** all underwent deuteration with mild to good deuterium incorporation, again at a single site. 6-Membered heterocycle pyrimidine **3o** proved amenable to deuteration at C-2, C-4 and C-6, albeit with only moderate incorporation. When 4-phenylpyrimidine **3p** was used, deuteration occurred at both C-2 and C-5 positions with significantly greater inclusion than the unsubstituted analogue.

To illustrate the utility and tolerance of this system with respect to complex targets, the deuteration procedure was successfully applied to several pharmaceutical and natural product structures (Table 1, lower). Purine **3r**, a compound ubiquitous to biological systems and common foodstuffs, reacted efficiently with incorporation at both C-2 and C-8. A further range of biologically active molecules including caffeine



Table 1 Iron-catalysed Site-selective Heteroarene C(sp²)-H H/D Exchange^a

^a Reaction conditions: arene (0.33 mmol), [dmpe₂FeCl₂] **1** (2.5 mol%), NaO^tBu (5 mol%), HBpin (5 mol%), THF (0.2 mL), CD₃OD (0.2 mL), blue-light irradiation, 15 h. Reported yields denote quantity of material recovered post-reaction. Deuterium incorporation determined by ¹H and/or ¹³C NMR spectroscopy. ^b Quantity of recovered product determined using 1,3,5-trimethoxybenzene as an internal standard. ^c Starting material **3e** = 4,4,5,5-tetramethyl-2-(furan-2-ylmethoxy)-1,3,2-dioxaborolane, free alcohol [D]-**3e** isolated following deprotection. ^d Performed on a 9.3 mmol scale, 48 h.

3s, histamine receptor antagonist cimetidine **3t** and antifungal compounds; miconazole **3u**, ketoconazole **3v** and imazalil **3w**, all reacted efficiently with predictable deuterium incorporation at the most acidic C(sp²)-H site. While the imidazole unit of **3w** underwent H/D exchange under the reaction conditions to give [D]-**3w**, the allylic ether was not deuterated. The functional group compatibility and regioselectivity shown illustrates the system is suitable for potential late-stage site-selective isotopic exchange of heteroarene units.

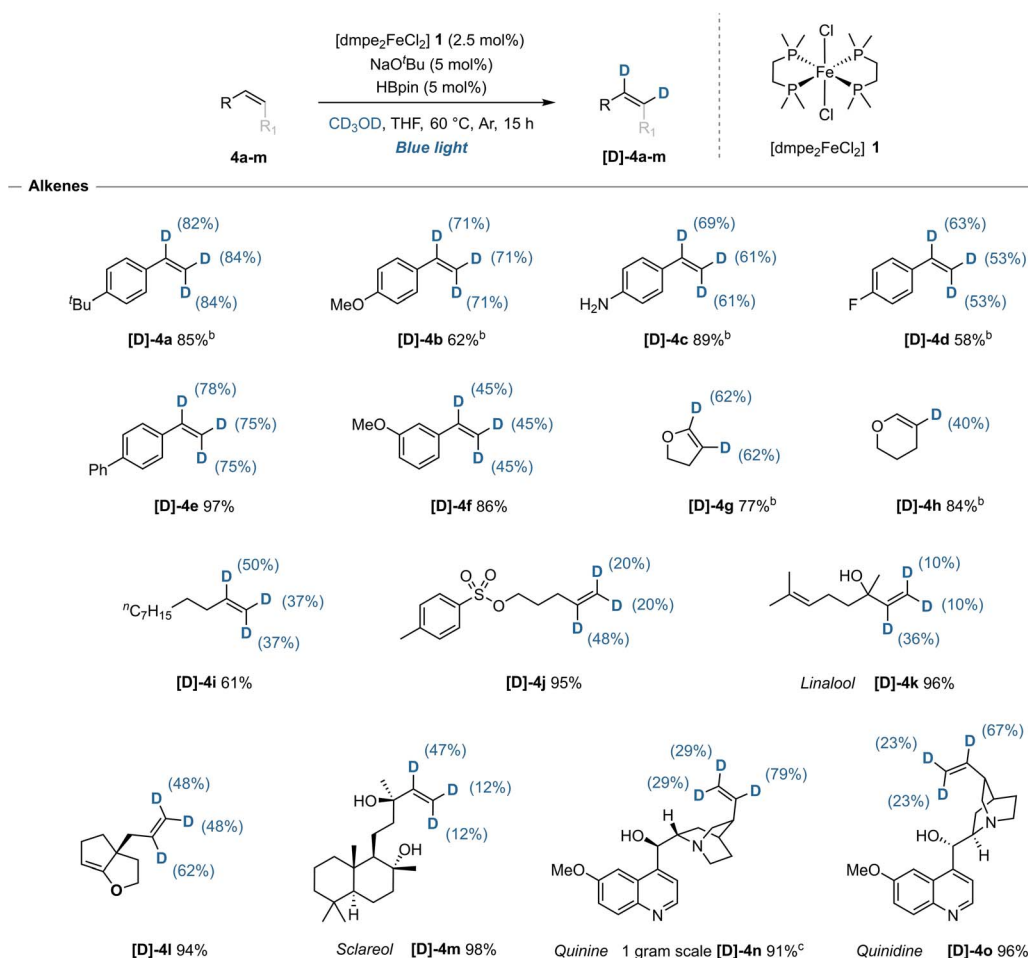
While high levels of deuterium incorporation were obtained using this system, it must be noted that an alternative alkoxide-mediated reaction exists for substrates with highly acidic C(sp²)-H bonds. Excluding benzoxazole **3l**, which achieved greater levels of deuterium incorporation in the absence of pre-catalyst and HBpin,¹³ all substrates underwent greater deuterium incorporation and selectivity under the iron-catalysed reaction conditions (see ESI, Table S8†).



Catalytic H/D exchange of alkenes

While H/D exchange reactions of alkenes with non-reductive sources of deuterium, *i.e.* CD₃OD, D₂O or C₆D₆, have been previously reported using precious metals catalysts (iridium,¹⁴ rhodium,¹⁵ ruthenium,¹⁶ and palladium¹⁷), Earth-abundant metal-mediated H/D exchange reactions of alkenes have so far been limited to either stoichiometric studies,¹⁸ or unwanted side reactions.¹⁹ Using this iron-catalysed system, styrene derivatives **4a–f** bearing both electron-donating- and electron-withdrawing groups were efficiently deuterated at all alkene positions with no detection of deuterium incorporation at any of the arene C(sp²)-H bonds. This represents the first reported example of an iron-catalysed H/D exchange reaction of alkenes (Table 2). It was observed that for the deuteration of styrene derivatives there was a slight trend for greater deuterium incorporation at the α position relative to both β positions, contrasting with results often seen with precious metal alternatives.^{14b,15b,17}

2,3-Dihydrofuran **4g** underwent deuteration at both alkene C(sp²)-H bonds while the 6-membered 2,3-dihydropyran **4h** was selectively deuterated at the 3-position. Monosubstituted acyclic alkenes undecene **4i** and *O*-tosyl alkene **4j** both underwent moderate deuterium incorporation. Naturally occurring allylic alcohols Linalool **4k** and anti-cancer agent Sclareol **4m**, both of which contain free alcohol groups, were deuterated with moderate deuterium incorporation. Cinchona alkaloid quinine **4n** and diastereoisomer quinidine **4o** were both successfully reacted and with exclusive deuteration of the alkene over the other five available C(sp²)-H sites. Minimal reactivity was displayed towards carbon substituted 1,2-*cis* alkenes including cyclohexene and cyclooctene, and no reactivity was observed for *trans*-, 1,1-disubstituted-, trisubstituted- or activated (*e.g.* acrylates or acrylamides) alkenes. Background, base-mediated H/D exchange was not observed for any alkene substrate (see ESI, Table S8†).²⁰

Table 2 Iron-catalysed selective alkene C(sp²)-H H/D Exchange^a

^a Reaction conditions: alkene (0.33 mmol), [dmpe₂FeCl₂] **1** (2.5 mol%), NaO^tBu (5 mol%), HBpin (5 mol%), THF (0.2 mL), CD₃OD (0.2 mL), blue-light irradiation, 15 h. Reported yields denote quantity of material recovered post-reaction. Deuterium incorporation determined by ¹H and/or ¹³C NMR spectroscopy. ^b Quantity of recovered product determined using 1,3,5-trimethoxybenzene as an internal standard. ^c Performed on a 3.4 mmol scale (1.0 g recovered), 48 h.



of $[\text{dmpe}_2\text{FeCl}_2]$ **1** were observed to exist as a 1 : 1 electrolyte of $[\text{dmpe}_2\text{Fe}(\text{HOMe})\text{Cl}]^+$ and Cl^- , as seen by ^{31}P NMR spectroscopy.²¹ Upon the addition of a stoichiometric amount of sodium *tert*-butoxide, the immediate generation of iron-hydride species, including $[\text{dmpe}_2\text{FeHCl}]$ and $[(\text{dmpe}_2\text{FeH})_2(\mu\text{-dmpe})]^{2+}$, were observed by ^1H and ^{31}P NMR spectroscopy. Following blue light irradiation, $[\text{dmpe}_2\text{FeH}_2]$ **2** was also observed in solution alongside an additional unknown iron hydride species. This unknown iron-hydride was not observed under standard activation conditions; sodium *tert*-butoxide and HBpin (see ESI,† Part 12).

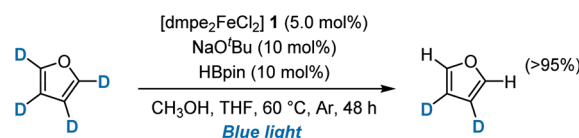
The formation of these catalytically active iron-hydrido complexes was proposed to proceed by *tert*-butoxide-mediated deprotonation of $[\text{dmpe}_2\text{Fe}(\text{HOMe})\text{Cl}]^+$ to generate an unstable iron methoxide complex, $[\text{dmpe}_2\text{Fe}(\text{OMe})\text{Cl}]$, which underwent β -hydride elimination releasing formaldehyde and generating $[\text{dmpe}_2\text{FeHCl}]$ (Scheme 2a, II). The formation of $[\text{dmpe}_2\text{FeHCl}]$ was also observed by ^1H and ^{31}P NMR spectroscopy when the reaction was performed in ethanol and benzyl alcohol, with benzaldehyde being formed and observed by ^{13}C NMR spectroscopy in the latter case. When the reaction was performed in CD_3OH , $[\text{dmpe}_2\text{FeDCl}]$, along with other iron-deuteride complexes, were observed by ^{31}P NMR spectroscopy (see ESI,† Part 12). The use of alcohols lacking available β -hydrogens, *tert*-butanol and phenol, resulted in no iron-hydride species being observed. Similar reactivity has been proposed for the analogous ruthenium-dmpe complexes.²² It should be noted that although activation to the catalytically active iron-hydride complexes can be achieved in the absence of HBpin, this activation was less controlled in terms of clean formation of $[\text{dmpe}_2\text{FeH}_2]$ under catalytic conditions.

$[\text{trans-dmpe}_2\text{Fe}(\text{H})(2\text{-methylfuryl})]$ *trans*-5, has previously been characterised in solution.^{11b} By careful tuning of the reaction and crystallization conditions, it was characterised in the solid-state by single-crystal X-ray diffraction (Scheme 2b, left). Significantly this reactivity was not limited to furan derivatives and was extended to the reaction of caffeine **3s** to give the corresponding complex, $[\text{cis-dmpe}_2\text{Fe}(\text{H})(\text{caffeine})]$ *cis*-6 (Scheme 2b, center). Although these species were crystallised as the *trans*- and *cis*-isomers, respectively, solution phase *cis-trans* isomerisation was reasonably proposed.²³ Rapid and quantitative exchange of hydride for deuteride was observed upon addition of excess CD_3OD (approx. 250 eq.) to a THF solution of $[\text{trans-dmpe}_2\text{Fe}(\text{H})(2\text{-methylfuryl})]$ *trans*-5 to give the deuterated isotopologue $[\text{trans-dmpe}_2\text{Fe}(\text{D})(2\text{-methylfuran})]$ [D]-*trans*-5 in the absence of blue light irradiation. Exchange of hydride for deuteride occurring by protonation of $[\text{trans-dmpe}_2\text{Fe}(\text{H})(2\text{-methylfuryl})]$ *trans*-5 with CD_3OD ,²⁴ to give the cationic complex $[\text{dmpe}_2\text{Fe}(\text{HD})(2\text{-methylfuryl})]^+$ which reversibly released CD_3OH (Scheme 2c, upper). Further monitoring of this solution by ^1H and ^{31}P NMR spectroscopy showed the slow generation of $[\text{dmpe}_2\text{FeD}_2]$ [D]-**2** and 2-methyl-5D-furan [D]-**3a** at room temperature in the absence of blue light irradiation. Additionally, no further intermediary species were observed, and similar reactivity was not observed when using $^t\text{BuOH}$. Presumably, turnover proceeded either through a stepwise cationic protonation and release of the arene, or by a concerted

sigma bond metathesis reaction with CD_3OD , both resulting in an $[\text{dmpe}_2\text{Fe}(\text{D})(\text{OMe})]$ intermediate which collapsed by β -hydride elimination to generate the photoactive complex $[\text{dmpe}_2\text{FeD}_2]$ [D]-**2** and formaldehyde (*vide ante*).

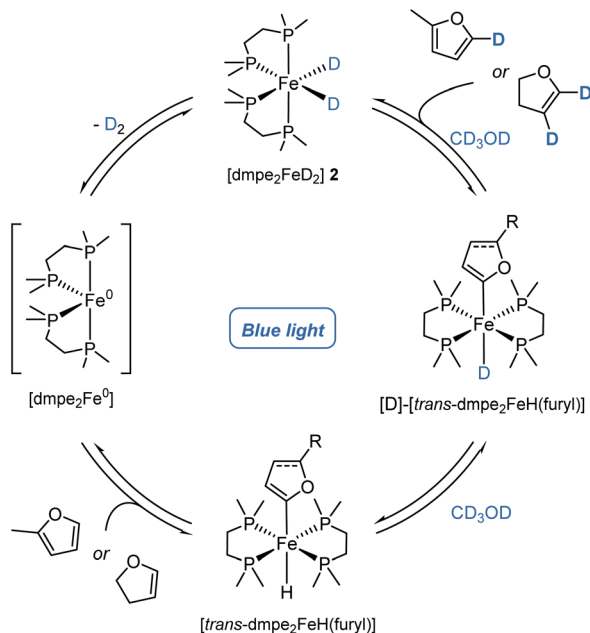
The reversible nature of deuterium incorporation led to it being questioned whether this process could be used for selective protodeuteration to give selectively deuterated products. *d*₄-Furan was regioselectively protodeuterated at the 2- and 5-positions to give *d*₂-[3D,4D]-furan with >95% incorporation using 5 mol% of Fe(II) pre-catalyst **2** and MeOH (Scheme 3). The synthesis of *d*₂-[3D,4D]-furan has only been previously prepared using a multistep sequence.²⁵

Considering the H/D exchange of alkenes, blue light irradiation of $[\text{dmpe}_2\text{FeH}_2]$ **2** in the presence of 2,3-dihydrofuran, led exclusively to the C-2C(sp²)-H metallation product, $[\text{trans-dmpe}_2\text{Fe}(\text{H})(2,3\text{-dihydrofuryl})]$ *trans*-7 (Scheme 2b, right). Despite reports of Fe-alkenyl C(sp²)-H metallation products being observed in the solution phase,^{5b} complex *trans*-7 represents the first example of an Fe-alkenyl complex characterised in the solid-state by single-crystal X-ray diffraction (Fe-C bond distance 1.338(25) Å, C=C bond distance 1.338(2) Å). This was in contrast to previous reports using the analogous bis(diethylphosphino)ethane ligand where C-3 metallation was proposed based on solution phase ^1H and ^{31}P NMR spectroscopy.²⁶ In analogy to aryl iron hydride *trans*-7, the alkenyl iron complex *trans*-7 displayed similar reactivity in the presence of CD_3OD ; quantitative conversion to the iron-deuteride isotopologue, [D]-*trans*-7, was observed upon the addition of excess CD_3OD in the absence of blue light irradiation. Slow conversion of $[\text{trans-dmpe}_2\text{Fe}(\text{H})(2,3\text{-dihydrofuryl})]$ *trans*-7 to $[\text{dmpe}_2\text{FeD}_2]$ [D]-**2** with the release of 2,3-dihydro-4D,5D-furan [D]-**4g** was observed by ^1H and ^{31}P NMR spectroscopy in the absence of blue light irradiation. The irradiation of $[\text{dmpe}_2\text{FeH}_2]$ **2** in the presence of 4-*tert*-butylstyrene **4a**, led to a complex mixture of products observed by ^1H and ^{31}P NMR spectroscopy. When performing the deuteration of *tert*-butylstyrene in the absence of blue light irradiation at 60 or 80 °C, a greater α : β ratio was observed to that under standard reaction conditions (see ESI, Table S6†). When the allylic ethers, 2,5-dihydrofuran and allyl benzyl ether, were reacted under standard conditions, alkene isomerisation to the vinyl ethers was observed producing 2,3-dihydrofuran (62%) and the benzyl propenyl ether (62%, 46 : 54 *Z* : *E*), respectively. Similarly, 4-allylanisole showed small amounts of isomerisation to (*Z*)-anethole (<10%) (see ESI,† Part 12). Control reactions ruled out any acid- or base-mediated



Scheme 3 Protodeuteration of *d*₄-furan. Reaction conditions: *d*₄-furan (0.33 mmol), $[\text{dmpe}_2\text{FeCl}_2]$ **1** (5.0 mol%), NaO^tBu (10 mol%), HBpin (10 mol%), THF (0.2 mL), CH_3OH (0.2 mL), blue-light irradiation, 48 h. Deuterium incorporation determined by ^1H and ^{13}C NMR spectroscopy.





Scheme 4 Proposed reaction mechanism for the iron-catalysed H/D exchange reaction of heteroarenes and alkenes.

isomerisation. The aforementioned observations, alongside previous work,^{5b,27} would suggest that the deuteration of alkenes is occurring through a combination of (direct) C–H metallation and hydrometallation mechanisms, with the latter observed to mediate alkene isomerisation alongside exchange (Scheme 4).

Conclusions

In summary, direct C–H metallation of heteroarenes and alkenes using an iron(II) hydride species has enabled the development of an iron-catalysed H/D exchange reaction using a bench-stable iron(II) pre-catalyst, and CD₃OD as the deuterium source. This method is mechanistically different from and complementary to previously described iron-catalysed strategies, and allows for precise and predictable formation of C–D bonds without the need for directing groups. Regioselectivity was obtained and controlled through highly selective C–H metallation by the proposed active catalyst. Significantly, the use of a non-reductive deuterium source (CD₃OD) has enabled extension to exchange of alkene C–H bonds and to molecules containing reducible functional groups. Isolation and characterisation, including single-crystal X-ray diffraction, of the key iron-aryl and iron-alkenyl intermediates allowed for mechanistic investigations that provided evidence for a reversible protonation of these iron C–H activation products. Further, a new mechanism of iron-hydride formation is presented in alcohol solvents.

Data availability

Experimental data is provided in the ESI.†

Author contributions

J. H. D. and S. P. T. conceived and discovered the reaction. L. B., J. H. D., J. S. and J. C. conducted the experimental work. G. S. N. conducted the X-ray crystallographic analysis. S. P. T. and A. P. D. advised investigations. All authors contributed to the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

All authors thank Dr Andrew Ashley and Lee J. Edwards for useful discussions. S. P. T. thanks The Royal Society for a University Research Fellowship (RF191015). J. H. D. and S. P. T. acknowledge GSK and EPSRC (P1110002) and The Royal Society (RF191015) for post-doctoral funding. L. B. acknowledges The Royal Society and The University of Edinburgh for a PhD studentship (RF191015).

Notes and references

- (a) I. V. Seregin and V. Gevorgyan, *Chem. Soc. Rev.*, 2007, **36**, 1173–1193; (b) M. M. Díaz-Requejo and P. J. Pérez, *Chem. Rev.*, 2008, **108**, 3379–3394; (c) J. Yamaguchi, A. D. Yamaguchi and K. Itami, *Angew. Chem., Int. Ed.*, 2012, **51**, 8960–9009; (d) Z. Huang, H. N. Lim, F. Mo, M. C. Young and G. Dong, *Chem. Soc. Rev.*, 2015, **44**, 7764–7786; (e) F. Roudesly, J. Oble and G. Poli, *J. Mol. Catal. A: Chem.*, 2017, **426**, 275–296; (f) D. J. Abrams, P. A. Provencher and E. J. Sorensen, *Chem. Soc. Rev.*, 2018, **47**, 8925–8967; (g) B. Liu, L. Yang, P. Li, F. Wang and X. Li, *Org. Chem. Front.*, 2021, **8**, 1085–1101.
- (a) R. Shang, L. Ilies and E. Nakamura, *Chem. Rev.*, 2017, **117**, 9086–9139; (b) P. Gandeepan, T. Muller, D. Zell, G. Cera, S. Warratz and L. Ackermann, *Chem. Rev.*, 2019, **119**, 2192–2452; (c) L. Ilies, *Bull. Chem. Soc. Jpn.*, 2021, **94**, 404–417; (d) J. Loup, U. Dhawa, F. Pesciaioli, J. Wencel-Delord and L. Ackermann, *Angew. Chem., Int. Ed.*, 2019, **58**, 12803–12818.
- (a) M.-A. Légaré, M.-A. Courtemanche, É. Rochette and F.-G. Fontaine, *Science*, 2015, **349**, 513–516; (b) K. Chernichenko, M. Lindqvist, B. Kótai, M. Nieger, K. Sorochkina, I. Pápai and T. Repo, *J. Am. Chem. Soc.*, 2016, **138**, 4860–4868; (c) J. Lv, X. Chen, X.-S. Xue, B. Zhao, Y. Liang, M. Wang, L. Jin, Y. Yuan, Y. Han, Y. Zhao, Y. Lu, J. Zhao, W.-Y. Sun, K. N. Houk and Z. Shi, *Nature*, 2019, **575**, 336–340; (d) T. He, H. F. T. Klare and M. Oestreich, *J. Am. Chem. Soc.*, 2022, **144**, 4734–4738.
- (a) S. F. McWilliams, D. L. J. Broere, C. J. V. Halliday, S. M. Bhutto, B. Q. Mercado and P. L. Holland, *Nature*, 2020, **584**, 221–226; (b) A. M. Messinis, L. H. Finger, L. Hu and L. Ackermann, *J. Am. Chem. Soc.*, 2020, **142**, 13102–13111; (c) A. M. Messinis, J. C. A. Oliveira, A. C. Stückl and L. Ackermann, *ACS Catal.*, 2022, **12**, 4947–4960; (d) S. L. Daifuku, M. H. Al-Afyouni, B. E. R. Snyder,



- J. L. Kneebone and M. L. Neidig, *J. Am. Chem. Soc.*, 2014, **136**, 9132–9143; (e) R. B. Bedford, P. B. Brenner, E. Carter, J. Clifton, P. M. Cogswell, N. J. Gower, M. F. Haddow, J. N. Harvey, J. A. Kehl, D. M. Murphy, E. C. Neeve, M. L. Neidig, J. Nunn, B. E. R. Snyder and J. Taylor, *Organometallics*, 2014, **33**, 5767–5780; (f) Y. Liu, M. Shi and L. Deng, *Organometallics*, 2014, **33**, 5660–5669; (g) T. E. Boddie, S. H. Carpenter, T. M. Baker, J. C. DeMuth, G. Cera, W. W. Brennessel, L. Ackermann and M. L. Neidig, *J. Am. Chem. Soc.*, 2019, **141**, 12338–12345.
- 5 (a) S. D. Ittel, C. A. Tolman, A. D. English and J. P. Jesson, *J. Am. Chem. Soc.*, 1976, **98**, 6073–6075; (b) M. V. Baker and L. D. Field, *J. Am. Chem. Soc.*, 1986, **108**, 7433–7434.
- 6 (a) R. Pony Yu, D. Hesk, N. Rivera, I. Pelczer and P. J. Chirik, *Nature*, 2016, **529**, 195–199; (b) J. Corpas, P. Viereck and P. J. Chirik, *ACS Catal.*, 2020, **10**, 8640–8647.
- 7 S. Garhwal, A. Kaushansky, N. Fridman, L. J. W. Shimon and G. d. Ruiter, *J. Am. Chem. Soc.*, 2020, **142**, 17131–17139.
- 8 W. Li, J. Rabeah, F. Bourriquen, D. Yang, C. Kreyenschulte, N. Rockstroh, H. Lund, S. Bartling, A.-E. Surkus, K. Junge, A. Brückner, A. Lei and M. Beller, *Nat. Chem.*, 2022, **14**, 334–341.
- 9 (a) J. Zhang, S. Zhang, T. Gogula and H. Zou, *ACS Catal.*, 2020, **10**, 7486–7494; (b) S. Kopf, H. Neumann and M. Beller, *Chem. Commun.*, 2021, **57**, 1137–1140; (c) F. Bourriquen, N. Rockstroh, S. Bartling, K. Junge and M. Beller, *Angew. Chem., Int. Ed.*, 2022, **61**, e202202423.
- 10 A. Tlahuext-Aca and J. F. Hartwig, *ACS Catal.*, 2021, **11**, 1119–1127.
- 11 (a) J. H. Docherty, J. Peng, A. P. Dominey and S. P. Thomas, *Nat. Chem.*, 2017, **9**, 595–600; (b) L. Britton, J. H. Docherty, A. P. Dominey and S. P. Thomas, *Molecules*, 2020, **25**, 905; (c) L. Britton, M. Skrodzki, G. S. Nichol, A. P. Dominey, P. Pawluć, J. H. Docherty and S. P. Thomas, *ACS Catal.*, 2021, **11**, 6857–6864.
- 12 M. Farizyan, A. Mondal, S. Mal, F. Deufel and M. van Gemmeren, *J. Am. Chem. Soc.*, 2021, **143**, 16370–16376.
- 13 Presumed to be a result of a lower concentration of base present in the reaction mixture.
- 14 (a) J. Zhou and J. F. Hartwig, *Angew. Chem., Int. Ed.*, 2008, **47**, 5783–5787; (b) M. Hatano, T. Nishimura and H. Yorimitsu, *Org. Lett.*, 2016, **18**, 3674–3677.
- 15 (a) B. Rybtchinski, R. Cohen, Y. Ben-David, J. M. L. Martin and D. Milstein, *J. Am. Chem. Soc.*, 2003, **125**, 11041–11050; (b) A. Di Giuseppe, R. Castarlenas, J. J. Pérez-Torrente, F. J. Lahoz and L. A. Oro, *Chem.–Eur. J.*, 2014, **20**, 8391–8403.
- 16 (a) G. Erdogan and D. B. Grotjahn, *J. Am. Chem. Soc.*, 2009, **131**, 10354–10355; (b) S. K. S. Tse, P. Xue, Z. Lin and G. Jia, *Adv. Synth. Catal.*, 2010, **352**, 1512–1522; (c) A. Bechtoldt and L. Ackermann, *ChemCatChem*, 2019, **11**, 435–438.
- 17 N. Camedda, A. Serafino, R. Maggi, F. Bigi, G. Cera and G. Maestri, *Synthesis*, 2020, **52**, 1762–1772.
- 18 (a) C. P. Lenges, M. Brookhart and B. E. Grant, *J. Organomet. Chem.*, 1997, **528**, 199–203; (b) J. Choi, L. Tang and J. R. Norton, *J. Am. Chem. Soc.*, 2007, **129**, 234–240.
- 19 (a) H. Fong, M.-E. Moret, Y. Lee and J. C. Peters, *Organometallics*, 2013, **32**, 3053–3062; (b) D. Zell, M. Bursch, V. Müller, S. Grimme and L. Ackermann, *Angew. Chem., Int. Ed.*, 2017, **56**, 10378–10382; (c) J.-F. Li, Z.-Z. Wei, Y.-Q. Wang and M. Ye, *Green Chem.*, 2017, **19**, 4498–4502.
- 20 T. R. Puleo, A. J. Strong and J. S. Bandar, *J. Am. Chem. Soc.*, 2019, **141**, 1467–1472.
- 21 J. M. Bellerby, M. J. Mays and P. L. Sears, *Dalton Trans.*, 1976, 1232–1236.
- 22 (a) J. R. Fulton, S. Sklenak, M. W. Bouwkamp and R. G. Bergman, *J. Am. Chem. Soc.*, 2002, **124**, 4722–4737; (b) X.-J. Dai and C.-J. Li, *J. Am. Chem. Soc.*, 2016, **138**, 5433–5440.
- 23 T. Dombay, C. G. Werncke, S. Jiang, M. Grellier, L. Vendier, S. Bontemps, J. B. Sortais, S. Sabo-Etienne and C. Darcel, *J. Am. Chem. Soc.*, 2015, **137**, 4062–4065.
- 24 M. V. Baker, L. D. Field and D. J. Young, *Chem. Commun.*, 1988, 546–548.
- 25 R. M. Spycher, L. Hausherr-Primo, G. Grassi and A. Bauder, *J. Mol. Struct.*, 1995, **351**, 7–17.
- 26 T. Morikita, M. Hirano, A. Sasaki and S. Komiya, *Inorg. Chim. Acta*, 1999, **291**, 341–354.
- 27 S. Komiya, N. Oyasato and T. Furukawa, *Bull. Chem. Soc. Jpn.*, 1989, **62**, 4078–4079.

