Homocoupling-free iron-catalysed twofold C–H activation/cross-couplings of aromatics via transient connection of reactants

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Abstract

Twofold C–H activation/cross-coupling of stoichiometric amounts of organic molecules, R^1–H and R^2–H, to form an R^1–R^2 product free of homocoupling products is a goal in the activation of unreactive C–H bonds, as it will dramatically simplify organic synthesis. No reliable strategy to eliminate the homocoupling side products effectively without recourse to the use of an excess of one reactant over another is known. We report herein that a transient connection of two reactants by an anionic group appended to one reactant achieves this goal under mildly oxidative iron-catalysed conditions, through the formation of a productive heteroleptic R^1–M–R^2 intermediate. We utilized a *N*-(quinolin-8-yl)amide anion for the temporary connection and cross-coupled a stoichiometric mixture of aromatics in high yield without any trace of homocoupling products. A short-step synthesis of several donor/acceptor thiophene compounds and carbon/sulfur-bridged flat conjugated systems illustrates the utility of this method to streamline organic synthesis.

Introduction

Metal catalysis aiming at C–H activation[1,2,3,4,5,6,7,8] for creation of new C–C bonds[9] has been a subject of intense research for decades with a common goal of cross-coupling stoichiometric amounts of two organic molecules, R^1–H and R^2–H, to form an R^1–R^2 product free of homocoupling products (R^1–R^1 and R^2–R^2) under mild oxidative conditions[10,11,12]. Such reactions obviate the need for prefunctionalization of reactants and thus, simplify the synthetic scheme. To achieve twofold C–H activation/cross-coupling[13,14,15,16,17,18,19] free of homocoupling[20], we need to generate a productive heteroleptic R^1–M–R^2 intermediate with the exclusion of homoleptic species (*i.e.*, R^1–M–

R^1 or R^2–M–R^2)[12]. No reliable strategy is yet known to suppress homocoupling entirely, and people have recourse to the use of one reactant in large excess[12,16,17]. Being aware that iron-catalysed C–H activation [21, 22] involves a Lewis acidic organoiron(III) intermediate[23,24,25], we considered that transient connection of the two reactants via a basic group (X in **I**, Fig. 1) generates an intermediate (**III**), and exclusively forms a cross-coupling product **V** through **IV**.

We report here that an iron-catalysed reaction of a stoichiometric mixture of a (hetero)arene and a (hetero)arene or an olefin bearing a *N*-(quinolin-8-yl)amide group[26,27] (*e.g.*, **1**) produces at 70 °C a cross-coupling product (**2**) in high yield without any homocoupling products (**4** and **5**, Fig. 2a). Here, the amide group acts both as a group to assist the first C–H cleavage (**I**)[28] and as a connector in **III**. An organozinc reagent ($Zn(CH_2SiMe_3)_2$) serves as a stoichiometric base (B in Fig. 1) to remove protons, 1,2-dichloropropane (DCP) as a mild oxidant, and a mixture of $Fe(acac)_3$ in combination with a conjugated bisphosphine (dppen) as a catalyst (Fig. 2a). Deuterium labeling experiments suggested a fast equilibrium between **II** and **III**, from which an irreversible deprotonation event slowly occurs to give a diorganoiron(III) intermediate (**IV**), and a cross-coupled intermediate after reductive elimination (**V**). The reaction is particularly effective for coupling one equivalent each of (hetero)arene (or alkene) carboxamides and thiophene derivatives[20,29,30], with the highest yield exceeding 90%. The multifold C–C coupling proceeded also with high efficiency, allowing us to synthesize carbon- and sulfur-bridged flat conjugated systems[31,32] (*e.g.*, **6** and **8**) in a few steps (Fig. 2b), and a variety of donor/acceptor thiophene compounds in one step (Fig. 5)[33].

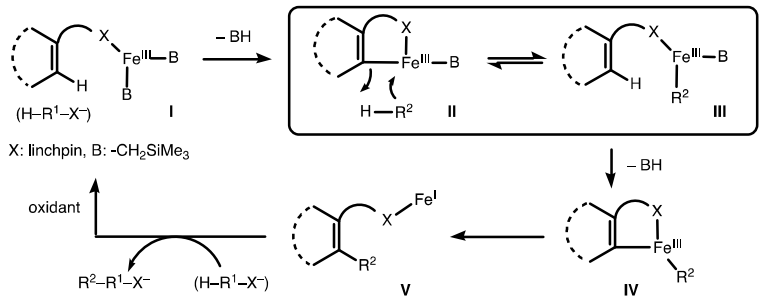

Fig. 1 | The mechanistic hypothesis of iron(III)-catalysed twofold C–H activation/cross-coupling with temporary connection strategy.

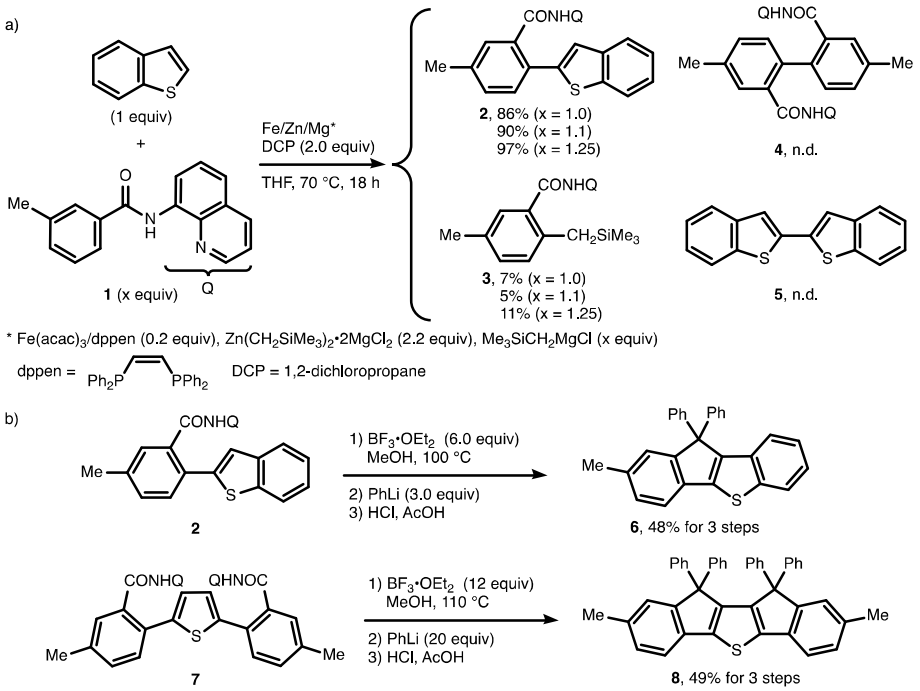

Fig. 2 | Iron-catalysed twofold C–H activation/cross-coupling and its application to material synthesis. a, Iron(III)-catalysed stoichiometric C–H/C–H coupling between 3-methyl-*N*-(quinolin-8-yl)benzamide and benzo[*b*]thiophene with exclusive selectivity for cross-coupling. n.d. = not detected. **b**, Transformation of C–H/C–H coupling products to carbon- and sulfur-bridged flat conjugated systems.

Results

Reaction conditions and the outcome. The reaction is illustrated for coupling of benzo[*b*]thiophene with 3-methyl-*N*-(quinolin-8-yl)benzamide (**1**, Fig. 2a). For twofold C–H activation and N–H deprotonation, the reaction requires three equivalents of a base, for which we found $Zn(CH_2SiMe_3)_2$ is the most suitable (see Supplementary Figure 1 for details). Here the only detectable side product was 2-(trimethylsilyl)methylated product (**3**, 7% yield) probably formed by reductive elimination of **II**. The use of methyl or phenyl reagent instead of the CH_2SiMe_3 group resulted in nearly exclusive ortho-methylation or ortho-phenylation of the carboxamide. Thus, we surmise that steric bulk of the $SiMe_3$ group suppressed this side reaction. A typical example is described first: a THF solution of (trimethylsilyl)methylmagnesium chloride (5.4 equiv) was added to a THF solution of **1** (0.20 mmol, 1.0 equiv) and zinc chloride (0.44 mmol, 2.2 equiv) to deprotonate the N–H proton and to generate 2.2 equiv of a diorganozinc base. Benzo[*b*]thiophene (0.20 mmol, 1.0 equiv), DCP (2.0 equiv), and a THF solution of $Fe(acac)_3$ (20 mol%) and *cis*-

1,2-bis(diphenylphosphino)ethene (dppen, 20 mol%) were sequentially added. The reaction mixture was stirred at 70 °C for 18 h because the reaction occurs very slowly; it is only half complete even after 9 h (Fig. 6b, c). After aqueous workup, the cross-coupled product **2** was obtained in 86% yield with no trace of homocoupling byproducts **4** and **5**, as analyzed by GC-MS and NMR (Fig. 2a). Homocoupling [34] of ((trimethylsilyl)methyl)magnesium chloride was not observed. The reaction exclusively took place at the C2 position on the thiophene ring[35]. Benzo[*b*]thiophene was recovered in 15% yield. The use of 10 mol% excess of **1** increased the yield of **2** to 90%, and 25 mol% excess of **1** increased the yield of **2** based on benzo[*b*]thiophene to 97% (see Supplementary Figure 3 for details). While we have so far not been able to reduce the catalyst loading beyond 20–25 mol% probably because of product inhibition, the dppen ligand was recovered in 89% yield with retention of the *Z*-geometry after aqueous workup due to its weak coordination to Lewis acidic Fe(III) species. Recoverability of phosphine ligand is a merit of using Lewis acidic iron over soft transition metals such as palladium, which often tend to bind strongly to the ligand, making recovery difficult. In the following experiments, we routinely used a 1:1 mixture of the two reactants (Fig. 3), while we used 1.25–1.33 equiv excess of carboxamides for each C–C bond formation in multifold C–C cross-coupling reactions shown in Fig. 5.

Scope of the reaction. Fig. 3 provides examples of single C–C bond-forming reactions under 1:1 stoichiometry, except for several examples (marked a, b, and c). In all cases, the formation of 2-(trimethylsilyl)methylated amide side products[36] (*cf.* **3**) accounted for the rest of the cross-coupling product to consume the amide starting material. Being prone to double arylation at the C2 and C5 positions (*cf.* **7**), thiophene gave monoarylated products **9** and **27** in good yields of 68% and 70%, respectively, when thiophene was used in fivefold excess to the amide partner (2-(trimethylsilyl)methylated amide accounted for the rest of the consumption of the amide starting material). Double arylation of the benzamide partner did not take place because arylation at the C2 position prevents the second arylation at the C6 position. Electron-rich and -deficient, C2-substituted thiophenes (**10**, **11**, **12**) reacted well, and **16** having a C3 phenyl substituent reacted exclusively at the C5 position, probably because of steric hindrance. Benzo[*b*]thiophenes also took part in the reaction well (**2** and **13–15** *etc*.). As for the carboxamide part, arene carboxamides bearing electron-donating substituents reacted smoothly (**14**, **15**), while arene carboxamides containing strong electron-withdrawing substituents (–F, –CF_3, ester)

were unsuccessful (see Supplementary Figure 4 for details). Indole-2-carboxamide (**17**) and thiophene-2-carboxamides (**18**–**21**) were coupled with thiophene derivatives to deliver bis-heteroarene compounds. Cyclic alkenamide (**22**) and acyclic ones (**23**, **24**) reacted stereospecifically to give the *Z*-isomer as the only product. The example of **23** illustrates a gram-scale synthesis performed in 76% yield. This catalytic cycle tolerates functional groups such as ether (**11**), ketone (**12**), tertiary amine (**14**), and aryl silane (**20**, **21**). The reaction took place on benzofuran (**28**), but not on indole derivatives (see Supplementary Figure 4 for details). 1-Methyl-1*H*-pyrazole regioselectively reacted at the C4 position in 29% yield with 1:1 stoichiometry (**29**), and in 49% yield with fivefold excess of the pyrazole substrate. The regioselectivity for 1-methyl-1*H*-pyrazole may be ascribed to the acidity of the C–H bond and/or steric effects caused by metal coordination on nitrogen atoms.

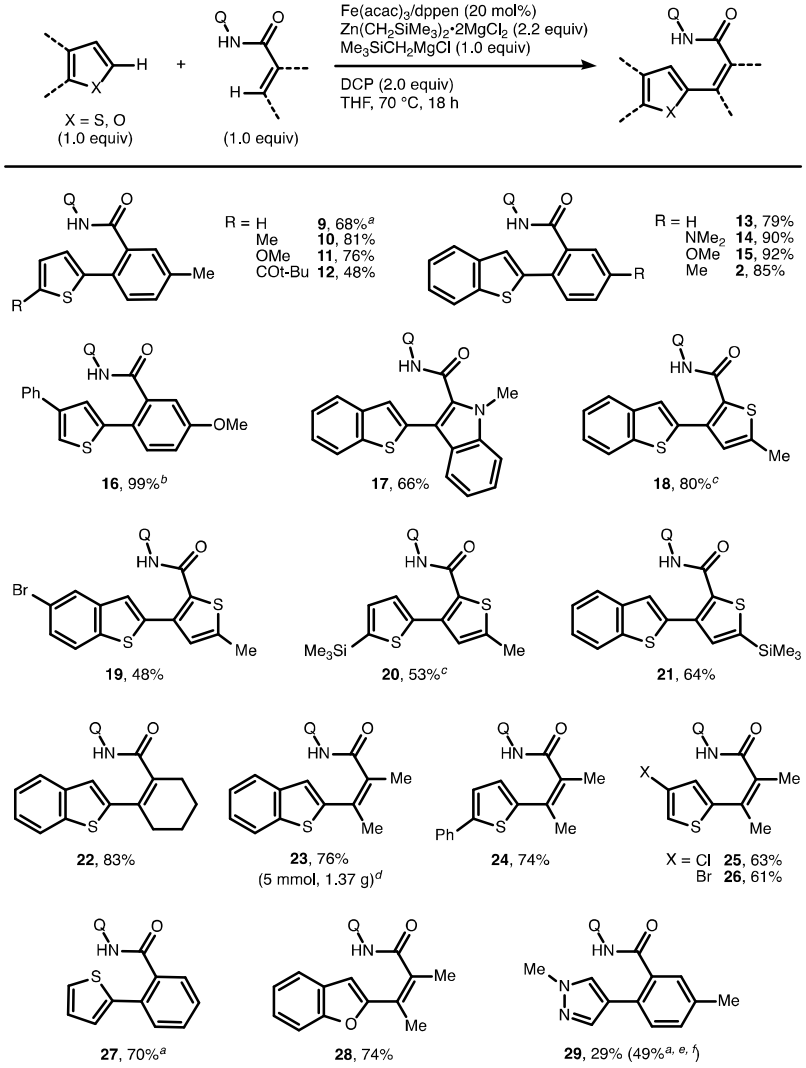

Fig. 3 | Reaction scope of iron-catalysed twofold C–H activation/cross-coupling of

heteroarenes with (hetero)aryl and alkenyl carboxamides. Reactions were performed using 1.0 equiv of heteroarene (0.30 mmol), *x* equiv of carboxamide, 20 mol% of $Fe(acac)_3$, 20 mol% of dppen, 2.2*x* equiv of $ZnCl_2$, 5.4*x* equiv of Me_3SiCH_2MgCl, and 2.0*x* equiv of DCP in THF at 70 °C for 18 h, where $x = 1.0$ unless otherwise noted below. The yield refers to the isolated, pure product. [a] 5.0 equiv of heteroarene was used. [b] $x = 1.25$, [c] $x = 1.5$, [d] 2-(Trimethylsilyl)methylated amide side product was obtained in 13% yield. [e] 24 h. [f] The yield was determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as an internal standard.

Benzene and halobenzene derivatives also took part in the reaction, albeit in low yield. Benzene reacted in 12% yield when used as a solvent mixed with THF (Fig. 4, **30**). The low reaction efficiency may be ascribed to the weak coordination ability of benzene to iron(III) catalyst and the low acidity of its C–H bond[37]. Halobenzenes, but not electron-rich benzene derivatives (*e.g.*, anisole), also afforded the desired cross-coupling products in 42–72% yields. The reaction with a 1:5 ratio of the amide **1**/1,2,3-trichlorobenzene produced a small amount of the cross-coupled product with no trace of the dimers of the amide nor the arene, giving back the amide and producing the side product **3**. The observed reactivity speaks against a Friedel–Crafts-type mechanism[38] and suggests that the success of the reaction depends on the acidity of the C–H bond to be cleaved (*cf.* thiophene vs furan and benzene)[37].

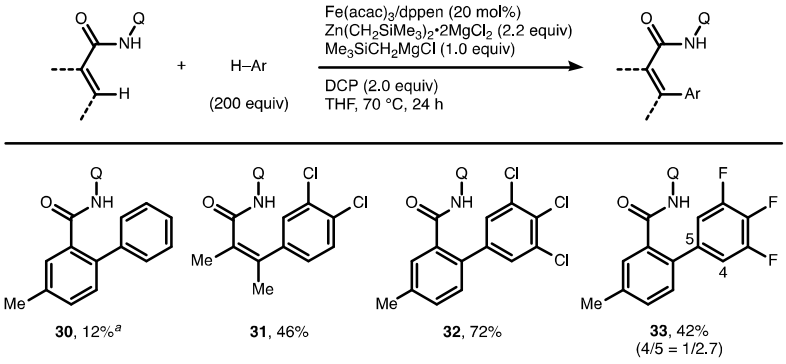

Fig. 4 | Reaction scope of iron-catalysed twofold C–H activation/cross-coupling of carboxamides with arenes. Reactions were performed using 1.0 equiv of carboxamide (0.30 mmol), 200 equiv of arene, 20 mol% of $Fe(acac)_3$, 20 mol% of dppen, 2.2 equiv of $ZnCl_2$, 5.4 equiv of Me_3SiCH_2MgCl, and 2.0 equiv of DCP in THF at 70 °C for 24 h. Unless otherwise noted, the yield refers to the isolated, pure product. [a] The yield was determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as an internal standard.

The efficiency of the temporary connection strategy led us to explore a short-step synthesis of multithiophene compounds of material interest, where we used 1.25–1.33 equiv of amide reagent for each C–C bond formation. Fig. 2b has already illustrated the utility of the products. Thiophene and two molecules of an arene carboxamide reacted smoothly to give 2,5-diarylated thiophene **7** in 92% yield; **7** was converted to a carbon/sulfur-bridged flat conjugated system in 49% yield in four steps from thiophene (Fig. 2b). 2,2′-Bithiophene was diarylated at the 5- and 5′-positions in 90% yield (**34**). Electron-rich 3,4-ethylenedioxythiophene (EDOT), used as a monomer unit in conductive polymers[39] and hole-transporting materials[40], was 2,5-diarylated in 99% yield (**35**). Thus, EDOT, which is sensitive to oxidation[41], survived perfectly under the present reaction conditions, attesting to the mildness of the oxidant (DCP) and the iron-catalytic cycle. (*E*)-1,2-Di(thiophen-2-yl)ethene was diarylated without affecting the double bond (**36**). 4,7-Di(thiophen-2-yl)benzo[*c*][1,2,5]thiadiazole, found often in organic photovoltaic materials [42], was derivatized in 93% yield (**37**). π-Extended benzo[1,2-*b*:4,5-*b*′]dithiophene regioselectively coupled with two benzamide units smoothly in 92% yield (**38**). Double C–H activation of furan on the C2- and C5-positions was achieved in 77% yield (**39**). Threefold chain extension from a central benzene ring via a thiophene linkage was achieved in high yield, as illustrated for 1,3,5-tri(thiophen-2-yl)benzene and benzo[1,2-*b*:3,4-*b*′:5,6-*b*″]trithiophene (**40**, **41**). Dppen ligand was recovered in 89% with retention of *Z*-geometry after aqueous workup in the synthesis of **41**.

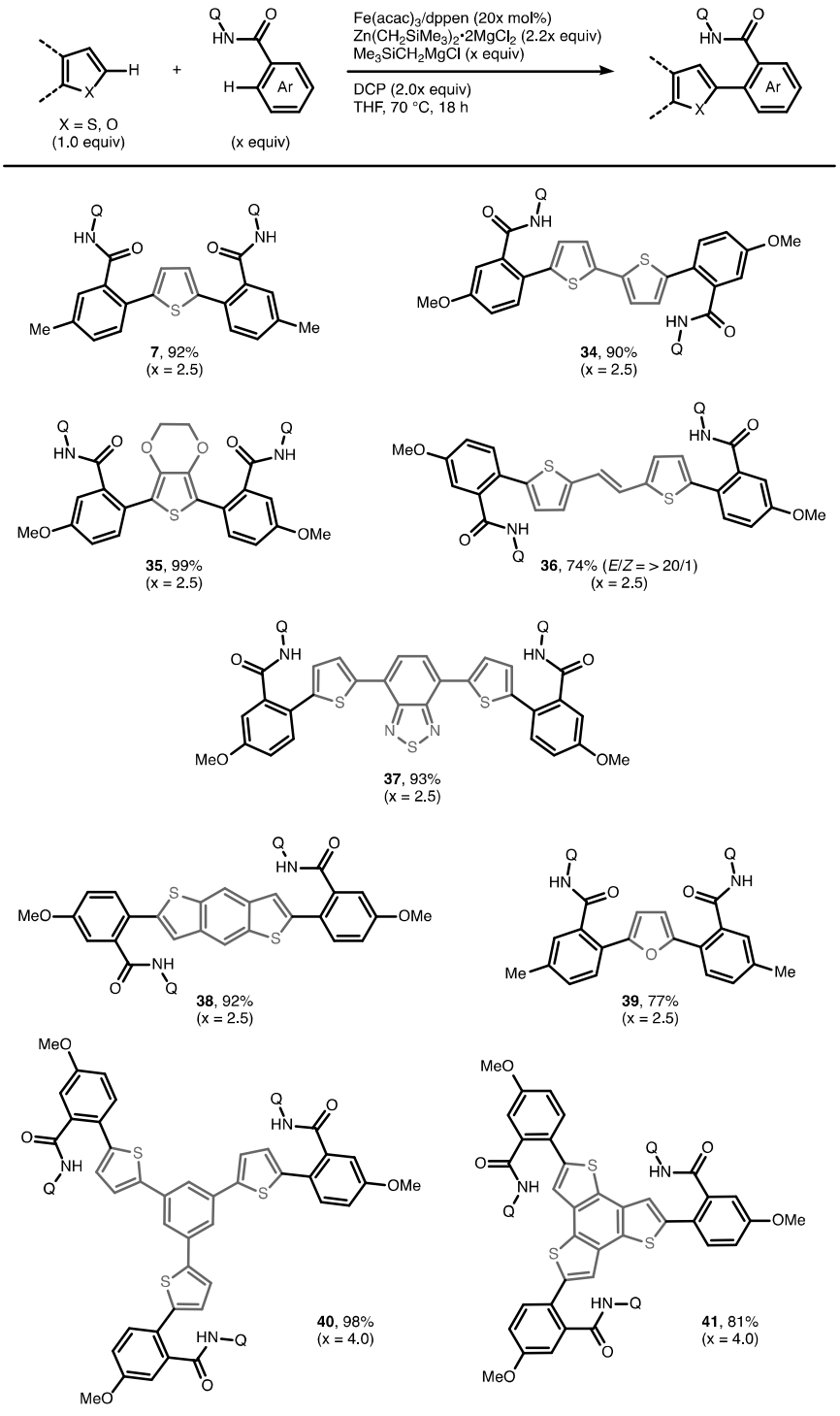

Fig 5| Iron-catalysed twofold C–H activation/cross-coupling using heteroarenes of interest in materials science. Reactions were performed using 1.0 equiv of heteroarene, *x* equiv of carboxamide (0.30 mmol), 20*x* mol% of $Fe(acac)_3$, 20*x* mol% of dppen, 2.2*x* equiv of $ZnCl_2$, 5.4*x* equiv of Me_3SiCH_2MgCl, and 2.0*x* equiv of DCP in THF at 70 °C for 18 h. The yield refers to the isolated, pure product.

Mechanistic investigation. Deuterium labeling experiments (Fig. 6a–c) provided experimental support for the equilibrium between **II** and the connected intermediate **III** in Fig. 1. Fig. 6d illustrates a plausible mechanism of the C–H activation (**B** and **C**, stereochemistry is tentative). The mechanism of the first C–H activation converting an amide anion **A** to an aza-metallacycle **B** has already been proposed[21,28,43]. In the absence of the benzamide reactant, protio benzo[*b*]thiophene was not deuterated under the same reaction conditions (Fig. 6a), and we suggest that aza-metallacycle **B** deprotonates the benzo[*b*]thiophene, as illustrated by **C** in Fig. 6d. The **B**-to-**C** conversion is supported by the reaction between benzo[*b*]thiophene-2-*d* and *N*-(quinolin-8-yl)benzamide (Fig. 6b) that resulted in partial deuteration of the product (29%-*d*) and the recovered benzamide (38%-*d*) upon *ca.* 50% conversion. Label-scrambling took place also between protio benzo[*b*]thiophene and *N*-(quinolin-8-yl)benzamide-2,3,4,5,6-*d*5 (Fig. 6c), indicating the occurrence of a reverse reaction, **C**-to-**B** (Fig. 6d in the box). For **C** to go into a product-forming path via **D**, **C** needs to undergo a conformational change allowing the $-CH_2SiMe_3$ group to irreversibly deprotonate the amide C–H group via **C′**. Given the very slow rate of the reaction, this latter step after the **B**-to-**C** equilibrium may be a slow step in the catalytic cycle. It should be noted the formation of thiophene-coordinated ferracycle intermediate (**B**) is probably inhibited by product, because product may coordinate to ferracycle competitively preventing formation of intermediate (**B**). This may be one of the reasons for high catalyst loading.

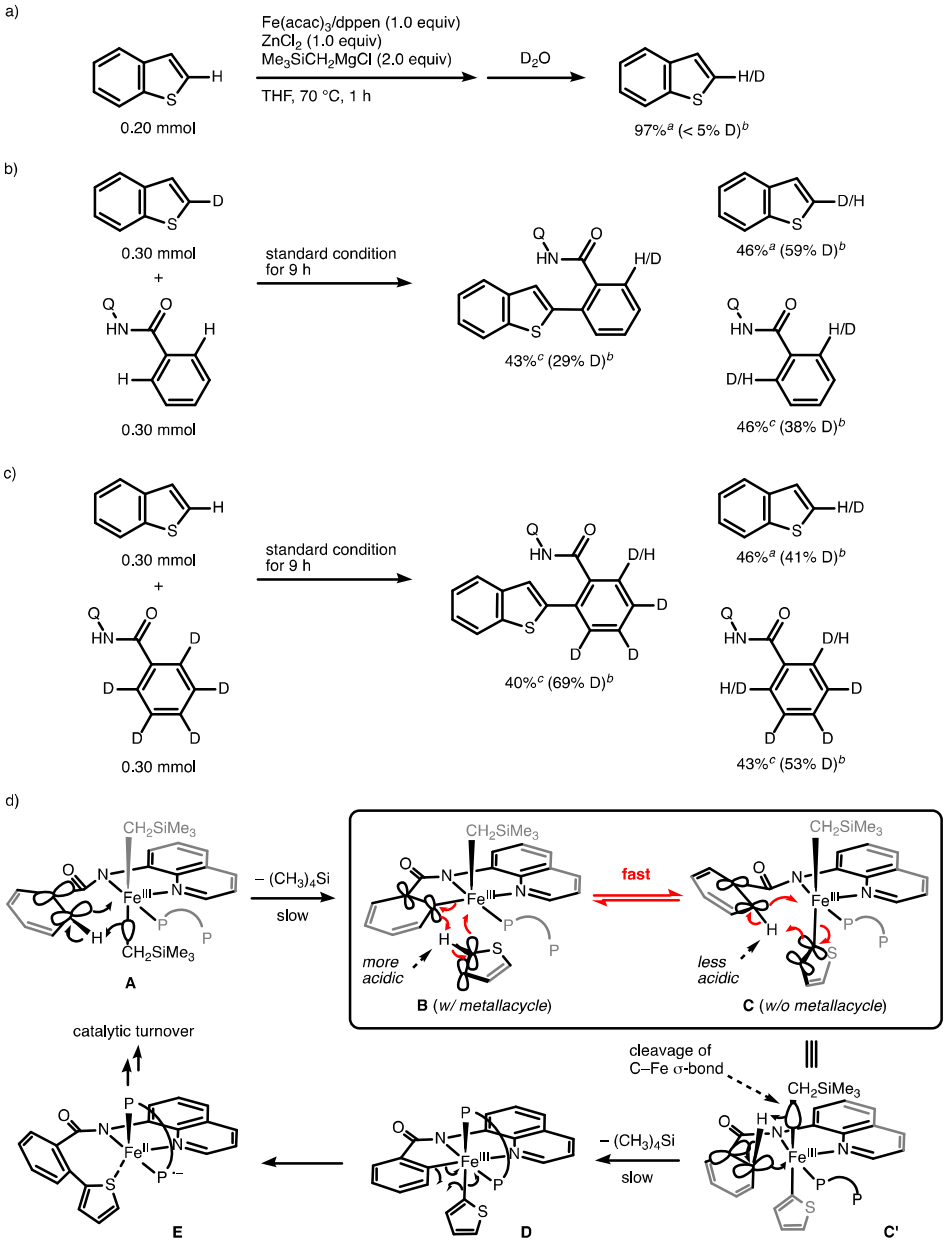

Fig. 6 | Mechanistic investigation. a–c, Deuterium labeling experiments reveal a "proton shuttle" effect of quinolinyl carboxamide substrates. [a] Yields were determined by GC using tridecane as an internal standard. [b] The amount of deuterium incorporation was determined by ^{1}H NMR. [c] Yields were determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as an internal standard. **d**, Mechanistic illustration with orbital analysis focusing on twofold C–H activation on the iron(III) centre.

Conclusions

In summary, we have developed a strategy using iron catalysis to carry out homocoupling-

free twofold C–H activation/cross-couplings of aromatics via transient connection of reactants. The excellent cross-coupling selectivity, using a stoichiometric amount of reactants, allowed us to synthesize thiophene derivatives of interest in materials science via multifold C–H activation/C–C cross-couplings. Other aromatics, including furan, pyrazole, and benzene derivatives also participated in the reaction. The reaction proceeds through sequential C–H activation steps via formation of a ferracycle followed by reversible C–H deprotonation of heteroarene by ferracycle to generate a transient species (**III** or **C**), where two reactants are connected by the coordination of the amide anion with iron. This equilibrating intermediate was experimentally verified by deuterium labeling experiments. We are further exploring the temporary connection strategy for selective twofold C–H activation/cross-coupling reactions using iron catalysis.

Methods

Full experimental details and characterization of the compounds are given in the Supplementary Methods.

General procedure illustrated for the synthesis of 2-(benzo[*b*]thiophen-2-yl)-5-methyl-*N*-(quinolin-8-yl)benzamide (2): In an oven-dried Schlenk tube was added 3-methyl-*N*-(quinolin-8-yl)benzamide (79 mg, 0.30 mmol) and a THF solution of $ZnCl_2$ (0.66 mL, 1.0 mol/L, 2.2 equiv). Then a THF solution of Me_3SiCH_2MgCl (1.53 mL, 1.06 mol/L, 5.4 equiv) was added dropwise at room temperature. After stirring for 10 minutes, benzo[*b*]thiophene (40 mg, 0.30 mmol) and 1,2-dichloropropane (58 μL, 0.60 mmol) were added, and then a solution of $Fe(acac)_3$ (21 mg, 0.060 mmol) and *cis*-1,2-bis(diphenylphosphino)ethene (dppen, 24 mg, 0.060 mmol) in THF (0.60 mL) was added dropwise, after which the colour of the reaction mixture became dark blue. The reaction mixture was stirred at 70 °C for 18 h and quenched by the addition of a saturated aqueous solution of potassium sodium tartrate (3 mL) and a saturated aqueous solution of NH_4Cl (3 mL). After stirring vigorously, the aqueous layer was extracted with EtOAc (3 mL x 3). The combined organic layer was passed through a pad of Florisil, concentrated *in vacuo*, and purified by silica gel chromatography (hexane: ethylacetate = 10: 1) to afford the product as white solid (101 mg, 85%).

Gram scale synthesis of (*E*)-2-methyl-*N*-(quinolin-8-yl)but-2-enamide

In an oven-dried Schlenk tube was added (*E*)-2-methyl-*N*-(quinolin-8-yl)but-2-enamide (1.13 g, 5.0 mmol) and a THF solution of $ZnCl_2$ (11.0 mL, 1.0 mol/L, 2.2 equiv). Then a THF solution of

Me_3SiCH_2MgCl (26.0 mL, 1.04 mol/L, 5.4 equiv) was added dropwise at r.t. After stirring for 10 minutes, benzo[*b*]thiophene (0.67 g, 5.0 mmol) and 1,2-dichloropropane (0.97 mL, 10 mmol) were added, and then a solution of $Fe(acac)_3$ (353 mg, 1.0 mmol) and *cis*-1,2-bis(diphenylphosphino)ethene (dppen, 396 mg, 1.0 mmol) in THF (10 mL) was added dropwise, after which the colour of the reaction mixture became dark purple. The reaction mixture was stirred at 70 °C for 18 h and quenched by the addition of a saturated aqueous solution of potassium sodium tartrate (50 mL) and a saturated aqueous solution of NH_4Cl (50 mL). After stirring vigorously, the aqueous layer was extracted with EtOAc (50 mL x 3). The combined organic layer was washed with brine, dried with Na_2SO_4, concentrated *in vacuo*, and purified by silica gel chromatography (hexane: ethylacetate = 7: 1 to 4: 1) to afford the product as white solid (1.37 g, 76 %) and 2-trimethylsilylmethylated alkenamide as colorless oil (0.20 g, 13%).

Data availability. All data supporting the findings of this study, including experimental procedures and compound characterization, are available within the paper and its Supplementary Information, or from the authors upon reasonable request.

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E.N. and R.S. guided the research and wrote the manuscript. T.D. performed the experiments to study the scope, application and mechanism. All authors contributed to designing the experiments, analyzing the data and editing the manuscript.

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Competing interests

The authors declare no competing interests.