Iron-catalysed cross-coupling of organolithium compounds with organic halides

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In past decades, catalytic cross-coupling reactions between organic halides and organometallic reagents to construct carbon–carbon bond have achieved a tremendous progress. However, organolithium reagents have rarely been used in cross-coupling reactions, due mainly to their high reactivity. Another limitation of this transformation using organolithium reagents is how to control reactivity with excellent selectivity. Although palladium catalysis has been applied in this field recently, the development of an approach to replace catalytic systems of noble metals with nonprecious metals is currently in high demand. Herein, we report an efficient synthetic protocol involving iron-catalysed cross-coupling reactions employing organolithium compounds as key coupling partners to unite aryl, alkyl and benzyl fragments and also disclose an efficient iron-catalysed release-capture ethylene coupling with isopropyllithium.
Transition metal-catalysed cross-coupling has emerged as a highly useful, selective and widely applicable method for synthesizing structurally diverse organic compounds via carbon–carbon bond formation. Since the discoveries of cross-coupling reactions, palladium-catalysed cross-coupling with organic halides and organometallic reagents, has dominated this area as an exceptionally powerful approach to assemble C–C bond (Fig. 1a). Although Murahashi et al. disclosed a palladium-catalysed cross-coupling reaction of alkenyl halides with various organolithium compounds, direct use of organolithium reagents in cross-coupling reactions has been neglected for a long time, mainly due to the high reactivity and low stability of organolithium reagents. Recently, Feringa and co-workers developed palladium-based catalytic systems to directly generate C–C bond using organolithium compounds as cross-coupling partners (Fig. 1b). Although palladium-based catalysts typically mediated such reactions, there are increasing concerns about their long-term sustainability in the synthetic community because of its high cost, low natural abundance, environmentally deleterious extraction, toxicity and competition for its use from the automotive and consumer electronics sectors. Therefore, there is a growing interest in replacing palladium-based catalysts with those more Earth-abundant elements. With its low cost, high natural abundance and low toxicity, iron is indeed a particularly appealing alternative, and accordingly, the development of iron-catalysed cross-coupling is undergoing an explosive growth. Herein, we develop an iron-catalysed cross-coupling strategy of organolithium reagents with organic halides to form C–C bonds, examples including C(sp²)–C(sp³) bonds, C(sp³)–C(sp³) bonds and a rare method to form a novel C(sp²)–C(sp³) bond via in-situ generation of ethylene from tetrahydrofuran (THF).

Results

Serendipity. Previously, we demonstrated that the rigid tetraphenylene (tetrabenzo[a,c,e,g]cyclooctatetraene) is a structurally and functionally exceptional molecule. To improve the efficiency of the coupling step, we proposed to synthesize tetraphenylene derivatives through a one-pot iron-catalysed intramolecular cross-coupling protocol. Although we obtained a trace amount of tetraphenylene, the serendipity is that 2-n-butylbiphenyl was observed (Fig. 2). Therefore, we recognized the potential utility of alkylithium reagents in iron-catalysed cross-coupling reactions.

Optimization. Encouraged by the reaction shown in Fig. 2, we attempted to couple 4-methoxybromobenzene (1a) with n-BuLi (2a) under the same condition. As expected, the target product p-methoxybutylbenzene (3a), together with a trace amount of the isomerized cross-coupling product (3a') were detected by gas chromatography-mass spectrometry (GC–MS), although the homo-coupling product (4) is the major product, together with dehalogenated product (5; Table 1, entry 1). In the absence of triethylamine (Et₃N) and at 22 °C, the ratio of the desired product was almost the same (Table 1, entries 2–3). Then, in the presence of FeCl₃ (10 mol%), ligands (20 mol%) and 1a (0.2 mmol) in THF (1.0 ml), several traditional bidentate ligands with different bite angles (for expanded screening results, see Supplementary Table 1) and monodentate electron-rich phosphine ligands (Fig. 3) were examined through a slow addition of dilute organolithium reagent 2a (0.3 mmol, 0.35 M) within 1 h at 22 °C using a syringe pump (Table 1, entries 4–11). To our delight, a distinct improvement was displayed by GC–MS. When trimethyl phosphite (L₂) was used as a ligand, the desired product was isolated in 68% yield (Table 1, entry 8). Further screening of iron salts revealed that iron(II) chloride gave a promising yield with trimethyl phosphite as the ligand (Table 1, entries 12–15). Recently, Fürstner pioneered the use of iron(III) acetylactonato-catalysed cross-coupling reactions with Grignard reagents; however, this iron catalyst demonstrated lower reactivity with lithium reagents (Table 1, entry 16). Surprisingly, upon addition of tetramethylethylenediamine (TMEDA, L₄) into the solution of iron(III) chloride in THF, the homo-coupling by-product (4) was suppressed dramatically (Table 1, entry 17). This catalytic system developed by Nakamura had been employed in cross-coupling reactions with Grignard reagents and arylzinc reagents. Therefore, the complex of TMEDA with iron(III) chloride was prepared according to Nakamura’s procedure for use in our next stage of optimization (Table 1, entries 18–24). When the cross-coupling reaction was conducted at 0 °C, the generation of the dehalogenated by-product (5) was reduced and the expected product was isolated in 85% (0.2 mmol scale; Table 1, entry 19). To further improve this procedure, we also screened the reaction media. A comparison of results obtained in THF revealed that the ratios of desired product were decreased in toluene and diethyl ether (Table 1, entries 20–21). When the catalyst loading was reduced to 3 and 1 mol%, respectively, the overall efficiency was not reduced in an obvious manner (Table 1, entries 22–23).

C(sp²)–C(sp³) cross-coupling of aryl halides with alkylithiums. To expand the scope of the iron-catalysed reactions, C(sp²)–C(sp³) cross-coupling of aryl halides with alkylithium reagents was further investigated. Initially, we compared the...
reactivity of different aryl halides (Table 2, 3a). 4-Methoxychlorobenzene (5% conversion) was more inert than 4-methoxybromobenzene (1a). The target product was generated exclusively, when 4-methoxyiodobenzene was used as a starting substrate. Unexpectedly, 4-methoxyphenyltrifluoromethanesulfonyl triflate (an aryl triflate) decomposed to the corresponding phenol (see note in Table 2). In consideration of their commercial availability, we made use of aryl bromides for further investigation (Table 2, 3b-3r). It was uncovered that varying the position of the methoxy group on the benzene ring led to a pronounced effect on the reaction outcome, presumably due to chelation of oxygen with lithium (Table 2, 3b-3c). In the case of bromobenzene, the GC yield was given due to the volatility issue (Table 2, 3d). Electron-donating and bulky functional groups facilitated cross-coupling reaction without sacrificing the yield of the corresponding products (Table 2, 3e-3g). However, a strongly electron-withdrawing substituent was found to lead to halogen-metal exchange (Table 2, 3h). Remarkably, a series of alkylolithiums were freshly prepared and were found to be compatible with this protocol, being able to couple with...
4-bromo-N,N-dimethylaniline (Table 2, 3i-3o). Polyaromatic compounds were found to undergo alkylation in moderate yields (Table 2, 3p-3q). In addition, a double alkylation product was obtained in 65% yield (Table 2, 3r).

Release-capture ethylene coupling with isopropyllithium. When isopropyllithium, a typical secondary organolithium, was utilized in the iron catalysis system with 4-methoxy-bromobenzene (1a), 1-isopentyl-4-methoxybenzene (3aTHF) was
obtained together with a trace amount of cross-coupling product 1-isopropyl-4-methoxybenzene. After prolonging the reaction time to overnight at 22 °C, the yield of 3aTHF was optimized up to 71% (Table 3, 3aTHF). To our best knowledge, this is an unusual example of transition metal-catalysed cross-coupling reaction involving freshly prepared ethylene generated by decomposing THF with isopropyllithium. Several aryl bromides were then investigated to explore the substituent effect at various positions of the benzene ring. Possible chelation effect and steric effect were demonstrated when the benzene ortho-position was occupied by a methoxy group or a bulky group (Table 3, 3bTHF and 3cTHF). It is noted that when FeCl₂ with P(OMe)₃ was used as the catalyst in place of [(FeCl₃)₂(TMEDA)], the yield of 3cTHF could be improved. Remote substituents could be tolerated, leading to the formation of the corresponding products in 37–77% yield (Table 3, 3dTHF-3fTHF). Moreover, a naphthyl compound was found to participate efficiently (Table 3, 3gTHF). On the basis of the previously reported reactions, we would like to propose a plausible pathway for this release-capture ethylene process. Thus, as shown in Fig. 4, THF is deprotonated at its 2-position by isopropyllithium to form 2-lithioTHF (I). Then, a subsequent intramolecular reverse [3 + 2] cycloaddition of the anion would release ethylene and generate the lithium enolate (II). Finally, the resulting ethylene could be caught in situ to give the doubly homologated lithium product (III). Moreover, further evidence for our proposed pathway was obtained from a relevant deuterium-labelled crossover experiment utilizing deuterated tetrahydrofuran (THF-d₈) as solvent. Thus, treatment of 4-methoxybromobenzene (1a) with isopropyllithium in THF-d₈ led to the release of ethylene-d₄. The expected deuterated product 3aTHF-d₄ (Table 3) was obtained in 61% yield.

Cross-coupling of alkyl bromides with organolithiums. We next extended the iron catalysis strategy to alkyl bromides with organolithium reagents. Typically, commercially available 1-bromo-3-phenylpropane was assessed with n-BuLi to explore the possibility of C(sp³)-C(sp³) cross-coupling. Gratifyingly, the reaction proceeded smoothly and the desired product was isolated in 77% yield (Table 4, 3a). Other organolithium reagents, such as cyclopropyllithium, 9H-fluoren-9-yllithium and (trimethylsilyl)methylolithium, were allowed to couple with 1-bromo-3-phenylpropane to provide the corresponding C(sp³)-C(sp³) cross-coupling products in good to excellent yields (Table 4, 3ab-3ad). Benzylic compounds, possessing a typical C(sp³)-Br bonds, were also used as coupling partners. As expected, the cross-coupling products with yields ranging from 11 to 71% were generated, when n-BuLi and (trimethylsilyl)methylolithium were used as coupling partners (Table 4, 3ae-3am). Under the same condition, 2-(3-bromopropyl)naphthalene was also alkylated (Table 4, 3an). Subsequently, bromocyclohexane successfully underwent a similar reaction to form the relevant coupling product in 44% yield (Table 4, 3ao).

Table 3 | Iron-catalysed release-capture ethylene coupling with isopropyllithium*.  

| Aryl | Br | Method A: FeCl₂ 10 mol%, P(OMe)₃ 10 mol%  
THF/THF-d₈, 22 °C, overnight  Method B: [(FeCl₃)₂(TMEDA)] 3 mol%  
| + | Li |  
| 3aTHF | 71%†  
MeO | Me |  
| 3bTHF trace |  
MeO | Me |  
| 3cTHF 71% (61%)†  
MeO | Me |  
| 3dTHF 37%  
MeO | Me |  
| 3eTHF 67%†  
MeO | Me |  
| 3fTHF 77%  
MeO | Me |  
| 3gTHF 85%†  
MeO | Me |  
| 3aTHF-d₄ 61%†  
MeO | Me |  

*Reaction conditions: Under – 78 °C, a solution of isopropyllithium (0.50 mmol) was added slowly into a solution of aryl bromides (0.2 mmol) in THF (1 ml). Subsequently, the mixture was added by a syringe pump in 1 h to a solution of [(FeCl₃)₂(TMEDA)] (3 mol%) in THF (1.0 ml) at 22 °C.  †Method A: FeCl₂ combined with P(OMe)₃ as catalyst was used in place of [(FeCl₃)₂(TMEDA)].  ‡Deuterated 3aTHF-d₄ was obtained in 61% when THF-d₈ was used in a deuterium-labelled experiment.  

Figure 4 | Possible pathway of release-capture ethylene. (I) 2-LithioTHF. (II) Lithium enolate. (III) Doubly homologated of isopropyllithium to generate the isopentyllithium in situ.
In summary, we have disclosed iron-catalysed cross-coupling of organolithium compounds to form diverse carbon–carbon bonds efficiently. These results are expected to expand the scope of iron catalysis as well as the use of organolithium reagents. We trust that these reactions would provide milder, cheaper and more environmentally friendly approaches towards cross-coupling products. An extension of this catalytic system to broaden its scope, and to investigate its mechanistic nature is underway in our laboratory.

**Discussion**

To provide a support against the involvement of trace amounts of other metal species, such as Pd, Pt, Co and Ni in our iron catalysts that would catalyse C–C bond formation, inductively coupled plasma mass spectrometry was performed on samples of FeCl₃ to detect the trace quantities of these metals (see Supplementary Information for details). Moreover, we conducted experiments to mimic the catalyst system to prove that relevant products were not isolated when the concentration of Co and Ni were as low as those present in the iron salts (see Supplementary Information for details). We also performed preliminary mechanistic analysis of this transformation utilizing several control experiments (see Supplementary Information for details). It was likely that the reaction involved radical species.

Noteworthy, the capability to procure useful product quantities for laboratory and industry usage through scalable routes is emerging as a very essential goal in catalytic reactions today. Therefore, we also confirmed the scalable feasibility of these iron-catalysed reactions, as shown in Fig. 5.

### Table 4 | Iron-catalysed cross-coupling of alkyl bromides with organolithium reagents*

| AlkylBr + Li[(FeCl₃)(TMEDA)₃] 3 mol% THF, r.t. overnight | AlkylR |
|--------------------------------------------------------|--------|
| ![Chemical structure 3aa](image1) 77% |
| ![Chemical structure 3ab](image2) 71% |
| ![Chemical structure 3ac](image3) 86% |
| ![Chemical structure 3ad](image4) 84% |
| ![Chemical structure 3ae](image5) 25% |
| ![Chemical structure 3af](image6) 30% |
| ![Chemical structure 3ag](image7) 37% |
| ![Chemical structure 3ah](image8) 60% |
| ![Chemical structure 3ai](image9) 48% |
| ![Chemical structure 3aj](image10) 71% |
| ![Chemical structure 3ak](image11) 53% |
| ![Chemical structure 3al](image12) 23% |
| ![Chemical structure 3am](image13) 11% |
| ![Chemical structure 3an](image14) 73% |
| ![Chemical structure 3ao](image15) 44% |

*Reaction conditions: 0.30 mmol organolithiums diluted with THF to a final concentration of (0.35 M) was added by syringe pump in 1 h to a 1.0 ml of THF solution of arylhalides (0.2 mmol), [(FeCl₃)(TMEDA)₃] (3 mol%), 0 °C.

**Figure 5 | Gram scale reactions.** Three model substrates were selected to scale up to 10 mmol scale and the corresponding target products were isolated in satisfied yields.
several typical scale-up reactions in multi-grain scales provided relevant desired products in satisfied yields.

**Methods**

**Iron-catalysed cross-coupling of 4-methoxybromobenzene (1a) and n-BuLi (2a).** To an oven-dried vial, equipped with a magnetic stirring bar, was charged with \([\text{FeCl}_3]_2(\text{TMEDA})_3\) (3.96 mg, 0.006 mmol, 3 mol%) in THF (1.6 ml) and the subsequent addition of 4-methoxybromobenzene (1a) (0.2 mmol) and FeCl₃·6H₂O (15 mg, 0.08 mmol, 4 mol%) in THF (1.0 ml). Then, after the sealed vial with a rubber stopper was taken out from the glove box, the reaction mixture was heated to 0 °C, n-BuLi (2a) (0.30 mmol, 1.6 M or 2.4 M in hexane, diluted with THF to a final concentration of 0.35 M) was added to the mixture using a syringe pump in 1 h. After the addition was completed, the reaction mixture was stirred at 0 °C for 1 h. Then, after quenching with a saturated solution of aqueous Na₂CO₃, the reaction mixture was extracted with CH₂Cl₂ three times. The combined organic solvent was evaporated under reduced pressure to afford the crude product, which was then purified by column chromatography on silica gel or preparative thin-layer chromatography.

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**Author contributions**

Z.J. performed the experiments and wrote the draft of the manuscript. Q.L. helped to perform experiments to assess scope of coupling-partners as well as to help preparing the manuscript. X.-S.P. and H.N.C.W. provided overall supervision. All authors discussed the results and commented on the manuscript.

**Additional information**

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Corrigendum: Iron-catalysed cross-coupling of organolithium compounds with organic halides

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Previous work by Cahiez et al. 2007 describing iron-catalysed cross-coupling of Grignard reagents was inadvertently omitted from the reference list of this Article. This work should have been cited following the sentence 'This catalytic system developed by Nakamura had been employed in cross-coupling reactions with Grignard reagents and arylzinc reagents'. Additionally, the formation of the TMEDA/iron(III) chloride complex was incorrectly attributed; the statement 'Therefore, the complex of TMEDA with iron(III) chloride was prepared according to Nakamura’s procedure' should read 'Therefore, the complex of TMEDA with iron(III) chloride was prepared according to Cahiez’s procedure (Cahiez et al. 2007)'.

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