

Ligand-Free Iron-Catalyzed Carbon (sp²)–Carbon (sp²) Oxidative Homo-Coupling of Alkenyllithiums

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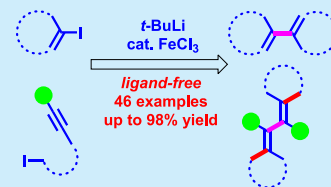
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Supporting Information

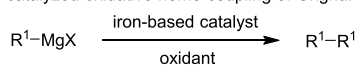
ABSTRACT: A new strategy was developed for the efficient synthesis of di-, tetra-, and hexa-substituted 1,3-butadienes. This one-pot procedure involves lithium–iodine exchange to generate the corresponding vinylolithium intermediates. A subsequent iron-catalyzed ligand-free oxidative homo-coupling eventually led to the formation of 1,3-butadienes in acceptable to excellent isolated yields.



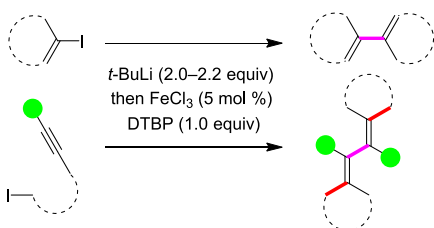
Iron is one of the most abundant metals on earth and consequently one of the most inexpensive and environmentally friendly ones.¹ Iron-based catalysts have been actively investigated for oxidative coupling reactions of Grignard reagents (Scheme 1a).² Although oxidative homo-coupling of

Scheme 1. Iron-Catalyzed Oxidative Homo-Coupling of Organometallic Reagents

a) Iron-catalyzed oxidative home-coupling of Grignard reagents



b) This work: iron-catalyzed oxidative homo-coupling of alkenyllithiums

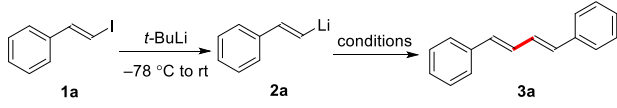


vinylolithium using a stoichiometric amount of FeCl₃ has been reported since 1969,³ efficient methods for iron-catalyzed oxidative coupling involving lithium reagents remain elusive. Conjugated 1,3-diene motifs appear in many biologically active natural products⁴ and participate in a variety of useful chemical syntheses.⁵ In connection with our continuing interest in iron-catalyzed coupling reactions of lithium reagents,⁶ herein we reported an efficient iron-catalyzed oxidative homo-coupling of alkenyllithiums, generated through either direct lithium–halide exchange or cyclization of acetylenic lithium reagents, affording

diversified 1,3-butadiene species, such as polycyclic or acyclic multisubstituted 1,3-butadienes (Scheme 1b).

Upon a lithium–iodine exchange between the vinyl iodide 1a and *t*-BuLi, the resulting vinylolithium moiety 2a was subjected to an iron-catalyzed oxidative homo-coupling. On the basis of the reports of iron-mediated oxidative homo-coupling of vinylolithium,³ a stoichiometric amount of FeCl₃ was employed at the beginning, forming the desired 1,3-butadiene (3a) in 86% yield (Table 1, entry 1). Various iron salts were uncovered to give the same result in lower or slightly lower yields than FeCl₃, such as FeF₃ (56%), FeBr₃ (52%), Fe(acac)₃ (70%), FeF₂ (25%), FeCl₂ (82%), and FeBr₂ (38%) (Table 1, entries 2–7). Next, we turned our attention to the use of catalytic amounts of FeCl₃. In the absence of an oxidant, decreasing loading of FeCl₃ led to a lower yield of 3a (Table 1, entry 8). Several commonly used oxidants were examined for this iron-catalyzed oxidative homo-coupling of vinylolithium (Table 1, entries 9–11). Considering the reaction yields and environmental friendly issue, di-*tert*-butyl peroxide (DTBP) was chosen as an oxidant in 86% yield (Table 1, entry 11). Although Et₃N was reported to be a successful additive in FeCl₂-catalyzed homo-coupling involving organolithium,⁷ it was not suitable for our reaction system (Table 1, entry 12). Changing the solvents or temperature led to no significant improvement to yields. Furthermore, we were able to reduce the catalyst loading to 5 mol % and shortened the reaction time to 30 min without sacrificing the yield (Table 1, entry 13). Due to the fact that vinylolithium was destroyed during the addition procedure with a syringe and that FeCl₃ can be dissolved well in THF, we chose to add a solution of FeCl₃ in

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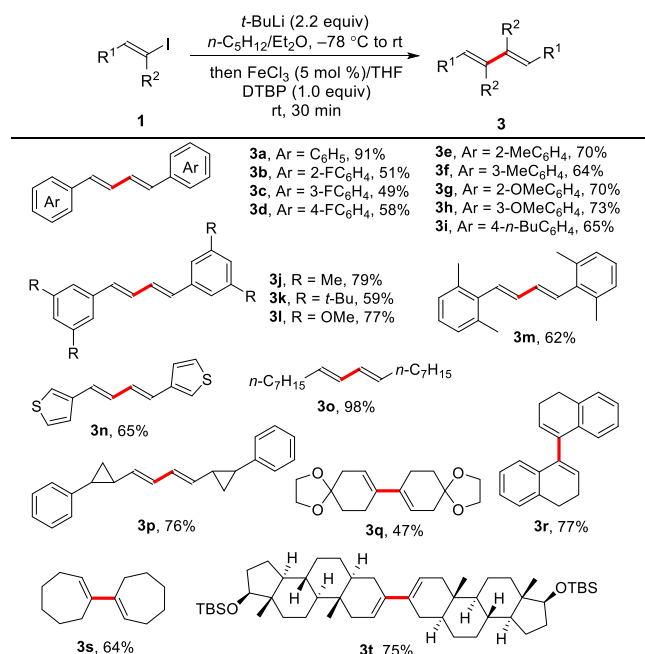
Table 1. Optimization of the Reaction Conditions^a


entry	iron salt (mol %)	additive	time (min)	yield ^b (%)
1	FeCl ₃ (100)	none	60	86
2	FeF ₃ (100)	none	60	56
3	FeBr ₃ (100)	none	60	52
4	Fe(acac) ₃ (100)	none	60	70
5	FeF ₂ (100)	none	60	25
6	FeCl ₂ (100)	none	60	82
7	FeBr ₂ (100)	none	60	38
8	FeCl ₃ (10)	none	60	29
9	FeCl ₃ (10)	O ₂ (balloon)	60	41
10	FeCl ₃ (10)	DCE (1.0 equiv)	60	84
11	FeCl ₃ (10)	DTBP (1.0 equiv)	60	86
12	FeCl ₂ (10)	Et ₃ N (1.0 equiv)	60	33
13	FeCl ₃ (5)	DTBP (1.0 equiv)	30	86
14 ^c	FeCl ₃ (5)	DTBP (1.0 equiv)	30	94

^aReaction condition: a solution of vinyl lithium (0.2 mmol) was added to a mixture of iron salts, additive (if applicable) in THF (1.0 mL) at rt. ^bGC-MS analysis. ^cTo a solution of vinyl lithium (0.2 mmol) were added a solution of FeCl₃ in THF (0.1 mL) and additive.

THF to vinyl lithium. Gratifyingly, this optimization increased the yield of diene 3a to 94% (Table 1, entry 14), and the isolated yield reached 91% (Scheme 2).

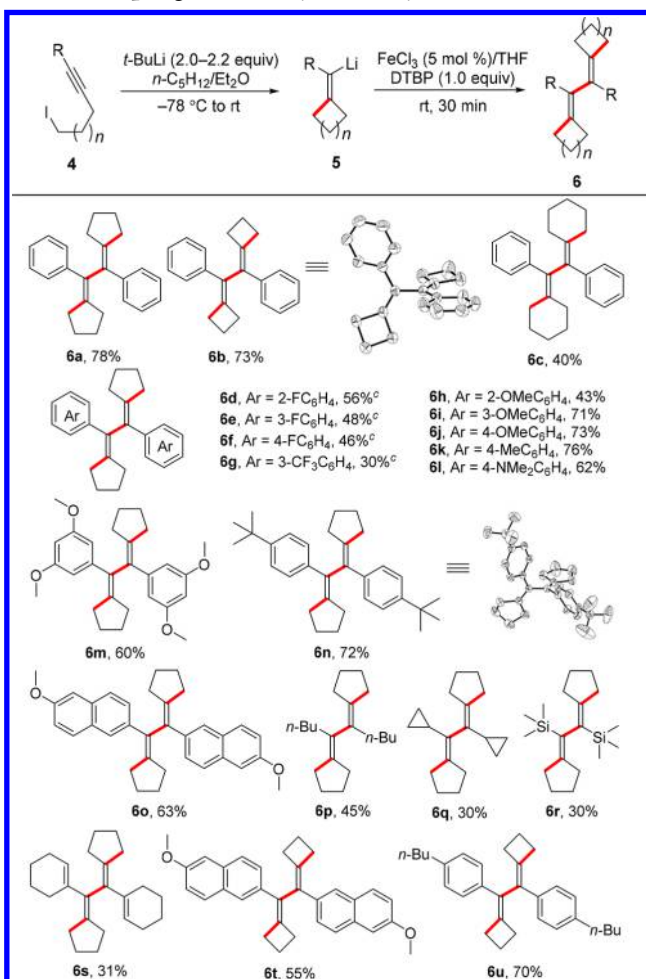
After the establishment of an acceptable optimal reaction condition, we turned our attention to examine the substrate scope of this oxidative homo-coupling. As shown in Scheme 2, homo-couplings of electron-deficient aryl groups were slightly disfavored, leading to 49–58% yields (3b–d). Electron-donating groups, such as methyl, *n*-butyl, and methoxyl, can

Scheme 2. Iron-Catalyzed Homo-Coupling from Alkenyl Iodides^{a,b}

^aReaction condition: 1 (0.2 mmol), *t*-BuLi (0.44 mmol). ^bIsolated yields.

be well tolerated on the aromatic rings with 64–73% yields (3e–i). Meanwhile, disubstituted aryl substrates and heteroaryl substrates were tested in 59–79% yields (3j–n). Notably, alkyl-substituted diene 3o was isolated in excellent yield (98%). Additionally, various polycyclic dienes (3p–t), especially a dimer of natural product derivative (3t), were obtained in acceptable to high yields (47–77%).

As organolithiums were well used in cyclization to form new carbon–carbon bonds,⁸ we next employed cyclization of acetylenic alkyl lithium to *in situ* generated vinyl lithium species, which then underwent oxidative homo-coupling to generate polycyclic all-substituted 1,3-butadienes. As can be seen in Scheme 3, 1,3-butadienes with two 5- or 4-membered rings

Scheme 3. Tandem Anionic Cyclization/Iron-Catalyzed Homo-Coupling from Acetylenic Alkyl Iodides^{a,b}

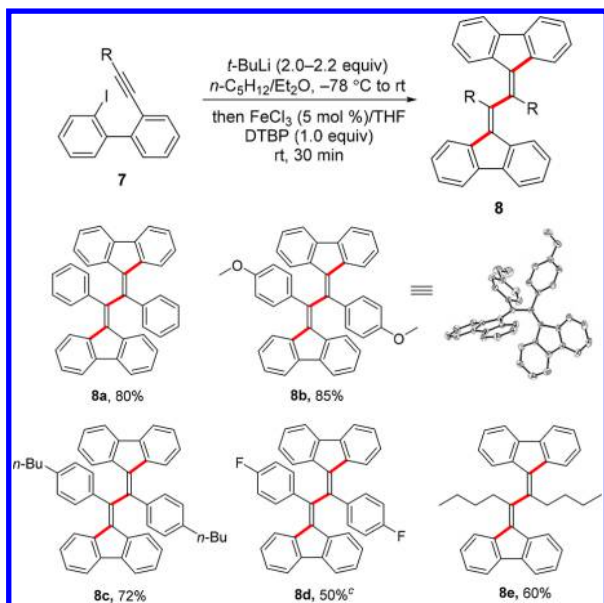
^aReaction condition: 4 (0.2 mmol), *t*-BuLi (0.44 mmol). ^bIsolated yields. ^c*t*-BuLi (0.4 mmol).

could be easily obtained in satisfactory yields (6a,b). In contrast, butadiene 6c with two 6-membered rings was formed in low yield because of allene formation.⁸ With electron-deficient aryl groups, the homo-couplings were slightly disfavored in 46–56% yields (6d–f). In particular, an aryl substrate with a stronger electron-withdrawing moiety CF₃ gave rise to diene 6g in a much lower yield (30%). Several electron-rich aryl groups were suitable for this reaction, providing the corresponding 1,3-butadienes (6i–o) in good yields (60–76%). However, substrate 4h, featuring an *ortho*-methoxy group on the phenyl

ring, gave **6h** in only 43% yield. This could be attributed to the steric hindrance effect. Moreover, electron-rich aryl groups were also able to provide 1,3-butadienes containing two 4-membered rings in moderate yields (**6t,u**). Unfortunately, this oxidative coupling process still suffers from lower yields under current conditions when aromatic groups were replaced by alkyl, silyl, or alkenyl groups (**6p–s**).

Finally, several acetylenic phenyl iodides **7** were allowed to generate butadienes **8** with two fluorene rings (Scheme 4). To

Scheme 4. Tandem Anionic Cyclization/Iron-Catalyzed Homo-Coupling from Acetylenic Phenyl Iodides^{a,b}



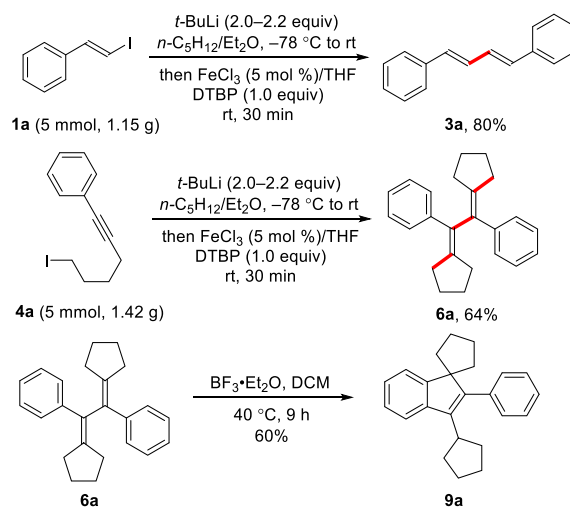
^aReaction condition: **7** (0.2 mmol), *t*-BuLi (0.44 mmol). ^bIsolated yields. ^c*t*-BuLi (0.4 mmol).

our delight, acetylenic phenyl iodides were able to undergo this tandem cyclization/oxidative coupling in higher yields than those of the corresponding acetylenic alkyl iodides, probably due to the stabilization of vinylolithium with the fluorene motif.

To demonstrate the practicality of this protocol, we carried out the coupling reaction with substrates **1a** (5 mmol, 1.15 g) and **4a** (5 mmol, 1.42 g) on a gram-scale reaction to afford diene compounds **3a** and **6a** in 80 and 64% yield, respectively (Scheme 5). Diene **3a** and its derivatives were rather useful in organic synthesis, for example, in Diels–Alder reaction⁹ and McCormack cycloaddition.¹⁰ Subsequent treatment of polycyclic diene **6a** with a Lewis acid led to an intramolecular Friedel–Crafts cyclization, forming the highly substituted indene **9a**.¹¹ Diene **8a** and its derivatives were applied to construct the corresponding dispirocycles bearing high fluorescence quantum yields, which were expected to be applicable in the field of optoelectronics.¹²

It is worth noting that butadienes with bulky substituents show axial chirality because of hindered rotation around the C2–C3 bond.¹³ Fortunately, single crystals of diene products (**6b**, **6n**, and **8b**) were obtained from hexane or hexane/ethyl acetate (Schemes 3 and 4), whose X-ray diffraction analysis revealed that the torsion angle of C1–C2–C3–C4 was 95.698(337), 80.275(318), and 69.432(227)°, respectively. Indeed, the current protocol for preparing nonplanar butadienes could help open up avenues for the synthesis and application of various axially chiral 1,3-butadienes.

Scheme 5. Scale-Up Syntheses and Transformation of Butadienes



In order to obtain mechanistic insights of this transformation, several control experiments were carried out (Table 2).

Table 2. Control Experiments^a

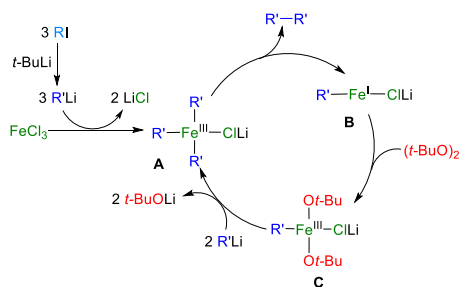
entry	iron (mol %)	oxidant	time (min)	yield ^b (%)
1	none	DTBP (1.0 equiv)	60	25
2	Fe (100)	none	60	0
3	Fe (10)	DTBP (1.0 equiv)	60	25

^aReaction condition: a solution of vinylolithium **2a** (0.2 mmol) was added to a mixture of iron and oxidant (if applicable) in THF (1.0 mL) at rt. ^bGC-MS analysis.

Experiments in entry 1 (Table 2) and entry 8 (Table 1) showed that both catalyst and oxidant were necessary for this reaction condition. One equivalent of FeCl₂ also worked well (Table 1, entry 6), but iron powder (1.0 equiv) did not work (Table 2, entry 2) in this oxidative homo-coupling. Moreover, a catalytic amount of iron powder and stoichiometric oxidant failed to initiate the catalytic cycle (Table 2, entry 3 vs entry 1). Therefore, we proposed Fe(I) as the lowest oxidation state in this homo-coupling. Since 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and 1,1-diphenylethylene (DPE) were known to interact directly with organolithium reagents,^{6a} these radical scavengers were not suitable if this reaction involves a radical pathway. Furthermore, radical clock experiments¹⁴ with cyclopropyl substrate **4q** to diene **6q** did not generate ring-opening products, which partially supported that the catalytic cycle of this transformation did not involve radical species.

On the basis of these experimental results and literature reports,¹⁵ we propose herein a plausible mechanism of oxidative homo-coupling in Scheme 6. At the beginning, catalytic amounts of FeCl₃ and vinylolithium reagents generate the tetra-coordinated complex A, which readily undergoes a reductive elimination of the homo-coupling product to form Fe(I) complex B.¹⁶ In the presence of DTBP, Fe(I) complex B would be oxidized to Fe(III) complex C. Subsequently, complex C would regenerate the reactive complex A with two more molecules of vinylolithium, thus completing the catalytic cycle. In

Scheme 6. Proposed Mechanism for Iron-Catalyzed Oxidative Homo-Coupling



order to shed light on the proposed mechanistic pathway, DFT computation (Supporting Information) and EPR spectroscopic experiments on the iron-catalyzed oxidative homo-coupling were performed. In the ESR experiments (Bruker EMX EPR spectrometer, pentane/Et₂O/THF at 10 K), a Fe(I) signal was observed (see Figure S5 in the Supporting Information), which partially supports the proposed mechanism.

In summary, we have developed an iron-catalyzed oxidative homo-coupling of vinylolithiums for the efficient synthesis of di-, tetra-, and hexa-substituted 1,3-butadienes. This reaction system, involving inexpensive and environmentally friendly iron catalysts, is easy to scale up and would help open up a new avenue to the synthesis and application of butadienes in chemical materials and asymmetric synthesis. The mechanistic study suggests that Fe(I) is the lowest oxidation state in this catalytic homo-coupling cycle. Relevant studies on the axial chirality and applications of these butadienes and their analogues as well as detailed mechanistic investigation are still in progress in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03893.

Experimental procedures and compound characterization (PDF)

Accession Codes

CCDC 1860059–1860060 and 1866387 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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