# Mild and Phosphine-Free Iron-Catalyzed Cross-Coupling of Nonactivated Secondary Alkyl Halides with Alkynyl Grignard Reagents

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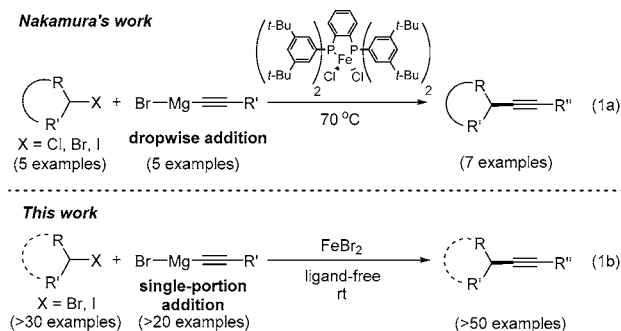
ⓢ Supporting Information

ABSTRACT: A simple protocol for iron-catalyzed cross-coupling of nonactivated secondary alkyl bromides and iodides with alkynyl Grignard reagents at room temperature has been developed. A wide range of secondary alkyl halides and terminal alkynes are tolerated to afford the substituted alkynes in good yields. A slight modification of the reaction protocol also allows for cross-coupling with a variety of primary alkyl halides.
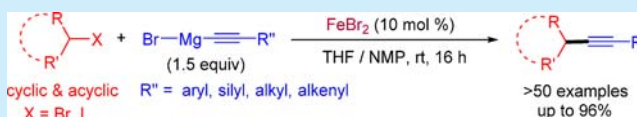
Alkynes are versatile intermediates in the syntheses of natural products, biologically active molecules, and functional materials.[1] Therefore, the development of streamlined and practical syntheses of substituted and functionalized alkynes is highly desirable. Whereas aryl- and vinyl-substituted alkynes are routinely prepared by palladium-catalyzed Sonogashira coupling,[1a,2] alkyl-substituted alkynes are harder to access through similar reactions due to two factors: (i) oxidative addition of alkyl halides is comparatively slow;[3] (ii) the competitive and nonproductive β-hydride elimination of alkyl group is facile in metal alkyl intermediates.[3] Until now, there have been less than a handful of reports of Pd-[4] and Ni-catalyzed[5] Sonogashira coupling of alkyl halides, the most advanced of which is Liu's Ni-based method to afford a broad range of secondary alkyl-substituted alkynes.[5b] Consequently, a number of alternatives of Sonogashira coupling have been developed to access alkyl-substituted alkynes.[6−12] Among them, alkyl−alkynyl organometallic coupling reactions are most straightforward and versatile.[6−8,10] These include the coupling of alkyl halides with organometallic reagents,[6,7] the coupling of haloalkynes with organometallic reagents,[8] and the oxidative coupling of alkynyl nucleophiles.[10] Despite the advances of the above-mentioned synthetic methodologies in the construction of $C(sp^3)−C(sp)$ bond, several limitations exist: (i) Coupling of nonactivated secondary alkyl halides remains difficult compared with primary ones. (ii) The terminal alkynes employed in the reported methods are generally limited to silylethynes and arylethynes, while the coupling of functionalized alkylethynes is challenging. (iii) The transition-metal-catalyzed reactions usually employ costly phosphine- and nitrogen-based ligands.

In the past decade, iron catalysis has generated significant interest for C−C cross-coupling reactions thanks to the abundance, low toxicity, and low cost character of iron.[13] Although iron catalysis has been widely employed for the formation of $C(sp^2)−C(sp^2)$, $C(sp^3)−C(sp^2)$, and $C(sp^3)−C(sp^3)$ bonds,[13] iron-catalyzed $C(sp^3)−C(sp)$ bond formation

is rare.[6a] To the best of our knowledge, there is only a single report by Nakamura on iron-catalyzed synthesis of substituted alkynes via the cross-coupling of secondary alkyl halides with alkynyl Grignard reagents (eq 1a).[6a] However, the reactions

required an iron complex with a bis(phosphine) ligand, an elevated temperature (70 °C), and a slow, dropwise addition of Grignard reagents over 2 h. Furthermore, only several examples of cyclic secondary alkyl halides and sterically hindered alkynes were demonstrated. Herein, we report the phosphine-ligand-free iron-catalyzed cross-coupling of nonactivated secondary alkyl bromides and iodides with alkynyl Grignard reagents at room temperature, exhibiting a broad scope on both alkyl halides and terminal alkynes (more than 50 examples, eq 1b).

We commenced our investigation by attempting the cross-coupling of iodocyclohexane with 1-propynylmagnesium bromide in N-methylpyrrolidone (NMP) solvent at room temperature (Table S1, Supporting Information). Various iron(III) and iron(II) salts were tested as the catalysts. While most of the iron salts catalyzed the reaction to yield the desired product, 1-propynylcyclohexane (**1**), iron(II) bromide was the optimal catalyst (Table S1, entry 10, Supporting Information).

Upon further optimization, we were able to achieve the highest yield of **1** (86%) in the presence of 10 mol % of FeBr$_2$ and 1.5 equiv of alkynyl Grignard reagent in a more diluted solution (Table S1, entry 19, Supporting Information). Significantly, a slow, dropwise addition of Grignard reagent as in the Nakamura protocol was unnecessary. The replacement of NMP with other solvents [for example, tetrahydrofuran (THF), 1,4-dioxane, and *N,N*-dimethylformamide (DMF)] only provided **1** in low yields.[14] While bis[2-(*N,N*-dimethylamino)-ethyl] ether (O-TMEDA)[6c] and tetramethylethylenediamine (TMEDA)[15] have been reported to enhance the yield of transition-metal-catalyzed alkylation of Grignard reagents, they did not promote the yield of **1** in our protocol (Table S1, entries 31 and 36, Supporting Information).[14] Thus, no additive is employed in our protocol. We further examined other transition-metal catalysts (Mn,[16] Co,[6b] Ni,[6c,d,7] Cu,[8b] Ag,[12] Cr,[17] and Pd[6e]) which have been employed in various C–C cross-coupling reactions (Table S1, entries 39–48, Supporting Information); however, they either promoted the reaction to afford **1** in a trace to modest yield or did not catalyze the reaction at all. Their catalytic inactivity further suggests that they are unlikely to be the metal impurities present in FeBr$_2$ to catalyze the reaction. Without FeBr$_2$, no product was observed (Table S1, entry 21, Supporting Information), further suggesting FeBr$_2$ as a genuine precatalyst.

With the optimized conditions in hand, we then explored the substrate scope (Scheme 1). This iron-catalyzed protocol tolerates a wide range of six-membered cyclic alkyl iodides, including cyclohexyl, bicyclo[2.2.1]heptyl, Boc-protected piper-idinyl, and tetrahydrofuranyl moieties. The cyclic rings bearing various substituents (alkyl, ester, carbamate, and functionalized aryl groups) (**2f–h,k,l,n,o,u–x**) are also suitable coupling partners. In the presence of higher loading of FeBr$_2$ (20 mol %) and O-TMEDA additive, bromocyclohexane gave a yield similar to that using iodocyclohexane (**2c**). In addition, a variety of aryl-, silyl-, and alkylethynes readily react with EtMgBr to generate the corresponding alkynyl Grignard reagents for subsequent cross-coupling reactions, affording the substituted alkynes in moderate to excellent yields. Electron-rich, -neutral, and -deficient arylethynes, as well as trialkylsilylethynes with varying steric properties (SiMe$_3$, SiEt$_3$, and Si^{i}Pr$_3$), are well tolerated. Furthermore, alkylethynes containing both simple hydrocarbon (hexyl, nonyl) and functionalized groups (tetrahydropyran, carbazole, morpholine, substituted aryl ether, and cyclohexenyl) couple efficiently. Double alkynylation of 1,4-diiodocyclohexnae proceeded smoothly when excess Grignard reagent was added (**2m**). The biologically related molecule, cholestene, can also be alkynylated (**2y**). The diastereomeric ratios of the alkyne products are enhanced compared to the corresponding alkyl iodides, especially when sterically hindered alkynyl groups are adopted (**2f,h,k,u,v,x**). However, the use of less bulky alkylethynyl groups results in a decrease of the diastereomeric ratio of the products (**2g,l,m,y**).[18] When extremely high purity (99.999%) FeBr$_2$ was used in the coupling reactions, similar yields of substituted alkyne products were obtained as compared to the use of FeBr$_2$ in 98% purity (**2o,s,w**), further supporting that FeBr$_2$ is the best catalyst to promote the reactions.

We then studied the scope of smaller and larger cyclic as well as acyclic alkyl halides (Scheme 2). Halo-substituted azetidine, cyclopentane, dihydroindene, cycloheptane, and cyclooctane were shown to be compatible coupling partners (**3a–e**) despite the ring strains and/or steric hindrance of these cyclic
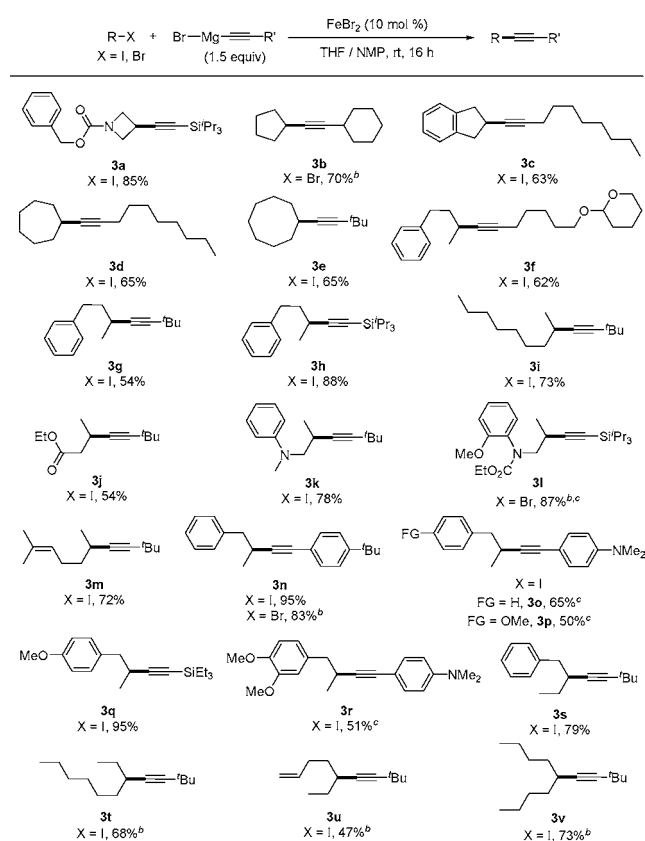
Scheme 1. Scope of Six-Membered Cyclic Alkyl Halides[a]
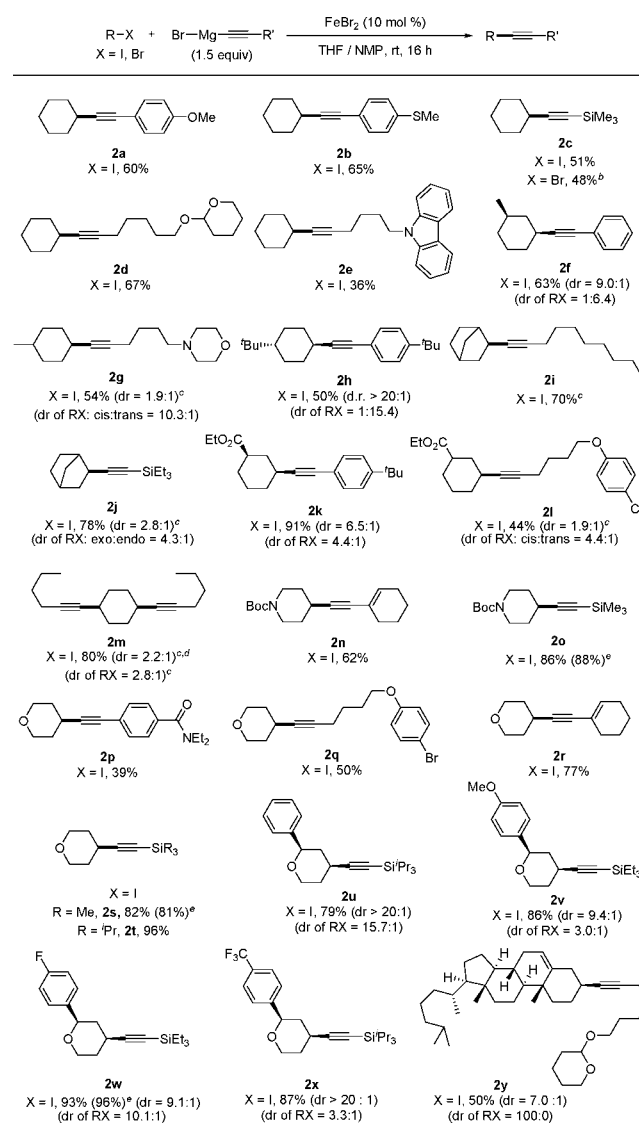
[a]Reaction conditions: alkyl halide (1 mmol), alkynyl-MgBr (0.5 M in THF, 1.5 mmol, 3 mL), FeBr$_2$ (98% purity, 10 mol %), NMP (4 mL), N$_2$ atm, rt, 16 h; yields are of isolated products; diastereomeric ratios (dr) of product and RX determined by ^{1}H NMR or GCMS; major diastereoisomers are shown. [b]FeBr$_2$ (20 mol %), O-TMEDA (2 equiv). [c]Major diastereoisomer could not be determined. [d]FeBr$_2$ (20 mol %), alkynyl-MgBr (0.5 M in THF, 3 mmol, 6 mL). [e]FeBr$_2$ (99.999% purity) used.

compounds. Further, acyclic alkyl halides, even when bearing aryl, ester, amine, carbamate, and olefin functional groups, reacted smoothly to yield the substituted alkynes (**3f–v**). The more sterically hindered acyclic alkyl iodides afforded the products in higher yields in the presence of higher loading of FeBr$_2$ and O-TMEDA (**3t–v**). To our knowledge, this method enables the first Fe-catalyzed cross-coupling of acyclic secondary alkyl halides with alkynyl Grignard reagents.

To demonstrate the practicality of this Fe-catalyzed alkynylation of secondary alkyl halides, the coupling was performed at higher mmol scales. Both 4-iodotetrahydropyran (eq 2a,b) and *tert*-butyl 4-iodopiperidine-1-carboxylate (eq 2c) (5–20 mmol, up to 4.2 g) reacted with (trimethylsilyl)-

Scheme 2. Scope of Cyclic and Acyclic Secondary Alkyl Halides.[a]

[a]Reaction conditions: alkyl halide (1 mmol), alkynyl-MgBr (0.5 M in THF, 1.5 mmol, 3 mL), FeBr$_2$ (98% purity, 10 mol %), NMP (4 mL), N$_2$ atm, rt, 16 h; yields are of isolated products. [b]FeBr$_2$ (20 mol %), O-TMEDA (2 equiv). [c]Reaction conditions: alkyl halide (0.5 mmol), alkynyl-MgBr (0.5 M in THF, 0.75 mmol, 1.5 mL), NMP (2.0 mL).
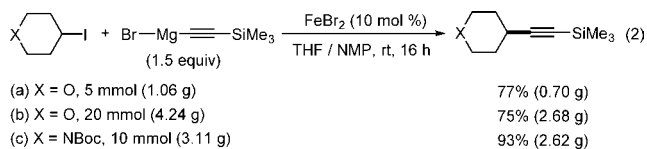
ethynylmagnesium bromide to give the corresponding substituted alkynes without significant diminishment of yields.

To gain mechanistic insight for the Fe-catalyzed coupling of secondary alkyl halides with alkynyl Grignard reagents, we employed enantioenriched (3-iodobutyl)benzene as the coupling partner (eq 3).[19] Only a racemic mixture of substituted alkynes was obtained. Additionally, a radical clock substrate, cyclopropylmethyl bromide, reacted to give the ring-opening product in the Fe-catalyzed alkynylation (eq 4). These results are consistent with the radical mechanism proposed in Fe-[6a,20] and Ni-catalyzed[5b,6c,21] C–C cross-coupling reactions with alkyl halides. The enhancement of diastereomeric ratios of substituted alkyne products in the Fe-catalyzed alkynylation of 3- and 4-substituted iodocyclohexanes further supports the radical pathway (Scheme 1), as similar results have been demonstrated in radical-based Ni-catalyzed coupling reactions.[5b,22] We propose that the reaction mechanism of this phosphine-free Fe-catalyzed protocol would be similar to that proposed in Nakamura's system.[6a] FeBr$_2$ first reacts with the alkynyl Grignard reagent to form an Fe(alkynyl-ate)
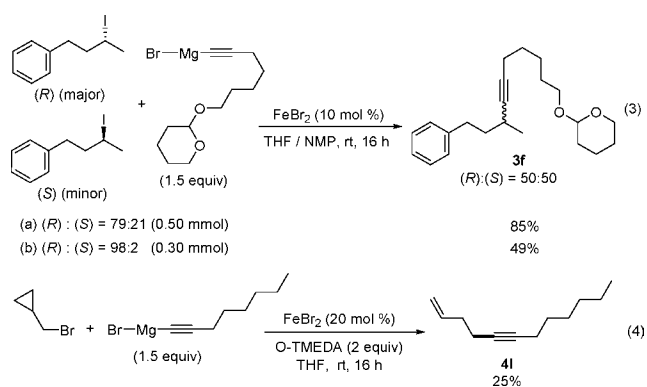
intermediate.[23] A single-electron transfer from the Fe center of the Fe–ate complex to alkyl halide initiates the carbon–halogen bond cleavage, generating an alkyl radical. The recombination of alkyl radical to the Fe(alkynyl-ate) intermediate forms an Fe(alkynyl-ate)(alkyl) species, which subsequently undergoes reductive elimination to generate the alkyl-substituted alkyne product. While the identity of the Fe species during catalysis is unclear, after the reaction the solution remained clear and no insoluble iron(0) particles were observed.

The application of this protocol to the cross-coupling of nonactivated primary alkyl halides was also examined. Further optimization of the original protocol showed that the use of THF solvent in conjunction with 2 equiv of O-TEMDA efficiently facilitated the coupling of primary alkyl halides with alkynyl Grignard reagents.[14] Under the modified conditions, a number of functionalized primary alkyl halides were found to couple with various arylethynyl-, silylethynyl-, and alkylethynylmagnesium bromides (Scheme 3).

In the Fe-catalyzed reaction protocols (Schemes 1–3), the cross-coupling of secondary alkyl iodides generally proceeds smoothly without the addition of O-TMEDA additive, whereas

Scheme 3. Scope of Primary Alkyl Halides[a]
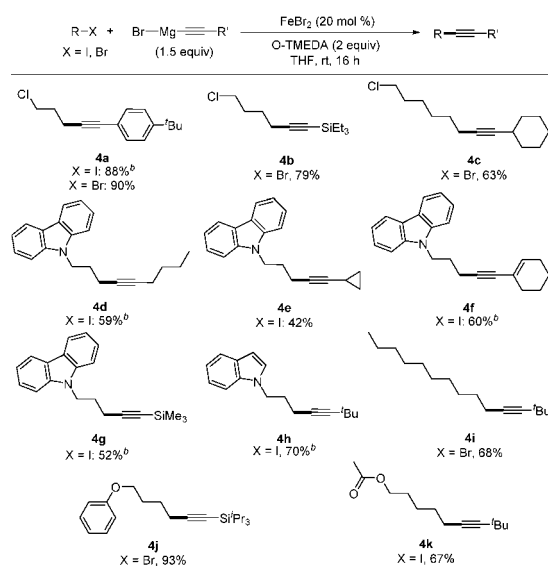
[a]Reaction conditions: alkyl halide (1 mmol), alkynyl-MgBr (0.5 M in THF, 1.5 mmol, 3 mL), FeBr$_2$ (98% purity, 20 mol %), O-TMEDA (2 mmol), THF (4 mL), N$_2$ atm, rt, 16 h; yields are of isolated products. [b]FeBr$_2$ (10 mol %).

the addition of O-TMEDA can promote the coupling with secondary alkyl bromides, primary halides, and sterically hindered alkyl iodides.[14] We propose that O-TMEDA would stabilize the reactive alkynyl Grignard reagents from decomposition,[6c] prior to the Fe-mediated activation of less reactive secondary alkyl bromides and primary alkyl halides as well as sterically hindered alkyl iodides to generate the corresponding alkyl radicals. Some reactions only generate moderate yields of products despite a 100% conversion, probably due to a competing β-hydride elimination from Fe−alkyl intermediate to give alkene and the Fe-mediated reduction of the alkyl halide to give akane.[24]

In summary, we have developed a general method for the iron-catalyzed cross-coupling reactions of nonactivated secondary alkyl halides with alkynyl Grignard reagents at ambient conditions. This method is compatible with a wide range of readily accessible secondary alkyl halides and terminal alkynes. Additionally, the modified reaction protocol can be utilized in the cross-coupling reactions of nonactivated primary alkyl halides. Thanks to the use of environmentally benign and inexpensive iron catalyst along with the mild conditions of this protocol, we anticipate that this chemistry will be applicable to the convenient synthesis of functionalized alkyne motifs in pharmaceutical and materials chemistry.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Spectral and experimental data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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(18) We propose that the Fe(alkynyl-ate) intermediate containing the less bulky alkynyl group could not sterically differentiate significantly the substituted cyclohexyl radical prior to the coupling reaction, thereby generating a lower diasteromeric ratio of the product.

(19) The deviation of the yields of 3f was presumably due to the use of different scales of enantioenriched substrates.

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(24) During the optimizations of reaction conditions, trace to modest amounts of alkene and alkane coproducts were often detected by GC−MS analysis. Moreover, for product 4e (Scheme 3), both alkane and alkene coproducts were detected by GC−MS, which probably led to the low yield of 4e.