Cross-Coupling

DOI: 10.1002/ange.201104125

Tuning Chemoselectivity in Iron-Catalyzed Sonogashira-Type Reactions Using a Bisphosphine Ligand with Peripheral Steric Bulk: Selective Alkynylation of Nonactivated Alkyl Halides**

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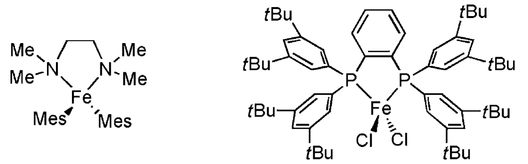
Alkynes are important structural units of various bioactive molecules and organic electronic materials as well as of versatile intermediates in organic synthesis.[1] We frequently rely on the Sonogashira reaction to incorporate alkynyl units into organic molecules in laboratory and industrial settings.[2] Despite their prevalent use in the chemical synthesis, nonactivated alkyl halides with β-hydrogen atoms have remained as difficult electrophiles for the cross-coupling reaction. Considerable efforts have been devoted to address this problem: Fu and co-workers recently employed a palladium/copper catalyst composite with a bulky N-heterocyclic carbene (NHC) ligand.[3] Glorius and co-workers[4] and Hu and co-workers[5] have expanded the substrate scope by using the palladium-NHC complex $[\{IBiox7PdCl_2\}_2]$[4] and the nickel-pincer complex $[(^{Me}NN_2)NiCl]$ (bis[(2-dimethylamino)phenyl]amine nickel(II) chloride),[5] respectively. Oshima and co-workers reported another noteworthy example of a Sonogashira-type coupling of alkyl halides with alkynyl Grignard reagents using a cobalt catalyst.[6] Based on the ability of iron to couple a nonactivated alkyl halide with various nucleophiles,[7–10] we would expect that iron would be an efficient catalyst for the Sonogashira-type coupling of our current focus. However, there has been no established method for the C_{sp}–C_{sp^3} coupling under iron catalysis, whereas several groups, including us, successfully developed iron-catalyzed Sonogashira-type C_{sp}–C_{sp^2} couplings of conventional unsaturated carbon electrophiles, such as aryl halides and alkenyl halides.[11] We report herein a highly C_{sp^3}-selective coupling reaction of nonactivated alkyl halides with alkynyl Grignard reagents using an iron catalyst possessing a bisphosphine ligand with peripheral steric bulk. This ligand switches the selectivity of the C–C bond formation from an unsaturated carbon center to a saturated carbon center.[8b,12]

A recent mechanistic study reported by Nagashima and our group showed that a diaryliron species, such as complex **A** (Scheme 1), is a catalytically active species in the iron-catalyzed cross-coupling of alkyl halides.[14] Complex **A** possesses the following characters: divalent oxidation state (+II), electronic charge neutrality, coordinative unsaturation (14 electrons), and high spin state ($S=2$). Complex **A** homolytically cleaves the C_{sp^3}–halogen bond by a radical mechanism, thus resulting in the observed high reactivity and selectivity towards nonactivated alkyl halides. In analogy, we designed new bisphosphine ligands bearing peripheral steric bulk (SciOPPs), and prepared a divalent iron bisphosphine complex **B** (Scheme 1). Complex **B** exhibits the above-mentioned properties of the catalytically active species and can be a good precatalyst for the coupling reaction; indeed, various coupling reactions were successfully catalyzed by this complex.[8n,15] The transmetalation reaction between **B** and alkynyl metal reagents should also give rise to a reactive alkynyliron intermediate for the desired Sonogashira-type coupling reaction; however, in our previous work, we have observed that the C_{sp}–C_{sp^2} coupling between an alkynyl Grignard reagent and an alkenyl triflate or bromide proceeded in the absence of a ligand or a coordinating additive.[11a] Thus, the issue of the chemoselectivity emerged as an interesting point to explore.



A
$[Fe(Mes)_2(tmeda)]$

B
$[FeCl_2(3,5\text{-}tBu_2\text{-}SciOPP)]$

Scheme 1. Divalent iron diamine and bisphosphine complexes relevant to iron-catalyzed cross-coupling of alkyl halides. Mes = 2,4,6-trimethylphenyl, tmeda = *N*,*N*,*N'*,*N'*-tetramethylethylene diamine, SciOPP = spin-control-intended *ortho*-phenylene bisphosphine.[13]

To study the chemoselectivity, C_{sp^3} center versus C_{sp^2} center, we treated 4-bromo-1-cyclohexen-1-yl trifluoromethanesulfonate **1** with alkynylmagnesium reagent **2a** in the presence of various iron catalysts (Table 1). Electrophile **1** has two potential reactive sites, C_{sp^3}–Br and C_{sp^2}–OTf. In the presence of 5 mol% of $FeCl_2$, the reaction between **1** and **2a** gave only 7% of C_{sp^3}-alkynylated **3**, and 64% yield of C_{sp^2}-alkynylated **4** and 7% of the doubly alkynylated product **5** (Table 1, entry 1). Slow addition of Grignard reagent **2a**

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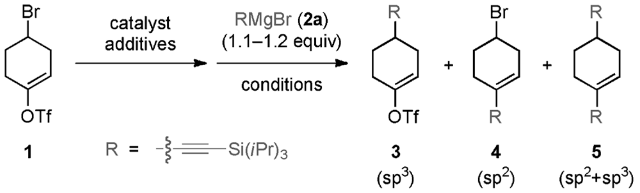
[**] This work is granted by the Japan Society for the Promotion of Science (JSPS) through the "Funding Program for Next Generation World-Leading Researchers (NEXT Program)," initiated by the Council for Science and Technology Policy (CSTP). Financial support from Tosoh Finechem Corporations, the Noguchi Institute, and a Grant-in-Aid for Scientific Research on Innovative Areas "Integrated Organic Synthesis" is also acknowledged.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201104125.

Table 1: Chemoselective iron-catalyzed cross-coupling of 4-bromo-1-cyclohexen-1-yl trifluoromethanesulfonate (**1**) with (*tert*-butyldimethylsilyl)ethynylmagnesium bromide (**2a**) in the presence of catalyst and additives.[a]

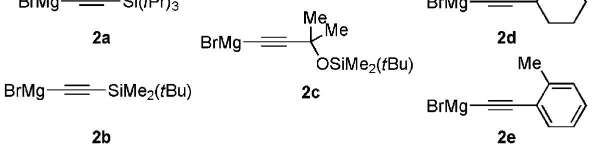


Entry	Catalyst [mol %]	Additives [mol %]	Solvent	T [°C]	t [h]	Yield [%][b] 3	4	5	Recovery of **1** [%][b]
1	$FeCl_2$ (5)	–	THF	60	2	7	64	7	19
2	$FeCl_2$ (5)	–	THF	60	2[c]	18	31	9	35
3	$FeCl_3$ (3)	LiBr (120)	THF	60	2	0	89[d]	5[e]	0
4	**B** (5)	–	THF	60	2[c]	65	4	12[e]	18
5	**B** (5)	**L1** (5)	THF	60	4[c]	70	1	2	27
6[f]	[{(π-allyl)PdCl}$_2$] (2.5)	IAd·HCl (5), CuI (5)	DMF/Et_2O	45	4	0	88	0	6[e]
7[f]	[(^{Me}NN$_2$)NiCl][g] (5)	CuI (5), NaI (20)	dioxane	120	16	0	26	0	30[e]
8	[Co(acac)$_3$] (5)	–	TMEDA	60	3	10[e]	3	13	71[e]

[a] Reactions were carried out on a 0.3–0.5 mmol scale. [b] Yields were determined by ^1H NMR analysis using CH_2Br_2 as an internal standard, unless otherwise noted. [c] Grignard reagent **2a** was added dropwise over the time indicated. [d] Yield of the isolated product. [e] Yields were determined by GLC analysis using decane as an internal standard. [f] Ethynyltriisopropylsilane and Cs_2CO_3 were used instead of **2a**. [g] Bis[(2-dimethylamino)-phenyl]amine nickel(II) chloride purchased from Sigma–Aldrich. acac = acetylacetonate, DMF = *N,N′*-dimethylformamide, Tf = trifluoromethanesulfonyl, THF = tetrahydrofuran.

slightly improved the yield of **3** (Table 1, entry 2).[8a] Addition of LiBr (1.2 equiv), known as an effective additive for the above-mentioned enyne coupling,[11a] resulted in the selective cleavage of C_{sp^2}–OTf to give **4** in 89 % yield (Table 1, entry 3). This chemoselectivity toward C_{sp^2} electrophiles can be rationalized by the formation of an alkynylferrate intermediate.[8i, 16] The reaction in the presence of the divalent iron complex **B** gave the desired C_{sp^3} coupling product **3** in 65 % yield along with the formation of small amounts of **4** and **5** (Table 1, entry 4). Addition of SciOPP ligand **L1** (5 mol %) and the prolongation of the addition period (2→4 h) of **2a** further improved the C_{sp^3} selectivity to give **3** in 70 % yield with the minimal formation of **4** (1 %) and **5** (2 %; Table 1, entry 5). Notably the literature methods for C_{sp}–C_{sp^3} coupling based on a Pd/Cu–NHC catalyst[3] and a Ni catalyst[5] gave the unexpected C_{sp^2}-alkynylated product selectively (Table 1, entries 6 and 7). The Co-catalyzed reaction[6] gave **3** in 10 % yield with 71 % recovery of the substrate **1** (Table 1, entry 8). These results clearly show that the combined use of an iron catalyst and the phosphine ligand is effective for the selective C_{sp}–C_{sp^3} coupling reaction.[17]

Table 2 exemplifies the coupling reaction between various alkyl halides and alkynyl Grignard reagents (**2a**–**e**; Scheme 2) under the optimized reaction conditions. The reactions of secondary alkyl bromides with alkynyl Grignard reagents **2a**–**e** gave the desired product in good to excellent yields (Table 2, entries 1–5). Notably the reactions with **2d** and **2e**, which bear a less-bulky substituent, required a higher catalyst loading and a longer addition period of the Grignard reagents for completion. A secondary alkyl chloride, one of the challenging substrates in the C_{sp}–C_{sp^3} coupling,[3–6] gave the desired product in an acceptable yield (Table 2, entry 7). In all the reactions examined, the reductive-cleavage by-product (alkane) and the elimination by-product (alkene) were obtained in 3–15 % yields. The coupling reaction of an alkyl bromide possessing an ethoxycarbonyl group occurred with preservation of the ester functionality (Table 2, entry 8). With 1-bromo-4-chlorobutane, C–Br bond cleavage took place in preference to C–Cl bond cleavage (Table 2, entry 9). 1-Bromo-4-(2-bromoethyl)benzene coupled with **2a** with selective C_{sp^3}–Br bond cleavage (Table 2, entry 10). Notably the C_{sp^2}–Br bond cleavage product was obtained in less than 1 % yield. The selective cleavage can be attributed to the radical character of the organoiron species (see above) and the difference in the stabilities of the resulting radical intermediates (alkyl versus aryl).

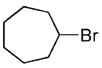
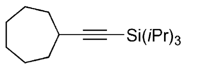
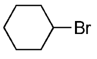
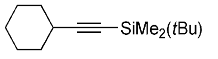
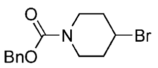
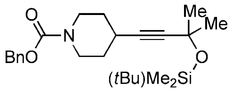
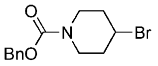
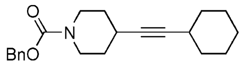
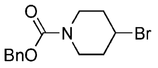
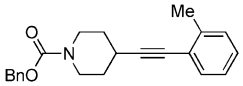
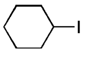
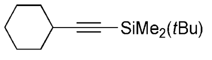
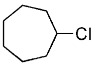
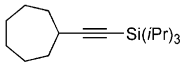
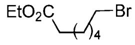
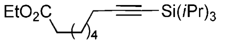
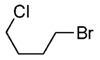
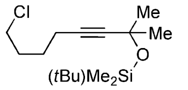
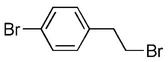
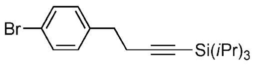
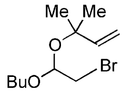
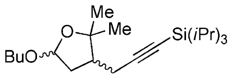
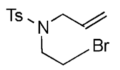
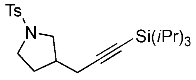


Scheme 2. Alkynyl Grignard reagents examined for the iron-catalyzed cross-coupling of alkyl halides. See reactions in Table 2.

Taking advantage of the generation of alkyl radical intermediates from the alkyl halide substrates, we carried out sequential cyclization/cross-coupling reactions[18] (Table 2, entries 11 and 12). 3-(2-Bromo-1-butoxyethoxy)-3-methyl-1-butene and *N*-(2-bromoethyl)-*N*-(2-propenyl)-4-methylbenzenesulfonamide reacted with **2a** to give the corresponding ring-closure products in 81 % and 92 % yields, respectively. The simple cross-coupling products without the cyclization were not obtained.

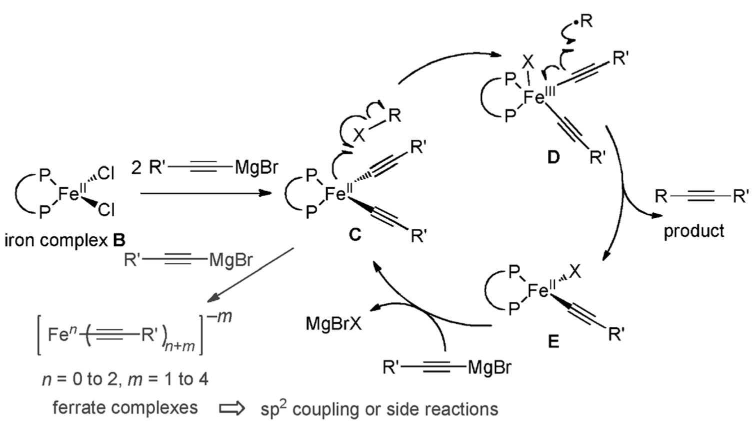
A possible catalytic cycle based on our mechanistic picture is shown in Scheme 3. The starting complex **B** is treated with two equivalents of alkynyl Grignard reagent to

Table 2: Cross-coupling of alkyl halides with alkynyl Grignard reagents.[a]

Entry	Alkyl halide	RMgBr	Product	Yield [%][b]
1		**2a**		88
2		**2b**		83
3		**2c**		86
4[c]		**2d**		64
5[c]		**2e**		68
6		**2b**		83
7		**2a**		69
8		**2a**		81
9		**2c**		73
10		**2a**		82
11		**2a**		81
12[d]		**2a**		92

[a] Reactions were carried out according to the procedure for entry 4 in Table 1 using 3–5 mol% of **B** on a 0.5–1.0 mmol scale, unless otherwise noted. [b] Yield of the isolated product. [c] Grignard reagent was added dropwise over 4 h in the presence of 20 mol% of **B** and 5 mol% of **L1** [d] Grignard reagent was added dropwise over 4 h in the presence of 10 mol% of **B**. bn = benzyl, Ts = *p*-toluenesulfonyl.

form dialkynyliron(II) **C**. Because we did not observe any trace formation of a diyne byproduct in the coupling reactions, we believe that the iron center is not reduced during the reaction and remains divalent in the ground state. The catalytic cycle, thus, starts with the homolytic cleavage of the C_{sp^3}–halogen bond of the alkyl halide by **C** to form an alkyl radical (R·) and Fe^{III} species **D**. This step is known as the initial process in metal-catalyzed living radical polymerization reactions.[19,20] The trivalent intermediate **D** reacts with the alkyl radical by release of the alkynyl radical, or much more likely, by an addition/elimination or substitution reaction of the alkyl radical at the ligating carbon center of the alkynyl group, and gives the product and alkynyliron(II) halide **E**. We cannot rule out the possibility of an alternative pathway, in which the alkyl radical (R·) adds to the iron center of **D** to form a Fe^{IV} intermediate, which may also undergo the reductive elimination to give the product and **E**. Transmetalation with an alkynyl Grignard reagent regenerates the reactive species **C** to complete the catalytic cycle. The peripheral steric bulk[21] of the SciOPP ligand as well as the slow addition of the Grignard reagents presumably suppresses the undesired ferrate formation and the side reactions, such as the C_{sp^2}–OTf cleavage.



Scheme 3. A possible catalytic cycle for the iron-catalyzed Sonogashira-type coupling.

In summary, we have demonstrated that a Sonogashira-type coupling of primary and secondary alkyl halides with alkynyl Grignard reagents can be achieved in a highly chemoselective manner by using an iron catalyst. The key to this success is the use of a bisphosphine ligand bearing peripheral steric bulk, which dramatically switches chemoselectivity from the C_{sp^2}-selective coupling to C_{sp^3}-selective coupling. The present reaction can be applicable to secondary alkyl halides, including less-reactive alkyl chlorides, which are difficult substrates in previous methods. These synthetic advantages, as well as the nonhazardous nature of the catalyst and reagents make the present reaction suitable for the practical synthesis of various functional molecules bearing alkyne moieties.

Experimental Section

(Triisopropylsilyl)ethynylmagnesium bromide (0.80 mL, 0.78 M in THF, 0.62 mmol) was added dropwise using a syringe pump over 2 h at 70 °C to a THF solution (1.6 mL) of bromocycloheptane (73.5 mg, 0.42 mmol) and iron complex **B** (12.7 mg, 12 μmol, 3.0 mol%). After addition of the Grignard reagent, the reaction mixture was quenched by the addition of a saturated aqueous solution of NH_4Cl at room temperature. The aqueous layer was extracted five times with Et_2O. The combined organic extracts were filtered through a pad of Florisil and then concentrated in vacuo. The crude product was purified by a reversed-phase column chromatography (C18-bonded silica gel; eluents 20% H_2O in MeOH and MeOH) to give (cycloheptylethynyl)triisopropylsilane in 88% yield (0.102 g, 98% pure by GC analysis).

Received: June 15, 2011

Keywords: alkynes · cross-coupling · homogeneous catalysis · iron

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