# Iron-Catalyzed Grignard Cross-Coupling Reaction with Alkyl Halides Possessing $\beta$-Hydrogens 

Takashi Nagano and Tamio Hayashi*<br>Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo, Kyoto 6068502, Japan.

## Supporting Data

General. All anaerobic and/or moisture sensitive manipulations were carried out with standard Schlenk techniques under predried nitrogen or with glovebox techniques under prepurified argon. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone-ketyl under nitrogen prior to use. NMP, 1-bromooctane (2n), 1-chlorooctane, 1-iodooctane, 1-bromo-4-phenoxybutane (20), and bromocyclohexane ( $\mathbf{2 q}$ ) were obtained from commercial suppliers and used without further purification. Tris(acetylacetonato)iron(III) ${ }^{1}, n$-octyl tosylate ${ }^{2}$, 2-bromooctane ( $\left.\mathbf{2 p}\right)^{3}$, and 1-bromo-5-phenylpentane ( $\left.\mathbf{2 m}\right)^{4}$ were prepared according to the literature methods. NMR spectra were recorded on a JEOL JNM LA500 spectrometer $\left({ }^{1} \mathrm{H}, 500 \mathrm{MHz}\right.$; $\left.{ }^{13} \mathrm{C}, 125 \mathrm{MHz}\right) .{ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C}$ chemical shifts are reported in ppm downfield of internal tetramethylsilane.

Synthesis of 1-bromo-3-(4-trifluoromethanesulfonyloxyphenyl)propane (7). To a mixture of 4-(3-bromopropyl)phenol ${ }^{5}(1.53 \mathrm{~g}, 7.1 \mathrm{mmol})$ and
 pyridine ( $0.97 \mathrm{~mL}, 12 \mathrm{mmol}$ ) in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(15 \mathrm{~mL})$ was added dropwise $\mathrm{Tf}_{2} \mathrm{O}(1.55 \mathrm{~mL}, 9.2 \mathrm{mmol})$ at $0{ }^{\circ} \mathrm{C}$, and the mixture was stirred at room temperature for 1 h . The resulting mixture was concentrated under reduced pressure and the residue was dissolved in benzene. The benzene solution was washed with 1 N HCl , saturated $\mathrm{NaHCO}_{3}$ and brine, and dried over anhydrous magnesium sulfate. The solvent was removed and the residue was chromatographed on silica gel (pentane/diethyl ether $=4: 1$ ) to give $7(2.47 \mathrm{~g}, 7.1$ mmol). Yield: $100 \%$. ${ }^{1} \mathrm{H}$ NMR $\left(\mathrm{CDCl}_{3}\right)$ : $\delta 2.14-2.19(\mathrm{~m}, 2 \mathrm{H}), 2.82(\mathrm{t}, J=7.5 \mathrm{~Hz}, 2 \mathrm{H}), 3.39$ $(\mathrm{t}, J=6.4 \mathrm{~Hz}, 2 \mathrm{H}), 7.20(\mathrm{~d}, J=8.7 \mathrm{~Hz}, 2 \mathrm{H}), 7.28(\mathrm{~d}, J=8.7 \mathrm{~Hz}, 2 \mathrm{H}) .{ }^{13} \mathrm{C}\left\{{ }^{1} \mathrm{H}\right\}$ NMR $\left(\mathrm{CDCl}_{3}\right)$ : $\delta 32.56,33.25,33.76,118.74\left(\mathrm{q}, J_{\mathrm{C}-\mathrm{F}}=320.0 \mathrm{~Hz}\right.$ ), 121.34, 130.26, 141.16, 148.01. Anal. Calcd for $\mathrm{C}_{10} \mathrm{H}_{10} \mathrm{O}_{3} \mathrm{~F}_{3} \mathrm{SBr}$ : C, 34.60; H, 2.90. Found: C, 34.80; H, 2.92.

Iron-Catalyzed Cross-Coupling Reaction. A mixture of 1-bromooctane ( 100 mg , $0.52 \mathrm{mmol})$ and $\mathrm{Fe}(\mathrm{acac})_{3}(9.0 \mathrm{mg}, 0.026 \mathrm{mmol})$ in $\mathrm{Et}_{2} \mathrm{O}(3 \mathrm{~mL})$ was warmed to reflux. To this was added p-tolylmagnesium bromide ( $1.67 \mathrm{M} \mathrm{in}^{2} \mathrm{Et}_{2} \mathrm{O}, 0.70 \mathrm{~mL}, 1.04 \mathrm{mmol}$ ), resulting in an immediate color change from red to black. The mixture was refluxed for 30 minutes and then poured into aqueous HCl solution ( 1 N ). It was extracted with $\mathrm{Et}_{2} \mathrm{O}$, and the extracts were dried over anhydrous magnesium sulfate. The solvent was removed and the residue was chromatographed on silica gel to give 1-(p-tolyl)octane (3an) ( $74.0 \mathrm{mg}, 0.36 \mathrm{mmol}$ ). Yield: $70 \%$. Registry No. of the known compounds are as follows: 3an, 7686-25-1; 3bn, 3307-19-5; 3cn, 28593-20-6; 3dn, 79835-99-7; 3am, 38425-25-1; 3ap, 90734-22-8; 3aq, 4501-36-4; 3en, 177969-49-2; 4, 1075-74-7; 5, 538-68-1; 6, 613-33-2. The characterization data of the new compounds are described below.

4-(4-phenoxybutyl)toluene (3ao). ${ }^{1} \mathrm{H}$ NMR $\left(\mathrm{CDCl}_{3}\right): \delta 1.74-1.84(\mathrm{~m}, 4 \mathrm{H}), 2.31$ (s,
 $3 \mathrm{H}), 2.64(\mathrm{t}, J=7.3 \mathrm{~Hz}, 2 \mathrm{H}), 3.95(\mathrm{t}, J=6.0 \mathrm{~Hz}, 2 \mathrm{H}), 6.87$ (d, $J=8.3 \mathrm{~Hz}, 2 \mathrm{H}$ ), $6.90-6.93(\mathrm{~m}, 1 \mathrm{H}), 7.08$ (singlet-like $\mathrm{m}, 4 \mathrm{H}), 7.24-7.28(\mathrm{~m}, 2 \mathrm{H}) .{ }^{13} \mathrm{C}\left\{{ }^{1} \mathrm{H}\right\}$ NMR $\left(\mathrm{CDCl}_{3}\right): \delta$ 20.96, 27.94, 28.87, 35.12, 67.64, 114.49, 120.48, 128.28, 128.98, 129.38, 135.16, 139.12, 159.07. Anal. Calcd for $\mathrm{C}_{17} \mathrm{H}_{20} \mathrm{O}: \mathrm{C}, 84.96 ; \mathrm{H}, 8.39$. Found: C, 85.13; H, 8.39.

1-(4-tolyl)-3-(4-trifluoromethanesulfonyloxyphenyl)propane (8). ${ }^{1} \mathrm{H}$ NMR $\left(\mathrm{CDCl}_{3}\right)$ : $\delta 1.90-1.96(\mathrm{~m}, 2 \mathrm{H}), 2.32(\mathrm{~s}, 3 \mathrm{H}), 2.60(\mathrm{t}, J=7.6 \mathrm{~Hz}$,
 $2 \mathrm{H}), 2.65(\mathrm{t}, J=7.8 \mathrm{~Hz}, 2 \mathrm{H}), 7.06(\mathrm{~d}, J=8.1 \mathrm{~Hz}, 2 \mathrm{H})$, $7.09(\mathrm{~d}, J=8.1 \mathrm{~Hz}, 2 \mathrm{H}), 7.16(\mathrm{~d}, J=8.6 \mathrm{~Hz}, 2 \mathrm{H}), 7.23(\mathrm{~d}$, $J=8.6 \mathrm{~Hz}, 2 \mathrm{H}) .{ }^{13} \mathrm{C}\left\{{ }^{1} \mathrm{H}\right\} \mathrm{NMR}\left(\mathrm{CDCl}_{3}\right): \delta 20.96,32.77$, $34.67,34.83,118.76\left(\mathrm{q}, J_{\mathrm{C}-\mathrm{F}}=320.6 \mathrm{~Hz}\right), 121.05,128.26$, 129.06, 130.06, 135.36, 138.64, 142.94, 147.73. Anal. Calcd for $\mathrm{C}_{17} \mathrm{H}_{17} \mathrm{O}_{3} \mathrm{~F}_{3} \mathrm{~S}: \mathrm{C}, 56.97$; H, 4.78. Found: C, 57.24; H, 4.82.

1-(4-tolyl)-3-(4-n-butylphenyl)propane (9). ${ }^{1} \mathrm{H}$ NMR $\left(\mathrm{CDCl}_{3}\right): \delta 0.92(\mathrm{t}, J=7.3 \mathrm{~Hz}$, $3 \mathrm{H}), 1.31-1.38(\mathrm{~m}, 2 \mathrm{H}), 1.55-1.61(\mathrm{~m}, 2 \mathrm{H}), 1.89-1.95$
 $(\mathrm{m}, 2 \mathrm{H}), 2.31(\mathrm{~s}, 3 \mathrm{H}), 2.55-2.62(\mathrm{~m}, 6 \mathrm{H}), 7.07-7.08$ $(\mathrm{m}, 8 \mathrm{H}) .{ }^{13} \mathrm{C}\left\{{ }^{1} \mathrm{H}\right\}$ NMR $\left(\mathrm{CDCl}_{3}\right): \delta 13.95,20.98$, $22.39,33.06,33.72,35.01,35.24,128.26,128.29$, 128.30, 128.95, 135.07, 139.28, 139.46, 140.18. Anal. Calcd for $\mathrm{C}_{20} \mathrm{H}_{26}$ : C, 90.16; H, 9.84. Found: C, 90.41; H, 9.88.

Determination of the amount of initially formed 4,4'-bitolyl in the reduction of $\mathrm{Fe}(\mathbf{a c a c})_{3}$. To a solution of $\mathrm{Fe}(\mathrm{acac})_{3}(90.0 \mathrm{mg}, 0.255 \mathrm{mmol})$ in $\mathrm{Et}_{2} \mathrm{O}(30 \mathrm{~mL})$ was added $p$ tolylmagnesium bromide ( $1.67 \mathrm{M} \mathrm{in}^{\mathrm{Et}} \mathrm{O}, 6.0 \mathrm{~mL}, 3.59 \mathrm{mmol}$ ) at $0{ }^{\circ} \mathrm{C}$. The mixture was stirred for 30 minutes and then poured into aqueous HCl solution ( $1 \mathrm{~N}, 30 \mathrm{~mL}$ ). It was extracted with $\mathrm{Et}_{2} \mathrm{O}$ and the extracts were dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel to give $4,4^{\prime}$-bitolyl ( $109.1 \mathrm{mg}, 0.599 \mathrm{mmol}$ ). On the other hand, it was determined that 6.0 mL of this Grignard reagent contained 64.2 mg of $4,4^{\prime}$-bitolyl by independent experiment (hydrolysis of the Grignard reagent). Thus the amount of initially formed 4,4-bitolyl in the reduction step is $44.9 \mathrm{mg}(109.1-64.2=44.9 \mathrm{mg}, 0.246 \mathrm{mmol})$. The molar ratio of $\mathrm{Fe}(\mathrm{acac})_{3} / 4,4^{\prime}$-bitolyl is 1.04 , which strongly suggests that catalytic active species is $\mathrm{Fe}(\mathrm{I})$ according to the following equation.

$$
2 \mathrm{ArMgBr}+\mathrm{Fe}^{\mathrm{III}} \mathrm{X}_{3} \longrightarrow \mathrm{Ar}-\mathrm{Ar}+2 \mathrm{MgBrX}+\mathrm{Fe}^{\mathrm{I}} \mathrm{X}
$$

Distribution of products in the reaction of 1a with $\mathbf{2 m}$ (Table 1). The reactions were carried out according to the general procedure (vide supra). The crude material was divided into two fractions by column chromatography using silica gel and pentane. The first fraction was composed of alkene 4 and alkane 5. The second fraction was composed of the crosscoupling product 3am and 4,4'-bitolyl (6). The amount of each component in each fraction was calculated by integral ratio in its ${ }^{1} \mathrm{H}$ NMR spectrum.

## References

(1) Charles, R. G.; Pawlikowski, M. A. J. Phys. Chem. 1958, 62, 440.
(2) Chatti, S; Bortolussi, M; Loupy, A. Tetrahedron 2001, 57, 4365.
(3) Alnajja, M. S.; Kuivila, H. G. J. Am. Chem. Soc. 1985, 107, 416.
(4) Van der Mey, M.; Hatzelmann, A.; Van Klink, G. P. M.; Van der Laan, I. J.; Sterk, G. J.; Thibaut, U.; Ulrich, W. R.; Timmerman, H. J. Med. Chem. 2001, 44, 2523.
(5) Bell, V. L.; Gidding, P. J.; Holmes, A. B.; Mock, G. A.; Raphael, R. A. J. Chem. Soc., Perkin Trans. 1 1986, 1515.

