11.963(2), $c = 22.865(4)$ Å, $V = 1945.7(3)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.271$ g cm^{-3}; $\mu = 8.942$ cm^{-1}; no absorption correction applied; Mo$_{K\alpha}$ radiation; $T = 293$ K; F scan (Stoe IPDS diffractometer); F range 0–250°; of 7483 reflections collected, 2983 were independent ($Rm = 0.074$) and 2037 were regarded as observed ($I > 2\sigma(I)$); 210 parameters refined; R/R_w 0.0424/0.0460, GOF = 1.104, $\Delta/\sigma = 0.041$; $[\Delta\rho]_{min}/[\Delta\rho]_{max}$ −0.37/0.56; Flack's parameter = 0.00(3). The structures of **5** and **8** were solved with the programs SIR92 and CRYSTALS. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-100607. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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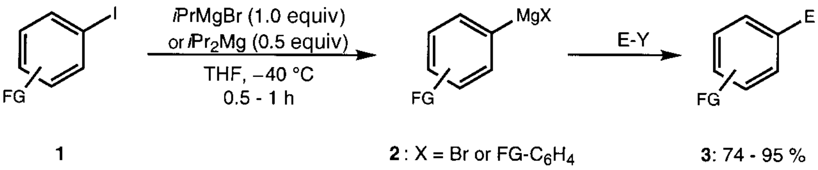
Preparation of Highly Functionalized Grignard Reagents by an Iodine – Magnesium Exchange Reaction and its Application in Solid-Phase Synthesis

Laure Boymond, Mario Rottländer, Gérard Cahiez,* and Paul Knochel*

In memoriam Henri Normant

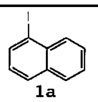
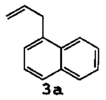
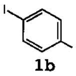
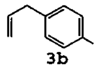
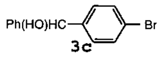
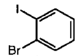
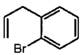
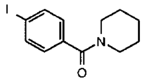
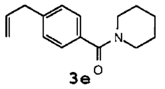
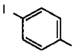
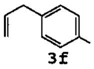
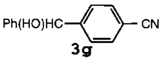
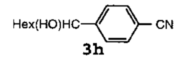
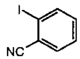
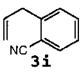
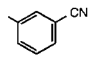
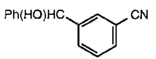
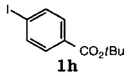
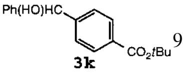
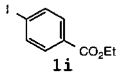
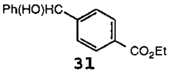
Organomagnesium reagents are extremely important in synthetic organic chemistry. Since their discovery, there has great interest in these versatile reagents, and numerous industrial applications have been reported.[1] Grignard reagents can be conveniently synthesized from organic halides and exhibit high reactivity and satisfactory chemoselectivity, which can be further improved by transmetalation.[2] However, very few functionalized organomagnesium reagents have been prepared due to the low functional-group tolerance of these reagents.[1] Here we report a general route to highly functionalized arylmagnesium halides of type **2**, which contain functional groups such as ester, amide, or cyano groups, or a halogenide substituent and were synthesized from functionalized aryl iodides of type **1** by an iodine – magnesium exchange reaction.[3] The reaction of **2** with electrophiles E – Y (aldehyde or allyl bromide) gave the expected aromatic products of type **3** in good to excellent yield (Scheme 1 and Table 1).



Scheme 1. Functional group (FG) = Br, CONR$_2$, CN, CO$_2$Et, CO$_2t$Bu; E – Y = aldehyde, allyl bromide.

Preliminary experiments showed that treatment of 1-iodonaphthalene (**1a**) with *i*PrMgBr or *i*Pr$_2$Mg in THF at 25 °C for 1 h or 0.5 h, respectively, gave the corresponding Grignard reagent **2a** in 90 % yield (GC analysis of aliquots of

Table 1. Synthesis of compounds **3** by iodine – magnesium exchange of aryl iodides **1 a – i** with *i*Pr$_2$Mg followed by reaction with an electrophile E – Y.

Entry	Aryl iodide **1**	T [°C]/t [h][a]	E – Y	Product **3**	Yield [%][b]
1	 **1a**	25/0.5	CH_2CHCH_2Br	 **3a**	80 (87)[c]
2	 **1b**	− 40/0.5	CH_2CHCH_2Br	 **3b**	79[d]
3		− 25/0.5	PhCHO	 **3c**	93
4	 **1c**	− 25/0.5	CH_2CHCH_2Br	 **3d**	95
5	 **1d**	− 25/0.5	CH_2CHCH_2Br	 **3e**	81
6	 **1e**	− 40/1	CH_2CHCH_2Br	 **3f**	75[d]
7		− 40/1	PhCHO	 **3g**	94
8		− 40/1	n-C_6H_{13}-CHO	 **3h**	74
9	 **1f**	− 40/0.5	CH_2CHCH_2Br	 **3i**	89
10	 **1g**	− 40/0.5	PhCHO	 **3j**	89
11	 **1h**	− 40/1	PhCHO	 **3k**	94 (91)[e]
12	 **1i**	− 40/1	PhCHO	 **3l**	90 (90)[e]

[a] Reaction conditions for iodine – magnesium exchange. [b] Yield of analytically pure product. [c] Yield obtained by performing iodine – magnesium exchange with ($cyclo$-C_5H_9)$_2$Mg. [d] The allylation was performed in the presence of CuCN · 2 LiCl (10 mol %). [e] *i*PrMgBr (1.05 equiv) was used in this case.

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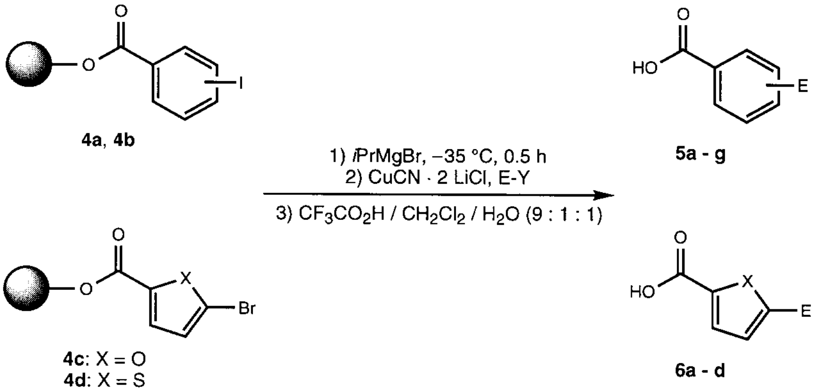
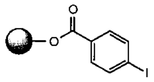
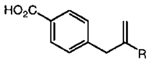
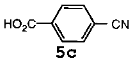
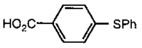
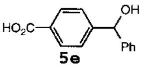
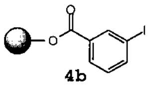
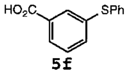
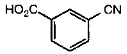
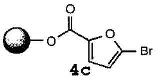
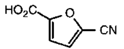
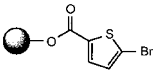
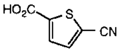
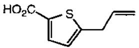
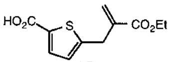
the reaction mixture after quenching with water). The stability of the Grignard reagent is lowered by the presence of the isopropyl iodide formed in the iodine–magnesium exchange reaction. Elimination of hydroiodic acid presumably occurs. This can be avoided by using dicyclopentylmagnesium, since the resulting cyclopentyl iodide less readily eliminates HI. Alternatively, the arylmagnesium reagents can be stabilized by using one equivalent of *i*Pr_2Mg instead of 0.5 equivalents; the excess is presumably used for the elimination reaction. Treatment of the Grignard reagent derived from 1-iodonaphthalene (**1a**) and *i*Pr_2Mg (0.53 equiv, THF, 25 °C, 0.5 h) with allyl bromide gave 1-allylnaphthalene (**3a**) in 80 % yield. When (*cyclo*-$C_5H_9)_2Mg$ was used for the exchange reaction (0.53 equiv, 25 °C, 3 h), **3a** was obtained in 87 % yield. Iodine–magnesium exchange can also be performed at −20 °C: the aryl iodide **1a** is converted into the magnesium compound **2a** in 4–5 h. Since Grignard reagents are unreactive towards many functional groups at low temperature, iodine–magnesium exchange opens the way for the preparation of functionalized Grignard reagents. Treatment of 4-bromoiodobenzene (**1b**) with *i*Pr_2Mg (THF, −40 °C, 0.5 h) afforded the corresponding Grignard reagent **2b** (>98 % conversion), which was quenched with allyl bromide (1.1 equiv) in the presence of CuCN · 2 LiCl[4] (10 mol %) to give **3b** in 79 % yield. No bromine–magnesium exchange product could be detected. Treatment of **2b** with benzaldehyde gave the corresponding alcohol **3c** in 93 % yield (Table 1, entry 3). The conversion of 2-bromoiodobenzene (**1c**) to the corresponding Grignard compound **2c** proceeds smoothly, and treatment with allyl bromide leads to the allylated product **3d** in 95 % yield (entry 4). As expected, an amide function as in **1d** does not affect the iodine–magnesium exchange reaction (entry 5). When the exchange reaction is carried out at −40 °C, nitrile groups in the *ortho*, *meta*, and *para* positions are tolerated (entries 6–10). Even ester groups are compatible with a carbon–magnesium bond in the same molecule; quenching with benzaldehyde gave the corresponding benzylic alcohols **3k**–**l** in 90–94 % yield (entries 11 and 12).

After these initial successes, we envisioned that this exchange reaction could be used to generate an aryl Grignard reagent on a polymer support and therefore have applications in combinatorial chemistry.[5] Various substituted aryl or heteroaryl iodides or bromides attached to Wang resin[6] through an ester function (**4a**–**d**) were treated with *i*PrMgBr (ca. 7 equiv) at −35 °C for 15-30 min. The desired Grignard reagents were formed with >95 % conversion, as indicated by quenching experiments with electrophiles such as allylic bromides, tosyl cyanide,[7] diphenyl disulfide, or an aldehyde (Scheme 2 and Table 2). After cleavage from the resin with trifluoroacetic acid, the expected products of type **5** or **6** were obtained in good to excellent purity. Remarkably, heteroaryl bromides such as **4c** and **4d** undergo a smooth bromine–magnesium exchange reaction under the same reaction conditions (−35 °C, 0.5 h, entries 8–11 of Table 2).



Scheme 2. For **4a**, **4b**, **5a**–**g**, **6a**–**d**, and E–Y, see Table 2.

Table 2. Synthesis of the compounds **5** and **6** obtained by solid-phase synthesis via an intermediate functionalized resin-bound Grignard reagent.

Entry	Resin-bound ester **4**	E–Y	Product **5** or **6**	Purity [%][a]
1	 **4a**	CH_2CHCH_2Br		98
2	**4a**	$CH_2C(CO_2Et)CH_2Br$	**5a**: R=H **5b**: R=CO_2Et	99
3	**4a**	TosCN	 **5c**	95
4	**4a**	PhSSPh	 **5d**	87
5	**4a**	PhCHO	 **5e**	95[b,c]
6	 **4b**	PhSSPh	 **5f**	87
7	**4b**	TosCN	 **5g**	92[b,d]
8	 **4c**	TosCN	 **6a**	94[b]
9	 **4d**	TosCN	 **6b**	91[b]
10	**4d**	CH_2CHCH_2Br	 **6c**	99
11	**4d**	$CH_2C(CO_2Et)CH_2Br$	 **6d**	94

[a] Purity determined by HPLC analysis (RP-18, $MeCN/H_2O$, 0.1 % CF_3CO_2H, UV detection at 254 nm). The yield in each case was >90 % as determined by weighing. [b] No CuCN · 2LiCl was used in this case. [c] After treatment of the cleaved product with aqueous solutions of NaOH and HCl and filtration of the product. [d] UV detection at 215 nm.

We have shown that the iodine–magnesium or bromine–magnesium exchange with *i*Pr_2Mg or *i*PrMgBr proceeds under mild conditions, tolerates various functional groups, and is therefore a widely applicable method for preparing highly functionalized magnesium compounds. The scope and limitations of this method are currently under investigation.[8]

Experimental Section

Typical procedure for an iodine–magnesium exchange reaction: Preparation of **31**: A solution of ethyl 4-iodobenzoate (552 mg, 2 mmol) in THF (20 mL) was cooled to $-40\,^{\circ}C$, and iPr_2Mg (2.3 mL, 1.06 mmol) in *tert*-butyl methyl ether was added. After 1 h at $-40\,^{\circ}C$, benzaldehyde (233 mg, 2.2 mmol) was added. After stirring for 3 h, the reaction mixture was worked up as usual to give a crude yellow oil, which was purified by flash chromatography (pentane/ether, 80/20) to give 460 mg of pure **31** (90% yield).

Typical procedure for an iodine–magnesium exchange reaction on the solid phase: Preparation of **5a**: Wang resin (100 mg) charged with 4-iodobenzoic acid (70 μmol) was dried for 2 h under vacuum (0.1 Torr) at 50 °C. After cooling to room temperature under an inert atmosphere, the resin was allowed to swell for 10 min in THF (2 mL). The heterogeneous mixture was cooled to $-35\,^{\circ}C$, and a solution of *i*PrMgBr (0.70 mL, 0.51 mmol, 0.73 M) in THF was added. After stirring for 15 min, a solution of $CuCN \cdot 2\,LiCl$ (0.70 mL, 0.7 mmol, 1.0 M) was added, followed, after a further 15 min, by allyl bromide (0.30 mL, 50 equiv). After stirring for 40 min, the reaction mixture was filtered, and the resin was successively washed with DMF, MeOH, and CH_2Cl_2 (six cycles) and treated with CF_3CO_2H (4 mL of $CF_3CO_2H/CH_2Cl_2/H_2O$, 9/1/1) for 20 min. After filtration and evaporation of the volatile materials under high vacuum, **5a** (10.8 mg, 95% yield) was isolated as a white solid. The HPLC purity was 98% (RP-18, $MeCN/H_2O$, 0.1% CF_3CO_2H; UV detection at 254 nm).

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Keywords: copper · Grignard reactions · iodine–magnesium exchange · magnesium · solid-phase synthesis

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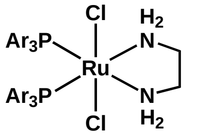
trans-[$RuCl_2$(phosphane)$_2$(1,2-diamine)] and Chiral *trans*-[$RuCl_2$(diphosphane)(1,2-diamine)]: Shelf-Stable Precatalysts for the Rapid, Productive, and Stereoselective Hydrogenation of Ketones[**]

Henri Doucet, Takeshi Ohkuma, Kunihiko Murata, Tohru Yokozawa, Masami Kozawa, Eiji Katayama, Anthony F. England, Takao Ikariya, and Ryoji Noyori*

We recently discovered that a system comprising [$RuCl_2$(phosphane)$_n$], 1,2-diamine, and an inorganic base is an excellent catalyst for the hydrogenation of simple ketones in 2-propanol, at high substrate/catalyst molar ratios (S/C) under mild conditions.[1] In addition to other features, this reaction is characterized by high diastereo-, enantio-, and C=O/C=C selectivity. However, the concentration of the catalytic species generated in situ remains unknown. Because the quantities of the metallic and organic components used are extremely small, it is possible that the intermolecular reactions may be incomplete. Furthermore, the catalytically active metal complexes may not be the only complexes formed. We speculated that the use of a pure, stable phosphane/diamine complex would significantly increase the catalytic efficiency. We describe here procedures for the preparation of Ru^{II} complexes with phosphane and diamine ligands from commercial or other readily available materials. As expected, these complexes proved to be exceedingly efficient hydrogenation precatalysts. The reaction rate and productivity were two orders of magnitude higher than those obtained from the complexes generated in situ.

Achiral Ru type **1** complexes with triarylphosphane, ethylenediamine, and chloro ligands were prepared by the addition of two equivalents of ethylenediamine to [$RuCl_2$(phosphane)$_3$][2] in CH_2Cl_2 at 25 °C. The mixture was stirred for three hours (method A). Type **2** chiral complexes were most



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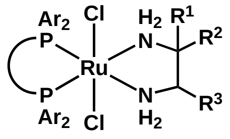

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