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A Grignard-type Phase-vanishing Method: Generation of Organomagnesium Reagent and Its Subsequent Addition to Carbonyl Compounds

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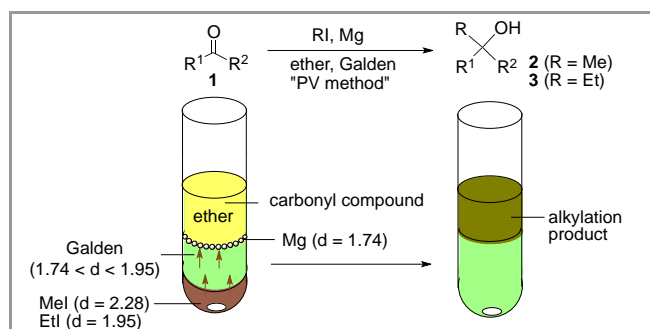
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Abstract: A quadruphase phase-vanishing system comprised of ether, magnesium, perfluoropolyether, and iodoalkane generated Grignard reagents efficiently, which subsequently added to carbonyl compounds in the ether layer to afford alkylated alcohols in good yields.

Key words: fluoruous solvent, phase-vanishing, Grignard reaction, Barbier reaction, magnesium, perfluoropolyether

Perfluorinated compounds are generally immiscible with most organic solvents and are denser than typical organic molecules.¹ By utilizing these characteristics, in conjunction with the Curran group, we developed a triphasic reaction system, termed the “phase-vanishing (PV) method”, where fluoruous media act as liquid membranes to transport reagents to the organic layer, which contains the substrates.² Since the first demonstration of the viability of the PV method,³ which was used for the bromination of alkenes with molecular bromine, various reactions have been carried out using the PV method by us⁴ as well as others.⁵ For example, in a photo-irradiative PV method,^{4e} hydrogen bromide was efficiently generated from a PV system comprised of an alkane, perfluorohexanes, and molecular bromine under irradiation; it was subsequently reacted with 1-alkanes to afford terminal bromides in high yields. Perfluorohexanes (FC-72[®], $d = 1.69$) are usually employed as the fluoruous phase and perfluoropolyethers such as Galden[®] have been used as well.⁶ Typical reagents utilized in PV systems are denser than fluoruous media ($d > 1.7$) and include Br₂, BBr₃, SnCl₄, CH₂I₂, etc. The PV method is suitable for controlling heat evolution in exothermic reactions, and the fluoruous phase regulates the transport of reagents by passive diffusion.

The Grignard reaction is one of the most important reactions in organic synthesis.⁷ Although some Grignard reagents are commercially available, researchers often prepare Grignard reagents from organic halides and magnesium in ethereal solvents. The slow addition of halides to magnesium is usually required to safely prepare Grignard reagents in good yields. Thus, we utilized the PV method to prepare Grignard reagents. The concept behind the “Grignard-type PV reaction” is shown in Scheme 1. Iodomethane ($d = 2.28$) and iodoethane ($d = 1.95$) were used as the reagent phase (bottom layer), since these iodides were denser than the fluoruous media. Diethyl ether was employed as the organic phase (top layer) and carbonyl compounds were added to the top layer. THF did not dissolve the methylmagnesium reagent, and FC-72 was miscible with diethyl ether; therefore, these solvents were not suitable in this system. As such, perfluoropolyethers (Galden[®]) were employed as the fluoruous phase. Tuning of the fluoruous phase was necessary since magnesium ($d = 1.74$) was required to be between the fluoruous and organic phases. The use of Galden HT135 ($d = 1.72$) as the fluoruous phase was attempted. However, this solvent was not heavy enough to float the magnesium on it. Therefore, Galden HT200 ($d = 1.79$) was subsequently employed as the fluoruous phase. This solvent kept the magnesium between the two phases; however, Galden HT200 prevented the diffusion of the iodoalkanes, since the kinetic viscosity of Galden HT200 is 2.4 times larger than that of Galden HT135.⁶ As such, we mixed Galden HT135 and Galden HT200 in a 1/1 (v/v) ratio. The mixed fluoruous solvent ($d = 1.75$) worked well, in that it was able to float magnesium in the appropriate position and it facilitated the transport of iodoalkanes to the magnesium phase via diffusion, as shown in Figure 1.



Scheme 1 Concept of Grignard-type phase-vanishing alkylation of carbonyl compounds

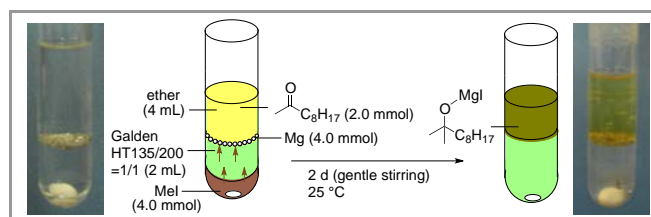


Figure 1 Grignard-type phase-vanishing methylation of 2-decanone.

With the optimized fluorosolvent in hand, we examined the generation of Grignard reagents from iodomethane and the subsequent addition of the Grignard reagent to 2-decanone as a model (Figure 1). In a test tube (13 mm ϕ), iodomethane (4 mmol) was covered with Galden HT135/200 (2 mL), which in turn was covered with an ether solution (4 mL) containing 2-decanone (**1a**, 2 mmol). Magnesium powder (4 mmol) was floated between the fluorosolvent and organic solution to form a quadruphasic system. The bottom layer was gently stirred at 25 °C, with care not to mix the four layers. After 2 d, the bottom layer vanished. The ether layer and magnesium salt were taken and quenched with dilute hydrochloric acid. The organic phase was collected, dried over Na_2SO_4 and concentrated. After column chromatography on silica gel, 2-methyl-2-decanol (**2a**) was obtained in 93% yield.

Table 1 Grignard-Type Phase-Vanishing Reaction with Carbonyl Compounds^a

Entry	RI	Substrate	Product	Isolated yield (%)
1	MeI			93
2	MeI			87
3	EtI			80
4	MeI			79
5	MeI			75
6	MeI			91
7	MeI			30 ^b
8 ^c	MeI			81
9 ^c	EtI			77
10 ^d	MeI			71

^aReaction conditions: substrate (2.0 mmol), Mg (2.0 equiv), RI (2.0 equiv), ether (4 mL), Galden HT135/200 = 1/1 (2 mL), 25 °C, 2 d. ^b1-Dodecanol (47%) was also obtained. ^cMg (4.0 equiv), RI (4.0 equiv). ^dMg (6.0 equiv), RI (6.0 equiv).

Table 1 demonstrates the generality of the Grignard-type PV reaction.⁸ Acyclic (entries 1–5) and cyclic (entry 6) ketones underwent addition of the methylmagnesium reagent to afford the corresponding carbinols in high yields. On the other hand, an aldehyde gave the corresponding carbinol in a low yield, as the reduction of the substrate with magnesium affording the corresponding primary alcohol was the dominant process (entry 7). The reactivity of iodoethane was slightly lower than that of iodomethane (entries 3 and 9). With an excess of the generated Grignard reagents, esters (entries 8–9) and a diester (entry 10) afforded the corresponding alcohols and diol in good yields, respectively.

The reactivity of the Grignard-type PV method was compared to that of the Barbier reaction.⁹ Methylation of carbonyl compounds under Barbier conditions was carried out as follows: a mixture of iodomethane (4 mmol), magnesium (4 mmol), and carbonyl compounds (2 mmol) in ether (10 mL) was stirred for 2 d at 25 °C, followed by the same workup as used in the PV method. As shown in Table 2, the Grignard-type PV method gave the corresponding carbinols in higher or similar yields with ketones (entries 1 and 2) or an ester (entry 4) respectively, while the Barbier conditions suppressed the reduction of the substrate with magnesium better than the PV method, and thereby afforded the addition product in a higher yield when an aldehyde was used (entry 3).

Table 2 Comparison of the Grignard-Type PV Method^a and the Barbier Reaction^b

Entry	Substrate	Product	Isolated yield (%)	
			PV	Barbier
1			93	63
2			91	67
3			30 ^c	62 ^d
4 ^e			77	89

^aReaction conditions: substrate (2.0 mmol), Mg (2.0 equiv), MeI (2.0 equiv), ether (4 mL), Galden HT135/200 = 1/1 (2 mL), 25 °C, 2 d. ^bReaction conditions: (2.0 mmol), Mg (2.0 equiv), MeI (2.0 equiv), ether (10 mL), 25 °C, 2 d. ^c1-Dodecanol (47%) was also obtained. ^d1-Dodecanol (27%) was also obtained. ^eMg (4.0 equiv), MeI (4.0 equiv).

We also examined the generation of alkynylmagnesium reagents¹⁰ using the Grignard-type PV method. 1-Octyne was added to the ether solution in the Grignard-type PV method, in which methylmagnesium iodide was reacted with 1-octyne to afford the 1-octynylmagnesium reagent in situ. After 2 d, carbonyl compounds were added to the ether solution and the mixture was gently stirred for 1 d at 25 °C. As shown in Table 3,^{11,12} ketones gave the corresponding alcohols **4** with an octynyl moiety in good yields (entries 1–3), while aldehydes resulted in complex mixtures and lower yields of the desired products (entries 4 and 5).

Table 3 Alkynylation of Carbonyl Compounds by the Grignard-Type PV Method^a

Entry	Substrate	Product	Isolated yield (%)
1			72
2			83
3			93
4			21
5			12 ^b

^aReaction conditions: 1-octyne (2.0 mmol), Mg (2.5 mmol), MeI (2.7 mmol), ether (4 mL), Galden HT 135/200 = 1/1 (2 mL), 25 °C, 2 d; then substrate (2.0 mmol), 25 °C, 1 d. ^bDetermined by ¹H-NMR.

In summary, by using mixed perfluoropolyethers as the fluoruous phase, we demonstrated the generation of Grignard reagents from iodomethane or iodoethane by floating magnesium between the organic and fluoruous layers. While aldehydes did not suitably undergo alkylation, ketones and esters gave the desired products in high yields. The Grignard-type PV method afforded superior or similar results to the Barbier reaction for the alkylation of ketones or esters, respectively. Generation of alkynylmagnesium reagents using this method was also carried out

successfully. It should be noted that using the PV method, Grignard-type reactions can be carried out in a simple apparatus, namely just a test tube.

Supporting Information for this article is available online at <http://www.thieme-connect.com/products>.

Acknowledgement

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- (6) Galden[®] HT135 and HT 200 are polyether-type perfluorinated solvents, which is commercially available from Solvay Solexis Inc. General structure of the solvents is shown in Figure 2. Kinetic viscosity of Galden HT135 and HT200 at 25 °C are 1.0 and 2.4 cSt, respectively.

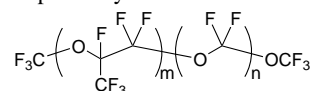


Figure 2

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- (8) **Typical Procedure for Grignard-Type Phase-Vanishing Alkylation of Carbonyl Compounds** (Table 1, entry 1): Galden HT135/200 = 1/1 (2 mL) was placed in a test tube (13 mm ϕ x 105 mm), to which MeI (571 mg, 4.0 mmol) was added slowly using a glass pipette under argon. Dry ether (1 mL) was added slowly; three layers were formed. Mg powder (98 mg, 4.0 mmol) was then added slowly, and floated between the Galden and ether layers; four layers were formed. Subsequently, a dry ether (3 mL) solution of 2-decanone (**1a**, 313 mg, 2.0 mmol) was added to the ether layer. The bottom layer was stirred slowly at 25 °C for 2 d, taking care not to mix the four layers. The ether solution and Mg salt were taken into a flask, to which hydrochloric acid (2 M) was added to quench the reaction, while cooling in an ice bath. The organic layer was separated, and the aqueous layer was extracted with ether. The organic layer collected was then dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography on silica gel with hexane–ether (3:1) to give 2-methyl-2-decanol (**2a**)¹³ as a colorless oil (320 mg, 93%); ¹H NMR (500 MHz, CDCl₃): δ 1.47 – 1.43 (m, 2H, C-CH₂), 1.34 – 1.28 (m, 12H, alkyl), 1.21 (s, 6H, C-CH₃×2), 0.88 (t, J = 7.1 Hz, 3H, CH₂-CH₃); ¹³C NMR (126 MHz, CDCl₃): δ 70.97, 43.95, 31.81, 30.12, 29.53, 29.20, 29.13, 24.28, 22.58, 14.01.
- (9) For example, see: Kürti, L.; Czako, B. *Strategic Applications of Named Reactions in Organic Synthesis*; Elsevier Academic Press: Burlington, **2005**, 38.
- (10) For example, see: Blagoev, B.; Ivanov, D. *Synthesis* **1970**, 615.
- (11) **Typical Procedure for Alkynylation of Carbonyl Compounds by the Grignard-Type Phase-Vanishing Method** (Table 3, entry 2): Galden HT135/200 = 1/1 (2 mL) was placed in a test tube (13 mm ϕ x 105 mm), to which MeI (391 mg, 2.7 mmol) was added slowly using a glass pipette under argon. Dry ether (1 mL) was added slowly; three layers were formed. Mg powder (61 mg, 2.5 mmol) was then added slowly, and floated between the Galden and ether layers; four layers were formed. Subsequently, a dry ether (3 mL) solution of 1-octyne (221 mg, 2.0 mmol) was added to the ether layer. The bottom layer was stirred slowly at 25 °C for 2 d, taking care not to mix the four layers. After confirming that the MeI layer vanished and Mg was consumed, a dry ether (1 mL) solution of dipentyl ketone (**1b**, 341 mg, 2 mmol) was slowly added to the organic layer. The mixture was then stirred at 25 °C for 1 d. The ether solution and Mg salt were taken into a flask, to which hydrochloric acid (2 M) was added to quench the reaction, while cooling in an ice bath. The organic layer was separated, and the aqueous layer was extracted with ether. The organic layer collected was then dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography on silica gel with hexane–ether (9:1) to give 6-(1-octynyl)-undecan-6-ol (**4b**) as a colorless oil (466 mg, 83%); ¹H NMR (500 MHz, CDCl₃): δ 2.19 (t, J = 7.1 Hz, 2H, -CH₂-C≡), 1.82 (s, 1H, OH), 1.61 – 1.57 (m, 6H, -CH₂-C-O×2 + -CH₂-CH₂-C≡), 1.51 – 1.46 (m, 6H, alkyl), 1.38 – 1.26 (m, 12H, alkyl), 0.91 – 0.86 (m, 9H, CH₃×3); ¹³C NMR (126 MHz, CDCl₃): δ 84.62, 83.19, 71.31, 42.24, 32.00, 31.50, 31.24, 28.66, 28.38, 23.93, 22.53, 18.54, 13.94; MS (EI, 70 eV): 280 (0.07), 262 (3), 209 (100), 195 (1), 177 (3), 163 (1), 135 (5%); HRMS (EI, 70 eV) calcd for C₁₉H₃₆O: 280.2766; found: 280.2764; IR (neat): ν 3424, 2932, 2238, 1378, 1342, 1140, 1025 cm⁻¹.
- (12) Spectroscopic data for new compounds, **4a**: ¹H NMR (500 MHz, CDCl₃): δ 2.18 (t, J = 6.9 Hz, 2H, -CH₂-C≡), 1.86 (s, 1H, OH), 1.63 – 1.59 (m, 2H, -CH₂-C-O), 1.50 – 1.40 (m, 5H, -CH₂-CH₂-C≡ + CH₃-C), 1.38 – 1.24 (m, 18H, alkyl), 0.90 – 0.86 (m, 6H, CH₃-CH₂×2); ¹³C NMR (126 MHz, CDCl₃): δ 84.10, 83.75, 68.36, 44.01, 31.88, 31.31, 30.13, 29.75, 29.55, 29.25, 28.68, 28.47, 24.79, 22.66, 22.54, 18.59, 14.10; MS (EI, 70 eV): 266 (0.3), 251 (35), 181 (2), 165 (3), 157 (5), 153 (100), 137 (6%); HRMS (EI, 70 eV) calcd for C₁₈H₃₃O[M-H]⁺: 265.2531; found: 265.2532; IR (neat): ν 3364, 2928, 2240, 1630, 1466, 1370, 1131, 930 cm⁻¹. **4d**: ¹H NMR (500 MHz, CDCl₃): δ 7.63 (d, J = 7.3 Hz, 2H, Ph), 7.35 (t, J = 7.6 Hz, 2H, Ph), 7.27 (t, J = 7.3 Hz, 1H, Ph), 2.30 (t, J = 7.1 Hz, 2H, -CH₂-C≡), 2.17 (s, 1H, OH), 1.98 – 1.85 (m, 2H, -CH₂-C-O), 1.54 – 1.42 (m, 4H, alkyl), 1.34 – 1.27 (m, 4H, alkyl), 0.95 – 0.89 (m, 6H, CH₃×2); ¹³C NMR (126 MHz, CDCl₃): δ 145.08, 127.95, 127.39, 125.56, 86.86, 82.38, 73.96, 38.49, 31.28, 28.66, 28.54, 22.53, 18.73, 14.01, 9.13; MS (EI, 70 eV): 244 (0.5), 227 (29), 215 (100), 185 (2), 167 (3), 157 (6), 144 (13%); HRMS calcd for C₁₇H₂₄O: 244.1827; found: 244.1820; IR (neat): ν 3424, 3060, 3028, 2932, 2243, 1666, 1600, 1448, 1329, 1213, 1051, 973, 758, 700 cm⁻¹. **4f**: ¹H NMR (500 MHz, CDCl₃): δ 4.34 (t, J = 5.6 Hz, 1H, CH-O), 2.19 (m, 2H, -CH₂-C≡), 1.67 – 1.64 (m, 2H, -CH₂-CH-O), 1.50 – 1.25 (m, 26H, alkyl), 0.90 – 0.86 (m, 6H, CH₃×2); ¹³C NMR (126 MHz, CDCl₃): δ 85.52, 81.33, 62.79, 38.22, 31.91, 31.32, 29.63, 29.56, 29.34, 28.63, 28.50, 25.20, 22.68, 22.54, 18.67, 14.10, 14.03; MS (EI, 70 eV): 294 (2), 237 (9), 209 (47), 181 (5), 167 (7), 153 (25), 139 (100%); HRMS (EI, 70 eV) calcd for C₂₀H₃₈O: 294.2923; found: 294.2917; IR (neat): ν 3357, 2925, 2234, 1701, 1465, 1033 cm⁻¹.
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