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Added-Metal-Free Catalytic Nucleophilic Addition of Grignard Reagents to Ketones

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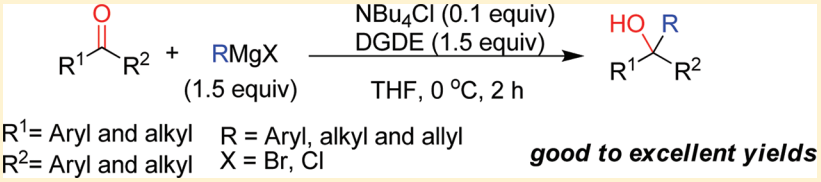
Supporting Information



ABSTRACT: On the basis of the investigation of the combinational effect of quaternary ammonium salts and organic bases, an added-metal-free catalytic system for nucleophilic addition reactions of a variety of Grignard reagents to diverse ketones in THF solvent has been developed to produce tertiary alcohols in good to excellent yields. By using tetrabutylammonium chloride (NBu_4Cl) as a catalyst and diglyme (DGDE) as an additive, this system strongly enhances the efficiency of addition at the expense of enolization and reduction. NBu_4Cl should help to shift the Schlenk equilibrium of Grignard reagents to the side of dimeric Grignard reagents to favor the additions of Grignard reagents to ketones via a favored six-membered transition state to form the desired tertiary alcohols, and DGDE should increase the nucleophilic reactivities of Grignard reagents by coordination. This catalytic system has been applied in the efficient synthesis of Citalopram, an effective U.S. FDA-approved antidepressant, and a recyclable version of this catalytic synthesis has also been devised.

INTRODUCTION

Nucleophilic addition reactions between Grignard reagents and ketones are among the most versatile methods for synthesizing tertiary alcohols.[1,2] However, because of competing β-hydride reduction and enolization of ketones, a large amount of byproducts are often produced along with the low yields of desired alcohols. Many methods have been developed to suppress these side reactions, including changing solvents,[3] adding stoichiometric or excess amounts of organic bases,[4] tetrabutyl ammonium bromide,[5] and inorganic salts[6−8] as additives.

Among these methods, several added-metal activated systems (Ln, Li, and Zn) have achieved high efficiencies for promoting the nucleophilic addition reactions of Grignard reagents to ketones in THF. The first highly useful system for this purpose, utilizing stoichiometric anhydrous $CeCl_3$, was developed by Imamoto and his co-workers.[7] Knochel also reported that homogeneous stoichiometric and catalytic amounts (30 mol %) of $LnCl_3{\cdot}2LiCl$ serve as superior promoters of the addition reactions of various Grignard reagents to ketones.[8] In addition, Ishihara and his co-workers[9] developed efficient homogeneous and heterogeneous stoichiometric $[R_3Mg]^-[Li]^+[LiX]$ or $[RMe_2Mg]^-[Li]^+[LiX]$ ate complexes, which undergo efficient additions to ketones.[9a] This group also described highly efficient methods for alkylation reactions of ketones using either RMgCl in the presence of catalytic amount of anhydrous $ZnCl_2$ or stoichiometric $[R_3Zn]^-[MgCl]^+[MgCl]_2$ ate complex.[9b,c] Unfortunately, these procedures are only applicable to RMgCl with an alkyl group, not RMgCl with an aryl group, RMgBr, and RMgI. As an improvement, a system employing $ZnCl_2$ (10 mol %)−Me_3SiCH_2MgCl (20 mol %)−LiCl (110 mol %) was developed, which can be used with diverse Grignard reagents (RMgX: R = alkyl, aryl; X = Cl, Br, I).[9d,e] However, the highly efficient techniques developed thus far all require the use of added metal ions to activate the carbonyl group of ketone. Although changing solvents and adding stoichiometric or excess amounts of organic additives have been reported to suppress the side reactions of Grignard addition reaction of ketone more or less, a general and efficient added-metal-free catalytic system for nucleophilic addition reactions of Grignard reagents to ketones has not been described to date.

According to the detailed studies on the mechanism of the Grignard reaction of ketone so far by Maruyama and others (Figure 1),[1,6a,10,11] the transition sate of Grignard reaction of ketone may involve a 1:1 complex comprised of a monomeric Grignard reagent and one molecule of ketone or a 2:1 complex comprised of two monomeric Grignard reagents or a dimeric Grignard reagent and one molecule of ketone. The 1:1 complex would prefer the competitive reduction and enolization via six-membered transitions states (Figure 1A,B) to the addition via a four-membered transition state (Figure 1C). In contrast, the 2:1 complex favors the addition, and this process occurs via a six-membered transition state as shown in Figure 1D,E.

It is well-known that the Schlenk equilibrium of Grignard reagents changes the structures of Grignard reagents in solution.[11−13] Therefore, an effect that facilitates the shifting of Schlenk equilibrium of Grignard reagents in solution to form dimeric Grignard reagents would favor the addition reaction.

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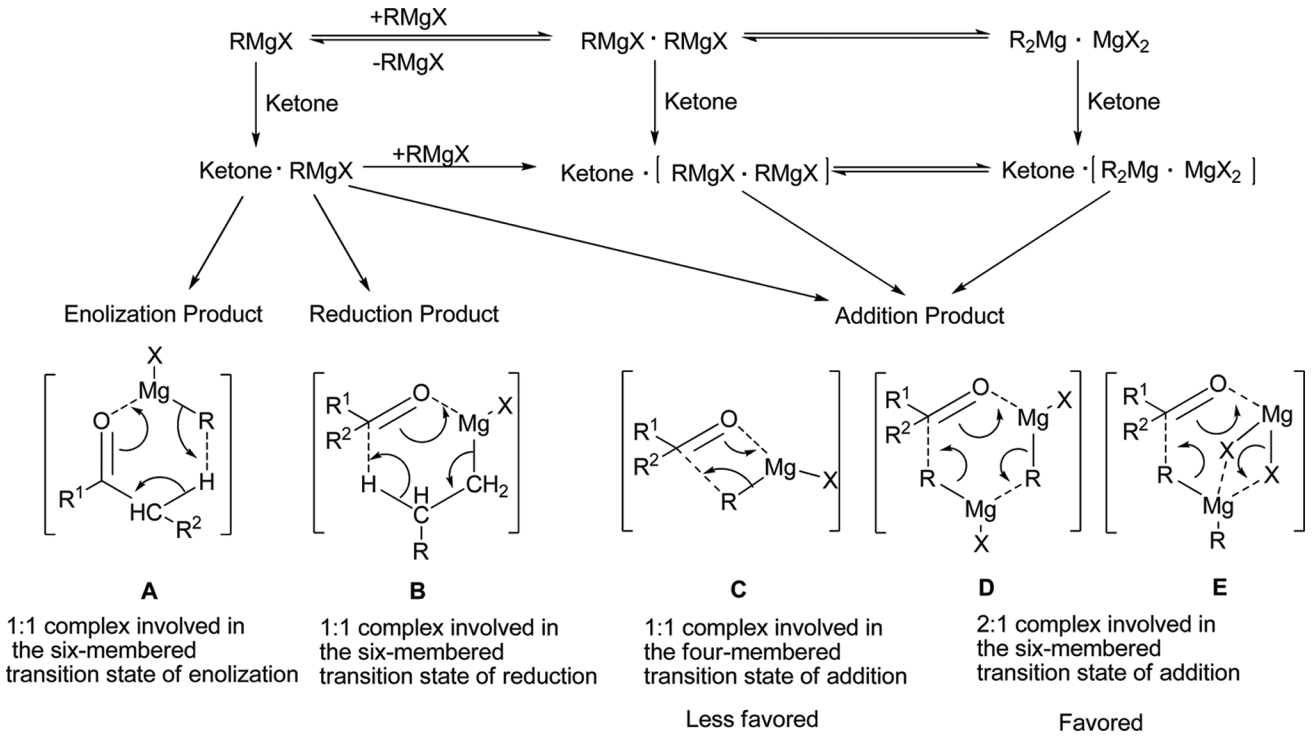

Figure 1. Simplified mechanism of the Grignard reaction of ketone.

In 1970, Chastrette reported that a stoichiometric amount of tetrabutylammonium bromide (NBu_4Br) could promote the addition reaction of di-isopropyl ketone with *n*-PrMgBr by forming a Grignard reagent−salt complex.[5] On the basis of the above mechanism, we envisaged that the formed Grignard reagent−salt complex should facilitate the bromide anion of NBu_4Br to bridge two molecules of Grignard reagent to form a dimeric Grignard reagent−salt complex so that the addition reaction is favored.

Because of the fact that the addition/byproduct ratio of a Grignard addition reaction can also be altered by adding different organic bases due to the varied solvation effects,[4] we consumed that a combinational effect of solvation and quaternary ammonium salt would lead to the highly favored formation of addition product, so that a highly useful system without the participation of added-metal-ion could be developed for the addition reactions of Grignard reagents to ketones. Herein, we describe the development of an efficient added-metal-free catalytic system for nucleophilic addition reactions of a variety of Grignard reagents to diverse ketones in THF solvent.

RESULTS AND DISCUSSION

To check our assumption, we explored the effect of different organic bases on the addition reaction between *n*-BuMgBr with acetophenone in THF at 0 °C (2 h) (Table 1, entries 1−8). In the absence of an added organic base, the reaction proceeded to give the desired addition product **2a** in 49% yield only. The THF solution of *n*-BuMgBr was clean in the presence of DME or DGDE at room temperature, and the reaction gave enhanced yields of **2a** (70 and 75%, respectively) due to the increased nucleophilicity of *n*-BuMgBr caused by coordination with DME or DGDE.[4] On the other hand, a lot of precipitation was immediately formed in this solution by adding TMEDA, BDMAEE, or PMDTA at the same temperature. Poor yields of **2a** were obtained accompanied by more byproducts formed. TMEDA, BDMAEE, or PMDTA should drive the Schlenk equilibrium to the side of R_2Mg by forcing $MgBr_2$ to be precipitated out from THF solution, and the formation of R_2Mg tends to give more byproducts.[12]

Next, we examined the effect of NBu_4Br on this reaction (Table 1, entries 9−12). With the use of 1.0 equiv of NBu_4Br only, the reaction could also be improved to give 81% yield of **2a**. In contrast, the addition reaction of *n*-BuMgBr with acetophenone in the presence of 1.0 equiv of NBu_4Br and 1.5 equiv of DGDE was found to generate **2a** in 91% yield. Moreover, changing the amount of NBu_4Br from 1.0 to 0.1 equiv had no obvious difference on the efficiency of formation of tertiary alcohol **2a**. These results indicate that the use of a catalytic amount of NBu_4Br along with DGDE is sufficient to promote clean reaction of *n*-BuMgBr with acetophenone.

The effect of 10 mol % of different quaternary ammonium salts along with DGDE as the additive (Table 2) on the addition of *i*-PrMgBr to acetophenone was investigated next. The data show that NBu_4Cl/DGDE (entry 3) is the best combination to use for this process, which gave an improved 82% yield of **2b** in contrast to a 39% yield associated with the uncatalyzed reaction (entry 1) and respective 65 and 75% yields when either DGDE (entry 2) or NBu_4Cl (entry 8) was used alone. The fact that the decreased yields of **2b** were obtained with the increased anion sizes from NBu_4Cl, NBu_4Br, and NBu_4I to NBu_4ClO_4 supports our vision that the beneficial effect of quaternary ammonium salt to the addition reaction should result from the formation of dimeric Grignard reagents bridged by the halide anions in solution. Because of its small anion size as compared with others in Table 2, NBu_4Cl is the best. As compared to NBu_4Cl, $N(CH_3)_4Cl$ (entry 7) gave a decreased yield of **2b** due to the less solubility of $N(CH_3)_4Cl$ than NBu_4Cl in THF, which resulted in a dilute solution of chloride anions.[14]

On the basis of our investigation above, the roles of NBu_4Cl and DGDE are proposed as follows: NBu_4Cl should help to shift the Schlenk equilibrium of Grignard reagents to the side of dimeric Grignard reagents to favor the additions of Grignard reagents to

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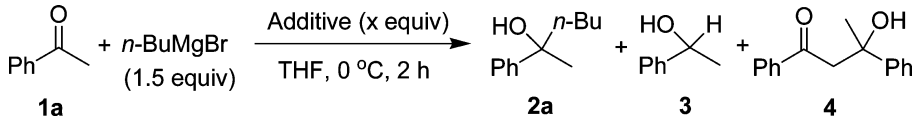
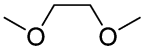
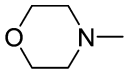
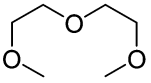
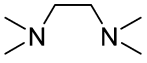
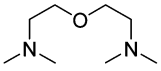
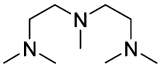
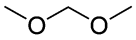
Table 1. Effect of Additives on the Addition Reaction of *n*-BuMgBr to Acetophenone

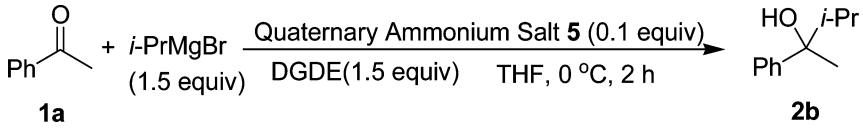


1a 2a 3 4

entry[a]	additive [x equiv]	yield (%)[b] of **2a**	entry[a]	additive [x equiv]	yield (%)[b] of **2a**
1	None	49	7	 DME [1.5]	70
2	 NMM [1.5]	51	8	 DGDE [1.5]	75
3	 TMEDA [1.5]	37	9	NBu_4Br [1.0]	81
4	 BDMAEE [1.5]	34	10	DGDE [1.5] + NBu_4Br [1.0]	91
5	 PMDTA [1.5]	20	11	DGDE [1.5] + NBu_4Br [0.5]	88
6	 DMM [1.5]	45	12	DGDE [1.5] + NBu_4Br [0.1]	89

[a]Reactions were carried out on a 1.0 mmol scale. [b]Isolated yield.

Table 2. Effect of Quaternary Ammonium Salts on the Addition Reaction of *n*-BuMgBr to Acetophenone



1a 2b

entry[a]	**5** and DGDE	yield (%)[b] of **2b**	entry[a]	**5** and DGDE	yield (%)[b] of **2b**
1	none	39	5	DGDE + NBu_4I	70
2	DGDE only	65	6	DGDE + NBu_4ClO_4	66
3	DGDE + NBu_4Cl	82	7	DGDE + $N(CH_3)_4Cl$	66
4	DGDE + NBu_4Br	75	8	NBu_4Cl only	75

[a]Reactions were carried out on a 1.0 mmol scale. [b]Isolated yield.

ketones to form the desired tertiary alcohols, and DGDE increased the nucleophilicity of Grignard reagents by coordination.

The general applicability of this catalytic system, probed by utilizing a variety of Grignard reagents and ketones, is demonstrated by the data displayed in Tables 3 and 4. Thus, by using NBu_4Cl as the catalyst and DGDE as the additive at 0 °C in THF for 2 h, addition reactions of acetophenone with diverse Grignard reagents (RMgX, R = aryl or alkyl or allyl, branched- or straight-chain; X = Br, Cl) occurred in good to excellent yields. In contrast, the reactions carried out in the absence of NBu_4Cl/DGDE (Table 3) have only normally poor to moderate efficiencies. The results also show that under these conditions *i*-PrMgBr reacted with a variety of ketones (aryl or alkyl, electron-withdrawing or -donating group substituted, and enolizable or hindered) in improved yields (Table 4). For example, the addition of *i*-PrMgBr to tetralone only gave a 22% yield of **2n**, but the yield of this process jumped to 65% when NBu_4Cl/DGDE was present (Table 4, entry 9). It should be noted that extending the reaction time for this process from 2 to 24 h had no effect on yield (Table 4, entry 10) but that doubling the concentration of the Grignard reagent and adding NBu_4Cl/DGDE enhanced the formation of addition product to 80% yield of **2n** (Table 4, entry 11).

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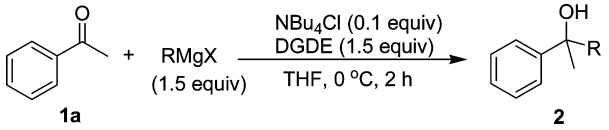
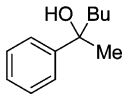
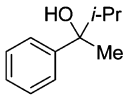
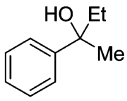
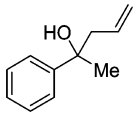
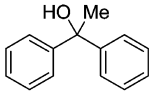
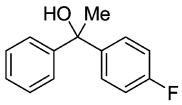
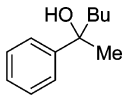
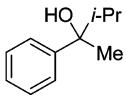
Table 3. Addition Reactions of Acetophenone with Different Grignard Reagents Using NBu_4Cl as the Catalyst and DGDE as the Additive



entry[a]	RMgX	product (2)		yield (%)[b] of 2 with NBu_4Cl/DGDE	yield (%)[b] of 2 without NBu_4Cl/DGDE
1	*n*-BuMgBr		**(2a)**	92	49
2	*i*-PrMgBr		**(2b)**	82	39
3	EtMgBr		**(2c)**	95	78
4	AllylMgBr		**(2d)**	>99	97
5	PhMgBr		**(2e)**	94	73
6	4-F-PhMgBr		**(2f)**	90	78
7	*n*-BuMgCl		**(2a)**	82	37
8	*i*-PrMgCl		**(2b)**	74	23

[a]Reactions were carried out on a 1.0 mmol scale. [b]Isolated yield.

Moreover, the respective 73 and 69% yields of **2m** with 0.1 and 1.0 equiv NBu_4Cl prove again that the use of a catalytic amount of NBu_4Br along with DGDE is sufficient (Table 4, entries 7–8).

Citalopram is a very selective inhibitor of serotonin (5-HT) reuptake and has been demonstrated to be an effective U.S. FDA-approved antidepressant.[15] Because of the fact that 4-[4-(dimethylamino)-1-(4′-fluorophenyl)-1-hydroxybutyl]-3-(hydroxymethyl)-benzonitrile diol **7** (Table 5) is a useful intermediate in the synthesis of racemic/enantiopure citalopram, we applied our conditions to carry both Grignard addition steps in the one-pot preparation of **7** described in a previous patent.[16] Accordingly, sequential addition of *p*-fluorophenyl magnesium chloride and 3-dimethylaminopropyl magnesium chloride to commercially available cyanobenzolactone **6** in the presence of NBu_4Cl (0.1 equiv)/DGDE (1.5 equiv) led to the formation of diol **7** in a 87% yield (Table 5, entry 3). The efficiency of this two-step process contrasts with the 67% yield of **7** obtained when the Grignard additions are carried out in the absence of catalyst and additive (Table 5, entry 1). In a preliminary effort aimed at enhancing the practicality of catalytic system, we have explored the use of the resin Dowex-1-chloride as a catalyst for these reactions. As the result given in entry 4 of Table 5 shows, sequential addition of *p*-fluorophenyl magnesium chloride and 3-dimethylaminopropyl magnesium chloride to **6** in the presence of solid Dowex-1-chloride and 1.5 equiv of DGDE took place to form **7** in a 83% yield. Although we have not yet established optimal reaction conditions for this solid-supported catalytic process, the preliminary result indicates that a recyclable catalytic system could be available for promoting efficient addition reactions between Grignard reagents and ketones.

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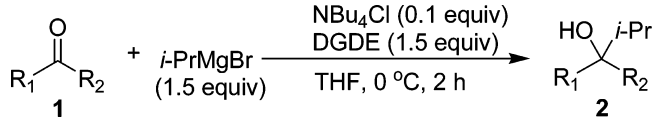
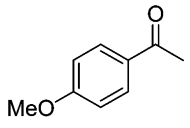
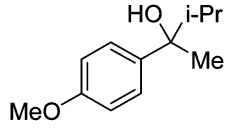
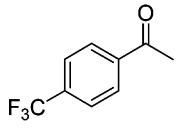
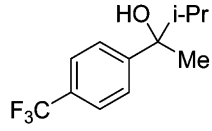
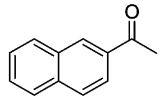
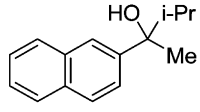
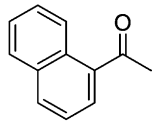
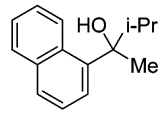
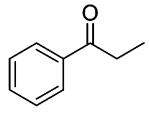
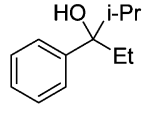
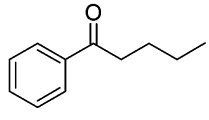
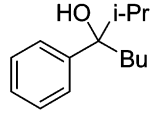
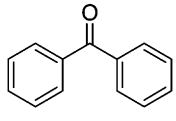
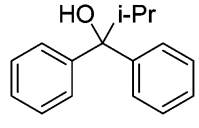
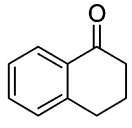
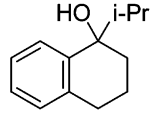
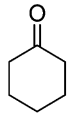
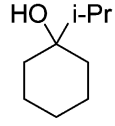
Table 4. Addition Reactions of *i*-PrMgBr with Different Ketones Using NBu_4Cl as the Catalyst and DGDE as the Additive



entry[a]	ketone (**1**)	product (**2**)		yield (%)[b] of **2** with NBu_4Cl/DGDE	yield (%)[b] of **2** without NBu_4Cl/DGDE
1			**(2g)**	82	41
2			**(2h)**	89	52
3			**(2i)**	80	48
4			**(2j)**	75	44
5			**(2k)**	92	53
6			**(2l)**	85	48
7			**(2m)**	69	55
8[c]				73	55
9			**(2n)**	65	22
10[d]				68	26
11[e]				80	34
12			**(2o)**	73	39

[a]Reactions were carried out on a 1.0 mmol scale. [b]Isolated yield. [c]1.0 equiv of NBu_4Cl was used. [d]Reaction time was 24 h. [e]*i*-PrMgBr (3.0 equiv) and DGDE (3.0 equiv) were used.

CONCLUSION

In summary, the effort described above has led to the development of a general and efficient catalytic system to carry out nucleophilic addition reaction of Grignard reagents to ketones by using NBu_4Cl as a catalyst and DGDE as an additive in THF. This system is cost-effective because it relies on the use

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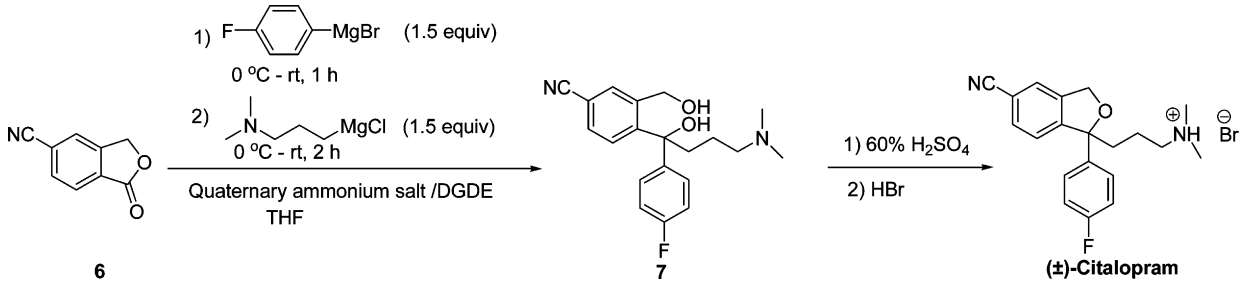
Table 5. Synthesis of the Important Tertiary Diol Intermediate in the Route to Citalopram



entry[a]	DGDE	quaternary ammonium salt	yield (%)[b] of 7
1	none	none	67
2	1.5 equiv	NBu_4Cl (1.0 equiv)	90
3	1.5 equiv	NBu_4Cl (0.1 equiv)	87
4	1.5 equiv	Dowex-1-chloride resin (300 mg/1 mmol of **6**)	83

[a]Reactions were carried out on a 1.0 mmol scale. [b]Isolated yield.

of commercially available and inexpensive NBu_4Cl and DGDE. Because THF is the widest used solvent for generating Grignard reagents and carrying out Grignard reactions, this system is applicable to a wide range of Grignard addition reactions. Moreover, this process is both practical and environmentally friendly since it avoids the use of added metal ions to active reaction and can potentially employ a solid supported, recyclable catalyst.

EXPERIMENTAL SECTION

General Methods. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$ solutions. Chemical shifts are reported in parts per million (ppm, δ) relative to $CDCl_3$ (δ 7.26 for ^{1}H NMR) or $CDCl_3$ (δ 77.1 for ^{13}C NMR). Multiplicities are indicated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). All experiments were carried out in dried glassware with magnetic stirring under an atmosphere of dry nitrogen. For thin-layer chromatography (TLC) analysis throughout this work, TLC plates (silica gel 60 F254, Qingdao Haiyang Chemical and Special Silica Gel Co., LTD) were used. The products were purified by column chromatography on silica gel 60 (300−400 mesh, Qingdao Haiyang Chemical and Special Silica Gel Co., LTD). Visualization was accomplished by UV light (254 nm), $KMnO_4$, and phosphomolybdic acid.

In experiments that required dry solvents, THF was distilled from sodium/benzophenone in prior to use. All ketones, organic bases, quaternary ammonium salts, allylmagnesium bromide (1.0 M in THF), isopropylmagnesium chloride (2.0 M in THF), butylmagnesium chloride (1.0 M in THF), 5-cyanophthalide, and 3-dimethylamino-propylchloride hydrochloride were purchased commercially. Unless otherwise stated, commercial reagents were used without further purification. Butylmagnesium bromide, isopropylmagnesium bromide, ethylmagnesium bromide, phenylmagnesium bromide, 4-fluorophe-nylmagnesium bromide, and (3-(dimethylamino)propyl) magnesium chloride were prepared by slow addition of the corresponding halide in anhydrous THF to magnesium turnings. All freshly prepared Grignard reagents were titrated with a solution of 1,10-phenanthoroline/*n*-BuLi/*s*-BuOH in benzene prior to use.

General Procedure for the Grignard Reactions of Ketones in THF. To a Schlenk tube equipped with a magnetic stirrer and charged with *n*-BuMgBr (1.5 mL, 1.5 mmol, 1.0 M in THF), acetophenone (**1a**, 120 mg, 1.0 mmol, 1.0 M in THF) was added dropwise over 30 min by a syringe at 0 °C. This reaction mixture was stirred at 0 °C for 2 h and then was quenched by saturated aqueous NH_4Cl (5 mL) and extracted with AcOEt (10 mL × 3). The combined extracts were washed by brine (5 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent: *n*-hexane/AcOEt, v/v = 20/1−5/1) to give the desired product **2a** as a colorless oil (49% yield, entry 1 in Table 1).

General Procedure for the Grignard Reactions of Ketones with Different Organic Bases Only in THF. To a Schlenk tube equipped with a magnetic stirrer and charged with *n*-BuMgBr (1.5 mL, 1.5 mmol, 1.0 M in THF), DGDE (0.21 mL, 201 mg, 1.5 mmol) was added at 0 °C, and this solution was stirred for 30 min. Then, acetophenone (**1a**, 120 mg, 1.0 mmol, 1.0 M in THF) was added dropwise over 30 min by a syringe at the same temperature. This reaction mixture was stirred at 0 °C for 2 h and then was quenched by saturated aqueous NH_4Cl (5 mL) and extracted with AcOEt (10 mL × 3). The combined extracts were washed by brine (5 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent: *n*-hexane/AcOEt, v/v = 20/1−5/1) to give the desired product **2a** as a colorless oil (75% yield, entry 8 in Table 1).

General Procedure for the Grignard Reactions of Ketones with Different Quaternary Ammonium Salts Only in THF. To a Schlenk tube equipped with a magnetic stirrer and charged with tetrabutylammonium bromide (NBu_4Br) (322 mg, 1.0 mmol) and *n*-BuMgBr (1.5 mL, 1.5 mmol, 1.0 M in THF), acetophenone (**1a**, 120 mg, 1.0 mmol, 1.0 M in THF) was added dropwise over 30 min at 0 °C, and the reaction mixture was stirred for 2 h. Then, the reaction was quenched by saturated aqueous NH_4Cl (5 mL) and extracted with AcOEt (10 mL × 3). The combined extracts were washed by brine (5 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent: *n*-hexane/AcOEt, v/v = 20/1−5/1) to give the desired product **2a** as a colorless oil (81% yield, entry 9 in Table 1).

General Procedure for the Grignard Addition Reactions of Ketones in the Presence of NBu_4Cl/DGDE in THF. To a Schlenk tube equipped with a magnetic stirrer and charged with tetrabutylammonium chloride (NBu_4Cl) (27.8 mg, 0.1 mmol), *n*-BuMgBr (1.5 mL, 1.5 mmol, 1.0 M in THF) and DGDE (0.21 mL, 201 mg, 1.5 mmol) were added, and the mixture was stirred for 30 min at 0 °C. Then, acetophenone (**1a**, 120 mg, 1.0 mmol, 1.0 M in THF) was added dropwise over 30 min by a syringe at the same temperature. The reaction mixture was stirred at 0 °C for 2 h. Then, the reaction was quenched by saturated aqueous NH_4Cl (5 mL) and extracted with AcOEt (10 mL × 3). The combined extracts were washed by brine (5 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent: *n*-hexane/AcOEt, v/v = 20/1−5/1) to give the desired product **2a** as a colorless oil (92% yield, entry 1 in Table 3).

2-Phenylhexan-2-ol (2a, Entry 1 in Table 3).[17] Colorless oil (92% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (m, 3H), 1.15−1.34 (m, 4H), 1.59 (s, 3H), 1.81−1.88 (m, 2H), 2.04 (s, 1H), 7.25−7.49 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 23.1, 26.2, 30.1, 44.0, 74.7, 124.8, 126.5, 128.3, 148.2.

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3-Methyl-2-phenylbutan-2-ol (2b, Entry 2 in Table 3).[9b] Colorless oil (82% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.82 (d, J = 6.9 Hz, 3H), 0.90 (d, J = 6.9 Hz, 3H), 1.53 (s, 3H), 1.73 (s, 1H), 2.03 (septet, J = 6.9 Hz, 1H), 7.20−7.45 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.2, 17.4, 26.7, 38.6, 76.7, 125.3, 126.4, 127.9, 147.8.

2-Phenylbutan-2-ol (2c, Entry 3 in Table 3).[18] Colorless oil (95% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.83 (t, J = 7.4 Hz, 3H), 1.58 (s, 3H), 1.77 (s, 1H), 1.87 (m, 2H), 7.24−7.47 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 8.3, 29.6, 36.7, 74.9, 124.9, 126.5, 128.1, 147.8.

2-Phenylpent-4-en-2-ol (2d, Entry 4 in Table 3).[19] Colorless oil (99% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.57 (s, 3H), 2.25 (s, 1H), 2.52 (dd, J = 8.2 Hz, 13.8 Hz, 1H), 2.70 (dd, J = 8.2 Hz, 13.8 Hz, 1H), 5.15 (m, 2H), 5.66 (m, 1H), 7.24−7.48 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.9, 48.5, 73.7, 119.4, 124.8, 126.6, 128.2, 133.8, 147.7.

1,1-Diphenylethanol (2e, Entry 5 in Table 3).[9b] White solid (94% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.96 (s, 3H), 2.25 (s, 1H), 7.25 (m, 2H), 7.32 (t, J = 7.19 Hz, 4H), 7.42 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.9, 76.2, 125.8, 127.0, 128.2, 148.0.

1-(4-Fluorophenyl)-1-phenylethanol (2f, Entry 6 in Table 3)[20]**.** White solid (90% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.95 (s, 3H), 2.67 (s, 1H), 7.02 (t, J = 8.7 Hz, 2H), 7.30−7.45 (m, 7H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.8, 75.8, 114.7 (d, J = 21.1 Hz), 125.7, 127.0, 127.5 (d, J = 8.0 Hz), 128.1, 143.7 (d, J = 3.2 Hz), 147.7, 160.4, 162.8. ^{19}F NMR (376 MHz, $CDCl_3$): δ −115.96.

3-Methyl-2-(4-methoxyphenyl)butan-2-ol (2g, Entry 1 in Table 4).[21] Colorless oil (82% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.82 (d, J = 6.9 Hz, 3H), 0.86 (d, J = 6.9 Hz, 3H), 1.50 (s, 3H), 1.69 (br, 1H), 1.98 (septet, J = 6.9 Hz, 1H), 3.80 (s, 3H), 6.84−6.89 (m, 2H), 7.30−7.36 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.2, 17.4, 26.4, 38.7, 55.2, 76.5, 113.1, 126.4, 139.9, 158.0.

3-Methyl-2-(4-(trifluoromethyl)phenyl)butan-2-ol (2h, Entry 2 in Table 4).[9e] Colorless oil (89% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.77 (d, J = 6.9 Hz, 3H), 0.91 (d, J = 6.9 Hz, 3H), 1.53 (s, 3H), 1.75 (br, 1H), 2.02 (septet, J = 6.9 Hz, 1H), 7.53 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.9, 17.3, 27.1, 38.5, 77.3, 123.0, 124.8 (q, J = 271.0 Hz), 125.7, 128.8 (q, J = 32.4 Hz), 151.8. ^{19}F NMR (376 MHz, $CDCl_3$): δ −62.38.

3-Methyl-2-(2-naphthalenyl)-2-butanol (2i, Entry 3 in Table 4).[9b] Colorless oil (80% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (d, J = 6.9 Hz, 3H), 1.02 (d, J = 6.9 Hz, 3H), 1.68 (s, 3H), 2.09 (s, 1H), 2.21 (septet, J = 6.9 Hz, 1H), 7.51−7.62 (m, 3H), 7.86−7.92 (m, 3H), 7.98 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.3, 17.6, 26.8, 38.5, 77.0, 123.8, 124.2, 125.7, 126.0, 127.5, 127.6, 128.3, 132.3, 133.2, 145.5.

3-Methyl-2-(1-naphthalenyl)-2-butanol (2j, Entry 4 in Table 4).[9b] Colorless oil (75% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85 (d, J = 6.9 Hz, 3H), 1.06 (d, J = 6.9 Hz, 3H), 1.78 (s, 3H), 2.12 (s, 1H), 2.88 (septet, J = 6.9 Hz, 1H), 7.44−7.56 (m, 4H), 7.80−7.93 (m, 2H), 8.87 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.2, 18.3, 25.2, 36.3, 79.0, 124.4, 124.7, 125.1, 127.3, 128.4, 129.3, 131.0, 135.1, 143.3.

2-Methyl-3-phenyl-3-pentanol (2k, Entry 5 in Table 4).[9b] Colorless oil (92% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.70 (t, J = 7.3 Hz, 3H), 0.72 (d, J = 6.9 Hz, 3H), 0.95 (d, J = 6.9 Hz, 3H), 1.59 (s, 1H), 1.89 (q, J = 6.9 Hz, 2H), 2.05 (septet, J = 6.9 Hz, 1H), 7.18−7.40 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 7.9, 16.6, 17.5, 32.0, 37.5, 79.3, 125.9, 126.1, 127.7, 145.0.

2-Methyl-3-phenyl-3-heptanol (2l, Entry 6 in Table 4).[22] Colorless oil (85% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.72 (d, J = 6.8 Hz, 3H), 0.83 (t, J = 7.3 Hz, 3H), 0.95 (m, 4H), 1.25 (m, 3H), 1.61 (d, J = 11.8 Hz, 1H), 1.85 (m, 2H), 2.04 (septet, J = 6.9 Hz, 1H), 7.20−7.38 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 16.6, 17.4, 23.2, 25.8, 37.8, 39.4, 79.0, 125.8, 126.1, 127.7, 145.5.

2-Methyl-1,1-diphenyl-1-propanol (2m, Entry 7 in Table 4).[9b] Colorless oil (69% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (d, J = 6.9 Hz, 6H), 2.10 (s, 1H), 2.93 (septet, J = 6.9 Hz, 1H), 7.18−7.55 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.1, 35.0, 80.4, 125.7, 126.3, 128.0, 146.7.

1-Isopropyl-1,2,3,4-tetrahydro-1-naphthol (2n, Entry 9 in Table 4).[9b] Colorless oil (65% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.66 (d, J = 6.9 Hz, 3H), 1.09 (d, J = 6.9 Hz, 3H), 1.62−1.89 (m, 5H), 2.40 (septet, J = 6.9 Hz, 1H), 2.60−2.84 (m, 2H), 7.08 (d, J = 7.5 Hz, 1H), 7.14−7.26 (m, 2H), 7.52 (d, J = 7.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.3, 18.4, 19.1, 30.3, 30.9, 37.4, 74.4, 126.1, 126.4, 126.8, 128.9, 137.8, 141.6.

1-Isopropyl-1-cyclohexanol (2o, Entry 12 in Table 4).[9b] Colorless oil (73% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (d, J = 6.9 Hz, 6H), 1.11 (s, 1H), 1.20−1.63 (m, 11H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.6, 21.9, 25.9, 34.1, 37.5, 73.1.

Synthesis of 4-(4-(Dimethylamino)-1-(4-fluorophenyl)-1-hydroxybutyl)-3-(hydroxymethyl)benzonitrile (7).

Method 1 (Entry 1 in Table 5). To 1 mL of THF solution of a Schlenk tube equipped with a magnetic stirrer and charged with 5-cyanophthalide (**6**, 157 mg, 1.0 mmol), 4-fluorophenylmagnesium bromide (1.5 mL, 1.5 mmol, 1.0 M in THF) was added dropwise over 30 min by a syringe at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 1 h and then cooled to 0 °C. The second freshly made Grignard reagent [3-(dimethylamino)-propyl)magnesium chloride (1.5 mL, 1.5 mmol, 1.0 M in THF)] was added dropwise over 30 min. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. Then, the reaction was quenched by saturated aqueous NH_4Cl (5 mL) and extracted with CH_2Cl_2 (10 mL × 3). The combined extracts were washed by brine (5 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to afford the crude product as a colorless oil. Purification by silica gel column chromatography (eluent: CH_2Cl_2/CH_3OH, v/v = 40/1) and recrystallization in heptane/isopropyl ether (v/v = 2/1) gave the pure compound (**7**) as a white solid (67% yield, entry 1 in Table 5).

Method 2 (Entry 2 in Table 5). To 1 mL of THF solution of a Schlenk tube equipped with a magnetic stirrer and charged with tetrabutylammonium chloride (278 mg, 1.0 mmol), 5-cyanophthalide (**6**, 157 mg, 1.0 mmol), and DGDE (0.21 mL, 201 mg, 1.5 mmol), 4-fluorophenylmagnesium bromide (1.5 mL, 1.5 mmol, 1.0 M in THF) was added dropwise over 30 min by a syringe at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 1 h and then cooled to 0 °C. The second freshly made Grignard reagent (3-(dimethylamino)propyl)magnesium chloride (1.5 mL, 1.5 mmol, 1.0 M in THF) was added dropwise over 30 min. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. Then, the reaction was quenched by saturated aqueous NH_4Cl (5 mL) and extracted with CH_2Cl_2 (10 mL × 3). The combined extracts were washed by brine (5 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to afford the crude product as a colorless oil. Purification by silica gel column chromatography (eluent: CH_2Cl_2/CH_3OH, v/v = 40/1) and recrystallization in heptane/isopropyl ether (v/v = 2/1) gave the pure compound (**7**) as a white solid (90% yield, entry 2 in Table 5).

Method 3 (Entry 4 in Table 5). To 1 mL of THF solution of a Schlenk tube equipped with a magnetic stirrer and charged with Dowex-1-chloride resin (300 mg), 5-cyanophthalide (**6**, 157 mg, 1.0 mmol), and diethylene glycol dimethyl ether (0.21 mL, 201 mg, 1.5 mmol), 4-fluorophenylmagnesium bromide (1.5 mL, 1.5 mmol, 1.0 M in THF) was added dropwise over 30 min by a syringe at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 1 h and then cooled to 0 °C. The second freshly made Grignard reagent (3-(dimethylamino)propyl)magnesium chloride (1.5 mL, 1.5 mmol, 1.0 M in THF) was added dropwise over 30 min. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. Then, the reaction was quenched by saturated aqueous NH_4Cl (5 mL) and extracted with CH_2Cl_2 (10 mL × 3). The combined extracts were washed by brine (5 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to afford the crude product as a colorless oil. Purification by silica gel column chromatography (eluent: CH_2Cl_2/CH_3OH, v/v = 40/1) and recrystallization in heptane/isopropyl ether (v/v = 2/1) gave the pure compound (**7**) as a white solid (83% yield, entry 4 in Table 5).

4-(4-(Dimethylamino)-1-(4-fluorophenyl)-1-hydroxybutyl)-3-(hydroxymethyl)benzonitrile (7, Table 5).[23,24] White solid, mp

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97−98 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.57 (m, 1H), 1.66 (m, 1H), 2.21 (s, 6H), 2.37 (m, 3H), 2.47 (m, 1H), 4.16 (d, J = 12.3 Hz, 1H), 4.42 (d, J = 12.3 Hz, 1H), 6.96 (dd, J = 8.4, 8.8 Hz, 2H), 7.30 (m, 2H), 7.59 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.2, 43.8, 44.7, 59.9, 64.0, 77.5, 111.3, 114.7 (d, J = 21.2 Hz), 118.6, 127.2, 127.6 (d, J = 8.0 Hz), 130.8, 135.6, 142.3, 142.8 (d, J = 3.2 Hz), 151.1, 160.3, 162.8. ^{19}F NMR (376 MHz, $CDCl_3$): δ −116.25.

■ ASSOCIATED CONTENT

Supporting Information

Copies of the ^{1}H and ^{13}C NMR spectra of products. 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.

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