Chemical Science

EDGE ARTICLE

View Article Online
View Journal | View Issue

Cite this: *Chem. Sci.*, 2024, **15**, 8569

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 11th March 2024
Accepted 29th April 2024

DOI: 10.1039/d4sc01659a

rsc.li/chemical-science

Zinc chloride-catalyzed Grignard addition reaction of aromatic nitriles†

Manabu Hatano, *[a] Kisara Kuwano,[a] Riho Asukai,[a] Ayako Nagayoshi,[a] Haruka Hoshihara,[a] Tsubasa Hirata, [a] Miho Umezawa,[b] Sahori Tsubaki,[b] Takeshi Yoshikawa *[b] and Ken Sakata *[b]

In the alkyl addition reaction of aromatic nitriles using Grignard reagents, ketones are formed after hydrolysis. However, this addition reaction is often slow compared to that using reactive organolithium(I) reagents. In this study, we improved the reaction by using zinc(II)ates, which are generated *in situ* using Grignard reagents and zinc chloride ($ZnCl_2$) as a catalyst. As a result, the corresponding ketones and amines were obtained *via* hydrolysis and reduction, respectively, in good yields under mild reaction conditions. Scale-up reactions are also demonstrated. Interestingly, using a catalytic amount of $ZnCl_2$ was more effective than using a stoichiometric amount of zinc(II)ates. Possible transition states are proposed on the basis of the active zinc(II)ate species, and DFT calculations were carried out to elucidate a plausible reaction mechanism.

Introduction

Aromatic nitriles are versatile compounds that are widely used in the synthesis of natural products, pharmaceuticals, agrochemicals, and industrial materials.[1] Nitriles are not only equivalents of carbonyl compounds, but also a valuable source of nitrogen, and they are easily transformed into amines, amidines, imino esters, triazines, amides, carboxylic acids, ketones, and aldehydes. Due to the low reactivity of aromatic nitriles, traditional organometallic reagents, such as highly reactive organolithium(I) compounds,[2] have often been used for the conversion of aromatic nitriles to alkylphenones. Although organomagnesium(II) reagents, *i.e.*, Grignard reagents,[3] have also been used for this purpose, reflux conditions are usually required because Grignard reagents are much less reactive than organolithium(I) reagents (Scheme 1a).[4] Moreover, α-deprotonation from imide intermediates to produce enamines often results in byproducts during long reactions. In the quest for more reactive alternatives to Grignard reagents, Cu(I) catalysts were found to promote the reaction;[5] however, heating conditions are still required. Subsequently, innovative methods involving solvent-free conditions,[6] aqueous conditions,[7] 2-methyltetrahydrofuran,[8] and flow-system conditions have been investigated with respect to their potential to replace Cu(I) catalyst systems. In this context, we have previously reported a highly effective zinc chloride ($ZnCl_2$)-catalyzed Grignard addition reaction of ketones under mild reaction conditions (Scheme 1c),[9,10] which stands in contrast to the noncatalyzed Grignard addition reactions of ketones that usually result in the formation of byproducts and the recovery of starting materials (Scheme 1b). Remarkably, since zinc(II)ates derived from $ZnCl_2$ and Grignard reagents have stronger nucleophilicity than basicity, alkyl transfer may proceed rather than the α-deprotonation of ketones that usually occurs when using Grignard reagents alone. Accordingly, we envisioned that $ZnCl_2$ could promote the Grignard addition reaction of aromatic nitriles under mild reaction conditions (Scheme 1d). Considering that Grignard reagents are relatively stable and commercially available, using Grignard reagents instead of relatively unstable organolithium(I) reagents for the alkyl addition to aromatic nitriles would be preferable both from a laboratory and industrial perspective. Herein, we report the $ZnCl_2$-promoted Grignard addition reaction of aromatic nitriles, which affords the corresponding ketones and amines.

Results and discussion

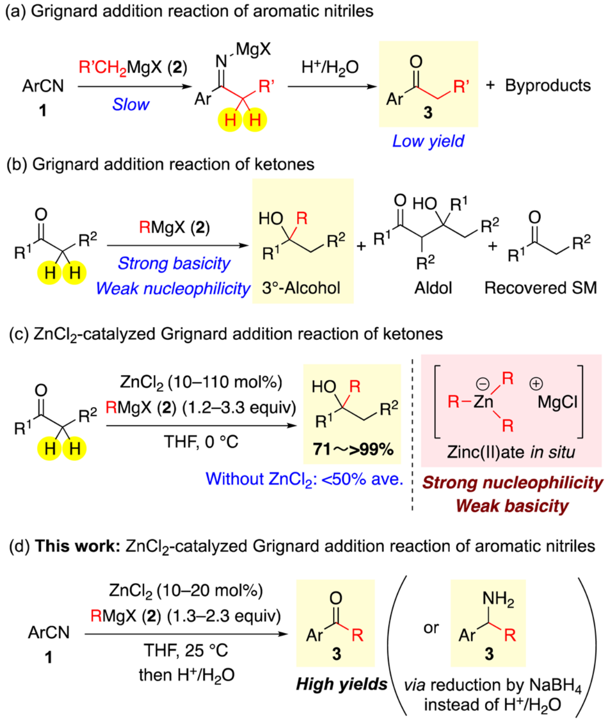
We started our investigation by examining the addition of *n*-butyl lithium(I) (*n*-BuLi) and magnesium(II) reagents (1.1–3.3 equiv.) to benzonitrile **1a** (1 equiv.) in the presence or absence of $ZnCl_2$ (0–1.1 equiv.) in tetrahydrofuran (THF) (Table 1). In the absence of $ZnCl_2$, the reaction using *n*-BuLi was completed within 1 h at −78 °C, and the corresponding ketone (**3aa**) was obtained in >99% yield after routine hydrolysis with aqueous

---

[a] *Faculty of Pharmaceutical Sciences, Kobe Pharmaceutical University, Higashinada, Kobe 658-8558, Japan. E-mail: mhatano@kobepharma-u.ac.jp*

[b] *Faculty of Pharmaceutical Sciences, Toho University, Miyama, Funabashi, Chiba 274-8510, Japan. E-mail: takeshi.yoshikawa@phar.toho-u.ac.jp; ken.sakata@phar.toho-u.ac.jp*

† Electronic supplementary information (ESI) available: Experimental procedure, characterization data, computational details, and copies of ^{1}H NMR and ^{13}C NMR spectra of compounds. See DOI: **https://doi.org/10.1039/d4sc01659a**

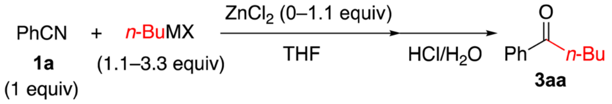


Scheme 1 Alkyl addition to aromatic nitriles and ketones with Grignard reagents.

HCl (entry 1). In contrast, the reaction using *n*-BuMgCl (**2a**), which is much less reactive than *n*-BuLi, did not proceed at −78 °C (entry 2). Unexpectedly, the combined use of **2a** (3.3 equiv.) and $ZnCl_2$ (1.1 equiv.), which can be expected to give the corresponding reactive zinc(II)ate (1.1 equiv.) *in situ*, did not promote the reaction at −78 °C (entry 3). However, the reaction proceeded at 25 °C to give **3aa** in 77% yield after 3 h (entry 4). Interestingly, reducing the amount of $ZnCl_2$ (0.2 equiv., 20 mol%) was more effective than using a stoichiometric amount of $ZnCl_2$ (1.1 equiv.), and **3aa** was obtained in an improved yield of 88% (entry 5). Furthermore, the amount of **2a** could be reduced from 3.3 to 2.3 equiv., affording almost the same yield (87%; entry 6). Finally, by extending the reaction time to 6 h, **3aa** was obtained in 95% yield (entry 7). Using *n*-BuMgBr (**2a′**) instead of **2a** afforded **3aa** in 93% yield (entry 8). For practical use, commercially available 0.5 M $ZnCl_2$ in THF and non-hygroscopic dichloro(*N*,*N*,*N*′,*N*′-tetramethylethylenediamine)zinc(II) ($ZnCl_2$(tmeda))[11] can be used in place of $ZnCl_2$, which provided **3aa** in 91% and 87% yield, respectively (entries 9 and 10). In contrast to inexpensive $ZnCl_2$, which is hygroscopic and requires melt-drying *in vacuo* before use, these forms of zinc(II) species are very convenient because they can be used without pre-treatment. We also examined the reactions of **1a** with **2a** or **2a′** alone as control experiments under the optimized conditions, which furnished **3aa** in 18–55% yield (entries 11–14). Overall, the addition of $ZnCl_2$ was found to effectively promote the Grignard addition reaction of aromatic nitrile **1a**.

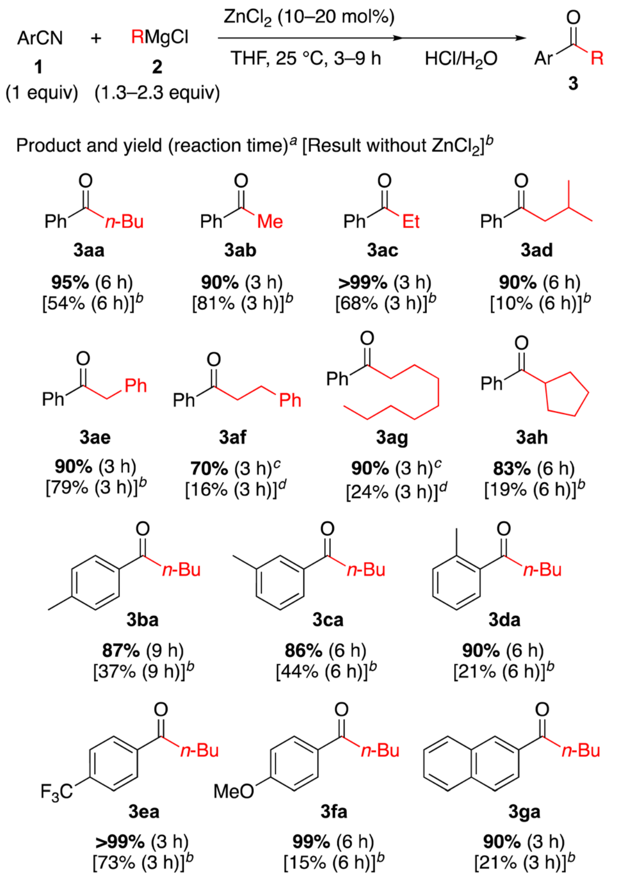
With the optimized reaction conditions in hand, various aromatic nitriles (**1**) and Grignard reagents (**2**) were investigated in the presence of 20 mol% of $ZnCl_2$ catalyst (Scheme 2). The primary alkyl Grignard reagents **2b** (Me), **2c** (Et), **2d** (i-Bu), **2e** (Bn), **2f** ($BnCH_2$), and **2g** (*n*-octyl) could be successfully applied to the reaction of **1a**, and the corresponding products (**3ab–ag**) were obtained in improved yield compared with the reactions

Table 1 Optimization of the reaction conditions of the Grignard addition reaction of aromatic nitrile **1a**[a]



Entry	Reagents	Conditions	Yield (%) of **3aa**[b]
1	*n*-BuLi (1.1 equiv.)	−78 °C, 1 h	>99
2	*n*-BuMgCl (**2a**) (1.1 equiv.)	−78 °C, 1 h	0
3	**2a** (3.3 equiv.) + $ZnCl_2$ (1.1 equiv.)	−78 °C, 1 h	1
4	**2a** (3.3 equiv.) + $ZnCl_2$ (1.1 equiv.)	25 °C, 3 h	77
5	**2a** (3.3 equiv.) + $ZnCl_2$ (0.2 equiv.)	25 °C, 3 h	88
6	**2a** (2.3 equiv.) + $ZnCl_2$ (0.2 equiv.)	25 °C, 3 h	87
7	**2a** (2.3 equiv.) + $ZnCl_2$ (0.2 equiv.)	25 °C, 6 h	95
8	*n*-BuMgBr (**2a′**) (3.3 equiv.) + $ZnCl_2$ (0.2 equiv.)	25 °C, 6 h	93
9[c]	**2a** (3.3 equiv.) + $ZnCl_2$ in THF (0.2 equiv.)	25 °C, 6 h	91
10[d]	**2a** (3.3 equiv.) + $ZnCl_2$(tmdea) (0.2 equiv.)	25 °C, 6 h	87
11	**2a** (1.1 equiv.)	25 °C, 3 h	18
12	**2a** (2.3 equiv.)	25 °C, 3 h	33
13	**2a** (2.3 equiv.)	25 °C, 6 h	54
14	**2a′** (2.3 equiv.)	25 °C, 6 h	55

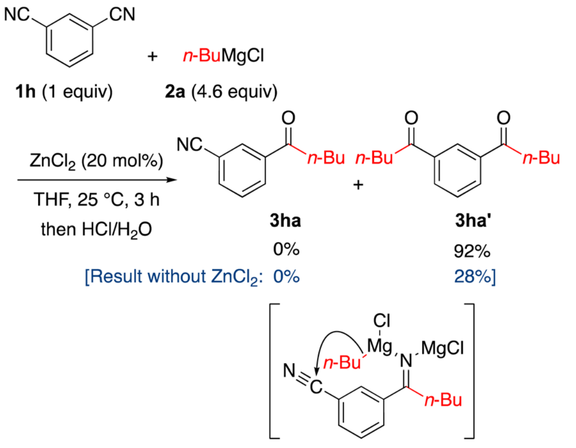
[a] The reaction was carried out using PhCN (**1a**; 2 mmol), *n*-BuMX (2.2–6.6 mmol), and $ZnCl_2$ (0–2.2 mmol) in THF at −78 °C or 25 °C for 1–6 h, unless otherwise noted. [b] Isolated yield. [c] 0.5 M $ZnCl_2$ in THF was used. [d] Dichloro(*N*,*N*,*N*′,*N*′-tetramethylethylenediamine)zinc(II) was used instead of $ZnCl_2$.



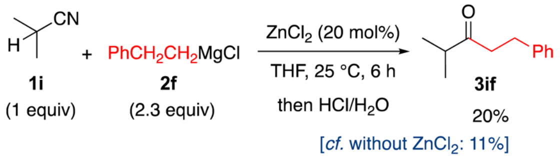
Scheme 2 ZnCl$_2$-catalyzed Grignard addition reaction of aromatic nitriles. [a] The reaction was carried out using ArCN (**1**; 2 mmol), RMgCl (**2**; 4.6 mmol), and ZnCl$_2$ (0.4 mmol, 20 mol%) in THF at 25 °C for 3–9 h, unless otherwise noted. The isolated yield is shown. [b] Results within brackets refer to the isolated yield of **3** in the absence of the ZnCl$_2$ catalyst using 2.3 equiv. (4.6 mmol) of **2**. [c] Isolated yield when using 10 mol% of ZnCl$_2$ and 1.3 equiv. (2.6 mmol) of **2**. [d] Isolated yield when using 1.3 equiv. (2.6 mmol) of **2**.

without ZnCl$_2$ catalyst (for details, see brackets *b* in Scheme 2). It is noteworthy that in the reactions giving **3af** and **3ag**, the amount of ZnCl$_2$ could be reduced from 20 to 10 mol% and that of the Grignard reagent could be reduced from 2.3 to 1.3 equiv. In particular, **3ad**, **3af**, and **3ag** were obtained in drastically improved yield, since **2d**, **2f**, and **2g** are less reactive than **2a–c** and **2e**. A sterically hindered and therefore less reactive secondary alkyl Grignard reagent (**2h**; *c*-pentyl), also furnished the corresponding product (**3ah**) in improved yield (83%) compared to the 19% yield obtained in the absence of ZnCl$_2$. Next, **1a** was replaced with **1b–d** in order to examine the effect of a simple methyl substituent at the *p*-, *m*-, or *o*-position of the benzonitrile. Even for the sterically demanding **1d**, which contains an *o*-Me substituent, the reactions proceeded smoothly in the presence of ZnCl$_2$ catalyst to produce **3ba–da** in 86–90% yield. The electron-donating methyl substituent probably decreases slightly the reactivity, and the yields of the reactions in the absence of the ZnCl$_2$ catalyst were lower (21–44%) than in the case of **1a** (54%). In this context, the reactions of reactive **1e** with an electron-withdrawing *p*-CF$_3$-substituent and of less reactive **1f** with an electron-donating *p*-MeO-substituent gave contrasting results; the noncatalyzed reaction with **2a** alone gave **3ea** in 73% yield and **3fa** in 15% yield, whereas **3ea** and **3fa** were obtained in quantitative yields (>99%) in the presence of ZnCl$_2$. In addition, substrate **1g** with a 2-naphthyl moiety, which would be less favored than **1a** due to steric and electronic reasons, was suitable for the present catalytic reaction, and the desired product (**3ga**) was obtained in 90% yield.

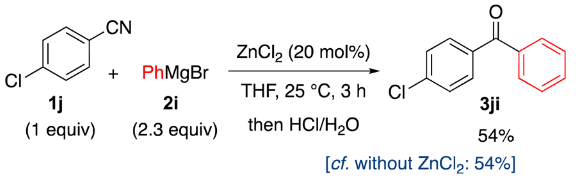
A ZnCl$_2$-catalyzed double alkyl addition to isophthalonitrile (**1h**) with **2a** was also carried out (eqn (1)), which afforded the desired double adduct (**3ha′**) in 92% yield; this stands in sharp contrast to the noncatalyzed version of the reaction (28% yield). Interestingly, the single alkyl adduct **3ha** was not obtained when using **2a** alone. This implies that a coordinating reagent at the adjacent imido group in pre-**3ha** would promote the alkyl transfer even without Zn(II) activation; thus, pre-**3ha** would be easily converted to pre-**3ha′**. For additional information, aliphatic nitriles were investigated instead of aromatic nitriles. However, even under ZnCl$_2$-catalyzed conditions, α-deprotonation of aliphatic nitriles occurred, resulting in almost complete recovery of substrates and/or α-addition to another nitrile (*e.g.*, aldol-type products). For example, the reaction of isobutyronitrile **1i** with **2f** afforded the desired product (**3if**) in merely 20% yield, whereas the noncatalyzed reaction gave **3if** in 11% yield (eqn (2)). In addition, using phenyl-magnesium(II) reagent **2i** instead of the alkylmagnesium(II) reagents in the reaction with 4-chlorobenzonitrile (**1j**) (eqn (3)) afforded **3ji** in 54% yield irrespective of the presence or absence of ZnCl$_2$. Although the reason is not clear at present, the failure to generate the corresponding triphenyl-zinc(II)ate and/or its low nucleophilicity could explain this result. Overall, the reactions with aliphatic nitriles and arylmagnesium(II) reagents are a limitation of the present ZnCl$_2$ catalysis.



(1)

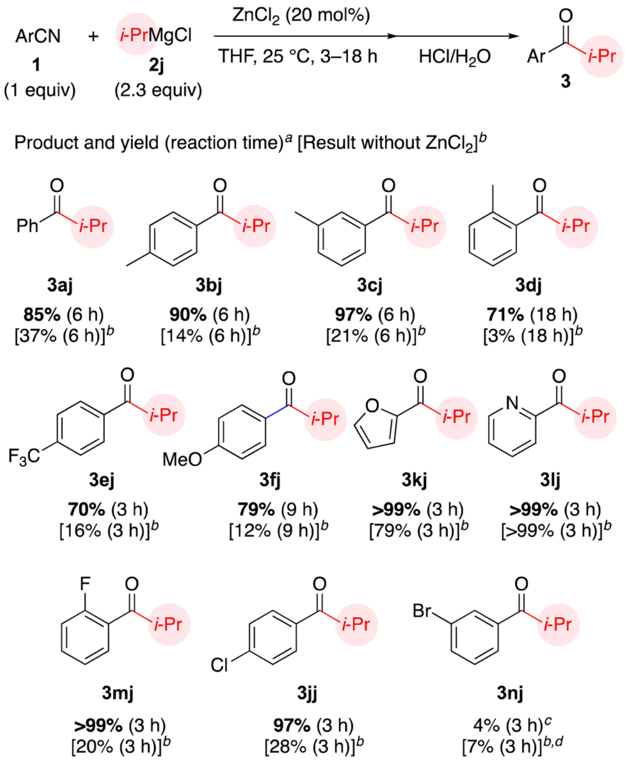


(2)



(3)

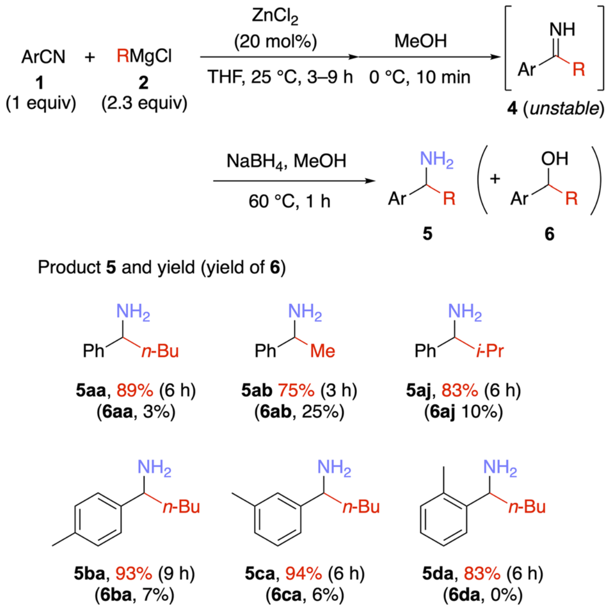
Next, encouraged by the results of the reaction giving **3ah** in Scheme 2, the isopropyl addition to aromatic nitriles (**1**) with i-PrMgCl (**2j**; 2.3 equiv.) in the presence of $ZnCl_2$ was examined, since reactions of secondary alkyl Grignard reagents are often sluggish due to steric effects (Scheme 3). For aryl or heteroaryl nitriles, the $ZnCl_2$-catalyzed reactions smoothly furnished the desired i-Pr-adducts (**3aj–fj** and **3jj–mj**) in 70–99% yield. These results stand in sharp contrast to those obtained in the absence of $ZnCl_2$ (see brackets *b* in Scheme 3).[12] It is also noteworthy that the differences in yield in the presence or absence of $ZnCl_2$ are larger than the difference in yield when using primary alkyl Grignard reagents (Scheme 2). It should furthermore be noted that halogen moieties are tolerated, and that 2-fluorobenzonitrile (**1m**) and 4-chlorobenzonitrile (**1n**) can be used. Unfortunately, the reaction with 3-bromobenzonitrile (**1n**) did not proceed well because a magnesium–halogen exchange reaction occurred exclusively,[13] and the corresponding protonated product PhCN (**1a**) was recovered in 96% yield.



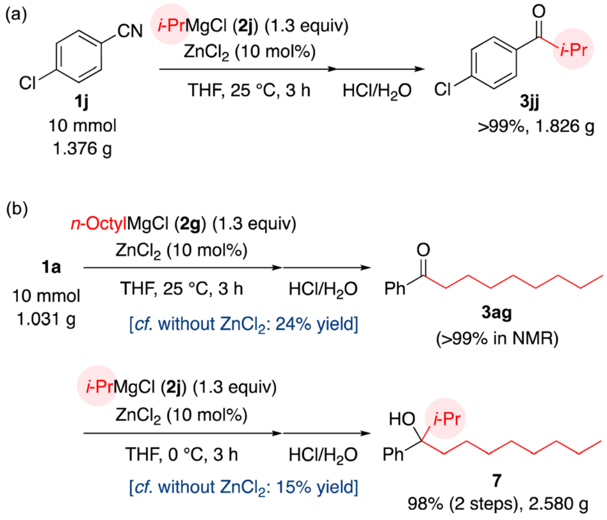
Scheme 3 $ZnCl_2$-catalyzed Grignard addition reaction of aromatic nitriles with i-PrMgCl. ^{a} The reaction was carried out using ArCN (**1**; 2 mmol), i-PrMgCl (**2j**; 4.6 mmol), and $ZnCl_2$ (0.4 mmol, 20 mol%) in THF at 25 °C for 3–18 h, unless otherwise noted. The isolated yield is shown. ^{b} Results within brackets refer to the isolated yield of **3** in the absence of $ZnCl_2$ using 2.3 equiv. (4.6 mmol) of **2j**. ^{c} **1a** was obtained in 96% yield. ^{d} **1a** was obtained in 92% yield.

Next, we examined the synthesis of amines *via* reduction using sodium borohydride ($NaBH_4$) instead of the routine hydrolysis under acidic conditions with aqueous HCl (Scheme 4). After alkylation of **1a** with **2a** in the presence of $ZnCl_2$, MeOH was added at 0 °C and the mixture was stirred for 10 min. Since unprotected imine **4aa** would be unstable, the residue obtained after rapid extraction with diethyl ether and water followed by concentration of the organic phase was treated with $NaBH_4$ in MeOH at 60 °C for 1 h. As a result, α-*n*-butylbenzylamine **5aa** was obtained in 89% yield, together with α-*n*-butylbenzylalcohol **6aa** in 3% yield as a byproduct. The reduction of hydrolysis product **3aa** derived from imine intermediate **4aa** afforded **6aa**. Reaction products derived from **1a** and **2b** or **2j** also provided the corresponding amine **5ab** in 75% yield or **5aj** in 83% yield. In addition, when *p*-, *m*-, or *o*-Me substituted benzonitriles **1b–d** were used with **2a** instead of **1a**, the corresponding amines (**5ba**, **5ca**, and **5da**) were obtained in 83–94% yield.

To demonstrate the synthetic utility of this catalytic reaction, some scale-up reactions were conducted (Scheme 5). The $ZnCl_2$-catalyzed reaction of 10 mmol (1.768 g) of 4-chlorobenzonitrile (**1j**) with i-PrMgCl (**2j**) proceeded smoothly even when using reduced amounts of both **2j** (from the usual 2.3 to 1.3 equiv.) and $ZnCl_2$ (from the usual 20 to 10 mol%), and the desired ketone (**3jj**) was obtained in quantitative yield (1.826 g) (Scheme 5a). In addition, the $ZnCl_2$-catalyzed reaction of 10 mmol (1.031 g) of PhCN (**1a**) with *n*-octylMgCl (**2g**; 1.3 equiv.) proceeded smoothly in the presence of 10 mol% of $ZnCl_2$. After a routine workup procedure, the resulting ketone (**3ag**) was used without purification for the subsequent $ZnCl_2$ (10 mol%)-catalyzed alkylation reaction of **3ag** with **2j** (1.3 equiv.) (Scheme 5b). As a result, the corresponding tertiary alcohol (**7**) was obtained in 98% yield (2.580 g) over two steps based on **1a.** $ZnCl_2$ was very effective in both steps shown in Scheme 5b, whereas the



Scheme 4 Amine synthesis *via* reduction with $NaBH_4$.



Scheme 5 Scalable $ZnCl_2$-catalyzed alkyl addition reactions of aromatic nitriles and sequential alkyl addition to a ketone.

product yield was low in the absence of $ZnCl_2$ (see brackets in Scheme 5; 24% and 15% yield, respectively).

Subsequently, we turned our attention to mechanistic aspects, and a plausible reaction mechanism is proposed in Fig. 1. In particular, Fig. 1a–d show the key results shown in Table 1, entries 11, 12, 4, and 6. In the case of 1.1 equiv. of *n*-BuMgCl (**2a**) alone (Fig. 1a), the nitrogen of the nitrile moiety would coordinate to the Mg(II) center, and the alkyl group (R = *n*-Bu) would attack the carbon atom of the nitrile moiety (TS-**8**). This would result in a slow reaction (18% yield) due to the relatively large distance between the nucleophilic R carbon atom and the electrophilic nitrile carbon atom. Meanwhile, in the case of 2.3 equiv. of **2a** alone (Fig. 1b), two molecules of **2a** would disproportionate and dimerize (TS-**9**).[3] As a result, the attack distance would be shortened and the yield slightly improved (33% yield). Furthermore, in the case of 3.3 equiv. of **2a** and 1.1 equiv. of $ZnCl_2$, which would produce 1.1 equiv. of the zinc(II)ate *in situ* (Fig. 1c), the Mg(II) center could be positively ionized and the Zn(II) center negatively ionized (TS-**10**).[14] This would greatly enhance both the nucleophilicity of the R carbon atom and the electrophilicity of the nitrile carbon atom, improving the yield in the case of Fig. 1c (77% yield), albeit the attack distance would not change compared to the case shown in Fig. 1b. Finally, in the case of 2.3 equiv. of **2a** and 20 mol% of $ZnCl_2$ (Fig. 1d), there would be an excess of **2a** given that the amount of zinc(II)ate depends on the amount of $ZnCl_2$ (20 mol%), which would integrate with the zinc(II)ate to form a trimer complex with two Mg(II) and one Zn(II) centers, to which the nitrile moiety could coordinate (TS-**11**). This trimeric structure can be also envisaged for the possible structures shown in Fig. 1b and c. Again, it is worth noting that the Mg(II) center would be positively ionized and the Zn(II) center would be negatively ionized in this structure. Moreover, the distance between the nucleophilic R carbon atom and the electrophilic nitrile carbon atom would be shortened. Therefore, despite using a catalytic amount of $ZnCl_2$, the yield was further improved (87% yield). After the alkyl transfer, the trimer complex with two Mg(II) and one Zn(II) centers would be regenerated in the presence of an excess of **2a**, thus closing the catalytic cycle.

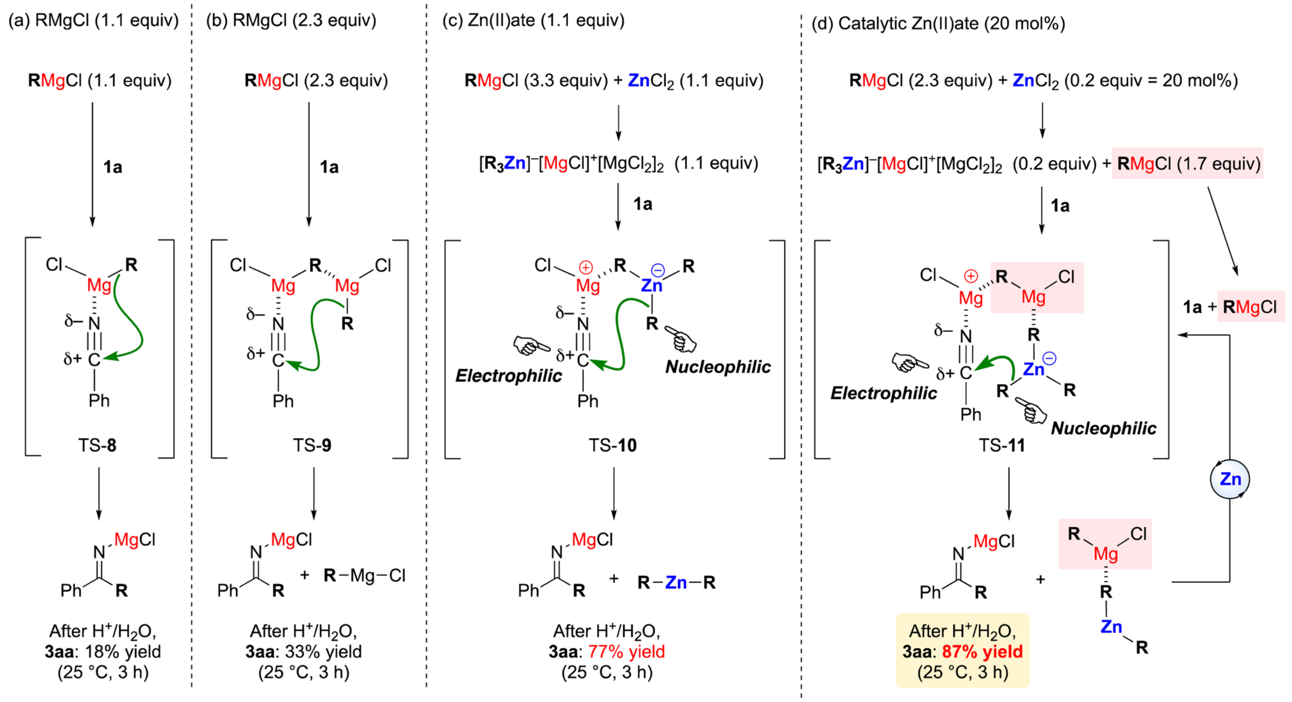


Fig. 1 Plausible reaction mechanism and the catalytic cycle (R = *n*-Bu). (a) Stoichiometric reaction using RMgCl (1.1 equiv.). (b) Stoichiometric reaction using RMgCl (2.3 equiv.). (c) Stoichiometric reaction using RMgCl (3.3 equiv.) and $ZnCl_2$ (1.1 equiv.) leading to 1.1 equiv. of zinc(II)ate. (d) Catalytic reaction using RMgCl (2.3 equiv.) and $ZnCl_2$ (0.2 equiv. = 20 mol%) leading to 1.1 equiv. of zinc(II)ate.

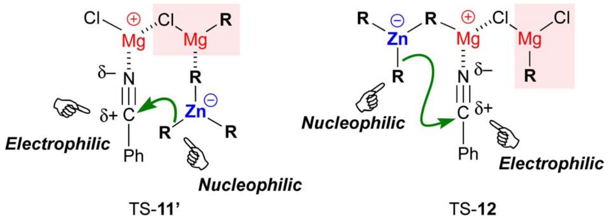


Fig. 2 Other possible transition states instead of TS-**11**.

As shown in Fig. 2, chloro-bridged TS-**11**′ could also be envisaged instead of TS-**11**. Moreover, an alternative geminal pathway *via* TS-**12** or a vicinal pathway *via* TS-**11** or TS-**11**′ cannot be ruled out. Therefore, to gain more insight into the reaction mechanism and to discriminate between the possible transition states, DFT calculations were conducted for the methyl addition to **1a** with **2b** using a catalytic amount of $ZnCl_2$ in THF. In general, solutions of Grignard reagents contain a variety of chemical molecules, such as MeMgCl, Me_2Mg, and $MgCl_2$, under the Schlenk equilibrium (eqn (4)).

$$2MeMgCl \rightleftharpoons Me_2Mg + MgCl_2 \tag{4}$$

Therefore, the formal reactant MeMgCl is a condensed representation of numerous mono-, di-, and polynuclear species that coexist in the Schlenk equilibrium. The crystal structure obtained by adding $ZnCl_2$ also suggests the formation of a more complex structure.[14] In addition, two mechanistic possibilities, *i.e.*, nucleophilic polar and radical mechanisms, have long been discussed (Fig. 3).[15] Although the mechanism of the Grignard addition reaction of nitriles is difficult to elucidate in detail, some theoretical studies on the mechanism of Grignard addition reactions of aldehydes and ketones have already been reported.[16–18] In computational studies on the Schlenk equilibrium, one of the pioneering studies on the Grignard reactions of carbonyl compounds with CH_3MgCl suggested that dinuclear species are more reactive than mononuclear species in a nucleophilic polar addition process.[17] In this regard, in the nucleophilic polar mechanism, the interaction between the vicinal Mg–CH_3 moiety and the C═O moiety, *i.e.*, a four-center interaction, facilitates the addition of the methyl group (Fig. 3a).

Moreover, in studies concerned with explicit solvent models,[18] molecular-dynamics simulations have shown that the Mg(II) centers of mono- and dinuclear species of CH_3MgCl can accommodate a variable number of solvent molecules in their first coordination spheres. In particular, for the Grignard addition reactions of aldehydes and ketones in THF, the possible pathways were examined on the basis of the Schlenk equilibrium for the mono- and dinuclear species, which showed that the conformational space including the explicit treatment of THF was important.[18] Indeed, THF molecules can effectively and flexibly bind to Mg(II) centers, thus stabilizing the nucleophilic polar pathway by compensating for the lack of chemical bonds on the Mg(II) centers. In addition, it has been noted that the radical reaction cannot occur unless a substrate with a low-lying π* (C═O) orbital, such as in fluorenone but not benzaldehyde, coordinates to the Mg(II) center.[18]

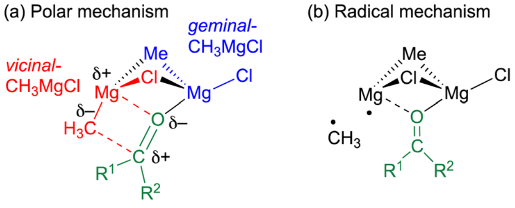
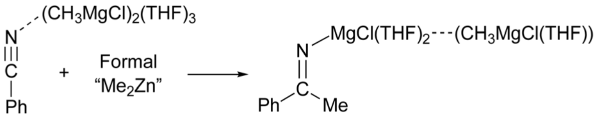


Fig. 3 Polar and radical mechanisms for the CH_3MgCl addition reaction of carbonyl compounds.

According to these previous studies,[16–18] we comprehensively examined in this study the $ZnCl_2$-catalyzed Grignard addition reaction between benzonitrile (**1a**) and CH_3MgCl (**2b**) explicitly including THF (eqn (5); for computational details, see Section 10 in the ESI†). Since the orbital energy of the π* orbital in benzonitrile (−1.25 eV) is slightly higher than that of benzaldehyde (−1.52 eV), the radical reaction pathway can be considered unlikely; instead, we focused on the nucleophilic polar mechanism.



(5)

Fig. 4 shows the reaction pathways examined for the model Grignard addition reaction of benzonitrile (**1a**) with mono- and dinuclear species of CH_3MgCl (**2b**). In complex **I**, the mononuclear Grignard species $CH_3MgCl(THF)_2$ is coordinated to **1a.** The methyl carbon atom in the Grignard species is 4.81 Å away from the nitrile carbon atom. A nucleophilic attack of the methyl carbon atom on the nitrile carbon atom would give the corresponding imine complex **V** *via* transition state **TS(I–V)** (Fig. S4†). The activation energy of **TS(I–V)** from **I** is relatively high (21.77 kcal mol^{-1}), although it is lower than that of the transition state without any THF molecules, *i.e.*, $\mathbf{TS(I–V)_0}$ (29.26 kcal mol^{-1}; Fig. S2†). This indicates that the coordination of THF to the Grignard reagent plays an important role in this reaction. The pathway *via* **TS(I–V)** corresponds to that *via* TS-**8** shown in Fig. 1a.

Next, we examined the reaction with dinuclear Grignard species in the presence of a large amount of Grignard reagents. Addition of one more $CH_3MgCl(THF)$ molecule to **I** gives a dinuclear reactant species with a bridged structure, *i.e.*, $\mathbf{II_g}$ ($\Delta G = -1.25$ kcal mol^{-1}) or $\mathbf{II_v}$ ($\Delta G = -0.93$ kcal mol^{-1}). In $\mathbf{II_g}$, two Mg(II) centers are bridged by one chloride ion and one THF molecule. The distance between the carbon atom in the geminal methyl group and the nitrile carbon atom is 3.76 Å, which is shorter than that in **I** (4.81 Å). This suggests that the geminal methyl group in $\mathbf{II_g}$ is more prone to attack the nitrile group than that in **I.** It should also be noted here that the ΔG of the transition state for the attack of the methyl group on the nitrile carbon to afford $\mathbf{VI_g}$, *i.e.*, $\mathbf{TS(II_g–VI_g)}$, is 16.75 kcal mol^{-1} (geminal pathway in Fig. 2), which is lower than that of **TS(I–V)**

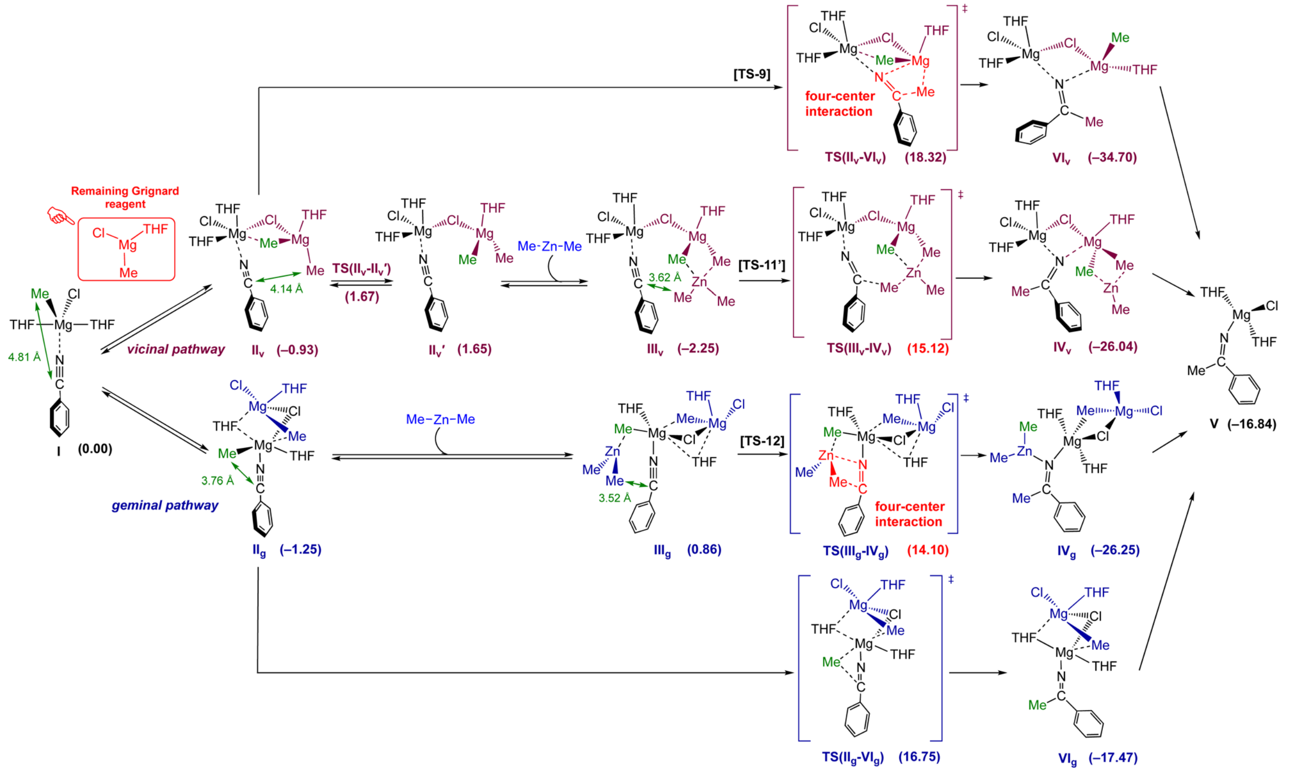


Fig. 4 Reaction pathways for the addition of a methyl group to **1a** with **2b** in the presence or absence of a catalytic amount of $ZnCl_2$ in THF. The Gibbs free energy values (ΔG; kcal mol^{-1}) are given relative to that of reactant I at 298.15 K and are shown in parentheses.

for the mononuclear Grignard species. Elimination of the unreacted Grignard species $CH_3MgCl(THF)$ from **VI$_g$** gives **V**. Meanwhile, in **II$_v$**, two Mg(II) centers are bridged by one chloride ion and one methyl group. The bridging methyl group in **II$_v$** could easily migrate to the other Mg(II) center *via* transition state **TS(II$_v$–II$_v'$)** ($\Delta G = 1.67$ kcal mol^{-1}) to give **II$_v'$** ($\Delta G = 1.65$ kcal mol^{-1}); thus, **II$_v$** and **II$_v'$** are in equilibrium. From **II$_v$**, the attack of the vicinal methyl group on the nitrile carbon atom would proceed *via* transition state **TS(II$_v$–VI$_v$)**, where the geminal methyl group transfers to the other Mg(II) center in parallel *via* a four-center interaction, to give **VI$_v$** (vicinal pathway in Fig. 2). The ΔG of **TS(II$_v$–VI$_v$)** is 18.32 kcal mol^{-1}, which is also lower than that of **TS(I–V)** for the mononuclear Grignard species. **TS(II$_v$–VI$_v$)** corresponds to TS-**9** in Fig. 1b. The results obtained using these dinuclear Mg(II) calculation models support the experimental results, indicating that a large amount of Grignard reagents facilitates the addition of the methyl group.

Next, we examined the reaction pathways of the Zn(II)-catalyzed system. Coordination of Me_2Zn to **II$_g$** or **II$_v'$** would give trimer complexes **III$_g$** ($\Delta G = 0.86$ kcal mol^{-1}) or **III$_v$** ($\Delta G = -2.25$ kcal mol^{-1}), respectively. In **III$_g$**, the Zn(II) center is coordinated to the geminal methyl group. The distance between the carbon atom in the methyl group of Me_2Zn and the nitrile carbon atom (3.52 Å) is even shorter than that of **II$_g$** (3.76 Å). The methyl group on the Zn(II) center could then attack the nitrile carbon atom *via* a transition state in which the Zn(II) center exhibits a trigonal-planar arrangement (**TS(III$_g$–IV$_g$)**), which corresponds to TS-**12** in Fig. 2, to give **IV$_g$** (geminal pathway in Fig. 4). In **TS(III$_g$–IV$_g$)**, a four-center interaction between the Zn–Me moiety and the C≡N bond is observed. The ΔG of **TS(III$_g$–IV$_g$)** (14.10 kcal mol^{-1}) is lower than that of **TS(II$_g$–VI$_g$)** (16.75 kcal mol^{-1}). In the pathway *via* **TS(III$_g$–IV$_g$)**, the methyl group bonded to the Mg(II) center migrates to the Zn(II) center in parallel with the attack of the methyl group. Subsequently, elimination of both Me_2Zn and $CH_3MgCl(THF)$ from **IV$_g$** would give **V**. In the case of **III$_v$**, the Zn(II) center is coordinated to the vicinal methyl group. The attack of the methyl group on the Zn(II) center on the nitrile carbon atom would afford **IV$_v$** *via* a transition state wherein the Zn(II) center adopts a tetrahedral arrangement (**TS(III$_v$–IV$_v$)**), which corresponds to TS-**11**′ in Fig. 2 (vicinal pathway in Fig. 4). The ΔG of **TS(III$_v$–IV$_v$)** (15.12 kcal mol^{-1}) is lower than that of **TS(II$_v$–VI$_v$)**. Since the last two pathways *via* **TS(III$_g$–IV$_g$)** or **TS(III$_v$–IV$_v$)** would correspond to the Zn(II)-catalyzed reaction using a large amount of Grignard reagents (TS-**11** in Fig. 1d and TS-**11**′ and TS-**12** in Fig. 2), the computational results strongly support that the Zn(II)-catalyzed system has higher reactivity than the noncatalytic version.

Conclusions

In summary, we have developed a $ZnCl_2$-catalyzed Grignard addition reaction of aromatic nitriles by virtue of the *in situ* generation of reactive zinc(II)ate species. The corresponding ketones and amines were successfully obtained *via* hydrolysis and reduction, respectively, in good yield under mild reaction conditions. A scale-up reaction of a ketone and sequential tertiary alcohol synthesis were also demonstrated by taking advantage of the this $ZnCl_2$ catalysis. Furthermore, computational DFT calculations were performed to propose plausible reaction mechanisms and transition states in order to investigate the origin of the higher efficiency of a catalytic amount of $ZnCl_2$ compared to the use of a stoichiometric amount of zinc(II)ates.

Data availability

All data associated with this article are available from ESI.†

Author contributions

M. Hatano conceived and directed the project and designed the experiments. M. Hatano, K. Kuwano, R. Asukai, A. Nagayoshi, H. Hoshihara, and T. Hirata performed the experimental studies and analyzed the results. M. Umezawa, S. Tsubaki, T. Yoshikawa, and K. Sakata performed the DFT calculations. M. Hatano, T. Yoshikawa, and K. Sakata prepared the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Financial support was partially provided by JSPS KAKENHI grant JP20H02735 and JP24K08419 (to M. H.). Some of the calculations were performed using resources of the Research Center for Computational Science, Okazaki, Japan (Project: 23-IMS-C047).

Notes and references

1 (*a*) Z. Rappoport, *The chemistry of the cyano group*, John Wiley & Sons, London, 1970; (*b*) A. J. Fatiadi, *Preparation and Synthetic Applications of Cyano Compounds*, ed. S. Patai and Z. Rappoport, Wiley-VCH, New York, 1983; (*c*) R. C. Larock, *Comprehensive Organic Transformations: A Guide to Functional Group Preparations*, Wiley-VCH, Weinheim, 1999, pp. 1621–1927; (*d*) P. Pollak, *Nitriles. Ullmann's Encyclopedia of Industrial Chemistry*, Wiley-VCH, Weinheim, 2000; (*e*) G. Yan, Y. Zhang and J. Wang, *Adv. Synth. Catal.*, 2017, **359**, 4068–4105.

2 For selected textbooks on organolithium(I) reagents, see:(*a*) B. J. Wakefield, *The Chemistry of Organolithium Compounds*, Pergamon Press, Oxford, 1974; (*b*) J. Clayden, *Organolithiums: Selectivity for Synthesis*, Pergamon, Oxford, 2002; (*c*) Z. Z. Rappoport and I. Marek, *The Chemistry of Organolithium Compounds: R-Li (Patai's Chemistry of Functional Groups)*, Wiley-VCH, Weinheim, 2004; (*d*) Z. Z. Rappoport and I. Marek, *The Chemistry of Organolithium Compounds: R-Li (Patai's Chemistry of Functional Groups)*, Wiley-VCH, Weinheim, 2006, vol. 2.

3 For selected reviews and textbooks on Grignard reagents, see:(*a*) Y.-H. Lai, *Synthesis*, 1981, 585–604; (*b*) B. J. Wakefield, *Organomagnesium Methods in Organic Chemistry*, Academic Press, San Diego, 1995; (*c*) G. S. Silverman and P. E. Rakita, *Handbook of Grignard Reagents*, Marcel Dekker, New York, 1996; (*d*) H. G. Richey Jr, *Grignard Reagents: New Development*, Wiley, Chichester, 2000; (*e*) P. Knochel, *Handbook of Functionalized Organometallics*, Wiley-VCH, Weinheim, 2005; (*f*) H. Yorimitsu, in *Science of Synthesis, Knowledge Updates (2011)*, George Thieme, Stuttgart, 2010, ch. 7.6.5.6, pp. 1–9; (*g*) H. Yorimitsu, in *Science of Synthesis, Knowledge Updates (2011)*, George Thieme, Stuttgart, 2010, ch. 7.6.10.9, pp. 11–19.

4 (*a*) L. S. Cook and B. J. Wakefield, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2392–2397; (*b*) F. J. Weiberth and S. S. Hall, *J. Org. Chem.*, 1986, **51**, 5338–5341.

5 (*a*) F. J. Weiberth and S. S. Hall, *J. Org. Chem.*, 1987, **52**, 3901–3904; (*b*) M. Ortiz-Marciales, L. M. Tirado, R. Colón, M. L. Ufret, R. Figueroa, M. Lebrón, M. DeJesús, J. Martínez and T. Malavé, *Synth. Commun.*, 1998, **28**, 4067–4075.

6 For the addition of RLi under solvent-free conditions, see: D. Elorriaga, F. Carrillo-Hermosilla, B. Parra-Cadenas, A. Antiñolo and J. García-Álvarez, *ChemSusChem*, 2022, **15**, e202201348.

7 For the addition of RLi in water and glycerol, see:(*a*) G. Dilauro, M. Dell'Aera, P. Vitale, V. Capriati and F. M. Perna, *Angew. Chem., Int. Ed.*, 2017, **56**, 10200–10203; (*b*) M. J. Rodríguez-Álvarez, J. García-Álvarez, M. Uzelac, M. Fairley, C. T. O'Hara and E. Hevia, *Chem.–Eur. J.*, 2018, **24**, 1720–1725.

8 For the addition of *n*-BuMgBr in 2-methyltetrahydrofuran, see: W. Zhong, Y. Wu and X. Zhang, *J. Chem. Res.*, 2009, **2009**, 370–373.

9 We have already reported the catalytic and stoichiometric use of $ZnCl_2$ with Grignard reagents for carbonyl compounds; for details, see:(*a*) M. Hatano, S. Suzuki and K. Ishihara, *J. Am. Chem. Soc.*, 2006, **128**, 9998–9999; (*b*) M. Hatano, S. Suzuki and K. Ishihara, *Synlett*, 2010, **2010**, 321–324; (*c*) M. Hatano, O. Ito, S. Suzuki and K. Ishihara, *Chem. Commun.*, 2010, **46**, 2674–2676; (*d*) M. Hatano, O. Ito, S. Suzuki and K. Ishihara, *J. Org. Chem.*, 2010, **75**, 5008–5016; (*e*) M. Hatano, K. Yamashita, M. Mizuno, O. Ito and K. Ishihara, *Angew. Chem., Int. Ed.*, 2015, **54**, 2707–2711; (*f*) M. Hatano, K. Yamashita and K. Ishihara, *Org. Lett.*, 2015, **17**, 2412–2415; (*g*) M. Hatano, M. Mizuno and K. Ishihara, *Org. Lett.*, 2016, **18**, 4462–4465.

10 Lanthanide halides are known as good additives in the Grignard addition reaction of ketones; for details, see:(*a*) T. Imamoto, N. Takiyama, K. Nakamura, T. Hatajima and Y. Kamiya, *J. Am. Chem. Soc.*, 1989, **111**, 4392–4398; (*b*) A. Krasovskiy, F. Kopp and P. Knochel, *Angew. Chem., Int. Ed.*, 2006, **45**, 497–500.

11 A $ZnCl_2$(tmeda)-catalyzed nucleophilic substitution reaction of chlorosilanes with RMgX has been reported by Oshima and coworkers; for details, see: K. Murakami, H. Yorimitsu and K. Oshima, *J. Org. Chem.*, 2009, **74**, 1415–1417.

12 The product yield for the noncatalyzed reactions of heteroaryl nitriles **1k** and **1l** with **2j** was relatively high, probably due to the presence of directing *O*- or *N*-moieties at the *ortho*-position, similar to the phenomena as seen in the reaction of **1h** (see eqn (1)).

13 (*a*) P. Knochel, W. Dohle, N. Gommermann, F. F. Kneisel, F. Kopp, T. Korn, I. Sapountzis and V. A. Vu, *Angew. Chem., Int. Ed.*, 2003, **42**, 4302–4320; (*b*) H. Shinokubo and K. Oshima, *Eur. J. Org Chem.*, 2004, **2004**, 2081–2091.

14 Since $ZnCl_2$ should be smoothly converted to anionic zinc(II) ates *in situ*, the corresponding Zn(II)-function as Lewis acid catalysts to activate the nitrile moiety can be reasonably excluded. D. R. Armstrong, W. Clegg, P. García-Alvarez, M. D. McCall, L. Nuttall, A. R. Kennedy, L. Russo and E. Hevia, *Chem.–Eur. J.*, 2011, **17**, 4470–4479.

15 (*a*) E. C. Ashby, *Pure Appl. Chem.*, 1980, **52**, 545–569; (*b*) E. C. Ashby and W. E. Becker, *J. Am. Chem. Soc.*, 1963, **85**, 118–119; (*c*) K. Maruyama and T. Katagiri, *J. Am. Chem. Soc.*, 1986, **108**, 6263–6270; (*d*) T. Holm, *Acta Chem. Scand.*, 1966, **20**, 2821–2828; (*e*) S. G. Smith and G. Su, *J. Am. Chem. Soc.*, 1964, **86**, 2750–2751; (*f*) E. C. Ashby, J. Laemmle and H. M. Newmann, *Acc. Chem. Res.*, 1974, **7**, 272–280; (*g*) H. Yamataka, T. Matsuyama and T. Hanafusa, *J. Am. Chem. Soc.*, 1989, **111**, 4912–4918.

16 M. Uchiyama, S. Nakamura, T. Ohwada, M. Nakamura and E. Nakamura, *J. Am. Chem. Soc.*, 2004, **126**, 10897–10903.

17 (*a*) S. Yamazaki and S. Yamabe, *J. Org. Chem.*, 2002, **67**, 9346–9353; (*b*) T. Mori and S. Kato, *J. Phys. Chem. A*, 2009, **113**, 6158–6165.

18 (*a*) R. M. Peltzer, O. Eisenstein, A. Nova and M. Cascella, *J. Phys. Chem. B*, 2017, **121**, 4226–4237; (*b*) R. M. Peltzer, J. Gauss, O. Eisenstein and M. Cascella, *J. Am. Chem. Soc.*, 2020, **142**, 2984–2994.