Synthetic Methods

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# C-Selective and Diastereoselective Alkyl Addition to β,γ-Alkynyl-α-imino Esters with Zinc(II)ate Complexes**

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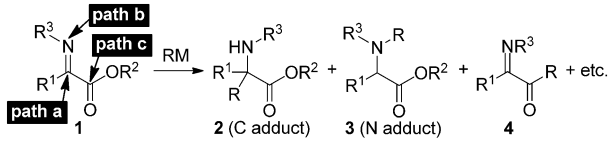
***Abstract:*** *Since umpolung α-imino esters contain three electrophilic centers, regioselective alkyl addition with traditional organometallic reagents has been a serious problem in the practical synthesis of versatile chiral α-amino acid derivatives. An unusual C-alkyl addition to α-imino esters using a Grignard reagent (RMgX)-derived zinc(II)ate was developed. Zinc(II)ate complexes consist of a Lewis acidic $[MgX]^+$ moiety, a nucleophilic $[R_3Zn]^-$ moiety, and 2 $[MgX_2]$. Therefore, the ionically separated $[R_3Zn]^-$ selectively attacks the imino carbon atom ,which is most strongly activated by chelation of $[MgX]^+$. In particular, chiral β,γ-alkynyl-α-imino esters can strongly promote highly regio- and diastereoselective C-alkylation because of structural considerations, and the corresponding optically active α-quaternary amino acid derivatives are obtained within 5 minutes in high to excellent yields.*

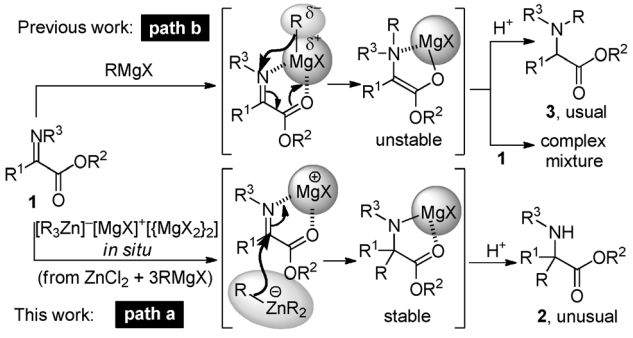
Alkyl addition to α-imino esters (**1**) with organometallic reagents (RM) is one of the most straightforward methodologies for synthesizing versatile N-substituted α-amino-acid derivatives (**2** and **3**; Scheme 1).[1] However, regioselective alkyl addition to **1** is problematic, since these conjugated umpolung compounds can react with organometallic reagents at three possible electrophilic centers: the imino carbon atom (path a to give **2**), imino nitrogen atom (path b to give **3**), and carbonyl carbon atom (path c to give **4**).[2] Usually, regioselectivity (paths a–c) depends on both the substrates and alkylating reagents, and the desired product is often obtained as part of a complex mixture.[3–5] Moreover, purification is laborious, since the obtained compounds often have similar chemical properties.




***Scheme 1.*** Alkyl addition to α-imino esters with organometallic reagents.

In a pioneering work, Kagan reported that Et-, Pr-, *i*Bu-, and $PhCH_2MgX$ react at the imino nitrogen atom (path b; Scheme 1), whereas *t*Bu- and allylMgX unusually react at the imino carbon atom (path a).[3a,b] Later, Yamamoto et al. investigated the addition of $ZnBr_2$, $Et_3Al$, $Ti(OiPr)_3Cl$, and $B(OMe)_3$ to $PhCH_2MgX$ and allylMgX to control the regioselectivity of these additions (paths a and b).[6c–e] Moreover, in a remarkable advance in this field, Niwa and Shimizu reported a tandem N-ethyl addition/oxidation/C-allyl addition (path b) to deliver N-PMP-α-ketimino esters (PMP = 4-$MeOC_6H_4$) using $Et_2AlCl/EtAlCl_2$, benzoyl peroxide, and allylbutyltin.[7] Later, Kozlowski and co-workers also reported a tandem reaction system (path b) with some electrophiles.[8] In sharp contrast, a practical and general methodology for the unusual C-alkyl addition to α-imino-esters (i.e., path a) has not yet been well-established. In particular, since a variety of Grignard reagents are commercially available or can be readily prepared in both the laboratory and industry,[9] a method for the highly regioselective C-alkyl addition to **1** with Grignard reagents is desired.

In this context, we envisioned that zinc(II)ate reagents ($[R_3Zn]^-[MgX]^+[\{MgX_2\}_2]$),[10–12] which are prepared in situ from Grignard reagents (RMgX) and $ZnCl_2$, would be highly attractive for use in a path a reaction (Scheme 2). The selective C-alkyl addition with zinc(II)ate reagents would be expected to offer both the increased nucleophilicity of an anionic $[R_3Zn]^-$ moiety and the increased Lewis acidity of a cationic $[MgX]^+$ moiety. While a chelated Grignard reagent with **1** would be unlikely to attack the most activated imino carbon atom beyond the adjacent imino nitrogen atom, an ionically separated zincate might attack the most activated imino carbon atom. Even though two or more molecules of the Grignard reagent compete, the hard and soft acids and




***Scheme 2.*** Regioselective alkyl addition at the imino nitrogen atom (path b) versus imino carbon atom (path a).

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bases (HSAB) concept might support the assumption. After the formation of a five-membered metallacycle resulting from N,O chelation with one RMgX, another molecule of soft RMgX or even $[RMgX_2]^-$ [12k] in Schlenk's equilibrium cannot easily attack the mismatched hard imino carbon atom.[2]

At the beginning of this study, we examined the addition of EtMgCl (3.3 equiv) to the α-aldimino ester **5a** and α-ketimino ester **5b** in either the presence or absence of $ZnCl_2$ (1.1 equiv) in THF (Table 1). For highly reactive **5a**, the reaction went to completion at −78 °C within 5 minutes, and the unusual ethyl (at C) adduct **6a** was successfully obtained in 94% yield in the presence of $ZnCl_2$ (entry 2), while the ethyl (at N) adduct **7a** was obtained in 95% yield in the absence of $ZnCl_2$, as reported by the groups of Shimizu[7] and Kozlowski[8] (entry 1). However, when the much less reactive **5b** was used, the reaction was very sluggish even with the use of $ZnCl_2$ at 0 °C, and the desired **6b** was obtained in 44% yield after 20 hours (entry 4).[13] During the course of our study, Shimizu and co-workers reported that N-PMP-protected β,γ-alkynyl-α-imino esters were effective for tandem N-alkyl addition/C acylation to give α-quaternary alkynyl amino esters.[14] Inspired by this timely report, we found that the β,γ-alkynyl-α-imino ester **5c** was much more reactive than **5b**.[15] As a result, the desired **6c** was obtained in 97% yield at −78 °C within 5 minutes when EtMgCl and $ZnCl_2$ were used (entry 6). Moreover, the $ZnCl_2$ method was effective with the less reactive *i*PrMgCl, and the corresponding and unusual adduct **6d** was obtained in 95% yield within 30 minutes (entry 8). In contrast, the reaction of **5c** with *i*PrMgCl in the absence of $ZnCl_2$ was slow, and the regioselectivity was low (entry 7). A 3:1 ratio of a Grignard reagent and $ZnCl_2$ is important to give the separated ion-pair zinc(II)ate complex $[iPr_3Zn]^-[MgCl]^+[\{MgCl_2\}_2]$, and the use of *i*PrMgCl (3.3 equiv) and $ZnCl_2$ (3.3 equiv), which would give the contact ion-pair reagent *i*PrZnCl·$MgCl_2$, was not effective (entry 9).[12f–j]

In general, α-ketimino esters are much less reactive than α-aldimino esters in terms of steric and electronic factors. To confirm the unexpectedly high reactivity of **5c**, we clarified the structural considerations for the first time by X-ray analysis of **5a–c** (Figure 1). As a result we found that, **5a** and

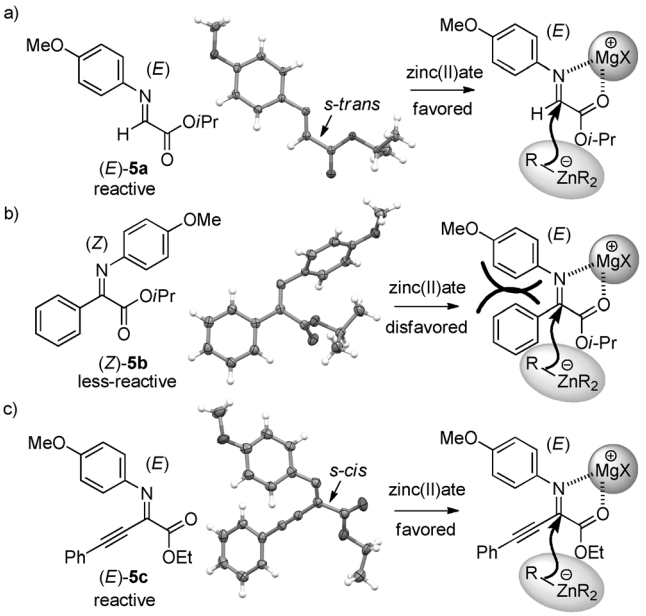
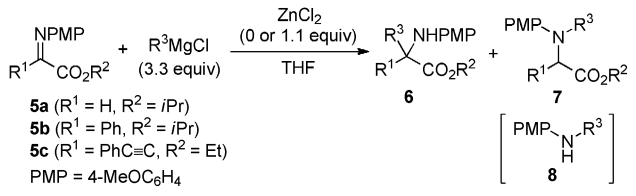



***Figure 1.*** X-ray analysis of α-imino esters and the postulated complexation with zinc(II)ate complex.

**5c** prefer an *E* geometry, while the much less-reactive **5b** prefers a *Z* geometry. The minimal steric constraints imposed by H or PhC≡C on the imino carbon atom of either **5a** or **5c** might be crucial for the *E* geometry, since these substituents would avoid the steric repulsion with PMP in the *E* geometry. Moreover, $^1H$ and $^{13}C$ NMR analyses of **5a–c** in $CDCl_3$ showed that each compound has either a pure *E* or *Z* geometry, and that the observed geometry is quite stable; there is no interconversion between the *E* and *Z* isomers even at room temperature. Preliminary DFT calculations (B3LYP/6-31G*) also supported a difference in the energy profiles of the *E* and *Z* isomers, and *s* rotation of N=C–C=O would be much easier than *E* to *Z* isomerization (see the Supporting Information). Overall, both (*E*)-**5a** and (*E*)-**5c** with *s-cis*- or *s-trans*-N=C–C=O might be suitable for $[MgX]^+$ chelation, as we show in Figure 1a and c.

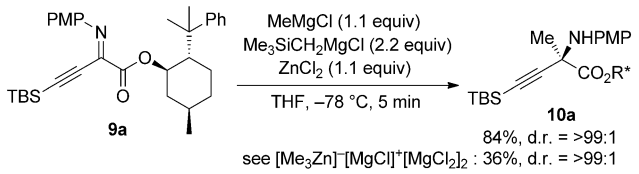
By taking advantage of the high reactivity and regioselectivity of zinc(II)ate reagents for **5c**, we next examined the diastereoselective methyl addition to the chiral 8-phenylmenthyl (R*) ester **9a** (Scheme 3).[6] However, the desired C-methyl addition to **9a** did not proceed selectively. Instead, N-methylation-derived compounds were obtained in considerable yields (>40%) along with the desired **10a** (36%). To overcome this problem, we next used more reactive mixed zinc(II)ate complexes $[R(Me_3SiCH_2)_2Zn]^-[MgX]^+[\{MgX_2\}_2]$, which we had previously developed,[11c,d] and **10a** was

***Table 1:*** Alkyl addition to α-imino esters.[a]

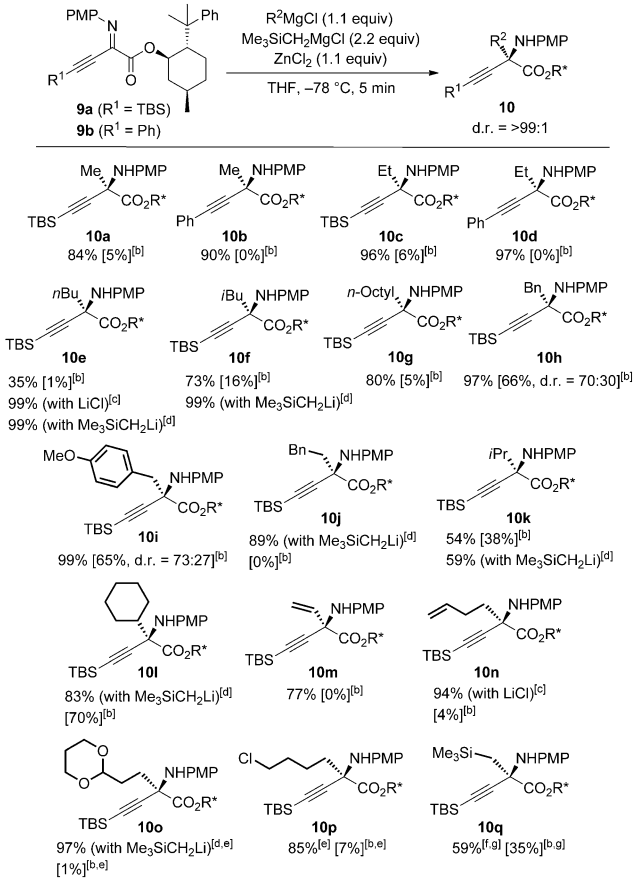



| Entry | 5 | Reagents | *T* [°C] | Time | 6/7/8 | Yield [%][b] 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|
| 1 | **5a** | EtMgCl | −78 | 5 min | **6a:7a:8a** | 0 | 95 | 0 |
| 2 | **5a** | EtMgCl + $ZnCl_2$ | −78 | 5 min | **6a:7a:8a** | 94 | 0 | 0 |
| 3 | **5b** | EtMgCl | 0 | 20 h | **6b:7b:8b** | 9 | 0 | 52 |
| 4 | **5b** | EtMgCl + $ZnCl_2$ | 0 | 20 h | **6b:7b:8b** | 44 | 0 | 6 |
| 5 | **5c** | EtMgCl | −78 | 5 min | **6c:7c:8c** | 8 | 0 | 71 |
| 6 | **5c** | EtMgCl + $ZnCl_2$ | −78 | 5 min | **6c:7c:8c** | 97 | 0 | 0 |
| 7 | **5c** | *i*PrMgCl | −78 | 30 min | **6d:7d:8d** | 35 | 0 | 27 |
| 8 | **5c** | *i*PrMgCl + $ZnCl_2$ | −78 | 30 min | **6d:7d:8d** | 95 | 0 | 0 |
| 9 | **5c** | *i*PrMgCl + $ZnCl_2$[c] | −78 | 30 min | **6d:7d:8d** | 9 | 0 | 46 |

[a] Unless otherwise noted, the reaction was conducted with the use of Grignard reagent (3.3 equiv) without $ZnCl_2$ or Grignard reagent (3.3 equiv) with $ZnCl_2$ (1.1 equiv) in THF. [b] Yields of isolated products. [c] *i*PrZnCl, which was prepared in situ from *i*PrMgCl (3.3 equiv) and $ZnCl_2$ (3.3 equiv), was used. THF = tetrahydrofuran.




***Scheme 3.*** Diastereoselective methyl addition (R* = 8-Ph-menthyl). PMP = *p*-methoxyphenyl.




***Scheme 4.*** Regio- and diastereoselective alkyl addition to chiral α-ketimino esters.[a] [a] Unless otherwise noted, the reaction was conducted with the use of Grignard reagent (1.1 equiv), $ZnCl_2$ (1.1 equiv), and $Me_3SiCH_2MgCl$ (2.2 equiv) in THF at −78 °C for 5 min (standard conditions). Yields of the isolated products are shown. [b] Yields of the isolated product are shown within brackets for reactions using the Grignard reagent (3.3 equiv) at −78 °C for 5 min. [c] LiCl (1.1 equiv) was added under standard reaction conditions. [d] $Me_3SiCH_2Li$ (2.2 equiv) was used in place of $Me_3SiCH_2MgCl$. [e] Grignard reagent (RMgBr) was prepared from Mg turnings and alkylbromide in advance. [f] $Me_3SiCH_2MgCl$ (3.3 equiv) and $ZnCl_2$ (1.1 equiv) were used. [g] The temperature was gradually increased from −78 °C to 0 °C over 4 h. R* = chiral 8-phenylmenthyl, TBS = *tert*-butyldimethylsilyl.

obtained in 84% yield with the use of MeMgCl, $Me_3SiCH_2MgCl$, and $ZnCl_2$.

We next investigated the scope of Grignard reagents for **9a** and **9b** (Scheme 4). Simple Grignard reagents with primary alkyl chains such as methyl, ethyl, *n*-butyl, isobutyl, *n*-octyl, benzyl, *p*-methoxybenzyl, and phenethyl magnesium chlorides could be used successfully, and the corresponding desired products (**10a–j**) were obtained in high to excellent yields (80–99%) within 5 minutes. In some cases, the cation effect of lithium(I) salts[11c,d] was effective for improving the reactivity and regioselectivity (i.e., C addition versus N addition). For example, the use of *n*BuMgCl/$Me_3SiCH_2MgCl$/$ZnCl_2$ gave **10e** in 35% yield, while the addition of LiCl (1.1 equiv) or the use of $Me_3SiCH_2Li$[11c,d] in place of $Me_3SiCH_2MgCl$ greatly improved the yield (99%) of **10e**. Grignard reagents with secondary alkyl chains such as isopropyl and cyclohexyl magnesium chlorides could be used, and the corresponding C adducts (**10k** and **10l**) were obtained in good yields (54–83%). Moreover, some ω-functionalized alkyl chains with olefin, acetal, chlorine, and trimethylsilyl could successfully transfer to **9a**, and the corresponding and unusual C adducts (**10m–q**) were exclusively obtained. It was noted that whenever zinc(II)ate complexes were used, perfect diastereoselectivities (> 99:1) were observed.[16] The excellent diastereoselectivity of the C-alkyl addition products can be understood in terms of the well-known paradigms.[6] The bulky chiral 8-phenylmenthyl group would shield the *re*-face and promote the attack of the *si*-face exclusively (Figure 2).

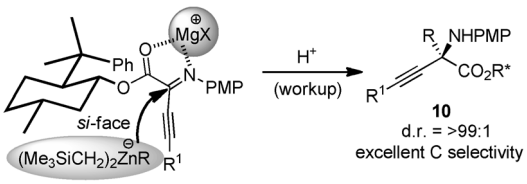
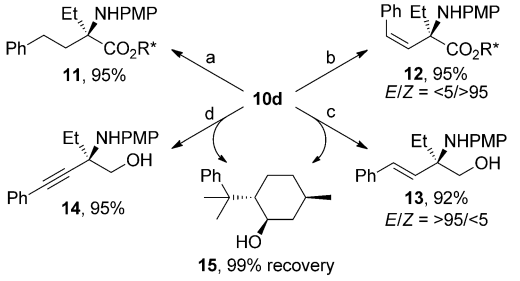



***Figure 2.*** Possible mechanism (R* = 8-Ph-menthyl).

To demonstrate the synthetic utility of the products, **10d** was reduced under typical reaction conditions (Scheme 5). Palladium on charcoal facilitated the selective hydrogenation of phenylacetylene to the phenethyl compound **11** in 95% yield. The *Z*-olefin **12** was selectively obtained in 95% yield by hydrogenation with Lindlar's catalyst, while the *E*-olefin **13** was selectively obtained in 92% yield with the use of sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) in THF at 60 °C. Moreover, the treatment of **10d** with lithium aluminum hydride in THF at 0 °C gave the β-alkynyl-β-amino alcohol **14**

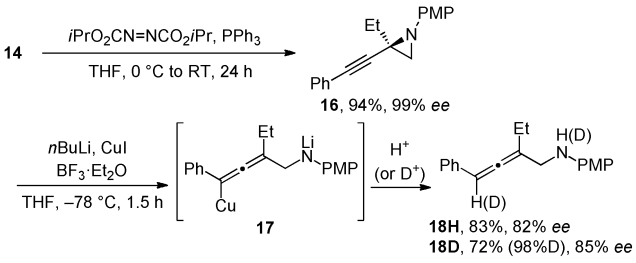



***Scheme 5.*** Transformation of alkyne and recovery of chiral auxiliary (R*OH, R* = 8-Ph-menthyl). Reaction conditions: a) $H_2$, 10 wt% Pd/C, MeOH, RT, 1 h; b) $H_2$, $Pd/CaCO_3/Pb(OAc)_2$, EtOH, RT, 1 h; c) Red-Al, THF, 0 °C to 60 °C, 12 h; d) $LiAlH_4$, THF, 0 °C, 2.5 h.

in 95% yield. The chiral 8-phenylmenthol **15** (R*OH) was recovered quantitatively with the generation of the optically pure alcohol **13** or **14**. For other useful transformations of **10c** into the optically pure oxazolidinones, see the Supporting Information.

Since optically pure aziridines are often important intermediates, particularly in pharmaceuticals, **14** was transformed into the 2-alkynyl aziridine **16** by the Mitsunobu reaction (Scheme 6). Furthermore, we found that a stereoselective




***Scheme 6.*** Transformation of **14** into the optically active 2-alkynyl aziridine **16** and trisubstituted allene **18**.

allene formation proceeded by ring-opening reduction, instead of the expected $S_N2'$ alkyl substitution, with the use of a Gilman-type cuprate[17] and the trisubstituted allene [H]-**18** was obtained in 83% yield with 82% *ee* after the protonation of **17**. The deuterated product [D]-**18**, which was obtained by $CD_3CO_2D$ work-up with 98% D content, supported the mechanism proposed by Alexakis et al. for the reductive metalation of propargylic epoxides with cuprates.[18]

In summary, we have developed an unusual C-selective alkyl addition to α-imino esters with Grignard-reagent-derived zinc(II)ate reagents. In particular, with the use of chiral (*E*)-β,γ-alkynyl-α-imino esters (**9**), highly regio- and diastereoselective C-alkyl addition successfully proceeded at −78°C within 5 minutes. Moreover, synthetically useful optically active compounds, such as *E* and *Z* olefins, amino alcohol, aziridine, allene, and oxazolidinones, were provided in high yields with the full recovery of (−)-8-Ph-menthol as a chiral auxiliary. Overall, this fundamental method will provide access to optically pure α,α-disubstituted α-quaternary amino acid derivatives.

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[1] For selected reviews on α-amino acid synthesis: a) R. O. Duthaler, *Tetrahedron* **1994**, *50*, 1539; b) C. Cativiela, M. D. Díaz-de-Villegas, *Tetrahedron: Asymmetry* **1998**, *9*, 3517; c) K. Maruoka, T. Ooi, *Chem. Rev.* **2003**, *103*, 3013; d) C. Nájera, J. M. Sansano, *Chem. Rev.* **2007**, *107*, 4584.

[2] For selected reviews and accounts: a) J. S. Dickstein, M. C. Kozlowski, *Chem. Soc. Rev.* **2008**, *37*, 1166; b) M. Shimizu, I. Hachiya, I. Mizota, *Chem. Commun.* **2009**, 874; c) K. Koyama, I. Mizata, M. Shimizu, *Pure Appl. Chem.* **2014**, *86*, 755.

[3] With Grignard reagents: a) J.-C. Fiaud, H. B. Kagan, *Tetrahedron Lett.* **1970**, *11*, 1813; b) J.-C. Fiaud, H. B. Kagan, *Tetrahedron Lett.* **1971**, *12*, 1019; c) P. Münster, W. Steglich, *Synthesis* **1987**, 223; d) P. Ermert, J. Meyer, C. Stucki, J. Schneebeli, J.-P. Obrecht, *Tetrahedron Lett.* **1988**, *29*, 1265; e) L. M. Harwood, K. J. Vines, M. G. B. Drew, *Synlett* **1996**, 1051; f) S.-E. Yoo, Y.-D. Gong, *Heterocycles* **1997**, *45*, 1251; g) Y. Niwa, K. Takayama, M. Shimizu, *Tetrahedron Lett.* **2001**, *42*, 5473; h) P. Calí, M. Begtrup, *Synthesis* **2002**, 63.

[4] With organozinc(II) reagents: a) M. R. P. van Vliet, J. T. B. H. Jastrzebski, W. J. Klaver, K. Goubitz, G. van Koten, *Recl. Trav. Chim. Pays-Bas* **1987**, *106*, 132; b) G. Courtois, L. Miginiac, *J. Organomet. Chem.* **1989**, *376*, 235; c) M. P. Bertrand, L. Feray, R. Nouguier, P. Perfetti, *Synlett* **1999**, 1148; d) K. P. Chiev, S. Roland, P. Mangeney, *Tetrahedron: Asymmetry* **2002**, *13*, 2205; e) S. Basra, M. W. Fennie, M. C. Kozlowski, *Org. Lett.* **2006**, *8*, 2659; f) M. Mitani, Y. Tanaka, A. Sawada, A. Misu, Y. Matsumoto, *Eur. J. Org. Chem.* **2008**, 1383; g) L. Lin, X. Fu, X. Ma, J. Zhang, R. Wang, *Synlett* **2012**, 2559; h) Y. Mizutani, H. Tanimoto, T. Morimoto, Y. Nishiyama, K. Kakiuchi, *Tetrahedron Lett.* **2012**, *53*, 5903.

[5] With organoaluminum(II) reagents: a) M. Shimizu, Y. Niwa, *Tetrahedron Lett.* **2001**, *42*, 2829; b) M. Shimizu, Y. Niwa, T. Nagai, I. Hachiya, *Heterocycles* **2007**, *72*, 127; c) M. Shimizu, H. Itou, M. Miura, *J. Am. Chem. Soc.* **2005**, *127*, 3296; d) M. Shimizu, H. Itou, T. Iwao, Y. Umeda, *Chem. Lett.* **2009**, *38*, 732; e) S. Hata, H. Koyama, M. Shimizu, *J. Org. Chem.* **2011**, *76*, 9670; f) M. Shimizu, D. Kurita, I. Mizota, *Asian J. Org. Chem.* **2013**, *2*, 208.

[6] a) E. J. Corey, H. E. Ensley, *J. Am. Chem. Soc.* **1975**, *97*, 6908; b) W. Oppolzer, M. Kurth, D. Reichlin, C. Chapuis, M. Mohnhaupt, F. Moffatt, *Helv. Chim. Acta* **1981**, *64*, 2802; c) Y. Yamamoto, W. Ito, K. Maruyama, *J. Chem. Soc. Chem. Commun.* **1985**, 1131; d) Y. Yamamoto, S. Nishii, K. Maruyama, T. Komatsu, W. Ito, *J. Am. Chem. Soc.* **1986**, *108*, 7778; e) Y. Yamamoto, W. Ito, *Tetrahedron* **1988**, *44*, 5415.

[7] Y. Niwa, M. Shimizu, *J. Am. Chem. Soc.* **2003**, *125*, 3720.

[8] a) J. S. Dickstein, M. W. Fennie, A. L. Norman, B. J. Paulose, M. C. Kozlowski, *J. Am. Chem. Soc.* **2008**, *130*, 15794; b) J. M. Curto, J. S. Dickstein, S. Berritt, M. C. Kozlowski, *Org. Lett.* **2014**, *16*, 1948; c) J. M. Curto, M. C. Kozlowski, *J. Org. Chem.* **2014**, *79*, 5359.

[9] Excellent textbooks for Grignard reagents: a) B. J. Wakefield, *Organomagnesium Methods in Organic Chemistry*, Academic Press, San Diego, CA, **1995**; b) G. S. Silverman, P. E. Rakita, *Handbook of Grignard Reagents*, Marcel Dekker, New York, **1996**; c) H. G. Richey, Jr., *Grignard Reagents: New Development*, Wiley, Chichester, **2000**; d) P. Knochel, *Handbook of Functionalized Organometallics*, Wiley-VCH, Weinheim, **2005**.

[10] a) M. Uchiyama, C. Wang, *Top. Organomet. Chem.* **2014**, *47*, 159; b) F. Mongin, A. Harrison-Marchand, *Chem. Rev.* **2013**, *113*, 7563.

[11] We have reported the catalytic and stoichiometric use of $ZnCl_2$ with Grignard reagents for alkyl addition to ketones: a) M. Hatano, S. Suzuki, K. Ishihara, *J. Am. Chem. Soc.* **2006**, *128*, 9998; b) M. Hatano, S. Suzuki, K. Ishihara, *Synlett* **2010**, 321; c) M. Hatano, O. Ito, S. Suzuki, K. Ishihara, *Chem. Commun.* **2010**, *46*, 2674; d) M. Hatano, O. Ito, S. Suzuki, K. Ishihara, *J. Org. Chem.* **2010**, *75*, 5008.

[12] Zinc(II)ate reagents in recent organic synthesis reports: a) T. Harada, T. Katsuhira, A. Osada, K. Iwazaki, K. Maejima, A. Oku, *J. Am. Chem. Soc.* **1996**, *118*, 11377; b) M. Uchiyama, S. Furumoto, M. Saito, Y. Kondo, T. Sakamoto, *J. Am. Chem. Soc.* **1997**, *119*, 11425; c) M. Uchiyama, M. Kameda, O. Mishima, N. Yokoyama, M. Koike, Y. Kondo, T. Sakamoto, *J. Am. Chem. Soc.*

  

**1998**, *120*, 4934; d) M. Uchiyama, S. Nakamura, T. Ohwada, M. Nakamura, E. Nakamura, *J. Am. Chem. Soc.* **2004**, *126*, 10897; e) K. Murakami, H. Yorimitsu, K. Oshima, *J. Org. Chem.* **2009**, *74*, 1415; f) E. Hevia, J. Z. Chua, P. García-Álvarez, A. R. Kennedy, M. D. McCall, *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 5294; g) D. R. Armstrong, W. Clegg, P. García-Alvarez, M. D. McCall, L. Nuttall, A. R. Kennedy, L. Russo, E. Hevia, *Chem. Eur. J.* **2011**, *17*, 4470; h) D. R. Armstrong, W. Clegg, P. García-Álvarez, A. R. Kennedy, M. D. McCall, L. Russo, E. Hevia, *Chem. Eur. J.* **2011**, *17*, 8333; i) C. Vidal, J. García-Álvarez, A. Hernán-Gómez, A. R. Kennedy, E. Hevia, *Angew. Chem. Int. Ed.* **2014**, *53*, 5969; *Angew. Chem.* **2014**, *126*, 6079; j) T. D. Bluemke, W. Clegg, P. García-Alvarez, A. R. Kennedy, K. Koszinowski, M. D. McCall, L. Russo, E. Hevia, *Chem. Sci.* **2014**, *5*, 3552. For the related constitution of Grignard reagent also see: k) S. Sakamoto, T. Imamoto, K. Yamaguchi, *Org. Lett.* **2001**, *3*, 1793.

[13] The expected N-alkyl adducts **7b–d** were not obtained since they are unstable under acidic workup conditions, and fully decomposed to **8b–d**.

[14] I. Mizota, Y. Matsuda, S. Kamimura, H. Tanaka, M. Shimizu, *Org. Lett.* **2013**, *15*, 4206.

[15] Preliminary results with some *n*BuMX for **9a** are shown in the Supporting Information.

[16] Unfortunately, the present method for alkynyl and aryl additions gives rise to a complex mixture. Further investigation is now in progress.

[17] F. Chemla, F. Ferreira, *Curr. Org. Chem.* **2002**, *6*, 539.

[18] a) A. Alexakis, I. Marek, P. Mangeney, J. F. Normant, *Tetrahedron Lett.* **1989**, *30*, 2391; b) A. Alexakis, I. Marek, P. Mangeney, J. F. Normant, *Tetrahedron* **1991**, *47*, 1677.

  