C- and N-Selective Grignard Addition Reactions of α-Aldimino Esters in the Presence or Absence of Zinc(II) Chloride: Synthetic Applications to Optically Active Azacycles

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S *Supporting Information*

ABSTRACT: Highly practical synthetic methods were developed for the C- and N-selective Grignard addition reactions of N-4-MeOC$_6$H$_4$-protected α-aldimino esters in the presence or absence of zinc(II) chloride. Diastereoselective C-alkyl addition, tandem C-alkyl addition–N-alkylation, and some transformations to synthetically useful optically active azacycles were demonstrated.
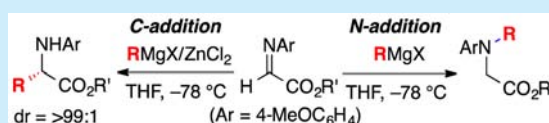
Umpolung α-imino esters, which are versatile α-amino acid precursors, have two adjacent reactive electrophilic centers on the C=N double bond. Therefore, the Grignard addition reaction[1] of α-imino esters usually provides a mixture of C- and N-adducts.[2] However, some N-aryl-protected (commonly, 4-MeOC$_6$H$_4$ (PMP)) α-ketimino esters **1** prefer N-alkyl addition to C-alkyl addition in the reaction with Grignard reagents, and N-adduct **3** rather than C-adduct **2** would be obtained as a major product (eq 1).[3,4] We recently developed an *unusual* C-selective
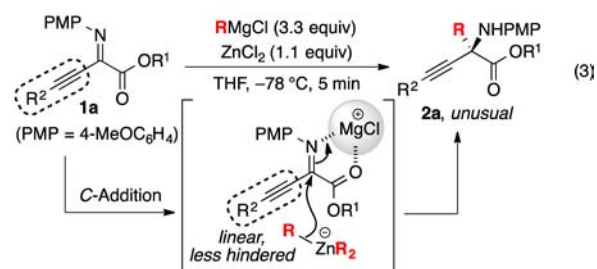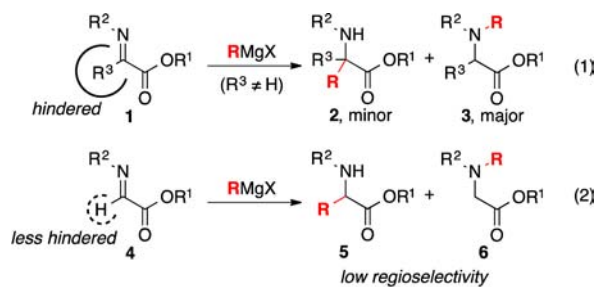
and diastereoselective alkyl addition to β,γ-alkynyl-α-imino esters (**1a**) with alkylzinc(II)ate complexes, which were prepared in situ from Grignard reagents and zinc(II) chloride (eq 3).[5–7] Since the alkylzinc(II)ate consists of a Lewis acidic [MgCl]$^+$ (or [Mg$_3$Cl$_5$]$^+$) moiety and a nucleophilic [R$_3$Zn]$^-$ moiety, the ionically separated [R$_3$Zn]$^-$ can selectively attack the imino
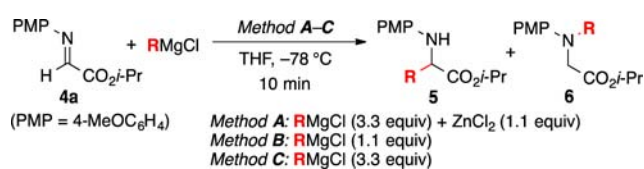
carbon atom, which is reasonably activated by the chelation of [MgCl]$^+$. As a result, the corresponding optically active α,α-disubstituted amino acid derivatives (**2a**) were obtained in high yields within 5 min. In sharp contrast, α-aldimino esters **4** are generally much more reactive and less regioselective than α-ketimino esters **1** due to the relief of steric and electronic factors, and C-adduct **5** and N-adduct **6** are often competitively obtained with low regioselectivity (eq 2).[8] Moreover, the regioselectivity on C- or N-alkyl addition generally depends on the α-aldimino esters, and respective practical methodologies for both the C- and N-alkyl additions to **4** with Grignard reagents have not yet been well-established.[9–11] In this context, we report here the C- and N-selective Grignard addition reactions of N-PMP-protected α-aldimino esters in the presence or absence of zinc(II) chloride.

First, we examined alkyl addition to N-PMP-α-aldimino ester **4a** with 1°-, 2°-, and 3°-alkylmagnesium chloride in the presence or absence of ZnCl$_2$ in tetrahydrofuran (THF) at −78 °C (Table 1). As a result, the reaction of **4a** (1 mmol) with alkylzinc(II)ate (1.1 equiv), which is prepared in situ from RMgCl (3.3 equiv) and ZnCl$_2$ (1.1 equiv) (method A), proceeded smoothly within 10 min, and the corresponding C-adducts **5a–c** were obtained in 92–96% yields selectively (entries 1, 4, and 7). On the other hand, 1.1 equiv of RMgCl without ZnCl$_2$ (method B) provided a complex mixture (entries 2, 5, and 8), which might be attributed to the highly reactive and unstable Mg(II)-enolate intermediates (**7**) via N-addition (eq 4). However, very interestingly, N-adduct **6a** was obtained in 95% yield when 3.3 equiv of EtMgCl was used (method C) (entry 3). This result strongly suggests that quick consumption of **4a** would prevent the reaction between intermediates **7a** and **4a** (eq 5). Reactions were scalable to 10 mmol of **4a** without serious problems (entries 1 and 3). Although 2°- and 3°-alkylmagnesium chloride (i.e., *i*-PrMgCl and *t*-BuMgCl, respectively) were less selective than EtMgCl as 1°-

## Table 1. Regioselective Alkyl Addition to α-Aldimino Ester 4a[a]

(PMP = 4-MeOC₆H₄)

Method A: RMgCl (3.3 equiv) + ZnCl₂ (1.1 equiv)
Method B: RMgCl (1.1 equiv)
Method C: RMgCl (3.3 equiv)

				yield (%)	
entry	RMgCl	method	5/6	5	6
1	EtMgCl	A	5a/6a	96 (>99)[b]	0 (0)[b]
2	EtMgCl	B	5a/6a	9	63
3	EtMgCl	C	5a/6a	0 (0)[b]	95 (92)[b]
4	i-PrMgCl	A	5b/6b	96	0
5	i-PrMgCl	B	5b/6b	9	19
6	i-PrMgCl	C	5b/6b	17	80
7	t-BuMgCl	A	5c/6c	92	0
8	t-BuMgCl	B	5c/6c	38	12
9	t-BuMgCl	C	5c/6c	34	54
10	allylMgCl	A	5d/6d	>99 (94)[c]	0 (0)[c]
11	allylMgCl	B	5d/6d	20	0
12	allylMgCl	C	5d/6d	11	0

[a]The reaction was conducted in THF at −78 °C for 10 min with method A, B, or C on a 1 mmol scale of **4a** unless otherwise noted. Method A: Grignard reagent (3.3 equiv) and ZnCl₂ (1.1 equiv). Method B: Grignard reagent (1.1 equiv). Method C: Grignard reagent (3.3 equiv). Isolated yields (%) are shown. [b]On a 10 mmol scale of **4a**. [c]On a 50 mmol scale of **4a**.
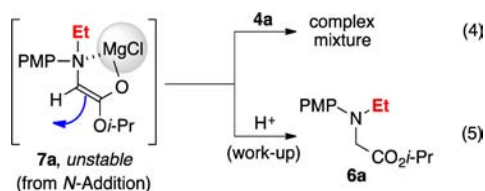
alkylmagnesium chloride, N-adducts **6b** and **6c** were obtained as major products (entries 6 and 9). Moreover, C-allyl addition to **4a** smoothly proceeded by method A on a 50 mmol scale, and C-adduct **5d** was obtained quantitatively (12.4 g) (entry 10). However, the expected N-adduct **6d** was not obtained by method C (entry 12). By methods B (entry 11) and C (entry 12), side reactions at the activated ester moiety almost consumed **4a**, probably due to a six-membered cyclic transition state of allylation.

C-Phenyl addition to **4b** was also examined with the use of PhMgBr and ZnCl₂ (Scheme 1). In place of routine acidic workup, treatment with chloroacetyl chloride, followed by 1,8-diazabicyclo[5.4.0]-7-undecene, was conducted in one pot. As a result, β-phenyl-β-alkoxycarbonyl-β-lactam (**8**) was obtained in 87% yield. PMP protection in **8** was readily cleaved by (NH₄)₂[Ce(NO₃)₆] (CAN), and β-lactam **9** was obtained in 92% yield. Ring opening of **8** by NaOMe gave the synthetically useful α-phenyl aspartic acid derivative[12] **10** in 47% yield.

We next examined regio- and diastereoselective alkyl and aryl addition to **11**, which has a bulky chiral 8-phenylmenthyl (R*) ester[13,14] (Table 2). As expected, the desired C-alkyl addition proceeded smoothly when alkylzinc(II)ate reagents were used (method A), and the corresponding (S)-C-adducts (**12**) were obtained as sole products with perfect diastereoselectivity (>99:1). Remarkably, alkylzinc(II)ate, method A, was highly effective with various Grignard reagents, such as ethyl (entry 1),

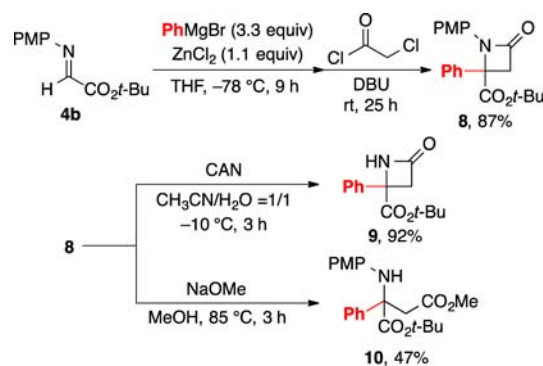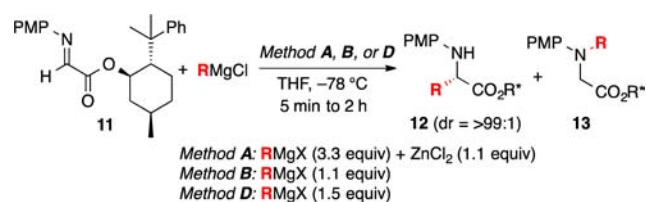## Scheme 1. C-Phenyl Addition for the Synthesis of β-Lactam 9 and Aspartic Acid Derivative 10

Table 2. Regio- and Diastereoselective Alkyl Addition to Chiral α-Aldimino Ester 11[a]

Method A: RMgX (3.3 equiv) + ZnCl₂ (1.1 equiv)
Method B: RMgX (1.1 equiv)
Method D: RMgX (1.5 equiv)

				yield (%)	
entry	RMgX	method	12/13	12	13
1	EtMgCl	A	12a/13a	99	0
2	EtMgCl	B	12a/13a	6	85
3	i-PrMgCl	A	12b/13b	97	0
4	i-PrMgCl	B	12b/13b	12	78
5	c-PrMgBr	A	12c/13c	83	0
6	c-PrMgBr	B	12c/13c	0	0
7[b]	t-BuMgCl	A	12d/13d	89	0
8[b]	t-BuMgCl	B	12d/13d	21	74
9	PhCH₂MgCl	A	12e/13e	99	0
10	PhCH₂MgCl	B	12e/13e	11	88
11[b]	o-BrC₆H₄CH₂MgBr	A	12f/13f	99	0
12	o-BrC₆H₄CH₂MgBr	B	12f/13f	19	53
13[b]	o-BrC₆H₄CH₂MgBr	D	12f/13f	0	87
14	PhCH₂CH₂MgCl	A	12g/13g	>99	0
15	PhCH₂CH₂MgCl	B	12g/13g	0	79
16[b]	PhCH₂CH₂MgCl	D	12g/13g	0	99
17	C₈H₁₇MgCl	A	12h/13h	96	0
18	C₈H₁₇MgCl	B	12h/13h	0	90
19	3-thienylMgI	A	12i/13i	73	0
20	3-thienylMgI	B	12i/13i	20	0

[a]The reaction was conducted in THF at −78 °C for 2 h with method A, B, or D on a 0.5 mmol scale of **11** unless otherwise noted. Method A: Grignard reagent (3.3 equiv) and ZnCl₂ (1.1 equiv). Method B: Grignard reagent (1.1 equiv). Method D: Grignard reagent (1.5 equiv). [b]Reaction time was 5 min.

isopropyl (entry 3), cyclopropyl (entry 5), tert-butyl (entry 7), benzyl (entries 9 and 11), homobenzyl (entry 14), and octyl (entry 17) magnesium halides. C-Aryl addition also proceeded when 3-thienyMgI and ZnCl₂ were used, and the corresponding C-adduct **12i** was obtained in 73% yield. Moreover, interestingly, when we used 1.1 equiv of Grignard reagents for **11** without ZnCl₂ (method B) (unlike 3.3 equiv for **4a** without ZnCl₂ by method C in Table 1), N-adducts **13** were selectively obtained in good to high yields. In some cases, the yields of **13** were

improved when 1.5 equiv of Grignard reagents were used by method D (entries 13 and 16). Unfortunately, N-aryl addition generally did not proceed well by method B, probably due to a steric reason between the transferable aryl moiety and PMP or other unsolved reasons which need further investigations (entry 20).

Based on the results in Table 2, the high N-selectivity with alkyl Grignard reagents might be inherent in aldimino ester **11**. In particular, unlike aldimino ester **4a**, highly sterically hindered Mg(II)-enolate intermediates **14** via N-alkyl addition to **11** would be stable, and **14** might be unlikely to undergo further problematic nucleophilic reactions with **11** even when 1.1 equiv of Grignard reagents is used (Figure 1).[14] Therefore, quick consumption of **11** by an excess amount of Grignard reagent would not be required in this case.
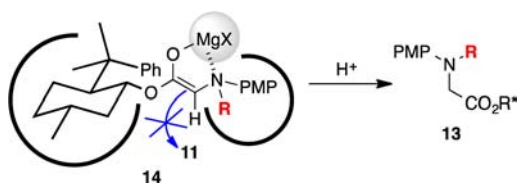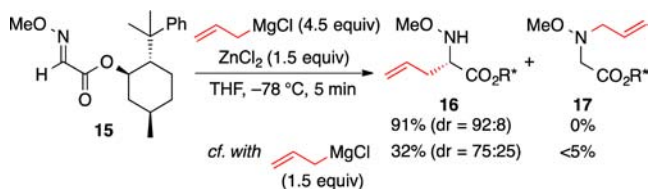

Figure 1. Possible stable intermediates via N-alkyl addition.

Similarly, C-selective alkyl addition to chiral α-oximino ester[13e,15] **15** with allylzinc(II)ate was conducted (Scheme 2).

Scheme 2. C-Allyl Addition to Chiral α-Oximino Ester 15

As expected, the corresponding C-adduct **16** was obtained in 91% yield with high diastereoselectivity (92:8) within 5 min. This result is comparable to the results with allylZn(II)Br (52% yield, dr = 87:13).[13e] Moreover, when Grignard reagent was used in the absence of ZnCl2, N-adduct **17** could not be obtained and **16** was obtained in 32% yield with lower diastereoselectivity (75:25).

To demonstrate the synthetic utility of the obtained optically active C-adducts, some transformations were examined. First, the chiral auxiliary R* (8-Ph-menthyl) was recovered quantitatively as R*OH from compound **12e** under treatment with LiAlH4 (Scheme 3). Subsequently, the corresponding amino alcohol **18** was transformed to oxazolidinones **19** and then **20** by the

Scheme 3. Recovery of Chiral Auxiliary and Transformation to Oxazolidinones 19 and 20 and Indoline 21
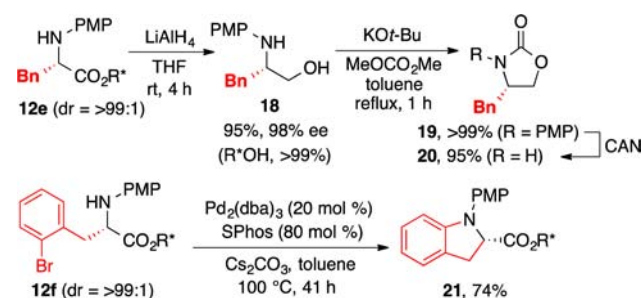
cleavage of PMP protection by CAN. Moreover, in the case of compound **12f**, Pd(0)/2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (SPhos)-catalyzed N-cyclization[16] provided synthetically useful indoline **21** in 74% yield.

We next focused on the transformation to cyclic α-amino acid derivatives based on synthetic and medicinal chemistry. In this context, Kozlowski reported the intramolecular tandem N-alkyl addition−C-alkylation of achiral ketimino esters, and racemic piperidine and azepane were obtained in one pot.[3a] Alternatively, we examined the intramolecular tandem C-alkyl addition−N-alkylation of chiral aldimino ester **11** with alkylzinc(II)ate reagents in one pot (Scheme 4). Fortunately, the desired

Scheme 4. Tandem C-Alkyl Addition−N-Alkylation
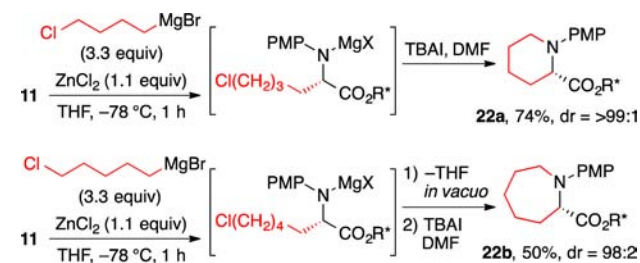
optically active N-heterocycles **22a** and **22b** were obtained in respective yields of 74 and 50% with excellent diastereoselectivities. The use of tetrabutylammonium iodide was crucial for promoting cyclization.

Finally, to demonstrate the versatility of the N-PMP moiety without deprotection, we used α-aldimino ester **23** with o-phenylethynyl-substituted PMP (Scheme 5). C-Selective and

Scheme 5. Transformation to Indoles 25
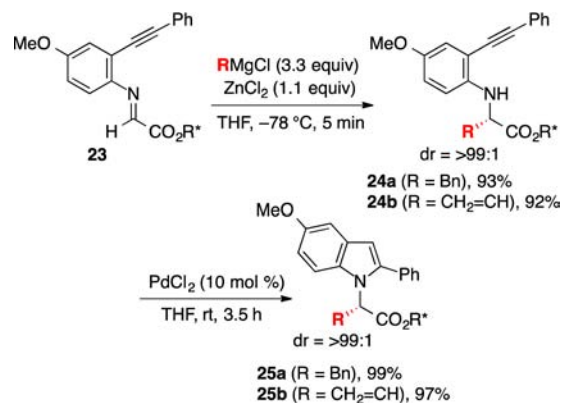
diastereoselective addition of benzyl and vinyl Grignard reagents was completed within 5 min, and **24a** and **24b** were obtained in respective yields of 93 and 92%. Subsequently, 10 mol % of PdCl2 catalyzed the cyclization,[17] and synthetically useful optically active N-indolyl acetic acid derivatives[18] (**25a** and **25b**) were obtained almost quantitatively. X-ray analysis of **25a** unambiguously showed the structure (see the Supporting Information).

In summary, we have developed a highly practical method for the C- and N-selective Grignard addition reaction of N-PMP-protected α-aldimino esters in the presence or absence of zinc(II) chloride. In particular, with the use of a chiral α-aldimino ester, diastereoselective C-alkyl addition and tandem C-alkyl addition−N-alkylation successfully proceeded with the use of alkylzinc(II)ate.[19] Moreover, some transformations of the C-

adducts to synthetically useful optically active azacycles, such as piperidine, azepane, indole, and indoline, were demonstrated. Overall, this simple procedure with Grignard reagents in the presence or absence of zinc(II) chloride might be attractive as one of the most simple methodologies for obtaining α-amino acid derivatives.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and characterization data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b00927.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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