Tetrahedron Letters, Vol. 34, No. 26, pp. 4227-4230, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

S_N2' Selective Alkylation of Allylic Chlorides and Mesylates with RZnX Reagents Generated from Grignard Reagents, Zinc Chloride, Lithium Chloride, and Cu(II)-Salts

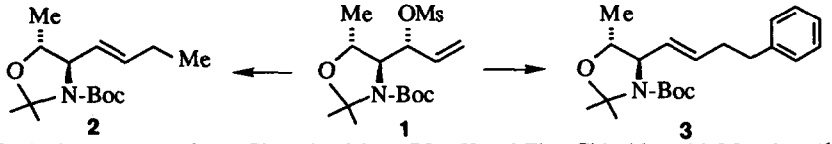
Nobutaka Fujii,* Kazuo Nakai, Hiromu Habashita, Hidenori Yoshizawa, and Toshiro Ibuka*
Faculty of Pharmaceutical Sciences, Kyoto University, Sakyo-ku, Kyoto 606, Japan

Fabrice Garrido and André Mann*
Laboratoire de Pharmacochimie Moléculaire, Centre de Neurochimie-CNRS, 5, rue Blaise Pascal, F-67084 Strasbourg Cedex, France

Yukiyasu Chounan and Yoshinori Yamamoto*
Department of Chemistry, Faculty of Science, Tohoku University, Sendai 980, Japan

Abstract: Treatment of RMgX (1 equiv. R = alkyl; X = Cl, Br) with $ZnCl_2$ (1 equiv.) in a mixed solvent of THF and Et_2O leads to a highly turbid white suspension. Addition of LiCl (1~2 equiv.) solubilizes the insoluble species to yield a colorless clear solution. Addition of a catalytic amount of a Cu(II)-salt followed by allylic halides or mesylates at *0* °C ~ room temperature yielded S_N2' products in high yields. Application for the synthesis of (*E*)-alkene dipeptide isosteres is also reported.

The growing importance of peptide mimetics in synthetic and medicinal chemistries has created a need for developing efficient synthetic routes to various isosteres.[1] Recently, we have shown that alkene dipeptide isosteres can be prepared in high yields by the reaction of γ-mesyloxy-α,β-enoates with typical organocopper reagents in the presence of boron trifluoride.[2] However, both regio- and stereo-chemical control in the alkylation of allylic halides and sulfonates for the synthesis of alkene dipeptide isosteres still need considerable improvement and optimization. Herein we report that alkylzinc halides[3] derived from Grignard reagents, zinc chloride, and lithium chloride[4] act as good nucleophiles enabling S_N2' selective alkylation by the addition of a catalytic amount of cupric salts[5] prior to their reaction with allylic substrates.



2 1 3

Table 1. Reaction of RZnCl, derived from RMgX and Zinc Chloride, with Mesylate (**1**)

Entry	Reagent*1	LiCl	$Cu(acac)_2$	Reaction Conditions	Product	Yield*2
1	MeZnCl·Mg(Br)Cl	none	none	0 °C, 1 h*3	2	< 0.5 %
2	MeZnCl·Mg(Br)Cl	2 mol equiv.	none	0 °C, 1 h	2	< 1.6 %
3	MeZnCl·Mg(Br)Cl	none	10 mol %	0 °C, 1 h*3	2	< 10 %
4	MeZnCl·Mg(Br)Cl	2 mol equiv.	10 mol %	0 °C, 30 min	2	92 %
5	$PhCH_2ZnCl·MgCl_2$	2 mol equiv.	10 mol %	0 °C, 30 min	3	88 %

*1 Four equivalents of the reagents were used. *2 All yields are based upon the isolated pure materials. *3 A white suspension.

Organozinc halides can be prepared by the reaction of Grignard reagents with zinc halides.[6] One of the advantages of using Grignard reagents for the preparation of RZnX is the ease of preparation of the Grignard reagents in comparison with organolithiums.[7] However, the dropwise addition of a THF or Et_2O solution of RMgX (R = alkyl, X = Cl or Br, 1 equiv.) to a solution of $ZnCl_2$ in Et_2O resulted in a white suspension.[8] It turned out that the sequential addition of zinc chloride (1 equiv.) in Et_2O and Grignard reagent(s) (1 equiv.) in either Et_2O or THF to a stirred suspension of LiCl (1~2 equiv.) in THF yields a colorless clear solution.[4,7]

Initially, we attempted the allylic substitution of the mesylate **1** with MeZnCl prepared from MeMgBr and $ZnCl_2$ at room temperature either in the absence or in the presence of LiCl. However, treatment of **1** with MeZnCl led to the nearly complete recovery of the starting material (Table 1, entries 1 and 2). In the absence of LiCl, the addition of a catalytic amount of $Cu(acac)_2$ to a suspension of MeZnCl prior to its reaction with **1** appears to be effective in promoting the desired reaction. However, the reaction was very slow and did not proceed to completion (Table 1, entry 3). As shown by entries 4 and 5 in Table 1, both LiCl and $Cu(acac)_2$ are essential additives for the clean reaction.

The addition of a catalytic amount of $Cu(OTf)_2$ to a solution of RZnCl·$MgCl_2$·nLiCl also permits alkylation of allylic chloride. The exposure of geranyl chloride **4**, neryl chloride **5**, and *p*-methoxycinnamyl chloride **9** to reagents prepared from RZnCl·$MgCl_2$·nLiCl and a catalytic amount of $Cu(OTf)_2$ gave rise to a mixture of S_N2' and S_N2 products. As shown in Table 2, the regioselectivities moderately favored the S_N2' products over the S_N2 products.

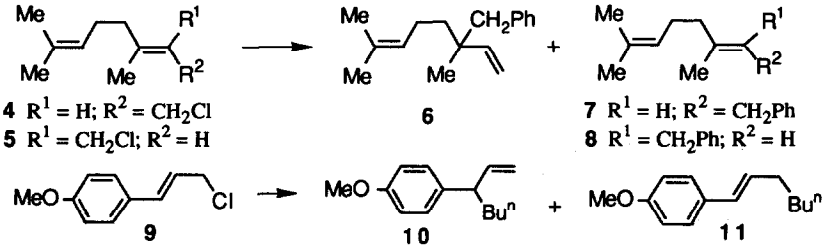
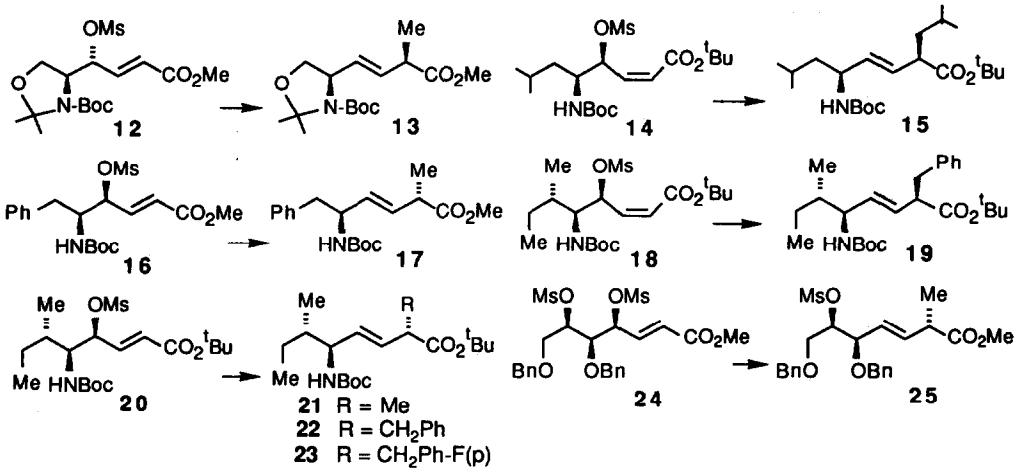


Table 2. Reaction of RZnCl with Allylic Halides **4**, **5**, and **9**[*1]

Entry	Substrate	Reagent[*1]	$Cu(OTf)_2$	Reaction Conditions	S_N2' (%)	S_N2 (%)
1	**4**	$PhCH_2ZnCl·MgCl_2·2LiCl$	3 mol %	THF-Et_2O (6:1), 0 °C, 5 h	**6** (71%)	**7** (13 %)
2	**5**	$PhCH_2ZnCl·MgCl_2·2LiCl$	3 mol %	THF-Et_2O (7:1), 0 °C, 7 h	**6** (75 %)	**8** (15 %)
3	**9**	*n*-BuZnCl·$MgCl_2$·LiCl	5 mol %	THF-Et_2O (5:1), 0 °C, 7 h	**10** (75 %)	**11** (4 %)

[*1] Three to four equivalents of the reagents were used. All yields are based upon the isolated pure materials.



The present method was extended to the synthesis of (*E*)-alkene dipeptide isosteres **13**, **15**, **17**, **19**, **21**, **22**, and **23**. The addition of a catalytic amount of cupric salts such as $CuBr_2$, $Cu(OTf)_2$, and $Cu(acac)_2$ to a solution of $RZnCl{\cdot}MgX_2{\cdot}nLiCl$ (n = 1 or 2) enhances the reactivity and permits synthesis of the (*E*)-alkene dipeptide isosteres in high yields *via* an anti-S_N2' pathway from both (*E*)- and (*Z*)-γ-mesyloxy-α,β-unsaturated esters as shown in Table 3.[9]

In addition, dimesylate **24** furnished only the methylation product **25** in 87 % yield by treatment with a reagent prepared from $MeZnCl{\cdot}MgCl_2{\cdot}2LiCl$ and 1 mol % of $Cu(OTf)_2$. Clearly, only the γ-mesyloxy group in **24** is involved in the reaction.

Table 3. Reaction of RZnCl derived from RMgX, $ZnCl_2$, and LiCl with Some Mesylates[*1]

Entry	Substrate	Reagent	Cupric Salt	Product	Yield[*2]	(diastereoselection)
1	**12**	$MeZnCl{\cdot}Mg(Br)Cl{\cdot}LiCl$	10 mol % $Cu(OTf)_2$	**13**	86 %	(> 99 : 1)
2	**12**	$MeZnCl{\cdot}Mg(Br)Cl{\cdot}2LiCl$	5 mol % $CuBr_2$	**13**	94 %	(> 99 : 1)
3	**14**	*Iso*-$BuZnCl{\cdot}MgCl_2{\cdot}2LiCl$	10 mol % $Cu(acac)_2$	**15**	86 %	(> 99 : 1)
4	**16**	$MeZnCl{\cdot}Mg(Br)Cl{\cdot}2LiCl$	10 mol % $Cu(acac)_2$	**17**	96 %	(> 99 : 1)
5	**18**	$PhCH_2ZnCl{\cdot}MgCl_2{\cdot}2LiCl$	5 mol % $Cu(OTf)_2$	**19**	75 %	(> 99 : 1)
6	**20**	$MeZnCl{\cdot}Mg(Br)Cl{\cdot}2LiCl$	3 mol % $CuBr_2$	**21**	91 %	(> 99 : 1)
7	**20**	$PhCH_2ZnCl{\cdot}MgCl_2{\cdot}LiCl$	5 mol % $Cu(OTf)_2$	**22**	96 %	(> 99 : 1)
8	**20**	(*p*)-$F\text{-}C_6H_4CH_2ZnCl{\cdot}MgCl_2{\cdot}LiCl$	5 mol % $Cu(OTf)_2$	**23**	91 %	(> 99 : 1)

[*1] All reactions were carried out in a mixed solvent of THF and Et_2O for 30 min~ 1 h and three to four equivalents of the reagents were used. [*2] All yields are based upon the isolated pure materials.

H-D-Phe-Gln-Trp-Ala-Val-Gly-His-Leu-ψ[CH_2NH]Leu-NH_2 **26**

H-D-Phe-Gln-Trp-Ala-Val-Gly-His-Leu-ψ[(E)-CH=CH]Leu-NH_2 **27**

The synthesis of the analogue **27** of the bombesin receptor antagonist **26**[10] was also carried out wherein the Leu-ψ[CH_2NH]Leu isosteric unit was replaced with the alkene isostere **15**. Thus, the protected isostere **15** was converted to an amino acid hydrochloride by treatment with TFA followed by 1 N HCl. The hydrochloride salt was transformed to an *N*-Boc-amino acid, which was condensed on a methylbenzhydrylamine resin. Finally, the peptide amide **27** was prepared by Boc-based solid phase peptide synthesis followed by deprotection with 1 M TMSOTf-thioanisole in TFA.[11]

It has recently been shown by Kuwajima and his co-workers that some copper(II) compounds are highly effective for the conjugate addition.[5] In the present allylic alkylations, although the exact oxidation state of the reactive copper species remains uncertain, the copper(II) salts that have been added to a solution of RZnCl would be reduced to copper(I) species by alkylzinc halides.[12] It should be noted that while these reagents work well for substitutions, it is not applicable to the other main mode of reactions, i.e., conjugate additions.

ACKNOWLEDGEMENT: Financial support from the CIBA-GEIGY Foundation (Japan) for the Promotion of Science is gratefully acknowledged.

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7. When organolithium derivatives are used, it is possible to start from a zinc chloride suspension in a mixed solvent of THF and Et_2O. The lithium salt which results from the rapid metal-metal exchange reaction is able to dissolve the organozinc halide reagents presumably by "ate" complex formation. Benzyllithium could be prepared by either the addition of *sec*-butyllithium to toluene (Screttas, C. G.; Estham, J. F.; Kamienski, C. W. *Chimia* **1970**, *24*, 109-111) or the reaction of a benzyltellurium compound with *n*-butyllithium (Hiiro, T.; Kambe, N.; Ogawa, A.; Sonoda, N. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 1187). The benzyllithium solutions, however, suffered from a serious disadvantage in that they were unstable over extended periods of time.
8. It is found that the filtered cake collected by filtration of the suspension in an argon atmosphere is active organometallic species. The addition of LiCl to a suspension of the filtered cake in THF resulted in a colorless clear solution. (see also ref. 22 in von dem Bussche-Hunnefeld, J. L.; Seebach, D. *Tetrahedron* **1992**, *48*, 5719-5730).
9. *The following procedure is typical* (Table 3, entry 5). Boc-Ile-ψ[(*E*)-CH=CH]Phe-OBu^t **19**
To a stirred suspension of LiCl (339 mg, 8 mmol) in 7 mL of dry THF at -78 °C, $ZnCl_2$ (8 mmol, 8 mL of a 1.0 M $ZnCl_2$ solution in Et_2O) and BnMgCl (8 mmol, 8 mL of a 0.65 M solution in THF) were added sequentially by syringe. The mixture was allowed to warm to 0 °C and then stirred at this temperature for 30 min. $Cu(OTf)_2$ (0.4 mmol, 144 mg) was added to the above clear mixture at 0 °C and the mixture was stirred for 5 min. A solution of α,β-enoate **18** (2 mmol, 842 mg) in dry THF (7 mL) was added dropwise to the above reagent at - 30 °C with stirring. The mixture was allowed to warm to 0 °C and the stirring was continued for 1 h. The usual work-up followed by recrystallization from a mixed solvent of *n*-hexane-CH_2Cl_2 (10 : 1) gave **19** (804 mg, 96 % yield) as colorless crystals. mp 60-61 °C. $[\alpha]^{15}_D$ - 63.03 ° (c 1.102, $CHCl_3$); Δε - 5.11 (222 nm, isooctane). The product shows the appropriate ^{1}H- NMR (in $CDCl_3$), IR (in $CHCl_3$) spectra and microanalytical data.
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(Received in Japan 5 April 1993)