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"Higher Order" Zinc Cuprates Involving Lithium Chloride: Synthesis of (*E*)-Alkene Dipeptide Isosteres Free from Reductive Elimination Products

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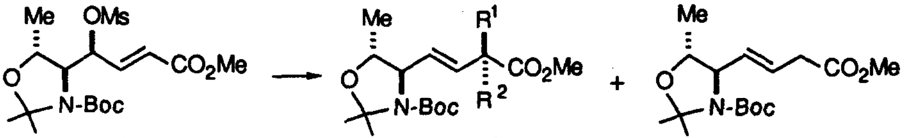
Abstract: The "higher order" organozinc cuprates, $R_2Cu(CN)(ZnCl)_2{\cdot}2Mg(X)Cl{\cdot}nLiCl$, *derived from admixture of LiCl (1~2 equiv.),* $ZnCl_2$ *(1 equiv.), RMgX (1 equiv.), and CuCN (0.5 equiv.) in a mixed solvent of THF and* Et_2O *exhibit high diastereoselection of up to > 99 : 1 in the synthesis of (E)-alkene dipeptide isosteres from γ-mesyloxy-α,β-unsaturated esters. Addition of lithium chloride is essential for the preparation of clear solutions of reagents.*

Organocoppers and their Lewis acid complexes have been utilized in a large number of chemical reactions and are finding growing application in the construction of biologically important compounds.[1)]

We recently described an efficient synthetic route to α-alkylated (E)-β,γ-unsaturated esters by the reaction of γ-mesyloxy-α,β-unsaturated esters with Lewis acid mediated organocyanocopper reagents, $RCu(CN)M.BF_3$ (M = Li or MgX).[2)] This *anti*-S_N2' allylic rearrangement reaction[3)] has been successfully used in key steps for the synthesis of several dipeptide isosteres[4)] and of a building block of rapamycin.[5)]



1

2 R^1 = H; R^2 = Me
3 R^1 = Me; R^2 = H

4

Scheme 1

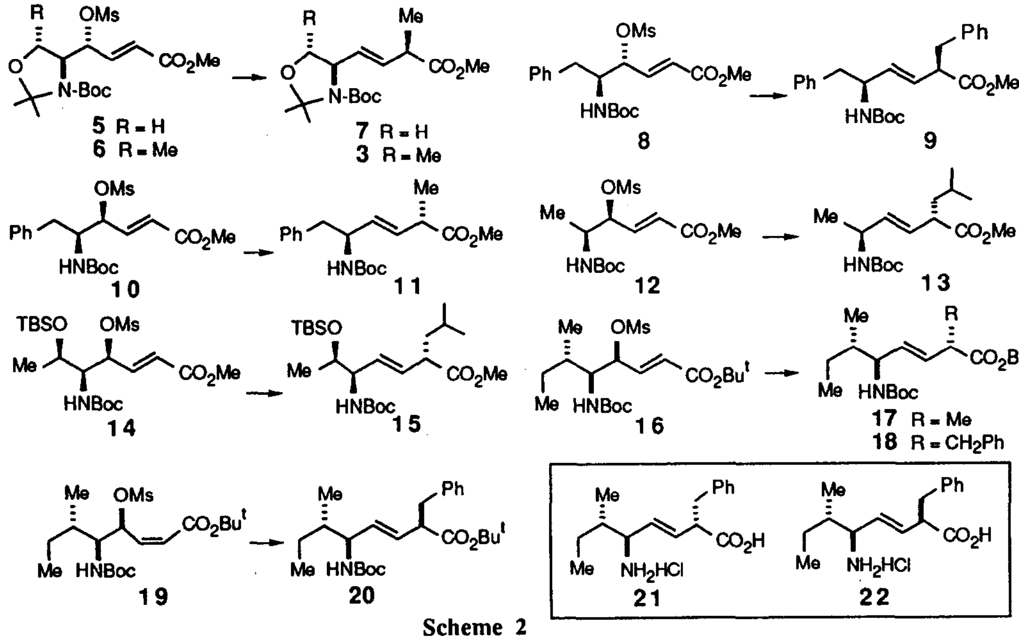
Table 1

Entry	Reagent	Chem. Yield (2 + 3 + 4)	(2 + 3)	:	4
1	$MeCu(CN)MgBr$	95 %	0	:	100
2	$MeCu(CN)MgBr{\cdot}3BF_3{\cdot}2LiCl$	89 %	64 *1	:	36
3	$MeCu(CN)MgBr{\cdot}3Me_3SiCl{\cdot}2LiCl$	85 %	51 *1	:	49
4	$Me_2Cu(CN)(ZnCl)_2{\cdot}2Mg(Br)Cl{\cdot}3LiCl$	85 %	100 *2	:	0

*1 A separable diastereoisomeric mixture of products. 2 : 3 = 96 : 4 . *2 2 : 3 = 76 : 24

Subsequent studies on the application of the reaction to the synthesis of some dipeptide isosteres uncovered one limitation. In the reaction of organocyanocopper reagents with substrates derived from serine and threonine, competing reductive elimination was observed leading to low chemical yields of the desired α-alkylation products. As atypical example, the γ-mesyloxy-α,β-unsaturated ester **1** gave exclusively the reductive elimination product **4** by treatment with MeCu(CN)MgBr (**Table 1**, entry 1). It has been well documented that the electron transfer properties of organocopper reagents are attenuated on addition of $BF_3{\cdot}Et_2O$[2,4] or Me_3SiCl.[6] In fact, the amount of the undesired product **4** could be reduced by addition of $BF_3{\cdot}Et_2O$ or Me_3SiCl, but the yield of the α-alkylated products (**2** + **3**) was still unsatisfactory (**Table 1**, entries 2 and 3). Therefore, there was a need for a reagent that would selectively transform γ-mesyloxy-α,β-enoates to α-alkyl-(E)-β,γ-enoates in a high yield under mild conditions.

We now report that the limitation can be surmounted by the use of a variant which employs the "higher order"[7] organozinc cuprates in the presence of lithium chloride.[8] Nearly complete suppression of the reduction product **4** was accomplished upon treatment of **1** with the higher order organozinc cuprate, $Me_2Cu(CN)(ZnCl)_2{\cdot}2Mg(Br)Cl{\cdot}3LiCl$ (**Table 1**, entry 4).[9] The exact structure of the "higher order" zinc cuprates is not known and the formula $R_2Cu(CN)(ZnCl)_2{\cdot}2MgCl(X){\cdot}nLiCl$ reflects its stoichiometry.[10]



Scheme 2

Admixture of an ethereal solution of $ZnCl_2$ (1 equiv.) and a THF solution of RMgX (R = alkyl, X = Cl or Br, 1 equiv.) at 0 °C resulted in a white suspension. The problem associated with limited solubility of organozinc reagents prepared from RMgX (1 equiv.) and $ZnCl_2$ (1 equiv.) was overcome by the addition of lithium chloride. One of the practical advantages of using Grignard reagents is the ease of preparation of Grignard reagents in comparison with organolithiums. *Thus, sequential addition of $ZnCl_2$ (1 equiv.) and RMgBr (1 equiv.) to a stirred suspension of LiCl (1 ~ 2 equiv.) in THF at 0 °C gave a colorless clear solution.* The order in which $ZnCl_2$ and RMgX are introduced to a suspension of LiCl is of no consequence in the preparation of the reagent involving MeZnCl. The "higher order" reagent was prepared by the addition of CuCN (0.5 equiv.) to the stirred clear solution of MeZnCl at 0 °C.

The same solubility of the suspension involving RZnCl, derived from Grignard reagent and $ZnCl_2$, could be promoted by the addition of LiBr to yield a clear solution. However, anhydrous LiBr is highly hygroscopic and much harder to handle.

Reactions monitored by TLC and GLC showed that lithium perchlorate is not an effective additive;

with very low conversion of **5** to (**2** + **3**) was realized after 3 h at 0 °C (**Table 2**, entry 1).

If the alkylation reaction is performed in the absence of either cuprous cyanide or lithium chloride, the reaction proceeds slowly and a substantial amount of the starting material remains unchanged along with unidentified byproducts (**Table 2**, entries 2, 3, and 11). These observations indicate that lithium chloride plays an important role.

Table 2. Synthesis of (*E*)-Alkene Dipeptide Isosteres by Reaction of δ-Aminated γ-Mesyloxy-α,β-unsaturated Esters with "Higher Order" Organozinc Cuprates.

Entry	Substrate	Reagent[*1]	Condition	Product	Yield[*2]	d.e.[*3]
1	**5**	$Me_2Cu(CN)(ZnCl)_2 \cdot 2Mg(Br)Cl \cdot 3LiClO_4$[*4]	0 °C, 3 h	**2** + **3**	< 0.5%	9
2	**5**	$MeZnCl \cdot Mg(Br)Cl \cdot LiCl$	0 °C, 1 h	**7**	13%[*5]	> 98
3	**5**	$Me_2Cu(CN)(ZnCl)_2 \cdot 2Mg(Br)Cl$[*4]	0 °C, 3 h	**7**	53%	> 98
4	**5**	$Me_2Cu(CN)(ZnCl)_2 \cdot 2Mg(Br)Cl \cdot 2LiCl$	0 °C, 30 min	**7**	96%	> 98
5	**5**	$Me_2Cu(CN)(ZnCl)_2 \cdot 2Mg(Br)Cl \cdot 4LiCl$	0 °C, 30 min	**7**	91%	> 98
6	**6**	$Me_2Cu(CN)(ZnCl)_2 \cdot 2Mg(Br)Cl \cdot 2LiCl$	0 °C, 30 min	**3**	96%	> 98
7	**8**	$(PhCH_2)_2Cu(CN)(ZnCl)_2 \cdot 2MgCl_2 \cdot 4LiCl$	0 °C, 30 min	**9**	95%	> 98
8	**10**	$Me_2Cu(CN)(ZnCl)_2 \cdot 2Mg(Br)Cl \cdot 2LiCl$	0 °C, 50 min	**11**	91%	> 98
9	**12**	$(iso\text{-}Bu)_2Cu(CN)(ZnCl)_2 \cdot 2MgCl_2 \cdot 2LiCl$	0 °C, 30 min	**13**	96%	> 98
10	**14**	$(iso\text{-}Bu)_2Cu(CN)(ZnCl)_2 \cdot 2MgCl_2 \cdot 2LiCl$	0 °C, 1 h	**15**	94%	> 98
11	**14**	$(iso\text{-}Bu)_2Cu(CN)(ZnCl)_2 \cdot 2MgCl_2$[*4]	0 °C, 1 h	**15**	75%	> 98
12	**16**	$Me_2Cu(CN)(ZnCl)_2 \cdot 2Mg(Br)Cl \cdot 4LiCl$	-30 ~ 0 °C, 1h	**17**	95%	> 98
13	**16**	$(PhCH_2)_2Cu(CN)(ZnCl)_2 \cdot 2MgCl_2 \cdot 2LiCl$	0 °C, 30 min	**18**	99%	> 98
14	**19**	$(PhCH_2)_2Cu(CN)(ZnCl)_2 \cdot 2MgCl_2 \cdot 4LiCl$	-30 ~ 0 °C, 1h	**20**	96%	> 98

[*1] Four equivalents of the reagents were used. [*2] All yields are based upon pure materials isolated by flash chromatography on SiO_2. [*3] Determined by ^1H-NMR, HPLC, or capillary GLC. [*4] A heterogeneous suspension. [*5] Ca. 52% of the starting material was recovered.

This chirality transfer reaction with "higher order" organozinc cuprates has been successfully applied to the synthesis of *trans*-alkene isosteres. We did not detect any reductive elimination product by treatment of the substrates (**5**, **6**, **8**, **10**, **12**, **14**, **16**, and **19**) with 4 molar equivalents of $R_2Cu(CN)(ZnCl)_2 \cdot 2MgX_2 \cdot nLiCl$ (n = 2 or 4) in a solvent involving THF at - 30 ~ 0 °C for 30 min ~ 1h. The results in **Scheme 2** and **Table 2** (entries 4 ~ 10 and 12 ~ 14) show that "higher order" organozinc cuprates are effective reagents for the synthesis of ψ[(*E*)CH=CH] isosteres from corresponding γ-mesyloxy-α,β-enoates in high chemical and optical yields. The protected isosteres **18** and **20** were readily transformed into amino acid hydrpchlorides **21** (mp 135-140 °C) and **22** (mp 160-164 °C), respectively, by treatment with TFA followed by 1 *N* HCl.

In summary, the relatively slow reaction of RZnX reagents, prepared from $ZnCl_2$ and Grignard reagents, with γ-mesyloxy-α,β-unsaturated esters can be accelerated by lithium chloride and cuprous cyanide to produce *E*-alkene dipeptide isosteres under mild conditions.

General Procedure using $R_2Cu(CN)(ZnCl)_2 \cdot 2MgX_2 \cdot nLiCl$. The following procedure for the preparation of **13** is representative for all reactions of δ-aminated-γ-mesyloxy-(*E*)-α,β-enoates with the "higher order" organozinc cuprates.

To a stirred suspension of LiCl (34 mg, 0.8 mmol) in THF (2 mL) at 0 °C were added sequentially

$ZnCl_2$ (0.80 mL, 0.80 mmol; 1M in Et_2O) and *iso*-BuMgCl (0.80 mL, 0.80 mmol; 1M in THF) and the mixture was stirred for 30 min. CuCN (36 mg, 0.4 mmol) was added to the colorless clear solution with stirring, and the stirring was continued for 30 min at 0 °C. To the resulting colorless clear solution was then added the substrate **12** (135 mg, 0.4 mmol) in 2 mL of THF. The mixture was stirred for 30 min at 0 °C, and then the reaction was quenched with 4 mL of 28% NH_4OH/sat.NH_4Cl solution with vigorous stirring at -78 °C. The usual workup followed by flash chromatography over silica gel with *n*-hexane-EtOAc (4 : 1) gave 116 mg (96 % yield) of **13**. Kugelrohr distillation, 160 °C (1 mm Hg); $[\alpha]_D^{20}$ +15.6° (c 1.10, $CHCl_3$); Capillary GC (ULBON HR 20, 50 M, 225 °C, 11.22 min); ^1H NMR (200 MHz, $CDCl_3$) δ 0.86 (d, J = 6.3 Hz, 3 H), 0.90 (d, J = 6.3 Hz, 3 H), 1.19 (d, J = 6.8 Hz, 3 H), 1.44 (s, 9 H), 3.08 (m, 1 H), 4.21 (broad s, 1 H), 4.39 (broad s, 1 H), 5.44 - 5.60 (m, 2 H). Anal. CHN

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References.

(1) a) Posner, G. H. *An Introduction to Synthesis using Organocopper Reagents*: Wiley: New York, 1980. b)Yamamoto, Y. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 947. c) Lipshutz, B. H. Synthesis **1987**, 325. d) Nakamura, E. *Synlett.* **1991**, 539. e) Ibuka, T.; Yamamoto, Y. *Synlett.* in print.

(2) Ibuka, T.; Nakao, T.; Nishii, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **1986**, *108*, 7420. Ibuka, T.; Tanaka, M.; Nishii, S.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1987**, 1596. Ibuka, T.; Tanaka, M.; Nishii, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4864. Ibuka, T.; Akimoto, N.; Tanaka, M.; Nishii, S.; Yamamoto, Y. *J. Org. Chem.* **1989**, *54*, 4055.

(3) For excellent reviews on S_N2 and S_N2'reactions, see: Magid, R. M. *Tetrahedron* **1980**, *36*, 1901. Marshall, J. A. *Chem. Rev.* **1989**, *89*, 1503, Marino, J. P.; Viso, A. *J. Org. Chem.* **1991**, *56*, 1349. For an anti-S_N2' reaction mechanism, see: Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1984**, *25*, 3063.

(4) a) Ibuka, T.; Habashita, H.; Funakoshi, S.; Fujii, N.; Oguchi, Y.; Uyehara, T.; Yamamoto, Y. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 801. b) Ibuka, T.; Habashita, H.; Otaka, A.; Fujii, N.; Oguchi, Y.; Uyehara, T.; Yamamoto, Y. *J. Org. Chem.* **1991**, *56*, 4370. c) D. J.; Wang, X. C.; Spanton, S. G. *Int. J. Protein Res.* **1991**, *38*, 237.

(5) Chen, S.-H.; Horvath, R. F.; Joglar, J.; Fisher, M. J.; Danishefsky, S. J. *J. Org. Chem.* **1991**, *56*, 5834.

(6) Smith, B. A. J.; Vellekoop, A. S. *Tetrahedron* **1989**, *45*, 517.

(7) Higher order cuprate: For a review of higher order cuprates see: Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *Tetrahedron* **1984**, *40*, 5005. For discussions on "higher order" cyanocuprates see, Bertz, S. H. *J. Am. Chem. Soc.* **1990**, *112*, 4031. Lipshutz, B. H.; Sharma, S.; Ellsworth, E. L. *J. Am. Chem. Soc.* **1990**, *112*, 4032. For higher order zinc cuprates see: Zhu, L.; Wehmeyer, R. M.; Rieke, R. D. *J. Org. Chem.* **1991**, *56*, 1445. Yamamoto, Y.; Tanaka, M.; Ibuka, T. *J. Org. Chem.* **1992**, *57*, 0000.

(8) For Li salt effects, see: Hallnemo, G.; Ullenius, C. *Tetrahedron Lett.* **1986**, *27*, 395. Lipshutz, B. H.; Whitney, S. Kozlowski, J. A.; Breneman, C. M. *Tetrahedron Lett.* **1986**, *27*, 4273. Lipshutz, B. H.; Ellsworth, E. L.; Dimock, S. H. *J. Am. Chem. Soc.* **1990**, *112*, 5869.

(9) For RZnCl-mediated reactions, see: Sekiya, K.; Nakamura, E. *Tetrahedron Lett.* **1988**, *29*, 5155. For $R_2CuZnCl$-mediated reactions, see: Nakamura, E.; Sekiya, K.; Arai, M.; Aoki, S. *J. Am. Chem. Soc.* **1989**, *111*, 3091.

(10) For organocopper reagents prepared from organozinc reagents, see: Knochel, P.; Yeh, M. C. P.; Berk, M. S.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2392. Tamaru, Y.; Tanuigawa, H.; Yamamoto, T.; Yoshida, Z. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 351. Knochel, P.; Rao, S. A. *J. Am. Chem. Soc.* **1990**, *112*, 6146. Rao, S. A.; Knochel, P. *J. Ant. Chem. Soc.* **1991**, *113*, 5735. Knoess, H. P.; Furlong, M. T.; Rozema, M. J. Knochel, P. *J. Org. Chem.* **1991**, *56*, 5974. For transition metal-catalyzed reaction of organozinc reagents, see: Morizawa, Y.; Oda, H.; Ohshima, K.; Nozaki, H. *Tetrahedron Lett.* **1984**, *25*, 1163. Ohshima, K., *Adv. in Metal-organic Chemistry*; Liebeskind, L. S. Ed.; JAI Press: London, **1991**, vol. 2, p 101-141.

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