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**CONJUGATE ADDITIONS OF GRIGNARD REAGENTS TO α,β -UNSATURATED
 KETONES MEDIATED BY DIAMINE ZINC(II) MONOALKOXIDES**

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Summary. A method for zinc-mediated 1,4-additions of Grignard reagents with alkoxides as non-transferable ligands is described. Using a chiral TMEDA analogue upto 14% enantiomeric excess was achieved.

Organozinc compounds have recently received much attention in studies aimed at the stereoselective additions of organo-metallic reagents.⁽¹⁾ These investigations have cumulated in methods for the 1,2-addition of dialkylzincs to aldehydes with excellent enantioselectivities.⁽²⁾ In contrast efficient and selective methods for 1,4-additions to α,β -unsaturated carbonyl compounds are mainly based on organocuprates⁽³⁾ whereas organozinc reagents have been scarcely studied for this purpose.

Facile conjugated additions were achieved with lithium-triorganozincates⁽⁴⁾. Kijonaa and coworkers⁽⁵⁾ reported that lithium alkyl dimethylzincates selectively transfer the alkyl group rather than the methyl group. Furthermore these authors found that a reagent (presumably a triorganozincate), prepared from 3 equivalents of Grignard reagent and 1 equivalent of $\text{ZnCl}_2/\text{N,N,N',N'}$ -tetramethylethylenediamine complex ($\text{TMEDA} \cdot \text{ZnCl}_2$) gave 1,4-addition products.⁽⁶⁾ A disadvantage of the latter system as compared to cuprates is the loss of two equivalents of the alkyl ligand to be transferred. In connection with our studies on selective organometallic addition reactions⁽⁷⁾ we investigated the zinc-mediated 1,4-addition of Grignard reagents and report now a new procedure using alkoxides as non transferable ligands for the zinc complexes.

First we studied the effect of tert-butoxide on $\text{TMEDA} \cdot \text{ZnCl}_2$ mediated Grignard additions of isopropylmagnesiumbromide to cyclohexenone. (scheme 1) The zinc complexes were prepared in situ by the addition of 0 to 2 equivalents of potassium tert-butoxide to $\text{TMEDA} \cdot \text{ZnCl}_2$ ⁽⁸⁾ followed by 1 to 3 equivalents of $i\text{-PrMgBr}$. The results are shown in scheme 1.⁽⁹⁾

scheme 1

n	m	2 (yield, %) ⁽¹⁰⁾
3	0	80
2	1	94
1	1	0
1	2	10

It is clear that 2 equivalents of Grignard reagent are necessary and sufficient for efficient 1,4-additions when TMEDA.ZnCl₂ is first treated with KtOBu. Furthermore a better yield of 2 is obtained with this reagent compared to the reagent prepared from 3 equivalents of *i*PrMgBr and TMEDA.ZnCl₂.⁽⁶⁾ Addition of 2 equivalents of KtOBu to TMEDA.ZnCl₂ blocks the 1,4-addition almost completely.

Encouraged by these results the 1,4-addition reactions of three representative ketones 3–5 were studied using TMEDA.ZnCl₂.KtOBu.RMgBr (1:1:2

ratio) reagents. Data are summarized in table 1.⁽⁹⁾

Table 1

entry	ketone	Grignard reagent (R in RMgBr)	procedure	product	isolated ¹⁰ yield (%)
1	<u>3</u>	Et	A		57
2	<u>3</u>	<i>i</i> Pr	A		94
3	<u>3</u>	Ph	A		14 ¹¹
4	<u>4</u>	Et	A		64
5	<u>4</u>	<i>i</i> Pr	A		75
6	<u>4</u>	Ph	A		17 ¹¹
7	<u>5</u>	Et	A		40 ¹¹
8	<u>5</u>	<i>i</i> Pr	A		95
9	<u>5</u>	Ph	A		27 ¹¹
10	<u>3</u>	<i>i</i> Pr	B		20
11	<u>3</u>	<i>i</i> Pr	C		85
12	<u>3</u>	Et	C		53
13	<u>3</u>	Ph	C		24

The results show that efficient 1,4-addition of Alkylgrignard reagents takes place with yields comparable to the G.C. yields reported for trialkylzincates.⁽⁶⁾ Arylgrignards gave low yields in the 1,4-addition reaction using our procedure. Furthermore the use of THF instead of diethylether strongly increases the yield (entries 2,10).

In order to gain insight into the nature of the zincate intermediates and to achieve enantioselective 1,4-additions the effects of a chiral alkoxide,

1-menthyloxymagnesiumbromide 6, and a chiral TMEDA analog ligand 7 were investigated.

The crystalline C_2 symmetric zinc complex 8 was prepared from S,S -(-)- N,N' -dimethyl- N,N' -bis(1-phenylethyl)-1,2-ethylenediamine 7⁽¹²⁾ using the procedure described for TMEDA. ZnCl_2 (scheme 2).⁽⁸⁾ The results of the enantioselective 1,4-additions are summarized in table 2.

Table 2

entry	ketone	zinc complex	i-PrMgBr (equiv.)	alkoxide (equiv.)	product: isolated yield % ⁽⁹⁾	ee % ⁽¹³⁾
1	<u>3</u>	<u>8</u>	3	—	65	5
2	<u>3</u>	<u>8</u>	2	KOtBu (1)	94	14
3	<u>3</u>	TMEDA. ZnCl_2	2	<u>6</u> (1)	80 ⁽¹¹⁾	9
4	<u>5</u>	TMEDA. ZnCl_2	2	<u>6</u> (1)	80 ⁽¹¹⁾	—

Low optical yields are obtained using triorganozincates prepared from the chiral TMEDA. ZnCl_2 analogue 8. (entry 1) It is evident that the use of 1 equivalent of *t*-butoxide as a non-transferable ligand improves both the yield and the enantioselectivity in this reaction. The enantioselectivity is comparable to results of the addition of lithiumtrialkylzincates to cyclohexenone using S,S -1,4-dimethylamino-2,3-dimethoxybutane as a chiral co-solvent.⁽¹⁴⁾ We propose that an alkoxy-(diamine)-monoalkylzinc complex is formed in analogy with recently proposed structures of zinc-catalysts for 1,2-additions.⁽²⁾ This complex binds one equivalent of Grignard compound to form the active reagent for 1,4-additions. The result with KOtBu and 8 (entry 2) as well as the results with 1-menthoxide as chiral non-transferable ligand in TMEDA. ZnCl_2 mediated additions (entry 3,4) support this mechanism.

Studies to improve the enantioselectivity in these 1,4-additions are in progress.

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 8. TMEDA.ZnCl₂ was prepared according to Isobe et al. in ref. 4.
 9. All product showed spectral data in accordance with those reported. Typical procedure **A**: 2.52g (10 mmol) of ZnCl₂.TMEDA was added to a stirred solution of 1.12g (10 mmol) KOtBu in 40 ml THF at 0°C under a nitrogen atmosphere. After 5 min. iPrMgBr (20 mmol; 8 ml of a 2.5N solution in diethylether) was added. The resulting mixture was stirred for 5 min. followed by the addition of 0.96g (10 mmol) of cyclohexenone. After 0.5 hr at 0°C the reaction mixture was poured into 50 ml 1N HCl and the product isolated by bulb to bulb distillation following a normal work-up using diethylether. **B**: same procedure except diethylether as solvent. **C**: THF, temperature -80°C to -20°C.
 10. Isolated yield; 100% starting material was recovered in entry 3, scheme 1.
 11. Purified by chromatography.
 12. L. Horner and K. Dickerhof, *Liebigs Ann. Chem.*, 1984, 1240; 8: $[\alpha]_D^{20}$ 54.8° (c 0.50, THF), mp 243.5-243.8, IR (KBr) 700, 735 cm⁻¹; ¹H-NMR (300 MHz, CDCl₃) 1.80 (d, 6H, J=6Hz) 1.92 (d, 2H, J=11Hz) 2.49 (s, 6H) 3.05 (d, 2H, J=11Hz) 4.30 (q, 2H, J=6Hz) 7.22-7.39 (m, 10H) ¹³C-NMR (300 MHz, CDCl₃) 19.32 (q) 36.11 (q) 54.57 (t) 66.23 (d) 128.34 (d) 128.68 (d) 129.47 (d) 135.12 (s), MS. M⁺-Cl: found: 395 (1.2%) 397 (1.05%) 399 (0.7%) 401 (0.2%); calc. : 395 (1.2%) 397 (1.10%) 399 (0.7%) 401 (0.2%), anal. C, H, Cl, N.
 - 13a Enantiomeric excess (ee) was determined by ¹³C-NMR of the diastereoisomeric (2R,3R)-(-)-2,3-butanediol ketals using the Hiemstra, Wynberg method: H. Hiemstra and H. Wynberg, *Tetrahedron Lett.*, 1977, 2183.
b entry 4; $[\alpha]_{578}^{20}$ =1.26 (c=6.75, CHCl₃).
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