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A Simple Method for Chelation Controlled Additions to α-Amino Aldehydes

Manfred T. Reetz*, Karin Rölfing and Nils Griebenow

Max-Planck-Institut für Kohlenforschung, Kaiser-Wilhelm-Platz 1, 45470 Mülheim/Ruhr, Germany

Abstract: *BOC- and Cbz-protected α-amino aldehydes derived from amino acids undergo stereoselective addition reactions with alkyl cuprates and manganese reagents, the chelation-controlled adducts being the major diastereomers (generally ds > 90%). Undesired racemization is not observed (ee > 99%).*

β-Amino alcohols constitute a pharmaceutically and biologically interesting class of compounds as such and as constituents of more complex molecules.[1] A popular synthetic approach involves the use of natural and unnatural amino acids as chiral non-racemic building blocks.[1-3] Accordingly, amino acids are converted into the corresponding protected amino aldehydes which are then reacted with C-nucleophiles. The basic problem is to control diastereoselectivity under conditions which do not lead to undesired racemization. The most commonly used protective groups are BOC (*t*-butyloxycarbonyl) and Cbz (benzyloxycarbonyl) residues. However, Grignard and Li-enolate additions to BOC or Cbz-protected α-amino aldehydes usually afford 1 : 2 or 1 : 3 mixtures of diastereomers,[2-4] partial racemization being possible.[5,6] The 9-phenyl-9-fluorenyl protective group imparts a high degree of configurational stability, but Grignard and Li-enolate additions provide 1 : 3 mixtures of diastereomers.[6] The Garner aldehyde derived from serine is a notable exception in that high levels of diastereoselectivity and little racemization (0 - 3%) result.[7] We have previously shown that *N,N*-dibenzylamino aldehydes react with RMgX, RLi, R_2CuLi, Me_3SiCN/ZnX_2, Li-enolates, and enolsilanes/$LiClO_4$ to provide the corresponding β-amino alcohols with >90% non-chelation control and no racemization.[3,8] Thus, the problem of non-chelation control has been solved in a general way, but inducing the opposite diastereoselectivity in favor of chelation control remains a challenge. Polt's one-pot use of α-imino esters derived from amino acids and benzophenone (O'Donnell's Schiff bases) in combination with $i Bu_2AlH/(iBu)_3Al$ and a three molar excess of RMgX or RLi is currently the most efficient way to obtain chelation controlled adducts for phenyl and vinyl-type additions (86 : 14 to >95 : <5 diastereomer ratios with essentially no racemization),[9] but alkylmetal reagents were not employed. We now describe a simple and general method for chelation controlled addition reactions of BOC- and Cbz-protected α-amino aldehydes **1** with alkyl cuprates and alkyl manganese[10] reagents.

Transmetalation of organolithium compounds with Cu- or Mn-salts provides reagents which add to aldehydes **1** with chelation control (Tables 1 and 2). Alkyl (but not vinyl or phenyl) reagents generally show diastereoselectivities of >90%.

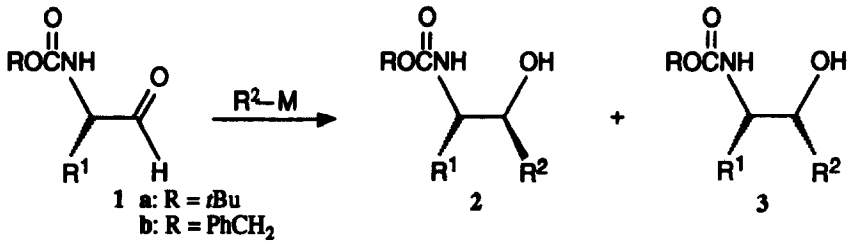

Table 1. Reactions of Organocopper Reagents with Aldehydes 1 in Diethylether[a].

Aldehyde	R^1	Reagent[b]	Temp./Time (°C / h)	% Conversion[c] (yield)	2 : 3[c]
1a	CH_3	3 CH_3Li	-78 / 3	88	46 : 54
1a	CH_3	1 $(CH_3)_2CuLi$	-55 / 3	84 (70)	96 : 4
1a	CH_3	3 *n*BuLi	-78 / 3	91	44 : 56
1a	CH_3	1.2 $(n\text{Bu})_2CuLi$	-78 / 4	93 (82)	91 : 9
1a	CH_3	3 *t*BuLi	-78 / 3	82	58 : 42
1a	CH_3	2.2 $(t\text{Bu})_2CuLi$	-78 / 3	94 (69)	97 : 3
1a	CH_3	3 $CH_2{=}C(CH_3)Li$	-78 / 3	93	48 : 52
1a	CH_3	2.2 $[CH_2{=}C(CH_3)]_2CuLi$	-78 / 3	94	80 : 20
1a	CH_3	3 PhLi	-78 / 3	92	66 : 34
1a	CH_3	2.2 Ph_2CuLi	-78 / 3	98	71 : 29
1b	CH_3	3 CH_3Li	-78 / 3	74	49 : 51
1b	CH_3	2 $(CH_3)_2CuLi$	-55 / 5	90 (62)	96 : 4
1b	CH_3	2 $[(CH_3CuCN)Li \cdot 2\ LiCl]$	-55 / 3	85	98 : 2
1b	CH_3	3 *n*BuLi	-78 / 3	86	48 : 52
1b	CH_3	2.2 $(n\text{Bu})_2CuLi$	-78 / 3	98	92 : 8
1a	$PhCH_2$	3 CH_3Li	-78 / 3	80	42 : 58
1a	$PhCH_2$	1.5 $(CH_3)_2CuLi$	-78 / 3	80 (68)	88 : 12
1a	$PhCH_2$	4.4 $[(CH_3CuCN)Li \cdot 2\ LiCl]$	-78 / 3	92	93 : 7
1a	$PhCH_2$	3 *n*BuLi	-78 / 3	92	38 : 62
1a	$PhCH_2$	1.5 $(n\text{Bu})_2CuLi$	-78 / 4	96 (80)	78 : 22
1a	$PhCH_2$	3 *t*BuLi	-78 / 3	77	60 : 40
1a	$PhCH_2$	2.2 $(t\text{Bu})_2CuLi$	-78 / 4	49 (26)	89 : 11
1a	$PhCH_2$	3 PhLi	-78 / 3	71	41 : 59
1a	$PhCH_2$	2.2 Ph_2CuLi	-78 / 3	94	69 : 31
1a	$(CH_3)_2CHCH_2$	3 CH_3Li	-55 / 3	81	51 : 49
1a	$(CH_3)_2CHCH_2$	1.5 $(CH_3)_2CuLi$	-55 / 3	94 (73)	93 : 7
1a	$(CH_3)_2CHCH_2$	3 $(CH_3)_2CuLi$	-55 / 3	99	95 : 5
1a	$(CH_3)_2CHCH_2$	4.4 $[(CH_3CuCN)Li \cdot 2\ LiCl]$	-78 / 3	92	97 : 3
1a	$(CH_3)_2CHCH_2$	3 *n*BuLi	-78 / 3	87	49 : 51
1a	$(CH_3)_2CHCH_2$	2.2 $(n\text{Bu})_2CuLi$	-78 / 3	94 (80)	89 : 11
1a	$(CH_3)_2CHCH_2$	3 *t*BuLi	-78 / 3	82	57 : 43
1a	$(CH_3)_2CHCH_2$	2.2 $(t\text{Bu})_2CuLi$	-78 / 4	84	96 : 4

[a] CuBr·SMe_2 was used to prepare R_2CuLi. [b] The numbers in front of the reagents indicate the amount of reagent used with respect to 1. [c] Conversion and diastereomer ratios were determined by GC analysis of the crude products. The numbers in parentheses refer to isolated pure products.

Table 2. Reactions of Organomanganese Reagents with Aldehydes 1 in THF.

Aldehyde	R^1	Reagent[a]	Temp./Time (°C / h)	% Conversion[b] (yield)	2 : 3[b]
1a	CH_3	2.2 CH_3Li	-78 / 2	76	40 : 60
1a	CH_3	2.2 CH_3MgI	-78 / 2	71	62 : 38
1a	CH_3	2.2 ($CH_3Li/MnCl_2$)	-78→-20 / 4	97	94 : 6
1a	CH_3	2.2 ($CH_3Li/MnBr_2$)	-55 / 3	90	95 : 5
1a	CH_3	2.2 (CH_3Li/MnI_2)	-78 / 3.5	41	81 : 19
1a	CH_3	2.2 (2 $CH_3Li/MnBr_2$)	-78 / 5	97 (66)	94 : 6
1a	CH_3	2.2 (*n*BuLi/$MnBr_2$)	-78 / 5	82	86 : 14
1a	CH_3	2.1 [(*n*BuLi/$MnBr_2$) · 2 LiBr]	-78→25/3	95 (63)	88 : 12
1a	CH_3	2.2 (PhLi/$MnBr_2$)	-55 / 17	88	78 : 22
1b	CH_3	2.2 ($CH_3Li/MnBr_2$)	-78 / 5.5	84	96 : 4
1b	CH_3	2.2 CH_2=CHMgBr	-78 / 4	77	56 : 44
1b	CH_3	2.2 (CH_2=CHMgBr/$MnBr_2$)	-78 / 5	62	66 : 34
1b	CH_3	2.2 (*n*BuLi/$MnBr_2$)	-78 / 3.5	82	93 : 7
1a	$PhCH_2$	2.2 CH_3MgI	-78 / 3	66	54 : 46
1a	$PhCH_2$	2.1 ($CH_3Li/MnBr_2$)	-55 / 2	85	89 : 11
1a	$PhCH_2$	2.2 (2 $CH_3Li/MnCl_2$)	-78 / 2.5	93	89 : 11
1a	$PhCH_2$	2.2 [(*n*BuLi/$MnBr_2$) · 2 LiBr]	-78 / 26	60	85 : 15
1a	$(CH_3)_2CHCH_2$	3 CH_3Li	-78 / 3	85	39 : 61
1a	$(CH_3)_2CHCH_2$	2.1 ($CH_3Li/MnBr_2$)	-50 / 3	97	96 : 4
1a	$(CH_3)_2CHCH_2$	2.2 (*n*-BuLi/$MnBr_2$)	-78 / 3	68	84 : 16

[a] The numbers in front of the reagents indicate the amount of reagent used with respect to 1.
[b] Conversion and diastereomer ratios were determined by GC analysis of the crude products. The numbers in parentheses refer to isolated pure products.

Control experiments show that the reactions proceed without any appreciable racemization (ee >99%).[11] Configurational assignment of adducts 2 was made by comparison with known compounds, chemical correlation and/or X-ray structural analysis.

In summary, alkylcopper and -manganese compounds are currently the most efficient reagents for chelation controlled Grignard-type additions to *N*-BOC or *N*-Cbz amino aldehydes, the reactions proceeding without any racemization. Diastereoselectivity is considerably lower in the case of phenyl and vinyl-type reagents, which means that our protocol[12] is complementary to Polt's method.[9]

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11. This was checked by GC (chiral phase) in the reactions of aldehyde **1a** ($R^1 = CH_3$). We thank F. Kobor and U. Häusig for help in the determination of the ee values and F. Sagheb for all other GC analyses.
12. **Typical procedure**: *Cuprate additions*: To a suspension of $CuBr{\cdot}SMe_2$ (3.8 mmol) in dry ether (30 ml) is added RLi (7.6 mmol, 1.6 M in ether or hexane) at -78°C under argon-atmosphere. After warming up until a clear solution is obtained the mixture is cooled to the given temperature and stirred for 30 min. Then the α-aminoaldehyde **1** (1.7 mmol) dissolved in 8 ml dry ether is added. After 3 - 4 h the reaction mixture is quenched with sat. NH_4Cl, diluted with ether, extracted once again with sat. NH_4Cl, sat. $NaHCO_3$, brine and dried over $MgSO_4$. The products are purified by flash chromatography.

    Manganese reagent additions: To a suspension of anhydrous MnX_2 (2.2 mmol) (and 4.4 mmol anhydrous LiX) in dry THF (10 ml) is added RLi (2.2 or 4.4 mmol, 1.6 M in ether or hexane) at 25°C under argon-atmosphere. The clear redbrown solution obtained is stirred for 30 min (for R = *n*-Bu; 1 min). After that the mixture is cooled to the given temperature and the α-aminoaldehyde **1** (1 mmol) dissolved in 8 ml dry THF is added. After the given time the reaction mixture is quenched with sat. NH_4Cl, diluted with ether, extracted with sat. aq. EDTA solution, sat. $NaHCO_3$, brine and dried over $MgSO_4$. Purification as above.

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