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ENANTIOSELECTIVE ADDITION OF (Z)- AND (E)-ALKENYLZINC BROMIDES TO ALDEHYDES: ASYMMETRIC SYNTHESIS OF SEC-ALLYLALCOHOLS

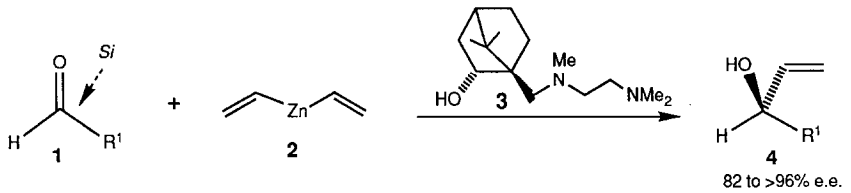
Wolfgang Oppolzer* and Rumen N. Radinov

Département de Chimie Organique, Université de Genève, CH-1211 Genève 4, Switzerland

Summary: *In situ* prepared (*Z*)- and (*E*)-1-alkenylzinc bromides **5** were added to various aldehydes **1** in the presence of lithiated (+)-*N*-methylephedrine or (+)-2-(*N*,*N*-dimethylamino)-1,2-diphenylethanol to give *sec.* allylalcohols **7** in high optical purity with simple recovery of the chiral aminol **6**.

Asymmetric ligand-controlled additions of diethyl- and dimethylzinc to aldehydes have been subject of numerous studies during the last five years. [1] Related additions of alkynylzinc reagents proceeded with variable π-face discrimination. [2] Uniformly high inductions were found in our laboratories on reaction of divinylzinc (**2**) with various aldehydes **1** in the presence of camphor-derived tridentate ligand **3** (Scheme 1). [3]

Scheme 1



We report here an even more attractive approach to synthetically important β-substituted, chiral allylalcohols. Our results are summarized in the Scheme 2 and the Tables 1,2. [4]

Scheme 2

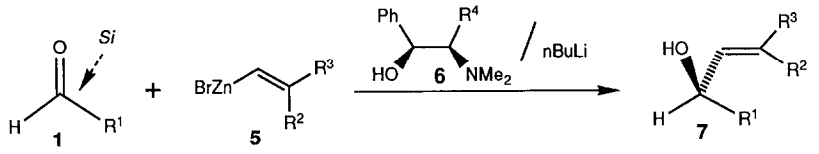


Table 1: Lithium (1*S*, 2*R*)-*N*-Methylephedrate-Promoted Enantioselective Additions of 1-Alkenylzinc Bromides to Aldehydes **1** + **5** → **7**.

		Aldehyde	Alkenyl Bromide		$ZnBr_2$ Molequiv	Allylalcohol Product **7**				
Entry	Series	R^1	R^2	R^3		Yield [%]	e.e.[a] [%]	Configuration	$[\alpha]_D$ found	$[\alpha]_D$ lit.
1	**a**	C_6H_5	CH_3	H	1.5	68	86	*S*	+167.7°	-101°[b]
2	**b**	*n*-C_4H_9	CH_3	H	1.5	75	78	*R*	+18.2°	----
3	**c**	*n*-C_6H_{13}	CH_3	H	1.5	72	78	*R*	+20.2°[c]	-27.1°[c]
4	**d**	*i*-C_4H_9	CH_3	H	1.5	70	86	*R*	+16.0°	+21.0°[d]
5	**e**	1-ethylpropyl	CH_3	H	1.5	65	92	*R*	-8.2°	----
6	**f**	cyclohexyl	CH_3	H	1.5	78	93	*R*	+26.3°	----
7	**g**	*t*-C_4H_9	CH_3	H	1.5	62	93	*S*	-24.9°	----
8	**h**	C_6H_5	H	CH_3	1.5	78	73	*S*	+50.3°	+12.5°[e]
9	**i**	*n*-$C_{12}H_{25}$	H	CH_3	1.5	76	85	*R*	+3.2°	+3.6°[f]
10	**j**	cyclohexyl	H	CH_3	1.5	73	83	*R*	-12.5°[g]	-13.6°[g]
11	**k**	*t*-C_4H_9	H	CH_3	1.5	48	>98	*S*	-19.3°	----
12	**l**	C_6H_5	*n*-C_6H_{13}	H	1.1	68	90	*S*	+168.7°	----
13	**m**	C_2H_5	*n*-C_6H_{13}	H	1.1	69	87	*R*	-19.5°[h]	-17.1°[h]
14	**n**	*n*-C_4H_9	*n*-C_6H_{13}	H	1.1	66	86	*R*	+15.6°	----
15	**o**	*n*-C_6H_{13}	*n*-C_6H_{13}	H	1.1	70	86	*R*	+17.9°	----
16	**p**	*i*-C_4H_9	*n*-C_6H_{13}	H	1.1	65	86	*R*	+14.7°	----
17	**q**	cyclohexyl	*n*-C_6H_{13}	H	1.1	73	95	*R*	+24.2°	----
18	**r**	*t*-C_4H_9	*n*-C_6H_{13}	H	1.1	67	97	*S*	-16.9°	----

a) Enantiomeric excess (e.e.) determined by HPLC (*Chiralcel OB*, entries *1*, *8*, *12*), or by ^{19}F-NMR of (*R*)-MTPA ester (entry *9*), or otherwise by GC of (1*S*)-camphanic acid esters. b) lit.: (*R*)-antipode, 61% e.e. [5] c) CH_2Cl_2, lit.: (*S*)-antipode 99% e.e. [6] d) lit.: 93% e.e. [7] e) lit.: 35% e.e. [5] f) lit.: 97% e.e. [8] g) EtOH, lit.: 98% e.e. [9] h) EtOH, lit.: >95% e.e. [10].

Lithiation of pure (*Z*)-1-bromo-1-propene with lithium metal in Et_2O, followed by transmetallation with $ZnBr_2$ (1.5 molequiv), successive addition of lithiated (1*S*, 2*R*)-*N*-methylephedrine (**6**, R^4 = Me, 1 molequiv) in toluene and benzaldehyde (1 molequiv) to the resulting (*Z*)-1-propenylzinc bromide solution at 0°C gave, after aq workup (*Z*,*S*)-(1-propenyl)benzenemethanol (68%) in 86% e.e. (Table 1, entry *1*).

Analogous lithium aminoalkoxide promoted addition of *in situ* prepared (*Z*)-1-propenylzinc bromide to straight-chain, β- and α-branched aliphatic aldehydes provided corresponding (*Z*)-allylalcohols **7**, R^3 = H in 78 to 93% e.e.. It appears that the π-face selectivity of the alkenylation increased with growing steric demand of the aldehyde (Table 1, entries *2* - *7*). A similar trend was observed on addition of (*E*)-1-propenylzinc bromide to various aldehydes in the presence of lithiated aminol **6**, R^4 = Me affording (*E*)-allylalcohols **7**, R^2 = H in 73 to >98% e.e. (entries *8* - *11*).

Extension of this approach to higher allylalcohols was exemplified by the addition of (*Z*)-1-*n*-octenylzinc bromide to a series of aldehydes proceeding with 86 to 97% aminoalkoxide-controlled face topicity (entries *12* - *18*). It thus follows that the (*Z*)/(*E*)-integrity of starting 1-alkenyl bromides is perfectly retained in the overall process. Nevertheless, several examples (*e.g.*, entries *2*, *3*, *8*) may call for further improvement of the face discrimination. It was gratifying to find that the addition of (*Z*)- or (*E*)-1-propenylzinc bromide in the presence of lithiated (*N*,*N*-dimethylamino)-1,2-diphenylethanol (**6**, R^4 = Ph) [11] resulted in significantly enhanced topicities (Table 2, *c.f.*, series **a**: 86 → 93% e.e.; series **c**: 78 → 86% e.e.; series **h**: 73 → 88% e.e.).

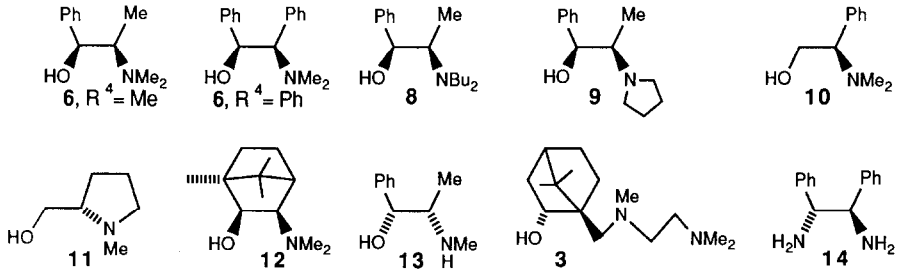
Table 2: Lithium (1*S*, 2*R*)-2-*N*,*N*-Dimethylamino-1,2-diphenylethoxide-Promoted Additions of 1-Alkenylzinc Bromides to Aldehydes: **1** + **5** → **7**

		Aldehyde	Alkenyl Bromide		$ZnBr_2$ Molequiv	Allylalcohol Product 7		
Entry	Series	R^1	R^2	R^3		Yield [%]	e.e.[a] [%]	Configuration
19	**a**	C_6H_5	CH_3	H	1.5	82	93	*S*
20	**c**	*n*-C_6H_{13}	CH_3	H	1.5	71	86	*R*
21	**f**	cyclohexyl	CH_3	H	1.5	62	91	*R*
22	**h**	C_6H_5	H	CH_3	1.5	63	88	*S*

a) Enantiomeric excess (e.e) determined by HPLC (*Chiralcel OB*, entries *19*, *22*) or by GC of (1*S*)-camphanic acid esters (entries *20*, *21*).

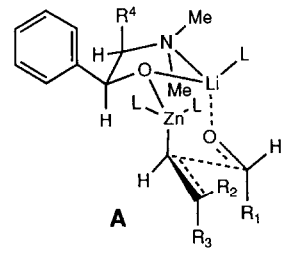
In contrast, other lithiated aminols or diamines (*e.g.*, **3**, **8** - **14**, Figure 1) exerted only modest induction (20 - 70% same sense of induction) in the reaction of (*Z*)-1-propenylzinc bromide with benzaldehyde.

Figure 1



The high aldehyde-*Si*-face preference consistently observed with ligands **6** (R^4 = CH_3 or Ph) is in agreement with transition state **A** (Figure 2).

Figure 2



We thus assume coordination of the aldehyde oxygen (*trans* to R^1) with the chelating lithium atom distal to the phenyl ring(s) and alkenyl-transfer *via* a six-centered bimetallic transition state.

It is worth noting that

1) both antipodes of *N*-methylephedrine as well as 2-amino-1,2-diphenyl-1-ethanol are commercially available allowing a convenient direction of the asymmetric induction in either sense.

2) The chiral source **6** can be easily recovered by simple extraction.

3) Only one molequiv of easily accessible alkenyl bromide is required so that an economic employment of more complex olefinic substrates can be expected.

Further exploration of catalytic alkenylzinc/aldehyde additions as a practical route to pivotal chiral allylalcohols is presently under way in our laboratories.

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4) All new compounds were characterized by IR, ^{1}H-NMR, ^{13}C-NMR and MS. $[\alpha]_D$-measurements in $CHCl_3$ unless otherwise specified (c = 0.3 to 1.7, T = 20 to 28°C). The following procedure is representative: Lithium, containing 2% Na (490 mg, 70 mmol) was obtained from the commercial 15% suspension in hexane (5.6 ml) by evaporation of the solvents in vacuum at rt. To the Li powder under argon was added dry ether (20 ml) and the suspension was cooled to -35°C. With stirring a solution of pure (>98%) (*Z*)-1-bromo-1-propene (1.70 g, 14 mmol) in ether (2 ml) was added dropwise. The mixture was stirred at -35°C for 2 h and filtered under argon. The 0.6 M (*Z*)-1-propenyllithium solution (17 ml, 10 mmol) was cooled to -35°C and treated dropwise with a 0.6 M solution of commercial zinc bromide in ether (25 ml, 15 mmol). The reaction mixture was stirred for an additional 1h at 0°C and then a solution of lithium (1*S*,2*R*)-*N*-methylephedrate, prepared by the addition of *n*-BuLi 1.6 M in hexanes (6.4 ml, 10 mmol) to a solution of (+)-*N*-methylephedrine (1.80 g, 10 mmol) in toluene (60 ml) at 0°C, was cannulated. The clear colorless solution was stirred for 1h at 0°C and cyclohexanecarboxaldehyde (1.20 ml, 10 mmol) was added neat. After stirring for 1h at 0°C the reaction was quenched by the addition of satd. aq ammonium chloride solution, the organic phase was separated and the aqueous phase was extracted with ether. The organic extracts were washed with a second portion of the ammonium chloride solution, dried (Na_2SO_4) and concentrated. Flash chromatography (SiO_2/ hexane - ether 10:1) and bulb-to-bulb distillation (130°C/ 0.01 mmHg) gave 1.20 g (78%) (*Z*,*R*)-α-(1-propenyl)cyclohexanemethanol (**7f**) of 93% ee.. $[\alpha]_D^{20}$ +26.3°, $[\alpha]_{578}^{20}$ +27.3°, $[\alpha]_{546}^{20}$ +31.0°, $[\alpha]_{436}^{20}$ 52.6°, $[\alpha]_{365}^{20}$ 83.0° (c 1.44, $CHCl_3$). (+)-*N*-Methylephedrine was recovered quantitatively and without loss of optical purity (1.798 g, 99.9%; $[\alpha]_D^{20}$ +30.0°, c = 4.51, MeOH) from the aqueous phases by basification with conc. aq NaOH solution (at pH 10-12 it crystallized out of the aqueous phase) and extraction in ether.

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