APPLIED ORGANOMETALLIC CHEMISTRY
Appl. Organometal. Chem. **13**, 481–486 (1999)

Asymmetric Alkylation of Aromatic Aldehydes with Dialkylzinc Catalyzed by Novel Amino Derivatives of Hydroxytetrahydropyran

Günther Oehme,[1] Irina Iovel[2] and Edmunds Lukevics[2]*
[1]Institut für Organische Katalyseforschung an der Universität Rostock eV, Buchbinderstr. 5–6, 18055 Rostock, Germany
[2]Latvian Institute of Organic Synthesis, 21 Aizkraukles Street, Riga, LV-1006, Latvia

Novel, specially prepared, tetrahydropyran-based γ-amino alcohols (*S*)-2-(aminomethyl)-3-hydroxy-6-ethoxy(phenoxy)-tetrahydropyrans (I) (amino = n-Bu$_2$N, piperidinyl, pyrrolidinyl, azetidinyl) were tested as catalysts in the asymmetric addition of Et$_2$Zn and n-Bu$_2$Zn to (hetero)aromatic aldehydes. In most cases the phenoxy derivatives of I acted more enantioselectively than the ethoxy ones. The dibutylamino derivaties showed the least enantioselectivity; the pyrrolidinyl derivatives were more active as catalysts than piperidinyl and azetidinyl compounds. The highest enantioselectivity was observed in the addition of Et$_2$Zn to benzaldehyde in the presence of (*S*)-2-(*N*-pyrrolidinylmethyl)-3-hydroxy-6-phenoxytetrahydropyran. The corresponding alcohol was prepared with 72% *ee* (*R*-configuration). The addition of dibutylzinc proceeded slowly and less selectively. The alkylation of (hetero)aromatic aldehydes with Et$_2$Zn and n-Bu$_2$Zn was also studied in the presence of the known optical inductor (1*S*,2*R*)-*N*,*N*-dibutylnorephedrine. Some chiral aromatic secondary alcohols were synthesized in high chemical yields and up to 93% *ee* enantioselectivity. Copyright © 1999 John Wiley & Sons, Ltd.

Keywords: Asymmetric catalysis; dialkylzinc; alkylation; chiral 1,3-amino alcohols; aromatic secondary alcohols

Received 4 June 1998; accepted 28 October 1998

INTRODUCTION

The synthesis of new effective chiral ligands is essential for efficient asymmetric catalysis development.[1–3] Although various kinds of chiral amino alcohols are used as catalysts and auxiliaries in enantioselective catalysis and asymmetric synthesis, these are mainly 1,2-amino alcohols.[1–7] Chiral 1,3-amino alcohols are rare and less studied. On the other hand, the enantioselective addition of organometallic reagents to aldehydes yielding valuable optically active secondary alcohols has both theoretical and practical importance.

Recently we have studied the preparation of optically active ligands and complexes and their behavior in various asymmetric catalytic reactions (hydrosilylation, hydrogen transfer reduction, trimethylsilylcyanation and alkylation).[8–11] Herein we report the results of alkylation of aldehydes with dialkylzinc using new chiral catalysts, namely tetrahydropyran 1,3-amino alcohols (**I**) synthesized from tri-*O*-acetyl-D-glucal in five-step procedures (Scheme 1). The compounds **I** were obtained as crystals or oils in 24–83% yields. The specific optical rotation and some other data for the compounds **I** are listed in Table 1. The ^{1}H NMR, ^{13}C NMR, GC–MS and IR spectra, as well as the elemental analyses, for compounds **1–8** have been found in good agreement with the structures of these aminocarbinols. Descriptions of the syntheses and spectral characteristics of the catalysts and intermediates will be published elsewhere.

EXPERIMENTAL

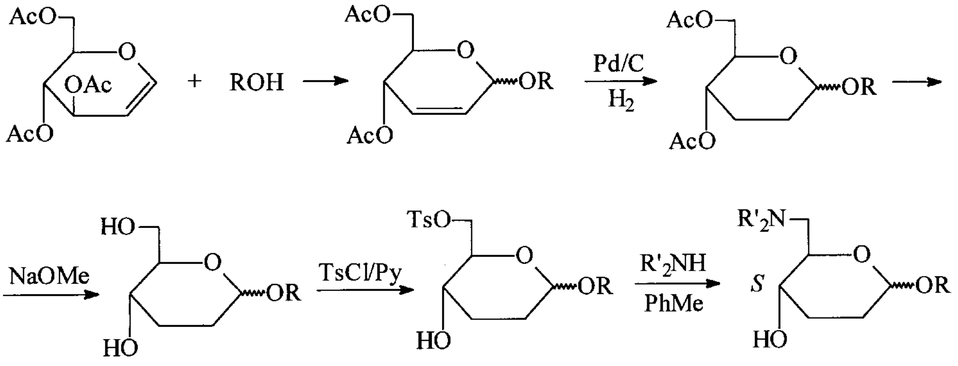
General procedure

The catalyst (0.06 mmol), 2.2 ml of dry toluene and

---

* Correspondence to: Edmunds Lukevics, Latvian Institute of Organic synthesis, 21 Aizkraukles Street, Riga, LV-1006, Latvia.

CCC 0268–2605/99/070481–06 $17.50



I (1–8)

Scheme 1 Synthesis of chiral catalyst **I** (**1–8**): R = Et, Ph; R′$_2$ = n-Bu$_2$, —(H$_2$C)$_n$— (n = 3–5).

Table 1 Characteristics of the compounds **I** (**1–8**)

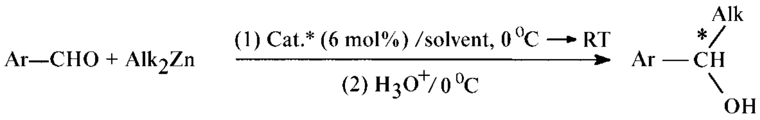
Compound	R	R′$_2$	n	Yield (%)	M.p. (°C)	[α]$_D$ (deg.) (c in CHCl$_3$) at 22–25 °C
1	Et	n-Bu$_2$	—	30	Oil	+33 (1.03)
2	Ph	n-Bu$_2$	—	32	Oil	+67 (0.97)
3	Et	—(H$_2$C)$_n$—	5	68	Oil	+63 (0.74)
4	Ph	—(H$_2$C)$_n$—	5	83	84	+107 (0.97)
5	Et	—(H$_2$C)$_n$—	4	38	Oil	+64 (0.81)
6	Ph	—(H$_2$C)$_n$—	4	42	Oil	+89 (0.97)
7	Et	—(H$_2$C)$_n$—	3	24	76	+78 (1.02)
8	Ph	—(H$_2$C)$_n$—	3	60	75	+135 (0.60)

aldehyde (1 mmol) were placed in a flame-dried Schlenk tube under an argon atmosphere. The mixture was stirred at room temperature for 15 min, then cooled to 0 °C and 2.2 ml (2.2 mmol) of a 1 M solution of diethylzinc in toluene or dibutylzinc in heptane was added. The reaction mixture was slowly warmed to room temperature. For workup the mixture was cooled to 0 °C, and the reaction was quenched by the addition of 1 M HCl (or saturated NH$_4$Cl solution in the case of heterocyclic substrates) for 2 h. The organic layer was separated and analyzed by means of GC, GC–MS and chiral GC.

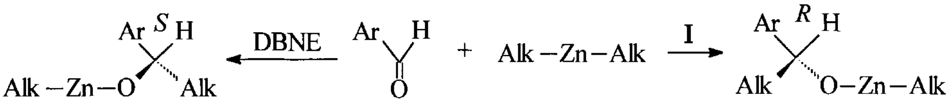
Materials and methods

Toluene was distilled from LiAlH$_4$ prior to use. Diethylzinc (1 M solution in toluene), dibutylzinc (1 M solution in heptane) and (1*S*,2*R*)-(−)-2-dibutylamino-1-phenyl-1-propanol (*N*,*N*-dibutyl-D-norephedrine, DBNE) were purchased from Fluka. The aldehydes (from Merck and Fluka) were distilled before use.

GC analysis was performed on an HP 5880-A chromatograph equipped with a flame-ionization detector, on a capillary column packed with HP-5 nonpolar phase (5% phenyl-substituted methyl polysiloxane, 30 m × 0.25 mm); the carrier gas was helium (1 ml min^{-1}) and the temperature program was set at 50 → 260 °C at 8 °C min^{-1}. GC–MS spectra were obtained by means of an HP 5890 (II) chromatograph on an HP 101 capillary column (methyl silicon fluid, 25 m × 0.2 mm), connected to an HP Engine 5989-A mass spectrometer (70 eV). The chiral separations were performed on an HP 5890 (II) gas chromatograph with Macherey–Nagel capillary columns containing various chiral phases: Cyclodex IP (50 m × 0.2 mm), Lipodex E (50 m × 0.2 mm), Chiraldex G-TA (30 m × 0.2 mm). The carrier gas was argon (1 ml min^{-1}) for the resolution of the ethyl derivatives, and hydrogen (1.5 ml min^{-1}) for the butyl derivatives.



Scheme 2 Asymmetric addition of dialkylzinc to (hetero) aromatic aldehydes: Ar = Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$, 4-$EtOC_6H_4$, 2-furyl (Fur), 2-thienyl (Th); Alk = Et, n-Bu; solvent = toluene or toluene/heptane (1:1); Cat* = **I** or DBNE; RT = room temperature.



Scheme 3 Directions of asymmetric induction in alkylation of aromatic aldehydes with Alk_2Zn catalyzed by DBNE and **I**.

RESULTS AND DISCUSSION

In our previous work[11] the addition of Et_2Zn to heterocyclic aldehydes HetCHO (Het = 2-furyl,2-thienyl,2-,3-,4-pyridyl) and benzaldehyde was studied in the presence of two known *β*-amino alcohols, (*S*)-2-amino-1-butanol (AB) and (1*S*,2*R*)-*N*,*N*-dibutylnorephedrine (DBNE); various chiral secondary heterocyclic alcohols of formula HetCH(OH)Et were synthesized in yields of 95–98% and up to 92% *ee* enantioselectivity.

In the present paper we report the results of asymmetric alkylation of a number of aromatic and heterocyclic aldehydes with Et_2Zn and n-Bu_2Zn catalyzed by novel 1,3-amino alcohols **I**, yielding the corresponding secondary chiral alcohols (Scheme 2).

The reactions of Scheme 2 were also carried out in the presence of DBNE, affording (hetero) aromatic alcohols with predominance of the *S*-configuration in accordance with the rule[3,11] (Scheme 3, left hand side). The alcohols with known absolute configuration were necessary as reference compounds for chiral GC analysis.

The absolute configuration and enantiomeric purity of the secondary alcohols synthesized were found by means of the GC method with chiral phase columns. Comparing GC spectra obtained for PhCH(OH)Et prepared in the presence of (a) a catalyst **6** and (b) DBNE, it can be seen in Fig. 1 that our catalyst induces *R* optical activity in contrast to DBNE.

In all cases catalysis by 1,3-amino alcohols **I** gave the optically active aromatic secondary alcohols of which the absolute configuration was opposite to that obtained with DBNE catalyst. This fact means that catalysts **1–8** induce the optical activity in the *R*-configuration (Scheme 3, right-hand side).

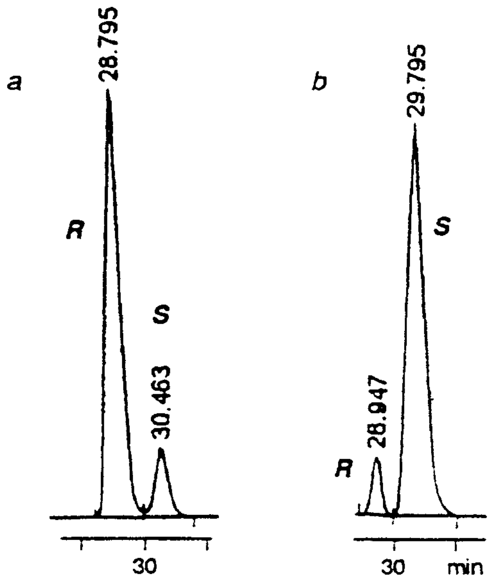


Figure 1 GC chiral separation of 1-phenyl-l-propanol synthesized in the presence of catalyst **6** (a) and DBNE (b). GC conditions: Cyclodex IP chiral phase (50 m × 0.2 mm), 110 °C, argon carrier gas (1 ml min^{-1}).

The alkylation of aldehydes with diethylzinc was studied in the presence of all the catalysts **I** synthesized (Table 2). The *ee* values fluctuated from 16% to 72%, depending on the aldehyde and catalyst structures. The dibutylamino derivatives (**1, 2**) were characterized by minimal enantioselectivity. In most cases the phenoxy derivatives (**4, 6, 8**) were more active than the corresponding ethoxy ones (**3, 5, 7**). The pyrrolidinyl (**5, 6**) derivatives were more active than the piperidinyl (**3, 4**) and azetidinyl (**7, 8**) compounds. The maximum enantioselectivity was observed in the addition of Et_2Zn to benzaldehyde catalyzed by (*S*)-2-(*N*-

Table 2 Alkylation of aldehydes with diethylzinc catalyzed by **I** (solvent, toluene; molar ratio ArCHO/Et_2Zn/**I** = 1:2.2:0.06; temperature, 0 °C → RT)

				Alcohol	
Ar	Catalyst	Reaction time (h)	Conversion (%)	Yield (%)[a]	*ee* (%)[b] (*R*-config.)
Ph	**1**	20	85	79	26
	2	20	90	71	16
	3	28	97	96	35
	4	70	99	96	45
	5	24	94	90	67
	6	45	96	88	72
	7	24	83	55	46
	8	46	91	82	69
4-ClC_6H_4	**3**	44	100	100	46
	4	32	97	93	50
	5	46	62	58	60
	6	32	87	76	68
	7	46	91	73	60
	8	22	90	82	71
4-$MeOC_6H_4$	**3**	22	78	75	41
	4	22	61	56	57
	5	28	44	28	58
	6	46	72	59	69
4-$EtOC_6H_4$	**3**	27	90	90	42
	4	22	60	60	55
	5	28	54	32	57
	6	46	64	42	54.5
	8	46	33	23	60.5
Fur	**3**	28	100	100	21
Th	**3**	28	57	55	33

[a] Determined by GC analysis (see Experimental Section).
[b] Determined by chiral GC (for the GC conditions, see Table 5).

pyrrolidinylmethyl)-3-hydroxy-6-phenoxytetrahydropyran (**6**); the corresponding alcohol (1-phenyl-1-propanol) was prepared with 72% *ee* enantioselectivity. The addition of dibutylzinc proceeded more slowly and less selectively (Table 3).

Table 3 Addition of dibutylzinc to benzaldehyde catalyzed by **I** (solvent, toluene/heptane (1:1), molar ratio PhCHO/n-Bu_2Zn/**I** = 1:2.2:0.06; temperature, 0 °C → RT)

			Alcohol	
Catalyst	Reaction time (h)	Conversion (%)[a]	Yield (%)[a]	*ee* (%)[b] (*R*-config.)
3	64	60	48	45
4	64	79	61	42

[a,b] See footnotes in Table 2.

The alkylation of (hetero)aromatic aldehydes with Et_2Zn and n-Bu_2Zn was also studied in the presence of DBNE, and the corresponding alcohols were obtained in high yields and 86–93% *ee* enantioselectivity (Table 4).

Chiral GC resolutions of the optically active secondary alcohols synthesized were performed on columns packed with different chiral chromatographic phases (Table 5). In contrast with all the propanols synthesized as well as the butyl derivative obtained from furfural FurCH(OH)Bu^n, the chiral separations of 1-phenyl- and 1-(2-thienyl)-1-pentanols were impossible by means of argon used as a carrier gas. Resolutions of these two compounds were successful on a column with Chiraldex G-TA phase using hydrogen as a carrier gas.

Mass spectra of the obtained chiral (hetero)aromatic secondary alcohols are listed in Table 6.

Table 4 Addition of dialkylzinc to aldehydes catalyzed by DBNE (solvent, toluene or toluene/heptane (1:1), molar ratio ArCHO/Alk$_2$Zn/DBNE = 1:2.2:0.06, temperature, 0 °C → RT)

				Alcohol	
Ar	Alk	Reaction time (h)	Conversion (%)[a]	Yield (%)[a]	*ee* (%)[b] (*S*-config.)
Ph	Et	44	100	98	90
	n-Bu	42	88	56	90
4-ClC$_6$H$_4$	Et	46	98	93	90
4-MeOC$_6$H$_4$	Et	22	96	91	92
4-EtOC$_6$H$_4$	Et	22	83	83	90
Fur	Et	70	98	96	86
	n-Bu	23	100	88	90
Th	Et	70	100	98	92
	n-Bu	23	85	67	93

[a,b] See footnotes in Table 2.

Table 5 Data on the chiral GC resolution of the secondary (hetero)aromatic alcohols ArCH(OH)Alk

Alcohol					Retention time (min)	
Ar	Alk	Chiral GC phase	Carrier gas (ml min^{-1})	Temp. Isothermal temperature regime (°C)	*R*-config.	*S*-config.
Ph	Et	Cyclodex IP	Ar (1.0)	110	28.7–29.0	29.7–30.5
4-CIC$_6$H$_4$	Et	Cyclodex IP	Ar (1.0)	140	24.1–24.3	24.8–30.0
4-MeOC$_6$H$_4$	Et	Cyclodex IP	Ar (1.0)	135	33.2–33.5	34.3–34.5
4-EtOC$_6$H$_4$	Et	Cyclodex IP	Ar (1.0)	135	43.5–43.9	45.1–45.5
Fur	Et	Lipodex E	Ar (1.0)	80	9.1–9.3	8.7–8.9
Th	Et	Cyclodex IP	Ar (1.0)	120	31.3–31.5	33.1–33.4
Ph	n-Bu	Chiraldex G-TA	H$_2$ (1.5)	105	15.1–15.3	15.6–15.8
Fur	n-Bu	Cyclodex IP	Ar (1.0)	115	21.6–21.8	20.7–21.0
Th	n-Bu	Chiraldex G-TA	H$_2$ (1.5)	60	22.6–22.9	23.3–23.5

Table 6 Mass spectra of aromatic and heterocyclic alcohols ArCH(OH)Alk[a]

Alcohol		*m*/*z* (rel. intensity, %)							
Ar	Alk	M$^+$	M$^+$−H$_2$O	M$^+$−Alk	ArC$^+$	(ArH+H$^+$)	Ar$^+$	PhOH$_2$$^+$	Ph
Ph	Et	136 (14)	—	107 (100)	—	79 (79)	77 (32)	—	—
4-CIC$_6$H$_4$	Et	170 (14)	—	141 (100)		113 (30)	111 (7)	—	77 (76)
4-MeOC$_6$H$_4$	Et	166 (14)	148 (10)	137 (100)		109 (36)	—	95 (25)	77 (20)
4-EtOC$_6$H$_4$	Et	180 (14)	162 (27)	151 (100)	133 (30)	109 (36)	—	95 (25)	77 (20)
Ph	n-Bu	164 (13)	—	107 (100)	—	79 (65)	77 (30)	—	—
Fur	n-Bu	154 (10)	—	97 (100)	—	69 (12)	—	—	—
Th	n-Bu	170 (8)	152 (8)	113 (100)	—	85 (34)	—	—	—

[a] Spectra of HetCH(OH)Et (Het = Fur, Th) are given in ref. 11.

CONCLUSIONS

Asymmetric addition of diethyl- and dibutyl-zinc to a number of (hetero)aromatic aldehydes has been studied in the presence of a series of new tetrahydropyran-based 1,3-amino alcohols synthesized from tri-*O*-acetyl-D-glucal as well as in the presence of DBNE catalyst. The influence of the structure of chiral auxiliaries and substrates on the enantioselectivity of the alkylation has been determined. Amongst the novel catalysts the phenoxypyrrolidinyl derivative exhibited the highest enantioselectivity (72% *ee*, *R*-configuration). Various chiral aromatic and heterocyclic secondary alcohols were synthesized with high yields and enantiomeric purities (up to 93% *ee*, *S*-configuration) in the presence of DBNE. In the course of this work different chiral phases and other optimal GC parameters have been found for the effective separation of the chiral alcohols prepared.

Acknowledgements The authors are grateful to Mrs H. Baudisch, Mrs M. Diehr and Mrs K. Kortus for assistance and for the performance of analyses.

REFERENCES

1. J. Seyden-Penne, *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*, Wiley, New York, 1995.
2. R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, 1994.
3. *Catalytic Asymmetric Synthesis*, I. Ojima, (ed.) VCH, New York, 1993.
4. *Stereoselective Synthesis* (Helmchen, G., Hoffman, R. W., Mulzer, J. and Schaumann, E.)(eds) *Methods of Organic Chemistry (Houben-Weyl)*, Vol. E21, Thieme, Stuttgart, 1995.
5. D. J. Ager, I. Prakash, and D. R. Schaad, *Chem. Rev.* **92**, 835 (1996).
6. A. Vidal-Ferran, A. Moyano, M. A. Perricas, and A. Riera, *J. Org. Chem.* **62**, 4970 (1997).
7. For reviews, see: (a) K. Tomioka, *Synthesis* 541 (1990); (b) R. Noyori, and M. Kitamura, *Angew. Chem. Int. Ed. Engl.* **30**, 49 (1991); (c) K. Soai, and S. Niva, *Chem. Rev.* **92**, 833 (1992); (d) G. Chelucci, *Gazz. Chim. Ital.* **122**, 89 (1992); (e) A. Togni, and L. M. Venanzi, *Angew. Chem.* **106**, 517 (1994); (f) D. J. Berrisford, C. Bolm, and K. B. Sharpless, *Angew. Chem. Int. Ed. Engl.* **34**, 1059 (1995); (g) P. Knochel, S. Vettel, and C. Eisenberg, *Appl. Organomet. Chem.* **9**, 175 (1995).
8. G. Oehme, I. Iovel, C. Facklam, and E. Lukevics, *Chem. Heterocycl. Comp.* **31**, 735 (1995).
9. I. Iovel, K. Rubina, J. Popelis, A. Gaukhman, and E. Lukevics, *Chem. Heterocycl. Comp.* **32**, 294 (1996).
10. I. Iovel, J. Popelis, M. Fleisher, and E. Lukevics, *Tetrahedron: Asymmetry* **8**, 1279 (1997).
11. I. Iovel, G. Oehme, and E. Lukevics, *Appl. Organomet. Chem.* **12**, 469 (1998).