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Novel 3,4-Diarylpyrrolidine-Based Chiral Ligands for the Asymmetric Reaction of Arylmagnesium Bromides with Aldehydes¶

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Utilizing novel chiral diamine ligands, asymmetric addition of arylmagnesium bromides to aldehydes provided the corresponding carbinols in 40-75% ee.

Design of the chiral ligand and its application to the asymmetric addition of organometallics to carbonyl compounds present a focused challenge of substantial international interest.[1-3] As part of a program approaching to the chiral ligand-mediated asymmetric reactions,[4] we designed two novel chiral diamines, 1 and 2. These diamines consist of two trans-3,4-diarylpyrrolidine units, 4 and 6, being bridged by ethylene chain. The C_2 symmetry of 1 and 2 would be effective in forming the well organized chelate complex with organometallics.[1c] Since arylmetals have been scarcely used in this type of asymmetric reactions, we describe herein chiral ligand-mediated asymmetric reactions of arylmagnesium bromides with aldehydes, which produced the corresponding carbinols in 40-75% ee.

Optically pure (3R,4R)-diphenylpyrrolidine (4: $[\alpha]_D^{20}$ -226° ($CHCl_3$)) was prepared in 71% overall yield from (2R,3R)-diphenyl-1,4-butanediol (3).[5,6] (3R,4R)-Dixylylpyrrolidine (6: $[\alpha]_D^{24}$ -176° (MeOH) for hydrochloride) was prepared in 40% overall yield via resolution of the corresponding dl-5[7] with (-)-phenethylamine.[8] Diamine ligands, 1 ($[\alpha]_D^{20}$ -143° ($CHCl_3$), ^1H NMR ($CDCl_3$) δ=2.6-3.6 (16H, m) and 7.16 (20H, s)) and 2 ($[\alpha]_D^{22}$ -135° ($CHCl_3$), ^1H NMR ($CDCl_3$) δ=2.25 (24H, s), 2.8-3.3 (16H, m), and 6.84 (12H, s)), were prepared in 48 and 65% yield, respectively,

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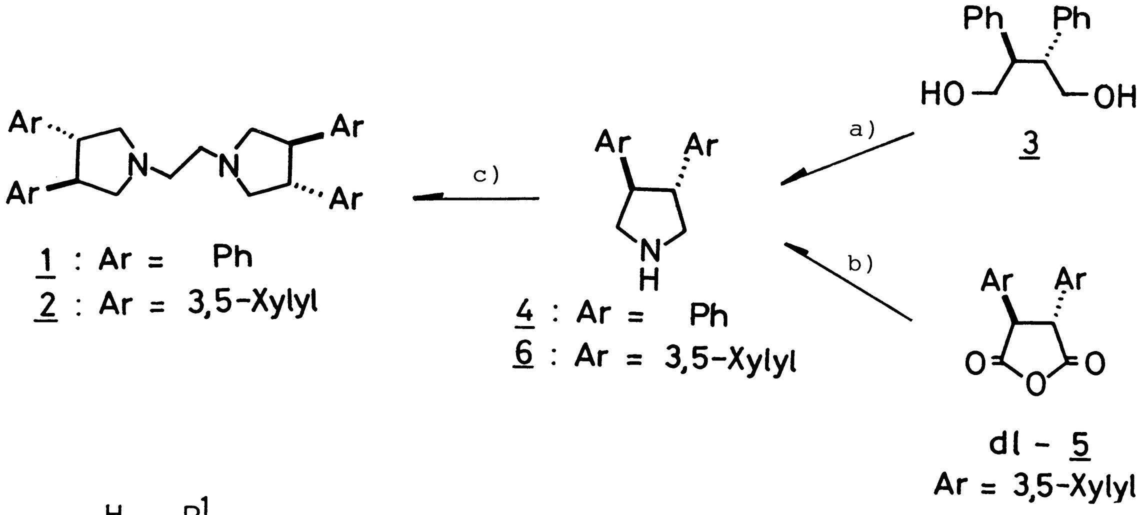
¶ This paper is dedicated to Professor Teruaki Mukaiyama on the occasion of his 60th birthday.

in two steps from the corresponding pyrrolidines (4, 6).

Typical reaction procedure is as follows. A solution of α-naphthylmagnesium bromide (2.0 mmol) in benzene-ether (2:1, 3 ml) was added to a stirred solution of 2 (2.4 mmol) in toluene (100 ml) at -78 °C. After 30 min stirring at the same temperature, the reagent solution was cooled to -100 °C and a solution of benzaldehyde (0.8 mmol) in toluene (5 ml) was added. The mixture was stirred at -100 °C for 1 h and quenched with 5% aqueous HCl. Usual work-up and following silica gel column chromatography afforded (S)-α-naphthylphenylcarbinol (94%) in 75% ee. The chiral diamine was recovered for reuse as its hydrochloride in a good yield by simple filtration.

As summarized in the Table 1, both diamines well mediated asymmetric reactions and the selectivities are in good relationships with the bulkiness of the aldehyde substituents. The possible origins of enantioface selection are probably related to the formulated structure 7.$^{9)}$

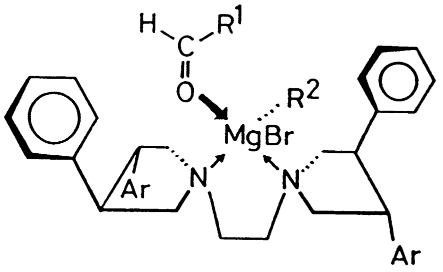
It is worthwhile to note that, as listed in the top three runs in the Table, a linear relationship between reciprocal of the reaction temperature and log (S-



1 : Ar = Ph
2 : Ar = 3,5-Xylyl

4 : Ar = Ph
6 : Ar = 3,5-Xylyl

3



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a) p-TsCl/Py; PhCH$_2$NH$_2$/xylene; 10% Pd/C-HCOOH/MeOH
b) PhMeCHNH$_2$/PhH; recrystallization from EtOH; AcOH-c. HCl; LAH/THF; 10% Pd/C-HCOOH/MeOH
c) ClCOCOCl-NEt$_3$/CH$_2$Cl$_2$; LAH/THF

Table 1. Asymmetric Reaction of Arylmagnesium Bromides with Aldehydes Mediated by Chiral Diamine Ligands (1 and 2)

$$R^1CHO + R^2MgBr \xrightarrow{\text{1 or 2}} R^1R^2CHOH$$

R^1	R^2	Ligand[a)]	Temp/°C	[α]/°	ee(%)(conf'n)	Yield/%
Ph	α-Nap[b)]	1	-100	-84.4[d)]	71(S)	92
Ph	α-Nap[b)]	1	-78	-76.0[d)]	64(S)	96
Ph	α-Nap[b)]	1	-45	-65.3[d)]	55(S)	94
Ph	α-Nap[b)]	2	-100	-88.0[d)]	75(S)	94
t-Bu	Ph	1[c)]	-100	-21.6[e)]	60(S)	82
c-Hex	Ph	2	-100	-15.6[e)]	55(S)	68
i-Pr	Ph	1[c)]	-100	-22.6[e)]	47(S)	68
Bu	Ph	1[c)]	-100	-14.3[e)]	40(S)	73

a) Ratio: R^1CHO/R^2MgBr/Ligand=1/2.5/3. b) α-naphthylmagnesium bromide. c) Ratio: R^1CHO/R^2MgBr/Ligand=1/1.25/1.5. d) NMR analysis of the acetate of the alcohol ($[\alpha]^{25}_{435}$ -76.0° (c 2.00, acetone)) in C_6D_6 in the presence of $Eu(hfc)_3$ indicated the optical purity of 64%. G. Wittig and U. Thiele, Justus Liebigs Ann. Chem., 726, 1 (1969). e) For the calculation of ee, reported maximum optical rotation was used. R^2=Ph, R^1 : t-Bu ($[\alpha]^{20}_D$ -36.2° (c 9.0, Et_2O)); c-Hex ($[\alpha]^{22}_D$ -28.3° (c 3.3, PhH)); i-Pr ($[\alpha]^{20}_D$ -47.7° (c 7.0, Et_2O)), R. Macleod, F. J. Welch, and H. S. Mosher, J. Am. Chem. Soc., 82, 876 (1960); Bu ($[\alpha]^{25}_D$ 35.7° (c 3.0, C_6H_6)), references 1c,h).

isomer/R-isomer) suggests the monomeric structure similar to 7[9)] to be an actual reactive species at temperature ranging from -45 to -100 °C. The difference in activation energies of the reactions leading to the S and R carbinols is estimated to be 0.15 kJ/mol (0.6 kcal/mol).

The novel chiral ligands, 1 and 2, characterized by the 3,4-diarylpyrrolidine units at the both end of ethylene bridge may offer the another choice of chiral catalyst.[1c)]

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6) Satisfactory spectroscopic (NMR, IR, MS) and combustion analytical data were obtained for all new compounds described herein.

7) Prepared from 3,5-dimethylphenylacetonitrile (A. Schonne, E. Braye, and A. Bruylants, Bull. Soc. Chim. Belg., 62, 155 (1953)) by the modification of the reported method for 2,3-diphenylsuccinic anhydride. R. B. Davis and J. A. Ward, Jr., Org. Synth., Coll. Vol. 4, 392 (1963).

8) The absolute configuration was established by converting to the known compound with definite absolute configuration. Details will be reported in due course.

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