Enantioselective Phenylation of Prochiral Aldehydes Using a Kinetically Formed Chiral Complex Between Grignard–Zinc Halide Reagent and *N,N*-Dibutylnorephedrine

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Optically active phenylmethanols have been synthesized in good to high enantiomeric excess (up to 82% e.e.) by the enantioselective addition of a kinetically formed complex (between phenyl Grignard–zinc halide and *N,N*-dibutylnorephedrine) to aliphatic, aromatic and α,β-unsaturated aldehydes.

Although chiral metal complexes have often been employed in enantioselective asymmetric syntheses,[1] the kinetic or thermodynamic conditions required for their formation has received little attention.[2] In contrast, enantioselective alkylation of aldehydes with organometallic reagents has attracted much attention.[3] However, the structure of organometallic reagents

Table 1 Effect of the conditions of complex formation and chiral ligands on the enantioselective phenylation of 2-naphthaldehyde **1a**

Entry[a]	Chiral ligand **3**	Complex formation[b] Time (Temp.)	Alcohol **4a** Yield (%)	E.e. (%)[c]
1	None	—	99	—
2[d]	(1*S*,2*R*)-**3a**	2 h (50 °C)	95	26
3	(1*S*,2*R*)-**3a**	30 min (r.t.)	44	67
4	(1*S*,2*R*)-**3a**	20 s (0 °C)	40	77
5[e]	(1*R*,2*S*)-**3a**	20 s (0 °C)	83	79
6	(1*S*,2*R*)-**3b**[f]	30 min (r.t.)	100	58
7	(1*S*,2*R*)-**3c**[f]	2 h (r.t.)	92	57
8	(1*S*,2*R*)-**3d**	20 s (0 °C)	91	1

[a] Molar ratio **1a**–**2**–**3**, 1:1:1. After the complex between **2** and **3** was formed, **1a** was added at room temperature. [b] Reaction time and temperatures of the complex formation between **2** and **3**. [c] Determined by HPLC analyses using a chiral column (Chiralcel OD, 250 mm; 254 nm UV detector; eluent 10% propan-2-ol in hexane; flow rate 0.7 cm^3/min); retention time/min for **4a**, 18.1 for major peak, 21.1 for minor peak. [d] After the complex formation, 1 further equiv. of **2** was added. [e] Molar ratio **1a**–**2**–**3a**, 1:2:3. [f] Prepared *in situ* by the reaction of **3a** with BuLi and Et_2Zn, respectively.

Table 2 Enantioselective phenylation of aldehydes **1a**–**e** in the presence of (1*R*,2*S*)-(+)-DBNE

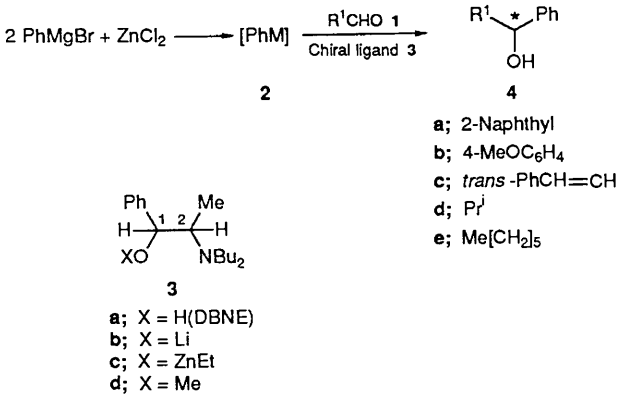
Entry	Aldehyde	Alcohol **4a**–**e** $[\alpha]_D$ (Temp./°C, *c*, solvent)	Yield (%)	E.e. (%)	Config.
1	**1a** **4a**	−4.0 (28, 1.0, C_6H_6)	83	79[a]	
2	**1b** **4b**	−12.8 (26, 0.9, C_6H_6)	41	68[b]	*S*
3	**1c** **4c**	+28.1 (27, 1.0, CH_2Cl_2)	90	82[c]	*R*[d]
4	**1d** **4d**	+37.4 (27, 1.7, Et_2O)	44	78[b]	*R*
5	**1e** **4e**	+30.0 (26, 0.7, $CHCl_3$)	43	79[e]	*R*[f]

[a] See footnote *c* in Table 1. [b] Based on the reported value of optical rotations. $[\alpha]_D^{25}$ −18.8° (*c* 5, C_6H_6) for (*S*)-**4b**, J. Capillon and J. P. Guétté, *Tetrahedron*, 1979, **35**, 1801; $[\alpha]_D^{20}$ +47.7° (*c* 7, Et_2O) for (*R*)-**4d**, R. Macleod, F. J. Welch and H. S. Mosher, *J. Am. Chem. Soc.*, 1960, **82**, 876. [c] Determined by HPLC analysis using a chiral column (Chiralcel OB, 250 mm; 254 nm UV detector; eluent 10% propan-2-ol in hexane; flow rate 0.7 cm^3/min); retention time/min for **4c**, 25.3 for minor peak, 31.1 for major peak. [d] Determined by the derivation (hydrogenation using Pd/C) of **4c** into (*R*)-(+)-1,3-diphenylpropan-1-ol, C. Belzecki and I. Pantil, *J. Org. Chem.*, 1979, **44**, 1212. [e] Determined by ^1H NMR analysis of the ester derived from (*S*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid. [f] Based on the sense of optical rotation, K. Soai, S. Niwa, T. Yamanoi, H. Hikima and M. Ishizaki, *J. Chem. Soc., Chem. Commun.*, 1986, 1018.

has been limited mostly to alkylmetals[4] and it is therefore challenging to find a method which employs reagents which are both sterically and electronically different.

We report here an enantioselective phenylation of prochiral aliphatic, aromatic and α,β-unsaturated aldehydes using a kinetically formed chiral complex between phenyl Grignard–zinc halide reagent and *N*,*N*-dibutylnorephedrine (DBNE).

Firstly, the effect of the conditions on the formation of the chiral complex between phenyl Grignard–zinc halide reagent (**2**, PhM)* and the chiral ligand (**3**, DBNE[5] derivatives) was examined in the enantioselective phenylation of 2-naphthaldehyde **1a**. The results are shown in Table 1. When PhM and DBNE **3a** were mixed for 2 h at 50 °C (thermodynamic control), the 2-naphthylphenylmethanol **4a** obtained showed a 26% e.e. (95% yield) (entry 2). However, a dramatic increase in e.e. was observed when the mixing time of the DBNE and PhM reagents was very short (0 °C, 20 sec, kinetic control). Under these conditions, compound **4a** was obtained in 40% yield with 77% e.e. (entry 4). This result suggests that the kinetically formed complex between DBNE and PhM is more enantioselective than the thermodynamically formed complex. The methyl ether of DBNE **3d** was not enantioselective (entry 8). The e.e. obtained from the kinetically formed complex was higher than that obtained using the lithium or the ethylzinc salt of DBNE



(**3b** and **3c**) (entries 6 and 7). Finally, the use of 3 equiv. of DBNE and 2 equiv. of PhM reagent with aldehyde **1a** raised the yield of **4a** to 83% (79% e.e.) (entry 5). The results of the addition to various aldehydes under these reaction conditions are shown in Table 2. Cinnamaldehyde **1c** was phenylated in 90% yield and 82% e.e. (entry 3).† Aliphatic aldehydes were phenylated in 78–79% e.e. (entries 4 and 5). When (1*R*,2*S*)-(+)-DBNE was

* A THF solution (0.94 mol dm^{-3}, 41.0 cm^3) of PhMgBr (38.6 mmol) was added dropwise to a zinc chloride (2.60 g, 19.1 mmol) solution in THF (8 cm^3) at room temperature. The mixture was stirred for 1.5 h and 1,4-dioxane (3.3 cm^3, 38.3 mmol) was added dropwise. After a further 0.5 h at room temperature, the precipitate was filtered off under an argon atmosphere and washed with THF (3 × 5 cm^3). The THF was evaporated under reduced pressure and then THF was again added until the volume of solution was 38.5 cm^3.

† A THF solution of **2** (0.5 mol dm^{-3}; 2.0 cm^3, 1.0 mmol) was added to (1*R*,2*S*)-(+)-DBNE (0.394 g, 1.5 mmol) in hexane (2 cm^3) at 0 °C. The cooling ice bath was removed after 20 s and **1c** (0.068 g, 0.51 mmol) was added and the mixture was stirred for 30 min at room temperature. HCl (1 mol dm^{-3}; 5 cm^3) was added to quench the reaction, the organic layer was separated and the aqueous layer was extracted with ethyl acetate (5 × 5 cm^3). The combined organic layers were washed with sat. brine and dried (Na_2SO_4). The solvent was evaporated under reduced pressure. Purification of the residue by silica gel TLC (eluent, hexane–AcOEt, 8:1, *v*/*v*) afforded (*R*)-**4c** (0.098 g, 0.47 mmol) in 90% yield.

used, aldehydes reacted with **2** from the *Si* face to afford (*S*)-**4b** and (*R*)-**4c–e**. These enantioselectivities are opposite to those observed with dialkylzinc reagents which react with aldehydes from *Re* face in the presence of (1*R*,2*S*)-(+)-DBNE.[5]

The PhM reagent is not considered to be diphenylzinc itself, because although PhMgBr and $ZnCl_2$ do form an equilibrium mixture of diphenylzinc and MgBrCl, when pure Ph_2Zn (crystalline) was used in the presence of DBNE, the reaction with **1a** at room temperature was very slow and hardly afforded **4a**. However, even without DBNE, PhM reagent affords **4a** in 99% yield in the reaction with **1a** (Table 1, entry 1).

Under thermodynamic conditions, all the hydroxy groups of DBNE are considered to become metal alkoxide groups by reaction with PhM. In contrast, under kinetic conditions, some of the hydroxy groups of DBNE are thought to remain. Kinetic coordination of the oxygen atom of the hydroxy group and the nitrogen atom of the dibutylamino group of DBNE with the metal atom of PhM may be an important factor for the present enantioselective phenylation of aldehydes.

As described, various aldehydes were phenylated enantioselectively using a kinetically formed chiral complex between Grignard–zinc halide reagent and DBNE.

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Paper 1/01171E
Received 5*th February* 1991
Accepted 13*th February* 1991