COMMUNICATION

A catalytic and enantioselective cyclopropylation of aldehydes using dicyclopropylzinc

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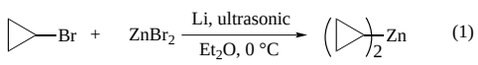
Enantioselective cyclopropylation of various aldehydes proceeds using dicyclopropylzinc in the presence of a catalytic amount of chiral amino alcohol or thiophosphoramidate with Ti(OPr^i)$_4$ to provide enantiomerically enriched cyclopropyl alkanols (up to 96.6% ee).

The catalytic enantioselective addition of diorganozincs to aldehydes is one of the most important methods for the synthesis of optically active secondary alcohols.[1] We have developed highly efficient chiral catalysts for enantioselective alkylations, namely chiral amino alcohols derived from norephedrines[2] and proline,[3] and chiral cyclic diamines (piperazines).[4] Moreover, we found that the chiral thiophosphoramidate[5] derived from norephedrine was also an effective catalyst in the enantioselective alkylation using diethylzinc with the aid of Ti(OPr^i)$_4$.[6]

We here report the first highly enantioselective cyclopropylation of aldehydes using dicyclopropylzinc.[7] The cyclopropyl group is of interest in synthetic methodologies.[8] The enantioselective reduction of phenyl cyclopropyl ketones has been reported to provide a chiral cyclopropyl alkanol[9] but alkylation is more convenient because various chiral cyclopropanols can be obtained depending on the choice of aldehyde.

Dicyclopropylzinc was prepared in 30% isolated yield from zinc bromide, cyclopropyl bromide and lithium under ultrasonic conditions [eqn. (1)] †,[10]



(1)

As a preliminary study, an enantioselective cyclopropylation of benzaldehyde was examined under several reaction conditions using diphenyl(1-methylpyrrolidin-2-yl)methanol (DPMPM) **1** and *N*-(*O*,*O*-dimethylthiophosphoryl)norephedrine (PHONE) **2** as chiral catalysts (Table 1).

Cyclopropylation proceeded in high yield (90.0%) and optical yield (83.3% ee) by the use of 5 mol% of DPMPM **1** in a mixed solvent of hexane and toluene (4 : 1.5) (Entry 1). Ee was decreased in toluene-free solvent (Entry 2). Lowering the reaction temperature (−18 °C) had almost no effect on optical yield (Entry 3), but it was slightly improved by increasing the amount of chiral catalyst (20 mol%) (Entry 4). Utilization of the lithium salt of **1** gave the same result as that of **1** itself (Entry 5). PHONE **2**, the thiophosphoramidate of norephedrine, was very

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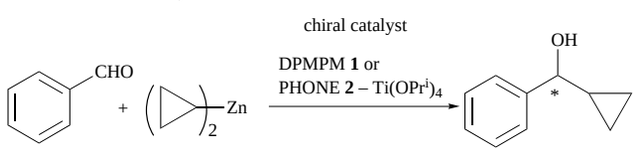
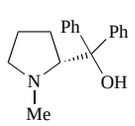
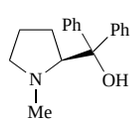
† Dicyclopropylzinc is known to be prepared from the zinc chloride and cyclopropyl Grignard reagent but in very low yield of *ca.* 10%.[7] The present method using lithium gave dicyclopropylzinc, which was purified by distillation, in an improved yield.

Table 1 Enantioselective cyclopropylation of benzaldehyde under various reaction conditions

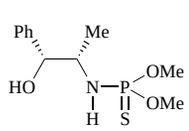




(*R*)-DPMPM **1**



(*S*)-DPMPM **1**

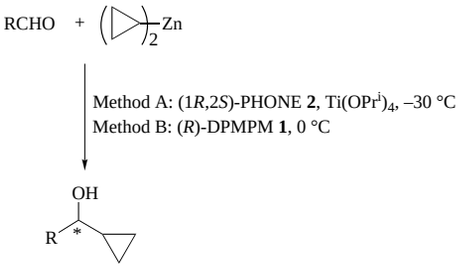


(1*R*,2*S*)-PHONE **2**

Entry[a]	Chiral catalyst (equiv.)	Solvent[b]	Temp./°C	Time/h	Yield (%)	Ee (%)[c]
1	(*R*)-**1** (0.05)	Hex–Tol	0	4	90.0	83.3 (*S*)
2	(*R*)-**1** (0.05)	Hex	0	4	86.9	76.5 (*S*)
3	(*R*)-**1** (0.05)	Hex–Tol	−18	4	86.5	84.4 (*S*)
4	(*S*)-**1** (0.20)	Hex–Tol	0	5	**90.1**	**85.8** (*R*)
5	(*S*)-**1**[d] (0.20)	Hex–Tol	0	6	81.6	84.8 (*R*)
6[e]	**2** (0.05)	Tol	−30	2	84.5	87.1 (*R*)
7[e]	**2** (0.15)	Tol	−30	2	**93.1**	**96.0** (*R*)

[a] Unless otherwise noted, molar ratio of aldehyde : dicyclopropylzinc was 1.0 : 3.0. [b] Hex = hexane, Tol = toluene. Ratio of mixed solvent Hex : Tol was 4 : 1.5. [c] Ee was determined by HPLC using a chiral column (Daicel Chiralcel OD, eluent: 2% propan-2-ol in hexane, flow rate: 1 ml min^{-1}) and the absolute configuration was determined by comparison of optical rotation in the literature [ref. 9(*a*)]. [d] Lithium alkoxide of **1** was used. [e] Molar ratio of aldehyde : Ti(OPr^i)$_4$: dicyclopropylzinc was 1.0 : 1.2 : 3.0.

Table 2 Enantioselective cyclopropylation of various aldehydes



Entry	R	Method[a]	Time/h	Yield (%)	Ee (%)[b]
1	Ph	A	2	93.1	96.0
		B[c]	5	90.1	85.8
2	4-MeO-C_6H_4	A	3	98.9	96.6
		B	3	96.7	86.2
3	4-Cl-C_6H_4	A	2	85.0	90.8
		B	2	96.7	84.1
4	1-Naphthyl	A	2	88.6	95.6
		B	2	93.7	78.2
5	PhCH=CH	A	1.5	94.1	63.6
		B	1.5	94.1	67.3
6	$PhCH_2CH_2$	B[c]	1	91.3	67.0
7	Cyclohexyl	B	2	86.6	70.5[d]

[a] Method A. Molar ratio of aldehyde:PHONE **2**:Ti(OPr^i)$_4$:dicyclopropylzinc was 1.0:0.15:1.2:3.0. Method B. Molar ratio of aldehyde:DPMPM **1**:dicyclopropylzinc was 1.0:0.05:3.0. [b] Ee was determined by HPLC using a chiral column. [c] 0.20 equiv. of DPMPM **1** was used. [d] Ee was determined as its benzoate by HPLC using a chiral column.

effective with the aid of Ti(OPr^i)$_4$ (Entry 6), especially when 15 mol% of **2** was used as a chiral catalyst. In this case 96.0% ee was reached (Entry 7).

Various aldehydes were submitted to the enantioselective cyclopropylation using PHONE **2** in coexistence of Ti(OPr^i)$_4$ (Method A)‡ or DPMPM **1** (Method B)§ (Table 2). In the cyclopropylation of aromatic aldehydes, PHONE **2** was more efficient than DPMPM **1** and very high optical yields (90.8–96.6% ee) were observed in each reaction (Entries 1–4). In the cases of cinnamaldehyde, the two methods gave almost the same results (Entry 5). It appears that DPMPM **1** is suitable for the cyclopropylation of aliphatic aldehydes, with the corresponding cyclopropyl alkanols being obtained with moderate ee (Entries 6 and 7).

We have developed a highly enantioselective cyclopropylation of aldehydes by dicyclopropylzinc with the use of a catalytic amount of chiral catalysts. Various chiral cyclopropyl alkanols were obtained from both aromatic and aliphatic aldehydes depending on the choice of catalyst. The present method provides a convenient and direct route for the preparation of optically active cyclopropyl alkanols.

‡ Typical experimental procedure for Method A (Table 2, Entry 1). A toluene solution (2 ml) of (1*R*,2*S*)-PHONE **2** (41.3 mg, 0.15 mmol) and Ti(OPr^i)$_4$ (0.36 ml, 1.2 mmol) was stirred for 20 min at room temperature. The reaction vessel was cooled to −30 °C and a 1 M toluene solution of dicyclopropylzinc (3 ml, 3 mmol) was injected into it. After the reaction mixture was stirred for 20 min, a toluene solution (2 ml) of benzaldehyde (106.1 mg, 1.00 mmol) was added at this temperature. After the mixture was stirred for 2 h, the reaction was quenched by the addition of sat. aq. NH_4Cl (15 ml), then the mixture was filtered using Celite and the filtrate was extracted with dichloromethane. The combined extracts were dried over anhydrous sodium sulfate and evaporated to dryness under reduced pressure. Purification of the crude product on silica gel TLC (thin-layer chromatography) (eluent: CH_2Cl_2) gave the pure cyclopropyl alkanol (137.9 mg, 0.931 mmol, 93.1%). Optical purity was determined to be 96.0% ee by HPLC analysis.

§ Typical experimental procedure for Method B (Table 2, Entry 1). To a hexane solution (4 ml) of (*R*)-DPMPM **1** (26.8 mg, 0.10 mmol) and benzaldehyde (52.7 ml, 0.50 mmol) was added a 1 M toluene solution of dicyclopropylzinc (1.5 ml, 1.5 mmol) at 0 °C. The quenching treatment and purification was the same as that of Method A and gave pure cyclopropyl alkanol (66.3 mg, 0.45 mmol, 90.1%). Optical purity was determined to be 85.8% ee by HPLC analysis.

Acknowledgements

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