Highly Diastereoselective 1,2-Asymmetric Addition of Dialkylzincs to Chiral 2-Phenylpropanal Catalyzed by Amino Alcohol

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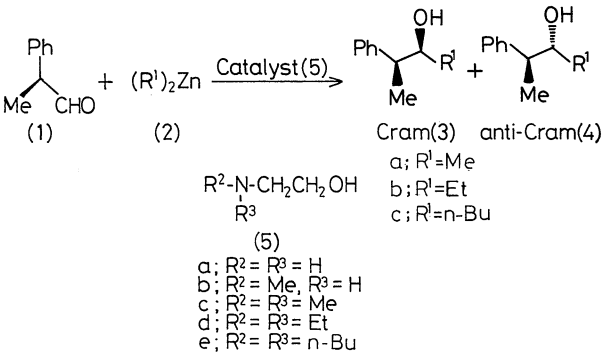
Synopsis. Diastereoselective addition of dialkylzinc reagents to 2-phenylpropanal using amino alcohol as catalyst afforded *erythro* alcohols (Cram-selectivity) in high diastereomeric excess (up to 88% d.e.).

Many efforts have been devoted to understanding 1,2-asymmetric alkylation of chiral carbonyl compounds, and useful models for predicting the relative stereochemistry have been provided.[1] Among chiral carbonyl compounds, 2-phenylpropanal (**1**) has been one of the most widely used fundamental indicators of the diastereoselectivity of 1,2-asymmetric induction (Cram's open-chain[2] and Felkin's[3] models) in addition reactions of organometallic reagents. However, from the standpoint of organic synthesis, diastereomeric excesses (d.e.'s) of Cram addition to **1** have been low to moderate, i.e., MeMgI,[2] EtMgBr,[2] MeZnX,[4] Et_2Zn–$TiCl_4$,[5] MeLi.[6] It is only recently that more diasetereoselective methods using organometallic reagents with certain auxiliaries, i.e., Bu_2CuLi–Me_3SiCl–crown ether,[7] MeLi–$TiCl_4$,[6] Et_4Pb–$TiCl_4$,[8] have been reported.[9] These methods require *stoichiometric* amounts of auxiliaries such as $TiCl_4$[10] and crown ether.



Scheme 1.

We report a highly *diastereoselective* addition to **1** with an organozinc reagent using a catalytic amount of auxiliary (catalyst). During our continuing study on the *enantioselective* addition of dialkylzincs to aldehydes,[11] we found that **1** is alkylated diastereoselectively in high d.e.'s with dialkylzincs (**2**) using amino alcohols (**5**)[12] as catalysts. When **1** was treated with Et_2Zn using 10 mol% of 2-dimethylaminoethanol (**5c**) in hexane at room temperature, 2-phenylpentan-3-ols (**3b**+**4b**) were obtained in a combined 64% isolated yield.[13] *Erythro*-**3b** (Cram selectivity) was formed predominatly in 86% d.e. (determined by GLC analysis) (Table 1, Entry 4). When the reaction was run at 0 °C, d.e. of **3b** increased to 88% d.e. (Entry 5). Tratment of **1** with dibutylzinc afforded Cram-**3c** in 84% d.e. (Entry 8). The Cram-selectivity obtained here is much higher than those of the existing organozinc methods [MeZnX (ca. 20% d.e.),[4] Et_2Zn–$TiCl_4$ (54% d.e.)[5]].

D.e. was also high when a lesser amount (5 mol%) of the catalyst (**5c**) was used (Entry 3). Both *primary*-amino (**5a**), *secondary*-amino (**5b**), and *tertiary*-amino (**5c**, **5d**, **5e**) alcohols act as catalysts to afford Cram-**3b** in high d.e.'s (Entries 1, 2, 4, 9, and 10).[15] The high

Table 1. Diastereoselective Alkylation of **1** with Dialkylzincs (**2**) Using Amino Alcohols (**5**) as Catalysts[a]

Entry	R^1 in **2**	Catalyst (**5**)		Alcohols (**3**+**4**) Yield (**3**+**4**),[b]/%	D.e.[Cram-**3**],[c]/%
1	Et	**a**	**b**	55	83
2	Et	**b**	**b**	45	83
3[d]	Et	**c**	**b**	53	85
4	Et	**c**	**b**	64	86
5[e]	Et	**c**	**b**	60	88
6[f]	Et	**c**	**b**	65	87
7	Me	**c**	**a**	55	74
8	*n*-Bu	**c**	**c**	37	84
9	Et	**d**	**b**	53	85
10	Et	**e**	**b**	45	84

a) Unless otherwise noted reactions were run in hexane at room temperature for 45—51 h. Molar ratio. **1**:**2**:**5**= 1.0:2.0:0.1. b) Isolated yields. c) Determined by GLC analyses. Conditions: FID detector, OV-1, 50 m capillary column, column temp. 120 °C. Retention time 15.7 min for **4a** (minor), 16.3 min for **3a** (major). Column temp. 105 °C. Retention time 46.0 min for **4b** (minor), 48.2 min for **3b** (major). PEG-20M 25 m capillary column, column temp. 125 °C. Retention time 16.5 min for **4c** (minor), 19.9 min for **3c** (major). d) Molar ratio. **1**:**2**:**5**=1.0:2.0:0.05. e) Reaction was run at 0 °C for 69 h. f) Reaction was run at 0 °C in a mixed solvent of hexane and toluene (2:1, v/v) for 44 h.

diastereoselectivity of the present R_2Zn with amino alcohol catalyst may results from the steric bulk of the activated organozinc reagent formed in situ by the complex formation of amino alcohol with R_2Zn. These bulky alkylating reagents are more diastereoselective probably because of their more effective steric interaction with the large Ph group substituent of **1**.

Experimental

GLC analyses were performed on a Shimadzu GC-4C gas chromatograph with Chromatopac C-R6A data processor. 2-Phenylpropanal (**1**) and amino alcohols (**5a—e**) were purchased from Tokyo Kasei, Inc. Diethylzinc (hexane solution) was purchased from Kanto Chemical Co. Dibutylzinc was prepared according to the literature procedure.[14]

Typical procedure (Table 1, Entry 5): To a solution of (**5c**)(13.5 mg, 0.15 mmol) in hexane (1.5 ml) was added (**1**) (0.2 ml, 202 mg, 1.5 mmol). The mixture was stirred at room temperature for 20 min. Then, Et_2Zn (3 mmol, 3.0 ml of 1 M hexane solution, M=mol dm^{-3}) was added at 0 °C. The reaction mixture was stirred at 0 °C for 69 h and was quenched with 1 M HCl. The mixture was extracted with dichloromethane, and the extract was dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by silica-gel TLC [hexane–AcOEt=4:1 (v/v) as developing solvent]. Alcohols (**3b** and **4b**) were obtained in 60% total yield (148 mg). NMR and IR spectra were identical with those of authentic samples. Conditions of GLC analyses are described in a footnote to Table 1.

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