Chem. Pharm. Bull. **45**(12) 2122—2124 (1997) Vol. 45, No. 12

ENANTIOSELECTIVE α-ALKYLATION OF PHENYLACETIC ACID USING A CHIRAL BIDENTATE LITHIUM AMIDE AS A CHIRAL AUXILIARY

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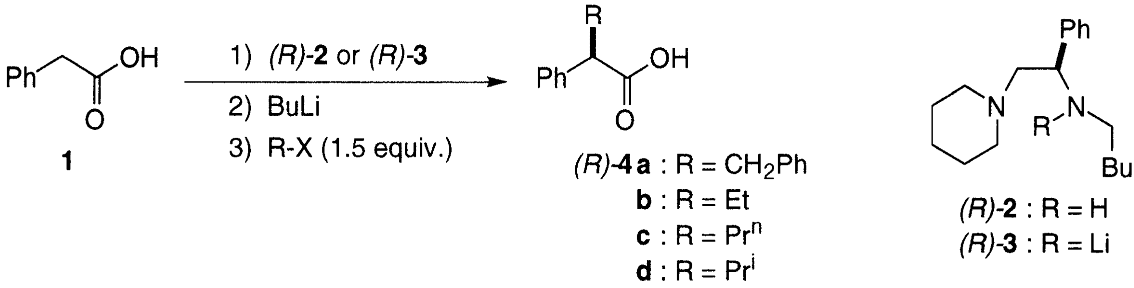
Enantioselective alkylation at the α-position of phenylacetic acid (**1**) can be realized in up to 68% ee by treating the dilithiated **1** with alkyl halides in the presence of a chiral bidentate lithium amide ((*R*)-**3**).

KEY WORDS dilithiated phenylacetic acid; enantioselective alkylation; chiral lithium amide; α-substituted phenylacetic acid

Lithium enolates are versatile intermediates as carbon nucleophiles in organic synthesis.[1] Among the various reactions of lithium enolates, alkylation of dilithiated carboxylic acids is a promising method for the synthesis of α-alkylated carboxylic acids, because dilithiated carboxylic acids are easily prepared and relatively reactive.[2] In the course of the studies on enantioselective reactions of achiral lithium enolates with achiral electrophiles in the presence of chiral external ligands,[3] we intended to examine the possibility of enantioselective α-alkylation of phenylacetic acid. To the best of our knowledge, there are only two reports on the enantioselective α-alkylation of carboxylic acids using chiral amines as chiral auxiliaries to obtain the products in up to 24% ee,[4] and in up to 46.2% ee.[5] We describe here a method to obtain the products in higher enantioselectivity in the α-alkylation of phenylacetic acid (**1**) using a chiral amine ((*R*)-**2**) or a chiral lithium amide ((*R*)-**3**) as a chiral auxiliary, as shown in Chart 1.

Chart 1



The reaction was examined under various conditions, as summarized in Table 1. By using 2.4 equivalents of (*R*)-**3**[6] followed by treatment of the resulting dianion of **1** with benzyl bromide, the chemical and optical yields of the product were found to be highly dependent on the solvents used (runs 1-6). Thus, chemical yields are higher in THF and DME, but lower in ether and toluene, while optical yields are lower in THF, DME, and ether, but higher in toluene. Since attempts to improve the

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chemical yield of the reaction in toluene were not successful, probably due to the low solubility of the dilithiated **1**, we used THF as the solvent in the following experiments.[7]

It was found that as the amount of *(R)*-**3** was increased, enantioselectivity of the reaction increased, whereas chemical yield became lower (runs 8-10).[8,9] The increase in enantioselectivity suggests that the chiral environment provided by the lithium amide (*(R)*-**3**) is more efficient than that provided by the corresponding amine (*(R)*-**2**) for the reaction. To obtain a solution of dilithium salt of **1** and *(R)*-**3**, a mixture of one equivalent of **1** and two equivalents of *(R)*-**2** was treated with four equivalents of butyllithium. Treatment of the resulting solution with benzyl bromide gave the product in 59% ee (42% yield) (run 11). Reactions with other alkyl halides were carried out similarly (runs 12-14).

Table 1. Enantioselective Alkylation of **1** to Give **4**[a]

								Product		
Run	*(R)*-**2** (equiv.)	*(R)*-**3** (equiv.)	BuLi (equiv.)	RX	Solvent	Temp. (°C)	Time (min)	**4**[b]	Yield (%)[c]	E.e. (%)[d]
1	0	2.4	0	$PhCH_2Br$	THF	-78	10	*(R)*-**4a**	69	34
2	0	2.4	0	$PhCH_2Br$	THF	-78	60	*(R)*-**4a**	86	30
3	0	2.4	0	$PhCH_2Br$	DME	-78	60	**4a**	89	1
4	0	2.4	0	$PhCH_2Br$	ether	-78	60	**4a**	4	0
5	0	2.4	0	$PhCH_2Br$	toluene	-78	60	*(R)*-**4a**	24	52
6	0	2.4	0	$PhCH_2Br$	THF-toluene (1:1)	-78	60	*(R)*-**4a**	83	26
7[e]	0	2.4	0	$PhCH_2Br$	THF	-78	60	**4a**	79	1
8	0	2.0	0	$PhCH_2Br$	THF	-78	60	*(R)*-**4a**	95	18
9	0	3.0	0	$PhCH_2Br$	THF	-78	60	*(R)*-**4a**	68	42
10	0	4.0	0	$PhCH_2Br$	THF	-78	60	*(R)*-**4a**	49	57
11	2.0	0	4.0	$PhCH_2Br$	THF	-78	10	*(R)*-**4a**	42	59
12	2.0	0	4.0	EtI	THF	-78	20	*(R)*-**4b**	38	68
13	2.0	0	4.0	^{n}PrI	THF	-78~-45	120	*(R)*-**4c**	70	47
14	2.0	0	4.0	^{i}PrI	THF	-78~0	240	*(R)*-**4d**	51	42

[a] For procedure, see the text. [b] Absolute configurations of optically active **4a**,[11a] **4b**,[11b] **4c**,[11c] and **4d**[11d] are known. [c] Determined by ^{1}H-NMR using triphenylmethane as an internal standard. [d] Determined by HPLC using a chiral column.[12] [e] The reaction mixture contains LiBr (2.6 equiv.) from the beginning.

A typical experimental procedure (run 11) is as follows. Under an argon atmosphere, a solution of *n*-butyllithium in hexane (1.55 *N*, 1.88 ml, 2.91 mmol) was added to a solution of the chiral amine (*(R)*-**2**) (410 mg, 1.49 mmol) and **1** (99 mg, 0.73 mmol) in THF (9.3 ml) at 0°C, and the resulting solution was stirred at 0°C for 15 min, and was then cooled down to -78°C. Benzyl bromide (0.13 ml, 1.09 mmol) in THF (2 ml) was added, and the whole mixture was stirred at -78°C for 10 min. The reaction mixture was quenched with 10% aqueous hydrochloric acid (5 ml), and then extracted with ether (20 ml x 3). The combined organic extracts were washed with water and brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo* to give a pale yellow residue. The chemical yield of **4a** (42%) was determined by ^{1}H-NMR using triphenylmethane as an internal standard. The pale yellow residue was subjected to column chromatography (silica gel, hexane-ether) to give a mixture of **1** and

4a. The ee of **4a** (59%) was determined by HPLC using a chiral column.[12] Further purification by preparative TLC gave **4a** of $[\alpha]_D^{25}$ -71.9 ° (c=0.57, acetone), with an excess of *(R)*-enantiomer.[11a] *(R)*-**2** was recovered quantitatively without any loss of optical purity.

Further studies on the stereochemical mechanism of the present enantioselective reaction are under way.

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7) Judging from the data from runs 1 and 2, partial racemization of the product may be occurring during the reaction in THF. Details are under investigation.

8) By using excess *(R)*-**3**, 1-bromo-1,2-diphenylethane was isolated from the reaction mixture.

9) Contrary to our previous reports[10] on the alkylation of ketone lithium enolates, addition of lithium bromide caused a dramatic decrease in the enantioselectivity of the reaction (run 7).

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12) The ees of the products were determined by HPLC using a chiral column (Daicel Chiralcel OJ®, hexane/isopropanol/trifluoroacetic acid (9/1/0.01)) for **4a**, and a chiral column (Daicel Chiralcel OD-H®, hexane/isopropanol/trifluoroacetic acid (100/2/0.1)) for **4b-d**.

(Received September 29, 1997; accepted October 20, 1997)