

Asymmetric Conjugate Addition of Grignard Reagents in the Presence of Tertiary Amines to α,β -Unsaturated Amides Derived from (*S*)-2-(1-Hydroxy-1-methylethyl)pyrrolidine or (*S*)-Prolinol

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In the presence of tertiary amines, diastereoselective conjugate addition of Grignard reagents to α,β -unsaturated amides affords 3-substituted carboxylic acids of high enantiomeric excess (up to 89% e.e.).

In order to develop effective asymmetric reactions, it is important to examine factors which affect product stereochemistry. Several examples are known of the asymmetric conjugate addition of organometallic reagents to α,β -unsaturated carbonyl compounds.¹ Although chiral amines (and their derivatives) have been utilised as chelating reagents in enantioselective conjugate addition of organometallic reagents, optical yields remain low to moderate.² Amines have rarely been utilised as chelating reagents in diastereoselective conjugate addition.³

We now report that tertiary amines effect diastereoselective 1,4-conjugate addition of Grignard reagents to α,β -

unsaturated amides (**1a–d**) derived from (*S*)-prolinol (and its derivatives). Conjugate addition of *n*-butylmagnesium bromide to the amide alcohol (**1a**), followed by acidic hydrolysis of the adduct (**2**), resulted in the formation of (*S*)-3-phenylheptanoic acid (**3a**) in low optical yields (16 and 37% enantiomeric excess, e.e., Table 1, entries 1 and 2).

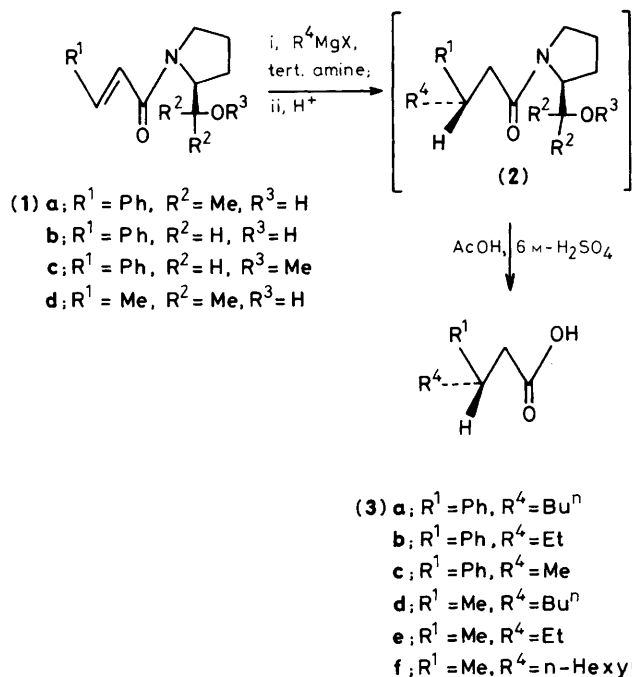
However, when the same addition was performed in the presence of a tertiary amine such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), *N,N,N',N'*-tetramethylethylenediamine (TMEDA), or (–)-sparteine, the optical yields of (**3a**) increased to 50–89% e.e. (Table 1, entries 3–8). This tendency for the

Table 1. Diastereoselective conjugate addition of Grignard reagents (R^4MgX)^a to (**1**) in the presence of tertiary amines.

Entry	(1)	R^4	Tert. amine ^b	Solvent ^c	(3)			
						Yield (%)	$[\alpha]^d$	% E.e. ^{e,f}
1	a	Bu ⁿ	—	B	a	33	+5.58°	16
2	a	Bu ⁿ	—	A	a	52	+12.82°	37
3	a	Bu ⁿ	DBU	A	a	81	+30.23°	88
4	a	Bu ⁿ	DBU	B	a	39	+30.46°	89
5	a	Bu ⁿ	DBU	C	a	62	+23.60°	69
6	a	Bu ⁿ	DBN	B	a	27	+17.06°	50
7	a	Bu ⁿ	TMEDA	B	a	30	+23.03°	67
8	a	Bu ⁿ	(–)-Sparteine	B	a	25	+23.85°	69
9	a	Bu ⁿ g	DBU	A	a	60	+25.38°	74
10	a	Et	DBU	A	b	66	+40.55°	82
11	a	Me	DBU	A	c	22	–36.39°	64 ^h
12	b	Bu ⁿ	DBU	A	a	29	+28.88°	84
13 ⁱ	a	i, Bu ⁿ Li ii, Bu ⁿ MgBr	DBU	B	a	21	+7.76°	23
14	c	Bu ⁿ	—	A	a	73	+4.82°	14
15	c	Bu ⁿ	DBU	A	a	23	+1.38°	4
16	d	Bu ⁿ	DBU	A	d	13	–2.10°	50
17	d	Et	DBU	A	e	27	+5.63°	69
18	d	<i>n</i> -Hexyl	DBU	A	f	23	–3.49°	68
19	d	<i>n</i> -Hexyl	—	A	f	33	–2.81°	55
20	d	<i>n</i> -Hexyl	TMEDA	A	f	22	–3.37°	66

^a X = Br unless otherwise noted. ^b For abbreviations, see the text. ^c A, Toluene; B, tetrahydrofuran, (THF); C, diethyl ether.

^d Conditions for the measurements: compound, wavelength/nm, *c*, solvent; (**3a**) 577, 5.66–8.06, benzene; (**3b**), Na D line, 7.04, benzene; (**3c**), Na D line, 6.97, benzene; (**3d–f**), Na D line, neat. ^e Based on the reported values of optical rotations: (**3a**), $[\alpha]_{577} -34.4^\circ$ (*c* 8, benzene), A. I. Meyers and C. E. Whitten, *Heterocycles*, 1976, **4**, 1687; (**3b**), $[\alpha]_D -49.66^\circ$ (*c* 7, benzene), L. Lardicci, R. Menicagli, and P. Savadori, *Gazz. Chim. Ital.*, 1968, **98**, 738; (**3c**), $[\alpha]_D + 57.23^\circ$ (*c* 9, benzene), V. Prelog and H. Scherrer, *Helv. Chim. Acta*, 1959, **42**, 2227; (**3d**), $[\alpha]_D^{27} -4.21^\circ$ (neat), P. A. Levene and R. E. Marker, *J. Biol. Chem.*, 1932, **95**, 1; (**3e**), $[\alpha]_D -8.15^\circ$ (neat), L. Lardicci and L. Conti, *Ann. Chim. (Rome)*, 1961, **51**, 823; (**3f**), $[\alpha]_D^{23} + 5.10^\circ$ (neat), A. I. Meyers, R. K. Smith, and C. E. Whitten, *J. Org. Chem.*, 1979, **44**, 2250. ^f (*S*) Configuration unless otherwise noted. ^g X = Cl. ^h (*R*) Configuration. ⁱ See footnote †.



e.e. to increase in the presence of tertiary amines was also observed with other combinations of amide (**1d**) and Grignard reagents (entries 18–20).

The change from the alcohols (**1a,b,d**) to the methyl ether (**1c**) in the reactions with Bu^nMgBr in the presence or absence of DBU led to a marked decrease in asymmetric induction (entries 14 and 15). Thus, in addition to the chelation of the tertiary amine to the Grignard reagent,^{2b} the chelation of the

tertiary amine to magnesium of the magnesium alkoxide of (**1a,b,d**)[†] is essential for the present asymmetric reaction.[‡]

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[†] Addition of Bu^nMgBr to the preformed lithium alkoxide of (**1a**) in the presence of DBU resulted in low asymmetric induction (Table 1, entry 13).

[‡] A typical procedure is as follows. To a toluene solution (8 ml) of (**1a**) (3.01 mmol) was added DBU (13.5 mmol) at room temperature under argon. The mixture was cooled to -40°C , and Bu^nMgBr (9.03 mmol, 0.82 M solution in THF) was added during 30 min. The mixture was allowed to warm to room temperature during 23 h with stirring, and saturated aqueous NH_4Cl (11 ml) was then added. The aqueous layer was extracted with chloroform and the extract dried (Na_2SO_4) and evaporated *in vacuo*. The residue was hydrolysed with refluxing acetic acid (7.5 ml)–6 M-sulphuric acid (15 ml) for 4 h. The mixture was extracted with chloroform, and the extracts were dried (Na_2SO_4) and evaporated under reduced pressure. The residue was distilled (bath temp. $140\text{--}200^\circ\text{C}$; 2 mmHg), and purified by t.l.c. on silica gel ($20 \times 20\text{ cm}$; $\text{CH}_2\text{Cl}_2\text{--MeOH}$, 50:1 v/v, as eluant). (*S*)-(+)-(**3a**) was obtained as oil (0.503 g, 81%; 88% e.e.) (Table 1, entry 3).