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

Kenso Soai,* Hideaki Machida, and Atsuhiro Ookawa

Department of Applied Chemistry, Faculty of Science, Science University of Tokyo, Kagurazaka, Shinjuku-ku, Tokyo 162, Japan

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]

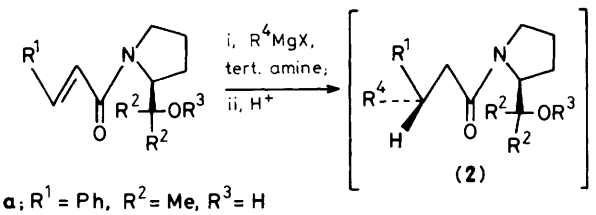
We now report that tertiary amines effect diastereoselective 1,4-conjugate addition of Grignard reagents to α,β-unsaturated amides (**1a—d**) derived from (*S*)-prolinol (and its derivatives). Conjugate addition of n-butylmagnesium bromide to the amide alcohol (**1a**), followed by acidic hydrolysis 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

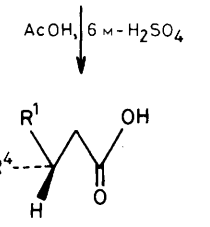
Table 1. Diastereoselective conjugate addition of Grignard reagents (R^4MgX)[a] to (**1**) in the presence of tertiary amines.

					(3)			
Entry	(1)	R^4	Tert. amine[b]	Solvent[c]		Yield (%)	[α][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^nLi ii, Bu^nMgBr	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**	n-Hexyl	DBU	A	**f**	23	−3.49°	68
19	**d**	n-Hexyl	—	A	**f**	33	−2.81°	55
20	**d**	n-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° (*c* 8, benzene), A. I. Meyers and C. E. Whitten, *Heterocycles*, 1976, **4**, 1687; (**3b**), $[\alpha]_D$ −49.66° (*c* 7, benzene), L. Lardicci, R. Menicagli, and P. Savadori, *Gazz. Chim. Ital.*, 1968, **98**, 738; (**3c**), $[\alpha]_D$ + 57.23° (*c* 9, benzene), V. Prelog and H. Scherrer, *Helv. Chim. Acta*, 1959, **42**, 2227; (**3d**), $[\alpha]_D^{27}$ −4.21° (neat), P. A. Levene and R. E. Marker, *J. Biol. Chem.*, 1932, **95**, 1; (**3e**), $[\alpha]_D$ −8.15° (neat), L. Lardicci and L. Conti, *Ann. Chim. (Rome)*, 1961, **51**, 823; (**3f**), $[\alpha]_D^{23}$ + 5.10° (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 †.



(1) **a**; R^1 = Ph, R^2 = Me, R^3 = H
b; R^1 = Ph, R^2 = H, R^3 = H
c; R^1 = Ph, R^2 = H, R^3 = Me
d; R^1 = Me, R^2 = Me, R^3 = H



(3) **a**; R^1 = Ph, R^4 = Bu^n
b; R^1 = Ph, R^4 = Et
c; R^1 = Ph, R^4 = Me
d; R^1 = Me, R^4 = Bu^n
e; R^1 = Me, R^4 = Et
f; R^1 = Me, R^4 = n-Hexyl

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.‡

This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, and Culture.

Received, 21st December 1984; Com. 1784

References

1 For a review, see K. Tomioka and K. Koga, 'Asymmetric Synthesis,' vol. 2, ed. J. D. Morrison, Academic Press, New York, 1983, p. 201.
2 (a) W. Langer and D. Seebach, *Helv. Chim. Acta*, 1979, **62**, 1710; T. Imamoto and T. Mukaiyama, *Chem. Lett.*, 1980, 45; F. Leyendecker, F. Jesser, and B. Rubland, *Tetrahedron Lett.*, 1981, 3601; (b) R. A. Kretchmer, *J. Org. Chem.*, 1972, **37**, 2744.
3 K. Soai, A. Ookawa, and Y. Nohara, *Synth. Commun.*, 1983, **13**, 27. For the use of amines for non-asymmetric conjugate addition of alkyl-lithium reagents, see J. E. Baldwin and W. A. Dupont, *Tetrahedron Lett.*, 1980, 1881.

† 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—200 °C; 2 mmHg), and purified by t.l.c. on silica gel (20 × 20 cm; CH_2Cl_2–MeOH, 50 : 1 v/v, as eluant). (*S*)-(+)-(**3a**) was obtained as oil (0.503 g, 81%; 88% e.e.) (Table 1, entry 3).