

The effect of pressure on the diastereoselectivity of the reaction of prenal with monoalkyl ylidenemalonates catalysed by homochiral secondary amines

Edward P. Serebryakov,* Albert G. Nigmatov and Mikhail A. Shcherbakov

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation.
Fax: +7 095 135 5328; e-mail: ser@cacr.ioc.ac.ru

10.1070/MC2001v011n05ABEH001502

The dienamine-mediated formation of 6-substituted cyclohexa-1,3-dienes from the title reactants catalysed by either (*S*)- or (*R*)-prolinol at 8 kbar proceeds with different net enantioselectivities depending on the structure of $RCH=C(CO_2H)CO_2Alk$ to give a product with the same configuration as that obtained at atmospheric pressure (if $R = Me_2C=CH$) or with a configuration opposite to the latter (if $R = Ph$); by contrast, with both dienophiles the sense of enantioselectivity does not change with pressure when (*S*)- α,α -diphenyl-2-pyrrolidinemethanol is used as the catalyst.

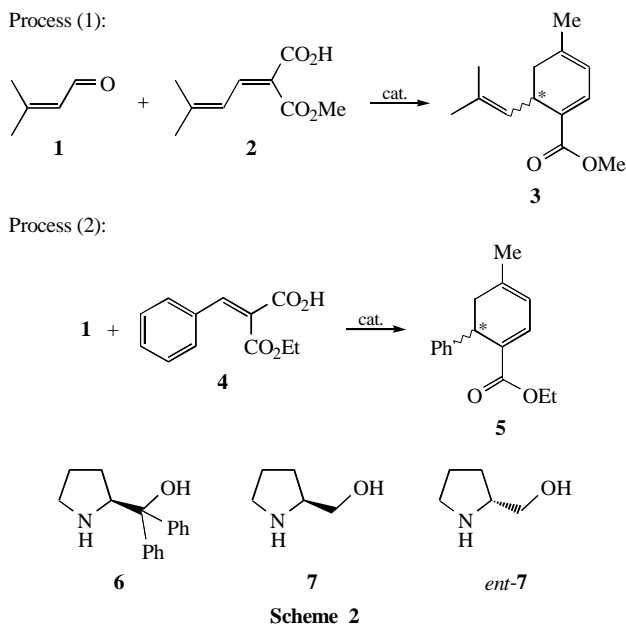
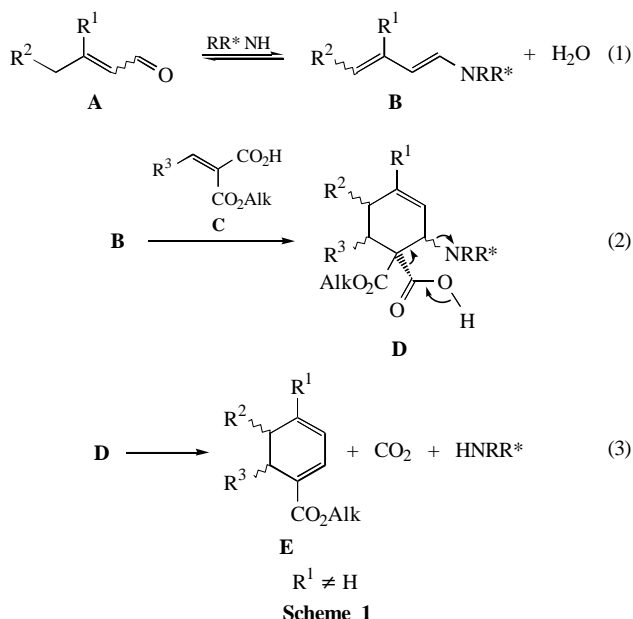
Recently, the catalytic synthesis of optically active cyclohexa-1,3-dienes from β -branched α,β -alkenals and various monoalkyl ylidenemalonates was described,¹ and factors affecting the apparent (net) enantioselectivity of this process were studied.² The reaction mechanism (Scheme 1)^{1–3} involves the transient formation of a dienamine followed by two consecutive, inherently diastereoselective reactions. One of them, intermolecular [4+2] cycloaddition, is strongly accelerated by pressure,⁴ whereas the other is believed to proceed *via* a six-membered transition state,⁵ which can also be affected by pressure.

Since the net enantioselectivity of cyclohexadiene formation diminishes with temperature,^{1,2} we used a high-pressure technique as an alternative to heating for accelerating the process without damaging the *ee* of its products. Scheme 2 demonstrates two examples examined.

The experiments were performed in dry toluene at $20 \pm 2^\circ C$ both under normal pressure (~ 1 bar) and at 8 kbar.[†] Enantiopure (*S*)- α,α -diphenyl-2-pyrrolidinemethanol **6**, (*S*)-prolinol **7** and (*R*)-prolinol *ent*-**7** (0.1 equiv. each) were used as catalysts. The results are shown in Table 1.

Table 1 indicates that the application of a high pressure results in diminished chemical yields of target products **3** and **5**. However, with all three catalysts, prolonged exposures of process (2) to high pressure markedly increased the *ee* of ester **5** (cf. runs 2.2–2.3, 2.5–2.6, 2.8–2.9); this trend can be useful from the preparative standpoint.

In process (1), the sense of its net enantioselectivity is not altered by a high pressure. The *ee* of ester (*S*)-**3** slightly diminishes when catalyst **6** is used, whereas a relatively high increase in *ee* is observed if this process is catalysed by **7** or *ent*-**7**.



[†] Experiments at 1 bar were carried out as described earlier,² however, dry toluene was used instead of benzene. Acid esters **2** (mp $84^\circ C$) and **4** (mp $95^\circ C$) were prepared as *Z* isomers of $\sim 100\%$ geometrical purity (1H and ^{13}C NMR data) according to refs. 2 and 6, respectively. Experiments at 8 kbar were performed using a thermostatted Barostat HP unit in 2 ml Teflon ampoules. The ampoules were filled at $0-5^\circ C$ first with dienophiles **2** or **4** (0.4–0.5 mmol) in 0.5 ml of PhMe and then with solutions of enal **1** (0.4–0.5 mmol) and a chiral amine (0.04–0.05 mmol) in toluene to the total volume of 2 ml. The time span between the application of the pressure and the attainment of a steady state was ~ 10 min. At both pressures, the work-up of the reaction mixture included its concentration *in vacuo*, the extraction of an oily residue with pentane, and the fractionation of the pentane-extracted solute by column chromatography (SiO_2). The purity of the products was controlled by TLC on Silufol plates (hexane–AcOEt, 6:1; R_f 0.55 for **3** and 0.45 for **5**) and by 1H NMR spectroscopy (Bruker AM-300 instrument, in d_6 -benzene). Enantiomer ratios (*er*) and the values of *ee* in scalemic **3** and **5** were determined by correlating the $[\alpha]_D$ of a specimen with the ratio of peak areas belonging to *R* and *S* antipodes in the 1H NMR spectrum recorded in the presence of (*S*)- or (*R*)-BINOL (for details, see refs. 1, 2). For the enantiomers of **3**, this correlation was linear in the whole range of *ee* (from ~ 0 to $\sim 100\%$). In the case of **5**, this correlation was also linear up to the largest *ee* attainable at atmospheric pressure (32%); further estimates of *ee* were made using $[\alpha]_D$ alone on the assumption that the linearity still holds. For (*S*)-**5** and (*R*)-**5** with 100% *ee*, an extrapolation gave $[\alpha]_D = 186^\circ$.

All $[\alpha]_D$ (measured in benzene at $20 \pm 4^\circ C$) and the corresponding enantiomer ratios and *ee* given in Table 1 are the mean values of three significantly close results. Material balances for processes (1) and (2) at both pressures revealed methyl 5-methylhexa-3,5-dienoate (from **2**) or ethyl cinnamate (from **4**) as main low-molecular-weight by-products (up to 3% at 1 bar and below 1.5% at 8 kbar), and polar polymers ($R_f < 0.05$), which are insoluble in pentane (up to 35% at normal pressure⁶ and up to 50% at 8 kbar in the case of dienophile **4**).

Table 1 The effect of pressure on the chemical yields and net enantioselectivities of processes (1) and (2) in the presence of amines **6**, **7** and *ent*-**7** in dry toluene at 20±2 °C.

Run	Amine	P/bar	t/h	Yield (%) ^a	[α] _D ^b	R:S ratio	ee (%)
Process (1): 1 + 2 → 3							
1.1	6	1.0	360	39	+296°	<2:98	> 96
1.2	6	8000	72	27	+238°	10:90	80
1.3	7	1.0	120	52	+53°	41:59	18
1.4	7	8000	96	18	+76°	37:63	26
1.5	<i>ent</i> - 7	1.0	120	54	-41°	57:43	14
1.6	<i>ent</i> - 7	8000	72	35	-82°	64:36	28
Process (2): 1 + 4 → 5							
2.1a	6	1.0	360	0	—	—	—
2.1b	6	1.0	20 ^c	7 ^c	+53° ^c	34:66	32 ^d
2.2	6	8000	48	5	+71°	31:69	38 ^d
2.3	6	8000	240	6	+167°	5:95	90 ^d
2.4	7	1.0	360	20	-14.5°	54.5:45.5	9 ^d
2.5	7	8000	24	6	+34°	41:59	18 ^d
2.6	7	8000	336	6.5	+60°	36:64	28 ^d
2.7	<i>ent</i> - 7	1.0	120	14	+17°	45:55	10 ^d
2.8	<i>ent</i> - 7	8000	24	3.5	-12.5°	53:47	14 ^d
2.9	<i>ent</i> - 7	8000	168	7	-74°	70:30	40 ^d

^aIsolated yield. ^bMeasured at 20±4 °C in dry benzene (c 1.0). ^cAt 50 °C, because at 20 °C process (2) is not observed. ^dFor a specimen with ee ~100%, it was extrapolated¹ that |[α]_D| = 186°.

The application of a high pressure to process (2) led to somewhat puzzling results. First, at 8 kbar, amine **7** catalysed the formation of dextrotatory ester (*S*)-**5**, while under atmospheric pressure it favoured the formation of levorotatory (*R*)-**5**. As the complement to this reversal, instead of (*S*)-**5**, which was obtained at 1 bar using *ent*-**7** as the catalyst, (*R*)-**5** was isolated when a mixture of **1**, **4** and *ent*-**7** was exposed to 8 kbar. With both catalysts, the reversal of net enantioselectivity increased at prolonged exposures to a high pressure. Second, while process (1) catalysed by bulky amine **6** at 8 kbar afforded a specimen of (*S*)-**3** with a lower ee than that attained at 1 bar, a specimen of (*S*)-**5**, which was isolated when process (2) was catalysed by **6** at 8 kbar, had a higher ee than that of an analogous specimen of (*S*)-**5** obtained at 1 bar.

Different patterns of the net enantioselectivity of processes (1) and (2) under high pressure imply that the preferred transition states of their pivotal steps are different. This difference may originate from different diastereofacial selectivities with which each of the two reactive conformations of transient dienamines (e.g., *s-cis*¹-**8a,b** and *s-cis*²-**8a,b** generated from enal **1** and amines **6** or **7**) approaches – in both *endo* and *exo* modes – the preferred conformations of dienophiles **2** or **4** (**F** and **G**, respectively, as determined using the PC MODEL program²) (Figure 1).

Note that, by contrast with pressure-assisted asymmetric Diels–Alder reactions of achiral 1,3-dienes with homochiral dienophiles,^{4(c)} analogous pressure-assisted processes involving conformationally flexible homochiral dienamines and achiral dienophiles rarely occur in high-pressure organic chemistry.

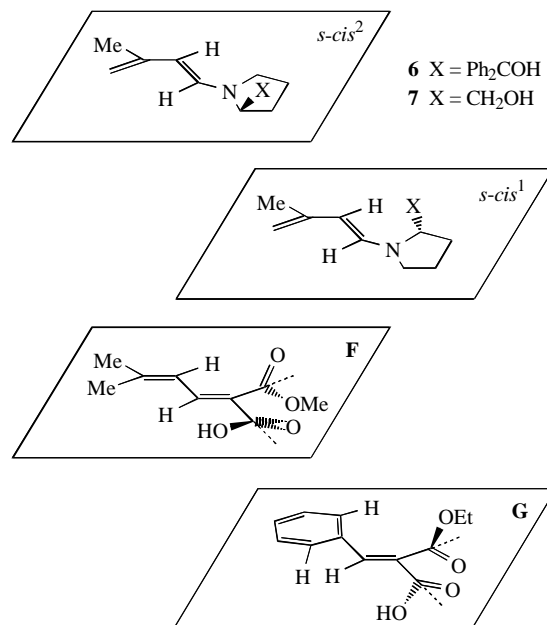


Figure 1

We thank Dr. M. I. Struchkova and Mr. A. V. Ignatenko (N. D. Zelinsky Institute of Organic Chemistry, Moscow) for their help in determining the ee of the products by the ¹H NMR–chiral solvating agent technique, and to Professor V. M. Zhulin and Dr. I. V. Zavarzin for their kind permission to use their high-pressure equipment. This work was supported by the Russian Foundation for Basic Research (grant nos. 96-03-33396 and 99-03-32992) and by INTAS (grant no. 96-1109).

References

- A. G. Nigmatov and E. P. Serebryakov, *Izv. Akad. Nauk, Ser. Khim.*, 1996, 663 (*Russ. Chem. Bull.*, 1996, **45**, 623).
- E. P. Serebryakov, A. G. Nigmatov, M. A. Shcherbakov and M. I. Struchkova, *Izv. Akad. Nauk, Ser. Khim.*, 1998, 84 (*Russ. Chem. Bull.*, 1998, **47**, 82).
- A. G. Nigmatov and E. P. Serebryakov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1991, 1079 (*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1991, **40**, 961).
- (a) G. Jenner, in *Organic High Pressure Chemistry*, ed. W. J. leNoble, Elsevier, Amsterdam, 1988, pp. 143–203; (b) R. van Eldik, T. Asano and W. J. leNoble, *Chem. Rev.*, 1989, **89**, 549; (c) G. Jenner, *Tetrahedron*, 1997, **53**, 2669; (d) M. Ciobanu and K. Matsumoto, *Liebigs Ann. Chem.*, 1997, 623; (e) L. F. Tietze, M. Henrich, A. Niklaus and M. Bubak, *Chem. Eur. J.*, 1999, **5**, 297.
- (a) C. Mannich and E. Ganz, *Ber.*, 1922, **55**, 3504; (b) N. Campbell and R. S. MacPherson, *J. Chem. Soc., Perkin Trans. 1*, 1974, 43.
- A. G. Nigmatov, I. N. Kornilova and E. P. Serebryakov, *Izv. Akad. Nauk, Ser. Khim.*, 1996, 154 (*Russ. Chem. Bull.*, 1996, **45**, 144).

Received: 13th July 2001; Com. 01/1828