Asymmetric C-C Bond Forming Reactions by Chiral Crown Catalysts; Darzens Condensation and Nitroalkane Addition to the Double Bond

Péter Bakó[a], Áron Szöllősy[b], Petra Bombicz[c] and László Tőke[a] *

[a] Department of Organic Chemical Technology, Technical University of Budapest, H-1521 Budapest, P. O. Box 91, Hungary, Fax: 36-1 463 3648, Email: P-Bako@ch.bme.hu

[b] NMR Laboratory of the Institute for General and Analytical Chemistry, Technical University of Budapest, H-1521 Budapest, Szt. Gellért tér 4, Hungary

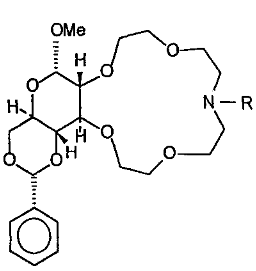
[c] Central Research Institute for Chemistry, Hung. Acad. of Sci., P.O.Box 17, H-1525 Budapest, Hungary

Received 20 December 1996

Abstract: A new, efficient crown ether **1** anellated to a sugar derivative has been prepared which shows significant asymmetric induction as phase transfer catalyst in the Michael addition of 2-nitropropane to chalcone (60% ee for the *S* antipode) and in the Darzens condensation of phenacyl chloride and benzaldehyde (64% ee), simultaneously changing the PT process from solid-liquid to liquid-liquid phase.

A number of papers have been published on the asymmetric C-C bond formation in the presence of chiral catalysts as phase transfer (PT) agents[1a-d]. Previously, we reported the asymmetric Michael addition of phenylacetate to acrylate catalyzed by chiral crown ethers incorporating two glucose units (85 % ee)[1d].

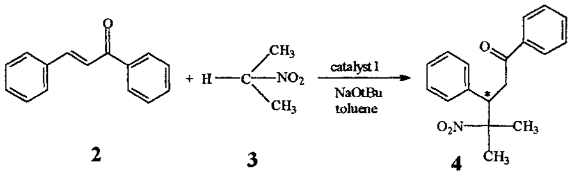
In this paper we wish to report the investigations of two new reactions: a Darzens condensation and the addition of nitroalkane to chalcone. It would bear great practical significance for both reactions (and reaction products) if asymmetric synthesis could be realized. Since the crown ethers having two glucoses[1d] have proved to be unsuccessful for these reactions, new catalysts have been synthesized[2]. These compounds are 15-membered monoaza-crown ethers **1** with one glycopyranoside unit, in which the substituents attached to the nitrogen exert a significant effect on the PT properties of the catalyst[2].



1

Compound	R
1a	C_6H_5
1b	$CH_2C_6H_5$
1c	$CH_3\text{-}(CH_2)_3$
1d	$CH_3\text{-}(CH_2)_9$
1e	CH_2CH_2OH
1f	C_6H_{11}
1g	$CH_2CO_2CH_3$

In the Michael addition the crown compounds **1** proved to be effective catalysts in the solid-liquid (SL) system, whereas in the Darzens condensation the medium had to be changed to a liquid-liquid (LL) system for appropriate results.



2 **3** **4**

The effect of certain catalysts on the stereoselective addition of nitroalkanes to methyl vinyl ketone[3a] and to enone[3b] was studied recently. The conventional addition of 2-nitropropane (**3**) to chalcone (**2**) to give the racemic nitroketone **4** is known in the literature[3c]. We studied this reaction in a binary SL system in the presence of various bases (35 mol %) and chiral catalysts (7 mol %)[4a]. The results obtained under such conditions are collected in Table 1.

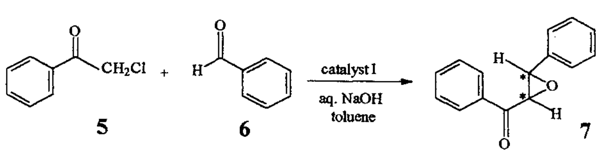
Table 1. Addition of 2-nitropropane (**3**) to chalcone (**2**) in toluene in the presence of catalysts **1**, at 20 °C

Entry	Catalyst	Base	Time (h)	Yield (%) [a]	$[\alpha]_D$ [b]	ee(%) [c]
1	**1b**	NaO-t-Bu	22	51	+38.4	46
2	**1f**	NaO-t-Bu	22	53	+39.1	48
3	**1g**	NaO-t-Bu	8	81	+43.0	52
4	**1g**	NaO-t-Bu	14	68	+43.4	53 [d]
5	**1e**	NaO-t-Bu	9	75	+49.1	60
6	**1e**	NaO-t-Bu	12	61	+44.5	58 [d]
7	**1e**	KO-t-Bu	5	80	+11.6	14
8	**1e**	KF	22	58	+8.2	10
9	**1e**	$KF+K_2CO_3$	3	81	+10.1	12

[a]Based on substance isolated by prep. TLC; [b] In CH_2Cl_2 (c 1.0) at ambient temperature; [c]Determined by ^1H-NMR spectroscopy in the presence of $Eu(hfc)_3$ as chiral shift reagent, [d] Reaction temperature: -10 °C.

In all cases the product with positive optical rotation was found to be in excess. It can be seen that under such conditions both chemical yield and optical purity depend on the substituent R of the catalyst. Compound **1e** ($R=CH_2CH_2OH$) showed the best asymmetric induction. The reaction was the fastest in the presence of $KF+K_2CO_3$ mixture (entry 9), but with low selectivity (12 % ee).

The greatest chiral induction could be achieved with NaO-t-Bu as a base: in the presence of catalyst **1e** at 20°C 60% ee was obtained for the (+)-antipode. The product of the highest optical purity was repeatedly recrystallized from toluene to prepare the pure enantiomer of positive optical rotation (purity was determined by ^1H-NMR)[4b]. The X-ray diffraction measurement of a single crystal of this substance[5] showed that the absolute configuration is *S*. The specific rotation of (+)-(*S*)-**4** is $[\alpha]_D^{20}$ + 80.8 (c = 1, CH_2Cl_2).



5 **6** **7**

The Darzens condensation taking place between phenacyl chloride (**5**) and benzaldehyde (**6**) could not be performed so far in a stereoselective manner[6]: in the presence of quininium benzyl chloride catalyst under PT conditions an optical purity of 8 % was the best result[7]. Using a SL system only a modest asymmetric induction (5 %) could be achieved in the presence of crown ethers **1**, consequently we changed the medium to a LL system[8](aqueous NaOH - toluene mixture , Table 2).

It can be seen that under such conditions both chemical yield and optical purity significantly depend on substituent R of the catalysts, **1e** (R = CH_2CH_2OH) has proved to be the most effective. The highest optical purity was obtained at -20°C (64 % ee with catalyst **1e**). This, on the basis of the optical rotation of the enantiomer corresponds to an absolute configuration of (2*R*,3*S*)[9]. The excellent properties of crown ether **1e** in both reactions are due most probably to the terminal OH group of substituent R (lariate ether type compound). The fact that catalysts **1** exerted no induction in SL system in the case of Darzens reaction, being effective in

LL system only, shows that the ion pair complexes leading to (2*R*,3*S*)-products are better stabilized under LL conditions.

Table 2. Asymmetric Darzens condensation of phenacyl chloride (**5**) with benzaldehyde (**6**) in the presence of chiral crown ethers **1**

Entry	Catalyst	Time(h)	Temp.(°C)	Yield(%)[a]	$[\alpha]_{578}$[b]	ee(%)[c]
1	**1a**	1	22	42.8	-8.4	4
2	**1b**	1	22	67.6	-26.9	13
3	**1c**	1	22	38.6	-24.5	11
4	**1c**	16	22	84.3	-45.3	21
5	**1d**	3	22	61.8	-11.6	5
6	**1e**	1	22	87.8	-87.3	41[d]
7	**1e**	4	22	92.5	-90.3	42
8	**1e**	2	-10	80.4	-107.0	50
9	**1e**	4	-10	88.6	-126.0	59[d]
10	**1e**	4	-20	76.5	-137.0	64[d]

[a]Based on substance isolated by prep. TLC; [b]Maximum value $[\alpha]_{578}$ -214 (c=1, in CH_2Cl_2) for pure enantiomer[9]; [c]Enantiomeric excess was determined by optical rotation; [d]Determined by ^1H- NMR spectroscopy in the presence of $Eu(hfc)_3$ as chiral shift reagent.

Acknowledgement: This work was partly supported by the Hungarian Academy of Sciences and the National Science Foundation (OTKA T015677).

Notes and References

(1) (a) Maarschalkerwaart, D. A. H. van; Willard, N. P.; Pandit, U. K. *Tetrahedron* **1992,** *48*, 8825. (b) Aoki, S.; Sasaki, S.; Koga, K. *Heterocycles* **1992,** *33*, 493, and references cited therein. (c) Brunet, E.; Poveda, A. M.; Rabasco, D.; Oreja, E.; Font, L. M.; Batra, M. S.; Rodriguez-Ubis, J. C. *Tetrahedron : Asymmetry* **1994,** *5*, 935. (d) Tõke, L.; Fenichel, L.; Albert, M. *Tetrahedron Lett.* **1995,** *36*, 5951, and references cited therein.

(2) Bakó, P; Tõke, L. *J. Incl. Phenom.* **1995,** *23*, 195.

(3) (a) Latvala, A.; Stanchev, S.; Linden, A.; Hesse, M. *Tetrahedron : Asymmetry* **1993,** *4*, 173. (b) Yamaguchi, M.; Shiraishi, T.; Igarashi, Y.; Hirama, M. *Tetrahedron Lett.* **1994,** *35*, 8233. (c) Ono, N.; Kamimura, A.; Kaji, A. *Synthesis* **1984,** 226, and references cited therein.

(4) (a) The Michael addition was performed as follows: 0.3 g (1.44 mmol) of chalcone and 0.3 mL (3.36 mmol) of 2-nitropropane were dissolved in 3 mL of anhydrous toluene, and then 0.1 mmol of crown ether and 0.5 mmol of base were added. The mixture was stirred under Ar atmosphere. After completing the reaction a mixture of 7 mL of toluene and 10 mL of water was added. The organic phase was processed in the usual manner. The product was purified on silica gel by preparative TLC with hexane-ethyl acetate (10:1) as eluent. (b) We found that at 0.2 mol $Eu(hfc)_3$/substrate ratio the induced upfield shift of the methyl signals were 0.09 and 0.13 ppm for the *R* enantiomer while these values for the *S* antipode were 0.10 and 0.11 ppm. These shift differences at 500 MHz make possible to determine the enantiomeric purity within the limits of the NMR spectroscopy as quantitative analytical tool. In the case of the optically pure compound **4** the doubling of any signal could not be observed even at 0.3 and 0.45 $Eu(hfc)_3$/substrate ratio, and minor signals were not showed.

(5) Crystal data: $C_{18}H_{19}NO_3$, formula weight 297.34, orthorhombic; space group $P2_12_12_1$, unit cell dimension a=5.935(1)Å, b=14.539(1)Å, c=198.242(1)Å, α=90.00°, β=90.00°, γ=90.00°, V=1574.1(3)$Å^3$, z=4, D_{calc}=1.255 g/cm^3, F(000)=632, μ (CuK_α)=0.69 mm^{-1}, independent reflections 3189, R=0.0419, R_w=0.1085.

(6) Juliá, S.; Guixer, J.; Masana, J.; Rocas, J.; Colonna, S.; Annunziata, R.; Molinari, H. *J. Chem. Soc. Perkin Trans. 1*, **1982,** 1317.

(7) Hummelen, J. C.; Wynberg, H. *Tetrahedron Lett.* **1978**, 1089.

(8) Typical experimental procedure for the asymmetric Darzens condensation: A toluene solution (3 mL) of 0.2 g (1.3 mmol) of phenacyl chloride was treated with 0.2 g (1.9 mmol) of benzaldehyde and 0.1 mmol of catalyst in 0.6 mL of 30 % NaOH solution. The mixture was stirred under Ar atmosphere. After completing the reaction 7 mL of toluene were added, the organic phase washed with water, dried over $MgSO_4$ and the solvent evaporated. The residue was chromatographed on a preparative silica gel plate of 2 mm thickness (Kieselgel 60 GF_{254}), using CH_2Cl_2 as eluent. ^1H-NMR (δ, 500 MHz, $CDCl_3$) 4.08 (1H, d, J 2 Hz), 4.29 (1H, d, J 2 Hz), 7.30-7.40 (5H, m aromatic), 7.48 (2H, t, aromatic), 7.60 (1H, t, aromatic), 8.01 (2H, m, aromatic).

(9) Marsman, B.; Wynberg, H. *J. Org. Chem.* **1979,** *44*, 2312.