Asymmetric Michael Addition of 2-Nitropropane to a Chalcone Catalyzed by Chiral Crown Ethers Incorporating a D-glucose Unit

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ABSTRACT

Michael addition of 2-nitropropane 4 to a chalcone 3 catalyzed by crown ethers incorporating two glucose units (of 1 type) afforded the adduct 5 with an R-enantiomer excess (28% ee) while the aza-crown ethers containing one glucose unit (of 2 type) gave the same adduct favoring the S-enantiomer under solid–liquid phase transfer conditions (SL-PT). It was proven that substituents at the N-atom of the crown ring in 2 have a significant effect on both the chemical yield and the enantioselectivity, and those having heteroatoms in the proper position of the side chain (2e, 2f) showed the best results in this reaction: 65% ee for the S-antipode. The absolute configuration of (+)-4-methyl-4-nitro-1,3-diphenyl-1-pentanone (5), determined by X-ray diffraction, is also presented in this article. © 1997 John Wiley & Sons, Inc.

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INTRODUCTION

One of the most attractive types of asymmetric synthesis is that in which chiral products are generated under the influence of chiral catalysts. Although many optically active crown ethers have been described in the literature [1], there have been relatively few attempts to use chiral crown ethers to catalyze asymmetric C–C bond formation reactions [2]. The Michael addition of carbon nucleophiles to conjugated enones is one of the most powerful methods for carbon–carbon bond formation. Due to its relevance in the synthesis of biologically active compounds, much effort has been centered on carrying out this reaction in a stereoselective way [3]. The effect of certain catalysts on the stereoselective addition of nitroalkanes to methyl vinyl ketone [4a] and to other enones [4b] was studied recently. The Michael addition of methyl phenylacetate to methyl acrylate had been described earlier by us, in a reaction in which the chiral crown ether catalyst 1b showed very significant chiral induction (R = Bu, 80% ee) [5].
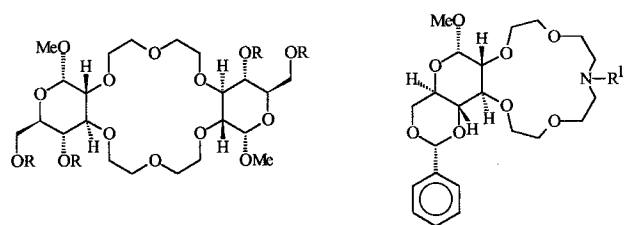
As part of our investigations in this area, we have synthesized the novel class of D-glucose–based crown ether derivatives **2**. These compounds are 15-membered mono-aza-crown ethers with one glucopyranoside unit, in which the substituents attached to the nitrogen exert a significant effect on the phase transfer (PT) properties of the catalyst [6].

RESULTS AND DISCUSSION

The catalytic activity of macrocycles **1** and **2** in the asymmetric Michael addition reaction of 2-nitropropane (**4**) to the chalcone **3** was studied under SL-PT conditions (Scheme 1). Of course, this reaction yields a racemic product by conventional procedures [7]. Our experiments were carried out in toluene, employing solid sodium tert-butoxide as a base in the presence of 7 mol% of catalyst. The asymmetric inductions expressed in terms of enantiomeric excess (ee %) values were determined by ^{1}H-NMR spectroscopy with Eu(hfc)$_3$ as a chiral shift reagent and using preparative TLC in the workup procedure. The reactions were repeated under a variety of conditions. From the results presented in Table 1, several salient aspects of the reaction may be noted. First,

the catalysts incorporating two glucopyranoside units **1a**, **1b** resulted in moderate chemical and relatively low optical yields for the R-enantiomer having negative rotatory power (runs 1–3). No conversion was observed in the presence of the tosyl-derivative **1c** (run 4). The highest optical purity (28% ee) was obtained at $-20°C$ with catalyst **1b** (R = Bu).

It is interesting to note that, by use of aza-crown ethers **2**, the products with opposite configurations (*S*) were obtained. The catalyst having a phenyl group at the N-atom of the crown ring (**2a**) gave the lowest chemical and optical yields (run 5). The following three of the catalysts (**2b**, **2c**, **2d**) exerted roughly the same chiral induction (46% to 48% ee at room temperature), regardless of the quality of the substituents R (runs 6–8). The chemical yields dramatically increased, and higher enantioselectivities were obtained in the presence of catalysts **2e** and **2f** both having heteroatoms with lone pairs of electrons in the N-substituents. Among all the catalysts tested, the compound **2f** (R = CH$_2$CH$_2$OH) proved to be the best: optical purity of 61% for the *S*-antipode and a chemical yield of 85% were obtained at 20°C (run 11), and this value of ee could be improved to 65% ee by an increase of the amount of the catalyst used (from 7 mol% to 14 mol%). The above given temperature seemed to be the optimal temperature for the reaction because under or above this value the enantioselectivity was lower (runs 10, 12, and 14).

1a R = Me

1b R = Bu

1c R = Ts

2a R^1 = Ph

2b R^1 = Bn

2c R^1 = Bu

2d R^1 = cyclohexyl

2e R^1 = CH$_2$COOCH$_3$

2f R^1 = CH$_2$CH$_2$OH

SCHEME 1

TABLE 1 Addition of 2-Nitropropane **4** to Chalcone **3** Catalyzed by Crown Ethers **1**[a] and **2**[b]

Run	Catalyst	Temp. (°C)	Time (h)	Yield (%)[c]	ee (%)[d]
1	**1a**	−20	42	31	9 (R)
2	**1b**	−20	30	44	28 (R)
3	**1b**	20	24	51	14 (R)
4	**1c**	20	68	0	—
5	**2a**	20	30	21	10 (S)
6	**2b**	20	22	39	46 (S)
7	**2c**	20	30	40	48 (S)
8	**2d**	20	22	42	47 (S)
9	**2e**	20	8	90	58 (S)
10	**2e**	−10	8	78	53 (S)
11	**2f**	20	9	85	61 (S)
12	**2f**	−10	10	71	55 (S)
13[e]	**2f**	22	8	91	65 (S)
14	**2f**	50	6	90	34 (S)
15[f]	**2f**	20	10	88	58 (S)

[a]Base: KF + K$_2$CO$_3$.
[b]Base: NaOBu^t.
[c]Based on substance isolated by preparative TLC.
[d]Determined by ^{1}H-NMR spectroscopy in the presence of Eu(hfc)$_3$ as chiral shift reagent; absolute configurations are given in parantheses.
[e]14 mol% of catalyst was used.
[f]Recovered catalyst was used; data are averages from two or more experiments and reproducible within 2%.

The crown amine catalysts **2** could be recovered from the reaction mixture by extracting them with aqueous hydrochloric acid, followed by treatment of the extracts with base. The last experiment of Table 1 (run 15) shows that the catalyst **2f** recovered by this procedure worked similarly as the original one in the reaction.

The effect of the quality of the bases with regard to the ee was examined, always with crown ether **2f** being used as the chiral source. The results of these experiments are presented in Table 2. It can be seen that the quality of the bases exerted significant influence on both the chemical yield and chiral induction. When a KF + K_2CO_3 mixture was used (run 2), the reaction was faster, and the chemical yield (91%) and selectivities (27% ee) were better than those in the case in which KF alone was used (run 1) (yield 58%, ee 22%). The application of the KOBu^t (run 3) and NaF + Na_2CO_3 mixture (run 4) resulted in a good chemical yield but showed very poor selectivities. The reaction was fast in the presence of NaH as well (run 6), but a series of by-products, so far not identified, were formed (yield 54%, ee 25%). The use of powdered NaOH resulted in a higher value of ee (41%) but with poor chemical yield (39%). The greatest degree of chiral induction could be achieved using NaOBu^t base at room temperature (61% ee). The increase of the amount of the base gave a somewhat lower selectivity (58% ee). The difference between influences of NaOBu^t (run 7) and KOBu^t (run 3) may be connected with the fact that crown ethers of type **2** form stronger complexes with Na ions than with K ions [6]. It can be seen that it is the *S*-enantiomer that is in excess in the products in all of the experiments listed in Table 2.

We also investigated the so-called deracemization of the racemic product (+/−)-**5** effected by chi-

ral crown ether-NaOBu^t complexes. As it had been observed earlier by us, the position of the protonation–deprotonation equilibria for chiral CH-acids in the presence of chiral crown catalysts is dependent on the quality of the chiral catalysts, so that one of the antipodes can be in an excess at this point [5]. However, no such effect could be observed in the presence of the catalysts **1** either with KF + K_2CO_3 or with KOBu^t bases. The compounds **2** did not exert such an effect on the racemate **5** at room temperature either, but at −10°C, only slightly dependent on the conditions of the reaction, an excess for the *R*-enantiomer of **5** (4–7% ee) could be detected. Taking into account this result, one can explain the lower ee value for the *S*-enantiomer in the experiment carried out at −10°C (runs 10 and 12, in Table 1).

The product **5** of the highest optical purity (65% ee for *S*) was repeatedly recrystallized from toluene to prepare the pure enantiomer of positive optical rotation (purity was checked by ^{1}H-NMR spectroscopy). The single-crystal X-ray analysis of this substance showed that its absolute configuration is S. The specific rotation of (+)-(S)-**5** is $[\alpha]_D^{20}$ + 80,8 (c = 1, in CH_2Cl_2).

The X-ray crystal structure and labeling of (*S*)-**5** can be seen at the 50% probability level in the ZORTEP [10] diagram (Figure 1). The packing of **5** in the unit cell is drawn in a space-filling model with the nonhydrogen atom skeleton of the molecule. The two phenyl rings in the molecule are nearly perpendicular to each other with an angle of 91.95 (7)°. No noticeable intermolecular interactions could be observed within the sum of the van der Waals radii on the basis of this crystal structure model.

To explain the stereochemical outcome of the reaction, we suppose that there exists an equilibrium between ion pair complexes formed by the enolate-

TABLE 2 Addition of 2-Nitropropane **4** to Chalcone **3** catalyzed by Crown Ether **2f** in the Presence of Various Bases[a]
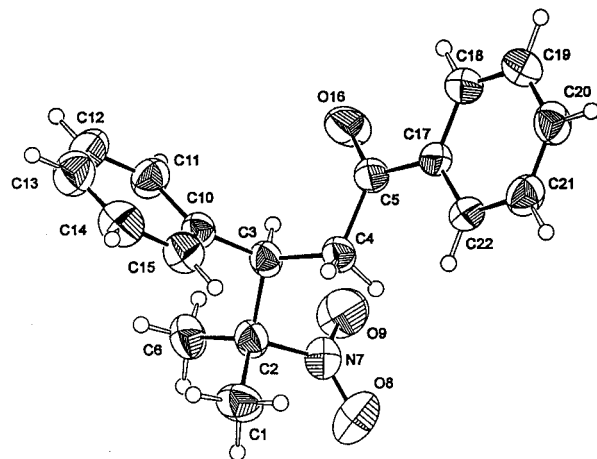
Run	Base	Time (h)	Yield (%)[b]	ee (%)[c]
1	KF	22	58	22 (S)
2	KF + K_2CO_3	3	91	27 (S)
3	KOBu^t	5	71	15 (S)
4	NaF + Na_2CO_3	10	82	12 (S)
5	NaOH	21	39	41 (S)
6	NaH	5	54	25 (S)
7	NaOBu^t	9	85	61 (S)
8[d]	NaOBu^t	8	89	58 (S)

[a]In toluene, at room temperature, 35 mol% of base was used.
[b]Based on substance isolated by prep. TLC.
[c]Determined by ^{1}H-NMR analysis.
[d]70 mol% of base was used.

FIGURE 1   ZORTEP diagram of (S)-**5**.

TABLE 3 Crystal Data and Structure Refinement for (S)-**5**

Empirical formula	$C_{18}H_{19}NO_3$
Formula weight	297.34
Temperature	293(2) K
Wavelength	1.54184 Å
Crystal system	Ørthorhombic
Space group	P $2_12_12_1$
Unit cell dimensions	a = 5.935(1) Å alpha = 90.000°
	b = 14.539(1) Å beta = 90.000°
	c = 18.242(1) Å gamma = 90.000°
Volume	1574.1(3) Å³
Z	4
Density (calculated)	1.255 Mg m^{-3}
Absorption coefficient	0.690 mm^{-1}
F(000)	632
Crystal size	0.35 × 0.18 × 0.09 mm
Theta range for data collection	3.89 to 74.92°
Index ranges	$-6 \Leftarrow h \Leftarrow 7, -18 \Leftarrow k \Leftarrow 18, -22 \Leftarrow l \Leftarrow 22$
Reflections collected	3824
Independent reflections	3189 [R(int) = 0.0128]
Absorption correction	semiempirical from ϕ-scan
Max. and min. transmission	0.940 and 0.771
Refinement method	full-matrix least-squares on F²
Data/restraints/parameters	3189/0/205
Goodness-of-fit on F 2	1.050
Final R indices [I > 2sigma(I)]	R1 = 0.0436, wR2 = 0.1129
R indices (all data)	R1 = 0.0630, wR2 = 0.1245
Absolute structure parameter	−0.1(3)
Largest diff. peak and hole	0.184 and −0.185 e Å^{-3}

metal ion-crown ether, and the result is believed to be controlled by the relative stability of these complexes. In this equilibrium, the ion pair with the lowest energy dominates. The anion of the ion pair is presumably trapped (so that the situation becomes frozen) by the attack of chalcone, resulting in the *S*-product excess.

The concepts of C_2 symmetry and catalyst-substrate steric interactions have played an important role in suggested mechanisms of asymmetric catalysis. The C_2 symmetry element often simplifies the synthesis of the catalysts and serves to reduce the number of competing diastereomeric intermediates in reactions involving their use. Most often, the models that adequately predict the stereochemical outcome of these reactions are based on the spatial orientation of groups within the disymmetric environment of the auxiliary or catalyst. Even so, examples of the electronic tuning of asymmetric catalysts are appearing in the literature with increasing

frequency [8]. Furthermore, in several cases, good enantioselectivities have been obtained using chiral ligands without C_2 symmetry. Our examples with use of the catalysts **2** belong to this latter case. Unfortunately, a clear delineation of the steric and electronic effects is not possible in these systems [8].

It can be seen that the catalysts **2e** and **2f** provided the best chemical yields and the highest chiral induction. These types of heterocycles consisting of a side arm containing ester and hydroxy groups, respectively, named lariat ethers or armed crown ethers, are known to display special complexation, high lipophilic character, and unique quest specificity via tethering-side arm cooperativity [9].

EXPERIMENTAL

¹H-NMR Spectra. BRUKER DRX-500 AVANCE (in CDCl₃), TMS as internal standard. Polarimeter: Perkin-Elmer 241. TLC: preparative silica gel plates (20 × 20 cm) of 2 mm thickness, DC-Fertig-platten Sil G-200 UV₂₅₄ (Macherey-Nagel), eluent hexane-ethyl acetate (10:1), development in UV light. Shift reagents: Eu(hfc)₃ (Aldrich).

Performance of The Michael Addition. Amounts of 0.3 g (1.44 mmol) of the chalcone and 0.3 mL (3.36 mmol) of 2-nitropropane were dissolved in 3 mL of anhydrous toluene, and the 0.1 mmol of crown ether and 0.5 mmol of base were added. The mixture was stirred under an Ar atmosphere. After completion of the reaction, a mixture of 7 mL of toluene and 10 mL of water was added. The organic phase was washed with water, dried over anhydrous MgSO₄, filtered, and the filtrate evaporated to dryness. The residue was purified by preparative TLC. The product **5** was a white crystalline solid, mp 146–148°C. ¹H-NMR (CDCl₃) δ 1.54 (3H, s, CH₃); 1.62 (3H, s, CH₃); 3.25–4.18 (3H, m, CH₂, and CH); 7.25 (5H, m, Ph); 7.52 (3H, m, Ph); 7.85 (2H, m, Ph).

The results of the experiments are presented in Tables 1 and 2. Data are averages of two or more experiments and are reproducible within 2%.

Determination of the Optical Purity. We found that at 0.2 mol Eu(hfc)₃/substrate ratio the induced upfield shifts of the methyl signals were 0.09 and 0.13 ppm for the R enantiomer, while those for the S antipode were 0.10 and 0.11 ppm. These shift differences at 500 MHz make it possible to determine the enantiomeric purity within the limits of the NMR spectroscopy as a quantitative analytical tool. In the case of the optically pure compound (*S*)-**5**, the doubling of any signal could not be observed, even at a 0.3 and 0.45 Eu(hfc)₃/substrate ratio, and minor signals were not in evidence.

X-ray Crystal Structure Determination of (*S*)-**5.** Determination of the unit cell parameters and collection of the symmetry-independent reflections of **5** were performed on an Enraf-Nonius CAD4 computer-controlled single-crystal diffractometer using graphite monochromated CuK_α radiation. The initial structure model was found by the direct method (program SHELXS86 [11]), with the structure refinement being carried out by SHELXL93 [12]. Anisotropic displacement parameters were refined for all of the nonhydrogen atoms. Hydrogen atoms were introduced in calculated positions and refined riding mode on the respective carbon atoms. Crystal data and structure refinements for (*S*)-**5** are listed in Table 3.

SUPPLEMENTARY MATERIAL

The fractional atomic coordinates with their anisotropic displacement parameters, full list of bond distances, angles and torsion angles, least-squares plane data, and F_0/F_c values are given in the supplementary material and are deposited at the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW England.

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