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Tetrahedron: *Asymmetry* 15 (2004) 3775–3781
Tetrahedron: *Asymmetry*

Synthesis of chiral pentacyclo-undecane macrocycles and their use in enantioselective Michael addition reactions

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Received 17 September 2004; accepted 11 October 2004

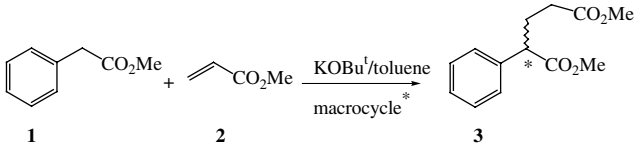
Abstract—The synthesis of a new class of chiral cage annulated macrocycles with five donor atoms and C_1 symmetry is reported. The ability of the chiral hosts to catalyse enantioselective Michael addition reactions were investigated. The cage annulated hosts catalysed the addition of 2-nitropropane to chalcone with high enantioselectivities (up to 92% ee) but with lower turnover rates than previously reported systems. Using sodium methoxide as a base resulted in a classical catalytic reaction for the addition of 2-nitropropane to chalcone. The reaction did not proceed in the absence of the macrocycle. The pentacyclo-undecane (PCU) hosts however, were unsuccessful in catalysing the addition of methyl phenylacetate to methyl acrylate. The structures and energies of the macrocycles with sodium methoxide were calculated using a high level density functional theory (DFT) calculation, which indicates that the complexes should be stable at room temperature. According to the DFT optimised complexes, it appears as if the PCU macrocycles are effectively shielding the base from sterically demanding reagents.

1. Introduction

The search for new chiral ligands to be used in asymmetric catalysis is of great interest in the field of synthetic chemistry.[1,2] Carbon–carbon bond formation reactions remain an active area of research[3] with one of the most popular reactions being the Michael addition.[4–7] We have recently reported the use of chiral pentacyclo-undecane (PCU) cage macrocycles as hosts for chiral ammonium ions,[8] and the application of chiral PCU derived amino alcohols in asymmetric catalysis.[9] However, the use of chiral PCU derived macrocycles for asymmetric Michael addition reactions has not yet been reported.

A considerable amount of effort has been devoted towards the development of the Michael addition reaction, since this reaction often leads to the formation of a stereogenic centre.[7] Cram and Sogah[10] first reported the use of crown ethers as chiral phase transfer catalysts for Michael addition reactions (Scheme 1).

Recently Bakó et al.[11,12] have reported some success with the use of sugar derived macrocycles. Although it is not explicitly mentioned in the literature, it appears



Scheme 1. The classical Michael addition reaction of methyl phenylacetate to methyl acrylate.

that the Michael addition reaction of methyl phenylacetate to methyl acrylate performs best in combination with macrocycles with six donor atoms[10,13–17] and with K^+ as the counter ion. Macrocycles with five donor atoms were, for example, used by Bakó et al.[11,12,18–21] for the catalytic addition of 2-nitropropane to chalcone with Na^+ as the counter ion (Scheme 2). 2-Nitropropane **4** and Na^+ are much smaller than methyl phenylacetate **1** and K^+, which suggests that the two model reactions are influenced[22] by steric factors exerted by the base and macrocyclic host complex. Herein we report the synthesis of PCU macrocycles with five donor atoms and their application in two Michael addition reactions (Schemes 1 and 2). Macrocycles **12**–**15** have C_1 symmetry, which is unique when compared to previously reported hosts utilised in Michael addition reactions.

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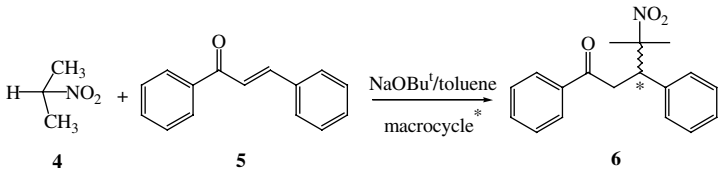
doi:10.1016/j.tetasy.2004.10.015



Scheme 2. Michael addition reaction of 2-nitropropane and chalcone.

2. Results and discussion

Amino alcohols **7**–**10**[9] were reacted with α,α-dibromo-*o*-xylene **11** and sodium hydride in tetrahydrofuran to afford the corresponding macrocycles **13**–**15**. Macrocycle **12** could not be isolated. Macrocycles **13**–**15** were isolated via column chromatography on silica gel using methanol, chloroform and ammonium hydroxide. The ammonium hydroxide was essential in order to minimise streaking of the product on the column (Scheme 3).

Interestingly a fifth ligand **16**[9] derived from proline was also used to attempt the cyclisation reaction above but only gave negligible yields possibly due to increased steric hindrance (Fig. 1).

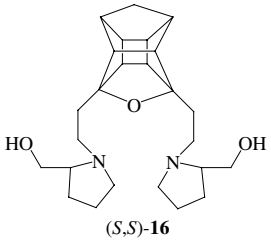


Figure 1. Proline derived ligand.

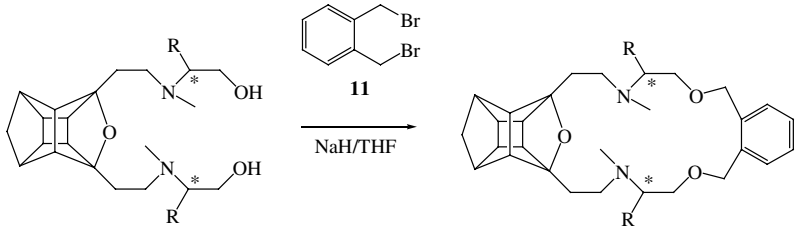
Spectroscopic evidence for product formation for **13**–**15** was evident. Infrared spectra of the macrocycles indicated the presence of C–O–C asymmetric stretching vibrations at ~1080 cm^{-1}. C–C stretching vibration peaks (skeletal bands) of the aromatic ring were present at ~1460 cm^{-1}. The ^1H NMR spectrum indicated the presence of the benzyl group with a peak at approximately 4.5 ppm. The ^{13}C spectrum showed peaks at ~70–71 ppm (CH_2 of the benzylic group) confirming the presence of the xylene substituent. A triplet peak at ~43 ppm represented the methylene bridge carbon of the cage substituent and two nonequivalent quartets at ~38.6 ppm for the methyl groups attached to the nitrogen atoms. Mass spectrometry confirmed the 1:1 ratio of cyclisation products with *m*/*z* peaks that support the respective formulae.

The only group that has reported the use of macrocycles with five donor atoms in Michael addition reactions is that of Bakó et al. As indicated above, they have used the macrocycles for the addition of 2-nitropropane to chalcone (see Scheme 2). It appears from literature that the general experimental conditions, that is, the order of adding reactants for the Michael addition reaction varies considerably.

The experimental conditions employed for macrocycles with six donor atoms (Cram and Sogah,[10] Penadés et al.,[16] Koga et al.,[17] Pandit et al.[23]) and five donor atoms (Bakó et al.[11,12,18–21]) were considered. The general procedure reported by Pandit et al.[23] was employed, wherein the base and nucleophile **1** were first complexed to the macrocycle and then reacted with the substrate **2** thereby eliminating any chance of the reaction proceeding in the absence of a chiral influence.

The catalytic abilities of the cage macrocycles **13**–**15** with the Michael addition reaction of methyl phenylacetate **1** to methyl acrylate **2** were investigated using 18-crown-6 as a control reaction. The ratio of base ($NaOBu^t$; $KOBu^t$ or NaOMe) to host (1:1 and 2:1), time and temperature (−70; 25 °C) were independently varied.

Both sodium and potassium *tert*-butoxide gave racemic product **3** in absence of the host. Although the control



(*R*,*R*)-**7** = CH_2CH_3
(*S*,*S*)-**8** = $CH(CH_3)_2$
(*S*,*S*)-**9** = $CH_2CH(CH_3)_2$
(*S*,*S*)-**10** = C_6H_5

(*R*,*R*)-**12** = CH_2CH_3
(*S*,*S*)-**13** = $CH(CH_3)_2$
(*S*,*S*)-**14** = $CH_2CH(CH_3)_2$
(*S*,*S*)-**15** = C_6H_5

Scheme 3. Proposed synthesis of novel cage annulated macrocycles **12**–**15**.

reaction with 18-crown-6 (−70 °C) proceeds, no yield (**3**) was obtained with any of the PCU macrocycles (five donor atoms) when the base to host ratio was 1:1. When excess base ($NaOBu^t$ or $KOBu^t$) was used (2:1), product **3** was obtained but with poor % ee indicating that the reaction proceeded in the absence of host, as the blank run confirmed.

Sodium methoxide was not able to initiate the reaction in the absence of the host. Product was obtained when NaOMe was used in presence of 18-crown-6 as a control catalyst, but no product was obtained with the PCU macrocycle as host. A control experiment without any host indicated that a mixture of by-products was obtained at temperatures higher that 30 °C. The results indicate that the PCU macrocycles with five donor atoms are unsuitable for the addition reaction of methyl phenylacetate **1** to methyl acrylate **2**.

The Michael addition reaction of 2-nitropropane **4** and chalcone **5**[24] in the presence of base was attempted next. The experimental procedure by Bakó et al.[21] was utilised, but the concentration of base was reduced to be equimolar with respect to the host with the order of adding the reagents was changed as discussed above. The type of base was also varied with the results obtained presented below.

A control experiment using the 'standard base'[21] for this reaction (sodium *tert*-butoxide) resulted in 24% product formation in the absence of host. The reaction gave 26% racemic product when 18-crown-6 was used and a very low yield (<5%) obtained in the presence of the cage macrocycles (Table 1). When excess base was used with the cage macrocycles, the yield increased but the enantioselectivity was very poor (Table 1).

It was argued that a smaller base, such as sodium methoxide, might reduce the steric hindrance between the complexed base and 2-nitropropane, resulting in better yields. Interestingly, a control reaction in absence of host failed to give product **6**, indicating that sodium methoxide is too weak a base to initiate the reaction by itself. The control host (18-crown-6) catalysed the reaction with 54% yield in 48 h when sodium methoxide was used as the base. The cage macrocycles indeed gave product (12% in 120 h) as well as high % ee (80–92%) in the presence of sodium methoxide as base (ratio for host:base:**4**:**5** was 0.05:0.05:2.3:1). It should be noted that when sodium methoxide is used, the 18-crown-6 and the PCU macrocycles gave approximately twice the turnover rate obtained than with sodium *tert*-butoxide.

The fact that sodium methoxide fails to initiate the reaction in the absence of the host, suggests that the reaction in the presence of a host represents a true catalytic cycle. When the concentration of the base (NaOMe) is increased to a factor of two with respect to the PCU host, the yield and ee were unchanged. The rate of the reaction also did not increase, indicating that the catalytic nature of the reaction is maintained. It is likely that a decrease in temperature[25] for the cage macrocyclic systems could result in a very high % ee (>92%) but this was not investigated since the reaction proceeded at too slow a rate.

Results presented by Bakó et al. on the application of chiral crown compounds with five donor atoms to catalyse the Michael addition of 2-nitropropane to chalcone at 25 °C resulted in yields ranging from 20% to 80% with ee values of 2–94% with the majority of systems displaying an ee between 40% and 60%. The best result by Bakó et al.[21] was obtained in the presence of sodium *tert*-butoxide (25 °C) and gave a yield of 43% with an ee value of 94% (ratio for host:base:**4**:**5** was 0.07:0.4:2.3:1). Although they[21] have used a ~5.7 times excess of the base (sodium *tert*-butoxide) with respect to host, the product obtained had a high ee (94%). This is an impressive result if one considers that when sodium *tert*-butoxide is used as the base, the reaction can proceed without the presence of a host to yield a racemic product. The influence of the chiral environment in Bakó's reaction appears to be sufficiently dominant that the excess base does not induce noticeable racemic product.

The results of our studies seem to indicate that steric hindrance may be an important factor in the catalytic ability of the relatively rigid PCU macrocycles:

- First, the addition reaction between methyl phenylacetate **1** and methyl acrylate **2** fails to proceed in the presence of the PCU macrocycles, even at elevated temperatures (−70; 25 °C) and with different bases ($NaOBu^t$; $KOBu^t$ or NaOMe) when the host to base ratio is 1:1. These results seems to indicate that the

Table 1. Michael addition reaction of 2-nitropropane **4** and chalcone **5** catalysed by base and different macrocycles at 25 °C

Host	None	18-C-6	**14**	None	18-C-6	**13**	**14**	**14**	**15**
Base	$NaOBu^t$	$NaOBu^t$	$NaOBu^t$	NaOMe	NaOMe	NaOMe	NaOMe	NaOMe	NaOMe
[Host][a]	None	0.03	0.03	None	0.03	0.03	0.03	0.03	0.03
[Base][a]	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.06	0.03
[4][a]	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3
[5][a]	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Time/h	48	12	96	48	48	120	120	120	120
Yield (%)	24	26	<5	0	54	12	12	~12	20
Ee/%	0	0	—[b]	0	0	92	92	92	80

[a] Concentration in mmol.

[b] Amount of product too small for accurate determination of the specific rotation.

base is forming a tightly shielded 1:1 complex with the PCU macrocycle, which effectively prevents initiation of the reaction by abstraction of the α-hydrogen of the phenylacetate **1**.[26] The reaction occurred in absence of the host for both sodium and potassium *tert*-butoxide, suggesting that the cage macrocycles are immobilising the base through steric hindrance.
- Second, the reaction between 2-nitropropane **4** and chalcone **5** gave very low yields (<5% in 96 h) when sodium *tert*-butoxide is used as base and the PCU macrocycles acts as host (1:1 ratio). When a smaller base (sodium methoxide) is used, the reaction proceeds, albeit with a low turnover rate (12% in 120 h).

In order to gain a better understanding about the steric factors involved when the base is complexed by the different macrocycles, a high level density functional theory (DFT) investigation was performed. The computational details are provided in Section 4. The optimised complexes of the two macrocycles with sodium methoxide are presented below (Fig. 2).

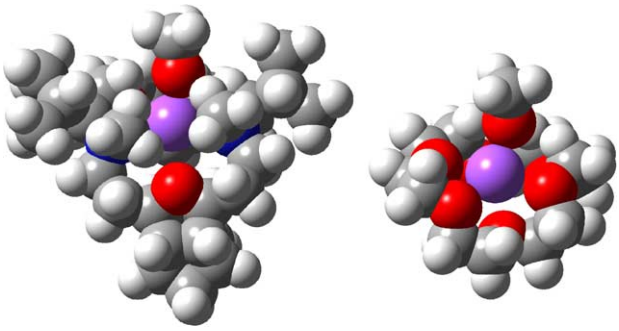


Figure 2. The DFT optimised structures for PCU complex **17** and 18-crown-6 complex **18**, both with sodium methoxide.

It is clear from the geometry of the calculated complex structures that the base (sodium methoxide) is much more shielded in PCU complex **17** than the corresponding base in 18-crown-6 complex **18**. The base should be accessible to abstract a proton from the reagent **1** or **4** in order to initiate the reaction. The approximate[27] heat of complexation was calculated and found to be $\sim -28\,\text{kcal mol}^{-1}$ for the PCU complex **17** and $\sim -35\,\text{kcal mol}^{-1}$ for the 18-crown-6 complex **18**. These results seem to fit the expected chemical interaction for these complexes as well as our experimental observations. The contribution of one donor atom towards stabilisation of the complex is $\sim 6\,\text{kcal mol}^{-1}$, which is of the same order of hydrogen bond stabilisation (3–6 kcal mol^{-1}).[28] Both complexes are also sufficiently stable to prevent dissociation at room temperature, since the molecules have only enough thermal and kinetic energy at room temperature to allow processes requiring up to 15–20 kcal mol^{-1}.[29] The base appears to be effectively shielded from the sterically demanding reagents in the PCU complex **17**. Steric hindrance and the stability of the complex at room temperature seem to provide a plausible explanation for the observation that the PCU macrocycles are immobilising the reaction (Schemes 1 and 2) when sterically demanding reagents are used.

3. Conclusion

Chiral PCU macrocycles with five donor atoms catalyse the Michael addition reaction of 2-nitropropane to chalcone with high ee (up to 92% ee) but low yield. Using sodium methoxide as a base, offers a classical catalytic reaction as no product is obtained in the absence of host. Steric hindrance appears to influence the reaction since a larger base, such as sodium *tert*-butoxide, gave very little product with the PCU host systems while a smaller base (sodium methoxide) gave approximately double the yields. The PCU hosts with five donor atoms did not catalyse the Michael addition reaction between methyl phenylacetate and methyl acrylate in the presence of a base. This Michael addition reaction is normally used with macrocycles with six donor atoms. The DFT computed structures of the PCU complex suggest that the base is effectively shielded from sterically demanding reagents. The PCU complexes are sufficiently stable at room temperature ($>25\,\text{kcal mol}^{-1}$) to immobilise the base from reagents, such as phenylacetate, while a smaller and much more acidic reagent (2-nitropropane) gives product.

In the context of the results presented in the literature, chiral hosts containing the PCU framework deserve further investigation as the system can be modified[9,30] to change the cavity size of the host macrocycle, which could be instrumental in investigating the effect of steric hindrance with this type of catalyst.

4. Experimental

Melting points are uncorrected. Optical rotations were taken on a Perkin–Elmer 341 polarimeter. All mass spectrometric analysis were carried out on a VG70-70E mass spectrometer. FAB mass spectra were obtained by bombardment of samples with xenon atoms (1 mA at 8 keV). *m*-Nitrobenzyl alcohol was used as the matrix. NMR spectra were recorded on a Varian Unity Inova-300 MHz spectrometer. Elemental microanalyses were obtained at the University of KwaZulu-Natal using a LECO CHNS-932 for carbon, hydrogen and nitrogen, and a LECO VTF-900 for oxygen. Tetrahydrofuran and toluene were freshly distilled over sodium benzophenone ketyl under a nitrogen atmosphere prior to its use.

4.1. General procedure for the synthesis of macrocycles 13–15

To a suspension of NaH (4 equiv) in THF (100 mL/0.5 g NaH) was added a solution of the diamino diol (**8**–**10** 1 equiv) and α,α-dibromo-*o*-xylene **11** (1 equiv) dropwise (8 h) under a nitrogen atmosphere at ambient temperature. The reaction mixture was stirred for a further 12 h after the addition had been completed. The solution was then filtered and concentrated in vacuo to give the

crude product as a highly viscous oil. This oil was chromatographed on silica gel by eluting with chloroform–methanol–ammonium hydroxide (96:2:2) to afford the pure macrocycles.

4.1.1. Macrocycle 13. Clear oil (17%). $[\alpha]_D^{20} = +2.1$ (*c* 2, $CHCl_3$); IR (KBr): ν_{max} 2952(vs), 1460(m), 1089(m), 744(m) cm^{-1}; FAB$^+$ MS (*m*-nitrobenzyl alcohol): *m/z* 548 $[M+H]^+$; ^1H NMR [$CDCl_3$, 300 MHz]: δ_H 0.90 (d, $J = 6.6$ Hz, 6H), 0.95 (d, $J = 6.6$ Hz, 6H), 1.49 (AB, $J_{AB} = 10$ Hz, 1H), 1.68–3.13 (m, 27H), 3.35–3.82 (m, 4H), 4.33–4.84 (m, 4H), 7.12–7.54 (m, 4H), ^{13}C NMR [$CDCl_3$, 75 MHz]: δ_C 19.52 (q), 21.09 (q), 28.26 (d), 28.41 (d), 29.67 (t), 38.44 (q), 38.81 (q), 41.24 (d), 41.39 (d), 43.48 (t), 42.79 (d), 43.88 (d), 47.08 (d), 48.61 (d), 50.15 (t), 50.52 (t), 57.89 (d), 59.29 (d), 68.82 (t), 70.79 (t), 70.87 (t), 94.61 (s), 127.58 (d), 127.89 (d), 127.99 (d), 128.19 (d); 136.08 (s), 136.27 (s). Anal. Calcd for $C_{35}H_{52}N_2O_3C$, 76.60; H, 9.55; N, 5.10; O, 8.75. Found C, 76.52; H, 9.49; N, 5.07; O, 8.80.

4.1.2. Macrocycle 14. Waxy solid (42%) $[\alpha]_D^{20} = +17.0$ (*c* 5, $CHCl_3$); IR (KBr): ν_{max} 2954(vs), 1464(m), 1088(m) cm^{-1}; FAB$^+$ MS (*m*-nitrobenzyl alcohol): *m/z* 576 $[M+H]^+$; ^1H NMR [$CDCl_3$, 300 MHz]: δ_H 0.85 (t, 12H), 1.10–1.35 (m, 4H), 1.37–1.51 (AB, $J_{AB} = 10$ Hz, 1H), 1.53–1.68 (m, 2H); 1.71–2.00 (m, 5H), 2.1–2.95 (m, 20H), 3.32–3.48 (m, 2H), 3.5–3.65 (m, 2H); 4.45–4.65 (m, 4H), 7.15–7.45 (m, 4H); ^{13}C NMR [$CDCl_3$, 75 MHz]: δ_C 22.78 (q), 22.98 (q), 25.29 (d), 30.30 (t), 30.47 (t), 37.79 (q), 37.91 (q), 38.06 (t), 38.16 (t), 41.33 (d), 41.41 (d), 43.49 (t), 43.90 (d), 47.59 (d), 48.53 (d), 50.19 (t), 50.51 (t), 58.15 (d), 59.08 (d), 60.49 (d), 60.55 (d), 70.84 (t), 70.97 (t), 71.08 (t), 71.12 (t), 94.78 (s), 127.39 (d), 127.47 (d), 128.21 (d), 128.37 (d), 136.52 (s). Anal. Calcd for $C_{37}H_{56}N_2O_3C$, 77.04; H, 9.78; N, 4.86; O, 8.32. Found C, 77.92; H, 9.73; N, 4.83; O, 8.40.

4.1.3. Macrocycle 15. Waxy solid (35%) $[\alpha]_D^{20} = +11.3$ (*c* 5, $CHCl_3$); IR (KBr): ν_{max} 2923(vs), 1452(m), 1088(m) cm^{-1}; FAB$^+$ MS (*m*-nitrobenzyl alcohol): *m/z* 617 $[M+H]^+$; ^1H NMR [$CDCl_3$, 300 MHz]: δ_H 1.49 (AB, $J_{AB} = 10.5$ Hz, 1H), 1.70–2.73 (m, 25H), 2.80–2.94 (m, 4H), 3.65–4.00 (m, 4H); 4.50–4.65 (m, 4H), 7.15–7.42 (m, 14H), ^{13}C NMR [$CDCl_3$, 75 MHz]: δ_C 30.28 (t), 39.70 (q), 39.79 (q), 41.31 (d), 41.52 (d), 43.53 (t), 43.88 (d), 43.90 (d), 47.34 (d), 48.64 (d), 50.08 (t), 50.24 (t), 57.98 (d), 59.27 (d), 68.31 (d), 70.98 (t), 71.08 (t), 72.28 (t), 94.99 (s), 95.04 (s), 127.18 (d), 127.23 (d), 127.31 (d), 127.57 (d), 128.19 (d), 128.22 (d), 128.25 (d), 128.32 (d), 128.40 (d), 128.43 (d), 128.46 (d), 128.49 (d), 128.52 (d), 128.58 (d), 136.24 (s), 136.43 (s). Anal. Calcd for $C_{41}H_{48}N_2O_3C$, 79.83; H, 7.84; N, 4.54; O, 7.78. Found C, 79.79; H, 7.82; N, 4.48; O, 7.82.

4.2. General procedure for the Michael addition reaction of methyl phenylacetate 1 to methyl acrylate 2

A mixture of the macrocycle (0.05 mmol) and base (0.05 mmol) in toluene (2 mL) was stirred for 30 min at ambient temperature under a nitrogen atmosphere. The reaction mixture was cooled to −78 °C at which point methyl phenylacetate (2 mmol) was added and stirred for 10 min, followed by the addition of methyl acrylate (1 mmol). The reaction was monitored via TLC (hexane–EtOAc = 9:1) and the spots were detected with UV light and anisaldehyde reagent (the product, **3**, orange coloured spot). The conditions were also individually varied as indicated in the text.

The reaction was quenched with saturated NH_4Cl (4 mL) and extracted with diethyl ether (4 mL). The solution was concentrated in vacuo and the product purified via column chromatograph (silica, hexane–EtOAc = 9:1). The enantiomeric excess was determined by dividing the specific rotation of the product by the specific rotation of the literature value.

4.3. General procedure for the Michael addition reaction between 2-nitropropane 4 and chalcone 5

The corresponding macrocycle (0.03 mmol) and sodium methoxide (0.03 mmol) was added to a solution of chalcone[24] (1.0 mmol) and 2-nitropropane (2.3 mmol) in dry toluene (3 mL). The mixture was stirred under an inert atmosphere at ambient temperature. After the desired reaction time, water (5 mL) and toluene (5 mL) were added. The organic phase was separated and dried over Na_2SO_4. The solvent was evaporated and the crude product **6** purified by column chromatography (silica, hexane–EtOAc = 9:1). The enantiomeric excess was determined by dividing the specific rotation of the product by the specific rotation of the literature value. Each experiment was performed twice and the average yield taken. Recycling of the host was achieved using column chromatography (~50%).

4.4. Details of the DFT optimised structures for the two complexes 17 and 18

The two complexes were optimised by using GAUSSIAN 03[31] utilising density functional theory (DFT) at the B3LYP level of theory with the 6-31+*G*(*d*) basis set. Diffuse functions are typically used for a more accurate description where lone pair electrons are involved, while polarisation functions remove some limitations of the basis set by expansion of the virtual space. Solvation effects were not considered in order to simplify the model.

To ensure that a complex structure as close as possible to the global minimum structure was obtained, a number of different starting structures were created and optimised. The distance between the donor atoms and sodium were initially fixed (using the 'modred' function) in order to maintain maximum interaction between the donor atoms and sodium, while the rest of the molecule was relaxed to find a low energy structure. All constraints were then released to enable the optimisation algorithm to find the lowest possible structure.

In order to calculate the approximate[27] heat of complexation ($\Delta H_{complexation} = E_{complex} - (E_{host} + E_{NaOMe})$, the free host was subjected to a series of molecular dynamics (MD) calculations using the MM3[33] forcefield in

Alchemy.[34] An MD simulation at 800 °C for 10 ps was performed and the energy was plotted against the time of simulation. The lowest energy structures were manually picked from the plot and subjected to a second MD simulation with the same settings. This procedure was repeated a third time. A total of between 10 and 30 low energy structures were manually picked from the three MD sequences and optimised using the MM3 forcefield. The five lowest energy structures were used as starting structures for a DFT optimisation. The order of energies remained unchanged, and the lowest energy structure was used to determine the heat of complexation. Sodium methoxide was also optimised with a DFT calculation.

The second-derivative analytical vibrational frequency calculation utilising the same methodology employed in the location of stationary point showed no negative frequencies, indicating that the complexes and free hosts were minimum structures.

Cartesian coordinates of the optimised complex structures are available from the corresponding author.

Acknowledgements

This work was supported by grants from the National Research Foundation Gun 2046819 (South Africa), the University of KwaZulu-Natal and the National Computational Science Alliance (USA) under grant number CHE010004 (NCSA IBM pSeries 690). Dr. Louis Fourie, University of Potchefstroom, is acknowledged for the MS analysis and Mrs. Anita Naidoo, University of KwaZulu-Natal for the elemental microanalysis.

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25. Cram and Sogah (see Ref. 10) reported 67% ee at 25 °C and 99% ee at −78 °C for the Michael addition reaction in Scheme 1. The PCU macrocycles gave 90–92% ee at 25 °C for the Michael addition reaction in Scheme 2 and, should in analogy to Cram's result, give a higher % ee at lower temperatures.
26. The fact that NaOMe, in the presence of the PCU macrocycles, is unable to initiate the reaction between methyl phenylacetate **1** and methyl acrylate **2**, but able to initiate the reaction between 2-nitropropane **4** and chalcone **5** is possible due to both steric and electronic factors. Phenyl acetate is sterically more hindered than 2-nitropropane. Its α-hydrogen is also less acidic than for 2-nitropropane.
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