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Asymmetric enolate alkylation via templation with chiral synthetic receptors

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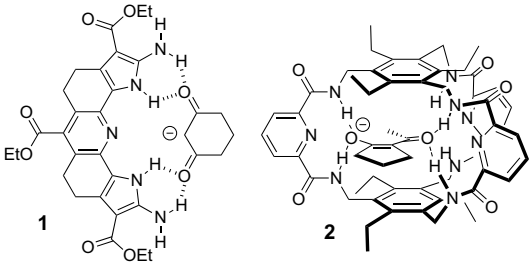
Abstract—C_3-Symmetric chiral receptors have been developed for enantioselective alkylation of sodium enolates of active methylene compounds. It has been demonstrated that a 1:1 binding complex forms between these receptors and sodium enolates in THF-d_8/CD_3CN by ^1H NMR titration experiments. Moderate enantiomeric enrichment of the benzylation product of 2-acetylcyclohexanone has been demonstrated using this strategy. Templation of enolate alkylation by synthetic receptors represents a new approach to asymmetric induction.

Stereoselectivity is an important aspect of reactions involving enolates, as enolates are synthetically useful intermediates in carbon–carbon bond forming reactions, such as Michael additions, aldol reactions, acylation and alkylation.[1] Controlling the stereoselectivity of enolate alkylation has received considerable attention, as this reaction is often used in the synthesis of natural products.[2] In most reactions involving enolates, the chirality of the carbon α to a carbonyl is lost upon conversion to the corresponding enolate due to the planar nature of the enolate. An enantiomerically enriched product is typically obtained through the use of a chiral auxiliary that is covalently bound to the enolate.[3] In comparison, there are fewer examples of enantioselective enolate alkylation reactions employing noncovalently bonded chiral ligands.[4] This is, in part, due to the lack of information about the interactions of the enolate and coordinating ligand in solution.

Our host design is based on previous studies with polyazacleft **1**[5] and bicyclic cyclophane **2**.[6] Compounds **1** and **2** were designed to form hydrogen bonds to the oxygen atoms of diketones, thereby increasing their acidity by stabilizing the resulting enolate anion. Molecular modelling suggests encapsulation of the enolate of 2-acetylcyclopentanone in bicyclic cyclophane



2 with two pairs of hydrogen bonds directed towards the π-system of the enolate guest.

Our studies with receptor **2** lead us to design a C_3-symmetric chiral host (**3**) for binding enolates of active methylene compounds. The design of our receptor includes six amide hydrogen bonds arranged on one face of a hexasubstituted benzene ring. It has been shown that steric interactions between adjacent substituents on a hexasubstituted benzene ring cause alternate substituents to be arranged above and below the ring.[7] In our receptor design, chiral substituents on the 1, 3 and 5 positions of the benzene ring are proposed to form a chiral cavity for enolate binding. A complex between the chiral host and a prochiral enolate is proposed to exist as a pair of diastereomers, depending on the facial orientation of the enolate guest with respect to the benzene ring. It is postulated that the lower energy diastereomeric complex will predominate in solution and result in a

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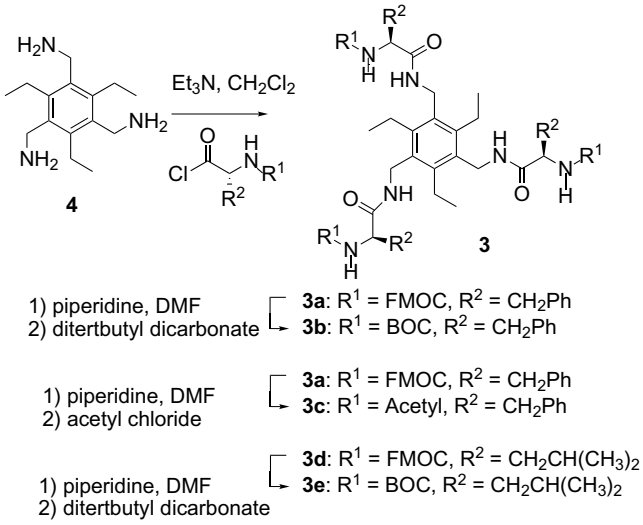
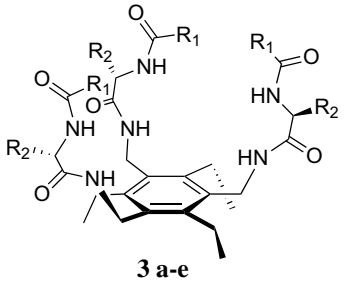


Scheme 1. General synthetic route to **3**.

face selective approach of an alkylating agent, as one face of the enolate will be blocked by the benzene scaffold. However, the possibility that alkylation will preferentially occur from the higher energy, more reactive diastereomeric complex in solution relative to the lower energy diastereomeric complex cannot be excluded.



A general synthesis of the chiral coordinating ligands is shown in Scheme 1. The synthesis of the hexasubstituted benzene scaffold, 1,3,5-tris(aminomethyl)-2,4,6-triethylbenzene (**4**), from 1,3,5-triethylbenzene is described elsewhere.[8] Fmoc protected L-phenylalanine, L-valine and L-leucine were converted to acid chlorides with thionyl chloride.[9] Coupling the acid chlorides with **4** yields chiral C_3-symmetric Fmoc protected receptors **3a** and **3d**. However, due to the insolubility of the these hosts, compounds **3b**, **3c** and **3e** were synthesized by first removing the Fmoc protecting group with piperidine in DMF and reprotecting the primary amines with di(*tert*-butyl) dicarbonate (**3b** and **3e**) or acetyl chloride (**3c**), respectively. Receptors **3b**, **3c** and **3e** were found to be soluble in a variety of organic solvents, including tetrahydrofuran and toluene.

Before evaluating the utility of hosts **3b**, **3c** and **3e** in directing enantioselective enolate alkylation, we determined the binding stoichiometry and association constant of receptor **3e** and **5** using a 400 MHz ^{1}H NMR titration experiment in THF-d_8, CD_3CN with 4.7 mM host. In order to separate the enolate from the sodium counterion and promote binding of the enolate to the host, a [2.2.1] cryptand was used to coordinate sodium.[10]

The association constant between receptor **3e** and enolate-sodium [2.2.1] cryptand guest **5** was determined from the downfield shift of the host amide N–H resonances with increasing concentration of the enolate-sodium [2.2.1] cryptand guest. A 1:1 binding stoichiometry was found, as shown in Figure 1. An association constant of $6.0\times10^3 \pm 1.0^3$ was found by analysis of the ^{1}H NMR chemical shift of the resonances of the host as a function of the guest concentration.[11]

For enolate alkylation studies, we chose cyclic enolates of active methylene compounds **6**, **7** and **8** because the conformation of these enolates is restricted to either the *Z*,*E* and *Z*,*Z* conformations, with the *Z*,*E* conformation being formed preferentially (Scheme 2). Benzylation of the enolates was performed in the presence of hosts **3b**, **3c** and **3e** in toluene. The ee's obtained were low, ranging between single digits to around 20 (Table 1). However, the enantioselectivity of the benzylation of **7** was greatly improved in the presence of host **3e** (42%).[12]

Because the highest ee was obtained with host **3e** and enolate **7**, we sought to test the origin of the enantioselectivity of this one reaction. As a control, **9** was synthesized from Boc-L-leucine *N*-hydroxysuccinimide ester in methylene chloride with triethylamine. Benzylation of **7** in the presence of **9** (Scheme 3) did not result

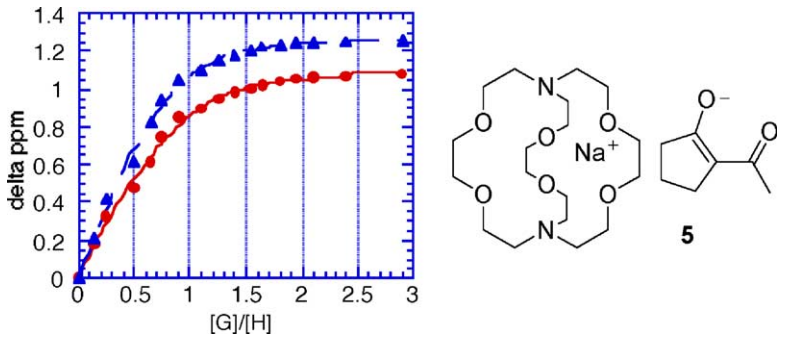
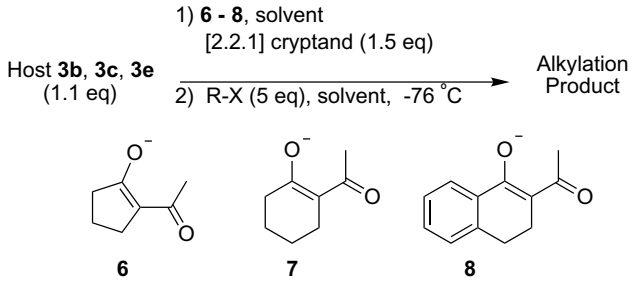


Figure 1. ^{1}H NMR titration of **3e** with **5**.



Scheme 2. Alkylation studies.

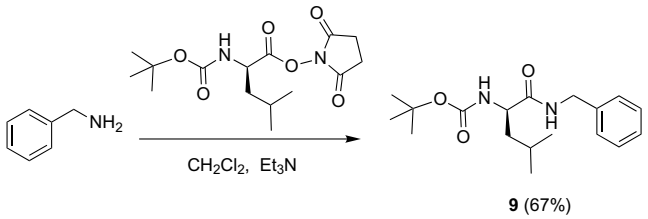
Table 1. Alkylation of enolates **6**–**8** with benzyl bromide in the presence of hosts **3b**, **3c** and **3e**

Host	Enolate	Time (h)	Solvent	*T* (°C)	Yield (%)	Ee[a]
None	**6**	8	THF	−78	54	0
None	**7**	6	THF	−65	80	0
None	**8**	12	THF	−78	76	0
3c	**7**	8	THF	−78	36	20
3b	**7**	8	Toluene	−78	57	10
3e	**7**	7	Toluene	−50	44	<3
3e	**7**	8	THF	−65	40	42
3e	**6**	10	THF	−78	54	<3
3e	**8**	12	THF	−78	62	4

[a] Ee was determined by chiral HPLC.

in any enantiomeric enrichment of the alkylation product. This suggests that the organization of the coordinating ligands on one face of the hexasubstituted benzene scaffold in **3** is responsible for forming a binding cavity for enolate recognition, thereby directing enolate alkylation enantioselectively.

In summary, we have shown that a hydrogen-bonding chiral receptor can act as a template for directing enolate alkylation.[13] In our case, a moderate enantiomeric enrichment of the product was obtained. Further studies must focus on improving the enantioselectivity of the reaction and broadening the scope of this concept to other reactions. However, the principle has been demonstrated, and it suggests that other hydrogen-bonding molecular receptors can be used in enolate reactions, hopefully significantly improving on the initial studies described herein.



Scheme 3.

Acknowledgements

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12. Typical experimental procedure: In a drybox under nitrogen, enolate 12 (30 mg, 0.20 mmol) was added to [2.2.1] cryptand (100 mg, 272 mmol). Receptor **7b** (180 mg, 0.20 mmol) in THF (20 mL) was added under Ar atmosphere followed by THF (20 mL). The solution was stirred for 30 min and cooled to −78 °C. Benzyl bromide (0.16 mL,1.35 mmol) in THF (10 mL) was added and the solution stirred for 8 h. The reaction was quenched with water (1 mL) and the THF was removed in vacuo. The residue was dissolved in methylene chloride and washed with water (30 mL × 1), saturated aqueous $NaHCO_3$ (30 mL × 1) and brine, and dried with $MgSO_4$. After filtration, the filtrate was concentrated in vacuo to give a yellow oil. This crude product was purified by flash chromatography (hexanes/ethyl acetate (90/10)) to give the desired product.
    Enantiomeric excess of the product was determined by HPLC under the following conditions: Chiralcel AD (hexane/2-propanol = 30/1, 1.0 mL/min, 260 nm).
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