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Per-6-amino-β-cyclodextrin as a Reusable Promoter and Chiral Host for Enantioselective Henry Reaction

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ABSTRACT

A highly efficient enantioselective Henry reaction has been carried out using per-6-ABCD as a supramolecular chiral host and promoter to give the corresponding adduct with high yield (up to 99%) and enantiomeric excess (up to 99%). Per-6-ABCD also promotes the diastereoselective Henry reaction in a syn-selective manner to give the adduct up to 99% yield with 99:1 syn/anti selectivity. The enantiomeric excess of the syn-adduct is 99%. The catalyst is recovered and reused without loss in its activity.

The ever-increasing demand for enantiopure chemicals continues to nurture the development of powerful synthetic methods that utilize highly efficient chiral catalysts and auxiliaries.[1] The requirements for a useful chiral catalyst are that it must provide only the target product in high yield and excellent enantiomeric excess and must have broad general applications.[2] However, the difficulties associated with the recovering and reusability of these expensive chiral catalysts is an important challenge.[3] Furthermore, the potential contamination of the products caused by metal leaching particularly from homogeneous catalysts is unacceptable for pharmaceuticals production.[4] One of the most promising ways to circumvent these difficulties is immobilization of these chiral catalysts using various strategies.[5] Many approaches developed so far for the immobilization of homogeneous catalysts are often flawed by reduced enantioselectivity, diminished catalytic activity, and poor reproducibility in the catalysis and/or tedious catalyst synthesis in comparison with their homogeneous counterparts.

There is increasing interest in developing catalytic asymmetric C−C bond-forming processes.[6] The Henry (nitroaldol) reaction is a powerful and atom-economical carbon−carbon bond-forming reaction that can be used to create a new stereogenic center at the β-position of a nitro functionality.[7,8] The resulting β-hydroxynitro compounds have been used in various beneficial organic transformations.[9] Consequently, increasing attention has recently been focused on the development of novel catalytic, asymmetric versions of the Henry reaction.[10]

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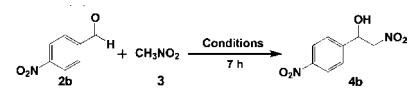
Cyclodextrins (CDs) are macrocyclic oligosaccharides possessing hydrophobic cavities that bind substrates selectively via noncovalent interactions.[11] Native β-CD has been employed as a catalyst for thiol[12] and aza-Michael addition[13] in water medium with poor chiral induction. Chemical modification of cyclodextrins is expected to improve the enantioselectivity in asymmetric catalysis,[14a] and in chiral NMR analysis.[14b] Per-amino-CDs are homogeneous CD derivatives modified by persubstitution at the primary face with amino pendant groups, which display combined hydrophobic and electrostatic bindings of guest molecules relative to native CDs. They are employed as biomimetic catalysts for Kemp elimination,[15a] deprotonation,[15b] and chiral recognition.[15c] Amino catalysts are also receiving greater attention in asymmetric Michael addition.[16] In our group, per-6-amino-β-cyclodextrin (per-6-ABCD, **1**) is used extensively as a supramolecular chiral host and a base catalyst for Cu-catalyzed *N*-arylation,[17a] for Michael addition of nitromethane and thiols to chalcones,[17b] and for the synthesis of pyranopyrazole derivatives under solvent-free conditions at room temperature.[17c] A novel, colorimetric, and ratiometric sensor is also developed for transition-metal cations Fe^{3+} and Ru^{3+} in water,[17d] using per-6-ABCD as a supramolecular host and *p*-nitrophenol as a spectroscopic probe. In the present work, we have successfully employed per-6-ABCD (**1**) as a chiral base and a host for addition of nitromethane (**3**)/nitroethane (**5**) to substituted aldehydes in ACN/water (1:1 v/v) medium at −20 °C with <99% ee. It is also interesting to note that the promoter can be recovered and reused several times.

The potential of per-6-ABCD (**1**) is optimized in an enantioselective Henry reaction using *p*-nitrobenzaldehyde (**2b**) and nitromethane (**3**) as test substrates, and the results are discussed in Table 1. When carried out in native β-cyclodextrin in water, there is no reaction (entry 1). When triethylamine is employed as an external base along with native β-CD, though good conversion is observed, the enantiomeric excess is very poor at room temperature (ee of 1.2%) and 4 °C (ee of 1.3%) (entry 2). On the other hand, per-6-ABCD (**1**) effectively promotes Henry reaction with quantitative yield but with only 65% enantioselectivity in 7 h at room temperature (entry 3).

Table 1. Enantioselective Henry Reaction of **2b** with **3** under Various Reaction Conditions[a]



entry	medium	ratio of **1**:**2**[b]	temp (°C)	yield[c] (%)	% ee[d]
1	water (β-CD)	1:1[e]	rt		
2	water (β-CD)	1:1[f]	rt (4 °C)	78 (76)	1.2 (1.3)
3	water	1:1	rt	99	65
4	methanol	1:1	rt	99	28
5	DMF	1:1	rt	99	34
6	ACN	1:1	rt	99	60
7	methanol/water	1:1	rt	99	56
8	DMF/water	1:1	rt	99	60
9	ACN/water	1:1	rt	99	88
10	ACN/water	1:1	−5, −10, −15, −20	99, 99, 99, 99	89, 92, 94, 99
11	ACN/water	1:1[g]	−20	96	22
12	ACN/water	0.25:1	−20	88	62
13	ACN/water	0.50:1	−20	90	71
14	ACN/water	0.75:1	−20	98	90
15	ACN/water	1:1	−20	99	99
16	ACN/water	2:1	−20	99	99

[a] All reactions were carried out on a 0.1 mmol scale with 0.1 mmol of per-6-ABCD, 0.1 mmol of aldehyde, and 0.1 mmol of nitromethane in ACN/H_2O (1:1 v/v) mixture at −20 °C for 7 h, unless otherwise noted. [b] Mole ratio. [c] Isolated yield. [d] Determined by HPLC analysis. [e] Mole ratio of β-CD/aldehyde. [f] Mole ratio of β-CD/aldehyde and triethylamine as the external base. [g] Mole ratio of mono-6-ABCD/aldehyde.

Influence of other experimental parameters such as solvent, temperature, and amount of per-6-ABCD (**1**) are also optimized. Among the different solvents screened, ACN shows quantitative yield and moderate enantiomeric excess when compared to other solvents such as water, methanol, and DMF (entries 3−6). Among the mixture of solvents, complete conversion and good enantiomeric excess are achieved in ACN/water at room temperature (entries 7−9).

The effect of temperature on enantioselectivity in the Henry reaction promoted by per-6-ABCD (**1**) is also studied (entries 9 and 10). At −20 °C, high yield and excellent enantiomeric excess (up to 99%) (entry 10) are obtained. The absolute configuration of the predominant enantiomer was assigned as *R* by comparison with literature data.[5−10,19] When mono-6-ABCD[18] was used instead of per-6-ABCD (**1**) at optimized conditions, although a good yield was realized, the ee was poor (entry 11). The reaction was also studied with different molar ratios of host and guest. Though very good conversions were observed, the ee was excellent only when the H/G ratio was ≥1 (entries 12−16).

This per-6-ABCD (**1**)-promoted Henry reaction is also successfully extended to different substituted aliphatic, aromatic, cyclic, and heterocyclic aldehydes. As depicted in Table 2, this reaction works very well for a wide range of para-substituted aldehydes with very good to excellent isolated yields and also with very high enantiomeric excess. When substituents are

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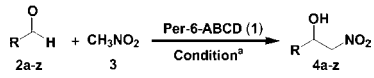
present in the *meta*- and *ortho*-positions, there is no change in the yield but the ee decreases considerably. The yield of the Henry product remains the same when more than one substituent is present in the phenyl ring, but the ee decreases (Table 2, entries 22−25). When the distance between the carbonyl carbon and phenyl ring increases (Table 2, entries 16 and 17), the yield as well as ee decrease considerably. These results clearly suggest that electronic factors play a limited role, but the presence of substituents at different positions plays a major role in enhancing the ee. Para-substituted aldehydes (which may ensure a stronger binding and deeper inclusion into the CD cavity) showed higher ee. To demonstrate the potential of this method for preparative purposes, the reaction was also carried out on a gram scale, giving isolated yields which are comparable to those obtained for a small-scale reaction.

Simultaneously, the recovery and reusability of per-6-ABCD (**1**) was also investigated. After completion of the reaction, products were extracted with ethyl acetate, dried with sodium sulfate, and concentrated under reduced pressure. Per-6-ABCD was washed three times with ethyl acetate, filtered, dried in vacuo, and reused. Even after seven consecutive reactions, the recovered per-6-ABCD retained its activity, resulting in 99−92% yield. The enantiomeric excess decreased considerably from the fifth run (Table 3) onward.

Table 2. Per-6-ABCD (**1**)-Promoted Enantioselective Henry Reaction of Nitromethane (**3**) with Different Aldehydes[a]



entry	aldehyde (R)	product	yield[b] (%)	% ee[c]
1	C_6H_5-	**4a**	98	90
2[d]	*p*-NO_2-C_6H_4-	**4b**	99	99
3	*m*-NO_2-C_6H_4-	**4c**	99	94
4	*o*-NO_2-C_6H_4-	**4d**	99	85
5	*p*-Cl-C_6H_4-	**4e**	99	99
6	*m*−Cl-C_6H_4-	**4f**	99	95
7	*o*-Cl-C_6H_4-	**4g**	99	90
8	*p*-Br-C_6H_4-	**4h**	99	99
9	*p*-OH-C_6H_4-	**4i**	99	95
10	*o*-OH-C_6H_4-	**4j**	98	89
11	*p*-OCH_3-C_6H_4-	**4k**	98	99
12	*m*-OCH_3-C_6H_4-	**4l**	96	88
13	*p*-CH_3-C_6H_4-	**4m**	92	98
14	*p*-*i*-Pr-C_6H_4-	**4n**	92	99
15	*p*-NMe_2-C_6H_4-	**4o**	99	99
16	C_6H_5-CH=CH-	**4p**	89	89
17	$C_6H_5CH_2$-	**4q**	93	85
18	2′-furanyl-	**4r**	99	92
19	2′-thiophenyl-	**4s**	99	99
20	2′-pyridinyl-	**4t**	99	98
21	cyclohexyl-	**4u**	99	97
22	*m, p*-Cl_2-C_6H_3-	**4v**	99	85
23	*p*-Cl-*m*-NO_2-C_6H_3-	**4w**	99	81
24	*m*-OCH_3-*p*-OH-C_6H_3-	**4x**	98	89
25	*m,m′*-$(OCH_3)_2$-*p*-OH-C_6H_2-	**4y**	96	92
26	$(CH_3)_2$CH-CH_2-	**4z**	72	52

[a] All reactions were carried out on a 0.1 mmol scale with 0.1 mmol of per-6-ABCD (**1**), 0.1 mmol of aldehyde, and 0.1 mmol of nitromethane (**3**) in ACN/H_2O (1:1 v/v) mixture at −20 °C for 7 h, unless otherwise noted. [b] Isolated yield. [c] Determined by chiral HPLC on chiral stationary phase (OD-H). Absolute configurations of nitroaldol adducts were assigned by comparison with literature data (refs 5−10 and 19). [d] Gram scale.

Table 3. Reusability of Per-6-ABCD (**1**) in Asymmetric Henry Reaction of Nitromethane with *p*-NO_2-C_6H_5CHO[a]

reuse	1	2	3	4	5	6	7
yield (%)	99	99	99	98	96	95	92
% ee[b]	99	99	96	94	90	92	91

[a] All of the reactions were carried out on a 0.1 mmol scale with 0.1 mmol of per-6-ABCD (**1**), 0.1 mmol of aldehyde, and 0.1 mmol of nitromethane (**3**) in ACN/H_2O (1:1 v/v) mixture at −20 °C for 7 h. [b] Determined by chiral HPLC on chiral stationary phase (OD-H).

The potential of the nitroaldol reaction for formation of multifunctional products bearing several stereocenters have been reported.[20,21] In most cases, however, expensive catalysts or silyl nitronates are required to achieve high yields and stereoselectivity.[22]

The above optimized host is also used in the diastereoselective Henry reaction involving nitroethane with different aldehydes. The observed results (Table 4) show that per-6-ABCD (**1**) promotes the Henry reaction between substituted aldehydes and nitroethane (**5**) with remarkable stereocontrol

Table 4. Per-6-ABCD (**1**)-Promoted Diastereoselective Henry Reaction of Nitroethane (**5**) with Different Aldehydes[a]

entry	aldehyde R	R′	product	yield (%)	dr (%) syn/anti[b]	ee (%) syn/anti[b]
1	C_6H_5-	CH_3	**6a**	92	97/3	95/70
2	*p*-NO_2-C_6H_4-	CH_3	**6b**	99	99/1	99/88
3	*m*-NO_2-C_6H_4-	CH_3	**6c**	98	97/3	95/76
4	*o*-NO_2-C_6H_4-	CH_3	**6d**	96	95/5	92/72
5	*p*-OCH_3-C_6H_4-	CH_3	**6e**	97	97/3	99/90
6	cyclohexyl	CH_3	**6f**	90	98/2	90/81
7	$C_6H_5CH_2$-	CH_3	**6g**	88	94/6	79/80
8	2′-furanyl-	CH_3	**6h**	98	97/3	94/89
9	2′-thiopheneyl-	CH_3	**6i**	98	98/2	88/80
10	2′-pyridinyl-	CH_3	**6j**	99	98/2	91/70

[a] All reactions were carried out on a 0.1 mmol scale with 0.1 mmol of per-6-ABCD (**1**), 0.1 mmol of aldehyde, and 0.1 mmol of nitroethane (**5**) in ACN/H_2O (1:1 v/v) mixture at −20 °C for 8 h, unless otherwise noted. [b] Determined by chiral HPLC on chiral stationary phase (OD-H). Absolute configurations of nitroaldol adducts were assigned by comparison with literature data (refs 20−22 and 19).

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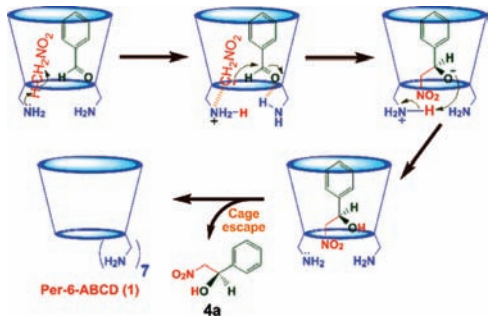
and favors formation of the syn diastereomer. This syn selectivity is in contrast to the results of Jorgensen's bis(oxazoline)-Cu(OTf)$_2$-catalyzed anti-selective Henry reaction with silyl nitronate.[23] Diastereoselectivity is also significant when the substituent is present in the para position of aldehyde. For example, the reaction of *p*-nitrobenzaldehyde (**2b**) with nitroethane (**5**) gave the product in 99% yield with 99:1 syn/anti selectivity. The enantiomeric excess of the syn adduct is 99% (Table 4, entry 2).[20,21]

The observed reactivity and enantioselectivity are rationalized by proposing a suitable mechanism. Addition of **3** to **2** to form the nitroaldol takes place inside the cavity of per-6-ABCD (**1**). The aldehydic carbonyl group is inside the cavity, and the phenyl part stays near the wider rim of **1** (Scheme 1). This type of inclusion (mode A, see the Supporting Information, Figure S4) with a lower complexation energy ($\Delta E = -30.70$ kcal M^{-1}) is preferred more than the other mode (mode B, see the Supporting Information, Figure S4), in which the aldehyde group penetrates inside the cavity and the phenyl group of the aldehydes stays outside ($\Delta E = -24.76$ kcal M^{-1}). Mode A is stabilized by hydrogen bonding between the carbonyl group of aldehyde (**2**) and amino groups of per-6-ABCD (**1**). During the addition of **3**, a ternary complex of **2** and **3** with **1** is formed (2546 M^{-1}), which is more stable than a binary complex (1852 M^{-1}) of **1** and **2**, which is also evident from molecular modeling studies. Formation of the binary and then ternary complexes are also evident from ESI-MS. The molecular ion peaks (*m*/*z* found 1296.0898, calcd 1296.0861; *m*/*z* found 1234.0710, calcd 1234.0697; see the Supporting Information, Figures S7 and S6, respectively) correspond to ternary complex of **2** and **3** with **1** and the binary complex of **3** and **1**, respectively.

Scheme 1. Proposed Mechanism for Asymmetric Henry Reaction Promoted by Per-6-ABCD (**1**)



In the proposed mechanism (Scheme 1), primary amino groups present in the narrow rim of **1** acting as an internal base (pK_a 6.5−8.9)[24] activate nitromethane (**3**) by abstracting a proton, resulting in nucleophilic attack on the included aldehyde. This occurs from the amino-functionalized narrow rim side of **1** leading to the formation of the major (*R*)-isomer, which is confirmed from the specific rotation[19] of the adduct. If the attack takes place from the wider rim of CD, it may lead to formation of the (*S*)-enantiomer, which is obtained in small excess in the β-CD-triethylamine system (Table 1, entry 2) and not observed with **1**. The complexation energies of two enantiomers of Henry adduct **4a** with per-6-ABCD are also calculated and confirm that the (*R*)-enantiomer forms a more stable complex ($\Delta E = -39.11$ kcal M^{-1}, mode C, see the Supporting Information, Figure S5) than the corresponding (*S*)-enantiomer ($\Delta E = -32.31$ kcal M^{-1}, mode D, see the Supporting Information, Figure S5).

Active participation and catalysis by the amino groups of **1** are also supported by the fact that per-6-amino-β-cyclodextrin hydrochloride fails to catalyze the addition of **3** to **2**. A control experiment carried out with per-6-ABCD/adamantanol complex as the catalyst (binding constant 2248 M^{-1}) gave a good yield of **4** without any ee, which confirms active participation of the chiral cavity of **1** in inducing enantiometric excess. We believe that the cooperative binding and tighter fit of guest inside the CD cavity ensure their proximity to the chiral centers in CD, which may have contributed to the high enantio- and diastereoselectivities.

In conclusion, per-6-ABCD (**1**) has been successfully employed in a dual role, acting both as a base to promote the reaction and as a chiral inductor by enhancing the enantiomeric excess in the asymmetric Henry reaction in ACN/H$_2$O medium. Henry adducts under mild conditions are formed in good yields and high enantioselectivities in a syn-selective manner. Both diastereomers are obtained with excellent enantiomeric excess. This procedure thus avoids environmentally hazardous organic solvents and has several other advantages; i.e., the reaction proceeds under simpler experimental conditions at −20 °C without metal salts or other harmful external acids or bases and the host can be easily recovered by simple filtration and reused several times without loss of activity.

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Supporting Information Available: General methods, experimental procedures, characterization data for all compounds, and copies of ^{1}H and ^{13}C NMR, HPLC trace, and ESI-MS. This material is available free of charge via the Internet at http://pubs.acs.org.

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