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A new catalytic enantioselective reducing reagent system from (−)-α,α-diphenylpyrrolidinemethanol and 9-borabicyclo[3.3.1]nonane, especially effective for hindered and substituted aralkylketones☆

Josyula V. B. Kanth and Herbert C. Brown*

Department of Chemistry, H. C. Brown Center for Borane Research, Purdue University, 1393 Brown Building, West Lafayette, IN 47907, USA

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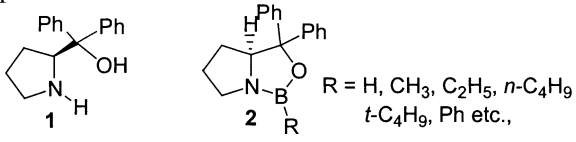
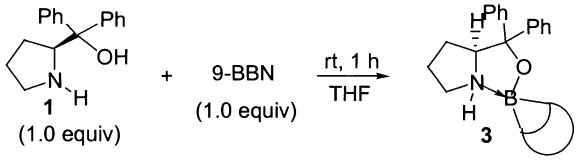
Abstract—New catalytic enantioselective reduction systems were prepared from aminoalcohols and dialkylboranes, for the enantioselective reductions of prochiral aromatic ketones. Among these, the system prepared from (−)-α,α-diphenylpyrrolidinemethanol with 9-borabicyclo[3.3.1]nonane proved especially promising for such reductions. This complex catalyzes the reduction of prochiral aralkyl ketones to the corresponding alcohols with BH_3–THF, with enantioselectivities 82–99.2%. Also, this catalyst is particularly effective for the more hindered and substituted aralkyl ketones. Various modifications in this new catalytic reduction system, such as changing reaction conditions, reducing agent and dialkylborane, were also examined.

Asymmetric reduction of prochiral ketones to obtain the corresponding optically active alcohols constitutes a very important step in the synthesis of several medicinally important compounds. The discovery of oxazaborolidines as catalytic reagents for enantioselective reduction of prochiral ketones by borane in tetrahydrofuran has been an important milestone in organic synthesis. The 'enzyme like' nature of these reagents has attracted the attention of chemists all over the world and several new reagents derived from various amino alcohols have been reported.[1] The aminoalcohol (−)-α,α-diphenylpyrrolidinemethanol (**1**), derived from L-proline has been widely accepted as superior.[2,3] However, the high synthetic utility of these oxazaborolidines in asymmetric synthesis necessitates the development of a reagent system that would serve as a general enantioselective reducing system for various classes of prochiral ketones.[3]



In continuation of our efforts in asymmetric organic synthesis, we became interested in developing a more convenient reagent system for such catalytic asymmetric reductions. The 9-borabicyclo[3.3.1]nonane (9-BBN) is a very useful bulky dialkylborane reagent. Its usage in conjunction with some chiral auxiliaries produced excellent asymmetric reduction agents, such as Alpine Borane®.[4] Though oxazaborolidines, prepared from aminoalcohols and alkylboronic acids, have proven to be excellent for asymmetric reductions, care must be taken to remove water completely from such condensations to avoid undesired effects.[5] It occurred to us that the catalyst prepared from aminoalcohol[2] (**1**) and 9-BBN would eliminate hydrogen, not water, and thereby avoid these problems.



(1)

Reaction of (−)-α,α-diphenylpyrrolidinemethanol (1 equiv.) with 9-BBN (0.5 equiv., dimer), rapidly evolves 1 equiv. of hydrogen. The ^{11}B NMR examination of the reaction mixture showed the disappearance of the peak due to 9-BBN (at δ +27 ppm) and the appearance of a new peak at δ +8.3 ppm (singlet). Evaporation of the solvent gave a white solid, mp 120–125°C, with the spectral data (^1H, ^{13}C NMR and mass) in accordance with the above structure **3**. This compound is stable in the presence of BH_3–THF with

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Keywords: chiral aminoalcohol; dialkylborane; enantioselective reductions; aromatic ketones; borane–Lewis base complexes.

* Corresponding author. Tel.: +1-765-494-5316; fax: +1-765-494-0239; e-mail: hcbrown@purdue.edu

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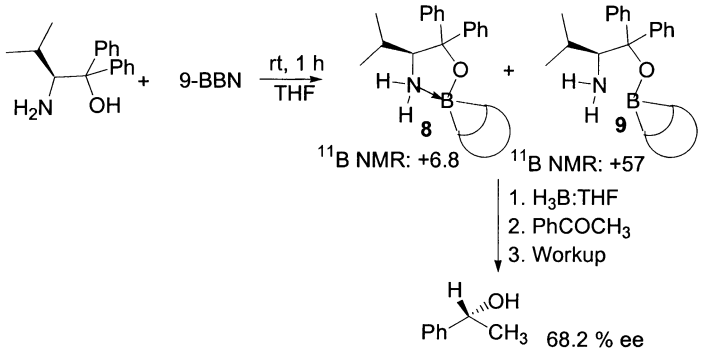
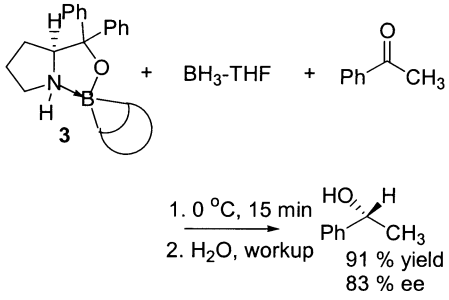


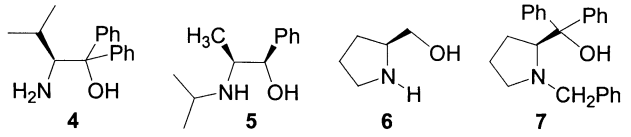
Scheme 1.

no N→B bond dissociation noted in ^{11}B NMR examination.[6] Upon the addition of acetophenone to the complex (**3**) in the presence of BH_3–THF, the ketone was reduced to the corresponding alcohol within 5 min and the enantiomeric purity of the (*R*)-alcohol obtained was 83% ee (Eq. (2)).



(2)

In order to achieve improved enantioselectivities, various modifications were made on the reagent system. Initially, several other amino alcohols (**4**–**7**) were tested as chiral auxiliaries.



With all the above amino alcohols, active asymmetric reduction catalysts were prepared by mixing the amino alcohol and 9-BBN in THF and the formation of the desired borinate complex, confirmed by measuring the hydrogen gas evolved and examining the ^{11}B NMR spectrum of the reaction mixtures. The reaction of *S*-(−)-diphenylvalinol (**4**) with 9-BBN readily evolved 1 equiv. of hydrogen. The ^{11}B NMR examination showed the presence of a mixture of both the N–B coordinated cyclic oxazaborolidine type 'ate' complex **8** (+6.8 ppm) and the dialkyloxyborane **9** (+56 ppm), indicating incomplete formation of the desired catalyst (Scheme 1). This mixture when treated with H_3B–THF and acetophenone, gave the corresponding alcohol in only 68% ee.

Table 1. Enantioselective reduction of acetophenone with H_3B/THF in the presence of catalyst prepared from various aminoalcohols and 9-BBN

S. No	Amino-alcohol	Reaction conditions	Ee (%)[a]
1	**1**	Rt/0.05 h	83.2
2	**4**	Rt/0.05 h	68.2
3	**5**	Rt/48 h	59.0
4	**6**	Rt/48 h[b]	83.0
5	**7**	Rt/0.5 h	52.4

To THF solution of amino alcohol (1 equiv.), 9-BBN (0.5 equiv., dimer) was added and H_3B–THF (0.6 equiv.) was added after the hydrogen evolution is complete (2–3 h) followed by acetophenone (1 equiv.).

[a] Enantiomeric excess was established using chiral HPLC analysis of the alcohol product on Chiralcel-OD column.

[b] Reduction is only 90% complete after 48 h.

The reaction of 9-BBN with *N*-isopropyl-(1*R*,2*S*)-norephedrin (**5**) gave the N–B coordinated ate complex essentially quantitatively (^{11}B NMR: +12.5). However, with the addition of H_3B–THF, the N–B coordination completely disappeared, as revealed by ^{11}B NMR examination, which showed signals corresponding to $\geq$N–BH_3 (q, −20.4 ppm), dialkyloxyborane (+56 ppm) and the signal at +12.5 completely vanished. The reduction of acetophenone with the resulting reagent system is very slow (48 h) and the enantioselectivity of the alcohol obtained is only 64.3%. Similar reactions with *S*(−)-*N*-benzyl-α,α-diphenylpyrrolidinemethanol (**7**) also gave 2-phenylethanol of 52.4% ee. The enantioselectivity obtained in the reduction of acetophenone with (*S*)-prolinol (**6**), 9-BBN and H_3B–THF system is comparable to that obtained for (−)-α,α-diphenylpyrrolidinemethanol, 9-BBN and H_3B–THF, 83% ee. However, with the (*S*)-prolinol system, the reduction is very slow and it is only 90% complete even after 48 h at room temperature. The results obtained with various amino alcohols, are summarized in Table 1.

From these initial results, it is clearly evident that the reagent system prepared from (−)-α,α-diphenylpyrrolidinemethanol and 9-BBN differs from the other derivatives in existing as the oxazaborolidine complex (**3**). Moreover, it is stable to H_3B–THF. Consequently, we selected this system for further study and possible optimization.

Initially, a number of experiments were carried out to see whether a change in reaction temperature would enhance the enantioselectivity. Unfortunately, no improvement in enantioselectivity was noted with change in temperature. Only the reduction time changed with the temperature change, with more time required at lower temperatures.

Also, in order to examine the catalytic efficiency of the present reagent system, the reduction of acetophenone (1 equiv.) was carried out in the presence of varying amounts of the catalyst **3** with BH_3–THF. In all these

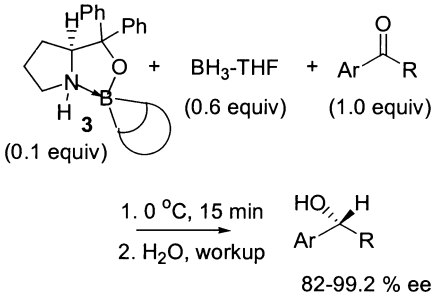
Table 2. Effect of temperature and amount of catalyst on the reduction of acetophenone using H_3B/THF in the presence of catalyst (*S*)-**3**

S. No	Amount of catalyst (**3**) equiv.	Reaction temperature (°C)	Reaction time (h)	Ee (%)[a]
1	1.0	−78	2.0	83.2
2	1.0	−15	1.5	82.8
3	1.0	0	0.25	83.1
4	1.0	25	0.05	83.5
5	0.5	0	0.25	83.2
6	0.25	0	0.25	82.5
7	0.1	0	0.25	82.7
8	0.05	0	0.25	79.2

To THF solution of **3** (0.1 equiv.), H_3B–THF (0.6 equiv.) was added followed by acetophenone (1.0 equiv.).
[a] Enantiomeric excess was established using chiral HPLC analysis of the alcohol product on Chiralcel-OD column.

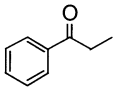
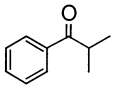
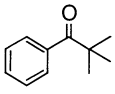
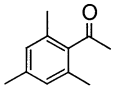
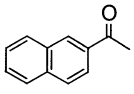
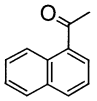
cases, the reductions are instantaneous with up to 10 mol% of the catalyst, the enantioselectivity achieved was in the neighborhood of 82%. However, lowering the amount of catalyst further affected the enantioselectivity only marginally. Table 2 summarizes the results.

Consequently, in all of these experiments, the enantioselectivity achieved for the acetophenone reduction is at best moderate. Unexpectedly we discovered that the reduction of certain modified aralkyl ketones gave considerably improved enantioselectivities when compared to acetophenone under optimized conditions. For example, the relatively hindered isobutyrophenone (entry 3, Table 3) gave 89.3% ee and 1′-acetonaphthone (entry 7, Table 3) gave 99.2% ee.



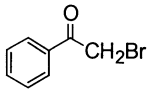
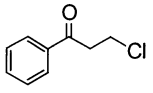
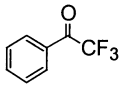
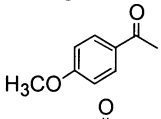
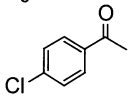
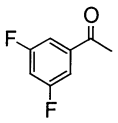
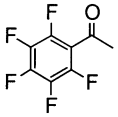
(3)

Table 3. Effect of steric factor on asymmetric reductions using the catalyst (*S*)-**3**

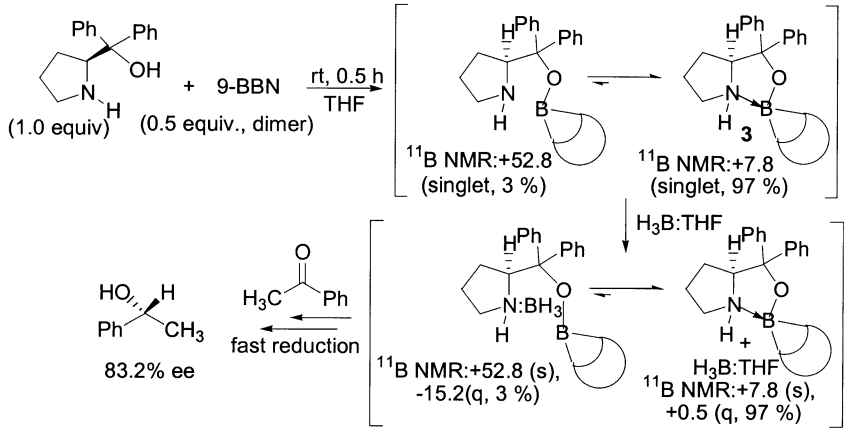
S. No	Aralkyl ketone	Ee (%)[a] (config)[b]
1		83.2 (*R*)
2		82.1 (*R*)
3		89.3 (*R*)
4		91.5 (*S*)
5		87.5 (*R*)
6		94.5 (*R*)
7		99.2 (*R*)

To THF solution of **3** (0.1 equiv.), H_3B–THF (0.6 equiv.) was added followed by aralkyl ketone (1.0 equiv.) at 0°C.
[a] Enantiomeric excess was established using chiral HPLC analysis of the alcohol product on Chiralcel-OD column.
[b] Configuration was established by comparing sign of rotation with literature reports.

Table 4. Effect of electronic and steric factors on asymmetric reductions using the catalyst (*S*)-**3**

S. No	Aralkyl ketone	Ee (%)[a] (config)[b]
1		95.5 (*S*)
2		93.2 (*R*)
3		93.1 (*S*)
4		94.7 (*R*)
5		91.0 (*R*)
6		91.5 (*R*)
7		91.2 (*R*)
8		73.2 (*R*)

To THF solution of **3** (0.1 equiv.), H_3B–THF (0.6 equiv.) was added followed by aralkyl ketone (1.0 equiv.) at 0°C.
[a] Enantiomeric excess was established using chiral HPLC analysis of the alcohol product on Chiralcel-OD column.
[b] Configuration was established by comparing sign of rotation with literature reports.



Scheme 2.

Accordingly, we undertook a systematic study of the effect of the steric factor in these enantioselective reductions with increasing bulk of both the alkyl and the aryl groups (Eq. (3)). The results are presented in Table 3. Also, changing the electronic factors on the aralkyl ketone also has considerable effect on the enantioselectivity. Halogen substitution on the alkyl side chain (entries 1–3, Table 4) or on the aromatic ring (entries 5–7, Table 4) achieves considerable improvement in enantioselectivity. Only 2,3,4,5,6-pentafluoroacetophenone, $F_5C_6COCH_3$, gave poorer results. These results are summarized in Table 4.

1. Asymmetric reduction of acetophenone using various reducing reagents in the presence of catalyst 3

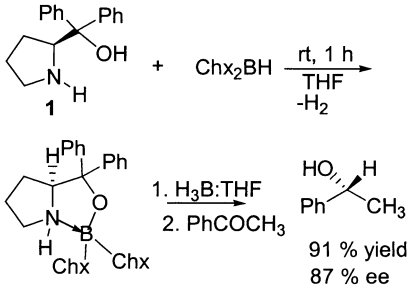
As mentioned earlier, the reduction of acetophenone using H_3B–THF in the presence of the catalyst prepared from α,α-diphenylpyrrolidinemethanol and 9-BBN, give only 83% ee under varying conditions. It was thought that a better understanding of the mechanism for this reaction might provide clues for the improvement of this reagent system. Accordingly, we have carried out several ^{11}B NMR studies during the course of the reaction at various stages. From these studies, the following may be a plausible path for the reaction (Scheme 2).

The formation of an intermediate wherein borane is complexed with the nitrogen atom (3%) of the diphenylprolinol may provide a handle for the interaction of the carbonyl group with the boron atom of the 9-BBN structure. The hydride may be delivered internally from the amine–borane or externally from H_3B–THF present in the system. In the case of other aminoalcohols, such as diphenylvalinol (**4**) and prolinol (**6**), the interaction between the the nitrogen and boron atom of the of 9-BBN moiety is disturbed and the major product obtained after the addition of H_3B–THF to the catalyst is the $>N–BH_3$ adduct, which reduced acetophenone very slowly. The faster reaction for the catalyst derived from diphenylprolinol indicates external hydride delivery from H_3B–THF. The low enantioselectivity in the case of acetophenone is probably due to the competitive uncatalysed reduction of acetophenone using H_3B–THF. It was of interest to see whether other less reactive reducing agents and other borane reagents having single hydride would give improved selectivities. Thus, in a bid to find a better reducing agent, various other borane reagents were tried in the reduction of acetophenone in the presence of catalyst **3**.

The reduction of acetophenone using *N*,*N*-diethylaniline-borane is very slow at 0°C. When H_3B–THF was replaced with *N*,*N*-diethylaniline–borane in catalytic enantioselective reductions using the catalyst **3**, the reduction is complete in 6 h and the corresponding alcohol was obtained in slightly improved ee (89%). However, with other slow reducing amine–boranes, such as triethylamine–borane and *N*,*N*-diisopropylethylamine–borane, the reduction is very slow at 0°C. When the reductions were carried at higher temperatures, the enantioselectivity realized was poor. Fortunately, dimethyl sulfide–BH_3 gave the best results, providing the 2-phenylethanol of 95.3% ee. The results are summarized in Table 5.

We have also tried to improve the catalyst by changing the dialkylborane. Thus, catalysts were prepared from diphenylprolinol and several other dialkylborane reagents in addition to 9-BBN. Dicyclohexylborane and both isomers of diisopinocamphylborane were used in these studies.

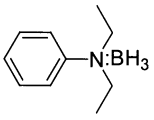
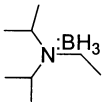
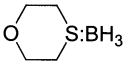
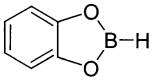
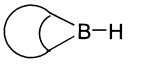
Both (+) and (−) isomers of diisopinocamphylborane readily reacted with the aminoalcohol **1**. However, the catalyst thus obtained is unstable and α-pinene is eliminated. Addition of H_3B–THF followed by acetophenone provided the alcohol in only 65% ee. On the other hand, reaction with dicyclohexylborane gave a stable catalyst and reduction of acetophenone with H_3B–THF in the presence of this catalyst gave 2-phenylethanol in 87% ee (Eq. (4)).



(4)

From the current study it is quite evident that the reagent

Table 5. Reduction of acetophenone using various reducing reagents in the presence of catalyst **3**

S. No.	Reducing agent	Reaction conditions	Ee (%)
1	BH_3/THF	0°C/10 min	83.2
2		0°C/6 h	89.2
3	$(CH_3)_2S-BH_2Cl$	0°C/4 h	62.5
4		50°C/2 h[a]	62
5	Et_3N-BH_3	50°C/2 h[b]	52
6	BH_3–DMS	0°C/5 h	95.3
7		0°C/5 h	75.2
8		0°C/2 h	72
9		0°C/2 h	86

To THF solution of **3** (0.1 equiv.), H_3B/LB (0.6 equiv.) was added followed by acetophenone (1.0 equiv.) at 0°C.
[a] At 0°C, the reduction is very slow and incomplete even after 48 h.
[b] The reduction does not occur at 0°C or even at room temperature.

system prepared form (−)-α,α-diphenylpyrrolidinemethanol (**1**), 9-BBN, H_3B–THF gives good results with both hindered aralkyl ketones and aralkyl ketones having electron-withdrawing groups either on the aromatic ring or on the alkyl side chain. In the case of acetophenone reduction, the use of DMS–BH_3 in place of H_3B–THF provides good enantioselectivities. Also, the easy preparation of this structurally well-defined catalyst should facilitate use of this reagent by synthetic chemists for the enantioselective reduction of such ketones.

2. Experimental

2.1. General

All glassware was oven-dried for several hours at 120°C, assembled while hot and cooled in a stream of dry nitrogen gas. Syringes were assembled and fitted with needles while hot and cooled under nitrogen gas. Techniques for handling air-sensitive compounds described elsewhere were followed.[7] All manipulations and reactions with air-sensitive compounds were carried out under nitrogen atmosphere. The amino alcohols, diphenylvalinol,[1c] prolinol,[8] (−)-*N*-benzyl-α,α-diphenylpyrrolidinemethanol, (−)-α,α-diphenylpyrrolidinemethanol[2] were prepared following the literature procedures. 9-BBN is a commercial product and dicyclohexylborane,[7,9] diisopinocamphylborane,[9] were prepared according to the reported procedures. All the borane–Lewis base complexes and aralkyl ketones utilized are commercial products. ^{1}H, ^{13}C and ^{11}B NMR spectra were recorded on a 300 MHz multinuclear instrument. The ^{11}B chemical shifts are in δ relative to boron trifluoride-diethyl etherate. HPLC analyses were carried out using Chiralcel-OD® column. Optical rotations were measured on a polarimeter.

2.1.1. Preparation of the catalyst (3). An oven-dried RB flask provided with a septum inlet and stirring bar, was cooled under dry nitrogen gas. Into the flask was placed, aminoalcohol **1** (10 mmol) and 9-BBN (5 mmol, dimer) in dry THF (10 mL). The outlet of the flask was connected to a gasimeter. The contents were stirred at room temperature for 1 h, by which time the evolution of one equivalent of hydrogen is complete and ^{11}B NMR examination (+7.8 ppm, singlet) showed the clean formation of the catalyst **3**, white solid, mp 120–125°C. The IR spectrum didn't show the characteristic hydroxy stretch around 3350 cm^{-1}, for starting aminoalcohol. ^{13}C NMR (δ): 24.2, 24.7, 24.8, 28.4, 31.4, 32.1, 32.9, 33.3, 33.7, 47.4, 69.7, 82.5, 126.0, 126.1, 126.5, 127.7, 127.8, 147.3, 150.0. Mass (70 eV, EI CI): 374 (M+1, 64.82%), 373 (M+, 26.98%), 372 (31.81%), 254 (base peak, 100%).

The catalyst **3**, thus obtained is indefinitely stable under inert atmosphere. It is moderately air and moisture sensitive. For the catalytic asymmetric reductions, the catalyst does not require any further purification. Pre-formed catalyst (**3**) as well as in situ generated catalyst (**3**) gave comparable results in the asymmetric reduction of acetophenone. Accordingly, in majority of the cases it was prepared in situ and used immediately for the reductions. However, with the other amino alcohols (**4**–**7**), reaction with 9-BBN gave mixture of products (as described in Scheme 2) and the mixture as such was used as the catalyst.

2.2. General reduction procedure

An oven-dried RB flask provided with a septum inlet and stirring bar, was cooled to 0°C under a continuous flow of dry nitrogen gas. The flask was charged with the aminoalcohol **1** (0.1 equiv.) and 9-BBN (0.05 equiv.) in anhydrous THF (10 mL). The contents were stirred at room temperature for 1 h. The reaction flask was cooled to 0°C and BH_3–THF (1 M, 0.6 equiv.) was added. The aralkyl ketone (1 equiv.) in THF (20 mL) was slowly added during 15 min at 0°C. The reduction is complete as soon as the addition of ketone is complete, as observed by ^{11}B NMR, which shows the disappearance of the peak due to borane (+0.3 ppm) and the appearance of a new peak due to dialkoxyborane (+21 ppm). The reaction was quenched with water and dil. HCl (2 M) and *n*-pentane were added to precipitate the catalyst. The clear organic layer was separated by filtration and dried over anhydrous magnesium sulfate. Evaporation of the organic layer provided essentially pure alcohol, which was further purified by passing through a silica gel pad. The enantiomeric purity of the alcohol was established by HPLC analysis on a Chiralcel-OD® column.

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