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ANOMALIES IN THE ASYMMETRIC HYDROBORATION OF OLEFINS WITH THE 1/1 ADDUCT OF (+)-α-PINENE AND $BH_3 \cdot THF$ *

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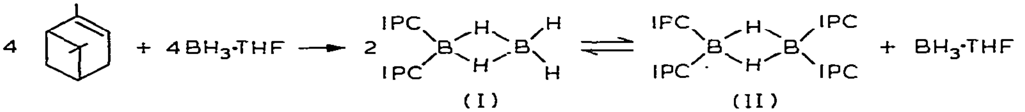
Summary

The hydroboration of *cis*-2-butene and *cis*-3-hexene with pure diisopinocampheylborane (IPC_2BH) and monoisopinocampheylborane ($IPCBH_2$), both prepared from (+)-α-pinene, were studied. In contrast to IPC_2BH, which yielded *R*-(—)-2-butanol and *R*-(—)-3-hexanol in 98.4 and 94.5% optical purities, $IPCBH_2$ yielded *S*-(+)-2-butanol and *S*-(+)-3-hexanol in 23.6 and 19.7% optical purities respectively. PMR examination of the methanolyzed products were utilized to establish the species present in the freshly prepared and aged 1/1 adduct from (+)-α-pinene and $BH_3 \cdot THF$. The results confirm the interpretation previously advanced for the major differences realized in asymmetric hydroboration with the fresh and aged 1/1 adducts.

Introduction

The hydroboration of α-pinene with borane in THF at 0°C in a 1/1 ratio was first reported by Brown and Klender to yield mostly unsymmetrical dimer 1,1-diisopinocampheyldiborane (I) in equilibrium with a small amount of symmetrical dimer, tetraisopinocampheyldiborane (II), and $BH_3 \cdot THF$ (eq. 1) [1].



(1)

A few years ago Katsuhara et al. [2] claimed to have prepared (+)-monoisopinocampheylborane in diglyme from a 1/1 mixture of (—)-α-pinene and borane (made from $NaBH_4$ and $BF_3 \cdot OEt_2$) and utilized the product for the

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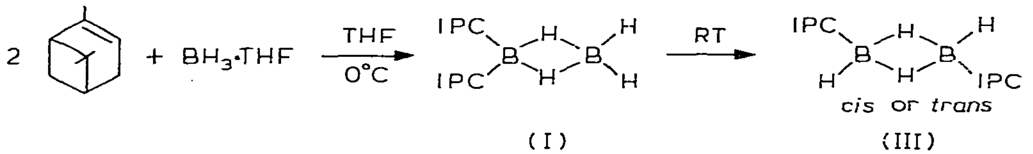
* Dedicated to Professor Herbert C. Brown in recognition of his contributions to chemistry.

asymmetric syntheses of (—)-menthol and (—)-isomenthol by hydroboration-oxidation of (+)-3-*p*-menthene.

Mislow and his coworkers, while studying the stereochemistry of 2-benznorbornenone, synthesized by the hydroboration-oxidation of benznorbornadiene followed by oxidation of the resulting *exo*-2-benznorbornenol reported an anomalous behavior of 1/1 adduct of (+)-α-pinene and $BH_3 \cdot THF$ in the asymmetric hydroboration of benznorbornadiene and *cis*-3-hexene [3,4]. Thus hydroboration of benznorbornadiene with a freshly prepared THF solution of the 1/1 adduct of (+)-α-pinene and $BH_3 \cdot THF$, followed by oxidation and acetylation, afforded (+)-*exo*-2-benznorbornenyl acetate, containing a 7.4% excess of 1*R*, 2*S* enantiomer. However, the opposite enantiomer, 1*S*, 2*R*, was produced in approximately the same excess when the hydroborating agent had been aged for 21 h at 25°C. Similarly, with fresh 1/1 adduct, *cis*-3-hexene gave *R*-(—)-3-hexanol in 20.6% optical purity, whereas the aged adduct gave *S*-(+)-3-hexanol in 10.7% optical purity.

The authors explained the result on the basis of a rearrangement or disproportionation of the initially formed I, as postulated by Brown et al., to a *cis*- or *trans*-1,2-diisopinocampheyldiborane (III) during aging at room temperature (eq. 2). They postulated that these two asymmetric hydroborating species can give rise to enantiomeric products.



(2)

Recently, Moore and his associates, while investigating the partial resolution of racemic allenes by the partial hydroboration with II, examined the utility of the fresh and aged 1/1 adduct of (—)-α-pinene and borane (made from $NaBH_4$ and $BF_3 \cdot OEt_2$ in diglyme) to such resolutions [5]. Thus, partial hydroboration of 1,3-diethylallene with the aged 1/1 adduct led to the recovery of *R*-allene, with a rotation approximately twice that obtained with the fresh 1/1 reagent. The explanation was that the initial reagent must have been a complex mixture of tetra-, tri-, di- and mono-isopinocampheyldiboranes, with reductions resulting from the more reactive, less substituted diboranes. Aging would shift the composition to III which would be somewhat more selective than the unsymmetrical derivatives.

It appeared that a precise understanding of these results would require a better understanding of the nature and behavior of the asymmetric hydroborating agents IPC_2BH and $IPCBH_2$ *, believed to be active intermediates involved in the asymmetric hydroboration of *cis*-olefins, such as *cis*-2-butene and *cis*-3-hexene.

Recently, we developed an improved synthesis of IPC_2BH [6,7] of exceptionally high purity, an excellent hydroborating agent for representative *cis*-olefins [6,8,9]. This reagent achieves the asymmetric hydroboration of *cis*-2-

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* Diisopinocampheylborane, IPC_2BH, and monoisopinocampheylborane, $IPCBH_2$, exists as dimers II and III in ether solvents, but we write the monomeric form for the sake of convenience.

butene to yield after oxidation *R*-(—)-2-butanol in an optical purity as high as 98.4% [6]. However, hydroboration of hindered (trisubstituted) olefins, such as 1-methyl cyclopentene and 1-methylcyclohexene, with IPC_2BH is slow, proceeding with partial displacement of α-pinene from the reagent and the alcohols exhibited lower optical purities [10]. Fortunately, this problem can be circumvented by the recent discovery of $IPCBH_2$ [11—13], a less hindered optically active reagent which is successfully utilized for the asymmetric hydroboration of trisubstituted olefins, such as 2-methyl-2-butene, 1-methylcyclopentene, and 1-methylcyclohexene, to yield alcohols of high optical purities [12]. Subsequently, we decided to utilize this reagent for the asymmetric hydroboration of *cis*-2-butene and *cis*-3-hexene and then couple these results with those obtained with IPC_2BH and the above olefins to account for the anomalous behavior of the 1/1 adduct of α-pinene and $BH_3 \cdot THF$, fresh and aged. Finally, we decided to undertake to establish by some means the composition of the fresh and aged 1/1 adduct. The result of this study is presented in this paper.

Results and discussion

We first decided to utilize fresh and aged 1/1 adduct of (+)-α-pinene and $BH_3 \cdot THF$ for the hydroboration of *cis*-2-butene and *cis*-3-hexene to check the reproducibility of the reported results. A fresh 1/1 adduct, made by allowing (+)-α-pinene to react with $BH_3 \cdot THF$ at 0°C for 0.5 h, was utilized to hydroborate *cis*-2-butene and *cis*-3-hexene at 0° C. Following oxidation, *R*-(—)-2-butanol and *R*-(—)-3-hexanol were realized in 25.0 and 31.6% optical purities, respectively.

The aged 1/1 adduct, obtained by allowing the fresh 1/1 adduct to come to room temperature and remain there for 24 h, under identical reaction conditions as above, yielded *R*-(—)-2-butanol and *R*-(—)-3-hexanol in 14.3 and 19.7% optical purities respectively. This results, however, did not reveal complete sign reversal in the configuration of the alcohol products of hydroboration with the fresh and aged 1/1 adduct, as previously reported, but it did indicate a significant decrease in the rotations of the alcohols accompanying the aging. These results are summarized in Table 1.

Our next effort was then directed to the hydroboration of *cis*-2-butene and *cis*-3-hexene with authentic IPC_2BH and $IPCBH_2$. (—)-IPC_2BH was prepared in THF at 0°C following the published procedure [6]. The hydroboration of *cis*-2-butene and *cis*-3-hexene revealed after oxidation *R*-(—)-2-butanol, $[\alpha]_D^{22.5}$ —13.29°, an optical purity of 98.4% [6], and *R*-(—)-3-hexanol, $[\alpha]_D^{27.5}$ —6.71°, an optical purity of 94.6%, respectively.

$IPCBH_2 \cdot NEt_3$ was prepared following the modified procedure involving neat thexylborane/triethylamine and α-pinene [13]. $IPCBH_2$ in THF was obtained by treatment of $IPCBH_2 \cdot NEt_3$ with $BH_3 \cdot THF$ at 0°C [12]. Hydroboration of *cis*-2-butene with $IPCBH_2$ in THF at —40°C for 1 h revealed after oxidation *S*-(+)-2-butanol, $[\alpha]_D^{26}$ + 3.33°, an optical purity of 23.6%. Alternatively, $IPCBH_2$ in pentane was obtained by treatment of $IPCBH_2 \cdot NEt_3$ with $BF_3 \cdot OEt_2$ at 25°C [13]. Hydroboration of *cis*-3-hexene yielded after oxidation *S*-(+)-3-hexanol, $[\alpha]_D^{27}$ + 1.40°, an optical purity of 19.7%. The results thus revealed that whereas the hydroboration-oxidation of *cis*-2-butene and *cis*-3-hexene with (—)-IPC_2BH from (+)-α-pinene gives the corresponding *R*-(—)-2-butanol and *R*-(—)-3-hexanol

TABLE 1

ASYMMETRIC HYDROBORATION OF (a) *cis*-2-BUTENE AND (b) *cis*-3-HEXENE WITH CHIRAL BORANE REAGENTS[a]

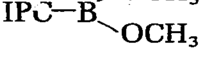
Hydroborating agent	Olefin	ROH		
		$[\alpha]_D$ (°)	Optical purity (%)	Configuration
IPC_2BH	(a) *cis*-2-Butene	−13.29	98.4	*R*
	(b) *cis*-3-Hexene	−6.71	94.6	*R*
$IPCBH_2$	(a) *cis*-2-Butene	+3.33	23.6	*S*
	(b) *cis*-3-Hexene	+1.40	19.7	*S*
1/1 Adduct of (+)-α-Pinene and $BH_3 \cdot THF$ (freshly prepared)	(a) *cis*-2-Butene	−3.39	25.0	*R*
	(b) *cis*-3-Hexene	−2.24	31.6	*R*
1/1 Adduct of (+)-α-Pinene and $BH_3 \cdot THF$ (aged)	(a) *cis*-2-Butene	−1.93	14.3	*R*
	(b) *cis*-3-Hexene	−1.40	19.7	*R*

[a] All the chiral reagents are prepared from (+)-α-pinene, $[\alpha]_D^{26.5}$ +48.7°, an optical purity of 95.2%.

in high optical purities, the similar sequence of reactions with $IPCBH_2$ from (+)-α-pinene yields the enantiomeric *S*-(+)-2-butanol and *S*-(+)-3-hexanol in lower optical purities (Table 1).

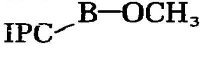
Based on the results obtained so far, it seemed reasonable to say that the fresh 1/1 adduct consists chiefly of I with a small amount of II. Therefore, much of the hydroboration involves BH_3 with only a portion proceeding through the asymmetric species, IPC_2BH. The result of aging will be a decrease in the BH_3 with accumulation of III (*cis* or *trans*), presumably by the rearrangement of I * in the aged 1/1 adduct. This will induce hydroboration with low optical activity, with an excess of the (+)-isomer, decreasing the overall negative rotation of the alcohols produced.

More definite proof of this interpretation would be provided if it were possible to analyze the relative amounts of I and III in the fresh and aged 1/1 adduct. PMR analysis of the methanolyzed products proved to be an effective means of such analysis. We made use of the fact that the methoxy protons of dimethyl monoisopinocampheylboronate (IV) and monomethyl diisopinocampheylborinate (V) are distinguishable in the PMR spectrum, the former appearing at δ 3.50 ppm, and the latter at δ 3.70 ppm.



$IPC{-}B(OCH_3)_2$

(IV)



$(IPC)_2B{-}OCH_3$

(V)

Hence, the analysis of IV and V in the fresh and aged 1/1 adduct after methanolysis would be possible following the removal of the more volatile other products. Benzene was used as an internal standard. A fresh 1/1 adduct of 20 mmol each

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* A time dependent rearrangement of a 1,1-dialkyldiborane to a 1,2-dialkyldiborane has been observed by Milkhailov [14].

of (+)-α-pinene and $BH_3 \cdot THF$ was made at 0°C for 0.5 h (at this time the whole of α-pinene reacted with borane) and then methanolyzed with 100% excess of methanol. Removal of volatiles and analysis of the reaction mixture revealed the presence of 3.0 mmol of IV (presumably coming from 1.5 mmol of III) and 8.6 mmol of V. The amount of methyl borate would then be 8.4 mmol [20 — (8.6 + 3.0)]. The result thus indicates that the fresh 1/1 adduct contains ~8.6 mmol of I and 1.5 mmol of III. Similar analysis of the aged 1/1 adduct revealed the presence of 9.0 mmol of IV and 5.6 mmol of V, thereby corresponding to 5.6 mmol of I and 4.5 mmol of III. Thus, we clearly see an increase in the amount of III in the aged 1/1 adduct which therefore accounts for the decrease in the negative rotations of the alcohol of the hydroboration reaction. It seems worthwhile to mention at this point that the report of Katsuhara et al. [2] of the synthesis of (+)-monoisopinocampheylborane from 1/1 (—)-α-pinene and borane in diglyme (although the exact experimental condition is not given) cannot be correct based on our results. The 1/1 adduct of α-pinene and borane in THF attains equilibrium after 48 h at 25°C and the equilibrium mixture is composed of 70% of $IPCBH_2$ and 15% each of IPC_2BH and BH_3.

Conclusions

The present study has indicated that IPC_2BH and $IPCBH_2$, obtained from (+)-α-pinene, hydroborate *cis*-olefins to yield enantiomeric alcohols. It also establishes that the anomalous behavior of fresh and aged 1/1 adduct of (+)-α-pinene and $BH_3 \cdot THF$ toward *cis*-olefins is due to the variable amounts of 1,1-diisopinocampheyldiborane (I) and 1,2-diisopinocampheyldiborane (III) present in the hydroborating agent. The study also offers promise for a simple synthesis of $IPCBH_2$ by the equilibration of such a 1/1 adduct of (+)-α-pinene and borane. We are actively exploring such possibility.

Experimental

Materials

The techniques described in Chapter 9 of ref. 15 were used extensively. THF and $BF_3 \cdot OEt_2$ were purified by standard procedures [15]. Borane in THF was prepared from $NaBH_4$ and $BF_3 \cdot OEt_2$ and standardized by hydrolyzing an aliquot of the solution with glycerin/water/THF mixture and measuring the hydrogen evolved [15]. *cis*-2-Butene was a product of Phillips Petroleum Co.: pure grade 99 mol% minimum. *cis*-3-Hexene (96%) was obtained from Chemical Samples Co. (+)-α-Pinene (Dragoco Co.) was used after distillation from $LiAlH_4$, which showed an optical rotation of $[\alpha]_D^{26.5}$ +48.7°, an optical purity of 95.2% *. The optical rotations were measured in a Zeiss polarimeter.

Reactions of (a) fresh and (b) aged 1/1 adduct of (+)-α-pinene and $BH_3 \cdot THF$ with cis-2-butene and cis-3-hexene

The reaction of 1/1 adduct of (+)-α-pinene and $BH_3 \cdot THF$ with *cis*-3-hexene would be representative. (a) 6.80 g (8.0 ml, 50 mmol) of (+)-α-pinene and 19.3

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* Based on highest rotation of $[\alpha]_D$ +51.1° for (+)-α-pinene [16].

ml of 2.59 *M* $BH_3 \cdot THF$ (50 mmol) were allowed to react at 0°C for 0.5 h. 4.2 g (6.25 ml, 50 mmol) of *cis*-3-hexene was added and the reaction mixture was stirred at 0°C for 3 h. The reaction mixture was then hydrolyzed with 4.0 ml of water. After adding 20 ml of 3 *M* NaOH, 20 ml of 30% aqueous hydrogen peroxide was added dropwise to oxidize the reaction mixture. The aqueous layer was saturated with anhydrous K_2CO_3 and the organic layer was extracted with ether and then dried over anhydrous magnesium sulfate. The solvents were removed by distillation using a 30 cm Widmer column. Distillation under reduced pressure yielded 3.1 g of 3-hexanol (>95% pure by GC), b.p. 68—69°C at 30 mmHg, a yield of 62%. Further purification through preparative GC (SE-30 column) afforded pure 3-hexanol, n_D^{20} 1.4158 $[\alpha]_D^{24}$ —2.24°, an optical purity of 31.6% *.

(b) In a separate experiment 6.80 g (8.0 ml, 50 mmol) of (+)-α-pinene and 19.3 ml of 2.59 *M* $BH_3 \cdot THF$ (50 mmol) were allowed to react at 0°C for 0.5 h and then it was stirred at 25°C for 24 h. 4.2 g (6.25 ml, 50 mmol) of *cis*-3-hexene was added and the solution stirred at 0°C for 3 h. Usual workup and purification as before yielded pure 3-hexanol, n_D^{20} 1.4156 $[\alpha]_D^{25}$ —1.40°, an optical purity of 19.7%.

Preparation of (—)-IPC$_2$BH and hydroboration of (a) cis-2-butene and (b) cis-3-hexene

(—)-IPC_2BH was prepared from (+)-α-pinene and $BH_3 \cdot THF$ at 0°C following procedure reported elsewhere [6].

(a) The hydroboration of *cis*-2-butene with (—)-IPC_2BH was carried out according to reported procedure [6]. The *R*-(—)-2-butanol exhibited $[\alpha]_D^{22.5}$ —13.29°, an optical purity of 98.4% [6].

(b) To a suspension of (—)-IPC_2BH (50 mmol) in THF at 0°C (made from 115 mmol of (+)-α-pinene and 50 mmol of $BH_3 \cdot THF$) was added 4.2 g (6.25 ml, 50 mmol) of *cis*-3-hexene. The reaction mixture was stirred at 0°C for 3 h and then diluted with 3.0 ml of water. Oxidation was carried out by the addition of 20 ml of 3 *M* NaOH solution followed by 20 ml of 30% hydrogen peroxide. After stirring at 40°C for 1 h the reaction mixture was cooled and the aqueous layer was saturated with anhydrous potassium carbonate. The organic layer was extracted with 3 × 30 ml portions of ether. The combined extracts were washed twice with saturated brine solution and dried over anhydrous magnesium sulfate overnight. Ether and THF were removed by distillation using a 30 cm Widmer column. 3-Hexanol and excess (+)-α-pinene were then distilled under aspirator vacuum (28 mmHg) to yield 5.95 g of mixture of these two reagents. After making correction for 15 mmol of excess (+)-α-pinene used, the yield of 3-hexanol would be 3.9 g (76.5%). Pure 3-hexanol was then separated from (+)-α-pinene by preparative GC using a SE-30 column. The material exhibited n_D^{30} 1.4160 and $[\alpha]_D^{27.5}$ —6.71°, an optical purity of 94.67%.

Preparation of IPCBH$_2$ in THF and hydroboration of cis-2-butene at —40°C

A solution of $IPCBH_2 \cdot NEt_3$ (85 mmol) in THF was prepared according to procedure reported elsewhere [8,10]. To this solution was added at 0°C 42.5 ml of 2 *M* BH_3 in THF (85 mmol). After 4 h at 0°C, the solution was cooled to

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* Based on highest rotation of $[\alpha]_D$ —7.13° for (—)-3-hexanol [17].

—40° and then diluted with 4.96 g (80 mmol) of *cis*-2-butene. After 1 h at —40°, the solution was brought to 0°C and 15 ml of methanol was added dropwise. About 90.5 mmol of hydrogen was evolved. Oxidation was done as usual. After oxidation the reaction mixture was heated under reflux for 12 h to complete hydrolysis of $BH_3 \cdot NEt_3$. The organic layer was extracted into ether and dried. Distillation provided 3.7 g of 2-butanol (2.2 g at 90—97°C and 1.5 g at 97.8°C, both at 751 mmHg) a yield of 62.5%. The alcohol was then purified through preparative GC (XE-60 column), n_D^{30} 1.3979, $[\alpha]_D^{26}$ +3.33°, an optical purity of 24.6%.

Preparation of IPCBH₂ in pentane and hydroboration of cis-3-hexene at —40°C

To 30.6 ml of 1.80 *M* $IPCBH_2 \cdot NEt_3$ in pentane (55 mmol) there was added at 25°C 6.77 ml of $BF_3 \cdot OEt_2$ (55 mmol). The reaction mixture was stirred at 25°C over a period of 15 min in which time two layers separated. On cooling the reaction in an ice-salt bath, the lower layer of $BF_3 \cdot NEt_3$ crystallized out. The free $IPCBH_2$ in pentane was then decanted off to another flask using a double-ended needle. The crystalline $BF_3 \cdot NEt_3$ was thoroughly washed with pentane (15 ml) and pentane washings transferred to main solution. The solution was cooled to —40°C and 6.25 ml of *cis*-3-hexene (50 mmol) was then added to it. Hydroboration was allowed to proceed for 2 h at —40°C. After the usual oxidation and workup procedure as above, *S*-(+)-3-hexanol n_D^{20} 1.4168. $[\alpha]_D^{27}$ +1.40° was obtained in 19.7% optical purity.

Analysis of the methanolyzed product of (a) fresh and (b) aged 1/1 adduct of (+)-α-pinene and $BH_3 \cdot THF$

(a) 2.72 g (3.2 ml, 20 mmol) of (+)-α-pinene and 7.72 ml of 2.59 *M* $BH_3 \cdot THF$ (20 mmol) were allowed to react at 0°C for 0.5 h in which time the whole of α-pinene was consumed. The reaction mixture was then methanolyzed with 3.2 ml of methanol. After about 0.5 h at 25°C, the volatiles (THF, methanol and methylborate) were removed under aspirator vacuum (14 mmHg). The residue was then diluted with 1.0 ml of carbon tetrachloride and 0.45 of benzene (5 mmol), used as an internal standard for PMR. The PMR revealed 3.0 mmol of $IPCB(OCH_3)_2$ and 8.6 mmol of IPC_2BOCH_3. The amount of $B(OCH_3)_3$ was calculated to be 8.4 mmol [20 — (8.6 + 3.0)].

(b) Similarly in a separate experiment, 2.72 g (3.2 ml, 20 mmol) of (+)-α-pinene and 7.72 ml of 2.59 *M* $BH_3 \cdot THF$ (20 mmol) were first allowed to react at 0°C for 0.5 h and then stirred at room temperature (25°C) for 24 h. The analysis of the reaction mixture as before revealed the presence of 9.0 mmol of $IPCB(OCH_3)_2$ and 5.6 mmol of IPC_2BOCH_3 and 5.4 mmol of $B(OCH_3)_3$.

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