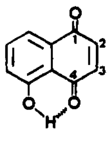
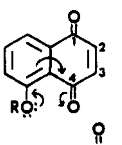
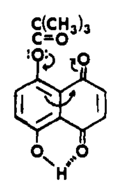


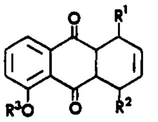
14



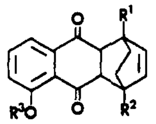
15, R=CH$_3\overset{O}{\overset{\|}{C}}$-
20, R=CH$_3$



19



16, R^1=R^3=H, R^2=OCOCH$_3$
17, R^1=OCOCH$_3$, R^2=H, R^3=COCH$_3$



18, R^1=R^3=H, R^2=OCH$_3$
21, R^1=OCH$_3$, R^2=H, R^3=CH$_3$
22, R^1=H, R^2=OCH$_3$ R^3=CH$_3$

consequence of activation of the C-4 carbonyl by intramolecular hydrogen bonding (see **14**). The C-4 carbonyl in **14** would thus[14] be the most electron-withdrawing substituent on the C-2,C-3 double bond and would determine the regiochemical outcome of the reaction.[15] To our knowledge Inhoffen, Muxfeldt, and coworkers have not offered a rationale for the regiochemical dichotomy embodied in the formation of **16** and **17**, but extension of the Birch-Powell thesis[14] suggests that the regiochemical reversal observed in the formation of **17** might result from selective electron feeding from the *peri*-acetoxy group (**15**, arrows)[16] to the C-4 carbonyl. Such resonance donation[18] into the C-4 carbonyl would render the C-1 carbonyl the most electron-withdrawing substituent on the C-2,C-3 double bond and thus the regiochemical director by default. Further extension of this hypothesis suggests that incorporation of both *peri*-acyloxy (or alkoxy)[16] and hydroxy groups into the same molecule so that their conflicting influences could operate in a complementary fashion (see **19**) would permit a high degree of orientational control in the Diels–Alder reaction of molecules such as **2** and **7**. The above results confirm this expectation and demonstrate the effectiveness of such long-range regiochemical control in the Diels–Alder reactions of naphthazarin derivatives.

Extension of this work is in progress and will be reported in due course.

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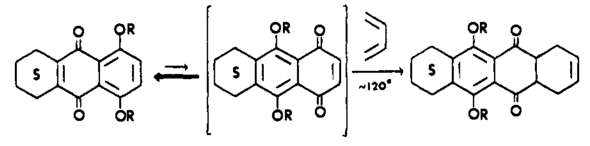
(8) That the **6** ⇄ **7** equilibrium strongly favors **6** is indicated by the position of the NMR resonance attributable to the C-ring hydrogens (δ^{CDCl_3} 7.20 (2 H, s)). The presence of **7** is undetectable by NMR (the C-ring hydrogens of **7** should[9] give a resonance at δ ~6.8).

(9) (a) St. Berger and A. Reiker in "The Chemistry of Quinonoid Compounds", S. Patai, Ed., Wiley, New York, N.Y., 1974, p 172; (b) S. Alvarado, F. Fariña, and J. L. Martin, *Tetrahedron Lett.*, 3377 (1970); (c) F. Fariña and J. C. Vega, *ibid.*, 1655 (1972).

(10) The expectation that the **6** ⇄ **7** equilibrium might exist and that **7** could be trapped selectively was suggested by the observations of Fariña and Vega[9c] that the *symmetrical* naphthazarin derivatives i and ii react in a similar fashion to give iii and iv, respectively. For additional examples of *acylwanderung*, see H. Brockmann, H. Greve, and A. Zeeck, *Tetrahedron Lett.*, *1929* (1971); and ref 9b.



i, R=H
ii, R=COCH$_3$
iii, R=H
iv, R=COCH$_3$

(11) Use of other oxidizing agents permits preservation of the epoxide ring.

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(16) Further support for this rationale is found in the observation (T. R. Kelly, unpublished results) that reaction (benzene, 80 °C) of juglone methyl ether (**20**) with 1-methoxycyclohexa-1,3-diene affords **21** and **22** in a 2.5:1 ratio. The regiochemistry of this reaction was demonstrated by conversion—tautomerization[17] (KO-t-Bu, THF; HCl), oxidation (Pb(OAc)$_4$), and pyrolysis (145°)—of the crude adduct to a mixture of 1,5- and 1,8-dimethoxyanthraquinone and comparison (NMR) with reference mixtures of authentic samples. The overall yield from **20** to the mixture of dimethoxyanthraquinones is ~80% after chromatography. This hypothesis is also supported by the fact that **14** is a significantly more reactive dienophile than **20** in competition experiments with 1-methoxycyclohexa-1,3-diene (reaction conducted in CDCl$_3$, monitored by NMR).

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(19) Recipient of NIH Research Career Development Award, 1975–1980.

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Monoisopinocampheylborane—a New Chiral Hydroborating Agent for Relatively Hindered (Trisubstituted) Olefins

Sir:

Optically active monoisopinocampheylborane-triethylamine (IPCBH$_2$·NEt$_3$), readily available via the reaction of optically active α-pinene with thexylborane-triethylamine, undergoes a rapid reaction with borane to yield free, optically active monoisopinocampheylborane in nearly quantitative yield. This new chiral monoalkylborane was successfully utilized for the asymmetric hydroboration of 1-methylcyclopentene to give after oxidation *trans*-2-methylcyclopentanol in an optical purity of 55.4%. Other hindered (trisubstituted) olefins, such as 2-methyl-2-butene and 1-methylcyclohexene, which resist hydroboration with diisopinocampheylborane, undergo facile

Table I. Asymmetric Hydroboration of Representative Hindered (Trisubstituted) Olefins with Diisopinocampheylborane (IPC_2BH) and Monoisopinocampheylborane ($IPCBH_2$)

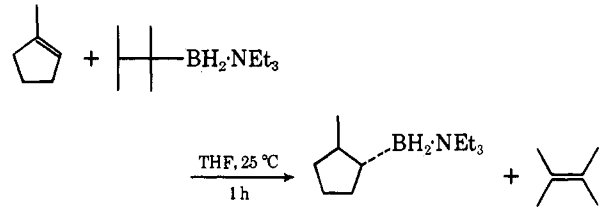
	IPC_2BH[a]		$IPCBH_2$[b]		
Olefin	$[\alpha]_D$, deg (ROH)	ee, %	$[\alpha]_D$, deg (ROH)	ee, %	Absolute confign
2-Methyl-2-butene	0.15	14[d]	2.33	53.4[d]	*S*
1-Methylcyclopentene	6.1[c]	22	24.3	55.4[e]	1*S*,2*S*
1-Methylcyclohexene			31.2	72.4[f]	1*S*,2*S*

[a] All results translated to (−)-IPC_2BH from (+)-α-pinene to facilitate comparison.[5] [b] From (+)-α-pinene, $[\alpha]^{26.5}_D$ +48.0°. [c] Reaction conditions: 25° for 60 h. [d] Based on $[\alpha]_D$ +5.34° for (+)-3-methyl-2-butanol: R. H. Pickard and J. Kenyon, *J. Chem. Soc.*, **103,** 1957 (1913). [e] Based on $[\alpha]_D$ +43.9° for *trans*-2-methylcyclopentanol.[3] [f] Based on maximum rotation of $[\alpha]^{20}_D$ +43.1° for (+)-*trans*-2-methylcyclohexanol: R. Bäckström and B. Sjöbers, *Ark. Kemi,* **26** (47), 549 (1967).

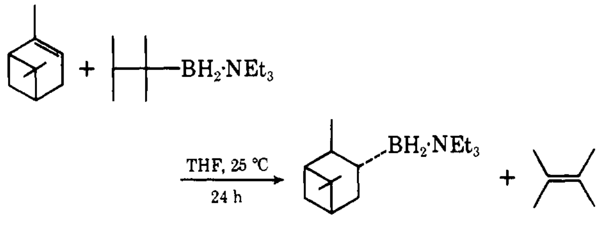
hydroboration with $IPCBH_2$, providing optically active alcohols with optical purities of 53 and 72.4%. In these three cases, the absolute configuration of the new asymmetric center at the alcohol position is consistently *S*. Consequently, this new reagent extends asymmetric hydroboration to such relatively hindered (trisubstituted) olefinic structures and offers promise of an asymmetric synthesis with defined stereochemistry.

Diisopinocampheylborane (IPC_2BH) is an excellent hydroborating agent for cis olefins.[1-3] Indeed, it has recently achieved the conversion of *cis*-2-butene into 2-butanol with an optical purity of 98.4%.[4] Unfortunately, the corresponding reactions of this reagent with more hindered (trisubstituted) olefins, such as 1-methylcyclopentene and 1-methylcyclohexene, are slow and mechanistically complicated, proceeding with partial displacement of α-pinene from the reagent. In such cases, the product alcohols reveal much lower optical purities, in the range of 17-22%.[5] It appeared desirable to discover a less hindered optically active hydroborating agent which could be used effectively with trisubstituted olefins of this type.

We recently observed that hindered olefins react readily with thexylborane-triethylamine at 25 °C to displace tetramethylethylene (TME) and produce the corresponding monoalkylborane-triethylamine (eq 1).[6] We subjected (+)-α-pinene ($[\alpha]^{26.5}_D$ 48.0°) to this reaction. Although the reaction is slower, it proceeds satisfactorily to the synthesis of the new compound, monoisopinocampheylborane-triethylamine (**1**) (eq 2). The volatile components (THF and TME) were removed under aspirator vacuum (15 mm) to leave essentially pure $IPCBH_2 \cdot NEt_3$ (97%) as a colorless viscous liquid. Oxidation with alkaline hydrogen peroxide following methanolysis yielded 97% isopinocampheol ($[\alpha]^{23}_D$ −34.3°, *c* 10, benzene) and 3% thexyl alcohol. Thus the displacement has proceeded without any racemization and the $IPCBH_2 \cdot NEt_3$ possesses the original activity, 96%, of the α-pinene used.



(1)



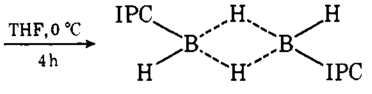
(2)

1

Hydroboration of 1-methylcyclopentene with this reagent proved to be slow at 0 °C—only 43% reaction after 24 h—and involved a small amount of displacement of α-pinene. The reaction could be completed in an additional 6 h at 25 °C, but, under these conditions, displacement of α-pinene is large. However, oxidation of the reaction product provided *trans*-2-methylcyclopentanol in an optical purity of 40%.

We attempted to facilitate the reaction by removing the Et_3N with boron trifluoride in THF to provide free $IPCBH_2$. However, the reaction proved to be disappointingly slow.[7] Fortunately, borane in THF provided a more effective means for removing the Et_3N from $IPCBH_2 \cdot NEt_3$. Thus, treatment of $IPCBH_2 \cdot NEt_3$ in THF at 0 °C with an equivalent amount of BH_3-THF results in the quantitative formation of free $IPCBH_2$ presumably present as the dimer **2** (eq 3). Fortunately, $H_3B \cdot NEt_3$ is inert toward hydroboration, except at elevated temperatures, and need not be removed.

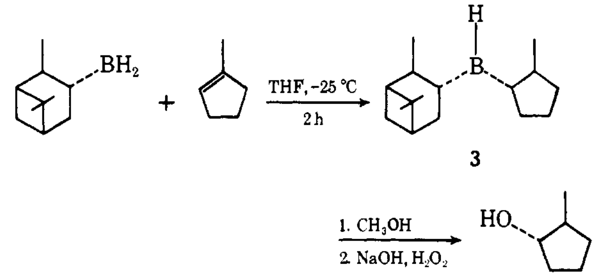
$IPCBH_2 \cdot NEt_3$ + $2BH_3 \cdot THF$



+ $H_3B \cdot NEt_3$ (3)

2

The hydroboration of 1-methylcyclopentene in this solution is complete at −25 °C within 2 h. Oxidation produces *trans*-2-methylcyclopentanol with an optical purity of 55.4% (eq 4).



3

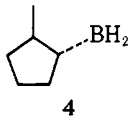
(4)

55.4% ee

In the same way, two other representative hindered olefins, 2-methyl-2-butene and 1-methylcyclohexene were hydroborated with $IPCBH_2$ and oxidized to optically active alcohols, ee (enantiomeric excess) 53% and 72.4%, respectively. The results are summarized in Table I. It should be noted that in the products from these three olefins the absolute configurations of the new asymmetric center is consistently *S*.

The experimental procedure follows. All operations were carried out under nitrogen. A 2 M solution of thexylborane in THF was prepared in the standard manner.[7,8] To 27.5 mL of this solution (55 mmol of $ThBH_2$) was added 8.4 mL (60 mmol of Et_3N, 10% excess). A 1.5 M solution of $ThBH_2 \cdot NEt_3$ in THF was obtained. To this solution was added 8.8 mL of α-pinene (55 mmol, $[\alpha]^{26.5}_D$ 48.0°,[9] 94% ee) and the reaction mixture was stirred at 25 °C for 24 h. TME and THF were removed under aspirator vacuum (15 mm), providing $IPCBH_2 \cdot NEt_3$, 55 mmol, as a viscous liquid. The product was dissolved in 20 mL of THF, followed by 25.0 mL of 2.0 M BH_3 in THF (50 mmol). After 4 h at 0 °C, the solution was cooled to −25 °C and 5.3 mL of 1-methylcyclopentene (50 mmol) was added. After 2 h at −25 °C, the solution was brought to 0 °C and 10 mL of methanol was added dropwise. Hydrogen, 49.8 mmol, evolved. The solution was treated with 20 mL of 30% aqueous sodium hydroxide, followed by 15 mL of 30% hydrogen peroxide added at such a rate that the temperature was maintained at ~40 °C. After an additional hour at 40 °C, the reaction mixtre was heated under reflux for 12 h to complete hydrolysis of $H_3B{\cdot}NEt_3$. The alcohol products were extracted into ether and dried. Distillation provided 4.0 g of *trans*-2-methylcyclopentanol, bp 72–74 °C (18 mm), 80% yield. The alcohol was then purified by GLC (SE-30 column): $n^{20}{}_D$ 1.4495, $[\alpha]^{27}{}_D$ +24.34°, an optical purity of 55.4%.[3]

Monoisopinocampheylborane, the first optically active monoalkylborane, is evidently an excellent hydroborating agent for hindered (trisubstituted) olefins. It also offers promise for the synthesis of other optically active hydroborating agents, such as **3**, and optically active *trans*-2-methylcyclopentylborane (**4**). Thus, this discovery opens the door to the exploration and development of numerous optically active boranes with considerable potential as hydroborating and reducing agents. It also offers promise of a valuable asymmetric synthesis producing products with defined stereochemistry.



4

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(9) We are indebted to Dr. E. Klein of the Dragaco Co., Holzminden, West Germany, for a generous gift of α-pinene of high rotation.

(10) Postdoctorate Research Associate on Grant GM 10937 from the National Institutes of Health.

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Necessity of Electron Transfer and a Radical Pair in the Nitration of Reactive Aromatics

Sir:

Aromatic nitration is the canonical example of an established mechanism,[1,2] and it is a model for electrophilic aromatic substitutions and for studies of aromatic reactivity.[2,3] It is the purpose of this paper to demonstrate that the established mechanism is incomplete, and that the "electrophilic" attack on reactive aromatics occurs by electron transfer, followed by radical-pair collapse.

The accepted mechanism of aromatic nitration is

$$H^+ + HNO_3 \overset{\text{fast}}{\rightleftharpoons} H_2ONO_2^+ \longrightarrow H_2O + NO_2^+$$

$$\xrightarrow{ArH} HArNO_2^+ \xrightarrow{\text{fast}} ArNO_2$$

Frequently formation of NO_2^+ is the rate-limiting step, and electrophilic attack by NO_2^+ on the aromatic is product determining.[1] For aromatics more reactive than toluene, the reaction with NO_2^+ is encounter limited,[4] so that all such aromatics react at the same rate. Yet, even though there is no intermolecular selectivity,[5] there is, paradoxically, intramolecular selectivity. If NO_2^+ is so reactive that it reacts at every encounter with a π system, what distinguishes the ortho and para positions, which have only a slightly greater π-electron density? It is expected that so reactive a species ought to show no selectivity; yet the intramolecular selectivity is ordinary—typical of electrophilic substitutions.[6] The paradox of intramolecular selectivity without intermolecular selectivity is usually interpreted in terms of the intermediacy of π complexes,[7] or oriented encounter pairs:[8]

$$NO_2^+ + ArH \xrightarrow[\text{controlled}]{\text{encounter}} [ArH \rightarrow NO_2^+] \longrightarrow HArNO_2^+$$

It is then asserted[5,7-9] that an oriented π complex can exhibit selectivity. Nevertheless the paradox remains, since it is still necessary to explain how NO_2^+, by virtue of being in a π complex, can acquire selectivity, which free NO_2^+ lacked. Moreover, the estimated lifetime of an encounter pair—10^{-10} s—is too short to accommodate the intramolecular selectivities that are observed. It has been noted[8b] that the intramolecular selectivity in pseudocumene can easily be accommodated if the rate constants for collapse to σ complex at C_6 and C_5 are 10^{11} and 10^{12} s^{-1}, respectively. (According to partial rate factors,[10] which account for the activating effects of methyl groups, C_6 ought to be at least 10 times as reactive as C_2 of toluene; so 10^{11} s^{-1} is a reasonable estimate.) Then both C_1 and C_3 of durene should be considerably more reactive, with rate constants for collapse to σ complex estimated at nearly 10^{13} s^{-1}. Since this is the theoretical maximum, both C_1 and C_3 should react at the same rate. (It has generally been agreed[4] that for sufficiently reactive aromatics the intramolecular selectivity must vanish.) Nevertheless, C_1 of durene is considerably more reactive, since no product resulting from initial attack at C_3 could be detected.[11] Furthermore, the intramolecular selectivity seems to persist even in pentamethylbenzene, which undergoes attack by NO_2^+ predominantly at C_2.[12]

We therefore wish to propose an alternative mechanism—electron transfer, followed by radical-pair collapse to the σ-complex intermediate:

$$NO_2^+ + ArH \xrightarrow[\text{controlled}]{\text{encounter}} \overline{NO_2^{\cdot} + ArH^{+\cdot}} \longrightarrow HArNO_2^+$$

Electron transfer has on occasion been suggested[13] in apparent electrophilic attack on aromatics, and both ESR and CIDNP have been observed.[14] Also, ionization potentials[15] support this suggestion; electron transfer from reactive aromatics to NO_2^+ is exothermic by 20-40 kcal/mol. Of course ionization potentials are gas-phase values, and preferential solvation of NO_2^+ (the smaller ion) decreases this exothermicity. As a result, the electron-transfer mechanism has never been creditable.

To determine the energetics of electron transfer, we have determined the anodic half-wave potentials for NO_2 and representative aromatics in CH_3CN. The experimental values are 1.82 (NO_2), 1.34 (naphthalene), 1.4 (anisole), 1.62 (mesitylene), 1.68 (*o*-xylene), and >1.9 V (toluene) vs. Ag|0.01 M $AgClO_4$. Even in such a polar solvent *electron transfer to* NO_2^+ *is exothermic for all aromatics more reactive than toluene.* Therefore we conclude that the π-complex description is inadequate for a species in which an electron has been transferred from aromatic to NO_2^+.

The electron-transfer mechanism provides a ready explanation for the encounter-limited nitration of aromatics more