Table I. Kinetic and Thermodynamic Data for Racemization of Substituted 1-Phenylbromoethanes in Acetone

substituent	k,[a] L/(mol·s)	$\Delta G^{\ddagger}$,[b] kJ/mol	$\Delta H^{\ddagger}$,[b] kJ/mol	$\Delta S^{\ddagger}$,[b] J/(deg·mol)
3,4-$(CH_3)_2$	7.74×10^{-3}	87.6 ± 1.5	54.2 ± 3.0	−110 ± 10
p-CH_3	7.90	86.9 ± 0.9	56.6 ± 1.5	−100 ± 5
p-H	3.65	88.4 ± 0.3	64.19 ± 0.09	−79.9 ± 0.7
p-Br	8.77	87.1 ± 0.9	66.2 ± 2.6	−69 ± 10
p-NO_2	16.75	84.8 ± 1.1	69.5 ± 1.8	−50 ± 8

[a] Observed value for [LiBr] = 0.002 M, T = 303.15 K. All reactions are kinetically second order, but the observed rate constants decrease with increasing lithium bromide concentration due to ion pairing of the salt (see ref 6). [b] Averages of the values obtained for several concentrations of lithium bromide between 5.00×10^{-4} and 1.000×10^{-2} M. The temperature range for each determination was 25-45 °C.

values in Table I are clearly inconsistent with that rationale.

If on the other hand we are dealing with an ionization process, perhaps to an ion pair,[7,8] it is the C–Br bond strength, moderated of course by solvation, that would determine $\Delta H^{\ddagger}$. The enthalpy of activation would then be expected to decrease progressively as the carbon becomes more able to support the developing positive charge; this is exactly what is found. Clearly an ionization model is a more acceptable one than the classical S_N2 transition state required by the usual rationale.

The decrease in enthalpy of activation with the increase in stability of the expected carbocation is compensated for by the entropy term which rapidly gets more negative. Such a "compensation effect" of enthalpic and entropic contributions is well-known and seems to be one of the reasons the Hammett and like equations are so broadly applicable.[5,9] Of course $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are not "independent" variables since changes in the former will affect the transition state structure and hence its solvation. It is usual to assume the bulk of the entropy of activation comes from the resolvation in going from the reactants to the transition state so that, if this assumption is valid, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are affected by the same factors.

Again, the observed range in $\Delta S^{\ddagger}$ with substituent is more consistent with a larger change in charge separation and hence in solvation than would be expected if the usual explanation for the nonlinear Hammett behavior of such systems is valid. Both the enthalpic and entropic data then are consistent with an ionization process rather than the one usually invoked.

Shiner and his colleagues[8] have done extensive studies of m- and p-substituted 1-phenylethyl halides and have concluded that internal return from an ion pair is important in alcoholysis and hydrolysis. From deuterium isotope effects, they concluded that for the solvolysis of unsubstituted 1-phenylethyl bromide in 80:20 ethanol–water and even of the p-nitro analogue in 5:95 acetone–water ionization was nearly complete at the transition state, with nucleophilic attack probably occurring at the contact ion-pair stage. Acetone is of course much less ionizing than aqueous ethanol or water and is incapable of hydrogen bonding, but his results lend support to our conclusions. Unfortunately Shiner did not report activation parameters.

There have, however, been a few reports of activation parameters, or data from which they can be calculated, for benzylic systems[2b,c,3b,c,f-h] but only two report data for a range of substituents and reactions that are at all comparable to the system reported here. The data of Sugden and Willis[3h] for the bromide–*radio*-bromide exchanges in ethylene diacetate show precisely the same pattern in and comparable values for the activation parameters. The results of Brown et al.[2c] for the solvolysis of p-nitrobenzoate esters of benzylic systems show similar patterns. Thus the dramatic dependence of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ on substituents is not limited to racemizations in the phenylethyl system or the solvents studied to date.

Clearly the nonlinearity of the Hammett equation is due to the fact that the enthalpic parameter is more than compensated for by the entropic one. In the system in question the range of $\Delta H^{\ddagger}$ is 15.3, that of $T\Delta S^{\ddagger}$ is 18.2 kJ/mol at 303.15 K. Undoubtedly for proponents of the usual rationale for the nonlinearity, it will be possible to "fit" the activation data to their mechanism,[10] but we feel that the data supports an ion-pair scheme. Obviously more data for benzylic systems must be obtained before any extensive mechanistic discussion is undertaken so that we conclude with a plea that such measurements be made. Rate and isotope effect measurements clearly are not enough to sort out the origins of the nonlinearity of Hammett $\sigma\rho$ correlations.

Acknowledgment. The financial assistance of Memorial University and the National Science and Engineering Research Council of Canada is gratefully acknowledged.

(7) R. A. Sneen and J. W. Larsen, *J. Am. Chem. Soc.*, **91**, 362, 6031 (1969).

(8) V. J. Shiner, Jr. in "Isotope Effects in Chemical Reactions", ACS Monograph 167, C. J. Collins and N. S. Bowman, Eds., Van Nostrand-Reinhold Co., New York, 1970, pp 105-118.

(9) (a) L. G. Hepler, *Can. J. Chem.*, **49**, 2803 (1971); (b) T. M. Krygowski and W. R. Fawcett, *ibid.*, **53**, 3622 (1975).

(10) For example, the changes in $\Delta S^{\ddagger}$ can be explained by assuming the transition state changes from "very tight" to "very loose" as the substituent changes from electron withdrawing to electron donating and considering the effects upon solvation. The fact that $\Delta H^{\ddagger}$ continues to increase markedly as the substituents become quite electron withdrawing is difficult to explain in this way though. In any event, when does a "loose" transition state with almost no bonding to the leaving group become an ion pair?

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Structure Determination of the Active Sulfhydryl Reagent in Gill Tissue of the Mushroom *Agaricus bisporus*[1]

Summary: The red pigment found in sporulating gill tissue of the mushroom *Agaricus bisporus*, which is a potent inhibitor of a number of enzymes containing sulfhydryl groups at their active sites, is shown to be 2-hydroxy-4-imino-2,5-cyclohexadienone (4).

Sir: A potent sulfhydryl reagent appears in the gill tissue of the mushroom *Agaricus bisporus* in the period prior to

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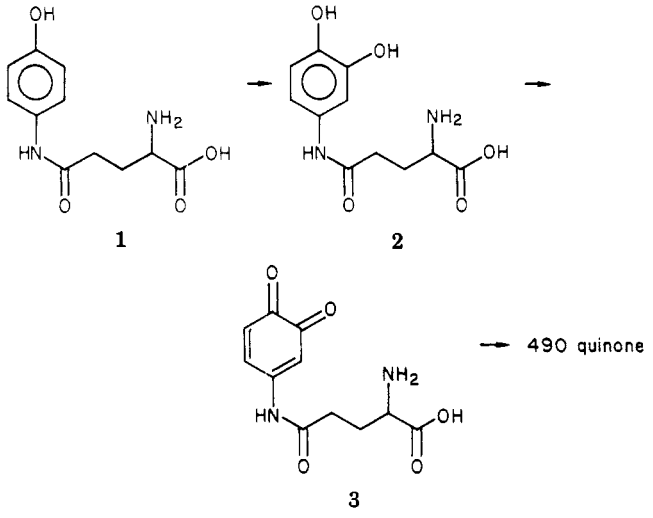
Scheme I

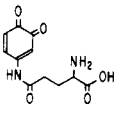
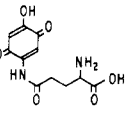


sporulation.[2] This compound, termed the 490 quinone because of its visible absorption maximum at 490 nm, has been postulated to play a role in the induction of cryptobiosis in the spore through inhibition of enzymes associated with both mitochondrial respiration[3] and DNA synthesis.[4] The 490 quinone has also been shown to be an antitumor agent in vitro against murine B-16 melanoma and murine L-1210 leukemia.[5] The elucidation of the structure of the mushroom quinone has been hampered by its instability at concentrations above 10^{-4} M.[6]

The identification[7] of γ-L-glutaminyl-4-hydroxybenzene (**1**) as the biological precursor of the 490 quinone led to an early hypothesis in formulating it as γ-L-glutaminyl-3,4-benzoquinone (**3**).[6] The quinone representing this latter structure was later synthesized by periodate oxidation of γ-L-glutaminyl-3,4-dihydroxybenzene (**2**) and was shown to have a chromophore of 440 nm, not 490 nm.[8] Both the catechol (**2**) and the compound **3** appeared to be intermediates in the biosynthesis of the 490 quinone since in the presence of tyrosinase they are both converted by oxygen to the natural quinone. In addition, the subsequent isolation[9] of γ-L-glutaminyl-3,4-dihydroxybenzene from *A. campestris* is in keeping with its role as a biosynthetic intermediate.

In a previous study, glutamic acid was identified in the acid hydrolysate of the 490 quinone.[6,10] This led us to assume that the glutaminyl side chain in **1**, **2**, and **3**, which are all established precursors of the 490 quinone (Scheme I), was retained in the structure of the latter. On the basis of this premise, the bathochromic shift observed in going from the *o*-benzoquinone **3** to the 490 quinone could be most reasonably accounted for by further oxidation of the quinone ring of **3** to generate structures such as those exemplified by **6**, **8**, or **10** (see Scheme II). This reasoning formed an initial basis for our further investigation.

Table I. Visible Absorption Maxima and Redox Potentials of Model Quinones[a]

	COMPOUND	$E_{1/2}$	λ_{max}
11		−165 mV	440 nm
3		−190 mV	440 nm
12		−220,550 mV	450 nm
13		95 mV	495 nm
6		85 mV	495 nm
4		110 mV	490 nm

[a] $E_{1/2}$ measured against Ag/AgCl reference electrode.

Model compounds **11**, **12**, and **13** were synthesized from the corresponding catechols by oxidation with either aqueous $NaIO_4$ (**11** and **12**) or air oxidation (**13**) in aqueous buffer pH 7.2 to test our hypothesis. The cyclic voltammograms, $E_{1/2}$ values,[11] and visible absorption spectra of these model compounds were compared to those of the natural quinone (see Table I). Inspection of these results shows that structure **8** is an unlikely candidate for the structure of the 490 quinone since its λ_{max} and $E_{1/2}$ values would have been expected to bear a close relation to the values obtain for the model compound **12**. However, 2-(acetylamino)-5-hydroxy-1,4-benzoquinone (**13**) has a visible absorption maximum at 495 nm and an $E_{1/2}$ of −95 mV, which are in reasonably close agreement with the values obtained for the 490 quinone and led us to consider structure **6**. Quinone **6** was synthesized by the oxidation of γ-L-glutaminyl-2,4,5-trihydroxybenzene (**5**)[12] with periodate. A careful comparison of the spectra of **6** and the 490 quinone indicated that significant differences existed in these two compounds in the UV spectral region and in their $E_{1/2}$ values (−110 mV for the 490 quinone and −85 mV for **6**) to indicate their nonidentity.

Two recent findings have led to the elucidation of the structure of the natural quinone. The first concerned the observation that the tyrosinase-catalyzed oxidation of the catechol **2** when carried out at pH 6.5 proceeded to give the 1,2-benzoquinone **3**. The second observation was that a dilute solution (10^{-5} M) of this latter quinone could be converted to the natural quinone when the pH was raised to values between 7.0 and 8.5, with or without tyrosinase being present.

This transformation suggested several remaining possibilities for the structure of 490, including its formation from **3** by nucleophilic attack on the quinone ring by the amino acid nitrogen to give a species **9** which could undergo further oxidation to the compound **10**. We, therefore,

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(3) Weaver, R. F.; Rajagopalan, K. V.; Handler, P. *Arch. Biochem. Biophys.* **1972**, *149*, 541.
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(6) Weaver, R. F.; Rajagopalan, K. V.; Handler, P.; Byrne, W. L. *J. Biol. Chem.* **1971**, *246*, 2015.
(7) Weaver, R. F.; Rajagopalan, K. V.; Handler, P.; Rosenthal, D.; Jeffs, P. W. *J. Biol. Chem.* **1971**, *246*, 2010.
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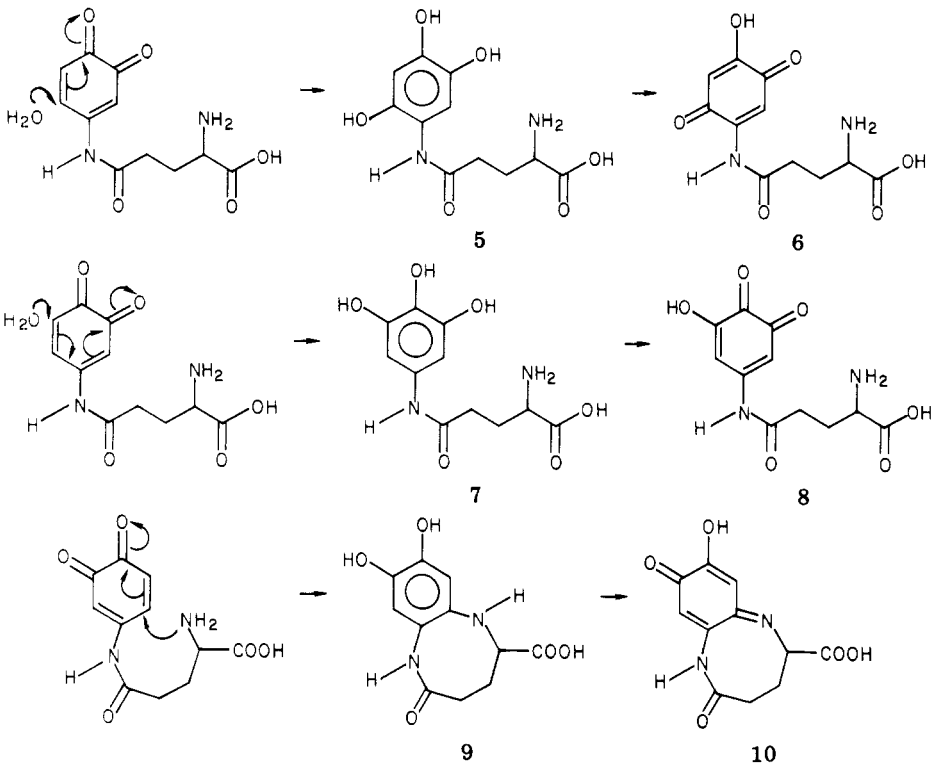
(10) Samples of 490 quinone obtained in the earlier study are now known to have been contaminated with γ-L-glutaminyl-4-hydroxybenzene, despite chromatographic purification on Sephadex. The latter compound was, in retrospect, the source of the glutamic acid identified in the hydrolysate.
(11) For a general review of voltammetry as applied to biological systems, see: Adams, R. N. *J. Pharm. Sci.* **1969**, *58*, 1171.
(12) The synthesis of this compound followed the same general procedures as reported previously[7] and will be detailed in the full paper.

Scheme II



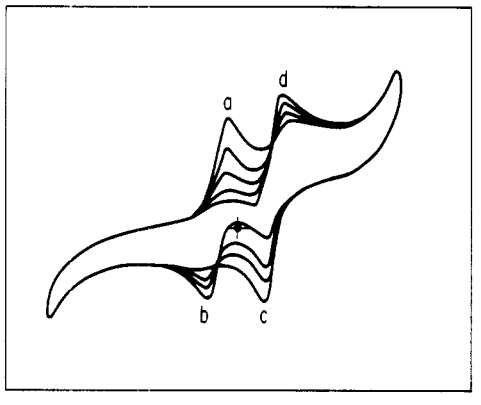
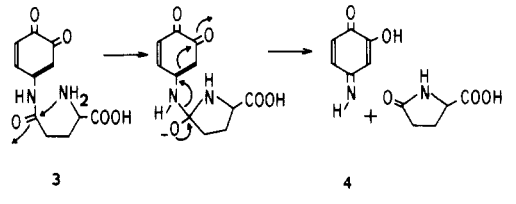


Figure 1. Transformation of 3 to 4 followed by cyclic voltammetry: a, peak for compound 2; b, peak for compound 3; c, peak for compound 4; d, peak for 4-aminocatechol.

undertook a careful examination of the oxygen dependency of the conversion of **3** to the 490 quinone by cyclic voltammetry.

The transformation of γ-L-glutaminyl-3,4-benzoquinone (**3**) to the 490 quinone was observed to take place in a rigorously deoxygenated solution at pH 7.8 (see Figure 1).[12] As the redox couple for the interconversion of **2** and **3** disappeared (peaks a and b), the redox couple for the 490 quinone appeared (peaks c and d). Since the reaction was conducted in an oxygen-free system, if intramolecular nucleophilic attack by the amino acid side chain on the quinone occurs, the *initial species* generated by such a reaction is the benzenoid compound **9**, and, therefore, it must suffer further oxidation in order to provide a quinonoid species. The absence of an oxidation step in the conversion of **3** to the 490 quinone was readily discounted by single-sweep cyclic voltammetry experiments. This may be understood as follows. If the conversion of **3** to the 490 quinone involves intramolecular cyclization to **9**, then in an oxygen-free environment the sampling of the species present should reveal only the redox couples associated with these two compounds. The advantage of the single-sweep experiment is that by sweeping either anodically or cathodically the concentrations present of reduced (phenolic) and oxidized species (quinone) are revealed. Figure 2 shows a single anodic and cathodic sweep of the reaction which ensued from quinone **3** in an oxygen-free solution at pH 7.8 at a point when all of the 1,2-benzoquinone **3** had been consumed (as revealed by multiple-sweep cyclic voltammetry). The single anodic sweep (curve A) showed an insignificantly small current,[13] indicating the absence of the phenolic species corresponding to the reduced 490 quinone. The complementary experiment in which the potential was swept in the cathodic direction (curve B) showed a large reduction peak at $E_{p,c}$ corresponding to that of the 490 quinone. These results established that quinone **3** is converted directly in a nonoxidative manner to the 490 quinone, indicating that this conversion is the result of a base-catalyzed reaction, and suggested that the structure of the 490 quinone is the iminoquinone **4**. The formation of **4** from **3** can be readily understood in terms of the mechanism given in Scheme III.

Scheme III



The structural assignment for the 490 quinone was confirmed by the air oxidation of 4-aminocatechol in aqueous solution at pH 7.8 to give the iminoquinone **4**. The 2-hydroxy-4-iminoquinone generated by this route had the same cyclic voltammogram and UV–visible spectrum as the natural quinone obtained from *A. bisporus*. Further

(13) The very small current at the $E_{p,a}$ of the 490 quinone which is observed at the start of the sweep is readily accounted for by the reduction of the 490 quinone at the electrode when the potential is applied at the start of the sweep. This can be seen to represent an insignificant concentration by comparing it with the $E_{p,a}$ seen at the end of the sweep.

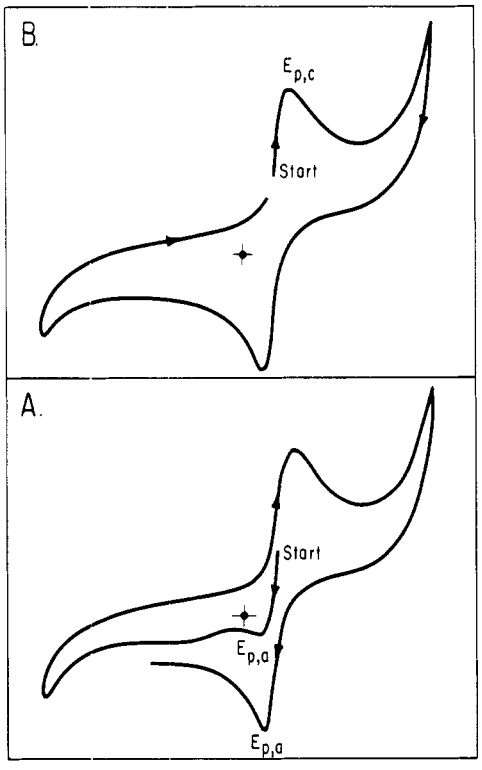


Figure 2. Single-sweep cyclic voltammetry of the 490 quinone performed on the product obtained directly from 3 in an aqueous solution at pH 7.8 (working electrode Au, reference electrode Ag/AgCl): A, anodic sweep; B, cathodic sweep.

confirmation of its structure was provided by the conversion of the natural quinone to 3,4-diacetoxyacetanilide by the following procedure: 15 mL of a 10^{-4} M solution of natural 490 quinone was reduced with an excess of $NaBH_4$, and the solution was acidified with 1 N HCl and taken to dryness under vacuum. The residue was acetylated in Ac_2O and pyridine at 50 °C for 2 h and the solvent removed under vacuum. The crude acetylated product after purification by high-performance LC was identical with authentic 3,4-diacetoxyacetanilide by TLC, high-performance LC, and GC–MS.

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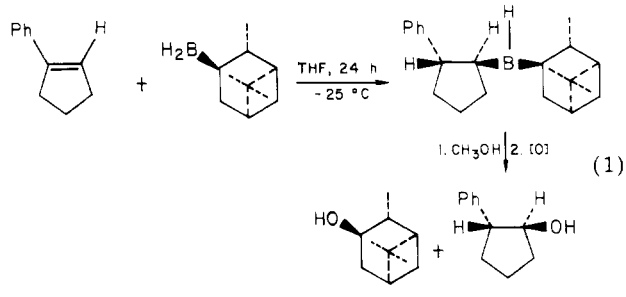
Monoisopinocampheylborane: An Excellent Chiral Hydroborating Agent for Phenyl-Substituted Tertiary Olefins. Synthesis of Alcohols Approaching 100% Enantiomeric Excess

Summary: Monoisopinocampheylborane ($IPCBH_2$), a less hindered chiral hydroborating agent, is highly effective for the hydroboration of phenyl-substituted tertiary olefins, such as 1-phenyl-1-cyclopentene, 1-phenyl-1-cyclohexene, (*E*)- and (*Z*)-2-phenyl-2-butenes, and (*E*)- and (*Z*)-3-phenyl-2-pentenes. Oxidation furnishes alcohols in the range of 81 to 100% ee. The new asymmetric center at the alcohol position is consistently enriched in *S* enantiomer, utilizing reagent prepared from (+)-α-pinene.

Sir: We have recently reported that $IPCBH_2$, a less hindered optically active borane reagent, is highly effective for the asymmetric hydroboration of hindered olefins, such as 1-methyl-1-cyclopentene, 1-methyl-1-cyclohexene, and 2-methyl-2-butene.[1,2] Diisopinocampheylborane (IPC_2BH), an excellent chiral hydroborating agent for cis olefins, hydroborates these hindered olefins only sluggishly, with displacement of α-pinene from the reagent, yielding the corresponding alcohols in only 17–22% ee.[3] In contrast, $IPCBH_2$ hydroborates these olefins cleanly to yield after oxidation the above alcohols in much higher isomeric purities, in the range of 53 to 75% ee. These observations encouraged us to explore the usefulness of $IPCBH_2$ for the hydroboration of other olefins having different steric and structural requirements.

We have now discovered that optically pure $IPCBH_2$, readily available in tetrahydrofuran (THF) by the reaction of $TMED{\cdot}2IPCBH_2$ with boron trifluoride etherate,[4] hydroborates phenyl-substituted tertiary cyclic or acyclic olefins smoothly to yield after oxidation the corresponding alcohols in exceptionally high optical purities. Thus, hydroboration of 1-phenyl-1-cyclopentene with $IPCBH_2$ in THF at −25 °C requires 24 h for near completion. Oxidation produces *trans*-2-phenylcyclopentanol with an optical purity of 100% ee (eq 1).



(1)

The hydroboration of 1-phenyl-1-cyclohexene with the reagent is much slower. Even at 0 °C, the reaction requires some 7 days to achieve 80% completion. Oxidation furnishes *trans*-2-phenylcyclohexanol in 88% ee.

$IPCBH_2$ is also effective for phenyl-substituted tertiary acyclic olefins. Thus (*E*)- and (*Z*)-2-phenyl-2-butenes are hydroborated with the reagent and yield, following oxidation, optically active (+)-(2*S*,3*R*)- and (−)-(2*S*,3*S*)-3-phenyl-2-butanols in 81% and 82% ee, respectively (eq 2 and 3).

Similarly, the hydroboration of (*E*)- and (*Z*)-3-phenyl-2-pentenes with $IPCBH_2$, followed by oxidation, yields (−)-(2*S*,3*R*)- and (+)-(2*S*,3*S*)-3-phenyl-2-pentanols in 85.5 and 85% ee, respectively.

At this time it is not clear why the results achieved with these phenyl-substituted tertiary olefins are more favorable than those with the corresponding methyl-substituted olefins.

The tosylate derivatives of the optically active 3-phenyl-2-butanols and 3-phenyl-2-pentanols have been

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