

A New Route to Chiral Compounds

Hydroboration of olefins with a derivative of α -pinene produces chiral intermediates that can be converted into many other compounds

A new technique for hydroboration of olefins provides a simple way to produce chiral alkyl boranes with essentially 100 percent optical purity. The technique, developed by Nobel laureate Herbert C. Brown and Bakthan Singaram of Purdue University, makes use of inexpensive and readily available reagents both for induction of the optically active center and for isolation of the borane. Furthermore, Brown says, since "It is now possible to transfer alkyl groups from boron to essentially all other elements of synthetic interest without observable racemization," the new approach should greatly simplify the synthesis of virtually all types of chiral compounds.

Interest in the synthesis of chiral compounds has intensified in recent years because of the need to produce hor-

Either isomer can be treated with borane to produce diisopinocampheylborane (di-Ipc), a crystalline solid. "If we put in 15 percent or so excess α -pinene," says Brown, "and let it stew for a day or two, the major isomer gets incorporated into the solid, the solid becomes 100 percent optically pure, and the minor isomer stays in solution."

This step can, however, be bypassed. "For hydroboration, we use mono-Ipc, and there we were lucky. If we take di-Ipc of 92 percent optical purity and simply treat it with tetramethylethylenediamine (TMEDA), we displace α -pinene and get the mono-Ipc adduct with TMEDA, with one molecule of mono-Ipc attached to each nitrogen. The adduct is a crystalline solid that separates out at 100 percent optical purity." Treat-

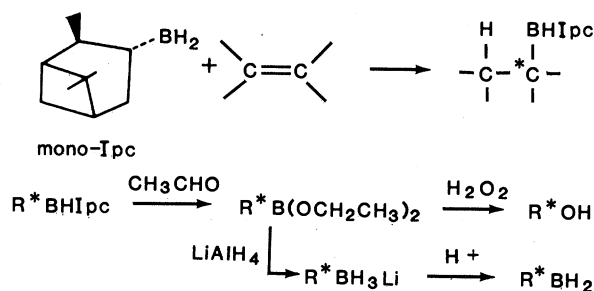
alkaline hydrogen peroxide or reduced to a chiral borane, R^*BH_2 , with lithium aluminum hydride and methanesulfonic acid. Using well-known techniques, the borane can then be converted into a wide variety of other chemicals, including acetylenes, *cis*-olefins, *trans*-olefins, alkenes, halides, nitriles, carboxylic acids, amines, aldehydes, and others, all with complete retention of optical activity. Brown also predicts that the alkyl boranes will be useful for forming asymmetric carbon-carbon bonds.

Brown and Singaram reported several examples of the use of their reagent. For instance, 1-methylcyclopentene was added to the stock solution in ethyl ether at $-35^\circ C$ and allowed to stand for 12 hours without stirring. Isopinocampheyl-*trans*-(2-methylcyclopentyl)borane crystallized in 65 percent yield. Oxidation produced *trans*-2-methylcyclopentanol of 100 percent optical purity. Oxidation of the mother liquor, in contrast, gave the same alcohol in only 12 percent optical purity, indicating that the major isomer becomes incorporated in the crystalline solid, leaving the minor isomer in solution.

In a similar fashion, hydroboration and oxidation of 1-methylcyclohexene produced *trans*-2-methylcyclohexanol in greater than 99 percent optical purity, and treatment of 2-methyl-2-butene yielded 3-methyl-2-butanol of 100 percent optical purity. Hydroboration of (*Z*)-3-phenyl-2-pentene gave somewhat different results, however. In this case, optically impure material crystallized as an amorphous solid, leaving the optically pure isomer in solution; nonetheless, *erythro*-3-phenyl-2-pentanol was obtained in 100 percent optical purity.

All of the alcohols reported in the paper were previously prepared by the conventional, relatively tedious route involving resolution of the brucine salts of the corresponding phthalate half-esters. "The present method," says Brown, "provides a far simpler route to these alcohols in high optical purity." Any of the intermediate boranes, furthermore, could equally as well have been converted into other functional groups. Concludes Brown: "For the first time we can, by a rational synthesis, undertake to make practically any compound with 100 percent optical purity."

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mones, insect pheromones, prostaglandins, antitumor agents, drugs, and many other analogues of naturally occurring compounds. Up to now only two good techniques for induction of a chiral center with high optical purity (*Science*, 22 July 1983, p. 351) have been available: chiral hydrogenation of olefins and chiral epoxidation of olefins. While these techniques have been very valuable, they are nonetheless useful in only a limited number of situations. In most other cases, investigators have had to resort to the more conventional technique of producing a racemic mixture of the desired compound and isolating the desired isomer, most often by crystallization as the salt of a chiral reagent such as brucine. The Brown approach, reported in the most recent issue of the *Journal of the American Chemical Society* [106, 1797 (1984)], should open the way to synthesis of a much wider variety of materials.

The key to the new synthetic approach is α -pinene, a terpene that is available commercially in about 92 percent optical purity in either its (+) or (–) form.

ment of the adduct with boron trifluoride etherate in ethyl ether yields a stock solution that is stable for at least 20 days at $0^\circ C$.

"When we react the stock solution with an olefin," Brown continues, we get anywhere from 60 to 90 percent optically pure material. But when we crystallize that, it comes out 100 percent optically pure." The crystallizing solvent is typically ethyl ether at $-35^\circ C$. What actually crystallizes is a diborane dimer that contains four optically active centers—two Ipc groups and the two chiral alkyl groups (R^*) that have been created in the hydroboration. It is apparently the large number of optically active centers that produces the differential crystallization.

The diborane dimer is then treated with acetaldehyde to cleave α -pinene, producing the boronic ester $R^*B(OCH_2CH_3)_2$. (The α -pinene released in this and the earlier step can be recovered and used again, thereby holding down costs for a commercial process.) This ester can be directly oxidized to a chiral alcohol with