Alkylation of Allylic Derivatives. 9.[1] On the Stereochemistry of Alkylation of Acyclic Allylic Alcohols by the Murahashi Method

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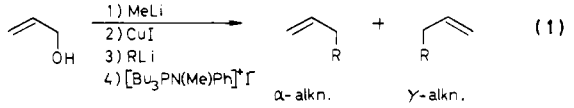
The stereochemistry of alkylation of optically active *trans*-α-methyl-γ-phenylallyl alcohol (3-OH) by the Murahashi procedure has been investigated. Alkylation with *n*-butyllithium results in almost exclusive syn γ-alkylation. With methyllithium, syn γ-alkylation also predominates. The syn stereochemistry in this acyclic system is opposite from that observed earlier in cyclic systems. Mechanistic implications of this reversal of stereochemistry are discussed.

Earlier studies[2,3] have shown that the Murahashi method for cross coupling allylic alcohols with alkyllithium reagents (eq 1) is regiospecific (γ-alkylation) in both cyclic and



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acyclic systems.[4] Stereochemical studies have been limited to cyclohexenyl systems in which anti γ-alkylation is observed.[2,3] The reaction pathway outlined in Scheme I has been proposed for this four-step process.[2]

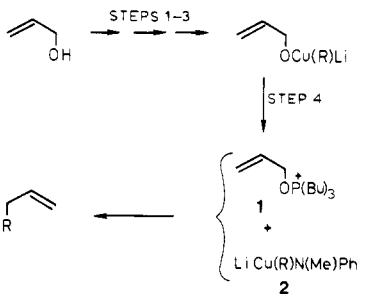
We have now investigated the stereochemistry of alkylation of optically active *trans*-α-methyl-γ-phenylallyl alcohol (3-OH) by this method and find that syn γ-alkylation predominates. Thus the stereochemistry in this acyclic system is opposite from that observed in cyclohexenyl systems.[2,3]

Results for alkylation of (*S*)-(−)-3-OH with *n*-BuLi are presented in Scheme II. Absolute configurations and rotations for 3-OH and 4-phenyloctane (**5**) were known from other work.[5] The product distribution was determined by capillary GC and components were identified by comparison with authentic racemic samples.[6] These results show that this reaction is almost completely regiospecific[7] and gives 99% of the unconjugated γ-alkylation product (**4**).

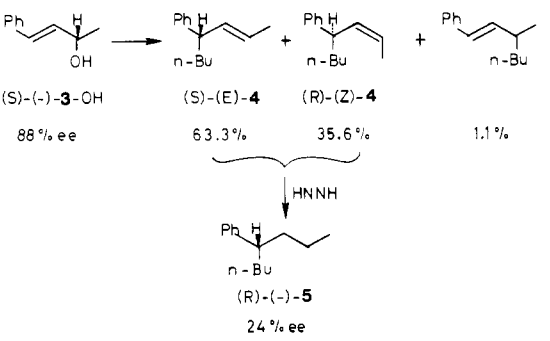
The configuration of the chiral center in **4** was determined by a method developed earlier[5] which involves diimide reduction to **5**. The latter was isolated in pure form by preparative GC and had $[\alpha]^{25}_{D}$ −2.05° (*n*-hexane). From the absolute configuration and rotation[5] it can be determined that this sample has the *R* configuration and an enantiomeric excess (ee) of 24%. Thus (*E*)-**4** has the *S* configuration as shown in the scheme. This establishes that the 3-OH → **4** transformation involves excess syn stereochemistry.

Presumably (*E*)- and (*Z*)-**4** are formed from the two reactive conformations of the product-forming intermediate derived from (*S*)-**3**-OH as illustrated in Scheme III. From this we conclude that these isomers have opposite configurations as indicated in Scheme II and are of equal optical purity. Reduction converts these to enantiomers.

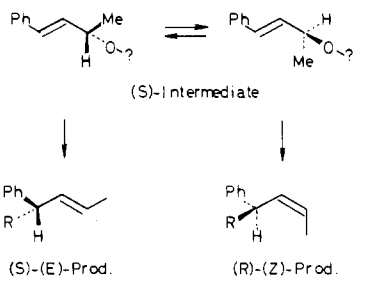
Scheme I



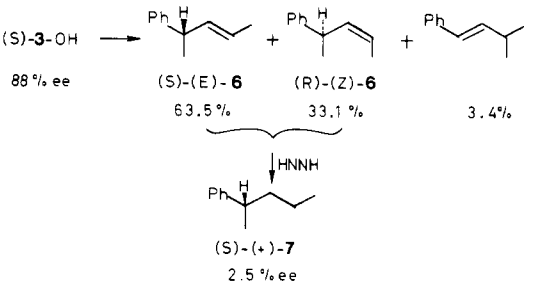
Scheme II



Scheme III



Scheme IV



Thus the ee for **5**, derived from the mixture of 64% (*S*)-(*E*)-**4** and 36% (*R*)-(*Z*)-**4**, is 72% less than that of (*E*)-

(1) Previous paper in this series: Goering, H. L.; Kantner, S. S. *J. Org. Chem.* **1984**, *49*, 422.
(2) Tanigawa, Y.; Ohta, H.; Sonoda, A.; Murahashi, S.-I. *J. Am. Chem. Soc.* **1978**, *100*, 4610.
(3) Goering, H. L.; Kantner, S. S. *J. Org. Chem.* **1981**, *46*, 2144.
(4) Regiospecificity depends on reaction conditions and is diminished if more than 1 equiv of alkyllithium is used in step 3.[3]
(5) Goering, H. L.; Kantner, S. S.; Tseng, C. C. *J. Org. Chem.* **1983**, *48*, 715.
(6) Goering, H. L.; Seitz, E. P., Jr.; Tseng, C. C. *J. Org. Chem.* **1981**, *46*, 5304.
(7) The term "regiospecific" is used as defined in ref 3 of: Goering, H. L.; Singleton, V. D., Jr. *J. Org. Chem.* **1983**, *48*, 1531.

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and (*Z*)-4. From the observed 24% ee for **5** it can be determined that that for (*E*)- and (*Z*)-4 is 86%, which is only slightly less than the ee of the starting (*S*)-3-OH. This shows that there is little, if any, loss of chirality and the reaction involves essentially exclusive syn γ-alkylation. Similar results were obtained in a totally independent experiment.

Results for alkylation of (*S*)-3-OH with MeLi are presented in Scheme IV. The product distribution is essentially the same as that found earlier for alkylation of racemic 3-OH.[3] The major product ((*E*)-**6**) was shown to have the *S* configuration by diimide reduction to (*S*)-(+)-2-phenylpentane (**7**).[5] Thus this reaction also involves excess syn alkylation.

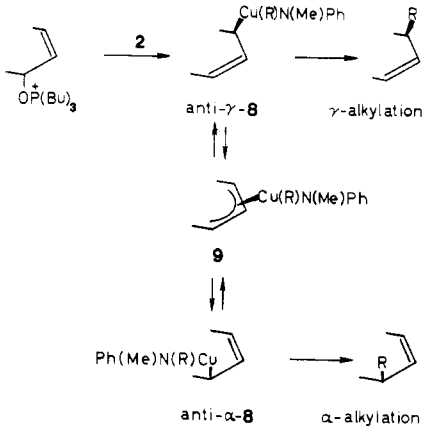
A homogeneous sample of (*S*)-(+)-**7**, isolated by preparative GC,[8] had $[\alpha]^{20}_D$ 0.49° (*n*-hexane), which corresponds to an ee of 2.5%.[5] From the composition of **6** (66% *E* and 34% *Z*) it can be seen that the enantiomeric excess for the reduction product (**7**) is 68% less than that for (*E*)- and (*Z*)-**6**. The observed ee of 2.5% for **7** corresponds to an ee of 8% for (*E*)- and (*Z*)-**5**. In this case syn alkylation predominates, but about 90% of the chirality is lost. Put another way, the 3-OH → **6** transformation involves 55% syn and 45% anti alkylation. Thus, alkylation of optically active 3-OH with MeLi is substantially less stereospecific and somewhat less regiospecific[7] than alkylation with *n*-BuLi.

The change in stereochemistry from anti in cyclic systems[2,3] to syn in 3-OH indicates that different mechanisms are involved. This change is also accompanied by increased regiospecificity[7] in the acyclic system. In earlier work we found that in the 5-methyl-2-cyclohexenyl system, Murahashi alkylation of the alcohol with MeLi is somewhat less regiospecific (88–93% γ-alkylation)[3] than alkylation of the acetate with LiCu(CN)Me (~97% γ-alkylation).[1] The situation is reversed in acyclic systems. For example, alkylation of 3-OAc with LiCu(CN)Me gives ~50% γ-alkylation[8] as compared to 97% (MeLi) and 99% (*n*-BuLi) γ-alkylation observed in the present work. In this system nonregiospecific[7] alkylations with R_2CuLi give ~94% of the conjugated α-alkylation product.[6]

The mechanism involved in cyclic systems presumably involves an intermolecular alkylation of an (allyloxy)-phosphonium ion (**1**) by a mixed cuprate (**2**) as indicated in Scheme I. In this connection it is important that reactions of this type (e.g., alkylation of allylic derivatives with alkylcuprates) in general proceed with anti stereochemistry in both cyclic[1,9] and acyclic systems.[8,10] It should also be noted that the regiochemistry and stereochemistry for alkylation of 5-methyl-2-cyclohexenyl alcohol with MeLi by the Murahashi method are similar to those for alkylation of the acetate with LiCu(Me)N(Me)Ph.[3]

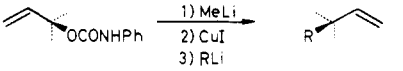
A refinement of the mechanism proposed earlier[3] for the intermolecular alkylation of **1** by **2** is shown in Scheme V.[11] Originally we thought that oxidative addition results in simultaneous formation of the S_N2' σ-allyl complex (*anti*-γ-**8**) and the π-allyl complex (**9**). For reasons discussed elsewhere[1,12] we now feel that this step gives only *anti*-γ-**8**, which subsequently isomerizes to **9** in competition with reductive elimination. The **8** ⇄ **9** isomerization results in loss of regiochemistry; however, stereochemistry is preserved.[1,8] This mechanism accommodates the pre-

Scheme V



dominating anti γ-alkylation of cyclic allylic alcohols[2,3] but not the syn γ-alkylation observed in the present work.

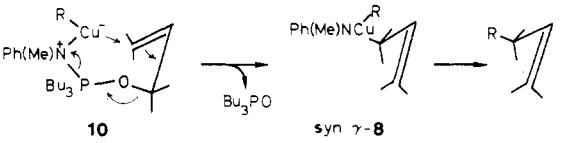
The syn stereochemistry and remarkable regiospecificity for alkylation of 3-OH suggest that a cyclic intramolecular process is involved. In other work[5] we found that alkylation of allylic *N*-phenylcarbamates by the three-step process shown by eq 2 gives exclusive syn γ-alkylation and



(2)

concluded that a cyclic internal process is involved. Alkylation of 3-OCONHPh with *n*-BuLi by this method[5] is similar to alkylation of 3-OH with *n*-BuLi (Scheme II) in that exclusive syn γ-alkylation results in each case. However, there is a marked difference in *E*/*Z* ratios for the two procedures—the ratio for 3-OH is 1.78 and that for 3-OCONHPh is 10.8. Another difference is that the *N*-phenylcarbamate method (eq 2) gives exclusive syn γ-alkylation in cyclic as well as in acyclic systems.[5]

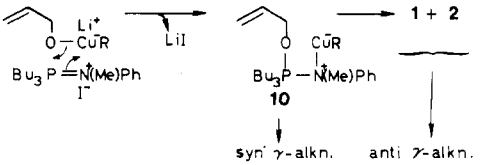
A plausible cyclic process that accounts for syn γ-alkylation of acyclic allylic alcohols is shown in eq 3.[11] This



(3)

involves a complex (**10**) that undergoes an intramolecular oxidative addition reaction to give the S_N2' σ-allyl complex (*syn*-γ-**8**). Reductive elimination converts the latter to the syn γ-alkylation product.

The complex (**10**) involved in the proposed cyclic process may be an intermediate in step 4 of the Murahashi procedure as shown in eq 4. In this case there are two routes



(4)

for conversion of **10** to product. One involves direct internal oxidative addition which leads to syn γ-alkylation (eq 3) and the other, dissociation to **1** and **2** followed by intermolecular oxidative addition which leads to anti alkylation with partial loss of regiochemistry (Scheme V).

According to this interpretation the cyclic intramolecular process is limited to acyclic systems. The reason may be that the conformation of **10** required for the cyclic process is strained in cyclic systems because of restricted rotation

(8) Goering, H. L.; Tseng, C. C. *J. Org. Chem.* **1983**, *48*, 3986.
(9) Kreft, A. *Tetrahedron Lett.* **1977**, 1035.
(10) Claesson, A.; Olsson, L.-I. *J. Chem. Soc., Chem. Commun.* **1978**, 621. Trost, B. M.; Klun, T. P. *J. Org. Chem.* **1980**, *45*, 4256.
(11) Organocopper species are shown as monomeric for simplicity. The extent and nature of aggregation of these species are not known.
(12) Goering, H. L.; Kantner, S. S. *J. Org. Chem.* **1983**, *48*, 721.

of the C_α–C_β bond. Put another way, in cyclic systems the intramolecular oxidative addition becomes a strained bicyclic process. The results for alkylation of 3-OH with MeLi (~55% syn and 45% anti γ-alkylation) indicate that both routes are involved in this case.

There is a discrepancy in our mechanistic proposals that evidently results from oversimplification.[11] Both intramolecular (eq 3) and intermolecular oxidative additions (Scheme V) are thought to give S_N2' (σ-allyl)copper(III) complexes exclusively. However, the intermediates derived by the two routes show different behavior and clearly differ in some unknown way. The complex involved in the cyclic process gives γ-alkylation product only.[5] In this case there is no evidence for isomerization to the (π-allyl)copper(III) complex (9). On the other hand, when the σ-allyl complex results from the intermolecular route, reductive elimination is accompanied by varying amounts (depending on the type of nontransferred ligand[1,3,8]) of isomerization to the π-allyl complex, which results in loss of regiochemistry. The difference in the σ-allyl complexes may be a matter of differences in aggregation or configuration of square-planar copper(III) complexes.

Experimental Section

Materials. (*S*)-(−)-α-Methyl-γ-phenylallyl alcohol (3-OH),[5] mp 57–59 °C, $[\alpha]^{30}_D$ −30.9° (*c* 5.2, $CHCl_3$) (88% ee), and (*N*-methyl-*N*-phenylamino)tri-*n*-butylphosphonium iodide[3] were prepared as reported earlier. Cuprous iodide was purified and solutions of methyllithium in ether and *n*-butyllithium in hexane were standardized by methods that have been described.[6] Authentic samples of alkylation products in Schemes II and IV and GC and spectral properties of these were available from an earlier study.[6]

Alkylation of (*S*)-(−)-3-OH with *n*-Butyllithium. In the experiment outlined in Scheme II, a stirred solution of 580 mg (3.9 mmol) of the above (*S*)-(−)-3-OH in 10 mL of dry THF at −40 °C was treated with 3.9 mmol of *n*-BuLi in 2.36 mL of hexane. The resulting lithium alkoxide solution was chilled to −78 °C and added (cannula) to a suspension of 746 mg (3.9 mmol) of CuI in 10 mL of dry THF which in turn was prepared in a nitrogen-flushed 100-mL flask equipped with a stirrer and septum. The mixture was stirred for 2.5 h at ca. −20 °C, the resulting homogeneous yellow solution was chilled to −78 °C, and 3.9 mmol of *n*-BuLi in hexane was added (this is step 3 in eq 1). After 10 min, 1.70 g (3.9 mmol) of (*N*-methyl-*N*-phenylamino)tributylphosphonium iodide in 16 mL of dry DMF was added. The resulting brown solution was stirred for 2.5 h at −20 °C and 3 h at room temperature after which the reaction was quenched with 20 mL of saturated aqueous NH_4Cl. The organic layer was separated and the remainder was extracted with ether. The extracts were combined, dried ($MgSO_4$), and concentrated by fractional distillation (Vigreux column). Vacuum distillation of the residue gave 0.57 g (78%) of clear colorless oil, bp 80–83 °C (1.4 mm). The composition of this product was determined by capillary GC (94 ft, UCON LB 550X, 130 °C and 299 ft, QF-1, 130 °C),[6] and components were identified by comparison of retention times with those for authentic samples.[6]

Diimide reduction of 0.50 g of the above product[5] gave 0.48 g (95%) of a colorless oil, bp 68–70 °C (1.5 mm). Spectral properties and capillary GC showed this to be mainly 4-phenyloctane (5). Purification by preparative GC (10 ft × $^3/_8$ in., 30% UCON on Chromosorb P, 130 °C) gave a pure sample of 5 that had the same IR and NMR spectral properties and GC retention time as those for an authentic sample of *dl*-5.[5] This sample of 5 had $[\alpha]^{25}_D$ −2.05° (*c* 5.91, *n*-hexane), which corresponds to 24% ee.[5]

Alkylation of (*S*)-(−)-3-OH with Methyllithium. The procedure for the experiment outlined in Scheme IV was the same as that above except that *n*-BuLi was replaced by MeLi in step 3. The alkylation product, bp 67–69 °C (8.8 mm), was isolated in 63% yield. The composition was determined by capillary GC (94 ft, UCON LB 550X, 80 °C and 196 ft, UCON LB 550X, 80 °C), and components were identified by comparison of retention times with those for authentic samples.[6]

Diimide reduction[5] of 0.27 g of the above product gave 0.23 g (84%) of 2-phenylpentane (7) contaminated with ~3% 3-methyl-1-phenylbutane. Purification by preparative GC (10 ft × $^3/_8$ in., 30% UCON on Chromosorb P, 65 °C) gave a homogeneous sample of 7 that had the same spectral properties (IR, NMR) and retention time as those for an authentic sample of *dl*-7.[5] This sample had $[\alpha]^{20}_D$ 0.49° (*c* 3.51, *n*-hexane), which corresponds to 2.5% ee[5].

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A Synthesis of 2-Fluoro-2-alkenes[1]

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A three-step method for the synthesis of 2-fluoro-2-alkenes from the parent methyl ketones has been developed. The yields of the sequence are fair, and no contamination of the products by the isomeric 2-fluoro-1-alkenes can be detected.

The reactivity of vinylic fluorides is a relatively unexplored area in organic synthesis. It has been clearly recognized that the substitution of a fluorine atom for a hydrogen atom can dramatically affect the physiological fate of biologically active molecules.[3] However, there has been limited exploration of the synthetic utility of selectively fluorinated molecules. Recent reports have shown vinylic fluorides to be highly regioselective in their reactions with electrophiles.[4–7] In particular, vinylic fluorides are more

(1) In memory of Professor Guido H. Daub, University of New Mexico, 1920–1984.
(2) Camille and Henry Dreyfus Teacher-Scholar, 1982–1987.
(3) Schlosser, M. *Tetrahedron* **1978**, *34*, 3 and references cited therein.
(4) Peterson, P. E.; Bopp, R. J. *J. Am. Chem. Soc.* **1967**, *89*, 1284.

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