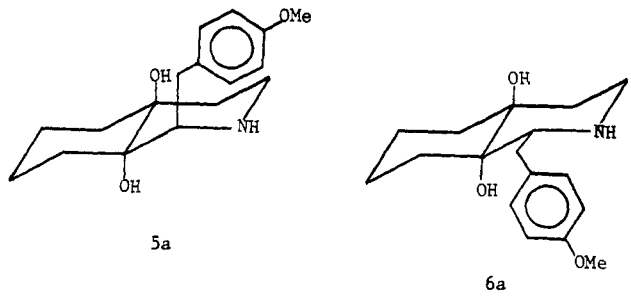

Figure 1.

showed that these compounds exist in the conformations shown in Figure 1. The stereochemistry of epoxides was deduced from the expected exclusive or preferential C-10 opening by analogy to previous results in the *N*-methyl series (**3e, 4e**) by Onda et al.[6] and in the *N*-methyloctahydroisoquinoline series by Grob and Wohl.[9]

Clearly, for the practical synthesis of 14-hydroxymorphinans a stereoselective C-9 opening of a suitable cis epoxide **4** to a diol **5** and an efficient cyclization of **5** to **7** were essential. The first indication that the cyclization step may be improved was obtained in the reaction of borane complex of **5a** with phosphoric acid. This reaction was cleaner (no destruction of starting material was observed), the reaction time was shorter (4–5 h), and the yield of **7a** was higher (14–16%). Finally, yields in both the epoxide opening and the diol cyclization were further dramatically improved with the introduction of various other substituents on the nitrogen atom as illustrated below for the synthesis of butorphanol.

Acylation of **2a** by a standard procedure readily afforded the amide **2c** (mp 89–91 °C). Epoxidation of **2c** with *m*-chloroperbenzoic acid gave a 1:4 mixture of **3c** (mp 118–120 °C) and **4c** (mp 77–78 °C), which was separable by column chromatography. Acid-catalyzed opening of **3c** gave stereoselectively the product of C-10 opening, the trans diol **5c** (mp 148–150 °C). The same diol was the major product of the reaction of the cis epoxide **4c** indicating a stereoselective opening at C-9. The ratio of **5c** to **6c** (mp 90–92 °C) was 7:3. When the mixture of epoxides (**3c** and **4c**) in 2-butanone was treated with 64% sulfuric acid for 16 h, followed by addition of water, removal of organic solvent by distillation, and heating of the aqueous phase under reflux for 1 h, the trans diol **5c** crystallized upon cooling in 75% overall yield from **2a.** Reduction of **5c** with $LiAlH_4$ gave **5d** (92%, mp 120–122 °C). Treatment of a solution of **5d** in THF with slight excess of BH_3–THF, followed by concentration and treatment of the residual solid borane complex with 15 parts of anhydrous phosphoric acid at 40–45 °C for 16 h gave, after workup, **7d,** in 65–70% yield. Demethylation of **7d** to **1a** has been described earlier.[2]

This synthesis was successfully repeated with optically active **2a,**[10] giving the optically active **7d,** thus eliminating costly last-step resolution in the original synthesis.[2]

The use of amine–borane complex in Friedel–Crafts-type cyclization, to the best of our knowledge, has not been previously recorded, although its use as a protective group in intermolecular oxidative phenol coupling[11] and transformation of proerythrinodienone to aporphine[12] has been described recently.

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Ivo Monković,* Carol Bachand, Henry Wong
Bristol Laboratories of Canada
Candiac, Quebec, Canada J5R 1J1
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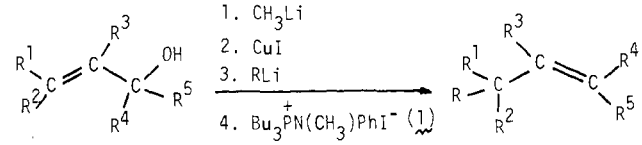
Regio- and Stereoselective γ Substitution of Allylic Alcohols with Alkyllithium Compounds by Using *N,N*-Methylphenylaminotributylphosphonium Iodide. Anti Stereochemistry of S_N2' Reaction[1]

Sir:

The carbon–carbon bond formation by direct substitution of a hydroxyl group of allylic alcohols with a carbon moiety is one of the most attractive pathways for synthesis of olefinic compounds, since allylic alcohols are often naturally occurring key intermediates[2] and many highly selective, potentially useful methods for synthesis of allylic alcohols have recently been explored.[3]

Previously, we reported that the regioselective synthesis of olefins by coupling of allylic alcohols with organolithium compounds using *N,N*-methylphenylaminotriphenylphosphonium iodide.[4] We now wish to report that the selective γ-alkylation of allylic alcohols with organolithium compounds in conjunction with *N,N*-methylphenylaminotributylphosphonium iodide (**1**) proceeds as depicted in eq 1. The alkylation provides an efficient single-step process for regio- and stereoselective synthesis of olefins from allylic alcohols. It is expected that the process will find widespread use and that in many instances it will be found superior to current procedures.[5-7]



(1)

Reagent **1** is easily prepared by the addition of the equivalent of phenyl azide to tributylphosphine in ether at reflux, followed by treatment with excess methyl iodide at reflux in 90% yield, mp 120–120.5 °C (recrystallized from ethyl acetate). The following procedure for the preparation of *trans*-5-undecene is representative of the alkylation. To a suspension of cuprous iodide (1.90 g, 10 mmol) in dry THF (20 mL) was added a solution of the lithium allyloxide, prepared in a separate flask from 1-hepten-3-ol (1.14 g, 10 mmol) and ethereal methyllithium (1.23 M, 8.2 mL) at 0 °C, with stirring at room temperature. After additional stirring for 30 min, the resulting green-brown solution was cooled to −78 °C, and then a solution of butyllithium in hexane (1.34 M, 7.4 ml) was added over a 5-min period. Subsequently, to the resulting brown suspension a solution of **1** (4.35 g, 10 mmol) in dry DMF (40 mL) was added at the same temperature, and the reaction mixture was allowed to warm to room temperature. The brown suspension became a homogeneous solution. After additional stirring for 3 h, ether and an aqueous saturated NH_4Cl solution were added to the reaction mixture (at 0 °C), which was then fil-

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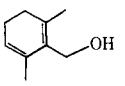
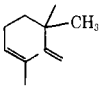
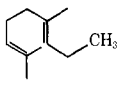
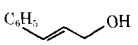
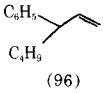
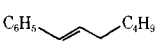
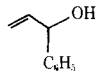
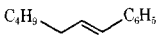
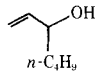
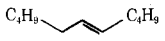
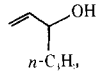
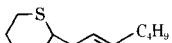
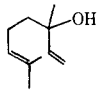
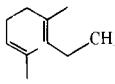
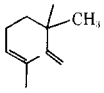
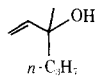
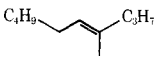
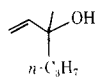
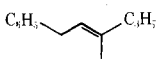
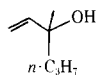
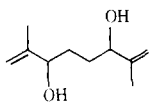
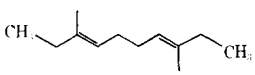
Table I. Alkylation and Arylation of Allylic Alcohols[a]

Entry	Substrate	Organolithium compounds[b]	Product[c] (relative ratio, %[d]) γ products	Product[c] (relative ratio, %[d]) α products	Stereochemistry,[d] *Z/E*	Bp, °C (mmHg)	Isold yield, %[e]
1		CH_3Li	 (82)	 (18)	0/100	88–90 (60)	75
2		*n*-C_4H_9Li	 (96)	 (4)	0/100	95–100 (15)	73
3		*n*-C_4H_9Li	 (100)		9/91	105–107 (5)	97
4		*n*-C_4H_9Li	 (100)		0/100	84–85 (45)	90
5			 (100)		0/100		56[f]
6		CH_3Li	 (92)	 (8)	36/64	126–128 (70)	80
7		*n*-C_4H_9Li	 (100)		32/68	52–55 (25)	39 (80)[g]
8		C_6H_5Li	 (100)		32/68		60[f,i]
9			 (100)		32/68		65[f]
10		CH_3Li	 (100)		36/64[h]	63–65 (20)	70

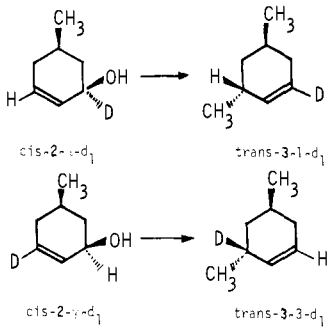
[a] Alkylation was carried out under the same reaction condition as described about a representative case. (THF–ether–DMF, −78 °C to room temperature, 2 h). [b] 1 molar equiv of organolithium was used. [c] All products exhibited satisfactory spectral and analytical data. [d] Determined by GLC. [e] Isolated yield by reduced distillation unless otherwise indicated. [f] By preparative TLC (silica gel). [g] GLC yield using dibenzyl ether as an internal standard. [i] Biphenyl was obtained. [h] *ZE/EE*.

tered and washed with 0.2 N HCl solution, and the ether extract was dried over anhydrous magnesium sulfate. Removal of the solvent and distillation gave 5-undecene (1.39 g, 90%), bp 84–85 °C (45 mmHg). The VPC analysis showed that 5-undecene consisted of over 99.5% trans isomer.

An examination of Table I indicates the full scope of this reaction. Excellent yields are obtained from primary, secondary, and tertiary allylic alcohols. Importantly, 1-substituted prop-2-en-1-ols, which are readily available, can be converted into *trans*-1,2-disubstituted olefins in a regio- and stereospecific manner (entries 3–5). Moreover, the alkylation of tertiary allylic alcohols occurs with predominant allylic rearrangement, giving trisubstituted olefins (entries 6–9). The stereochemistry of this alkylation to a trisubstituted olefin may be worth noting. The cis/trans ratios of the olefins obtained are dependent neither upon the substituent of the tertiary allylic alcohols nor on the organolithium compounds, giving constant values of 32–36/68–64. 1,5-Dienes are readily prepared regioselectively upon treatment of octa-1,7-diene-3,6-diol[6b] with 2 equiv of alkyllithium compounds (entry 10). The wide diversity of organolithium compounds evidently enhances the synthetic utility of the reaction. For instance, the reaction with an equivalent of 2-lithio-1,3-dithiane (entries 5 and 9) gave valuable intermediates of *trans*-allyl-1,3-dithiane.

Next, we examined the stereochemistry of the γ-alkylation of alcohols. The bimolecular nucleophilic substitution with allylic rearrangement (S_N2') has been of interest from the standpoints of both mechanistic considerations[9] and potential utility for organic synthesis;[10] however, definitive experimental investigations of the stereochemistry are limited to a few cases.[10-12] We chose the Goering system[5b] of using a mixture of *cis*- and *trans*-5-methyl-2-cyclohexen-1-ols (**2**) as the substrate for the alkylation. The methylation with methyllithium gives 1,3-dimethylcyclohexene (**3**) selectively with inversion of configuration in 88% yield. Thus, from the mixture of *cis*-**2** (92%) and *trans*-**2** (8%) was obtained the mixture of *trans*-**3** (87%) and *cis*-**3** (13%). The conversion of **2**-α- and -γ-*d* to **3** was investigated to determine the amount of allylic rearrangement in this unbiased system. *cis*-**2**-α- and -γ-*d* were prepared by the $LiAlH_4$–$LiAlD_4$ and $LiAlD_4$–$LiAlH_4$ reductions of 3-ethoxy-5-methyl-2-cyclohexenone according to Goering's method.[5b,13] A mixture of *cis*-**2**-α-d_1 (92%) and *trans*-**2**-α-d_1 (8%), both of which contain d_1 in over 98% yield, gave a mixture of *trans*-**3** (87%) and *cis*-**3** (13%). Total deuterium contents were determined from mass spectra.[14] The NMR (100 MHz) showed that *trans*-**3** consisted of *trans*-**3**-

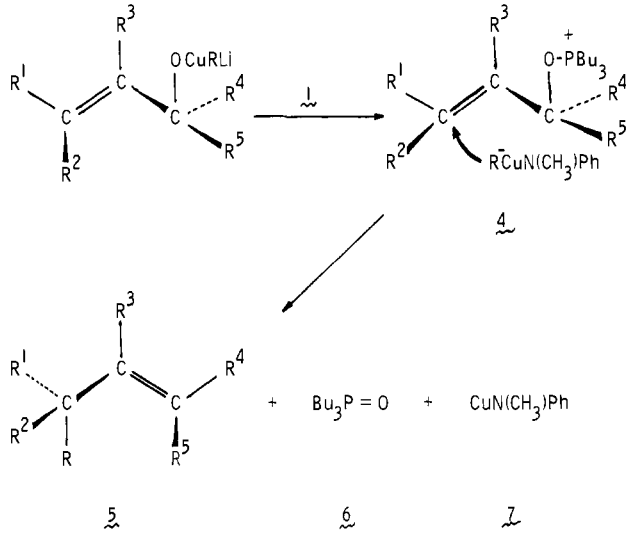
1-d_1 (92%) and *trans*-**3**-*3*-d_1 (8%), while *cis*-**3** consisted of *cis*-**3**-*1*-d_1 (92%) and *cis*-**3**-*3*-d_1 (8%). These results clearly show that the transformation from **2** to **3** proceeds predominantly via an S_N2'-type reaction. It is assumed that *trans*-**3**-*3*-d_1 was formed from *cis*-**2**-α-d_1 via an S_N2 reaction; calculations show that the transformation of **2** to **3** consisted of 86% anti S_N2' and 6% syn S_N2' reactions. Similar methylation



of a mixture of *cis*-**2**-γ-d_1 (92%) and *trans*-**2**-γ-d_1 (8%) gave **3** which consisted of *trans*-**3**-*3*-d_1 (82%), *trans*-**3**-*1*-d_1 (4%), *cis*-**3**-*1*-d_1 (1%), and *cis*-**3**-*3*-d_1 (13%). These results also show that the reactions proceed as follows: 88% anti S_N2', 7% syn S_N2', and 5% S_N2. Although this system is unbiased with regard to substitution with and without allylic rearrangement, the methylation proceeds with 92% allylic rearrangement (S_N2') in contrast to the nonselective conversion (with and without rearrangement, 50:50) of the acetates of **2** to **3** with lithium dimethylcuprate.[5b] The predominant anti stereochemistry of the S_N2' reaction (94% anti) may be due to an inconspicuous steric bias, unique to the cyclohexyl system.[5b,15,16]

The course of the reaction can be rationalized by assuming that the nucleophilic attack of R, from the counterion derived from the aminocuprate, at the γ carbon of allyloxy group of the intermediate **4** gives olefin **5** along with tributylphosphine oxide (**6**) and *N*,*N*-methylphenylaminocopper (**7**) as shown in Scheme I.

Scheme I



Work is currently in progress on the extention of this reaction to other systems and application to the synthesis of natural products.

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Yoshio Tanigawa, Hiroyuki Ohta
Akio Sonoda, Shun-Ichi Murahashi*
Department of Chemistry
Faculty of Engineering Science, Osaka University
Machikaneyama, Toyonaka, Osaka, Japan, 560
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Electron Spin Resonance Studies of Sulfur-Based Donor Heterocycles: ^{33}S Couplings

Sir:

Although the theory of low dimensional solids[1,2] has led to a qualitative understanding of the electronic and magnetic solid-state properties of highly conducting organic donor and

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