located in the equatorial plane.[9] This, along with the probable slightly greater apicophilicity of the primary OC5′ group over that of the secondary OC3′ substituent,[11] imparts the *thermodynamic* stability to the O5′ apical structure which results in its being lower in energy than its O3′ apical counterpart. This difference is depicted in Scheme I (structures **8T** and **9T**).

On the other hand **9T** should be *kinetically* more labile towards scission of the apical O–P bond than **8T**, because the p orbital electron pair on O5′ in **9T** is lined up parallel to the apical bonding system to assist *stereoelectronically*[10] with the scission of the O3′–P bond to give 5′-AMP. In this view **9T** would immediately give 5′-AMP, and pseudorotation to form **8T** would not occur (see the scheme). The predominance of 3′-AMP then most likely results from the kinetically as well as thermodynamically more favored formation of 5′O apical **8T**, generated concertedly on attack by HO^- or immediately from kinetically favored chair form **8**, **8C** (5′O apical).[12] In that case, and if **8T** decays rapidly to 3′-AMP, the difference of activation energy for the two pathways ($\Delta\Delta G^{\ddagger}$) is 0.8 kcal/mol. Indeed, since **8T** and especially **9T** are both set up for apical departure of good leaving groups, there is no reason to think that they should be rapidly equilibrated prior to scission (Hammett–Curtin-based product distribution). Nonetheless, it is conceivable that some of the 5′-AMP results from conversion of **8T** to **9T** in competition with scission of **9T** to 5-AMP. In that instance the selectivity for **8** vs **9** formation would be greater than 0.8 kcal/mol.

These ideas are at variance with those expressed recently[13] concerning the relative amounts of P–O3′ and P–O5′ scission on hydrolysis of cyclic 3′,5′-phosphoramidate ($P(O)NMe_2$) derivatives of cAMP and its 5′-Me-substituted analogues. Those studies, however, certainly appear to show the sensitivity of product distribution to small changes in stabilities of intermediates.

Acknowledgment. Support of this research by Grant R01 CA11045 from the NCI of the PHS is gratefully acknowledged.

Supplementary Material Available: Preparation of **5** and tables for the X-ray structure of **5** of crystal data, positional parameters, bond lengths, bond distances, torsional angles, and thermal parameters (19 pages); listing of structure factors (10 pages). Ordering information given on any current masthead page.

(9) Hoffmann, R.; Howell, J. M.; Muetterties, E. L. *J. Am. Chem. Soc.* **1972**, *94*, 3047.
(10) For an extensive converage of such ideas see Gorenstein, D. G. *Chem. Rev.* **1987**, *87*, 1047. Transition-state effects are normally greater than ground-state effects.
(11) Trippett, S. *Phosphorus Sulfur* **1976**, *1*, 89.
(12) Although **8C** does not benefit energetically from the placement of the O3′ lone pair equatorial, it nonetheless has the primary, presumably more apicophilic, O5′–C bond apical.
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Enantioselective Wittig–Horner Reaction in the Solid State

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Summary: Wittig–Horner reactions in the solid state of the inclusion compound of 4-methyl- or 3,5-dimethylcyclohexanone and an optically active host compound with (carbethoxymethylene)triphenylphosphorane gave optically active 4-methyl- and 3,5-dimethyl-1-carbethoxymethylene)cyclohexane, respectively.

We have previously presented very efficient enantioselective photoreactions of prochiral compounds in inclusion complexes with optically active host compounds in the solid state.[1] We recently also reported that usual organic reactions such as pinacol rearrangement,[2] Baeyer–Villiger oxidation,[3] $NaBH_4$ reduction,[4] and $FeCl_3$-assisted phenol coupling[5] occur efficiently in the solid state and that even enantioselective reactions occur in the solid state when the reactant is complexed with an optically active host.

For example, treatment of the inclusion compound of ketones and (−)-*trans*-2,3-bis(hydroxydiphenylmethyl)-1,4-dioxaspiro[4.4]nonane (**1b**),[6] (−)-1,6-bis(*o*-chlorophenyl)-1,6-diphenylhexa-2,4-diyne-1,6-diol (**2**),[6] or β-cyclodextrin[7] with a borane–ethylenediamine complex or $NaBH_4$ in the solid state gave optically active alcohols of up to 59% ee. These reactions involve enantioselective hydride attack. We have further found that the Wittig–Horner reagent **3** also attacks prochiral ketones enantioselectively when the substrates are included in an optically active host, giving optically active olefins.

For example, when a mixture of finely powdered 1:1 inclusion compound of **1b** and 4-methylcyclohexanone (**4a**) (1.5 g) and (carbethoxymethyl)triphenylphosphorane (**3**) (2.59 g) was kept at 70 °C, the Wittig–Horner reaction was completed within 4 h. To the reaction mixture was added ether–petroleum (1:1), and the precipitated solid (triphenylphosphine oxide and excess **3**) was removed by filtration. The crude product left after evaporation of the solvent of the filtrate was distilled in vacuo to give (−)-4-methyl-1-(carbethoxymethylene)cyclohexane (**5a**) of 42.3% ee in 73.0% yield (Table I). The optical purity of **5a** was determined by measuring the ^1H NMR spectrum in the presence of the chiral shift reagent, tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III).[8]

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(8) $En(hfc)_3$ (99+%) is available from Aldrich Co. Ltd., Milwaukee, WI. The methylene proton signal of the carbethoxy group of **5a** and its (+)-enantiomer appeared at δ 5.24 and 5.28 ppm in $CDCl_3$, respectively, in the presence of 0.1 molar equiv of $Eu(hfc)_3$.

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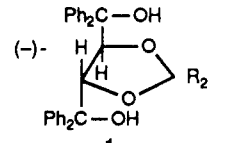
Table I. Enantioselective Wittig Reactions of Cyclohexanone Derivatives (4-6) in the 1:1 Inclusion Complex with Optically Active Hosts (1, 2)

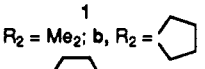
host	ketone	reaction conditions		product		
		reaction temp, °C	reaction temp, h		yield, %	optical purity,[a] % ee
1a	4a	70	4	5a	50.8	42.8
1b	4a	70	4	5a	73.0	42.3
1c	4a	80	4	5a	47.5	39.0
2	4a	70	4	5a	30.0	8.6
1b	4b	70	4	5b	72.5	45.2
1c	4b	80	4	5b	58.0	44.4
1c	6	80	2	7	58.0	56.9
2	6	80	8	7	28.1	5.5

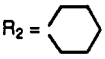
[a] All optical purities were determined by ^{1}H NMR analysis in $CDCl_3$ by using the chiral shift reagent, tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III), Eu(hfc)$_3$.[8]

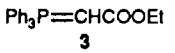
The absolute configuration of **5a** was determined to be *R*, because its hydrolysis gave the (*R*)-carboxylic acid derivative.[9]



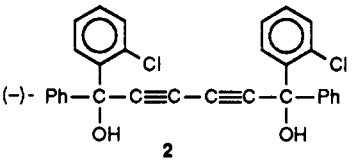
1

a, $R_2 = Me_2$; b, R_2 = 

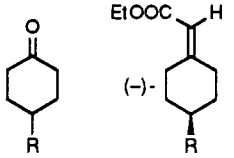
c, R_2 = 



3

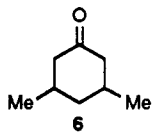


2

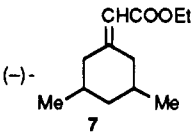


4 5

a, R = Me; b, R = Et



6



7

Although the host (−)-*trans*-3,5-bis(hydroxydiphenylmethyl)-2,2-dimethyl-1,3-dioxacyclopentane (**1a**)[10] and (−)-*trans*-2,3-bis(hydroxydiphenylmethyl)-1,4-dioxaspiro[5.4]decane (**1c**)[11] are also effective for the enantioselective Wittig–Horner reaction of **4a**, **2** is not effective (Table I). The enantioselective reaction is also applicable to 3-ethylcyclohexanone (**4a**) and 3,5-dimethylcyclohexanone (**6**), and (−)-4-ethyl-1-(carbethoxymethylene)cyclohexane (**5b**) and (−)-3,5-dimethyl-1-carbethoxymethylene)cyclohexane (**7**) were obtained, respectively (Table I). The optical purity of **5b** and **7** was also determined by measuring ^{1}H NMR spectra in the presence of Eu(hfc)$_3$.[12] The absolute configuration of **5b** was also determined to be *R*, but that of **7** was not determined. In the reactions of **4b** and **6**, **2** is again not effective (Table I). The enantioselectivity of the Wittig–Horner reaction is not very high; however, it may be valuable because the procedure is very simple.

To the best of our knowledge, only three enantioselective variants of the Wittig reaction have been reported. Tomoskoz and Janzso have reported that the reaction of **4a** with a Wittig reagent bearing an optically active substituent gives optically active 4-methyl-1-methylenecyclohexane of about 50% ee.[13] Bestmann and Lienert have reported that the reaction of **4a** with **3** in the presence of a chiral carboxylic acid gives optically active **5a** of less than 10% ee.[14] Hanessian and his co-workers have reported that the reaction of **4a** and its derivatives with optically active bicyclic phosphonamide reagents gives optically active cyclohexene derivatives of up to 90% ee.[15] In comparison with these precedents, our method using the host–guest inclusion compound is much simpler. Furthermore, our results suggest that the method is applicable to many other organic reactions.

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Palladium-Catalyzed Heteroannulation of 1,3-Dienes by Functionally Substituted Aryl Halides

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Summary: Heteroatom-containing aryl iodides react with 1,3-dienes in the presence of a palladium catalyst and an appropriate base to afford a variety of oxygen and nitrogen heterocycles.

The ability to append a heteroatom-containing unit onto existing functionality (heteroannulation) is one of the most important routes to heterocyclic compounds. Many such palladium-based processes have recently been reported,[1]

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