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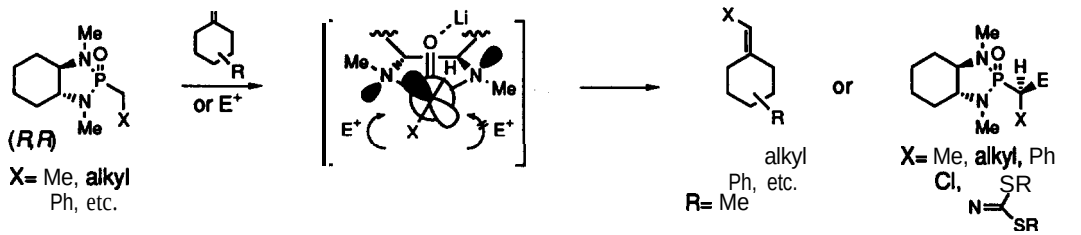
STUDIES IN ASYMMETRIC OLEFINATIONS – THE SYNTHESIS OF ENANTIOMERICALLY PURE ALLYLIDENE, ALKYLIDENE, AND BENZYLIDENE CYCLOHEXANES

Stephen Hanessian* and Serge Beaudoin
Department of Chemistry, Université de Mont&I
P.O. Box 6128, Station A, Montréal, P.Q. CANADA, H3C3J7

Abstract: Treatment of alkyl cyclohexanones with topologically unique bicyclic phosphonamides derived from the C_2 symmetrical (*R,R*)- and (*S,S*)-N,N'-dimethyl1,2-*trans*-cyclohexane diamine leads to enantiomerically pure allylidene and benzylidene alkylcyclohexanes.

The past decade has witnessed a burgeoning activity in the area of asymmetric organic reactions.[1] Today, an increasing number of known bond-forming processes have their "asymmetric" counterparts, usually with impressive levels of enantiomeric or diastereomeric purities. In spite of such developments in the field, the subject of a direct asymmetric olefmation of cycloalkanones has received little attention.2

In 1984. we reported our preliminary results on the design and reactivity3 of anions derived from topologically unique chiral bicyclic phosphonamides of the type shown in Figure 1.4 These showed high stereoselectivity in the ethylidenation (X=Me) of substituted cyclohexanones, and more recently5 in alkylation reactions (X=Me, Ph, alkyl, CI, N=SR$_2$, etc.) to produce enantiomerically pure (or highly enriched) α-substituted-a-alkylphosphonic acids. We now report further studies on the asymmetric olefination



Benzylidene alkyl cyclohexanes - Reaction of 4-methylcyclohexanone 2 with the (R,R)-bicyclic benzylphosphonamide **1** (BuLi, THF, -78°C, 1 h; AcOH quench, –78°C→25°C), led to the corresponding (*aR*)-(4-methylcyclohexane) benzylidene **4**[6] in excellent yield and optimal enantioselectivity (Scheme 1). The facile

isolation of the intermediate β-hydroxyphosphonamide[4a,b] 3 and its structure elucidation by single crystal X-ray analysis[7], allowed a definitive assessment of the optical purity of the product after elimination. It also led to some important insights into the mechanism of the reaction with the following conclusions: a. the disposition of the phosphoryl appendage reflects a preferential "equatorial" attack on the carbonyl group as shown in 3. b. the orientation of the a-phenyl group is the one expected from an attack on the *pro-S* face of the anion by the electrophile as originally predicted from the model[3] (Figure 1). c. the enantiomeric purity of the olefin obtained in one step is essentially identical to that resulting from a two-step sequence (via the β-hydroxyphosphonamide), thus demonstrating the extremely high stereodifferentiation in the olefination reaction.

Scheme 1

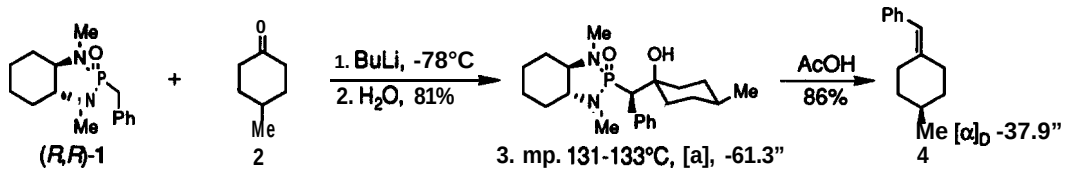
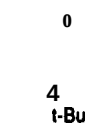
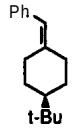
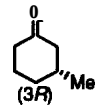
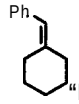
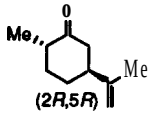
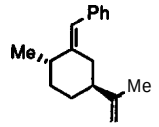
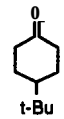
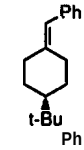
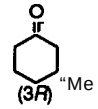
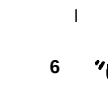
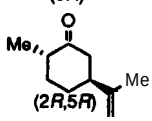
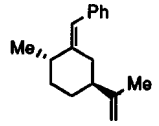


Table 1 lists several examples of asymmetric benzylidenations of various alkyl cyclohexanones with the a-benzylphosphonamide reagents (*R,R*)-**1** and (*S,S*)-**1**.

Table 1

Entry	Ketone	Reagent	Product	Yield*	Ratio	$[\alpha]_D$ (EtOH)[c]
1		(*R,R*)-1		91% (*aR*)	>99:1	-33.3" (c 1.12)
2		(*R,R*)-1		82% (E,3*R*)	98:2[b]	-72.0" (c 1.08)
3		(*R,R*)-1		06% (E,2*R*,5*R*)	99:1[b]	-86.0" (c 1 .10)
4		(*S,S*)-1		89% (*aS*)	99:1	+32.3° (c 1.39)
5		(W - 1	6 	75% (Z,3*R*)	98:2[b]	+30.3° (c 0.98)
6		(*S,S*)-1		66% (E,2*R*,5*R*)	61:39[b]	

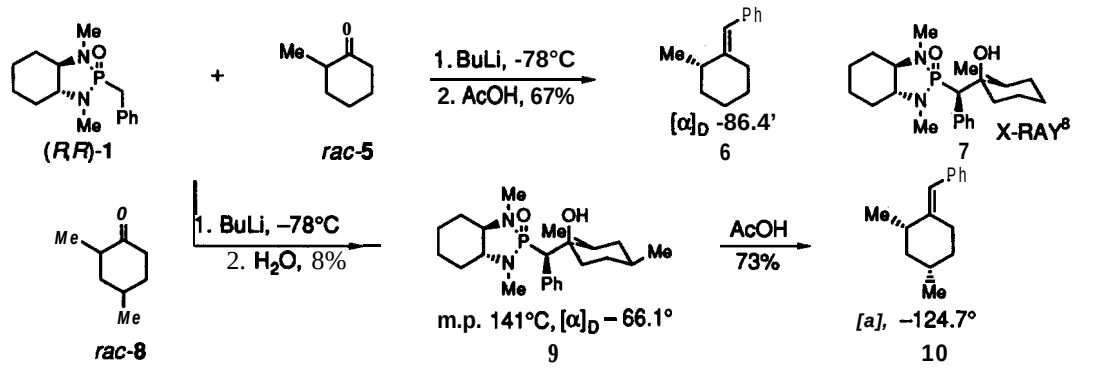
a Isolated yields. **b. Ratios evaluated** by capillary GC; c. Optical rotations measured at 25°C.

The inherent preference for the formation of the (*aR*)- and (*aS*)-benzylidene alkyl cyclohexanes from the (*R,R*)-and (*S,S*)-reagents respectively is evident, as predicted by the model[3] (entries l-5). A deviation can be

seen in entry 6, where the proportion of the Z-olefinic product expected from the **(*S*,*S*)-reagent** is greatly diminished due to an unfavorable ***syn*-interaction** hetween the phenyl and **2-methyl** groups.

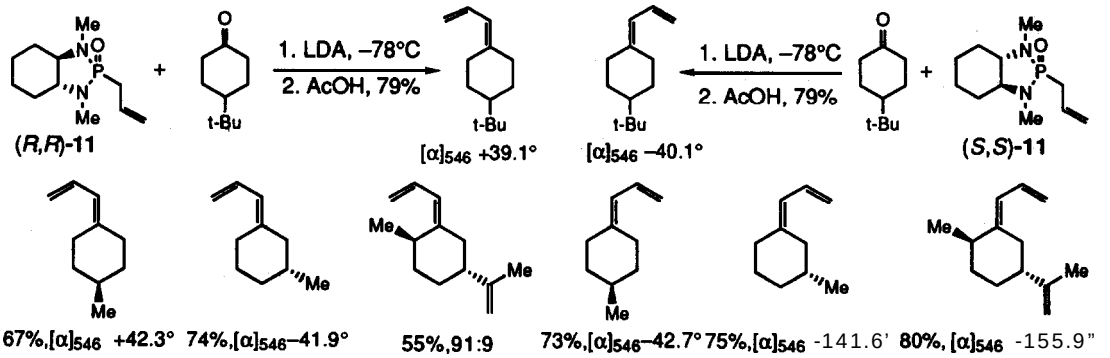
Kinetic Resolution - Based on the proposed model in Figure 1 and the result in entry **6,** it was of interest to attempt asymmetric benzylidenations with **appropriate** alkyl cyclohexanones, where **stereodifferentiation** could be maximized in the transition state, thus allowing a kinetic resolution. Treatment of **(*d*,*l*)-2-methylcyclohexanone** 5 **(1** mmole) with the anion of **1 (0.5** mmole, **-78°C,** THF, 1 **h; AcOH,** -78°C) gave **(*E*,2*S*)-(2-methylcyclohexane)** benzylidene 6. and the Z-isomer **(>98:2,** cap. GC, 63% based on the reagent) (Scheme 2). The enantiomeric (&X)-derivative was obtained in 67% yield, **$[\alpha]_D$ +83.9°** from the **(*S*,*S*)-reagent.** An identical reaction with **(*d*,*l*)-*cis*-2,4-dimethylcyclohexanone** 8 and the (R&)-reagent (0.5 mmole) gave the **(*E*,2*R*,4*R*)-(2,4-**dimethylcyclohexane) benzylidene via the corresponding Phydroxyphosphonamide 9 in 60% overall yield and **>99%** enantiomeric purity. Benxylidenation of **(*d*,*l*)-2-methylcyclopentanone** with the **(*R*,*R*)** reagent was less efficient, resulting in the formation of the **(2*S*)-** and **(2*R*)-*E*/*Z*-(2-methylcyclopentane)benzylidene (80:20,** cap. GC, 53%).

Scheme 2



Allylidene and Propylidene Alkyl Cyclohexanes - Elegant studies by Walborsky and coworkers9 have led to the synthesis of isomers of enantiomerically pure (and enriched) allylidene alkyl cyclohexanes via the intermediacy of alkylidene carboxylic acids[10] which were resolved and further manipulated. We now show that the treatment of alkyl cyclohexanones with the **(*R*,*R*)** and **(*S*,*S*)-bicyclic** allylphosphonamide reagents

Scheme 3



11 give, respectively, the corresponding enantiomerically pure allylidene alkyl cyclohexanes in one step.11 Scheme 3 lists a number of relevant examples where this trend is consistently observed, even in the case of 2-substituted cyclohexanone (compare Table 1, entry 6).

A structural and stereochemical correlation with allylic alcohols obtained from the previously reported route[9] was possible with the dienes resulting from 4-methyl and 3-methyl cyclohexanone via selective hydroxylation of the terminal double bond followed by oxidative cleavage with periodate and reduction to the allylic alcohol.

It is of interest that with one exception, all the examples shown in Scheme 3 involved attack at the a-position of the allylic anion[4a] to account for the major product. In the case of bulky ketones such as dihydrocarvone, the diene (55%. 91:9) was accompanied by another product resulting from attack of the γ-position on the carbonyl group (39%).

Asymmetric propylidenation of 4-*t*-butylcyclohexanone was best achieved using the N,N'-dibenzyl reagent corresponding to 1 (BuLi, THF, -78°C, then H_2O at -78°C). The crude β-hydroxyphosphonamide was shown by ^{31}P NMR to have a de of >84%. Recrystallization from hexane afforded a single isomer, mp. 148°C, $[\alpha]_D$ -10.0' (c, 1.03, $CHCl_3$).[12]

Acknowledgments.

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12. Unless otherwise mentioned, optical rotations were measured at a concentration of 1.0. All products showed the expected analytical and spectroscopic characteristics.

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