

Kinetic Resolution of α -Substituted Ketones by Wittig Reaction using a Chiral Tricyclic Phosphonate

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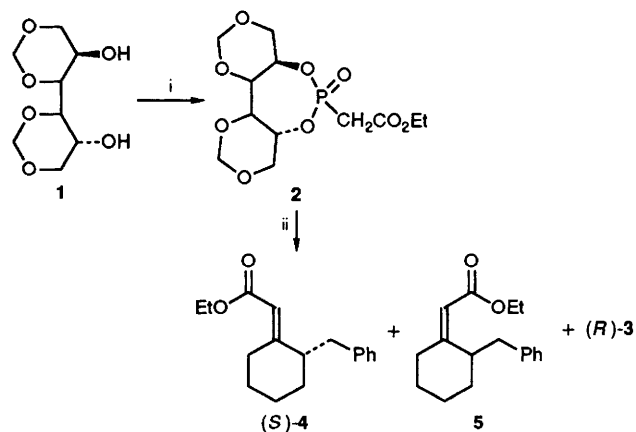
Wittig reactions of α -substituted ketones using a chiral phosphonate derived from mannitol afford chiral olefins by kinetic resolution.

The Wittig reaction is one of the most important methods for olefin formation. Nevertheless little effort has been expended for the development of asymmetric Wittig olefination, although phosphorus-stabilized benzylic carbanions can be stereoselectively alkylated.¹ Hanessian *et al.* have reported the only notable result in which axially dissymmetric (alkylcyclohexylidene)ethanes were produced with up to 90% optical purity from cyclohexanone derivatives and a chiral bicyclic phosphonamide.² Kinetic resolution of racemic compounds is one possible method to obtain chiral products albeit yields cannot exceed 50%. If the resolution proceeds along with racemization of the substrate, then more than half of the starting material can be converted into the desired enantiomer.³

In this paper we report on the kinetic resolution of racemic α -substituted carbonyl compounds by Wittig reaction between α -substituted ketones and a chiral cyclic phosphonate prepared from mannitol.

Natural D-mannitol was converted into the C_2 -axis symmetrical dimethylene acetal **1** by transacetalization of dimethoxymethane.^{4,5} Chiral tricyclic phosphonate **2** was prepared from ethyl (dichlorophosphoryl)acetate and chiral diol **1**. We first examined the reaction between racemic α -benzylcyclohexanone **3** and the chiral phosphonate **2** that led to chiral olefins **4** and **5** along with recovered **3** (Scheme 1).

Analysis of their respective ¹H NMR NOESY spectra revealed the geometry of **4** and **5**. The absolute configuration of **4** was determined as (*S*) by comparison of the optical rotation of ketone **3**, which was obtained by ozonolysis of the chiral olefin, to the literature value of the pure (*R*)-enantiomer.⁶



Scheme 1 Reagents: i, $\text{Cl}_2\text{P}(\text{O})\text{CH}_2\text{CO}_2\text{Et}$, 5 equiv. NEt_3 , cat. DMAP, CH_2Cl_2 ; ii, $\text{PhCH}_2\text{CHC}(\text{O})[\text{CH}_2]_3\text{CH}_2$ (\pm)-**3**, base

Table 1 The effect of base, solvent and additive on enantioselectivity

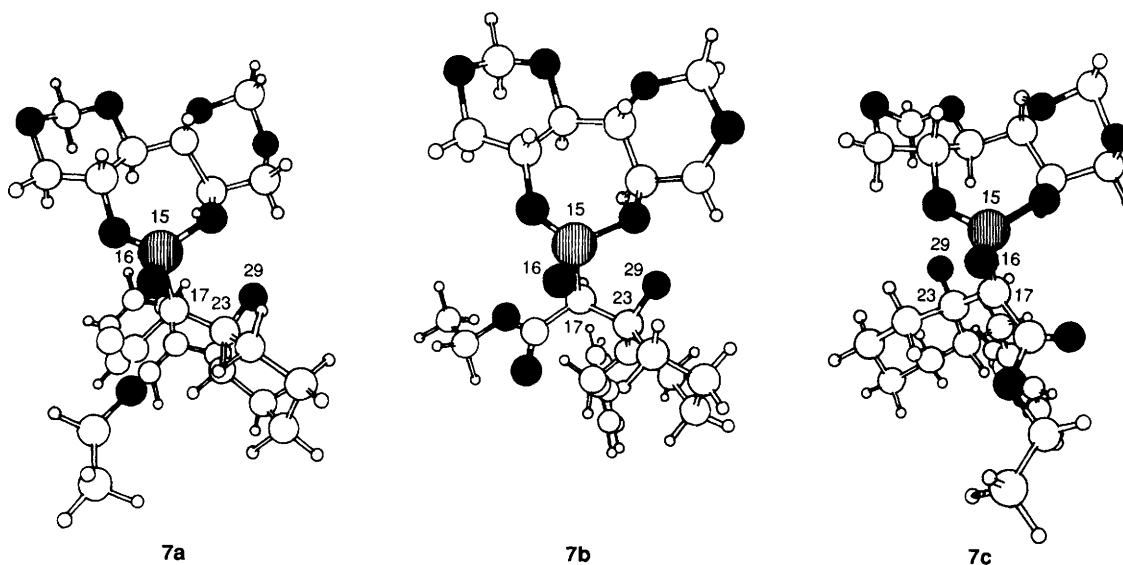
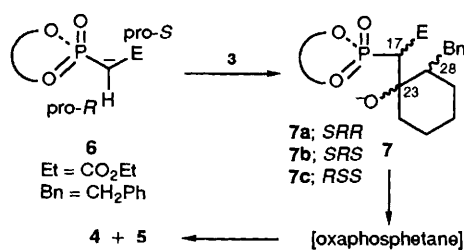
| Entry | Base ^a | Solvent ^b | Additive | T/°C ^a | t/h | Yield (%) (Optical purity % e.e.) | | |
|-------|--------------------|----------------------|-----------------------------|-------------------|---------|-----------------------------------|----|---------|
| | | | | | | 4 | 5 | 3 |
| 1 | KH | THF | None | R.t. | 26 | 9 (64) | 3 | 89 (4) |
| 2 | KH | DME | None | R.t. | 29 | 10 (56) | 2 | 83 (7) |
| 3 | Bu ^t OK | THF | None | 0 | 72 | 14 (51) | 4 | 79 (4) |
| 4 | Bu ^t OK | THF | 1 equiv. HMPA | 0 | 72 | 19 (46) | 5 | 75 (7) |
| 5 | NaH | DMF | None | R.t. | 24 | 26 (57) | 7 | 59 (23) |
| 6 | NaH | DMF | None | R.t. | 39 | 18 (56) | 7 | 53 (9) |
| 7 | LDA | THF | None | 0 | 72 | 37 (40) | 10 | 50 (34) |
| 8 | LDA | THF | 5 equiv. LiClO ₄ | R.t. | 41 | 9 (39) | 2 | 85 (7) |
| 9 | LDA | THF | 1 equiv. HMPA | 0 | 73 | 38 (89) | 7 | 56 (32) |
| 10 | LDA | THF | 1 equiv. HMPA | 0 | 34 days | 56 (81) | 11 | 29 (3) |

^a Molar ratio of ketone : phosphonate : base is 1 : 1.1 : 1.2. ^b DME = 1,2-dimethoxyethane; DMF = dimethylformamide. ^c R.t. = room temp.

Table 2 The effect of molar ratio of reactants^a

| Entry | Molar ratio | | | t/h | Yield (%) (Optical purity % e.e.) | | |
|-------|-------------|-----|------|-----|-----------------------------------|---|---------|
| | 3: | 2: | LDA | | 4 | 5 | 3 |
| 1 | 1.0 | 1.0 | 0.95 | 72 | 28 (76) | 5 | 60 (41) |
| 2 | 1.0 | 1.1 | 1.2 | 73 | 38 (89) | 7 | 56 (32) |
| 3 | 1.0 | 1.1 | 1.7 | 72 | 42 (89) | 7 | 39 (13) |

^a The reactions were carried out at 0 °C in THF-HMPA.

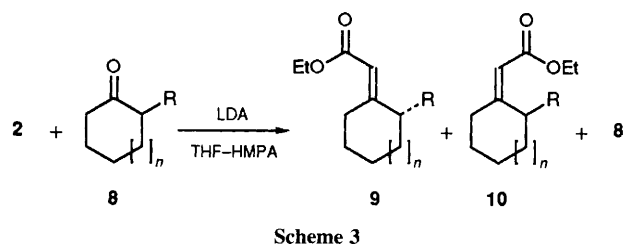
**Fig. 1** Calculated conformations of favoured oxanions 7**Scheme 2** *R* and *S* assignments for 1 refer to the absolute configurations at C17, C23 and C28, respectively

The optical purity of unsaturated ester 4 was measured after conversion to the epoxy alcohol [i, diisobutylaluminium hydride (DIBALH), ii, Bu^tOOH, cat. VO(acac)₂ (Hacac = pentane-2,4-dione)]. Then integration of the OMe signals from the ¹³C NMR spectra of the corresponding diastereoisomeric (+)-MTPA [(+)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid] ester⁷ (peaks at δ 27.03 and 27.13) was directly related to the optical purity.

The effect of bases, solvents and additives on the enantioselectivity was studied in detail, and the results are listed in Table 1. In most cases, the *E* isomer was obtained predominantly, and the highest enantioselectivity [89% enantiomeric

Table 3 Selected conformational features in oxyanion **7**

| | Energy/ Kcal ^a | Distances/Å O(29)–P(15) | Dihedral angles (°) | | | Resulting olefin |
|-----------|------------------------------|----------------------------|-----------------------------|-----------------------------|-----------------------------|------------------------|
| | | | O(16)–P(15)– C(23)–O(29) | O(16)–P(15)– C(17)–C(23) | P(15)–C(17)– C(23)–O(29) | |
| 7a | 92 | 3.44 | –136.6 | –84.7 | –60.7 | (<i>R</i>)- 4 |
| 7b | 103 | 3.28 | –153.1 | –100.0 | –56.9 | (<i>S</i>)- 4 |
| 7c | 95 | 3.35 | 156.4 | 114.8 | 51.9 | (<i>S</i>)- 4 |
| | | Optimal values: ±180 | | ±180 | 0 | |



excess (e.e.), 38% chemical yield] was achieved when the reaction was carried out in tetrahydrofuran (THF) at 0 °C for 73 h using lithium diisopropylamide (LDA) as a base and hexamethylphosphoramide (HMPA) as an additive (entry 9). In this reaction, the optical purity of recovered ketone **3** was 32%.

The yield of the olefinated products (*E* and *Z*) increased to 67% by prolonging the reaction time (to 1 month), with the optical purity of the *E* isomer being 81%. In addition, the recovered ketone **3** was still racemic (entry 10). These results indicate that the kinetic resolution proceeds in high enantioselectivity and with racemization of unconverted **3**.

To racemize the unconverted starting material much faster, we examined the molar ratio of LDA to the chiral phosphonate **2** (Table 2). With 0.95 mol equiv. of LDA to **3**, racemization of **3** hardly occurred (entry 1). On the other hand, addition of an excess of LDA facilitated the racemization and the recovered starting material showed only 13% e.e. (entry 3). Moreover, **4** was obtained with the same high optical purity as that of entry 2 irrespective of the amount of excess of LDA. According, the excess of LDA racemizes the unconverted ketone **3** but does not racemize the resulting α,β -unsaturated ester **4** at all.

We used molecular mechanics calculations to evaluate conformational and constitutional equilibria of the oxyanion **7** obtained by addition of the phosphonate carbanion **6** to the carbonyl group of **3**. The computer program used, GENMOL,^{8,9} which is derived from Allinger's MM2 parametrization, is suitable for the calculation of molecules containing heteroatoms like O and P, and π systems. Force field calculations and geometry optimization indicate that out of the eight possible diastereoisomers of **7**, three are energetically much favoured (Scheme 2, Fig. 1).

Both **7b** and **7c** lead to (*S*)-**4**. They result from the attack of pro-*R* carbanion **6** on the equatorial side (opposite to the Bn substituent) of the carbonyl group of ketone (*S*)-**3** (**7c**), and from the attack of the pro-*S* carbanion on the axial side of ketone (*S*)-**3** (**7b**). Oxyanion **7a** arises from the equatorial attack of pro-*S* carbanion **6** on ketone (*R*)-**3**. Conformational studies show that **7b** and **7c** have much better molecular geometries than **7a** to undergo ring closure towards the oxaphosphetane, then the olefin (Fig. 1, Table 3).

Since high enantioselectivity was achieved by employing the chiral phosphonate **2**, we investigated the enantioselective Wittig reaction of various racemic α -substituted cyclo-

Table 4 The Wittig reaction between **2** and various α -substituted ketones^a

| <i>n</i> | R | | <i>t</i> /h | Yield (%) | | | (Optical purity % e.e.) |
|----------|-------------------------------------|-----------|-------------|-----------|-----------|----------|-------------------------|
| | | | | 9 | 10 | 8 | |
| 1 | PhCH ₂ | 3 | 73 | 38 (89) | 7 | 56 (32) | |
| 1 | Ph(CH ₂) ₃ | 8a | 72 | 21 (77) | 2 | 73 | |
| 0 | PhCH ₂ | 8b | 139 | 16 (66) | 7 (44) | 67 | |
| 1 | Bu ^t Me ₂ SiO | 8c | 40 | 41 (31) | 28 (15) | 12 | |

^a Molar ratio of ketone **8**: phosphonate **2**: LDA was 1:1.1:1.2, and the reaction was carried out in THF–HMPA at 0 °C.

alkanones and **2**, in the presence of LDAs in THF–HMPA (Scheme 3, Table 4).

The reactions of 2-(3-phenylpropyl)cyclohexanone **8a** and 2-benzylcyclopentanone **8b**, afford good enantioselectivities, although the chemical yields could be improved. In the case of **8c**, which bears an electron withdrawing *tert*-butyldimethylsiloxy group α to the carbonyl, the chemical yield is good, but the optical yield is poor.

To conclude with, the Wittig reaction of racemic α -substituted cycloalkanones and chiral phosphonate **2** proceeds through kinetic resolution and racemization of the unconverted starting carbonyl compound, to produce chiral *E*-olefins in good enantioselectivities.

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