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Asymmetric Wittig reaction of chiral arsonium ylides — I. Asymmetric olefination of 4-substituted cyclohexanones [†]

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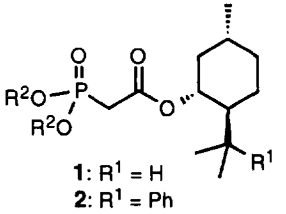
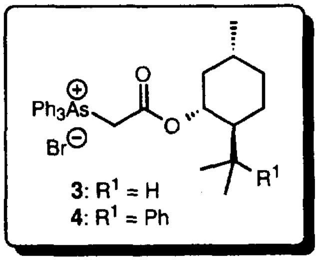
Abstract: Asymmetric Wittig-type olefination of 4-substituted cyclohexanones with chiral ligand-modified stable arsonium ylides has been examined. The 8-phenylmenthol-derived chiral arsonium ylide of **4** reacted with prochiral ketones **9a–d** at −15°C to give the 4-substituted cyclohexylideneacetates **11a–d** in 58–69% yield and in up to 80% diastereomeric excess (de). © 1997 Elsevier Science Ltd

The Wittig reaction[1a] of phosphonium ylides has been extensively used in organic synthesis for the preparation of olefins from aldehydes or ketones.[1] An important variation of the Wittig reaction is the Hornor–Wadsworth–Emmons (HWE) reaction which relies on the use of phosphonates and other phosphonic acid derivatives.[1b] The first asymmetric Wittig-type olefination was demonstrated in 1962 by the reaction of 4-*tert*-butylcyclohexanone or 4-methylcyclohexanone with the menthol-derived chiral phosphonate **1** (R^2=Et).[2] Advances in asymmetric Wittig-type reactions have been made recently focusing on the development of chiral HWE reagents.[3] The 8-phenylmenthol-modified chiral phosphonate **2** has been used for the reactions with chiral or prochiral substrates and for kinetic resolution.[4] Higher diastereoselectivity is generally achieved with **2** compared to the menthol derivative **1**.[4b,5] However, the Wittig reaction of **2** with 4-*tert*-butylcyclohexanone provided an unsatisfactory asymmetric induction of 28% de.[4d] We report here some preliminary results of asymmetric Wittig olefination of chiral arsonium ylides derived from the salts **3** and **4** with 4-substituted cyclohexanones. Diastereoselectivity up to 80% was achieved.



1: R^1 = H
2: R^1 = Ph



3: R^1 = H
4: R^1 = Ph

In contrast to phosphonium ylides, which react with carbonyl compounds at elevated temperature, the corresponding arsonium ylides are much reactive toward Wittig olefination and their synthetic applications have been documented.[6] Optically active tertiary arsines with stereogenic arsenic atoms or with stereogenic center(s) at the substituent have been prepared.[7] Only a few of them have been used for asymmetric synthesis[7] including catalytic hydrogenation, catalytic hydrosilylation, and benzylidene transfer. Optically active epoxides up to 41% enantiomeric excess (ee) were obtained from aldehydes and chiral arsonium ylides possessing a stereogenic arsenic atom.[8] To the best of our knowledge asymmetric Wittig-type olefination using chiral arsonium ylides has not been reported so

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[†] Dedicated to Hangzhou University on the occasion of the 100th anniversary.

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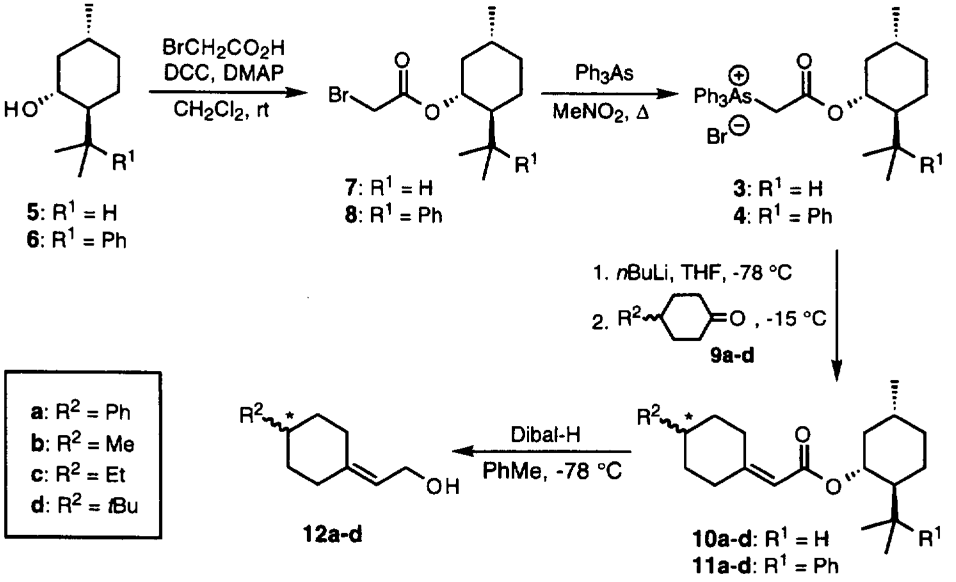
far. In order to explore this new field, we synthesized the chiral arsonium salts **3** and **4** from Ph_3As and chiral esters **7** and **8** (Scheme 1).[9] Condensation of (−)-menthol **5** and (−)-8-phenylmenthol **6** with bromoacetic acid (DCC–DMAP, CH_2Cl_2, rt, 3 h) gave chiral bromoacetates **7** and **8** in quantitative yield. Refluxing a solution of **7** or **8** with Ph_3As in CH_3NO_2 (16–22 h) provided chiral arsonium salt **3** (54%) or **4** (63%). Deprotonation of **3** and **4** with 1 mole equivalent of *n*BuLi in THF at −78°C formed the corresponding chiral arsonium ylides **13** which reacted, without isolation, with a number of prochiral 4-substituted cyclohexanones **9a–d** at −15°C to afford α,β-unsaturated esters **10a–d** and **11a–d**, respectively (Scheme 1, Table 1). Reactions of **13** carried out below −15°C were very slow. In general, the bulky arsonium ylide **13** (R^1=Ph) of **4** reacted slowly with the ketones but gave better diastereoselectivities than the menthol-derived **13** (R^1=H) of **3** (Table 1, Entries 5–8 *vs*. Entries 1–4). This can be attributed to the shielding effect of the phenyl group in 8-phenylmenthyl ligand as observed in numerous precedents.[5] Substituents at the C4 position of cyclohexanones **9a–d** affected diastereoselectivity with the following trend of Ph (80%) > *t*Bu (72%) > Me (65%) > Et (47%) for the reactions of arsonium ylide of **4** (Entries 5–8). The diastereomeric ratios of **10a–d** and **11a–d** were determined by ^1H NMR on a 600 MHz instrument. Integrations of the *gem*-dimethyl groups were used in the calculations. The absolute stereochemistry of the major diastereomers of **10a–d** and **11a–d** was assigned by chemical correlation to chiral 4-substituted cyclohexylideneethanols **12a–d** (Scheme 1). Comparison of the sign of specific rotation of **12b** and **12d** with the known (*R*)-(−)-enantiomer[10] lead to the assignment of *R* configuration for the newly established stereogenic center in **10b,d** and **11b,d**. The analogous alcohols (−)-**12a** and (−)-**12c** are also suggested to have *R* configuration. Thus the major diastereomers of **10a,c** and **11a,c** should possess the same absolute stereochemistry as that of **10b,d** and **11b,d**.



Scheme 1.

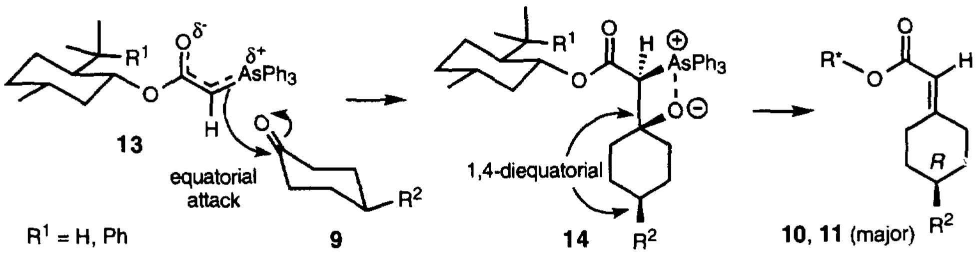
In order to understand the asymmetric olefination of the chiral arsonium ylides, a working hypothesis is proposed (Scheme 2). It is known that arsonium β-carbonyl ylides favor the *Z* configuration in solution presumably due to coulombic interaction between $As^{\delta+}$ and $O^{\delta-}$.[11] Attack of ylide **13** from the least shielded face at 4-substituted cyclohexanones **9** from the equatorial direction gives the betaine intermediate or the four-membered ring transition state **14** in which a favorable 1,4-diequatorial relationship of $-CHCO_2R^*(As^+Ph_3)$ with R^2 is maintained. *Syn*-elimination of $Ph_3As{=}O$ from **14** should afford (*R*)-**10** and (*R*)-**11** as the major product. Reaction of **13** with **9** through the unfavorable

Table 1. Asymmetric olefination of 4-substituted cyclohexanones **9a–d** with **3** and **4**[a]

Entry	Salt	Ketone	t (h)	Yield (%)	de%[b]	**12**; $[\alpha]_D^{20}$ (c)[c]	Configuration[e]
1	**3**	**9a**	38.5	**10a** (86)	12.8	**12a**; -1.43 (1.26)	*R*
2	**3**	**9b**	40.5	**10b** (81)	12.8	**12b**; -2.03 (0.35)[d]	*R*
3	**3**	**9c**	68	**10c** (73)	9.0	**12c**; -0.77 (1.03)	*R*
4	**3**	**9d**	52	**10d** (72)	3.6	**12d**; -0.56 (1.08)	*R*
5	**4**	**9a**	61.5	**11a** (58)	80.0	**12a**; -10.98 (0.50)	*R*
6	**4**	**9b**	59	**11b** (67)	65.4	**12b**; -7.44 (0.43)[d]	*R*
7	**4**	**9c**	69	**11c** (60)	47.4	**12c**; -4.68 (1.02)	*R*
8	**4**	**9d**	91	**11d** (69)	72.0	**12d**; -6.37 (1.34)	*R*

[a] Ratio of salt:nBuLi:ketone is 1.25:1.25:1. [b] Determined by ^{1}H NMR at 600 MHz in $CDCl_3$. [c] Recorded in EtOH unless otherwise stated. [d] Recorded in $CHCl_3$. [e] Determined by the sign of specific rotation. The reported data for (*R*)-(-)-**12b** and (*R*)-(-)-**12d** are $[\alpha]_{Hg}^{25.5}$ -9.84 ± 0.16 (c 3.18, $CHCl_3$; 84.7% ee) and $[\alpha]_{Hg}^{25}$ -8.02 ± 0.34 (c 1.45, EtOH; 91% ee), respectively (see ref. 10).

conformer possessing an axial R^2 at C4 should lead to the minor (*S*)-diastereomer. However, the observed diastereoselectivity does not strictly follow the conformational preference of cyclohexanones **9a–d** which should be determined by bulkiness of the C4 substituent. Isomerization at α carbon of the ester moiety in **14** and attack of ylide **13** from the blocked face are the possible pathways for formation of the minor (*S*)-diastereomer. Nevertheless, our working hypothesis illustrated in Scheme 2 is consistent with our experimental results given in Table 1. A similar model was proposed for Wittig-type olefination of chiral phosphonate **2** with prochiral cycloalkanones.[3]



Scheme 2.

In summary, we have examined the Wittig-type olefination of 4-substituted cyclohexanones **9a–d** with chiral arsonium ylides in situ derived from **3** and **4**. Encouraging levels of asymmetric induction up to 80% de were achieved with the 8-phenylmenthol-modified arsonium ylide of **4**. This is a better result compared to asymmetric induction of the analogous chiral phosphonate **2**.[4d,12] We are currently working on the solvent and metal counterion effects on the olefination of chiral arsonium ylides as well as on developing a catalytic[13] enantioselective Wittig olefination using chiral arsonium ylide possessing a stereogenic arsenic atom.[14]

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