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Asymmetric Wittig reactions of chiral arsonium ylides. Part 3: Reversal of stereochemistry caused by metal cation in enantioselective olefination of 4-substituted cyclohexanones using a C_2-symmetric chiral arsine†

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Abstract—A novel C_2-symmetric chiral arsine was synthesized from (*S*)-(−)-1,1′-bi-2-naphthol in three steps. It was employed in the enantioselective olefination of 4-substituted cyclohexanones via a stabilized ylide formed in situ from the corresponding arsonium salt. Enantioselectivity up to 40% was obtained. Moreover, a reversal in the stereochemistry of the product was observed simply by changing the counter cation of the base from lithium to potassium.

1. Introduction

The Wittig and related reactions[1] are the most useful olefination methods using carbonyl compounds as the starting materials. A variety of phosphorus-derived reagents including phosphonium ylides (Wittig reagents), phosphine oxides (Horner reagents), and phosphonates and other phosphonic acid derivatives (Horner–Wadsworth–Emmons, HWE reagents) have been employed. Among them, the HWE reagents possessing stereogenic sub-unit(s) have been a great success in the asymmetric versions of the olefination of carbonyl compounds.[2,3] Moreover, the asymmetric HWE reactions using external chiral reagents have been reported very recently.[4] Although Wittig-type olefinations of aldehydes can be carried out using a catalytic amount of *n*-Bu_3As[5a] or organic tellurides,[5b–e] a catalytic asymmetric Wittig reaction is still lacking.

In 1997, we reported the first asymmetric Wittig reaction of prochiral 4-substituted cyclohexanones using chiral arsonium ylides modified by (−)-menthol and (−)-8-phenylmenthol.[6a] Diastereomeric ratios of up to 90:10 were achieved. With similar chiral arsonium ylides, we performed a kinetic resolution of axially chiral *N*,*N*-dialkyl 2-formyl-1-naphthamides, giving diastereomeric ratios of up to 88:12.[6b] The advantage of arsonium ylides over the phosphonium counterparts is the enhanced reactivity toward carbonyl substrates so that olefinations of arsonium ylides with both aldehydes and ketones can be performed at low temperature. We report here on our results from studies on enantioselective Wittig reactions of prochiral 4-substituted cyclohexanones using a chiral arsonium ylide derived from a novel C_2-symmetric chiral tertiary arsine.

2. Results and discussion

In order to avoid creating a stereogenic arsenic atom after formation of the arsonium salt, we designed the C_2-symmetric chiral tertiary arsine **4** possessing the 1,1′-binaphthyl-2,2′-bis(methylene) backbone (Scheme 1). Similar compounds containing oxygen,[7] nitrogen,[8] sulfur,[9] silicon,[10] tin,[11] boron,[11a] and phosphorus[12] have been prepared and used in various asymmetric reactions and for asymmetric catalysis. We prepared the (*S*)-2,2′-dimethyl-1,1′-binaphthyl **3** from (*S*)-(−)-**1** via the bistriflate **2** according to the reported procedure.[12c,13] Metalation of **3** was carried out using *tert*-BuLi–TMEDA in Et_2O[8k,10,11a] to form the dilithio species which reacted with $PhAsBr_2$[14] to afford **4** in 52% yield.

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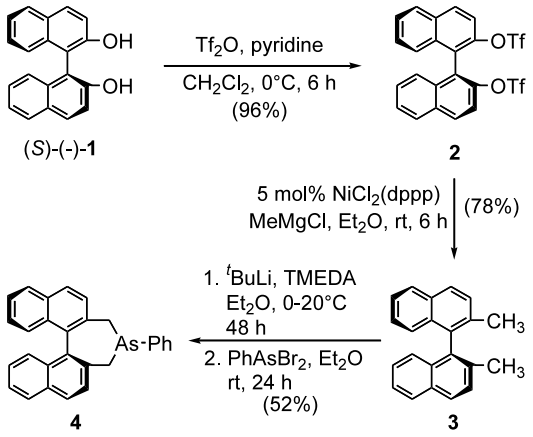
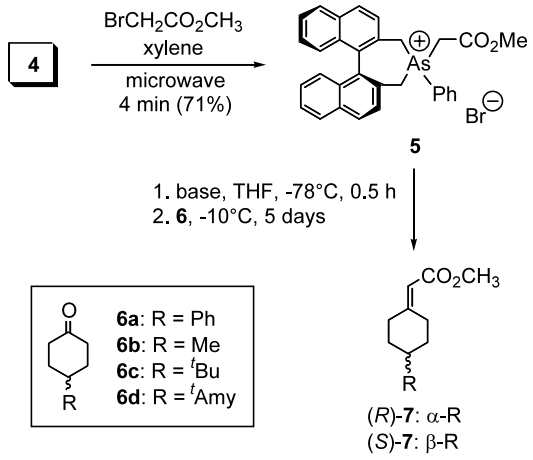


Scheme 1. Synthesis of novel C_2-symmetric chiral arsine **4**.



Scheme 2. Enantioselective Wittig reaction of chiral arsonium ylide.

The chemical structure of **4** was unambiguously confirmed by X-ray crystal structural analysis of its arsonium salt **5**, as shown in Scheme 2 and Fig. 1.[15]

Formation of the arsonium salt **5** was effected by microwave irradiation of a mixture of **4** and methyl bromoacetate in xylene in a pressure tube. The salt was collected by precipitation in 71% yield (Scheme 2). Deprotonation of **5** using *n*-BuLi in THF at −78°C[6a] formed the arsonium ylide, which was reacted without isolation with the 4-substituted cyclohexanones **6a–d** at −10°C by standing in a freezer for 5 days. The products (*R*)-**7a–d** were isolated through flash column chromatography over silica gel in 53–92% yields (entries 1–4, Table 1). The enantioselectivity of the reactions (25.4–40.0% ee) was determined by HPLC analysis using a chiral stationary phase. The absolute stereochemistry of (*R*)-**7a–c** was assigned by comparing the sign of the specific rotations with the reported values.[16] The absolute configuration of (*R*)-**7d** was assigned by its similar specific rotation data to **7c**.

In an attempt to examine the effect of counter ion of the base on enantioselectivity, we found that the absolute stereochemistry of the product reversed from *R* to *S* when NaHMDS and KHMDS were used for the formation of the ylide (entries 5–7, Table 1). For 4-phenylcyclohexanone **6a**, (*R*)-**7a** of 29.7% ee was obtained using LiHMDS as the base. In contrast, (*S*)-**7a** of 25.8% and 40.4% ee was obtained when NaHMDS and KHMDS were used for ylide formation, respectively. The counter ion effect was also observed for KH, KO^{t}Bu, $ZnEt_2$, and $CsCO_3$ to form (*S*)-**7a** with enantioselectivities in the range of 5.7–42.3% ee (entries 11–15, Table 1). It is interesting to note that a similar level of enantioselectivity was achieved for the Wittig reaction at room temperature (entry 15, Table 1). For other 4-substituted cyclohexanones **6b–d**, (*S*)-products

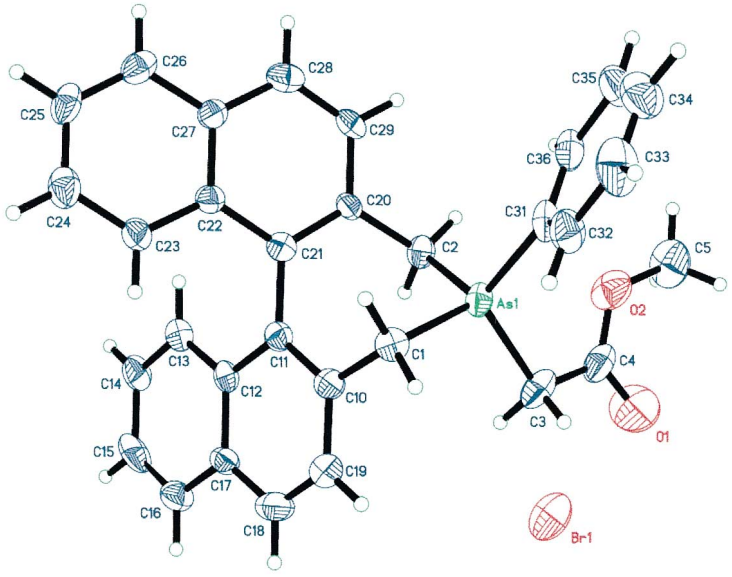
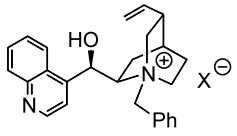


Figure 1. X-Ray crystal structure of chiral arsonium salt **5**.

Table 1. Enantioselective Wittig reaction of 4-substituted cyclohexanones **6** with the chiral arsonium ylide in situ formed from the chiral arsonium salt **5**[a]

Entry	Substrate	Base	Product (%)[b]	ee (%)[c]	Entry	Substrate	Base	Product (%)[b]	ee (%)[c]
1	**6a**	^{n}BuLi	(*R*)-**7a**: 92	25.4	11	**6a**	KH	(*S*)-**7a**: 55	36.0
2	**6b**	^{n}BuLi	(*R*)-**7b**: 53	33.5	12	**6a**	KO^{t}Bu	(*S*)-**7a**: 62	34.7
3	**6c**	^{n}BuLi	(*R*)-**7c**: 60	40.0	13	**6a**	$ZnEt_2$	(*S*)-**7a**: 36	5.7
4	**6d**	^{n}BuLi	(*R*)-**7d**: 77	39.2	14	**6a**	$CsCO_3$ (THF, 4°C)	(*S*)-**7a**: 50	42.3
5	**6a**	LiHMDS	(*R*)-**7a**: 76	29.7	15	**6a**	$CsCO_3$ (THF, rt)	(*S*)-**7a**: 41	38.4
6	**6a**	NaHMDS	(*S*)-**7a**: 65	25.8	16	**6a**	$CsCO_3$ (PhH, rt)	(*S*)-**7a**: 42	43.5
7	**6a**	KHMDS	(*S*)-**7a**: 76	40.4	17	**6a**	$CsCO_3$ (**8**, PhH, rt)	(*S*)-**7a**: 48	39.7
8	**6b**	KHMDS	(*S*)-**7b**: 55	27.7	18	**6a**	$CsCO_3$ (**9**, PhH, rt)	(*S*)-**7a**: 40	44.6
9	**6c**	KHMDS	(*S*)-**7c**: 48	36.2	19	**6a**	$CsCO_3$ (CH_3CN, rt)	(*S*)-**7a**: 34	8.5
10	**6d**	KHMDS	(*S*)-**7d**: 63	30.4					



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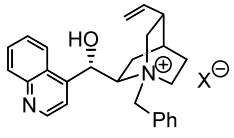

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[a] Reactions were carried out in THF at −10°C for entries 1–13.

[b] Isolated yield and not optimerized. Loss of materials during sample drying may occur due to the low molecular weights of the liquid products **7b–d**.

[c] Determined by HPLC analysis over one or two Chiralcel OD column(s) eluted with hexane–2-propanol (98:2) at 0.5 mL/min using UV detector at 230 nm.

were also produced in the ees of 27.7 (Me), 36.2 (*tert*-Bu), and 30.4% (*tert*-Amyl) (entries 8–10, Table 1). However, it should be emphasized that the counter ion effect on enantioselectivity was not observed in the reactions of the menthol-modified chiral arsonium ylides.[6b]

We investigated solvent effects on the Wittig reaction of **6a** carried out at room temperature in the presence of $CsCO_3$. A slight enhancement in the enantioselectivity was obtained in benzene over THF, whereas the use of acetonitrile resulted in a dramatic loss in the asymmetric induction (entries 16 and 19 versus entry 15, Table 1). The results imply that a tight association of the counter ion with the reagent(s) is favored for maintaining a rigid transition state, leading to better stereodifferentiation. We tried two chiral phase transfer catalysts **8** and **9**[4d] in the reactions of **6a**. However, no significant improvement in enantioselectivity was observed (entries 17–18, Table 1). This reflects the different structural features of arsonium ylides compared to HWE reagents.[4d]

We suggest a mechanism for the enantioselective Wittig reactions of the chiral arsonium ylide, as depicted in Fig. 2. Among various possible isomers and conformations of the ylide, two low energy structures are assumed on the basis of the X-ray crystal structure of its precursor salt **5**. As shown in **I** and **II**, the ylide possesses *Z* configuration as a consequence of coulombic interaction between the oppositely charged arsenic and oxygen atoms.[6,17] The $As^{\delta+}$–CH–C(OMe)–$O^{\delta-}$ moiety in **I** is perpendicular to the plane of Ph–$As^{\delta+}$–CH which bisects the 1,1′-binaphthyl-2,2′-bis(methylene) backbone. On the other hand, a coplanar alignment is seen for Ph–$As^{\delta+}$–CH–C(OMe)–$O^{\delta-}$ in **II**. Attack of the ylide should occur from the equatorial position of the cyclohexanones to form a 1,4-diequatorial cyclohexane species which undergoes *syn* elimination of As=O to give the olefin.[6a] In the absence of strong chelating metal ions, the Wittig reaction should take place through pathway **I**, where the ketone substrate is bisected by the Ph–$As^{\delta+}$–CH plane. (*R*)-**7a–d** are

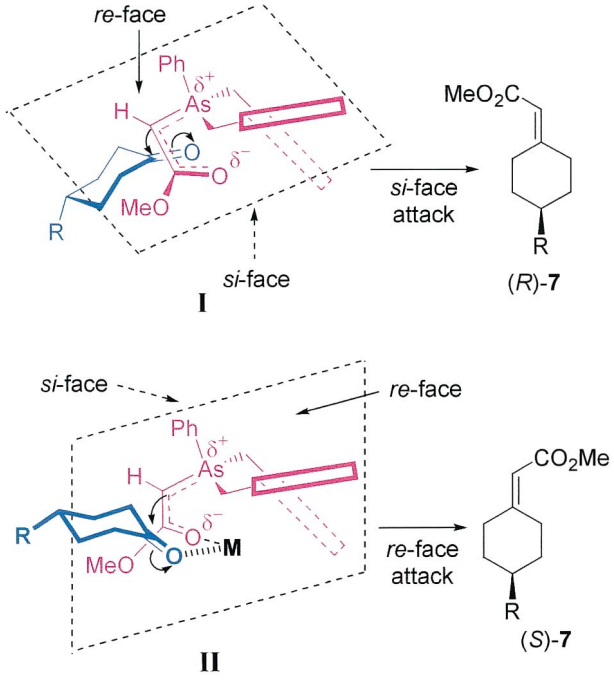

Figure 2. Proposed pathways for the enantioselective Wittig reaction.

expected to form as the major products, as observed in the Wittig reactions using *n*-BuLi and LiHMDS as the base. Alternatively, chelating metal ions such as Na, K, and Cs favor the reaction pathway **II**, where the ketone substrate suffers from a minimum steric interaction with the 1,1′-binaphthyl-2,2′-bis(methylene) backbone, leading to the formation of (*S*)-**7a**–**d** as the major enantiomers. The observed solvent effect on the enantioselectivity, in the order of PhH (43.5% ee)>THF (38.4% ee)>CH_3CN (8.5% ee), is consistent with the chelation model shown in **II**. Less polar solvents promote chelation and lead to higher enantioselectivity. It should be emphasized that the above discussion is based on the assumption that the addition of the chiral arsonium ylide to the ketone is the rate-determining step. Other possibilities cannot be ruled out at this stage.

In summary, we have designed and synthesized the first example of a C_2-symmetric chiral tertiary arsine possessing the 1,1′-binaphthyl-2,2′-bis(methylene) backbone and applied it in the enantioselective Wittig reactions of prochiral 4-substituted cyclohexanones. The change in enantioselectivity and the reversal of stereochemistry caused by metal cations are discussed in terms of the conformational flexibility of the chiral arsonium ylide derived from **5**. Future work should be aimed at increasing the conformational rigidity of the arsonium ylide in order to improve the enantioselectivity of the Wittig reactions.

Acknowledgements

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