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The Asymmetric Horner-Emmons Reaction using a Benzopyrano-Isoxazolidine Auxiliary

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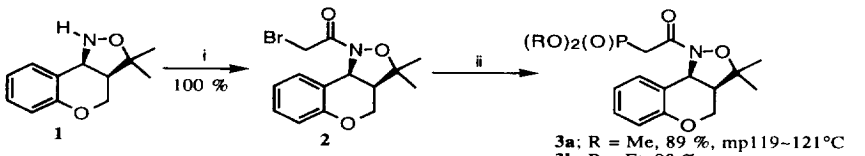
Abstract: The asymmetric Horner-Emmons reaction of the phosphonate derived from a chiral benzopyrano-isoxazolidine (with 4-substituted cyclohexanones) proceeded in high diastereoselectivity with the aid of KHMDS and 18-crown-6 ether. Enantiomerically pure, axially dissymmetric cyclohexylidene alcohols, aldehydes and ketones were obtained from the diastereomerically pure Horner-Emmons products in a single step.

The synthesis of axially dissymmetric olefins has attracted much attention over the past decade.[1] One straightforward approach to this problem is the application of a Wittig-type reaction, and in fact recent publications record the asymmetric Horner-Emmons reaction using an ester with a chiral alcohol moiety or a chiral phosphonate.[2] During the course of our investigation on chiral benzopyrano-[4,3-c]-isoxazolidine derivatives (e. g., see **1**) as auxiliaries for asymmetric alkylation,[3] it became evident that the phosphonate reagent **3** derived from **1** could be advantageously used for the asymmetric Horner-Emmons reaction. This note describes the following findings: (1) the Horner-Emmons reaction of **3** with 4-substituted cyclohexanones indeed proceeded smoothly with high diastereoselectivity, (2) the products, cyclohexylidenecarbonyl derivatives, were readily obtained in diastereomerically pure form, and (3) the conversion of the products to the corresponding enantiomerically pure alcohols, aldehydes, and ketones with concomitant cleavage of the auxiliary was executed in a single step.

The phosphonate reagents **3** were prepared by the standard Arbuzov reaction from the bromoacetamide derivative (**2**) of **1**. Thus, heating a mixture of **2** and a phosphite (trimethyl, triethyl or triisopropyl phosphite) in toluene (or xylene) at reflux for several hours afforded the corresponding phosphonate **3a**, **3b** or **3c** in high yield. (**3a** was obtained in crystalline form.) For the preparation of **3d**,[4] diphenyl methyl phosphite was used. (Scheme 1)

Scheme 1



1 **2**

3a; R = Me, 89 %, mp119~121°C
3b; R = Et, 98 %
3c; R = iPr, 95 %
3d; R = Ph, 48 %

Key: i) $BrCOCH_2Br$, Et_3N, CH_2Cl_2 ii) $(RO)_3P$, heat in toluene (for **3a**), or in xylene (for **3b**, **3c**, **3d**).

Several sets of reaction conditions were examined with 4-*tert*-butylcyclohexanone as a substrate. Although the use of NaH, LiCl-DBU, or $Sn(OTf)_2$-DBU resulted in disappointingly low selectivities (Table 1), the reaction of **3a** with KHMDS in the presence of 18-crown-6 ether in THF afforded a high level of asymmetric induction (96 : 4; Table 2, Entry 1). Use of the bulkier phosphonates **3b** and **3c** caused significant decreases in both reactivity and selectivity (Table 2, Entries 2, 3). The phenyl phosphonate **3d** exhibited high selectivity, but the reactivity was lower than **3a** (Table 2,Entry 4). Surprisingly, the solvent (toluene, ether, THF, DME) and the amount of the crown ether (from 1 to 5 equiv of the phosphonate) did not affect the selectivity. (Table 2, Entries 5~10)

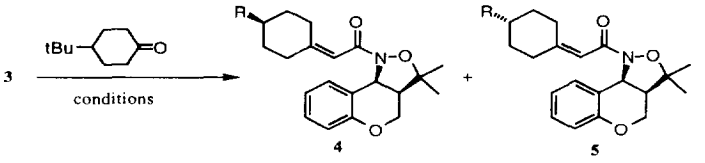


Table 1: Asymmetric Horner-Emmons reaction of **3** with 4-*tert*-butylcyclohexanone

Entry	Phosphonate **3**	Conditions	**4** : **5**
1	**3a** (R = Me)	NaH, THF, -20 °C, 14 h	61 : 39
2	**3a** (R = Me)	NaH, DMF, -20 °C, 14 h	85 : 15
3	**3c** (R = iPr)	NaH, THF, 0 °C, 14 h	41 : 59
4	**3c** (R = iPr)	NaH, DMF, 0 °C, 14 h	47 : 53
5	**3a** (R = Me)	LiCl-DBU, MeCN, -20 °C, 14 h	26 : 74
6	**3b** (R = Et)	LiCl-DBU, THF, -20 °C, 14 h	43 : 57
7	**3c** (R = iPr)	LiCl-DBU, MeCN, 0 °C, 14 h	27 : 73
8	**3c** (R = iPr)	LiCl-DBU, THF, 0 °C, 14 h	42 : 58
9	**3a** (R = Me)	$Sn(OTf)_2$-DBU, THF, -20 °C, 14 h	31 : 69
10	**3b** (R = Et)	$Sn(OTf)_2$-DBU, THF, -20 °C, 14 h	27 : 73
11	**3c** (R = iPr)	$Sn(OTf)_2$-DBU, THF, -20 °C, 14 h	23 : 77
12	**3d** (R = Ph)	$Sn(OTf)_2$-DBU, THF, -20 °C, 14 h	77 : 23

Table 2: Asymmetric Horner-Emmons reaction of **3** with KHMDS and 18-crown-6.

Entry	Phosphonate **3**	Solvent	Conditions	Crown ether (eq)	**4** : **5**
1	**3a** (R = Me)	THF	-20 °C, 14 h	2	96 : 4
2	**3b** (R = Et)	THF	0 °C ~ r t, 14 h	2	89 : 11
3	**3c** (R = iPr)	THF	0 °C ~ r t, 14 h	2	83 : 17
4	**3d** (R = Ph)	THF	0 °C, 64 h	2	95 : 5
5	**3a** (R = Me)	Et_2O	-20 °C, 14 h	2	96 : 4
6	**3a** (R = Me)	toluene	-20 °C, 14 h	2	96 : 4
7	**3a** (R = Me)	DME	-20 °C, 14 h	2	96 : 4
8	**3a** (R = Me)	THF	-20 °C, 14 h	1	96 : 4
9	**3a** (R = Me)	THF	-20 °C, 14 h	3	96 : 4
10	**3a** (R = Me)	THF	-20 °C, 14 h	5	96 : 4

Under the optimal reaction conditions (Table 2, Entry 1), the Horner-Emmons reaction of **3a** with several 4-substituted cyclohexanones proceeded with high selectivity. The pure diastereomers of the reaction products were isolated readily and in high yield by chromatography and/or recrystallization (Table 3).

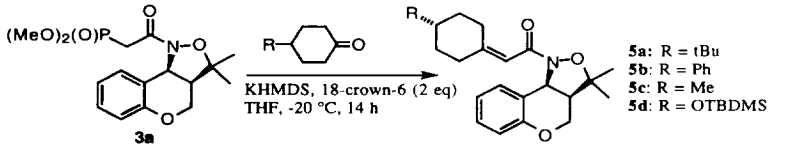


Table 3: Asymmetric Horner-Emmons reaction of **3a** with 4-substituted cyclohexanones.

Entry	5	aS : aR	isolated yield of 5	mp	$[\alpha]_D$ (in $CHCl_3$)
1	**5a** (R = t-Bu)	96 : 4	91 %	177~178 °C	246.7 (c 1.01)
2	**5b** (R = Ph)	93 : 7	90	149~151	241.2 (c 1.00)
3	**5c** (R = Me)	92 : 8	89	119~120	240.7 (c 1.00)
4	**5d** (R = OTBDMS)	90 : 10	85	167~168	186.4 (c 1.00)

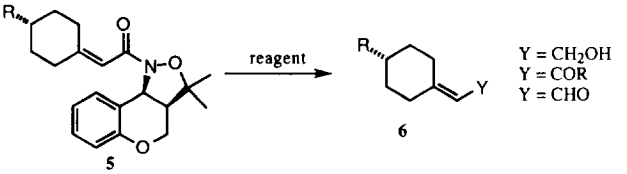


Table 4: Syntheses of axially chiral cyclohexylidene compounds.

Entry	R	Reagent	Product **6** (Y)	yield (%)	$[\alpha]_D$ (in $CHCl_3$)
1	**5** (R = tBu)	$LiBH_4$-EtOH, Ether	CH_2OH	95	8.8 (c 3.60)
2	**5** (R = tBu)	MeMgBr, Ether	COMe	93	87.3 (c 1.54)[a]
3	**5** (R = tBu)	BuMgBr, Ether	COBu	90	66.6 (c 3.79)
4	**5** (R = tBu)	PhMgBr, Ether	COPh	82	50.1 (c 1.01)[a]
5	**5** (R = tBu)	DIBAH	CHO	79	32.0 (c 2.79)
6	**5** (R = Ph)	$LiBH_4$-EtOH, Ether	CH_2OH	100	15.9 (c 1.42)
7	**5** (R = Ph)	MeMgBr, Ether	COMe	83	136.0 (c 1.21)
8	**5** (R = Ph)	PhMgBr, Ether	COPh	55	81.6 (c 1.35)[a]
9	**5** (R = Me)	$LiBH_4$-EtOH, Ether	CH_2OH	93	10.7 (c 2.27)
10	**5** (R = Me)	MeMgBr, Ether	COMe	75	77.1 (c 2.51)
11	**5** (R = Me)	PhMgBr, Ether	COPh	75	34.1 (c 2.00)[b]

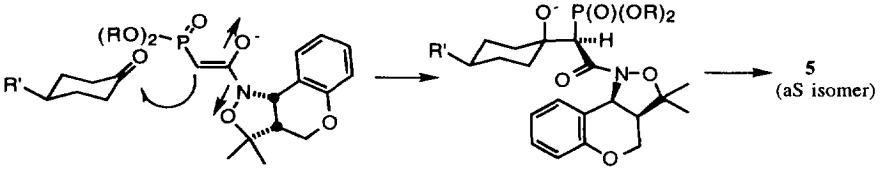
a) ref. 1. e); b) ref. 1. f).

The notable advantage of the benzopyrano-isoxazolidine auxiliary is a single step transformation to the corresponding alcohols, aldehydes and ketones without racemization. The Horner-Emmons products were subjected to the standard conditions of the transformations[3]; $LiBH_4$-EtOH, Grignard reagent, and DIBAH afforded the corrsponding dissymmetric alcohols, ketones and aldehydes, respectively. The absolute configuration of each product was determined (or assumed) to be *aS* by comparison with the reported sign of the optical rotation. (Table 4)

The high diastereoselectivity achieved for the Horner-Emmons reaction is rationalized as shown in Scheme

2. It may be assumed that the phosphonate anion prefers the conformation, in which the dipole-dipole repulsion between the C-O and N-O bonds (indicated by the arrows) is minimized, and this bulky nucleophile attacks the carbonyl group from the equatorial side preferentially. Elimination of the phosphate anion then follows immediately without equilibration. The degree of the equatorial attack is dependent on the bulkiness of the substituent on the 4-position of the ketone (tBu>Ph>Me>OTBDMS), as well documented.

Scheme 2



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