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ARTICLE TYPE

Addition of Optically Pure *H*-Phosphinate to Ketones: the Selectivity, Stereochemistry and Mechanism

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Aromatic methyl ketones and cyclic asymmetric ketones underwent hydrophosphorylation with P-stereogenic H-P species in the presence of potassium carbonate to produce P,C-stereogenic tertiary α-hydroxyl phosphinates in excellent yields and up to 99:1 dr. The diastereoselectivity was induced by reversible conversion of less stable stereomer of product to more stable one via an equilibrium, which was confirmed by aldehyde/ketone exchanging reaction. As attacking reagents to the exchanging, aliphatic or aldehyde carbonyl showed more active than aromatic or ketone ones, respectively. The stabilities difference between two diastereomers-was controlled by the sizes of substituents linking to phosphorus or α-carbon.

Introduction

Because of potential applications as biological active substances[1] and precursors of ligands for asymmetric catalysis,[2] the optically active phosphorus compounds attracted extensive attention in recent years. For example, α-hydroxyl phosphonic acid derivatives have been used as the inhibitors of HIV protease, polymerase,[3] and renin,[4] also these compounds have been found to show anti-virus and anti-cancer activities.[5] The optically enriched these compounds are mainly obtained through enzymatic methods,[6] such as kinetic resolution of racemic mixture by bacteria, fungi, or lapses,[7] or through asymmetric reduction of α-keto phosphonate with baker's yeast, fungi or other catalysts.[6,8,9]

Another available chemical method[10] include asymmetric oxidation of benzyl phosphonates.[11] The addition of P-H species to carbon oxygen double bonds, known as Pudovik reaction,[12] is frequently used for the formation of α-hydroxyl phosphorus compounds, and the relevant asymmetric approaches are also developed by several research groups. These reported methods either use special reagents that are difficult to handle, or have very limited substrate scope. Most catalyzed methods employ asymmetric catalysts that involved in heavy metal or difficultly accessible ligands.[13] Furthermore, the reported methods are only suitable for the synthesis of optically active secondary α-hydroxyl phosphonic acid derivatives. Acquirement of tertiary these compounds in high stereoselectivity is still a challenging task for organic chemists.[13a,14]

P-stereogenic P-H species have attracted growing attention because of their applications in construction of asymmetric P-C bonds.[15] Theoretically, when these species are used in Pudovik reaction, cleavage of P-H bond and formation of P-C bond were involved,[16] and four stereomers were probably formed due to carbon and phosphorus chiral centers. The reported asymmetric Pudovik reactions are usually committed the formation of *C*-stereogenic α-hydroxyl phosphorus compounds via addition of non-chiral P-H species to pre-chiral aldehydes. Addition of phosphorus reagents that contained two or three chiral alkoxyl or amino groups to aldehydes also afforded *C*-stereogenic α-hydroxyl phosphorus compounds.[17b] The early synthesis of *P*- or *P,C*-stereogenic these compounds via Pudovik reactions either employed unseparated chiral P-H starting materials or affoded diastereomeric mixtures of products. Owing to poor induction effect of *P*-stereogenic centre to the formation of chiral carbon,[9b,17] the simultaneous formations of carbon and phosphorus chiral centers in excellent stereoselectivity are quite limited. Zhao and co-workers prepared *P,C*-stereogenic α-hydroxyl phosphinates,[14b] as a diastereomeric mixture derived from *R*/*S* configuration on phosphorus. Recently, Montchamp's group reported the preparation of *P,C*-stereogenic α-hydroxyl phosphinates in 94% de by means of Wittig rearrangement.[18]

Thermodynamic-controlled reactions are frequently applied for asymmetric synthesis to selectively obtain stable enantiomers. If a chemical equilibrium between two stereomers can be readily established, the less stable stereomer will be converted to the more stable one, thereafter the latter was afforded in high stereoselectivity. However, the stereoselective acquirement of phosphorus-containing compounds utilizing stability-difference of products was rather rare[19].

The importance of *P*-stereogenic compounds[9,20] and the deficiency of satisfied method for acquiring them encourage us to investigate the asymmetric Pudovik reaction employing *P*-stereogenic R_P-(*L*)-menthyl phenylphosphinate **1a**.[15c,21] On the basis of a reversible equilibrium,[19] the addition of P-H species to aldehydes or ketones afford adducts in two diastereomers that showed different thermodynamic stabilities and could be

converted. The reaction of **1a** with aliphatic or aromatic ketones was undertaken in the presence of potassium carbonate, affording S_PR_C-stereomers of tertiary α-hydroxyl phosphinates predominantly, in moderate to excellent yields. The aldehydes/ketones exchanging for α-hydroxyl phosphinates, as well as their affinities to phosphorus, was explored. The interactions between various substituents linking to phosphorus or α-carbon of adducts, such as alkoxyl, aryl or methyl, were also examined.

Results and Discussion

1. Hydrophosphorylation of ketones with 1a.

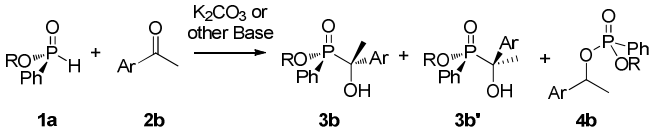
Under neat condition, the hydrophosphorylation of aldehydes with **1a** afforded secondary α-hyderoxyphosphinate in high yield but poor diastereoselectivity.[16b,22] Similar reaction of ketones **2** occurred sluggishly without catalyst. In the presence of potassium carbonate, *p*-bromoacetophenone **2b** reacted to **1a** at room temperature affording α-hydroxyl phosphinate **3b** in high yield. To our surprise, besides the stereochemistry at phosphorus kept integral just as the reaction of aldehydes,[20,22] α-chiral carbon was generated in some diastereoselectivity. For example, in DMF, **3b**/**3b'** were formed in 92% yield and 90:10 ratio (entry 2 of Table 1). The two diastereomers **3b**/**3b'** were confirmed to have S_PR_C and S_PS_C structures, respectively (vide infra). The consequence encouraged us to further optimize the reaction conditions, and the results were summarized in Table 1.

The solvents had significant influence on the yield and dr_C (diastereomeric ratio on carbon, assigned as **3b**:**3b'**). When K_2CO_3 was used as catalyst, DMF and DMSO gave better yields and dr_C than other solvents such as NMP, pyridine, acetonitrile and THF (entries1-9, 13). In DMSO, **3b** was afforded in 97% yield and 98:2 dr_C. The mixed solvents containing DMSO also improved the reaction results (entries 10 and 11). Base was essential to the reaction. However, increasing amount of K_2CO_3 resulted in side reaction to afford *O*-phosphorylated product **4b** via Phospha-Brook rearrangement (entries 14 and 15).[20,23] At elevated temperature, formation of **4b** became significantly and yield of **3b** became poor (entry 17). When the reaction was carried out under air, yield and dr_C of **4b** wasn't decreased obviously (entry 16).

Pyridine and calcium hydroxide also promoted the addition, giving unsatisfied dr_C in DMSO. Other bases including sodium bicarbonate, triethylamine didn't show catalysis activities (entries 21-22). The stronger bases such as KOH or tetrabutylammonium hydroxide resulted in predominately formation of **4b** (entries 23-24).

The additions of **1a** to various ketones **2** were examined. In Table 2, stereospecifically *P*-retention adduct **3** were obtained in more than 99:1 dr_P. Most aryl methyl ketones having either electron withdrawing or donating groups at *para*-position, gave excellent yield and dr_C of **3**. The results of *p*-fluoroacetophenone **2d** were slight lower than others, affording **3d** in 87% and 84:16 dr_C (entry 4). *o*-Chloroacetophenone formed **3** only in a trace amount. At elevated temperature, *O*-phosphorylated product **4** was obtained as major product (entry 5). *m*-Bromoacetophenone afforded **3e**/**3e'** in poor dr_C (entry 6). For nitro-substituted acetophenones, dr_C can be improved significantly in concentrated solution (entries 7-8). In the case of *m*-nitroacetophenone **2g**, **3g'** was formed as major diastereomer, exhibited reversing dr_C to other aromatic ketones.

Table 1. Hydrophosphorylation of **2b** with **1a** under various reaction conditions.



1a **2b** **3b** **3b'** **4b**

R = (*L*)-menthyl; Ar = *p*-BrC_6H_4

entry	solvent	Base/(mol%)	time/h	yield % **3b**/**3b'**[a]
1	No	No	48	4
2	DMF	50	24	92 (90:10)
3	NMP	25	26	8 (44:56)
4	NMP	100	22	61 (44:56)
5	CH_3CN	25	26	4 (40:60)
6	CH_3CN	100	22	27 (43:57)
7	THF	25	24	31 (52:48)
8	THF	25	16	30 (60:40)[b]
9	pyridine	25	24	16 (37:63)
10	pyridine/DMSO	25	22	85 (77:23)
11	DMF/DMSO	25	24	88 (97:3)
12	DMSO	No	24	NR
13	DMSO	25	24	97 (98:2)
14	DMSO	50	24	90 (97:3)
15	DMSO	100	12	88 (98:2)
16	DMSO	25	24	93 (97:3)[c]
17	DMSO	25	24	55 (94:6)[d]
18	DMSO	25	24	94 (95:5)[e]
19	DMSO	25	24	99 (83:17)[f]
20	DMSO	$Ca(OH)_2$/25	48	52 (49:51)
21	DMSO	Et_3N/100	24	NR
22	DMSO	$NaHCO_3$/100	24	NR
23	DMSO	KOH/50	36	90 (45:55)[g]
24	DMSO	Bu_4NOH/25	13	98[g,h] (10:10:42:38)

[a] Typical procedure: 0.36 mmol **1a** and 0.36 mmol **5b** were stirred in 1 ml DMSO in the presence of base at room temperature. [b] To run the reaction at 65°C. [c] To run the reaction under air. [d] To run the reaction at 55°C. [e] To run the reaction in DMSO (2 ml). [f] To run the reaction in DMSO (0.5 ml). [g] Two stereomers of **4b** were formed, whose structures weren't confirmed. [h] **1a** was partly epimerized to **1a**/**1a'** that afforded four stereomers of **4b** via reaction with **2b**.

Table 2. Hydrophosphorylation of ketones with **1a**.

entry	R^1-CO-R^2, **2**	time /h	yield % dr_C (**3/3'**)[a]
1	Ph, Me, **2a**	40	**3a**, 75 (90:10)
2	*p*-BrC_6H_4, Me, **2b**	24	**3b**, 97 (98:2)
3	*p*-ClC_6H_4, Me, **2c**	68	**3c**, 90 (99:1)
4	*p*-FC_6H_4, Me, **2d**	54	**3d**, 87 (84:16)
5	*o*-ClC_6H_4, Me	24	Trace[b]
6	*m*-BrC_6H_4, Me, **2e**	60	**3e**, 70 (67:33)
7	*p*-$NO_2C_6H_4$, Me, **2f**	40	**3f**, 48 (94:6)[c]
8	*m*-$NO_2C_6H_4$, Me, **2g**	72	**3g'**, 71 (12:88)[c]
9	*p*-$CH_3C_6H_4$, Me, **2h**	90	**3h**, 93 (99:1)
10	*p*-$CH_3OC_6H_4$, Me, **2i**	96	**3i**, 94 (99:1)
11	*p*-PhC_6H_4, Me, **2j**	88	**3j**, 87 (97:3)
12	*p*-HOC_6H_4, Me	72	NR
13	*m*-$NH_2C_6H_4$, Me, **2k**	24	**3k**, 35 (63: 37)
14	Ph, CF_3, **2l**	76	**3l**, 97 (36:64)[d,e]
15	α-Tetralone	48	Trace
16	2-Furyl, Me, **2m**	107	**3m**, 47 (53:47)[e]
17	1-Naphyl, Me, **2n**	48	**3n**, 19 (46:54)[e]
18	1,1'-Diacetylferrocene, **2o**	24	**3o**, 24 (50:50)[e,f]
19	Acetylferrocene	40	Trace
20	$(CH_2)_5$, **2p**	24	**3p**, 99
21	$(CH_2)_4$, **2q**	44	**3q**, 98
22	Me, Me, **2r**	24	**3r**, 99
23	Et, Et, **2s**	96	**3s**, 54
24	Et, Me, **2t**	65	**3t**, 98 (27:73)[e]
25	*i*Bu, Me, **2u**	24	**3u**, 83 (68:32)
26	*i*Pr, Me, **2v**	100	**3v**, 54 (51:49)[e]
27	2-Me-cyclohexanone, **2w**	16	**3w**, 90 (5:50:7:38)[e]
28	2-*cyclo*Pentyl-cyclopentanone,**2x**	24	**3x**, 24 (42:58)[e,f]

[a] Typical procedure: 0.36 mmol (R_P)-**1a** and 0.36 mmol **2b** were stirred in 1 ml DMSO in the presence of K_2CO_3 (25 % molar) at rt. Yield and dr_C were estimated by ^{31}P-NMR spectroscopy. Dr_C were assigned as **3**/**3'** except for unconfirmed stereomers. [b] When the reaction was carried out at 60°C, only **4** was detected. [c] DMSO was used in 0.5 ml. When 1 ml of DMSO was used, **3f** and **3g**' were formed in 86% (84:16) and 82% (15:85), respectively. [d] The reaction was carried out in diethyl ether without base. Under typical condition, only **4l** was formed. [e] The structures of stereomers weren't confirmed. [f] *t*BuOK was used as base.

Some electron donating groups linking to acetophenones resulted in formation of **3** took longer time, but in good dr_C. *p*-Hydroxyacetophenone cannot afford **3** even at elevated temperature or in the presence of stronger base such as KOH (entry 12). In entry 13, *m*-aminoacetophenone **2k** afforded **3k** in quite poor yield and dr_C. Under typical condition, trifluoro acetophenone **2l** afforded **4l** predominantly. In the absence of base, **3l**/**3l**' was obtained in 97% yield and 36:64 dr_C (entry 14). Other aromatic ketones including α-tetralone, 2-acetyl furans, 1-acetylnaphthalene, acetylferrocene and 1,1'-diacetylferrocene, as seen in entries 15-19, gave poor results for formation of **3**.

Some aliphatic ketones also showed excellent activities to the reaction. As expected, symmetric ketones gave only one diastereomer because no chiral carbon was generated (entries 20 to 23). The addition of **1a** to acyclic asymmetric ketones showed weak selectivity (entries 24 and 26). For cyclic asymmetric ketones, racemic 2-methyl cyclohexanone **2w** afforded four stereomers of **3w** in the ratio of 5:50:7:38. Two enantiomers of **2w** reacted to **1a** respectively, forming two pairs of diastereomers, either in more than 20:80 dr_C (entry 27). More bulky 2-cyclopentylcyclopentanone **2x** cannot react to **1a** in the presence of K_2CO_3. When catalyzed by *t*BuOK, two stereomers of **3x** were stereospecifically obtained from the two enantiomers of racemic **2x**, in 42:58 ratio and 24% yield.

Significant epimerization of **1a** to **1a**/**1a'** wasn't detected during the above addition. We believed that **1a** was stable toward K_2CO_3 or KOH in the presence of active ketone. However, when **1a** was excess or inactive ketone was used, epimerization of **1a** was observed. As seen in Table 2, low conversion for inactive ketones always accompanied by poor dr_C (or increasing formation of **4**), which might be partly ascribed to the epimerization of **1a**.

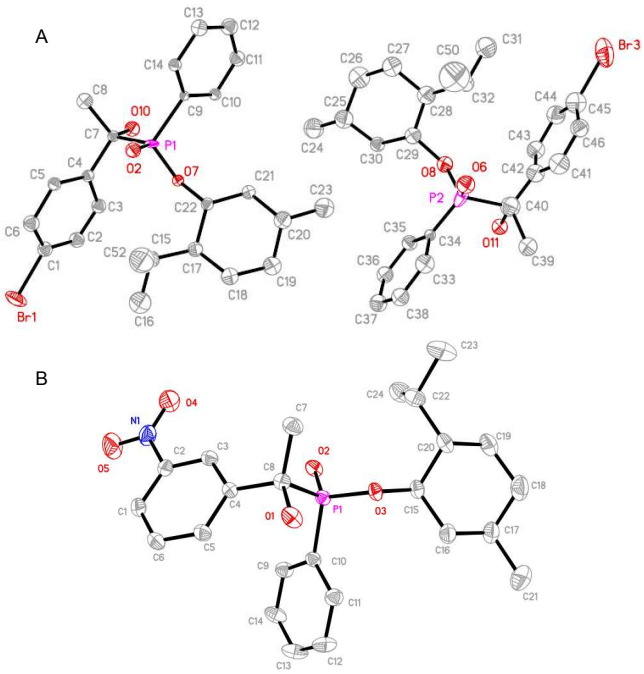


Figure 1. ORTEP drawing for S_PR_C-**3b** (A) and S_PS_C-**3g'** (B).

The structure of **3** was determined based on crystallography

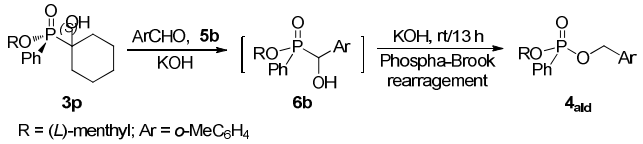
and ^{31}P-NMR spectroscopy. Formation of sole diastereomer from symmetric ketone and **1a** exhibited integral stereochemistry on phosphorus, and the S_P configuration of **3p**[24] indicated *P*-retention mechanism. The *R* configuration on α-carbon was confirmed by X-ray diffraction of **3b**, **3i** and **3j** (Figure 1). **3g'** was similarly confirmed to have $S_PS_{\alpha\text{-}C}$ structure (Part B of Figure 1). On ^{31}P-NMR spectroscopy, the peaks of S_PR_C-**3** located at lower field than S_PS_C-**3'**. For asymmetric aliphatic ketones, except for S_PR_C-**3u** (entry 25), the structures of other adducts were not confirmed.

2. Aldehyde/ketone Exchanging Reaction and Proposed Mechanism.

In some cases of Table 2, a trace amount of unconsumed **1a** was detected during addition to **2**, even if excess **2** was used. The consequence exhibited reversible reaction.[21] For to further confirm the mechanism, aldehydes or ketones-exchanging reaction was examined. When **3b** was stirred with ketone **2** in the presence of K_2CO_3, phosphorus moiety was combined to **2** to form new kind of **3**. As seen in entries 1-2 of Table 3, both aromatic and aliphatic ketones can accept transferring phosphorus from **3**. The ketone-exchanging depended on the structure and concentration of additional ketone. For example, cyclohexanone **2p** was more active than *p*-methoxyacetophenone **2i**. Two equiv **2p** formed more exchanged adduct **3p** (entries 2-3). The reaction of a mixture of **3b**/**3b'** to **2p** afforded **3p**, which also confirmed the different configuration on α-carbons of **3b** and **3b'**.

Exchanging also occurred for aldehydes. R_PR_C-**6a** was obtained from addition of S_P-**1a'** to benzaldehydes **5a**.[22] When reacted with **2p**, its *R*-phosphorus moved to cyclohexanone and kept retention, affording R_P-**3p** (entry 4). In a similar reaction to *o*-anisaldehyde **5b**, four peaks from 35.0 to 36.2 ppm were observed on ^{31}P-NMR spectroscopy, two of the them were assigned as unconsumed R_PR_C-**6a** and its epimerized partner R_PS_C-**6a**, and the two others, in 29% yield and 24:76 ratio, were assigned as newly formed R_PR_C-**6b** and R_PS_C-**6b** via aldehyde exchanging (entry 6). However, as shown in entry 7, aromatic ketone cannot accept phosphorus from R_PR_C-**6a**.

Catalyzed by either K_2CO_3 or KOH, aliphatic ketones can also be exchanged (entries 8-11). For example, **3p** and acetone **2r** afforded **3r** in 10-13% yield. However, aromatic aldehydes difficultly accepted phosphorus combined to aliphatic ketones. When *o*-anisaldehyde **5b** was stirred with **3p** in the presence of K_2CO_3, expected **6b** wasn't detected. In the presence of stronger base KOH, *O*-phosphorylated aldehyde $\mathbf{4_{ald}}$ was obtained, probably via irreversibly Phospha-Brook rearrangement of **6b** (entries 10- 11 and Scheme 1).



Scheme 1. Formatio of $\mathbf{4_{ald}}$ in the presence of KOH.

These results exhibited aliphatic ketones combined to phosphorus more firmly than aromatic ketones. As attacking reagents, aliphatic carbonyl exhibited more active than aromatic carbonyl, and aldehyde carbonyl more active than ketone carbonyl. The orders also indicated their affinities to phosphorus. As leaving moieties, the above orders of carbonyl were reversed.

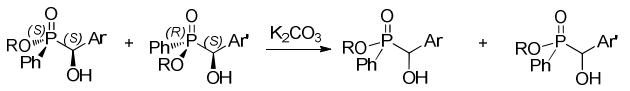
Table 3. Ketone or aldehyde exchanging reaction for **3** or **6**.

3: R^1, R^2=alkyl
6: R^1=alkyl; R^2=H
2: ketone
5: aldehyde
another **3** or **6**

entry	**3** or **6**	aldehyde or ketone	base/time(h)	Yield % (dr_P)(dr_C)[a]
1	*p*-BrC_6H_4, Me, **3b**	*p*-$MeOC_6H_4$, Me, **2i** (2 eq)	K_2CO_3/48	**3i**, 13 (>99:1) (>99:1)
2	**3b**	$(CH_2)_5$, **2p** (2 eq)	K_2CO_3/24	**3p**, 70 (>99:1)
3	**3b/3b'** (59:41)	**2p** (1 eq)	K_2CO_3/24	**3p**, 31 (>99:1)
4	Ph, H R_PR_C-**6a**	$(CH_2)_5$, **2p** (5 eq)	K_2CO_3/48	R_P-**3p**, 15 (<1:99)
5	Ph, H R_PR_C-**6a**	*o*-$MeOC_6H_4$, H, **5b** (1 eq)	none/24	NR[b]
6	Ph, H R_PR_C-**6a**	**5b** (2 eq)	K_2CO_3/24	R_PR_C-**6b**/R_PS_C-**6b**, 29 (<1:99)(24:76)
7	Ph, H **6a**[c]	**2a** (3 eq)	K_2CO_3/24	NR
8	$(CH_2)_5$ **3p**	Me, Me, **2r**, (2 eq)	K_2CO_3/24	**3r**, 10 (>99:1)
9	$(CH_2)_5$ **3p**	**2r**, (2 eq)	KOH/24	**3r**, 13 (>99:1)
10	$(CH_2)_5$ **3p**	**5b** (2 eq)	K_2CO_3/24	$\mathbf{4_{ald}}$ (trace)
11	$(CH_2)_5$ **3p**	**5b** (2 eq)	KOH/13	$\mathbf{4_{ald}}$, 91

[a] Typical procedure: the mixture of optically pure **3b** and **2i** was stirred in DMSO in the presence of K_2CO_3 (25% mol) for 48 h at room temperature. The yield, dr_P (in first parentheses, the ratio of S_P/R_P) and dr_C (in second parentheses, if applicable, the ratio of R_C/S_C) were estimated by ^{31}P-NMR spectroscopy. [b] The two reactants were heated in neat state at 80°C. [c] The mixture of four stereomers was used.

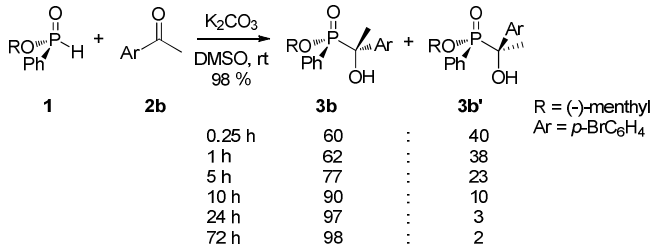
When a mixture of S_PS_C-**6a** and R_PS_C-**6c** (Ar=*p*-tolyl) was stirred in the presence of K_2CO_3, eight peaks on ^{31}P-NMR spectroscopy were observed from 34.9 to 36.4 ppm, which indicated facile exchange between aromatic aldehydes. The phosphorus having R_P and S_P configuration, respectively, added to two kinds of aromatic aldehydes, forming two kinds of adducts **6a** and **6c**, both in four stereomers (Scheme 2).



Scheme 2. Cross-exchanging reaction of aldehydes between **6a** and **6c**.

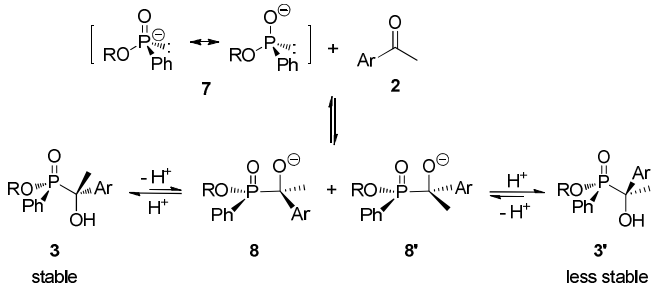
In the absence of base, no exchanging occurred between R_PR_C-

6a and **2b** (entry 5), which indicated the addition of **1a** to aldehydes or ketones was reversible under alkali condition. The variation of dr_C over time also confirmed this mechanism. When the mixture of **3b/3b'**, which was isolated from the reaction of **1a** to **3b** for 30 minutes, was stirred with K_2CO_3 for 1.5 and 5 hours, the initial 59:41 dr_C was improved to 94:6 and 97:3, respectively. At the same time, a trace amount of **1a** was detected by ^{31}P NMR spectroscopy. In fact, the reaction of **1a** to **2b** was completed within 1 hour, and prolonged reaction time only improved the ratio of **3b/3b'**. As seen in Scheme 3, dr_C of **3b/3b'** was observed in as 60:40, 90:10, and 97:3 when **1a** and **3b** were stirred for 0.25, 10, and 24 hours, respectively.[25]



Scheme 3. Improvement for dr_C of **3a/3a'** with reaction time.

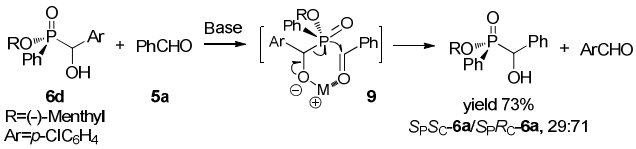
On the basis of these consequences, we believed the different thermodynamic stabilities between **3** and **3'**. As seen in Scheme 4, **1a** was converted to anion **7** by base,[26] which added to electropositive carbonyl carbon from two sides to afford adducts **8** and **8'**. Protonation of **8** and **8'** afforded **3** and **3'**, respectively. In the presence of base, more unstable **3'** would have stronger tendency to become back to **1a** and **2** through alkoxyl anion **8'**, which then was further converted to **3** through **8** after enough time.



Scheme 4. Supposed reversible mechanism for addition of **1** to ketones **2**.

During the exchanging of R_PR_C-**6a** with *o*-aisaldehyde **5b**, we noticed the formation of adduct **6b** showed 24:76 dr_C. As contrast, when **1a** and **5b** were stirred under similar condition (K_2CO_3/DMSO), **6b** was formed only in 50:50 dr_C.[22] In a separated experiment, the alkoxyl lithium salt of **6d** (Ar=*p*-chlorophenyl, mixture of two diastereomers) and benzaldehydes (2 equiv) afforded exchanging product **6a** in 73% yield and 29:71 dr_C.

The obvious selectivities for formation of **6a** and **6b** promoted us to suppose a possible alternative route for the exchanging reaction. As seen in Scheme 5, except for the above exchanging via reversible addition, directly substitution of aldehydes from phosphorus might take place. The attacking aldehyde approached to phosphorus as electrophilic reagent, meanwhile P-C bond was broken and original aldehyde was replaced as leaving group. In a possible *six*-member intermediate **9**, the crowded groups around phosphorus resulted in enhanced induction of (-)-menthyl to formation of chiral α-carbon in **6a**. To the best of our knowledge, although the bimolecular electrophilic substitution (S_E2) on phosphorus hasn't been reported, it can be explained by traditional S_N2 reaction except the electronic properties for attacking and accepting roles were reversed. During this process, the configuration on phosphorus kept retention, which was different to S_N2 reaction occurred at carbon atom.

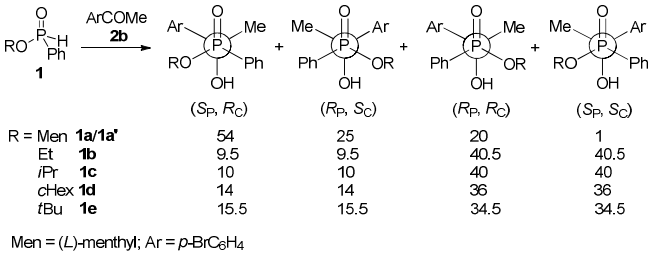


Scheme 5. Supposed bimolecular electrophilic substitution (S_E2) mechanism for aldehyde-exchanging..

3. Diastereoselectivity of the Hydrophosphorylation.

The *H*-phosphinates **1b** to **1e** containing various alkoxyl groups were prepared and employed to further explore the selctivity of hydrophosphorylation (Scheme 6). When **1d** was used to react with **2b** under the above optimized condition, two peaks at 39.4 and 39.7 ppm were observed on ^{31}P-NMR spectroscopy. The former one was confirmed as (*l*)-**3db**[27] by X-ray diffraction results (Figure 2). The ratio of (*u*/*l*)-stereomers also was improved with prolonged time, reaching 28:72 after 72 h. For the reactions of **1b-1e**, (*l*)-stereomers were also dominatly formed, whose peaks located at upfield on ^{31}P-NMR spectroscopy, and dr (ratio of *u*/*l*) were improved to 30:70-20:80 with time.

The predominantly formation of (*l*)-stereomers of **3bb-3eb** from **1b-1e**, to our surprise, was contrary to the formation of S_PR_C or (*u*)-**3b** in 98:2 dr_C (Table 2, entry 2). When the mixture of **1a**/**1a'** reacted to **2b**, four stereomers of product gave peaks at 37.8, 38.3, 38.4, and 38.7 ppm on ^{31}P-NMR spectroscopy, in the ratio of 54:25:1:20. Among those, the ratio of 54:1 for the peaks at 37.8 and 38.4 ppm, ascribed to **3b**/**3b'**, were quite coherent to 98:2 in Table 2. Meanwhile, (S_P)-**1a'** gave **3b''**/**3b'''** in even poorer ratio (25:20 or 20:25, did not confirmed) than reactions of **1b-1e**.



Scheme 6. Additions to **2b** by various *H*-phosphinates **1**.

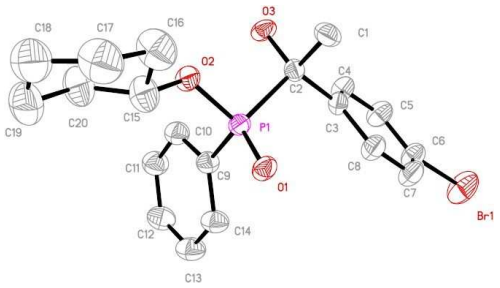


Figure 2. ORTEP drawing for (*l*)-**3db**.

The time-dependences of dr for reactions of **1a-1e** were presented in Figure 3. In the case of **1b**, yield of **3bb** became worse after reached a top, owing to the formation of *O*-phosphorylated product **4bb** via Phospha-Brook rearrangement, which lead the calculation of dr was not quite accurate. **1b-1e** showed distinctly reversed selectivity to **1a**. It seemed that dr became worse with increasing volume of alkoxyl. For (S_P)-**1a'**, the worst ratio of **3b''**/**3b'''** kept around 50:50, and was not improved with time.

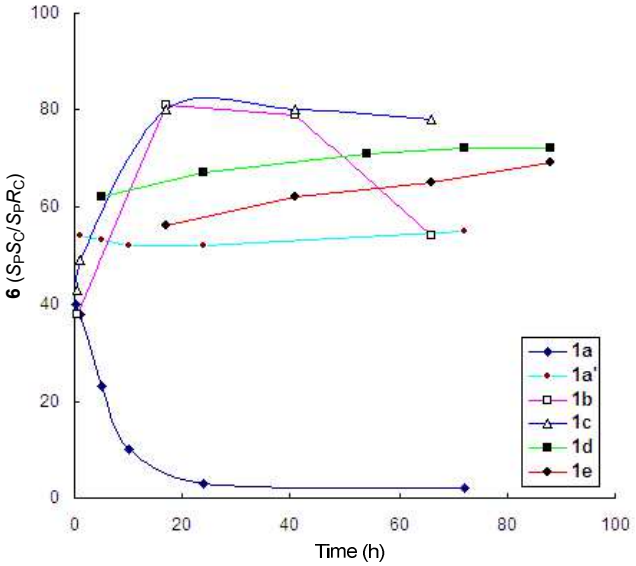


Figure 3. Time-dependences of dr for hydrophosphorylation of **2b** with **1a-1e**.

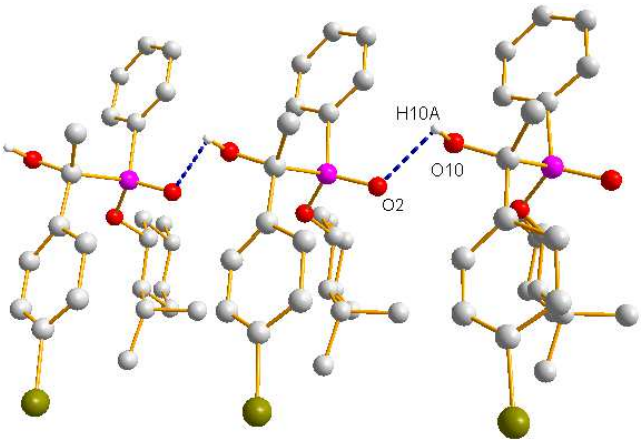


Figure 4. One-dimensional chain structure of **3b**.

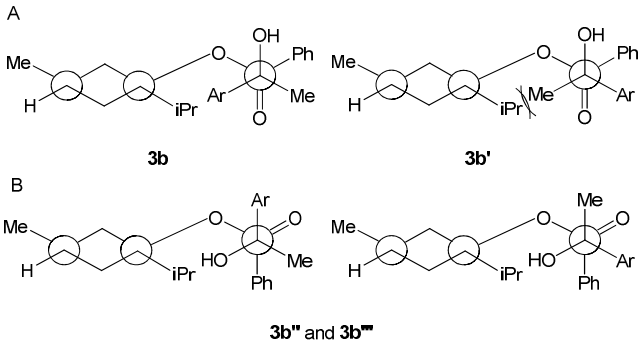


Figure 5. Supposed conformation of **3b/3b'** (A) and **3b''/3b'''** (B).

The unusual consequences of Figure 3 indicated the diastereoselectivities greatly depended on alkoxyl groups of **1**. As shown in Figure 4, intermolecular hydrogen bond between α-hydroxyl and P=O consisted one-dimensional chain structure of **3b**, in which the two oxygen atoms located at against positions of a cross conformation. Because of the restriction of *six*-member ring of menthyl, *ortho*-isopropyl located near to α-carbon of **3**. In the ORTEP drawing for **3b** (Part A of Figure 1), benzene ring of acetophenone moiety faced to the isopropyl with its plane, and two methyl of isopropyl oriented far to benzene ring. In this manner, the spatial repulsion between isopropyl to aryl might be weaker than that to methyl (Figure 5).

We supposed approaching of *ortho*-isopropyl to α-methyl lead lower stability of **3b'**. In the adduct **6** obtained from **1a** and aldehydes, the spatial interaction between isopropyl to α-hydrogen was not significant, therefore formation of **6** showed poor dr_C.[22] For **1b-1e**, the similar *ortho*-effect of isopropyl wasn't existed. Weakened repulsion between alkoxyl to α-methyl resulted in (*l*) or R_PR_C+S_PS_C stereomers **3bb-3eb** were more stable. Big alkxoyl such as in **1e**, tended to form more (*u*)-stereomer and give poor *u/l* ratio.

The even poorer dr for formation of **3b''/3b'''** from (S_P)-**1a'** might also be ascribed to the size of menthoxyl. As shown in Part B of Figure 5, the long distance between isopropyl to α-aryl or α-methyl in **3b''** and **3b'''** lead weak or negligible interaction between them. We believed menthoxyl in **1a'** has similar size to phenyl, so that the stabilities difference between **3b''** and **3b'''** was insignificant.

Aryl groups of **2** also influenced dr_C of **3**/**3'**. For big aryl, the planar orientation of benzene ring toward isopropyl might be hindered. The increased repulsion of isopropyl to aryl lead decreased stability-difference between two diastereomers **3**/**3'**. For example, *meta*-substituted acetophenones afforded **3e** and **3k**, respectively, in less than 70:30 dr_C (entries 6 and 13 of Table 2). *ortho*-Chloroacetophenone cannot form corresponding *C*-phosphorylated product **3** (entry 5 of Table 2). In the reaction of *m*-nitroacetophenone **2g** with **1a**, **3g'** even was afforded as major product, in reversed dr_C 12:88 (entry 8 of Table 2).

Density functional calculations of **3b/3b'** and **3g/3g'** supported the above assumption. As shown in Table 4, the single point energy of **3b** was lower than **3b'** by 14.25 kcal/mol, and **3g'** was lower than **3g** by 0.15 kcal/mol (for details, please see SI). Theses results were consistent with the observation of dr_C for the two compounds, as shown in Table 2.

Table 4. Density functional calculations of **3b/3b'** and **3g/3g'**.[a]

Compounds	$E_{SpRc\text{-}opt}$	$E_{SpSc\text{-}opt}$	$E_{SpRc\text{-}opt}$ - $E_{SpSc\text{-}opt}$ (kcal/mol)
3b/3b' [b]	-4075.3727 a.u.	-4075.3500 a.u.	-14.25
3g/3g' [b]	-1706.0739 a.u.	-1706.0742 a.u.	0.15

[a] The whole calculations were performed in Gaussian 09 using the B3LYP density functional. [b] Structures of **3b** and **3g'** were referred from X-ray diffraction results.

Additionlly, dr_C were also influenced by solubility-difference between two stereomers **3**/**3'**. When the mixture of **3b**/**3b'** (59:41) was stirred in DMSO, according the concentration of typical procedure of Table 2, the ratio of **3b**/**3b'** was detected as 22:78 and 62:38 in solution and unsolvable solid, respectively. These results indicated **3b'** was more solvable than **3b**, and have more chance being converted back to **1a** and **2b**. The dr_C for formations of **3f**/**3f'** and **3g**/**3g'** were obviously improved when reactions were carried out in concentrated solution (entries 7-8 of Table 2). However, in some cases such as entry 6, **1a** and **2e** in DMSO formed a clear solution, **3e**/**3e'** was generated still in 67:33 dr_C. We believed thermodynamic stability took more important role than solubility to the diastereoselectivity.

Conclusions

The hydrophosphorylation of ketones **2** with optically pure *H*-phosphinate **1a** was catalyzed by potassium carbonate, affording *P,C*-stereogenic tertiary α-hydroxyphosphinates **3**. During the reaction, the configuration on phosphorus stereospecifically kept retention, and the diastereoselectivities for formation of chiral α-carbon depended on the structures of ketones **2**. Excellent dr_C and yields were realized for most aryl methyl ketones and cyclic asymmetric ketones. Acyclic aliphatic ketones showed weak selectivities.

Reversible addition and stabilities-differences between two diastereomers of adducts were contributed to the selectivities. Aldehydes/ketones exchanging reaction only took place in the presence of base, which confirmed the reversible mechanism. During the exchanging, phosphorus was stereospecifically transferred in retention configuration. As attacking reagents, aliphatic or aldehyde carbonyl was more active than aromatic or ketone carbonyl. The two diastereomers **3**/**3'** showed different stabilities, the more stable stereomer was converted to less stable one via the reversible addition, so that dr_C were obviously improved over reaction time.

The thermodynamic stabilities of two diastereomers of adducts were examined. For most adducts obtained from **1a**, S_PR_C stereomers were more stable than S_PS_C ones. For **1b** to **1e**, (*l*) or R_PR_C+S_PS_C adducts were stable. Addition by **1a** showed excellent dr_C that was attributed to *ortho*-isopropyl on menthyl. The approaching and repulsion between *ortho*-isopropyl to α-methyl within **3** resulted in the lower stabilities of S_PS_C diastereomers. Alkoxyl in **1b**-**1e** were thought as smaller than phenyl, so that these compounds exhibited reversed dr_C to **1a**. The worst selectivity for **1a'** was explained by the similar sizes of menthoxyl to phenyl.

Although thermodynamic controlled reactions are widely applied in asymmetric synthesis, the similar *P*-involved reversible equilibrium, to the best of our knowledge, hasn't been reported. Our research employed simple catalysts to realize diastereoselective hydrophosphorylation of ketones and preparation of *P,C*-stereogenic α-hydroxyphosphinates. The consequences of the stereochemistry on both phosphorus and carbon atoms are hoped to deeply reveal the mechanism of *P*-involved asymmetric reactions.

Notes and references

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† Electronic Supplementary Information (ESI) available: [Experimental procedures, spectral data for products, and crystallographic information are included]. See DOI: 10.1039/b000000x/

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