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One-Pot Process That Efficiently Generates Single Stereoisomers of 1,3-Bisphosphinylpropanes Having Five Chiral Centers

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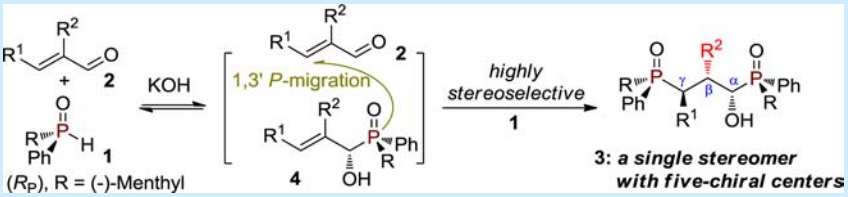
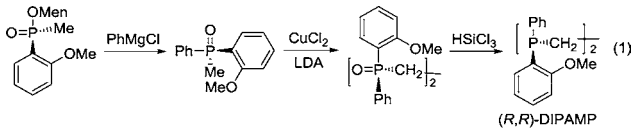
Supporting Information



ABSTRACT: *P,C*-Stereogenic 1,3-bisphosphinylpropanes **3** that have up to five stereogenic centers could be obtained stereoselectively in high yields by a one-step reaction of (R_P)-menthylphenylphosphine oxide **1** with α,β-unsaturated aldehydes **2** catalyzed by KOH at room temperature. A mechanism was proposed as to involve a stereoselective intermolecular 1,3′-phosphorus migration from the 1,2-adduct of **1** with **2** to another **2** generating a 1,4-adduct that subsequently reacts with **1** to produce **3**.

P-Stereogenic phosphorus compounds attracted extensive attention in recent years because of their wide applications as biologically active chemicals[1] and excellent chiral ligands or organocatalysts[2] in asymmetric synthesis,[3,4] as exemplified by the famous (*R,R*)-DIPAMP synthesized by Knowles who was recognized with the Nobel Prize in Chemistry in 2001 (eq 1).[5]



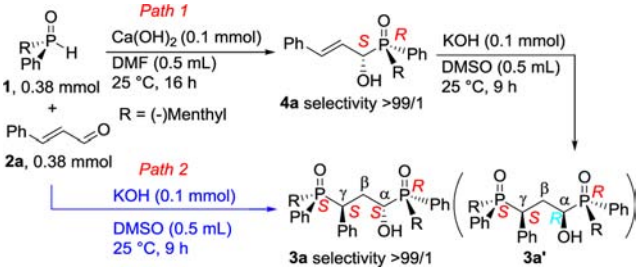
As represented by DIPAMP, in order to acquire high stereoselectivity, a chelating ligand with more than one chiral center is usually employed.[4] However, the preparation of such ligands is time-consuming and difficult because of multistep synthetic procedures and tedious resolution processes.[2−6]

Herein we report a one-pot reaction of the readily prepared (R_P)-menthylphenyl phosphine oxide[7] **1** with α,β-unsaturated aldehydes **2** affording, stereoselectively, 1,3-bisphosphinylpropanes **3** in high yields. This simple process can almost exclusively produce *a single stereoisomer* **3** having up to *five* chiral centers (eq 2). Although the bioprocess can generate compounds having

multiple stereocenters efficiently, to the best of our knowledge, such an anthropogenic process, that can generate so many chiral centers selectively by such a simple reaction, is hardly known.[8]

Compound **1** (0.38 mmol) and *trans*-cinnamaldehyde **2a** (0.38 mmol) were dissolved in DMF (0.5 mL). As expected,[9] at room temperature, in the presence of $Ca(OH)_2$ (0.1 mmol), the addition of the P(O)H compound to the aldehyde proceeded highly diastereoselectively to produce the corresponding 1,2-adduct **4a** quantitatively after 16 h (path 1, Scheme 1). Although

Scheme 1. Stereoselective Formation of $S_{\gamma\text{-}C}$-3a



analogue base-catalyzed addition of P(O)H compounds to α,β-unsaturated carbonyl compounds was known to give both the 1,2-adduct and 1,4-adduct, no such 1,4-adduct was detected under the current conditions.[10] Interestingly, however, on further pursuing the reaction, we found that a bisphosphinylation product **3a** was obtained by treating **4a** with a stronger base such as KOH at room temperature. Thus, the isolated **4a** (0.33 mmol) was treated with KOH (0.12 mmol) in DMSO at room temperature for 9 h; compound **4a** completely disappeared to

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produce **3a** in 78% isolated yield (based on **1**). It was more surprising that the very high stereoselectivity at **3a** was achieved; i.e., **3a** with four chiral centers was obtained almost as a pure single stereoisomer having a configuration of $R_{\alpha\text{-P}},S_{\alpha\text{-C}},S_{\gamma\text{-C}},S_{\gamma\text{-P}}$.

As followed by ^{31}P NMR spectroscopy, the treatment of **4a** with KOH produced, at the early stage of the reaction (0.5 h), two pairs of new signals at δ 50.21, 43.29 and 49.46, 42.11 ppm, respectively, with a ratio of 14/86. The former was assigned to **3a′** with the *R* configuration at α-carbon, and the latter was due to **3a** with the *S* configuration at the α-carbon (vide infra). Signals due to **3a′** gradually disappeared and were negligible after 9 h.[11] Therefore, the high stereoselectivity was achieved by retention of configurations at the two phosphorus atoms and selective generation of two new chiral carbon centers, C_γ and C_α, with the latter being formed thermodynamically.[9]

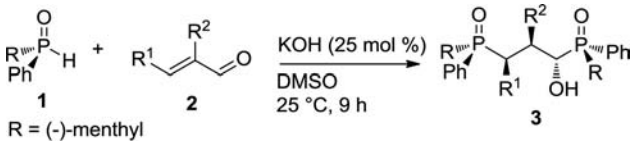
As shown in Scheme 1 (path 2), **3a** could be more conveniently prepared stereoselectively directly from **1** (0.38 mmol) and **2a** (0.38 mmol) in the presence of KOH (0.1 mmol) (76% isolated yield, >99:1 stereoselectivity). Surprisingly, the molar ratio of the P(O)H compound **1** to *trans*-cinnamaldehyde **2a** is pivotal to the stereoselectivity of **3a**. More or less of **1** resulted in a decreased selectivity of **3a**. For example, **3a** was formed in only about 50% yield, accompanied by other stereoisomers, when the ratio of **1**/**2a** was either 1:2 or 2:1. In these cases, the stereoisomers having various configuration on γ-carbon atom were supposed to be formed simultaneously with **3a** and **3a′**, which resulted in complicated NMR spectral. The detailed discussion about diastereoselectivies on α- and γ-carbon could be found in the Supporting Information.

This reaction could be easily applied to other vinyl aldehydes **2** to efficiently produce the corresponding 1,3-bisphosphinylalkanes highly stereoselectively (>99:1, Table 1). Thus, in addition to **2a**, other substituted cinnamaldehydes having methyl (runs 1 and 2), methoxy (runs 3 and 4), and halogen atoms (runs 6 and 7) on the benzene ring, all gave high yields of the bisphosphinylation products selectively. Similarly, an aliphatic crotonaldehyde (run 8) also smoothly produced the corresponding bisphosphinylation adduct **3h** highly selectively in 76% isolated yield. A more surprising result was obtained from the reaction of 2-methyl cinnamaldehyde (run 9); i.e., the product **3i** having up to five chiral centers was also obtained almost as a pure stereoisomer by this one-pot reaction.[12] A mixture of *E* and *Z* citral afforded two stereoisomers of **3j** in 1:1 ratio (run 10), and one of them was isolated in 30% yield.

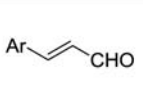
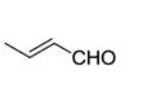
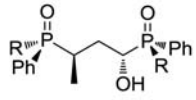
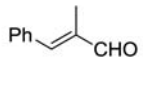
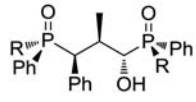
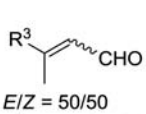
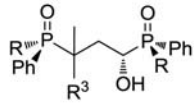
As to the determination of the stereochemistry of **3**, as described above, ^{1}H and ^{31}P NMR spectroscopies could clearly distinguish the predominantly formed diastereomers with the minor one (Supporting Information). Fortunately, good crystals were obtained from **3c**, and its absolute configuration was determined by X-ray analysis, unambiguously showing that the compound has $R_{\alpha\text{-P}},S_{\alpha\text{-C}},S_{\gamma\text{-C}},S_{\gamma\text{-P}}$ configuration (Figure 1).

Careful mechanistic studies revealed an interesting path for the stereoselective formation of **3a** (Scheme 2). Thus, the reaction did not proceed via the known Michael 1,4-addition of **1** with **2a**[10] forming **5a**, which then gave **3a** via 1,2-addition of **1** to the aldehyde (route B). Rather, the reaction was proposed to take place by 1,2-addition of **1** to **2a** forming **4a** first (route A). A highly stereoselective intermolecular phosphinyl migration, perhaps via an intermediate **9**, afforded **5a** which reacted further with **1** to selectively produce **3a**. Although such an intermediate **9** was not captured successfully, experiments showed that **4a** did stereoselectively change to **3a** (Scheme 2). Moreover, monitoring the reaction of **1** with **2a** catalyzed by KOH using

Table 1. Stereoselective Preparation of 3 from Vinyl Aldehydes and 1



1 2 3

Run	2	3	Isolated yield %[a]
1		Ar = Ph,	**3a**, 76
2		Ar = *o*-MeC$_6$H$_4$,	**3b**, 75
3		Ar = *p*-MeC$_6$H$_4$,	**3c**, 79
4		Ar = *o*-MeOC$_6$H$_4$,	**3d**, 81
5		Ar = *m*-MeOC$_6$H$_4$,	**3e**, 82
6		Ar = *p*-ClC$_6$H$_4$,	**3f**, 70
7		Ar = *p*-FC$_6$H$_4$,	**3g**, 80
8			**3h**, 76
9			**3i**, 50[b]
10			**3j-A**, 30[c]

E/*Z* = 50/50
R^3 = Me$_2$C=CHCH$_2$CH$_2$

[a]A typical procedure: **1** (0.38 mmol) and **2a** (0.38 mmol) were stirred in DMSO (0.5 mL) in the presence of KOH (25 mol %) at room temperature for 9 h. Aqueous saturated ammonium chloride solution (2 mL) was added. The resulting solid was collected by filtration, dried under air, and purified by recrystallization. The yields were calculated on the basis of **1**. [b]One stereoisomer of **3i** was formed. The absolute configuration on β-C was tentatively assigned to *S* (ref 12). [c]Two stereoisomers were formed in a 1:1 ratio, and one of them was isolated in 30% yield. The absolute configuration was not determined.

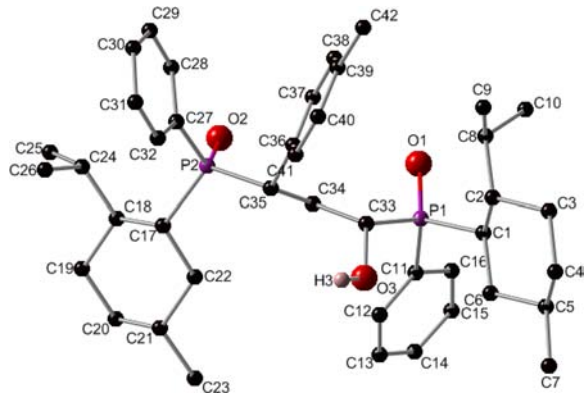


Figure 1. X-ray crystal structure of **3c**.

^{31}P NMR spectroscopy also showed that **4a** was quickly formed as the major product at the early stage of the reaction, which then changed to **3a**.

Strong evidence supporting the above proposal come from the experiments using 4-phenyl-3-buten-2-one **6** as the substrate (Scheme 3), in which due to the steric hindrance, 1,2-addition

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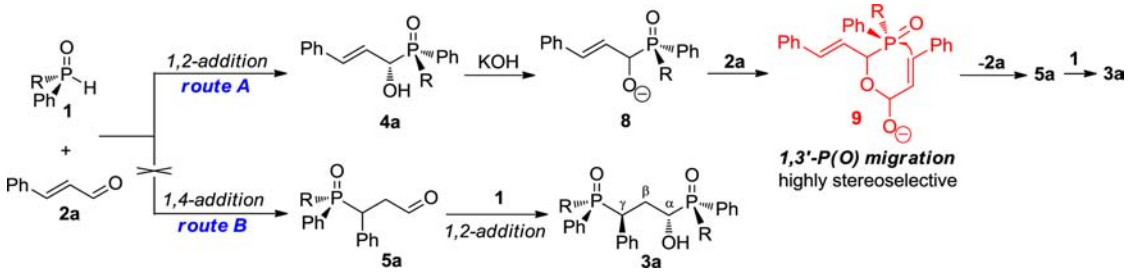
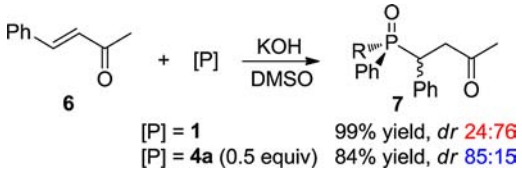
Scheme 2. Proposed Mechanism for Formation of 3a



Scheme 3. Reactions of 4-Phenyl-3-buten-2-one 6 with Phosphorus Reagents



product was not produced under this reaction conditions.[9] First, the diastereoselectivity for the direct 1,4-addition was low. Thus, a DMSO (0.5 mL) solution of **6** (0.38 mmol) and **1** (0.38 mmol) was stirred at room temperature for 5 h to produce the 1,4-addition product **7** with a poor diastereoselectivity of 24:76. Interestingly, under similar conditions, replacing **1** with **4a** also produced 84% yield of **7**. However, the diastereoselectivity was 85:15, a reversed selectivity to that of the direct 1,4-addition. This result showed that an intermolecular phosphinyl migration is possible which should operate in the formation of **3**.

Thus, as shown in Scheme 2, **4a** was converted to alkoxide anion **8** that might attack the carbonyl of **2a** to generate **9**. Within **9**, the phosphorus shifted from 1-position of one molecule of **2a** to the 3-position of another, via a possible *six*-membered cyclic intermediate, to form the 1,4-adduct **5a**. We assume that perhaps the vacant *d*-orbital of amphiphilic phosphorus interacts with the alkenyl double bond, forming a pentacoordinated structure and the excellent asymmetric induction effect of the crowded chiral phosphinyl group leads to the stereoselective formation of the chiral carbon of **5a**, which then reacted with **1** to give the single stereoisomer of **3a**[13] through an equilibrium.[9] During the migration of phosphorus, the configuration was retained.

The possibility of intramolecular phosphinyl migration within **4a** was also examined. When treated with *n*-BuLi, **4a** was similarly converted to alkoxide anion **8**. A phospha-Brook rearrangement, i.e., phosphinyl migration to oxygen,[9a] probably occurred to afford phosphinate that might be further converted to **3a** via intramolecular phosphinyl migration. However, the expected **3a** was not detected in this experiment. Therefore, route A via intermediate **9** was supposed as more possible for formation of **3a**, within which the attacking of phosphorus to carbon−carbon double bond took place more easily. Importantly, our recently reported reaction of secondary phosphine oxides with α,β-unsaturated aldehydes confirmed the formation of intermediate **9**.[14]

In summary, the single stereoisomer of 1,3-bisphosphinylalkanes that has up to five stereogenic centers was synthesized from secondary phosphine oxide **1** and α,β-unsaturated aldehydes. A novel intermolecular migration of phosphorus via a *six*-membered cyclic intermediate was proposed to take place. During the process, chiral β- and γ-carbon atoms were generated; meanwhile, the configuration of two phosphorus atoms was retained. The high stereoselectivity of the chiral α-carbon benefited from a reversible addition of **1** to the aldehydes. Our research provided a quite short and convenient route for the preparation of the useful multiple *P,C*-stereogenic 1,3-bisphosphinylalkanes that can be potentially converted to the highly useful chiral 1,3-bisphosphinoalkanes via well-established modification of hydroxyl and reduction of phosphinyl.[15] Further studies on the clarification of the mechanism and applications of the products are in progress in this laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, full spectroscopic data, and copies of ^{1}H, ^{31}P, and ^{13}C spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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(11) This conversion of *R* configuration of the carbon to *S* configuration was due to the reversible addition of **1** to the aldehyde which has been observed recently (ref 9).

(12) On the basis of the structure of **3c** and the Cram rule, the *β*-methyl of **3i** was supposed to occupy the position far away from the big phenyl group, and thus, **3i** is assumed to have a $R_{\alpha\text{-P}},S_{\alpha\text{-C}},S_{\beta\text{-C}},S_{\gamma\text{-C}},S_{\gamma\text{-P}}$ configuration.

(13) All attempts to identify **5a** failed due to its high reactivity. For example, when **4a** and an excess amount of isobutyraldehyde were treated with KOH, **3a** was obtained predominantly together with a trace amount of the product by the addition of **1** to isobutyraldehyde (ca. 2% yield). In addition, although an aldehyde-exchange reaction takes place for other *α*-hydroxyl phosphinates, **3a** kept unchanged and the expected **5a** could not be detected at all when mixing **3a** with *o*-chlorobenzaldehyde (ref 9b). We assumed that the high reactivity of **5a** might be ascribed to a hypervalent bond between the carbonyl oxygen and phosphorus, through the *p*-electron filling of the vacant *d*-orbital of phosphorus via a *five*-membered cycle, to activate the C═O bond. For similar hypervalence bonds, see: Akiba, K.-y.; Okada, K.; Ohkata, K. *Tetrahedron Lett.* **1986**, *27*, 5221−5224.

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