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# A One-Pot *O*-Phosphinative Passerini/Pudovik Reaction: Efficient Synthesis of Highly Functionalized α-(Phosphinyloxy)amide Derivatives

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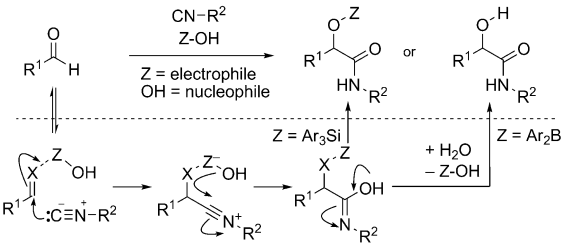
**Abstract:** A one-pot *O*-phosphinative Passerini/Pudovik reaction has been developed, based on reacting aldehydes, isocyanides, and phosphinic acids followed by the addition of second aldehydes to form the corresponding α-(phosphinyloxy)amide derivatives. This is the first reported instance of a Passerini-type, isocyanide-based multicomponent reaction using a phosphinic acid instead of a carboxylic acid. The nucleophilicity of the phosphinate group allows a subsequent catalytic Pudovik-type reaction, affording the highly functionalized α-(phosphinyloxy)amide derivative in high yield. A wide range of aldehydes and isocyanides are applicable to this reaction.

## Introduction

The multicomponent reactions of isocyanides represent convergent processes in which three or more starting materials are combined to generate a new product in practical, time-saving, one-pot operations, by applying combinatorial strategies or parallel synthesis. Historically, the reaction of an isocyanide with an aldehyde and a carboxylic acid to generate an α-acyloxy amide was discovered by Passerini in 1921.[1] Subsequently, various modifications to this reaction were developed,[2] although only recently have other species been substituted for the carboxylic acid. The carboxylic acid is typically a crucial component of the mixture due to the specific mechanism by which the Passerini reaction progresses. This mechanism has been widely studied and appears to involve activation of the aldehyde by the carboxylic acid, followed by addition of the isocyanide and trapping of the resulting nitrilium intermediate by the carboxylate to afford the final product by migration of the acyl group onto the oxygen atom derived from the aldehyde. The carboxylic acid is, therefore, generally a necessity during the reaction of an isocyanide with an aldehyde, or with an imine, as in the Ugi reaction. The requirement to use a carboxylic acid unfortunately limits the application of this reaction to the synthesis of a narrow range of molecules. Only a few examples using other components in place of the carboxylic acid have been reported to date. One example is the *O*-arylative Passerini reaction using nitrophenol derivatives, developed by El Kaim and Grimaud in 2006.[3] Taguchi also reported the direct alkylative Passerini reaction of an aldehyde, an isocyanide and a free aliphatic alcohol, catalyzed by $In^{III}$.[4] Acetals and ketals are also useful for the reaction of isocyanides when catalyzed by Lewis or Brønsted acids, affording α-alkoxyimidates.[5] As described above, the acyl group in a carboxylic acid acts as an electrophile while its OH group works as a nucleophile to the nitrilium intermediate during the Passerini reaction. Thus, other molecules containing both electrophilic and nucleophilic groups (Z-OH) could potentially act in a similar manner to the carboxylic acid during the Passerini reaction. Based on this hypothesis, we have previously developed an *O*-silylative Passerini reaction and the borinic acid catalyzed α-addition of an isocyanide (Scheme 1).[6] We initially examined whether phosphinic acid was able to participate in a three-component coupling reaction with an aldehyde and an isocyanide to afford the corresponding α-(phosphinyloxy)-amide [Eq. (1), step 1]. We further investigated the reaction of the resulting α-(phosphinyloxy)amide with aldehydes to generate α-hydroxyphosphinate derivatives [Eq. (1), step 2]. It has been established that α-hydroxyphosphinic acid and its deriva-




**Scheme 1.** The *O*-silylative Passerini reaction and the borinic acid catalyzed α-addition of an isocyanide.

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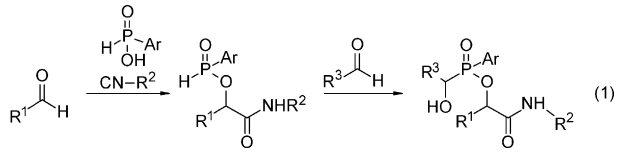
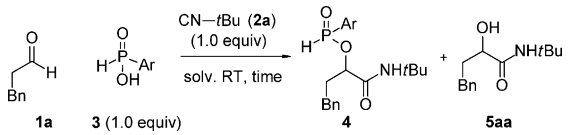
tives, such as the α-hydroxyphosphinates, can function as very useful enzyme inhibitors.[7] For example, α-hydroxyphosphinate-derived peptides have been applied as inhibitors of human immunodeficiency virus (HIV) protease[8] and renin,[9] as well as GABA antagonists[10] and herbicides.[11] The addition of a phosphite to an aldehyde, known as the Pudovik reaction, is the most versatile synthetic pathway to the α-hydroxyphosphinates. Herein, we describe the first example of a one-pot phosphinative Passerini/Pudovik reaction, consisting of the reaction between an aldehyde, an isocyanide and a phosphinic acid followed by the addition of a second aldehyde to give the corresponding α-hydroxyphosphinate derivative [Eq. (1)].




## Results and Discussion

Our initial studies used a combination of phenylpropionaldehyde (**1a**), *tert*-butyl isocyanide (**2a**) (1.0 equiv), and phenylphosphinic acid (**3a**) (1.0 equiv) in toluene at room temperature (Table 1, entry 1). We were pleased to observe that the expected α-(phosphinyloxy)amide (**4aaa**) was obtained in 81% yield as a mixture of diastereomers after 3 h with little or no generation of side products under these conditions. This reaction proceeded efficiently in both dichloromethane and diethyl ether to afford **4aaa** in high yields (entries 2 and 3). The use of the cyclic ether THF as the solvent was less effective, resulting in the formation of α-hydroxyamide (**5aa**) in 13% yield, likely due to the hydrolysis of **4aaa** (entry 4). Methanol, which has been used in the Ugi reaction as a protic solvent, produced a very sluggish reaction from which only **5aa** was obtained, in 55% yield, after 24 h (entry 5). Increasing the amount of the isocyanide or the phosphinic acid to 1.5 equivalents did not lead to any improvement in yield (entries 6 and 7), which indicated that 1.0 equiv of both the isocyanide and the phosphinic acid are sufficient to obtain the desired product in high yield (entry 2). After having established an efficient method for the *O*-phosphinative Passerini reaction, we then set out to evaluate the effectiveness of phosphinic acids bearing other substituents (entries 8–11). When employing either (4-methoxyphenyl)-phosphinic acid (**3b**), (4-tolyl)phosphinic acid (**3c**), or (4-chlorophenyl)phosphinic acid (**3d**), the product was obtained in good yields (entries 8–10), while **5aa** was the major product when using (4-nitrophenyl)phosphinic acid (**3e**) (entry 11).

**Table 1.** Results of the *O*-phosphinative Passerini reaction under varying conditions.




**1a** **3** (1.0 equiv) **4** **5aa**

| Entry | Ar | Solvent | *t* [h] | Yield of **4** [%] | Yield of **5aa** [%] |
|---|---|---|---|---|---|
| 1 | Ph (**3a**) | toluene | 3 | 81 (**4aaa**) | – |
| 2 | Ph (**3a**) | $CH_2Cl_2$ | 3 | 96 (**4aaa**) | – |
| 3 | Ph (**3a**) | $Et_2O$ | 4 | 90 (**4aaa**) | – |
| 4 | Ph (**3a**) | THF | 2 | 62 (**4aaa**) | 13 |
| 5 | Ph (**3a**) | MeOH | 24 | – | 55 |
| 6[a] | Ph (**3a**) | $CH_2Cl_2$ | 4 | 94 (**4aaa**) | – |
| 7[b] | Ph (**3a**) | $CH_2Cl_2$ | 4 | 94 (**4aaa**) | – |
| 8 | 4-$MeOC_6H_4$ (**3b**) | $CH_2Cl_2$ | 5 | 75 (**4aab**) | 14 |
| 9 | 4-$MeC_6H_4$ (**3c**) | $CH_2Cl_2$ | 4 | 79 (**4aac**) | 14 |
| 10 | 4-$ClC_6H_4$ (**3d**) | $CH_2Cl_2$ | 4 | 86 (**4aad**) | 11 |
| 11 | 4-$O_2NC_6H_4$ (**3e**) | $CH_2Cl_2$ | 2 | 39 (**4aae**) | 59 |

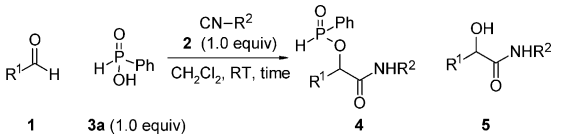
[a] Using 1.5 equiv of **2a**. [b] Using 1.5 equiv of **3a**.

We also attempted to expand the range of isocyanides and aldehydes applicable to the present *O*-phosphinative Passerini reaction, utilizing phenylphosphinic acid (**3a**) in all cases, with the results shown in Table 2. Throughout these trials, the optimal amounts of the aldehydes **1a**–**e** (1.0 equiv) and the isocyanides **2a**–**g** (1.0 equiv) were used in the presence of 1.0 equiv of phenylphosphinic acid (**3a**). The results demonstrate that these conditions allow the reaction to proceed when employing a wide variety of aldehydes and isocyanides, and that most reactions were complete within 24 h. The reactions of aliphatic isocyanides ($R^2$ = *t*Oct, *c*Hex, and Bn) with **1a** and **3a** gave the products in good to high yields (Table 2, entries 2–4). Aldehyde **1a** was consumed within 7 h when *tert*-octyl isocyanide (**2b**) and cyclohexyl isocyanide (**2c**) were used, generating the products in 89 and 86% yields, respectively (entries 2 and 3). In the case of benzyl isocyanide (**2d**), the desired product **4ada** was afforded in 98% yield without any of the hydrolyzed product **5ad** (entry 4). Aromatic isocyanides were also employed in this reaction (entries 5–7). When phenyl isocyanide (**2e**) was used, the corresponding α-hydroxyamide **4aea** was obtained in 67% yield (entry 5). An aromatic isocyanide bearing an electron-donating methoxy group at the *para* position also exhibited high reactivity, forming the corresponding product in 80% yield (entry 6). In the case of an aromatic isocyanide bearing an electron-withdrawing group bromo at the *para* position, however, the reaction generated a complex mixture of products (entry 7).

The reactivity of various aldehydes with *tert*-butyl isocyanide (**2a**) was next examined. Aliphatic aldehydes **1b** and **1c** gave the products in 84 and 61% yields, respectively (entries 8 and 9). Cinnamaldehyde (**1d**) and benzaldehyde (**1e**) both demonstrated very low reactivities, and their reactions did not produce any of the desired product (entries 10 and 11).

During the course of this investigation, we anticipated that the subsequent coupling of a fourth component could be accomplished by exploiting the nucleophilic phosphorus atom in the phosphinate group of **4**. Since we had already found that the α-(phosphinyloxy)amides are relatively unstable during silica gel column chromatography, the conversion of **4** to more stable compounds would have an additional practical advantage. We focused on the Pudovik-type reaction of aldehydes, which involves the addition of dialkylphosphites to carbonyl

**Table 2.** Range of isocyanides and aldehydes applicable to the *O*-phosphinative Passerini reaction.



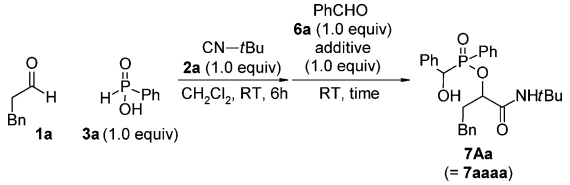

| Entry | $R^1$ | $R^2$ | *t* [h] | Yield of **4** [%] | Yield of **5** [%] |
|---|---|---|---|---|---|
| 1 | $BnCH_2$ (**1a**) | *t*Bu (**2a**) | 4 | 96 (**4aaa**) | – |
| 2 | $BnCH_2$ (**1a**) | *t*-Oct (**2b**) | 7 | 89 (**4aba**) | 8 (**5ab**) |
| 3 | $BnCH_2$ (**1a**) | *c*-Hex (**2c**) | 5 | 86 (**4aca**) | 13 (**5ac**) |
| 4 | $BnCH_2$ (**1a**) | Bn (**2d**) | 5 | 98 (**4ada**) | – |
| 5 | $BnCH_2$ (**1a**) | Ph (**2e**) | 24 | 67 (**4aea**) | 22 (**5ae**) |
| 6 | $BnCH_2$ (**1a**) | 4-$MeOC_6H_4$ (**2f**) | 5 | 80 (**4afa**) | 10 (**5af**) |
| 7 | $BnCH_2$ (**1a**) | 4-$BrC_6H_4$ (**2g**) | 24 | complex | – |
| 8 | *c*-Hex (**1b**) | *t*Bu (**2a**) | 24 | 84 (**4baa**) | 9 (**5ba**) |
| 9 | *t*Bu (**1c**) | *t*Bu (**2a**) | 20 | 61 (**4caa**) | 18 (**5ca**) |
| 10 | 2-phenylethenyl (**1d**) | *t*Bu (**2a**) | 24 | n.r. | – |
| 11 | Ph (**1e**) | *t*Bu (**2a**) | 24 | n.r. | – |

compounds to generate α-hydroxyphosphonates and is a powerful and direct means of forming C–P bonds. To date, a variety of catalysts have been applied to this reaction, including cesium fluoride,[12] triethylamine,[13] 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU)[14] and lithium diisopropylamide (LDA),[15] as well as $BF_3$·$OEt_2$,[16] TMSCl,[17] and trifluoroacetic acid (TFA).[18] We therefore began by surveying suitable catalysts for a one-pot phosphinate Passerini/Pudovik reaction aimed at obtaining the relatively stable α-hydroxyphosphinate derivatives.

To this end, 1.0 equiv of various additives along with 1.0 equiv of benzaldehyde (**6a**) were added to the reaction vessel subsequent to the completion of the phosphinate Passerini reaction of **1a**, **2a**, and **3a**. Using TMSCl or $BF_3$·$OEt_2$ as the additive, the intermediate species **4A** (equivalent to **4aaa**) was consumed after 24 h, and the desired α-hydroxyphosphinate **7Aa** (or **7aaaa**) was obtained in good yield (Table 3, entries 1 and 2). When using $Ti(OiPr)_4$ or other Lewis acids, however, the Pudovik reaction did not proceed at all (entry 3). The effects of basic additives on this one-pot reaction were evaluated next (entries 4–7). When cesium fluoride was employed, the reaction was very sluggish and produced **7Aa** only a 23% yield in the same time frame (entry 4). Interestingly, when using organic bases (entries 5 and 6), the reactions were complete within 6 h and afforded the product in 95 and 96% yields. Finally, we found that the use of 20 mol% $Et_3N$ afforded the desired α-hydroxyphosphinate **7Aa** in 92% yield as a mixture of four diastereomers (entry 7).

Having established an efficient method for the combined, one-pot *O*-phosphinative Passerini/Pudovik reaction, we next investigated the scope of this multicomponent reaction, using a variety of aldehydes ($R^3CHO$) in conjunction with phenylphosphinic acid (**3a**) (Table 4). It was gratifying to find that our reaction system was indeed applicable to a wide range of aldehydes when using 20 mol% $Et_3N$ in $CH_2Cl_2$ at room temperature. Both 1-naphthaldehyde (**6b**) and 2-naphthaldehyde (**6c**) were found to work well as substrates

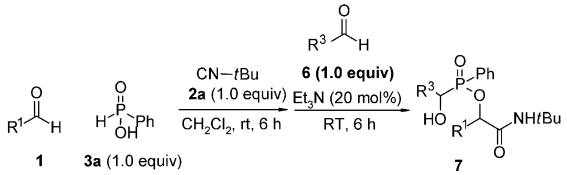
**Table 3.** One-pot phosphinate Passerini/Pudovik reactions.




| Entry | additive | *t* [h] | Yield [%] |
|---|---|---|---|
| 1 | TMSCl | 24 | 79 |
| 2 | $BF_3$·$OEt_2$ | 24 | 59 |
| 3 | $Ti(OiPr)_4$ | 21 | n.r. |
| 4 | CsF | 6 | 23 |
| 5 | DMAP | 6 | 95 |
| 6 | $Et_3N$ | 6 | 96 |
| 7 | $Et_3N$[a] | 6 | 92 |

[a] 20 Mol% $Et_3N$ was used. DMAP = 4-dimethylaminopyridine.

**Table 4.** Range of aldehydes applicable to the *O*-phosphinative Passerini/Pudovik reactions.

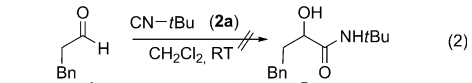



| Entry | $R^1$ | $R^3$ | Yield [%] |
|---|---|---|---|
| 1 | $BnCH_2$ (**1a**) | Ph (**6a** = **1e**) | 92 (**7Aa**) |
| 2 | $BnCH_2$ (**1a**) | 1-naphthyl (**6b**) | 87 (**7Ab**) |
| 3 | $BnCH_2$ (**1a**) | 2-naphthyl (**6c**) | 87 (**7Ac**) |
| 4 | $BnCH_2$ (**1a**) | 2-$MeC_6H_4$ (**6d**) | 86 (**7Ad**) |
| 5 | $BnCH_2$ (**1a**) | 2-$ClC_6H_4$ (**6e**) | 90 (**7Ae**) |
| 6 | $BnCH_2$ (**1a**) | 3-$ClC_6H_4$ (**6f**) | 85 (**7Af**) |
| 7 | $BnCH_2$ (**1a**) | 4-$ClC_6H_4$ (**6g**) | 85 (**7Ag**) |
| 8 | $BnCH_2$ (**1a**) | 4-$BrC_6H_4$ (**6h**) | 88 (**7Ah**) |
| 9 | $BnCH_2$ (**1a**) | 4-$CF_3C_6H_4$ (**6i**) | 79 (**7Ai**) |
| 10 | $BnCH_2$ (**1a**) | 4-$MeC_6H_4$ (**6j**) | 72 (**7Aj**) |
| 11 | $BnCH_2$ (**1a**) | 4-$MeOC_6H_4$ (**6k**) | 65 (**7Ak**) |
| 12 | $BnCH_2$ (**1a**) | 2-pyridyl (**6l**) | 81 (**7Al**) |
| 13 | $BnCH_2$ (**1a**) | 2-furyl (**6m**) | 88 (**7Am**) |
| 14 | $BnCH_2$ (**1a**) | 2-phenylethenyl (**6n** = **1d**) | n.r. |
| 15 | $BnCH_2$ (**1a**) | 2-phenylethynyl (**6o**) | 75 (**7Ao**) |
| 16 | $BnCH_2$ (**1a**) | 2-phenylethyl (**6p** = **1a**) | 78 (**7Ap**) |
| 17 | $BnCH_2$ (**1a**) | *c*-Hex (**6q** = **1b**) | 65 (**7Aq**) |
| 18[a] | *c*-Hex (**1b**) | Ph (**6a** = **1e**) | 82 (**7baaa**) |
| 19[b] | $BnCH_2$ (**1a**) | Ph (**6a** = **1e**) | 96 (**7aada**) |
| 20[c] | *i*Pr (**1f**) | Ph (**6a** = **1e**) | 93 (**7fcda**) |
| 21[d] | *i*Pr (**1f**) | Ph (**6a** = **1e**) | 88 (**7fdaa**) |

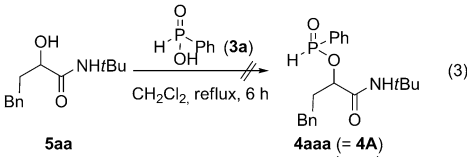
[a] Reaction time of the second step was 26 h. [b] **3d** was used instead of **3a**. [c] **2c** and **3d** were used instead of **2a** and **3a**, respectively. [d] **2d** was used instead of **2a**.

and the respective products **7Ab** and **7Ac** were obtained in 87% yield (Table 4, entries 2 and 3). The *ortho*-substituted benzaldehydes **6d** and **6e** were also applicable to this reaction (entries 4 and 5). We examined substituted benzaldehydes bearing electron-withdrawing groups (entries 5–9). Regarding the substitution pattern of the benzaldehydes, the 2-, 3-, and 4-chloro substituents were all tolerated, furnishing the corresponding α-hydroxyphosphinate in high yields (entries 5–7). Similar reactivities were observed with 4-bromo and 4-(trifluoromethyl)benzaldehydes (**6h** and **6i**) (entries 8 and 9). The reactions of relatively deactivated 4-methylbenzaldehyde (**6j**) and 4-methoxybenzaldehyde (**6k**) showed lower reactivities to afford the products in 72 and 65% yields, respectively (entries 10 and 11). The heteroaromatic aldehydes 2-pyridinecarboxaldehyde (**6l**) and furfural (**6m**) were also shown to be applicable to this reaction, without any loss of efficiency in the process (entries 12 and 13). Although cinnamaldehyde **6n** (=**1d**) was not effective in this reaction (entry 14), phenylpropargyl aldehyde (**6o**) was shown to be a reactive substrate and afforded the product **7Ao** in 75% yield (entry 15). Aliphatic aldehydes **6p** (equivalent to **1a**) and **6q** (=**1b**) were also useful in this reaction (entries 16 and 17). Finally, when the combination of **1b**, **2a**, **3a**, and **6a** was tested, the corresponding product **7baaa** was obtained in 82% yield (entry 18). The other combination of aldehyde, isocyanide, and phosphinic acid were also useful in this reaction to afford the products **7aada**, **7fcda**, and **7fdaa** in high yield (entries 20–22).

To assist in elucidating the reaction mechanism, we conducted a series of controlled experiments. These trials showed that the addition reaction of isocyanide **2a** to aldehyde **1a** in the absence of phenylphosphinic acid (**3a**) did not proceed in $CH_2Cl_2$ over a period of 24 h [Eq. (2)]. In addition, when the reaction of α-hydroxyamide **5aa** with phosphinic acid **3a** was attempted in $CH_2Cl_2$ with reflux, none of the desired product, **4aaa**, was obtained and **5aa** was instead recovered [Eq. (3)]. This result indicates that the α-(phosphinyloxy)amide cannot be formed by a dehydration reaction between the α-hydroxyamide **5** and the phosphinic acid **3**.

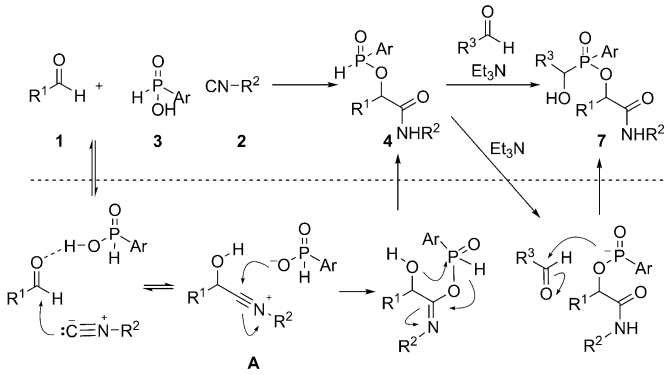



(2)




(3)

Based on these findings, we propose the mechanism for the present *O*-phosphinative Passerini reaction shown in Scheme 2. In this mechanism, the aldehyde is activated by the acidic proton of the phosphinic acid ($pK_a = 1.75$ in $H_2O$)[19] through coordination with the carbonyl oxygen. Subsequently, nucleophilic attack of the isocyanide at the carbonyl group provides the nitrilium intermediate **A**. This intermediate is subsequently trapped by the phosphinate anion to afford the adduct **4** through migration of the phosphinate group onto the oxygen atom originating from the aldehyde. Finally, after the deprotonation of the phosphinyloxy group by the catalytic base, nucleophilic attack at the second aldehyde proceeds, generating the corresponding α-(phosphinyloxy)amides (Scheme 2).




**Scheme 2.** Proposed reaction mechanism.

## Conclusion

In summary, we have developed a one-pot *O*-phosphinative Passerini/Pudovik reaction, in which combination of aldehydes, isocyanides, and a phosphinic acids are first reacted, followed by the addition of a second aldehydes to give the corresponding highly functionalized α-(phosphinyloxy)amides in high yields. This reaction is the first reported demonstration of an isocyanide-based multicomponent reaction using a phosphinic acid in place of a carboxylic acid. A wide range of aldehydes and isocyanides are applicable to this reaction. Further studies on this reaction are in progress in our laboratory.

## Experimental Section

### General

$^1$H NMR spectra were recorded on a JEOL ECS 400 (400 MHz) NMR spectrometer. Chemical shifts $\delta$ are reported in ppm using TMS as an internal standard. Data are reported as follows: Chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (*J*) and integration. $^{13}$C NMR spectra were recorded on JEOL ECS 400 (100 MHz) NMR spectrometer. The chemical shifts were determined in the δ-scale relative to $CDCl_3$ ($\delta = 77.0$ ppm). $^{31}$P NMR spectra were recorded on JEOL ECS 400 (162 MHz) NMR spectrometer. The chemical shifts were determined in the δ-scale relative to $H_3PO_4$ ($\delta = 0$ ppm) as an external standard. The IR spectra were measured on JASCO FT/IR-230 spectrometers. The MS spectrum was recorded with JEOL SX-102A mass spectrometer. All of the melting points were measured with YANAGIMOTO micro melting-point apparatus. Dehydrated solvents were purchased for the reactions and used without further desiccation. Flash column chromatography was performed by using Cica silica gel 60N, spherical neutral (37563–84).

### General procedure for the *O*-phosphinative Passerini reactions

Compound **3** (0.5 mmol) was added to a solution of **1** (0.5 mmol) and **2** (0.5 mmol) in $CH_2Cl_2$ (1 mL) and the whole mixture was stirred at room temperature. After the reaction was completed (monitored by TLC analysis), the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography to give the corresponding products.

**1-(*tert*-Butylamino)-1-oxo-4-phenylbutan-2-yl phenylphosphinate (4aaa)**: Silica gel column chromatography (hexane/ethyl acetate = 3:1 ~ 1:2) gave **4aaa** (182 mg, 95% yield) as a colorless oil. Diastereomeric ratio was determined to be 6:4 by $^{31}$P NMR spectroscopy. $^1$H NMR ($CDCl_3$): $\delta$ = 1.30 (s, 9H), 1.38 (s, 9H), 2.13 (m, 2H), 2.31 (m, 2H), 2.64 (t, $J$ = 7.8 Hz, 2H), 2.78 (t, $J$ = 7.8 Hz, 2H), 4.62 (m, 1H), 4.74 (m, 1H), 6.39 (brs, 1H), 6.42 (brs, 1H), 7.09 (d, $J$ = 6.9 Hz, 2H), 7.15–7.30 (m, 8H), 7.52–7.58 (m, 4H), 7.67 (d, $J$ = 571 Hz, 1H), 7.66 (m, 2H), 7.74 (d, $J$ = 571 Hz, 1H), 7.75–7.81 ppm (m, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 28.4, 28.5, 30.3, 30.6, 34.6 (d, $J$ = 3.8 Hz), 34.9 (d, $J$ = 3.8 Hz), 51.3, 51.4, 76.2 (d, $J$ = 7.6 Hz), 76.5 (d, $J$ = 7.6 Hz), 126.1 (d, $J$ = 10.5 Hz), 128.3, 128.3 (d, $J$ = 5.7 Hz), 128.4 (d, $J$ = 5.7 Hz), 129.1 (d, $J$ = 13.5 Hz), 129.5 (d, $J$ = 19.1 Hz), 130.5 (d, $J$ = 12.3 Hz), 133.6, 133.7, 140.5, 167.9 (d, $J$ = 2.9 Hz), 168.2 ppm (d, $J$ = 2.9 Hz); $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ = 27.5, 27.8 ppm; IR (neat): $\tilde{\nu}$ = 3430, 2970, 2370, 1680, 1590, 1520, 1460, 1440, 1360, 1230, 1130, 960 cm$^{-1}$; HRMS-FAB (*m/z*): calcd for $C_{20}H_{27}NO_3P$: 360.1729 [$M^+$+H]; found: 360.1726.

### General procedure for the one-pot *O*-phosphinative Passerini/Pudovik reactions

Compound **3** (0.5 mmol) was added to a solution of **1** (0.50 mmol) and **2** (0.5 mmol) in $CH_2Cl_2$ (1 mL) and the whole mixture was stirred at room temperature. After the reaction was completed (monitored by TLC analysis), the solvent was removed under reduced pressure. The residue was diluted by $CH_2Cl_2$ (0.1 mL) and triethylamine (0.01 mmol) and aldehyde (0.5 mmol) were added to the solution. The whole mixture was stirred at room temperature. After the reaction had reached completion (monitored by TLC analysis), water was added and organic layer was separated. The aqueous layer was extracted by $CHCl_3$ (5 mL ×3), and the combined organic layers were washed with brine followed by drying over $Na_2SO_4$. The residue was purified by silica gel column chromatography.

**1-(*tert*-Butylamino)-1-oxo-4-phenylbutan-2-yl [hydroxy(phenyl)methyl](phenyl)phosphinate (7Aa)**: Silica gel column chromatography (chloroform/diethyl ether = 6:1) gave **7Aa** (208 mg, 92% yield) as a white amorphous solid. The diastereomeric mixture was further separated by recycle HPLC (hexane/AcOEt = 2:1) for analysis. Diastereomeric ratio was determined to be 2:1:1:2 by $^{31}$P NMR spectroscopy.

*Diastereomer* ***1***: $^1$H NMR ($CDCl_3$): $\delta$ = 1.24 (s, 9H), 2.18 (m, 2H), 2.70 (m, 2H), 3.64 (brs, 1H), 4.53 (m, 1H), 5.16 (d, $J$ = 8.7 Hz, 1H), 6.30 (brs, 1H), 7.19 (m, 2H), 7.24–7.29 (m, 8H), 7.38–7.43 (m, 2H), 7.56 (m, 1H), 7.65 ppm (m, 2H); the OH proton was not observed clearly; $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 28.4, 30.2, 35.2 (d, $J$ = 1.9 Hz), 51.2, 73.5 (d, $J$ = 184.8 Hz), 76.1 (d, $J$ = 7.6 Hz), 125.9, 126.0, 127.2 (d, $J$ = 4.8 Hz), 128.3, 128.4, 128.5, 132.5 (d, $J$ = 9.5 Hz), 133.1 (d, $J$ = 2.8 Hz), 135.7, 141.1, 168.6 ppm (d, $J$ = 3.8 Hz); $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ = 38.9 ppm; IR (KBr): $\tilde{\nu}$3280, 2970, 1670, 1540, 1450, 1370, 1220, 1050 cm$^{-1}$; HRMS-ESI (*m/z*): calcd for $C_{27}H_{32}NO_4PNa$: 488.1967 [$M^+$+Na]; found: 488.1956.

*Diastereomer* ***2***: $^1$H NMR ($CDCl_3$): $\delta$ = 1.37 (s, 9H), 2.00 (m, 1H), 2.17 (m, 1H), 2.58 (m, 2H), 4.66 (m, 1H), 5.15 (d, $J$ = 6.9 Hz, 1H), 6.78 (brs, 1H), 7.02 (d, $J$ = 6.9 Hz, 2H), 7.19–7.28 (m, 8H), 7.37 (m, 2H), 7.54–7.67 ppm (m, 3H); the OH proton was not observed clearly; $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 28.6, 30.4, 34.9 (d, $J$ = 3.8 Hz), 51.5, 73.6 (d, $J$ = 177.6 Hz), 75.2 (d, $J$ = 8.6 Hz), 126.0, 127.3 (d, $J$ = 4.8 Hz), 128.3, 128.4, 128.5, 132.5 (d, $J$ = 9.5 Hz), 133.1 (d, $J$ = 1.9 Hz), 135.4, 141.0, 168.9 ppm (d, $J$ = 2.9 Hz); $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ = 39.8 ppm.

*Diastereomer* ***3***: $^1$H NMR ($CDCl_3$): $\delta$ = 1.25 (s, 9H), 1.79 (brs, 1H), 2.25 (m, 2H), 2.69 (m, 2H), 4.56 (m, 1H), 5.16 (d, $J$ = 9.6 Hz, 1H), 6.21 (brs, 1H), 7.18 (d, $J$ = 7.3 Hz, 2H), 7.24–7.30 (m, 8H), 7.35 (m, 2H), 7.49–7.56 ppm (m, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 28.5, 30.2, 35.0, 51.3, 73.3 (d, $J$ = 182.3 Hz), 76.0 (d, $J$ = 7.6 Hz), 126.0, 126.9 (d, $J$ = 4.8 Hz), 128.3, 128.4, 128.5, 133.0 (d, $J$ = 8.6 Hz), 133.2, 136.1, 141.0, 168.4 ppm (d, $J$ = 4.8 Hz); $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ = 39.1 ppm.

*Diastereomer* ***4***: $^1$H NMR ($CDCl_3$): $\delta$ = 1.38 (s, 9H), 2.07 (m, 1H), 2.21 (m. 1H), 2.63 (t, $J$ = 8.2 Hz, 2H), 4.93 (m, 1H), 5.10 (d, $J$ = 8.2 Hz, 1H), 5.38 (brs, 1H), 7.00 (brs, 1H), 7.05 (d, $J$ = 7.4 Hz, 2H), 7.12–7.25 (m, 8H), 7.33 (m, 2H), 7.49–7.53 ppm (m, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 28.6, 30.6, 35.4 (d, $J$ = 4.8 Hz), 51.7, 73.1 (d, $J$ = 171.1 Hz), 74.3 (d, $J$ = 7.6 Hz), 126.1, 127.0 (d, $J$ = 5.7 Hz), 127.9, 128.0, 128.0, 128.1, 128.3, 128.4, 132.4 (d, $J$ = 9.5 Hz), 132.8, 135.6, 140.8, 170.0 ppm; $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ = 40.5 ppm.

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