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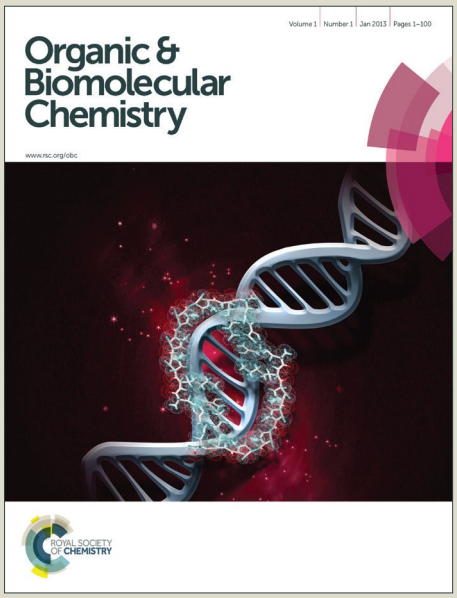

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Brønsted Base-Catalyzed Three-Component Coupling Reaction of α-Ketoesters, Imines, and Diethyl Phosphite Utilizing [1,2]-Phospha-Brook Rearrangement

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A three-component coupling reaction of α-ketoesters, imines, and diethyl phosphite under Brønsted base catalysis was developed by utilizing the [1,2]-phospha-Brook rearrangement. The reaction involves the generation of ester enolates via the *umpolung process*, i.e., the chemoselective addition of diethyl phosphite to α-ketoesters followed by the [1,2]-phospha-Brook rearrangement, and the trapping of the resulting enolates by imines preferentially over α-ketoesters and protons. This operationally simple reaction can provide densely functionalized β-amino acid derivatives including an oxygen functionality at the α-position in good yields. The diastereoselectivity is highly dependent on the substrates and reaction temperature, which is attributed to the reversibility of the addition of the ester enolates to the imines. The methodology was further extended to the reaction of α-ketoesters, β-nitrostyrenes, and diethyl phosphite.

Introduction

The [1,2]-phospha-Brook rearrangement involves the migration of the dialkoxyphosphoryl moiety of the alkoxide of an α-hydroxyphosphonate from carbon to oxygen to generate an α-oxygenated carbanion.[1,2] This rearrangement proceeds smoothly, especially with an alkoxide possessing an electron stabilizing group at the α-position. Whereas the generation of α-oxygenated carbanions using other methods requires several preparative steps, the alkoxide that is the precursor for the [1,2]-phospha-Brook rearrangement is easily accessible by various methods, including the deprotonation of α-hydroxyphosphonates, the addition of cyanide to acylphosphonates, and the addition of the anion of secondary phosphites to carbonyl compounds. Therefore, the generation of the carbanion by using the [1,2]-phospha-Brook rearrangement is potentially a useful methodology for developing new carbon-carbon bond forming reactions. Indeed, in recent years, a few types of carbon-carbon bond forming reactions utilizing the [1,2]-phospha-Brook rearrangement have been developed, such as the benzoin-type condensation of acylphosphonates[3] and the aldol-type reaction of α-hydroxyphosphonates.[4] In addition, very recently, the remarkable enantioselective three-component coupling reactions of isatins or benzylidene pyruvates, aldehydes and dialkyl phosphites were achieved by using chiral organobase catalysts, which can also be categorized as aldol-type reactions.[5] While the utility of the methodology has been gradually established, the types of reactions and the scope of carbanion precursors and electrophiles applicable to the reactions are still limited.

We have been focusing on the [1,2]-phospha-Brook rearrangement as a useful tool for the development of novel synthetic reactions under Brønsted base catalysis.[6] Specifically, our studies on new carbon-carbon bond forming reactions utilizing the [1,2]-phospha-Brook rearrangement are characterized by catalytic direct generation of enolates of less acidic amides and esters from α-ketoamides and α-ketoesters via the *umpolung process*, i.e., the addition of dialkyl phosphite to a keto moiety followed by the [1,2]-phospha-Brook rearrangement. Previously, we successfully utilized the resulting enolates of such less acidic pronucleophiles for intramolecular addition to alkynes to construct heterocyclic and carbocyclic frameworks.[6b,d] As the next stage of our studies, we envisioned the development of intermolecular addition reactions of the enolates of less acidic pronucleophiles to unsaturated compounds. During the course of our studies on the α-oxygenation of carbonyl compounds utilizing the [1,2]-phospha-Brook rearrangement, we discovered the addition reaction of ester enolates to imines, in which the enolate was generated from diethylphosphonoacetate through α-oxidation followed by the [1,2]-phospha-Brook rearrangement.[6c] Based on this result, we proposed a new three-component coupling reaction of α-ketoesters, imines, and diethyl phosphite under Brønsted base catalysis, involving the Mannich-type process, i.e., the addition of ester enolates to imines. Generally, in direct Mannich reactions under Brønsted base catalysis, easily-enolizable

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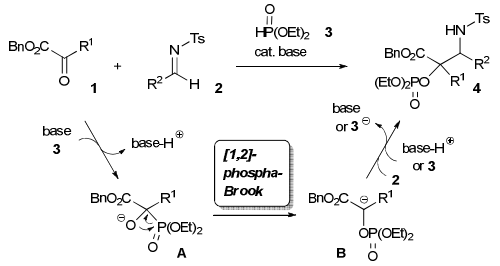
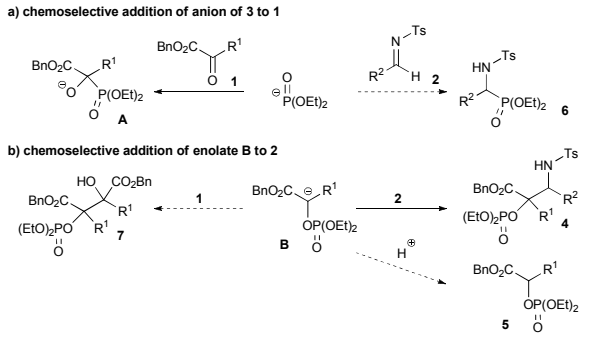


Scheme 1 Proposed reaction system.

carbonyl compounds possessing a highly acidic α proton, such as β-dicarbonyls and related compounds, are employed as pronucleophiles, which facilitates the catalyst turnover by the smooth protonation after the carbon-carbon bond forming step.[7] On the other hand, the catalytic reactions of less acidic pronucleophiles, such as simple esters, are rather limited because of the difficulty of the catalyst turnover,[8,9] and a stoichiometric amount of strong bases, such as LDA, are more commonly used for the addition of those pronucloephiles. Therefore, the present methodology could provide an alternative approach toward the catalytic addition of the enolate of less acidic pronucleophiles.

Our proposed reaction system is shown in Scheme 1. First, the deprotonation of diethyl phosphite (**3**) by a Brønsted base followed by the addition of the resulting anion to a keto moiety of α-ketoester **1** provides alkoxide **A**. Next, the [1,2]-phospha-Brook rearrangement proceeds to generate ester enolate **B**. Finally, the addition of the enolate to an imine **2** and the smooth protonation, which is the key step for establishing the catalytic cycle, by the conjugated acid of the Brønsted base or diethyl phosphite provides the desired adduct **4** along with the regeneration of the Brønsted base or the anion of **3**. In order to achieve the designed reaction, some issues of chemoselectivity must be overcome (Scheme 2). For instance, the generation of the ester enolates **B** requires the chemoselective addition of diethyl phosphite (**3**) to an α-ketoester **1** in the presence of an electrophilic imine **2** (Scheme 2a). In contrast, the resulting enolate **B** should react with an imine **2** in the presence of an α-ketoester **1** for the formation of **4** (Scheme 2b). Furthermore, the carbon-carbon bond formation should proceed in preference to the protonation of



Scheme 2 Challenging issues of chemoselectivity. The normal arrows indicate the desired reactions, while the dashed arrows indicate undesired side reactions.

enolate **B**, which is a competing side reaction arising from the basicity of **B**. Once the corresponding ester **5** is formed by the protonation of **B**, it cannot re-enter the catalytic cycle via deprotonation due to its low acidity. Indeed, the catalytic three-component coupling reactions reported to date are limited to those involving the generation of the enolates of relatively acidic pronucleophiles probably because of avoiding the protonation issue.[5] Herein, we report the results of our investigation on the challenging three-component coupling reaction of α-ketoesters **1**, imines **2**, and diethyl phosphite (**3**) under Brønsted base catalysis,[10] providing densely functionalized β-amino acid derivatives including an oxygen functionality at the α-position, which are important building blocks for bioactive molecules.[11]

Results and Discussion

Investigation of reaction conditions

The initial study was conducted with benzyl phenylglyoxylate (**1a**), tosylimine **2a**, and diethyl phosphite (**3**). Equimolar amounts of **1a**, **2a**, and **3** were treated with 10 mol% of *t*BuOLi in THF at −20 °C. As a result, the desired three-component coupling product **4aa** was obtained as the major product in 50% yield with 86:14 dr along with by-products **5a** (7%) and **6a** (42%). **5a** was formed by the protonation of the enolate, while **6a** was formed by the direct addition of diethyl phosphite to imine **2a**. This promising result prompted us to investigate the reaction conditions further (Table 1). Brønsted bases were screened first (entries 1-10). Surprisingly, the countercation of *t*-butoxide dramatically influenced both the chemoselectivity and diastereoselectivity (entries 1-3). Among alkaline metal *t*-butoxides, *t*BuONa was the best and the desired product **4aa** was obtained in 81% yield with 83:17 dr along with 4% of **5a** and 15% of **6a** (entry 2). LHMDS and NaHMDS provided almost identical results to those obtained with *t*BuOLi and *t*BuONa, indicating that the countercation of the reaction intermediates, such as the anion of diethyl phosphite and the enolate, would play a key role in determining the chemoselectivity, as well as the diastereoselectivity, of the reaction (entries 4 and 5). Several organic bases were also tested (entries 6-10). Phosphazene bases, which are known as organosuperbases, provided the desired three-component product. However, significant amounts of by-products were formed in each case (entries 6-8). Interestingly, the yield of the desired **4aa** was increased with decreased basicity of the phosphazene bases, and thus the weakest P1-*t*Bu provided the best result. On the other hand, the use of organic bases weaker than phosphazene bases, such as MTBD and DBU, facilitated the protonation of the enolate and **5a** was obtained as the major product along with a trace amount of **4aa** (entries 9 and 10). Next, a variety of solvents were screened (entries 11-16). Diethyl ether and aprotic polar solvents, such as DMF, acetonitrile, and ethyl acetate, provided **4aa** in similar yields, albeit in significantly lower diastereoselectivities than that obtained in THF (entries 11-14). In contrast, less polar solvents, such as dichloromethane and toluene, were less effective and

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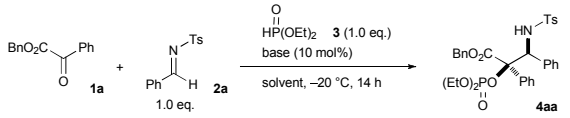
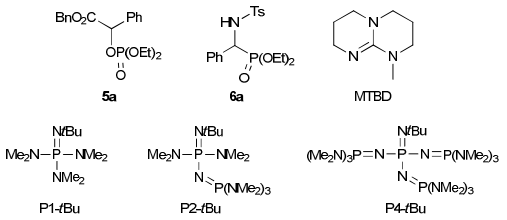
Table 1 Initial screening of reaction conditions[a]



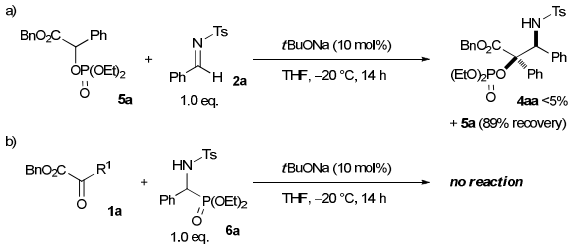
entry	base	solvent	yield (%)[b] 4aa	dr of 4aa[c]	5a	6a
1	*t*BuOLi	THF	50	86:14	7	42
2	*t*BuONa	THF	81	83:17	4	15
3	*t*BuOK	THF	74	69:31	6	18
4	LHMDS	THF	50	84:16	4	41
5	NaHMDS	THF	80	84:16	4	15
6	P4-*t*Bu	THF	10	75:25	50	36
7	P2-*t*Bu	THF	48	77:23	25	22
8	P1-*t*Bu	THF	64	83:17	8	27
9	MTBD	THF	5	-	63	29
10	DBU	THF	<1	-	68	32
11	*t*BuONa	Et_2O	80	59:41	8	12
12	*t*BuONa	DMF	80	64:36	2	16
13	*t*BuONa	CH_3CN	85	56:44	2	10
14	*t*BuONa	AcOEt	77	69:31	4	15
15	*t*BuONa	CH_2Cl_2	66	50:50	15	16
16	*t*BuONa	toluene	64	46:54	12	24
17[d]	*t*BuONa	THF	87 (77)	79:21	3	20[e]

[a] Reaction conditions: **1a** (0.10 mmol), **2a** (0.10 mmol), **3** (0.10 mmol), base (0.010 mmol), solvent (1.0 mL), –20 °C, 14 h. [b] NMR yields. Bn_2O was used as the internal standard. Isolated yield is shown in parentheses. [c] Determined by ^1H NMR and ^{31}P NMR analysis of the crude mixtures. [d] 1.1 equivalents of **2a** and **3** were used. [e] Based on the amount of **1a**.



the yield of by-product **5a** was increased (entries 15 and 16). Finally, the use of a slight excess of the imine and diethyl phosphite improved the yield of **4aa** to 87%, although the diastereoselectivity was slightly decreased (entry 17). The structure of the major diastereomer of **4aa** was confirmed by single-crystal X-ray diffraction analysis.[12]

At this point, control experiments shown in Scheme 3 were conducted. In order to clarify whether **5a** was the intermediate for the formation of **4aa**, **5a** was treated with *t*BuONa in the presence of imine **2a** in THF at −20 °C (Scheme 3a). Only a trace amount of **4aa** was detected in the crude reaction mixture and most of **5a** was recovered. This result clearly indicates that the carbon-carbon bond formation that provides **4aa** occurred directly between the enolate generated via the [1,2]-phospha-Brook rearrangement and imine **2a**, and **5a** was not the intermediate for the formation of **4aa** presumably due to the difficulty of the deprotonation of less acidic **5a** by NaO*t*Bu. Thus, this experiment demonstrates the usability of the [1,2]-phospha-Brook rearrangement for the generation of



Scheme 3 Control experiments.

the enolate of less acidic pronucleophiles, such as esters, in intermolecular carbon-carbon bond forming reactions. The reversibility of the formation of 6a was also examined (Scheme 3b). Treatment of 6a with *t*BuONa in THF at −20 °C in the presence of 1a resulted in no reaction. This result suggests that 6a cannot re-enter the catalytic cycle via a retro process once it is formed.

Scope of α-ketoesters and imines

The scope of α-ketoesters and imines was investigated under the optimum reaction conditions (Table 2). First, the scope of the α-ketoesters was examined (entries 1-9). In this reaction, the substituents on the keto moiety significantly influenced both chemical yield and diastereoselectivity of **4**. A substrate possessing an electron-donating group, such as a methoxy group, at the para position of the benzene ring provided the corresponding product **4ba** in moderate yield with low diastereoselectivity (entry 1). In this case, a significant amount of **6a** was formed. In contrast, the reaction of substrates having electron-deficient aryl groups such as **1c** and **1d** provided the corresponding products **4ca** and **4da** in high yields with relatively good diastereoselectivities (entries 2 and 3). These results suggest that the chemoselectivity for the generation of enolates, i.e., the addition of diethyl phosphite to α-ketoester **1**, is highly sensitive to the relative electrophilicity of α-ketoester **1** to imine **2**, and electron-deficient α-ketoesters are more suitable than electron-rich ones for this three-component reaction. Meta-methoxy-phenyl-substituted **1e** underwent the reaction without any problems to afford **4ea** in good yield (entry 4). However, ortho-tolyl-substituted **1f** resulted in low yield of **4fa** along with the formation of considerable amounts of **5f** and **6a** (entry 5). This result indicates that the steric hindrance of the substituent detrimentally affected not only the addition of diethyl phosphite to **1f** but also the addition of the enolate to imine **2a**. 2-Naphthyl and 2-thienyl groups were applicable to the reaction (entries 6 and 7). The reactions of substrates having primary and secondary alkyl substituents, **1i** and **1j**, were also attempted. In these cases, however, the protonation of the enolates proceeded preferentially to afford **5a** as the major product (54% and 58%, respectively), and the desired **4ia** and **4ja** were formed only in modest yields (entries 8 and 9).

Next, the scope of imines **2** was examined (entries 10-21). The substituents of the imines also strongly affected the chemical yield and diastereoselectivity. For instance, the reaction with

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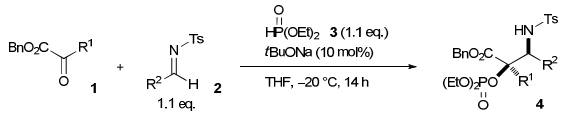
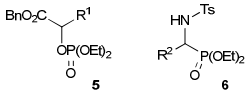
2b, which has an electron-donating methoxy group at the para position of the benzene ring, afforded the desired product **4ab**

Table 2 Scope of α-ketoesters and imines[a]



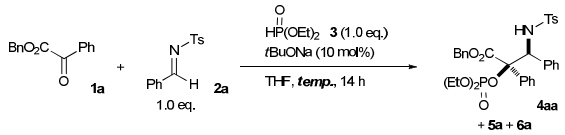
entry	R^1	R^2	4	yield (%)[b] 4	dr of 4[c]	5	6[d]
1	4-MeO-C_6H_4	Ph	**4ba**	62 (52)	56:44	2	44
2	4-Cl-C_6H_4	Ph	**4ca**	84 (82)	79:21	3	12
3	4-F-C_6H_4	Ph	**4da**	91 (80)	74:26	2	17
4	3-MeO-C_6H_4	Ph	**4ea**	80 (77)	79:21	2	24
5	2-Me-C_6H_4	Ph	**4fa**	40 (27[e])	68:32	19	44
6	2-naphthyl	Ph	**4ga**	74 (62)	82:18	2	21
7	2-thienyl	Ph	**4ha**	88 (88)	72:28	2	15
8	$PhCH_2CH_2$	Ph	**4ia**	32 (32)	73:27	54	19
9	*c*C_6H_{11}	Ph	**4ja**	30 (26)	77:23	58	19
10	Ph	4-MeO-C_6H_4	**4ab**	93 (93)	83:17	5	5
11	Ph	4-Cl-C_6H_4	**4ac**	67 (56)	61:39	2	36
12	Ph	4-NO_2-C_6H_4	**4ad**	50 (42)	50:50	6	54
13	Ph	3-MeO-C_6H_4	**4ae**	83 (82)	83:17	5	20
14	Ph	2-MeO-C_6H_4	**4af**	84 (84)	83:17	12	14
15	Ph	1-naphthyl	**4ag**	65 (62)	74:26	12	29
16	Ph	2-naphthyl	**4ah**	86 (76)	74:26	5	12
17	Ph	2-furyl	**4ai**	91 (81)	53:47	3	14
18	Ph	3-pyridyl	**4aj**	48 (48)	50:50	7	49
19	Ph	*n*C_6H_{13}	**4ak**	60 (58)	50:50	33	15
20	Ph	*c*C_6H_{11}	**4al**	60 (57)	80:20	22	25
21	Ph	*t*Bu	**4am**	<1	-	75	31

[a] Reaction conditions: **1a** (0.10 mmol), **2a** (0.11 mmol), **3** (0.11 mmol), *t*BuONa (0.010 mmol), THF (1.0 mL), −20 °C, 14 h. [b] NMR yields. Bn_2O was used as the internal standard. Isolated yields are shown in parentheses. [c] Determined by ^{1}H NMR and ^{31}P NMR analysis of the crude mixtures. [d] Based on the amount of **1a**. [e] Isolated yield of the major diastereomer.



in high yield with good diastereoselectivity (entry 10). In contrast, employment of imines possessing electron-deficient aryl groups, such as **2c** and **2d**, resulted in the formation of **4ac** and **4ad** in only moderate yields with low diastereoselectivities along with the formation of a significant amount of corresponding **6** (entries 11 and 12). These differences in the yields of **4** can also be rationalized by considering the relative electrophilicity of α-ketoester **1** to imine **2**. Thus, electron-rich imines, which facilitate the chemoselective addition of diethyl phosphite to α-ketoesters, were more suitable than electron-deficient imines for this reaction. The reaction with meta-methoxyphenyl- and 2-naphthyl-substituted imines proceeded without any problem to provide the products **4ae** and **4ah**, respectively, in good yields with good diastereoselectivities (entries 13 and 16). Sterically hindered imines, such as **2f** and **2g**, slightly retarded the carbon-carbon bond formation with the enolate and as a result, the yield of by-product **5a** was increased (entries 14 and 15). Heteroaryl groups, such as 2-furyl and 3-pyridyl groups, were compatible under the reaction conditions to provide the corresponding products **4ai** and **4aj**,

Table 3 Temperature effect



entry	temp.	yield (%)[a] 4aa	dr of 4aa[b]	5a	6a
1	−20 °C	81	83:17	4	15
2	0 °C	72	83:17	10	15
3	rt	0	-	78	19
4	−40 °C	83	47:53	3	13

[a] NMR yields. Bn_2O was used as the internal standard. [b] Determined by ^{1}H NMR and ^{31}P NMR analysis of the crude mixtures.

respectively, the yields of which were highly dependent on the electronic nature of those groups (entries 17 and 18). Finally,aliphatic imines were tested (entries 19-21). The primary and secondary alkyl-substituted imines provided the corresponding products in moderate yields (entries 19 and 20) while *t*Bu-substituted imines only afforded by-products **5a** and **6m** (entry 21).

Temperature effect

In the course of investigating the reaction conditions, a remarkable temperature effect was observed. When the reaction temperature was increased to 0 °C, the yield of **4aa** was decreased, and instead, the yield of **5a** was increased (entry 2). Furthermore, when the reaction was conducted at room temperature, the desired **4aa** was not observed and **5a** was obtained as the major product in high yield (entry 3). In contrast, when the reaction temperature was decreased to −40 °C, **4aa**, **5a**, and **6a** were obtained in yields similar to those obtained at −20 °C. However, the diastereoselectivity of **4aa** was dramatically reduced to 47:53 (entry 4). Our previous study suggested that the formation of **4** through the addition of the ester enolate to the imine followed by protonation could be reversible under Brønsted base catalysis.[6c] Therefore, in order to clarify the origin of the temperature effect, the reversibility of the formation of **4** under the three-component coupling conditions and its influence on the diastereoselectivity were investigated by conducting several control experiments (Scheme 4). First, the major diastereomer of **4aa** was treated with 10 mol% of *t*BuONa in THF at room temperature for 14 h (Scheme 4a). As a result, **5a** was obtained in 83% yield along with 13% recovery of the starting **4aa**. This result suggested that the irreversible retro-Mannich-type reaction of **4aa** would dominate at room temperature, and therefore **4aa** was not observed when the reaction was performed at room temperature (Table 3, entry 3). Next, the major diastereomer of **4aa** was treated with 10 mol% of *t*BuONa in the presence of imine **2c** at −20 °C (Scheme 4b). As a result, three-component products **4aa** and **4ac** were

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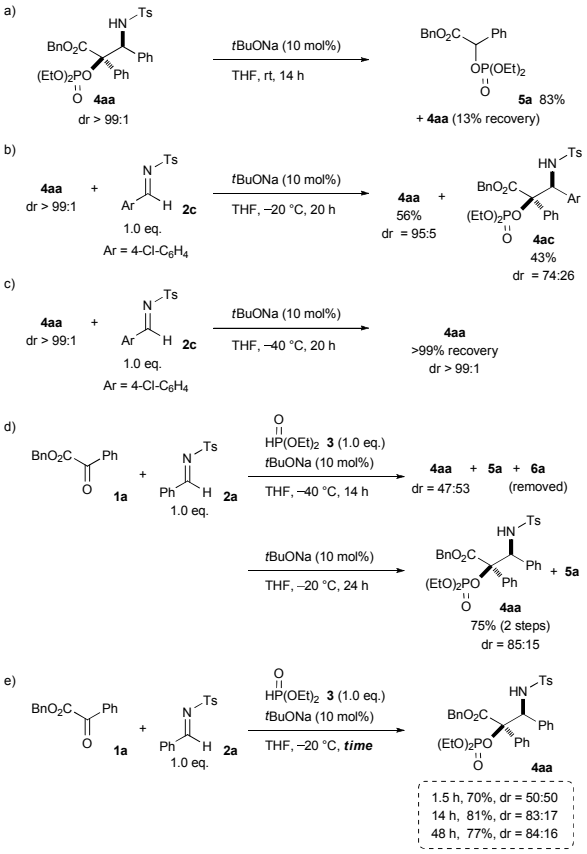
obtained as a mixture of diastereomers. Interestingly, **5a** was not obtained at all in this case, in contrast to the reaction at room temperature. This result indicates that the formation of

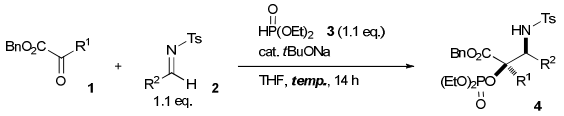


Scheme 4 Control experiments.

4 under the three-component coupling conditions is reversible even at −20 °C, whereas the protonation of the enolate intermediate is rather slow compared to the carbon-carbon bond formation at that temperature. In other words, the effect of decreasing the reaction temperature from room temperature to −20 °C is the suppression of the competing side reaction, the protonation of the enolate intermediate, against the desired carbon-carbon bond formation reaction. A similar experiment was also conducted at −40 °C (Scheme 4c). In this case, **4aa** was fully recovered as a single diastereomer, which showed that the formation of **4** is nearly irreversible at that temperature. The difference between the results obtained at −20 °C and −40 °C suggests that the reversibility of the formation of **4** is responsible for the diastereoselectivity. Thus, we conducted the experiment shown in Scheme 4d. First, the reaction was conducted at −40 °C to provide **4aa** in a 47:53 diastereomeric ratio. After removing the by-product **6a**, **4aa** with a tiny amount of **5a** thus obtained was re-subjected to the reaction conditions at − 20 °C. As a result, the diastereomeric ratio of **4aa** was increased to 85:15, which is almost the same ratio as that obtained in the reaction at − 20 °C. Furthermore, when the reaction was quenched before reaching full conversion (after 1.5 h, Scheme 4e), the diastereomeric ratio was 50:50, which is similar to that obtained in the reaction at −40 °C. In contrast, increasing the reaction time to 48 h did not change the diastereomeric ratio from that obtained after 14 h (Scheme 4e). These results provide a tentative profile of the formation of **4aa** at −20 °C. At the beginning of the reaction, the addition of the enolate generated by the [1,2]-phospha-Brook rearrangement to the imine proceeded with low diastereoselectivity under kinetic control, and then the diastereomeric ratio was gradually improved through the reversible process aforementioned under thermodynamic control.

During the examination of the substrate scope, the diastereoselectivity was found to be highly dependent on the choice of α-ketoesters and imines, which is now attributed to the difference in the rate of the reversible retro-Mannich-type process among the corresponding products **4**. Therefore, if this process could be accelerated, the diastereoselectivity would be improved. Based on this idea, the reaction conditions were modified in two ways: by increasing the catalyst loading and by increasing the reaction temperature. The results are summarized in Table 4. As the initial attempt for improvement in diastereoselectivity, the amount of *t*BuONa was increased from 10 mol% to 20 mol% in the reaction of **1a** with **2a** (entry 1). As we expected, the diastereoselectivity was improved from 79:21 to 84:16 without loss of the yield (entry 1 vs Table 1, entry 17). This strategy was also applied to the reaction of **1a** with **2c**, in which the original diastereomeric ratio was 61:39 (entries 2 and 3 vs Table 2, entry 11). In this case, while 20 mol% of *t*BuONa improved the diastereomeric ratio to 72:28, the employment of 30 mol% of *t*BuONa further accelerated the reversible process and provided the product with 81:19 dr. Increasing the reaction temperature to 0 °C was also found to be an efficient strategy to improve the diastereoselectivity; the reaction with 20 mol% of *t*BuONa at 0 °C gave a comparable result to that with 30 mol% of *t*BuONa at −20 °C (entry 4). Next, the reaction of **1a** with **2d** was examined (entries 5 and 6). In this case, employment of an increased amount of *t*BuONa did not improve the diastereomeric ratio, indicating the retro-Mannich-type

Table 4 Investigation toward improvement of the diastereomeric ratio



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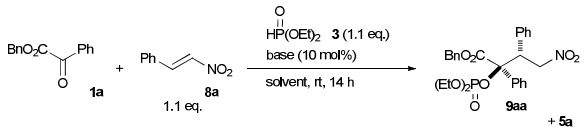
entry	R^1	R^2	*t*BuONa (mol%)	temp. (°C)	**4**	yield (%)[a]	dr[b]
1	Ph	Ph	20	−20	**4aa**	85	84:16
2	Ph	4-Cl-C_6H_4	20	−20	**4ac**	67	72:28
3	Ph	4-Cl-C_6H_4	30	−20	**4ac**	67	81:19
4	Ph	4-Cl-C_6H_4	20	0	**4ac**	65	82:18
5	Ph	4-NO_2-C_6H_4	30	−20	**4ad**	47	55:45
6	Ph	4-NO_2-C_6H_4	20	0	**4ad**	38	79:21
7	Ph	2-furyl	30	−20	**4ai**	78	78:22
8	Ph	2-furyl	20	0	**4ai**	75	83:17
9	4-MeO-C_6H_4	Ph	30	−20	**4ba**	57	56:44
10	4-MeO-C_6H_4	Ph	30	0	**4ba**	48	85:15

[a] NMR yields. Bn_2O was used as the internal standard. [b] Determined by ^1H NMR and ^{31}P NMR analysis of the crude mixtures.

Table 5 Screening of reaction conditions[a]



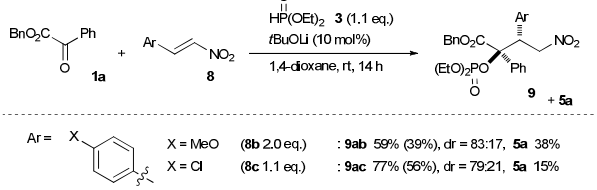
entry	base	solvent	yield (%)[b] **9aa**	dr of **9aa**[c]	**5a**
1	*t*BuONa	THF	57	80:20	40
2	*t*BuOLi	THF	54	74:26	46
3	*t*BuOK	THF	19	74:26	10
4	NaHMDS	THF	59	80:20	38
5	P2-*t*Bu	THF	33	50:50	50
6	P1-*t*Bu	THF	18	50:50	77
7	*t*BuONa	Et_2O	31	73:27	53
8	*t*BuONa	1,4-dioxane	55	85:15	33
9	*t*BuONa	DMF	1	-	12
10	*t*BuONa	CH_3CN	6	-	14
11[d]	*t*BuONa	THF	61	80:20	19
12[d]	*t*BuONa	1,4-dioxane	54	85:15	5
13[d]	*t*BuOLi	THF	63	73:27	36
14[d]	*t*BuOLi	1,4-dioxane	78 (59)	81:19	22

[a] Reaction conditions: **1a** (0.10 mmol), **8a** (0.11 mmol), **3** (0.11 mmol), base (0.010 mmol), solvent (1.0 mL), rt, 14 h. [b] Yields based on ^{31}P NMR analysis of crude reaction mixture. $P(O)(OMe)_3$ was used as the internal standard. Isolated yield of the major diastereomer is shown in parentheses. [c] Determined by ^1H NMR and ^{31}P NMR analysis of the crude mixtures. [d] 2.0 equivalents of **8a** were used.

process does not occur at −20 °C (entry 5 vs Table 2, entry 12). However, upon increasing the reaction temperature to 0 °C with 20 mol% of *t*BuONa, the product was obtained with 79:21 dr (entry 6). The yield was slightly decreased due to the competing protonation of the enolate intermediate. The diastereomeric ratios of the reactions of **1a** with **2i** and **1b** with **2a** were also substantially improved by employing the same strategies (entries 7-10 vs Table 2, entries 1 and 17).

Investigation of three-component coupling reaction of α-ketoesters, β-nitrostyrenes, and diethyl phosphite

In order to expand the scope of the newly developed methodology, alternative electrophiles to imines were explored. After screening of a variety of electrophiles, β-nitrostyrene was found to be a suitable candidate. The reaction of **1a**, β-nitrostyrene (**8a**), and diethyl phosphite (**3**) under the optimum conditions for the previous reaction provided the desired adduct **9aa** in 28% yield with 79:21 dr along with the formation of 5% of **5a**. In this reaction, the compound formed by the direct addition of diethyl phosphite to β-nitrostyrene was not observed. While substantial amounts of **1a** and **3** remained after 14 h, β-nitrostyrene was fully consumed, probably because the polymerization of β-nitrostyrene is initiated by basic species. When the reaction was conducted at room temperature, the yield of **9aa** was improved to 57% (Table 5, entry 1). Based on this result, the screening of bases and solvents was carried out at room temperature (Table 5). Screening of the bases showed that *t*BuONa and *t*BuOLi were the most suitable bases for this



Scheme 5 Three-component reaction with β-nitrostyrene derivatives **8**. Yields are NMR yields. Isolated yields of the major diastereomers are shown in parentheses.

reaction (entries 1-6). Again, NaHMDS provided almost identical results to that obtained with *t*BuONa (entry 1 vs entry 4). Screening of solvents with *t*BuONa was then carried out (entries 7-10). As a result, ethereal solvents were the solvents of choice. In particular, the reaction in 1,4-dioxane resulted in good diastereoselectivity. Employment of 2.0 equivalents of **8a** improved the ratio of **9aa** and **5a** (entries 11 and 12). However, a substantial amount of **1a** remained (12% and 27%, respectively). Finally, the combination of *t*BuOLi with 1,4-dioxane as a solvent was found to be the optimum reaction conditions (entry 14). The structure of the major diastereomer of **9aa** was confirmed by single-crystal X-ray diffraction analysis.[13] With these reaction conditions in hand, β-nitrostyrene derivatives having a substituent at the para position of the benzene ring were examined (Scheme 5). The reaction with para-methoxy-substituted β-nitrostyrene **8b** provided the product **9ab** in moderate yield. In this case, a significant amount of by-product **5a** was formed. On the other hand, β-nitrostyrene **8c** having an electron-deficient para-chlorophenyl group provided the product **9ac** in good yield. As a control experiment, the treatment of **5a** with **8a** in the presence of a catalytic amount of *t*BuOLi did not provide three-component coupling product **9aa** and **5a** was fully recovered, clearly indicating that the enolate generated via the [1,2]-phospha-Brook rearrangement directly underwent the addition reaction to β-nitrostyrene as was the case in the reaction with imines.

Conclusions

In conclusion, we have developed a three-component coupling reaction of α-ketoesters, imines, and diethyl phosphite under

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Brønsted base catalysis by utilizing the [1,2]-phospha-Brook rearrangement. This reaction involves the generation of an ester enolate via the *umpolung process*, i.e., the chemoselective addition of diethyl phosphite to α-ketoesters followed by the [1,2]-phospha-Brook rearrangement, and the trapping of the resulting enolates by imines preferentially over α-ketoesters and protons. This operationally simple reaction can provide densely functionalized β-amino acid derivatives including an oxygen functionality at the α-position in good yields. The diastereoselectivities are highly dependent on the substrates, as well as the reaction temperature, which is attributed to the reversibility of the addition of the enolates to imines. In addition, the methodology was extended to the reaction of α-ketoesters, β-nitrostyrenes, and diethyl phosphite. Further investigation of this methodology, including the development of an enantioselective version, is in progress.

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Notes and references

1 For early studies, see: (a) S. J. Fitch and K. Moedritzer, *J. Am. Chem. Soc.*, 1962, **84**, 1876-1879; (b) L. A. R. Hall, C. W. Stephenes and J. J. Drysdals, *J. Am. Chem. Soc.*, 1957, **79**, 1768-1769; (c) W. F. Barthel, B. H. Alexander, P. A. Giang and S. A. Hall, *J. Am. Chem. Soc.*, 1955, **77**, 2424-2427; (d) A. M. Mattson, J. T. Spillane and G. W. Pearce, *J. Agric. Food Chem.*, 1955, **3**, 319-321; (e) W. Lorenz, A. Henglbin and G. Schrader, *J. Am. Chem. Soc.*, 1955, **77**, 2554-2556.

2 For selected examples, see: (a) M. Hayashi and S. Nakamura, *Angew. Chem. Int. Ed.*, 2011, **50**, 2249-2252; (b) D. Coffinier, L. El Kaim and L. Grimaud, *Synlett*, 2008, 1133-1136; (c) A. S. Demir, Ö. Reis, I. Esiringü, B. Reis and S. Baris, *Tetrahedron*, 2007, **63**, 160-165; (d) A. S. Demir and S. Eymur, *J. Org. Chem.*, 2007, **72**, 8527-8530; (e) L. El Kaïm, L. Gaultier, L. Grimaud and A. Dos Santos, *Synlett*, 2005, 2335-2336; (f) K. Pachamuthu and R. R. Schmidt, *Chem. Commun.*, 2004, 1078-1079; (g) R. Ruel, J.-P. Bouvier and R. N. Young, *J. Org. Chem.*, 1995, **60**, 5209-5213; (h) M. Kuroboshi, T. Ishihara and T. Ando, *J. Fluorine Chem.*, 1988, **39**, 293-298.

3 (a) C. C. Bausch and J. S. Johnson, *Adv. Synth. Catal.*, 2005, **347**, 1207-1211; (b) A. S. Demir, Ö. Reis, A. Ç. İğdir, İ. Esiringü and S. Eymur, *J. Org. Chem.*, 2005, **70**, 10584-10587; (c) A. S. Demir, I. Esiringü, M. Göllü and Ö. Reis, *J. Org. Chem.*, 2009, **74**, 2197-2199; (d) A. S. Demir, B. Reis, Ö. Reis, S. Eymür, M. Göllü, S. Tural and G. Saglam, *J. Org. Chem.*, 2007, **72**, 7439-7442.

4 M. Corbett, D. Uraguchi, T. Ooi and J. S. Johnson, *Angew. Chem. Int. Ed.*, 2012, **51**, 4685-4689.

5 (a) M. A. Horwitz, N. Tanaka, T. Yokosaka, D. Uraguchi, J. S. Johnson and T. Ooi, *Chem. Sci.*, 2015, **6**, 6086-6090; (b) M. A. Horwitz, B. P. Zavesky, J. I. Martinez-Alvarado and J. S. Johnson, *Org. Lett.*, 2016, **18**, 36-39.

6 (a) A. Kondoh and M. Terada, *Org. Lett.*, 2013, **15**, 4568-4571; (b) A. Kondoh, T. Aoki and M. Terada, *Org. Lett.*, 2014, **16**, 3528-3531; (c) A. Kondoh and M. Terada, *Org. Chem. Front.*, 2015, **2**, 801-805; (d) A. Kondoh, T. Aoki and M. Terada, *Chem. Eur. J.*, 2015, **21**, 12577-12580.

7 For selected reviews, see: (a) S. Kobayashi, Y. Mori, J. S. Fossey and M. M. Salter, *Chem. Rev.*, 2011, **111**, 2626-2704; (b) S. Kobayashi and H. Ishitani, *Chem. Rev.*, 1999, **99**, 1069-1094; (c) J. M. M. Verkade, L. J. C. Van Hemert, P. J. L. Quaedflieg and F. P. J. T. Rutjes, *Chem. Soc. Rev.*, 2008, **37**, 29-41; (d) R. G. Arrayás and J. C. Carretero, *Chem. Soc. Rev.*, 2009, **38**, 1940-1948.

8 (a) Y. Yamashita, H. Suzuki and S. Kobayashi, *Org. Biomol. Chem.*, 2012, **10**, 5750-5752; (b) A. Kondoh, M. Oishi, T. Takeda and M. Terada, *Angew. Chem. Int. Ed.*, 2015, **54**, 15836-15839.

9 The reaction of ester equivalents under Brønsted base catalysis was reported. See: (a) R. Matsubara, F. Berthiol and S. Kobayashi, *J. Am. Chem. Soc.*, 2008, **130**, 1804-1805; (b) S. Kobayashi and R. Matsubara, *Chem. Eur. J.*, 2009, **15**, 10694-10700; (c) J. Nakano, K. Masuda, Y. Yamashita and S. Kobayashi, *Angew. Chem. Int. Ed.*, 2012, **51**, 9525-9529.

10 During the preparation of this manuscript, the related stoichiometric reaction was reported. The reaction involves the generation of ester enolates by treating α-ketoesters with diethyl phosphite in the presence of a stoichiometric amount of NaHDMS or LHDMS and the subsequent entrapment of the generated enolates by adding imines in a one-pot fashion. See: J. Jiang, H. Liu, C.-D. Lu and Y.-J. Xu, *Org. Lett.*, 2016, **18**, 880-883.

11 For selected synthetic study of α-hydroxy-β-amino acid derivatives, see: (a) A. Clerici, N, Pastori and O. Porta, *J. Org. Chem.*, 2005, **70**, 4174-4176; (b) A. Guerrini, G. Varchi and A. Battaglia, *J. Org. Chem.*, 2006, **71**, 6785-6795; (c) W. Hu, X. Xu, J. Zhou, W. J. Liu, H. Huang, J. Hu, L. Yang and L. Z. Gong, *J. Am. Chem. Soc.*, 2008, **130**, 7782-7783; (d) Z. Sun, H. Liu, Y.-M. Zeng, C.-D. Lu and Y.-J. Xu, *Org. Lett.*, 2016, **18**, 620-623, and references cited therein.

12 CCDC No. 1046578. See ref. 6c.

13 CCDC No. 1450154. See the supporting information for details.