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Diethyl Phosphite Initiated Coupling of α-Ketoesters with Imines for Synthesis of α-Phosphonyloxy-β-amino Acid Derivatives and Aziridine-2-carboxylates

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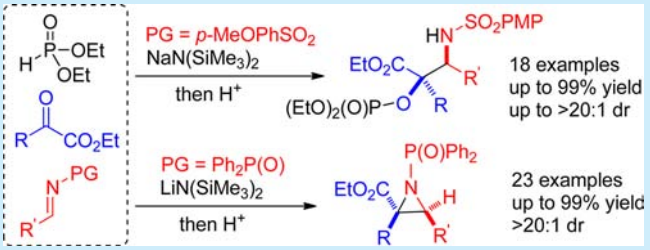
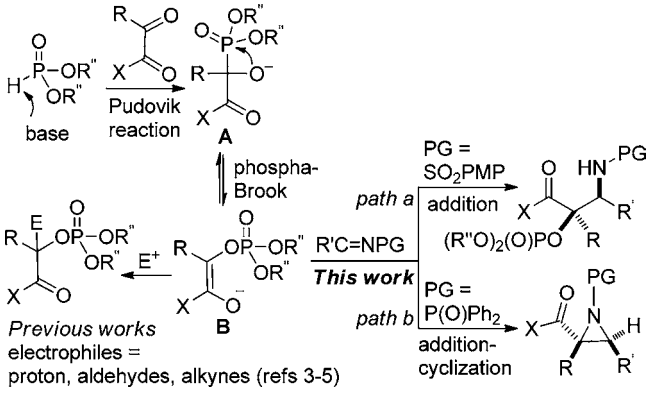
Supporting Information

ABSTRACT: Coupling of α-ketoesters with imines initiated by diethyl phosphite in the presence of alkaline metal hexamethyldisilazides is reported. Base-promoted addition of diethyl phosphite to α-ketoesters, followed by [1,2]-phosphonate/phosphate rearrangement, generates α-phosphonyloxy enolates that are subsequently intercepted by imines. The use of suitable azomethine coupling partners allows selective construction of *syn*-α-hydroxy-β-amino acid derivatives or *trans*-aziridine-2-carboxylates in high yields with excellent diastereoselectivities.



Nucleophilic addition of phosphites to a carbon atom in polarized π-bonds, such as in aldehydes, imines, and 1,4-Michael acceptors, is a well-established method for constructing a C−P bond.[1] Adding phosphite diester to carbonyl compounds provides adduct **A**, which can undergo phosphoryl migration from carbon to oxygen under alkaline conditions. This [1,2]-phosphonate−phosphate rearrangement, also known as [1,2]-phospha-Brook rearrangement,[2] generates the reactive α-phosphonyloxy enolate **B**, which can be intercepted intramolecularly by alkynes,[3] or intermolecularly by electrophiles such as protons[4] and aldehydes[5] (Scheme 1, lower left). Using suitable chiral bases, researchers have extended these late transformations to enantioselective versions of protonation and aldolization. However, similar three-component cascade transformations involving Mannich addition in which azomethines serve as electrophiles have not been reported. Terada and co-workers have recently published an alternative approach to the enolate **B** involving α-oxygenation of α-phosphonyl esters with oxaziridines and subsequent trapping of **B** by an *N*-Ts imine generated *in situ* from deoxygenation of oxaziridines. This procedure gives α-phosphonyloxy-β-amino esters in high yield with moderate diastereoselectivity.[6]

Scheme 1. Trapping α-Phosphonyloxy Enolates with Imines



Given our continuing interest in rapidly constructing nitrogen-containing structural motifs using cascade reactions that involve Brook rearrangement,[7] we wanted to examine whether using imines to trap the phospha-Brook rearrangement intermediate **B** might open the door to novel reactions. In particular, we wanted to know whether we could achieve (a) Mannich coupling with imine to yield α-hydroxy-β-amino acid derivatives (path a), which are important building blocks in bioactive agents such as taxoids,[8] and (b) an aza-Darzens reaction that would take advantage of the α-phosphonyloxy group as a good leaving group[9] (path b), which would generate aziridine-2-carboxylates, which are key subunits or precursors of useful nitrogen-containing compounds.[10] Here we describe our efforts in using *N*-substituted imines to achieve these two reaction pathways.

Initially, we tried to achieve the proposed transformations by adding the *N*-Ts imine **3** to a reaction mixture containing 3.0 equiv of diethyl phosphite (**1**), ethyl benzoylformate (**2a**), and lithium hexamethyldisilazide (LHMDS) at −15 °C. To our delight, the three-component product α-phosphonyloxy-β-amino ester **6** was obtained in high yield and 15:1 dr (Table 1, entry 1). The diastereoselectivity of the coupling reaction was sensitive to reaction temperature. When we repeated and quenched the reaction at −78 °C, reversal of diastereoselectivity was observed (1:2.2 dr, entry 2). Gradually warming the reaction

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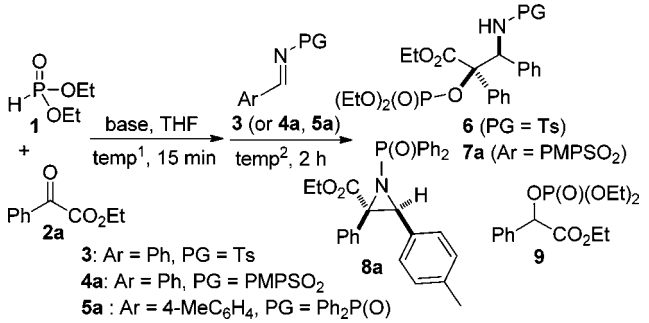
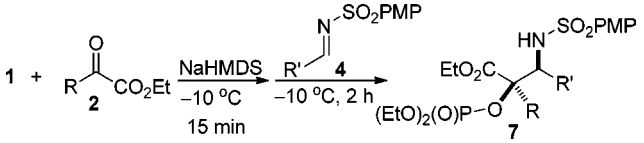
Table 1. Screening Reaction Conditions for Coupling Diethyl Phosphite (1), α-Ketoesters, and Imines[a]



entry	imine	base, temp[1], temp[2] (°C)	product, yield (%),[b] dr[c]
1	**3**	LHMDS, −15, −15	**6**, 93, 15:1
2	**3**	LHMDS, −78, −78	**6**, 84, 1:2.2
3	**3**	LHMDS, −78, −78 to −10	**6**, n.i., 15:1
4	**3**	*t*BuOK, −10, −10	**6**, n.i., 5:1
5	**3**	KHMDS, −10, −10	**6**, n.i., 3:1
6	**3**	NaHMDS, −10, −10	**6**, 99, >20:1
7	**4a**	NaHMDS, −10, −10	**7a**, 99, >20:1
8	**5a**	LHMDS, −15, −15	**8a**, 77, >20:1
9	**5a**	LHMDS, −40, −40 to rt	**8a**, 94, >20:1

[a]Diethyl phosphite (0.61 mmol), ketoester **2a** (0.60 mmol), base (0.61 mmol), and imine (0.20 mmol) in anhydrous THF under argon. [b]Entries 1−2 and 6: calculated yield based on the total measured mass of product **6** contaminated by **9**, after adjusting for the ratio of **6** to **9** determined by ^{1}H NMR measurement. Entries 7−9: isolated yield. [c]Ratios were determined by ^{1}H NMR analysis of crude reaction mixtures. PMP = *p*-methoxyphenyl, LHMDS = $LiN(SiMe_3)_2$, NaHMDS = $NaN(SiMe_3)_2$, KHMDS = $KN(SiMe_3)_2$. n.i. = not isolated.

Table 2. Three-Component Coupling of Diethyl Phosphite, α-Ketoesters, and *N*-Sulfonyl Imines[a]



entry	ester **2** (R)	imine **4** (R′)	7, yield (%)[b], dr[c]
1	**2a** (Ph)	**4a** (Ph)	**7a**, 99,[d] >20:1[d]
2	**2a** (Ph)	**4b** (4-MeC_6H_4)	**7b**, 92, >20:1
3	**2a** (Ph)	**4c** (3-MeC_6H_4)	**7c**, 99, >20:1
4	**2a** (Ph)	**4d** (2-MeC_6H_4)	**7d**, 99, >20:1
5	**2a** (Ph)	**4e** (4-ClC_6H_4)	**7e**, 99, >20:1
6	**2a** (Ph)	**4f** (4-BrC_6H_4)	**7f**, 92, >20:1
7	**2a** (Ph)	**4g** (2-thienyl)	**7g**, 99, >20:1
8	**2a** (Ph)	**4h** (1-naphthyl)	**7h**, 91, >20:1
9	**2a** (Ph)	**4i** (*i*-butyl)[e]	**7i**, 62, >20:1
10	**2a** (Ph)	**4j** (cyclohexyl)[f]	**7j**, 90, >20:1
11	**2a** (Ph)	**4k** (*t*Bu)[f]	**7k**, 59, >20:1
12	**2b** (4-MeC_6H_4)	**4a** (Ph)	**7l**, 99, >20:1
13	**2c** (3-MeC_6H_4)	**4a** (Ph)	**7m**, 95, >20:1
14	**2d** (2-MeC_6H_4)	**4a** (Ph)	**7n**, 66, 1:1
15	**2e** (4-ClC_6H_4)	**4a** (Ph)	**7o**, 91, >20:1
16	**2f** (4-FC_6H_4)	**4a** (Ph)	**7p**, 94, >20:1
17	**2g** (2-thienyl)	**4a** (Ph)	**7q**, 68, >20:1
18	**2h** (cyclohexyl)	**4a** (Ph)	**7r**, 84, 2.5:1

[a]**1** (0.61 mmol), **2** (0.60 mmol), and **4** (0.20 mmol) in anhydrous THF under argon at −10 °C. [b]Isolated yield. [c]Ratios (*syn*/*anti*) were determined by ^{1}H NMR analysis of crude reaction mixtures. [d]10-fold scale-up (1.41 g synthesis of **7a**). [e]α-Amido sulfone was used as precursor of aliphatic *N*-Ts imine. [f]*N*-Ts imine was used.

mixture from −78 to −10 °C afforded product with the same dr as when the reaction was conducted at −15 °C (15:1 dr, entry 3). When we isolated the major isomer of product **6** from the reaction mixture in entry 2 and treated it with 1.0 equiv of LHMDS in THF at −10 °C for 2 h, efficient *syn*/*anti* isomerization of **6** occurred, and the dr changed from 0:1 to 13:1 (not shown in Table 1).[11] These results suggest that the Mannich and retro-Mannich pathways are in equilibrium under our experimental conditions. A screening of bases (entries 4−6) showed that sodium hexamethyldisilazide (NaHMDS) provided the best yield and diastereoselectivity. Decreasing the amount of diethyl phosphate and α-ketoester led to lower yields.

We were unable to separate the Mannich addition product derived from *N*-Ts imine **3** from the protonation byproduct **9** by silica-gel column chromatography since they had identical R_f values. To solve this problem, we increased the polarity of the coupling product by replacing the *N*-substituent of the imine from a tosyl group to a *p*-methoxyphenylsulfonyl group (entry 7).[12]

Using *N*-DPP imine **5a** generated the addition/cyclization product **8a** rather than the aforementioned three-component coupling product (entry 8). The fact that the nitrogen anion of the Mannich addition intermediate internally displaced the diethoxyphosphate[9] indicates that a secondary nitrogen anion bearing a DPP group is more nucleophilic than one bearing sulfonyl groups. Fine-tuning the reaction temperature led to aziridine **8a** in 94% yield with >20:1 dr (entry 9).[13]

Reactions for 1-g syntheses of **7a** and **8a** gave comparable yields and diastereoselectivities (Table 2, entry 1; Table 3, entry 1). Attempts to extend these protocols to chiral *tert*-butanesulfinylimines[14] failed to give any coupling products, leaving the imines intact. This presumably reflects the diminished electrophilicity of the sulfinyl imines. Control experiments showed that reacting 3.0 equiv of **9** with imine **4a** in the presence of NaHMDS gave product **7a** in 70% yield, while reacting 3.0 equiv of **9** with imine **5a** in the presence of LHMDS gave **8a** in 84% yield. In both cases, the dr was >20:1.

Next, the reactivity of a range of α-ketoesters and *N*-4-methoxyphenylsulfonyl imines was examined for this phosphate diester-initiated three-component coupling reaction. Under the optimized reaction conditions, *N*-sulfonyl imines derived from aryl and heteroaryl aldehydes participated in the cascade reaction, affording α-phosphonyloxy-β-amino esters **7a**−**h** with excellent diastereoselectivities and yields (entries 1−8).[15] The enalizable and nonenalizable alphatic imines derived from isovaleraldehyde, cyclohexanecarboxaldehyde, and pivaldehyde underwent coupling smoothly to give products with high diastereoselectivities in moderate to high yields (entries 9−11). Various α-ketoesters with different α-substitutions known to be suitable coupling partners afforded the corresponding coupling products **7l**−**r** in moderate to good yields (entries 12−18). The diastereoselectivities were excellent except in the case of α-ketoesters bearing *ortho*-substituted phenyl and cyclohexyl groups at the α-position (entries 14 and 18).[16]

We also evaluated the scope of the aziridination transformations of *N*-DPP imines with α-ketoesters **2** in the presence of LHMDS with the assistance of diethyl phosphite (**1**). As shown in Table 3, all coupling partners tested underwent

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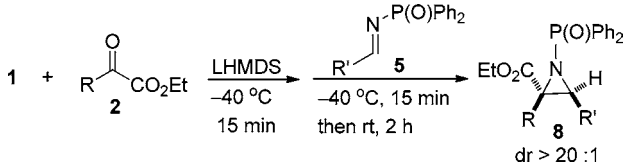
Table 3. Diethyl Phosphite-Initiated Coupling of α-Ketoesters and *N*-Diphenylphosphinyl Imines[a]



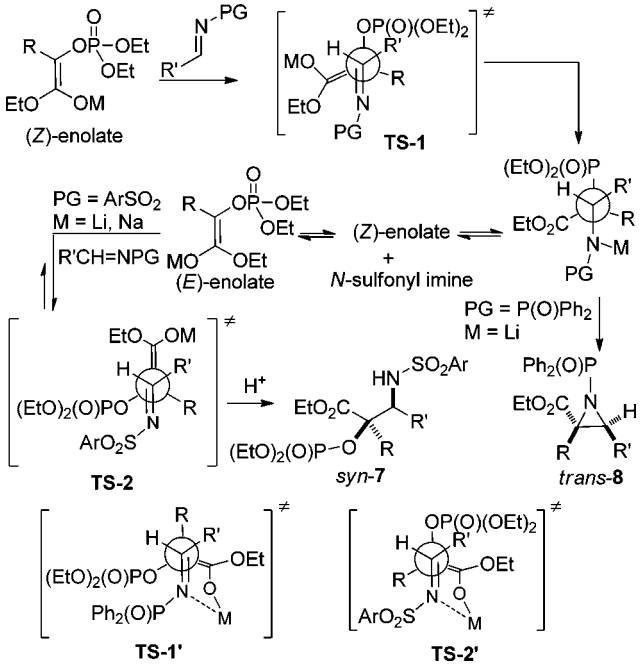
entry	ester **2** (R)	imine **5** (R′)	**8**, yield (%)[b]
1	**2a** (Ph)	**5a** (4-MeC$_6$H$_4$)	**8a**, 94 (93)[c]
2	**2a** (Ph)	**5b** (Ph)	**8b**, 91
3	**2a** (Ph)	**5c** (3-MeC$_6$H$_4$)	**8c**, 81
4	**2a** (Ph)	**5d** (2-MeC$_6$H$_4$)	**8d**, 52
5	**2a** (Ph)	**5e** (4-MeOC$_6$H$_4$)	**8e**, 93
6	**2a** (Ph)	**5f** (4-BrC$_6$H$_4$)	**8f**, 92
7	**2a** (Ph)	**5g** (4-ClC$_6$H$_4$)	**8g**, 72
8	**2a** (Ph)	**5h** (4-FC$_6$H$_4$)	**8h**, 87
9	**2a** (Ph)	**5i** (1-naphthyl)	**8i**, 60
10	**2a** (Ph)	**5j** (2-furyl)	**8j**, 90
11	**2a** (Ph)	**5k** (2-thienyl)	**8k**, 88
12	**2a** (Ph)	**5l** (*i*Bu)	**8l**, 52
13	**2a** (Ph)	**5m** (cyclohexyl)	**8m**, 62
14	**2a** (Ph)	**5n** (*t*Bu)	**8n**, 86
15	**2b** (4-MeC$_6$H$_4$)	**5b** (Ph)	**8o**, 97
16	**2c** (3-MeC$_6$H$_4$)	**5b** (Ph)	**8p**, 99
17	**2d** (2-MeC$_6$H$_4$)	**5b** (Ph)	**8q**, 90
18	**2i** (4-MeOC$_6$H$_4$)	**5b** (Ph)	**8r**, 89
19	**2j** (4-BrC$_6$H$_4$)	**5b** (Ph)	**8s**, 99
20	**2e** (4-ClC$_6$H$_4$)	**5b** (Ph)	**8t**, 85
21	**2f** (4-FC$_6$H$_4$)	**5b** (Ph)	**8u**, 88
22	**2g** (2-thienyl)	**5b** (Ph)	**8v**, 61
23	**2h** (cyclohexyl)	**5b** (Ph)	**8w**, 87

[a] **1** (0.61 mmol), **2** (0.60 mmol), and **5** (0.20 mmol) in anhydrous THF under argon. Ratios (*trans*/*cis*) were determined by ^{1}H NMR analysis of crude reaction mixtures. [b] Yield of isolated product. [c] 10-fold scale-up (1.34 g synthesis of **8a**).

reaction to give the desired products with excellent diastereocontrol (>20:1 dr) and mostly high yield.[17]

Using single-crystal X-ray analysis, we determined the relative configuration of the α-hydroxy-β-amino acid derivative **7m** to be *syn* and that of the trisubstituted *N*-DPP aziridine **8a** to be *trans*.[18] The stereochemistry of other products was assigned by analogy. We proposed the models in Scheme 2 to rationalize the observed stereochemical outcomes. The reactive intermediate (*Z*)-enolate generated by the addition/rearrangement cascade (Scheme 1)[19] undergoes nucleophilic addition to the imine via an open transition state **TS-1**, which minimizes nonbonding interactions between the protecting group on the imine and the phosphonyloxy and ester group of the enolate. The result is a new C−C bond, affording a nitrogen anion intermediate.[20] In the case of *N*-DPP imines, subsequent *3-exo-tet* cyclization of the nitrogen anion gives *trans*-aziridine products **8**. In the case of *N*-sulfonyl imines, the relatively weak nucleophilicity of the nitrogen anion retards the aziridination, allowing a retro-Mannich reaction[21] to occur at higher reaction temperatures. Subsequent enolate isomerization and equilibration, followed by (*E*)-enolate coupling with imine via **TS-2**, yield the product *syn*-**7**. At this time, we are unable to rule out the existence of a corresponding chelated chairlike transition state **TS-1′** on the reaction pathway proceeding via **TS-1**, or the existence of the corresponding state **TS-2′** on the pathway proceeding via **TS-2**.

Scheme 2. Proposed Models to Explain Diastereoselectivity



In summary, we have described an efficient protocol for synthesizing *syn*-α-hydroxy-β-amino acid derivatives and *trans*-aziridine-2-carboxylates via phosphate diester initiated coupling of α-ketoesters with imines. In this approach, the intermediate derived from phosphate addition/[1,2]-phospha-Brook rearrangement is trapped by imines through Mannich addition or aza-Darzens reaction. These pathways can be tuned by employing imines with different *N*-substitutions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00273.

Experimental details, characterization data of all new compounds (PDF)
X-ray crystal structure of compounds **7m** (CIF)
X-ray crystal structure of compounds **8a** (CIF)

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Notes

The authors declare no competing financial interest.

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(10) For recent reviews of aziridines, see: (a) Degennaro, L.; Trinchera, P.; Luisi, R. *Chem. Rev.* **2014**, *114*, 7881. (b) Callebaut, G.; Meiresonne, T.; De Kimpe, N.; Mangelinckx, S. *Chem. Rev.* **2014**, *114*, 7954. (c) Pellissier, H. *Adv. Synth. Catal.* **2014**, *356*, 1899. For a recent example of trisubstituted aziridine synthesis via aza-Darzens reaction, see: (d) Moragas, T.; Churcher, I.; Lewis, W.; Stockman, R. A. *Org. Lett.* **2014**, *16*, 6290.

(11) Treating compound **6** with 1.0 equiv of LHMDS at rt for 24 h resulted in complete decomposition of the starting material, which is consistent with results reported in ref 6.

(12) For synthetic applications of *N*-*p*-methoxyphenylsulfonyl imines, see: Hashimoto, T.; Sakata, K.; Tamakuni, F.; Dutton, M. J.; Maruoka, K. *Nat. Chem.* **2013**, *5*, 240.

(13) Reactions carried out at −40 °C or below did not provide aziridines; instead, the main products were α-phosphonyloxy-β-amino esters. Attempts to isolate these products in analytically pure form failed.

(14) For a review on *tert*-butanesulfinylimine chemistry, see: Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600.

(15) Reference 6 reports the use of $LiAlH_4$ to convert the diethoxyphosphoryloxy group and ester in α-phosphonyloxy-β-amino acid derivative **6** to hydroxyl groups, furnishing 3-amino-1,2-diol.

(16) In the reaction of *N*-sulfonyl imine **4a**, replacing α-ketoester **2a** with ethyl pyruvate (R′ = Me) did not lead to any three-component coupling product; instead, imine hydrophosphonylation occurred.

(17) In the reaction of *N*-DPP imine **5a**, replacing α-ketoester **2a** with ethyl pyruvate (R′ = Me) gave the corresponding aziridine with 5:4 dr, based on ^{1}H NMR analysis of the crude product. Pure product could not be obtained by silica-gel column chromatography.

(18) See the Supporting Information for X-ray crystal structures of compounds **7m** and **8a**.

(19) For preferential formation of (*Z*)-enolate during addition of phosphite diester to α-ketoester and subsequent phosphoryl migration, see refs 5b, c.

(20) For precedents of the proposed open transition state in the addition of homoenolate to imine, see: (a) Lettan, R. B.; Woodward, C. C.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 2294. (b) Lettan, R. B.; Galliford, C. V.; Woodward, C. C.; Scheidt, K. A. *J. Am. Chem. Soc.* **2009**, *131*, 8805.

(21) For examples of retro-Mannich transformations, see: Giubellina, N.; Mangelinckx, S.; Törnroos, K. W.; De Kimpe, N. *J. Org. Chem.* **2006**, *71*, 5881. Also see ref 6.

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