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Catalytic Mannich-type reaction of phosphorylimidates

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ABSTRACT

Phosphorylimidates reacted with *N*-Boc imines in the presence of a catalytic amount of potassium hexamethyldisilazide, to afford the corresponding Mannich-type adducts in high yields. It was shown that, like sulfonylimidates, phosphorylimidates can function as ester equivalents. In contrast to sulfonylimidates however, phosphorylimidates exhibited high *anti*-selectivity even in low polar solvents. An explanation for the *anti*-selectivity is given.

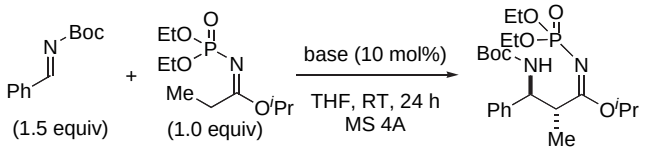
1. Introduction

Mannich-type reactions have been widely used over the past two decades for the synthesis of nitrogen containing compounds.[1] Most of these reactions utilize preformed enolates and their derivatives as nucleophiles, while the development of direct-type reactions, i.e., the in situ generation and use of carbonyl nucleophiles, has only recently become a focus area of research.[2] Given the synthetic versatility of aldehydes and esters, the development of the use of these substrates as nucleophiles is especially important. While the catalytic Mannich-type reaction in which aldehydes are used as nucleophiles has been realized using enamine catalysis, there are only a few examples of the use of ester nucleophiles bearing no activating α-substituents, such as COR, Ar, CN or OH. This is because of the high pK_a value of the ester α-proton.[3] In order to solve this problem the pK_a value of the α-proton must be reduced—either dynamically, by employing a Lewis acidic metal catalyst to activate the carbonyl group, or statically, by designing suitable esters or ester derivatives.[4] We have recently reported on the Mannich-type reaction of sulfonylimidates with *N*-Boc imines, under either DBU- or alkali earth metal alkoxide/amide-catalyzed conditions, to afford the corresponding adducts in good yields and with high diastereoselectivity.[5] The reaction can proceed to afford either the *syn* or *anti* isomers, depending on the choice of solvent and catalyst. As part of an ongoing investigation into imidate chemistry, we now wish to report on the use of a phosphorylimidate as a novel nucleophile in a catalytic Mannich-type reaction of *N*-Boc imines.

2. Results and discussion

We set out to investigate the behavior of phosphorylimidates[6] by exposing this type of substrate to Mannich-type reaction conditions developed in our laboratory and varying the Brønsted base catalysts. The results are summarized in Table 1. While a strong organic base, such as DBU, did not catalyze the reaction (entry 1), the use of 10 mol % potassium *tert*-butoxide (KO^{t}Bu) afforded the desired adduct in 69% yield and with high diastereoselectivity in favor of the *anti* product (entry 2). Alkali earth metal alkoxides and amides generally afforded moderate yields (entries 3–9). The best

Table 1
Effect of bases



Entry	Base	Yield (%)	*anti*/*syn*[a]
1	DBU	0	—
2	KO^{t}Bu	69	87/13
3	Mg(O^{t}Bu)$_2$	0	—
4	Ba(O^{t}Bu)$_2$	62	67/33
5	Ca(O^{i}Pr)$_2$	47	80/20
6	Sr(O^{i}Pr)$_2$	43	71/29
7	Ba(O^{i}Pr)$_2$	69	67/33
8	Ca(HMDS)$_2$	9	85/15
9	1/2[Sr(HMDS)$_2$]$_2$	72	76/24
10	Na(HMDS)	84	86/14
11	K(HMDS)	89	85/15

[a] Determined by ^{1}H NMR spectroscopy of the crude products.

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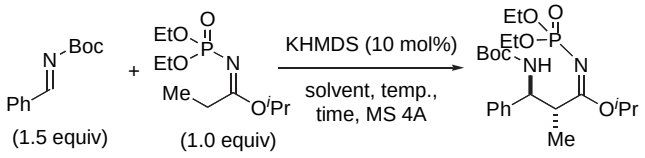
yield and *anti*-selectivity was obtained by using potassium hexamethyldisilazide (KHMDS) as a catalyst (entry 11). Such *anti*-selectivity is in contrast to what we observed with sulfonylimidates, which always gave *syn*-selectivity in THF, irrespective of the metal catalysts used.[3i]

Further investigations were carried out (see Table 2). Since we know from our sulfonylimidate chemistry that *anti*-selectivity is favored when the metal enolate ion pair is dissociative,[3j] 18-crown-6 was added to bind the potassium cation. This afforded the formation of a naked aza-enolate (entry 2). As expected, higher *anti*-selectivity was observed (*anti*/*syn*=92/8). Decreasing the reaction temperature further increased the selectivity (entries 3 and 4). As a result of solvent screening, toluene was also found to be a good solvent (entry 5); the desired product was obtained in 92% yield, albeit with lower selectivity (*anti*/*syn*=87/13). On the other hand, use of dichloromethane (DCM) shut down the reaction (entry 6). DMF is the best solvent to use for achieving high *anti*-selectivity in sulfonylimidate chemistry, and it proved to be equally good with the phosphoryimidates; use of DMF as solvent afforded high *anti*-selectivity, even in the absence of 18-crown-6 (entries 7–10).

Table 2
Optimization of reaction conditions



Entry	Solvent	Temp	Time (h)	Yield (%)	*anti*/*syn*[a]
1	THF	rt	24	89	85/15
2[b]	THF	rt	24	74	92/8
3[b]	THF	0 °C	24	73	96/4
4[b]	THF	0 °C	48	80	94/6
5	Toluene	0 °C	48	92	87/13
6	DCM	0 °C	48	Trace	—
7	DMF	rt	24	72	93/7
8	DMF	0 °C	24	79	95/5
9	DMF	0 °C	48	88	96/4
10	DMF	0 °C	72	88	95/5

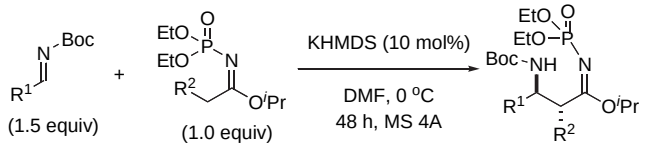
[a] Determined by ^{1}H NMR spectroscopy of the crude products.
[b] 18-Crown-6 (10 mol %) was added.

Having determined the optimized reaction conditions in hand (Table 2, entry 9), the substrate generality was examined next (Table 3). Besides propionimidate (entry 1), butyrimidate can also be used (entry 2). The use of acetimidate led to a mixture of mono- and double-addition products (entry 3). This phenomenon was previously observed with sulfonylimidates,[3g] but it was possible to suppress it by using an excess amount of phosphorylacetimidate (5 equiv). Various aromatic aldehyde-derived Boc imines, including heteroaromatics, provide the corresponding adducts in good to high yields and with high selectivity (entries 4–13). Enolizable isovaleraldehyde-derived Boc imine could also be used, as shown in entry 14. Moreover, it was noted that the sterically demanding pivaldehyde-derived Boc imine was tolerated and afforded the desired product in high yield and with high selectivity (entry 15).

The Mannich-type adducts were readily converted to amides under acidic conditions; the adduct was treated with sulfuric acid at 100 °C for 3 h to afford the corresponding *N*-phosphorylamide in 88% yield. No epimerization was observed during this transformation (Scheme 1).

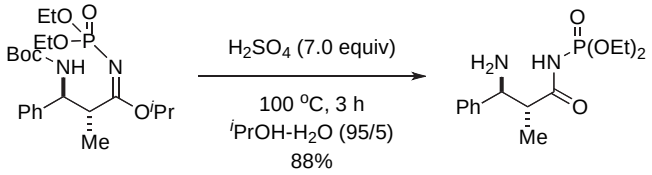
In contrast to the metal-catalyzed addition reactions of sulfonylimidates, phosphorylimidates afforded the corresponding adducts with *anti*-selectivity in all the reactions investigated in this study. In our sulfonylimidate studies, a combination of experimental results and X-ray diffraction analyses suggested that the

Table 3
Mannich-type reactions of phosphorylimidates



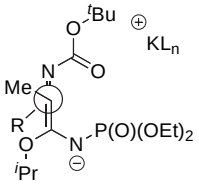
Entry	R^1	R^2	Yield (%)	*anti*/*syn*[a]
1	Ph	Me	88	96/4
2	Ph	Et	94	96/4
3[b]	Ph	H	59	—
4	*p*-MeO-C_6H_4	Me	88	94/6
5	*p*-F-C_6H_4	Me	86	93/7
6	*p*-Cl-C_6H_4	Me	71	96/4
7	*p*-Me-C_6H_4	Me	80	95/5
8	*m*-Me-C_6H_4	Me	92	95/5
9	*o*-Me-C_6H_4	Me	91	94/6
10	1-Naphthyl	Me	93	95/5
11[c]	2-Furyl	Me	70	79/21
12	2-Thienyl	Me	77	90/10
13	3-Pyridyl	Me	38	86/14
14[d]	^{i}Bu	Me	31	88/12
15[d]	^{t}Bu	Me	87	98/2

[a] Determined by ^{1}H NMR spectroscopy of the crude products.
[b] Phosphorylimidate (5.0 equiv) and imine (1.0 equiv) were used. Reaction time was 10 min.
[c] KO^{t}Bu (10 mol %) was used.
[d] Imine (2.0 equiv) was used.



Scheme 1. Conversion to *N*-phosphorylamide.

anti-selectivity observed could be explained by a transition state model wherein metal coordination with the aza-enolate nitrogen and *N*-Boc imine oxygen is not involved; otherwise, when metal coordination is possible, *syn*-selectivity resulted.[7] Applying this explanation to phosphorylimidate chemistry, it is therefore appropriate to reason that the addition reactions of phosphorylimidates proceeded via a noncoordinating transition state, even in less polar solvents such as toluene and THF. Although this is still speculative, we believe that the Lewis basic P=O oxygen atom may have a high tendency to coordinate to the metal cation, either in a uni- or multi-molecular fashion. As a result, coordination between the metal cation and the *N*-Boc imine oxygen is less favored in the transition state for both steric and electronic reasons. The assumed transition state model for the Mannich-type reaction of phosphorylimidates is given in Figure 1.



(L = DMF, 18-crown-6 or phosphorylimidate)

Figure 1. Assumed transition state model for the Mannich-type reaction of phosphorylimidates.

3. Conclusion

In summary, in an ongoing study of the development of novel nucleophiles, phosphorylimidates have been successfully used in the catalytic, direct Mannich-type reactions. In contrast to sulfonylimidates, phosphorylimidates afford high *anti*-selectivity, even in less polar solvents. An explanation for the *anti*-selectivity is given. Further application of this methodology as well as development of its asymmetric variant is ongoing in our laboratory.

4. Experimental

4.1. Preparation of phosphorylimidates

HCl gas was bubbled into a mixture of a nitrile (400 mmol) and 2-propanol (400 mmol) for 10–20 min (exothermic). The mixture was then left for 3–10 h under an Ar atmosphere. Removal of all the volatiles by evaporation afforded an almost pure imidate HCl salt in 40–80% yield. This product could be used in the next reaction without further purification but, if required, further purification could be carried out by washing the solid with dry Et_2O. The imidate HCl salts were hygroscopic, but could be stored under an inert gas atmosphere in the refrigerator.

To a solution of *iso*-propylpropionimidate HCl salt (5.39 g, 35.57 mmol) in DCM (82.5 mL) was added Et_3N (15.0 mL, 106.72 mmol) dropwise at room temperature (rt). To the resultant suspension were added $(EtO)_2(O)PCl$ (4.75 mL, 35.57 mmol) and DMAP (367.5 mg, 3.557 mmol). The mixture was stirred until $(EtO)_2(O)PCl$ was consumed (ca. 24 h). The mixture was poured into water and extracted with DCM. The organic fraction was dried over anhydrous Na_2SO_4. Filtration and evaporation of the solvents afforded the crude product, which was purified by column chromatography on SiO_2 to give *iso*-propyl *N*-diethoxyphosphorylpropionimidate (7.087 g, 86% yield).

4.1.1. iso-Propyl N-diethoxyphosphoryl-propionimidate. Colorless oil. ^{1}H NMR (C_6D_6) δ=5.06 (1H, quint, J=6.2 Hz), 4.10–4.00 (4H, m), 2.79 (2H, q, J=7.8 Hz), 1.14–1.11 (9H, m), 1.00 (6H, d, J=6.2 Hz); ^{13}C NMR (C_6D_6) δ=176.24 (d, J=17.3 Hz), 69.25, 62.14 (d, J=5.8 Hz), 28.94 (d, J=2.9 Hz), 21.23, 16.45 (d, J=7.2 Hz), 11.07; ^{31}P NMR (C_6D_6) δ=4.34; IR (neat) 3550, 2982, 2360, 1648, 1466, 1375, 1297, 1230, 1110, 1034, 968, 763, 606, 506 cm^{-1}; HRMS (DART); exact mass calcd for $C_{10}H_{23}NO_4P$ $[M+H]^+$, 252.1365. Found 252.1372.

4.1.2. iso-Propyl N-diethoxyphosphoryl-butyrimidate. Colorless oil. ^{1}H NMR (C_6D_6) δ=5.09 (1H, quint, J=6.2 Hz), 4.10–4.02 (4H, m), 2.81 (2H, t, J=7.6 Hz), 1.69 (2H, td, J=14.4, 7.1 Hz), 1.14 (6H, t, J=6.9 Hz), 1.02 (6H, d, J=6.2 Hz), 0.88 (3H, t, J=7.6 Hz); ^{13}C NMR (C_6D_6) δ=175.20 (d, J=17.3 Hz), 69.15, 62.07 (d, J=5.8 Hz), 36.98 (d, J=4.3 Hz), 21.26, 20.42, 16.43 (d, J=5.8 Hz), 13.76; ^{31}P NMR (C_6D_6) δ=4.21; IR (neat) 2980, 2366, 1650, 1467, 1372, 1290, 1255, 1110, 1035, 965, 775, 608, 512 cm^{-1}; HRMS (DART); exact mass calcd for $C_{11}H_{25}NO_4P$ $[M+H]^+$, 266.1521. Found 266.1515.

4.1.3. iso-Propyl N-diethoxyphosphorylacetimidate. Colorless oil. ^{1}H NMR (C_6D_6) δ=5.06 (1H, quint, J=6.5 Hz), 4.08–4.01 (4H, m), 2.28 (3H, s), 1.16 (6H, t, J=7.2 Hz), 1.03 (6H, *d*, J=6.2 Hz); ^{13}C NMR (C_6D_6) δ=172.45 (*d*, J=15.9 Hz), 69.43, 21.29 (*t*, J=4.3 Hz), 16.39 (d, J=7.2 Hz); ^{31}P NMR (C_6D_6) δ=4.56; IR (neat) 3542, 2982, 2361, 1654, 1375, 1282, 1110, 1056, 965, 909, 837, 767, 618, 505 cm^{-1}; HRMS (DART); exact mass calcd for $C_9H_{21}NO_4P$ $[M+H]^+$, 238.1208. Found 238.1205.

4.2. General procedure for the addition reactions of phosphorylimidates to imines

A mixture of imine (0.45 mmol), phosphorylimidate (0.3 mmol), and MS 4 Å (50 mg) in DMF (0.4 mL) was cooled to 0 °C, and a solution of KHMDS (10 mol %) in DMF (0.2 mL) was added to the mixture. The mixture was stirred for 48 h at this temperature and then quenched with satd NH_4Cl (aq) and diluted by the addition of Et_2O and H_2O. The mixture that was obtained was washed with water (three times) and then dried over anhydrous Na_2SO_4. Filtration and removal of solvents afforded the crude product. The diastereomer ratio was determined by ^{1}H NMR analysis of the crude product. Purification of the crude product was conducted by chromatography on SiO_2, to afford the desired product.

4.2.1. iso-Propyl anti-3-(tert-butoxycarbonylamino)-N-(diethoxyphosphoryl)-2-methyl-3-phenylpropionimidate. Colorless oil. ^{1}H NMR (C_6D_6) δ=7.62 (1H, d, J=8.9 Hz), 7.54 (2H, d, J=7.6 Hz), 7.09 (2H, t, J=7.6 Hz), 7.00 (1H, t, J=7.6 Hz), 5.20 (1H, quint, J=6.2 Hz), 5.03 (1H, dd, J=10.3, 10.3 Hz), 4.20–4.15 (2H, m), 4.02–3.92 (3H, m), 1.34 (9H, s), 1.29–1.25 (6H, m), 1.09 (3H, d, J=6.2 Hz), 1.05 (3H, t, J=7.2 Hz), 0.96 (3H, d, J=6.2 Hz); ^{13}C NMR (C_6D_6) δ=177.40 (d, J=15.9 Hz), 155.10, 142.36, 128.82, 127.86, 127.64, 78.16, 70.33, 62.60 (d, J=5.8 Hz), 58.90, 46.70 (d, J=4.3 Hz), 28.44, 21.15, 20.95, 16.43 (d, J=5.8 Hz), 16.30 (d, J=5.8 Hz), 15.01; ^{31}P NMR (C_6D_6) δ=6.51; IR (neat) 3289, 2979, 2935, 2363, 1715, 1640, 1520, 1455, 1365, 1289, 1246, 1171, 1106, 1034, 970, 916, 879, 852, 765, 703, 637, 614, 573, 517 cm^{-1}; HRMS (DART); exact mass calcd for $C_{22}H_{38}N_2O_6P$ $[M+H]^+$, 457.2468. Found 457.2445.

4.2.2. iso-Propyl syn-3-(tert-butoxycarbonylamino)-N-(diethoxyphosphoryl)-2-methyl-3-phenylpropionimidate. White solid. ^{1}H NMR (C_6D_6) δ=7.71 (2H, d, J=7.6 Hz), 7.15 (2H, d, J=7.6 Hz), 7.01 (1H, t, J=7.2 Hz), 6.13 (1H, d, J=8.9 Hz), 5.36 (1H, t, J=10 Hz), 4.83 (1H, quint, J=6.2 Hz), 4.53–4.49 (1H, m), 4.06–43.99 (2H, m), 3.87–3.83 (2H, m), 1.56 (3H, d, J=6.9 Hz), 1.42 (9H, s), 1.12–1.07 (6H, m), 0.90 (3H, d, J=6.2 Hz), 0.70 (3H, d, J=6.2 Hz); ^{13}C NMR (C_6D_6) δ=176.02 (d, J=17.3 Hz), 155.86, 142.60, 128.46 (d, J=2.9 Hz), 127.87, 127.36, 78.39, 69.46, 62.34 (d, J=7.2 Hz), 62.19 (d, J=5.8 Hz), 57.59, 44.61 (d, J=4.3 Hz), 28.55, 20.96, 20.54, 16.45, 16.37 (t, J=7.9 Hz); ^{31}P NMR (C_6D_6) δ=2.99; IR (neat) 3734, 3269, 2979, 2360, 1709, 1650, 1525, 1455, 1366, 1240, 1172, 1107, 1038, 969, 770, 701, 624, 501 cm^{-1}; HRMS (DART); exact mass calcd for $C_{22}H_{38}N_2O_6P$ $[M+H]^+$, 457.2468. Found 457.2454. Mp 115–116 °C.

4.2.3. iso-Propyl anti-3-(tert-butoxycarbonylamino)-N-(diethoxyphosphoryl)-2-ethyl-3-phenylpropionimidate. Colorless oil. ^{1}H NMR (C_6D_6) δ=7.69 (1H, d, J=8.9 Hz), 7.56 (2H, d, J=7.6 Hz), 7.09 (2H, t, J=7.6 Hz), 7.00 (1H, t, J=7.2 Hz), 5.22 (1H, quint, J=6.2 Hz), 5.06 (1H, dd, J=10.3, 10.3 Hz), 4.22–4.15 (2H, m), 4.06–4.02 (1H, m), 3.97–3.90 (1H, m), 3.82 (1H, t, J=11.3 Hz), 1.74–1.63 (1H, m), 1.34 (9H, s), 1.31–1.25 (6H, m), 1.22–1.14 (1H, m), 1.09 (3H, d, J=6.2 Hz), 1.07 (3H, t, J=7.2 Hz), 0.75 (3H, t, J=7.2 Hz); ^{13}C NMR (C_6D_6) δ=176.75 (d, J=15.9 Hz), 155.06, 142.79, 128.81, 127.84, 127.60, 78.05, 70.23, 62.59 (q, J=6.7 Hz), 58.10, 54.79 (d, J=4.3 Hz), 28.43, 23.32, 21.13, 21.04, 16.43 (d, J=5.8 Hz), 16.30 (d, J=7.2 Hz), 12.00; ^{31}P NMR (C_6D_6) δ=6.75; IR (neat) 3293, 2978, 2935, 2364, 1715, 1639, 1520, 1455, 1389, 1365, 1303, 1247, 1171, 1106, 1034, 970, 866, 799, 760, 703, 635, 610, 574, 522 cm^{-1}; HRMS (DART); exact mass calcd for $C_{23}H_{40}N_2O_6P$ $[M+H]^+$, 471.2624. Found 471.2632.

4.2.4. iso-Propyl 3-(tert-butoxycarbonylamino)-N-(diethoxyphosphoryl)-3-phenylpropionimidate. Colorless oil. ^{1}H NMR (C_6D_6) δ=7.51 (1H, d, J=8.9 Hz), 7.43 (2H, d, J=7.6 Hz), 7.07 (2H, *t*, J=7.6 Hz), 6.98 (1H, t, J=7.2 Hz), 5.51–5.47 (1H, m), 5.12 (1H, quint, J=6.2 Hz), 4.21–4.14 (2H, m), 3.96–3.89 (2H, m), 3.58 (1H, t, J=12.4 Hz), 2.72 (1H, dd, J=13.1, 4.8 Hz), 1.39 (9H, s), 1.24 (3H, t, J=6.9 Hz), 1.20 (3H, d, J=6.2 Hz), 1.05–1.03 (6H, m); ^{13}C NMR (C_6D_6) δ=173.42 (d, J=15.9 Hz), 155.38, 143.50, 128.81, 127.85, 127.40, 78.26, 70.37, 62.54 (d, J=5.8 Hz), 53.37, 42.90 (d, J=4.3 Hz), 28.46, 21.24, 20.95, 16.44 (d, J=7.2 Hz), 16.25 (d, J=5.8 Hz); ^{31}P NMR (C_6D_6) δ=6.35; IR (neat) 3882, 3850, 3734, 3646, 3280, 2980, 2361, 1714, 1649, 1519, 1455, 1365, 1298, 1246, 1173, 1108, 1033, 969, 774, 700, 626, 516 cm^{-1};

HRMS (DART); exact mass calcd for $C_{21}H_{36}N_2O_6P$ $[M+H]^+$, 443.2311. Found 443.2304.

4.2.5. iso-Propyl anti-3-(tert-butoxycarbonylamino)-N-(diethoxyphosphoryl)-3-(p-methoxyphenyl)-2-methylpropionimidate. Colorless oil. ^{1}H NMR (C_6D_6) δ=7.54 (1H, d, J=9.6 Hz), 7.46 (2H, d, J=8.2 Hz), 6.68 (2H, d, J=8.9 Hz), 5.21 (1H, quint, J=6.2 Hz), 5.01 (1H, dd, J=10.3, 10.3 Hz), 4.22–4.15 (2H, m), 4.04–3.93 (3H, m), 3.26 (3H, s), 1.36 (9H, s), 1.30 (3H, d, J=6.2 Hz), 1.26 (3H, t, J=6.9 Hz), 1.10 (3H, d, J=6.2 Hz), 1.07 (3H, t, J=7.2 Hz), 1.01 (3H, d, J=6.9 Hz); ^{13}C NMR (C_6D_6) δ=177.63 (d, J=17.3 Hz), 159.50, 155.14, 134.42, 128.92, 114.33, 78.14, 70.32, 62.63 (d, J=5.8 Hz), 58.38, 54.70, 46.84 (d, J=4.3 Hz), 28.49, 21.19, 20.99, 16.46 (d, J=5.8 Hz), 16.33 (d, J=5.8 Hz), 15.12; ^{31}P NMR (C_6D_6) δ=6.48; IR (neat) 3888, 3872, 3855, 3840, 3824, 3804, 3747, 3678, 3652, 3295, 2979, 2361, 1713, 1642, 1514, 1456, 1366, 1293, 1247, 1173, 1105, 1035, 970, 832, 766, 620 cm^{-1}; HRMS (DART); exact mass calcd for $C_{23}H_{40}N_2O_7P$ $[M+H]^+$, 487.2573. Found 487.2559.

4.2.6. iso-Propyl anti-3-(tert-butoxycarbonylamino)-N-(diethoxyphosphoryl)-3-(p-fluorophenyl)-2-methylpropionimidate. Colorless oil. ^{1}H NMR (C_6D_6) δ=7.60 (1H, d, J=8.9 Hz), 7.34 (2H, dd, J=8.2, 5.5 Hz), 6.71 (2H, t, J=8.6 Hz), 5.18 (1H, quint, J=6.2 Hz), 4.95 (1H, dd, J=10.3, 10.3 Hz), 4.21–4.13 (2H, m), 4.02–3.85 (3H, m), 1.36 (9H, s), 1.29–1.23 (6H, m), 1.08 (3H, d, J=6.2 Hz), 1.05 (3H, t, J=7.2 Hz), 0.91 (3H, d, J=6.9 Hz); ^{13}C NMR (C_6D_6) δ=177.21 (d, J=15.9 Hz), 155.07, 138.10 (d, J=2.9 Hz), 129.51 (d, J=7.2 Hz), 127.84, 115.53 (d, J=21.7 Hz), 78.32, 70.39, 62.65 (d, J=5.8 Hz), 58.14, 46.63 (d, J=4.3 Hz), 28.41, 21.11, 20.91, 16.39 (d, J=7.2 Hz), 16.26 (d, J=5.8 Hz), 14.91; ^{31}P NMR (C_6D_6) δ=6.46; IR (neat) 3855, 3734, 3672, 3275, 2980, 2936, 2365, 1714, 1639, 1509, 1456, 1390, 1366, 1290, 1225, 1173, 1107, 1035, 970, 880, 838, 767, 620, 567, 528 cm^{-1}; HRMS (DART); exact mass calcd for $C_{22}H_{37}FN_2O_6P$ $[M+H]^+$, 475.2373. Found 475.2364.

4.2.7. iso-Propyl anti-3-(tert-butoxycarbonylamino)-3-(p-chlorophenyl)-N-(diethoxyphosphoryl)-2-methylpropionimidate. White solid. ^{1}H NMR (C_6D_6) δ=7.64 (1H, d, J=8.9 Hz), 7.26 (2H, d, J=8.9 Hz), 6.99 (2H, d, J=8.2 Hz), 5.18 (1H, quint, J=6.2 Hz), 4.90 (1H, dd, J=10.7, 9.3 Hz), 4.21–4.13 (2H, m), 4.02–3.97 (1H, m), 3.94–3.90 (1H, m), 3.86–3.82 (1H, m), 1.36 (9H, s), 1.29–1.23 (6H, m), 1.07 (3H, d, J=6.2 Hz), 1.05 (3H, t, J=7.2 Hz), 0.88 (3H, d, J=6.9 Hz); ^{13}C NMR (C_6D_6) δ=177.05 (d, J=15.9 Hz), 155.03, 140.84, 133.38, 129.26, 128.91, 78.34, 70.37, 62.64 (d, J=2.9 Hz), 62.60 (d, J=2.9 Hz), 58.24, 46.46 (d, J=4.3 Hz), 28.41, 21.12, 20.90, 16.41 (d, J=7.2 Hz), 16.28 (d, J=5.8 Hz), 14.82; ^{31}P NMR (C_6D_6) δ=6.56; IR (neat) 3850, 3734, 3289, 2979, 2935, 2361, 1714, 1648, 1519, 1492, 1456, 1389, 1365, 1288, 1246, 1169, 1089, 1035, 970, 878, 825, 767, 617, 519 cm^{-1}; HRMS (DART); exact mass calcd for $C_{22}H_{37}ClN_2O_6P$ $[M+H]^+$, 491.2078. Found 491.2056. Mp 67 °C.

4.2.8. iso-Propyl anti-3-(tert-butoxycarbonylamino)-N-(diethoxyphosphoryl)-3-(p-methylphenyl)-2-methylpropionimidate. White solid. ^{1}H NMR (C_6D_6) δ=7.58 (1H, d, J=9.6 Hz), 7.45 (2H, d, J=8.2 Hz), 6.91 (2H, d, J=8.2 Hz), 5.20 (1H, quint, J=6.2 Hz), 5.02 (1H, dd, J=10.3, 10.3 Hz), 4.22–4.15 (2H, m), 4.03–3.92 (3H, m), 2.03 (3H, s), 1.35 (9H, s), 1.29 (3H, d, J=6.2 Hz), 1.26 (3H, t, J=6.9 Hz), 1.09 (3H, d, J=6.2 Hz), 1.06 (3H, t, J=6.9 Hz), 1.00 (3H, d, J=6.9 Hz); ^{13}C NMR (C_6D_6) δ=177.55 (d, J=17.3 Hz), 155.11, 139.47, 136.99, 129.53, 128.19, 78.11, 70.29, 62.59 (d, J=5.8 Hz), 58.67, 46.71 (d, J=4.3 Hz), 28.48, 21.17, 20.98 (d, J=2.9 Hz), 16.46 (d, J=7.2 Hz), 16.32 (d, J=7.2 Hz), 15.08; ^{31}P NMR (C_6D_6) δ=6.51; IR (neat) 3855, 3840, 3735, 3672, 3647, 3293, 2979, 2361, 1715, 1644, 1518, 1455, 1365, 1289, 1246, 1172, 1106, 1034, 970, 818, 765, 620, 520 cm^{-1}; HRMS (DART); exact mass calcd for $C_{23}H_{40}N_2O_6P$ $[M+H]^+$, 471.2624. Found 471.2608. Mp 59–60 °C.

4.2.9. iso-Propyl anti-3-(tert-butoxycarbonylamino)-N-(diethoxyphosphoryl)-3-(m-methylphenyl)-2-methylpropionimidate. Colorless oil. ^{1}H NMR (C_6D_6) δ=7.61 (1H, d, J=9.6 Hz), 7.40 (1H, d, J=8.2 Hz), 7.37 (1H, s), 7.05 (1H, t, J=7.6 Hz), 6.85 (1H, d, J=7.6 Hz), 5.20 (1H, quint, J=6.2 Hz), 5.04 (1H, dd, J=10.3, 10.3 Hz), 4.22–4.15 (2H, m), 4.02–3.92 (3H, m), 2.03 (3H, s), 1.35 (9H, s), 1.30 (3H, d, J=6.2 Hz), 1.26 (3H, t, J=7.2 Hz), 1.09 (3H, d, J=6.9 Hz), 1.04 (3H, t, J=7.2 Hz), 1.00 (3H, d, J=6.9 Hz); ^{13}C NMR (C_6D_6) δ=177.51 (d, J=17.3 Hz), 155.09, 142.30, 138.28, 128.81, 124.93, 78.13, 70.29, 62.58 (d, J=5.8 Hz), 58.89, 46.71 (d, J=4.3 Hz), 28.44, 21.26, 21.15, 20.95, 16.43 (d, J=5.8 Hz), 16.26 (d, J=5.8 Hz), 15.04; ^{31}P NMR (C_6D_6) δ=6.54; IR (neat) 3855, 3734, 3672, 3293, 2979, 2935, 2361, 1714, 1639, 1519, 1455, 1365, 1288, 1241, 1169, 1106, 1035, 970, 847, 764, 704, 621, 582, 445 cm^{-1}; HRMS (DART); exact mass calcd for $C_{23}H_{40}N_2O_6P$ $[M+H]^+$, 471.2624. Found 471.2623.

4.2.10. iso-Propyl anti-3-(tert-butoxycarbonylamino)-N-(diethoxyphosphoryl)-3-(o-methylphenyl)-2-methylpropionimidate. Colorless oil. ^{1}H NMR (C_6D_6) δ=7.85 (1H, d, J=7.6 Hz), 7.60 (1H, d, J=9.6 Hz), 7.07 (1H, t, J=7.2 Hz), 6.97–6.93 (2H, m), 5.42 (1H, dd, J=10.0, 10.0 Hz), 5.20 (1H, quint, J=6.2 Hz), 4.22–4.14 (2H, m), 4.05–3.93 (3H, m), 2.57 (3H, s), 1.33 (9H, s), 1.29–1.24 (6H, m), 1.08–1.05 (6H, m), 0.97 (3H, d, J=6.9 Hz); ^{13}C NMR (C_6D_6) δ=177.45 (d, J=15.9 Hz), 155.28, 141.33, 136.41, 130.36, 128.16, 78.12, 70.30, 62.59 (d, J=5.8 Hz), 53.89, 47.42, 28.42, 21.12, 20.92, 20.03, 16.43 (d, J=5.8 Hz), 16.31 (d, J=7.2 Hz), 14.08; ^{31}P NMR (C_6D_6) δ=6.59; IR (neat) 3855, 3734, 293, 2979, 2935, 2360, 1713, 1648, 1519, 1456, 1365, 1291, 1247, 1174, 1107, 1035, 970, 878, 762, 733, 633, 615, 579, 520, 458 cm^{-1}; HRMS (DART); exact mass calcd for $C_{23}H_{40}N_2O_6P$ $[M+H]^+$, 471.2624. Found 471.2616.

4.2.11. iso-Propyl anti-3-(tert-butoxycarbonylamino)-N-(diethoxyphosphoryl)-2-methyl-3-(naphthalen-1-yl)propionimidate. Colorless oil. ^{1}H NMR (C_6D_6) δ=8.84 (1H, br s), 8.00 (1H, br s), 7.79 (1H, br s), 7.58 (1H, d, J=8.2 Hz), 7.50 (1H, d, J=8.2 Hz), 7.37 (1H, br s), 7.20 (1H, q, J=8.2 Hz), 6.06 (1H, br s), 5.25 (1H, quint, J=6.2 Hz), 4.32 (2H, br s), 4.26–4.18 (2H, m), 4.05–3.94 (2H, m), 1.37 (3H, d, J=6.2 Hz), 1.31 (9H, s), 1.28 (3H, t, J=7.2 Hz), 1.10 (3H, d, J=6.2 Hz), 1.05 (3H, t, J=6.9 Hz), 0.92 (3H, d, J=6.9 Hz); ^{13}C NMR (C_6D_6) δ=177.45 (d, J=15.9 Hz), 155.27, 129.00, 128.29, 127.84, 126.49, 126.04, 125.77, 78.20, 70.45, 62.60 (d, J=5.8 Hz), 28.40, 21.17, 21.03, 16.46 (d, J=5.8 Hz), 16.31 (d, J=7.2 Hz), 14.86; ^{31}P NMR (C_6D_6) δ=6.33; IR (neat) 3855, 3839, 3734, 3672, 3646, 3630, 3295, 2979, 2935, 2361, 1714, 1649, 1556, 1509, 1455, 1390, 1365, 1289, 1237, 1170, 1033, 970, 780, 637, 607, 577, 521 cm^{-1}; HRMS (DART); exact mass calcd for $C_{26}H_{40}N_2O_6P$ $[M+H]^+$, 507.2624. Found 507.2601.

4.2.12. iso-Propyl anti-3-(tert-butoxycarbonylamino)-N-(diethoxyphosphoryl)-3-(2-furyl)-2-methylpropionimidate. Orange oil. ^{1}H NMR (C_6D_6) δ=7.15 (1H, s), 7.00 (1H, s), 6.22 (1H, d, J=3.4 Hz), 5.96 (1H, s), 5.26 (1H, dd, J=10.0 , 10.0 Hz), 5.15 (1H, quint, J=6.5 Hz), 4.22–4.11 (3H, m), 4.05–3.94 (2H, m), 1.36 (9H, s), 1.26–1.21 (6H, m), 1.09–1.03 (9H, m); ^{13}C NMR (C_6D_6) δ=176.53 (d, J=17.3 Hz), 155.11, 154.01, 142.19, 110.38, 107.94, 78.50, 70.39, 62.68 (d, J=5.8 Hz), 52.30, 44.33 (d, J=4.3 Hz), 28.41, 21.09, 20.92, 16.41 (d, J=7.2 Hz), 16.31 (d, J=5.8 Hz), 14.94; ^{31}P NMR (C_6D_6) δ=5.51; IR (neat) 3855, 3839, 3734, 3672, 3646, 3630, 3295, 2979, 2935, 2361, 1714, 1649, 1556, 1509, 1455, 1390, 1365, 1289, 1237, 1170, 1033, 970, 780, 637, 607, 577, 521 cm^{-1}; HRMS (DART); exact mass calcd for $C_{20}H_{36}N_2O_7P$ $[M+H]^+$, 447.2260. Found 447.2239.

4.2.13. iso-Propyl anti-3-(tert-butoxycarbonylamino)-N-(diethoxyphosphoryl)-2-methyl-3-(2-thienyl)propionimidate. Colorless oil. ^{1}H NMR (C_6D_6) δ=7.43 (1H, d, J=9.6 Hz), 7.07 (1H, d, J=3.4 Hz), 6.77 (1H, d, J=5.5 Hz), 6.64 (1H, t, J=4.5 Hz), 5.37 (1H, dd, J=10.3, 10.3 Hz), 5.15 (1H, quint, J=6.2 Hz), 4.18–4.11 (2H, m), 4.06–3.93 (3H, m), 1.35 (9H, s), 1.24–1.22 (6H, m), 1.10–1.03 (9H, m); ^{13}C NMR (C_6D_6) δ=176.73 (d, J=15.9 Hz), 155.06, 145.78, 126.97, 125.67, 124.60, 78.47, 70.36, 62.63

(q, J=3.4 Hz), 54.21, 46.96 (d, J=4.3 Hz), 28.43, 21.10, 20.91, 16.42 (d, J=5.8 Hz), 16.34 (d, J=7.2 Hz), 15.29; ^{31}P NMR (C_6D_6) δ=6.10; IR (neat) 3855, 3839, 3734, 3672, 3647, 2979, 2935, 2360, 1714, 1649, 1519, 1455, 1366, 1287, 1238, 1169, 1105, 1035, 968, 764, 700, 630, 586, 516 cm^{-1}; HRMS (DART); exact mass calcd for $C_{20}H_{36}N_2O_6PS$ $[M+H]^+$, 463.2032. Found 463.2030.

4.2.14. iso-Propyl anti-3-(tert-butoxycarbonylamino)-N-(diethoxyphosphoryl)-2-methyl-3-(3-pyridyl)propionimidate. Colorless oil. ^{1}H NMR (C_6D_6) δ=8.93 (1H, s), 8.40 (1H, d, J=3.4 Hz), 7.72 (2H, t, J=8.2 Hz), 6.68 (1H, q, J=4.1 Hz), 5.16 (1H, quint, J=6.2 Hz), 5.00 (1H, dd, J=10.0, 10.0 Hz), 4.12–4.11 (2H, m), 3.97–3.87 (3H, m), 1.34 (9H, s), 1.26–1.21 (6H, m), 1.05 (3H, d, J=6.2 Hz), 1.03 (3H, t, J=7.2 Hz), 0.85 (3H, d, J=6.9 Hz); ^{13}C NMR (C_6D_6) δ=176.84 (d, J=15.9 Hz), 155.09, 149.97, 149.41, 137.44, 134.36, 123.73, 78.50, 70.4, 62.68 (d, J=5.8 Hz), 56.62, 46.29 (d, J=4.3 Hz), 28.37, 21.06, 20.88, 16.38 (d, J=5.8 Hz), 16.25 (d, J=7.2 Hz), 14.79; ^{31}P NMR (C_6D_6) δ=6.40; IR (neat) 3902, 3888, 3882, 3866, 3855, 3840, 3824, 3803, 3747, 3734, 3672, 3647, 3631, 2980, 2361, 1714, 1649, 1519, 1455, 1365, 1236, 1170, 1034, 766, 623 cm^{-1}; HRMS (DART); exact mass calcd for $C_{21}H_{37}N_3O_6P$ $[M+H]^+$, 458.2420. Found 458.2405.

4.2.15. iso-Propyl anti-3-(tert-butoxycarbonylamino)-N-(diethoxyphosphoryl)-2,5-dimethylhexanimidate. Colorless oil. ^{1}H NMR (C_6D_6) δ=6.44 (1H, d, J=9.6 Hz), 5.12 (1H, quint, J=6.2 Hz), 4.18–4.08 (3H, m), 4.03–3.92 (2H, m), 3.56–3.53 (1H, m), 1.92–1.86 (1H, m), 1.45 (9H, s), 1.30–1.21 (8H, m), 1.12 (3H, d, J=6.9 Hz), 1.09–1.06 (6H, m), 1.04 (3H, d, J=6.2 Hz), 0.84 (3H, d, J=6.9 Hz); ^{13}C NMR (C_6D_6) δ=177.64 (d, J=17.3 Hz), 155.73, 77.79, 70.17, 62.40 (d, J=7.2 Hz), 52.43, 46.26 (d, J=5.8 Hz), 44.12, 28.56, 24.93, 24.19, 22.02, 21.18, 21.09, 16.47 (d, J=7.2 Hz), 16.37 (d, J=7.2 Hz), 15.23; ^{31}P NMR (C_6D_6) δ=5.86; IR (neat) 3855, 3839, 3734, 3672, 3646, 3289, 2978, 2361, 1714, 1649, 1524, 1455, 1389, 1365, 1288, 1241, 1176, 1103, 1036, 1004, 968, 766, 619, 516 cm^{-1}; HRMS (DART); exact mass calcd for $C_{20}H_{42}N_2O_6P$ $[M+H]^+$, 437.2781. Found 437.2778.

4.2.16. iso-Propyl anti-3-(tert-butoxycarbonylamino)-N-(diethoxyphosphoryl)-2,4,4-trimethylpentanimidate. Colorless oil. ^{1}H NMR (C_6D_6) δ=6.29 (1H, d, J=10.3 Hz), 5.03 (1H, quint, J=6.2 Hz), 4.10–4.05 (2H, m), 4.03–3.91 (3H, m), 3.85 (1H, dd, J=10.3, 7.6 Hz), 1.46 (9H, s), 1.31 (3H, d, J=6.9 Hz), 1.18 (6H, m), 1.09 (3H, t, J=7.2 Hz), 1.06–1.02 (12H, m); ^{13}C NMR (C_6D_6) δ=177.71 (d, J=15.9 Hz), 156.04, 77.92, 70.19, 62.36 (d, J=2.9 Hz), 61.63, 41.59 (d, J=2.9 Hz), 36.31, 28.54, 27.50, 21.12, 21.01, 17.96, 16.36 (d, J=5.8 Hz); ^{31}P NMR (C_6D_6) δ=4.32; IR (neat) 3855, 3839, 3734, 3672, 3647, 3464, 3293, 2977, 2361, 1719, 1649, 1504, 1390, 1366, 1247, 1174, 1035, 1000, 954, 764, 608, 522 cm^{-1}; HRMS (DART); exact mass calcd for $C_{20}H_{42}N_2O_6P$ $[M+H]^+$, 437.2781. Found 437.2795.

4.3. Conversion to *N*-phosphorylamide (Scheme 1)

A mixture of phosphorylimidate, 2-propanol and H_2O (95/5), and concentrated H_2SO_4 (ca. 7.0 equiv) was stirred at 100 °C for 3 h. After cooling to room temperature, the mixture was diluted with CH_2Cl_2 and neutralized by a satd aq solution of $NaHCO_3$. All volatiles were evaporated and the residue was diluted with CH_2Cl_2 and filtered. After evaporation, the crude product was purified by column chromatography (silica gel).

4.3.1. anti-3-Amino-N-(diethoxyphosphoryl)-2-methyl-3-phenylpropionamide. Orange oil. ^{1}H NMR (C_6D_6) δ=7.48 (2H, d, J=7.4 Hz), 7.04 (1H, t, J=7.2 Hz), 6.23 (2H, s), 4.20–4.15 (4H, m), 3.31 (1H, s), 1.35 (1H, d, J=6.2 Hz), 1.14–1.11 (6H, m), 1.04 (3H, d, J=6.2 Hz); ^{13}C NMR (C_6D_6) δ=128.80, 128.29, 64.34 (dd, J=32.5, 5.1 Hz), 59.41, 47.83 (d, J=11.6 Hz), 23.34, 16.17 (d, J=7.2 Hz), 15.88; ^{31}P NMR (C_6D_6) δ=−1.15; IR (neat) 3865, 3854, 3839, 3734, 3672, 3646, 3630, 2981, 2361, 1698, 1649, 1557, 1541, 1455, 1396, 1242, 1032, 969, 866, 766, 702, 548, 418 cm^{-1}; HRMS (DART); exact mass calcd for $C_{14}H_{24}N_2O_4P$ $[M+H]^+$, 315.1474. Found 315.1486.

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References and notes

1. (a) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069; (b) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044; (c) Friestad, G. K.; Mathies, A. K. *Tetrahedron* **2007**, *63*, 2541; (d) Kobayashi, S.; Ueno, M. In *Comprehensive Asymmetric Catalysis, Supplement 1*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 2004; Chapter 29.5, p 143.
2. For reviews on direct Mannich or Mannich-type reactions, see: (a) Verkade, J. M. M.; van Hemert, L. J. C.; Quaedflieg, P. J. L. M.; Rutjes, F. P. J. T. *Chem. Soc. Rev.* **2008**, *37*, 29; (b) Ting, A.; Schaus, S. E. *Eur. J. Org. Chem.* **2007**, 5797; (c) Marques, M. M. B. *Angew. Chem., Int. Ed.* **2006**, *45*, 348.
3. For examples of catalytic direct-type Mannich-type reactions using substrates bearing no activating groups at α-position, see acetonitrile as a nucleophile: (a) Kumagai, N.; Matsunaga, S.; Shibasaki, M. *Tetrahedron* **2007**, *63*, 8598; (b) Kumagai, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 13632; Trichloromethylketone as a nucleophile: (c) Morimoto, H.; Wiedemann, S. H.; Yamaguchi, A.; Harada, S.; Chem, Z.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 3146; (d) Morimoto, H.; Lu, G.; Aoyama, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 9588; (e) Morimoto, H.; Yoshino, T.; Yukawa, T.; Lu, G.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *47*, 9125; (*N*-Boc)acylanilide as a nucleophile: (f) Saito, S.; Tsubogo, T.; Kobayashi, S. *Chem. Commun.* **2007**, 1236; Sulfonylimidate as a nucleophile: (g) Matsubara, R.; Berthiol, F.; Kobayashi, S. *J. Am. Chem. Soc.* **2008**, *130*, 1804; (h) Matsubara, R.; Kobayashi, S. *Synthesis* **2008**, 3009; (i) Nguyen, H. V.; Matsubara, R.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 5790; (j) Matsubara, R.; Berthiol, F.; Nguyen, H. V.; Kobayashi, S. *Bull. Chem. Soc. Jpn.* **2009**, *82*, 1083.
4. Matsubara, R.; Kobayashi, S. *Chem.—Eur. J.* **2009**, *15*, 10694.
5. After the publications on the use of sulfonylimidate as a nucleophile by our group (Refs. 3g–j), the catalytic asymmetric Michael reaction of sulfonylimidates was reported. Maasa, A.; Utsumi, N.; Barbas, C. F., III. *Tetrahedron Lett.* **2009**, *50*, 145.
6. Phosphorylimidates were prepared according to a procedure similar to that used for the sulfonylimidates. For details, see Experimental.
7. For a detailed explanation of the stereoselectivities in sulfonylimidate reactions, see Ref. 3j.