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Chiral *N*-phosphonyl imine chemistry: asymmetric additions of malonate-derived enolates to chiral *N*-phosphonyl imines for the synthesis of β-aminomalonates

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ABSTRACT

Chiral *N*-phosphonyl imines attached by 1-naphthyl group were found to react with lithium malonate enolates smoothly to give chiral β-aminomalonates. Good yields and excellent diastereoselectivity were achieved for sixteen examples. The chiral auxiliary can be readily removed by treating with trifluoroacetic acid (TFA) to give free amino malonates. The absolute structure has been unambiguously determined by converting one of the products into an authentic sample.

β-Aminomalonates and β-amino acids belong to important building blocks for the study of natural products, pharmaceuticals and peptides, and copolymers.[1–6] They serve as direct precursors to chiral amino alcohols that are also chemically and biologically important.[7,8] In recent years, there has been a continuing interest in asymmetric synthesis of β-amino acids and their derivatives in organic and medicinal chemistry, among them the asymmetric Mannich reaction has become a powerful and practical protocol for this purpose.[9] Although a significant progress has been made in the development of asymmetric Mannich reactions using enolate nucleophiles derived from enolsilane,[10] β-ketoesters,[11a–c] and 1,3-diketones,[11] a practical Mannich reaction of dialkyl malonate-derived enolates with simple imines remains less explored. Recently, Marigo et al.[12] reported the Mannich reaction of malonates with *N*-tosyl-imino esters that showed enantioselectivity of 39–87% ee. Deng and co-workers have developed an efficient enantioselective direct Mannich reactions of *N*-Boc-protected imines with malonates under mild conditions by using bifunctional cinchona alkaloids as catalysts.[13]

Very recently, we have established novel phosphoramide and chiral *N*-phosphonyl imine chemistry and have been successful in utilizing *N*-phosphonyl imines for asymmetric aza-Darzens reaction,[14] aza-Henry reaction,[15] asymmetric Mannich reaction with ketone enolates,[16] and ester enolates.[17] These asymmetric reactions provided an easy access to chiral aziridines, vicinal amino nitroalkanes, β-aminoketones, and β-amino esters. As a continuing effort on this chiral *N*-phosphonyl imine chemistry, herein we would like to report the asymmetric addition of alkyl malonates onto chiral phosphonyl imines for the synthesis of chiral β-amino malonates (Scheme 1).

In our previous studies,[16,17] *N*-phosphonyl imines attached with 1-naphthylmethyl group had been proven to show higher diastereoselectivity as compared with their benzyl counterparts due to a larger steric effect on asymmetric induction process. Sometimes, they are even more effective than *iso*-propyl group attached *N*-phosphonyl imines.[16] In the present Letter, the 1-naphthyl group attached *N*-phosphonyl imine **1a** was thus chosen for the model reaction to react with dialkyl malonate enolates. The reaction procedure is similar to those we reported earlier[14–17] in that *N*-phosphonyl imines (**1a**, 1.0 equiv) were added into preprepared lithium dialkyl malonate enolate (2.0 equiv) in THF solution at −78 °C. The resulting mixture was stirred for 1 h at this temperature and then raised to −30 °C and stirred for additional 6 h to furnish the reaction.

Several different bases, such as LDA, LiHMDS, $(Me_3Si)_2NK$, and *n*-BuLi, were utilized for generation of metal enolates. As shown in Table 1, among these bases, LDA was found to be the best choice for the present reaction. Other bases gave either poor diastereoselectivity or low chemical yields. $(Me_3Si)_2NK$ gave a slightly higher diastereoselectivity (91:9) but in a lower yield of 70%. Surprisingly, *n*-BuLi resulted in a diastereoselectivity of 93:7, but in a poor yield of 25%.

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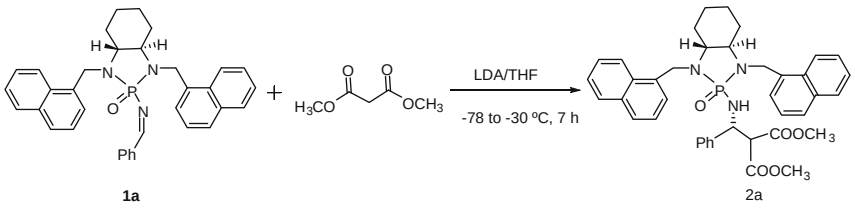


Scheme 1. Addition of dimethyl malonate enolate to *N*-phosphonyl imine.

Table 1
Effects of solvents and bases on the reaction outcomes[a]

Entry	Base	Solvent	Yield (%)	dr[b]
1	LDA	THF	88	90:10
2	LiHMDS	THF	54	87:13
3	$(Me_3Si)_2NK$	THF	70	91:9
4	*n*-BuLi	THF	25	93:7
5	LDA	Toluene	79	88:12
6	LDA	$CHCl_3$	55	90:10
7	LDA	Et_2O	84	83:17

[a] Reaction condition: 0.1 mmol of imine, 0.3 mmol of ester, 0.2 mmol of base in 3.5 mL of solvent.
[b] Determined by ^{31}P NMR of crude products.

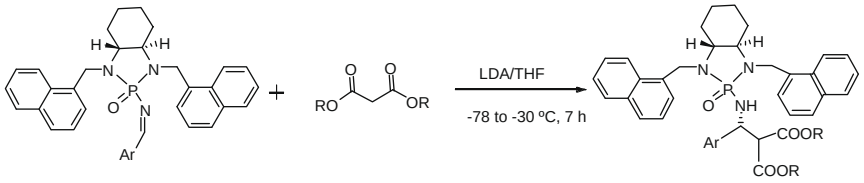
The solvent effect was also examined for this reaction. It was found that the two polar and Lewis base solvents, THF and ethyl ether, resulted in higher chemical yields than other two less polar solvents, toluene and $CHCl_3$. THF was thus chosen as the solvent for this reaction.

Under the above optimized conditions, a series of substrates were examined to find the scope of generality. As shown in Table 2, a variety of phosphonyl imines derived from benzaldehyde derivatives attached with electron-withdrawing groups or electron-donating groups on their aromatic rings and 1-naphthaldehyde are all suitable for this reaction. For all cases, excellent diastereoselectivity and good to high chemical yields have been achieved after purification via flash column chromatography or recrystallization. For entries 3, 5, 6, and 14, their crude products were even determined to show excellent diastereoselectivity. In fact, a single diastereoisomer was observed for each of these cases as revealed by crude ^{31}P NMR. For the rest of the examples, except for entries 1 and 14, high diastereoselectivities ranging from 94:4 to 97:3 were obtained. Obviously, for the present reaction, the most phosphonyl imines displayed higher diastereoselectivity than those of ester enolate-based reactions.[17]

The alkyl group of dialkyl malonates was found to have a substantial effect on chemical yields. As showed by cases 4, 6, 8, and 15, diethyl malonate-derived enolate resulted in significant yield enhancement up to 36%, at the same time, to retain diastereoselectivity at the same level as those when using dimethyl malonate-derived enolate. Surprisingly, when di-*tert*-butyl malonate-derived lithium enolate was employed for the reaction, good to excellent yield (75–93%) can still be obtained. However, diastereoselectivity was diminished to a range of 52/48–62/38. This phenomenon is similar to the observations of Michael addition of di-*tert*-butyl malonate esters to nitroolefins[18] and to chalcone derivatives in the presence of a chiral phase-transfer catalysts.[19]

It is noteworthy that in the present reaction, almost all products can be readily purified by flash column chromatography or recrystallization from ethanol solution to give single isomers.

Table 2
Results of asymmetric additions of alkyl malonates to chiral *N*-phosphonyl imines[a]



Entry	Imine	Ar	R	Prod.	Yield[b] (%)	dr[c]
1	**1a**	Ph	CH_3	**2a**	88	>99:1[e] (90:10)
2	**1b**	2-OCH_3–Ph	CH_3	**2b**	54	97:3
3	**1c**	4-OCH_3–Ph	CH_3	**2ca**	50	>99:1
4	**1c**	4-OCH_3–Ph	Et	**2cb**	67	>99:1[d] (96:4)
5	**1d**	2-CH_3–Ph	CH_3	**2da**	62	>99:1
6	**1d**	2-CH_3–Ph	Et	**2db**	80	>99:1
7	**1e**	2-F–Ph	CH_3	**2ea**	55	97:3
8	**1e**	2-F–Ph	Et	**2eb**	76	>99:1
9	**1f**	4-F–Ph	CH_3	**2f**	62	>99:1[e] (94:6)
10	**1g**	2-Br–Ph	CH_3	**2g**	67	>99:1[d] (93:7)
11	**1h**	4-Br–Ph	CH_3	**2h**	68	>99:1[e] (93:7)
12	**1i**	2-NO_2–Ph	CH_3	**2i**	66	97:3[e] (94:6)
13	**1j**	4-Ph–Ph	CH_3	**2j**	73	99:1[e] 93:7
14	**1k**	4-OBn–Ph	CH_3	**2ka**	47	>99:1
15	**1k**	4-OBn–Ph	Et	**2kb**	83	(>99:1)[d] 94:6
16	**1l**	2-Naphthyl	CH_3	**2l**	90	(>99:1)[d] 88:12

[a] Reaction conditions:[21] 0.4 mmol imine, 0.12 mmol ester, 0.8 mmol base, 7 mL solvent, −78 to −30 °C.
[b] Isolated yields after column.
[c] dr in bracket was determined by ^{31}P NMR spectra of crude samples; Otherwise, purified dr is the same as crude dr; >99:1 means only one isomer observed.
[d] Diastereoselectivities in the bracket were determined by ^{31}P NMR after purified by column.
[e] Diastereoselectivity was determined by ^{31}P NMR after purified by recrystallization.

The absolute stereochemistry of this reaction has been determined by converting a product to a known sample.[22] In this procedure, **2a** was subjected to deprotection reaction with TFA/MeOH–H_2O at room temperature followed by protection using $(Boc)_2O$ in the presence of $NaHCO_3$. The in situ procedure resulted in 2-(*tert*-butoxycarbonylamino-phenyl-methyl)-malonic acid dimethyl ester.[20] An overall yield of 80% was obtained under these convenient conditions; the effectiveness of this procedure enables the present method an efficient approach to β-aminomalonates.

The resulting stereochemistry revealed that the asymmetric induction of this reaction is similar to that of the previous asymmetric reactions as we reported,[14–17] that is, the enolates approach the electrophilic center of *N*-phosphonyl imines from their *Si* faces to give β-*S* amino products.

In summary, chiral *N*-phosphonyl imines were found to react with lithium dialkyl malonate enolates smoothly to give chiral β-amino malonates in excellent diastereoselectivity and good chemical yields. The reaction shows good substrate scope in that aromatic phosphonyl imines with both electron-withdrawing and electron-donating groups on their rings can be utilized. The resulting products can be readily purified by both flash column chromatography and recrystallization. The resulting products will be converted into other important building blocks in due course.

Acknowledgment

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21. *Typical procedure for the synthesis of chiral amino malonates*: Into an oven-dried vial flushed with N_2 were loaded dialkyl malonates (1.2 mmol) and 3.0 mL of dry THF. The loaded vial was cooled to −78 °C and 0.4 mL of 2 LDA solution in THF (2.0 M) was added dropwise with stirring over 10 min, and the resulting solution was stirred at −78 °C for additional 30 min. Into the resulting mixture was added dropwise 4.0 mL of THF of phosphonyl imine **1** (0.4 mmol) and was stirred at −78 °C for 1 h. The reaction temperature was then raised to −30 °C. After the reaction mixture has been stirred for 6 h at this temperature, 1.0 mL of saturated NH_4Cl solution was added and followed by 5.0 mL water to quench the reaction. The mixture was transferred into a separation funnel, and the aqueous layer was extracted with 2×20 mL of ethyl acetate. Combined organic layers were dried on anhydrous sodium sulfate. Sodium sulfate was filtered off and evaporated the organic solvent. Purification by column chromatography obtained adducts **2**.*Selected data of* **2a**: White solid, mp 147–150 °C. $[\alpha]_D^{25}$ −18.7 (*c* 0.475, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 8.04–8.02 (m, 1H), 7.94–7.68 (m, 7H), 7.57–7.42 (m, 6H), 7.32–7.25 (m, 2H), 7.11–7.04 (m, 3H), 5.08–4.98 (m, 1H), 4.80–4.69 (dd, *J* = 13.2 Hz, 16.5 Hz, 1H), 4.47–4.30 (m, 3H), 3.50 (s, 3H), 3.59–3.54 (m, 1H), 3.42 (s, 3H), 3.41–3.89 (m, 1H), 3.14–2.88 (m, 2H), 1.74–0.90 (m, 8H).^{13}C NMR ($CDCl_3$, 125 MHz): δ 168.09, 167.42, 141.53, 135.39, 135.34, 134.27, 134.23, 133.51, 133.34, 131.06, 130.63, 128.67, 128.53, 128.26, 127.62, 127.27, 127.24, 127.02, 125.91, 125.55, 125.48, 125.41, 125.40, 125.25, 125.12, 124.74, 122.76, 122.71, 64.75, 64.67, 63.47, 63.40, 58.23, 58.17, 55.19, 52.36, 52.29, 44.11, 44.07, 43.92, 43.89, 29.80, 29.74, 29.58, 29.50, 24.22, 24.19. ^{31}P NMR: ($CDCl_3$, 202 MHz): δ 26.27.
22. Removal of *N*-phosphonyl group of **2a** and synthesis of *N*-Boc-protected β-amino malonate**:** Into a 50 mL round bottomed flask were loaded **2a** (335 mg, 0.5 mmol), methanol (15.0 mL), and H_2O (5.0 mL). To the resulting mixture was added 10 equiv of trifluoroacetic acid; the reaction was stirred at rt for 24 h. The reaction was monitored by TLC. Volatiles were removed to give a yellow oil, to which were added MeOH (15.0 mL), H_2O (5.0 mL), and $NaHCO_3$ (5.0 mmol) at room temperature. To the resulting mixture was added di-*tert*-butyl dicarbonate (0.654 g, 3.0 mmol) and stirred at room temperature overnight. The crude reaction mixture obtained after standard aqueous work-up was purified by using silica gel column chromatography with 10% ethyl acetate in hexanes as the eluent. *N*-Boc β-amino malonate was obtained as a white solid in 80% yield (114 mg). $[\alpha]_D^{25}$ −47.0 (*c* 0.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.33–7.22 (m, 5H), 6.13 (s, br, 1H), 5.49 (s, br, 1H), 3.93 (d, *J* = 4.2 Hz, 1H), 3.75 (s, 3H), 3.64 (s, 3H), 1.42 (s, 9H).