Nucleophilic Carbene-Mediated Hydrophosphonylation of Aldimines

Zhi-Hua Cai, Guang-Fen Du,* Bin Dai, Lin He*

Key Laboratory for Green Processing of Chemical Engineering of Xinjiang Bingtuan and School of Chemistry and Chemical Engineering, Shihezi University, Xin Jiang 832000, P. R. of China
Fax +86(993)2057270; E-mail: helin@shzu.edu.cn; E-mail: duguangfen@shzu.edu.cn

Received 26 October 2011; revised 31 December 2011

Abstract: Aldimines undergo efficient hydrophosphonylation reactions with dimethyl phosphite in the presence of nucleophilic heterocyclic carbenes (NHCs) as organocatalysts to give the corresponding (α-aminoalkyl)phosphonates in moderate-to-excellent yields.

Key words: catalysis, carbenes, imines, phosphonylations, phosphonates

α-Aminophosphoric acids and their esters have recently attracted considerable attention because of their intriguing biological activities.[1] These compounds have been successfully used in the pharmaceutical field as inhibitors of enzymes,[2] as catalytic antibodies,[3] as antibacterial agents,[4] as peptide mimetics,[5] and as anti-HIV agents.[6] The addition of a phosphite to an imine, known as the Pudovik reaction,[7] is the most versatile and atom-economic protocol for the preparation of α-aminophosphoric acids and their derivatives. Owing to the significance of the Pudovik reaction in the construction of C–P bonds, considerable efforts have been made to develop catalytic methods for these reactions.[8] In the last decade, several organocatalysts, such as chiral thioureas,[9] cyclic phosphoric acids,[10] and cinchona alkaloids,[11] have been successfully used in the asymmetric hydrophosphonylation of imines.

As an important group of organocatalysts for umpolung reactions, N-heterocyclic carbenes (NHCs) have been widely used to construct C–C bond in unusual ways by means of the benzoin reaction, the Stetter reaction, or other transformations.[12] NHCs have also been found to be highly efficient nucleophilic catalysts for promoting a variety of 1,2-addition reactions, such as the trifluoromethylation of aldehydes,[13] cyanation reactions,[14] and Mukaiyama aldol reactions,[15] as well as several other reactions.[16] However, NHCs-promoted C–P bond-formation reactions have been far less intensively studied. We recently reported that NHCs can be used to promote hydrophosphonylation of aldehydes to give α-hydroxyphosphonates in high yields.[17] Encouraged by this finding, we applied NHCs catalysts to the addition reaction of alkyl phosphites with imines to give the corresponding (α-aminoalkyl)phosphonates directly in high yield. Here, we describe our latest research findings with regard to C–P bond-forming reactions.

Initially, we examined the addition of dimethyl phosphite (**7**) to *N*-tosylbenzaldimine [**6a**; 4-methyl-*N*-(phenylmethylene)benzenesulfonamide] in the presence of the stable NHC 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (IPr, **1**).[18] The reaction proceeded smoothly to give the desired (α-aminomethyl)phosphonate **8a** in 91% isolated yield (Table 1, entry 1). Inspired by this result, we screened several different types of NHC generated in situ from the corresponding precursor and a base. Interestingly, all the NHCs investigated for the reaction promoted the addition reaction efficiently, giving the desired adduct in good-to-excellent yield (entries 2–9). A brief survey of other solvents showed that toluene, dichloromethane, and diethyl ether are all suitable media for the reaction (entries 10–12). Reducing the catalyst loading to 5 mol% led to a small decrease in the yield (entry 13). Finally, a control experiment (entry 14) showed that the hydrophosphonylation does not occur in the absence of the NHC catalyst.

Because of the commercial availability and stability of NHC **1**, we proceeded to evaluate the scope of the reaction with respect to the aldimine under the optimized reaction conditions (10 mol% **1**, THF, r.t.) and the results are summarized in Table 2.

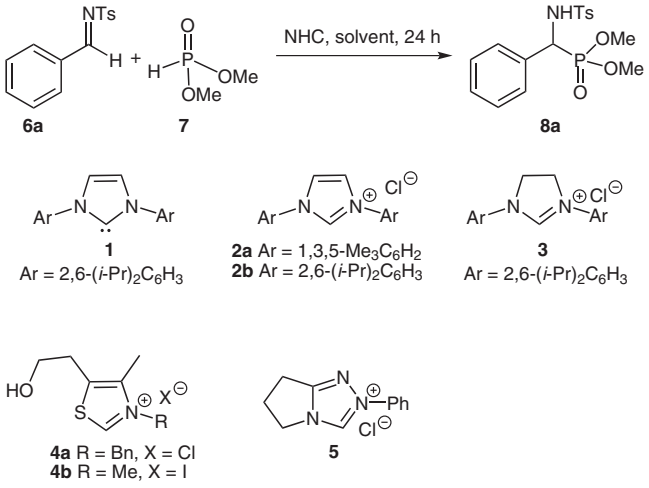
Tosyl arylimines bearing both electron-donating and electron-withdrawing groups worked well to give the corresponding hydrophosphonylation adducts in high yields (entries 1–9). *N*-Tosyl-1-(2-furyl)methanimine (**6j**) and *N*-tosyl-1-(2-naphthyl)methanimine (**6k**) were also suitable substrates for the reaction (entries 10 and 11). However, because of the instability of alkylimines under the reaction conditions, the linear substrate **6l** gave only a low yield of the corresponding alkyl-substituted α-aminophosphonate (entry 12). To our delight, however, the branched alkylimine **6m** proved to be very good reactant, affording the desired product in excellent yield (entry 13). Aldimines bearing *N*-protecting groups other than tosyl were also examined as substrates for the reaction. 4-Nitrophenylsulfonyl, *N*-*tert*-butoxycarbonyl, and benzyl aldimines coupled smoothly with dimethyl phosphite in the presence of 10 mol% **1** as the catalyst, but gave relatively low yields of the corresponding products (entries 14–16).

We also attempted an asymmetric hydrophosphonylation of *N*-tosylbenzaldimine (**6a**) in the presence of the chiral NHC generated from the imidazolium salt **9**, but unfortunately the reaction showed no enantioselectivity (Scheme 1).

SYNTHESIS 2012, 44, 694–698
Advanced online publication: 03.02.2012
DOI: 10.1055/s-0031-1289690; Art ID: H101011SS

On the basis of pioneering work on NHC-catalyzed 1,2-addition reactions,[19,20] two hypothetical mechanisms for our hydrophosphonylation reaction are outlined in Scheme 2. In path **I**, the NHC functions as a carbon-centered Brønsted base.[19] The phosphite anion/imidazolium ion pair **A** is formed after deprotonation of dimethyl phosphite by the NHC, possibly triggering subsequent addition of the imine and giving, after proton transfer, the desired (α-aminoalkyl)phosphonate. In the second mechanism, the NHC attacks the imine to form adduct **C**;[20] subsequent proton transfer from the phosphite to **C** leads to the formation of intermediate **D**, which undergoes nucleophilic substitution to afford the final product with release of the NHC.

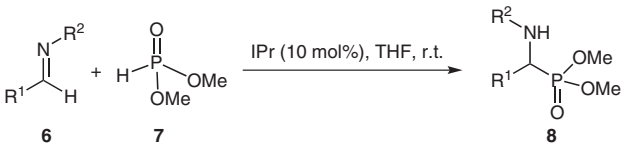
Table 1 NHC-Catalyzed Hydrophosphonylation of *N*-Tosylbenzaldimine



Entry[a]	NHC	Solvent	Yield (%)[b]
1	**1**	THF	91
2	**2a**, Cs_2CO_3 (10 mol%)	THF	72
3	**2b**, Cs_2CO_3 (10 mol%)	THF	82
4	**3**, Cs_2CO_3 (10 mol%)	THF	85
5	**4a**, Cs_2CO_3 (10 mol%)	THF	80
6	**4b**, Cs_2CO_3 (10 mol%)	THF	51
7	**5**, Cs_2CO_3 (10 mol%)	THF	90
8	**2b**, *t*-BuOK (10 mol%)	THF	84
9	**2b**, DBU (10 mol%)	THF	83
10	**1**	toluene	85
11	**1**	CH_2Cl_2	83
12	**1**	Et_2O[c]	76
13	**1**[d]	THF	78
14	no catalyst	THF	–

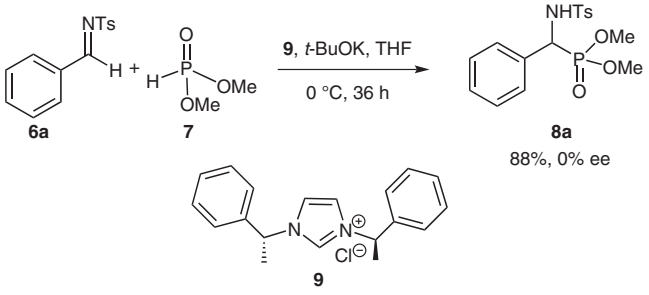
[a] Reaction conditions: **6a** (1.0 equiv, 0.15 M), **7** (1.5 equiv), NHC (10 mol%), r.t., 24 h.
[b] Isolated yield.
[c] Et_2O (4 mL).
[d] **1** (5 mol%).

Table 2 NHC-Catalyzed α-Aminophosphonylation of Aldimines



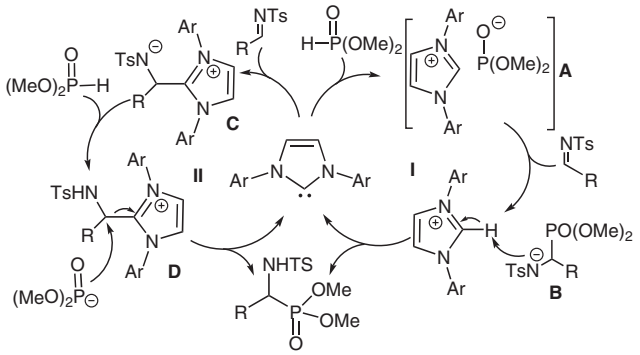
Entry[a]	R^1	R^2	Time (h)	Product	Yield (%)[b]
1	Ph	Ts	24	**8a**	91
2	4-Tol	Ts	24	**8b**	74
3	4-$MeOC_6H_4$	Ts	70	**8c**	95
4	4-ClC_6H_4	Ts	24	**8d**	77
5[c]	4-$O_2NC_6H_4$	Ts	24	**8e**	99
6	2-ClC_6H_4	Ts	24	**8f**	96
7	2,4-$Cl_2C_6H_3$	Ts	24	**8g**	91
8	3-BrC_6H_4	Ts	24	**8h**	66
9	3-$O_2NC_6H_4$	Ts	70	**8i**	76
10	2-furyl	Ts	48	**8j**	74
11	2-naphthyl	Ts	24	**8k**	79
12	Pr	Ts	40	**8l**	48
13	Cy	Ts	24	**8m**	93
14	Ph	4-Ns[d]	48	**8n**	42
15	Ph	Boc	48	**8o**	51
16	Ph	Bn	48	**8p**	40

[a] Reaction conditions: aldimine (0.3 mmol), phosphite (0.45 mmol), THF (2.0 mL), r.t.
[b] Isolated yield.
[c] THF (4 mL), –78 °C to r.t.
[d] 4-Nitrophenylsulfonyl.



Scheme 1 Attempted asymmetric hydrophosphonylation catalyzed by a chiral NHC

In summary, we have demonstrated an efficient protocol for the hydrophosphonylation of aldimines. The environmentally friendly organocatalysts, the mild reaction con-



Scheme 2 Two possible mechanisms for the hydrophosphonylation reaction

ditions, and the simple procedure provide a valuable approach for the synthesis of (α-aminoalkyl)phosphonates. Further exploration and development of this catalytic strategy are currently underway in our laboratory.

Unless otherwise indicated, all reactions were conducted under N_2 in oven- dried glassware with a magnetic stirring bar. Column chromatograph was performed with silica gel (200–300 mesh) and analytical TLC was performed on silica gel 60-F254. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker DMX 400 spectrometer in $CDCl_3$ or DMSO-d_6, with TMS as an internal standard. IR spectra were recorded on a Nicolet FT/IR-360 spectrophotometer. Anhyd THF, toluene, and Et_2O were distilled from sodium, and the imines were synthesized according to the literature procedures. Other starting materials were obtained from commercial suppliers and used as received. PE, where used, had a boiling range of 60–90 °C.

Dimethyl (α-Aminoalkyl)phosphonates: General Procedure

N-Sulfonylimine (0.3 mmol) was dissolved in anhyd THF (2 mL) and the soln was cooled to 0 °C. Dimethyl phosphite (0.45 mmol, 42 μL) was added from a syringe under N_2 and then IPr (**1**; 10 mol%) was subsequently added and the soln was stirred at r.t. until the reaction was complete (TLC). The crude product was then purified by flash column chromatography [silica gel, PE–EtOAc (1:1)].

Dimethyl [(Tosylamino)(phenyl)methyl]phosphonate (8a)[21]

White solid; yield: 101 mg (91%); mp 163–164 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 (d, *J* = 8.3 Hz, 2 H), 7.26–7.19 (m, 3 H), 7.16–7.05 (m, 3 H), 6.95 (d, *J* = 8.0 Hz, 2 H), 4.85 (dd, *J* = 24.2, 9.9 Hz, 1 H), 3.88 (d, *J* = 10.8 Hz, 3 H), 3.40 (d, *J* = 10.6 Hz, 3 H), 2.26 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.7, 137.9, 133.3, 128.9, 128.2, 128.2, 127.8 (d, *J* = 2.0 Hz), 127.0, 54.9 (d, *J* = 157.0 Hz), 54.6 (d, *J* = 8.0 Hz), 53.9 (d, *J* = 7.0 Hz), 21.3.

Dimethyl [(4-Tolyl)(tosylamino)methyl]phosphonate (8b)[21]

White solid; yield: 110 mg (74%); mp 187–189 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 (d, *J* = 8.2 Hz, 2 H), 7.19–6.86 (m, 6 H), 6.82 (br s, 1 H, NH), 4.78 (dd, *J* = 23.9, 9.8 Hz, 1 H), 3.84 (d, *J* = 10.8 Hz, 3 H), 3.41 (d, *J* = 10.6 Hz, 3 H), 2.29 (s, 3 H), 2.25 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.7, 137.8 (d, *J* = 4.0 Hz), 130.2, 128.97, 128.94, 128.0 (d, *J* = 6.0 Hz), 127.0, 54.6 (d, *J* = 156.0 Hz), 54.4 (d, *J* = 7.0 Hz), 53.9 (d, *J* = 7.0 Hz), 21.3, 21.0.

Dimethyl [(4-Methoxyphenyl)(tosylamino)methyl]phosphonate (8c)[21]

White solid; yield: 103 mg (95%); mp 160–161 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 (d, *J* = 8.3 Hz, 2 H), 7.12 (dd, *J* = 8.6, 1.8 Hz, 2 H), 7.00 (d, *J* = 8.0 Hz, 2 H), 6.72 (br s, 1 H, NH), 6.63 (d, *J* = 8.5 Hz, 2 H), 4.77 (dd, *J* = 24.6, 10.1 Hz, 1 H), 3.85 (d, *J* = 10.8 Hz, 3 H), 3.73 (s, 3 H), 3.42 (d, *J* = 10.6 Hz, 3 H), 2.29 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.3 (d, *J* = 3.0 Hz), 142.8, 137.8 (d, *J* = 2.0 Hz), 129.3 (d, *J* = 6.0 Hz), 129.0, 127.0, 125.3, 113.7 (d, *J* = 2.0 Hz), 55.2, 54.4 (d, *J* = 7.0 Hz), 54.2 (d, *J* = 157.0 Hz), 53.9 (d, *J* = 7.0 Hz), 21.3.

Dimethyl [(4-Chlorophenyl)(tosylamino)methyl]phosphonate (8d)[21]

White solid; yield: 99 mg (77%); mp 198–199 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 (d, *J* = 8.3 Hz, 2 H), 7.20 (br s, 1 H, NH), 7.17–7.10 (m, 2 H), 7.04 (d, *J* = 8.3 Hz, 2 H), 6.99 (d, *J* = 8.0 Hz, 2 H), 4.82 (dd, *J* = 24.4, 9.9 Hz, 1 H), 3.91 (d, *J* = 10.8 Hz, 3 H), 3.47 (d, *J* = 10.7 Hz, 3 H), 2.31 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.2, 137.6 (d, *J* = 2.0 Hz), 134.0 (d, *J* = 4.0 Hz), 131.9, 129.5 (d, *J* = 5.0 Hz), 129.0, 128.4 (d, *J* = 2.0 Hz), 127.0, 54.3 (d, *J* = 157.0 Hz), 54.8 (d, *J* = 7.0 Hz), 53.9 (d, *J* = 7.0 Hz), 21.3.

Dimethyl [(4-Nitrophenyl)(tosylamino)methyl]phosphonate (8e)[21]

White solid; yield: 121 mg (99%); mp 207–208 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.98 (d, *J* = 8.3 Hz, 1 H), 7.94 (d, *J* = 8.7 Hz, 2 H), 7.50 (dd, *J* = 8.8, 2.0 Hz, 2 H), 7.44 (d, *J* = 8.3 Hz, 2 H), 7.07 (d, *J* = 8.3 Hz, 2 H), 5.09 (dd, *J* = 25.4, 10.3 Hz, 1 H), 3.69 (d, *J* = 10.7 Hz, 3 H), 3.49 (d, *J* = 10.8 Hz, 3 H), 2.19 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 146.7 (d, *J* = 4.0 Hz), 142.8, 142.2, 138.0, 129.6 (d, *J* = 5.0 Hz), 129.2, 126.8, 122.9 (d, *J* = 1.0 Hz), 54.2 (d, *J* = 7.0 Hz), 53.6 (d, *J* = 7.0 Hz), 53.4 (d, *J* = 154.0 Hz), 20.9.

Dimethyl [(2-Chlorophenyl)(tosylamino)methyl]phosphonate (8f)

White solid; yield: 110 mg (96%); mp 223–224 °C.

IR (KBr): 3152, 2954, 1449, 1334, 1239, 1156, 1065, 1033 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52 (d, *J* = 8.2 Hz, 2 H), 7.47 (d, *J* = 7.8 Hz, 1 H), 7.18 (d, *J* = 7.9 Hz, 2 H), 7.05 (t, *J* = 7.4 Hz, 1 H), 6.96 (d, *J* = 8.0 Hz, 3 H), 5.50 (dd, *J* = 24.6, 10.1 Hz, 1 H), 3.95 (d, *J* = 10.8 Hz, 3 H), 3.44 (d, *J* = 10.7 Hz, 3 H), 2.25 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.9, 137.2, 133.3 (d, *J* = 7.0 Hz), 131.6, 129.6 (d, *J* = 4.0 Hz), 129.1 (d, *J* = 2.0 Hz), 129.0, 126.9, 126.8 (d, *J* = 3.0 Hz), 54.8 (d, *J* = 7.0 Hz), 54.0 (d, *J* = 7.0 Hz), 50.5 (d, *J* = 158.0 Hz), 21.3.

HRMS (ESI): *m/z* calcd for $C_{16}H_{19}ClNNaO_5PS$ [M + Na]$^+$: 426.0308; found 426.0313.

Dimethyl [(2,4-Dichlorophenyl)(tosylamino)methyl]phosphonate (8g)

White solid; yield: 120 mg (91%); mp 185–187 °C.

IR (KBr): 3152, 2958, 2883, 1588, 1477, 1342, 1247, 1164, 1061, 1033, 903, 871, 807, 720 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51 (d, *J* = 8.3 Hz, 2 H), 7.32 (dd, *J* = 8.4, 2.4 Hz, 1 H), 7.22 (dd, *J* = 2.1, 1.1 Hz, 1 H), 7.03 (d, *J* = 8.4 Hz, 2 H), 6.94 (dd, *J* = 8.5, 2.0 Hz, 1 H), 6.77 (br s, 1 H), 5.40 (dd, *J* = 24.5, 9.8 Hz, 1 H), 3.93 (d, *J* = 10.9 Hz, 3 H), 3.51 (d, *J* = 10.8 Hz, 3 H), 2.32 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.6, 137.0, 134.5 (d, *J* = 3.0 Hz), 134.1 (d, *J* = 8.0 Hz), 130.5 (d, *J* = 4.0 Hz), 130.3, 129.2, 128.9 (d, *J* = 2.0 Hz), 127.2 (d, *J* = 3.0 Hz), 126.9, 54.9 (d, *J* = 7.0 Hz), 54.0 (d, *J* = 7.0 Hz), 50.1 (d, *J* = 158.0 Hz), 21.4.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{16}H_{18}Cl_2NNaO_5PS$: 459.9918; found 459.9917.

Dimethyl [(3-Bromophenyl)(tosylamino)methyl]phosphonate (8h)
White solid; yield: 89 mg (66%); mp 129–131 °C.

IR (KBr): 3108, 2950, 2879, 1600, 1465, 1338, 1239, 1168, 1025, 918, 804, 724.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 (d, *J* = 8.3 Hz, 2 H), 7.41 (d, *J* = 6.1 Hz, 1 H, NH), 7.27–7.16 (m, 3 H), 7.01–6.95 (m, 3 H), 4.81 (dd, *J* = 24.6, 10.1 Hz, 1 H), 3.96 (d, *J* = 10.8 Hz, 3 H), 3.48 (d, *J* = 10.7 Hz, 3 H), 2.28 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.1, 137.5 (d, *J* = 2.0 Hz), 135.3, 131.1 (d, *J* = 6.0 Hz), 130.8 (d, *J* = 2.0 Hz), 129.8 (d, *J* = 2.0 Hz), 129.0, 126.9, 122.5 (d, *J* = 2.0 Hz), 55.0 (d, *J* = 7.0 Hz), 54.6 (d, *J* = 157.0 Hz), 54.1 (d, *J* = 7.0 Hz), 21.4.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{16}H_{19}BrNNaO_5PS$: 471.9782; found 471.9767.

Dimethyl [(3-Nitrophenyl)(tosylamino)methyl]phosphonate (8i)
White solid; yield: 121 mg (76%); mp 162–164 °C.

IR (KBr): 3105, 2954, 2883, 1532, 1465, 1358, 1334, 1243, 1168, 1085, 1057 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (d, *J* = 1.8 Hz, 1 H), 7.92 (d, *J* = 8.1 Hz, 1 H), 7.84 (br s, 1 H), 7.54 (d, *J* = 7.4 Hz, 1 H), 7.44 (d, *J* = 8.3 Hz, 2 H), 7.31 (t, *J* = 7.9 Hz, 1 H), 6.88 (d, *J* = 8.3 Hz, 2 H), 5.00 (dd, *J* = 25.0, 10.9 Hz, 1 H), 4.03 (d, *J* = 10.8 Hz, 3 H), 3.57 (d, *J* = 10.8 Hz, 3 H), 2.18 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.9, 143.2, 137.6, 135.3, 134.3 (d, *J* = 6.0 Hz), 129.0 (d, *J* = 2.0 Hz), 128.9, 126.9, 123.1 (d, *J* = 6.0 Hz), 122.6 (d, *J* = 3.0 Hz), 55.4 (d, *J* = 3.0 Hz), 54.4 (d, *J* = 148.0 Hz), 54.1 (d, *J* = 7.0 Hz), 21.1.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{16}H_{19}N_2NaO_7PS$: 437.0548; found 437.0538.

Dimethyl [(2-Furyl)(tosylamino)methyl]phosphonate (8j)[21]
White solid; yield: 106 mg (74%); mp 163–164 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57 (d, *J* = 8.4 Hz, 2 H), 7.19–7.07 (m, 3 H), 6.32–6.01 (m, 3 H), 4.92 (dd, *J* = 24.1, 10.1 Hz, 1 H), 3.85 (d, *J* = 10.8 Hz, 3 H), 3.58 (d, *J* = 10.8 Hz, 3 H), 2.35 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.5, 143.1, 142.6 (d, *J* = 3.0 Hz), 137.3, 129.2, 126.9, 110.6 (d, *J* = 2.0 Hz), 109.7 (d, *J* = 7.0 Hz), 54.6 (d, *J* = 7.0 Hz), 53.9 (d, *J* = 7.0 Hz), 48.5 (d, *J* = 163.0 Hz), 21.4.

Dimethyl [(2-Naphthyl)(tosylamino)methyl]phosphonate (8k)
White solid; yield: 116 mg (79%); mp 172–173 °C.

IR (KBr): 3437, 3108, 2950, 1457, 1326, 1235, 1164, 1057, 1029 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (d, *J* = 8.0 Hz, 1 H), 7.60 (s, 1 H), 7.54 (d, *J* = 8.5 Hz, 1 H), 7.50 (d, *J* = 8.0 Hz, 1 H), 7.46–7.34 (m, 5 H), 7.29 (br s, 1 H, NH), 6.69 (d, *J* = 8.0 Hz, 2 H), 5.02 (dd, *J* = 24.2, 10.0 Hz, 1 H), 3.96 (d, *J* = 10.8 Hz, 3 H), 3.43 (d, *J* = 10.6 Hz, 3 H), 1.94 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.8, 137.7 (d, *J* = 2.0 Hz), 132.8 (d, *J* = 2.0 Hz), 132.7 (dd, *J* = 6.0, 2.0 Hz), 130.3, 128.7, 128.1 (d, *J* = 1.0 Hz), 127.9, 127.8 (d, *J* = 8 Hz), 127.3, 126.9, 126.2, 126.0, 125.6 (d, *J* = 4.0 Hz), 55.3 (d, *J* = 157.0 Hz), 54.8 (d, *J* = 7.0 Hz), 54.0 (d, *J* = 7.0 Hz), 20.9

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{20}H_{22}NNaO_5PS$: 442.0854; found 442.0871.

Dimethyl [1-(Tosylamino)butyl]phosphonate (8l)[21]
White solid; yield: 63 mg (48%); mp 117–118 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 8.2 Hz, 2 H), 7.29 (d, *J* = 8.2 Hz, 2 H), 5.40 (br s, 1 H, NH), 3.66 (d, *J* = 1.3 Hz, 3 H), 3.63 (d, *J* = 1.1 Hz, 3 H), 2.42 (s, 3 H), 1.77–1.60 (m, 1 H), 1.58–1.32 (m, 2 H), 1.31–1.18 (m, 2 H), 0.79 (dt, *J* = 7.3, 1.9 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.3, 138.3, 129.4, 127.0, 53.5 (d, *J* = 7.0 Hz), 52.9 (d, *J* = 7.0 Hz), 49.7 (d, *J* = 157.0 Hz), 32.5 (d, *J* = 3.0 Hz), 21.5, 18.7 (d, *J* = 10.0 Hz), 13.6.

Dimethyl [(Cyclohexyl)(tosylamino)methyl]phosphonate (8m)
White solid; yield: 108 mg (93%); mp 160–161 °C.

IR (KBr): 3152, 2950, 2922, 2847, 1465, 1322, 1235, 1152, 1105, 1057, 1013 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 8.0 Hz, 2 H), 7.39–7.18 (m, 2 H), 5.18 (dd, *J* = 9.5, 4.1 Hz, 1 H), 3.59 (d, *J* = 10.7 Hz, 3 H), 3.53 (d, *J* = 10.7 Hz, 3 H), 2.42 (s, 3 H), 1.80–1.55 (m, 6 H), 1.22–1.00 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.2, 138.4, 129.3, 127.1, 54.8 (d, *J* = 151.0 Hz), 52.8 (d, *J* = 7.0 Hz), 52.7 (d, *J* = 6.0 Hz), 39.2 (d, *J* = 4.0 Hz), 30.4 (d, *J* = 11.0 Hz), 28.0 (d, *J* = 3.0 Hz), 26.1 (d, *J* = 1.0 Hz), 26.0, 25.7, 21.5.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{16}H_{26}NNaO_5PS$: 398.1167; found 398.1142.

Dimethyl [{[(4-Nitrophenyl)sulfonyl]amino}(phenyl)methyl]phosphonate (8n)
Yellow solid; yield: 50 mg (42%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.28 (d, *J* = 6.4 Hz, 1 H), 7.96–7.90 (m, 2 H), 7.76–7.69 (m, 2 H), 7.23 (br s, 1 H, NH), 7.21 (d, *J* = 1.7 Hz, 1 H), 7.16–7.02 (m, 3 H), 4.94 (dd, *J* = 24.4, 10.2 Hz, 1 H), 4.02 (d, *J* = 10.9 Hz, 3 H), 3.42 (d, *J* = 10.7 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.3, 146.8 (d, *J* = 2.0 Hz), 132.5, 128.5 (d, *J* = 3.0 Hz), 128.4 (d, *J* = 2.0 Hz), 128.3 (d, *J* = 6.0 Hz), 128.2, 123.3, 55.2 (d, *J* = 158.0 Hz), 54.8 (d, *J* = 7.0 Hz), 54.3 (d, *J* = 8.0 Hz).

Dimethyl {[(*tert*-Butoxycarbonyl)amino](phenyl)methyl}phosphonate (8o)[8f]
White solid; yield: 48 mg (51%); mp 110.5–113.0 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.30 (m, 5 H), 5.54 (br s, 1 H, NH), 5.15 (dd, *J* = 21.4, 9.9 Hz, 1 H), 3.77 (d, *J* = 10.7 Hz, 3 H), 3.50 (d, *J* = 10.6 Hz, 3 H), 1.43 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.8 (d, *J* = 9.0 Hz), 135.1, 128.7, 128.1 (d, *J* = 3.0 Hz), 127.7 (d, *J* = 5.0 Hz), 80.5, 53.7 (d, *J* = 7.0 Hz), 53.6 (d, *J* = 7.0 Hz), 51.4 (d, *J* = 153.0 Hz), 28.2.

Dimethyl [(Benzylamino)(phenyl)methyl]phosphonate (8p)[8f]
Oil; yield: 36 mg (40%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.26 (m, 9 H), 7.25 (s, 1 H), 4.05 (d, *J* = 20.2 Hz, 1 H), 3.81 (d, *J* = 13.2 Hz, 1 H), 3.73 (d, *J* = 10.6 Hz, 3 H), 3.56 (s, 1 H), 3.54 (d, *J* = 10.5 Hz, 3 H), 2.67 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.1, 135.3 (d, *J* = 4.0 Hz), 128.63, 128.61, 128.5, 128.4, 128.3, 128.0 (d, *J* = 3.0 Hz), 127.2, 59.2 (d, *J* = 154.0 Hz), 53.8 (d, *J* = 7.0 Hz), 53.4 (d, *J* = 6.0 Hz), 51.1 (d, *J* = 17.0 Hz).

Attempted Asymmetric Hydrophosphonylation of *N*-Tosylbenzaldimine (6a)

The chiral NHC precursor **9** (12% mol) and *t*-BuOK (10% mol) were dissolved in THF (2 mL) and the soln was stirred for 30 min at r.t. then cooled to 0 °C. *N*-Tosylbenzaldimine (**6a**; 0.3 mmol) and dimethyl phosphite (**7**; 0.45 mmol, 42 μL) were added and the mixture was kept at r.t. until the reaction was complete (TLC). The crude product was then purified by flash column chromatography [silica gel, PE–EtOAc (1:1)] to give **8a** as a white solid; yield: 97 mg (88%); mp 163–164 °C; 0% ee [HPCL: Daicel Chiralpak OJ-H, 0.50 mL/min; *i*-PrOH–hexane (10:90); retention times: 22.5 and 49.2 min].

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 (d, *J* = 8.3 Hz, 2 H), 7.26–7.19 (m, 3 H), 7.16–7.05 (m, 3 H), 6.95 (d, *J* = 8.0 Hz, 2 H), 4.85 (dd, *J* = 24.2, 9.9 Hz, 1 H), 3.88 (d, *J* = 10.8 Hz, 3 H), 3.40 (d, *J* = 10.6 Hz, 3 H), 2.26 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.7, 137.9, 133.3, 128.9, 128.2, 128.2, 127.8 (d, *J* = 2.0 Hz), 127.0, 54.9 (d, *J* = 157.0 Hz), 54.6 (d, *J* = 8.0 Hz), 53.9 (d, *J* = 7.0 Hz), 21.3.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

Acknowledgment

This work was supported by Shihezi University.

References

(1) For reviews of the biological activity of α-amino phosphonic acids, see: (a) Kafarski, P.; Lejczak, B. *Phosphorus, Sulfur Silicon Relat. Elem.* **1991**, *63*, 193. (b) Hiratake, J.; Oda, J. *Biosci., Biotechnol., Biochem.* **1997**, *61*, 211. (c) Kafarski, P.; Lejczak, B. *Curr. Med. Chem.: Anti-Cancer Agents* **2001**, *1*, 301. (d) Grembecka, J.; Kafarski, P. *Mini-Rev. Med. Chem.* **2001**, *1*, 133.

(2) (a) Allen, M. C.; Fuhrer, W.; Tuck, B.; Wade, R.; Wood, J. M. *J. Med. Chem.* **1989**, *32*, 1652. (b) Bartlett, P. A.; Hanson, J. E.; Giannousis, P. G. *J. Org. Chem.* **1990**, *55*, 6268. (c) Oleksyszyn, J.; Powers, J. C. *Biochemistry* **1991**, *30*, 485. (d) Smith, W. W.; Bartlett, P. A. *J. Am. Chem. Soc.* **1998**, *120*, 4622.

(3) Hirschmann, R.; Smith, A. B. III; Taylor, C. M.; Benkovic, P. A.; Taylor, S. D.; Yager, K. M.; Sprengeler, P. A.; Venkovic, S. J. *Science (Washington, D. C.)* **1994**, *265*, 234.

(4) (a) Allen, J. G.; Atherton, F. R.; Hall, M. J.; Hassall, C. H.; Holmes, S. W.; Lambert, R. W.; Nisbet, L. J.; Ringrose, P. S. *Nature (London)* **1978**, *272*, 56. (b) Atherton, F. R.; Hassall, C. H.; Lambert, R. W. *J. Med. Chem.* **1986**, *29*, 29. (c) Pratt, R. F. *Science (Washington, D. C.)* **1989**, *246*, 917.

(5) Lejczak, B.; Kafarski, P.; Sztajer, H.; Mastarlerz, P. *J. Med. Chem.* **1986**, *29*, 2212.

(6) (a) Stowasser, B.; Budt, K.-H.; Jian-Qi, L.; Peyman, A.; Ruppert, D. *Tetrahedron Lett.* **1992**, *33*, 6625. (b) Alonso, E.; Alonso, E.; Solís, A.; del Pozo, C. *Synlett* **2000**, 698.

(7) For reviews, see: (a) Pudovik, A. N.; Konovalova, I. V. *Synthesis* **1979**, 81. (b) Kolodiazhnyi, O. I. *Tetrahedron: Asymmetry* **1998**, *9*, 1279.

(8) For recent reviews see: (a) Ma, J.-A. *Chem. Soc. Rev.* **2006**, *35*, 630. (b) Merino, P.; López, E. M.; Herrera, R. P. *Adv. Synth. Catal.* **2008**, *350*, 1195. For recent examples of aminophosphonylation reactions see: (c) Gröger, H.; Saida, Y.; Arai, S.; Martens, J.; Sasai, Hiroaki.; Shibasaki, M. *Tetrahedron Lett.* **1996**, *37*, 9291. (d) Gröger, H.; Saida, Y.; Sasai, H.; Yamaguchi, K.; Martens, J.; Shibasaki, M. *J. Am. Chem. Soc.* **1998**, *120*, 3089. (e) Saito, B.; Katsuki, T. *Angew. Chem. Int. Ed.* **2005**, *44*, 4600. (f) Saito, B.; Egami, H.; Katsuki, T. *J. Am. Chem. Soc.* **2007**, *129*, 1978. (g) Palacios, F.; Olszewski, T. K.; Vicario, J. *Org. Biomol. Chem.* **2010**, *8*, 4255.

(9) Joly, G. D.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 4102.

(10) (a) Akiyama, T.; Morita, H.; Itoh, J.; Fuchibe, K. *Org. Lett.* **2005**, *7*, 2583. (b) Akiyama, T.; Morita, H.; Bachu, P.; Mori, K.; Yamanaka, M.; Hirata, T. *Tetrahedron* **2009**, *65*, 4950. (c) Shi, F.-Q.; Song, B.-A. *Org. Biomol. Chem.* **2009**, *7*, 1292.

(11) (a) Pettersen, D.; Marcolini, M.; Bernardi, L.; Fini, F.; Herrera, R. P.; Sgarzani, V.; Ricci, A. *J. Org. Chem.* **2006**, *71*, 6269. (b) Nakamura, S.; Nakashima, H.; Yamamura, A.; Shibata, N.; Torua, T. *Adv. Synth. Catal.* **2008**, *350*, 1209. (c) Nakamura, S.; Hayashi, M.; Hiramatsu, Y.; Shibata, N.; Funahashi, Y.; Toru, T. *J. Am. Chem. Soc.* **2009**, *131*, 18240.

(12) For recent reviews, see: (a) Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534. (b) Zeitler, K. *Angew. Chem. Int. Ed.* **2005**, *44*, 7506. (c) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606. (d) Marion, N.; Díez-González, S.; Nolan, S. P. *Angew. Chem. Int. Ed.* **2007**, *46*, 2988. (e) Nair, V.; Vellalath, S.; Babu, B. P. *Chem. Soc. Rev.* **2008**, *37*, 2691.

(13) Song, J. J.; Gallou, F.; Reeves, J. T.; Tan, Z. L.; Yee, N. K.; Senanayake, C. H. *J. Org. Chem.* **2006**, *71*, 1273.

(14) (a) Zhang, J.; Du, G.-F.; Xu, Y.-K.; He, L.; Dai, B. *Tetrahedron Lett.* **2012**, in press. (b) Suzuki, Y.; Abu Bakar, M. D.; Muramatsu, K.; Sato, M. *Tetrahedron* **2006**, *62*, 4227. (c) Suzuki, Y.; Muramatsu, K.; Yamauchi, K.; Morie, Y.; Sato, M. *Tetrahedron* **2006**, *62*, 302. (d) Kano, T.; Sasaki, K.; Konishi, T.; Mii, H.; Maruoka, K. *Tetrahedron Lett.* **2006**, *47*, 4615. (e) Fukuda, Y.; Maeda, Y.; Ishii, S.; Kondo, K.; Aoyama, T. *Synthesis* **2006**, 589. (f) Fukuda, Y.; Kondo, K.; Aoyama, T. *Synthesis* **2006**, 2649. (g) Fukuda, Y.; Maeda, Y.; Kondo, K.; Aoyama, T. *Synthesis* **2006**, 1937. (h) Fukuda, Y.; Maeda, Y.; Kondo, K.; Aoyama, T. *Chem. Pharm. Bull.* **2006**, *54*, 397.

(15) (a) Song, J.; Tan, Z.; Reeves, J. T.; Yee, N. K.; Senanayake, C. H. *Org. Lett.* **2007**, *9*, 1013. (b) Du, G.-F.; He, L.; Gu, C.-Z.; Dai, B. *Synlett* **2010**, 2513.

(16) (a) Wu, J.; Sun, X.; Xia, H. G. *Eur. J. Org. Chem.* **2005**, 4769. (b) Wu, J.; Sun, X. Y.; Ye, S. Q.; Sun, W. *Tetrahedron Lett.* **2006**, *47*, 4813. (c) Sun, X.; Ye, S.; Wu, J. *Eur. J. Org. Chem.* **2006**, 4787. (d) Liu, Y. K.; Li, R.; Yue, L.; Li, B. J.; Chen, Y. C.; Wu, Y.; Ding, L. S. *Org. Lett.* **2006**, *8*, 1521.

(17) Cai, Z.-H.; Du, G.-F.; He, L.; Gu, C.-Z.; Dai, B. *Synthesis* **2011**, 2073.

(18) Arduengo, A. J. III; Krafczyk, R.; Schmutzler, R.; Craig, H. A.; Goerlich, J. R.; Marshall, W. J.; Unverzagt, M. *Tetrahedron* **1999**, *55*, 14523.

(19) (a) Song, J. J.; Tan, Z. L.; Reeves, J. T.; Fandrick, D. R.; Yee, N. K.; Senanayake, C. H. *Org. Lett.* **2008**, *10*, 877. (b) Movassaghi, M.; Schmidt, M. A. *Org. Lett.* **2005**, *7*, 2453.

(20) He, L.; Jian, T.-Y.; Ye, S. *J. Org. Chem.* **2007**, *72*, 7466.

(21) Das, B.; Balasubramanyam, P.; Krishnaiah, M.; Veeranjaneyulu, B.; Reddy, G. C. *J. Org. Chem.* **2009**, *74*, 4393.

