Tetrahedron: *Asymmetry* 19 (2008) 1886–1890

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Chiral *N*-thiophosphoryl imine-induced diastereoselective aza-Morita–Baylis–Hillman reaction

Aidang Lu, Xinyuan Xu, Peng Gao, Zhenghong Zhou *, Haibin Song, Chuchi Tang

State Key Laboratory of Elemento-Organic Chemistry, Institute of Elemento-Organic Chemistry, Tianjin 300071, People's Republic of China

ARTICLE INFO

Article history:
Received 30 May 2008
Accepted 5 August 2008
Available online 29 August 2008

ABSTRACT

In the presence of an effective air-stable nucleophilic trialkylphosphine organocatalyst, 1,3,5-triaza-7-phosphaadamantane, a chiral *N*-thiophosphoryl imine bearing a (*S*)-binaphthalene skeleton induced a diastereoselective aza-MBH reaction with fair chemical yields and moderate to excellent diastereoselectivities (up to >99% de).

1. Introduction

The Morita–Baylis–Hillman (MBH) reaction is an effective and potentially useful carbon–carbon bond forming reaction, giving densely multifunctional adducts under mild conditions.[1] Due to its enormous potential in organic synthesis, it has received much research interest.[2] Recent efforts on this reaction have been directed toward the following two aspects: asymmetric MBH reaction catalyzed by chiral catalysts,[3] and aza-MBH reaction.[4,5] For the latter, major efforts have been focused on the scope of the reaction and a search for practical catalysts[4] including chiral catalysts for an asymmetric version of the aza-MBH reaction.[5] In 1984, Perlmutter reported the first example of an aza-MBH reaction of *N*-tosyl imines and ethyl acrylate catalyzed by DABCO.[4a] However, this report did not attract much attention in the following decade, and only ver recently did new reports emerge.[4d–p] For example, Yamamoto first explored the aza-MBH reaction of *N*-methoxycarbonyl-protected imines;[4b] Bertendshaw established a three-component version of an aza-MBH reaction from an activated olefin, aldehyde, and N-protected amine;[4c] Adolfsson applied Lewis base or Lewis acid as a cocatalyst to aza-MBH reaction;[4g,h] Shi made significant contributions to this reaction by expanding the scope of the substrate activated olefin,[4f,l,n,p] and employing tertiary phosphines[4i,j,m] as catalysts and *N*-diphenylphosphinoylimines[4i] as an alternative imine substrate. Over the past decades, a catalytic asymmetric version of the aza-MBH reaction has undergone remarkable progress.[5d–w] However, only a few reports have dealt with a chiral auxiliary-induced diastereoselective aza-MBH reaction.[5a–c] Kündig reported a DABCO-catalyzed coupling reaction of methyl acrylate and acrylonitrile with planar chiral arylaldimine tricarbonylchromium complexes, in which the de values varied in a range of 68–95%.[5a] Using chiral *N*-sulfinylimines as the electrophile, Shi[5b] and Aggarwal[5c] developed another variation of the diastereoselective aza-MBH reactions, with diastereoselectivities up to 86% and 64% de being observed, respectively.

Recently, we have developed a convenient method for the preparation of *N*-thiophosphoryl imines,[6] which have been successfully employed as novel electrophiles in some organic transformations.[7] Compared to *N*-diphenylphosphinoyl imines, the former exhibit great advantages with their stability and ease of preparation. In the preliminary report, it was found that in the presence of an air-stable trialkylphosphine, 1,3,5-triaza-7-phosphaadamantane (PTA), *N*-thiophosphoryl imines demonstrate fair reactivity in the coupling of methyl vinyl ketone (MVK) and methyl acrylate (MA) (Scheme 1).[8] The unique characteristics of *N*-thiophosphoryl imines, a tetradentate structure around the phosphorus(V) atom, would provide a full opportunity to realize the diastereoselective version of this reaction. Herein, we report the diastereoselective version of this *N*-thiophosphoryl imine-based aza-MBH reaction.

2. Results and discussion

2.1. Synthesis of chiral *N*-thiophosphoryl imines

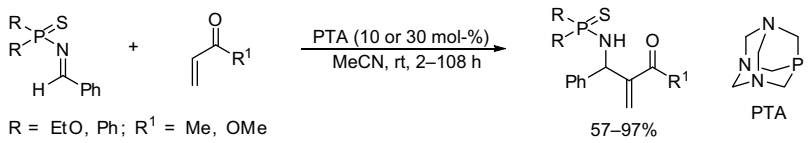
According to the reported procedure, chiral *N*-thiophosphoryl imine **1** containing an adjacent stereogenic phosphorus atom and chiral *N*-thiophosphoryl imines **2** bearing a (*S*)-binaphthalene scaffold were synthesized in good to excellent yield through thermal condensation of acetals and the corresponding thiophosphoramides (Scheme 2).[6]

2.2. PTA-catalyzed diastereoselective aza-MBH reaction between chiral *N*-thiophosphoryl imines 1 and 2 and MVK

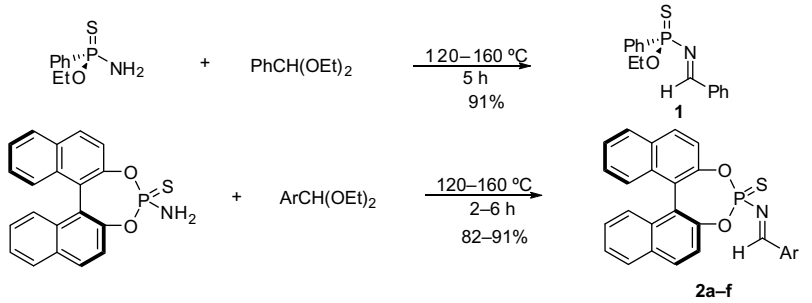
With these imines in hand, their chiral induction ability in the coupling with MVK was investigated. Firstly, diastereoselective aza-MBH reaction between chiral imine **1** with an adjacent

* Corresponding author. Tel.: +86 22 23504232; fax: +86 22 23508939.
E-mail address: z.h.zhou@nankai.edu.cn (Z. Zhou).

0957-4166/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2008.08.010

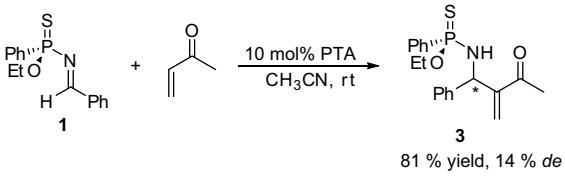


Scheme 1. PTA-catalyzed aza-MBH reaction of *N*-thiophosphoryl imines.



Scheme 2. Synthesis of chiral *N*-thiophosphoryl imines.

stereogenic phosphorus atom and MVK was performed in the presence of 10 mol % of PTA. The reaction ran smoothly to afford the corresponding aza-MBH adducts with satisfactory yields, albeit in quite low diastereoselectivities (Scheme 3).



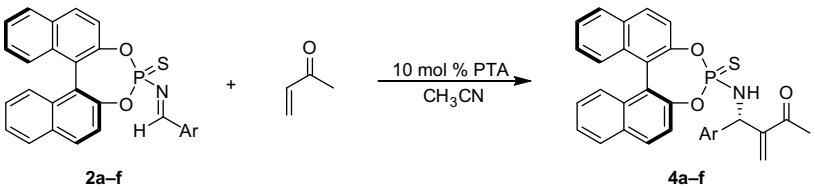
Scheme 3. PTA-catalyzed diastereoselective aza-MBH reaction of imine **1** with MVK.

We then turned our attention to the chiral *N*-thiophosphoryl imine **2** bearing a bulky (*S*)-binaphthalene scaffold. It is noteworthy that under otherwise identical conditions, a dramatic improvement in diastereoselectivity was obtained for the diastereoselective aza-MBH reaction of chiral thiophosphorylimine **2** derived from (*S*)-1,1′-binaphthyl-2,2′-diol and MVK. The results are summarized in Table 1.

As shown in Table 1, in all cases, the coupling of chiral imines **2** with MVK ran smoothly in the presence of 10 mol % of PTA to give the corresponding aza-MBH adducts **4** in satisfactory yields. The diastereoselectivity of this reaction was influenced by the nature of the substrate imine. For example, only moderate diastereoselectivities were observed for imines **3b**, **3c**, and **3e** (Table 1, entries 2, 3, and 5; 50%, 42%, and 48% de, respectively), while almost perfect diastereoselectivity was obtained for imine **3f** bearing a trifluoromethyl group at the *para*-position on the benzene ring (Table 1, entry 6, >99% de). The diastereoselectivity of this type of reaction was obviously higher than that of the coupling of a chiral imine **1** and MVK (Scheme 2, 14% de). This means that the chiral induction of chiral imine containing an adjacent stereogenic phosphorus atom is far less effective than that of the chiral imine with a bulky (*S*)-binaphthalene scaffold.

Theoretically, the reaction of **2** with MVK will provide a pair of diastereomers of adduct **4**. With the exception of **4f**, the ^{31}P NMR analysis of **4** clearly showed two singlets (near 80 ppm) corresponding to these two diastereomers. In all cases, the separation is sufficient to determine the de value by integration. In addition, it is possible to analyze these adducts by ^{1}H NMR, where many signals (particularly the acetyl group) could be differentiated between the two diastereomers. With the exception of **4f**, in all cases, the

Table 1
PTA-catalyzed diastereoselective aza-MBH reaction between **2** and MVK



Entry	**2** or **4**	Ar	Time (day)	Yield[a] (%)	de[b] (%)	Configuration
1	**a**	Ph	4	64	90	(*S*,*S*)
2	**b**	4-MeC_6H_4	5	65	50	(*S*,*S*)
3	**c**	4-MeOC_6H_4	5	70	42	(*S*,*S*)
4	**d**	2-ClC_6H_4	2	75	82	(*S*,*R*)
5	**e**	4-BrC_6H_4	4	72	48	(*S*,*S*)
6	**f**	4-F_3CC_6H_4	3	66	>99	(*S*,*S*)

[a] Isolated yield.
[b] Determined by ^{31}P NMR and ^{1}H NMR.

acetyl protons (2.2–2.4 ppm) are clearly distinguished by ^{1}H NMR analysis. Integration of the two signals also allows the determination of its de value.

In order to determine the absolute configuration of the newly generated stereogenic center, single crystals suitable for X-ray crystallographic analysis were obtained from compound **4f** bearing a trifluoromethyl group. The absolute configuration of **4f** was assigned to be (*S*) for the nitrogen-connecting carbon (Fig. 1).[9] At the same time, NMR analysis showed that the signal corresponding to the major diastereomer always appeared at downfield in the ^{31}P NMR spectra, and the signal of the acetyl protons corresponding to the major isomer always appeared upfield in the ^{1}H NMR spectra. Therefore, the other adducts **4** should have the same (*S*)-configuration as compound **4f**, except for **4d** in which the priority of the four groups is changed when chloro is introduced at the *ortho*-position on the benzene ring.

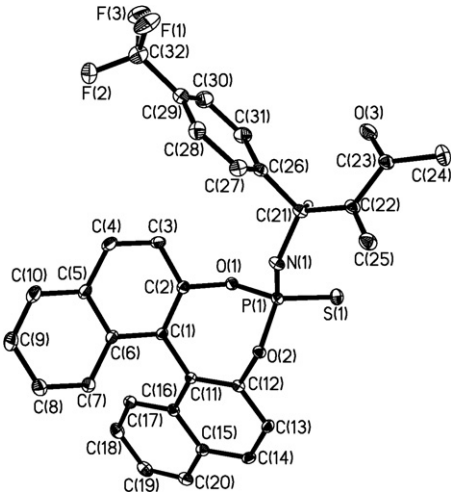


Figure 1. X-ray structure of enantiomerically pure **4f**. Thermal ellipsoids are shown at 30% probability. Solvent (CH_2Cl_2) has been omitted for clarity.

3. Conclusion

In conclusion, we have developed a novel chiral *N*-thiophosphoryl imine-induced diastereoselective aza-MBH reaction. The corresponding aza-MBH adducts were obtained in fair to excellent yields with moderate to excellent diastereoselectivities (>99% de) in the presence of an efficient air-stable nucleophilic trialkylphosphine organocatalyst—PTA.

4. Experimental

4.1. Synthesis of chiral *N*-thiophosphoryl imines 1 and 2

A mixture of acetal and the corresponding phosphoramide (with a molar ratio of 1.3:1) was placed in a round-bottomed flask equipped with a distilling apparatus. The resulting mixture was gently heated (the bath temperature was gradually raised to ca. 160 °C) with stirring. The reaction was completed until no more released ethanol was distilled off from the reaction mixture (2–6 h). After removal of the excess acetal, the crude product was purified via recrystallization or column chromatography on silica gel (200–300 mesh, gradient eluted with petroleum ether and ethyl acetate).

For **1**: Pale yellow liquid, 91% yield, n_D^{16} 1.6100, $[\alpha]_D^{20} = -102.2$ (*c* 1.0, $CHCl_3$), ^{31}P NMR (161.7 MHz, $CDCl_3$): δ 87.3; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32 (t, 3H, J = 7.2 Hz, CH_3), 4.07–4.15 (m, 2H, OCH_2), 7.44–7.55 (m, 6Harom), 7.98 (d, 2Harom, J = 7.2 Hz), 8.07–8.03 (m, 2Harom), 9.23 (d, 1H, J = 38.8 Hz, CH). Anal. Calcd for $C_{15}H_{16}NOPS$: C, 62.27; H, 5.57; N, 4.84. Found: C, 62.43; H, 5.45; N, 4.72.

For **2a**: White solid, 82% yield, mp 208–211 °C, $[\alpha]_D^{20} = +288.5$ (*c* 1.0, $CHCl_3$), ^{31}P NMR (161.7 MHz, $CDCl_3$): δ 90.74; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (t, 2Harom, J = 7.6 Hz), 7.43–7.52 (m, 7Harom), 7.63 (d, 2Harom, J = 8.4 Hz), 7.93 (d, 2Harom, J = 7.6 Hz), 7.98 (dd, 2Harom, J = 8.4, 3.6 Hz) 8.02 (d, 1Harom, J = 8.8 Hz), 8.08 (d, 1Harom, J = 8.8 Hz), 9.39 (d, J = 40.4 Hz, CH). Anal. Calcd for $C_{27}H_{18}NO_2PS$: C, 71.83; H, 4.02; N, 3.10. Found: C, 71.65; H, 3.86; N, 2.91.

For **2b**: White solid, 91% yield, mp 210–211 °C, $[\alpha]_D^{20} = +153.9$ (*c* 1.0, $CHCl_3$), ^{31}P NMR (121.3 MHz, $CDCl_3$): δ 91.41; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.44 (s, 3H, CH_3), 7.28–7.35 (m, 4Harom), 7.42–7.52 (m, 5Harom), 7.63 (dd, 1Harom, J = 8.7 and 1.2 Hz), 7.82 (d, 2Harom, J = 8.4 Hz), 7.96–8.09 (m, 4Harom), 9.34 (d, 1H, J = 40.5 Hz, CH). Anal. Calcd for $C_{28}H_{20}NO_2PS$: C, 72.24; H, 4.33; N, 3.01. Found: C, 72.01; H, 4.12; N, 2.86.

For **2c**: White solid, 88% yield, mp 182–184 °C, $[\alpha]_D^{20} = +103.5$ (*c* 1.0, $CHCl_3$), ^{31}P NMR (121.3 MHz, $CDCl_3$): δ 91.84; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.89 (s, 3H, CH_3), 6.96 (d, 2Harom, J = 8.7 Hz), 7.29–7.34 (m, 2Harom), 7.42–7.52 (m, 5Harom), 7.63 (dd, 1Harom, J = 8.7 and 1.2 Hz), 7.88 (d, 2Harom, J = 8.7 Hz), 7.96–8.08 (m, 4Harom), 9.29 (d, 1H, J = 40.5 Hz, CH). Anal. Calcd for $C_{28}H_{20}NO_3PS$: C, 69.84; H, 4.19; N, 2.91. Found: C, 69.65; H, 4.04; N, 2.67.

For **2d**: White solid, 90% yield, mp 118–122 °C, $[\alpha]_D^{20} = +228.5$ (*c* 1.0, $CHCl_3$), ^{31}P NMR (121.3 MHz, $CDCl_3$): δ 89.65; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43–7.52 (m, 9Harom), 7.92–8.10 (m, 7Harom), 9.88 (d, 1H, J = 39.6 Hz, CH). Anal. Calcd for $C_{27}H_{17}ClNO_2PS$: C, 66.74; H, 3.53; N, 2.88. Found: C, 66.37; H, 3.16; N, 2.49.

For **2e**: White solid, 90% yield, mp 208–211 °C (recrystallization from methanol), $[\alpha]_D^{20} = +99.5$ (*c* 1.0, $CHCl_3$), ^{31}P NMR (121.3 MHz, $CDCl_3$): δ 90.14; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30–7.35 (m, 2Harom), 7.40–7.53 (m, 5Harom), 7.60–7.65 (m, 3Harom), 7.78 (d, 2Harom, J = 8.4 Hz) 7.96–8.09 (m, 4Harom), 9.33 (d, J = 39.9 Hz, CH). Anal. Calcd for $C_{27}H_{17}BrNO_2PS$: C, 61.14; H, 3.23; N, 2.64. Found: C, 60.97; H, 3.04; N, 2.51.

For **2f**: White solid, 83% yield, mp 205–207 °C, $[\alpha]_D^{20} = +254.4$ (*c* 1.0, $CHCl_3$), ^{31}P NMR (121.3 MHz, $CDCl_3$): δ 89.19; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31–7.36 (m, 2Harom), 7.41–7.54 (m, 5Harom), 7.63 (dd, 1Harom, J = 9.0 and 1.2 Hz), 7.75 (d, 2Harom, J = 8.1 Hz), 7.98–8.11 (m, 6Harom), 9.43 (d, 1H, J = 39.6 Hz, CH). Anal. Calcd for $C_{28}H_{17}F_3NO_2PS$: C, 64.74; H, 3.30; N, 2.70. Found: C, 64.59; H, 3.05; N, 2.52.

4.2. General procedure for the PTA-catalyzed diastereoselective aza-MBH reaction

A mixture of chiral imine (1.0 mmol), MVK (3.0 mmol), and PTA (0.10 mmol) in 3.0 mL of acetonitrile was stirred at room temperature until almost total consumption of imine (monitored by TLC). After removal of solvent, the residue was purified by column chromatography on silica gel (200–300 meshes, gradient eluted with petroleum ether/ethyl acetate) to afford the product.

For **3**: Pale yellow oil, 68% yield, 14% de, ^{31}P NMR (161.7 MHz, $CDCl_3$): δ 74.73 (major), 75.93 (minor); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 (t, 1.71 H, J = 7.2 Hz, CH_3), 1.32 (t, 1.29 H, J = 7.2 Hz, CH_3), 2.17 (s, 1.56H, CH_3), 2.21 (s, 1.15H, CH_3), 3.80–3.86 (m, 0.56H, CH), 3.95–4.01 (m, 0.45H, CH), 4.10–4.24 (m, 2H, OCH_2), 5.20 (t, 0.56H, J = 11.6 Hz, NH), 5.20 (t, 0.43 H, J = 11.6 Hz, NH), 5.91 (s, 0.52 H, $=CH_2$), 6.01 (s, 0.52 H, $=CH_2$), 6.14 (s, 0.39H, $=CH_2$), 6.16 (s, 0.38H, $=CH_2$), 7.11–7.25 (m, 5Harom), 7.36–7.48 (m, 3Harom), 7.75–7.85 (m, 2Harom). Anal. Calcd for $C_{19}H_{22}NO_2PS$: C, 63.49; H, 6.17; N, 3.90. Found: C, 63.16; H, 5.83; N, 3.62.

For **4a**: White solid, 64% yield, mp 242–245 °C, $[\alpha]_D^{20} = +339.3$ (*c* 1, $CHCl_3$), 90% de, ^{31}P NMR (121.3 MHz, $CDCl_3$): δ 82.09 (minor), 82.21 (major); ^1H NMR (400 MHz, $CDCl_3$): δ 2.27 (s, 2.85H, CH_3), 2.35 (s, 0.15H, CH_3), 4.60 (dd, 1H, J = 8.0 and 10.8 Hz, CH), 5.63 (dd, 1H, J = 10.8 and 13.2 Hz, NH), 6.12 (s, 1H, =CH_2), 6.21 (s, 1H, =CH_2), 6.97–7.00 (m, 1Harom), 7.27–7.58 (m, 12Harom), 7.85–8.03 (m, 4Harom); ^{13}C NMR (100.6 MHz, $CDCl_3$): 26.67, 59.14, 59.18, 121.12, 121.51, 122.10, 122.27, 122.30, 125.60, 125.72, 126.49, 126.64, 126.68, 126.99, 127.13, 127.47, 127.53, 128.37, 128.48, 128.54, 130.55, 130.83, 131.56, 131.86, 132.32, 132.35, 140.97, 141.02, 146.34, 146.43, 147.37, 147.51, 147.67, 147.72, 199.21. Anal. Calcd for $C_{31}H_{24}NO_3PS$: C, 71.39; H, 4.64; N, 2.69. Found: C, 71.15; H, 4.64; N, 2.74.

For **4b**: White solid, 65% yield, mp 105–110 °C, $[\alpha]_D^{20} = +282.5$ (*c* 0.5, $CHCl_3$), 50% de, ^{31}P NMR (121.3 MHz, $CDCl_3$): δ 81.03 (minor), 81.19 (major); ^1H NMR (300 MHz, $CDCl_3$): δ 2.26 (s, 2.25 H, CH_3), 2.30 (s, 0.75H, CH_3), 2.34 (s, 0.74H, CH_3), 2.37 (s, 2.38H, CH_3), 4.64 (dd, 0.74H, J = 8.1 and 10.8 Hz, CH), 4.75 (dd, 0.25H, J = 8.1 and 10.8 Hz, CH), 5.48 (dd, 0.26H, J = 10.8 and 13.2 Hz, NH), 5.59 (dd, 0.73 H, J_{H-H} = 10.8 and 13.2 Hz, NH), 6.09 (s, 0.75H, =CH_2), 6.16 (s, 0.25H, =CH_2), 6.19 (s, 0.72H, =CH_2), 6.27 (s, 0.23H, =CH_2), 7.02–7.20 (m, 7Harom), 7.33–7.59 (m, 6Harom), 7.86–8.03 (m, 3Harom); ^{13}C NMR (75 MHz, $CDCl_3$): 21.06, 26.68, 58.99, 59.04, 121.21, 121.55, 121.58, 122.13, 122.33, 125.58, 125.70, 125.99, 126.47, 126.58, 126.65, 127.04, 127.11, 127.19, 128.36, 128.48, 129.20, 130.50, 130.80, 131.60, 131.90, 132.38, 137.19, 138.02, 138.09, 146.43, 146.54, 147.45, 147.63, 147.99, 148.05, 199.22. Anal. Calcd for $C_{32}H_{26}NO_3PS$: C, 71.76; H, 4.89; N, 2.62. Found: C, 71.55; H, 4.68; N, 2.43.

For **4c**: White solid, 70% yield, mp 108–112 °C, $[\alpha]_D^{20} = +133.5$ (*c* 0.5, $CHCl_3$), 42% de, ^{31}P NMR (121.3 MHz, $CDCl_3$): δ 80.90 (minor), 81.10 (major); ^1H NMR (300 MHz, $CDCl_3$): δ 2.26 (s, 2.12H, CH_3), 2.34 (s, 0.87H, CH_3), 3.77 (s, 0.81H, OCH_3), 3.84 (s, 2.03H, OCH_3), 4.61 (dd, 0.65H, J_{H-H} = 8.1 and 10.5 Hz, CH), 4.75 (dd, 0.27H, J_{H-H} = 8.1 and 10.5 Hz, CH), 5.47 (dd, 1H, J_{H-H} = 10.5 and 12.6 Hz, NH), 5.59 (dd, 1H, J_{H-H} = 10.5 and 12.6 Hz, NH), 6.08 (s, 0.66H, =CH_2), 6.15 (s, 0.27H, =CH_2), 6.18 (s, 0.65H, =CH_2), 6.26 (s, 0.26H, =CH_2), 6.80–6.91 (m, 2Harom), 6.99–7.10 (m, 2Harom), 7.30–8.59 (m, 8Harom) 7.86–8.04 (m, 4Harom); ^{13}C NMR (100.6 MHz, $CDCl_3$): 27.00, 27.07, 55.49, 55.54, 55.58, 55.65, 58.74, 58.88, 114.00, 114.12, 120.97, 121.41, 121.78, 122.36, 122.56, 125.89, 126.00, 126.77, 126.97, 127.26, 127.40, 127.53, 128.18,128.66, 128.76, 130.80, 131.11, 131.82, 132.11, 132.59, 133.42, 133.46, 146.61, 146.70, 147.63, 147.77, 148.11, 148.16, 158.99, 159.20, 199.53, 199.61. Anal. Calcd for $C_{32}H_{26}NO_4PS$: C, 69.68; H, 4.75; N, 2.54. Found: C, 69.41; H, 4.48; N, 2.26.

For **4d**: White solid, 75% yield, mp 115–119 °C, $[\alpha]_D^{20} = +216.6$ (*c* 1, $CHCl_3$), 82% de, ^{31}P NMR (121.3 MHz, $CDCl_3$): δ 80.14 (minor), 80.69 (major); ^1H NMR (300 MHz, $CDCl_3$): δ 2.25 (s, 2.67H, CH_3), 2.27 (s, 0.26H, CH_3), 4.81 (dd, 1H, J = 9.0 and 10.8 Hz, CH), 6.01 (dd, 1H, J = 10.8 and 13.5 Hz, NH), 6.25 (s, 1H, =CH_2), 6.26 (s, 1H, =CH_2), 7.30–7.43 (m, 4Harom), 7.46–7.59 (m, 8Harom), 7.86 (d, 1Harom, J = 8.7 Hz), 7.93 (d, 2Harom, J = 8.7 Hz), 8.01 (d, 1Harom, J = 8.7 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 26.74, 56.08, 56.13, 120.38, 121.05, 121.43, 121.52, 121.55, 122.05, 122.08, 122.33, 122.36, 125.61, 125.74, 126.51, 126.61, 126.71, 126.80, 126.99, 127.15, 128.35, 128.42, 128.48, 128.67, 128.75, 128.95, 129.30, 129.49, 129.61, 129.87, 130.70, 130.53, 130.85, 131.60, 131.87, 132.33,132.42,132.75, 132.92, 138.01, 138.06, 199.39. Anal. Calcd for $C_{31}H_{23}ClNO_3PS$: C, 66.96; H, 4.17; N, 2.52. Found: C, 66.78; H, 4.05; N, 2.34.

For **4e**: White solid, 72% yield, mp 108–112 °C, $[\alpha]_D^{20} = +168.7$ (*c* 1, $CHCl_3$), ^{31}P NMR (121.3 MHz, $CDCl_3$): δ 80.90 (minor), 80.96 (major); ^1H NMR (300 MHz, $CDCl_3$): δ 2.26 (s, 2.22H, CH_3), 2.36 (s, 0.78H, CH_3), 4.66–4.84 (m, 1H, CH), 5.43–5.59 (m, 1H, NH), 6.11 (s, 0.62H, =CH_2), 6.19 (s, 0.22H, =CH), 6.21 (s, 0.65H, =CH_2), 6.30 (s, 0.22H, =CH), 7.20–7.22 (m, 2Harom), 7.33–7.36 (m, 3Harom), 7.44–7.55 (m, 6Harom), 7.91–8.06 (m, 5Harom); ^{13}C NMR (75 MHz, $CDCl_3$): 26.59, 58.99, 59.05, 120.96, 121.00, 121.46, 125.66, 125.81, 126.54, 126.78, 127.02, 127.18, 127.82, 127.97, 128.32, 128.43, 128.49, 130.62, 130.90, 131.47, 131.59, 131.64, 131.93, 132.36, 132.45, 140.05, 140.12, 147.34, 199.16. Anal. Calcd for $C_{31}H_{23}BrNO_3PS$: C, 62.01; H, 3.86; N, 2.33. Found: C, 61.84; H, 3.67; N, 2.08.

For **4f**: White solid, 66% yield, mp 123–127 °C, $[\alpha]_D^{20} = +216.6$ (*c* 0.5, $CHCl_3$), >99% de, ^{31}P NMR (121.3 MHz, $CDCl_3$): δ 80.95; ^1H NMR (300 MHz, $CDCl_3$): δ 2.27 (s, 3H, CH_3, CH_3), 4.77 (dd, 1H, J = 8.4 and 10.8 Hz, CH), 5.64 (dd, 1 H, J = 10.8 and 13.2 Hz, NH), 6.16 (s, 1H, =CH_2), 6.25 (s, 1H, =CH_2), 7.10 (d, 1Harom, J = 8.7 Hz), 7.31–7.36 (m, 3Harom), 7.43–7.49 (m, 4Harom), 7.52–7.64 (m, 4Harom), 7.92–7.99 (m, 3Harom), 8.03 (d, 1Harom, J = 8.7 Hz); ^{13}C NMR (75.0 MHz, $CDCl_3$): 26.52, 59.25, 59.30, 120.86, 121.43, 122.07, 122.10, 122.34, 126.63, 126.87, 126.96, 127.02, 127.19, 128.48, 128.56, 130.70, 130.97, 131.68, 131.95, 132.36, 132.48, 145.02, 145.09, 146.34, 146.46, 147.05, 147.11, 147.34, 147.53, 199.22. Anal. Calcd for $C_{32}H_{23}F_3NO_3PS$: C, 65.19; H, 3.93; N, 2.38. Found: C, 65.02; H, 3.67; N, 2.11.

4.3. General procedure for acidic methanolysis of the aza-MBH adducts

A mixture of aza-Morita–Baylis–Hillman adduct **4a** (0.52 g, 1 mmol) in 20 mL of 3.75 M HCl/MeOH was stirred at room temperature for 3 h. After removal of solvent, the pale yellow viscous residue was washed with ether (3 × 20 mL), and then recrystallized from ether/chloroform to provide the desired product.

3-[Amino(phenyl)methyl]but-3-en-2-one hydrochloride: White solid, 0.13 g, 60% yield, mp 153–156 °C, ^1H NMR (400 MHz, D_2O): δ 2.19 (s, 3H, CH_3), 5.23 (s, 1H, CH), 6.05 (s, 1H, =CH_2), 6.51 (s, 1H, =CH_2), 7.21–7.38 (m, 5Harom).

Acknowledgment

We are grateful to the National Natural Science Foundation of China (Nos. 20472033, 20772058) for generous financial support for our programs.

References

1. (a) Morita, K.; Suzuki, Z.; Hirose, H. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2815; (b) Baylis, A. B.; Hillman, M. E. D. *Ger. Offen.* 2155113; *Chem. Abstr.* **1972**, *77*, 34174g.
2. For reviews of MBH reaction, see: (a) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001; (b) Ciganek, E. *Org. React.* **1997**, *51*, 201; (c) Langer, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 3049; (d) Cai, J. X.; Zhou, Z. H.; Tang, C. C. *Chem. Res. (in Chinese)* **2001**, *12*, 54; (e) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811; (f) Masson, G.; Housseman, C.; Zhu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 4614; Basavaiah, D.; Rao, K. V.; Reddy, R. J. *Chem. Soc. Rev.* **2007**, *36*, 1581.
3. (a) Barrett, A. G. M.; Dozzo, P.; White, A. J. P.; Williams, D. J. *Tetrahedron* **2002**, *58*, 7303; (b) Hayashi, Y.; Tamura, T.; Shoji, M. *Adv. Synth. Catal.* **2004**, *346*, 1106; (c) Iwabuchi, Y.; Hatakeyama, S. *J. Synth. Org. Chem. Jpn.* **2002**, *60*, 1; (d) Shi, M.; Jiang, J. K. *Tetrahedron: Asymmetry* **2002**, *13*, 1941; (e) Krishina, P. R.; Kannan, V.; Reddy, P. V. N. *Adv. Synth. Catal.* **2004**, *346*, 603; (f) Shi, M.; Jiang, J. K.; Li, C. Q. *Tetrahedron Lett.* **2002**, *43*, 127; (g) Imbriglio, J. E.; Vasbinder, M. M.; Miller, S. J. *Org. Lett.* **2003**, *5*, 3741; (h) Yang, K. S.; Lee, W. D.; Pan, J. F.; Chen, K. M. *J. Org. Chem.* **2003**, *68*, 915; (i) Aroyan, C. E.; Vashinder, M. M.; Miller, S. J. *Org. Lett.* **2005**, *7*, 3849; (j) Walsh, L. M.; Winn, C. L.; Goodman, J. M. *Tetrahedron Lett.* **2002**, *43*, 8219; (k) McDougal, N. T.; Trevellini, W. L.; Rodgen, S. A.; Kliman, L. T.; Schaus, S. E. *Adv. Synth. Catal.* **2004**, *346*, 1231; (l) Sohtome, Y.; Tanatani, A.; Hashimoto, Y.; Nagasawa, K. *Tetrahedron Lett.* **2004**, *45*, 5589; (m) McDougal, N. T.; Schaus, S. E. *J. Am. Chem. Soc.* **2003**, *125*, 12094; (n) Nakano, A.; Ushiyama, M.; Iwabuchi, Y.; Hatakeyama, S. *Adv. Synth. Catal.* **2005**, *347*, 1790; (o) Wang, J.; Li, H.; Yu, X.; Zu, L.; Wang, W. *Org. Lett.* **2005**, *7*, 4293; (p) Pereira, S. I.; Adrio, J.; Silva, A. M. S.; Carretero, J. C. *J. Org. Chem.* **2005**, *70*, 10175; (q) Tang, H. Y.; Zhao, G. F.; Zhou, Z. H.; Zhou, Q. L.; Tang, C. C. *Tetrahedron Lett.* **2006**, *47*, 5717; (r) Tang, H. Y.; Gao, P.; Zhao, G. F.; Zhou, Z. H.; He, L. N.; Tang, C. C. *Catal. Commun.* **2007**, 1811; (s) Tang, H. Y.; Zhao, G. F.; Zhou, Z. H.; Gao, P.; He, L. N.; Tang, C. C. *Eur. J. Org. Chem.* **2008**, 126.

4. (a) Perlmutter, P.; Teo, C. C. *Tetrahedron Lett.* **1984**, *25*, 5951; (b) Yamamoto, K.; Takagi, M.; Tsuji, J. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 319; (c) Bertenshaw, S.; Kahn, M. *Tetrahedron Lett.* **1989**, *30*, 2731; (d) Kamimura, A.; Gunjigake, Y.; Mitsudera, H.; Yokeyama, S. *Tetrahedron Lett.* **1998**, *39*, 7323; (e) Richter, H.; Jung, G. *Tetrahedron Lett.* **1998**, *39*, 2729; (f) Shi, M.; Xu, Y. M. *Chem. Commun.* **2001**, 1876; (g) Balan, D.; Adolfsson, H. *J. Org. Chem.* **2001**, *66*, 6498; (h) Balan, D.; Adolfsson, H. *J. Org. Chem.* **2002**, *67*, 2329; (i) Shi, M.; Zhao, G. L. *Tetrahedron Lett.* **2002**, *43*, 4499; (j) Shi, M.; Xu, Y. M. *Eur. J. Org. Chem.* **2002**, 696; (k) Azizi, N.; Saidi, M. R. *Tetrahedron Lett.* **2002**, *43*, 4305; (l) Shi, M.; Xu, Y. M.; Zhao, G. L.; Wu, X. F. *Eur. J. Org. Chem.* **2002**, 3666; (m) Huang, J. W.; Shi, M. *Adv. Synth. Catal.* **2003**, *345*, 953; (n) Shi, M.; Xu, Y. M. *J. Org. Chem.* **2003**, *68*, 4784; (o) Back, T. G.; Rankic, D. A.; Sorbetti, J. M.; Wulff, J. E. *Org. Lett.* **2005**, *7*, 2377; (p) Zhao, G. L.; Shi, M. *J. Org. Chem.* **2005**, *70*, 9975; (q) Shi, Y. L.; Shi, M. *Eur. J. Org. Chem.* **2007**, 2905.
5. (a) Kündig, E. P.; Xu, L.-H.; Schnell, B. *Synlett* **1994**, 413; (b) Shi, M.; Xu, Y. M. *Tetrahedron: Asymmetry* **2002**, *13*, 1195; (c) Aggarwal, V. K.; Castro, A. M. M.; Mereu, A.; Adams, H. *Tetrahedron Lett.* **2002**, *43*, 1577; (d) Genisson, Y.; Massardier, C.; Gautier-Luneau, I.; Greene, A. E. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2869; (e) Shi, M. l.; Xu, Y. M. l. *Angew. Chem., Int. Ed.* **2002**, *41*, 4507; (f) Shi, M.; Chen, L. H. *Chem. Commun.* **2003**, 1310; (g) Kawahara, S.; Nakano, A.; Esumi, T.; Iwabuchi, Y.; Hatakeyama, S. *Org. Lett.* **2003**, *5*, 3103; (h) Balan, D.; Adolfsson, H. *Tetrahedron Lett.* **2003**, *44*, 2521; (i) Shi, M.; Xu, Y. M.; Shi, Y. L. *Chem. Eur. J.* **2005**, *11*, 1794; (j) Matsui, K.; Takizawa, S.; Sasai, H. *J. Am. Chem. Soc.* **2005**, *127*, 3680; (k) Shi, M.; Chen, L. H.; Tang, W. D. *Adv. Synth. Catal.* **2005**, *347*, 1781; (l) Shi, M.; Chen, L. H.; Li, C. Q. *J. Am. Chem. Soc.* **2005**, *127*, 3790; (m) Buskens, P.; Klankermayer, J.; Leitner, W. *J. Am. Chem. Soc.* **2005**, *127*, 16762; (n) Shi, M.; Li, C. Q. *Tetrahedron: Asymmetry* **2005**, *16*, 1385; (o) Raheen, I. T.; Jacobsen, E. N. *Adv. Synth. Catal.* **2005**, *347*, 1701; (p) Matsui, K.; Tanaka, K.; Horii, A.; Takizawa, S.; Sasai, H. *Tetrahedron: Asymmetry* **2006**, *17*, 578; (q) Matsui, K.; Takizawa, S.; Sasai, H. *Synlett* **2006**, 761–765; (r) Liu, Y. H.; Chen, L. H.; Shi, M. *Adv. Synth. Catal.* **2006**, *348*, 973; (s) Ito, K.; Nishida, K.; Gotanda, T. *Tetrahedron Lett.* **2007**, *48*, 6147; (t) Shi, Y. L.; Shi, M. *Adv. Synth. Catal.* **2007**, *349*, 2129; (u) Qi, M. J.; Ai, T.; Shi, M.; Li, G. *Tetrahedron* **2008**, *64*, 1181; (v) Liu, Y. H.; Shi, M. *Adv. Synth. Catal.* **2008**, *350*, 122; (w) Guang, X. Y.; Jiang, Y. Q.; Shi, M. *Eur. J. Org. Chem.* **2008**, 2150.
6. (a) Xu, X. Y.; Wang, C. G.; Zhou, Z. H.; Zeng, Z. B.; Ma, X. P.; Zhao, G. F.; Tang, C. C. *Lett. Org. Chem.* **2006**, *3*, 640; (b) Xu, X. Y.; Wang, C. G.; Zhou, Z. H.; Zeng, Z. B.; Ma, X. P.; Zhao, G. F.; Tang, C. C. *Heteroatom Chem.* **2008**, *19*, 238.
7. Ma, X. P.; Xu, X. Y.; Wang, C. G.; Zhao, G. F.; Zhou, Z. H.; Tang, C. C. *J. Organomet. Chem.* **2007**, *692*, 3685.
8. Xu, X. Y.; Wang, C. G.; Zhou, Z. H.; Tang, X. F.; He, Z. J.; Tang, C. C. *Eur. J. Org. Chem.* **2007**, 4487.
9. Crystal data for enantiomerically pure **8f** $C_{32}H_{23}F_3NO_3PS{\cdot}CH_2Cl_2$ (674.47), orthorhombic, space group $P2_12_12_1$, $a = 8.0179(3)$, $b = 10.2679(4)$, $c = 37.4726(13)$ Å, $V = 3085.0(2)$ Å^3, $Z = 4$, specimen, $0.22 \times 0.20 \times 0.18$ mm^3, $T = 113(2)$ K, Rigaku Saturn CCD area detector, absorption coefficient 0.384 mm^{-1}, reflections collected/unique 27,246/7338 [$R_{int} = 0.0455$], refinement by full-matrix least-squares on F^2, data/restraints/parameters 7338/100/423, Goodness-of-fit on $F^2 = 1.045$, final R indices [$I > 2\sigma(I)$] $R_1 = 0.0420$, $wR_2 = 0.0930$, R indices (all data) $R_1 = 0.0459$, $wR_2 = 0.0954$, absolute structure parameter $-0.05(5)$, largest difference in peak and hole 0.361 and -0.385 e Å^{-3}.