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A Novel Selective Aza-Morita–Baylis–Hillman (aza-MBH) Domino Reaction and Aza-MBH Reaction of N-Sulfonated Imines with Acrolein Catalyzed by a Bifunctional Phosphine Organocatalyst

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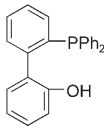
A practical and efficient construction of highly functionalized and diversified molecules from simple starting materials is highly desirable and remains a great challenge. The domino process is a very appealing strategy as it favors the formation of complex molecules starting from readily available substrates in two or more steps without isolation of intermediates.[1] These reactions avoid time-consuming and costly processes, including the purification of intermediates and steps involving the protection and deprotection of functional groups, and they are environmental friendly and often proceed with excellent stereoselectivities.[2] Thus, considerable efforts have been made to develop catalytic domino transformations catalyzed by an organocatalyst,[3] one of the most successful class of organocatalysts used for this purpose are secondary amines and usually initiated reactions are Michael additions.[3] Although, significant advances have been made in the development of two-step domino reactions,[4] the development of a new catalyst for a new domino reaction and a multicomponent three-step domino reaction proved to be a challenging task, especially since such processes are rare.[5,6] To the best of our knowledge, a domino sequence starting with aza-Morita–Baylis–Hillman (aza-MBH) reaction, followed by an intermolecular Michael addition and aldol/dehydration reaction has not been reported so far.[7] Herein, we report for the first time a novel selective aza-MBH domino reaction and aza-MBH reaction of N-sulfonated imines with acrolein catalyzed by a bifunctional phosphine organocatalyst.

The Baylis–Hillman reaction, first reported in 1972 by Baylis and Hillman, is an important carbon–carbon bond-forming process that affords densely functionalized products.[8] However, this reaction has traditionally suffered from low reaction rates and limited substrate scopes. Recently, Chong and Shi reported that octanol and *p*-nitrophenol can accelerate Baylis–Hillman reaction, respectively.[9] Sasai and Shi also reported several bifunctional organocatalysts, which can efficiently catalyze the aza-MBH reaction.[10] This promoted us to search for an easy synthesis and high efficient bifunctional phosphine organocatalyst for the aza-MBH reactions. (2′-Hydroxy-biphenyl-2-yl)-diphenylphosphane (see below) was first reported in 1994 by Takaya and co-workers.[11] It can also be easily prepared in high yields from 2-phenylphenol and usually applied to Rh-catalyzed hydrogenation and hydroformylation reactions.[12] Although, it incorporates a basic and an acidic moiety in one molecule and can be used as a Lewis base–Brønsted acid (LBBA) bifunctional organocatalyst, there have been no reports on its utility as a bifunctional organocatalyst to catalyze the aza-MBH reaction thus far. On the other hand, acrolein, different from methyl vinyl ketones and methyl acrylate, is an interesting and more activated Michael acceptor, which is rarely used as the conjugated carbonyl substrate in Baylis–Hillman reaction, clearly because of its propensity to form oligomers or polymers under the basic catalysis employed.[13] Recently, more and more reports are available on the aza-MBH reaction using acrolein as Michael acceptor.[14] So, it is very important to study the aza-MBH reaction using acrolein as Michael acceptor catalyzed by bifunctional organocatalysts (LBBA).



LBBA

We first studied the reaction of *N*-(2-chlorobenzylidene)-4-methylbenzenesulfonamide (**1a**) with acrolein (1.5 equiv) in the presence of 20 mol% LBBA in THF at room temperature. As indicated by TLC, the reaction proceeded smoothly. One hour later, **1a** disappeared and a new compound was obtained in high yield (90%) (Scheme 1i). The product was characterized by ^{1}H NMR and ^{13}C NMR spectroscopy

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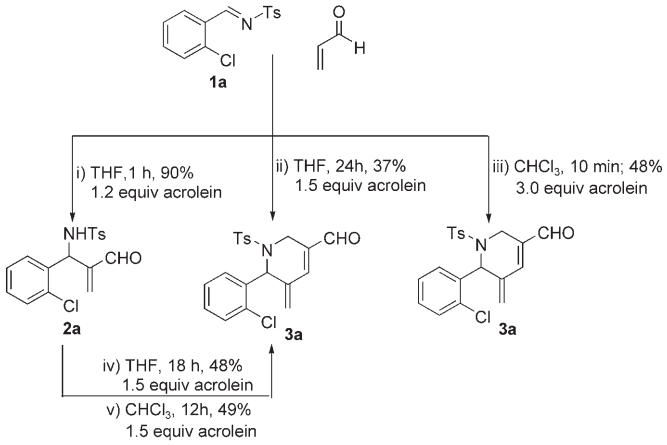
as a normal aza-MBH product **2a**. To our delight, when the reaction time was extended, according to TLC, **2a** was slowly reduced and another new product was formed (Scheme 1ii). After 24 h, unfortunately only 37% yield of



Scheme 1. i) LBBA (20% mol), THF, 1 h; ii) LBBA (20% mol), THF, 24 h; iii) LBBA (20% mol), $CHCl_3$, 10 min; iv) LBBA (20% mol), THF, 18 h; v) LBBA (20% mol), $CHCl_3$, 12 h.

the new product was isolated. The new product was also characterized by ^1H NMR and ^{13}C NMR spectra. There are two doublets ($J = 19$ Hz) at δ 3.33 and 4.43 ppm in the ^1H NMR and one peak at δ 38.20 ppm in the ^{13}C NMR spectrum (see supporting information). These NMR spectral data indicate that the new product is not the regular aza-MBH reaction product. Further confirmation of the structure of this new product was obtained by X-ray diffraction measurements. The ORTEP diagram is shown in Figure 1.[15] A tetrahydropyridine derivative **3a** was formed.

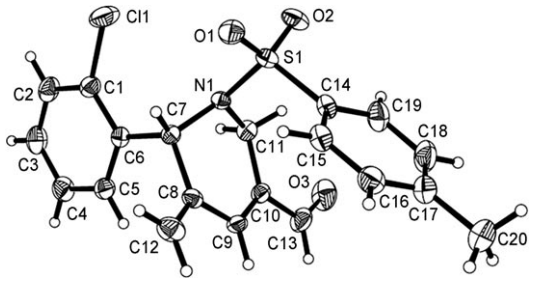
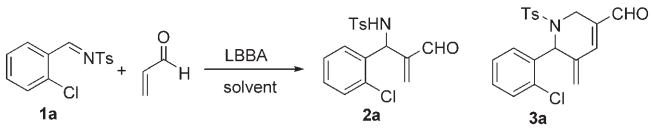


Figure 1. X-ray structure of **3a**.

With these results at hand, we next examined how to control this reaction to selectively form different products. Thus, we have studied the solvent effect, the results are shown in the Table 1. When THF was used as the solvent, the reaction is finished in one hour to give aza-MBH product **2a** in high yields using 1.2 equiv acrolein (entry 1), if the reaction time was prolonged. The aza-MBH domino reaction product was obtained in the almost same yields (entries 2,3) whether the ratio of the substrates was 1:1.5 or 1:3. When the reaction was carried out in a more polar solvent such as DMF, the aza-MBH product **2a** was obtained in 70% yield within 10 min (entry 4). In less polar solvents such as CH_3CN, CH_2Cl_2, $CHCl_3$ (entries 5, 6, 7), all reactions exclusively gave the aza-MBH domino reaction product **3a** in a short reaction time (10 min); also no aza-MBH product **2a** was found. The highest yield of **3a** was obtained in $CHCl_3$. Therefore, $CHCl_3$ was selected as the best solvent for the aza-MBH domino reaction product **3a** (Scheme 1iii) and THF was used as the best solvent for the aza-MBH reaction product **2a** (Scheme 1i). Although the exact reason for the solvent effect is not known (THF or DMF), it can be assumed that the oxygen atom of the solvent could stabilize the reaction intermediate anion by a hydrogen bond, and then the intermediate can easily be converted to the aza-MBH product **2a**. However, when the reaction was carried out in solvents such as CH_3CN, CH_2Cl_2, $CHCl_3$, the reaction intermediate can not be stabilized by a hydrogen bond, so that the intermediate has a high reactivity and yields the aza-MBH domino reaction product **3a**.

Table 1. LBBA-catalyzed domino reaction and aza-MBH reaction of **1a** and acrolein.[a]

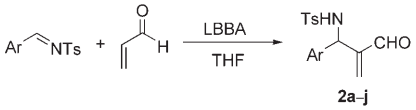


Entry	Solvent	t [min]	Product[b]	
			Yield [%] **2a**	Yield [%] **3a**
1[c]	THF	60	90	0
2[d]	THF	24 h	0	37
3[e]	THF	24 h	0	38
4[e]	DMF	10	70	0
5[e]	CH_3CN	10	0	31
6[e]	CH_2Cl_2	10	0	42
7[e]	$CHCl_3$	10	0	48

[a] All reactions were performed on a 0.5 mmol scale with LBBA (20 mol%) as the catalyst with the use of 2 mL of solvent. [b] Product isolated by flash chromatography. [c] 1.2 equiv of acrolein were used. [d] 1.5 equiv of acrolein were used. [e] 3.0 equiv of acrolein were used.

Under identical conditions for **2a** and **3a**, we then examined a range of N-sulfonated imines **1** to explore the generality of this novel catalyst (LBBA) for the aza-MBH reaction and the domino reaction. The results are summarized in Tables 2 and 3. As can be seen in Table 2, it was observed that all reactions proceeded smoothly in THF under the mild conditions to afford the corresponding aza-MBH reaction products **2** in high yields. The results exhibited the scope with respect to a range of N-sulfonated imines substituted with both electron-donating (Table 2, entry 8) and electron-withdrawing (Table 2, except entry 8) groups to afford the desired aza-MBH products in excellent yields in a short time. From Table 3, the one-pot three component domino reaction of N-sulfonated imines with acrolein can also be catalyzed by the bifunctional organocatalyst (LBBA) efficiently in $CHCl_3$. In these reactions, a range of N-sulfonated imines react with acrolein by way of a cata-

Table 2. LBBA-catalyzed aza-MBH reaction.

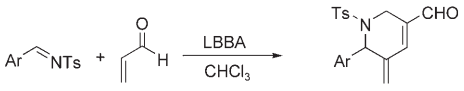


2a–j

Entry	Ar	Compound	t [h]	Yield **2** [%][a,b]
1	2-ClC_6H_4	**1a**	1	90 (**2a**)
2	3-ClC_6H_4	**1b**	1	85 (**2b**)
3	4-ClC_6H_4	**1c**	1	88 (**2c**)
4	2,4-$Cl_2C_6H_3$	**1d**	1	80 (**2d**)
5	4-$NO_2C_6H_4$	**1e**	0.5	95 (**2e**)
6	3-$NO_2C_6H_4$	**1f**	0.5	92 (**2f**)
7	4-BrC_6H_4	**1g**	1	91 (**2g**)
8	4-$CH_3C_6H_4$	**1h**	1.5	86 (**2h**)
9	4-FC_6H_4	**1i**	1	80 (**2i**)
10	C_6H_5-CH=CH	**1j**	1	85 (**2j**)

[a] Isolated yields. [b] 1.2 equiv of acrolein were used.

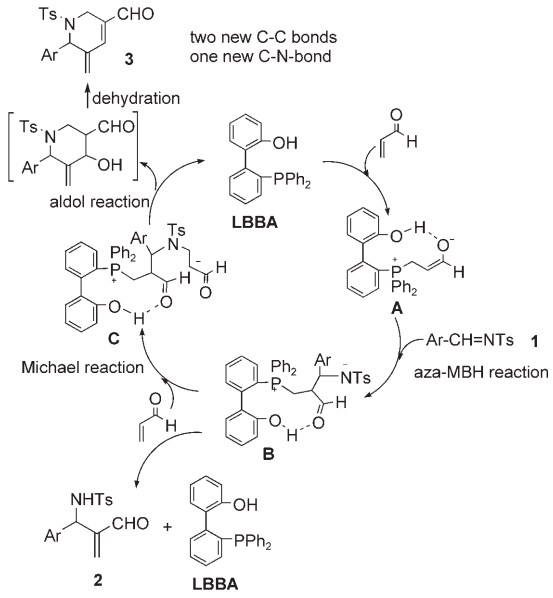
Table 3. LBBA-catalyzed domino reaction.



3a–j

Entry	Ar	Compound	t [min]	Yield **3** [%][a,b]
1	2-ClC_6H_4	**1a**	10	48 (**3a**)
2	3-ClC_6H_4	**1b**	10	45 (**3b**)
3	4-ClC_6H_4	**1c**	10	50 (**3c**)
4	2,4-$Cl_2C_6H_3$	**1d**	10	50 (**3d**)
5	4-$NO_2C_6H_4$	**1e**	5	49 (**3e**)
6	3-$NO_2C_6H_4$	**1f**	5	46 (**3f**)
7	4-BrC_6H_4	**1g**	10	48 (**3g**)
8	4-$CH_3C_6H_4$	**1h**	15	50 (**3h**)
9	4-FC_6H_4	**1i**	10	46 (**3i**)
10	C_6H_5-CH=CH	**1j**	10	41 (**3j**)

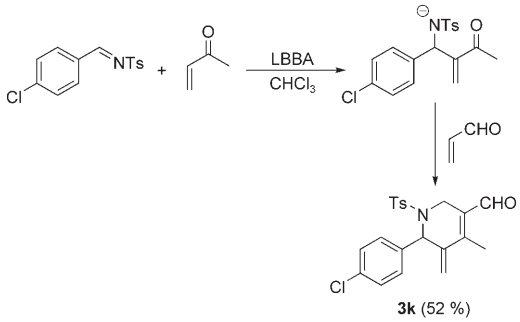
[a] Isolated yields [b] 3.0 equiv of acrolein were used.



Scheme 2. Proposed catalytic cycle of the domino reactions and aza-MBH reaction.

lyzed aza-MBH/Michael/aldol/dehydration domino sequence affording the tetrahydropyridine derivatives with good yields (41–50%). Moreover, one new C–C bond, one C–N bond and one new C=C bond were formed under mild and rapid reaction conditions. This methodology provides a new protocol for the construction of a variety of tetrahydropyridine derivatives with different substituents.

To extend the scope of this reaction, cross aza-MBH domino reactions of two different Michael acceptors were investigated (Scheme 3). The aza-MBH reaction of **1a** with methyl vinyl ketone (MVK) (1.2 mmol) catalyzed by LBBA in $CHCl_3$ was performed at room temperature for one hour; after **1a** had disappeared and a new product had formed acrolein (1.5 equiv) was added to the reaction mixture. After 12 h, the reaction was finished and the new aza-MBH domino reaction product **3k** was obtained in 52% yield. This reaction demonstrates the potential utility of this novel domino reaction for the efficient synthesis of other tetrahydropyridine derivatives.



Scheme 3. The LBBA catalyzed cross aza-MBH domino reaction.

In order to obtain more information for the study of the aza-MBH domino reaction, we first carried out the ^{31}P NMR spectroscopic measurements of the bifunctional catalyst LBBA in the absence and presence of acrolein in $CDCl_3$ and $[D_8]$THF, respectively, The ^{31}P NMR spectra of LBBA showed a signal at δ −12.98 ($CDCl_3$) and −47.32 ppm ($[D_8]$THF), but the ^{31}P NMR spectra of LBBA and acrolein (molar ratio = 1:8) gave a new signal at δ +32.03 ($CDCl_3$) and −5.52 ppm ($[D_8]$THF), which appears to correspond to the phosphonium enolate **A** (Scheme 2). The difference in the ^{31}P NMR spectrum for $CHCl_3$ and THF indicated that intermediate **A** may have a different reactivity, and yields product **2** and **3**. Secondly, the reaction of **2b** with acrolein (1.5 equiv) in the presence of 20 mol% LBBA in THF and $CHCl_3$ at room temperature was carried out (Scheme 1iv, v). As indicated by TLC, after 18 h, the tetrahydropyridine derivative **3b** was obtained in 48% yield in THF(Scheme 1iv). A similar result was obtained with 49% yield in $CHCl_3$ after 12 h. On the base of these results, though in contrast to the literature,[10b] a proposed mechanism for the domino reaction and the aza-MBH reaction is shown in Scheme 2, in which LBBA acts as a bifunctional catalyst in this reaction. The phosphine acts as a Lewis base

and the phenolic OH group acts as a Brønsted acid.[10b] In the first step, LBBA reacts with acrolein to produce intermediate **A**; the OH group is utilized to stabilize the intermediate **A** through hydrogen bonding. The following Michael addition of **A** with N-sulfonated imine gives intermediate **B**, when THF is used as the solvent. Elimination of the catalyst LBBA from **B** gave aza-MBH product **2**. However, in the case of $CHCl_3$ as the solvent, intermediate **B** did not stop at this step to give the aza-MBH product **2**, but continued to react rapidly with another acrolein, which undergoes an intermolecular Michael addition to give another zwitterionic intermediate **C**. In the subsequent third step, the intermediate **C** undergoes an intramolecular aldol condensation and dehydration to regenerate catalyst LBBA to give the tetrahydropyridine derivative **3**.

In conclusion, we have developed an efficient, bifunctional phosphine organocatalyst catalyzed aza-MBH reaction and aza-MBH domino reaction between N-sulfonated imines and acrolein under mild conditions in moderate to excellent yields. The aza-MBH/Michael/aldol/dehydrate domino reaction also provides an efficient method to synthesise tetrahydropyridine derivatives which can be used as building blocks in organic synthesis. Further investigations are underway to expand the scope and application of the bifunctional phosphine organocatalyst LBBA and this new efficient domino process.

Experimental Section

General procedure of aza-MBH domino reaction for synthesis the tetrahydropyridine derivatives: Acrolein (1.5 mmol) was added to a solution of *N*-(2-chlorobenzylidene)-4-methylbenzenesulfonamide (0.5 mmol) and catalyst LBBA (0.1 mmol) in $CHCl_3$ (2 mL). The stirring was maintained at room temperature until completion of the reaction (the reaction was monitored by TLC plate). The residue was purified by a flash column chromatography to yield **3a** as a colorless solid.

General procedure for the aza-MBH reaction: Acrolein (0.6 mmol) was added to a solution of *N*-(2-chlorobenzylidene)-4-methylbenzenesulfonamide (0.5 mmol) and catalyst **LBBA** (0.1 mmol) in THF (2 mL) at room temperature. The reaction mixture was monitored by TLC plate. After 1 h, the residue was purified by a flash column chromatography to yield **2a** as a colorless solid.

Acknowledgements

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Keywords: aldol reaction · domino reactions · Michael reaction · Morita–Baylis–Hillman reaction · organocatalysis

[1] For reviews, see a) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115; b) L. F. Tietze, U. Beifuss, *Angew. Chem.* **1993**, *105*, 137; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 131; c) L. F. Tietze, G. Brasche, K. Gericke, Domino Reactions in Organic Synthesis, Wiley-VCH, Weinheim, **2006**; d) H.-C. Guo, J.-A. Ma, *Angew. Chem.* **2006**, *118*, 362; *Angew. Chem. Int. Ed.* **2006**, *45*, 354.

[2] D. Enders, M. R. M. Huttl, C. Grondal, G. Raabe, *Nature* **2006**, *441*, 861.

[3] For recent reviews on organocatalytic domino reactions, see for example: D. Enders, C. Grondal, M. R. M. Hüttl, *Angew. Chem.* **2007**, *119*, 1590; *Angew. Chem. Int. Ed.* **2007**, *46*, 1570.

[4] For recent examples of two step domino reaction see: a) S. Cabrera, J. Aleman, P. Bolze, S. Bertelsen, K. A. Jørgensen, *Angew. Chem.* **2008**, *120*, 127; *Angew. Chem. Int. Ed.* **2008**, *47*, 121; b) J. Xie, W. Chen, R. Li, M. Zeng, W. Du, L. Yue, Y. Chen, Y. Wu, J. Zhu, J. Deng, *Angew. Chem.* **2007**, *119*, 393; *Angew. Chem. Int. Ed.* **2007**, *46*, 389; c) G.-L. Zhao, J. Vesely, R. Rios, I. Ibrahem, H. Sunden, A. Cordova, *Adv. Synth. Catal.* **2008**, *350*, 237; d) M. Marigo, T. Schulte, J. Franzen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2007**, *129*, 15710; e) H. Li, J. Wang, H. Xie, L. Zu, W. Jiang, E. N. Duesler, W. Wang, *Org. Lett.* **2007**, *9*, 965; f) J. Wang, H. Li, H. Xie, L. Zu, X. Shen, W. Wang, *Angew. Chem.* **2007**, *119*, 9208; *Angew. Chem. Int. Ed.* **2007**, *46*, 9050; g) M. Marigo, S. Bertelsen, A. Landa, K. A. Jørgensen, *J. Am. Chem. Soc.* **2006**, *128*, 5475; h) S. Brandau, E. Maerten, K. A. Jørgensen, *J. Am. Chem. Soc.* **2006**, *128*, 14986; i) H. Xie, L. Zu, H. Li, J. Wang, W. Wang, *J. Am. Chem. Soc.* **2007**, *129*, 10886; j) H. Li, L. Zu, H. Xie, J. Wang, W. Jiang, W. Wang, *Org. Lett.* **2007**, *9*, 1833; k) D. Enders, A. A. Narine, T. R. Benninghaus, G. Raabe, *Synlett* **2007**, 1667; l) J. Zhou, B. List, *Synlett* **2007**, 2037; m) J. Zhou, B. List, *J. Am. Chem. Soc.* **2007**, *129*, 7498; n) R. Rios, J. Vesely, H. Sunden, I. Ibrahem, G.-L. Zhao, A. Cordova, *Tetrahedron Lett.* **2007**, *48*, 5835; o) H. Sunden, I. Ibrahem, G.-L. Zhao, L. Eriksson, A. Cordova, *Chem. Eur. J.* **2007**, *13*, 574; p) H. Sunden, R. Rios, I. Ibrahem, G.-L. Zhao, L. Eriksson, A. Cordova, *Adv. Synth. Catal.* **2007**, *349*, 827; q) Y. Hayashi, T. Okano, S. Aratake, D. Hazelard, *Angew. Chem.* **2007**, *119*, 5010; *Angew. Chem. Int. Ed.* **2007**, *46*, 4922.

[5] For selected examples of three step domino reaction see: a) Y. Huang, A. M. Walji, C. H. Larsen, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 15051; b) D. Enders, M. R. M. Huttl, G. Raabe, J. W. Bats, *Adv. Synth. Catal.* **2008**, *350*, 267; c) D. Enders, M. R. M. Huttl, J. Runsink, G. Raabe, B. Wendt, *Angew. Chem.* **2007**, *119*, 471; *Angew. Chem. Int. Ed.* **2007**, *46*, 467; d) H. Jiang, J. B Nielsen, M. Nielsen, K. A. Jørgensen, *Chem. Eur. J.* **2007**, *13*, 9068; e) A. Carlone, S. Cabrera, M. Marigo, K. A. Jørgensen, *Angew. Chem.* **2007**, *119*, 1119; *Angew. Chem. Int. Ed.* **2007**, *46*, 1101.

[6] For selected examples of Brøsted acid catalyzed domino reactions see: a) Y. Hoashi, T. Yabuta, Y. Takemoto, *Tetrahedron Lett.* **2004**, *45*, 9185; Y. Hoashi, T. Yabuta, P. Yuan, H. Miyabe, Y. Takemoto, *Tetrahedron* **2006**, *62*, 365; b) M. Rueping, A. P. Antonchick, T. Theissmann, *Angew. Chem.* **2006**, *118*, 3765; *Angew. Chem. Int. Ed.* **2006**, *45*, 3683; c) J. W. Yang, M. T. Hechavarria Fonseca, N. Vignola, B. List, *Angew. Chem.* **2005**, *117*, 110; *Angew. Chem. Int. Ed.* **2005**, *44*, 108; d) R. I. Storer, D. E. Carrera, Y. Ni, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2006**, *128*, 84.

[7] a) M. J. Lee, D. Y. Park, K. Y. Lee, J. N. Kim, *Tetrahedron Lett.* **2006**, *47*, 1833; b) W. Wang M. Yu, *Tetrahedron Lett.* **2004**, *45*, 7141; c) S. Mix, S. Blechert, *Org. Lett.* **2005**, *7*, 2015.

[8] For recent reviews on the Morita-Baylis–Hillman reaction, see a) Y.-L. Shi, M. Shi, *Eur. J. Org. Chem.* **2007**, 2905; b) D. Basavaiah, K. V. Rao, R. J. Reddy, *Chem. Soc. Rev.* **2007**, *36*, 1581; c) G. Masson, C. Housseman, J. Zhu, *Angew. Chem.* **2007**, *119*, 4698; *Angew. Chem. Int. Ed.* **2007**, *46*, 4614; d) D. Basavaiah, A. J. Rao, T. Satyanarayana, *Chem. Rev.* **2003**, *103*, 811; e) P. Langer, *Angew. Chem.* **2000**, *112*, 3177; *Angew. Chem. Int. Ed.* **2000**, *39*, 3049.

[9] a) K. S. Park, J. Kim, H. Choo, Y. Chong, *Synlett* **2007**, 395; b) M. Shi, Y. H. Liu, *Org. Biomol. Chem.* **2006**, *4*, 1468.

[10] a) K. Matsui, S. Takizawa, H. Sasai, *Synlett* **2006**, 761; b) M. Shi, L. H. Chen, C. Q. Li, *J. Am. Chem. Soc.* **2005**, *127*, 3790.

[11] T. Higashizima, N. Sakai, K. Nozaki, H. Takaya, *Tetrahedron Lett.* **1994**, *35*, 2023.

[12] G. Keglevich, A. Kerenyi, H. Szelke, L. Krisztina, T. Kortvelyesi, *J. Organomet. Chem.* **2006**, *691*, 5038.

[13] G. M. Strunz, R. Bethell, G. Samplson, P. White, *Can. J. Chem.* **1995**, *73*, 1666.
[14] a) Y. H. Liu, L. H. Chen, M. Shi, *Adv. Synth. Catal.* **2006**, *348*, 973; b) K. Matsui, K. Tanaka, A. Horii, S. Takizawa, H. Sasai, *Tetrahedron: Asymmetry* **2006**, *17*, 578; c) M. Shi, L. H. Chen, *Pure Appl. Chem.* **2005**, *77*, 2105; d) M. V. R. Reddy, M. T. Rudd, P. V. Ramachandran, *J. Org. Chem.* **2002**, *67*, 5382.
[15] CCDC 656007 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

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