ChemComm

Cite this: *Chem. Commun.*, 2011, **47**, 9227–9229

www.rsc.org/chemcomm

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A bifunctional spiro-type organocatalyst with high enantiocontrol: application to the aza-Morita–Baylis–Hillman reactions†

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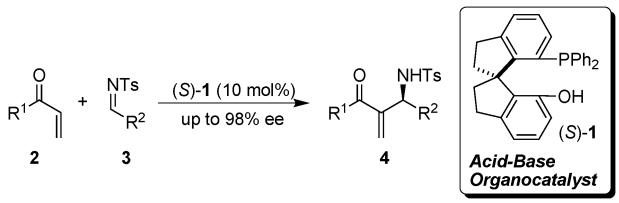
Received 12th May 2011, Accepted 4th July 2011
DOI: 10.1039/c1cc12784e

A unique spiro-type Brønsted acid–Lewis base organocatalyst has been developed. The new bifunctional organocatalyst promoted aza-Morita–Baylis–Hillman reactions to yield adducts with up to 98% ee.

Enantioselective organocatalysis has been recognized as an environmentally benign and practical methodology for asymmetric synthesis.[1] With organocatalysts, metal contamination of products does not occur because these catalysts contain no toxic or expensive metals. So far, numerous enantioselective organocatalysts derived from chiral natural products and chiral BINOL derivatives have been prepared and applied in various asymmetric reactions.[2] Over a decade, we have studied the design and synthesis of chiral spiro compounds that can be used either as ligands or catalysts.[3] As a continuation of our study, this communication investigates the first spiro-type organocatalyst with Brønsted acid and Lewis base units (**1**) for the enantioselective aza-Morita–Baylis–Hillman (aza-MBH) reaction (Scheme 1). Spiro organocatalyst **1** exhibited high asymmetric induction yielding adduct **4** with up to 98% ee.

The aza-MBH reaction of an electron-deficient alkene with an imine promoted by Lewis base catalysts, such as nucleophilic amines or phosphines, is recognized as one of the most useful and atom-economical carbon–carbon bond-forming reactions.[4] The aza-MBH adducts are highly functionalized allylic amines, which are valuable building blocks for medicinal chemistry.[5] We previously developed (*S*)-3-(*N*-isopropyl-*N*-3-pyridinylaminomethyl)BINOL[6a,b,d,e] and (*S*)-3-[2-(diphenylphosphino)phenyl]BINOL[6c,d] as the Brønsted acid–Lewis base organocatalysts for the aza-MBH reaction. In these catalyses, the acid–base moieties act cooperatively to activate substrates (enones and *N*-tosylimines), thus facilitating a carbon–carbon bond-forming reaction that occurs with high enantioselectivity. Owing to our interest in the development of novel acid–base organocatalysts, we focused on 1,1-spirobiindane as a potential platform for these bifunctional organocatalysts.[7] Although the 1,1-spirobiindane backbone is well-established in metal catalysis,[8] spiro organocatalysts containing the Brønsted acid and Lewis base units have not yet been reported.

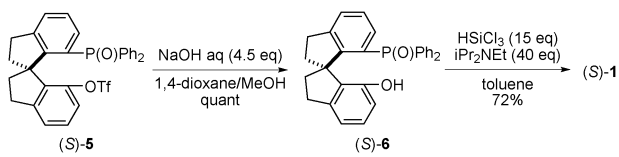


Scheme 1 Spiro-type acid–base organocatalyst (*S*)-**1** for the aza-MBH reaction.

As shown in Scheme 2, the synthesis of spiro-type organocatalyst **1** was achieved in 72% overall yield after two simple steps starting from the known compound (*S*)-**5**.[8a] To confirm the catalytic activity of organocatalyst **1**, we studied the effects of solvent and temperature on the reaction of methyl vinyl ketone (**2a**) with *p*-chlorophenyl *N*-tosylimine (**3a**) (Table 1). We found that the solvent effects were critical to accelerate the reaction (entries 1–4). The addition of 3 Å molecular sieves (MS 3 Å) was beneficial to suppress the decomposition of moisture-sensitive *N*-tosylimines (**3a**, entries 5 and 6). Lowering the reaction temperature improved enantioselectivity and the ee value of **4a** reached 91% (entry 8).

Furthermore, using chloroform at −10 °C with MS 3 Å afforded the best outcome; **4a** was obtained in 86% yield with 92% ee (Table 2, entry 1). Under the optimal conditions as shown in Table 2, organocatalyst **1** promoted the aza-MBH reaction with high enantioselectivities for various substituted phenyl *N*-tosylimines with **2a**. 2-Naphthyl tosylimine (**3m**) was also found to be a suitable substrate (entry 13). The reaction of ethyl vinyl ketone (**2b**) afforded the corresponding adduct **4n** with excellent enantioselectivity (entry 14).

Shi *et al.* reported that (*R*)-2′-(diphenylphosphino)-1,1′-binaphthyl-2-ol (**7**)[9] functioned as an acid–base organocatalyst for the aza-MBH reaction. Interestingly, in almost all cases, spiro-type organocatalyst **1** yielded **4** with enantioselectivities



Scheme 2 Synthesis of (*S*)-**1**.

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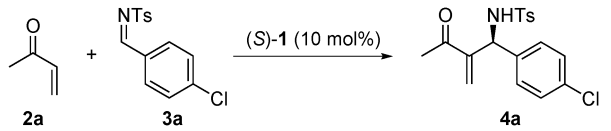
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c1cc12784e

Table 1 Optimization of the reaction conditions[a]

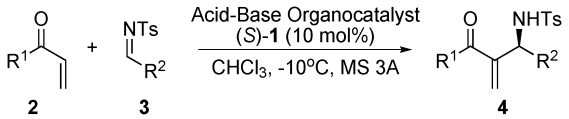


2a 3a 4a

Entry	Solvent	Temp/°C	Time/days	Additive	Yield[b] (%)	ee[c] (%)
1[d]	THF	Rt	3	—	2	—
2[d]	Et_2O	Rt	3	—	Trace	—
3[d]	Toluene	Rt	3	—	18	—
4[d]	CH_2Cl_2	Rt	1	—	27	—
5	CH_2Cl_2	0	4	—	49	81
6	CH_2Cl_2	0	4	MS 3 Å	91	89
7	CH_2Cl_2	−5	4	MS 3 Å	82	90
8	CH_2Cl_2	−10	4	MS 3 Å	75	91

[a] 3 eq. of **2a** were used. [b] Isolated yield. [c] Determined by HPLC (Daicel Chiralpak AS). [d] *Rac*-**1** was used.

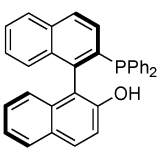
Table 2 Substrate scope of the aza-MBH reaction[a]



2 3 4

Entry	3: R^1	4: R^2	Time/days	Yield[b] (%)	ee[c,d] (%)
1	Me (**2a**)	4-Cl-C_6H_4 (**3a**)	4	**4a**, 86	92 (94)
2	**2a**	3-Cl-C_6H_4 (**3b**)	9	**4b**, 86	93 (88)
3	**2a**	2-Cl-C_6H_4 (**3c**)	8	**4c**, 72	95 (61)
4	**2a**	4-Br-C_6H_4 (**3d**)	9	**4d**, 83	94 (83)
5	**2a**	4-F-C_6H_4 (**3e**)	6	**4e**, 79	87 (81)
6	**2a**	4-CN-C_6H_4 (**3f**)	5	**4f**, 99	90 (—)
7	**2a**	3-CN-C_6H_4 (**3g**)	4	**4g**, 97	93 (—)
8	**2a**	2-CN-C_6H_4 (**3h**)	4	**4h**, 92	97 (—)
9	**2a**	4-NO_2-C_6H_4 (**3i**)	5	**4i**, 97	96 (94)
10	**2a**	3-NO_2-C_6H_4 (**3j**)	4.5	**4j**, 94	94 (90)
11	**2a**	2-NO_2-C_6H_4 (**3k**)	6	**4k**, 91	93 (84)
12	**2a**	Ph (**3l**)	8	**4l**, 95[e]	88 (83)
13	**2a**	2-Naphthyl (**3m**)	9	**4m**, 94[e]	85 (—)
14	Et (**2b**)	**3i**	7	**4n**, 73	98 (88)

[a] 3 eq. of **2** were used. [b] Isolated yield. [c] Determined by HPLC (Daicel Chiralpak AS for **4a** and **4k**; Daicel Chiralpak AD-H for **4b–j** and **4l–n**). [d] Values in parentheses are results obtained using catalyst **7**.[9] [e] 20 mol% of (*R*)-**1** was used.



Shi's catalyst (**7**)

higher than those achieved using catalyst **7** (Table 2, ee values in parentheses). A spiro organocatalyst would provide a geometrically distinct and more rigid chiral pocket than its BINOL-derived counterpart. The rigid spiro catalyst backbone could reduce the conformational flexibility in the transition state for the catalyzed reactions resulting in the formation of the aza-MBH adducts with excellent enantioselectivities.[3b]

In summary, we have developed a new spiro-type organocatalyst with the Brønsted acid and Lewis base units for the enantioselective aza-MBH reaction. Spiro organocatalyst **1** was found to show high asymmetric induction to yield products with up to 98% ee. Further investigations to expand the reaction scope and application in organic synthesis are currently underway.

This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan. We thank the technical staff of the ISIR Comprehensive Analysis Center at Osaka University.

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