Synlett H.-L. Cui et al. Letter

Asymmetric [3+2] Cycloaddition of Olefins with Morita–Baylis–Hillman Carbonates Catalyzed by BINOL-Based Bifunctional Phosphine

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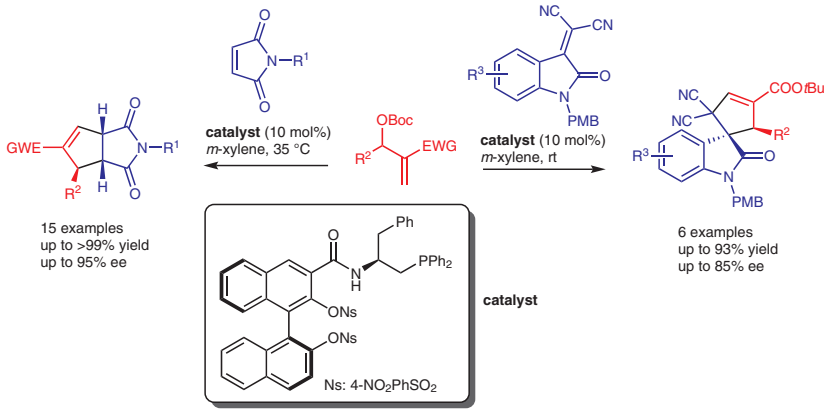

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Abstract We have developed a series of novel BINOL-based phosphines. These bifunctional organocatalysts can be used in the [3+2] cycloaddition of electron-deficient olefins and Morita–Baylis–Hillman (MBH) carbonates. Moderate to excellent yields (up to >99%) and good to excellent enantioselectivities (up to 95% ee) can be obtained in the cycloaddition reaction of maleimides and MBH carbonates. The application of these novel phosphines can be further extended to the asymmetric synthesis of chiral spirooxindoles (up to 85% ee). The results in this study indicate that the BINOL moiety plays an important role in stereocontrol.

Key words BINOL, phosphine, organocatalyst, Morita–Baylis–Hillman derivative, cycloaddition

The past few years have witnessed great progress in the field of phosphine catalysis. A range of powerful phosphine catalysts have been designed and thus a large number of elegant asymmetric reactions have been disclosed.[1] Consequently, on the basis of these developments, easy constructions of structurally diversified chiral molecules have been realized. Accordingly, increasing attention has been paid to the design and application of novel phosphine-based organocatalysts. Bifunctional organocatalysts as a combination of functional units enable two activation modes that could activate both nucleophile and electrophile in the catalytic system synergistically, thus providing enantioenriched molecules efficiently.[2] Recently, several research groups have made intensive efforts to design bifunctional phosphine catalysts.[3–9] For example, Shi and co-workers disclosed their achievements on the design of bifunctional phosphines based on the combination of Lewis base and Brønsted acid. These BINOL-derived catalysts have been used widely in asymmetric aza-Morita–Baylis–Hillman (MBH) reactions and the transformations of MBH derivatives.[3a–e] Later, Sasai and Ito independently reported their studies on the development of BINOL-based chiral phosphines.[3f,3g] These new bifunctional phosphines were found to be efficient catalysts that enabled aza-MBH reactions to proceed with high levels of enantiocontrol. In 2007, the Miller group reported an asymmetric version of Lu's [3+2] cycloaddition of allenoate esters and enones mediated by an α-amino acid based multifunctional phosphine.[4] Jacobsen et al. have prepared a new family of phosphinothiourea catalysts for the enantioselective imine-allene [3+2] cycloaddition, affording substituted 2-aryl-2,5-dihydropyrroles.[5] Zhao and co-workers developed simple bifunctional N-acyl aminophosphines that could efficiently promote the asymmetric [3+2] cycloaddition of allenoates and activated olefins.[6] The Lu group has designed a variety of amino acid-based phosphines and many attractive methodologies have been developed based on these novel phosphines.[7] Notably, the dipeptidic backbone-derived phosphine catalysts have shown a fascinating capacity to provide stereochemical control in a wide range of asymmetric reactions. Zhang and co-workers reported a ferrocene-derived bifunctional phosphine-catalyzed asymmetric [4+2] cycloaddition of allenones and enones.[8] These novel catalysts have significantly broadened the application scope of phosphines as organocatalysts in the field of organic synthesis. As a result of these achievements, various new methodologies and complex chiral molecules of great importance have been created.

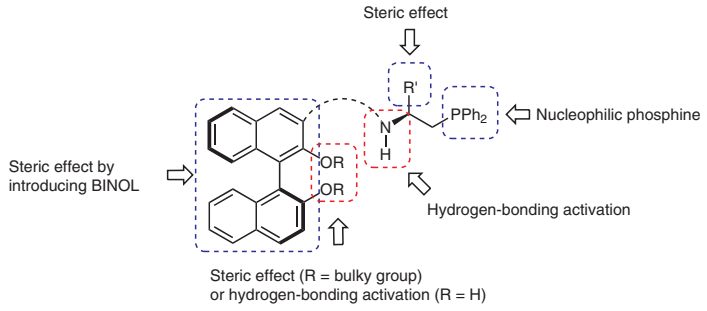


Figure 1 Our design for the BINOL-based bifunctional phosphine

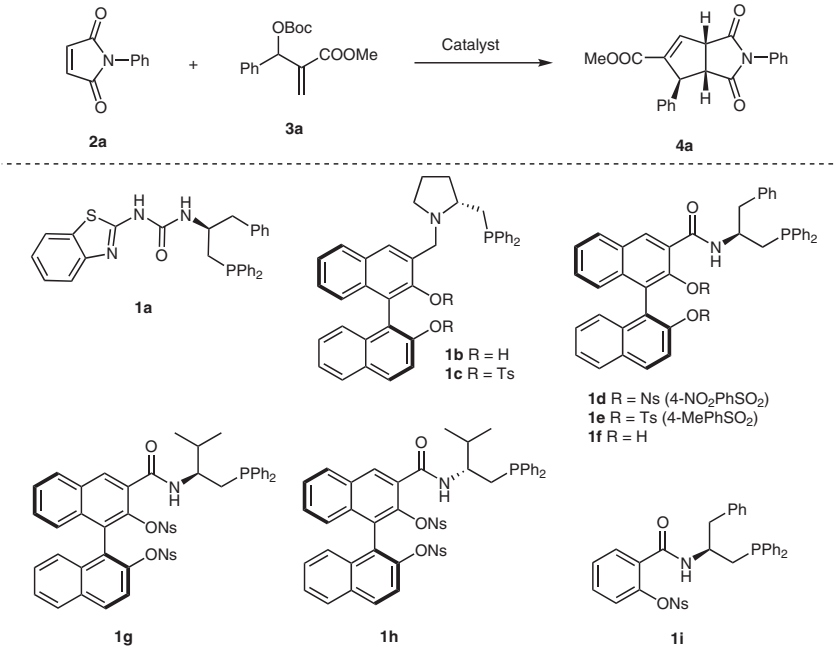
Inspired by these pioneering achievements,[3–9] we aimed to design novel 1,1′-bi-2-naphthol (BINOL) derived bifunctional catalysts for nucleophilic catalysis. As shown in Figure 1, our design principle is to combine BINOL and amino phosphine, enabling further stereocontrol through steric effects and/or hydrogen-bonding interactions caused by a modified BINOL moiety. The introduction of BINOL into amino phosphines may provide effective steric effects as well as hydrogen-bonding interactions, thus activating substrates synergistically and achieving satisfactory levels of enantiocontrol. In addition, the tunability of BINOL would be beneficial for further novel catalyst design. Here, we report our results on the design of novel BINOL-derived phosphine catalysts and their application in the [3+2] cycloaddition of MBH carbonates and electron-deficient olefins.

Initially, the [3+2] cycloaddition of electron-deficient olefin N-phenyl maleimide **2a** and MBH carbonate **3a** was selected as the model reaction to test the catalytic capability of the newly designed catalysts.[10–12] The Lu group and the Shi group have employed dipeptide-based bifunctional phosphine and multifunctional thiourea-phosphine, respectively, to catalyze the same [3+2] cycloaddition reaction, giving excellent enantioselectivities.[10a,10b] Very recently, Zhong and co-workers developed bifunctional ferrocenylphosphines and excellent enantiocontrol was achieved under the catalysis of the novel chiral phosphines.[10c] As shown in Table 1, new urea-based catalyst **1a** and BINOL-derived catalysts **1b–c**, developed in our group, were tested and were found to be ineffective in this system (Table 1, entries 1–3, <5% yields). We reasoned that methylene-tethered catalyst lacked sufficient structural rigidity for enantiocontrol. We then tested catalysts **1d–f**, with an amide group as linkage. The amide group in these catalysts linked the phosphine moiety and the BINOL moiety, possibly generating the necessary chiral environment. As expected, better enantiocontrol was achieved and excellent enantioselectivities can be reached in the reactions catalyzed by **1d** and **1e** (entries 4 and 5, 97% ee and 94% ee, respectively). A trace amount of product was observed when **1f** was used as catalyst, indicating that the hydroxyl groups of the BINOL moiety failed to interact effectively with substrate through hydrogen-bonding, probably because of a side reaction with MBH carbonate (entry 6). The use of catalyst **1g**, bearing an L-valinol backbone, afforded 82% ee, while D-valinol-derived phosphine gave the opposite enantiomer of compound **4a** as the major isomer (entries 7 and 8, 82% ee versus –71% ee). As control experiment, catalyst **1i** gave poor ee value, indicating that the presence of BINOL is critical for stereocontrol (entry 9, 10% ee). The obtained results suggest that amino acid-derived backbones play a significant role in the determination of absolute configuration, while the BINOL unit in the catalyst is important for the generation of high enantioselectivity. The amide group is also essential to tether the BINOL moiety and amino phosphine moiety for enantiocontrol.

Further optimization studies were then conducted to improve the yield and enantioselectivity. Higher reaction temperature (50 °C) afforded better reaction yield and slightly decreased ee value (entry 10, 64% yield, 94% ee). Screening of solvent was then performed at 50 °C, but no improvement on yield was achieved, although good enantioselectivities were obtained in all cases (entries 11–14, 90–94% ee). It seems that the enantioselectivity is not sensitive to the choice of solvent. The employment of two equivalents of MBH carbonate **3a** significantly increased the reaction yield, while the use of an excess amount of N-phenyl maleimide **1a** led to reduced yield (entries 15 and 16, 21% versus 91%). Further lowering the reaction temperature to 35 °C could slightly improve the reaction yield and enantioselectivity (entry 17, 92% yield, 95% ee). The addition of 4 Å MS had a negative effect on reaction yield, while showing no influence on ee value (entry 18, 85% yield, 95% ee).

Having established the optimized reaction conditions, we next examined the generality of this catalytic system. Good diastereoselectivities were observed in most cases and we only isolated the major product in this study. As shown in Scheme 1, variation of MBH carbonates on the electron-withdrawing groups and phenyl ring was successful. Both methyl and ethyl acrylate derived MBH carbonates were employed successfully, giving excellent enantioselectivities (Scheme 1, **4a** and **4b**, 95% ee and 93% ee, respectively). Generally, good yields and enantioselectivities were

Table 1 Optimization of Reaction Conditions of Asymmetric Synthesis of **4a**[a,b]



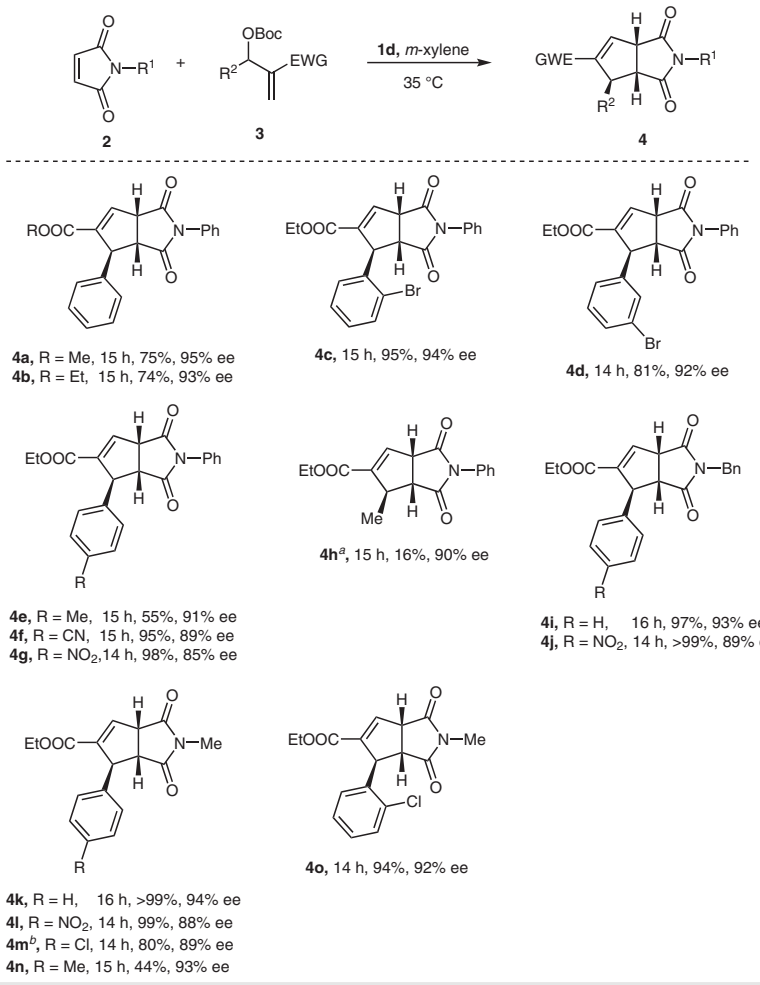
Entry	Cat.	Sol	*T* (°C)	*t* (h)	dr[c]	Yield (%)[c]	ee[d]
1	**1a**	*m*-xylene	rt	20	–	<5	–
2	**1b**	*m*-xylene	rt	20	–	<5	–
3	**1c**	*m*-xylene	rt	21	–	<5	<5
4	**1d**	*m*-xylene	rt	23	>20:1	15	97
5	**1e**	*m*-xylene	rt	20	>20:1	18	94
6	**1f**	*m*-xylene	rt	20	–	<5	–
7	**1g**	*m*-xylene	rt	20	>20:1	40	82
8	**1h**	*m*-xylene	rt	20	>20:1	33	–71
9	**1i**	*m*-xylene	rt	23	>20:1	5	10
10	**1d**	*m*-xylene	50	6	>20:1	64	94
11	**1d**	THF	50	6	>20:1	20	90
12	**1d**	DCE	50	6	>20:1	12	94
13	**1d**	PhCl	50	6	>20:1	35	94
14	**1d**	$PhCF_3$	50	6	>20:1	25	94
15[e]	**1d**	*m*-xylene	50	5	>20:1	21	94
16[f]	**1d**	*m*-xylene	50	5	>20:1	91	94
17[f]	**1d**	*m*-xylene	35	12	>20:1	92	95
18[f,g]	**1d**	*m*-xylene	35	12	>20:1	85	95

[a] Reaction conditions: **2a** (0.05 mmol), **3a** (0.06 mmol), catalyst (10 mol%) and solvent (0.5 mL).
[b] The yield of major product was determined by ^{1}H NMR analysis using CH_2Br_2 as internal standard.
[c] Determined by ^{1}H NMR spectroscopic analysis.
[d] Determined by HPLC analysis on a chiral stationary phase.
[e] Using 0.1 mmol of **2a** and 0.05 mmol of **3a**.
[f] Using 0.1 mmol of **3a** (2 equiv).
[g] Adding 50 mg of 4 Å MS.

observed irrespective of the position of the substituents on the phenyl ring (**4c–g**, 85–94% ee). However, the use of ethyl 2-(((*tert*-butoxycarbonyl)oxy)(*p*-tolyl)methyl)acrylate gave a decreased yield (**4e**, 55% yield), suggesting the electron-donating group substituent of MBH carbonate has a negative effect on the reaction yield. Aliphatic aldehyde derived MBH carbonate gave lower yield compared with other cases (**4h**, 16% yield, 90% ee). We reasoned that the instability of the intermediate generated from catalyst and MBH carbonate should be responsible for the low yield of compound **4h**. The employment of methyl and benzyl maleimides afforded the corresponding bicyclic imides **4i–o** in moderate to excellent yields (44–99%) and good to excellent ee values (88–94%).

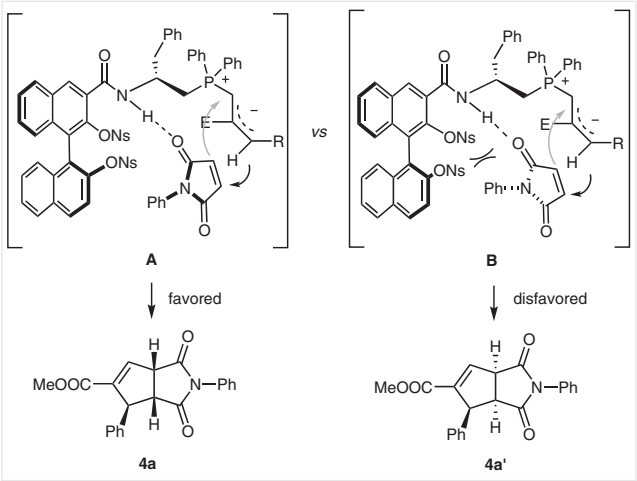
As shown in Scheme 2, we proposed a possible transition state for this reaction. Cycloaddition through transition mode **A** would deliver the desired product **4a** through *Re*-attack triggered Michael–Michael–elimination cascade. While transition mode **B** through *Si*-face attack and subsequent Michael–elimination cascade is disfavored because of the steric repulsion of the Ns moiety next to the amide group with the phenyl group of maleimide. In addition to the hydrogen-bonding interaction provided by the amide group in the catalyst, a π-π stacking effect may also exist in the transition state between the naphthalene ring of the catalyst and the maleimide.

To further investigate the catalytic effect of these BINOL-based organocatalysts, [3+2] cycloaddition of isatin-derived α,α-dicyanoalkene and MBH carbonates was then studied.[7a,13] As shown in Scheme 3, spirooxindole **6** can be obtained in good yields (69–93%) and good enantioselectivities (74–85% ee) in the presence of catalyst **1d**.[14] Good diastereoselectivities were also observed in most cases. These results indicate that the BINOL-derived catalyst can be used



Scheme 1 Examination of substrate scope. Reaction conditions: **2** (0.1 mmol), **3** (0.2 mmol) and **1d** (10 mol%) in *m*-xylene (1.0 mL) at 35 °C. Isolated yield of the major product given. The ee was determined by HPLC analysis on a chiral stationary phase. [a] Performed at 50 °C for 15 h; The yield of **4h** was determined by ^{1}H NMR analysis using CH_2Br_2 as internal standard. [b] Relative configuration of compound **4m** was determined according to reported HPLC analysis results and other products were assigned by analogy.[10b]

to promote the reaction successfully for the construction of two contiguous quaternary centers and the introduction of BINOL moiety is beneficial for controlling the stereochemistry.[7a,13,14]



Scheme 2 Proposed transition modes

In conclusion, we have developed a series of novel BINOL-derived organocatalysts. These multifunctional phosphines can be used in the [3+2] cycloaddition of electron-deficient olefins and MBH carbonates. Moderate to excellent yields (up to >99% yield) and good to excellent enantioselectivities (up to 95%ee) can be obtained. The results obtained in this study indicate that the BINOL moiety plays an important role in stereocontrol. The application of these novel phosphines to asymmetric reaction development and to the synthesis of chiral heterocycles is under way in our laboratory.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611752.

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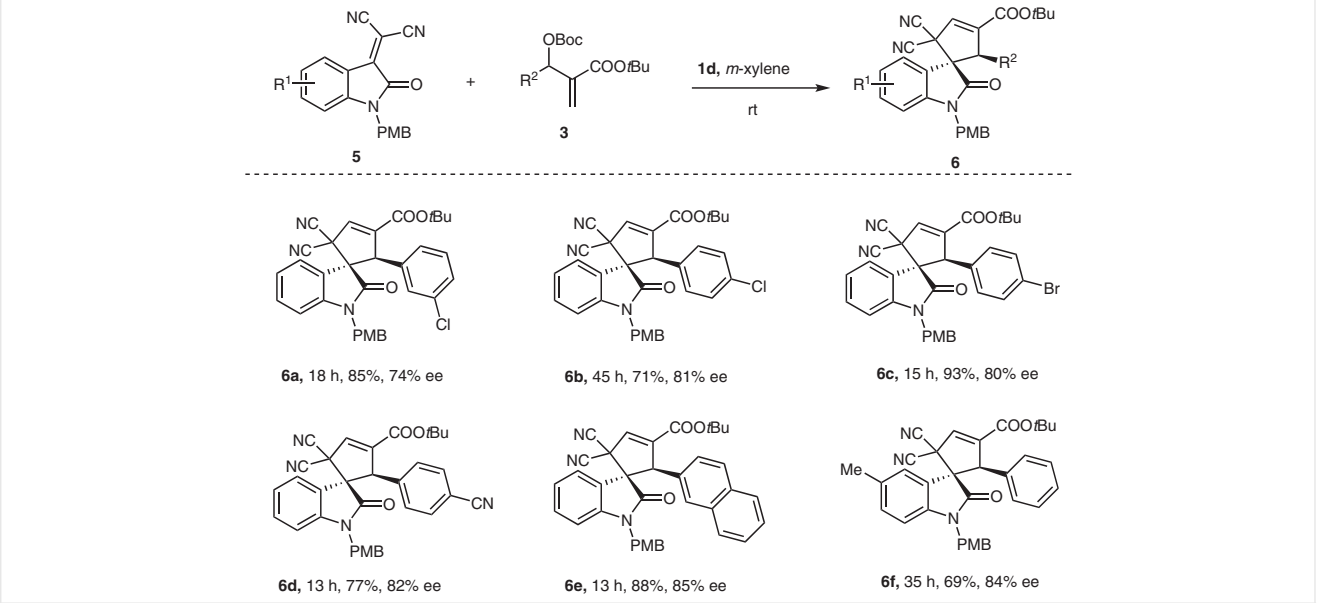

Scheme 3 Application of BINOL-based catalysts for the synthesis of chiral spirooxindoles. Reaction conditions: **5** (0.1 mmol), **3** (0.2 mmol) and **1d** (10 mol%) in *m*-xylene (1.0 mL) at r.t. Isolated yield of the major product given. The ee was determined by HPLC analysis on a chiral stationary phase. Relative configuration of compound **6f** was determined according to reported HPLC analysis results and other products were assigned by analogy.[7a]

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