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Chiral Naphthyl-C2-Indole as Scaffold for Phosphine Organocatalysis: Application in Asymmetric Formal [4 + 2] Cycloaddition Reactions

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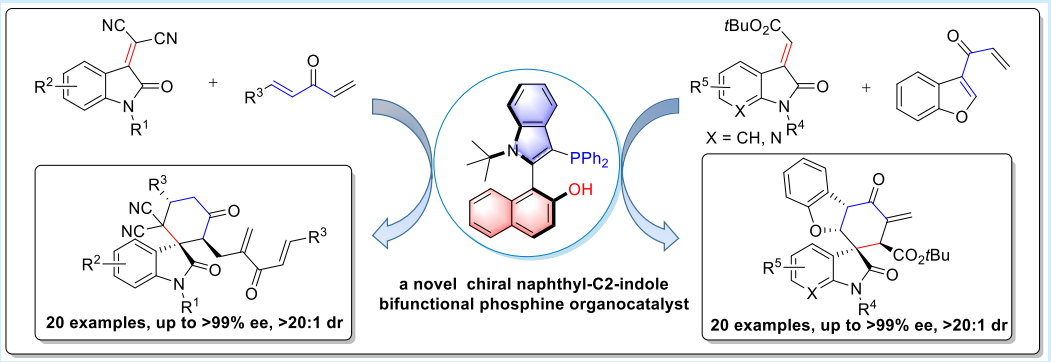
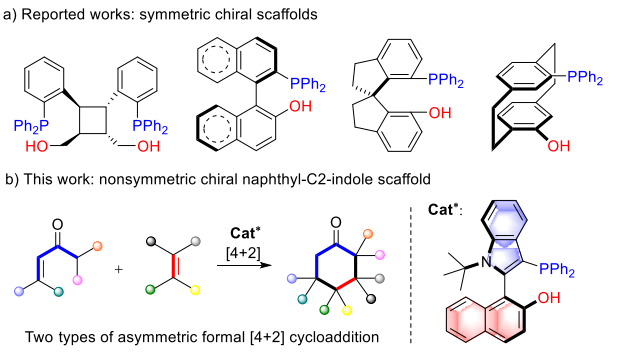


ABSTRACT: The applications of a newly designed chiral naphthyl-C2-indole bifunctional phosphine organocatalyst in stereoselective formal [4 + 2] cycloaddition reactions were reported. The chiral naphthyl-C2-indole skeleton was introduced to bifunctional phosphine organocatalysis for the first time, and excellent stereocontrol was achieved in two types of formal [4 + 2] cycloaddition reactions. With the optimal catalyst, a series of chiral spirooxindole and hydrodibenzofuran architectures were produced in moderate to good yields with excellent stereoselectivities (up to >99% ee, >20:1 dr).

Chiral phosphine organocatalysis[1] has evolved into a powerful and reliable tool for the construction of diverse chiral molecular frameworks. Numerous reactions such as Morita−Baylis−Hillman (**MBH**) reactions, Rauhut−Currier reactions, addition reactions, and multifarious annulations have been innovatively developed to provide multiple paths toward numerous chiral adducts.[2] In particular, a chiral phosphine catalyst bearing a phenolic hydroxyl group has gained much attention due to its Lewis base and Brønsted acid (**LBBA**) properties.[3] As shown in Scheme 1a, several scaffolds have been introduced as the core backbones of such catalyst. A C_2-symmetric bisphosphine catalyst with a cyclobutane backbone[3a,d,e] was investigated as the organocatalyst, but its catalytic performance was unsatisfactory in an aza-**MBH** reaction.[3d] Currently, C_2-symmetric binaphthyl skeletons have been identified as the most efficient chiral scaffolds for phosphine catalysts bearing a phenolic hydroxy group, and many protocols have been reported since the pioneering works on **MBH** reactions reported by Shi in 2003.[3b,c,d,f] With the efforts to seek satisfactory chiral scaffolds for asymmetric phosphine organocatalysts, chiral [2.2]paracyclophane[3h,i] and spiro-type backbones[3g] have been installed to a series of **LBBA** phosphine organocatalysts and successfully applied to the aza-

Scheme 1. Reported Works and This Work



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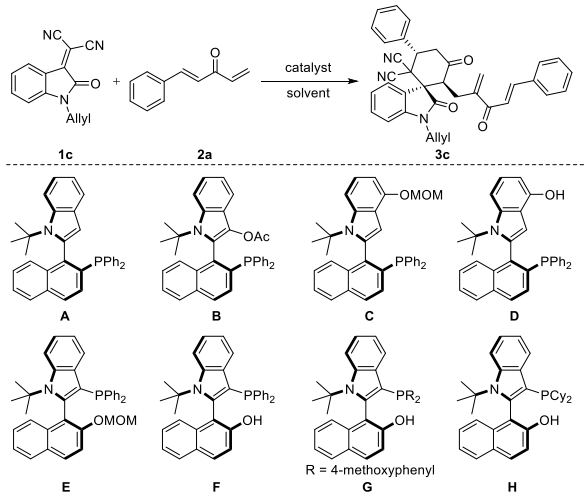
MBH reaction. To date, the backbones used in **LBBA** phosphine organocatalysts have mostly been symmetric scaffolds, whereas nonsymmetric scaffolds containing a heterocyclic ring have rarely been investigated. As a kind of prevalent heterocycle, indole has been used as the catalyst[4] alone or as a key skeleton in some heterobiaryl systems[5−7] and has showed structural and synthetic advantages. Achiral indole-aryl-derived phosphine has been utilized as a unique ligand for Pd-catalyzed cross-coupling reactions[5] or as organocatalyst in a [4 + 1] cyclization reaction.[6] Meanwhile, the axially chiral indole-containing heterobiaryl backbones have been applied as chiral ligands[7] in asymmetric synthesis. However, the non-symmetric chiral aryl-C2-indole skeleton has never been installed into phosphine ligands or organocatalysts, probably due to the lack of an atroposelective procedure for constructing such architectures. Recently, several procedures for the enantioselective preparation of chiral indole biaryl systems have been established,[8] and a series of axially chiral indole derivatives have been prepared. In particular, some practical procedures for producing chiral aryl-C2-indole systems have been well established,[8f,j,n] so that the evaluation of such scaffolds in **LBBA** phosphine organocatalysis can be realized. Considering our continuing interests in organo-catalysis,[9] we intended to develop a novel **LBBA** phosphine catalytic system based on axial chiral aryl-C2-indole skeletons and then to investigate their applications in two types of formal [4 + 2] cycloaddition reactions (Scheme 1b).

Spirooxindole architecture was first selected as the target because such a scaffold widely exists in a number of natural products and biologically active molecules.[10] In 2014, Shi reported a phosphine-catalyzed formal [4 + 2] tandem cyclization of activated dienes with isatylidenemalononitriles.[11] We were encouraged to perform the reaction under the catalysis of our newly designed and synthesized chiral phosphines containing an axially chiral naphthyl-C2-indole scaffold. We began our study with isatylidenemalononitrile **1c** and activated diene **2a** as the substrate in the presence of phosphine catalyst **A** in toluene. The reaction achieved −79% ee in <10% yield (Table 1, entry 1). This preliminary result encouraged us to evaluate catalysts with different substituents in indole part. Disappointingly, catalysts **B**, **C**, and **D** did not significantly improve the yield and stereocontrol of the reaction (Table 1, entries 2−4). Next, the catalyst with a phosphine part in the indole moiety (catalyst **E**) was tested under the same reaction conditions. Interestingly, when the phosphine functionality shifted to the indole part, the enantiomeric isomer of product **3c** was revised to its counterpart, and even the absolute configuration of the catalyst was retained. Moreover, the reaction yield was significantly increased, albeit the ee value of the product was decreased (Table 1, entry 5). This result revealed that attaching a phosphine part into the indole moiety could dramatically increase the reaction output. The low enantioselectivity was probably caused by the lack of a hydrogen-donor site between the catalyst and the substrate. On the basis of this phenomenon, catalysts **F**, **G**, and **H** were designed to bear a free hydroxyl group in the naphthalene ring. To our delight, the reaction proceeded smoothly in the presence of all three catalysts, and the stereoselectivities were obviously increased. Among them, catalyst **F** was found to give better stereo-selectivity in terms of enantio- and diastereoselectivities (98% ee, >20:1 dr). The further evaluation of the solvents (Table 1, entries 9−13), temperature (Table 1, entries 14−18), and

Table 1. Optimization of Reaction Conditions[a]



entry	cat.	solvent	T (°C)	yield (%)[b]	ee (%)[c]	dr[d]
1	**A**	toluene	25	<10	−79	
2	**B**	toluene	25	<10	−85	
3	**C**	toluene	25			
4	**D**	toluene	25	<10	−49	
5	**E**	toluene	25	94	5	>20:1
6	**F**	toluene	25	95	98	>20:1
7	**G**	toluene	25	89	97	18:1
8	**H**	toluene	25	90	98	18:1
9	**F**	$PhCF_3$	25	93	98	>20:1
10	**F**	CH_2Cl_2	25	85	98	15:1
11	**F**	$CHCl_3$	25	88	98	18:1
12	**F**	THF	25	88	97	15:1
13	**F**	CH_3CN	25	96	93	>20:1
14	**F**	toluene	35	95	98	>20:1
15	**F**	toluene	50	95	97	>20:1
16	**F**	toluene	10	94	99	>20:1
17[e]	**F**	toluene	0	94	>99	>20:1
18[e]	**F**	toluene	−10	85	>99	>20:1
19[e,f]	**F**	**toluene**	**0**	**93**	**>99**	**>20:1**
20[e,g]	**F**	toluene	0	65	>99	>20:1

[a]Reaction conditions: **1c** (0.10 mmol), **2a** (0.25 mmol), and catalyst (10 mol %) in the solvent (2.0 mL) for 12 h under N_2, unless otherwise specified. [b]Isolated yield. [c]Determined by HPLC analysis using a chiral stationary phase. [d]dr = diastereoselectivity ratio, determined by ^{1}H NMR. [e]24 h. [f]5 mol % catalyst. [g]2.5 mol % catalyst.

catalyst loading amount (Table 1, entries 19 and 20) revealed that the best reaction performance could be achieved under the reaction conditions as follows: **1c** (0.10 mmol), **2a** (0.25 mmol), and 5 mol % catalyst **F** in toluene (2.0 mL) at 0 °C for 24 h under N_2.

With the optimized reaction conditions in hand (Table 1, entry 19), the substrate scope of the established enantiose-lective formal [4 + 2] cascade cyclization reaction was investigated (Scheme 2). First, different substituent groups on the nitrogen atom of isatylidenemalononitriles were tested, and methyl, methyloxymethyl (−MOM), allyl, benzyl, and phenyl were demonstrated to be compatible with the reaction conditions and gave products **3a−e** in good yields with high stereoselectivities (up to >99% ee, >20:1 dr). Next, different electronic properties and positions of the substituent groups attached to the phenyl ring of isatylidenemalononitriles did not significantly affect the stereocontrol of the reactions, and

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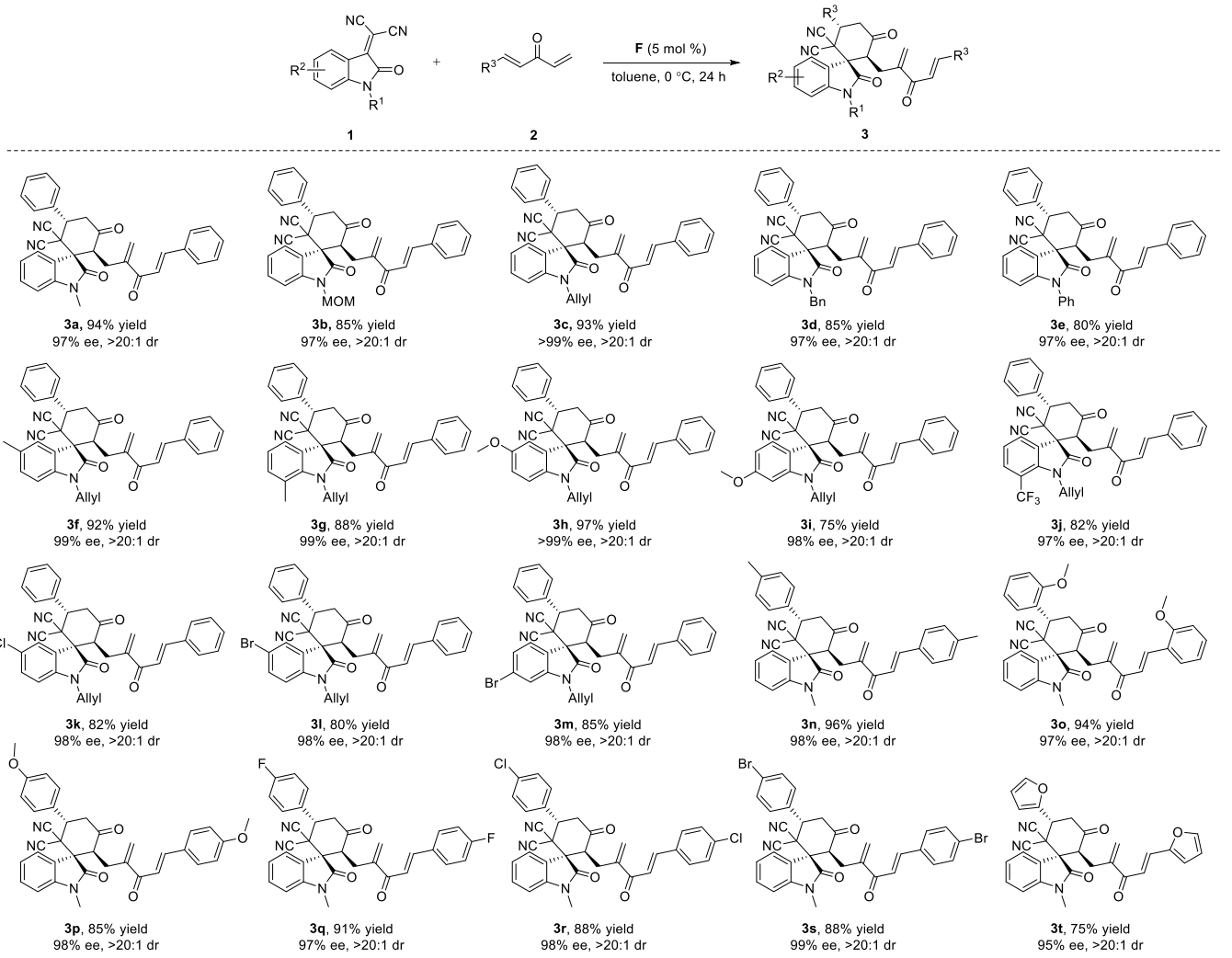
Scheme 2. Substrate Scope[a]



[a]Reaction conditions: **1** (0.10 mmol), **2** (0.25 mmol), and catalyst **F** (5 mol %) in toluene (2.0 mL) at 0 °C for 24 h under N_2.

cascade products **3f−m** were obtained with excellent stereoselectivities (up to >99% ee, >20:1 dr), although the reaction yield was slightly decreased when a methoxyl group was installed to the C6 position of isatylidenemalononitrile (**3i**). The absolute configuration of **3m** was determined by X-ray crystallography analysis of its dihydroxyl derivative (see the SI), and others were assigned by analogy. Moreover, dienes **2** with both electron-donating and -withdrawing groups attached to the different positions of phenyl rings were found to be suitable substrates for the reactions and gave the desired products **3n−s** in high yields (up to 96% yield) with excellent enantiopurities (up to 99% ee, >20:1 dr). Interestingly, when the benzene ring of activated diene was replaced by a heterocycle such as a furan ring, the corresponding substrate was also tolerant of the reaction conditions and afforded product **3t** in moderate yield with high optical purity (95% ee, >20:1 dr).

After the phosphine-catalyzed formal [4 + 2] tandem cyclization of activated dienes with isatylidenemalononitriles was established, we intended to explore an asymmetric dearomative formal [4 + 2] cycloaddition[12] between 3-benzofuranyl vinyl ketone and activated alkenes with the same catalytic system. After a regular condition screening (see SI), the optimal reaction conditions were identified as follows: **4e** (0.075 mmol), **5** (0.05 mmol), and 5 mol % catalyst **F** in toluene (1.0 mL) at 25 °C for 12 h under N_2; **5** was added in two portions at 1 h intervals. Under the optimal reaction conditions, the substrate scope and limitations were investigated. Substrates **4** with different *N*-substitutions were tested in the reaction with **5** (Scheme 3) and products **6a−h** were afforded in moderate to high yields with excellent strereocontrol (up to >99% ee, >20:1 dr). Next, a methyl group was attached to substrates **4** at different positions of the benzene ring of 3-olefinic oxindoles, and products **6i** and **6j** were obtained in moderate yields with excellent optical purities (>99% ee, >20:1 dr). Moreover, the dimethyl-substituted substrate **4k** also smoothly afforded the corresponding product **6k** with excellent stereoselectivity (>99% ee, >20:1 dr). In addition, a methoxyl group was also compatible with the reaction conditions when it was installed at different positions of the benzene ring of substrates **4**; products **6l** and **6m** were obtained in moderate yields with excellent optical purities (up to >99% ee, >20:1 dr). Next, halides such as fluoro, chloro, and bromo were attached to various positions of the benzene ring of substrates **4**, and adducts **6n−s** were formed in moderate yields with excellent stereoselectivities (up to 99% ee, >20:1

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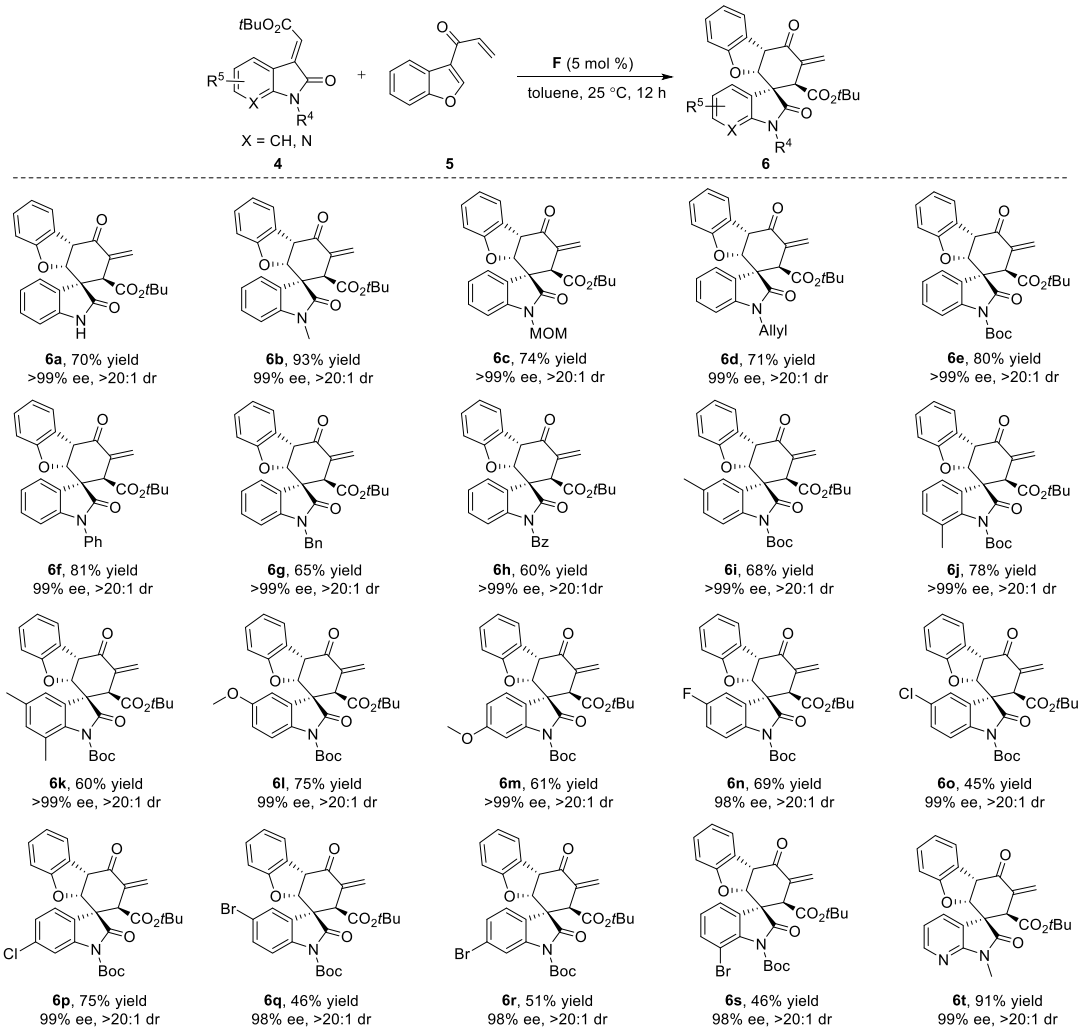
Scheme 3. Substrate Scope[a]



[a]Reaction conditions: **4** (0.15 mmol), **5** (0.10 mmol), and catalyst **F** (5 mol %) in toluene (2.0 mL) at 25 °C for 12 h under N_2; substrate **5** was added in two portions at 1 h intervals.

dr). Interestingly, after substituting the benzene ring of substrates **4** with a heterocycle, the desired pyridine-containing derivative **6t** was successfully produced in 91% yield with excellent enantio- and diastereoselectivity (99% ee, >20:1 dr).

In summary, we prepared a series of newly designed phosphine organocatalysts containing a chiral naphthyl-C2-indole scaffold and investigated their applications in two types of stereoselective formal [4 + 2] cycloaddition reactions. Chiral naphthyl-C2-indole was demonstrated to be an excellent scaffold for **LBBA** phosphine organocatalysis. First, a series of multistereogenic spirooxindole architectures were constructed through the asymmetric cyclization of activated dienes with isatylidenemalononitriles in moderate to good yields with excellent stereoselectivities (up to >99% ee, >20:1 dr). Second, an asymmetric dearomative formal [4 + 2] cycloaddition reaction of 3-benzofuranyl vinyl ketone and 3-olefinic oxindoles was also achieved through a domino cross-Rauhut−Currier/Michael addition. Furthermore, efforts to elucidate the catalytic model of this kind of naphthyl-C2-indole-containing **LBBA** phosphine and its applications in other asymmetric transformations are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02519.

Experimental procedure and characterization data for all of the products (PDF)

Accession Codes

CCDC 2023965 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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