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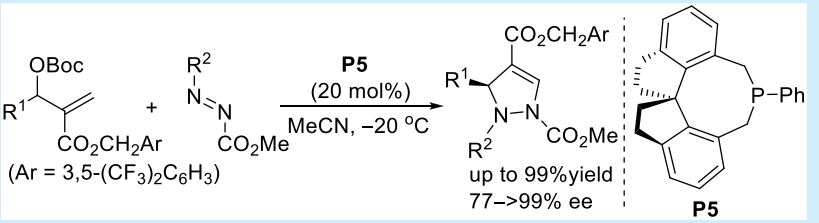
Phosphine-Catalyzed Asymmetric Cycloaddition Reaction of Diazenes: Enantioselective Synthesis of Chiral Dihydropyrazoles

Chang Wang, Yuehua Chen, Jingyu Li, Leijie Zhou, Bo Wang, Yumei Xiao, and Hongchao Guo*

Department of Applied Chemistry, China Agricultural University, Beijing 100193, P. R. China

Supporting Information



ABSTRACT: Although carbon−carbon, carbon−nitrogen, and carbon−oxygen double bonds or their combinations have extensively been applied in phosphine-catalyzed asymmetric cycloaddition, a nitrogen−nitrogen double bond has never been investigated in chiral phosphine catalysis. In this paper, we present phosphine-catalyzed asymmetric [3+2] cycloaddition of diazenes with Morita−Baylis−Hillman (MBH) carbonates to give chiral dihydropyrazoles in high yields with excellent enantioselectivities. Various MBH carbonates and diazenes worked well under the mild reaction conditions.

The pyrazole[1] and pyrazoline[2] system are privileged structures in numerous pharmaceuticals and agrochemicals. Among them, many compounds exhibit bioactivities.[3] Some of them serve as medicines (Figure 1). For example,

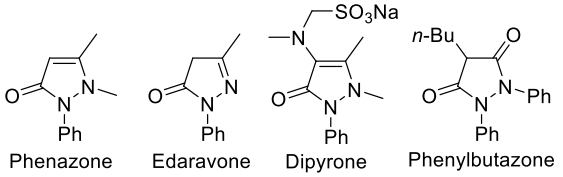
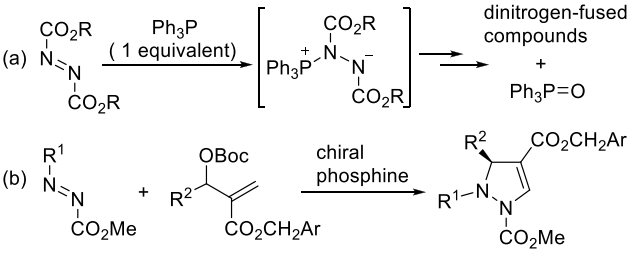


Figure 1. Several bioactive pyrazole and pyrazoline derivatives.

phenazone is a medicine for relieving pain and fever.[4] Edaravone is an intravenous medication used to help with recovery following a stroke and was approved by the U.S. Food and Drug Administration in 2017 to treat amyotrophic lateral sclerosis (ALS).[5] Phenylbutazone displayed anti-inflammatory activity.[6] Dipyrone was used as an analgesic and an antipyretic.[7] Therefore, developing novel synthetic methods for pyrazole and pyrazoline systems, especially chiral molecules, is highly desirable.

Over the past two decades, asymmetric phosphine catalysis has emerged as a practical and reliable tool for the construction of chiral molecular frameworks and synthesis of natural products.[8] Numerous asymmetric organic transformations such as kinetic resolution of secondary alcohols,[9] Rauhut−Currier reactions,[10] Morita−Baylis−Hillman (MBH) reactions,[11] addition reactions,[12] and multifarious annulations[13] have innovatively been developed through chiral phosphine catalysis, providing plentiful access to chiral molecules. In the asymmetric phosphine catalysis, the catalysis cycle normally runs through the addition of the chiral phosphine catalyst to the electrophilic phosphine acceptors such as alkenes, alkynes, and allenes to form zwitterionic intermediates, which then react with electrophilic coupling partners to complete various transformations.[8] To date, hundreds of reports of asymmetric phosphine catalysis have been focused on the discovery of electrophilic coupling partners incorporating electron-deficient carbon−carbon,[10,12a,b,13c,e,g,j] carbon−nitrogen,[11a,c,d,12c,d,13b,f,j] and carbon−oxygen[11b,e,13a] double bonds or their combinations,[13k,n,q] and the fantastic success has been attained in developing asymmetric reactions.[8] However, phosphine-catalyzed asymmetric transformations involving a nitrogen−nitrogen double bond have never been reported. Actually, diazenes such as diethyl azodicarboxylate (DEAD) and its analogues had often been used as achiral phosphine acceptor for the synthesis of dinitrogen-fused compounds, albeit with the use of equivalents of phosphines (Scheme 1a).[14] Recently,

Scheme 1. Nitrogen−Nitrogen Double Bond in Phosphine-Promoted Reactions



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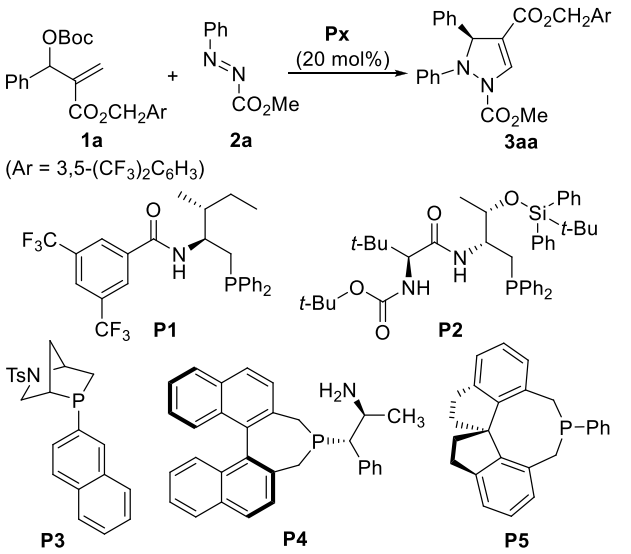
Bu_3P-catalyzed [3+2] cycloaddition/aromatization reaction of MBH carbonates with diazenes was described for the synthesis of pyrazole derivatives.[15] On the basis of these works and our continuous efforts on phosphine catalysis,[16] we envisioned that a nitrogen−nitrogen double bond having electron-deficient properties may work in chiral phosphine-catalyzed asymmetric reactions and thus intensely studied its application in asymmetric phosphine catalysis. Herein, we present our initial results on the first phosphine-catalyzed asymmetric [3+2] cycloaddition reaction of MBH carbonates with diazenes to give pharmaceutically interesting functionalized chiral dihydropyrazoles (Scheme 1b).

Initially, MBH carbonate **1a** and methyl 2-phenyldiazene-1-carboxylate **2a** were employed as model substrates to examine the optimized catalytic system for the expected [3+2] cycloaddition. Several easily accessible chiral phosphines **P1**−**P5** were screened with CH_2Cl_2 as the solvent at room temperature (Table 1, entries 1−5, respectively). Unexpectedly, all of these phosphines promoted the reaction to give the desired product. Among them, spirocyclic chiral phosphine **P5** gave the best results (95% yield with 86% ee) (entry 5). Subsequently, with the use of **P5** as the catalyst, the solvent effect was explored (entries 6−9). The THF solvent was not applicable, affording a trace of the product (entry 7). Toluene behaved like CH_2Cl_2 and 1,2-dichloroethane (DCE), providing similar results (entry 8 vs entries 5 and 6). In particular, in the polar solvent acetonitrile, the [3+2] cycloaddition reaction was completed in 40 min, providing product **3aa** in 99% yield with 87% ee (entry 8). Further improvement of enantioselectivity was accomplished with a decrease in reaction temperature (entries 6−9). When the reaction was performed at −20 °C, both the yield and the enantioselectivity were excellent (99% yield and 97% ee) (entry 10). On the basis of the screening results mentioned above, the optimal reaction conditions were determined as follows: in acetonitrile at −20 °C with 20 mol % phosphine **P5** as the chiral catalyst.

With the optimized reaction conditions in hand, we then performed the cycloaddition of various MBH carbonates **1** with methyl 2-phenyldiazene-1-carbonate **2a** (Table 2). In general, the reaction worked pretty well, tolerating MBH carbonates **1** with various substituents (Table 2, entries 1−20). The desired transformations were extremely efficient when R was aryl or heteroaryl, furnishing the corresponding [3+2] cycloadducts **3** in 93−99% yields with 94−99% ees (entries 1−18). For substituted phenyl groups, the substituent on the phenyl (regardless of electronic properties, substituted position, or its number) has no virtually obvious effect on yield and ee value (entries 2−16). Both 2-naphthyl- and 2-thienyl-substituted MBH carbonates (**1q** and **1r**, respectively) displayed good performance, giving products **3qa** and **3ra** in 98% yield and 99% ee and 83% yield and 95% ee, respectively (entries 17 and 18, respectively). Gratifyingly, the alkyl-

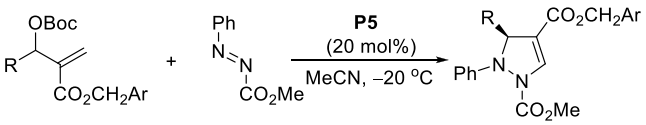
Table 1. Optimization of Reaction Conditions[a]



entry	P*x*	solvent	*T* (°C)	*t*	yield (%)[b]	ee (%)[c]
1	**P1**	CH_2Cl_2	25	3 h	48	−37
2	**P2**	CH_2Cl_2	25	2 days	46	−33
3	**P3**	CH_2Cl_2	25	40 min	72	51
4	**P4**	CH_2Cl_2	25	2 days	19	40
5	**P5**	CH_2Cl_2	25	1.5 h	95	86
6	**P5**	$(CH_2Cl)_2$	25	1 h	98	84
7	**P5**	THF	25	3 days	trace	–
8	**P5**	toluene	25	4 h	94	86
9	**P5**	MeCN	25	40 min	99	87
10	**P5**	MeCN	−10	1.5 h	99	95
11	**P5**	MeCN	−20	5 h	99	97
12	**P5**	MeCN	−30	16 h	95	97

[a]Unless otherwise indicated, reactions of **1a** (0.10 mmol) and **2a** (0.15 mmol) were carried out in the presence of chiral phosphine (0.02 mmol) in 1 mL of the solvent. [b]Isolated yield. [c]Determined by chiral HPLC analysis.

Table 2. Scope of MBH Carbonates[a]



1 (Ar = 3,5-$(CF_3)_2C_6H_3$) **2a** **3**

entry	R in **1**	*t* (h)	**3**/yield (%)[b]	ee (%)[c]
1	C_6H_5 (**1a**)	5	**3aa**/99	97
2	2-FC_6H_4 (**1b**)	10	**3ba**/97	96
3	3-FC_6H_4 (**1c**)	3	**3ca**/95	95
4	4-FC_6H_4 (**1d**)	4.5	**3da**/96	96
5	3-ClC_6H_4 (**1e**)	4	**3ea**/95	98
6	4-ClC_6H_4 (**1f**)	9	**3fa**/98	97
7	2-BrC_6H_4 (**1g**)	12	**3ga**/99	96
8	3-BrC_6H_4 (**1h**)	2	**3ha**/99	98
9	4-BrC_6H_4 (**1i**)	5	**3ia**/95	98
10	4-$NO_2C_6H_4$ (**1j**)	3	**3ja**/93	>99
11	3-MeC_6H_4 (**1k**)	2	**3ka**/96	98
12	4-MeC_6H_4 (**1l**)	4	**3la**/95	98
13	2-$OMeC_6H_4$ (**1m**)	12	**3ma**/93	94
14	3-$OMeC_6H_4$ (**1n**)	3	**3na**/96	98
15	4-$OMeC_6H_4$ (**1o**)	4	**3oa**/99	96
16	3,4-$OMe_2C_6H_3$ (**1p**)	12	**3pa**/98	99
17	2-naphthyl (**1q**)	6	**3qa**/98	99
18	2-thienyl (**1r**)	11	**3ra**/83	95
19	Et (**1s**)	48	**3sa**/97	77
20	*i*-Pr (**1t**)	48	**3ta**/91	80

[a]Unless otherwise stated, all reactions were performed with **2a** (0.1 mmol), **1** (0.15 mmol), and **P5** (0.02 mmol) in 1 mL of MeCN at −20 °C. [b]Isolated yield. [c]Determined by HPLC analysis using a chiral stationary phase.

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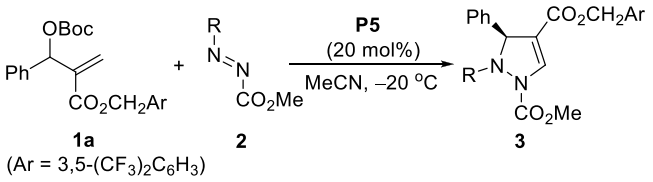
substituted MBH carbonates (**1s** and **1t**) were suitable substrates for the [3+2] cycloaddition, providing pyrazoline **3** in excellent yield with good ee (entries 19 and 20). The absolute configuration of the product has been verified through single-crystal X-ray analysis of product **3ha**.[17]

As indicated in Table 3, a range of diazenes were found to be compatible substrates for the cycloaddition reaction. Generally,

Table 3. Scope of Diazenes[a]



1a (Ar = 3,5-$(CF_3)_2C_6H_3$) **2** **3**

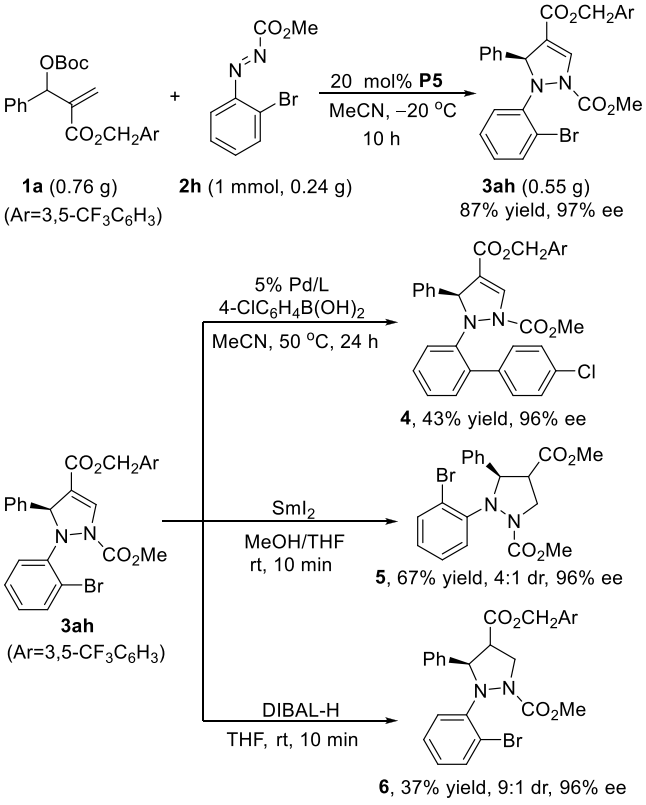
entry	R in **2**	t (h)	**3**/yield (%)[b]	ee (%)[c]
1	2-FC_6H_4 (**2b**)	4	**3ab**/ 97	90
2	3-FC_6H_4 (**2c**)	3.5	**3ac**/99	97
3	4-FC_6H_4 (**2d**)	6	**3ad**/96	91
4	3,4-$F_2C_6H_3$ (**2e**)	3	**3ae**/95	92
5	3-ClC_6H_4 (**2f**)	12	**3af**/87	98
6	4-ClC_6H_4 (**2g**)	2	**3ag**/94	95
7	2-BrC_6H_4 (**2h**)	5	**3ah**/91	97
8	3-BrC_6H_4 (**2i**)	5	**3ai**/96	91
9	4-BrC_6H_4 (**2j**)	3	**3aj**/99	95
10	4-$CF_3C_6H_4$ (**2k**)	48	**3ak**/35	92
11	2-MeC_6H_4 (**2l**)	10	**3al**/99	95
12	3-MeC_6H_4 (**2m**)	4	**3am**/96	98
13	4-MeC_6H_4 (**2n**)	6	**3an**/99	96
14	2,4-$Me_2C_6H_3$ (**2o**)	24	**3ao**/92	96
15	4-EtC_6H_4 (**2p**)	6	**3ap**/99	97
16	3-$OMeC_6H_4$ (**2q**)	4	**3aq**/97	98
17	4-$OMeC_6H_4$ (**2r**)	12	**3ar**/98	96
18	2-naphthyl (**2s**)	2.5	**3as**/99	99
19	6-Br-2-naphthyl (**2t**)	3	**3at**/99	96

[a]Unless otherwise indicated, all reactions were carried out with **2** (0.1 mmol), **1a** (0.15 mmol), and **P5** (0.02 mmol) in 1 mL of MeCN at −20 °C. [b]Isolated yield. [c]Determined by HPLC analysis using a chiral stationary phase.

with respect to variations on the phenyl group of the diazenes, the [3+2] cycloaddition reactions proceed efficiently with excellent enantioselectivity (90−99% ee) for a series of substitution patterns (Table 3, entries 1−19). By employing phenyldiazenes **2** bearing a halogen (**2b**−**2j**), alkyl (**2l**−**2p**), or alkoxyl (**2q** and **2r**) group on the phenyl group to this cycloaddition, dihydropyrazole derivatives **3** were obtained in great yields (87−99%) and with excellent ee values (90−98%, entries 1−9, 11−15, and 16 and 17, respectively). In addition, *p*-trifluoromethyl-substituted phenyldiazene **2k** produced cycloadduct **3ak** with 92% ee, albeit in 35% yield (entry 10). To our delight, the cycloaddition of 2-naphthyl- and bromonaphthyl-substituted diazenes (**2s** and **2t**, respectively) occurred under the optimized conditions with excellent yields and enantioselectivities (entries 18 and 19, respectively).

Having determined the scope of phosphine-catalyzed asymmetric [3+2] cycloaddition of diazenes, we then carried out an experiment to further showcase the application of this methodology in organic synthesis. As shown in Scheme 2, the cycloaddition reaction on the 1 mmol scale worked smoothly, affording pyrazoline derivative **3ah** without a remarkable loss of yield and enantioselectivity, compared with the reaction at

Scheme 2. Scale-Up Synthesis and Synthetic Transformations



0.1 mmol. Cycloadduct **3ah** was further converted into biphenyl heterocyclic product **4** through the coupling reaction in the presence of $Pd(Ph_3P)_4$. Treatment of **3ah** with SmI_2 led to hydrogenation/transesterification, giving tetrahydropyrazole derivative **5** in 67% yield with 96% ee. Reduction of **3ah** with aluminum diisobutyl hydride (DIBAL-H) in THF furnished tetrahydropyrazole derivative **6** in 37% yield with 96% ee.

In summary, we have disclosed that the nitrogen−nitrogen double bond could conduct chiral phosphine-catalyzed asymmetric cycloaddition reaction, resulting in enantioselective synthesis of chiral dihydropyrazoles. The mild reaction conditions and commercially available chiral catalyst make this reaction a feasible way toward chiral dihydropyrazoles. This example demonstrates that nitrogen−nitrogen double bonds may function like carbon−carbon and carbon−nitrogen double bonds for various asymmetric transformations and thus will potentially have a large application in organocatalyst and metal-catalyzed asymmetric catalysis. Further investigations on the application of a nitrogen−nitrogen double bond in the asymmetric reactions are in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02800.

Experimental procedure, characterization data, HPLC analysis dada, NMR spectra, and X-ray crystallographic data (PDF)

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Accession Codes

CCDC 1940604 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.

AUTHOR INFORMATION

Corresponding Author

*E-mail: hchguo@cau.edu.cn.

ORCID

Chang Wang: 0000-0003-2870-6518

Hongchao Guo: 0000-0002-7356-4283

Notes

The authors declare no competing financial interest.

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(17) Crystallographic data for **3ha** have been deposited with the Cambridge Crystallographic Data Centre as deposition number CCDC 1940604.

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Org. Lett. XXXX, XXX, XXX−XXX