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Cu(I)-Catalyzed Highly Enantioselective [3 + 3] Cycloaddition between Two Different 1,3-Dipoles, Phthalazinium Dicyanomethanides and Iminoester-Derived Azomethine Ylides

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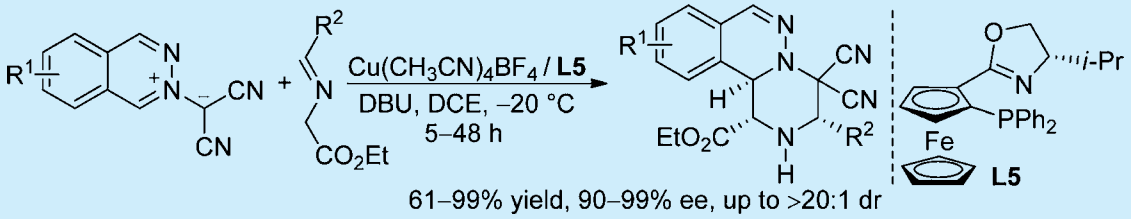
Supporting Information



ABSTRACT: The Cu(I)-catalyzed highly enantioselective [3 + 3] cycloaddition between two different 1,3-dipoles, phthalazinium dicyanomethanides and iminoester-derived azomethine ylides, has been achieved under mild reaction conditions, providing novel chiral heterocyclic compounds, 2,3,4,11b-tetrahydro-1*H*-pyrazino[2,1-*a*]phthalazine derivatives, in high yields with excellent diastereo- and enantioselectivies (up to 99% yield, 99% ee, >20:1 dr).

1,3-Dipolar cycloaddition reactions represent an important class of synthetic methods for the convergent synthesis of a wide range of heterocycles.[1] Among various cycloadditions, [3 + 3] cycloaddition reactions have attracted much attention during the past decade[2,3] and have emerged as an important alternative tool to the [4 + 2] cycloaddition for the synthesis of six-membered heterocycles and total synthesis of natural products.[2,3] However, successful examples of metal-catalyzed [3 + 3] cycloadditions, especially enantioselective [3 + 3] cycloadditions, are still limited.[4,5]

Generally, [3 + 3] cycloaddition occurs via stepwise reaction of a stable 1,3-dipole with reactive dipolar species.[2,4,5] To achieve a [3 + 3] cycloaddition, making a compatible combination of stable dipoles with reactive dipolar species is key. Through reactions of the phosphonium ylide formed in situ from a phosphine and allenoate or electron-deficient alkene with the stable dipole, azomethine imines, we developed several phosphine-catalyzed cycloadditions, not only [3 + 3] but also [3 + 2], [4 + 3], and [3 + 2 + 3] cycloadditions, leading to a broad range of dinitrogen-fused heterocycles.[6] In 2013, we reported the first copper-catalyzed highly diastereo- and enantioselective [3 + 3] cycloaddition of azomethine ylides formed in situ with nother stable dipole azomethine imines, providing a concise and expedient excess of a variety of optically active hexahydro-8*H*-pyrazolo[1,2-*a*][1,2,4]triazin-8-one derivatives with potential biological activity.[5h] As a continuation of our research on cycloaddition reactions, we are anticipating to find new cycloaddition reactions by using a combination of a stable 1,3-dipole with reactive dipolar species.

Numerous heteroatom-containing 1,3-dipoles such as nitrone, azomethine imine, azomethine ylide, carbonyl ylide, nitrile imine, nitrile oxide, azide, diazoalkane, diazoacetate, and carbonyl oxide, are available for cycloaddition chemistry, thus providing a diverse dipole source for the development of [3 + 3] cycloaddition.[1] Among these 1,3-dipoles, phthalazinium dicyanomethanide is a particularly attractive one as a result of its stability, easy preparation, and favorable reactivity. Its thermal [3 + 2] cycloaddition reactions with alkenes, alkynes, phosphaalkynes, or thiones have intensively been studied.[7] Besides these thermal cycloadditions, in 2011, Carrillo and Vicario reported an imidazolidinone-catalyzed enantioselective [3 + 2] cycloaddition of phthalazinium dicyanomethanide with α,β-unsaturated aldehydes, affording highly substituted chiral pyrrolo-phthalazines.[8] As a classic Sustmann type-II 1,3-dipole,[9] phthalazinium dicyanomethanide may conduct a cycloaddition reaction via dipole HOMO-control or dipole LUMO-control mode depending on the dipolarophile that it encounters.[7c−e] On the basis of this behavior, we reasoned that [3 + 3] cycloaddition of phthalazinium dicyanomethanide with other 1,3-dipoles might occur when both dipoles are encountered. Iminoester-derived azomethine ylide, which was generated in situ and has functioned as a versatile metalated 1,3-dipole in various 1,3-dipolar cycloadditions,[10] would be an ideal candidate to pair with phthalazinium dicyanomethanide for an interesting [3 + 3] cycloaddition. Herein, we report a novel Cu(I)-catalyzed enantioselective [3 + 3] cycloaddition of two different 1,3-dipoles, phthalazinium dicyanomethanide and iminoester-derived azomethine ylide, to give chiral heterocycles under mild reaction conditions (Scheme 1).

Our initial investigations focused on the reactions of phthalazinium dicyanomethanide **1a** with α-iminoester **2a**

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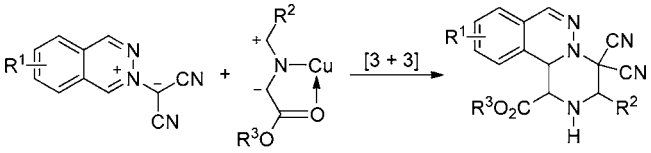
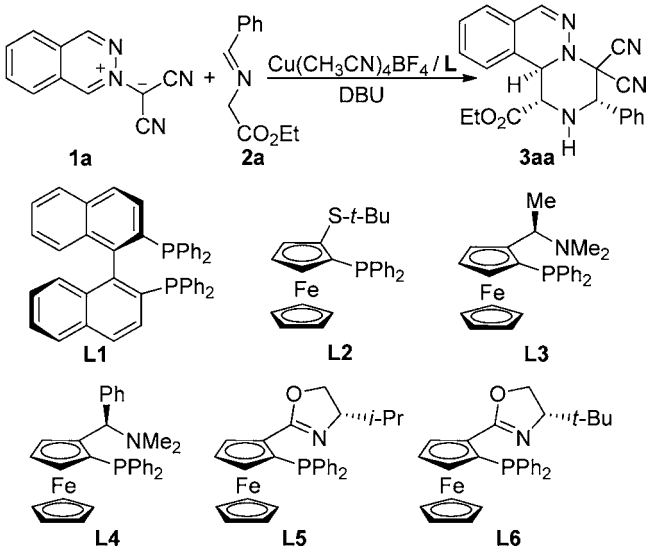
Scheme 1. Copper-Catalyzed [3 + 3] Cycloaddition Reactions of Phthalazinium Dicyanomethanides with Iminoester-Derived Azomethine Ylides



(Table 1). The dipole **1a** is a stable ylide and was easily prepared in almost quantitative yield by treating phthalazine with

Table 1. Screening of the Reaction Conditions[a]



entry	L	solvent	t (°C)	t/h	yield (%)[b]	ee (%)[c]
1	**L1**	DCM	0	12	85	61[d]
2	**L2**	DCM	0	5	89	60
3	**L3**	DCM	0	12	67	80[d]
4	**L4**	DCM	0	12	65	−47[d]
5	**L5**	DCM	0	12	82	95
6	**L6**	DCM	0	12	87	84
7	**L5**	$CHCl_3$	0	24	75	44
8	**L5**	DCE	0	5	86	96
9	**L5**	DCE	−10	6	90	95
10	**L5**	DCE	−20	8	89	97
11	**L5**	DCE[e]	−20	8	91	99
12[f]	**L5**	DCE	−20	32	83	97

[a]Unless otherwise stated, reactions of **1a** (0.1 mmol) and **2a** (0.2 mmol) were carried out in the presence of $Cu(CH_3CN)_4BF_4$ (0.01 mmol), Ligand (0.01 mmol), and DBU (0.02 mmol) in 5 mL of the solvent. [b]Isolated yield. [c]Unless otherwise stated, dr is >20:1, determined by ^1H NMR analysis. Ee was determined by chiral HPLC analysis. [d]Entry 1, dr 15:1; entry 3, dr 10:1; entry 4, dr 8:1. [e]For entry 17, 3 mL of DCE were used. [f]5 mol % catalyst was used.

tetracyanoethyl-eneoxide in THF at rt.[11] We first examined the reaction in dichloromethane (DCM) at 0 °C in the presence of 10 mol % of $Cu(CH_3CN)_4BF_4$, 10 mol % of chiral ligand, and 20 mol % of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Since the solubility of phthalazinium dicyanomethanide is poor in the solvent, the reaction is heterogeneous. As the reaction proceeds, the substrate slowly dissolves and is exhausted. Using 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl (BINAP) (**L1**) as a chiral ligand, the desired product **3aa** was obtained in 85% yield and 61% ee (entry 1). The P,S-ligand **L2** could also promote the reaction to give the product in 89% yield and 60% ee (entry 2). The use of ferrocenyl P,N ligand **L3** resulted in the product **3aa** in 67% yield with increased 80% ee and >20:1 dr. The homologous ligand **L4** provided the product in similar 65% yield, but in low 47% ee. Gratifyingly, iPr-Phosferrox **L5** displayed high activity and excellent enantio- and diastereoselectivity, providing the product **3aa** in 82% yield, 95% ee and >20:1 dr (entry 5). Using tBu-Phosferrox **L6** as chiral ligand, the product **3aa** was obtained in 87% yield and >20:1 dr, albeit in lower 84% ee (entry 6). With the use of $Cu(CH_3CN)_4BF_4$/**L5** as the catalyst, two haloalkane solvents, $CHCl_3$ and 1,2-dichloroethane (DCE), were tried. Both solvents were compatible for catalysis. However, in chloroform, the reaction gave the desired product in lower yield and moderate ee (75% yield and 44% ee) (entry 7); in the contrast, DCE gave excellent results (86% yield, 96% ee, >20:1 dr) (entry 8). Lowering the reaction temperature to −10 and −20 °C respectively, gave a little increased yield of product (entries 9−10). When the volume of solvent was reduced from 5 to 3 mL, the yield and ee were slightly increased to 91% and 99%, respectively (entry 11 vs 10). Reducing the catalyst loading to 5 mol % still afforded an 83% yield of product in 97% ee (entry 12), albeit requiring 32 h of reaction time. Such a significantly longer reaction time is probably attributed to the heterogeneous nature of the reaction. On the basis of the above observations, subsequent reactions were performed at −20 °C using $Cu(CH_3CN)_4BF_4$/**L5** (10 mol %) and DBU (20 mol %) in 3 mL of DCE.

With the optimized conditions identified, we investigated the [3 + 3] cycloaddition of a variety of α-iminoesters **2** with phthalazinium dicyanomethanide **1a**. As shown in Table 2, a wide range of aryl substituted α-iminoesters reacted smoothly with phthalazinium dicyanomethanide to afford the desired cycloaddition products in high yields (87−99%) with excllent enantioselectivities (90−99% ee) and good to excellent diastereoselectivity (14:1 to >20:1 dr) (entries 1−22). Both electron-donating and -withdrawing substituents on the benzene ring of the α-iminoesters were well tolerated in the cycloaddition reactions, and the substitution pattern had no significant influence on the activity and stereoselectivity (entries 1−20). In particular, those α-iminoesters with electron-donating substituents on the benzene ring yielded the cycloaddition products in high yields with uniformly excellent stereoselectivites (97−99% ee, >20:1 dr) (entries 12−20). Both naphthyl and thienyl-substituted iminoesters are also compatible substrates for the reaction, providing the corresponding product in high yields and excellent enantioselectivities (entries 21−22). Moreover, cinnamyl-substituted iminoesters underwent the cycloaddition reaction to give the cycloadduct in 90% yield with 96% ee and >20:1 dr (entry 23). It is worth noting that alkyl-substituted substrates also displayed satisfactory activity and excellent enantioselectivity (entry 24). Compared with aryl-substituted iminoesters, the alkyl-substituted substrate is relatively inert and required more basic inorganic base to promote the reaction. The absolute and relative configurations as depicted were determined by X-ray diffractional analysis of the cycloaddition product **3ah**.[12]

We next studied the reaction of several phthalazinium dicyanomethanide **1** with α-iminoesters **2a**.[11] As indicated in Table 3, all phthalazinium dicyanomethanides afforded the cycloaddition products in high yields (80−93%) and with excellent enantioselectivities (90−99% ee), regardless of the electronic properties and substitution pattern of substituents on the phthalazine ring (entries 1−4). However, it is noteworthy

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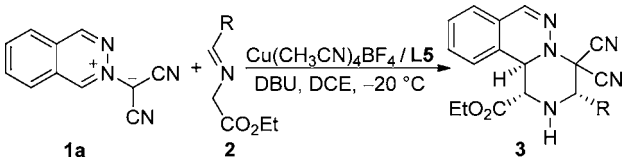
Table 2. Scope of Iminoester-Derived Azomethine Ylides[a]



entry	2	R	t/h	3	yield (%)[b]	ee (%)[c]
1	2a	C_6H_5	8	3aa	91	99
2	2b	2-FC_6H_4	5	3ab	84	94
3	2c	3-FC_6H_4	8	3ac	95	94
4	2d	4-FC_6H_4	12	3ad	86	95[d]
5	2e	2-ClC_6H_4	7	3ae	87	92
6	2f	3-ClC_6H_4	9	3af	84	90
7	2g	4-ClC_6H_4	7	3ag	93	97
8	2h	2-BrC_6H_4	12	3ah	94	90
9	2i	3-BrC_6H_4	48	3ai	85	92
10	2j	4-BrC_6H_4	24	3aj	99	97
11	2k	4-PhC_6H_4	7	3ak	95	95
12	2l	2-MeC_6H_4	24	3al	86	98
13	2m	3-MeC_6H_4	8	3am	87	97
14	2n	4-MeC_6H_4	7	3an	99	97
15	2o	4-EtC_6H_4	12	3ao	95	98
16	2p	2-$OMeC_6H_4$	24	3ap	90	97
17	2q	4-$OMeC_6H_4$	8	3aq	90	99
18	2r	4-$SMeC_6H_4$	8	3ar	95	98
19	2s	2,4-diMeC_6H_3	7	3as	92	98
20	2t	3,4-diMeC_6H_3	20	3at	93	98
21	2u	2-naphthyl	12	3au	95	99
22[e]	2v	2-thienyl	12	3av	80	95[d]
23	2w	cinnamyl	12	3aw	90	96
24[f]	2x	*i*-Bu	48	3ax	61	92[d]

[a]Unless otherwise stated, reactions of **1a** (0.1 mmol), **2** (0.2 mmol), $Cu(CH_3CN)_4BF_4$ (0.01 mmol), **L5** (0.01 mmol), and DBU (0.02 mmol) were carried out in DCE (3 mL) at −20 °C. [b]Isolated yields. [c]Unless otherwise stated, dr is >20:1, determined by ^1H NMR analysis. Ee was determined by chiral HPLC analysis. [d]Entry 4, dr: 14:1; entry 22, dr: 18:1; entry 24, dr: 5:1. [e]The reaction was performed at −30 °C. [f]2 equiv of Cs_2CO_3 were used.

Table 3. Scope of Phthalazinium Dicyanomethanides[a]

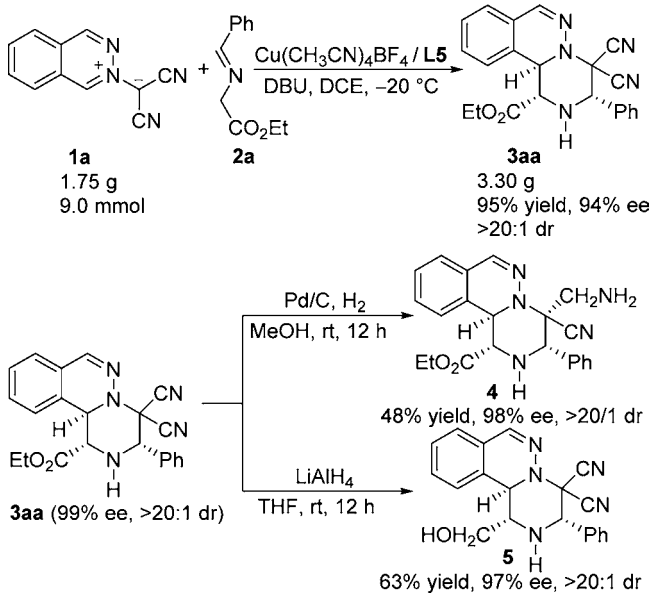
entry	1	3	yield (%)[b]	dr[c]	ee (%)[d]
1	**1b** (R = 5-OMe)	**3ba**	91	9:1	90
2	**1c** (R = 8-OMe)	**3ca**	93	15:1	91
3	**1d** (R = 6,7-2Me)	**3da**	90	>20:1	97
4	**1e** (R = 5-Cl)	**3ea**	87	>20:1	99

[a]Reactions of **1** (0.1 mmol), **2a** (0.2 mmol), $Cu(CH_3CN)_4BF_4$ (0.01 mmol), **L5** (0.01 mmol), and DBU (0.02 mmol) were carried out in DCE (3 mL) at −20 °C. For entries 1 and 2, the reactions of **1b** and **1c** were performed in one pot by using the mixture of **1b** and **1c** as the substrates, and then the resulting products were separated by flash column. The yields were calculated according to the ratio of two substrates obtained from HPLC analysis. For entry 4, a similar procedure had been used. [b]Isolated yields. [c]Determined by 1H NMR analysis. [d]Determined by chiral HPLC analysis.

that the substitution pattern of substituents on phthalazine ring seems to have a certain influence on the diastereoselectivity. For example, the cycloaddition reaction of 5-OMe substituted phthalazinium dicyanomethanide (**1b**) led to the corresponding product **3ba** with 9:1 dr, while an 8-OMe substituted substrate (**1c**) yielded the heterocyclic product **3ca** with 15:1 dr (entry 1 vs 2).

We also performed the present asymmetric reaction on the gram scale. As shown in Scheme 2, in the presence of 10 mol % of

Scheme 2. Gram-Scale Synthesis and Further Transformations of the Cycloadduct



Cu(I) catalyst, asymmetric [3 + 3] cycloadddition of phthalazinium dicyanomethanide **1a** (1.75 g) with *α*-iminoester **2a** delivered the desired chiral 2,3,4,11b-tetrahydro-1*H*-pyrazino[2,1-*a*]phthalazine **3aa** in 95% yield (3.30 g) with 94% ee, demonstrating the synthetic potential of the present asymmetric reaction. Further treatment of the product **3aa** with H_2/Pd/C led to reduction of a cyano group to an amine, affording the corresponding derivative **4** in 48% yield with 98% ee and >20:1 dr, and an unidentified ring-opening product. With the use of $LiALH_4$, the ester group of **3aa** was reduced to give the corresponding derivative **5** in 63% yield with 97% ee and >20:1 dr.

In summary, a highly enantioselective [3 + 3] cycloaddition of phthalazinium dicyanomethanides and iminoester-derived azomethine ylides has been developed with the use of a phosphine−oxazoline−Cu(I) complex as the chiral catalyst, leading to chiral 2,3,4,11b-tetrahydro-1*H*-pyrazino[2,1-*a*]phthalazine derivatives in high yields with excellent dr and ee values. A variety of iminoester-derived azomethine ylides and phthalazinium dicyanomethanides are compatible with the mild reaction conditions, making this reaction a highly valuable method for the diversity-directed synthesis of biologically important chiral heterocyclic compounds.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectral data, and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(11) For the preparation of phthalazinium dicyanomethanide, see ref 7. For details on the preparation of the phthalazinium dicyanomethanide **1**, see the Supporting Information. For nonsymmetric substituted phthalazine, since there are two nitrogen atoms, both which can attack tetracyanoethyleneoxide, two positional isomeric phthalazinium-2-dicyanomethanide derivatives were produced. These two isomers could not be separated by flash column. Fortunately, the [3 + 3] annulation products from the mixture of two isomeric substrates could be separated by using flash column. The cycloaddition yields were calculated on the basis of HPLC analysis of two isomeric substrates.

(12) Crystallographic data for **3aa** and **3ah** have been deposited with the Cambridge Crystallographic Data Centre as deposition numbers CCDC 995194 and 995195.