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Catalytic Asymmetric Three-Component 1,3-Dipolar Cycloaddition of Aldehydes, Hydrazides, and Alkynes

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Supporting Information

ABSTRACT: Catalytic asymmetric 1,3-dipolar cycloadditions offer expeditious ways to afford synthetically important chiral heterocycles. Although a variety of 1,3-dipoles can be employed in this context, the use of acyclic azomethine imines as a facile means to give chiral pyrazolines and pyrazolidines remains completely unexplored. We report herein the first catalytic asymmetric 1,3-dipolar cycloaddition of terminal alkynes with acyclic azomethine imines generated in situ from the corresponding aldehydes and hydrazides, which was realized using Cu(I)/pybox and axially chiral dicarboxylic acid cocatalysts.

Catalytic asymmetric multicomponent reactions (MCRs) have been widely investigated as an attractive strategy for constructing complex chiral molecules in a single operation.[1] Apart from minimizing the overall number of manipulations, the implementation of MCRs is advantageous in terms of exploiting labile chemical species that are not suitable for isolation. In this context, we recently developed chiral Brønsted acid-catalyzed three-component asymmetric reactions using aldehydes, hydrazides, and nucleophiles such as diazoacetate and isocyanide,[2] wherein the in situ generation of acyclic azomethine imines as unstable electrophiles plays a pivotal role (Figure 1).

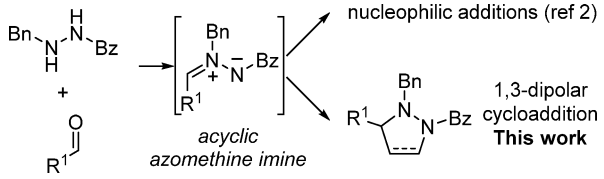

Figure 1. In situ generation of acyclic azomethine imines.

Our next step was to use these labile species in catalytic asymmetric three-component 1,3-dipolar cycloadditions (1,3-DCs),[3] exploiting their innate 1,3-dipolar nature. The reaction would provide a novel and rapid process for synthesizing chiral pyrazolines and pyrazolidines, an important class of heterocycles that appear in biologically active compounds[4,5] and also serve as synthetic intermediates for chiral 1,3-diamines. In sharp contrast to the extensive utility of 1,3-DCs in every aspect of organic synthesis,[6] this catalytic asymmetric transformation has yet to be realized.[7] Previously, only preformed, isolable N,N′-cyclic and C,N-cyclic azomethine imines, which have intrinsic limitations in terms of structural flexibility and diversity, have been used for this purpose.[8,9] At present, the catalytic asymmetric [3 + 2] cycloaddition of hydrazones and reactive alkenes is the only method that offers an alternative.[10]

As a synthetically attractive and challenging dipolarophile that would be compatible with in situ generation of acyclic azomethine imines, we selected catalytically generated copper acetylide (Figure 2) to afford chiral pyrazolines, a strategy

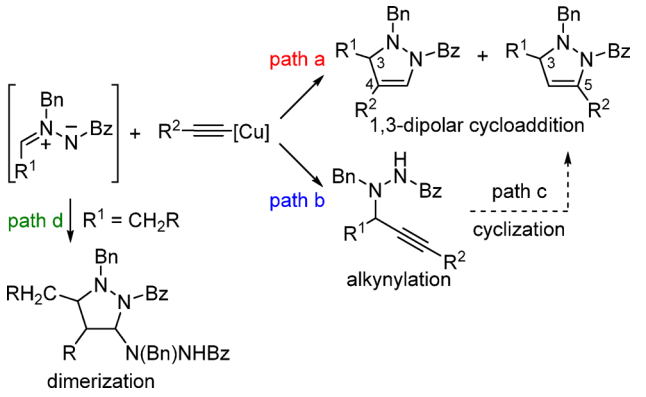

Figure 2. 1,3-Dipolar cycloaddition of acyclic azomethine imines and copper acetylide.

initially introduced in catalytic asymmetric 1,3-DC of N,N′-cyclic azomethine imines by Fu.[8a,b] The major concern in implementing this three-component 1,3-DC is the possible formation of three different compounds: two regioisomeric cycloadducts stemming from 1,3-DC (path a) and a propargyl hydrazide via alkynylation (path b).[11,12] Understandably, one of the two regioisomers from path a can also be generated by sequential alkynylation/cyclization (paths b and c), as evidenced by recent studies by Fujii and Ohno[13] and Kobayashi.[14]

Our optimal catalyst system was composed of Cu(I)/pybox and axially chiral dicarboxylic acid cocatalysts,[15,16] which gave rise to 3,4-disubstituted pyrazolines in high yields with excellent enantioselectivities and also exhibited broad substrate scope with respect to the aldehyde, the alkyne, and even the hydrazide. While the reaction generally proceeded in a regiospecific manner, the reaction pathway had to be controlled by the judicious choice of a catalyst system to favor 1,3-DC over alkynylation. In addition, it was also necessary to suppress the dimerization of the acyclic azomethine imine when a linear aliphatic aldehyde was used as the substrate (Figure 2, path d).

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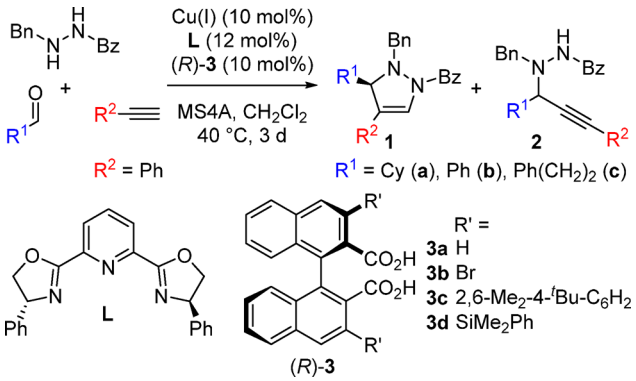
At the beginning of this study, the reaction of cyclohexanecarbaldehyde, *N*′-benzylbenzohydrazide, and phenylacetylene was carried out in the presence of CuOAc/(*R*,*R*)-Ph-pybox (**L**) in CH_2Cl_2 at room temperature (rt) (Table 1). Use of

Table 1. Optimization of the Reaction Conditions[a]



entry	R^1	Cu(I)	**3**	yield (%)[b]	**1**:**2**[c]	ee (%)[d]
1[e]	Cy	CuOAc	–	16	60:40	82
2[e]	Cy	CuCl	–	71	58:42	83
3[e]	Cy	CuBr	–	68	37:63	68
4[e]	Cy	CuI	–	71	64:36	63
5[e]	Cy	CuOTf	–	45	79:21	97
6	Cy	CuOTf	–	81	87:13	97
7	Ph	CuOTf	–	74	93:7	78
8	Ph	CuOTf	**3a**	50	85:15	78
9	Ph	CuOTf	**3b**	80	>95:5	89
10	Ph	CuOTf	**3c**	68	>95:5	84
11	Ph	CuOTf	**3d**	91	93:7	92
12[f]	Ph	CuOTf	**3d**	91	93:7	55
13	Cy	CuOTf	**3d**	89	93:7	99
14[g]	$Ph(CH_2)_2$	CuOTf	**3d**	n.d.[h]	–	–
15[g]	$Ph(CH_2)_2$	CuOAc	**3d**	87	>95:5	>99
16	Cy	CuOAc	**3d**	92	>95:5	>99
17	Ph	CuOAc	**3d**	89	>95:5	96

[a]Performed with *N*′-benzylbenzohydrazide (0.10 mmol), aldehyde (0.12 mmol), phenylacetylene (0.12 mmol), copper catalyst (0.01 mol), **L** (0.012 mmol), and (*R*)-**3** (0.01 mmol). [b]Combined yield of **1** and **2**. [c]Determined by ^{1}H NMR analysis of the crude material. [d]Determined by chiral HPLC analysis. [e]Performed at rt. [f]Performed with (*S*,*S*)-Ph-pybox (*ent*-**L**). [g]Performed at rt for 1 day. [h]n.d. = not detected.

4 Å molecular sieves (MS4A) was necessary to scavenge water generated by the condensation of the aldehyde and the hydrazide. This 1,3-DC gave 3,4-disubstituted pyrazoline **1a** regiospecifically with 82% ee, although the conversion was still low after 3 days (entry 1). Furthermore, a nearly equal amount of the alkynylation product **2a** was observed, thereby urging us to identify conditions that selectively provide the cycloadduct. In the first optimization, the effect of the Cu source was examined (entries 2–5). Among those, the use of CuOTf led to the preferential formation of **1a** with modest conversion and high enantioselectivity (entry 5). Full conversion without deterioration of the enantioselectivity was attained by running the reaction at 40 °C (entry 6).

Benzaldehyde was then used as substrate to clarify the generality of the reaction conditions. Whereas pyrazoline **1b** was obtained with a good product ratio, the enantioselectivity was only modest (entry 7). As a facile means to improve it,[17] we turned our attention to the use of axially chiral dicarboxylic acid (*R*)-**3** as a cocatalyst,[11] expecting that it would interact with the azomethine imine via hydrogen bonding (entries 8–11).[2] This strategy was found to be effective in increasing not only the enantioselectivity but also the product ratio, especially when (*R*)-**3d** with 3,3′-disilyl groups was used (entry 11).[18] The mismatched chiral pair using (*S*,*S*)-Ph-pybox (*ent*-**L**) and (*R*)-**3d** gave the pyrazoline with 55% ee (entry 12).

Even though this cocatalysis was also successfully applied to cyclohexanecarbaldehyde (compare entries 6 and 13), we faced another problem in a further attempt to use hydrocinnamaldehyde as a typical linear aliphatic aldehyde (entry 14). In this case, only a dimer of the azomethine imine was obtained (see Figure 2, path d). As this dimerization is known to proceed under acidic conditions,[2a] we planned to attenuate it by returning to a less acidic copper source, CuOAc, while using the cocatalyst system. This finally led us to the optimized conditions, which have very broad generality. When CuOAc/**L** and (*R*)-**3d** were used as cocatalysts, hydrocinnamaldehyde was transformed to the desired product **1c** in high yield with excellent enantioselectivity at rt (entry 15). Gratifyingly, this cocatalysis uniformly provided excellent results when other aldehydes were used at 40 °C (entries 16 and 17).

With the optimized conditions in hand, we examined the substrate scope using a variety of aldehydes with phenylacetylene as a fixed reaction partner at a catalyst loading of 5 mol % on a 0.2 mmol scale (Chart 1). Although the catalyst loading was reduced to half compared with the optimization study in Table 1, the representative aldehydes (cyclohexanecarbaldehyde, benzaldehyde, and hydrocinnamaldehyde) all were converted to the corresponding pyrazolines **1a**–**c** in high yields and selectivities. A series of aromatic aldehydes could be utilized to give pyrazolines **1d**–**f** in high yields, enantioselectivities, and product ratios, irrespective of the electronic property and position of the functionality. The use of 2-furfural led to a slight decrease in the enantioselectivity (**1g**). As for aliphatic aldehydes, the enantioselectivities of the products **1h**–**l** were no less than 98% ee, and the exclusive formation of pyrazolines was observed in all of the reactions using linear aliphatic aldehydes. In some cases, it was preferable to reduce the loading of (*R*)-**3d** to 2.5 mol % to minimize the formation of the azomethine imine dimer.

Next, the alkyne scope was evaluated (Chart 2). The reactions of aromatic and aliphatic alkynes using cyclohexanecarbaldehyde as a reaction partner gave rise to pyrazolines **1m**–**p** with exceptionally high enantioselectivities and minimal erosion of the product ratio. Ethyl propiolate was also a good substrate, exclusively giving pyrazoline **1q** having ester functionality. As shown by the reaction of hydrocinnamaldehyde and 1-hexyne to give pyrazoline **1r**, the reaction using other aldehydes also proceeded without difficulty. The absolute configuration of **1m** was determined by X-ray crystallography to be *R* (see the Supporting Information). The only limitation of this reaction system was the combination of sterically demanding substrates such as cyclohexanecarbaldehyde and 2-tolylacetylene, for which alkynylation became a competing pathway (data not shown).

This three-component 1,3-DC was also compatible with various substituents on the hydrazide moiety. The reactions using *N*′-butyl hydrazide and *N*-Cbz hydrazide gave rise to the corresponding pyrazolines **4** and **5** in good yields with over 90% ee (Scheme 1). Accordingly, the method developed herein can be used as a general way to form at will pyrazolines having four different functionalities.

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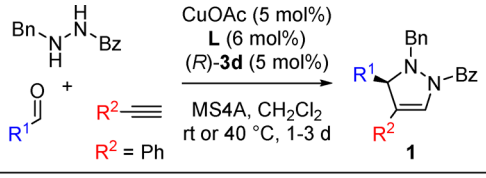
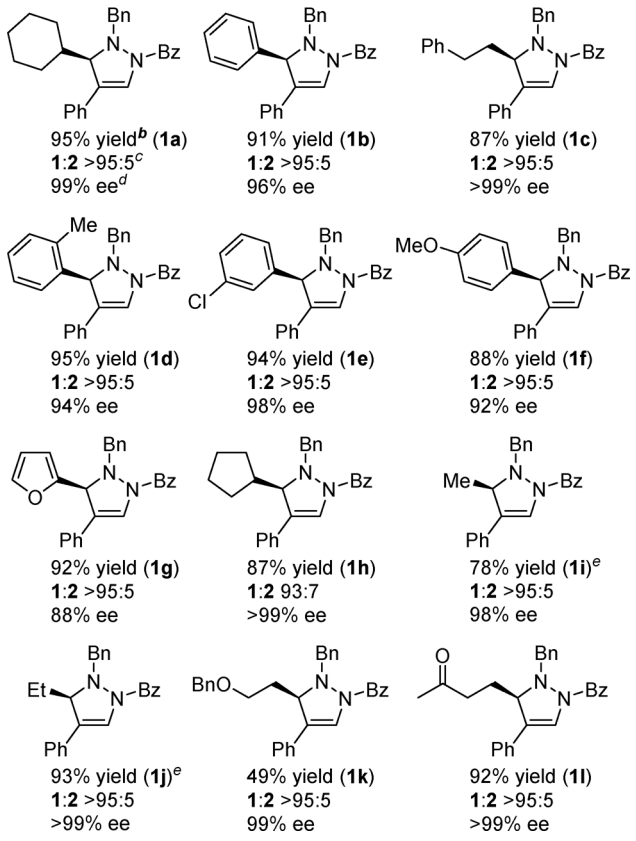
Chart 1. Substrate Scope Using Various Aldehydes[a]



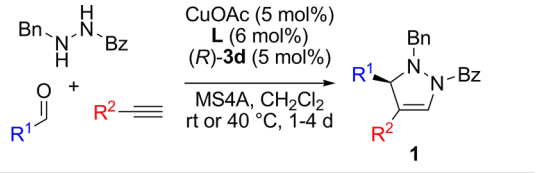


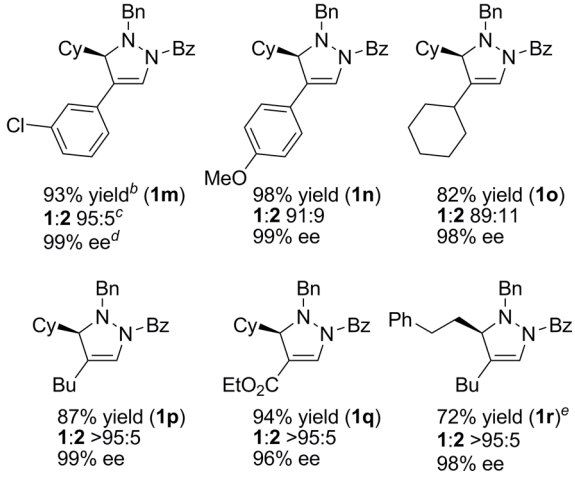
[a]Performed with *N*′-benzylbenzohydrazide (0.20 mmol), aldehyde (0.24 mmol), phenylacetylene (0.20 mmol), CuOAc (0.01 mol), **L** (0.012 mmol), and (*R*)-**3d** (0.01 mmol). [b]Combined yield of **1** and **2**. [c]Determined by ^{1}H NMR analysis of the crude material. [d]Determined by chiral HPLC analysis. [e]Performed with 2.5 mol % (*R*)-**3d** (0.05 mmol).

To demonstrate the utility of 3,4-disubstituted pyrazolines, we conducted two transformations generating an additional stereocenter (Scheme 2). In one reaction, the benzoyl moiety of **1b** was removed under basic conditions to give pyrazoline **6** having two phenyl groups oriented in a trans fashion. Formation of the trans isomer is assumed to be thermodynamically controlled, as some amount of the cis isomer was observed in the early stage of the reaction. On the other hand, hydrogenation of **1b** furnished pyrazolidine **7** bearing two phenyl groups in a cis fashion. Furthermore, acyclic 1,3-diamine **8** could be synthesized by SmI_2-mediated cleavage of the N−N bond in **7**.

In conclusion, we have developed the first catalytic asymmetric three-component 1,3-DC of aldehydes, hydrazides, and terminal alkynes, exploiting acyclic azomethine imines as key species.[19] Two major obstacles to attaining this goal were control of the reaction pathway toward 1,3-DC while suppressing undesired alkynylation and identification of general reaction conditions applicable to both aromatic and aliphatic aldehydes. As a solution, we opted for the use of CuOAc/Ph-pybox and axially chiral dicarboxylic acid cocatalysts, with which a variety of 3,4-

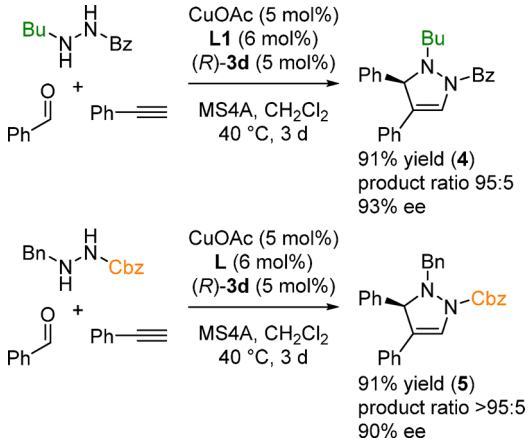
Chart 2. Substrate Scope Using Various Alkynes[a]



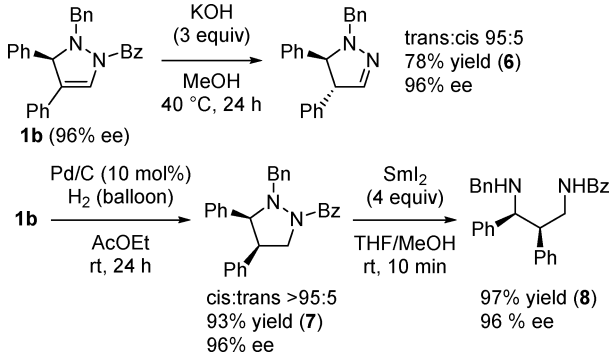


[a]Performed with *N*′-benzylbenzohydrazide (0.20 mmol), aldehyde (0.24 mmol), alkyne (0.20 mmol), CuOAc (0.01 mol), **L** (0.012 mmol), and (*R*)-**3d** (0.01 mmol). [b]Combined yield of **1** and **2**. [c]Determined by ^{1}H NMR analysis of the crude material. [d]Determined by chiral HPLC analysis. [e]Performed with 2.5 mol % (*R*)-**3d** (0.05 mmol).

Scheme 1. Use of Other Hydrazides



Scheme 2. Synthetic Applications



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disubstiuted pyrazolines could be obtained with high enantioselectivities. This asymmetric transformation also has a tolerance with regard to the hydrazide functionality, opening up a new direct way to construct a diverse array of chiral pyrazolines.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization 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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(19) An example using an N,N′-cyclic azomethine imine under our optimized conditions is available in the Supporting Information.