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Diastereoselective 1,3-Dipolar Cycloadditions of *N,N′*-Cyclic Azomethine Imines with Iminooxindoles for Access to Oxindole Spiro-*N,N*-bicyclic Heterocycles

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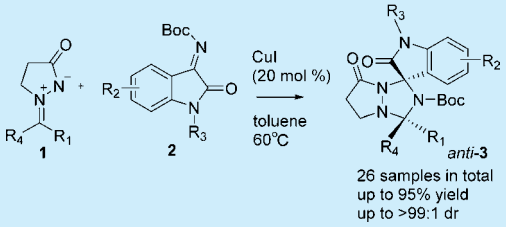
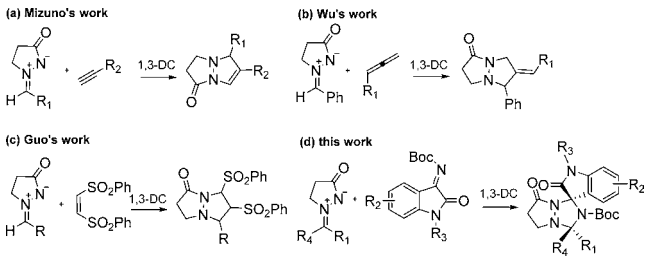
Supporting Information

ABSTRACT: In the presence of CuI, 1,3-dipolar cycloadditions of *N,N′*-cyclic azomethine imines with iminooxindoles proceeded readily and furnished novel oxindole spiro-*N,N*-bicyclic heterocycles in moderate to excellent chemical yields with excellent diastereoselectivities.



N,N′-Cyclic azomethine imines constitute a class of stable and easily accessible 1,3-dipoles and act as versatile and robust building blocks in numerous 1,3-dipolar cycloadditions (1,3-DCs) for the construction of structurally diverse *N,N*-bicyclic heterocycles with potential biological activities.[1] As reported in the literature, these kinds of 1,3-dipoles have been widely applied in 1,3-DCs with diverse and highly functionalized alkynes,[2] allenes,[3] and alkenes.[4] For example, in 2011, Mizuno and co-authors established the $Cu(OH)_x/Al_2O_3$-catalyzed 1,3-DC of *N,N′*-cyclic azomethine imines with terminal alkynes, furnishing *N,N*-bicyclic pyrazolidinones (Scheme 1a).[5] Later,

Scheme 1. *N,N′*-Cyclic Azomethine Imines Involved in 1,3-Dipolar Cycloadditions



Wu and co-workers developed the gold-catalyzed 1,3-DC of *N,N′*-cyclic azomethine imines with *N*-allenyl amides, delivering pyrazolyl-based bicyclic heterocycles (Scheme 1b).[6] In 2014, Guo and co-workers discovered the phosphine-catalyzed 1,3-DC of *N,N′*-cyclic azomethine imines with electron-deficient alkenes, yielding *N,N*-bicyclic heterocycles (Scheme 1c).[7] Moreover, in this context, some enantioselective variants have been built for the construction of enantioenriched *N,N*-bicyclic heterocycles under the catalysis of chiral Lewis acids and organocatalysts.[8] Therefore, excellent advances have been achieved with *N,N′*-cyclic azomethine imines in 1,3-DCs in recent years. However, exploration of 1,3-DCs of *N,N′*-cyclic azomethine imines with synthetically important and useful iminooxindoles,[9] which can produce oxindole spiro-*N,N*-bicyclic heterocycles with spirooxindole derivatives with potential bioactivities,[10] has not been reported in the literature to date.

On the basis of the above-mentioned findings and developments in the chemistry of *N,N′*-cyclic azomethine imines, we designed unknown 1,3-DCs using *N,N′*-cyclic azomethine imines as dipoles and iminooxindoles as dipolarophiles.[11] Our studies demonstrated that 1,3-DCs between *N,N′*-cyclic azomethine imines and iminooxindoles proceed readily, thus furnishing the desired novel oxindole spiro-*N,N*-bicyclic heterocycles bearing potential bioactivities in moderate to excellent chemical yields with excellent diastereoselectivities. To the best of our knowledge, such a work has not been reported in the literature so far.

First, we screened the effect of a wide range of catalysts on the 1,3-DC between *N,N′*-cyclic azomethine imine **1a** and iminooxindole **2a** at room temperature, as shown in Table 1. These catalysts could promote the 1,3-DC through the different activation modes, for example, metal chelation,[12] hydrogen bonding,[13] conjugated nucleophilic addition,[7,14] etc. Remarkably, the used catalysts affected the chemical yield significantly and the diastereoselectivity slightly. In the case of most catalysts, they gave product **3aa** in excellent diastereoselectivity (Table 1, entries 1, 3, 5−13, 19, and 20). Even without catalyst, the distereoselectivity of 1,3-DC still reached >99:1 dr (Table 1, entry 21). Consequently, we deduced that the diastereoselectivity of 1,3-DC has no close relation to the

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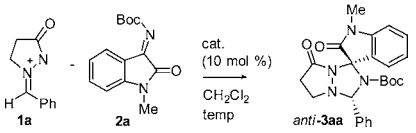
Table 1. Screening of Catalysts[a]



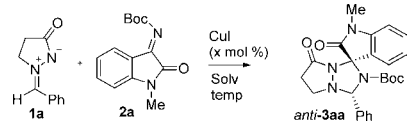
entry	cat.	temp	time (h)	yield[b] (%)	dr[c]
1	CuI	rt	40	42	>99:1
2	$Cu(OAc)_2$	rt	40	38	>80:20
3	$CuBF_4$	rt	40	40	>99:1
4	$Yb(OTf)_3$	rt	40	trace	
5	$Zn(OTf)_2$	rt	40	32	>99:1
6	$SnCl_2$	rt	40	37	>99:1
7	CuCl	rt	40	23	>99:1
8	CuBr	rt	40	32	>99:1
9	Na_2CO_3	rt	40	28	>99:1
10	K_2CO_3	rt	40	23	>99:1
11	NaOAc	rt	40	25	>99:1
12	Et_3N	rt	40	14	>99:1
13	quinine	rt	40	11	>99:1
14	DABCO	rt	40	nr[d]	
15	TFA	rt	40	nr[d]	
16	*p*-TSA	rt	40	nr[d]	
17	stearic acid	rt	40	nr[d]	
18	HOAc	rt	40	nr[d]	
19	CuI	40 °C	20	47	>99:1
20	CuI	60 °C	20	51	>99:1
21		rt	40	16	>99:1

[a]Reactions were carried out with 0.12 mmol of **1a** and 0.1 mmol of **2a** in the presence of 10 mol % of catalyst in 1.0 mL of CH_2Cl_2 at specified temperature. [b]Isolated yield. [c]Determined by ^1H NMR spectroscopy. [d]No reaction.

organocatalysts used. By comparison, the chemical yield of **3aa** highly depended on the structural nature of the catalysts examined. Using DABCO, TFA, *p*-TSA, stearic acid, and HOAc as catalysts did not produce product **3aa** in 40 h (Table 1, entries 14−18). Catalyzed by $Yb(OTf)_3$, the 1,3-DC yielded **3aa** in a trace amount in 40 h (Table 1, entry 4). For other catalysts, the chemical yield of **3aa** ranged from 11 to 42% (Table 1, entries 1−3 and 5−13). Moreover, it was noted that increasing the reaction temperature could increase the chemical yield of **3aa** in the different degrees (Table 1, entries 1 vs 19 and 20).

In the presence of 10 mol % of CuI at 60 °C, we explored the effect of various organic solvents on the 1,3-DC between *N,N′*-cyclic azomethine imine **1a** and iminooxindole **2a** as presented in entries 1−7 of Table 2. Noticeably, the used solvents influenced the chemical yield of **3aa** largely and did not change the diastereoselectivity of **3aa** at all. In all the solvents checked, the 1,3-DC reaction went smoothly, thus furnishing **3aa** in excellent diastereoselectivity (Table 2, entries 1−7). Regarding the chemical yield of **3aa**, it was significantly affected by the solvent used. For example, use of EtOH gave **3aa** in a trace amount after 20 h (Table 2, entry 2). In the case of THF and 1,4-dioxane, **3aa** was obtained in similar chemical yields (Table 2, entries 4 and 6). With respect to other solvents, the chemical yield of **3aa** changed from 41 to 77% (Table 2, entries 1, 3, 5, and 7). Simultaneously, the catalytic loading of CuI was screened in the range from 10 to 50 mol %, and **3aa** was obtained in the highest yield when CuI was loaded in 20 mol % (Table 2, entries 1 and 8−10). Moreover, the increase in the reaction

Table 2. Screening of Solvents[a]



entry	solv.	temp (°C)	time (h)	CuI (*x* mol %)	yield[b] (%)	dr[c]
1	toluene	60	20	10	77	>99:1
2	EtOH	60	20	10	trace	
3	1,2-DCE	60	20	10	60	>99:1
4	THF	60	20	10	29	>99:1
5	$CHCl_3$	60	20	10	68	>99:1
6	1,4-dioxane	60	20	10	28	>99:1
7	CH_3CN	60	20	10	41	>99:1
8	toluene	60	20	20	88	>99:1
9	toluene	60	20	30	80	>99:1
10	toluene	60	20	50	77	>99:1
11	toluene	80	10	20	50	>99:1
12	toluene	100	6	20	10	>99:1

[a]Reactions were carried out with 0.12 mmol of **1a** and 0.1 mmol of **2a** in the presence of *x* mol % of CuI in 1.0 mL of solvent at specified temperature. [b]Isolated yield. [c]Determined by ^1H NMR spectroscopy.

temperature dramatically decreased the chemical yield of **3aa** (Table 2, entries 8 vs 11 and 12). Therefore, at the current stage, we determined the optimal reaction conditions: **1a**/**2a**/CuI = 1.2:1:0.2, toluene, 60 °C.

Next, under the optimal reaction conditions, we extended the reaction scope of 1,3-DC between *N,N′*-cyclic azomethine imines **1** and iminooxindoles **2**, as outlined in Table 3. In most cases, the 1,3-DCs gave rise to products **3** in excellent diastereoselectivities (Table 3, entries 1−26). In comparison, the chemical yield of the 1,3-DCs was clearly affected by substrates **1** and **2**. Reaction of **1p** with **2a** did not take place at all in 40 h (Table 3, entry 27). The same negative result was observed with the reaction between **1q** and **2a** (Table 3, entry 28). The 1,3-DCs of **1h** with **2a** and **1l** with **2a** generated products **3ha** and **3la** in similar chemical yields (Table 3, entries 19 vs 23). In the case of the rest of the 1,3-DCs examined, the chemical yield of **3** ranged from 80 to 95% (Table 3, entries 1−18, 20−22, and 24−26). Simultaneously, the relative configuration of **3aa** was determined by single-crystal X-ray analysis, as depicted in Figure 1. On the basis of the relative stereochemistry of **3aa**, we similarly assigned the relative configurations of other **3** products as shown in Table 3.[15] Moreover, we carried out 1,3-DC of **1i** and **2a** on a gram scale, and **3ia** was obtained in 97% yield (see details in Supporting Information, SI). Meanwhile, the asymmetric catalytic 1,3-DC of **1a** and **2a** was attempted using chiral Lewis acids and organocatalysts; however, **3aa** was isolated as a racemate in all cases (see details in SI).

Conformational analysis of **3aa** indicated that its *N,N*-bicyclic moiety adopts a concave conformation. By virtue of the nonplanar structure of the *N,N*-bicyclic subunit, the two protons of the NCH_2 group in the pyrazolidinone ring become chemically nonequivalent: one proton resides in the deshielding area of the monosubstituted benzene ring of 1,2,4-triazolidine; the other one positions at the shielding area of the same benzene ring. As a consequence, the two protons should exhibit quite different behaviors in ^1H NMR. Actually, this assumption was in full agreement with the obtained ^1H

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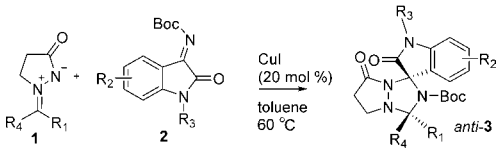
Table 3. Extension of the Reaction Scope[a]



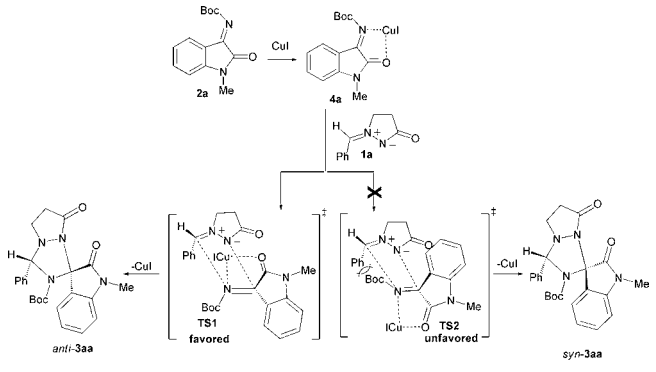
entry	1 (R_1, R_4)	2 (R_2, R_3)	time (h)	3	yield[b] (%)	dr[c]
1	**1a** (C_6H_5, H)	**2a** (H, Me)	20	**3aa**	88	>99:1
2	**1a** (C_6H_5, H)	**2b** (5-F, Me)	20	**3ab**	92	>99:1
3	**1a** (C_6H_5, H)	**2c** (5-Cl, Me)	12	**3ac**	90	>99:1
4	**1a** (C_6H_5, H)	**2d** (5-OMe, Me)	20	**3ad**	87	>99:1
5	**1a** (C_6H_5, H)	**2e** (5-Me, Me)	20	**3ae**	94	>99:1
6	**1a** (C_6H_5, H)	**2f** (5-Br, Me)	12	**3af**	91	>99:1
7	**1a** (C_6H_5, H)	**2g** (5-NO_2, Me)	20	**3ag**	90	>99:1
8	**1a** (C_6H_5, H)	**2h** (6-Cl, Me)	20	**3ah**	83	>99:1
9	**1a** (C_6H_5, H)	**2i** (6-Br, Me)	12	**3ai**	85	>99:1
10	**1a** (C_6H_5, H)	**2j** (H, Bn)	20	**3aj**	87	>99:1
11	**1a** (C_6H_5, H)	**2k** (H, allyl)	20	**3ak**	83	>99:1
12	**1a** (C_6H_5, H)	**2l** (H, MOM)	20	**3al**	88	>99:1
13	**1b** (4-F-C_6H_4, H)	**2a** (H, Me)	20	**3ba**	83	>99:1
14	**1c** (3-F-C_6H_4, H)	**2a** (H, Me)	40	**3ca**	94	>99:1
15	**1d** (2-F-C_6H_4, H)	**2a** (H, Me)	40	**3da**	85	>99:1
16	**1e** (4-Cl-C_6H_4, H)	**2a** (H, Me)	20	**3ea**	80	>99:1
17	**1f** (2-Cl-C_6H_4, H)	**2a** (H, Me)	40	**3fa**	86	>99:1
18	**1g** (3-Cl-C_6H_4, H)	**2a** (H, Me)	20	**3ga**	91	>99:1
19	**1h** (4-Br-C_6H_4, H)	**2a** (H, Me)	12	**3ha**	78	>99:1
20	**1i** (2-Br-C_6H_4, H)	**2a** (H, Me)	12	**3ia**	95	>99:1
21	**1j** (4-Me-C_6H_4, H)	**2a** (H, Me)	40	**3ja**	88	>99:1
22	**1k** (3-Me-C_6H_4, H)	**2a** (H, Me)	40	**3ka**	81	>99:1
23	**1l** (4-MeO-C_6H_4,H)	**2a** (H, Me)	40	**3la**	77	>99:1
24	**1m** (3-MeO-C_6H_4, H)	**2a** (H, Me)	40	**3ma**	82	>99:1
25	**1n** (3,4-di-MeO-C_6H_3, H)	**2a** (H, Me)	40	**3na**	80	>99:1
26	**1o** (4-pyridine, H)	**2a** (H, Me)	20	**3oa**	86	>99:1
27	**1p** (2-thiophene, H)	**2a** (H, Me)	40	**3pa**	nr[d]	
28	**1q** (Me, Me)	**2a** (H, Me)	40	**3qa**	nr[d]	

[a]Reactions were carried out with 0.12 mmol of **1** and 0.1 mmol of **2** in the presence of 20 mol % of CuI in 1.0 mL of toluene at 60 °C. [b]Isolated yield. [c]Determined by ^{1}H NMR spectroscopy. [d]No reaction.

Figure 1. X-ray single-crystal structure of **3aa** (with thermal ellipsoils shown at the 50% probability level).

NMR experimental results (see details in SI): one proton resonates at 3.17 ppm, and the other one signals at 3.43 ppm. Moreover, we shed light on the diastereoselective formation of *anti*-**3aa** on the basis of the proposed reaction mechanism as described in Scheme 2. First, the chelation interaction of **2a** to CuI affords **4a**. Then, **4a** will attack **1a** by the two different orientations, as shown in transition states **TS1** and **TS2**, which lead to the formation of *anti*-**3aa** and *syn*-**3aa**, respectively. With the aid of the molecular model, we found strong steric repulsion between the benzene ring and Boc group in **TS2**. Compared to **TS2**, the same destabilizing effect does not exist at all in **TS1**. As a consequence, transition state **TS1** should be more stable than **TS2** and mainly accounts for the formation of *anti*-**3aa**. According to literature,[16] it is

Scheme 2. Proposed Mechanism for the Formation of 3aa



assumed that 1,3-DC of **1a** and **2a** follows a concerted process. Moreover, DFT calculations have located the concerted transition states **TS1** and **TS2** and disclosed that the formation of *anti*-**3aa** is kinetically and thermodynamically favored (see details in SI).

In conclusion, in the presence of 20 mol % of CuI, the 1,3-dipolar cycloadditions of *N,N′*-cyclic azomethine imines **1** with iminooxindoles **2** proceeded efficiently and provided easy access to the oxindole spiro-*N,N*-bicyclic heterocycles in

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moderate to excellent chemical yields with excellent diastereoselectivities. Furthermore, exploration of new cycloadditions of *N*,*N*′-cyclic azomethine imines with various structurally diverse and complex dipolarophiles is ongoing in our organic lab and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00139.

Experimental details and NMR spectra for the obtained compounds **3** (PDF)
X-ray data for **3aa** (CIF)

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Notes

The authors declare no competing financial interest.

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