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Group 11 Metal Amide-Catalyzed Asymmetric Cycloaddition Reactions of Azomethine Imines with Terminal Alkynes

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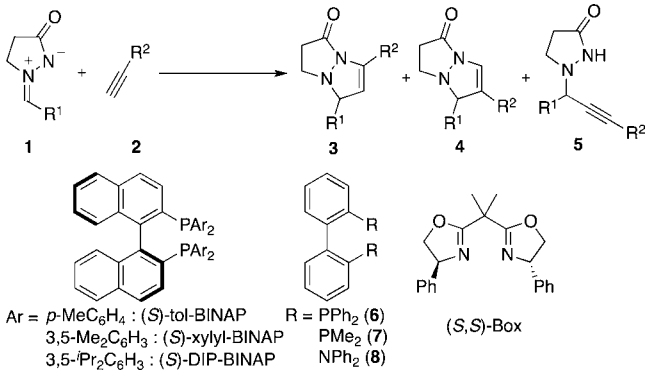
Supporting Information

ABSTRACT: We developed a 1,3-dipolar cycloaddition reaction of azomethine imines with terminal alkynes catalyzed by group 11 metal amides to provide *N,N*-bicyclic pyrazolidinone derivatives. This reaction afforded the cycloadducts in a unique 5,7-disubstituted manner. Furthermore, we succeeded in applying this catalysis to asymmetric reactions, and the desired heterocycles were produced in high yields with exclusive regioselectivity and high enantioselectivity. Mechanistic studies elucidated a stepwise reaction pathway and critical features that determine the regioselectivity.

Metal and metalloid catalysts have attracted great interest in the field of acid/base catalysis in the past two decades.[1] Among the various acid/base catalysts that have been intensively studied, Lewis acid catalysts have displayed unique reactivity and selectivities, especially enantioselectivity.[2] These catalysts have often been used for C−C bond-forming reactions via proton transfer, which usually start with carbanion formation using a catalytic amount of base.[3] In many cases, external bases have been employed in the presence of Lewis acid catalysts, causing the available Lewis acids to be limited because they must be base-compatible in this situation. Moreover, the range of substrates for the reactions is reasonably dependent upon the basicity of the employed bases. We envisioned that a more effective and general catalytic system would be produced if metal catalysts that have both Lewis acidic and strong Brønsted basic character could be developed.[4] Our group recently reported silver amide as such a metal catalyst. It promotes the 1,3-dipolar cycloaddition of azomethine ylides to alkenes, affording pyrrolidine derivatives in high yields with high diastereo- and enantioselectivity.[5] Proton transfer reactions using highly Brønsted basic catalysts have been recognized to be difficult because their conjugate acids display very high pK_a values. However, silver amide can realize an effective catalytic cycle under these conditions.

Group 11 metals are well-known for their specific ability to coordinate with C−C multiple bonds to generate π complexes. We therefore focused on the cooperative activation of terminal alkynes using the Lewis acidity and Brønsted basicity of group 11 metal amides to generate active acetylide species. Herein we describe a 1,3-dipolar cycloaddition reaction of azomethine imines with terminal alkynes catalyzed by the group 11 metal amides silver amide and copper amide, in which acetylide formation is a key step (Scheme 1).

Scheme 1. General Scheme of the Reaction of Azomethine Imines with Terminal Alkynes



The synthesis of heterocycles is of great importance because of their various applications as pharmaceutical, agricultural, and engineering materials.[6] Among the numerous methods for the preparation of heterocycles, 1,3-dipolar cycloaddition reactions have played important roles because various kinds of heterocyclic compounds can be synthesized by the combination of 1,3-dipoles and dipolarophiles.[7] 1,3-Dipolar cycloadditions of azomethine imines **1** derived from 3-pyrazolidinone to terminal alkynes **2** afford five-membered ring structures containing N−N bonds, which are typical motifs found in biologically active compounds.[8,9] However, to our knowledge, there had been no report of an asymmetric variant of this reaction before the article by Fu et al.[9b] describing cycloadditions of *N,N*-cyclic azomethine imines **1** to terminal alkynes catalyzed by a Cu(I)−phosphaferrocene complex to afford *5,6-disubstituted* bicyclic compounds **4** with high enantioselectivity. There has been no report of highly regioselective reactions affording *5,7-disubstituted* products **3**.

In an initial investigation, the reaction of azomethine imine **1a** with phenylacetylene (**2a**) was examined (Table 1). In the presence of 10 mol % silver bis(trimethylsilyl)amide (AgHMDS) in tetrahydrofuran (THF), the reaction proceeded slowly at 20 °C to afford the 1,2-adduct **5aa** alone in poor yield (8%, entry 1). When the reaction temperature was increased to 40 °C, the reaction proceeded smoothly even at a lower concentration, providing a ca. 1:1 mixture of the 1,2-adduct **5aa** and cycloadduct **3aa** (entry 2). Interestingly, the regioselectivity of the cycloadduct was the reverse of that in the previously reported reaction, and 5,7-disubstituted adduct **3aa** was

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Table 1. 1,3-Dipolar Cycloaddition of Azomethine Imine 1a to Alkyne 2a Using a Silver Catalyst[a]

entry	solvent	T (°C)	conc. (M)	yield (%)	**3aa**/**5aa**
1	THF	20	0.4	8	<1/>99
2	THF	40	0.2	97	45/55
3	Et_2O	40	0.2	87	42/58
4	toluene	40	0.2	32	<1/>99
5[b]	THF	40	0.2	nr	–
6[c]	THF	40	0.2	55	<1/>99
7[d]	THF	40	0.2	23	<1/>99
8[e]	THF	40	0.2	90	82/18
9[e,f]	THF	40	0.2	92	99/1

[a]Reaction conditions: **1a** (R^1 = Ph, 0.40 mmol), **2a** (R^2 = Ph, 0.80 mmol), AgHMDS (0.040 mmol), and *rac*-BINAP (0.044 mmol) in the solvent for 24 h, unless otherwise noted. [b]AgOAc was used instead of AgHMDS. [c]AgOTf and DBU were used instead of AgHMDS. [d]AgOTf and KO^{t}Bu were used instead of AgHMDS. [e]MS 5A (50 mg) was added. [f]**2a** (0.44 mmol) was used.

obtained exclusively. It is noteworthy that this is the first known example of the regioselective synthesis of the regioisomer **3aa**. We then tested other solvents, but the results were not promising (entries 3 and 4). Furthermore, no product was obtained when a less basic silver source, AgOAc, was used (entry 5); even the combination of AgOTf and an external base [1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or KO^{t}Bu] showed lower reactivity, and no cyclized product was obtained (entries 6 and 7). The stronger basicity of AgHMDS was found to be essential for this cyclization. The addition of 5 Å molecular sieves (MS 5A) and a decrease in the amount of the alkyne gave **3aa** almost exclusively in high yield (92%, 99/1; entry 9).

We found a broad substrate scope with respect to substituents on the aromatic rings of both the azomethine imine and the phenylacetylene (Table 2). Electron-donating

Table 2. Azomethine Imine and Alkyne Substrate Scope[a]

entry	R^1	R^2	yield (%)	**3**/**5**
1	Ph (**1a**)	Ph (**2a**)	92	99/1
2	*p*-MeC_6H_4 (**1b**)	Ph (**2a**)	98	>99/<1
3	*p*-$MeOC_6H_4$ (**1c**)	Ph (**2a**)	84	>99/<1
4	*p*-ClC_6H_4 (**1d**)	Ph (**2a**)	92	>99/<1
5	1-Nap (**1e**)	Ph (**2a**)	96	>99/<1
6	Ph (**1a**)	*p*-MeC_6H_4 (**2b**)	90	>99/<1
7	Ph (**1a**)	*p*-$MeOC_6H_4$ (**2c**)	88	>99/<1
8	Ph (**1a**)	*p*-ClC_6H_4 (**2d**)	93	>99/<1
9	Ph (**1a**)	*p*-FC_6H_4 (**2e**)	96	>99/<1

[a]Reaction conditions: **1** (0.40 mmol), **2** (0.44 mmol), AgHMDS (0.040 mmol), *rac*-BINAP (0.044 mmol), and MS 5A (50 mg) in THF (2 mL) at 40 °C for 24 h.

substituents (*p*-methyl or -methoxy) and electron-withdrawing substituents (*p*-chloro) on the ring in the azomethine imine did not affect the reactivity or regioselectivity (entries 2–4). Steric bulkiness on this aromatic ring was also tolerated (entry 5). With respect to substituents on the phenylacetylene, various electronic and steric characters did not decrease the reactivity or selectivity (entries 6–9), although in the previous report, electron-rich terminal alkynes required a longer reaction time because of low reactivity.[9b]

Having established the exclusive regioselective reaction conditions for the silver amide-catalyzed cyclization of azomethine imines and terminal alkynes, we turned our attention to asymmetric catalysis (Table 3). Unfortunately,

Table 3. Asymmetric 1,3-Dipolar Cycloaddition Reaction of 1a with 2a[a]

entry	M	ligand	yield (%)	**3aa**/**5aa**	ee of **3aa** (%)
1	Ag	(*S*)-BINAP	95	99/1	24
2	Cu	(*S*)-BINAP	96	>99/<1	50
3	Cu	(*S*)-Tol-BINAP	94	>99/<1	57
4	Cu	(*S*)-Xylyl-BINAP	93	>99/<1	60
5	Cu	(*S*)-DIP-BINAP	93	>99/<1	83
6[b]	Cu	(*S*)-DIP-BINAP	97	>99/<1	90
7[b,c]	Cu	(*S*)-DIP-BINAP	94	>99/<1	90

[a]Reaction conditions: **1a** (0.40 mmol), **2a** (0.44 mmol), MHMDS (0.040 mmol), ligand (0.044 mmol), and MS 5A (50 mg) in THF at 40 °C (2 mL) for 24 h, unless otherwise noted. [b]CPME was used as the solvent. [c]Catalyst 5 mol%. **2a** was added slowly over 16 h.

despite intensive screening of ligands, chiral AgHMDS displayed poor enantioselectivity (24% ee; entry 1). Therefore, we switched to copper amide catalysis. The desired heterocycle was produced with moderate enantioselectivity in the presence of 10 mol % CuHMDS[10] and (*S*)-BINAP (50% ee; entry 2).[11] The more sterically bulky ligands tol-BINAP and xylyl-BINAP afforded the desired products with higher enantioselectivity than BINAP (entries 3 and 4). (*S*)-DIP-BINAP led to cycloaddition in high yield with good enantioselectivity and exclusive regioselectivity (entry 5). Finally, the desired adduct **3aa** was obtained exclusively in 97% yield with 90% ee when cyclopentyl methyl ether (CPME) was used as the solvent (entry 6).[12]

Wide substrate scope was confirmed in the chiral CuHMDS-catalyzed cycloaddition. With respect to the imine portion of the azomethine imine, the reaction tolerated electron-deficient and -rich aryl, alkenyl, and alkyl groups on the carbonyl carbons, furnishing the products in high yields with high enantioselectivity (Table 4, entries 1–9). With regard to the terminal alkyne, the reactions proceeded cleanly when alkynes with electron-deficient and electron-rich aromatic, alkyl, silyl, and protected alcohol groups were employed (entries 10–17).

To obtain a better understanding of the reaction mechanism, several experiments were conducted. As described above, the 1,2-adduct **5aa** was produced in the reaction of azomethine imine **1a** with terminal alkyne **2a**. When **5aa** was treated under the reaction conditions, cycloadduct **3aa** was obtained quantitatively (Scheme 2). In addition, the ee values of **5aa** and **3aa** were almost identical under the said conditions, even when racemic ligands were used. On the other hand, this transformation did not proceed without the transition metal. Furthermore, we investigated the use of isolated copper acetylide. When a catalytic amount of copper acetylide species was employed instead of the metal amide, the reactivity decreased slightly without loss of enantioselectivity. When HMDS was added to this reaction system, the reactivity was recovered.[13] These results indicate that the conjugate acid of MHMDS plays an important role in the catalytic cycle. Therefore, we propose that the cyclized compounds are not

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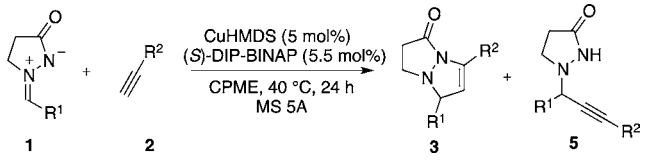
Table 4. Azomethine Imine and Alkyne Substrate Scope for the Asymmetric Reaction[a]

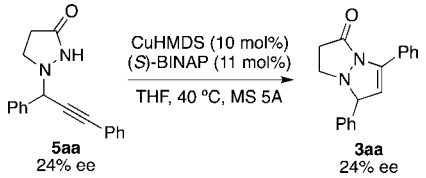


1 2 3 5

entry	R^1	R^2	yield (%)	3/5	ee of 3 (%)
1	Ph (**1a**)	Ph (**2a**)	94	>99/<1	90
2	*p*-MeC_6H_4 (**1b**)	Ph (**2a**)	98	>99/<1	92
3	*p*-$MeOC_6H_4$ (**1c**)	Ph (**2a**)	84	>99/<1	93
4	*p*-ClC_6H_4 (**1d**)	Ph (**2a**)	92	>99/<1	88
5	1-Nap (**1e**)	Ph (**2a**)	87	>99/<1	93
6	*p*-CNC_6H_4 (**1f**)	Ph (**2a**)	96	>99/<1	90
7	PhCH=CH (**1g**)	Ph (**2a**)	88	>99/<1	89
8	^{n}Pr (**1h**)	Ph (**2a**)	92	>99/<1	92
9	^{c}Hex (**1i**)	Ph (**2a**)	94	>99/<1	95
10	Ph (**1a**)	*p*-MeC_6H_4 (**2b**)	90	>99/<1	87
11	Ph (**1a**)	*p*-$MeOC_6H_4$ (**2c**)	88	>99/<1	88
12	Ph (**1a**)	*p*-ClC_6H_4 (**2d**)	93	>99/<1	90
13	Ph (**1a**)	*p*-FC_6H_4 (**2e**)	96	>99/<1	91
14	Ph (**1a**)	^{n}Bu (**2f**)	88	>99/<1	90
15	Ph (**1a**)	^{c}Hex (**2g**)	90	>99/<1	88
16	Ph (**1a**)	TES[b] (**2h**)	92	>99/<1	93
17	Ph (**1a**)	CH_2OBn (**2i**)	83	>99/<1	82

[a]Reaction conditions: **1** (0.40 mmol), **2** (0.44 mmol), CuHMDS (0.020 mmol), (*S*)-DIP-BINAP (0.022 mmol), and MS 5A (50 mg) in CPME (2 mL) at 40 °C for 24 h. **2** was added slowly over 16 h. [b]TES = triethylsilyl.

Scheme 2. Transformation of the 1,2-Adduct into the Cycloadduct



5aa 24% ee → **3aa** 24% ee

produced via a concerted pathway as proposed in previous reports[9] but instead are formed via a stepwise reaction mechanism involving 1,2-addition of the metal acetylide to the azomethine imines followed by intramolecular cyclization with the alkyne activated by the Lewis acid (Scheme 3). The Lewis acidity of the metal amide is utilized for activation of C–C multiple bonds in both the formation of the metal acetylide and the intramolecular cyclization. It is noted that basic reaction conditions, in which no active proton source exists, effectively promoted the intramolecular cyclization. The conjugate acids of the bases with less Brønsted basicity ($DBUH^+$, ^{t}BuOH) could protonate the alkynylated intermediate and inhibit intramolecular cyclization (Table 1, entries 5 and 6). This proposed pathway can also explain the unique regioselectivity of the products.

Finally, it was interesting to find that the regioselectivity could be changed by using different ligands (Table 5). Complete reversal of the regioselectivity was observed when bisoxazoline (Box)-type and 2,2′-bipyridyl ligands were used

Scheme 3. Proposed Catalytic Cycle

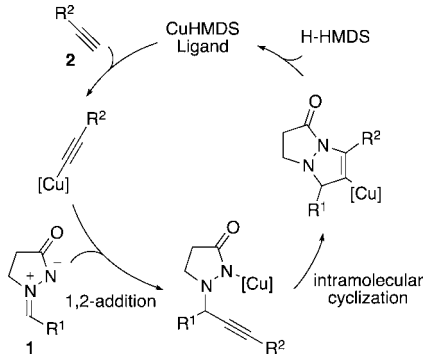


Table 5. Effect of the Ligand on the Regioselectivity[a]

entry	ligand	yield (%)	**3aa**/**4aa**
1	(*S*)-BINAP	96	>99/<1
2	(*S*,*S*)-Box	>99	<1/>99
3	2,2′-bipyridine	>99	<1/>99
4	**6**	>99	86/14
5	**7**	>99	22/78
6	**8**	98	73/27

[a]Reaction conditions: **1a** (0.40 mmol), **2a** (0.44 mmol), CuHMDS (0.040 mmol), ligand (0.044 mmol), and MS 5A (50 mg) in CPME (2 mL) at 40 °C for 24 h. **2a** was added slowly over 16 h.

(entries 2 and 3). Three types of BIPHEP-type ligands (**6**–**8**) were also employed in this reaction to examine the steric and electronic effects of the ligand on the regioselectivity. BIPHEP **6** produced a mixture of two regioisomers with a **3aa**/**4aa** ratio of 84/16 (entry 4). By contrast, the sterically less bulky BIPHEP analogue **7** led to a reversed **3aa**/**4aa** ratio of 22/78 (entry 5). When *N*,*N*,*N*′,*N*′-tetraphenyl-2,2′-diaminobiphenyl ligand **8** (the N analogue of BIPHEP) was used, the reaction proceeded smoothly to afford the cycloaddition products in high yield with **3aa**/**4aa** = 73/27 (entry 6). These results indicate that the steric character of the ligand has much more influence on the regioselectivity than the type of atom coordinating to the metal.

In conclusion, we have developed a silver amide-catalyzed cycloaddition reaction of azomethine imines with terminal alkynes to afford 5,7-disubstituted adducts in high yields with excellent selectivities. To our knowledge, this is the first description of the synthesis of 5,7-disubstituted cycloadducts with exclusive regioselectivity. We have also succeeded in applying this catalysis to asymmetric reactions, and the desired cycloadducts were obtained in high yields with high regio- and enantioselectivity using CuHMDS and the DIP-BINAP ligand. Mechanistic studies revealed that the reactions proceed via a stepwise pathway and that the steric character of the ligand controls the reaction pathway to determine the regioselectivity. Further investigations of the detailed reaction mechanism and expansion of the substrates scope are ongoing.

■ ASSOCIATED CONTENT

Supporting Information

Mechanistic study and experimental details. 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) To the best of our knowledge, this is the first example of a reaction (either asymmetric or racemic) using CuHMDS as a catalyst. We have also found that chiral CuHMDS is an excellent catalyst for asymmetric Mannich-type reactions.

(12) The absolute configuration of the product **3aa** was determined to be *S* (for details, see the Supporting Information).

(13) See Table S-1 in the Supporting Information.