Communication

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

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

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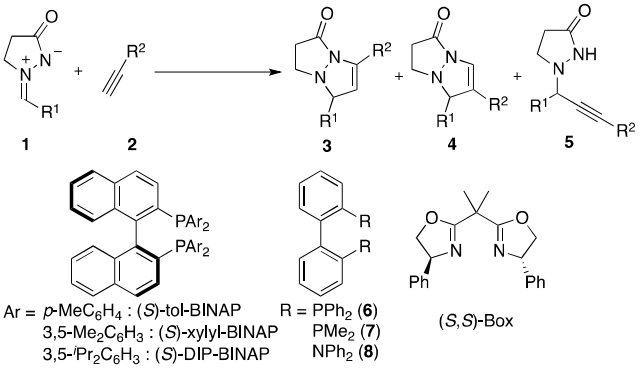
Supporting Information Placeholder

ABSTRACT: We developed 1,3-dipolar cycloaddition reactions 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 carbon–carbon bond-forming reactions *via* proton transfer, which usually start from carbanion formations using catalytic amounts of bases.[3] In many cases, external bases were employed in the presence of Lewis acid catalysts, causing available Lewis acids to be limited because the Lewis acids should 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 characters were developed.[4] As such a metal catalyst, our group recently reported silver amide, which 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 the 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 carbon–carbon multiple bonds to generate π-complexes. We therefore focused on the cooperative activation of terminal alkynes using Lewis acidity and Brønsted basicity of group 11 metal amides to generate active acetylide species. Herein, we describe 1,3-dipolar cycloaddition reactions of azomethine imines with terminal alkynes catalyzed by group 11 metal amides, silver amide and copper amide, in which acetylide formation is a key step (Scheme 1).

Scheme 1. General Scheme of Reactions 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 nitrogen–nitrogen bonds, which are typical motifs found in biologically active compounds.[8,9] However, to our knowledge, there had been no report on an asymmetric variant of this reaction before Fu's article.[9b] Fu et al. described cycloadditions of *N*,*N*-cyclic azomethine imines **1** to terminal alkynes catalyzed by a copper(I)–phosphaferrocene complex to afford *5,6-disubstituted* bicycle compounds **4** with high enantioselectivity. However, 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 phenyl acetylene **2a** was examined (Table 1). In the presence of 10 mol% of silver bis(trimethylsilyl)amide (AgHMDS), 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 mixture of the 1,2-adduct **5aa** and cycloadduct **3aa** (ca. 1:1, entry 2). Interestingly, the regioselectivity of the cycloadduct was the reverse of that of the previously reported reaction, and *5,7-disubstituted* adduct **3aa** was obtained exclusively. It is noteworthy that this is the first known example of the regiose-

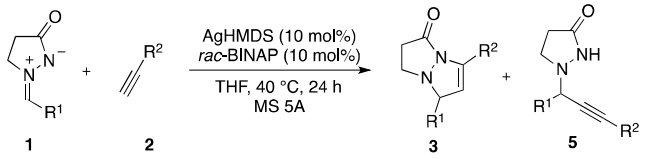
lective synthesis of the regioisomer **3aa**. We then tested other solvents, but the results were not promising (entries 3, 4). Furthermore, no product was obtained by using a less basic silver source (AgOAc, entry 5), and even the combination of AgOTf and an external base (DBU or KO^{t}Bu) showed lower reactivity, and no cyclized product was obtained (entries 6 and 7). Stronger basicity of AgHMDS was found to be essential for this cyclization. The addition of molecular sieves (MS) 5A and a decrease in the amount of the alkyne gave the cycloadduct **3aa** almost exclusively in high yield (92%, 99/1, entry 9).

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

Entry	Solv.	Temp. (°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	n.r.	–
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: The reaction of azomethine imine **1a** (R^1=Ph, 0.40 mmol) with phenyl acetylene **2a** (R^2=Ph, 0.80 mmol) was conducted using AgHMDS (0.040 mmol) and *rac*-BINAP (0.040 mmol) for 24 h. [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 used. [f]**2a** (0.44 mmol) was used.

Table 2. Substrate Scope: Azomethine Imine and Alkyne[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: The reaction of azomethine imine **1** (0.40 mmol) with alkyne **2** (0.44 mmol) was conducted using AgHMDS (0.040 mmol), *rac*-BINAP (0.040 mmol), and MS 5A (50 mg) in THF (2 mL) at 40 °C for 24 h.

We have revealed that the scope of substrates is broad for substituents on the aromatic rings of both azomethine imines and phenyl acetylenes (Table 2). Electron-donating substituents (*para*-methyl or -methoxy) and electron-withdrawing substituents (*para*-chloro) on the azomethine imine part did not affect the reactivity or regioselectivity (entries 2–4). Steric bulkiness of the aromatic ring was tolerated for this cyclization (entry 5). With respect to substituents on phenyl acetylenes, various electronic and steric characters could 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 silver amide-catalyzed cyclization of the azomethine imine **1** and terminal alkyne **2**, we turned our attention to asymmetric catalysis (Table 3). Unfortunately, despite the 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% of CuHMDS[10] and (*S*)-BINAP (50% ee, entry 2).[11] More sterically bulky BINAP ligands, namely tol-BINAP and xylyl-BINAP, afforded the desired products with higher enantioselectivity than that with BINAP (entries 3 and 4). (*S*)-DIP-BINAP led to the 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]

Table 3. Asymmetric 1,3-Dipolar Cycloaddition Reaction of Azomethine **1a** Imine with Terminal Alkyne **2a**[a]

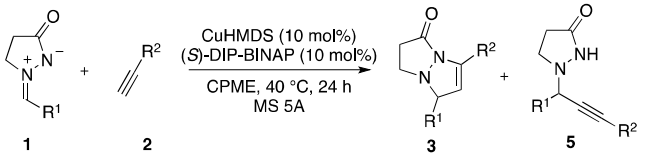
Entry	M	Ligand	Yield (%)	**3aa**/**5aa**	ee (%, **3aa**)
1	Ag	(*S*)-BINAP	95	99/1	24
2	Cu	(*S*)-BINAP	96	>99/<1	50
3	Cu	(*S*)-Tol-BINAP	94	>99/<1	57
4	Cu	(*S*)-Xylyl-BINAP	93	>99/<1	60
5	Cu	(*S*)-DIP-BINAP	93	>99/<1	83
6[b]	Cu	(*S*)-DIP-BINAP	97	>99/<1	90
7[b,c]	Cu	(*S*)-DIP-BINAP	94	>99/<1	90

[a]Reaction conditions: The reaction of azomethine imine **1a** (0.40 mmol) with phenyl acetylene **2a** (0.44 mmol) was conducted using metal HMDS (0.040 mmol), a ligand (0.040 mmol), and MS 5A (50 mg) in THF at 40 °C (2 mL) for 24 h. [b]CPME was used as the solvent. [c]**2a** was added slowly over 16 h.

Wide substrate scope was confirmed in the chiral CuHMDS-catalyzed cycloaddition. With respect to the imine portions of the azomethine imines, 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 terminal alkynes, the reactions proceeded cleanly by employing alkynes with electron-deficient and electron-rich aromatic, alkyl, silyl, and protected alcohol groups (entries 10–17).

For better understanding of the reaction mechanism, several experiments were conducted. As we described above, the 1,2-adduct **5aa** was produced in the reaction of azomethine imine **1a** with terminal alkyne **2a**. It was confirmed that when **5aa** was treated under the reaction conditions, the cycloadduct **3aa** was obtained quantitatively (Scheme 2). In addition, the ee values of **5aa** and **3aa** were almost identical under the said conditions even using racemic ligands. On the other hand, this transformation did not proceed without the transition metals. Furthermore, we investigated the use of isolated copper acetylide. We employed a catalytic amount of copper acetylide species instead of the metal amides in this reaction, and found that the reactivity decreased slightly without loss of enantioselectivity. When hexamethyldisilazane was added to this reaction system, the reactivity was recovered.[13] These results indicate that the conjugate acid of the metal HMDS played an important role in the catalytic cycle. Therefore, it was proposed that the cyclized compounds were produced not *via* a concerted pathway as proposed in previous reports,[9] but *via* a stepwise reaction mechanism: 1,2-addition of metal acetylides to azomethine imines took place, followed by intramolecular cyclization with alkynes activated by Lewis acid (Scheme 3). The Lewis acidity of the metal amides was utilized for activation of carbon–carbon multiple bonds in both formation of metal acetylides and 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.

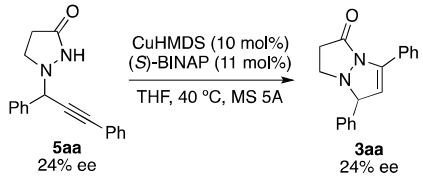
Table 4. Reaction Scope for Asymmetric Reaction: Azomethine Imine and Alkyne[a]



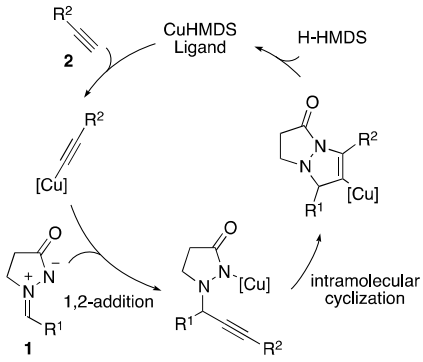
Entry	R^1	R^2	Yield (%)	**3**/**5**	ee (%, **3**)
1	Ph (**1a**)	Ph (**2a**)	92	99/1	90
2	*p*-MeC_6H_4 (**1b**)	Ph (**2a**)	98	>99/<1	92
3	*p*-$MeOC_6H_4$ (**1c**)	Ph (**2a**)	84	>99/<1	93
4	*p*-ClC_6H_4 (**1d**)	Ph (**2a**)	92	>99/<1	88
5	*p*-CNC_6H_4 (**1f**)	Ph (**2a**)	96	>99/<1	90
6	1-Nap (**1e**)	Ph (**2a**)	87	>99/<1	93
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: The reaction of azomethine imine **1** (0.40 mmol) with alkyne **2** (0.44 mmol) was conducted using CuHMDS (0.040 mmol), (*S*)-DIP-BINAP (0.040 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 to the Cycloadduct



Scheme 3. Proposed Catalyst Cycle



Finally, it was interesting to find that the regioselectivity was changed by the ligands employed (Table 5). Complete reversal of the regioselectivity was observed by using the bisoxazoline (Box)-type ligand and 2,2′-bipyridyl ligand (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 ligands on the regioselectivity. BIPHEP **6** produced a mixture of two regioisomers with **3aa**/**4aa** = 84/16 (entry 4). By contrast, the sterically less bulky BIPHEP analogue **7** led to the reverse ratio of **3aa**/**4aa** = 22/78 (entry 5). When *N*,*N*,*N*′,*N*′-tetraphenyl-2,2′-diaminobiphenyl ligand **8** (*N*-analogue of BIPHEP) was used, the reaction proceeded smoothly to afford the cycloaddition products in high yield with **3aa**/**4aa** = 73/27 regioselectivity (entry 6). These results indicate that the steric character of the ligands has much more influence on the regioselectivity than the type of atom coordinating to the metal.

Table 5. Effect of the Ligands on 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: The reaction of azomethine imine **1a** (0.40 mmol) with alkyne **2a** (0.44 mmol) was conducted using CuHMDS (0.040 mmol), a ligand (0.040 mmol), and MS 5A (50 mg) in CPME (2 mL) at 40 °C for 24 h. **2a** was added slowly over 16 h.

In conclusion, we have developed silver amide-catalyzed cycloaddition reactions of azomethine imines **1** with terminal alkynes **2** to afford 5,7-disubstituted adducts **3** 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 proceeded *via* a stepwise pathway, and that the steric character of the ligands controlled the reaction pathway to determine the regioselectivity. Further investigations of the detailed reaction mechanism and expansion of the scope of substrates are ongoing.

ASSOCIATED CONTENT

Supporting Information

Mechanistic study and experimental details are available free of charge via the Internet at http://pubs.acs.org.

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[7] For recent reviews on catalytic asymmetric [3+2] cycloadditions, see: a) *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products* (Ed.: Padwa, A.; Pearson, W. H.), Wiley, New York, **2002**; b) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 865-910; d) Pandy, G.; Banerjee, P.; Gadre, S. R. *Chem. Rev.* **2006**, *106*, 4484-4517; e) Pellissier, H. *Tetrahedron* **2007**, *63*, 3235-3285; f) Stanley, L. M.; Sibi, M. P. *Chem. Rev.* **2008**, *108*, 2887-2902;

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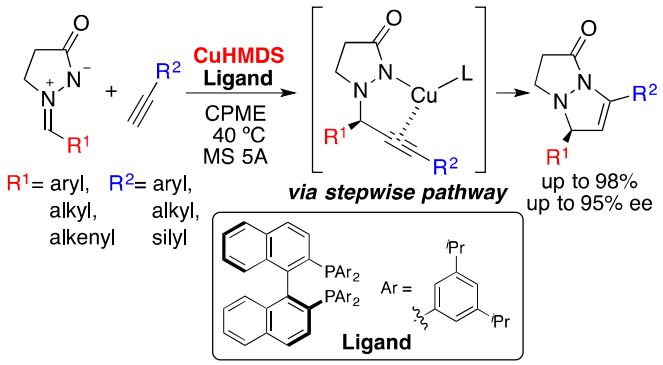
[11] To the best of our knowledge, this is the first example of reactions (not only asymmetric reactions but also racemic reactions) using CuHMDS as a catalyst. We have also found that chiral CuHMDS is an excellent catalyst for asymmetric Mannich-type reactions.

[12] The absolute configuration of the product **3aa** was determined to be *S*. Details are shown in Supporting Information.

[13] See Supporting Information (Table S-1).


CuHMDS
Ligand
CPME
40 °C
MS 5A
R1= aryl, alkyl, alkenyl
R2= aryl, alkyl, silyl
via stepwise pathway
up to 98%
up to 95% ee
PAr2
PAr2
Ar =
iPr
iPr
Ligand