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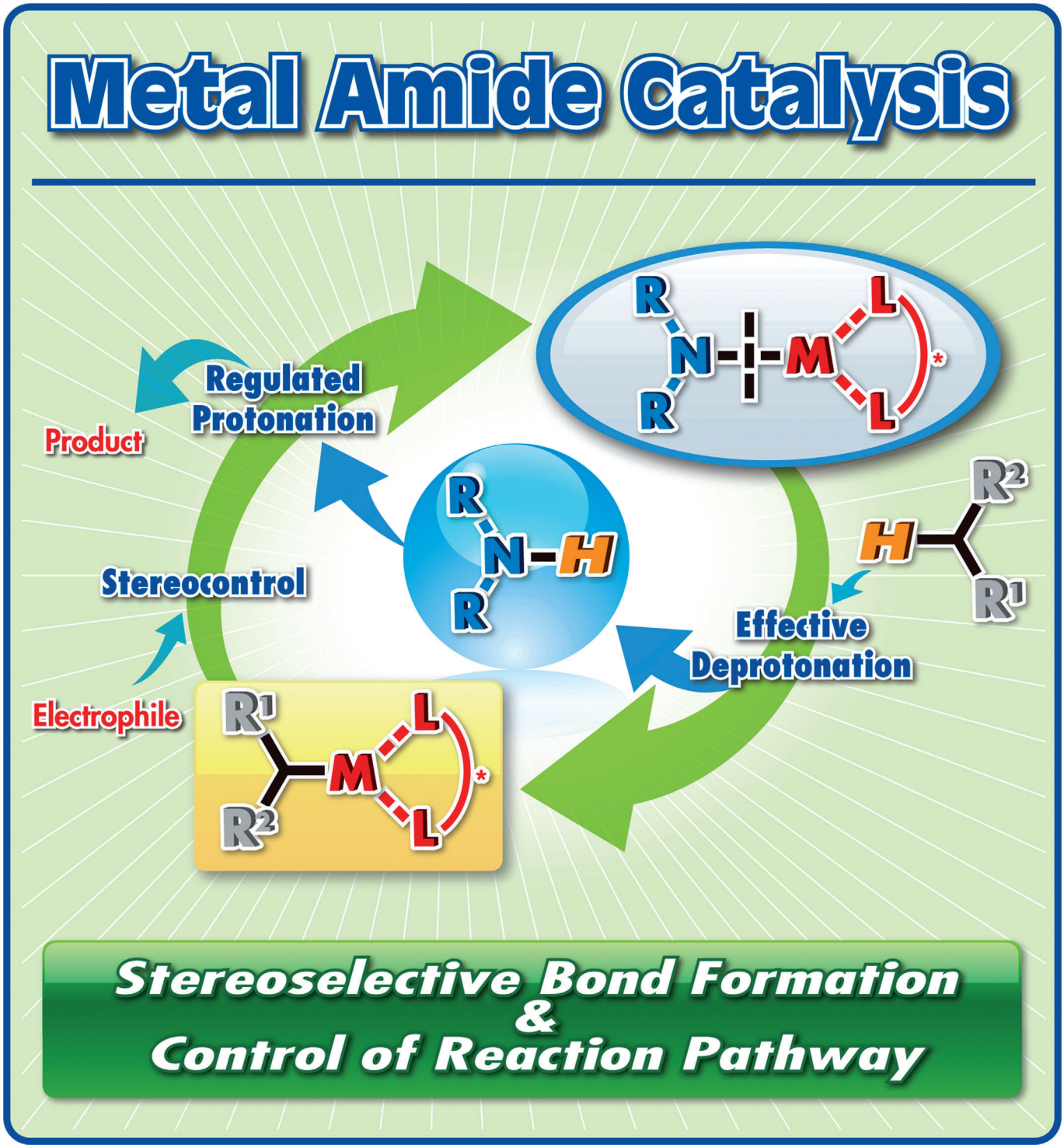
Metal Amides as the Simplest Acid/Base Catalysts for Stereoselective Carbon–Carbon Bond-Forming Reactions

Yasuhiro Yamashita and Shū Kobayashi*[a]



Abstract: In this paper, new possibilities for metal amides are described. Although typical metal amides are recognized as strong stoichiometric bases for deprotonation of inert or less acidic hydrogen atoms, transition-metal amides, namely silver and copper amides, show interesting abilities as one of the simplest acid/base catalysts in stereoselective carbon–carbon bond-forming reactions.

Keywords: asymmetric synthesis · Brønsted base · catalyst · Lewis acid · metal amide

Introduction

Acid/base catalysis has been well explored in synthetic organic chemistry. Among these catalysts, Lewis acid/Brønsted base catalysts can achieve atom-economical bond-forming processes through only proton transfer.[1] In particular, a combination of metal or metalloid Lewis acid and Brønsted base is a promising catalyst system in carbon–carbon bond-forming reactions, because control of reactivity and stereoselectivity by modified metal Lewis acid and deprotonation of active hydrogen by Brønsted base under Lewis acid activation of substrates are quite efficient for the formation of reactive and stereoselective carbanion species.

In the long history of metal catalysis, Lewis acid catalysis has been of great interest because it enables unique reactivity and stereoselectivities, especially enantioselectivities, to be attained under mild reaction conditions.[2] To obtain higher reactivities and selectivities, a target is stronger Lewis acids, which are prepared by combining more Lewis acidic metals or metalloids with less nucleophilic centers. Through this approach, ligands (counteranions) have evolved from halides to perchlorate, triflate, triflimide, etc., leading to stronger Lewis acids. However, strong Lewis acids are not always suitable for acid/base catalysis. In Lewis acid catalysis using strong Lewis acids, electrophile/Lewis acid complexes are formed in transition states, and if the complexes are too stable, Lewis acid catalysts might be trapped by electrophiles, which suppress the catalyst turnover. Moreover, a strong Lewis acid could easily interact with basic species to deactivate them and shut down the acid/base-catalyzed reactions. To achieve efficient acid/base catalysis, the use of an appropriate combination of Lewis acid and Brønsted base species is crucial.

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In Lewis acid/Brønsted base catalysis, the most familiar catalyst system is composed of metallic compounds and external basic compounds, such as tertiary amines. These species do not interact significantly with each other and work simultaneously to deprotonate substrates. On the other hand, metallic compounds including basic counteranions are also recognized as good candidates for Lewis acid/Brønsted base catalysts, because in acid/base systems using external bases, the deprotonation step proceeds in an intermolecular fashion. However, the deprotonation step proceeds in an intramolecular-like fashion when metallic compounds including basic counteranions are used (Figure 1). This means that

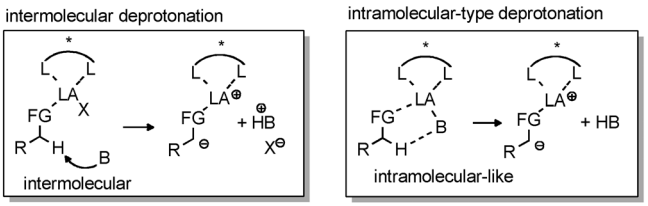


Figure 1. Intermolecular- and intramolecular-type deprotonation by a Lewis acid/base system.

metallic compounds including basic counteranions could promote acid/base-mediated reactions much more smoothly. The structures of those metallic compounds are very simple, and much flexibility exists in modification of the metal center by using coordinative ligands for reactivity and stereochemical control of reactions. To date, several types of Lewis acid/Brønsted base catalysts, such as metal acetates, phenoxides, and alkoxides, have been developed and employed in several stereoselective acid/base catalyses;[3] however, metal amides have not received the same attention as effective Lewis acid/Brønsted base catalysts in stereoselective carbon–carbon bond-forming reactions.

Metal amides, mainly alkaline metal amides, have been used as stoichiometric strong Brønsted base species in organic transformation reactions.[4] However, the difficulty in modification of alkaline metal amides by using external ligands because of the lower Lewis acidic nature of the metals, and also the acidity of the conjugate acid, a secondary amine, prevent the application of those metal amides to catalytic stereoselective reactions. Other metal amides, such as alkaline earth metal amides and transition-metal amides, have also been employed in some catalytic reactions such as hydroamination reactions[5] and hydroaminoalkylation reactions;[6] however, use of those species in catalytic stereoselective carbon–carbon bond-forming reactions has been very limited. Those metal amides may show a less Brønsted basic nature because the Lewis acidic metal part and the basic amide part sometimes interact with each other and are deactivated; therefore, the choice of metals could be an important factor in developing effective active metal amides as catalysts. However, some combination of metal and amide

could show good Lewis acid/Brønsted base catalysis with effective basicity. If so, metal amides could be one of the simplest acid/base catalysts in synthetic reactions. Here, we describe a new concept in metal amide chemistry in stereoselective Lewis acid/Brønsted base catalysis (Figure 2).

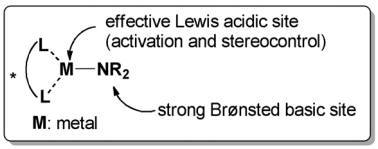


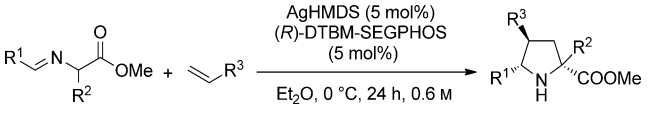
Figure 2. Concept in metal amide chemistry.

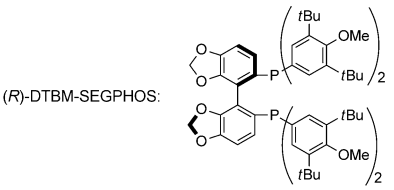
Catalytic Asymmetric [3+2] Cycloaddition Reactions of α-Aminoester Schiff Bases by Using a Chiral Silver Amide

Silver (Ag) is in Group 11 between copper (Cu) and gold (Au). Except for cases requiring exchange of counteranions (AgCl forms in most cases), silver salts, such as AgOTf, $AgSbF_6$, and $AgClO_4$, have mainly been used as Lewis acid catalysts to activate carbonyls, imines, and carbon–carbon multiple bonds in synthetic organic chemistry.[7] When silver salts are combined with chiral ligands, excellent asymmetric environments can be created; for example, AgOTf with chiral bidentate ligands, such as 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), have been successfully used in asymmetric catalysis. In contrast, silver species as chiral Brønsted bases are very limited. To date, chiral silver Brønsted bases have mostly been prepared by silver acetate or the combination of an appropriate silver salt with an external tertiary amine base, which could show high stereoselectivities in some asymmetric reactions; however, its activity as a Brønsted base has been insufficient.[2] On the other hand, a silver amide such as silver hexamethyldisilazide (AgHMDS) is a promising candidate as a base catalyst. Although AgHMDS has been prepared and evaluated in inorganic chemistry,[8] its use in stereoselective base catalysis has never been reported. We anticipated that, if the silver cation worked as an effective Lewis acid and at the same time the amide anion worked as a strong Brønsted base, the silver amide might work as an efficient catalyst to achieve asymmetric catalysis with appropriate ligands.

Based on this concept, silver hexamethyldisilazide (AgHMDS) was successfully employed in catalytic asymmetric [3+2] cycloaddition reactions of Schiff bases with olefins. [3+2] cycloaddition reactions of Schiff bases of glycine with olefins are among the most useful methods for constructing highly substituted pyrrolidine derivatives, which are important basic molecular skeletons in biologically active molecules.[9] To date, several types of Lewis acid/base catalysts and organocatalysts have been successfully employed, and high control of stereochemistry has been achieved. However, there are some limitations in substrate scope, especially in the reactions of less reactive Schiff bases prepared from aliphatic aldehydes. It was found that the chiral silver amide prepared from AgHMDS and a chiral bisphosphine ligand, DTBM-SEGPHOS, showed excellent reactivity and stereoselectivity in the [3+2] cycloaddition reaction (Table 1). The desired reaction of glycine methyl ester benzaldehyde Schiff base with methyl acrylate proceeded in high yield with high *exo*- and enantioselectivity in the presence of the chiral AgHMDS catalyst. The substrate scope of the reaction was also found to be wide, and several types of Schiff bases bearing aromatic groups, alkenyl groups, and olefins bearing an electron-withdrawing group were successfully employed to afford the desired [3+2] cy-

Table 1. Asymmetric [3+2] cycloaddition reactions of the Schiff base of α-aminoesters with olefins.



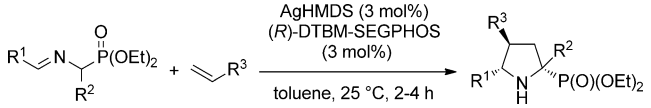


Entry	R^1	R^2	R^3	Yield [%]	*exo*/*endo*	*ee* (%, *exo*)
1	Ph	H	CO_2Me	91	99:1	98
2	4-MeC_6H_4	H	CO_2Me	90	>99:<1	99
3	2-MeC_6H_4	H	CO_2Me	91	>99:<1	99
4	4-$MeOC_6H_4$	H	CO_2Me	93	>99:<1	98
5	4-FC_6H_4	H	CO_2Me	82	>99:<1	95
6	4-ClC_6H_4	H	CO_2Me	86	>99:<1	90
7	4-BrC_6H_4	H	CO_2Me	88	97:3	92
8	4-$CF_3C_6H_4$	H	CO_2Me	90	>99:<1	91
9	4-NCC_6H_4	H	CO_2Me	98	>99:<1	96
10	3-pyridyl	H	CO_2Me	92	>99:<1	90
11	2-furyl	H	CO_2Me	90	>99:<1	94
12	2-thiophenyl	H	CO_2Me	88	>99:<1	82
13	1-naphthyl	H	CO_2Me	97	94:6	99
14	2-naphthyl	H	CO_2Me	96	>99:<1	92
15	*trans*-PhCH=CH	H	CO_2Me	90	>99:<1	98
16	Ph	Me	CO_2Me	78	>99:<1	97
17	Ph	*i*Bu	CO_2Me	87	97:3	94
18	Ph	Bn	CO_2Me	81	94:6	90
19	Ph	H	$CO(N(CH_2)_2O(CH_2)_2$-)	92	>99:<1	96
20	Ph	H	$CONMe_2$	97	>99:<1	95
21	Ph	H	COMe	82	>99:<1	97
22	Ph	H	SO_2Ph	83	>99:<1	97
23	Ph	H	$P(O)(OEt)_2$	80	>99:<1	98
24	Ph	H	CN	96	>99:<1	99
25	*c*-C_6H_{11}	H	CO_2Me	71	>99:<1	97
26	*i*Pr	H	CO_2Me	43	>99:<1	80
27	*i*Bu	H	CO_2Me	64	>99:<1	88
28	$PhCH_2CH_2$	H	CO_2Me	70	>99:<1	92
29	*n*Pr	H	CO_2Me	60	>99:<1	79
30	$CH_3(CH_2)_5$	H	CO_2Me	62	>99:<1	82
31	$CH_3(CH_2)_9$	H	CO_2Me	36	>99:<1	84

cloadduct in high yields with high *exo*- and enantioselectivities. Remarkably, Schiff bases bearing alkyl groups reacted with methyl acrylate in good to high yields with good to high stereoselectivities when using the chiral AgHMDS catalyst, while no reaction occurred when the AgOTf–1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), $-Et_3N$, or AgOAc system was employed instead of the AgHMDS system in the reaction shown in Table 1, entry 30. This result indicates that the AgHMDS system shows significantly strong basicity compared with the traditional silver Lewis acid/base systems.

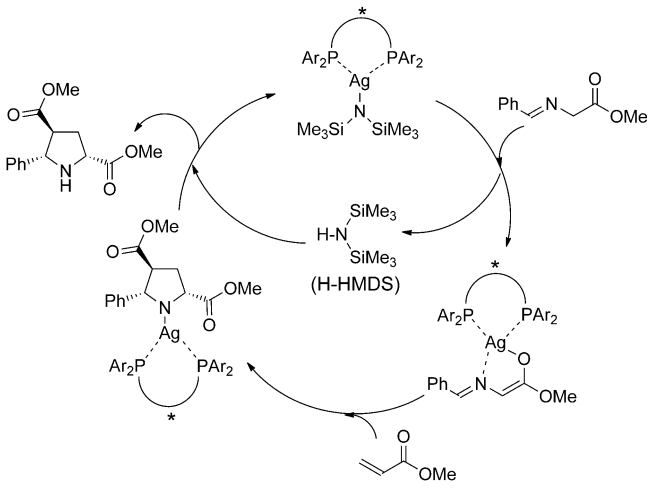
Furthermore, it was found that the chiral AgHMDS catalyst system was applicable for the [3+2] cycloadditions of Schiff bases of α-aminophosphonates (Table 2). It is known that Schiff bases of α-aminophosphonates are phosphonate analogues of those of glycine esters and less reactive than Schiff bases of glycine esters because of the less acidic nature of the α-hydrogen atom. Although a few examples using Schiff bases of α-aminophosphonates have been reported, catalytic asymmetric reactions using them are still rare. As expected, the AgHMDS catalyst worked well in the [3+2] cycloaddition reactions. The desired reactions of several Schiff bases of α-aminophosphonate-derived aldehydes proceeded smoothly to afford the cycloadducts in high yields with high *exo*- and enantioselectivities by using DTBM-SEGPHOS as a ligand. In this reaction, the silver amide system played a crucial role, and the typical related chiral silver Lewis acid–tertiary amine system, AgOTf–Et_3N system, or AgOTf–DBU system, did not work at all. The substrate scope of the reaction was also wide, and several types of Schiff bases bearing aromatic groups, alkenyl groups, and olefins bearing electron-withdrawing groups were successfully employed with high *exo*- and enantioselectivities.

Table 2. Asymmetric [3+2] cycloaddition reactions of the Schiff base of α-aminophosphonates with olefins.



Entry	R^1	R^2	R^3	Yield [%]	*exo*/*endo*	*ee* (%, *exo*)
1	Ph	H	CO_2tBu	94	>99:<1	96
2[a]	Ph	H	CO_2tBu	94	>99:<1	96
3	4-MeC_6H_4	H	CO_2tBu	99	>99:<1	94
4[c,d]	4-$MeOC_6H_4$	H	CO_2tBu	91	>99:<1	96
5	4-FC_6H_4	H	CO_2tBu	94	>99:<1	97
6	4-BrC_6H_4	H	CO_2tBu	93	>99:<1	95
7	4-$CF_3C_6H_4$	H	CO_2tBu	91	>99:<1	95
8[b]	1-naphthyl	H	CO_2tBu	80	94:6	>99
9	2-naphthyl	H	CO_2tBu	85	>99:<1	97
10	3-pyridyl	H	CO_2tBu	74	>99:<1	90
11[b]	*trans*-PhCH=CH	H	CO_2tBu	77	>99:<1	97
12[c,e]	*i*Pr	H	CO_2tBu	56	>99:<1	82
13[c,e]	*c*-C_6H_{11}	H	CO_2tBu	73	>99:<1	86
14[c,e]	*i*Bu	H	CO_2tBu	43	97:3	90
15[b,f]	Ph	Me	CO_2tBu	81	>99:<1	98
16[b,f]	Ph	*i*Bu	CO_2tBu	80	>99:<1	91
17[b,f]	Ph	Bn	CO_2tBu	72	>99:<1	90
18	Ph	H	CO_2Et	95	>99:<1	97
19	Ph	H	$CO(NCH_2CH_2OCH_2CH_2-)$	93	>99:<1	99
20	Ph	H	$CONMe_2$	97	>99:<1	98
21	Ph	H	COMe	81	>99:<1	99
22	Ph	H	SO_2Ph	98	>99:<1	99
23	Ph	H	$P(O)(OEt)_2$	85	>99:<1	98
24	Ph	H	CN	91	>99:<1	97

[a] Catalyst 1 mol%. [b] Catalyst 5 mol%. [c] Catalyst 10 mol%. [d] 20 h. [e] 0 °C for 4 d. [f] 15 h.



Scheme 1. Proposed catalytic cycle of the [3+2] cycloaddition reaction of the Schiff base of glycine ester with methyl acrylate.

A proposed catalytic cycle is shown in Scheme 1. The chiral silver amide deprotonates the Schiff base substrate to form a silver enolate species, which reacts with an olefin to afford a product–silver amide species. The intermediate should be protonated by the conjugate acid, H-HMDS, to regenerate the chiral silver amide and to release the desired cycloadduct.

It is notable that less reactive substrates such as Schiff bases of glycine esters derived from primary aliphatic aldehydes or Schiff bases of α-aminophosphonates were applicable to the catalytic asymmetric [3+2] cycloaddition reactions by using the silver amide as a catalyst.[10] This is an obvious advantage of a chiral silver amide as an enantioselective strong acid/base catalyst.

In this section, it was shown that metal amides are promising species for catalytic asymmetric carbon–carbon bond-

forming reactions when using a substrate bearing a less acidic proton. Cooperation of Lewis acidity of the metal part for activation/stereocontrol and effective Brønsted basicity of the amide part could provide a route to highly efficient asymmetric catalysis. This is an advanced concept in acid/base catalysis.

Catalytic Asymmetric [3+2] Cycloaddition Reactions of Azomethine Imines with Terminal Alkynes by Using a Silver or Copper Amide

Catalytic activation of terminal alkynes by using a metal Lewis acid and Brønsted base system is a typical and common methodology to promote addition reactions with aldehydes, imines, and related compounds to form products bearing alkynyl groups.[11] For this purpose, copper(I), silver, zinc, and indium compounds have been successfully employed. In those systems, tertiary amines were sometimes employed to enhance the reactions under mild conditions. We envisioned that activation of terminal alkynes might proceed through an intramolecular-like proton-transfer process by using a metal amide as a catalyst (Figure 3).

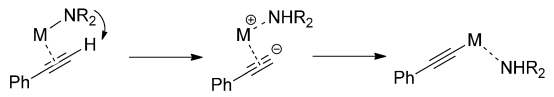
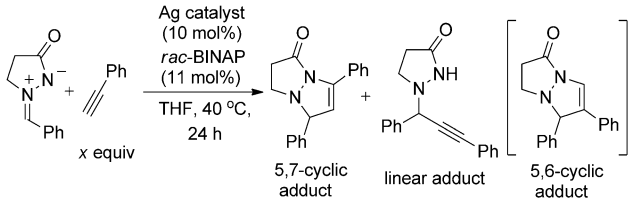


Figure 3. Intramolecular-like deprotonation of a terminal alkyne.

The AgHMDS system has been successfully applied to a [3+2] cycloaddition reaction of azomethine imines with terminal alkynes. [3+2] cycloadditions of azomethine imines derived from 3-pyrazolidinone to terminal alkynes afford five-membered-ring structures containing nitrogen–nitrogen bonds, which are typical motifs found in biologically active compounds. However, examples of catalytic asymmetric synthesis of these compounds are quite limited, and only one successful example has been reported. Fu et al. reported successful catalytic asymmetric [3+2] cycloaddition reactions of the azomethine imines with terminal alkynes by using a chiral copper system derived from CuI, a chiral phosphaferrocene–oxazoline ligand, and dicyclohexylmethylamine to afford 5,6-disubstituted bicyclic products exclusively with high enantioselectivities.[12] As the first investigation, the AgHMDS–BINAP system was employed as a catalyst (Table 3). In this reaction system, it was interestingly found that not a 5,6-disubstituted bicyclic product but a 5,7-disubstituted bicyclic product was obtained as the major product accompanying a certain amount of linear 1,2-addition product. On the other hand, a silver catalyst system with a less basic counteranion or using an external base, AgOAc–BINAP or AgOTf–BINAP–DBU systems, afforded no product or only the linear 1,2-addition product. It was remarkable that only the AgHMDS system afforded the cyclic product. Formation of the 1,2-addition product was suppressed under less protic reaction conditions, excluding proton sources, such as using dehydrating agents, molecular sieves, and also using smaller amounts of reactants, terminal alkynes.

Table 3. [3+2] cycloaddition reaction of an azomethine imine with phenylacetylene.

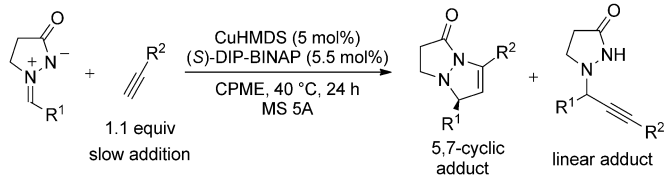


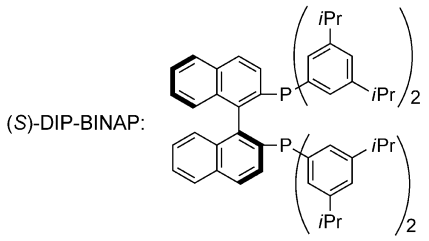
Entry	Catalyst system	*x*	Yield [%]	5,7-Cyclic/linear adduct
1	AgHMDS	2.0	97	45:55
2	AgOAc	2.0	no reaction	–
3	AgOTf+DBU	2.0	55	<1:>99
4	AgOTf+KO*t*Bu	2.0	23	<1:>99
5	AgHMDS+MS 5 Å	2.0	90	82:18
6	AgHMDS+MS 5 Å	1.1	92	99:1

The reaction could also be expanded into asymmetric catalysis (Table 4). Although a chiral AgHMDS system did not achieve high enantioselectivity, a copper amide, CuHMDS,[13] with a chiral bisphosphine ligand was found to be effective, and use of the bulkier BINAP system, DIP-BINAP, afforded good enantioselectivity. In further optimization of the reaction conditions, use of cyclopentyl methyl ether (CPME) improved enantioselectivity, and slow addition of the terminal alkyne improved the catalyst turnover without decreasing the selectivities. A wide substrate scope was observed in the reaction system; not only azomethine imines derived from aromatic aldehydes, but also those from aliphatic aldehydes were successfully employed. Furthermore, terminal alkynes with aromatic substituents, as well as those with aliphatic substituents, worked well to afford the desired products with high regio- and enantioselectivities.

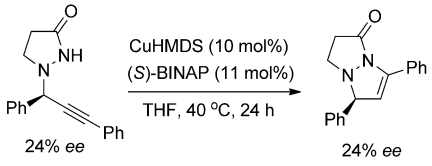
In a mechanistic study, it was indicated that the desired reaction affording the 5,7-disubstituted products proceeded via a stepwise pathway, namely 1,2-addition of terminal alkyne to the azomethine imine and intramolecular cyclization. This was supported by the fact that the linear 1,2-addition product was successfully converted into the 5,7-disubstituted bicyclic product in the presence of the chiral CuHMDS catalyst without any change of enantioselectivity (Scheme 2). The complete difference in the regioselectivity from the previously reported reaction catalyzed by a copper catalyst system[12] prepared from CuI, a chiral phosphaferrocene–oxazoline ligand, and a tertiary amine could be explained by a steric effect of the ligand (Scheme 3). In the CuHMDS system, while 2,2′-bis(diphenylphosphino)-1,1′-biphenyl and 2,2′-bis(diphenylamino)-1,1′-biphenyl mainly afforded the 5,7-disubstituted product, 2,2′-bis(dimethylphosphino)biphenyl predominantly afforded the 5,6-disubstituted product. These results indicate that the bulkiness of the employed ligands controlled the regioselectivity.

Table 4. Asymmetric [3 + 2] cycloaddition reactions of azomethine imine with terminal alkyne.





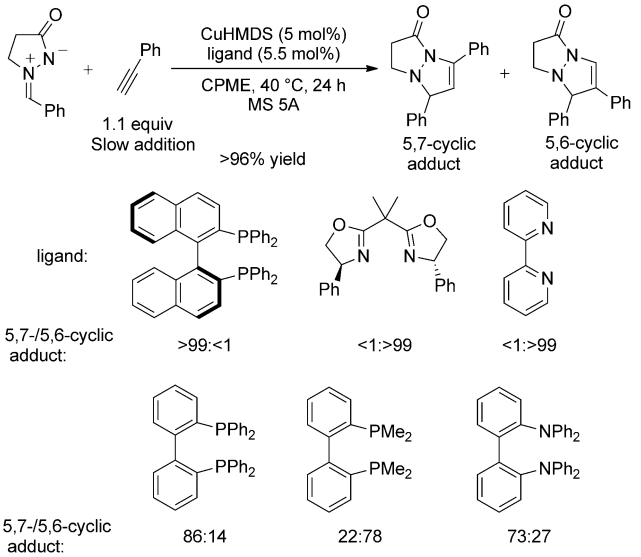
Entry	R^1	R^2	Yield [%]	5,7-Cyclic/ linear	*ee* [%]
1	Ph	Ph	94	99:1	90
2	4-MeC_6H_4	Ph	98	>99:<1	92
3	4-$MeOC_6H_4$	Ph	84	>99:<1	93
4	4-ClC_6H_4	Ph	92	>99:<1	88
5	4-NCC_6H_4	Ph	96	>99:<1	90
6	1-naphthyl	Ph	87	>99:<1	93
7	*trans*-PhCH=CH	Ph	88	>99:<1	89
8	*n*Pr	Ph	92	>99:<1	92
9	*c*-C_6H_{11}	Ph	94	>99:<1	95
10	Ph	4-MeC_6H_4	90	>99:<1	87
11	Ph	4-$MeOC_6H_4$	88	>99:<1	88
12	Ph	4-ClC_6H_4	93	>99:<1	90
13	Ph	4-FC_6H_4	96	>99:<1	91
14	Ph	*n*Bu	88	>99:<1	90
15	Ph	*c*-C_6H_{11}	90	>99:<1	88
16	Ph	Et_3Si	92	>99:<1	93
17	Ph	CH_2OBn	83	>99:<1	82



Scheme 2. Cyclization of the linear adduct.

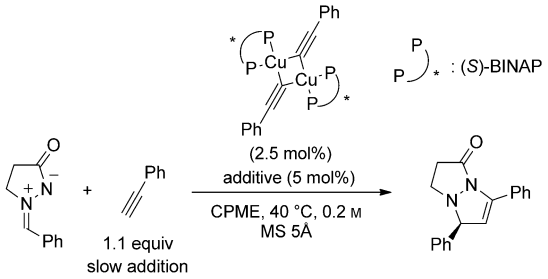
Furthermore, it was also indicated that the counteranion part of the metal HMDS played an important role in the catalytic cycle (Table 5). When an isolated chiral copper acetylide–BINAP was employed, the reaction proceeded in moderate yield; however, if $HN(SiMe_3)_2$ (H-HMDS) was added to the same reaction system, the yield was significantly improved, while addition of other Brønsted/Lewis bases showed no effect on the yields. This means that H-HMDS protonated the bicyclic alkyl copper intermediate to accelerate the catalytic turnover.

A proposed catalytic cycle is shown in Scheme 4. The chiral group 11 metal amide deprotonates the terminal

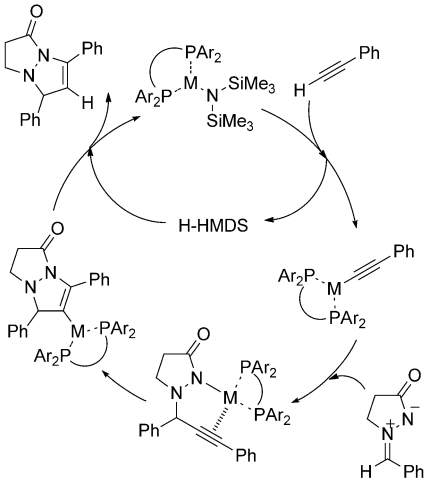


Scheme 3. Effect of ligand.

Table 5. Effect of additives.



Entry	Additive	Yield [%]	*ee* [%]
1	none	43	51
2	H-HMDS	78	50
3	Et_3N	45	50
4	PPh_3	51	38



Scheme 4. Proposed catalytic cycle.

alkyne to form a metal acetylide species, which reacts with the azomethine imine in a 1,2-addition to afford a linear 1,2-adduct intermediate. The intermediate further cyclizes in an intramolecular fashion to afford the metallated desired product, which is protonated by H-HMDS to regenerate the metal amide species with release of the bicyclic product. It is important to mention that proton sources, including not only a trace amount of water but also conjugate acids of the base catalyst ($DBUH^+$ or *t*BuOH) and even terminal alkyne, significantly prevented the intramolecular cyclization; this means that the acidity of H-HMDS is highly appropriate not for protonating the metallated linear 1,2-adduct intermediate but for protonating the metallated bicyclic product for promotion of the desired catalytic cycle.

It was shown that the use of silver or copper HMDS is very important in this reaction. Their advantages in this reaction system are 1) suppression of linear 1,2-adduct formation and enhancement of the intramolecular cyclization and 2) acceleration of the reaction rate by efficient protonation. These advantages are due to the less acidic but not neutral nature of the hydrogen of H-HMDS. Silver or copper HMDS could control the whole reaction system effectively.[14]

In this section, metal amides were also found to be a promising species for acid/base-catalyzed asymmetric carbon–carbon bond-forming reactions. A less acidic conjugate acid of the metal amide, a secondary amine, could play key roles in accelerating the catalytic cycle and controlling the reaction pathway effectively. This is another advanced concept in metal amide chemistry in acid/base catalysis.

Summary and Outlook

In this manuscript, we described new possibilities of metal amides as one of the simplest Lewis acid/Brønsted base catalysts in stereoselective carbon–carbon bond-forming reactions based on our recent results. Metal amides, especially alkaline metal amides, have been recognized as strong bases for deprotonation of inert or less acidic hydrogen atoms to form anionic organic molecules, but their application for catalytic carbon–carbon bond formation has been very limited because of the difficulty of their regeneration as catalysts due to their strong basicity. However, it has been shown that transition-metal amides have interesting abilities and possibilities as catalysts. The points shown here are 1) effective Lewis acid/Brønsted base cooperative activation and stereocontrol of the less reactive substrate and 2) control of the reaction pathway by the less acidic nature of its conjugate acid, a secondary amine. These findings are based on traditional theory but indicate their hidden promising potential. Such use of metal amides would open a door to a new generation of stereoselective acid/base catalysis.

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