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COMMUNICATION

Enantioselective intramolecular propargylic amination using chiral copper-pybox catalyst

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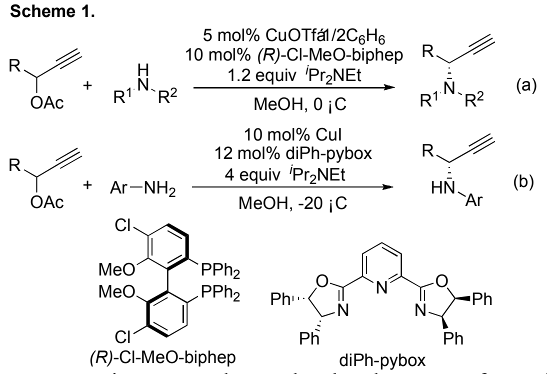
Intramolecular propargylic amination of propargylic acetates bearing an amino group at the suitable position in the presence of chiral copper-pybox complexes proceeds enantioselectively to give optically active 1-ethynyl-isoindolines (up to 98% *ee*). The method described in this paper provides a useful synthetic approach to the enantioselective preparation of nitrogen containing heterocyclic compounds with an ethyl group at the α-position.

Heterocycles containing nitrogen atom such as pyrrolidines, tetrahydroquinolines and isoindolines and their derivatives are widely found in many natural products and biologically active compounds.[1] In addition to classical synthetic approaches to these heterocycles, a variety of preparative methods catalyzed by transition metal complexes have been reported including its asymmetric version for the optically active heterocycles.[1,2]

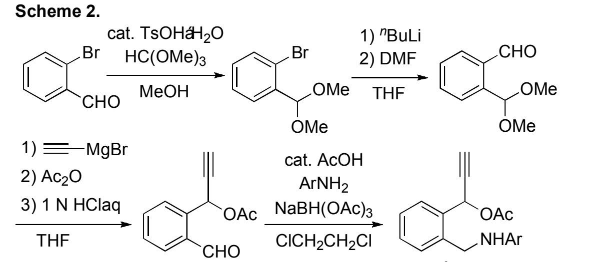
Scheme 1.



As our continuous study on the development of transition metal-catalyzed propargylic substitution reactions of propargylic alcohol derivatives with various nucleophiles including their enantioselective versions,[3,4] we have recently disclosed the copper-catalyzed propargylic amination of propargylic esters with amines via copper-allenylidene complexes as key reactive intermediates.[5-7] In our reaction system, (*R*)-Cl-MeO-biphep was found to work as an effective ligand toward the propargylic amination with secondary amines such as *N*-methylaniline (Scheme 1 (a)),[5] in contrast to the van Maarseveen's reaction system, where the propargylic amination with primary amine was achieved by using diPh-pybox as a chiral ligand (Scheme 1 (b)).[6] Based on these research backgrounds, we have envisaged the application of this reaction system to the preparation of heterocycles containing nitrogen atom via an intramolecular cyclization of propargylic esters bearing an amine moiety at a suitable position. In fact, we have succeeded in obtaining chiral 1-ethynyl-isoindolines in good to high yields with up to 98% *ee*. Preliminary results are described here.

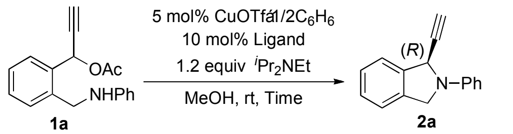
We have designed 1-phenylpropargylic acetates bearing an aminomethyl group at the *ortho*-position of the benzene ring **1**, which were prepared via four steps from 2-bromobenzaldehyde as shown in Scheme 2. After the protection of the original formyl group in 2-bromobenzaldehyde, the introduction of another formyl group and sequential ethynylation of the formyl group gave 1-(2-formylphenyl)prop-2-yn-1-yl acetate in a good yield. Then, reductive amination with various aniline derivatives led to the formation of **1** in high yields.

Scheme 2.



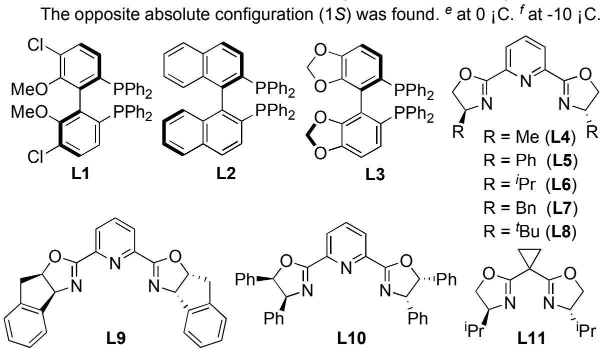
Treatment of 1-(2-((phenylamino)methyl)phenyl)prop-2-yn-1-yl acetate (**1a**) in methanol at room temperature for 14 h in the presence of 5 mol% of CuOTf·1/2(C_6H_6) and 10 mol% of (*R*)-Cl-MeO-biphep[8] (**L1**) gave 1-ethynyl-2-phenylisoindoline (**2a**) in 17% yield with 57%ee (Table 1, entry 1). Typical results are shown in Table 1. The use of related diphosphines such as (*R*)-binap[9] (**L2**) and (*R*)-segphos[10] (**L3**) as chiral ligands afforded only low yields of **2a** (Table 1, entries 2 and 3). When pyboxs were used as chiral ligands under the same reaction conditions, the intramolecular amination proceeded smoothly to give **2a** in good to high yields with a high enantioselectivity. The use of a larger amount (2 equiv to Cu atom) of pyboxs slightly increased the enantioselectivity in all cases. (*S*)-Me-pybox[11] (**L4**) was found to work as an effective chiral ligand to achieve the highest enantioselectivity such as 89%ee (Table 1, entry 4) although the use of related pyboxs such as Ph-pybox[11] (**L5**), *i*Pr-pybox[11] (**L6**), and Bn-pybox[11] (**L7**) gave high enantioselectivities (85%ee, 82%ee, and 80%ee, respectively) (Table 1, entries 5-7). Other pyboxs such as *t*Bu-pybox[11] (**L8**), indan-pybox[11] (**L9**), and diPh-pybox[6] (**L10**) did not work as effective ligands, with only low to moderate enantioselectivities (56%ee, 50%ee, and 23%ee, respectively) (Table 1, entries 8-10). When a bis(oxazoline) ligand[12] (**L11**) was used as a chiral ligand, the amination did not occur smoothly to afford **2a** with only a low enantioselectivity (Table 1, entry 11). A higher enantioselectivity was observed when the cyclic amination was carried out at a lower reaction temperature by using **L4** and **L5** as chiral ligands. The highest enantioselectivity was achieved at 0 °C and -10 °C by using **L4** (Table 1, entries 12 and 13). A slightly lower enantioselectivity was observed in the reaction at 0 °C by using **L5** as a chiral ligand (Table 1, entry 14).

Table 1. Intramolecular propargylic amination of **1a** in the presence of chiral copper complexes.[a]



Entry	Ligand	Time (h)	Yield of **2a** (%)[b]	*ee* (%)[c]
1	**L1**	14	17	57[d]
2	**L2**	4	19	55[d]
3	**L3**	20	2	17[d]
4	**L4**	4	80	89
5	**L5**	4	83	85
6	**L6**	4	81	82
7	**L7**	8	87	80
8	**L8**	20	25	56
9	**L9**	4	49	50
10	**L10**	4	82	23
11	**L11**	4	34	20[d]
12[e]	**L4**	8	87	93
13[f]	**L4**	20	87	93
14[e]	**L5**	8	91	90

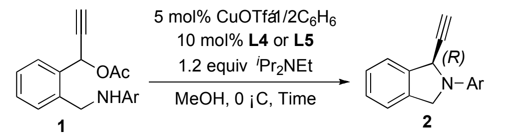
[a] Reactions of **1a** (0.2 mmol) in the presence of CuOTfá1/$_2$C$_6$H$_6$ (0.01 mmol), ligand (0.02 mmol), and ^{i}Pr$_2$NEt (0.24 mmol) were carried out in MeOH at room temperature. [b] Isolated yield. [c] Determined by HPLC. [d] The opposite absolute configuration (1*S*) was found. [e] at 0 ¡C. [f] at -10 ¡C.



Intramolecular cyclic amination of various propargylic acetates bearing an aminomethyl group was investigated by using **L4** and **L5** as chiral ligands. Typical results are shown in Table 2. The presence of a substituent such as methyl, fluoro, or bromo group at the *para*-position of the benzene ring in the amino group decreased the reactivity, a longer reaction time (20-30 h) being necessary to obtain the corresponding 1-ethynyl-isoindolines in high yields with a high enantioselectivity (Table 2, entries 1-6). The highest enantioselectivity was achieved in the reaction of **1d** as a substrate by using **L5** (Table 2, entry 8). After one recrystallization of crude cyclic product, the enantiomerically pure **2d** was isolated and its absolute configuration (1*R*) was determined by X-ray analysis (Figure 1).[13]

Next, we investigated the nature of substituent on the aromatic scaffold linking the propargylic acetate. Typical results are shown in Scheme 3. The introduction of a fluoro group at the 5-position and two methoxy groups at the 4- and 5-positions substantially increased the enantioselectivity under the same reaction conditions.

Table 2. Intramolecular propargylic amination of **1** in the presence of chiral copper complexes.[a]



Entry	**1**, Ar	L	Time (h)	Yield of **2** (%)[b]	*ee* (%)[c]
1	**1a**, C_6H_5	**L4**	8	87	93
2	**1a**, C_6H_5	**L5**	8	91	90
3	**1b**, 4-MeC_6H_4	**L4**	20	79	92
4	**1b**, 4-MeC_6H_4	**L5**	20	70	92
5	**1c**, 4-FC_6H_4	**L4**	30	79	95
6	**1c**, 4-FC_6H_4	**L5**	30	77	88
7	**1d**, 4-BrC_6H_4	**L4**	30	89	93
8	**1d**, 4-BrC_6H_4	**L5**	30	89	96

[a] Reactions of **1** (0.2 mmol) in the presence of CuOTfá1/$_2$C$_6$H$_6$ (0.01 mmol), **L4** or **L5** (0.02 mmol), and ^{i}Pr$_2$NEt (0.24 mmol) were carried out in MeOH at 0 ¡C. [b] Isolated yield. [c] Determined by HPLC.

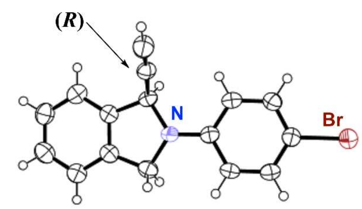
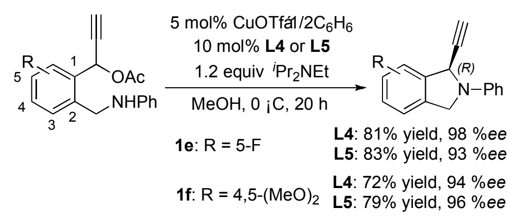


Figure 1. Ortep drawing of optically active **2d**.

Scheme 3.



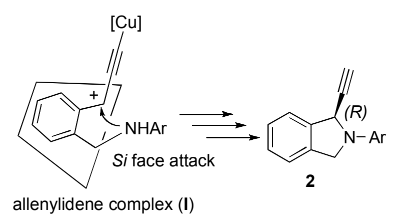
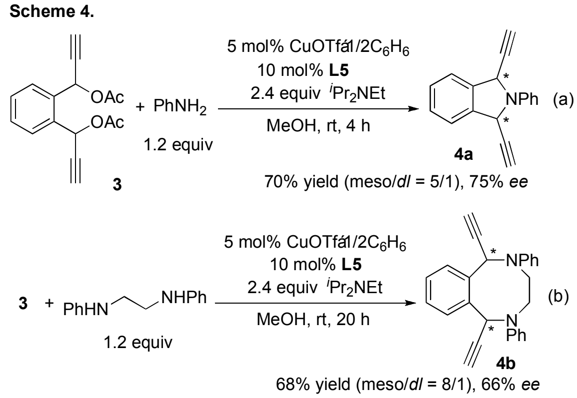


Figure 2. Copper-allenylidene complex as a key reactive intermediate.

As described in our previous work, the intermolecular propargylic amination proceeded via copper-allenylidene complex (**I**),[5,6,14] which was generated from the copper-pybox complex with the propargylic acetate. At present, we consider that the intramolecular amination also proceeds via a similar reaction pathway. The absolute configuration at the propargylic position in **2** indicates that the intramolecular attack of an amino group on the cationic γ-carbon in **I** occurs from the *Si* face (Figure 2).

The successful results of the intramolecular cyclic amination prompted us to investigate double propargylic amination including sequential inter- and intra-molecular amination (Scheme 4). The reaction of 1,1'-(1,2-phenylene)-bis(prop-2-yne-1,1-diyl) diacetate (**3**) with aniline in methanol at room temperature in the presence of 5 mol% of $CuOTf\cdot 1/2(C_6H_6)$ and 10 mol% of **L5** proceeded smoothly to give 1,3-di(ethynyl)-2-phenylisoindoline (**4a**) in 70% yield as a mixture of two diastereoisomers (*meso*-isomer/*dl*-isomer = 5/1) (Scheme 4 (a)). The minor *dl*-isomer was obtained with 75%*ee*. On the other hand, the reaction of **3** with *N*,*N'*-diphenylethane-1,2-diamine under the same reaction conditions afforded 1,6-diethynyl-2,5-diphenyl-1,2,3,4,5,6-hexahydrobenzo[*f*][1,4]diazocine (**4b**) in 68% yield as a mixture of two diastereoisomers (*meso*-isomer/*dl*-isomer = 8/1) (Scheme 4 (b)). The minor *dl*-isomer was obtained with 66%*ee*. The low selective formation of *dl*-isomers in the both reaction systems indicates that the first intermolecular amination of **3** took place with only a low enantioselectivity. This low selectivity was not surprising based on the results found by van Maarseveen and co-workers in the intermolecular amination with primary aniline by using Ph-pybox.[6]

Scheme 4.



In summary, we have disclosed the copper-catalyzed intramolecular propargylic amination of propargylic acetates bearing an amine moiety at a suitable position to give optically active 1-ethynyl-isoindolines. In the present reaction system, copper-pybox complexes have been found to work as effective catalysts toward the propargylic amination (up to 98%*ee*). We believe that the present method provide a useful synthetic approach to the enantioselective preparation of optically active nitrogen containing heterocyclic compounds with an ethynyl group at the α-position with a high enantioselectivity as an application of the copper-catalyzed propargylic amination. Further studies on the transition metal-catalyzed propargylic substitution reactions are currently in progress.

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† Electronic Supplementary Information (ESI) available.

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