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Enantioselective intramolecular propargylic amination using chiral copper–pybox complexes as catalysts†

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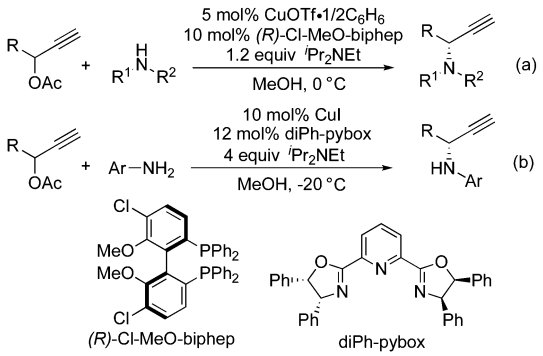
Intramolecular propargylic amination of propargylic acetates bearing an amino group at the suitable position in the presence of chiral copper–pybox complexes proceeds enantioselectively to give optically active 1-ethynyl-isoindolines (up to 98% ee). The method described in this communication provides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

Heterocycles containing a 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 obtain these heterocycles, a variety of preparative methods catalyzed by transition metal complexes have been reported including their asymmetric version for the optically active heterocycles.[1,2]

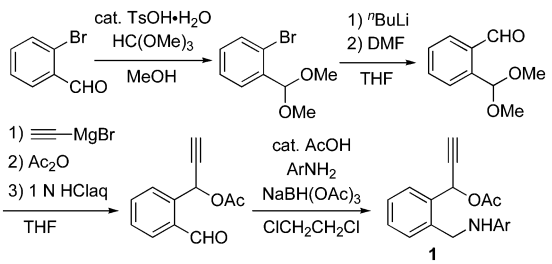
In continuation of our study on the development of transition metal-catalyzed propargylic substitution reactions of propargylic alcohol derivatives with various nucleophiles including their enantioselective versions,[3,4] we have recently disclosed the copper-catalyzed propargylic amination of propargylic 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 van Maarseveen's reaction system, where the propargylic amination with primary amines was achieved by using diPh-pybox as a chiral ligand (Scheme 1(b)).[6] Based on these research backgrounds, we envisaged the application of this reaction system to the preparation of heterocycles containing a 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.



Scheme 1

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.

Treatment of 1-(2-((phenylamino)methyl)phenyl)prop-2-yn-1-yl acetate (**1a**) in methanol at room temperature for 14 h in



Scheme 2

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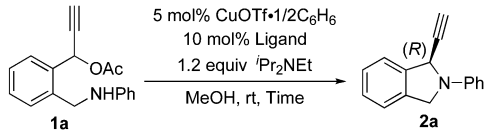
Table 1 Intramolecular propargylic amination of **1a** in the presence of chiral copper complexes[a]

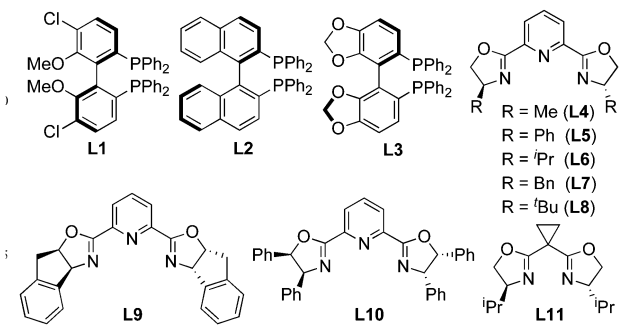


1a 2a

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 CuOTf·1/2(C_6H_6) (0.01 mmol), ligand (0.02 mmol), and $^iPr_2NEt$ (0.24 mmol) were carried out in MeOH at room temperature. [b] Isolated yield. [c] Determination by HPLC. [d] The opposite absolute configuration (1*S*) was found. [e] At 0 °C. [f] At −10 °C.

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, *i.e.* 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, affording **2a** with only a low enantioselectivity (Table 1, entry 11). A higher enantioselectivity was observed



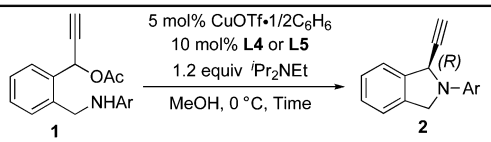
when the cyclic amination was carried out at a lower reaction temperature by using **L4** and **L5** as chiral ligands. The highest enantioselectivity was achieved at 0 °C and −10 °C by using **L4** (Table 1, entries 12 and 13). A slightly lower enantioselectivity was observed in the reaction at 0 °C by using **L5** as a chiral ligand (Table 1, entry 14).

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 a 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 (Fig. 1).[13]

Next, we investigated the nature of substituents 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.

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

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



1 2

Entry	**1**, Ar	Ligand	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 CuOTf·1/2(C_6H_6) (0.01 mmol), **L4** or **L5** (0.02 mmol), and $^iPr_2NEt$ (0.24 mmol) were carried out in MeOH at 0 °C. [b] Isolated yield. [c] Determination by HPLC.

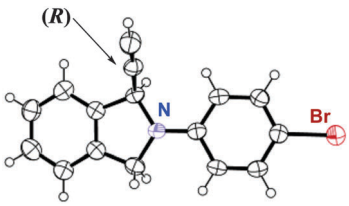
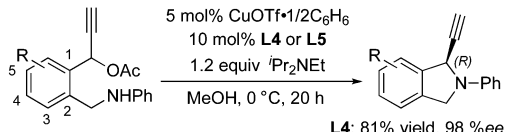


Fig. 1 Ortep drawing of optically active **2d**.



Scheme 3

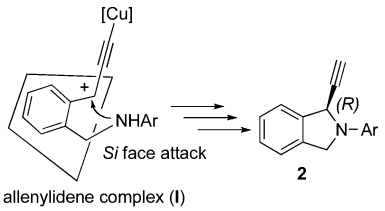
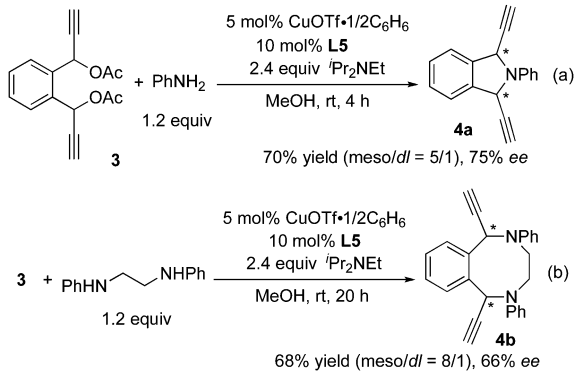


Fig. 2 Copper–allenylidene complex as a key reactive intermediate.

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 (Fig. 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·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 for the intermolecular amination with primary aniline by using Ph-pybox.[6]

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 provides 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.



Scheme 4

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