

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

Masashi Shibata, Kazunari Nakajima and Yoshiaki Nishibayashi*

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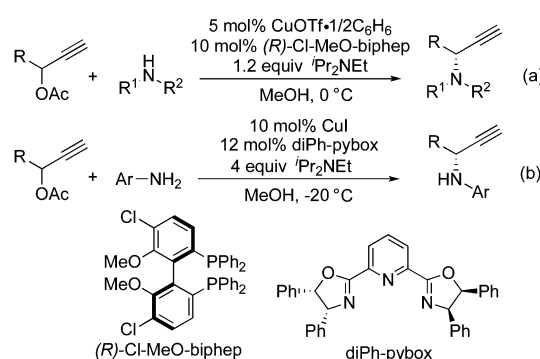
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Intramolecular propargylic amination of propargylic acetates bearing an amino group at the suitable position in the presence of chiral copper–pybox complexes proceeds enantioselectively to give optically active 1-ethynyl-isoidolines (up to 98% ee). 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

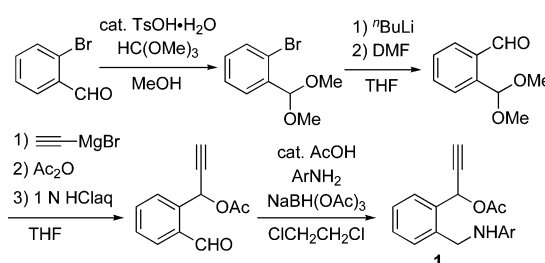


Scheme 1

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.

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

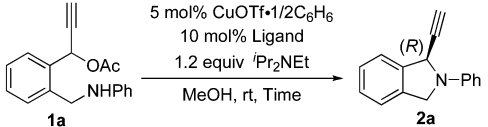


Scheme 2

Institute of Engineering Innovation, School of Engineering, The University of Tokyo, Yayoi, Bunkyo-ku, Tokyo, 113-8656, Japan. E-mail: ynishiba@sogo.t.u-tokyo.ac.jp; Fax: +81 3 5841-1175

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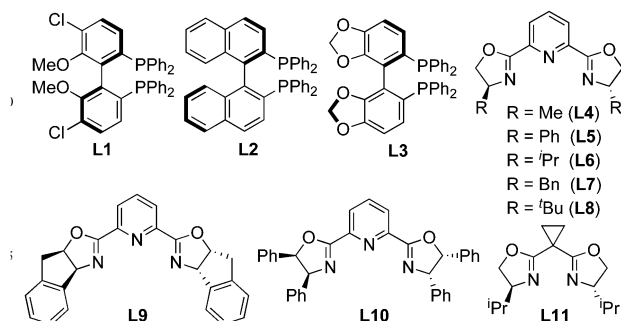


Table 1 Intramolecular propargylic amination of **1a** in the presence of chiral copper complexes^a


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 CuOTf·1/2(C₆H₆) (0.01 mmol), ligand (0.02 mmol), and ⁱPr₂NEt (0.24 mmol) were carried out in MeOH at room temperature. ^b Isolated yield. ^c Determination by HPLC. ^d The opposite absolute configuration (**1S**) was found. ^e At 0 °C. ^f At –10 °C.

the presence of 5 mol% of CuOTf·1/2(C₆H₆) and 10 mol% of (*R*)-Cl-MeO-biphep⁸ (**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*)-binap⁹ (**L2**) and (*R*)-segphos¹⁰ (**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-pybox¹¹ (**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-pybox¹¹ (**L5**), ⁱPr-pybox¹¹ (**L6**), and Bn-pybox¹¹ (**L7**) gave high enantioselectivities (85% ee, 82% ee, and 80% ee, respectively) (Table 1, entries 5–7). Other pyboxs such as *t*Bu-pybox¹¹ (**L8**), indan-pybox¹¹ (**L9**), and diPh-pybox⁶ (**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) ligand¹² (**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

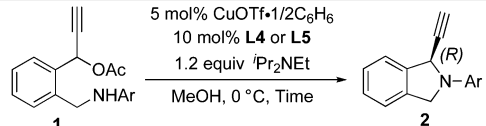


when the cyclic amination was carried out at a lower reaction temperature by using **L4** and **L5** as chiral ligands. The highest enantioselectivity was achieved at 0 °C and –10 °C by using **L4** (Table 1, entries 12 and 13). A slightly lower enantioselectivity was observed in the reaction at 0 °C 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 (*1R*) was determined by X-ray analysis (Fig. 1).¹³

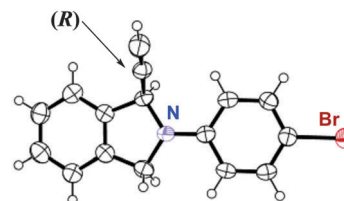
Next, we investigated the nature of substituents on the aromatic scaffold linking the propargylic acetate. Typical results are shown in Scheme 3. The introduction of a fluoro group at the 5-position and two methoxy groups at the 4- and 5-positions substantially increased the enantioselectivity under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

As described in our previous work, the intermolecular propargylic amination proceeded *via* copper-allenyldiene 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


Entry	1 , Ar	Ligand	Time (h)	Yield of 2 ^b (%)	ee ^c (%)
1	1a , C ₆ H ₅	L4	8	87	93
2	1a , C ₆ H ₅	L5	8	91	90
3	1b , 4-MeC ₆ H ₄	L4	20	79	92
4	1b , 4-MeC ₆ H ₄	L5	20	70	92
5	1c , 4-FC ₆ H ₄	L4	30	79	95
6	1c , 4-FC ₆ H ₄	L5	30	77	88
7	1d , 4-BrC ₆ H ₄	L4	30	89	93
8	1d , 4-BrC ₆ H ₄	L5	30	89	96

^a Reactions of **1** (0.2 mmol) in the presence of CuOTf·1/2(C₆H₆) (0.01 mmol), **L4** or **L5** (0.02 mmol), and ⁱPr₂NEt (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**.

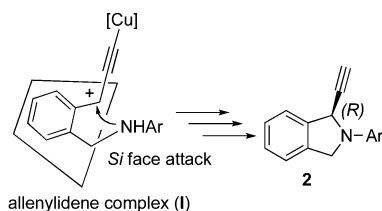
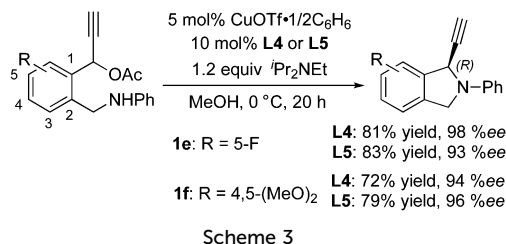
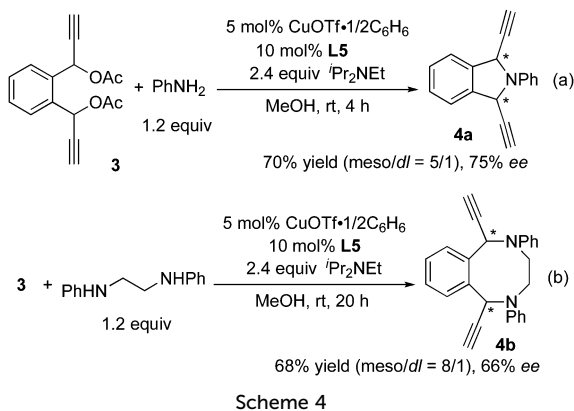


Fig. 2 Copper–allenylidene complex as a key reactive intermediate.

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(C₆H₆) 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.

Notes and references

- For reviews, see: (a) M. Chrzanowska and M. D. Rozwadowska, *Chem. Rev.*, 2004, **104**, 3341; (b) Y.-G. Zhou, *Acc. Chem. Res.*, 2007, **40**, 1357; (c) S. Anas and H. B. Kagan, *Tetrahedron: Asymmetry*, 2009, **20**, 2193; (d) M. Ahamed and M. H. Todd, *Eur. J. Org. Chem.*, 2010, 5935; (e) V. Sridharan, P. A. Suryavanshi and J. C. Menéndez, *Chem. Rev.*, 2011, **111**, 7157.
- For enantioselective synthesis of isoindolines, see: (a) Y. Sato, T. Nishimata and M. Mori, *J. Org. Chem.*, 1994, **59**, 6133; (b) Y. Sato, T. Nishimata and M. Mori, *Heterocycles*, 1997, **44**, 443; (c) D. Enders, A. A. Narine, F. Toulgoat and T. Bisschops, *Angew. Chem., Int. Ed.*, 2008, **47**, 5661; (d) C. Wang, X.-H. Chen, S.-M. Zhou and L.-Z. Gong, *Chem. Commun.*, 2010, **46**, 1275; (e) S. Takizawa, N. Inoue, S. Hirata and H. Sasai, *Angew. Chem., Int. Ed.*, 2010, **49**, 9725; (f) R. Morán-Ramallal, V. Gotor-Fernández, P. Laborda, F. J. Sayago, C. Cativiela and V. Gotor, *Org. Lett.*, 2012, **14**, 1696.
- For our recent reviews, see: (a) Y. Miyake, S. Uemura and Y. Nishibayashi, *ChemCatChem*, 2009, **1**, 342; (b) Y. Nishibayashi, *Synthesis*, 2012, 489.
- For recent reviews by other research groups, see: (a) R. J. Detz, H. Hiemstra and J. H. van Maarseveen, *Eur. J. Org. Chem.*, 2009, 6263; (b) C.-H. Ding and X.-L. Hou, *Chem. Rev.*, 2011, **111**, 1914; (c) O. Debleds, E. Gayon, E. Vrancken and J.-M. Campagne, *Beilstein J. Org. Chem.*, 2011, **7**, 866; (d) E. B. Bauer, *Synthesis*, 2012, 1131.
- For our recent papers of enantioselective propargylic amination, see: (a) G. Hattori, H. Matsuzawa, Y. Miyake and Y. Nishibayashi, *Angew. Chem., Int. Ed.*, 2008, **47**, 3781; (b) G. Hattori, A. Yoshida, Y. Miyake and Y. Nishibayashi, *J. Org. Chem.*, 2009, **74**, 7603; (c) G. Hattori, Y. Miyake and Y. Nishibayashi, *ChemCatChem*, 2010, **2**, 155; (d) G. Hattori, K. Sakata, H. Matsuzawa, Y. Tanabe, Y. Miyake and Y. Nishibayashi, *J. Am. Chem. Soc.*, 2010, **132**, 10592; (e) A. Yoshida, M. Ikeda, G. Hattori, Y. Miyake and Y. Nishibayashi, *Org. Lett.*, 2011, **13**, 592; (f) A. Yoshida, G. Hattori, Y. Miyake and Y. Nishibayashi, *Org. Lett.*, 2011, **13**, 2460.
- For recent papers of enantioselective propargylic amination reported by van Maarseveen and co-workers, see: (a) R. J. Detz, M. M. E. Delville, H. Hiemstra and J. H. van Maarseveen, *Angew. Chem., Int. Ed.*, 2008, **47**, 3777; (b) R. J. Detz, Z. Abiri, R. le Griel, H. Hiemstra and J. H. van Maarseveen, *Chem. – Eur. J.*, 2011, **17**, 5921.
- For recent papers of enantioselective propargylic amination reported by other research groups, see: (a) C. Zhang, Y.-H. Wang, X.-H. Hu, Z. Zheng, J. Xu and X.-P. Hu, *Adv. Synth. Catal.*, 2012, **354**, 2854; (b) T. Mino, H. Taguchi, M. Hashimoto and M. Sakamoto, *Tetrahedron: Asymmetry*, 2013, **24**, 1520.
- (*R*)-Cl-MeO-biphep = (*R*)-5,5'-dichloro-6,6'-dimethoxy-2,2'-bis(diphenylphosphino)-1,1'-biphenyl: (a) R. R. Huddleston, H.-Y. Jang and M. J. Krische, *J. Am. Chem. Soc.*, 2003, **125**, 11488; (b) H.-Y. Jang, F. W. Hughes, H. Gong, J. Zhang, J. S. Brodbelt and M. J. Krische, *J. Am. Chem. Soc.*, 2005, **127**, 6174; (c) J. U. Rhee and M. J. Krische, *J. Am.*



- Chem. Soc.*, 2006, **128**, 10674; (d) E. Skucas, J. R. Kong and M. J. Krische, *J. Am. Chem. Soc.*, 2007, **129**, 7242.
- 9 (R)-binap = (R)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl: R. Noyori and H. Takaya, *Acc. Chem. Res.*, 1990, **23**, 345 and references therein.
- 10 (R)-segphos = (R)-5,5'-bis(diphenylphosphino)-4,4'-bi-1,3-benzodioxole: H. Shimizu, I. Nagasaki, K. Matsumura, N. Sayo and T. Saito, *Acc. Chem. Res.*, 2007, **40**, 1385 and references therein.
- 11 pybox = Pyridine-2,6-bis(oxazolines): G. Desimoni, G. Faita and P. Quadrelli, *Chem. Rev.*, 2003, **103**, 3119.
- 12 For a recent review on bis(oxazoline) ligands, see: G. Desimoni, G. Faita and K. A. Jørgensen, *Chem. Rev.*, 2006, **106**, 3561.
- 13 See ESI† for Experimental details.
- 14 (a) The copper–allenylidene complexes have not yet been isolated and characterized until now although silver- and gold–allenylidene complexes have already been reported by Bertrand and Hashmi, respectively; (b) M. Asay, B. Donnadieu, W. W. Schoeller and G. Bertrand, *Angew. Chem., Int. Ed.*, 2009, **48**, 4796; (c) M. M. Hansmann, F. Rominger and A. S. K. Hashmi, *Chem. Sci.*, 2013, **4**, 1552.

