Organic LETTERS

Letter

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Enantioposition-Selective Copper-Catalyzed Azide–Alkyne Cycloaddition for Construction of Chiral Biaryl Derivatives

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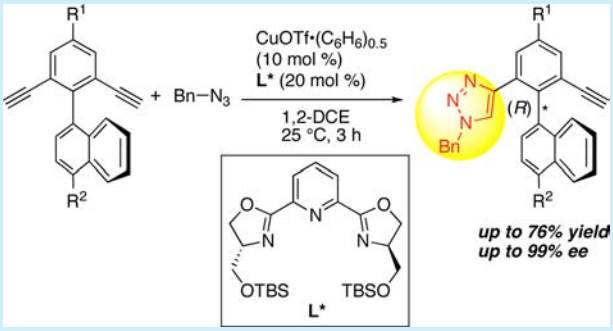
Supporting Information

ABSTRACT: A highly enantioposition-selective copper-catalyzed azide–alkyne cycloaddition (CuAAC) of dialkynes bearing prochiral biaryls has been developed for the construction of 1,2,3-triazoles bearing axially chiral biaryl groups in up to 76% yield and up to 99% ee.



The copper-catalyzed azide–alkyne cycloaddition (CuAAC) reaction, also known as the Huisgen reaction, has been recognized as a click reaction[1] and is widely used in the construction of 1,2,3-triazoles in the synthesis of a wide variety of functional molecules.[2] Compared with the significant development of the CuAAC, scant attention has been paid to the asymmetric version of this reaction. Fokin and Finn reported a kinetic resolution of α-benzylic azides and the asymmetric desymmetrization of *gem*-diazides through an enantioposition-selective CuAAC with a modest level of the enantioselectivity.[3] Recently, Zhou and co-workers achieved a highly enantioposition-selective CuAAC of prochiral oxindole group-containing 1,6-heptadiynes to give the 1,2,3-triazoles containing quaternary stereogenic carbon centers in the oxindole moiety in high yields and excellent enantioselectivities (84–98% ee).[4] However, despite the considerable potential of CuAAC to achieve asymmetric induction, the range of substrates with which highly enantioselective CuAAC can occur remains limited to oxindole-based 1,6-heptadiynes. Therefore, enantioselective CuAAC is still an immature reaction and major challenges remain in broadening its synthetic utility.

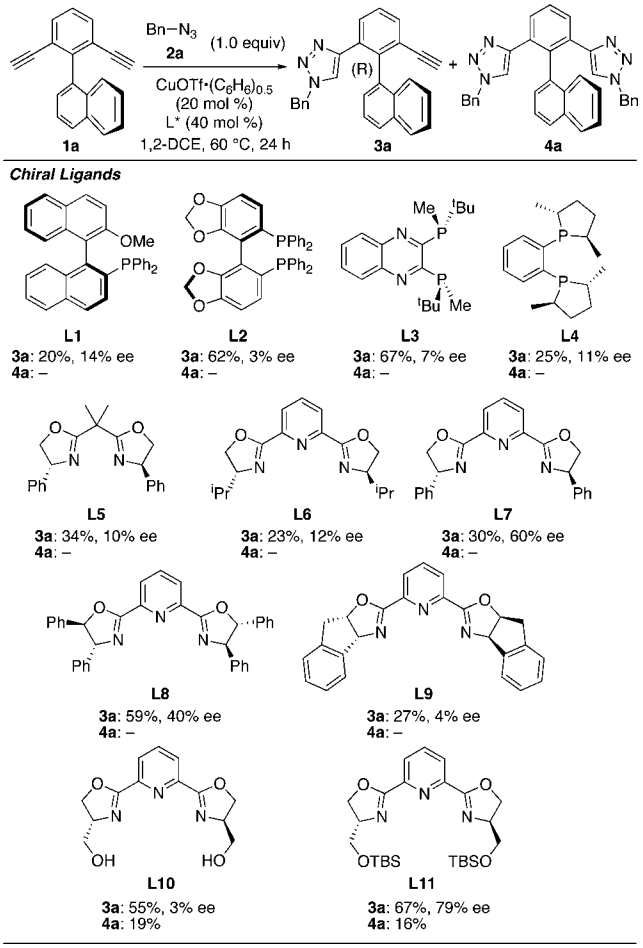
Axially chiral biaryl derivatives are important and useful compounds and are widely found in valuable organic compounds, including biologically active compounds, chiral ligands, and chiral Brønsted acids.[5] Because of their versatility as excellent chiral units, much effort has been devoted to the development of efficient methods for constructing axially chiral biaryl derivatives.[6−8] Asymmetric desymmetrization of C_s-symmetric achiral biaryls is a particularly efficient strategy for the construction of axially chiral biaryl derivatives.[8] As part of our continuing efforts to develop copper catalysis,[9] we hypothesized that the application of the asymmetric CuAAC reaction to the desymmetrization of C_s-symmetric achiral biaryls might provide a new method for enantioselective construction of axially chiral biaryls. Here, we report the development of enantioposition-selective copper-catalyzed azide–alkyne cycloaddition of azides with dialkynes bearing prochiral biaryl groups to give 1,2,3-triazoles bearing axially chiral biaryl groups with high enantioselectivities.

We chose 1-(2,6-diethynylphenyl)naphthalene (**1a**) as a model substrate for the enantioposition-selective copper-catalyzed azide–alkyne cycloaddition (CuAAC) of achiral biaryls, and we screened the effects of various chiral ligands (Scheme 1). The reaction of diyne **1a** with benzyl azide (**2a**) in the presence of CuOTf·$(C_6H_6)_{0.5}$ (20 mol %) and a chiral phosphine ligand **L1**–**4** (40 mol %) in 1,2-dichloroethane (1,2-DCE) at 60 °C for 24 h gave the desired monotriazole **3a** in 20–67% yield with low enantioselectivity (≤14% ee). The reaction in the presence of the chiral bidentate bisoxazoline (Box) ligand **L5** also showed low enantioselectivity. We then screened the effects of a series of tridentate bis(oxazolinyl)pyridine (PyBox) ligands **L6**–**9**. Whereas the isopropyl-substituted PyBox **L6** was not effective in asymmetric induction, the use of a phenyl-substituted PyBox improved the enantioselectivity toward **3a** to 60% ee. The use of more sterically congested PyBox ligands **L8** and **L9** did not enhance the enantioselectivity. Reaction in the presence of the L-serine-derived PyBox ligand **L10**[10] gave monotriazole **3a** in 55% yield and 3% ee, together with a 19% yield of bistriazole **4a**. Protection of the hydroxy groups of **L10** as *tert*-butyl(dimethyl)silyl (TBS) groups in **L11**[10] significantly improved both the yield and enantioselectivity. The desired

Received: September 19, 2014
Published: October 31, 2014

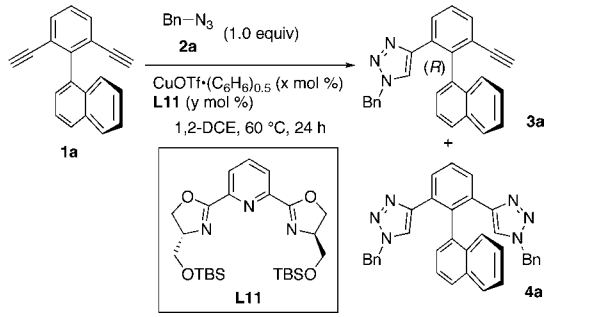
dx.doi.org/10.1021/ol502778j | *Org. Lett.* 2014, 16, 5866–5869

Scheme 1. Chiral Ligand Screening[a]



[a]Reaction conditions: **1a** (0.125 mmol), **2a** (0.125 mmol), CuOTf·$(C_6H_6)_{0.5}$ (20 mol %), **L1**–**11** (40 mol %), 1,2-DCE, 60 °C, 24 h. Isolated yields are reported. The ee values were determined by HPLC on a chiral stationary column (DAICEL CHIRALPAK IA). The absolute configuration of **3a** was tentatively determined to be *R* (see below).

Table 1. Condition Optimization[a]



			3a		4a
entry	Cu (mol %)	**L11** (mol %)	yield[b] (%)	ee[c] (%)	yield[b] (%)
1	20	40	67	79	16
2	10	20	65	78	14
3	5	10	60	70	10
4	10	11	52	70	19
5	10	30	65	73	17
6[d]	10	20	72	84	14
7[e]	10	20	65	80	11
8[f]	10	20	64	91	32

[a]Reaction conditions: **1a** (0.125 mmol), **2** (0.125 mmol), CuOTf·$(C_6H_6)_{0.5}$, **L11**, 1,2-DCE, 60 °C, 24 h, unless otherwise noted. [b]Isolated yield. [c]The ee values were determined by HPLC on a chiral stationary column (DAICEL CHIRALPAK IA). The absolute configuration of **3a** was tentatively determined to be *R* (see below). [d]The reaction was performed at 25 °C. [e]The reaction was performed at 25 °C for 3 h. [f]The reaction was performed at 25 °C for 3 h. **2a** (0.188 mmol, 1.5 equiv) was used.

monotriazole **3a** was then obtained in 67% yield and 79% ee, together with a 16% yield of bistriazole **4a**.

Having identified the optimal chiral ligand (**L11**), we further screened the reaction conditions for the enantioposition-selective CuAAC (Table 1). When the reaction of dialkyne **1a** with azide **2a** was performed in the presence of a combination of CuOTf·$(C_6H_6)_{0.5}$ (10 mol %) and **L11** (20 mol %), the chiral mono(triazole) **3a** was obtained in 65% yield with retention of enantioselectivity (78% ee; Table 1, entry 2). Further reductions in the loading of both copper and the ligand (5 mol % for Cu and 10 mol % for **L11**) resulted in a slight loss of enantioselectivity (entry 3). Changing the Cu/**L11** ratio to 1:1.1 or 1:3 afforded **3a** in 70% and 73% ee, respectively (entries 4 and 5). The reaction at 25 °C improved both the yield and ee, giving **3a** in 72% yield and 84% ee (entry 6). The reaction time could be reduced to 3 h without significant loss of yield and enantioselectivity (65% yield and 80% ee, entry 7). The use of 1.5 equiv of benzyl azide (**2a**) further improved the ee of **3a** to 91% ee with an acceptable yield (64%), although the yield of **4a** increased to 32% (entry 8).

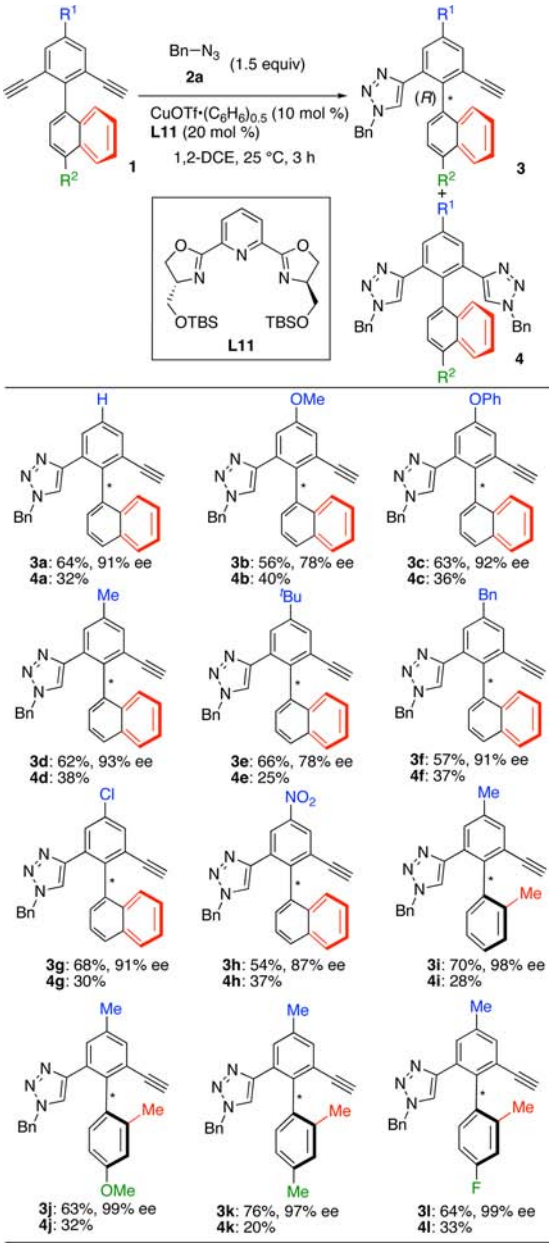
We then examined the substrate scope for dialkynes **1** in the enantioposition-selective CuAAC under the optimized conditions (Scheme 2). 1-(2,6-Diethynylphenyl)naphthalenes **1b**–**f** bearing electron-donating substituents such as methoxy, phenoxy, or alkyl groups on the phenyl rings underwent the enantioposition-selective CuAAC to give the corresponding chiral monotriazoles **3b**–**f** in 56–66% yield and 78–91% ee. Substituents such as chloro and nitro on the phenyl rings (**1g** and **1h**) were also tolerated in the reaction, and chiral monotriazoles **3g** and **3h** were obtained in 68% and 54% yield and 91% and 87% ee, respectively. Dialkynes **1i**–**l** bearing prochiral biphenyl groups [2,6-diethynyl-2′,4-dimethylbiphenyls] also underwent the enantioposition-selective CuAAC to provide the corresponding monotriazoles **3i**–**l** bearing axially chiral biphenyl groups in 63–76% yield and 97–99% ee.[11]

The absolute stereochemistry of chiral monotriazole **3g** was determined to have an *R*-configuration by means of X-ray crystallographic analysis (Scheme 3).[12] The chiral monotriazole **3g** was converted into the asymmetric bistriazole **5** by CuAAC with 4-methylbenzyl azide. The crystal structure of **5** showed that the conformation of the axial chirality was retained during the CuAAC.

The resulting axially chiral monotriazoles **3** can be used as synthetic intermediates. For example, monotriazole **3a** was readily converted into the optically active ethyl derivative **6** without loss of the enantioselectivity by catalytic hydrogenation in the presence of an amphiphilic resin dispersion of platinum (ARP-Pt), and the phenylethynyl derivative **7** was

dx.doi.org/10.1021/ol502778j | Org. Lett. 2014, 16, 5866–5869

Scheme 2. Substrate Scope for Dialkynes 1[a]

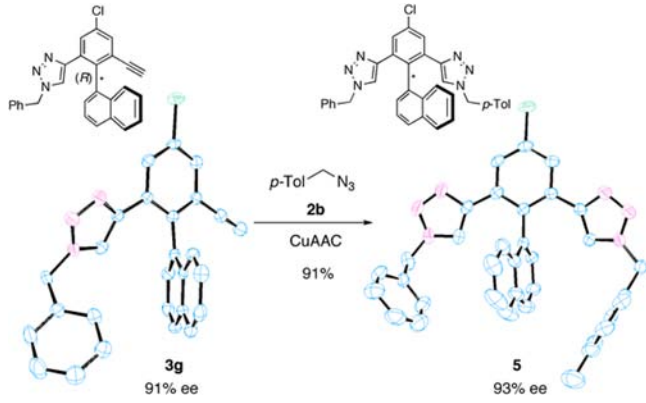


[a]Reaction conditions: **1** (0.125 mmol), **2a** (0.188 mmol), CuOTf·$(C_6H_6)_{0.5}$ (10 mol %), **L11** (20 mol %), 1,2-DCE, 25 °C, 3 h. Isolated yields are reported. The ee values were determined by HPLC on a chiral stationary column. The absolute configuration of **3g** was determined to be *R* by X-ray crystallographic analysis, and those of **3a–l** were tentatively assigned based on the mechanistic similarity of the asymmetric induction.

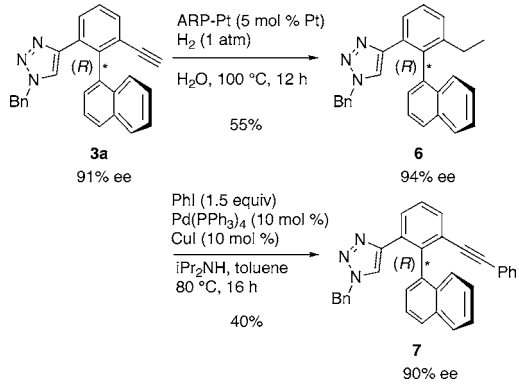
prepared enantioselectively by the Sonogashira reaction (Scheme 4).

In conclusion, we have developed a highly enantioposition-selective copper-catalyzed azide–alkyne cycloaddition (CuAAC) of benzyl azide with dialkynes bearing prochiral biaryl groups to give 1,2,3-triazoles bearing axially chiral biaryl groups in up to 76% yield and up to 99% ee. This asymmetric transformation provides a novel and efficient method for the construction of axially chiral biaryl derivatives. Further investigation for the substrate scope and the mechanistic study will be reported elsewhere.

Scheme 3. Determination of the Absolute Structure



Scheme 4. Derivatization of Chiral Mono(triazole) 3a



■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, analytical and spectroscopic data, ^1H and $^{13}C\{^1H\}$ NMR and HPLC spectra, and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the JST-CREST (Creation of Innovative Functions of Intelligent Materials on the Basis of Element Strategy). We appreciate the partial funding from the JSPS (Grant-in-Aid for Scientific Research on Innovative Area No. 2105; Grant-in-Aid for Young Scientists (B) Nos. 22750141, 26810099) and from Shionogi & Co., Ltd. (Shionogi Award in Synthetic Organic Chemistry).

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(11) Unfortunately, the scope of the azide in the highly enantioposition-selective CuAAC was limited to benzyl azide. The use of *para*-substituted benzyl azides (*p*-OMe, *p*-CH_3, *p*-CF_3), octyl azide, or phenyl azides provided the corresponding monotriazoles with low levels of enantioselectivity (up to 35% ee). Details will be reported elsewhere.

(12) For details, see Supporting Information. CCDC deposition numbers: 1020680 (**3h**) and 1020681 (**5**).

dx.doi.org/10.1021/ol502778j | *Org. Lett.* 2014, 16, 5866−5869