Synthesis of Atropisomeric Triazoles with Vicinal 1,5-Diaxes via Rhodium-Catalyzed Click Chemistry

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Abstract

Axially chiral scaffolds, namely atropisomers, are widely found in natural products, pharmaceuticals, functional materials as well as chiral catalysts and ligands. Over the past decades, the construction of axial chirality has become one of hot topics in organic chemistry, and remarkable advances have been achieved. However, these studies mainly focus on the preparation of atropisomers with a single axis, while the synthesis of atropisomers with more than one axes remains elusive, probably owing to the formidable challenges in establishing multi-axes with high chiral control. Herein we report a practical and modular platform technology of click chemistry for the construction of biaxial atropisomers. In this protocol, a wide range of readily available internal alkynes and azides could rapidly assemble to a variety of atropisomeric triazoles with vicinal 1,5-C−N/C−C-diaxes through Rh-catalysis in excellent yields with high regioselectivities, diastereoselectivities and enantioselectivities. This click technology features broad substrate scope, very mild reaction conditions, high efficiency and scalability, demonstrating tremendous potential in chemistry and biology.

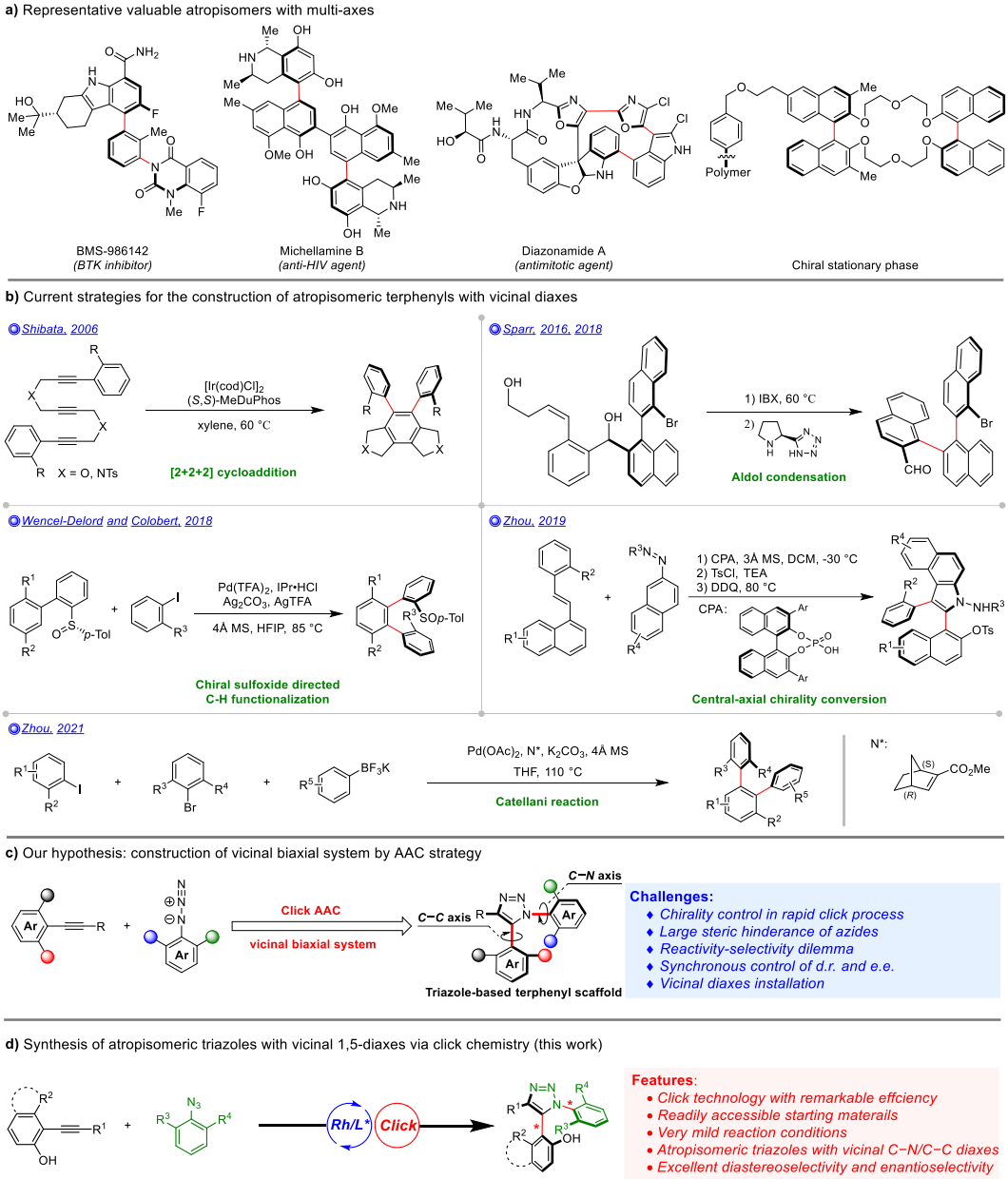
Introduction

Axial chirality, arising from restricted rotation around a single bond by electronic and/or steric effects which results in a pair of conformational enantiomers denoted as atropisomers, represents a unique mode of stereochemistry[1,2]. Atropisomers are ubiquitously distributed in a myriad of natural products[3-5], pharmaceuticals[6], functional materials[7] as well as chiral catalysts and ligands[8,9], showing great significance in various areas of science. Given the relevance of axial chirality, numerous efforts have been dedicated to the synthesis of atropisomers, and remarkable advances have been achieved during the past few decades[10-17]. Nevertheless, these achievements mainly focus on the preparation of atropisomers with a single axis[18-28], while the synthesis of atropisomers with more than one axes are rarely reported although Hayashi reported the catalytic asymmetric synthesis of diaxes compounds back to 1989[29], probably owing to the formidable challenges in establishing multi-axes with efficient chiral control[30-32]. Multi-axes are also widely found in biologically valuable molecules (Scheme. 1a). For example, BMS-986141, whose structure bears a couple of *meta*-C−C/C−N diaxes, is a reversible inhibitor of Bruton's tyrosine kinase (BTK)[33]; Michellamine B and Diazonamide A, two natural products containing multi-axial system, are served as an anti-HIV agent and an antimitotic agent, respectively[5,34]. Among the multi-axial systems, terphenyl scaffolds with vicinal diaxes are

typical structures, and to the best of our knowledge, the syntheses of these atropisomers remain limited up to now (Scheme. 1b). In 2006, Shibata and co-workers reported an intramolecular [2+2+2] cycloaddition of triynes, generating atropisomeric biaryls with vicinal 1,2-diaxes in good yields with high enantioselectivities for the first time[35]. Sparr and co-workers reported the synthesis of oligo-1,2-naphthylenes with vicinal diaxes through intramolecular aldol condensation[36]. In 2018, Wencel-Delord and Colobert developed a chiral sulfoxide directed asymmetric C-H arylation toward terphenyl atropisomers with 1,2-diaxes[37]. In 2019, Zhou and co-workers designed a three-step cascade reaction of successive chiral phosphoric acid catalyzed asymmetric [3+2] cycloaddition, *p*-tosylation and DDQ oxidation to realize a central-axial chirality conversion, delivering 2,3-diarylbenzoindole structures with vicinal diaxes efficiently[38]. In 2021, Zhou reported an elegant work about Pd-catalyzed synthesis of atropisomeric terphenyls with adjacent 1,2-diaxes via axial-to-axial diastereoinduction through Catellani reaction[39]. Very recently, Shi reported a Co-catalyzed intramolecular C-H annulation to constitute the isoquinolinone-based terphenyls with vicinal diaxes[40]. Despite being effective, these methods suffer from individually obvious limitations, such as relatively special starting materials, limited structural diversity of products, lengthy multi-step preparation and high reaction temperature. Additionally, the biaxial systems in most of these diaxially chiral skeletons consist of a pair of vicinal C-C axes, thus showing the lack of axial diversity. In this context, developing practical and general approach towards novel terphenyl type scaffolds with vicinal diaxes under mild conditions is of high-demand and challenging.

Click chemistry has long been recognized as a classical process of ‘ideal synthesis’ owing to high efficiency, broad scope, simple reaction conditions and process treatment, which can be used as modular and practical tools for rapidly assembling structures of interest[41-43]. Since the first definition by Sharpless *et al* in 2001, click chemistry has attracted considerable attentions, and become a powerful synthetic technique in chemistry, biology, material sciences and drug discovery[44-49]. Typically, azide-alkyne cycloaddition (AAC), also known as Huisgen reaction, has evolved into an uncontested flagship of click chemistry due to flexible structural diversity of products, excellent fidelity and biocompatibility[50-51]. Remarkable progress has been achieved in chemoselective AAC reactions. For instance, various classes of AAC reactions, including Cu-catalyzed azide–alkyne cycloaddition (CuAAC)[52],Ru-catalyzed azide–alkyne cycloaddition (RuAAC)[53] and strain promoted azide–alkyne cycloaddition (SPAAC)[54], have been well developed to constitute triazole skeletons with high regioselectivities. Notably, Fokin and Finn, Zhou, Topczewski, Xu, and Fossey independently demonstrated the enantioselective AAC reactions for accessing enantiotropic triazoles by dynamic kinetic resolution[55-59], or desymmetrization of diynes[60-62]. Very recently, Xu[63], Li[64] and our group[65] individually disclosed the atroposelective AAC reactions for the synthesis of axially chiral triazoles, which successfully implement click chemistry into the area of axial chirality. On the basis of these works, we envisioned that aryl alkynes with steric hinderance and aromatic azides with flanking substituents in the click AAC reaction may bring opportunities to construct biaxial systems, leading to a novel type of triazole-based terphenyl scaffolds with a couple of C-C/C-N vicinal diaxes (Scheme 1c). To this end, several challenges are confronted: 1) it is unpredictable to control the chirality in very rapid click process; 2) the reactivity of 2,6-

disubstituted aromatic azides would be severely diminished due to the increasing steric hindrance, thus bringing the reactivity-selectivity dilemma; 3) the synchronous control for both diastereoselectivity and enantioselectivity needs high accuracy. Herein, we successfully overcome these challenges and report a practical and modular platform technology of click AAC reaction for the construction of atropisomeric triazoles containing a pair of adjacent 1,5-C-N/C-C-diaxes under Rh-catalysis in excellent efficiency, diastereoselectivities and enantioselectivities (Scheme. 1d).

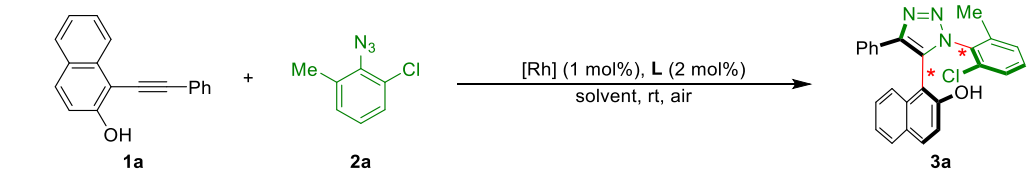


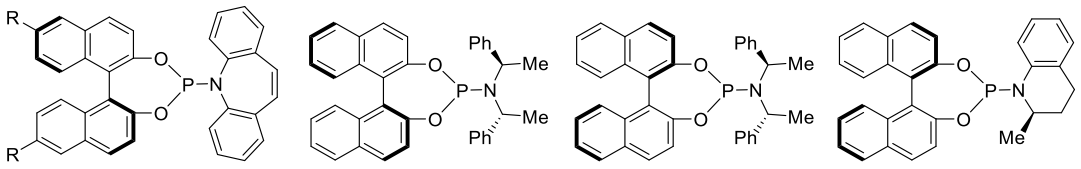
Scheme 1 Valuable atropisomers with multi-axes and synthetic strategies for the synthesis of terphenyl atropisomers with vicinal diaxes. a, Representative valuable atropisomers with multi-axes. **b**, Current strategies for the construction of atropisomeric terphenyls with vicinal diaxes. **c**, Our hypothesis: construction of vicinal biaxial system by AAC strategy. **d**, Synthesis of atropisomeric triazoles with vicinal 1,5-diaxes via click chemistry (this work).

Results and Discussion

Reaction Condition Optimizations. We first prepared 1-phenylethyl-2-naphthol **1a** and 2-chloro-3-methyl phenyl azide **2a** as model substrates to test our hypothesis. Typical reaction condition optimizations are summarized in Table 1. Initially, we mixed **1a**, **2a** and $[Rh(cod)OH]_2$ (1 mol%) in dichloromethane at room temperature under air, and a triazole **3a** bearing a couple of vicinal 1,5-diaxes could be rapidly formed in an almost quantitative yield with moderate diastereoselectivity (entry 1, 99% yield, 8:1 *d.r.*). This preliminary result prompted us to further explore the reaction. We then test the use of $[Rh(cod)OH]_2$ in combination with various commercially available chiral phosphoramidite ligands **L1–L5** (entries 2–6). To our delight, when Carreira-type ligand **L1** was used, the reaction could be completed in an hour with excellent diastereoselectivity and enantioselectivity [entry 2, 99% yield, >20:1 *d.r.* (^{1}H NMR), 40:1 *d.r.* (HPLC), 95% *e.e.*]. **L2** was another effective ligand in this click reaction to deliver the desired diaxially chiral triazole product with slightly diminished *e.e.* value (entry 3, 99% yield, >20:1 *d.r.*, 93% *e.e.*), while ligands **L3-L5** would significantly decrease the reaction rate, diastereoselectivity and enantioselectivity (entries 4-6). When $[Rh(cod)Cl]_2$ was used as the catalyst, the results would be inferior with poor diastereoselectivity and enantioselectivity (entry 7, 80% yield, 12.5:1 *d.r.*, 30% *e.e.*). Next, a survey of solvents showed significant distinctions in outcomes. When Et_2O was utilized as the solvent, the reaction gave the best result [entry 8, 99% yield, >20:1 *d.r.* (^{1}H NMR), >99:1 *d.r.* (HPLC), 95% *e.e.*]. Using DCE, $CHCl_3$, EtOAc, toluene or dioxane as the solvent could furnish the desired triazole in excellent *d.r.* but with slightly lower *e.e.* values (entries 9-14), while the utilization of MeOH, MeCN, DMF and THF would diminish the *d.r.* values significantly, albeit in good *e.e.* values (entries 15-18).

Table 1 Reaction condition optimizations[a].





Entry	[Rh]	L	Solvent	Yield (%)	*d.r.* [b]	*e.e.* (%)[d]
1	$[Rh(cod)OH]_2$	-	DCM	99	8:1	0
2	$[Rh(cod)OH]_2$	**L1**	DCM	99	>20:1 (40:1)[c]	95
3	$[Rh(cod)OH]_2$	**L2**	DCM	99	>20:1	93
4	$[Rh(cod)OH]_2$	**L3**	DCM	61	12.5:1	13
5	$[Rh(cod)OH]_2$	**L4**	DCM	94	12.5:1	3
6	$[Rh(cod)OH]_2$	**L5**	DCM	79	12.5:1	8

7	$[Rh(cod)Cl]_2$	**L1**	DCM	80	12.5:1	30
8	$[Rh(cod)OH]_2$	**L1**	Et_2O	99	>20:1 (>99:1)[c]	95
9	$[Rh(cod)OH]_2$	**L1**	acetone	99	30:1	94
10	$[Rh(cod)OH]_2$	**L1**	DCE	99	40:1	94
11	$[Rh(cod)OH]_2$	**L1**	$CHCl_3$	99	>20:1	93
12	$[Rh(cod)OH]_2$	**L1**	EtOAc	99	>20:1	93
13	$[Rh(cod)OH]_2$	**L1**	toluene	99	>20:1	94
14	$[Rh(cod)OH]_2$	**L1**	dioxane	99	>20:1	94
15	$[Rh(cod)OH]_2$	**L1**	MeOH	99	5:1	96
16	$[Rh(cod)OH]_2$	**L1**	MeCN	94	3:2	88
17	$[Rh(cod)OH]_2$	**L1**	DMF	86	1:1	91
18	$[Rh(cod)OH]_2$	**L1**	THF	90	6:1	84

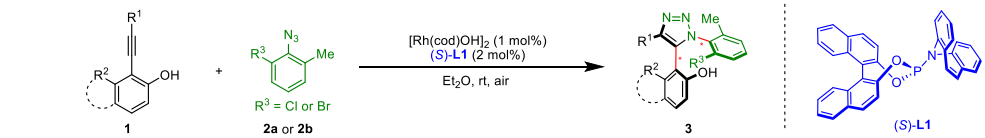
cod, 1,5-cyclooctadiene; DCM, dichloromethane; DCE, 1,2-dichloroethane; DMF, *N*,*N'*-dimethyl formamide; THF, tetrahydrofuran; HPLC, high-performance liquid chromatography.

[a]Reaction conditions: **1a** (0.1 mmol, 1 equiv.), **2a** (0.12 mmol, 1.2 equiv.), catalyst (1 mol%), Ligand (2 mol%), in solvent (1 mL) at rt under air. Yields refer to isolated products. [b]*d.r.* values are determined by crude ^{1}H NMR of the reaction.

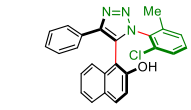
[c]*d.r.* values in parentheses are determined by HPLC analysis.

[d]*e.e.* values are determined by analysing the crude reaction in HPLC with a chiral stationary phase.

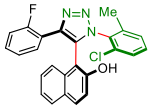
Substrate scope of alkynes. Having the optimized reaction conditions in hand, we set out to study the substrate scope of alkyne component (Scheme 2). The terminal fragment of 1-alkynyl-2-naphthol type alkynes was firstly varied. A series of benzene ring with various substituted groups, such as fluorine, methyl, pentyl, methoxy and chlorine, in different positions were well compatible with this click process to deliver the corresponding diaxially chiral triazoles in excellent yields with high *d.r* and *e.e.* values (**3b-3h**). The configuration of **3g** was unambiguously confirmed by X-ray single crystal diffraction analysis, showing that the hydroxy and chlorine were located in the same side. 2-Naphthyl, 3-thienyl and cyclohexenyl were also tolerable in this process, leading to excellent results (**3i-3k**). The aliphatic tertiary butyl was tested as well, and the corresponding diaxially chiral triazole 3l could be isolated in satisfactory yield and *d.r.* value, but with a slightly lower 89% *e.e.* value. Subsequently, numerous 1-alkynyl-2-naphthols with diverse substituents at different positions in the naphthalene ring were found to be suitable for this atroposelective click process to furnish desired diaxially chiral triazoles in decent yields with high *d.r.* as well as *e.e.* values (**3m-3w**). Functional groups, including methyl, bromo, phenyl, phenylethynyl, formyl, cyano and methoxy, were found compatible. Notably, when the naphthol scaffold was shifted to those privileged skeletons, such as quinolin-6-ol, 1,2,3,4-tetrahydroquinolin-6-ol and tetrahydronaphthol, the atroposelective click reaction could also proceed well, giving the corresponding diaxially chiral triazole products in excellent yields with high chemoselectivities (**3x-3z**). Noteworthy, *ortho*-alkynyl phenols with flanking substituents, such as chlorine, acetal and olefin, were amenable to this click process, delivering the desired diaxially chiral triazoles in remarkable outcomes (**3aa-3ac**).



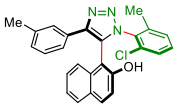
◎ *alkyne scope*



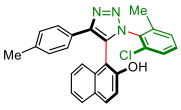
3a, 99% yield
>99:1 *d.r.*, 95% *e.e.*



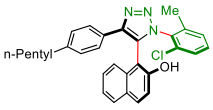
3b, 99% yield
96:4 *d.r.*, >99% *e.e.*



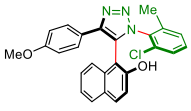
3c, 99% yield
96:4 *d.r.*, 96% *e.e.*



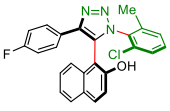
3d, 98% yield
97:3 *d.r.*, 93% *e.e.*



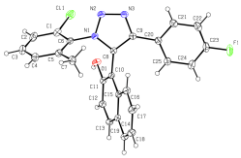
3e, 98% yield
97:3 *d.r.*, 95% *e.e.*



3f, 96% yield
96:4 *d.r.*, 95% *e.e.*



3g, 99% yield
97:3 *d.r.*, 97% *e.e.* (x-ray)



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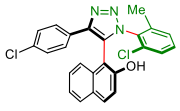
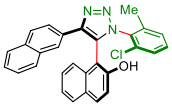
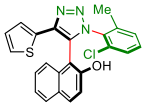


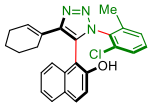
3h, 99% yield
96:4 *d.r.*, 96% *e.e.*



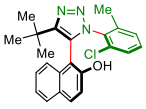
3i, 98% yield
96:4 *d.r.*, 94% *e.e.*



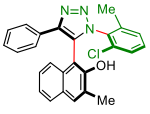
3j, 92% yield
95:5 *d.r.*, 90% *e.e.*



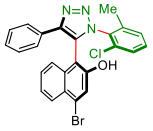
3k, 88% yield
97:3 *d.r.*, 95% *e.e.*



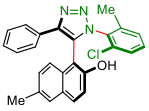
3l[a], 93% yield
99:1 *d.r.*, 89% *e.e.*



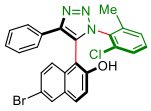
3m, 99% yield
98:2 *d.r.*, 96% *e.e.*



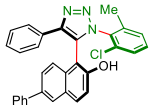
3n, 99% yield
98:2 *d.r.*, 95% *e.e.*



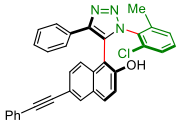
3o, 94% yield
>99:1 *d.r.*, 96% *e.e.*



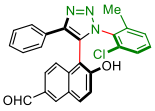
3p, 99% yield
96:4 *d.r.*, 94% *e.e.*



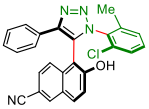
3q, 99% yield
96:4 *d.r.*, 94% *e.e.*



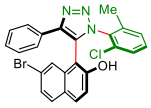
3r, 96% yield
96:4 *d.r.*, 95% *e.e.*



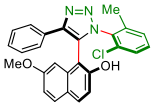
3s, 94% yield
95:5 *d.r.*, 95% *e.e.*



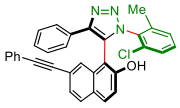
3t, 91% yield
95:5 *d.r.*, 96% *e.e.*



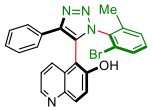
3u, 99% yield
97:3 *d.r.*, 94% *e.e.*



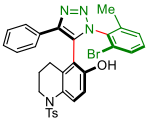
3v, quant.
98:2 *d.r.*, 96% *e.e.*



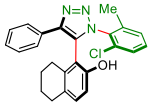
3w, 97% yield
96:4 *d.r.*, 94% *e.e.*



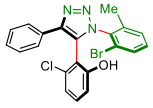
3x[a], 88% yield
91:9 *d.r.*, 90% *e.e.*



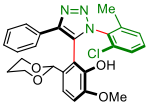
3y[a], 99% yield
99:1 *d.r.*, 98% *e.e.*



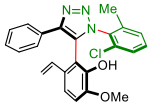
3z, 96% yield
95:5 *d.r.*, 98% *e.e.*



3aa, 94% yield
98:2 *d.r.*, 90% e.e.



3ab, 97% yield
93:7 *d.r.*, >99% *e.e.*

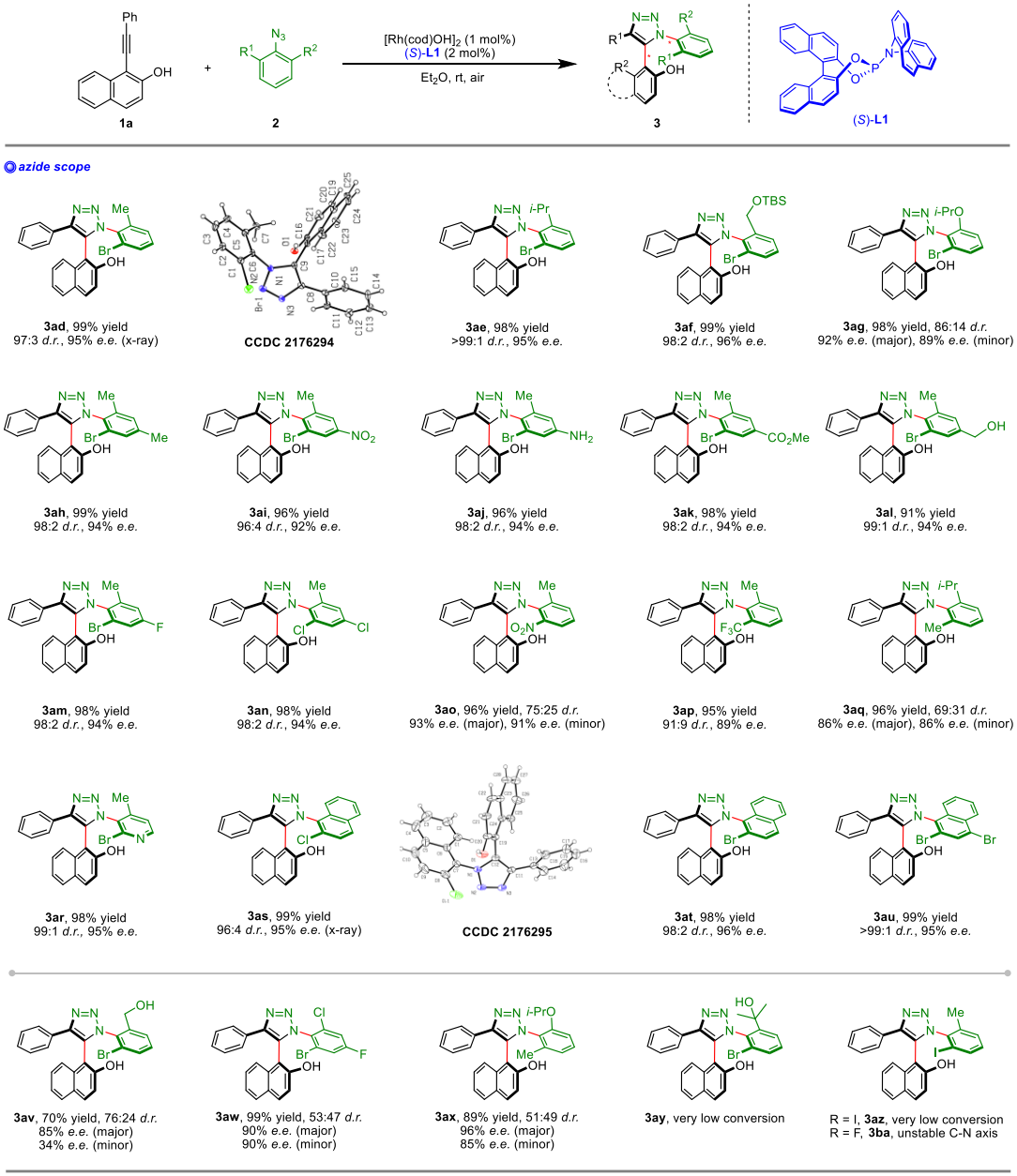


3ac, 92% yield
>99:1 *d.r.*, 97% *e.e.*

Scheme 2 Substrate scope of alkynes. Reactions were performed on 0.2 mmol scale. The yields refer to isolated products. The *d.r.* and *e.e.* values were determined by analysing crude reactions via HPLC. [a]DCM as the solvent. TBS: *tert*-butyldimethylsilyl.

Substrate scope of azides. Next, the scope of azide component was explored (Scheme 3). A variety of *ortho*-bromo/chloro phenyl azides with sterically hindered groups, such as methyl, isopropyl, protected hydroxymethyl and isopropoxy, at another *ortho*-position were found tolerable with this reaction to furnish corresponding diaxially chiral triazoles in excellent yields with high *d.r.* and *e.e.* values (**3ad-3an**), and the configuration of **3ad** was

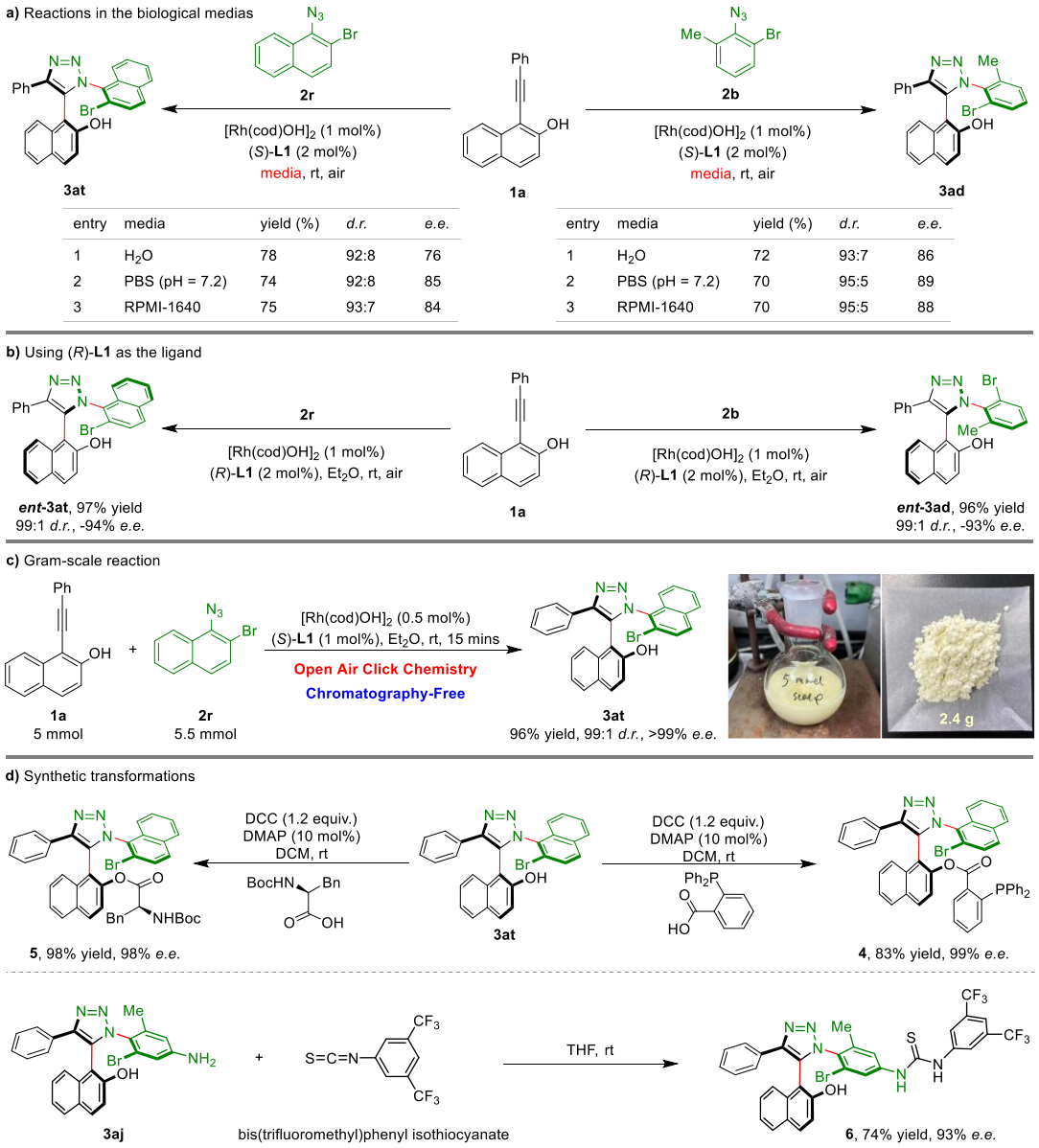
undoubtedly verified by X-ray single crystal diffraction analysis. An array of functional groups in the benzene ring, such as nitro, amino group, ester, hydroxyl, fluorine and chlorine, were all well compatible, which provides good opportunities to further enrich the structural diversity of products. Furthermore, when phenyl azides were substituted with an *ortho*-methyl and an electron-withdraw groups, such as nitro and trifluoromethyl, at another *ortho* position, the diaxially chiral triazoles could be formed in 75:25 and 91:9 *d.r.*, respectively (**3ao-3ap**). These outcomes indicated that the electronic distinction between two *ortho* substituted groups was a significant factor for triggering the diastereoselectivity. Of note, 2-methyl-6-isopropylphenyl azide could participate the reaction smoothly, generating the diaxially chiral triazole in good yield with moderate 69:31 *d.r.*, and 86% *e.e.* values for both diasiomers (**3aq**), which revealed that the steric hinderance difference between two flanking groups was another induced factor for the diastereoselectivity. In addition to phenyl azides, various substituted heteroaryl and naphthyl azides were tested. For example, 3-azido-2-bromo-4-methylpyridine could participate this click reaction efficiently, leading to the corresponding diaxially chiral triazole product in an excellent yield with high *d.r.* and *e.e.* values (**3ar**, 98% yield, 97:3 *d.r.*, 93% *e.e.*). 2-Chloro-1-naphthyl azide, 2-bromo-1-naphthyl azide and 2,4-dibromo-1-naphthyl azide were suitable as well to deliver corresponding diaxially chiral triazole products with excellent diastereoselectivities and enantioselectivities (**3as-3au**), among which **3as** was analysed by X-ray single crystal diffraction to confirm the structure and configuration. It is worth noting that although this atroposelective click process showed remarkable efficiency for a broad range of azides, several substrates would give unsatisfactory outcomes. A phenyl azide with a methyl and an unprotected hydroxymethyl at respective *ortho*-positions could furnish corresponding triazole product in 70% yield with a moderate 76:24 *d.r.* value, and the two diastereomers represented an 85% and a low 34% e.e. values, respectively (**3av**). Phenyl azide with a bromine and chlorine at two *ortho* positions would deliver product in high yield with decreased *d.r.* value (**3aw)**, probably due to the similar electronic effect of flanking groups neutralizing the diastereoselectivity. Using 2-methyl-6-isopropoxy phenylazides in this click reaction would shut down the *d.r.* value (**3ax**), which further implied the key role of an electron-withdraw group at *ortho* position of the aromatic azides for the diastereoselectivity. Furthermore, 2,6-disubstitued phenyl azides containing steric hindered 2-hydroxypropan-2-yl and iodine were found unsuitable for this click reaction (**3ay-3az**). When 2-fuloro-6-methylphenyl azide was used, the corresponding biaxial triazole product with a unstable C−N axis could be formed efficiently, (**3ba**). These results collectively demonstrated that both steric hinderance and electronic effect of flanking substituted groups at *ortho* positions of azides exerted obvious influences to the efficiency and chemoselectivites in this click reaction.



Scheme 3 Substrate scope of azides. Reactions were performed on 0.2 mmol scale. The yields refer to isolated products. The *d.r.* and *e.e.* values were determined by analysing crude reactions via HPLC.

Universality Study. To further demonstrate the universality of this asymmetric click reaction, a set of experiments were conducted (Scheme 4). First, alkyne **1a** was tested with azide **2b** and **2r** in several biocompatible medias, such as water, PBS solution and RPMI-1640 culture solution, and the heterogeneous reactions could still proceed smoothly to give the corresponding products **3ad** and **3at** with slightly lower yields, *d.r.* and *e.e.* values (Scheme 4a). These results showed the good potential of implementing this asymmetric click technology into the bioorthogonal chemistry and chemical biology. Meanwhile, by using the (*R*)-**L1** as the ligand, alkyne **1a** could react with azides **2b** and **2r** to furnish the enantiotropic products ***ent*-3ad** and ***ent*-3at** in excellent yields with high *d.r.*

and *e.e.*, which indicated that this click chemistry could selectively prepare specific configurational diaxially chiral triazoles (Scheme 4b). Furthermore, a 5 mmol scale reaction of **1a** and **2r** was performed, and the reaction could be completed in 15 minutes. More importantly, by simple manipulation of filtration, product **3at** could be obtained with remarkable efficiency and chemoselectivities (2.4 g, 96% yield, 99:1 *d.r.*, >99% *e.e.*), which represented not only the good scalability, but also typical characteristics of click chemistry (Scheme 4c). Moreover, a variety of synthetic transformations were then performed based on the representative diaxially chiral triazole products (Scheme 4d). For example, **3at** could be easily linked to valuable carboxylic acids, such as 2-(diphenylphosphino)benzoic acid and (*L*)-phenylalanine, for leading to the single configurational derivatives **4** and **5** respectively; Upon the treatment with bis(trifluoromethyl)phenyl isothiocyanate, **3aj** could be transformed to an atropisomeric thiourea **6** (74% yield, 93% *e.e.*) with retention of enantiopurity, which could potentially serve as an organocatalyst in asymmetric synthesis.



Scheme 4 Universality study of this click reaction. a, Reactions in biological meidas. **b**, Using (*R*)-**L1** as the ligand. **c**, Gram-scale reaction. **d**, Synthetic transformations.

Thermal stabilization study. To test the configurational stability of biaxially chiral triazole products, **3at** (98:2 d.r., 96% e.e.), whose structure potentially contained four configurations (Figure 1a), was selected as model substrate to conduct the thermal stabilization study (for details, see supplementary information). When the *i*-PrOH solution of **3at** was stirred at ambient temperature, the d.r. and e.e. values remained unchanged after 72 h. When the solution was kept at 90 °C, the d.r. value smoothly dropped to 50:50 in 140 mins, and changed to 29.5:70.5 after continuous heating to 360 mins. At the same time, the e.e. value of major diastereomer dropped obviously to 52%, while the e.e. value of minor diastereomer slowly decreased from 49% to 40% after 360 mins. When the solution was kept at 120 °C, the d.r. value rapidly decreased to 50:50 in 20 mins, and changed to an equilibrium level of 25:75 after continuous heating to 240 mins. we calculated the barriers to diastereoisomers inversion to be $\Delta G^{\ddagger}$ (120 °C) = 30.49 kcal·mol^{-1} [for (*S,S*),(*R,R*) to (*S,R*),(*R,S*) inversion] and $\Delta G^{\ddagger}$ (120 °C) = 29.63 kcal·mol^{-1}[for (*S,R*),(*R,S*) to (*S,S*),(*R,R*) inversion] (Figure 1b). The e.e. value of major diastereomer dropped significantly to 23%, and the e.e. value of minor diastereomer slowly decreased from 45% to 28% after 240 mins, from which the barriers to enantiomerization were calculated to be $\Delta G^{\ddagger}$ (120 °C) = 30.92 kcal·mol^{-1} [for (*S,R*) to (*R,S*) inversion, $t_{1/2}$ = 112 mins] (figure 1c) and $\Delta G^{\ddagger}$ (120 °C) = 31.70 kcal·mol^{-1} [for (*S,R*) to (*R,S*) inversion, $t_{1/2}$ = 304 mins] (figure 1d), respectively. These experimental results demonstrated the good stability of both C-C and C-N axis.

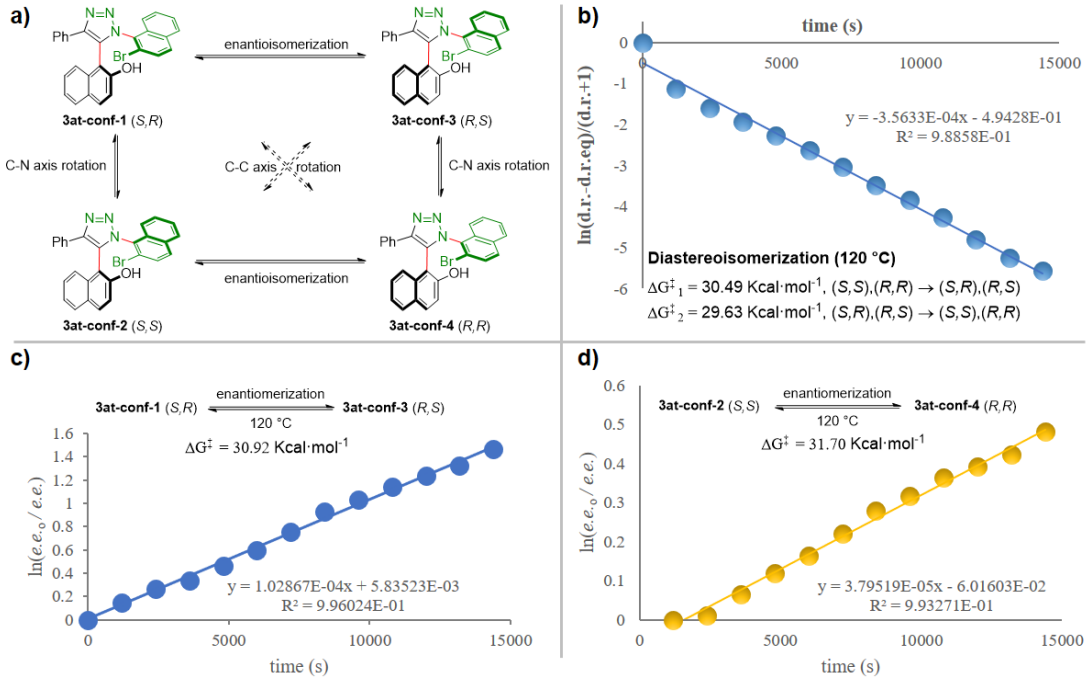


Figure 1 Thermal stabilization experiments of 3at. a, Four configurations of diaxial trizaole **3at**. **b**, Equilibration of diastereomers versus time. **c**, Linear relationship of e.e. and time for major diastereomer. **d**. Linear relationship of e.e. and time for minor diastereomer

Conclusion

In conclusion, we have established a Rh-catalyzed click reaction for the synthesis of atropoisomeric triazoles with a couple of vicinal 1,5-C-N/C-C-diaxes. The reaction features easily accessible starting materials, very mild reaction conditions, scalability as well as remarkable efficiency, diastereoselectivity and enantioselectivity, providing a robust and facile access to novel triazole-based diaxially chiral terphenyl scaffolds. The biocompatible potential of this click technology would find wide applications in medicinal chemistry and chemical biology.

Methods

General information. Commercially available reagents and solvents were used without further purification. ^{1}H nuclear magnetic resonance (NMR) and ^{13}C NMR ^{19}F NMR and ^{31}P NMR spectra were recorded at room temperature in DMSO-d_6 or $CDCl_3$ on a 400 MHz instrument. Flash column chromatography was performed on silica gel (200–300 mesh). All reactions were monitored by thin-layer chromatography or NMR analysis. High-resolution mass spectrometry data were obtained with an Agilent Technologies 6546-LC/Q-TOF mass spectrometer (ESI-TOF). *d.r.* and *e.e.* values were determined by HPLC analysis on a chiral stationary phase on Agilent 1010 instruments

General procedure for the synthesis of diaxially chiral triazoles. A mixture of alkynes **1** (0.2 mmol, 1 equiv.), azides **2** (0.24 mmol, 1.2 equiv.), $[Rh(cod)(OH)]_2$ (0.9 mg, 1 mol%) and (*S*)-**L1** (2.1 mg, 2 mol%) in Et_2O (2 mL) was stirred at room temperature until the alkyne was consumed (monitor by TLC, most of reactions were completely within 1 hour). The mixture was concentrated and purified by silica gel column chromatography to give corresponding triazole products **3**. For several alkyne substrates, DCM was used as the solvent due to the bad solubility in Et_2O, for details, see the description of each case in supplementary information.

Data availability

The data that support the findings of this study are available within the article and its Supplementary Information. Crystallographic data for compounds **3g**, **3ad** and **3as** were deposited on the Cambridge Structural Database and are freely available via the Cambridge Crystallographic Data Centre under CCDC numbers 2071993 (for **3g**) 2176294 (for **3ad**) and 2070176 (for **3as**).

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spectrometry, and Mr. Jiyong Liu (Department of Chemistry, Zhejiang University) for X-ray crystallographic analysis assistance.

Author contributions

S.C. and L.Z. conceived the idea. L.Z. performed the most experiments, analysed the data and drafted the manuscript. J.L. and Y.H. performed a part of experiments. S.C. and F.Z. supervised the project and revised the manuscript. All authors discussed the results and commented on the manuscript.

Competing interests

The authors declare no competing interests.

Materials & Correspondence

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