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Enantioselective Cu(I)-Catalyzed Cycloaddition of Prochiral Diazides with Terminal or 1-Iodoalkynes

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Cite This: https://dx.doi.org/10.1021/acs.orglett.9b04522 Read Online

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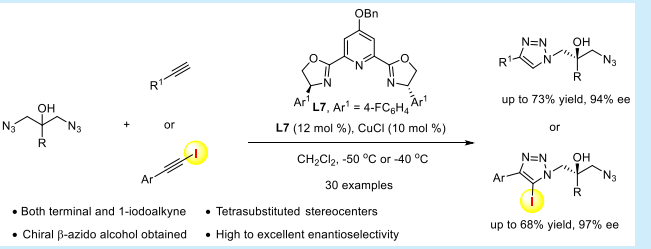
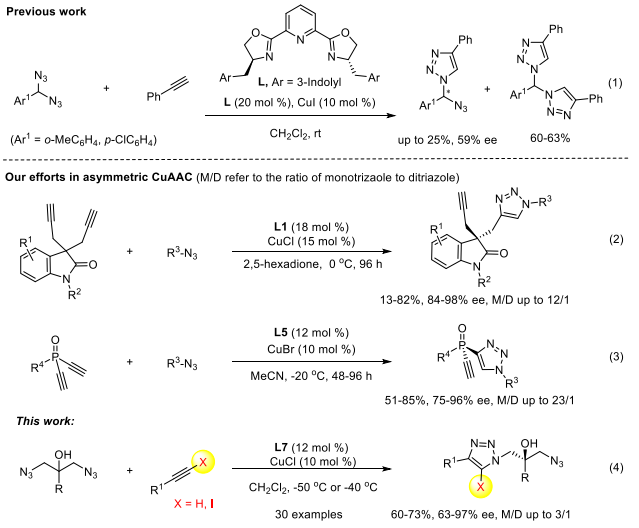
ABSTRACT: We report an unprecedented highly enantioselective desymmetric Cu(I)-catalyzed 1,3-dipolar cycloaddition of diazides with terminal alkynes and 1-iodoalkynes, affording tertiary alcohols bearing a 1,2,3-triazole moiety in high yield and excellent ee value. PYBOX ligands with a C4 shielding group once again show the promising ability to achieve higher enantioselectivity.



Although the Cu(I)-catalyzed azide−alkyne cycloaddition (CuAAC), independently discovered by Meldal[1] and Sharpless,[2] has found numerous applications in many research fields,[3] its potential for the catalytic enantioselective synthesis of chiral triazoles, alkynes, and azides remains largely undeveloped.[4] In 2005, Fokin and Finn pioneered asymmetric CuAAC via the desymmetrization of *gem*-diazides and the kinetic resolution of racemic α-azides (eq 1, Scheme 1).[5] Later

Scheme 1. Desymmetric CuAAC Reactions



in 2013, we reported the first highly enantioselective CuAAC by desymmetrizing prochiral diynes to access quaternary oxindoles (eq 2).[6a] The groups of Uozumi[6c,d] and Stephenson[6h] elegantly demonstrated the potential of desymmetric CuAAC of prochiral diynes to construct axial and planar chirality, respectively. In these protocols using pyridine-2,6-bis(oxazolines) (PYBOX) ligands, substantial side achiral ditriazole formation occurred. However, axially chiral multistereogenic ligands with a deep chiral cavity, developed by Xu et al, showed notable capacity of suppressing ditriazole formation.[6e,f] Based on these meaningful studies, we recently reported that PYBOX with a C4 bulky shielding group to enhance the chiral pocket could effectively inhibit such side reaction while achieving excellent enantioselectivity in the desymmetrization of diethynylphosphine oxides (eq 3).[6g]

In contrast to the progress in accessing chiral alkynes via CuAAC,[6] limited attention was paid to the synthesis of chiral azides, although Topczewskiet et al. recently made a breakthrough in achieving a highly enantioslective dynamic kinetic resolution of racemic azides via CuAAC as well as a kinetic resolution of secondary azides.[7] To our knowledge, highly enantioselective desymmetrization of prochiral diazides via CuAAC is unknown. In addition, reported desymmetric CuAACs are all based on terminal alkynes, the use of 1-iodoalkynes to access chiral 5-iodo-1,2,3-triazoles is unexplored.[8] In view of the importance of optically active azides as building blocks, along with the current interest in their catalytic enantioselective synthesis,[9] we explored the desymmetric CuAAC of diazides. Here, we report a highly enantioselective version to construct chiral 1,2-azido-alcohols, using both terminal alkynes and 1-iodoalkynes (eq 4).

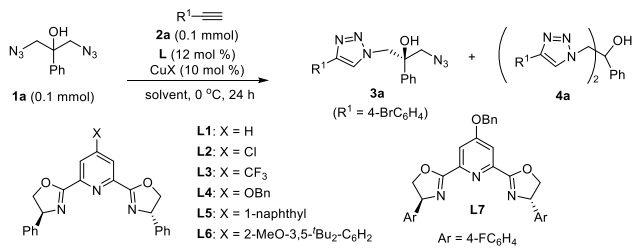
The desymmetrization[10] of prochiral azides is a potentially useful strategy to access multifunctional chiral azides, as shown by intramolecular desymmetric cyclization of diazides to chiral

Received: December 17, 2019

https://dx.doi.org/10.1021/acs.orglett.9b04522
Org. Lett. XXXX, XXX, XXX−XXX

5,6-dihydro-1,4-oxazin-2-ones developed by Gu et al.[11] However, exploiting intermolecular desymmetrization of diazides is very challenging because it is difficult to achieve excellent enantiotopic group discrimination while suppressing side difunctionalization, due to the linear shape of azide group without bulky shielding group. This is clearly demonstrated by the only precedent shown in eq 1.[5,12] To examine whether our recently developed PYBOX ligands bearing a bulky shielding group offer a flexible solution to develop asymmetric CuAAC,[6a,g] we first designed a prochiral diazido alcohol **1** for reaction development. It is worth mentioning that this protocol constitutes an attractive method for catalytic enantioselective synthesis of multifunctional tertiary alcohols bearing both an azido and a triazole moiety.[13,14] Notably, chiral azido alcohols are valuable for the synthesis of pharmaceutical products.[15i,j] While there are some catalytic enantioselective methods to 1,2-azido alcohols,[15] most are based on asymmetric ring opening of epoxides with azides, and importantly, few allowed access of tertiary alcohols bearing an azido moiety.[15f,6h] The reaction of **1a** with 1.0 equiv *p*-bromophenylacetylene **2a** was undertaken to evaluate the potency of PYBOX with different C4 shielding groups, and typical results are shown in Table 1.

Table 1. Optimization of Reaction Conditions



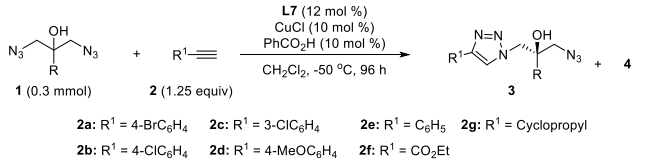
entry	L	CuX	solvent	yield of **3a**[a] (%)	ee of **3a**[b] (%)	**3a**/**4a**[a]
1	**L1**	CuCl	CH_3CN	26	57	1:1.1
2	**L2**	CuCl	CH_3CN	25	60	1:1.3
3	**L3**	CuCl	CH_3CN	15	53	1:1.7
4	**L4**	CuCl	CH_3CN	19	70	1:1.7
5	**L5**	CuCl	CH_3CN	15	53	1:2.5
6	**L6**	CuCl	CH_3CN	24	65	1:1.6
7	**L7**	CuCl	CH_3CN	22	77	1:1.4
8	**L7**	CuCl	Et_2O	34	80	2.4:1
9	**L7**	CuCl	CH_2Cl_2	57	81	2.8:1
10	**L7**	CuCl	DCE	55	81	2.7:1
11	**L7**	CuBr	CH_2Cl_2	53	78	2.2:1
12	**L7**	CuI	CH_2Cl_2	28	79	1.6:1
13	**L7**	$Cu(OAc)_2$	CH_2Cl_2	54	80	2.7:1
14[c]	**L7**	CuCl	CH_2Cl_2	66	92	2.8:1

[a]Determined by ^1H NMR using CH_2Br_2 as an internal standard. [b]Determined by chiral HPLC analysis. [c]0.3 mmol scale, 1.25 equiv of **2a**, and 10 mol % $PhCO_2H$ were used at −50 °C for 96 h.

PYBOX **L1**, without a C4 shield group, was first examined. Although it in combination with CuCl achieved excellent enantioselectivity in the desymmetrization of oxindole-based diyne (eq 2),[6a] it was insufficient in this reaction, because chiral tertiary alcohol **3a** was obtained in only 57% ee with 26% yield as well as a poor ratio of mono- and ditriazole **3a**/**4a** (entry 1). With an electron-withdrawing group, either a chloro or a bulkier CF_3 substituent, ligands **L2** and **L3** gave a diminished **3a**/**4a** ratio (entries 2 and 3). Gratifyingly, the use of ligand **L4** with a flexible OBn group obviously improved the ee of **3a** to 70% but afforded a poor **3a**/**4a** of 1:1.7 (entry 4). However, further increasing the steric hindrance of the shielding group, by using ligand **L5** and **L6**, led to poorer results (entries 5 and 6), although both ligands were powerful in the construction of *P*-chiralgenic center.[6g] We next varied the phenyl group of the ligand to a 4-fluorophenyl group, and the corresponding ligand **L7** afforded slightly improved 77% ee and a poor **3a**/**4a** ratio of 1/1.4 (entry 7). These results are generally unsatisfactory, further showing the challenging in developing asymmetric desymmetrization of prochiral diazides. To improve the outcome, we examined the solvent effects (entries 8−10) and found that CH_2Cl_2 was the solvent of choice, delivering **3a** in 57% yield, 81% ee, and 2.8/1 **3a**/**4a** ratio (entry 9). Screening of copper salts gave no better results than CuCl (entries 11−13). Finally, increasing the usage of alkyne **2a** from 1.0 to 1.25 equiv with the addition of 10 mol % $PhCO_2H$, and the reaction performed at −50 °C could afford chiral **3a** in 66% yield with 92% ee, and 2.8/1 **3a**/**4a** ratio (entry 14). For details of the condition optimization, see the Supporting Information.

Under the above established conditions, we examined the scope of this protocol, as shown in Table 2. First, diazido alcohols **1** with differently substituted phenyl rings were studied. A wide range of functional groups at the *para* position could be tolerated, no matter the electron-withdrawing F, Cl, and CF_3 group or electron-donating methyl and methoxyl group, giving the desired products **3b**−**3f** in 62−73% yield with 83−91% ee and 2.5/1−2.9/1 M/D ratio (entries 2−6). With *meta*-substituted phenyl rings, diazido alcohols **1g**−**i**

Table 2. Reaction of Azides with Terminal Alkynes



entry	**1**	**2**	**3**	yield of **3**[a] (%)	ee of **3**[b] (%)	**3**/**4**[c]
1	**1a**: R = C_6H_5	**2a**	**3a**	66	92	2.8:1
2	**1b**: R = 4-FC_6H_4	**2a**	**3b**	62	85	2.5:1
3	**1c**: R = 4-ClC_6H_4	**2a**	**3c**	62	83	2.8:1
4	**1d**: R = 4-$CF_3C_6H_4$	**2a**	**3d**	73	90	2.9:1
5	**1e**: R = 4-MeC_6H_4	**2a**	**3e**	69	91	2.9:1
6	**1f**: R = 4-$MeOC_6H_4$	**2a**	**3f**	71	90	2.8:1
7	**1g**: R = 3-ClC_6H_4	**2a**	**3g**	69	94	2.7:1
8	**1h**: R = 3-MeC_6H_4	**2a**	**3h**	66	94	2.2:1
9	**1i**: R = 3,5-$(MeO)_2C_6H_3$	**2a**	**3i**	68	92	2.8:1
10	**1j**: R = 2-naphthyl	**2a**	**3j**	67	90	2.9:1
11	**1k**: R = 2-thienyl	**2a**	**3k**	69	92	2.8:1
12	**1l**: R = CH_2CH_2Ph	**2a**	**3l**	68	63	2.8:1
13	**1a**: R = C_6H_5	**2b**	**3m**	66	93	2.5:1
14	**1a**: R = C_6H_5	**2c**	**3n**	72	95	2.8:1
15	**1a**: R = C_6H_5	**2d**	**3o**	60	90	2.4:1
16	**1a**: R = C_6H_5	**2e**	**3p**	68	91	2.8:1
17	**1a**: R = C_6H_5	**2f**	**3q**	69	79	2.6:1
18	**1a**: R = C_6H_5	**2g**	**3r**	68	85	2.4:1
19[d]	**1a**: R = C_6H_5	**2a**	**3a**	73	89	3.0:1

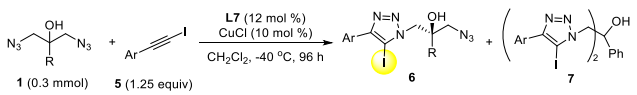
[a]Isolated yield. [b]Determined by chiral HPLC. [c]Determined by the yield of **3**/**4**. [d]1.0 mmol scale.

https://dx.doi.org/10.1021/acs.orglett.9b04522
Org. Lett. XXXX, XXX, XXX−XXX

afforded the corresponding adducts **3g–i** in slightly higher ee values (entries 7–9). 2-Naphthyl- and 2-thienyl-substituted diazides **1j–1k** also furnished products **3j** and **3k** in 67% yield and 90% ee, 69% yield, and 92% ee, respectively (entries 10 and 11). However, diazido alcohol **1l** with an alkyl group gave the corresponding product **3l** in 68% yield and obviously lower 63% ee (entry 12). Second, terminal alkynes **2b–2e** bearing differently substituted phenyl rings were tried, and the corresponding chiral products **3m–3p** were obtained in 60–72% yield, 90–95% ee, and 2.4–2.8/1 M/D ratio (entries 13–16). In addition, the ester- and alkyl-substituted terminal alkynes **2f** and **2g** were also workable, affording the corresponding **3q** and **3r** in 69% yield, 79% ee with 2.6:1 M/D ratio, and 68% yield, 85% ee with 2.4:1 M/D ratio, respectively (entries 17 and 18). Finally, the reaction could be scaled up to 1.0 mmol, giving **3a** in 73% yield with a slightly decreased 89% ee, and a M/D ratio of 3.0:1 (entry 19). The absolute configuration of **3a** was determined to be *S* by X-ray diffraction.

Encouraged by the above results, we next examined whether 1-iodoalkynes were viable substrates under this condition, as shown in Table 3. To our delight, a variety of aryl diazido

Table 3. Reaction of Azides with 1-Iodoalkynes



5a: Ar = 4-BrC$_6$H$_4$ **5b**: Ar = 4-ClC$_6$H$_4$ **5c**: Ar = 3-ClC$_6$H$_4$ **5d**: Ar = 4-MeOC$_6$H$_4$ **5e**: Ar = C$_6$H$_5$

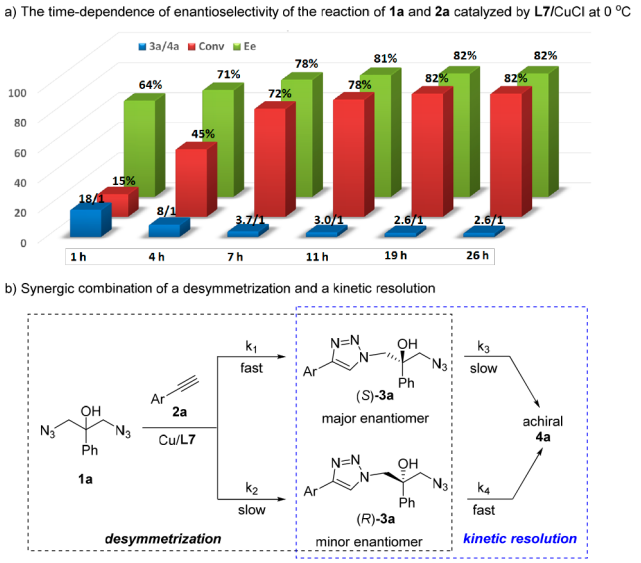
entry	1	5	6	yield of 6[a] (%)	ee of 6[b] (%)	6/7[c]
1	**1a**: R = C$_6$H$_5$	**5a**	**6a**	65	93	2.4:1
2	**1d**: R = 4-CF$_3$C$_6$H$_4$	**5a**	**6b**	68	92	2.8:1
3	**1e**: R = 4-MeC$_6$H$_4$	**5a**	**6c**	65	93	2.6:1
4	**1f**: R = 4-MeOC$_6$H$_4$	**5a**	**6d**	60	96	2.2:1
5	**1i**: R = 3,5-(MeO)$_2$C$_6$H$_3$	**5a**	**6e**	63	93	2.7:1
6	**1j**: R = 2-naphthyl	**5a**	**6f**	67	91	2.8:1
7	**1k**: R = 2-thienyl	**5a**	**6g**	64	92	2.5:1
8	**1l**: R = CH$_2$CH$_2$Ph	**5a**	**6h**	60	74	2.6:1
9	**1a**: R = C$_6$H$_5$	**5b**	**6i**	65	92	2.7:1
10	**1a**: R = C$_6$H$_5$	**5c**	**6j**	67	97	2.8:1
11	**1a**: R = C$_6$H$_5$	**5d**	**6k**	64	82	2.7:1
12	**1a**: R = C$_6$H$_5$	**5e**	**6l**	63	93	2.5:1

[a]Isolated yield. [b]Determined by chiral HPLC. [c]Determined by the yield of **6**/**7**.

alcohols worked well with 1-iodoalkyne **5a** to give the desired chiral 1,2-azido alcohols **6a–6g** in reasonable yield with excellent enantioselectivity (entries 1–7). The reaction of alkyl substituted **1l** with1-iodoalkyne **5a** gave a higher 74% ee than the reaction with terminal alkyne **2a** (entry 8). Good to excellent enantioselectivity was also be achieved in the reaction of **1a** with 1-iodoalkynes **5b–5e** bearing different phenyls (entries 9–12). However, the electron-donating methoxyl group seemed to be less favorable, resulting in a slightly lower 82% ee (entry 11). Notably, this presents the first enantioselective Cu(I)-catalyzed 1,3-dipolar cycloaddition of diazides with 1-iodoalkynes.

The obtained high enantioselectivity was related to the synergic combination of a desymmetrization and a kinetic resolution, similar to Uozumi's result.[6d] As shown in Scheme 2a, the time-dependent enantioselectivity of the reaction of **1a**

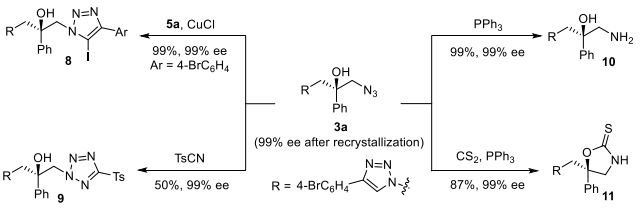
Scheme 2. Study of Reaction Mechanism



and **2a** catalyzed by **L7**/CuCl at 0 °C showed that the ee value of **3a** gradually increased with the proceeding of the reaction; meanwhile, the **3a**/**4a** ratio decreased sharply. This implied that the formation of the achiral ditriazole **4a** was helpful to increase the enantioselectivity of **3a**. In the presence of **L7**/CuCl, the consumption of the minor enantiomer (*R*)-**3a**, formed in the initial step of desymmetrization, was faster than that of the major enantiomer (*S*)-**3a** (Scheme 2b). Therefore, the reaction of **1a** and **2a** was a favorable scenario to obtain (*S*)-**3a** with high ee value, where $k_1 > k_2$ and $k_4 > k_3$.[16]

The thus-obtained chiral tertiary alcohols bearing a triazole moiety are interesting targets for medicinal chemistry research.[17] In addition, they could be readily elaborated by using the azido moiety as a synthetical handle. As shown in Scheme 3, the 1,3-dipolar cycloaddition of **3a** (99% ee after

Scheme 3. Synthetic Elaboration of 3a



recrystallization) with 1-iodoalkyne **5a** or TsCN delivered **8** or **9** in 99% and 50% yield, respectively. By a Staudinger reaction, **3a** was easily reduced to 1,2-amino alcohol **10** in 99% yield; if using the combination of CS_2 and PPh_3, the 1,3-oxazolidine-2-thione **11** was obtained in 87% yield and 99% ee.

In conclusion, we have developed a highly enantioselective desymmetric CuAAC of prochiral diazides for the synthesis of *β*-azido tertiary alcohols bearing a 1,2,3-triazole moiety. Once again, PYBOX ligands with a C4 shielding group on the pyridine showed a promising ability to achieve higher enantioselectivity. This process also features the first example of using nonterminal alkynes for catalytic enantioselective CuAAC. The development of new PYBOX ligands with various shielding groups to develop enantioselective CuAAC reactions for the diverse synthesis of chiral alkynes, azides, and triazoles is ongoing in our laboratory.

https://dx.doi.org/10.1021/acs.orglett.9b04522
Org. Lett. XXXX, XXX, XXX–XXX

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04522.

Experimental procedures, characterization data and spectra (PDF)

Accession Codes

CCDC 1968889 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from NSFC (21672068, 21725203), the Ministry of Education (PCSIRT), and the Fundamental Research Funds for the Central Universities is highly appreciated.

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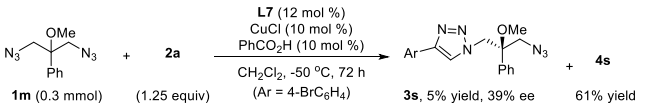

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https://dx.doi.org/10.1021/acs.orglett.9b04522
Org. Lett. XXXX, XXX, XXX−XXX