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Asymmetric Copper(I)-Catalyzed Azide–Alkyne Cycloaddition to Quaternary Oxindoles

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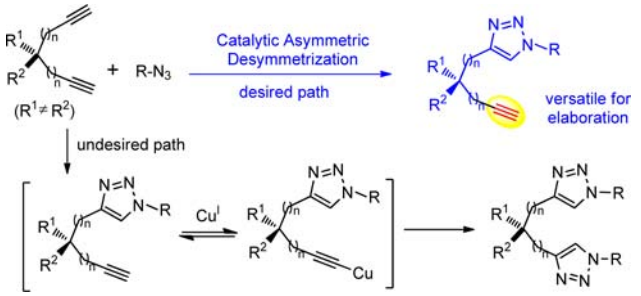
Supporting Information

ABSTRACT: We report a highly enantioselective Cu(I)-catalyzed azide–alkyne cycloaddition via asymmetric desymmetrization of oxindole-based 1,6-heptadiynes, which furnishes quaternary oxindoles bearing a 1,2,3-triazole-containing moiety with 84–98% ee.

Since Kolb, Finn, and Sharpless introduced the concept of click chemistry,[1] Cu(I)-catalyzed azide–alkyne cycloaddition (CuAAC), independently discovered by the Meldal[2a] and Sharpless[2b] laboratories, has been intensively studied and has found applications in many areas of research.[3] Apart from serving as a powerful strategy for the modular assembly of new molecular entities, CuAAC provides a facile and selective synthesis of 1,4-disubstituted 1,2,3-triazoles, which have proven to be a unit of significant pharmacophoric activity,[3a] and a variety of pharmaceutically active compounds featuring a 1,2,3-triazole-containing moiety at the chiral center have been identified.[3b] In view of the versatility of CuAAC in medicinal chemistry and life and material sciences, it is very important and urgent to explore the corresponding catalytic asymmetric studies, as a highly enantioselective CuAAC would facilitate the synthesis of related biologically active compounds and chiral materials, provide a better understanding of the mechanism of this highly useful bond-forming reaction, and helpfully open up new synthetic opportunities for CuAAC.

Very surprisingly, despite the significant achievements in click chemistry, asymmetric CuAAC is largely unexplored. To date, only one example has been reported, in which Fokin and Finn pioneered the kinetic resolution of α-azides and the catalytic desymmetrization of *gem*-diazides with modest selectivity.[4] In the latter case, the desired monotriazole products were obtained in up to 25% yield with 59% ee, as the formation of achiral ditriazoles dominated. Distinct from their research, we envisioned that enantioselective desymmetrization of prochiral dialkynes would be a promising strategy for the development of a highly enantioselective CuAAC (Scheme 1). The attractive features of this approach include ready access to various types of prochiral dialkynes and, more importantly, the installation of a versatile alkyne-containing moiety on the resulting stereogenic carbon centers[5] after the selective conversion of a terminal alkyne group to a 1,2,3-triazole moiety. If both R^1 and R^2 are carbon-based substituents, an all-carbon quaternary stereogenic center is formed, the catalytic asymmetric construction of which is a formidable task in the field of asymmetric catalysis.[6]

Scheme 1. Desymmetrization of Dialkynes by CuAAC



Two major challenges had to be tackled to accomplish the desired reaction. First, excellent enantiotopic group discrimination in the unprecedented catalytic intermolecular desymmetrization of prochiral dialkynes had to be realized. It is well-known that enantioselective catalysis based on functionalization of C–C triple bonds is very challenging,[7] and previous work in catalytic desymmetrization of dialkynes focused on intramolecular transformations.[8] Since the pioneering work of Tanaka and Fu,[8a] several successful desymmetrizations of diynes via intramolecular cyclization have been independently reported by the groups of Yamada,[8b] Czekelius,[8c] and Hennecke,[8d] but to the best of our knowledge, the corresponding intermolecular process remains unexplored to date. Second, the formation of undesired ditriazole products had to be suppressed. Because of the rapid interaction between Cu^I and the alkyne group, the desired chiral monotriazole product can further react with an azide to form the achiral ditriazole. This is a severe problem, as evidenced by the mechanistic studies by Fokin and Finn showing that statistical mixtures of mono- and ditriazoles were obtained in the CuAAC of a malonate derived 1,6-heptadiyne.[9] In view of these challenges, we carried out a research program to explore asymmetric CuAAC. Herein we disclose a highly enantioselective CuAAC involving catalytic desymmetrization of oxindole-based 1,6-heptadiynes to furnish quaternary oxindoles.

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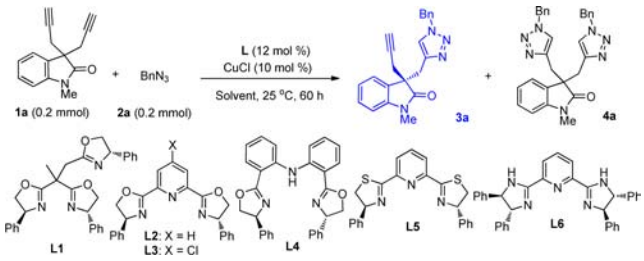
The need for privileged scaffolds in medicinal research has recently provided an impetus to develop diverse syntheses of 3,3-disubstituted oxindoles,[10] which are widely present in natural products, drugs, and pharmaceutically active compounds. In particular, the development of catalytic asymmetric methods has received considerable attention,[11] as both the substituent and the configuration of the C3 position significantly influence the biological activity. During our continuous efforts devoted to the synthesis of quaternary oxindoles,[12] we designed oxindole-based 1,6-heptadiyne **1** to initiate the study of asymmetric CuAAC, as the resulting quaternary oxindole **3** featuring a 1,2,3-triazole-containing substituent at C3 would be interesting for medicinal research.[13] Accordingly, the reaction of dialkyne **1a** and benzyl azide (**2a**) was chosen for optimization, and some typical results are summarized in Table 1.

Table 1. Optimization of the Conditions



entry	L	solvent	yield of **3a** (%)[a]	ee of **3a** (%)[b]	**3a**:**4a**[a]
1	–	CH_2Cl_2	10	–	1:3
2	**L1**	CH_2Cl_2	17	−6	1:1
3	**L2**	CH_2Cl_2	11	67	1:4
4	**L3**	CH_2Cl_2	11	64	1:4
5	**L4**	CH_2Cl_2	5	2	1:9
6	**L5**	CH_2Cl_2	6	23	1:9
7	**L6**	CH_2Cl_2	8	0	1:5
8	**L2**	acetone	20	75	1:2
9	**L2**	2-butanone	21	77	1:2
10	**L2**	2-pentanone	22	75	1:2
11	**L2**	3-pentanone	21	84	1:2
12	**L2**	cyclopentanone	24	60	1:2
13	**L2**	2,5-hexanedione	32[c]	90	1:1
14[d]	**L2**	2,5-hexanedione	50[c]	85	2:1
15[e]	**L2**	2,5-hexanedione	77[c]	90	7:1

[a]Determined by ^{1}H NMR spectroscopy using CH_2Br_2 as an internal standard. [b]Determined by HPLC analysis. [c]Isolated yield. [d]0.24 mmol of **1a** was used. [e]0.24 mmol of **1a**, 15 mol % CuCl, and 18 mol % **L2** were used at 0 °C for 96 h.

Of all the cuprous salts screened under ligand-free conditions, CuCl proved to be the best in terms of reactivity. However, even in the presence of 10 mol % CuCl, the reaction of equal amounts of **1a** and **2a** proceeded slowly in CH_2Cl_2 at 25 °C and gave the desired product **3a** in only 10% yield (Table 1, entry 1). Not unexpectedly, the unwanted ditriazole **4a** was obtained as the major product. Next, various chiral ligands in combination with CuCl were examined. To our disappointment, all of the ligands accelerated the formation of **4a** except for trisoxazoline **L1**,[14a] which improved the **3a**/**4a** ratio from 1:3 to 1:1; however, **3a** was obtained with only 6% ee (entry 2). PYBOX ligand **L2**[14b] proved to be the most promising in terms of enantioselectivity, affording **3a** in 11% yield with 67% ee and a **3a**/**4a** ratio of 1:4 (entry 3). Unfortunately, endeavors to tune the steric and electronic properties of PYBOX-type ligands to inhibit the side reaction and improve the ee of **3a** ended in vain (entries 4−7).

We then carefully optimized other reaction parameters to improve the reaction outcome. The reaction solvent was found to play a pivotal role, and using acetone as the solvent not only noticeably improved the ee of the desired product **3a** to 75% but also enhanced the **3a**/**4a** ratio to 1:2 (entry 8). This result encouraged us to try other ketone solvents (entries 9−13). Remarkably, when 2,5-hexanedione was used as the solvent, the enantioselectivity and yield of **3a** improved to 90% ee and 32%, respectively, with a **3a**/**4a** ratio of 1:1 (entry 13). Varying the **1a**/**2a** ratio from 1:1 to 1.2:1 resulted in an increase in the **3a**/**4a** ratio to 2:1, although the ee of **3a** slightly decreased to 85% (entry 14). On the basis of this variation, further lowering the reaction temperature to 0 °C and using a 15 mol % loading of the chiral Cu(I) catalyst afforded **3a** in 77% yield with 90% ee and a **3a**/**4a** ratio of 7:1 (entry 15). It is worth mentioning that to our knowledge the use of 2,5-hexanedione as the solvent to improve the enantioselectivity of an asymmetric reaction is unprecedented to date.

The scope of this reaction was then evaluated with respect to substituted oxindole-derived dialkynes **1** and azides **2** under the optimized conditions (Table 2). The reactions were carried out in 2,5-hexanedione at 0 °C using 15 mol % chiral Cu(I) catalyst and a **1**/**2** ratio of 1.2:1.0. The effects of the *N*-protecting group on the oxindole were evaluated first. The products **3a**−**d** were obtained with excellent enantioselectivity irrespective of whether the *N*-protecting group was an alkyl or acetyl group (entries 1−4). However, the electron-withdrawing acetyl protecting group seemed to be less favorable, resulting in increased formation of the undesired ditriazole (entry 4 vs entries 1−3). Both alkyl- and aryl-substituted azides proved to be viable substrates in the reaction with *N*-benzyloxindole **1b**. The reactions of benzyl-type azides **2b**−**i** generally worked well, giving the desired products **3e**−**l** in 70−82% yield with 88−95% ee and good **3**/**4** ratios (entries 5−12). Good to excellent ee (86−98%) was also achieved in the reactions of functionalized alkyl azides **2j**−**l**, although the yield and/or the **3**/**4** ratio were somewhat less satisfactory (entries 13−15). In the case of phenyl azide (**2m**), the desired product **3p** was obtained with 84% ee in a modest yield of 35%, but the **3p**/**4p** ratio was moderate (entry 16). Finally, it was found that the presence of either electron-withdrawing or electron-donating substituents on the oxindole framework had no big influence on the enantioselectivity, as dialkynes **1e**−**k** reacted with 2-(azidomethyl)phenol (**2h**) to give products **3q**−**w** in reasonable yields with 93−95% ee and good **3**/**4** ratios (entries 17−23). The absolute configuration of product **3v** was determined to be *S* by X-ray diffraction analysis.

With an alkyne group as a synthetically versatile handle, the thus-obtained quaternary oxindoles **3** could be readily elaborated. For example, oxindole **3b** was readily converted without loss of enantioselectivity to **5**−**8**, quaternary oxindoles of considerable interest in medicinal research, via transformations based on the alkyne group, including [3 + 2] cycloaddition, Sonogashira coupling, and full or partial hydrogenation, respectively (Scheme 2).

Since the pioneering kinetic studies by Fokin and Finn to elucidate the mechanism,[9a] the possible involvement of dinuclear copper intermediates as the catalytically active species in CuAAC has been supported by both experimental evidence and theoretical calculations.[9b−e] We envisioned that the highly

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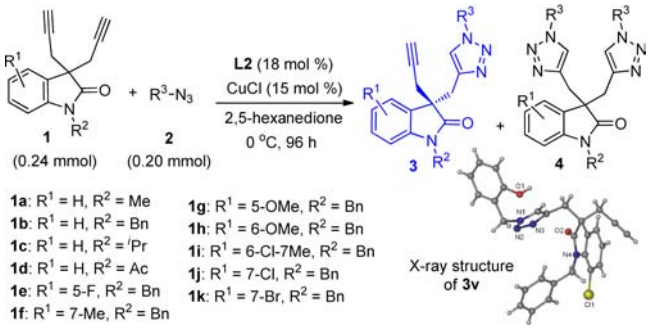
Table 2. Substrate Scope of the Asymmetric CuAAC



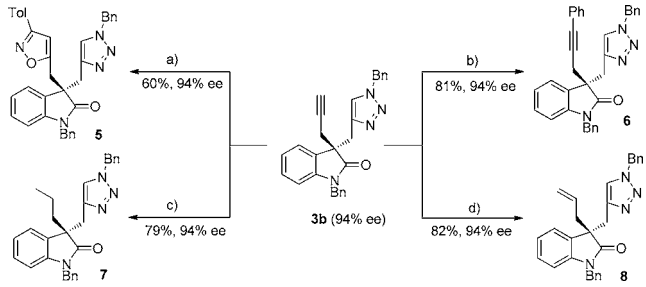
entry	1	2	3	yield of 3 (%)[a]	ee of 3 (%)[b]	3:4[c]
1	1a	2a: R^3 = Bn	3a	77	90	7:1
2	1b	2a: R^3 = Bn	3b	70	94	7:1
3	1c	2a: R^3 = Bn	3c	70	95	6:1
4	1d	2a: R^3 = Bn	3d	64	90	4:1
5	1b	2b: R^3 = 2-$FC_6H_4CH_2$	3e	70	92	10:1
6	1b	2c: R^3 = 3-$FC_6H_4CH_2$	3f	82	89	12:1
7	1b	2d: R^3 = 4-$ClC_6H_4CH_2$	3g	79	88	10:1
8	1b	2e: R^3 = 2-$MeC_6H_4CH_2$	3h	77	93	11:1
9	1b	2f: R^3 = 3-$MeC_6H_4CH_2$	3i	78	93	12:1
10	1b	2g: R^3 = 4-$MeC_6H_4CH_2$	3j	82	93	10:1
11	1b	2h: R^3 = 2-$OHC_6H_4CH_2$	3k	75	95	6:1
12	1b	2i: R^3 = 4-$OHC_6H_4CH_2$	3l	77	94	8:1
13	1b	2j: R^3 = CH_2CO_2Bn	3m	49	89	3:1
14[d]	1b	2k: R^3 = 	3n	56	98	11:1
15	1b	2l: R^3 = *c*-hexyl	3o	13	86	---
16	1b	2m: R^3 = Ph	3p	35	84	2:1
17	1e	2h: R^3 = 2-$OHC_6H_4CH_2$	3q	71	94	10:1
18	1f	2h: R^3 = 2-$OHC_6H_4CH_2$	3r	81	95	10:1
19	1g	2h: R^3 = 2-$OHC_6H_4CH_2$	3s	62	95	8:1
20	1h	2h: R^3 = 2-$OHC_6H_4CH_2$	3t	48	95	7:1
21	1i	2h: R^3 = 2-$OHC_6H_4CH_2$	3u	81	95	9:1
22	1j	2h: R^3 = 2-$OHC_6H_4CH_2$	3v	78	93	7:1
23	1k	2h: R^3 = 2-$OHC_6H_4CH_2$	3w	76	95	11:1

[a]Isolated yields. [b]Determined by chiral HPLC analysis. [c]Determined from the isolated yields of **3** and **4**. [d]At 25 °C.

enantioselective CuAAC developed in the present work might offer a useful probe for mechanistic investigations of this important bond-forming reaction by means of a nonlinear effect (NLE) study.[15] Indeed, a strong negative NLE was observed in the reaction of **1a** and **2a** (Figure 1). Such asymmetric depletion might be rationalized by the hypothesis that the homochiral dimeric species is less reactive than the corresponding heterodimer. Studies of the exact nature of the catalytic species are currently underway.

In conclusion, we have developed the first highly enantioselective CuAAC via desymmetrization of oxindole-based 1,6-heptadiynes to furnish chiral quaternary oxindoles bearing a 1,2,3-triazole moiety, which are interesting targets for medicinal research. Our reaction also features an unprecedented highly enantioselective intermolecular desymmetrization of dialkynes, which demonstrates the great potential of this strategy in the construction of stereogenic carbon centers with an alkyne group. The results further indicate the power of the desymmetrization strategy in the construction of quaternary carbon stereogenic centers.[16] The extension of this methodology to other classes of prochiral dialkynes for the development of highly enantioselective CuAAC reactions, together with the catalytic asymmetric intermolecular desymmetrization of dialkynes by other types of reactions, is ongoing in our laboratory.

Scheme 2. Synthetic Elaboration of 3b[a]



[a]Conditions: (a) *N*-Hydroxy-4-methylbenzimidoyl chloride (2.5 equiv), Et_3N (2.5 equiv), CH_2Cl_2, 10 h. (b) PhI (1.5 equiv), $Pd(PPh_3)_4$ (5 mol %), CuI (5 mol %), Et_3N (10.0 equiv), DMF, 4 h. (c) Raney Ni, MeOH, H_2, 4 h. (d) Lindlar's catalyst, quinine (10.0 equiv), MeOH, H_2, 5 h.

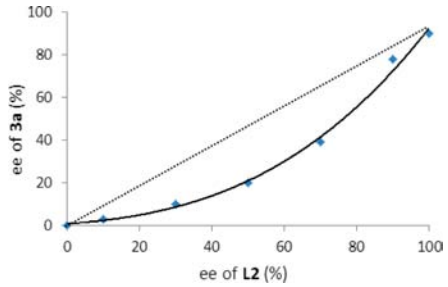


Figure 1. Negative NLE in the reaction of **1a** and **2a** using 15 mol % CuCl/**L2**.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, characterization data, NMR spectra, and HPLC traces for all compounds. 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.

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