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Kinetic Resolution of Cyclic Secondary Azides, Using an Enantioselective Copper-Catalyzed Azide−Alkyne Cycloaddition

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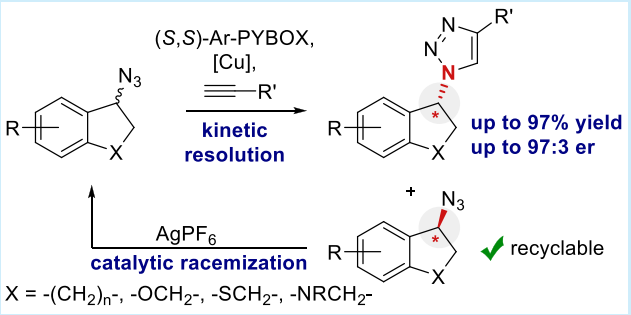
Supporting Information

ABSTRACT: An enantioselective copper-catalyzed azide−alkyne cycloaddition (E-CuAAC) is reported by kinetic resolution. Chiral triazoles were isolated in high yield with limiting alkyne (up to 97:3 enantiomeric ratio (er)). A range of substrates were tolerated (>30 examples), and the reaction was scaled to >1 g. The er of a triazole product could be enhanced by recrystallization and the recovered scalemic azide could be racemized and recycled. Recycling the azide allows efficient use of the undesired azide enantiomer.



The copper(I) catalyzed azide−alkyne cycloaddition reaction (CuAAC)[1,2] is an important transformation. Applications for CuAAC penetrate numerous subdisciplines, including chemical biology, medicinal chemistry, and polymer chemistry.[3−5] This click reaction[6] is operationally simple, functional-group-tolerant, high yielding, and broad in scope. Furthermore, the triazole ring is gaining recognition as a protease-resistant peptidomimetic.[4] Biologically active α-chiral triazoles have been reported (Figure 1).[7−12] Because of the

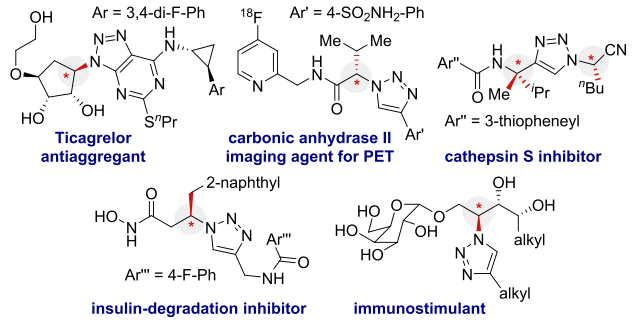
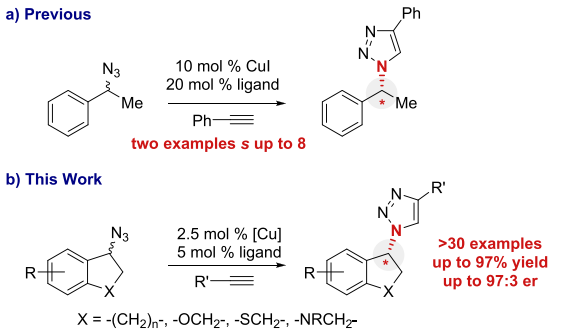


Figure 1. Representative bioactive α-*N*-chiral triazoles.

prevalence of α-amino acid-derived amides, an enantioselective CuAAC (E-CuAAC) reaction would be useful for accessing α-*N*-chiral triazoles. However, E-CuAAC has proven challenging in part because (i) both cycloaddition components have linear geometries, (ii) CuAAC does not require a ligand, and (iii) the product triazole is a competent CuAAC ligand.[13] Therefore, E-CuAAC must kinetically outcompete the background CuAAC reaction.

A few reports describe kinetic resolution,[14−16] dynamic kinetic resolution,[17] or desymmetrization[18−21] for E-CuAAC.[22] The majority of successful E-CuAAC reactions generate α-*C*-chiral triazoles, where the new stereocenter is *alkyne*-derived.[15,16,18,20,21] The original E-CuAAC reported by Fokin and Finn is the state-of-the-art E-CuAAC kinetic resolution for α-*N*-chiral triazole formation, where the new stereocenter is derived from the *azide* component (Scheme 1a).[14] The authors

Scheme 1. Azide Kinetic Resolution by E-CuAAC



provided only two examples of kinetic resolution with a selectivity factor (s) of 3.2 and 8, respectively (ca. 70:30 er and 84:16 er, assuming 40% conversion of the azide). Using the same conditions, the desymmetrization of two *bis*-azides were reported to result predominantly in the formation of *bis*-triazole (not shown).

Our laboratory became interested in using the unique properties of allylic azides to establish α-*N*-chiral centers though dynamic kinetic resolution.[23−25] Recently, we reported the first E-CuAAC reaction that proceeded by dynamic kinetic resolution.[17] This work prompted an exploration of E-CuAAC

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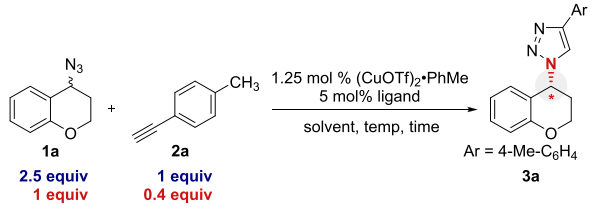
by azide kinetic resolution for *α*-*N*-chiral triazole synthesis (Scheme 1b). Reported herein is a successful expansion of the kinetic resolution by E-CuAAC.

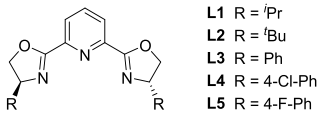
Our investigation began with azide **1a**, alkyne **2a**, and commercially available PYBOX ligands (Table 1, entries 1−3).

Table 1. E-CuAAC Optimization by Kinetic Resolution[a]



entry	ligand	solvent	temperature (°C)	yield[b] (%)	enantiomeric ratio, er[c]
1	(*R*)-L1	CH_2Cl_2	rt[d]	88 (35)	55:45
2	(*R*)-L2	CH_2Cl_2	rt[d]	55 (22)	50:50
3	(*R*)-L3	CH_2Cl_2	rt[d]	92 (37)	22:78
4	(*R*)-L4	CH_2Cl_2	rt[d]	95 (38)	21:79
5	(*S*)-L5	CH_2Cl_2	rt[d]	96 (38)	80:20
6[e]	(*S*)-L5	CH_2Cl_2	0	84 (34)	84:16
7[e,f]	(*S*)-L5	CH_2Cl_2	−15	64 (26)	86:14
8[e,g]	(*S*)-L5	CH_2Cl_2	−20	34 (14)	89:11
9[e,f]	(*S*)-L5	DME	−15	87 (35)	86:14
10[e,f]	(*S*)-L5	$PhCF_3$	−15	92 (37)	88:12
11[e,h]	(*S*)-L5	$PhCF_3$	−15	92 (37)	88:12

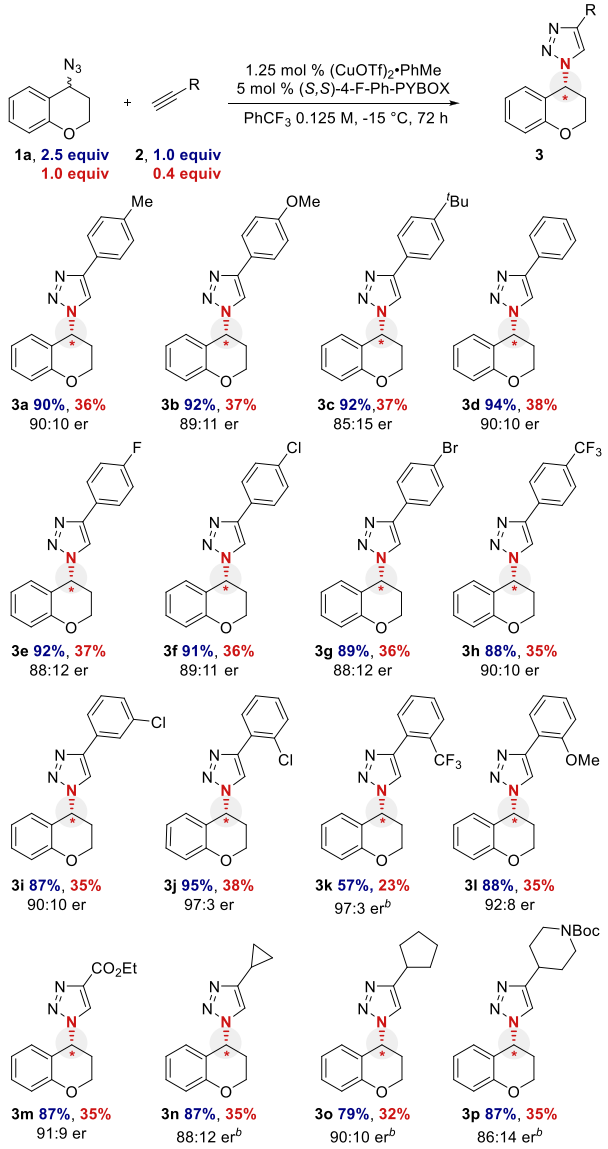
[a]Reactions conducted with azide **1a** (0.125 mmol) and alkyne **2a** (0.05 mmol) at 0.1 M in varying solvent with $(CuOTf)_2$·PhMe (0.62 *μ*mol) and varying ligand (2.5 *μ*mol). All yield and er values reflect the average of duplicate trials. [b]Yield determined using calibrated GC with triphenylmethane as an internal standard. The yield is calculated based on either the *alkyne* (limiting reagent) or *azide* (kinetic resolution component). [c]Chiral HPLC was used to determine er. [d]rt = room temperature. [e]Concentration was 0.125 M. [f]Time = 72 h. [g]Time = 96 h. [h]Time = 48 h.



Minimal enantioselectivity was observed with these ligands, confirming the report from Fokin and Finn.[14] A wide variety of chiral ligands were screened consisting of numerous ligand classes (see Table 1, entries 4 and 5, as well as the Supporting Information). Only the aryl-PYBOX ligands provided reasonable enantioselectivity, with ligand **L5** providing the best selectivity among the ligands screened. The data obtained are reported here with er instead of the selectivity parameter *s* because (i) er is more synthetically meaningful, (ii) er is directly obtained by chiral HPLC, and (iii) several kinetic assumptions are made when deriving *s*, which are likely faulty for E-CuAAC, based on reported CuAAC kinetics.[26,27] One could convert the reported er to a presumed *s* by assuming 40% conversion for reactions approaching completion. Lowering the reaction temperature resulted in an increase in enantioselectivity, albeit at the cost of conversion (Table 1, entries 6−8). The reaction was faster in DME or $PhCF_3$ as the solvent, relative to CH_2Cl_2, and the enantioselectivity was maintained. When using $PhCF_3$ as the solvent, the reaction was complete within 48 h (entry 11; see the Supporting Information for additional optimization).

With the optimized conditions in hand, the scope of the alkyne coupling partner was investigated (Scheme 2). The

Scheme 2. Substrate Scope of Alkyne Coupling Partner[a]



[a]Isolated yields are reported. The yield is calculated based on either the *alkyne* (limiting reagent) or *azide* (kinetic resolution component). Enantiomeric ratio (er) was determined by chiral HPLC. Yield and er values are the average of duplicate trials. [b]2.5 mol % $(CuOTf)_2$·PhMe, 10 mol % (*S*,*S*)-4-F-Ph-PYBOX, and 0.1 M in $PhCF_3$.

model substrate was isolated in comparable yield and er as expected (**3a**). Other aryl alkynes were tolerated with electron-rich (**3b** and **3c**), electron-neutral (**3d** and **3e**), and electron-deficient substituents (**3f**−**3h**) on the arene. Substituents positioned *meta* and *ortho* on the aryl alkyne provided good enantioselectivity (**3i**−**3l**). Ethyl propiolate (**3m**), cycloalkyl alkynes (**3n** and **3o**), and a heterocyclic alkyne (entry **3p**) were tolerated, although several substrates required higher catalyst loadings or longer reaction times to reach higher conversion. Note that long reaction times are not uncommon for other E-CuAAC reactions.[15,18,19]

The scope of the azide component that could be kinetically resolved was explored (Scheme 3). Substituents on the

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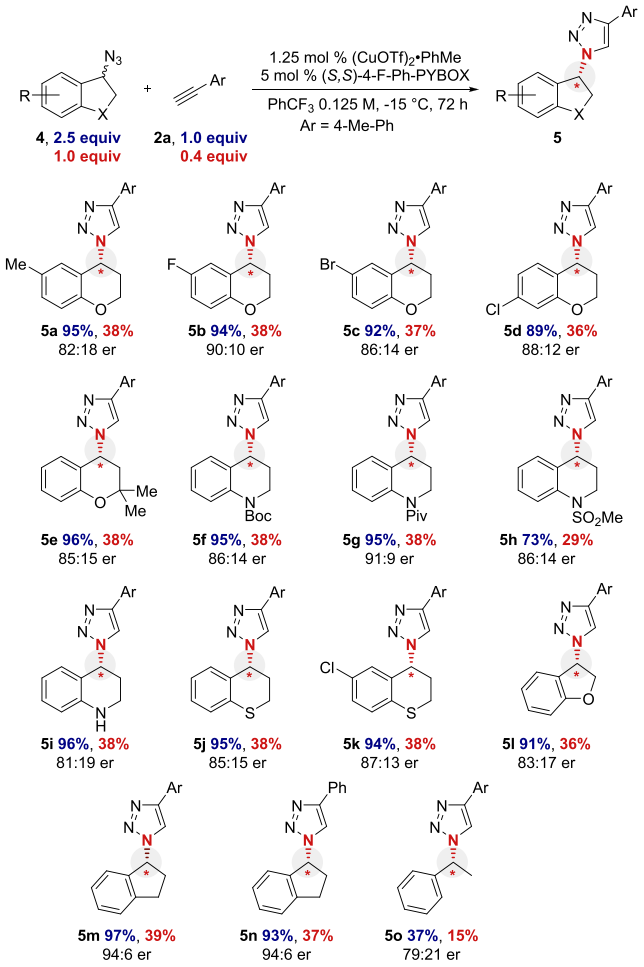
Scheme 3. Substrate Scope of Azide Coupling Partner[a]



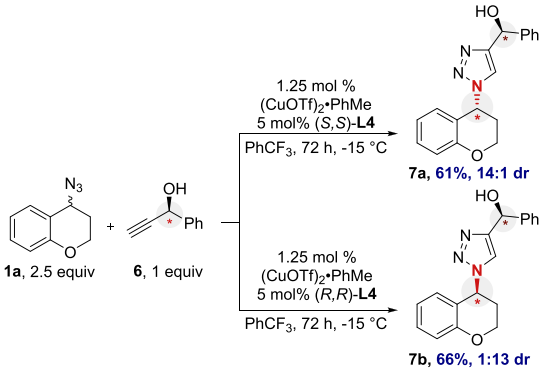
[a]Isolated yields are reported. The yield is calculated based on either the *alkyne* (limiting reagent) or *azide* (kinetic resolution component). Enantiomeric ratio (er) was determined by chiral HPLC. Yield and er values are the average of duplicate trials.

chromane arene core were tolerated, including methyl (**5a**) and halogens (**5b**–**5d**). Groups could also be added α to the oxygen atom (**5e**). Azido-tetrahydroquinolines with various *N*-protecting groups (**5f**–**5h**) and the free NH (**5i**) provided triazoles in high yield and acceptable enantioselectivity. Azido-thiochromanes (**5j** and **5k**), azido-dihydrobenzofuran (**5l**), and azido-indane (**5m** and **5n**) could also be resolved. Substrates **5m** and **5n** are noteworthy because the original E-CuAAC reported by Fokin and Finn described this as a problematic substrate (s < 1.3).[14] Acyclic substrate **5o** provided slower conversion and slightly reduced selectivity.

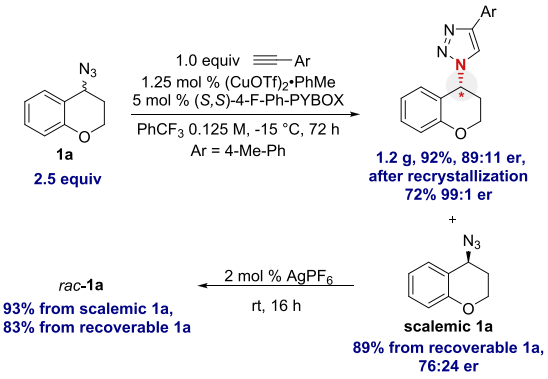
Chiral alkyne **6** was used to test for matched/mismatched behavior (Scheme 4). Treating azide *rac*-**1a** with chiral alkyne **6** and either enantiomer of ligand **L4** resulted in moderate yield with opposite diastereoselectivity (14:1 and 1:13). This reversal of diastereoselectivity indicates this reaction is under catalyst control.

The kinetic resolution could be successfully scaled to provide more than 1 g of triazole product (Scheme 5). The initial enantioselectivity was 89:11 er, which corresponds to an s = 13.5. The enantiopurity could be enhanced upon recrystallization (99:1 er). The excess azide was recovered (76:24 er) and racemized upon exposure to catalytic $AgPF_6$.[28]

Scheme 4. Matched/Mismatched Experiment



Scheme 5. Gram-Scale Reaction and Racemization of Recovered Azide



The azide could then be recycled and used in a subsequent reaction. The ability to recycle the recovered azide improves the overall efficiency of the reaction. The (*R*)-**1a** enantiomer preferentially reacted with the catalyst derived from ligand (*S*,*S*)-**L5**. This was determined by analyzing scalemic azide recovered from the reaction. The scalemic azide was compared to a sample of (*S*)-**1a** which was accessed via diazo transfer from commercially available (*S*)-3,4-dihydro-2H-chromen-4-amine. The same analysis was conducted with azide recovered in the synthesis of triazoles **3j** and **3p**, which confirmed the absolute configuration of the product. The configuration of the other triazole products were assigned based on analogy.

This report describes an expanded scope for both the azide and alkyne coupling partners in an E-CuAAC. The products of this kinetic resolution are α-*N*-chiral triazoles and can be obtained in up to 97% yield and up to 97:3 er. The reaction can be conducted to isolate more than 1 g of product and the excess azide can be recovered, racemized, and recycled. The er of the product triazoles can be readily improved to 99:1 with a single recrystallization.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01556.

Procedures, characterization, and spectral and chromatographic data (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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