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Kinetic resolution by copper-catalyzed azide–alkyne cycloaddition

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Abstract—The use of chiral pybox ligands imparts enantioselectivity to the Cu^{I}-catalyzed azide–alkyne cycloaddition reaction, in the form of kinetic resolution of α-chiral azides and desymmetrization of *gem*-diazides. While levels of selectivity are modest, the results show unequivocally that the process benefits from ligand-accelerated catalysis.

The copper(I)-catalyzed 1,3-dipolar cycloaddition of azides and alkynes[1] has emerged as a useful process to connect diverse building blocks for chemical synthesis, drug discovery, biological chemistry, and materials science.[2] In the course of our initial catalyst screening and mechanistic efforts, we observed strong ligand-accelerated catalysis of the process by a number of different heterocyclic chelates.[3] Such a situation is well-suited for the imposition of enantioselectivity on a metal-catalyzed process, and we report here the first examples of asymmetric kinetic resolution for the azide–alkyne cycloaddition reaction. Apart from an expansion of the synthetic applications that this may provide, the study is most useful for its relevance to questions of reaction mechanism.

Copper complexes of the bis(oxazolinyl)pyridine (pybox) family of ligands are well established as catalysts for a number of asymmetric transformations.[4] While most of these applications derive from the Lewis acidic properties of Cu(II) complexes, two recent examples involve Cu(I)–acetylide species.[5] A selection of pybox ligands, **4**–**12**, was screened in the kinetic resolution of racemic azide **1**, as shown in Figure 1. Each showed an acceleration rate with respect to the reaction in the absence of chelating ligand. A range of effectiveness in kinetic resolution was observed up to maximum enantiomer selectivity factors of approximately 3 for the 5-substituted structures **5** and **12**, showing that the ligand is involved in the copper-catalyzed process. Aromatic substitution at or near the 5-position of each oxazole ring appears to be required with substrate **1**, since ligands lacking such a substituent were ineffective (**4**, **6**, and **10**). The faster-reacting enantiomer of **1** was found to be the same for all ligands except *ent*-**7** and **8**, suggesting that the sense of asymmetric recognition is determined by the absolute configuration at the 5-position of the oxazole.

We surveyed the effect of various reaction conditions on the kinetic resolution of phenethyl azide (**13**) using ligand **12**. The source of Cu^{I} was found to be important, with cuprous iodide giving a much improved system ($s = 5.9$). Increasing the concentration of the catalyst provided more conversion but made relative little difference to the enantiomeric selectivity (Table 1). Catalytic activity was found to be more sensitive to solvent than is the case for standard Cu-catalyzed azide–alkyne cycloaddition reactions, with dichloromethane providing the best rates and selectivities.[6] Catalytic activity was also substantial in acetonitrile and methanol solutions, in which CuOTf was more effective than CuI.

The existence of ligand-accelerated catalysis by **12** was further revealed in an examination of kinetic resolution with varying Cu:**12** ratios (Table 2). The presence of excess copper eroded, but did not eliminate, kinetic resolution, demonstrating that Cu–**12** complexes are more active than the ligand-free catalyst. Reaction rates peaked at Cu:**12** ratios of 1:2, and diminished in the presence of greater amounts of ligand, more dramatically with cuprous triflate than cuprous iodide. A 1:1 mixture of **12** and 4,4′-dimethyl-1,1′-bipyridine provided an *s* value of only 1.3. The Cu–bipy catalyst itself

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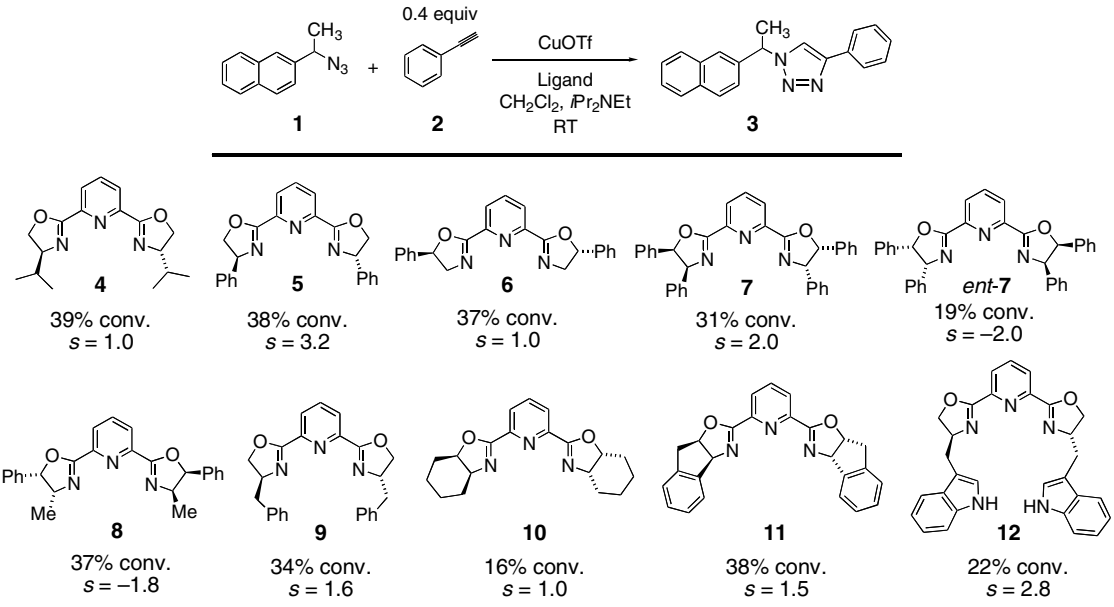
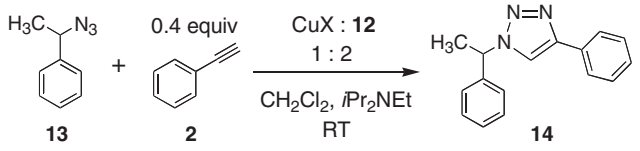


Figure 1. Results for reactions of **1** and **2** using 10 mol% CuOTf and 20 mol% ligand with respect to **2**, under the indicated conditions. For all data in this letter, the relative rate ratio for kinetic resolution is given by $s = k_{fast}/k_{slow}$ with experimental error of ±10% of the reported value; the maximum percentage conversion is 40%, based on the limiting reagent **2**.

Table 1. Dependence on Cu^I source and concentration for the reaction of **13**+**2** in CH_2Cl_2 using 2 equiv of ligand **12** with respect to Cu



Cu complex[a]	% Conv[b]	*s*	mol% CuI · **12**[c]	% Conv[b]	*s*
Cu(OTf)	40	3.4	3	17	5.3
$Cu(MeCN)_4PF_6$	9	2.3	5	21	5.3
CuBr	38	4.1	10	27	6.0
CuCl	37	2.9	20	32	5.5
CuI	37	5.9	30	34	5.4
$CuSO_4$[d]	29	3.8			

[a] [Cu] = 10 mol% with respect to azide and alkyne.
[b] % Conversion, maximum is 40% corresponding to the limiting reagent **2**.
[c] With respect to azide and alkyne; a 2:1 ratio of **12**:CuI.
[d] With 2 equiv sodium ascorbate with respect to Cu; reaction in a 2:1 *t*-BuOH:H_2O.

showed approximately the same degree of reactivity as Cu–**12**. These observations suggest that bipy is a strongly competitive ligand for Cu^I and/or that the species of the formulation (Cu·**12**·bipy) is not enantioselective.[7]

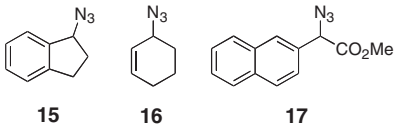
Table 2. Kinetic resolution for **13**+**2** in the presence of a constant amount of CuI or CuOTf (0.1 equiv with respect to alkyne) and varying amounts of **12** (CH_2Cl_2, room temperature)

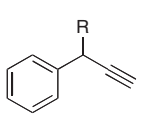
CuI:**12**	% Conv[a]	*s*	CuOTf:**12**	% Conv[a]	*s*
4:1	96	1.9			
2:1	88	4.0			
1:1	91	4.6			
1:2	86	5.4	1:2	96	3.4
1:3	87	5.6	1:4	30	3.1
1:4	81	5.8	1:6	1	—

[a] % Conversion, maximum is 40% corresponding to limiting **2**.

The maximum level of kinetic resolution thus far achieved for the reaction of **13**+**2** ($s = 8 \pm 0.4$) was observed for the CuI·$(\mathbf{12})_2$ catalyst upon cooling to 0 °C, near-complete reaction requiring approximately 24 h.[8] The recovered starting material was compared with enantiopure **13** prepared from commercially available *R*-phenethyl alcohol[9] to reveal *R*-**13** to be the faster-reacting enantiomer. The attempted extension of kinetic resolution to substrates **15**–**17** using a selection of ligands was unsuccessful, with *s* values all <1.3.[6] The 1-phenylpropargylic compounds **18**–**22** were even more resistant to kinetic resolution, with no enantiomeric discrimination observed whatsoever ($s = 1.0$).

The reactions of geminal diazides **23** and **26** with **2**, mediated by the best catalyst in the above studies, have so far





Cpd	R
18	OH
19	OAc
20	OEt
21	OCOPh
22	NHAc

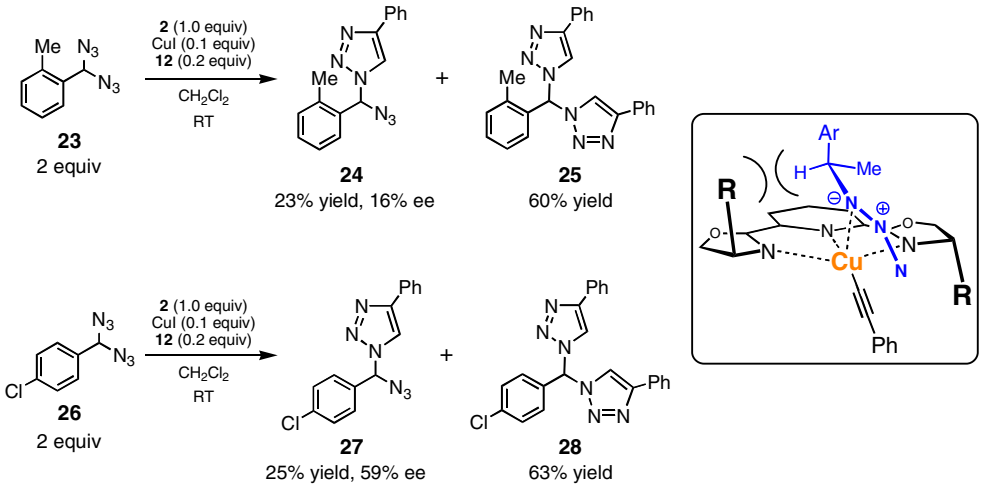


Figure 2. (Left) Desymmetrization of *gem*-diazides. (Right) Proposed interaction of ligand and azide stereogenic centers.

resulted in the formation of the corresponding bis(triazoles) **25** and **28** as major products, even in the presence of a deficiency of alkyne (Fig. 1). A similar phenomenon has been observed with 1,2- and certain 1,3-diazides, and is believed to be a function of the high reactivity of a Cu–organometallic intermediate, as described elsewhere.[10] While the production of monotriazoles in this type of reaction is not synthetically useful, a moderate level of asymmetric induction was achieved in the desymmetrization of **26**. The absolute stereochemistry of the chiral product has not yet been established.

The absolute sense of kinetic resolution of benzylic azides and the lack of resolution of enantiomeric alkynes are consistent with an arrangement of reacting species shown in Figure 2. We suggest that copper–pybox complexes engage azide so as to place the azide α-carbon directly over the ligand plane and therefore in a position to be influenced by its chiral environment. Such a Cu–azide interaction has been predicted on the basis of density functional theory calculations[11] and implicated in kinetic studies of the ligand-free reaction,[10] although the precise coordination environment of the metal center and the role of counterion are not yet understood.[12] Orienting the aryl group away from the ligand plane and the H-atom toward the more sterically demanding quadrant occupied by the ligand *R*-group defines a better arrangement for the *R*-azide. The propargylic stereogenic center in such compounds as **18**–**22** will be farther away from the chiral ligand if the reaction occurs through a Cu–acetylide intermediate, providing poor enantiomeric discrimination.

We have demonstrated here the first asymmetric induction in the Cu-catalyzed azide–alkyne cycloaddition process, both in kinetic resolution and desymmetrization. The achievement of more highly enantioselective systems, a target being currently pursued, will aid the synthesis of useful biologically active compounds since the triazole is emerging as a unit of significant pharmacophoric activity,[13] and will assist in the development of a better understanding of the mechanism of this highly useful bond-forming process.

Acknowledgements

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Supplementary data

Synthetic details, a complete table of solvent effect studies, and a survey of substrate versus ligand are available online with the paper in ScienceDirect. Supplementary data associated with this article can be found, in the online version at doi:10.1016/j.tetlet.2005.05.019.

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6. See Supporting Information for details.
7. Nonlinear effects in mixed-ligand systems are certainly possible and are under investigation.
8. Typical procedure (no precautions were taken to exclude oxygen): A mixture of ligand **12** (95 mg, 0.2 mmol) and CuI (19 mg, 0.1 mmol) in 15 mL CH_2Cl_2 was sonicated at room temperature for 10 min, and stirred until the solution became clear. Alkyne **2** (102 mg, 1 mmol) in 10 mL CH_2Cl_2 was added and the solution was stirred at room temperature for 30 min before cooling to 0 °C. A cooled solution of azide **13** (368 mg, 2.5 mmol) in 10 mL CH_2Cl_2 was added at 0 °C, followed by one drop of iPr$_2$NEt. The resulting solution was stored at 0–4 °C for 24 h. The solvent was removed and the mixture was analyzed without purification to determine kinetic selectivity. When desired, pure components were obtained by silica gel column chromatography, eluting with hexanes to recover the azide and with a 10:1 hexanes:EtOAc to elute the product (**14**). Values of enantiomeric excess were determined by HPLC using a Chiralcel OD–H column.
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12. Kinetic studies show the catalytic reaction to be second order in copper, and azide to bind competitively to the metal center.[10] The Cu–pybox structure in Figure 2 is meant only to illustrate the idea that the azide stereogenic center is positioned close to a pybox ligand by virtue of Cu interaction with its proximal N atom, and not to represent a proposed catalyst structure. Since Cu^{I} is most often found in tetrahedral coordination environments, bonds from the pyridine and oxazoline nitrogen atoms are shown as dotted lines to indicate that not all are expected to be formed. A $[Cu_2(pybox)_2]^{2+}$ system has been structurally characterized, showing an intriguing helical structure in the solid phase and in solution Gelalcha, F. G.; Schulz, M.; Kluge, R.; Sieler, J. *J. Chem. Soc. Dalton Trans.* **2002**, 2517–2521.
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