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Goldberg Active Template Synthesis of a [2]Rotaxane Ligand for Asymmetric Transition-Metal Catalysis

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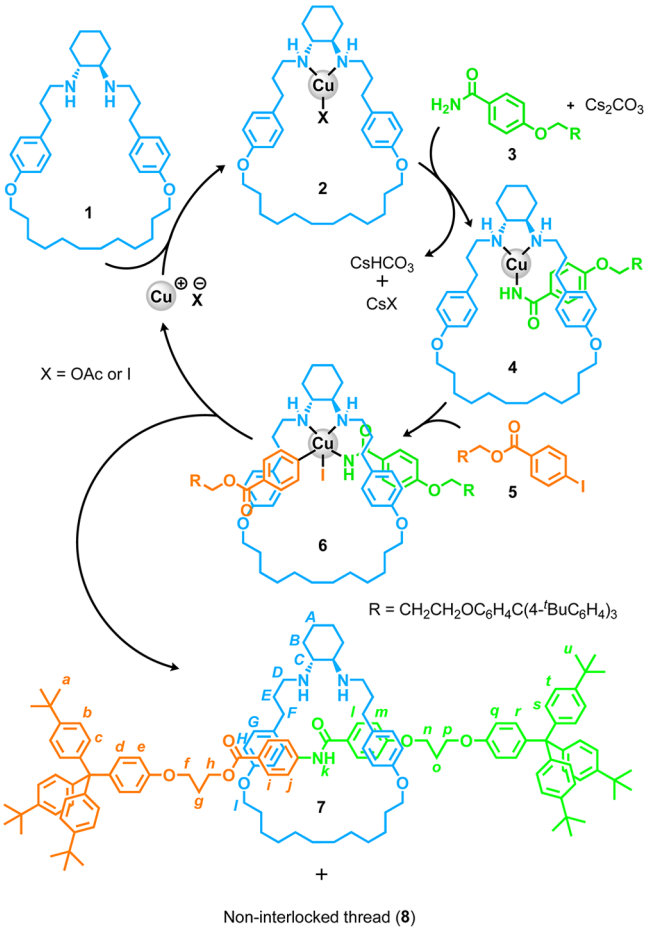
Supporting Information

ABSTRACT: We report on the active template synthesis of a [2]rotaxane through a Goldberg copper-catalyzed C−N bond forming reaction. A C_2-symmetric cyclohexyldiamine macrocycle directs the assembly of the rotaxane, which can subsequently serve as a ligand for enantioselective nickel-catalyzed conjugate addition reactions. Rotaxanes are a previously unexplored ligand architecture for asymmetric catalysis. We find that the rotaxane gives improved enantioselectivity compared to a noninterlocked ligand, at the expense of longer reaction times.

The active metal template synthesis of rotaxanes utilizes both a metal ion's preferred coordination geometry (to direct the assembly of a threaded intermediate) and its ability to catalyze chemical reactions (to covalently capture the interlocked molecular architecture).[1] Advantages of this approach compared to classical "passive" metal template synthesis include that (i) the traditionally separate "threading" and "covalent capturing" processes are combined in a single reaction and (ii) the metal catalyst can often turn over, meaning that only substoichiometric quantities of the template may be required.[2] In addition, it is unnecessary to have a permanent ligand set on the axle of the rotaxane in active template synthesis, making it easier for rotaxanes to be designed that can bind metal ions without saturating all of their coordination sites.[3] Furthermore, the orthogonal orientation of the threaded components should embed a coordinated metal ion within a binding pocket where the shape and surface topography is well-defined in all three dimensions. In principle, these latter two features could be exploited to assemble well-expressed chiral environments for catalysis. Here we report on the synthesis and efficacy of the first rotaxane ligand employed in asymmetric transition-metal catalysis.[4]

To introduce asymmetry close to the metal center in a target rotaxane ligand, we searched for reactions that might form rotaxanes with a chiral C_2-symmetric *trans*-*N*,*N*′-dialkyl-1,2-cyclohexanediamine macrocycle, **1**. Buchwald et al. have described an effective strategy for the amidation of aryl halides—the Goldberg reaction[5]—employing a copper catalyst bound to a cyclohexyldiamine ligand, and we envisaged that this could be adapted for active template synthesis (Scheme 1).[6] In the proposed catalytic cycle, macrocycle **1** coordinates the copper ion endotopically to generate complex **2**. Subsequently the anion is displaced by the stoppered nucleophile **3**, generating **4**. Oxidative insertion into the C−I bond of aryl iodide **5** should occur preferentially from the other face of the macrocycle to give threaded Cu(III) species **6**. Reductive elimination should then liberate [2]rotaxane **7**, concurrently regenerating Cu(I) and allowing its re-entry into the catalytic cycle. Reactions catalyzed by copper ions not bound to **2**, or coordinated outside of the cavity, would produce the noninterlocked thread **8** instead.

Scheme 1. Proposed Catalytic Cycle for the Goldberg Active Metal Template Synthesis of [2]Rotaxane 7 from 1, 3, and 5



We started our investigation of the Goldberg active metal template rotaxane-forming reaction using conditions reported by Buchwald et al.[6] A screen of reaction parameters found toluene to be the optimal solvent when Cs_2CO_3 was employed

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as the base, and $Cu(OAc)_2$ was identified as the most effective copper source. We optimized these conditions for [2]rotaxane formation (Table 1). Extending the reaction time from 8 to 20

Table 1. Optimization of [2]Rotaxane Synthesis by Active Template Goldberg C–N Bond Formation[a]

entry	$Cu(OAc)_2$ (equiv)	time (h)	temp (°C)	conv. of **5** (%)	rotaxane **7** (conv. %)[b]
1	0.5	8	110	26	6
2	0.5	20	110	78	15
3[c]	0.5	20	110	99	21
4[c]	0.1	20	110	65	14
5[c]	2	20	110	82	11
6[c,d]	0.5	48	110	74	51
7[c,d]	0.5	48	90	51	51
8[c,e]	0.9	15	120	99	57 (50[f])

[a]Performed with macrocycle **1** (1.0 equiv), aryl amide **3** (1.5 equiv), aryl iodide **5** (1.0 equiv), and Cs_2CO_3 (2 equiv) in toluene (0.0725 M). [b]Conversion to rotaxane **7** determined by ^{1}H NMR. [c]0.15 M concentration. [d]Aryl amide **3** (4.5 equiv), aryl iodide **5** (4.0 equiv) and Cs_2CO_3 (8.0 equiv). [e]Performed with aryl amide **3** (5.5 equiv), aryl iodide **5** (5.0 equiv) and Cs_2CO_3 (10 equiv). [f]Isolated yield.

h improved the yield of **7** from 6% to 15% (Table 1, entries 1 and 2). Increasing the reaction concentration to 0.15 M, close to the limit of solubility of **3**, increased the rotaxane yield to 21% (Table 1, entry 3). While a decrease in the loading of the copper catalyst (from 0.5 to 0.1 equiv) slowed the reaction rate (Table 1, entry 4), higher copper loadings reduced the amount of rotaxane **7** formed (Table 1, entry 5), probably by increasing the rate of the nonligated-Cu(I)-catalyzed reaction to form **8**. Using a higher ratio of the axle components **3** and **5** to macrocycle **1** increased the yield of [2]rotaxane to a synthetically viable 50% (Table 1, entries 6–8).

The rotaxane architecture of **7** was confirmed by mass spectrometry and NMR spectroscopy (see Supporting Information). The ^{1}H NMR spectra of [2]rotaxane **7** and its components (**1** and **8**) also provided insight into the interactions and relative positions of the components within the rotaxane (Figure 1). Resonances for protons associated with, or proximate to, the amide group of the axle (H_k, H_l, and H_j) are shifted dramatically downfield in the rotaxane (Figure 1b) compared to the noninterlocked thread (Figure 1c), with H_k shifting nearly 3 ppm. This is indicative of the axle being held in position by intercomponent hydrogen bonding between the amide H-bond donor of the axle and the H-bond acceptor amines of the macrocycle. Several proton resonances for the macrocycle are doubled in the rotaxane (e.g., H_G, Figure 1b), a consequence of the threaded unsymmetrical axle rendering the faces of the macrocycle inequivalent.

Having established that the Goldberg reaction could be used to prepare a chiral [2]rotaxane with an embedded metal ion binding pocket with vacant coordination sites, our attention turned to evaluating the efficacy of **7** as a ligand in enantioselective metal catalysis (Table 2). As a proof-of-concept, we examined the well-studied metal-catalyzed enantioselective Michael addition of diethyl malonate (**9**) to *trans*-β-nitrostyrene (**10a**).[7] Evans has demonstrated[8] the utility of chiral cyclohexyldiamine ligands in $NiBr_2$-promoted variants of this reaction to afford **11a**, and we compared the effectiveness of acyclic ligand **12** (Table 2, entry 1) and [2]rotaxane **7** (Table 2, entry 2) in this process. Pleasingly, both ligands catalyzed the reaction between **9** and **10a**.

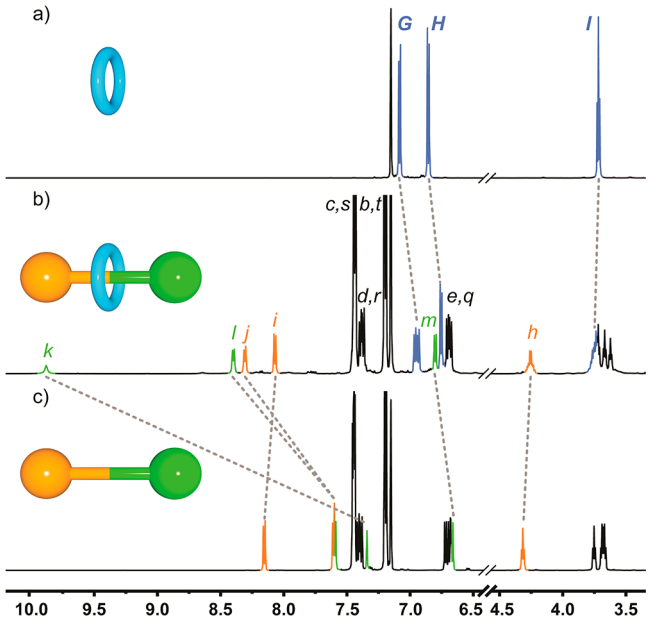
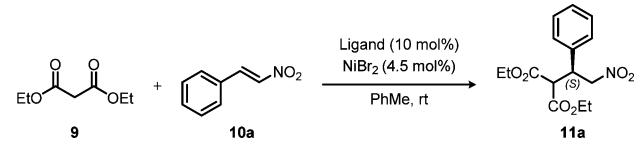
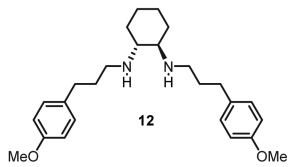


Figure 1. ^{1}H NMR spectra (600 MHz, C_6D_6, 298 K) of (a) macrocycle **1**, (b) rotaxane **7**, (c) thread **8**. The assignments correspond to the lettering shown in Scheme 1.

Table 2. Ligand-Nickel-Catalyzed Enantioselective Michael Addition of Diethyl Malonate 9 and *trans*-β-Nitrostyrene 10a[a]



9 **10a** **11a**

ligand	time (d)	conv. (%)[b]	er (*S*:*R*)[c]
 **12**	2	>98	68:32
Rotaxane **7**	27	>98	93:7

[a]Reaction conditions: **10a** (1.0 equiv), **9** (1.2 equiv), ligand (10 mol %), and $NiBr_2$ (4.5 mol %) in toluene (1 M) at rt. [b]Reactions were run to full conversion as determined by ^{1}H NMR. [c]Enantiomeric ratios determined by HPLC using a Chiralpak IC column. In the absence of $NiBr_2$, diamine **12** gives >98% conversion to **11a** over 4 days with er 49:51 (consistent with the diamine acting as a base, as with other amines in this type of reaction).[8b]

However, they exhibited significant differences in catalytic behavior and stereochemical outcome of the reaction. Although acyclic ligand **12** facilitated rapid formation of **11a**, only modest enantiomeric enrichment (68:32 er) was observed. In contrast, despite more sluggish activity (10× longer reaction times than for **12**), [2]rotaxane **7** afforded product **11a** in good yield (>98% conversion) and enantioselectivity (93:7 er). This behavior is consistent with the rotaxane providing a much more structurally defined 3D pocket for the metal ion and substrate, improving the expression of chirality of the ligand and reducing the degrees of freedom (in terms of conformation and orientation) that the substrate can adopt upon binding to the

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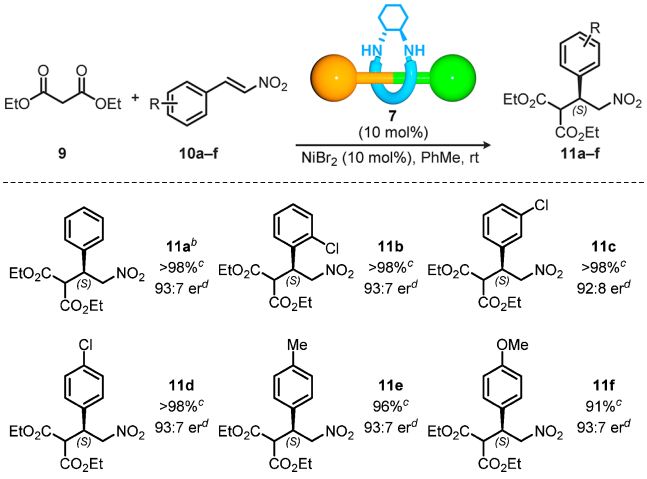
catalytic center.[9] However, burying the metal ion deeper in the ligand structure apparently reduces its accessibility and availability for catalysis, increasing the reaction time needed for full conversion to product.

The substrate scope of the rotaxane-nickel-catalyzed reaction was investigated (Table 3), with high levels of enantiomeric enrichment obtained regardless of substitution pattern (**11b–d**) or electronic properties (**11e,f**) of the nitrostyrene employed.

Table 3. Scope of the Rotaxane-Nickel-Catalyzed Enantioselective Michael Addition of Diethyl Malonate 9 and *trans*-β-Nitrostyrenes 10a–f.[a]



[a]Reaction conditions: **10a–f** (1.0 equiv), **9** (2.0 equiv), **7** (10 mol %), and $NiBr_2$ (10 mol %) in toluene (0.2 M) at rt. [b]Reactions were performed under the conditions used for Table 2. [c]Conversions determined by ^1H NMR. [d]Enantiomeric ratios determined by HPLC using a Chiralpak IC column.

In conclusion, we have demonstrated that the Goldberg copper-catalyzed amidation of an aryl iodide provides an effective means of introducing a C_2-symmetric chiral cyclohexyldiamine macrocycle into a [2]rotaxane architecture. Once the rotaxane is assembled, the ligand remains active in promoting asymmetric transition-metal-catalyzed reactions, giving markedly higher enantioselectivities compared to a noninterlocked analogue, albeit at the expense of significantly longer reaction times.

Enzymes often perform asymmetric catalysis within deep binding pockets of well-defined shape and surface topography. It can be difficult to construct three-dimensional cavities in which the chirality is similarly well-expressed using conventional small-molecule structures. The orthogonal arrangement of the mechanically interlocked components of rotaxanes, which can conveniently incorporate chiral C_2-symmetric (and other) macrocyclic ligands through active template synthesis, offers an intriguing way of assembling chiral three-dimensional binding pockets that have a ligated transition-metal ion with accessible coordination sites at the core. Tuning of the structure of rotaxane ligand **7**, by shortening the thread (to further restrict the freedom of movement of the interlocked components) and varying the axle constitution, is ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Synthetic procedures, characterization data, and catalysis studies. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b04726.

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Notes

The authors declare no competing financial interest.

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(3) The available metal coordination site in active template rotaxanes has been used to promote further threading to form higher order

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(9) The ability of **12** to confer enantioselectivity in the conjugate addition increases at reduced ligand stoichiometry (e.g., 1:1) and concentration. Rotaxane **7** is much less sensitive to changes in these reaction parameters.

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