

An Unusual Nickel–Copper-Mediated Alkyne Homocoupling Reaction for the Active-Template Synthesis of [2]Rotaxanes

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Abstract: We report on an unusual Ni-/Cu-mediated alkyne homocoupling reaction, directed through the cavity of a bidentate macrocyclic ligand by chelated metal ions to furnish [2]rotaxanes in excellent (up to 95%) yields. This is the first active metal template reaction to employ an octahedral coordination geometry metal ion, Ni(II), and the study provides some interesting mechanistic insights into the mixed bimetallic reaction mechanism. The mixed-metal catalyst system was discovered serendipitously when Cu(I) was added to a Ni(II)-catalyzed alkyne homocoupling reaction in an attempt to facilitate chloride–acetylide ligand exchange. The role of Cu(I) in the reaction is, in fact, quite different from that originally intended. The effectiveness of having both nickel and copper present can be rationalized by the nature of a π -activated, σ -bonded, bimetallic intermediate in which the substitution of Ni(II) for one Cu(I) ion in the classic bimetallic Glaser reaction mechanism apparently aids reductive elimination of the acetylide ligands. The system may prove useful for the development of general mixed-metal protocols for catalytic alkyne coupling reactions as well as being a highly effective route to rotaxanes with bis-acetylene threads, which are potentially useful for materials applications (insulated molecular wires) and in molecular machines (rigid, nonfolding axles).

Introduction

Traditional transition-metal template routes to mechanically interlocked molecular-level architectures rely on well-defined recognition motifs on each of the components to be interlocked and efficient, structurally tolerant, reactions to covalently capture the threaded structure.¹ Among the reactions used to assemble rotaxanes, metal-catalyzed alkyne homocouplings have proved popular² because they are generally high yielding, compatible with the conditions used to maximize the intercomponent interactions responsible for template effects, and give rise to a conjugated, relatively rigid axle which can have useful structural and electronic properties.

In active-template³ syntheses the metal plays a dual role in the rotaxane-forming reaction, acting as both a template for the interlocked architecture and as a catalyst to mediate covalent bond formation between the axle building blocks.⁴ There are several potentially attractive features of active-template assembly including: the inherent efficiency of having the macrocycle–metal complex perform multiple functions during the reaction; the lack of requirement for permanent recognition elements on each component of the interlocked product; in some cases only substoichiometric quantities of the active template may be required; and the coordination requirements during key stages of the catalytic cycle can provide useful insights into the mechanism of the metal-catalyzed reaction. The active-template strategy has been successfully applied to the Cu(I)-catalyzed Huisgen–Meldal–Fokin CuAAC

‘click’ reaction of azides with terminal alkynes,^{4a,d,i,j} the Pd(II)-catalyzed oxidative Heck reaction,^{4c} Pd(II)-catalyzed Michael additions,^{4g} Lewis-acid-promoted Diels–Alder reactions^{4k} and copper-catalyzed C–S bond formation.^{4b} As

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with classical 'passive' metal template routes to interlocked molecules, some of the most potentially useful⁵ active-template reactions have been based on Cu(I)^{4b,f,g,i} and Pd(II)^{4e}-catalyzed alkyne coupling reactions. However, all of the active template alkyne homocoupling reactions investigated thus far are accompanied by the formation of significant amounts of non-interlocked thread, arising from metal-catalyzed reaction of the building blocks that occurs *exo*- to the macrocyclic cavity. Clearly there is great scope for improved efficiency of this transformation through the investigation of related reactions with different coordination geometries, catalytic mechanisms, and activities.

Metal-Catalyzed Alkyne Homocouplings and Their Application in Rotaxane Synthesis. Since the first report of oxidative coupling of Cu(I)-acetylides in air by Glaser,^{6a} alkyne-alkyne couplings⁶ have become a standard construction tool in organic

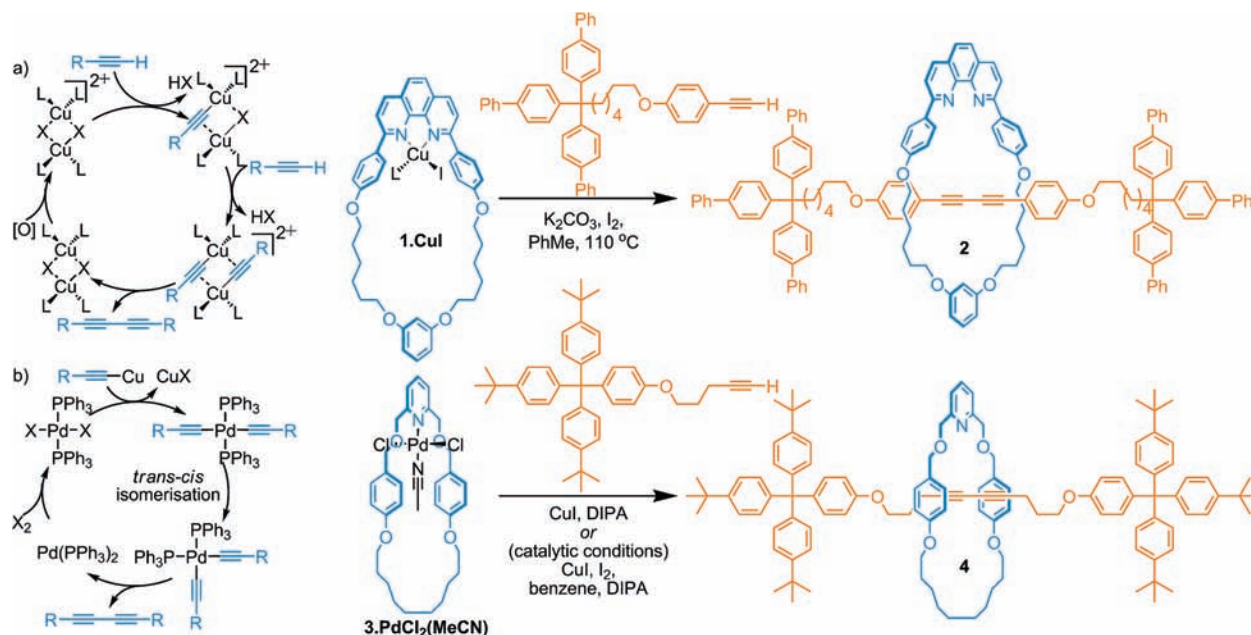
synthesis. Their use has intensified in recent years due to the interest in the electronic and optical properties of π -conjugated systems⁷ and, as a result, new variations and methodologies are constantly being developed^{6b-j} to overcome the synthetic challenges presented by increasingly complex systems. The generally accepted mechanism of the Glaser reaction is that proposed by Bohlmann and co-workers in 1964.⁸ The coordination of Cu(I) ions to the alkyne triple bond activates it to deprotonation which is followed by formation of a dinuclear Cu(II)-acetylide complex that collapses to give the oxidatively coupled product (Scheme 1a).

Widely used alternatives to Glaser-type alkyne homocouplings are palladium-catalyzed methods.⁹ Palladium-promoted terminal alkyne couplings were first observed as a side reaction during the coupling of terminal alkynes with aryl or vinyl halides.^{9a} The reaction was later optimized by Rossi and co-workers, using a mixture of CuI and [Pd(PPh₃)₄] as a catalyst for coupling aryl and alkyl alkynes.^{9b} Since then Pd-catalyzed alkyne couplings to give 1,4-disubstituted diynes have been widely used.^{9c-o} The generally accepted mechanism (Scheme 1b) involves transmetalation of a Cu(I)-acetylide (generated *in situ* from a Cu(I) source, a terminal acetylene and an amine base) to give a dialkynyl-Pd(II) intermediate. Subsequent reductive elimination gives the coupled product and a Pd(0) species, which is reoxidized by I₂.^{9c}

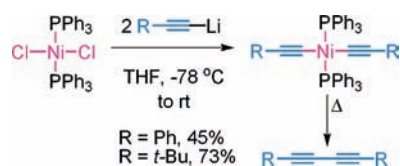
Compared to copper- and palladium-mediated synthesis of 1,4-diynes, however, there has been very little investigation¹⁰ of the potential of nickel to promote the homocoupling of terminal alkynes and no mechanistic studies on the reaction. In 1969 Rhee and co-workers observed the formation of a 1,4-diyne from the reaction of lithium phenyl acetylide with Ni(CO)₄ (Scheme 2).^{10a} Homocoupling of Li-acetylides in the presence of NiCl₂(PPh₃)₂ has been reported,^{10b,c} and the Ni(II)-promoted homocoupling of alkynes in supercritical water has also been described.^{10d}

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Scheme 1. Cu(I)- and Pd(II)-Catalyzed Alkyne Homocouplings and Their Application to Active-Template Rotaxane Synthesis^a

^a (a) Proposed mechanism of the Cu(I)-catalyzed Glaser coupling⁶ and its application to the active-template synthesis of [2]rotaxane 2.^{4b} (b) Proposed mechanism of Pd(II)-catalyzed oxidative homocoupling⁹ of terminal alkynes and its application to the active-template synthesis of [2]rotaxane 4.^{4c} DIPA = diisopropylamine. (a) X = Cl⁻, AcO⁻; (b) X = Cl or I.

Scheme 2. Ni(II)-Promoted Coupling of Alkynyl Lithium Derivatives^{10a}

We were intrigued as to whether the Ni(II) alkyne homocoupling reaction could be applied to active-template rotaxane synthesis. The use of octahedral metal ions in active-template reactions is unprecedented, but we thought that the changes in oxidation state and ligand geometry around the nickel ion, or ions, could assist the alkyne coupling to proceed through the macrocycle to form a rotaxane rather than *exo*- to the cavity to form the non-interlocked thread. This reasoning was based on the observation that when bipyridyl macrocycle 5 was employed in the Pd(II)-mediated active-template-alkyne homocoupling it was found to be significantly less efficient than its monodentate pyridyl analogue, 3, using stoichiometric quantities of the metal: only 10% of the corresponding rotaxane was obtained with 2.5 equiv of the stoppered alkyne.^{4e} This is probably due to the square-planar geometry of the Pd(II) center in a bidentate macrocycle not being conducive to threading during the transmetalation step. Indeed, in the solid-state structure¹¹ of complex 5·PdCl₂ both chloride ligands protrude from the same face of the macrocycle; thus, transmetalation with a Cu–acetylide might be expected to lead predominantly to the unthreaded complex.

Nickel is more geometrically flexible than palladium¹² (as well as being inexpensive, readily available as many different

salts, and easily removed from the products of a reaction¹³), and so we investigated the homocoupling of terminal alkynes mediated by macrocyclic bipyridine complex 5·NiCl₂. Although the acyclic bipyridine complex 6·NiCl₂ has a tetrahedral structure in the solid state,¹⁴ we were pleased to find that the X-ray structure of a bipyridyl macrocycle complex 5·NiCl₂, grown from a saturated acetonitrile solution, has the Ni(II) center in a pseudo-octahedral geometry, with the nickel(II) weakly coordinated to the benzylic ether oxygen atoms of the macrocycle (Figure 1). The Cl–Ni–Cl angle is 161°, with the chloride ligands pointing directly out of the plane of the bipyridyl unit on either side of the plane of the macrocycle. Thus, unlike the analogous palladium complex 5·PdCl₂,¹¹ 5·NiCl₂ seems ideally suited to an active metal template reaction in which the chloride ligands are replaced by metalated acetylenes prior to reductive elimination to form a substituted 1,4-diyne product. This is provided, of course, that the ligand-bound Ni(II) salt actually catalyzes the alkyne–alkyne coupling reaction.

Ni(II)-Mediated Alkyne Homocouplings and Active-Template Rotaxane Formation. To test the efficacy of ligand-bound NiCl₂ for a Ni(II)-promoted terminal alkyne coupling reaction, acyclic bipyridyl compound 6 and macrocycle 5 were employed as ligands using Li-phenylacetylide (formed *in situ* from phenylacetylene and *n*-BuLi) as the substrate (Scheme 3). The NiCl₂ complexes were prepared *in situ* by stirring equimolar quantities of ligand and NiCl₂·DME (dimethoxyethane) in tetrahydrofuran (THF) at 80 °C.¹⁵ The reaction was unsuccessful in the presence of 6·NiCl₂ and only 5% coupling of Li-phenylacetylide was observed in the presence of 5·NiCl₂ (Scheme 3). By contrast the control reaction, in which NiCl₂·DME was used without an added ligand, resulted in complete conversion to the homocoupled product (Scheme 3). We reasoned that the use of

(11) For the X-ray crystal structure of 5·PdCl₂(MeCN) see the Supporting Information of ref 4e.

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(15) Reactions were carried out in crimp-sealed vials, allowing THF to be used as a solvent above its boiling point at atmospheric pressure.

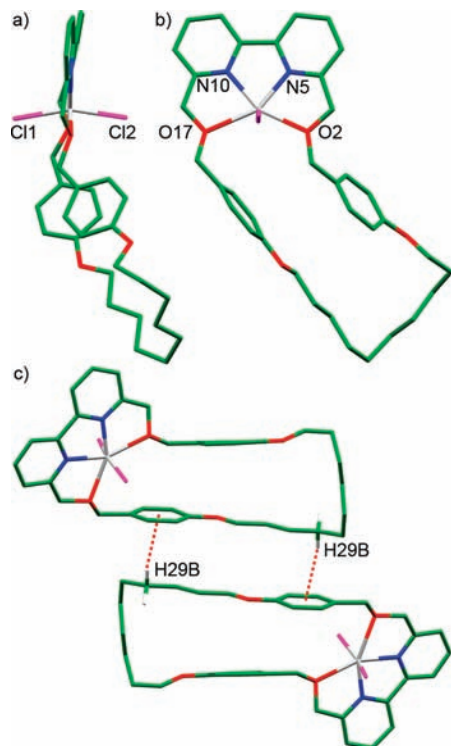
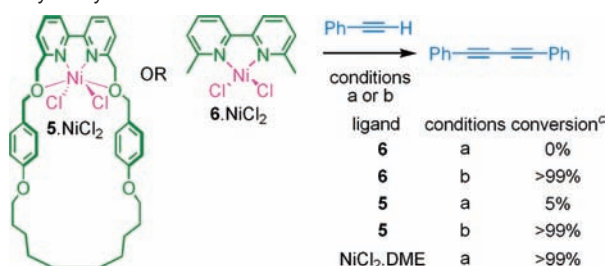


Figure 1. X-ray crystal structure of $5 \cdot \text{NiCl}_2$, from a single crystal obtained by slow cooling of a saturated acetonitrile solution: (a) viewed side-on; (b) viewed along the Cl–Ni–Cl axis; (c) viewed to show C–H– π interactions present in the extended crystal lattice. Carbon atoms are shown in green, selected hydrogen atoms in white, nitrogen atoms in blue, oxygen atoms in red, chlorine atoms in pink, and nickel in gray. Selected bond lengths [Å] and angles [deg]: N10–Ni 2.01, N5–Ni 2.02, O17–Ni 2.25, O2–Ni 2.41, Cl1–Ni 2.32, Cl2–Ni 2.33, H29B– π (centroid) 2.73, C29– π (centroid) 3.59, N5–Ni–N1079.8, O2–Ni–O17131.7, Cl1–Ni–Cl2161.4, C29–H29B– π (centroid) 146.6.

Scheme 3. Ligand-Complexed-Ni(II)-Catalyzed Dimerization of Phenylacetylene^{a,b,c}

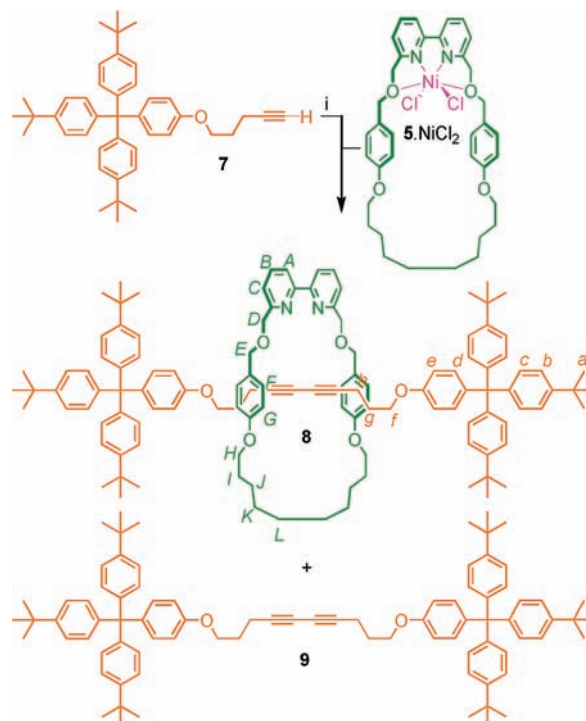


^a Reagents and conditions: (a) (i) Phenylacetylene (0.05 mmol), *n*-BuLi (0.05 mmol), THF, $-78^\circ\text{C} \rightarrow 0^\circ\text{C}$, (ii) $5 \cdot \text{NiCl}_2$ or $6 \cdot \text{NiCl}_2$ (0.025 mmol, in THF), $-78^\circ\text{C} \rightarrow \text{RT}$; (b) (i) phenylacetylene (0.05 mmol), *n*-BuLi (0.05 mmol), THF, $-78^\circ\text{C} \rightarrow 0^\circ\text{C}$, (ii) CuI (0.05 mmol), 0°C , (iii) $5 \cdot \text{NiCl}_2$ or $6 \cdot \text{NiCl}_2$ (0.025 mmol, in THF), $-78^\circ\text{C} \rightarrow \text{RT}$. ^b $5 \cdot \text{NiCl}_2$ and $6 \cdot \text{NiCl}_2$ were prepared *in situ* from equimolar quantities of the appropriate ligand and $\text{NiCl}_2 \cdot \text{DME}$ in THF at 80°C . ^c The conversion of phenylacetylene to the coupled product was determined from ^1H NMR of the reaction mixture

a softer nucleophile might be required to form the necessary Ni(II)–diacetylide, and we were pleased to find that transmetalation of the Li–acetylide to the Cu–acetylide using CuI prior to addition of $5 \cdot \text{NiCl}_2$ or $6 \cdot \text{NiCl}_2$ did indeed result in smooth and quantitative homocoupling of the substrate.

By using a terminal alkyne bearing a stoppering group larger than the cavity of the macrocycle, the reaction was successfully extended to the active-template synthesis of a [2]rotaxane (Scheme 4). Treatment of a solution of alkyne **7** with an

Scheme 4. Active-Template Synthesis of a [2]Rotaxane by Ni(II)–Cu(I)alkyne Homocoupling^a



^a Reagents and conditions: (i) *n*-BuLi, CuI, THF, $-78^\circ\text{C} \rightarrow 80^\circ\text{C}$. Experimental procedure is provided in the Supporting Information.

equimolar quantity of *n*-BuLi to give the corresponding Li–acetylide, followed by addition of CuI, generated the copper acetylide.¹⁶ Addition of a solution of $5 \cdot \text{NiCl}_2$ resulted in formation of the [2]rotaxane **8** in 10–48% yield, along with 5–30% of the noninterlocked thread **9** (Scheme 4). Unfortunately, however, under these conditions the reaction proved capricious, and in order to improve both the rotaxane yield and the reliability of the reaction some optimization of the experimental protocol was required.

The irreproducibility of the reaction turned out, somewhat surprisingly, to be related to the order of addition of the reagents. When copper iodide was added last, rather than prior to $5 \cdot \text{NiCl}_2$, the reaction became consistently high yielding. This seemed strange as the intended role of the Cu(I) was simply to aid chloride–acetylide exchange at the Ni(II) center of $5 \cdot \text{NiCl}_2$. Nevertheless the following procedure was adopted: Alkyne **7** (2.0 equiv) was treated with *n*-BuLi (2.0 equiv) at -78°C , followed by stirring at 0°C for 30 min, to allow formation of the Li–acetylide. This solution was cooled to -78°C , and a solution of $5 \cdot \text{NiCl}_2$ added. After warming to room temperature, CuI (2.0 equiv) was added (accompanied by a change of color in the reaction mixture from pale yellow to deep orange), and the reaction mixture was subsequently heated at 80°C for 48 h. This procedure gave [2]rotaxane **8** reproducibly in 67% yield (Table 1, entry 1). Varying the amount of CuI present showed that less than a stoichiometric quantity (with respect to **7**) proved detrimental to the yield (Table 1, entries 2–4). Comparison of the total conversion of acetylene **7** to products (both rotaxane

(16) A yellow paste was observed as Cu(I)–acetylides are generally complex extended multi-atom aggregates, at least in the solid state and in the absence of good nitrogen ligands. See: Mykhalichko, B. M., Temkin, O. N., Mys'kiv, M. G. *Russ. Chem. Rev.* **2000**, *69*, 957–984.

Table 1. The Effect of the Amount of CuI on the Conversion of Alkyne **7** to Rotaxane **8** and Non-interlocked Thread **9**

entry	equiv of 7	equiv of 5·NiCl ₂	equiv of CuI	yield of rotaxane 8 ^d (%)	total conversion of 7 to (8 + 9) ^e (%)
1 ^a	2.0	1.0	2.0	67 ^b	99 ^b (32% of 9 ^b)
2 ^a	2.0	1.0	1.5	63 ^c	>99 ^c
3 ^a	2.0	1.0	1.0	32 ^c	52 ^c
4 ^a	2.0	1.0	0.5	23 ^c	27 ^c

^a Reaction carried out at 16.7 mM concentration with respect to 5·NiCl₂; experimental procedures provided in the Supporting Information. ^b Isolated yield. ^c Determined by ¹H NMR analysis of the reaction mixture. ^d Relative to macrocycle **5**. ^e Relative to alkyne **7**.

Table 2. Experiments to Determine the Conversion of Alkyne **7** to Rotaxane **8** and Non-interlocked Thread **9** under a Range of Conditions

entry	equiv of 7	equiv of <i>n</i> -BuLi	equiv of 5	equiv of NiCl ₂ ·DME	equiv of CuI	conversion to rotaxane 8 ^d (%)	total conversion of 7 to (8 + 9) ^e (%)
1 ^a	2.0	2.0	1.0	1.0	2.0	67 ^{b,h}	99 ^{b,h} (32% of 9 ^b)
2 ^a	2.0	2.0	1.0	—	2.0	13 ^{c,h}	45 ^{c,h}
3 ^f	2.0	2.0	1.0	1.0	—	5 ^{c,h}	5 ^{c,h}
4 ^{a,f}	2.0	—	1.0	1.0	2.0	0 ^{c,h}	0 ^{c,h}
5 ^{a,f}	4.0	2.0	1.0	2.0	2.0	95 ^{b,g}	66 ^c

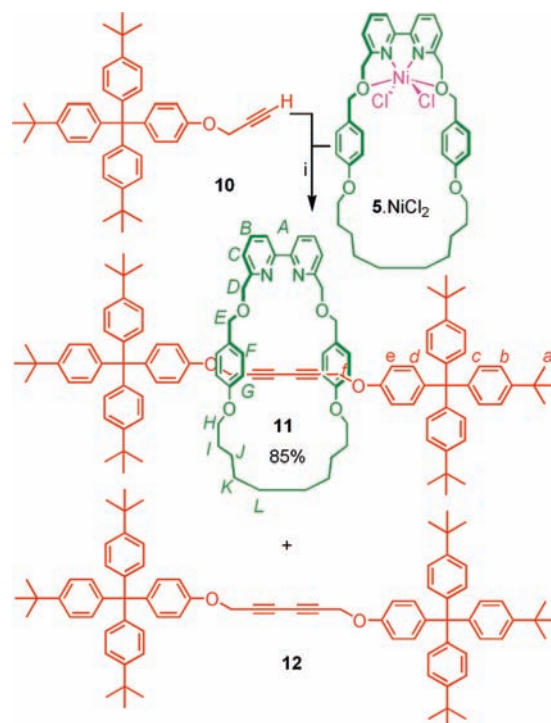
^a Reaction carried out at 16.7 mM concentration with respect to **5**; experimental procedures are provided in the Supporting Information. ^b Isolated yield. ^c Determined by ¹H NMR analysis of the reaction mixture. ^d Relative to macrocycle **5**. ^e Relative to alkyne **7**. ^f Where macrocycle **5** and NiCl₂·DME are both present, these were added as a solution of the complex 5·NiCl₂. ^g After 86 h at 80 °C. ^h After 48 h at 80 °C.

8 and noninterlocked thread **9**) shows that the reaction is selective for the rotaxane over the thread, but is slower (lower yielding after 48 h) when less CuI is used (Table 1).

A further series of experiments was carried out to probe the necessity of each reagent in the reaction (Table 2). The intrinsic importance of both metals to the active-template reaction is illustrated by the poor yield of rotaxane when either nickel or copper is omitted (Table 2, entries 2 and 3). Comparison of the rate of reaction under the optimized conditions with that of a solely Cu-catalyzed coupling shows that the reaction is greatly assisted by the presence of the nickel. After 48 h at 80 °C the bimetallic system has reached its maximum conversion to products (Table 2, entry 1) while the corresponding reaction in the absence of Ni(II) has only formed 13% (based on **5**) of rotaxane **8** and 45% (based on **7**) noninterlocked thread **9** (Table 2, entry 2), showing that the Cu-mediated reaction is both much slower and exhibits low selectivity for formation of interlocked over noninterlocked product. The presence of Ni(II) is essential for rotaxane formation in an appreciable yield in the same time frame. A 2-fold increase in the amount of alkyne used results in a near quantitative yield of [2]rotaxane **8** (Table 2, entry 5). No coupling was observed in the absence of *n*-BuLi (Table 2, entry 4).¹⁷

In order to extend the substrate scope of the reaction we applied it to propargylic ether **10** and were delighted to obtain [2]rotaxane **11** (which could not be prepared by Pd(II) active-template homocoupling because of competitive Pd-mediated cleavage of the propargylic ether) in 85% yield (Scheme 5).

¹H NMR Characterization of [2]Rotaxanes. Characteristic upfield shifting of H_D and H_E of [2]rotaxanes **8** and **11** in the ¹H NMR spectrum relative to those of the free macrocycle meant that the progress of reactions could readily be followed by ¹H

Scheme 5. Active-Template Synthesis of a [2]Rotaxane by Ni(II)–Cu(I)alkyne Homocoupling of Propargylic Ether **10**^a

^a (i) 5·NiCl₂ (1 equiv), **10** (4.0 equiv), *n*-BuLi (2 equiv), CuI (2 equiv), THF, −70 °C → 80 °C. Experimental procedure is provided in the Supporting Information

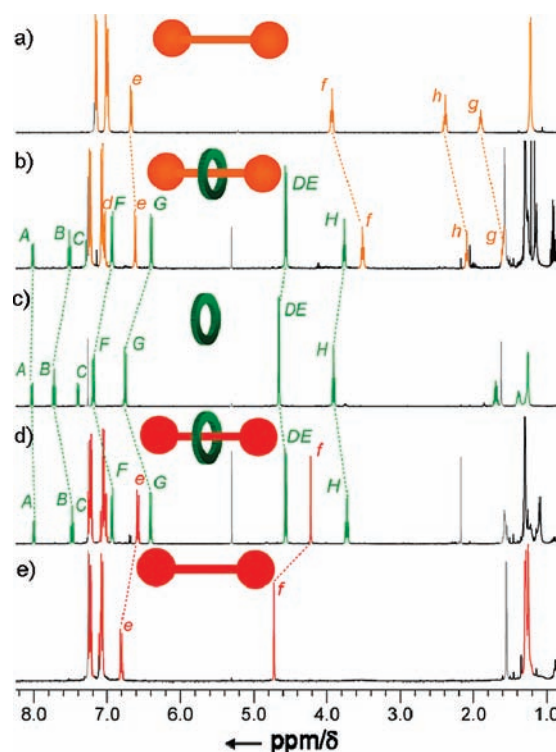
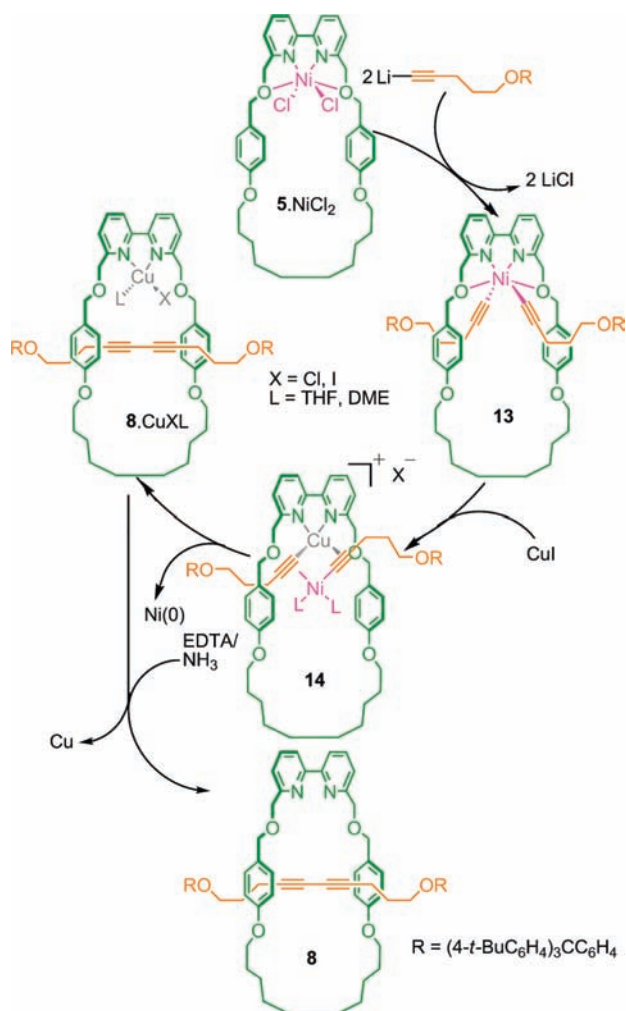


Figure 2. Partial ¹H NMR spectra (400 MHz, CDCl₃, 300 K) of (a) thread **9**, (b) [2]rotaxane **8**, (c) macrocycle **5**, (d) [2]rotaxane **11**, (e) thread **12**. The assignments correspond to the lettering shown in Schemes 4 and 5.

NMR spectroscopy (Figure 2). Characteristic upfield shifting of the aromatic protons of the macrocycle (H_B, H_C, H_F, and H_G) and the protons in the axle (H_{e–h} for rotaxane **8** and H_{e–f}

(17) Yin, W.; He, C.; Chen, M.; Zhang, H.; Lei, A. *Org. Lett.* **2009**, *11*, 709–712.

Scheme 6. Proposed Mechanism for the Ni(II)/Cu(I)-Mediated Assembly of [2]Rotaxane



for rotaxane **11**) is a result of face-on alignment of the component π -systems and confirms the interlocked nature of both rotaxanes **8** and **11** (Figure 2).

Mechanism of the Nickel–Copper-Mediated Active-Template-Alkyne Homocoupling Reaction. Very recently, oxidative alkyne hetero- and homocouplings mediated by CuI and NiCl₂·6H₂O, O₂, and a bidentate nitrogen ligand, tetramethylenediamine (TMEDA), were reported by Lei et al.¹⁷ However, unlike the heterocoupling mechanism proposed by Lei and co-workers—in which transmetalation of the acetylide from Cu to Ni is proposed—our findings suggest a different role for the copper in the active-template reaction. The alkyne homocoupling mechanism appears to be that of a bimetallic system, where the Cu(I) displaces the Ni(II) from the macrocyclic cavity to form a bimetallic five-component intermediate, **14**, from which nickel can be reductively eliminated (Scheme 6).

Such a mechanism explains the increased reliability of the reaction when the copper source was added last, allowing the Ni(II)–diacetylide complex **13** to form first. In our early experiments with phenylacetylene (Scheme 3) no conversion to the homocoupled product was observed in the absence of Cu(I). Using the mechanism proposed in Scheme 6, this can be explained by the failure of nickel to eliminate from the intermediate Ni–diacetylide. This ‘switching off’ of the reaction by a bipyridyl ligand is not unreasonable, given that phosphine-ligated Ni(II)–diacetylide

species are isolable and stable in air and above room temperature.^{10c,18} Nitrogen-containing ligands are harder donors than their phosphine counterparts, which could explain the extra stability of the complex and subsequent degradation back to the starting alkyne upon removal of the metal on aqueous work up. A change of color from pale yellow (presumed complex **13**) to deep orange upon addition of CuI is an indication of the formation of intermediate **14** in which Cu(I), not Ni(II), is directly coordinated to the macrocycle. Heating an equimolar solution of macrocycle **5** and CuI also gives a deep orange solution in THF, whereas **5**·NiCl₂ gives a pink solution in the same solvent. No reaction occurs in the absence of *n*-BuLi (Table 2, entry 4). It is known that Cu–acetylides can form in the absence of strong base, as a π -bonding interaction between the Cu(I) and the acetylene activates the triple bond, decreasing the p*K*_a of the acetylenic proton sufficiently to allow deprotonation. Therefore, if formation of a Cu–acetylide was the first step of the reaction, we would expect some degree of rotaxane formation in the absence of a strong base. This is not what was observed.

Conclusions

The nickel–copper-mediated reaction reported here is the highest-yielding active-template-alkyne homocoupling reaction developed to date and the first to utilize a metal in an octahedral coordination geometry. The mixed-metal catalyst system was discovered somewhat by accident when Cu(I) was added to the Ni(II)-catalyzed reaction in an attempt to facilitate chloride–acetylide ligand exchange. However, varying the reaction protocol established that the role of Cu(I) is quite different from the one originally envisaged. The effectiveness of having both nickel and copper present in the reaction can be rationalized by the nature of a proposed π -activated, σ -bonded, bimetallic intermediate **14**, in which the substitution of Ni(II) for one Cu(I) ion in the classic bimetallic Glaser reaction mechanism (Scheme 1a) appears to aid reductive elimination of the acetylide ligands. The system may prove useful for the development of general mixed-metal protocols for catalytic alkyne coupling reactions as well as being a highly effective route to rotaxanes with bis-acetylene threads, which are potentially useful for materials applications (insulated molecular wires^{2b}) and in molecular machines (molecular shuttles with rigid, nonfolding, axles¹⁹). The development of other active-template reactions for improved rotaxane synthesis—and insights that the requirements for active-template synthesis can reveal about reaction mechanism^{4d}—are currently being pursued by our group.

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Supporting Information Available: Experimental procedures and the supplementary crystallographic data in CIF format. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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