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Synthesis of Readily Cleavable Immobilized 1,10-Phenanthroline Resins

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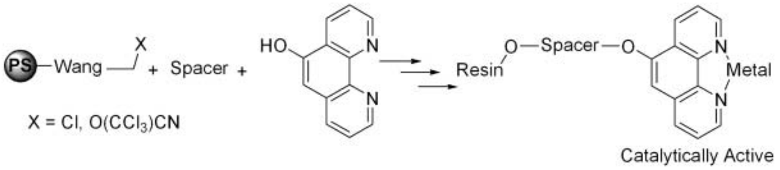
ABSTRACT



1,10-Phenanthroline is derivatized and ultimately immobilized on two different polystyrene/divinylbenzene solid supports using convenient methodology. All syntheses are amenable to semiautomatic processing and are scalable for high-throughput screening. A domino copper-catalyzed coupling–cyclization reaction is used to illustrate applicability in catalytic studies.

The development of high-throughput screening technology for metal catalyst development continues to be a very active area of research. Methods as diverse as solid-phase catalyst immobilization,[1] mass spectral analysis of reactive catalyst intermediates,[2] and focused libraries of catalyst mixtures[3] have all been utilized in this regard. Although 1,10-phenanthroline is a venerable ligand in coordination chemistry, its use in catalytic reactions has only recently attracted significant attention.[4] The disposition of the nitrogen atoms within the fused aromatic system makes phenanthroline a nearly universal ligand for d- and f-block metals.[5] With these considerations in mind, it would be a significant achievement to find fast, flexible, and convenient methods to screen the catalytic properties of 1,10-phenanthroline complexes. We therefore chose to pursue the solid-phase immobilization strategy. This report summarizes our work leading toward a semiautomatic method for the preparation of custom phenanthroline resins on polystyrene-divinylbenzene beads.

Resins with immobilized 1,10-phenanthroline or 2,2′-bipyridyl ligands have been prepared previously. For instance, Neckers[6] immobilized 2,2′-bipyridyl on polystyrene through a carbanion coupling procedure. This resin, presumably substituted at the 2-position, was inert to cleavage agents, and analysis could only be done indirectly with metal complexation and subsequent metal analysis. Other examples

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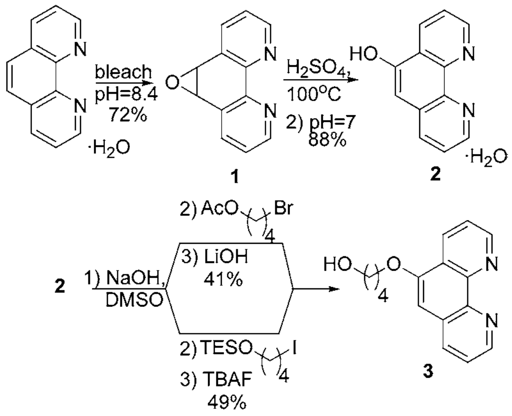
10.1021/ol049101i CCC: $27.50

Scheme 1

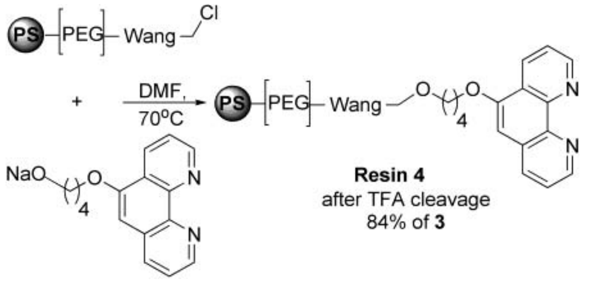


of immobilized 1,10-phenanthrolines on polymers[7] and silica gel[8] have also been reported and studied in metal-catalyzed reactions. These examples, however, point out issues that we wished to address in the context of modern combinatorial constructs. First, we desired an immobilization regime that avoided the 2- and 9-positions on the phenanthroline system in order to avoid interferences with metal coordination. Second, we desired a specific cleavage site that used either a Wang or SASRin linker so that trifluoroacetic acid (or DDQ) cleavage would assay constituents on the resin. Finally, we anticipated a semiautomatic procedure by which systematic syntheses of the spacer group on the resin[9] and phenanthroline itself can be achieved.

Our immobilization method uses 5-hydroxy-1,10-phenanthroline, **2**, as the fundamental building block. The literature procedure for **2** is difficult to replicate,[10] and therefore, we developed a reliable H_2SO_4-catalyzed rearrangement of 5,6-dihydo-5,6-epoxy-phenanthroline, **1**.[10a] Low solubility and the acid−base characteristics of **2** made it a difficult material to manage in solid-phase preparations; therefore, the phenanthrolate ion was generated with NaOH and alkylated with either 4-bromobutyl acetate or triethyl(4-iodobutoxy)silane[11] (Scheme 1). Cleavage of either the acetate or silyl ether gave **3** as a stable white solid which smoothly coupled with commercial resins.

The basic nature of phenanthroline required all solid-phase reactions to be conducted under basic conditions. Treatment of **3** with NaH in DMF yielded the sodium alkoxide which alkylated ArgoGel-Wang-Cl (0.35 mmol/g, declared substitution). This gave a pale yellow resin that incorporated the phenanthroline ligand (Scheme 2).[12] Treatment of resin **4** with neat TFA cleaved the resin and released **3** in 84% yield.

Scheme 2



Subsequently, a second resin was prepared using a more highly substituted Wang resin (1.75 mmol/g). The Lewis base character of **3** proved incompatible with the BF_3·etherate-catalyzed trichloroimidate substitution reaction.[13] To circumvent this problem, we used the TBS protected 2-(4-hydroxyphenyl)ethanol,[14] **6**, to replace the trichloroimidate group and yet provide an appropriate site for a Mitsunobu coupling with **3** (Scheme 3). Ether formation between ArgoPore-Wang **5** and alcohol **6** resulted in resin **7**. This reaction showed complete replacement of the imidate group as evidenced by the absence of an IR band at 1664 cm^{-1}. After removal of the TBS group, Mitsunobu coupling of resin **7** with **3** proceeded smoothly in 90% yield. Cleavage of resin

Scheme 3

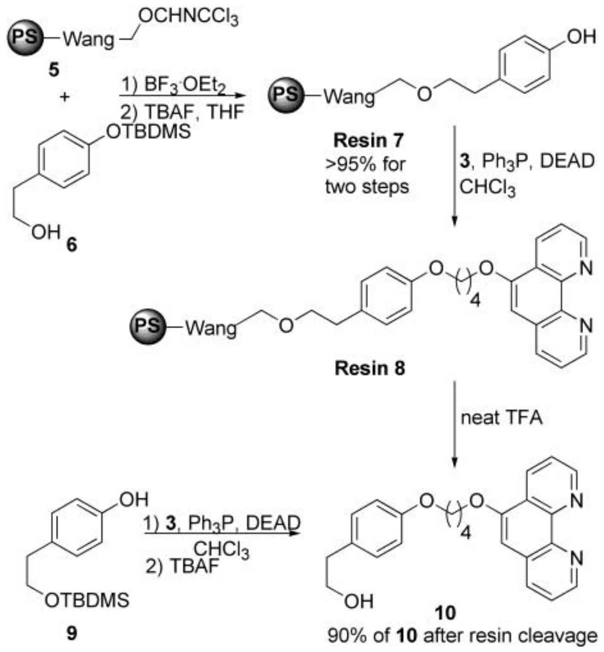


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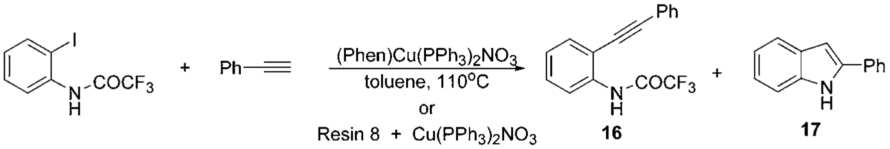
Table 1. Comparative Catalytic Properties of Homogeneous Copper Catalyst and Copper Activated Resin **8**



domino copper-catalyzed coupling−cyclization					yield **16**/ **17**[b] (%)		
entry	catalyst[a]	solvent	time (h)	T (°C)	cycle 1	cycle 2	cycle 3
1	[Phen]Cu$(PPh_3)_2NO_3$	toluene	12.0	110	16:73		
2	resin **8** + Cu$(PPh_3)NO_3$	toluene	12.0	110	29:56	24:60	21:70

[a] All catalyses used 0.027 mmol of active catalyst in reactions that were 10 mol % mixtures. [b] Gas chromatographic yields by standard curve method.

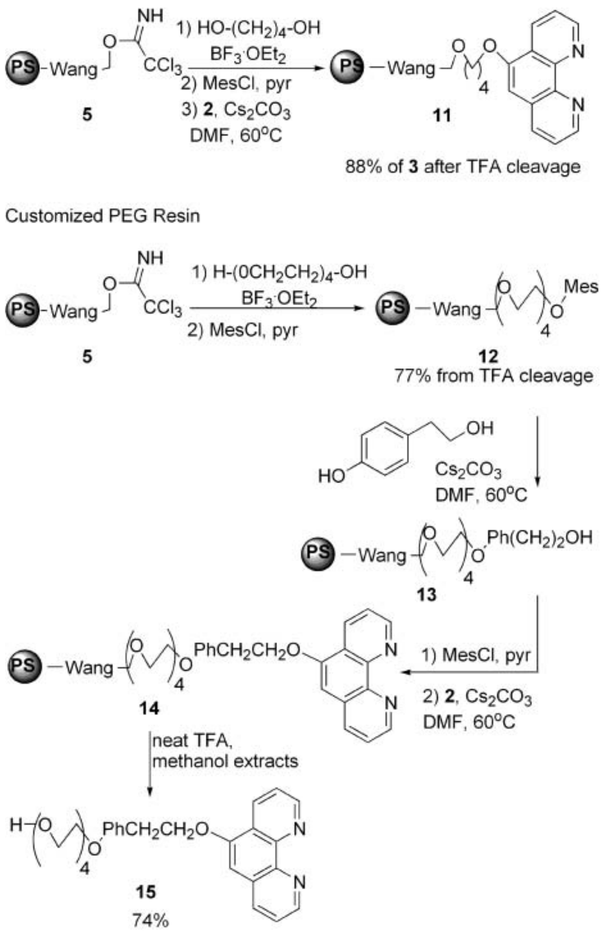
8 with TFA gave phenanthroline derivative **10**, which was verified by independent synthesis from phenol **9**.[15]

With our experience with resins **4** and **8**, we next developed a protocol capable of automated synthesis. We envisioned that 5-hydroxy-1,10-phenanthroline, **2**, could cap a customized spacer group prepared by a linear synthesis. An elementary and a customized PEG resin synthesis are illustrated in Scheme 4. Trichloroimidate replacement by a symmetric diol, in the illustrative case 1,4-butanediol, yielded a 1° alcohol that smoothly reacted with methanesulfonyl chloride in pyridine.[16] The resulting mesylate reacted with **2** in the presence of Cs_2CO_3 yielding a stable resin in high yield. Cleavage of the 1,4-butanediol resin with neat TFA gave **3** in 88% yield. A further simplification of this synthesis using a Mitsunobu reaction gave unsatisfactory results. Approximately 40% of the butyl residues alkylated properly during the Mitsunobu reaction while a majority of the product showed the addition of both the diazo dicarboxylate reagent and 1,10-phenanthroline to the resin.

The customized PEG resin, shown in Scheme 4, illustrates the flexibility of our semiautomated synthesis. The ability to customize the spacer allows one to tailor specific swelling and hydrophilic properties of the phenanthroline resin.[17] Difficulties with the Mitsunobu reaction continued throughout this scheme, and therefore we used simple mesylation and alkylation technology to prepare the PEG resin. Imidate replacement and mesylation provided a reliable scaffold for all further transformations. Infrared analysis of resin **12** showed no band at 1660 cm^{-1} and only a weak OH stretch at 3448 cm^{-1}. Alkylation of resin **12** with 4-hydroxy-β-phenethyl alcohol in the presence of Cs_2CO_3 gave a new resin which blends hydrophilic and hydrophobic properties. Repetition of the mesylation and alkylation cycle with 5-hydroxy-1,10-phenanthroline gave a maroon colored resin in 74% yield (TFA cleavage gave **15**, 493, M$^+$+1). Unreacted tetraethylene glycol was the only other material observed by LCMS.

With immobilized 1,10-phenanthroline resins in hand it is incumbent to demonstrate that these materials have potential for use in catalytic reactions. As a brief test case, we provide data for catalysis based on Cacchi's domino copper-catalyzed coupling-cyclization reaction.[18] Cacchi noted a distinct solvent effect in this indole synthesis, and therefore we report the results from use of the nonpolar, hydrophobic resin **8**. Parallel reactions of homogeneous catalyst (Phen)Cu$(PPh_3)_2NO_3$ (0.027 mmol, 10 mol %) and resin **8** (same catalyst loading) gave the results summarized

Scheme 4



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in Table 1. The homogeneous catalyst gave results comparable to those of Cacchi. The catalytic species generated with resin **8** produced **16** and **17** very efficiently, but the ratio of these compounds was partially skewed toward **16**. This same catalytic species exhibited persistent catalytic effect through three batches of substrate.

The simplicity and speed of our resin preparations and our initial catalytic study with immobilized 1,10-phenanthroline all augur well for a high-throughput screening regime. Our ability to customize properties associated with a polystyrene-based solid support and our ability to add chiral diversity on the phenanthroline subunit[19] indicate that we may be able to develop an efficient screening system for asymmetric catalysis.[20] Results from this strategy will be reported in due course.

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Supporting Information Available: Details for the preparation and spectral characterization of compounds **2**−**4**, **8**, **11**, and **14** and details pertaining to immobilized catalyst preparation and catalyst recycling. This material is available free of charge via the Internet at http://pubs.acs.org.

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