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Solid-Supported Copper Catalysts for Atom-Transfer Radical Cyclizations: Assessment of Support Type and Ligand Structure on Catalyst Performance in the Synthesis of Nitrogen Heterocycles

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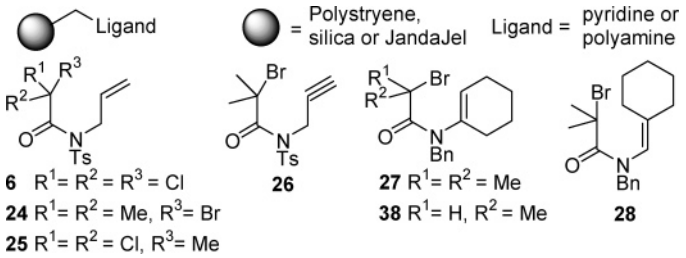

A range of solid supported pyridinemethanimine **9**−**11** and polyamine **12**−**15** ligands have been prepared on silica, polystyrene, and JandaJel supports. The CuCl and CuBr complexes of these supported ligands have been used to assess both the effect of the ligand type and the nature of the support upon a representative range of copper-mediated atom transfer 5-*exo*-*trig* **6**, **24**−**25**, 5-*exo*-*dig* **26**, 4-*exo*-*trig* **28**, and 5-*endo*-*trig* **27**, **38** radical cyclizations to give nitrogen heterocycles. In addition, the effect of the nature of the support on the stereochemical outcome of the 5-*exo* cyclization of **25** has been probed. Generally, it was found that the type of support (e.g., polystyrene, silica, or JandaJel) had very little effect upon the efficiency and selectivity of the processes but that the nature of the ligand type immobilized was the important factor. Thus, the 5-*exo* cyclization of **6** and **24**−**26** proceeded more rapidly with the PMI ligands **9**−**11**, whereas 4-*exo* cyclizations **28** and 5-*endo* radical polar crossover reactions **27** and **38** proceeded more efficiently with the JJ-TEDETA ligand **15**. The efficiency of the supported ligands was also compared to their solution counterparts **4** and **5**. The reusability of P-PMDETA ligand system **13** was assessed in the cyclization of **6**.

Introduction

Transition-metal-catalyzed atom transfer radical *cyclization* (ATRC)[1] and *polymerization* (ATRP)[2] reactions have been extensively studied over the past few years. The driving force for this research has been the desire to find nonreductive catalytic alternatives to organotin hydrides in mediating radical cyclization reactions in organic synthesis, and the need to prepare living polymers with a high degree of control for novel materials applications. Active catalysts for both cyclization and polymerization processes are derived mainly from ruthenium,[3] iron,[4] or copper[1a] complexes with those based upon the coordination chemistry of copper being the most popular. A whole range of copper catalysts based upon the coordination

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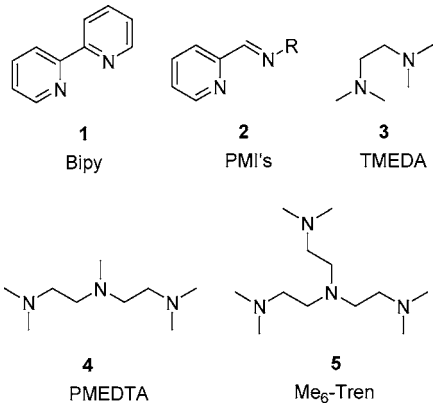
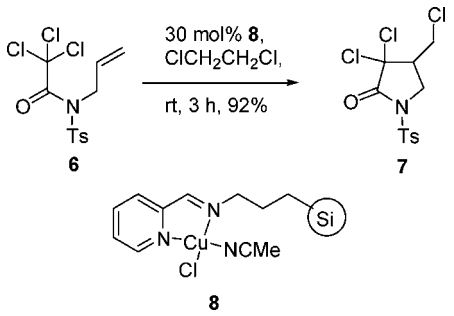


FIGURE 1. Ligands for atom-transfer radical cyclization.

of the ligands bipyridine[5] (Bipy) **1**, pyridylmethanimines[6] (PMIs) **2**, tetramethylethylenediamine[7] (TMEDA) **3**, *N*,*N*,*N*′,N′,N″-pentamethyldiethylenetriamine[8] (PMDETA) **4**, and tris(*N*,*N*-2-dimethylamino)ethylamine[8b,9] **5** (Me_6-Tren) have been explored for ATRC applications, Figure 1. Different ligands often show different reactivities and selectivities.

In ATRP, the removal of the copper catalysts from the synthesized polymer can be problematic. For industrial polymer applications, where the removal of copper residues is necessary, perfluorous catalysts[10] and solid-supported reagents[11] have been explored to overcome this. However, the use of a perfluorous reagent can be costly, and solid-supported reagents tend not to be as selective or as efficient in living polymerizations compared to their solution counterparts.[12] The reason for this is the requirement for both the large living polymer to interact with the active catalyst which is itself attached to a macromolecular assembly. On the other hand, in organic synthetic applications, ATRC reactions often involve relatively small molecular weight substrates, and consequently mass transport, selectivity, and efficiency should be less compromised. One of the drivers for the development of copper-mediated ATRC catalysts was their potential replacement of tin hydrides in industrial radical applications. In light of the proven ability of ATRC reactions to generate a range of medicinally active heterocyclic scaffolds,[1] it is surprising that only one type of solid-supported reagent (e.g., **8**) has been evaluated in ATRC reactions (Scheme 1).[13] In this paper, we wish to report our studies into the effect of the nature of the support (cross-linked polystyrene (P), silica (Si), or JandaJel (JJ)), along with the type of ligand conjugated to the support (PMI **2**, PMEDTA **4**, or Me_6-Tren **5** analogues) on the radical cyclization of a range of substrates to furnish nitrogen heterocycles.

SCHEME 1. ATRC Using Silica-Supported PMI Ligand



Results and Discussion

We decided to investigate how the nature of the polymeric support and the type of ligand effected the rate and selectivity of a range of simple cyclization reactions. We chose to prepare solid-supported ligands that could be synthesized in only a few steps from commercial sources. By far the most studied solid-supported ligands in ATRP reactions are those derived from

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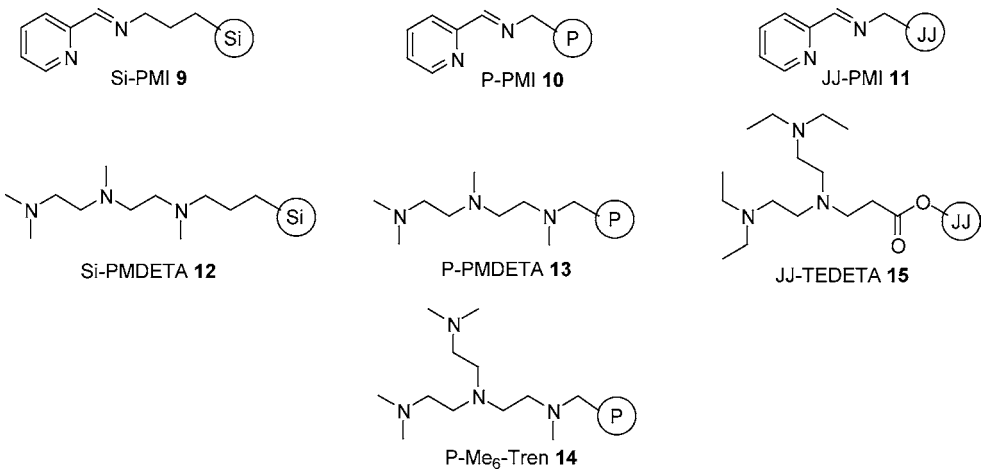
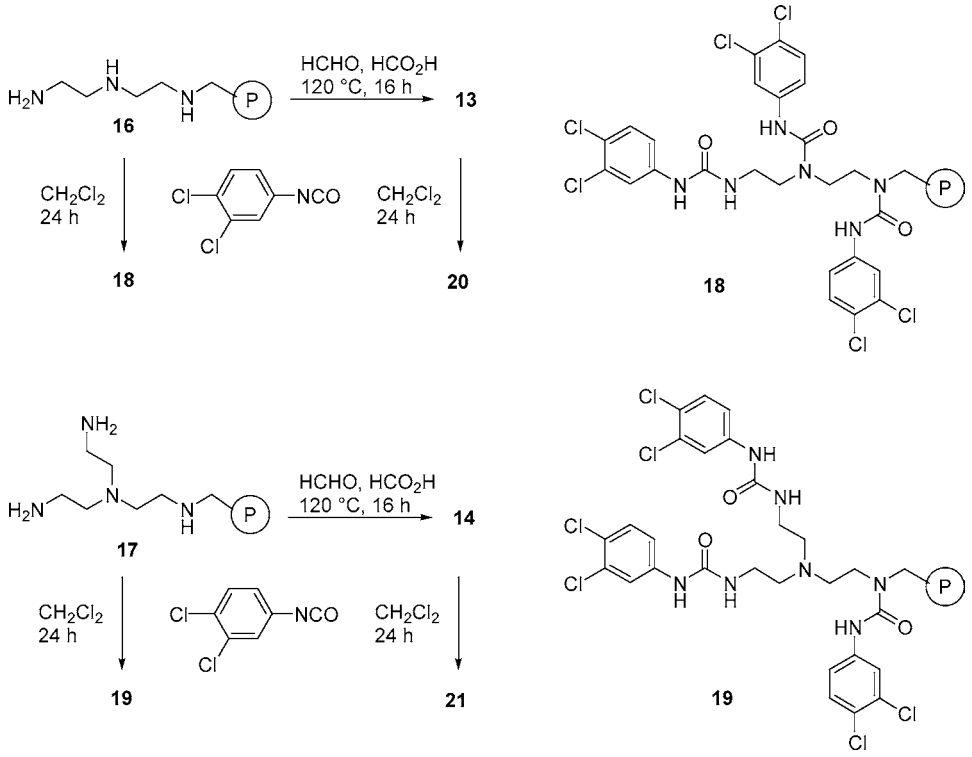


FIGURE 2. Solid-supported ligands **9**−**15**.

SCHEME 2. Preparation and Functionalization of Resins 13 and 14



PMI ligands **2**.[11g−i,12a,b] Thus, we chose to investigate the effect of three different supports (**9**−**11**) on the ATRC reactions of this ligand. The incorporation of **9** into the study would allow us to compare our results with those previously published. As conventional solution cyclization reactions can be influenced by the nature of the ligand (with rate enhancements generally following the order Me_6-Tren **5** > PMEDTA **4** > PMI **2**), we chose to prepare a range of supported analogues of these ligands, namely **12**−**15**, Figure 2.[8b]

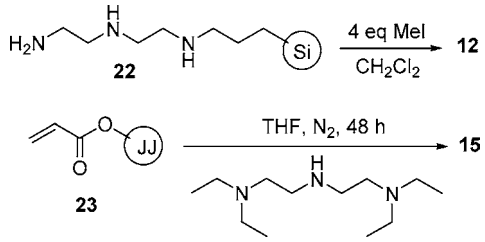
Preparation of Solid-Supported Ligands 9−**15**. We prepared the silica-PMI **9**, the 1% divinylbenzene cross-linked polystyrene-PMI **10**, and the JandaJel-PMI **11** using previously published procedures from aminopropylated silica gel (1.26 mmol of $-NH_2$/g),[13] aminopolystyrene (70−90 mesh, 1.66 mmol of $-NH_2$/g),[12b] and JandaJel-NH_2 (0.635 mmol of $-NH_2$/g),[11i] respectively. The latter has been reported to have increased solvent compatibility and site accessibility compared to divinylbenzene cross-linked polystyrene resins in ATRP.[11i] Ligand loadings were calculated for each resin using elemental analysis,[14] and all three polymers exhibited infrared spectra similar to those already reported.

Polystyrene PMDETA **13** and Me_6-tren **14** analogues were prepared by Eschweiler−Clarke[15] permethylation of commercially available **16** (2.72 mmol of ligand/g) or **17** (1.18 mmol of ligand/g) respectively, Scheme 2. Heating **16** or **17** with a 10-fold excess of formic acid and formaldehyde at 120 °C furnished the desired permethylated supported ligands **13** or **14**, respectively. The novel supports were washed with Et_3N, DCM, and MeOH and dried to constant weight.

(14) All numerical values obtained were the average of duplicate microanalysis results.

(15) (a) Ciampolini, M.; Nardi, N. *Inorg. Chem.* **1996**, *41*, 42. (b) Thomas, E. W.; Cudahy, M. M.; Spilman, C. H.; Dinh, D. M.; Watkins, T. L.; Vidmar, T. J. *J. Med. Chem.* **1992**, *35*, 1233.

SCHEME 3. Preparation of Resins 12 and 15



To determine qualitatively the degree of methylation, both resins **13** and **14** were reacted with a 15-fold excess of the highly reactive electrophile 3,4-dichlorophenyl isocyanate in anhydrous DCM for 16 h to give **20** and **21**.[16] This allowed any remaining NH groups to be functionalized as ureas. As a control, the unmethylated starting resins **16** and **17** also were reacted in this way to give **18** and **19**. The resins produced were then analyzed for chlorine content by elemental analysis. Comparison of their chlorine content indicated that on average 0.7 of the 4 possible methylation sites of **16** and 0.7 of the 5 methylation sites of **17** remained unmethylated. As expected from this analysis, both resins gave a negative Kaiser test (indicating that no primary amines were left unreacted) but did show positive *p*-chloroanil tests indicative of some free secondary amines.[17] Infrared analysis also confirmed these conclusions.[18]

Attempts at preparing the analogous silica supported resin **12** from commercially available **22** (1.28 mmol/g) using the same Eschweiler−Clarke procedure furnished a product resin with a very low nitrogen content, indicating that significant quantities of ligand were cleaved from the silica support under the reaction conditions (Scheme 3). As an alternative approach, unmethylated resin **22** was reacted with 4 equiv of MeI in DCM at room temperature overnight. After being washed with Et_3N, the product resin was found to contain iodine (6.59%) indicating the presence of quaternary ammonium salts. Reaction of **12** with 3,4-dichlorophenyl isocyanate indicated a significant level of unfunctionalized secondary amines in **12**. Finally, the JandaJel analogue **15** was prepared from **23** using an established literature procedure.[11i]

Preparation of Copper Complexes. To prepare the active copper catalysts, each solid-supported ligand **9**−**15** was added to a stirred acetonitrile solution of an excess of either CuCl or CuBr. After addition, the resins were filtered, washed with acetonitrile, dried, and stored under nitrogen. In light of our difficulty in preparing the silica PMDETA analogue **12** we prepared the copper chloride complexes of the unmethylated commercially available silica triamine ligand **22** instead. Analysis of the polymers by infrared spectroscopy, elemental analysis, and ICP was undertaken to determine the copper loading and the ligand-to-copper ratio and to provide evidence for copper complexation by the supported ligand, Table 1. While the copper complexes of ligands **9**−**11** and **15** have been prepared before, evidence for copper complexation of the supported ligands **12**−**14** was obtained by comparison of their infrared spectra. In solution, the main changes upon complexation of the free ligand **4** with either CuCl or CuBr are shown in Figure 3. A shift to higher wavenumbers of the C−H stretching frequencies is observed in the 2700−3000 cm^{-1} range. The shift is accompanied by the merging of the two main sets of absorbances into a broader single set. This change was also observed for the supported ligands **12**−**14**, Figure 4. In this case, the C−H stretch region of the spectrum is more complicated as it is made up of the absorbances from both the ligand as well as the polystyrene backbone, but the broadening and merging of bands is still observable.

TABLE 1. Ligand and Copper Loadings

resin	ligand[a] loading (mmol/g)	loading[a] copper (mmol/g)
Si-PMI **9**:CuCl	0.87	0.81
Si-PMI **9**:CuBr	1.16	0.69
P-PMI **10**:CuCl	1.19	0.51[b]
P-PMI **10**:CuBr	1.16	0.53[b]
JJ-PMI **11**:CuCl	0.53	0.26[b]
JJ-PMI **11**:CuBr	0.52	0.46
P-PMDETA **13**:CuCl	1.81	1.98[c]
P-PMDETA **13**:CuBr	1.57	1.78[c]
P-Me_6-Tren **14**:CuCl	0.86	1.27[c]
P-Me_6-Tren **14**:CuBr	0.84	1.07[c]
JJ-TEDETA **15**:CuCl	0.45	0.43
JJ-TEDETA **15**:CuBr	0.45	0.43
Si-DETA **22**:CuCl	1.10	1.09
Si-DETA **22**:CuBr	1.07	0.97

[a] All numerical values are the average of duplicate microanalysis results. [b] Ratio of Cu:ligand approximately 1:2. [c] Copper loading is greater than ligand loading.

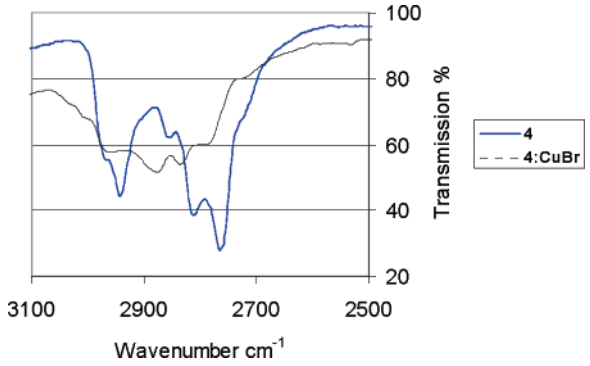


FIGURE 3. IR of solution PMDETA **4** and **4**:CuBr.

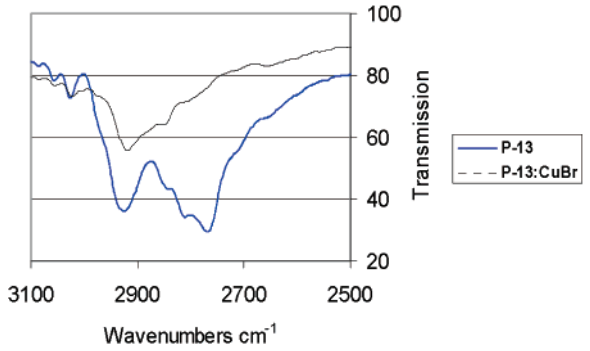


FIGURE 4. IR of P-PMDETA **13** and **13**:CuBr.

Reactions of Solid-Supported Copper Catalysts. Our initial experiments focused upon the cyclization of the trichloroacetamide substrate **6**.[5a] Thus, reacting **6** with 30 mol % of the supported reagents **9**−**15** and **22** at room temperature in DCE produced the expected atom-transfer product **7** with varying levels of efficiency, Table 2. The reactions were repeated at

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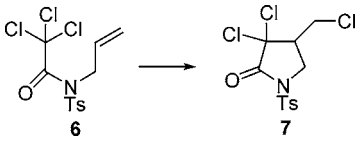
TABLE 2. Cyclization of 6 with Resins



resin	time	yield of **7**[a] (%)
Si-PMI **9**	3 h	92[b]
P-PMI **10**	3 h	98
JJ-PMI **11**	3 h	100
P-PMEDTA **13**	120 h	80[c]
Me_6-Tren **5**	5 min	93[d]
P-Me_6-Tren **14**	40 h	93[c]
JJ-TEDETA **15**	80 h	61[c]
Si-DETA **22**	80 h	0[e]

[a] Conducted at room temperature in DCE. [b] Reference 13. [c] 100% after 30 min at reflux. [d] Solution ligand. [e] Starting material recovered.

reflux using the same supported reagents **9**−**15**. This time, all of the reactions went to completion in quantitative yields after 30 min.

There was some concern that the activity of complex P-PMEDTA **13** may have been due to significant uncomplexed Cu(I) since the loading of the copper on the support exceeded that of the ligand. However, when the reaction was repeated using the equivalent of "free" Cu(I)Cl, no cyclization was observed. Interestingly, the polyamine-functionalized supports **13**−**15** were less efficient in cyclizing the test substrate than the immobilized PMI ligands **9**−**11**. This is the reverse behavior to that observed in solution.[8b] In light of the inability of the silica-functionalized support to mediate the reaction of **6,** this catalyst was not evaluated further. We next investigated the reusability of the polyamine supports P-PMDETA **13**:CuCl and P-Me_6-Tren **14**:CuCl. Reactions were performed using a 0.12 M concentration of **6** in DCE with 30 mol % (Cu) of catalysts at reflux under nitrogen. The reactions were monitored by the removal of aliquots from the reaction mixture at regular intervals. Once each reaction had reached completion the catalysts were filtered, washed well with DCE, dried to constant weight, and then reused with a fresh batch of substrate **6**. The reactions were repeated a total of seven times for each catalyst. Both catalysts retained their activity even after seven runs with the P-Me_6-Tren **14**:CuCl support requiring 4.5 h to reach completion and the P-PMDETA **13**:CuCl support requiring 9 h after the final run (the initial reaction was over in less than 30 min for both catalysts). A pseudo-first-order rate plot for the reaction mediated by P-PMDETA **13**:CuCl is shown in Figure 5. For both catalysts P-PMDETA **13**:CuCl and P-Me_6-Tren **14**:CuCl, the copper content was determined after the seventh run. Analysis indicated a leeching of 34% and 27% of Cu, respectively.

We next investigated the reactions of a variety of other substrates to probe the efficiency of the catalysts. Test substrates were picked in order to investigate 5-*exo-trig* cyclization of less activated substrates **24**[13] and **25**[3b] (the latter being chosen in order to determine if the stereochemical outcome of the reaction would be effected by the nature of the supported catalyst), as well as probing 5-*exo-dig* **26**,[8b] 5-*endo-trig* **27**,[13] and 4-*exo-trig* **28** cyclizations, Figure 6.

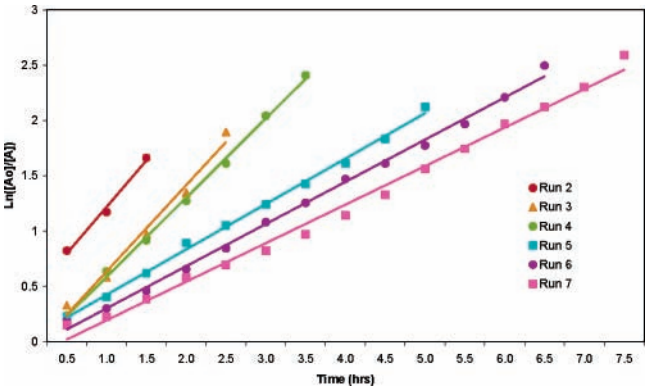


FIGURE 5. Rate Plots for P-PMDETA **13**:CuCl.

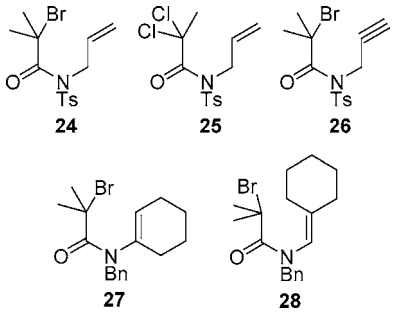
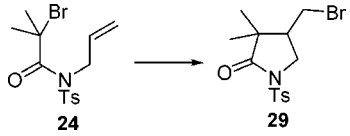


FIGURE 6. Cyclization substrates **24**−**28**.

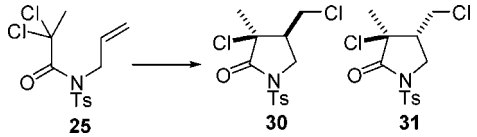
TABLE 3. Cyclization of 24



ligand	*T* (°C)	time (h)	yield (%)
PMDETA **4**	18	0.5	99
P-PMDETA **13**	18	48	0
P-PMDETA **13**	83	0.5	95
Me_6-Tren **5**	18	<0.1	97
P-Me_6-Tren **14**	18	92	95
P-Me_6-Tren **14**	83	0.5	95
JJ-TEDETA **15**	83	3	92
Si-PMI **9**	22	24	31
P-PMI **10**	22	24	30
JJ-PMI **11**	22	24	27

Cyclization of Substrates 24−25. Cyclizations of both substrates **24** and **25** were undertaken using PMI **9**−**11** and polyamine **13**−**15** catalysts (Table 3). In addition, the solution ligand counterparts PMDETA **4** and Me_6-Tren **5** of the solid-supported reagents P-PMDETA **13** and P-Me_6-Tren **14** were also investigated in order to compare homogeneous versus heterogeneous catalyst rates and selectivities. The homogeneous catalysts PMDETA **4** and Me_6-Tren **5** were found to effect cyclization of substrates **24** and **25** at room temperature in less than 5 min and in 1 h, respectively (with catalyst **4** providing a de of 73% and catalyst **5** a de 75% for the cyclization of **25**). On the other hand, the solid-supported analogues P-PMDETA **13** and P-Me_6-Tren **14** failed to mediate any cyclization of either substrate even after 1 h. More detailed studies carried out at room temperature indicated the cyclization of **24** with P-Me_6-Tren **14**:CuBr was more efficient than with P-PMDETA **13**:CuBr paralleling the homogeneous reactivities of these ligands.

TABLE 4. Cyclization of 25



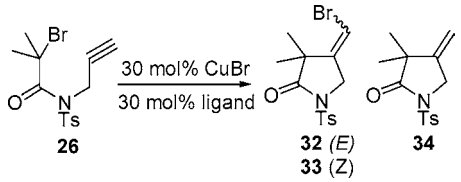
ligand	*T* (°C)	time (h)	yield (%) (de, %)
PMDETA **4**	18	1	98 (73)
P-PMDETA **13**	83	1	91 (65)
Me_6-Tren **5**	20	1	88 (75)
P-Me_6-Tren **14**	83	24	93 (63)
JJ-TEDETA**15**	83	24	58 (31)
Si-PMI **9**	83	18	94 (64)
P-PMI **10**	83	18	92 (62)
JJ-PMI **11**	83	18	93 (60)

Yet again, however, the most reactive catalysts were those derived from PMI ligands **9**−**11** (all providing >95% yield in only 30 min at reflux). Comparing the effect of the support type (polystyrene versus JandaJel) on the rate of cyclization of **24** with PMI ligands at room temperature (Table 3) indicated that the JandaJel resin with its flexible cross-linker provided no advantage over the analogous polystyrene or silica catalyst. Upon reflux, all of the catalysts mediated the cyclization of **24** to completion in 30 min with the exception of the JJ-TEDETA·CuBr complex, which took 3 h.

Cyclization of the dichloroamide **25** indicated a different order of reactivity (Table 4). While cyclization of **25** with PMDETA **13**:CuCl and PS-Me_6-Tren **14**:CuCl again paralleled their solution reactivities, catalyst **14** was particularly active. As before, the PMI ligands **9**−**11** all performed similarly. All reagents showed a decrease in diastereoselectivity compared to their solution counterparts. The JJ-TEDETA **15**:CuBr complex was again one of the least efficient, giving a relatively low yield of product (58%) with an extremely low diastereoselectivity (de 31%).

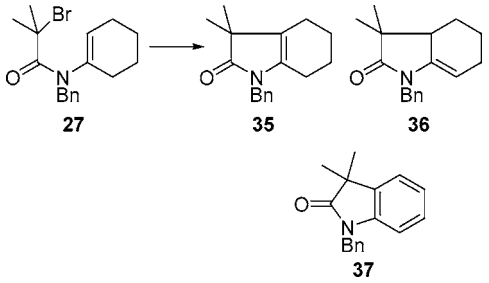
Effect of Reduction versus Atom Transfer in the Cyclization of Alkyne 26. Copper-mediated atom transfer 5-*exo*-*dig* cyclizations onto alkynes have been reported to be difficult with the nature of the ligand being crucial to the success of the reaction.[7d] Previous work has shown that PMI ligands **2** mediate the reaction of **26** to give an inseparable mixture of the vinyl bromides **32**/**33** as well as the reduced alkene **34**. The reduced alkene **34** is thought to arise via reduction of the intermediate vinyl radical by H abstraction from either the ligand or the solvent or from both.[7d] That the nature of the ligand used in this homogeneous catalyzed reaction can affect both the amount of **34** obtained as well as the *E*/*Z* ratio of the vinyl bromides **32**/**33** was ascertained by reacting **26** with the solution catalysts obtained by mixing 30 mol % of CuBr and 30 mol % of PMI **2**, PMDETA **4**, or Me_6-Tren **5** as ligand in DCE. Substantial amounts of reduced product **34** (29%) was obtained when the PMDETA **4** or Me_6-Tren **5** ligands were used (29% for both) but only a trace was obtained with the PMI ligand **2** (4%). To a certain degree, this reflects the relative ease of H atom donor ability of the respective ligands with the polyamine ligands being better donors. The *E*/*Z* ratio of the vinyl bromides **32**/**33** obtained were also somewhat different for the polyamine ligands **4** and **5** (3.7:1.0) compared to the pyridine-based ligand system **2** (2.5:1.0). The solid-supported catalysts followed the same reactivity trends as those observed in the other supported 5-*exo* cyclizations with the PMI catalysts being more reactive than the polyamine ones. However, in all cases, the *E*/*Z* selectivity was eroded compared to the reactions with the solution catalysts. This may be due to the greater steric bulk of the polymer-supported reagents which led to a significantly retarded rate of atom transfer at the most hindered site (giving rise to **32**) in the intermediate vinyl radical.

TABLE 5. Cyclization of 26



ligand	time (h)	yield of **32**/**33** (%), ratio *E*/*Z*	yield of **34** (%)
PMDETA **4**	0.5	70, 3.7:1.0	29
P-PMDETA **13**	48	88, 2.4:1.0	11
Me_6-Tren **5**	0.5	70, 3.8:1.0	29
P-Me_6-Tren **14**	48	93, 2.4:1.0	6
JJ-TEDETA **15**	24	90, 2.4:1.0	8
Si-PMI **9**	24	98, 2.2:1.0	0
JJ-PMI **11**	24	93, 2.2:1.0	6

TABLE 6. Cyclization of 27



ligand	ratio of **35**:**36**	yield of **35** + **36** (%)
P-PMEDTA **13**	1.2:1.0	42
P-Me_6-Tren **14**	1.0:1.0	50
JJ-TEDETA **15**	1.1:1.0	100
Si-PMI **9**	1.0:1.0	78
JJ-PMI **11**		15[a]

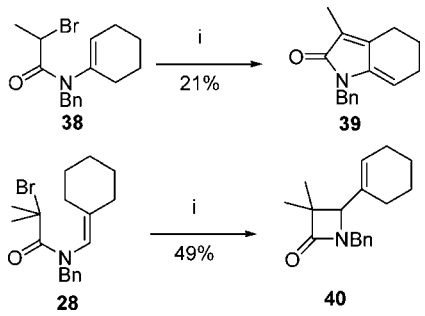
[a] Yield of **37**.

While all supported ligands showed reduced stereoselectivity they also provided significantly lower amounts of the undesired reduced alkene **34**. Presumably, the supported ligands are less sterically accessible for H atom donation compared to their solution analogues (Table 5). Thus, higher overall yields of atom-transfer products could be obtained when using the heterogeneous Si-PMI **9** ligand system compared to the homogeneous catalysts.

Mediation of 4-*exo* and 5-*endo* Radical Polar Crossover Reactions. Efficient 5-*endo* radical polar crossover reactions of tertiary bromide precursors have been reported to be mediated in solution by Me_6-Tren **5**:CuX complexes.[9a] Hence, precursor **27** has been shown to furnish a 1:1 mixture of **35** and **36** in an overall yield of 82% after 20 min at room temperature (Table 6). This reaction has also been reported to be mediated by the Si-PMI **9**:CuBr complex[13] at reflux giving the same 1:1 mixture of isomers albeit in an extended reaction time (24 h) and reduced yield (78%).

Interestingly, attempts to mediate the cyclization of **27** with the analogue JJ-PMI **11** only furnished the oxindole **37** in 15%

SCHEME 4. Cyclization of 28 and 38[a]



[a] Key: (i) 30 mol % of JJ-TEDETA **15**:CuBr, DCE, reflux.

yield[19] (the remaining mass balance being unreacted starting material). Both P-PMDETA **13** and P-Me_6-Tren **14** did facilitate the reaction, but neither went to completion even after 48 h. Most surprising, however, was that the JJ-TEDETA **15** complex was now the most efficient, providing a quantitative yield of both regioisomers **35** and **36** in 48 h. Encouraged by this result, we wondered whether it would be possible to mediate the 5-*endo* cyclization of secondary halides, such as **38**, using this reagent. Previous work has shown that polyamine ligands such as Me_6-Tren **5** will not mediate this cyclization in solution, and instead, more active multidentate pyridine ligands such as tripyridylamine are necessary for successful reaction.[20] Thus, it came as no surprise that neither the P-PMDETA **13** or P-Me_6-Tren **14** ligands facilitated the cyclization of **38**. In both cases, only starting material was recovered from the reactions. However, heating **38** with JJ-TEDETA **15**:CuBr for 48 h at reflux did provide the cyclized diene **39** in low yield (21%) along with recovered starting material. It remains unclear why the JJ-TEDETA **15** ligand should be so effective at mediating these 5-*endo* cyclizations but is one of the least efficient resins in mediating 5-*exo* cyclizations. In addition, we determined that the JJ-TEDETA **15** was the only resin to mediate the 4-*exo* cyclization of **28** to give **40** (all the other resins providing only recovered starting material) (Scheme 4).

Conclusions

We have shown that a range of supported pyridinemethanimine **9**−**11** and polyamine **13**−**15** ligand/copper complexes will mediate 4-*exo*-*trig*, 5-*exo*-*trig*, 5-*exo*-*dig*, and 5-*endo*-*trig* radical cyclizations of a representative set of substrates. The rates of reaction of all the supported reagents were significantly slower than for their corresponding solution analogues. In addition, the effect of the nature of the supported ligand upon the cyclization of **6** indicated that the pyridinemethanimine ligands **9**−**11** were more effective than the polyamine ligands **12**−**15**. This was unexpected in light of the reverse result for their behavior in solution.[8b] In general, the PMI catalysts **9**−**11** were more efficient in 5-*exo* cyclizations with the JJ-TEDETA catalyst being the least efficient. This situation was reversed, however, when examining the 4-*exo* and 5-*endo* cyclizations of **28**, **27**, and **38**. In fact, the JJ-TEDETA catalyst was the only system to mediate the cyclization of **28** and **38**. The reason for this difference in reactivity is unclear at this stage. A potential advantage in using solid-supported reagents in the cyclization onto alkynes (e.g., **26**) was indicated by the fact that cyclization of **26** led to significantly less of the undesired reduced product **34** compared to the corresponding homogeneous catalyzed processes.[8b] The reusability of the ligands was briefly probed with the P-PMDETA ligand system **13**. This indicated that in the cyclization of **6** the catalyst system was capable of reuse up to the seven runs investigated. The decrease in reactivity observed in each consecutive run is likely to arise from both leaching of the copper from the support as well as oxidative deactivation to unreactive copper(II) complexes. Generally, it was found that the type of support (e.g., polystyrene, silica, or JandaJel) had very little effect upon the efficiency and selectivity of the processes but that the nature of the ligand type immobilized was the important factor.

Experimental Section

General Procedures. *N*-Allyl-*N*-4-toluenesulfonyl-2,2,2-trichloroacetamide **6**,[5a] *N*-allyl-*N*-4-toluenesulfonyl-2-bromo-2-methylpropionamide **24**,[13] *N*-allyl-*N*-4-toluenesulfonyl-2,2-dichloropropionamide **25**,[3b] *N*-propargyl-*N*-4-toluenesulfonyl-2-bromo-2-methylpropionamide **26**,[8b] and *N*-benzyl-2-methyl-2-bromo-*N*-cyclohexyl-1-enylpropionamide **27**[13] were prepared by literature procedures. 4-Chloromethyl-3,3-dichloro-1-toluene-4-sulfonylpyrrolidin-2-one **7**,[5a] 4-bromomethyl-3,3-dimethyl-1-toluene-4-sulfonylpyrrolidin-2-one **29**,[13] (3*S**,4*R**)-4-chloromethyl-3-chloro-3-methyl-1-toluene-4-sulfonylpyrrolidin-2-one **30**,[3b] (3*S**,4*S**)-4-chloromethyl-3-chloro-3-methyl-1-toluene-4-sulfonylpyrrolidin-2-one **31**,[3b] (*E*)-4-bromomethylene-3,3-dimethyl-1-toluene-4-sulfonylpyrrolidin-2-one **32**,[8b] (*Z*)-4-bromomethylene-3,3-dimethyl-1-toluene-4-sulfonylpyrrolidin-2-one **33**,[8b] 3,3-dimethyl-4-methylene-1-toluene-4-sulfonylpyrrolidin-2-one **34**,[8b] 1-benzyl-3,3-dimethyl-1,3,4,5,6,7-hexahydroindol-2-one **35**,[13] 1-benzyl-3,3-dimethyl-1,3,3a,4,5,6-hexahydroindol-2-one **36**,[13] and 1-benzyl-3,3-dimethyl-1,3-dihydroindol-2-one **37**[19] exhibited spectroscopic details identical to those already reported. Nuclear magnetic resonance, ^{1}H NMR, were recorded at 300 or 400 MHz and ^{13}C NMR recorded at 75.5 or 100.6 MHz with residual solvent as internal standard; infrared spectra (IR) were recorded as solutions or neat; and mass spectra were recorded using either electron impact or chemical ionization (NH_3). All reactions were carried out under nitrogen unless otherwise stated.

Synthesis of Supported Ligands. Si−PMI 9. A mixture of aminopropylated silica gel (1.26 mmol of $-NH_2$/g) (4.00 g, 5.04 mmol) and pyridine-2-carboxaldehyde (4.26 mL, 45.0 mmol) in dry toluene (100 mL) was heated to reflux for 24 h with a Soxhlet containing crushed 4 Å molecular sieves (10.0 g). The orange solid was filtered, washed with toluene (3 × 50 mL), DCM (3 × 20 mL), and ethanol (10 mL), and dried in vacuo to give (Si-NPMI) **9** as an orange solid (4.35 g): ν_{max} (solid)/cm^{-1} 1045, 796. Found: C, 15.25; H, 1.78; N, 3.54; 1.26 mmol of ligand/g.

P-PMI 10. A mixture of (aminomethyl)polystyrene (1% cross linked; 1.66 mmol of $-NH_2$/g) (4.50 g, 7.47 mmol) and pyridine-2-carboxaldehyde (6.41 mL, 67.5 mmol) in dry toluene (100 mL) was heated to reflux for 24 h with a Soxhlet containing crushed 4 Å molecular sieves (10.0 g). The resin was filtered, washed with anhydrous toluene (10 × 25 mL), and dried in vacuo to give P-PMI **10** as an orange solid (4.97 g): ν_{max} (solid)/cm^{-1} 3057, 3025, 2919, 2850, 2320, 1700, 1646, 1594, 1492, 1452, 1361, 1152, 1072, 1025, 994, 755, 697. Found: C, 88.13; H, 7.29; N, 3.30; 1.18 mmol of ligand/g.

JJ-PMI 11. A mixture of JandaJel-NH_2 (0.635 mmol of $-NH_2$/g) (5.08 g, 3.22 mmol) and pyridine-2-carboxaldehyde (613 μL, 6.45 mmol) in dry toluene (100 mL) was heated to reflux for 16 h with a Soxhlet containing crushed 4 Å molecular sieves (5.0 g). The resin was filtered, washed with anhydrous toluene (10 × 25 mL), and dried in vacuo to give JJ-NPMI **11** as a yellow solid

(19) Trifonov, L. S.; Orahovats, A. S. *Helv. Chim. Acta* **1987**, *70*, 1732.
(20) Clark, A. J.; Dell, C. P.; McDonagh, J. P. *C. R. Acad. Sci. Ser IIc: Chim.* **2001**, *4*, 575.

(5.02 g): ν_{max} (solid)/cm^{-1} 3058, 3025, 2917, 2850, 1645, 1601, 1510, 1493, 1452, 1368, 1239, 1178, 1111, 1024, 906, 825, 754, 695. Found: C, 89.10; H, 7.64; N, 1.46; 0.521 mmol of ligand/g.

Attempted Synthesis of Si-PMDETA 12, Method A. 3-Propyldiethylenetriamine-functionalized silica gel (1.28 mmol of triamine/g) (4.50 g, 5.76 mmol) was cooled to 0 °C in an ice bath. Formic acid (11.0 mL, 294 mmol) was added by syringe over 10 min, followed by aqueous formaldehyde (19.4 mL, 36% aqueous solution, 259 mmol). The reaction mixture was heated to reflux for 16 h. The mixture was cooled and the resin filtered through a pre-tared filter funnel. The resin was washed repeatedly with 19:1 DCM/MeOH and was dried in vacuo at room temperature to give a white solid (3.75 g): ν_{max} (solid)/cm^{-1} 3245, 1591, 1044, 795. Found: C, 7.45; H, 1.90; N, 1.79. Kaiser test (solid initially colorless, stains pale black after 30 s); *p*-chloranil test (silica stained dark green). **Method B.** Methyl iodide (1.27 mL, 20.4 mmol) was added to a suspension of 3-propyldiethylenetriamine-functionalized silica gel (4.00 g, 5.10 mmol) in anhydrous DCM (40 mL) at room temperature under nitrogen. After 16 h, the solid was filtered through a pretared filter funnel, washed repeatedly with 19:1:0.5 DCM/MeOH/Et_3N, and dried in vacuo at room temperature to give a white solid (4.43 g). Found: C, 12.26; H, 2.72; N, 4.80; I, 6.59.

P−PMDETA 13. Stratospheres PL-DETA (diethylenetriamine) resin (2.72 mmol of triamine/g) (4.50 g, 12.2 mmol) was cooled to 0 °C in an ice bath. Formic acid (23.4 mL, 622 mmol) was added by syringe over 10 min, followed by aqueous formaldehyde (41.2 mL, 36% aqueous solution, 549 mmol). The reaction mixture was heated to reflux for 16 h. The mixture was cooled and the resin filtered through a pretared filter funnel. The resin was washed well with Et_3N (3 × 5 mL), water (3 × 5 mL), DCM (3 × 5 mL), MeOH (3 × 5 mL), DMF (3 × 5 mL), and MeOH (3 × 5 mL) and was dried in vacuo at room temperature to give P-PMDETA **13** (5.07 g) as a white solid: ν_{max} (solid)/cm^{-1} 3024, 2924, 2764, 1673, 1602, 1489, 1448, 1361, 1285, 1119, 1025, 788, 760, 699. Found: C, 78.90; H, 9.24; N, 9.88; 2.35 mmol of triamine/g; Kaiser test (resin colorless); *p*-chloranil test (resin stained orange brown then green).

P-Me$_6$-tren 14. Tris(2-aminoethyl)amine polystyrene (1.18 mmol tetramine/g) (3.00 g, 3.53 mmol) was cooled to 0 °C in an ice bath. Formic acid (6.79 mL, 180 mmol) was added by syringe over 10 min, followed by aqueous formaldehyde (11.9 mL, 36% aqueous solution, 154 mmol). The reaction mixture was heated to reflux for 16 h. The mixture was cooled and the resin filtered through a pretared filter funnel. The resin was washed well with Et_3N (3 × 5 mL), water (3 × 5 mL), DCM (3 × 5 mL), MeOH (3 × 5 mL), DMF (3 × 5 mL), and MeOH (3 × 5 mL) and was dried in vacuo to give **14** (2.99 g) as a white solid: ν_{max} (solid)/cm^{-1} 3057, 3023, 2920, 2847, 2766, 1679, 1599, 1491, 1448, 1361, 1113, 1025, 754, 695. Found: C, 84.34; H, 8.54; N, 5.69; Cl, 0.14; 1.02 mmol of tetramine/g; Kaiser test (resin colorless); *p*-chloranil test (resin stained blue).

JJ-TEDETA 15. *N*,*N*,*N*′,*N*′-Tetraethyldiethylenetriamine (5.00 mL, 19.4 mmol) was added to a suspension of JandaJel-supported acrylate (JJ-Acrylate)[11i] (4.50 g, 8.69 mmol) in anhydrous THF (100 mL) at room temperature under nitrogen. After 48 h, the solids were filtered, washed several times with THF, and dried in vacuo to give JJ-TEDETA **15** (4.42 g) as an orange solid: ν_{max} (solid)/cm^{-1} 3296, 3060, 3025, 2920, 2848, 1724, 1602, 1493, 1448, 1374, 1244, 1175, 1065, 1027, 908, 815, 753, 696. Found: C, 83.97; H, 8.02; N, 2.09; 0.497 mmol of ligand/g.

Kaiser Test for Determining Primary Amines on Solid Supports. One drop of each of the following solutions was added to 1−2 mg of solid: (i) 5 g of ninhydrin in 100 mL of ethanol, (ii) 80 g of phenol in 20 mL of ethanol, and (iii) 2 mL of 0.001 M KCN (aq) mixed with 98 mL of pyridine. The mixture was heated for a few seconds. Coloration of the solid indicates the presence of primary amines on the solid support.

***p*-Chloranil Test for Determining Secondary Amines on Solid Supports.** One drop of each of the following solutions was added to 1−2 mg of solid: (i) 2% acetaldehyde in DMF, (ii) 2% *p*-chloranil (tetrachloro-1,4-benzoquinone) in DMF, and (iii) 2 mL 0.001 M KCN (aq) and 98 mL of pyridine. The mixture was allowed to stand for 5 min at room temperature. Coloration of the solid indicates the presence of secondary amines on the solid support.

Determination of Free Amine Content and Reaction of Resins with 3,4-Dichlorophenyl Isocyanate. To the resin was added to a solution of 3,4-dichlorophenyl isocyanate (15 equiv) in anhydrous DCM (10 mL) under nitrogen. After 16 h at room termperature, the reaction mixture was filtered through a pretared filter funnel. The resin was washed well with with Et_3N (3 × 5 mL), water (3 × 5 mL), DCM (3 × 5 mL), MeOH (3 × 5 mL), DMF (3 × 5 mL), and MeOH (3 × 5 mL) and was dried in vacuo at room temperature to give the functionalized resin.

General Synthesis of CuCl- and CuBr-Supported Catalysts. To the supported ligand was added a stirred solution of CuCl or CuBr (1.2 equiv) in dry acetonitrile (10 mL) at room temperature under nitrogen. After 30 min, the dark resin was filtered, washed with acetonitrile (3 × 20 mL), and dried in vacuo.

***N*-Benzyl-2-bromo-*N*-cyclohexylidenemethyl-2-methylpropionamide 28.** A stirred solution of cyclohexanecarboxaldehyde (7.27 mL, 60.0 mmol) and benzylamine (6.55 mL, 60.0 mmol) in toluene (40 mL) was heated to reflux in a Dean−Stark apparatus for 24 h. The reaction mixture was concentrated in vacuo (12.1 g, 100%). The crude product (3.22 g, 16 mmol) was dissolved in anhydrous toluene (90 mL), and *N*,*N*-diethylaniline (2.55 mL, 16.0 mmol) was added. To this mixture was added 2-bromoisobutyryl bromide (1.98 mL, 16.0 mmol) dropwise over 10 min at 0 °C. After being stirred for 16 h at room temperature, the reaction mixture was washed with water (40 mL) and then 1 M HCl (40 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (SiO_2, 9:1, petroleum ether/ethyl acetate) to give **28** as a colorless oil (4.86 g, 87%): R_f (5:1 petroleum ether/ethyl acetate) 0.44; IR (film) (film) 2928, 2853, 1636 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 7.33−7.20 (5H, m), 6.30 (1H, s), 4.67 (2H, s), 2.13−2.06 (4H, m), 1.98 (6H, s), 1.58−1.46 (6H, m); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.0, 141.5, 137.7, 128.8 (×2), 128.3 (×2), 127.5, 123.2, 58.9, 55.5, 33.2, 32.7, 29.0, 27.9, 26.6, 26.5; HRMS (EI) calcd for $C_{18}H_{24}Br^{81}NO$ 352.1099, found 352.1111; CI-MS *m*/*z* 350 $(M)^+$, 270, 200, 91. Anal. Calcd for $C_{18}H_{24}BrNO$: C, 61.7; H, 6.9; N, 4.0; Br, 22.8. Found: C, 61.7; H, 6.9; N, 4.0; Br, 22.7.

***N*-Benzyl-2-bromo-*N*-cyclohex-1-enylpropionamide 38.** 2-Bromopropionyl bromide (1.68 mL, 16.0 mmol) was added dropwise over 10 min to a solution of benzylcyclohexylideneamine[20] (3.00 g, 16.0 mmol) and *N*,*N*-diethylaniline (2.55 mL, 16.0 mmol) in anhydrous toluene (90 mL) at 0 °C. After stirring for 16 h at room temperature, the reaction mixture was washed with water (40 mL) and then 1M HCl (40 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (SiO_2, 9:1, petroleum ether/ethyl acetate) to give **38** as an off-white solid (3.59 g, 70%): mp 87−88 °C; R_f (5:1 petroleum ether/ethyl acetate) 0.29; IR (film) ν_{max} 2931, 1656 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28−7.18 (5H, m), 5.48 (1H, br s), 4.70−4.45 (3H, m), 2.22−1.84 (4H, m), 1.78 (3H, d, J = 8.0 Hz), 1.70−1.58 (2H, m), 1.56−1.47 (2H, m); ^{13}H NMR (75.5 MHz, $CDCl_3$) δ 169.7, 138.0, 137.8, 129.4, 129.0 (×2), 128.7 (×2), 127.7, 50.4, 39.9, 28.4, 25.1, 23.1, 21.7, 22.6; HRMS (EI) calcd for $C_{16}H_{20}Br^{79}NO$ 321.0728, found 321.0734; CI-MS *m*/*z* 322 $(MH)^+$, 242, 152, 91. Anal. Calcd for $C_{16}H_{20}BrNO$: C, 59.6; H, 6.3; N, 4.35; Br, 24.8. Found: C, 59.6; H, 6.2; N, 4.4; Br, 24.8.

General Procedure for Homogeneous Cyclization Reactions. To a solution of the cyclization substrate (0.120 mmol) and ligands **4** and **5** (0.036 mmol) in anhydrous dichloroethane (1 mL) under nitrogen was added copper(I) chloride or copper(I) bromide (0.0360 mmol). The mixture was stirred at an appropriate temperature and was monitored by TLC or NMR until no further change in reaction composition was observed. The crude reaction mixture was filtered

through a short plug of silica, which was washed with CH_2Cl_2 and then EtOAc. The filtrate was concentrated in vacuo and the crude residue purified by flash column chromatography.

General Procedure for Solid-Supported Cyclization Reactions. The polymer-supported copper chloride or copper bromide complex (0.0360 mmol of Cu) was added to a solution of the cyclization substrate (0.120 mmol) in anhydrous dichloroethane (1 mL) under nitrogen. The mixture was stirred at an appropriate temperature and was monitored by TLC or ^{1}H NMR until no further change in reaction composition was observed. The crude reaction mixture was filtered, and the resin was washed well with CH_2Cl_2 and then EtOAc. The filtrate was concentrated in vacuo and was characterized by ^{1}H NMR. Reaction products were purified by flash column chromatography where necessary.

1-Benzyl-3-methyl-1,4,5,6-tetrahydroindol-2-one 39: pale yellow oil; yield 21%; R_f (5:1 petroleum ether/ethyl acetate) 0.26; IR (film) ν_{max} 2922, 2856, 1682, 1653 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32−7.18 (5H, m), 5.42 (1H, t, J = 4.5 Hz), 4.76 (2H, s), 2.53 (2H, m), 2.24 (2H, m), 1.89 (3H, s), 1.78 (2H, m); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 171.5, 140.4, 139.4, 138.3, 123.8, 128.9 (×2), 127.6 (×2), 127.5, 108.9, 43.2, 24.7, 23.7, 22.9, 8.8; *m*/*z* (EI) 239 $(M)^+$, 216, 122, 105, 91, 77, 65; HRMS (EI) calcd for $C_{16}H_{17}NO$ 239.1310, found 239.1310; EI-MS *m*/*z* 239 $(M)^+$, 216, 122, 105, 91.

1-Benzyl-4-cyclohex-1-enyl-3,3-dimethylazetidine-2-one 40: clear oil; R_f (3:1 petroleum ether/ethyl acetate) 0.31; IR (film) ν_{max} 2927, 1751, 1642 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.21 (5H, m), 5.57 (1H, m), 4.83 (1H, d, J = 14.9 Hz), 3.86 (1H, d, J = 14.9 Hz), 3.36 (1H, s), 2.14−2.05 (2H, m), 1.85−1.45 (6H, m), 1.26 (3H, s), 1.06 (3H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 174.8, 136.6, 133.2, 129.1 (×2), 128.8 (×2), 127.9, 123.7, 66.7, 44.8, 33.2, 27.7, 25.2, 22.9, 22.7, 17.1; HRMS (FAB) calcd for $C_{18}H_{24}NO$ 270.1858, found 270.1859; *m*/*z* (EI) 270 $(MH)^+$, 200, 136, 121, 91.

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Supporting Information Available: Microanalysis data for supported ligands **9**−**15** and **18**−**21**, and CuCl and CuBr complexes of **9**−**15** and **22** as well as representative ^{1}H NMR data for **28** and **38**−**40**. Data for the re-usability of catalyst **13**:CuCl in the cyclization of **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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