Solid-Supported Catalysts for Atom-Transfer Radical Cyclization of 2-Haloacetamides

Andrew J. Clark,*,† Robert P. Filik, David M. Haddleton, Arnaud Radigue, and Christopher J. Sanders

Department of Chemistry, University of Warwick, Coventry CV4 7AL, U.K.

Gerard H. Thomas

Research and Development, Knoll Pharmaceuticals, Pennyfoot Street, Nottingham, NG1 1GF, U.K.

Mark E. Smith

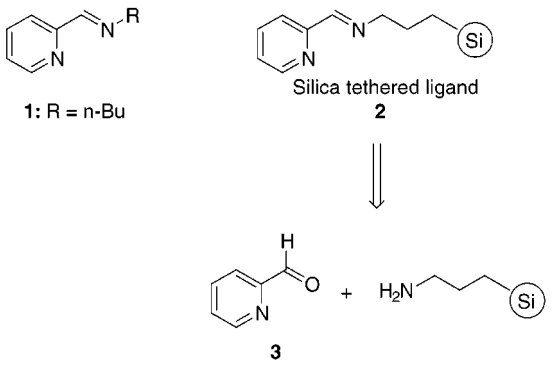
Department of Physics, University of Warwick, Coventry CV4 7AL, U.K.

Received June 2, 1999

Introduction

With the renaissance in solid-supported chemistry the design and use of novel solid-supported reagents has become an area of great interest.[1] In the area of free radical chemistry the vast majority of radical cyclization reactions are initiated by organotin hydride reduction of carbon−halogen bonds.[2] As a consequence the use of solid-supported organotin hydride reagents has been reported by Neumann and others.[3] These have been shown to mediate efficient radical cyclization reactions; however, the reductive nature of these cyclizations is a major disadvantage. Consequently in recent years the growth of transition-metal-mediated free radical processes has gained importance.[4] In particular the atom-transfer radical cyclization reactions (ATRC) of 2,2,2-trichlorinated carbonyl compounds have been reported with a range of metal catalysts including $RuCl_2(PPh_3)_3$,[5] $FeCl_2(P(OEt)_3)_3$,[6] CuCl(bipyridine),[7] CuCl(TMEDA),[8] and CuCl(*N*,*N*′,*N*′,*N*″-pentamethyldiethylenetriamine).[9]

We have recently reported that *N*-alkyl-2-pyridylmethanimines **1** can act as good ligands for copper-mediated atom-transfer radical polymerization reactions[10] and that these ligands can be readily immobilized onto solid supports.[11] In addition we have shown that copper(I) complexes of *N*-alkyl-2-pyridylmethanimines **1** can act as efficient catalysts in atom-transfer radical cyclization reactions of a range of 2-haloacetamides.[12] The nature of the *N*-alkyl substituent in **1** was found to affect the efficiency of the catalysis, with ligands bearing primary substituents (R = *n*-Bu) being the most active. We report here that copper(I) halide complexes **4a**,**b** of silica-supported ligands **2** based upon *N*-alkyl-2-pyridylmethanimines **1** tethered to silica via a primary *N*-alkyl group are efficient mediators of the cyclization of a range of activated and unactivated 2-haloacetamides.



Results and Discussion

The solid-supported catalysts were prepared by reacting 9% functionalized aminopropyl silica gel (Aldrich) with an excess of pyridine-2-carboxaldehyde (**3**) in toluene at reflux for 24 h (with a Soxhlet containing crushed 4 Å molecular sieves to remove water). After careful isolation of the light orange solid-supported ligand **2** (by filtration and repeated washing with solvent to remove unattached absorbed ligand), it was characterized by infrared spectroscopy, elemental analysis, and solid-state ^{13}C CP/MAS NMR. The active catalysts **4a** and **4b** were then prepared by reaction of the solid-supported ligand **2** with either CuCl or CuBr dissolved in acetonitrile (Scheme 1). After the solution was stirred for 1 h and washed with a large excess of acetonitrile, the dark brown solid catalysts **4a**,**b** were isolated. ICP analysis indicated that they contained

† E-mail: msrir@csv.warwick.ac.uk. Fax: +44-1203 524112.

(1) (a) Brown, A. R.; Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Synlett* **1998**, 817. (b) Blackburn, C. *Biopolymers* **1998**, *47*, 351. (c) Brown, R. C. D, *J. Chem. Soc., Perkin Trans. 1* **1998**, *19*, 3293.

(2) (a) Fossey, J.; Lefort, D.; Sorba, J. *Free Radicals in Organic Synthesis*; Chichester: Wiley, 1995. (b) Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, pp 716 and 779.

(3) (a) Schumann, H.; Pachaly, B. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 1043. (b) Gerigk, U.; Gerlach, M.; Neumann, W. P.; Robert, V.; Weintritt, V. *Synthesis* **1990**, 448. (c) Neumann, W. P. *J. Organomet. Chem.* **1992**, *437*, 23. (d) Gerlach, M.; Jördens, F.; Kuhn, H.; Neumann, W. P.; Peterseim, M. *J. Org. Chem.* **1991**, *56*, 5971.

(4) Iqbal, J.; Bhatia, B.; Nayyar, N. K. *Chem. Rev.* **1994**, *94*, 519.

(5) (a) Pirrung, F. O. H.; Hiemstra, H.; and Speckamp, W. N. *Tetrahedron* **1994**, *50*, 12415. (b) Rachita, M. A.; Slough, G. A. *Tetrahedron Lett.* **1993**, *43*, 6821. (c) Slough, G. A. *Tetrahedron Lett.* **1993**, *43*, 6825. (d) Hayes, T. K.; Villani, R.; Weinreb, S. M. *J. Am. Chem. Soc.* **1988**. *110*, 5533. (e) Phelps, J. C.; Bergbreiter, D. E.; Lee, G. M.; Villani, R.; Weinreb, S. M. *Tetrahedron Lett.* **1989**, *30*, 3915. (f) Lee, G. M.; Weinreb, S. M. *J. Org. Chem.* **1990**, *55*, 1281. (g) Nagashima, H.; Wakamatsu, H.; Ozaki, N.; Ishii, M.; Watanabe, M.; Tajima, T.; Itoh, K. *J. Org. Chem.* **1992**, *57*, 1682. (h) Nagashima, H.; Ara, K.; Wakamatsu, H.; Itoh, K. *J. Chem. Soc., Chem. Commun.* **1985**, 518.

(6) Lee, G. M.; Parvez, M.; Weinreb, S. M. *Tetrahedron* **1988**, *44*, 4671.

(7) (a) Udding, J. H.; Tuijp, K. C. J. M.; Vanzanden, M. N. A.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron* **1994**, *50*, 1907. (b) Baldovini, N.; Bertrand, M.-P.; Carrière, A.; Nougier, R.; Plancher, J.-M. *J. Org. Chem.* **1996**, *61*, 3205. (c) Nagashima, H.; Ozaki, N.; Ishii, M.; Seki, K.; Washiyama, M.; Itoh, K. *J. Org. Chem.* **1993**, *58*, 464.

(8) (a) Forti, L.; Ghelfi, F.; Pagnoni, U. M. *Tetrahedron Lett.* **1996**, *37*, 2077. (b) Benedetti, M.; Forti, L.; Ghelfi, F.; Pagnoni, U. M.; Ronzoni, R. *Tetrahedron* **1997**, *53*, 14031.

(9) De Campo, F.; Lastécouères, D.; Verlhac, J.-B. *J. Chem. Soc., Chem. Commun.* **1998**, 2117.

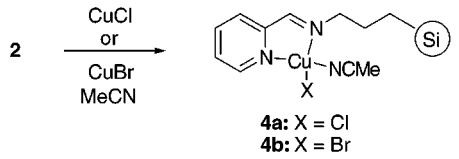
(10) (a) Haddleton, D. M.; Duncalf, D. J.; Kukulj, D.; Shooter, A. J.; Clark, A. J. *J. Mater. Chem.* **1998**, *8*, 1525. (b) Haddleton, D. M.; Clark, A. J.; Crossman, M. C.; Duncalf, D. J.; Morsley, S. R., Heming, A. M.; Shooter, A. J. *J. Chem. Soc., Chem Commun.* **1997**, 1173.

(11) Haddleton, D. M.; Kukulj, D.; Radigue, A. P. *J. Chem. Soc., Chem. Commun.* **1999**, 99.

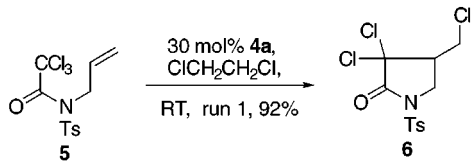
(12) (a) Clark, A. J.; Duncalf, D. J.; Filik, R. P.; Haddleton, D. M., Thomas, G. H.; Wongtap, H. *Tetrahedron Lett.* **1999**, *40*, 3807. (b) Clark, A. J.; Filik, R. P.; Thomas, G. H. *Tetrahedron Lett.* **1999**, *40*, 4885.

10.1021/jo9908896 CCC: $18.00
Published on Web 11/03/1999

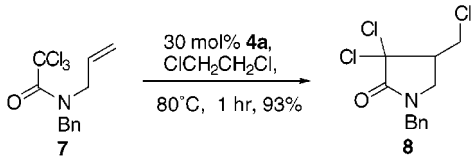
Scheme 1



Scheme 2



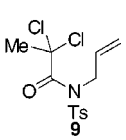
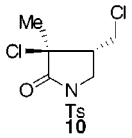
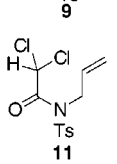
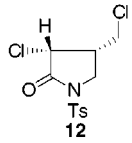
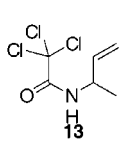
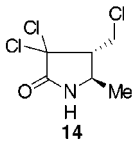
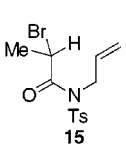
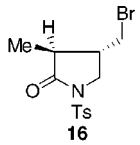
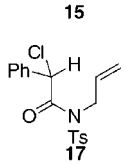
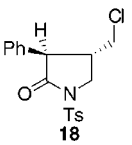
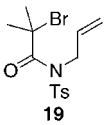
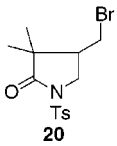
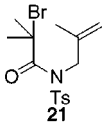
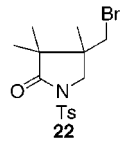
Scheme 3



4.3% and 4.7% copper, respectively. While the copper is likely to be bound directly to the attached ligand, the possibility that it is adsorbed onto the surface of the silica (i.e., bound to the SiOH groups) cannot be completely discounted. However, catalyst **4a** mediated atom-transfer polymerization of methyl methacrylate (toluene, 90 °C, ethyl 2-bromoisobutyrate as initiator) twice as fast as a support prepared from CuBr adsorbed onto the surface of silica that did not contain any attached ligand. The difference in reactivity between these two systems provides tentative evidence that the copper is interacting with the covalently bound ligand in **2** and not with any surface SiOH groups.

Reaction of the solid-supported catalyst **4a** (30 mol % based upon 4.3% copper content) with *N*-tosyl-*N*-allyl-2,2,2-trichloroacetamide[7c] (**5**) in dichloromethane at room temperature for 3 h furnished the expected atom-transfer radical cyclization product **6** in 92% yield after purification (Scheme 2). The catalyst was reclaimed by filtration from the reaction mixture and was then reused with a new batch of **5** under identical conditions (second run; 90% in 18−24 h). After filtration the catalyst was recycled a third time to give **6** in 86% in 24−36 h. The dramatic increase in the time required for complete reaction was not found to be due to any leeching of the copper from the solid support as ICP analysis indicated that even after the third recycling the catalyst still contained 4.3% copper. During the course of these successive runs, the color of the solid support gradually changed from brown to green, and the deactivation of the catalyst is therefore likely due to the formation of an inactive $CuCl_2$ complex. Whether this deactivated copper complex remains bound to the ligand or is extracted from the ligand by the surface silanol groups remains unclear. Cyclization of the less activated *N*-allyl-*N*-benzyl-2,2,2-trichloro precursor[5b] **7** required elevated temperatures but proceeded smoothly to give **8** in high yield after only 1 h at 80 °C (Scheme 3). However, the rates of these cyclizations were much slower than those obtained using 30 mol % CuCl and ligand **1** in dichloromethane under homogeneous catalysis conditions (**5** furnished **6** in less than 1 min at room temperature, while **7** furnished **8** in 2 h at room temperature under these conditions).

Table 1. Atom-Transfer Radical Cyclization of Haloacetamides

Entry	Substrate	Product[a]	Time (hr)	Yield[b] (%)
1	 **9**	 **10**	18	94[c]
2	 **11**	 **12**	24	96[d]
3	 **13**	 **14**	48	75[e]
4	 **15**	 **16**	24	92[f]
5	 **17**	 **18**	22	94[g]
6	 **19**	 **20**	24	92
7	 **21**	 **22**	36	90

[a] All reactions were carried out in $ClCH_2CH_2Cl$ at reflux with 30 mol % catalyst. [b] Combined yield of both diastereomers, major diastereomer shown. [c] de = 64%. [d] de = 55%. [e] de = 72%. [f] de = 64%. [g] de = 66%.

To determine the scope of the new solid-supported methodology, we screened both the catalysts **4a** and **4b** with a number of substrates (Table 1), using 30 mol % catalyst in refluxing 1,2-dichloroethane at 80 °C. While cyclization of the *N*-allyl-*N*-benzyl-2,2,2-trichloro precursor **7** proceeded smoothly at 80 °C, the more deactivated 2,2-dichloroacetamide derivatives **9** (entry 1) and **11** (entry 2) required 18 h (94%, de = 64%) and 24 h (96%, de = 55%), respectively. The major product produced from the cyclization of **9** was identical to that reported for the related Ru-mediated atom-transfer cyclization,[5b] while that from **11** was found to be of the sense opposite that previously reported.[5b] The selectivities were slightly poorer than those obtained using homogeneous catalysis mediated by CuCl and **1**.[12]

Cyclization of the unsubstituted amide **13** (entry 3) under the same reaction conditions also proved unproblematic, although an extended reaction time of 2 days was now required. The diastereoselectivity of the reaction was again similar to that reported for the related CuCl(bipyridine) cyclization.[7c] Having established that the

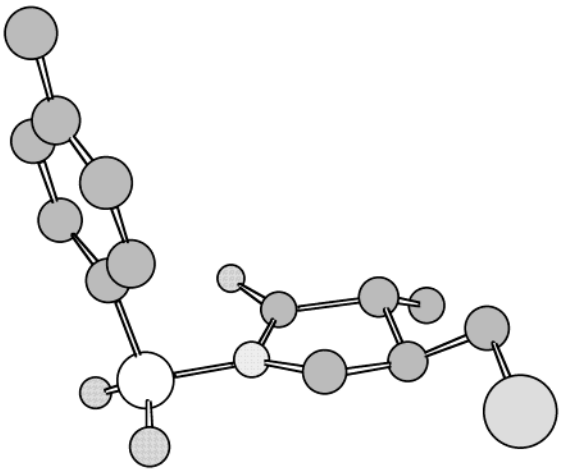
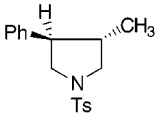


Figure 1. X-ray structure of compound **16**.

solid-supported catalyst was active in mediating the cyclization of the known trichloro- and dichloroacetamides **9**, **11**, and **13**, we next turned our attention to mediating the reaction of monohaloacetamides **15**, **17**, **19**, **21**, and **23**. Pleasingly it was possible to mediate the cyclization of a range of relatively deactivated monohaloacetamides (see Table 1).

Cyclization of mono-halo derivatives **15** and **17** gave rise to the trans isomers **16** and **18** as the major products (entries 4 and 5, Table 1). The stereochemistry of the major isomer **18** was determined by chemical correlation to the known pyrrolidine **25**,[13] while that of **16** was



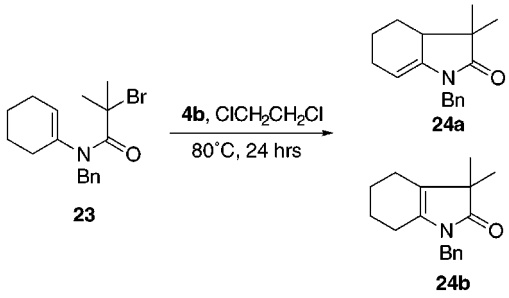
25

determined by X-ray analysis (Figure 1). Cyclization of the dimethyl-substituted precursors **19** and **21** were unproblematic (entries 6 and 7) and gave the expected 5-exo products **20** and **22** in 92% and 90% yields, respectively. The success of the latter cyclizations indicated that steric hindrance at both the radical site and the radical acceptor site were tolerated by the solid-supported reagent. Once again these reactions were much slower than those conducted under homogeneous catalysis using CuBr and ligand **1**. Under these conditions substrates **19** and **21** underwent complete conversion in 12 h at room temperature and did not require heating.

It was also possible to mediate the 5-endo cyclization of enamine **23** in a highly efficient manner. Cyclization proceeded via a 5-endo reaction pathway to give the two alkene derivatives **24a**,**b** in 78% yield as a 1:1 mixture of double bond regioisomers (Scheme 4). While these isomers could be separated by column chromatography, they underwent rapid equilibration back to a 1:1 mixture in $CDCl_3$. Presumably 5-endo cyclization followed by oxidation of the heterostabilized tertiary radical to the cation and elimination of H^+ leads to the observed products.[14]

(13) Denmark, S. E.; Marcin, L. R. *J. Org. Chem.* **1993**, *58*, 3857.
(14) Cassayre, J.; Quiclet-Sire, B.; Saunier, J.-B.; Zard, S. Z. *Tetrahedron* **1998**, *54*, 1029.

Scheme 4



In conclusion we have shown that efficient 5-exo and 5-endo atom-transfer radical cyclizations can be mediated by solid-supported Schiff base copper complexes **4a**,**b** and that these catalysts can be reused, albeit with a substantial drop in activity. It was possible to mediate the cyclization of trichloro- and dichloroacetamides as well as the relatively unactivated monobromoacetamides. The effect of the type of support as well as the tether length used in immobilizing the ligand to the support is currently being examined as is the use of end-capped silica derivatives to remove any potential deactivating copper−SiOH interactions.

Experimental Section

General Procedures. *N*-Allyl-*N*-4-toluenesulfonyl-2,2,2-trichloroacetamide (**5**),[7c] *N*-allyl-*N*-benzyl-2,2,2-trichloroacetamide (**7**),[7c] *N*-allyl-*N*-4-toluenesulfonyl-2,2-dichloro-2-methylacetamide (**9**),[5b] *N*-allyl-*N*-4-toluenesulfonyl-2,2-dichloroacetamide (**11**),[5b] and *N*-(1-buten-3-yl)trichloroacetamide (**13**)[7c] were prepared by literature procedures. 4-Chloromethyl-3,3-dichloro-1-toluene-4-sulfonylpyrrolidin-2-one (**6**),[7c] 4-chloromethyl-3-chloro-3-methyl-1-toluene-4-sulfonylpyrrolidin-2-one (**10**),[5b] 4-chloromethyl-3-chloro-1-toluene-4-sulfonylpyrrolidin-2-one (**12**),[5b] and 4-chloromethyl-3,3-dichloro-5-methylpyrrolidin-2-one (**14**)[7c] exhibited spectroscopic details identical to those already reported. All reagents used were purchased from Sigma-Aldrich Chemical Co. Nuclear magnetic resonance (NMR) spectra were recorded at 250, 300, or 400 MHz with residual solvent as internal standard, infrared spectra (IR) were recorded as solutions ($CHCl_3$) or neat, mass spectra were recorded using either electron impact or chemical ionization (NH_3). All reactions were conducted under nitrogen unless otherwise stated.

General Procedure for the Preparation of *N*-Toluene-4-sulfonamide Cyclization Precursors. 15, **17**, **19**, **and 21**. A solution of *n*-BuLi (2.24 cm^3, 2.5 M in hexanes, 5.6 mmol) was added dropwise over 5 min to a stirred solution of *N*-allyl-*N*-toluenesulfonamide (2.4 mmol) in dry tetrahydrofuran (30 cm^3) at −78 °C under nitrogen, and the mixture was stirred for 30 min at this temperature. The appropriate acid chloride (6.2 mmol) or acid bromide (6.2 mmol) was added and the mixture stirred for 2 h at −78 °C. The reaction was quenched with ammonium chloride (5 cm^3) and allowed to warm to room temperature. The mixture was extracted with CH_2Cl_2 (2 × 30 cm^3) and washed with saturated sodium bicarbonate (2 × 30 cm^3). The organic extracts were dried over $MgSO_4$, and the solvent was evaporated under reduced pressure to give the products **15**, **17**, **19**, and **21**. The crude compounds were purified by column chromatography on silica using petroleum ether−ethyl acetate (4:1) as eluent.

***N*-2-Propenyl-*N*-toluenesulfonyl-2-bromopropionamide (15)**: yield (70%); white crystalline solid; mp 39−40 °C; IR ($CHCl_3$, cm^{-1}) 2925, 1703, 1645, 1596; ^1H NMR (250 MHz, $CDCl_3$) δ 7.84 (2 H, d, J = 8.5 Hz), 7.32 (2 H, d, J = 8.5 Hz), 5.97−5.81 (1 H, m), 5.26−5.20 (2 H, m), 4.82 (1 H, q, J = 6.5 Hz), 4.67 (1 H, ddt, J = 17.4, 4.8, 1.8 Hz), 4.38 (1 H, ddt, J = 17.4, 5.5, 1.8 Hz), 2.42 (3 H, s, Me), 1.71 (3 H, d, J = 6.5 Hz); ^{13}C (75 MHz, $CDCl_3$) δ 169.8, 145.6, 135.9, 133.1, 130.1 (×2), 128.6 (×2), 118.3, 49.1, 40.0, 22.1, 21.5. HRMS calcd for $C_{13}H_{16}BrNO_3S$ 345.0035, found 345.0040; EI-MS *m*/*z* 345 (6%, M^+), 155

(70), 91 (100). Anal. Calcd for $C_{13}H_{16}BrNO_3S$: C, 45.10; H, 4.66; N, 4.05. Found: C, 45.26; H, 4.69; N, 3.74.

***N*-2-Propenyl-*N*-toluenesulfonyl-2-chloro-2-phenylacetamide (17):** yield (65%); white crystalline solid: mp 70−71 °C; IR ($CHCl_3$, cm^{-1}) 2925, 1702, 1593; ^1H NMR (250 MHz, $CDCl_3$) δ 7.69 (2 H, d, J = 8.2 Hz), 7.37−7.25 (7 H, m), 6.13 (1 H, s), 5.86−5.71 (1 H, m), 5.24−5.16 (2 H, m), 4.50−4.27 (2 H, m), 2.43 (3 H, s); ^{13}C (75 MHz, $CDCl_3$) δ 162.7, 145.6, 135.9, 133.1, 132.3, 130.1 (×2), 129.8, 129.4 (×2), 128.9 (×2), 128.6 (×2), 119.0, 58.8, 49.1, 22.1; HRMS calcd for $C_{18}H_{18}ClNO_3S$ 363.0684, found 363.0696; EI-MS *m*/*z* 362 (5), 328 (23), 155 (80), 91 (100). Anal. Calcd for $C_{18}H_{18}ClNO_3S$: C, 59.42; H, 4.95; N, 3.85. Found: C, 59.22; H, 4.95; N, 3.75.

***N*-Allyl-*N*-4-toluenesulfonyl-2-bromo-2-methylpropionamide (19):** yield (72%); white crystalline solid; mp 83−84 °C; IR ($CHCl_3$, cm^{-1}) 2925, 1682, 1597; ^1H NMR (250 MHz, $CDCl_3$) δ 7.83 (2 H, d, J = 8.3 Hz), 7.26 (2 H, d, J = 8.3 Hz), 6.01−5.86 (1 H, m), 5.39−5.26 (2 H, m), 4.91 (2 H, dt, J = 4.6, 1.8 Hz), 2.37 (3 H, s), 1.83 (6 H, s); ^{13}C(67.8 MHz, $CDCl_3$) δ 170.7, 145.0, 136.5, 133.9, 129.6 (×2), 129.2 (×2), 118.6, 57.4, 51.0, 32.4 (×2), 22.1; CI-MS *m*/*z* 360 (72, $M^+ + H$), 282 (100), 218 (55). Anal. Calcd for $C_{14}H_{18}BrNO_3S$: C, 46.67; H, 5.04; N, 3.89. Found: C, 46.36; H, 5.08; N, 3.55.

***N*-2-Methyl-2-propenyl-*N*-toluenesulfonyl-2-bromo-2-methylpropionamide (21):** yield (75%); oil; IR (neat, cm^{-1}) 2936, 1680, 1597; ^1H NMR (250 MHz, $CDCl_3$) δ 7.78 (2 H, d, J = 8.5 Hz), 7.21 (2 H, d, J = 8.5 Hz), 4.95 (2 H, br s), 4.73 (2 H, br s), 2.32 (3 H, s), 1.72 (6 H, s); ^{13}C (67.8 MHz, $CDCl_3$) δ 170.8, 145.1, 140.9, 136.2, 129.5 (×2), 129.1 (×2), 112.4, 58.0, 53.7, 32.4 (×2), 22.1, 20.7; EI-MS *m*/*z* 373 (2, M^+), 155 (82), 91 (100). Anal. Calcd for $C_{15}H_{20}BrNO_3S$: C, 48.13; H, 5.35; N, 3.74. Found: C, 48.19; H, 5.38; N, 3.40.

***N*-Benzyl-2,2-dimethyl-2-bromo-*N*-cyclohex-1-enylacetamide (23).** To cyclohexanone (2.94 g, 30 mmol) in toluene (15 cm^3) was added benzylamine (3.22 g, 30 mmol), and the mixture was stirred under reflux in a Dean−Stark apparatus for 5 h. The solvent was removed in vacuo to give the crude imine (5.1 g, 91%). The crude imine (0.75 g, 4 mmol) was then dissolved in dry toluene (2 cm^3), and added dropwise to a stirred solution of 2-bromo-2-methylpropionyl bromide (1.00 g, 4.4 mmol) at 0 °C. The mixture was stirred for 1 h at room temperature, and then triethylamine (1.21 g 12 mmol) was added at 0 °C. The mixture was stirred for a further 2 h and then poured into saturated sodium carbonate and left for another 3 h at room temperature. The crude mixture was extracted with ether, dried over magnesium sulfate, and concentrated to give a yellow oil. Purification by column chromatography (4:1 petroleum ether−ethyl acetate) furnished the desired product as a clear oil: yield 0.93 g (68%); clear oil; IR ($CHCl_3$, cm^{-1}) 2984, 1627; ^1H NMR (250 MHz, $CDCl_3$) δ 7.28−7.18 (5 H, m), 5.58 (1 H, m), 4.95 (1 H, br s), 4.27 (1 H, br s), 2.18 (2 H, m), 2.02 (8 H, m), 1.67 (2 H, m), 1.55 (2 H, m); ^{13}C (75 MHz, $CDCl_3$) δ 170.8, 138.1, 129.9, 128.8 (×2), 128.6 (×3), 127.6, 58.8, 52.8, 35.0, 33.0, 28.4, 24.9, 22.9, 21.7; CI-MS *m*/*z* 338 ($Br^{81}MH^+$, 33), 336 ($Br^{79}MH^+$, 38), 256 (89), 186 (30), 91 (100); Anal. Calcd for $C_{17}H_{22}BrNO$: C, 60.71; H, 6.54; N, 4.16. Found: C, 60.88; H, 6.61; N, 4.26.

Preparation of Solid Supported Catalysts 4a,b. A mixture of aminopropylated silica (2.00 g, 9% functionalized) and pyridinecarboxaldehyde (2.4 g, 22.5 mmol) in dry toluene (50 cm^3) was heated at reflux for 24 h with a Soxhlet containing crushed 4 Å molecular sieves (5.0 g). The crude orange supported ligand was washed with toluene (3 × 25 cm^3), CH_2Cl_2 (3 × 10 cm^3), and ethanol (5 cm^3), and then dried to constant weight in an oven at 100 °C to give an orange powder. The solid-supported ligand (1.00 g) was added to either CuCl (0.17 g, 1.7 mmol) or CuBr (0.17 g, 1.2 mmol) in dry MeCN (10 cm^3) and the mixture stirred for 30 min. During this time the solid support turned dark brown. The support was filtered under argon and washed repeatedly with dry MeCN (10 × 15 cm^3) to give 1.0812 and 1.1300 g of catalysts **4a** and **4b**, respectively (**4a**, ICP indicated 4.3% Cu; **4b**, ICP indicated 4.7% Cu).

General Procedure for Solid-Supported Atom- Transfer Cyclization Reactions. To a solution of the substrate (0.14 mmol) in 1,2-dichloroethane (1.25 mL) was added the solid-supported catalyst (62 mg for Cl substrates or 58 mg for Br substrates). The mixture was then refluxed for the appropriate time and the solid-supported catalyst filtered off under nitrogen. Removal of the solvent under reduced pressure furnished the cyclization precursors.

***trans*-4-Bromomethyl-3-methyl-1-toluene-4-sulfonylpyrrolidin-2-one (16):** yield 92%; white crystalline solid; mp 124−125 °C; IR ($CHCl_3$, cm^{-1} 2933, 1739, 1597; ^1H NMR (250 MHz, $CDCl_3$) δ 7.85 (2 H, d, J = 8.3 Hz), 7.27 (2 H, d, J = 8.3 Hz), 4.04 (1 H, m), 3.51 (2 H, m), 3.31 (1 H, m), 2.37 (3 H, s), 2.27 (2 H, m), 1.14 (3 H, d, J = 6.8 Hz); ^{13}C (67.8 MHz, $CDCl_3$) δ 174.4, 145.7, 135.3, 130.2 (×2), 128.5 (×2), 49.9, 43.1, 42.2, 33.1, 22.1, 13.9. Anal. Calcd for $C_{13}H_{16}BrNO_3S$: C, 45.10; H, 4.65; N, 4.05. Found: C, 45.44; H, 4.68; N, 3.65.

4-Chloromethyl-3-phenyl-1-toluene-4-sulfonylpyrrolidin-2-one (18): yield 94%; oil; IR ($CHCl_3$, cm^{-1}) 2922, 1736, 1595; ^1H NMR (250 MHz, $CDCl_3$) (major isomer) δ 7.95 (2 H, d, J = 8.6 Hz), 7.24−7.35 (5 H, m), 7.06 (2 H, d, J = 8.6 Hz), 4.20 (1 H, dd J = 10.2, 7.7 Hz), 3.71 (1 H, dd, J = 10.2, 8.7 Hz), 3.64 (1 H, dd, J = 11.6, 3.5 Hz), 3.58 (1 H, d J = 10.5 Hz), 3.50 (1 H, dd, J = 11.6, 6.6 Hz), 2.75−2.84 (1 H, m), 2.44 (3 H, s); ^{13}C (67.8 MHz, $CDCl_3$) δ 172.3, 145.9, 135.3, 133.2, 130.2 (×2), 129.9, 129.0 (×2), 128.9 (×2), 128.8 (×2), 53.0, 48.4, 44.3, 43.2, 22.1; Anal. Calcd for $C_{18}H_{18}ClNO_3S$: C, 59.42; H, 4.99; N, 3.85. EI-MS *m*/*z* 362 (8, $M^+ - H$), 328 (32), 155 (100), 91 (80). Found: C, 59.32; H, 4.93; N, 3.58.

4-Bromomethyl-3,3-dimethyl-1-toluene-4-sulfonylpyrrolidin-2-one (20): yield 92%; white crystalline solid; mp 132−133 °C (from ethyl acetate); IR (Nujol, cm^{-1}) 2923, 1738; ^1H NMR (250 MHz, $CDCl_3$) δ 7.89 (2 H, d, J = 8.2 Hz), 7.32 (2 H, d, J = 8.2 Hz), 4.14 (1 H, dd, J = 10.4, 7.3 Hz), 3.49−3.39 (2 H, m), 3.19 (1 H, t, J = 10.4 Hz), 2.42 (3 H + 1 H, s and m), 1.15 (3 H, s), 0.88 (3 H, s); ^{13}C (67.8 MHz, $CDCl_3$) δ 175.8, 144.3, 133.8, 128.7 (×2), 126.9 (×2), 47.7, 44.4, 44.0, 28.7, 22.4, 20.7, 16.8; HRMS (EI) calcd for $C_{14}H_{18}Br^{79}NO_3S$ 359.0191, found 359.0180; EI-MS *m*/*z* 359 (2, M^+), 279 (32), 149 (100), 91 (34).

4-Bromomethyl-3,3-dimethyl-4-methyl-1-toluene-4-sulfonylpyrrolidin-2-one (22): yield 90%; white crystalline solid; mp 175−176 °C (from ethyl acetate); IR ($CHCl_3$, cm^{-1}) 2936, 1738; ^1H NMR (300 MHz, $CDCl_3$) δ 7.88 (2 H, d, J = 8.3 Hz), 7.31 (2 H, d, J = 8.3 Hz), 3.83 (1 H, d, J = 10.7 Hz), 3.54 (1 H, d, J = 10.7 Hz), 3.06−3.27 (2 H, m), 2.41 (3 H, s), 1.06 (3 H, s), 1.02 (3 H, s), 0.94 (3 H, s). ^{13}C(67.8 MHz, $CDCl_3$) δ 177.4, 145.7, 135.3, 130.1 (×2), 128.3 (×2), 54.5, 48.9, 43.0, 38.9, 22.1, 21.3, 19.5, 18.9; EI-MS *m*/*z* 374 (M^+, 1), 309 (100), 155 (51), 91 (86). Anal. Calcd for $C_{15}H_{20}BrNO_3S$: C, 48.13; H, 5.35; N, 3.74. Found: C, 48.43; H, 5.54; N, 3.58.

1-Benzyl-3,3-dimethyl-1,3,3a,4,5,6-hexahydroindol-2-one (24a) and 1-Benzyl-3,3-dimethyl-1,3,4,5,6,7-hexahydroindol-2-one (24b): yield 78% (1:1 mixture); clear oil; IR (cm^{-1}) (mixture) 2931, 1702, 1654, 1621; EI-MS (mixture) *m*/*z* 255 (M^+, 37), 240 (29), 91 (100); HRMS (EI) calcd for $C_{17}H_{21}NO$ 255.1623, found 255.1625; ^1H NMR (300 MHz, C_6D_6) (**24a**) δ 7.28−7.07 (5H, m), 4.67 (1H, s), 4.65 (1H, d, J = 15.2 Hz), 4.55 (1H, d, J = 15.2 Hz), 2.18 (1H, m), 1.90 (2H, m), 1.61 (1H, m), 1.37 (1H, m), 1.26 (3H, s), 1.14 (2H, m), 0.99 (3H, s); ^{13}C (67.8 MHz, C_6D_6) (**24a**) δ 179.8, 140.3, 138.0, 128.9 (×4), 127.5, 97.6, 46.0, 43.8, 42.9, 23.7, 23.4, 22.6, 22.1, 20.9; ^1H NMR (300 MHz, C_6D_6) (**24b**) δ 7.16−7.07 (5H, m), 4.55 (2H, s), 1.79 (4H, m), 1.40 (4H, m), 1.28 (6H, s); ^{13}C (67.8 MHz, C_6D_6) (**24b**) δ 183.0, 139.5, 134.2, 129.1, 128.9 (×2), 127.4 (×2), 120.4, 46.2, 43.1, 23.0, 22.9, 22.6, 21.8, 20.9.

Supporting Information Available: Solid-state ^{13}C CP/MAS NMR for the solid-supported ligand **2**, ^1H NMR for compounds **12**, **20**, **22**, **24a**, **24b**, and **25**, X-ray data for compound **16**, and experimental procedures for the intermediates in the chemical correlation of **18** to **25**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO9908896