JOC The Journal of Organic Chemistry

Featured Article

pubs.acs.org/joc

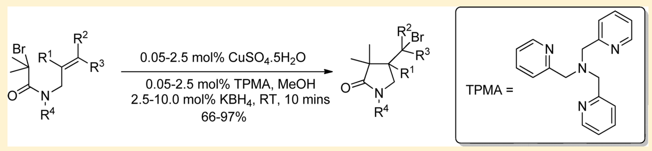
Atom-Transfer Cyclization with $CuSO_4/KBH_4$: A Formal "Activators Generated by Electron Transfer" Process Also Applicable to Atom-Transfer Polymerization

Andrew J. Clark,* Alana E. C. Collis, David J. Fox, Lauren L. Halliwell, Natalie James, Rachel K. O'Reilly, Hemal Parekh, Andrew Ross, Andrew B. Sellars, Helen Willcock, and Paul Wilson

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

Ⓢ *Supporting Information*

ABSTRACT: The 4-*exo* and 5-*exo-trig* atom-transfer cyclizations of **1**, **8a–e**, **9**, **12**, and **13** can be mediated with as little as 0.05 mol % of Cu(TPMA)SO_4·$5H_2O$ in the presence of 2.5 mol % of borohydride salts in 10 min at room temperature in air. This formal "activators generated by electron transfer" (AGET) procedure utilizes a cheap and oxidatively stable copper source ($CuSO_4$·$5H_2O$) and can be carried out in environmentally benign solvents (EtOH). It is possible to alter the product distribution in the 5-*endo* radical–polar crossover reactions of **10a,b** and **11** by tailoring the amount of borohydride. Cyclization onto alkynes **14** and **15** is also possible in only 20 min. Controlled radical polymerization of styrene, with increased rates over conventional atom-transfer radical polymerization (ATRP), can be carried out in a controlled fashion (Mn, PDI) using either CuBr or $CuSO_4$·$5H_2O$ and Bu_4NBH_4.

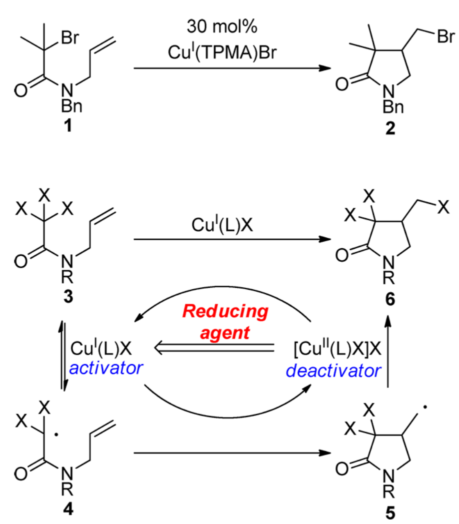


■ INTRODUCTION

Copper(I) halide catalyzed atom-transfer radical addition (ATRA),[1] polymerization (ATRP),[2] and cyclization (ATRC)[3] reactions have been extensively studied. The majority of ATRC reactions utilize CuCl (5–30 mol %) in combination with bipyridine[4] or TMEDA[5] to generate radicals from reactive trichloro- or dichloroacetamide derivatives. Recently, a "ligand free" process was reported for the 5-*exo-trig* cyclization of dichloroacetamides using CuCl (5–20 mol %) in DMF as solvent,[5b] but in general, nitrogen-based ligands are preferred because they are cheap and they provide the scope to fine-tune catalyst reactivity.[6] Polydentate ligands, such as tris(2-pyridylmethyl)amine[7] (TPMA), mediate the cyclization of less reactive monohalides (e.g., **1** → **2**). However, one disadvantage is that elevated temperatures (50–110 °C) and high catalyst loadings (~30 mol %) are still required. Some "difficult" cyclizations (e.g., onto alkynes)[7b] often require stoichiometric amounts of copper mediators. The mechanism of ATRC has been postulated to be similar to ATRA and ATRP in that the $Cu^I(L)X$ complex (the "activator") reversibly abstracts a halogen atom from **3** to give radical **4** which then undergoes cyclization **4** → **5**. The oxidized form of the catalyst ([Cu^{II}(L)X][X]) then transfers a halogen to the more reactive cyclized radical **5** regenerating the *activator*.[8] In related ATRA and ATRP it has been shown that the halide atom transfers occur through a concerted mechanism via an inner-sphere electron transfer.[1a,9]

In the related areas of ATRA and ATRP a number of strategies have been employed to lower catalyst loadings and/or facilitate purification and recycling of copper catalysts in order to make the reactions more industrially attractive.[1,2,10]

Scheme 1. ATRC of 1 and Postulated Mechanism of CuI(L)X-Mediated ATRC



Some of these, such as the use of biphasic fluorous solvents[10b,11] or solid supported reagents[10b,12] have also been employed in ATRC.[13] It has been suggested that relatively high catalyst loadings are required in ATRC because of a buildup of the *deactivator* species ([Cu^{II}(L)X][X]) during the course of the reaction. This may be due to "parasitic" radical–radical coupling, disproportionation, or reductive side reactions.[10]

Received: July 9, 2012
Published: August 6, 2012

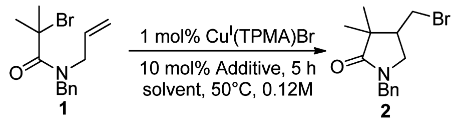
Alternatively, product **6** can be produced by a competitive nonmetal-mediated atom-transfer reaction by direct abstraction of a C−X bond in **3** by the reactive radical **5** or electron transfer; this also leads to accumulation of the *deactivator*.[14] Useful procedures to lower catalyst loadings in ATRP−ATRA include the addition of reducing agents to the catalytic cycle to regenerate the *activator* from the *deactivator*, Scheme 1. The two most common techniques are the "activators regenerated by electron transfer" process (ARGET)[15] and the "initiators for continuous activator regeneration" protocol (ICAR).[16] Both have been extended to cyclization reactions. ARGET−ATRC has been used to reduce copper catalyst loadings to 2 mol % in the cyclization of **3** (X = Cl, Cl, Me, R = Bn) with Cu(PMDETA)Cl and 2.5 mol % of ascorbic acid/Na_2CO_3 as reductant.[5a] Monobromoacetamide **1** can be cyclized using the ICAR−ATRC protocol with as little as 1 mol % of Cu(TPMA)Br if 10 mol % AIBN is used as an additive.[17] A closely related approach to mediate atom-transfer reactions, the "activators generated by electron transfer" protocol (AGET), has been little applied to ATRC reactions.[17] This approach utilizes $[Cu^{II}(L)X][X]$ and a reductant at the start of the reaction rather than the oxidatively less stable $Cu^{I}(L)X$ species.[18] We report a new class of AGET system based upon $CuSO_4{\cdot}5H_2O$ reduction with borohydrides in alcohol solvents. This allows highly efficient atom-transfer cyclization of the monobromoacetamide **1** → **2** with as little as 0.05 mol % of $CuSO_4{\cdot}5H_2O$/2.5 mol % of KBH_4 in air. This challenges the current wisdom that copper halides are required for efficient copper-mediated atom-transfer cyclization and that these should be carried out under an inert atmopshere. We also extend the Cu(L)$SO_4{\cdot}5H_2O$/borohydride concept to the controlled radical polymerization of styrene. Polymerization proceeds at increased rates when borohydride reagents are added but with maintained control of polymerization. It is expected that this new reagent combination will also show utility in ATRA reactions.

■ RESULTS AND DISCUSSION

We screened the ATRC reaction **1** → **2** using typical ARGET reagents previously reported in ATRP namely, phenols,[19] D-glucose,[20] L-ascorbic acid,[21,5a] and hydrazine (Table 1).[22] This allowed us to compare their efficiency as additives to AIBN (ICAR−ATRC)[17] and conventional ATRC. We investigated the reaction in two solvents, CH_2Cl_2 and MeOH. Although ascorbic acid has been reported to mediate the cyclization of dichloroacetamides,[5a] it has not been applied to the cyclization of monosubstituted halides.

Reaction of CuBr with TPMA in MeOH (run 1) produced a faint blue solution indicative of $[Cu^{II}(TPMA)Br][Br]$. It is known that Cu(TPMA)Br disproportionates to give Cu^0 metal and $[Cu^{II}(TPMA)Br][Br]$ in polar solvents such as methanol or DMSO.[23] In ATRP, this dissociation mechanism leads to reaction via a single-electron radical polymerization (SET-LRP) where the actual catalytic species is Cu^0.[24] Reaction of substrate **1** led to 14% conversion over 5 h at 50 °C, indicating that the corresponding single-electron-transfer cyclization process is relatively inefficient but superior to the normal ATRC process (run 2). At 50 °C in MeOH only L-ascorbic acid (run 11) was found to be more reactive than the previously published ICAR reagent AIBN in MeOH. In the phenol series, the order of reactivity paralleled their acidity (4-$CF_3C_6H_4OH$ > C_6H_5OH > 4-$MeOC_6H_4OH$) with better conversions in CH_2Cl_2. On the other hand, sodium borohydride showed remarkable reactivity with 100% conversion in only 10 min at room temperature. As

Table 1. Screening of Additives in the Reaction of 1 → 2



run	additive[a]	solvent	conv (%)	yield (%)
1		MeOH	14	13
2		CH_2Cl_2	5	*b*
3	C_6H_5OH	MeOH	10	*b*
4	C_6H_5OH	CH_2Cl_2	91	83
5	4-$MeOC_6H_4OH$	MeOH	5	*b*
6	4-$MeOC_6H_4OH$	CH_2Cl_2	18	15
7	4-$CF_3C_6H_4OH$	MeOH	19	19
8	4-$CF_3C_6H_4OH$	CH_2Cl_2	100	51
9	AIBN	MeOH	50	43
10	AIBN	CH_2Cl_2	100	84
11	L-ascorbic acid	MeOH	55	9
12	L-ascorbic acid	CH_2Cl_2	19	18
13	NH_2NH_2	MeOH	14	11
14	D-glucose	MeOH	23	17
15	**$NaBH_4$**	**MeOH**	**100**	**82**[c]

[a]A 0.01 M stock solution of Cu(TPMA)Br in MeOH or CH_2Cl_2 was used as the copper source. [b]Not measured due to low conversion. [c]Reaction time 10 min at room temperature.

a consequence, we briefly screened a range of different borohydride reducing agents at room temperature. The most reactive are shown in Table 2.

Table 2. Screening of Borohydrides as Additives in the Reaction of 1 → 2

run	time (min)	additive[a] (mol %)	temp (°C)	conv (%)	yield (%)
1	60	$LiBH_4$ (10)	rt	24	18
2	10	$NaBH_4$ (5)	rt	67	52
3	**10**	**KBH_4 (5)**	**rt**	**100**	**74**
4	10	$NaB(OAc)_3H$ (5)	rt	100	72
5	10	$Ca(BH_4)_2{\cdot}2THF$ (5)	rt	88	73
6	10	$[Bu_4N][BH_4]$ (5)	rt	36	31
7	**60**	**KBH_4 (10)**[b]	**rt**	0	0

[a]A 0.01 M stock solution of Cu(TPMA)Br in MeOH was used as the copper source. [b]No Cu(TPMA)Br was added.

Both the counterion of the borohydride and the solvent proved to be critical for conversion with KBH_4 > $NaB(OAc)_3H$ > $CaBH_4$ > $NaBH_4$ > $[Bu_4N][BH_4]$ > $LiBH_4$ in MeOH. No reactions were observed in dry THF. A range of other conventional 'hydride' reducing agents did not mediate the formation of **2** in either MeOH or dry THF ($NaAlH_4$, $Na(OMe)_2AlH_2$, DIBAL, $Li(^tBuO)_3BH$, $Li(NMe_2)BH_3$, 9-BBN, BH_3.THF, Et_3SiH, or $[Me_4N][BH_4]$). Traditionally borohydride reagents are normally used in 'hydride' delivery processes[25] but less common is their participation in radical chain mechanisms leading to dehalogenation, radical cyclization or addition. Beckwith and others[26] have studied the 5-*exo trig* radical cyclization of aryl halides with both $LiAlH_4$ and $NaBH_4$ and a range of initiators (light, peroxides), while $NaCNBH_3$ has been used to mediate hydroxymethylation of alkyl iodides via alkyl radical addition to CO.[27] It should be highlighted that these reactions were terminated by a reduction ($R^\bullet + BH_4^- \rightarrow RH + BH_3^{\bullet -}$) not by atom transfer. In light of this we carried

dx.doi.org/10.1021/jo301429a | J. Org. Chem. 2012, 77, 6778−6788

out a control reaction (run 7) in which we left out the Cu(TPMA)Br complex. After 1 h there was no conversion and only starting material was recovered, indicating that both Cu(TPMA)Br and KBH_4 were necessary to mediate the cyclization. We also determined that TPMA was a superior ligand to others used in ATRC namely bipy, PMDETA, or Me_6-tren. Results with 1 mol % of Cu(ligand)Br and 10 mol % of KBH_4 indicated the trend in conversion TPMA (100%) > Me_6-tren (77%) > PMDETA (0%) > bipy (0%).

Upon addition of the borohydride reagent, the solution immediately turned from faint blue to brown, then over 4−6 min changed again to a faint green color. This occurred both in the presence and absence of the substrate **1**. As the reactions were carried out in MeOH as solvent, and the initial Cu(TPMA)Br would have disproportionated to $[Cu^{II}(TPMA)Br][Br]$ and Cu^0, we decided to investigate whether other Cu^{II} salts could be used as precatalysts in an AGET−ATRC protocol, Table 3.

Table 3. Screening of Metal Salts in the Reaction of 1 → 2

run	MX (mol %)[a]	KBH_4 (mol %)	conv (%)	yield of B (%)
1	$FeBr_2$ (1)	10	0	*b*
2	$NiBr{\cdot}H_2O$ (1)	10	5	*b*
3	$CrBr_3{\cdot}6H_2O$ (1)	10	0	*b*
4	AgBr (1)	10	7	*b*
5	$CoBr{\cdot}H_2O$ (1)	10	7	*b*
6	CuBr (1)	10	100	68
7	$CuBr_2$ (1)	10	100	84
8	CuBr (0.1)	5	23	18
9	$CuBr_2$ (0.1)	5	0	*b*
10	CuOAc (0.1)	5	16	12
11	$Cu(OAc)_2{\cdot}H_2O$ (0.1)	5	16	14
12	$Cu(CF_3acac)_2$ (0.1)	5	43	33
13	Cu(OTf) (0.1)	5	92	82
14	$Cu(OTf)_2$ (0.1)	5	100	85
15	**$CuSO_4{\cdot}5H_2O$ (0.1)**	**5**	**100**	**97**
16	$Cu(acac)_2$ (0.1)	5	100	83
17	$Cu(ClO_4)_2{\cdot}6H_2O$ (0.1)	5	100	85
18	$Cu(NO_3)_2{\cdot}H_2O$ (0.1)	2.5	32	27
19	$Cu(acac)_2$ (0.05)	2.5	49	42
20	$Cu(OTf)_2$ (0.05)	2.5	47	40
21	$CuSO_4{\cdot}5H_2O$ (0.05)	2.5	40	35
22	$Cu(ClO_4)_2{\cdot}6H_2O$ (0.05)	2.5	54	50

[a]Reactions carried out in MeOH at rt for 10 min at 0.12 M concentration. [b]Not measured due to low conversion.

We also briefly investigated the effect of other metals (Ni, Cr, Co, and Ag) and a range of other Cu^I salts, Table 3. The results indicate that the Cu^{II} salts $Cu(acac)_2$, $Cu(OTf)_2$, $CuSO_4{\cdot}5H_2O$, and $Cu(ClO_4)_2{\cdot}6H_2O$ (runs 14−17) are superior to either CuBr or $CuBr_2$ (runs 8 and 9). In all four cases, atom transfer occurred with 100% conversion with 0.1 mol % of Cu^{II} salt/TPMA and 5 mol % of KBH_4 in 10 min. It was possible to drop the metal loading even further to 0.05 mol % of Cu^{II} salt and 2.5 mol % of KBH_4 (a 600-fold improvement on conventional procedures) (runs 19−22) and still obtain reasonable activities (40−54% conversion). Crucially, it was not necessary to use anhydrous salts or exclude moisture from the reactions. Out of these four salts, $CuSO_4{\cdot}5H_2O$ was chosen for further study because of its low cost (~\$0.16 per kilo).

The nature of the active catalyst is uncertain, but reaction between $Cu(TPMA)SO_4$ and KBH_4 is likely to lead initially to a $Cu(TPMA)BH_4$ complex, eq 1, where some or all of the active hydrogens may be displaced by the solvent (e.g., $Cu(TPMA)B(OMe)_nH_{4-n}$). The facts that the cyclization reactions are severely retarded or do not take place in CH_2Cl_2 or dry THF suggest that this exchange reaction is likely to be important. $CuBH_4$ was first reported in 1952 from the reaction of $LiBH_4$ and CuCl at −20 °C in ether, and on warming to 0 °C it decomposed to copper hydride and diborane.[28] The stoichiometries of the reactions between $LiBH_4$ and $CuCl_2$ at room temperature and at −45 °C were determined by Klingen (eqs 2 and 3).[29] They also discovered that pure $CuBH_4$ decomposed at −12 °C to give Cu^0, diborane, and hydrogen, eq 4.

$$CuSO_4 + 2KBH_4 \underset{rt}{\rightarrow} CuBH_4 + K_2SO_4 + 0.5B_2H_6 + 0.5H_2 \quad (1)$$

$$CuCl_2 + 2LiBH_4 \underset{rt}{\rightarrow} Cu + 2LiCl + B_2H_6 + H_2 \quad (2)$$

$$CuCl_2 + 2LiBH_4 \xrightarrow[-45°C]{} CuBH_4 + 2LiCl + 0.5B_2H_6 + 0.5H_6 \quad (3)$$

$$CuBH_4 \xrightarrow[-12°C]{} Cu + B_2H_6 + H_2 \quad (4)$$

If $Cu(TMPA)BH_4$ is formed upon reaction of $Cu(TPMA)SO_4$ and KBH_4 (eq 1), then this too could decompose to liberate Cu^0 (eq 4). The difference between this and the SET−ATRC process (Table 1, run 1) is that it is not a disproportionation ($Cu^I \rightarrow Cu^{II} + Cu^0$) but ultimately leads to complete production of Cu^0 and gaseous products ($Cu^{II} \rightarrow Cu^I \rightarrow Cu^0$). If this occurs, then a buildup of Cu^0 may be responsible for the enhanced catalysis. Two factors mitigated against this. First, we did not observe the formation of copper metal during the reaction, although this is hardly conclusive. More convincing however, was that no reaction took place when **1** was exposed to a previously prepared and aged solution of $Cu(TPMA)SO_4$ and KBH_4 (45 min). In order to probe this further, we followed the formation and decomposition of the "catalyst" via UV/vis spectrometry in both the presence and absence of substrate **1**. The main area of interest was in the visible region 400−1100 nm. Addition of KBH_4 to the reaction mixture had a profound effect on the absorption profile. The characteristic $Cu^{II}(TPMA)SO_4$ absorbance between 900 and 950 nm was replaced by an absorbance around 400−500 nm. After 30 min, the characteristic Cu^{II} absorptions were found to begin to return and for the next 90 min there was little change.

Recently, more thermally stable complexes containing phenanthroline **7** and phosphine ligands have been developed, with $CuBH_4(Ph_3P)_2$ being commercially available.[30] Typically, phosphine complexes, such as $CuBH_4(Ph_3P)_2$, are much more stable than their phenanthroline counterparts **7** with the former able to undergo outersphere charge transfer to phenanthroquinone.[31] Interestingly, it was possible to mediate the reaction **1** → **2** (50% conversion, 84% mass balance) with 1.0 mol % of $(Ph_3P)_2CuBH_4$ and 20 mol % of KBH_4.

The 2,9-dimethyl-1,10-phenanthroline **7** complex of $CuBH_4$ has been reported to exhibit BH_4^- to phenanthroline ligand-to-ligand charge transfer at 465 nm.[30a] This observation, together with the fact that the transformation **1** → **2** did not occur if

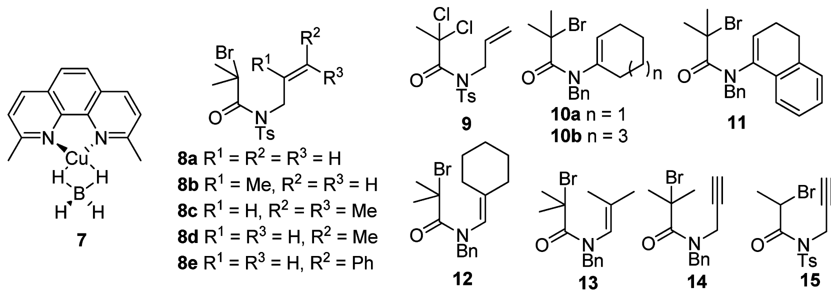
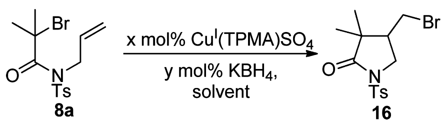


Figure 1. Phenanthroline $CuBH_4$ complex **7** and cyclization substrates **8**−**15**.

aged catalyst was used, indicates that the "active" catalyst is the species responsible for the visible spectrum (400−500 nm) and is similar in structure to **3** (but with TPMA as ligand).

We next investigated the scope and limitation of this new process in a range of 5-*exo-trig* **8**−**9**, 4-*exo-trig* **12**−**13**, 5-*endo-trig* **10**−**11**, and 5-*exo-dig* **14**−**15** cyclizations (Figure 1) as well as in the controlled radical polymerization of styrene. Electron-withdrawing *N*-protecting groups are known to increase the efficiency and yields of 5-*exo* cyclizations of acetamides.[4f,5a] We therefore investigated the cyclization of the *N*-tosyl derivatives **8** and **9**. Interestingly, reaction of **8a** under the standard conditions (0.1 mol % of $Cu(TPMA)SO_4$ and 10 mol % of KBH_4) led to only 33% conversion to **16**. Increasing the time of the reaction to 1 h made no difference to the conversion or yield of the isolated product, presumably because the active complex has fully decomposed after 15−30 min. Increasing the amount of KBH_4 to 50 mol % led to 94% conversion; however, the concentration of the reaction proved to be the key to lowering the amounts of metals required, Table 4. Increasing the concentration to 0.51 M allowed the transformation to occur with just 1 mol % of $Cu(TPMA)SO_4$ and 5 mol % of KBH_4 (run 7). The substrate **8a** was not completely soluble in MeOH at concentrations higher than 0.12 M, and as a consequence, it was necessary to use either EtOH (a renewable solvent) or a mixed solvent of MeOH and CH_2Cl_2 (1−2 drops).

Table 4. Screening of Reaction of 8a → 16



run	$CuSO_4$ (mol %)	conc of **8a** (M)	KBH_4 (mol %)	conv (%)	yield (%)
1	0.1	0.12	10	33	27
2	0.1	0.12	50	94	74
3	2.5	0.16	5	69	60
4	**2.5**	**0.30**[a]	**5**	**100**	**85**
5	1.0	0.30[a]	5	58	49
6	1.0	0.30[b]	5	46	43
7	**1.0**	**0.51**[a]	**5**	**100**	**90**
8	0.5	0.82[a]	5	76	69

[a]Reactions carried out in MeOH over 10 min with one drop of CH_2Cl_2 to help solubilize substrate **8a**. [b]Reaction carried in ethanol.

Reaction of a (0.30 M) solution of **8b**,**c** with 2.5 mol % of $Cu(TPMA)SO_4$ and 5 mol % of KBH_4 for 10 min occurred as expected and gave **17** and **18** in 40% and 70%, respectively. The relatively slower cyclization of **8b** required 10 mol % of KBH_4 to obtain a reasonable yield in 10 min (72%). A similar yield of **19** (74%, 2.0:1.0 mixture of diastereomers, major isomer shown) was obtained by reacting **9** under identical conditions. This compares to a ratio of 5.3:1.0 with 30 mol % $Cu(Me_6$-tren)Cl at rt for 30 min and 2.7:1.0 for $RuCl_2(PPh_3)_3$ in benzene at reflux.[32] The differing ratios are a consequence of the equilibration of both diastereomers of **19** *via* reversible removal/attachment of the α-chloro substituent under the different reaction conditions with different efficiencies. Reaction of both **8d**,**e** furnished **20** (diastereomer ratio, 3.8:1.0) and **21** (diastereomer ratio, 5.0:1.0) in 91% and 80% yields, respectively. In these cases the diastereoselectivities (major isomer shown) are similar to those previously reported using the ICAR procedure (**20**, 3.5:1.0 and **21**, 6.0:1.0).[17] Here the different ratios are likely due to the difference in temperature between the two procedures (AGET = rt, ICAR = 50 °C.)[17] It was possible to crystallize the major isomer of **21** and show from X-ray crystallography that it exhibited the stereochemistry shown in Figure 2.

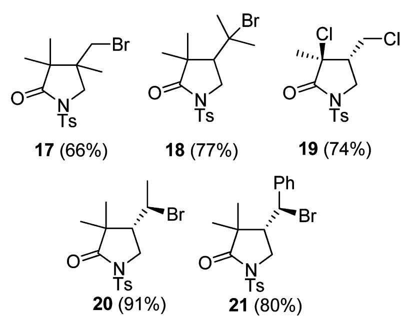
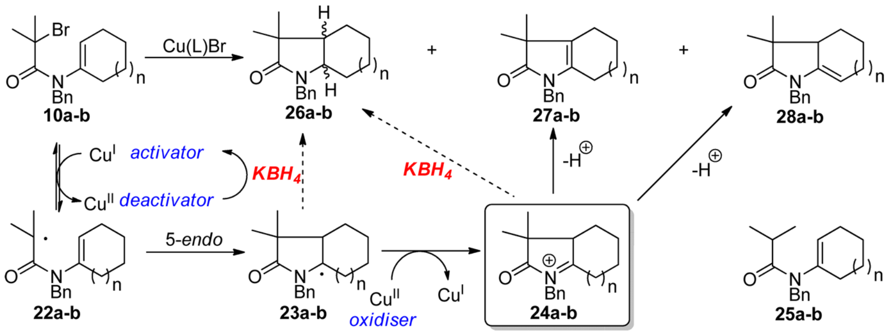


Figure 2. Products from the cyclization of substrates **8b**−**e** and **9**.

The ability to sequence a radical transformation followed by a separate reaction mediated by a polar (anionic or cationic) intermediate is known as a radical−polar crossover reaction.[33,34] There are two classes of radical−polar crossover reaction; an oxidative radical−polar crossover reaction, where the intermediate radical is oxidized to a cation, and a reductive reaction where the intermediate radical is reduced to an anion. These transformations can be mediated by metals[35] or by electron transfer from organic systems.[34] In particular, 5-*endo* oxidative transformations have been mediated mainly by metal complexes (e.g., manganese,[36] copper,[37,13a] and nickel[38]). Hence, reaction of **10a** with 30 mol % of $Cu(Me_6$-Tren)Br in CH_2Cl_2 furnishes a 1:1 ratio of **27a** and **28a** in 82% yield.[37b] These reactions are generally thought to follow the mechanism outlined in Scheme 2. Initiation by Cu(L)Br furnishes radical **22** which is predisposed to cyclize in a 5-*endo* fashion to give initially **23** but after oxidation to the acyl iminium ion **24**, (by rapid electron transfer from the Cu(L)Br[Br] formed in the

Scheme 2. Radical−polar Crossover Reaction of 10a and Possible Mechanism in the Presence of KBH_4



first step), is terminated by elimination to give **27a** and **28a**. Large amounts of copper salts (30−100 mol %) are normally required to mediate these 5-*endo* cyclizations, and this has been postulated to be necessary due to the release of HBr during the reaction;[5l] in fact, stoichiometric amounts of K_2CO_3 or Na_2CO_3 are sometimes added to the reactions to increase efficiency.[5a] We were intrigued to determine if it would be possible to mediate these transformations reductively after oxidation by in situ trapping of the acyl iminium ion with the borohydride reagent (KBH_4 or $Cu(TPMA)BH_4$). Of course, the excess borohydride might suppress oxidation of **23** → **24**, but this would not be problematic for the overall process because (i) intermediate radical **23** may be reduced directly by BH_4 in a process similar to that described by Beckwith[26] and (ii) the activator will be regenerated by borohydride reduction not oxidation. Another complication is that the acyl iminium ion intermediate **24** may be trapped by the nucleophilic solvent required (ROH).

Initial reactions focused on reacting a 0.12 M solution of **10a,b** and **11** in MeOH with 1 mol % of $Cu(TPMA)SO_4$ and 1 equiv of KBH_4 in MeOH at room temperature for 30 min. For **10b**, minor amounts of the reduced compound **26b** (as a 1:1 mixture of diastereomers in 11% yield) and oxidatively terminated enamide **27b** (6%) were isolated with the major product being **28b** (69%). Similar results were found for **10a** and **11** under the same reaction conditions (Table 5).

Table 5. Reactions of 10a,b

compd	conc[a] (M)	KBH_4 (equiv)	yield (%) of 25:26:27:28	ratio of 27 + 28:26[b]
10a	0.12	1	0:12:24:47	6.0:1.0
10b	0.12	1	0:11:6:69	6.5:1.0
11	0.12	1	18:52[c]	2.9:1.0[d]
10b	0.12	10	30:32:16[e]	2.0:1.0
10b	0.02	1	82:10:3:5[e]	1.5:1.0

[a]MeOH as solvent, 1.0 mol % of $Cu(TPMA)SO_4$. [b]Ratio determined from 400 MHz ^1H NMR of crude mixture. [c]Yields of **29**:**30**. [d]Ratio of **30**:**29** determined from 400 MHz ^1H NMR of crude mixture. [e]Ratio determined from 400 MHz ^1H NMR spectroscopy.

Increasing the amount of KBH_4 to 10 equiv in the reaction of **10b**, in the hope of competitively trapping out acyl iminium ion **24b** reductively to give **26b**, was partially successful (**26b**, 32%), but a significant amount of the precyclized reduced product **25b** was now also isolated (30%). Decreasing the concentration of the reaction (0.12 M → 0.02 M) now led to **25b** as the major product (83%), although minor amounts of **26b** (10%) and **27b**−**28b** (8%, 1.7:1 = **27b**:**28b**) were also detected in the crude ^1H NMR spectrum. It was not possible to find reaction conditions that led to high yields of **26b** but by changing the solvent to EtOH it was possible to suppress both reductive cyclization **26b** and precyclization **25b** to less than 5%. No trapping of the intermediate acyl iminium ion by MeOH or EtOH was detected. Reaction of tetralone derivative **11** with 2.5 mol % of $Cu(TPMA)SO_4$ and 20 mol % of KBH_4 occurred with a 25% conversion only (1:2.9 ratio of **29**:**30**). It seems that 1 equiv of KBH_4 is required for 100% conversions of the substrates **10a,b** and **11**. The fact that significant reductive termination is not observed could suggest that KBH_4 is acting in a dual role as a Cu(II) reductant and as a scavenger of the HBr liberated in the radical−polar crossover reaction (Figure 3).

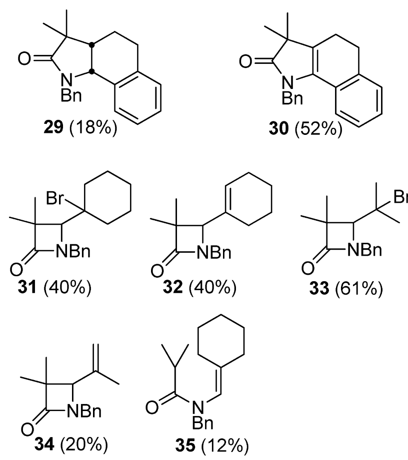
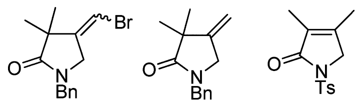


Figure 3. Products from the cyclizations of substrates **11**−**13**.

The 4-*exo* substrates **12** and **13** were next examined to apply the chemistry to *β*-lactam synthesis. Examination of the crude NMR spectra obtained during the cyclization of **12** indicated that the atom-transfer product **31** was the major product; however, during chromatography elimination of HBr from the tertiary bromide partially occurred, which also led to the isolation of the alkene **32**. This was also observed in the reaction of **13**. If 1 equivalent of KBH_4 was used in the reaction of **12** a minor amount of the reduced precyclized compound **35** (12%) was also produced (**31** 40%, **32** 40%, **35** 12%).

We next turned our attention to the previously reported 5-*exo-dig* cyclizations of the substrates **14** and **15** (Figure 4). They have been reported to be approximately 100 times slower than the corresponding 5-*exo* cyclization of **8a**.[7b] Using standard conditions (30 mol % of Cu(TPMA)Br), it was necessary to reflux **14** at 50 °C for 24 h for 100% conversion.



36 37 38

Figure 4. Products from the cyclizations of substrates **14** and **15**.

With the published ICAR–ATRC protocol,[17] it was possible to lower the loading to 1 mol % of Cu(TPMA)Br with 10 mol % of AIBN, but it was necessary to heat for 24 h in toluene at reflux (110 °C) to obtain 52% yield of **36**:**37** as a 1:1 mixture. Using the new protocol, 2.5 mol % of Cu(TPMA)SO_4 and 20 mol % of KBH_4 were required to give a 90% conversion (ratio of **36**:**37** = 1:1) in only 20 min at rt. Decreasing the amount of $CuSO_4$ to 1.0 mol % but increasing the amount of KBH_4 to 100 mol % doubled the relative amount of reduction product (67%, **36**:**37** = 1:2). Cyclization of the less reactive secondary bromide **15** under the same reaction conditions furnished sulphonamide **38** in 45% yield after 10 min at rt.

We next investigated the polymerization (ATRP)[2] of styrene with either Cu(NBipy)Br or Cu(NBipy)$SO_4 \cdot 5H_2O$ with Bu_4NBH_4 (0.1 equiv with respect to Cu salt) as the borohydride reagent and compared the results to that obtained without added Bu_4NBH_4.[39] Even though Bu_4NBH_4 proved to be one of the least efficient borohydride salts screened in the reaction of **1** (Table, 2), it was necessary to use a reagent that dissolved in the bulk monomer. Initial studies focused on the reaction of Cu(NBipy)Br, with styrene in bulk at 110 °C with ethyl(bromoisobutyrate) as initiator (180.0 equiv of styrene, 1.00 equiv of initiator, 1.02 equiv of CuBr, 2.56 equiv of NBipy), with or without added Bu_4NBH_4 (0.10 equiv). The rate of polymerization was followed by removal of aliquots for analysis by ^{1}H NMR to calculate conversion of monomer. These aliquots were then passed through a plug of silica gel to remove the Cu(NBipy)Br complex and were subsequently analyzed by GPC analysis. The kinetic plot (Figure 5) and molecular weight plot (Figure 6) prove that the polymerization is well-controlled, the linear first-order kinetic plot of monomer consumption indicates a constant number of active species, and the linear increase of molecular weight with conversion is characteristic of a controlled polymerization process. The addition of Bu_4NBH_4 increased the rate of polymerization, which is consistent with other reported reactions where reducing agents have been added.[40] After 5 h the PDI of the polymer obtained with added Bu_4NBH_4 was slightly increased compared to the standard system (1.20 compared to 1.12) as was the M_n (Bu_4NBH_4 = 16.8 KDa, no Bu_4NBH_4 = 11.3 KDa). The increase in PDI may be due to the increase in observed rate compared to the standard system which leads to a loss of control in the polymerization.

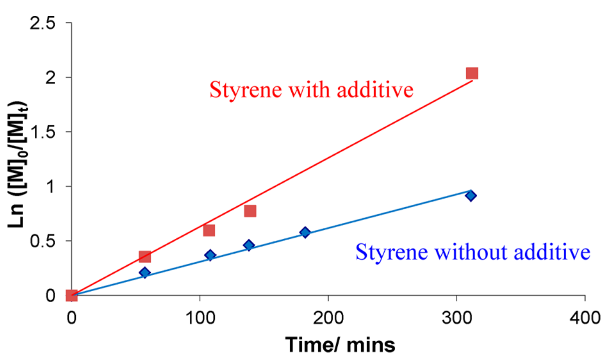


Figure 5. Linear first-order kinetic plots of monomer consumption for the polymerization of styrene with and without Bu_4NBH_4 (0.1 equiv with respect to Cu(NBipy)Br).

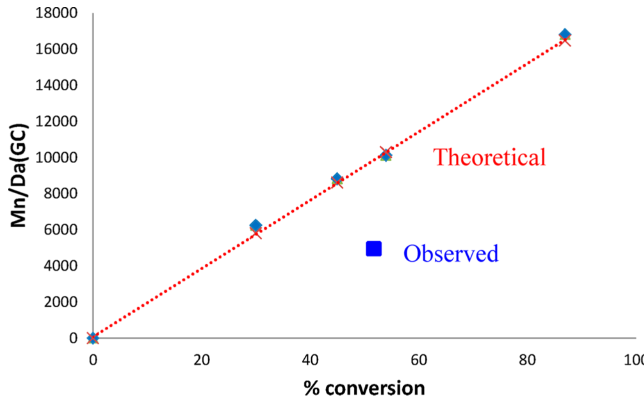


Figure 6. Plot of M_n versus percent conversion for polymerization of styrene with 0.1 equiv of Bu_4NBH_4 additive.

Changing the copper source to Cu(NBipy)$SO_4 \cdot 5H_2O$ for the bulk styrene reaction (100.0 equiv of styrene, 1.00 equiv of initiator, 1.02 equiv of $CuSO_4 \cdot 5H_2O$, 2.56 equiv of NBipy, 0.4 equiv of Bu_4NBH_4) again resulted in an increased rate of polymerization compared to the standard system (Cu(NBipy)Br without Bu_4NBH_4)[39] and yielded a relatively well-defined polymer with good correlation between theoretical and measured molecular weight. After 5 h, the PDI of the resultant polymer was slightly increased compared to the standard system (1.19). End group analysis by ^{1}H NMR (64% end group fidelity) and elemental analysis (53% end group fidelity) indicated the expected termination by a bromine atom for the $CuSO_4 \cdot 5H_2O$-mediated polymerization, and no sulfur was detected by elemental analysis. The relatively low end group fidelity may indicate that reduction of the end group is occurring; this would also explain the slight rise in PDI compared to the standard system of polymerization. No polymerization was observed with Cu(NBipy)$SO_4 \cdot 5H_2O$ in the absence of Bu_4NBH_4 or with Bu_4NBH_4 in the absence of Cu(NBipy)$SO_4 \cdot 5H_2O$.

■ CONCLUSIONS

In conclusion, we have shown that KBH_4 is an efficient AGET reagent for ATRC when used in conjunction with Cu(TPMA)-$SO_4 \cdot 5H_2O$. While conventional ATRC of **1** requires long reaction times (24 h) and high copper loadings (30 mol % of Cu(TPMA)Br), the same reaction can be mediated with 0.1 mol % of Cu(TPMA)$SO_4 \cdot 5H_2O$ in the presence of 5 mol % of KBH_4 in only 10 min (a 300 decrease of copper catalyst and a 144 decrease in reaction time). It is applicable to a range of 5-*exo* and 4-*exo* cyclizations as well as 5-*endo* cyclizations. While the "reductive" conditions can be used to mediate oxidative radical-polar crossover reactions, it was not possible to alter the reaction manifold to terminate the cyclizations reductively by increasing the amount of borohydride added without significant side reactions. Cyclization onto alkynes (traditionally difficult to achieve with copper catalysis 24 h, 110 °C)[7b] is possible in only 20 min at room temperature, although higher amounts of metal species are required to facilitate acceptable yields. Eglinton or Hay[41] type copper mediated sp/sp coupling reaction of terminal alkynes (typically observed in some ATRC procedures) were not observed. For 4-*exo* and 5-*exo*

dx.doi.org/10.1021/jo301429a | J. Org. Chem. 2012, 77, 6778−6788

cyclizations high loadings of KBH_4 (1 equivalent) led to reduced starting amides as byproduct (e.g., **12** → **35**); however, no reduced products were observed when low loadings of KBH_4 were used (<5 mol %). We have extended the concept to ATRP, and have shown that styrene can be polymerized in a controlled fashion with good control over M_n and PDI. The addition of Bu_4NBH_4 as reducing agent causes an increase in the rate of polymerization, although the PDI in the reaction of styrene with $Cu(TPMA)SO_4{\cdot}5H_2O$ or Cu(Nbipy)Br is slightly higher than conventional reactions without borohydride additives. This new class of AGET reagent system may also have application in ATRA and it is more efficient in ATRC than conventional ARGET and AGET additives routinely employed in these areas.[5a,17]

EXPERIMENTAL SECTION

General Methods. ^{1}H NMR were recorded at 300, 400, or 500 MHz and ^{13}C NMR recorded at 75.5, 100, or 125 MHz with residual solvent as internal standard; infrared spectra (IR) were recorded as neat solutions or solids; and mass spectra were recorded using electron impact or electrospray ionization techniques. Gel permeation chromatography (GPC) was carried out using 2X mixed D columns and a 5 μm guard column.

Synthesis of Known Compounds by Literature Procedures. *N*-Allyl-*N*-(2-bromo-2-methylpropionyl)-4-methylbenzenesulfonamide **8a**,[7e] 2-bromo-2-methyl-*N*-[(4-methylphenyl)sulfonyl]-*N*-(2-methyl-2-propenyl)propanamide **8b**,[7e] *N*-allyl-*N*-(2,2-dichloro-2-methylpropionyl)-4-methylbenzenesulfonamide **9**,[7e] *N*-benzyl-2-bromo-*N*-(cyclohex-1-enyl)-2-methylpropionamide **10a**,[42] *N*-benzyl-2-bromo-*N*-(cyclooct-1-enyl)-2-methylpropionamide **10b**,[43] *N*-benzyl-2-bromo-*N*-(3,4-dihydronaphthalen-1-yl)-2-methylpropionamide **11**,[43] and *N*-benzyl-2-bromo-*N*-(methylenecyclohexane)-2-methylpropionamide **12**[13a] were prepared by literature procedures and exhibited ^{1}H and ^{13}C NMR spectroscopic details identical to those previously reported. ^{1}H NMR was used to check the purity of all the compounds.

General Procedure for the Formation of *N*-Benzylpropanamides 1 and 14. Et_3N (0.7 mL, 5.0 mmol) was added to a solution of *N*-allyl-*N*-benzylamine (0.43 g, 2.92 mmol) or *N*-2-propyny-*N*-benzylamine (0.42 g, 2.92 mmol) in Et_2O (25 mL) at 0 °C. After 20 min, 2-bromoisobutyryl bromide (0.36 mL, 2.92 mmol) was added, and the reaction mixture was allowed to warm to room temperature. After 4 h, the reaction was quenched with satd NH_4Cl (10 mL) and partitioned between satd $NaHCO_3$ (50 mL) and Et_2O (50 mL). The organic layer was collected, and the aqueous layer was extracted using Et_2O (2 × 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to yield **1** and **14** as a mixture of rotamers.

N-Allyl-N-benzyl-2-bromo-2-methylpropanamide (1): yield 0.72 g (84%), colorless oil; mixture of rotamers; R_f (1:1 petroleum ether/EtOAc) 0.84; ν_{max} (film)/cm^{-1} 2980, 2932, 1633; δ_H (toluene-d_8, 400 MHz, 363 K) 7.16−7.06 (5H, m), 5.69−5.61 (1H, m) 5.01 (1H, dd, *J* 10.3, 1.4 Hz), 4.98 (1H, dd, *J* 17.2, 1.4 Hz), 4.67 (2H, s), 4.02 (2H, d, *J* 5.5 Hz), 1.86 (6H, s); δ_C (toluene-d_8, 125 MHz, 363 K) 170.3, 137.6, 133.5, 128.7, 127.8, 127.4, 117.4, 57.7, 50.6, 50.3, 33.1; *m*/*z* (ESI) 318 ([M]$^+$Na), found [M]$^+$Na 318.0465 $C_{14}H_{18}BrNONa$ requires 318.0469.

2-Bromo-2-methyl-N-(phenylmethyl)-N-2-propynylpropanamide (14): yield 0.86 g (99%), pale yellow oil; mixture of rotamers; R_f (1:1 petroleum ether/EtOAc) 0.91; ν_{max} (film)/cm^{-1} 2980, 2932, 1636; δ_H ($CDCl_3$, 300 MHz) 7.35−7.22 (5H, m), 4.87 (2H, br s), 4.27 (2H, br s), 2.24 (1H, s), 2.00 (6H, s); δ_C (toluene-d_8, 125 MHz, 363K) 169.4, 137.0, 128.2, 127.6, 127.2, 72.0, 56.8, 50.3, 37.1, 32.4, 31.8; *m*/*z* (CI) 293 [M]$^+$, found [M]$^+$ 293.0420 $C_{14}H_{16}BrNO$ requires 293.0415.

General Procedure for the Formation of 2-Bromo-2-methyl-*N*-[(4-methylphenyl)sulfonyl]propanamides 8c−e. To a suspension of K_2CO_3 (2.80 g, 20.0 mmol) in acetone (100 mL) at room temperature was added *p*-toluenesulfonamide (3.40 g, 20.0 mmol). After 15 min, either 3,3-dimethylallyl bromide (to give **8c**), crotyl bromide (to give **8d**), or cinnamyl bromide (to give **8e**) (16.1 mmol) was added. The reaction was stirred overnight and the acetone removed in vacuo. The resulting residue was dissolved in a 1:1 v/v ether/water mixture (100 mL) and extracted with ether (2 × 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to yield the crude sulfonamides. *n*-BuLi (1.6 M in hexanes, 3.75 mL, 6.0 mmol) was added dropwise to the crude sulfonamide (5.3 mmol) in dry THF at −78 °C. After 30 min, 2-bromoisobutyryl bromide (0.87 mL, 7.0 mmol) was added. The reaction was allowed to warm room temperature overnight. The reaction was quenched with saturated NH_4Cl (10 mL) and partitioned between saturated $NaHCO_3$ (100 mL) and DCM (100 mL). The residue was extracted using DCM (2 × 100 mL), and the combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to yield a crude product which was purified by flash chromatography.

2-Bromo-2-methyl-N-[(4-methylphenyl)sulfonyl]-N-2-prenylpropanamide (8c): yield 1.07 g (53%); white solid; mp 86−88 °C; R_f (3:1 petroleum ether/EtOAc) 0.64; ν_{max} (film)/cm^{-1} 2969, 2934, 1676; δ_H ($CDCl_3$, 300 MHz) 7.85 (2H, d, *J* 8.3 Hz), 7.28 (2H, d, *J* 8.3 Hz), 5.24−5.22 (1H, m), 4.90 (2H, d, *J* 6.0 Hz), 2.42 (3H, s), 1.90 (6H, s), 1.76 (6H, d, *J* 4.8 Hz); δ_C ($CDCl_3$, 75.5 MHz) 170.2, 143.9, 135.9, 135.6, 128.5, 128.3, 119.9, 56.2, 46.8, 31.2, 31.1, 25.0, 21.1, 17.8; *m*/*z* (ESI) 410 ([M]$^+$Na), found ([M]$^+$Na) 410.0396, $C_{16}H_{22}BrNO_3S$ requires ([M]$^+$Na) 410.0401.

2-Bromo-2-methyl-N-[(4-methylphenyl)sulfonyl]-N-2-crotylpropanamide (8d): yield 1.14 g (56%), 6:1 *E*:*Z* isomers; white solid; mp 80−81 °C; R_f (3:1 petroleum ether/EtOAc) 0.64; ν_{max} (film)/cm^{-1} 2938, 1677; δ_H ($CDCl_3$, 300 MHz) 7.85 (2H, d, *J* 8.3 Hz), 7.28 (2H, d, *J* 8.3 Hz), 5.86−5.78 (1H, m), 5.61−5.53 (1H, m), 4.85 (2H, d, *J* 5.4 Hz), 2.41 (3H, s). 1.88 (6H, s), 1.73 (3H, dd, *J* 6.3, 1.2 Hz); δ_C ($CDCl_3$, 75.5 MHz) 170.7, 144.6, 136.5, 130.3, 129.2, 129.1, 126.2, 57.1, 50.3, 32.1, 21.8, 17.9; *m*/*z* (ESI) 396 ([M]$^+$Na), found ([M]$^+$Na) 396.0239, $C_{15}H_{20}BrNO_3S$ requires ([M]$^+$Na) 396.0245.

2-Bromo-2-methyl-N-[(4-methylphenyl)sulfonyl]-N-2-cinnamylpropanamide (8e): yield 1.32 g (56%); yellow solid; mp 101−102 °C; R_f (3:1 petroleum ether/EtOAc) 0.62; ν_{max} (film)/cm^{-1} 2968, 2923, 1676; δ_H ($CDCl_3$, 300 MHz) 7.88 (2H, d, *J* 8.4 Hz), 7.32−7.25 (7H, m), 6.69 (1H, dt, *J* 16.1, 1.2 Hz), 6.25 (1H, dt, *J* 16.1, 5.7 Hz), 5.11 (2H, dd, *J* 5.7, 1.5 Hz), 2.41 (3H, s), 1.94 (6H, s); δ_C ($CDCl_3$, 75.5 MHz) 170.6, 144.7, 136.2, 136.0, 133.7, 129.2, 129.1, 128.7, 128.1, 126.6, 124.4, 56.9, 50.5, 32.0, 21.7; *m*/*z* (ESI) 458 ([M]$^+$Na), found ([M]$^+$Na) 458.0396, $C_{20}H_{22}BrNO_3S$ requires ([M]$^+$Na) 458.0401.

***N*-Benzyl-2-bromo-*N*-isobutenyl-2-methylpropionamide (13).**[7c] Benzylamine (2.94 g, 27.5 mmol) and isobutyraldehyde (1.98 g, 27.5 mmol) in dry toluene were heated using a Dean−Stark apparatus overnight. The crude mixture was cooled to 0 °C, and 2-bromoisobutyryl bromide (6.33 g, 27.5 mmol) was added followed by diethylaniline (4.10 g, 27.5 mmol). After 4 h, the reaction was quenched with 2 M HCl (50 mL), extracted with Et_2O (3 × 100 mL), dried ($MgSO_4$), filtered, and evaporated to dryness. The crude product was purified by flash chromatography, 9:1 petroleum ether/EtOAc to afford **13**: yield 4.84 g, 57%), clear oil; R_f (3:1 petroleum ether/EtOAc) 0.74; ν_{max} (film)/cm^{-1} 2975, 2933, 1637; δ_H ($CDCl_3$, 400 MHz) 7.38−7.27 (5H, m), 6.36 (1H, s), 4.72 (2H, s), 1.99 (6H, s), 1.75 (3H, s), 1.63 (3H, s); δ_C ($CDCl_3$, 100 MHz) 170.6, 137.3, 134.9, 128.4, 127.9, 127.2, 125.8, 58.3, 54.4, 32.1, 21.8, 18.2; *m*/*z* (ESI) 334 ([M]$^+$Na), 310 [M]$^+$, found ([M]$^+$Na) 332.0620, $C_{15}H_{20}BrNO$ requires ([M]$^+$Na) 332.0626.

2-Bromo-*N*-[(4-methylphenyl)sulfonyl]-*N*-2-propynylpropanamide (15). 4-Methyl-*N*-prop-2-ynylpropanamide (1.02 g, 4.9 mmol) was dissolved in dry THF (50 mL) and cooled to −78 °C. *n*-BuLi (1.6 M in hexanes, 4.70 mL, 7.5 mmol) was added dropwise. After 30 min, 2-bromoisbutyryl bromide (0.79 mL, 7.5 mmol) was added. The reaction was allowed to warm room temperature overnight. The reaction was quenched with saturated NH_4Cl (10 mL) and partitioned between saturated $NaHCO_3$ (100 mL) and DCM (100 mL). The residue was extracted using DCM (2 × 100 mL), and the combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to yield a crude product which was purified by flash chromatography (5:1 petroleum ether/EtOAc): yield 0.89 g, (53%), pale yellow oil; R_f (3:1 petroleum ether/EtOAc) 0.50; ν_{max} (film)/cm^{-1} 2972, 2937, 1698, 1599; δ_H ($CDCl_3$, 300 MHz) 7.91 (2H, d, *J* 8.4 Hz,) 7.34 (2H, d, *J* 8.4 Hz), 4.97 (1H, q, *J* 6.6 Hz), 4.84 (1H, dd, *J* 18.6, 2.5 Hz), 4.60 (1H, dd, *J* 18.6, 2.5 Hz), 2.44 (3H, s), 2.34 (1H, t, *J* 2.5 Hz), 1.74 (3H, d, *J* 6.6 Hz); δ_C ($CDCl_3$, 75.5 MHz) 168.9, 145.5, 135.3, 129.8, 128.4, 77.7, 73.5, 39.3, 35.7, 21.1, 20.2; *m/z* (ESI) 365 ([M]$^+$Na), found ([M]$^+$Na) 365.9770, $C_{13}H_{14}BrNO_3S$ requires ([M]$^+$Na) 365.9775.

General Procedure for $CuSO_4 \cdot 5H_2O/KBH_4$-Mediated Cyclization. A 0.01 M stock solution of $CuSO_4 \cdot 5H_2O$ and TPA in MeOH was prepared, and the appropriate amount was added to the substrate (typically 0.5−2.0 mmol) dissolved in the preferred amount of MeOH to make up the desired concentration (typically 0.12−0.30 M). If necessary, 1−2 drops of DCM were added to solubilize the substrate (up to a 6:1 ratio of MeOH/DCM). To this solution was added KBH_4 (typically 2.5−100 mol %). An immediate color change was observed. The mixture was allowed to stir at room temperature for 10−30 min. The mixture was filtered through a silica plug using DCM (50 mL) as eluent, and the resulting filtrate was washed with water (30 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo to give the crude product, which was further purified by chromatography. A typical example is given below for the synthesis of compound **2**.

3,3-Dimethyl-4-bromomethyl-1-(phenylmethyl)pyrrolidin-2-one (2). A stock solution of 0.01 M Cu(TPMA)SO_4 was prepared (249 mg of $CuSO_4 \cdot 5H_2O$ and 276 mg of TPMA were dissolved in 100 mL of MeOH in a volumetric flask). To substrate **1** (106 mg, 0.36 mmol) in MeOH (2.6 mL) was added Cu(TPMA)SO_4 (1 mol %, 3.6 × 10^{-3} mmol, 0.36 mL of 0.01 M stock solution) followed by KBH_4 (∼10 mol %, 2 mg). After 15 min the crude solution was filtered through a silica plug (50 mL DCM) and washed with water (30 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo to give the crude product which was further purified by chromatography on silica (3:1 petroleum ether/EtOAc): yield 76 mg, (72%), colorless oil; R_f (3:1 petroleum ether/EtOAc) 0.30; ν_{max} (film)/cm^{-1} 2964, 1684; δ_H ($CDCl_3$, 300 MHz) 7.32−7.15 (5H, m, Ar), 4.52 (1H, d, *J* 14.4 Hz), 4.35 (1H, d, *J* 14.4 Hz), 3.46 (1H, dd, *J* 10.0, 4.8 Hz), 3.35 (1H, dd, *J* 10.0, 7.5 Hz), 3.22 (1H, t, *J* 10.5 Hz), 2.88 (1H, t, *J* 10.2 Hz), 2.40 (1H, m), 1.24 (3H, s), 0.99 (3H, s); δ_C ($CDCl_3$, 75.5 MHz) 178.5, 136.3, 128.8, 128.1, 127.7, 48.9, 46.7, 46.1, 44.0, 31.5, 24.3, 19.6, found ([M]$^+$Na) 318.0464, $C_{14}H_{18}BrNO$ requires ([M]$^+$Na) 318.0469.

3,3-Dimethyl-4-bromomethyl-1-(*p*-toluenesulfonyl)-pyrrolidin-2-one (16). Conditions: Cu(TPMA)SO_4 1.0 mol %, KBH_4 5 mol % (3:1 MeOH/DCM, 0.50M); yield 109 mg (90%); white solid; mp 131−132 °C; spectroscopic data matched that previously reported;[7e] R_f (3:1 petroleum ether/EtOAc) 0.21; ν_{max} (film)/cm^{-1} 2960, 1757, 1595; δ_H ($CDCl_3$, 400 MHz) 7.92 (2H, d, *J* 8.3 Hz), 7.34 (2H, d, *J* 8.3 Hz), 4.15 (1H, dd, *J* 10.3, 7.4 Hz), 3.47 (1H, dd, *J* 10.2, 8.7 Hz), 3.44 (1H, dd, *J* 10.2, 4.8 Hz), 3.21 (1H, t, *J* 10.3 Hz), 2.46 (1H, m), 2.44 (3H, s), 1.17 (3H, s), 0.90 (3H, s); δ_C ($CDCl_3$, 100 MHz) 177.1, 145.5, 135.0, 129.9, 128.1, 48.9, 45.6, 45.2, 30.1, 23.5, 21.8, 18.0; *m/z* (ESI) (360 [M]$^+$Na). Anal. Calcd for $C_{14}H_{18}BrNO_3S$: C, 46.7; H, 5.0; N, 3.9. Found: C, 47.1; H, 5.0; N, 3.8.

3,3-Dimethyl-4-methyl-4-bromomethyl-1-(*p*-toluenesulfonyl)pyrrolidin-2-one (17). Conditions: Cu(TPMA)-SO_4 2.5 mol %, KBH_4 10 mol % (6:1 MeOH/DCM, 0.30 M); yield 88 mg (66%); white solid; mp 174−176 °C; spectroscopic data matched that previously reported;[7e] R_f (3:1 petroleum ether/EtOAc) 0.48; ν_{max} (film)/cm^{-1} 2982, 2937, 1722, 1596; δ_H ($CDCl_3$, 400 MHz) 7.91 (2H, d, *J* 8.3 Hz), 7.34 (2H, d, *J* 8.3 Hz), 3.85 (1H, d, *J* 10.8 Hz), 3.57 (1H, d, *J* 10.8 Hz), 3.27 (1H, d, *J* 10.5 Hz), 3.22 (1H, d, *J* 10.5 Hz), 2.44 (3H, s), 1.09 (3H, s), 1.07 (3H, s), 0.97 (3H, s); δ_C ($CDCl_3$, 100 MHz) 177.0, 145.3, 135.0, 129.7, 128.0, 54.1, 48.5, 48.2, 38.5, 21.7, 20.0, 19.1, 18.5; *m/z* (ESI) (396 [M]$^+$Na), 374 ([M]$^+$H), found ([M]$^+$Na) 396.0244, $C_{15}H_{20}BrNO_3S$ requires ([M]$^+$Na) 396.0245.

3,3-Dimethyl-4-(2-bromoisopropyl)-1-(*p*-toluenesulfonyl)-pyrrolidin-2-one (18). Conditions: Cu(TPMA)SO_4 2.5 mol %, KBH_4 5 mol % (6:1 MeOH/DCM, 0.30 M); yield 107 mg, (77%); white solid; mp 118−119 °C; R_f (3:1 petroleum ether/EtOAc) 0.60; ν_{max} (film)/cm^{-1} 2970, 1720, 1595; δ_H ($CDCl_3$, 300 MHz) 7.92 (2H, d, *J* 8.3 Hz), 7.34 (2H, d, *J* 8.3 Hz), 4,15 (1H, dd, *J* 10.0, 7.6 Hz), 3.80 (1H, t, *J* 10.2 Hz), 2.43 (3H, s), 2.27 (1H, dd, *J* 10.3, 7.6 Hz), 1.86 (6H, d, *J* 5.5 Hz), 1.28 (3H, s), 1.05 (3H, s); δ_C ($CDCl_3$, 75.5 MHz) 177.1, 145.3, 134.6, 129.8, 128.0, 65.2, 54.9, 47.7, 46.7, 35.9, 32.9, 26.1, 21.8, 18.9; *m/z* (ESI) 410 ([M]$^+$Na), found ([M]$^+$Na) 410.0396, $C_{16}H_{22}BrNO_3S$ requires ([M]$^+$Na) 410.0401.

3-Chloro-4-(chloromethyl)-3-methyl-1-(*p*-toluenesulfonyl)-pyrrolidin-2-one (19). Cu(TPMA)SO_4 2.5 mol %, KBH_4 10 mol % (6:1 MeOH/DCM, 0.30 M); yield 65 mg (66%); white solid; mp 161−162 °C; spectroscopic data matched that previously reported.[7e] Mixture of diastereoisomers (ratio 1.96:1.00 *cis*:*trans*): ν_{max} (film)/cm^{-1} 2924, 1735; δ_H ($CDCl_3$, 400 MHz) *cis* 7.92 (2H, d, *J* 8.4 Hz), 7.35 (2H, d, *J* 8.4 Hz), 4.21 (1H, dd, *J* 10.0, 7.0 Hz), 3.77 (1H, dd, *J* 11.5, 5.5 Hz), 3.63 (1H, dd, *J* 11.5, 9.0 Hz), 3.44 (1H, t, *J* 10.0 Hz), 2.60−2.50 (1H, m), 2.45 (3H, s), 1.72 (3H, s); *trans* 7.91 (2H, d, *J* 8.4 Hz), 7.35 (2H, d, *J* 8.4 Hz), 4.14 (1H, dd, *J* 10.6, 6.6 Hz), 3.87 (1H, dd, *J* 10.6, 3.6 Hz), 3.65 (1H, dd, *J* 11.5, 4.3 Hz), 3.37 (1H, dd, *J* 11.5, 8.5 Hz), 2.89−2.80 (1H, m), 2.45 (3H, s), 1.60 (3H, s); δ_C ($CDCl_3$, 75.5 MHz) *mixture* 169.3, 169.1, 146.3 (× 2), 134.4, 134.1, 130.3 (× 2), 130.2 (× 2), 128.6 (2C × 2), 128.5 (× 2), 71.4, 69.4, 47.7, 47.6, 47.4, 47.2, 42.3, 41.4, 24.2 (× 2), 22.2 (× 2). Anal. Calcd for $C_{13}H_{15}Cl_2NO_3S$: C, 46.4; H, 4.5; N, 4.2. Found: C, 46.5; H, 4.5; N, 3.9.

3,3-Dimethyl-4-(±)-(1-bromoethyl)-1-(*p*-toluenesulfonyl)-pyrrolidin-2-one (20).[17] Conditions: Cu(TPMA)SO_4 2.5 mol %, KBH_4 10 mol % (6:1 MeOH/DCM, 0.30 M); yield 122 mg (91%, 3.8:1 mixture of diastereomers); white solid; mp 128−130 °C. Data for major isomer ((±) *S,S*): R_f (3:1 petroleum ether/EtOAc) 0.59; ν_{max} (film)/cm^{-1} 2969, 1723, 1597; δ_H ($CDCl_3$, 300 MHz) 7.86 (2H, d, *J* 8.4 Hz), 7.26 (2H, d, *J* 8.4 Hz), 4.10 (1H, dd, *J* 10.5, 7.7 Hz), 4.01 (1H, ddd, *J* 8.6 Hz) 3.40 (1H, dd, *J* 10.5, 8.6 Hz), 2.37 (3H, s), 2.20 (1H, q, *J* 8.5 Hz), 1.71 (3H, d, *J* 6.7 Hz), 1.17 (3H, s,), 0.87 (3H, s); δ_C ($CDCl_3$, 100 MHz) 177.1, 145.3, 134.9, 129.7, 128.1, 50.5, 48.9, 48.8, 45.4, 25.7, 25.1, 21.7, 17.5; *m/z* (ESI) 396 ([M]$^+$Na); found ([M]$^+$Na) 396.0239, $C_{20}H_{22}BrNO_3S$ requires ([M]$^+$Na) 396.0245.

3,3-Dimethyl-4-(±)-(1-bromophenyl)methyl-1-(*p*-toluenesulfonyl)pyrrolidin-2-one (21).[17] Conditions: Cu-(TPMA)SO_4 2.5 mol %, KBH_4 50 mol % (6:1 MeOH/DCM, 0.30 M); yield 125 mg (80%, 5.0:1 unseparable mixture of diastereomers); white solid; mp 182−183 °C. Data for major isomer ((±) *S,S*): R_f (3:1 petroleum ether/EtOAc) 0.57; ν_{max} (film)/cm^{-1} 2961, 1728, 1597; δ_H ($CDCl_3$, 400 MHz) 7.88 (2H, d, *J* 8.3 Hz), 7.30−7.26 (7H, m), 4.84 (1H, d, *J* 11.3 Hz), 4.32 (1H, dd, *J* 10.4, 2.9 Hz), 3.45 (1H, t, *J* 10.5 Hz), 2.93−2.85 (1H, m), 2.38 (3H, s), 0.76 (3H, s), 0.45 (3H, s); δ_C ($CDCl_3$, 100 MHz) 177.2, 145.3, 139.7, 134.9, 129.8, 129.4, 129.0, 128.1, 127.8, 53.6, 49.9, 49.6, 45.8, 23.4, 21.7, 17.8; *m/z* (ESI) 458 ([M]$^+$Na); found ([M]$^+$Na) 458.0396, $C_{20}H_{22}BrNO_3S$ requires ([M]$^+$Na) 458.0401.

Cyclization of *N*-Benzyl-2-bromo-*N*-(cyclohex-1-enyl)-2-methylpropionamide 10a. Conditions: Cu(TPMA)SO_4 1.0 mol %, KBH_4 100 mol % (MeOH, 0.12 M). Purified by silica gel chromatography 9:1 petroleum ether/EtOAc. **1-Benzyl-3,3-dimethyl-1,3,3a,4,5,6,7,7a-octahydroindol-2-one (26a):** yield 11 mg (12%, as a 1:1 mixture of diastereomers); clear oil; R_f (3:1 petroleum ether/EtOAc) 0.56; ν_{max} (film)/cm^{-1} 2924, 2855, 1680; δ_H ($CDCl_3$, 400 MHz) 7.31−7.20 (5H, m, both diastereomers), 5.00 (1H, d, *J* 12.5 Hz, one diastereomer), 4.82 (1H, d, *J* 12.5 Hz, one diastereomer), 4.05 (1H, d, *J* 12.5 Hz, one diastereomer), 3.91 (1H, d, *J* 12.5 Hz, one diastereomer), 3.50 (1H, app q, 3.5 Hz, one diastereomer), 2.81 (1H, ddd, *J* 10.5, 6.5, 3.0 Hz, one diastereomer), 2.01−1.99 (1H, m, one diastereomer), 1.89 (1H, m, one diastereomer), 1.81−1.77 (3H, m, both diastereomers), 1.58−1.13 (5H, m, both diastereomers), 1.17, (3H s, one diastereomer), 1.13 (3H, s, one diastereomer), 1.10 (3H, s, one diastereomer) 0.90 (3H, s, one diastereomer); δ_C ($CDCl_3$, 125 MHz) 181.1, 180.7, 137.5, 137.2, 128.6, 128.5, 127.9, 127.8, 127.3, 127.2, 58.7, 53.1, 52.5, 44.6, 43.9, 43.7, 42.9, 42.5, 29.8, 29.7, 26.1, 26.0, 24.5, 23.9, 23.6, 23.3, 23.2, 20.7, 19.4, 17.0; *m/z* (ESI) 280 ([M]$^+$Na), 258 ([M]$^+$H), found ([M]$^+$Na) 280.1672, $C_{17}H_{23}NO$ requires ([M]$^+$Na) 280.1677. **1-Benzyl-3,3-dimethyl-1,3,4,5,6,7-hex-**

ahydroindol-2-one (27a): yield 22 mg (24%), clear oil; spectroscopic data matched that previously reported;[13a] R_f (3:1 petroleum ether/EtOAc) 0.48; ν_{max} (film)/cm^{-1} 2924, 2855, 1680; δ_H ($CDCl_3$, 400 MHz) 7.31−7.16 (5H, m), 4.63 (2H, s), 1.97 (2H, m), 1.64−1.47 (6H, m), 1.26 (6H, s); δ_C ($CDCl_3$, 100 MHz) 181.1, 138.7, 133.6, 128.5, 17.9, 127.3, 121.4, 42.7, 28.5, 24.8, 22.6, 22.5, 21.9, 22.2; *m/z* (ESI) 278 ([M]$^+$Na), 256 ([M]$^+$H), found ([M]$^+$Na) 278.1515, $C_{17}H_{21}NO$ requires ([M]$^+$Na) 278.1521. **1-Benzyl-3,3-dimethyl-1,3,3a,4,5,6-hexahydroindol-2-one (28a):** yield 43 mg (47%); clear oil; spectroscopic data matched that previously reported;[13a] R_f (3:1 petroleum ether/EtOAc) 0.67; ν_{max} (film)/cm^{-1} 2962, 1669; δ_H ($CDCl_3$, 400 MHz) 7.35−7.22 (5H, m), 4.81 (1H, dd, *J* 6.8, 3.0 Hz), 4.66 (1H, d, *J* 15.6 Hz), 4.56 (1H, d, *J* 15.6 Hz), 2.48−2.39 (1H, m), 2.10−1.95 (2H, m), 1.95−1.85 (1H, m), 1.82−1.71 (1H, m), 1.58−1.30 (2H, m), 1.26 (3H, s), 0.99 (3H, s); δ_C ($CDCl_3$, 100 MHz) 180.6, 139.7, 137.0, 128.7, 128.5, 127.2, 98.5, 45.8, 43.6, 43.0, 23.5, 23.1, 22.2, 21.9, 20.8; *m/z* (ESI) 278 ([M]$^+$Na), 256 ([M]$^+$H), found ([M]$^+$Na) 278.1515, $C_{17}H_{21}NO$ requires ([M]$^+$Na) 278.1521. ***N*-cyclohex-1-enyl-*N*-benzyl-2-methylpropionamide (25a).** Conditions: Cu(TPMA)SO_4 1.0 mol %, KBH_4 1000 mol % (MeOH, 0.12M); crude 2.1:1.0: mixture of **25a**:**26a**; spectroscopic data matched that previously reported;[42] yield 39 mg (42%); pale yellow solid; mp 78−80 °C; R_f (3:1 petroleum ether/EtOAc) 0.8; ν_{max} (film)/cm-1 2929, 1634; δ_H ($CDCl_3$, 400 MHz) 7.32−7.21 (5H, m), 5.40 (1H, s), 4.59 (2H, s), 2.81 (1H, quin, *J* 6.7 Hz), 2.04−1.90 (4H, m), 1.70−1.59 (2H, m), 1.57−1.45 (2H, m), 1.12 (6H, d, *J* 6.5 Hz); δ_C ($CDCl_3$, 75.5 MHz) 177.0, 138.6, 138.5, 128.7, 128.2, 127.5, 127.0, 49.7, 31.4, 28.8, 24.7, 22.9, 21.5, 20.2; *m/z* (ESI) 280.2 ([M]$^+$Na) 258.1 [M]$^+$, found ([M]$^+$Na) 280.1672, $C_{17}H_{23}NO$ requires ([M] + Na) 280.1677.

Cyclization of *N*-Benzyl-2-bromo-*N*-(cyclooct-1-enyl)-2-methylpropionamide (10b). Conditions: Cu(TPMA)SO_4 1.0 mol %, KBH_4 100 mol %, (MeOH, 0.12M); purified by silica gel chromatography 9:1 petroleum ether/EtOAc. **1-Benzyl-3,3-dimethyl-(1-cyclooctyl)pyrrolidin-2-one (26b):** yield 11 mg, (11%), clear oil. Crude NMR shows a 1:1 mixture of diastereomers. It was possible to partially remove one of the isomers by chromatography a second time to give a 2:1 mixture of isomers. Data for mixture: R_f (3:1 petroleum ether/EtOAc) 0.30; ν_{max} (film)/cm^{-1} 2924, 2854, 1755, 1596; δ_H ($CDCl_3$, 400 MHz) 7.35−7.17 (5H, m), 5.04 (1H major, d, *J* 16.0 Hz), 5.02 (1H minor, d, *J* 16.0 Hz), 3.97 (1H major, d, *J* 16.0 Hz), 3.90 (1H minor, d, *J* 16.0 Hz), 3.38 (1H minor, app t, *J* = 8.0 Hz), 3.12 (1H, major app dt, *J* 9.5, 5.0 Hz), 2.12−2.02 (1H, m), 1.89−1.26 (11H, m), 1.17 (3H major, s), 1.15 (3H minor, s), 1.07 (3H minor, s), 0.95 (3H major, s), 0.81 (1H, m); δ_C ($CDCl_3$, 100 MHz) 179.9, 179.0, 137.0, 137.0, 128.7, 128.6, 128.1, 127.9, 127.4, 127.3, 603, 59.4, 48.9, 46.9, 44.2, 44.0, 43.7, 43.6, 32.1, 29.7, 28.6, 27.5, 27.4, 27.0, 26.7, 25.5 (× 2), 25.4, 25.2, 24.06, 22.74, 21.9, 20.9, 19.6 ; *m/z* (ESI) 308 ([M]$^+$Na), 286 ([M]$^+$H), found:([M]$^+$Na) 308.1985, $C_{19}H_{27}NO$ requires ([M]$^+$Na) 308.1990. **1-Benzyl-3,3-dimethyl(1-cyclooct-1-enyl)pyrrolidin-2-one (27b):**[37b] yield 6 mg (6%); clear oil; R_f (3:1 petroleum ether/EtOAc) 0.63; ν_{max} (film)/cm^{-1} 2925, 2855, 1755, 1596; δ_H ($CDCl_3$, 400 MHz) 7.35−7.12 (5H, m), 4.68 (2H, s), 2.40−2.15 (4H, m), 1.70−1.35 (8H, m), 1.20 (3H, s); δ_C (C_6D_6, 100 MHz) 184.3, 139.6, 135.6, 129.2, 127.7, 127.4, 121.7, 47.7, 43.5, 30.7, 27.6, 26.4, 26.3, 23.4, 23.1; *m/z* (ESI) 306 ([M]$^+$Na), 284 ([M]$^+$H); found ([M]$^+$Na) 306.1828, $C_{19}H_{25}NO$ requires ([M]$^+$Na) 306.1834. **1-Benzyl-3,3-dimethyl(1-cyclooct-2-enyl)pyrrolidin-2-one (28b):**[37b] yield 70 mg (69%); clear oil; R_f (3:1 petroleum ether/EtOAc) 0.74; ν_{max} (film)/cm^{-1} 2926, 2854, 1702; δ_H (C_6D_6, 400 MHz) 7.33−7.10 (5H, m, Ar), 4.78−4.70 (2H, m), 4.59 (1H, d, *J* 15.1 Hz), 2.45 (1H, dd, *J* 12.5, 3.0 Hz), 2.21−1.90 (2H, m), 1.70−0.90 (8H, m) 1.25 (3H, s), 1.18 (3H, s); δ_C (C_6D_6, 100 MHz) 179.8, 143.2, 138.0, 129.6, 128.0, 127.7, 101.2, 47.7, 44.0, 43.9, 32.6, 30.2, 28.0, 26.1, 25.7, 24.4, 19.1; *m/z* (ESI) 306 ([M]$^+$Na), 284 ([M]$^+$H), found ([M]$^+$Na) 306.1829, $C_{19}H_{25}NO$ requires ([M]$^+$Na) 306.1834.

Conditions: Cu(TPMA)SO_4 1.0 mol %, KBH_4 1000 mol %, (MeOH, 0.12 M);1.0:1.0:0.5 mixture of **25b**:**26b**:**27b+28b**. Purified by silica gel chromatography 9:1 petroleum ether/EtOAc. ***N*-Cyclooct-1-enyl-*N*-benzyl-2-methylpropionamide (25b):** yield 21 mg, (20%); white crystalline solid; mp 64−65 °C; R_f (9:1 petroleum ether/EtOAc) 0.28; ν_{max} (film)/cm^{-1} 2929, 2847, 1639; δ_H ($CDCl_3$, 400 MHz) 7.33−7.20 (5H, m, Ar), 5.30 (1H, t, *J* 8.0 Hz), 4.69 (1H, br s), 2.91 (1H, sept *J* 6.0 Hz), 2.31 (2H, br s), 2.05 (2H, br s) 1.63−1.40 (8H, m), 1.13 (6H, d, *J* 6.0 Hz); δ_C ($CDCl_3$, 100 MHz) 177.4, 140.8, 138.8, 129.5, 128.3, 127.0, 50.6, 31.7, 31.5, 29.1, 28.9, 26.4, 26.0 (x2), 20.1; *m/z* (ESI) 308 ([M]$^+$Na), 286 ([M]$^+$H), found ([M]$^+$Na) 308.1990, $C_{19}H_{27}NO$ requires ([M]$^+$Na) 308.1990.

Cyclization of *N*-Benzyl-2-bromo-*N*-(3,4-dihydronaphthalen-1-yl)-2-methylpropionamide (11). Conditions: Cu(TPMA)-SO_4 1.0 mol %, KBH_4 100 mol %, (MeOH, 0.12M). Purified by silica gel chromatography gradient 9:1 petroleum ether: EtOAc → EtOAc. **1-Benzyl-3,3-dimethyl-4-(2,4,5,6-tetrahydronaphthalen)-2-one (29):** yield 20 mg (18%); colorless oil; R_f (3/1 petroleum ether/EtOAc) 0.48; ν_{max} (film)/cm^{-1} 2927, 1679; δ_H ($CDCl_3$, 400 MHz) 7.33−6.98 (9H, m), 4.99 (1H, d, *J* 15.5 Hz), 4.63 (1H, d, *J* 6.0 Hz), 3.63 (1H, d, *J* 15.5 Hz), 2.70 (1H, dt, *J* 16.1, 5.5 Hz), 2.68 (1H, dt, *J* 16.1, 5.5 Hz), 2.26 (1H, dd, *J* 13.0, 6.5 Hz), 1.72 (2H, dd, *J* 13.1, 6.5 Hz), 1.34 (3H, s), 1.24 (3H, s); δ_C ($CDCl_3$, 100 MHz) 179.8 139.7, 137.3, 131.8, 131.1, 128.7, 128.6, 128.2, 127.5, 127.1, 125.7, 61.8, 55.8, 43.5, 43.4, 28.1, 22.9, 25.1, 20.1; *m/z* (ESI) 328 ([M]$^+$Na), found ([M]$^+$Na) 328.1672, $C_{21}H_{23}NO$ requires ([M]$^+$Na) 328.1677. 1-Benzyl-3,3-dimethyl-1,3,4,5-tetrahydrobenzo[*g*]indol-2-one (**30**): yield 57 mg (52%); white crystalline solid; mp 94−96 °C; R_f (9/1 petroleum ether/EtOAc) 0.23; ν_{max} (film)/cm^{-1} 2929, 1697; δ_H ($CDCl_3$, 400 MHz) 7.31 (2H, t, *J* 8.2 Hz), 7.26−7.14 (5H, m), 7.10 (1H, t, *J* 7.3 Hz), 7.03 (1H, t, *J* 7.6 Hz), 5.06 (2H, s), 2.84, (2H, t *J* 7.9 Hz), 2.31 (2H, t, *J* 7.9 Hz), 1.31 (6H, s); δ_C ($CDCl_3$, 100 MHz) 185.0, 138.0, 136.7, 134.5, 128.8, 128.4, 127.5, 127.2, 127.1, 126.8, 126.6, 126.3, 121.6, 46.1, 45.5, 29.4, 22.5, 19.2; *m/z* (ESI) 326, ([M]$^+$Na); found ([M]$^+$Na) 326.1515, $C_{21}H_{21}NO$ requires ([M]$^+$Na) 326.1521]. Anal. Calcd for $C_{21}H_{21}NO$: C, 83.2; H, 7.0; N, 4.6. Found: C, 82.9; H, 6.9; N, 4.5.

Cyclization of *N*-Benzyl-2-bromo-*N*-(methylenecyclohexane)-2-methylpropionamide (12). Conditions: Cu(TPMA)SO_4 1.0 mol %, KBH_4 100 mol % (MeOH, 0.12 M). Purified by silica gel chromatography 9:1 petroleum ether/EtOAc. ***N*-Benzyl-4-bromo-4-cyclohexyl-3.3-dimethylazetidin-2-one (31):** yield 50 mg (40%); clear oil; spectroscopic data matched that previously reported;[13a] R_f (3:1 petroleum ether/EtOAc) 0.33; ν_{max} (film)/cm^{-1} 2929, 1736; δ_H ($CDCl_3$, 300 MHz) 7.40−7.15 (5H, m), 4.92 (1H, d, *J* 15.6 Hz), 4.15 (1H, d, *J* 15.6 Hz), 3.50 (1H, s), 2.15−1.41 (10H, m) 1.50 (3H, s), 1.29 (3H, s); δ_C ($CDCl_3$, 100 MHz) 175.0, 136.2, 127.8, 128.4, 127.7, 74.4, 72.7, 55.5, 45.5, 37.6, 25.0, 22.6, 22.4, 21.9, 24.5, 18.4; *m/z* (ESI) 372 ([M]$^+$Na); found ([M]$^+$Na) 372.0933, $C_{18}H_{24}BrNO$ requires ([M]$^+$Na) 372.0939. ***N*-Benzyl-4-cyclohex-1-enyl-3.3-dimethylazetidin-2-one (32):** yield 39 mg, (40%); clear oil; spectroscopic data matched that previously reported;[13a] R_f (3:1 petroleum ether/EtOAc) 0.41; ν_{max} (film)/cm^{-1} 2929, 1736; δ_H ($CDCl_3$, 300 MHz) 7.40−7.15 (5H, m), 5.56 (1H, br s), 4.80 (1H, d, *J* 14.8 Hz), 3.85 (1H, d, *J* 14.8 Hz), 3.37 (1H, s), 2.15−1.48 (8H, m) 1.24 (3H, s), 1.07 (3H, s); δ_C ($CDCl_3$, 100 MHz) 174.4, 136.2, 132.8, 128.7, 128.4. 127.6, 123.4, 66.4, 54.9, 44.4, 27.3, 24.8, 22.4, 22.3, 22.5, 16.8; *m/z* (ESI) 292 ([M]$^+$Na), 270 ([M]$^+$H); found ([M]$^+$H) 270.1852, $C_{18}H_{22}NO$ requires ([M]$^+$H) 270.1858. ***N*-Benzyl-*N*-(methylenecyclohexane)-2-methylpropionamide (35):** yield 12 mg (12%); clear oil; R_f (3:1 petroleum ether/EtOAc) 0.57; ν_{max} (film)/cm^{-1} 2931, 2855, 1639; δ_H ($CDCl_3$, 400 MHz) 7.30−7.21 (5H, m), 5.74 (1H, br s), 4.59 (2H, s), 2.83 (1H, sept, *J* 6.8 Hz), 2.06 (2H, br t, *J* 5.8 Hz), 1.90 (2H, t, *J* 5.8 Hz), 1.50 (4H, tt, *J* 5.8, 2.7 Hz), 1.29−1.23 (2H, m), 1.06 (6H, d, *J* 6.8 Hz); δ_C ($CDCl_3$, 100 MHz) 177.6, 143.2, 137.7, 128.9, 128.3, 127.1, 120.1, 51.0, 33.0, 30.9, 27.9, 26.4, 26.3, 20.7; *m/z* (ESI) 294 ([M]$^+$Na), 272 ([M]$^+$H); found ([M]$^+$H) 272.2009, $C_{18}H_{26}NO$ requires ([M]$^+$H) 272.2014.

Cyclization of *N*-Benzyl-2-bromo-*N*-(methylenecyclohexane)-2-methylpropionamide (13). Conditions: Cu(TPMA)SO_4 1.0 mol %, KBH_4 100 mol %, (MeOH, 0.12 M); purified by silica gel chromatography 9:1 petroleum ether/EtOAc. ***N*-Benzyl-4-(2-methyl-2-bromoethyl)-3,3-dimethylazetidine-2-one (33):** yield 68 mg, (61%); clear oil; R_f (3:1 petroleum ether/EtOAc) 0.46; ν_{max}

(film)/cm^{-1} 2962, 2925, 1751; δ_H ($CDCl_3$, 400 MHz) 7.30−7.15 (5H, m), 4.86 (1H, d, *J* 15.1 Hz), 4.16 (1H, d, *J* 15.1 Hz), 3.54 (1H, s), 1.74 (6H, d, *J* 4.7 Hz), 1.32 (3H, s), 1.21 (3H, s); δ_C ($CDCl_3$, 100 MHz) 174.1, 135.9, 128.1, 127.9, 127.0, 72.2, 64.6, 54.7, 44.4, 30.7, 23.4, 17.2; *m/z* (ESI) 332 ($[M]^+Na$); found ($[M]^+Na$) 332.0628, $C_{15}H_{20}BrNO$ requires ($[M]^+Na$) 332.0626]. ***N*-Benzyl-4-(isoprop-1-enyl)-3,3-dimethylazetidine-2-one (34):** yield 18 mg (20%); colorless oil; R_f (3:1 petroleum ether/EtOAc) 0.23; ν_{max} (film)/cm^{-1} 2962, 2925, 1751; δ_H ($CDCl_3$, 400 MHz) 7.30−7.15 (5H, m), 4.99 (1H, br s), 4.81 (1H, br s), 4.79 (1H, d, *J* 14.6 Hz), 3.81 (1H, d, *J* 14.6 Hz), 3.34 (1H, s), 1.55 (3H, s), 1.20 (3H, s), 1.04 (3H, s); δ_C ($CDCl_3$, 100 MHz) 168.4, 136.2, 135.9, 128.8, 128.4, 127.7, 111.9, 66.2, 44.4, 31.2, 29.7, 21.0, 16.6; *m/z* (ESI) 252 ($[M]^+Na$), 230 ($[M]^+H$); found ($[M]^+Na$) 252.1361, $C_{15}H_{19}NO$ requires ($[M]^+Na$) 252.1364].

Cyclization of 2-Bromo-2-methyl-*N*-(phenylmethyl)-*N*-2-propynylpropanamide (14). Conditions: Cu(TPMA)SO_4 1.0 mol %, KBH_4 100 mol % (MeOH, 0.12 M); purified by silica gel chromatography 9:1 petroleum ether/EtOAc. 3,3-Dimethyl-4-bromo-methylene-1-(phenylmethyl)-2-pyrrolidinone (**36**) and 3,3-dimethyl-4-methylene-1-(phenylmethyl)-2-pyrrolidinone (**37**):[17] yield 86 mg (82%) as an inseparable mixture (**36**:**37** = 1:2); colorless oil; R_f (3:1 petroleum ether/EtOAc) 0.57; ν_{max} (film)/cm^{-1} 2966, 2926, 1693; δ_H ($CDCl_3$, 300 MHz) 7.39−7.20 (10H, m, 36 and 37), 6.11 (1H, t, *J* 2.7 Hz, 36), 5.03 (1H, t, *J* 2.4 Hz, 37), 4.96 (1H, t, *J* 2.0 Hz, 37), 4.53 (2H, s, 36), 4.51 (2H, s, 37), 3.84−3.80 (4H, m, 36 and 37), 1.31 (6H, s, 36 and 37), 1.27 (6H, s, 36 and 37); δ_C ($CDCl_3$, 75.5 MHz) 177.5, 148.8, 146.1, 136.3, 135.9, 128.9, 128.8, 128.1, 127.8, 127.6, 106.7, 100.9, 50.1, 49.6, 46.3, 46.2, 44.4, 44.0, 25.6, 25.2; *m/z* (ESI) 316 ($[M]^+Na$) 294 ($[M]^+H$) (36); found ($[M]^+Na$) 316.0307, $C_{20}H_{22}BrNO_3S$ (36) requires ($[M]^+Na$) 316.0313.

3-Methyl-4-methyl-1-(*p*-toluenesulfonyl)pyrrolidin-3-en-2-one (38). Conditions: Cu(TPMA)SO_4 1.0 mol %, KBH_4 100 mol % (MeOH, 0.12 M); purified by silica gel chromatography 5:1 petroleum ether/EtOAc; yield 76 mg (80%); pale yellow oil; R_f (3:1 petroleum ether/EtOAc) 0.23; ν_{max} (film)/cm^{-1} 2923, 2858, 1709; δ_H ($CDCl_3$, 400 MHz) 7.94 (2H, d, *J* 8.5 Hz), 7.32 (2H, d, *J* 8.5 Hz), 4.23 (2H, s), 2.41 (3H, s), 1.98, (3H, s) 1.70 (3H, s); δ_C ($CDCl_3$, 100 MHz) 169.8, 150.8, 144.9, 135.6, 128.5, 129.7, 128.0, 53.4, 21.7, 13.5, 8.3; *m/z* (ESI) 288 ($[M]^+Na$); found ($[M]^+Na$) 288.0665, $C_{13}H_{15}NO_3S$ requires ($[M]^+Na$) 288.0670.

General Procedure for the Polymerization of Styrene with CuBr. To a mixture of 2,2′-nonylbipyridyl (Nbipy, 2.56 equiv), CuBr (1.02 equiv), and Bu_4NBH_4 (0.1 equiv) under nitrogen was added degassed styrene monomer (n equiv). To the solution at 110 °C was added ethyl α-bromoisobutyrate (1.00 equiv) to initiate polymerization. The mixture was stirred at 110 °C and aliquots were taken at regular intervals to assess the extent of polymerization. Aliquots were passed through a plug of silica to remove the Cu/Nbipy complex and precipitated into cold methanol to remove residual monomer. Polymers were then analyzed by 400 MHz ^1H NMR and GPC. The % conversion was calculated using the integrals of the vinyl peaks at 5.15 and 5.65 ppm compared to those of the aromatic region (6.10 − 7.50 ppm).

Conditions with Cu(Nbipy)Br (no Bu_4NBH_4, 180 equiv of styrene): GPC (THF + 2% TEA) M_n = 11.4 kDa, PDI = 1.12. δ_H ($CDCl_3$, 400 MHz), 7.30−6.20 (5H, br m, backbone), 4.60−4.00 (1H, br m, end group) 3.70−3.30 (2H, br m, CH_2 end group), 2.60−0.80 (3H, br m, backbone and end group).

Conditions with Cu(Nbipy)Br (Bu_4NBH_4, 180 equiv of styrene): GPC (THF + 2% TEA) M_n = 16.8 kDa, PDI = 1.20. δ_H ($CDCl_3$, 400 MHz), 7.30−6.20 (5H, br m, backbone), 4.60−4.00 (1H, br m, end group) 3.70−3.30 (2H, br m, CH_2 end group), 2.60−0.80 (3H, br m, backbone and end group).

End Group analysis. Conditions with Cu(Nbipy)Br (no Bu_4NBH_4, 50 equiv of styrene), GPC (THF + 2% TEA) M_n = 3.2 kDa, PDI = 1.08. Anal. Calcd for $C_{302}H_{307}BrO_2$: C, 89.59; H, 7.64; Br, 1.97 (Br content indicates 83% and ^1H NMR analysis indicates 60% end group fidelity). Found: C, 89.68; H, 7.68; Br, 1.64.

Polymerization of Styrene with $CuSO_4$·$5H_2O$. To a mixture of 2,2′-nonylbipyridyl (Nbipy, 2.56 equiv), CuBr (1.02 equiv), and Bu_4NBH_4 (0.4 equiv) under nitrogen was added degassed styrene monomer (100 equiv). Heating at 110 °C caused a vigorous reaction resulting in a brown solution. Ethyl α-bromoisobutyrate (1.00 equiv) was added to initiate the polymerization. The mixture was stirred at 110 °C, and aliquots were taken at regular intervals to assess the extent of polymerization. Aliquots were passed through a plug of silica to remove the Cu/Nbipy complex and precipitated into cold methanol to remove residual monomer, yielding polystyrene as a white solid.

Conditions with $CuSO_4$·$5H_2O$: 100 equiv of styrene, GPC (THF + 2% TEA) M_n = 7.3 KDa, PDI = 1.19; δ_H ($CDCl_3$, 400 MHz), 7.30−6.20 (5H, br m, backbone). 4.60−4.00 (1H, br m, end group) 3.70−3.30 (2H, br m, CH_2 end group), 2.60−0.80 (3H, br m, backbone and end group). Anal. Calcd for $C_{550}H_{555}BrO_2$: C, 90.78; H, 7.69; Br, 1.10; S, 0.00 (Br content indicates 64% and ^1H NMR analysis indicates 53% end group fidelity). Found C, 91.38; H, 7.73; Br, 0.70; S, <0.1.

■ ASSOCIATED CONTENT

Supporting Information

^1H NMR spectra for **1** (at 298 and 363 K), **2**, **8c−e**, **13−21**, **25−38**, and polystyrene prepared by ATRP using CuBr or $CuSO_4$·$5H_2O$ and Bu_4NBH_4. ^{13}C NMR spectra for **1** (at 298 and 363 K), **2**, **8c−e**, **13−15**, **17−18**, **20−21**, **25−26**, **27b**, **28b**, **29−30**, **33**, and **35−38**, and X-ray data for **21** (CIF). Visible spectra of Cu(TPMA)SO_4/**1** in MeOH with/without KBH_4 and the decomposition of the "active catalyst". This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: a.j.clark@warwick.ac.uk.

■ ACKNOWLEDGMENTS

We thank the University of Warwick and the Engineering and Physical Science Research Council for funding this work. The Oxford Diffraction Gemini XRD system was obtained through the Science City Advanced Materials project: Creating and Characterizing Advanced Materials, with support from Advantage West Midlands (AWM) and in part funded by the European Regional Development Fund (EDRF).

■ REFERENCES

(1) (a) Eckenhoff, W. T.; Pintauer, T. *Catal. Rev. Sci. Eng.* **2010**, *52*, 1−59. (b) Bellus, D. *Pure Appl. Chem.* **1985**, *57*, 1827−1838.

(2) (a) Di Lena, F.; Matyjaszewski, K. *Prog. Polym. Chem.* **2010**, *35*, 959−1021. (b) Pintauer, T.; Matyjaszewski, K. *Chem. Soc. Rev.* **2008**, *37*, 1087−1097.

(3) Clark, A. J. *Chem. Soc. Rev.* **2002**, *31*, 1−11.

(4) (a) Nagashima, H.; Isono, Y.; Iwamatsu, S. *J. Org. Chem.* **2001**, *66*, 315−319. (b) Davies, D. T.; Kapur, N.; Parsons, A. F. *Tetrahedron Lett.* **1999**, *40*, 8615−8618. (c) Iwamatsu, S.; Matsubara, K.; Nagashima, H. *J. Org. Chem.* **1999**, *64*, 9625−9631. (d) Baldovini, N.; Bertand, M.-P.; Carriere, A.; Nouguier, R.; Plancher, J.-M. *J. Org. Chem.* **1996**, *61*, 3205−3208. (e) Udding, J. H.; Tuijp, C. J. M.; van Zanden, M. N. A.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1994**, *59*, 1993−2003. (f) Nagashima, H.; Ozaki, N.; Ishii, M.; Seki, K.; Washiyama, M.; Itoh, K. *J. Org. Chem.* **1993**, *58*, 464−470. (g) Pirrung, F. O. H.; Steeman, W. J. M.; Hiemstra, H.; Speckamp, W. N.; Kaptein, B.; Boesten, W. H. J.; Schoemaker, H. E.; Kamphius, J. *Tetrahedron Lett.* **1992**, *33*, 5141−5144. For ATRP, see: (h) Wang, J.; Matyjaszewski, K. *J. Am. Chem. Soc.* **1995**, *117*, 5614−5615.

(5) (a) Casolari, R.; Felluga, F.; Frenna, V.; Ghelfi, F.; Pagnoni, U. G.; Parsons, A. F.; Spinelli, D. *Tetrahedron* **2011**, *67*, 408−416. (b) Pattarozzi, M.; Roncaglia, F.; Giangiordano, V.; Davoli, P.; Prati, F.; Ghelfi., F. *Synthesis* **2010**, 694−700. (c) Ghelfi, F.; Pattarozzi, M.; Roncaglia, F.; Parsons, A. F.; Felluga, F.; Pagnoni, U. M.; Valentin, E.; Mucci, A.; Bellesia, F. *Synthesis* **2008**, 3131−3141. (d) Bellesia, F.;

Danieli, C.; De Buyck, L.; Galeazzi, R.; Ghelfi, F.; Mucci, A.; Orena, M.; Pagnoni, U. M.; Parson, A. F.; Roncaglia, F. *Tetrahedron* **2006**, *62*, 746−757. (e) De Buyck, L.; Danieli, C.; Ghelfi, F.; Pagnoni, U. M.; Parsons, A. F.; Pattarozzi, M.; Roncaglia, F. *Tetrahedron* **2005**, *61*, 2871−2877. (f) Cagnoli, R.; Ghelfi, F.; Pagnoni, U. M.; Parsons, A. F.; Schenetti, L. *Tetrahedron* **2003**, *59*, 9951−9960. (g) Ghelfi, F.; Parsons, A. F. *J. Org. Chem.* **2000**, *65*, 6249−6253. (h) Bellesia, F.; Forti, L.; Ghelfi, F.; Ghirardini, G.; Libertini, E.; Pagnoni, U. M.; Pinetti, A.; Prochilo, N. *Synth. Commun.* **1999**, *29*, 3739−3748. (i) Benedetti, M.; Forti, L.; Ghelfi, F.; Pagnoni, U. M.; Ronzoni, R. *Tetrahedron* **1997**, *41*, 14031−14042.

(6) Clark, A. J.; Battle, G. M.; Hemings, A. M.; Haddleton, D. M.; Bridge, A. *Tetrahedron Lett.* **2001**, *42*, 2003−2005.

(7) (a) Clark, A. J.; Geden, J. V.; Thom, S. *J. Org. Chem.* **2007**, *72*, 5923−5926. (b) Clark, A. J.; Battle, G.; Bridge, A. *Tetrahedron Lett.* **2001**, *42*, 1999−2001. (c) Clark, A. J.; Battle, G.; Bridge, A. *Tetrahedron Lett.* **2001**, *42*, 4409−4412. (d) Clark, A. J.; Dell, C. P.; McDonagh, J. P. *C. R. Acad. Sci. Ser IIc: Chim.* **2001**, *4*, 575−579. (e) Clark, A. J.; De Campo, F.; Deeth, R. J.; Filik, R. P.; Gatard, S.; Hunt, N. A.; Lastécouères, D.; Thomas, G. H.; Verlac, J.-B.; Wongtap, H. *J. Chem. Soc., Perkin Trans. 1* **2000**, 671. (f) de Campo, F.; Lastécouères, D.; Verlhac, J−B. *Chem. Commun.* **1998**, 2117−2118.

(8) Nagashima, H.; Seki, K.; Ozaki, N.; Wakamatsu, H.; Itoh, K.; Tumo, Y.; Tsuji, J. *J. Org. Chem.* **1990**, *55*, 985−900.

(9) Lin, C. Y.; Coote, M. L.; Gennaro, A.; Matyjaszewski, K. *J. Am. Chem. Soc.* **2008**, *130*, 12762−12774.

(10) (a) Pintauer, T.; Matyjaszewski, K. *Chem. Soc. Rev.* **2008**, *79*, 1087−1097. (b) Tsarevsky, N. V.; Matyjaszewski, K. *Chem. Rev.* **2007**, *107*, 2270−2799.

(11) (a) Lu, N.; Lin, C. I.; Chen., T. C. *J. Appl. Polym. Sci.* **2008**, *110*, 2531−2537. (b) Haddleton, D. M.; Jackson, S. G.; Bon, S. A. F. *J. Am. Chem. Soc.* **2000**, *122*, 1542−1543.

(12) (a) Jones, C. W.; Nguyen, J. V. *J. Polym. Sci., Polym. Chem.* **2004**, *42*, 1367−1383. (b) Honigfort, M. E.; Brittain, W. J. *Macromolecules* **2003**, *36*, 3111−3114. (c) Hong, S. C.; Matyjaszewski, K. *Macromolecules* **2002**, *35*, 7592−7605. (d) Shen, Y.; Zhu, S. *Macromolecules* **2001**, *34*, 8603−8609. (e) Haddleton, D. M.; Duncalf, D. J.; Kukulj, D.; Radique, A. P. *Macromolecules* **1999**, *32*, 4769−4775.

(13) (a) Clark, A. J.; Geden, J. V.; Thom, S. *J. Org. Chem.* **2006**, *71*, 1471−1479. (b) de Campo, F.; Lastecoures, D.; Vincent, J. M.; Verlhac, J.-B. *J. Org. Chem.* **1999**, *64*, 4946−4971.

(14) (a) Curran, D. P.; Guthrie, D. B.; Geib, S. J. *J. Am. Chem. Soc.* **2008**, *130*, 8437−8445. (b) Newcomb, M.; Curran, D. P. *Acc. Chem. Res.* **1988**, *21*, 206−214.

(15) (a) Taylor, M. J. W.; Eckenhoff, W. E.; Pintaur, T. *Dalton Trans.* **2010**, *39*, 11475−11482. (b) Dong, H.; Matyjaszewski, K. *Macromolecules* **2008**, *41*, 6868−6870. (c) Matyjaszewski, K.; Jakubowski, W.; Min, K.; Tang, H; Huang, J.; Braunecker, K.; Tsarevsky, N. V. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 15309−15314. (d) Min, K.; Matyjaszewski, K.; Jakubowski, W. *Macrol. Rapid Commun.* **2006**, *27*, 594−598. (e) Tang, H.; Radosz, M.; Shen, Y. *Macrol. Rapid Commun.* **2006**, *27*, 1127−1131. (f) Dong, H.; Matyjaszewski, K. *Macromolecules* **2008**, *41*, 6868−6870.

(16) Matyjaszewski, K.; Jakubowski, W.; Min, K.; Tang, H; Huang, J.; Braunecker, K.; Tsarevsky, N. V. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 7440−7441.

(17) Clark, A. J.; Wilson, P. *Tetrahedron Lett.* **2008**, *49*, 4848−4850.

(18) (a) Zhou, Y.; Qui, L.; Deng, Z.; Texter, J.; Yan, F. *Macromolecules* **2011**, *44*, 7948−7955. (b) Min, K.; Gao, H.; Matyjaszewski, K. *J. Am. Chem. Soc.* **2005**, *127*, 3825−3830.

(19) Wright, P. M.; Mantovani, G.; Haddleton, D. M. *J. Polym. Sci., Part A: Polym. Chem.* **2008**, *46*, 7376−7385.

(20) Jakubowski, W.; Matyjaszewski, K. *Macromolecules* **2006**, *39*, 39−45.

(21) Min, K.; Gao, H.; Matyjeszewski, K. *J. Am. Chem. Soc.* **2005**, *127*, 3825−3830.

(22) Matyjaszewski, K.; Jakubowski, W.; Min, K.; Tang, H; Huang, J.; Braunecker, K.; Tsarevsky, N. V. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 15309−15314.

(23) (a) Lligadas, G.; Ladislaw, J. S.; Guliashvili, T.; Percec., V. *J. Polym. Sci., Part A: Polym. Chem.* **2008**, *46*, 278−288. (b) Monteiro, M. J.; Guliashvili, T.; Percec., V. *J. Polym. Sci., Part A: Polym. Chem.* **2007**, *45*, 1835−1847.

(24) (a) Lligadas, G.; Rosen, B. M.; Monteiro, M. J.; Percec, V. *Macromolecules* **2008**, *41*, 8360−8364. (b) Matyjaszewski, K.; Tsarevsky, N. V.; Braunecker, W. A.; Dong, H.; Huang, J.; Jakubowski, W.; Kwak, Y.; Nicolay, R.; Tang, W.; Yoon, J. A. *Macromolecules* **2007**, *40*, 7795−7806.

(25) Trost, B. M.; Fleming, I. *Comprehensive Organic Synthesis*; Elsevier Ltd.: New York, 1991; Vol. *8*, Reduction, pp 1−107.

(26) (a) Beckwith, A. L. J.; Abeywickrema, A. N. *Tetrahedron Lett.* **1986**, 109−112. (b) Beckwith, A. L. J.; Goh, S. H. *Chem. Commun.* **1983**, 905−906. (c) Beckwith, A. L. J.; Goh, S. H. *Chem. Commun.* **1983**, 907−908. (d) Beckwith, A. L. J.; Gara, W. B. *J. Am. Chem. Soc.* **1969**, *91*, 5689−5691. (e) Liu., Q.; Han, B.; Zhang, W.; Yang, L.; Liu, Z.-L.; Yu, W. *Synlett* **2005**, 2248−2250. (f) Kropp, M.; Schuster, G. B. *Tetrahedron Lett.* **1987**, *28*, 5295−5298.

(27) (a) Kawamoto, T.; Fukuyama, T.; Ryu, I. *J. Am. Chem. Soc.* **2012**, *134*, 875−877. (b) Kobayashi, S.; Kawamoto, T.; Uehara, S.; Fukuyama, T.; Ryu, I. *Org. Lett.* **2010**, *12*, 1548−1551. (c) Ryu, I.; Uehara, S.; Hirao, H.; Fukuyama, T. *Org. Lett.* **2008**, *10*, 1005−1008.

(28) Wiberg, E.; Henle, W. *Naturforsch. Teil B.* **1952**, *7*, 582.

(29) Klingen, T. J. *Inorg. Chem.* **1964**, *3*, 1058−1059.

(30) (a) Spokas, R. J.; James, B. D. *Inorg. Chim. Acta* **1986**, *118*, 99−104. (b) Kunkely, H.; Volger, A. *Inorg. Chem. Commun.* **2002**, *5*, 239−241.

(31) Kunkely, H.; Volger, A. *J. Photochem. Photobiol., A* **2002**, *147*, 149−152.

(32) (a) Rachita, M. A.; Slough, G. A. *Tetrahedron Lett.* **1993**, *43*, 6821−6824. (b) Slough, G. A. *Tetrahedron Lett.* **1993**, *43*, 6825−6828.

(33) Bashir, N.; Patro, B.; Murphy, J. A. *Advances in Free Radical Chemistry*; Zard, S. Z., Ed.; JAI Press: Stamford, CT, 1999; Vol. *2*, p 123.

(34) Murphy, J. A. *Pure Appl. Chem.* **2000**, *72*, 1327−1334.

(35) Iqbal, J.; Bhatia, B.; Nayyar, N. K. *Chem. Rev.* **1994**, *94*, 519−564.

(36) Davies, D. T.; Kapur, N.; Parsons, A. F. *Tetrahedron* **2000**, *56*, 3941−3944.

(37) (a) Davies, D. T.; Kapur, N.; Parsons, A. F. *Tetrahedron Lett.* **1999**, *40*, 8615−8618. (b) Clark, A. J.; Dell, C. P.; Ellard, J. M.; Hunt, N. A.; McDonagh, J. M. *Tetrahedron Lett.* **1999**, *40*, 8619−8623.

(38) (a) Cassayre, J.; Quiclet−Sire, B.; Sauniers, J. B.; Zard, S. Z. *Tetrahedron Lett.* **1998**, *39*, 8995−8998. (b) Cassayre, J.; Dauge, D.; Zard, S. Z. *Synlett* **1999**, 501−503. (c) Cassayre, J.; Dauge, D.; Zard, S. Z. *Synlett* **2000**, 471−474.

(39) Kajiwara, A.; Matyjaszewski, K.; Kamachi, M. *Macromolecules* **1998**, *31*, 5695−5701.

(40) Matyjaszewski, K.; Jakubowski, W.; Min, K.; Tang, W.; Huang, J.; Braunecker, W. A.; Tsarevsky, N. V. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 15309−15314.

(41) (a) Eglinton, G.; Galbraith, A. R. *J. Chem. Soc.* **1959**, 889−896. (b) Hay, A. S. *J. Org. Chem.* **1962**, *27*, 3320−3321.

(42) Clark, A. J.; Curran, D. P.; Geden, J. V.; James, N.; Wilson, P. *J. Org. Chem.* **2011**, *76*, 4546−4551.

(43) Guthrie, D. B.; Damodaran, K.; Curran, D. P.; Wilson, P.; Clark, A. J. *J. Org. Chem.* **2009**, *74*, 4262−4266.