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Copper mediated atom transfer radical cyclisations with AIBN

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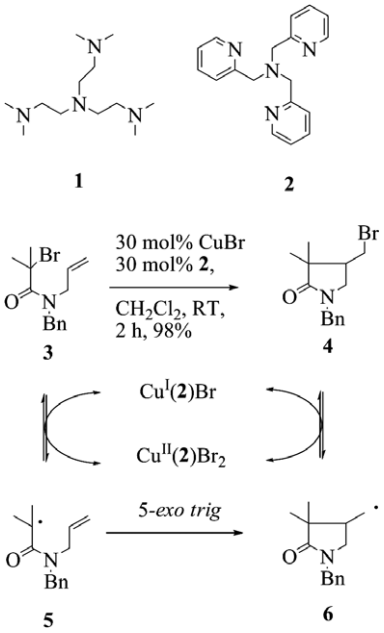
ABSTRACT

We have shown that it is possible to mediate a range of 5-*exo trig* and 5-*exo dig* atom transfer radical cyclisations of bromoacetamides using 0.1–1 mol % CuBr or $CuBr_2$ in conjunction with 0.1–1 mol % tri(pyridin-2-ylmethyl)amine and 10 mol % AIBN. This equates to a 30–300-fold reduction in the amount of catalyst previously reported for these reactions and allows cyclisation to be carried out with the more oxidatively stable $CuBr_2$ without the requirement of an inert atmosphere.

Copper(I) halide catalysed atom transfer radical cyclisation (ATRC) reactions have been extensively studied.[1] The majority of the published reactions utilise CuCl in combination with bipyridine[2] or TMEDA[3] to generate precursor radicals from reactive trichloro derivatives. We have shown that alternative ligands such as Me_6-tren[4] **1** or tripyridylamine (TPA)[5] **2** facilitate the cyclisation of less activated substrates (e.g., monobromide precursor **3**, Scheme 1). However, relatively high levels of CuBr are required (e.g., 30 mol %).[1] Some particularly 'difficult' reactions (e.g., cyclisations onto alkynes) often require stoichiometric amounts of Cu mediators at elevated temperature although the reason for this is unclear.[5b,d] For industrial applications, any reaction utilising a large catalyst loading will be unattractive and is likely to require the separation and recycling of the CuBr. As a consequence, a range of polymeric supported Cu reagents have been reported that mediate ATRC reactions.[6] However, in all cases moving the reaction from a homogeneous to a heterogeneous manifold decreases the rate of the reactions leading to higher temperatures and/or even larger 'catalyst' loadings for successful reactions. Although it has been shown that polymeric supported reagents can be re-used, their activities drop after subsequent reaction runs. This may be due to either leaching of the CuBr from the polymeric support or by competing oxidation of the CuBr active species and build up of $CuBr_2$ complexes under the reaction conditions or via adventitious oxygen.[6]

In order to lower catalyst loadings and to potentially allow reactions to be carried out under aerobic conditions we investigated modifying the reaction to include an additive that would reduce any built-up $CuBr_2$ complex to the active CuBr. A number of potential additives have been used to reduce $CuBr_2$ complexes in the related atom transfer radical polymerisation (ATRP) reactions



Scheme 1. Atom transfer radical cyclisation of **3**.

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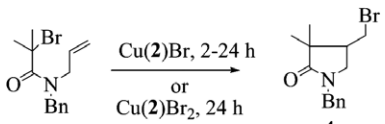
including phenols, hydrazine[7] and glucose.[8] We chose to investigate the role of AIBN as a reducing agent, as the by-products should be volatile and facilitate work-up. This approach has shown promise in intermolecular atom transfer radical additions (ATRA).[9] Initial studies focussed on the 5-*exo* cyclisation of the monobromide **3** with CuBr and TPA **2**, Table 1. Utilising conventional conditions (30 mol % Cu(**2**)Br, CH_2Cl_2, rt) the expected atom transfer product was produced in 98% yield after 2 h (entry 1). Lowering the catalyst loading to 1 mol % Cu(**2**)Br decreased the conversion to only 5% over a 24 h period at room temperature (entry 2) or 14% at 50 °C (entry 3). On the other hand, if 10 mol % AIBN was added (entry 4) the reaction proceeded to completion to give an 84% yield of **4**. The reaction also proceeded in toluene at reflux (entry 8). In order to check that the AIBN was not mediating the reaction on its own we repeated the process using 10 mol % AIBN *without* added Cu(**2**)Br (entry 5). We were pleased to observe that the reaction did not proceed at all. Attempts at lowering the loading of AIBN (5 mol %, entry 6) and Cu(**2**)Br (0.1 mol %, entry 7) met with mixed success. Finally, we investigated the effect of changing the oxidation state of the copper salt from CuBr to $CuBr_2$, (entry 9). This change furnished the product in the greatest yield (97%) and is noteworthy in that it shows that either CuBr or $CuBr_2$ can be utilised under these reaction conditions.[10]

It is known that different ligand complexes can mediate the same cyclisation with different efficiencies.[1] The rate of cyclisation of the related monobromide **7a** proceeds with 30 mol % CuBr and ligands in the order of TPA **2** > Me_6-Tren **1** > pentamethyldiethylenetriamine (PMDETA)[11] **9** > bipyridine **10**.[4,12] These reactivity orders were observed when using our AIBN modification and substrate **3**, Table 2. Heating substrate **3** under the standard conditions chosen from Table 1 (entry 4) indicated that ligands **2** and **1** were more reactive than pentamethyldiethylenetriamine (PMDETA) **9** which in turn was more reactive than bipyridine **10**, Table 2 (entries 1–4). Shortening the reaction time to just 2 h allowed us to determine that the ligand **2** was superior to **1** thus confirming the order of reactivity. In conclusion we managed to lower the catalyst loading from (30 mol %, rt, 2 h) by a factor of 30 (1 mol %, 50 °C, 6 h) without compromising the yield (Scheme 2).

We next investigated the scope and limitation of the reaction by investigating a range of relatively facile 5-*exo trig* cyclisations **7a–e** as well as cyclisations known to be much harder to facilitate such as 5-*exo dig* cyclisations onto alkynes[5d] **13a–b** and 5-*exo trig* cyclisations of secondary bromide **16**. The cyclisations of **7a–e** proceeded as expected. Thus, cyclisation of compounds **7a–c** was over in less than 1 h and furnished the atom transfer products **8a–c** in excellent yields (95–100%). It has been reported that the nature of the N-protecting group can control the efficiency of 5-*exo* cyclisations of acetamides.[1,2b] Of the two possible amide conformers of acetamides, only the *anti* conformer has the correct geometry for cyclisation. Large or electron withdrawing N-substituents favour the *anti* conformer and so facilitate cyclisation. Changing the *N*-Ts group **7d** to an *N*-Bn group **7e** would be expected to retard the rate of cyclisation. This was observed and even after 24 h the reactions had only proceeded with 14% conversion. This low conversion was observed irrespective of whether CuBr or $CuBr_2$ was utilised in the reaction. Increasing the temperature and performing the reaction in toluene at reflux allowed the reaction to proceed at an acceptable rate (standard conditions entry 8, Table 1). However, cyclisation of **7e** now produced the two alkene regioisomers **11** and **12** in a 1:2 ratio, respectively. Presumably this is formed by elimination of HBr from the unobserved 3° bromide atom transfer product **8e** under the reaction conditions. Once again there was little change in yield or reaction efficiency when either CuBr or $CuBr_2$ was utilised. As already highlighted, cyclisations of the *N*-Ts compounds **7a–c** were more rapid than the *N-Bn* compounds **3** and **7e**. Thus it was possible to mediate these reactions at even lower catalyst loadings. Hence, reaction of **7b** with 0.1 mol % Cu(**2**)Br and 10 mol % AIBN furnished the expected product **8b** in 99% yield after 24 h with the same diastereoselectivity (Fig. 1, Table 3).

Table 1
Effect of Cu(**2**)Br and AIBN loadings on conversion



3 **4**

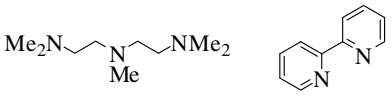
Entry	Solvent	Temp (°C)	AIBN (mol %)	Cu(**2**)Br (mol %)	Conv[a] (%)	Mass balance (%)
1	CH_2Cl_2	rt	—	30.0	100	98
2	CH_2Cl_2	rt	—	1.0	5	98
3	CH_2Cl_2	50	—	1.0	14	99
4[b]	*CH_2Cl_2*	*50*	*10.0*	*1.0*	*100*	*84*
5	CH_2Cl_2	50	10.0	—	0	98
6	CH_2Cl_2	50	5.0	1.0	95	99
7	CH_2Cl_2	50	10.0	0.1	40	89
8[b]	*Toluene*	*110*	*10.0*	*1.0*	*100*	*87*
9[b]	*CH_2Cl_2*	*50*	*10.0*	*1.0*[c]	*100*	*97*

[a] Determined by 300 MHz ^{1}H NMR. Reaction time for entry 1, 2 h.
[b] Italicized rows indicate the conditions chosen for further experiments.
[c] 1.0 mol % of $CuBr_2$ was used.

Table 2
Effect of ligand on reaction conversion **3** to **4**

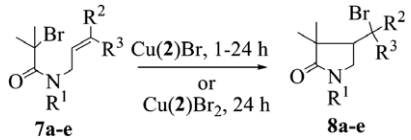
Entry[a]	Ligand	Time (h)	Conv[b] (%)
1	**1**	24	100
2	**2**	24	100
3	**9**	24	85
4	**10**	24	5
5	**1**	6	100
6	**2**	6	100
7	**2**	2	15
8	**1**	2	5

[a] Reactions were carried out using 1 mol % CuBr and 1 mol % ligand in CH_2Cl_2 at 50 °C with substrate **3** (0.17 M).
[b] Determined by 300 MHz ^{1}H NMR. Only starting material and product detected.



9 **10**

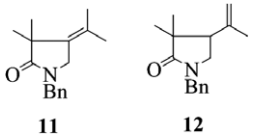
Table 3
5-*Exo trig* cyclisation of compounds **7a–e**



7a-e **8a-e**

Compound	Temp (°C)	Solvent	R^1	R^2	R^3	Cu Source	Yield[a] (%)
7a	50	CH_2Cl_2	Ts	H	H	CuBr	95
7b	50	CH_2Cl_2	Ts	Me	H	CuBr	100[b]
7c	50	CH_2Cl_2	Ts	Ph	H	CuBr	99[c]
7d	50	CH_2Cl_2	Ts	Me	Me	CuBr	99
7e	50	CH_2Cl_2	Bn	Me	Me	CuBr	14[d]
7e	110	Toluene	Bn	Me	Me	CuBr	80[e]
7e	50	CH_2Cl_2	Bn	Me	Me	$CuBr_2$	13[d]
7e	110	Toluene	Bn	Me	Me	$CuBr_2$	88[e]

[a] All reactions of **7a–c** were complete within 1 h, **7e** required 24 h.
[b] 3.5:1.0 mixture of diastereomers.
[c] 6.0:1.0 mixture of diastereomers.
[d] Remaining mass balance is recovered starting material.
[e] 1.0:2.0 mixture **11**:**12**.



11 **12**

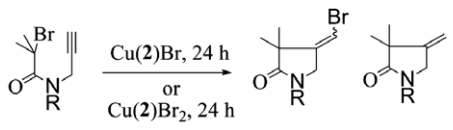
Figure 1. Alkene regioisomers produced in ATRC of **7e**.

We next turned our attention to the previously reported 5-*exo dig* cyclisation of the alkyne **13a**.[5d] This has been reported to be approximately 100 times slower than for the correponding 5-*exo trig* cyclisation of **7a**. Indeed, cyclisation under the conditions highlighted in grey in Table 1 (24 h) proceeded to only give a 33% and 9% combined yield of the expected products **14a** and **15a** with CuBr or $CuBr_2$, respectively. Switching to toluene at reflux allowed the reactions to proceed at a reasonable rate (Table 4, entries 3 and 4). The same pattern of reactivity was observed with the *N*-benzyl analogue **13b**. The ratio of the atom transfer products **14** to reduced products **15** has been reported to be solvent and ligand dependent and so the variation in the ratio between CH_2Cl_2 and toluene was expected.[4c] Vinyl bromides **14a–b** were produced as a 9:1 mixture of *E*:*Z* isomers in all cases. The ratio was determined by comparison to authentic samples.[4c]

Finally, we investigated the cyclisation of the secondary bromide **16**. Cyclisation rates of secondary bromides are known to be slower than the corresponding tertiary bromide derivatives, presumably due to the Thorpe–Ingold effect.[4c] Heating **16** in toluene at reflux under the standard conditions determined for substrate **3** (Table 1, entry 8) produced a 90% yield of the expected atom transfer product as a 4:1 mixture of diastereomers (de 60%). The major diastereomer was identified as **17a** based upon comparison of spectral details with authentic samples.[4c] The diastereoselectivity was slightly eroded compared to that reported (de 76%) for the cyclisation of **16** with 30 mol % Cu(**1**)Br at rt.[4c]

In conclusion, we have shown that it is possible to mediate a range of relatively slow 5-*exo trig* and 5-*exo dig* atom transfer radical cyclisations of tertiary and secondary bromoacetamides using 1 mol % Cu(**2**)Br in conjunction with 10 mol % AIBN as an additive. This allows for a 30-fold reduction in the amount of metal catalyst previously required to mediate these reactions efficiently. This coupled with the fact that the reactions can be mediated with either CuBr or the more oxidatively stable $CuBr_2$ without the need for an inert atmosphere should make the atom transfer radical cyclisation approach more attractive for use in industrial applications. Cyclisation of the more reactive *N*-Ts compounds (e.g., **7b**) proceeded with an order of magnitude less catalyst (0.1 mol %). It is likely that for the even more reactive trichloroacetyl derivatives, even lower catalyst loadings will be possible. By applying the AIBN protocol in conjunction with solid supported atom transfer catalysts,[6] it now should be possible to make efficient heterogeneous catalysts that can be recycled efficiently and re-used (Scheme 2).

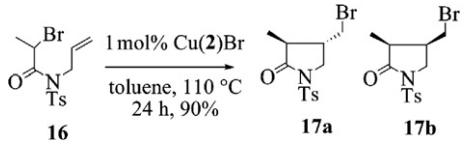
Table 4
5-*Exo dig* cyclisation of compounds **13a–b**



13a R = Ts, **13b** R = Bn — **14a** R = Ts, **14b** R = Bn — **15a** R = Ts, **15b** R = Bn

Entry	Comp	Temp (°C)	Solvent	Cu Source	Ratio **14**[a]**:15**	Yield[b] (%)
1	**13a**	50	CH_2Cl_2	CuBr	1:2	33
2	**13a**	50	CH_2Cl_2	$CuBr_2$	2:3	9
3	**13a**	110	Toluene	CuBr	1:1	67
4	**13a**	110	Toluene	$CuBr_2$	1:1	80
5	**13b**	50	CH_2Cl_2	CuBr	3:2	30
6	**13b**	110	Toluene	CuBr	1:1	51

[a] 9:1 mixture of *E*:*Z* isomers.
[b] Remaining mass balance is recovered starting material.



16 **17a** **17b**

Scheme 2. Cyclisation of secondary bromide **16**.

Acknowledgement

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10. A typical procedure is illustrated for entry 4, Table 1. *N*-Allyl-*N*-(phenylmethyl)-*N*-2-bromo-2-methylpropanamide **3** was dissolved in dry CH_2Cl_2 at room temperature (123 mg, 0.42 mmol in 2 ml, 0.21 M). AIBN (7 mg, 0.042 mmol) was added followed by a 0.01 M solution of CuBr/TPA in dry CH_2Cl_2 (0.42 ml, 0.0042 mmol, final concentration of **3** 0.17 M) solution and the mixture was heated at reflux for 6 h. The mixture was allowed to cool then passed through a silica plug and washed with CH_2Cl_2 (2 × 50 ml). The solvent was removed in vacuo to yield the crude product which was purified by flash chromatography, 9:1 pet ether/EtOAc, to yield 3,3-dimethyl-4-bromomethyl-1-(phenylmethyl)-pyrrolidin-2-one **4** (103 mg, 0.35 mmol, 84%). Data for **4**: R_f (3:1 petrol/EtOAc) 0.30; ν_{max} 2964, 2929, 1684, 1427, 1269, 699 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.29 (5H, m), 4.52 (1H, d, 14.6 Hz), 4.35 (1H, d, 14.6 Hz), 3.46 (1H, dd, 10.0, 4.8 Hz), 3.35 (1H, dd, 10.0, 7.5 Hz), 3.22 (1H, app t, 10.0 Hz), 2.88 (1H, app t, 10.0 Hz), 2.40 (1H, m), 1.24 (3H, s), 0.99 (3H, s); δ_C (75.5 MHz, $CDCl_3$) 178.5, 136.3, 128.8 (×2), 128.1 (×2), 127.7, 48.9, 46.7, 46.1, 44.0, 31.5, 24.3, 19.6; ESI [Na^+] found 318.0464, $Na^+C_{14}H_{18}NO^{79}Br$ requires 318.0469.
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