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Ligand Geometry Effects in Copper Mediated Atom Transfer Radical Cyclisations.

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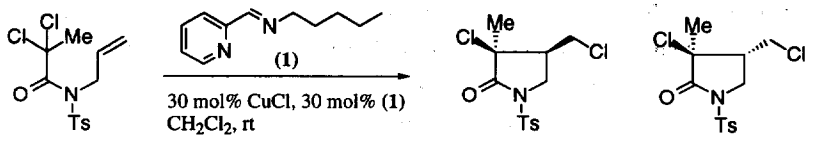
Abstract: The relative rate of copper (I) mediated atom transfer radical cyclisation of (**11**) with a range of ligands at room temperature has been screened. The most active ligands were found to be multidentate amine ligands (**6-7**).

Keywords: Radicals, addition, copper, lactam.

In recent years the growth of transition metal mediated free radical processes has gained in importance. Atom transfer radical cyclisation reactions of α,α,α,-trichlorinated carbonyl compounds with a range of metal catalysts have been reported.[1] In particular, the use of copper catalysts in both atom transfer radical cyclisation (ATRC)[2] and polymerisation (ATRP)[3] reactions has been the focus of great interest. Among the most successful catalysts reported for cyclisation reactions are CuCl(bipyridine),[2a-c] CuCl(TMEDA)[2d-e] and CuCl(*N,N,N',N',N"* - pentamethyldiethylenetriamine).[2f] We recently reported that CuCl(N-pentyl-2-pyridylmethanimine)[4] was an effective mediator of the cyclisation of a range of α,α,-dihaloacetamide and α-monohaloacetamide precursors at room temperature. These ligands were designed as potentially tuneable mimics of bipyridine and we reported how the reactivity of the ligands could be fine-tuned by varying the nature of the N-alkyl group. While a range of different ligand systems has been investigated by a number of groups, no direct comparative study on how the changes in the ligand structure effect the rate of cyclisation has appeared. We wish to report in this letter one such study that shows that multi-dentate amine ligands mediate the cyclisation of haloacetamides much faster than aromatic derived amine ligands.

We initially investigated the effect of the CuCl to ligand ratio on the rate of cyclisation of (**2**) using our N-pentyl-2-pyridylmethanimine ligand (**1**), See Graph.



(**2**) **Scheme 1** (**3**) (**4**)

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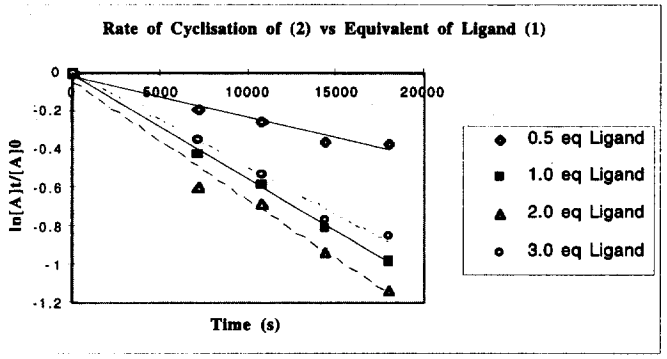
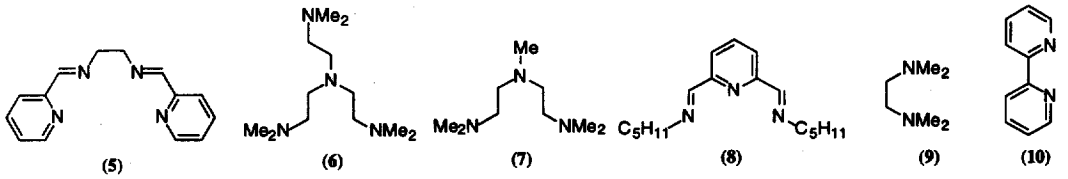
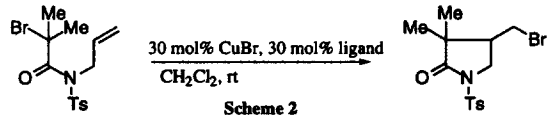


Keeping the concentration of CuCl constant and assuming the reaction is pseudo-first order with respect to reactant A (substrate **2**) a plot of $\ln[A]_t/[A]_0$ against time for each run (0.5, 1.0, 2.0 and 3.0 equiv of ligand to CuCl) furnishes the graph opposite. The fastest rate of cyclisation is when the ligand (**1**):CuCl ratio is 2:1. This is similar to the optimum ratio found for the ATRP of methyl methacrylate using this ligand system.[5] The active catalyst is therefore likely to be a tetrahedral $CuCl[(\mathbf{1})]_2$ complex. Indeed X-ray structures of related 2:1 CuCl[ligand] complexes have recently been published.[3h] The fact that co-ordination of 4 nitrogen substituents seemed optimal prompted us to screen the tetradentate ligands (**5-6**)[6,7] to see if they would also enhance the rate of atom transfer cyclisation reactions. In addition to these ligands we also screened the previously reported ligands (**7, 9-10**)[2f, 2d-e, 2a-c] in the cyclisation of the bromoacetamide (**11**). Hence to a 0.1M solution of (**11**) in CH_2Cl_2 at room temperature was added 30 mol% of ligand (**1, 5-10**) and 30 mol% of CuBr. The solution was stirred at room temperature for 30 min and then the sample was quickly eluted through a small silica plug (CH_2Cl_2) by suction to remove the CuCl(ligand) complex. The ratio of starting material to product was determined by 250 MHz ^{1}H NMR. In all cases the mass balances for the reactions were excellent (90-98%) and the reactions were clean with only starting material (**11**) and product (**12**) peaks observable in the NMR.





Scheme 2

As can be seen from Table 1 the catalysts derived from bipyridine (**10**), PMDETA (**7**), and tren-Me_6 (**6**) were particularly active with 75%, 100% and 100% conversion to products respectively. Particularly notable is that the N-pentyl-2-pyridylmethanimine ligand (**1**) was much slower than bipyridine (**10**) in the cyclisation of (**11**). This result is in contrast to that previously reported by us for the cyclisation of the trichloroacetate-O-allyl ester for which bipyridine (**10**) was found to give poorer product:starting material ratios.[4] The conditions for this latter reaction however were very different (toluene, 110°C) indicating that the solvent may have a crucial role to play in controlling the reactions presumably by affecting the solubility of the complex. Repeating the reactions with PMDETA (**7**) and tren-Me_6 (**6**) at lower catalyst loadings and lower concentrations (for 2 hours) allowed us

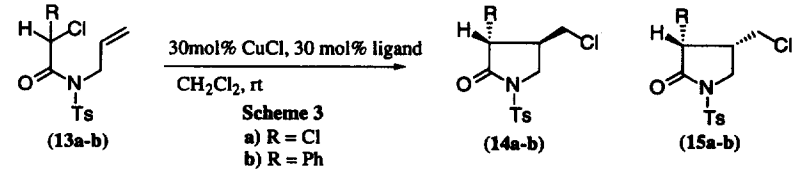
to determine that the tetradentate ligand (**6**) was at least ten times faster at mediating the cyclisation of (**11**) than tridentate ligand (**7**). Interestingly the tetra- and tri-dentate amine ligands (**6-7**) were found to be more active than the tetra- and tri-dentate pyridine/imine hybrid ligands (**5**) and (**8**).[8] In parallel to our results Matyjaszewski[9] has recently indicated that the rate of ATRP of methacrylates increases in the order TMEDA (**9**)<PMTEDA (**7**)<Tren-Me_6 (**6**) and that multi-dentate amine ligands generally catalyse polymerisation reactions much faster than bipyridine (**10**). This could be explained by the lower redox potential of copper amine complexes compared to copper pyridine derived complexes.[10]

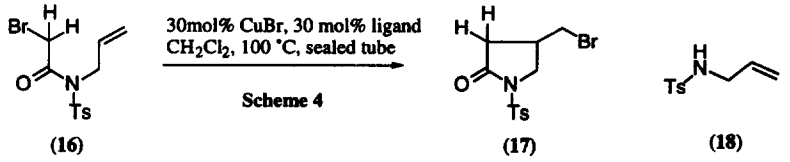
Ligand	Conversion[a]	Mass Balance
1	11%	98%
5	<2%	98%
6	100%	92%
7	100%	92%
8	20%	98%
9	5%	98%
10	75%	92%
6	20%[b]	94%
7	<2%[b]	90%

Table 1

[a] 30 mol% CuBr, 30 mol% ligand, 0.12M
[b] 10 mol% CuBr, 10 mol% ligand, 0.03M

Having determined that the fastest cyclisation rate occurred with the tetradentate amine ligand (**6**) we next investigated the use of this ligand system in ATRC of three particularly deactivated precursors. Hence, while cyclisation of the dichloro derivative (**13a**) (R = Cl) proceeded slowly at room temperature (72 h, 15% conversion, de 72% in favour of (**15a**)) with ligand (**1**) the reaction was over in less than 2 hours (90%, de 66%)[11] with the tren-Me_6 ligand (**6**). Cyclisation of the phenyl derivative (**13b**) (R = Ph) also proceeded efficiently at room temperature (86% yield, 9:1 mixture of diastereomers). Attempts to cyclise the most deactivated substrate (**16**) with the N-pentyl-2-pyridylmethanimine ligand (**1**) failed completely even after extended reaction times (24 h) at 100 °C in benzene (sealed tube). However, with the tren-Me_6 (**6**) it was possible to achieve cyclisation to give (**17**), albeit in low yield (18%) under forcing conditions, 100 °C, sealed tube, 24 h. In addition to the cyclised product a significant amount of (**18**) was isolated from the reaction. While the yield was poor the result is significant in that Nagashima and Itoh reported that CuCl(bipyridine) failed to cyclise the related N-allyl-N-benzyliodoacetamide.[12]





In conclusion we have shown that the rate of copper mediated atom transfer radical cyclisation reactions is heavily dependant upon both ligand and solvent effects.[4] It is highly likely that both effects alter the redox potential and solubility of the catalyst system and this in turn will effect the efficiency of the cyclisation. Simple copper amine complexes have been reported to have lower redox potentials than related pyridine derived ligands although more information is needed before firm conclusions can be drawn.[7] The major difference between the efficiency of

TMEDA (**9**) and tren-Me_6 (**6**) suggests that the geometry of the ligand may also be an important controlling factor. Assuming that the rate limiting step in the cyclisation reactions is the removal of a halogen atom from the starting material by a Cu(I)Cl[ligand] complex to furnish a radical and a $Cu(II)Cl_2$[ligand] complex then ligands which stabilise the preferred geometry of Cu(II) complexes (e.g square pyramidal, trigonal bipyramidal and distorted octahedral) relative to Cu(I) complexes (tetrahedral) should also facilitate cyclisation. Tren-Me_6 (**6**) is known to co-ordinate to copper in a trigonal bipyramidal arrangement[7] which may explain why it is so reactive a ligand in ATRC.

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