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LETTERS

N-Alkyl-2-pyridylmethanimines as Tuneable Alternatives to Bipyridine Ligands in Copper Mediated Atom Transfer Radical Cyclisation.

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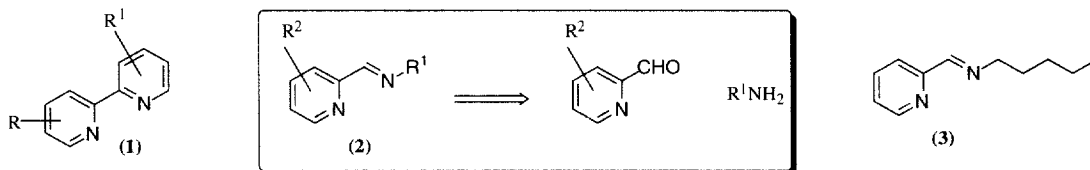
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Abstract: Copper halide complexes of N-alkyl-2-pyridylmethanimines (**3**, **11-14**) catalyse atom transfer radical cyclisation reactions of activated (**6a-b**) and unactivated α -haloallylacetamides (**9**) at room temperature.

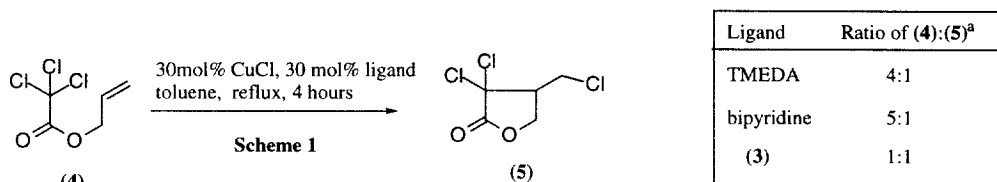
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In recent years the growth of transition metal mediated free radical processes has gained in importance.¹ In particular atom transfer radical cyclisation reactions of α,α,α -trichlorinated carbonyl compounds with a range of metal catalysts have been reported (RuCl₂(PPh₃)₃,² FeCl₂(P(OEt)₃)₃,³ CuCl(bipyridine),⁴ CuCl(TMEDA)⁵ and CuCl(*N,N,N',N',N''*-pentamethyldiethylenetriamine).⁶ However, even with these catalysts both high temperatures 60-160°C, and activated carbon-halogen bonds (e.g. α,α,α -trihaloacetyl or α,α -dihaloacetyl groups) as initiators are generally required. The cyclisation of α,α,α -trichloroacetamides by CuCl(bipyridine)⁷ has been shown to be an efficient process occurring at room temperature and was extended to the sequencing of both intramolecular and intermolecular reactions.⁸ However most of the reported examples of cyclisation reactions utilise activated α,α,α -trichloro- or α,α -dichloroacetamide derivatives with the latter requiring elevated temperatures for reaction. While a range of ligand systems have been investigated by a number of groups²⁻⁸ no study on the modification of existing ligands to elucidate structure-activity relationships has been undertaken. More active catalysts might be designed if the bipyridine ligand was modified electronically or sterically. However, the preparation of modified bipyridine ligands (**1**) is not trivial and we consequently decided to study whether the related class of bidentate ligands (**2**) (readily prepared from pyridine caboxaldehydes and amines) would also function as versatile atom transfer catalysts. If successful this approach could lead to the relatively easy synthesis of solid supported catalysts (e.g. (**2**) R¹ =solid support).



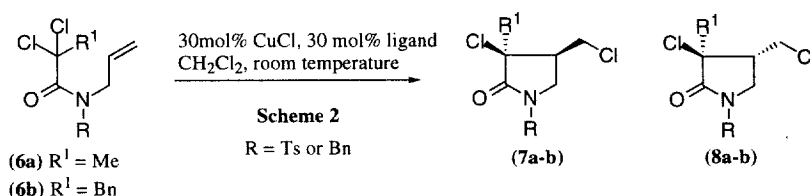
We have recently reported the use of the *N*-pentyl-2-pyridylmethanimine ligand (**3**) in atom transfer radical polymerisation reactions⁹ and as a consequence we prepared this ligand to investigate its activity as a catalyst in atom transfer cyclisation reactions. Reaction of pyridine carboxaldehyde with 1. equivalent of pentylamine in THF in the presence of MgSO₄ furnished the desired ligand in 72% yield after distillation. Initial work to determine the efficiency of the CuCl complex of this ligand as an atom transfer catalyst involved investigating the known cyclisation of α,α,α -trichloroallylacetate (**4**). Reaction of this ester under atom transfer conditions using CuCl(bipyridine) has been previously reported and hence a comparison could be made.



^a ratio determined by ¹H 250MHz NMR

Table 1

Reaction of (**4**) with 30 mol% CuCl and 30 mol% of either (**3**), TMEDA, or bipyridine as ligand in refluxing toluene was then attempted. After four hours the reactions were quenched and the ratio of product (**5**) to starting material (**4**) was determined, (Table 1). We were pleased to discover that ligand (**3**) showed a moderate rate enhancement over the other two ligands investigated. This prompted us to investigate the use of this catalyst in a range of other reactions. Most reported cyclisations of α,α -dichloro- α -alkyl-allylacetamides e.g. (**6**) require elevated temperatures.^{2b,2c,5,6} For example Ghelfi⁵ recently reported the cyclisations of *N*-benzyl- α,α -dichloro- α -alkyl-allylacetamides ((**6a-b**) R=Bn), with CuCl(TMEDA) at 60°C while Slough^{2b,c} reported the cyclisations of the related *N*-tosyl- α,α -dichloro- α -alkyl-allylacetamides ((**6a-b**) R=Ts), with RuCl₂(PPh₃)₃ at 80-100°C. The latter reported selectivities for the cyclisation of (**6a**) and (**6b**) (R=Ts) to be (**7a:8a**) = 27:73 and (**7b:8b**) = 95:5 respectively at 100°C after 4 hours. They also reported that this diastereoselectivity varied with temperature, concentration and time and showed that the diastereomers can interconvert under the reaction conditions, (i.e. the selectivity is thermodynamically controlled). The enhanced activity of our catalyst system to that of CuCl(bipyridine) in the cyclisation of (**4**) prompted us to re-examine the cyclisation of the substrates ((**6a-b**) R = Ts) at room temperature. As can be seen from table 2, conversion and yields were high with little or no erosion in selectivity to that previously reported.^{2b} Selectivities could be improved if required by heating the reactions or if the reaction time was increased.



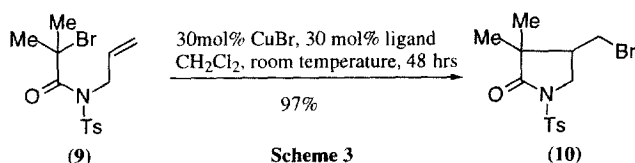
In addition the catalyst prepared from ligand (**3**) and CuBr was active enough to mediate the cyclisation *N*-tosyl- α -bromo- α,α -dimethyl-allylacetamide (**9**) also at room temperature, albeit rather slowly (48 hrs). Alternatively heating at 40°C in CH₂Cl₂ allowed cyclisation in a matter of a few hours (95%).

R ¹	TEMPERATURE	TIME	RATIO (7):(8) ^a	YIELD
Me	RT	24hrs	28:72	90%
Me	40°C	3hrs	33:67	^b
Me	40°C	40hrs	16:84	95%
Bn	RT	24hrs	94:6	93%

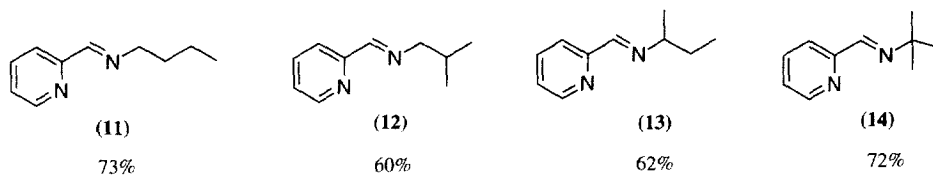
^aRatio determined by 250MHz ¹H NMR. Major isomers identical to that reported in ref 2c.

^bAnalysis of aliquot from reaction

Table 2



As our ultimate aim was to investigate how catalyst structure related to catalyst activity, and then to design new atom transfer catalysts that could be immobilised onto solid supports¹⁰ we examined the effect of the nature of the imine alkyl group (R¹ in (2)) on the activity of the catalyst. We envisaged that this position in the ligand might act as a good linking point to any solid support. Hence any information as to the scope and limitations of the type of group possible at this position would be beneficial. We therefore prepared a range of ligands of varying steric hindrance shown below (11-14) (yields given below).



The activity of each catalyst in the cyclisation of (6a), (Scheme 2) was determined. The optimum copper to ligand ratio was found to be 1:2 which is in line with an active catalyst containing two bidentate ligands. Hence, 60 mol% of ligand and 30 mol% CuCl were added to a 0.112M solution of (6a) in CH₂Cl₂. Aliquots were taken from the reaction mixture at varying times and the relative amounts of starting material to products determined by ¹H NMR. The diastereoselectivities of the products were measured after 48 hours irrespective of whether the reactions had gone to completion. The relative rate for each ligand in converting (6a) to products is indicated in table 3. The most sterically demanding catalyst derived from ligand (14) mediated the reaction extremely slowly (41% conversion after 48 hrs). In addition the diastereoselectivity of this reaction was very poor. As the steric hindrance at the N-alkyl substituent decreases the activity of the catalyst increases as does the diastereoselectivity. It therefore follows that to obtain good rates and conversions there is a requirement for a sterically unencumbered

primary N-substituent in the ligands. This information suggests that tethering to solid supports via this position will be practical providing the tether is primary and relatively unencumbered.

LIGAND	RELATIVE RATE ^a	(10a:10b) ^b
(12)	45	82:18
(13)	28	28:72
(14)	3	32:68
(15)	1	51:49

^a Relative rate with respect to the reaction of ligand (15).

^b Determined after 48 hours at RT (by ¹H 250MHz NMR)

electronic effects in the ligands modify reactivity and this will be published in due course. In addition the relative ease of the synthesis of this class of ligands should allow for the development of solid supported radical catalysts attached to supports via tethering to the imine nitrogen substituent.

In conclusion we have reported the use of the readily available N-alkyl-2-pyridylmethanimines as ligands for atom transfer radical cyclisation of both activated and unactivated α -haloacetamides. The nature of the N-alkyl substituent is crucial in obtaining activated catalysts. Although the catalysts react in a similar way to the previously reported CuCl(bipyridine) complex^{4,7} they have the advantage that they can be readily modified sterically to fine-tune their reactivity. Work is currently underway investigating how

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