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ARTICLE

Supramolecularly regulated copper-bisoxazoline catalysts for the efficient insertion of carbenoid species into hydroxyl bonds†

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The catalytic insertion of copper carbenoids into O–H bonds affords synthetically useful α-alkyl/aryl-α-alkoxy/aryloxy derivatives. Herein, the design, preparation and application of supramolecularly regulated copper(I) complexes of bisoxazoline ligands is reported. We have demonstrated that the catalytic performance of these systems can be modulated by the use of an external molecule (*i.e.* the regulation agent), which interacts with a polyethyleneoxy chain on the ligand (*i.e.* the regulation site) *via* supramolecular interactions. This approach has been applied to an array of structurally diverse alcohols (cycloalkyl, alkyl and aryl derivatives). Moreover, we have used this methodology to synthesise advanced synthetic intermediates of biologically relevant compounds.

Pressure is increasing on chemists to replace expensive noble metal catalysts with earth abundant metals. Although the number of papers describing the use of such metals in catalysis is growing, many synthetic transformations lack efficient catalysts of this type.[1] α-Alkyl/aryl, α-alkoxy/aryloxy carboxylate moieties are common in biologically active compounds[2] and their preparation by earth abundant metal catalysis has gained research attention.[3] Early studies by Yates *et al.*[4] showed the catalytic insertion of copper carbenoids into O–H bonds. Following this work, several studies were published,[5] with the enantioselective copper catalysts developed by Fu[6] and Zhou[7] deserving mention. Although high enantioselectivities were obtained, the scope of the reaction was limited: Reactions between phenyldiazoacetates and substituted phenols are understudied,[3] and carbenoid insertions into electron-deficient phenols or cycloalkyl alcohols are unreported.[8]

Inspired by nature, non-natural allosteric catalysts have been developed in past years.[9] Our research group has contributed to this area of research by reporting supramolecularly regulated catalysts[10] that contain polyethyleneoxy chains as regulation sites and stereogenic phosphite motifs for catalysis.[10b,f-i] Our regulation mechanism is triggered by the addition of a regulation agent (RA) capable of interacting with the regulation site *via* supramolecular interactions. The choice of RA determines the rigidity and conformational flexibility of the whole catalytic system, which translates into a modulation of the (stereo)selectivity in the transformation of interest.

Given the efficacy of regulation in previous transformations, we postulated that this strategy could be implemented to improve the copper-catalysed insertion of carbenoids into O–H bonds. In particular, an oxazoline[11] group, regularly used in copper catalysis, could act as a coordinating motif while the polyethyleneoxy motif is maintained in the regulation site. Our catalyst design incorporates two oxazoline units linked by a polyethyleneoxy chain at the α and ω positions (Figure 1).[12] We envisaged that the binding of the RA by the polyethyleneoxy moiety would not only serve to bring together the two ligating groups, but would also serve to modify the geometry and flexibility of the catalytic site. With regard to the RA, alkali metal BArF derivatives[13] (BArF = [B(3,5-$(CF_3)_2C_6H_3)_4$]) were selected due to their good performance as RAs in our previous studies.[10] Herein, we report the results of the synthesis of copper-bisoxazoline complexes that can be structurally modified by an external RA. We also describe the application of these catalysts for the insertion of copper carbenoids into O–H bonds, affording synthetically useful α-alkyl/cycloalkyl/aryl-α-alkoxy/aryloxy derivatives.

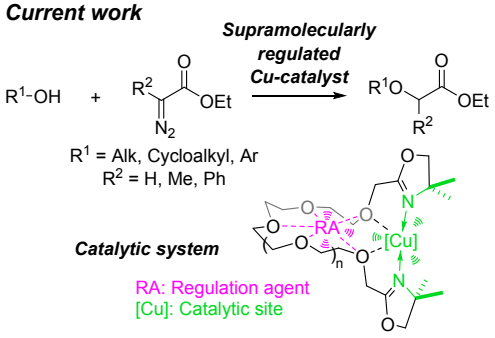

Figure 1. Supramolecularly regulated insertion of Cu-carbenoids into O–H bonds

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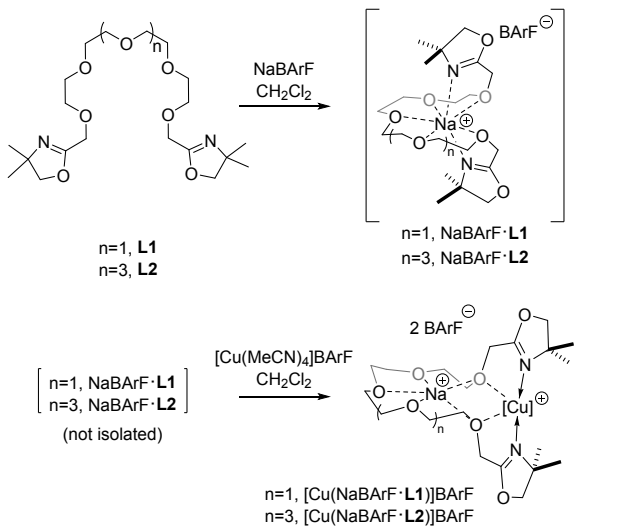
Our investigations began with the preparation of the ligands and desired supramolecular complexes (Scheme 1). Bisoxazoline ligands **L1** and **L2** were straightforwardly synthesised[14] and the corresponding supramolecular complexes were prepared by addition of substoichiometric quantities of ligand to NaBArF.[14] Binding constants for **L1** and BArF salts were calculated by nonlinear curve fitting[15] of the NMR titration data assuming a 1:1 binding model and were found to be $K > 10^3$ M^{-1} at 25 ºC in $CDCl_3$.[14] Single crystal X-ray diffraction confirmed the complexation of NaBArF to the polyethyleneoxy motif in NaBArF·**L1**.[14] The target Cu(I) complexes were prepared from NaBArF·**L1** or NaBArF·**L2** and $[Cu(MeCN)_4]BArF$[16] (Scheme 1) and characterised with standard spectroscopic techniques.[14] Unfortunately, single crystals of [Cu(NaBArF·**L1**)]BArF or [Cu(NaBArF·**L2**)]BArF were not obtained. However, when the synthetic protocol indicated in Scheme 1 was followed with PF_6 derivatives, single crystals of the corresponding complexes were obtained. X-Ray analysis confirmed the coordination of both oxazoline units to the copper centre and the coordination of sodium within the metallacrown structure (Figure 2).[14]

With a method for the preparation of supramolecular copper(I) catalysts in hand, we set about evaluating their activity and selectivity in the insertion of copper carbenoids into O–H bonds. The reactions were performed generating the copper catalysts from 5 mol% of $[Cu(MeCN)_4]BArF$, 6 mol% of **L1** or **L2** and 8 mol% of the RA[17] prior to substrate addition. Initial experiments demonstrated that Cu(I)-complexes derived from **L1** catalysed the insertion of the carbenoids formed from **2a** into the O–H bond of **1a** in the absence of the RA in 67% yield. The diazoester **2a** was fully consumed and no C–H insertion products were detected in the crude reaction mixtures.[14] In order to decouple activation effects that were not related to the envisioned regulation mechanism, several control experiments were performed (Table SI-1[14]). For instance, NaBArF displayed negligible activity in the reaction.[14] The effects in the reaction of the $[Cu(MeCN)_4]BArF$ alone (or in combination with two equivalents of the monodentate 4,4-dimethyl-4,5-dihydrooxazole ligand) were also studied, with the O–H product **3a,a** being obtained in lower yield (*ca.* 47%)[14] than with the Cu(I)-complex derived from **L1** (67%, Table SI-1). Temperature and solvents affected the yield of the reaction, with chloroform at 40 °C providing the highest yields.[14] We next evaluated whether the use of different RAs would translate into improved yields of the desired ester **3a,a**. Of all the RAs tested for **1a**, the catalyst incorporating RbBArF ([Cu(RbBArF·**L1**)]BArF) gave the best results (85% yield, Table SI-2[14]), even though LiBArF provides similar yield. Yield curves for the O–H insertion product derived from **1a** and **2a** were recorded by ^{1}H NMR analyses at different reaction times (see Figure 3) and then used to calculate turnover frequency numbers at *ca*. 50% conversion ($TOF_{1/2}$). Interestingly, a comparison of the $TOF_{1/2}$ numbers in the presence ($TOF_{1/2}$ = 400 h^{-1}) or absence ($TOF_{1/2}$ = 34 h^{-1}) of RA demonstrate the rate acceleration effects induced by RbBArF in the reaction between **1a** and **2a**. The supramolecular catalyst remained active after one reaction cycle: A second batch of reagents **1a** and **2a** was converted to product **3a,a** without any loss of selectivity and yield,[14] which demonstrates that no deactivation of the copper catalyst is taking place. Copper catalysts derived from **L2** provided lower yields than those obtained with ligand **L1** (Table SI-2).[14] Thus, ligand **L1** was used in subsequent catalytic studies.



Scheme 1. Synthesis of complexes [Cu(NaBArF·**L1**)]BArF and [Cu(NaBArF·**L2**)]BArF.

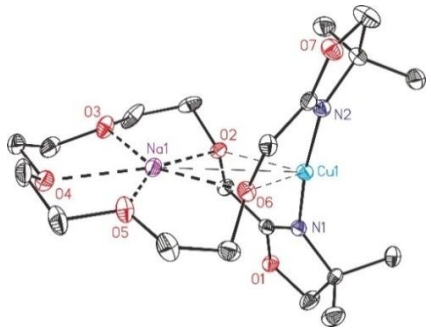


Figure 2. ORTEP drawing of the crystal structure of $[Cu(NaPF_6·L1)]PF_6$. Hydrogen and PF_6 groups have been omitted for clarity.

Having demonstrated that the yield of the transformation involving reaction partners **1a** and **2a** can be maximised by the choice of the RA, we decided to explore the substrate scope of the reaction with an array of structurally and electronically diverse phenols. Reaction partners that are typically challenging, such as phenols substituted with electron-withdrawing groups were also included in this study. In order to determine which RA was the most favourable for each phenol, the complete set of alkali metal BArF salts was tested, with the yield indicated in Scheme 2 being the highest one.[14]

In terms of position effects, yields were higher for products with substituents at the *para* position with respect to the *meta* and *ortho* analogues (87%, 69% and 59% for compounds **3d,a**; **3c,a** and **3b,a**). Pronounced electronic effects were observed, with the lowest yield within the series obtained for the most electron-deficient phenols (41% yield for **3f,a**). Rapid tailoring of the catalyst system to each substrate can be achieved through the RA approach, with yields being improved by the addition of a RA in most cases. The greatest improvements

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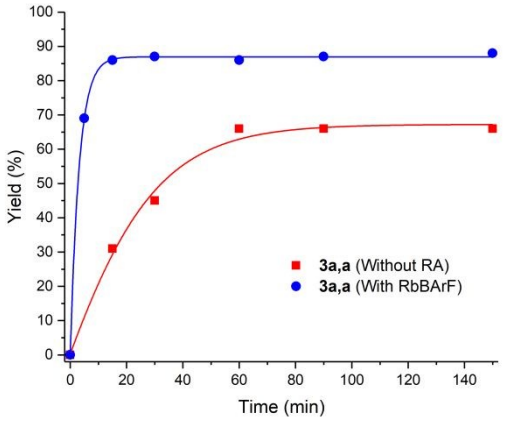
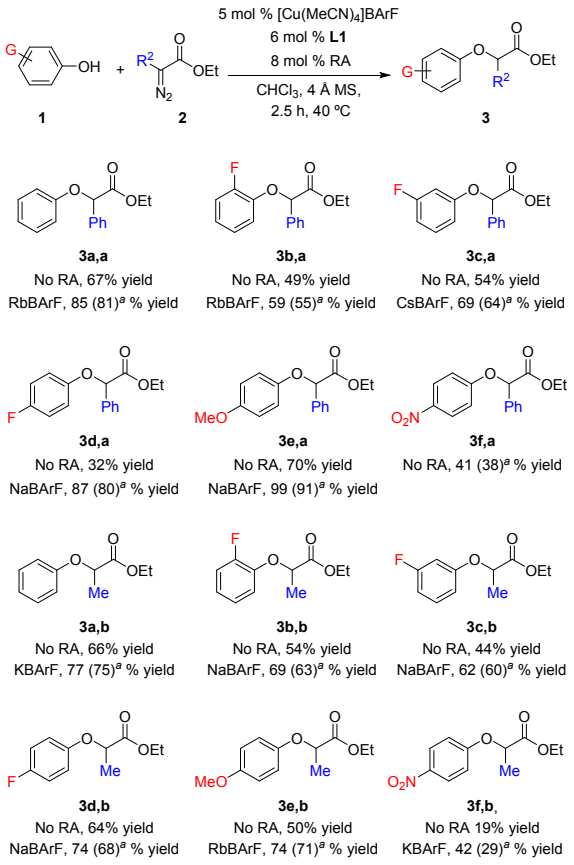


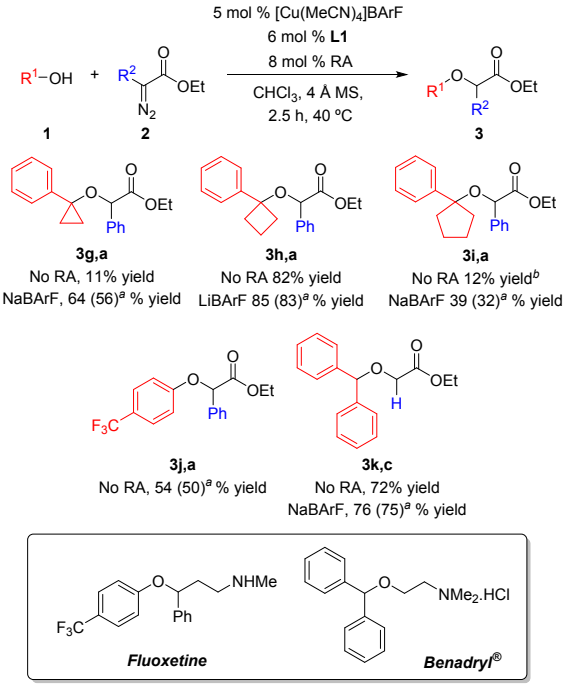
Figure 3. Yield for product **3a,a** plotted against reaction time (solid lines correspond to eye guidelines).

were observed for the *p*-fluoro-substituted product **3d,a** with an increase from 32% with no agent RA to 87% when NaBArF was used. We also performed an analogous study with ethyl 2-diazopropanoate **2b** as the carbenoid precursor and obtained similar outcomes to those described for **2a** (Scheme 2). The results obtained in this study indicate that the catalysts derived from **L1** mediate O–H insertions in all the substrates studied, regardless of the nature of the substituents.



Scheme 2. Supramolecularly regulated insertion reactions into O–H bonds. Reactions were performed employing a **1a** : [Cu] : **L1** : RA : **2a** ratio equal to 500 : 5 : 6 : 8 : 100. Yields were determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as the internal standard. [a] Isolated yields.

The practicality of our catalysts was further demonstrated by the preparation of the insertion products derived from several tertiary cycloalkanols (products **3g,a**; **3h,a** and **3j,a**; Scheme 3). This is a challenging transformation, as insertions of Cu-carbenoids into the O–H groups of cycloalkanols are limited and with ring opening products generally being obtained instead.[8] The use of NaBArF (Scheme 3) maximised the yield of the compounds **3g,a** (64%) and **3i,a** (39%), while LiBArF enhanced the yield of **3h,a** (85%). The preparation of advanced synthetic intermediates of biologically relevant compounds was also studied. Substrates **3j,a** and **3k,c** were selected to access advanced synthetic intermediates of fluoxetine or Prozac® (an SSRI antidepressant, which was marketed as a racemate[18]) and Benadryl® (an antihistaminic drug[19]), respectively. Regarding the preparation of fluoxetine precursor **3j,a**, reaction between 4-(trifluoromethyl)phenol and **2a** under optimised reaction conditions afforded the O–H insertion product in good yield (Scheme 3). For this particular substrate, the absence of regulation agent gave the best yield. Subsequent reduction of the ester group with $LiAlH_4$ afforded the corresponding alcohol, whose transformation into fluoxetine has been reported in the literature.[20] In an analogous manner for Benadryl®, an advanced synthetic intermediate **3k,c** was synthesised by reacting diphenylmethanol and **2a** in the presence of catalyst derived from **L1** and NaBArF. The reduction of **3k,c** with $LiAlH_4$ afforded the corresponding alcohol, which can be transformed into Benadryl® following an already published synthetic protocol.[21] Our chemistry therefore constitutes new formal syntheses of these active pharmaceutical ingredients.



Scheme 3. Extension of the supramolecular regulation strategy. [a] See footnotes to Scheme 2. [b] Reaction time was 24 h.

In conclusion, catalysts containing linear polyethyleneoxy chains as regulation sites and oxazoline units as coordinating groups for copper centres have been designed, prepared and characterised. These supramolecular copper complexes have found application in the catalysed insertion of copper carbenoids into the O–H groups of an array of structurally diverse alcohols to afford synthetically useful α-alkyl/aryl-α-alkoxy/aryloxy derivatives in yields ranging from 41% to 99% (seventeen examples). Our regulation approach, which consists of screening a set of regulation agents to obtain the highest yield for the substrate of interest, has been demonstrated. The rapid tailoring of the catalyst system to each substrate has been achieved and the practicality of this transformation has been expanded by preparing advanced synthetic intermediates of relevant APIs.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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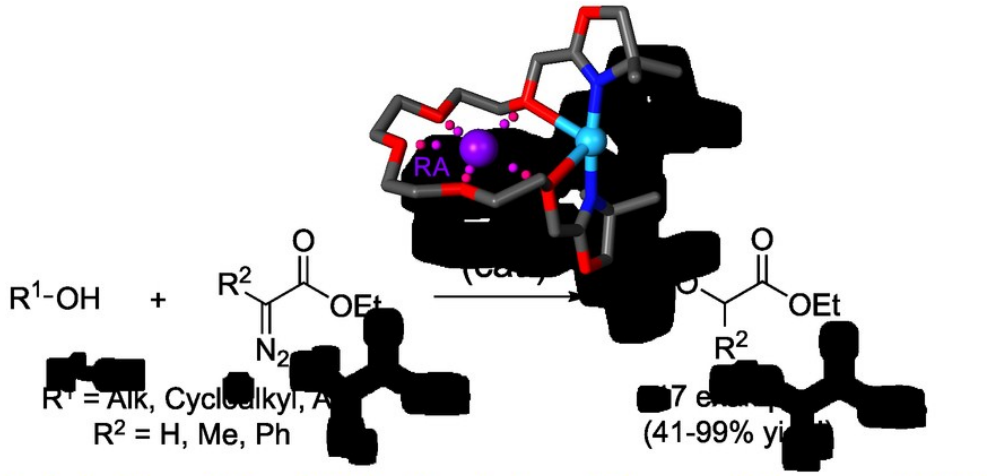

Maximisation of the yield by the choice of the regulation agent (RA)

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