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Copper(I) catalysed cyclisation of unsaturated *N*-benzoyloxyamines: an aminohydroxylation *via* radicals

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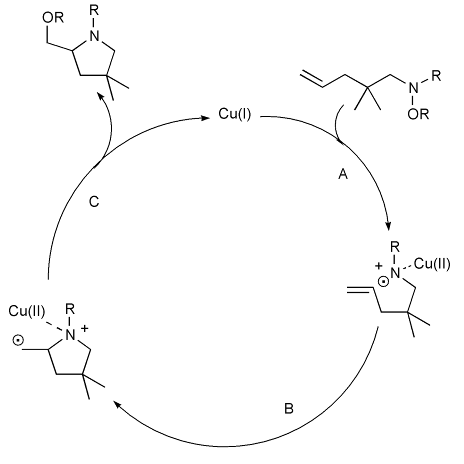
A new catalytic aminohydroxylation *via* radicals has been developed leading to cyclic aminoalcohols.

Aminoalcohols are important substructures of a variety of natural- and pharmacologically active products[1] and are extensively used for ligand synthesis.[2] Because of their importance, the catalytic aminohydroxylation of simple alkenes developed by Sharpless[3] has found broad interest. Even though this is a very efficient process, to date there are still unsolved problems concerning the regiochemistry and the substrate range[4] of this reaction. In the course of our ongoing studies towards the catalytic addition of nitrogen-heteroatom bonds to double bonds[5] we envisioned, that nitrogen–oxygen bonds could be added to double bonds *via* aminyl radicals, thereby enabling us to perform the first aminohydroxylation of alkenes *via* a radical pathway. Here we want to present our results towards this goal.

Even though N–O bonds are much less reactive than the N–Cl bonds we used previously, we hoped to find conditions that allow a catalytic reaction as shown below (Scheme 1).

In a first step (A) the N–O-bond is reduced by copper(I), leading to the formation of an aminyl radical. This can add to the double bond efficiently when activated by a Lewis acid (B). The carbon radical thus generated is quickly oxidised (C) by copper(II) *via* a ligand transfer, regenerating the catalyst and leading to the product.[6]

In our first experiments we found that simple hydroxylamines and their ethers are not reactive enough to achieve the anticipated reaction. We therefore turned our attention to more reactive substrates like oxaziridines, which have been used by Aube for the generation of aminyl radicals before.[7] However these were too reactive, and even when we used the conditions reported by Aube we observed various side reactions and were not able to isolate more than 40% of the cyclisation product.[8] Therefore oxaziridines seemed to be too reactive for our purpose. A N–O bond of intermediate reactivity is found in the easily accessible[9] *N*-benzoyloxyamines,[10] as the carbonyl group withdraws electrons and thereby renders the N–O bond more reactive towards reduction.

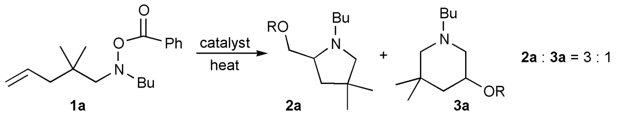


Scheme 1 Anticipated catalytic cycle.

This approach seemed more promising and in our first experiment we were able to isolate the 2-benzoyloxymethylpyrrolidine **2a** and the 3-benzoyloxypiperidine **3a** in a 3 : 1 ratio from benzoyloxyamine **1a** in 13% yield under copper(I) acetate catalysis together with unreacted starting material (Scheme 2).

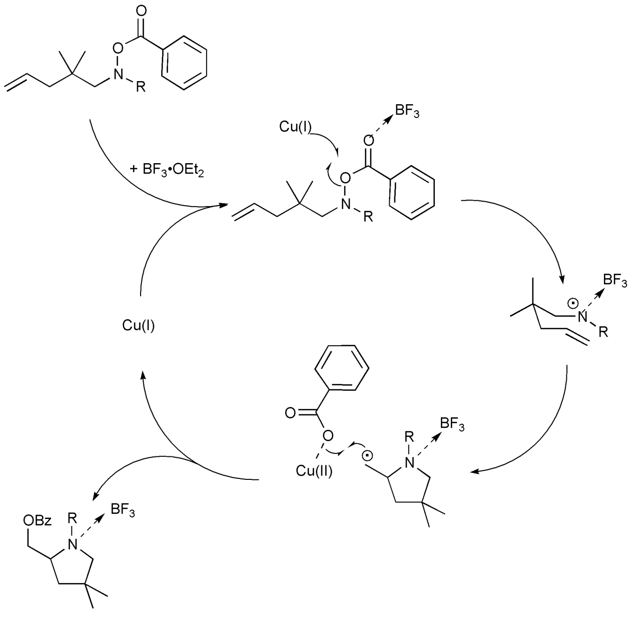
Using the more Lewis-acidic copper(I) hexafluorophosphate[11] and increasing the reaction temperature did not improve the yield. We therefore tried to activate the N–O bond further by adding an oxophilic (Lewis) acid that might coordinate to the benzoyloxy carbonyl oxygen and withdraw electron density, thereby increasing the reactivity of the N–O bond. This approach was successful and we tested various acids for this purpose, some examples are given in Scheme 2.[12]

Amongst these the cheap BF_3–etherate produced the best yields when used in equimolar amounts in toluene at 100 °C. To



catalyst	solvent	temperature	yield
10% Cu(OAc)	THF	reflux	*13%*
10% $CuPF_6$	THF	reflux	*15%*
10% $CuPF_6$ + 10% BF_3*OEt_2	CCl_4	reflux	*18%*
10% $CuPF_6$ + 100% BF_3*OEt_2	CCl_4	reflux	*42%*
10% $CuPF_6$ + 100% BF_3*OEt_2	toluene	100ºC	*79%*
10% $CuPF_6$ + 100% $Sc(OTf)_3$	toluene	100ºC	*25%*
10% $CuPF_6$ + 100% HOBz	toluene	100ºC	*28%*
10% AIBN + 100% BF_3	toluene	100ºC	*13%*

Scheme 2 Optimisation of the reaction conditions.



Scheme 3 Proposed catalytic cycle.

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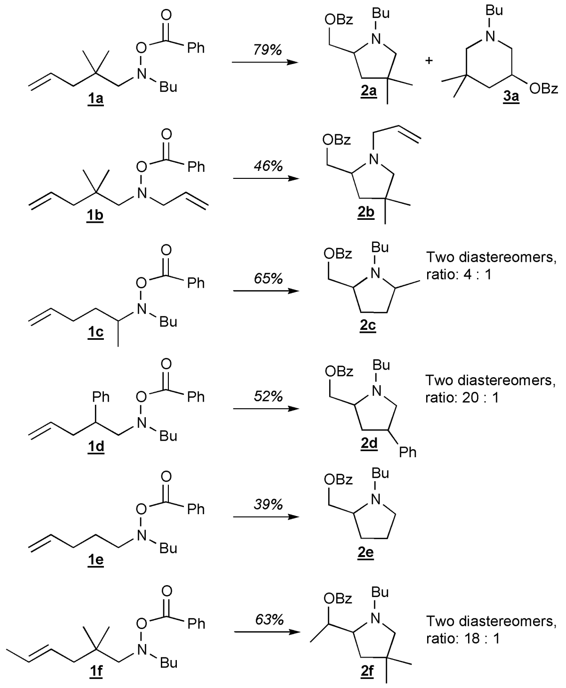
prove that this is not a polar reaction, initiated by the Lewis acid and proceeding *via* nitrenium ions, we submitted **1a** to the reaction conditions without a copper catalyst. In this case only traces of the cyclisation product were isolated together with more than 70% of the starting material. Next we wanted to know whether copper(I) is only an initiator or whether the intermediately formed copper(II) species is involved in the oxidation of the carbon radical (Scheme 1).[6] We therefore used 10% of AIBN instead of copper(I) as an initiator. However only 13% of the addition product, together with unreacted starting material, was isolated under these conditions. We therefore believe, that a copper(II) complex is involved in the oxidation of the intermediate carbon radical and thereby allows the efficient catalysis. The proposed catalytic cycle is shown in Scheme 3.

To check the generality of this new aminohydroxylation, we synthesised a set of benzoyloxyamines and subjected them to the reaction conditions. In all cases moderate to good yields of pyrrolidines were obtained (Scheme 4).

Surprisingly in none of these reactions was the piperidine derivative formed. We supposed that **2a** and **3a** might be in an equilibrium under the reaction conditions, however upon subjecting the pure isomers to the reaction conditions again or simply heating them, none of the corresponding regioisomer was formed. Therefore piperidine **3a** must be formed *via* an unusual 6-endo radical cyclisation. This surprising result might be related to the influence of the two alkyl groups on the rotamer distribution in the substrate (*gem* dialkyl effect)[13] or on the bond angles (Thorpe–Ingold effect).[14]



Scheme 4 Applying the conditions to other benzoyloxyamines.

In summary we have presented the first radical aminohydroxylation of double bonds. We believe that this new catalytic procedure will prove highly valuable for the synthesis of natural products like aminoalcohols and azasugars.

Further studies on this new reaction and towards other catalytic nitrogen-heteroatom bond additions to double bonds are currently being performed in our laboratory.

Notes and references

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