Cu(I)/Cu(II)-catalyzed allylic amination of alkenes

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ABSTRACT

Allylic hydrocarbons are selectively converted to the corresponding allyl amines in good to excellent yield by reaction with aryl hydroxylamines catalyzed by a 1:1 mixture of CuCl and $CuCl_2$ (10 mol %). Under these conditions unsymmetrical olefins react highly regioselectively with N-functionalization at the less substituted vinylic carbon. Trapping experiments indicate that a free nitrosoarene is not an intermediate in these reactions.
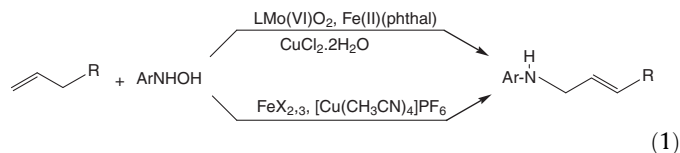
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1. Introduction

The selective formation of the C–N bond is of fundamental importance in organic synthesis with important application in the production of natural products, pharmaceuticals, and new materials.[1] Traditionally, the introduction of C–N bonds is largely based on functional group interconversions. In contrast, transition metal-catalyzed C–N bond formation by the activation of C=C and C–H bonds of hydrocarbons represents an attractive and atom economical approach to the synthesis of amines.[2]

Over the past several years, substantial efforts have been made in order to effect amination via a C–H bond activation strategy, particularly with regard to allylic and benzylic C–H bonds.[3–7] Direct methods for allylic amination include alkene reactions with S/Se-imido reagents[8] and *ene*-reactions with azo-,[9] N-carboalkoxy-nitroso[10] and N-sulfinylcarbamate derivatives.[11]

We and others contributed to the early development of metal-catalyzed aminations with the discovery of Mo(VI)[12] and Fe(II,III)[13,14]-catalyzed allylic aminations of alkenes by aryl hydroxylamines (Eq. 1). Further work by our group and the Cenini–Ragaini group led to metal-catalyzed allylic aminations using nitroarenes[15] and aminoarenes[16] as the aminating agents. In recent independent communications, our group[17] and Lau's group[18] found that the Cu-catalyzed reactions of olefins with aryl hydroxylamines produce moderate yields of allyl amines regioselectively, with N-functionalization at the less substituted original olefinic carbons. Lau's group also reported the α-amination of saturated ketones catalyzed by Cu(II) salts.[18]

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$$\text{(1)}$$

Our earlier mechanistic probes of allylic amination reactions catalyzed by Cu(I) suggested the involvement of a coordinated organonitrogen species as the ArN-transfer agent.[19] Various experimental and molecular modeling observations, coupled with the distinctive regioselectivity, led us to suggest a reaction pathway for the Cu-catalyzed allylic amination reactions.[19,20] Initially, Cu(II) is likely generated by Cu(I)-reduction of the ArNHOH; the available Cu(II) then oxidizes PhNHOH to PhNO with the formation of a Cu–C-nitroso complex. A redox reaction that interconverts Cu(I) and Cu(II) seems to be an essential feature for the reaction to proceed catalytically. In view of this analysis, we were of opinion that the use of a mixture of Cu(I) and Cu(II) salts (a redox couple) as catalyst would enhance the efficiency and product yield by limiting the production of the aromatic amine $ArNH_2$ from the Cu(I) reduction of ArNHOH. Testing this hypothesis forms the subject of the present work.

2. Results and discussion

Slow addition of the aryl hydroxylamine to a 1,2-dichloroethane solution at 100–120 °C (bath temperature) containing excess olefin and 10 mol % of 1:1 CuCl:$CuCl_2$ (**1**) produces N-aryl-N-allyl amines in good to excellent yields along with a small amount of N-containing byproducts including aniline, azobenzene, and azoxybenzene (Eq. 2). The effect on product yield of employing the mixed catalyst

Table 1
Mixed metal (Cu$^+$/Cu^{2+})-catalytic allylic amination of alkenes

Alkene	Allylamine	Yield[*] (%)	N-selectivity (%)
		73 (63)	90
		54	69
		62 (44)	74
		11	22
		24	44
		54	64
		41	50
		86	99
		88	99

[*] G.C. yield using sensitivity factor versus naphthalene internal standard; (isolated yield).

1 compared to CuCl or CuCl$_2$ alone was substantial; compare runs 1–3 with 38%, 45%, and 30% with Cu(I) and 40% (run 3) with Cu(II) from Table 1, and the product yield increased substantially.

$$\text{(2)}$$
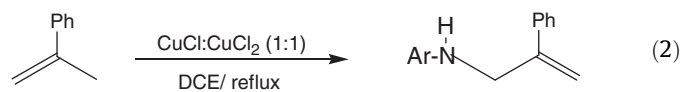
This prompted us to explore the scope and selectivity of the reaction with a range of allylic substrates under optimized conditions. The following conclusions can be made from Table 1: (i) double bond transposition (*ene*-reaction) occurs in unsymmetrical alkenes leading to allylic amines, (ii) disubstituted and trisubstituted alkenes produce the highest yields (N-functionalization) amination, and (iii) the reaction is highly regiospecific producing

Scheme 1.
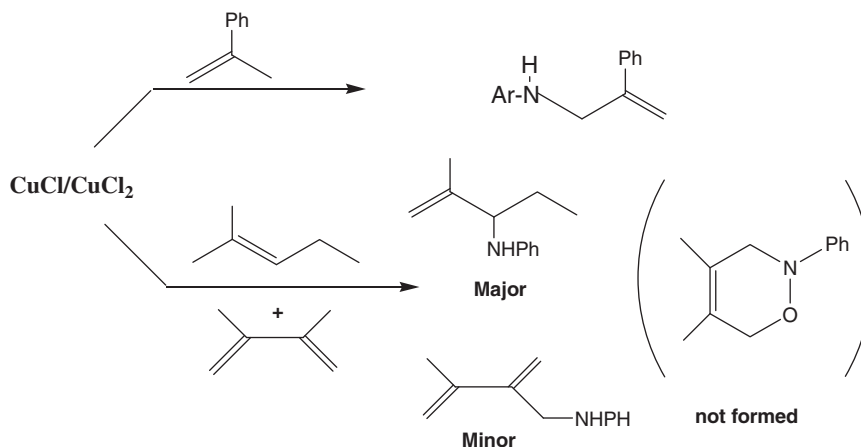
only single regioisomers. The reactivity and chemoselectivity features of the reaction are comparable to the Mo-[12], Fe-[13,14] Cu(II)[17], and Cu(I) –catalyzed[18–20] reactions reported earlier. However, the product yield is much higher in the present case. The high yield of reactions catalyzed by **1** compared to Cu(I) or Cu(II) alone can be explained by the presence of both Cu(I) and Cu(II) with **1** from the beginning to complete the redox cycle. On the other hand, a redox couple is not available in the Cu(I)-catalyzed system at the launch of the reaction and probably some hydroxylamine is reduced to ArNH$_2$ by Cu(I), thus limiting the reaction yield.

To probe whether the Cu(I)/Cu(II)-catalyzed and Cu(I)-catalyzed allylic aminations[19,20] proceed via the same reaction pathway, we employed the hetero Diels–Alder reaction of nitrosobenzene with 2,3-dimethylbutadiene as a trapping test for PhNO, a reactive enophile that could account for the reactivity/selectivity features of the aminations.[21] The effective Diels–Alder trapping of PhNO by 2,3-dimethylbutadiene at 120 °C (bath temperature) in the presence of 2-methyl-2-pentene in dichloroethane was first established (Scheme 1). When the amination reaction of 2-methyl-2-pentene by phenyl hydroxylamine catalyzed by **1** (10 mol %) was carried out in the presence of 2,3-dimethylbutadiene the allyl amines derived from the alkene (major) and diene (minor), and a trace amount of 3,4-dimethyl-N-phenylpyrrole were formed; the Diels–Alder adduct (trapping product from PhNO) was not detected (Scheme 1). In a separate experiment the D–A adduct was shown to be stable under the catalytic conditions employed. Thus both the Cu(I)/Cu(II)- and Cu(I)-only catalyzed reactions give the same results, that is, no Diels–Alder adduct is formed. The results further substantiate our earlier work,[19,20] which argues against the intermediacy of free PhNO in the catalysis by **1**, and in support of the involvement of Cu(I)/Cu(II) redox cycle. The mechanistic details can be found in our earlier work.[19,20]

3. Conclusion

In conclusion, an equimolar mixture of Cu(I)/Cu(II), **1**, catalyzes the regioselective allylic amination of alkenes using hydroxylamine as a nitrogen fragment donor in a much higher yield than what was obtained when Cu(I) or Cu(II) was used. Furthermore, the result substantiated our earlier findings, which argue against the intermediacy of free PhNO in the catalysis by **1**, and in support of the involvement of Cu(I)/Cu(II) redox cycle.

4. Experimental section

4.1. Representative procedure for the amination of olefins by aryl hydroxylamines catalyzed by CuCl/CuCl$_2$ 1

A 1,2-dichloroethane (2 mL) solution of olefin (4.6 mmol) and an equimolar mixture of anhydrous CuCl and CuCl$_2$ **1** (5 mol % each) was refluxed (under N$_2$/Ar). A phenyl hydroxylamine (0.75 mmol) solution in dichloroethane (8 mL) was delivered with a syringe pump to the heated solution over a period of 5–6 h. After cooling, the volatiles were removed under vacuum and the residue was dissolved in diethyl ether. Column chromatography was carried out on silica gel using dichloromethane/petroleum ether as eluant to afford the N-aryl allylamines (Table 1). The allyl amines were characterized by comparison of their spectroscopic data with authentic samples as described in the literature.[12–20]

Acknowledgments

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