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Copper-Catalyzed Intramolecular C–H Amination

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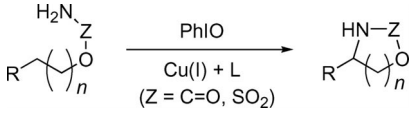
The amino-functionalization of tertiary, secondary and benzylic C–H bonds of tethered carbamates and sulfamates by iodosobenzene is catalyzed by Cu^{I}-diimine complexes in moderate to good yield. Employing homochiral imine-Cu catalysts affords oxazolidinones and oxathiazinanes with modest enantioselectivity.

Introduction

The nearly ubiquitous presence of nitrogen in both natural and synthetic bioactive compounds continues to drive the development of new C–N bond-forming reactions.[1] In recent years various nitrogenation methods have focused on C–H bond activation for introduction of the amino functional group.[2] Such reactions typically involve the reaction of a suitable nitrogen precursor, e.g. an azide,[3] iminoiodinane,[4] *N*-*O*-sulfonate[5] or *N*-halosulfonamide[6] with a metal pre-catalyst to presumably generate a nitrene (imido)-transition metal complex which inserts into the substrate C–H bond. Sulfonylimino-iodinanes and carbamoyliminoiodinanes, typically derived from in situ oxidation of sulfamates and carbamates with $PhI(OAc)_2$, have been used as reagents in intramolecular cycloamidation reactions of saturated C–H bonds catalyzed by dirhodium,[7] ruthenium-porphyrin[8] and -pybox,[9] Mn-salen[10] and disilver[11] complexes. Generally, moderate to good efficiencies and variable enantioselectivity have been achieved with catalysts having chiral ligands. Realization of the synthetic potential of such reactions calls for continuing efforts to develop new, selective and economical catalysts and reagents and to establish the scope, selectivity, and mechanism of such processes.

Results and Discussion

As part of an ongoing project to discover and elucidate new nitrogenation reactions of hydrocarbons catalyzed by non-precious metal catalysts, we focused first on the intermolecular amination of benzylic substrates by copper complexes. Diimine (Schiff base) ligands in combination with commercial $[Cu(CH_3CN)_4]PF_6$ were found to provide efficient catalysts for the intermolecular benzylic amination by anhydrous chloramine-T.[12] Mechanistic probes, both experimental and computational, support a reaction pathway involving a LCu-imido species as the active aminating agent which, as a ground state triplet, transfers the -NTs unit via a stepwise, radical process.[13] This contribution reports on the use of carbamates and sulfamates as substrates for *cycloamination* to produce *N*,*O*-heterocycles (Scheme 1) via Cu-catalyzed reactions employing commercially available iodosylbenzene as oxidant.



Scheme 1. Cu-catalyzed cycloamination.

In initial screening experiments the reactivity of carbamate **1** towards the oxidants $PhI(OAc)_2$ and PhIO, with prospective catalysts $Cu^{II}Cl_2$ and $[Cu^{I}(CH_3CN)_4]PF_6$ in various solvents was assessed. From this initial study the combination PhIO/$[Cu(CH_3CN)_4]PF_6$ (10 mol-%) in acetonitrile (45 °C, 12 h) was found to be the most effective, providing a modest 26% conversion to oxazolidinone **2** from **1** (Scheme 2). In the absence of the copper complex no oxazolidinone was produced. Having demonstrated the viability of Cu-catalyzed intramolecular benzylic amination the effects of auxiliary ligands on the reaction was evaluated as a means of improving the catalyst activity and controlling stereoselectivity. Reactions of **1** were conducted in the presence of representative ligand types under the same conditions as with the "unligated" $[Cu(CH_3CN)_4]PF_6$ (1:1 Cu/L) and the yield of oxazolidinone **2** was determined by NMR integration and/or isolation; the results are summarized in Table 1.

Substantial improvements in conversion and yield were found with phenanthroline and electron-poor diimine **A** while PPh_3 and electron-rich **B** were less effective than the CH_3CN-ligated Cu catalyst. Access to diverse diimine li-

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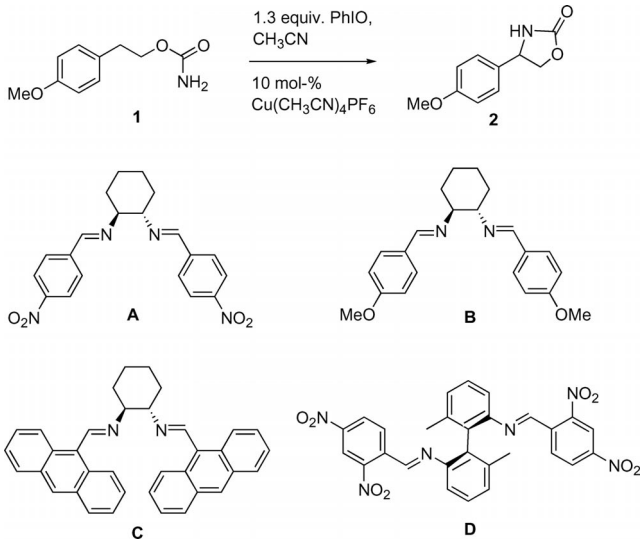


Scheme 2. Ligand effects on the cyclization of carbamate **1**.

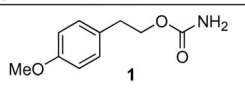
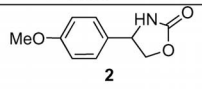
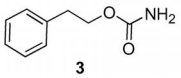
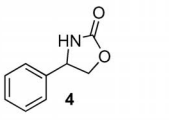
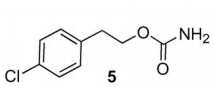
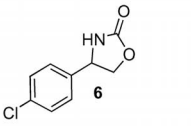
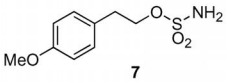
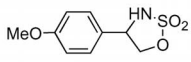
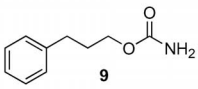
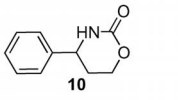
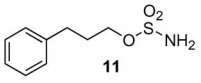
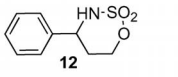
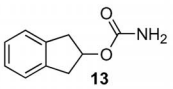
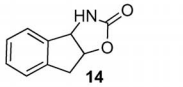
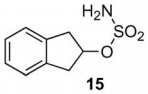
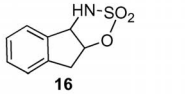
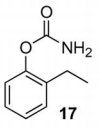
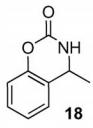
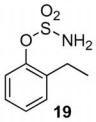
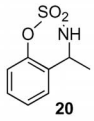
Table 1. Effect of ligands on the amination of **1**.

Entry	Ligand	Time [h]	% Yield (NMR)
1	CH_3CN	12	26
2	PPh_3	12	15
3	phenanthroline	12	48
4	**B**	12	15
5	**A**	12	62

gands from diamine and aldehyde building blocks provides a convenient set of ligands for catalyst tuning so these ligands were employed in follow-up studies.

An assessment of the scope of the amination of benzylic substrates was conducted with a set of representative sulfamates and carbamates using ligand **A** with $Cu(CH_3CN)_4PF_6$. The substrates were efficiently prepared from the corresponding alcohols by reaction with trichloroacetyl isocyanate (for carbamates) and $ClSO_2NH_2$ (for sulfamates), respectively.[14] The amination reactions were conducted under the same conditions established for the carbamate **1** {CH_3CN, room temp., 6–12 h, 0.1 equiv. [$Cu(CH_3CN)_4PF_6$]/0.1 equiv. L}; the results are summarized in Table 2. Moderate to good yields of cyclized amine derivatives were obtained with several of the substrates. Important features of the reactions include: 1) an increasing efficiency and conversion rate with more electron rich aromatic carbamates (entries 1–3); 2) failure of the sulfamate **7** to form the five-membered product **8** (entry 1 vs. 4); 3) the longer chain derivatives **9** and **11** both readily form the six-membered products (entries 5 and 6); 4) the more constrained indane derivatives **13** and **15** both efficiently cyclized to the five-membered products (entries 7,8); and 5) phenolic carbamate **17** failed to produce the six-membered **18**, whereas sulfamate **19** afforded the corresponding **20** with moderate efficiency. The sometimes divergent carbamate/sulfamate cyclization behavior (e.g. entries 1/4, 9/10) is probably a result of geometric differences between the trigonal carbamate and tetrahedral sulfamate functionalities, the former providing a less strained five-membered transition state and product, whereas the latter is less strained for six-membered ring formation.

Table 2. Cu-catalyzed amination of benzylic substrates.

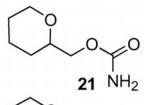
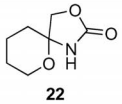
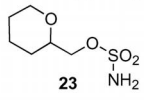
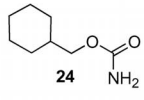
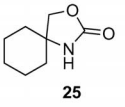
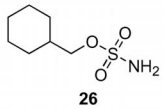
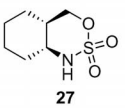
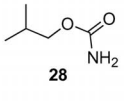
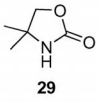
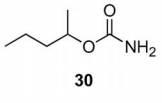
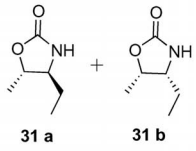
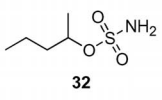
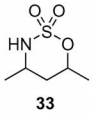
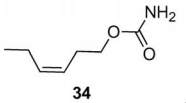
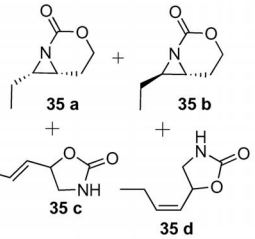
Entry	Substrate	Product	% Yield (conv.)
1			62 (67)
2			42 (44)
3			32
4			no reaction
5			54 (57)
6			56 (59)
7			62 (68)
8			70 (72)
9			no reaction
10			57

[a] Isolated yield after chromatography. [b] Conversion determined by NMR integration of substrate/product in the unpurified reaction mixture.

Prior studies of Cu-catalyzed *inter*molecular aminations (with chloramine-T) revealed little reactivity towards unactivated (non-benzylic, allylic) C–H bonds.[15] It was thus of interest to determine whether *intra*molecular insertions into less reactive aliphatic C–H bonds would be facilitated entropically. A set of aliphatic tethered carbamates and sulfites were prepared and subjected to **A**-Cu-catalyzed amination. Indeed, substrates possessing secondary and tertiary C–H centers are cyclized effectively (Table 3). Key features of these reactions are: 1) the efficient C–H amination of tertiary aliphatic carbamates (entries 1,3,5) to form oxazolidinones; 2) less efficient amination of secondary C–H

bonds (entries 4,6,7); 3) selective formation of five-membered (oxazolidinone) rings from carbamate precursors (entries 1,3,5,6); 4) selective formation of six-membered oxathiazinanes from sulfamate precursors (entries 4,7); 5) modest diastereoselectivity in the cycloamination of substrates **30** and **32** (entries 6,7); and 6) competitive C–H amination and azirdination of olefinic substrate **34** with low stereoselectively (entry 8). The regio- and diastereoselectivity of the Cu-catalyzed reactions are comparable to those found in other metal-catalyzed intramolecular aminations.[7–11] The limited chemoselectivity observed with carbamate **34** (entry 8), however, contrasts with the corresponding Rh_2- and Ag_2-catalyzed reactions in which C–H amination predominates with preservation of the double bond geometry. The *E*/*Z*-mixture obtained from **34** in the Cu-catalyzed reaction is indicative of a stepwise C–H insertion process. Our computational results from the corresponding intermolecular amination reactions support this picture[13] with the primary reactive species likely to be the triplet (diimine)-Cu(NZ)$^+$ complex, which reacts as an *N*-centered radical, effecting insertion by a stepwise process. This contrasts with the Rh_2-catalyzed intramolecular reactions which apparently proceed by concerted insertion of the nitrene complex.[7g]

Table 3. Cu-catalyzed amination of aliphatic substrates.

Entry	Substrate	Product	% Yield[a] (conv.)[b]
1	 **21**	 **22**	80 (86)
2	 **23**		no reaction
3	 **24**	 **25**	76 (79)
4	 **26**	 **27**	5 (9)
5	 **28**	 **29**	67 (72)
6	 **30**	 **31 a** **31 b**	47 (52) **a**:**b** = 2.2:1
7	 **32**	 **33**	12 (20) *syn*:*anti*: 1.8:1
8	 **34**	 **35 a** **35 b** **35 c** **35 d**	42 (51) **a**:**b**:**c**:**d** = 3.4:2.7:2.4:1

[a] Isolated yield after chromatography. [b] Conversion determined by NMR integration of substrate/product in the unpurified reaction mixture.

After establishing the ability of the ligated-Cu systems to catalyze C–H amination, the homochiral ligands **A**, **C** and **D** were tested for their ability to mediate enantioselective aminations of the prochiral benzylic substrates **1**, **13** and **15**. All reactions were conducted under the previously established conditions with 1:1 L*/Cu (PhIO, CH_3CN, 45 °C). The optical purity of the isolated amination products was determined by chiral HPLC; the results are shown in Table 4. In each case a low but significant enantioselectivity was observed, comparable in magnitude to the corresponding Cu-catalyzed *inter*molecular reactions.[12] These results could reflect ineffective stereoinduction by the L*Cu-imido intermediate and the stepwise C–H insertion process.

Table 4. Enantioselective amination with chiral diimines.

Entry	Ligand	Product	% *ee*
1	**A**	**16**	16[a]
2	**D**	**14**	13[b]
3	**C**	**14**	18[b]
4	**A**	**8**	14[a]

[a] Chiralcell OD-H, 10% 2-propanol/90% hexane. [b] Chiralcell OJ-H, 10% 2-propanol/90% hexane.

Conclusions

In summary, we have developed a catalytic method employing economical copper-diimine catalysts for the oxidative cyclization of carbamates and sulfamates to corresponding five- and six-membered *N*,*O*-heterocycles. Both benzylic and less reactive saturated substrates are effectively cycloaminated, in contrast to corresponding (diimine)Cu-catalyzed intermolecular reactions which are typically ineffective for unactivated hydrocarbons. The hydrolytic convertibility of these products to 1,2- and 1,3-amino alcohol derivatives further amplifies their synthetic value and portends their valuable application in the stereoselective synthesis of complex molecules.[16]

Experimental Section

General Procedure for Preparing Carbamate Substrates: The aryl carbamates were prepared by dissolving the alcohol precursor (1 equiv.) in dry $ClCH_2CH_2Cl$ (12 mL) in a flask under an argon atmosphere. The trichloromethylisothiocyanate (1.2 equiv.) was then added slowly to the reaction mixture at 0 °C. The reaction was monitored by TLC until all the starting material was consumed. After 5 h K_2CO_3 (0.1 equiv.) was added and stirring was continued for 10 min. Methanol (12 mL) was then added slowly

to the mixture with vigorous stirring. After stirring the mixture overnight, it was poured into saturated aqueous NH_4Cl and extracted three times with CH_2Cl_2. The separated organic phase was dried with $MgSO_4$ and concentrated by rotary evaporation. H-NMR analysis indicated that the product carbamates were formed in > 95% purity and were thus used without further purification.

General Procedure for Preparing Sulfamate Substrates: Formic acid (283 μL, 7.5 mmol) was added to neat $ClSO_2NCO$ (653 μL, 7.5 mmol) at 0 °C with vigorous stirring; the mixture gradually solidified. To the resulting white mass was added 5.0 mL of dry acetonitrile and the contents were warmed to room temperature. After stirring for 5 h, the solvent was removed by rotary evaporation. In a separate flask the alcohol precursor (3.0 mmol) was treated with NaH (3.5 mmol) in 10 mL of DMF. The $ClSO_2NH_2$ produced above was then added to the alkoxide mixture at 0 °C with vigorous stirring. The mixture was warmed to room temp. and stirred overnight. The reaction was quenched by the addition of 15 mL of H_2O and extracted with ethyl acetate and saturated brine. The combined organic extracts were dried with $MgSO_4$, and concentrated under reduced pressure. H-NMR analysis indicated that the product sulfamates were obtained in > 95% purity and were thus used without further purification.

Procedure for Cu-Catalyzed Amination: Commercial $Cu(CH_3CN)_4$-PF_6 (28 mg, 0.073 mmol), the ligand (0.073 mmol) and 5 mL of dry CH_3CN were added to a round-bottomed flask containing dry molecular sieves (4 Å, ca. 200 mg) under argon. To the well-stirred suspension carbamate 1 (0.10 g, 0.73 mmol) was added. Anhydrous iodosylbenzene (0.20 g, 0.95 mmol) was added after 30 min and the mixture was stirred at 45 °C overnight. The mixture was then filtered through Celite and the filtrate was concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (4:1 dichloromethane/ethyl acetate).

Characterizational Data for New Compounds: (1) ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.12 (t, J = 2.4 Hz, 2 H), 6.83 (dd, J = 3, 1.8 Hz, 2 H), 4.63 (s, 1 H), 4.22 (t, J = 7.2 Hz, 2 H), 3.77 (s, 3 H), 2.86 (t, J = 7.2 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 158.2, 156.7, 129.8, 131.2, 113.8, 65.7, 55.2, 34.5 ppm. ESI-MS calcd. m/z [M + Na] 218.0793, found 218.0789. (2) White solid, R_f = 0.34, EtOAc/CH_2Cl_2 (1:4). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.2 (d, J = 6.3 Hz, 2 H), 6.86 (d, J = 8.7 Hz, 2 H), 5.34 (s, 1 H), 4.84 (t, J = 7.7 Hz, 1 H), 4.64 (t, J = 8.8 Hz, 1 H), 4.1 (t, J = 7.8 Hz, 1 H), 3.75 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 160.0, 159.3, 131.2, 127.4, 114.5, 72.7, 55.9, 30.9 ppm. ESI-MS calcd. m/z [M + Na] 216.0636, found 216.0642. (5) white solid, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27 (d, J = 9 Hz, 2 H), 7.16 (dd, J = 2.4, 1.5 Hz, 2 H), 4.57 (s, 2 H), 4.26 (t, J = 6.7 Hz, 2 H), 2.91 (t, J = 6.7 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 156.6, 136.3, 132.3, 130.2, 128.6, 65.2, 34.7 ppm. ESI-MS calcd. m/z [M + Na] 222.0298, found 222.0290. (6) white solid, R_f = 0.24, EtOAc/CH_2Cl_2 (1:4). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32 (d, J = 8.7 Hz, 2 H), 7.24–7.19 (m, 2 H), 5.46 (s, 1 H), 4.88 (t, J = 8.1 Hz, 1 H), 4.67 (t, J = 8.4 Hz, 1 H), 4.08 (dd, J = 8.6, 6.9 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 159.1, 137.8, 134.8, 129.4, 127.4, 55.7, 30.9 ppm. ESI-MS calcd. m/z [M + Na] 220.0141, found 220.0137.

Supporting Information (see also the footnote on the first page of this article): General procedures for preparing carbamate and sulfamate substrates, characterizational data for all oxazolidinone and oxathiazinane products.

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