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Copper(II) Carboxylate Promoted Intramolecular Carboamination of Alkenes for the Synthesis of Polycyclic Lactams

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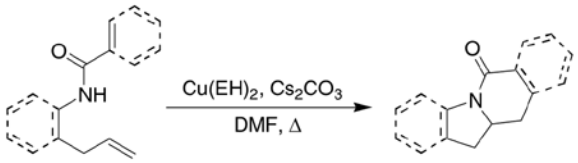
Abstract

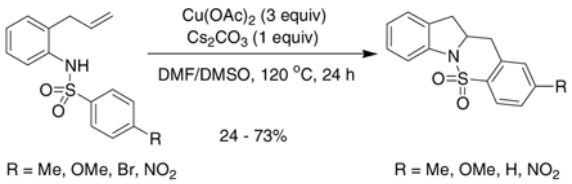


$Cu(EH)_2$ = Copper(II) Ethylhexanoate

The copper(II) carboxylate promoted intramolecular carboamination reactions of variously substituted γ-alkenyl amides have been investigated. These oxidative cyclization reactions efficiently provide polycyclic lactams, useful intermediates in nitrogen heterocycle synthesis, in good to excellent yields. The efficiency of the carboamination process is dependent upon the structure of the amide backbone as well as the nitrogen substituent.

Nitrogen heterocycles are useful intermediates in complex molecule synthesis, as well as an abundant class of biologically active molecules. The rapid assembly of such molecules and the search for new molecular scaffolds provides a constant challenge to the synthetic and medicinal chemist, thus, new methods of entry into these systems are especially useful.[1] One particularly attractive method is the intramolecular carboamination reaction of alkenes.[2]

In 2004, our lab disclosed the first copper(II) carboxylate promoted intramolecular carboamination reaction of *N*-arylsulfonyl 2-allyl anilines (Eq 1).[2c] More recently we reported further substrate versatility and diastereoselectivity, and provided an experimental analysis of the reaction mechanism.[2f]



R = Me, OMe, Br, NO_2 R = Me, OMe, H, NO_2

(1)

In both of these accounts, a variety of γ and δ alkenyl *N*-aryl sulfonamides were shown to undergo the oxidative cyclization in the presence of copper(II) carboxylates to produce the

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corresponding polycyclic sultams in modest to good yield.[2c, 2f] In an effort to expand the utility of the method, a variety of aryl-, vinyl-, and aliphatic γ-alkenyl amides were investigated in the copper(II) promoted carboamination reaction. The results of our findings are described in this report.

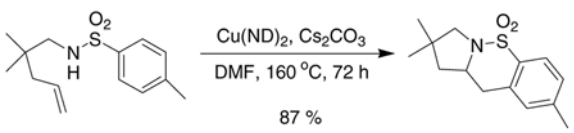
Under our original reaction conditions (e.g. Eq 1), 2-allyl aniline amides were poor substrates for the copper(II) carboxylate promoted intramolecular carboamination reaction, significantly less reactive in comparison to their aryl sulfonamide counterparts (Table 1, entries 1 and 2).[2f] Success in this matter was subsequently realized when *N*-benzoyl-2-allyl aniline was treated with more organic soluble copper(II) salts and slightly higher reaction temperatures, providing polycyclic lactam **2a** in moderate yield (Table 1). The organic soluble copper salts, Cu(II) neodecanoate [$Cu(ND)_2$] and Cu(II) ethylhexanoate [$Cu(EH)_2$], were shown to be more reactive than $Cu(OAc)_2$ (Table 1, entries 3 and 4).[2f, 3] $Cu(EH)_2$ was subsequently used throughout the substrate screening because of its lower cost and ease of use [$Cu(EH)_2$ is purchased as a solid whereas $Cu(ND)_2$ is purchased as a solution in toluene].

A variety of 2-allyl aniline amides were oxidatively cyclized in an efficient manner using the optimized reaction conditions (Table 2). The mildly electron deficient halogenated substrates **1b** and **1c** reacted efficiently (Table 2, entries 2 – 4 and 7). Worth noting, the flourine was displaced with dimethylamine when the reaction was run in DMF (Table 2, entry 3) (dimethylamine presumably arises from thermally decomposed DMF). When *tert*-butyl benzene was used as solvent, the carboamination adduct was obtained in good yield with the fluorine intact (Table 2, entry 4). 4-Cyano and 4-methoxy arylamides displayed comparatively lower reactivity (Table 2, entries 5 and 6). Meta-substituted aryl amides demonstrated a preference (ca. 1.8:1) for the ortho addition product over the para (Table 2, entries 7 and 8). This ortho preference is consistent with that of meta-substituted aryl sulfonamides[2c, 2f] and provides evidence for C-C bond formation via the addition of a carbon radical to an aromatic ring.[2f, 4]

2-Allyl aniline derived vinyl amides are reactive carboamination substrates as well (Table 3). Interestingly, the unsubstituted vinyl amides **9a – c** cyclized in 6-*endo* fashion at 140 °C to provide the polycyclic α,β-unsaturated lactones **10a – c** in good yield (Table 3, entries 1–3). These observations are in contrast to similar palladium catalyzed processes where the 5-*exo* cyclization product (similar to **11**) was the only observed regioisomer.[2d,5] Increasing the reaction temperature to 190 °C, however, resulted in a 1.2:1 mixture of the 6-*endo* to 5-*exo* carboamination adducts (Table 3, entry 4). The 5-*exo* product **11a** terminated in hydrogen atom capture rather than olefin formation. This observation presents an intriguing example of temperature control of regiochemistry.

Disappointingly, the more substituted vinyl amides **12** and **14** were less reactive (Table 3, entries 5 and 6). These substrates required higher reaction temperature (190 °C) in order to consume most of the substrate, but in doing so, resulted in the concomitant formation of a mixture of 5-*exo* cyclization products and isomerized olefin starting material.

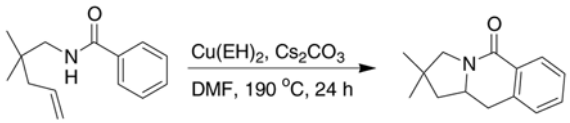
Our previous studies showed that the copper(II) carboxylate promoted intramolecular carboamination reaction is effective in cyclizing a variety of aliphatic *N*-aryl sulfonamides (e.g. Eq 2).[2f]



(2)

This prompted us to investigate the cyclization reaction of a corresponding *N*-benzoyl aliphatic amide (Eq 3). Unfortunately, this substrate was shown to be unreactive upon heating to 190 ° C for 24 h.

This result led us to examine a variety of structurally different imides and amides as shown Table 4. Imide **17** cyclized in high yield while the amide substrate in Eq. 3 did not react. This indicates that an sp^2 hybridized

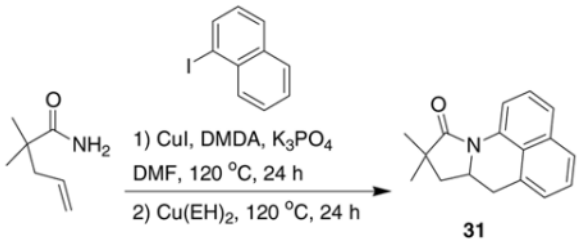


(3)

carbon in the substrate's backbone decreases the activation energy for cyclization. (This could be due to lower relative torsional strain in the five-membered ring of the transition state and product for substrate **17**.) In addition, imide **17** cyclized at lower temperature and in higher yield and selectivity than its benzyl amide counterpart **19** (Table 4, entries 1 and 2). Thus, the imide is more reactive than the alkyl amide. Substrates with geminally disubstituted carbon backbones cyclized more efficiently due to the Thorpe-Ingold effect (compare entries 6 and 7, Table 4).[6]

The aryl amides **22** and **25** were able to undergo the cyclization in an efficient manner albeit with the formation of the hydroamination byproducts (Table 4, entries 3 and 4). In order to reduce hydroamination and maximize carboamination, a less hydrogen atom donating solvent, i.e. *t*-butyl benzene, was used. Although increased selectivity for carboamination was observed, formation of the hydroamination byproduct still occurred. Regardless, these are the first examples where two fused 5-membered rings are formed in the copper(II) carboxylate promoted intramolecular carboamination reaction. Substrate **28**, which lacks the geminal methyl groups in the backbone, only produced hydroamination adduct **29** (Table 4, entry 5). Because of the apparent difficulty in forming a 5-membered ring with the aryl substituent[7] (vide supra), naphthalene substrates **30** and **32** were investigated. Gratifyingly, both substrates underwent the oxidative cyclization in good yield without the simultaneous formation of the hydroamination byproduct (Table 4, entries 6 and 7).

During the synthesis of naphthalene substrate **30**, an interesting observation was made. When the corresponding amide was treated under the coupling reaction conditions developed by Buchwald et al.[8] (5 mol% CuI, DMDA, iodonaphthalene, K_3PO_4, in DMF at 120 °C), trace amounts of carboamination (ca. 2–3%) product (**31**) are observed in the ^{1}H NMR. This occurrance is easily explained by the ability of Cu(I) to disproportionate into Cu(II) and Cu (0).[9] Thus, in an effort to exploit this reactivity, a one-pot arylation/carboamination reaction was performed. Upon completion of the coupling reaction, 3 equivalents of $Cu(EH)_2$ was added to the reaction mixture. After 24 h the carboamination adduct was obtained in 71% yield (Eq 4).



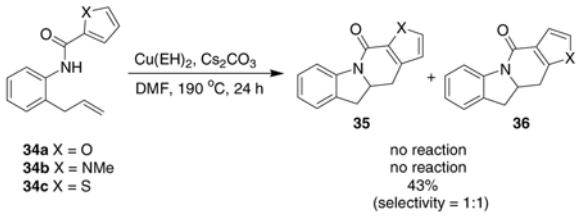
31

71 %

(4)

Another interesting observation was made when performing the carboamination reaction on heteroaromatic ring amides. Both the amido furan **34a** and the amido pyrrole **34b** derivatives of 2-allyl aniline were unreactive substrates. The amido thiophene **34c** cyclized in 43% yielding *two* carboamination products **35c** and **36c** in a 1:1 ratio (Eq 5).

This observation can be rationalized based on the mechanism shown in Scheme 1. Thus, syn aminocupration followed by homolysis of the resulting



(5)

unstable organocopper intermediate gives primary radical **A**.[2f] This radical can either add 1,6 to give the carboamination product **35c** after oxidation of the aryl radical intermediate **B**, or 1,5 (*ipso*) giving rise to carboamination product **36c** via intermediate **C**, radical migration and oxidative re-aromatization as shown in Scheme 1.[10] Rearrangement of intermediate **C** via a carbocation is also possible.

In conclusion, the intramolecular copper(II) carboxylate promoted carboamination reaction is an efficient method to form a variety of polycyclic lactams. The substrate scope has been expanded from sulfonamides, to include not only aryl amides, but vinyl amides and alkyl imides as well. Furthermore, a simple one-pot arylation/carboamination reaction sequence was achieved. The synthetic utility of this methodolgy and its application in natural product as well as biologically active molecule synthesis is currently ongoing in our lab and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We thank Mr. Dov Shalman (Northwestern University), Ms. Fatima Sequiera (University at Buffalo, ACS administered PRF Summer Scholar 40968-G1), and Ms. Melantha Jackson (from Utica College, NSF REU Fellowship at SUNY, Buffalo, CHE-0453206) for preliminary studies. This work was

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C-C bond formation, see Chemler SR, Fuller PH. Chem Soc Rev 2007;36:1153. [PubMed: 17576482] and references therein

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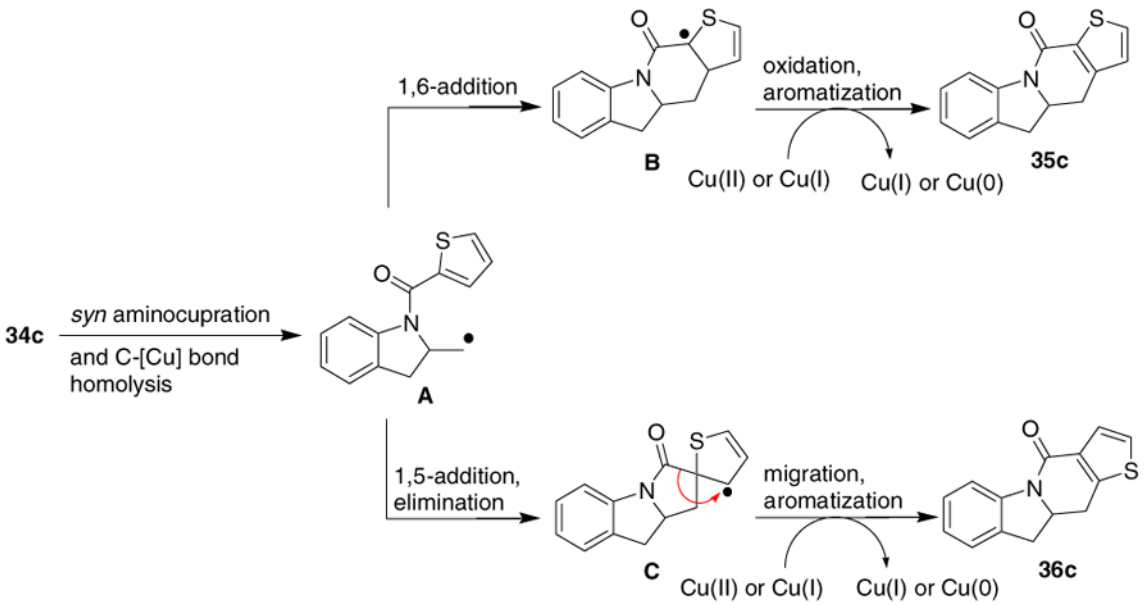
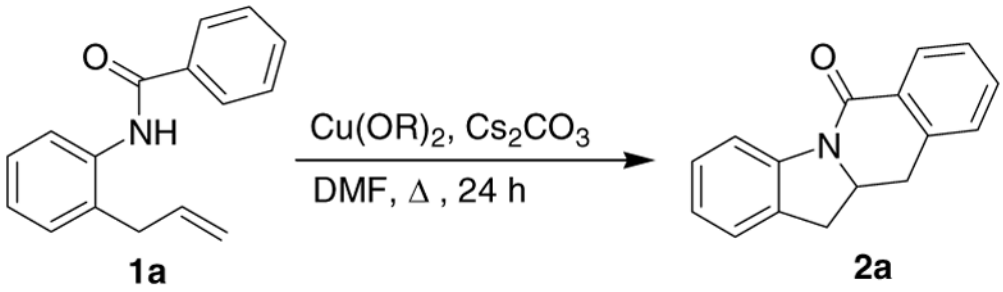


Scheme 1.
Mechanistic rational for carboamination product **36c**.

Table 1

Reaction optimization.[a]



1a 2a

entry	copper salt	temperature	yield[b]
1[c]	$Cu(OAc)_2$	170 °C	16%
2[c]	$Cu(OAc)_2$	190 °C	39%
3	$Cu(ND)_2$	190 °C	59%
4	$Cu(EH)_2$	190 °C	61%

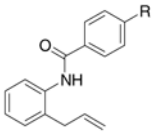
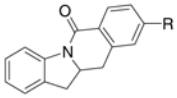
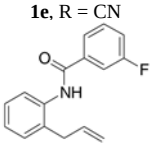
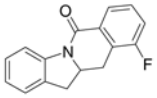
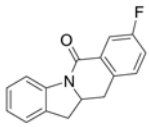
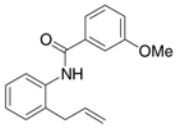
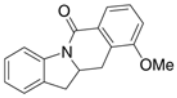
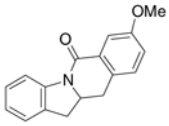
[a] Conditions: Substrate in DMF (0.1 M) was treated with $Cu(OR)_2$ (3 equiv) and Cs_2CO_3 (1 equiv). The mixture was heated to the indicated temperature for 24 h in a pressure tube.

[b] Yields refer to product isolated by chromatography on SiO_2.

[c] DMSO (4 equiv) was used. The remainder of the material was either starting olefin or olefin-isomerized starting material. $Cu(EH)_2$ = copper(II) ethylhexanoate, $Cu(ND)_2$ = copper(II) neodecanoate.

Table 2

Carboamination of *o*-allyl aryl amides[a]

entry	substrate	product(s)	yield[b](selectivity)
			
1	**1a**, R = H	**2a**, R = H	61%
2	**1b**, R = Cl	**2b**, R = Cl	63%
3	**1c**, R = F	**2c**, R = NMe_2	73%
4[c]	**1c**, R = F	**2d**, R = F	71%
5	**1d**, R = OMe	**2e**, R = OMe	56%
6	**1e**, R = CN	**2f**, R = CN	42%
7	 **3**	 **4**	58%**4:5** = 1.7:1  **5**
8	 **6**	 **7**	44%**7:8** = 1.9:1  **8**

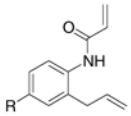
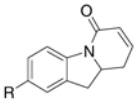
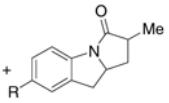
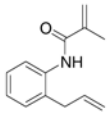
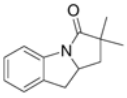
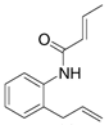
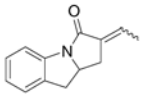
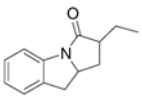
[a]Conditions. Substrate in DMF (0.1 M) was treated with $Cu(EH)_2$ (3 equiv) and Cs_2CO_3 (1 equiv). The mixture was heated to 190 °C for 24 h in a pressure tube.

[b]Yields refer to the sum of products isolated by chromatography on SiO_2. The remainder of the material was either starting olefin or olefin-isomerized starting material.

[c]*t*Butyl benzene was used as solvent. The structures of the products (e.g., regioisomer) were assigned by analysis of the aromatic region of the ^1H NMR spectra.[1]

Table 3

Carboamination of *o*-allyl vinyl amides[a]

entry	substrate	product(s)		yield[b](selectivity)
				
1	**9a**, R = H	**10a**, R = H	**11a**, R = H	72%(**10a:11a** = >20:1)
2	**9b**, R = OMe	**10b**, R = OMe	**11b**, R = OMe	74%(**10b:11b** = >20:1)
3	**9c**, R = Cl	**10c**, R = Cl	**11c**, R = Cl	71%(**10c:11c** = >20:1)
4[c]	**9a**, R = H	**10a**, R = H	**11a**, R = H	56%(**10a:11a** = 1.2:1)
5[c]	 **12**	 **13**		38%
6[c]	 **14**	 **15**	 **16**	49%(**15:16** = 2.5:1)

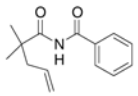
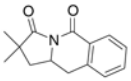
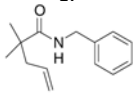
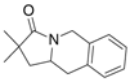
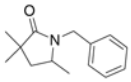
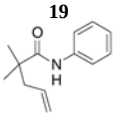
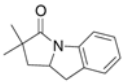
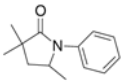
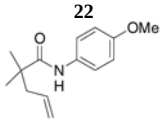
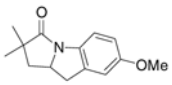
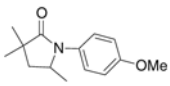
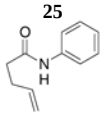
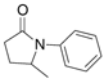
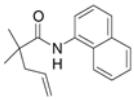
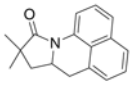
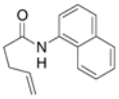
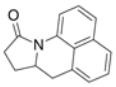
[a] Conditions. Substrate in DMF (0.1 M) was treated with $Cu(EH)_2$ (3 equiv) and Cs_2CO_3 (1 equiv). The mixture was heated to 140 °C for 24 h in a pressure tube.

[b] Yields refer to the sum of products isolated by chromatography on SiO_2. The remainder of the material was either starting olefin or olefin-isomerized starting material.

[c] Heated to 190 °C for 24 h.

Table 4

Carboamination of aliphatic imides and amides.[a]

entry	substrate	product(s)		yield[b](selectivity)
1	 **17**	 **18**		81%
2[c,d]	 **19**	 **20**	 **21**	70%(**20:21** = 1.6:2)
3[c,e]	 **22**	 **23**	 **24**	83%(**23:24** = 3.3:1)
4[c,e]	 **25**	 **26**	 **27**	79%(**26:27** = 3.4:1)
5[c]	 **28**	 **29**		56%
6	 **30**	 **31**		81%
7[c]	 **32**	 **33**		74%

[a] Conditions. Substrate in DMF (0.1 M) was treated with $Cu(EH)_2$ (3 equiv) and Cs_2CO_3 (1 equiv). The mixture was heated to 120 °C for 24 h in a pressure tube.

[b] Yields refer to the sum of products isolated by chromatography on SiO_2. The remainder of the material was either starting olefin or olefin-isomerized starting material.

[c] Heated to 190 °C.

[d] Reaction run for 72 h.

[e] *t*butyl benzene was used as solvent.