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Evolution of copper(II) as a new alkene amination promoter and catalyst

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Abstract

Copper(II) carboxylates and chiral copper(II) triflate-bis(oxazoline) complexes promote and catalyze intramolecular alkene carboamination, diamination and aminooxygenation reactions, creating an array of nitrogen heterocycles. High diastereoselectivity and enantioselectivity can be achieved in these transformations. This account reviews the discovery and development of these useful and interesting reactions.

Keywords

Alkene; Carboamination; Diationation; Aminooxygenation; Enantioselective; Copper

1. Introduction

Copper-promoted and catalyzed C–N bond forming reactions provide useful and relatively inexpensive entry into diverse and valuable organic products. Most commonly, these reactions involve Ullman-type reactions [1–4] with aryl or vinyl halides, cross-coupling with aryl- or vinylboronates [2] or additions to alkynes involving copper-acetylide intermediates [5,6]. Recently we found that copper(II) carboxylates can promote the intramolecular addition of electron-deficient amines onto unactivated alkenes [7]. The discovery was surprising as such alkene aminations have historically been conducted with Pd(II) catalysts using Cu(II) as stoichiometric oxidant to regenerate the Pd-catalyst (aza-Wacker conditions) [8,9]. We recently found, however, that copper(II) carboxylates are sufficient to promote intramolecular amine additions to alkenes at more elevated temperatures (90–120 °C) and the products of these reactions are net difunctionalizations such as carboamination [7,10], diamination [11] and aminooxygenation [10,12].

2. Copper(II)-promoted and catalyzed intramolecular alkene carboamination

The simultaneous formation of C–N and C–C bonds across an alkene, heretofore referred to as carboamination, is an attractive method for the synthesis of nitrogen heterocycles [13–15]. Nitrogen heterocycles are common components of bioactive molecules.

2.1. Copper(II)-promoted intramolecular alkene carboamination

We reported the discovery of the copper(II) acetate promoted intramolecular carboamination of terminal alkenes in 2004 [7]. This reaction yielded polycyclic indoline sultams **2** from *N*-aryl-sulfonyl-2-allylaniline substrates **1** (Scheme 1). A survey of aryl-sulfonamide substituents revealed that electron-donating groups increased reactivity compared to

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electron-withdrawing substituents (when R = CF₃, no reaction, unpublished result). Interestingly, meta-substituted arylsulfonamides **3** provided ca. 2:1 mixtures of ortho and para-substituted carboamination adducts **4** and **5**, respectively. The slight preference for ortho substitution indicated that electronic, rather than steric factors, dominated the regioselectivity in the C–C bond forming step. Such selectivity has been observed in radical additions to aromatic rings [16–18].

We proposed two possible mechanistic pathways for this transformation. Path A involves N–Cu coordination followed by intramolecular cis-aminocupration onto the olefin to form an unstable organocopper(II) intermediate **7**. Subsequent C–Cu(II) homolysis to the primary carbon radical **9** and carbon radical addition to the aryl ring forms aryl radical **10**. Aryl radical oxidation by Cu(II) and loss of H⁺ provides the sultam product **2a**. Alternatively (Path B), N–Cu intermediate **6** could undergo homolysis to generate nitrogen radical **8**. 5-Exo trig cyclization could generate the primary carbon radical **9** and intramolecular radical addition to the aryl ring followed by re-aromatization could provide sultam **2a**.

That electron-rich sulfonamides are more reactive than electron poor sulfonamides (Scheme 1) could be the result of either poor amine nucleophilicity, slowing down path A, or poor oxidation potential, slowing down path B. The substituent could also influence the rate of the aromatic addition step. [Subsequent to these studies, we found that a chiral Cu(OTf)₂·bis(oxazoline) complex can engender chiral carboamination products (*vide infra*). If the reaction promoted by Cu(II) carboxylates is largely similar to the reaction catalyzed by the Cu(OTf)₂·bis(oxazoline) complex, as we believe, then the ability to induce asymmetry in this manner unequivocally excludes a path involving metal-free nitrogen radical addition to the alkene, as in Path B.]

The scope of the *N*-arylsulfonyl-2-allylaniline-type substrate class was recently expanded to include 5-allyl-*N*-sulfonylated coumarins and quinolones [19]. We expanded the scope of the carboamination reaction further to include aliphatic sulfonamides and demonstrated that both pyrrolidines and piperidines could be obtained especially when more organic soluble copper(II) carboxylates, e.g., copper(II) neodecanoate [Cu(ND)₂] or copper(II) 2-ethylhexanoate [Cu(EH)₂], are used (Scheme 3) [10]. The yields range from moderate to good (43–87%) and the reaction temperatures are high (160–210 °C). Internal olefins do not provide carboamination adducts, they are less reactive and tend to give oxidative amination products (e.g., **19**).

Diastereoselective reactions were performed. While no selectivity was observed with the 2-phenyl-substituted γ -alkenylsulfonamide **20**, the γ -substituted γ -alkenyl sulfonamide **22** gave a 3:1 ratio favoring the trans diastereomer, and α -substituted sulfonamides **24** gave >20:1 selectivity for the 2,5-cis pyrrolidines **25** (Eqs. (1)–(4)). Several of these reactions suffered from a competing hydroamination process (to give products like **15**, Scheme 3). The hydroamination product is thought to arise from hydrogen atom abstraction from the solvent by the carbon radical intermediate. (Indeed, use of DMF-d₇ as solvent gave deuterium incorporation in the hydroamination product [20]). We subsequently found that most of these reactions can be run with Cu(2-ethylhexanoate)₂ as promoter in aromatic solvents like xylenes and PhCF₃ at 120 °C (Eq. (4), unpublished results). The lower temperature conditions allow for greater selectivity of carboamination over hydroamination.

(1)

(2)

(3)

(4)

Equations (1)–(4). Copper(II) carboxylate promoted diastereoselective carboaminations. Cu(ND)_2 = copper(II) neodecanoate. Cu(EH)_2 = copper(II) 2-ethylhexanoate.

Polycyclic lactams can also be synthesized via copper(2-ethyl-hexanoate)₂ promoted intramolecular carboamination of γ -alkenyl amides and imides (Scheme 4) [21].

2.2. Reactivity trends as mechanism probes

2.2.1. Evidence for the presence of a primary carbon radical—We provided evidence for the presence of a primary carbon radical intermediate (c.f. **9**, Scheme 2) by 1) generating the radical independently from an alkylbromide and observing the same regiochemical product distribution as in our copper-promoted reaction (Eqs. (5) and (6)) and 2) trapping the carbon radical with tetramethyaminopyridyl radical (TEMPO), a stable oxygen radical (Eq. (7)) [10]. A stereospecifically labeled deuterated substrate also produced

a 1:1 ratio of diastereomeric products (Eq. (8)), indicating the presence of an sp^2 -hybridized intermediate, the primary carbon radical. This experiment also indicates that the carbon radical does not revert back to substrate **11-D** as the starting alkene is recovered from the reaction conditions without alkene isomerization having occurred.

(5)

(6)

(7)

(8)

Equations (5)–(8). Evidence for the primary carbon radical. $\text{Cu}(\text{ND})_2 = \text{Cu}(\text{II})$ neodecanoate.

2.2.2. Stereochemical trends to analyze the alkene amination step—Since stereochemical information is lost in the proposed C–Cu homolysis step (see diastereomer mixture, Eq. (8)), we were unable to use deuterium-labeled substrates to infer a *cis* or *trans* aminocupration process. This tool is commonly used in the mechanistic analysis of palladium-catalyzed reactions [22–24]. However, since we observed the carboamination reaction was highly diastereoselective with α -substituted γ -alkenyl sulfonamide substrates, generating 2,5-*cis* pyrrolidine products (Eqs. (3) and (4)), we were able to compare our reaction to other reactions that generate 2,5-disubstituted pyrrolidines in alkene cyclization reactions. We considered mechanisms involving 1) *trans*-aminometallation (path A), 2) *cis*-aminometallation (path B) and 3) nitrogen radical cyclization (path C, Scheme 5).

By surveying a number of literature reports and observing results of additional reactions conducted in our own lab [10], we found that for intramolecular alkene aminations of secondary amines, the nitrogen radical [25–27] and the trans-amino-metallation mechanisms [28,29] generally favor formation of 2,5-trans pyrrolidines while cis-aminometallation mechanisms [22,30–32] favor formation of 2,5-cis pyrrolidines.

This analysis led to our working hypothesis that the reaction involves N–Cu coordination, cis-aminocupration, homolysis of the C–Cu bond and addition of the radical to the neighboring aromatic ring (Path B, Scheme 5). The cis pyrrolidine selectivity can be rationalized by minimization of steric interactions between the N-substituent and the α -substituent leading to a preferred anti-arrangement of these two groups (Fig. 1). This preferred anti-arrangement can be accommodated by the chair-like transition state **A** or the boat-like transition state **B**, both of which lead to the cis-pyrrolidine (Fig. 1). Further, we believe that the cis-aminocupration step is the stereochemistry-determining and rate-limiting step in the mechanism. This is supported by the fact that the rate of the reaction is highly substrate dependent where substrates predisposed to cyclize due to entropy factors (e.g., 2-allyl aniline-derived, gem-dialkyl backbone and smaller ring size) are more reactive than less cyclization prone substrates. We have also observed internal olefins are significantly less reactive than terminal olefins [10], which we believe is due to a steric deterrent in the N–C bond forming step, likely the steric demands of the copper(II) salt. Kinetic data currently being gathered to evaluate the reaction mechanism is consistent with this hypothesis.

2.3. Catalysis and asymmetric catalysis in the carboamination reaction

Since we believed copper to be present in the nitrogen-carbon bond forming step, we were optimistic a catalytic enantioselective method using chiral ligands on copper could be developed. The first step toward this goal involved identifying an oxidant that could turn over Cu(I) to Cu(II) in aprotic organic solvent in the presence of base. After screening a number of oxidants, we found that manganese (IV) oxide (MnO_2 , <5 micron activated, 85%) can be used as an inexpensive, readily available oxidant that can be easily removed and potentially recycled. Thus, 300 mol% MnO_2 , 20 mol% $\text{Cu}(\text{OTf})_2$ and 20 mol% bipyridine as ligand in toluene (120 °C, pressure tube) provided an efficient carboamination reaction of γ -alkenyl sulfonamide **11** (Table 1, entry 1)). PhCF_3 proved a superior solvent to PhCH_3 for reducing the hydroamination side product **39** (entry 2). Aromatic solvents were used since they are generally good solvents for MnO_2 and can provide elevated reaction temperatures (110–120 °C). A screen of bis(oxazoline) ligands revealed that the commercially available ligand 2,2-bis[(4*R*)-4-phenyl-2-oxazolin-2-yl]propane, (*R,R*)-Ph-box, gave the best yield and %ee (entry 6).

A range of γ - and δ -alkenyl sulfonamides undergo intra-molecular carboamination to give chiral sultams with 46–94% ee, depending on the substrate (Table 2) [33]. X-Ray crystal structure of two products established their absolute configuration, the rest were assigned by analogy.

The proposed catalytic cycle is shown in Scheme 6. A sulfonamide is key to obtaining enantioselectivity in these reactions as γ -alkenyl amides [34] and *N*-aryl-2-allylanilines [35] provide racemic products under the same conditions (unpublished results). The key stereocontrolling element in these reactions is likely a rate-determining cis-aminocupration, wherein the N-substituent adopts a position anti to the closest bis(oxazoline) substituent. The copper(II) is thought to be four coordinate and square planar, and the overall cyclic transition state adopts a chair-like conformation. Theoretical calculations to further examine the origin of enantio-selectivity in these reactions are currently being performed.

2.4. Applications in bioactive compound synthesis

The chiral 2-benzyl-pyrrolidine **42**, an intermediate used in the synthesis of a potent calcium-sensing receptor antagonist **43** [36], was synthesized efficiently using this enantioselective carboamination reaction. Carboamination of γ -alkenyl benzenesulfonamide **40** gave **41** in 77% yield and 82% ee. Removal of SO₂ via dissolving metal reduction provided the pyrrolidine intermediate **42** (3 steps from commercially available material) thereby demonstrating the utility of the methodology [33] (Scheme 7).

We further demonstrated the utility of this methodology in the enantioselective total synthesis of (*S*)-(+)-tylophorine (**46**), a promising anti-cancer compound with excellent in vitro activity in a broad range of cancer cell lines [37,38]. Our synthesis (Scheme 8) of tylophorine is 8 steps from commercially available starting material, making this enantioselective synthesis one of the shorter preparations of this compound [38].

3. Copper(II)-promoted and catalyzed intramolecular alkene diaminations

Vicinal diamines are common moieties in bioactive compounds as well as useful ligands for transition-metal catalysis [39–43]. The diamination of alkenes is a transformation that has attracted a number of researchers in the past several decades [43].

3.1. Copper(II)-promoted intramolecular alkene diamination

3.1.1. Doubly intramolecular alkene diamination—We reported a novel copper(II) acetate promoted intramolecular diamination of terminal alkenes in 2005 [11]. The reaction forms bicyclic sulfamides from γ -alkenyl and δ -alkenyl sulfamides (Table 3). High diastereoselectivity was observed with an allylic alcohol substrate. The cyclic sulfamide products can be converted to the free diamine by reduction with LiAlH₄ (Eq. (9)).

(9)

Equation (9). Conversion to the free diamine.

We subsequently further optimized the reaction conditions and expanded the substrate scope to include α - and γ -substituted γ -alkenylsulfamides as well as some γ - and δ -alkenyl sulfamides that previously decomposed under the copper(II) acetate promoted conditions (Table 4). Ureas and α -amidopyrroles also participated in the new diamination reaction. By changing the copper carboxylate to copper(II) neodecanoate and conducting the reaction in dichloroethane, a more mild and reactive protocol resulted, allowing for substrate expansion (Table 4) [44]. Consistent with our diastereoselective carboamination reactions, α -substituted sulfamides provided 2,5-cis-pyrrolidines as the major diastereomers (>20:1) while allylic substituted substrates gave products with modest (3:1) 4,5-trans selectivity.

A mechanism for this diamination reaction was proposed as follows (Scheme 9): 1) the sulfamide amine coordinates to Cu(II) to give **48**; 2) rate-determining and stereochemistry-determining cis-aminocupration via **49** generates an unstable organocopper(II) intermediate **50**; 3) homolysis of the carbon-copper(II) bond provides a primary carbon radical **51**; 4) the carbon radical adds to another Cu(II) complex to form a Cu(III) complex; 5) the remaining amine coordinates to Cu(III) to give **52**; and 6) reductive elimination ensues, forming the second C–N bond and generating cyclic sulfamide **53**. It is also possible the distal amine

may already be coordinated to another copper(II), making radical addition to it all the more facile. An alternative S_N2 mechanism for the second C–N bond formation cannot be ruled out. Invoking Cu(III) in this mechanism is consistent with other copper-promoted and catalyzed processes [45–47].

Like the carboamination reaction, diamination of deuterium-labeled alkene **54-D** gave a 1:1 mixture of diastereomers **55-D** (Eq. (10)), which provides evidence for an sp^2 -hybridized carbon radical intermediate.

(10)

Equation (10). Isotopic labeling study.

This diamination reaction was more resistant than the carboamination reaction to being rendered catalytic. The sulfamide and urea substrates were unreactive when treated with catalytic amounts of copper(II) salts and stoichiometric amounts of MnO_2 . Other oxidants such as O_2 and hypervalent iodine reagents were tried, without success.

3.1.2. Intra- and intermolecular copper(II)-promoted diamination of alkenes—A breakthrough came when we found that the copper(II)-promoted diamination reaction could be rendered intra/intermolecular (Table 5). A range of urea, sulfonamide and amido γ -alkenyl substrates were found to undergo copper(II)-promoted diamination with a range of external amine nucleophiles serving as the second amine component (anilines, NaN_3 , sulfonamides, amides) [48].

3.2. Copper(II)-catalyzed intramolecular alkene diamination

Importantly, we were able to render the intra/intermolecular alkene diamination reaction catalytic in copper with *N*-sulfonyl-2-allylaniline and *N*-allylurea substrates **56** and **58** (these are two of the more reactive substrates) using MnO_2 as the stoichiometric oxidant (Eqs. (11) and (12)). We next challenged the reaction to asymmetric catalysis using the Cu(OTf)_2 -(*R,R*)-Ph-box complex and obtained a promising 64% yield of vicinal diamine **57a** in 71% ee (Eq. (13), absolute stereochemistry tentatively assigned *S* based on analogy) [33]. This is the first example of a catalytic enantioselective intramolecular diamination reaction and thus a promising solution to a long-standing problem. Although similar reactions have been catalyzed by palladium, nickel and gold salts [24,49–52], no enantioselective reactions have yet been reported with these other catalysts. Efforts to further optimization this reaction are ongoing.

(12)

(13)

Equations (11)–(13). Catalytic intra/intermolecular diaminations.

4. Copper(II)-promoted and catalyzed intramolecular aminooxygenation of alkenes

Vicinal amino alcohols are useful building blocks in the synthesis of bioactive compounds and have been utilized as ligands and catalysts in organic reactions [53]. Due to the considerable interest of the products, the alkene aminooxygenation (aminohydroxylation, aminoetherification, aminoacetoxylation) has been actively developed by a number of research groups [54,55].

4.1. Copper(II)-catalyzed enantioselective aminooxygenation

During the course of our study on the copper(II)-promoted carboamination mechanism, we provided evidence for a carbon radical intermediate by trapping the proposed intermediate with tetra-methylaminopyridyl radical (TEMPO, vide supra, Eq. (7)) [10]. This reaction is very efficient and constitutes a net intramolecular alkene aminooxygenation. We subsequently developed the first catalytic asymmetric intramolecular alkene aminooxygenation reaction by using the (4*R*,5*S*)-bis-Ph-box ligand complexed to Cu(OTf)₂ in conjunction with 300 mol% TEMPO as the oxygen source and sole oxidant [21]. The more reactive *N*-sulfonyl-2-allylaniline substrates underwent efficient aminooxygenation at 110 °C to provide chiral alkoxyindolines in 61–97% yield with 50–91% ee (Table 6).

(14)

(15)

The slightly less reactive aliphatic sulfonamides benefited from use of O₂ (1 atm) as co-oxidant and slightly higher temperature (120 °C), and generated chiral pyrrolidines in 74–97% yield and 75–92% ee (Table 7).

We demonstrated that the free alcohol **59** could be liberated by treatment with Zn and NH₄Cl, the free amino alcohol **60** could be liberated by sequential dissolving metal reactions (Li, NH₃ then Zn, NH₄Cl) and the aldehyde **61** could be directly generated by oxidation with mCPBA. The free amino alcohol **60** is a known ligand used in asymmetric catalysis and our route to it is more efficient than the previously published route [56] (Scheme 10).

4.2. Copper(II)-promoted diastereoselective aminooxygenation

We subsequently demonstrated the efficient and diastereoselective synthesis of pyrrolidines via a copper(2-ethylhexanoate)₂ promoted intramolecular alkene aminooxygenation procedure [12]. The reaction is selective for formation of the 2,5-cis pyrrolidines (*dr* >20:1) using α -substituted substrates (Eq. (14)). The 4,5-trans pyrrolidine **65** is the major products of a γ -substituted γ -alkenyl sulfonamide (*dr* 3:1, Fig. 2) and the trans aminooxygenation product **67** was obtained from a cyclopentene precursor (Fig. 2). Note that **67** was obtained via reaction of an internal alkene. This is one of the few reactions where the copper(II)-catalyzed amination provides the difunctionalized product as the major adduct (instead of oxidative amination analogous to **19**, vide supra Scheme 3). We were able to select for the 2,5-trans pyrrolidine diastereomer by tethering the amine to the alpha substituent (Eq. (15)). We rationalize these diastereoselectivities using cyclic transition states where the cyclic aminocupration transition state determines the relative stereochemistry.

Equations (14) and (15). Diastereoselective aminooxygenations.

We demonstrated the utility of this method by converting 2,5-cis pyrrolidine **68** to aldehyde **69** via mCPBA oxidation. Aldehyde **69** is an intermediate in Bäckvall's synthesis of (+)-monomorine (**70**), an ant pheromone [57,58]. Current work includes development of a catalytic diastereoselective aminooxygenation protocol and detailed mechanistic analysis of the aminooxygenation reaction using isotope effects, isotopic labeling, kinetics and molecular modeling (Scheme 11).

5. Summary and future outlook

The copper(II)-promoted and catalyzed intramolecular alkene amination reactions described herein have considerable synthetic potential. The dual organometallic and radical nature of the organocopper intermediates makes them quite versatile for introducing divergent reactivity depending upon the reaction conditions, components and structures of the substrates. We have found that various nitrogen heterocycles can be synthesized via copper(II)-promoted or catalyzed cyclization of sulfonamides, amides, imides, ureas and *N*-aryl anilines onto terminal, and in a few cases, internal, alkenes. The kind of

difunctionalization that occurs, carboamination, diamination, or aminooxygenation, depends largely on the reaction components. In general, trapping the primary radical intermediate is most rapid with TEMPO, leading to amino-oxygenation. In the absence of TEMPO, but presence of additional amine nucleophile, diamination becomes the most favored process. In the absence of both TEMPO and additional amine nucleophiles, carboamination ensues via cyclization of the radical onto a nearby π -bond (arene or alkene). A number of additional reaction developments using this chemistry are underway in our lab and applications in drug discovery and natural product synthesis will be forthcoming.

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Proposed Major Transition States, Cis Pyrrolidine Formation

Proposed Minor Transition States, Trans Pyrrolidine Formation

Fig. 1.
Origin of 2,5-cis-diastereoselectivity with α -substituted substrates.

Fig. 2.
Other products, selectivities (see Eq. (14) for conditions).

Scheme 1. Copper(II)-promoted intramolecular carboamination of *N*-arylsulfonyl-2-allylanilines.

Scheme 2.

Two initially proposed potential mechanisms for the carboamination reaction.

Scheme 3.

Carboamination of *N*-arylsulfonyl- γ - and δ -alkenes. $\text{Cu}(\text{ND})_2$ = copper(II) neodecanoate.

Scheme 4.

Carboaminations of γ -alkenyl amides and imides. $\text{Cu}(\text{EH})_2$ = copper(II) 2-ethylhexanoate.

Scheme 5.

Possible mechanistic scenarios for C–N bond formation.

Scheme 6.
Proposed enantioselective carboamination catalytic cycle.

Scheme 7.

Synthesis of a calcium-sensing receptor antagonist intermediate.

Scheme 8.
Synthesis of (S)-(+)-tylophorine.

Scheme 9.

Proposed doubly intramolecular alkene diamination mechanism.

Scheme 10.
Conversion to alcohol, aldehyde and amine.

Scheme 11.
Formal synthesis of (+)-monomorphine.

Table 1

Ligand screening for the copper-catalyzed enantioselective carboamination.

Entry	Solvent	Ligand	Yield 12 (%)	ee (%)
1	PhCH ₃	bipyridine	59 (+ 12% 39)	--
2	PhCF ₃	bipyridine	60	--
3	PhCF ₃	(S,S)- <i>t</i> -Bu-box	50	24
4	PhCF ₃	(S,S)-Bn-box	55	82
5	PhCF ₃	(S,S)-Ph-box	75	86
6	PhCF ₃	(R,R)-Ph-box	85	-92

Table 2

Copper-catalyzed enantioselective carboamination substrate scope.

Table 3

Copper(II)-promoted doubly intramolecular alkene diamination.

Table 4

Improved conditions, expanded scope.

Table 5

Copper(II)-promoted intra- and intermolecular alkene diamination.

Table 6

Synthesis of chiral indolines via copper catalysis.

X	R	Yield (%)	ee (%)
H	Ts	97	90
4-F	Ts	83	89
4-Cl	Ts	73	91
4-OMe	Ts	82	86
4-CN	Ts	75	85
4-Me	Ts	88	76
3-OMe	Ts	61	87
H	Ns	75	61
H	Ms	57	50

Table 7

Catalytic aminooxygenation for chiral pyrrolidines.