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Stereoselective Synthesis of Isoxazolidines via Copper-Catalyzed Alkene Diamination

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Abstract

A convenient copper-catalyzed intramolecular/intermolecular alkene diamination reaction to synthesize 3-aminomethyl-functionalized isoxazolidines under mild reaction conditions and with generally high levels of diastereoselectivity was achieved. This reaction demonstrates that previously underutilized unsaturated carbamates are good [Cu]-catalyzed diamination substrates. Sulfonamides, anilines, benzamide, morpholine, and piperidine can serve as the external amine source. This relatively broad amine range is attributed to the mild reaction conditions. Reduction of the N–O bond could also be achieved, revealing the corresponding 3,4-diamino-1-alcohols efficiently.

Graphical abstract

Keywords

isoxazolidine; diamination; copper; alkene; electron-rich amines

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Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.7b01362. Experimental procedures, tabulated characterization data and copies of NMR spectra for all new compounds (PDF)

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Notes

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Because of the significant utility of vicinal 1,2-diamines, the diamination of alkenes is a reaction that has inspired the development of many synthetic methodologies.¹ In particular, several powerful transition-metal-catalyzed alkene diamination reactions have been developed over the past decade.¹ Palladium-catalyzed alkene diaminations have enabled the synthesis of cyclic ureas, amides, and carbamates with good regioselectivity and enantioselectivity.^{1b,c,2} Copper-catalyzed alkene diaminations reported by our group,³ and others,^{1b,4} have enabled both diastereoselective^{3a} and enantioselective^{3a,4a} synthesis of vicinal diamines containing sulfonamides and ureas. Enantioselective diamination of styrenes enabled by chiral hypervalent iodine catalysts have also been introduced.⁵ In the majority of examples, the exogenous amine nucleophile is uniformly electron-deficient. More recently, attention has been given to expansion of the alkene and amine scope, with an emphasis on the ease of amine functionalization. A [Rh]-catalyzed tandem aziridination/aziridine opening of a range of alkenes with sulfamides has contributed in this respect.⁶ More-recent copper-catalyzed alkene diaminations employing unsaturated oximes or hydroxylamines as the alkene component have enabled the scope of the amine nucleophile to be expanded to more electron-rich amines.^{7,8} Electron-rich amine nucleophiles pose a particular challenge to [Cu]-catalyzed diamination catalysis as they may succumb to oxidation themselves.⁹ Given the continued interest in vicinal diamines, we pursued expansion of our copper-catalyzed alkene diamination reaction to the synthesis of variously substituted 3-aminomethyl isoxazolidines with a range of external amine nucleophiles.

The synthesis of isoxazolidines is worth pursuing, because of their value as synthetic intermediates and their attractive biological activities.¹⁰ Until now, no alkene diamination strategy has been developed for the synthesis of isoxazolidine rings. Previous strategies employed for the synthesis of isoxazolidines include intermolecular [3 + 2] dipolar cycloaddition reactions^{11,12} and intramolecular addition of the hydroxylamines onto alkenes and allenes.^{13,14} However, these previous methods do not directly produce 3-aminomethyl isoxazolidines.

We have recently disclosed the stereoselective synthesis of *N*-sulfonyl 3-methyleneoxy isoxazolidines via copper-catalyzed alkene aminooxygenation of *N*-sulfonyl-*O*-butenyl hydroxyl amines with yields up to 92% and diastereomeric ratio (dr) values up to >20:1.¹⁵ We observed these substrates to be reactive at much lower temperature (e.g., 60 °C) than other previously explored substrates including *N*-sulfonyl-2-allylanilines and *N*-sulfonyl-4-pentenylamines (which reacted at 100–110 °C).³ Herein, we report the first alkene diamination strategy to access 3-aminomethyl isoxazolidines. This reaction extends the scope of our diastereoselective copper-catalyzed intra/intermolecular alkene diamination reaction.³ With respect to both the intramolecular amine (alkenylamine) component, the use of unsaturated *N*-carbamoyl amines is enabled for the first time.^{16a,b} Carbamates have demonstrated considerable utility in organic synthesis and medicinal chemistry.^{16c} With respect to the exogenous amine component, the use of anilines, morpholine, piperidine, and benzamide under our [Cu]-catalyzed alkene diamination conditions³ was enabled for the first time. A key factor in the increased range observed in these reactions appears to be the innate superior reactivity of the unsaturated hydroxylamine substrates, which allows the comparatively less-reactive unsaturated carbamates to undergo copper-catalyzed cyclization and also enables an overall lower reaction temperature (60–85 °C, compared to 100 or

110 °C previously required with *N*-sulfonyl-2-allylanilines and 4-pentenylsulfonamides), which likely contributes to the better catalyst turnover and stability with otherwise challenging electron-rich amine nucleophiles (vide infra).

We launched our study by subjecting hydroxylamine **1a** and TsNH₂ to various reaction conditions (Table 1). To our delight, this Cbz-protected substrate **1a** showed reactivity, for the first time, in copper-catalyzed alkene difunctionalization chemistry, and the desired 3-aminomethyl isoxazolidine **2a** was obtained in 22% isolated yield (>90% conversion) using copper(II) 2-ethylhexanoate (20 mol %), MnO₂ (85%, <5 μ) and 2,6-di-*tert*-butyl-4-methylpyridine at 95 °C (Table 1, entry 1). Decreasing the temperature to 85 °C enabled an increase in the isolated yield to 75% (Table 1, entry 2), which suggests that the substrate decomposes at higher temperatures.

The use of less-soluble bases such as Cs₂CO₃ or K₂CO₃ resulted in lower isolated yield (14% and 48%, respectively, Table 1, entries 3 and 4). In these examples, a hydroamination side product, likely the result of a Brønsted-acid-catalyzed alternative pathway, was observed (see Supporting Information (SI) for spectral data).^{3b} Using 2 equiv instead of 3 equiv of the tosyl amine lowered the yield to 59% (Table 1, entry 5). Removal of 4 Å molecular sieves also diminished the isolated yield of **2a** (Table 1, entry 6). Further lowering of the temperature to 75 °C reduced the yield to 68% for this substrate (Table 1, entry 7). No product was obtained by the use of di-*tert*-butylperoxide (DTBP) as an oxidant (Table 1, entry 8). Use of O₂ (1 atm) as terminal oxidant enabled only 15% isolated yield of diamine **2a**, along with multiple other products (Table 1, entry 9). When Cu(OTf)₂ and 1,10-phenanthroline were used as catalyst and ligand, respectively, a 35% yield of **2a** was obtained, along with at least two other side products (Table 1, entry 10).

With the optimal conditions in hand (Table 1, entry 2), we moved forward to establish the sulfonamide nucleophile scope (Chart 1). The *N*-Cbz α -phenyl substrate **1a** underwent coupling with electron-rich (*p*-Me, *p*-OMe) as well as electron-deficient (*p*-CF₃, *p*-NO₂) aryl sulfonamides to afford the corresponding isoxazolidines **2a–2d** in moderate to good yields. Alkyl sulfonamides 2-trimethylsilylethylsulfonamide and cyclopropylsulfonamide provided the corresponding isoxazolidines **2e** and **2f** in moderate yields. Isoxazolidines **2g** and **2h** were obtained from the *N*-tosyl substrate **1b**. In all cases, good to excellent 3,5-*cis* diastereoselectivity was observed (relative stereochemistry assigned by NOE of **2b** and by analogy).

We further expanded the scope of the diamination reaction with more electron-rich amines (Chart 2). Halogenated anilines (*p*-CF₃, *p*-chloro, *o*-chloro, *p*-bromo, and *p*-fluoro) provided compounds **2i–2m** in moderate to high yield and uniformly high diastereoselectivity. The secondary amine, *N*-methyl-*p*-chloroaniline, could also be used as a coupling partner, forming isoxazolidine **2n** efficiently and selectively. The use of aniline as a nucleophile provided isoxazolidine **2o** in moderate yield and good diastereoselectivity (54% yield, dr = 10:1). Use of the slightly more electron-rich *p*-*t*-butylaniline provides **2p** in 40% yield, while the use of *p*-methoxyaniline gave <20% conversion (not shown).

When morpholine was used as the external amine, it provided isoxazolidines **2q** and **2r** in moderate yields (45% and 34%, respectively; see Chart 2). In these examples, the remainder of the mass was unreacted starting material, possibly due to catalyst poisoning by the exogenous amine. An initial attempt to couple piperidine with *N*-tosyl hydroxylamine **1b** led to the formation of an undesired chlorine atom transfer side product (aminochlorination).^{14a} Changing the solvent to PhCF₃ enabled formation of the desired diamine **2s** in low conversion. To minimize the ability of piperidine to complex with the catalyst, the copper(2-ethylhexanoate)₂ (20 mol %) was treated with diethylsalicylamide (40 mol %) prior to addition of the substrate.^{16b,17} Gratifyingly, 50% of the desired diamine product **2s** was then obtained (Chart 2). Finally, the use of benzamide as nucleophile afforded **2t** in a modest 34% yield.

Many different heterocyclic and alkyl-substituted hydroxylamines **1** were also tested for their reactivity in our diamination reaction (Chart 3). Good yields were obtained for the formation of furanyl and the thienyl isoxazolidines **2u** and **2v**. Alkyl-substituted substrates were also amenable for the diamination reaction, although lower yields of their respective adducts **2u–2w** were obtained. The TBDPS-protected substrate formed isoxazolidine **2z** in good yield but moderate diastereoselectivity. While 3,5-*cis*-diastereoselectivity was favored with 2-substituted hydroxylamines, 3,4-*trans*-isoxazolidine **2aa** was observed when a 3-phenyl hydroxylamine underwent cyclization and coupling (stereochemistry assigned by NOE). The unsubstituted hydroxylamine produced isolazolidine **2bb** in 51% yield, indicating that backbone substituents are not required.

A catalytic enantioselective diamination protocol was also explored (eq 1). A brief substrate and solvent screen led us to

(1)

use 3,5-di-*tert*-butyl-4-methoxysulfonyl hydroxylamine **1c** in PhCF₃/*t*-BuOH (9:1) in an enantioselective diamination using [Cu(*R,R*)-Ph-box](OTf)₂ as the chiral catalyst.^{3b} While the yield and enantioselectivity of **2cc** are low (20% yield, 11% ee), this result indicates feasibility and supports that the initial C–N bond formation could occur via aminocupration (vide infra, Scheme 1), in analogy to our previously reported diamination reactions,^{3,18} since some ligand-induced selectivity is observed. The comparatively low enantioselectivity may indicate some reversibility in the C–N bond-forming step (vide infra) or a small energy difference between competing pro-*R* and pro-*S* transition states.

The proposed reaction mechanism is outlined in Scheme 1. Upon [N–Cu] bond formation to give **I**, a *cis*-aminocupration occurs via seven-membered chairlike transition state **II** that gives the unstable organocopper(II) intermediate **III**. The diastereoselectivity observed with

substituted hydroxylamines originates from placement of the substituent in the pseudo-equatorial position in transition state **II**. Homolysis of the carbon–copper(II) bond gives [Cu(I)] and the carbon radical intermediate **IV**, which then adds to [Cu(II)]. The resulting amine-coordinated [Cu(III)] intermediate **V** then leads to **2** and [Cu(I)] via reductive elimination. Oxidation of [Cu(I)] to [Cu(II)] by MnO₂ completes the catalytic cycle. The involvement of radical **IV** is implicated based on isotopic labeling studies performed in analogous diamination reactions.^{3a}

One more clue regarding the reaction mechanism emerged from an attempted diamination of 1,1-disubstituted alkene **3** (Scheme 2). This alkene previously underwent aminooxygenation under copper catalysis in the presence of (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) and O₂ to provide isoxazolidine **4** (Scheme 2).¹⁵ To our surprise, when subjected to the copper-catalyzed diamination conditions, only oxidative amination product **5** was obtained (Scheme 2). Taken together, these results indicate that carbon radical intermediate **IV'** could be in equilibrium with aminyl radical **VI** and that the relative rates of TEMPO radical trapping (of **IV'**) versus C–N bond formation (with regard to **IV'**, [Cu(II)] and TsNH₂) are different and impact the product distribution. Thus, endo cyclization of aminyl radical **VI** onto its 1,1-disubstituted alkene to produce a tertiary carbon radical (not shown) that suffers oxidation to give alkene **5** is more favorable than the C–N bond formation involving carbon radical **IV'**, which would lead to a diamine product.¹⁹ The presence of a ring-opening pathway (such as **IV'** to **VI**) could also account, at least in part, for the low observed enantioselectivity (eq 1), since the aminyl radical would produce a racemic product upon exocyclization to give a carbon radical like **IV** (Scheme 1). We have previously observed low enantioselectivity in related reactions where substrates can access a more-stabilized aminyl radical and where the carbon radical must engage in a relatively higher energy subsequent bond formation.^{17b}

To demonstrate further synthetic utility, isoxazolidines **2b** and **2z** were converted to 3,4-diamino-1-alcohols **3a** and **3b** by reduction of the N–O bond with NaBH₄ in the presence of Mo(CO)₆ (Scheme 3).^{13e,20} These conditions proved far more effective than [Pd]-catalyzed hydrogenation.¹⁵ This new diamination methodology, in conjunction with N–O reduction, may well prove useful for the synthesis of 3,4-diamino-1-alcohols such as those found in bioactive natural products.^{21,22}

In summary, a broad range of 3-aminomethyl isoxazolidines **2** can be formed in moderate to good yields and with moderate to high diastereoselectivity via copper-catalyzed intramolecular/ intermolecular alkene diamination. The unsaturated hydroxylamine substrates **1** can bear Cbz and sulfonyl groups on the amine, and the intermolecular amine component can range from electron-deficient to more electron-rich. The higher reactivity of the hydroxylamine substrates **1**, compared to 2-allylaniline and 4-pentenylamines previously explored,³ is possibly due to the greater nucleophilicity of the hydroxylamine, its greater ability to accommodate spin (or unpaired electron)^{18a} or to a lower transannular strain at the transition state (e.g., **II**; see Scheme 1). This higher reactivity enables a lower reaction temperature that, in turn, appears to enable a broader amine scope. Thus, electron-rich amines are not inherently incompatible with copper-catalyzed alkene diaminations that occur under oxidative conditions; rather, milder reaction conditions, especially with respect to

reaction temperature, can facilitate their successful application.²³ The added ligand, diethylsalicylamide, also served to enable diamination with piperidine, perhaps by preventing catalyst poisoning. Further scope expansion and exploration of enantioselective conditions are in progress and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

DCE	1,2-dichloroethane
Ts	toluene sulfonyl
Ns	<i>p</i> -nitrobenzenesulfonyl
PMBS	<i>p</i> -methoxybenzenesulfonyl
TBDPS	<i>t</i> -Bu-diphenylsilyl
Cbz	carboxybenzyl
SES	2-trimethylsilylethylsulfonyl

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Scheme 1.
Proposed Reaction Mechanism

Scheme 2.
Attempted Diamination Gives Oxidative Amination

Scheme 3.
N–O Bond Reduction

Chart 1. Scope of the Sulfonamide Nucleophiles^{a,b,c,d}

^aFor reaction conditions, see Table 1, entry 2. ^bIsolated yield. ^cDiastereomeric ratios were determined by crude ¹H NMR. ^dDiastereoselectivity assigned by NOE of **2b** and by analogy.

Chart 2. External Amine Nucleophile Scope^{a,b,c,d}

^aFor reaction conditions, see Table 1, entry 2. ^bIsolated yield. ^cDiastereomeric ratios were determined by crude ¹H NMR. ^dRelative configuration assigned by NOE of **2n** and **2t** and by analogy. ^e200 mol % of amine nucleophile was used. ^fReaction run at 60 °C. ^gReaction was run with 40 mol % diethylsalicylamide in PhCF₃ for 48 h.

Chart 3. Alkene Scope^{a,b,c,d}

^aFor reaction conditions, see Table 1, entry 2. ^bIsolated yield. ^cDiastereomeric ratios were determined by crude ¹H NMR. ^dRelative configuration of **2z** and **2aa** assigned by NOE, or by analogy. ^eThe reaction was run for 6 h.

Table 1

Optimization of the Reaction Conditions^a

entry	temperature (°C)	base	yield ^b (%)	diastereomeric ratio, dr ^c
1	95	2,6-di- <i>t</i> -Bu-4-Me-pyridine	22	10:1
2	85	2,6-di- <i>t</i> -Bu-4-Me-pyridine	75	10:1
3	85	CS ₂ CO ₃	14	10:1
4	85	K ₂ CO ₃	48	10:1
5 ^d	85	2,6-di- <i>t</i> -Bu-4-Me-pyridine	59	10:1
6 ^e	85	2,6-di- <i>t</i> -Bu-4-Me-pyridine	53	10:1
7	75	2,6-di- <i>t</i> -Bu-4-Me-pyridine	68	10:1
8 ^f	85	2,6-di- <i>t</i> -Bu-4-Me-pyridine	complex mixture	
9 ^g	85	2,6-di- <i>t</i> -Bu-4-Me-pyridine	15	10:1
10 ^h	85	2,6-di- <i>t</i> -Bu-4-Me-pyridine	35	5:1

^aReaction conditions: **1a** (0.134 mmol), Cu(2-ethylhexanoate)₂ (20 mol %), TsNH₂ (300 mol %), MnO₂ (270 mol %), base (100 mol %), DCE (0.2 M, 0.7 mL), flame activated 4 Å mol. sieves (13 mg), 85 °C, 24 h.

^bIsolated yield, chromatography by preparatory TLC on silica gel.

^cDetermined by analysis of the crude ¹H NMR.

^dSulfonamide (200 mol %).

^eNo molecular sieves.

^fDTBP (di-*tert*-butylperoxide) (300 mol %) was used instead of MnO₂.

^gOxygen (1 atm, balloon) was used instead of MnO₂.

^hCu(OTf)₂ (20 mol %) and 1,10-phenanthroline (25 mol %) were used instead of Cu(2-ethylhexanoate)₂.