

Copper(II) Acetate Promoted Intramolecular Diamination of Unactivated Olefins

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Nitrogen heterocycles containing the vicinal diamine unit are ubiquitous in biologically active small molecules and are also common ligands for inorganic as well as organic catalysts.¹ An intramolecular alkene diamination offers a direct method for the synthesis of cyclic vicinal diamines. Herein is presented the first intramolecular diamination of unactivated olefins. This method is general for the formation of both five- and six-membered heterocycles, and substrate-based asymmetric induction has been achieved.

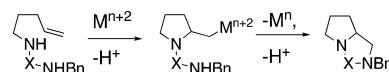
The direct diamination of olefins is an important method for the synthesis of 1,2-diamines¹ and is analogous to the highly useful olefin dihydroxylation reaction.² Current methods for the intermolecular olefin diamination are primarily limited to the use of stoichiometric amounts of late transition metal salts, which are both expensive and toxic.³ A Pd^{II}-catalyzed intermolecular diamination has been reported recently; however, this method is limited to conjugated diene substrates.^{3h} We sought a solution to this problem using an inexpensive alternative to bring about the diamination of isolated alkenes.

We envisioned the diamination would occur optimally via an intramolecular strategy, where the two nitrogen nucleophiles are tethered (Scheme 1). In this reaction design, a transition metal must activate the olefin toward nucleophilic attack by the first nitrogen, then become displaced by the second nitrogen nucleophile (a net $M^{n+2} \rightarrow M^n$ reduction). An intramolecular aminocarbonation reaction recently discovered in our labs indicated that copper(II) could perform such oxidative cyclization chemistry.⁴

Gratifyingly, we found that Cu(OAc)₂ is an excellent promoter for the intramolecular diamination of olefins using sulfamide substrates, such as **1a** (Table 1). Treatment of *N*-(2-allylphenyl)-*N'*-benzyl sulfamide **1a** with Cu(OAc)₂ (1.2 equiv) in the presence of K₂CO₃ at elevated temperature (90 °C) provided the desired diamination adduct **2a** in up to 92% yield. We screened several solvents, bases, and copper(II) salts in order to define the reaction parameters. We found the polar solvent DMF to be superior to THF and CH₃CN, and added DMSO increased the reaction yield in DMF, possibly due to increased Cu(OAc)₂ solubility (entries 1–4). These reactions were conducted in pressure tubes, and stirring was controlled so as to keep the copper salt in solution. The sulfamide functional group proved to be a significantly superior dinitrogen source compared to the urea **1b**, possibly indicating a sensitivity to the electron density or coordinating ability of nitrogen (compare entries 4 and 5). Use of base (2 equiv) was also necessary for optimal conversion (compare entry 7 to entry 4, Table 1), and K₂CO₃ proved slightly superior to Cs₂CO₃.

The nature of the ligands and the oxidation state of copper profoundly affect the reaction outcome. Copper(II) acetate was infinitely superior to Cu(OTf)₂ and CuF₂ as no diamination product was observed in the crude ¹H NMR spectra of the latter two reactions (entries 8 and 9, Table 1). Other copper(II) halide salts (CuBr₂, CuCl₂) were not further investigated as they have been

Scheme 1

Table 1. Olefin Diamination Reaction Optimization^a

entry	tether	Cu ⁿ (equiv)	base (2 equiv)	solvent ^b	% yield ^c
1	X = SO ₂	Cu(OAc) ₂ (1.2)	K ₂ CO ₃	THF	43
2	X = SO ₂	Cu(OAc) ₂ (1.2)	K ₂ CO ₃	CH ₃ CN	38
3	X = SO ₂	Cu(OAc) ₂ (1.2)	K ₂ CO ₃	DMF	78
4	X = SO ₂	Cu(OAc) ₂ (1.2)	K ₂ CO ₃	DMF/DMSO	92
5	X = C=O	Cu(OAc) ₂ (1.2)	K ₂ CO ₃	DMF/DMSO	no rxn
6	X = SO ₂	Cu(OAc) ₂ (1.2)	Cs ₂ CO ₃	DMF/DMSO	84
7	X = SO ₂	Cu(OAc) ₂ (1.2)	none	DMF/DMSO	34
8	X = SO ₂	Cu(OTf) ₂ (1.2)	K ₂ CO ₃	DMF/DMSO	no rxn
9	X = SO ₂	CuF ₂ (1.2)	K ₂ CO ₃	DMF/DMSO	no rxn
10	X = SO ₂	CuOAc (1.0)	K ₂ CO ₃	DMF/DMSO	22
11	X = SO ₂	CuOAc (3.0)	K ₂ CO ₃	DMF/DMSO	54

^a Pressure tube, Ar atmosphere, dry solvent. ^b When DMSO was included, 10 equiv was used. ^c Remainder of material is recovered substrate **1**.

shown previously to provide aminohalogenation rather than diamination products.⁴ Treatment of sulfamide **1a** with CuOAc (3.0 equiv) under argon atmosphere (to prevent air oxidation of Cu^I) provided 54% of the cyclized product **2a**, while the reaction of **1a** with 1 equiv of CuOAc gave only 22% of **2a**. The partial conversion can be explained by the disproportionation of CuOAc to Cu(OAc)₂ and Cu⁰, thus enabling the oxidative cyclization.⁵ This oxidative cyclization requires a stoichiometric amount (1–3 equiv) of Cu(OAc)₂ for optimal conversion. Copper(II) acetate is inexpensive and relatively nontoxic. Cross-coupling and oxidation methods mediated by stoichiometric and, in some cases, catalytic Cu^{II} are of recognized importance in organic synthesis.^{4,6}

With the optimized reaction conditions in hand, a variety of substrates were surveyed to explore the scope of the reaction (Table 2). The intramolecular diamination reaction occurred with complete regioselectivity (exo vs endo cyclization) in all cases, generating the smaller ring size. Both five- and six-membered rings can be formed efficiently. These substrates required 1–3 equiv of Cu(OAc)₂ and a temperature range of 90–120 °C for optimal conversion. The geminal disubstituted aliphatic amine **3** underwent conversion to cyclic sulfamide **4** in 73% yield. The styrenyl substrate **5** provided the benzylic diamine **6** in 56% yield. Geminal olefin substitution is also tolerated. The 1,1-disubstituted olefin **7** provided the tertiary amine **8** upon cyclization in 57% yield. The allylic alcohol substrate **9** provided the diamination product **10** with >20:1 diastereoselectivity (71% yield). This example also illustrates

Table 2. Intramolecular Diamination of Olefins^a

entry	substrate	product(s) ^b	yield (%) ^c
1 ^d			73
	3, R = H	4	
2 ^d			56
3			57
4			71
	9	10	
		selectivity = >20:1	
5 ^d			83
	11	12	
6 ^d			34
	13	14	
		15	
		selectivity = 1.2 : 1	

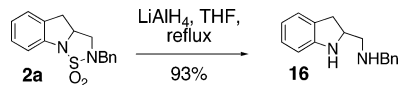
^a Reaction conditions: 3 equiv of Cu(OAc)₂, 2 equiv of K₂CO₃, DMF (0.08–0.1 M), DMSO (10 equiv), 90 °C, 48 h. ^b Selectivity determined by analysis of the crude ¹H NMR spectrum and by amount of the isolated adducts. ^c Yield refers to amount of product isolated by chromatography on silica gel. ^d Reaction was conducted at 120 °C.

that an acid-sensitive group (a benzylic, allylic secondary alcohol) can survive the mild diamination reaction conditions.

The isoquinoline **12** was formed in 83% yield upon cyclization of the 2-allylbenzylamine sulfamide **11**. Cyclization of the branched benzylic sulfamide **13** led to a 1.2:1 mixture of diastereomeric isoquinolines **14** and **15**, albeit only in 34% yield. Reaction of substrate **13** is both entropically and sterically challenging, and side reactions included loss of the substrate's sulfamide group (Bn-NHSO₂–) under the reaction conditions.

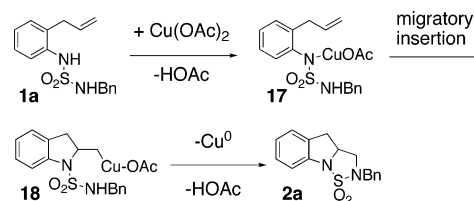
The *trans*-methyl-1,2-disubstituted olefin derivative of **3** (R = Me) and *N*-benzyl-*N'*-(2-cyclopent-2-enylethyl)sulfamide failed to provide the diamination products; primarily starting compounds with and without the sulfamide group were obtained. Clearly, steric hindrance on the terminal position of the olefin affects the reactivity of the substrate.

The free diamine can be obtained by reduction of the sulfamide with LiAlH₄ (cf. **2a** → **16**, 93% yield).



A working hypothesis for the diamination mechanism is proposed in Scheme 2. The reaction is likely initiated by coordination of the

Scheme 2



sulfamide nitrogen to Cu(OAc)₂, providing intermediate **17**. Migratory insertion would then form the new sp³ N–C bond, giving **18**.^{4,7} The organocopper species **18** may undergo ligand exchange with the remaining nitrogen, followed by reductive elimination, providing sulfamide **2a**. Yet another mechanistic scenario would involve homolysis of the carbon–copper bond of **18** followed by copper(II)-promoted oxidative coupling for N–C bond formation.

The method communicated herein expands the olefin diamination concept to include an intramolecular process and new copper(II) chemistry, thereby yielding a number of cyclic diamines. The cyclic sulfamide adducts are valuable entities to medicinal chemistry and material science,⁸ and the free diamine is easily liberated using LiAlH₄. Further expansion of the substrate scope and mechanism studies are underway.

Acknowledgment. This research was supported by the University at Buffalo, SUNY and the donors of the Petroleum Research Fund (PRF 40968-G1).

Supporting Information Available: Procedures and characterization data for all new products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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JA053335V