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Copper(II) Carboxylate Promoted Intramolecular Diamination of Terminal Alkenes: Improved Reaction Conditions and Expanded Substrate Scope

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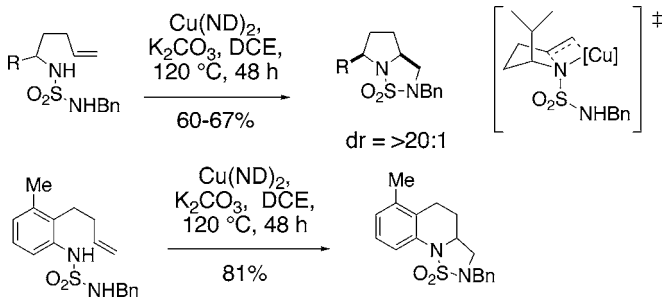
ABSTRACT



The copper(II) carboxylate promoted diamination reaction has been improved by the use of the organic soluble copper(II) neodecanoate [$Cu(ND)_2$]. $Cu(ND)_2$ allowed the less-polar solvent dichloroethane (DCE) to be used, and as a consequence, decomposition of less-reactive substrates could be avoided. High diastereoselectivity was observed in the synthesis of 2,5-disubstituted pyrrolidines. Ureas, bis(anilines), and α-amido pyrroles derived from 2-allylaniline could also participate in the diamination reaction.

Nitrogen heterocycles that contain vicinal amines are privileged biologically active structures.[1] Compounds containing vicinal diamines have demonstrated a range of activity that includes antiparasitic [e.g., (*R*)-Praziquantel, Oxamniquine],[2] antidepressant (e.g., Mianserin),[3] anticancer [(−)-quinocarcin],[4] adenosine kinase,[5] and protease inhibitory activity (Figure 1).[6] Cyclic sulfamides, which are especially accessible via the technology described in this paper, appear frequently as components of small molecule enzyme inhibitors (Figure 1).[7]

The synthesis of vicinal diamines via olefin diamination is an active area of research.[1,8,9] The intramolecular diamination of alkenes provides a direct entry into the cyclic vicinal diamine motif.[9b,c] We recently reported a novel intramolecular alkene diamination protocol promoted by copper(II) ace-

(1) Kotti, S. R. S. S.; Timmons, C.; Li, G. *Chem. Biol. Drug Des.* **2006**, *67*, 101.

(2) (a) Andrews, P.; Thomas, H.; Pohlke, R.; Seubert, J. *Med. Res. Rev.* **1983**, *3*, 147. (b) Reich, M. R.; Govindaraj, R. *Health Policy* **1998**, *44*, 1. (c) Fenwick, A.; Keiser, J.; Utzinger, J. *Drugs Future* **2006**, *31*, 413.

(3) Brogden, R. N.; Heel, R. C.; Speight, T. M.; Avery, G. S. *Drugs* **1978**, *16*, 273.

(4) Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669.

(5) Bauser, M.; Delapierre, G.; Hauswald, M.; Flessner, T.; D'Urso, D.; Hermann, A.; Beyreuther, B.; De Vry, J.; Spreyer, P.; Reissmuller, E.; Meier, H. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1997.

(6) (a) Bachand, B.; Tarazi, M.; St-Denis, Y.; Edmunds, J. J.; Winocour, P. D.; Leblond, L.; Siddiqui, M. A. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 287. (b) St-Denis, Y.; Levesque, S.; Bachand, B.; Edmunds, J. J.; Leblond, L.; Preville, P.; Tarazi, M.; Winocour, P. D.; Siddiqui, M. A. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1181. (c) Bursavich, M. G.; Rich, D. H. *J. Med. Chem.* **2002**, *45*, 541.

(7) Winum, J.-Y.; Scozzafava, A.; Montero, J.-L.; Supuran, C. T. *Med. Res. Rev.* **2006**, *26*, 767.

(8) For reviews for olefin diamination: (a) Kemp, J. E. G. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 7, p 469. (b) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580. (c) Mortensen, M. S.; O' Doherty, G. A. *Chemtracts: Org. Chem.* **2005**, *18*, 555.

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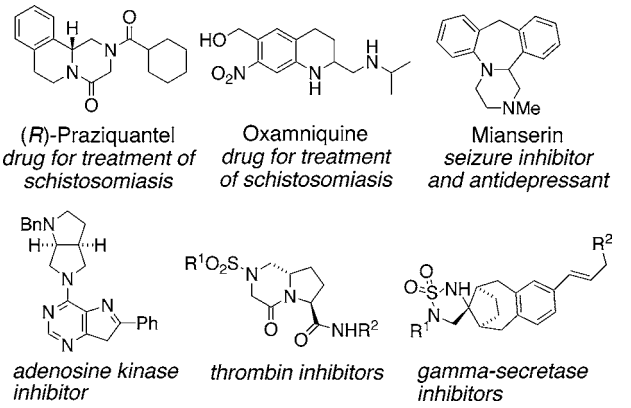
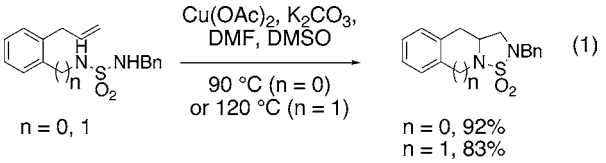


Figure 1. Biologically active cyclic vicinal diamines.

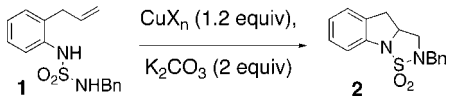
tate.[9b] This protocol provided efficient synthesis of fused cyclic sulfamide pyrrolidines and piperidines (eq 1). This reaction is a member of a growing class of copper(II)-promoted oxidative cyclizations that also includes the intramolecular copper(II)-promoted alkene carboamination reaction.[10]



We report herein an expansion of the diamination substrate scope to include substrates with other linked ($RNHX_nNHR$) bis(amino) units. In addition, the diastereoselectivity in the oxidative cyclization of alkyl-substituted pent-4-enyl sulfamides and a deuterated alkene substrate was examined. The substrate expansion was enabled by the use of an organic soluble copper(II) salt, copper(II) neodecanoate [$Cu(ND)_2$], and the less-polar solvent dichloroethane (DCE). The level and direction of observed diastereoselectivity, and comparison to the mechanistically similar copper(II)-promoted carboamination reaction, provided insight into a plausible reaction mechanism (vide infra).

The effect of solvent, copper(II) ligand, and heating method (oil bath vs microwave) was systematically examined as shown in Table 1. We quickly found that the solubility of the copper(II) carboxylate in the organic solvent was important to the efficiency of the reaction. In initial experiments, we used $Cu(OAc)_2$ with polar solvents (DMF) and an additive (4 equiv of DMSO, 90 °C, 48 h) (entries 1 and 2, Table 1).[9b] We subsequently found that the use of more organic soluble copper(II) carboxylates, e.g., copper(II) neodecanoate [$Cu(ND)_2$], allowed shorter reaction times (90 °C, 24 h) than the use of less-polar solvents (dichloroethane, toluene). The reaction time could be further reduced by the use of microwave heating (120 °C for 20 min, entry 4, Table 1). All of these reactions are carried out in pressure tubes.

Table 1. Temperature, Solvent, and Ligand Effects[a]

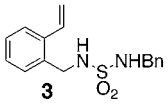
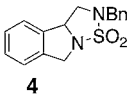
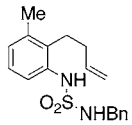
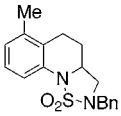


entry	CuX_n	solvent	temp, time	yield (%)[b]
1	$Cu(OAc)_2$	DMF	90 °C, 48 h	78
2	$Cu(OAc)_2$	DMF/DMSO	90 °C, 48 h	92
3	$Cu(ND)_2$	DMF	90 °C, 24 h	94
4	$Cu(ND)_2$	DMF	120 °C (μW), 20 min	90
5	$Cu(OAc)_2$	CH_3CN	90 °C, 48 h	38
6	$Cu(ND)_2$	CH_3CN	90 °C, 24 h	94
7	$Cu(ND)_2$	DCE	90 °C, 24 h	73
8	$Cu(ND)_2$	toluene	90 °C, 24 h	40
9	$Cu(OAc)_2$	*tert*-amylOH	90 °C, 48 h	38

[a] All reactions were run in sealed tubes at 0.1 M w/r to **1**. $Cu(ND)_2$ = copper(II) neodecanoate. [b]Yield refers to amount of product isolated after purification by flash chromatography on silica gel.

Under the new reaction conditions [$Cu(ND)_2$, $(CH_2Cl)_2$], the reactions of substrates **3**, **5**, and **7** were significantly improved (Table 2). At 120 °C or above, these less-reactive, more entropically challenging substrates tended to undergo decomposition (removal of the sulfamide) using the Cu-

Table 2. Diamination of Challenging Substrates

entry	substrate	product	conditions[a]	yield (%)[b]
1			A	56
2	**3**	**4**	B	81
3			A	43
4			B	**86**
5			C	55
6	**5**	**6**	D	48
7			A	*decomp*
8	**7**	**8**	B	81

[a] Reaction conditions A: 3 equiv of $Cu(OAc)_2$, 2 equiv of K_2CO_3, DMF (0.1 M), DMSO (10 equiv), 120 °C, 48 h, sealed tube. Conditions B: 3 equiv of $Cu(ND)_2$, 2 equiv of K_2CO_3, DCE (0.1 M), 120 °C, 48 h, sealed tube. Conditions C: Same as B except $Cu(OAc)_2$ was used instead of $Cu(ND)_2$. Conditions D: Same as B except DMF was used instead of DCE. [b]Yield refers to amount of product isolated after purification by flash chromatography on silica gel.

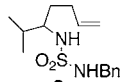
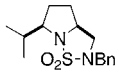
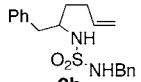
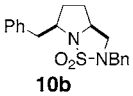
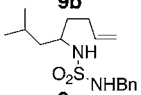
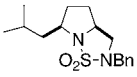
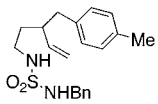
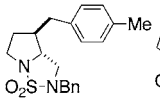
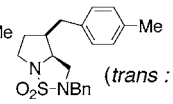
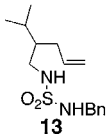
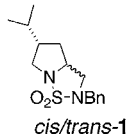
(9) Recent metal-facilitated olefin diaminations: (a) Bar, G. L. J.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *J. Am. Chem. Soc.* **2005**, *127*, 7308. (b) Zabawa, T. P.; Kasi, D.; Chemler, S. R. *J. Am. Chem. Soc.* **2005**, *127*, 11250. (c) Streuff, J.; Hovelmann, C. H.; Nieger, M.; Muniz, K. *J. Am. Chem. Soc.* **2005**, *127*, 14586. (d) Du, H.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 762. (e) Wei, H.-X.; Kim, S. H.; Li, G. *J. Org. Chem.* **2002**, *67*, 4777.

(10) (a) Sherman, E. S.; Chemler, S. R.; Tan, T. B.; Gerlits, O. *Org. Lett.* **2004**, *6*, 1573. (b) Sherman, E. S.; Fuller, P. H.; Kasi, D.; Chemler, S. R. *J. Org. Chem*, **2007**, ASAP. (c) Chemler, S. R.; Fuller, P. H. *Chem. Soc. Rev.* **2007**, DOI: 10.1039/B607819M.

$(OAc)_2$, DMSO, and DMF reaction conditions. It is possible that DMF or its decomposition product (Me_2NH) could promote sulfamide decomposition. Under the new conditions, the isoindoline adduct **4** was obtained in 81% yield. The unsubstituted, aliphatic sulfamide **5** cyclized efficiently to provide pyrrolidine **6** in 86% yield. The *N*-2-γ-butenyl-3-methylphenyl-*N*′-benzylsulfamide (**7**) cyclized to form the tetrahydroquinoline adduct **8** in 81% yield.

The use of $Cu(ND)_2$ and dichloroethane as solvent was especially important in the case of monosubstituted *N*-pent-4-enyl-*N*′-benzyl sulfamides **9**, **11**, and **13** (Table 3).

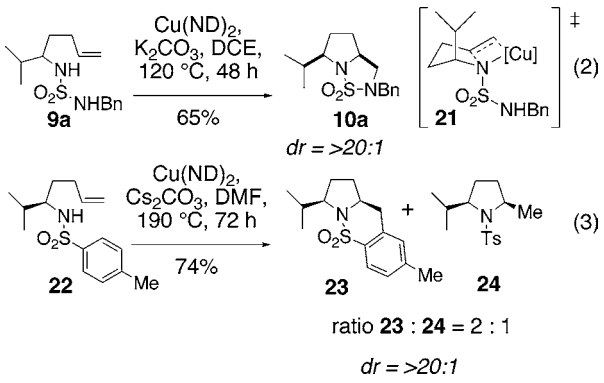
Table 3. Diastereoselectivity in Cyclizations of Pent-4-enyl Sulfamides[a]

entry	substrate	product	yield (%)[b] (selectivity)[c]
1	 **9a**	 **10a**	65 (dr >20 : 1)
2	 **9b**	 **10b**	60 (dr >20 : 1)
3	 **9c**	 **10c**	67 (dr > 20 : 1)
4	 **11**	 *trans*-**12**  *cis*-**12**	88 (*trans* : *cis* = 3 : 1)
5	 **13**	 *cis/trans*-**14**	83 (*trans* : *cis* = 1 : 1)

[a] Reaction conditions: 3 equiv of $Cu(ND)_2$, 2 equiv of K_2CO_3, DCE (0.1 M), 120 °C, 48 h, sealed tube. [b]Yield refers to amount of product isolated upon purification by flash chromatography on silica gel. [c]Selectivity determined by analysis of the crude ^1H NMR spectrum.

Good to excellent levels of diastereoselectivity were observed with these substrates (Table 3). Reactions of substrates **9** with substitution α to the sulfamide unit were highly diastereoselective, generating the *cis*-pyrrolidine core **10** with >20:1 selectivity (entries 1−3, Table 3). The high degree of *cis*-pyrrolidine selectivity is similar to that observed in the copper(II) carboxylate promoted carboamination reaction.[10b] Pent-4-enyl sulfonamide **11** containing an allylic stereocenter also provided a diastereoselective reaction (dr = 3:1) favoring the *trans* diastereomer (entry 4, Table 3). The 2-substituted pent-4-enyl sulfamide **13** afforded pyrrolidines *cis*-**14** and *trans*-**14** in a 1:1 ratio of diastereomers (entry 5, Table 3). Discussion of the reaction diastereoselectivity is provided in eq 2 (vide infra) and in the Supporting Information. We have previously demonstrated that sulfur dioxide can be reductively removed to reveal the diamine if desired.[9b]

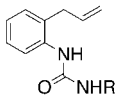
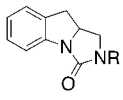
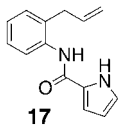
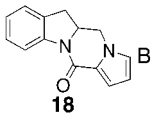
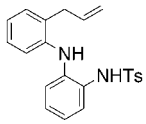
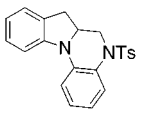
The generality of the intramolecular diamination protocol was further examined as illustrated in Table 4. Although the



N-2-allylphenyl-*N*′-benzyl sulfamide **1** reacted at the lowest temperature of all the substrates examined (90 °C, Table 1), the reaction could be extended at higher temperature (120 °C) to analogous substrates with different diamine units such as ureas, bis(anilines), and α-amidopyrroles. Diamination with the urea substrates **15a**−**c** produced bicyclic ureas **16a**−**c**, whereas cyclization of the α-amidopyrrole **17** and the bis(aniline) **19** produced 1,4-diazines **18** and **20**. Cyclic ureas and 1,4-diazines are common components in biologically active compounds. The *N*-tosyl urea **15d** and aliphatic γ-pentenylureas were unreactive under the reaction conditions.

Upon the basis of the high diastereoselectivity of the diamination reactions with α substituents, wherein the *cis*-pyrrolidines are highly favored, we propose that the first C−N bond is formed via a *syn*-aminocupration (e.g., transition state **21**), in analogy to the mechanistically similar copper(II)-promoted intramolecular carboamination reaction

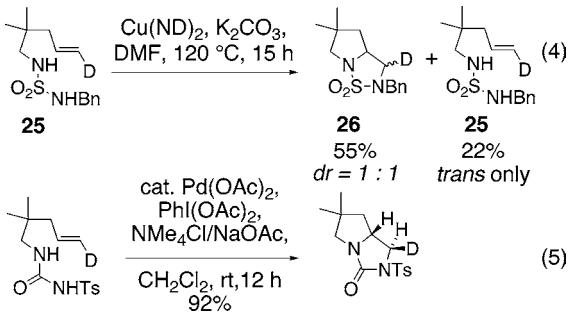
Table 4. Formation of Cyclic Ureas and 1,4-Diazines

entry	substrate	product	conditions[a]	yield (%)[b]
				
1	**15a**, R = Bn	**16a**	A	69
2	**15b**, R = Ph	**16b**	B	68
3	**15c**, R = Pr	**16c**	A	59
4	**15d**, R = Ts	**16d**	A	*no rxn*
5	**15d**, R = Ts	**16d**	B	*decomp*
6	 **17**	 **18**	B	61
7	 **19**	 **20**	B	61[c]

[a] Reaction conditions A: 3 equiv of $Cu(ND)_2$, 2 equiv of K_2CO_3, DCE (0.1 M), 120 °C, 48 h, sealed tube. Conditions B: same as A except DMF was used as solvent instead of DCE. [b]Yield refers to amount of product isolated after purification by flash chromatography on silica gel. [c]11% of the carboamination product was also formed (see Supporting Information).

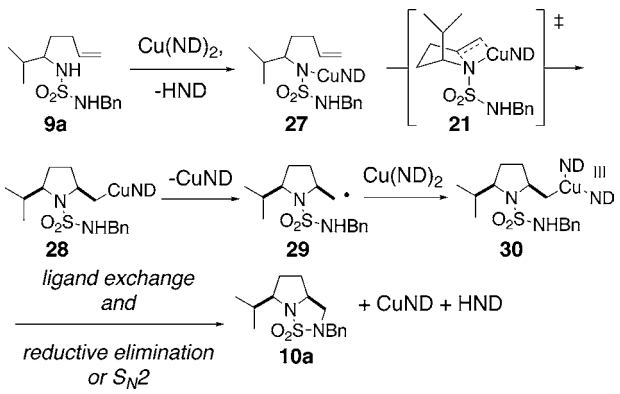
(eqs 2 and 3).[10b] By comparing the direction and degree of diastereoselectivity in the carboamination reaction to the preferences found in analogous reactions, we argued that a *syn*-aminocupration mechanism (analogous to transition state **21**) best accounted for the observed diastereoselectivity.

To probe the mechanism of the second C−N bond-forming step, we submitted the *trans*-deuteroalkene **25** to the diamination conditions (eq 4). Partial conversion to diamination adduct **26** allowed for the recovery and examination of the remaining starting material **25**. We found that adduct **26** is formed in a 1:1 ratio of diastereomers. This is in contrast to the analogous study by Muniz and co-workers, who found that this bond is formed stereospecifically in their palladium-catalyzed diamination reaction (eq 5).[9c]



The proposed reaction mechanism for the copper(II) carboxylate promoted intramolecular alkene diamination is illustrated in Scheme 1. The stereorandom formation of

Scheme 1. Proposed Diamination Mechanism



deuterated diamination adducts **26** (eq 4) indicates the presence of an intermediate with an sp^2 hybridized deuterium-substituted carbon, possibly a primary radical (e.g., **29**, Scheme 1).[11] Thus, ligand exchange in the reaction of **9a** with $Cu(ND)_2$ would provide for N−Cu bond formation (cf. **9a** → **27**, Scheme 1). Syn aminocupration would occur in stereoselective fashion via transition state **21**, forming the *cis*-pyrrolidine. The unstable organocopper(II) intermediate **28** would undergo C−Cu bond homolysis, generating primary radical **29**. Organocopper(II) species are known to be unstable due to the paramagnetic nature of copper(II).[12,13] The primary radical does not revert back to the starting material, as indicated by the fact that the recovered deuterated alkene **25** can be isolated without olefin isomerization (vide supra, eq 4). Because another electron must be lost from the substrate in this net two-electron oxidation process, it seems necessary that copper be involved in the second C−N bond-forming process. One likely scenario would involve combination of the primary radical with $Cu(ND)_2$. The affinity of carbon radicals for Cu(II) has previously been studied.[13] The resulting Cu(III) intermediate **30** could then undergo ligand exchange and reductive elimination or S_N2 to provide the observed product. Prior coordination of $Cu(ND)_2$ to the second sulfamide nitrogen and intramolecular delivery to the carbon radical may also be operative. Because copper carboxylate salts can easily disproportionate, an adequate amount of Cu(II) can be provided for the entire process.

An alternative mechanism would involve ligand exchange and reductive elimination or S_N2 of organocopper(II) intermediate **28**, but the stereorandom formation of the second C−N bond would still have to be accounted for. Although a mechanism involving a primary carbocation intermediate could also account for the stereorandom second C−N bond formation, such a species seems unlikely as no rearrangement or elimination products are observed. Also, Kochi has previously observed that copper(II) salts do not promote carbocation formation unless a stable carbocation can be formed.[13b]

In summary, we have identified milder reaction conditions that allow an expanded substrate scope in the copper(II) carboxylate promoted intramolecular diamination of terminal alkenes. Stereochemical probes have been used to identify a probable reaction mechanism. The copper(II) carboxylate promoted protocol has demonstrated the highest levels of diastereoselectivity among intramolecular alkene diaminations to date.

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

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(11) Attempts to trap the radical intermediate with TEMPO have been frustrated by starting material decomposition. Reactions performed in the presence of O_2 gave only diamination.

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