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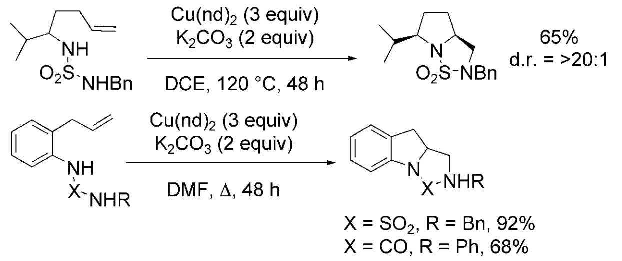
Copper Catalysis

Copper-Promoted and Copper-Catalyzed Intermolecular Alkene Diamination**

*Fatima C. Sequeira, Benjamin W. Turnpenny, and Sherry R. Chemler**

Olefin diamination methods provide powerful access to vicinal diamines that are useful in drug discovery, materials, and catalysis.[1] A number of impressive diastereoselective, enantioselective, and catalytic olefin diamination methods have been recently reported.[2–7]

Intramolecular olefin diaminations form nitrogen heterocycles directly and has predominantly been accomplished by using tethered amine nucleophiles wherein both amine additions occur in an intramolecular fashion (Scheme 1). This olefin diamination strategy has been successfully employed by using palladium,[4a] nickel,[4b] and gold[4c] catalysts, and stoichiometric copper reagents,[3] and has resulted in the synthesis of a number of interesting compounds, such as bicyclic sulfamides, ureas, and guanidines. An intra/intermolecular alkene diamination procedure would result in the convergent formation of one new nitrogen heterocycle along with the installation of a differently functionalized amine substituent. In a recent report, Michael and co-workers found that the use of a palladium catalyst in combination with *N*-fluorobenzenesulfonimide led to the formation of nitrogen heterocycles with $CH_2N(SO_2Ph)_2$ functionalization.[5] Herein, we report a new copper(II)-promoted intra- and intermolecular diamination of alkenes that tolerates a wide range of internal and external amine sources for the formation of differently functionalized and various nitrogen heterocycles. Importantly, we report the first intramolecular diamination procedure where catalyst-based asymmetric induction has been observed. Impressive catalytic enantioselective intermolecular olefin diaminations have been reported,[2] but no enantioselective intramolecular variant has yet been reported.[8] Herein, we report our progress towards this elusive transformation.



Scheme 1. Previous tethered diaminations. nd = neodecanoate, Bn = benzyl, DCE = 1,2-dichloroethane, DMF = *N*,*N*-dimethylformamide.

These copper(II)-promoted intra- and intermolecular alkene diamination procedures are an advance on earlier studies by our group, which involved the synthesis of bicyclic sulfamides and ureas using a tethered-olefin diamination approach (Scheme 1).[3] We have recently found that we can expand this process to involve the participation of an external amine source in the second C–N bond-forming step (Table 1).

Thus, heating 1-allyl-1-benzyl-2-phenyl urea (**1a**) in the presence of copper(II) 2-ethylhexanoate (Cu(eh)$_2$, 3 equiv), Cs_2CO_3, and aniline (1.5 equiv) in $PhCF_3$ for 24 hours provided imidazolidin-2-one **2a** in 92% yield (Table 1, conditions A). Other copper-promoted processes, such as intramolecular carboamination,[9] aminoacetoxylation,[9e] and hydroamination[9b] can occur with the substrates used in this study (see the Supporting Information), but the intra/intermolecular diamination is favored when the reaction is run in the presence of an external amine nucleophile.

A number of substituted anilines (substitutents = Cl, CF_3, Me, F, OMe, *i*Pr, NO_2) also participated as the external amine in this diamination process, thus providing **2b**–**2i** in good to excellent yields (Table 1, entries 2–9). The amount of substituted aniline had to be increased to 3 equivalents (conditions B) in order to minimize the competitive formation of **2a**, from $PhNH_2$, itself formed from partial decomposition of **1a**. In addition, at least 2 equivalents of Cu(eh)$_2$ was necessary to minimize the formation of a hydroamination side-product (for reaction optimization, see the Supporting Information). NaN_3,[10] benzamide and *p*-TolSO$_2$NH$_2$ were also good nucleophiles (Table 1, entries 10–12).

The 4,4-disubstituted imidazolidin-2-one **4** was formed efficiently from diamination/cyclization of the corresponding urea **3** (Scheme 2). Chiral imidazolidin-2-ones **6** were formed with high 4,5-*trans* selectivity from their corresponding alkenyl ureas **5** (Scheme 3). Formation of the *trans* diastereomer is rationalized by transition-state **A**, where the substituent adopts a pseudo-equatorial position.

N-aryl-γ-pentenyl amides, and sulfonamides with different γ-alkenyl backbones, were also good substrates in this intra- and intermolecular diamination reaction (Table 2).

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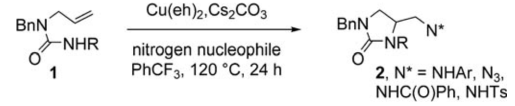
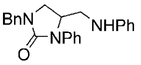
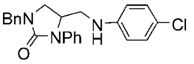
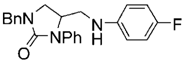
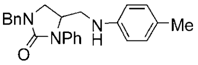
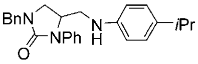
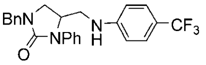
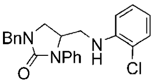
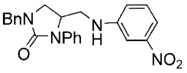
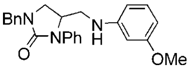
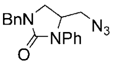
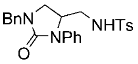
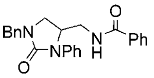
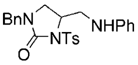
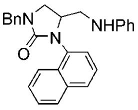
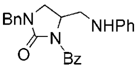
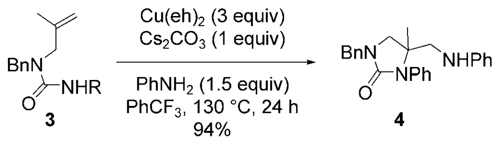
Table 1: Copper(II)-promoted diamination of *N*-allyl ureas.

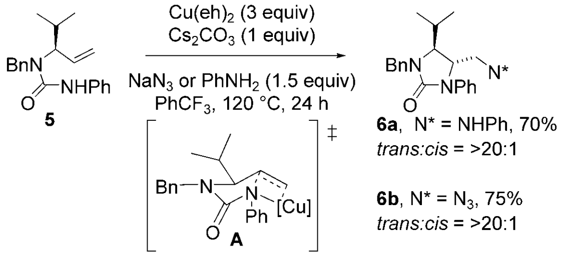


Entry	**1** (R)	Nitrogen nucleophile		Product	Yield [%]
1[a]	**1a** (Ph)	PhNH$_2$	**2a**		92
2[b]	**1a**	*p*-Cl-C$_6$H$_4$NH$_2$	**2b**		86
3[b]	**1a**	*p*-F-C$_6$H$_4$NH$_2$	**2c**		76
4[b]	**1a**	*p*-Me-C$_6$H$_4$NH$_2$	**2d**		72
5[a,c]	**1a**	*p*-*i*Pr-C$_6$H$_4$NH$_2$	**2e**		85
6[b]	**1a**	*p*-CF$_3$-C$_6$H$_4$NH$_2$	**2f**		97
7[b]	**1a**	*o*-Cl-C$_6$H$_4$NH$_2$	**2g**		72
8[b]	**1a**	*m*-NO$_2$-C$_6$H$_4$NH$_2$	**2h**		82
9[b]	**1a**	*m*-MeO-C$_6$H$_4$NH$_2$	**2i**		70
10[a]	**1a**	NaN$_3$	**2j**		85
11[b]	**1a**	TsNH$_2$	**2k**		86
12[b]	**1a**	BzNH$_2$	**2l**		65
13[b]	**1b**, (Ts)	PhNH$_2$	**2m**		60
14[b]	**1c** (1-naph-thyl)	PhNH$_2$	**2n**		76
15[b]	**1d** (Bz)	PhNH$_2$	**2o**		60

[a] Conditions A: *N*-allylurea **1** (0.15 mmol), Cu(eh)$_2$ (3 equiv), nitrogen nucleophile (1.5 equiv), Cs$_2$CO$_3$ (1 equiv), PhCF$_3$ (0.2 M with respect to **1**), 120 °C, 24 h, pressure tube. [b] Conditions B: Same as A except 3 equiv nitrogen nucleophile and 2 equiv Cu(eh)$_2$ were used. [c] Reaction run with 1 equiv nitrogen nucleophile. Cu(eh)$_2$ = copper(II) 2-ethylhexanoate, Ts = *para*-toluenesulfonyl, Bz = benzoyl.

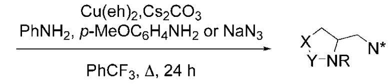


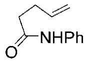
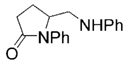
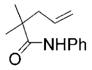
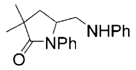
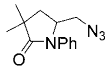
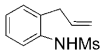
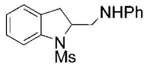
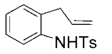
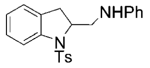
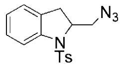
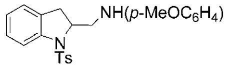
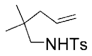
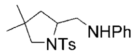
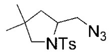
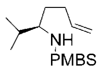
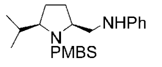
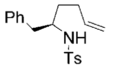
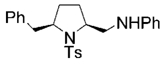
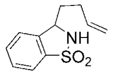
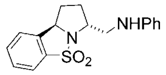
Scheme 2. Diamination of a 1,1-disubstituted alkenyl urea. eh = 2-ethylhexanoate.



Scheme 3. High diastereoselectivity for allylic-substituted ureas.

Table 2: Copper(II)-promoted diamination of γ-alkenyl amides and sulfonamides.[a]



Entry		Substrate		Product	Yield [%]
1[a,b]	**7**		**8**		87
2[a]	**9**		**10a**		83
3[a]	**9**		**10b**		89
4[c]	**11a**		**12a**		82
5[c]	**11b**		**12b**		83
6[a]	**11b**		**12c**		80
7[c]	**11b**		**12d**		42
8[a]	**13**		**14a**		70
9[a]	**13**		**14b**		92
10[a,d]	**15**		**16**		78 d.r. > 20:1
11[a,d]	**17**		**18**		82 d.r. > 20:1
12[a,d]	**19**		**20**		63 d.r. > 20:1

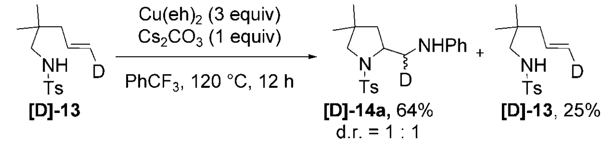
[a] Conditions A (see Table 1). [b] Reaction run at 150 °C for 48 h. [c] Conditions B (see Table 1). [d] Reaction run at 130 °C. PMBS = *para*-methoxybenzene sulfonyl, Ms = methanesulfonyl.

Both 2,5-*cis*- and 2,5-*trans*-pyrrolidines were formed with high diastereoselectivity (Table 2, entries 10–12).

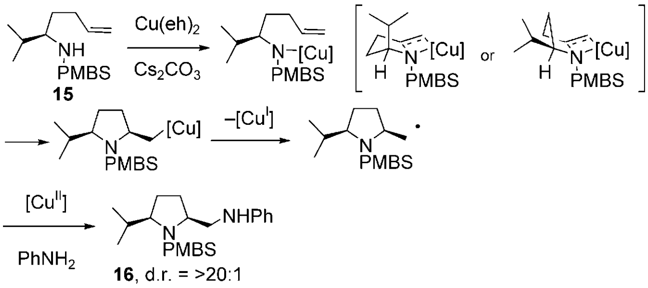
In general, electron-deficient anilines are better coupling partners than electron-rich anilines in this reaction. For example, the electron-deficient *para*-trifluoromethylaniline provided the highest yield with **1a**, giving 97 % of **2f** (Table 1, entry 6), whilst only the substrate-decomposition product **2a** was observed from the attempted diamination of *para*-methoxyaniline with **1a**. *para*-Methoxyaniline was marginally more successful in the diamination reaction with *N*-tosyl-

ortho-allylaniline (which cannot undergo the same decomposition), giving **12d** in 42% yield (Table 2, entry 7). Electron-rich amines may bind too tightly to the copper promoter, thereby inhibiting either or both of the C–N bond-forming steps.

To gain insight into the formation of the second C–N bond, we subjected the *trans*-deuterated alkene **[D]-13**[9b] to the diamination reaction (Scheme 4). Partial conversion led to isolation of a 1:1 ratio of the diamination diastereomers of **[D]-14a** (64% combined yield) along with 25% of recovered **[D]-13** without alkene isomerization. We interpret this observation to indicate the irreversible formation of a transient primary carbon radical (as in Scheme 5), a result of C–Cu^{II} bond homolysis.[3,9b] This radical can then recombine with copper(II) to generate a C–Cu^{III} intermediate that may then undergo RNH_2 addition and reductive elimination to produce the observed diamine product (Scheme 5).



Scheme 4. Isotopic labeling experiment.



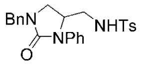
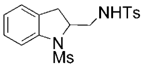
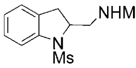
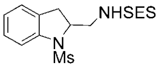
Scheme 5. Origin of 2,5-*cis*-pyrrolidine diastereoselectivity. PMBS = *para*-methoxybenzene sulfonyl.

We interpret the 2,5-*cis*-pyrrolidine selectivity shown in products **16** and **18** to be the result of the first C–N bond-formation proceeding through either chair-like or boat-like transition states in Scheme 5, where the dominant stereochemistry-determining interaction is avoidance of steric hindrance between the α substituent and the N substituent.[9] This diastereoselectivity can be switched to favor the 2,5-*trans*-pyrrolidine (cf. **20**) by connecting these two substituents directly to one another.[11]

Our initial attempts to render this diamination reaction catalytic in copper(II) using MnO_2 as a stoichiometric oxidant with either *N*-allyl urea **1a** or *N*-sulfonyl *ortho*-allylaniline **11a**, and aniline or NaN_3 as nucleophiles led to no reaction. MnO_2 was a competent oxidant in our previously reported copper-catalyzed carboamination reaction.[9c,e]

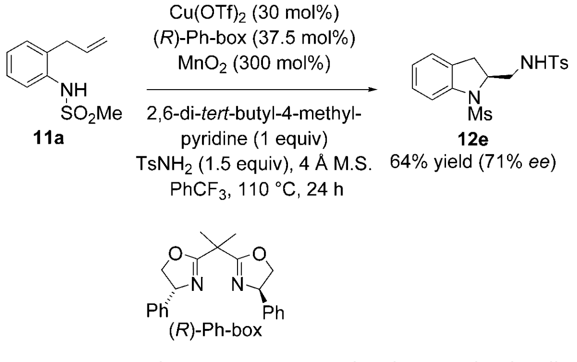
Sulfamide and urea substrates, such as those shown in Scheme 1, also failed to undergo the copper-catalyzed doubly intramolecular alkene diamination. However, to our delight, when *p*-$TolSO_2NH_2$ was used as the nucleophile with substrates **1a** and **11a**, the catalytic intra- and intermolecular alkene diamination reactions proceeded efficiently (Table 3). Superior yields (87% versus 72%; Table 3, entry 1) were obtained when 2,6-di-*tert*-butyl-4-methyl pyridine was used as the base instead of Cs_2CO_3.

Table 3: Copper(II)-catalyzed intra/intermolecular diamination of alkenes.[a]

Entry	Substrate	Nucleophile		Product	Yield [%]
1[a,b]	**1a**	$TsNH_2$	**2k**		87 (72)
2[a]	**11a**	$TsNH_2$	**12e**		83
3[a,c]	**11a**	$MeSO_2NH_2$	**12f**		69
4[a,c]	**11a**	$SESNH_2$	**12g**		80

[a] **1a** or **11a** (0.24 mmol), $Cu(eh)_2$ (20 mol%), 2,6-di-*tert*-butyl-4-methylpyridine (1 equiv), MnO_2 (300 mol%), and an amine nucleophile (2.2 equiv) were dissolved in $PhCF_3$ (0.2 M with respect to **1a** or **11a**) and treated with activated 4 Å M.S. and heated at 100°C in a pressure tube for 24 h. [b] Yield in parentheses is with 1 equiv Cs_2CO_3 as base. [c] Reaction run at 110°C. SES = trimethylsilylethylsulfonyl.

We next attempted to perform the reaction enantioselectively. When a copper(II) triflate (30 mol%) complex with (*R*)-Ph-bis(oxazoline) ligand (37.5 mol%) was used, diamination adduct **12e** was obtained in 64% yield and 71% *ee* (Scheme 6). The major enantiomer was tentatively assigned to be *S* by analogy to previous work.[9c] This is a promising result for development of the elusive catalytic enantioselective intramolecular alkene diamination reaction. Mechanistically, this reaction clearly demonstrates that copper is present in the C–N bond-forming step (as indicated in Scheme 3 and Scheme 5). Further optimization of the catalytic enantioselective process is underway in our laboratory.



Scheme 6. Enantioselective copper(II)-catalyzed intramolecular alkene diamination (*ee* determined by HPLC on a chiral stationary phase).

Experimental Section

Representative procedure (Table 1, entry 2): **1a** (40 mg, 0.15 mmol) was placed in a glass pressure tube equipped with a magnetic stir bar and was treated with Cs_2CO_3 (48.8 mg, 0.15 mmol) and $Cu(eh)_2$ (105 mg, 0.30 mmol). $PhCF_3$ (0.75 mL) and 4-chloroaniline (41 μL, 0.45 mmol) were added via syringe. The tube was capped and the reaction mixture was stirred in a 120°C oil bath. After 24 h, the mixture was cooled to 23°C, diluted with EtOAc (10 mL), and washed with sat. aq. Na_2EDTA (2×10 mL) and 2 M NaOH (2×10 mL). The aqueous layers were each washed with EtOAc and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. Flash chromatography of the crude oil on SiO_2 (0–40% EtOAc/hexanes gradient) provided 50.3 mg (86%) of **2b** (yellow oil).

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[1] For reviews on diamination reactions, see: a) J. E. G. Kemp in *Comprehensive Organic Synthesis*, *Vol. 7* (Eds.: B. M. Trost, I. Fleming), Permagon, Oxford, **1991**, p. 469; b) D. Lucet, T. Le Gall, C. Mioskowski, *Angew. Chem.* **1998**, *110*, 2724–2772; *Angew. Chem. Int. Ed.* **1998**, *37*, 2580–2627; c) M. S. Mortensen, G. A. O'Doherty, *Chemtracts: Org. Chem.* **2005**, *18*, 555; d) F. Cardona, A. Goti, *Nat. Chem.* **2009**, *1*, 269–275; e) R. M. de Figueiredo, *Angew. Chem.* **2009**, *121*, 1212–1215; *Angew. Chem. Int. Ed.* **2009**, *48*, 1190–1193.

[2] For catalytic enantioselective intermolecular alkene diamination reactions, see: a) H. F. Du. , W. C. Yuan, B. G. Zhao, Y. A. Shi, *J. Am. Chem. Soc.* **2007**, *129*, 11688–11689; b) H. F. Du, B. G. Zhao, Y. Shi, *J. Am. Chem. Soc.* **2008**, *130*, 8590–8591; c) L. Zu, Y. Shi, *J. Org. Chem.* **2008**, *73*, 749–751; d) H. F. Du, B. G. Zhao, W. C. Yuan, Y. Shi, *Org. Lett.* **2008**, *10*, 4231–4234; An osmium-promoted enantioselective alkene diamination: e) L. Almodovar, C. H. Hovelmann, J. Streuff, M. Nieger, K. Muniz, *Eur. J. Org. Chem.* **2006**, 704–712.

[3] For recent copper-promoted intramolecular alkene diaminations, see: a) T. P. Zabawa, D. Kasi, S. R. Chemler, *J. Am. Chem. Soc.* **2005**, *127*, 11250–11251; b) T. P. Zabawa, S. R. Chemler, *Org. Lett.* **2007**, *9*, 2035–2038.

[4] For recent palladium, nickel, and gold-catalyzed intramolecular alkene diaminations, see: a) J. Streuff, C. H. Hovelmann, M. Nieger, K. Muniz, *J. Am. Chem. Soc.* **2005**, *127*, 12586–12587; b) K. Muñiz, J. Streuff, C. H. Hovelmann, A. Nunez, *Angew. Chem.* **2007**, *119*, 7255–7258; *Angew. Chem. Int. Ed.* **2007**, *46*, 7125–7127; c) A. Iglesias, K. Muniz, *Chem. Eur. J.* **2009**, *15*, 10563–10569; d) K. Muñiz, C. Hovelmann, J. Streuff, E. Campos-Gomez, *Pure Appl. Chem.* **2008**, *80*, 1089–1096.

[5] For palladium-catalyzed intra/intermolecular alkene diaminations, see: a) P. A. Sibbald, F. E. Michael, *Org. Lett.* **2009**, *11*, 1147–1149; b) P. A. Sibbald, C. F. Rosewall, R. D. Swartz, F. E. Michael, *J. Am. Chem. Soc.* **2009**, *131*, 15945–15951.

[6] For other recent metal-catalyzed alkene diaminations, see: a) G. L. J. Bar, G. C. Lloyd-Jones, K. I. Booker-Milburn, *J. Am. Chem. Soc.* **2005**, *127*, 7308–7309; b) H.-X. Wei, S. H. Kim, G. Li, *J. Org. Chem.* **2002**, *67*, 4777–4781; c) B. Wang, H. F. Du, Y. Shi, *Angew. Chem.* **2008**, *120*, 8348–8351; *Angew. Chem. Int. Ed.* **2008**, *47*, 8224–8227.

[7] For selected recent reports on the metal-mediated and catalyzed methods for the synthesis of vicinal diamines, see: a) B. M. Trost, D. R. Fandrick, *J. Am. Chem. Soc.* **2003**, *125*, 11836–11837; b) J. A. Fritz, J. S. Nakhla, J. P. Wolfe, *Org. Lett.* **2006**, *8*, 2531–2534; c) J. A. Fritz, J. P. Wolfe, *Tetrahedron* **2008**, *64*, 6838–6852; d) Y. Fukuta, T. Mita, N. Fukuda, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2006**, *128*, 6312–6313; e) D. E. Olson, J. Du Bois, *J. Am. Chem. Soc.* **2008**, *130*, 11248–11249; f) H. Li, R. A. Widenhoefer, *Org. Lett.* **2009**, *11*, 2671–2674; g) C. T. Hoang, V. Alezra, R. Guillot, C. Kouklovsky, *Org. Lett.* **2007**, *9*, 2521–2524.

[8] S. R. Chemler, *Org. Biomol. Chem.* **2009**, *7*, 3009–3019.

[9] a) E. S. Sherman, S. R. Chemler, T. B. Tan, O. Gerlits, *Org. Lett.* **2004**, *6*, 1573–1575; b) E. S. Sherman, P. H. Fuller, D. Kasi, S. R. Chemler, *J. Org. Chem.* **2007**, *72*, 3896–3905; c) W. Zeng, S. R. Chemler, *J. Am. Chem. Soc.* **2007**, *129*, 12948–12949; d) P. H. Fuller, S. R. Chemler, *Org. Lett.* **2007**, *9*, 5477–5480; e) E. S. Sherman, S. R. Chemler, *Adv. Synth. Catal.* **2009**, *351*, 467–471.

[10] These reactions were run using no more than 15 mg of NaN_3. Care should be taken with this reaction as NaN_3 is potentially explosive when heated or exposed to metals and their salts.

[11] M. C. Paderes, S. R. Chemler, *Org. Lett.* **2009**, *11*, 1915–1918.