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Complementary Regioselectivity in the Cu(I)-Catalyzed Diamination of Conjugated Dienes To Form Cyclic Sulfamides

Richard G. Cornwall, Baoguo Zhao, and Yian Shi*

Department of Chemistry, Colorado State University, Fort Collins,
Colorado 80523, United States

yian@lamar.colostate.edu

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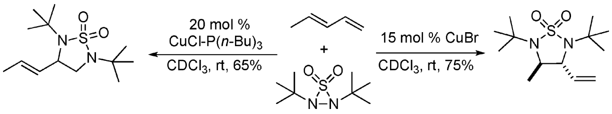
ABSTRACT



This paper describes the regioselective diamination of conjugated dienes using inexpensive Cu(I) as catalyst and *N*,*N*-di-*tert*-butylthiadiaziridine 1,1-dioxide as nitrogen source. The regioselectivity of diamination is likely due to dual mechanistic pathways which are greatly influenced by reaction conditions and the nature of the diene. A variety of useful internal and terminal cyclic sulfamides can be obtained in good yield.

Metal-catalyzed diamination of olefins presents an attractive strategy for the synthesis of vicinal diamines which are important functional moieties present in various biologically active compounds and chiral ligands used in asymmetric synthesis.[1] Various metal-mediated and metal-catalyzed processes to construct vicinal diamines from olefins have been reported.[1−8] We previously reported the diamination of conjugated dienes using Pd(0)[9] or Cu(I)[10] as a catalyst and di-*tert*-butyldiaziridinone (**1**)[11] as a nitrogen source (Figure 1). The Pd(0)-catalyzed reaction is proposed to proceed through a concerted mechanism, affording diamination of the internal double bond, whereas the Cu(I)-catalyzed reaction is proposed to proceed through a stepwise

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(1) For leading reviews, see: (a) Michalson, E. T.; Szmuszkovicz, J. *Prog. Drug Res.* **1989**, *33*, 135. (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. (d) Kotti, S. R. S. S.; Timmons, C.; Li, G. *Chem. Biol. Drug Des.* **2006**, *67*, 101. (e) Kizirian, J.-C. *Chem. Rev.* **2008**, *108*, 140. (f) Lin, G.-Q.; Xu, M.-H.; Zhong, Y.-W.; Sun, X.-W. *Acc. Chem. Res.* **2008**, *41*, 831. (g) de Figueiredo, R. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 1190. (h) Cardona, F.; Goti, A. *Nat. Chem.* **2009**, *1*, 269.

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(4) For Rh(II)-, Cu(I)-, and Fe(III)-catalyzed diamination with $TsNCl_2$ or $TsNBr_2$, see: (a) Li, G.; Wei, H.-X.; Kim, S. H.; Carducci, M. D. *Angew. Chem., Int. Ed.* **2001**, *40*, 4277. (b) Wei, H.-X.; Kim, S. H.; Li, G. *J. Org. Chem.* **2002**, *67*, 4777. (c) Han, J.; Li, T.; Pan, Y.; Kattuboina, A.; Li, G. *Chem. Biol. Drug. Des.* **2008**, *71*, 71.

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(8) For related Ni(II)-catalyzed intramolecular diamination of olefins, see: (a) Muñiz, K.; Streuff, J.; Hövelmann, C. H.; Núñez, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 7125. (b) Muñiz, K.; Hövelmann, C. H.; Streuff, J.; Campos-Gómez, E. *Pure Appl. Chem.* **2008**, *80*, 1089.

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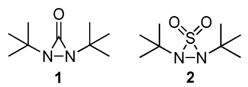
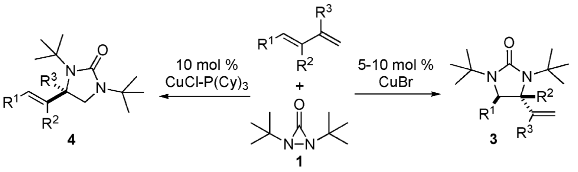


Figure 1. Nitrogen sources.

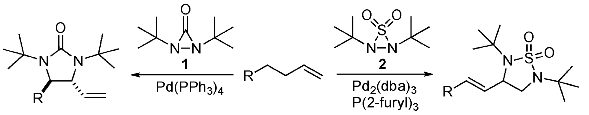
radical mechanism, yielding predominantly the terminal diamination product. Very recently, we found that the regioselectivity of diamination of conjugated dienes can be highly influenced by reaction conditions, choice of Cu(I) catalyst, and substrates used (Scheme 1).[12] It is proposed that the regioselectivity of this diamination is a result of dual mechanistic pathways. Complementary to the previously reported conditions using CuCl-L$_n$[10a] yielding terminal diamination, it was shown that with 5−10 mol % CuBr as catalyst, the internal double bond of conjugated dienes could be efficiently diaminated with very high selectivity.[12] While the terminal diamination products are consistent with a stepwise radical process, the internal diamination products are consistent with a mechanism similar to that of the proposed, concerted Pd(0)-catalyzed diamination of conjugated dienes.[9a] The mechanistic duality of the Cu(I)-catalyzed reaction prompted us to investigate the use of alternate nitrogen sources on the regioselectivity of diamination.

Scheme 1. Cu(I)-Catalyzed Regioselective Diamination Using **1**



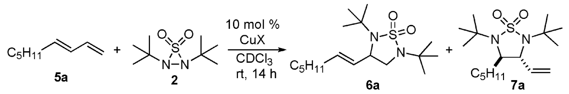
We have reported in our earlier studies that *N*,*N*-di-*tert*-butylthiadiaziridine 1,1-dioxide[13] (**2**) exhibits unique reactivity as an effective nitrogen source for diamination.[14,15] For example, terminal olefins were diaminated at the allylic and homoallylic carbons using Pd(0) and **1**, whereas the use of **2** resulted in dehydrogenation across the allylic and homoallylic carbons with diamination occurring at the terminal double bond (Scheme 2). In addition, cyclic sulfamides are functional moieties present in medicinal and biologically active molecules, including antibacterial agents and protease inhibitors.[16] They have also been employed as chiral ligands in asymmetric synthesis.[17] All of these factors led us to examine the behavior of compound **2** toward various dienes under Cu(I) catalysis conditions. Herein we report our preliminary studies on this topic.

Scheme 2. Pd(0)-Catalyzed Diamination of Terminal Olefins with **1** or **2**



Studies began with (*E*)-nona-1,3-diene (**5a**) as substrate and by varying reaction conditions. As shown in Table 1, both regioisomers can be formed and selectivity is dependent upon the choice of catalyst as well as reaction concentration. The terminal product was predominately obtained when P(Cy)$_3$ or P(*n*-Bu)$_3$ was used with CuCl (Table 1, entries 1−2 vs 6) and further favored when a more concentrated reaction mixture was used (Table 1, entry 2 vs 3). Alternatively, internal diamination was favored when CuBr was used without ligand (Table 1, entry 7). Addition of P(*n*-Bu)$_3$ to CuBr reaction conditions resulted in the reversal of selectivity (Table 1, entry 7 vs 9). It was also observed that internal diamination is further favored with a more dilute reaction concentration (Table 1, entry 7 vs 8).

Table 1. Effect of Reaction Conditions on Regioselectivity of Cu(I)-Catalyzed Diamination of Dienes[a]



entry	conditions	conv (%)	**6a:7a**
1	CuCl-P(Cy)$_3$ (1:1)	44	14:1[d]
2	CuCl-P(*n*-Bu)$_3$ (1:1)	47	14:1[d]
3[b]	**CuCl-P(*n*-Bu)$_3$ (1:1)**	**65**	**>25:1**[d]
4	CuCl-P(PPh)$_3$ (1:1)	40	1:1[e]
5	CuCl-dppe (1:1)	23	2:1[e]
6	CuCl	39	1:3[e]
7	CuBr	70	1:10[d]
8[c]	**CuBr**	**76**	**1:19**[d]
9	CuBr-P(*n*-Bu)$_3$ (1:1)	24	1.7:1[e]

[a] All reactions were carried out with olefin **5a** (0.20 mmol), **2** (0.24 mmol), and Cu(I) catalyst (0.020 mmol) in CDCl$_3$ (0.3 mL) under Ar at rt for 14 h unless otherwise stated. [b] 0.1 mL of CDCl$_3$ was used. [c] 0.6 mL of CDCl$_3$ was used. [d] When the selectivity is high, an accurate ratio of **6a** to **7a** was difficult to obtain by ^{1}H NMR analysis of the crude reaction mixture due to baseline noise interference. The ratio was then obtained by ^{1}H NMR analysis after flash chromatography (**6a** and **7a** were nearly inseperable). [e] When the selectivity is low, the ratio of **6a** to **7a** was determined by ^{1}H NMR analysis of the crude reaction mixture.

With optimal reaction conditions obtained, investigation into the substrate scope for terminal as well as internal diamination was pursued. As shown in Table 2, the terminal

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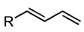
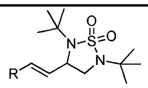
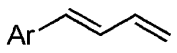
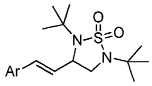
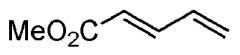
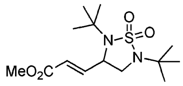
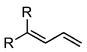
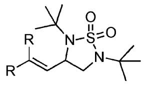
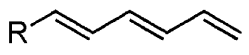
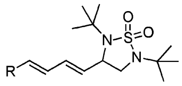
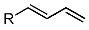
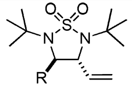
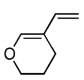
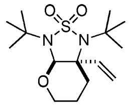
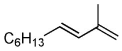
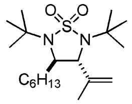
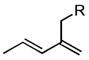
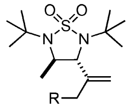
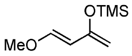
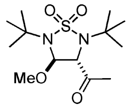
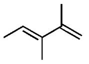
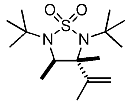
Table 2. CuCl-Catalyzed Regioselective Diamination[a]

entry	substrate (5)	product (6)	yield (%)[g]
			
1[b]	**5a**, R = $\mathrm{C_5H_{11}}$	**6a**	61
2[c]	**5b**, R = Me	**6b**	65
			
3	**5c**, Ar = Ph	**6c**	97
4	**5d**, Ar = p-$\mathrm{MeOC_6H_4}$	**6d**	93
5	**5e**, Ar = p-$\mathrm{NO_2C_6H_4}$	**6e**	94
6	**5f**, Ar = 2-furyl	**6f**	80
			
7[d]	**5g**	**6g**	67
			
8	**5h**, R = Ph	**6h**	95
9[e]	**5i**, R = Me	**6i**	89
			
10	**5j**, R = Me	**6j**	74
11[f]	**5k**, R = $\mathrm{C_5H_{11}}$	**6k**	83

[a] All reactions were carried out with olefin **5** (0.40 mmol), CuCl/P(*n*-Bu)$_3$ (1:1) complex (0.020 mmol), and **2** (0.48 mmol) in $\mathrm{CDCl_3}$ (0.1 mL) under Ar at rt unless otherwise stated. Reaction times: for entry 1, 24 h; entry 2, 48 h; entry 3, 3.5 h; entry 4, 8 h; entry 5, 12 h; entry 6, 20 h; entry 7, 48 h; entry 8, 12 h; entry 9, 24 h; entry 10, 36 h; entry 11, 8 h. [b] Olefin **5a** (0.20 mmol), CuCl/P(*n*-Bu)$_3$ (1:1) complex (0.040 mmol), and **2** (0.24 mmol). [c] CuCl/P(*n*-Bu)$_3$ (1:1) complex (0.080 mmol) and **2** (0.80 mmol). [d] CuCl/P(*n*-Bu)$_3$ (1:1) complex (0.080 mmol) and **2** (0.60 mmol). [e] CuCl/P(*n*-Bu)$_3$ (1:1) complex (0.040 mmol) and **2** (0.60 mmol). [f] **2** (0.6 mmol). [g] Isolated yield.

Table 3. CuBr-Catalyzed Regioselective Diamination[a]

entry	substrate (5)	product (7)	yield (%)[c]
			
1	**5a**, R = $\mathrm{C_5H_{11}}$	**7a**	70 (75)[d] (1:19)[e]
2	**5b**, R = Me	**7b**	75
			
3	**5l**	**7l**	62
			
4	**5m**	**7m**	63
			
5	**5n**, R = TMS	**7n**	74
6	**5o**, R = Me	**7o**	81
			
7	**5p**	**7p**	75
			
8[b]	**5q**	**7q**	65

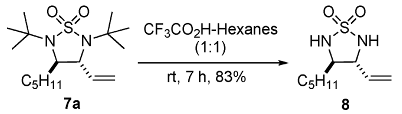
[a] All reactions were carried out with olefin **5** (0.20 mmol), CuBr (0.030 mmol), and **2** (0.24 mmol) in $\mathrm{CDCl_3}$ (0.6 mL) under Ar at rt for 24 h, unless otherwise stated. For entry 1, 0.040 mmol of CuBr was used. For entry 8, the reaction was carried out on double scale. [b] Diamination product **7q** is acid sensitive and was obtained by crystallization from hexanes. [c] Isolated yield. [d] The reaction was carried out with 8 mmol of olefin **5a**. [e] The ratio of **6a** to **7a** was determined by ^{1}H NMR analysis after flash chromatography.

diamination exhibited excellent substrate adaptability. Various substituted dienes and trienes can be smoothly diaminated at room temperature. Both electron-deficient (Table 2, entries 5 and 7) and electron-rich (Table 2, entries 4 and 6) dienes can be diaminated under the reaction conditions. Compared with alkyldienes (Table 2, entries 1−2), aryldienes and trienes (Table 2, entries 3−6, 8, 10−11) exhibited higher activity and could be diaminated with lower catalyst loading (5 mol %). The reaction exhibited excellent regioselectivity, and all the diaminations occurred at the terminal double bond. The internal regioisomer, if there was any, was barely detectable by ^{1}H NMR analysis.

Using CuBr as catalyst, the substrate investigation for internal diamination is shown in Table 3. Various 1-monosubstituted (Table 3, entries 1, 2), 1,2- (Table 3, entry 3) and 1,3-disubstituted (Table 3, entries 4−7), and 1,2,3-trisubstituted (Table 3, entry 8) dienes can be readily diaminated at the internal double bond with high regioselectivity. When Danishefsky's diene (**5p**) was subjected to the diamination conditions, internal diamination was observed and desilylation occurred during purification on silica gel yielding the ketone product **7p** (Table 3, entry 7). The diamination occurred highly regioselectively, and in most cases only the internal regioisomer was formed as judged by ^{1}H NMR analysis. The diamination can be carried out on gram scale (Table 3, entry 1). Removal of the *tert*-butyl groups from internal diamination products is demonstrated in Scheme 3. Treatment of **7a** with a mixture of $\mathrm{CF_3CO_2H}$−hexanes (1:1) at rt resulted in deprotected product **8** in 83% yield.

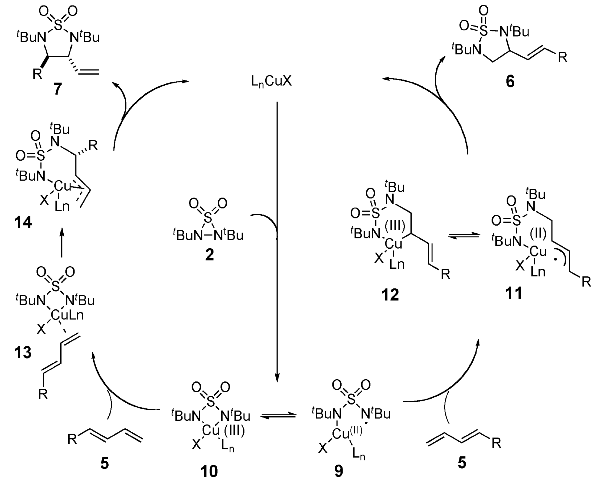
Although further mechanistic studies are needed, it is proposed that the mechanism of diamination proceeds *via* dual

Scheme 3. Deprotection of Diamination Product **7a**



mechanistic pathways analogous to that of the Cu(I)-catalyzed diamination using **1** as a nitrogen source.[12] As shown in Scheme 4, insertion of the Cu(I) catalyst into the N−N bond of **2** results in the formation of Cu(III) species **10** in equilibrium with Cu(II) radical species **9**. Terminal diamination is likely to proceed *via* a radical pathway.[10a] The addition of **9** into the terminal double bond of diene **5** forms radical species **11** and/or Cu(III) species **12** which subsequently results in terminal diamination product **6** and regeneration of the Cu(I) catalyst. The alternate diamination pathway involving Cu(III) species **10** likely results in the formation of internal diamination product **7**.[18] Coordination of diene **5** to Cu(III) species **10** forms the olefin complex **13** which is then converted to intermediate **14** *via* migratory insertion of the nitrogen to the internal double bond of the diene. Intermediate **14** then undergoes reductive elimination to give the internal diamination product **7** and regenerate the Cu(I) catalyst.

Scheme 4. Proposed Mechanistic Cycle for the Cu(I)-Catalyzed Diamination of Conjugated Dienes Using **2**



As shown in the above studies, the regioselectivity is greatly dependent upon diene substrate and reaction conditions. Conjugated dienes with radical stabilizing groups, such as arylbutadienes and trienes, are especially efficient for terminal diamination (Table 2, entries 3−6, 8, and 10−11), due to their ability to stabilize radical intermediate **11**. Electron-rich dienes, including polysubstituted dienes (Table 3, entries 3−8), have shown high regioselectivity for internal diamination using CuBr as a catalyst, analogous to Pd(0)-catalyzed diamination.[9a] The substituents on the terminal olefins of entries 4−8 (Table 3) could also play a role in sterically favoring the internal diamination over the terminal diamination. Alkyl dienes present a class of compounds which are efficient for both terminal and internal diamination. The regioselectivity of the diamination can be controlled by changing the reaction conditions. Addition of a phosphine ligand favors terminal diamination. This is likely due to the coordination of the ligand to the Cu center, favoring the formation of radical species **9** while hindering the coordination of olefin **5** to Cu(III) species **10**.[12]

In summary, a variety of conjugated dienes have been internally diaminated using CuBr and terminally diaminated using CuCl-P(n-Bu)$_3$, with *N*,*N*-di-*tert*-butylthiadiaziridine 1,1-dioxide (**2**) as a nitrogen source, giving various cyclic sulfamides in good yield. Cyclic sulfamides are useful functional motifs in medicinal and biologically important molecules. The reaction conditions, as well as the diene substrate, play a large role in the regioselectivity of the diamination. A dual mechanistic pathway involving Cu(II)/Cu(III) species is proposed for this diamination. The terminal diamination likely proceeds *via* a radical mechanism involving a Cu(II) species while the internal diamination likely undergoes a concerted pathway involving a Cu(III) species. Further mechanistic investigation as well as the development of an asymmetric process is ongoing.

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Supporting Information Available: Experimental procedures, characterization data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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