

## Cu(I)-Catalyzed Regioselective Diamination of Conjugated Dienes via Dual Mechanistic Pathways

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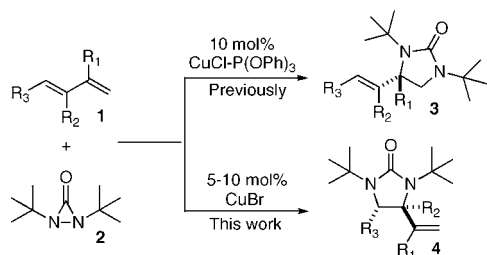
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**Abstract:** This paper describes the Cu(I)-catalyzed regioselective diamination of conjugated dienes using di-*tert*-butyldiaziridinone as nitrogen source. The internal diamination and terminal diamination likely proceed via two mechanistic pathways. Various dienes can be efficiently diaminated at the internal double bonds with high regio- and diastereoselectivity in good yield using inexpensive CuBr as catalyst.

Diamination of olefins presents an effective strategy to access vicinal diamine moieties which are contained in various biologically active molecules and are widely used as chiral control elements in asymmetric synthesis.<sup>1</sup> Various metal-mediated and metal-catalyzed diamination processes have been reported.<sup>1–8</sup> In our earlier studies, we have shown that conjugated dienes can be regioselectively diaminated using Pd(0)<sup>9</sup> and Cu(I)<sup>10</sup> as catalysts and di-*tert*-butyldiaziridinone (**2**)<sup>11,12</sup> as nitrogen source. The Pd(0)-catalyzed diamination occurred regioselectively at the internal double bonds of dienes,<sup>9</sup> and the Cu(I)-catalyzed diamination occurred primarily at the terminal double bonds with 10 mol % CuCl–P(OPh)<sub>3</sub> (Scheme 1).<sup>10</sup> The Cu(I)-catalyzed diamination was proposed to proceed via a stepwise radical mechanism involving a Cu(II) species. During our ongoing studies, it was a surprise to find that the Cu(I)-catalyzed diamination could occur regioselectively at the internal double bond under certain conditions (e.g., with CuBr as catalyst) (Scheme 1). The reaction is likely to proceed via a concerted mechanism involving a four-membered Cu(III) species. Herein, we report our preliminary studies on this subject.

### Scheme 1



Studies began with the investigation of the effect of reaction conditions on the diamination of (*E*)-penta-1,3-diene (**1a**). As shown in Table 1, diene **1a** can be selectively diaminated on either double bond. The regioselectivity is highly dependent on the reaction conditions. Terminal diamination product **3a** was increased with more phosphorus ligand present (Table 1, entry 2 vs 1). When PCy<sub>3</sub> was used, the diamination occurred predominately on the terminal double bond (Table 1, entry 4). On the other hand, internal diamination product **4a** was favored in the absence of ligand (Table 1, entries 5 and 6). Essentially only **4a** was formed with 5 mol %

**Table 1.** Effect of Reaction Conditions on the Regioselectivity of Cu(I)-Catalyzed Diamination of Dienes<sup>a</sup>

entry	substrate	catalyst	conv. (%) <sup>b</sup>	3:4 <sup>d</sup>
1		CuCl–P(OPh) <sub>3</sub> (1:1.2)	92	34:66
2	<b>1a</b>	CuCl–P(OPh) <sub>3</sub> (1:2)	92	42:58
3	<b>1a</b>	CuCl–PCy <sub>3</sub> (1:1.2)	61	78:22
4	<b>1a</b>	CuCl–PCy <sub>3</sub> (1:1.5)	100 (53%) <sup>c</sup>	<b>97:3</b>
5	<b>1a</b>	CuCl	100	17:83
6	<b>1a</b>	CuBr	100 (99%) <sup>c</sup>	<b>1:99</b>
7		CuCl–PCy <sub>3</sub> (1:1.5)	100 (99%) <sup>c</sup>	<b>&gt;99:1</b>
8	<b>1b</b>	CuBr	100 (97%) <sup>c</sup>	<b>9:91</b>

<sup>a</sup> All reactions were carried out with olefin **1a** (0.20 mmol), di-*tert*-butyldiaziridinone (**2**) (0.40 mmol), and catalyst [0.020 mmol, complex CuCl–P was prepared *in situ* from CuCl (0.02 mmol) and the corresponding ligand by stirring at room temperature for 1 h] in C<sub>6</sub>D<sub>6</sub> (0.2 mL) under Ar at room temperature for 10 h unless otherwise stated. For entry 5, CDCl<sub>3</sub> was used. For entry 4, the reaction was carried out with olefin **1a** (2.0 mmol) and **2** [0.20 mmol, dissolved in C<sub>6</sub>D<sub>6</sub> (0.1 mL), slow addition over 7 h] at room temperature for 10 h (total). For entry 6, the reaction was carried out with olefin **1a** (0.20 mmol), di-*tert*-butyldiaziridinone (**2**) (0.22 mmol), and CuBr (0.010 mmol) in CDCl<sub>3</sub> (0.4 mL) at 0 °C for 20 h. For entry 7, C<sub>6</sub>D<sub>6</sub> (0.05 mL) was used to dissolve olefin **1b**. For entry 8, the reaction was carried out with olefin **1b** (0.20 mmol), **2** (0.22 mmol), and CuBr (0.010 mmol) in CDCl<sub>3</sub> (1.0 mL) at –20 °C for 40 h. <sup>b</sup> The conversion was based on olefin **1** and determined by analysis of the <sup>1</sup>H NMR spectrum of the crude reaction mixture, except for entry 4, for which the conversion was based on **2**. <sup>c</sup> Isolated yield based on olefin **1** for entries 6–8 and based on **2** for entry 4. <sup>d</sup> The ratio of **3** to **4** was determined by analysis of the <sup>1</sup>H NMR spectrum of the crude reaction mixture.

CuBr as catalyst in CDCl<sub>3</sub> at 0 °C (Table 1, entry 6). The control of regioselectivity by simply changing reaction conditions was also observed for additional substrates such as 3-methyl-1-phenylbuta-1,3-diene (**1b**) (Table 1, entries 7 and 8).

While the Cu(I)-catalyzed terminal diamination of conjugated dienes has been previously shown to be an effective process for various substrates,<sup>10</sup> internal diamination did not appear to be a viable process under those conditions. The observation that the internal double bond can be regioselectively diaminated with CuBr prompted us to further explore the substrate scope. As shown in Table 2, various 1-substituted (entries 1 and 2), 1,2-disubstituted (entries 3–9), 1,3-disubstituted (entries 10–12), and 1,2,3-trisubstituted (entries 13 and 14) dienes can be efficiently diaminated at the internal double bonds with high regioselectivity and yield. Cyclic substrates can also be selectively diaminated in high yield (Table 2, entries 5–9). In the case of entry 9, only one diastereoisomer

Table 2. CuBr-Catalyzed Regioselective Diamination of Dienes<sup>a</sup>

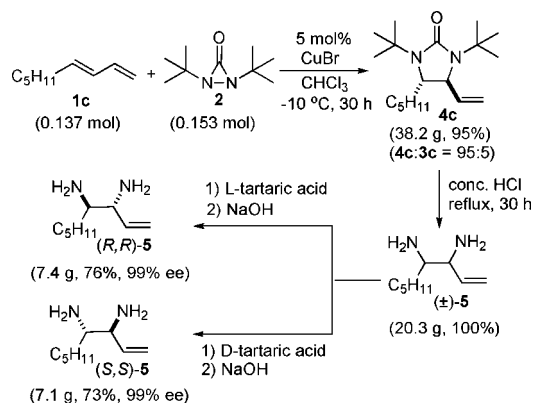
entry	substrate ( <b>1</b> )	product ( <b>4</b> )	yield (%) <sup>b</sup>
1	<b>1c</b> C <sub>5</sub> H <sub>11</sub>		97 (96:4) <sup>c</sup>
2	<b>1d</b> MeO		95
3	<b>1e</b> , R = Et		81
4	<b>1f</b> , R = Ph		92 (97:3) <sup>c</sup>
5	<b>1g</b> , n = 1		95
6	<b>1h</b> , n = 2		99
7	<b>1i</b> , n = 3		94
8	<b>1j</b> 		85
9	<b>1k</b> OTMS		95 (97:3) <sup>c,d</sup>
10	<b>1l</b> , R = Me		98
11	<b>1m</b> , R = Ph		96 (89:11) <sup>c</sup>
12	<b>1n</b> TMS		94
13	<b>1o</b>		90
14	<b>1p</b> Ph, Et		95

<sup>a</sup> All reactions were carried out with olefin **1** (0.20 mmol), di-*tert*-butyldiaziridinone (**2**) (0.22 mmol), and CuBr (0.010 mmol) in CDCl<sub>3</sub> (0.4 mL) under Ar with vigorous stirring at 0 °C for 20 h unless otherwise stated. For entry 1, **1c** (0.19 mmol) was used. For entry 2, olefin **1d** (0.25 mmol, *EZ* = 15.7:1, *E* isomer: 0.24 mmol) and **2** (0.2 mmol) were used. For entry 7, the reaction was carried out on 0.40 mmol scale. For entry 9, CuBr (0.020 mmol) was used. <sup>b</sup> Isolated yield based on **1** except for that of entry 2, which was based on **2**. <sup>c</sup> The ratio of **4** to **3** was determined by analysis of the <sup>1</sup>H NMR spectrum of the crude reaction mixture. <sup>d</sup> The stereochemistry was tentatively assigned on the basis of sterics.

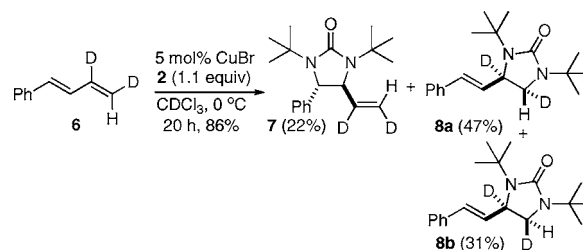
was observed in the <sup>1</sup>H NMR spectrum. In most cases, essentially one regioisomer was formed, and the other regioisomer was barely detectable (if there was any) in the <sup>1</sup>H NMR spectrum of the crude reaction mixture. The reaction is also highly diastereoselective, and essentially only one diastereoisomer was obtained in all cases.

The CuBr-catalyzed diamination can be carried out on a relatively large scale (Scheme 2). For example, 38.2 g of diamination product

Scheme 2



Scheme 3

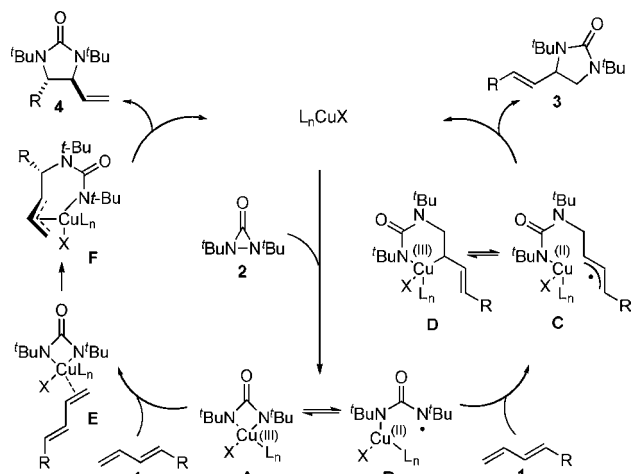
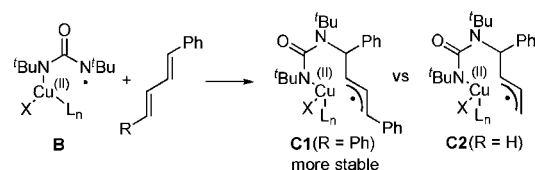


**4c** was readily obtained using 5 mol % CuBr as catalyst. The *tert*-butyl groups and the carbonyl group were cleanly removed by treatment of **4c** with concentrated HCl at reflux to give free diamine (±)-**5** in quantitative yield. Resolution of racemic diamine **5** with L- and D-tartaric acids gave chiral diamines (*R,R*)-**5** (99% ee) and (*S,S*)-**5** (99% ee) in good yield.<sup>13</sup>

Effective substrates require a terminal double bond. Internal dienes such as 1,4-diphenylbutadiene gave an insignificant amount of diamination products. Substrates such as 1-phenylbutadiene gave a mixture of both internal and terminal diamination products. When deuterated 1-phenylbutadiene (**6**) was used, two deuterium isomers, **8a** and **8b**, were obtained for the terminal diamination, while no deuterium isomerization was observed for the internal diamination (Scheme 3). These results suggest that the internal diamination and terminal diamination likely proceed via two different mechanisms.

While a precise reaction mechanism awaits further study, a plausible dual mechanism is shown in Scheme 4. The CuX first reductively cleaves the N–N bond of diaziridinone **2** to form four-membered Cu(III) species **A** and Cu(II) nitrogen radical **B**, which are likely in equilibrium. As proposed previously,<sup>10a</sup> radical **B** adds to the terminal double bond of the diene to form Cu(II) allyl radical species **C** and/or Cu(III) intermediate **D**, which subsequently undergo the second C–N bond formation to give the terminal diamination product **3** and regenerate the Cu(I) catalyst. Radical **B** preferentially adds to the terminal double bond, likely due to sterics and the formation of a relatively more stable allyl radical **C**. The formation of isomers **8a** and **8b** from deuterated 1-phenylbutadiene (**6**) (Scheme 3) is consistent with the proposed radical mechanism for the terminal diamination.

The fact that no significant amount of diamination product was obtained with internal dienes such as 1,4-diphenylbutadiene suggests that addition of radical **B** to an internal double bond is unfavorable, even in the presence of a radical-stabilizing phenyl group, possibly due to sterics (Scheme 5). A terminal diene should be even less favorable for the addition of radical **B** to the internal double bond since it does not have the radical-stabilizing phenyl group (radical **C2** is less stable than **C1**) (Scheme 5). Therefore, it is unlikely that the

**Scheme 4.** Proposed Dual Mechanisms for the Cu(I)-Catalyzed Diamination of Conjugated Dienes**Scheme 5.** Addition of Radical **B** to the Internal Double Bond

observed internal diamination of terminal dienes proceeds via a radical pathway. The absence of deuterium isomerization in internal diamination product **7** (Scheme 3) also argues against a radical mechanism.

The internal diamination likely proceeds via four-membered Cu(III) species **A**,<sup>14</sup> analogous to the case of Pd-catalyzed diamination.<sup>9</sup> Intermediate **A** coordinates with diene **1** to form complex **E**, which undergoes a migratory insertion and a subsequent reductive elimination to give internal diamination product **4** and regenerate the Cu(I) catalyst (Scheme 4).

The competition between the two pathways depends on the reaction conditions and types of substrates used. Adding more ligand to the reaction system appears to facilitate the formation of Cu(II) radical **B** and/or hinder the coordination of diene **1** to Cu(III) species **A**, thus leading to more terminal diamination product **3**. On the other hand, the absence of the ligand may favor Cu(III) species **A** and subsequent internal diamination to give product **4**. The counteranion of the Cu(I) catalyst also has a large influence on the regioselectivity. It appears that CuBr is more favorable toward the internal diamination than CuCl. Substrates with radical-stabilizing groups such as 1-phenylbutadiene facilitate the formation of radical **C**, thus increasing the amount of terminal diamination product **3** even with CuBr. Generally, introduction of electron-donating groups, such as alkyl chains, appears to be more favorable toward formation of the internal diamination product **4**.

In summary, studies have shown that the regioselectivity of the Cu(I)-catalyzed diamination of conjugated dienes using di-*tert*-butyldiaziridinone (**2**) as nitrogen source can be altered by simply tuning the reaction conditions. Various dienes can be efficiently diaminated at the internal double bonds with high regioselectivity and good yield using 5–10 mol % of inexpensive CuBr. The diamination is also amenable to large scale. Chiral diamines can be readily obtained in high optical purity by simple resolution with tartaric acids. Studies also show that the internal diamination and terminal diamination likely proceed via two mechanistic pathways involving Cu(III) and Cu(II) species, respectively. The mechanistic duality of the Cu species displayed in this diamination may provide

useful insights for Cu-promoted reaction processes.<sup>15</sup> Further mechanistic studies and development of an asymmetric diamination process are currently underway.

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**Supporting Information Available:** Experimental procedures, characterization of diamination products, data for determination of enantiomeric excess of diamine **5**, and <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra of **3–5**, **7**, and **8**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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