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Cu(I)-Catalyzed Asymmetric Diamination of Conjugated Dienes

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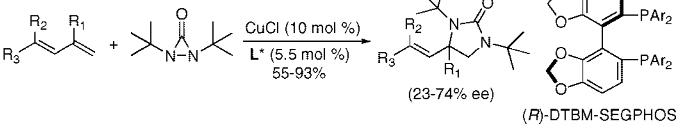
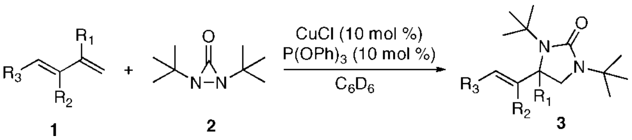
ABSTRACT



A Cu(I)-catalyzed asymmetric diamination for a variety of conjugated dienes and a triene with encouraging ee's has been effectively achieved using (*R*)-DTBM-SEGPHOS as a chiral ligand and di-*tert*-butyldiaziridinone as the nitrogen source.

Direct diamination of olefins provides an efficient approach to the synthesis of vicinal diamines, which are biologically and chemically important functional moieties.[1] While various metal-mediated and catalyzed diaminations have been achieved,[2−8] catalytic asymmetric diamination of olefins has been less well developed and still remains a challenge in organic synthesis. Earlier, Muñiz and co-workers reported chiral auxiliary based[9a] and chiral Lewis acid catalyzed[9b] asymmetric diamination using bisimidoosmium as reagent. Recently, we reported Pd(0)-catalyzed asymmetric diamination of conjugated dienes[10a,b] and asymmetric allylic and homoallylic C−H diamination of terminal olefins.[10c] Previously, we have shown that Cu(I)-catalyzed diamination of conjugated dienes and triene using di-*tert*-butyldiaziridinone (**2**)[11,12] as the nitrogen source occurs regioselectively at the terminal double bond under mild reaction conditions (Scheme 1),[8a] which provides complementary regioselectivity to the Pd(0)-catalyzed diamination.[7] It is highly desirable to develop an asymmetric version of this diamination process to enhance its synthetic utility. However, the Cu(I)-catalyzed diamination likely proceeds via a radical mechanism (Figure 1).[8,13−15] The involvement of radical intermediates presents a challenge for asymmetric control.

Scheme 1



1 **2** **3**

Asymmetric diamination was initially investigated using 10 mol % of CuCl with various commercially available or

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(1) For leading reviews, see: (a) Lucet, D.; Gall, T. L.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580. (b) Mortensen, M. S.; O'Doherty, G. A. *Chemtracts: Org. Chem.* **2005**, *18*, 555. (c) Kotti, S. R. S. S.; Timmons, C.; Li, G. *Chem. Biol. Drug Des.* **2006**, *67*, 101.

(2) For examples of metal-mediated diaminations, see: Co: (a) Becker, P. N.; White, M. A.; Bergman, R. G. *J. Am. Chem. Soc.* **1980**, *102*, 5676. Hg: (b) Barluenga, J.; Alonso-Cires, L.; Asensio, G. *Synthesis* **1979**, 962. Mn: (c) Fristad, W. E.; Brandvold, T. A.; Peterson, J. R.; Thompson, S. R. *J. Org. Chem.* **1985**, *50*, 3647. Os: (d) Chong, A. O.; Oshima, K.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 3420. (e) Muñiz, K. *Eur. J. Org. Chem.* **2004**, 2243. Pd: (f) Bäckvall, J.-E. *Tetrahedron Lett.* **1978**, 163. Tl: (g) Aranda, V. G.; Barluenga, J.; Aznar, F. *Synthesis* **1974**, 504.

(3) For recent Cu(II)-mediated intramolecular diamination, see: (a) Zabawa, T. P.; Kasi, D.; Chemler, S. R. *J. Am. Chem. Soc.* **2005**, *127*, 11250. (b) Zabawa, T. P.; Chemler, S. R. *Org. Lett.* **2007**, *9*, 2035.

(4) For Rh(II)- and Fe(III)-catalyzed diamination with $TsNCl_2$, 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.

(5) For a recent Pd(II)-catalyzed intermolecular diamination of conjugated dienes, see: Bar, G. L. J.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *J. Am. Chem. Soc.* **2005**, *127*, 7308.

(6) For recent Pd(II)- and Ni-catalyzed intramolecular diamination of olefins, see: (a) Streuff, J.; Hövelmann, C. H.; Nieger, M.; Muñiz, K. *J. Am. Chem. Soc.* **2005**, *127*, 14586. (b) Muñiz, K.; Streuff, J.; Hövelmann, C. H.; Núñez, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 7125. (c) Muñiz, K. *J. Am. Chem. Soc.* **2007**, *129*, 14542. (d) Muñiz, K.; Hövelmann, C. H.; Streuff, J. *J. Am. Chem. Soc.* **2008**, *130*, 763.

10.1021/ol801605w CCC: $40.75

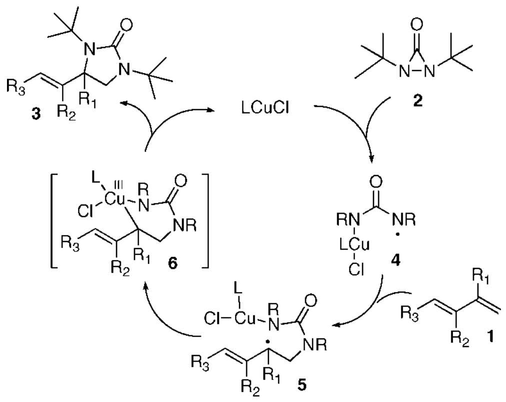
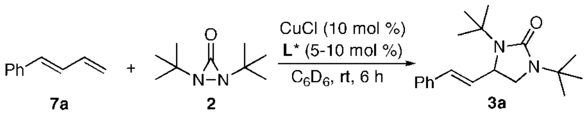


Figure 1. Proposed catalytic cycle for Cu(I)-catalyzed diamination.

Scheme 2



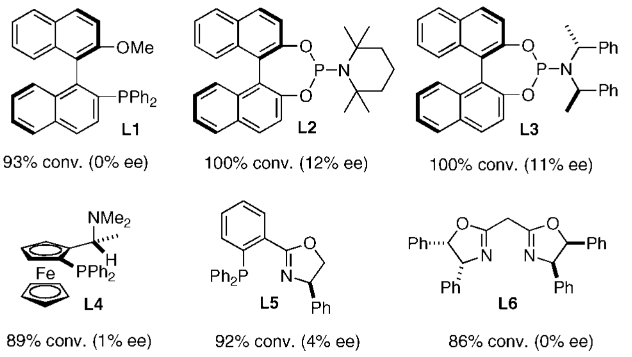


Figure 2. Asymmetric diamination of diene **7a** with selected monophosphorus and nitrogen-containing ligands.[18]

easily prepared chiral monophosphorus and nitrogen-containing ligands[16] and *trans*-1-phenylbutadiene (**7a**) as a test substrate at room temperature for 6 h (Scheme 2). As shown in Figure 2, all the reactions went smoothly to give diamination product **3a** with high conversions, but with 0 to 12% ee. To search for more promising ligands, a series of commercially available chiral bisphosphine ligands[17] were subsequently studied for the diamination of *trans*-1-phenylbutadiene (**7a**) with a 2/1 ratio of CuCl and ligand. It was found that steric bulkiness on the phosphine atoms had a large impact on the enantioselectivities (Figure 3). Encouragingly, the diamination of **7a** with (*R*)-DTBM-SEGPHOS (**L12**)[17f] gave 90% conversion and 56% ee (Figure 3).

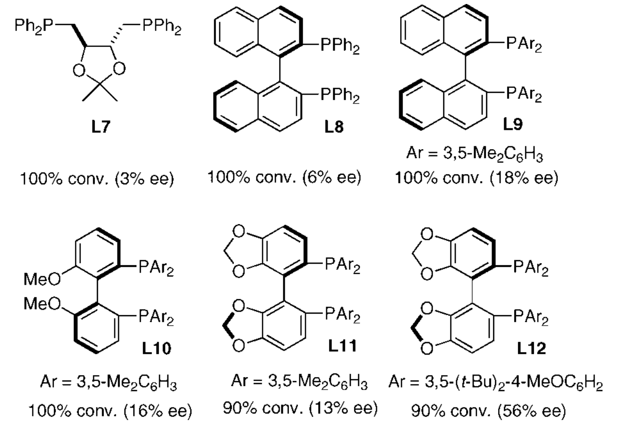


Figure 3. Asymmetric diamination of diene **7a** with selected bisphosphine ligands.[19]

To improve the enantioselectivity, the reaction conditions, including solvent, temperature, and the ratio of ligand and

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(7) For Pd(0)-catalyzed intermolecular diamination, see: (a) Du, H.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 762. (b) Xu, L.; Du, H.; Shi, Y. *J. Org. Chem.* **2007**, *72*, 7038. (c) Du, H.; Yuan, W.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 7496.

(8) For Cu(I)-catalyzed intermolecular diamination, see: (a) Yuan, W.; Du, H.; Zhao, B.; Shi, Y. *Org. Lett.* **2007**, *9*, 2589. (b) Zhao, B.; Yuan, W.; Du, H.; Shi, Y. *Org. Lett.* **2007**, *9*, 4943. (c) Zhao, B.; Du, H.; Shi, Y. *Org. Lett.* **2008**, *10*, 1087.

(9) For leading references on asymmetric diamination using bisimidoosmium as reagent, see: (a) Muñiz, K.; Nieger, M. *Synlett* **2003**, 211. (b) Muñiz, K.; Nieger, M. *Chem. Commun.* **2005**, 2729.

(10) (a) Du, H.; Yuan, W.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 11688. (b) Xu, L.; Shi, Y. *J. Org. Chem.* **2008**, *73*, 749. (c) Du, H.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2008**, *130*, 8590.

(11) Greene, F. D.; Stowell, J. C.; Bergmark, W. R. *J. Org. Chem.* **1969**, *34*, 2254.

(12) For a leading review on diaziridinone, see: Heine, H. W. In *The Chemistry of Heterocyclic Compounds*; Hassner, A., Ed.; John Wiley & Sons, Inc.: Hoboken, NJ, 1983; p 547.

(13) For a leading review on metal-promoted radical reactions, see: Iqbal, J.; Bhatia, B.; Nayyar, N. K. *Chem. Rev.* **1994**, *94*, 519.

(14) For leading reviews on CuX-catalyzed atom transfer reactions see: (a) Patten, T. E.; Matyjaszewski, K. *Acc. Chem. Res.* **1999**, *32*, 895. (b) Clark, A. J. *Chem. Soc. Rev.* **2002**, *31*, 1.

(15) For a leading review on nitrogen-centered radicals, see: Stella, L. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001; Vol. 2, p 407.

(16) For leading references on **L1**–**L6**, see: (a) Hattori, T.; Shijo, M.; Kumagai, S.; Miyano, S. *Chem. Express* **1991**, *6*, 335. (b) Ref 10a. (c) Sewald, N.; Wendisch, V. *Tetrahedron: Asymmetry* **1998**, *9*, 1341. (d) Hayashi, T.; Yamamoto, K.; Kumada, M. *Tetrahedron Lett.* **1974**, *15*, 4405. (e) von Matt, P.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 566. (f) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726. (g) Lowenthal, R. E.; Masamune, S. *Tetrahedron Lett.* **1991**, *32*, 7373.

(17) For leading references on **L7**–**L12**, see: (a) Kagan, H. B.; Dang, T.-P. *J. Am. Chem. Soc.* **1972**, *94*, 6429. (b) Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7932. (c) Mashima, K.; Matsumura, Y.-i.; Kusano, K.-h.; Kumobayashi, H.; Sayo, N.; Hori, Y.; Ishizaki, T.; Akutagawa, S.; Takaya, H. *J. Chem. Soc., Chem. Commun.* **1991**, 609. (d) Lipshutz, B. H.; Noson, K.; Chrisman, W. *J. Am. Chem. Soc.* **2001**, *123*, 12917. (e) Hatano, M.; Terada, M.; Mikami, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 249. (f) Lipshutz, B. H.; Lower, A.; Noson, K. *Org. Lett.* **2002**, *4*, 4045.

(18) The reactions were carried out with *trans*-1-phenylbutadiene (0.20 mmol), di-*tert*-butyldiaziridinone (**2**) (0.30 mmol), CuCl (0.02 mmol), and ligand **L1**–**L5** (0.02 mmol), except for **L6** (0.01 mmol) in benzene-d_6 (0.60 mL) at room temperature for 6 h. The conversions were determined by crude ^{1}H NMR, and the ee's were determined by chiral HPLC.

(19) The same conditions as ref 18 except for **L7**–**L12** (0.01 mmol).

CuCl, were further investigated. It was found that solvent has a significant effect on both reactivity and enantioselectivity (Table 1, entries 1−7), and benzene-d_6 proved to be the best solvent. The ratio of ligand and CuCl was also very important, and only 24% conversion was obtained with slightly higher ee when 1:1 CuCl and **L12** were used (Table 1, entry 8). Lowering the temperature improved the enantioselectivity (Table 1, entries 9−13), increasing to 65% ee at 0 °C (a small amount of toluene was added to avoid solidification of benzene-d_6). Overall, the best reaction conditions involve 10 mol % of CuCl and 5.5 mol % of **L12** in benzene-d_6 with a small amount of toluene at 0 °C (Table 1, entry 10).

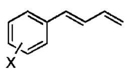
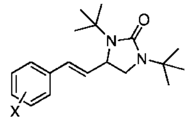
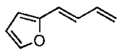
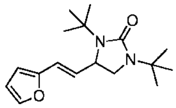
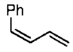
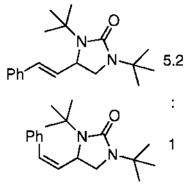
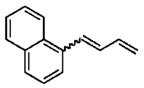
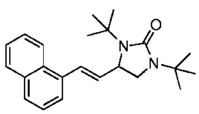
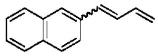
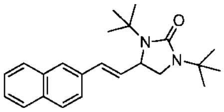
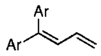
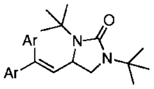
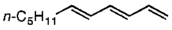
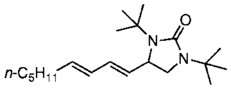
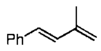
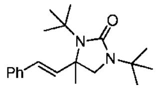
Table 1. Studies on Reaction Conditions for Asymmetric Diamination of **7a**[a]

entry	CuCl (mol %)	**L12** (mol %)	solvent	conv. (%)[b]	ee (%)[c]
1	10	5	DME	63	44
2	10	5	Et_2O	43	42
3	10	5	$CDCl_3$	78	19
4	10	5	CD_2Cl_2	100	35
5	10	5	THF	21	33
6	10	5	toluene-d_8	77	53
7	**10**	**5**	$\mathbf{C_6D_6}$	**90**	**56**
8	10	10	C_6D_6	24	58
9	10	5	$C_6D_6/PhCH_3$ (11/1, v/v)	73	63
10	**10**	**5.5**	$\mathbf{C_6D_6/PhCH_3}$**(11/1, v/v)**	**72**	**65**
11	12	5	$C_6D_6/PhCH_3$ (11/1, v/v)	74	61
12	15	5	$C_6D_6/PhCH_3$ (11/1, v/v)	89	56
13	10	5.5	$PhCH_3$	30	65

[a] All the reactions were carried out with *trans*-1-phenylbutadiene (**7a**) (0.20 mmol), di-*tert*-butyldiaziridinone (**2**) (0.30 mmol), and solvent (0.60 mL). For entries 1−8, the reactions were carried out at rt for 6 h. For entries 9−13, the reactions were carried out at 0 °C for 20 h. [b] The conversion was determined by crude ^1H NMR. [c] The ee was determined by chiral HPLC (Chiralpak AD-H column).

Under the optimized conditions, a variety of conjugated dienes can be regio- and enantioseletively diaminated at the terminal double bond in 59−93% yield with 62−74% ee's (Table 2, entries 1−10). The ee could be further improved after recrystallization (Table 2, entry 2). For *cis*-1-phenylbutadiene, isomerization of the *cis* double bond occurred during the reaction and mainly gave *E*-isomer product in 70% ee which was a little higher than direct diamination of *trans*-1-phenylbutadiene (Table 2, entry 1 vs 5). When a mixture of *trans*- and *cis*-dienes was subjected to the reaction conditions, the diamination product of the *E* isomer was formed predominately with only a trace amount of *Z* isomer (Table 2, entries 6 and 7). Asymmetric diamination of 1,1-disubstituted butadienes gave slightly higher ee's (Table 2, entries 8−10). When a triene was diaminated at room temperature in benzene-d_6, the diamination product was obtained in 58% ee (Table 2, entry 11). Asymmetric diamination of *trans*-1-phenyl-3-methylbutadiene led to 90% yield with only 23% ee (Table 2, entry 12), suggesting that the steric effect and radical stability are important factors for the enantioselectivity.

Table 2. Catalytic Asymmetric Diamination of Dienes and Triene[a]

entry	substrate	product	yield (%)[b]	ee (%)[f]
1	 X = H		69	65
2	X = 4-OMe		76	67 (>99)[g]
3	X = 2-OMe		70	67
4			80	62
5			60[c]	70 nd[h]
6	 *E*/*Z* = 1.9/1		65[d]	66
7	 *E*/*Z* = 4.1/1		78[d]	66
8	 Ar = Ph		93	72
9	Ar = *p*-tolyl		59	74
10	Ar = 2-thienyl		79	66
11			55[e]	58
12			90	23

[a] All the reactions were carried out with olefin (0.20 mmol), di-*tert*-butyldiaziridinone (**2**) (0.30 mmol), CuCl (0.02 mmol), **L12** (0.011 mmol), benzene-d_6 (0.55 mL), and toluene (0.050 mL) at 0 °C under argon for 20 h unless otherwise stated. [b] Isolated yield based on diene or triene. [c] The ratio was determined by ^1H NMR. [d] Only a trace amount of isomer was observed by ^1H NMR. [e] The reaction was carried out in benzene-d_6 at rt for 20 h. [f] The ee was determined by chiral HPLC (Chiralpak AD-H column). [g] The ee after recrystallization from hexanes. [h] Not determined.

In summary, catalytic asymmetric diamination for a variety of conjugated dienes and a triene with encouraging ee's has been achieved using CuCl/**L12** as the catalyst and di-*tert*-butyldiaziridinone as the nitrogen source. These results show that Cu(I)-catalyzed asymmetric diamination is feasible despite the fact that the diamination likely involves radical intermediates. Ligand (*R*)-DTBM-SEGPHOS (**L12**) provides a very promising lead for further improvement. Searches for more effective chiral ligands, studies of different nitrogen sources, and expansion of the substrate scope will be carried out.

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Supporting Information Available: The asymmetric diamination procedure, the characterization of the diamination products, and data for the determination of enantiomeric excess of diamination products along with the NMR spectra of diamination products. This material is available free of charge via the Internet at http://pubs.acs.org.

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