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Catalytic Asymmetric Synthesis of Cyclic Sulfamides from Conjugated Dienes

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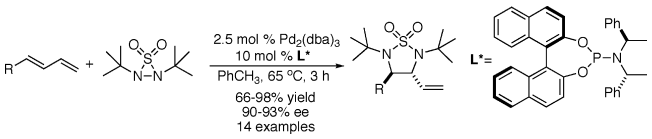
ABSTRACT



This paper describes the catalytic asymmetric diamination of alkyl dienes using *N,N′*-di-*tert*-butylthiadiaziridine 1,1-dioxide in the presence of Pd(0) and a chiral phosphoramidite ligand to give cyclic sulfamides in high yield and high ee. The diamination is also amenable to gram scale.

Vicinal diamines are found throughout biologically active molecules and are important chiral control agents in asymmetric synthesis.[1] The synthesis of vicinal diamines through the metal-promoted diamination of olefins presents an attractive and efficient strategy to access these important functional motifs, and various methods have been reported.[1−10] We have previously reported Pd(0)-[11] and Cu(I)-catalyzed[12] methods for the regioselective diamination of conjugated dienes using *N,N′*-di-*tert*-butyldiaziridinone

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(**1**) (Figure 1) as nitrogen source.[13] Asymmetric variations of these reactions have also been disclosed.[14,15] A related analogue, *N*,*N*′-di-*tert*-butylthiadiaziridine 1,1-dioxide (**2**),[16] has also shown to be an effective nitrogen source in the synthesis of cyclic sulfamides using Pd(0),[17] CuCl,[18,19] or CuBr[19] as catalyst. The resulting cyclic sulfamides are important functional motifs present in medicinal and biologically active

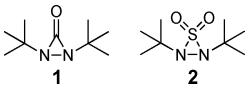

Figure 1. Nitrogen sources for diamination.

molecules including HIV protease inhibitors, anti-inflammatory agents, antibacterials, blood pressure regulators, enzyme inhibitors, and treatments for Alzheimer's disease (Figure 2).[20] Cyclic sulfamides have also shown promise as chiral auxiliaries (Figure 2).[21] Due to their biological and synthetic importance, an asymmetric synthesis of cyclic sulfamides is highly desirable. Commonly used methods employ multistep syntheses from chiral amino acids,[22] or more recently, the asymmetric hydrogenation of thiadiazole

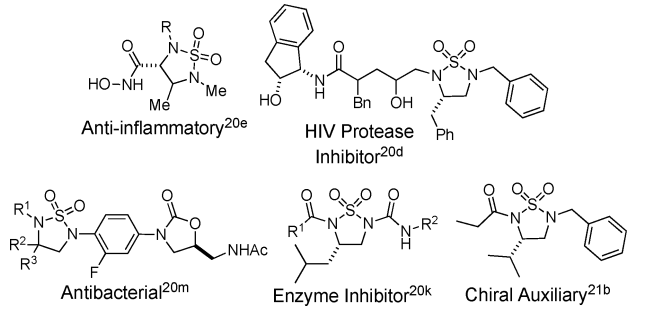

Figure 2. Cyclic sulfamides as biologically active molecules and chiral auxiliaries.

1,1-dioxides, which are synthesized via reaction of α-hydroxy aryl ketones with sulfamide.[23] Herein we wish to report the direct synthesis of optically active cyclic sulfamides via the catalytic asymmetric diamination of conjugated dienes with *N*,*N*′-di-*tert*-butylthiadiaziridine 1,1-dioxide (**2**).

Using *trans*-nona-1,3-diene as test substrate, thiadiaziridine **2** as nitrogen source, and catalysts generated from $Pd_2(dba)_3$ and a chiral ligand, the reactivity and selectivity of diamination was investigated (Scheme 1). No reaction was observed using bidentate ligand *R*-BINAP (**L1**).[24] Of the ligands screened,[25−28] BINOL-based phosphoramidite ligands displayed the most promising selectivity, and diamination was found to be highly regioselective for the internal double bond of the diene. Somewhat surprisingly, ligands **L5**[14a] and **L6**,[29] which were found to induce high

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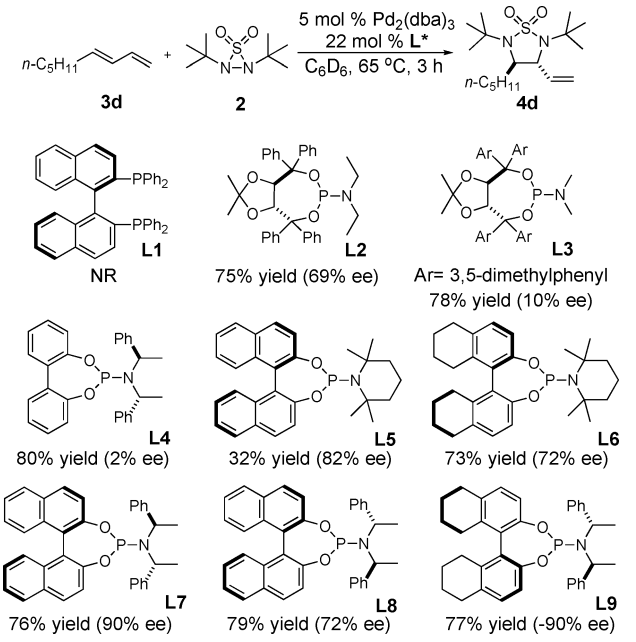
Scheme 1. Initial Screening for Asymmetric Diamination



selectivity for catalytic asymmetric diaminations using **1**, exhibited lower selectivity in the current system. On the contrary, (*R*,*R*,*R*) ligand **L7** was found to be optimal for both yield and selectivity providing the corresponding cyclic sulfamide in 76% yield and 90% ee, whereas *ent*-**L7** had previously displayed poor reactivity using **1**. As also shown in Scheme 1, (*R*,*S*,*S*) ligand **L8** displayed decreased selectivity from that of **L7**, indicating that a matched relationship between the BINOL and amine portions of the ligand are important for high asymmetric induction. In both cases, the product configuration is determined by the BINOL skeleton and not the amine portion of the ligand. H_8−BINOL-derived phosphoramidite ligand **L9** also resulted in high ee, yielding the opposite enantiomer of the product sulfamide.

With optimal ligand in hand, the substrate scope was subsequently investigated. As shown in Table 1, a variety of alkyl-substituted conjugated (*E*)-dienes[30] can be efficiently diaminated in 66−98% yield and 90−93% ee with 2.5 mol % $Pd_2(dba)_3$ and 10 mol % **L7** in toluene at 65 °C for 3 h. Alkyl chains can contain silyl (Table 1, entry 6), and aryl groups (Table 1, entries 7−9) as well as ethers (Table 1, entries 10−12). Double bonds in the alkyl groups remained unreacted in geometrically pure form (Table 1, entries 13 and 14). The catalytic asymmetric diamination is also amenable to gram scale and catalyst loading can be further reduced to 1.4 mol % $Pd_2(dba)_3$ (Table 1, entry 8). In all

Table 1. Catalytic Asymmetric Diamination of Conjugated Dienes to Form Cyclic Sulfamides[a]

entry	diene (**3**)	product (**4**)[b]	yield (%)[c]	ee (%)[d]
1	**3a**, R= Me	**4a**	97	90
2	**3b**, R= *n*-Pr	**4b**	79	90
3	**3c**, R= *i*-Bu	**4c**	84	90
4	**3d**, R= *n*-C_5H_{11}	**4d**	91	91
5	**3e**, R= $(CH_2)_2Cy$	**4e**	89	91
6	**3f**, R= $(CH_2)_2TMS$	**4f**	98	91
7	**3g**	**4g**	90	93[e]
8[f]	**3h**, Ar= Ph	**4h**	88	92[e]
9	**3i**, Ar= 4-MeOPh	**4i**	77	90[e]
10	**3j**, R= *n*-C_6H_{13}	**4j**	69	93
11[g]	**3k**, R= Ph	**4k**	81	93[h]
12	**3l**	**4l**	66	91
13	**3m**	**4m**	98	91
14	**3n**	**4n**	93	91

[a] All reactions were carried out with diene **3** (0.20 mmol), **2** (0.30 mmol), $Pd_2(dba)_3$ (0.005 mmol), and **L7** (0.02 mmol) in toluene (0.10 mL) under Ar at 65 °C for 3 h, unless otherwise stated. [b] For entries 4 and 7, the absolute configurations (*R*,*R*) were determined by comparison of the optical rotations with reported ones after complete deprotection to the free diamine (refs 12b, 14a). For all other entries, the absolute configurations were not determined and the stereochemistry indicated represents relative stereochemistry. [c] Isolated yield. [d] The ee was determined by chiral HPLC (Chiralpak IC column) after removal of the *t*-Bu groups, unless otherwise stated. [e] The ee was determined without removal of the *t*-Bu groups. [f] Reaction was carried out with diene **3h** (6.96 mmol), **2** (9.03 mmol), $Pd_2(dba)_3$ (0.10 mmol), and **L7** (0.46 mmol) in toluene (3.5 mL) under Ar at 65 °C for 3 h. [g] Reaction time, 6 h. [h] The ee was determined by chiral HPLC (Chiralpak IA column).

cases, the reaction occurs with high regioselectivity toward the internal double bond (Figure 3) and other regioisomers were barely detectable by ^1H NMR analysis if there was any. The diamination most likely proceeds through a concerted reaction mechanism analogous to the previously reported catalytic cycle using **1** (Scheme 2).[11a,c] Insertion of the chiral Pd(0) complex into the N−N bond of **2** forms four-membered Pd(II) complex **5**, which coordinates to diene **3** to give complex **6**. The migratory insertion of **6** leads to π-allyl Pd complex **7**. Upon reductive elimination,

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cyclic sulfamide **4** is formed with regeneration of the chiral Pd(0) catalyst.

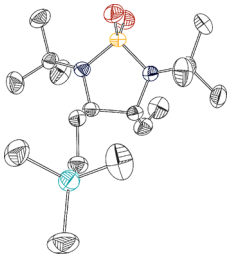
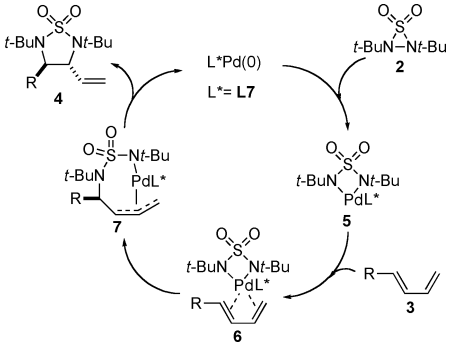


Figure 3. X-ray structure of **4f**.

Scheme 2. Proposed Catalytic Cycle for the Asymmetric Diamination of Dienes Using **2**



As shown in Scheme 3, removal of the *t*-Bu groups is accomplished in a mixture of CF_3CO_2H-hexanes at room temperature, allowing possible further derivatization of the nitrogens. Complete removal of the *t*-Bu groups and the sulfone moiety in one step is also realized in aqueous HBr at elevated temperature to unmask the free diamine.[31]

In summary, we have developed the direct and efficient synthesis of chiral cyclic sulfamides from conjugated

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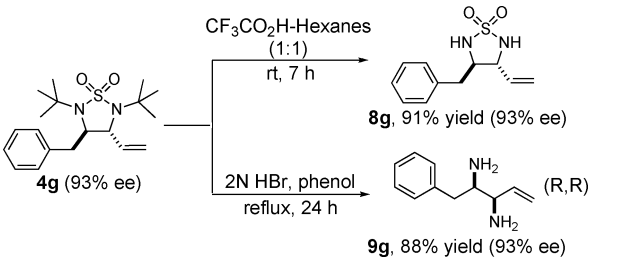
Scheme 3. Representative Deprotection of Cyclic Sulfamides



dienes using $Pd_2(dba)_3$ and chiral phosphoramidite ligand **L7** as catalyst and *N*,*N*′-di-*tert*-butylthiadiaziridine 1,1-dioxide (**2**) as nitrogen source. Various alkyl-substituted conjugated dienes are smoothly diaminated in high yields and high selectivities, providing cyclic sulfamides with two adjacent chiral centers and the pendent vinyl group allows possible further functionalization. The reaction is amenable to gram scale and can produce the resulting cyclic sulfamides in multigram quantity. The resulting cyclic sulfamides can be deprotected via removal of the *t*-Bu groups and the corresponding free diamines can also be obtained without loss of ee. Cyclic sulfamides are valuable moieties in biologically relevant molecules and the described process provides a viable route to access a broad range of diverse analogues for future study.

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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.

The authors declare no competing financial interest.