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Asymmetric Synthesis of N-Fused 1,3-Oxazolidines via Pd-Catalyzed Decarboxylative (3+2) Cycloaddition

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Abstract. Efficient synthesis of optically active N-fused 1,3-oxazolidines containing quaternary and tertiary stereocenters was achieved via Pd-catalyzed asymmetric (3+2) cycloadditions of sulfamate-derived cyclic imines and vinylethylene carbonates. Using a chiral phosphoramidite ligand, the cycloadditions proceeded effectively providing sulfamidate-fused 1,3-oxazolidines in high yields (up to 96%) with stereoselectivities (up to 25:1 dr; >99% ee). Additionally, the scale-up reaction and further transformations of the product were also achieved demonstrating the synthetic utility toward the construction of useful heterocycles such as chiral oxazoline bearing a quaternary stereocenter.

Keywords: Oxazolidines; Cycloaddition; Asymmetric catalysis; Sulfamidates; Quaternary stereocenter

Fused heterocyclic scaffolds containing an 1,3-oxazolidine are found in a considerable number of natural products and bioactive molecules such as quinocarcin, tetrazomine, and jadomycin alkaloids (Figure 1).[1] Enantioenriched 1,3-oxazolidines are also commonly utilized as chiral auxiliaries in pharmaceutical synthesis as well as ligands in transition metal catalysis.[2] Consequently, stereospecific and stereoconvergent synthetic methods toward optically active 1,3-oxazolidines have been extensively explored over the last decades.[3] However, the synthesis of chiral oxazolidine derivatives fused with nitrogen heterocycles has not been studied. The incorporation of versatile functional groups into the oxazolidines, which can be converted into various types of fused ring systems, such as cyclic sulfamidate, is highly desirable.

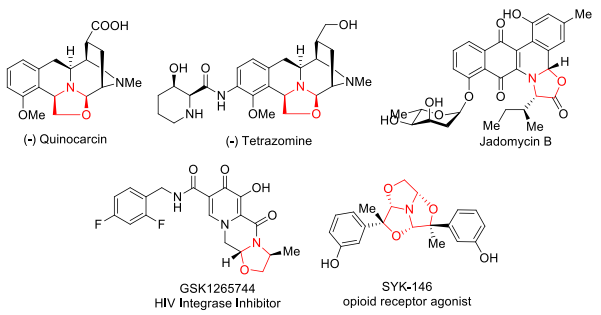

Figure 1. Representative alkaloids and pharmacologically active molecules containing N-fused 1,3-oxazolidines

Cyclic sulfamidates have attracted considerable attention not only in medicinal chemistry for improving pharmacological properties but also in organic chemistry for synthetic application to construct various heterocycles.[4] Therefore, sulfamidate-fused 1,3-oxazolidines are attractive synthetic targets for new drug designs and are useful intermediates in organic synthesis. Catalytic asymmetric methods for synthesizing several sulfamidate-fused N-heterocycles such as piperidines, piperidinones, dihydropyrroles, imidazolines, and tetrahydroquinazolines have been developed;[5] however, enantioselective synthesis of sulfamidates-fused 1,3-oxazolidines has not been reported. Recently, an elegant example to access sulfamidate-fused 1,3-oxazolidines via Pd-catalyzed (3+2) cycloadditions of sulfamate-derived cyclic imines and vinyloxiranes was developed by Guo et al. (Scheme 1a).[6] In this report, vinyloxiranes acted as three- or five-atom synthons to furnish (3+2) or (5+2) cycloadditions depending on the substituents using the Pd(0) catalyst and DPEphos ligands. Similarly, Pd-catalyzed (3+2) cycloadditions of sulfamate-derived cyclic imines and vinylaziridines have been also reported, affording cyclic imidazolidines.[7] Considering the importance of quaternary centers in bioactive compounds,[8] we attempted to construct

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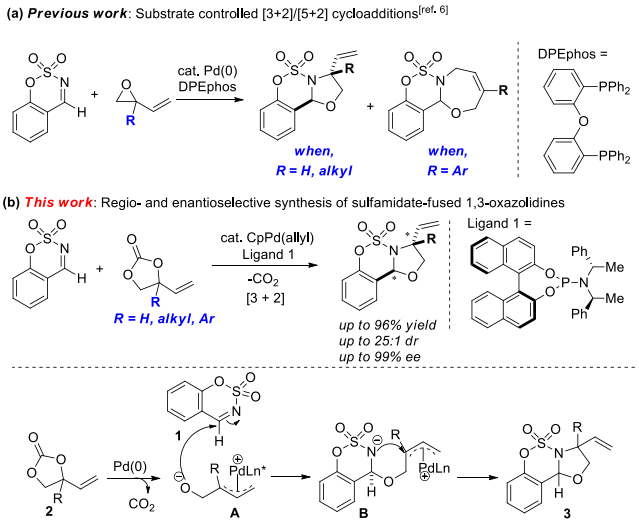
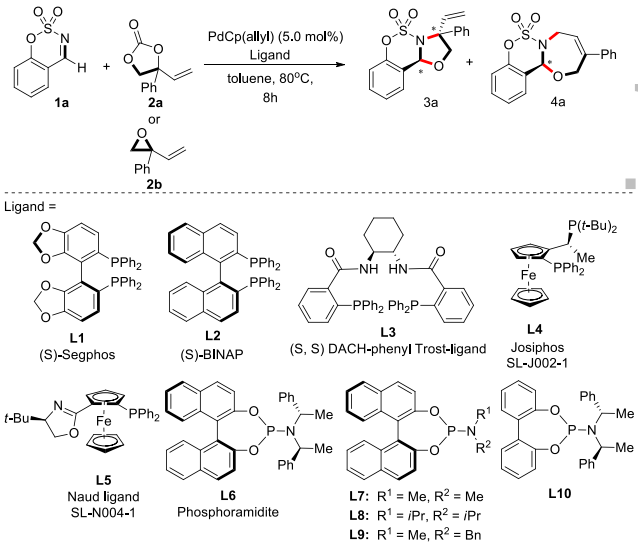
sulfamidate-fused 1,3-oxazolidines bearing a quaternary stereocenter with various substituents and focused on the use of readily accessible vinylethylene carbonates (VECs) instead of vinyloxiranes. VECs have emerged as stable dipole precursors in Pd-catalyzed decarboxylative cycloadditions producing zwitterionic π-allyl palladium species that could act as O-nucleophilic/C-electrophilic 1,3-dipole or 1,5-dipole equivalents.[9] Herein, we disclose the Pd-catalyzed asymmetric (3+2) cycloadditions of sulfamate-derived cyclic imines and VECs providing enantioenriched sulfamidate-fused 1,3-oxazolidines bearing a quaternary center (Scheme 1b). The zwitterionic π-allyl Pd intermediate **A** would be generated from VECs under the palladium catalyst, then the oxygen anion react with electrophilic imines to give intermediate **B**. Subsequently, the intramolecular N–C bond formation leads to the oxazolidines **3** bearing a quaternary carbon center.[3a,7]



Scheme 1. Pd-catalyzed asymmetric (3+2) cycloaddition

Initially, the asymmetric cycloaddition of sulfate-derived cyclic imine **1a** and 4-phenyl-4-vinyl-1,3-dioxolan-2-one (**2a**) was chosen as the model reaction to produce 1,3-oxazolidine with a quaternary center (Table 1, Table SI). Initial experiments revealed that the selectivity of 1,3-oxazolidine **3a** and 1,3-oxazepine **4a** was largely affected by ligands in the presence of 5 mol% of PdCp(allyl). As previously described,[6] 1,3-oxazepine **4a** was obtained as the major compound via (5+2) cycloaddition with several chiral bisphosphine and monophosphine ligands such as **L1**, **L2**, and **L5** (entries 1-2, 5). Changing the ligand to **L3** altered the selectivity of the product and selectively produced 1,3-oxazolidine **3a** in 42% yield with moderate stereoselectivity (4:1 dr., 56% ee) (entry 3). After the screening of chiral ligands **L4**-**L6**, the yield of **3a** could not only be increased to 94% but the enantioselectivity of **3a** could also be improved to 78% ee by using ligand **L6** (entry 6). Under the same reaction conditions, 2-phenyl-2-vinyloxirane (**2b**) selectively underwent a (3+2) cycloaddition, but its reactivity and the enantioselectivity of **3a** were relatively lower compared with the reaction using **2a** (entry 7). Performing the reaction of **1a** and **2a** at room temperature resulted in a considerable increase of enantioselectivity to 94% ee without decrease in the yield (entry 8). Other phosphoramidite ligands **L7**-**L10** were also examined at room temperature (entries 9-12). Some of ligands showed better reactivity (**L8**) and dr. (**L7**, **L9**), but the enantioselectivity was not improved compared to ligand **L6**.

Table 1. Optimization of Reaction Conditions.[a]



Entry	Ligand (mol%)	2	Yield (%)[b] 3a	Yield (%)[b] 4a	dr[c] 3a	ee (%)[d] 3a or 4a
1	**L1** (5.5)	**2a**	0	51	-	**4a**, 60
2	**L2** (5.5)	**2a**	0	21	-	**4a**, 45
3	**L3** (5.5)	**2a**	42	0	4:1	**3a**, 56
4	**L4** (5.5)	**2a**	30	0	5:1	**3a**, 90
5	**L5** (11)	**2a**	8	25	2:1[e]	**4a**, 71
6	**L6** (11)	**2a**	94	0	3:1	**3a**, 78
7	**L6** (11)	**2b**	85	0	3:1	**3a**, 56
8[f]	**L6** (11)	**2a**	89	0	3:1	**3a**, 94
9[f]	**L7** (11)	**2a**	80	0	7:1	**3a**, 50
10[f]	**L8** (11)	**2a**	99	0	3:1	**3a**, 50
11[f]	**L9** (11)	**2a**	52	0	18:1	**3a**, 40
12[f]	**L10** (11)	**2a**	29	0	2:1	**3a**, 60

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.5 mmol), PdCp(allyl) (5 mol%), and ligand in toluene (2.0 mL) at 80°C for 8 h under Ar. [b] Isolated yield. [c] Diastereomers of **3a** were not separated by the column chromatography. Diastereomeric ratio (dr) was determined by ^{1}H NMR analysis. [d] Determined by HPLC using a chiral stationary phase. [e] 82% ee was obtained for the **3a**. [f] The reaction was performed at room temperature for 20 h.

Under the optimized reaction conditions, the generality of these asymmetric (3+2) cycloadditions was investigated using various sulfamate-derived cyclic imines **1** (Table 2). The reactions of cyclic imines **1** bearing electron donating groups, such as methoxy and methyl substituents, on different

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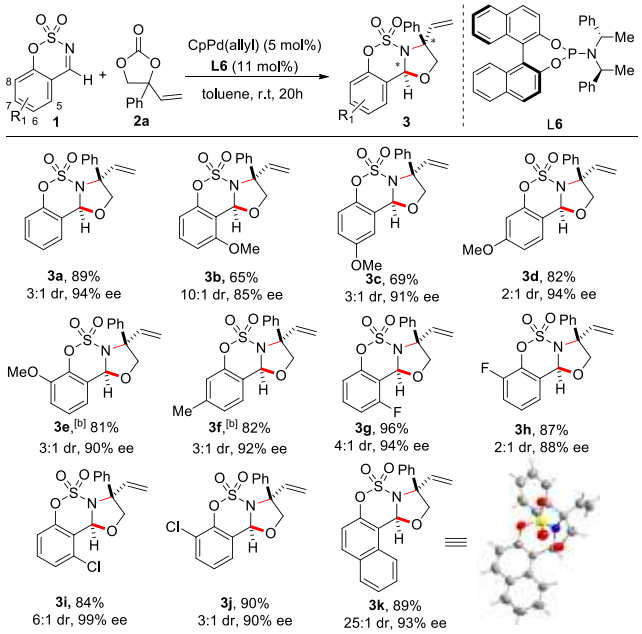
positions of the benzene ring with **2a** were well tolerated to produce the desired products **3b-3f** with yields up to 82% with excellent enantioselectivities (83-94% ee) and moderate to good diastereoselectivities (2:1 to 17:1 dr). In general, the stereoselectivities of these reactions were good regardless of the position of the substituents; however, the reactivity considerably decreased when the –OMe group was at the 8-position of benzene. On the other hands, the reactions proceeded more effectively with substrates **1** bearing electron-withdrawing groups, such as –F and –Cl, irrespective of the substituent positions providing **3g-3j** in high yields (84%-96%) with excellent enantioselectivities (88%-99% ee). The naphthyl-substituted cyclic imine **1k** smoothly reacted with **2a** to afford the corresponding product **3k** with an 89% yield with almost a single diastereomer and 93% ee. The structure of the major diastereomer of **3k** was unambiguously assigned by X-ray diffraction,[10] and those of the other oxazolidines **3** were assigned by analogy.

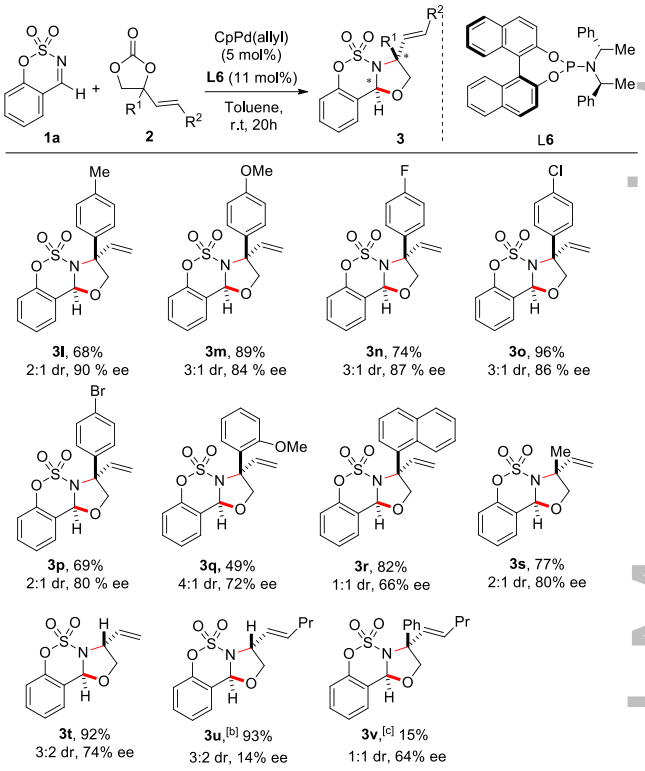
Table 2. Scope of sulfamate-derived cyclic imines.[a]



[a] The reactions were carried out with **1** (0.2 mmol), **2a** (0.5 mmol), PdCp(allyl) (5 mol%), and **L6** (11 mol%) in toluene (2.0 mL) at room temperature for 20 h under Ar. [b] The reaction was performed at 60°C.

Subsequently, a variety of substituted vinylethylene carbonates **2** were tested under the standard reaction conditions for asymmetric (3+2) cycloadditions (Table 3). Various aryl-substituted VECs having different electronic and steric properties were reacted with **1a** to afford corresponding products **3l-3r** in excellent yields up to 96% with good stereoselectivities (up to 86% ee; 4:1 dr). The substituents at the 4-position of VECs were not limited to aryl; a methyl substituted VEC was also tolerated providing **3s** in good yield with good enantioselectivity. Vinylethylene carbonate without a quaternary center was also feasible in this asymmetric cycloaddition producing **3t** in 92% yield with slightly reduced enantioselectivity (74% ee). The reactions of **1a** and terminal alkyl-substituted VECs were also examined to test the feasibility of olefin moiety instead of vinyl group. The corresponding oxazolidines **3u** and **3v** were obtained in 93% and 15% yields, respectively.

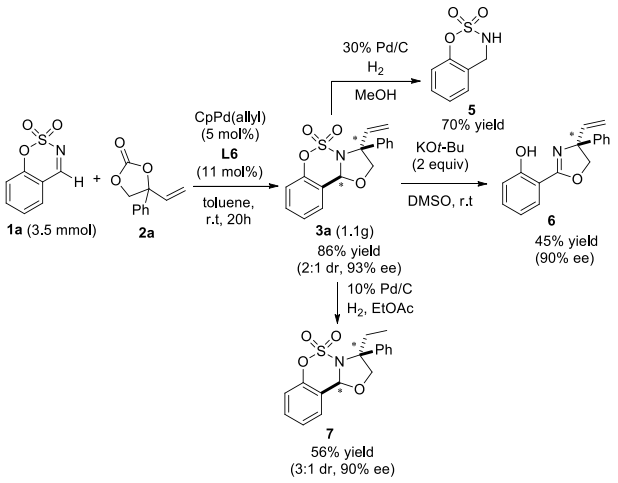
Table 3. Scope of vinylethylene carbonates.[a]



[a] The reactions were carried out with **1a** (0.2 mmol), **2** (0.5 mmol), PdCp(allyl) (5 mol%), and **L6** (11 mol%) in toluene (2.0 mL) at room temperature for 20 h under Ar. [b] When reacted at 80°C using **L4** ligand instead of **L6**, 29% yield with 4:1 dr and 89% ee were obtained for the **3u**. For more details, see the SI. [c] The reaction was performed at 60°C.

To demonstrate the utility of sulfamidate-fused 1,3-oxazolidines in synthesis and the potential of scaling-up the protocol, the (3+2) cycloaddition of **1a** and **2a** was performed on a gram-scale under the standard conditions. As shown in scheme 2, the desired product **3a** was obtained in 86% yield with 2:1 dr and 93% ee, regardless of the reaction scale, and it was tested for various transformations. The selective cleavage of C–N and C–O bonds on oxazolidine ring was achieved by using $LiAlH_4$, which provided cyclic sulfamidate **5** in 44% yield. Interestingly, in the presence of H_2 and 30% Pd/C, the sulfamidate **5** was also obtained in 70% yield. In contrast, the SO_2 extrusion and the formation of C=N double bond were accomplished by treating KO*t*-Bu in DMSO, and an enantiomerically enriched

oxazoline **6**, which is one of the most important families of chiral ligands,[11] was obtained without losing enantioselectivity. The versatile vinyl group on **3a** could be converted to ethyl by the hydrogenation, which afforded N-fused oxazolidine **7** while maintaining the stereoselectivity.



Scheme 2. Gram-scale synthesis of sulfamidate-fused 1,3-oxazolidine **3a** and its further applications

In conclusion, we developed a highly efficient and enantioselective (3+2) cycloaddition between sulfamate-derived cyclic imines and VECs under the palladium catalysis. A range of optically active N-fused 1,3-oxazolidines bearing a quaternary stereocenter were obtained in good yields (up to 96% yield) and diastereoselectivities (up to 25:1 dr) with excellent enantioselectivities (up to 99% ee) using a chiral phosphoramidite ligand. The cycloaddition adducts, sulfamidate-fused 1,3-oxazolidines, could be converted to structurally useful scaffolds such as sulfamidate and chiral oxazoline via selective ring opening. In addition, the vinyl group on the desired product could be conveniently converted to ethyl, which indicated that the substituents on the quaternary carbon could be easily controlled.

Experimental Section

Typical Procedure for Synthesizing Optically Active Sulfamidate-Fused 1,3-Oxazolidines 3: To a flame-dried Schlenk tube, sulfamate-derived cyclic imines **1** (0.2 mmol), CpPd(allyl) (2.13 mg; 5 mol%), and phosphoramidite **L6** (11.9 mg; 11 mol%) were added in a glove box. Then, vinyl ethylene carbonate **2** (0.5 mmol) and anhydrous toluene (2.0 mL) were added under an argon atmosphere. The reaction mixture was stirred at room temperature for the corresponding reaction time. After the reaction was completed, the solvent was evaporated, and the desired product **3** was isolated by silica gel column chromatography.

Acknowledgements

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[10] CCDC 1965924 (**3k**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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