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Pd-Catalyzed Asymmetric Decarboxylative Cycloaddition of Vinylethylene Carbonates with Imines

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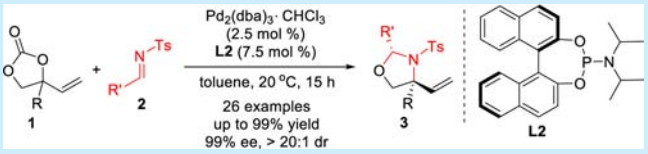
Supporting Information

ABSTRACT: An efficient method for the enantioselective synthesis of β-tertiary β-amino alcohol derivatives through Pd-catalyzed decarboxylative cycloaddition of vinylethylene carbonates with imines was developed. By using a palladium complex generated in situ from $[Pd_2(dba)_3]\cdot CHCl_3$ and phosphoramidite **L2** as a catalyst under mild reaction conditions, the process provided 4-substituted-4-vinyloxazolidines in good to high yields with high levels of enantio- and diastereoselectivities.



The transition metal-catalyzed asymmetric allylic amination is one of the powerful methods for the formation of valuable chiral α-secondary allylic amine derivatives.[1] However, for the regioselective construction of chiral α-tertiary amines, which are important motifs for a wide variety of medicinally relevant agents and natural products,[2,3] the asymmetric allylic amination of 1,1- or 3,3-disubstituted allylic donors remains an unmet challenge. Trost and co-workers reported Pd-catalyzed asymmetric allylic amination of isoprene oxide to afford β-substituted β-vinylglycinols in high efficiency.[4] The related transformations, that is, asymmetric cycloaddition of isoprene oxide with carbondiimides[5] and imines,[6] have also been developed for the synthesis of β-tertiary β-amino alcohol derivatives, but the enantioselectivities are not satisfactory. Recently, Nguyen and Arnold reported Rh-catalyzed allylic amination of 1,1-disubstituted allylic trichloroacetimidates furnishing β-substituted β-vinylglycinols in good to high enantioselectivities.[7] However, all of these approaches are limited to providing β-methyl β-vinylglycinol derivatives. For vinyl epoxides, isoprene oxide can be readily made from abundant feedstock, isoprene. However, 2-vinyloxiranes bearing diverse 2-substituents are not readily accessible by the epoxidation process because the corresponding 2-substituted butadiene compounds are not easy to access. Although 2-substituted 2-vinyloxiranes can be synthesized from the corresponding α-halogenated ketones,[8] this type of epoxides is somewhat unstable.[9] Most recently, we have presented a useful synthetic strategy for the construction of quaternary stereocenters via Pd-catalyzed asymmetric decarboxylative cycloaddition of racemic vinylethylene carbonates (VECs), which are stable substrates and readily synthesized from the corresponding α-hydroxy ketones, with unsaturated electrophiles.[10,11] The process allows rapid access to tertiary vinylglycols, 4,4-disubstituted oxazolidinones, and multifunctional tetrahydrofurans with vicinal quaternary stereocenters in very high efficiency. Based on our continuous efforts on the development of effective methods for the enantioselective construction of quaternary stereocenters with diverse functionalities, we are interested in the decarboxylative cycloaddition of VECs with imines. The transformation could provide 4-substituted 4-vinyloxazolidines **3** through allylpalladium intermediates **A** and **B** under the Pd-catalyzed decarboxylative cycloaddition process (Scheme 1).

Optically active oxazolidines are important structural motifs in a number of biologically active natural products.[12] Chiral oxazolidines are also used as chiral auxiliaries and chiral ligands in a variety of asymmetric transformations.[13] Nevertheless, asymmetric synthesis of chiral oxazolidines mainly relies on the chiral pool synthesis using chiral 1,2-amino alcohols, which are generated from natural amino acids. The catalytic enantioselective routes to oxazolidines are largely unexplored.[14] On the other hand, the process (Scheme 1) provided oxazolidines **3** which would be useful precursors of chiral β-tertiary β-amino alcohols, which are important structure motifs in a wide range of natural products and medicinal interesting agents.[15] Although various methods for the asymmetric synthesis of β-tertiary β-amino alcohol derivatives have been developed, most of them are based on the stoichiometric use of chiral auxiliary, chiral pool or stereospecific methods.[16] In contrast, the catalytic enantioselective routes to these compounds are largely unexplored.[17] Therefore, the development of efficient approaches to chiral β-tertiary β-amino alcohol derivatives, with advantage in terms of operational simplicity, and the use of readily available and stable starting materials is highly desired. Herein we disclose the palladium-catalyzed decarboxylative

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Scheme 1. Pd-Catalyzed Asymmetric Decarboxylative Cycloaddition of VECs with Imines

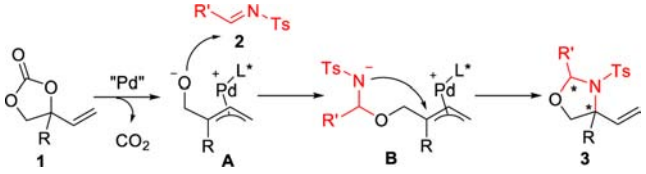
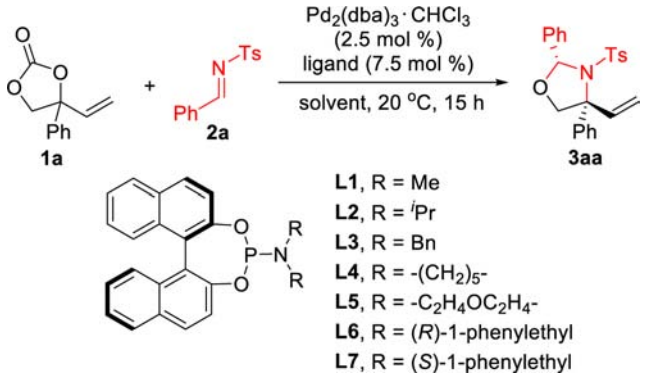


Table 1. Condition Optimization[a]



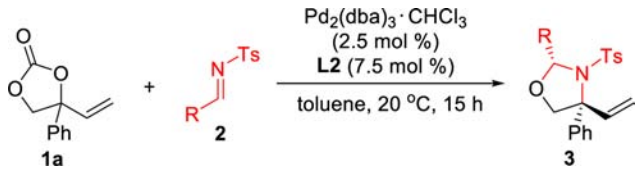
entry	ligand	solvent	yield[b] (%)	dr[c]	ee[d] (%)
1	**L1**	THF	26		
2	**L2**	THF	95	16:1	92
3	**L3**	THF	69	12:1	82
4	**L4**	THF	NR		
5	**L5**	THF	NR		
6	**L6**	THF	trace		
7	**L7**	THF	trace		
8	(*R*)-BINAP	THF	33		
9	Trost ligand[e]	THF	38		
10	**L2**	toluene	92	15:1	94
11	**L2**	CH_2Cl_2	98	11:1	94
12	**L2**	2-MeTHF	90	11:1	94
13	**L2**	dioxane	89	16:1	90
14	**L2**	CH_3CN	89	5:1	93

[a]Reaction conditions: **1a** (0.22 mmol), **2a** (0.20 mmol), $Pd_2(dba)_3CHCl_3$ (0.005 mmol), ligand (0.015 mmol), solvent (1.0 mL), 20 °C, 15 h. [b]The yields are of isolated materials for the mixtures of the diastereomers. [c]Determined by ^1H NMR of crude reaction mixture. [d]Determined by HPLC using a chiral stationary phase. [e](*R*,*R*)-DACH-phenyl Trost ligand.

cycloaddition of VECs with imines, a general and effective protocol that allows rapid access to 4-substituted 4-vinyloxazolidines in good to high yields with high levels of enantio- and diastereoselectivities.

Initial studies focused on the examination of the decarboxylative cycloaddition of Ph-VEC **1a** with (*E*)-*N*-benzylidenetosylamide (**2a**) as standard reaction partners using palladium(0) catalysts bearing different chiral phosphoramidite ligands (Table 1). To our delight, the reaction proceeded smoothly with ligand **L2** in THF at 20 °C for 15 h, affording oxazolidine **3aa** in 95% yield with high levels of enantio- and diastereoselectivities (entry 2). The reaction efficiency decreased obviously when ligand **L3** (entry 3) was used, and the reaction was less effective using other phosphoramidite ligands (entries 1 and 4−7). Low conversions were observed when the reaction was carried out with (*R*)-BINAP or Trost standard ligand. By means of further screening reaction

Table 2. Pd-Catalyzed Decarboxylative Cycloaddition of Ph-VEC 1a with Imines 2[a]



entry	2	3	yield[b] (%)	dr[c]	ee[d] (%)
1	**2a** (R = Ph)	**3aa**	92	15:1	94
2	**2b** (R = 4-MeC_6H_4)	**3ab**	89	11:1	96
3	**2c** (R = 2-MeC_6H_4)	**3ac**	80	2:1	80
4	**2d** (R = 4-MeOC_6H_4)	**3ad**	82	11:1	94
5	**2e** (R = 3-MeOC_6H_4)	**3ae**	91	10:1	91
6	**2f** (R = 3-BrC_6H_4)	**3af**	94	13:1	90
7	**2g** (R = 4-$CF_3C_6H_4$)	**3ag**	96	11:1	89
8	**2h** (R = 2-$NO_2C_6H_4$)	**3ah**	74	2:1	73
9	**2i** (R = 4-Br-3-$NO_2C_6H_4$)	**3ai**	99	17:1	96
10	**2j** (R = 1-naphthyl)	**3aj**	77	6:1	94
11	**2k** (R = 2-furanyl)	**3ak**	93	>20:1	97
12	**2l** (R = cyclohexyl)	**3al**	87	9:1	88

[a]Reaction conditions: **1a** (0.22 mmol), **2** (0.20 mmol), $Pd_2(dba)_3CHCl_3$ (0.005 mmol), **L2** (0.015 mmol), toluene (1.0 mL), 20 °C, 15 h. [b]The yields are of isolated materials for the mixtures of the diastereomers. [c]Determined by ^1H NMR of crude reaction mixture. [d]Determined by HPLC using a chiral stationary phase. The absolute configuration of **3ai** was determined by X-ray crystallography (see Figure 1); those of the other products were assigned by analogy.

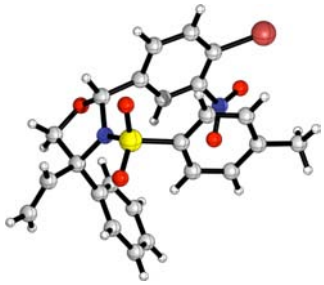


Figure 1. X-ray structure of **3ai**.

solvents, we found that the reaction proceeded well in other solvents (entries 10−14), and the reaction in toluene gave best results, providing oxazolidine **3aa** in 92% yield with 94% ee and a 15:1 diastereomeric ratio. We also attempted the reaction of **1a** with the corresponding imines with different *N*-substituents, for example, *N*-Boc or *N*-Cbz. However, the reactions did not proceed under the standard conditions.

With the optimal conditions in hand, the generality of this protocol was evaluated by the reaction of Ph-VEC **1a** with various imines **2**. As shown in Table 2, the reactions with imines derived from arylaldehydes bearing different steric and electronic natures proceeded quite well to afford the corresponding oxazolidines **3** in high yields and high levels of enantio- and diastereoselectivities (entries 1−10). However, the diastereoselectivities decreased remarkably with the reaction with imines derived from 2-substututed benzaldehydes **2c** and **2h** (entries 3 and 8). The cycloaddition reaction was also effective with imine **2k** from furfural to furnish oxazolidine **3ak** in high yield with 97% ee and with almost a single diastereomer (entry 11). The imine **2l** derived from aliphatic aldehyde was also a suitable substrate for the reaction to give oxazolidine **3al**

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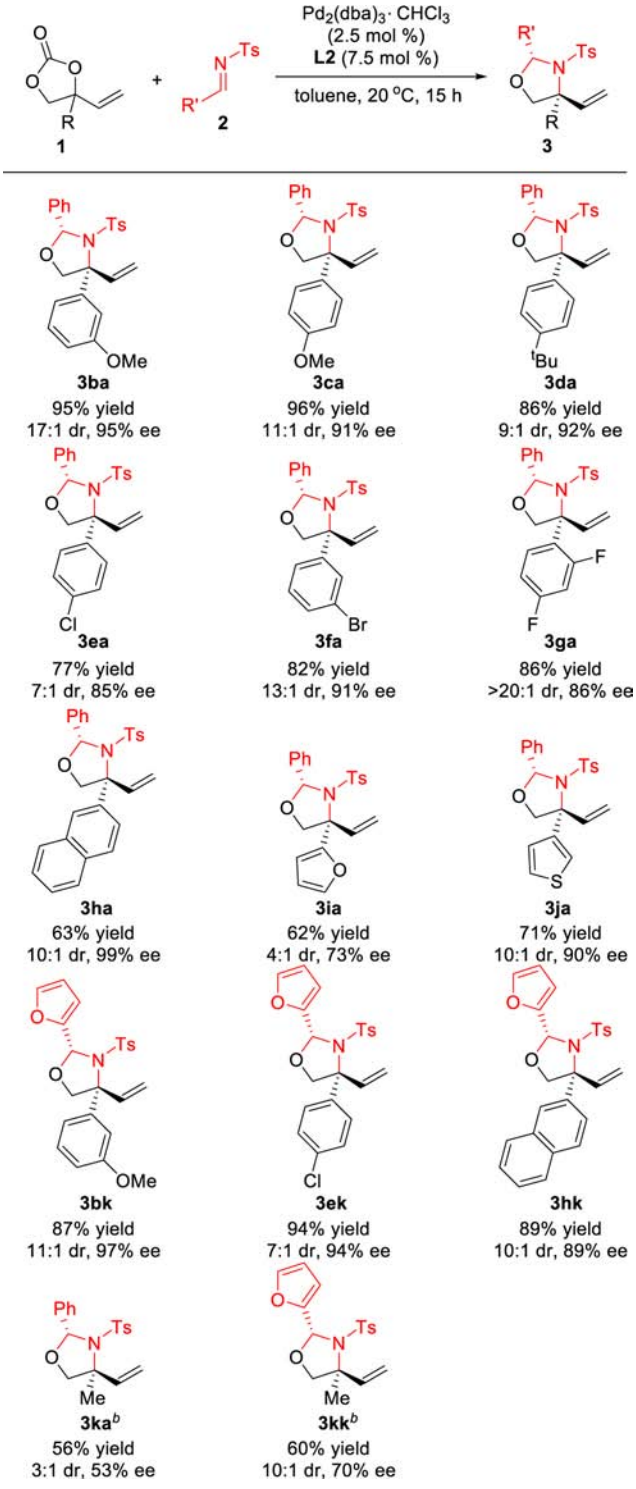
Scheme 2. Pd-Catalyzed Decarboxylative Cycloaddition of VECs 1 with Imines 2[a,b]

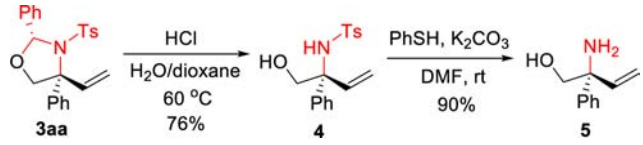


[a]As described in Table 2. [b]The reactions were carried out in THF at 40 °C for 15 h.

in acceptably high efficiency (entry 12). The absolute configuration of **3ai** was unambiguously assigned by X-ray crystallography (Figure 1), and those of the other products were assigned by analogy.

After the successful realization of the cycloaddition of Ph-VEC **1a** with various imines, we subsequently turned our attention toward the examination of the cycloaddition of various 4-substituted VECs **1** with imines **2**. As revealed in Scheme 2, various substituted aryl VECs having different electronic and steric properties were converted into the corresponding oxazolidines **3ba**–**ga** in high yields with high levels of enantio- and diastereoselectivities. The reaction of VECs with a naphthyl group also proceeded smoothly to afford oxazolidine **3ha** in good yield with excellent enantioselectivity. The reaction of VEC **1j** with a 3-thiophene-yl group was effectively converted to the oxazolidine **3ja** in good yield with high levels of diastereo- and enantioselectivity. However, lower efficiency was obtained when the reaction was carried out with VEC **1i** bearing a 2-furanyl group. The versatile 2-furanyl group can be installed by the reaction of VECs with imine **2k** derived from furfural to afford the corresponding 2-(2-furanyl)-oxazolidines in high yields with high enantio- and diastereoselectivities. The reaction efficiency decreased markedly for the reaction of Me-VEC **1k** with imine **2a**, giving oxazolidine **3ka** in moderate yield with 53% ee. The diastereo- and enantioselectivity could be improved for the reaction of Me-VEC **1k** with (*E*)-*N*-2-furanylmethylenetosylamide (**2k**).

Scheme 3. Elaboration of Oxazolidine 3aa



To further demonstrate the synthetic utility of the present protocol, we elaborated the oxazolidine **3aa** into the corresponding *β*-tertiary *β*-amino alcohol (Scheme 3). Straightforward hydrolysis of **3aa** under acidic conditions afforded tosylated amino alcohol **4** in good yield. The deprotection of the *N*-tosyl group of **4** was achieved under known conditions[14b] to furnish 2-phenyl-2-vinylglycinol **5** in high yield.

In conclusion, we have developed an efficient method for the diastereo- and enantioselective synthesis of 4-substituted 4-vinyloxazolidines through Pd-catalyzed asymmetric decarboxylative cycloaddition of VECs with imines. By using palladium complex generated in situ from $[Pd_2(dab)_3]\cdot CHCl_3$ and phosphoramidite ligand **L2** as a catalyst under mild reaction conditions, the process furnished 4-substituted-4-vinyloxazolidines in high yields with good to excellent diastereo- and enantioselectivities. The utility of the process was demonstrated by an example of the elaboration of oxazolidines into corresponding *β*-tertiary *β*-amino alcohols. Further studies to extend the scope of the decarboxylative cycloaddition of VECs are currently underway and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03218.

Detailed experimental procedures, characterization data of all of the new compounds, copies of HPLC chromatograms, and ^1H and ^{13}C NMR spectra of the products (PDF)

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Notes

The authors declare no competing financial interest.

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