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Highly efficient and diastereoselective synthesis of 1,3-oxazolidines featuring a palladium-catalyzed cyclization reaction of 2-butene-1,4-diol derivatives and imines

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ABSTRACT

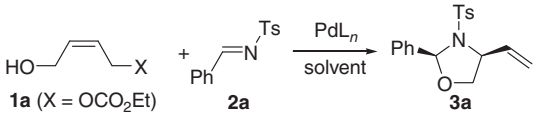
A palladium-catalyzed protocol for effective synthesis of 1,3-oxazolidines has been reported. This method is featured by the high diastereoselectivity (dr up to >98/2) and using the readily available 2-butene-1,4-diol derivatives and imines as substrates.

Nitrogen-containing molecules are critical building blocks in pharmaceuticals, catalysts, and materials.[1] Among them, 1,3-oxazolidine derivatives are of particular interest because of their wide applications in organic synthesis, chiral auxiliaries or ligands, and drug designing such as the anticancer prodrugs doxoform, doxazolidine, and doxaz carbamate.[2] Therefore, it is highly desirable to develop new methods for the efficient construction of 1,3-oxazolidine moieties.

1,3-Oxazolidines are usually prepared by condensation of 1,2-amino alcohols with aldehydes or ketones,[3] the [3+2] cycloaddition of azomethine ylides and carbonyl compounds,[4] palladium-catalyzed [3+2] cycloaddition reactions,[5] Lewis acid-catalyzed [3+2] cycloaddition reactions of aziridines,[6] and in other ways.[7] Recently, Yoon's group has reported an efficient method for establishing 1,3-oxazolidines through iron- or copper-catalyzed aminohydroxylation of olefins.[8] As elegant as these syntheses, use of rather expensive starting materials and low diastereoselectivity left some room for improvement. As part of our interests to develop new cyclization reactions initiated by allylpalladium intermediates,[9] herein, we report a highly efficient and diastereoselective protocol for the synthesis of 1,3-oxazolidine motifs featuring a palladium-catalyzed cyclization reaction of the readily available 2-butene-1,4-diol derivatives and imines.

Our initial optimization of the proposed cyclization reaction started with the reaction between 2-butene-1,4-diol derivatives **1a** and imine **2a** (Table 1). Using 5 mol % of $Pd(PPh_3)_4$ as a catalyst, the reaction did give 1,3-oxazolidine product **3a** in 65% yield, albeit in two isomers at a ratio of 37:63 (entry 1, Table 1). Similar result was observed in the case of $Pd(OAc)_2$ as a catalyst precursor, while $Pd(dba)_2$ gave slightly better yield (entries 2 and 3 Table 1). As we know, ligands play an important role in the Pd-catalyzed reactions, then, we checked the effects of the ligands on this cyclization reaction employing $Pd(dba)_2$ as a palladium catalyst. Among the ligands we examined, PCy_3 was totally ineffective for the

Table 1
Optimization of the reaction conditions[a]



Entry	Catalyst	Ligand	Solvent	Yield[b] (%)	Cis/trans[c]
1	$Pd(PPh_3)_4$	No	THF	65	37/63
2	$Pd(OAc)_2$	PPh_3	THF	63	30/70
3	$Pd(dba)_2$	PPh_3	THF	69	38/62
4	$Pd(dba)_2$	$(o\text{-Tol})_3P$	THF	21	49/51
5	$Pd(dba)_2$	PCy_3	THF	<5	—
6	$Pd(dba)_2$	DPEphos	THF	86	31/69
7	$Pd(dba)_2$	dppf	THF	89	67/33
8	$Pd(dba)_2$	dppb	THF	85	94/6
9	$Pd(dba)_2$	dppp	THF	92	97/3
10	$Pd(dba)_2$	dppe	THF	87	>98/2
11	$Pd(dba)_2$	dppe	Dioxane	83	91/9
12	$Pd(dba)_2$	dppe	DMF	76	88/12
13	$Pd(dba)_2$	dppe	Toluene	88	93/7
14	$Pd(dba)_2$	dppe	THF	84[d]	>98/2

[a] All the reactions were run with **1a** (48 mg, 0.30 mmol) and **2a** (65 mg, 0.25 mmol) in the presence of 5 mol % of catalyst and 20 mol % of monophosphines (10 mol % of bisphosphines) at 50 °C.
[b] Combined yields of cis- and trans-isomers.
[c] Cis/trans ratios were determined by ^1H NMR.
[d] *E*-**1a** was used as a substrate.

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transformation, and $(o\text{-tol})_3P$ also showed less activity, which therefore led to **3a** only in 21% yield (entries 4 and 10, Table 1).

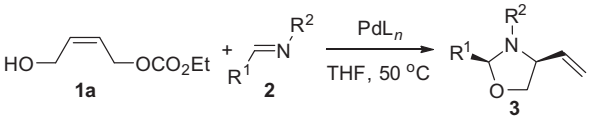
In contrast, the combined usage of 5 mol % of $Pd(dba)_2$ and 10 mol % of diphenylphosphinoethane (dppe) dramatically increased the yield of **3a** to 87% (entry 10, Table 1). More importantly, only single cis-isomer was detected, which could be deduced by NOE analysis, and further confirmed by X-ray diffraction study of cis-**3a**. Other bisphosphine ligands, such as dppb, dppf, and DPEphos, produced similar yields, accompanying with a relative low diastereoselectivity (entries 6–9, Table 1). Of the solvents we screened, including toluene, tetrahydrofuran (THF), dimethylforamide (DMF), and dioxane, THF turned out to be the best solvent, while other solvents resulted in relative lower stereoselectivity (entries 11–13, Table 1). Slightly slower reaction was observed employing **1b** (X = OAc) as a substrate and no reaction occurred when using **1c** (X = Cl) as a substrate. The reaction of *E*-**1a**, an *E*-2-butene-1,4-diol derivative, afforded **3a** in 84% yield and excellent diastereoselectivity (entry 14, Table 1). Finally, we chose 5 mol % of $Pd(dba)_2$, 10 mol % of dppe, THF as the solvent, and 50 °C for the optimized reaction conditions.

With the optimal reaction conditions in hand, we then explored the scope and limits of the cyclization reaction using a variety of imine substrates. The results were summarized in Table 2.

As shown in Table 2, although the reaction of the imine **2b** was sluggish somehow, the reaction could be successfully extended to other activated imines especially the *N*-sulfonylimines. 1,3-Oxazolidines **3b** and **3c** were obtained from **2b** and **2c** in 59% and 90% yield, respectively, while no desired 1,3-oxazolidine product was observed employing *tert*-butylphenylsulfinimine **2d** as a substrate (entries 2–4, Table 2). The more activated imine **2e** was subjected to the standard reaction conditions to give the 1,3-oxazolidine **3e** in moderate yield, however, an obvious decrease in diastereoselectivity was detected (entry 5, Table 2). Attempts to the extension of the reaction to other imines, such as ketimines and *N*-arylimines, did not give any of the desired 1,3-oxazolidines.

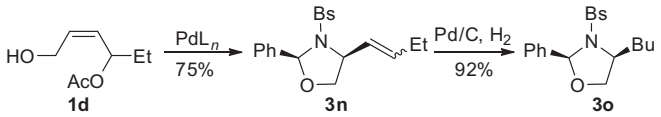
Thus, the *N*-sulfonyl imines appeared to be the most suitable substrates for the cyclization reaction. Both aromatic *N*-benzenesulfonylimine and aliphatic *N*-benzenesulfonylimine are good reaction partners, although the aliphatic *N*-benzenesulfonylimine **2l** led to a decrease of yield to 51% (entry 12, Table 2). All the aromatic *N*-benzenesulfonylimines resulted in 1,3-oxazolidine products with good yields and excellent diastereoselectivity,

Table 2
Pd-catalyzed cyclization of **1a** with various imines[a]



Entry	2	R^1	R^2	3	Yield[b] (%)	dr[c]
1	**2a**	Ph	Ts	**3a**	87	>98/2
2	**2b**	Ph	Ms	**3b**	59	>98/2
3	**2c**	Ph	Bs	**3c**	90	>98/2
4	**2d**	Ph	$S(O)Bu^t$	**3d**	NR	—
5	**2e**	Ph	Piv	**3e**	57	53/47
6	**2f**	*p*-OMe-C_6H_4	Bs	**3f**	87	>98/2
7	**2g**	*p*-Me-C_6H_4	Bs	**3g**	88	>98/2
8	**2h**	*p*-Br-C_6H_4	Bs	**3h**	80	>98/2
9	**2i**	*p*-OMe-C_6H_4	Ts	**3i**	85	>98/2
10	**2j**	*p*-Cl-C_6H_4	Bs	**3j**	86	>98/2
11	**2k**	*p*-F-C_6H_4	Bs	**3k**	80	>98/2
12	**2l**	Pent	Bs	**3l**	51	>98/2
13	**2m**	Furyl	Bs	**3m**	85	>97/3

[a] All the reactions were run under optimal reaction conditions.
[b] Isolated yields.
[c] Determined by ^1H NMR. Piv = $COBu^t$.



Scheme 1.

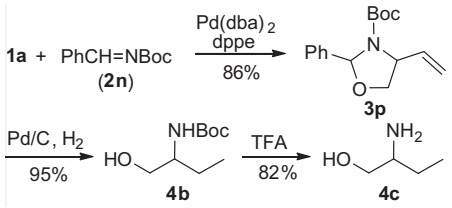
producing the cis-isomer with >97:3 selectivity. For example, imine **2f** and **2g**, two electron-rich aromatic ring containing imines, gave 1,3-oxazolidine **3f** and **3g** in 87% and 88% yields, respectively (entries 6 and 7, Table 2). The aromatic imine **2k**, substituted by electron-withdrawing group such as fluoride atom, led to 1,3-oxazolidine **3k** in 80% yield as a single isomer (entry 11, Table 2). In addition, the furyl possessing imine **2m** also reacted smoothly with **1a** to afford 1,3-oxazolidine **3m** in 85% yield and in a highly diastereoselective fashion (dr >97:3, entry 13, Table 2). Moreover, the halides in the aromatic ring were intact under the reaction conditions, which may permit further chemical transformations such as transition-metal-catalyzed coupling reactions for the introduction of other functional groups.

Then, we further checked the scope and limits of the reaction, and found that **1d**, another 2-butene-1,4-diol derivatives, also underwent the Pd-catalyzed cyclization to give the 1,3-oxazolidine **3n** in 75% yield (*E*/*Z* = 9:1). The excellent diastereoselectivity was confirmed by the NMR analysis of the hydrogenated product **3o** (Scheme 1).

1,2-Amino alcohols and their derivatives have attracted numerous attentions because of the potential biological activity and building blocks for the synthesis of nitrogen-containing natural products.[10] Thus, we extended this protocol to synthesize certain of 1,2-amino alcohols or their derivatives. For example, *N*-tosyl-2-amino-3-butenol **4a** was prepared in 71% yield via TFA-mediated ring opening of 1,3-oxazolidines **3a**. As we known, C=C bond is a good potential functional group in organic synthesis, therefore functionalized amino alcohol derivatives may be synthesized through further chemical transformations from the C=C bond possessing 1,3-oxazolidines.

The synthetic application of this protocol was well illustrated in the efficient synthesis of aminobutanol, a key building block for the synthesis of ethambutol.[11] Palladium-catalyzed cyclization of **1a** with *N*-Boc imine **2n** gave 1,3-oxazolidine **3p** in 86% yield. Pd/C catalyzed hydrogenation not only reduced the C=C bond, but also cleaved the ring of 1,3-oxazolidines to give *N*-Boc-aminobutanol in 95% yield. Then, deprotection of Boc in the presence of TFA yielded aminobutanol in 82% yield. Thus, aminobutanol could be prepared in 67% overall yield over three steps (Scheme 2).

On the other hand, Pd-catalyzed asymmetric allylation reactions[12] have made great breakthrough in recent years, and number of chiral ligands could produce excellent asymmetric induction. The reaction presented herein is thought to be a typical Pd-catalyzed reaction involving allylpalladium intermediates, therefore, it is highly possible to generate chiral amino alcohols learning from the Pd-catalyzed asymmetric allylation reactions. What is more, the tuning of chiral ligands may result in the enantioselective synthesis of D-amino alcohol, which is quite difficult to obtain by traditional methods.



Scheme 2.

In conclusion, we have developed a highly efficient and diastereoselective protocol for the synthesis of 1,3-oxazolidine derivatives via a palladium-catalyzed tandem cyclization reaction of imines and rather cheap 2-butene-1,4-diol derivatives. To the best of our knowledge, it is the first highly diastereoselective (dr >97:3) synthetic route to 1,3-oxazolidines, which may also permit the formation of 1,2-amino alcohols in a simple and efficient way. Further efforts in asymmetric reaction study for the enantioselective synthesis of 1,2-aminol alcohols are undergoing in this group.

Acknowledgment

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Supplementary data

Supplementary data (experimental details, NMR spectra, and analytical data) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.07.087.

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