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Palladium-Catalyzed Asymmetric [3 + 2] Cycloaddition of 5-Vinyloxazolidinones with Imines Using Chiral Ammonium-Phosphine Hybrid Ligand

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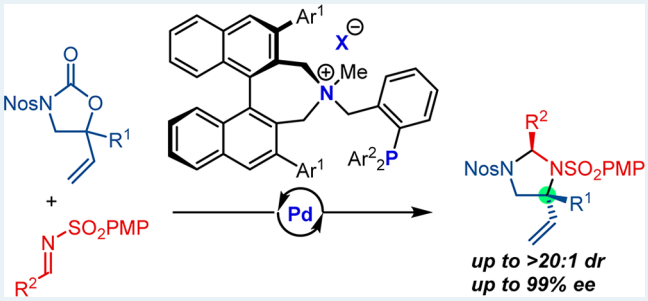
Supporting Information

ABSTRACT: A palladium-catalyzed asymmetric [3 + 2] annulation reaction between racemic 5-vinyloxazolidinones and *N*-sulfonyl imines was established. Under the influence of the palladium complex with a chiral ammonium-phosphine hybrid ligand, the cycloaddition proceeded smoothly to yield imidazolidines bearing α-amino quaternary stereocenters in high yields with excellent diastereo- and enantioselectivities.



KEYWORDS: *asymmetric catalysis, palladium, ammonium ion, phosphine, cycloaddition, imidazolidine*

Chiral imidazolidines represent a structural motif that is frequently found in natural products, biologically active compounds, catalysts, and ligands. Accordingly, stereochemically defined imidazolidine derivatives could serve as versatile building blocks with a wide array of potential applications in organic chemistry and biochemistry.[1] A representative method to construct this nitrogen-containing cyclic framework is the 1,3-dipolar cycloaddition[2] of azomethine ylides and imines.[3] To date, a few enantioselective cycloadditions have been successfully developed on the basis of either metal or organic catalysts, facilitating efficient access to multisubstituted chiral imidazolidines.[4] However, these methodologies suffer from limited scope and are applicable only to the syntheses of imidazolidines with tertiary stereocenters. Therefore, efforts aimed at the development of novel protocols, especially for the direct and selective generation of these heterocycles with quaternary stereocenters, should prove valuable.

In line with our recent research on the design and application of ion-paired chiral ligands for asymmetric palladium catalysis,[5] we have delineated that phosphine ligands with pendant chiral ammonium salts (**1·X** in Figure 1) are extremely powerful in achieving the asymmetric [3 + 2] annulation of racemic 5-vinyloxazolidinones with activated trisubstituted alkenes (Scheme 1).[6,7] A remarkable feature of this catalytic system resides in the precise asymmetric construction of three contiguous stereocenters including two quaternary centers, each of which is individually controlled by the chiral ammonium-phosphine ligand. For instance, the stereochemical outcome in the installation of the C(4) stereocenter that originates from the oxazolidinone is not affected by the

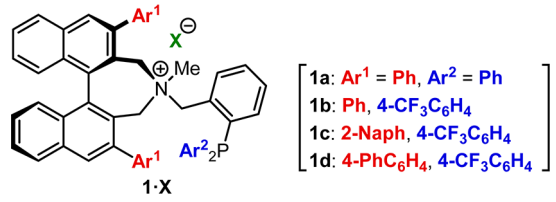
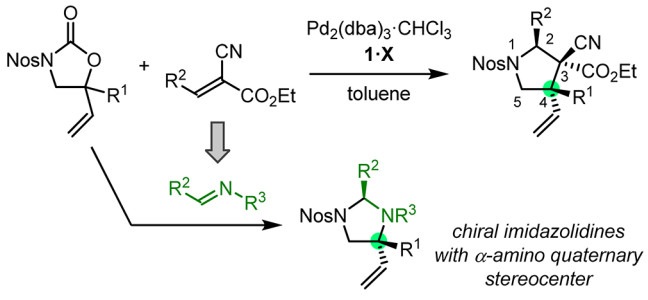


Figure 1. Chiral ammonium-phosphine hybrid ligands in this study.

Scheme 1. Palladium-Catalyzed Asymmetric [3 + 2] Cycloadditions of 5-Vinyloxazolidinones



structure of the alkene. This characteristic prompted us to envisage that the palladium catalysis with **1·X** might also be effective for the assembly of other five-membered *N*-hetero-

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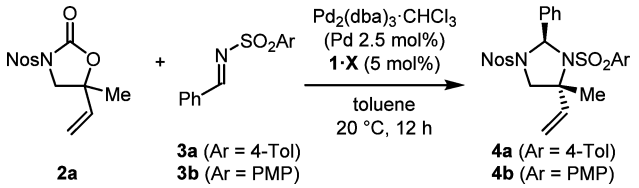
cycles through the asymmetric [3 + 2] cycloaddition of vinyloxazolidinones with different dipolarophiles such as aldimines. Herein, we report the successful demonstration of this possibility in the context of providing a straightforward yet stereoselective route toward chiral imidazolidines bearing α-amino quaternary stereocenters.

Initially, the reaction between vinyloxazolidinone **2a** and *N*-4-toluenesulfonyl (Ts) imine **3a** was carried out under the influence of $Pd_2(dba)_3{\cdot}CHCl_3$ and ion-paired chiral ligand **1a·Br** in toluene at 20 °C. The corresponding cycloadduct **4a** was isolated in 80% yield after 12 h of stirring with negligible diastereoselectivity and low-to-moderate enantioselectivity of each diastereomer (Table 1, entry 1). Although examination of

Table 1. Optimization of Reaction Parameters[a]



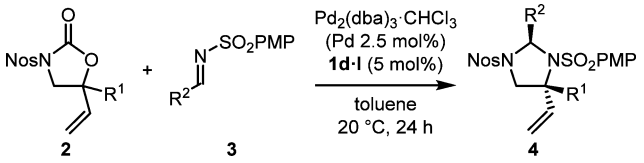
entry	1·X	3	yield (%)[b]	dr[c]	ee (%)[d]
1	**1a·Br**	**3a**	80	1:1	72/30
2	**1a·Br**	**3b**	92	1.1:1	74/35
3	**1a·Cl**	**3b**	91	1:1.3	72/37
4	**1a·I**	**3b**	92	3.2:1	76/27
5	**1b·I**	**3b**	99	15:1	92/26
6	**1c·I**	**3b**	99	19:1	90/nd
7	**1d·I**	**3b**	99	>20:1	96/nd

[a]Reactions were conducted with vinyloxazolidinone **2a** (0.1 mmol) and imine **3** (0.2 mmol) under the influence of $Pd_2(dba)_3{\cdot}CHCl_3$ (Pd 2.5 mol %), ligand **1·X** (5 mol %) in toluene (1 mL) at 20 °C for 12 h. [b]Isolated yield of the mixture of diastereomers. [c]Determined on the basis of ^{1}H NMR analysis of crude reaction mixture. [d]Determined by chiral HPLC. nd = not determined.

the effect of the imine protecting group revealed that the cycloaddition with *N*-(4-methoxy)benzenesulfonyl imine **3b** proceeded with high efficiency, the improvement in stereoselectivity was only marginal (entry 2). Notably, the identity of the halide ion of **1·X** was associated with its stereocontrolling ability, as we observed in our previous study.[6] Although stereoselectivities remained at a similar degree with chloride variant (**1a·Cl**), use of ammonium phosphine paired with an iodide ion (**1a·I**) delivered a promising increase in diastereoselectivity (entries 3 and 4). Then, the structural modifications of the aromatic substituents of **1·I** were undertaken. Introduction of the strongly electron-withdrawing trifluoromethyl group onto phosphorus benzene (Ar^2) (**1b·I**) induced a substantially higher level of diastereo- and enantiocontrol (entry 5). Additional manipulation of the phenyl appendages at the 3,3′-positions of the binaphthyl unit (Ar^1) led to the identification of **1d·I** as the best ligand; its palladium complex promoted the annulation to afford **4b** quantitatively with excellent diastereo- and enantioselectivity (entry 7).

Under the optimized reaction conditions, the scope of this asymmetric [3 + 2] cycloaddition protocol was explored with a range of vinyloxazolidinones **2** and imines **3**. The results are summarized in Table 2. With respect to the vinyloxazolidinones, significant variation of the 5-alkyl substituent was feasible, and the corresponding imidazolidines (**4c**–**4f**) were

Table 2. Substrate Scope[a]



entry	R^1	R^2	4	yield (%)[b]	dr[c]	ee (%)[d]
1	Et	Ph	**4c**	90	>20:1	96
2	*n*Bu	Ph	**4d**	99	>20:1	96
3[e]	*i*Bu	Ph	**4e**	99	>20:1	94
4	$(CH_2)_2$Ph	Ph	**4f**	92	11:1	92
5	Me	2-MeC_6H_4	**4g**	93	>20:1	99
6	Me	2-$MeOC_6H_4$	**4h**	92	>20:1	97
7	Me	2-ClC_6H_4	**4i**	92	19:1	95
8	Me	4-$MeOC_6H_4$	**4j**	80	7:1	96
9	Me	2-furyl	**4k**	99	14:1	95
10	Me	1-naphthyl	**4l**	94	>20:1	98
11	Me	*c*Hex	**4m**	99	>20:1	98
12	Me	*i*Pr	**4n**	99	>20:1	98
13	Me	*i*Bu	**4o**	99	6:1	92

[a]Unless otherwise noted, reactions were conducted with vinyloxazolidinone **2** (0.1 mmol) and imine **3** (0.2 mmol) under the influence of $Pd_2(dba)_3{\cdot}CHCl_3$ (Pd 2.5 mol %), ligand **1d·I** (5 mol %) in toluene (1 mL) at 20 °C for 24 h. [b]Isolated yield of the mixture of diastereomers. [c]Determined on the basis of ^{1}H NMR analysis of crude reaction mixture. [d]Determined by chiral HPLC, and % ee of major diastereomer is indicated. [e]Performed with $Pd_2(dba)_3{\cdot}CHCl_3$ (Pd 5 mol %), ligand **1d·I** (10 mol %) for 48 h.

obtained in nearly quantitative yields with high-to-excellent diastereo- and enantioselectivities (entries 1–4). An array of aromatic imines **3**, with electron-donating or electron-withdrawing groups at the *ortho* position of the benzene ring, reacted with oxazolidinone **2a** to give the cycloadducts **4g**–**4j** in high yields with almost complete stereocontrol (entries 5–7). With 4-methoxyphenyl-substituted imine, a decrease in the reaction efficiency and diastereoselectivity was observed, but a high level of enantioselectivity was retained (entry 8). In addition, hetero- and fused aromatic imines were well tolerated (entries 9 and 10). The present system was found to be applicable to reactions with aliphatic imines possessing secondary alkyl substituents, resulting in the quantitative production of **4m** and **4n** with rigorous control of the relative and absolute stereochemistry (entries 11 and 12). Primary alkyl-substituted imines also appeared to be amenable to this catalytic process, albeit with diminished diastereoselectivity (entry 13). The absolute configuration of **4g** was confirmed by X-ray crystal structure analysis,[8] and the stereochemistries of the remaining examples were assumed by analogy.

The synthetic potential of this method was demonstrated by the product derivatization to 1,2-diamines and biologically intriguing imidazolidin-2-ones[9,10] with quaternary stereocenters, as exemplified in Scheme 2. Deprotection of the 4-nitrobenzenesulfonyl (Nos) group[11] of cycloadduct **4b** under well-established conditions gave the corresponding monoprotected 1,2-diamine **5** in 80% yield. The formation of cyclic urea framework was executed by treating **5** with triphosgene under basic conditions, and subsequent deprotection of the PMP sulfonyl group in the presence of magnesium furnished chiral imidazolidinone **6** without the concomitant loss of enantiomeric purity.

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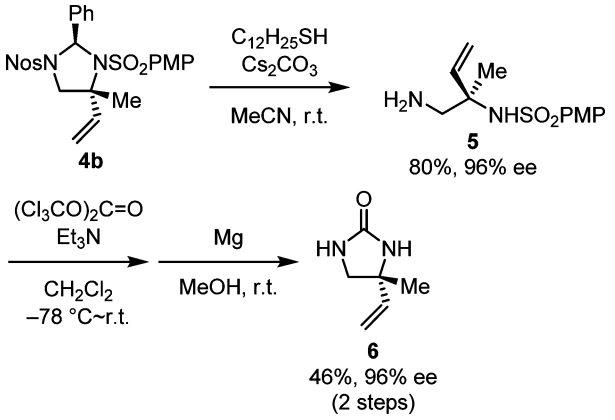
Scheme 2. Synthetic Transformations of Cycloadduct 4b



In conclusion, a highly enantio- and diastereoselective [3 + 2] annulation reaction between 5-vinyloxazolidinones and *N*-sulfonyl imines was developed using a palladium complex bearing a chiral ammonium-phosphine hybrid ligand, which allowed for the efficient and stereoselective construction of structurally diverse imidazolidines with α-amino quaternary stereocenters. Investigations regarding mechanistic details and further applications of the present methodology are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The following files are available free of charge on the ACS Publications website at DOI: 10.1021/cs501369z.

Representative experimental procedures, additional experimental data, analytical data for new compounds (PDF).

Crystallographic data for **4g** (CIF).

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Notes

The authors declare no competing financial interest.

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