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A Novel and Effective Route to 1,3-Oxazolidine Derivatives. Palladium-Catalyzed Regioselective [3 + 2] Cycloaddition of Vinylic Oxiranes with Imines

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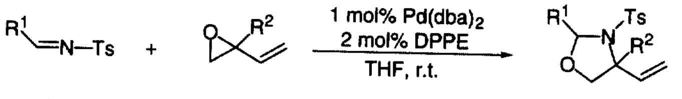
Abstract: *Palladium-catalyzed intermolecular reaction of imines 1 with vinylic oxiranes 2 gives the regioselective [3 + 2] cycloaddition products, 1,3-oxazolidine derivatives 3, in good to excellent yields. The present reaction permits the use of unconventional starting materials for the synthesis of 1,3-oxazolidines 3.* © 1999 Elsevier Science Ltd. All rights reserved.

The palladium-catalyzed [3 + 2] cycloaddition reaction of vinylic oxiranes with heterocumulenes ($X^{\delta-} = Y^{\delta+} = Z$) has been considered to be a versatile tool for constructing certain heterocycles in organic synthesis.[1] For example, heterocumulenes such as isocyanate,[2] carbon dioxide,[3] and carbodiimide[4] afforded oxazolidin-2-one, cyclic carbonate, and oxazolidin-2-one derivatives, respectively, in good to high yields. Recently, we reported that the palladium-catalyzed regioselective [3 + 2] cycloaddition of vinylic oxiranes with certain activated olefins, $C^{\delta+} = C^{\delta-}(EWG)_2$, in which EWG should be an electron-withdrawing group such as CN, SO_2R, or Meldrum's acid, gave polysubstituted tetrahydrofuran derivatives in good yields.[5] It now becomes clear that not only polarized heterocumulenes but also polarized carbon electrophiles of certain Michael acceptors can be used as a counterpart of vinylic oxiranes. It occurred to us that 1,3-oxazolidines would be obtained if imines are able to be used as a counterpart, instead of the activated C = C bond. The most popular method for the synthesis of 1,3-oxazolidines is the condensation of 1,2-amino alcohols with carbonyl compounds (or their corresponding acetals) in the presence of acid catalysts.[6-11] Accordingly, the N and O atom of the resulting 1,3-oxazolidine framework comes from the 1,2-amino alcohol, and the carbon between the N and O atom of the heterocycle comes from the carbonyl carbon of the counterpart. It was expected that the imine incorporated [3 + 2] cycloaddition would produces 1,3-oxazolidines via combination of the two substrates entirely different from the well-known combination. Here we describe that the palladium-catalyzed intermolecular reaction of imines **1** with vinylic oxiranes **2** gives the regioselective [3 + 2] cycloaddition products, 1,3-oxazolidine derivatives **3**, in good to excellent yields (eq 1).



1 a-g **2 a-b** **3 a-i** (1)

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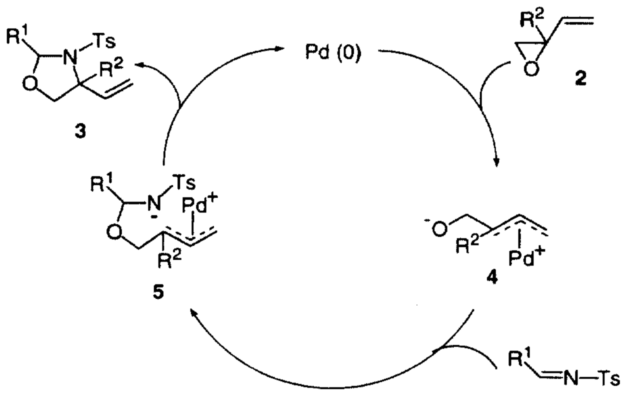
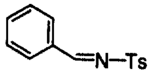
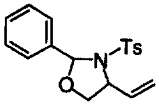
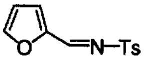
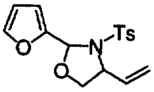
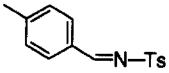
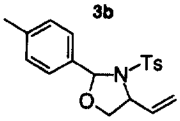
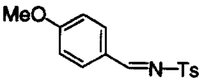
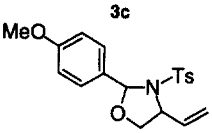
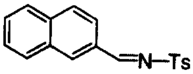
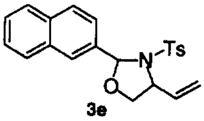
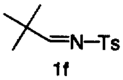
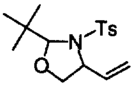
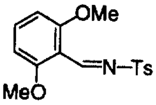
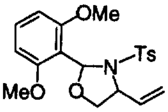
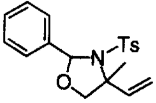
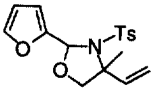
Our initial studies focused on the development of optimal reaction conditions for this transformation. At the outset, we undertook the reaction of imine **1a** with vinyl oxirane **2a** in THF using 3 mol % $Pd(PPh_3)_4$ at room temperature. After 2 h, the starting imine **1a** was consumed completely. As expected, ^1H NMR analysis of the reaction mixture revealed that the corresponding 1,3-oxazolidine **3a** was produced in 97 % yield. Polar and nonpolar solvents such as DMF, CH_3CN, toluene and CH_2Cl_2 gave the cycloaddition product **3a** in essentially quantitative yield, while the use of 1,4-dioxane as a solvent did not afford the cyclized product at all. Next, several other catalysts and catalytic systems were investigated to reduce the amounts of catalyst. Although $Pd(PPh_3)_4$ or $Pd(dba)_2$-$4PPh_3$ was an active catalyst, $Pd(dba)_2$-2DPPE system was the most effective catalyst for the present transformation. Interestingly, even the use of 1 mol % of the catalyst afforded the desired product **3a** in 97 % yield (entry 1 in Table 1), while the use of 1 mol % of $Pd(PPh_3)_4$ did not produce any of the cycloaddition product **3a** for 2 h. The results obtained for various substrates are summarized in Table 1. The imines **1a-b** possessing a phenyl or a furyl substituent reacted effectively with vinyl oxirane **2a** to afford the 1,3-oxazolidines **3a-b**, respectively, in excellent yields (entries 1-2). In addition, aromatic imines **1c-d** containing electron-donating substituents at the para position were converted smoothly to the five-membered heterocycles **3c-d**, respectively, in essentially quantitative yields (entries 3-4). Naphthyl imine **1e** gave **3e** in high yield (entry 5). Even the imines **1f-g,** having sterically crowding substituents as the R^1 group, afforded **3f-g** in 82 % and 75 % yields, respectively (entries 6-7). Meanwhile, in order to understand the effect of a substituent of vinylic oxiranes, we examined the reaction of a substituted vinylic oxirane **2b**. Although the reaction of **2b** was sluggish in comparison with that of **2a** (entries 8-9), the regioselective [3 + 2] cycloaddition products **3h-i** were obtained from **1a** and **1b** in 78 % and 74 % yields, respectively, although 3 mol % of the catalyst were needed. Diminished reaction rates and chemical yields in these cases are presumably attributed to the steric congestion of a π-allylpalladium intermediate **5** (vide post). In the above reactions, seven-membered heterocycles were not obtained.

A key step of the present [3 + 2] cycloaddition is the nucleophilic addition of an oxygen anion **4**, which is generated by the reaction of vinylic oxirane **2** with palladium, to imine **1**. It is noteworthy that the regioselective [3 + 2] cycloaddition reported here is accomplished by using activated tosyl imines, whereas other ordinary imines such as methyl, phenyl, and phophinoyl gave no cycloaddition products at all.



Phosphine omitted for clarity

Table 1. Pd-Catalyzed Regioselective [3 + 2] Cycloaddition of 1 with 2.[a]

Entry	Imine 1	Vinylic Oxirane 2	Time	Product 3	Yield,[b] (%)
1	 1a	 2a	2 h	 3a	97 (73 : 27)[c,d]
2	 1b	2a	2 h	 3b	96 (88 : 12)[c,d]
3	 1c	2a	4 h	 3c	>99 (70 : 30)[c]
4	 1d	2a	3 h	 3d	>99 (60 : 40)[c,d]
5	 1e	2a	3 h	 3e	93 (62 : 38)[c]
6	 1f	2a	3 h	 3f	82 (55 : 45)[c]
7	 1g	2a	4 h	 3g	75 (90 : 10)[c]
8[e]	1a	 2b	1 d	 3h	78 (57 : 43)[c]
9[e]	1b	2b	1 d	 3i	74 (50 : 50)[c]

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[a] All reactions were conducted in THF at room temperature. [b] Isolated yields based on 1. [c] Diastereomeric ratios were indicated in parentheses. [d] The configuration of the major isomer was cis (by means of 500 MHz NOE studies). In the other cases, the stereochemistries of the diastereoisomers were not determined. [e] 3 mol % of catalyst were used.

Palladium-catalyzed regioselective [3 + 2] cycloaddition of imine **1a** with vinyl oxirane **2a** is representative. To a solution of Pd(dba)$_2$ (0.003 g, 1 mol %), DPPE (0.004 g, 2 mol %) and **1a** (0.129 g, 0.5 mmol) in THF (5.0 mL) was added vinyl oxirane **2a** (0.046 mL, 1.2 equiv.) under Ar atmosphere. The reaction mixture was stirred at room temperature and the reaction progress was monitored by TLC. When the starting substrate **1a** was consumed completely, the reaction mixture was filtered through a short celite column using diethyl ether as an eluent. After the usual workup, analytically pure product **3a** was isolated in 97 % yield (0.159 g) by column chromatography on silica gel using *n*-hexane - ethyl acetate (15 : 1) as eluent.

In summary, we have developed a novel and effective route to 1,3-oxazolidine derivatives **3** by the successive addition reactions of the O and N atoms of vinyl oxiranes with imines. The present palladium-catalyzed intermolecular regioselective [3 + 2] cycloaddition of imines **1** with vinylic oixiranes **2** is a new version of 1,3-dipolar cycloadditions affording the five-membered heterocycles and permits the use of unconventional starting materials for the synthesis of 1,3-oxazolidines **3**.

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