Communications to the Editor

The First Enantiospecific Palladium-Catalyzed Cycloaddition of Aziridines and Heterocumulenes. Novel Synthesis of Chiral Five-Membered Ring Heterocycles

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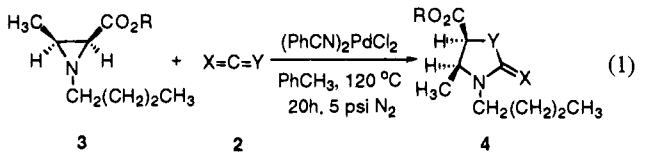
Cycloaddition reactions of three-membered ring heterocycles with heterocumulenes have been extensively studied because of the potential biological activity of the products.[1−13] In this regard, the development of enantiospecific approaches to the above reactions would be a significant development in this area. To our knowledge, there are no examples of enantioselective metal-catalyzed cycloaddition reactions involving small-ring heterocycles and heterocumulenes. Consequently, we have investigated cycloaddition reactions of stereochemically defined aziridines (including chiral, optically active derivatives) with heterocumulenes (carbodiimides, isocyanates, and isothiocyanates) in the presence of a Pd(II) catalyst.

Recent work on bis(benzonitrile)palladium dichloride-catalyzed cycloaddition reactions of aziridines or azetidines with heterocumulenes has resulted in the development of highly effective, regio- and stereospecific routes to a variety of five- and six-membered ring heterocycles containing two identical or different heteroatoms.[14−17] Herein, we report the first highly effective stereo- and enantiospecific cycloaddition reactions enabling one to obtain either enantiomeric product in optically pure form.

In light of the results of our study of the palladium(II)-catalyzed reaction of 1,2-disubstituted aziridines with carbodiimides, which regiospecifically gave imidazolidinimines in high yield,[14] we investigated the corresponding reactions of stereochemically defined 1,2,3-trisubstituted aziridines with heterocumulenes in order to determine the stereoselectivity of the cycloaddition process. Treatment of *cis*-1-isopropyl-3-methyl-2-phenylaziridine (**1**) with heterocumulenes such as diphenylcarbodiimide, phenyl isocyanate, or *p*-chlorophenyl isothiocyanate under various reaction conditions, using catalytic quantities of bis(benzonitrile)palladium(II) dichloride, resulted in recovery of the aziridine **1**.

The inertness of **1** may be due, in part, to the combined steric effect of the substituent groups (isopropyl, phenyl, methyl) which can inhibit complexation to palladium.[17] It is also conceivable that the presence of an electron-attracting substituent at an aziridine carbon atom could weaken the C−N bond and thus enhance reactivity. Consequently, *cis*-1-*n*-butyl-2-carboalkoxy-3-methylaziridines (**3**), which contain an ester group, were subjected to the cycloaddition reaction. Indeed, when aziridine **3** (R = CH_3) was treated with *p*-chlorophenyl isocyanate (**2**, X = O, Y = *p*-ClC_6H_4N) in toluene at 120 °C for 20 h in the presence of a catalytic amount of bis(benzonitrile)palladium dichloride (10 mol %), cycloaddition occurred efficiently, affording *cis*-1-*n*-butyl-3-(*p*-chlorophenyl)-4-carbomethoxy-5-methylimidazolidin-2-one (**4**, R = CH_3, X = O, Y = *p*-ClC_6H_4N) in 80% yield (eq 1). The reaction is



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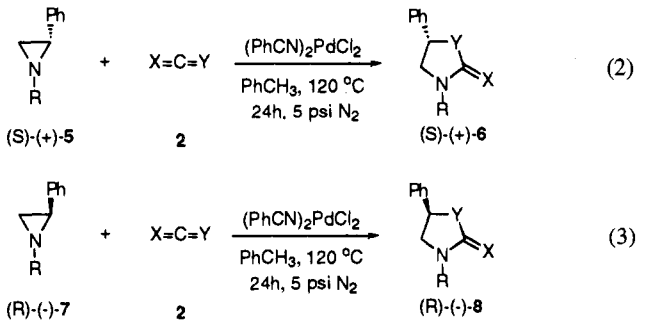
both regio- and stereospecific, the cycloaddition occurring with retention of stereochemistry at the heterocyclic carbon centers bearing the substituent groups. In other words, *cis*-**3** (R = CH_3) affords *cis*-**4** (R = CH_3, X = O, Y = *p*-ClC_6H_4N). The configuration of the 4,5-protons of the imidazolidine ring follows from the coupling constant (J = 8.0 Hz), characteristic of *cis*-vicinal proton coupling.[18]

Aryl isocyanates and isothiocyanates reacted with aziridine **3** (R = CH_3, CH_2CH_3) in the presence of $(PhCN)_2PdCl_2$ to form imidazolidinones and thiazolidinimines in good yields. The results of these reactions are presented in Table 1. These new compounds were characterized by analytical and spectral methods (see supplementary material).

In order to determine the enantioselectivity of the cycloaddition reaction, several known, as well as new, optically pure aziridines were prepared from commercially available enantiomers of 2-phenyloxirane (see supplementary material) and then studied in cycloaddition reactions. The palladium(II)-catalyzed cycloaddition reaction of (*S*)-(+)-*n*-butyl-2-phenylaziridine (**5**, R = *n*-C_4H_9) with phenyl isocyanate (**2**, X = O, Y = PhN) gave (+)-1-*n*-butyl-3,4-diphenylimidazolidin-2-one (**6**, R = *n*-C_4H_9, X = O, Y = PhN) ($[\alpha]^{23}_D$ + 31.7° (*c* 5.4, $CHCl_3$)) in 82% yield (eq 2). Similarly, the (−)-enantiomer **8** (R = *n*-C_4H_9,



X = O, Y = PhN) ($[\alpha]^{23}_D$ −31.0° (*c* 5.0, $CHCl_3$)) was obtained in 81% yield when (*R*)-(−)-*n*-butyl-2-phenylaziridine (**7**, R = *n*-C_4H_9) was treated with phenyl isocyanate (eq 3). The

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Table 1. Reaction of 1,2,3-Trisubstituted Aziridines with Heterocumulenes Catalyzed by $(PhCN)_2PdCl_2$[a]

3, R	2 X	2 Y	yield of 4[b] (%)
CH_3	C_6H_5N	C_6H_5N	60
CH_3	O	C_6H_5N	72
CH_3	O	*p*-ClC_6H_4N	80
C_2H_5	O	*p*-ClC_6H_4N	86
CH_3	*p*-ClC_6H_4N	S	70
CH_3	*p*-$NO_2C_6H_4N$	S	72
C_2H_5	*p*-ClC_6H_4N	S	75

[a] Reaction conditions: aziridine (1.0 mmol), heterocumulene (1.0 mmol), $(PhCN)_2PdCl_2$ (0.1 mmol), $PhCH_3$ (2.0 mL), 120 °C, 20 h, 5 psi N_2. [b] Isolated yield of pure materials.

imidazolidin-2-ones obtained were characterized by ^1H and ^{13}C NMR spectra as well as by IR, mass spectra, and elemental analysis (see supplementary material). To determine the optical purities of products (+)-**6** and (−)-**8** (R = *n*-C_4H_9, X = O, Y = PhN), the protons attached to the chiral carbons at position 4 in imidazolidin-2-ones were resolved by ^1H NMR using $Eu(hfc)_3$ as the chiral shift regent (see supplementary material). The europium-resolved ^1H NMR spectra clearly show that the products obtained by cycloaddition reactions are optically pure. Also, the specific rotations of the enantiomers are nearly equal in magnitude but opposite in sign (see above and supplementary material).

The absolute configuration of the asymmetric carbon of (+)-1-*n*-butyl-3-(*p*-chlorophenyl)-4-phenylimidazolidin-2-one (**6**, R = *n*-C_4H_9, X = O, Y = *p*-ClC_6H_4N), which was prepared by reaction of (*S*)-(+)-1-*n*-butyl-2-phenylaziridine with *p*-chlorophenyl isocyanate, was determined by single-crystal X-ray analysis. The chiral center has the (*S*) configuration. These results unequivocally demonstrate that the palladium(II)-catalyzed cycloaddition reactions of aziridines with heterocumulenes occur enantiospecifically and with retention of the configuration of the asymmetric center.

A series of chiral aziridines were reacted with heterocumulenes to give the corresponding five-membered ring heterocycles in high yields (eqs 2 and 3). The results are summarized in Tables 2 and 3. This cycloaddition reaction constitutes a simple, novel method for the synthesis of chiral imidazolidinones, imidazolidinimines, and thiazolidinimines not accessible by other means.

In conclusion, Pd(II)-catalyzed reactions of 1,2,3-trisubstituted aziridines, containing appropriate substituents, with heterocumulenes provide a simple and efficient route to five-membered ring heterocycles. These reactions occur both regio- and stereospecifically with retention of the stereochemistry of substituents in the aziridine ring. Enantiomerically pure 1,2-disubstituted aziridines react with heterocumulenes, affording the corresponding chiral five-membered ring heterocycles, the reactions proceeding with retention of configuration. This clearly is not only an excellent enantiospecific, general method for the chiral syntheses of imidazolidinones, imidazolidinimines, and thiazolidinimines but is also of considerable potential for the preparation of other chiral heterocycles by metal-catalyzed cycloaddition reactions.

Table 2. Reaction of (*S*)-(+)-1-Alkyl-2-phenylaziridines with Heterocumulenes Catalyzed by $(PhCN)_2PdCl_2$[a]

5, R	2 X	2 Y	yield of (*S*)-(+)-6[b] (%)
n-C_4H_9	*p*-ClC_6H_4N	*p*-ClC_6H_4N	90
n-C_4H_9	O	C_6H_5N	82
n-C_4H_9	O	*p*-ClC_6H_4N	87
1-adamantyl	C_6H_5N	S	85
1-adamantyl	*p*-ClC_6H_4N	S	83

[a] Reaction conditions: as in footnote a of Table 1, except for the reaction time (24 h). [b] Isolated yield of pure materials.

Table 3. Reaction of (*R*)-(−)-1-Alkyl-2-phenylaziridines with Heterocumulenes Catalyzed by $(PhCN)_2PdCl_2$[a]

7,R	2 X	2 Y	yield of (*R*)-(−)-8[b] (%)
n-C_4H_9	*p*-ClC_6H_4N	*p*-ClC_6H_4N	88
n-C_4H_9	O	C_6H_5N	81
n-C_4H_9	O	*p*-ClC_6H_4N	84
1-adamantyl	C_6H_5N	S	82
1-adamantyl	*p*-ClC_6H_4N	S	80

[a] Reaction conditions: as in footnote a of Table 1, except for the reaction time (24 h). [b] Isolated yield of pure materials.

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Supplementary Material Available: Experimental procedures and characterization data for reaction products, including NMR chiral shift reagent studies; experimental details; tables of atomic parameters (*x*, *y*, *z*, and B_{iso}), bond distances, and angles and for **6** (R = *n*-C_4H_9, X = O, Y = *p*-ClC_6H_4N) (34 pages); listing of observed and calculated structure factors for **6** (25 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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