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Articles

Room Temperature Ring-Opening Cyclization Reactions of 2-Vinylaziridines with Isocyanates, Carbodiimides, and Isothiocyanates Catalyzed by $[Pd(OAc)_2]/PPh_3$

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2-Vinylaziridines undergo cycloaddition reactions with various heterocumulenes, in the presence of $[Pd(OAc)_2]$ and PPh_3, at room temperature and 1 atm pressure, regioselectively affording five-membered ring products in moderate to high yields. The mixture of stereoisomers obtained by reactions employing *cis*-1-butyl-2-vinyl-3-methylaziridine as the reactant provides evidence for a mechanism involving a $\eta^3-\eta^1-\eta^3$ interconversion of a (π-allyl)palladium intermediate.

Introduction

The synthesis of five-membered heterocyclic rings by nucleophilic ring-opening of three-membered heterocycles has been extensively studied, especially because of the potential biological activity of some of the products.[1] For example, the ring-opening cycloaddition reactions of 1,2- and 1,2,3-substituted aziridines with various heterocumulenes catalyzed by $[PdCl_2(PhCN)_2]$ proceed both regio- and stereoselectively to give the corresponding five-membered ring heterocycles in reasonable to excellent yields.[2] A drawback of this system is that the reactions generally require relatively high temperatures (50−120 °C depending on substrates) to proceed to completion.

Recently, it has been shown that 2-vinyloxiranes can undergo stereoselective palladium(0)-catalyzed asymmetric cycloaddition with isocyanates and carbodiimides[3] to form oxazolidinones and oxazolidinoneimines, respectively (Scheme 1). The presence of chiral ligands such as BINAP and p-TolBINAP enables one to prepare the noted products in high enantiomeric excess.

These transformations are readily achieved at room temperature and low pressure and likely occur by a (π-allyl)palladium complex as the intermediate. The ring-opening carbonylation of 1-*N*-alkyl-2-vinylaziridines employing catalysts such as $[Fe(CO)_5]$[5] (light-induced) and [Pd(0)][6] has been briefly explored, and the driving force for these reactions is also tentatively explained by the presence of an intermediate (π-allyl)metal complex. In an effort to extend the cycloaddition methodology to an analogous aziridine system, we investigated the previously unstudied reaction of 2-vinylaziridines with several heterocumulenes.

(1) El Ali, B.; Alper, H. in *Transition Metal Catalyzed Reactions*; Murahashi, S.-I., Davies, S. G., Eds.; Blackwell Science: Malden, MA, 1999; p 261, and references therein. See also (b) Katrizky, A. R., Rees, C. W. In *Comprehensive Heterocyclic Chemistry*; Pergamon Press: Oxford, 1984; Parts 1 and 4B.

(2) Baeg, J. O.; Bensimon, C.; Alper, H. *J. Am. Chem. Soc.* **1995**, *117*, 4700. (b) Baeg, J. O.; Alper, H. *J. Org. Chem.* **1992**, *57*, 157. (c) Maas, H.; Bensimon, C.; Alper, H. *J. Org. Chem.* **1998**, *63*, 17.

(3) Larksarp, C.; Alper, H. *J. Am. Chem. Soc.* **1997**, *119*, 3709.

(4) Larksarp, C.; Alper, H. *J. Org. Chem.* **1998**, *63*, 6229.

(5) Aumann, R.; Frohlich, K.; Ring, H. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 275.

(6) Spears, G. W.; Nakanishi, K.; Ohfune, Y. *Synlett* **1991**, 91. (b) Tanner, D.; Somfai, P. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2415.

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Scheme 1

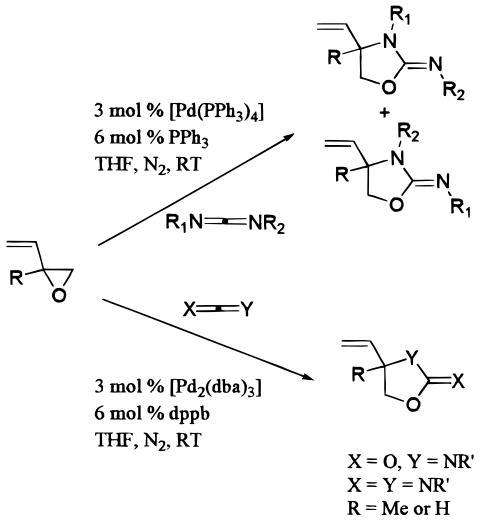


Table 1. Cycloaddition of 1-Alkyl-2-vinylaziridines with Various Heterocumulenes Catalyzed by $[Pd(OAc)_2]/PPh_3$

aziridine	heterocumulene	reaction time (h)	product	yield[a] (%)
1a	**2a**	2	**5a**	89
1a	**2b**	2	**5b**	82
1a	**2c**	2	**5c**	88
1a	**3a**	2	**6a**	60
1a	**3b**	20	**6b**	61
1a	**3c**	20	**6c**	36
1a	**4**	20	**7**	96
1b	**2a**	2	**5d**	67
1b	**2b**	2	**5e**	34
1b	**2c**	2	**5f**	61
1c	**2a**	2	**5g**	74[b,c]
1c	**2b**	2	**5h**	97[c]

[a] Isolated yields. Purities assessed by ^1H NMR, ^{13}C NMR, IR, and HRMS (EI^+ mode). [b] Reaction performed at 0 °C. [c] Product isolated as an approximately 2:1 mixture of cis and trans isomers.

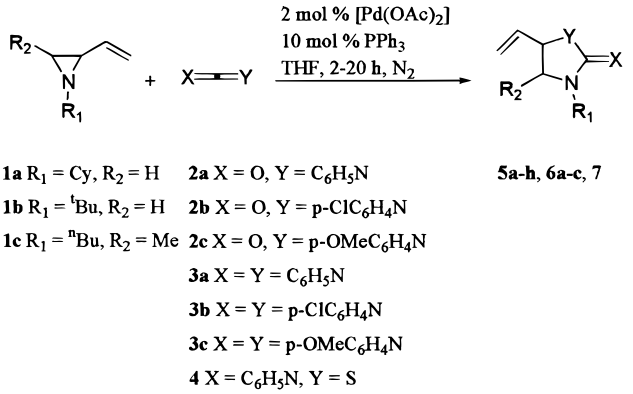
Results and Discussion

The vinyl aziridines **1a**−**c** were prepared according to a literature procedure,[7] and **1c** was obtained as a racemic mixture ((2*R*,3*S*) and (2*S*,3*R*)) of its cis stereoisomer. Resolution of the latter was not attempted.

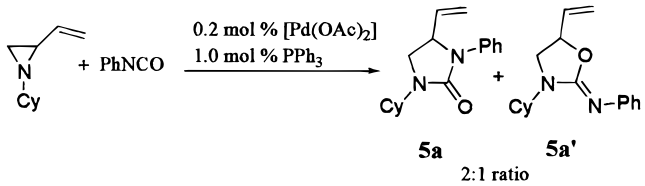
Treatment of a 2 mol % solution (anhydrous THF) of $[Pd(OAc)_2]$ containing 10 mol % of triphenylphosphine, with 2-vinylaziridine **1a**−**c** followed by heterocumulene **2a**−**c**, **3a**−**c**, or **4** at room temperature afforded the corresponding five-membered heterocycles **5a**−**h**, **6a**−**c**, and **7** in 34−97% yields (Table 1). Isocyanates, isothiocyanates, and carbodiimides were employed as heterocumulenes to give imidazolidinones, imidazolidinethiones, and imidazolidineimines, respectively, as products (Scheme 2).

For isocyanates, the reaction was complete after stirring for only 2 h (corresponding to a catalytic turnover number of 25 mol/mol [Pd]/h); however, for carbodiimides and isothiocyanates, 20 h was usually required for completion. The difference in reactivity of the latter may be explained by the relatively reduced nucleophilic

Scheme 2



Scheme 3



character at nitrogen and sulfur, respectively, in these substrates. It is notable that in the absence of palladium, the reaction of **1a** with **2a** did not occur under these conditions, which demonstrates the requirement for a catalyst. The regioselectivity of these reactions is excellent, with cycloaddition occurring between the *N*-1 and C-2 (vinyl-substituted) bond of the aziridine, giving a single regioisomer. However, when the catalyst concentration was reduced to 0.2 mol %, it was found that an inseparable (by TLC) mixture of structural isomers was obtained as products. For example, when isocyanate **2a** and aziridine **1a** are employed as substrates with 0.2 mol % $[Pd(OAc)_2]$ and 1 mol % PPh_3, over a period of 20 h, an approximately 2:1 mixture of **5a** ($m/z = 270$, ν (C=O) = 1698 cm^{-1}) and **5a′** (oxazolidinimine, $m/z = 270$, ν (C=N) = 1671 cm^{-1})[3] was obtained (Scheme 3).

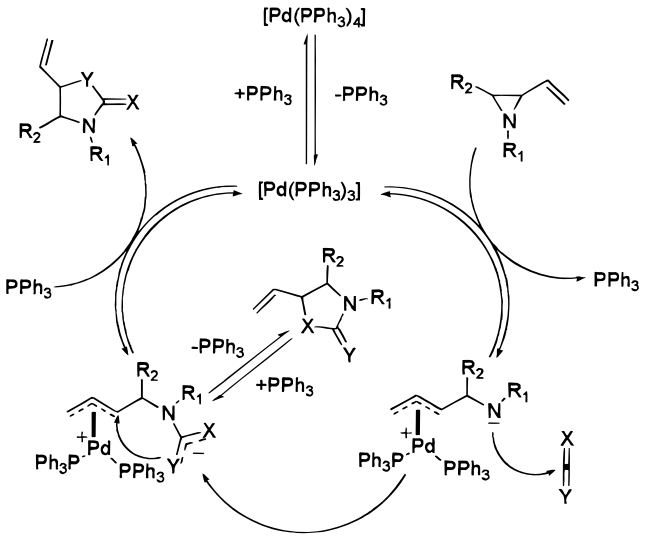
At reduced catalyst loads, Trost et al. also encountered *N*- and *O*-alkylated products from reactions of vinyloxiranes with isocyanates.[8] However, upon exposure to zerovalent palladium, the *O*-alkylated heterocycle could be isomerized to the anticipated product. It is likely that both products are formed in these reactions, but with sufficient catalyst present, the isomerization step can occur more efficiently, masking the formation of **5a′**. The internal cyclization would be in equilibrium with ring opening of the five-membered heterocycle and would eventually yield only the more thermodynamically favorable product, **5a**.

It is noteworthy that isocyanate reactivity is apparently unaffected by the electronic influence of the aromatic substituent. For example, *p*-chloro and *p*-methoxyphenyl isocyanate are similarly reactive, yet have quite different inductive characteristics (it might be expected that the *p*-chloro derivative should stabilize the negative charge on the nitrogen atom of the isocyanate group, enhancing reactivity, while the *p*-methoxy derivative should stabilize the negative charge on the oxygen atom of the isocyanate group making the nitrogen atom less reactive toward nucleophilic ring closing).

(7) Borel, D.; Gelas-Mialhe, Y.; Vessiere, R. *Can. J. Chem.* **1976**, *54*, 1582. For analogous preparation of vinyl aziridines, see also; Ibuka, T.; Mimura, N.; Aoyama, H.; Akaji, M.; Ohno, H.; Miwa, Y.; Taga, T.; Nakai, K.; Tamamura, H.; Fujii, N. *J. Org. Chem.* **1997**, *62*, 999.

(8) Trost, B. M.; Sudhakar, A. R. *J. Am. Chem. Soc.* **1987**, *109*, 3792.

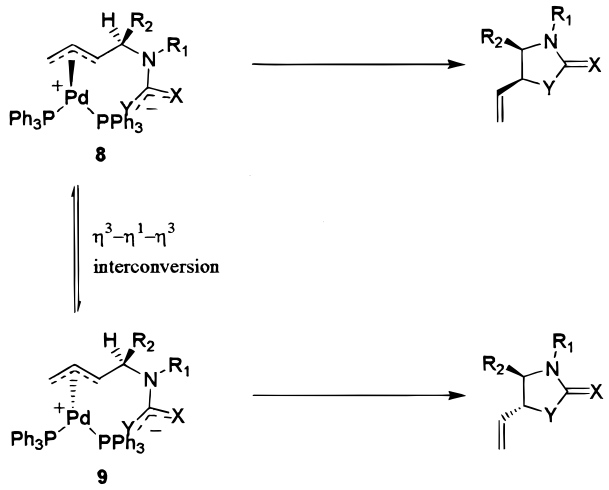
Scheme 4



Scheme 4 outlines the envisioned mechanistic pathway. Alkene coordination with a 16 electron palladium(0) complex leading to a η^3 intermediate is likely to be aided by the relatively strong coordinating effect of the nitrogen lone pair of the aziridine (in a recent publication, coordination of nitrogen was noticed to occur preferentially to that of the alkene group in some vinyl and allyl aziridine complexes of palladium(II)[9]). The highly nucleophilic nitrogen of the resulting intermediate should react readily with the electrophilic heterocumulene carbon atom giving rise to a further intermediate, cyclization of which affords the two possible five-membered heterocyclic rings, and regenerates the original palladium(0) complex. The equilibrium between the ring closing and opening steps enables subsequent isomerization to afford the more thermodynamically stable product.

It was observed that employment of *cis*-**1c** resulted in products containing an approximately 2:1 mixture of cis and trans stereoisomers. This lack of stereospecificity can be explained by the facile interconversion between intermediates **8** and **9** via a well established $\eta^3-\eta^1-\eta^3$ mechanism[10] (Scheme 5), which occurs at a much faster rate than intermolecular attack of the nitrogen nucleophile. This means that nucleophilic ring closing can *effectively* occur on either side of the (π-allyl)palladium intermediate, resulting in a mixture of cis and trans isomers. The distribution of this mixture should be dependent upon the immediate steric environment. Efforts were therefore made to control the stereochemistry of this reaction by cooling and employing bulkier phosphine ligands such as dppb. An isomeric mixture was obtained in all cases. Use of prochiral phosphine ligands ((*R*) and (*S*) BINAP and (*R*) and (*S*) Tol-BINAP) in reactions involving **1c** gave racemic products.

Scheme 5



Conclusions

The catalyst system comprising 2 mol % palladium acetate and 10 mol % PPh_3 is highly effective for the synthesis of imidazolidinones, imidazolidinethiones and imidazolidineimines by ring-opening cyclization of 2-vinylaziridines with isocyanates, isothiocyanates, and carbodiimides, respectively. The reaction occurs at room temperature and pressure and is simple in execution and workup, affording products in 34−97% yields.

Experimental Section

General Methods. All reactions and manipulations of chemicals were carried out using standard Schlenk techniques under an atmosphere of dinitrogen. THF was dried over Na/benzophenone and distilled prior to use. Isocyanates and isothiocyanates were obtained from commercial sources and were used as received without further purification. Carbodiimides were prepared according to the literature procedure[11] and purified by distillation under reduced pressure. [$Pd(OAc)_2$] and phosphines were obtained from Strem Chemical Co. and were used as received. All NMR spectra were recorded using $CDCl_3$ as the solvent and referenced to residual $CHCl_3$ (^1H at 7.24 ppm) and $CDCl_3$ (^{13}C at 77.0 ppm).

General Procedure for the Palladium-Catalyzed Cycloaddition Reaction of 2-Vinylaziridines and Heterocumulenes. The following procedure is representative. [$Pd(OAc)_2$] (4.5 mg, 0.020 mmol) was weighed into a Schlenk tube of 15−20 cm^3 internal volume under a stream of nitrogen. THF (12.0 cm^3) was added, and dissolution was effected by magnetic stirring. The solution was degassed by bubbling with dinitrogen. Triphenylphosphine (26.2 mg, 0.100 mmol) was added, and following dissolution, 3.0 cm^3 of this stock solution was transferred by syringe to a separate Schlenk tube whereupon 1-*N*-cyclohexyl-2-vinylaziridine (38 mg, 0.25 mmol), followed by phenylisocyanate (30 mg, 0.25 mmol) were added in succession. In this manner, the remaining stock solution of 2 mol % solution of [$Pd(OAc)_2$] containing 10 mol % PPh_3 can be used in three other reactions as required.

The progress of the reactions was followed by GC; they were judged to be complete when either of the starting materials was observed to be completely consumed.

Workup. On completion, the yellow-orange solutions were exposed to air, reduced to dryness in vacuo, redissolved in a small quantity of CH_2Cl_2 and subjected to either column or preparative thin-layer chromatography using an appropriate mixture of Et_2O/pentane as eluant or developer. After collection, the fractions were redissolved in Et_2O (if preparative TLC

(9) Cheikh, R. B.; Chaabouni, R.; Bonnet, M. C.; Dahan, F. *Polyhedron* **1998**, *17*, 185.

(10) Godleski, S. A. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon Press: Oxford, U.K., 1991; Vol. 4, Chapter 3.3, pp 585−662. (b) Trost, B. M.; Hung, M.-H. *J. Am. Chem. Soc.* **1984**, *106*, 6837. (c) Trost, B. M.; Bunt, R. C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 99. (d) Dawson, G. J.; Williams, J. M. J.; Coote, S. J. *Tetrahedron Lett.* **1995**, *36*, 461. (e) Auburn, P. R.; Mackenzie, P. B.; Bosnich, B. *J. Am. Chem. Soc.* **1985**, *107*, 2033. (f) Trost, B. M.; Krische, M. J.; Radinov, R.; Zanoni, G. *J. Am. Chem. Soc.* **1996**, *118*, 6297. (g) Trost, B. M.; Murphy, D. J. *Organometallics* **1985**, *4*, 1143.

(11) Campbell, T. W.; Monagle, J. J.; Foldi, V. *J. Am. Chem. Soc.* **1962**, *84*, 3673.

was the method of choice), dried with $MgSO_4$, decolorized with charcoal, filtered, and reduced to a colorless oil or a solid in vacuo. Yields reported are for the pure isolated compounds.

1-Cyclohexyl-3-phenyl-4-vinyltetrahydro-2*H*-imidazolidin-2-one (5a): 89% yield; colorless oil; IR (neat) ν (C═O) 1701 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.0−1.2 (br, 1H), 1.3−1.5 (m, br, 4H), 1.6−1.9 (br, 5H), 3.10 (dd, 1H, J = 8.6 and 5.9 Hz), 3.60 (t, 1H, J = 8.9 Hz), 3.7−3.9 (br, 1H), 4.62 (q, 1H, J = 7.4 Hz), 5.22 (m, 2H), 5.78 (m, 1H), 7.00 (t, 1H, J = 7.3 Hz), 7.27 (t, 2H, J = 7.8 Hz), 7.42 (d, 2H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$) δ 157.12, 139.41, 136.61, 128.43, 122.78, 120.13, 118.17, 56.59, 51.36, 44.50, 30.15, 25.50; MS (*m*/*e*) 270 $[M]^+$; EIHRMS calcd for $C_{17}H_{22}N_2O$ 270.1732, found 270.1755.

1-Butyl-5-methyl-3-phenyl-4-vinyltetrahydro-2*H*-imidazolidin-2-one (5g) (ca. **2:1 mixture of cis and trans):** 74% yield; colorless oil; IR (neat) ν (C═O) 1704 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (t, 4.5H, J = 7.1 Hz), 1.15 (d, 1.5H, J = 6.6 Hz), 1.29 (d, 3H, J = 6.1 Hz), 1.3−1.6 (m, 6.5H), 3.1 (m, 1.5H), 3.4 (m, 2.5H), 3.9 (m, 0.5H), 4.07 (t, 1H, J = 7.1 Hz), 4.57 (t, 0.5H, J = 8.2 Hz), 5.27 (m, 3H), 5.75 (m, 1.5H), 7.04 (m, 1.5H), 7.27 (m, 3H), 7.44 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 157.57, 139.43, 136.27, 133.35, 128.40, 123.02, 122.72, 120.53, 120.18, 118.85, 64.88, 61.18, 54.86, 52.13, 41.21, 40.90, 29.86, 29.64, 20.05, 17.56, 14.30, 13.80; MS (*m*/*e*) 258 $[M]^+$; EIHRMS calcd for $C_{16}H_{22}N_2O$ 258.1732, found 258.1731.

***N*-(1-Cyclohexyl-3-phenyl-4-vinyltetrahydro-2*H*-imidazol-2-ylidene)aniline (6a):** 60% yield; colorless solid mp 68 °C; IR (neat) ν (C═N) 1638 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.0−1.2 (br, 1H), 1.2−1.5 (br, 4H), 1.6−2.0 (br, 5H), 3.15 (dd, 1H, J = 8.8 and 6.4 Hz), 3.63 (t, 1H, J = 9.5 Hz), 3.9 (br, 1H), 4.18 (q, 1H, J = 7.0 Hz), 5.20 (m, 2H), 5.92 (m, 1H), 6.6 (m, 3H), 6.82 (m, 3H), 6.96 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 151.33, 149.61, 141.93, 137.80, 128.00, 127.85, 125.09, 124.30, 122.23, 119.63, 117.96, 64.25, 52.81, 46.25, 30.14, 28.98, 25.77, 25.68, 25.38; MS (*m*/*e*) 345 $[M]^+$; EIHRMS calcd for $C_{23}H_{27}N_3$ 345.2205, found 345.2220.

***N*-(3-Cyclohexyl-5-vinyl-1,3-thiazolidin-2-ylidene)aniline (7):** 96% yield; colorless oil; IR (neat) ν (C═N) 1619 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.0−1.2 (br, 1H), 1.2−1.5 (br, 4H), 1.6−2.0 (br, 5H), 3.35 (dd, 1H, J = 9.8 and 7.3 Hz), 3.68 (dd, 1H, J = 9.8 and 6.5 Hz), 4.06 (q, 1H, J = 7.4 Hz), 4.2 (br, 1H), 5.15 (m, 2H), 5.84 (m, 1H), 6.93 (m, 2H), 7.01 (d, 1H J = 7.4 Hz), 7.24 (2H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$) δ 157.65, 152.25, 135.49, 128.61, 122.73, 122.04, 117.53, 54.12, 51.68, 45.78, 30.63, 29.67, 25.67, 25.60; MS (*m*/*e*) 286 $[M]^+$; EIHRMS calcd for $C_{17}H_{22}N_2S$ 286.1521, found 286.1496.

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Supporting Information Available: Characterization data for compounds **5b**−**f**, **5h**, and **6b**,**c**, and ^1H and ^{13}C NMR spectra for compounds **5a**−**h**, **6a**−**c**, and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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