Synthesis of 1,3-Oxazine Derivatives by Palladium-Catalyzed Cycloaddition of Vinyloxetanes with Heterocumulenes. Completely Stereoselective Synthesis of Bicyclic 1,3-Oxazines

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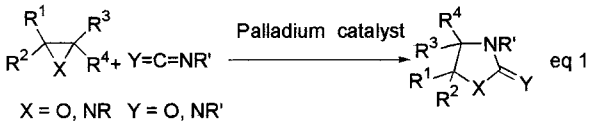
1,3-Oxazines were prepared by palladium−phosphine-catalyzed cycloaddition reactions of vinyloxetanes with heterocumulenes. 4-Vinyl-1,3-oxazin-2-imines were obtained in fine yields by the reaction of 2-vinyloxetanes with carbodiimides in THF at rt for 12 h using 1.5 mol % $Pd_2(dba)_3 \cdot CHCl_3$ and 3 mol % bidentate phosphine ligands (dppe or dppp). When isocyanates were utilized in the reaction, moderate to good yields of 4-vinyl-1,3-oxazin-2-ones were achieved within 1−2 h at rt. Palladium-catalyzed cycloaddition of fused-bicyclic vinyloxetanes with heterocumulenes proceeds in a highly stereoselective fashion affording only the *cis*-3-aza-1-oxo-9-vinyl[4.4.0]decane derivatives in 43−98% yield.

Introduction

The synthesis of 1,3-oxazines has attracted attention in the past because of their potential as antibiotics,[1a−d] antitumor,[1e−g] analgesics,[1h,i] and anticonvulsants.[1j] Several methods for the preparations of 1,3-oxazine derivatives have previously been reported,[1k,l] including the use of heterocumulenes.[2]

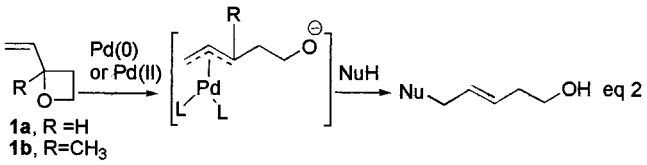
The cycloaddition reaction of heterocumulenes with three-membered heterocycles are of value for the formation of five-membered ring heterocycles.[3] We previously reported the use of isocyanates and carbodiimides as substrates for cycloaddition reactions with oxiranes (X = O)[4] or aziridines (X = NR)[5] (eq 1) catalyzed by



eq 1

palladium complexes, thus affording oxazolidine or imidazolidine derivatives, respectively. Also, palladium-catalyzed reaction of carbodiimides with vinyloxiranes in the presence of BINAP or TolBINAP affords oxazolidinimines in high enantiomeric excess.[4]

Furthermore, when enantiomerically pure aziridines are used in the palladium-catalyzed reaction with heterocumulenes, the cycloaddition reaction proceeds with retention of configuration.[5] Several methods have been described for the preparation of 1,3-oxazines by cycloaddition of heterocumulenes with oxetanes.[6] For example, Baba and co-workers[6a,b] employed organotin halide−base complexes as the catalyst for the addition of isocyanates to an oxetane to form oxazines. The reaction of oxetane with carbodiimides in the presence of triethylamine has been described in a US patent.[6c] However, relatively high reaction temperatures (100−200 °C) were needed in most cases. Larock et al.[7] have observed the palladium(0)-catalyzed nucleophillic ring opening of 2-vinyloxetanes in the synthesis of homoallyllic alcohols (eq 2). A π-allyl complex may be a reaction intermediate, in analogy to the 2-vinyloxiranes/heterocumulenes process.[4] Therefore, 2-vinyloxetanes could, in principle, be used for cycloaddition with heterocumulenes to prepare 4-vinyl-1,3-oxazines.



eq 2

Given the complete regio- and stereoselective nature of the noted vinyloxirane−heterocumulene reactions, we

(1) (a) Haneishi, T.; Okazaki, T.; Hata, T.; Tamura, C.; Nomura, M., Naito, A., Seki, I.; Arai, M. *J. Antibiot.* **1971**, *24*, 797. (b) Sasaki, K.; Kusakabe, Y.; Esumi, S. *J. Antibiot.* **1972**, *25*, 151. (c) Kusakabe, Y.; Nagatsu, J.; Shibuya, M.; Kawaguchi, O.; Hirose, C.; Shirato, S. *J. Antibiot.* **1972**, *25*, 44. (d) Kupchan, S. M.; Komoda, Y.; Court, W. A.; Thomas, G. J. Smith, R. M. Karim, A.; Gilmore, C. J.; Haltivanger, R. C.; Bryan, R. F. *J. Am. Chem. Soc.* **1972**, *94*, 1354. (e) Wani, M. C.; Taylor, H. L. Wall, M. E. *Chem. Soc., Chem. Commun.* **1973**, 390. (f) Johnson, P. Y.; Silver, R. B. *J. Heterocycl. Chem.* **1975**, *10*, 1029. (g) Renullard, S.; Rebhun, L. I. Havic, G. A.; Kupchan, S. M. *Science*, **1975**, *189*, 1002. (h) Urbański, T.; Ghrne, D.; Szczerek, I.; Modaski, M. Polish Patent, 54, 007, **1967**. (i) Lesher, G. Y.; Surrey, A. R. *J. Am. Chem. Soc.* **1955**, *77*, 636 (j) Mosher, H. S.; Frankel, M. B.; Gregory, M. *J. Am. Chem. Soc.* **1953**, *75*, 5326. (k) Sainsbury, M. In *Comprehensive Heterocyclic Chemistry*; Boulton, A. J., Mckillop, A., Eds.; Pergamon Press: Canada, 1984; Vol. 3, Part 2B, p 995. (l) Khumtaveeporn, K.; Alper, H. *J. Org. Chem.* **1995**, *60*, 8142.

(2) (a) Eckstein, Z.; Urbański, T. *Adv. Heterocycl. Chem.* **1963**, *2*, 311. (b) Eckstein, Z.; Urbański, T. *Adv. Heterocycl. Chem.* **1978**, *23*, 1. (c) Kato, T.; Katagiri, N.; Yamamoto, Y. *Heterocycles* **1980**, *14*, 133.

(3) (a) Osaki, S. *Chem. Rev.* **1972**, *72*, 457. (b) Gunar, V. I.; Ovechkina, L. F.; Zavyalov, S. I. *Chem. Abstr.* **1965**, *63*, 8346 g. (c) Pietsch, H.; Clauss, K.; Schmidt, E.; Jensen, H. *Chem. Abstr.* **1976**, *84*, 135684f. (d) Fukui, K.; Kitano, T. *Kogyo Kagaku Zasshi*, **1980**, *63*, 2062. (e) Hassner, A.; Rasmussen, J. K. *J. Am. Chem. Soc.* **1975**, *97*, 1451. (f) Karikomi, M.; Yamazaki, T.; Toda, T. *Chem. Lett.* **1993**, 1965. (g) Trost, B. M.; Sudhakar, A. R. *J. Am. Chem. Soc.* **1988**, *110*, 7933. (h) Baba, A.; Fujiwara, M.; Matsuda, H. *Tetrahedron Lett.* **1986**, *27*, 77. (i) Fujiwara, M.; Baba, A.; Matsuda, H. *J. Heterocycl. Chem.* **1988**, *25*, 1351. (j) Baba, A.; Seki, K.; Matsuda, H. *J. Heterocycl. Chem.* **1990**, *27*, 1925.

(4) (a) Larksarp, C.; Alper, H. *J. Am. Chem. Soc.* **1997**, *119*, 3709. (b) Larksarp, C.; Alper, H. *J. Org. Chem.* **1998**, *63*, 6229.

(5) (a) 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.

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(7) (a) Larock, R. C.; Stolz-Dunn, S. K. *Tetrahedron Lett.* **1989**, *30*, 3487. (b) Larock, R. C.; Ding, S.; Chi, T. *Synlett* **1993**, 145. (c) Larock, R. C.; Stolz-Dunn, S. K. *Synlett* **1990**, 341.

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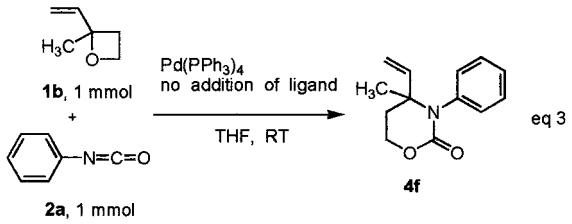
investigated the palladium-catalyzed cycloaddition reaction of vinyloxetanes with heterocumulenes. We now report that not only is the reaction of considerable scope for monocyclic oxetanes, but we were gratified to observe that bicyclic oxetanes reacted in a totally stereoselective manner with heterocumulenes to form 3-aza-1-oxo-*cis*-bicyclo[4.4.0]decanes.

Results and Discussion

Cycloaddition Reaction of Vinyloxetanes with Heterocumulenes. To determine the viability of the cycloaddition reaction of vinyloxetanes with heterocumulenes, we initially examined the reaction of 2-vinyloxetane (**1b,** R = CH_3**)** with phenyl isocyanate (**2a)** in anhydrous THF (Table 1) by using 5 mol % of $Pd(PPh_3)_4$ (eq 3). The latter has been used in the nucleophilic ring opening reaction of 2-vinyloxetane with hard nucleophiles to obtain allylic alcohol.[7a] The desired product, 4-vinyl-



1,3-oxazine-2-one (**4f**) was obtained in 47% yield (Table 1, entry 1). We then investigated the optimum amount of catalyst for this reaction by reducing the amount of palladium catalyst, $Pd(PPh_3)_4$ (without additional of any phosphine ligands), to 3 mol % (57% isolated yield of **4f**), 2 mol % (53% isolated yield of **4f**), and 1 mol % (38% isolated yield of **4f**). Therefore, 2−3 mol % of palladium catalyst was used in the cycloaddition reactions.

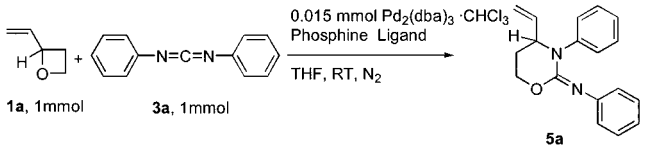
Table 1. Determination of the Optimum Amount of Palladium Catalyst for the Cycloaddition Reaction of 2-Methyl-2-vinyloxetane (1b) with Phenyl Isocyanate (2a)[a]

entry	mol % of $Pd(PPh_3)_4$ to 1 mol of phenyl isocyanate	isolated yield of **4f** (%)[b]
1	5	47
2	*3*	*57*
3	*2*	*53*
4	1	38
5	0	0

[a] Reaction conditions: 2-methyl-2-vinyloxetane **1b** (1.0 mmol), phenyl isocyanate **2a** (1.0 mmol), $Pd(PPh_3)_4$, 5 mL of THF, room temperature, N_2 atmosphere. [b] Purified by preparative TLC.

The presence of phosphine ligands was essential for the reaction, as no conversion of heterocumulenes was observed in the absence of a phosphine ligand.[8] To investigate the effect of the added phosphine ligands in the reaction, different types of phosphine ligands were employed when 2-vinyloxetane **1a** was treated with diphenylcarbodiimide **3a** to form *N*-phenyl-3-phenyl-4-vinyl-1,3-oxazin-2-imine, **5a** (see Table 2). Triphenylphosphine and dpppentane[9] were found to be less effective than dppe,[10] dppp,[11] and dppb[12] for the palladium-catalyzed reaction. This may be due to the lower basicity

Table 2. Effect of Added Phosphine Ligands in the Cycloaddition Reactions of 2-Vinyloxetane 1a with Diphenylcarbodiimides 3a Using 1.5 mol% $Pd_2(dba)_3{\cdot}CHCl_3$[a]



entry	ligands	reaction time (h)[b]	isolated yield of **5a** (%)[c]
1	0.06 mmol of PPh_3	12	79
2	0.03 mmol of dppe	12	*97*
3	0.03 mmol of dppp	12	*98*
4	0.03 mmol of dppb	12	94
5	0.03 mmol of dpppentane	24	78

[a] Reaction conditions: 2-Vinyloxetane **1a** (1.0 mmol), diphenylcarbodiimide **3a** (1.0 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (0.015 mmol), 0.03 mmol of bidentate ligand or 0.06 mmol of PPh_3, room temperature, 5 mL of THF, N_2 atmosphere. [b] Reaction times were based on the complete conversion of the carbodiimide. [c] Isolated yield by preparative TLC.

of PPh_3 and dpppentane which can enhance dimerization or trimerization of the carbodiimide.[13] Therefore, dppe and dppp are ligands of choice in the cycloaddition reactions.

The cycloaddition reaction was successfully carried out by treatment of 2-vinyloxetane (**1a**, R = H, **1b**, R = CH_3) with heterocumulenes **2** or **3** in the presence of 2−3 mol % $Pd_2(dba)_3{\cdot}CHCl_3$ and 2 equiv of phosphine ligands in anhydrous THF at room temperature. The reaction times were 12 h when carbodiimides were utilized in the cycloaddition, whereas in the case of isocyanates the reaction times were always shorter (1−1.5 h).[14] All reactions were performed by using dppe and dppp and some reactions utilized PPh_3 in order to compare the yields. The results are illustrated in Table 3 (for isocyanates) and Table 4. (for carbodiimides).

The cycloaddition reaction involving vinyloxetanes may proceed in the same manner as for vinyloxirane,[15,4] i.e., via zwitterionic π-allyl palladium intermediate **6** generated by oxidative addition of vinyloxetane **1** to a palladium(0) complex followed by reaction with heterocumulenes. Intramolecular attack of the nitrogen nucleophile at C-3 carbon of **7** would afford the six-membered-ring, 1,3-oxazine derivatives. (Scheme 1).

When using isocyanates for the reactions, product yields were considerably less than using carbodiimides as the substrate. The reaction conditions used might enhance the rate of dimerization and/or trimerization of isocyanates relative to the rate of cyclization. Lowering the reaction temperature to 0 °C (68% yield), −20 °C (65% yield), and −78 °C (40% yield) so as to reduce the rate of

(8) The reaction was performed by using 1 mmol of **1b** and 1 mmol of **2a** in the presence of 0.015 mmol of $Pd_2(dba)_3{\cdot}CHCl_3$ (no phosphine ligand was added) in THF and was stirred under nitrogen atmosphere for 24 h.

(9) dpppentane = 1, 5-bis(diphenylphosphino)pentane.

(10) dppe = 1, 2-bis(diphenylphosphino)ethane [Diphos].

(11) dppp = 1, 3-bis(diphenylphosphino)propane.

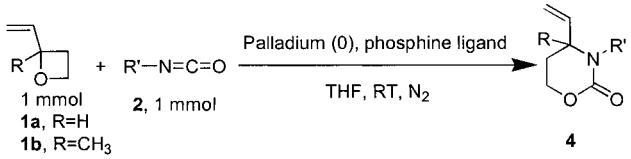
(12) dppb = 1, 4-bis(diphenylphosphino)butane.

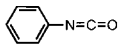
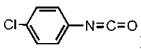
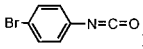
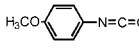
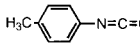
(13) (a) Trost, B. M.; Sudhakar, A. R. *J. Am. Chem. Soc.* **1987**, *109*, 3792. (b) Rahman, M. M.; Liu, H.-Y.; Eriks, K.; Prock, A.; Giering, W. P. *Organometallics* **1989**, *8*, 1.

(14) Reaction times were based on the complete conversion of the heterocumulenes (monitored by the shift of the IR absorption band of the carbodiimide unit at ~2100 cm^{-1} to the region of 1600 cm^{-1}; the absorption band of the isocyanate at about 2200 cm^{-1} was replaced by the carbonyl absorption in the region of 1700 cm^{-1}).

(15) (a) Hayashi, T.; Yamamoto, A.; Hagihara, T.; Ito, Y. *Tetrahedron Lett.* **1986**, *27*, 191. (b) Hayashi, T.; Yamamoto, A.; Ito, Y. *Chem. Lett.* **1987**, 177. (c) Hayashi, T.; Konishi, M.; Kumada, M. *Chem. Soc., Chem. Commun.* **1984**, 107. (d) Fiaud, J.-C.; Legros, J.-Y. *J. Org. Chem.* **1990**, *55*, 4840. (e) Tsuji, J. *Pure Appl. Chem.* **1982**, *54*, 197.

Table 3. Cycloaddition Reactions of 2-Vinyloxetanes 1 with Isocyanates 2 in the Presence of a Palladium(0) Complex and a Phosphine Ligand[a]



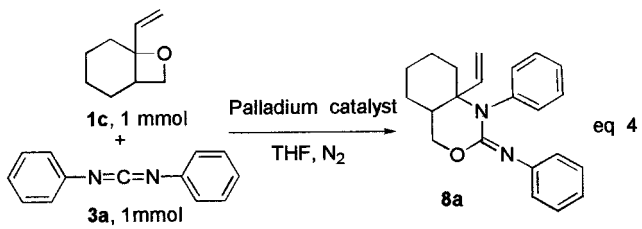
entry	1	R′-N=C=O	catalyst (mmol)	ligand (mmol)	reaction time, h	product	isolated yield (%)[b]
1	**1a**	 **2a**	$Pd_2(dba)_3$•$CHCl_3$ (0.015)	dppp (0.03)	2	**4a**	83
2				PPh_3 (006)	2	**4a**	69
3				dppb (0.03)	2	**4a**	52
4	**1a**	 **2b**	$Pd(PPh_3)_4$ (0.02)	PPh_3 (0.04)	2	**4b**	62
5			$Pd_2(dba)_3$•$CHCl_3$ (0.01)	dppe (0.02)	2	**4b**	27
6				dppp (0.02)	2	**4b**	17
7	**1a**	 **2c**	$Pd(PPh_3)_4$ (0.02)	PPh_3 (0.04)	2	**4c**	61
8	**1a**	 **2d**	$Pd_2(dba)_3$•$CHCl_3$ (0.015)	dppp (0.03)	2	**4d**	45
9	**1a**	 **2e**	$Pd_2(dba)_3$•$CHCl_3$ (0.01)	dppp (0.02)	1	**4e**	34
10				dppe (0.02)	1	**4e**	34
11	**1b**	**2d**	$Pd_2(dba)_3$•$CHCl_3$ (0.01)	dppe (0.02)	1	**4f**	39
12				dppp (0.02)	1	**4f**	25
13	**1b**	**2e**	$Pd_2(dba)_3$•$CHCl_3$ (0.01)	dppp (0.02)	2	**4g**	45
14				dppe (0.02)	2	**4g**	37

[a] Refer to the Experimental Section for General Procedure. [b] Purified by preparative TLC.

dimerization and/or trimerization proved to have no beneficial effect on the rate of cyclization.[16] In comparison with reactions utilizing isocyanates containing a halogen at the *para*-position of the phenyl ring, PPh_3 was shown to be the best ligand (entries 4 and 7, Table 3). Using dppp as the added ligand gives better product yields in most cases. However, reaction of *p*-methoxyphenyl isocyanate **2d** with **1b**, and dppe afforded a higher yield of isolated product (entry 8).

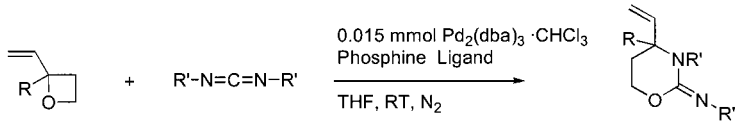
In the reaction using carbodiimides, good to excellent isolated yields of the desired products were obtained with 1.5 mol % of $Pd_2(dba)_3$•$CHCl_3$ and 3 mol % of dppp being the best catalytic system in most cases. In the reaction using carbodiimides having halogen at the *para*-position of the phenyl rings, dppe proved to be the best ligand for the reactions (entries 5, 9, and 12, Table 4). The reaction times were always longer when 2-vinyloxetanes were used which contained a vinylic substituent (entries 11−15, Table 4).

Cycloaddition Reaction of Bicyclic Vinyloxetanes with Heterocumulenes. The synthesis of homoallylic alcohols by palladium-catalyzed ring opening of fused-bicyclic vinyloxetanes has been described by Larlock and co-workers.[8] The reaction was found to proceed via a π-allyl palladium intermediate. Reaction of bicyclic vinyloxetanes with heterocumulenes is a simple route to bicyclic oxazines. We first performed the reaction using 1 mmol each of **1c** and diphenylcarbodiimide, **2a** (eq 4), and the reaction conditions were identical to those used for monocyclic vinyloxetanes (**1a**,**b**) (entry 1, Table 5), but no conversion of the carbodiimides was observed. Increasing the amount of the palladium catalyst to 2.5 mol % and the reaction temperature to 50 °C (entry 2) also gave recovered heterocumulenes. However, complete conversion occurred using 4.5 mol % of $Pd_2(dba)_3$•$CHCl_3$ and 9 mol % of dppp at 50 °C, with **8a** isolated in 52% yield (entry 4).



(16) Repeating reaction in entry 1, Table 3, but with stirring at lower temperature after addition of **1a** and **2a** to the mixture of $Pd_2(dba)_3$•$CHCl_3$ and dppp in THF.

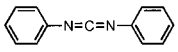
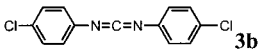
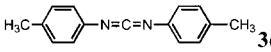
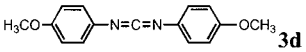
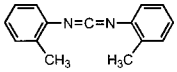
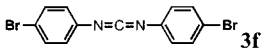
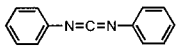
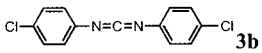
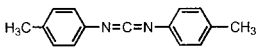
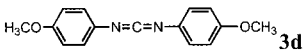
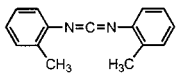
Table 4. Cycloadducts Obtained from the Reactions of 2-Vinyloxetanes 1 and Carbodiimides 3 in the Presence of 1.5 mol % $Pd_2(dba)_3 \cdot CHCl_3$ and a Phosphine Ligand[a]



1mmol
1a, R = H
1b, R = CH_3

3, 1mmol

5a

entry	1	R′-N=C=N-R′ (3)	ligand	reaction time, h	product	isolated yield (%)[b]
1	**1a**	 **3a**	dppp	12	**5a**	98
2			PPh_3	12	**5a**	88
3			dppe	12	**5a**	97
4			dppb	12	**5a**	94
5	**1a**	 **3b**	dppe	12	**5b**	86
			dppp	12	**5b**	68
6	**1a**	 **3c**	dppp	12	**5c**	94
7	**1a**	 **3d**	dppp	12	**5d**	98
8	**1a**	 **3e**	dppp	12	**5e**	98
9	**1a**	 **3f**	dppe	12	**5f**	65
10			dppp	12	**5f**	45
11	**1b**	 **3a**	dppp	48	**5g**	83
12	**1b**	 **3b**	dppe	36	**5h**	62
13			dppp	36	**5h**	52
14	**1b**	 **3c**	dppp	48	**5i**	92
15	**1b**	 **3d**	dppp	15	**5j**	77
16	**1b**	 **3e**	dppp	24	**5k**	78

[a] Refer to the Experimental Section for the General Procedure. [b] Yield of isolated product after silica gel TLC.

The yield increased to 70% when the reaction was carried out in a glass autoclave with 5 psi N_2 at 80 °C (entry 5). Increasing the reaction temperature to 100 °C resulted in the formation of palladium black, and **8a** was formed in reduced yield.

Trans- and *cis*-fused bicyclic oxazine-2-imines (**8a**) (Figure 1) are possible reaction products.

Spectral results[17] and a single-crystal X-ray diffraction determination (Figure 2) established the structure as *cis*-**8a**. Consequently, the cycloaddition proceeds with complete stereochemical control.

A series of heterocumulenes **2** and **3** were reacted with bicyclic vinyloxetanes **1c**, **1d**, and **1e** using $Pd_2(dba)_3 \cdot CHCl_3$ and a bidentate phosphine ligand as the catalytic system (eq 5), and the results are summarized in Table

(17) After complete conversion of **2a** (monitored by IR), the reaction solution was concentrated and separated by preparative silica gel TLC. Only one isomer of the desired product was observed by TLC.

Scheme 1

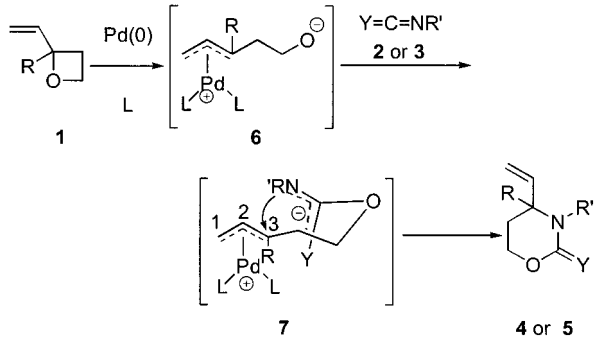


Table 5. Optimization of Reaction Conditions for the Cycloaddition of Bicyclic Vinyloxetane 1c with Diphenylcarbodiimide 3a[a]

entry	conditions	isolated yields,[b] %
1	0.015 mmol of $Pd_2(dba)_3{\cdot}CHCl_3$, 0.03 mmol of dppp, RT, 48 h	0
2	0.025 mmol of $Pd(PPh_3)_4$, 0.025 mmol of PPh_3, 50 °C, 48 h	0
3	0.045 mmol of $Pd_2(dba)_3{\cdot}CHCl_3$, 0.09 mmol of dppp, RT, 48 h	0
4	0.045 mmol of $Pd_2(dba)_3{\cdot}CHCl_3$, 0.09 mmol of dppp, 50 °C, 48 h	52
5	0.045 mmol of $Pd_2(dba)_3{\cdot}CHCl_3$, 0.09 mmol of dppp, 80 °C, 48 h[c]	70

[a] Reaction conditions: **1c** (1 mmol), **3a** (1 mmol), THF (10 mL), under N_2 atmosphere. [b] Isolated yield of **8a** (by preparative TLC). [c] Reaction was stirred in a glass autoclave at 5 psi N_2.

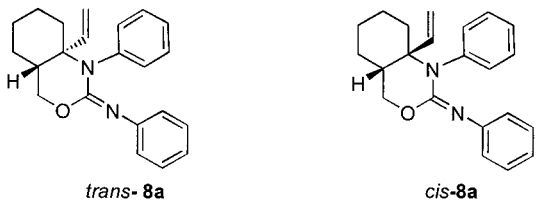


Figure 1. Two possible cycloaddition products which could be obtained from the reaction.

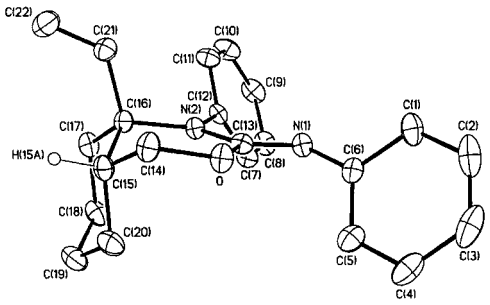
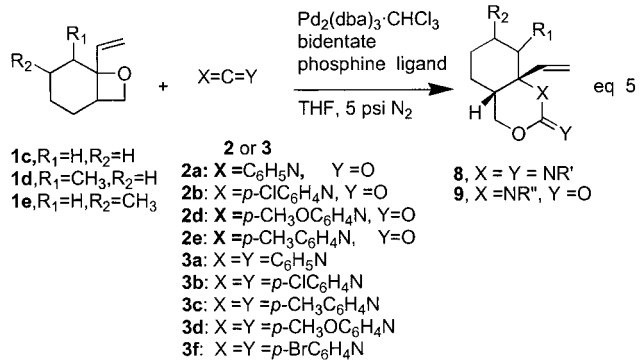


Figure 2. X-ray structure of **8a**.

6. The reactions were carried out in a glass autoclave under 5 psi N_2 using 1 mmol of **1c**, **1d**, or **1e** with 1 equimolar of heterocumulene (**2** or **3**) in the presence of 4−4.5 mol % of $Pd_2(dba)_3{\cdot}CHCl_3$ and 8−9 mol % of bidentate phosphine ligand (using carbodiimides), whereas a mixture of 3.0 mol % of $Pd_2(dba)_3{\cdot}CHCl_3$ and 6 mol % of bidentate phosphine ligand was used for reactions involving isocyanates. The reaction mixture was stirred at 80 °C for carbodiimides and 50 °C for isocyanates, until conversion of heterocumulenes was complete (monitored by IR). The yields of the bicyclic *cis*-oxazin-2-imine (**8**) were significantly higher using dppe than dppp for the reaction of bicyclic oxetanes with carbodiimides (entries 2, 4, 6, and 8, Table 6). However, dppp was a superior ligand for the reaction of **1a** with isocyanates. Lower isolated product yields were observed using isocyanates than carbodiimides in the cycloaddition reactions, analogous to results observed using monocyclic vinyloxetanes.



The selective formation of *cis*-fused bicyclic [4.4.0] heterocycles (**8** or **9**) may be due to a preference for the formation of **10** rather than **11** (Scheme 2). Intramolecular nucleophilic addition in **10** may occur from the side opposite to π-allyl palladium moiety resulting in the formation of the *cis*-product.

The cycloaddition of bicyclic vinyloxetanes **1d** and **1e** bearing a methyl substituent on the cyclohexyl ring was also stereoselective. An X-ray determination of the structure of **8f** revealed a *trans* relationship of the methyl and vinyl groups in the *cis*-bicyclic oxazine imine (Figure 3). Excellent yields resulted from reactions of **1d** or **1e** with carbodiimides **3a**−**c** (entries 14−18, Table 6). What these results demonstrate is the ability to achieve complete regio- and stereoselective cycloaddition processes using nonchiral ligands.

Conclusions

Mono and bicyclic oxazin-2-ones and oxazin-2-imines were isolated in fine yields by the cycloaddition reaction of 2-vinyloxetanes with heterocumulenes catalyzed by palladium complexes and phosphine ligands. This process is completely regioselective and stereoselective. A particularly novel feature of the cycloaddition process is its use for the construction of bicyclic [4.4.0] systems by use of $Pd_2(dba)_3{\cdot}CHCl_3$ and a achiral ligand such as dppe. The new reaction provides access to stereochemically defined mono and bicyclic compounds some of which may prove to exhibit significant pharmaceutical activity.

Experimental Section

General Methods. $Pd(PPh_3)_4$ and isocyanates were purchased from commercial sources and were used as received. Carbodiimides[18] and $Pd_2(dba)_3{\cdot}CHCl_3$[19] were prepared according to literature procedures. Organic solvents were dried and distilled prior to use. Vinyloxetanes **1a** and **1b** were prepared according to literature methods.[20] Bicyclic vinyloxetanes, **1c**−**e**, were obtained by modification of literature procedures[21]

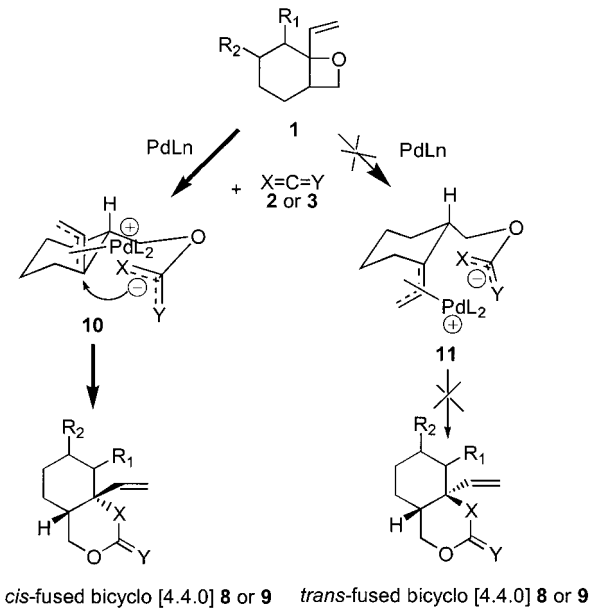
(18) Campbell, T. W.; Monagle, J. J.; Foldi, V. *J. Am. Chem. Soc.* **1962**, *84*, 3673.
(19) Ukai, T.; Kawazura, H.; Ishii, Y. *J. Organomet. Chem.* **1974**, *65*, 253.
(20) Portnyagin, Y, M.; Pak, N. E. *J. Org. Chem. USSR* **1971**, *7*, 1691.
(21) Portnyagin, Y, M.; Sova, V. V. *J. Org. Chem. USSR* **1968**, *4*, 1515.

Table 6. Cycloaddition Reaction of Fused-Ring 2-Vinyloxetanes 1c−e with Heterocumulenes 2 or 3 Catalyzed by $Pd_2(dba)_3$·$CHCl_3$ and Bidentate Phosphine Ligands[a]

entry	1	X=C=Y	$Pd_2(dba)_3$·$CHCl_3$ (mmol)	ligand (mmol)	reaction time, h	product	isolated yield,[b] %
1	**1c**	**3a**	0.045	dppp (0.09)	24	**8a**	70
2				dppe (0.09)	24		98
3	**1c**	**3b**	0.04	dppp (0.08)	48	**8b**	65
4				dppe (0.08)	48		85
5	**1c**	**3c**	0.04	dppp (0.08)	48	**8c**	20
6				dppe (0.08)	48		86
7	**1c**	**3d**	0.04	dppp (0.08)	48	**8d**	22
8				dppe (0.08)	48		66
9	**1c**	**3f**	0.045	dppe (0.09)	48	**8e**	86
10	**1c**	**2a**	0.03	dppp (0.06)	24	**9a**	51
11	**1c**	**2b**	0.03	dppp (0.06)	12	**9b**	46
12	**1c**	**2d**	0.03	dppp (0.06)	12	**9c**	55
13	**1c**	**2e**	0.03	dppp (0.06)	12	**9d**	43
14	**1d**	**3b**	0.45	dppe (0.09)	12	**8f**	80
15	**1d**	**3a**	0.45	dppe (0.09)	24	**8g**	77
16	**1d**	**3c**	0.45	dppe (0.09)	24	**8h**	70
17	**1e**	**3b**	0.45	dppe (0.09)	24	**8i**	98
18	**1e**	**3c**	0.45	dppe (0.09)	24	**8j**	82

[a] See the Experimental Section for General Procedure for the Cycloaddition Reaction of Bicyclic Vinyloxetanes with Heterocumules. [b] Purified by column chromatography using silica gel.

Scheme 2



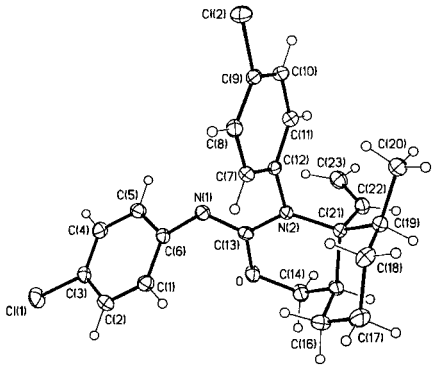


Figure 3. X-ray structure of **8f**.

(procedures and spectral data of **1c−e** are available in Supporting Information).

General Procedure for the Palladium-Catalyzed Cycloaddition Reaction of 2-Vinyloxetanes (1a,b) with Heterocumulenes. A mixture of the palladium complex and a phosphine ligand [$Pd(PPh_3)_4$ (0.02 mmol) and PPh_3 (0.04 mmol), or $Pd_2(dba)_3$·$CHCl_3$ (0.01−0.015 mmol) and a bidentate phosphine ligand (0.02−0.03 mmol)] and THF (5 mL), was stirred in a three-neck round-bottom flask under nitrogen at room temperature for 30 min. The vinyloxetane **1a** or **1b** (1.0 mmol) and heterocumulene (1.0 mmol) were added, and the mixture was then stirred under nitrogen at room temperature until the conversion of the heterocumulenes was complete [monitored by disappearance of the N=C=N IR-absorption band in the free carbodiimide (~2100 cm^{-1}) and the appearance of the C=N band in the region of 1620−1630 cm^{-1}; the absorption of the isocyanate (~2200 cm^{-1}) is replaced by the carbonyl band at 1680−1690 cm^{-1}]. After the reaction was complete, the orange yellow solution was then concentrated by rotary evaporation, and the residue was purified by silica gel TLC using a mixture of pentane/ether as the developer. Melting points, IR, NMR, MS, and analytical data for selected samples of **4** and **5** are as follows (see Supporting Information for all others **4** and **5**).

***N*-Phenyl-4-vinyl-1,3-oxazin-2-one (4a)** (R = H, R′ = C_6H_5): mp = 60−61 °C; IR (C=O) 1695 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.97 (m, 1H), 2.30 (m, 1H), 4.31 (m, 3H), 5.15 (m, 2H), 5.71 (m, 1H), 7.13−7.34 (m, 5H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 27.63, 60.13 63.67, 118, 126.67, 126.94, 128.72, 135.97, 141.53, 152.63 (C=O); MS (*m*/*e*) 203 $[M]^+$. Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found C, 71.28; H, 6.44; N, 6.70.

***N*-(*p*-Chlorophenyl)-4-vinyl-1,3-oxazin-2-one (4b)** (R = H, R′ = *p*-ClC_6H_4): mp = 68−69 °C; IR (C=O) 1696 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.06 (m, 1H), 2.40 (m, 1H), 4.41 (m, 3H), 5.17 (d, 1H, *J* = 15.9 Hz), 5.23 (d, 1H, *J* = 8.9 Hz), 5.79 (m, 1H), 7.20−7.37 (m, 4H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 27.82, 60.38, 63.89, 118.59, 128.46, 129.04, 135.82, 131.84, 140.10, 152.59 (C=O); MS (*m*/*e*) 237 $[M]^+$. Anal. Calcd for $C_{12}H_{12}ClNO_2$: C, 60.64; H, 5.09; N, 5.89. Found C, 60.54; H, 5.06; N, 6.04.

***N*-Phenyl-3-phenyl-4-vinyl-1,3-oxazin-2-imine (5a)** (R = H, R′ = C_6H_5): mp = 90−91 °C; IR (C=N) 1636 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$), δ 2.05 (m, 1H), 2.39 (m, 1H), 4.25 (m, 2H), 4.44 (m, 1H), 5.20 (m, 2H), 5.87 (m, 1H), 6.86−7.41 (m, 10H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 29.03, 59.23, 63.29, 117.51, 121.05, 123.32. 125.70, 127.03, 128.18, 128.73, 137.61, 143.74, 148.12, 148.97 (C=N); MS (*m*/*e*) 277 $[M - 1]^+$, 278 $[M]^+$. Anal. Calcd for $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52; N, 10.06. Found C, 77.40; H, 6.42; N, 10.02.

***N*-(*p*-Chlorophenyl)-3-(*p*-chlorophenyl)-4-vinyl-1,3-oxazin-2-imine (5b)** (R = H, R′ = *p*-ClC_6H_4): mp = 99−100 °C; IR (C=N) 1630 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.08 (m, 1H), 2.40 (m, 1H), 4.32 (m, 3H), 5.18 (m, 2H), 5.84 (m, 1H), 7.11−7.34 (m, 4H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 28.82, 59.46, 63.47, 118.09, 124.67, 128.17, 128.67, 128.96, 137.02, 126.59, 129.21, 141.91, 146.43, 149.04 (C=N); MS (*m*/*e*) 345 $[M-1]^+$,

346 $[M]^+$. Anal. Calcd for $C_{18}H_{16}Cl_2N_2O$: C, 62.26; H, 4.64; N, 8.07. Found C, 62.26; H, 4.68; N, 8.03.

General Procedure for the Cycloaddition Reaction of Bicyclic Vinyloxetanes (1c−e) with Heterocumulenes Catalyzed by $Pd_2(dba)_3$·$CHCl_3$ and a Bidentate Phosphine. A mixture of $Pd_2(dba)_3$·$CHCl_3$ (0.03−0.045 mmol) and 2 equiv of a bidentate phosphine ligand in THF (5 mL) was stirred in a glass autoclave under nitrogen at room temperature for 30 min. The bicyclic vinyloxetane **1c**−**e** (1.0 mmol), heterocumulene (1.0 mmol), and another 5 mL of THF were added. The glass autoclave was sealed and then pressurized with N_2 to 5 psi. The reaction mixture was then stirred (see Table 6 for reaction time and temperature in each case) until the conversion of the heterocumulene was complete (monitored by IR). The resulting solution was then concentrated by rotary evaporation, and the residue was purified by silica gel column chromatography using mixture of pentane/ether as the eluant. Melting points, IR, NMR, MS, and analytical data for selected samples of **8** and **9** are as follows (see Supporting Information for all others **8** and **9**).

3-Aza-1-oxo-3-phenyl-*N*-phenyl-9-vinylbicyclo[4.4.0]-decan-2-imine (8a) (R_1 = H, R_2 = H, X = Y = C_6H_5N): mp = 122−123 °C; IR (C═N) 1627 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.30−2.25 (m, 9H), 4.05 (d,1H, J = 10.6 Hz), 4.55 (dd, 1H, J = 10.6 and 2.9 Hz), 5.43 (d, 1H, J = 5.09 Hz), 5.50 (d, 1H, J = 1.47 Hz), 6.03 (dd, 1H, J = 17.5 and 10.5 Hz), 6.88−7.50 (m,10H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 20.90, 24.45, 25.67, 33.20, 38.25, 61.76, 68.44, 116.99, 121.67, 123.66, 126.68, 128.16, 130.23, 139.93, 143.95, 149.97 (C═N); MS (*m*/*e*) 331 $[M - 1]^+$, 332 $[M]^+$. Anal. Calcd for $C_{22}H_{24}N_2O$: C, 79.48; H, 7.28; N, 8.43. Found C, 79.48; H, 7.17; N, 8.37.

3-Aza-1-oxo-3-(*p*-chlorophenyl)-*N*-(*p*-chlorophenyl)-9-vinylbicyclo[4.4.0]decan-2-imine (8b) (R_1 = H, R_2 = H, X = Y = *p*-ClC_6H_4N): mp = 142−143 °C; IR (C═N) 1622 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.31−1.90 (m, 9H), 3.95 (dd, 1H, J = 10.8 and 1.4 Hz), 4.48 (dd, 1H, J = 10.8 and 2.8 Hz), 5.41 (d, 1H, J = 13.0 Hz), 5.46 (d, 1H, J = 6.6 Hz), 6.00 (dd, 1H, J = 17.2 and 10.8 Hz), 6.80 (d, 2H), 7.16 (d, 2H), 7.35 (m, 4H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 20.78, 24.43, 25.57, 33.14, 38.07, 61.65, 68.37, 117.00, 124.73, 126.20, 128.08, 131.36, 131.94, 138.80, 143.88, 147.10, 149.44. (C═N); MS (*m*/*e*) 400 $[M]^+$. Anal. Calcd for $C_{22}H_{22}Cl_2N_2O$: C, 65.84; H, 5.53; N, 6.98. Found C, 66.05; H, 5.60; N, 6.96.

3-Aza-1-oxo-*N*-(phenyl)-9-vinylbicyclo[4.4.0]decan-2-one (9a) (R_1 = H, R_2 = H, X = C_6H_5N, Y = O): mp = 162−163 °C; IR (C═O) 1683 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.54−2.30 (m, 9H), 4.41 (dd, 1H, J = 11.22 and 1.46 Hz), 4.96 (dd, 1H, J = 10.80 and 2.2 Hz), 5.76 (m, 2H), 6.31 (dd, 1H, J = 17.3 and 10.7 Hz), 7.61−7.73 (m, 5H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 20.66, 24.22, 25.25, 32.75, 37.47, 62.78, 68.22, 116.71, 126.99, 128.11, 129.10, 138.53, 143.30, 153.36. (C═O); MS (*m*/*e*) 257 $[M]^+$. Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found C, 74.65; H, 7.48; N, 5.45.

3-Aza-1-oxo-*N*-(*p*-chlorophenyl)-9-vinylbicyclo[4.4.0]-decan-2-one (9b) (R_1 = H, R_2 = H, X = *p*-ClC_6H_4N, Y = O): mp = 167−168 °C; IR (C═O) 1676 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.52−2.21 (m, 9H), 4.45 (d, 1H, J = 10.8 Hz), 4.98 (dd, 1H, J = 10.8 and 2.2 Hz), 5.74 (d, 1H, J = 17.3 Hz), 5.86 (d, 1H, J = 10.8 Hz), 6.35 (dd, 1H, J = 17.3 and 10.8 Hz), 7.70 (s, 4H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 20.71, 24.23, 25.26, 32.77, 37.49, 62.95, 68.35, 117.14, 120.83, 130.85, 131.39, 137.71, 143.07, 153.20. (C═O); MS (*m*/*e*) 291 $[M]^+$. Anal. Calcd for $C_{16}H_{18}ClNO_2$: C, 65.86; H, 6.22; N, 4.80. Found C, 66.03; H, 6.28; N, 4.78.

Single-Crystal X-ray Diffraction Study of 8a and 8f. Suitable crystals were selected, mounted on thin glass fibers using viscous oil, and cooled to the data collection temperature. Data were collected on a Bruker AX SMART 1k CCD diffractometer using 0.3° ω-scans at 0, 90, and 180° in ϕ. Unit-cell parameters were determined from 60 data frames collected at different sections of the Ewald sphere. No absorption corrections were required.

No symmetry higher than triclinic was evident from the diffraction data. Solution in *P*-1 yielded chemically reasonable and computationally stable results of refinement. The structures were solved by direct methods, completed with difference Fourier syntheses, and refined with full-matrix least-squares procedures based on F^2. All non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were treated as idealized contributions. All scattering factors and anomalous dispersion factors are contained in the SHEXTL 5.1 program library (Bruker AXS, 1997, Madison, WI).

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Supporting Information Available: The procedures for the preparations, spectral data, and ^1H and ^{13}C NMR spectra of **1c**−**e**; spectral data of compounds **4c**−**g**, **5c**−**k**, **8c**−**j**, and **9c**−**d**; ^1H and ^{13}C NMR spectra of compounds **4c**, **4g**, **5d**, **5e**, **8i**, **8j**, **9c**. Text giving full details of the X-ray structures of **8a** and **8f** including the experimental procedures, tables of crystal data, structure refinements, coordination parameters, bond lengths, bond angles, and anisotropic displacement parameters. This material is available free of charge via the Internet at http://pubs.acs.org.

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