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Decarboxylative Ring Contractions and Olefin Insertions of Vinyl Oxazinanones

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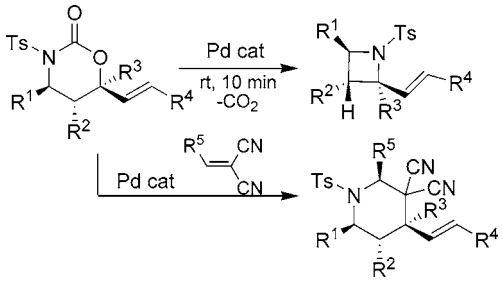
ABSTRACT



6-Vinyl oxazinanones undergo catalytic, diastereoselective, decarboxylative ring contraction to form vinyl azetidines in good yield. Performing the decarboxylation in the presence of Michael acceptors results in decarboxylative olefin insertion to provide diastereoenriched substituted vinyl piperidines.

Decarboxylative coupling is emerging as a powerful method for the formation of C−C and C−N bonds.[1,2] We recently reported that acyclic allylic carbamates undergo decarboxylative coupling under mild conditions to produce allylic amines.[2] On the basis of these experiments, it was expected that a related cyclization would allow facile generation of nitrogen-containing heterocycles that are common components of pharmaceuticals.

To begin, we addressed the challenge of developing a catalytic route from 1,3-amino alcohols to azetidines. Synthesis of azetidines by intramolecular substitution of 1,3-amino halide or 1,3-amino alcohol derivatives is often hampered by the slow kinetics for four-membered ring closure.[3] Thus, substitution reactions of this type often require long reaction times even when treated with a strong base at high temperatures.[4] Activation of 1,3-amino alcohols by PPh_3 in Mitsunobu-type reactions proceeds under milder conditions; however, yields are generally moderate (40−70%), and these reactions require stoichiometric phosphine activators in the presence of an oxidant (DEAD, Br_2, or CCl_4).[5] In addition to the poor atom economy of these reactions, the phosphine oxide byproduct is notorious for complicating product purification. Herein, we report that 2-vinylazetidines are readily available via diastereoselective ring contraction of 6-vinyl-1,3-oxazinanones where CO_2 is the only byproduct. Furthermore, 4-vinylpiperidines are available through decarboxylative cycloaddition of 6-vinyl-1,3-oxazinanones to Michael acceptors.

Initial experiments focused on the 6-vinyl-1,3-oxazinanone substrate **1a** which was prepared from the 1,3-amino alcohol by treatment with carbonyl diimidazole.[6] It is known that 6-vinyl-1,3-oxazinanones undergo ring opening and decar-

(1) (a) Rayabarapu, D. K.; Tunge, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 13510. (b) Burger, E. C.; Tunge, J. A. *Org. Lett.* **2004**, *6*, 4113. (c) Nakamura, M.; Hajra, A.; Endo, K.; Nakamura, E. *Angew. Chem., Int. Ed.* **2005**, *44*, 7248. (d) Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 17180. (e) Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M.; *Angew. Chem., Int. Ed.* **2005**, *44*, 6924. (f) Myers, A. G.; Tanaka, D.; Mannion, M. R. *J. Am. Chem. Soc.* **2002**, *124*, 11250. (g) Lou, S.; Westbrook, J. A.; Schaus, S. E. *J. Am. Chem. Soc.* **2004**, *126*, 11440. (h) Tsuda, T.; Chujo, Y.; Nishi, S.-I.; Tawara, K.; Saegusa, T. *J. Am. Chem. Soc.* **1980**, *102*, 6381. (i) Shimizu, I.; Yamada, T.; Tsuji, J. *Tetrahedron Lett.* **1980**, *21*, 3199.

(2) Mellegaard-Waetzig, S. R.; Rayabarapu, D. K.; Tunge, J. A. *Synlett* **2005**, 2759.

(3) (a) de Kimpe, N. *Comprehensive Heterocyclic Chemistry II*; 1996; 1B, p 507. (b) Yoda, H.; Uemura, T.; Takabe, K. *Tetrahedron Lett.* **2003**, *44*, 977.

(4) Huszthy, P.; Bradshaw, J. S.; Krakowiak, K. E.; Wang, T.; Dalley, N. K. *J. Heterocycl. Chem.* **1993**, *30*, 1197.

(5) (a) Stoilova, V.; Trifonov, L. S.; Orahovats, A. S. *Synthesis* **1979**, 105. (b) Freeman, J. P.; Mondron, P. J. *Synthesis* **1974**, 894.

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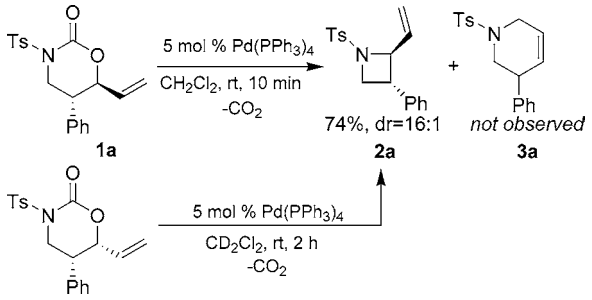
boxylation in the presence of palladium catalysts, and the intermediate palladium allyl complexes have been trapped by pendant nucleophiles and CO.[7] Previous results from this group suggested that such substrates would also undergo C−N bond formation in the absence of CO.[2] Indeed, allowing *trans*-**1a** (>19:1 dr) to react in the presence of 5 mol % of $Pd(PPh_3)_4$ in CH_2Cl_2 at 25 °C led to rapid evolution of CO_2 and formation of the vinyl azetidine **2a** in 74% yield with no observable formation of the tetrahydropyridine **3a** (Scheme 1).[8a] Interestingly, the ratio of diastereomers in the product

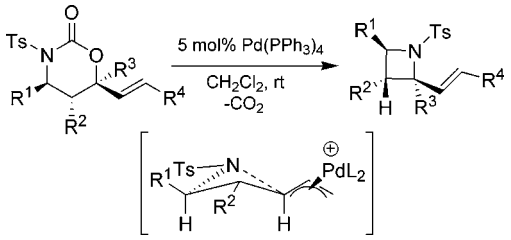
Scheme 1



azetidine (16:1) is slightly smaller than that of the starting material. This suggested that the diastereomers were interconverting on the time scale of the cyclization. To test this hypothesis, *cis*-**1a** was prepared and subjected to the same reaction conditions. Although the rate of the reaction with *cis*-**1a** was somewhat slower than that with *trans*-**1a**, the product was identical. Thus, epimerization through $\pi-\sigma-\pi$ allyl interconversion is faster than cyclization.[9] This is an important observation because it allows the synthesis of highly diastereoenriched azetidines from diastereomixtures of the cyclic allylic carbamates **1** (i.e., **2g**,**h**; Table 1).

Rapid formation of the vinyl azetidine can be explained by one of two possible mechanisms (Scheme 2). First, nitrogen may coordinate to palladium to form a five-membered metallacycle **A** that would give rise to the azetidine upon reductive elimination.[10] Second, a free nitrogen anion might preferentially undergo backside attack at the 4-carbon of π-allyl complex **B**. The two mechanisms are readily distinguished by the stereochemistry of the cyclization. Reductive elimination from a five-membered

Table 1. Yields and Diastereoselectivities for Decarboxylative Ring Contractions[a]

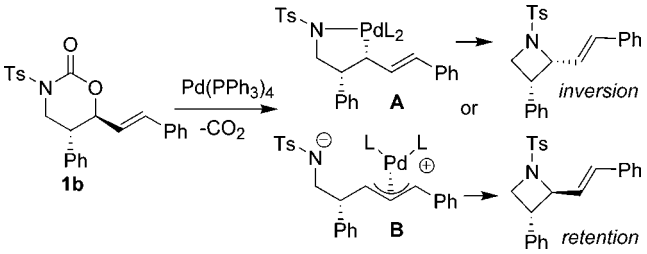


product	R^1	R^2	R^3	R^4	yield (dr)[b]
2a	H	Ph	H	H	74 (16:1)
2b	H	Ph	H	Ph	62 (>19:1)
2c	H	H	Ph	H	<1
2d	H	H	CH_3	H	<5
2e	H	*p*-ClC_6H_4	H	H	78 (>19:1)
2f	H	*p*-$MeOC_6H_4$	H	H	84 (14:1)
2g	H	CH_2Ph	H	H	60 (8.5:1)[c]
2h	H	$CH(CH_3)_2$	H	H	93 (>19:1)[c]
2i	Ph	H	H	H	92 (>19:1)
2j	CH_3	H	H	H	78 (8:1)

[a] Conditions. [b] Yield and dr of isolated product. [c] Prepared from ca. 1:1 *syn*/*anti*-**1**.

metallacycle should give overall inversion of stereochemistry, and backside attack by an amide anion should result in overall retention of stereochemistry.[11]

Scheme 2



The stereochemical analysis of the ring contraction can only be performed if the substrate does not epimerize. Therefore, substrate **1b** was chosen for study because the initial stereochemistry of the allyl alcohol cannot be lost by a $\pi-\sigma-\pi$ epimerization mechanism that is common for terminally unsubstituted π-allyl complexes. The azetidine formed from **1b** under our standard reaction conditions was shown to be the anti isomer by nOe experiments, indicating that the reaction proceeds with overall retention of stereochemistry. Thus, the reaction likely proceeds by backside attack of the amide anion on the π-allyl ligand.

Regarding the preferential four-member cyclization, Rutjes and Hiemstra have suggested a stereoelectronic origin for the regioselectivity of related cyclizations of β-aminoallenes.[8a] Monosubstituted palladium π-allyl complexes can adopt two

(6) (a) Liotta, D.; Zima, G.; Saindane, M. *J. Org. Chem.* **1982**, *47*, 1258. (b) Bando, T.; Tanaka, S.; Fugami, K.; Yoshida, Z.; Tamaru, Y. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 97.

(7) (a) Bando, T.; Tanaka, S.; Fugami, K.; Yoshida, Z.-i.; Tamaru, Y. *Bull. Chem. Soc. Jpn*. **1992**, *65*, 97. (b) Cook, G. R.; Shanker, P. S. *Tetrahedron Lett.* **1998**, *39*, 3405. (c) Cook, G. R.; Sund, L. *Org. Lett.* **2004**, *6*, 2481.

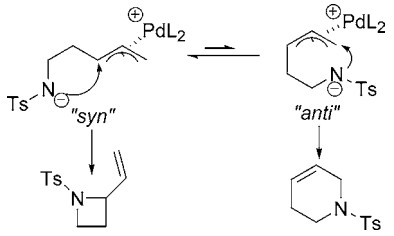
(8) Reductive cyclization of amino allenes can form mixtures of vinyl azetidines and tetrahydropyridines. (a) Rutjes, F. P. J. T.; Tjen, K. C. M. F.; Wolf, L. B.; Karstens, W. F. J.; Schoemaker, H. E.; Hiemstra, H. *Org. Lett*. **1999**, *1*, 717. (b) Anzai, M.; Toda, A.; Ohno, H.; Takemoto, Y.; Fujii, N.; Ibuka, T. *Tetrahedron Lett*. **1999**, *40*, 7393.

(9) Auburn, P. R.; Mackenzie, P. B.; Bosnich, B. *J. Am. Chem. Soc.* **1985**, *107*, 2033.

(10) Syn- and anti-addition mechanisms are competitive in intermolecular allylic amination reactions. (a) Cerezo, S.; Cortes, J.; Moreno-Manas, M.; Pleixats, R.; Roglans, A. *Tetrahedron* **1998**, *54*, 14869. (b) Trost, B. M.; Keinen, E. *J. Am. Chem. Soc*. **1978**, *100*, 7779.

(11) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc*. **1980**, *102*, 4730.

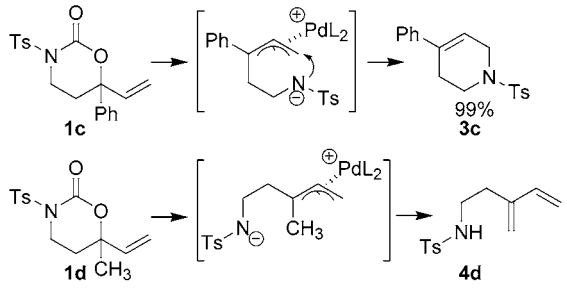
Scheme 3



conformations, and the syn conformation is thermodynamically favored because it avoids A1,3-strain (Scheme 3). Although the syn conformation can readily give rise to the vinyl azetidine, the anti conformation is required for formation of the tetrahydropyridine derivative.

To probe this mechanistic hypothesis, a 6-phenyl vinyloxazinanone **1c** was prepared. Such a substrate should prefer to place the sterically smaller amino alkyl fragment in the anti position and thus would be expected to preferentially form the tetrahydropyridine isomer (Scheme 4) if the Rutjes

Scheme 4

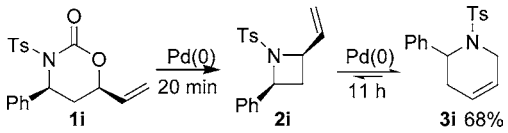


mechanism is correct. Indeed, treatment of **1c** under standard reaction conditions produced tetrahydropyridine **3c** in quantitative yield. Furthermore, scrutiny of the reaction progression by ^{1}H NMR spectroscopy showed no evidence for intermediate azetidine formation. Thus, it appears that, in contrast to the previous reactions that provide vinyl azetidines, tetrahydropyridine **3c** is the kinetic product. Similarly, the 6-methyl-substituted derivative **1d** was prepared and allowed to react with 5 mol % of $Pd(PPh_3)_4$ in CH_2Cl_2. In this case, deprotonation is favored, and diene **4d** is the only observable product of the reaction.

Although the above considerations obviate the formation of tertiary C−N bonds via decarboxylative ring contraction, other substitution patterns are allowed. For example, both 5-alkyl- and 5-aryl-substituted 1,3-oxazinanones provide good yields and selectivities for *trans*-1,2-vinyl azetidines (Table 1). The 4-substituted vinyl oxazinanones react similarly, but they provide the *syn*-1,3-vinyl azetidines with good diastereoselectivity. The stereochemical outcome for either case can be rationalized on the basis of the preference for substituents to occupy the pseudoequatorial positions of the four-membered transition state for cyclization.

On the basis of literature reports, the formation of vinyl azetidines is expected to be reversible.[8a,12,13] In accord, treatment of **1i** for 20 min at room temperature provides the vinyl azetidine **2i**;[14] however, prolonged standing in the presence of the Pd(0) catalyst results in complete conversion to the thermodynamically more stable tetrahydropyridine isomer **3i** (Scheme 5). Thus, the rapid reaction rate and mild

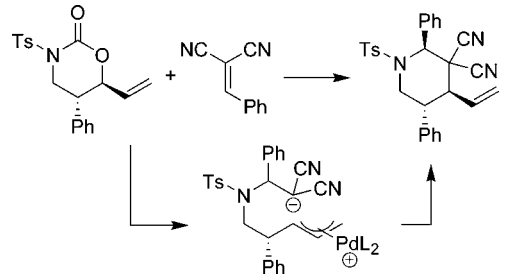
Scheme 5



conditions of azetidine formation are important because they obviate isomerization which can be significant at elevated temperatures.[8a]

In addition to the decarboxylative ring contractions, it was envisioned that the zwitterionic π-allyl intermediates would lend themselves to decarboxylative olefin insertion if the intermediate amide anion could be intercepted by a suitably electrophilic Michael acceptor.[15,16] The resulting stabilized carbanion could undergo addition to the π-allyl palladium fragment which would give rise to 4-vinyl piperidines (Scheme 6). Indeed, treatment of *rac*-**1a** with benzylidene

Scheme 6



malononitrile produced the vinyl piperidine as a single diastereomer in excellent yield.[17] The reaction is rapid, and vinyl azetidines are not observed as intermediates when the

(12) (a) Martorella, A.; Inman, G. A.; Alper, H. *J. Mol. Catal. A* **2003**, 91. (b) Satake, A.; Ishii, H.; Shimizu, I.; Inoue, Y.; Hasegawa, H.; Yamamoto, A. *Tetrahedron* **1995**, *51*, 5331.

(13) (a) Ibuka, T.; Mimura, N.; Aoyama, H.; Akaji, M.; Ohno, H.; Miwa, Y.; Taga, T.; Nakai, K.; Tamamura, H.; Fujii, N.; Yamamoto, Y. *J. Org. Chem.* **1997**, *62*, 999. (b) Ishii, K.; Ohno, H.; Takemoto, Y.; Osawa, E.; Yamaoka, Y.; Fujii, N.; Ibuka, T. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2155.

(14) Lowering the catalyst loading to 0.8 mol % of $Pd(PPh_3)_4$ led to quantitative conversion in 2 h.

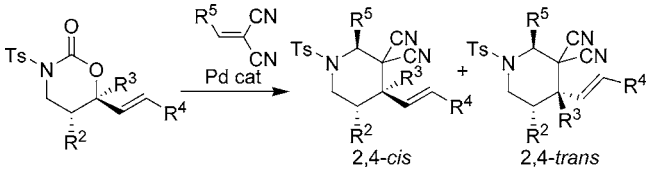
(15) Wang, C.; Tunge, J. A. *Org. Lett.* **2005**, *7*, 2137.

(16) For related cycloadditions, see: (a) Aoyagi, K.; Nakamura, H.; Yamamoto, Y. *J. Org. Chem.* **2002**, *67*, 5977. (b) Sekido, M.; Aoyagi, K.; Nakamura, H.; Kabuto, C.; Yamamoto, Y. *J. Org. Chem.* **2001**, *66*, 7142.

(17) Yamamoto has reported a similar cycloaddition of vinyl aziridines and methylene malononitriles that gives rise to pyrrolidine derivatives; however, the diastereoselectivities were low (3.3−1.2:1; see ref 16).

reaction is monitored by ^{1}H NMR spectroscopy. Once again, *cis*-**1a** provides the same product as *trans*-**1a**, indicating that π-allyl epimerization is faster than cyclization. Although the stereocontrol is good when the vinyl oxazinanone is substituted at C4, C5, or C6, the stereocontrol is not high when the vinyl oxazinanone is unsubstituted (i.e., **5j**,**k** trans/cis ~3:1, Table 2).

Table 2. Yields and Diastereoselectivities for Decarboxylative Olefin Insertions



product	R^2	R^3	R^4	R^5	yield (dr)[a,b]
5a	*p*-$MeOC_6H_4$	H	H	Ph	88 (>19:1)
5b	*p*-$MeOC_6H_4$	H	H	*p*-$AcOC_6H_4$	81 (>19:1)
5c	*p*-ClC_6H_4	H	H	Ph	87 (>19:1)
5d	*p*-ClC_6H_4	H	H	*p*-$AcOC_6H_4$	96 (>19:1)
5e	Ph	H	H	Ph	94 (>19:1)
5f	Ph	H	H	*p*-$AcOC_6H_4$	76 (>19:1)
5g	Ph	H	Ph	Ph	54 (10:1)
5h	Ph	H	Ph	*p*-$AcOC_6H_4$	53 (>19:1)
5i	Bn	H	H	Ph	66 (8.3:1)
5j	H	H	H	Ph	85 (1:3)
5k	H	H	H	*p*-$AcOC_6H_4$	99 (1:2.8)
5l	H	CH_3	H	Ph	99 (1:2)
5m	H	CH_3	H	*p*-$AcOC_6H_4$	92 (1:2)
5n	H	Ph	H	Ph	87 (1:>19)

[a] Yield and syn/anti ratio of isolated product. [b] >19:1 indicates that the minor diastereomer was not detected by ^{1}H NMR spectroscopy.

Although the preference for formation of 2,4-trans products, as determined by nOe experiments, from unsubstituted vinyl oxazinanones is difficult to explain, the diastereoselectivity of the substituted derivatives is straightforward. In these cases, the product is the result of cyclization through a conformation that places the larger groups in equatorial positions (Figure 1). Such an interpretation requires that the Michael addition is reversible, allowing the diastereoselectivity to be controlled by the relative barriers for cyclization.

Finally, the above cycloaddition can be applied to an annulation of cyanocoumarin (Scheme 7). Although the product was isolated in lower yield than other substrates, investigation of the reaction by ^{1}H NMR spectroscopy shows clean formation of **5n** in high yield. Furthermore, the annulation sets three contiguous stereocenters with high diastereoselectivity for syn addition to the coumarin.

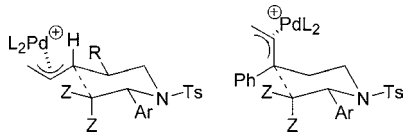
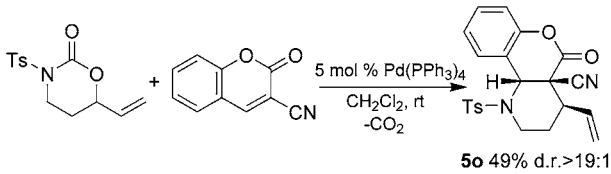


Figure 1. Preferred conformations.

Scheme 7



5o 49% d.r.>19:1

In summary, we have developed a unique ring contraction of cyclic carbamates that diastereoselectively produces vinyl azetidines. Moreover, decarboxylation of the vinyl oxazinanones in the presence of Michael acceptors results in cycloaddition to form highly substituted piperidines with good diastereoselectivity. Importantly, the reactions proceed under mild conditions and produce CO_2 as the only byproduct.

Acknowledgment. The authors thank the National Science Foundation (CHE-0548081) and the Petroleum Research Fund (44453-AC1) for financial support.

Supporting Information Available: Experimental procedures, spectroscopic data of all compounds, and crystal structures of **5n** and **5o**. This material is available free of charge via the Internet at http://pubs.acs.org.

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