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Catalytic Asymmetric Intramolecular Aminopalladation: Enantioselective Synthesis of Vinyl-Substituted 2-Oxazolidinones, 2-Imidazolidinones, and 2-Pyrrolidinones

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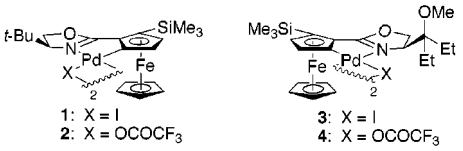
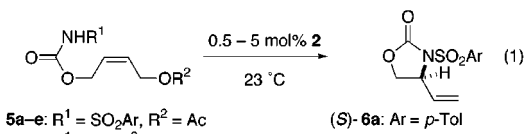
A variety of useful reactions are catalyzed by Pd(II) complexes.[1] Although the first example was described by Murahashi over 20 years ago,[2] only within the past few years has the potentially rich catalytic asymmetric chemistry of Pd(II) received wide attention.[3] In 1999 we reported that ferrocenyloxazoline palladacycles **2** and **4** were excellent catalysts for asymmetric rearrangement of prochiral allylic imidates to form enantioenriched allylic amides.[4] Intramolecular aminopalladation of the double bond is undoubtedly a central event in this rearrangement,[5] as it is in syntheses of numerous nitrogen heterocycles.[6] The use of ferrocenyloxazoline palladacycles (FOP catalysts) **2** and **4** to catalyze the asymmetric synthesis of five-membered nitrogen heterocycles is disclosed herein.



We began by studying the formation of 4-vinyloxazolidin-2-ones from readily available derivatives of (*Z*)-2-buten-1,4-diol (eq 1).[7] To keep the leaving group and the anionic ligand of the catalyst the same, the cyclization of allylic *N*-tosylcarbamate trifluoroacetate, **7**, with FOP trifluoroacetate catalyst **2** (generated in situ by deiodination of **1** with silver trifluoroacetate) was examined initially. Although vinyloxazolidinone (*S*)-**6a** could be formed in up to 79% ee (5 mol % catalyst, CH_2Cl_2, room temperature), the lability of the allylic trifluoroacetate group made this synthesis impractical. Bis-*N*-tosylcarbamate **8** also cyclized in CH_2Cl_2 at room temperature in the presence of 5 mol % of **2** to provide (*S*)-**6a** (72% yield and 79% ee),[8] comparable to the outcome achieved (95% yield and 78% ee) in the cyclization of alcohol precursor **9**. Cyclizations of allylic *N*-tosylcarbamate acetate **5a** were significantly better, providing (*S*)-**6a** in 96% yield and 86% ee under similar conditions. Further optimization showed that enantioselectivity was enhanced in more polar solvents, a 1:1 mixture of $CH_2Cl_2-MeNO_2$ being optimal in terms of both yield and enantioselection (>95% yield and 91−93% ee). Changing the anionic ligand by activating precatalyst **1** with other silver salts was also examined; however, all silver salts screened provided catalysts that were less satisfactory than **2**.[9]



5a–e: $R^1 = SO_2Ar$, R^2 = Ac
7: R^1 = Ts, $R^2 = COCF_3$
8: R^1 = Ts, R^2 = CONHTs
9: R^1 = Ts, R^2 = H
10: R^1 = *p*-$NO_2C_6H_4$, R^2 = Ac

(*S*)-**6a**: Ar = *p*-Tol
6b: Ar = Ph
6c: Ar = *o*-MeC_6H_4
6d: Ar = *p*-ClC_6H_4
6e: Ar = *p*-FC_6H_4

Table 1. Catalytic Asymmetric Synthesis of 3-Arylsulfonyl-4-vinyloxazolidin-2-ones (**6a**−**e**)

concentration (*M*)	catalyst (mol %)	product	yield (%)[b]	ee (%)[b,c]
1.0	**2** (5.0)	(*S*)-**6a**	96	91
	2 (1.0)		91	90
	2 (0.5)		86	91
2.0	**2** (5.0)		98	93
0.2			98	92
	4 (5.0)	(*R*)-**6a**	80	92
	2 (5.0)	**6b**	98	92
		6c	88	91
		6d	91	89
		6e	98	92

[a] Reactions conducted in 1:1 $CH_2Cl_2-MeNO_2$ at room temperature for 10−20 h; the starting (*Z*)-allylic carbamate was >98% isomerically pure. [b] Mean of 2−4 experiments. [d] HPLC analysis using a Chiracel OD-H column (±2%).

As summarized in Table 1, the efficient, highly enantioselective conversion of **5a** → (*S*)-**6a** can be accomplished under practical conditions: substrate concentrations up to 2 M, reaction times at room temperature of 10−20 h, and catalyst loadings as low as 0.5 mol %. Cyclization of **5a** with the pseudoenantiomeric FOP trifluoroacetate catalyst **4** delivered (*R*)-**6a** in similar high yield and enantioselectivity. Contributing to the practicality of this method, iodide-bridged dimers **1** and **3** are air- and moisture-stable precatalysts, which are activated in situ by reaction with silver trifluoroacetate.[10] High yields and enantioselectivities were realized in cyclizations of *N*-arylsulfonylcarbamates containing a range of aryl substituents (Table 1). The lack of reaction of substrates such as *p*-nitrophenylcarbamate **10** under identical conditions suggests that a highly acidic nitrogen nucleophile is required.[11] Also required is the *Z* configuration of the starting allylic *N*-arylsulfonylcarbamate, as the *E* stereoisomer of **5a** was transformed extremely slowly at room temperature (22% yield after 4 days, 5 mol % of **2**) to give (*R*)-**6a** of moderate enantiopurity (65% ee). The absolute configuration of (*S*)-**6a** was established by conversion to (*S*)-4-vinyloxazolidin-2-one;[12] the absolute configurations of **6b**−**6e** were assigned in analogy.

It is most convenient to form the allylic *N*-arylsulfonylcarbamate in situ by reaction of an allylic alcohol with an arylsulfonyl isocyanate. This modification is particularly useful with tertiary allylic alcohols whose derived allylic *N*-arylsulfonylcarbamates are prone to eliminate. Using this procedure, spirocyclic 4-vinyloxazolidin-2-ones **13a** and **13b** were prepared in high enantiopurity and good overall yield from cyclohexanone and *N*-*tert*-butoxyoxycarbonyl-4-piperidone (Scheme 1). To minimize competing ionization of the tertiary allylic *N*-tosylcarbamate intermediate, the cyclization step was carried out in CH_2Cl_2 using 5 mol % of the FOP trifluoroacetate catalyst. The high enantioselectivity (97−99% ee) realized in these reactions appears to be a general feature of catalytic asymmetric cyclizations of tertiary allylic *N*-tosylcarbam-

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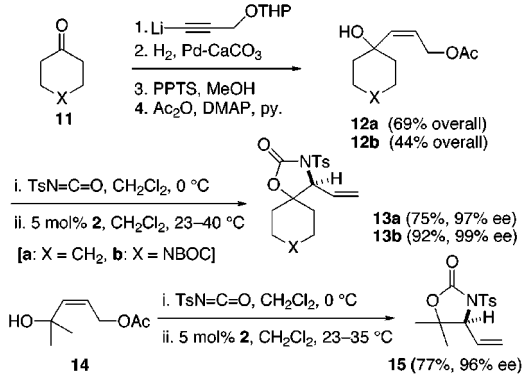
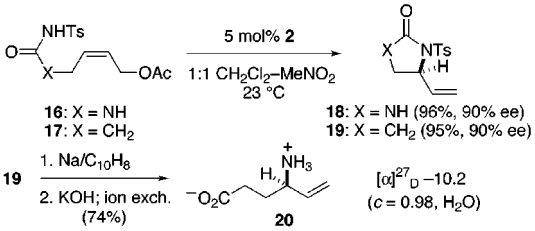
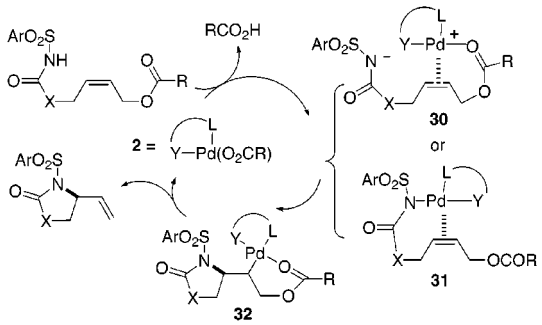
Scheme 1



Scheme 2



Scheme 3



ates with FOP trifluoroacetate catalysts, as **14** was converted to vinyloxazolidin-2-one **15** of 96% ee under identical conditions.[13−15]

Enantioenriched 2-pyrrolidinones and 2-imidazolidinones can be prepared in similar fashion (Scheme 2). The absolute configuration of pyrrolidinone **19** was secured by converting this product to the unnatural enantiomer of the powerful GABA inhibitor vigabatrin **20**,[16] whereas the absolute configuration of **18** was secured by single-crystal X-ray analysis.[14]

At least two general mechanisms can be considered for these catalytic asymmetric cyclization reactions (Scheme 3).[17] In one, the new C−N bond would be formed by aminopalladation of the alkene (**30** → **32**). In the other, it would be formed by insertion of the alkene into the Pd−N bond of **31**.[18] Alternative pathways involving η^3-allyl species and palladacyclic Pd(II) and Pd(IV) intermediates, or a conventional Pd(0)/Pd(II) catalytic cycle (the Pd(0) catalyst being some degradation product of the original palladacycle),[19] are unlikely.[20]

In summary, a new catalytic asymmetric synthesis of five-membered nitrogen heterocycles was developed. This synthesis employs palladacyclic Pd(II) catalysts and likely proceeds by a novel mechanism. We anticipate additional applications of FOP catalysts and other chiral Pd(II) complexes for catalytic asymmetric construction of heterocycles and carbocycles.

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Supporting Information Available: Preparation of representative rearrangement substrates (**5a**, **12a**, and **16**), representative catalytic asymmetric cyclizations (formation of (*S*)-**6a**, **13a**, and **18**), copies of HPLC traces used to determine enantiopurity, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) For examples of preparing nitrogen heterocycles by aminopalladation−deoxypalladation reactions using achiral Pd(II) catalysts, see: Hirai, Y.; Watanabe, J.; Nozaki, T.; Yokoyama, H.; Yamaguchi, S. *J. Org. Chem.* **1997**, *62*, 776−777 and references therein.

(8) Similar moderate enantioselection (77% ee in the best case) was reported earlier by Hayashi and Ito for cyclizations of bis-*N*-arylcarbamates of (*Z*)-2-buten-1,4-diol with Pd(0) catalysts having (hydroxyalkyl)ferrocenyldiphosphine ligands: Hayashi, T.; Yamamoto, A.; Ito, Y. *Tetrahedron Lett.* **1988**, *29*, 99−102.

(9) The following silver salts were examined: AgOAc, AgOBz, AgOTf, $AgBF_4$, $AgSbF_6$, $AgCB_{11}H_6Br_6$, and Ag(acac).

(10) In situ IR monitoring of this ligand exchange in CH_2Cl_2 indicated that 4 equiv of $Ag(OCOCF_3)$ were required to fully transform **1** into **2**. Control experiments established that **5a** (0.4 M in 1:1 CH_2Cl_2−$MeNO_2$) was unchanged when exposed at room temperature to 30 mol % of $Ag(OCOCF_3)$ for 18 h.

(11) $pK_a \approx 5$, see: Schaaf, T. K.; Hess, H.-J. *J. Med. Chem.* **1979**, *22*, 1340−1346.

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(13) The absolute configuration of **15** was determined by X-ray crystallography;[14] **13a** and **13b** were assigned by analogy.

(14) Absolute configuration was assigned by analysis of the anomalous dispersion using the Rogers's η parameter, see: Flack, H. D. *Acta Crystallogr*. **1983**, *A39*, 876−881.

(15) The acetyl regioisomer of **14**, (*Z*)-4-acetoxy-4-methyl-2-penten-1-ol analogue, gave 3-tosyl-4-(2-methylpropenyl)-oxazolidin-2-one in 95% yield, albeit in 25% ee, under similar conditions.

(16) For the state-of-the art in catalytic asymmetric synthesis of this agent, see: Trost, B. M.; Bunt, R. C.; Lemoine, R. C.; Calkins, T. L. *J. Am. Chem. Soc.* **2000**, *122*, 5968−5976.

(17) These mechanisms are undoubtedly oversimplified. The enantioselective step could involve interaction with a catalyst dimer; the FOP acetylacetonate catalyst, although kinetically competent for the **5a** → **6a** conversion, delivers **6a** as a racemate.

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(20) Evidence for this conclusion includes: (1) FOP catalysts are more reactive when they contain nondonor anionic ligands (RCO_2^-, TsO^-, NO_3^-, BF_4^-). (2) The reactions reported here take place under acidic conditions (added HOAc, 1−5 equiv has negligible effect on rate or ee). (3) Stereoisomeric alkene substrates cyclize in the presence of **2** to give enantiomeric 4-vinyloxazolidin-2-one products, whereas both alkene stereoisomers give the same 4-vinyloxazolidin-2-one enantiomer in related Pd(0)-catalyzed cyclization reactions.[8]

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