Palladium(II) Catalysed 5-*endo-trigonal* Cyclization of 2-Hydroxybut-3-enylamines: Synthesis of Five-membered Nitrogen Heterocycles

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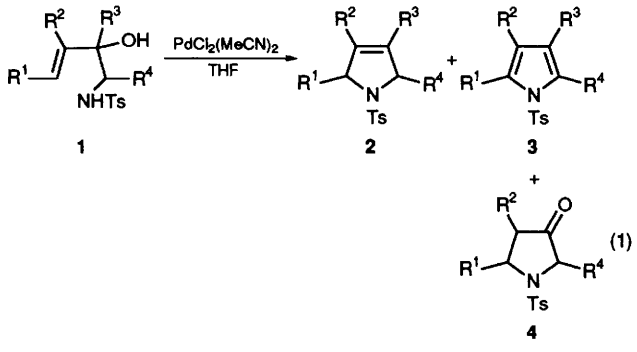
2-Hydroxybut-3-enylamines **1** undergo a novel Pd^{II}-catalysed 5-*endo-trigonal* cyclization to provide pyrrolines **2**, pyrroles **3**, and/or 3-oxopyrrolidines **4** in good to moderate combined isolated yields; the hydroxy group is essential for the cyclization.

Transition metal catalysed heterocyclic syntheses *via* intramolecular addition of heteronucleophiles to double and triple bonds have been well documented.[1] Among these studies, examples showing a 5-*endo-trig* mode of cyclization[2] are very scarce.[3] Here we disclose that 2-hydroxybut-3-enylamines **1** undergo an aminocyclization in a 5-*endo-trig* manner under the catalysis of palladium salts and provide five-membered nitrogen heterocycles, pyrrolines **2** and/or pyrroles **3** [eqn (1)]. In some cases, 3-oxopyrrolidines **4** are also formed as minor products.

For the cyclization of **1** to proceed, the allylic hydroxy group is essential. *N*-Tosyl-2-hydroxybut-3-enylamine **1a** underwent



cyclization to provide a mixture of pyrroline **2a** (55%) and pyrrole **3a** (22%)† when exposed to 0.2 equiv. of $PdCl_2(MeCN)_2$ in THF at room temp. for 21 h (run 1, Table 1), while *N*-tosylbut-3-enylamine, a dehydroxy derivative of **1a**, provided an intractable mixture of products that contained no cyclization products by treatment with 0.2–0.8 equiv. of $PdCl_2(MeCN)_2$. Furthermore, the cyclization depends on the kind of electrophiles. For example, no cyclization took place when **1a** was treated with some typical electrophiles, such as *N*-bromosuccinimide[4] (1.3 equiv. in THF–H_2O 10:1, room temp. 4 h) and PhSeCl[5] (1.0 equiv. in THF, room temp., 13 h, then 50 °C for 24 h).

The present Pd^{2+}-catalysed cyclization seems to be general and applicable to a variety of amines **1** with substituents at any skeletal carbon, and give **2**–**4** in good to moderate isolated yields (Table 1). Especially rewarding is the chemoselective cyclization that **1e** and **1f** display (runs 8–14). Since **1e** and **1f** possess allylic alcohol and allylic amine moieties at the same time, both the aminocyclization to provide **2**–**4** and the oxycyclization[3a] to furnish five-membered oxygen heterocycles, such as tetrahydrofurans and furans, are conceivable. However, **1e** and **1f** provided only the nitrogen heterocycles. No oxygen heterocycles were detected at all.

Chloride ion plays a crucial role in this cyclization. No reaction took place when $Pd(OAc)_2$ was used in place of $PdCl_2(MeCN)_2$ (runs 1 and 9, footnote *c*, Table 1). Excess

Table 1 Palladium(II) catalysed aminocyclization of 2-hydroxybut-3-enylamines **1**[a]

Run		Substrate **1** R¹	R²	R³	R⁴	Catalyst and additive (equiv.)	Reaction conditions *T*/°C (*t*/h)	Product[b] (% isolated yield) 2	3	4
1	**1a**	H	H	H	H	$PdCl_2(MeCN)_2$ (0.2)[c]	r.t.[d] (21)	**2a** (55)	**3a** (22)	
2	**1b**	Me	H	H	H	$PdCl_2(MeCN)_2$ (0.2)[e]	r.t. (22)	**2b** (77)	**3b** (5)	**4b** (4)
3	**1b**	Me	H	H	H	$PdCl_2(MeCN)_2$ (0.1) $CuCl_2$ (2.0)	r.t. (20)	**2b** (72)	**3b** (24)	
4	**1c**	H	Me	H	H	$PdCl_2(MeCN)_2$ (1.0)	r.t. (24), 50 (8)	**2c** (28)	**3c** (16)	
5	**1c**	H	Me	H	H	$PdCl_2(MeCN)_2$ (0.2) $CuCl_2$ (2.0)	r.t. (21), 50 (4)		**3c** (41)	
6	**1c**	H	Me	H	H	$PdCl_2(MeCN)_2$ (0.1) benzoquinone (1.0)	r.t. (40), 50 (4)	**2c** (18)	**3c** (40)	
7	**1d**	H	H	Me	H	$PdCl_2(MeCN)_2$ (0.3)	r.t. (24)		**3d** (78)	
8	*erythro*-**1e**	H	H	H	$CH=CH_2$	$PdCl_2(MeCN)_2$ (0.1)[f]	r.t. (1.5)	**2e** (83)	**3e** (7)	
9	*threo*-**1e**	H	H	H	$CH=CH_2$	$PdCl_2(MeCN)_2$ (0.1)[c]	r.t. (45)		**3e** (27)	
10	*threo*-**1e**	H	H	H	$CH=CH_2$	$PdCl_2(MeCN)_2$ (0.1)[g] $CuCl_2$ (2.0)	r.t. (25)	**2e** (18)	**3e** (47)	
11	*threo*-**1e**	H	H	H	$CH=CH_2$	$PdCl_2(MeCN)_2$ (0.1) benzoquinone (1.0)	r.t. (15)	**2e** (35)	**3e** (29)	
12	*threo*-**1e**	H	H	H	$CH=CH_2$	$PdCl_2(MeCN)_2$ (0.1) 1 atm. O_2	r.t. (22), 50 (4)	**2e** (19)	**3e** (41)	
13	*erythro*-**1f**	Me	H	H	$CH=CH_2$	$PdCl_2(MeCN)_2$ (0.5)[h]	r.t. (21)	*trans*-**2f** (19) *cis*-**2f** (12)		
14	*threo*-**1f**	Me	H	H	$CH=CH_2$	$PdCl_2(MeCN)_2$ (0.4)[h]	r.t. (20)	*cis*-**2f** (50)		*trans*-**4f** (9)

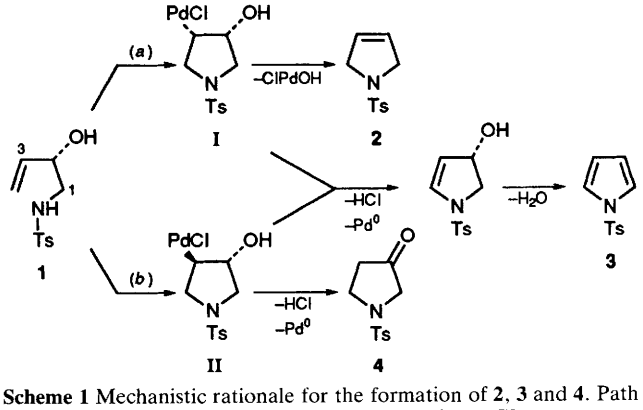
[a] Usual reaction conditions: **1** (1 mmol) in dry THF (5 ml, 15 ml for runs 3, 5 and 10) in the presence of the indicated amounts of catalysts and additives. [b] Isolated yields for the spectroscopically homogeneous products. [c] Complete recovery of **1** by the use of $Pd(OAc)_2$ (0.2 equiv. in THF) in place of $PdCl_2(MeCN)_2$. [d] r.t. = room temp. [e] **2b** (16%) and **3b** (9%) by an external addition of silver triflate (0.4 equiv., room temp. for 19 h, then 50 °C for 10 h). [f] Complete recovery of *threo*-**1e** in acetonitrile in place of THF. Intractable mixture of products in *N*,*N*-dimethylformamide. [g] No reaction by an external addition of LiCl (8.0 equiv. room temp., 24 h). [h] Scheme 2. [i] *N*-Tosyl-2-ethylidene-5-methyl-3-pyrrolidinone (4%) in addition to *cis*-**2f** and *trans*-**4f**.

chloride ion, externally added as LiCl (run 10, footnote *c*, Table 1), completely inhibits the reaction. Sequestration of chloride ion by silver cation causes diminution in the yield (run 2, footnote *d*, Table 1).

Selection of solvents is also important. Dry THF and 1,2-dimethoxyethane may be used successfully; however, solvents with high coordinating ability either retard (*e.g.* acetonitrile, run 8, footnote *e*, Table 1) or deteriorate the reactions (*e.g.* *N*,*N*-dimethylformamide, run 8, footnote *e*, Table 1).

Among the amines **1** examined, **1c** and *threo*-**1e** are exceptionally reluctant. For the completion of the reaction of **1c**, a stoichiometric amount of $PdCl_2(MeCN)_2$ and higher temperatures were required (run 4, Table 1). For such cases, $CuCl_2$ turned out to be effective promoters of the reaction and improved the isolated yields (runs 3, 5, and 10). Benzoquinone and molecular oxygen may be utilized with similar efficiency (runs 6, 11, and 12). These additives seem not only to serve as oxidants of Pd^0 to Pd^{II}, but also to affect the product distribution (Schemes 1 and 2).

The above-mentioned results suggest that the present cyclization starts with the coordination of Pd^{II} to the C3–C4 double bond of **1** and may be rationalized according the reaction paths outlined in Scheme 1.‡ The selective formation of **2** (runs 1, 2, 3, 8, 13 and 14) suggests a preferential *si*-face addition of $PdCl_2$ to form an intermediate **I**, which undergoes *syn*-dehydroxypalladation[6] to give **2** and Pd^{II}. Since Pd^{II} is regenerated, the transformation of **1** to **2** might be catalytic with respect to palladium.

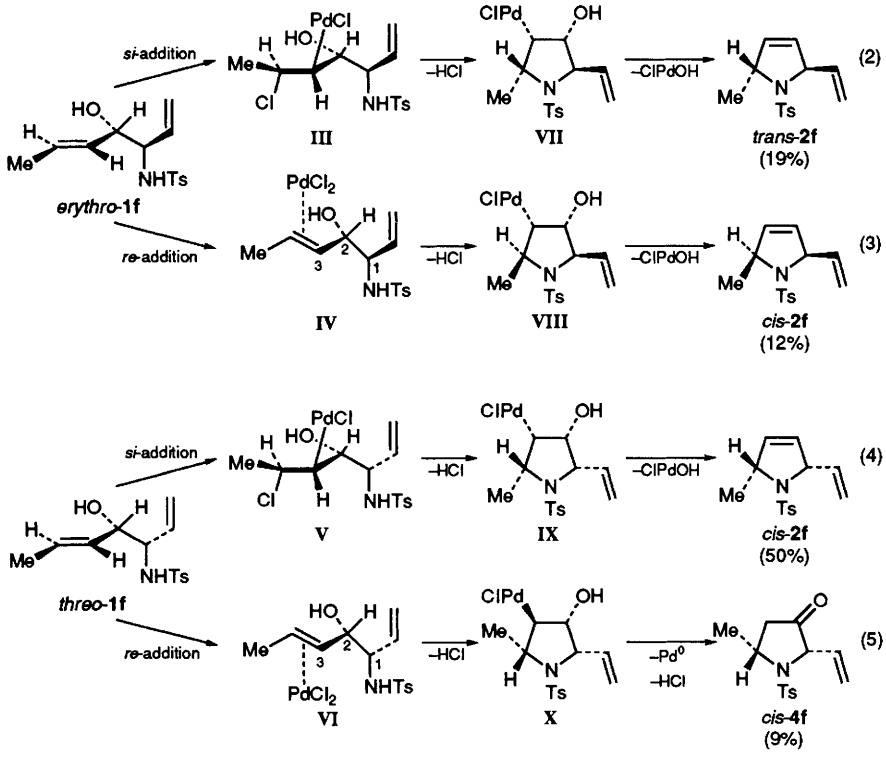


Scheme 1 Mechanistic rationale for the formation of **2**, **3** and **4**. Path (*a*) = *si*-addition; path (*b*) = *re*-addition of $PdCl_2$ at C3.

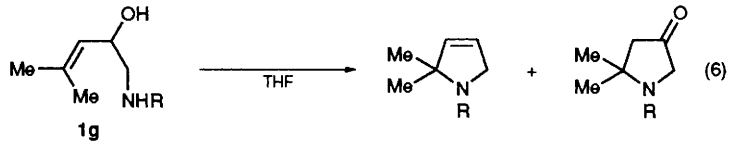
Pyrroles **3** seem to be formed through rather complex mechanisms. Two routes involving intermediates **I** and **II** are shown in Scheme 1. Both accompany a reduction of Pd^{II} to Pd^0 and should be stoichiometric with respect to Pd^{II}. Curiously, however, in some cases (*e.g.* runs 7 and 9, Table 1), pyrroles **3** are formed in larger amounts than the amount of $PdCl_2(MeCN)_2$ employed. Formation of **3** *via* an aromatization of **2** through an autoxidation or a Pd-catalysed dehydrogenation is unlikely, since **2c** was recovered when exposed to air in THF or to $PdCl_2(MeCN)_2$ (0.3 equiv. in THF) under either nitrogen or oxygen atmosphere. Furthermore, molecular hydrogen, expected to be evolved in an aromatization process, was not detected by VPC analyses (run 7, Table 1).

In order to shed more light on the reaction mechanism, a pair of stereoisomers of **1f**[7] were examined in detail (runs 13 and 14, Table 1 and Scheme 2). The formation of *trans*- and *cis*-**2f** from *erythro*-**1f** is the result of the selective *si*-face addition of $PdCl_2$ at C3 carbon [eqns. (2) and (3), Scheme 2], which may be attributed to the high electrophilic reactivity of the double bond in an eclipsing conformation with respect to the C2 hydroxy group,[8] and an approach of $PdCl_2$ to C3 from the less-hindered face of the double bond in the conformer. The formation of *trans*-**2f** is correlated through *trans* chloropalladation followed by a nucleophilic substitution of nitrogen for chlorine [eqn. (2)], while *cis*-**2f** through *trans* aminopalladation[9] *via* a coordination complex **IV** [eqn. (3)]. The formation of *cis*-**2f** and *cis*-**4f** from *threo*-**1f** may also be rationalized in a similar manner, where the minor product *cis*-**4f** stems from the unfavourable *re*-face *trans* aminopalladation through a complex **VI** [eqn. (5)].

Finally, the reaction of **1g** is remarkable [eqn. (6)], not only because it generates a quaternary C–N bond, but also because the usually least reactive acid amide nitrogen nucleophile[9]



Scheme 2 Mechanistic rationale for the cyclization of *erythro*- and *threo*-**1f**



$PdCl_2(MeCN)_2$ (0.5 equiv. room temp. 26h) **2g** R = Ts (22%) **4g** R = Ts (26%)
$PdCl_2(MeCN)_2$ (0.2 equiv. room temp. 20h) **2g** R = CO_2CH_2Ph (59%)
$PdCl_2(MeCN)_2$ (0.3 equiv. room temp. 26h) **2g** R = COPh (95%)

gives **2g** (R = COPh) in much greater yields than the sulfonamide and carbamate nitrogen nucleophiles.

The origin of product selectivity among **2–4**, *si- vs. re*-face selectivity, and one-sided aminocyclization rather than oxycyclization of **1e** and **1f**, as well as the selectivity of chloropalladation *vs.* aminopalladation, giving stereoisomeric intermediates, *e.g.* **VII** and **VIII**, respectively, is a subject to be pursued further.

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Footnotes

† All new compounds showed satisfactory spectral and analytical data.
‡ All reactions were undertaken with racemic **1**. For simplicity, only 2-(*R*)-isomers are indicated.

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