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Palladium-Catalyzed Cyclization of Unsaturated β-Amino Alcohols: A New Access to Enantiopure Bicyclic Oxazolidines

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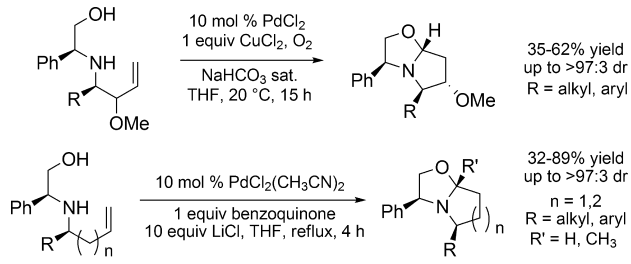
ABSTRACT



Chiral unsaturated β-amino alcohols possessing a dialkylamino function cyclize in the presence of Pd(II) catalysts and reoxidants to afford enantiopure bicyclic oxazolidines with total regio- and stereocontrol. The scope and limitations of this transformation have been studied.

Bicyclic oxazolidines are important intermediates in both synthetic and pharmaceutical chemistry. These compounds are interesting building blocks for the construction of nitrogen-containing heterocycles that constitute a tremendous class of biologically active compounds.[1,2]

The methodologies reported by Husson,[3] Katritzky,[4] and Higashiyama,[5] using bicyclic oxazolidines as key intermediates, have allowed enantioselective syntheses of many natural or unnatural derivatives containing a piperidine or a pyrrolidine framework and showed the relevance of developing new asymmetric syntheses of such products. In a previous paper, we reported the diastereoselective synthesis of various β-amino alcohols via addition of methoxyallyl anions on (*S*)-phenylglycinol-derived oxazolidines.[6] β-Amino alcohols **1**, obtained by addition of methoxyallyllithium, cyclized spontaneously in acidic medium to give bicyclic oxazolidines **2**. These appeared as good substrates for the asymmetric synthesis of proline derivatives **3** (eq 1).[7] On the other hand, addition of methoxyallylzinc bromide provided β-amino alcohols **4** bearing a terminal alkene function. We anticipated that **4** might cyclize in the presence of palladium(II) complexes and reoxidants to give trisubstituted bicyclic oxazolidines **5** (eq 2). Herein we describe our results concerning the development of this reaction and its application to a series of unsaturated β-amino alcohols.

(1) For the pioneering work in this field, see:(a) Meyers, A. I.; Harre, M.; Garland, R. *J. Am. Chem. Soc.* **1984**, *106*, 1146. (b) Meyers, A. I.; Lefker, B. A.; Sowin, T. J.; Westrum, L. J. *J. Org. Chem.* **1989**, *54*, 4243.

(2) Kadouri-Puchot, C.; Agami, C. *Asymmetric Synthesis of Nitrogen Heterocycles*; Royer, J., Ed.; Wiley-VCH, 2009; p 223, and references cited therein.

(3) Husson, H.-P.; Royer, J. *Chem. Soc. Rev.* **1999**, *28*, 383.

(4) Katritzky, A. R.; Cui, X.-L.; Yang, B.; Steel, P. J. *J. Org. Chem.* **1999**, *64*, 1979.

(5) Higashiyama, K.; Inoue, H.; Takahashi, H. *Tetrahedron* **1994**, *50*, 1083.

(6) Alladoum, J.; Roland, S.; Vrancken, E.; Kadouri-Puchot, C.; Mangeney, P. *Synlett* **2006**, 1855.

(7) Alladoum, J.; Roland, S.; Vrancken, E.; Mangeney, P; Kadouri-Puchot, C. *J. Org. Chem.* **2008**, *73*, 9771.

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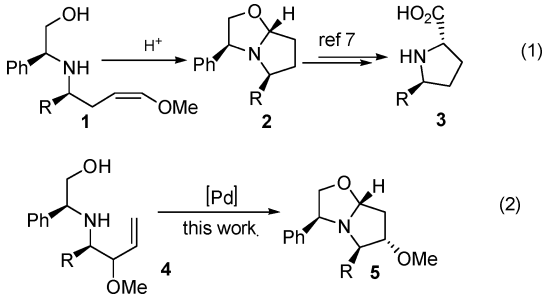
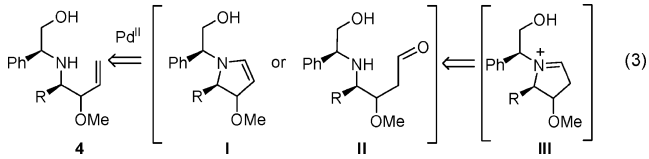
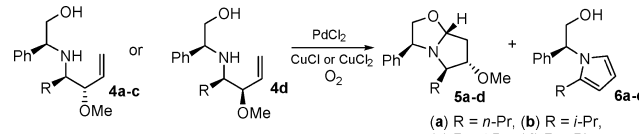


Since the pioneering works of Hegedus and co-workers,[8] the palladium-catalyzed intramolecular cyclization of unsaturated amines is a well-known method to synthesize azaheterocycles.[9] To the best of our knowledge, this reaction was not investigated with β-amino alcohols such as **4** having a homoallylic secondary amino group.[10] We expected that the enamine **I** or the aldehyde **II** could be obtained from **4** by an aza-Wacker or a Wacker reaction, respectively, and lead to the formation of the iminium ion **III**, which is a direct precursor of **5** (eq 3).[11] Examples of aza-Wacker reactions involving primary or secondary amino groups are relatively scarce.[12] Less basic acylated, tosylated, or aromatic amines are usually used for this transformation.[9] In the case where a Wacker reaction would be involved (formation of **II**), the oxidation must take place at the external terminal carbon of the double bond. It is known that oxidations of terminal alkenes under Wacker-type conditions generally afford the methyl ketone.[13] However, the preferential formation of the aldehyde was observed in some cases.[9c] For example, Nokami and co-workers obtained γ-butyrolactols through a regioselective oxidation of substituted 1-alken-4-ols at the terminal position of the alkene.[14]



This prompted us to study the cyclization of **4** under similar conditions ($PdCl_2$ 10 mol %, $CuCl_2$, O_2, DMF, 20 °C) (Table 1). This procedure proved to be efficient for the cyclization of **4a**−**d** and led to the formation of the expected oxazolidines **5** and/or pyrroles **6** with complete conversions (Table 1, entries 1−4). However, the pyrroles **6** were obtained as the major products together with a maximum of 30% of **5**. We assumed that the in situ formation of **6** could be favored by the presence of HCl, which is released during the reaction.

Table 1. Cyclization of Compounds **4** in the Wacker-Type Conditions: Effect of Bases on the Product Distribution



(**a**) R = *n*-Pr, (**b**) R = *i*-Pr, (**c**) R = *t*-Bu, (**d**) R = Ph

entry	sm	base (equiv)	solvent	**4/6/5** (%)[a,b]
1	**4a**	none	DMF	0/100/0
2	**4b**	none	DMF	0/90/10
3	**4c**	none	DMF	0/85/15
4	**4d**	none	DMF	0/70/30
5	**4b**	NaOH 2 M (5)	DMF	100/0/0
6	**4b**	AcONa 1 M (5)	DMF	0/48/52
7	**4b**	AcONa 2 M (3)	DMF	15/5/80
8	**4b**	$NaHCO_3$ sat.	DMF	0/5/95
9	**4b**	$NaHCO_3$ sat.	THF	0/0/**100** (35%)[c]
10	**4c**	$NaHCO_3$ sat.	THF	0/0/**100** (62%)[c]
11	**4d**	$NaHCO_3$ sat.	THF	0/0/**100** (54%)[c]

[a] Conditions: $PdCl_2$ 10 mol %, $CuCl_2$, O_2, 20 °C, 15 h. [b] Determined by ^1H NMR of the crude mixture [c] Isolated yield after chromatography.

A second set of experiments was then performed with **4b** in the same conditions by adding various bases (Table 1, entries 5−8). The reaction was completely inhibited in the presence of NaOH (entry 5), but the use of sodium acetate allowed the yield of **5b** to increase significantly and limited the formation of the pyrrole **6b** (entries 6 and 7). The best results were obtained when an aqueous $NaHCO_3$ solution was added to the reaction mixture. In this case, a 95:5 ratio of **5b/6b** was obtained (entry 8). Finally, changing the solvent from DMF to THF afforded exclusively the expected oxazolidine **5b** (entry 9). This protocol proved to be also efficient for the transformation of **4c**−**d** into the oxazolidines **5c**−**d** (entries 10 and 11). The expected oxazolidines **5b**−**d** were isolated in 35−62% yields. A single diastereoisomer is detectable by ^1H NMR of the crude reaction mixtures. The configurations of bicyclic oxazolidine **5b** were established from the DIFNOE ^1H NMR data which demonstrate that the three substituents *i*-Pr, Ph, and H are located in the same half-space. The relative configuration of compound **5d** was assigned from an X-ray analysis. Surprisingly, a cis relationship between the three substituents *i*-Pr, Ph, and H was also found in this case indicating that an inversion of configuration at the carbon bearing the methoxy substituent occurred during the reaction.[15,16]

(8) (a) Hegedus, L. S. *Organometallic in Synthesis*; Schlosser, M., Ed.; John Wiley& Sons, 2002; p 1137. (b) Hegedus, L. S.; McKearin, J. M. *J. Am. Chem. Soc.* **1982**, *104*, 2444. (c) Harrington, P. J.; Hegedus, L. S. *J. Org. Chem.* **1984**, *49*, 2657. (d) Harrington, P. J.; Hegedus, L. S.; McDaniel, K. F. *J. Am. Chem. Soc.* **1987**, *109*, 4355.

(9) For recent reviews on aminopalladation, see:(a) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285. (b) Minatti, A.; Muñiz, K. *Chem. Soc. Rev.* **2007**, *36*, 1142. (c) Beccali, E. M.; Broggini, G.; Martinelli, M.; Sottocornolla, S. *Chem. Rev.* **2007**, *107*, 5318.

(10) Cyclizations of β-amino alcohols having an allylic amine moiety have been reported. In this case, cyclic acetals or hemiacetals are obtained through nucleophilic attack of the hydroxy group at the double bond. See: Lai, J.-Y.; Shi, X.-X; Gong, Y.-S.; Dai, L.-X. *J. Org. Chem.* **1993**, *58*, 4775.

(11) Several strategies, reported in the literature for the synthesis of bicyclic oxazolidines, are based on the transient formation of cyclic iminium ions. For a review, see :Royer, J.; Bonin, M.; Micouin, L. *Chem. Rev.* **2004**, *104*, 2311–2352.

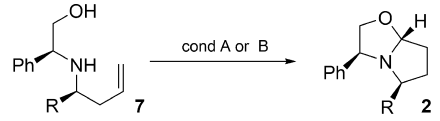
(12) Pugin, B.; Venanzi, L. M. *J. Am. Chem. Soc.* **1983**, *105*, 6877.

(13) For a recent review of the Wacker oxidation, see:Cornell, C. N.; Sigman, M. S. *Inorg. Chem.* **2007**, *46*, 1903.

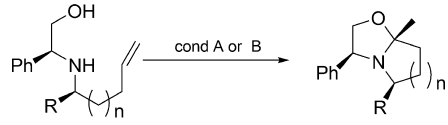
(14) Nokami, J.; Ogawa, H.; Miyamoto, S.; Mandai, T.; Wakabayashi, S.; Tsuji, J. *Tetrahedron Lett.* **1988**, *29*, 5181.

Encouraged by these results, we decided to study the scope and the limitations of this reaction. A series of chiral β-amino alcohols **7**−**9** without a methoxy group at the allylic position were synthesized. These compounds differ in the length of the chain bearing the double bond and in the nature of the R-group. The cyclizations of **7**−**9** were performed using two catalytic systems: the classic Wacker-type conditions (conditions A) and conditions using $PdCl_2(CH_3CN)_2$ as the catalyst, reported by Hegedus, which proved to be efficient for the intramolecular amination of olefins (conditions B).[8]

Table 2. Pd^{II}-Catalyzed Cyclization of β-Amino Alcohols **7**, **8**, and **9**



(a) R = H, **(b)** R = *i*-Pr, (**c**) R = *t*-Bu, (**d**) R = Ph



8 n = 1
9 n = 2

10 n = 1
11 n = 2

(b) R = *i*-Pr, (**c**) R = *t*-Bu, (**d**) R = Ph

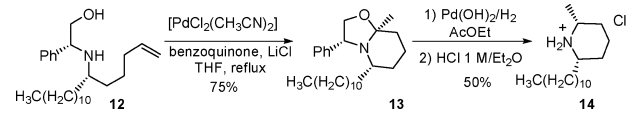
entry	amino alcohol	oxazolidine	yield[a, b]
1	**7a**	**2a**[c,d]	traces
2	**7b**	**2b**	58[d], 89[e]
3	**7d**	**2d**	84[d], 75[e]
4	**8b**	**10b**	75[e]
5	**8c**	**10c**	86[e]
6	**8d**	**10d**	65[e,f]
7	**9b**	**11b**	32[d], 80[e]
8	**9c**	**11c**	77[e]
9	**9d**	**11d**	76[e]

[a] After purification by flash silica gel chromatography. [b] Only one diastereoisomer was observed by ^1H NMR spectra of the crude mixture. [c] A complex mixture was obtained in which **2a** and **7a** were detectable. [d] Conditions A: $PdCl_2$ (0.1 equiv), $CuCl_2$ (1 equiv), AcONa 2 M (3 equiv), DMF, rt, 15 h. [e] Conditions B: $[PdCl_2(CH_3CN)_2]$ (0.1 equiv), benzoquinone (1 equiv), LiCl (10 equiv), THF, reflux, 4 h. [f] Isolated together with 8% of a nonidentified byproduct (not separable).

The results, presented in Table 2, show the importance of the R substituent. No selectivity was observed when the cyclization was performed from **7a** (R = H, entry 1). On the other hand, the methoxy group initially present in **4** is not essential. When R is an alkyl or aryl group, the bicyclic oxazolidines **2**, **10**, and **11** were obtained in 32−89% yields as single diastereomers (entries 2−9). Comparison of the two catalytic systems using **7b**, **7d**, and **9b** showed that the Hegedus conditions led to comparable or significantly higher yields than the Wacker-type conditions (entries 2, 3, and 7). Conditions B applied to **7**−**9** afforded the oxazolidines in 65−89% isolated yields (entries 2−9). For $n = 1$ and 2, the reaction gave in good yields, respectively, the bicyclic oxazolidines 5/5 **10** and 5/6 **11** containing an angular methyl group. These cyclizations occurred with total stereoselectivity: substituents R, R′, and Ph are in a *cis*-position.[15]

To illustrate the efficiency of this cyclization, we synthesized (2*R*,6*S*)-isosolenopsine A[17] in two steps from amino alcohol **12** (Scheme 1). Treatment of **12** with catalytic $PdCl_2(CH_3CN)_2$ in the presence of benzoquinone and LiCl produced the bicyclic oxazolidine **13** with an excellent diastereoselectivity (de > 93%) and in 75% yield. Hydrogenolysis with the Pearlman catalyst led to isosolenopsine **14** in an enantiomerically pure form.

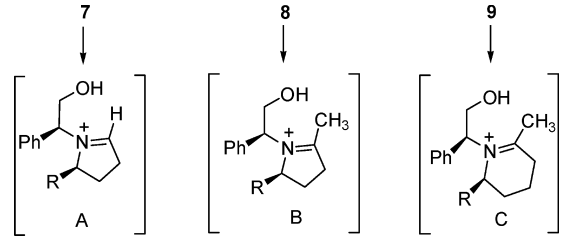
Scheme 1. Asymmetric Synthesis of (−)-Isosolenopsine A **14**



Although our data cannot clearly establish the mechanism of these transformations (Wacker or aza-Wacker-type reactions), a route involving the preferential formation of the iminium ions (**A**, **B**, and **C**) leading to the more stable bicyclic oxazolidines (respectively, **2**, **10**, and **11**), can account for the regio- and stereoselectivity of these cyclizations (Scheme 2).

Concerning the regioselectivity, five-membered rings (iminiums **A** and **B**, respectively from **7** and **8** leading to [5,5] oxazolidines **2** and **10**) and six-membered rings (iminium **C** from **9** leading to [5,6] oxazolidine **11**) are likely favored. The stereoselective formation of the stereocenter at the ring junction leads also to the more stable bicyclic oxazolidines where the carbon−oxygen bond is formed in an anti position relative to the phenyl and R substituents.[11]

Scheme 2. Iminium Ions Probably Involved in the Cyclization Reactions



In summary, the catalyzed reactions described herein provide access to valuable structures with total control of

(15) CCDC719372 for **5d** and CCDC719373 for **10b** contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(16) A reversible β-elimination involving the hydrogen atom on the carbon bearing the methoxy group and leading finally to the more stable oxazolidine **5d** could explain the epimerization observed during the cyclization of **4d**.

(17) For examples, see:(a) Singh, O.; Han, V. H. *Org. Lett.* **2004**, *6*,

selectivity. Further explorations of this palladium chemistry and studies on the synthetic applications of the bicyclic oxazolidines are actively in progress.

3067. (b) Amat, M.; Llor, N.; Hidalgo, J.; Escolano, C.; Bosch, J. *J. Org. Chem.* **2003**, *68*, 1919. (c) Monfray, J.; Gelas-Mialhe, Y.; Gramain, J.-C.; Remuson, R. *Tetrahedron: Asymmetry* **2005**, *16*, 1025. (d) Wang, X.; Dong, Y.; Sun, J.; Xu, X.; Li, R.; Hu, Y. *J. Org. Chem.* **2005**, *70*, 1897. (e) González-Gómez, J. C.; Foubelo, F.; Yus, M. *Synlett* **2008**, 2777. (f) Ciblat, S.; Besse, P.; Papastergiou, G. I.; Veschambre, H.; Canet, J. -L.; Troin, Y. *Tetrahedron: Asymmetry* **2000**, *11*, 2221.

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Supporting Information Available: Experimental procedure and characterization data of amino alcohols and bicyclic oxazolidines. This material is available free of charge via the Internet at http://pubs.acs.org.

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