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Communications

Synthesis of *N*-Boc-Protected 1-Amino-3-alken-2-ols from Allylic Carbamates via Palladium(II)-Catalyzed Oxidative Cyclization

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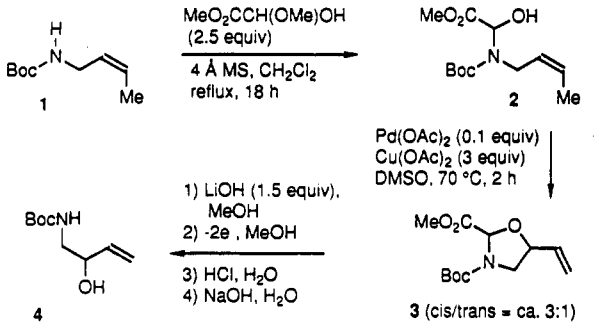
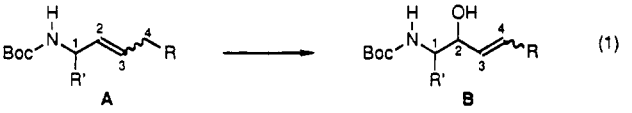
Summary: Methyl glyoxylate adducts of *N*-Boc-protected allylic amines cyclize in the presence of catalytic $Pd(OAc)_2$ and excess $Cu(OAc)_2$ in DMSO to 5-(1-alkenyl)-2-(methoxycarbonyl)oxazolidines. These heterocycles are readily converted to unsaturated *N*-Boc-protected β-amino alcohols through anodic oxidation and mild hydrolysis.

A highly successful method for controlling the regio- and stereochemistry of olefin functionalization reactions is the intramolecular approach employing a detachable connection at the allylic position. There are numerous examples of this concept for both electrophile-induced nucleophilic cyclizations[1] and radical cyclization processes.[2,3] The selectivity of this methodology is, at least partly, due to the considerable preference of 5-hexenyl nucleophiles and 5-hexenyl radicals to cyclize in the 5-exo mode. Palladium(II)-mediated oxidative cyclizations of 5-hexen-1-ols also show a high preference for 5-membered-ring formation, viz. oxygen-containing heterocycles.[4] We now wish to report the use of this Pd(II)-mediated cyclization for the selective functionalization of the double bond of *N*-Boc-protected allylic amines.[5]

Scheme I



The key transformation of this paper is schematically shown in eq 1. The *N*-Boc-protected allylic amine **A** is



(1)

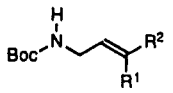
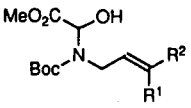
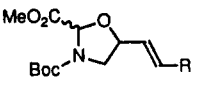
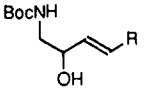
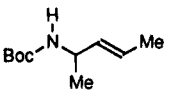
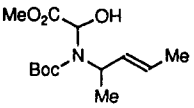
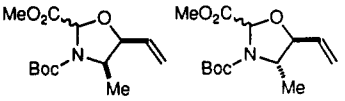
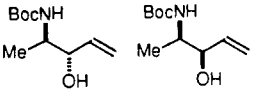
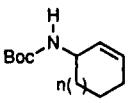
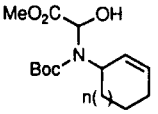
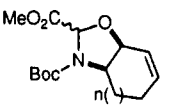
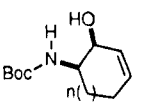
converted into the corresponding homoallylic amine through a shift of the double bond with concomitant introduction of a hydroxyl function at C-2. Important features of this transformation are the geometry of the double bond in **A** and **B** and the relative configuration at C-1 and C-2 in **B**.

To illustrate the individual steps, the use of *N*-Boc-protected (*Z*)-3-butenylamine **1** as starting material will be discussed in detail. Carbamate **1** was treated with an excess (2.5 equiv) of the methanol hemiacetal of methyl glyoxylate in CH_2Cl_2 containing 4-Å molecular sieves to give the stable adduct **2**[6] in 68% yield after flash chromatography. On stirring the adduct **2** for 5 h in DMSO

(1) Review: Cardillo, G.; Orena, M. *Tetrahedron* **1990**, *46*, 3321.
(2) Review: Stork, G. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 149.
(3) (a) Nishiyama, H.; Kitajima, T.; Matsumoto, M.; Itoh, K. *J. Org. Chem.* **1984**, *49*, 2298. (b) Tamao, K.; Maeda, K.; Yamaguchi, T.; Ito, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4984. (c) Koot, W. J.; Van Ginkel, R.; Kranenburg, M.; Hiemstra, H.; Louwrier, S.; Moolenaar, M. J.; Speckamp, W. N. *Tetrahedron Lett.* **1991**, *32*, 401. (d) Stork, G.; Suh, H. S.; Kim, G. *J. Am. Chem. Soc.* **1991**, *113*, 7054.
(4) Review: Hosokawa, T.; Murahashi, S.-I. *Heterocycles* **1992**, *33*, 1079.
(5) For earlier examples of the selective functionalization of allylic carbamates, see, e.g.: (a) Pauls, H. W.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1980**, *102*, 3956. (b) Overman, L. E.; McCready, R. J. *Tetrahedron Lett.* **1982**, *23*, 4887. (c) Parker, K. A.; O'Fee, R. *J. Am. Chem. Soc.* **1983**, *105*, 654. (d) Cardillo, G.; Orena, M.; Sandri, S. *J. Org. Chem.* **1986**, *51*, 713. (e) Cardillo, G.; Orena, M.; Sandri, S.; Tomasini, C. *Tetrahedron* **1985**, *41*, 163.
(6) For the synthesis and other applications of such adducts, see: Esch, P. M.; Hiemstra, H.; De Boer, R. F.; Speckamp, W. N. *Tetrahedron* **1992**, *48*, 4659 and references cited therein.

0022-3263/92/1957-6083$03.00/0

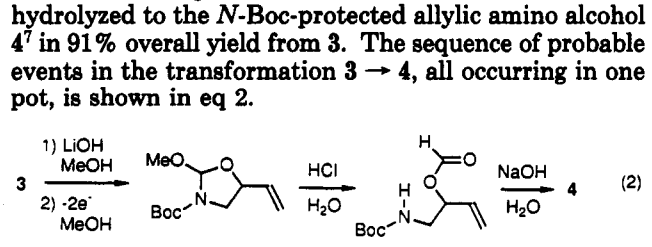
Table I. Synthesis of *N*-Boc-Protected 1-Amino-3-alken-2-ols from Allylic Carbamates[a]

starting allylic carbamate	*N,O*-hemiacetal (% yield, isomer ratio)	Pd(II)-mediated cyclization: reaction time[b] (h)	Pd(II)-mediated cyclization: product (% yield, isomer ratio)	product of anodic oxidation and hydrolysis (% yield)
				
1 R^1=Me, R^2=H	**2** (68)	2	**3** R=H (76, 3:1)	**4** R=H (91)[d]
5 R^1=H, R^2=Me	**6** (58)	5	**3** R=H (64, 1:1)	[c]
7 R^1=Pr, R^2=H	**8** (78)	10	**9** R=Et (80, 3:1)	**10** R=Et (87)[e]
11 R^1=H, R^2=Pr	**12** (83)	24	**9** R=Et (56, 1:1)	[c]
13 R^1=Me, R^2=Me	**14** (78)	>24	no cyclization	
				
15	**16** (64, 1:1)	7	**17** (32, 3:2) **18** (46, 3:2)	**19** (93) **20** (93)
				
21 n=0	**22** (76, 1:1)	1	**23** (85, 1:1)	**24** (92)[f]
25 n=1	**26** (80, 1:1)	5	**27** (70, 1:1)	**28** (88)
29 n=3	**30** (35, 1:1)	24[g]	**31** (49, 3:1)	**32** (76)[h]

[a] For reaction conditions see text and Scheme I; yield refers to yields of isolated and purified (flash chromatography) products; isomer ratios are given for inseparable isomers and are determined by ^{1}H NMR (OC*H*CH=C signals integrated); stereochemical assignments are based on NOE experiments. [b] For a complete reaction according to TLC. [c] Products with different isomer ratio's were mixed prior to anodic oxidation. [d] Mp 48–50 °C. [e] Mp 56–58 °C. [f] Mp 33–35 °C. [g] Reaction not complete. [h] Mp 122–123 °C.

at 70 °C in the presence of 0.1 equiv of $Pd(OAc)_2$ and excess of the oxidant $Cu(OAc)_2$ the key cyclization took place in 76% yield. The vinyl-substituted oxazolidine **3**[7] was obtained as a ca. 3:1 mixture of isomers. No 6-membered-ring cyclization products could be detected indicating the great preference for the 5-exo cyclization mode.[4] Furthermore, no other double-bond isomers were formed. The conditions used could be important for obtaining such a clean reaction, as it is well-known that DMSO enhances the regioselectivity of alkene formation,[4,8] while the use of acetate salts suppresses Pd-catalyzed olefin isomerization.[4]

For the removal of the acetic ester moiety connecting N and O the employment of an electrochemical method appeared most convenient. The methyl ester **3** was first saponified with a slight excess of LiOH in methanol. The resulting lithium salt was subjected to anodic oxidation[9] in methanol to provide an ortho ester which was then hydrolyzed to the *N*-Boc-protected allylic amino alcohol **4**[7] in 91% overall yield from **3**. The sequence of probable events in the transformation **3** → **4**, all occurring in one pot, is shown in eq 2.



(2)

The broad applicability of the transformation **A** → **B** (eq 1) is illustrated in Table I. The use of (*E*)-olefin **6** led to the same cyclization products **3**, now in a ca. 1:1 mixture of isomers. Interestingly, the cyclization of the (*E*)-olefin proceeded more slowly than the (*Z*)-olefin, the former requiring 5 h for complete reaction according to TLC. A similar rate difference was found in the cyclization of the precursors from (*E*)- and (*Z*)-hexenyl carbamates **7** and **11**. The olefin geometry in the starting material appeared inconsequential for the olefin geometry in the product, as (*E*)-**10**[7] was eventually obtained as the sole product. The trisubstituted olefin **14** failed to cyclize.

The methyl glyoxylate adduct **16** from racemic **15** cyclized to a mixture of four isomeric 2,4,5-trisubstituted oxazolidines. The 4,5-cis/trans ratio 17/18 appeared to be 43:57. This was proven through conversion of the mixture of four isomers into an inseparable mixture of the *anti*- and *syn*-amino alcohol derivatives **19** and **20** in high yield.[10] Via rather tedious flash chromatography a small amount of **17** and **18** could be obtained pure. Either isomer mixture **17** and **18** was also individually transformed into **19** and **20**, respectively.

Contrary to the *linear* carbamate **15**, the cyclization precursors derived from *cyclic* carbamates **21**, **25**, and **29** gave ring closure with very high cis-stereoselectivity. Thus, the *N*-Boc-protected β-amino alcohols **24**, **28**, and **32** were eventually obtained as single isomers. The *cis*-stereochemistry of **28** was confirmed through hydrogenation (H_2, 10% Pd/C, MeOH) to the known *N*-Boc-protected *cis*-2-aminocyclohexanol (mp 101–103 °C (lit.[11] mp 103–104 °C)).

(7) New compounds were appropriately characterized by using IR and ^{1}H and ^{13}C NMR spectroscopy and showed correct high-resolution mass data and/or combustion analyses.

(8) Semmelhack, M. F.; Kim, C. R.; Dobler, W.; Meier, M. *Tetrahedron Lett.* **1989**, *37*, 4925.

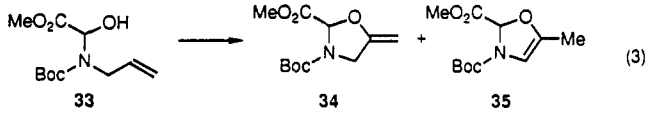
(9) See, e.g.: Seebach, D.; Charczuk, R.; Gerber, C.; Renaud, P.; Berner, H.; Schneider, H. *Helv. Chim. Acta* **1989**, *72*, 401 and references cited therein.

(10) For a different approach to this type of structure, see: Evans, P. A.; Holmes, A. B.; Russell, K. *Tetrahedron Asymmetry* **1990**, *1*, 593.

(11) Herranz, E.; Biller, S. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1978**, *100*, 3596.

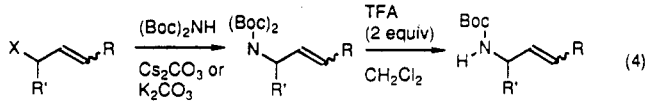
Remarkably, the cyclization to cyclopentene **23** appeared to be the fastest of all substrates tried, while cyclization to cyclooctene **31** was very slow. Clearly, the rate of the Pd(II)-mediated cyclization process is very sensitive to geometrical factors.

The reaction behavior of the parent allylcarbamate **33** was also briefly examined. Although in this case the usual elimination direction was not available (eq 3), cyclization did proceed (same conditions, 3 h) to give the 5-methyleneoxazolidine **34**[7] in 52% yield and a small amount of the double bond isomer **35** (ca. 5%).



(3)

The starting allylic carbamates were best prepared by using di-*tert*-butyl imidodicarbonate[12] as the nucleophile in an allylic substitution reaction on the corresponding halides with K_2CO_3 or Cs_2CO_3 as the base, followed by treatment with TFA for clean removal of one Boc-group (eq 4).[13,14]



(4)

(12) Ragnarsson, U.; Grehn, L. *Acc. Chem. Res.* **1991**, *24*, 285. For a convenient large-scale synthesis of this nitrogen nucleophile, see: Grehn, L.; Ragnarsson, U. *Synthesis* **1987**, 275.

(13) Connell, R. D.; Rein, T.; Åkermark, B.; Helquist, P. *J. Org. Chem.* **1988**, *53*, 3845.

To summarize, we have shown that allylic amines can be converted into 1-amino-3-alken-2-ols in a short reaction sequence involving three key steps: (1) *N,O*-hemiacetal formation from methyl glyoxylate, (2) Pd(II)-mediated oxidative cyclization, and (3) anodic oxidation (see Scheme I). The regioselectivity of the transformation is high in all cases, while the stereoselectivity is only high when starting from 3-aminocycloalkenes. When compared to the halocyclocarbamation route,[5] the advantage of the present method is the great ease and selectivity of olefin formation.[15] Applications of this methodology to enantiopure systems from α-amino acids and to natural products like the sphingosines[16] will be reported in due course.

Acknowledgment. We thank Professor P. W. N. M. van Leeuwen for useful discussions and the Innovation Oriented Research Program on Catalysis of the Dutch Ministry of Economic Affairs for financial support.

Supplementary Material Available: General experimental procedures for hemiacetal formation, cyclization, and anodic oxidation and spectral and analytical data for new compounds (10 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(14) Details of these synthesis will be provided in a full paper.

(15) The same type of unsaturated β-amino alcohol has been prepared from 1,3-dienes: Garigipati, R. S.; Weinreb, S. M. *J. Am. Chem. Soc.* **1983**, *105*, 4499.

(16) See, e.g.: Dondoni, A.; Fantin, G.; Fogagnolo, M.; Pedrini, P. *J. Org. Chem.* **1990**, *55*, 1439 and references cited therein.

Prismene: A Theoretically Predicted Target for Experimental Studies

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Summary: Two isomers of dehydroprismane with different positions of the double bond are calculated by quantum mechanical ab initio methods as minima on the C_6H_4 potential energy surface, and the most stable one with a double bond between a four-membered and a three-membered ring should be detectable in appropriate experiments.

The successful violation of bonding rules is a well-respected discipline in synthetic chemistry, challenging the skills of the inventive chemist. One example concerns the so-called Bredt's rule,[1] which implies the prohibition of bridgehead double bonds. Theoretical studies of strained molecules[2] and experimental efforts to synthesize molecules which violate Bredt's rule have led to the direct or indirect detection of a large number of highly strained compounds.[3] Such efforts are not only valuable for sharpening the skills of the synthetic chemists, they are also important to find out the limits of molecular stabilities. An important milestone to probe the validity of Bredt's rule is 1,2-didehydrocubane (cubene), which was predicted in 1988[4] by quantum mechanical calculations as an observable molecule. This prediction was subsequently confirmed by the synthesis of the highly strained cubene.[5]

In this paper, we report the results of ab initio calculations[6] which predict that the even higher strained and stronger pyramidalized dehydroprismane **1** is an observable species which should be detectable by appropriate experiments. The dehydrogenation of prismane may yield two isomeric alkenes, the tent-shaped prismene[7] (**1a**), in

(1) Bredt, J.; Thouet, H.; Schnitz, J. *Liebigs Ann. Chem.* **1924**, *437*, 1.

(2) Borden, W. T. *Chem. Rev.* **1989**, *89*, 1095.

(3) (a) Szeimies, G. In *Reactive Intermediates*; Abramovitch, R. A., Ed.; Plenum Press: New York, 1983; Vol. 3, p 299. (b) Warner, P. M. *Chem. Rev.* **1989**, *89*, 1067. (c) Hassenrück, K.; Martin, H.-D.; Walsh, R. *Chem. Rev.* **1989**, *89*, 1125. (d) Billups, W. E.; Haley, M. M.; Lee, G.-A. *Chem. Rev.* **1989**, *89*, 1147.

(4) Hrovat, D. A.; Borden, W. T. *J. Am. Chem. Soc.* **1988**, *110*, 4710.

(5) Eaton, P. E., Maggini, M. *J. Am. Chem. Soc.* **1988**, *110*, 7230.

(6) The geometries and vibrational frequencies were calculated at HF/6-31G(d) and MP2/6-31G(d) using GAUSSIAN 90: Frisch, M. J., Head-Gordon, M.; Trucks, G. W.; Foreman, J. B.; Schlegel, H. B.; Raghavachari, K.; Robb, M. A.; Binkley, J. S.; Gonzalez, C.; DeFrees, D. J.; Fox, D. J.; Whiteside, R. A.; Seeger, R.; Melius, C. F.; Baker, J.; Martin, R.; Kahn, L. R.; Stewart, J. J. P.; Topiol, S.; Pople, J. A. Gaussian Inc., Pittsburgh, PA, 1990. Geometry optimizations have also been carried out with a two-configuration (TCSCF) wave function and a 6-31G(d) basis set using the program GAMESS: Dupuis, M.; Spengler, D.; Wendolowski, J. I. NRCC QG01, Berkeley, 1980. Present version: Schmidt, M. W.; Baldridge, K. K.; Boatz, J. A.; Jensen, J. H.; Koseki, S.; Gordon, M. S.; Nguyen, K. A.; Windus, T. L.; Elbert, S. T. North Dakota State University, 1990.

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