

A Stereoselective Approach to 1,3-Amino Alcohols Protected as Cyclic Carbamates: Kinetic vs. Thermodynamic Control

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Dedicated to Barry M. Trost on the occasion of his 65th birthday

Keywords: Palladium / Allylation / 1,5-Diols / Carbamates / Aldol reactions

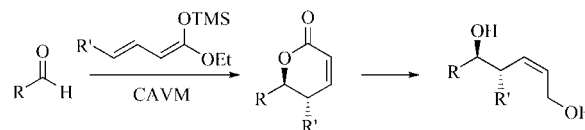
Direct enantiocontrolled access to 1,3-amino alcohols protected as cyclic carbamates is described. The approach is based on the addition of a silyl dienolate to aldehydes in the presence of 10 % of Carreira's catalyst (vinylogous Mukaiyama-aldol addition). The obtained δ -hydroxyesters were reduced to pent-2-ene-1,5-diols, which were converted into the corresponding dicarbamates with tosyl isocyanate. Stereose-

lective cyclization of these dicarbamates proceeded with 1,3-asymmetric induction under either thermodynamic or kinetic control to afford enantioselectively six-membered-ring cyclic carbamates. Calculations enabled us to rationalize the observed stereoselectivity.

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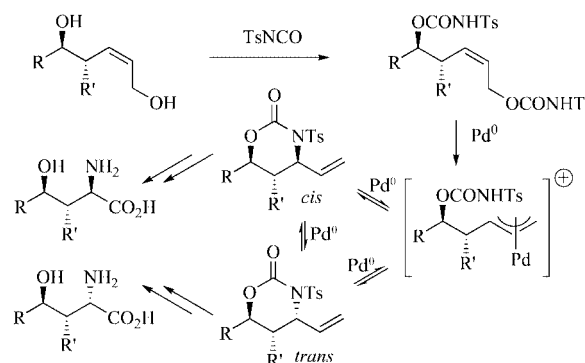
Introduction

Catalytic methods for the stereoselective formation of new chiral centers are used extensively in organic synthesis.^[1] In some cases, the success of these approaches has overcome the traditional use of chiral auxiliaries.^[2] Nevertheless, transferring chirality by substrate control is probably still the most common way to create stereocenters. In this context and as a part of a program directed at the synthesis of polyols^[3] and hydroxy amino acids,^[4] we were interested in the development of catalytic addition processes that could generate an initial chiral center that, in turn, could transfer its chirality to the neighboring atoms. Particularly, we focused our attention on the synthesis of 1,3-amino alcohols and γ -hydroxy α -amino acid substructures. Our idea for the generation of the first chiral center was based on our experience in the catalytic and asymmetric vinylogous Mukaiyama reactions (CAVM, Scheme 1).^[5] These types of additions have already proved to be very effective in yielding highly enantioenriched 2-alkene-1,5-diols via an α,β -unsaturated δ -lactone.^[6]



Scheme 1. Catalytic asymmetric vinylogous Mukaiyama-aldol addition.

We expected these diols to react with tosyl isocyanate to give the corresponding dicarbamates, which could be cyclized to 1,3-oxazinan-2-ones with 1,3-asymmetric induction (Scheme 2). Indeed, on the basis of related previous work,^[7] we anticipated that the stereochemistry of the final product would be thermodynamically driven by equilibration through the π -allyl intermediate. If this was the case,



Scheme 2. Pd⁰ cyclization.

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the stereochemical outcome of the reaction could be deduced from the relative stability of the two stereoisomers (*cis* and *trans*).

Results and Discussion

Before embarking on the synthesis of these compounds, our initial efforts were directed towards the determination of the relative energy of the possible diastereoisomeric oxazinan-2-ones, and, hence, the prediction of the thermodynamic stereoselectivity of the cyclization by computational means (DFT methods).^[8] Calculations were carried out on representative cyclized products **1–4** (Figure 1) having an aryl or alkyl substituent at the 6-position and a methyl group (*anti*) or a hydrogen atom at the 5-position.^[9] The chiral centers at the 5- and 6-positions were fixed and the two epimers at C-4 were explored (named as *cis* and *trans* indicating the C-4–C-6 relative configuration).

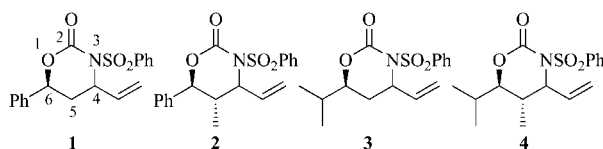


Figure 1. Cyclic carbamates.

First, we examined the conformational equilibrium of compounds **1–4** in either their *cis* or *trans* configuration (Table 1). This study revealed that, in all cases, the substituent at the 6-position (Ph/*i*Pr) prefers to be pseudoequatorial, especially for the *trans* isomers. A detailed analysis of the structures (see Supporting Information) indicates that the preference for this pseudoequatorial position can mainly be accounted for by the presence of a 1,3-diaxial interaction in the pseudoaxial conformer. A 1,3-diaxial destabilizing interaction of R¹ with the aromatic phenylsulfonyl group is also possible.

Another important structural feature is the presence of a stabilizing C–H···O hydrogen bond between one oxygen atom of the sulfonyl group and the pseudo-axial vinylic substituent (see Supporting Information) in the case of a pseudoaxial positioning of this later. Additionally, in conformers having the vinylic substituent in a pseudoequatorial position a destabilizing *gauche* interaction is present. These two interactions contribute to an additional relative stabilization of the conformers having the vinylic substituent in the pseudoaxial position (e.g. *cis*-pseudoaxial and *trans*-pseudoequatorial structures), which accounts for the larger axial/equatorial discrimination in the case of the *trans* conformers.

Having determined the lowest-energy conformer for each diastereoisomer, we investigated the *trans/cis* equilibrium (Table 2). Computed relative energies for the two diastereoisomers of the oxazinan-2-ones indicated a systematic higher stability for the *trans* isomer (over the *cis*). This lower energy of the *trans* isomer can mainly be explained by

Table 1. Conformational analysis of **1–4**.^[8]

Entry	R ¹	R ²	Isomer	ΔE [kcal/mol] ^[a]
1	Ph	H	<i>cis</i> - 1	2.2
2	Ph	H	<i>trans</i> - 1	4.2
3	Ph	Me	<i>cis</i> - 2	3.2
4	Ph	Me	<i>trans</i> - 2	6.6
5	<i>i</i> Pr	H	<i>cis</i> - 3	2.7
6	<i>i</i> Pr	H	<i>trans</i> - 3	2.8
7	<i>i</i> Pr	Me	<i>cis</i> - 4	1.8
8	<i>i</i> Pr	Me	<i>trans</i> - 4	4.2

[a] $\Delta E = E_{\text{(equatorial)}} - E_{\text{(axial)}}$.

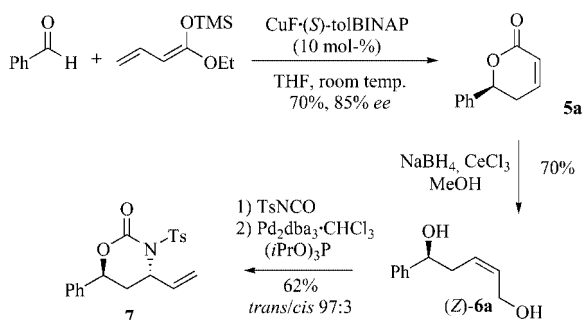
the preference of the vinylic group to be in the pseudoaxial position (vide supra), which is the case in the *trans* isomers (and not in the *cis* ones).

Table 2. Calculation of the *trans/cis* equilibrium.^[8]

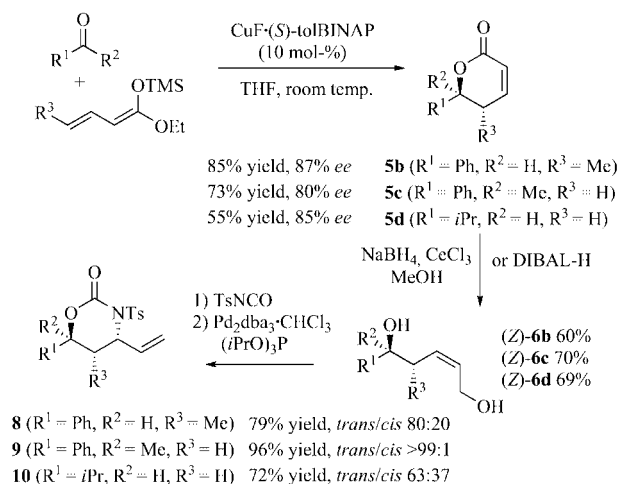
Entry	R ¹	R ²	Product	<i>cis</i> [kcal/mol]	<i>trans</i> [kcal/mol]	Predicted <i>trans/cis</i> ^[a]
1	Ph	H	1	1.4	0	91:9
2	Ph	Me	2	0.7	0	76:24
3	<i>i</i> Pr	H	3	0.9	0	80:20
4	<i>i</i> Pr	Me	4	0.1	0	54:46

[a] Ratio predicted at room temp.

From the above calculations one can conclude that if thermodynamically controlled the synthesis of the cyclic carbamates should be, in most cases, stereoselective, especially for product **1**. Therefore, the synthesis of **7** (related to **1**) was first attempted (Scheme 3). α,β -Unsaturated lactone **5a** was obtained by using a CAVM reaction in 70% yield and 85% *ee*. Reduction of the lactone was then carried out in the presence of NaBH₄/CeCl₃, which led to 1,5-diol (*Z*)-**6a**. Treatment of the diol with an excess of tosyl isocyanate, followed by a palladium-catalyzed Tsuji–Trost reaction,^[10] led to a clean conversion to the corresponding cyclic carbamate in 62% yield and a 97:3 *trans/cis* ratio.^[11] This result was in good agreement with the computed thermodynamic selectivity (91:9 *trans/cis* ratio; Table 2) and thus supported our hypothesis that the diastereoselectivity in the cyclization was under thermodynamic control.

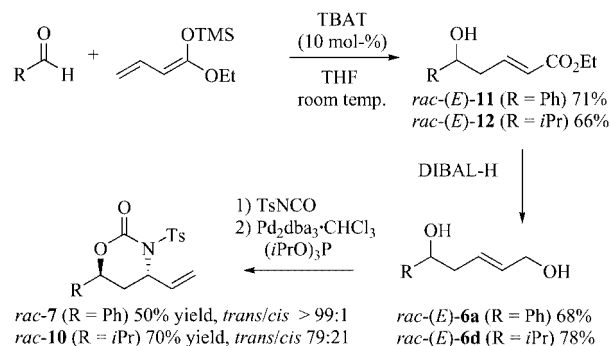
Scheme 3. Synthesis of **7**.

Encouraged by these positive preliminary results, the syntheses of **8**, **9** (possessing a chiral tertiary alcohol), and **10** were next investigated (Scheme 4). α,β -Unsaturated lactones **5b–d** were obtained in good yields and enantioselectivities from the corresponding aldehydes (or ketones) and were next reduced to 1,5-diols (**Z**)-**6b–d**. Cyclizations were carried out in the presence of $\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3$ to give cyclic carbamates **8**, **9**, and **10** in 79, 96, and 72% yield, respectively. Once again stereoselectivities were in good agreement with calculations, resulting in a 80:20, >99:1, and 63:37,^[12] *trans/cis* ratio, respectively.^[11]

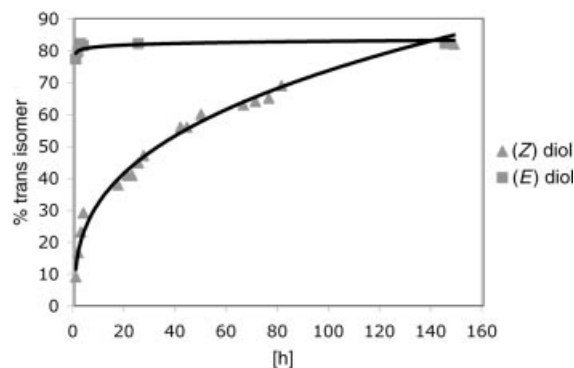
Scheme 4. Synthesis of cyclic carbamates **8–10**.

To obtain further evidence in support of the thermodynamic control of the *trans/cis* ratio, the cyclization of racemic 1,5-diols (**E**)-**6a** and (**E**)-**6d** was next investigated. Indeed, because an (**E**)- or (**Z**)-allylic system initially generates different π -allyl intermediates, which would lead to different carbamates, an influence of the stereochemistry of the olefin on the kinetic selectivity should be expected.

Diols (**E**)-**6a** and (**E**)-**6d** were obtained in two steps by using a racemic TBAT-mediated vinylogous Mukaiyama reaction followed by DIBAL-H reduction.^[5d] The cyclization of the diols with the use of the TsNCO diprotection–Pd-cyclization sequence gave cyclic carbamates (*rac*)-**7** and (*rac*)-**10** in a >99:1 and 79:21 *trans/cis* ratio, respectively (Scheme 5).

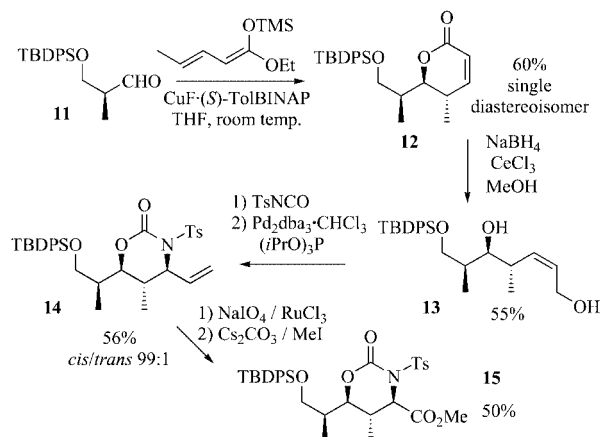
Scheme 5. (**E**)-Diols cyclization.

As shown, cyclization of 1,5-diol (**E**)-**6d** gave a higher *trans/cis* ratio than the corresponding (**Z**)-**6d** isomer (79:21 vs. 63:37), but closer to the predicted (by calculations) thermodynamic selectivity (80:20). This result either indicates that cyclization of (**Z**)-**6d** was mainly ruled by kinetic control or that the 66 h reaction time was not sufficient to reach thermodynamic equilibrium. Thus, we decided to monitor the cyclization–isomerization process of (**Z**)-**6d** and (**E**)-**6d** in $[\text{D}_8]\text{THF}$ by ^1H NMR spectroscopy (Figure 2). As shown, the (**E**) diol gave a high *trans* ratio immediately, whereas the (**Z**) isomer initially gave the *cis* isomer, but it then isomerized into the *trans* isomer very slowly (it took 145 h to reach the equilibrium and gave a 82:18 *trans/cis* ratio). This experiment thus demonstrated that the kinetic product in the cyclization of (**Z**) diols was the *cis* isomer but that equilibration occurred under reaction conditions leading to the more stable isomer; the *trans* cyclic carbamate. In the case of (**E**) diol cyclizations, the *trans* oxazinan-2-ones appeared to be both the kinetic and thermodynamic product.

Figure 2. Monitoring of the cyclization–isomerization process of the (**E**)-**6d** and (**Z**)-**6d** isomers.

The above experiment suggested that, in certain cases, the control of the final relative stereochemistry could be achieved under kinetic conditions, leading to the *cis* isomer. The requirements should be fast cyclization to the *cis* isomer and slow *cis*-to-*trans* isomerization. We anticipated that a good candidate would be a (**Z**)-1,5-diol with a large group at C-6 and a methyl group at C-5, which would hinder the isomerization.

Keeping this idea in mind, we prepared lactone **12** as a single diastereoisomer by starting from enantiomerically pure TBDPS-protected Roche's aldehyde **11** in 60% yield (Scheme 6). Reduction of the lactone to 1,5-diol **13**, followed by the protection–cyclization sequence led to cyclized product **14** in 56% yield and a deserving 99:1 *cis/trans* ratio.^[11,13]



Scheme 6. Carbamate **14**.

The high *cis* selectivity (99:1) observed in the first place in the case of **14** can thus be accounted for by: (1) a low thermodynamic discrimination between the two isomers (see calculations: Table 2, Entry 4) and (2) a large decrease in the rate of the equilibration reaction. This decrease in rate may well be due to the increase in sterics in the proximity of the double bond; in the pseudoequatorial conformer (the more stable one), the methyl indeed hinders one face of the double bond, whereas the tosyl group hinders the other one (see Figure 3 for the structure of **4**, which is closely related to **14**).

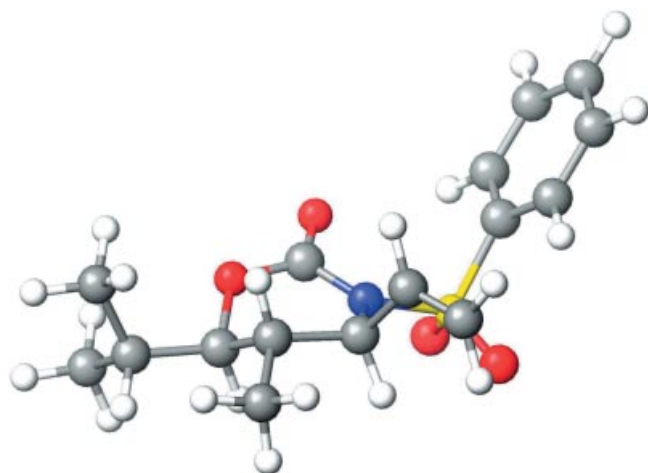


Figure 3. Lowest energy conformer of **4**.

Finally, in a desire to explore the development of new compounds with antidiabetic properties and structurally related to 4-hydroxyisoleucine,^[14] we envisaged the conversion of the protected amino alcohol **14** into the protected γ -hydroxy- α -amino acid **15** (Scheme 6). Thus, an oxidative

cleavage of the terminal double bond of **14**, followed by the esterification of the corresponding carboxylic acid, led to the protected γ -hydroxy- α -amino acid **15** in a (nonoptimized) yield of 50%.

Conclusions

Cyclic carbamates **7–10** can be easily obtained by a three-step process: (1) CAVM stereoselective addition of a silyl dienolate to aldehydes (or ketones), (2) reduction of the obtained lactone to a pent-2-ene-1,5-diol, and (3) dicarbamate formation followed by an *in situ* Pd⁰-mediated cyclization. These types of cyclizations seemed to be thermodynamically controlled under the used cyclization conditions, leading selectively to the *trans* cyclic carbamates. Nevertheless, it was possible to slow down the isomerization process that leads to the thermodynamic stereoisomer in some sterically crowded substrates such as carbamate **14** and, therefore, the kinetic stereoisomer (*cis*) can be isolated.

Experimental Section

Typical Procedure for the Pd-Catalyzed Cyclization of 1,5-Diols: *p*-Toluenesulfonyl isocyanate (92.4 μ L, 0.61 mmol, 2.5 equiv.) was added to a solution of diol **6** (0.24 mmol, 1 equiv.) in anhydrous THF (1.2 mL) under an atmosphere of N₂ at room temp. When the reaction was complete (TLC monitoring), the catalyst solution was added by cannula. This catalyst solution was prepared by adding (iPrO)₃P (21.4 μ L, 87.2 μ mol, 0.36 equiv.) to (dba)₃Pd $\cdot$ CHCl₃ (15 mg, 14.5 μ mol) in anhydrous THF (1.2 mL) and stirring at room temp. for 90 min. until a yellow color was obtained. The reaction mixture was stirred at room temp. for 24 h. The solvent was removed, and the residue was purified by flash column chromatography (heptane/EtOAc) to give the corresponding cyclic carbamates.

Supporting Information (see footnote on the first page of this article): Full computational details, optimized cartesian coordinates, and corresponding energies for all species discussed in the text, and characterizations for cyclized compounds **8**, **9**, **10**, **14**, and **15**.

Acknowledgments

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- [8] Calculations were carried out at the B3LYP/6-311+G**//B3LYP/6-31G* level of theory, including a continuum description of the THF solvent for both the geometry optimization and the single-point calculations by using the Jaguar 6.5 program package (Jaguar 6.5, Schrödinger, LLC, New York, NY, **2005**). Relative energies correspond to electronic energies. See Supporting Information for full computational details.
- [9] The systematic positioning of the methyl at the 5-position and the substituent at the 6-position in the *trans* relative configuration was based on previous results showing that the Mukaiyama-aldol addition occurs with high *anti* selectivity (see ref.^[5]).
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- [11] The *cis/trans* configurational assignments of the diastereoisomers were achieved by 2D NOESY spectroscopic experiments.
- [12] The reaction of **6d** was quenched after 66 h at room temp.
- [13] When compound **14** with a 99:1 *cis/trans* ratio was resubmitted to equilibration conditions [Pd₂(dba)₃, (*i*PrO)₃P in THF under reflux], a 70:30 *cis/trans* mixture was recovered. A longer reaction time generated significant amounts of decomposition products.
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