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New and Efficient Synthesis of Azabicyclo[4.4.0]alkane Amino Acids by Rh-Catalyzed Cyclohydrocarbonylation

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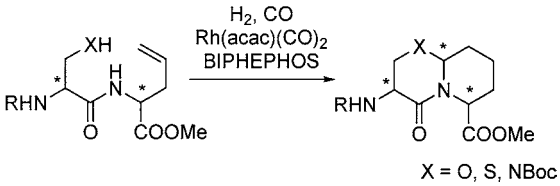
ABSTRACT



Highly efficient syntheses of azabicyclo[4.4.0]alkane amino acids were achieved by Rh-catalyzed cyclohydrocarbonylation of dipeptides bearing a terminal olefin moiety and a heteroatom nucleophile.

Recently, the importance of azabicyclo[*X*.*Y*.0]alkane amino acids as conformationally restricted dipeptide surrogates has been recognized among medicinal and peptide chemists in the design of peptides and peptidomimetics for enzyme inhibitors and receptor antagonists or agonists.[1−9]

Azabicyclo[*X*.*Y*.0]alkane amino acids also serve as peptide *β*-turn mimetics for controlling peptide secondary structures.[10,11] These scaffolds can also serve as excellent units for making combinatorial libraries. Accordingly, efficient and versatile methods for the syntheses of this class of compounds are currently in strong demand. Various approaches have been studied to develop relevant synthetic methods toward this goal.[1−3] However, to the best of our knowledge, no synthetic route has been developed based on a catalytic cyclization process.

We describe here the first and efficient catalytic method for the syntheses of enantiomerically pure azabicyclo[4.4.0]-alkane amino acids using highly regioselective cyclohydrocarbonylation catalyzed by a Rh-diphosphite complex.

We have reported[12] that the cyclohydrocarbonylation of *N*-acylallylglycinate catalyzed by Rh-BIPHEPHOS proceeds via extremely regioselective hydroformylation, followed by cyclization to form the corresponding hemiamidal. This hemiamidal readily generates *N*-acyliminium ion, which may accept the addition of an alcohol (in alcohol solvent) or isomerize to *N*-acylenamine (in aprotic solvent).[11] Accordingly, if a nucleophile is located within the substrate, a second cyclization should occur via the *N*-acyliminium intermediate as shown in Scheme 1.[13]

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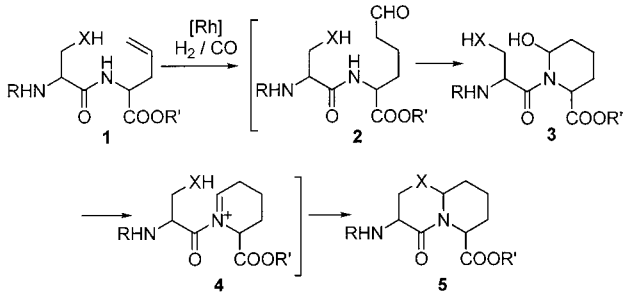
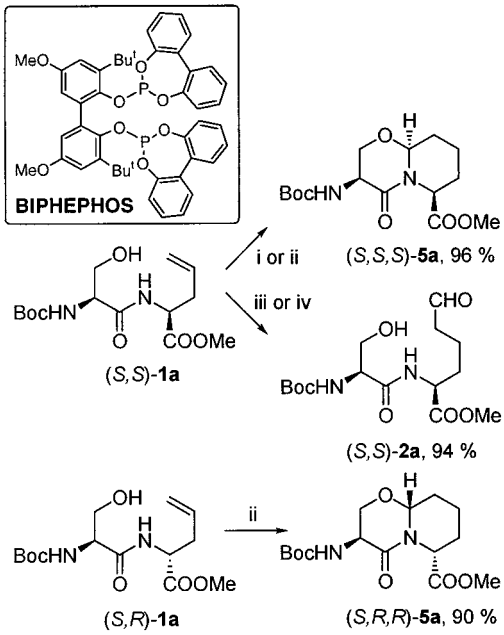
Scheme 1



As Scheme 2 illustrates, the cyclohydrocarbonylation of Boc-(*S*)-Ser-(*S*)-(allyl)Gly-OMe [(*S*,*S*)-**1a**] catalyzed by

Scheme 2[a]

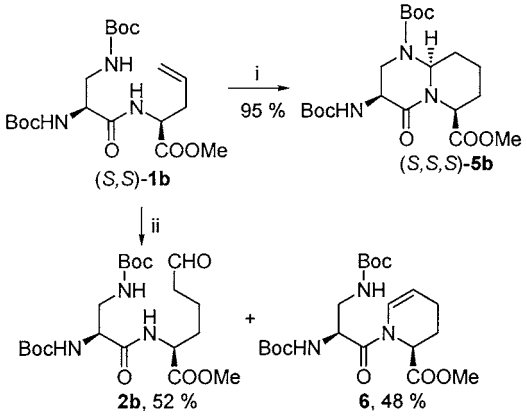


[a] Reagents and conditions: $Rh(acac)(CO)_2$ (2 mol %), BIPHEPHOS (4 mol %), H_2 (2 atm), CO (2 atm), 65 °C, 20 h; (i) toluene; (ii) toluene, PTSA (10 mol %); (iii) toluene, DMAP (10 mol %); (iv) THF.

$Rh(acac)(CO)_2$-BIPHEPHOS proceeded smoothly in toluene under mild conditions (CO/H_2 1/1, 4 atm, 60 °C). The generated aldehyde cyclized spontaneously in situ to afford the bicyclic dipeptide (*S*,*S*,*S*)-**5a** as the single product in 93% yield.[14] When the reaction was run in THF the cyclization did not occur, but gave aldehyde **2a** in 94% yield. The cyclization also did not take place in the presence of a small amount of 4-(dimethylamino)pyridine (DMAP) even when toluene was used as the solvent. On the contrary, addition of a catalytic amount of *p*-toluenesulfonic acid (PTSA) accelerated the cyclization to give (*S*,*S*,*S*)-**5a** in 96% yield. In the same manner, the reaction of (*S*,*R*)-**1a** in toluene in the presence of PTSA gave (*S*,*R*,*R*)-**5a** as the single product in 90% yield (Scheme 2). The stereochemistry of the newly formed bridgehead position C-6 of (*S*,*S*,*S*)-**5a** as well as (*S*,*R*,*R*)-**5a** was determined by NOESY analyses.

In the reaction of dipeptide (*S*,*S*)-**1b** bearing a β-aminoalanine (BAA)[15] moiety, the cyclization did not occur *in the absence of* PTSA as shown in Scheme 3. The reaction

Scheme 3[a]



[a] Reagents and conditions: (i) $Rh(acac)(CO)_2$ (2 mol %), BIPHEPHOS (4 mol %), H_2 (2 atm), CO (2 atm), PTSA (10 mol %), toluene, 65 °C, 20 h; (ii) same as (i), but without PTSA.

afforded linear aldehyde **2b** (52%) and *N*-acylenamine **6** (48%). The latter product **6** was formed by dehydration of a hemiamidal intermediate **3** via *N*-acyliminium intermediate **4**. This indicates that the nucleophilic addition of the Boc-amino group to the iminium bond does not compete with isomerization of **4**, resulting in the formation of acylinamine **6** under neutral conditions. In fact the reaction proceeded efficiently *in the presence of* PTSA to give (*S*,*S*,*S*)-**5b** as the single product in 95% yield (Scheme 3). The (3*S*,6*S*,10*S*) stereochemistry of **5b** was determined by X-ray crystallographic analysis (Figure 1). It should be noted that no 1-azabicyclo[4.3.0] product was formed although either Boc-amino group in the BAA residue could react with the acyliminium intermediate **4** (R = Boc, X = BocN).

In the case of a dipeptide substrate bearing a cysteine moiety, an *S*-trityl derivative was used to avoid undesirable

(13) Jackson et al. reported a facile bicyclization of an alkenyldiamine under classical hydroformylation conditions. This reaction is likely to proceed thorough an iminium ion intermediate. See: Campi, E. M.; Jackson, W. R.; McCubbin, Q. J.; Trnacek, A. E. *Aust. J. Chem.* **1994**, *47*, 1061−1070.

(14) **Typical procedure:** In a 10-mL round-bottomed flask was placed dipeptide **1** (0.100 mmol) in 2 mL of toluene under N_2. In a 25-mL reaction vessel were placed $Rh(acac)(CO)_2$ (0.5 mg, 2.0 μmol) and BIPHEPHOS (3 mg, 4 μmmol), and toluene (1 mL) was added by syringe under N_2. The catalyst mixture was stirred until it became a homogeneous solution. Then, the substrate solution was transferred to the catalyst solution via syringe. The reaction vessel was placed in a 300-mL stainless steel autoclave. The autoclave was flushed with CO several times then filled with 2 atm of CO and 2 atm of H_2. The autoclave was immersed into an oil bath that was maintained at 60−65 °C and kept for 20 h with magnetic stirring. Then, the autoclave was cooled to room temperature and pressure was slowly released. Solvent was evaporated to give a viscous oil, which was purified by flash chromatography on silica gel to give **5**.

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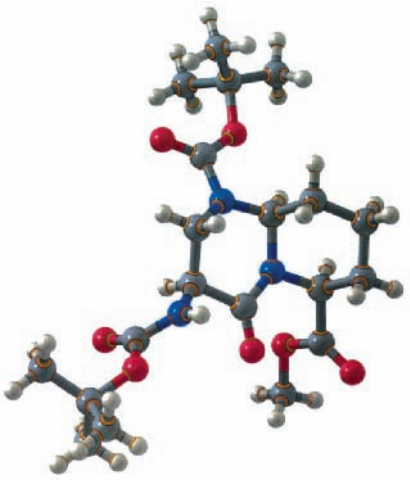
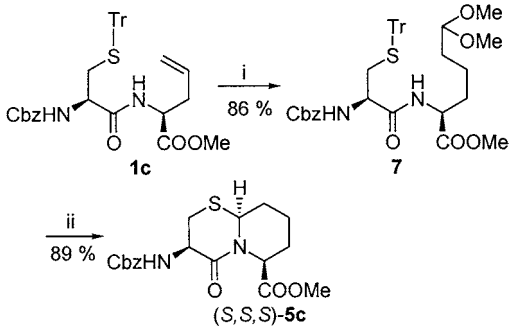


Figure 1. Single-crystal X-ray structure of (*S*,*S*,*S*)-**5b**.

S−S bond formation as well as possible deactivation of an active catalyst species during the reaction (Scheme 4). Since the thiol group is protected, a spontaneous cyclization cannot take place, which is likely to lead the reaction to undesirable *N*-acylenamine formation (see **6** in Scheme 3). Accordingly, the reaction of *S*-Tr-*N*-Cbz-(*S*)-Cys-(*S*)-(allyl)Gly-OMe [(*S*,*S*)-**1c**] was carried out in MeOH to trap the resulting aldehyde moiety by converting it in situ to the corresponding acetal (Scheme 4). The reaction of (*S*,*S*)-**1c** in MeOH was run under the standard conditions to give acetal **7** in high yield. The subsequent deprotection−cyclization with a catalytic amount of trifluoroacetic acid (TFA) afforded bicyclic dipeptide (*S*,*S*,*S*)-**5c** in 89% isolated yield (Scheme 4).

Scheme 4[a]

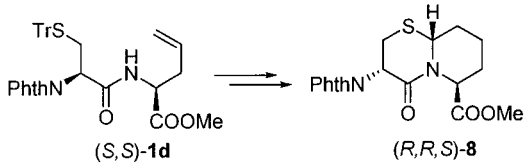


[a] Reagents and conditions: (i) $Rh(acac)(CO)_2$ (2 mol %), BIPHEPHOS (4 mol %), H_2 (2 atm), CO (2 atm), MeOH, 65 °C, 20 h; (ii) TFA (cat.), CH_2Cl_2, rt, 30 min.

In the same manner, the reaction of *S*-Tr-*N*-phthalyl-(*S*)-Cys-(*S*)-(allyl)Gly-OMe [(*S*,*S*)-**1d**] was carried out under the same conditions to afford the corresponding bicyclic dipeptide **8** (60% isolated yield for 2 steps) (Scheme 5).

To our surprise, however, the X-ray crystallographic analysis revealed that the product **8** possesses (3*R*,6*R*,10*S*) stereochemistry as shown in Figure 2, i.e., epimerization of the *N*-phthalylserine moiety took place. This result provides useful insight into the mechanism of cyclization in this process.

Scheme 5



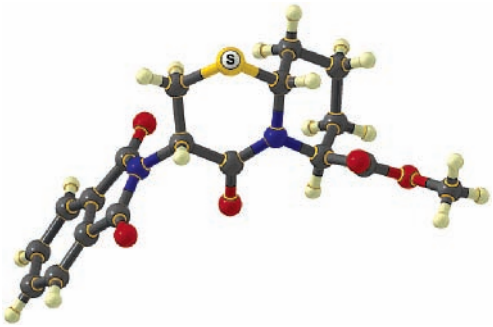
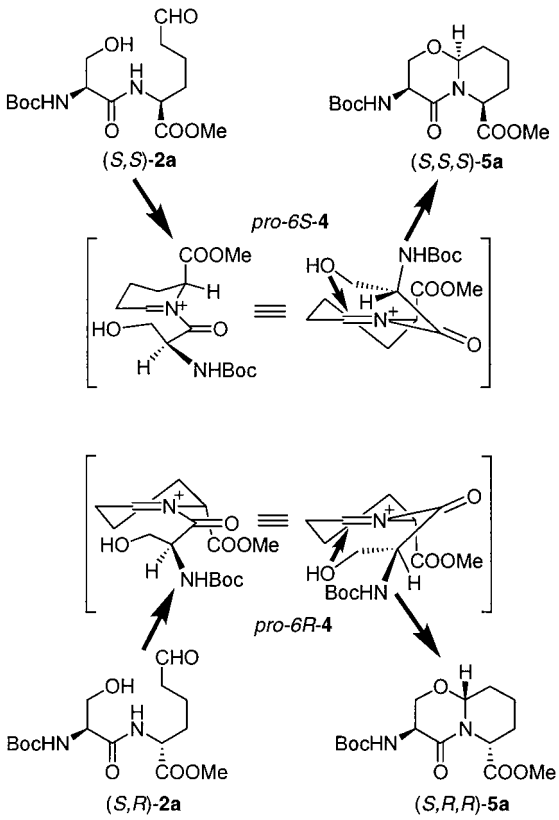


Figure 2. Single-crystal X-ray structure of (*R*,*R*,*S*)-**8**.

As Scheme 6 illustrates, the extremely diastereoselective cyclization of (*S*,*S*)-**2a** and (*S*,*R*)-**2a**, generating a new chiral

Scheme 6

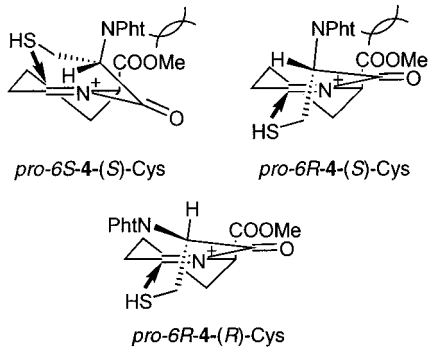


center at the bridgehead C-6 position in (*S*,*S*,*S*)-**5a** and (*S*,*R*,*R*)-**5a**, can be nicely explained by taking into account the $A^{1,3}$-strain in the *N*-acyliminium intermediate **4** at the cyclization step. It is very clear that the C-2 position of the pipecolate moiety serves as the stereogenic center, which takes an axial position to avoid the $A^{1,3}$-strain, in the transition state of the cyclization. Thus, the *S* and *R* configurations are exclusively induced at the C-6 position of **5a** from *S*-pipecolate (*pro-6S*-**4**) and *R*-pipecolate (*pro-6R*-**4**), respectively. Naturally, the formations of (*S*,*S*,*S*)-**5b** and (*S*,*S*,*S*)-**5c** should have followed the *pro-6S*-**4** pathway. As Figure 1 implies, flipping of the quasi-chair−chair bicyclic framework of **5** takes place to accommodate the most favorable conformation during or after the cyclization.

In the case of the formation of bicyclic dipeptide **8**, it is reasonable to assume that the rigid and bulky phthalimido group blocks the *pro-1S*-**4** approach of the *N*-phthalimido-cystein moiety, leading to the formation of *S* configuration at the C-6 position, i.e., *pro-6R*-**4**-(*S*)-Cys approach (Scheme 7). At this stage, it is obvious that the axial phthalimido group is sterically very unfavorable. Thus, epimerization at the C-3 position, which has an acidic hydrogen, takes place to make the phthalimido group equatorial, yielding (*R*,*R*,*S*)-**8** as the sole product. Another possibility is that the stereochemistry of the *N*-phthalyl-cystein moiety is flexible due to rapid epimerization or enol formation under the reaction conditions and only the (*R*)-Cys-isomer undergoes cyclization via the *pro-6R*-**4**-(*R*)-Cys pathway (Scheme 7).

In conclusion, a new and highly efficient catalytic method for the syntheses of azabicyclo[4.4.0]alkane amino acids **5** has been developed by means of Rh-catalyzed cyclohydrocarbonylation of dipeptides **1** bearing a terminal olefin moiety. This method provides enantiomerically pure product through extremely diastereoselective cyclization of *N*-acyliminium intermediates **4** wherein the C-2 position of the pipecolate moiety in **4** serves as the stereogenic center. Plausible mechanisms for the extremely stereoselective cyclization step are proposed. Further studies on the scope and applications of this method are actively underway in these laboratories.

Scheme 7



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Supporting Information Available: The characterization data of compounds **5** and **8**, as well as the X-ray crystallographic analysis data for (*S*,*S*,*S*)-**5b** and (*R*,*R*,*S*)-**8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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