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Synthesis of Bicyclic Cyclopropylamines by Intramolecular Cyclopropanation of *N*-Allylamino Acid Dimethylamides

Bin Cao, Dong Xiao, and Madeleine M. Joullié*

Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104-6323

mjoullie@sas.upenn.edu

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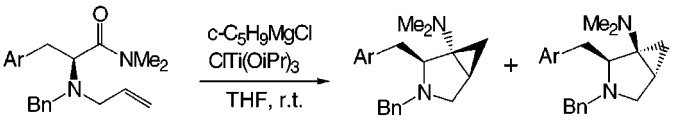
ABSTRACT



Ar = phenyl, 4-hydroxyphenyl, indole

Cyclopropylamines and substituted cyclopropylamines are important building blocks or substituents in a variety of biologically active compounds. Here, we report the facile syntheses of cyclopropylamines by Ti(II)-mediated intramolecular coupling of a terminal olefinic moiety and the *N,N*-dimethylcarboxamide moiety of amino acid derivatives. The products have novel and strained bicyclic structures. The yields were good (78–83%) for all three substrates with diastereomeric ratios of about 3:1.

The synthesis of molecules containing cyclopropane rings has been a synthetic challenge to organic chemists for a long time. The cyclopropane ring is not only a unique moiety in organic synthesis but it is also a template or substituent in a variety of biologically active compounds. Probably the most abundant cyclopropyl compound in nature is aminocyclopropane carboxylic acid (ACC).[1] The broad-spectrum antibiotic ciprofloxacin contains a cyclopropyl substituent on nitrogen.[2] Another example is the natural peptide lactone hormaomycin, which contains two (2′-nitrocyclopropyl)-alanine moieties.[3] Among the most important precursors for such compounds are cyclopropylamine and substituted cyclopropylamines.

The original Kulinkovich hydroxycyclopropanation protocol[4] was applied by de Meijere to *N,N*-dialkylamides in order to develop a facile preparation of *N,N*-dialkylcyclopropylamines.[5] Since the discovery of the ligand exchange for the generation of various substituted titanacyclopropane intermediates,[6] this methodology had been further improved and the scope of the reaction had been extended.[7] Cha reported a variant of this reaction utilizing Ti(II)-mediated coupling of esters or *N,N*-dialkylamides and monosubstituted olefins, as well as the intramolecular cyclopropanation of ω-vinyl esters and ω-vinyl amides.[8]

Here, we would like to report the syntheses of *N,N*-dimethylcyclopropylamines by Ti(II)-mediated intramolecular coupling of terminal olefins and *N,N*-dimethylcarboxamides. The intermediates are made from the proteinogenic amino acids, i.e., phenylalanine, tyrosine, and tryptophan. The products have novel and strained bicyclic structures. The key reaction, mechanism, and stereoselectivity are illustrated in Scheme 1. Reaction of $ClTi(OiPr)_3$ with 2 equiv of cyclopentylmagnesium chloride furnishes titanacyclopropane

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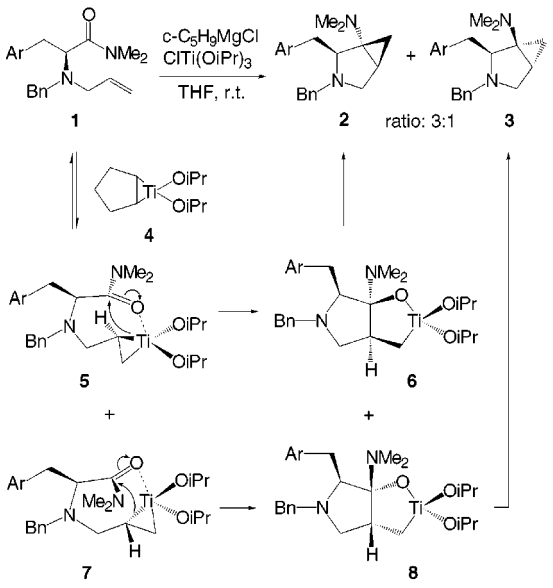
Scheme 1. Reaction Mechanism and Diastereomeric Selectivity

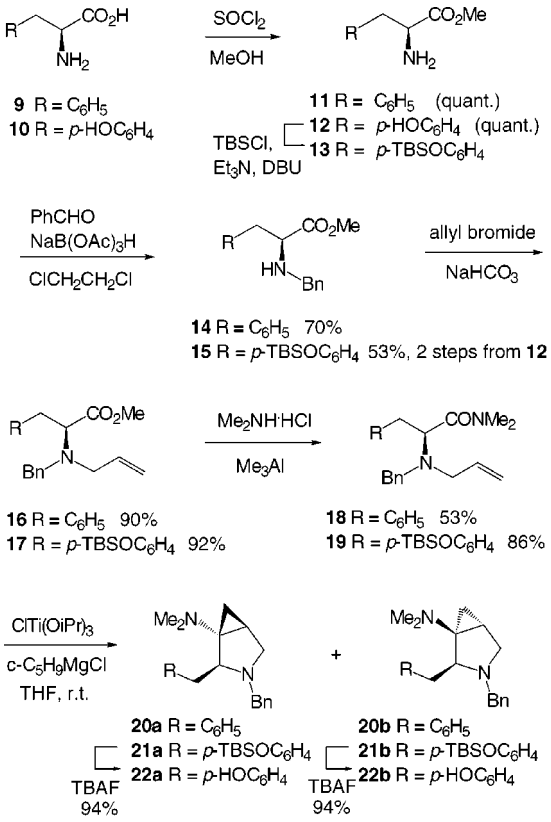


intermediate **4**. Then, olefin exchange with allyl compound **1** leads to titanacyclopropane intermediates **5** and **7**.[6,8] The next step, **5** to **6** and **7** to **8**, involves position-selective expansion of the titanacyclopropane ring by insertion of the amide carbonyl group between Ti and the more substituted carbon. The most favorable conformation (**5**) for the formation of the presumed titanaoxacyclopentane intermediate has the α-substituent of the amide group in a *β*-position and *anti* to the hydrogen of the most substituted carbon of the titanacyclopropane. This carbon retains its stereochemical integrity in the bicyclic intermediate (**6**).[9] Conversion of **6** to product **2** with retention of configuration of the carbon carrying the dimethylamino group may be explained by the intermediacy of an iminium ion, followed by reinstatement of the chiral center during the formation of the cyclopropane ring.

The reason for choosing aromatic amino acid derivatives for the reaction is based on the following considerations. First, we wanted to apply this reaction to make some novel bioactive molecules. It is believed that the basic pharmacophore which elicits dopaminergic activity contains an amine (typically tertiary) held at a certain distance from a *π*-system (such as an aromatic ring).[10] The generated *N*,*N*-dimethylcyclopropylamines satisfy this structural feature. Second, the bicyclic compounds are rigid and highly strained and would permit determination of the active conformation in the drug-receptor complex if the compounds exhibited biological activity, thus facilitating the modification and optimization of the lead compound.

To perform the aminocyclopropanation reaction, the carboxylic acid groups of phenylalanine, tyrosine, and tryptophan had to be converted to the corresponding amides and the amino groups substituted with benzyl and allyl groups. Schemes 2 and 3 show the detailed reactions.

Scheme 2



Thus, L-phenylalanine **9** was converted to methyl ester **11** in nearly quantitative yield. Reductive amination with benzaldehyde and sodium borohydride triacetate afforded secondary amine **14**. Treatment with allyl bromide and $NaHCO_3$ afforded compound **16**. Treatment of **16** with $AlMe_3$ and $Me_2NH{\cdot}HCl$ converted the ester to amide **18.** Cyclopentylmagnesium chloride (4.5 equiv) was added slowly at room temperature to a THF solution of amide **18** and $ClTi(OiPr)_3$ (1.0 equiv). The intramolecular aminocyclopropanation reaction afforded two diastereomeric bicyclic compounds, **20a** (major) and **20b** (minor), in good yields. The diastereomeric ratio was 72:28, as determined by ^1H NMR. Compounds **22a** and **22b** were obtained in the same manner from L-tyrosine with protection of the phenolic hydroxyl group.

Scheme 3 shows the application of the aminocyclopropanation reaction on L-tryptophan. It should be noticed that the indole nitrogen in tryptophan does not need to be protected.

These reactions proceeded in similar yields and diastereomeric ratios (approximately 3:1), and the results for the three reactions are shown in Table 1.

To determine the absolute configuration of the bicyclic compounds, **22a** was crystallized and its structure determined

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Scheme 3

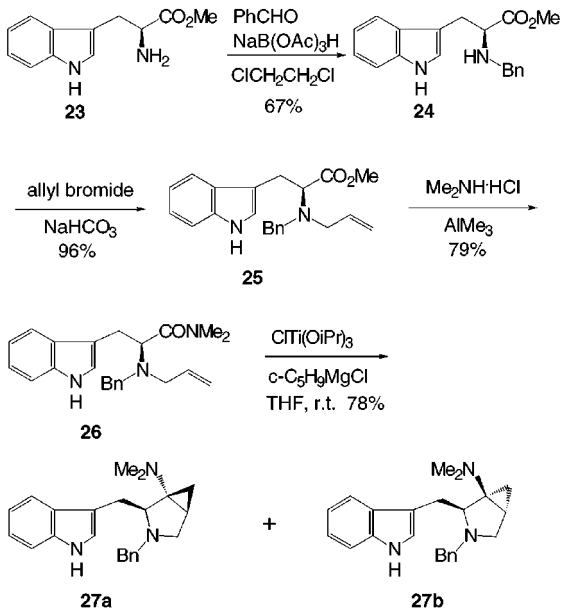

Table 1. Yields and Diastereomeric Ratios for the Aminocyclopropanation Reactions

compds	yield (%) [a]	diastereomeric ratio[b]
20a and **20b**	83	72:28
22a and **22b**	83	72:28
27a and **27b**	78	74:26

[a] Isolated yields based on olefinic amide intermediates. [b] The ratio of diastereomers was determined by ^{1}H NMR.

by X-ray crystallography. Figure 1 shows the ORTEP drawing of **22a**. The configuration of the other diastereomer was assigned according to its NMR spectrum.

In conclusion, this report describes the synthesis of a series of *N*,*N*-dimethylcyclopropylamines by Ti(II)-mediated intramolecular coupling of a terminal olefinic moiety and an *N*,*N*-dimethylcarboxamide moiety of amino acid derivatives. The yields were good for all three of aromatic amino acid

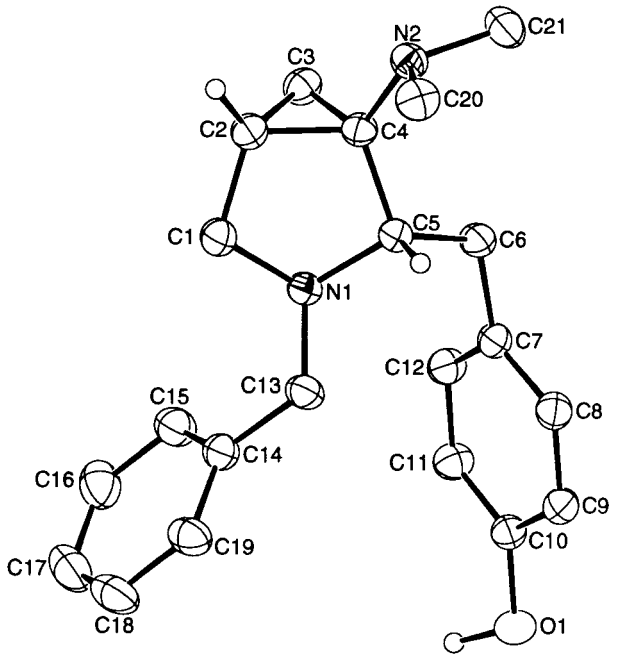

Figure 1. ORTEP drawing of compound **22a**.

derivatives. Biological activity tests on the six *N*,*N*-dimethylcyclopropylamines **20a**, **20b**, **22a**, **22b**, **27a**, and **27b** are currently in progress.

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Supporting Information Available: General experimental procedure for the aminocyclopropanation reaction and ^{1}H NMR, ^{13}C NMR, rotation, and mass spectra of compounds **20a**, **20b**, **22a**, **22b**, **27a**, and **27b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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