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trans-Cyclopropyl β-Amino Acid Derivatives via Asymmetric Cyclopropanation Using a (Salen)Ru(II) Catalyst

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Abstract: *trans*-Cyclopropyl β-amino acid derivatives can be synthesized in five steps with excellent enantioselectivities using a chiral (Salen)Ru(II) cyclopropanation catalyst in the key asymmetry-induction step. This facile synthesis proceeds with high overall yield and can be used to prepare a number of carbamate-protected (Cbz and Boc are demonstrated) β-amino acid derivatives.

The enantioselective synthesis of β-amino acids has recently attracted considerable attention[1−4] due to their interesting structural properties and significant pharmacological activities.[5,6] β-Amino acids are found in numerous biologically active compounds including β-peptides,[7−9] which have been shown to organize into well-defined folded secondary and tertiary structures in aqueous solution, similar to that observed for natural proteins.[10−14] β-Amino acids are also crucial structural features of multiple natural products,[15−21] β-lactams,[22] and other pharmaceutical candidate compounds.[23,24]

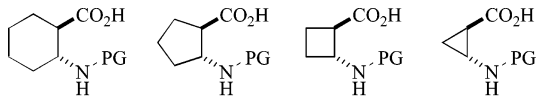

FIGURE 1. N-Protected cycloalkyl β-amino acid derivatives.

Having an extra carbon atom between the N- and C-termini, β-amino acids have a much greater potential for structural diversity beyond that of monosubstituted α-amino acids. In general, β-amino acids are also more metabolically stable than their α-amino counterparts[25] and have also been used for the preparation of modified peptides.[10,26,27] In particular, the nonnatural cyclic *trans*-cyclohexyl and -cyclopentyl β-amino acids[28] (Figure 1, **1** and **2** respectively), which restrict conformational mobility, have been successfully incorporated into β-peptide designs by Gellman and co-workers.[10]

Synthetic approaches toward the smaller-ring conformationally constrained analogues, β-aminocyclobutyl carboxylic acid **3**[29] and β-aminocyclopropyl carboxylic acid (β-ACC) **4**,[29,30] have been reported. Reiser and co-workers arrive at the N-protected derivative of **4** through the ozonolytic cleavage of a N-protected pyrrole that has been singly cyclopropanated in low yield with methyl diazoacetate. The isomers are then kinetically resolved (allowing for a maximum 50% yield of the desired optically pure isomer) by hydrolysis of the cyclopropylcarboxylic methyl ester in the presence of lipase.[31] We note that the Reiser laboratory has also developed methods to incorporate **4** into peptides.[32,33]

Additionally, the Csuk and Ortuño groups have each reported synthetic routes to enantiomerically enriched **4**.[34,35] These syntheses differed primarily in the cyclopropane-forming steps but both utilized pig liver esterase

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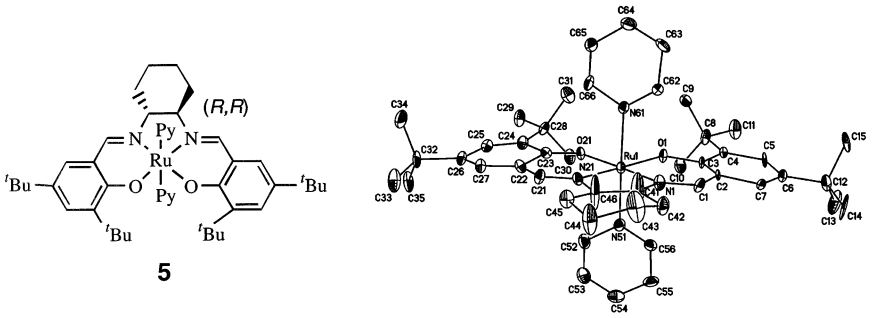


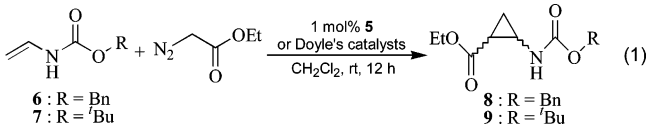
FIGURE 2. (left) (Salen)Ru(II) cyclopropanation catalyst **5**. (right) An ORTEP view of the crystal structure of **5** showing atom labeling scheme.[38] Thermal ellipsoids are drawn at 50% probability. Hydrogen atoms are omitted for clarity.

to arrive at the optically active product (through resolution of the two enantiomers of the *cis*-cyclopropane). Unfortunately, isomerization and racemization, presumably caused by heating in the synthetic pathway, led to less than desirable ee's for the final products. Low total yields were also noted for both syntheses (50% loss in the resolution step alone). Hence, a more straightforward synthesis of *trans*-*β*-ACC **4** is desired.

Herein we report a high-yield synthesis of *trans*-*β*-ACC derivatives**,** where the amino group is protected as the N-Cbz (**4a**) and N-Boc (**4b**) moieties, employing the highly enantioselective (salen)Ru(II) cyclopropanation catalyst **5**[36] developed in our laboratory (Figure 2).[37]

It has been established that the amino group of **4** needs to be protected with an electron-withdrawing group such as a carbamate because of its vicinal donor−acceptor substitution pattern, which can result in rapid ring opening and subsequent hydrolysis or condensation reactions.[29,39,40] Thus, we selected the benzyl carbamate (Cbz) and *tert*-butyl carbamate (Boc) N-protected cyclopropanes (**4a** and **4b**, respectively) as our synthetic targets. Cbz and Boc protecting groups were chosen on the basis of their contrasting chemical stabilities (N-Cbz is stable to most acidic conditions and is cleaved by catalytic hydrogenolysis, whereas N-Boc is stable to most basic conditions and is cleaved by acidic hydrolysis) and ease of introduction.[41]

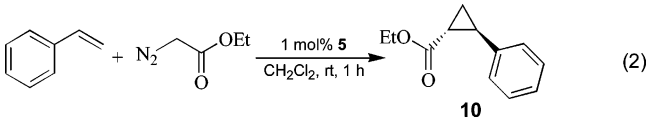
Our first attempt to produce the enantiomerically pure *trans*-*β*-ACC derivatives employed the direct cyclopropanation of the corresponding vinyl carbamates **6** and **7** with ethyl diazoacetate (EDA) in the presence of **5** (eq 1). While cyclopropanation of the Boc-protected olefin **7** resulted in no reaction, the Cbz-protected olefin **6** can



(1)

be cyclopropanated in good yields but with poor diastereoselectivity and no enantioselectivity. In our hands, a series of commercially available Doyle's chiral dirhodium catalysts[42] (containing the MEPY, MIPPM, and MEOX ligands) showed similar results (low diastereoselectivity and no enantioselectivity). These poor results prompted us to investigate other methods to synthesize the target *trans*-cyclopropyl *β*-amino acids.

We postulated that it would be advantageous to exploit the outstanding combination of diastereoselectivity (*cis:trans* = 1:11) and enantioselectivity (96% ee for *cis*, 99% ee for *trans*) in the cyclopropanation of styrene with EDA using our (salen)Ru(II) catalyst **5** (eq 2).[36] The product



(2)

of this reaction, chirally pure cyclopropane **10**, can be obtained in quantitative yield (99%) and serve as an excellent intermediate for our planned synthesis (Scheme 1). Oxidative degradation of the phenyl moiety of **10** to a carboxylic acid employing ruthenium tetraoxide, as described by Sharpless and co-workers[43] and applied to a phenyl-substituted cyclopropane by Jørgensen and Sydnes,[44] would furnish a *pseudo*-C_2 symmetric *trans*-acid ester, which can be transformed to an azide and undergo Curtius rearrangement to an isocyanate, with retention of configuration. The cyclopropyl isocyanate could then be converted to the target carbamate via reaction with an alcohol of choice (e.g., ^{t}BuOH or BnOH).

Indeed, application of the Sharpless oxidative degradation of the phenyl group of phenyl cyclopropane **10** with ruthenium tetroxide furnishes the cyclopropane ester-

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(38) Single crystals of **5** were obtained by slow diffusion of methanol into a toluene solution of **5** at low temperature inside a drybox. The catalyst crystallized in an orthorhombic unit cell, space group $Pna2_1$ with formula weight = 1078.45, a = 19.208(3) Å, b = 15.746(2) Å, c = 19.587(3) Å, and D_{calc} = 1.209 g/cm^3 for Z = 4, T = −100 °C.

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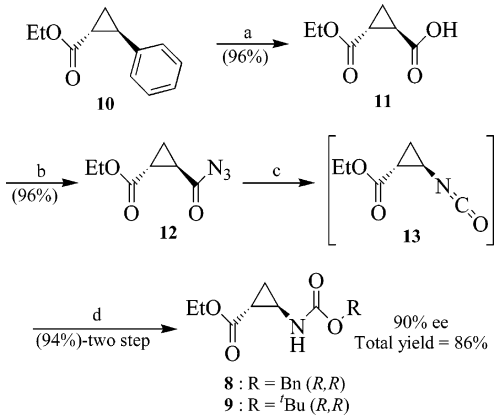
SCHEME 1. Scheme for *trans*-Cyclopropyl *β*-Amino Acid Derivative Synthesis[a]



[a] Conditions: (a) $RuCl_3 \cdot xH_2O$, $NaIO_4$, $CCl_4/CH_3CN/H_2O$, rt, 3 days. (b) (i) EtOC(O)Cl, Et_3N, acetone, 0 °C, 1 h; (ii) NaN_3, H_2O, rt, 1 h. (c) Toluene, 85 °C, 1 h. (d) CuCl, ROH, toluene/DMF, rt, 1.5 h.

acid **11** in near quantitative yield (96%) (Scheme 1, (a)). Azide transfer to **11** (Scheme 1, (b)) was attempted with diphenyl phosphoryl azide (DPPA)[34] but yielded no product. However, the acyl azide intermediate **12** can be obtained in high yield (96%) using ethyl chloroformate in the presence of triethylamine followed by reaction with sodium azide in a one-pot synthesis.[35] The Curtius rearrangement of the acyl azide **12** (Scheme 1, (c)) was carried out thermally in a toluene solution. Precise control of reaction time and temperature is crucial in order to preserve the optical purity of the *β*-amino acid derivatives. To optimize conditions for this reaction, it was followed closely by solution IR spectroscopy. Disappearance of the azide stretching peak at 2148 cm^{-1} corresponds simultaneously to the appearance of the isocyanate stretching peak at 2279 cm^{-1}. With this monitoring, optimal reaction time was found to be 1 h at 85 °C. Both longer reaction times and higher reaction temperature resulted in a loss of ee in the final products due to racemization, which is in accordance with observations by others where thermally induced racemization of the cyclopropane results in an overall loss in optical purity.[34,35]

After the Curtius rearrangement, the toluene solution of **13** was used directly for the carbamate synthesis (Scheme 1, (d)) without isolation. Initially, direct nucleophilic attack of the alcohols on **13** was attempted without a catalyst. This proved to be an inefficient process that was plagued by low yields (<30% for reaction of BnOH and <10% with ^{t}BuOH) and enantioselectivity due to the necessary heating required for carabamate formation. In an effort to improve the overall carbamate yield while at the same time reducing the need for heating, we decided to make use of a Lewis acid catalyst for this reaction. Employing samarium diiodide as a catalyst with HMPA at low temperatures showed no improvement over the noncatalyzed reaction, although this catalyst system has been found to be effective for carbamate synthesis with other substrates.[45] However, copper(I) chloride-catalyzed addition of the alcohol[46] to **13** proved to be highly successful for both BnOH and ^{t}BuOH. This high-yield (94%) reaction proceeds at room temperature, thus minimizing the chance of isomerization or racemization. Analysis of the final N-Cbz- and N-Boc-protected (1*R*,2*R*)-*trans*-cyclopropyl *β*-amino acid derivatives **8** and **9** by chiral HPLC and GC, respectively, showed a slight decrease in ee (99% to 90% ee) in comparison to that of **10**. This is most likely due to a small amount of racemization that presumably occurred via thermal rearrangement.[34,35] Following the synthesis in Scheme 1 with further *trans*-enriched cyclopropane **10** (*cis*:*trans* ratio of 1:17, obtained by vacuum distilling off a small amount of predominately the *cis* isomer, which has a higher vapor pressure) also yielded final enantiomeric excesses of 90% for the *trans* isomer with no change in the product *cis*:*trans* ratio.

We note that use of the (*S*,*S*)-cyclohexyl analogue of catalyst **5** in the styrene cyclopropanation reaction (eq 2) results, as expected, in the same selectivities but opposite product absolute configurations. Thus, use of the (*S*,*S*)-**5** would allow for easy production of the (*S*,*S*) enantiomers of the *trans*-cyclopropyl *β*-amino acid derivatives synthesized in Scheme 1.

In conclusion, chiral (salen)Ru(II) cyclopropanation catalysts can be successfully used in the key chirality-induction step for the synthesis of highly enantiomerically enriched *trans*-cyclopropyl *β*-amino acid derivatives. Our high-yield synthesis proceeds with a large amount of retention of the high enantio- and diastereoselectivities introduced initially in the cyclopropanation of styrene with EDA by **5**. Further saponification and in situ N-deprotection of these cyclopropyl *β*-amino acid derivatives could lead to a number of synthetically and biologically important products.

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Supporting Information Available: General procedures for the syntheses and characterization of the cyclopropanes (together with all GC and HPLC methods) and the X-ray structural data for **5**. A combined X-ray crystallographic file for the structure determination of **5** is available in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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