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SYNTHESIS OF BICYCLIC CYCLOPROPYLAMINES FROM AMINO ACID DERIVATIVES†

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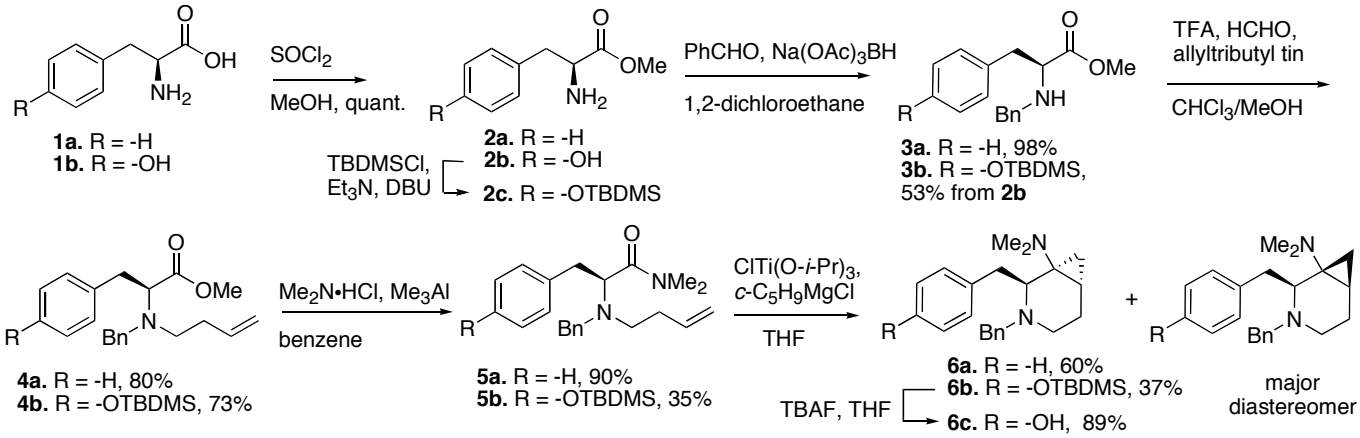
Abstract – The synthesis of novel [3.1.0] bicyclic cyclopropylamines from differently substituted amino acids using Ti(II)-mediated coupling and the extension of this methodology to provide [4.1.0] systems is described.

Cyclopropylamines and substituted cyclopropylamines are important structural elements in a variety of biologically active compounds. We have previously reported the Ti(II)-mediated coupling of a terminal olefin and the *N,N*'-dimethyl carboxamide moiety of aromatic amino acid derivatives to synthesize a series of *N, N*'-dimethylcyclopropylamines, by applying the Kulinkovich reaction to modified amino acids, and found that a tyrosine derivative was a weak dopamine receptor antagonist.[1] Here, we present an extension of our previous approach to the formation of bicyclic [4.1.0] cyclopropylamines, and to the synthesis of additional [3.1.0] systems using differently substituted amino acids.

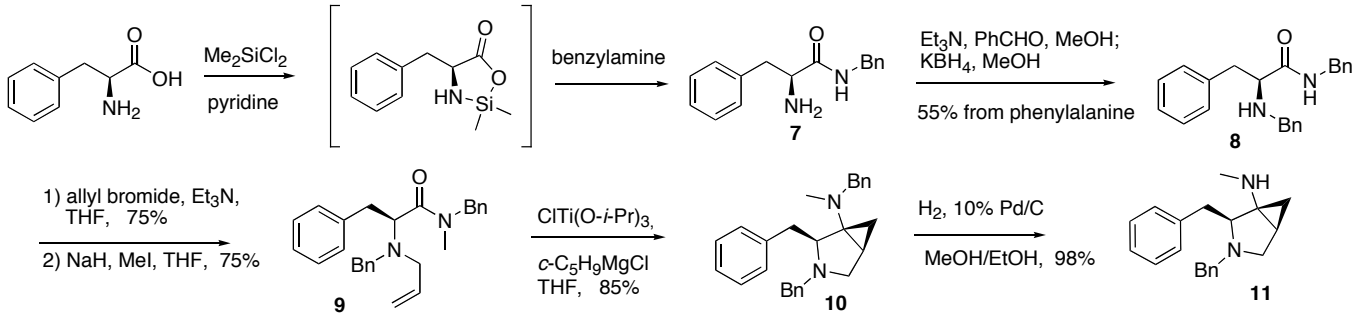
The [4.1.0] systems, obtained from a homoallylated amine, displayed greater diastereomeric selectivity than the [3.1.0] systems with an approximate 9:1 ratio of diastereomers (**Scheme 1**).[2]



Scheme 1. Nitrogen-containing [4.1.0] bicycles from L-tyrosine and L-phenylalanine.

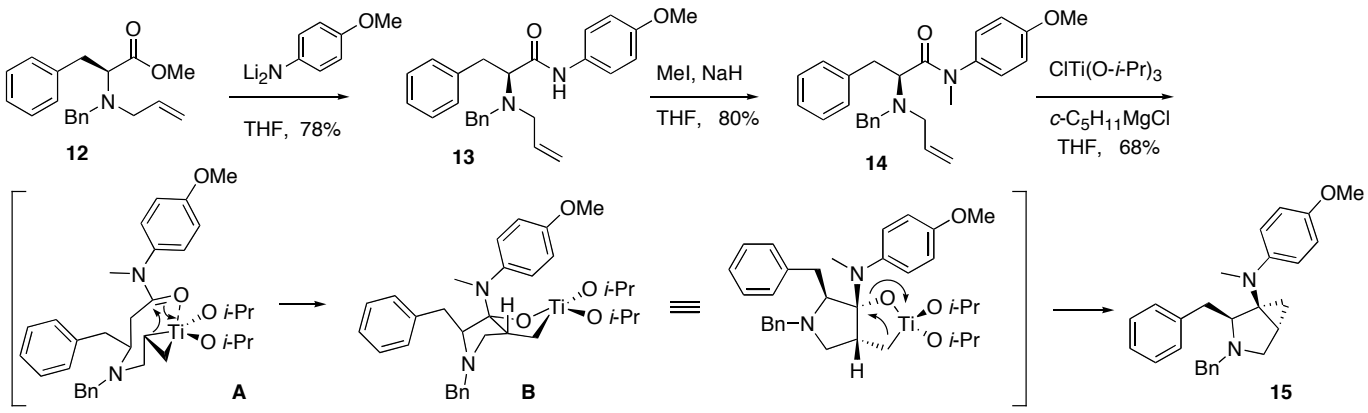
† Dedicated to Professor Barry M. Trost on the occasion of his 65th birthday.

In an effort to modify the substituents on the exocyclic amino group, and thereby extend the application of the bicycles, we explored alternate amidation procedures. We used a very efficient reaction developed by Liskamp *et al*. to produce benzyl amides directly from unprotected amino acids.[3] Though the yield suffered on a larger scale, dichlorodimethylsilane was highly successful in generating benzyl amides from all the amino acids we used, including proline, which was expected to be difficult for steric reasons. The benzyl amide (**8**) was then converted to an appropriately substituted compound for cyclization (**Scheme 2**). It should be noted that when **10** was exposed to hydrogenation conditions, only the more labile benzylmethylamine was deprotected. We assumed that the resulting free amine poisoned the palladium catalyst preventing further reaction.



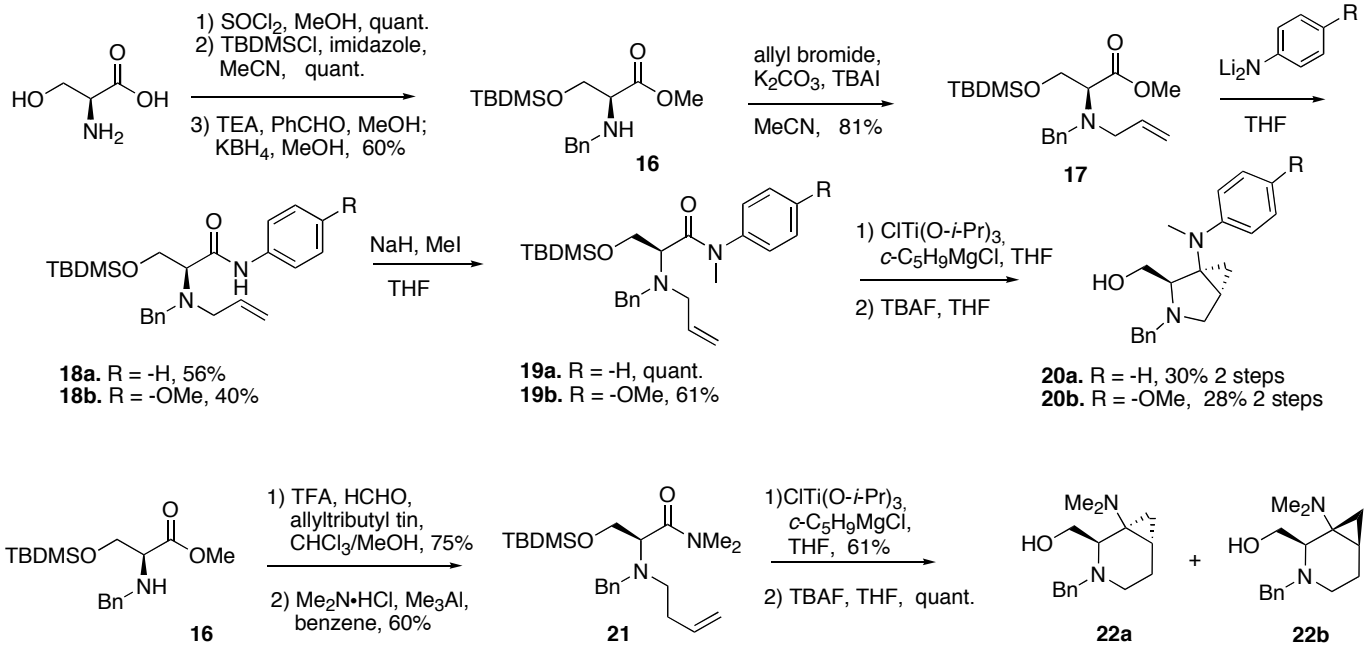
Scheme 2. Synthesis of dibenzyl-substituted aminocyclopropane.

In addition to benzyl-substitution, it was desirable to synthesize aromatic substituted aminocyclopropanes to alter the electronic properties of the exocyclic amine. Because of their weak nucleophilicity, the coupling of aniline or anisidine to an *N, N'*-allylbenzylphenylalanine acid failed to yield an amide. An aromatic bislithium amide was, therefore, chosen for aminolysis.[4] As shown in **Scheme 3**, the addition of a bislithium amide produced from anisidine gave the desired product which was then methylated and cyclized. Compound (**13**) can also be protected with a benzyl group in excellent yield. Although other substrates gave diastereomeric mixtures, in this case only a single diastereomer could be isolated.[5] We attribute the selectivity to greater steric hindrance in the presumed intermediate **A**.



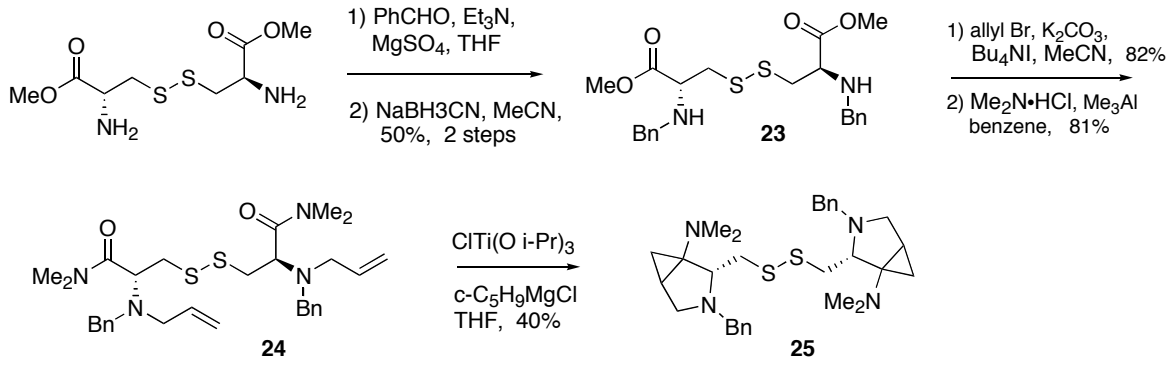
Scheme 3. Installation of a *p*-methoxyphenyl group.

We also attempted to synthesize similar bicycles containing a heteroatom. This modification was accomplished with serine and cystine, the dimer of cysteine. We envisioned protecting serine and cysteine as an oxazole and thiazolidine, respectively. This approach would negate the need for the benzyl protecting group, thus shortening the synthesis. Unfortunately, neither of these heterocycles survived the conditions for amidation. Serine, therefore, was protected as a TBDMS ether and carried through the described sequence of steps to cyclization and deprotected to give azabicyclo[3.1.0]hexyl methanol (**20**) as well as azabicyclo[4.1.0]heptyl methanol (**22**).[6] In the former example, it was found that the bislithium amidolysis gave higher yields than the conventional Weinreb approach.[7]



Scheme 4. L-Serine-derived [3.1.0] and [4.1.0] bicycles.

The protection of the sulfur in cysteine proved difficult, thus, the bicycle was synthesized as a dimer from cystine. A milder reducing agent, sodium cyanoborohydride, was needed in the benzylation step to prevent cleavage of the sulfur-sulfur bond. Compound (**23**) was then suitably modified to give disulfide (**25**).



Scheme 5. L-Cystine-derived bicycle.

In summary, a number of novel bicyclic cyclopropylamines have been synthesized from amino acid derivatives. Innovative amidation routes were successfully applied to achieve various amino substitutions of the cyclopropylamines. We are investigating the biological activity as well as the ring opening reactions of these interesting molecules.

ACKNOWLEDGEMENTS

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