Asymmetric synthesis of proline-based conformationally constrained tryptophan mimetic†

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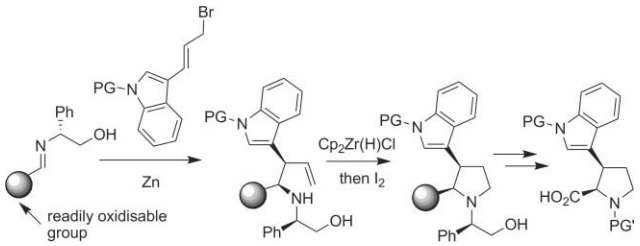
The synthesis of an optically pure proline-based tryptophan mimetic is described. The strategy involves the *in situ* generation of an unprecedented allylmetal species containing the indole moiety, and its coupling with a chiral imine. The construction of the 3-substitued proline skeleton is then achieved through a hydrozirconation/iodination sequence applied to the resulting homoallylic amine.

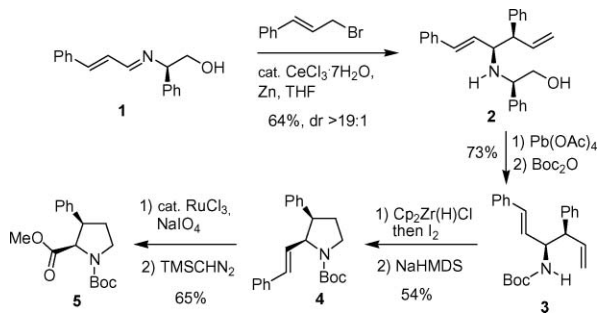
Substituted prolines exhibit significant biological activity, and are of marked interest for medicinal chemistry.[1] Among them, proline chimeras, incorporating proteinogenic amino acid chains at the 3-position, are valuable tools for biological investigations.[2] Such compounds are used as probes in SAR studies of biologically active peptides.[3] For example, their incorporation into peptides already proved to be an efficient approach to mimicking the natural β-turn of types I, II and II′ found in proteins.[4] They have also been employed with a view to developing protein–protein interaction inhibitors.[5] Although several syntheses of proline chimeras have been reported,[6] the development of efficient synthetic methods opening the way to optically pure compounds, and particularly those possessing an aromatic substituent at the 3-position, is valuable.

As part of our work on a hydrozirconation-based asymmetric approach to 5- and 6-membered N-heterocycles,[7] we recently developed an efficient synthesis of optically pure *cis*-2,3-disubstituted pyrrolidines.[8] In pursuit of this work, we describe herein a simple method for the diastereoselective construction of proline chimeras having an indolic fragment at the 3-position. The synthetic strategy applied for this purpose involves: (i) diastereoselective allylation of a chiral phenylglycinol-derived imine; (ii) hydrozirconation of the resulting homoallylic amine,[9] followed by iodination to promote pyrrolidine ring formation; (iii) direct oxidation of the 2-substituent to a CO_2H group (Scheme 1).



Scheme 1

Following this approach, the possibility of synthesizing proline-phenylalanine mimetic **5** was first checked out (Scheme 2). In the beginning, Barbier-type cinnamylation of cinnamaldehyde-derived imine **1** was performed in THF at room temperature, by using cinnamyl bromide (2.5 equiv.), Zn powder (2.5 equiv.) and a catalytic amount of $CeCl_3$.[10] As a result, homoallylic amine **2** was obtained as the sole (branched) regioisomer in a highly diastereoselective fashion (≥95% de) in 64% isolated yield. Subsequent $Pb(OAc)_4$-mediated chiral auxiliary removal and Boc-protection[11] provided **3**.[12] Selective hydrozirconation of



Scheme 2

the terminal C=C double bond, and *in situ* iodination gave the iodo intermediate, which after treatment with NaHMDS afforded the compound **4**. The successive Ru-mediated oxidation of the cinnamyl group, followed by diazomethane esterification provided the target proline-phenylalanine derivative **5** in the orthogonally protected form. Compound **5** was obtained as a unique *syn* (2*S*,3*R*) stereoisomer, based on the literature data (^{1}H, ^{13}C NMR and $[\alpha]_D$).[13]

We initially envisioned to start the synthesis of a (3-indolyl)proline analogue in the way similar to that followed for the preparation of **5**, *i.e.* by employing a Barbier-type protocol for the allylation step. Thus, the synthesis of 3-bromo-3-indolylpropene was first undertaken. However, all attempts to prepare this previously unreported starting material (in the *N*-Boc or *N*-Bn protected form) failed, presumably due to its instability resulting from the strong electron-donating effect of the indolyl moiety. We then turned to another possible way of generating allylmetal species, which would bypass the use of an unstable bromide. It was based on the Taguchi and Hanzawa protocol for the preparation of allylic zirconium species by reaction of a zirconocene equivalent "Cp_2Zr" with allylic ethers.[14,15] This reaction typically uses Cp_2Zr-butene, generated *in situ* from Cp_2ZrCl_2 and 2 equiv. of *n*-BuLi, and involves the formation of zirconacyclopropane through ligand exchange followed by β-alkoxy elimination (Scheme 3).

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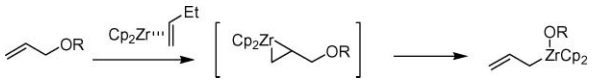
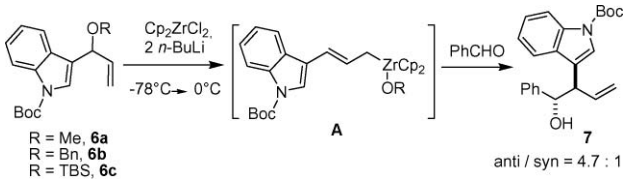


Scheme 3

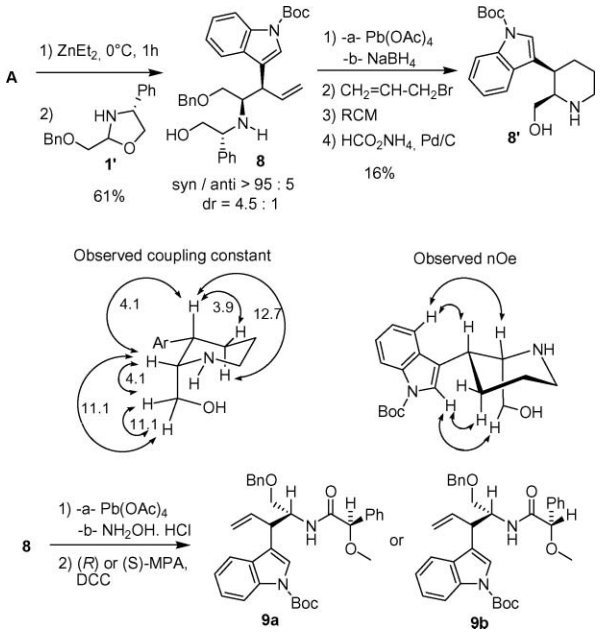


Scheme 4

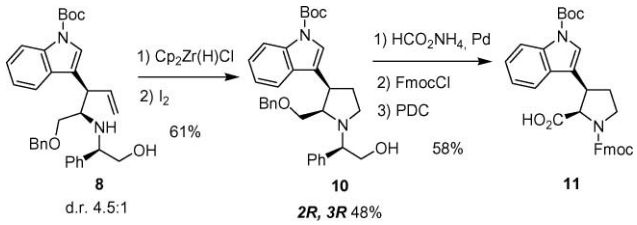
The indole-containing allylic ether **6** was easily prepared in 3 steps in 75% overall yield, from indole-3-carboxaldehyde (see ESI†). Compound **6** was added to the mixture of Cp_2ZrCl_2 (1 equiv.) and *n*-BuLi (2 equiv.) at −78 °C, and the temperature was raised to rt within 3 h. To check whether the allylic zirconocene **A** was efficiently generated, benzaldehyde was added. The expected homoallylic alcohol **7** was obtained in 86% yield as 4.7 : 1 *anti*/*syn* mixture of diastereomers (Scheme 4). Allylic metals bearing a heteroaromatic moiety are uncommon; to our knowledge, no allylmetals bearing the indole moiety have been reported. The formation and possible synthetic uses of **A** are worthy of note.

The preparation of a corresponding homoallylic amine was next envisioned, in the light of only a few examples involving allylzirconocene additions with imines.[16,17] Although the low reactivity of **A** towards imines could be anticipated,[18] the possibility of carrying out the reaction and preparing the *syn* adduct might be however achieved through transmetalation.[19] According to Taguchi's recent work on Cu(I) mediated addition of dialkoxyallylic zirconium species with imines,[20] we first examined the possibility of carrying out the reaction in Zr-to-Cu transmetalation conditions. These reactions were conducted in THF by using CuI, CuBr or CuCN as additive. However, no allylation product was obtained but only complex reaction mixtures were formed in all cases.

Recent advances in Zr-to-Zn transmetalations (typically using Me_2Zn or Et_2Zn) from alkenylzirconocenes,[21a] and allylzirconocenes,[21b] led to a number of synthetically useful transformations. Thus, Et_2Zn was added to 0 °C to *in situ* generated allylzirconocene **A**, prior to the addition of **1′**,[22] and the reaction was carried out at room temperature for 6 h. In these conditions, the expected compound **8** was formed and isolated in 61% yield as a mixture of two diastereomers (dr = 4.5 : 1) (Scheme 5). The use of Me_2Zn instead of Et_2Zn gave identical result. We noticed that the reaction took also place when using $ZnBr_2$ as additive, however with a lower yield of 42%. Moreover, the size of the OR group has been demonstrated to not affect the diastereoselectivity which remains almost constant for R = Me, Bn and TBDMS.[23] The *syn* stereochemistry in **8** was unambiguously established after conversion of the mixture of diastereomers **8** into the piperidine **8′** (Scheme 5). First, **8′** was obtained as a single isomer, thus indicating a unique relative configuration in **8**. Secondly, the *syn* stereochemistry was deduced from coupling constant values and NOESY experiment performed on compound **8′**. Finally, the 2*R*,3*R* configuration was assigned to compound **8** based on ^{1}H NMR data for the α-methoxy-α-phenylacetic amides (MPA) **9a** and **9b** (for details, see ESI†).[24] The observed facial selectivity in



Scheme 5



Scheme 6

the allylation step can be explained by a classical six-membered chair-like transition state.

The homoallylic amine **8** in hand, the target prolino-tryptophan analogue **11** was obtained in 4 steps (Scheme 6). The one-pot hydrozirconation–iodination sequence starting from **8** (4.5 : 1 mixture of diastereomers) afforded **10** in 61% isolated yield. At this stage the major isomer was easily isolated by flash chromatography. The simultaneous *N*- and *O*- debenzylation with ammonium formate[25] followed by Fmoc protection and oxidation provided enantiopure and orthogonally protected amino acid **11**.

Conclusions

In summary, we have described a diastereoselective method for the preparation of an optically pure proline-based tryptophan mimetic. The key steps are (i) diastereoselective allylmetallation of phenylglycinol-derived imines *via* Zr to Zn transmetallation of an *in situ* generated allylzirconocene, and (ii) the pyrrolidine ring construction through a hydrozirconation–iodination sequence. Other pyrrolidine (proline) derivatives with heteroaromatic substituents at the β-carbon could be available. The possibility of using allylic zirconiums bearing a heteroaromatic moiety opens the way to various synthetic applications.

Acknowledgements

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