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Access to Enantiomerically Enriched *cis*-2,3-Disubstituted Azetidines via Diastereoselective Hydrozirconation

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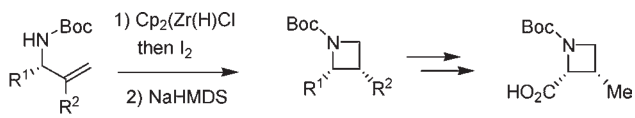
ABSTRACT



An asymmetric variant of the hydrozirconation reaction has been established starting from Boc-protected chiral allylic amines. The resulting diastereoselectively formed N-functionalized organozirconiums can be considered as promising chirons. In this case, they have been transformed into enantiomerically enriched *cis*-2,3-disubstituted azetidines through a iodination/cyclization sequence.

Azetidines are valuable building blocks for the preparation of both naturally occurring[1] and synthetic molecules[2] of biological interest and for the design of new organocatalysts[3] or ligands.[4] One of the modern mimicking approaches to enhance recognition of biological receptors is based on conformational constraint. Therefore, small-size rings, and among them the azetidine framework, constitute potent tools for SAR studies.[5] Although several syntheses of azetidine derivatives have been reported,[6] the development of simple synthetic strategies opening the way to optically pure compounds is still important.

The hydrozirconation of alkenes with the Schwartz reagent, $Cp_2Zr(H)Cl$, is a well-known reaction with important synthetic potential, owing to wide functional group tolerance, as well as marked regioselectivity and *syn*-stereoselectivity.[7,8] It represents one of the most practical methods for the formation of C−Zr bonds, which can be further transmetalated, linking zirconium chemistry with that of many other metals. In this context, an almost total

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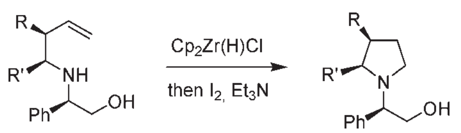
lack of alkene asymmetric hydrozirconation is surprising. To our knowledge, the only reported reactions deal with the hydrozirconation of enantiopure 1-alkenyl boranes to afford optically active 1,1-bimetallic species.[9] An efficient asymmetric hydrozirconation, particularly applied to the generation of functionalized organozirconium intermediates, would open new routes to a number of optically active molecules.

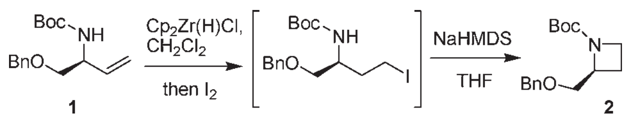
Our recent discovery that the hydrozirconation reaction can be carried out in the presence of secondary amino groups made it possible to develop new stereoselective approaches to pyrolidines (Scheme 1).[10] However, with this strategy, the formation of the stereogenic carbon center(s) is controlled prior to the hydrozirconation step.

Scheme 1. Synthesis of 2,3-Disubstituted Pyrrolidines



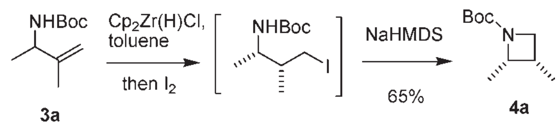
We report herein that hydrozirconation can proceed with high diastereofacial selectivity, making the preparation of optically pure 2,3-disubstituted azetidines possible. We first checked the feasibility of building the azetidine framework, starting from an amine with a protecting group that could further stereodirect the approach of the Schwartz reagent. For this purpose, we decided to use N-Boc protected allylamine[11] **1** (Scheme 2).

Scheme 2. Construction of the Azetidine Skeleton



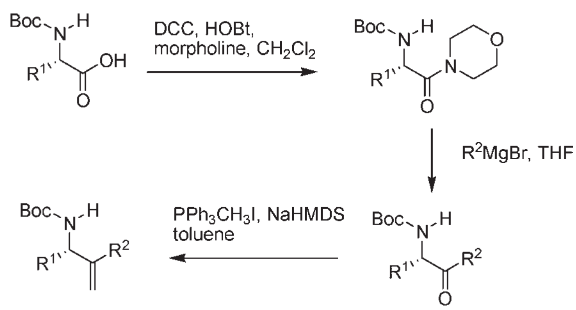
In a model experiment, **1** was first hydrozirconated within 1 h by using 3 equiv of the Schwartz reagent in CH_2Cl_2 at room temperature.[12] Treatment of the hydrozirconated intermediate with iodine afforded the corresponding iodocarbamate, isolated in 65% yield. Subsequent addition of NaHMDS in THF to promote the cyclization afforded **2** in 55% yield over the two steps, thus validating the strategy to build the azetidine. The diastereoselectivity of the hydrozirconation reaction was next studied by using a simple amine **3a** with two methyl groups. In this case, the hydrozirconation reaction was found to be effective in toluene at 80 °C,[13] and the azetidine **4a** was obtained with almost total diastereoselectivity in favor of the *cis* isomer[14] (dr ≥95:5) in 65% isolated yield (Scheme 3).

Scheme 3. Diastereoselective Access to Azetidine **4a**



The methodology was further explored by employing a series of enantiomerically enriched substituted allylic amines **3**. These compounds were easily obtained from the corresponding natural N-Boc protected L-amino acids or derivatives, following the sequence[15-17] shown in Scheme 4 (see the Supporting Information for details).

Scheme 4. Synthesis of Boc-Protected Allylamines **3**



Applied to **3a**−**f**, the hydrozirconation/iodination sequence and a subsequent NaHMDS-promoted cyclization afforded *cis*-2,3-disubstituted azetidines **4a**−**f** (Table 1).

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(12) When using 1 or 2 equiv of the Schwartz reagent, the starting material was recovered.

(13) When using CH_2Cl_2 as solvent, the hydrozirconation does not take place.

(14) The cis stereochemistry in **4a** was assigned based on the NOESY experiment (see the Supporting Information).

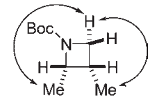

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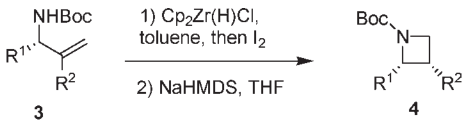
Table 1. Synthesis of Azetidines **4**



entry	R^1	R^2	dr[c]	compd (yield)
1[a]	Me	Me	94:6	**4a** (65%)
2	Bn	Bu	96:4	**4b** (75%)
3	Bn	Me	95:5	**4c** (65%)
4	*i*-Pr	Me	50:50	**4d** (68%)
5[b]	Ph	Me	73:27	**4e** (80%)
6	CH_2OTBS	Me	92:8	**4f** (65%)

[a] Reaction carried out starting from a racemic substrate. [b] Reaction carried out starting from (*R*)-enantiomer. [c] Determined by ^1H NMR of the crude reaction mixture.

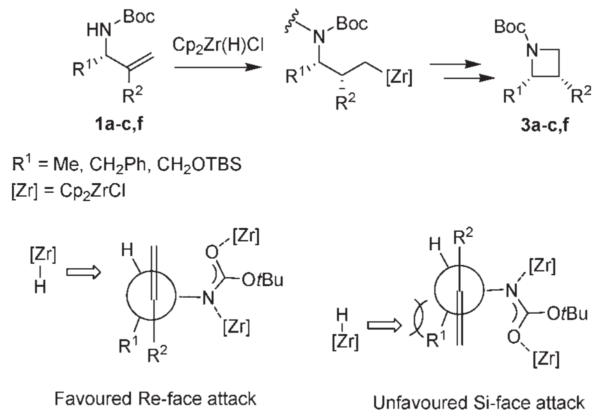


Figure 1. Plausible Origin of the Stereoselectivity.

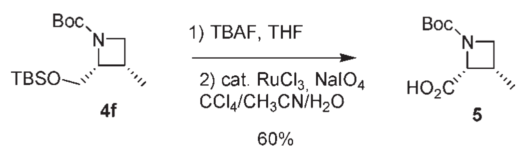
Thus, azetidines bearing two alkyl groups (entries 1−4, 6) and also an alkyl (R^2) and an aryl (R^1) substituent (entry 5) were prepared. These reactions proceeded with high diastereoselectivity except for **3d** and **3e** (R^1 = *i*-Pr, Ph, R^2 = Me, entries 4 and 5). The lack of stereoselectivity in these cases is not entirely clear at present, but might be due to steric reasons. The reaction did not take place starting from the allylamine with R^2 = Ph. A possible explanation could involve a thermodynamically favored dehydrozirconation.

Due to the 3 equiv of the Schwartz reagent required to perform the C=C bond hydrozirconation, one may assume that the first equivalent acts as a base, and the second coordinates to the N-Boc (on the O or N). Therefore, a protecting group-assisted approach of the hydride is probably not involved.

To account for the observed stereoselectivity, we assumed that conformations locating the large Zr-coordinated N-Boc fragment in a pseudoaxial orientation with respect to the double C=C bond plan prevail when R^1 is a medium-sized substituent. The selectivity may thus be rationalized by a more favorable accessibility of the Re face (Figure 1). This scenario is altered if the stereogenic center bears two large groups (R^1 = *i*-Pr or Ph and N-Boc). In such a case, their competition to adopt the pseudoaxial position renders the above simple conformationnal duality less likely.

The introduction of an alkoxy group at the α carbon of the chain (in R^1, entry 6) opens the way for further functionalizations. The presence of an azetidine-2-carboxylic acid moiety in a number of natural products and derivatives,[18] and the recent use of such acids for preparing the conformationally constrained peptides has to be underlined.[19] Rapid access to nonracemic azetidine-2-carboxylic acids is exemplified here by a simple preparation of the amino acid **5**, a rigid valine analogue, from **4f** through alcohol deprotection and ruthenium-based oxidation (Scheme 5).

Scheme 5



In conclusion, we have presented an asymmetric variant of the hydrozirconation reaction applied to N-Boc protected allylamines. The organozirconium species thus generated appear as versatile intermediates for synthetic applications, as exemplified by the stereoselective synthesis of *cis*-2,3-disubstituted azetidines.

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Supporting Information Available. Experimental procedures and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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