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Stereoselective Synthesis of Pyrrolidines from *N*-Allyl Oxazolidines via Hydrozirconation–Cyclization

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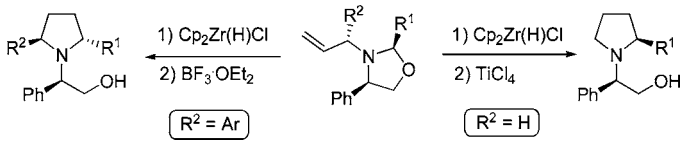
ABSTRACT



A new diastereoselective synthesis of pyrrolidines from readily available chiral *N*-allyl oxazolidines is presented. The construction of the pyrrolidine ring is achieved via a tandem hydrozirconation–stereoselective Lewis acid mediated cyclization sequence.

The pyrrolidine ring is common to numerous natural products[1] and medicinal drugs. Enantiopure pyrrolidines have been used as synthetic building blocks, chiral auxiliairies,[2] catalysts, and ligands for asymmetric synthesis.[3] Although many syntheses of pyrrolidines have been reported,[4] there is still a need for the development of general and simple methods for the preparation of optically pure compounds. Among the strategies implying an intramolecular cyclization to build the pyrrolidine ring, only a few methods involve carbon−carbon bond-forming reactions.[5] Carbon−nitrogen bond-forming reactions are most common, including in situ reduction reactions,[6] electrophilic C−C double bond activations,[7] metal carbenoid N−H insertions,[8] metal-catalyzed hydroamination reactions,[9] and those requiring the presence of a leaving group.[10]

Here we present a synthetic methodology that allows the preparation of enantiopure pyrrolidines via a carbon−carbon

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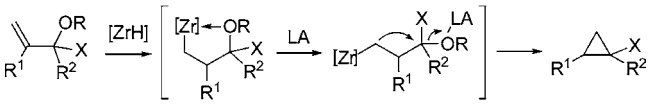
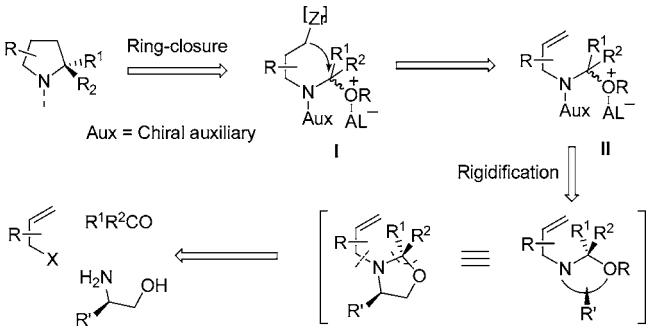
bond-forming cyclization reaction. To our knowledge, no such approach involving a C-metalated aminal intermediate has been reported. Recently, our group described a new diastereoselective synthesis of di- and trisubstituted cyclopropanes from allylic ethers and acetals.[11] This reaction involves a hydrozirconation followed by the Lewis acid promoted deoxygenative ring formation (Scheme 1).

Scheme 1. Synthesis of Cyclopropanes from Allylic Ethers and Acetals



We envisioned that in an analogous way oxazolidines might be transformed into pyrrolidines. The retrosynthetic approach is depicted in Scheme 2. The pyrrolidine ring could

Scheme 2. Retrosynthetic Approach



be thus constructed by the Lewis acid promoted ring closure starting from the zirconocene intermediate **I**, preformed from **II**. The stereochemistry at the α-position would be controlled by using a rigid *N*-allyl oxazolidine as chiral auxiliary. According to this strategy, the required allyl side chain should be preinstalled by alkylation of a relevant amino alcohol.[12]

The model oxazolidine **1a** was prepared in two steps from readily available (*R*)-2-phenylglycinol (Scheme 3). The reaction with allyl bromide and subsequent condensation with benzaldehyde afforded **1a** in 79% isolated yield, in the almost pure diastereomeric form according to ^{1}H NMR. The hydrozirconation of **1a** was carried out at room temperature in CH_2Cl_2 by using 1 equiv of Schwartz reagent. The reaction went to completion within 1 h, as proven by deuteriolysis, without alteration of the diastereoselectivity.

To achieve the ring-closure step, several Lewis acids were tested (Table 1). A complete conversion was observed using a stoechiometric amount of BF_3·OEt_2 at room temperature

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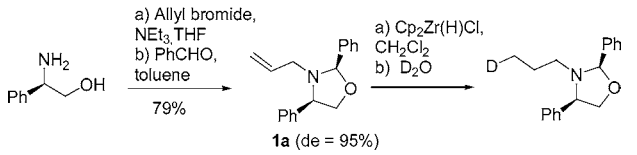
Scheme 3. Synthesis and Hydrozirconation of *N*-Allyloxazolidines

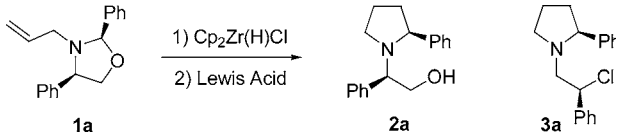


or 0 °C with 2:1 or 3.2:1 diastereomeric ratios, respectively, in favor of **2a** (entries 1 and 2). The selectivity could be further increased by lowering the reaction temperature to −70 °C; unfortunately the yield dropped to 43% (entry 3). When TMSOTf, $AlCl_3$, and $AlMe_3$ were used as Lewis acids, the pyrrolidine was obtained in good yields but with a moderate diastereoselectivity of 2:1, 2.7:1, and 3:1, respectively (entries 4−6). The level of stereoselectivity could be increased to 6:1 when $ZnCl_2$ was used (entry 7). The best diastereoselectivity of 10:1 was obtained with $TiCl_4$. In this case, when an equimolar quantity of $TiCl_4$ was employed, the chloride **3a** was obtained instead of **2a** (entry 8). We noticed, however, that the reaction also took place with a substoichiometric amount (15 mol %) of $TiCl_4$. By using this procedure, **2a** was isolated in 62% yield and with the same 10:1 diastereoisomeric ratio (entry 9). Finally, the catalytic process also proved to operate with BF_3·OEt_2 (entry 10).

To further explore the reaction, various oxazolidines were tested (Table 2). Oxazolidines bearing phenyl or substituted phenyl groups (entries 1−3) as well as heteroaromatic groups (entries 4 and 5) on the C2 atom afforded 2-substituted pyrrolidines (**2a**−**e**) in moderate to good yields. In the case of **2d** and **2e** the low yields originate from the competitive reduction of the aminal function.

The reaction could also be accomplished with oxazolidines bearing C2-alkyl substituents, i.e., *n*-C_5H_{11} and *i*-Pr (entries

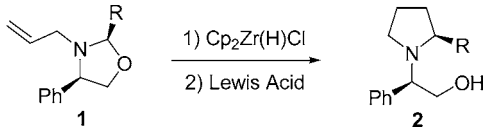
Table 1. Effect of Lewis Acid on the Ring-Closure Step



entry	Lewis acid (mol %)	T (°C)	dr	product yield (%)
1	BF_3·OEt_2 (100)	20	2:1	**2a**[a] (65)[b]
2	BF_3·OEt_2 (100)	0	3.2:1	**2a** (60)[b]
3	BF_3·OEt_2 (100)	−70	6.3:1	**2a** (43)[c]
4	TMSOTf (100)	20	2:1	**2a** (58)[c]
5	$AlCl_3$ (100)	20	2.7:1	**2a** (60)[c]
6	$AlMe_3$ (100)	20	3:1	**2a** (55)[c]
7	$ZnCl_2$ (100)	20	6:1	**2a** (51)[c]
8	$TiCl_4$ (100)	20	10:1	**3a** (69)[c,d]
9	$TiCl_4$ (15)	20	10:1	**2a** (62)[b]
10	BF_3·OEt_2 (15)	0	3:1	**2a** (64)[c]

[a] The optical rotation of the main diastereoisomer was identical to that previously reported.[13] [b] Isolated products. [c] NMR yield. [d] Configuration assigned by analogy.

Table 2. Synthesis of 2-Substituted Pyrrolidines



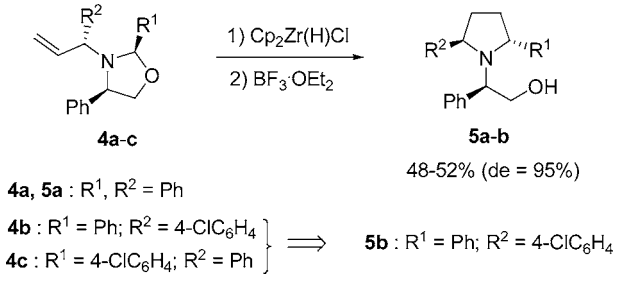
entry[a]	R	Lewis acid	dr	product yield (%)[b,c]
1	Ph	$TiCl_4$	10:1	**2a** (62)
2	2-BrC_6H_4	$TiCl_4$	7.4:1	**2b** (53)
3	2-$MeOC_6H_4$	$TiCl_4$	4:1	**2c** (55)
4	2-furyl	$TiCl_4$	>12:1	**2d** (31)
5	3-furyl	$TiCl_4$	>12:1	**2e** (43)
6	$^nC_5H_{11}$	$TiCl_4$	5.5:1	**2f** (52)
7	^{i}Pr	$TiCl_4$	7:1	**2g** (49)
8	^{i}Pr	$BF_3{\cdot}OEt_2$	1:4	**2g** (48)

[a] Conditions: 1 equiv of $Cp_2Zr(H)Cl$, 15 mol % of the Lewis acid, 0 °C, CH_2Cl_2. [b] Yields refer to isolated products starting from *N*-allylphenylglycinol. [c] Yield refers to combined isomers.

6−8). With $TiCl_4$ as a Lewis acid, 2-substituted pyrrolidines **2a**−**f** were obtained with a generally good diastereoselectivity. A reversal of diastereoselectivity with $BF_3{\cdot}OEt_2$ vs $TiCl_4$ was observed for the oxazolidine with the *i*-Pr group on the C2 atom (entries 7 and 8). In most cases, the diastereomeric pyrrolidines could easily be separated by column chromatography. The chiral auxiliary could be removed after reaction leading to N-deprotected pyrrolidines. As example, diastereoisomerically pure **2f** was submitted to hydrogenolysis (H_2, Pd/C) to afford (*R*)-2-pentylpyrrolidine in 76% yield.[14]

We noticed that the title reaction is not limited to the preparation of 2-substituted pyrrolidines. When using oxazolidines with an α-substituted *N*-allyl chain, 2,5-disubstituted pyrrolidines could be obtained. Examples are given in Scheme 4. In contrast to the results obtained with the

Scheme 4. Stereoselective Synthesis of 2,5-Disubstituted Pyrrolidines



oxazolidines bearing a nonsubstituted *N*-allyl chain, the use of $TiCl_4$ led to nonstereoselective reactions (dr ≅ 1:1) and low yields. However, when $BF_3{\cdot}OEt_2$ was employed, the pyrrolidines **5a** and **5b** were formed with a complete selectivity as *trans* isomers. Accordingly, the oxazolidines **4b** and **4c** with the transposed R^1 and R^2 groups afforded solely the same pyrrolidine **5b**. Therefore, $BF_3{\cdot}OEt_2$ appeared to be an appropriate Lewis acid to achieve highly *trans*-stereoselective formation of 2,5-disubstituted pyrrolidines.

To account for the observed stereoselectivity, we tentatively assumed that two competing mechanistic pathways were involved in the cyclization step. Whereas the minor diastereoisomer would result from an iminium intermediate with a formal retention of configuration, the major diastereoisomer would result from either a highly stereoselective S_N2-like process or an iminium intermediate with inversion of configuration (Figure 1). According to our results and as

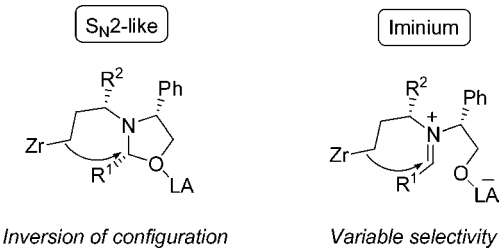


Figure 1. Competing reaction pathways: S_N2-like versus iminium

far as oxazolidines with a nonsubstituted *N*-allyl chain are concerned, the iminium-involving pathway would be generally favored with $BF_3{\cdot}OEt_2$, whereas an S_N2-like process would be enhanced with $TiCl_4$. Within this context, the inversion of stereoselectivity with $BF_3{\cdot}OEt_2$ versus $TiCl_4$ for the major stereoisomer obtained from the oxazolidine bearing a ramified substituent (*i*-Pr) on C2 (entries 7 and 8) could be due to a marked facial discrimination. Starting from oxazolidines with an α-substituted *N*-allyl chain, *trans* 2,5-pyrrolidines were exclusively obtained when $BF_3{\cdot}OEt_2$ was used as a Lewis acid. A unique and highly stereoselective iminium-involving pathway could operate in these cases, resulting in the formal retention of the configuration on the C2 atom. Additional studies are desirable, however, to give a better insight into the stereochemical outcome of these reactions.

In conclusion, we have described a new carbon−carbon bond-forming cyclization reaction that allows a stereoselective construction of the pyrrolidine ring. Simplicity of the procedure, readily available starting materials and a possible stereocontrol of the reaction are noteworthy. Work aimed at further exploring its synthetic scope is currently underway.

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

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