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Synthesis of Cyclic and Acyclic β-Amino Acids via Chelation-Controlled 1,3-Dipolar Cycloaddition

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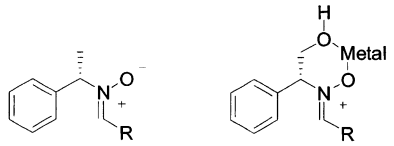
Abstract: Isoxazolidines have been synthesized in diastereomeric excess up to 94% via a $MgBr_2$-induced chelation-controlled 1,3-dipolar cycloaddition reaction with *N*-hydroxyphenylglycinol as a chiral auxiliary. The diastereomerically pure isoxazolidines were further transformed into cyclic and acyclic β-amino acid derivatives.

The 1,3-dipolar cycloaddition (1,3-DC) reaction has emerged as a powerful tool in organic synthesis. The isoxazolidines formed through 1,3-DC reactions are important intermediates in the preparation of natural products, such as alkaloids and β-amino acids. Up to three continuous stereocenters can be formed through 1,3-DC reactions and the challenge of controlling the absolute and relative stereochemistry has attracted much attention in recent years.[1]

Although some powerful enantioselective synthetic methodologies have been reported,[2] diastereoselective approaches have proven to be reliable competitive synthetic strategies.[1] The diastereoselective 1,3-DC approach relies on the effective chirality transfer induced by the chiral auxiliary, which can be located at the nitrone[3] or alkene.[4] Of the two options, the chiral nitrone strategy has proven to be more flexible for further transformations. One prominent nitrone auxiliary is *N*-hydroxy-α-methylbenzylamine, which can be easily cleaved by hydrogenation.[5] However, *N*-hydroxy-α-methylbenzylamine nitrones **1** (Figure 1) behave poorly with unsubstituted alkenes, and moderate diastereoselectivities are quite common in such 1,3-DC reactions.[6]



1 **2**

FIGURE 1. Intermediate chiral nitrone.

The poor selectivity is likely due to the conformational flexibility of the intermediate chiral nitrone **1**. We became interested in the possibility of increasing the diastereoselectivity of such 1,3-DC reactions by conformationally constraining the intermediate chiral nitrone, while an easily cleavable auxiliary was maintained. The *N*-hydroxyphenylglycinol nitrone **2** (Figure 1) fulfills this requirement nicely.[7] The primary hydroxyl group and the polarized oxygen in **2** are ideally placed for a tight chelation with an appropriate metal, and the required *N*-hydroxyphenylglycinol **4** can be easily synthesized in both enantiomeric forms from commercially available phenylglycinol.[8] To test this hypothesis, we synthesized aldehyde **3** and the *N*-hydroxyphenylglycinol **4** according to literature procedures.[9] When **3** was reacted with *N*-hydroxyphenylglycinol **4** in CH_2Cl_2 in the absence of any chelating metals, isoxazolidines **5** and **6** were isolated in a ratio of 63:37. The observed lack of selectivity is consistent with similar ratios observed with nitrone **1**. However, we were quite pleased to observe dramatic improvements in the selectivity upon the addition of $MgBr_2$ (Table 1).[10] When the same reaction was performed in the presence of anhydrous $MgBr_2$, the ratio drastically improved to 93:7 (**5**:**6**).

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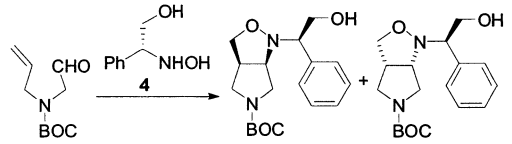
TABLE 1. Optimization of 1−3 DC Reaction



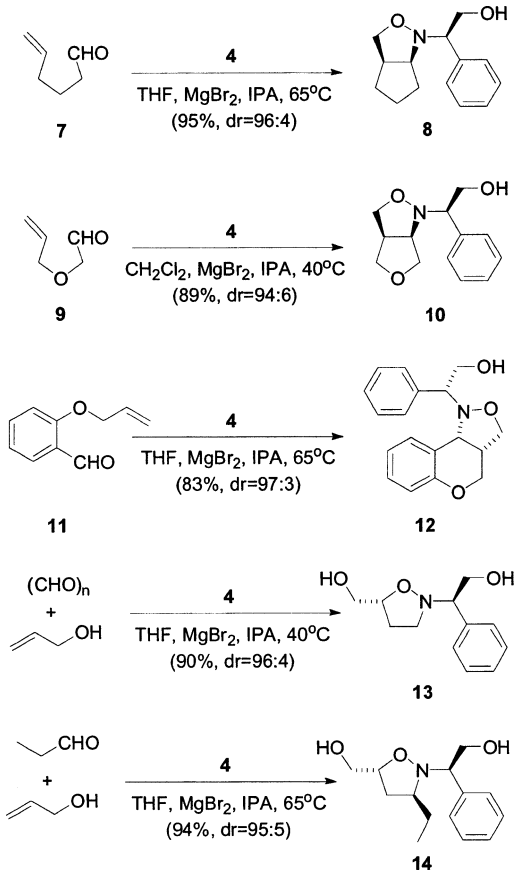
3 5 6

entry	metal	solvent[a]	additive	5:6[b]
1		THF (0.47 M)		59:41
2		CH_2Cl_2 (0.47 M)		63:37
3	$MgBr_2$	THF (0.47 M)		87:13
4	$MgBr_2$	CH_2Cl_2 (0.47 M)		93:7
5	$MgBr_2$	toluene (0.47 M)		86:14
6	$MgBr_2$	MeCN (0.47 M)		88:12
7	$MgBr_2$	CH_2Cl_2 (0.47 M)	IPA	94:6
8	$MgBr_2$	CH_2Cl_2 (0.23 M)	IPA	96:4

[a] Concentration based on *N*-hydroxyphenylglycinol. [b] The ratio was determined by HPLC and ^{1}H NMR of the crude reaction mixture.

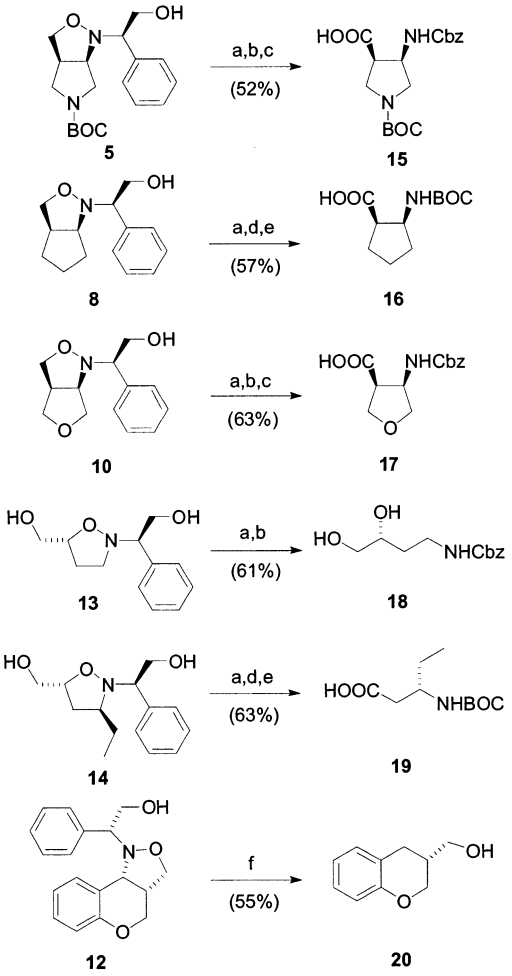
The ratio could be further improved by performing the reaction in the presence of 2-propanol as an additive[11] and under diluted conditions to provide an optimized 96:4 ratio. It is interesting to note that the $MgBr_2$ source

SCHEME 1. Examples of 1,3-DC Reactions[a]



[a] The ratio was determined by HPLC and ^{1}H NMR of the crude reaction mixture run with and without $MgBr_2$.

SCHEME 2. Conversion of 1,3-DC Adducts[a]



[a] Reaction conditions: (a) H_2, $Pd(OH)_2$ on C, MeOH; (b) Cbz-Cl, $NaHCO_3$, THF−H_2O; (c) $NaClO_2$, NaOCl, Tempo; (d) $(BOC)_2O$, $NaHCO_3$, THF−H_2O; (e) $RuCl_3$, $NaIO_4$, MeCN−H_2O; (f) H_2, $Pd(OH)_2$ on C, AcOH.

[commercially available $MgBr_2$ (diethyl etherate), anhydrous $MgBr_2$, or freshly prepared $MgBr_2$] had no significant effect on the selectivity.

To test the generality of the chelation-controlled 1,3-DC reaction, we applied the new protocol to the syntheses of several important pharmaceutical intermediates (Scheme 1).[12]

Importantly, the protocol could be applied to cyclic and acyclic cases, yielding isoxazolidines in high yields and diastereomeric ratios ≥94:6. The power of the chelation-controlled 1,3-DC reaction was well illustrated in the synthesis of adducts **8**, **12**, and **13**, which have been previously reported in the literature using *N*-hydroxy-α-methylbenzylamine as a chiral auxiliary.[13] The chelation-controlled 1,3-DC reaction provided selectivities up to 97:3, compared to between 50:50 and 65:35 as reported

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(11) (a) The exact role of 2-propanol as an additive is not clear; however, we believe it increases the solubility and overall homogeneity of the intermediate chelated nitrone **2**. (b) For a review on additives in asymmetric synthesis: Vogl, E. M.; Gröger, H.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 1570−1577.

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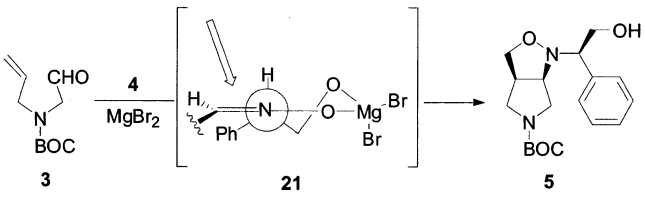
for the non-chelation-controlled *N*-hydroxy-α-methylbenzylamine auxiliary.

The cyclic 1,3-DC adducts were converted to the corresponding *β*-amino acid derivatives[14] via hydrogenation and subsequent oxidation,[15] thereby confirming the absolute configuration as depicted in Scheme 2.

The isoxazolidines **13** and **14** from the acyclic series were similarly converted to known derivatives **18**[16] and **19.**[17] Isoxazolidine **12** was fully hydrogenated over Perlman's catalyst to 3-hydroxymethylcromane (**20**),[13b] which is an important intermediate in the synthesis of α-adrenergic blocking agents.

Mechanistic Considerations. On the basis of the obtained absolute configurations, the stereochemical outcome can be best rationalized by a magnesium-chelated nitrone intermediate **21** (Scheme 3), in which the alkene approaches from the less hindered side.[18] In the case of the acyclic 1,3-DC products, NOE experiments on **14** clearly established the relative configuration, which

SCHEME 3. Possible Mechanistic Explanation for Chelation Controlled 1,3-DC Reaction



is consistent with a magnesium-chelated endo approach of the allyl alcohol to the intermediate *N*-hydroxphenylglycinol nitrone **21**.

In conclusion, a highly diastereoselective 1,3-DC reaction has been developed on both cyclic and acyclic systems with up to 97:3 dr. A predictive mechanistic model has been presented to explain the observed stereochemical outcome. Finally, the chelate-controlled 1,3-DC reaction should find wide application in the synthesis of cyclic and acyclic *β*-amino acids.

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Supporting Information Available: Experimental procedures and spectral data for compounds **5**, **8**, **10**, and **12**−**20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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