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# Asymmetric 1,3-Dipolar Cycloaddition of Nitrones with Ketene Acetals Catalyzed by Chiral Oxazaborolidines

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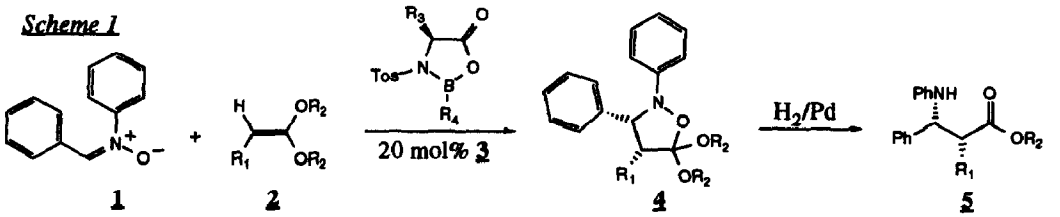
***Abstract** : Asymmetric 1,3-dipolar cycloaddition of nitrones with ketene acetals is strongly catalyzed by chiral oxazaborolidines derived from N-tosyl-L-α-amino acids. The 5,5-dialkoxyisoxazolidines are obtained regioselectively in high yield with high stereoselectivity and moderate enantioselectivity up to 62% ee. Mild hydrogenolysis of the N-O bond yields quantitatively the corresponding β-amino-ester.*

The asymmetric 1,3-dipolar cycloaddition of nitrones has received much attention in the last decade and plays an important role in natural product synthesis[1]. Most advances have been made with chiral nitrones or chiral dipolarophiles[2]. To the best of our knowledge, the effect of chiral catalysts (e.g. Lewis acids) has never been reported[3]. We rationalized that (chiral) Lewis acid catalysts, which have found wide application in various organic reactions[4], may activate the nitrone by complexing the oxygen atom of the nitrone and lowering the LUMO energy. For this reason an electron-rich alkene (e.g. ketene O,O-dialkyl acetal[5a] or enol ether[5b]) is expected to give a LUMO(nitrone) - HOMO(alkene) controlled catalyzed 1,3-dipolar cycloaddition with enhanced reaction rate. Enantioface discrimination by chiral Lewis acid catalysts may eventually allow the smooth introduction of chirality in the cycloadduct.

We decided to test chiral oxazaborolidines **3**[6], derived *in situ* from cheap and easily available N-tosyl-*L*-α-amino acids. Our experiments were oriented on 1,3-dipolar cycloadditions of C-phenyl-N-phenyl nitrone **1** (Scheme 1) and the more reactive and rigid 3,4-dihydroisoquinoline N-oxide **6**[7] with ketene acetals **2**[8] (Scheme 2). Without catalyst these reactions require high temperatures (> 100 °C) to proceed quantitatively[9]. At room temperature the cycloadditions were very slow but indeed could be catalyzed by several non-chiral Lewis acids e.g. 20 mol% $EtAlCl_2$, $Et_2AlCl$, $ZnCl_2$ and $ZnI_2$, of which the latter gave regioselectively the corresponding 5,5-dialkoxyisoxazolidine in quantitative yield after two days. A strong accelerating effect on the reaction rate was observed with 20 mol% of chiral oxazaborolidines **3** ($R_4$ = H). The reaction was complete after 5-24 hours at -78 °C. After aqueous workup the 5,5-dialkoxyisoxazolidines **4** or **7** were isolated as the only product[10]. Enantioselectivities were determined by HPLC analysis using Daicel chiral columns OD and AD. In order to study systematically the factors determining the enantioselectivity we varied the structure of the ketene acetal ($R_1$ and $R_2$), the side-chain substituent ($R_3$) of the oxazaborolidine and the substituent at the boron atom ($R_4$). One of our aims was to find out whether the position of a phenyl ring in the side-chain substituent $R_3$ could determine the enantioselectivity in a similar way as was found for the Diels-Alder reaction of acroleines with cyclopentadiene[6]. The experimental results are summarized in Table 1 and Table 2.

*Scheme 1*

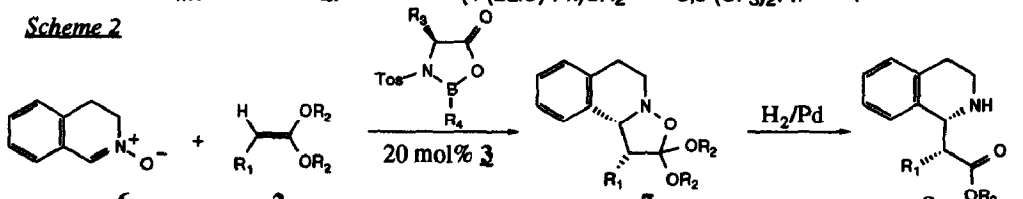


**1** **2** **4** **5**

*Table 1.* *Catalytic asymmetric 1,3-dipolar cyloaddition of C-phenyl-N-phenyl nitrone **1** with ketene acetals **2**[a]*

| entry | $R_1$ | $R_2$ | $R_3$ | $R_4$ | e.e. (%)[b] |
|---|---|---|---|---|---|
| 1 | H | Et | (4-(BzlO)-Ph)$CH_2$ | H | 4 |
| 2 | H | Et | (4-(BzlO)-Ph)$CH_2$ | *n*-Bu | 74[c] |
| 3 | H | Et | Ph | 3,5-$(CF_3)_2$Ph | 0 |
| 4 | H | Et | $PhCH_2$ | 3,5-$(CF_3)_2$Ph | 44 |
| 5 | H | Et | (4-(BzlO)-Ph)$CH_2$ | 3,5-$(CF_3)_2$Ph | 44 |
| 6 | Me | Et | Ph | H | 20[d] |
| 7 | Me | Et | $PhCH_2$ | H | 50 |
| 8 | Me | Et | $PhCH_2CH_2$ | H | 10 |
| 9 | Me | Et | (4-(BzlO)-Ph)$CH_2$ | H | 62 |
| 10 | Me | Et | (4-(BzlO)-Ph)$CH_2$ | 3,5-$(CF_3)_2$Ph | 4 |

*Scheme 2*



**6** **2** **7** **8**

*Table 2.* *Catalytic asymmetric 1,3-dipolar cyloaddition of 3,4-dihydroisoquinoline N-oxide **6** with ketene acetals **2**[a]*

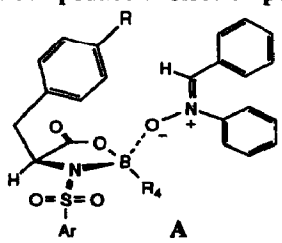
| entry | $R_1$ | $R_2$ | $R_3$ | $R_4$ | e.e. (%)[b] |
|---|---|---|---|---|---|
| 11 | H | Et | Ph | *n*-Bu | 12[d,e] |
| 12 | H | Et | $PhCH_2$ | *n*-Bu | 12 |
| 13 | H | Et | (4-(BzlO)-Ph)$CH_2$ | *n*-Bu | 6 |
| 14 | Me | Me | Ph | H | 12 |
| 15 | Me | Me | $PhCH_2$ | *n*-Bu | 24 |
| 16 | Me | Me | (4-(MeO)-Ph)$CH_2$ | *n*-Bu | 36 |
| 17 | Me | Me | (4-(BzlO)-Ph)$CH_2$ | *n*-Bu | 44 |
| 18 | Me | Et | (4-(BzlO)-Ph)$CH_2$ | H | 12 |
| 19 | Me | Et | $PhCH_2$ | *n*-Bu | 20 |
| 20 | Me | Et | (4-(BzlO)-Ph)$CH_2$ | *n*-Bu | 22 |

[a] all reactions were performed in dichloromethane ($R_4$ =H) or in propionitrile ($R_4$ =*n*-Bu, 3,5-$(CF_3)_2$Ph) at -78 °C for ca. 5-24 hours untill quantitative conversion of nitrone; absolute configuration of products is arbitrarily chosen ; [b] determined with chiral HPLC (Chiralcel OD and Chiralpak AD), *n*-hexane/*i*-PrOH 98/2;[c] ca. 10% chemical yield at room temperature in propionitrile; [d] reaction in tetrahydrofuran; [e]reversal of enantioselectivity.

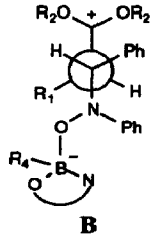
Borane-derived oxazaborolidines ($R_4$ = H) gave quantitative conversion of both nitrones at -78 °C, whereas the less acidic *n*-butyl-boron substituted oxazaborolidines gave low conversion of nitrone **1** but were still strong enough to catalyze 1,3-dipolar cycloadditions of the more reactive cyclic nitrone **6** at -78 °C. Quantitative conversion of nitrone **1** was observed at -78 °C with 3,5-bis(trifluoromethyl)phenylboronic acid[11] derived oxazaborolidines. Table 1 shows that for nitrone **1** the enantioselectivity depends on the position of a phenyl ring in the side-chain substituent ($R_3$) of the chiral oxazaborolidine. Best results were

found for $R_3$=$PhCH_2$ (entry 4 and 7). Further optimization is achieved with tyrosine-(OBzl)-derived oxazaborolidines ($R_3$=(4-BzlO-Ph)$CH_2$, entry 5 and 9). However, these results are also dependent on substituents $R_1$ and $R_2$ of the ketene acetal and $R_4$ of the boron catalyst. For nitrone 6 (Table 2) the substituent effects are less pronounced. Again, best enantioselectivities were obtained with tyrosine-(OBzl)-derived oxazaborolidines (entry 17 and 20), dependent on substituents $R_1$, $R_2$ and $R_4$. From our results we have deduced a "working model" **A** which can be used for further optimization of the catalyst. Enantioface discrimination of the nitrone can be explained by possible "attractive π-π interactions" between the electron-rich phenylring in the side-chain substituent $R_3$ and the C-phenyl part of the nitrone which becomes electron-poor by complexing the Lewis acid to the nitrone oxygen atom. The effects of the substituents $R_1$, $R_2$ and $R_4$ on the stereo- and enantioselectivity can only be understood further when the mechanism of the cycloaddition (concerted or via a dipolar intermediate) is known. The selective formation of the cis-5,5-dialkoxy-4-methyl-3-phenyl-isoxazolidines is in accordance with a dipolar transition state **B**, arising from the most favourable transoid approach of the ketene acetal to the E-nitrone moiety, as described analogously for the polar [2+2]-cycloaddition of ketene acetals to carbonyl compounds or electron-poor imines[12].

"working model"
*Si*-face shielding of *E*-nitrone
(R = H, OBzl)



**A**



**B**

This first example of catalytic asymmetric 1,3-dipolar cycloadditions of nitrones with ketene acetals provides a simple route for the asymmetric synthesis of β-amino esters. Mild hydrogenolysis of the N-O bond of *cis*-5,5-dimethoxyisoxazolidine 4 ($R_1$=$R_2$=Me; m.p. 112 °C) with 1 atm. $H_2$/Pd(C) for 30 min. at room temperature yielded the known *syn*-β-amino ester 5 ($J_{H2,H3}$ = 5.0 Hz, m.p. 98 °C; lit.[13] 98-99 °C). In a similar manner 5,5-diethoxyisoxazolidine 7 ($R_1$=H, $R_2$=Et) was converted into tetrahydroisoquinoline ethyl ester 8, a versatile intermediate in the synthesis of various biologically active compounds[14].

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10. General procedure: The chiral oxazaborolidines (0.2 mmol) were prepared *in situ* from N-tosyl-*L*-α-amino acids[6] at room temperature under inert nitrogen atmosphere by addition of equimolar amounts of $BH_3$.THF, or *n*-BuB$(OH)_2$ or 3,5-$(CF_3)_2$PhB$(OH)_2$ in the presence of powdered 4Å molecular sieves, in dry solvent (4 ml). Nitrone (1.0 mmol) was added at room temperature, the mixture cooled to -78 °C and the ketene acetal (2-3 eq.) was added. After 5-24 hours the reaction mixture was quenched with saturated aqueous bicarbonate, extracted with dichloromethane and diethyl ether, dried with sodium sulphate and concentrated under vacuum. The crude isoxazolidine was isolated and purified by flash chromatography on silica gel or alumina using ether:*n*-hexane (1:1-4) as eluens (containing 1% $Et_3N$). Yields: ca. 80-99%.
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