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DIASTEREOSELECTIVITY IN THE SYNTHESIS OF MANNICH BASES

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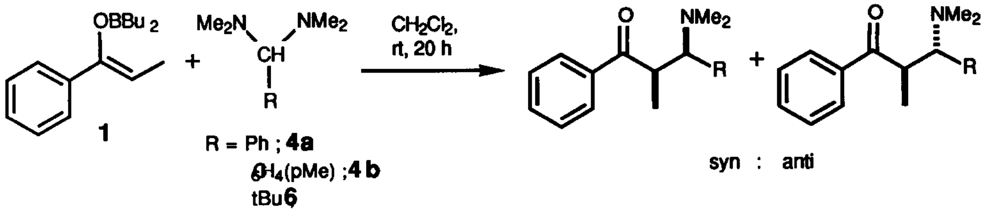
Summary: Diastereoselectivity has been observed in the Mannich reaction between boron enolates and aminals.

The Mannich reaction can be viewed as the imino analogue of the aldol reaction. Stereoselective aldol chemistry has been the focus of a great deal of attention, yet there has been scant attention directed to the stereoselective Mannich reaction outside of the ketene acetal-imine condensation.[1] While the classic Mannich condensation[2] utilized only formaldehyde as the imino component, Katritzky[3] and Seebach[4] have extended the variability of the imino component to othe aldehydes by employing benzotriazole aminals and trichlorotitanium dialkylamino-alkoxides, respectively. As the use of acetals has proved interesting in the aldol field, we have explored the use of aminals in the Mannich reaction.[5]

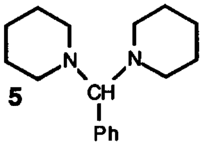
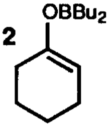
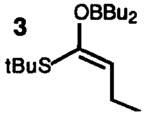
We have observed diastereoselectivity in the reaction between boron enolates and aminals[6] in dichloromethane producing β-aminocarbonyl compounds, see the general reaction below. The reactions herein described are limited to non-enolizable aminals due to the propensity of acyclic aminals to undergo elimination to the enamine.



Yields were quite good (61-95%) for the aromatic aminals, **4** and **5**, at room temperature, se the table. For the β-aminoketones equilibration typically afforded good diastereoselectivity, however the β-aminothiolester showed no selectivity under kinetic or thermodynamic conditions. The major diastereomers from the thermodynamic reactions of **1** with the phenyl aminal **4a** and the t-butyl aminal **6** were identified by the syn-elimination of the tertiary amine N-oxide, generated with MCPBA, to yield the known E and Z-alkenes.[7]

While the trichlorotitanium enolate[8] of the parent ketones of **1** and **2** provided Mannich bases upon reaction with **5**, the yields were somewhat lower, 49% (2.6:1 syn:anti) and 23% (7.5:1 ds) respectively. The less Lewis acidic lithium enolates were unreactive with these aminals in dichloromethane, tetrahydrofuran, and benzene.

Table. Reaction of Boron Enolates **1** - **3** with Aminals **4** - **6**

Enolates	Aminals	Conditions[a]	Yield (%)[b]	Diastereoselectivity (ds)[c]
1	**4a**	A	33	4 : 1, syn : anti
1	**4a**	rt, 6 hr	90	1 : 1
1	**4a**	B	95	1 : 17, syn : anti
1	**5** 	A	31	1 : 1.2[d]
1	**5**	B	86	1.3 : 1[d]
1	**6**	A	21	4 : 1, syn : anti
1	**6**	B	34	14 : 1, syn : anti
2 	**4b**	A	21	1.4 : 1[d]
2	**4b**	B	37	15 :1[d]
2	**5**	B	72	4.3 : 1[d]
3 	**4b**	B	61	1.2 : 1[d]
3	**5**	B	69	2.2 : 1[d]

[a] Conditions: Boron enolate : Aminal = 1.0 : 1.2, in CH_2Cl_2 (0.5 M); A = $^{-}78^{\circ}C$, 5-20 min. B = rt, 16-20 hr. [b] Isolated yield. [c] Diastereoselectivity (ds) determined by ^{1}H-NMR. [d] Major diastereomer not identified.

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