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Factors Influencing the Stereoselectivity in the Cycloaddition of Imino-Dienophiles Derived from Amino Ethers, Amino Alcohols, and Amino Acid Esters

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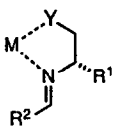
Summary: Imino dienophiles derived from amino ethers, amino alcohols and amino esters undergo Lewis acid promoted cycloaddition with Danishefsky's diene. Cyclic chelation between the imine and oxygen atom increases the stereoselectivity of the reaction.

Construction of nitrogen heterocycles through the use of imino-dienophiles in Diels-Alder reactions has received much attention in recent times.[1-6] The use of Lewis acids to counteract the low reactivity has further increased their potential in synthesis.[2] The diastereoselectivity of this reaction has been investigated with α-alkoxy imines[3], imines with carbohydrate templates[4], and imines derived from esters of amino acids.[5] The most recent progress in this area has been made through the use of chiral Lewis acids in asymmetric aza Diels-Alder reactions.[6] In some of these cases, an addition-cyclization pathway was suggested while in others, a cycloaddition pathway was suggested.

Our own investigation in this area focuses on factors which influence the stereoselectivity in imino-dienophiles that have the capacity to form a cyclic chelate as in structure **1**.[7] The cyclic chelate formed with Lewis acids would give a predictable conformation of the dienophile.



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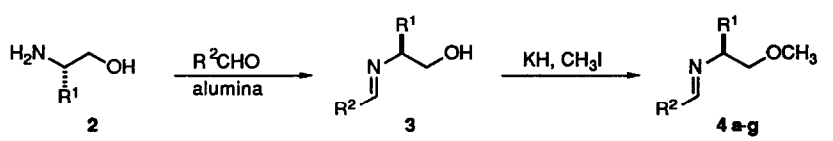
For the purpose of these investigations a variety of imines were synthesized. The imines **4a-4g** (Y=OCH_3) were synthesized from amino alcohols derived from amino acids (Scheme). The amino alcohols were condensed with the corresponding aldehydes followed by alkylation of the hydroxy group to obtain the desired imines in 54-88% yield.[8] Attempted synthesis of imine **4h** (R^1=R^2=*i*-Pr, Figure 1) by this method resulted in extensive cyclized product in the alkylation step. This led us to synthesize imine **4h** in a more indirect manner from **4b** (1. 1N HCl, 2. *i*-PrCHO, $MgSO_4$). Imines **4i** - **4l** and **4n** were synthesized from the corresponding amines and aldehydes. Alkylation of **4l** (LDA, CH_3I) led to imine **4m**.

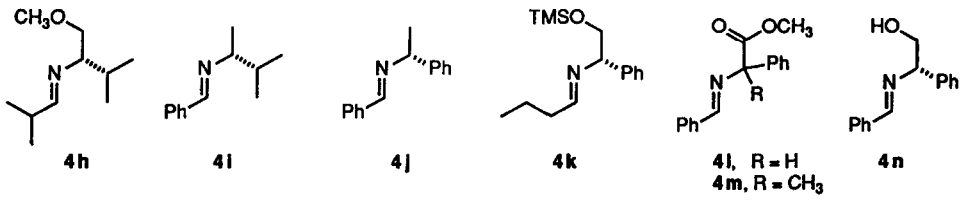
Scheme



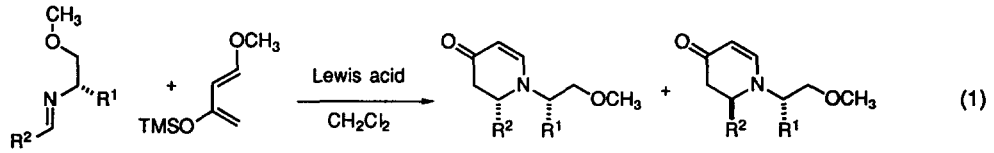
2 **3** **4 a-g**

4a, R^1= *i*-Pr, R^2 = Ph
4b, R^1= CH_3, R^2 = Ph
4c, R^1= CH_2Ph, R^2 = Ph
4d, R^1= Ph, R^2 = Ph
4e, R^1= *i*-Pr, R^2 = *p*-Ph-NO_2
4f, R^1= *i*-Pr, R^2 = *p*-Ph-OCH_3
4g, R^1= *i*-Pr, R^2 = *t*-Bu

Figure 1



For our initial studies, we chose to assay cycloaddition diastereoselectivity as a function of Lewis acid promoter. We selected cycloadditions of imine **4a** with Danishefsky's diene (Equation 1).[9] Representative results using a series of Lewis acids appear in the Table (entries 1-6).[10] The cycloaddition was carried out employing 1-1.5 eq of Lewis acid in dichloromethane at room temperature. Similar results were obtained with $BF_3{\cdot}Et_2O$, $Zn(OTf)_2$[11], and $SnCl_2$(entries 3-5). We chose $BF_3{\cdot}Et_2O$ and $Zn(OTf)_2$ for the rest of our investigations.



(1)

Comparison of the cycloaddition results show some interesting trends. The steric requirement of the stereodirecting R^1-group has a direct influence on the stereoselectivity. As the size of the directing appendage increases (methyl, isopropyl, phenyl group), the stereoselectivities are enhanced (entries 7, 8, 3, 4, and 11). In comparing aldimines, there is little difference between aliphatic or aromatic groups (entries 3, 4, 15, and 16). Electron donating or withdrawing groups on the aromatic aldimines also had little influence (entries 3, 4, 12, and 13). However, no cycloaddition was observed with the bulky *t*-butyl group (entry 14).

The second chelation site has a definitive effect on the stereoselectivity. For example, imine **4i**, which cannot form a cyclic chelate, gave lower stereoselectivity than imine **4a** (entry 17 vs. 4).[12] Imine **4j**, which also cannot form a cyclic chelate, gives lower stereoselectivity than its counterparts, imines **4d** and **4n** (entry 18 vs entries 11 and 22).[4b] Imines with a second chelation site that is more Lewis basic (Y = CO_2CH_3, OH) gave higher diastereoselectivity than imines with a less Lewis basic site (Y = OTMS, entries 21 and 22 vs. 19).[13] Imines with intermediate Lewis basicity (Y = OCH_3) gave corresponding intermediate stereoselectivity.

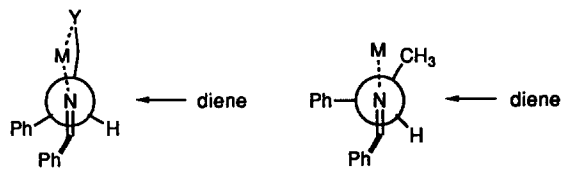
It is interesting to note that under our conditions, imine **4l** (R = H) gave only small amounts of the desired product along with numerous other compounds.[14] Upon replacing the hydrogen with a methyl group (**4m**, R = CH_3), a clean reaction occured in 60% yield, indicating that enolization may have been the problem with **4l**. The sense of stereoselectivity is identical for imines which form cyclic chelates and those which cannot. For the compounds which can form a cyclic chelate, the approach of the diene can be rationalized by the transition state **8** (Figure 2).[15] The modified Felkin-Anh model **9** rationalizes the approach of the diene in the acyclic chelate.[16] Theoretical calculations suggest that the diene approach exo to the nitrogen lone pair.[17]

Table. Cycloaddition of Imines **4a-4n**

Entry	Imine	R^1	R^2	Y	Lewis Acid	6 : 7	Yield(%)
1	**4a**	*i*-Pr	Ph	OCH_3	Et_2AlCl	72 : 28	24
2	**4a**	*i*-Pr	Ph	OCH_3	Me_3Al	--	--
3	**4a**	*i*-Pr	Ph	OCH_3	$BF_3{\cdot}Et_2O$	79 : 21	55
4	**4a**	*i*-Pr	Ph	OCH_3	$Zn(OTf)_2$	87 : 13	67
5	**4a**	*i*-Pr	Ph	OCH_3	$SnCl_2$	83 : 17	66
6	**4a**	*i*-Pr	Ph	OCH_3	$ZnCl_2$[a]	76 : 24	33
7	**4b**	CH_3	Ph	OCH_3	$BF_3{\cdot}Et_2O$	53 : 47	54
8	**4b**	CH_3	Ph	OCH_3	$Zn(OTf)_2$	59 : 41	63
9	**4c**	CH_2Ph	Ph	OCH_3	$BF_3{\cdot}Et_2O$	73 : 27	53
10	**4c**	CH_2Ph	Ph	OCH_3	$Zn(OTf)_2$	73 : 27	47
11	**4d**	Ph	Ph	OCH_3	$Zn(OTf)_2$	87 : 13	51
12	**4e**	*i*-Pr	*p*-Ph-NO_2	OCH_3	$BF_3{\cdot}Et_2O$	77 : 23	57
13	**4f**	*i*-Pr	*p*-Ph-OCH_3	OCH_3	$Zn(OTf)_2$	82 : 18	79
14	**4g**	*i*-Pr	*t*-Bu	OCH_3	$Zn(OTf)_2$	--	--
15	**4h**	*i*-Pr	*i*-Pr	OCH_3	$BF_3{\cdot}Et_2O$	77 : 23	48
16	**4h**	*i*-Pr	*i*-Pr	OCH_3	$Zn(OTf)_2$	72 : 28	50
17	**4i**	*i*-Pr	Ph	H	$Zn(OTf)_2$	72 : 28	60
18	**4j**	Ph	Ph	H	$Zn(OTf)_2$	80 : 20	69
19	**4k**	Ph	*n*-Pr	OTMS	$Zn(OTf)_2$	58 : 42	45
20	**4l**	H	Ph	CO_2CH_3	$Zn(OTf)_2$	--	--
21	**4m**	CH_3	Ph	CO_2CH_3	$Zn(OTf)_2$	>95 : <5 [b]	60
22	**4n**	Ph	Ph	OH	$BF_3{\cdot}Et_2O$	>95 : <5 [b]	60

[a] The reaction was carried out in THF. [b] One isomer was detected by ^1H NMR (360 MHz).

Figure 2



8 **9**

In summary, we have shown that chelation between the imine and the Y-group improves the stereoselectivity. There is a correlation between the Lewis basicity of the Y-group and the stereoselectivity. Under our conditions $BF_3{\cdot}Et_2O$ and $Zn(OTf)_2$ were excellent Lewis acids. The directing appendage R^1-group has a direct influence on the selectivity while the substituent on the carbon side of the imine had little effect, with the exception of the bulky *t*-butyl group. Imines derived from phenylalanine should be especially useful since the nitrogen can be deprotected via hydrogenolysis.[18]

Acknowledgment. We acknowledge partial support of this work by the SUNY Research Foundation.

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