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Studies on the role of Lewis basicity of the aldehydes utilized in the enantioselective Mukaiyama aldol reaction promoted by chiral 1,3,2-oxazaborolidin-5-ones

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Abstract

N-Tosyl-2-1,3,2-oxazaborolidin-5-one **1** was used to probe the role of the Lewis basicity of aldehydes utilized in Mukaiyama aldol reactions promoted by oxazaborolidin-5-ones. Eight aldehydes were each allowed to undergo a Mukaiyama aldol reaction with ketene silyl acetal derived from methyl isobutanoate. Lewis basicity of the aldehydes was determined computationally. The best results were obtained with isobutyl aldehyde and 3,4,5-trimethoxy benzaldehyde (91% and 85% *ee*). The best fit of *ee* as a function of Lewis basicity gave a correlation of R^2=0.79 [when two *ortho*-substituted aldehydes were excluded] suggesting that Lewis basicity of O_{CHO} can play a role in reactions of aldehydes promoted by **1**. © 1999 Elsevier Science Ltd. All rights reserved.

Chiral *N*-sulphonylated 1,3,2-oxazaborolidin-5-ones (e.g. **1**, Fig. 1) are known as efficient catalysts and promotors for asymmetric Diels–Alder,[1] Mukaiyama aldol,[2] and 1,3-dipolar cycloaddition[3] of nitrones to ketene acetals. The active substance (**1**, R=H; Fig. 1) was thought to form when borane (R=H; Fig. 1) or a boronic acid (R=alkyl; Fig. 1) is allowed to react with the corresponding *N*-sulphonylated amino acid.[1]

Various aldehydes were used as starting material in the reactions mentioned earlier, but how important the Lewis basicity of O_{CHO} is, appears not to be known.[4] The aim of this study was to shed light on this topic. Mukaiyama aldol reactions [using **1** (R=H, R′=*i*-Pr); Fig. 1] were carried out with one aliphatic and seven aromatic aldehydes (**2a**–**h**; Fig. 1). The silylated aldols were desilylated by treating them with dilute HCl. Formation of the aldols **3a**–**h** (Fig. 1) was confirmed by ^{1}H NMR and the *ee* values were determined using HPLC.[5]

Lewis basicity of the aldehydes was estimated computationally using the widely available semi-empirical AM1 method as implemented in the Spartan program.[6] In one of the aromatic *ortho*-substituted aldehydes (**2c**) the π-system of the CHO group was found, as expected, to be out of the plane of the ring (other π-systems including **2e** and **2h** were fully planar). Results shown in Table 1 (and illustrated in

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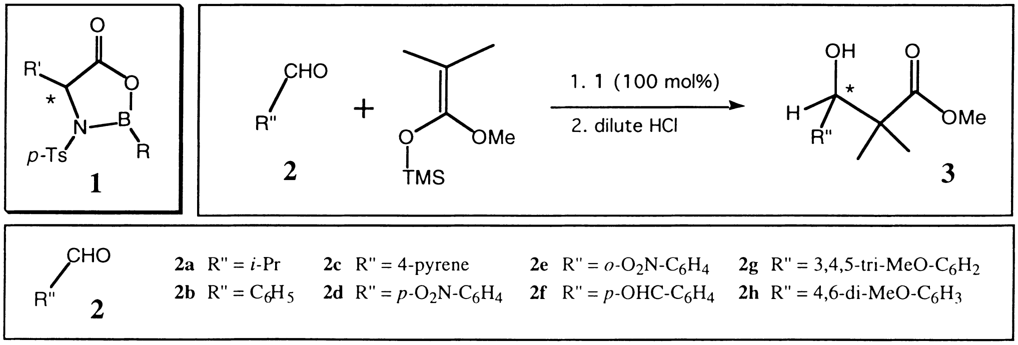

Figure 1. Coding of aldehydes (**2**) studied as substrates of Mukaiyama aldol (giving rise to the formation of **3**) promoted by **1** (R=H, R′=*i* -Pr). Aldol adducts of these aldehydes (the Scheme) are coded accordingly [i.e. R″ (**2**)=R″ (**3**)]

Table 1

Determined *ee* values[a] and chemical yields[b] of **3a**–**h** with charges[c] of O_{CHO} of **2a**–**h**[d]

Aldehyde	**3** (e.e. %)[a]	**3** (Yield %)[b]	Q (O_{CHO})[c]	Aldehyde	**3** (e.e. %)[a]	**3** (Yield %)[b]	Q (O_{CHO})[c]
2a	91	70	-0.466	**2e**	72	50	50
2b	83	76	-0.448	**2f**	80	42	42
2c	56	74	-0.459	**2g**	85	73	73
2d	77	40	-0.421	**2h**	34	35	35

[a] Enantiomeric excesses (ref. 5). [b] Isolated yields (ref. 5). [c] Atomic charges (electrostatic fit) of O_{CHO} (ref. 6). [d] Fig. 1.

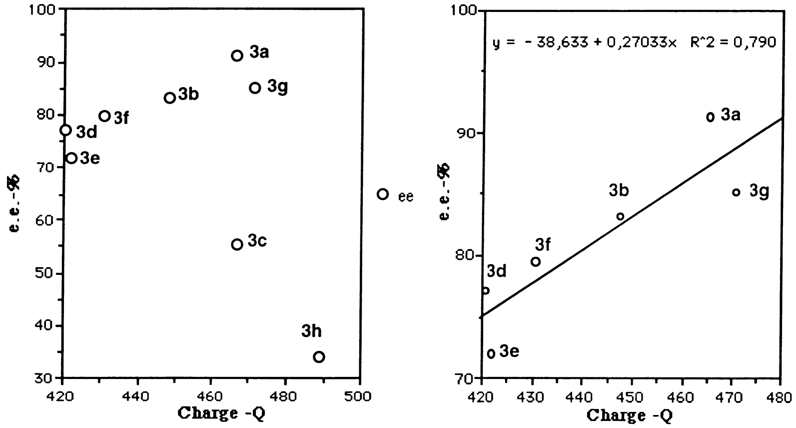

Figure 2. Correlation of the negative charges [Q(O_{CHO}), Table 1] with the observed enantioselectivity (*ee*, Table 1)

Fig. 2) indicate that in the case of **2a**, **b** and **2d**–**g** the observed *ee* values correlate considerably well (R^2=0.79; Fig. 2, on the right) with the Lewis basicity of O_{CHO}. On this basis it looks as if the Lewis basicity would be a factor of some significance in the case of Mukaiyama aldols promoted by **1** (R=H; Fig. 1).

The values of **3c** and **3h** do not fit this correlation, possibly because their *ortho*-position is bearing bulky groups, which are potentially oriented to directions in which they hamper coordination of RCHO to **1**. Both *O*-NO_2 and CHO groups of **2e**, however, appear to reside in the plane of the aromatic ring (the O_{NO_2} and H_{CHO} atoms in a *syn*-arrangement). Thus, the *ortho*-effect is much smaller in the case of **2e** than in **2c** or **2h**. Therefore, we consider the behavior of **2c** and **2h** to be related to repulsive steric factors which blur the enantiocontrol provided by attractive interactions. Further studies on these chiral promoters are in progress.

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References

1. Dias, L. C. J. *Braz. Chem. Soc.* **1997**, *8*, 289.
2. Kiyooka, S.-I.; Kira, H.; Hena, M. A. *Tetrahedron Lett*. **1996**, *37*, 2597.
3. Seerden, J.-P. G.; Scholte op Reimer, A. W. A.; Scheeren, H. W. *Tetrahedron Lett*. **1994**, *35*, 4419.
4. Simpura, I.; Nevalainen, V. *Proceedings of the 12th ICOS Meeting*, Venezia, Italy, 1998.
5. All aldols gave the expected proton NMR spectra. Enantioselectivities (*ee*) were determined using HPLC (CHIRALGEL OJ).
6. Wavefunction Inc., Irvine, CA, USA, 1996.