Reagent Control of Cram-type Selectivity in the Mukaiyama Aldol Catalysed by Supersilylating Agents

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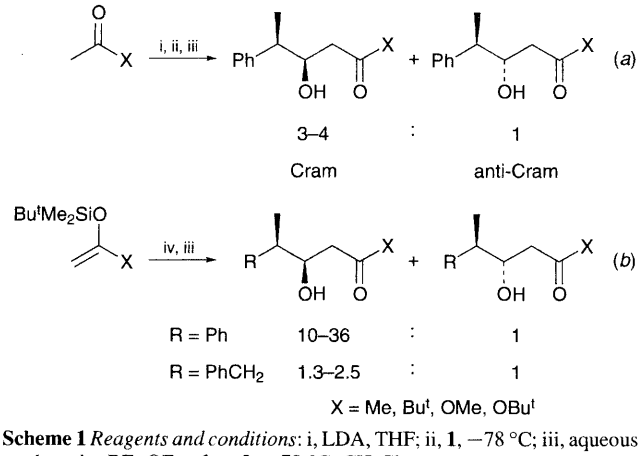
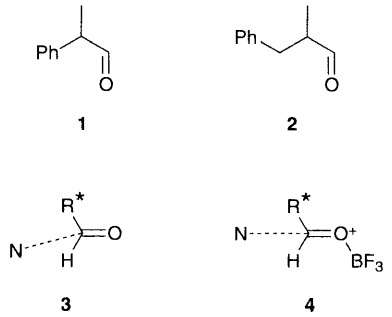
In the addition of silyl enol ethers **8** to α-asymmetric aldehydes **1** and **2**, catalysed by 'supersilylating agents' $R_3SiB(OTf)_4$,† the level of Cram-type selectivity correlates with the steric bulk of the silyl group; use of the triisopropylsilyl enol ether **8d** results in unprecedented levels of 1,2-asymmetric induction.

The control of stereochemistry in additions to unfunctionalised α-asymmetric aldehydes is a long-standing problem in acyclic stereoselection.[1–5] For alkyl or aryl organometallic reagents, 'Cram-type' selectivities may be optimised by modifications at the metallic centre, which is directly attached to the nucleophilic carbon atom.‡[2] However, for 'π-nucleophiles' (*e.g.* enolates) which are activated by remote metal atoms, this strategy is less likely to be effective while any alteration at the nucleophilic centre itself must necessarily change the constitution of the product.[3]

During the 1980's C. H. Heathcock and his collaborators developed an intriguing approach to this problem based on the concept of 'trajectory analysis'.[4] In an initial publication[4a] they reported that, whereas α-unsubstituted lithium enolates reacted with rather poor Cram-selectivity [*e.g.* Scheme 1, eqn. (*a*)], use of the BF_3-promoted Mukaiyama addition produced a substantial improvement [Scheme 1, eqn (*b*)].[5] As shown, diastereoisomeric ratios (d.r.) could be raised to impressive levels with aldehyde **1**, while appreciable (though still modest) selectivities could be obtained with the far more challenging substrate **2**. To explain these results, they proposed that coordination of the Lewis acid to the aldehyde might divert the path of an approaching nucleophile such that it passes closer to the asymmetric centre (*i.e.* **4** *vs.* **3**). The principle was later validated through experiments on acetals[4e] and thionium ions.[4c,d] However, for lack (presumably) of a suitable system it was never applied to the further improvement of additions to *aldehydes*, and the BF_3-mediated reaction remained the optimal method for such transformations.

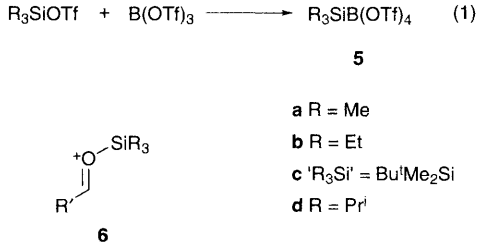


Scheme 1 *Reagents and conditions*: i, LDA, THF; ii, **1**, −78 °C; iii, aqueous workup; iv, $BF_3.OEt_2$, **1** or **2**, −78 °C, CH_2Cl_2



In a recent study, we found that treatment of $B(OTf)_3$ with Me_3SiOTf in dichloromethane or chloroform gave solutions containing a potent silylating agent formulated as $Me_3SiB(OTf)_4$ **5a** [eqn. (1), Tf = SO_2CF_3].[6] This species was shown to catalyse the addition of allyltrimethylsilane to aldehydes with remarkable efficiency, 3–4 orders of magnitude greater than that of Me_3SiOTf. Presuming that the allylation was proceeding *via* generation of silyloxonium intermediates **6a**, we reasoned that variation of R should be feasible, allowing control over the steric bulk of the activating moiety. It might thus be possible, for the first time, to apply Heathcock's concept systematically to an aldehyde addition reaction, and thereby make significant improvements to the levels of Cram-selectivity possible with π-nucleophilic reagents.

A plausible mechanism for the 'silicon-catalysed' allylation is shown in Scheme 2 (X = CH_2, R″ = H). Although this may not be correct in every detail, we felt safe in assuming that, as indicated, the silyl group in **5** and **6** would be derived partly from the added supersilylating agent and partly from the nucleophilic reagent **7**. Accordingly we chose to use the same silyl group in both components, and began by generating the highly hindered supersilylating agent **5d** and testing its ability to catalyse the addition of allyltriisopropylsilane to **1** in CH_2Cl_2 at room temperature. Disappointingly, the reaction was slow and gave a complex mixture of products. However, on changing to the Mukaiyama aldol, employing the silyl enol ether **8d** as nucleophile, we obtained a more pleasing result. As shown in Scheme 3, the addition of **8d** to **1** catalysed by **5d** (5 mol%)§ proceeded smoothly at low temperature to give **9d** and **10d** in a



Scheme 2 Possible mechanism for $R_3SiB(OTf)_4$ catalysis of (*a*) the allylation of aldehydes by allyltrimethylsilane (X = CH_2, R″ = H; see ref. 6), and (*b*) the Mukaiyama addition of silyl enol ethers to aldehydes (X = O; *cf.* ref. 7)

ratio of *ca.* 97 : 1 and an acceptable yield of 71%. A similar experiment with aldehyde **2** as substrate yielded **11d** and **12d** in the ratio 7 : 1. *As far as we are aware, these are the highest selectivities recorded for additions of 2-unsubstituted enolates to these aldehydes.*¶

To demonstrate that the steric bulk of the silyl group was indeed the factor controlling the stereoselectivity, we carried out additions to **1** and **2** using the supersilylating agents **5a–c** as catalysts and the corresponding silyl enol ethers **8a–c** as nucleophiles. The reactions proceeded in a satisfactory fashion to give, after aqueous workup, the corresponding aldols and/or their silylated derivatives **9–12** with varying degrees of diastereoselectivity. The full set of results is summarised in Table 1. Given the limitations of the analytical method used (NMR integration) we cannot be confident of the distinction between the Et_3Si and Bu^tMe_2Si reagent combinations, especially in the case of substrate **2**. However the general trend is as expected, there being a clear correlation between the size of the trialkylsilyl group and the stereoselectivity.

Treating Scheme 2 (X = O, R″ = Ph) as a working mechanistic hypothesis, one might expect that the 5 mol% of added **5** would be overwhelmed by the 'R_3Si^+' groups derived from the nucleophile. We have indeed found that, under our standard conditions, it is the silyl group present in **8** which dominates the stereochemical outcome. Thus addition of **8d** to **2** catalysed by 5 mol% of **5a** resulted in an 83% yield of **11d** and **12d** in the expected ratio of 7 : 1. This result highlights (but does not answer) an important mechanistic question; does the controlling effect of the trialkylsilyl group derive from its presence in silyloxonium ion **6** (as originally hypothesised), or in the attacking nucleophile **8**? Molecular modelling on **6** (R = Pr^i) lends credibility to the former option, by showing that the steric 'umbrella' provided by the Pr^i_3Si group could indeed affect the trajectory of an approaching nucleophile. Experimentally, the issue is being addressed through reactions employing stoichiometric quantities of the supersilylating agents.

In conclusion, we have shown that 'supersilylating agents' $R_3SiB(OTf)_4$ can be used to catalyse the Mukaiyama addition to unfunctionalised α-asymmetric aldehydes with unprecedented levels of 'Cram-type' selectivity.

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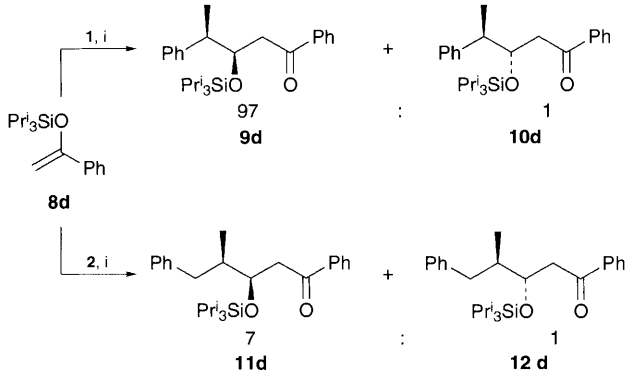

Scheme 3 *Reagents and conditions*: i, $Pr^i_3SiB(OTf)_4$ **5d** (5 mol%), CH_2Cl_2, −80 °C

Table 1 Additions of enolsilanes **8** to aldehydes **1** and **2** catalysed by supersilylating agents **5**[a]

Reagent combination	'R$_3$Si'	Aldehyde	D.r. (Cram : Anti-Cram)[b]	Yield (%)
5/8a	Me_3Si	**1**	8 : 1	44[c]
5/8b	Et_3Si	**1**	18 : 1	60[c]
5/8c	Bu^tMe_2Si	**1**	25 : 1	82[d]
5/8d	Pr^i_3Si	**1**	97 : 1	71[d]
5/8a	Me_3Si	**2**	1.8 : 1	45[c]
5/8b	Et_3Si	**2**	2.3 : 1	71[e]
5/8c	Bu^tMe_2Si	**2**	2.4 : 1	70[d]
5/8d	Pr^i_3Si	**2**	7 : 1	71[d]

[a] All reactions took place over 1 h in CH_2Cl_2 at −80 °C, employing 5 mol% of **5** as catalyst, and quenching at low temp. with sat. aq. $NaHCO_3$. [b] Determined by NMR integration. Cram's rule was assumed to hold for both substrates, and was used to assign product stereochemistries. [c] Hydroxy-ketone products. [d] Silyloxy-ketone products. [e] Mixture of hydroxy- and silyloxy-ketones.

Footnotes

† 'R_3Si' is used in this paper as a general designation for a trialkylsilyl group, and should be taken to include groups such as Bu^tMe_2Si in which the three alkyl groups are dissimilar.

‡ References 2*a–e* report quite satisfactory levels of Cram-type selectivity in additions to aldehyde **1**, (d.r.'s in the region of 20–30 : 1). However, it may be noted that selectivities with aldehyde **2**, where reported, are considerably lower; see *e.g.* ref. 2*c*, where a BuLi–crown ether complex is reported to give *d.r.* ≥30 : 1 with **1**, but only 2 : 1 with **2**.

§ The addition of silyl enol ethers and silyl ketene acetals to aldehydes has previously been catalysed by conventional silylating agents.[7] However, in the present case it seems that the extra potency of the supersilylating agent is indeed necessary, as Pr^i_3SiOTf proved to be completely ineffective in a control reaction under our standard conditions.

¶ It might be argued that acetophenone-derived silyl enol ethers, which were not employed in ref. 4*a*, might have a particular ability to undergo Cram-selective additions. However, in our hands the $BF_3.OEt_2$-induced addition of **8c** to **2** [Scheme 1, eqn. (*b*), X = Ph, R = $PhCH_2$] gave Cram and anti-Cram products in the ratio of only 2.7 : 1.

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