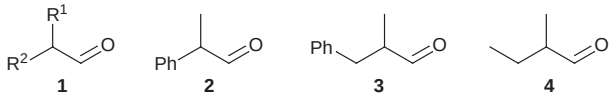
# The triisopropylsilyl effect: exceptional Cram-type selectivity in Mukaiyama aldol reactions of a silyl ketene thioacetal

**Anthony P. Davis,*† Stephen J. Plunkett and Jayne E. Muir**

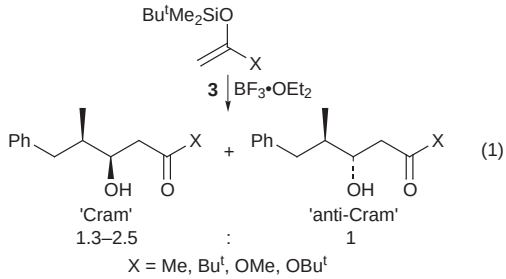
*Department of Chemistry, Trinity College, Dublin 2, Ireland*

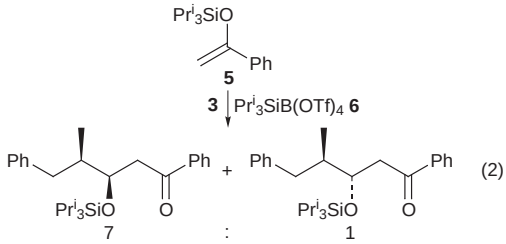
**The level of 1,2-asymmetric induction in the $BF_3{\cdot}OEt_2$-promoted addition of silyl ketene thioacetals to α-asymmetric aldehydes is affected by the bulk of the silyl group; unprecedented Cram-type selectivity is given by the triisopropylsilyl derivative 8a.**

The optimisation of 1,2-asymmetric induction in additions to aldehydes **1** still presents challenges in stereoselective synthesis. Effective methodology is available for substrates with heteroatom-based substituents,[1] while good 'Cram-type' selectivity can now be obtained with α-aryl aldehydes, or where $R^1$ and $R^2$ are alkyl groups of greatly differing steric bulk.[2,3] However, in cases where the α-substituents are more subtly differentiated, it is still difficult to achieve acceptable levels of selectivity. We now describe a variant of the Mukaiyama aldol addition which provides useful Cram-type selectivities with even the most 'difficult' of aldehydic substrates.

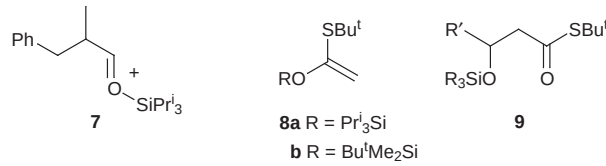



The new method is related to the conventional Mukaiyama addition as explored by Heathcock and Flippin [*e.g.* eqn. (1)],[3a] and to our subsequent development exemplified by eqn. (2).[3f]

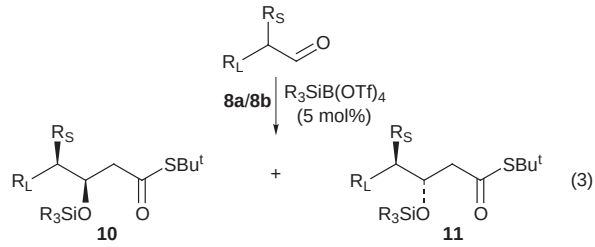



The Heathcock study yielded good selectivities (up to 36 : 1) with 2-phenylpropanal **2**, but modest results with the more challenging **3**. In our own methodology, use of triisopropylsilyl enol ether **5**, and 'supersilylating agent' **6**[4] gave a selectivity of *ca.* 100 : 1 with **2** and [as shown in eqn. (2)] a useful level of 7 : 1 with **3**. The improvement was thought to be due to the bulk of the $Pr^i_3Si$ group in intermediate **7**, requiring the nucleophile to pass close to the asymmetric centre.[5] Control experiments employing $BF_3{\cdot}OEt_2$ catalysis, and **3** as substrate, gave lower selectivities (*ca.* 3 : 1) that did not depend substantially on the bulk of the silyl group in the enolate.[3f,6]




The present work was aimed at extending the scope of our earlier method, specifically by employing a nucleophile of more general utility than **5**. Silyl ketene thioacetals **8** seemed especially attractive due to the versatility of the thioester groups in aldol products **9**.[3e] Accordingly, we prepared the triisopropylsilyl derivative **8a** and, for comparison, the *tert*-butyldimethylsilyl analogue **8b**, by treatment of *tert*-butyl thioacetate with LDA/THF/DMPU followed by $Pr^i_3SiOTf$ and $Bu^tMe_2SiCl$ respectively.‡ Reaction of **8a**/**8b** with aldehydes **2**–**4**, catalysed by the corresponding supersilylating agents under the conditions reported previously,[3f] gave the expected β-silyloxy thioesters **10** and **11** [eqn. (3), $R_L$ = large, $R_S$ = small] with the



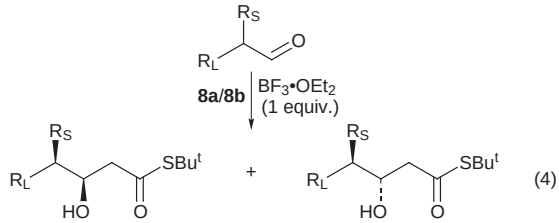

yields and diastereoselectivities shown in Table 1. Although not startling, the results were pleasing in that they generalised the earlier discovery (dependence of selectivity on steric bulk of $SiR_3$), registered an acceptable selectivity of 5 : 1 for aldehyde **3**, and confirmed that even the exceptionally challenging substrate **4** could be transformed with significant selectivity (3.5 : 1) using reagent **8a**.

**Table 1** Additions of silyl ketene thioacetals **8a**/**8b** to α-asymmetric aldehydes **2**–**4** catalysed by $R_3SiB(OTf)$[a]

| Aldehyde | Nucleophile | Yield (%) | **12** : **13**[b] |
|---|---|---|---|
| **2** | **8b** | 80 | 27 : 1 |
| **2** | **8a** | 79 | 77 : 1 |
| **3** | **8b** | 58 | 3.6 : 1 |
| **3** | **8a** | 78 | 5.5 : 1 |
| **4** | **8a** | 88 | 3.5 : 1 |

[a] Reaction conditions: $R_3SiB(OTf)_4$ (5 mol%), $CH_2Cl_2$, −80 °C, 1 h, quenching at low temp. with sat. aq. $NaHCO_3$. [b] Determined by NMR integration. Cram's rule was assumed to hold for all substrates, and was used to assign product stereochemistries.

By contrast, a surprise awaited when, for completeness, we repeated the reactions employing the conventional promoter $BF_3{\cdot}OEt_2$ [eqn. (4)]. On the basis of the earlier results with the




(+ **10** + **11** in some cases; see Table 2)

silyl enol ethers, we expected inferior diastereoselectivity with little dependence on $R_3Si$. In fact, as shown in Table 2, the method produced *higher* selectivities, which *did* increase with the bulk of the silyl group. The analysis was complicated by small amounts of **10** and **11** which appeared in some cases in addition to the expected products **12** and **13**. However, whether or not these were taken into account, *the discrimination achieved by the triisopropylsilyl reagent* **8a** *was quite outstanding*. For aldehyde **2** the selectivity was raised to the point where the minor isomer was difficult to detect with certainty, while for **3** and **4** the ratios were superior to those achieved in any previously reported additions.[7]

Although some aspects of this behaviour remain mysterious, a partial explanation is possible based on computer-based molecular modelling.[8] Systematic conformational searches on **8a** and **8b** reveal preferred structures in which the bulky But(S) and $R_3Si$(O) groups are held above and below the plane of the C=C bond, effectively shielding the nucleophilic carbon from attack by electrophiles (Fig. 1). As both faces are affected, these nucleophiles appear highly hindered and might be expected to react with unusual diastereoselectivity. The $R_3Si$ appears to be the more flexible of the two blocking groups,§ suggesting that attack may occur through the face *anti* to But(S) and providing an explanation for the sensitivity of the reactions to the steric bulk of $R_3Si$. In contrast, **5** adopts conformations in which one face of the C=C bond is shielded, but the other is essentially free (Fig. 1). It therefore attacks **3**·$BF_3$ with moderate selectivity, which does not depend greatly on the bulk of $R_3Si$. This analysis does *not* explain why catalysis by $R_3SiB(OTf)_4$ does not lead to even greater selectivity with **8**, as it does with **5**. We can only assume that the combination of an exceptionally hindered nucleophile **8** and a similarly hindered electrophile **7** causes a change in mechanism which degrades selectivity.

In conclusion, we have discovered an addition to aldehydes which takes place with unprecedented Cram-type selectivity, and gives products which can serve as versatile intermediates for organic synthesis. Our results further highlight the special utility of the triisopropylsilyl group as a tool for directing reactivity through long-range steric intervention.[9]¶

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**Table 2** Additions of silyl ketene thioacetals **8a**/**8b** to **2**–**4** catalysed by $BF_3{\cdot}OEt_2$[a]

| Aldehyde | Nucleophile | Yield (%) | **12**:**13**[b] |
|---|---|---|---|
| **2** | **8b** | 84 | 54:1 |
| **2** | **8a** | 76 | ~130:1 |
| **3** | **8b** | 43 (51)[c] | 5.8:1 (5.5:1)[c] |
| **3** | **8a** | 78 (81)[c] | 13:1 (12:1)[c] |
| **4** | **8a** | 77 (90)[c] | 5.4:1 (5.0:1)[c] |

[a] Reaction conditions: $BF_3{\cdot}OEt_2$ (1 equiv.), $CH_2Cl_2$, −80 °C, 30 min, quenching at low temp. with aqueous phosphate buffer (pH 7). [b] NMR integration; see Table 1. [c] Major products **12** and **13** were accompanied by minor quantities of **10** and **11**. Unbracketed figures refer to **12**/**13** only, while bracketed figures include contributions from the silylated products.

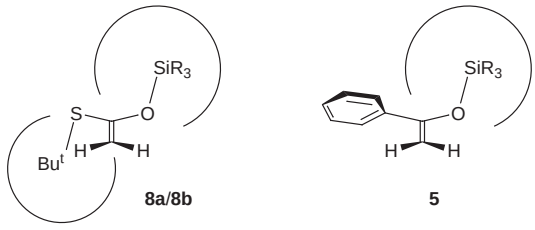


**Fig. 1** Schematic views of **8a**/**8b** and **5** in their preferred conformations, as predicted by computer-based molecular modelling

## Notes and References

† E-mail: adavis@tcd.ie

‡ Conveniently, the $Pr^i_3Si$ derivative **8a** could be purified by flash chromatography (hexane–$Et_2O$, 40:1). Substantial losses were incurred when the same technique was applied to **8b**.

§ Conformations in which the silicon atom is roughly in the plane of C=C bond appear at energies ⩾11 kJ $mol^{-1}$ above baseline.

¶ An alternative might be the *tert*-butyldiphenylsilyl group. However, a limited series of experiments indicates that, in this system, its effective bulk lies between that of $Pr^i_3Si$ and TBDMS.

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