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Silane-Controlled Diastereoselectivity in the Tris(pentafluorophenyl)borane-Catalyzed Reduction of α-Diketones to Silyl-Protected 1,2-Diols

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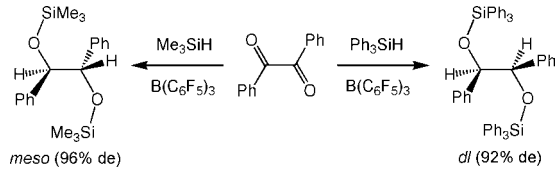
ABSTRACT



$B(C_6F_5)_3$-catalyzed bis(hydrosilylation) of α-diketones can give high diastereomeric excess of either *meso/anti* (small silanes and disilane reagents) or *dl/syn* (bulky silanes) silyl-protected 1,2-diols. This easily tuned diastereoselectivity is rationalized based on the classic Felkin−Anh model applied to a mechanism relying on Si−H abstraction by the electrophilic borane reagent.

Setting the relative stereochemistry at adjacent chiral centers in a molecule is a fundamental goal in synthetic chemistry. One strategy employs the reduction of α-diketones (or α-hydroxy ketones) to generate 1,2-diol reagents that are useful not only as chiral building blocks in complex natural product synthesis but also more generally as chiral auxiliaries or ligands in asymmetric catalysis. Varying degrees of enantio- and diastereoselectivity have been reported for a wide range of methods for the reduction of α-diketones,[1] but very few highly enantioselective routes are accompanied by high diastereoselectivity,[2] and among diastereoselective routes, there is often an inherent preference for formation of the *meso* or *anti* (for symmetric or unsymmetric diols, respectively) stereoisomer.[3] We describe here bis(hydrosilylation) reactions of α-diketones catalyzed by the electron-deficient borane, $B(C_6F_5)_3$, in which high selectivity for either the *meso* (*anti*) or the *dl* (*syn*) isomer of silyl-protected 1,2-diol products can be obtained simply by varying the substituents at the silane reagent under identical reaction conditions.

The highly electrophilic Lewis acid $B(C_6F_5)_3$ has been shown to catalyze the hydrosilylation of carbonyl groups in ketones, aldehydes, and esters, giving high yields under mild conditions and with low catalyst loadings.[4] We recently reported $B(C_6F_5)_3$-catalyzed hydrosilylation and heterodehydrocoupling reactions of *sym*-dihydridodisilanes that proceed with absolute chemoselectivity for Si−H over Si−Si activation.[5] We have now extended these studies to include the bis(hydrosilylation) of α-diketones, which gives quantitative conversion to 1,2-disilacyclic products such as **1**−**3** (Table 1). ^{13}C and ^{1}H NMR indicate the presence of a single diastereomer in samples of **1** (entry 1), and conversion to the corresponding, known 1,2-diol, hydrobenzoin,[6] confirmed the exclusive formation of the *meso* isomer in this reaction. This selectivity drops only slightly for the analogous reductions of 1-phenyl-2,3-propanedione and 2,3-butanedione (entries 2 and 3). These novel disilacycles can be isolated

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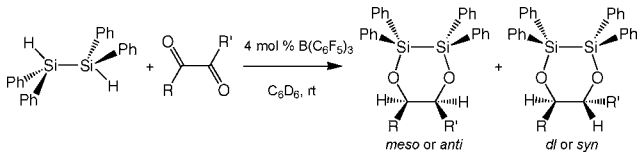
Table 1. Hydrosilylation of α-Diketones by *sym*-Tetraphenyldisilane[a]



entry	R	R′	product	*meso*/*dl* (*anti*/*syn*)
1	Ph	Ph	**1**	100:0
2	Me	Ph	**2**	(91:9)
3	Me	Me	**3**	86:14

[a] Product ratios determined by ^{1}H NMR. All reactions gave complete conversion to products within 1 h. Results averaged over two to three trials.

in 70−80% yield with the diastereomer ratios shown in Table 1; susbsequent recrystallization provides **2** as >99% *anti* and **3** as ∼96% *meso*. The molecular structure of the major, *meso* diastereomer of **3**, obtained from a single-crystal X-ray diffraction study (Figure 1), shows clearly the plane of

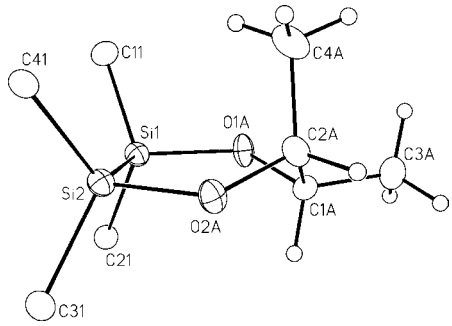
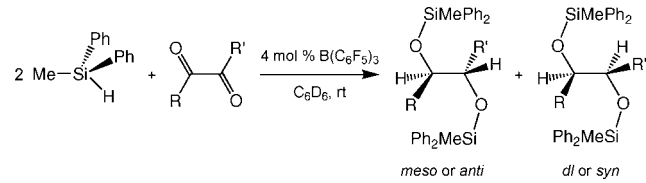


Figure 1. Molecular structure of *meso*-**3**. Only the ipso carbons of the phenyl rings are shown. Non-hydrogen atoms are represented by Gaussian ellipsoids at the 20% probability level. Hydrogen atoms are shown with arbitrarily small thermal parameters except for phenyl hydrogens, which are not shown.

symmetry in this reduced diketone, as well as an enforced eclipsed conformation along the Si−Si bond in this constrained, protected diol.

The diastereomer ratios in Table 1 can be rationalized on the basis of steric constraints associated with ring-closing (vide infra), but we were surprised to discover that bis(hydrosilylation) of benzil by the monosilane substrate $MePh_2SiH$ also proceeds stereoselectively (Table 2, entry 1). Even more interestingly, deprotection of the product, **4**,[6] showed that the major stereoisomer in this case is *dl*: an inversion of preferred stereochemistry relative to that observed for the disilane substrates. The same reaction performed using a variety of different α-diketones (Table 2) showed minimal impact of the steric and electronic features of these substrates on the diastereomer ratios. On the other hand, we observed a profound influence of the structure of the monosilane on diastereoselectivity in the hydrosilylation

Table 2. Hydrosilylation of α-Diketones by $MePh_2SiH$[a]



entry	R	R′	product	*meso*/*dl* (*anti*/*syn*)
1	C_6H_5	C_6H_5	**4**	17:83
2	CH_3	C_6H_5	**5**	(21:79)
3	CH_3	CH_3	**6**	19:81
4	*p*-$C_6H_4CH_3$	*p*-$C_6H_4CH_3$	**7**	11:89
5	*p*-$C_6H_4OCH_3$	*p*-$C_6H_4OCH_3$	**8**[b]	22:78[b]
6	*p*-C_6H_4F	*p*-C_6H_4F	**9**	12:88
7	*p*-C_6H_4Br	*p*-C_6H_4Br	**10**	14:86

[a] Product ratios determined by ^{1}H NMR. Unless otherwise noted, all reactions gave quantitative conversion to listed products within 1 h. Results averaged over three to five trials. [b] For this reaction we observed several side products by ^{1}H NMR, giving an overall ∼70% yield of **8**.[7]

of benzil catalyzed by $B(C_6F_5)_3$ (Figure 2). While Me_3SiH gave a very high ratio of the *meso* product (98:2, same preferred diastereomer as observed for *sym*-tetraphenyldisilane), Ph_3SiH gave a similarly high proportion of the *dl* diastereomer (4:96). The least stereodifferentiating silane was Et_3SiH. This trend in selectivity correlates very well with a simple change in bulk of the α-siloxy substituent.[8,9]

The established mechanism for hydrosilylation of carbonyl groups catalyzed by $B(C_6F_5)_3$ relies on partial abstraction of the silane Si−H bond by the borane, as demonstrated by

(1) Examples include the following, and references therein. Reactions of metal hydride reagents: (a) Li, X.; Zhao, G.; Cao, W. G. *Chin. J. Chem.* **2006**, *24*, 1402. (b) Clerici, A.; Pastori, N.; Porta, O. *Eur. J. Org. Chem.* **2002**, 3326. (c) Abernethy, C. D.; Cole, M. L.; Davies, A. J.; Jones, C. *Tetrahedron Lett.* **2000**, *41*, 7567. (d) Ravikumar, K. S.; Sinha, S.; Chandrasekaran, S. *J. Org. Chem.* **1999**, *64*, 5841. Biocatalytic methods: (e) Edegger, K.; Stampfer, W.; Seisser, B.; Faber, K.; Mayer, S. F.; Oehrlein, R.; Hafner, A.; Kroutil, W. *Eur. J. Org. Chem.* **2006**, 1904. (f) Demir, A. S.; Hamamci, H.; Ayhan, P.; Duygu, A. N.; Igdir, A. C.; Capanoglu, D. *Tetrahedron: Asymmetry* **2004**, *15*, 2579. (g) Kihumbu, D.; Stillger, T.; Hummel, W.; Liese, A. *Tetrahedron: Asymmetry* **2002**, *13*, 1069. (h) Buisson, D.; Elbaba, S.; Azerad, R. *Tetrahedron Lett.* **1986**, *27*, 4453. Organocatalyzed hydroboration: (i) Shimizu, M.; Tsukamoto, K.; Matsutani, T.; Fujisawa, T. *Tetrahedron* **1998**, *54*, 10265. Metal-catalyzed hydrogenation: (j) Toukoniitty, E.; Busygin, I.; Leino, R.; Murzin, D. Y. *J. Catal.* **2004**, *227*, 210. (k) Zhou, D. Q.; He, M.; Zhang, Y. H.; Huang, M. Y.; Jiang, Y. Y. *Polym. Adv. Technol.* **2003**, *14*, 287. (l) Li, Y.; Liu, H. F. *Chin. Chem. Lett.* **2001**, *12*, 127. (m) Hattori, K.; Sajiki, H.; Hirota, K. *Tetrahedron* **2001**, *57*, 4817. Metal-catalyzed transfer hydrogenation: (n) Ikariya, T.; Hashiguchi, S.; Murata, K.; Noyori, R.; Wipf, P.; Amantini, D. *Org. Synth.* **2005**, *82*, 10. (o) Wu, X. F.; Li, X. H.; Zanotti-Gerosa, A.; Pettman, A.; Liu, J. K.; Mills, A. J.; Xiao, J. L. *Chem.—Eur. J.* **2008**, *14*, 2209. Catalytic hydrosilylation: (p) Tsuhako, A.; He, J. Q.; Mihara, M.; Saino, N.; Okamoto, S. *Tetrahedron Lett.* **2007**, *48*, 9120. (q) Nadkarni, D.; Hallissey, J.; Mojica, C. *J. Org. Chem.* **2003**, *68*, 594. (r) Kuwano, R.; Sawamura, M.; Shirai, J.; Takahashi, M.; Ito, Y. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 485. (s) Corriu, R. J. P.; Lanneau, G. F.; Yu, Z. F. *Tetrahedron* **1993**, *49*, 9019.

(2) References 1g and 1n stand out in this respect but are limited in diketone scope.

(3) Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191.

(4) (a) Parks, D. J.; Piers, W. E. *J. Am. Chem. Soc.* **1996**, *118*, 9440. (b) Parks, D. J.; Blackwell, J. M.; Piers, W. E. *J. Org. Chem.* **2000**, *65*, 3090. (c) Asao, N.; Ohishi, T.; Sato, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2001**, *123*, 6931. (d) Bach, P.; Albright, A.; Laali, K. K. *Eur. J. Org. Chem.* **2009**, 1961.

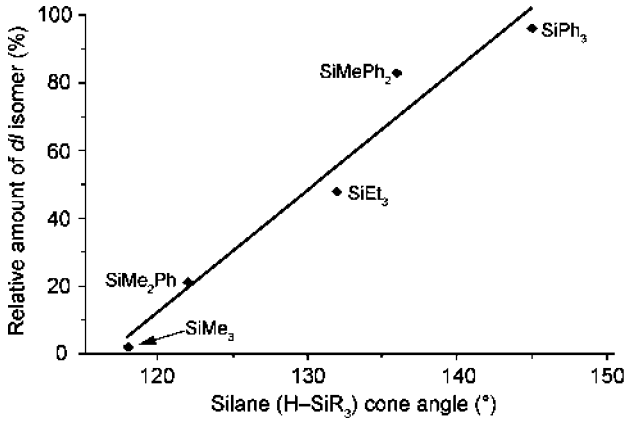
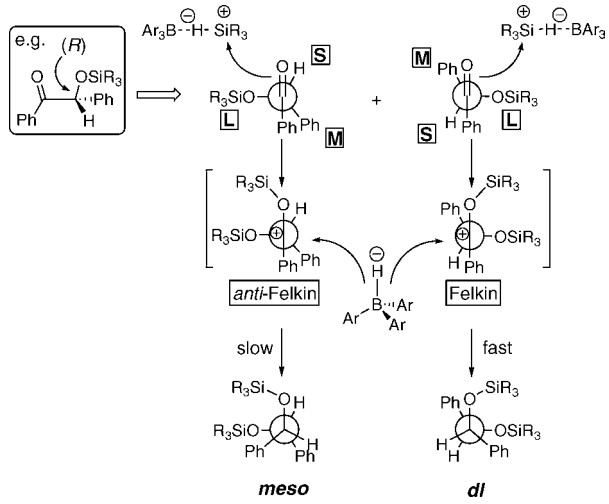


Figure 2. Variation in diastereoselectivity as a function of the size of the silane reagent.

Piers et al. using isotopic labeling experiments and computational studies, along with ^{1}H, ^{29}Si, and ^{19}F NMR experiments.[4b] The resulting silylium-like fragment is then highly susceptible to nucleophilic attack at silicon by the carbonyl oxygen, and ultimately the free borate anion delivers hydride to the carbonyl carbon. Scheme 1 illustrates how the

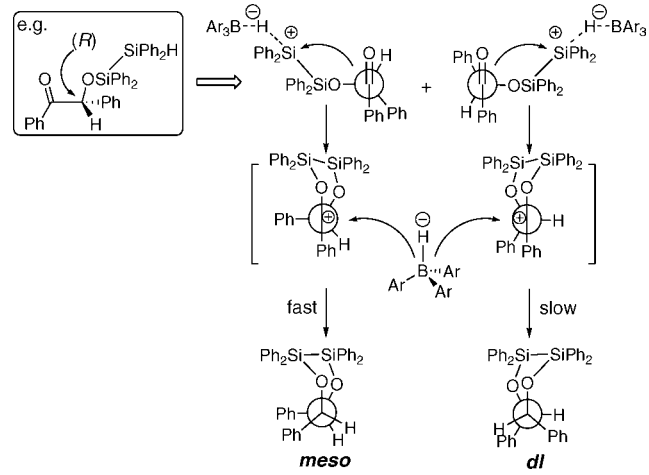
Scheme 1. Proposed Source of Diastereoselectivity for Bulky Silane Reagents, Illustrated for the (*R*)-Enantiomer of a Racemic α-Chiral Ketone Mixture



Felkin−Anh model for nucleophilic addition at carbonyl groups[3] plays out for this mechanism in the reduction of benzil by bulky monosilane substrates. The first hydrosilylation step gives a racemic mixture of the α-chiral ketone, in which the preferred conformation places the largest substituent (L) orthogonal to the remaining carbonyl double bond.[10] Thus, one diastereotopic face of the carbonyl group in each enantiomer is blocked by the α-siloxy group, while the other diastereotopic face is defined by the proximity of either the medium-sized substituent (M = Ph) or the smallest substituent (S = H) to the incoming nucleophile. A key feature is the bulk of the borate anion that delivers the hydride to the carbonyl carbon, which promotes the formation of the Felkin as opposed to the *anti*-Felkin product. The loss or inversion of stereoselectivity observed for smaller silanes corresponds to a switch in the L and M assignments in this mechanism: the small α-OSiMe$_3$ group (M) gives the most extreme Felkin induction for L = Ph. The approximately 1:1 ratio of diastereomers obtained for the reduction of benzil with HSiEt$_3$ indicates the comparable bulk of the OSiEt$_3$ and Ph groups.

Scheme 2 shows that the *meso*/*anti* selectivity exhibited in the disilane reactions (Table 1) arises from a variation on

Scheme 2. Proposed Source of Diastereoselectivity for Disilane Reagents, Illustrated for the (*R*)-Enantiomer of a Racemic α-Chiral Ketone Mixture



the Cram-chelate model:[3,11] the disilanyl fragment Ph$_2$Si−SiPh$_2$ generates a six-membered "chelate" intermediate, at which hydride delivery from the borate anion occurs preferentially from the H-side of the carbocation, instead of the Ph- (or Me-) side, giving the *anti*-Felkin product.[12]

Thus we have found a one-step reaction for controlling the relative stereochemistry at protected 1,2-diol reagents that

(5) Harrison, D. J.; Edwards, D. R.; McDonald, R.; Rosenberg, L. *Dalton Trans.* **2008**, 3401.

(6) Addition of excess tetrabutylammonium fluoride (TBAF) in THF gave quantitative conversion to diols in ≤5 h at rt as determined by ^{1}H NMR.

(7) We have not yet identified these side products but presume that the broader product distribution observed for this reaction results from the catalyst binding to the *p*-OMe groups in the substrate. This highlights a potential limitation in the scope of diketones suitable for this method. The formation of unwanted borane adducts at remote donor sites in the substrate may simply inhibit catalysis, giving lower yields or requiring higher catalyst loading (e.g., the reduction of 1,2-bis(pyridyl)-1,2-dione under comparable conditions requires up to 15 mol % borane), but at worst the coordinated borane will cause competing reactions that degrade the substrate. See, e.g., ref 4b and: Welch, G. C.; Masuda, J. D.; Stephan, D. W. *Inorg. Chem.* **2006**, *45*, 478 (nucleophilic ring opening of B(C$_6$F$_5$)$_3$-coordinated THF).

(8) Silane cone angles (θ) refer to R$_3$Si-H analyzed as for R$_3$P-M: (a) Tolman, C. A. *Chem. Rev.* **1977**, *77*, 313. (b) Hester, D. M.; Sun, J. M.; Harper, A. W.; Yang, G. K. *J. Am. Chem. Soc.* **1992**, *114*, 5234. This metric shows the *relative* steric influence of α-siloxy groups, although the added Si−O distance tempers the absolute bulk experienced by the adjacent carbonyl group.

relies on simple variation of a silane reagent in the catalytic reduction of α-diketones with both alkyl and aryl substituents. We are now exploring extension of this method to the enantioselective synthesis of protected 1,2-diols. In addition to evaluating the induction provided by chiral silane reagents, this ongoing work presents the interesting challenge of identifying chiral boranes that preserve the high activity of $B(C_6F_5)_3$.[13]

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Supporting Information Available: Experimental details and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) The larger silane *t*-$BuPh_2SiH$ ($\theta = 157°$) did not react, probably because the Si-H abstraction step was inhibited (see ref 4b). Two silanes with smaller cone angles gave product mixtures; for $(EtO)_3SiH$ ($\theta = 109°$) these probably result from competing de-ethanative coupling to give siloxanes: (a) Chojnowski, J.; Rubinsztajn, S.; Cella, J. A.; Fortuniak, W.; Cypryk, M.; Kurjata, J.; Kazmierski, K. *Organometallics* **2005**, *24*, 6077. For (*n*-hexyl)SiH_3 ($\theta \sim 106°$), ^1H NMR suggests competing formation of macrocyclic and/or 5-membered ring hydrosilylation products (see ref 1s).

(10) In some cases, electron-withdrawing groups occupy the L site, regardless of steric bulk (ref 3). Our results, especially the distinct selectivities observed for the electronically comparable $HSiMe_3$ and $HSiEt_3$, suggest either that this electronic effect is not important or that the $OSiR_3$ groups we studied all have electron-withdrawing abilities comparable to those of Ph.

(11) Reetz, M. T. *Acc. Chem. Res.* **1993**, *26*, 462.

(12) Similar *anti* selectivity was observed for intramolecular hydrosilylation of α-diketones employing a primary aminoarylsilane (ref 1s), but deprotection of the resulting 2,5-dioxa-1-silacyclopentane ring to the corresponding diol was not possible.

(13) Morrison, D. J.; Piers, W. E.; Parvez, M. *Synlett* **2004**, 2429.