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# Stereochemically divergent pathways for the allylation and crotylation reactions of *anti*- and *syn*-β-hydroxy-α-methyl aldehydes with allyl- and crotyltrifluorosilanes

Sherry R. Chemler and William R. Roush *

*Department of Chemistry, University of Michigan, Ann Arbor, MI 48109-1055, USA and Department of Chemistry, Indiana University, Bloomington, IN 47405, USA*

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**Abstract**

Allylation and crotylation reactions of 2,3-*anti*-β-hydroxy-α-methyl aldehydes **10** and **11** with allyl and crotyltrifluorosilanes **2**, **8** and **9** proceed with high selectivity via the bicyclic chelated transition states **3** and **30**. In contrast, analogous allylation and crotylation reactions of the 2,3-*syn*-β-hydroxy-α-methyl aldehydes **12** and **13** with **2**, **8** and **9** are generally less selective and proceed preferentially by way of the normal Zimmerman–Traxler transition states **6** and **32**. 

We recently disclosed the results of reactions of *anti*-α-methyl-β-hydroxy aldehydes **1** and (*Z*)-crotyltrifluorosilane **2**, which provide the *anti,anti*-dipropionate stereotriad **4** with high selectivity.[1] These reactions were designed to proceed by way of the internally chelated transition state **3**,[2–4] with bond formation occurring *anti* to the aldehyde α-methyl group, thereby generating the often elusive 3,4-*anti*-4,5-*anti*-dipropionate stereotriad.[5] We also reported that the (*Z*)-crotylation of 2,3-*syn*-α-methyl-β-hydroxy aldehydes **5** under comparable conditions gave product mixtures inconsistent with this bicyclic chelated pathway; the major products contained 3,4-*syn*-stereochemistry, as illustrated in **7**, suggesting that the crotylation of the *syn*-β-hydroxy aldehydes proceeds via the normal Zimmerman–Traxler transition state **6**[6,7] rather than a transition state analogous to **3**.

* Corresponding author. Address correspondence to this author at the University of Michigan address.
E-mail: roush@umich.edu

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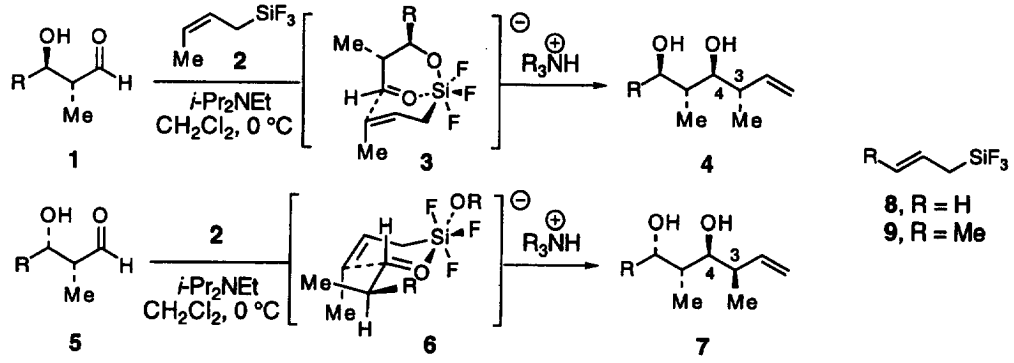


In order to probe the generality of this allylation process as well as to gain additional insight into the striking stereodivergent behavior of the 2,3-*anti*- vs. 2,3-*syn*-β-hydroxy aldehydes, we have examined the reactions of aldehydes **10–13**[1] with the allyl- and (*E*)-crotyltrifluorosilane reagents **8** and **9**. Reagents **8** and **9** are readily available from allyltrichlorosilane precursors by reaction with antimony trifluoride.[8,9] Allyltrichlorosilane is commercially available (Aldrich), while isomerically pure (*E*)-crotyltrichlorosilane is prepared from (*E*)-crotyl chloride.[8]

Table 1

Reaction of allyl- and (*E*)-crotyltrifluorosilane (**8** and **9**) with β-hydroxy-α-methyl chiral aldehydes[a]

| entry | reagent | aldehyde[b] | major products | | dr[c,d] (yield)[e] |
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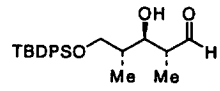
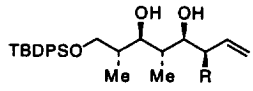
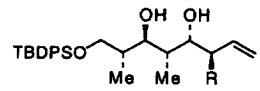
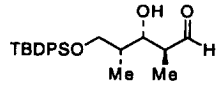
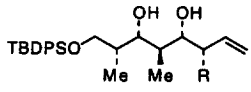
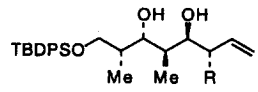
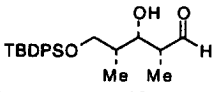
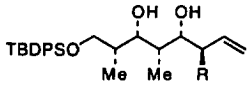
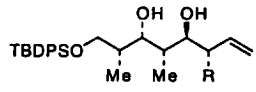
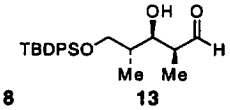
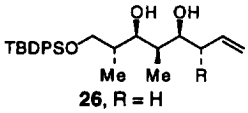
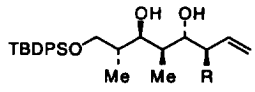
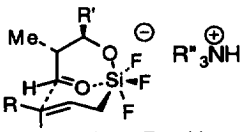
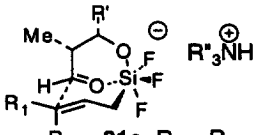
| | |  |  |  | |
| 1 | 8 | **10** | **14**, R = H | **15**, R = H | 90 : 10 (73% yield) |
| 2 | 9 | | **16**, R = Me | **17**, R = Me | 95 : 5 (75% yield) |
| | |  |  |  | |
| 3 | 8 | **11** | **18**, R = H | **19**, R = H | 90 : 10 (74% yield) |
| 4 | 9 | | **20**, R = Me | **21**, R = Me | 93 : 5 : 2 (76% yield) |
| | |  |  |  | |
| 5 | 8 | **12** | **22**, R = H | **23**, R = H | 52 : 48 (71% yield) |
| 6[f] | 9 | | **24**, R = Me | **25**, R = Me | 89 : 9 : 2 (80% yield) |
| | |  |  |  | |
| 7 | 8 | **13** | **26**, R = H | **27**, R = H | 58 : 42 (71% yield) |
| 8 | 9 | | **28**, R = Me | **29**, R = Me | 72 : 14 : 14 (42% yield) |

[a]All reactions were run with 3 equiv of **8** or **9** and 3 equiv of *i*-$Pr_2NEt$ in $CH_2Cl_2$ (0.08 M in aldehyde) at 0°C in the presence of 4 Å mol. sieves for 36 h, unless noted otherwise. [b]Aldehydes **10–13** were prepared by sequential dihydroxylation (cat. $OsO_4$/NMO) and oxidative cleavage ($NaIO_4$) as described by Chemler, S. R. and Roush, W. R.,[1] or by ozonolysis of the corresponding terminal olefins (see Hung, D. T.; Nerenberg, J. B.; Schreiber, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 11054). [c]Product ratios were determined by $^1H$ NMR analysis (400 or 500 MHz) of the crude, unseparated mixture of products. [d]Diastereomer ratios (dr) refer to the two major products and the sum of all other diastereomers obtained. The first column of structures are the major products of each experiment summarized in this table. [e]Combined yields of isolated diastereomeric products. [f]This reaction was performed for 72 h with 7 equiv of **9** and 5 equiv of *i*-$Pr_2NEt$.

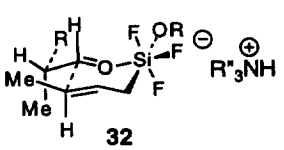
Allylation reactions (summarized in Table 1) of aldehydes **10–13** with the allyl- and (*E*)-crotyltrifluorosilanes **8** and **9** were performed using the optimal conditions previously described for the (*Z*)-crotylation of these substrates with (*Z*)-crotyltrifluorosilane **2**.[1] We found that the reactions of 2,3-*anti*-aldehydes **10** and **11** with reagents **8** and **9** were generally quite selective for the 4,5-*anti*-adducts **14** and **16** (from **10**, Table 1, entries 1 and 2) and **18** and **20** (deriving from **11**, Table 1, entries 3 and 4).[10] In all four of these reactions the major products, obtained with selectivity ranging from 90:10 to 95:5, are consistent with pathways involving chelated bicyclic transition structures **30a** and **30b**, analogous to **3**.



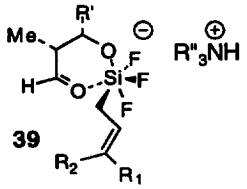
**30a**, R = H
**30b**, R = Me



**31a**, $R_1 = R_2 = H$
**31b**, $R_1 = Me$, $R_2 = H$
**31c**, $R_1 = H$, $R_2 = Me$



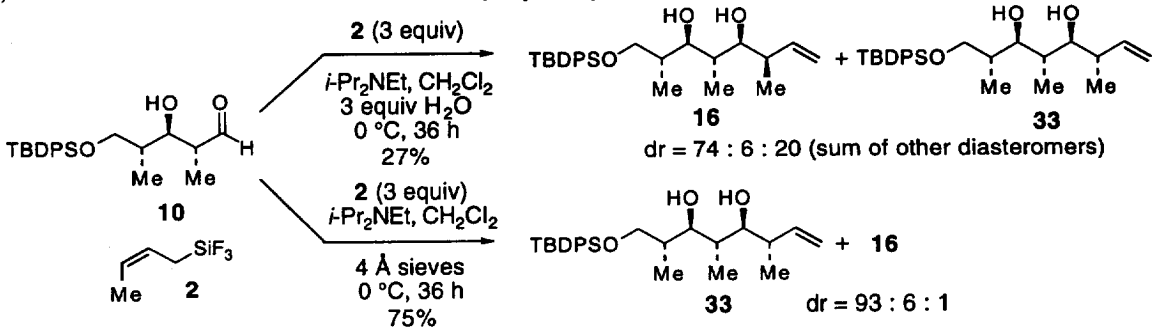
**32**



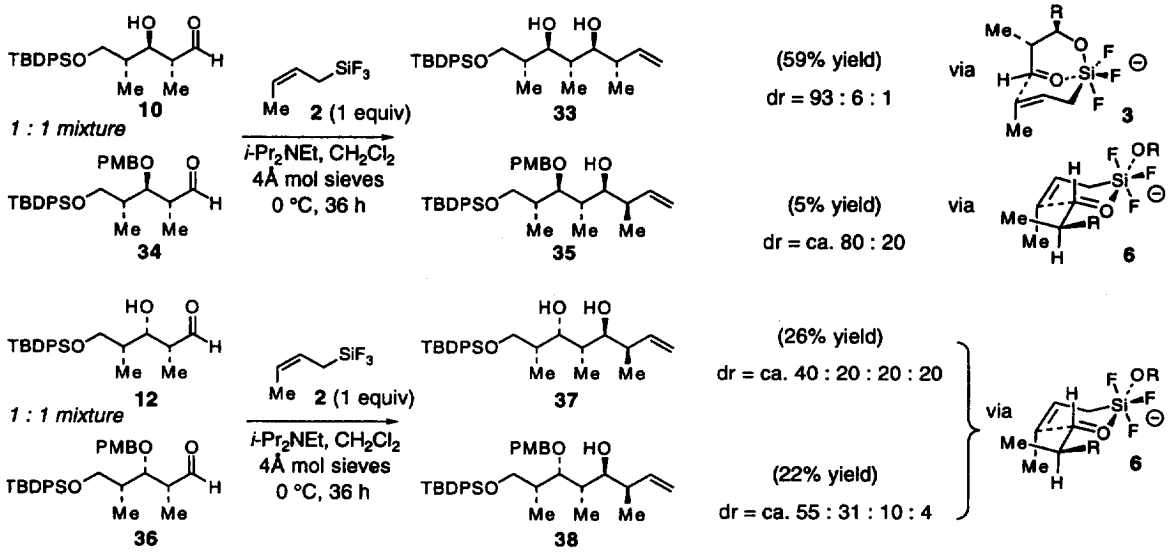
**39**

In contrast to the excellent results with **10** and **11**, the allylation reactions of the 2,3-*syn*-aldehydes **12** and **13** were virtually non-selective (Table 1, entries 5 and 7). Although the (*E*)-crotylations of **12** and **13** with reagent **9** were reasonably selective for **24** and **28** (Table 1, entries 6 and 8), these products possess 3,4-*anti*-stereochemistry and cannot arise by way of the chelated bicyclic transition structure **31b**. Rather, **24** and **28** must arise by way of the normal Felkin Zimmerman–Traxler transition state **32**.[6,7]

Insight into the divergent behavior of the 2,3-*anti*- vs. the 2,3-*syn*-aldehydes in these reactions was provided by the observation that these allylations must be performed under rigorously anhydrous conditions in order to obtain optimal stereoselectivity. For example, when the (*Z*)-crotylsilylation of **10** was performed with 3 equiv of **2** in the presence of 3 equiv of water, the 3,4-*syn*-4,5-*anti*-diastereomer **16** is the predominant product.[11] This result is in contrast to the stereoselectivity when the reaction is performed in the presence of 4 Å molecular sieves, in which case the *anti,anti*-diastereomer **33** is the major product (93:6:1 selectivity).[1] This striking reversal of stereoselectivity indicates that water may be capable of activating the allyltrifluorosilane by nucleophilic addition to the trifluorosilane unit to give a hypervalent allylsilicate species,[12] which then reacts with the aldehyde preferentially by way of a non-chelated pathway involving the Zimmerman–Traxler transition state **6** (where –OR = –OH). It is well known that allyltrifluorosilanes (and also allyltrichlorosilanes) require activation by an external nucleophile (e.g., CsF, ROH, $R_2NH$, phosphonamides, etc.) in order to react with carbonyl compounds.[2,8,12–18] These observations suggested to us that the aberrant behavior of the 2,3-*syn*-aldehydes **12** and **13** could be explained by assuming that one molecule of **12** or **13** (or one of the crotylation products, or even an adventitious nucleophile like fluoride ion) activates the reagent, and the resulting pentacoordinate allylsilicate then reacts with a second molecule of **12** or **13** via a non-chelated transition state (e.g., **6** or **32**, where –OR is a second molecule of the β-hydroxy aldehyde substrate).



Competition experiments were performed to probe this hypothesis.[19,20] Treatment of a 1:1 mixture (1 equiv of each) of β-hydroxy aldehyde **10** and the corresponding *p*-methoxybenzyl (PMB) ether **34** with 1 equiv of (*Z*)-crotyltrifluorosilane **2** under standard conditions gave a 59% isolated yield of products deriving from **10** (e.g., **33**) and only 5% of products deriving from **34**. Additionally, the stereochemistry of **35**, the main product of the reaction of **34** and **2**, was determined to be 3,4-*syn*-4,5-*anti*, implying that the crotylation of **34** proceeded through the usual[6,7] anti-Felkin Zimmerman–Traxler transition structure **6**.




In contrast, similar treatment of a 1:1 mixture of **12** and the corresponding PMB ether **36** with 1 equiv of **2** provided a 26% isolated yield of products deriving from **12** and 22% yield of products deriving from **36**. The 3,4-*syn*-4,5-*anti*-stereochemistry of the major adducts **37** and **38** (from **12** and **36**, respectively) indicates that both aldehydes reacted substantially through the non-chelated anti-Felkin Zimmerman–Traxler transition state **6**.

These results lead to the unambiguous conclusion that the 2,3-*syn*-aldehydes **12** and **13** react preferentially by way of the non-chelated Zimmerman–Traxler mode **6/32**, whereas the 2,3-*anti*-β-hydroxy aldehydes **10** and **11** react by way of the bicyclic chelated transition states **3/30**. What is not obvious at present is if the different behavior of these two classes of substrates is due to the inability of the 2,3-*syn*-β-hydroxy aldehydes to form an initial 6-centered chelate (see **39**) with the allylsilane reagent, owing to the requirement that one alkyl substituent must be axial in the 6-membered chelate, or if the problem resides with non-bonded interactions that develop in the chelated transition state **31**. Attempts to resolve these questions via NMR analysis of suitable chelate models and by semi-empirical molecular modeling of the bicyclic chelated transition structures **3**, **30** and **31** are underway.

In conclusion, we have demonstrated that the 2,3-*syn*-stereochemistry of β-hydroxy aldehydes plays a crucial role in determining the mechanism, and ultimately the stereoselectivity, of their reactions with allyl- and crotyltrifluorosilanes **2**, **8** and **9**. Anti-Felkin adducts (e.g., **14**, **16** and **33**) are formed with excellent selectivity from the 2,3-*anti*-aldehydes **10** and **11**, in a manner that is complementary to other methods.[6] Efforts to devise a highly stereoselective protocol for allylation of the 2,3-*syn*-β-hydroxy aldehydes continue and will be reported in due course.

## Acknowledgements

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## References

1. Chemler, S. R.; Roush, W. R. *J. Org. Chem.* **1998**, *63*, 3800.
2. Sato, K.; Kira, M.; Sakurai, H. *J. Am. Chem. Soc.* **1989**, *111*, 6429.
3. Wang, Z.; Meng, X.-J.; Kabalka, G. W. *Tetrahedron Lett.* **1991**, *32*, 1945.
4. Brzezinski, L. J.; Leahy, J. W. *Tetrahedron Lett.* **1998**, *39*, 2039.
5. Hoffmann, R. W.; Dahmann, G.; Andersen, M. W. *Synthesis* **1994**, 629.
6. Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 2, pp. 1.
7. Roush, W. R. *J. Org. Chem.* **1991**, *56*, 4151.
8. Kira, M.; Hino, T.; Sakurai, H. *Tetrahedron Lett.* **1989**, *30*, 1099.
9. Mironov, V. F. *Bull. Acad. Sci. USSR (Engl. Trans.)* **1962**, 1797.
10. The stereochemistry at C(4) of **14–29** was assigned by analysis of the $^{1}H$ and $^{13}C$ NMR spectra of the 4,6-acetonides generated from **14–29** (see Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511). The stereochemistry at C(3) of the crotylation products **16**, **17**, **20**, **21**, **24**, **25**, **28** and **29** was similarly assigned by analysis of the $^{1}H$ NMR spectra of the terminal 1,3-acetonides prepared from the corresponding triols (in turn generated by oxidative cleavage of the terminal olefins with $O_3$ followed by reduction with $NaBH_4$).
11. The low yield of **16** and **33** from the crotylation reaction of aldehyde **10** with reagent **2** in the presence of water is due to the competitive formation of aldehyde dimer (a 4-hydroxy-1,3-dioxane derivative), a side product commonly observed in these reactions. The amount of dimer generated in this experiment was far greater than usually observed in experiments performed under anhydrous conditions in the presence of molecular sieves (omitted in this case).
12. Kira, M.; Sato, K.; Sakurai, H. *J. Am. Chem. Soc.* **1988**, *110*, 4599.
13. Kira, M.; Kobayashi, M.; Sakurai, H. *Tetrahedron Lett.* **1987**, *28*, 4081.
14. Kira, M.; Sato, K.; Sakurai, H. *J. Am. Chem. Soc.* **1990**, *112*, 257.
15. Kira, M.; Sato, K.; Sekimoto, K.; Gewald, R.; Sakurai, H. *Chem. Lett.* **1995**, 281.
16. Kobayashi, S.; Nishio, K. *Tetrahedron Lett.* **1993**, *34*, 3453.
17. Denmark, S. E.; Coe, D. M.; Pratt, N. E.; Griedel, B. D. *J. Org. Chem.* **1994**, *59*, 6161.
18. Iseki, K.; Kuroki, Y.; Takahashi, M.; Kobayashi, Y. *Tetrahedron Lett.* **1996**, *37*, 5149.
19. Frye, S. V.; Eliel, E. L.; Cloux, R. *J. Am. Chem. Soc.* **1987**, *109*, 1862.
20. Paquette, L. A.; Mitzel, T. M. *J. Am. Chem. Soc.* **1996**, *118*, 1931.