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# DIASTEREOSELECTIVE ALDOL SYNTHESIS USING ACETAL TEMPLATES

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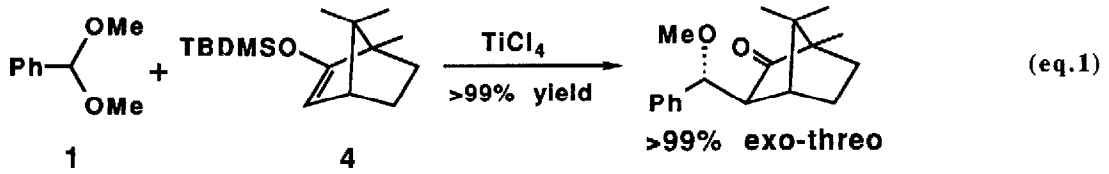
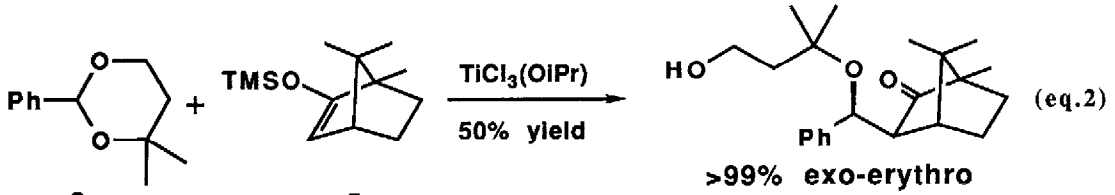
Summary: Stereoselectivity of the Mukaiyama reaction is dramatically changed by the steric features of acetal structures.

Aldol reactions are divided into two categories depending on the method of activation of the enolates and carbonyl substrates. Most reactions proceed via a six-membered chelated transition state assembled by a metal enolate and carbonyl compound.[1] In this case, the aldol stereoselectivity is heavily dependent on the geometry of the enolate double bond: (E)-enolates giving, generally, threo aldols and (Z)-enolates erythro products. The other reactions proceed through acyclic transition states, and both (E)- and (Z)-enolates give the erythro adducts selectively.[1,2] Very little is known, however, of the stereochemistry of the titanium mediated coupling of enol silyl ethers with aldehydes (Mukaiyama reaction),[3] despite its broad utility in organic synthesis. We report herein results of our investigations on unprecedented selectivities in the reaction of enol silyl ethers with a variety of acetal templates.



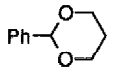

1 4 (eq.1)




3 5 (eq.2)

We chose to investigate the stereoselectivity of the aldol formation from benzaldehyde acetal and the enol silyl ether of D-camphor, an enol silane of high steric demand. Thus, a solution of benzaldehyde dimethyl acetal **1** in dichloromethane was cooled to -78°C and titanium tetrachloride was added dropwise. Enol silane **4** was then added, and the mixture was stirred for 15 min. After usual workup, the exo-threo product was obtained almost exclusively (eq. 1).[4] In dramatic contrast, however, similar reaction conditions but with the acetal of type **3** gave the exo-erythro isomer exclusively (eq. 2)![4] This reversal strongly suggests a crucial role for the acetal structure on the selectivity of the reaction and prompted us to investigate the course of the reaction with a wide variety of acetals under various reaction conditions. Some of our results are summarized in Table 1.

Table 1. Condensation of Enol Silanes of D-Camphor with Benzaldehyde Acetals

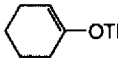
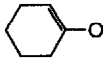
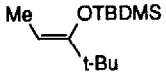
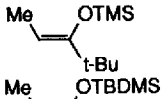
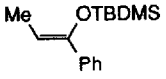
| Acetal[a] | Enol Silane[a] | Lewis Acid[a] | Temp. (°C) | Product (% Yield)[b] | Isomer Ratio[c] E : T[d] |
|---|---|---|---|---|---|
| **1** | **4** | $TiCl_4$ | -78 | >99 | < 1 : 99 |
| **1** | **5** | $TiCl_3(OiPr)$ | -78 | 99 | 24 : 76[e] |
| $PhCH(OCH_2)_2$ | **5** | $TiCl_3(OiPr)$ | -78 | 72 | 27 : 73 |
|  **2** | **4** | $TiCl_4$ | 0 | 61 | 9 : 91 |
| **2** | **5** | $TiCl_3(OiPr)$ | -78 | 87 | 33 : 67 |
| **2** | **5** | $TiCl_3(OiPr)$ | -90 | 43 | 37 : 63 |
| **3** | **5** | $TiCl_3(OiPr)$ | -78 | 50[f] | >99 : 1[g] |

[a]Acetal : Enol Silane : Lewis Acid = 1.0 : 1.2 : 1.2. [b]Isolated yield. [c]The structural assignment was based on $^1H$ NMR analysis and ratios were determined by HPLC assay. [d]E=erythro, T=threo. [e]The ratio was determined by the isolation of each isomer by chromatography. [f]28% yield of the aldol product was also produced in this case. [g]Ratio was determined by $^1H$ NMR analysis.

In order to explore the generality and scope of the above reversal stereoselectivity on aldol-type synthesis based on acetal structures, some enol silyl ethers were prepared and their

reactions examined with various acetals. The results are shown in Table 2. In the type **1** acetals, most reactions[5] stereoselectively afforded an erythro product independent of the

Table 2. Condensation of Enol Silanes with Acetals

| Acetal[a] | Enol Silane[a] | Lewis Acid[a] | Product[b] (% Yield)[c] | Isomer Ratio[d] E : T[g] | A[e] E : T[g] | B[f] E : T[g] |
|---|---|---|---|---|---|---|
| **1** |  | 9-BBNOTf | 95 | 78 : 22 | 92 : 8 | |
| | | $TiCl_4$ | 95 | 76 : 24 | | |
| **2** | | 9-BBNOTf | 83 | 73 : 27 | | |
| | | $TiCl_4$ | 39 | 54 : 46 | | |
| **3** |  | 9-BBNOTf | 59 | 15 : 85 | | 25 : 75[h] |
| | | $TiCl_4$ | 73 | 14 : 86 | | |
| **1** |  | 9-BBNOTf | 99 | 6 : 94[i] | 5 : 95[i] | |
| **2** | | $TiCl_4$ | 73 | 3 : 97 | | |
| **3** |  | $TiCl_3$(OiPr) | 43 | 3 : 97 | | 5 : 95 |
| **1** |  | 9-BBNOTf | 99 | 86 : 14 | 84 : 16 | |
| **2** | | 9-BBNOTf | 64 | 79 : 21 | | |
| **3** | | 9-BBNOTf | 55 | 73 : 27 | | 47 : 53 |

[a]Acetal : Enol Silane : 9-BBNOTf = 1.0 : 1.2 : 1.0 or Acetal : Enol : Silane : $TiCl_4$ = 1.0 : 1.2 : 1.2. [b]Reaction at -78°C. [c]Isolated yield. [d]In the reaction of **1**, the stereochemistry was determined by an independent synthesis of each isomer. For other cases, the ether bond was cleaved by oxidation-elimination sequence to produce the corresponding aldols which were analyzed by $^1H$ NMR. Isomer ratio was determined by HPLC analysis. [e]ref. 6. [f]ref. 7. [g]E=erythro, T=threo. [h]ref. 3. [i]ref. 5.

geometry of the enolate double bond.[6] These results are consistent with the reaction of enol silyl ether and aldehyde dimethyl acetal in the presence of trimethylsilyl triflate developed by Noyori et al.[6] On the other hand, the results from acetal **3** showed a trend similar to that discussed by Heathcock et al. for the reaction of titanium catalyzed coupling of enol silyl ethers with aldehyde.[7]

The question of why each acetal reacts with enol silyl ethers with such diverse selectivity is most intriguing but far from answerable at present in view of the lack of knowledge of the nature of coordinated acetals in solution.[8]

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**References and Notes**

1. Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. J. Org. Chem. **1980**, 45, 1066 and references cited therein, Evans, D. A.; Nelson, J. R.; Vogel, E.; Taber, T. R. J. Am. Chem. Soc. **1981**, 103, 3099 and references cited therein.
2. Noyori, R.; Nishida, I.; Sakata, J. J. Am. Chem. Soc. **1981**, 103, 2106.
3. Mukaiyama, T.; Banno, K.; Narasaka, K. J. Am. Chem. Soc. **1974**, 96, 7503.
4. The aldol reaction of the D-camphor enolate with benzaldehyde was reported to proceed with an unusual stereoselectivity, see Harlow, R. L.; Simonsen, S. H. Cryst. Struct. Comm. **1976**, 5, 471. In fact, under the reaction conditions of Noyori (ref. 6) the exo-threo product was the major product (78:22). On the other hand, the reaction conditions of Heathcock (ref. 7) gave the exo-erythro product almost exclusively (<1:99). Thus, these results are consistent with the mechanism of the scheme in the text.
5. The anti configuration (threo) of this particular reaction was reported by Heathcock. See, Heathcock, C. H., In "Asymmetric Synthesis, Vol. 3, Part B," Ed by Morrison, J. D., Academic Press, 1984, pp 138-139.
6. Murata, S.; Suzuki, M.; Noyori, R. J. Am. Chem. Soc. **1980**, 102, 3248.
7. Heathcock, C. H.; Davidsen, S. K.; Hug, K. T.; Flippin, L. A. J. Org. Chem. **1986**, 51, 3027.
8. The mechanistic studies of these reactions will be published in due course.

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