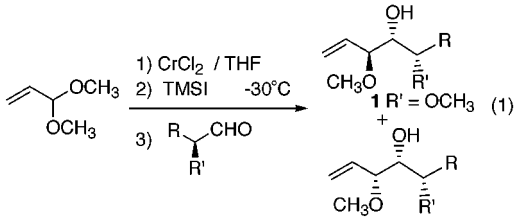
A Variant of the Takai−Utimoto Reaction of Acrolein Acetals with Aldehydes Catalytic in Chromium: A Highly Stereoselective Route to Anti Diol Derivatives

Robert K. Boeckman, Jr.,* and Raymond A. Hudack, Jr.

Department of Chemistry, University of Rochester, Rochester, New York 14627-0216

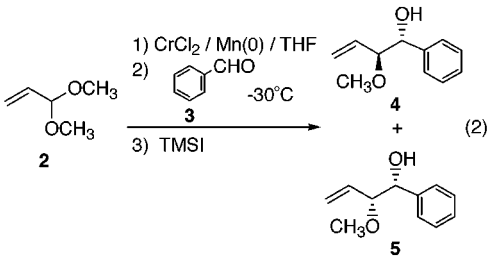
Received January 30, 1998

The multitude of variants of the aldol reaction and the reactions of allylmetal derivatives with aldehydes have provided a potent arsenal of methods useful for the stereoselective construction of arrays of acyclic stereogenic centers.[1,2] However, certain stereochemical relationships among vicinal stereogenic centers are much more difficult to access with high levels of diastereoselectivity, limited in some cases by the lack of practical access to the necessary precursors.[1,2] Among these are anti relationships in stereo duads and anti/syn relationships in stereo triads as exemplified by the general structure **1**, in which the nucleophilic component bears a protected heteroatom and the anti relationship is created during the C−C bond-forming step.[1,2] The Takai−Utimoto reaction of acrolein acetals with aldehydes mediated by TMSI and $Cr(II)Cl_2$ is effective for the generation of 1,2-anti diol derivatives (eq 1).[3] However, we have observed that substrate-based control over diastereofacial selectivity is problematic during generation of anti/syn triol derivatives (vide infra).



To explore a reagent-based strategy for stereocontrol in the generation of anti/syn triol derivatives utilizing the Takai−Utimoto reaction, a chiral ligand system for chromium must be developed to permit the generation of the required chiral γ-alkoxyallylchromium species.[4,5] Prior to undertaking such an effort, we felt it necessary and useful to investigate methods to obtain such species under conditions catalytic in chromium since use of more than stoichiometric quantities of chromium, as previously described by Takai and Utimoto, would be impractical.[3] Our experience with reactions employing stoichiometric γ-alkoxyallyl chromium reagents suggested that these species had limited stability under the reaction conditions and would require the use of excess chiral ligand to observe useful levels of de owing to the facility of ligand exchange in chromium(II) species.[3,4] In this connection, we have exploited the recent observations of Fürstner, who developed a redox couple between chromium(II) and manganese(0) permitting the use of catalytic amounts of chromium(II) to generate vinyl- and allylchromium species in situ.[6] The results of our studies are detailed below.

Our preliminary noncatalytic experiments, intended to determine whether the Cr(II)−Mn(0) redox couple would be effective in this system, employed conditions that were related to those employed by Fürstner.[6] A mixture of 1.5 equiv of chromium(II) chloride ($CrCl_2$) and 2 equiv of Mn powder in anhyd THF initially at −30 °C was combined sequentially with acrolein dimethyl acetal (**2**) (∼4 equiv), benzaldehyde (**3**) (1 equiv), and TMSI (3 equiv), followed by warming slowly to room temperature, which afforded the expected mixture of syn and anti alcohols **4** and **5** (∼2−3:1 anti/syn) in excellent yield (eq 2). Repetition of this reaction



at −30 °C with quenching at that temperature afforded **4** and **5** in 92% yield but with a disappointing selectivity (4.1:1 anti/syn). By comparison, the optimal stoichiometric reaction afforded **4** and **5** in a 7.3:1 ratio (anti/syn).[3a] Nevertheless, it appeared that the Cr(II)−Mn(0) couple could function effectively to produce the required (γ-alkoxyallyl) chromium intermediate(s) **6**.

Of greater concern was the observation that use of less than stoichiometric amounts of $CrCl_2$ (0.5 equiv), while holding the relative stoichiometry of the remainder of the components and the reaction conditions including the temperature (−30 °C) constant, led to only 20−40% conversion to **4** and **5** with considerable amounts of byproduct formation and substantial amounts of benzaldehyde (**3**) remaining. During the latter experiment, a significant exothermic reaction was noted upon addition of the TMSI. Repetition of this experiment with addition of the TMSI slowly over 1 h, however, did not significantly alter the composition of the product mixture. We speculated that the difficulty lay in the instability of the presumed intermediate α- and/or γ-methoxyallyl iodides **7** and **8**, generated from the reaction of **2** with TMSI, under the reaction conditions. Given the expected sensitivity of **7** and **8** to acid and reduction, it seemed plausible that the lower concentration of $CrCl_2$ would be insufficient to permit consumption of **7** and **8** rapidly enough to avoid decomposition or side reactions assuming **7** and **8** are formed rapidly. As a test of this hypothesis, a control experiment determined that, at −30 °C, the consumption of **2** upon reaction with TMSI was virtually complete within 3 min (GC analysis). Thus, use of $CrCl_2$ in truly catalytic quantities required the development of conditions to generate the iodide(s) **7** and **8** sufficiently slowly to permit efficient conversion to the γ-alkoxyallyl chromium intermediate(s) **6**.

(1) (a) Franklin, A. S.; Paterson, I. *Contemp. Org. Synth.* **1994**, *1*, 317−338. (b) Braun, M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 24. (c) Boeckman, R. K., Jr.; Connell, B. T. *J. Am. Chem. Soc.* **1995**, *117*, 12368−9 and references therein.

(2) (a) Hoppe, D.; Roush, W. R.; Thomas, E. J. *Houben-Weyl, Methods of Organic Chemistry "Stereoselective Synthesis"; Thieme: Stuttgart, 1995; Vol. E21b, pp 1357−1602. (b) Roush, W. R. In Comprehensive Organic Synthesis; Trost, B., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, pp 1−73.*

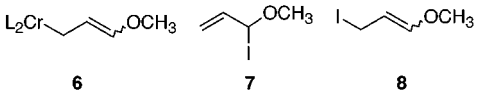
(3) (a) Takai, K.; Nitta, K.; Utimoto, K. *Tetrahedron Lett.* **1988**, *29*, 5263. (b) Fujimura, O.; Takai, K.; Utimoto, K. *J. Org. Chem.* **1990**, *55*, 1705. (c) Takai, K.; Kataoka, Y.; Utimoto, K. *Tetrahedron Lett.* **1989**, *30*, 4389.

(4) For studies of asymmetric allylation using organochromium reagents see: (a) Sugimoto, K.; Aoyagi, S.; Kibayashi, C. *J. Org. Chem.* **1997**, *62*, 2322−2323. (b) Chen, C.; Tagami, K.; Kishi, Y. *J. Org. Chem.* **1995**, *60*, 5386. (c) Cazes, B.; Verniere, C.; Goré, J. *Synth. Commun.* **1983**, *13*, 73.

(5) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.

(6) Fürstner, A.; Shi, N. *J. Am. Chem. Soc.*, **1996**, *118*, 12349−57.

S0022-3263(98)00160-1 CCC: $15.00
Published on Web 05/12/1998



6 7 8

Prior work by Sakurai and Olah on the in situ generation of TMSI suggested that this reagent could be generated slowly by use of TMSCl and NaI.[7,8] Control experiments established that TMSCl alone did not function effectively to generate the (γ-alkoxyallyl)chromium intermediate(s) **6**. To establish the validity of the idea, a mixture of $CrCl_2$ (0.5 equiv), Mn powder (2.5 equiv), and NaI (1.5 equiv) in anhyd THF at −30 °C was treated sequentially with **2** (4 equiv), **3** (1 equiv), and TMSCl (3 equiv). Upon addition of the TMSCl, a thick, difficultly stirrable slurry of NaCl was formed after a short time. Analysis of the resulting products indicated essentially complete conversion of **3** to a 7.4:1 (anti/syn) mixture of **4** and **5**, equivalent to that reported previously.[3] However, the level of diastereoselectivity observed using 0.5 equiv of $CrCl_2$ was variable owing to the difficulties with efficient mixing of the thick slurry of NaCl. Ultimately, it was found that these difficulties could be avoided by use of catalytic quantities of both NaI and $CrCl_2$ in an ~2.5:1 ratio.

Further experimentation led to the following optimized conditions: a mixture of $CrCl_2$ (0.07 equiv), Mn(0) powder (2.5 equiv), and NaI (0.2 equiv) in anhyd THF at room temperature is stirred for 20 min under argon, followed by cooling to −30 °C and sequential addition of **2** (2.3 equiv) and **3** (1 equiv) in single portions. Finally, TMSCl (3.2 equiv) is freed of acid by passage neat through a plug of basic alumina with washing by a small amount of anhyd THF, and the resulting solution is added to the reaction mixture in one portion. The resulting reaction mixture is stirred at −30 °C for 20 h, followed by quenching with 1 M aqueous HCl, warming to room temperature, and product isolation by ether extraction. Under these conditions, **4** and **5** were obtained in 77−88% yield having diastereomeric ratios of 10.9−11.5:1 (anti/syn), consistently higher than previously reported.[3a] The higher selectivity may arise from better control of the exotherm resulting from the reaction of **2** and TMSI, since Takai and Utimoto had observed a significant temperature dependence on selectivity in the stoichiometric reaction.[3a] As previously observed, for preparative purposes it is impractical to conduct the reaction much below −30 °C, even though higher diastereoselectivities might possibly be obtained.[3,4]

A plausible sequence of events for coupling the catalytic cycles is outlined in Figure 1. The iodide necessary to carry on the catalytic cycle by conversion of TMSCl to TMSI would appear insufficient unless any MnICl or MnI_2 produced during the reduction of $Cr(III)X_3$ reacts readily with TMSCl (or less likely with $TMSOCH_3$) to regenerate TMSI.

This procedure has been found to be quite generally applicable. A variety of structural types of aldehydes have been employed including aromatic, aliphatic, and α,β-unsaturated systems as shown in Table 1. One limitation encountered, thus far, is the somewhat diminished yields and diastereoselectivities observed for α,β-unsaturated aldehydes. Also, preliminary studies of aldehydes bearing α stereogenic centers, including cases bearing an α heteroatom (Table 1), show only modest diastereofacial selectivity in addition to the aldehyde (yields unoptimized), suggesting the absence of metal coordination between the reagent and the

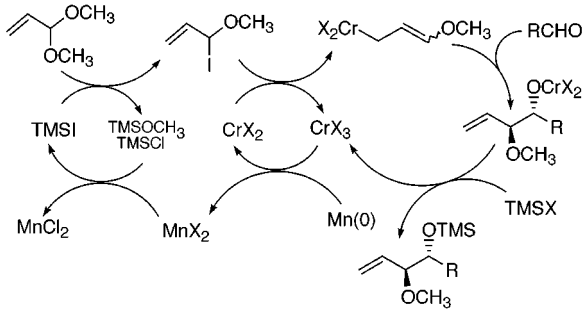
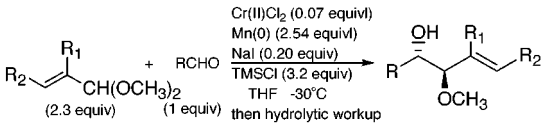
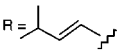
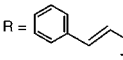
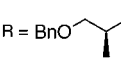
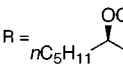


Figure 1.

Table 1



Reactants Product(s)	Yield (%)	Anti/Syn Ratio
R = Ph; $R_1 = R_2 = H$	88	10.9:1
R = C_6H_{11}; $R_1 = R_2 = H$	93	8.4:1
R = nC_3H_7; $R_1 = R_2 = H$	90	9.9:1
R = nC_6H_{13}; $R_1 = R_2 = H$	92	10.1:1
R = iC_3H_7; $R_1 = R_2 = H$	90	10.7:1
R = tC_4H_9; $R_1 = R_2 = H$	86	1:1.5
R =  ; $R_1 = R_2 = H$	62	3.9:1
R =  ; $R_1 = R_2 = H$	61	4.5:1
R = Ph; R_1 =CH_3; $R_2 = H$	94	8:1
R = iC_3H_7; $R_1 = CH_3$; $R_2 = H$	68	8.2:1
R =  ; $R_1 = R_2 = H$	46	~20:20:1:1[a]
R =  ; $R_1 = R_2 = H$	50	~20:20:1:1[a]

[a] The stereochemistry in this case is 3,4-*anti*-4,5-*syn*:*anti*-*anti*:3,4-*syn*-4,5-*anti*:*syn*-*syn*.

α heteroatom substituent.[9] Efforts are underway to remove these limitations, the former resulting, in part, from pinacol coupling in the cases involving α,β-unsaturated aldehydes, as shown by appropriate controls. The reaction is applicable to α-substituted acrolein acetals as has been previously observed (Table 1). We are continuing our studies aimed at the expansion of the scope of this catalytic variant of the Takai−Utimoto reaction, including investigation of the utility of ketones as acceptors and the development of chiral ligand systems for chromium to mediate a catalytic asymmetric variant of this process and to provide means to secure reagent-based control over facial selectivity in addition to aldehydes bearing α stereogenic centers.[4,5]

Acknowledgment. We are grateful to the National Institute of General Medical Sciences (NIGMS) and the National Cancer Institute (NCI) of the National Institutes of Health for research grants (GM-29290, GM-30345, and CA-29108) in support of these studies.

Supporting Information Available: A detailed general experimental procedure is provided along with characterization data and ^1H NMR spectra for the new compounds in the Table 1 (17 pages).

JO980160H

(7) (a) Morita, T.; Okamoto, Y.; Sakurai, H. *J. Chem. Soc., Chem. Commun.* **1978**, 874. (b) Morita, T.; Okamoto, Y.; Sakurai, H. *Tetrahedron Lett.* **1978**, 2523. (c) Morita, T.; Yoshida, S.; Okamoto, Y.; Sakurai, H. *Synthesis* **1979**, 379.

(8) (a) Olah, G. A.; Narang, S. C.; Gupta, B. G. B.; Malhotra, R. *Synthesis* **1979**, 61. (b) Olah, G. A.; Narang, S. C.; Gupta, B. G. B.; Malhotra, R. *J. Org. Chem.* **1979**, *44*, 1247.

(9) (a) Mulzer, J.; Schulze, T.; Strecker, A.; Denzer, W. *J. Org. Chem.* **1988**, *53*, 4098−103. (b) Martin, S. F.; Li, W. *J. Org. Chem.* **1989**, *54*, 6129−33.