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# CHELATION CONTROL ASSOCIATED WITH ORGANOMETALLIC ADDITION REACTIONS IN WATER. THE HIGH STEREOSELECTIVITY OFFERED BY α- AND β-HYDROXYL SUBSTITUENTS OBVIATES THE NEED FOR PROTECTING GROUPS[1]

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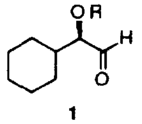
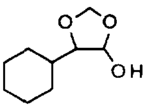
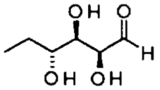
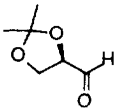
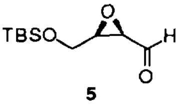
**Abstract:** High stereoselectivities have been observed for indium-promoted allylations of α- and β-hydroxy aldehydes in aqueous media, with strong implication that chelate control can continue to operate in water.

The Cram chelate model, put forward more than two decades ago as a predictor of the stereochemical course of organometallic additions to α-alkoxy ketones in anhydrous solvents,[2] has been applied extensively in synthesis.[3] According to this paradigm, the intervention of a preorganized complex is followed by nucleophilic attack from the less sterically hindered π-face of the carbonyl group. Relevantly, the determining factors for α-induction have been defined uniquely for anhydrous conditions. In view of the fact that the metal indium can promote effective carbon-carbon bond formation in aqueous media without concern for hydrolytic destruction of the organoindium reagent,[4] delineation of the impact of this substantive solvent change on chelation control has now been made. Although progression to a significantly more polar, hydrogen-bonding medium could effectively damp stereoselectivity, coordination of the substrate to the indium ion can indeed override such solvation forces, especially when the neighboring functionality is a free hydroxyl substituent.

A group of four cyclohexaneacetaldehydes containing α-oxy subtituents of widely differing basicity (**1a-d**) was examined first (Table I). Conversion to syn product following treatment with allyl bromide and indium would implicate chelation-controlled addition. Where **1a** and **1b** are concerned, the bulky nature of their R groups is sufficient to favor formation of anti product predominantly. Although the allylations performed in water or aqueous THF proceed significantly faster than in pure THF, the diastereoselectivity in these two examples is either constant or decreases modestly and gives no evidence for chelate control under any circumstances. In **1c**, the added binding capa-

**Table I.** C-Allylation of α-Oxy Aldehydes with Indium in Various Solvents: Syn/Anti Ratios.

| Compd | | $H_2O$ | (1:1) $H_2O$-THF | THF |
|---|---|---|---|---|
|  **1** | **a**, R = $SiMe_2t$-Bu | 1:3.9 | 1:4.2 | 1:4.0 |
| | **b**, R = $CH_2Ph$ | 1:1.2 | 1:2.2 | 1:3.9 |
| | **c**, R = $CH_2OCH_3$ | 2.1:1 | 1.7:1 | 1.6:1 |
| | **d**, R = H | 9.8:1 | 9.5:1 | ---- |
|  **2** | | 2.3:1 | 2.3:1 | [a] |
|  **3** | | 10.2:1 | 8.2:1 | 3.0:1 |
|  **4** | | 1:3.2 | 1:3.9 | 1:5.9 |
|  **5** | | 1:2.0 | 1:2.0 | 1:5.2 |

[a] No reaction.

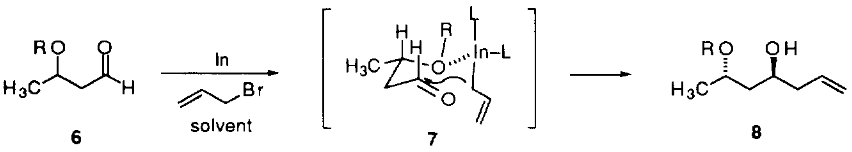
bility of a second oxygen in the MOM sidechain lends itself to a reversal in the preferred trajectory of attack. When a free hydroxyl is present as in **1d**, a syn-facial preference of approximately 10:1 is realized. While unprotected derivatives of this type, which include carbohydrates such as *D*-arabinose (**3**), cannot normally be utilized in most organometallic reactions due to rapid proton transfer, they excel in guiding the course of indium-catalyzed reactions in water.

The response of hemiacetal **2** is similar to that of the MOM derivative **1c**, signaling that its reactive open form likely has not yet lost formaldehyde or it would have behaved as **1d**. Rather unexpectedly, the neighboring acetal and oxiranyl centers in **4** and **5** exhibit no demonstrable capacity for coordination to the indium cation.

The effect of variation of experimental conditions on diastereofacial selectivity was examined on several fronts. The standard manner in which the allylations were performed was met with a gradual increase in acidity to approximately pH 2.5. When reactions were conducted under strictly controlled pH conditions, the product distributions achieved at pH 7.0 or 4.0 were seen not to differ significantly from the data in Table I, despite the much slower rate of allylation under neutral conditions. The one exception was **2**, which responded at low pH by generating a 9.8:1 syn/anti product mixture, presumably because of complete hydrolysis to **1d** prior to allylation.

Maximal stereoselectivity was achieved when tetraethylammonium bromide (13.5:1) or tetrabutylammonium iodide (7:1) were added at the 1 mol equiv level to aqueous reaction mixtures containing **3**. When processed analogously, **1c** was also transformed at an increased level to syn product (8.3:1). Lithium bromide and magnesium chloride did not lend themselves to a comparable synergistic effect. Consistent with the product distribution evidence for chelated intermediates, especially for **1d** and **3**, the rate of addition to **1d** is substantially faster than the allylations of **1a**, **1c**, and **5**. This relative ordering was established by means of competition experiments wherein amounts of the two reagents were allowed to vie for a limited quantity of allyl bromide and indium in water.

The prospects that a free hydroxyl positioned β to a carbonyl group undergoing indium-promoted allylation might be equally well exploited surfaced rapidly (Table II).[5] Aldehydes **6a-d** were chosen because of their structural simplicity and because of the almost identical changes in R compared to **1**. The product distribution data reveal in fact that a very good correlation exists between the two series. Although a methoxyl group is indeed capable of chelation control, it is again the free hydroxyl derivative that exhibits the most pronounced face selectivity.



The stereoselectivities documented here lift the limitations imposed by our current knowledge base, which has largely been confined to observations made in the strict absence of moisture. Interest in synthetic applications of indium metal has increased significantly in recent years.[4,6-10] The present systematic exercise, which demonstrates strong facial control when free hydroxyl groups are in close proximity to the reaction center, delineates the fact that organometallic reactions conducted in water make protection-deprotection tactics unnecessary, and in fact undesirable, at least for oxygenated functional groups. The extent to which this principle shall apply to other heteroatomic substituents is under investigation.

**Table II.** Anti/Syn Ratios for Allylindium Additions to **6**.

| Compd | | $H_2O$ | (1:1)<br>$H_2O$-THF | THF |
|---|---|---|---|---|
| **6a** | R = $SiMe_2t$-Bu | 1:1 | 1:1.2 | 1:1.7 |
| **b** | R = $CH_2Ph$ | 1:1 | 1:1 | 1:1 |
| **c** | R = $CH_3$ | 4:1 | 4:1 | 3.3:1 |
| **d** | R = H | 8.5:1 | 8.2:1 | [a] |

[a] No reaction.

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