

Remarkable 1,6-Acyclic Diastereoselection in the Coupling of a Novel Butadienyl Di-indium Compound with Aldehydes

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Reactions leading to the control of the relative stereochemistry of two stereogenic centers are of great synthetic importance. Numerous reactions have been developed for effective 1,2- and 1,3-stereoselection. As the separation of the two stereogenic centers extends further, stereoselection becomes more difficult, especially for acyclic systems.¹

Recently, organoindium chemistry has attracted considerable interest.² In particular, indium mediates the coupling of allyl³ and propargyl⁴ bromide with aldehydes to give the corresponding adduct alcohols in high yields under mild conditions in aqueous media. Furthermore, the reaction shows good regioselectivity⁵ and diastereoselectivity by steric⁵ or chelation control.⁶ 1,2-, 1,3-, and even 1,4-stereoselection were possible. However, in the latter case, the stereoselection was not as pronounced.^{6c} We report here our observation of a remarkable 1,6-acyclic stereoselection in an indium-mediated carbon-carbon bond formation reaction where essentially only one diastereomer was obtained.⁷

We have previously reported⁸ that indium mediated the coupling of 1,4-dibromobutene (**1**) with aldehydes (**2**) in aqueous media to give good yields of 1,3-butadien-2-ylmethanols (**3**) according to Scheme 1. However, when 2 equiv of the aldehyde was used in the reaction, a complex mixture was obtained. Using *p*-chlorobenzaldehyde (**2c**) as the typical example, the product mixture contained compound **3c**, the acetylenic diol **4c**, the allenylic diol **5c**, and the butadienylic diol **6c**. In the case of **5c** and **6c**, the compounds were obtained as mixtures of diastereomers, which were not unexpected. However, much to our surprise, compound **4c** was obtained as only one diastereomer according to its ¹H and ¹³C NMR spectra. The same mixtures were obtained when other aldehydes were used in the reaction. In all cases, compound **4** was formed as one single diastereomer. We were able to obtain an X-ray crystal structure of compound **4a** (R = *n*-C₅H₁₁), which showed that **4a** has the *anti*-stereochemistry (Figure 1). The same *anti*-stereochemistry was therefore assigned to other compounds **4** because of their similar NMR spectra. In an effort to improve the yield of **4**, we examined the reaction of **2c** in different solvents, including ethanol, 2-propanol, DMF, ether, THF, 1,4-dioxane, ethylene glycol dimethyl ether, 2-methoxy ethyl ether, methoxyethanol, water, and mixed systems (see Supporting Information). Even though in alcoholic or ether solvents, compound **4c** could be obtained as the major product of the reaction, the yield was moderate (up to 44%) nevertheless, and meticulous chromatography separation was required for its isolation.

Because in the indium-mediated allylation reaction, we were able to prove the formation of the allylindium intermediate by NMR,⁹ we decided to examine the reaction of 1,4-dibromobutene (**1**) with indium in THF-*d*₈ by ¹H NMR. It was found that, at room temperature, the signals due to the starting bromide slowly declined. After one night, the starting bromide had disappeared completely, and two single signals appeared at 6.33 and 5.56 ppm along with several other weak signals. To determine and characterize the new

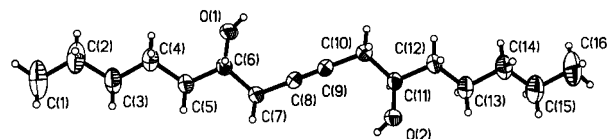
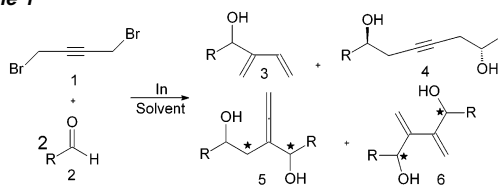


Figure 1. X-ray structure of compound **4a**.

Scheme 1

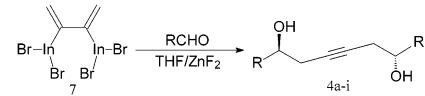


species, a series of experiments were performed. ¹H-¹H COSY spectra displayed a weak correlation, which indicated that the two signals are in close proximity. Carbon NMR spectra showed two major signals at 164.36 and 130.80 ppm. A subsequent DEPT experiment indicated that the peak at 130.80 ppm was a methylene group and the signal at 164.36 ppm had no proton attachment. Heteronuclear single quantum correlation (HSQC) and heteronuclear multiple bond correlation (HMBC) experiments showed that the 130.80 ppm carbon correlated with the above two types of protons, whereas the 164.36 ppm carbon correlated with these protons through three or four bonds. These NMR data were therefore consistent with a 2,3-butadienyldiindium structure. When this organoindium intermediate was quenched with water, the hydrolysis product was found to be butadiene. Finally, electrospray ionization MS of the intermediate gave a major cluster of peaks which, by isotopic distribution, was assigned to be [C₄H₄In₂Br₅]. We therefore assigned the molecular composition of the organoindium intermediate to be C₄H₄In₂Br₄, with the molecular structure as 2,3-butadienyldiindium tetrabromide (**7**).

This novel di-indium compound was remarkably stable in THF and can be stored as a THF solution and kept in a refrigerator for months without obvious changes. The reaction between **7** and different carbonyl compounds gave almost exclusively the acetylenic diol **4**. The reactions, however, were slow, but could be accelerated with the addition of zinc fluoride as the Lewis acid.¹⁰ Under these reaction conditions, the reactions gave excellent yields of the diols **4**, again as single diastereomers (Table 1). It is noteworthy that the reaction worked equally well for aryl, alkyl, and heteroaryl aldehydes. Furthermore, the nitro function was not reduced under the reaction conditions¹¹ (entry 4), and the addition reaction to the aldehyde function took place smoothly.

These results suggest that in the direct reaction of indium-mediated coupling of **1** with aldehyde **2**, a number of organoindium intermediates may have been formed (Scheme 2),¹² leading variously to products **3**, **4**, **5**, and **6**. By reacting indium with **1** first to give eventually mainly intermediate **7**, a high yield of **4** could be obtained, presumably via the first adduct **8**. The stereoselection

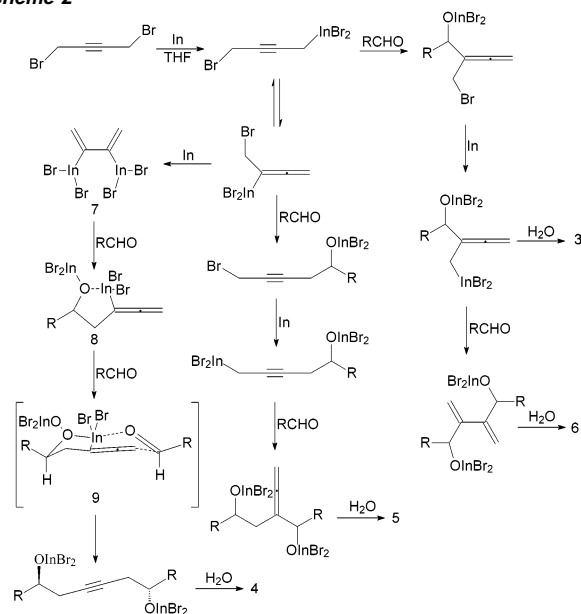
Table 1. 1,6-Diastereoselective Reactions of Aldehydes with Butadienyl Di-indium(III) Compound **7** in THF in the Presence of Zinc Fluoride



entry	aldehyde	R	product	yield (%) ^a
1	2a	<i>n</i> -C ₅ H ₁₁	4a	80
2	2b	Ph	4b	75
3	2c	(<i>p</i> -Cl)Ph	4c	96
4	2d	(<i>p</i> -O ₂ N)Ph	4d	92
5	2e	(<i>p</i> -MeO)Ph	4e	52 (84) ^b
6	2f	(<i>p</i> -MeO ₂ C)Ph	4f	99
7	2g	<i>c</i> -C ₆ H ₁₁	4g	73
8	2h	2-furyl	4h	89
9	2a + 2f	<i>n</i> -C ₅ H ₁₁ + (<i>p</i> -MeO ₂ C)Ph	4a/4f/4i	4/29/19

^a Isolated yields. ^b Yield based on the aldehyde consumed.

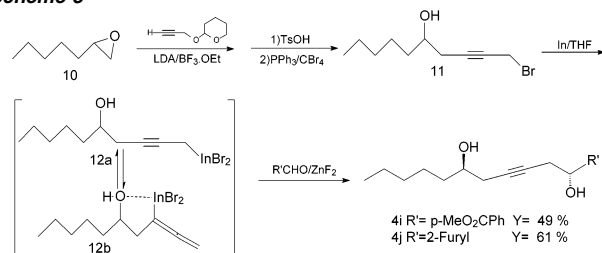
Scheme 2



can then be rationalized by the chelation of the allenylindium with the oxyanion as illustrated in **8**. Coupling of **8** with the second aldehyde will proceed through a bicyclic transition state **9** with chelation control. In this bicyclic structure, the R group of the aldehyde will prefer to be in the pseudoequatorial conformation leading to the observed *anti*-product, whereas there may be an interaction between pseudoaxial R and the bromine ligand on indium.

While the present reaction is useful in preparing symmetrical 1,6-diols, it is not practical for the synthesis of unsymmetrical diols. Indeed, when the di-indium reagent **7** was reacted with equal amounts of methyl 4-formylbenzoate **2f** and hexanal **2a** in a one-pot procedure, it gave a mixture of the symmetrical diols **4a** and **4f** and the unsymmetrical diol **4i** in yields of 4, 29, and 19%, respectively. However, the same unsymmetrical diols **4i** (and **4j**) can be selectively synthesized by taking advantage of the knowledge

Scheme 3



gained here. Thus, the mono bromo compound **11**, prepared in good yield from readily available precursors using literature procedures for similar compounds,¹³ reacted with indium and methyl 4-formyl benzoate (**2f**) or 2-furaldehyde (**2h**) to afford the acetylenic diols **4i** and **4j**, respectively, as one diastereomer in good yields (Scheme 3).¹⁴ This proved that the same intermediate **8** was operative in the control of diastereoselection.

In summary, we have demonstrated the formation of a novel organodiindium reagent **7** and its efficacy in displaying remarkable 1,6-acyclic diastereoselection in its reaction with aldehydes. Such diastereoselection can be achieved in other examples as well if the necessary chelation intermediate **8** can be generated.

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Supporting Information Available: X-ray single-crystal analysis data of **4a** as well as experimental details and characterization of compounds (PDF and CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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