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INDIUM-MEDIATED COUPLING REACTIONS OF δ-OXYGENATED ALLYL HALIDE DERIVATIVES WITH ALDEHYDES IN AQUEOUS MEDIA

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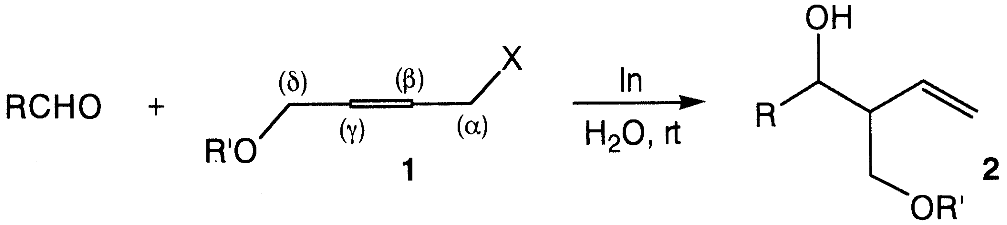
Indium-mediated coupling reactions of δ-oxygenated allyl halide derivatives **1** with aldehydes in aqueous media proceeded at the γ-position to give diol derivatives **2**. Compound **1** is equivalent to an allylic carbanion **4** with a neighboring oxygen functional group generated in aqueous media.

KEY WORDS indium; aqueous media; allylation; allyl halide

C-C bond formation promoted by allylic metals is one of the fundamental processes in organic synthesis, and a variety of metallic elements are employed for this purpose.1) Recently, indium has been shown to be an efficient mediator in the coupling reaction of allyl halide with carbonyl compounds in aqueous media, and its potential usefulness has been disclosed by reactions with various types of substituted carbonyl compounds in water giving homoallyl alcohol derivatives.2) In these reactions, preclusion of anhydrous reaction conditions offers practical convenience. In contrast to carbonyl substrates, somewhat limited types of allyl halide partners have been examined in the indium-mediated reactions in aqueous media. That is, although reactions of allyl halides having a substituent at the β- or γ-position have been reported,2) δ-functionalized allyl halides, in particular δ-oxygenated allyl halides,3) have not been utilized as an allyl component in the indium-mediated reaction. We report here the indium-mediated coupling reactions of δ-oxygenated allyl halides derivatives **1** with aldehydes in aqueous media to give diol derivatives **2**.4)



The extremely simple reaction procedures under atmospheric conditions are as follows: a mixture of the δ-oxygenated allyl halide (**1**, 1 mmol) and the aldehyde (1.5 mmol) in water (6 ml) was rapidly stirred. To this mixture indium {indium powder from SOEOKA CHEMICALS (99.9%, 325 mesh) ; 1.5–3 mmol} was added. The reaction mixture was stirred at room temperature for 14 h–4 d, and then extracted with ether. The solvent was evaporated and the product was purified by column chromatography.

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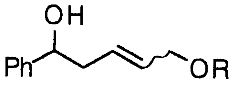
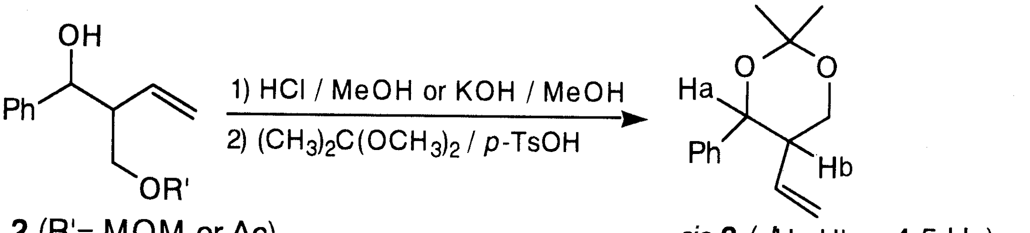
Table 1. Indium-Mediated Coupling Reactions of **1** with Aldehydes in Aqueous Media

Entry	Aldehyde	Allyl halide **1**		Yield of **2** (*anti* : *syn*)
1	R = Ph	R'= MOM	X = Cl (*Z*)	76% (1.7 : 1)
2	R = Ph	R'= MOM	X = Br (*Z*)	84% (2.5 : 1)
3	R = Ph	R'= Ac	X = Cl (*Z*)	54% (1.2 : 1)
4	R = Ph	R'= Ac	X = Br (*Z*)	54% (1.5 : 1)
5	R = Ph	R'= Bn	X = Cl (*Z*)	80% (1.9 : 1)
6	R = *n*-C_7H_{15}	R'= MOM	X = Cl (*Z*)	90% (1.9 : 1)
7	R = *n*-C_7H_{15}	R'= Bn	X = Cl (*Z*)	92% (1.5 : 1)
8	R = Ph	R'= MOM	X = I (*E*)	80% (4.0 : 1)[a]
9	R = Ph	R'= TBDMS	X = I (*E*)	30% (26.0 : 1)[a]

[a] The α-coupling products were obtained in approximately 20% yields, respectively.



(R' = MOM, TBDMS)

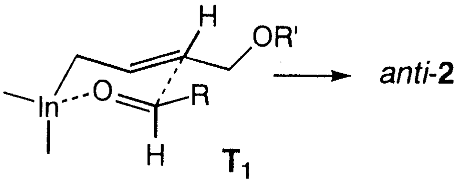


2 (R'= MOM or Ac)

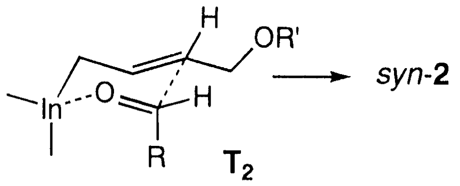
cis-**3** (*J*Ha-Hb = 4.5 Hz)
trans-**3** (*J*Ha-Hb = 10.6 Hz)

Allyl halides **1** bearing δ-methoxymethoxy (MOMO), -acetoxy (AcO), -benzyloxy (BnO), and -*tert*-butyldimethylsilyloxy (TBDMSO) groups were used as substrates. The results are shown in Table 1. The stereochemistry of the product was deduced by chemical transformation to the corresponding acetonide **3**. Removal of the protecting group (R') in **2** followed by the reaction with 2,2-dimethoxypropane gave **3**. The vicinal coupling constants (J = 4.5 Hz and J = 10.6 Hz) of ring protons (H_a and H_b) in *cis*-**3** and *trans*-**3** were related back to the *anti*- and *syn*-stereochemistry of **2**, respectively. With the (*Z*)-**1** (entries 1–7), the indium-mediated coupling reaction of benzaldehyde or octyl aldehyde in water gave diol derivatives **2** in good yields (54–92%). When THF was used as a solvent instead of water as in the case of entry 1, no apparent reaction was observed at room temperature. The indium-mediated reaction of (*Z*)-**1** was γ-regioselective but poorly diastereoselective, giving a mixture of *anti*- and *syn*-isomers of **2**. The ratio of *anti*-**2** : *syn*-**2** was in the range of 1.2 : 1–2.5 : 1. In entries 8 and 9, (*E*)-allyl iodides **1** gave the γ-coupling products **2** in 80% and 30% yields along with the α-coupling products, respectively. Worthy of note is that the bulky δ-TBDMS group in (*E*)-**1** improved the diastereoselectivity to give *anti*-**2** predominantly (*anti* : *syn* = 26.0 : 1).

The diastereoselectivity observed in the γ-coupling reaction of (*E*)-**1** can be explained by considering the cyclic transition states ($\mathbf{T_1}$ and $\mathbf{T_2}$, R'= TBDMS or MOM) with the coordination of the carbonyl oxygen to indium. C-C bond formation through the transition state $\mathbf{T_1}$ involving the substituents in the equatorial positions to *anti*-**2** would appear to be more favorable. Since the reaction of (*E*)-**1** (R'= TBDMS) to *syn*-**2** through the transition state **T_2** may occur with difficulty owing to steric hindrance from the bulky TBDMS group, the *anti*-diastereoselectivity was enhanced significantly. In cases of (*Z*)-**1**, the reaction may proceed through several possible cyclic transition states involving **T_1** (R'= MOM, Ac, and Bn), and is accompanied by a drop-off in the level of the *anti*-product.$^{5)}$

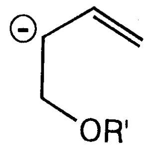


T_1



T_2

In conclusion, the indium-mediated coupling reaction of δ-oxygenated allyl halide derivatives **1** with aldehydes proceeds smoothly in aqueous media to give diol derivatives **2**. This reaction implies that δ-oxygenated allyl halide derivatives **1** function as synthons of allylic carbanions **4** with the neighboring δ-oxgen functional group in aqueous media. The present C-C bond formation is advantageous since the corresponding allylic carbanion **4** often induces competitive elimination of the δ-oxgen functional group in conventional reactions using alkali and alkaline earth metals in organic solvent.



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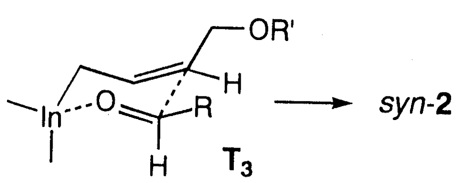
3) Very recently, indium-promoted coupling reactions of oxygen-substituted allylic bromides with aldehydes in aqueous solution and their stereoselectivity were investigated; *a*) Maguire R. J., Mulzer J., Bats J. W., *J. Org. Chem.*, **61**, 6936-6940 (1996); *b*) Paquette L. A., Bennett G. D., Chhatriwalla A., Isaac M. B., *J. Org. Chem.*, **62**, 3370-3374 (1997).

4) This work was presented at the 117th Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, March 1997, Abstracts of Papers, Part 2, p. 86.

5) At the present time, there is no evidence to suggest that the allyl indium species underwent *Z-E* equilibration during the formation from (*Z*)-allyl halides **1**. However, (*Z*)-allyl indium would provide the completely reversed *syn*-diastereoselectivity through the energetically more favorable transition state (**T_3**). Furthermore, the comparable diastereoselectivity in entries 1–7 with entry 8 may suggest that the *Z*-double bond isomerizes to some extent to the thermodynamically more stable *E*-double bond prior to the coupling.



T_3

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