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Development of a highly α-regioselective indium-mediated allylation reaction in water

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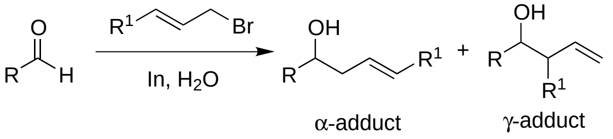
Abstract—Linear α homoallylic alcohol adducts were obtained with high regioselectivities in moderate to good yields using allylic indium reagents in the presence of 10 M water. The exceptionally high regioselectivities observed were neither steric nor electronic in origin from the results presented in this paper. © 2001 Elsevier Science Ltd. All rights reserved.

The addition of allylic metals to carbonyl compounds has become one of the most important reactions in organic synthesis. This is because the homoallylic alcohols generated are versatile building blocks for the synthesis of many biologically active molecules such as macrolides, polyhydroxylated natural products and polyether antibiotics.[1,2] Among the many metal-mediated allylation reactions, indium-mediated allylation has gained popularity in view of the possibility of carrying out the reaction in water.[3,4] The use of water as a solvent to carry out organic reactions offers practical convenience as it alleviates the need to handle flammable and anhydrous organic solvents. It also simplifies the tedious protection–deprotection sequences for certain functional groups containing acidic protons, which leads to an increase in overall synthetic efficiency.[5]

Although these reactions have been found to be highly regio- and stereoselective, one severe limitation inherent to this strategy is the difficulty in obtaining the α-adduct when γ-substituted allylic metals are employed (Scheme 1). Except for some special cases, the indium-mediated allylation of aldehydes with γ-substituted allylic indiums occurs regioselectively at the γ-position of the allylic metal reagent.[6,7] For example, the allylation of crotyl bromide with benzaldehyde produces solely the γ-adduct. This severely limits access to the corresponding α-homoallylic alcohol adducts. In this paper, we report a general method for indium-mediated allylation reactions that affords the α-adducts with high selectivities.



Scheme 1.

In view of our interest in the application of indium-mediated allylation for the synthesis of complex molecules, efforts were directed toward exploring the effect of solvents on the reactivity, as well as the diastereoselectivity of the indium-mediated allylation reaction. In our initial study, the reaction of cyclohexane carboxaldehyde with crotyl bromide in water was investigated. To our surprise, when the amount of water added was decreased while stirring was prolonged, we consistently detected a significant amount of the α-adduct.

This interesting result prompted us to study further the effect of solvents on the regioselectivity (α-adduct versus γ-adduct). The results are summarized in Table 1.

Among the various solvents examined, the reactions carried out in DMF, THF, ethanol and water (0.5 M) afforded only the γ-homoallylic alcohols (entries 1, 2, 5 and 10). The addition of equal amounts of water to THF or DMF does not improve the regioselectivity. However, water (10 M) and water/dichloromethane (10 M/10 M) distinguished themselves by exhibiting excellent α-selectivity (entries 3, 4 and 8).[8]

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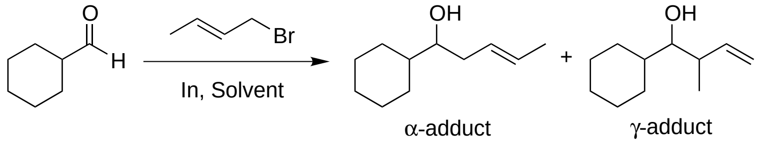
Table 1. The effect of solvent on the indium-mediated allylation of cyclohexanecarboxaldehyde with crotyl bromide[a]



Entry	Solvent	Amount (M)	Time (h)	Yield %[d] (α:γ)[c]
1[b]	DMF	10	72	65 (0:100)
2	H_2O	0.5	72	90 (0:100)
3[b]	H_2O	10	24	85 (99:1)
4	H_2O	10	72	87 (86:14)
5	THF	10	72	20 (0:100)
6	CH_2Cl_2	10	24	–[e]
7	THF/H_2O	10:10	72	95 (0:100)
8	CH_2Cl_2/H_2O	10:10	24	68 (>99:1)
9[b]	DMF/H_2O	10:10	72	80 (0:100)
10	CH_3CH_2OH	10	72	97 (0:100)

[a] All reactions were performed with aldehyde (1 mmol), crotyl bromide (1.2 mmol) and indium (1.5 mmol) at room temperature unless otherwise noted.

[b] The reactions were carried out at 40°C for 12 h.

[c] Determined by ^{1}H NMR.

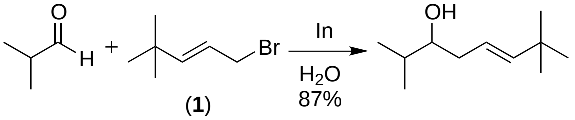
[d] Combined yield.

[e] Neither the γ- nor α-adduct was observed.

It is important to note that the amount of water added is crucial for the α-selectivity. Higher α-regioselectivity was observed when the amount of water was 10 M. When the reaction was carried out in the presence of 0.5 M of water, no α-adduct was observed even after the reaction was stirred for 72 h. Furthermore, the regioselectivity increased when a higher temperature was applied (entry 3).

To our best knowledge, this is the first example where the α-homoallylic alcohol adduct was synthesized via an indium-mediated allylation without the use of a sterically hindered substituent at the bromide and aldehyde. A previous publication by Chan et al.[9] revealed that a steric effect operates in determining the regioselectivity. In general, the reaction gives the γ-adduct, exclusively, if no sterically bulky carbonyl or allyl bromide substituent is presented. For example, Chan et al. found that the reaction of isopropyl aldehyde with bromide **1** gives the α-adduct in an 87% yield (Scheme 2).

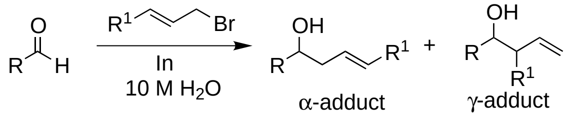
With the unveiling of water (10 M solution) as an important criterion for obtaining the α-homoallylic alcohol adduct, we extended the reaction to a variety of substrates and the results are shown in Table 2. In all cases, the α-adducts were obtained with high selectivities in moderate to good yields.



Scheme 2.

It was found that the reaction of benzaldehyde with crotyl bromide gave the α-regioisomer almost exclusively (entry 1). Using 10 M of water as the solvent, a totally different regioisomer was obtained as compared to previously published results using water or other solvents. Furthermore, the reaction of hydrocinnamaldehyde and hexanal with crotyl bromide also gave very good α-regioselectivity (entries 3 and 4). The results shown in Table 2 suggest that indium-mediated allylation can give the α-homoallylic alcohol adducts regardless of the substituents. Accordingly, an increase in the steric bulkiness of the aldehyde and bromide

Table 2. Indium-mediated allylation of aldehydes with crotyl bromide and cinnamyl bromide[a]



Entry	R	R^1	Time (h)	Yield %[c] (α:γ)[b] (E/Z)[b]
1	Ph	Me	36	60 (99:1) (55/45)
2	c-C_6H_{11}	Me	24	85 (99:1) (70/30)
3	n-C_5H_{11}	Me	36	75 (98:2) (65/35)
4	$PhCH_2CH_2$	Me	18	67 (97:3) (55/45)
5	Ph	Ph	72	66 (98:2) (E)
6	c-C_6H_{11}	Ph	72	73 (96:4) (98/2)
7	n-C_5H_{11}	Ph	85	71 (99:1) (90/10)
8	$PhCH_2CH_2$	Ph	160	50 (99:1) (95/5)

[a] All reactions were performed with aldehyde (1 mmol), bromide (1.2 mmol) and indium (1.5 mmol) with water (0.10 mL) at room temperature for 12 h, followed by heating to 40°C, unless otherwise noted.

[b] Determined by ^{1}H and ^{13}C NMR.

[c] Total yield.

gave no significant improvement in the α-regioselectivity. This type of reaction seems to be quite general irrespective of the allylic bromides used. Even when cinnamyl bromide was used, the α-adducts were obtained with excellent selectivities and good yields.

In conclusion, a general and new method for obtaining α-adducts by the indium-mediated allylation has been developed. By using 10 or 0.5 M water, the regioselectivity of the allylation can be completely inverted. Further mechanistic studies of this α-regioselective indium-mediated allylation are reported in the following paper.

A representative procedure for the preparation of α-homoallylic alcohol adducts: To a mixture of cyclohexane carboxaldehyde (0.11 g, 1 mmol) and indium powder (0.17 g, 100 mesh, 1.5 mmol) in H_2O (0.10 mL) was added crotyl bromide (0.16 g, 1.2 mmol) slowly at room temperature. The reaction mixture was stirred for 12 h followed by heating at 40°C for a further 12 h. Diethyl ether was added to dilute the reaction mixture followed by 1 M HCl to quench the reaction. The mixture was extracted with diethyl ether. The combined organic layer was washed with brine and dried over anhydrous magnesium sulfate, filtered and the solvent was removed in vacuo. The crude product was purified by column chromatography to afford the linear α-homoallylic alcohol adduct as a colorless oil.

R_f 0.45 (4:1, hexane:ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$) mixture of *E* and *Z* isomer: δ 5.61–5.38 (m, 2H), 3.39–3.29 (m, 1H), 2.24 (t, $J=8.4$ Hz, 1H), 2.05 (t, $J=8.4$ Hz, 1H), 1.69 (d, $J=5.6$ Hz, 3H), 1.87–0.94 (m, 11H). ^{13}C NMR (75.4 MHz, $CDCl_3$) *E* isomer: δ 128.7, 127.6, 74.9, 42.9, 37.4, 29.0, 28.1, 26.5, 26.2, 26.1, 18.0; *Z* isomer: δ 127.0, 126.6, 75.5, 42.59, 37.46, 31.7, 29.0, 28.1, 26.5, 26.2, 26.1. FTIR (film) 3591, 3422, 3020, 2925, 2854, 1625, 1448, 1261, 1086, 1065, 1030, 968, 892 cm^{-1}. HRMS calcd for $C_{11}H_{20}O$ [M$^+$]: 168.1514. Found: 168.1520.

Acknowledgements

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