

Development of a Highly α -Regioselective Metal-Mediated Allylation Reaction in Aqueous Media: New Mechanistic Proposal for the Origin of α -Homoallylic Alcohols

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Abstract: This paper described a general method to obtain α -adduct homoallylic alcohols using indium, zinc, and tin in water. A new mechanism was proposed to account for the formation of these synthetically difficult-to-obtain molecules. Generally, this method can be performed with a wide range of aldehydes and allylic halides with just 6 equiv of water added, giving the α -adduct in high selectivities. To account for the origin of the α -homoallylic alcohol, the reaction mechanism was carefully studied using ^1H NMR, a crossover experiment, and the inversion stereochemical studies of 22β γ -adduct homoallylic sterol to the 22α α -adduct homoallylic sterol. From the results of mechanism studies, it is possible that two mechanism pathways coexisted in the metal-mediated α -regioselective allylation. The metal salts formed from the metal-mediated allylation can catalyze the γ -adduct to undergo a bond cleavage to generate the parent aldehyde in situ followed by a concerted rearrangement, perhaps a retroene reaction followed by a 2-oxonia[3,3]-sigmatropic rearrangement to furnish the α -adduct. The α -adduct can also be synthesized via the formation of an oxonium ion intermediate between the γ -adduct and the unreacted aldehyde. The proposed mechanisms were further supported by experimental findings from the addition of InBr_3 to γ -adduct under similar conditions.

Introduction

Being important building blocks and versatile synthons, homoallylic alcohols are highly featured in the organic syntheses of many biological active molecules such as macrolides, polyhydroxylated natural products, and polyether antibiotics.¹ Among the existing means to construct these synthetically and biologically important molecules, metal-mediated allylation² is one of the easiest and most convenient. Furthermore, with the intensive and further development of catalytic stereo- and enantioselective synthesis of homoallylic alcohol,³ one or two

stereocenters can be assembled in a single step. This is highly efficient in terms of atom economics,⁴ as all of the carbons form the scaffold of the desired molecules.

However, many metal-mediated allylations involving allyl-magnesium and allyllithium are often very difficult to handle because the reactions have to be performed under strictly anhydrous, oxygen-free, and low temperature conditions. The metal-mediated Barbier type allylation reaction has provided an alternative to overcome these problems by adding reagents and metal together at room temperature using environmentally benign solvents such as water and/or ethanol. Metals such as indium,⁵ zinc,⁶ and tin⁷ are always used in typical metal-mediated Barbier type allylations with carbonyl compounds and allylic halides. The use of water as a solvent to carry out organic

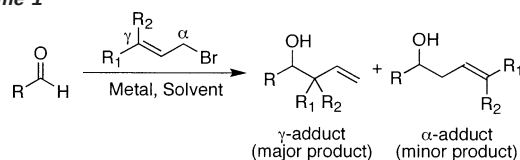
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- (1) (a) Nicolaou, K. C.; Kim, D. W.; Baati, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 3701. (b) Nicolaou, K. C.; Ninkovic, S.; Sarabia, F.; Vourloumis, D.; He, Y.; Vallberg, H.; Finlay, M. R. V.; Yang, Z. *J. Am. Chem. Soc.* **1997**, *119*, 7974. (c) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 3. (d) Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985**, *41*, 3569. (e) Gernay, O.; Kumar, N.; Thomas, E. J. *Tetrahedron Lett.* **2001**, *42*, 4969. (f) Romo, D.; Meyer, S. D.; Johnson, D. D.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 9345.
- (2) (a) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H. Pergamon Press: Oxford, 1991; Vol. 2, p 1. (b) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207.
- (3) For some reviews and examples of stereoselective synthesis of homoallylic alcohols, see: (a) Bode, J. W.; Gauthier, D. R.; Carreira, E. M. *Chem. Commun.* **2001**, 2560. (b) Yanagisawa, A.; Nakashima, H.; Ishiba, A.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 4723. (c) Roush, W. R.; Ando, K.; Powers, D. B.; Palkowitz, A. D.; Halterman, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 6339. (d) Faller, J. W.; Sams, D. W. I.; Liu, X. *J. Am. Chem. Soc.* **1996**, *118*, 1217. (e) Yanagisawa, A. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Vol. 2, p 965. (f) Bach, T. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 417. (g) Hoveyda, A. H.; Morken, J. P. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1262.

- (4) (a) Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695. (b) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259. (c) Trost, B. M. *Science* **1991**, *254*, 1471.
- (5) For reviews and examples, see: (a) Li, C. J.; Chan, T. H. *Organic Reactions in Aqueous Media*; John Wiley & Sons: New York, 1997. (b) Li, C. J.; Chan, T. H. *Tetrahedron* **1999**, *55*, 11149. (c) Li, C. J.; Chan, T. H. *Tetrahedron Lett.* **1991**, *32*, 7017. (d) Wang, R. B.; Lim, C. M.; Tan, C. H.; Lim, B. K.; Sim, K. Y.; Loh, T. P. *Tetrahedron: Asymmetry* **1995**, *6*, 1825. (e) Paquette, L. A.; Mittzel, T. M. *Tetrahedron Lett.* **1995**, *36*, 6863.
- (6) (a) Majee, A.; Das, A. R.; Ranu, B. C. *Indian J. Chem., Sect. B* **1998**, *37*, 731. (b) Killinger, T. A.; Boughton, N. A.; Wolinsky, J. J. *Organomet. Chem.* **1977**, *124*, 131. (c) Luche, J. L.; Damiano, J. C. *J. Am. Chem. Soc.* **1980**, *102*, 7926. (d) Sprich, J. D.; Lewandos, G. S. *Inorg. Chim. Acta* **1983**, *76*, L241. (e) Patrier, C.; Luche, J. L. *J. Org. Chem.* **1985**, *50*, 910. (f) Petrier, C.; Einhorn, J.; Luche, J. L. *Tetrahedron Lett.* **1985**, *26*, 1449. (g) Luche, J. L. *J. Organomet. Chem.* **1987**, *322*, 177. (h) Wilson, S. R.; Guazzaroni, M. E. *J. Org. Chem.* **1989**, *54*, 3087. (i) Shono, T.; Ishifune, M.; Kashimura, S. *Chem. Lett.* **1990**, 449. (j) Lu, W. S.; Chan, T. H. *J. Org. Chem.* **2000**, *65*, 917.

Scheme 1



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 molecules containing acidic protons, which leads to an increase in overall synthetic efficiency.⁸

Although this metal-mediated Barbier type allylation reaction has been found to be highly regio- and stereoselective, one severe limitation inherent in this reaction is the difficulty in obtaining the α -adduct when allylic metals are employed. Apart from some exceptions, the metal-mediated allylation of carbonyl compounds with α -substituted allylic halide occurs regioselectively at the γ -position (Scheme 1). Therefore, the direct synthesis of α -adduct using allylic halide, metal, and carbonyl compound in aqueous media has become one of the major synthetic challenges to organic chemists.

In our previous studies, the reaction of aldehydes with different allylic bromides and indium powder in water was investigated.⁹ To our surprise, when the amount of water added was decreased and the reaction time was lengthened, we consistently detected a significant amount of the α -adduct.¹⁰ This interesting result prompted us to study the regioselectivity of the reaction (α -adduct versus γ -adduct). After the successful development and understanding of α -regioselective indium-mediated allylation in water, we extended this reaction to different metals. In this paper, we report a general strategy to obtain α -homoallylic alcohols using three different metals, indium, tin, and zinc, in water. Through detailed mechanism studies described, a mechanism was proposed to account for the formation of this α -adduct.

Results and Experiments

Syntheses of α -Homoallylic Alcohols by Indium Metal. The indium-mediated α -regioselective allylation was first explored and tested with different solvents that were believed to give high yield. Among the various solvents examined, the reactions carried out in DMF, THF, ethanol, and water (2 mL) afforded only the γ -homoallylic alcohols (Table 1, entries 1, 2, 5, and 10). The addition of equal amounts of water to THF or DMF did not improve the regioselectivity. However, water (6 equiv) and water/dichloromethane (6 equiv/6 equiv) distinguished themselves by exhibiting excellent α -selectivity (entries 4 and 8). We also tried to perform the reaction of cyclohexane

Table 1. The Effect of Solvent on the Indium-Mediated Allylation of Cyclohexanecarboxaldehyde with Crotyl Bromide^a

entry	solvent	amount (equiv)	time (h)	yield % ^d (α : γ) ^c
1 ^b	DMF	6	72	65 (0:100)
2	H ₂ O	2 mL	72	90 (0:100)
3 ^b	H ₂ O	6	24	85 (99:1)
4	H ₂ O	6	72	87 (86:14)
5	THF	6	72	20 (0:100)
6	CH ₂ Cl ₂	6	24	— ^e
7	THF/H ₂ O	6:6	72	95 (0:100)
8	CH ₂ Cl ₂ /H ₂ O	6:6	24	68 (>99:1)
9 ^b	DMF/H ₂ O	6:6	72	80 (0:100)
10	CH ₃ CH ₂ OH	6	72	97 (0:100)
11	neat		24	— ^c

^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 room temperature for 12 h, followed by heating to 40 °C. ^c Determined by ¹H NMR. ^d Combined yield. ^e Neither the γ - nor the α -adduct was observed.

carboxyaldehyde with crotyl bromide under solvent-free conditions (entry 11); however, neither the γ - nor the α -adduct was acquired.¹¹

It is important to note that the amount of water added is crucial for the α -selectivity. The highest α -regioselectivity was observed when the amount of water used was 6 equiv. When the reaction was carried out in the presence of 12 equiv of water, no α -adduct was detected even after the reaction was stirred up to 72 h. Furthermore, regioselectivity increased significantly when a higher temperature was applied (entry 3).

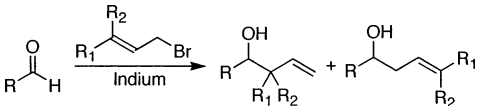
The results were pretty surprising, because α -homoallylic alcohols can be obtained in very high selectivity and yield in this condition. Previously reported results¹² showed that α -adducts could be obtained directly only when very bulky aldehyde and allylic halide were applied in the reaction. The addition of only a small amount of water has completely altered the reaction pathway and given virtually different regioisomers.

With the unveiling of water (6 equiv) as an important criterion for obtaining the α -adduct, we extended the reaction to a variety of substrates, and the results are as shown in Table 2. In all cases, the α -adducts were obtained with high selectivities in moderate to good yields.

It was found that the reaction of benzaldehyde with crotyl bromide gave the α -regio isomer almost exclusively (entry 1). Using 6 equiv of water as the solvent, we obtained a totally different regioisomer 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 suggested that indium-mediated allylation can give the homoallylic alcohol adducts regardless of the substituents. Accordingly, an increase in the steric bulkiness of the aldehyde and bromide gave no significant improvement in the α -regioselectivity. When cinnamyl bromide was used, the α -adducts were obtained with excellent selectivities and good yields (entries 5–8). Even relatively unreactive ethyl 4-bromo crotonate can be used to synthesize the desired α -adduct (entries

- (7) For examples on Barbier-type tin allylation, see: (a) Nokami, J.; Otera, J.; Sudo, T.; Okawara, R. *Organometallics* **1983**, *2*, 191. (b) Nokami, J.; Wakabayashi, S.; Okawara, R. *Chem. Lett.* **1984**, 869. (c) Zhou, J. Y.; Chen, Z. G.; Wu, S. H. *Chem. Commun.* **1994**, 2783.
 (8) (a) Chan, T. H.; Li, C. J. *Chem. Commun.* **1992**, 747. (b) Kim, E.; Gordon, D. M.; Schmid, W.; Whitesides, G. M. *J. Org. Chem.* **1993**, *58*, 5500. (c) Loh, T. P.; Cao, G. Q.; Pei, J. *Tetrahedron Lett.* **1998**, *39*, 1457. (d) Loh, T. P.; Hu, Q. Y.; Vittal, J. J. *Synlett* **2000**, 523. (e) Loh, T. P.; Lye, P. L. *Tetrahedron Lett.* **2001**, *42*, 3511.
 (9) (a) Loh, T. P.; Tan, K. T.; Yang, J. Y.; Xiang, C. L. *Tetrahedron Lett.* **2001**, *42*, 8701. (b) Loh, T. P.; Tan, K. T.; Hu, Q. Y. *Tetrahedron Lett.* **2001**, *42*, 8705.
 (10) For some isolated cases that produce α -adducts from an indium-mediated reaction, see: (a) Araki, S.; Ito, H.; Katsumura, N.; Butsugan, Y. *J. Organomet. Chem.* **1989**, *369*, 291. (b) Araki, S.; Katsumura, N.; Butsugan, Y. *J. Organomet. Chem.* **1991**, *415*, 7.

- (11) For an indium-mediated reaction under neat condition, see: Yi, X. H.; Heberman, J. X.; Li, C. J. *Synth. Commun.* **1998**, *28*, 2999.
 (12) Isaac, M. B.; Chan, T. H. *Tetrahedron Lett.* **1995**, *36*, 8957.

Table 2. Indium-Mediated Allylation of Aldehydes with Different Bromides^a


entry	R	R ₁	R ₂	time (h)	yield % ^c (α:γ) ^b (E:Z) ^b
1	Ph	Me	H	36	60 (99:1)(55/45)
2	<i>c</i> -C ₆ H ₁₁	Me	H	24	85 (99:1)(70/30)
3	<i>n</i> -C ₅ H ₁₁	Me	H	36	75 (98:2)(65/35)
4	PhCH ₂ CH ₂	Me	H	18	67 (97:3)(55/45)
5	Ph	Ph	H	72	66 (98:2)(E)
6	<i>c</i> -C ₆ H ₁₁	Ph	H	72	73 (96:4)(98/2)
7	<i>n</i> -C ₅ H ₁₁	Ph	H	85	71 (99:1)(90/10)
8	PhCH ₂ CH ₂	Ph	H	160	50 (99:1)(95/5)
9 ^e	<i>c</i> -C ₆ H ₁₁	CO ₂ Et	H	96	80 (80:20)(80/20) ^f
10 ^{d,e}	Me	CO ₂ Et	H	192	56 (85:15)(90/10) ^f
11 ^e	<i>c</i> -C ₆ H ₆	Me	Me	15	30 (95:5)

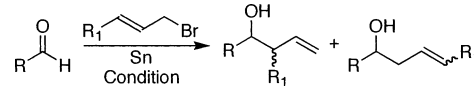
^a All reactions were performed with aldehyde (1 mmol), bromide (1.2 mmol), and indium (1.5 mmol) with water (0.108 mL) at room temperature for 12 h, followed by heating to 40 °C, unless otherwise noted. ^b Determined by ¹H and ¹³C NMR. ^c Total yield. ^d Because of the highly volatility of the aldehyde, an excess of acetyl aldehyde was added. ^e Two equivalents of water was used. ^f Z isomer was isolated as lactone.

9 and 10). However, the reaction of aldehyde with prenyl bromide only afforded a moderately low yield (entry 11).¹³ In short, this type of reaction can be applied generally irrespective of the allylic bromides and aldehydes used.

To study the scope and limitations of the reaction, two other metals, zinc and tin, which are known to work well in water, were used to test the feasibility of the conditions. We used the same condition as that used for indium to carry out the reaction. With little surprise, zinc and tin also gave us similar results. However, some modifications to the conditions were necessary to give higher selectivity and yield.

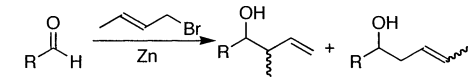
Tin- and Zinc-Mediated α-Regioselective Allylation. For tin-mediated allylation, aliphatic aldehydes such as hexanal, cyclohexanecarboxaldehyde, and trimethylacetaldehyde provided much higher α-regioselectivities in moderate to good yields (Table 3, entries 2, 4, and 5, respectively). Generally, an increase in the steric bulkiness of the aldehyde from hexanal to trimethylacetaldehyde resulted in significant improvements of the α-regioselectivity. These results suggested that tin-mediated allylation could also give α-homoallylic alcohol adducts regardless of the substituents on the aldehyde. Strikingly, when crotyl bromide was replaced by cinnamyl bromide, no organic co-solvent was required to run the reaction (entries 6–8).¹⁴ The reaction could also be performed in aqueous media (1 mL). For the case of cinnamyl bromide, the reaction did not exhibit any significant selectivity due to steric bulkiness.

Our investigations using zinc revealed that allylic zinc is much less reactive in aqueous media.¹⁵ For all of the aldehydes used, none reached completion, which accounted for the moderate yields obtained. In the zinc system, however, it was found that

Table 3. Tin-Mediated Crotylation of Aldehydes


entry	R	R ₁	condition ^{a,b}	yield (%) ^d	γ(syn:anti):α(E:Z) ^e
1	Ph	Me	A	83	45(50:50):55(75:25)
2	<i>n</i> -C ₅ H ₁₁	Me	A	81	20(61:39):80(55:45)
3	PhCH ₂ CH ₂	Me	A	82	29(37:63):71(53:47)
4	<i>c</i> -C ₆ H ₁₁	Me	A	78	5(23:77):95(67:33)
5	<i>t</i> -Bu	Me	A	42	1(–:–):99(83:17)
6	<i>n</i> -C ₅ H ₁₁	Ph	B	60	5(–:–):95(100:0)
7	<i>c</i> -C ₆ H ₁₁	Ph	B	54	1(–:–):99(100:0)
8 ^e	Ph	Ph	B	80	1(–:–):99(100:0)

^a Condition A: The reactions were performed with aldehyde (1 mmol), crotyl bromide (1.2 mmol), and tin (1.5 mmol) in water (0.108 mL) and CH₂Cl₂ (0.385 mL) at room temperature for 48 h unless otherwise noted. ^b Condition B: The reactions were performed with aldehyde (1 mmol), cinnamyl bromide (1.2 mmol), and tin (1.5 mmol) in water (1 mL) at room temperature for 24 h unless otherwise noted. ^c Determined by ¹H NMR and ¹³C NMR. ^d Combined yield. ^e The reaction was stirred for 3 days with 3 mmol of cinnamyl bromide.

Table 4. Zinc-Mediated Crotylation of Aldehydes^a


entry	R	yield (%) ^c	γ(syn:anti):α(E:Z) ^b
1	<i>t</i> -Bu	34	55(10:90):45(62:38)
2	<i>n</i> -C ₅ H ₁₁	55	10(88:12):90(54:46)
3	<i>c</i> -C ₆ H ₁₁	66	5(32:68):95(73:27)
4	PhCH ₂ CH ₂	58	6(35:65):94(60:40)
5	Ph	50	3(50:50):97(77:23)

^a All reactions were performed with aldehyde (1 mmol), bromide (1.2 mmol), and zinc (1.5 mmol) in water (0.036 mL) and CH₂Cl₂ (0.128 mL) at room temperature for 120 h. ^b Determined by ¹H NMR and ¹³C NMR. ^c Combined yield.

excellent α-regioselectivities were observed when a mixture of water (2 equiv) and dichloromethane (2 equiv) was used as the solvent. The results were summarized in Table 4.

Such interesting results displayed by the indium-, tin-, and zinc-mediated allylation reactions prompted us to investigate the mechanism in greater detail. To the best of our knowledge, all of the reported procedures for highly α-regioselective metal-mediated allylation reactions in water or an organic solvent are usually coupled with additives, such as Lewis acids. Reported examples include the addition of a stoichiometric amount of AlCl₃ to a Grignard reaction¹⁶ and the reaction of crotyl tributylstannanes with aldehydes in the presence of a Lewis acid.¹⁷ Furthermore, highly α-selective allylation can also be achieved by the reaction with aldehydes of allylic barium,¹⁸ allylic cerium reagents,¹⁹ and Me₃SiCl/NaI/H₂O.²⁰ There are also a few special cases where the magnesium and indium-mediated allylation reaction produces α-adducts. However, these isolated cases provided insufficient data, and further investigation was called for.

- (13) A small amount of THF (0.3 equiv) must be added to suppress the formation of side product to afford 78% yield with an α to γ ratio of 70/30. This is because the corresponding α-adduct undergoes an oxonium-ene cyclization with aldehyde immediately once the α-adduct was synthesized. For reference, see: Loh, T. P.; Hu, Q. Y.; Tan, K. T.; Cheng, H. S. *Org. Lett.* **2001**, 3, 2669.
- (14) We also tried to add 6 equiv of water to the reaction; yet, a lower yield was obtained. For example, reaction of hexanal aldehyde with cinnamyl bromide in 6 equiv of water for 24 h afforded only 22% yield with no change in regioselectivity.
- (15) The zinc powder was used directly from the bottle purchased from Merck.

- (16) Yamamoto, Y.; Maruyama, K. *J. Org. Chem.* **1983**, 48, 307.
- (17) (a) Keck, G. E.; Abbott, D. E.; Boden, E. P.; Enholm, E. J. *Tetrahedron Lett.* **1984**, 25, 3927. (b) Yamamoto, Y.; Maeda, N.; Maruyama, K. *Chem. Commun.* **1983**, 48, 1564. (c) Gambaro, A.; Gains, P.; Marton, D.; Peruzzo, V.; Tagliavini, G. *J. Organomet. Chem.* **1982**, 231, 307.
- (18) (a) Yanagisawa, A.; Habaue, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, 113, 8955. (b) Yanagisawa, A.; Habaue, S.; Yasue, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, 116, 6130.
- (19) (a) Guo, B. S.; Doubleday, W.; Cohen, T. *J. Am. Chem. Soc.* **1984**, 106, 4710. (b) Cohen, T.; Matz, J. R. *J. Am. Chem. Soc.* **1980**, 102, 6900.
- (20) Kanagawa, K.; Nishiyama, Y.; Ishii, Y. *J. Org. Chem.* **1992**, 57, 6988.

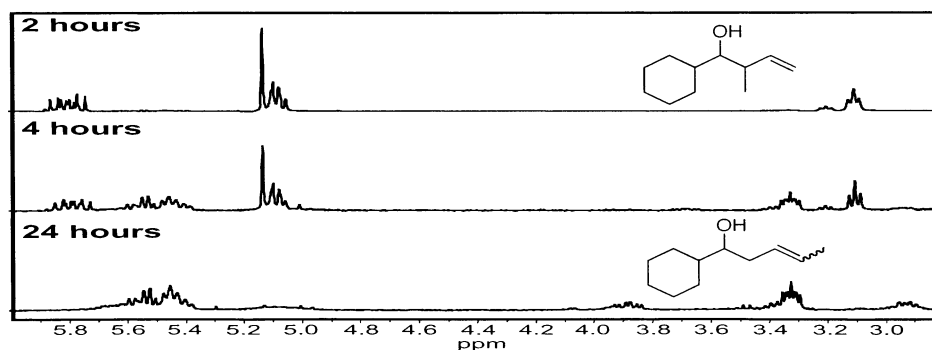
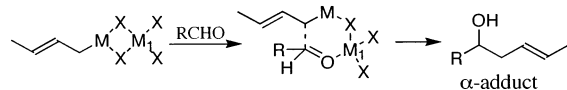
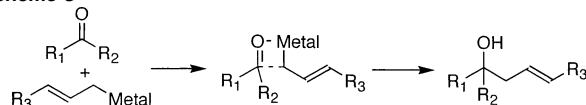


Figure 1. ^1H NMR study for indium-mediated allylation.

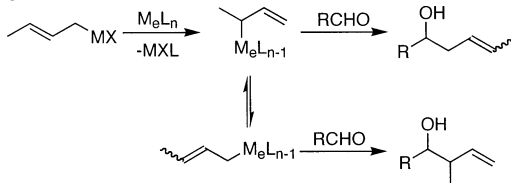
Scheme 2



Scheme 3



Scheme 4



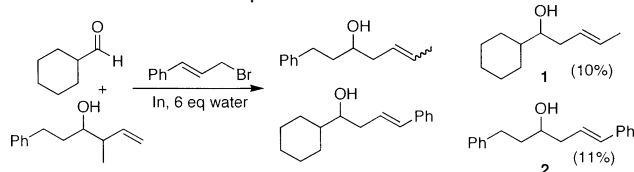
Mechanism Study of Metal-Mediated α -Regioselective Allylations. Three mechanisms have been proposed to account for the high α -selectivities observed for the known systems. They can generally be grouped into three categories: (i) The external activator or Lewis acid is involved in the formation of a six-membered transition state to afford the α -adduct directly as shown in Scheme 2; (ii) direct attack of the allylic metal on the α -position via a four-membered transition state (Scheme 3);^{21,22} and (iii) transmetalation of the allylic metal species with its external activator or Lewis acid to generate a new allylic species which undergoes a γ -attack to afford the α -adduct (Scheme 4).

^1H NMR Study for Indium- and Tin-Mediated Allylation.

To understand the origin of these linear homoallylic alcohol adducts, the progress of the indium-mediated allylation of cyclohexanecarboxaldehyde with crotyl bromide was monitored by ^1H NMR after workup at various intervals. The spectra were taken at 2, 4, and 24 h, respectively (Figure 1).

It was observed that the reaction proceeded very rapidly to afford the kinetically favored γ -homoallylic alcohol, which slowly converted to the thermodynamic α -homoallylic alcohol (24 h).²³ By the second hour, the γ -homoallylic alcohol adduct was obtained as the sole product with no sign of any α -isomer.

Scheme 5. Crossover Experiment



By the fourth hour, the α -adduct started to appear, as can be seen in the ^1H NMR spectrum, the peaks around δ 5.5 and 3.3 ppm being assigned as the internal double bond and the α -hydroxyl protons of the α -adduct. If the reaction was stirred further, after 24 h, all of the γ -adducts were arranged to the thermodynamically more stable α -adduct with complete consumption of the aldehyde, as indicated by the disappearance of the peaks at δ 5.8, 5.1, and 3.1 ppm.

A similar ^1H NMR study (Figure 2) was carried out as well with benzaldehyde and crotyl bromide using tin and zinc as the metals. The ^1H NMR spectra for tin-mediated allylation worked up at 2, 4, 8, 24, and 48 h, respectively, were shown. It was found that the reaction proceeded smoothly to give the kinetically favored γ -homoallylic alcohol initially, which slowly converted to the thermodynamic α -adduct. Similar observations were obtained with the zinc system. These results of the NMR studies suggested that the mechanisms for indium-, tin-, and zinc-mediated allylation reactions are likely to be similar, if not the same.

Crossover Experiment. A crossover experiment was conducted using indium (Scheme 5). After the reaction, column chromatography revealed the crossover products **1** and **2** in 10 and 11% yields, respectively. This proved that the rearrangement of this γ -adduct to its isomer α -adduct is an intermolecular process that may involve the cleavage of the γ -adduct to form the aldehyde substituent and an allyl fragment.

Stereochemical Investigation of the Reaction. In addition to the NMR studies and crossover experiment, the indium, tin, and zinc systems were tested using a steroidal aldehyde to investigate the stereochemistry of the reaction (Table 5). The initial attempt made using indium-mediated allylation of the steroidal aldehyde **3** with cinnamyl bromide afforded the 22 β γ -homoallylic alcohol **4** which rearranged to the 22 α α -homoallylic alcohol **5** with complete inversion of stereochemistry (the

(21) With hindered ketones such as di-*tert*-butyl ketone or di-*iso*-propyl ketone, the α -adducts might be formed from fission of the C–C bond or directly from the ketone and the crotyl Grignard via a four-center transition state, see: Benkeser, R. A.; Siklosi, M. P.; Mozden, E. C. *J. Am. Chem. Soc.* **1978**, *100*, 2134.

(22) Besides obvious steric effects, regioselectivity in the carbanionic addition is also governed by the relative electron densities and negative charge at the α - and γ -position in the highest occupied molecular orbital (HOMO) of the ambient allylic anion, see: Gompper, R.; Wagner, H. U. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 321.

(23) Process which converts readily available kinetic products to their less readily accessible thermodynamic isomers, see: (a) Barbot, F.; Miginiac, P. *Tetrahedron Lett.* **1975**, 3829. (b) Gedye, R. N.; Arora, P.; Khalil, A. H. *Can. J. Chem.* **1975**, *53*, 1943. (c) Tatsuta, K.; Tamura, T.; Mase, T. *Tetrahedron Lett.* **1999**, *40*, 1925. For an example of a γ -adduct rearranging to its α -adduct, see: (d) Hong, B. C.; Hong, J. H.; Tsai, Y. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 468.

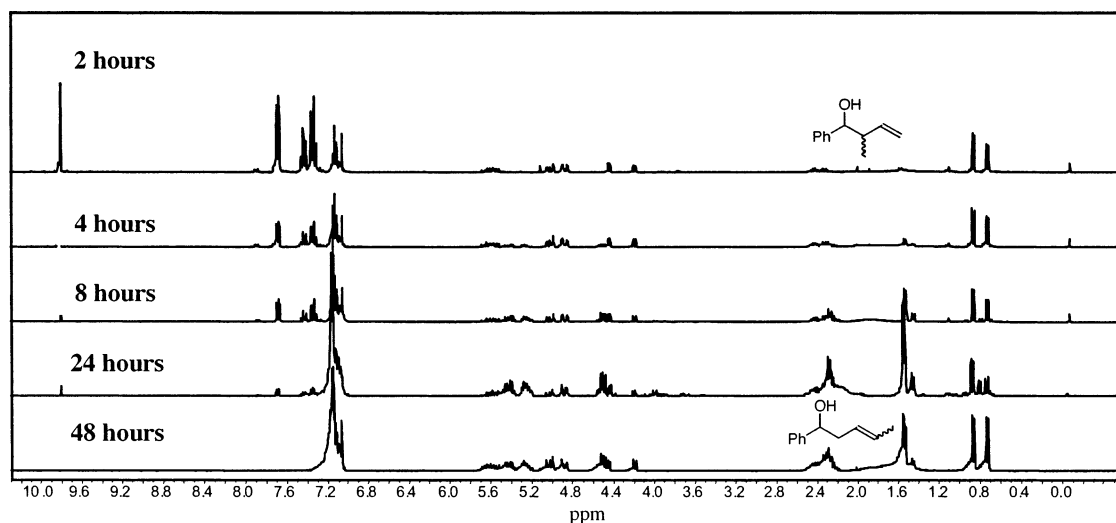


Figure 2. ^1H NMR study for tin crotylation of benzaldehyde.

Table 5. Stereochemical Study of Metal-Mediated α -Regioselectivity Allylation

entry	metal	R	time (h)	yield ^a (%)	SM recovered (%)	4(syn:anti):5(E:Z)
1	In	Ph	48	54	30	1 (-:-):99 (99:1)
2 ^a	Sn	Me	96	50	5	52(9:91):48(99:1)
3 ^a	Zn	Me	120	40	20	78(35:65):22(99:1)

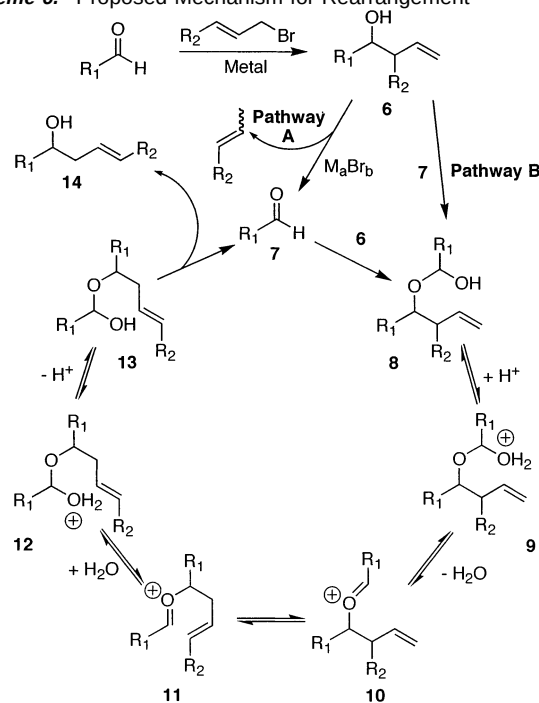
^a Convergent yield.

relative stereochemistry was determined by single-crystal X-ray diffraction analysis).²⁴ In other words, the allyl fragment re-attaches to the steroid in an *anti*-Cram manner, which excludes the possibility of allyl anion re-addition to the aldehyde.

Unexpectedly, for the tin-mediated reaction, no α -allylation adduct was observed in the reaction mixture even after 96 h. A ^1H NMR study of the tin-steroidal system revealed that the steroidal aldehyde was totally depleted after just 24 h. We believed that the absence of the aldehyde might be the key to the negative result. Indeed, using just a slight excess (0.1 mmol) of steroidal aldehyde in the reaction, we successfully obtained the desired α -homoallylic alcohol along with the γ -adducts. Furthermore, the α -homoallylic alcohol was found with complete inversion of stereochemistry at C22 with respect to the γ -products. Such *anti*-Cram allylation α -adducts could not possibly be obtained if these adducts were formed via the direct attack of the allylic species on the aldehyde. The reaction of steroidal aldehyde with crotyl bromide in the presence of zinc metal also gave the desired α -homoallylic alcohol in a mixture of products. Similarly, complete inversion of configuration at C22 was observed.

Proposed Mechanism for Metal-Mediated Allylation. In view of the similarity between the indium-, tin-, and zinc-mediated allylation reactions, the mechanisms for the formation of the α -homoallylic alcohols are believed to be the same. On the basis of the results of the ^1H NMR and stereochemical

Scheme 6. Proposed Mechanism for Rearrangement



studies, a new mechanism (Scheme 6) was proposed for this metal-mediated allylation reaction in aqueous media. In opposition to previously proposed mechanisms, our investigations suggested that the reaction took place in two stages. The first stage involves the metal-mediated allylation of the aldehyde to form the γ -adduct **6**. This initially formed the γ -adduct, which then underwent a retroene reaction,²⁵ followed by a 2-oxonia [3,3]-sigmatropic rearrangement in the presence of the aldehyde **7** to give the α -adduct **14** in the second stage.²⁶ The steps in the second stage are likely to be facilitated by the presence of residual metal salts generated from the first stage of the reaction. In addition, the aldehyde required in the second stage could either be unreacted aldehyde in the reaction²⁷ (pathway B) or

(25) For a recent review, see: Ripoll, J. L.; Vallée, Y. *Synthesis* **1993**, 659.

(26) An alternative mechanism for the formation of α -adduct via an intramolecular [1,3]-sigmatropic rearrangement, contradicting the results from the crossover experiment, which points towards an intermolecular rearrangement. For reference, see: Wilson, S. T. *Org. React.* **1993**, 43, 93.

(24) The single-crystal X-ray diffraction analysis data have been published, see: ref 10b and Loh, T. P.; Hu, Q. Y.; Ma, L. T. *Org. Lett.* **2002**, 4, 2389.

be aldehyde regenerated in situ from metal salt-catalyzed bond cleavage of the γ -adduct (pathway A).²⁸

The proposed mechanism clearly illustrates the role of water in the reaction. Besides being a good solvent for the metal-mediated allylation of the aldehyde in the first stage, 6 equiv of water is necessary in the second stage of the reaction for the optimal formation of the crucial oxonium intermediate **10** and the subsequent quenching of the rearranged intermediate **11**. The use of 12 equiv of water is believed to completely suppress the formation of oxonium intermediate **10**, causing the reaction to truncate in the first stage and resulting only in the γ -adduct.

Because of the great importance of water in the second stage, reactions carried out in other solvents did not give any desired α -adducts (see Table 1, entries 1, 5, 6, and 10). In addition, the use of water as a cosolvent with DMF and THF (entries 7 and 9) did not reverse the selectivity as it did with dichloromethane (entry 8). It is thus believed that the DMF or THF actually complexes strongly with indium salts essentially for the formation of intermediates **8–13**, which then led again to the truncation of the reaction in the first stage. The absence of the second stage in the presence of DMF and THF is further supported by experimental findings from the addition of InBr_3 ²⁹ to the γ -adduct under similar conditions.³⁰

- (27) (a) Nokami, J.; Yoshizane, K.; Matsuura, H.; Sumida, S. *J. Am. Chem. Soc.* **1998**, *120*, 6609. (b) Nokami, J.; Anthony, L.; Sumida, S. *Chem.-Eur. J.* **2000**, *6*, 2909. (c) Nokami, J.; Ohga, M.; Nakamoto, H.; Matsubara, T.; Hussain, I.; Kataoka, K. *J. Am. Chem. Soc.* **2001**, *123*, 9168. (d) Loh, T. P.; Hu, Q. Y.; Chok, Y. K.; Tan, K. T. *Tetrahedron Lett.* **2001**, *42*, 9277. (e) Loh, T. P.; Lee, C. L. K.; Tan, K. T. *Org. Lett.* **2002**, *4*, 2985. (28) Loh, T. P.; Tan, K. T.; Hu, Q. Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 2921. (29) We found that In(I)Br can catalyze the rearrangement of γ -adducts to their corresponding α -adducts too.

Conclusion

In conclusion, a general α -regioselective metal-mediated allylation reaction has been developed. We have demonstrated that indium, tin, and zinc can be used to carry out this reaction, giving moderate to good yields and selectivities. The mechanism proposed is supported by the experimental results from ^1H NMR, crossover experiment, stereochemical studies using steroidal aldehyde, and rearrangement investigations involving indium metal salts. These studies have led to a new mechanistic proposal for the origin of the high α -selectivity. This study showed that the origin of the α -homoallylic alcohols from many of the reported metal-mediated allylation reactions with or without activators warrants further studies to clarify their mechanisms.

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Supporting Information Available: Complete experimental details, including characterization of all new compounds (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (30) We tried to effect the rearrangement of the γ -adduct (formed from cyclohexane carboxyaldehyde and crotyl bromide) to its α -adduct by adding 0.5 equiv of InBr_3 to the γ -adduct in various solvents, including 6 equiv of water, DMF, and THF. Results revealed that after 72 h at room temperature, only the mixture in 6 equiv of water showed signs of rearrangement (γ : $\alpha \approx 78$:22), while those in DMF and THF showed no progress. In fact, when 12 equiv of water was used, no rearrangement was observed as well.