Pergamon

Tetrahedron Letters 42 (2001) 8705–8708

TETRAHEDRON LETTERS

A new mechanistic proposal for the origin of α-homoallylic alcohols in indium-mediated allylation reactions in water

Teck-Peng Loh,* Kui-Thong Tan and Qi-Ying Hu

Department of Chemistry, National University of Singapore, 3 Science Drive 3, Singapore 117543

Received 28 August 2001; revised 21 September 2001; accepted 5 October 2001

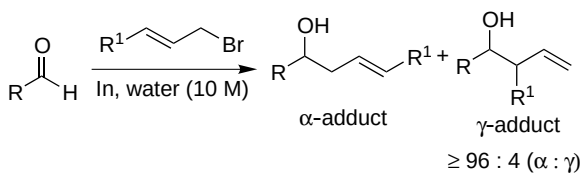
Abstract—A new mechanism is proposed for the α-regioselective indium-mediated allylation reaction in water. Based on the results and observations obtained from an NMR study, a cross-over experiment and the complete inversion of the stereochemistry of 22β γ-adduct homoallylic sterols to the 22α α-adduct homoallylic sterols, it is suggested that the initially formed γ-adduct undergoes a bond cleavage to generate the parent aldehyde in situ followed by a concerted rearrangement, perhaps a retro-ene reaction followed by a 2-oxonia [3,3]-sigmatropic rearrangement to furnish the α-adduct. © 2001 Elsevier Science Ltd. All rights reserved.

In the previous paper, we have successfully demonstrated that the indium-mediated allylation reaction of aldehydes proceeds smoothly with crotyl and cinnamyl bromides in water (10 M) to give almost exclusively the α-homoallylic alcohol adducts in moderate to good yields (Scheme 1). As far as we know, this is in fact the first general procedure by which linear homoallylic alcohols can be obtained with high α-regioselectivity in an aqueous media.[1] The high α-regioselectivity of this abnormal Barbier-type, indium-mediated, allylation has prompted us to investigate the mechanism further.

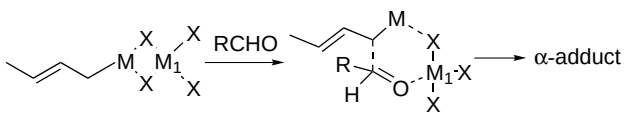
To the best of our knowledge, the development of a general procedure for highly α-regioselective metal-mediated allylation reactions in water has never been reported. Nevertheless, there are a few metal-mediated allylation methods that have been reported to achieve high α-regioselectivities in an organic solvent. Reported examples include the addition of a stoichiometric amount of $AlCl_3$ to a Grignard reaction[2] and the reaction of crotyl tributylstannanes with aldehydes in the presence of a Lewis acid.[3] Furthermore, highly α-selective allylation can also be achieved by the reaction with aldehydes of allylic barium,[4] and allylic cerium[5] reagents and $Me_3SiCl/NaI/H_2O$.[6] There are also a few special cases where the indium-mediated allylation reaction produces α-adducts.[7] However, these isolated cases provide insufficient data and further investigation is called for.

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 6-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).[8] (iii) Transmetallation of the allylic metal species with the external activator or Lewis acid to generate a new allylic species which undergoes γ-attack to afford the α-adduct (Scheme 4).

In our initial study of this α-regioselective indium-mediated allylation, low regioselectivities were obtained if stirring of the reaction mixture was not prolonged. The best selectivity was obtained, when the reaction was



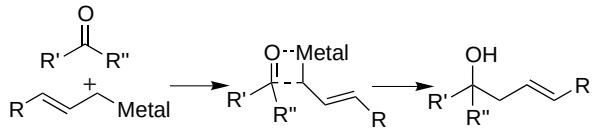
Scheme 1.



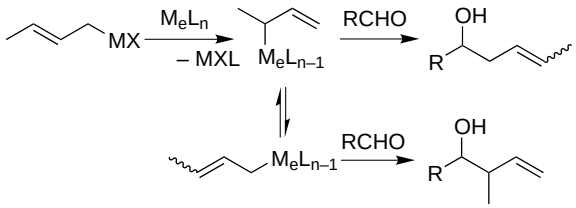
Scheme 2.

* Corresponding author. Tel.: +65-874-1781; fax: +65-779-1691; e-mail: chmlohtp@nus.edu.sg

PII: S0040-4039(01)01884-6



Scheme 3.



Scheme 4.

stirred for up to 72 h for cyclohexane carboxaldehyde with crotyl bromide.

In order to understand the origin of these linear homoallylic alcohol adducts, the progress of the reaction of cyclohexane carboxaldehyde with crotyl bromide was monitored by ^{1}H NMR after work-up at various intervals. The spectra were taken at 2, 4 and 24 h, respectively (Fig. 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).[9] After 2 h, the γ-homoallylic alcohol adduct was obtained as the sole product with no sign of any α-isomer. By the fourth hour, the α-adduct started to appear, as can be seen in the ^{1}H 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 the γ-adducts were rearranged 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.

Furthermore, a cross-over experiment was conducted (Scheme 5). After the reaction, column chromatography provided the cross-over products **1** and **2** in 10 and 11% yields, respectively. This proved that the rearrangement of this γ-adduct to its isomeric α-adduct may involve the cleavage of the γ-adduct to the aldehyde substituent and an allyl fragment.

With the establishment of the reaction conditions for obtaining the α-adduct, the application to the construction of a steroidal side chain was effected. Especially noteworthy is that the indium-mediated allylation of the steroidal aldehyde **3** with cinnamyl bromide afforded the 22β γ-homoallylic alcohols which rearrange to the 22α α-products with complete inversion of stereochemistry. (The relative stereochemistry was

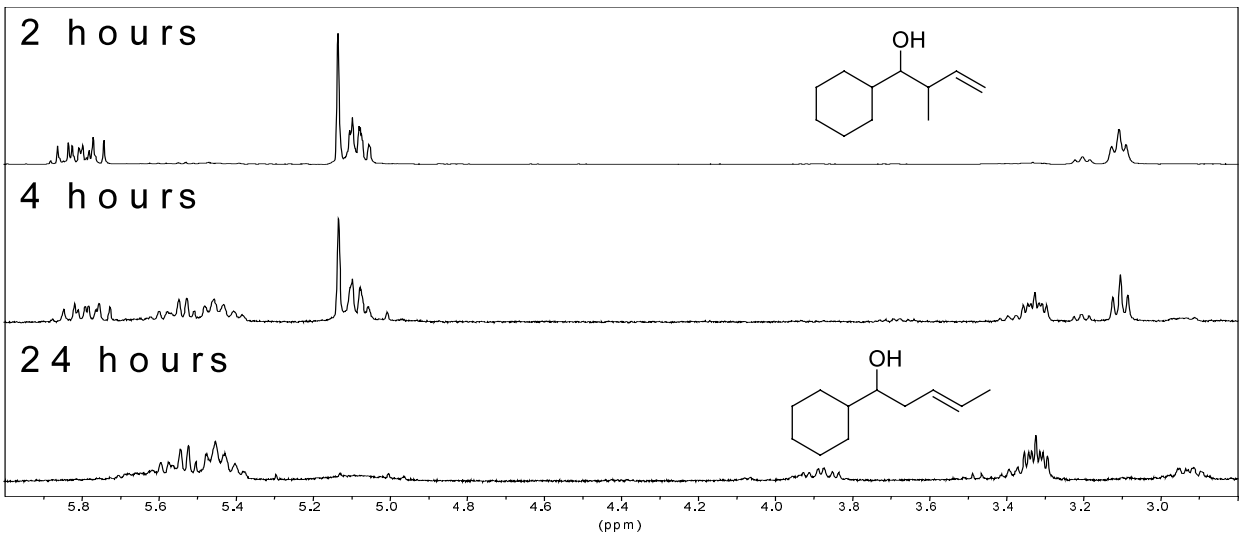
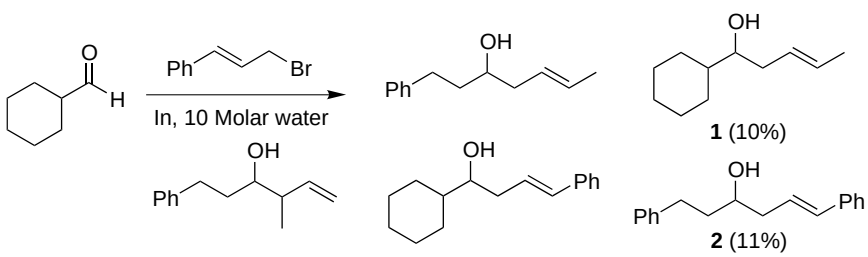
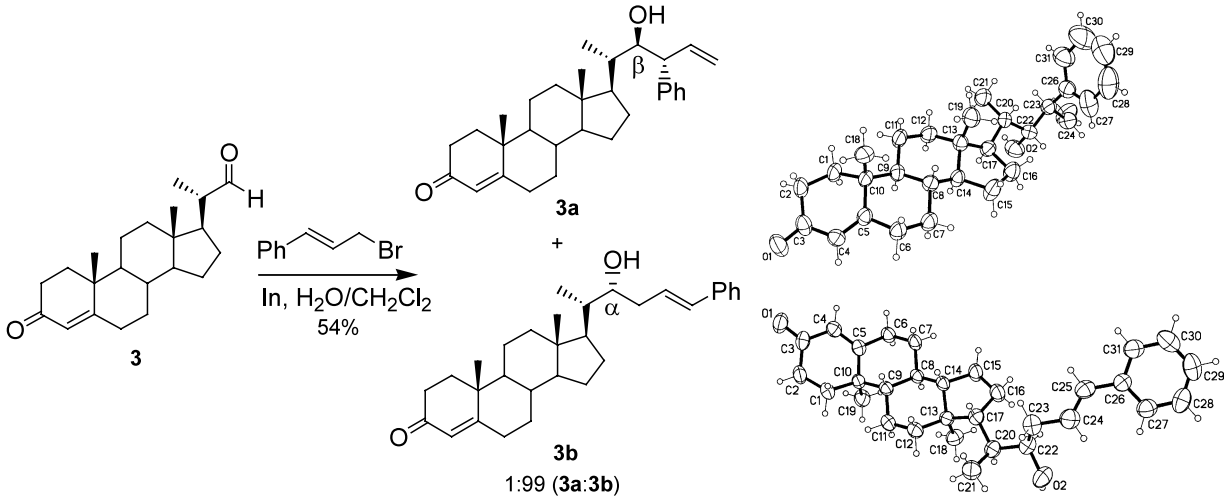


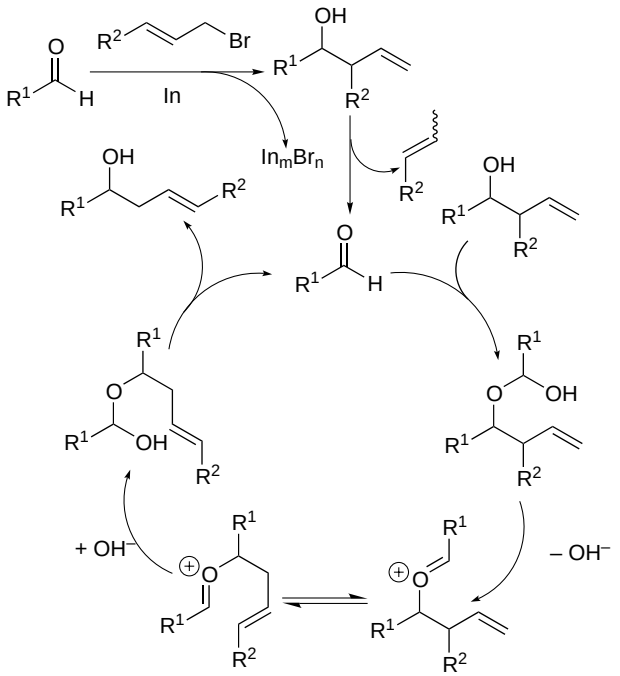
Figure 1. NMR xtudy of indium-mediated allylation.



Scheme 5. Cross-over experiment.



Scheme 6. Inversion of the steroid stereochemistry.



Scheme 7. Proposed mechanism for rearrangement.

determined by single crystal X-ray diffraction analysis,[10,11] Scheme 6.) In other words, the allyl fragment reattaches to the steroid in an *anti*-Cram manner, which excludes the possibility of allyl anion re-addition to the aldehyde.

Based on the results and observations presented above, a new mechanism (Scheme 7) was proposed for this indium-mediated allylation reaction in water (10 M). As opposed to the allyl anion transfer mechanism[2,3] or steric effect[7c,8] previously proposed to account for the formation of the α homoallylic alcohol adduct, our study suggested that the initially formed γ-adduct underwent a bond cleavage to generate the parent aldehyde in situ and subsequently proceeded via a concerted rearrangement, perhaps by a retro-ene[12] followed by a 2-oxonia [3,3]-sigmatropic rearrangement.[13]

This indicates the possibility of the concurrent involvement of both mechanisms for the generation of thermodynamic α-adducts in various allylation reactions. It should be noted that the indium complexes (In_mX_n)[14,15] generated after the C–C bond formation function as Lewis acids to catalyze this conversion.

In conclusion, a general and new method for obtaining α-adducts in indium-mediated allylation has been developed. Detailed mechanistic studies have led to a new mechanistic proposal for the origin of this exceptionally high α-selectivity. Mechanistic understanding of the process leads to predictable stereochemistry for the α-adduct and the possible design of α-selectivity in other allyl transfer reactions.[16]

Furthermore, 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.

Acknowledgements

We thank the National University of Singapore for generous financial support. We also thank Dr. Jagadese J. Vittal and Ms. Tan Geok Kheng for determining the crystal structures of **3a** and **3b**.

References

1. There are reported examples using aqueous and organic co-solvent to carry out α-selective allylation, see: Ito, A.; Kishida, M.; Kurusu, Y.; Masuyama, Y. *J. Org. Chem.* **2000**, *65*, 494.
2. Yamamoto, Y.; Maruyama, K. *J. Org. Chem.* **1983**, *231*, 307.

3. (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.
4. (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.
5. (a) Guo, B. S.; Doubleday, W.; Cohen, T. *J. Am. Chem. Soc*. **1984**, *109*, 4710; (b) Cohen, T.; Matz, J. R. *J. Am. Chem. Soc*. **1980**, *102*, 6900.
6. Kanagawa, K.; Nishiyama, Y.; Ishii, Y. *J. Org. Chem*. **1992**, *57*, 6988.
7. (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; (c) Isaac, M. B.; Chan, T. H. *Tetrahedron Lett*. **1995**, *36*, 8957.
8. 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.; Mozdzen, E. C. *J. Am. Chem. Soc*. **1978**, *100*, 2134.
9. For an example of a γ-adduct rearranging to its α-adduct, see: Hong, B. C.; Hong, J. H.; Tsai, Y. C. *Angew. Chem., Int. Ed. Engl*. **1998**, *37*, 468.
10. (a) Loh, T.-P.; Hu, Q.-Y.; Vittal, J. J. *Synlett* **2000**, 523; (b) X-ray data for **3a**: $f_w = 463.15$; monoclinic, space group $C2$; $a = 30.578(3)$, $b = 8.2267(8)$, $c = 11.5660(12)$ Å; $V = 2909.0(5)$ Å^3; $Z = 4$; $R_1 = 0.0946$; $wR_2 = 0.2373$; GOF = 1.026 for 4991 observations with $I > 2\sigma(I)$.
11. X-ray data for **3b**: $f_w = 446.65$; orthorhombic, space group $P2_12_12_1$; $a = 10.4991(7)$, $b = 11.7800(8)$, $c = 20.6984(14)$ Å; $V = 2560.0(3)$ Å^3; $Z = 4$; $R_1 = 0.0540$; $wR_2 = 0.0775$; GOF = 1.022 for 7473 observations with $I > 2\sigma(I)$.
12. For a recent review, see: Ripoll, J. L.; Vallée, Y. *Synthesis* **1993**, 659.
13. The rearrangement of γ-homoallylic alcohols to their α-adducts using an external carbonyl compound has been demonstrated elegantly by Nokami, see: (a) Nokami, J.; Yoshizane, K.; Matsuura, H.; Sumida, S. I. *J. Am. Chem. Soc*. **1998**, *120*, 6609; (b) Sumida, S. I.; Ohga, M.; Mitani, J.; Nokami, J. *J. Am. Chem. Soc*. **2000**, *122*, 1310; (c) For rearrangement of γ-homoallylic alcohols to their α-adducts without the additive of an external carbonyl compound refer to: Loh, T. P.; Tan, K.-T.; Hu., Q.-Y. *Angew. Chem., Int. Ed. Engl*. **2001**, *40*, 2921.
14. For recent reviews of indium(III) complexes, see: (a) Chauhan, K. K.; Frost, C. G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3015; (b) Babu, G.; Perumal, P. T. *Aldrichim. Acta* **2000**, *33*, 16. For examples, see: (c) Li, X.-R.; Loh, T.-P. *Tetrahedron: Asymmetry* **1996**, *7*, 1535; (d) Loh, T. P.; Li, X. R. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 980; (e) Loh, T. P.; Wei, L. L. *Tetrahedron Lett*. **1998**, *39*, 323; (f) Loh, T. P.; Chua, G. L.; Vittal, J. J.; Wong, M. W. *Chem. Commun*. **1998**, 861; (g) Loh, T. P.; Huang, J. M.; Goh, S. H.; Vittal, J. J. *Org. Lett*. **2000**, *2*, 1291; (h) Loh, T.-P.; Hu, Q.-Y.; Ma, L.-T. *J. Am. Chem. Soc*. **2001**, *123*, 2450; (i) Loh, T.-P.; Hu, Q.-Y.; Tan, K.-T.; Cheng, H.-S. *Org. Lett*. **2001**, *3*, 2669; (j) Yang, J.; Li, C.-J. *Synlett* **1999**, 717.
15. We found that both $InBr_3$ and InBr can also catalyze the rearrangement of γ-adducts to their α-adducts in water:
16. Samoshin, V. V.; Smoliakova, I. P.; Hank, M. M.; Gross, P. H. *Mendeleev Commun*. **1999**, *6*, 219.