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The First Example of Enantioselective Allyl Transfer from a Linear Homoallylic Alcohol to an Aldehyde

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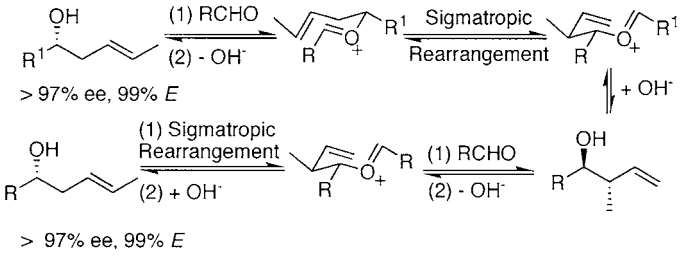
ABSTRACT

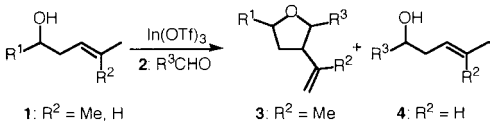


The first example of enantioselective linear homoallylic alcohol transfer reaction was revealed. In all cases, the whole rearrangement is thermodynamically favorable and a steric effect is the driving force of this reaction. The preservation of the stereocenter and olefin geometry together with the isolation of γ-adduct homoallylic alcohols in one isomeric form have warranted the proposed mechanism.

In the past few years, indium complexes have found widespread application in organic syntheses including their application for the catalysis of various C−C bond formation reactions in aqueous media.[1] Besides our interest in indium chemistry,[2] our group has also exploited the special characteristics of indium complexes to catalyze a wide variety of organic transformations.[3]

In a recent paper, we reported a novel $In(OTf)_3$-catalyzed (3,5)-oxonium-ene-type cyclization for the facile construction of various multisubstituted tetrahydrofurans and tetrahydropyrans.[4] It was noted that a disubstituted double bond of a homoallylic alcohol is essential for this oxonium-ene-type cyclization. During the course of our studies on the scope and limitations of this oxonium-ene reaction, we carried out the reaction of homoallylic alcohol **1** with a different aldehyde in the presence of a catalytic amount of indium triflate. To our surprise, homoallylic alcohol **1** (R^2 = H) gave not the desired tetrahydrofuran product **3** but instead another α-adduct linear homoallylic alcohol **4** (Scheme 1). Herein, we report an unprecedented pathway leading to this α-adduct linear homoallylic alcohol.

Scheme 1



The treatment of various linear homoallylic alcohols[5] and 3-phenylpropanal **2a** (2.5:1) with 10 mol % $In(OTf)_3$ in CH_2Cl_2 at room temperature was initially examined to test

(1) (a) Li, C. J.; Chan, T. H. *Tetrahedron* **1999**, *55*, 11149. (b) Li, C. J.; Chan, T. H. *Organic Reactions in Aqueous Media*; Wiley & Sons: New York, 1997.

(2) (a) Wang, R. B.; Lim, C. M.; Tan, C. H.; Lim, B. K.; Sim, K. Y.; Loh, T. P. *Tetrahedron: Asymmetry* **1995**, *6*, 1825. (b) Loh, T. P.; Li, X. R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 980. (c) Loh, T. P.; Chua, G. L.; Vittal, J. J.; Wong, M. W. *Chem. Commun.* **1998**, 861.

(3) Loh, T. P.; Tan, K. T.; Hu, Q. Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 2921.

(4) (a) Loh, T. P.; Hu, Q. Y.; Ma, L. T. *J. Am. Chem. Soc.* **2001**, *123*, 2450. (b) Loh, T. P.; Hu, Q. Y.; Tan, K. T.; Cheng, H. S. *Org. Lett.* **2001**, *3*, 2669.

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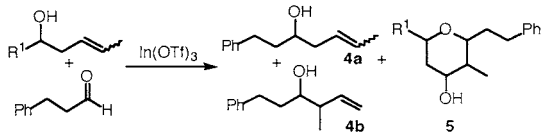
the feasibility of the allyl transfer reaction. The results are summarized in Table 1.

Table 1. Allyl-Transfer from α-Adduct Linear Homoallylic Alcohols to 3-Phenylpropanal **2a** Catalyzed by $In(OTf)_3$[a,b]



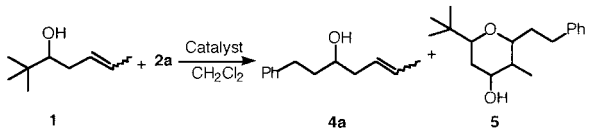
entry	R^1	*T* (°C)[d]	time (h)	% yield[e] (**4a**:**4b**) (*E*/*Z*)[f]
1[c]	*c*-C_6H_{11}	25	5.0	25 (>95%) (80/20)
2	$(CH_3)_2CH$	40	5.0	23 (>95%) (80/20)
3	*n*-C_8H_{17}	40	6.0	25 (76:24) (80/20)
4	Ph	25	1.5	45 (>95%) (80/20)
5	*c*-C_6H_{11}	25	2.0	49 (>95%) (80/20)
6	*t*-Bu	25	2.0	69 (>95%) (80/20)

[a] Reactions were performed with linear homoallylic alcohol (*E*/Z = 80/20, 1.25 mmol), **2a** (0.5 mmol), and $In(OTf)_3$ (10 mol %) in CH_2Cl_2 (3 mL), unless otherwise stated. [b] Yields of **5** were found to be between 5 and 10% in all cases mentioned. [c] The amount of homoallylic alcohol used was 0.5 mmol. [d] Reactions were made to reflux after stirring for 18 h at rt. [e] Combined yield based on **2a**. [f] Determined by ^1H NMR and ^{13}C NMR.

This preliminary study produced not only the desired α-adduct linear homoallylic alcohol **4a** but also a small amount of Prins cyclization product **5**.[6] Using a more sterically congested substrate (entry 6) provided a remarkable yield of the α-adduct product.[7] Switching the substrate to the nonyl fragment (entry 3) proved to be interesting, as a substantial amount of the γ-adduct was isolated.

Given the success of the development of a standard substrate for the allyl-transfer, Table 2 demonstrates a broad scope of the effect of catalysts on this allylation. The failure of the initial attempts with several catalysts[8] was quite puzzling. Perhaps the Lewis acidities of these catalysts were not sufficiently suitable for this demanding allyl transfer reaction. In the case of $Yb(OTf)_3$, the allyl transfer to 3-phenylpropanal gave excellent *E*/*Z* selectivity, though a rather low yield and regioselectivity were observed. Performing the reaction using either $Sn(OTf)_2$ or $In(OTf)_3$[9] gave the products in good yields and excellent regioselectivities in which the *E*/*Z* selectivity was almost preserved in most cases.

Table 2. Effect of Catalyst on the Allylation of 3-Phenylpropanal **2a** with 2,2-Dimethyl-5-hepten-3-ol **1**[a]

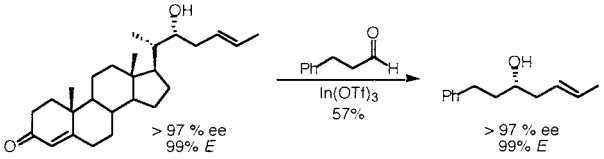


entry	catalyst	*T* (°C)[b]	time (h)	% yield **4a**[c] (α:γ)[d] (*E*/*Z*)[d]	% yield **5**[c]
1	$Yb(OTf)_3$	25	48	15 (75:25) (>95%)	5
2	$Cu(OTf)_2$	25	5	22 (23:77) (80/20)	3
3	$Sc(OTf)_3$	40	18	40 (>95%) (82/18)	28
4	$Sn(OTf)_2$	25	4	55 (>95%) (80/20)	23
5	$In(OTf)_3$	25	3	69 (>95%) (80/20)	10

[a] Reactions were performed with **1** (*E*/Z = 80/20, 1.25 mmol), **2a** (0.5 mmol), and catalyst (10 mol %) in CH_2Cl_2 (3 mL), unless otherwise stated. [b] Reactions were made to undergo reflux when TLC shows no desired product after stirring for 18 h at rt. [c] Combined yield based on **2a**. [d] Determined by ^1H NMR and ^{13}C NMR.

To understand the mechanism of this allyl transfer reaction, an optically active steroid α-adduct homoallylic alcohol (de > 97%) was used to study the stereochemistry of this reaction (Scheme 2). It is interesting to note that the enantioselectivity

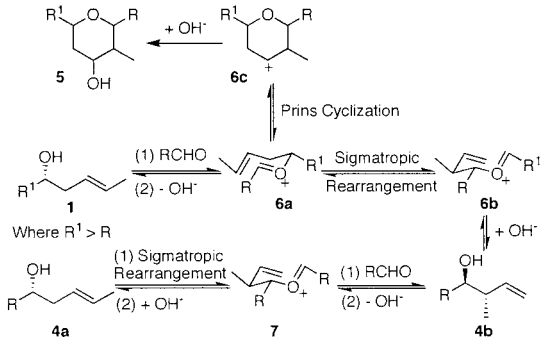
Scheme 2. Stereochemical Study of the Allyl Transfer Reaction



(ee > 97%) and the regiochemistry (99% *E*) of the product were preserved.[10] Furthermore, a trace amount of the γ-adduct in the anti form was obtained in the reaction.

From the reactions and results illustrated in Scheme 2 and Tables 1 and 2, we propose a plausible mechanism as shown in Scheme 3.

Scheme 3. Mechanistic Rationale for the α-to-α Allyl-Transfer and Prins Cyclization Reaction

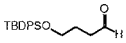


Scheme 3 outlines a mechanistic rationale based upon the following: (i) the branched γ-adduct homoallylic alcohol

(5) For examples of preparation of α-adduct linear homoallylic alcohol, see: (a) Loh, T. P.; Tan, K. T.; Yang, J. Y.; Xiang, C. L. *Tetrahedron Lett.* **2001**, *42*, 8701. (b) Ito, A.; Kishida, M.; Kurusu, Y.; Masuyama, Y. *J. Org. Chem.* **2000**, *65*, 494. (c) Yamamoto, Y.; Maeda, N.; Maruyama, K. *Chem. Commun.* **1983**, *48*, 1564. (d) Yanagisawa, A.; Habaue, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 8955.

(6) For some examples of Lewis acid-catalyzed Prins cyclizations, see: (a) Cloninger, M. J.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 1092. (b) Nishizaw, M.; Shigaraki, T.; Takao, H.; Imagawa, H.; Sugihara, T. *Tetrahedron Lett.* **1999**, *40*, 1153. (c) Yang, X. F.; Mague, J. T.; Li, C. J. *J. Org. Chem.* **2001**, *66*, 739. (d) Rychnovsky, S. D.; Marummoto, S.; Jaber, J. J. *Org. Lett.* **2001**, *3*, 3815. (e) Metzger, J. O.; Biermann, U. *Bull. Soc. Chim. Belg.* **1995**, *103*, 393.

Table 3. Allyl-Transfer from 2,2-Dimethyl-5-hepten-3-ol **1** to Various Aldehydes **2**[a]

Entry	2	Time (h)	Yield[d, e] %(E/Z)	ee%[g]
1		2	69 (>95%)	> 97[b, f]
2		3	41 (>95%)	> 97[b]
3		6	52 (>95%)	> 97[c, h]
4		2	35 (>95%)	> 97[c, f]

[a] Reactions were performed with **1** (*E*/Z > 95%, ee% > 97%, 1.25 mmol), **2** (0.5 mmol), and $In(OTf)_3$ (10 mol %) in CH_2Cl_2 (3 mL) at rt, unless otherwise stated. [b] Determined by chiral HPLC. [c] Determined by ^{19}F NMR of the Mosher derivative. [d] Combined yield based on **2**. [e] Only α-adduct was obtained. [f] Absolute stereochemistry was determined by comparison with literature values. See refs 10d and 12b. [g] Compound **1** was recovered with no decrease in ee%. [h] Compounds **1** (0.5 mmol) and **2** (1.25 mmol) were used.

4b was generated from the $In(OTf)_3$-promoted allyl transfer reaction from the α-adduct linear homoallylic alcohol **1**, perhaps through a 2-oxonia [3,3]-sigmatropic rearrangement. Following that, **4b** underwent a thermodynamic conversion to the preferred linear regioisomer **4a**, plausibly by a concerted rearrangement similar to that mentioned previously. (ii) The stereochemistry was retained after the allyl transfer from steroid homoallylic alcohol. (iii) The steric effect is very important, and the whole rearrangement process was driven by the difference in steric bulk of the two substrates, with the less bulky substrate being more stable. (iv) The Prins product was derived from the oxonium ions **6a**, which can cyclize to give a stable cation **6c**, which reacts with a hydroxyl equivalent generated in situ to give **5**.

With such understanding of the reaction, we then tried this enantioselective allyl transfer reaction with four different aldehydes using **1** with ee > 97% and an *E*/*Z* ratio >95%.[11] As shown from Table 3, the regio- and stereochemistry remained unchanged after the reaction. This allyl transfer reaction can also work with lactol (entry 3). Especially noteworthy is the stereoselective allyl transfer of **1** with aldehyde in entry 4, which provides easy assembly of the C15−C22 fragment of the (+)-Amphidinolide K (Figure 1).[12]

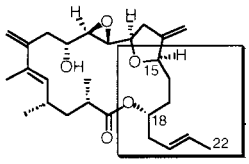


Figure 1. (+)-Amphidinolide K.

In conclusion, the first example of Lewis acid-catalyzed enantioselective linear homoallylic alcohol transfer, from sterically hindered starting material to its sterically less hindered analogue via its γ-adduct intermediate, has been developed. In all cases, the steric effect is the driving force behind this reaction.

Acknowledgment. We thank the National University of Singapore for generous financial support. Chi-Lik Ken Lee is grateful to Chemical Process and Engineering Center (CPEC) for a graduate scholarship.

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

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(7) We found that this allyl transfer reaction was largely dependent on the steric effect of the substituent on allylic alcohol and aldehyde. In many cases, the improved yields of the desired α-adduct linear homoallylic alcohol arose because the amount of the Prins product decreased.

(8) CSA, PTSA, $InBr_3$, $Ag(OTf)_3$, $La(OTf)_3$, and $Lu(OTf)_3$ gave no desired α-adduct homoallylic alcohol **4**.

(9) The solvent effect on the $In(OTf)_3$-catalyzed allyl transfer reaction of 3-phenylpropanal with **1** was investigated. H_2O, THF, and DMF showed no reaction. Hexane, $CHCl_3$, and CH_2Cl_2 gave 15, 30, and 69% α-adduct, respectively, together with 37, 10, 10% of prins product, respectively.

(10) For some examples of allyl transfer from its kinetic γ-adduct to its thermodynamically stable α-adduct, see: (a) Nokami, J.; Yoshizane, K.; Matsuura, H.; Sumida, S. *J. Am. Chem. Soc.* **1998**, *120*, 6609. (b) Sumida, S.; Ohga, M.; Mitani, J.; Nokami, J. *J. Am. Chem. Soc.* **2000**, *122*, 1310. (c) Nokami, J.; Anthony, L.; Sumida, S. *Chem. Eur. J.* **2000**, *6*, 2909. (d) Nokami, J.; Ohga, M.; Nakamoto, H.; Matsubara, T.; Hussain, I.; Kataoka, K. *J. Am. Chem. Soc.* **2001**, *123*, 9168.

(11) **1** (ee > 97%) was prepared using a procedure described by Nokami et al.; see ref 10d.

(12) (a) William, D. R.; Meyer, K. G. *J. Am. Chem. Soc.* **2001**, *123*, 765. (b) Loh, T. P.; Hu, Q. Y.; Chok, Y. K.; Tan, K. T. *Tetrahedron Lett.* **2001**, *42*, 9277.