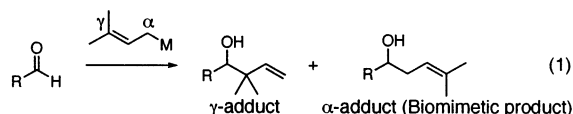# A Novel and General α-Regioselective and Highly Enantioselective Prenylation of Aldehydes
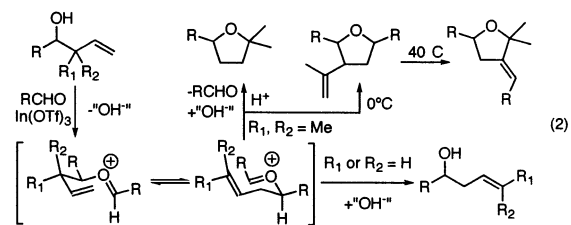
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The prenyl fragment is featured widely in many drugs and natural products such as alkanin, shikonin, and inotodiol as well as in biosynthetic intermediates.[1] Among the methods, the addition of prenyl substituent to carbonyl compounds or double bonds provides an easy and efficient entry into this class of compounds. However, despite the wealth of this class of compounds, prenylation of carbonyl compounds is still not well developed.[2] This is because the commonly employed method using the addition of allylic metals to carbonyl compounds is γ-regioselective except for a few special cases (eq 1). Therefore, the development of a general enantioselective α-selective prenyl addition to carbonyl compounds is one of most precious, yet challenging, endeavors in organic synthesis.[3] Hence, in this communication, we will describe a general and highly regioselective and enantioselective prenylation of aldehydes.[1]

It has been demonstrated recently by our group that the α-prenyl alcohol is labile in the presence of aldehyde and acid, undergoing facile oxonium-ene cyclization to form tetrahydrofuran derivatives (eq 2).[4] As a result, the prenyl moiety distinctively gives the cyclization product, in contrast to the γ-adducts of crotyl and cinnamyl alcohols, which do not cyclize, and hence can easily rearrange to the corresponding α-adducts.[5]

From the mechanism of oxonium-ene cyclization, we envisage that if we can suppress the oxonium-ene cyclization, the valuable α-prenyl alcohol can be obtained. However, our initial attempts by changing solvents or using a more bulky alcohol to obtain the prenyl alcohol were not successful. Next, we turned our attention toward trapping the oxonium intermediate with a hydroxyl group to form a ketal which, upon hydrolysis, will yield the desired prenyl alcohol. With this design in mind, γ-prenyl-1,5-diol **2**, easily obtained from a zinc-mediated prenylation of the corresponding lactol, was chosen as the prenyl source.[6,7]
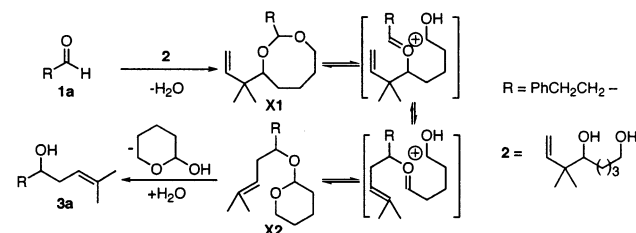
Initial experiments carried out using aldehyde, **1a**, (1 equiv), a γ-prenyl-1,5-diol (**2**, 2 equiv) and a catalytic amount of In(OTf)$_3$

Table 1. Prenyl Transfer in Various Solvents and Acids[a]

entry	catalyst	solvent	time/h	yield(%)[b]
1	Sn(OTf)$_2$	CH$_2$Cl$_2$	13	42
2	Cu(OTf)$_2$	CH$_2$Cl$_2$	120	25
3	pTSA	CH$_2$Cl$_2$	90	20
4[c]	In(OTf)$_3$	CH$_2$Cl$_2$	11	35
5	In(OTf)$_3$	CH$_2$Cl$_2$	11	61
6	In(OTf)$_3$	hexane	11	62
7	In(OTf)$_3$	CHCl$_3$	11	62
8	In(OTf)$_3$	toluene	11	25
9	In(OTf)$_3$	DMF	11	0
10	TfOH	CH$_2$Cl$_2$	20	35
11	TfOH	hexane	12	87[d]

[a] Reactions were performed by treating **1** (0.5 mmol, 1 equiv) and **2**(1.0 mmol, 2 equiv) in 20 mL solvent with acid (0.05 mmol, 0.1 equiv). The reaction mixtures were stirred for 11 h at 25 °C. 15 mL of MeOH was then added and stirred for 3 h. [b] Isolated yield. [c] The 1,4-diol was used instead of 1,5-diol, **2**. It was synthesized with identical condition as the **2**. [d] 40% of the total amount of **2** (i.e. 80% of the excess **2**) was recovered.

in dichloromethane afforded the desired α-prenyl product **3a** in 50% isolated yield, with 11% in the THP-protected form, **X2**. **X2** was then readily deprotected in situ, by stirring with methanol for an additional 3 h before workup. Comparison of the 1,5-diol **2** and the 1,4-diol (entries 4 and 5, respectively) revealed that the former is more efficient in the prenyl transfer, presumably due to the formation of the more stable six-membered ring in **X2**.

This preliminary result encouraged us to investigate the various reaction conditions in an attempt to improve the yield of the reaction. The results are summarized in Table 1.
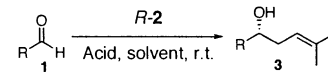
After screening several Lewis acids and Brønsted acids in various solvents, we found that In(OTf)$_3$, in both polar and nonpolar solvents, afforded the product in moderate yield (Table 1, entries 5, 6, and 7). Interestingly, triflic acid in hexane gave the product in highest yield (87%) (Table 1, entry 11).

With these results, we proceeded to investigate the asymmetric prenyl transfer using optically pure 1,5-diols, R-**2** and S-**2**, which were easily obtained via resolution.[7]

Various α-prenyl alcohols were successfully obtained using the optimized condition, as shown in Table 2. In all cases, the α-prenyl

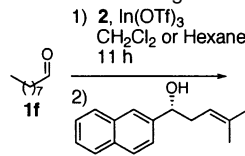**Table 2.** Asymmetric α-Prenylation of Various Aldehydes

Entry	R	Acid	Solvent	3	Yield[a]/ %	ee/ %
1	Ph-	In(OTf)₃	CH₂Cl₂	3 b	53	40
2	2-Napthyl-	In(OTf)₃	CH₂Cl₂	3 h	60	42
3	PhCH₂CH₂-	In(OTf)₃	CH₂Cl₂	3 a	62	90
4	CH₃(CH₂)₇-	In(OTf)₃	CH₂Cl₂	3 f	63	90
5	Ph-	TfOH	hexane	3 b	75	93[b]
6	BnO(CH₂)₄-	TfOH	hexane	3 c	95	98
7	BnO(CH₂)₃-	TfOH	hexane	3 d	85	92
8	BnO(CH₂)₂-	TfOH	hexane	3 e	60	94
9	PhCH₂CH₂-	TfOH	hexane	3 a	87	95
10	CH₃(CH₂)₇-	TfOH	hexane	3 f	71	95
11	EtO₂C ⟍⟋⟍₃	TfOH	hexane	3 g	89	98
12	2-Napthyl-	TfOH	hexane	3 h	61	87

[a] Isolated yield. [b] The absolute configuration was assigned as R by comparing the optical rotation with that of the known product.[8]

Scheme 1. Monitoring Enantiomeric Excess of **3h** with HPLC

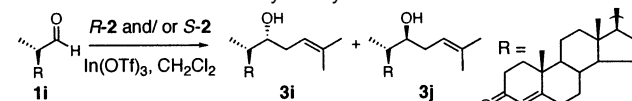| Time /h	in CH₂Cl₂ ee/%	in hexane ee/%
0	87	87
7	51	86
20	24	86
36	< 5	-
60	-	85

alcohols were obtained in moderate to high yields. It is also worth noting that this reaction is highly chemoselective, reacting selectively with the aldehyde without affecting the enone[9] and the α,β-unsaturated ester functionalities.

Surprisingly, when the reaction was performed in dichloromethane in the presence of In(OTf)₃, the aromatic aldehydes afforded a much lower enantiomeric excess (entries 1−2), in sharp contrast to the aliphatic counterparts (entries 3−4). On the other hand, the enantioselectivities were surprisingly high for both aromatic and aliphatic aldehydes in reactions using TfOH in hexane (entries 5−12).

To investigate this discrepancy, optically active aromatic **3h** was injected into two parallel reactions using In(OTf)₃ in hexane and dichloromethane respectively, and the optical purity was monitored with HPLC over time (Scheme 1). It was found that the optical purity decreased much more dramatically in dichloromethane than in hexane.[10,11]

To study the diastereoselectivity of the substrate, both enantiomers of **2** were used in the prenylation of steroidal aldehyde, **1i** (Scheme 2). We found that the absolute stereochemistry depends solely upon the stereochemistry of **2** (entries 1 and 2), and that the anti-Cram product was the major product when racemic **2** was employed (entry 3). The reasons for these observations are currently being investigated.

In summary, the study of the mechanism of the intramolecular oxonium-ene cyclization has led to the establishment of a general α-regioselective and highly enantioselective prenylation of aldehydes. Further studies disclosed the facile racemization of aromatic alcohols in dichloromethane in the presence of In(OTf)₃. This

Scheme 2. Stereoselectivity Study[a]

Entry	2	Yield (%)	Ratio of 3i:3j
1	R-2	80	> 98 : 2
2	S-2	80	< 2 : 98
3	R-2:S-2 =1:1	80	65: 35

[a] The condition CH₂Cl₂/ In(OTf)₃ was chosen other than hexane/ TfOH for the concern of the solubility of steroidal aldehyde.

racemization can be overcome by carrying out the reaction in hexane. Studies using chiral aldehyde have shown that the stereochemistry of the product was solely dependent on the stereochemistry of the prenyl source. Further application of this chemistry for natural product synthesis is in progress.

Supporting Information Available: Spectroscopic and analytical data for all compounds and the representative procedure (PDF). This material is available free of charge via the Internet at http:// pubs.acs.org.

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(6) The γ-prenyl can be easily obtained in 75% yield from a one-pot synthesis by generating lactol in situ from DHP in acidic aqueous media, followed by zinc-mediated prenylation of the corresponding lactol.

(7) It was done by chiral resolution with (S)-O-acetylmandelic acid. Whitesell, J. K.; Reynolds, D. *J. Org. Chem.* **1983**, *48*, 3548. Enantiomeric excess for both *R*-2 and *S*-2 was 99%. (*R*)-Mosser acid di-protection of *R*-2 and *S*-2 give ¹⁹F NMR at 4.73, 3.89 and 4.84, 3.89, respectively.

(8) [α]D = +53.3 (c =0.15 in C₆H₆); literature value: *R* isomer, [α]D = +50.2 (c =1.16 in C₆H₆). Ishihara, K.; Mouri, M.; Gao, Q.; Muruyama, T.; Furuta, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 11490−11495.

(9) Refer to Scheme 2 for the steroidal enone moiety.

(10) To validate this observation, naphthalene-2-carbaldehyde, **1h**, was reacted with In(OTf)₃ in hexane. Indeed, the product, **3h**, was obtained in 61% yield, 93% enantiomeric excess.

(11) For racemization under other conditions, see: (a) Crosby, S. R.; Harding, J. R.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2001**, *4*, 3407−3410. (b) Rychnovsky, S. D.; Marumoto, S.; Jaber, J. J. *Org. Lett.* **2001**, *3*, 3815−3818. (c) Marumoto, S.; Jaber, J. J.; Vitale, J. P.; Rychnovsky, S. D. *Org. Lett.* **2002**, *4*, 3919−3922.

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