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General and practical approach to the syntheses of linear homoallylic alcohols*

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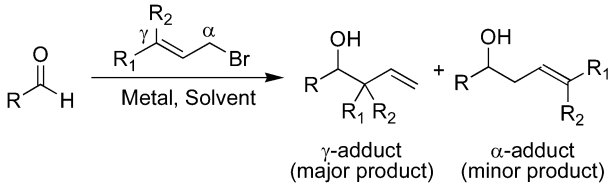
Abstract: We have demonstrated that metal-mediated allylation of aldehydes can afford γ-homoallylic alcohols or α-linear homoallylic alcohols by judicious choice of the solvents. A new mechanism has been proposed to account for this new α-selective metal-mediated allylation reaction. On the other hand, the metal-mediated prenylation under the same conditions to obtain α-prenyl alcohols was unsuccessful. Detailed mechanistic studies have resulted in the discovery of a new method to obtain compounds with diverse structures via an oxonium-ene cyclization. Suppressing the oxonium-ene reaction during the reaction has resulted in the formation of α-prenyl alcohols. A highly enantioselective process to obtain α-prenyl product in high optical purity has also been accomplished.

Keywords: Homoallylic alcohols; metal-mediated allylation; prenylation; α-selectivity; oxonium-ene cyclization.

Homoallylic alcohols are important building blocks in organic syntheses, since the alkene functionality can be readily transformed into a wide variety of functional groups such as aldehydes (via ozonolysis), δ-lactones (via a facile hydroformylation), epoxides, and other olefinic compounds (via cross-olefin metathesis) [1]. Furthermore, they are also featured widely in many biological active molecules such as macrolides, polyhydroxylated natural products, and polyether antibiotics [2].

Among the many methods available for the synthesis of homoallylic alcohols, metal-mediated allylation of aldehydes is one of the most common and efficient. Although many metals across the periodic table have been demonstrated to mediate the allylation, only a few of these metals (Sn, Zn, In) have been found to work in aqueous media. However, these reactions usually give γ-branched homoallylic alcohols except for a few cases (Scheme 1). Hence, the direct synthesis of linear homoallylic alcohol from carbonyl compound poses a challenging problem to organic chemists. In this paper, we report two general methods to obtain α-selective linear homoallylic alcohols.



Scheme 1

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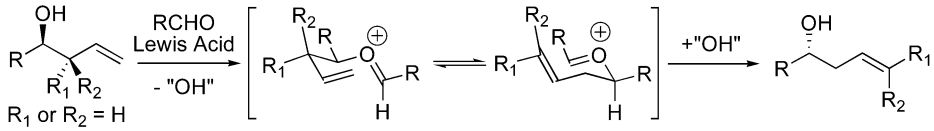
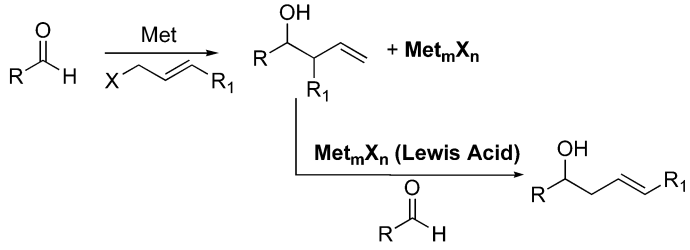
Based on the recent report by Nokami on the possibility of converting γ-branched homoallylic alcohols to linear homoallylic alcohols via 2-oxonia[3,3]-sigmatropic rearrangement in the presence of a catalytic amount of aldehyde and Lewis acid (Scheme 2) [3], we envisage that the metal halide generated during the reaction could act as a Lewis acid which could, in a tandem manner, catalyze the allyl transfer to produce linear homoallylic alcohols (Scheme 3). It is important to note that while water is required for the metal-mediated allylation reaction, too much water will be detrimental to the subsequent allyl-transfer reaction.



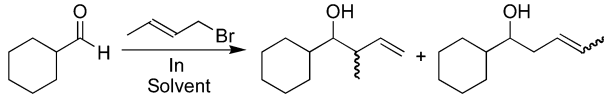
Scheme 2



Scheme 3

With these problems in mind, the indium-mediated allylations of cyclohexanecarbaldehyde with crotyl bromide were carried out in different solvents. The results were shown in Table 1 [4].

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

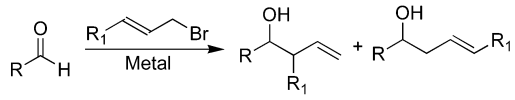


Entry	Solvent	Amount (equiv)	Time (h)	Yield %[d] (α:γ)[c]
1[b]	DMF	6	72	65 (0:100)
2	H_2O	2 ml	72	90 (0:100)
3[b]	H_2O	6	24	85 (99:1)
4	H_2O	6	72	87 (86:14)
5	CH_2Cl_2	6	24	–[e]
6	THF/H_2O	6:6	72	95 (0:100)
7	CH_2Cl_2/H_2O	6:6	24	68 (>99:1)
8[b]	DMF/H_2O	6:6	72	80 (0:100)
9	CH_3CH_2OH	6	72	97 (0:100)

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

To our expectation, excellent α-regioselectivity was achieved when the reaction was conducted in water (6 equiv) and water/dichloromethane (6 equiv/6 equiv) (entries 3 and 7). Subsequently, using these optimized conditions, we extended the reaction to a wide variety of aldehydes and allylic bromides. The results are summarized in Table 2.

Table 2 Metal-mediated allylation of aldehydes with bromides.



Entry	R	R_1	Metal	Condition[a]	Time (h)	Yield %[c] (α:γ)[b] (*E*/*Z*)[b]
1	Ph	Me	In	A	36	60 (99:1) (55/45)
2	*c*-C_6H_{11}	Me	In	A	24	85 (99:1) (70/30)
3	*n*-C_5H_{11}	Me	In	A	36	75 (98:2) (65/35)
4	$PhCH_2CH_2$	Me	In	A	18	67 (97:3) (55/45)
5	Ph	Ph	In	A	72	66 (98:2) (100/0)
6	*c*-C_6H_{11}	Ph	In	A	72	73 (96:4) (98/2)
7	*n*-C_5H_{11}	Ph	In	A	85	71 (99:1) (90/10)
8	$PhCH_2CH_2$	Ph	In	A	160	50 (99:1) (95/5)
9	*c*-C_6H_{11}	CO_2Et	In	A[e]	96	90 (80:20) (80/20)[f]
10	Me	CO_2Et	In	A[d,e]	192	56 (85:15) (90/10)[f]
11	Ph	Me	Sn	B	48	83 (55:45) (75/25)
12	*n*-C_5H_{11}	Me	Sn	B	48	81 (80:20) (55/45)
13	$PhCH_2CH_2$	Me	Sn	B	48	82 (71:29) (53/47)
14	*c*-C_6H_{11}	Me	Sn	B	48	78 (95:5) (67/33)
15	*t*-Bu	Me	Sn	B	48	42 (99:1) (83/17)
16	*n*-C_5H_{11}	Ph	Sn	C	24	60 (95:5) (100/0)
17	*c*-C_6H_{11}	Ph	Sn	C	24	54 (99:1) (100/0)
18[g]	Ph	Ph	Sn	C	24	80 (99:1) (100/0)
19	*t*-Bu	Me	Zn	D	120	34 (45:55) (62/38)
20	*n*-C_5H_{11}	Me	Zn	D	120	55 (90:10) (54/46)
21	*c*-C_6H_{11}	Me	Zn	D	120	66 (95:5) (73/27)
22	$PhCH_2CH_2$	Me	Zn	D	120	58 (94:6) (60/40)
23	Ph	Me	Zn	D	120	50 (97:3) (77/23)

[a]Condition A: 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. Condition B: The reactions were performed with aldehyde (1 mmol), crotyl bromide (1.2 mmol), and tin (1.5 mmol) in water (0.108 ml) and CH_2Cl_2 (0.385 ml) at room temperature for 48 h unless otherwise noted. Condition C: 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. Condition D: All reactions were performed with aldehyde (1 mmol), bromide (1.2 mmol), and zinc (1.5 mmol) in water (0.036 ml) and CH_2Cl_2 (0.128 ml) at room temperature for 120 h.

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

[c]Total yield.

[d]Due to the highly volatility of the aldehyde, an excess of acetyl aldehyde was added.

[e]2 equiv of water were used.

[f]*Z*-isomer was isolated as lactone.

[g]The reaction was stirred for 3 days with 3 mmol of cinnamyl bromide.

In all cases, the products were obtained in excellent α-selectivities with good yields. Similarly, tin and zinc were also found to afford α-adducts under similar conditions (Table 2).

MECHANISTIC STUDIES

i. TLC and ^{1}H NMR studies of the indium-, tin-, and zinc-mediated allylation showed that the reaction proceeded to afford the kinetically favored branched homoallylic alcohol first, which slowly converted to the thermodynamic linear homoallylic alcohol (Fig. 1). Furthermore, excess aldehyde is not necessary for the conversion of γ-branched homoallylic alcohols to the linear homoallylic alcohols.

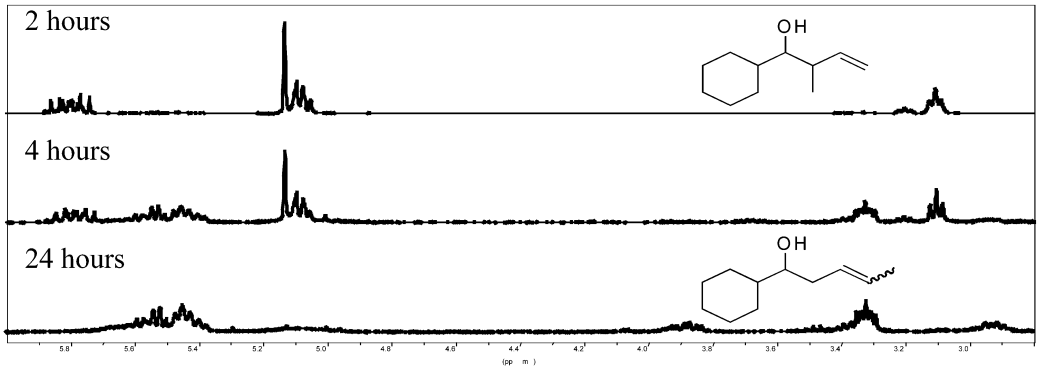
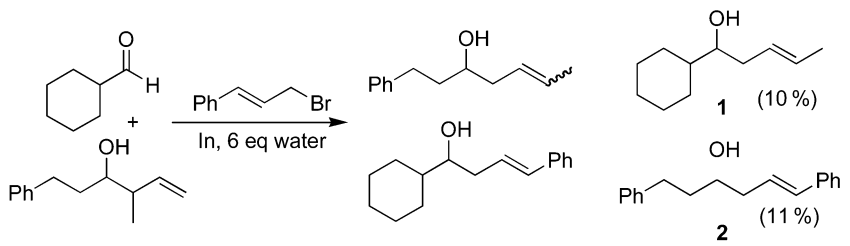


Fig. 1 ^{1}H NMR study for indium-mediated allylation.

ii. Prolonged stirring resulted in the formation of α-linear homoallylic alcohols. Surprisingly, a trace amount of aldehyde was detected at the end of the reaction. This result suggested the possibility of a retro-cleavage (retro-ene) process involving γ-branched homoallylic alcohols in the reaction to generate a trace amount of aldehyde, which was required for the subsequent transformation. Indeed, when we subjected the γ-branched homoallylic alcohols to various indium complexes, including indium triflate and indium tribromide, we found that in contrast to the results reported by Nokami, the rearrangement can be effected without the addition of the aldehyde.

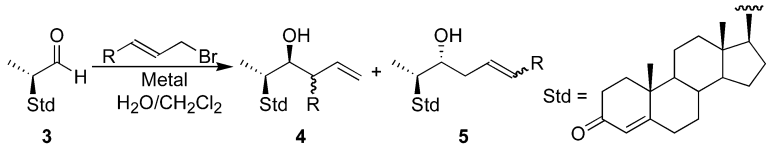
iii. Next, a cross-over experiment was conducted using indium (Scheme 4). After the reaction, column chromatography revealed the cross-over products **1** and **2** in 10 and 11 % yields, respectively. This proved that the rearrangement of this γ-adduct to its isomer α-adduct is an intermolecular process that may involve the cleavage of the γ-adduct to form the aldehyde and an allyl fragment.



Scheme 4 Cross-over experiment.

iv. Lastly, to rule out the possibility of the mechanism involving the retroclevage followed by recombination of the allylic metal species, stereochemical studies were carried out. Therefore, the indium, tin, and zinc systems were tested using a steroidal aldehyde to investigate the stereochemistry of the reaction (Table 3). In all cases, the allyl fragment reattaches to the steroid in an *anti*-Cram manner, which excludes the possibility of allyl anion re-addition to the aldehyde.

Table 3 Stereochemical study of metal-mediated α-regioselective allylation.

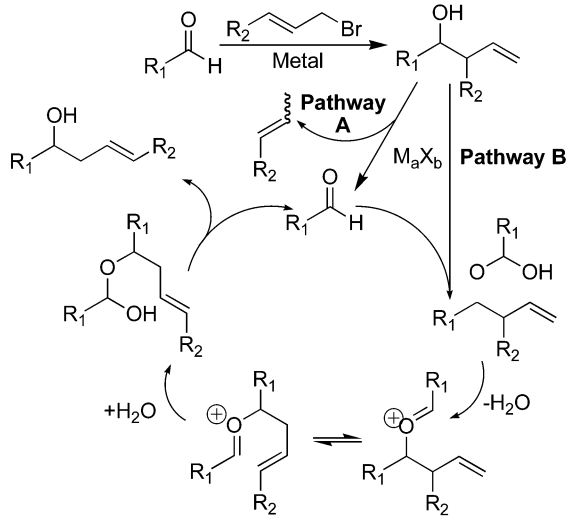


3 4 5

Entry	Metal	R	Time (h)	Yield* (%)	SM recovered (%)	**4** (*syn:anti*):**5** (*E:Z*)
1	In	Ph	48	54	30	1 (–:–):99 (99:1)
2*	Sn	Me	96	50	5	52 (9:91):48 (99:1)
3*	Zn	Me	120	40	20	78 (35:65):22 (99:1)

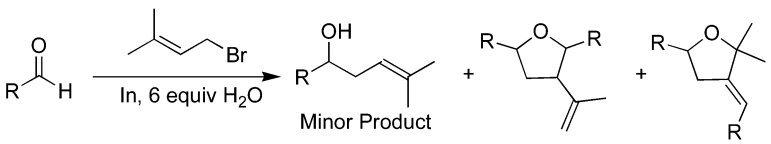
*Conversion yield.

Hence, a new mechanism (Scheme 5) was proposed for these highly α-regioselective metal-mediated allylation reactions. As opposed to previously proposed mechanisms, our investigations suggested that the initially formed γ-adduct underwent a bond cleavage to generate the parent aldehyde in situ (pathway A), and, subsequently, the reaction proceeded via a concerted rearrangement, perhaps by a retro-ene [5] followed by a 2-oxonia [3,3]-sigmatropic rearrangement [6]. Moreover, it is also possible that the metal salt can catalyze the formation of α-adduct as well via an oxonium ion intermediate **6** between the γ-adduct and unreacted aldehyde [3,7], with no fission of the γ-adduct's C–C bond by retro-ene reaction (pathway B).

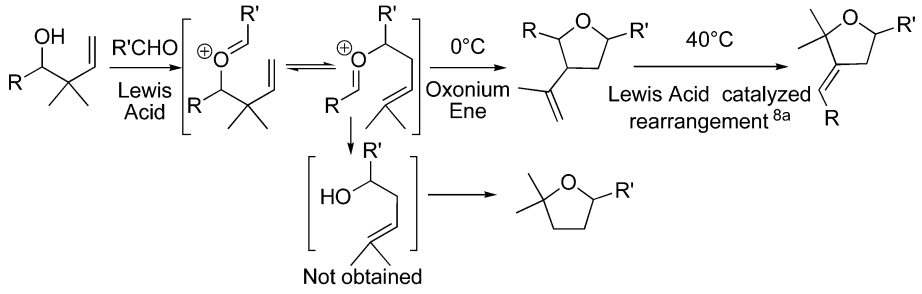


Scheme 5 Proposed mechanism for rearrangement.

When this strategy was extended to the α-prenylation of aldehydes with the above conditions, we obtained a mixture of compounds. Although the γ-branched prenyl product can be obtained easily using the classic method, the α-prenyl product was only obtained in low yield.

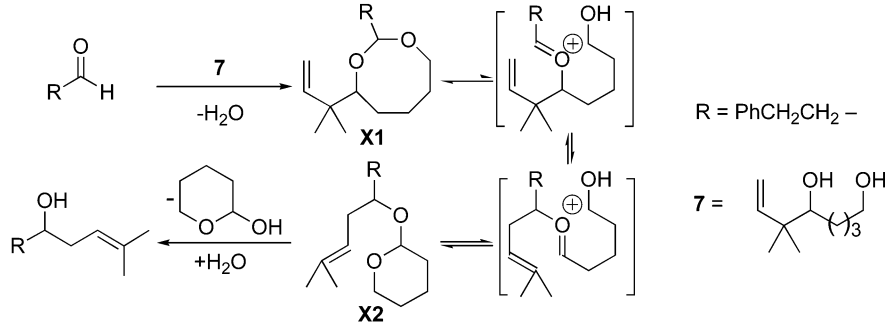


Despite being similar in structure, the prenyl group exhibited rather different chemistry in the allyl-transfer reaction. A project was undertaken to study the oxonium-[3,3]-sigmatropic rearrangement of the pure γ-branched homoallylic alcohols in the presence of a catalytic amount of Lewis acid and excess aldehyde. Interesting, depending on the reaction conditions employed, we were able to obtain different compounds of diverse structures. Detailed mechanism studies showed that after the sigmatropic rearrangement, the intermediate is in a facile orientation to carry out an intramolecular oxonium-ene reaction (Scheme 6). Hence, it undergoes a facile oxonium-ene cyclization to form tetrahydrofuran derivatives [8].



Scheme 6

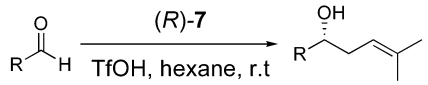
Based on this information, we envisage that if we can suppress the oxonium-ene cyclization, the valuable α-prenyl alcohol can be obtained cleanly (Scheme 7) [9]. This could be achieved by quenching the oxonium intermediate with a hydroxyl group to form a ketal, which, upon hydrolysis, yields the desired prenyl alcohol.



Scheme 7

To test our working hypothesis, (***R***)-**7** was used and was found to afford the various α-prenyl alcohols cleanly (Table 4). In all cases, the α-prenyl 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.

Table 4 Asymmetric α-prenylation of various aldehydes.



Entry	R	Yield[a]/%	ee/%
1	Ph–	75	93
2	$BnO(CH_2)_4$–	95	98
3	$BnO(CH_2)_3$–	85	92
4	$BnO(CH_2)_2$–	60	94
5	$PhCH_2CH_2$–	87	95
6	$CH_3(CH_2)_7$–	71	95
7	EtO_2C 	89	98
8	2-Napthyl–	61	87

[a]Isolated yield.

In conclusion, we have demonstrated that metal-mediated allylation can afford the γ-homoallylic alcohols or the α-linear homoallylic alcohols by the judicious choice of the solvents. A new mechanism has been proposed to account for this new α-selective metal-mediated allylation reaction. This new mechanism provides another possible explanation for the many reported α-selective metal-mediated allylation reactions. The retro-cleavage observed in this reaction has also resulted in the development of a new method to rearrange γ-branched homoallylic alcohols to the linear homoallylic alcohols in the presence of catalytic amount of Lewis acid without the need to add excess aldehyde.

On the other hand, the metal-mediated prenylation using the above conditions to obtain the α-prenyl alcohols was unsuccessful. Detailed mechanistic studies have resulted in the discovery of a new method to obtain compounds with diverse structures. An oxonium-ene process was found to be involved. Suppressing the oxonium-ene reaction during the reaction has resulted in the formation of the α-prenyl alcohols. A highly enantioselective process has been developed to afford α-prenyl product in high optical purity.

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