Racemization of Homoallyl Alcohols via an Allyl-transfer Reaction

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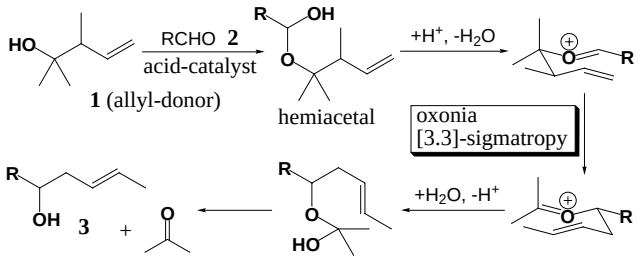
Received 18 January 2002

Abstract: Acid-catalyzed asymmetric allylation of 3-phenylpropanal **2a** via an allyl-transfer reaction from a chiral allyl donor, (1*R*,2*S*,5*R*)-1-allylmenthol, gave (*R*)-1-phenylhex-5-en-3-ol **3b** enantioselectively. The optical yield (ee) of (*R*)-**3b**, however, decreased with increasing chemical yield, and the chemical yield increased with increasing reaction time. The racemization takes place via an acid-catalyzed allyl-transfer reaction from (*R*)-**3b** to **2a**.

Key words: allyl-transfer reaction, homoallylic alcohol, asymmetric synthesis, racemization

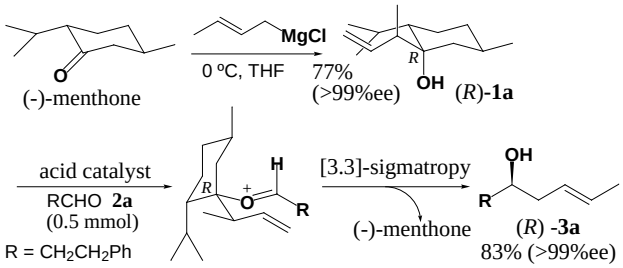
The enantioselective allylation of aldehydes with an allyl(ic)-nucleophile is one of the most attractive reactions in asymmetric synthesis. Not only is the functionalization of the product (homoallylic alcohol) of such a reaction extremely versatile,[1] but also the allylmetallic reagents, which serve as allyl-nucleophiles, can be easily prepared.[1,2]

On the other hand, we recently discovered an interesting reaction in which the homoallylic alcohol **1** serves as a crotyl-donor to the aldehyde **2** in the presence of an acid-catalyst to give the homoallylic alcohol **3**. In this reaction, the allylic unit in the donor homoallylic alcohol **1** is stereoselectively transfered to the aldehyde **2** via a six-membered chair-form cyclic transition state (oxonia [3,3]-sigmatropic rearrangement) in the absence of an allylmetallic reagent, as shown in Scheme 1.[3a,b]



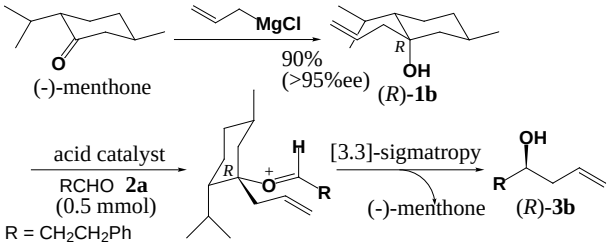
Scheme 1

We successfully applied this reaction in an asymmetric crotylation of aldehydes using a chiral crotyl-donor (homoallylic alcohol **1a**), prepared from (–)-menthone with crotylmagnesium chloride, to give (5*E*,3*R*)-1-phenylhept-5-en-3-ol **3a** in 83% yield with >99% ee.[2] See Scheme 2.



Scheme 2

To obtain further information on the allyl-transfer reaction, a chiral allyl-donor, (1*R*,2*S*,5*R*)-1-allylmenthol (**1b**, >95% ee: NMR spectroscopically pure), was reacted with 3-phenylpropanal **2a** in the presence of an acid catalyst, as shown in Scheme 3. The results are summarized in Table 1.



Scheme 3

The treatments of **1b** with **2a** in the presence of *p*-toluenesulfonic acid monohydrate (TSA·H_2O, 10 mol%) in CH_2Cl_2 at 20 °C, for 1.5, 2, 5, 10, and 15 h afforded *(R)*-1-phenylhex-5-en-3-ol, (*R*)-**3b**, in 37% (83% ee), 50% (78% ee), 60% (71% ee), 68% (70% ee), and 72% (68% ee) yields, respectively (entries 1–5). These results clearly show that the optical yield (ee) of (*R*)-**3b** decreases with increasing chemical yield of **3b**, and the yield of **3b** increases with increasing reaction time. However, from the reaction mechanism proposed for the asymmetric crotylation,[2] we must assume that the mechanism for the allyl-transfer from the chiral allyl-donor to the aldehyde is the same throughout the reaction.

Therefore, we considered that the ee of (*R*)-**3b**, derived by the allyl-transfer from the chiral allyl-donor **1b** to **2a**, decreases under the reaction conditions, especially in the presence of 3-phenylpropanal (**2a**, 10 mol%). The results derived by the reaction with various other acid catalysts are shown in Table 2.

Synlett 2002, No. 4, 29 03 2002. Article Identifier:
1437-2096,E;2002,0,04,0640,0642,ftx,en;Y01302ST.pdf.

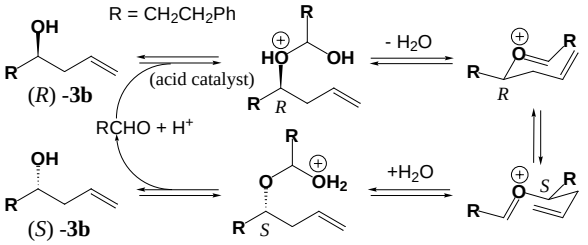
ISSN 0936-5214

Table 1 Allylation of Aldehyde via Allyl-transfer Reaction from Chiral Allyl-donor (*R*)-**1b**[a]

Entry	Catalyst[b] (mol%)	Temp (°C)	Time (h)	Yield (%)[c]	Optical purity (% ee)[d]
1[e]	TSA·H_2O (10)	20	1.5	37	83
2	TSA·H_2O (10)	20	2.0	50	78
3	TSA·H_2O (10)	20	5.0	60	71
4	TSA·H_2O (10)	20	10.0	68	70
5	TSA·H_2O (10)	20	15.0	72	68
6	HCl/Et_2O (100)	0	3.0	62	56
7[f]	$Sn(OTf)_2$ (10)	0	2.0	37	49
8	$HNTf_2$ (10)	0	2.0	22	64

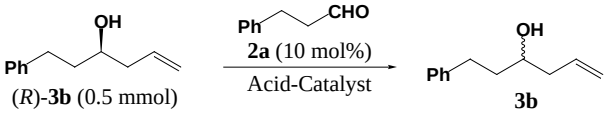
[a] All reactions were performed with 3-phenylpropanal (**2a**, 0.5 mmol) and (*R*)-**1b** (1 mmol) in CH_2Cl_2 (2 mL) unless otherwise noted. [b] TSA: *p*-toluenesulfonic acid; HCl: hydrogen chloride ether solution. [c] Isolated yield based on the aldehyde. [d] Determined by HPLC (Chiralcel OD). [e] The reaction was performed with **2a** (5 mmol) and (*R*)-**1b** (10 mmol) in CH_2Cl_2 (20 mL). [f] In the presence of molecular sieves (4 A, 25 mg).

As shown in entry 1, the aldehyde rapidly accelerated the racemization (decrease of ee) of (*R*)-**3b**, although the ee only slightly decreased in the absence of the aldehyde (entry 2). The role of the aldehyde in the racemization is very reasonable, because the allyl-transfer reaction from (*R*)-**3b** to **2a** gives (*S*)-**3b** via a six-membered chair-form cyclic transition state, as shown in Scheme 4. The very slight decrease of ee in the absence of the aldehyde would also be caused by the allyl-transfer from (*R*)-**3b** to a very small amount of the aldehyde that would be formed by an acid-catalyzed retro-ene reaction from (*R*)-**3b**.[4] $Sn(OTf)_2$ and $HNTf_2$ served as effective catalysts, and BF_3·OEt_2 and hydrogen chloride (HCl·OEt_2) were reasonable catalysts in the racemization caused by an allyl-transfer at 0 °C (entries 3–7). Metal chlorides served as weak catalysts, but Ti(*i*-PrO)$_4$ and $Sc(OTf)_3$ did not catalyze the reaction (entries 8–12).



Scheme 4

Table 2 Acid-catalyzed Racemization of Homoallylic Alcohol via Allyl-transfer Reaction[a]



Entry	Catalyst (mol%)	Solvent (mL)	Temp. (°C)	Time (h)	Recovery of **3b** %[b]	Optical purity (% ee)[c]
1	TSA·H_2O (10)	CH_2Cl_2 (2.0)	20	2	87	37.3 (59.)
2[d]	TSA·H_2O (10)	CH_2Cl_2 (2.0)	20	2	93	56.6 (59.3)
3	$Sn(OTf)_2$ (10)	CH_2Cl_2 (2.5)	0	1	87	41.6 (82.7)
4	BF_3·Et_2O (100)	CH_2Cl_2 (5.0)	–78	3	84	81.1 (82.7)
5	BF_3·Et_2O (100)	CH_2Cl_2 (5.0)	0	3	77	68.5 (79.7)
6	HCl·Et_2O (100)	CH_2Cl_2 (5.0)	0	3	70	32.6 (76.0)
7	$HNTf_2$ (1)	CH_2Cl_2 (5.0)	0	2	85	19.6 (48.6)
8	Me_2SiCl_2 (20)–DMF (20)	C_2H_5CN (2.0)	20	24	52	64.3 (82.7)
9[e]	$TiCl_4$ (20)–BINOL (20)	CH_2Cl_2 (2.5)	20	20	62	57.8 (64.1)
10	$TiCl_2$(*i*-PrO)$_2$ (20)–BINOL (20)	CH_2Cl_2 (2.5)	20	20	84	65.5 (69.5)
11	Ti(*i*-PrO)$_4$ (10)–BINOL (20)	CH_2Cl_2 (1.25)	20	20	66	74.4 (74.8)
12	$Sc(OTf)_2$ (5)–H_2O (150)	CH_2Cl_2 (2.5)	20	20	75	73.5 (74.8)
13	$Sc(OTf)_2$ (5)	CH_2Cl_2 (2.5)	20	20	90	42.8 (78.8)

[a] All reactions were performed with (*R*)-**3b** (0.5 mmol) in the presence of 3-phenylpropanal (**2a**, 10 mol%) and an acid-catalyst unless otherwise noted. [b] After isolation by column chromatography on silica gel. [c] Determined by HPLC (Chiralcell OD). Optical purities of the starting (*R*)-**3b** are shown in parentheses. [d] In the absence of 3-phenylpropanal. [e] In the presence of molecular sieves (4 Å, 500 mg).

In conclusion, attention should be given to an acid-catalyzed asymmetric allylation, because it will compete with the racemization of the product via an allyl-transfer reaction from the product to aldehyde. Subsequently, asymmetric allylations by an allyl-transfer reaction from a chiral allyl-donor will not be as easy as the crotylation.[5]

Acknowledgement

This work was financially supported by the Japan Securities Scholarship Foundation, and a Grant in Aid for Scientific Research from the Ministry of Education, Science, Culture, and Sports, Japan (No. 12450357).

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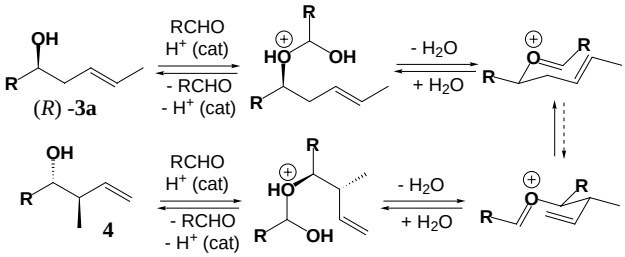
(4) Loh et al. also observed an allyl-transfer reaction in the absence of aldehyde in their indium-promoted allyl-transfer reaction: Loh, T.-P.; Tan, K.-T.; Hu, Q.-Y. *Tetrahedron Lett.* **2001**, *42*, 8705.
(5) Homocrotyl alcohol **3a** will be much more stable than homoallyl alcohol **4**, because **3a** has a thermodynamically more stable internal olefin and sterically less hindered structure. For example, we observed no racemization of **3a** (Scheme 5) after treatment with 3-phenylpropanal (**2a**, 10 mol%) in the presence of TSA·H_2O (10 mol%) at 20 °C for 20 h (recovery: 92%).



Scheme 5