The First and Highly Enantioselective Crotylation of Aldehydes via an Allyl-Transfer Reaction from a Chiral Crotyl-Donor

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The enantioselective allylation of aldehydes is one of the most popular reactions for constructing homoallylic alcohols with a chiral center by C−C bond formation.[1] This is because the reaction gives a high enantio excess of homoallylic alcohols, which provide more functionalized building blocks after functionalizations of the double bond of the introduced allylic unit.

Many methods to prepare highly optically active homoallyl(ic) alcohols have been proposed that utilize more than the stoichiometric amount of allyl(ic) metal compounds *in the presence of a chiral catalyst,*[1,2] or *together with more than the stoichiometric amount of chiral auxiliaries*.[1,3] However, in these asymmetric allylations, a number of problems remain. For example, in the case of catalytic reactions, (1) Preparation of an effective catalyst and/or an efficient catalysis system is not easy; (2) In many cases, more than the stoichiometric amount of allyl(ic)tributyltin[1,2a−d] is required as an allyl-donor (in particular, tributyltin residues are environmentally unfriendly), although attempts to use allyl(ic)silanes[1,2e−h] have been made; (3) The reaction mechanism is not clear in most of the catalytic enantioselective reactions; (4) The degree of enantioselectivity greatly depends on the substituents of the aldehydic carbon (low substrate tolerance); (5) Many of the 'catalytic' reactions require more than catalytic amount of chiral ligands (or additives); (6) The reactions usually have to be performed under precisely controlled reaction conditions.

Moreover, in the case of noncatalytic reactions,[1,3] (7) the preparation of an effective chiral auxiliary, which plays an important role together with allyl(ic) metals in determining the enantioselectivity, requires at least a few steps from naturally occurring optically pure compounds. The exceptions are (+)-, (−)-dialkyl tartrate in Roush's reagents and (+)-, (−)-α-pinene or (+)-carene in Brown's reagents,[1c,d] which can be effectively used as chiral auxiliaries as they are. In addition, (8) almost all of the allylation reactions, including the cases using a (3-substituted)allylmetal reagent, proceed with allylic transposition and give a (1-substituted)allyl product (e.g. 1-methylallyl adduct).[4] No asymmetric (3-substituted)allylation reactions such as crotylation reaction to aldehydic carbonyl have been reported.[5]

These facts prompted us to investigate an asymmetric crotylation reaction, which is very convenient to use, has a low cost, and does not require difficult techiques.

Recently, we discovered[6] a new crotylation reaction of aldehyde **2** via an acid-catalyzed allyl-transfer reaction from the 2-methylated-homoallylic alcohol (e.g., 2,3-dimethylpent-4-en-2-ol **1a**) to give the corresponding crotylated product **3**, specifically.[6a] It has been proposed that the reaction proceeds via the most stable comformational six-membered cyclic transition state ($\mathbf{T_{1-2}}$) to give an *E*-olefin selectively, while maintaining the optical purity (>98% ee).[6b] The reaction is shown in Scheme 1.

This result strongly suggested that we would be able to provide the first efficient enantioselective crotylation reaction, if we could conveniently prepare an enantiomerically or diasteromerically pure crotyl-donor.

We thus examined (1-methyl)allylation of (−)-menthone **4**,[7] derived from the artificial (−)-menthol (>99% purity),[8] by a Grignard reaction with (*E*)-crotylmagnesium chloride to give **5a** in a sterically pure form after separation of the diastereoisomeric mixture in good isolated yield (77%).[9] The major product (*R*)-**5a** (assignment by analogy) was then used as a crotyl-donor in an allyl-transfer reaction with 3-phenylpropanal in the presence of acid-catalyst. Surprisingly, we discovered that (5*E*,3*R*)-1-phenylhept-5-en-3-ol **3a**[6b] was obtained in good yield with very high e.e., as shown in Scheme 2[10] (Table 1), when *p*-toluenesulfonic acid monohydrate (TSA·H_2O) served as an effective catalyst.[6]

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(7) Commercially available (−)-menthone (90% purity, containing ca. 5% of isomenthone) was unsuitable for our purpose, because it reacted with crotylmagnesium chloride to give a mixture of inseparable stereoisomers of the crotyl-donors (**5**), which gave **3a** in 90−95% ee.

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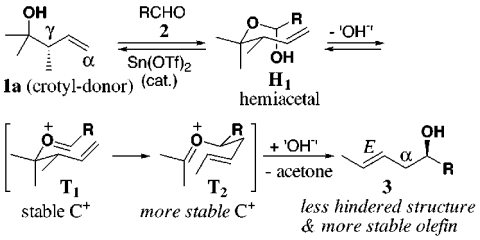
Scheme 1. Crotylation of Aldehydes via Allyl-Transfer Reaction from Crotyl-Donor **1a** to Aldehydes 2



Scheme 2. Asymmetric Crotylation of Aldehyde **2a**

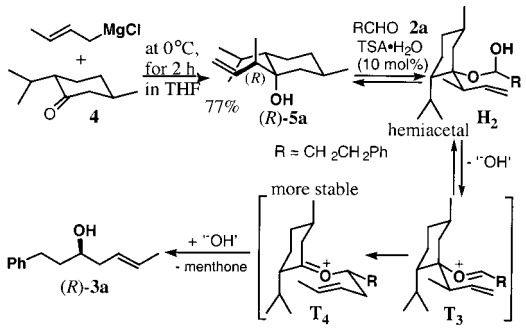


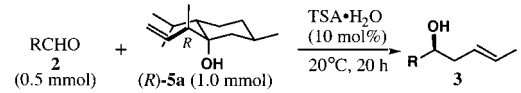
Table 1. Reaction of (*R*)-**5a** with 3-phenylpropanal (**2a**)[a]

run	(*R*)−**5a**/mmol (equiv. to **2a**)	catalyst[b] (equiv. to **2a**)	**3a** yield[c]/%	%ee[d]	recovery of (*R*)-**5a**/%[e]
1	0.5 (1)	TSA·H_2O (0.1)	62	>99	39 (14)
2	1.0 (2)	TSA·H_2O (0.1)	83	>99	55
3[f]	1.0 (2)	TSA·H_2O (0.1)	53	>99	56 (40)
4	0.5 (0.5)	TSA·H_2O (0.1)	67[g]	>99	16 (39)
5[h]	1.0 (2)	TSA·H_2O (0.1)	71	>99	
6[i]	1.0 (2)	*N*-HOBSA (1.0)	34	>99	39
7	1.0 (2)	BSA (0.1)	82	>99	45
8	1.0 (2)	CSA (0.8)	83	>99	49
9	1.0 (2)	$Sn(OTf)_2$ (0.4)	39	97	53
10	1.0 (2)	$Sn(OTf)_2$ (0.4)[j]	31	97	70 (10)

[a] The reaction was performed in CH_2Cl_2 (5 mL), at 20 °C, for 20 h unless otherwise noted. [b] Camphorsulfonic acid (CSA), *N*-hydroxybenzenesulfonamide (*N*-HOBSA), *p*-toluenesulfonic acid monohydrate (TSA·H_2O), benzenesulfonic acid (BSA). [c] Isolated yield based on **2a**, except run 4. [d] Determined by HPLC analysis (CHIRALCEL OD, 5% PriOH in hexane as eluent. [e] Recovery of **2a** was shown in parentheses (%). [f] Performed at 0 °C. [g] Isolated yield based on (R)-**5a**. [h] In the presence of H_2O (0.5 mmol). [i] Performed in $(CH_2Cl)_2$ (5 mL) at 65 °C. [j] In the presence of MS4 Å (25 mg).

It is noteworthy that the degree of asymmetric induction (% e.e.) was constantly very high throughout the investigation, and the highest yield was recorded when TSA·H_2O was used as a catalyst. The handling of this reaction was quite easy. That is, to a solution of (*R*)-**5a** and 3-phenylpropanal (**2a**) in dichloromethane was added TSA·H_2O (10 mol %) at 20 °C and the reaction mixture was gently stirred for 20 h under nitrogen. An excess amount (2 equiv to aldehyde) of (*R*)-**5a** was required to give **3a** in good (83%) yield. The unreacted (*R*)-**5a**, however, could be recovered in a pure form and was used again for the same reaction. A small quantity of water (e.g. 1 equiv to aldehyde) did not prevent the reaction, and only slightly reduced the yield (entry 5). Moreover, we surprisingly found that the crude (*R*)-**5a** (71% de) gave (5*E*,3*R*)-**3a** in satisfactory yield with 97% ee.[11] On the other hand, (5*E*,3*S*)-**3a** was obtained in 88% yield with >99% e.e. from the enantiomer of (*R*)-**5a**, derived from (+)-menthol.

Table 2. Reaction of (R)-**5a** with Various Aldehydes[a]



entry	**2**	R	**3**	yield[b] (%)	%ee(config.)[c]
1[d]	**b**	Ph	**b**	48	>99[e] (*S*)
2	**c**	$BnO(CH_2)_5$	**c**	75	>99[e] (*R*)
3	**d**	$PhCH(CH_3)$	**d**	64	>99[e] (*S*)
4	**e**	$PhS(CH_2)_2$	**e**	78	>99[e] (*S*)
5	**f**	$(CH_3CH_2)_2CH$	**f**	71	>99[f] (*S*)
6	**g**	$CH_2{=}CH(CH_2)_8$	**g**	71	>99[f] (*R*)
7	**h**	citroneral	**h**	0	−
8	**i**	$CH_3(CH_2)_4CH{=}CH$	**i**	0	−

[a] All the reactions were performed with (*R*)-**5a** (1.0 mmol) and **2** (0.5 mmol) in the presence of 10 mol % of TSA·H_2O in CH_2Cl_2 (5 mL), at 20 °C for 20 h unless otherwise noted. [b] Isolated yield based on the aldehyde. [c] Assignment by analogy based on the configuration of **3a**. [d] Performed in 2.5 mL of CH_2Cl_2. [e] Determined by HPLC analysis (CHIRALCEL OD, 5% *i*-PrOH in hexane as eluent). [f] Determined by HPLC analysis (CHIRALCEL AD, 5% *i*-PrOH in hexane as eluent) of the corresponding MTPA ester derived from (+)-MTPA.

The reaction with various aldehydes also gave the corresponding crotyl products in good yield and in high e.e. with a few exceptions, as shown in Table 2. Citoronellal was fast converted to 2-isopropylidene-5-methylcyclohexanol, isopuregol, via acid-catalyzed cyclization (entry 7). α,β-Unsaturated aldehyde did not react with the crotyl-donor **5a** (or with **1a**) (entry 8). In the case of R is R′-CH=CH in RCHO, we assume that the oxonium ion T_3 (T_1) is too stable to give T_4 (T_2). This is because the cation, T_3 (T_1) will be highly stabilized by a conjugation with the neighboring π-bond.

Finally, we attempted to apply this concept to an asymmetric allylation of aldehydes. Optically pure 1-allylmenthol (**6a**, >99% ee, 1 mmol) was treated with 3-phenylpropanal (**2a**, 0.5 mmol) for 2, 5, 10, and 15 h, in the presence of TSA·H_2O (10 mol %) in CH_2Cl_2 (5 mL) at 20 °C. We obtained (*R*)-1-phenylhex-5-en-1-ol (**7**) in 50% (78% e.e.), 60% (71% e.e.), 68% (70% e.e.), and 72% (68% e.e.) chemical and optical yields, respectively. This means that the asymmetric allylation by an allyl-transfer reaction is not as easy as the asymmetric crotylation.[12]

We believe that the allyl-transfer reported here is the first and highly enantioselective crotylation of aldehydes, and introduces the following advantages. Both of the enantiomers of the chiral crotyl-donors are very easily obtained by the Grignard reaction with (−)- or (+)-menthones derived from the corresponding menthols. The reagents are very easy to handle, and are environmentally friendly.

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Supporting Information Available: Experimental procedures and complete characterization (^1H and ^{13}C NMR, IR, and mass spectra) for compounds, **3b**−**g**, **4**, **5a**−**b**, and **6a**, the stereochemistry of (*R*)-**5a**, the racemization of (*R*)-**7**, and some additional references. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) A referee suggested an alternative explanation involving acyclic transition states. However, the methyl ether of (*R*)-**5a** was quantitatively recovered after treatment of the ether with **2a** at 20 °C for 24 h in CH_2Cl_2 in the presence of 10 mol % of TSA·H_2O. This shows that the formation of hemiacetal ($\mathbf{H_2}$) and the sequential six membered cyclic transition state ($\mathbf{T_{3-4}}$) is essential for this allyl-transfer reaction.

(11) In addition to (*R*)-**5a**, the crude product contained the diastereoisomer (*S*)-**5a** and 1-crotylmenthol. We are assuming that (*R*)-**5a** will be more reactive with aldehyde than the isomer(s).

(12) This means that (*R*)-**7** served as an allyl-donor under the reaction conditions to give racemic **7** by an allyl-transfer reaction of the allyl-unit of (*R*)-**7** into **2a** via the six-membered chair-form transition state. This is discussed in the Supporting Information.