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A Novel Enantioselective (2*Z*)-Alk-2-enylation of Aldehydes via an Allyl-Transfer Reaction from Chiral Allyl Donors Prepared from (+)-Isomenthone

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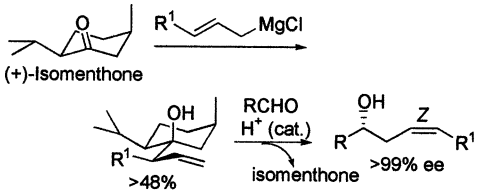
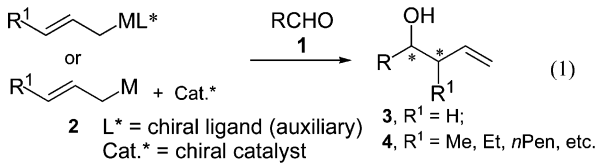
ABSTRACT



A highly enantioselective (2*Z*)-alk-2-enylation of aldehydes was successfully achieved by an allyl-transfer reaction from a chiral allyl donor, which was easily obtained by separation of a diastereomeric mixture of the corresponding homoallylic alcohol γ-adducts derived from (+)-isomenthone with alk-2-enylmagnesium chloride.

Asymmetric allylation of aldehydes (**1**, RCHO) is one of the most useful carbon−carbon bond formation reactions in organic synthesis because of the high and reactive functionality and high stereoselectivity.[1] For example, highly optically active homoallylic alcohols **3** [RC*H(OH)CH_2CH=CH_2] have been prepared by using allylic organometallic reagents **2** (CH_2=$CHCH_2$M; M = metal) with a stoichiometric amount of a chiral auxiliary[2] or a catalytic amount of a chiral promoter.[3] Furthermore, allylation reactions with γ-substituted organometallic reagent **2** (RCH=$CHCH_2$M; R = alkyl), in the presence of a chiral auxiliary or catalyst, afford the γ-adduct **4** diastereo- and enantioselectively.[4] This C−C bond formation reaction is particularly useful for the construction of vicinal stereogenic centers in a flexible hydrocarbon chain [eq 1].



Recently, we discovered an efficient stereoselective alk-2-enylation reaction of aldehydes to give the α-adduct **5**, in which no allyl(ic) metal nucleophiles are required and a homoallylic alcohol **6** served as an allyl donor in the presence of an acid catalyst. To understand this unusual allylation reaction, we proposed a reaction mechanism via a 2-oxonium [3,3]-sigmatropic rearrangement with a six-membered chair-like transition state (**TS-1**) as shown in Scheme 1, which we termed an "allyl-transfer reaction." [5a]

We succeeded in employing the allyl-transfer reaction to highly enantioselective (*E*)-alk-2-enylation of aldehydes to give optically pure (*E*)-α-adducts of homoallylic alcohols (*E*)-**7** using optically pure menthone as a chiral auxiliary.[5d,f] In this reaction, chiral allyl-donors **8** (γ-adducts of homoallylic alcohols) were prepared by reaction of alk-2-enylme-

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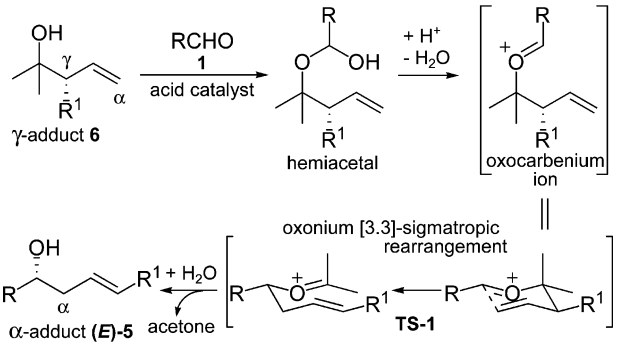
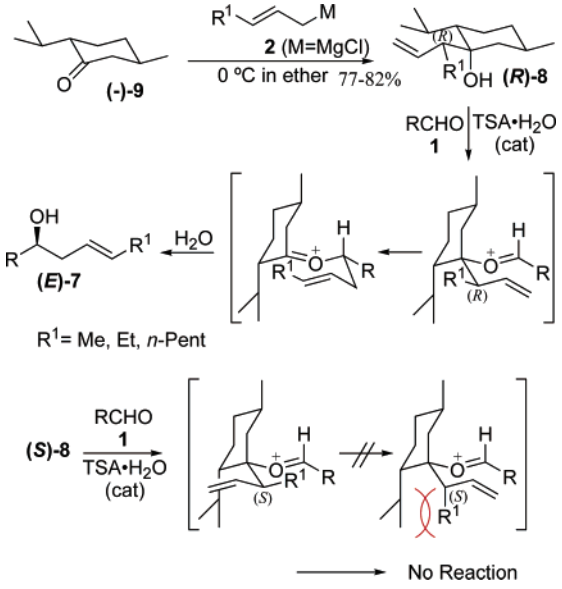
Scheme 1. Stereospecific Allyl-Transfer Reaction from γ-Adduct **6** to Aldehyde **1** to Give α-Adduct **(*E*)-5**



tallic reagents **2** (R ≠ H; M = MgCl, ZnBr, Ti(O*i*Pr)$_3$) with optically pure (−)- or (+)-menthone **9**, in which the desired chiral allyl donors (*R*)-**8** (assignment by analogy) were selectively obtained in 77−82% yield after column chromatography on silica gel. The minor product (*S*)-**8** did not react with aldehyde at all (Scheme 2).

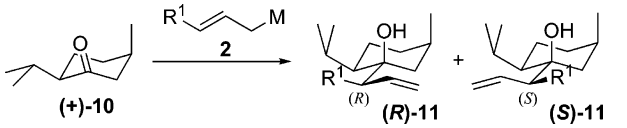
Scheme 2. Allyl-Transfer Reaction from **(*R*)-8** to Give **(*E*,*R*)-7**



In this paper, to extend the applicability of this asymmetric allyl-transfer reaction further, we used (+)-isomenthone **10** derived from inexpensive (+)-(1*S*,2*R*,5*R*)-isomethol (>99% ee) as a chiral auxiliary. Reaction of (+)-isomenthone **10** with alk-2-enylmetallic reagents **2** did not give a γ-adduct selectively, but gave an easily separable diastereomeric mixture of the corresponding γ-adducts **11** in good yield as shown in Table 1.

Surprisingly, we discovered that one of the isolated isomers served as an allyl donor for the (*Z*)-alk-2-enylation to give only the (*Z*)-olefin of the corresponding α-adduct (*Z*)-**5**, and the other isomer gave the corresponding (*E*)-olefin,

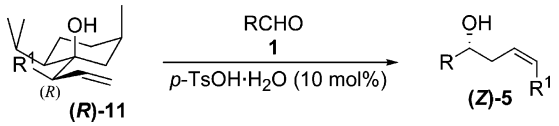
Table 1. Preparation of Allyl Donor **11** from (+)-Isomenthone[a]



			11 yield/%[b] (R_f value)[c]		
entry	R^1		**(*R*)-11**	**(*S*)-11**	*R*/*S*
1	Me	**b**	61 (0.41)	35 (0.51)	64/36
2	Et	**c**	52 (0.49)	40 (0.59)	56/44
3	*n*-Pent	**d**	48 (0.54)	47 (0.63)	51/49

[a] Reactions were performed with (+)-isomenthone (10 mmol) and alk-2-enylmagnesium chloride, derived from magnesium (15 mmol) and 1-chloroalk-2-ene (15 mmol), in THF at 0 °C for 2 h. [b] Isolated yield. [c] R_f value on TLC (Merk silica gel 60 F254, aluminum sheet) using a mixed solvent (hexane/ether = 10/1) as the eluent.

Table 2. Allyl-Transfer Reaction from **(*R*)-11** to Give Homoallylic Alcohol α-Adduct **(*Z*)-5**[a]

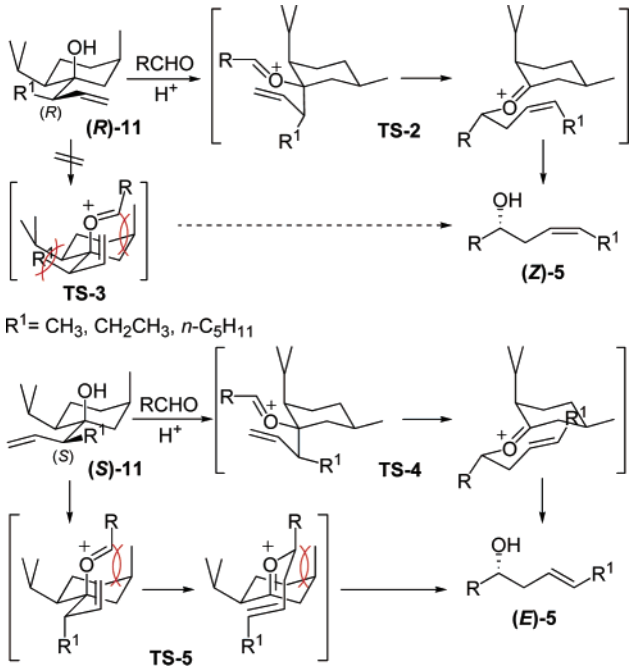


	(*R*)-11		RCHO **1**		**(*Z*)-5**	
entry	R^1	mol equiv	R		yield, %[b,c]	
1	**b** CH_3	1.0	**u**	$PhCH_2CH_2$	**5bu**	69 (>99)
2	**b** CH_3	2.0	**u**	$PhCH_2CH_2$	**5bu**	88 (>99)
3[d]	**b** CH_3	2.0	**v**	Ph	**5bv**	68 (>99)
4	**b** CH_3	2.0	**w**	$BnO(CH_2)_5$	**5bw**	88 (>99)
5	**b** CH_3	2.0	**x**	$PhSCH_2CH_2$	**5bx**	90 (>99)[e]
6	**c** C_2H_5	1.0	**u**	$PhCH_2CH_2$	**5cu**	88 (>99)
7	**c** C_2H_5	2.0	**u**	$PhCH_2CH_2$	**5cu**	92 (>99)
8[d]	**c** C_2H_5	2.0	**v**	Ph	**5cv**	74 (>99)
9	**c** C_2H_5	1.0	**w**	$BnO(CH_2)_5$	**5cw**	77 (>99)
10	**c** C_2H_5	1.5	**w**	$BnO(CH_2)_5$	**5cw**	90 (>99)
11	**c** C_2H_5	1.0	**x**	$PhSCH_2CH_2$	**5cx**	77 (>99)[e]
12	**c** C_2H_5	1.5	**x**	$PhSCH_2CH_2$	**5cx**	88 (>99)[e]
13	**d** n-C_5H_{11}	1.0	**u**	$PhCH_2CH_2$	**5du**	89 (>99)
14[d]	**d** n-C_5H_{11}	2.0	**v**	Ph	**5dv**	78 (>99)
15	**d** n-C_5H_{11}	1.0	**w**	$BnO(CH_2)_5$	**5dw**	90 (>99)
16	**d** n-C_5H_{11}	1.0	**x**	$PhSCH_2CH_2$	**5dx**	93 (>99)[e]

[a] Reactions were performed with allyl donor **11**, 1 mmol (2.0 equiv), 0.75 mmol (1.5 equiv), or 0.5 mmol (1.0 equiv), aldehyde (0.5 mmol), and *p*-TsOH·H_2O (10 mol % to aldehyde) in CH_2Cl_2 (1 mL), at 20 °C for 20 h, unless otherwise noted. [b] Isolated yield. [c] Values in parentheses show % ee of the product, determined by HPLC analysis (CHIRALCEL OD, 5% ^{i}PrOH in hexane as the eluent) unless otherwise noted. >99 means that no signal of the corresponding enantiomer was observed. [d] *p*-TsOH·H_2O (40 mol %) was used. [e] Determined by HPLC analysis (CHIRALCEL OJ, 2% ^{i}PrOH in hexane as the eluent).

(*E*)-**5**. We believe that the former is the first, direct, and enantioselective (*Z*)-alk-2-enylation reaction of an aldehyde to give the corresponding enantiomerically pure (*Z*)-homoallylic alcohol. Here, we predict that (*R*)-**11** serves as the allyl donor, as shown in Scheme 3. The (*E*)-alk-2-enylation is similar to an allyl-transfer reaction derived from (2*R*,5*R*)-

Scheme 3. Configuration of **11** (Assignment by Analogy) which Gives **(*Z*)-5** via Allyl-Transfer Reaction



(+)-menthone having the 5-epi configuration of (2*R*,5*S*)-(+)-isomenthone. From this, it is very reasonable to assume that (*S*)-**11** will give (*E*)-**5**.

Note that if the methyl substituent takes an equatorial configuration in a transition state such as **TS-2**, the isopropyl substituent has to be an axial conformation. In this case, there is a strong steric hindrance preventing the transition state **TS-3**, due to both the methyl and isopropyl substituents on the isomenthane ring. Therefore, the formation of (*Z*)-**5** via transition state **TS-2** is the most reasonable route. The formation of (*E*)-**5** via both transition states **TS-4** and **TS-5** seems to be favorable.

In summary, an asymmetric alk-2-enylation reaction of aldehydes by a *p*-TsOH·H_2O catalyzed allyl-transfer reaction from (+)-isomenthone adducts as chiral allyl-donors gave (*E*)- and (*Z*)-homoallylic alcohol α-adducts, via a six-membered chairlike transition state, in good yield with >99% ee. This is the first example of an asymmetric (*Z*)-alk-2-enylation of aldehydes. The chiral allyl donors were conveniently prepared using an environmentally friendly Grignard reagent with easily available (+)-isomenthone. Therefore, there was no need to prepare an allylmetallic reagent such as allyltin by transmetalation with a Grignard reagent and so on. Finally, it is noteworthy that the conformational analysis of the six-membered chairlike transition state is

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useful to estimate the reactivity and stereochemistry of this reaction.

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Supporting Information Available: Experimental procedures and complete characterization (^{1}H and ^{13}C NMR, IR, and mass spectra or elemental analysis) for compounds **5** and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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