Allyl-Transfer Reactions

Highly Enantioselective Alk-2-enylation of Aldehydes through an Allyl-Transfer Reaction**

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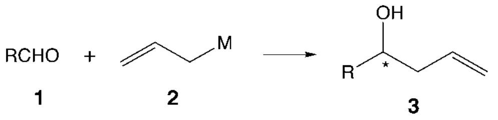
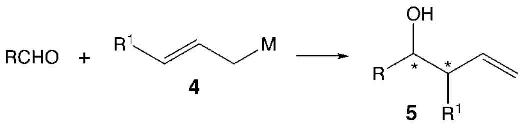
The enantioselective allylation of aldehydes to prepare optically pure homoallylic alcohols is one of the most attractive and popular methods for the construction of stereogenic centers [Eq. (1)].[1,2d] Not only can this type of reaction provide homoallylic alcohols with high enantiomeric purity, it can also provide modified chiral building blocks after suitable functionalization of the C–C double bond in the introduced allylic unit.



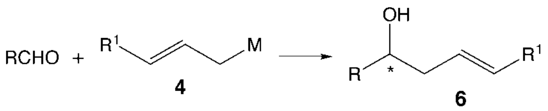
(1)

Highly enantiopure homoallylic alcohols have been prepared by using allylic organometallic reagents ($MCH_2CH{=}CH_2$; M = metal) and a stoichiometric amount of a chiral auxiliary[3] or a catalytic amount of a chiral promoter.[4] Furthermore, allylation reactions with γ-substituted organometallic reagents **4** in the presence of a chiral auxiliary or catalyst afford the γ adduct **5** diastereo- and enantioselectively.[5] This C–C-bond-formation reaction is particularly useful for the construction of vicinal stereogenic centers in a flexible hydrocarbon chain [Eq. (2)].



(2)

However, to the best of our knowledge, no asymmetric alk-2-enylation reaction (e.g. crotylation) of aldehydes to give 4-substituted homoallylic alcohols **6** (α adduct) has yet been reported [Eq. (3)]. This is because the allylation reactions by alk-2-enyl metal reagents **4** proceed, without exception, with allylic transposition via a six-membered cyclic transition state, affording exclusively the γ adduct **5**.[6]



(3)

Recently we discovered an efficient and stereoselective nucleophilic alk-2-enylation reaction of aldehydes that produces the desired α adduct **6**. In this procedure, no allylic metal nucleophiles are involved, and a homoallylic alcohol **7** acts as an allyl donor. This unusual allylation reaction appears to proceed through a 2-oxonium [3,3] sigmatropic rearrangement, as shown in Scheme 1.[2a] The acid-catalyzed reaction of aldehyde **1** with the homoallylic alcohol (γ adduct) **7** stereoselectively gave the homoallylic alcohol α adduct **6** by an allyl transfer from **7** via hemiacetal ($\mathbf{H}_1$) and oxonium cations $\mathbf{T}_1$ and $\mathbf{T}_2$.

More importantly, the $Sn(OTf)_2$-catalyzed (10 mol%) reaction of 3-phenylpropanal (**1a**) with optically pure allyl donor (3*R*,4*S*)-1-phenyl-4-methylhex-5-en-3-ol (**5a**; > 99% *ee*) gave (3*S*)-1-phenylhept-5-en-3-ol (**6a**) in 85% yield with > 98% *ee* (Scheme 2).[2b,c]

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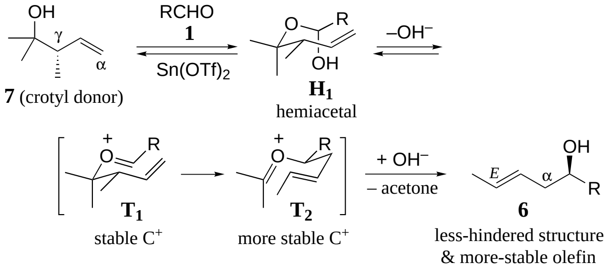
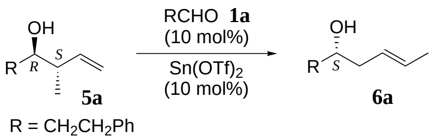
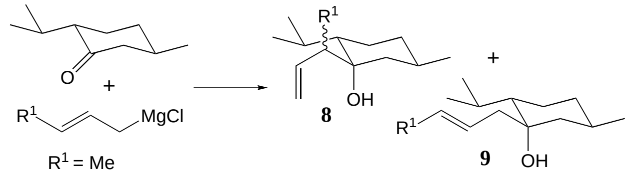


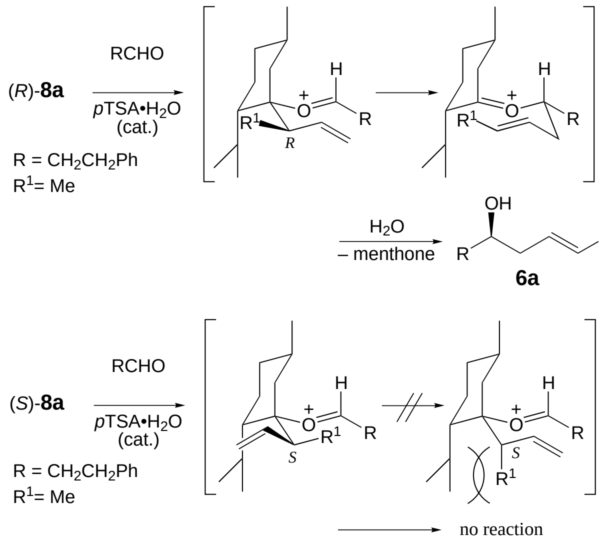
Scheme 1. Crotylation of aldehydes by an allyl-transfer reaction from crotyl donor **7** to aldehyde **1**.



Scheme 2. Conversion of a γ adduct into the α adduct through an allyl-transfer reaction.



Scheme 3. Stereoselctive reaction of (−)-menthone with alk-2-enylmagnesium chloride.



Scheme 4. Stereospecific allyl-transfer reaction from (*R*)-**8a** to aldehyde **1a**.

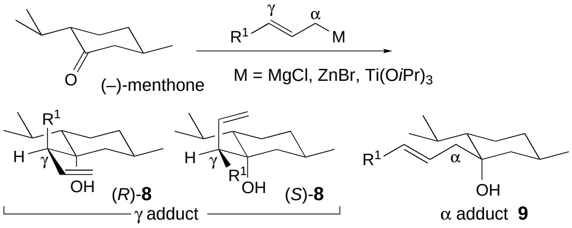
This result suggested that more broadly applicable chiral alk-2-enyl donors could be prepared from cheap and readily available optically pure ketones such as (−)- or (+)-menthone. Thus, reaction of (*E*)-but-2-enylmagnesium chloride **4a** (R^1 = Me) with (2*S*,5*R*)-(−)-menthone gave a mixture of 1-substituted menthols in good yield. Based on the reported stereochemistry of the addition of Grignard reagents to menthone,[7,8] the major product, isolated in 70–77 %, was determined to be one of the diastereomers of axial alcohols (*R*)- or (*S*)-**8a** (Scheme 3).

Both the diastereomers of **8a** were readily separated and independently used as crotyl donors in the allyl-transfer reaction with 3-phenylpropanal **1a** in the presence of *p*-toluenesulfonic acid monohydrate (*p*TSA·H_2O) as the catalyst. Remarkably, whilst the major isomer gave (5*E*,3*R*)-1-phenylhept-5-en-3-ol **6a** in good yield with > 99 % *ee*, the minor isomer did not react at all. Therefore, the configuration of the major isomer could be assigned as (*R*)-**8a** as shown in Scheme 4.[2d]

To investigate this asymmetric allylation further, we prepared other chiral alk-2-enyl-donors, from (−)-menthone[9] as shown in Table 1. These chiral alk-2-enyl-donors have substituents R^1 (R^1 = Et, *n*Pent, $(CH_2)_3Cl$, CH=CH_2 in **8** in place of the methyl substituent (R^1 = Me) in crotyl donor **8a**.

In all cases, the addition of the allylic metal reagent to the carbonyl of (−)-menthone involved an equatorial attack (favoring the carbonyl face *trans* to the isopropyl group) to give the corresponding homoallylic alcohol γ adducts **8b–e** selectively. Moreover, stereochemically pure **8b–d** were readily isolated in good yields by chromatography on silica gel. The structures of the minor by-products were assigned as the corresponding

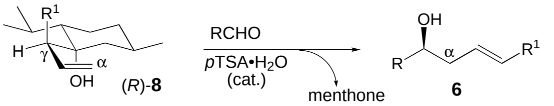
Table 1: Preparation of chiral allyl donors **8** from (−)-menthone.



Entry	Allylic nucleophile			*T* [°C]		Yield [%][a]		
	R^1	M	[equiv]			(*R*)-**8**	(*S*)-**8**	**9**
1[b]	Et	MgCl	1.5	0	**b**	79	11	trace
2[b]	*n*Pent	MgCl	1.5	0	**c**	82	11	1.3
3[c]	$Cl(CH_2)_3$	ZnBr	2.0	0	**d**	66	0	21
4[d]	CH_2=CH	Ti(O*i*Pr)$_3$	2.0	−78	**e**	70[e]		5.0

[a] Yield of isolated product. [b] The reaction was performed with (−)-menthone (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. [c] The reaction was performed with (−)-menthone (0.5 mmol) and 1-bromo-6-chlorooct-2-ene (1 mmol), Zn (1 mmol), NH_4Ac (1 mmol), in THF (2 mL) at 0 °C for 4 h. [d] The reaction was performed with (−)-menthone (5 mmol) and pentadienyltitanium reagent (derived from KO*t*Bu (10 mmol), *n*BuLi (10 mmol), penta-1,3-diene (15 mmol), and ClTi(O*i*Pr)$_3$ (10 mol) in hexane) in THF at −78 °C. [e] The allylic carbon atom is not stereogenic.

Table 2: Homoallylic alcohol α adducts **6** by allyl-transfer reaction from allyl-donors **8**.[a]



Entry		Allyl donor 8		Aldehyde		Product 6[b]	
		R^1	[equiv]	R		Yield [%][c]	*ee* [%][d]
1	**a**	Me	2	$Ph(CH_2)_2$	**a**	83 (70)	> 99 (97.0)
2	**a**	Me	1	$Ph(CH_2)_2$	**a**	75	> 99
3	**b**	Et	1	$Ph(CH_2)_2$	**b**	85	> 99
4	**b**	Et	2	Ph	**c**	61	> 99
5	**b**	Et	1	$BnO(CH_2)_5$	**d**	88	> 99
6	**b**	Et	2	PhCHMe	**e**	68	> 99
7	**b**	Et	1	$PhS(CH_2)_2$	**f**	90	> 99
8	**b**	Et	2	Et_2CH	**g**	71	> 99[e]
9	**b**	Et	1	$CH_2{=}CH(CH_2)_8$	**h**	75	> 99[e]
10	**c**	*n*Pent	1	$Ph(CH_2)_2$	**i**	92 (89)	> 99 (99.2)
11	**c**	*n*Pent	2	Ph	**j**	72	99.4
12	**c**	*n*Pent	1	$BnO(CH_2)_5$	**k**	93	> 99
13	**c**	*n*Pent	1	$PhS(CH_2)_2$	**L**	88	> 99
14	**d**	$Cl(CH_2)_3$	1	$Ph(CH_2)_2$	**m**	92	> 99
15	**d**	$Cl(CH_2)_3$	1	$BnO(CH_2)_5$	**n**	96	> 99
16	**d**	$Cl(CH_2)_3$	1	$PhS(CH_2)_2$	**o**	95	> 99
17	**e**	$CH_2{=}CH$	2	$Ph(CH_2)_2$	**p**	83	> 99
18	**e**	$CH_2{=}CH$	2	$BnO(CH_2)_5$	**q**	83	> 99
19	**e**	$CH_2{=}CH$	2	$PhS(CH_2)_2$	**r**	63	> 99

[a] The reactions were performed with allyl donor **8**, (1 mmol, 2 equiv or 0.5 mmol, 1 equiv), aldehyde (0.5 mmol), and *p*TSA·H_2O (10 mol%) in CH_2Cl_2 (1 mL), at 20 °C for 20 h, unless otherwise noted. [b] Yield and *ee* value of the corresponding product derived from the crude **8** are shown in parentheses. [c] Yield of isolated product. [d] Determined by HPLC analysis (CHIRALCEL OD, *i*PrOH (5%) in hexane as eluent) unless otherwise noted. > 99 means that no signal of the corresponding enantiomer. [e] Determined by HPLC analysis (CHIRALPAK AD, *i*PrOH (5%) in hexane as eluent) of the corresponding MTPA ester derived from (+)-MTPA. MTPA = α-methoxy-α-(trifluoromethyl)benzeneacetyl chloride.

diastereoisomer (*S*)-**8** and α-adducts (−)-menthol derivative **9**. A trace of a γ adduct formed by axial attack of (−)-menthone could also be detected.

Asymmetric 2-alkenylation of aldehydes by the allyl transfer reaction from these chiral allyl donors **8b–e** was successfully carried out using *p*TSA·H_2O as the catalyst. In all cases, the desired, optically pure α adducts were obtained in excellent yields.[2d] These results are summarized in Table 2.

Notably, allyl-transfer reactions using a crude mixture of **8** (containing all the other stereoisomers) and 3-phenylpropanal gave the desired product in good yield and with high *ee* values (Table 2, entries 1, 10). This result suggests that the major isomer is far more reactive than the other stereoisomers.

Finally, highly enantioselective 2,4-pentadienylation of aldehydes with **8e** were carried out (Table 2, entries 17–19).[10] Although the allylic carbon atom of **8e** is not stereogenic, only the *E* isomer of the final adduct is obtained. These results show that only one of the diastereotopic vinyl groups of **8e** is transferred. This observation reinforces even further our proposed transition state, implying the *R* absolute stereochemistry at the γ-stereogenic center of allyl-donors **8**.

In summary, we have discovered a novel asymmetric alk-2-enylation reaction, using (−)- and (+)-menthone as the chiral auxiliaries, which gives the homoallylic alcohols in a *p*TSA·H_2O-catalyzed allyl-transfer reaction in good yield and with > 99% *ee*. To the best of our knowledge, this is the first report of such an asymmetric alk-2-enylation of aldehydes.[3] The chiral allyl donors are conveniently prepared from simple alk-2-enyl metal reagents (e.g. Grignard reagents) and inexpensive (−)- and (+)-menthone. Finally, the absolute stereochemistry of the final adducts can be readily predicted from the conformational analysis of the six-membered-ring chair-like transition state depicted in Scheme 4.

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Keywords: alcohols · aldehydes · allylation · asymmetric synthesis · homogeneous catalysis

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