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Allylation of Aldehydes Promoted by the Cerium(III) Chloride Heptahydrate/Sodium Iodide System: the Dependence of Regio- and Stereocontrol on the Reaction Conditions

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Abstract: The cerium(III) chloride heptahydrate/sodium iodide complex ($CeCl_3 \cdot 7\,H_2O$/NaI) acts as a useful promoter in the carbon-carbon bond forming reaction by addition of allyltributylstannanes to aldehydes. The reaction of 2-butenyltributylstannane shows that the regio- and the stereochemical outcomes depend on the reaction conditions. When the promoter is adsorbed on a solid support (aluminum oxide), a highly prevalent formation of the γ-adduct is observed in solvent-free conditions. Conversely, when the reaction is carried out in acetonitrile as the solvent, the α-adduct largely prevails. In the last case, a complete stereocontrol is observed, the less stable (*Z*)-isomer being obtained in high geometrical purity.

Keywords: allylation; cerium; diastereoselectivity; Lewis acids; stannanes; synthetic methods

Introduction

The addition of allylic metal compounds to aldehydes to yield homoallylic alcohols[1] is a useful transformation in organic synthesis and consequently has received considerable attention in recent years.[2] For this purpose, allylstannanes have been extensively employed since these reagents offer an attractive combination of stability and high reactivity.[3] In widespread available methodologies, the reaction with γ-substituted allylstannanes generally proceeds with γ-regioselectivity.[4] Conversely, only few protocols for the regioselective synthesis of α-adducts have been reported, because almost all allylic metal derivatives react with aldehydes to give the γ-adducts exclusively. Therefore, much effort has been recently devoted to solve this problem. However, a complete α-regioselectivity can hardly be achieved since it varies depending on the nature not only of the allylic metal reagents, but also of aldehydes, promoters, and reaction conditions.[5] Appreciably high α-selective allylation is observed in the reaction of aldehydes with allylic barium,[6] and allylic cerium reagents.[7] However, these metal-mediated allylations are very difficult to handle because the reactions have to be performed under strictly anhydrous, oxygen-free, and low temperature conditions. In order to set up more practical procedures, efficient protocols based on the use of allylstannanes in the presence of appropriate additives have been developed. For example, cobalt(II) chloride[8] and tin(II) halides[9] promote the reaction of allylstannanes with aldehydes to give the prevalent formation of α-adducts. These methodologies allow the preferential insertion of the 2-butenyl group in the more stable (*E*)-structure. This is due to the combination of two factors: a) the 2-butenyltributylstannane is easily available in the (*E*)-configuration, or in a 75:25 mixture of (*E*)/(*Z*)-isomers respectively, owing to the high tendency of (*Z*)-compounds to isomerize to the more stable (*E*)-isomer; b) the transfer of an alkenyl moiety generally proceeds with retention of configuration at the Δ^2 position.[10] In conclusion, the synthesis of a (*Z*)-allyl alcohol is still an unsolved problem.[11]

During our program to develop new synthetic uses of the $CeCl_3 \cdot 7\,H_2O$/NaI[12] combination in promoting C–C bond formation,[13] we found that this system strongly facilitates the addition of allyltributylstannane to aldehydes in CH_3CN.[14] We report now that by this protocol a highly regio- and stereoselective addition of the 2-alkenyltributyltin derivative is accomplished surprisingly leading to the prevalent formation of the α-adduct in the less stable (*Z*)-configuration.

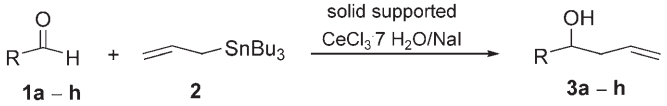
Furthermore, we report our studies on the same reaction carried out in solvent-free conditions in the presence of the promoter supported on neutral alumina.

The adoption of these different conditions gave completely different results, the almost exclusive formation of the γ-adduct having been observed.

Results and Discussion

Before analyzing the regio- and stereocontrol observed in the addition of crotyltributylstannane to aldehydes in various reaction conditions, we wish to report our investigations on the ability of the $CeCl_3 \cdot 7\ H_2O$/NaI system adsorbed on a solid support to promote the allylation of aldehydes by examining at first the reaction of aldehydes **1** with the simple allyltributylstannane **2** (Scheme 1).

Since several studies on the use of rare earth compounds supported on silica gel have been reported in the literature,[15] we tested our allylation reaction on a silica gel surface in solvent-free conditions.[16] Unfortunately, the reaction of benzaldehyde (**1a**) with allyltributylstannane **2** in the presence of $CeCl_3 \cdot 7\ H_2O$/NaI-SiO_2 does not work, only the unaffected **1a** being recovered even after prolonged reaction times. This is consistent with the well-documented[17] instability of allylstannanes under acidic conditions, owing to their high tendency to undergo protodestannylation. We thought to solve this problem by changing the inorganic material support. It is known, in fact, that alumina is a particularly interesting metal oxide widely used to carry out surface organic chemistry.[18] With this in mind, the $CeCl_3 \cdot 7\ H_2O$/NaI system was immobilized on neutral Al_2O_3[19] (Fluka, neutral, Brockman activity, grade 1, 150 mesh) and the activity of the resulting supported promoter was tested in the reaction of allyltributylstannane **2** with benzaldehyde (**1a**; Scheme 1).



Scheme 1.

We examined the influence of the reactants ratio and of the relative combination of the two promoter components on the reaction. We found that the best choice was a 1:1 ratio between **1a** and **2** in the presence of 1 equiv. of $CeCl_3 \cdot 7\ H_2O$ and 0.1 equiv. of NaI on Al_2O_3 (1 g/mmol aldehyde).

The reaction temperature is also important. In fact, the process is sluggish at room temperature, with low conversion yields (40%) being obtained after 3 days. It was necessary to increase the temperature to 50 °C to have the reaction completed in acceptable times (24 h). A further increase in the temperature produced an increase of undesired side products.[20] This procedure proved to be general and could be applied to a broad range of aldehydes (see Table 1). Good results were in fact obtained with aromatic, aliphatic and heterocyclic aldehydes.[21]

Also an acid-sensitive aldehyde such as furfural (**1i**) is converted into the corresponding homoallylic alcohol in good yield using this procedure (Table 1, entry 9). It is noteworthy that cinnamaldehyde (**1h**) undergoes regioselective 1,2-addition exclusively.

As expected, the reactivity of aryl aldehydes is strongly dependent on the nature of the substituents on the aromatic ring. Electron-withdrawing groups (Table 1, entries 4 and 5) accelerate the addition process, while electron-donating ones show a strong deactivating effect (Table 1, entries 2 and 3). For these reasons, the allylation of 4-methoxybenzaldehyde (**1c**) is effected in very low yields since in this case side processes become competitive.

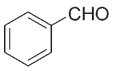
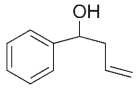
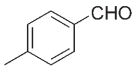
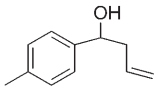
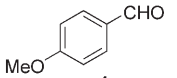
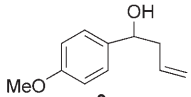
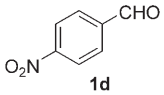
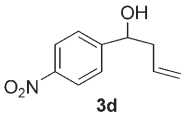
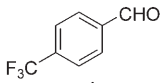
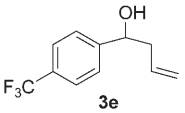
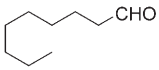
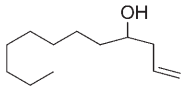
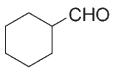
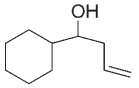
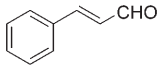
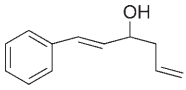
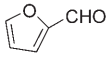
The presence of NaI and the use of the promoter supported on Al_2O_3 are essential for the efficiency of the process. In fact, in the absence of NaI or in the presence of unsupported $CeCl_3 \cdot 7\ H_2O$/NaI system in solvent-free conditions the process becomes very sluggish and side processes largely prevail. Very likely, Al_2O_3 acts as a carrier to increase the surface area available for the heterogeneous reaction, and cerium salt interacts with oxygen atoms at the surface of the support, forming new active sites on the alumina local structure. The water also plays an important role in this allylation reaction. In fact, the reaction works only in the presence of hydrated $CeCl_3$, while with dry $CeCl_3$ no allylation product is detected. However, it is still not clear how water molecules participate in the reaction.[22]

We wish to outline that the present methodology represents a very useful improvement with respect to the process carried out in CH_3CN, because it provides a more practical work-up procedure[20] (see Experimental Section). Moreover, we found that the activity of the catalyst supported on Al_2O_3 is not weakened by absorption of moisture from the air, and the catalyst can be stored for long periods without any appreciable loss of activity.

Regio- and Stereoselective Control in the Reaction with Crotyltributylstannane (4)

The reaction of benzaldehyde (**1a**) with 1 equiv. of a 85:15 mixture of (*E*)- and (*Z*)-2-butenyltributylstannane (**4**)[23] in the presence of $CeCl_3 \cdot 7\ H_2O$/NaI combination supported on Al_2O_3 at 50 °C (Method A) leads to the exclusive formation of the γ-adduct **6a**, (Table 2, entry 1). The high preference towards the γ-adduct is confirmed by the reaction of **4** with other aldehydes, (Table 2, entries 3, 5, 8, 12 and 13). However, the regiocontrol was strongly affected by the reactivity of the substrate. In fact, with highly reactive aldehydes, such as **1a**, **1e** and **1h** (Table 2, entries 1, 8 and 12), only the for-

Table 1. Allylation reaction of aldehydes promoted by $CeCl_3 \cdot 7\,H_2O$/NaI system supported on Al_2O_3 at 50 °C.[a]

Entry	Aldehyde[b]	Time [h]	Product[c]	Yield [%][d]
1	 **1a**	24	 **3a**	85
2	 **1b**	48	 **3b**	81
3	 **1c**	48	 **3c**	12[e]
4	 **1d**	15	 **3d**	79
5	 **1e**	17	 **3e**	91
6	 **1f**	18	 **3f**	85
7	 **1g**	17	 **3g**	86
8	 **1h**	20	 **3h**	78
9	 **1i**	18	 **3i**	81

[a] Reactions performed at 50 °C in the presence of 1.0 equiv. of $CeCl_3 \cdot 7\,H_2O$ and 0.1 equiv. of NaI supported on neutral alumina (1.00 g/mmol aldehyde **1**).
[b] All starting aldehydes were commercially available.
[c] All products were identified by their IR, NMR, and GC-MS.
[d] Yields of products isolated by column chromatography over silica gel.
[e] Yield by GC-MS analysis.

hyde **1h** exclusively underwent 1,2-addition and 4-methoxybenzaldehyde (**1c**) did not react.

We observed that the α/γ ratio is not influenced by the double bond configuration of the allyl moiety, because similar results are obtained by using 2-butenyltributylstannane in complete (*E*)-configuration.[24]

Although it is known that both (*E*)- and (*Z*)-2-butenylmetal reagents predominantly give *syn*-γ-adducts in Lewis acid-promoted reactions, the present reaction suffers from poor stereoselectivity. In most cases, in fact, approximately equal yields for *syn* and *anti* homoallylic alcohols are obtained.

Conversely, opposite results were obtained when the reaction was carried out in a solvent. For example, the addition of **4** to benzaldehyde (**1a**) in CH_3CN in the presence of $CeCl_3 \cdot 7\,H_2O$/NaI complex at room temperature[14] (Method B) yielded a 90:10 mixture of α- and γ-adducts, respectively, in 70% global yields. The high preference toward α-attack is confirmed by results obtained with other aldehydes (see Table 2, entries 4, 6, 7, 9–11 and 14).

As already observed in the case of Method A, even under the experimental conditions adopted in Method B, the formation of the minor γ-adduct is not a stereocontrolled process, an almost 1:1 *syn*/*anti*-mixture being obtained in all cases.

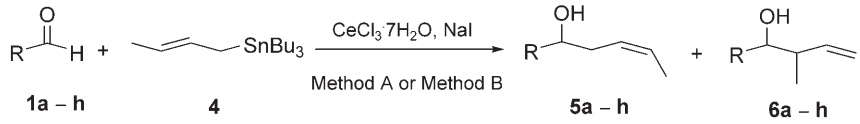
On the contrary, the process of the α-adduct formation surprisingly proceeds with very high stereocontrol giving in all cases the (*Z*)-alcohol in very high purity, as shown by accurate GC-MS and NMR analysis.[25] These results are very remarkable, since the formation of the (*E*)-stereoisomer generally prevails in this kind of reactions.

We wish to outline that, besides the great relevance originated by the novelty of the unexpected stereochemical outcome, the present reaction appears very interesting from a synthetic point of view. The α- and γ-regioisomers in fact can be easily separated by column chromatography, and then this method provides a useful access to difficultly available (*Z*)-alcohols **5**.

mation of the γ-adduct **6** was observed, while with less reactive substrates, such as **1b** and **1i** (Table 2, entries 3 and 13), an appreciable amount of α-adduct **5** was also detected.

In agreement with what was observed in the reaction with allyltributylstannane (**2**), α,β-unsaturated alde-

Table 2. Regioselective allylation of aldehydes promoted by $CeCl_3 \cdot 7\,H_2O$-NaI system.[a]



1a – h **4** **5a – h** **6a – h**

Entry	Aldehyde	Method[b]	Time [h]	Product	Regioisomeric Ratio[c] α/γ	*syn*:*anti*[d]	Yield [%][e]
1	**1a**	A	24	**6a**	0:100	50:50	85
2	**1a**	B	38	**5a**+**6a**	90:10	50:50	70
3	**1b**	A	30	**5b**+**6b**	42:58	46:54	77
4	**1b**	B	48	**5b**+**6b**	89:11	50:50	81
5	**1c**	A	24				0
6	**1c**	B	50	**5c**+**6c**	81:19	50:50	81
7	**1d**	B	26	**5d**+**6d**	85:15	50:50	93
8	**1e**	A	24	**6e**	0:100	50:50	91
9	**1e**	B	19	**5e**+**6e**	85:15	50:50	99
10	**1f**	B	36	**5f**+**6f**	81:19	50:50	79
11	**1g**	B	24	**5g**+**6g**	86:14	50:50	71
12	**1h**	A	18	**6h**	0:100	50:50	74
13	**1i**	A	21	**5i**+**6i**	28:72	36:64	80
14	**1i**	B	22	**5i**	100:0		85

[a] The allylation of aldehydes (1 mmol) by (*E*)-2-butenyltributylstannane **4** (1 mmol) was carried out with $CeCl_3 \cdot 7H_2O$ (1 mmol) and NaI (0.1 mmol).
[b] A: The $CeCl_3 \cdot 7\,H_2O$-NaI combination supported on neutral alumina (1.00 g/mmol aldehydes **1**). B: A suspension of $CeCl_3 \cdot 7\,H_2O$-NaI in acetonitrile.
[c] The regioisomeric ratio was determined by GLC and ^1H NMR spectroscopy.
[d] The stereochemistry was determined by ^1H and ^{13}C NMR spectroscopy.
[e] Total yield of products isolated by column chromatography over silica gel.

Mechanistic Considerations

Owing to the complexity of the obtained results, it is very difficult to completely rationalize the observed stereochemical outcome, especially in the case of the reactions carried out in CH_3CN (Method B), which lead to the prevalent unexpected formation of (*Z*)-α-adducts. Our difficulties arise from the fact that the various mechanisms proposed for other similar allylations of aldehydes do not fit our results (see below). However, a reasonable explanation of our findings is tentatively proposed.

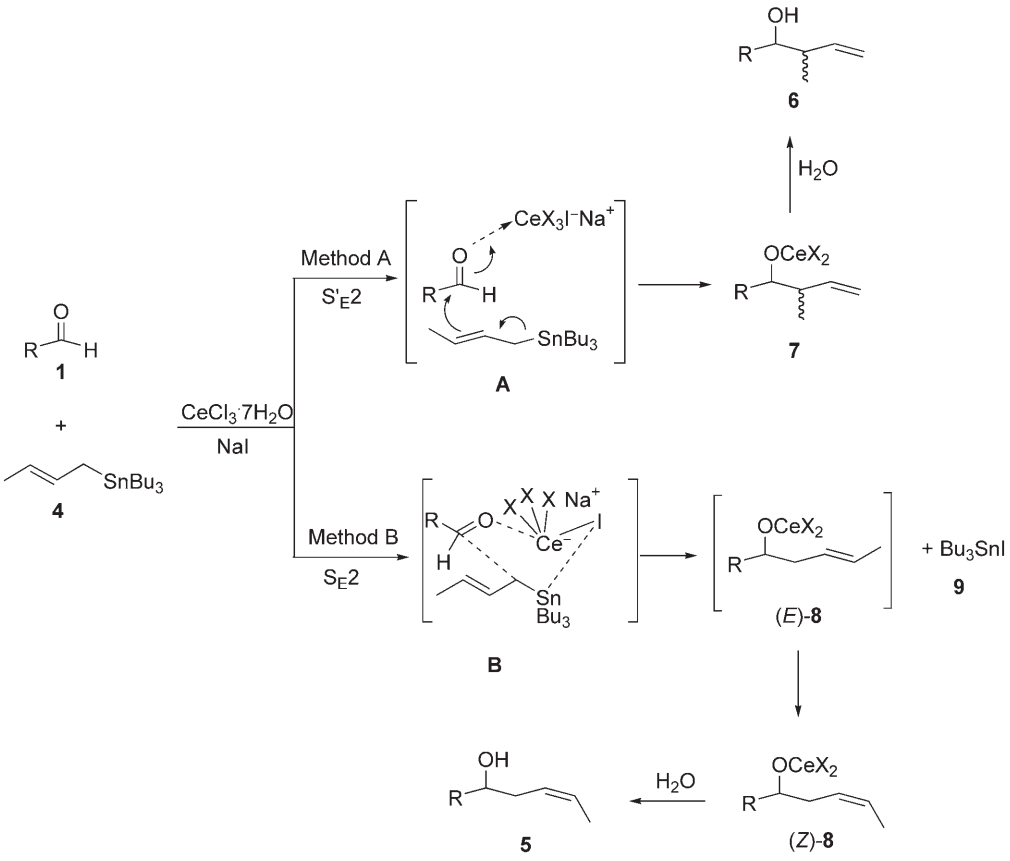
It is well known that a carbonylic function can undergo attack from C1 or C3 carbon of **4**.[26] This process is facilitated by the presence of Lewis acids, like Ce(III) derivatives, able to coordinate the oxygen atom of the carbonyl group.[27]

In this context, the exclusive formation of the γ-adduct **6** in the process carried out with supported catalyst (Method A) can be rationalized on the basis of an initial formation of a complex between the aldehyde **1** and the Lewis acid species adsorbed on Al_2O_3, which undergoes a nucleophilic attack by the C3 carbon of **4** to give alcoholate **7** *via* an S'_E2 pathway.[28] The lack of stereocontrol (see Table 2) observed could be attributed to the reversibility of the addition of **4** to **1**, analogously to the hydrated cerium(III) salt-promoted addition of γ-substituted allylmetal compounds to imine derivatives.[29] However, we think that the poor selectivity can be more reasonably attributed to a weak stereocontrol in the open chain transition state **A**.

It is more difficult to explain the formation of the (*Z*)-α-adduct **5**, when the reaction is carried out according to Method B. The simplest explanation is consistent with the hypothesis that in the presence of the solvent the interaction between **4** and the aldehyde proceeds *via* an S_E2 pathway according to a cyclic transition state **B** to give the linear alcoholate **8**. According to this mechanism, the reaction must produce also Bu_3SnI (**9**). In fact, the GC-MS analysis of the reaction mixture revealed the presence of small amounts of Bu_3SnI and of Bu_3SnOH, but not of Bu_3SnCl. Bu_3SnOH is very likely formed by reaction of Bu_3SnI with the water present in the reaction mixture. This hydrolysis process releases the iodide ion and this accounts for the fact that the use of a catalytic amount of sodium iodide is sufficient to promote the reaction.[14]

Moreover, this mechanistic assumption is strengthened by the fact that during the drafts of this work, a paper appeared in the literature, in which the authors proposed a mechanism similar to that depicted in Scheme 2 to explain the product distribution observed in the allylation of aldehydes catalyzed by carboxylic acids.[30]

As above mentioned, it is very difficult to rationalize the formation of the (*Z*)-isomer **5**. We can assume that the addition of **4** to **1** through the cyclic transition state **B** produces at first the alcoholate (*E*)-**8**, which under-



Scheme 2.

goes an isomerization promoted by an interaction between Ce(III) and the carbon-carbon double bond. This hypothesis is based on a recent study[31] which firmly established the ability of rare earth derivatives to coordinate alkenes. On the other hand, the alternative hypothesis that alcoholate (*Z*)-**8** is directly formed from an interaction of **1** with **4** seems less plausible, because it should imply a too severe stereocontrol in the cyclic transition state **B**. However, we do not have any conclusive evidence supporting this mechanistic interpretation. In fact, we were unable to isolate or synthesize compound (*E*)-**8** in order to verify if, under our reaction conditions, it can undergo a facile isomerization to (*Z*)-**8**. Furthermore, it is impossible to follow the course of the reaction *via* NMR spectroscopy, owing to the presence of paramagnetic Ce(III) species.[32]

Various other mechanistic hypotheses have been proposed to explain the formation of the α-adducts in other allylation reaction systems. However, all these interpretations are ruled out in our system by some unequivocal experimental evidence. In fact, the alternative hypothesis that the reaction in CH_3CN proceeds through a preliminary transmetallation process[33] between stannane **4** and the Ce(III) complex is excluded by our previous findings[14] in which we demonstrated, through a direct spectroscopic analysis, that such a transmetallation process does not occur under the adopted experimental conditions. Otherwise, it is not conceivable to assume the formation of an allylcerium species since it is well known that organocerium compounds are rapidly hydrolyzed by water. On the other hand, it has been proved that the presence of water is essential to promote the reaction.

Another possible explanation, which has been recently proposed to account for the formation of linear α-adducts is based on the hypothesis that the reaction proceeds through two separate steps. The first one implies that the Ce(III) complex-promoted interaction between the aldehyde **1** and **4** gives the γ-adduct **6**. In the second step, **6** is converted to α-adduct **5** through an initial formation of a hemiacetal by addition to unreacted aldehyde **1** followed by a Lewis acid-promoted retroene reaction,[34] and then by a 2-oxonia [3,3]-sigmatropic rearrangement.[35]

However, this mechanism can be completely excluded by the following findings. The treatment of γ-adduct **6e**, (prepared with Method A), with a small or stoichiometric amount of the parent aldehyde **1e** in the presence of $CeCl_3 \cdot 7\,H_2O$/NaI system in CH_3CN at room temperature, did not isomerize to the corresponding α-adduct **5e**. The treatment of **6e** with a more reactive aldehyde, such as 3-phenylpropanal, gave analogously unsuccessful results.

Finally we wish to outline that the opposite regiochemistry shown by Method A with respect to Method B can be attributed to the fact that a highly organized cyclic transition state of type **B** is unlike to be arranged on the Al_2O_3 surface.

Conclusion

In conclusion, regardless of the mechanistic details, the experimental simplicity of our $CeCl_3 \cdot 7\ H_2O$/NaI promoted reaction, the low cost and ease of access to the required reagents, and the high regioselectivity observed provide a convenient and practical method of allylation of aldehydes. Furthermore, the combination of these advantages with the possibility to obtain (*Z*)-α-adducts without isomerization to the more stable (*E*)-configuration, makes our procedure a very efficient method for the preparation of this important class of compounds.

The role of $CeCl_3 \cdot 7\ H_2O$ and NaI is intriguing and complex because the exact nature of the intermediate obtained by the interaction of the reagents with the $CeCl_3 \cdot 7\ H_2O$/NaI system is not yet known.[12a] Further studies are in progress in our laboratories to analyze in more detail the mechanistic outcome of the reaction. Unfortunately, first attempts to extend this reaction to other γ-substituted allylstannanes such as cinnamyltributylstannane, met with failure. We hope that under optimized conditions most undesired side reactions (polymerization and rapid protodestannylation) will be eliminated. The development of this new protocol also prompted us to investigate further applications of our reagent system in new schemes of synthesis, and at present experiments for the preparation of biologically important substances are in progress in our laboratories.

Experimental Section

Typical Experimental Procedure for Allylation

Method A: Neutral alumina (1 g) was added to a mixture of $CeCl_3 \cdot 7\ H_2O$ (0.373 g, 1.0 mmol) and NaI (0.015 g, 0.1 mmol) in acetonitrile (10 mL), and the mixture was stirred overnight at room temperature. The acetonitrile was removed by rotary evaporation and the resulting mixture stored in a bottle at room temperature.

To the $CeCl_3 \cdot 7\ H_2O$-NaI combination supported on neutral alumina (1.388 g) prepared as above was added successively 4-(trifluoromethyl)benzaldehyde (**1e**; 1.0 mmol, 0.174 g, 0.14 mL) and 2-butenyltributylstannane (**4**; 1.0 mmol, 0.313 g) at room temperature. The resulting reaction mixture was then stirred at that temperature until the disappearance of the starting material (24 hours, checked by TLC and GC analyses). After addition of Et_2O the mixture was passed through a short pad of Celite and the filtrate was stirred for 1 h with 10% KF in H_2O (10 mL). The organic phase was separated and washed with brine, dried with Na_2SO_4 and concentrated at reduced pressure. The crude material was purified by flash chromatography on a silica gel column (eluent, hexanes-ethyl acetate, 80:20) to give a mixture of *syn*- and *anti*-2-methyl-1-[4-(trifluoromethyl)phenyl]-3-buten-1-ol (**6e**); yield: 0.187 g (91%).

Method B: To a suspension of $CeCl_3 \cdot 7\ H_2O$ (0.373 g, 1.0 mmol) and NaI (0.015 g, 0.1 mmol) in acetonitrile (12 mL) was added successively 4-(trifluoromethyl)benzaldehyde (**1e**; 1.0 mmol, 0.174 g, 0.14 mL) and 2-butenyltributylstannane (**4**; 1.0 mmol, 0.313 g) at room temperature. The resulting reaction mixture was stirred at that temperature until the disappearance of the starting material (19 hours, checked by TLC and GC analyses), then was quenched with 0.1 N HCl solution. The aqueous layer was extracted with diethyl ether and the combined organic layers were stirred for 1 h with 10% KF in H_2O (10 mL). The organic phase was separated and washed with brine, dried with Na_2SO_4 and concentrated at reduced pressure. The mixture of two diastereomers was separated by silica gel chromatography (eluent, hexanes: ethyl acetate 80/20) to furnish 0.173 (84%) g of (*Z*)-1-[4-(trifluoromethyl)phenyl]-3-penten-1-ol (**5e**) and 0.031 g (15%) of a mixture of *syn*- and *anti*-2-methyl-1-[4-(trifluoromethyl)phenyl]-3-buten-1-ol (**6e**).

All obtained products, except **5c**, are known compounds and were identified by comparison of ^1H and ^{13}C NMR spectra with literature data. Spectroscopic data of **5c** are given below.

(*Z*)-1-(4-Methoxyphenyl)-3-penten-1-ol (5c): IR (neat): ν = 3400, 3017, 1648, 1541 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 1.61 (d, 3H, J_{HH} = 6.6 Hz), 2.21 (bs, 1H, OH), 2.40–2.62 (m, 2H), 3.98 (s, 3H), 4.78 (t, 1H, J_{HH} = 6.4 Hz), 5.38–5.47 (m, 1H), 5.58–5.68 (m, 1H), 6.89 (d, 2H, J_{HH} = 8.4 Hz), 7.30 (d, 2H, J_{HH} = 8.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.0, 31.6, 56.0, 73.4, 114.3, 122.6, 129.5, 130.6, 131.7, 160.6; MS (70 eV, EI): *m/z* = 192 (M^+), 137 (100), 109, 107, 77 , 51, 41, 39; anal. calcd. (%) for $C_{12}H_{16}O_2$ (192.115): C 74.97, H 8.39; found: C 74.95, H 8.27.

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