Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 4163–4169

TETRAHEDRON: *ASYMMETRY*

Titanium catalysed enantioselective addition of allyltributyltin to aldehydes: a simple and easily reproducible procedure

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Received 3 September 2000; accepted 15 September 2000

Abstract

We describe here an extremely simple procedure for the enantioselective addition of allyltributyltin to aldehydes in the presence of a binaphthol–titanium complex. In toluene or pentane, the reaction can be performed at room temperature in the absence of molecular sieves without a decrease in the enantioselectivity. Enantiomeric excesses of up to 99% can be obtained in the most favourable cases.

1. Introduction

Chiral homoallylic alcohols are useful but not easily accessible compounds. They are difficult to obtain by enantioselective reduction of enones;[1] enantioselective allylation of aldehydes remains the most attractive method for the preparation of such compounds.[2–4] The Lewis acid-promoted addition of allyltributyltin to aldehydes is the most common procedure to perform this reaction.[5] The general conditions used to carry out the titanium catalysed allylation are to employ dichloromethane as a solvent in the presence of 4 Å molecular sieves at low temperature (−78°C).[6] If the reaction is conducted by skillful operators, with dry dichloromethane and 4 Å molecular sieves oven dried at 250°C for 12 hours at 0.1 Torr, high enantiomeric excesses can be obtained.[6a,b] But this binaphthol–titanium complex seems to be extremely water-sensitive and, in dichloromethane, even under dry conditions, the catalyst decomposes after a few hours. We have also observed that, if the solvent and the sieves are not perfectly dry, much lower enantiomeric excesses and lower yields are obtained. Despite many attempts, we have not been able to obtain reproducible results with these operating conditions. Moreover, to the best of our knowledge, the ability of this titanium catalyst to give very high enantiomeric excesses at room

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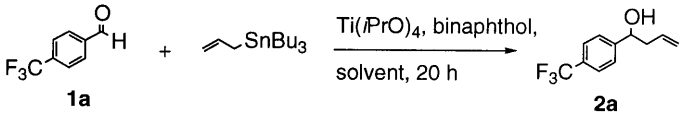
0957-4166/00/$ - see front matter
PII: S0957-4166(00)00374-8

temperature has never been demonstrated.[7] Our objective was to find a simpler procedure to perform this reaction that can be easily reproduced by any synthetic organic chemist. We decided to study the influence of three parameters for this reaction: the solvent, the temperature and the importance of the molecular sieves.

2. Results and discussion

We began by investigating the influence of the solvent and the temperature and found that the most suitable solvents for the reaction are toluene or pentane. In these solvents the stability of the active catalytic titanium species is much higher than in dichloromethane and the reaction can be performed at room temperature without decomposition of the catalyst and without loss of enantioselectivity. The addition of allyltributyltin to 4-trifluoromethylbenzaldehyde in the presence of 10% ((*R*)-binaphthol)Ti(O*i*Pr)$_2$ in pentane or toluene at 25°C led to complete conversion after 20 hours and to 92 and 94% *ee*s, respectively (Scheme 1).

The second problem for the reproducibility of this reaction is the presence of the molecular sieves. It is generally very difficult to know the exact dryness of the sieves and even storing dry sieves in a desiccator with P_2O_5 results in progressive degradation of their performance.[6b] In order to simplify the procedure we decided to study the influence of the sieves in toluene and pentane at room temperature on the reaction rate and on the *ee*s. We observed that, under these conditions, 4 Å molecular sieves have almost no influence on the reaction rate and on the *ee*s. With 10% catalyst, complete conversions are observed in the absence or presence of molecular sieves. Moreover, the *ee*s observed in toluene in the absence and presence of molecular sieves are 95 and 94%, respectively. In the presence of 5% catalyst in toluene or pentane, the *ee*s are even slightly higher in the absence of molecular sieves (Table 1).



Scheme 1.

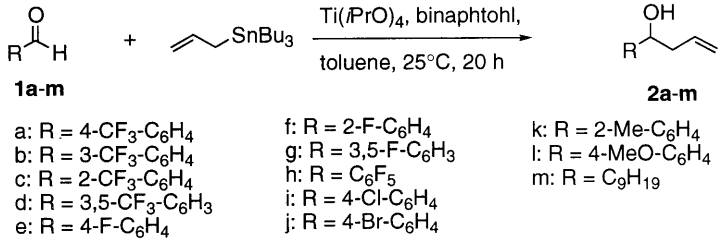
We next examined various aldehydes using these conditions: room temperature, toluene and absence of molecular sieves (Scheme 2). Aldehydes bearing an electron withdrawing, *para* or *meta* aryl substituent gave good yields of addition products, and excellent enantiomeric excesses. 4-Trifluoromethylbenzaldehyde **1a**, 3-trifluoromethylbenzaldehyde **1b** and 4-fluorobenzaldehyde **1e** gave 97% *ee*s and 96–100% yields. The di-*ortho*-substituted 3,5-bistrifluoromethyl **1d** and 3,5-difluorobenzaldehyde **1g** led to lower *ee*s: 91 and 90%, respectively. Pentafluorobenzaldehyde **1h** gave a moderate yield but an excellent *ee* of 99%. Conversely the reaction rate was dramatically decreased when an aldehyde with electron-releasing aryl *para*-substituent was employed. With 4-methoxybenzaldehyde, only a trace of coupling product was observed. A significant steric effect was also observed with the *ortho*-substituted aldehydes **1c**, **1f** or **1k**, which gave lower enantiomeric excesses and only a small amount of adducts **2c** and **2k**. In the case of 2,4-dimethoxybenzaldehyde, no trace of the coupling product was observed. Addition to decanal gave the addition product **2m** in good yield and excellent *ee*: 98%. In all cases, similar

Table 1
Addition to 4-trifluoromethylbenzaldehyde **1a**: influence of the solvent and of the molecular sieves[a]

Solvent	Catalyst (%)	Conversion[c] (%)	*ee* (%)
CH_2Cl_2	10	95	20–82[d]
CH_2Cl_2	5[b]	58	41
Toluene	50	100	90
Toluene	50[b]	100	97
Toluene	10	100	94
Toluene	10[b]	100	95
Toluene	5	68	68
Toluene	5[b]	99	76
Pentane	10[b]	100	92
Pentane	5	100	78
Pentane	5[b]	100	84

[a] Conditions: 4-trifluoromethylbenzaldehyde (2 mmol), allyltributyltin (2.2 mmol), ((*R*)-binaphthol)Ti(*i*PrO)$_2$, solvent 5 mL, molecular sieves 4 Å, 25°C, 20 h.
[b] Reaction without molecular sieves.
[c] Conversion determined by GC and NMR.
[d] Not reproducible *ee*s.

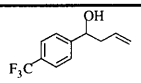
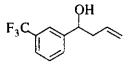
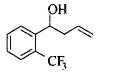
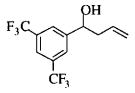
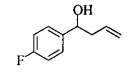
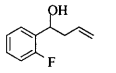
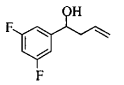
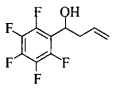
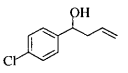
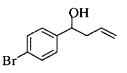
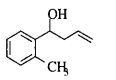
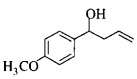
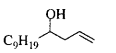
or higher enantiomeric excesses were obtained at room temperature in toluene without molecular sieves than at −78°C in dichloromethane in the presence of molecular sieves. The results are summarised in Table 2.



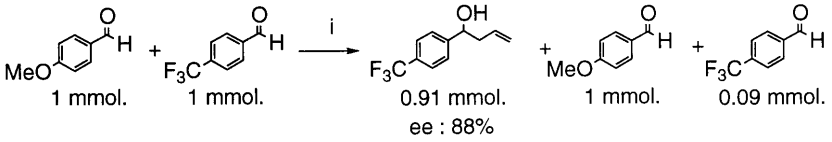
Scheme 2.

Finally we tried to clarify the difference in reaction rates between electron-withdrawing and electron-releasing substituted benzaldehydes. The slow reaction rate observed with 4-methoxybenzaldehyde could be due either to poisoning of the catalyst by coordination of the methoxy function to the complex or to an electronic effect. The addition of allyltributyltin to an equimolar mixture of 4-methoxybenzaldehyde and 4-trifluoromethylbenzaldehyde in the presence of (binaphthol)Ti(OiPr)$_2$ led exclusively to 1-(4-trifluoromethylphenyl)-3-buten-1-ol **2a** (Scheme 3). The same tendency was observed in the presence of an equimolar mixture of 4-fluorobenzaldehyde and 4-trifluoromethylbenzaldehyde. A higher conversion of 4-trifluoromethylbenzaldehyde was observed. These results indicate that the difference in reaction rate does not come from poisoning, but more probably from electronic factors.

Table 2
Titanium catalysed allylation: influence of the aldehyde

aldehyde	product		solvent	temp. °C	yield (%)[b]	ee (%)
1a		**2a**	toluene	25	94	97
			CH_2Cl_2 [a]	25	95	87
			CH_2Cl_2 [a]	-78	99	90
1b		**2b**	toluene	25	96 [c]	97
			CH_2Cl_2 [a]	-78	100	95
1c		**2c**	toluene	25	100	37
1d		**2d**	toluene	25	92 [c]	91
1e		**2e**	toluene	25	95 [c]	97
			CH_2Cl_2 [a]	-78	98	97
1f		**2f**	toluene	25	80 [c]	87
			CH_2Cl_2 [a]	-78	93	31
1g		**2g**	toluene	25	24 [c]	90
1h		**2h**	toluene	25	45 [c]	99
1i		**2i**	toluene	25	3	96
1j		**2j**	toluene	25	58 [c]	97
			CH_2Cl_2 [a]	-78	72	88
1k		**2k**	toluene	25	4	39
1l		**2l**	toluene	25	traces	-
1m		**2m**	toluene	25	80 [c]	98

Conditions: binaphthol 0.55 eq. / Ti(*i*PrO)$_4$ 0.5 eq., aldehyde 1 eq., allyltributyltin 1.2 eq, 20 h, [a] reaction in the presence of molecular sieves 4-Å, [b] Yield determined by GC and NMR, [c] isolated yields.



i =Ti(*i*PrO)$_4$ 0.25 mmol, binaphthol 0.26 mmol, $SnBu_3$ 2.2 mmol, toluene, 25 °C, 20 h.

Scheme 3.

3. Conclusion

We report here an extremely simple procedure for the enantioselective addition of allyltributyltin to aldehydes in the presence of a titanium catalyst. We observed that in toluene or

pentane the stability of the active catalytic titanium species is much higher than in dichloromethane, the solvent generally used for this reaction. In these solvents the reaction can be performed at room temperature in the absence of molecular sieves without decrease of the enantioselectivity. We have also observed important effects of the electronic and steric factors on the rate of the addition.

4. Experimental

4.1. General

Reactions were conducted under a dry argon atmosphere, using standard vacuum line techniques. NMR spectra were recorded on a Varian Gemini 200 and a Bruker AC200 or AMX 400 spectrometer. Gas chromatography analyses were performed on a Hewlett Packard HP 4890A. Reactions were carried out in solvents distilled from standard drying agents. Aldehydes were distilled under reduced pressure before use.

4.2. Preparation of [(R)-(+)-1,1′-bi(2-naphthol)]titanium isopropoxide complex

In a Schlenk tube, 2 mL of degassed toluene was added to 60 mg (0.21 mmol) of (*R*)-(+)-1,1′-bi(2-naphthol), then 59 μL (0.20 mmol) of titanium tetraisopropoxide was added. After stirring for 1 hour, the solvent was removed. These complexes are *not air stable* and were stored in Schlenk tubes under argon. For the catalytic allylation reactions the complexes were prepared just before use.

4.3. Catalytic allylation, general procedure

To 0.2 mmol of a solution of [(*R*)-(+)-1,1′-bi(2-naphthol)]titanium isopropoxide complex in toluene in a Schlenk tube were added 0.4 mmol of aldehyde and 0.45 mmol of allyltributyltin. The solution was stirred at 20°C over 20 hours, quenched with 1 mL of water, 10 mL of ether was added to the mixture, then the organic layer was washed with water and was dried over $MgSO_4$. After evaporation of the solvent, the product was purified by chromatography on silica gel (pentane/ether).

4.4. ^1H NMR (200 MHz, $CDCl_3$) spectra of the products

1-(4-Trifluoromethylphenyl)-3-buten-1-ol **2a**: $\delta = 7.58$ (d, $^3J(H,H) = 8.2$ Hz, 2H), 7.43 (d, $^3J(H,H) = 8.2$ Hz, 2H), 5.75 (m, 1H), 5.2–5.0 (m, 2H), 4.75 (t, $^3J(H,H) = 5.4$ Hz, 1H), 2.50 (m, 3H); 1-(3-trifluoromethylphenyl)-3-buten-1-ol **2b**: δ 7.65–7.35 (m, 4H), 5.75 (m, 1H), 5.2–5.0 (m, 2H), 4.75 (t, $^3J(H,H) = 5.4$ Hz, 1H), 2.47 (m, 2H); 1-(2-trifluoromethylphenyl)-3-buten-1-ol **2c**: $\delta = 7.9$–7.3 (m, 4H), 5.86 (m, 1H), 5.2–4.9 (m, 2H), 4.88 (t, $^3J(H,H) = 5.4$ Hz, 1H), 2.50 (m, 3H); 1-(3,5-bistrifluoromethylphenyl)-3-buten-1-ol **2d**: $\delta = 7.9$–7.5 (m, 3H), 5.77 (m, 1H), 5.20–4.80 (m, 3H), 2.50 (m, 3H); 1-(4-fluorophenyl)-3-buten-1-ol **2e**: $\delta = 7.3$ (m, 2H), 7.0 (m, 2H), 5.78 (ddt, $^3J(H,H) = 16.0$, 7.4 and 5.4 Hz, 1H), 5.15 (d, $^3J(H,H) = 7.4$ Hz, 1H), 5.14 (d, $^3J(H,H) =$ 16.0 Hz, 1H), 4.72 (t, $^3J(H,H) = 6.2$ Hz, 1H), 2.50 (m, 2H); 1-(2-fluorophenyl)-3-buten-1-ol **2f**:

$\delta = 7.5$–6.9 (m, 4H), 5.75 (ddt, $^3J(H,H) = 15.7$, 9.2 and 6.0 Hz, 1H), 5.13 (d, $^3J(H,H) = 15.7$ Hz, 1H), 5.0 (m, 1H), 4.70 (d, $^3J(H,H) = 6.0$ Hz, 1H), 2.50 (m, 2H); 1-(3,5-difluorophenyl)-3-buten-1-ol **2g**: $\delta = 7.00$ (m, 2H), 6.75 (m, 1H), 5.77 (m, 1H), 5.3–5.0 (m, 2H), 4.72 (t, $^3J(H,H) = 7.0$ Hz, 1H), 2.50 (m, 2H); 1-(pentafluorophenyl)-3-buten-1-ol **2h**: $\delta = 5.75$ (ddt, $^3J(H,H) = 15.5$, 7.8 and 7.0 Hz, 1H), 5.20 (d, $^3J(H,H) = 7.8$ Hz, 1H), 5.19 (d, $^3J(H,H) = 15.5$ Hz, 1H), 5.18 (m, 1H), 2.45 (m, 2H); 1-(4-chlorophenyl)-3-buten-1-ol **2i**: $\delta = 7.95$ (d, $^3J(H,H) = 8.3$ Hz, 2H), 7.30 (d, $^3J(H,H) = 8.3$ Hz, 2H), 5.75 (ddt, $^3J(H,H) = 16.0$, 8.0 and 6.3 Hz, 1H), 5.15 (d, $^3J(H,H) = 16.0$ Hz, 1H), 5.13 (d, $^3J(H,H) = 8.0$ Hz, 1H), 4.72 (t, $^3J(H,H) = 6.2$ Hz, 1H), 2.50 (m, 2H); 1-(4-methoxyphenyl)-3-buten-1-ol **2l**: $\delta = 7.27$ (d, $^3J(H,H) = 7.5$ Hz, 2H), 6.82 (d, $^3J(H,H) = 7.5$ Hz, 2H), 5.79 (ddt, $^3J(H,H) = 17.4$, 7.7 and 6.3 Hz, 1H), 5.14 (d, $^3J(H,H) = 7.7$ Hz, 1H), 5.13 (d, $^3J(H,H) = 17.4$ Hz, 1H), 4.72 (t, $^3J(H,H) = 6.4$ Hz, 1H), 3.90 (s, 3H), 2.50 (m, 2H).

4.5. Determination of enantiomeric excesses (Table 3)

Table 3
Determination of enantiomeric excesses by gas chromatography[a]

Alcohol	Oven temp. (°C)	Retention time of the enantiomers (min)[b]	
1-(4-Trifluoromethylphenyl)but-3-en-1-ol	140	**14.7**	16.1
1-(3-Trifluoromethylphenyl)but-3-en-1-ol	130	**18.9**	20.2
1-(2-Trifluoromethylphenyl)but-3-en-1-ol	130	**15.2**	15.9
1-(3,5-Bistrifluoromethylphenyl)but-3-en-1-ol	110	**35.7**	37.0
1-(4-Fluorophenyl)but-3-en-1-ol	120	**35.0**	37.0
1-(2-Fluorophenyl)but-3-en-1-ol	130	17.2	**18.3**
1-(3,5-Difluorophenyl)but-3-en-1-ol	115	**46.0**	48.0
1-(2,3,4,5,6-Pentafluorophenyl)but-3-en-1-ol	120	**15.8**	18.0
1-(4-Chlorophenyl)but-3-en-1-ol	130	24.0	**25.0**
1-(4-Bromophenyl)but-3-en-1-ol	150	**32.6**	34.5
1-(4-Methoxyphenyl)but-3-en-1-ol	135	**44.0**	46.0
1-(2-Methylphenyl)but-3-en-1-ol	125	**38.8**	39.9
Tridec-1-en-3-ol	130	**35.4**	37.0

[a] Using a column Chrompack WCOT Fused Silica, CP-Chirasil-DEX CB, 25 meters, injector temperature: 200°C, detector temperature: 250°C, inlet pressure 13 psi.

[b] Times in bold represent the major peaks obtained with [(*R*)-(+)-1,1′-bi(2-naphthol)]titanium isopropoxide complex as catalyst and should be *R* in all cases.

Acknowledgements

We thank the CNRS for providing financial support.

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