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for the Preparation
of Organic Compounds

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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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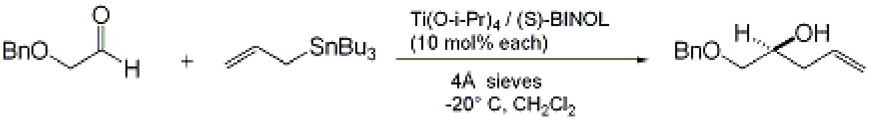
CATALYTIC ASYMMETRIC ALLYLATION REACTIONS: (S)-1-(PHENYLMETHOXY)-4-PENTEN-2-OL

[4-Penten-2-ol, 1-(phenylmethoxy)-, (S)-]



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Checked by William R. Roush and Melissa L. Reilly.

1. Procedure

A 250-mL, round-bottomed flask (Note 1) equipped with a stirring bar and a rubber septum is charged with (S)-(−)-1,1'-bi-2-naphthol [(S)-BINOL] (1.14 g, 4.0 mmol) (Note 2) and methylene chloride (Note 3) (40 mL). The suspension is stirred until the binaphthol is completely dissolved. Powdered 4 Å molecular sieves (16.0 g) (Note 4) are then added. To the resultant suspension is added a 1 M methylene chloride solution of titanium tetraisopropoxide (4.0 mL, 4.0 mmol) (Note 5) by syringe at ambient temperature. The resulting orange-red suspension is heated at reflux for 1 hr (Note 6). The red-brown mixture is cooled to ambient temperature and a methylene chloride (6 mL) solution of benzyloxyacetaldehyde (Note 7) (6.0 g, 40 mmol) is injected via syringe. The resulting mixture is stirred for 5 min at ambient temperature, then cooled to −78°C. To the reaction mixture is added allyltributylstannane (Note 8) (15.9 g, 14.9 mL, 48 mmol) via syringe. The resulting reaction mixture is then kept in a freezer at −20°C for 60 hr without stirring. Even after 60 hr a small amount of unreacted aldehyde is detected (TLC analysis) (Note 9). The reaction mixture is quenched with saturated aqueous sodium hydrogen carbonate solution (50 mL), diluted with methylene chloride (50 mL), and stirred at ambient temperature for 2 hr. The molecular sieves are removed by filtration through a pad of Celite, and the aqueous layer is extracted with methylene chloride (2 × 25 mL). The combined organic extracts are dried over sodium sulfate and evaporated under reduced pressure. Chromatography over silica gel (Note 10) gives 6.16-6.69 g (80-87%) of (S)-1-(phenylmethoxy)-4-penten-2-ol (Note 11), (Note 12), (Note 13). The enantiomeric purity is 94-96% ee by HPLC analysis using a chiral column (Note 14), (Note 15).

2. Notes

1. The reaction flask, needles, and syringes were stored in an oven at 120°C overnight prior to use.
2. S-(−)-1,1'-Bi-2-naphthol is purchased from the Aldrich Chemical Company, Inc.
3. Methylene chloride is distilled from calcium hydride before use.
4. Powdered 4 Å molecular sieves are purchased from the Aldrich Chemical Company, Inc., and activated by storing in an oven at 120°C for several days.
5. Titanium tetraisopropoxide [titanium(IV) isopropoxide] is purchased from the Aldrich Chemical Company, Inc.
6. The reaction mixture is refluxed gently using an oil bath.
7. Benzyloxyacetaldehyde is purchased from the Aldrich Chemical Company Inc. , and distilled under vacuum before use.
8. Allyltributylstannane is commercially available (Aldrich Chemical Company Inc.) or can be easily prepared following an *Org. Synth.* procedure.[2] [3]
9. Thin layer chromatography is performed on Merck Kieselgel silica gel 60 F-254 plates eluting with 30% acetone/hexanes , visualized by a 254-nm UV lamp and stained with an ethanolic 12-phosphomolybdic acid solution followed by heating at ca. 250°C on a hot plate. Observed R_f's were 0.30 for aldehyde and 0.38 for product.
10. A 25 × 17-cm silica gel (Davisel 633) column is used. Initially, hexanes are used as eluant to elute recovered allyltributylstannane, then 9 : 1 hexane:acetone is used as eluant to isolate the product.

Further elution of the column with 8 : 2 hexane:acetone gives 0.9 g (80%) of crude recovered BINOL which can be further purified by chromatography over silica gel to give 0.8 g (70%) of pure BINOL.

11. The submitters obtained 6.79 g (88%) of product.

12. The optical rotations for the R- and S- isomers of this compound have been reported in the literature with the same (−) sign.[4] [5] The submitters established the absolute stereochemistry of this compound using the Mosher method,[6] and for the S-isomer measured $[\alpha]_D^{23}$ 1.96° ($CHCl_3$, *c* 2.3). The optical rotation determined by the checkers for the S isomer is $[\alpha]_D$ 23 −1.87° ($CHCl_3$, *c* 2.3). Thus the same situation was encountered in the present case. Upon exchange of samples, the submitters measured a *positive* rotation for the checker's sample. The discrepancy was traced to the chloroform ($CHCl_3$) used: The submitters used EM Science Spectral Grade $CHCl_3$, which does not contain ethanol (EtOH) as a stabilizer, while the checkers used Mallinckrodt $CHCl_3$ which contained 0.75% EtOH as stabilizer. The submitters measured $[\alpha]_D^{23}$ −2.9° (*c* 2.5) in absolute ethanol ; other experiments that involved adding small amounts of EtOH to the EM Science $CHCl_3$ showed that the presence of small amounts of EtOH affected the rotation quite markedly. This is clearly a case where the measured rotations are so small as to be of limited value in making unambiguous assignments.

13. (S)-1-(Phenylmethoxy)-4-penten-2-ol prepared by this procedure gave the following spectroscopic data: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.28 (m, 2 H), 3.38 (dd, 1 H, J = 9.43, 7.55), 3.52 (dd, 1 H, J = 9.43, 3.46), 3.88 (m, 1 H), 4.58 (s, 2 H), 5.11 (m, 2 H), 5.82 (m, 1 H), 7.34 (m, 5 H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 37.9, 69.7, 73.4, 73.9, 117.6, 127.68, 127.73, 128.4, 134.2, 138.0 ; IR spectrum (neat) cm^{-1}: 3450, 3080, 3041, 2979, 2920, 1648, 1461, 1268, 1105, 1065 ; mass spectrum (low resolution, DCI/NH_3) 192 m/z .

14. CHIRALCEL OD-H is available from Chiral Technologies Inc. The checkers used a 15-cm column, with a 97 : 3 hexane/2-propanol mixture as eluant, a flow rate of 0.5 mL/min, and detection by RI detector. The t_R of the R-isomer (17.0 min) is shorter than that of the major S-isomer (17.8 min). The submitters used a 25-cm column with a 94 : 6 mixture of hexane/2-propanol as eluant and a flow rate of 0.5 mL/min. Under the latter conditions, the t_R's of the R- and S-isomers are 17.9 min and 19.4 min, respectively.

15. The submitters reported the enantiomeric purity of the product as 94% e.e.

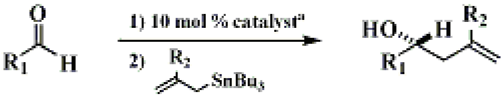
Waste Disposal Information

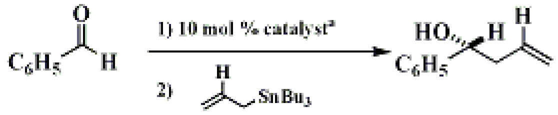
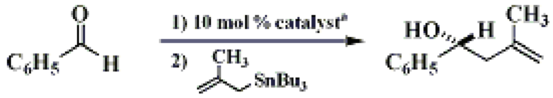
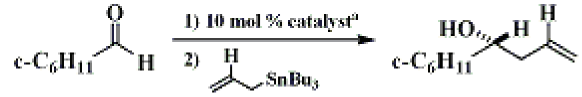
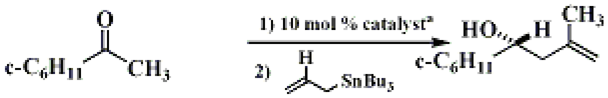
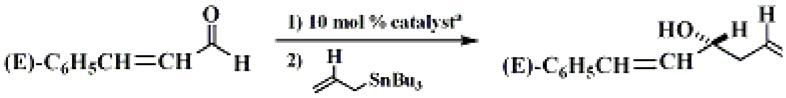
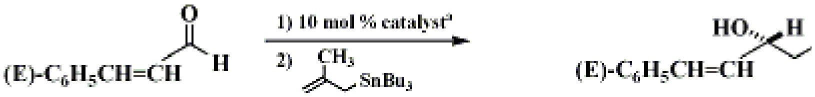
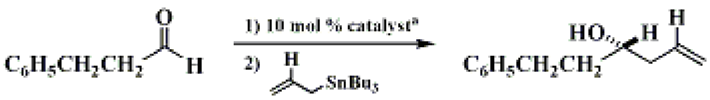
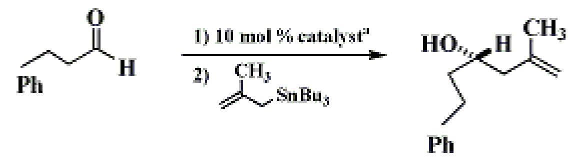
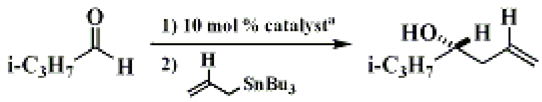
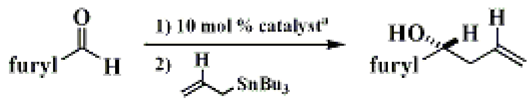
All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

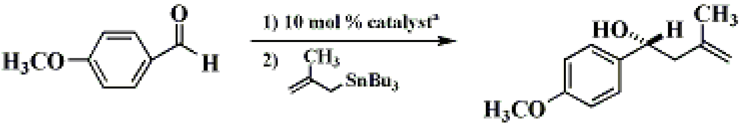
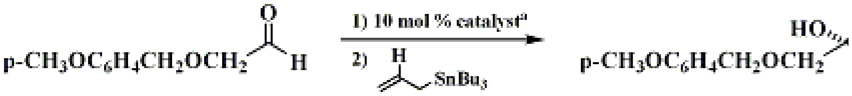
3. Discussion

This procedure describes the preparation and use of an effective chiral catalyst for the asymmetric allylation of aldehydes. A previous synthesis of optically pure 1-(phenylmethoxy)-4-penten-2-ol requires seven steps from D-mannitol .[7] This procedure has been employed successfully with other aldehydes,[8] and also with methallyltributylstannane [8] (see Table). Catalysts prepared from (R)- or (S)-BINOL and $Ti(O\text{-}i\text{-}Pr)_4$ at 2:1 stoichiometry have also proven useful in these reactions.[9,10] The olefinic products may be regarded as latent aldol products between aldehydes and the enolate of actetaldehyde or acetone. In all cases examined thus far, enantioselectivity is consistent with the observation that (R)-BINOL gives R-product with benzaldehyde. Thus addition occurs to the *re* face of substrate with this catalyst prepared using (R)-BINOL.

TABLE
CATALYTIC ASYMMETRIC ALLYLATION REACTIONS WITH OTHER ALDEHY

R_1	R_2	T, °C (time, hr)		Yield,[b] %

C_6H_5	H	−20 (70)		88
	CH_3	−20 (60)		75
c-C_6H_{11}	H	−20 (70)		66
	CH_3	−20 (48)		50
(E)-C_6H_5CH=CH	H	−20 (70)		42
	CH_3	−20 (12)		68
$C_6H_5CH_2CH_2$	H	−20 (70)		93
	CH_3	−20 (40)		97
i-C_3H_7	H	−20 (70)		89
	H	−20 (70)		

			73
furyl	CH_3	−20 (12)	
			99
p-$CH_3OC_6H_4$	CH_3	−20 (48)	
			61
p-$CH_3OC_6H_4CH_2OCH_2$	H	−20 (70)	
			81

[a]See experimental procedure for catalyst preparations. [b]Isolated yields of the product. [c]Determined NMR with $Eu(hfc)_3$. [d]Determined by ^{19}F NMR of the Mosher ester.

References and Notes

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

(S)-1-(Phenylmethoxy)-4-penten-2-ol:
4-Penten-2-ol, 1-(phenylmethoxy)-, (S)- (11); (88981-35-5)

(S)-(−)-1,1'-Bi-2-naphthol:
(S)-BINOL:
[1,1'-Binaphthalene]-2,2'-diol, (S)-(−)- (8),
[1,1'-Binaphthalene]-2,2'-diol, (S)- (9); (18531-99-2)

Titanium tetraisopropoxide:
Titanium(IV) isopropoxide:
Isopropyl alcohol, titanium(4+) salt (8);

2-Propanol, titanium(4+) salt (9); (546-68-9)

Benzyloxyacetaldehyde:
Acetaldehyde, (phenylmethoxy)- (9); (60656-87-3)

Allyltributylstannane:
Stannane, allyltributyl- (8);
Stannane, tributyl-2-propenyl- (9); (24850-33-7)