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Enantioselective synthesis of propargylic alcohols by addition of enantiopure cyclopentadienyldialkoxyallyltitanium complexes to acetylenic aldehydes

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Abstract

The enantioselective synthesis of propargylic alcohols was achieved by enantioselective allyltitanation of acetylenic aldehydes.

Keywords: allyltitanation; acetylenic aldehydes; propargylic alcohols.

The production of enantiomerically enriched intermediates from achiral starting materials by means of chiral reagents and catalysts has been of increasing interest in recent years.[1] One of the most widely studied goals in this field has been an efficient synthesis of enantioenriched carbinols. Recently, we became interested in the synthesis of chiral secondary propargylic alcohols as these compounds are useful building blocks for the synthesis of biologically[2] and structurally interesting compounds.[3] The methods that have been used for the synthesis of such alcohols involve the enantioselective alkynylation of aldehydes.[4] Stoichiometric reduction of acetylenic ketones with chirally modified metal hydrides[5] as well as catalytic asymmetric reduction[6] or enzymatic reduction[7] of acetylenic ketones have also been employed to produce these alcohols. Other methods such as cleavage of chiral acetylenic acetals,[8] enantioselective carbonyl-ene reactions with glyoxylates,[9] and enantioselective aldol addition reaction to α,β-ynals,[10] in the presence of a chiral catalyst have also found applications.

Additions of chiral allylboranes to α,β-acetylenic aldehydes[11] is one of the more general routes to enantioenriched propargylic alcohols. Here, we report a related approach which utilizes the

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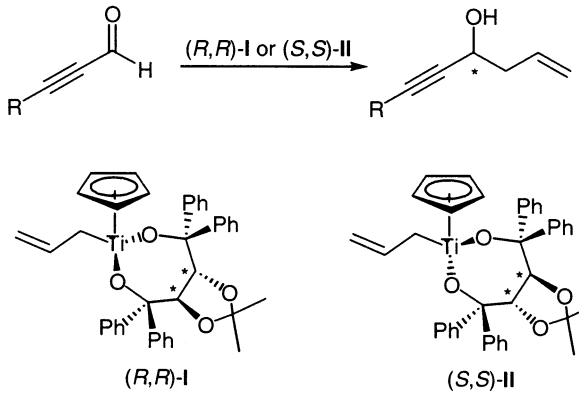
cyclopentadienyldialkoxyallyltitanium complexes (*R*,*R*)-**I** or (*S*,*S*)-**II**[12] in such additions. These reagents exhibit remarkably high facial discrimination for such aldehydes despite the relatively small steric requirements of the alkynyl group.



The asymmetric allyltitanation proceeds under neutral conditions at −78°C. Aldehydes **1**[13] (1 mmol, 1 equiv.) were added to an etheral solution of the cyclopentadienyldialkoxyallyltitanium complex (1.1 equiv.). After 3 h, the reaction mixture was quenched and the propargylic alcohols **2** were isolated in moderately high yield and excellent enantiomeric excess. For each propargylic alcohol, the enantiomeric purity was determined by chiral HPLC.[14] The results are reported in Table 1.

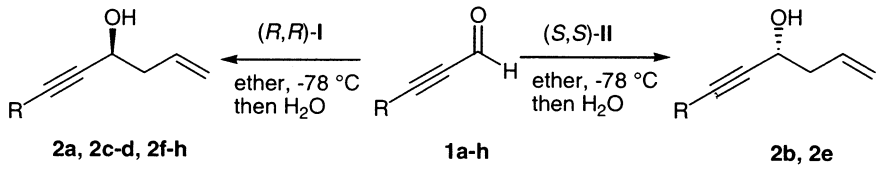


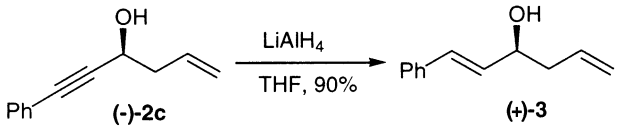
Table 1
Enantioselective allyltitanation of acetylenic aldehydes

Entry	Aldehyde **1**	Reagent	Product **2**			
	R		Yield (%)	$[\alpha]_D$[d]	Ee (%)[14]	Configuration
a	*t*-Bu$(CH_3)_2$Si–	(*R*,*R*)-**I**	53	−28	96	(*S*)[a]
b	*t*-Bu$(CH_3)_2$Si–	(*S*,*S*)-**II**	64	+27	95	(*R*)[b]
c	Ph–	(*R*,*R*)-**I**	70	−11	93	(*S*)[c]
d	CH_3–$(CH_2)_6$–	(*R*,*R*)-**I**	71	−19	98	(*S*)[a]
e	CH_3–$(CH_2)_6$–	(*S*,*S*)-**II**	55	+12	95	(*R*)[a]
f	TrO–$(CH_2)_2$–	(*R*,*R*)-**I**	70	−5	93	(*S*)[a]
g	THPO–CH_2–	(*R*,*R*)-**I**	60	−18	95	(*S*)[a]
h	*o*-AcO–C_6H_4–	(*R*,*R*)-**I**	61	−23	95	(*S*)[a]

[a] Determined by ^{1}H NMR analysis of the *O*-methylmandelates.
[b] Determined by comparison of the $[\alpha]_D$ of (−)-**2a** and (+)-**2b**.
[c] Determined by chemical correlation.
[d] The optical rotations for compounds **2a**–**h** were recorded in $CHCl_3$ at 25°C, with a similar concentration ($c = 1$).

When the propargylic aldehyde **1a** was treated with the (*R*,*R*)-**I** complex, alcohol (−)-**2a** was isolated in 53% yield (ee = 96%). The absolute configuration was determined by analysis of the ^{1}H NMR spectra of the corresponding *O*-methylmandelates.[15] The allylic protons of the (*R*)-*O*-methylmandelate appear at higher field than those of the (*S*)-*O*-methylmandelate (0.3 ppm) consistent with the (*S*) configuration for the propargylic alcohol. In a similar manner, when **1c**, **1d**, **1f**, **1g**, and **1h** were treated with the (*R*,*R*)-**I** complex, the corresponding propargylic alcohols were isolated in 60–70% yield with high enantioselectivity (ee>93%).

In each case, the absolute configuration was determined as before by analysis of the corresponding *O*-methylmandelates except for alcohol (−)-**2c**. For this compound, the determination of the absolute configuration was achieved by reduction of the propargylic alcohol (−)-**2c** with $LiAlH_4$ in THF and the vinylcarbinol (+)-**3** was obtained in 90% yield ($[\alpha]_D = +18$, *c* 2, ether; lit.[16]: compound (−)-**3**, $[\alpha]_D = -19.3$, *c* 1.33, ether). This chemical correlation allowed us to attribute the (*S*) configuration to compound (−)-**2c**.



Addition of the (*S*,*S*)-**I** complex to aldehyde **1b** led to alcohol (+)-**2b** in 60% yield (ee = 95%). By comparison of the $[\alpha]_D$ of (−)-**2a** ($[\alpha]_D = -28$) and (+)-**2b** ($[\alpha]_D = +27$), we can assign the (*R*) configuration to (+)-**2b**. When aldehyde **1e** was treated with (*S*,*S*)-**II**, the propargylic alcohol (+)-**2e** with the (*R*) configuration (determined from the *O*-methylmandelate derivatives),[15] was obtained in 55% yield.

Allyltitanation of α,β-acetylenic aldehydes with the (*R*,*R*)-**I** and (*S*,*S*)-**II** complexes proceeds with consistent and predictable stereochemistry to give propargylic alcohols of high optical purity (93–98%). The use of this reaction for the synthesis of biologically active compounds is in progress and will be reported in due course.

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14. The enantiomeric excess of propargylic alcohol **2a**–**h** was determined by HPLC analysis (Waters 590 chromatograph coupled with a Varian UV detector, $\lambda = 220$ nm). For (−)-**2a** and (+)-**2b**: Chiralpak-AD_2 column, (hexane/isopropanol: 99.2/0.8); For (−)-**2c**: Chiralpak-AD_2 column, (hexane/isopropanol: 93/7); For (−)-**2d** and (+)-**2e**: Chiralpak-OD-H column, (hexane/isopropanol: 99/1); For (−)-**2f**: Chiralcel-OD-H column, (hexane/isopropanol: 95/5); For (−)-**2g**: Chiralcel-OD-H column, (hexane/isopropanol: 90/10); For (−)-**2h**: Chiralcel-OD-H column, (hexane/ethanol: 94/6).
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