Enantioselective Catalyzed Addition of Substituted Indens to Unsaturated Epoxides

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Unsaturated aromatic epoxides can be regioselectively opened by substituted indenes in the presence of catalytic amounts of (R)-1,1'-bi-2,2'-naphthotitanium diisopropoxide (1 mol%). The reaction proceeds and enables the synthesis of (1R,2R)-2-(5-bromo-1H-inden-3-yl)-2-phenyl-1-[(prop-2-yn-1-yl)oxy]propan-1-ol with moderate yield and high enantioselectivity (ee up to 97%).

Introduction

Most biologically active compounds, including pharmaceuticals, possess chiral molecular structures. Organic compounds containing an indene fragment have a wide range of practical applications. Structural analogues of such substances are important products in the pharmaceutical industry [1]. Synthesized chiral indenyl-containing compounds can also serve as biologically active agents [2, 3].

Typically, Friedel–Crafts reactions are carried out using catalytic or stoichiometric amounts of Lewis acids [4]. However, the literature has recently reported interesting methods for the preparation of optically active compounds containing aromatic systems [5]. Unsaturated aromatic epoxides are ideal substrates, as they can be readily opened by nucleophiles, enabling the synthesis of functionally diverse compounds.

A reaction involving a chiral organic catalyst promotes the interaction of substituted indenes with unsaturated aromatic epoxides, potentially forming isomeric hydroxy compounds and leading to partial racemization.

Results and discussion

In this work, we report a straightforward (R)-1,1'-bi-2,2'-naphthotitanium diisopropoxide (L1)-catalyzed reaction of substituted indenes with unsaturated epoxides, affording products in moderate yields and high enantioselectivities (ee up to 97%; see **Scheme 1**).

Previous studies describe ring-opening reactions of unsaturated epoxides with substituted indenes carried out under high pressure (10 kbar) or in the presence of SiO_2 [6, 7]. High-pressure conditions require specialized equipment and several days to achieve good conversion. In fact, starting materials typically react after one week, yielding final products with only 88% efficiency. Under these conditions, slight racemization occurs due to partial benzyl carbocation formation.

We found that, in the presence of catalytic amounts of (R)-1,1'-bi-2,2'-naphthotitanium diisopropoxide, substituted indenes can be added to unsaturated aromatic epoxides under mild conditions (1 mol% catalyst, room temperature, 8–18 h). We previously reported the synthesis of such unsaturated aromatic epoxides [8].

The chiral catalyst plays a vital role in both catalytic activity and stereoselectivity in these asymmetric reactions.

The catalyst loading – optimally 1 mol% – proved essential for reaction efficiency. Notably, (R)-1,1'-bi-2,2'-naphthotitanium diisopropoxide was effective even at low concentrations. After chromatographic separation, the regioisomer 1-(1H-substituted inden-3-yl)-2-phenylethanol, resulting from nucleophilic attack of substituted indenes on the more substituted carbon, was isolated in 11% yield. Generally, substituted indenes bearing electron-donating groups exhibited higher reactivity, affording the corresponding alcohols in moderate yields (compounds **3–6**, **Table 1**).

In contrast, electron-withdrawing groups (**7,8**) significantly decreased the reactivity of substituted indenes. For example, when 5-nitro-substituted indenes were used as nucleophiles, lower yields (69–92%) and partial racemization (ee of 92%) were observed (compounds **8** and **9**, **Table 1**). **Table 1** also illustrates the effects of solvent and reaction time on yield and enantioselectivity. Enantiomeric excesses were determined by chiral HPLC chiral stationary phase (Daicel Chiralcel AD-H column, 95:5 e.r. shown; column temperature 20°C, Chiralcel OD-H column, 95:5 hexane/*i*PrOH, 1.0 mL/min, 254 nm).

The formation of (1R,2R)-2-(5-bromo-1H-inden-3-yl)-2-phenyl-1-(prop-2-yn-1-yl)oxypropan-1-ol proceeds in a stereospecific manner. The absolute configurations of substituted indenyl compounds **1–8** were determined by NMR spectroscopy. The ^{1}H NMR spectrum confirms the formation of a single diastereomer with (1R,2R) configuration. In the ^{1}H NMR spectrum of (1R,2R)-2-(5-bromo-1H-inden-3-yl)-2-phenyl-1-[(prop-2-yn-1-yl)oxy]ethan-1-ol (3), the methine protons of the CHC=C group appear as a doublet at 4.45 ppm (J = 6.6 Hz), and the proton of the OCHO group appears as a doublet at 3.89 ppm (J = 6.6 Hz).

In summary, we have developed a new method for the preparation of enantiomerically pure substituted indenyl derivatives via chiral organic catalyst-promoted ring opening of unsaturated epoxides.

When comparing the ^{1}H NMR spectra of the synthesized products with that of indene itself, the disappearance of the vinyl proton signal at higher fields (δ 6.87) is clearly observed. This further confirms the alkylation of unsaturated epoxides with substituted indenes.

Experimental part

Chemical shifts in the ^{1}H NMR spectra are reported in δ (ppm) relative to tetramethylsilane (TMS) as an internal standard, and coupling constants (J) are given in hertz (Hz). The data are presented as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, br=broad, m= multiplet).

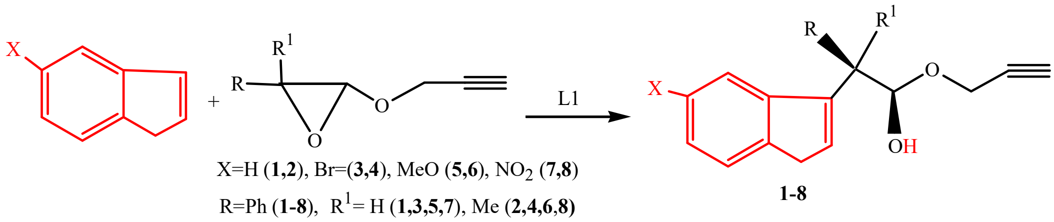
^{13}C NMR spectra were recorded with complete proton decoupling. Chemical shifts are reported in ppm relative to the internal standard (solvent): $CDCl_3$ at δ 77.0 ppm or DMSO-d_6 at δ 39.0 ppm.

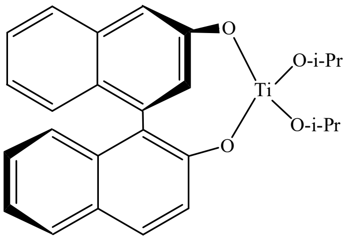
After solvent removal, the residue was purified by column chromatography on silica gel using petroleum ether as the eluent.

Elemental analysis was performed using a CHNOS analyzer. Infrared (İR) spectra were recorded on a Sapphire-ATR spectrophotometer, with absorption bands reported in cm^{-1}.

High-performance liquid chromatography (HPLC) was carried out using a Daicel Chiralcel OD column (0.46 cm×25 cm i.d.) from Daicel Inc. Optical rotations were measured in a 1 mL cell with a 10 mm path length (Na D-line).

Typical experimental procedure for direct ring opening of unsaturated aromatic epoxides involving (R)-1,1'-Bi-2,2'-naphthotitanium Diisopropoxide. To a dehydrated two-neck flask under nitrogen atmosphere, 3 mL of anhydrous CH_2Cl_2, (R)-1,1'-andi-2,2'-naphthotitanium diisopropoxide (5.5 mg, 0.015 mmol) and 2.25 mmol of substituted indene were added. The mixture was stirred for several minutes, and then 1.5 mmol of unsaturated aromatic epoxides was added. This clear solution was then stirred at room temperature until the unsaturated aromatic epoxides disappeared (8-16 hours, verified by GC). The reaction was then neutralized with saturated $NaHCO_3$ solution and extracted with Et_2O. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure and the crude mixture was purified by flash chromatography.



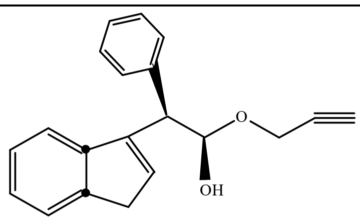
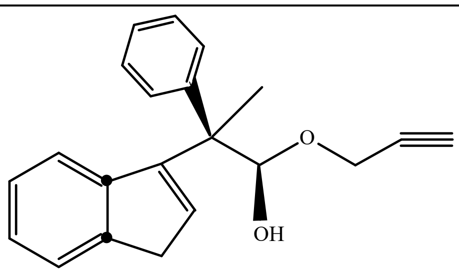
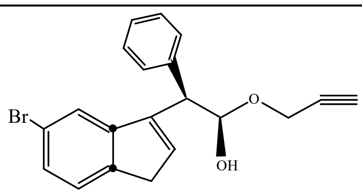
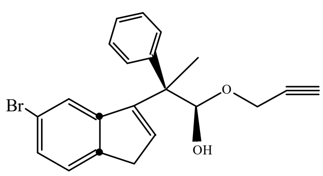


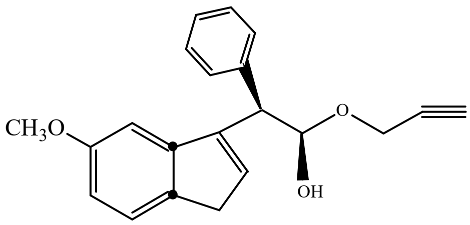
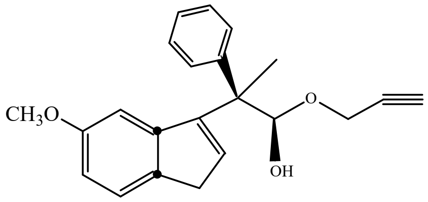
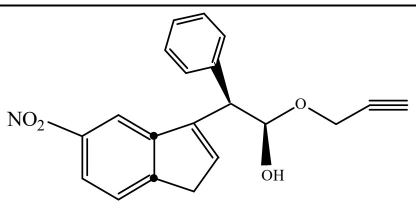
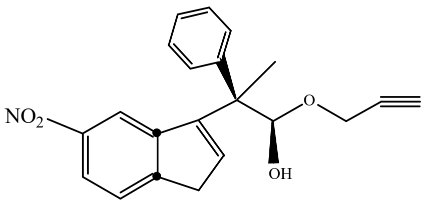
(L1)

(R)-1,1'-bi-2,2'-naphthotitanium diisopropoxide

Scheme 1.

Table 1. Enantioselective catalyzed Friedel-Crafts addition of substituted indens to unsaturated aromatic epoxides

Entry	Product	Solvent	Time, (h)	Yield, (%)[a]	ee, (%)[b]
1		DCM (dichloromethane)	1	78	96
2		DCM(dichloromethane)	1	76	92
3		THF (tetrahydrofuran)	1	79	94
4		DCM(dichloromethane)	1	84	97

5		THF THF (tetrahydrofuran)	1	79	92
6		Et_2O (diethyl ether)	1	81	82
7		PhMe(toluol)	1	72	90
8		MTBE(methyl tert-butyl ether)	1	69	92

[a] Isolated yield;

[b] Determined by HPLC analysis on a chiral stationary phase.

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