

Article

# Iron-Promoted 1,5-Substitution Reaction of Endocyclic Enyne Oxiranes with MeMgBr: A Stereoselective Method for the Synthesis of Exocyclic 2,4,5-Trienol Derivatives

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**Abstract:** The iron-promoted 1,5-substitution reaction of endocyclic oxiranes with MeMgBr yields exocyclic 2,4,5-trienols with high diastereomeric ratios of up to 100:0. However, for the method's success, the oxirane ring must have a *trans*-configuration. The reactions exhibit strong stereoselectivity concerning the methylation mode and the configuration of the resulting exocyclic double bond. Enantiomerically pure enyne oxiranes can be synthesized through Sharpless asymmetric dihydroxylation and subsequent manipulations. With these reagents, it has been possible to produce exocyclic 2,4,5-trienols in enantiopure forms. Importantly, this process maintains chirality without degradation during the center-to-axis transfer of chirality.

**Keywords:** enyne oxiranes; vinylallenes; 2,4,5-trienols; iron-catalyzed; 1,5-substitution; enantiopure allenes



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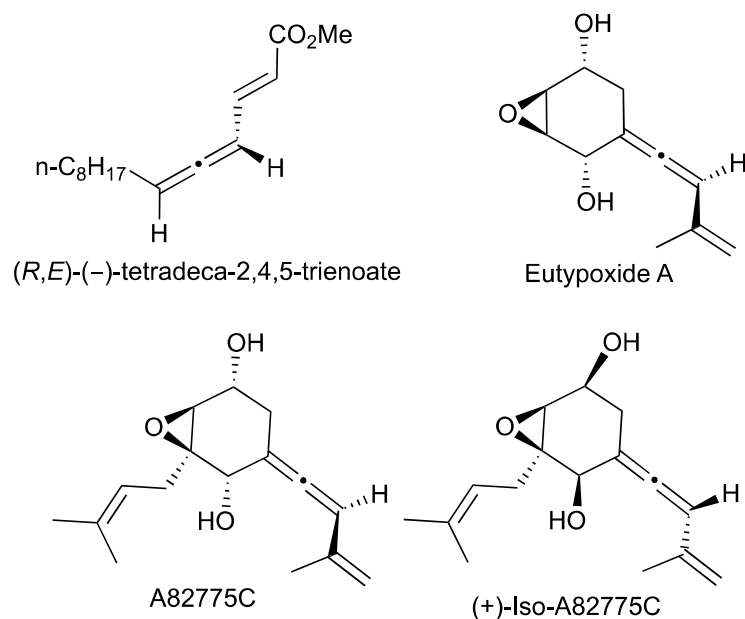
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## 1. Introduction

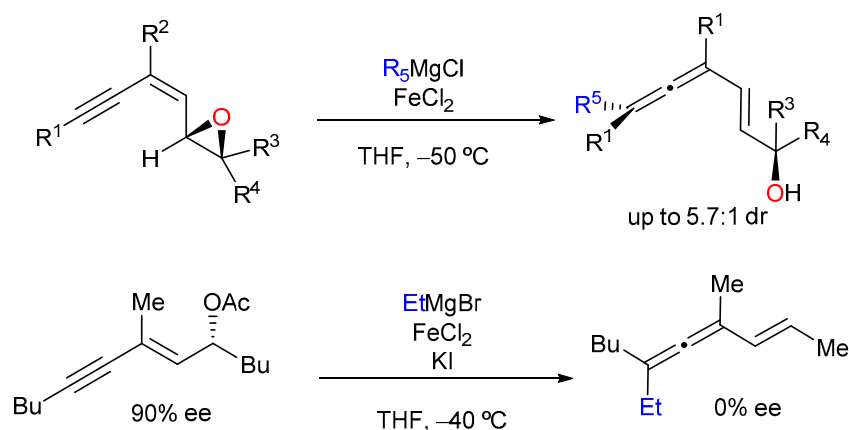
The combined use of iron compounds and Grignard reagents has been widely preferred in metal-mediated nucleophilic substitution [1–10] and addition [11–20] reactions. Both reagents are readily available, environmentally friendly, and relatively low in cost.

We have previously reported that the acetates of 2-en-4-yne alcohols and the conjugated enyne oxiranes undergo 1,5-substitution ( $S_N2''$ ) reactions with Grignard reagents in the presence of an iron compound, yielding vinyl-substituted allenes, commonly referred to as vinylallenes [10]. Vinylallenes [21–44] represent highly valuable synthetic intermediates [45–47] extensively utilized in various chemical processes, including electrocycloaddition [48–50], cycloaddition [35,51–59], cyclization [60–64], and isomerization [65]. Moreover, they play a significant role in the synthesis of numerous natural compounds [66–70]. Notably, various naturally occurring molecules feature vinylallene motifs [71–73] (Figure 1).

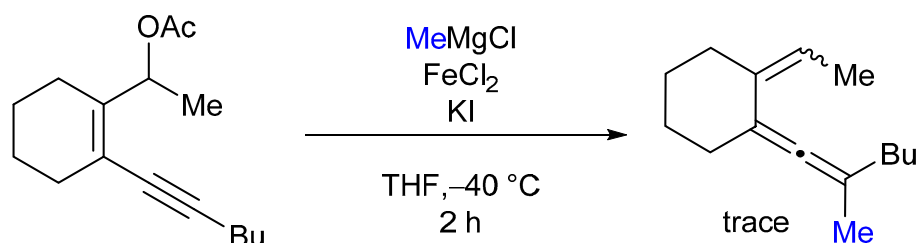
In our previous study, we observed that the method generally had low stereoselectivity [10]. An enantiomerically pure enyne acetate converted to racemic products and the reaction of enyne oxiranes resulted in products with low diastereomeric ratios (dr) (Scheme 1). Additionally, the method did not apply to endocyclic enyne acetates (Scheme 2). However, we now present evidence that, in contrast to their enyne acetate counterparts, endocyclic enyne oxiranes are suitable for the methylation method. Moreover, reactions with these reagents yield exocyclic 2,4,5-trienols with high dr levels, provided that the oxirane moiety is in the *trans*-configuration.



**Figure 1.** Some natural compounds with vinylallene moieties.



**Scheme 1.** Iron-promoted reaction of acyclic enyne oxiranes and an enantiomerically pure enyne acetate with Grignard reagents.



**Scheme 2.** Iron-promoted reaction of an endocyclic enyne acetate with MeMgCl.

## 2. Materials and Methods

### 2.1. General

The dimethylformamide (DMF) used was dried using a solvent purification system (SPS, MBRAUN 800). The solvents, CH<sub>2</sub>Cl<sub>2</sub> and CHCl<sub>3</sub>, were dried over a 3Å molecular sieve preactivated by heating at 400 °C for 24 h and cooled under an argon atmosphere before use. Tetrahydrofuran (THF) was distilled from benzophenone-ketyl under a nitrogen atmosphere for synthesizing starting materials. However, in metal-catalyzed reactions,

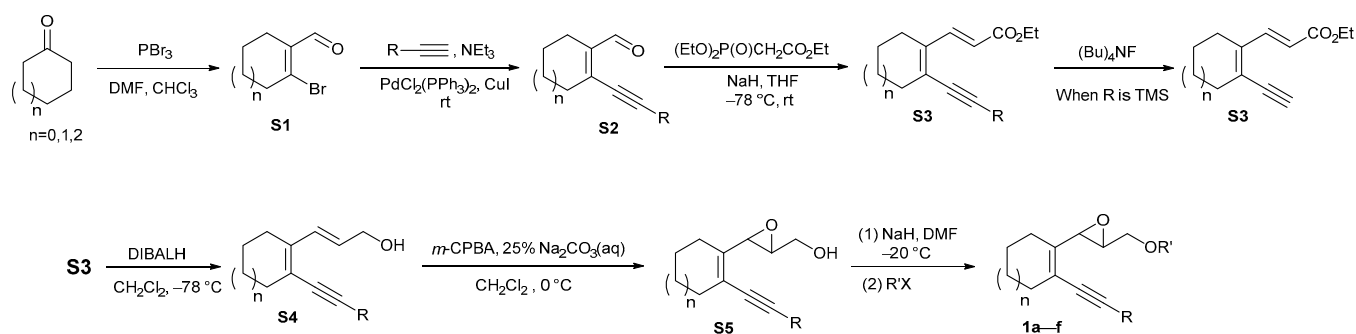
THF was distilled after refluxing for at least 3 h over  $\text{LiAlH}_4$  (300–350 mg/400 mL) under high-purity grade-6 argon gas. The argon gas was passed through a  $\text{KOH-P}_2\text{O}_5$  line just before use.

The synthesized enyne oxiranes were purified on triethylamine-deactivated silica gel with a mesh size of 200, while all other materials were purified on columns containing silica gel with a particle size of 35–70  $\mu\text{m}$ .

Pure samples were analyzed using GC/MS, NMR, and HRMS techniques. The NMR spectra were recorded on a Varian VnmrJ 400 spectrometer using  $\text{C}_6\text{D}_6$  as the NMR solvent for vinylallene products and  $\text{CDCl}_3$  for all other materials. Partial resolution of diastereomeric proton signals was achievable in the  $^1\text{H-NMR}$  spectra when recorded in  $\text{C}_6\text{D}_6$ . As a result, we were able to determine the diastereomeric ratios of the products using the NMR method.

## 2.2. Synthesis of Racemic Enyne Oxiranes

The synthesis of methoxy, benzyloxy, and silyloxy-substituted racemic endocyclic enyne oxiranes was carried out, starting from cycloalkanones (Scheme 3): to a mixture of DMF (12 mL, 153 mmol) and chloroform (80 mL) cooled to  $0^\circ\text{C}$  was added  $\text{PBr}_3$  (14 mL, 138 mmol) dropwise and stirred at this temperature for 1 h. Subsequently, 60 mmol of cycloalkanone was added dropwise to this mixture, and the entire mixture was refluxed overnight. After completion, the reaction was terminated with an ice-water mixture and carefully neutralized with  $\text{NaHCO}_3(\text{aq})$ . The organic phase was separated, and the aqueous phase was washed with  $\text{CH}_2\text{Cl}_2$ . The extract was then dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated under reduced pressure. The crude product was purified using silica gel column chromatography to obtain **S1** as a pale-yellow oil (hexane/EtOAc; yield:  $n = 0$ , 67%;  $n = 1$ , 72%;  $n = 2$ , 74%) [74].



**Scheme 3.** The methods applied for the synthesis of racemic endocyclic enyne oxiranes.

**S1** (25 mmol),  $\text{PdCl}_2(\text{PPh}_3)_2$  (2 mol% Pd, 355 mg, 0.5 mmol), and  $\text{CuI}$  (2 mol%, 95 mg, 0.5 mmol) were added to a degassed solution of  $\text{Et}_3\text{N}$  (50 mL) and stirred at room temperature (rt) for 10 min. A terminal alkyne (3.5 mL, 30 mmol) was then slowly added to this mixture, and the resulting mixture was magnetically stirred at rt under an inert gas. The reaction was monitored through gas chromatography (GC). After the reactant was completely consumed, the reaction was terminated by adding a saturated solution of  $\text{NH}_4\text{Cl}(\text{aq})$  and then extracted with  $\text{Et}_2\text{O}$ . The combined organic phases were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and evaporated under reduced pressure. The crude mixture was subsequently purified using silica gel column chromatography to yield endocyclic enyne aldehydes **S2** as a pale-yellow oil (hexane/EtOAc; yield:  $\text{R} = \text{Bu}$ ,  $n = 0$ , 88%;  $n = 1$ , 91%;  $n = 2$ , 90%;  $\text{R} = \text{Ph}$ ,  $n = 1$ , 67%;  $\text{R} = \text{TMS}$ ,  $n = 1$ , 92%) [75].

To a suspension of  $\text{NaH}$  (528 mg, 22 mmol) in a dry THF (50 mL) at  $0^\circ\text{C}$ , triethyl phosphonoacetate (4.8 mL, 24 mmol) was added dropwise and stirred at rt for 1 h. **S2** (3.8 g, 20 mmol) dissolved in 10 mL of THF was then added dropwise to this mixture at  $-78^\circ\text{C}$ . The mixture was stirred at this temperature for 1 h and then brought to rt. The reaction was monitored using GC. The reaction was terminated upon completion by adding a saturated

$\text{NH}_4\text{Cl}$ (aq) solution, extracted with  $\text{Et}_2\text{O}$ , and dried over  $\text{Na}_2\text{SO}_4$ . The crude mixture was concentrated under reduced pressure and purified using silica gel column chromatography to yield **S3** as a colorless oil (hexane/EtOAc; R = Bu, n = 0, 77%; n = 1, 82%; n = 2, 84%; R = Ph, n = 1, 82%; R = TMS, n = 1, 81%) [76].

For the desilylation of trimethylsilyl (TMS)-substituted dienyne ester, a solution of TMS-**S3** (828 mg, 3 mmol) in 10 mL of dry THF at 0 °C, was prepared. To this solution,  $(\text{Bu})_4\text{NBr}$  (1.3 equiv, 3.9 mL, 3.9 mmol, 1 M in THF) was added dropwise and stirred for 1 h. The reaction progress was monitored using TLC and was terminated by adding a saturated  $\text{NH}_4\text{Cl}$ (aq) solution. The organic phase was separated, and the aqueous phase was extracted with  $\text{Et}_2\text{O}$ . The combined organic phases were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated under reduced pressure. The crude product was subsequently purified using silica gel column chromatography to yield the desilylated product as a pale-yellow oil (hexane/EtOAc; 92%).

To the solution of **S3** (10 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (60 mL) cooled to  $-78$  °C, diisopropyl aluminium hydride (DIBALH) (3 equiv, 30 mL, 1.0 M in  $\text{CH}_2\text{Cl}_2$ ) was added dropwise and stirred at this temperature. The reaction was monitored using TLC, and upon completion, the mixture was quenched with a saturated Rochelle's salt (sodium-potassium tartarate) solution. The quenched mixture was stirred for additional 3 h at rt. The organic phase was separated, and the aqueous phase was washed with  $\text{CH}_2\text{Cl}_2$ . The combined organic phases were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and evaporated under reduced pressure. The crude mixture was purified using silica gel column chromatography to obtain **S4** as a colorless oil (hexane/EtOAc; yield: R = Bu, n = 0, 81%; n = 1, 89%; n = 2, 82%; R = Ph, n = 1, 81%; R = H, n = 1, 88%) [33].

To the solution of dienynol **S4** (2 mmol) in 30 mL of  $\text{CH}_2\text{Cl}_2$  cooled to 0 °C, 12 mL of 25%  $\text{Na}_2\text{CO}_3$ (aq) solution and *m*-chloroperbenzoic acid (MCPBA) (762 mg, 3.4 mmol,  $\leq 77\%$ ) were added successively. The reaction was monitored using TLC, and upon completion, the mixture was diluted with water, extracted with  $\text{CH}_2\text{Cl}_2$ , dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated under reduced pressure. The residue was purified through column chromatography using  $\text{NEt}_3$ -deactivated silica gel, and enyne oxirane **S5** was obtained as a pale-yellow oil (hexane/EtOAc; yield: R = Bu, n = 0, 27%; n = 1, 83%; n = 2; 55%; R = Ph, n = 1, 75%; R = H, n = 1, 53%) [33].

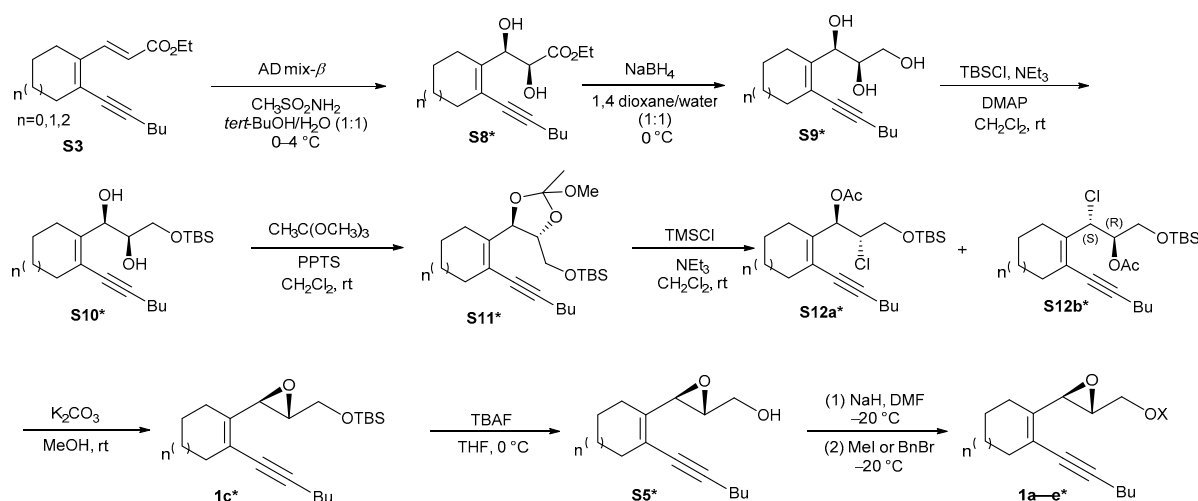
The compound **S5** (1 mmol) was added dropwise to the mixture of DMF (2 mL) and NaH (26.4 mg, 1.1 mmol) under an argon atmosphere at  $-20$  °C. After stirring this mixture for 0.5 h at the same temperature, MeI (75 mL, 1.2 mmol) was added and stirred for 1 h. The reaction progress was monitored through TLC and terminated with the addition of 10 mL of water/methanol mixture (1:1). The methyl-substituted structure **1** was purified through column chromatography using  $\text{NEt}_3$ -deactivated silica gel as a pale-yellow oil (hexane/EtOAc; R = Bu, **1d**, n = 0, 91%; **1a**, n = 1, 88%; **1e**, n = 2, 82%; **1g**, R = Ph, n = 1, 89%; **1f**, R = H, n = 1, 88%).

A DMF (1 mL) solution of compound **S5** (n = 1, 1 mmol) was added to a DMF (2 mL) solution of NaH (26.4 mg, 1.1 mmol) dropwise under an argon atmosphere at  $-20$  °C. After stirring this mixture for 0.5 h at the same temperature, BnBr (143  $\mu\text{L}$ , 1.2 mmol) was added and stirred for an additional 1 h. The reaction was monitored through TLC and terminated with the addition of 10 mL of water/methanol mixture (1:1). The benzyl-substituted structure **1b** was purified through column chromatography using  $\text{NEt}_3$ -deactivated silica gel as a pale-yellow oil (hexane/EtOAc; 81%).

**S5** (n = 1, 234 mg, 1 mmol) was dissolved in 15 mL of  $\text{CH}_2\text{Cl}_2$  under a nitrogen atmosphere. To this solution, *tert*-butyldimethylsilyl chloride (TBDMSCl, 1.2 equiv., 181 mg, 1.2 mmol),  $\text{Et}_3\text{N}$  (1.25 equiv, 0.2 mL, 1.25 mmol), and a catalytic amount of 4-dimethylaminopyridine (DMAP, 12.5 mg, 0.1 mmol) were added, respectively, and stirred for 24 h. The reaction was monitored using TLC, extracted with  $\text{CH}_2\text{Cl}_2$ , dried over  $\text{Na}_2\text{SO}_4$ , and filtered. The silyl-substituted compound **1c** was purified through column chromatography using  $\text{NEt}_3$ -deactivated silica gel (pale-yellow oil; hexane/EtOAc; 87%).

### 2.3. Synthesis of Enantiopure *Trans*-Enyne Oxiranes

Sharpless asymmetric dihydroxylation was the key step in synthesizing enantiopure substrates in this study [77] (Scheme 4): to a mixture of 80 mL water/*tert*-BuOH (1:1) at rt, 9.2 g of AD mix- $\beta$  and  $\text{CH}_3\text{SO}_2\text{NH}_2$  (760 mg, 8 mmol) were added and stirred until the solution became clearer (about 15 min after AD mix- $\beta$  was added, the mixture became a diphasic heterogeneous red mixture, but after some stirring, it became a clear, pale-red solution). Then, the mixture was cooled to 0 °C, and **S3** (8 mmol) was added. The reaction flask was kept in a refrigerator at 4 °C.



**Scheme 4.** The methods applied for the synthesis of enantiopure endocyclic *trans*-enyne oxiranes.

When the reaction was complete (approximately 3–10 days, as determined through TLC analysis), 12 g of  $\text{Na}_2\text{S}_2\text{O}_3$  was added, and the mixture was stirred for 1 h at rt. The reaction medium was diluted with water, extracted using EtOAc, dried over  $\text{Na}_2\text{SO}_4$ , filtered, and evaporated under reduced pressure. The crude mixture was purified using silica gel column chromatography, resulting in the isolation of **S8\*** as a white solid (hexane/EtOAc; yield:  $n = 0$ , 55%;  $n = 1$ , 78%, 96.5% ee;  $n = 2$ , 75%).

The compound **S8\*** (4 mmol) was dissolved in a 1,4-dioxane/water mixture (40 mL, 1:1 ratio) and cooled down to 0 °C, and  $\text{NaBH}_4$  (3 equiv, 454 mg, 12 mmol) was added incrementally to the mixture. The mixture was stirred at this temperature until **S8\*** was completely consumed, as determined through TLC. The reaction was then quenched by adding 0.1 M HCl, and the product was extracted with EtOAc, dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated under reduced pressure. The resulting residue was purified using silica gel column chromatography, yielding **S9\*** as a white paste (hexane/EtOAc;  $n = 0$ , 80%;  $n = 1$ , 95%;  $n = 2$ , 87%).

To a solution of **S9\*** (3.8 mmol) in 15 mL of  $\text{CH}_2\text{Cl}_2$ , TBDMSCl (1.2 equiv, 689 mg, 4.56 mmol),  $\text{NEt}_3$  (1.25 equiv, 0.7 mL, 4.75 mmol), and a catalytic amount of 4-dimethylaminopyridine (DMAP, 25 mg, 0.2 mmol) were added. The mixture was stirred at rt for 24 h. The reaction progress was monitored through TLC, and upon completion, the reaction mixture was diluted with water, extracted with  $\text{CH}_2\text{Cl}_2$ , dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated under reduced pressure. The silylated product **S10\*** was purified using column chromatography, resulting in a yellow oil (hexane/EtOAc; yield:  $n = 0$ , 70%;  $n = 1$ , 81%;  $n = 2$ , 77%).

The diol compound **S10\*** (0.2 mmol) was dissolved in 1 mL of dry  $\text{CH}_2\text{Cl}_2$  under an argon atmosphere. To this solution, 0.5 mg of pyridinium *p*-toluene sulfonate (PPTS) and trimethyl orthoacetate (1.2 equiv, 32 mL, 0.24 mmol) were added. The reaction progress was monitored using TLC, and once the reagent was completely converted, the reaction mixture was evaporated at rt under reduced pressure. The crude mixture was further evaporated using a vacuum pump for 5 min to remove volatile by-products completely. Subsequently, 1 mL of dry  $\text{CH}_2\text{Cl}_2$  was added to the flask, followed by the sequential addition of  $\text{NEt}_3$

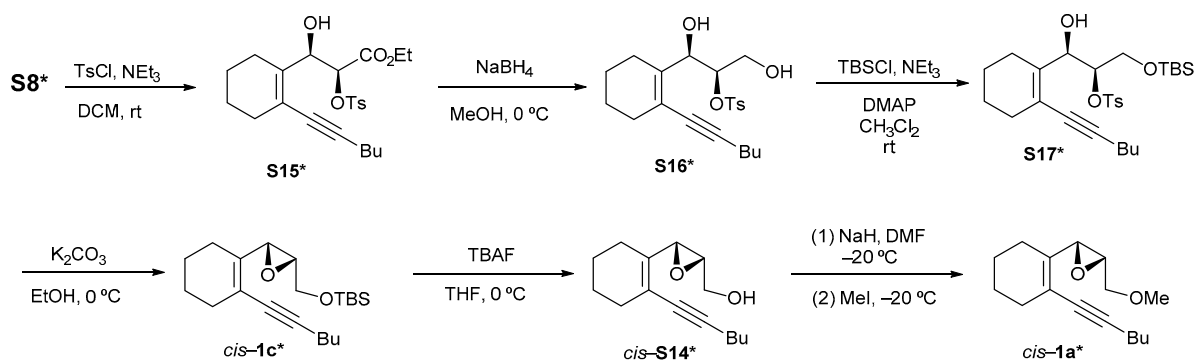
(2 mL, 10% mmol) and TMSCl (1.2 equiv, 31 mL, 0.24 mmol). The progress of the reaction was monitored using TLC, and upon depletion of the reactant, the reaction mixture was evaporated under reduced pressure at rt. In the final step of this one-pot synthesis, 1 mL of dry MeOH and K<sub>2</sub>CO<sub>3</sub> (4 equiv, 110 mg, 0.8 mmol) were added to the crude product under an argon atmosphere, and the mixture was stirred at rt until complete conversion. The residue was purified through column chromatography using silica gel treated with NEt<sub>3</sub> to yield the *trans*-configured **S13\*** compound as a pale-yellow oil (hexane/EtOAc; yield of the three steps: n = 0, 47%; **1c\***, n = 1, 63%; n = 2, 56%) [78]. The synthesis of **S13\*** was repeated to obtain a sufficient amount of the substrate.

To a solution of **S13\*** (0.2 mmol) in 10 mL of dry THF at 0 °C, TBAF (1.3 equiv, 0.26 mL, 0.26 mmol, 1 M in THF) was added dropwise and stirred for 1 h. The reaction was monitored using TLC and terminated with the addition of a saturated NH<sub>4</sub>Cl(aq) solution. The organic phase was separated, and the aqueous phase was extracted with Et<sub>2</sub>O. The combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude product was purified through column chromatography using NEt<sub>3</sub>-deactivated silica gel to yield **S14\*** products as a pale-yellow oil (hexane/EtOAc; n = 0, 87%; n = 1, 92%; n = 2, 91%). The synthesis of **S14\*** was repeated to obtain a sufficient amount of the substrate.

The compound **S14\*** (1 mmol) was added dropwise to a 2 mL solution of DMF in the presence of NaH (26.4 mg, 1.1 mmol) under an argon atmosphere at −20 °C. After stirring the mixture for 0.5 h at the same temperature, MeI (75 mL, 1.2 mmol) or BnBr (1.2 mmol) was added and stirred until the reaction was complete (~1 h) as confirmed through a TLC analysis. The reaction was terminated with the addition of a 10 mL water/methanol (1:1) mixture. The resulting compound **1\*** was purified through column chromatography using NEt<sub>3</sub>-treated silica gel, yielding a pale-yellow oil (hexane/EtOAc; **1d\***, n = 0, 91%; **1a\***, n = 1, 88%; **1e\***, n = 2, 82%; **1b\***, 93%).

#### 2.4. Synthesis of Enantiopure *Cis*-Enyne Oxiranes

A dry CH<sub>2</sub>Cl<sub>2</sub> solution (10 mL) of **S8\*** (1.47 g, 5 mmol, 96.5% ee), NEt<sub>3</sub> (1.25 equiv, 0.9 mL, 6.25 mmol), and TsCl (1.2 equiv., 1.33 g, 6 mmol) was stirred 1 h under N<sub>2</sub> at rt. Then, the reaction medium was extracted using EtOAc, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude product was purified using silica gel column chromatography to obtain **S15\*** as a pale-yellow oil (hexane/EtOAc; 97%) (Scheme 5).



**Scheme 5.** The synthesis of enantiopure endocyclic enyne oxirane *cis*-**1a\***.

In a 20 mL MeOH solution of **S3\*** (4 mmol), NaBH<sub>4</sub> (3 equiv, 454 mg, 12 mmol) was added in portions at 0 °C and stirred until the reduction process was complete, as determined through TLC. The reaction was terminated by adding 0.1 M HCl(aq) solution; then, it was extracted with EtOAc, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated under reduced pressure. The residue was purified over silica gel column chromatography to yield **S16\*** as a white paste (hexane/EtOAc; 95% yield).

Under an inert gas atmosphere, **S16\*** (3.8 mmol) was dissolved in dry  $\text{CH}_2\text{Cl}_2$  (15 mL). Subsequently, TBDMSCl (1.2 equiv, 689 mg, 4.56 mmol),  $\text{NEt}_3$  (1.25 equiv, 0.7 mL, 4.75 mmol), and a catalytic amount of 4-dimethylamino pyridine (DMAP, 25 mg, 0.2 mmol) were added, and the reaction mixture was stirred for 24 h. The reaction was terminated using water, extracted with  $\text{CH}_2\text{Cl}_2$ , dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated under reduced pressure. The silylated product **S17\*** was purified using silica gel column chromatography, yielding a pale-yellow oil (hexane/EtOAc; 87% yield).

For the epoxidation process, a 15 mL EtOH solution of **S17\*** (1.44 g, 3 mmol) and  $\text{K}_2\text{CO}_3$  (3 equiv, 1.24 g, 9 mmol) was stirred for 3 h at 0 °C. Upon completion, 20 mL of water was added to the reaction mixture, which was then extracted using  $\text{Et}_2\text{O}$ , dried over  $\text{Na}_2\text{SO}_4$ , filtered, and evaporated under reduced pressure. The residue was purified through column chromatography using  $\text{NEt}_3$ -deactivated silica to obtain *cis-1c\** as a pale-yellow oil (hexane/EtOAc; 83% yield) [79].

In a dry THF (10 mL) solution of *cis-1c\** (2 mmol), TBAF (1.3 equiv, 2.6 mL, 2.6 mmol, 1 M in THF) was added dropwise at 0 °C under a nitrogen atmosphere. The mixture was stirred for 1 h, and the reaction was terminated with water, followed by its extraction using  $\text{Et}_2\text{O}$ , drying over  $\text{Na}_2\text{SO}_4$ , filtration, and evaporation under reduced pressure. The compound **S18\*** was isolated through column chromatography using  $\text{NEt}_3$ -deactivated silica (pale-yellow oil; hexane/EtOAc; 92% yield). The methylation of the hydroxyl group was performed as described for the synthesis of **1a** (colorless oil; hexane/EtOAc; 86%).

**S8\*** (n = 1):  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 4.96 (dd,  $J = 6.7, 4.3$  Hz, 1H), 4.35–4.21 (m, 3H), 3.04 (d,  $J = 6.0$  Hz, 1H), 2.69 (d,  $J = 6.9$  Hz, 1H), 2.32 (t,  $J = 7.0$  Hz, 2H), 2.28–2.06 (m, 4H), 1.64–1.37 (m, 8H), 1.31 (t,  $J = 7.1$  Hz, 3H), 0.91 (t,  $J = 7.3$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 173.0, 141.5, 117.9, 95.3, 79.4, 74.4, 73.5, 62.1, 30.9, 30.6, 24.6, 22.2, 22.1, 22.0, 19.2, 14.1, 13.6; HPLC: OJ-H, hexane/IPA = 98.0:2.0, 1.0 mL/min, 220 nm,  $\text{RT}_1 = 9.05$  (major),  $\text{RT}_2 = 9.9$  (minor), ee%: 96.5.

**1a\***:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 3.88 (d,  $J = 2.2$  Hz, 1H), 3.69 (ddd,  $J = 11.4, 3.0, 0.6$  Hz, 1H), 3.45–3.35 (m, 1H), 3.40 (s, 3H), 3.12 (dt,  $J = 5.3, 2.7$  Hz, 1H), 2.34 (t,  $J = 6.8$  Hz, 2H), 2.20–2.11 (m, 2H), 2.08–1.88 (m, 1H), 1.72–1.34 (m, 9H), 0.98–0.90 (m, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 137.3, 121.7, 94.2, 79.5, 73.0, 59.1, 56.2, 55.2, 31.6, 30.9, 22.4, 22.2, 21.9, 21.7, 19.1, 13.6; specific rotation:  $[\alpha]_D^{24} = 10.3$  (c = 1.165 in  $\text{CHCl}_3$ ); HPLC: OJ-H, hexane, 1 mL/min, 254 nm,  $\text{RT}_1 = 8.56$  (major),  $\text{RT}_2 = 11.75$  (minor), ee%: 96.7.

*Cis-1a\**:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) 3.80 (d,  $J = 2.2$  Hz, 1H), 3.69 (d,  $J = 11.8$ , 1H), 3.45–3.31 (m, 1H), 3.40 (s, 3H), 3.12 (dt,  $J = 5.4, 2.7$  Hz, 1H), 2.34 (t,  $J = 6.8$  Hz, 2H), 2.23–2.11 (m, 2H), 2.08–1.88 (m, 1H), 1.72–1.34 (m, 9H), 0.94 (t,  $J = 7.2$  Hz, 3H).

**1b\***:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.38–7.23 (m, 5H), 4.59 (q,  $J = 12.0$  Hz, 2H), 4.01 (d,  $J = 2.3$  Hz, 1H), 3.81 (dd,  $J = 11.5, 2.9$  Hz, 1H), 3.47 (dd,  $J = 11.5, 6.0$  Hz, 1H), 3.28–3.21 (m, 1H), 2.31 (t,  $J = 6.9$  Hz, 2H), 2.19–2.05 (m, 2H), 2.01–1.87 (m, 1H), 1.73–1.29 (m, 9H), 0.87 (t,  $J = 7.2$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 138.0, 137.3, 128.4, 127.73, 127.70, 121.8, 94.3, 79.5, 73.2, 70.7, 56.4, 55.4, 30.94, 30.89, 22.4, 22.2, 22.0, 21.7, 19.2, 13.6; specific rotation:  $[\alpha]_D^{24} = -0.97$  (c = 4.11 in  $\text{CHCl}_3$ ); HPLC: OJ-H, hexane/IPA = 99.0:1.0, 1 mL/min, 254 nm,  $\text{RT}_1 = 6.29$  (major),  $\text{RT}_2 = 7.69$  (minor), ee%: 95.8.

**1c\***:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 3.99 (d,  $J = 2.3$  Hz, 1H), 3.87 (dd,  $J = 12.9, 2.9$  Hz, 1H), 3.64 (dd,  $J = 11.9, 4.7$  Hz, 1H), 3.10 (dt,  $J = 5.0, 2.6$  Hz, 1H), 2.29 (t,  $J = 6.9$  Hz, 2H), 2.18–2.05 (m, 2H), 2.00–1.85 (m, 1H), 1.72–1.29 (m, 9H), 0.87 (t,  $J = 7.2$  Hz, 3H), 0.86 (s, 9H), 0.04 (s, 6H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 137.5, 121.4, 94.0, 79.5, 63.5, 57.0, 56.3, 30.95, 30.93, 25.8, 22.4, 22.3, 22.0, 21.7, 19.2, 18.3, 13.6, -5.35, -5.41; specific rotation:  $[\alpha]_D^{24} = 11$  (c = 0.22 in  $\text{CHCl}_3$ ) HPLC: OD-3, hexane, 1 mL/min, 254nm,  $\text{RT}_1 = 7.025$  (major),  $\text{RT}_2 = 15.177$  (minor), ee%: 97.5.

**1d\***:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 3.77 (d,  $J = 2.1$  Hz, 1H), 3.71 (dd,  $J = 11.4, 3.0$  Hz, 1H), 3.41–3.36 (m, 4H), 3.23 (dt,  $J = 5.3, 2.9$  Hz, 1H), 2.47 (t,  $J = 6.7$  Hz, 2H), 2.35 (t,  $J = 6.8$  Hz, 2H), 2.18–2.08 (m, 1H), 1.83 (q,  $J = 7.8$  Hz, 2H), 1.45 (dq,  $J = 37.1, 7.0$  Hz, 4H), 0.90 (t,  $J = 7.3$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 143.4, 126.3, 96.4, 75.8, 72.8, 59.2, 56.4, 53.0, 37.7, 30.8, 30.6, 22.1, 21.9, 19.3, 13.6; specific rotation:  $[\alpha]_D^{28} = 1.302$  (c = 3.07 in  $\text{CHCl}_3$ );

HPLC: OJ-H, hexane/IPA = 99.0:1.0, 1 mL/min, 254 nm, RT<sub>1</sub> = 10.80 (major), RT<sub>2</sub> = 15.93 (minor), ee%: 98.6.

**1e**\*: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 3.96 (d, *J* = 2.3 Hz, 1H), 3.74 (dd, *J* = 11.5, 2.8 Hz, 1H), 3.42–3.33 (m, 4H), 3.04–2.99 (m, 1H), 2.32 (d, *J* = 6.9 Hz, 2H), 1.96–1.82 (m, 2H), 1.74–1.66 (m, 2H), 1.56–1.24 (m, 10H), 0.89 (t, *J* = 7.2 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ: 143.7, 127.0, 95.1, 80.7, 72.8, 59.1, 55.8, 55.1, 35.7, 32.5, 30.9, 26.2, 26.1, 25.2, 21.9, 19.3, 13.6; specific rotation:  $[\alpha]_D^{28} = -11.428$  (*c* = 2.45 in CHCl<sub>3</sub>); HPLC: OJ-H, hexane/IPA = 99:1, 1 mL/min, 254 nm, RT<sub>1</sub> = 7.94 (major), RT<sub>2</sub> = 11.30 (minor), ee%: 94.2.

**1f**: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 3.99–3.93 (m, 1H), 3.72 (ddd, *J* = 11.4, 3.0, 1.1 Hz, 1H), 3.41–3.35 (m, 4H), 3.22–3.17 (m, 1H), 3.13 (s, 1H), 2.20–2.18 (m, 2H), 2.01–1.96 (m, 1H), 1.74–1.49 (m, 5H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ: 141.1, 120.1, 82.6, 81.1, 72.9, 59.2, 55.9, 55.3, 30.3, 22.5, 22.0, 21.5.

**1g**: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 7.44–7.29 (m, 5H), 4.09 (d, *J* = 2.3 Hz, 1H), 3.76 (dd, *J* = 11.4, 3.1 Hz, 1H), 3.45 (d, *J* = 5.9 Hz, 1H), 3.42 (s, 3H), 3.26 (dt, *J* = 5.2, 2.6 Hz, 1H), 2.30 (s, 2H), 2.08–2.04 (m, 1H), 1.84–1.55 (m, 5H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ: 139.5, 131.3, 128.3, 128.1, 123.5, 121.1, 93.3, 88.3, 72.9, 59.2, 56.3, 55.5, 30.5, 22.7, 22.2, 21.6.

### 2.5. Iron-Catalyzed Reaction Protocol

All the glassware equipment used in the reaction were kept in an oven for 24 h at 120 °C and then cooled under an argon atmosphere before use. The catalyst precursor, Fe(acac)<sub>3</sub>, was placed in a Schlenk flask held under a 6-grade argon-filled balloon, and 2 mL of dry THF was added. After stirring the mixture for 1 min at rt, the Schlenk flask was cooled to −50 °C. The Grignard reagent (3 equiv, MeMgBr, 3 M in THF) was added to the reaction mixture dropwise and then stirred for 15 min. The enyne oxirane reagent (0.1 mmol in 1 mL dry THF) was introduced into the reaction medium via a syringe pump over 30 min. The reaction was allowed to continue after the addition of the Grignard solution was complete. Once the reaction was deemed complete as determined through TLC, it was terminated with a saturated NH<sub>4</sub>Cl solution. The mixture was then extracted using Et<sub>2</sub>O, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated under reduced pressure. The crude material was purified through silica gel column chromatography (resulting in a pale-yellow oil; hexane/EtOAc). Enantiomeric excess was analyzed through HPLC using suitable chiral columns, and the diastereomeric ratios were determined with the NMR technique using C<sub>6</sub>D<sub>6</sub> as the solvent. HRMS analyses were carried out using a Q-TOF LC/MS system.

**2a**\*: <sup>1</sup>H NMR (400 MHz, C<sub>6</sub>D<sub>6</sub>) δ: 5.74 (d, *J* = 8.0 Hz, 1H), 4.67–4.57 (m, 1H), 3.18–3.10 (m, 2H), 2.99 (s, 3H, minor), 2.98 (s, 3H, major), 2.37–2.22 (m, 3H), 2.22–2.10 (m, 2H), 2.00–1.81 (m, 2H), 1.65 (s, 3H, major), 1.64 (s, 3H, minor), 1.55–1.23 (m, 8H), 0.86 (t, *J* = 7.3 Hz, 3H, major), 0.85 (t, *J* = 7.3 Hz, 3H, minor); <sup>13</sup>C NMR (100 MHz, C<sub>6</sub>D<sub>6</sub>) δ: 197.7, 139.6, 123.7, 104.8, 98.6, 76.6, 67.0, 58.2, 34.0, 31.9, 29.8, 28.7, 26.2, 25.8, 22.3, 19.2, 13.9; M.S. (E.I. *m/z*): 264.2 (37.31, M<sup>+</sup>), 219.1 (36), 201.2 (26.30), 177.2 (14.85), 163.1 (29.37), 159.1 (17.87), 145.1 (51.69), 133.1 (92.06), 131 (54), 119 (45), 105 (100), 91 (88), 77 (39), 57 (21); HRMS (*m/z*, (M+H)<sup>+</sup>): 265.2162 (calculated), 265.2140 (found); specific rotation:  $[\alpha]_D^{24} = -38.23$  (*c* = 1.21 CHCl<sub>3</sub>); HPLC: IC, hexane/IPA = 95:5, 1 mL/min, 254 nm, RT<sub>1</sub> = 6.14 (major), RT<sub>2</sub> = 6.55 (minor), ee%: 95.2.

**2b**\*: <sup>1</sup>H NMR (400 MHz, C<sub>6</sub>D<sub>6</sub>) δ: 7.18–7.02 (m, 5H), 5.76 (d, *J* = 8.1 Hz, 1H), 4.65 (td, *J* = 7.8, 4.1 Hz, 1H), 4.21 (s, 2H, minor), 4.20 (s, 2H, major), 3.32–3.21 (m, 2H), 2.30–2.21 (m, 3H), 2.14–2.06 (m, 1H), 1.96–1.82 (m, 2H), 1.63 (s, 3H, major), 1.62 (s, 3H, minor), 1.53–1.16 (m, 9H), 0.84 (t, *J* = 7.3 Hz, 3H); <sup>13</sup>C NMR (100 MHz, C<sub>6</sub>D<sub>6</sub>) δ: 197.7, 139.6, 138.4, 128.2, 127.5, 123.7, 104.8, 98.6, 74.3, 72.9, 67.2, 34.0, 31.9, 29.8, 28.7, 26.1, 25.7, 22.3, 19.3, 13.9; HRMS (ESI) C<sub>23</sub>H<sub>33</sub>O<sub>2</sub> (M+Na)<sup>+</sup>: 363.2295 (calculated), 363.2280 (measured); M.S. (E.I. *m/z*): 340.2 (6.42, M<sup>+</sup>), 219 (15), 203 (8), 189 (13), 175.1 (8), 161 (11), 149 (10), 133 (19), 119 (20), 105 (30), 91 (100), 77 (14); specific rotation:  $[\alpha]_D^{24} = -28.10$  (*c* = 1.21 CHCl<sub>3</sub>); HPLC: IC, hexane/IPA = 95:5, 1 mL/min, 254 nm, RT<sub>1</sub> = 6.12 (minor), RT<sub>2</sub> = 6.55 (major), ee%: 95.8.

**2c**\*:  $^1\text{H}$  NMR (400 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  5.76 (d,  $J = 8.1$  Hz, 1H, major), 5.74 (d,  $J = 7.6$  Hz, 1H, minor), 4.56–4.49 (m, 1H), 3.56–3.49 (m, 2H, minor), 3.52–3.42 (m, 2H, major), 2.40–2.21 (m, 4H), 1.98–1.83 (m, 2H), 1.65 (s, 3H, major), 1.63 (s, 3H, minor), 1.51–1.25 (m, 9H), 0.87 (t,  $J = 7.3$  Hz, 3H), 0.85 (s, 9H),  $-0.06$  (s, 6H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$ : 197.7 (major), 197.6 (minor), 139.6 (major), 139.5 (minor), 124.0 (minor), 123.9 (major), 105.0 (minor), 104.9 (major), 98.6 (major), 98.4 (minor), 68.8 (minor), 68.7 (major), 67.3, 34.1 (major), 34.0 (minor), 31.9 (major), 31.9 (minor), 29.8 (major), 29.7 (minor), 28.8, 26.2 (minor), 26.1 (major), 25.8 (major), 25.8 (minor), 25.7, 22.3 (major), 22.2 (minor), 19.4 (major), 19.2 (minor), 18.1, 13.9,  $-5.7$ ,  $-5.6$ ; MS(EI  $m/z$ ): 364.4 ( $<5$ ,  $\text{M}^+$ ), 291 (26), 203 (20), 157 (30), 145 (16), 131 (23), 177 (27), 105 (19), 101 (29), 91 (40), 77.0 (17), 75 (100), 59 (26); specific rotation:  $[\alpha]_D^{24} = 32.84$  ( $c = 0.28$  in  $\text{CHCl}_3$ ).

**2d**\*:  $^1\text{H}$  NMR (400 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  5.83 (dt,  $J = 8.2, 2.4$  Hz, 1H), 4.54 (td,  $J = 8.0, 4.1$  Hz, 1H), 3.18–3.08 (m, 2H), 2.98 (s, 3H, minor), 2.96 (s, 3H, major), 2.38 (t,  $J = 7.2$  Hz, 2H), 2.33–2.22 (m, 1H), 2.11 (dtd,  $J = 10.2, 7.7, 2.6$  Hz, 1H), 1.91 (td,  $J = 7.2, 2.2$  Hz, 2H), 1.64 (s, 3H, major), 1.63 (s, 3H, minor), 1.51–1.21 (m, 7H), 0.82 (t,  $J = 7.3$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$ : 195.4, 142.6, 119.9, 105.7, 103.8, 76.4, 69.3, 58.2, 34.2, 31.7, 30.0, 29.8, 25.0, 22.4, 18.8, 13.8; M.S. (E.I.,  $m/z$ ): 250 ( $<5$ ,  $\text{M}^+$ ), 205 (98), 187 (46), 145 (80), 131 (53), 117 (58), 105 (77), 91 (98), 79 (63), 57 (45), 45 (47); specific rotation:  $[\alpha]_D^{28} = -46.51$  ( $c = 0.301$  in  $\text{CHCl}_3$ ); HPLC: AS-H, hexane, 1 mL/min, 254 nm,  $\text{RT}_1 = 24.05$  (major),  $\text{RT}_2 = 24.54$  (minor), ee%: 99.3.

**2e**:  $^1\text{H}$  NMR (400 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  5.83 (d,  $J = 8.1$  Hz, 1H), 4.61 (td,  $J = 8.1, 4.0$  Hz, 1H), 3.28–3.06 (m, 2H), 2.97 (s, 3H, minor), 2.96 (s, 3H, major), 2.31–2.18 (m, 4H), 1.90 (tq,  $J = 14.8, 7.3$  Hz, 2H), 1.64 (s, 3H, major), 1.62 (s, 3H, minor), 1.59–1.16 (m, 11H), 0.84 (t,  $J = 7.3$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$ : 199.8, 142.7, 124.6, 108.2, 99.1, 76.7, 67.5, 58.2, 34.0, 33.0, 31.4, 30.2, 29.8, 29.7, 29.2, 22.4, 18.9, 13.8; M.S. (EI  $m/z$ ): 278.3 ( $<5$ ,  $\text{M}^+$ ), 147 (6), 133 (6), 117 (12), 105 (9), 91 (31), 79 (14), 67 (9), 55 (21), 45 (100); HRMS ( $m/z$ ,  $(\text{M}+\text{H})^+$ ): 279.2319 (calculated), 279.2327 (found); specific rotation:  $[\alpha]_D^{19} = -47.61$  ( $c = 2.16$   $\text{CHCl}_3$ ); HPLC: OD-3, hexane/IPA: 99.5:0.5, 1 mL/min, 254 nm,  $\text{RT}_1 = 11.60$  (major),  $\text{RT}_2 = 12.73$  (minor), ee%: 91.6.

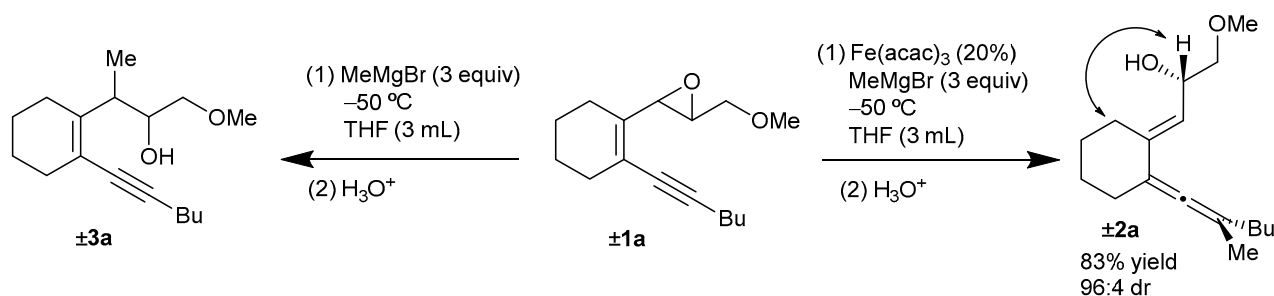
**2f**:  $^1\text{H}$  NMR (400 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$ : 5.72 (d,  $J = 8.1$  Hz, 1H), 5.10–5.03 (m, 1H), 4.64–4.56 (m, 1H), 3.15–3.06 (m, 2H), 2.96 (s, 3H), 2.33–2.17 (m, 4H), 2.13–2.01 (m, 1H), 1.51 (d,  $J = 7.0$  Hz, 3H), 1.47–1.39 (m, 2H), 1.36–1.22 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$ : 201.3, 138.6, 124.4, 104.9, 85.0, 76.5, 66.9, 58.2, 31.4, 28.5, 25.8, 25.6, 14.6; MS (EI  $m/z$ ): 208 (9), 175 (5), 163 (100), 145 (36), 121 (32), 117 (31), 105 (29), 91 (62), 79 (33) 77 (34), 55 (38).

### 3. Results and Discussion

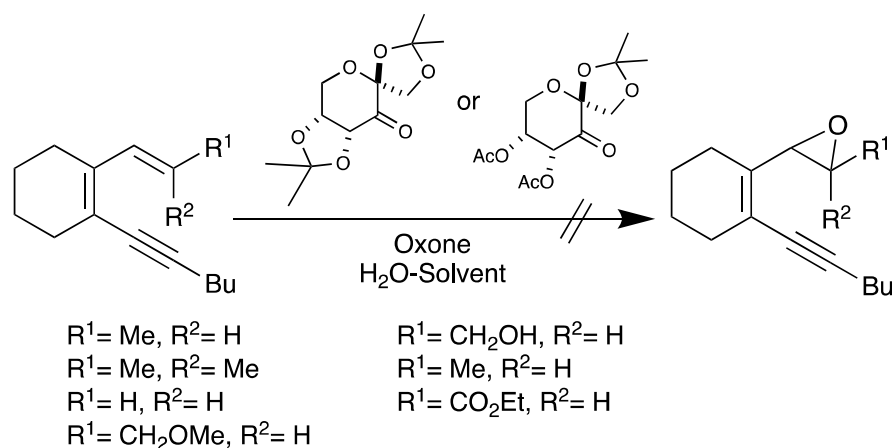
The addition of the enyne oxirane **1a** to a mixture of  $\text{Fe}(\text{acac})_3$  (20%) and  $\text{MeMgBr}$  (3 equiv) in  $\text{LiAlH}_4$ -dried THF via a syringe pump for over 30 min at  $-50$  °C and further stirring for 1 h at the same temperature provided the desired product **2a** in a high yield and high dr (Scheme 6). When no iron compound was present, the reaction predominantly yielded an  $\text{S}_{\text{N}}2$  product, with no observed formation of **2a**. The configuration of the alkenyl moiety of the product was determined to be (*E*) through NOE studies. Using  $\text{FeCl}_2$  as the catalyst and  $\text{MeMgCl}$  as the Grignard reagent resulted in variable outcomes (see the Supplementary File). On the other hand, reactions conducted in  $\text{Et}_2\text{O}$ , hexane, toluene, and DME solvents consistently yielded complex mixtures.

Encouraged by this result, we used this method to obtain enantiopure vinylallene products. This synthesis was made possible by the transfer of chirality from the center to the axial position during the reaction cycle, using enantiopure enyne oxiranes. In pursuit of this goal, we explored potential routes for direct asymmetric epoxidation methods to produce enantiopure enyne oxiranes. Unfortunately, the application of either Shi's asymmetric epoxidation method [80–82] to various dienyne reagents with different functionalities on the alkenyl moiety (Scheme 7) or Sharpless' method [83,84], a valuable technique for the asymmetric epoxidation of allylic alcohols, to alkynyldienol and bromodienol reagents

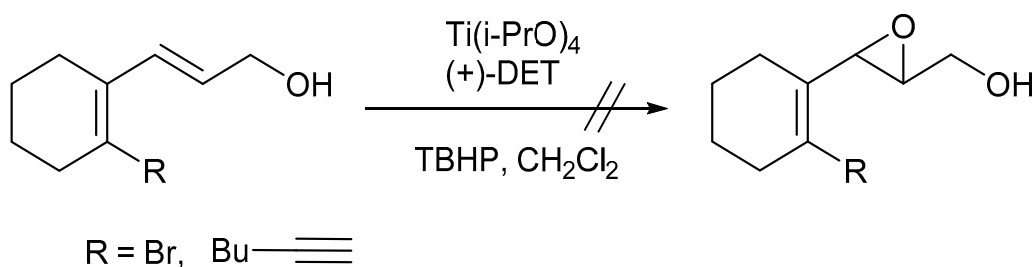
(Scheme 8), all proved unsuccessful in yielding epoxide products with reasonable yields and ees.



**Scheme 6.** Iron-promoted reaction of racemic **1a** with MeMgBr.



**Scheme 7.** Attempts of asymmetric epoxidation using Shi's methods.

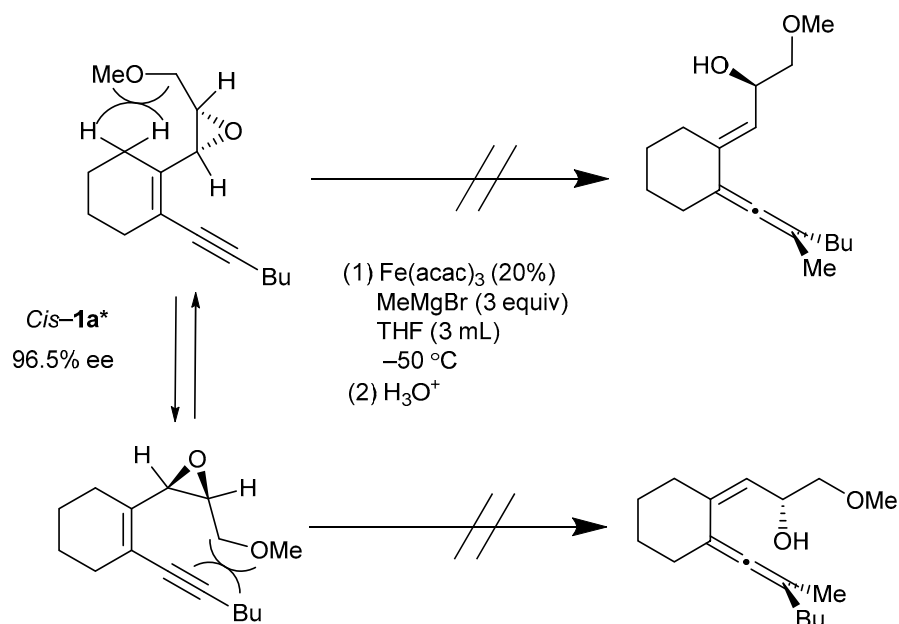


**Scheme 8.** Attempts of asymmetric epoxidation using Sharpless' method.

After numerous unsuccessful attempts at direct asymmetric epoxidation, our focus shifted to indirect methods. Utilizing the Sharpless asymmetric dihydroxylation method [77], we achieved the dihydroxylation of an endocyclic diene molecule with a high ee level (Scheme 4). The substantial steric congestion on the endocyclic alkenyl moiety allowed for selective hydroxylations at the  $\alpha$  and  $\beta$  positions, in contrast to the previously reported procedures typically applied to conjugated diene esters [85,86]. Subsequently, the  $\alpha$ -hydroxyl group was selectively sulfonated, the ester functionality was modified, and finally, an intramolecular substitution process was carried out, resulting in the desired enantiopure substrate with a *cis*-configured oxirane moiety (Scheme 5).

It is noteworthy that the standard reaction with the *cis*-configured oxirane **1a**\* substrate resulted in the full recovery of *cis*-**1a**\*. However, upon raising the reaction temperature to  $-20$  °C, a complex mixture emerged, and the formation of the desired vinylallene product became completely imperceptible. This outcome strongly indicates that this method is exclusively effective for *trans*-configured enyne oxiranes. The likely explanation for this

result can be attributed to steric congestion, which hinders the necessary conformers from participating in the reaction (Scheme 9).



**Scheme 9.** The iron-promoted reaction of *cis*-**1a**\* with MeMgBr.

In our pursuit, we sought a suitable method for synthesizing **1a**\* in the *trans*-configuration. Indeed, we were fortunate to observe that the Sharpless' group achieved a successful conversion of diols to epoxides while maintaining the original configuration [80]. This method hinges on the substitution of one hydroxyl group with an inverted configuration. The process involves converting the diol into its cyclic orthoacetate form, followed by the formation of an acetate chlorohydrin via the acetoxonium ion (Scheme 4). Ultimately, through base-mediated intramolecular substitution, we were able to obtain the desired *trans*-epoxides with a high degree of enantiomeric excess. This method proved instrumental in synthesizing enantiomerically pure enyne oxiranes featuring five- to seven-membered ring structures.

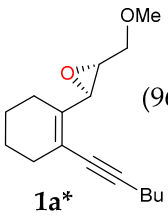
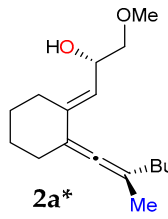
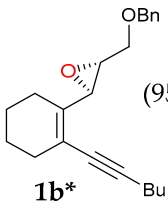
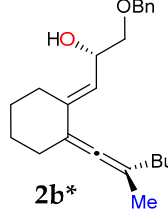
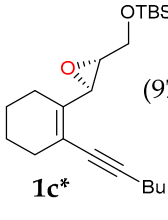
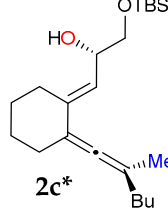
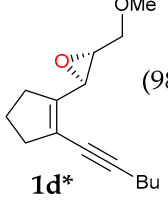
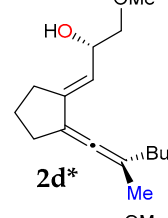
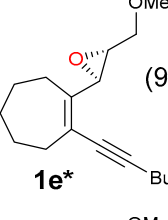
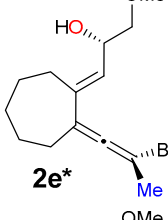
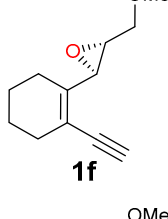
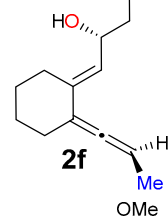
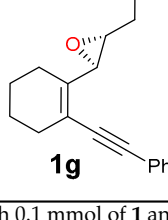
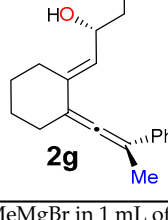
Table 1 presents the outcomes of reactions involving various racemic and enantiopure endocyclic enyne oxiranes with MeMgBr. Typically, these reactions proceeded in an *anti*-mode and demonstrated a remarkable degree of center-to-axial chirality transfer. Notably, we were able to synthesize the six-membered exo-cyclic vinylallene **2a**\* with a commendable yield and a remarkably high ee (95.2%). This achievement was realized through the reaction of enantiopure enyne oxirane **1a**\* with MeMgBr (entry 1).

The Lowe–Brewster rule was employed to correlate the sign of optical rotation with the absolute configuration of allenes [87–89]. This correlation is supported by numerous reported allene assemblies [37,53,90,91], including those found in natural compounds as illustrated in Figure 1 [72,73,92–94], as well as enantiopure allenols with a chirality center [95,96].

Modifying the pendant oxygen functionality to a benzyloxy group had no discernible impact on the reaction's outcome (entry 2). However, when a silyl protection strategy was employed, a significant decline in stereoselectivity was observed. As a consequence, the product **2c**\* was primarily formed through *syn*-mode addition, with a notably low dr (entry 3). It is likely that the diminished selectivity is attributable to steric crowding induced by the substantial size of the silyl group.

Satisfactory results can also be achieved when working with substrates featuring five- or seven-membered ring structures, although with slightly lower diastereomeric ratios (drs). These substrates led to the formation of the corresponding vinylallene products, **2d**\* and **2e**\*, with diastereomeric ratios of 90:10 and 92:8, respectively (entries 4 and 5).

**Table 1.** Fe-promoted reactions of endocyclic enyne oxiranes and MeMgBr \*.

Entry	Epoxide (ee%)	Product	Yield (%)	dr/ee%
1	 (96.7) <b>1a*</b>	 <b>2a*</b>	82	96:4/95.2
2	 (95.8) <b>1b*</b>	 <b>2b*</b>	74	95:5/93.8
3	 (97.5) <b>1c*</b>	 <b>2c*</b>	67	70:30/N.D.
4	 (98.6) <b>1d*</b>	 <b>2d*</b>	75	90:10/99.3
5	 (94.2) <b>1e*</b>	 <b>2e*</b>	71	92:8/91.6
6	 (±) <b>1f</b>	 <b>2f</b>	72	100:0/(±)
7	 (±) <b>1g</b>	 <b>2g</b>	C.M.	N.D.

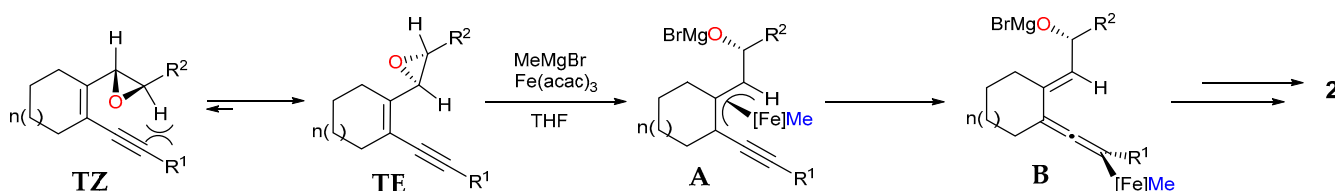
\* Performed with 0.1 mmol of **1** and 3 equiv of MeMgBr in 1 mL of dry THF at  $-50\text{ }^{\circ}\text{C}$ .

Substrate **1f**, having a terminal alkynyl group, was also found to be amenable to the method. Despite the presence of an acidic hydrogen atom, it underwent conversion into the corresponding vinylallene exclusively in a single diastereomeric form, as demonstrated in

entry 6. In contrast, the use of a reagent with a phenyl-substituted alkynyl group resulted in the formation of complex mixtures (entry 7).

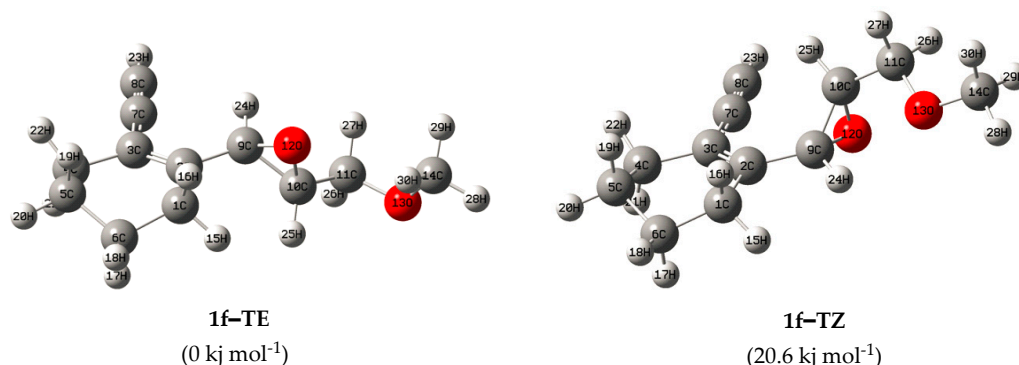
The method only applies to methyl Grignard reagents. Using other Grignard reagents, such as EtMgBr, EtMgCl, BuMgBr, PhMgBr, or BnMgCl, resulted in intricate mixtures. Only with EtMgBr and PhMgBr could the formation of corresponding vinylallenes be detected, yielding in the range of 30–40% (see the Supplementary File). The observed negative results with alkylMgBr reagents are likely due to competing  $\beta$ -hydride elimination from an initially formed organoiron intermediary. However, it should be noted that the methyl groups are the most prevalent alkyl substituents in natural compounds, and most small pharmaceutical products contain at least one methyl group [92,93]. Consequently, C-methylation has gained popularity as a prevalent structural modification frequently employed in medicinal chemistry [97–101].

While the precise reaction mechanism remains unclear, the exclusive formation of (*E*)-configured vinylallenes underscores the importance of the reacting compound **1** adopting the **TE** conformation before engaging in the reaction (Scheme 10). Otherwise, it would yield (*Z*)-configured vinylallenes via the **TZ** conformer.



**Scheme 10.** Plausible mechanism.

A conformational analysis conducted on **1f** validated that the **1f-TE** conformer occupies the lowest energy state, as illustrated in Figure 2. In contrast, the **1f-TZ** conformer, which would lead to the formation of the (*Z*)-configured **2f** structure upon reaction, exhibits an energy level 20.6 kJ mol<sup>−1</sup> higher than the **1f-TE** conformer. This significant energy disparity aligns with the diastereoselectivity observed in the exocyclic alkenyl moiety's formation, implying that the **TZ** conformer imposes greater steric demands on the reaction.



**Figure 2.** Optimized conformers for **1f** (the energy values are relative energies). Here, **1f-TE** is the lowest energy conformer overall and has the potential to produce **2f** with an (*E*)-configured exocyclic alkenyl moiety.

Based on our prior studies [10], our hypothesis suggests that the reaction involves a  $\pi$ -allyl iron intermediate identified as **A** and formed in an *anti*-mode (Scheme 10). This intermediate originates from compound **1**, assumed to be in the **TE** conformation. For an effective *p* orbital overlap across the  $\pi$ -allyl ligand carbons, compound **1** should ideally assume either the **TZ** or **TE** conformation. However, the **TZ** conformation is less likely due to its higher energy requirement. Additionally, the inherent steric congestion in **TZ** impedes the penetration of organoiron clusters, thereby favoring the occurrence of the oxidative addition step in the **TE** conformation.

The subsequent transfer of the iron atom to the distal alkynyl carbon leads to the formation of a  $\sigma$ -allenyl iron complex, denoted as **B**, followed by reductive elimination. The introduction of acid at the conclusion of the reaction is expected to yield the desired product **2**.

Notably, the nucleophilic [Fe]Me species involved in the reaction is believed to exist as large clusters [102,103], making the process particularly sensitive to steric constraints. On the other hand, the inherently more congested nature of endocyclic substrates has enhanced the method's stereoselectivity concerning the configurations of the alkenyl and allenyl moieties, as compared to its acyclic counterparts [10].

#### 4. Conclusions

Enantiomerically pure endocyclic enyne oxiranes were synthesized and reacted with MeMgBr in the presence of Fe(acac)<sub>3</sub>. These reactions followed a 1,5-substitution (S<sub>N</sub>2'') mechanism, exhibiting a remarkable center-to-axial chirality transfer. As a result, they exclusively produced (*E*)-configured exocyclic methyl-substituted vinylallenes with a high degree of enantiomeric excess and diastereomeric ratio. The largely *anti*-mode progression of the reactions and the conformational bias of the substrates within the reaction cycle appear to be the main reasons for the high stereoselectivity observed. The method appears to be sensitive to steric factors in both the substrate and Grignard reagent, which significantly influence the outcome.

**Supplementary Materials:** The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/chemistry5040173/s1>. The iron-catalyzed protocol, optimization studies, copies of NMR spectra, HPLC data, and computational details.

**Author Contributions:** Conceptualization, M.K. and L.A.; Methodology, M.K., C.O., S.K. and L.A.; Investigation, M.K., C.O. and S.K.; Software, S.K.; Resources, L.A.; Writing—original draft preparation, M.K., C.O. and L.A.; Writing—review and editing, L.A.; Visualization, M.K., C.O., S.K. and L.A.; Supervision, L.A.; Project administration, L.A.; Funding acquisition, L.A. All authors have read and agreed to the published version of the manuscript.

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**Data Availability Statement:** The data presented in this study are available upon request from the corresponding author and co-authors.

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**Conflicts of Interest:** The authors declare no conflict of interest.

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