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Synthetic applications of ortho esters*

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Abstract: The zirconocene-catalyzed rearrangement of epoxy esters to give 2,7,8-trioxabicyclo[3.2.1]octanes (ABO-esters) adds a new modification to carboxylic acid chemistry. Acid/base-sensitive α-amino, α-hydroxy and β-bromo acid derivatives are converted in high yield to ABO-esters using this protocol. This strategy is complementary to the OBO-ester technology, and orthogonal methods for the deprotection of ABO-and OBO-esters have been developed. Using chiral epoxy alcohol derivatives, a convenient and general asymmetric synthesis of bicyclic ortho esters can be achieved. New applications of ABO-esters in organic synthesis include conjugate additions to α,β-unsaturated ortho esters and their use as homoenolate equivalents as well as the preparation of tertiary alcohols.

USE OF ORTHO ESTERS AS PROTECTIVE GROUPS

In contrast to acetal derivatives of carbonyl compounds, ortho esters have found surprisingly limited use in organic synthesis [1]. Since ortho esters are among the few carboxylic acid protective groups that demonstrate a high level of stability toward strong nucleophiles and bases, most current applications are limited to protective group chemistry [2]. Compared to a carboxylic acid, the ortho ester removes the acidic hydroxyl group as well as the electrophilic carbonyl function and reduces the acidity of the α-hydrogens by many orders of magnitude. Historically, a broad use of ortho esters has been complicated by the difficulty and low yields in their preparation from acids or nitriles and alcohols. The Pinner reaction, followed by ortho ester exchange processes, represents a useful general strategy (eqn 1, [3]). Corey's OBO-ester protocol, e.g. the BF_3-etherate mediated preparation of the 2,6,7-trioxabicyclo[2.2.2]octane ring system from oxetanyl esters, greatly facilitated the synthesis of ortho esters of functionalized carboxylates and stimulated their use as protective groups in organic synthesis (eqn 2, [2,4]).

The ready access to 2,7,8-trioxabicyclo[3.2.1]octanes (ABO-esters) by cationic zirconocene-catalyzed rearrangement of epoxy esters provides new opportunities for the use of ortho esters in synthetic methodology and as chiral auxiliaries [5]. In the presence of 1–5 mol% of silver(I) salts with noncoordinating counterions, abstraction of chloride ions from Cp_2ZrCl_2 provides cationic metallocene with a high selectivity toward Lewis-basic oxiranes [6]. The ortho ester is the kinetic product of the neighboring group-assisted opening and rearrangement of an acyloxy oxirane, whereas under thermodynamic control or with stronger Lewis acids a tetrahydrofuran is formed [5,7]. In either case, the cationic zirconocene complex is regenerated in the catalytic cycle. Acid or base-sensitive α-amino and α-hydroxy acid derivatives are converted in high yield to ABO-esters using this protocol. The protection/deprotection strategy is complementary to the OBO-ester technology, and orthogonal methods for the deprotection of ABO-and OBO-esters have been developed [5]. Pertinent examples for the use of ABO-esters in organic synthesis are the preparation of γ-hydroxyleucine lactone, a component of toxins of the green death-cap mushroom, and the nonproteinogenic amino acid (*S*)-vinyl glycine [5].

Recently, we have used an ABO-ester derived homoenolate equivalent for the preparation of a butyrolactone in a model study toward the *Stemona* alkaloid tuberostemonine. After conversion of the proline ester **1** to the corresponding aldehyde, use of zinc-homoenolate **2** [8] provided < 10% of a mixture

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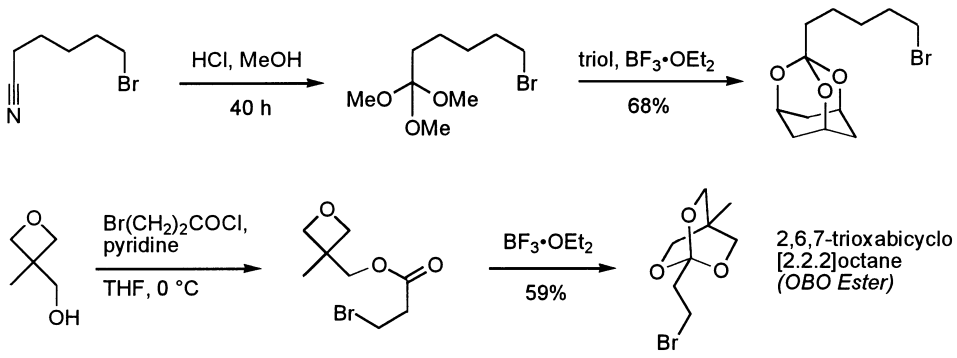


Scheme 1

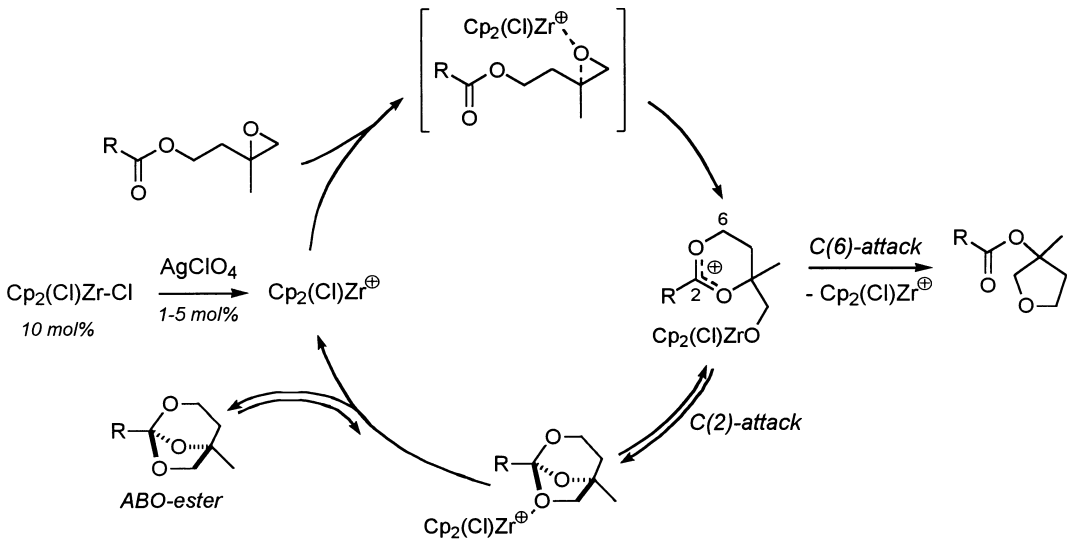
of diastereomers of lactone **3**. In contrast, addition of the lithiated ortho ester **4** to the Weinreb amide gave ketone **5** in excellent yield. Reduction with L-selectride provided a ≈ 7:1 ratio of the desired Felkin-Ahn addition product and its epimer, which was converted in a kinetically controlled cyclization to a single lactone isomer upon acidolytic removal of the ABO-ester. The stereochemistry of butyrolactone **6** was confirmed by NOE studies, and this compound was obtained in an excellent 76% overall yield from proline ester **1**.

Preparation of ortho ester **4** was straightforward starting from methyl (*S*)-3-hydroxy-2-methyl-propanoate **7**. After epoxidation of homoallylic ester **10**, cationic zirconocene-catalyzed epoxy ester rearrangement provided the β-bromo ABO-ester **12** in an excellent 73% overall yield from **7**. Subsequent treatment with naphthyl radical anion [9] provided homoenolate equivalent **4**.

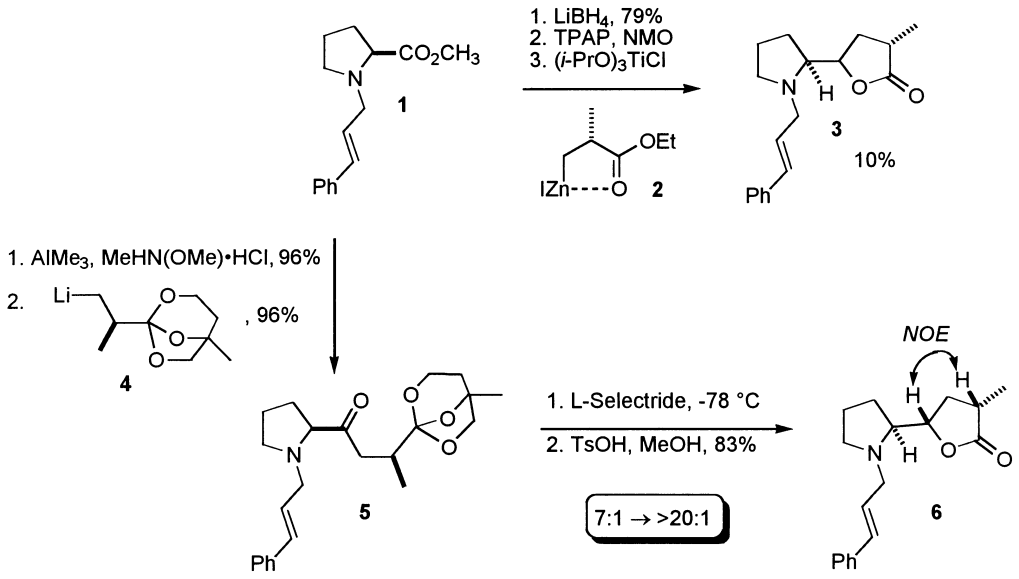
With α,β-unsaturated esters, the epoxy ester–ortho ester rearrangement has to be carefully controlled to avoid thermodynamic equilibration that primarily leads to acyloxy tetrahydrofurans. The use of 1 mol% of $AgSbF_6$ in toluene/MeCN at −30 °C provides an optimum conversion to the desired α,β-unsaturated ortho esters.

USE OF ORTHO ESTERS IN SYNTHETIC METHODOLOGY

Beyond their protective group chemistry, only few applications of ortho esters in synthetic methodology have been reported. Among the nicest and most recent results are studies by Ito & Taguchi on the formation of an acrolein anion equivalent by zirconocene-mediated elimination of vinyl ortho esters [10], the cyclocondensation of ortho esters and amino alcohols to give oxazolines [11], and the synthesis



Scheme 2

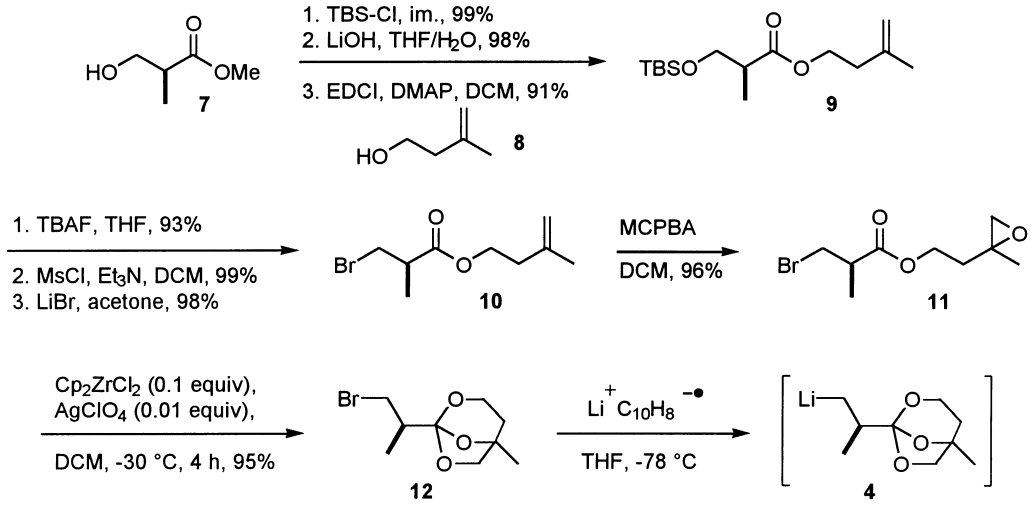


Scheme 3

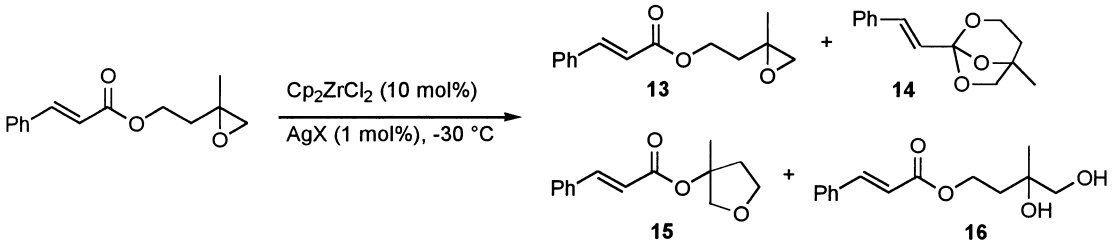
of *myo*-inositol derivatives [12]. We have recently demonstrated the first copper-catalyzed conjugate addition reactions to ortho esters. Treatment of ortho ester **14** with excess Grignard reagent in the presence of 10 mol% of Cu(I)-salts provided the β-branched ortho esters **17** in 63–71% yield. Since the ortho ester functionality is retained in this Michael addition, we postulate a mechanism that is S_N2'-like and regenerates the ortho ester after mild aqueous workup. Under more acidic conditions, complete cleavage to carboxylic acids **18** occurs.

Another novel application of ABO-esters is the formation of tertiary alcohols by Lewis acid-assisted double substitution with Grignard reagents. Treatment of **19** with MeMgBr, followed by TMS-Cl/$TiCl_4$-assisted cleavage of acetal **20** with EtMgBr provides tertiary ether **22** which is readily converted to tertiary alcohol **23**.

To date, there are only a handful of examples for the use of ortho esters as chiral auxiliaries in stereoselective transformations. Dubé *et al*. [13] obtained high diastereoselectivities in the reduction of a tartrate-derived ortho ester, and Langlois and co-workers used a five-membered ortho ester-derived dioxolanylium cation as a dienophile in Diels–Alder reactions [14]. In contrast to OBO-esters, ABO-esters contain two asymmetric carbon atoms; the unsubstituted bicyclic scaffold is in itself chiral. Using

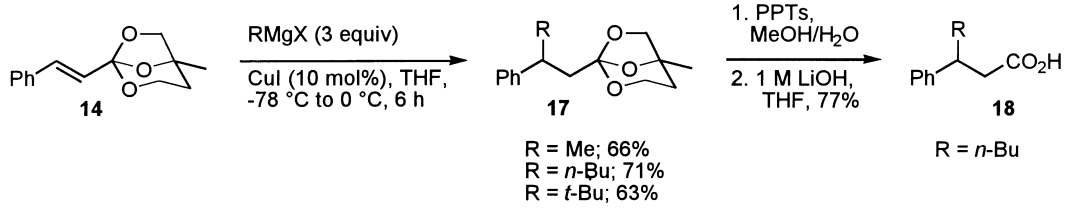


Scheme 4

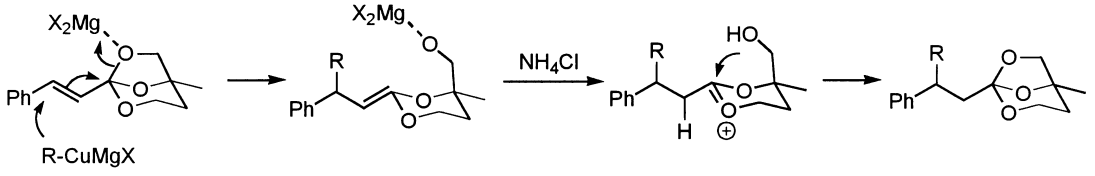


AgX	Solvent	Ratio of **13** : **14** : **15** : **16**
$AgClO_4$	toluene	0 : 64 : 10 : 26
$AgAsF_6$	toluene	0 : 55 : 21 : 24
$AgSbF_6$	toluene	0 : 65 : 12 : 23
AgOTf	toluene	0 : 11 : 89 (**15+16**)
$AgSbF_6$	toluene/MeCN	6 : 73 : 6 : 15
$AgSbF_6$	MeCN	15 : 67 : 0 : 18
$AgSbF_6$	THF	11 : 48 : 4 : 37
$AgSbF_6$	DME	0 : 26 : 0 : 74

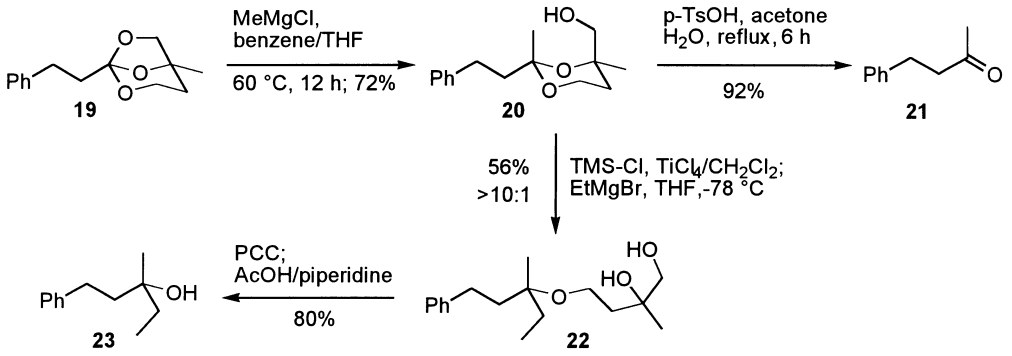
Scheme 5



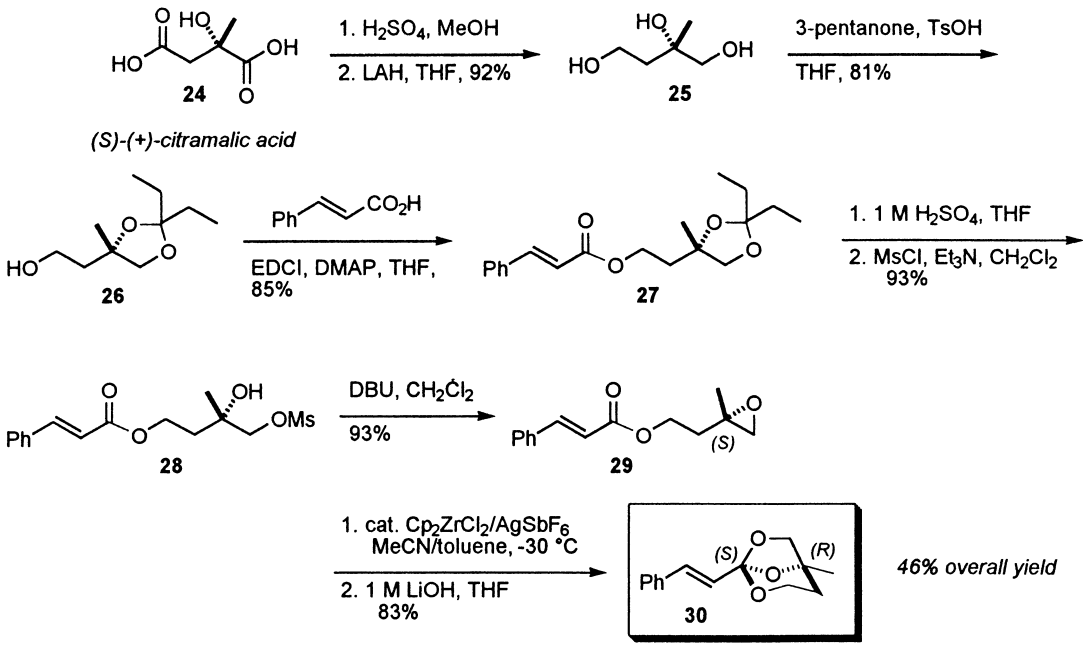
Proposed Mechanism:



Scheme 6



Scheme 7

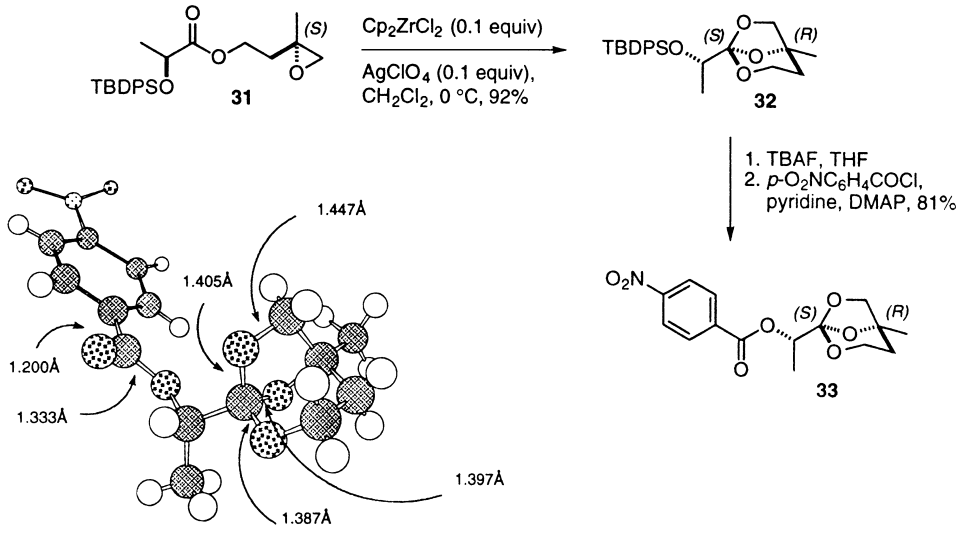


Scheme 8

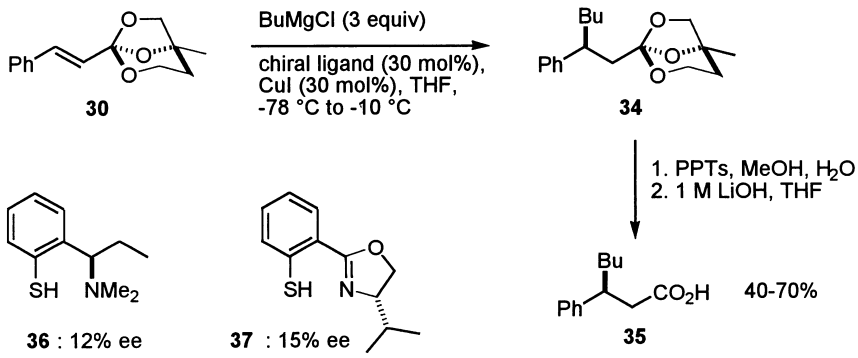
enantioenriched epoxy alcohol derivatives, a convenient and general asymmetric synthesis of bicyclic ortho esters can been achieved. In addition to asymmetric catalysis, starting materials from the chiral pool can be used for the synthesis of the (*R*)- or (*S*)-3-methyl-3,4-epoxy-1-butanol component of the epoxy ester–ortho ester rearrangement. For example, commercially available citramalic acid **24** is readily converted to cinnamate **29** in seven steps and in 46% overall yield.

The cationic zirconocene-catalyzed rearrangement of **29–30** proceeds with inversion of configuration at the quaternary carbon; this was clearly demonstrated by an X-ray analysis of ortho ester **33** derived from lactate **31**. Interestingly, the axial C–O bond in **33** is significantly elongated (1.405 Å) vs. the other two ortho ester C–O bonds in the six-membered ring (1.387 Å and 1.397 Å). In comparison, the ester C–O bond measures 1.333 Å, the C=O bond 1.200 Å, and an unactivated ether C–O bond is 1.447 Å.

The elongation of the ortho ester C–O bond and the preferential kinetic lability of the axial ether in



Scheme 9



Scheme 10

the presence of Lewis acids are consistent with the existence of a double anomeric effect in the chair 1,3-dioxane [15].

In preliminary studies of the chemistry of chiral ortho ester derivatives, we have investigated asymmetric versions of the copper(I)-catalyzed conjugate addition reaction to ortho esters. Interestingly, no induction is observed for either enantiomerically pure ABO-esters **30** or the use of racemic compounds **14** in the presence of chiral ligands. In contrast, combination of **30** with catalytic amounts of chiral thiophenols **36** [16] and **37** [17] provided acid **35** in modest inductions of up to 15% ee after conjugate addition of butyl magnesium bromide and hydrolysis of **34**. We are currently extending our ligand screening to identify more effective catalytic asymmetric conditions.

In conclusion, the synthetic potential of ortho esters is still largely unexplored and offers great promise for future important discoveries. Ortho esters are attractive protective groups for carboxylic acids in basic and nucleophilic reaction media, and facile manipulation of the structure of bicyclic ortho esters is accomplished by variation of starting materials and preparative protocols. The chemical stability and, accordingly, deprotection conditions can be broadly varied depending on the ring size and substitution pattern of bicyclic ortho esters. The zirconocene-catalyzed epoxy ester–ortho ester rearrangement allows the use of readily available epoxides in ortho ester synthesis under mild reaction conditions. In addition, recent research demonstrates that ortho esters are useful substrates for the development of new synthetic methodologies for C,C-bond formations. Chiral ortho esters represent promising new building blocks for asymmetric synthesis.

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