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The Evans-Tishchenko Reaction: Scope and Applications**

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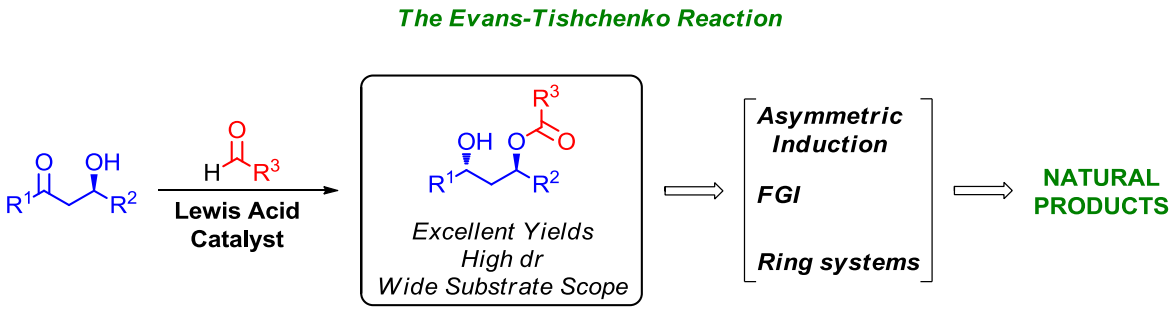
Graphical abstract:



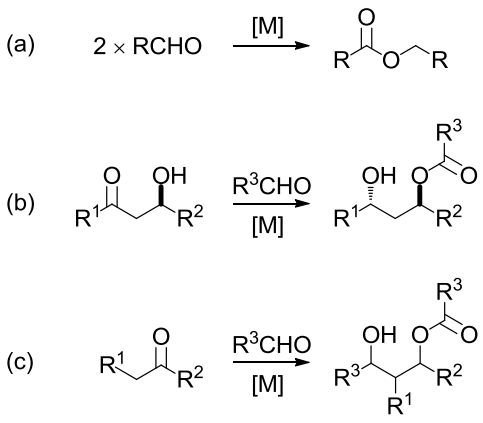
Keywords:
Evans-Tishchenko reaction; *anti*-1,3-diols; diasteroselectivity; Lewis acids; samarium; natural products

Abstract

The Evans-Tishchenko reaction provides a highly diastereoselective route towards the synthesis of 1,3-*anti* diol monoesters, and therefore has found prominent use in a number of synthetic applications. This review summarizes recent applications of the Evans-Tishchenko reaction in natural product synthesis, and examines scope in terms of substrate range, functional group tolerance, and catalyst.

1. Introduction

The Tishchenko reaction was first described in 1906 and entails the Lewis acid mediated condensation of two molar equivalents of an aldehyde to form an ester (**Scheme 1a**).[1] In 1990, Evans and Hoveyda reported an important variant of this reaction,[2] which has subsequently become known as the Evans-Tishchenko reaction. This transformation involves a preformed β-hydroxyketone and an aldehyde undergoing a Lewis acid catalyzed condensation to generate a 1,3-*anti* diol monoester (**Scheme 1b**). Importantly, the Evans-Tishchenko reaction provides a highly regio- and diastereo-selective route to these ubiquitous structural units; and the reaction itself is remarkably mild and can be carried out in the presence of a number of (often sensitive) functional groups. The resultant 1,3-*anti* diol monoesters may be retained as a selectively protected diol; serve as a means of fragment coupling; or be readily transformed into other interesting structural motifs. These features have rendered the Evans-Tishchenko reaction a key step in a number of natural product syntheses.



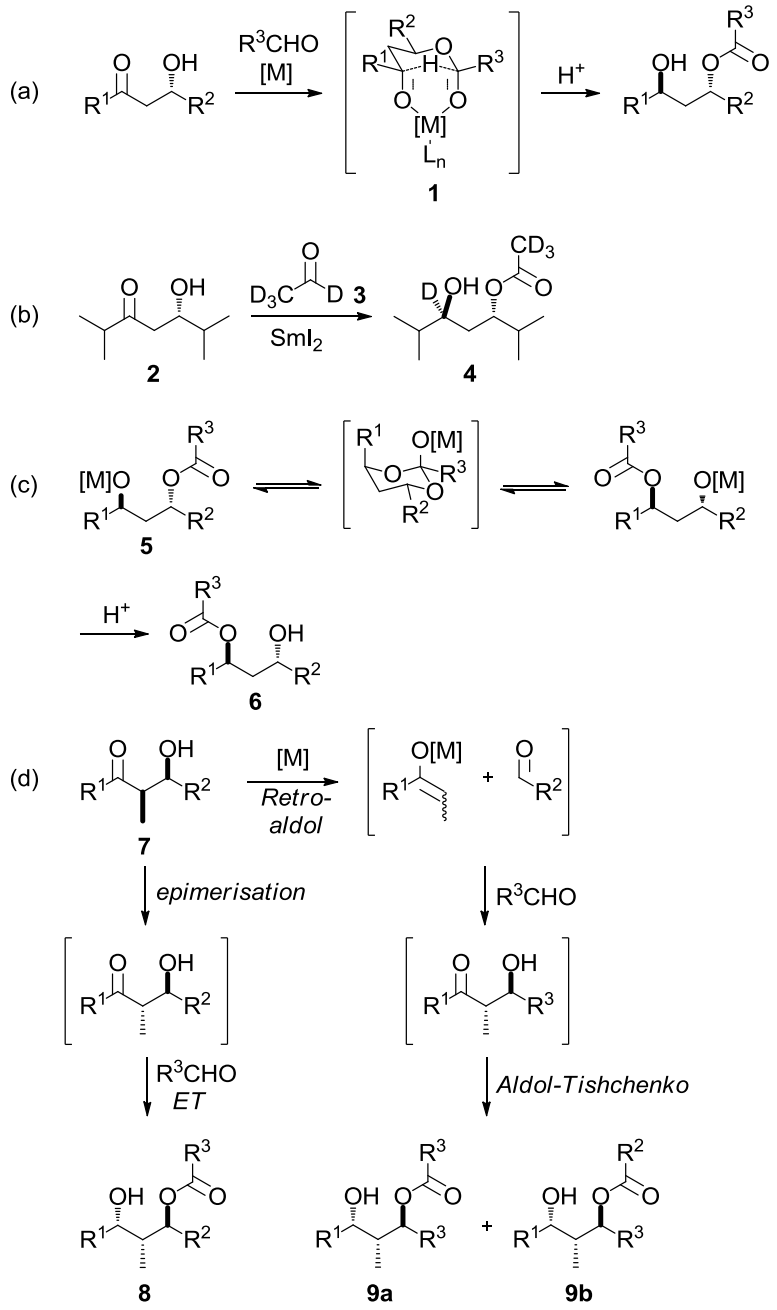
Scheme 1. (a) Tishchenko, (b) Evans-Tishchenko and (c) aldol-Tishchenko Reactions.

This review discusses the scope of the Evans-Tishchenko reaction in terms of the range of catalysts/promoters and its functional group tolerance, and highlights the versatility of the reaction in terms of its application to natural product synthesis. The closely-related Tishchenko and aldol-Tishchenko (**Scheme 1c**) reactions are not covered, as both have been the subject of recent surveys.[3,4]

2 Reaction Mechanism and Catalyst Scope

2.1 Reaction Mechanism

In the first reported Evans-Tishchenko reaction a samarium-based Lewis acid catalyst was generated *in situ*; under these conditions 1,3-*anti* diol monoesters were generated in excellent yield (>85%) and diastereoselectivity (>99:1).[2] The mechanism proposed to explain this selectivity involves Lewis acid promoted hemiacetal formation (**Scheme 2a**), followed by intramolecular hydride transfer from the aldehyde to the newly formed carbinol centre *via* a 6,6-chair-type transition state **1**.[2] The hydride transfer mechanism is supported by deuterium labeling studies in which d_4-acetaldehyde **3** was shown to selectively label the carbon backbone at the newly-formed hydroxyl stereocentre (**2** $\rightarrow$ **4**, **Scheme 2b**).[2] Although the reaction is generally both very highly diastereoselective and regioselective, two common side-reactions are known. Where the Evans-Tishchenko reaction results in ester products which are sterically crowded, Lewis acid catalyzed transesterification between the two hydroxyl of the 1,3-*anti* diol may occur (**5** $\rightarrow$ **6**, **Scheme 2c**).[5,6] In addition, there is often a delicate interplay with a second pathway in which an epimerisation/Evans-Tishchenko reaction,[5,7] or alternatively a Lewis acid catalyzed retro-aldol/aldol-Tishchenko (RAAT) reaction takes place.[8] This latter pathway may result in the scrambling of the α-stereocentre, with the net generation of the thermodynamically favoured *anti* aldol adduct with 1,3-*anti* diol stereochemistry (**9**, **Scheme 2d**). The extent to which this pathway competes with the Evans-Tishchenko reaction depends upon the nature of the Lewis acid catalyst used, as discussed in the following sections.

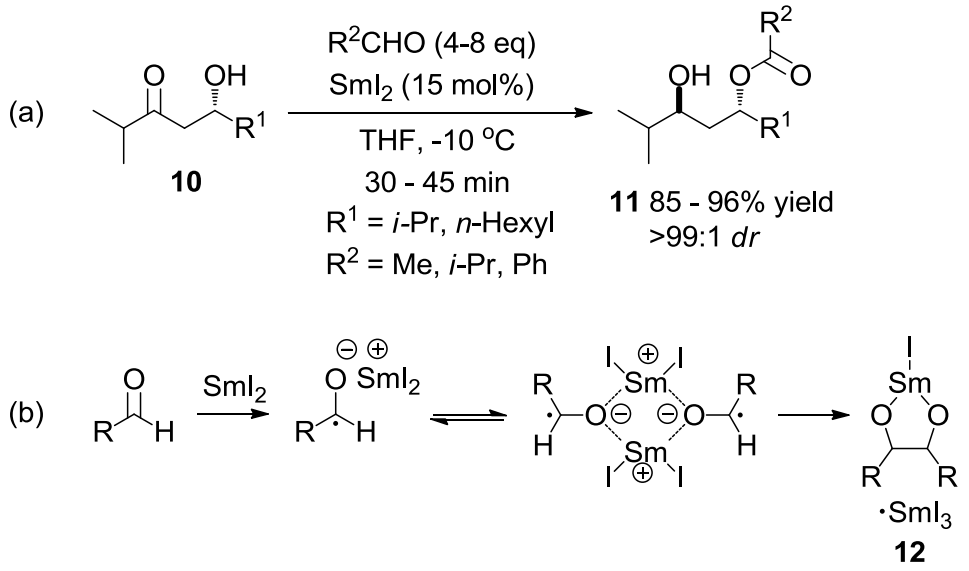


Scheme 2. (a) General mechanism for the Evans-Tishchenko reaction. (b) d_4-Acetaldehyde labelling study. Common side-reactions: (c) transesterification; (d) (i) epimerisation/Evans-Tishchenko and (ii) retro-aldol/aldol-Tishchenko (RAAT).

2.2 Samarium

The first example of the Evans-Tishchenko reaction was reported by Evans and Hoveyda,[2] who utilized a catalytic quantity (15 mol%) of samarium diiodide in the presence of an excess of the reacting aldehyde to generate the active Lewis acid catalyst (**Scheme 3a**). It has since been suggested[9] that samarium-pinacol

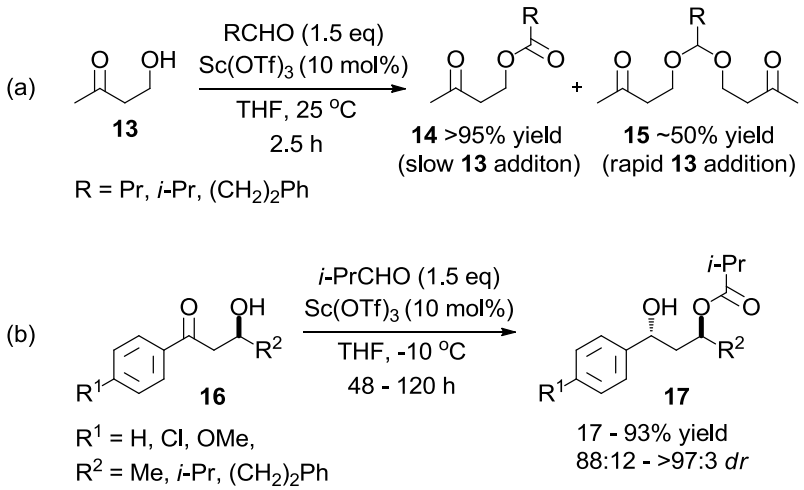
species **12** [$(RCHO)_2SmI{\bullet}SmI_3$] generated from reaction of samarium diiodide and either the reactive, or a sacrificial aldehyde, is responsible for catalysis (**Scheme 3b**). Typically quite high catalytic loadings of samarium diiodide are used (15-30 mol%), generating 7-15 mol% of the active species *in situ*. A survey of other samarium species has shown that samarium triiodide, samarium trichloride and $Sm(acac)_3$ are not effective catalysts for the reaction.[2] The pinacolate Lewis acid generated from samarium diiodide and a reactive aldehyde is a widely-used catalyst for Evans-Tishchenko reactions, and most reactions in the following sections make use of catalysts of this type. Unfortunately, samarium diiodide is air- and moisture-sensitive,[9d] and although commercially available, a number of methods for generating samarium diiodide *in situ* have been developed to counter the inherent difficulties in long-term storage. Reacting an excess of metallic samarium with elemental iodine at elevated temperature,[10] under ultrasonic vibration[11] or through use of microwave irradiation[12] in (typically) THF is sufficient to generate solutions of the precatalyst comparatively rapidly (<3 h) and on a gram scale for use in Evans-Tishchenko reactions, or alternative applications.[9,13] Other iodide sources have also been used, including diiodomethane,[14] iodoform[15] 1,2-diiodoethane,[16] and sodium iodide/chlorotrimethylsilane[17] but the low cost, improved atom economy and ready availability of elemental iodine have rendered these approaches less widespread. Despite the prominent use of samarium diiodide, a number of other metal catalysts have also been successfully been employed in Evans-Tishchenko coupling as discussed in the following sections.



Scheme 3. (a) First example of the samarium-catalyzed Evans-Tishchenko reaction. (b) Generation of a catalytically active samarium(III) pinacolate, Lewis acid catalyst.

2.3 Scandium

Scandium triflate has been identified as a promising Lewis acid in organic synthesis,[18] and has been shown to be effective in the Evans-Tishchenko reaction.[19] The primary alcohol **13** was successfully converted to the Evans-Tishchenko product **14** in excellent yield (95%) in the presence of 10 mol% scandium triflate, albeit requiring slow addition (2.5 h) of the β-hydroxyketone to circumvent formation of acetal byproducts (e.g. **15**, **Scheme 4a**). Conversely, secondary alcohols **16** underwent Evans-Tishchenko reduction smoothly (without the necessity for careful addition) to give the corresponding 1,3-*anti* diol monoesters **17** in moderate to excellent yield (17-93%) and diastereoselectivity (86:12 to >97:3 *dr*). The main disadvantage of the protocol was the requirement for long reaction times (48 to 120 h) in contrast to the samarium pinacolate catalyzed reactions which are typically complete within a much shorter timeframe (20 min to 1 h). However, the reaction takes place under comparable conditions to samarium mediated protocols (–10 °C, THF solvent), avoids the use of a radioactive metal and carries other key advantages of air- and moisture-stability when compared to other protocols. Scandium triflate could therefore provide a useful alternative where stringently dry conditions are difficult to achieve, for example where crude samples of reactant aldehydes or β-hydroxyketones must be used without purification due to problems of instability.



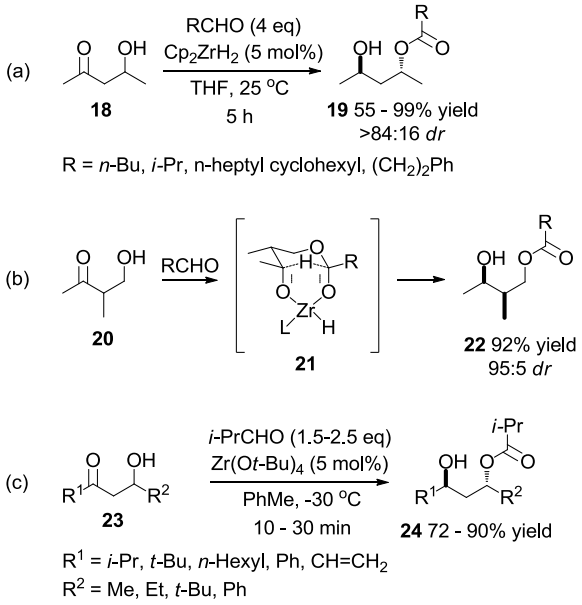
Scheme 4. Scandium-based Lewis acid catalyzed Evans-Tishchenko reactions.

2.4 Zirconium

Zirconocene catalyst Cp_2ZrH_2 was the first zirconium Lewis acid to be used successfully in the Evans-Tishchenko reaction.[20] Treatment of β-hydroxyketone **18** with 4 equivalents of alkyl aldehydes and a catalytic quantity (5 mol%) of Cp_2ZrH_2 (**Scheme 5a**) gave the corresponding 1,3-*anti* diol monoesters **19** in good to excellent yields (55-98%). Interestingly, benzaldehyde and crotonaldehyde failed to react, a feature of the

reaction that was attributed to the electron-withdrawing effect of these groups which would impede transfer of the hydride to the carbonyl group.[20] Furthermore, reaction of racemic α-methyl β-hydroxyketone **20** led to excellent *syn*-selectivity (95:5 *dr*) in the product **22** (**Scheme 5b**). This was attributed to the presumed equatorial placement of the methyl group that would occur during the transition state **21**, as opposed to axial placement which would give the *anti*-product.

The zirconium alkoxide Lewis acid, $Zr(O^tBu)_4$ has also been successfully employed as a catalyst for the Evans-Tishchenko reaction,[7] and offers similar reactivity to samarium pinacolate catalysts for alkyl aldehydes which react smoothly to give the corresponding 1,3-*anti* diol monoester products **24** (**Scheme 5c**). The reaction is carried out in the presence of catalytic quantities of $Zr(O^tBu)_4$ (5-10 mol%) at low temperature (–30 °C) with an excess of the aldehyde (1.5-2.5 equivalents). But in contrast to most samarium-mediated protocols, the reaction is conducted in toluene.[7] As with the zirconocene hydride based catalysts, aromatic and α,β-unsaturated aldehydes yielded only trace amounts of products. In addition, when α-substituted β-hydroxyketones were employed as substrates, substantial levels of epimerization at the α-sterocentre were observed. This indicated that retro-aldol, or epimerization, reactions took place at a rate competitive with the desired Evans-Tishchenko reduction; and hence that the conditions were not suitable for the synthesis of polypropionate-derived 1,3-polyols.

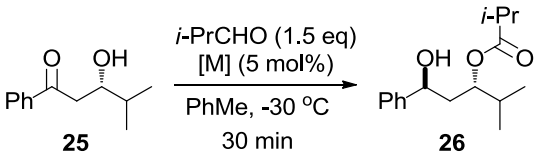


Scheme 5. Zirconium-based Lewis acid catalysis of the Evans-Tishchenko reaction: (a) and (b) Cp_2ZrH_2; (c) $Zr(O^tBu)_4$.

2.5 Other Metals

Although they have not received very much attention, the use of hafnium-, magnesium- and ytterbium-based Lewis acid catalysts are worthy of mention as they have also shown activity in the Evans-Tishchenko reaction.

During their study of zirconium catalysts Schneider *et al.* showed that hafnium(IV) *tert*-butoxide and dibutyl magnesium showed high diastereoselectivity (>99:1 *dr*) and conversion (>77%) with similar activity to the zirconium catalyst, while yttrium(III) isopropoxide showed moderate activity as a catalyst in the Evans-Tishchenko reaction (51% yield, 90:10 *dr*) between isobutyraldehyde and β-hydroxyketone **25** (**Scheme 6**).[7] Although only used in screening, it is clear that they have potential in future studies of the Evans-Tishchenko reaction, and indeed yttrium has already been employed in the related aldol-Tishchenko reaction.[21] The success achieved with the use of magnesium-based catalysts is particularly noteworthy given the relatively low cost of magnesium when compared to expensive rare-Earth transition metals.

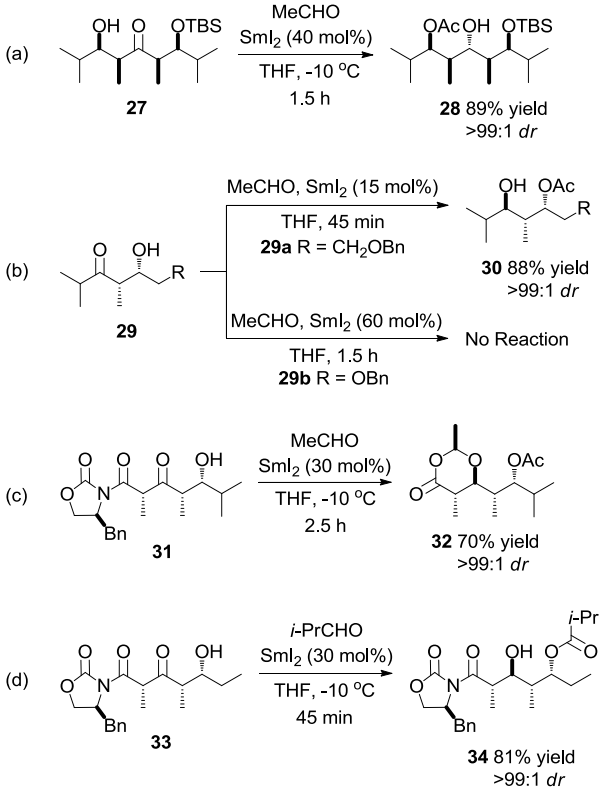


Scheme 6. Other metal mediated Evans-Tishchenko reactions.

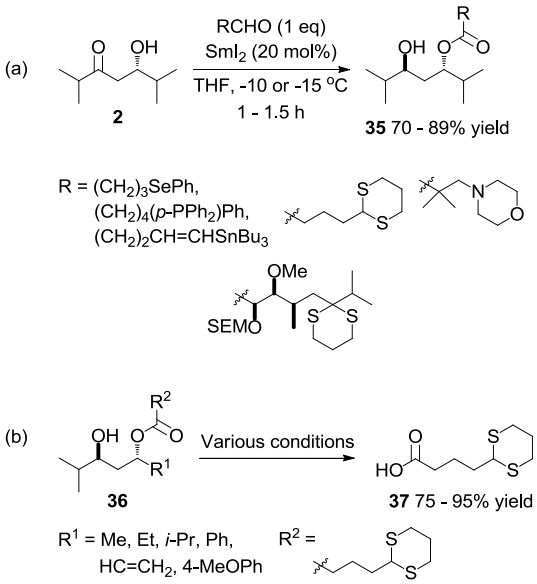
3 Substrate Scope

The first samarium-catalyzed Evans-Tishchenko reaction[2] made use of alkyl aldehydes and α-unsubstituted β-hydroxyketones (**Scheme 3**, above). However, sterically hindered substrates **27** and **29a** also react smoothly to give their corresponding 1,3-*anti* diol monoesters (**28** and **30** respectively), albeit requiring higher catalyst loadings (up to 40 mol% SmI_2; **Scheme 7ab**). In contrast, no reaction was observed in the case of the benzyl ether **29b**, even with a high catalyst loading (60 mol%). Presumably competitive chelation of the samarium catalyst by the benzyl ether inhibited the Evans-Tishchenko coupling, an effect which was also observed with an analogous *p*-methoxybenzyl ether in the total synthesis of (+)-crocacin C.[22] Surprisingly, oxazolidinone **31** also did not react as expected, leading to the formation of dioxalone **32**. Curiously however, the very minor structural changes in oxazolidinone **33** allowed formation of the expected product **34**, perhaps due to the shorter reaction time, subtle modulation of steric hindrance, or the enhanced nucleophilicity of the methoxy group *vs*. its isopropoxy counterpart (**Scheme 7cd**). In addition to alkyl and aryl substituents on the aldehyde, a range of electron rich heteroatom substituents have also been shown to react successfully. Smith *et al.*[23] demonstrated that sulfur, phosphorus, silicon, selenium and tin containing aldehydes successfully couple to give 1,3-*anti* diol monoesters **35** (**Scheme 8a**). They also showed that a range of dithiane-containing esters **36** synthesized via the Evans-Tishchenko reaction could be converted using a number of different conditions

(including base hydrolysis, rhodium/palladium catalysis and oxidative cleavage) to the corresponding carboxylic acid **37**; thus providing a mild, albeit two-step, method of aldehyde oxidation which leaves the oxidation-sensitive thioacetal moiety intact (**Scheme 8b**).[24]

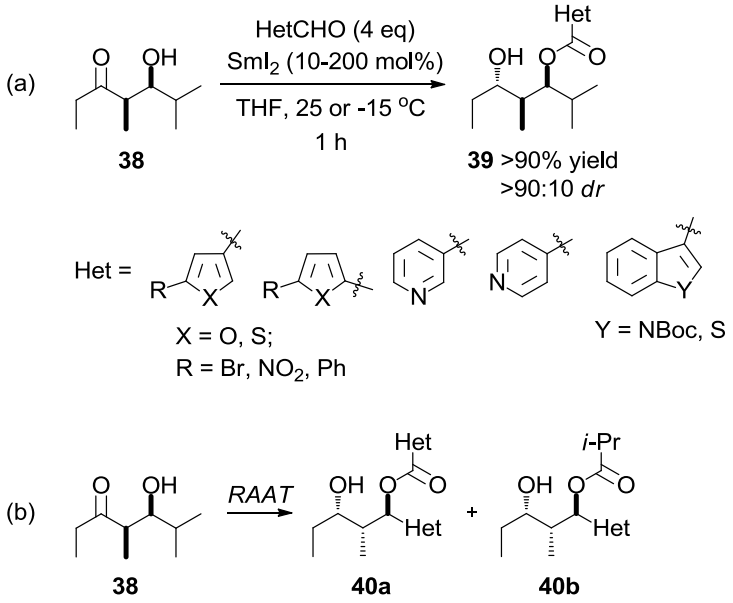


Scheme 7. Reaction of sterically hindered and polyketo β-hydroxyketones.



Scheme 8. (a) Coupling of a β-hydroxyketone and electron rich aldehydes in the Evans-Tishchenko reaction. (b) Conversion of dithiane containing 1,3-*anti* diol monoesters to the corresponding carboxylic acid.

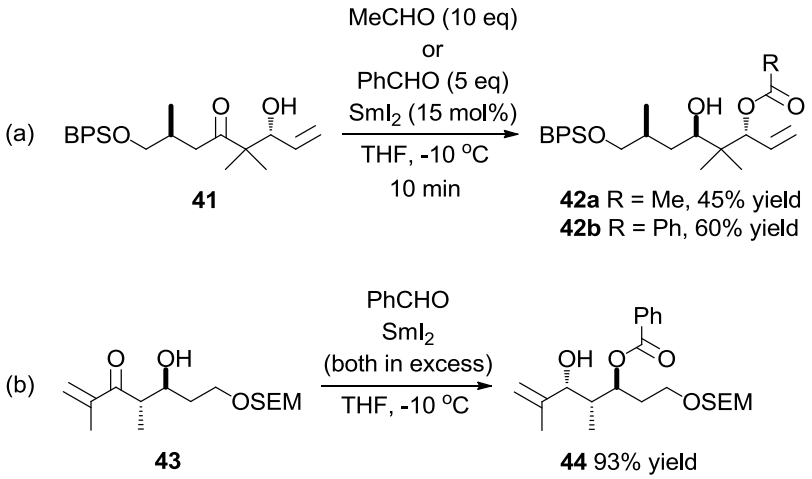
A number of studies have utilized alkyl and aryl aldehydes in the Evans-Tishchenko reaction (see **Section 4**), but heteroaryl aldehydes have also been shown to be good substrates. Research from our own laboratories[8] recently demonstrated this using a number of electron-rich and electron-poor heteroaryl aldehydes (**Scheme 9a**). Electron-deficient aldehydes (for example, 3- and 4-formylpyridine) reacted with β-hydroxyketone **38** in the presence of comparatively low loadings of the samarium diiodide precatalyst (10 mol%), to give the corresponding 1,3-*anti* diol monoesters **39** in excellent yield (>93%) and diastereoselectivity (>90:10 *dr*) even at room temperature. Electron-rich heteroaryl aldehydes (for example furans and thiophenes) also gave high yields of the 1,3-*anti* diol monoesters (>95%), albeit requiring the presence of stoichiometric loadings of the samarium pinacolate species (derived from 200 mol% samarium diiodide precatalyst) and lower temperature coupling conditions to circumvent competitive RAAT side-reactions (**38** → **40**, **Scheme 9b**).



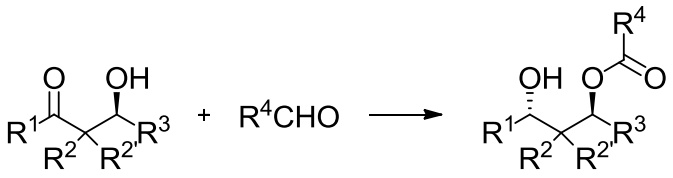
Scheme 9. (a) Evans-Tishchenko coupling of heteroaryl aldehydes. (b) RAAT byproducts observed for electron-rich heteroaryl aldehydes with sub-stoichiometric loadings of the samarium catalyst.

The examples above demonstrate the use of α-unsubstituted and α-monosubstituted β-hydroxyketones in the Evans-Tishchenko reaction, combined with alkyl substitution on the distal side of the ketone functionality. However, relatively few examples exist of α,α-disubstituted systems; in their total synthesis of polycavernoside A, White *et al*.[25] showed that *gem*-dimethyl substituents are tolerated, albeit leading to slightly diminished yields (45-60%) of the resulting 1,3-*anti* diol monoesters **42**, (**Scheme 10a**). Only a catalytic quantity (15 mol%) of SmI_2 was required to effect the transformation, and a short reaction time (10 min) was used. Therefore despite obtaining only moderate yields, there is clearly scope for improvement of the conditions which would allow higher yields to be obtained. Conversely, excellent product yields have been obtained with α,β- unsaturated ketones.[26,27] Kirschning *et al*.[27] showed that β-hydroxyenone **43** reacted

successfully in the Evans-Tishchenko reaction implying that conjugation is of little consequence in terms of reactivity (**Scheme 10b**). Indeed, the Evans-Tishchenko reaction, as demonstrated, is widely applicable and seldom fails even in the presence of a range of functionalities attached to each of the reactant carbon centres. A summary of the substrate scope as discussed in the current section is shown in **Table 1**.



Scheme 10. Evans-Tishchenko of (a) α,α-disubstituted β-hydroxyketones; and (b) a β-hydroxyenone.



Group	Functionality Tolerated
R^1	Alkyl, alkenyl, aryl; some O/N/Si[a] containing groups.
$R^2/R^{2'}$	H, alkyl.
R^3	H, alkyl, alkenyl, alkynyl,[a] (some) benzyl, Br containing.[a]
R^4	Alkyl, aryl, heteroaryl, N/O/P/S/Si containing.
[a]See examples in **Section 4**, below.	

Table 1. Summary of viable substrates for the Evans-Tishchenko reaction.

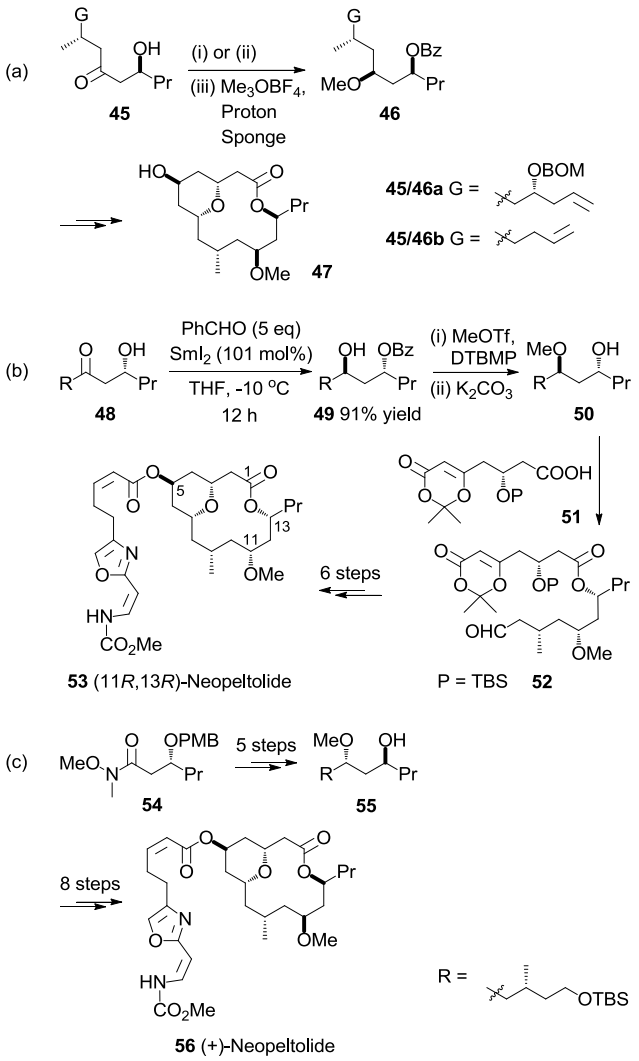
4. Application in Natural Product Synthesis

Given that the Evans-Tishchenko reaction may be performed with a high degree of stereoselectivity on chiral β-hydroxyketones, and that it is tolerant of a wide range of functional groups, it is no surprise that it has found frequent application in natural product synthesis. The following section categorizes these reactions and details some recent uses of the Evans-Tishchenko reaction in the synthesis of natural products.

4.1. Protection/Asymmetric Induction

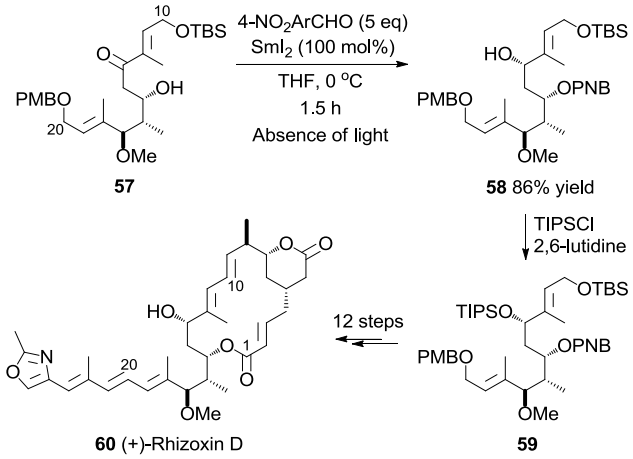
By far the most common use of the Evans-Tishchenko reaction is in tandem protection and asymmetric induction. There are a number of advantages associated with this strategy: first and foremost, a 1,3-*anti* diol is generated stereoselectively from the masked β-hydroxy ketone precursor; secondly, protection of the newly-formed hydroxyl group (*e.g.* as a silyl ether or benzyl ether) gives an orthogonally protected diol motif. Alternatively, esterification of the resulting 1,3-*anti* diol monoester lends itself to simultaneous hydrolytic deprotection at a later stage, which may help to streamline the total synthesis of such diol-containing natural products.

The synthesis of the macrolactone segment **47** of (+)-neopeltolide[28] **56** provides an excellent example of the use of this strategy and indeed this approach has been used in at least three attempted syntheses of the cyclic core (**Scheme 11a**). In the first synthetic route,[28a] β- hydroxyketone **45a** was reacted with benzaldehyde in the presence of SmI_2 to give the corresponding 1,3-*anti* diol monoester **46a** (>20:1 *dr*). Critically, this gave the free alcohol, which allowed installation of the C(11) methoxy group present in the natural product, while simultaneously installing a benzoyl protecting group. An identical functional group pairing was introduced in the Hong's[28b] total synthesis of the macrolactone **47**, utilizing β-hydroxyketone **45b**. In both cases, later removal of the benzoyl protecting group facilitated a key lactonisation and subsequent completion of the putative macrolactone core **47**. In exploring the total synthesis of neopeltolide,[28c] Scheidt *et al.* also made use of an Evans-Tishchenko reaction to generate the C(11) methoxy group and provide a hydroxyl group for esterification to form key intermediate **52** (**Scheme 11b**). However, completion of the synthesis using this material revealed that this route provided a neopeltolide diastereomer **53** whose spectral data did not match the natural product. A second approach by this group, using the closely related monomethylated diol **55** generated the (11*S*,13*S*) stereochemistry and spectral data was found to match that of the natural product, leading to the reassignment of these stereocentres (**Scheme 11c**).



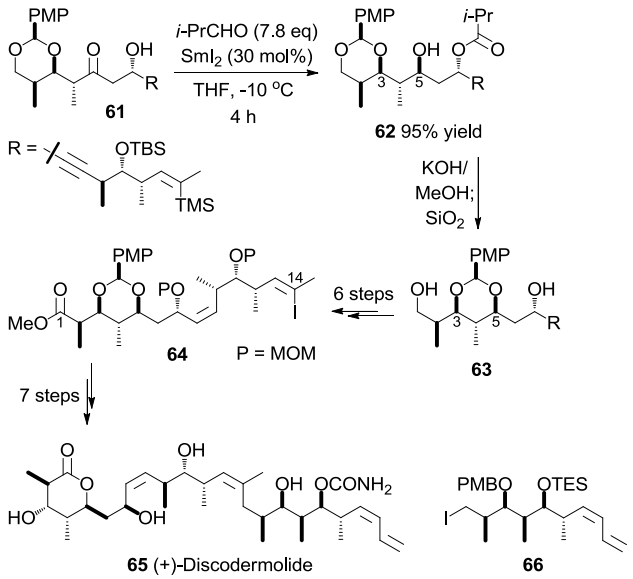
Scheme 11. Synthesis of (a) neopeltolide scaffold **53** using (i) **45a**, PhCHO (6 eq), SmI_2 (50 mol%), THF, –10 °C, 5 h, 80%;[28a] or (ii) **45b**, PhCHO (5 eq), SmI_2 (50 mol%), THF, 0 °C, 3 h, 87%;[28b] (b) (11*R*, 13*R*)-bisepineopeltolide **53**; and (c) (+)-neopeltolide **56**.

A SmI_2 mediated Evans-Tishchenko coupling was also employed in the stereoselective total synthesis of (+)-Rhizoxin D;[29] 1,3-*anti* diol formation followed by hydroxyl protection generated the fully protected C(10)-C(20) subunit (**Scheme 12**). In this case, *p*-nitrobenzaldehyde was coupled to the β-hydroxyketone **57** to generate the PNB (*p*-nitrobenzoyl) protected 1,3-diol **58** with a stoichiometric loading of SmI_2. Notably this particular Evans-Tishchenko reaction was performed in the absence of light: (a) to carefully control the reducing ability of SmI_2 (that can be enhanced in the presence of light);[30] and (b) to minimize the potential for reduction of the nitro functionality.[31] The reaction proceeded in excellent yield (86%) and subsequent protection of the free hydroxyl group as the silyl ether **59** allowed selective cleavage of the PNB group (DIBAL-H). Removal of the silyl group was carried out in the final step (HF/Pyridine) to generate the natural product **60**.



Scheme 12. Evans-Tishchenko coupling in the synthesis of (+)-rhizoxin D.

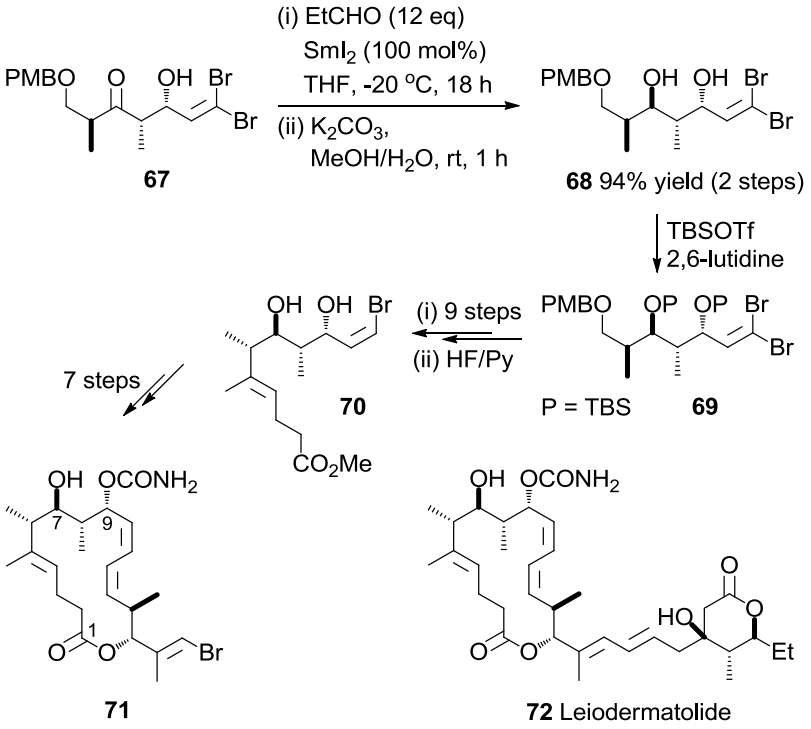
The synthesis of the key C(1)-C(14) subunit **64** of (+)-discodermolide **65**[32] highlights another example of tandem-protection and asymmetric induction in natural product synthesis (**Scheme 13**). In this synthetic sequence, coupling of a propargylic β-hydroxyketone **61** with sacrificial propionaldehyde gave the corresponding 1,3-*anti* diol monoester **62** in excellent yield (95%) and, critically, allowed subsequent selective migration of the PMP acetal protecting group to the *syn*-related C(3) and C(5) hydroxyl groups (**62** → **63**, **Scheme 13**). This sequence demonstrated both the compatibility of the Evans-Tishchenko reaction with various functional groups (silyl ethers, a hindered PMP group, alkyne and alkenes) and its effectiveness at maintaining the stereochemical integrity of neighbouring chiral centres. Completion of the C(1)-C(14) subunit **64** was achieved in 6 steps; and (+)-discodermolide was synthesized in a further 7 steps by coupling with fragment **66** and subsequent protecting group cleavage.



Scheme 13. Evans-Tishchenko coupling in the synthesis of (+)-discodermolide **65**.

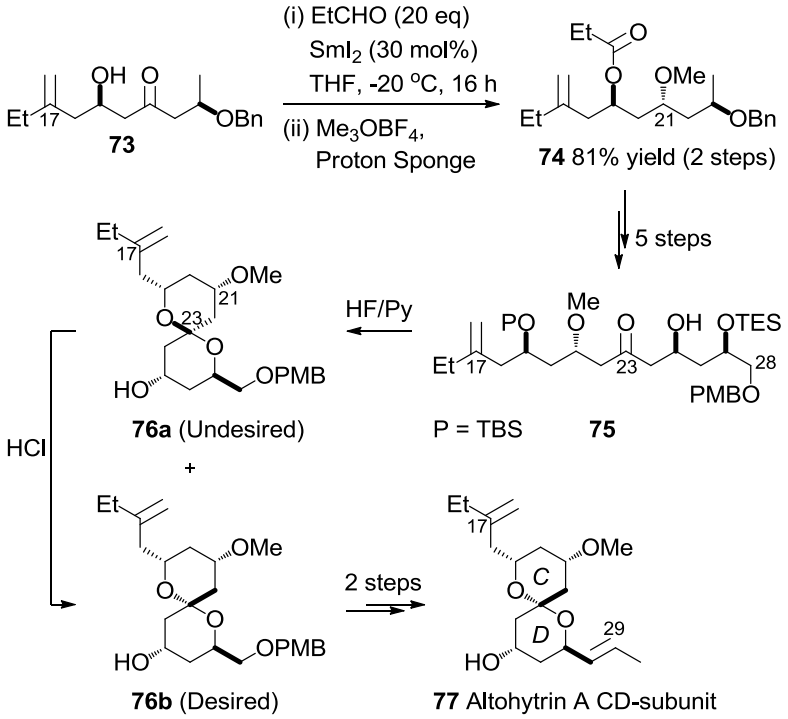
Although the use of protecting groups has become commonplace in organic synthesis, they are often criticized for their low atom economy and the increased cost and synthetic complexity which they impart.[33] However, deprotection strategies where multiple groups are removed simultaneously can help to reduce these disadvantages somewhat and provide a more streamlined route to the synthesis of polyols. In this context, the most obvious choice of dual protection would be to convert the hydroxyl formed as a result of the Evans-Tishchenko reaction to an ester, thus generating a 1,3-*anti* diol diester. However, this strategy does not appear to have been adopted, most probably due to the comparative instability of the resultant diester and the lack of orthogonality with other deprotection strategies required for complex natural product synthesis. However, silyl protecting groups have been used in at least two studies, and these demonstrate that there is potential for the use of the Evans-Tishchenko reaction as part of an simultaneous deprotection strategy.

In pursuing the synthesis of the macrocyclic core **71** of leiodermatolide[34] **72** the Paterson group used such a simultaneous deprotection strategy, hoping to achieve subsequent regioselective generation of the C(7)/C(9) β-hydroxycarbamate motif (**Scheme 14**). An initial SmI_2 mediated Evans-Tishchenko coupling of **67** with sacrificial propionaldehyde (>20:1 *dr*), followed by basic workup (K_2CO_3) to facilitate ester cleavage, and TBS-protection of the resulting diol **68** gave the *bis*-silyl ether **69**. Simultaneous deprotection of both hydroxyls with HF/pyridine to reveal the diol **70** was performed 9 steps later, during which time the chirality was preserved through two periodinane-mediated oxidations and two Grignard additions. The synthesis of the macrocycle **71** was successfully completed in 7 steps from this diol **70**.



Scheme 14. Simultaneous diol deprotection in the synthesis of leiodermatolide.

A second example of streamlined deprotection facilitated by the conversion of the ester resulting from an Evans-Tishchenko reaction to a silyl protecting group has been reported in the synthesis of the altohyrtin A CD-spiroacetal subunit **77** (**Scheme 15**).[35] Reaction of **73** with sacrificial propionaldehyde, followed by methylation of the free alcohol generated methyl ether **74**. Exchange of the propionate ester for a silyl ether was found to be facile (91% over 2 steps), and conversion of the C(23) benzyl-protected alcohol to a ketone gave the substrate for a key boron mediated acetate aldol reaction which generated the linear C(16)-C(28) fragment **75** with excellent diastereoselectivity (>97:3 *dr*). Simultaneous deprotection of the C(19) and C(27) hydroxyls of **75** with HF/pyridine led to spiroketal formation albeit with poor selectivity (1:5) for the desired spiroketal **76b**. Fortunately, the reaction proceeded in excellent yield (88%) and the diastereoisomers were readily equilibrated (HCl) to give a 1:1 mixture of the two isomers **76**, which were easily separated by chromatography thus providing a reliable route to the altohytrin A CD-spiroacetal subunit **77**.[36]

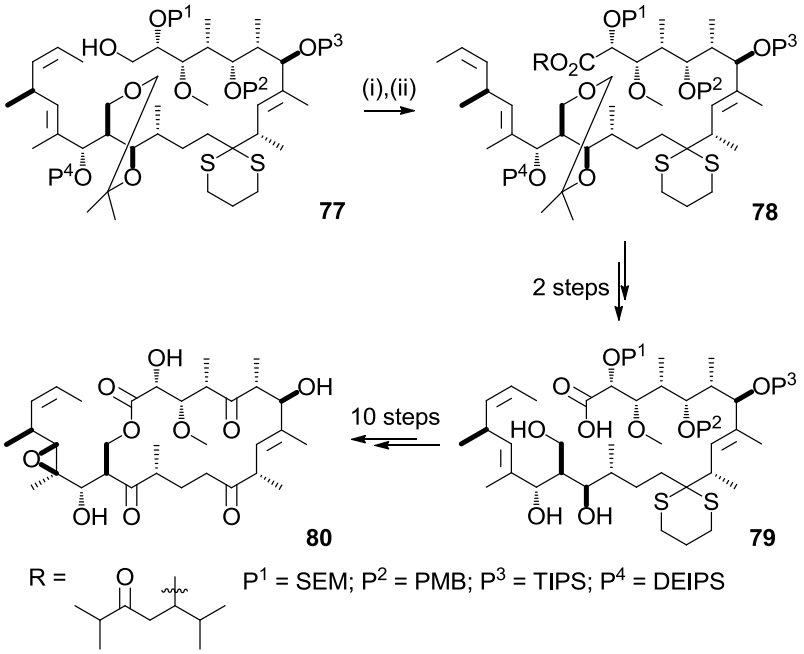


Scheme 15. Simultaneous deprotection in the synthesis of the altohytrin CD-spirocyclic subunit.

4.2 Functional Group Interconversion

As highlighted in **Section 3** the Evans-Tishchenko reaction can be used as a two-step oxidation protocol. Although it is perhaps a more costly and less atom economical method when compared to standard protocols, its use can circumvent problems of substrate sensitivity. An example of such an Evans-Tishchenko oxidation process was published in the synthesis of (+)-13-deoxytedanolide[37] **80** (**Scheme 16**). In this synthetic

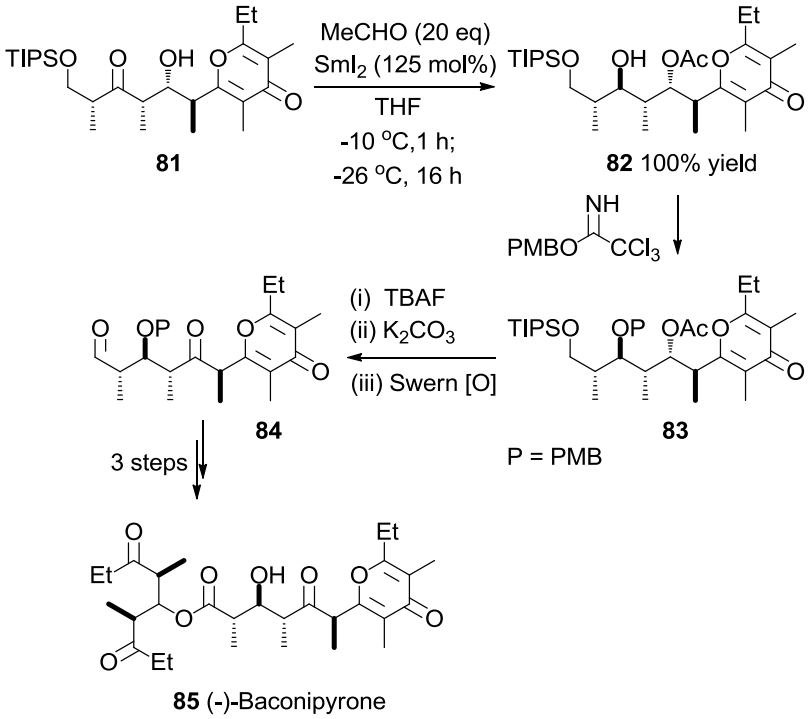
sequence, oxidation of the alcohol **77** to a carboxylic acid was required in the presence of both a number of double bonds and the oxidation-sensitive dithiane moiety. Model studies had shown that a number of standard oxidants including Dess-Martin Periodinane, TPAP/NMO and PCC led to decomposition or over-oxidation of the dithiane. However, following oxidation of alcohol **77** to the aldehyde, the Evans-Tishchenko reaction with a sacrificial β-hydroxyketone furnished the corresponding ester **78**. Despite the need to use the intermediate aldehyde in an unpurified form (due to its instability), this example of the samarium-mediated Evans-Tishchenko reaction still gave a good yield of the desired product **78** (78%) for the two steps. Acetal deprotection and subsequent hydrolysis of the ester functionality furnished the Yamaguchi lactonisation precursor, *seco*-acid **79**, which provided access to the desired natural product **80** in a further 10 steps.



Scheme 16. Use of the Evans-Tishchenko reaction as a mild oxidation in the synthesis of (+)-13-deoxytedanolide **80**. Reagents and conditions: (i) SO_3•Py, DMSO; (ii) ROH (1 eq), SmI_2 (35 mol%), THF, –10 – 0 °C, absence of light, 78% yield over 2 steps.

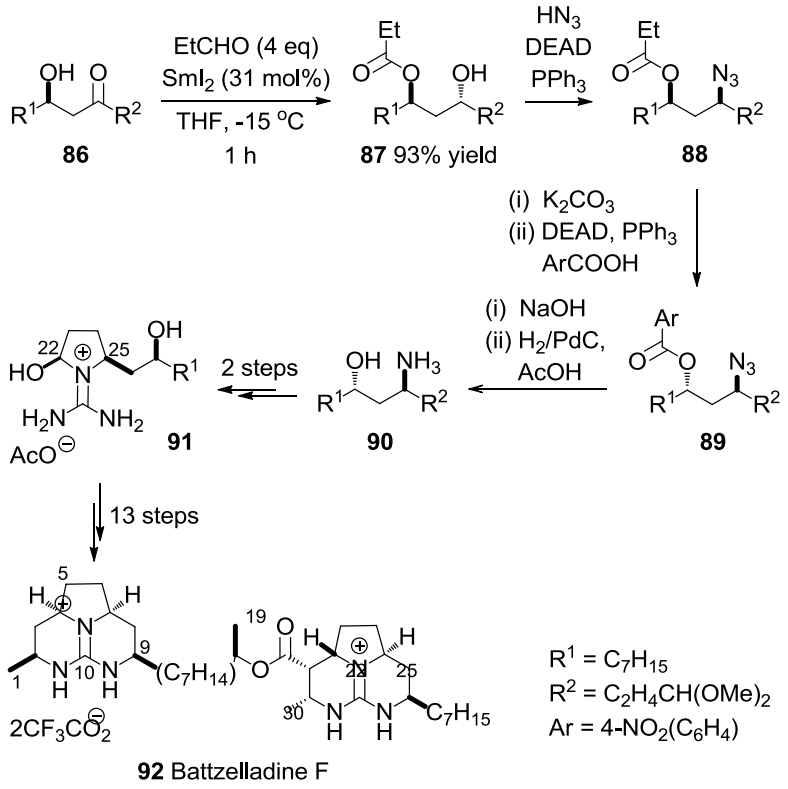
An obvious transformation that may be required by synthetic chemists tackling a complex natural product synthesis is the ability to switch the positions of the alcohol and ketone groups in a β-hydroxyketone with a high degree of stereoselectivity. This can be achieved through use of the Evans-Tishchenko reaction, albeit requiring a multi-step process; an example of such a transformation is seen in the first total synthesis of the polyketide (–)-baconipyrone **85** (**Scheme 17**).[38] Sacrificial acetaldehyde was used to generate the ester **82** from β-hydroxyketone **81** under samarium-catalyzed Evans-Tishchenko conditions. PMB protection of the resulting alcohol gave ether **83** which, after silyl ether deprotection of the primary alcohol, was subjected to

base-mediated ester cleavage and Swern oxidation to the corresponding keto-aldehyde **84**. Although this β-hydroxyl to ketone switch takes place with inversion of the sense of hydroxyl stereochemistry, the inclusion of a Mitsunobu reaction[39] could potentially generate the fully reversed β-hydroxyketone, and indeed this approach is discussed in the remainder of this sub-section.



Scheme 17. Inversion of hydroxyl and ketone groups in the total synthesis of (–)-baconipyrone **85**.

Perhaps as important as inverting the functionality in a β-hydroxyketone, is reversal of stereochemistry in the diol diastereomer generated. This is made possible using the Evans-Tishchenko reaction by exploiting the differing reactivity of the resulting ester and hydroxyl groups; as demonstrated in the synthesis of battzeladine F **92**.[40] Following Evans-Tishchenko coupling of **86** with propanal (**Scheme 18**), a Mitsunobu reaction with hydrazoic acid was used to generate the corresponding azide **88** from the alcohol functionality. After liberation of the hydroxyl group from the ester, a second Mitsunobu reaction (with 4-nitrobenzoic acid) led to reversal of the enantiomeric configuration of the stereocentres while providing a straightforward means of later generating the free amino-alcohol **90**. This was critical in the synthesis of the key C(22)-C(29) guanidinium ring system **91**, which was converted stepwise to the desired product **92** (**Scheme 18**).



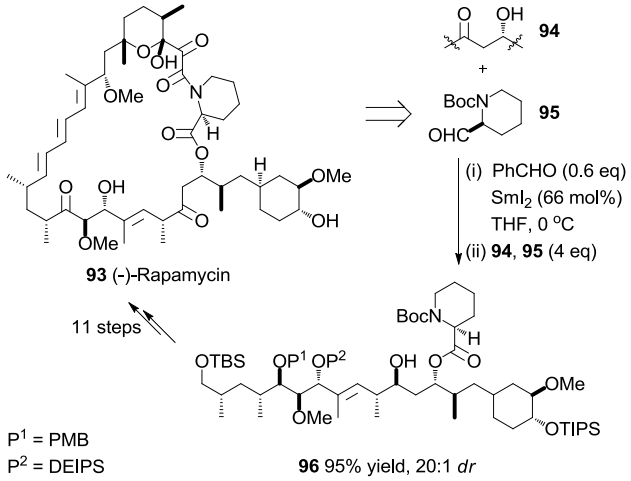
Scheme 18. Use of the Evans-Tishchenko reaction and functional group interconversions in the synthesis of battzelladine F **92**.

4.3. Fragment Linkage and Ring Formation

Linking small, easily synthesized fragments to form part of a larger framework of a natural product is a strategy that is commonplace and almost universally carried out in modern organic syntheses. For this convergent approach to work effectively a high-yielding, selective and reliable reaction is required to bring the components together and hence reactions such as palladium catalyzed couplings are often employed. The ability to construct rings efficiently also plays an essential role in natural product synthesis. The Evans-Tishchenko reaction has also been used in both these types of transformation, albeit in a somewhat limited capacity.

The first reported Evans-Tishchenko reaction in natural product synthesis was that used in the total synthesis of (–)-rapamycin.[41] The retrosynthesis included a SmI_2 mediated Evans-Tishchenko coupling between β-hydroxyketone **94** and the Boc-protected piperidine aldehyde **95** (**Scheme 19**). This reaction proceeded smoothly with 30 mol% of the preformed $(PhCHO)_2SmI{\bullet}SmI_3$ pinacolate catalyst [formed by treatment of sacrificial benzaldehyde (0.6 eq relative to **94**) with SmI_2 (66 mol%, relative to **94**)] to give the corresponding 1,3-*anti* diol monoester **96** in excellent yield (95%) and diastereoselectivity (20:1 *dr*). Later chain extension, deprotection and cyclisation of the linear monomer gave the natural product **93**. Aside from playing a key role

in the synthesis of the desired product, this reaction demonstrated the potential of the Evans-Tishchenko reaction in fragment linkage; with successful SmI_2 mediated coupling taking place in the presence of a number of protecting groups, ether linkages, a double bond and the pipiridine nitrogen atom.

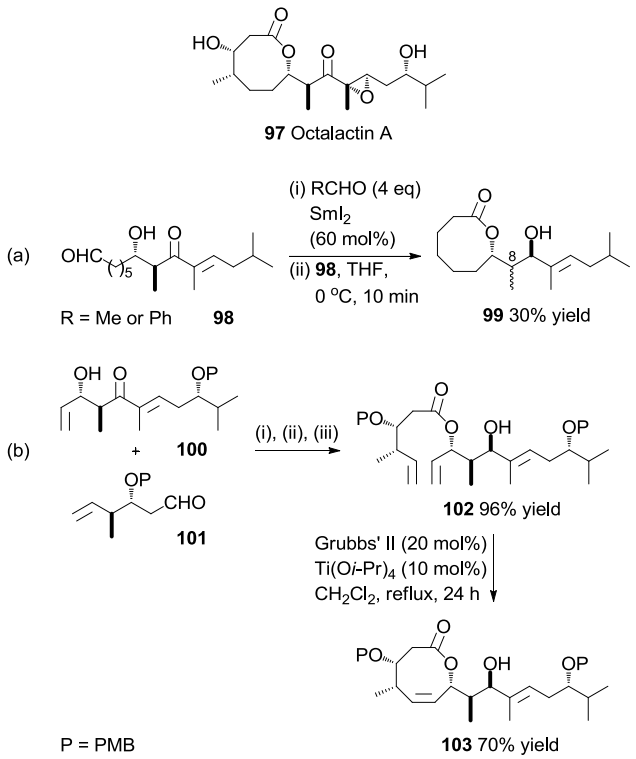


Scheme 19. Use of the Evans-Tishchenko reaction in the synthesis of (–)-rapamycin **93**.

The use of the Evans-Tishchenko reaction in the formation of macrolactone rings is one which has been explored with varying degrees of success. Two possible approaches to the synthesis of macrolactones using this methodology are: i. an intramolecular Evans-Tishchenko reaction to form the lactone directly; or ii. an initial Evans-Tishchenko esterification followed by ring-closure to the give the desired macrolactone through the use of orthogonal chemistry *e.g.* ring closing metathesis. The high diastereoselctivity imparted by the Evans-Tishchenko reaction combined with typically high yields and the fact that the reaction only reveals the second, potentially competing, hydroxyl during the reaction process makes this approach to macrolactone synthesis very attractive in complex natural product synthesis.

The first intramolecular Evans-Tishchenko reaction was carried out in model studies aimed at the synthesis of the cytotoxic marine natural product octalactin A.[26] Octalactin A **97** contains a medium lactone ring (8-membered) which has proven difficult to cyclise under standard conditions (*e.g.* macrolactonisation under high dilution).[42] Treatment of model cyclisation precursor **98** (**Scheme 20a**), which contains both aldehyde and β-hydroxyenone functionalities, with 30 mol% of a pre-formed pinacolate samarium catalyst at 0 °C led to formation of the 8-membered ring lactone **99**, albeit in poor yield (30%). Unfortunately, the generation of a 1:1 mixture of diastereomers rendered the route non-viable for construction of octalactin A **97**. However, NMR studies showed that this diastereomeric mixture arose from epimerisation of the C(8) methyl group due to the comparative instability of the β-hydroxyenone under the extended reaction times required for closure of a disfavoured medium ring, rather than low selectivity in the Evans-Tishchenko reaction. Therefore, the

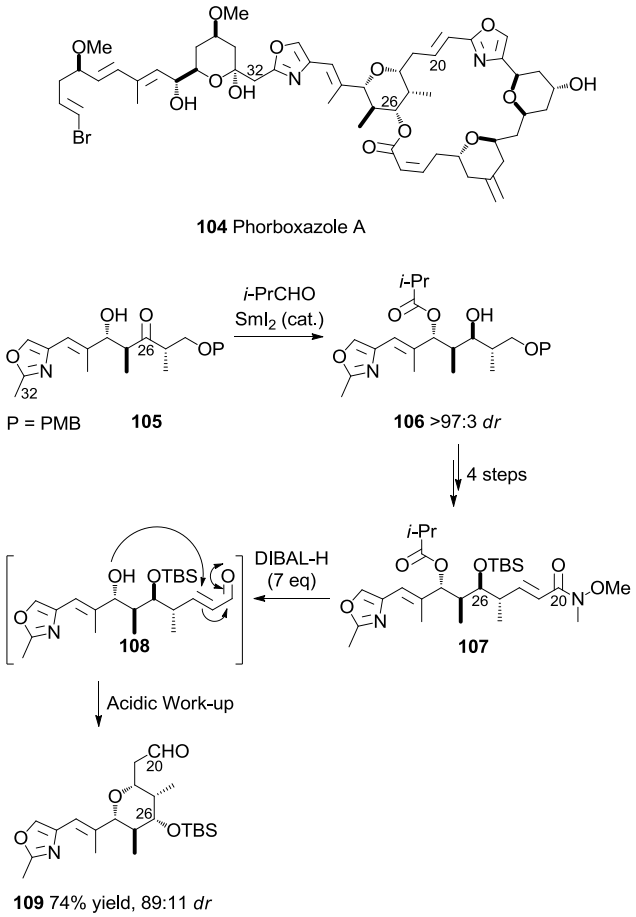
intramolecular Evans-Tishchenko reaction remains a potentially useful, highly diastereoselective alternative to more traditional means of lactonisation.



Scheme 20. (a) Intramolecular Evans-Tishchenko reaction; and (b) Evans-Tishchenko ring-closing metathesis approach toward the synthesis of octalactin A **97**. (i) PhCHO (0.5 eq), SmI_2 (61 mol%), THF, 0 °C, 30 min; (ii) **101** (2 eq), 30 min; (iii) **100**, 30 min.

Fortunately, a number of methods exist for the generation of medium sized rings, and the combination of the Evans-Tishchenko reaction with ring-closing metathesis provides a useful route to the synthesis of such lactones. The Hulme group[43] demonstrated this approach in a later synthesis of the 8-membered lactone core of octalactin A (**Scheme 20b**). Evans-Tishchenko coupling of β-hydroxyenone **100** with the aldehyde **101** (itself bearing an alkene functionality) provided the required metathesis precursor **102**. Ring-closing metathesis under Fürstner's modified conditions[44] (to circumvent deleterious side-reactions caused by internal chelation of the metallocarbene) allowed the successful generation of key lactone **103** and provided a straightforward two-step approach to the synthesis of the ring system. Indeed, the highly convergent nature of this approach allowed intermediate **103** to be generated in only 8 steps longest linear sequence providing a promising route to the synthesis of octalactin A.

A second class of ring that has been constructed from the products of an Evans-Tishchenko reaction is the tetrahydropyran motif. Pyran-type systems may be readily accessed through stereoselective reaction of the hydroxyl group formed in the Evans-Tishchenko reaction with an appropriate electrophilic sink. This synthetic strategy was exploited in the Paterson group synthesis of the C(20)-C(32) subunit **109** of phorboxazole A **104**.[45] A *cis*-tetrahydropyran ring system was introduced through use of the Evans-Tishchenko reaction to generate the key hydroxyester **106**, which could be converted to Weinreb amide **107** in 4 steps (**Scheme 21**). Ester-to-alcohol reduction and concomitant amide partial reduction to the intermediate δ-hydroxyenal **108** using an excess (7 eq) of DIBAL-H gave the required donor (hydroxyl group) and acceptor (enal) moieties for an intramolecular Michael reaction. This was realised through straightforward acidic aqueous work-up to give a high yield (74%) and diastereoselectivity (89:11 *dr*) of the product tetrahydropyran. Key to this process was the Evans-Tishchenko reaction which formed the 1,3-*anti* diol monoester in high *dr*, allowed selective protection of the hydroxyl group with a bulky TBS ether to aid subsequent selective *cis*-pyran ring formation, and provided an ester which could be readily deprotected under orthogonal conditions to generate the Michael donor moiety. Although the total synthesis of phorboxazole A was not completed using this methodology,[46] it provides an outstanding example of the versatility of the 1,3-*anti* diol monoester products generated *via* the Evans-Tishchenko reaction.



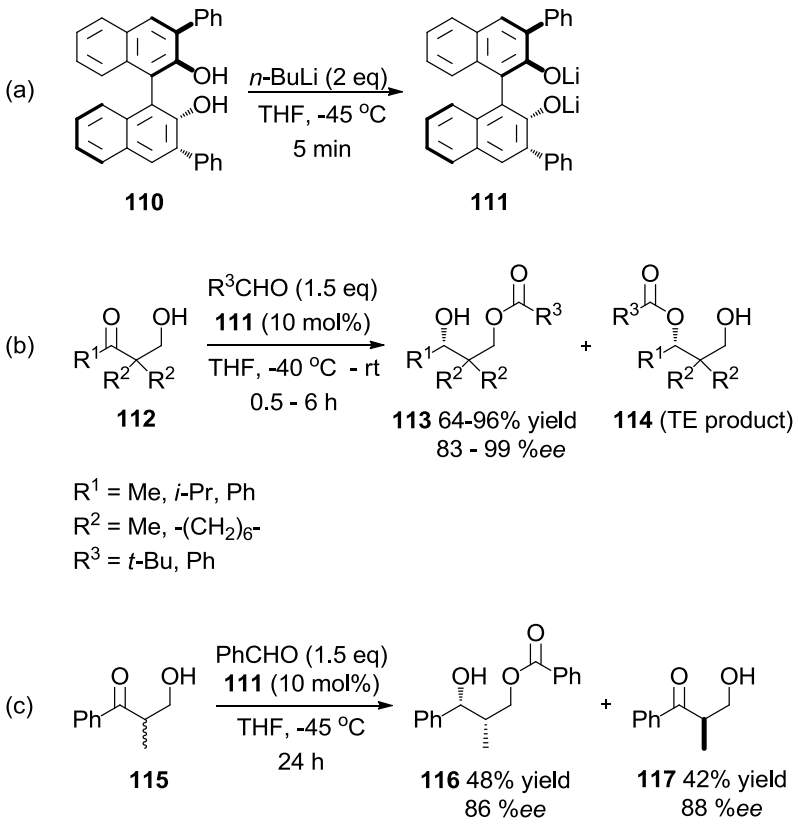
Scheme 21. Tetrahydropyran ring formation in the C(4)-C(32) subunit **109** of phorboxazole A **104**.

5. Future Perspectives

Since the Evans-Tishchenko reaction was first published in 1990, it has proved to be an important tool in the stereoselective generation of 1,3-*anti* diols and their derivatives. The reaction, in particular when performed in the presence of Lewis acidic catalysts derived from samarium diiodide, has already shown remarkable tolerance in terms of substrate scope and has been successfully demonstrated with a range of electron-rich, electron-poor and sterically hindered substrates. These attributes, as well as the versatility of the resulting 1,3-*anti* diol monoesters, have proved invaluable in the synthesis of natural products.

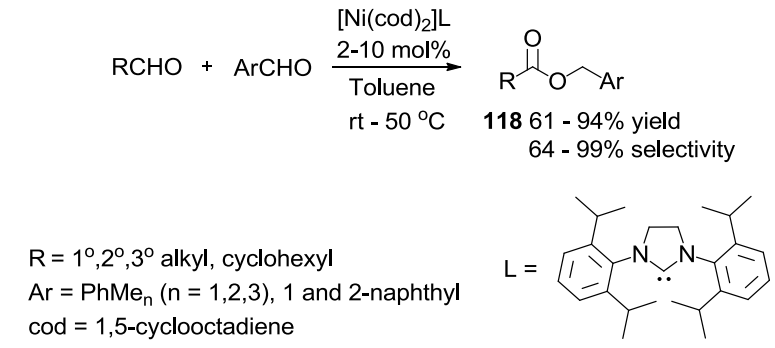
Future work in the development of the Evans-Tishchenko reaction should focus on the use of alternative Lewis acid catalysts. These must be less expensive and/or more readily handled on large scale than current samarium diiodide based methodologies. A number of alternative catalysts have been used in the related aldol-Tishchenko reaction; these include lithium,[47] lanthanum,[48] titanium,[49] yttrium[21] and ytterbium.[50] As the second step in the aldol-Tishchenko reaction is believed to have a similar transition state to the Evans-Tishchenko reaction, these metals would be worthy of study in efforts to identify those which can successfully catalyze the coupling of aldehydes and β-hydroxyketones without accompanying retro-aldol aldol-Tishchenko (RAAT) or epimerization aldol-Tishchenko reactions (*c.f.* **Section 2.1**). Although the use of inexpensive main group metals and transition metals such as iron, copper and zinc remain an ideal goal, much work is required in order to identify a catalyst or promoter which is as effective or offers other advantages or attributes over the samarium diiodide protocol.

The development of a widely-applicable asymmetric variant of the Evans-Tishchenko reaction would also be an extremely important advance in the field. To date only a very limited number of examples of this kind of transformation have been published. Chiral lithium binaphtholates have recently been shown to convert achiral β-hydroxyketones to the corresponding chiral 1,3-diol monoesters (**Scheme 22**).[5] Thus reaction of terminal β-hydroxyketones **112** with benzaldehyde or pivaldehyde in the presence of 10 mol% of the lithium binaphtholate catalyst **111** (generated *in situ* from **110**) led to the corresponding products **113** in generally excellent yields (64-96%) and enantioselectivities (>83 %*ee*). In some instances this product was accompanied by the undesired transesterification product **114** (*c.f.* **Section 2.1**). One example of the kinetic resolution of a racemic α-methyl-β-hydroxyketone **115** with the lithium binaphtholate catalyst **111** was also reported by Nakajima *et al.*.[5] Although attractive, these methods for the stereoselective generation of 1,3-diol monoesters and kinetic resolution of racemic α-substituted-β-hydroxyketones clearly lack generality and a greater understanding of both the reaction mechanism and substrate scope, are required before they can be widely adopted.



Scheme 22. (a) Generation of the lithium binaphtholate catalyst **111**. Lithium mediated (b) asymmetric Evans-Tishchenko reactions; and (c) Evans-Tishchenko kinetic resolution.

In addition to the use of chiral BINOL-type ligands to induce asymmetry, a further intriguing possibility has been raised by recent reports of nickel catalysts with NHC ligands for related crossed-Tishchenko reactions.[51] Under these conditions crossed alkanoate-benzyl esters **118** are selectively generated from the corresponding alkyl and aryl aldehydes (**Scheme 23**). Some mechanistic details of the reaction have been determined, but the extension of this catalytic system to the Evans-Tishchenko reaction, and the possibility of using chiral NHC ligands have yet to be explored.



Scheme 23. Nickel-catalyzed Tishchenko reaction.

To date, the Evans-Tishchenko reaction has predominantly been used in the construction of polyketides or the polyketide portion of mixed polyketide-NRPS natural products. However, when used in tandem with the Mitsunobu reaction (as demonstrated in the synthesis of battzeladine F[40] in **Section 4.2**) the reaction provides an excellent means of introducing a number of functional groups, including nitrogen, stereoselectively. Hence in future a wider range of applications to include other natural product target classes might be expected. In addition, an intra- or inter-molecular Mitsunobu reaction with an acidic group following Evans-Tishchenko coupling would also provide an interesting, straightforward general method of generating lactones and other oxygen or nitrogen containing ring systems.[52] Finally, substrate expansion to encompass the use of β-hydroxy imines is another unexplored area for the Evans-Tishchenko reaction; if suitable conditions were found this could add a complementary approach to the *anti*-specific reduction of β-hydroxy-*N*-sulfinyl imines reported by Ellman et al.[53]

It is clear that the generation of medium- and large-ring lactones using the intramolecular Evans-Tishchenko reaction remains an underdeveloped area of research. Similarly, further examples of Evans-Tishchenko reactions between alkene- or alkyne-containing aldehydes and alkenyl- or alkynyl-substituted β-hydroxyketones followed by ring-closing metathesis as a high yielding and highly diastereoselective route to unsaturated ring systems might be anticipated. In this review we have highlighted instances of the use of the Evans-Tishchenko reaction as a method of fragment linkage (**Section 4.3**). However, this strategy is still underutilized when compared with, for example, palladium catalyzed coupling reactions; this is especially surprising considering the relative ease of synthesis of both the reactive partners. Given that the 1,3-diol monoester, and related 1,3-derivatives are commonplace, and the Evans-Tishchenko reaction is particularly mild and tolerant of functionality, more syntheses could be built around an application of the Evans-Tishchenko reaction to join fragments in large natural products.

6 Conclusion

The Evans-Tishchenko reaction provides a reliable, mild, versatile and highly diastereoselective method of generating 1,3-*anti* diol monoesters and will continue to find application in the synthesis of natural products and other biologically relevant structures. Future work should focus on the development of cheaper alternative catalysts (metal, organocatalysts etc.), asymmetric induction and kinetic resolution, extension of the substrate scope (*e.g.* to encompass β-hydroxythioketones/imines, β-thio/aminoketones) and the use of synthetic plans which exploit the enormous potential of the 1,3-*anti* diol monoesters which result from the Evans-Tishchenko reaction.

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