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Rationally Designed Chiral Synthons Enabling Asymmetric *Z*- and *E*-Selective Vinylogous Aldol Reactions of Aldehydes

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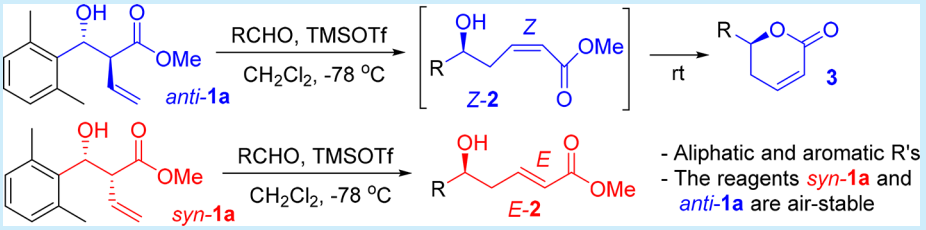
Supporting Information

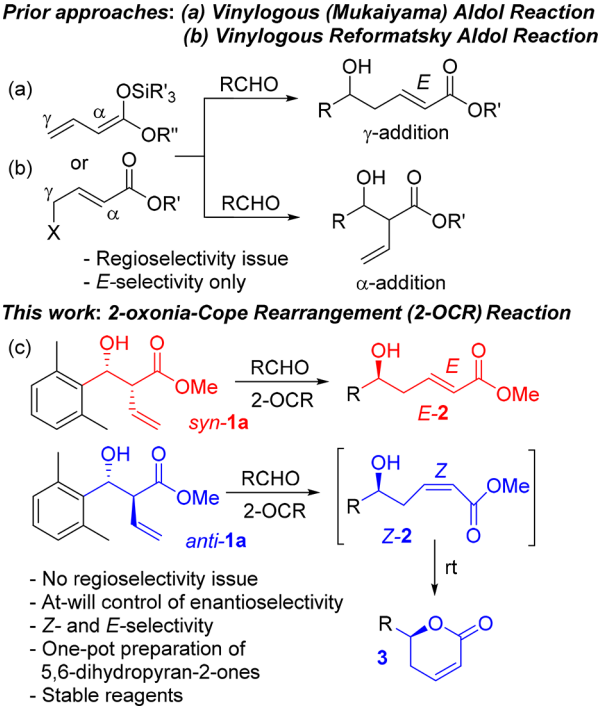


ABSTRACT: In a conceptually different approach, highly stereoselective 2-*oxonia*-Cope rearrangement reactions between rationally designed nonracemic vinylogous aldolation synthons and aldehydes are described to provide δ-hydroxy-α,β-unsaturated esters with excellent enantioselectivities and, for the first time, unprecedented *Z*- and *E*-selectivities without the regioselectivity issue.

δ-Hydroxy-α,β-unsaturated carbonyl functionalities occupy a privileged status in organic synthesis due to their prevalence in many natural and artificial products as well as their versatile synthetic utilities as intermediates toward other (more complex) useful structures.[1−5] As such, a plethora of asymmetric methodologies have been put forth, the vast majority of which rely on the asymmetric vinylogous (Mukaiyama) aldol reaction employing dienolates/dienol ethers in combination with chiral catalysts[1−4] or chiral auxiliary-based dienol ethers in the presence of Lewis acids.[5] Recently, an enantioselective Ir-catalyzed vinylogous Reformatsky aldol reaction was reported to circumvent some drawbacks associated with the vinylogous (Mukaiyama) aldol reaction, such as the formation and tractability of the required silyl dienol ethers as well as potential background reactions catalyzed by racemic silyl cations formed in the reaction.[6] Even though good to excellent enantioselectivities have been obtained in some cases, there still exists significant room for improvement with respect to the scope of dienol ethers and (functionalized) aliphatic aldehydes, and the regioselectivity problem is an intrinsic shortcoming of the aforementioned approaches (Scheme 1a,b). Furthermore, these methods are inherently unable to control the double bond configuration of enoate products. The *Z*- and *E*-selectivity issue has not been addressed to date and, thus, represents a significant literature gap, particularly considering that both 2*Z*- and 2*E*-δ-hydroxy-α,β-unsaturated carbonyl functionalities have been found in natural products,[7] and they often exhibit disparate behaviors in organic reactions.[8]

In a distinctly different approach, we herein report the development of rationally designed nonracemic synthons enabling the at-will control of not only enantioselectivity, but also *Z*- and *E*-selectivity without the regioselectivity concern in the vinylogous aldol reaction of aldehydes, which operate through a 2-*oxonia*-[3,3]-Cope rearrangement (2-OCR)

Scheme 1. Approaches for the Asymmetric Synthesis of δ-Hydroxy-α,β-Unsaturated Carbonyl Functionalities



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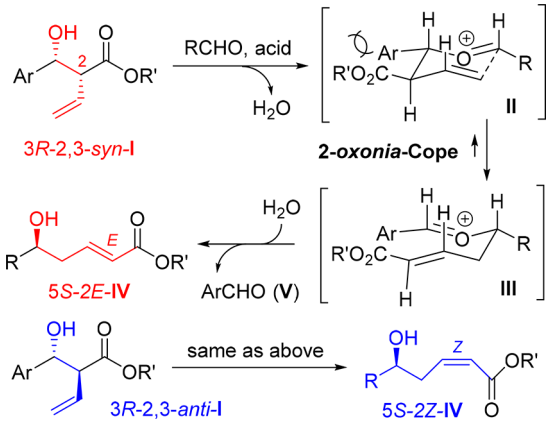
mechanism (Scheme 1c).[9] Also described is a convenient one-pot asymmetric synthesis of 5,6-dihydropyran-2-ones,[7] which exploits the unprecedented *Z*-selective vinylogous aldolation.[10]

Scheme 2 describes the mechanism of the 2-OCR reaction between vinylogous aldolation synthons 3*R*-2,3-*syn*-**I** and

Scheme 2. Mechanism and Chirality Transfer of 2-*Oxonia*-Cope Rearrangement Reaction between Aldehydes and the Synthons I

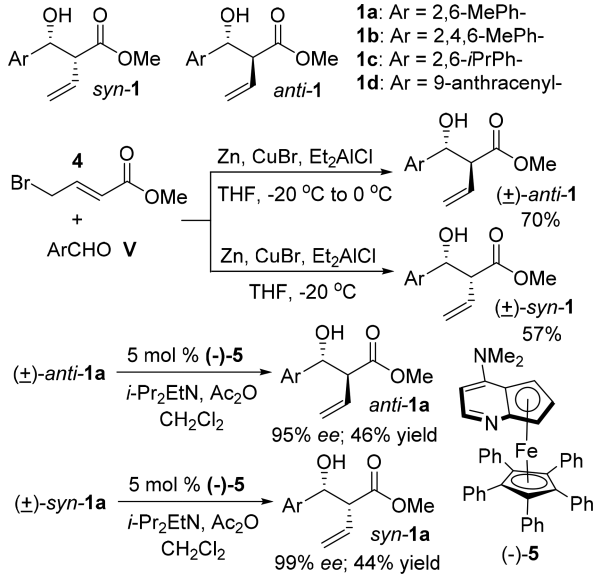


aldehydes under acidic conditions employing the Zimmerman–Traxler-type analysis of transition states.[11] Assuming that the key step in the mechanism is the [3,3]-sigmatropic rearrangement of the initially formed oxocarbenium ions **II** to the product-side oxocarbenium ions **III**, the relative stability of **III** to **II** as well as the steric repulsion between the aryl group and the ester group of **II** are expected to provide a major driving force for the reaction. This led us to conjecture that installing an aryl group with appropriate substituents at the C3 position of **I** could increase the relative stability of **III** to **II** and the steric repulsion, driving the equilibrium reaction to the product side. Sterically hindered aryl groups, such as a 2,6-disubstituted phenyl group, would be most appropriate in this regard. Moreover, the steric encumbrance by the 2,6-substituents can prevent the aryl aldehyde byproducts **V** from interfering with the desired 2-OCR reaction. The mechanism also shows that the chirality of 3*R*-2,3-*syn*-**I** can be specifically transferred to that of 5*S*-2*E*-**IV**. This analysis, when combined with a similar analysis for 3*R*-2,3-*anti*-**I**, strongly indicates that the C5 stereochemistry and the C2 double configuration of **IV** can be *easily predicted and controlled* by the absolute and relative stereochemistry of the C2 and C3 of **I**, respectively. The synthons 3*R*-2,3-*syn*-**I** and 3*R*-2,3-*anti*-**I** are expected to be air-stable and thus easy to handle.

Despite these attractive traits, a convenient and general platform, such as **I**, which can enable efficient 2-*oxonia*-Cope rearrangement reactions to deliver δ-hydroxy-α,β-unsaturated carbonyl compounds **IV** in a highly stereoselective fashion, is not currently available. In related work introducing bispropionates to aldehydes, the McDonald group recently reported the synthons containing a phenyl group tethered with a silyloxy group, which was required not only to drive 2-OCR to the product side, but also to facilitate purification; a synthon with a phenyl group only did not work. Contrary to the synthons **I**, their synthons worked in two stages through the formation of acetal intermediates, followed by a 2-OCR, and only aliphatic aldehydes were used.[12a]

On the basis of the above reasoning, the vinylogous aldolation synthons **1a–d** are devised, and their synthesis is shown in Scheme 3. A Reformatsky reaction between 2,6-

Scheme 3. Preparation of Vinylogous Aldolation Synthons



dimethylbenzaldehyde and methyl 4-bromocrotonate at either −20 or −20 to 0 °C generated the desired *syn*- and *anti*-aldol products, respectively.[13] When (±)-2,3-*syn*- and (±)-2,3-*anti*-**1a** were subjected to the kinetic resolution conditions employing Fu's catalyst (−)-**5**,[14] delightfully, the respective *syn*- and *anti*-**1a** were obtained with >95% ee for both cases. The synthons (±)-**1b–d** were similarly prepared.

With (±)-*anti*-**1a–d** in hand, their 2-OCR reactions with *n*-hexanal were studied to determine the best aryl group and the optimal reaction conditions by screening various acids [TMSOTf, TfOH, $BF_3{\cdot}OEt_2$, $SiCl_4$, $SnCl_4$, $TiCl_4$, $Sn(OTf)_2$, and $Sc(OTf)_3$] and temperatures (−78, −20, 0 °C, and rt). The conditions employing (±)-*anti*-**1a** and TMSOTf in CH_2Cl_2 at −78 °C were determined to be optimal. Under the optimal conditions, *anti*-**1a** (95% ee) delivered the expected *Z*-**2a** in 87% reaction yield with 94% ee and >25:1 *Z*/*E*-selectivity, indicating nearly perfect chirality transfer in the reaction.

The determined optimal 2-OCR conditions involving *anti*-**1a** and TMSOTf in CH_2Cl_2 at −78 °C are applied to a diverse array of aldehydes, and the results are displayed in Table 1. Linear, β-branched, α-branched, and cyclic aliphatic aldehydes all worked well (entries 1–4). Sterically hindered pivalaldehyde also reacted smoothly (entry 5). In the aliphatic aldehyde cases studied, excellent reaction yields (≥87%) were obtained, and chirality transfer was nearly perfect, as judged by the exceptional *Z*/*E*- and enantioselectivities obtained. With benzaldehyde, a diminished yield was observed due to the formation of the corresponding 5,6-dihyropyran-2-one (entry 6), but the *Z*/*E*- and enantioselectivities remained excellent. Particularly notable are almost exclusive *Z*-selectivities observed, which are not possible by any other vinylogous aldol reactions.

Table 2 describes a one-pot synthesis of 5,6-dihydropyran-2-ones **3** via the *Z*-selective 2-OCR reaction between *anti*-**1a** and aldehydes. After completing 2-OCR reactions at −78 °C, as judged by TLC, the temperature was raised, and the initial

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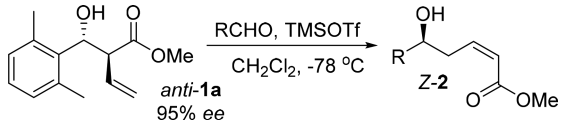
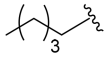
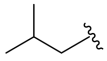
Org. Lett. XXXX, XXX, XXX–XXX

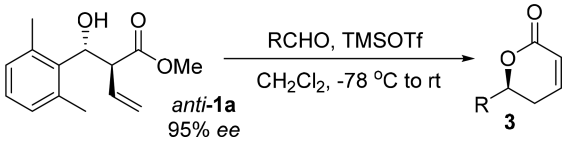
Table 1. Enantio- and *Z*-Selective Vinylogous Aldol Reactions between Aldehydes and *anti*-1a[a]

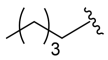
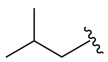


entry	R-	product	yield (%)[b]	*Z*/*E*[e]	*ee* (%)
1		***Z*-2a**	87	>25:1	94[f]
2		***Z*-2b**	90	>25:1	93[f]
3		***Z*-2c**	91	>25:1	95[f]
4		***Z*-2d**	97[c]	>25:1	96[g]
5		***Z*-2e**	88	>25:1	95[g]
6		***Z*-2f**	63[d]	>25:1	>92[f]

[a]*anti*-**1a** (0.213 mmol), aldehyde (2.00 equiv), and TMSOTf (1.50 equiv) in DCM (4 mL) at −78 °C for 60 min. [b]Isolated yields. [c]Yield at 1 mmol scale. [d]The corresponding 5,6-dihydropyran-2-one was obtained in 26% yield. [e]Determined by ^{1}H NMR. [f]Determined by measuring the ee's of the corresponding 5,6-dihydropyran-2-ones by chiral HPLC. [g]Determined by chiral HPLC

Table 2. Enantioselective One-Pot Synthesis of 5,6-Dihydropyran-2-ones via the 2-OCR Reaction of *anti*-1a[a]



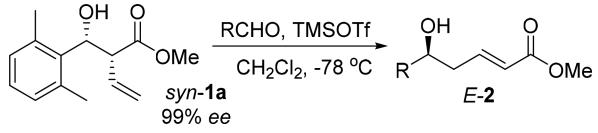
entry	R-	product	yield (%)[b]	condition A or B[a]	*ee* (%)
1		**3a**	71	A	94[d]
2		**3b**	75	A	93[d]
3		**3c**	72	A	95[d]
4		**3d**	77[c]	A	96[e]
5		**3e**	68	A	95[e]
6		**3f**	70	B	>92[d]

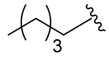
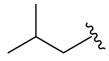
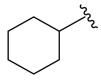
[a]Conditions A: same as Table 1 at −78 °C to rt for 5 h. Conditions B: at −78 to −30 °C for 90 min. [b]Isolated yields. [c]Yield at 1 mmol scale. [d]Determined by chiral HPLC. [e]See Table 1, entries 4 and 5.

products *Z*-**2** spontaneously cyclized into the corresponding 5,6-dihydropyran-2-ones without compromising enantioselectivities. The one-pot operation and excellent enantioselectivities of the 2-OCR reactions, followed by spontaneous cyclization, attest their superb synthetic efficiency, when compared with other synthetic methods for the 5,6-dihydropyran-2-one ring structures that have typically employed a three-step sequence of aldehyde allylation/acylation/ring-closing metathesis (RCM)[15] or aldehyde allylation/*Z*-selective cross-metathesis (CM)/cyclization.[16]

Depicted in Table 3 are enantio- and *E*-selective vinylogous aldol reactions between *syn*-**1a** and aldehydes. As in the cases of

Table 3. Enantio- and *E*-Selective Vinylogous Aldol Reactions between Aldehydes and *syn*-1a[a]



entry	R-	product	yield (%)[b]	*E*/*Z*[d]	*ee* (%)[e]
1		***E*-2a**	90	>25:1	99
2		***E*-2b**	90	>25:1	99
3		***E*-2c**	85	>25:1	99
4		***E*-2d**	97[c]	>25:1	99
5		***E*-2e**	83	>25:1	99
6		***E*-2f**	83	>25:1	99

[a]*syn*-**1a** (0.213 mmol), aldehyde (2.00 equiv), and TMSOTf (1.50 equiv) in CH_2Cl_2 (4 mL) at −78 °C for 60 min. [b]Isolated yields. [c]Yield at 1 mmol scale. [d]Determined by ^{1}H NMR. [e]Determined by chiral HPLC

anti-**1a** in Table 1, excellent enantioselectivities and *E*-selectivities were obtained with all aliphatic and aromatic aldehydes. A notable difference is that the 2-OCR reactions of aldehydes by *syn*-**1a** proceeded faster than those by *anti*-**1a**, which is consistent with the analysis in Scheme 2.

As shown Scheme 4, functionalized aldehydes could be used in the 2-OCR reaction. For example, 3-(benzyloxy)propanal (**6**)[17] reacted well with *anti*- and *syn*-**1a** to give the corresponding 2*Z*- and 2*E*-*δ*-hydroxy-*α*,*β*-unsaturated esters, *Z*- and *E*-**7** (Scheme 4a).[18] As anticipated, upon raising the temperature, *Z*-**7** spontaneously cyclized to the corresponding 5,6-dihyropyran-2-one **8** in 85% yield and with 99% ee (Scheme 4a), which had been previously synthesized from **6** by the asymmetric aldehyde allylation/acylation/cross metathesis sequence[19a] and used as an intermediate in the asymmetric synthesis of natural products.[19]

To further demonstrate the power and synthetic utility of the developed 2-OCR reaction by *anti*-**1a**, two stereoisomers of euscapholide, *syn*-**11** and *anti*-**11**, were prepared (Scheme 4b).

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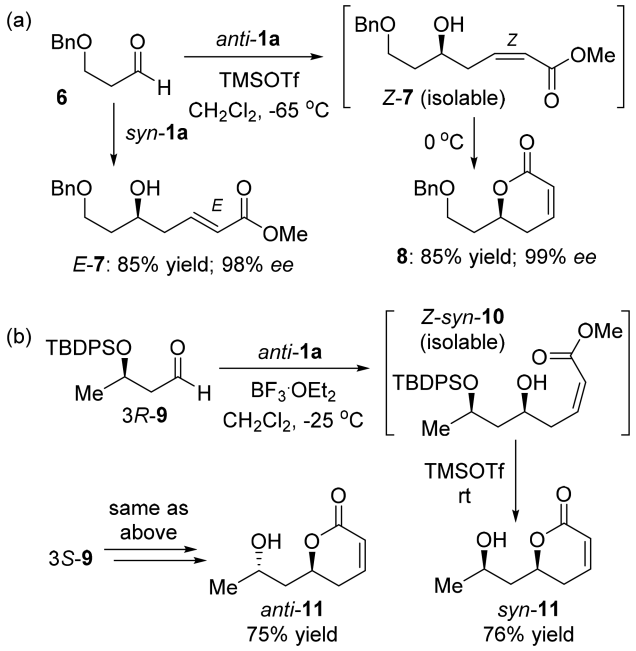
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 4. Synthetic Applications Utilizing *syn*- and *anti*-1a



Euscapholide (*ent-syn*-**11**) has shown anti-inflammatory activity[20a] and is the core structure of many natural products with interesting biological activities, such as anticancer, antibacterial, and antigerminating.[20] A 2-OCR reaction between nonracemic aldehyde with a stereocenter 3*R*-**9** and *anti*-**1a** in the presence of $BF_3{\cdot}OEt_2$ at −25 °C initially gave rise to *Z-syn*-**10**, which was isolable. Upon treating with TMSOTf and raising the temperature, *Z-syn*-**10** spontaneously cyclized into *syn*-**11** with concomitant deprotection of the TBDPS group.[21] On the other hand, an application of the same reaction sequence to 3*S*-**9** delivered *anti*-**11** in one-pot operation; the intermediate *Z-anti*-**10** was also isolable.[21] These results indicate that the stereochemistry of the above OCR reactions is entirely controlled by the chirality of the synthon *anti*-**1a**, overcoming the stereochemical bias by the existing C3 chiral center of **9**.

In summary, new chiral synthons for the asymmetric vinylogous aldolation of aldehydes have been devised and prepared from commercially available compounds through two easy catalytic reactions. Contrary to other vinylogous aldol reactions, the synthons operate through the 2-*oxonia*-Cope rearrangement mechanism, and for the first time, enable the at-will control of both enantioselectivity and *Z*/*E*-selectivity without the regioselectivity concern. Exceptional chirality transfer, operational simplicity, ready availability, and air-stability of the developed synthons should warrant their wide applications in organic synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00230.

Procedures, characterization data, HPLC chromatograms, and $^1H/^{13}C$ NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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