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Highly Stereoselective 2-Oxonia-Cope Rearrangement: A Platform Enabling At-Will Control of Regio-, Enantio-, and Diastereoselectivity in the Vinylogous Aldol Reactions of Aldehydes

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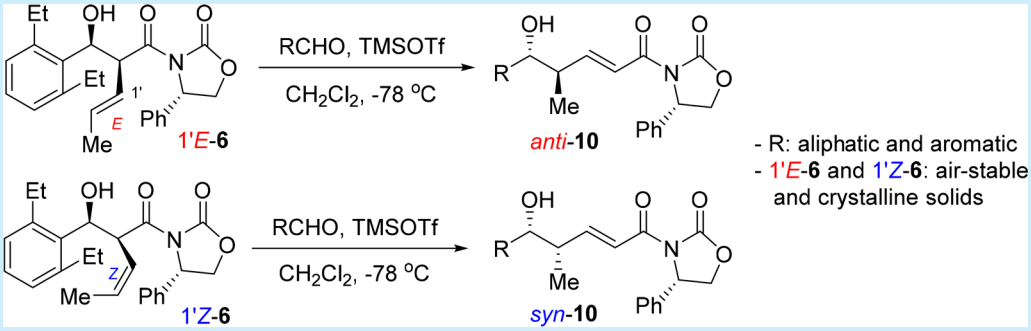
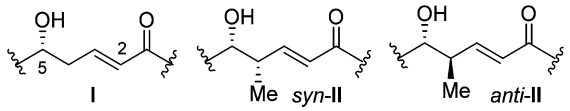
Supporting Information



ABSTRACT: A distinctly different approach for the vinylogous aldolation of aldehydes is described, which exploits 2-oxonia-Cope rearrangement reactions between two readily available partners, a set of rationally designed chiral homoallylic alcohol synthons and aldehydes, under simple conditions. In these processes, chirality transfer from the former to the latter is nearly perfect, giving rise to excellent enantio- and diastereoselectivity without the regioselectivity issue associated with traditional vinylogous aldol reactions.

5-Hydroxy-2,3-unsaturated carbonyl compounds **I** and their "crotyl" analogues **II** are valuable synthetic targets, both as final structures and as intermediates in the total synthesis of (bio)chemically relevant compounds, particularly polyketide natural products.[1,2] The vinylogous (Mukaiyama) aldol reaction employing enolates/dienol ethers in combination with chiral catalysts has been most widely used,[2] and other innovative protocols such as iridium-catalyzed vinylogous Reformatsky reaction[3] and Kobayashi aldol reactions employing Evans' chiral auxiliary-based silyl dienyl *N,O*-acetals[4] have been put forth in recent years. Excellent regio- and enantioselectivities have been obtained with a diverse array of aliphatic and aromatic aldehydes in the case of **I**.[5,6]



In contrast, the synthesis of **II** has proven to be challenging due to the requirement to control diastereoselectivity in addition to regio- and enantioselectivity. As shown in Figure 1, a literature survey surprisingly revealed a lack of a general platform to control all three selectivities simultaneously. Chiral silicon-catalyzed vinylogous Mukaiyama aldol reactions gave rise to only *anti*-**II** and, more significantly, did not work with aliphatic aldehydes (Figure 1a).[6] In the chiral boron-catalyzed vinylogous Mukaiyama aldol reactions, only *syn*-**II** was obtained from both 4*E*- and 4*Z*-methyl-substituted silyl dienyl acetals, and the scope of aldehydes was limited with respect to diastereoselectivity (Figure 1b).[7] Vinylogous aldol reactions utilizing chiral crotylsilanes led to only *syn*-**II**, and modest diastereoselectivities were observed with most aldehydes used (Figure 1c).[8] Finally, Kobayashi vinylogous aldol reactions using Evans' chiral auxiliary-based silyl dienyl *N,O*-acetals deliver either *syn*- or *anti*-**II** depending upon the reaction conditions and the starting materials employed.[4b,c] The diastereoselectivity issue still persists with aliphatic aldehydes,[4b] and acetals (or in situ formation of acetals) need to be used for the generation of *syn*-**II** (Figure 1d).[4c]

In this paper, we describe a distinct, general method enabling the enantio- and diastereoselective synthesis of both **I** and **II** without the regioselectivity issue, which takes advantage of underexploited 2-oxonia-Cope rearrangement (2-OCR) reactions[9] between rationally designed homoallylic alcohol synthons **III** and aldehydes (Figure 2). If the 2-OCR reaction follows the Zimmerman−Traxler model employing "closed" six-membered ring transition states,[10] the chirality of **III** is expected to be specifically transferred to that of **VI**: 1′*E*-**III** to *anti*-**VI** and 1′*Z*-**III** to *syn*-**VI** along with the control of the C5 stereochemistry of **VI** by the C3 stereochemistry of **III**. In addition, since the overall transformation of **III** to **VI** is mainly governed by the [3,3]-sigmatropic rearrangement of **IV** to **V**, selective stabilization of **V**

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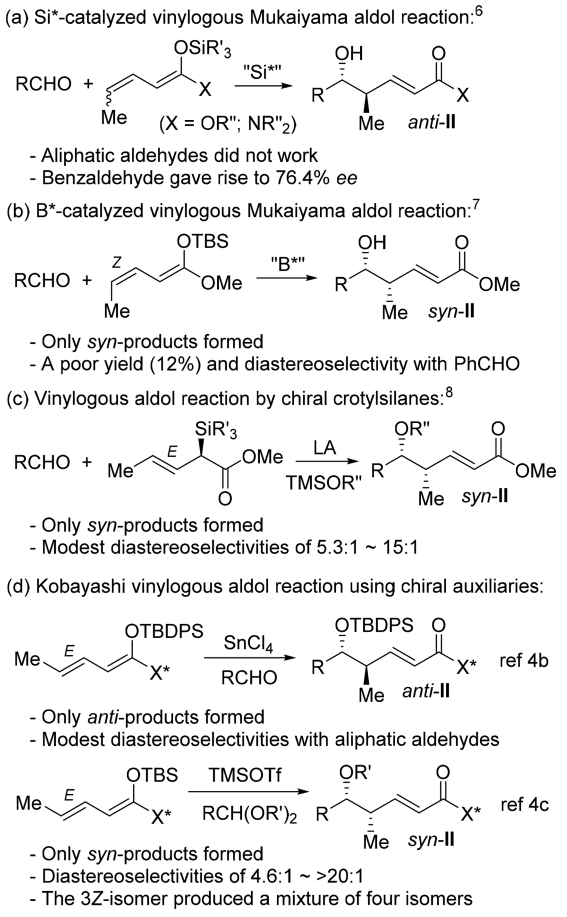


Figure 1. Prior approaches for the asymmetric synthesis of **II** and their drawbacks.

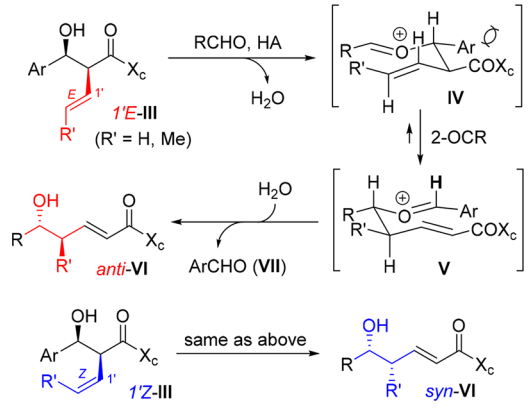
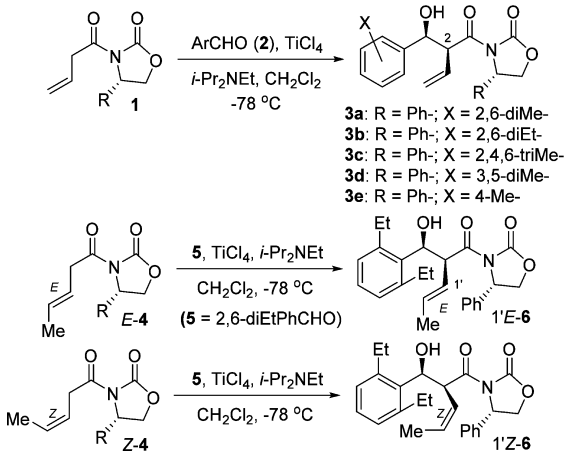


Figure 2. Stereospecific 2-oxonia-Cope rearrangement reaction between the chiral synthons **III** and aldehydes.

over **IV** is necessary to drive the reaction to the product side. We envisioned that such a selective stabilization could be attained by equipping the chiral synthons **III** with an aryl group with strategically positioned substituents to create more favorable electronic and steric environments for the formation of **V**.[9,11]

On the basis of the above reasoning, the chiral synthons **3** and **6** containing a substituted phenyl group were designed, wherein an Evans' chiral auxiliary was also incorporated for their convenient asymmetric synthesis (Scheme 1). The synthons **3** were prepared by the aldol reactions between aromatic aldehydes and the Evans-type imides **1** (Scheme 1).[12] After numerous

Scheme 1. Asymmetric Synthesis of the Synthons 3 and 6



experiments using different Evans' auxiliaries (R= *i*-Pr-, Bn-, Ph-) and B-/Ti-enolates in the deconjugative aldol reactions between **1** and 2,6-dimethylbenzaldehyde, the reaction conditions involving the Ti enolates of **1** derived from 4-phenyloxazolidin-2-one was determined to be optimal in terms of Evans *syn* selectivity and reaction yield. The use of 1.1−1.2 equiv of $TiCl_4$ relative to **1** was also found to be crucial for high stereoselectivities. All other synthons were similarly prepared from either **1** or **4**. In the aldol reactions of **4**, the C3 geometry of **4** was maintained without isomerization and rearrangement. The synthons **3** and **6** are crystalline solids and can be stored at ambient temperatures under air without any precautions.

With the synthons **3a**−**e** in hand, we set out to explore their 2-OCR reactions with benzaldehyde under the reaction conditions involving TfOH in CH_2Cl_2 at −78 °C previously determined for similar 2-OCR reactions.[13] When the synthon **3a** was used, the corresponding 4-hydroxy-2,3-unsaturated imide **7** was obtained in 83% yield (Table 1, entry 1). Lewis acids such as $BF_3{\cdot}OEt_2$, $SiCl_4$, $TiCl_4$, $Sn(OTf)_2$, $Sc(OTf)_3$, and TMSOTf were also screened (entries 2−7),[8] and TMSOTf was determined to be a choice of acids, giving rise to **7** in 93% yield and with 99:1 dr (entry 7). Under the optimal conditions, the synthon **3b** produced as high a reaction yield and dr as did **3a** but resulted in a faster 2-OCR reaction than **3a** (entry 8). The other synthons, **3c**−**e**, were found to be inferior to **3a** and **3b**. During the optimization study, it was found that the "endogenous" aldehydes, which were generated from the synthons used in the 2-OCR reactions, also participated in the reactions to produce byproducts **8** (entries 9−11), and epimerization took place to some extent at the benzylic position in the case of **3c**. These results indicate that **3a** and **3b** are sterically and electronically well-balanced in that their 2,6-dialkyl-substituted phenyl group is a sufficient oxocarbenium stabilizer to facilitate the 2-OCR reaction but not as strong as to cause epimerization at the benzylic position. Furthermore, the steric encumbrance by the 2,6-substituents can not only facilitate the rearrangement, but also prevent the endogenous aldehydes from interfering with the desired 2-OCR reaction. Otherwise mentioned, the synthons derived from 2,6-diethylbenzaldehdye (**3b**, 1′*E*-**6**, and 1′*Z*-**6**) were used in the 2-OCR reactions with aldehydes.

The determined optimal 2-OCR conditions involving **3b** and TMSOTf in CH_2Cl_2 at −78 °C are applied to a diverse array of aldehydes, and the results are displayed in Table 2. Linear and functionalized linear aliphatic aldehydes worked well (entries 1, 6, and 7). *β*-Branched, *α*-branched, and cyclic aliphatic aldehydes

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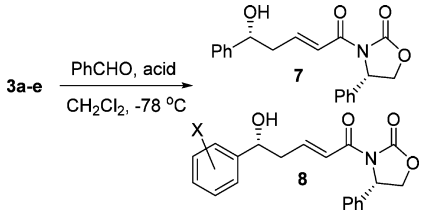
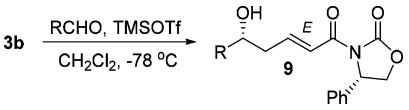
Table 1. Determination of the Optimal Reaction Conditions for the 2-OCR Reaction between 3a and Benzaldehyde[a]

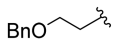


entry	synthon	acid	7/8[c]	yield[d] (%)	dr of 7[e]
1	**3a**	TfOH	>25:1	83	ND[g]
2	**3a**	$BF_3{\cdot}OEt_2$[b]	>25:1	83	ND
3	**3a**	$SiCl_4$	NR[f]	ND	ND
4	**3a**	$TiCl_4$	NR	ND	ND
5	**3a**	$Sn(OTf)_2$	NR	ND	ND
6	**3a**	$Sc(OTf)_3$	NR	ND	ND
7	**3a**	TMSOTf	>25:1	93	99:1
8	**3b**	TMSOTf	>25:1	93	99:1
9	**3c**	TMSOTf	20:1	76	95:5[c]
10	**3d**	TMSOTf	7:3	83	ND
11	**3e**	TMSOTf	6:4	73	ND

[a]**3a–e** (0.15 mmol), benzaldehyde (1.1 equiv), and acid (1.50 equiv) in CH_2Cl_2 (3 mL). [b]2.50 equiv of the acid was used at −50 °C. [c]Determined by ^1H NMR. [d]Combined yields of **7** and **8**. [e]Determined by chiral HPLC. [f]No reaction. [g]Not determined.

Table 2. Asymmetric 2-Oxonia-Cope Rearrangement Reactions between 3b and Aldehydes[a]

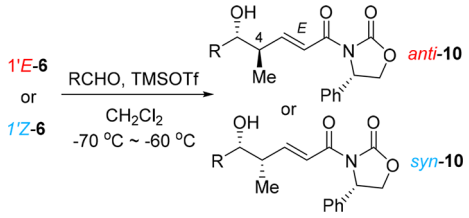


entry	R-CHO	product	yield (%)[b]	dr of **9**[c]
1		**9a**	96	99:1
2		**9b**	97	99:1
3		**9c**	94	98:2
4		**9d**	95[d]	98:2
5		**9e**	95	98:2
6		**9f**	89	98:2
7		**9g**	92	99:1
8		**9h (= 7)**	93	99:1

[a]**3b** (0.15 mmol), aldehyde (2.0 equiv to suppress the competing reaction by 2,6-diethylbenzaldehyde generated), and TMSOTf (1.0 equiv) in CH_2Cl_2 (4 mL). [b]Isolated yields. [c]Determined by chiral HPLC. [d]Yield at 1 mmol scale.

performed as well (entries 2–4). Even sterically hindered pivalaldehyde reacted smoothly. In all cases studied, excellent reaction yields (≥89%) were obtained, and chirality transfer was nearly perfect as evidenced by exceptional dr's (≥98:2) and exclusive *E*-selectivities.

Table 3. Asymmetric *Anti*- and *Syn*-Selective 2-Oxonia-Cope Rearrangement Reactions by 1′*E*-6 and 1′*Z*-6[a]



entry	R-	synthon	product	yield (%)[b]	*anti*/*syn*[c]
1		1′*E*-**6**	*anti*-**10a**	78	>25:1
2		1′*Z*-**6**	*syn*-**10a**	74	1:>25
3		1′*E*-**6**	*anti*-**10b**	75	>25:1
4		1′*Z*-**6**	*syn*-**10b**	72	1:>25
5		1′*E*-**6**	*anti*-**10c**	86	>25:1
6		1′*Z*-**6**	*syn*-**10c**	83	1:>25
7		1′*E*-**6**	*anti*-**10d**	94[e]	>25:1
8		1′*Z*-**6**	*syn*-**10d**	93[e]	1:>25
9[d]		1′*E*-**6**	*anti*-**10e**	50	>25:1
10[d]		1′*Z*-**6**	*syn*-**10e**	45	1:>25
11		1′*E*-**6**	*anti*-**10f**	83	>25:1
12		1′*Z*-**6**	*syn*-**10f**	75	1:>25

[a]**6** (0.15 mmol), aldehyde (2.0 equiv), and TMSOTf (1.5 equiv) in CH_2Cl_2 (4 mL). [b]Isolated yields. [c]Determined by ^1H and ^{13}C NMR. [d]1.5 equiv of TMSOTf at −15 to +4 °C (180 min). [e]Yield at 1 mmol scale.

Table 3 describes the asymmetric *anti*-selective 2-OCR reactions between 1′*E*-**6** and aldehydes. As in the case of **3b** in Table 2, structurally diverse aliphatic and aromatic aldehydes were well accommodated to give good reaction yields and excellent diastereoselectivities (entries 1, 3, 5, 7, 9, and 11). As expected, the 1′*E* geometry and 2,3-*syn* stereochemistry of the synthon 1′*E*-**6** were specifically transferred to the 4,5-*anti* stereochemistry and 2*E* geometry of **10**, respectively.

Table 3 also describes the asymmetric *syn*-selective 2-OCR reactions between 1′*Z*-**6** and aldehydes. Again, the scope of the 2-OCR reaction was quite broad, accommodating diverse structural variations of aliphatic and aromatic aldehydes (entries 2, 4, 6, 8, 10, and 12). In addition to good reaction yields and exclusive *E*-selectivities, excellent 4,5-*syn* selectivities (>25:1) were obtained in all cases studied.

The results in Table 3, taken together with the data in Table 2, convincingly indicate that the 2-OCR reactions of the developed chiral synthons (**3b**, 1′*E*-**6**, and 1′*Z*-**6**) proceed with nearly perfect chirality transfer, permitting total control of enantio- and diastereoselectivity without the regioselectivity issue; this is not possible with all other reported methods. A priori predictability of the reaction stereochemistry is an additional advantage of the 2-OCR reaction.

As synthetic applications and to determine the stereochemistry of **9** and **10**, **9a**, *anti*-**10c**, and *syn*-**10c** were converted to the corresponding δ-lactones through a hydrogenation reaction followed by an acid-catalyzed lactonization reaction in

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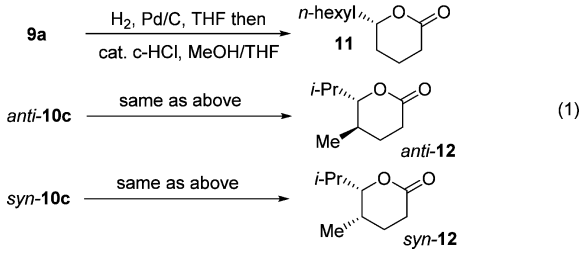
an one-pot operation (eq 1); the analytical data of **11**, *anti*-**12**, and *syn*-**12** were consistent with those of the known compounds.[1h,14] Since δ-lactones are the core structures of, and synthetic precursors for, many natural products,[15] the presented 2-OCR-hydrogenation–lactonization strategy can be of synthetic value.



(1)

In summary, novel chiral synthons enabling at-will control of regio-, enantio-, and diastereoselectivity in the vinylogous aldol reactions of aldehydes have been described. Combined with the versatile synthetic utilities of **I** and **II**, exceptional chirality transfer, operational simplicity, and ready availability 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.7b03895.

Experimental procedures and spectroscopic data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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