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Alkene Metathesis Approach to β-Unsubstituted *Anti*-Allylic Alcohols and Their Use in Ene−Yne Metathesis

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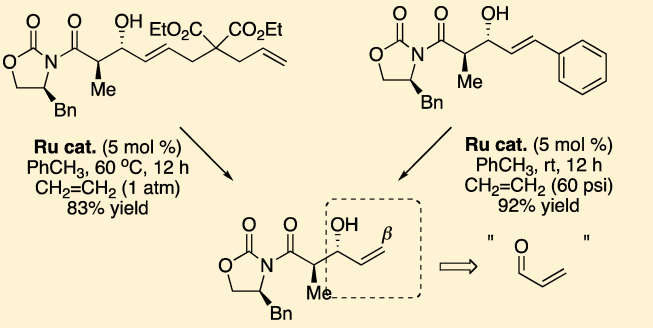
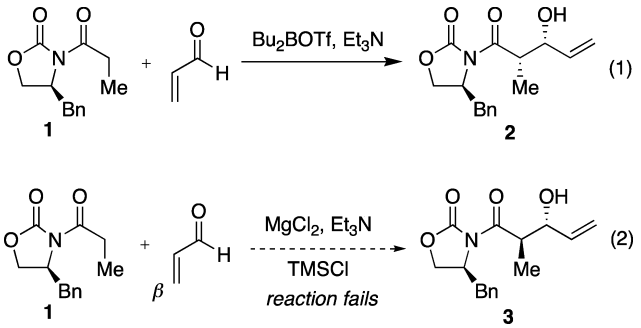
Supporting Information

ABSTRACT: The synthesis of β-unsubstituted, *anti*-allylic alcohols using a catalytic Evans aldol reaction conjoined with a relay-type ring-closing alkene metathesis is reported. The metathesis step serves to remove a β-alkenyl group, which facilitated the aldol step. The β-substituted enals serve as acrolein surrogates. The products were employed in ene−yne cross metathesis.



Asymmetric carbon−carbon bond formations mediated by chiral auxiliaries have made a significant impact in organic synthesis. Evans initially reported the use of *N*-acyloxazolidinones for *syn*-diastereoselective aldol reactions with dialkylboron and chlorotitanium enolates with high yields and diastereoselectivities (eq 1).[1] More recently Evans reported a

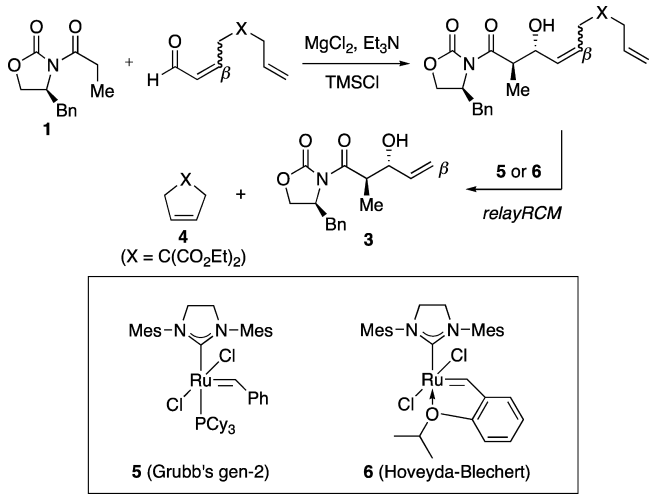


highly diastereoselective *anti*-aldol reaction with chiral acyloxyazolidinones promoted by *catalytic* amounts of $MgCl_2$ in the presence of chlorotrimethylsilane and triethylamine.[2] This simple and practical procedure does not work for acrolein, such that β-unsubstituted *anti* allylic alcohols cannot be accessed by this catalytic aldol procedure. We required access to both *syn* and *anti* aldols obtained by stereoselective aldol reaction to evaluate diastereoselectivity in cross ene−yne metathesis. In this report, we provide a simple method to extend the catalytic Evans enolization conditions to access *anti*-aldols for subsequent use in a metathesis reaction.

We sought a temporary β-substituent in the enal to suppress undesired side reactions in the aldol reaction step. In our hands, the Lewis acidic reaction conditions in eq 2 failed to deliver the desired *anti*-aldol product using acrolein. We envisioned that a β-substituent bearing a pendant terminal olefin could undergo a subsequent ring-closing metathesis (RCM) reaction which would replace CHR with a CH_2 group by extruding a cyclic alkene. Recent work suggests that alkenes bearing allylic chiral centers should be broadly applicable in cross metathesis chemistry.[3]

The approach to β-unsubstituted *anti*-aldols is envisioned in Scheme 1. *Anti*-selective aldol bond construction via generated

Scheme 1. Two-Step, *anti*-Aldol/RCM Approach



magnesium enolate should access the *anti*-aldol product without competing polymerization of the enal reactant. In a

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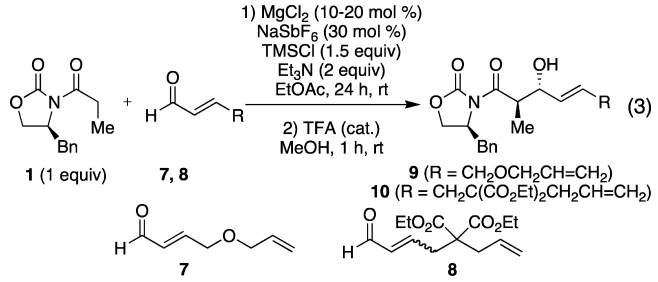
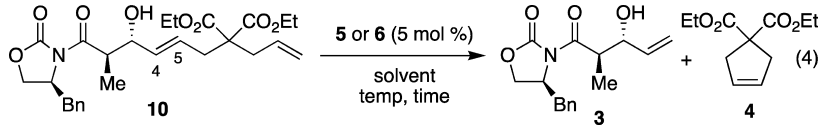
Table 1. Catalytic, Diastereoselective Aldol Reaction with β-Substituted Enals



entry	aldehyde (equiv)	$MgCl_2$ (mol %)	% yield of **9**	% yield of **10**	recovered **1** (%)
1	**7** (1.2)	10	26		54
2	**8** (1.2)	20	27		
3	**8** (1.2)	20		74	
4	**8** (1.3)	20		92[a]	

[a] >20:1 *anti*/*syn* (^{1}H NMR spectroscopy); see text.

Table 2. RCM Removal of β-Substituent



entry	catalyst	ethylene (1 atm)	solvent	T (°C)	time (h)	isolated yield of **3** (%)
1	**5**	Y	DCE	40	12	56
2	**5**	N	DCE	40	12	61
3	**5**	N	DCE	60	12	10
4	**5**	Y	DCE	60	12	7
5	**6**	Y	DCE	40	12	69
6	**6**	Y	DCE	60	12	62
7	**6**	N	DCE	60	12	12
8	**6**	Y	$PhCH_3$	60	12	83
9	**6**	N	$PhCH_3$	60	12	46
10	**6**	Y	$PhCH_3$	60	3	77
11	**6**	Y	$PhCH_3$	60	6	74

second step, addition of Grubbs catalysts (**5** or **6**) would trigger a ring-closing metathesis. This is similar to a relay ring-closing metathesis (rRCM) which was conceived by Hoye[4] specifically to form ruthenium carbenes that are normally hard to make. In the present case, the remote initiation site is used to remove the β-substituent, which would have served its role as a blocking group in the catalytic aldol step. The relay metathesis would free the unsubstituted unsaturated aldol from its β-tether, releasing cycloalkene **4** as a coproduct.

Two readily accessible aldehydes were employed as acrolein surrogates in the diastereoselective *anti*-aldol reaction with oxazolidinone **1** (eq 3). Aldehyde **7** was synthesized by the procedure of Garcia-Gomez and Moreto.[5] The allylic alcohol precursor to **8** was made as described by Doyle et al.[6] followed by a PCC oxidation to access malonate **8**, obtained as a 3:2 mixture of *E*/*Z* isomers. We found that aldehyde **7** did not perform well in the diastereoselective *anti*-aldol reaction using the standard Evans conditions (Table 1).[2] Doubling the concentration of $MgCl_2$ did not lead to improved yields (entry 2). This poor reactivity could be due to a Lewis acid promoted γ-deprotonation/polymerization in the enal prior to aldol reaction or due to debilitating coordination by the alkyl ether. The malonate enal **8** gave improved yields of the *anti*-aldol **10** (entries 3 and 4). The diastereomer ratio of aldol product **10** was determined to be >20:1 *anti*/*syn*.[7] Because of the superior performance of aldehyde **8**, it was used for the remainder of the study.

To obtain the acrolein-derived *anti*-aldol **3**, RCM was performed on **10** using a catalytic amount of Grubbs' catalysts **5** or **6**. Treating **10** with the Grubbs' second-generation catalyst **5** resulted in cleavage of the β-substituent to give 4,4-dicarboethoxycyclopentene (**4**) and alkene **3**. Screening catalyst and reaction conditions led to optimal reaction conditions with yields up to 83% (Table 2). Temperature played a critical role when using the Grubbs catalyst **5**. In contrast to elevated temperatures (entries 3 and 4), lower temperatures gave increased product yields (entries 1 and 2). The presence of ethylene did not seem to benefit reactions catalyzed by Grubbs' catalyst **5**. Using the Hoveyda−Grubbs complex **6** led to an increase in yield (entries 5−11). Increasing the temperature to 60 °C and changing the solvent from 1,2 DCE to toluene improved yield (entry 5 vs 8). At 60 °C, ethylene played a crucial role in achieving higher yields with Hoveyda−Grubbs complex **6** (entry 9 vs 8). Additionally, when Hoveyda−Grubbs complex **6** in toluene was used at 60 °C, increasing the reaction time from 3 h to overnight only had a slight effect on yield (entry 10 vs 8). The byproduct **4** was isolated in entry 10 (using ethylene) in 79% yield. This illustrates that ethylene does not directly cleave the $\Delta^{4,5}$ alkene by ethenolysis (vide infra).[8] The beneficial role of ethylene is most likely due to

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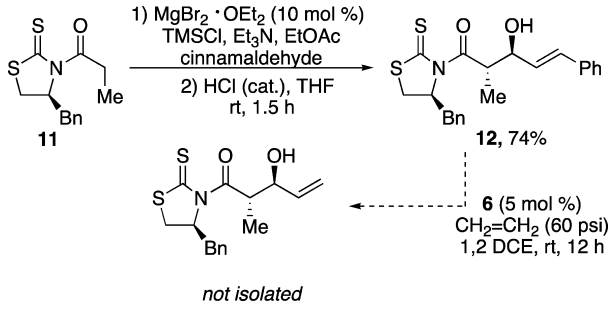
improved efficiency of methylene transfer to the newly formed alkylidene once the cyclopentene group is lost.[9,10]

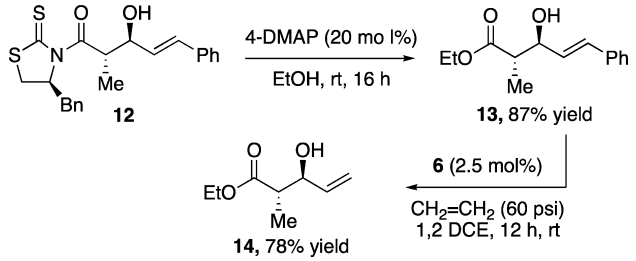
We wondered whether the antipodal stereodyads could be accessed using the aldol reaction between *N*-acyl thiazolidinethiones and β-cinnamaldehyde. The data in Table 2 showed that the linker cleavage benefitted from ethylene; this suggested that a direct cleavage of the linker using ethylene may be possible. This would represent an additional strategy to cleaving a β-blocking group. An earlier application of this concept was demonstrated by Piscopio et al. in a cleavage/release strategy for product removal from solid support.[11] Here, we envisioned using ruthenium carbenes to directly cleave the C=C double bond using ethylene without a ring-closing metathesis (Scheme 2).

Scheme 2. Attempted Route To Obtain Thiazolidinethione-Derived *anti*-Aldol



Though the aldol proceeded uneventfully, attempts to cleave the styrene to an unsubstituted alkene proved fruitless (cat. **6**, ethylene, 60 psi). Presumably, the thione moiety poisons the Grubbs catalyst.[12] Attempts to sequester the thione by use of Lewis acids were unsuccessful.

Scheme 3. Route To Obtain the Thiazolidinethione-Derived *anti*-Aldol

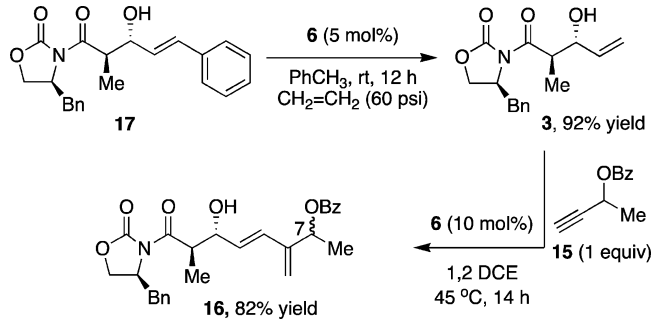


Cleavage of the β-styrenyl group using ethenolysis proved possible if the thiazolidinethione auxiliary was removed prior to ethenolysis.[13] The chiral auxiliary was cleaved to the ethyl ester prior to metathesis using an acyl transfer method introduced by Olivo et al.[14] (Scheme 3). This high yielding sequence provided ethyl ester **13**. To obtain the desired *anti*-aldol product, internal alkene **13** was subjected to Hoveyda–Grubbs catalyst **6** and 60 psi of ethylene over 12 h, giving enantiopure allylic alcohol **14** in 78% isolated yield. Importantly, the enantiopure aldol **14** has the opposite absolute configuration to that of the products obtained in Tables 1 and 2 using the *N*-acyloxazolidinones, illustrating that stereodivergence from *S*-phenylalanine is possible through the aldol/RCM sequence.

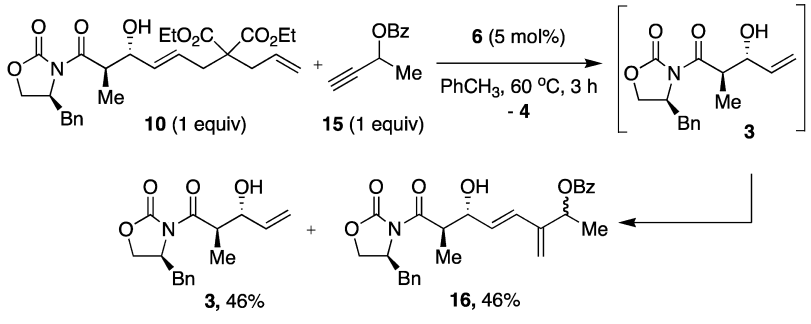
The *anti*-aldols performed well in a "one-pot" β-linker extrusion/cross ene–yne metathesis sequence. In a previous study, we found that *syn*-aldols underwent efficient cross metathesis at nearly equimolar ratio.[3] We predicted that functionalized *anti*-alkene **3** would display different reactivity from that of the *syn*-diastereomer (not shown; see ref 3). To test this hypothesis, a tandem one-pot reaction was developed to remove the β-substituent and subsequently trigger the cross ene–yne metathesis between alkene **3** with alkyne **15** (Scheme 4). To our delight, functionalized diene **16** was obtained in 46% yield, and 46% of the *anti*-alkene was recovered as well.[15] Slow addition of alkyne **15** using 10 mol % of **6** gave a higher chemical yield of **16** (75%) in the one-pot procedure. Both reactions resulted in complete consumption of the alkyne. For the one-pot transformation, alkyne oligomerization appears to be the major competing process.

Higher yielding access to **16** was achieved in a two-step ethenolysis/cross ene–yne metathesis sequence (Scheme 5). The *anti*-aldol product **17** can be synthesized via Evans' procedure[2] in 90% yield. Ethenolysis of **17** followed by removal of ruthenium[16] from the crude product gave **3** in 92% isolated yield. Subsequent ene–yne metathesis cross-coupling[3] of **3** (1.3 equiv) with **15** gave **16** as a mixture of two inseparable C7 diastereomers in 82% yield (Scheme 5).[17] Ethenolysis of **17** under 1 atm of ethylene was not sufficient to give good conversion

Scheme 5. Two-Step Ethenolysis/Cross Ene–Yne Metathesis Sequence



Scheme 4. An Efficient "One-Pot" Cleavage/Cross Ene–Yne Metathesis



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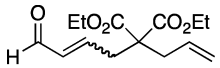
to the desired product **3**. It was found that 60 psi of ethylene was necessary for complete ethenolysis of **17** to give **3**.

In conclusion, two methods have been developed to access *anti*-aldols formally derived from acrolein. The presence of a removable β-substituent in the enal resulted in a high yielding catalytic aldol step. Unmasking of the β-blocking group was accomplished through a ring-closing metathesis triggered by a pendant alkene. Alternatively, with β-styrenyl groups, direct ethenolysis also worked well. Excellent yields were obtained through either method, providing flexibility in the metathesis cleavage step. The β-substituted aldols participate in cross ene−yne metathesis which could be conducted consecutively or in "one pot." The ability to use *anti*-allylic alcohols successfully in cross metathesis provides a catalytic method for cross coupling of alkynes with stereochemically complex (and unprotected) alkenols. Further use of *anti*-stereodyads in synthetic applications is ongoing in our laboratories and will be reported in due course.

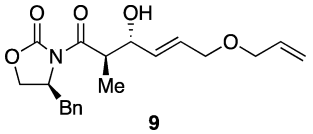
EXPERIMENTAL SECTION

General Information. Unless otherwise stated, reactions were conducted with oven-dried glassware under an atmosphere of argon. Solvents were dried by passage through alumina (dichloromethane) or alumina and Q5 (toluene, benzene) and stored under argon. Dichloroethane was dried over calcium hydride and distilled prior to use. Grubbs' ruthenium carbene complexes **5** and **6** were purchased or obtained from commercial suppliers and used as received (unless otherwise noted). The polar isocyanide KO_2CCH_2NC was prepared and used for quenching metathesis reactions as reported.[16] Ethylene (polymer grade) was used without further purification. Flash column chromatography was carried out on untreated silica gel 60 (230−400 mesh) under air pressure. Thin-layer chromatography was performed on glass-backed silica plates (F254, 250 μm thickness), visualized with UV light or stained with iodine, ceric ammonium molybdate, or $KMnO_4$ stains. ^{1}H NMR spectra were recorded at 400 or 500 MHz, and ^{13}C NMR spectra were recorded at 75 MHz. Optical rotations were measured at the indicated concentration and temperature using the sodium D line.



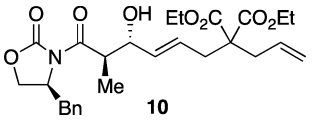
8

*Diethyl 2-Allyl-2-(4-oxobut-2-enyl)malonate (**8**).* The 5,5-bis(carbethoxy)-*cis*-2,7-octadien-1-ol was prepared according to the procedure developed by Doyle et al.[6] The alcohol was subsequently dissolved in 5 mL of dichloromethane (2.0 g, 7.4 mmol) and oxidized via dropwise addition to stirred pyridinium chlorochromate (2.7 g, 12.6 mmol) in 10 mL of dichloromethane at room temperature. The resulting dark orange slurry was stirred for 1 h until thin layer chromatography revealed full conversion to the aldehyde. The crude mixture was plug filtered through Celite/silica gel using 200 mL of diethyl ether as the eluent. The solvent was concentrated in vacuo (rotary evaporator) to obtain analytically pure **8** (3:2 *E*/*Z* mixture) as a colorless oil (1.53 g, 77%). Analytical TLC: R_f 0.16 (5% ethyl acetate in petroleum ether). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 10.05 (d, J = 7.8 Hz, 0.6H), 9.51 (d, J = 7.8 Hz, 0.4H), 6.76 (dt, J = 15.6, 7.3 Hz, 0.4H), 6.53 (dt, J = 11.2, 8.3 Hz, 0.6H), 6.15 (dd, J = 15.6, 7.8 Hz, 0.4H), 6.07−6.03 (m, 0.6H), 5.69−5.61 (m, 1H), 5.18−5.13 (m, 2H), 4.26−4.17 (m, 4H), 3.17 (d, J = 8.1 Hz, 1.2H), 2.88 (d, J = 7.6 Hz, 0.8H), 2.71 (d, J = 7.3 Hz, 1.2H), 2.69 (d, J = 7.3 Hz, 0.8H), 1.27 (t, J = 6.8 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 193.4, 190.5, 170.0, 152.0, 145.6, 135.8, 132.6, 131.5, 120.0, 61.7, 56.9, 37.6, 37.3, 35.9, 30.7, 14.1. FT-IR (thin film, cm^{-1}): 3077, 2983, 2929, 2815, 2746, 1732, 1691, 1446, 1368, 1144, 1042, 927, 858. High-resolution MS (EI$^+$, m/z): molecular ion calcd for $C_{14}H_{20}O_5$ 268.1305, found 268.1308, error 1.0 ppm.



9

*(S)-3-((2R,3R,E)-6-(Allyloxy)-3-hydroxy-2-methylhex-4-enoyl)-4-benzyloxazolidin-2-one (**9**).* Based on the Evans' procedure.[2] Into a dry round-bottom flask were dissolved oxazolidinone **1** (0.462 g, 1.98 mmol), $MgCl_2$ (38 mg, 0.40 mmol), sodium hexafluoroantimonate (0.154 g, 0.59 mmol), triethylamine (0.55 mL, 3.96 mmol), aldehyde **7** (0.300 g, 2.38 mmol), and chlorotrimethylsilane (0.38 mL, 2.97 mmol) in 4 mL of ethyl acetate, and the mixture was stirred at room temperature for 24 h. The cloudy yellow solution was filtered through a plug of silica gel using diethyl ether as the eluent. The solution was concentrated in vacuo (rotary evaporator), and 10 mL of methanol was added along with two drops of trifluoroacetic acid. The solution was stirred at room temperature for 30 min and concentrated in vacuo to give a clear yellow/orange oil. The oil was purified by silica gel flash chromatography using gradient elution (0−30% ethyl acetate in petroleum ether) to provide analytically pure **9** as a colorless oil (182 mg, 26% yield). Analytical TLC: R_f 0.31 (33% ethyl acetate in petroleum ether). $[\alpha]^{22.5}_D$ +21.6 (c = 1.7, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.33 (t, J = 7.3 Hz, 2H), 7.29−7.26 (m, 1H), 7.24 (d, J = 7.8 Hz, 2H), 5.94−5.81 (m, 3H), 5.28 (d, J = 17.6 Hz, 1H), 5.18 (d, J = 10.3 Hz, 1H), 4.72−4.67 (m, 1H), 4.31 (q, J = 6.8 Hz, 1H), 4.22−4.15 (m, 2H), 4.00 (dd, J = 15.1, 4.0 Hz, 5H), 3.30 (dd, J = 13.7, 2.9 Hz, 1H), 2.80−2.74 (m, 2H), 1.21 (d, J = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 176.2, 153.5, 135.2, 134.6, 132.6, 129.5, 129.4, 129.0, 127.3, 117.1, 75.0, 71.2, 69.8, 66.0, 55.5, 43.1, 37.8, 14.5. FT-IR (thin film, cm^{-1}); 3477, 3085, 3027, 2970, 2909, 2852, 1785, 1695, 1454, 1381, 1205, 1111, 760. High-resolution MS (EI$^+$, m/z): molecular ion calcd for $C_{20}H_{25}O_5N$ 359.1727, found 359.1730, error 0.7 ppm.



10

*Diethyl 2-Allyl-2-((4R,5R,E)-6-((S)-4-benzyl-2-oxooxazolidin-3-yl)-4-hydroxy-5-methyl-6-oxohex-2-enyl)malonate (**10**).* Based on the Evans' procedure.[2] Under argon, in a clean and dry round-bottom flask were dissolved oxazolidinone **1** (0.700 g, 3.0 mmol), $MgCl_2$ (38 mg, 0.40 mmol), sodium hexafluoroantimonate (0.233 g, 0.90 mmol), triethylamine (0.84 mL, 6.0 mmol), aldehyde **8** (3:2 *E*/*Z* mixture, 1.02 g, 3.8 mmol), and chlorotrimethylsilane (0.57 mL, 4.5 mmol) in 7 mL of ethyl acetate, and the mixture was stirred at room temperature for 24 h. The yellow and cloudy solution was filtered through a plug of silica gel using diethyl ether as the eluent. The solution was concentrated in vacuo (rotary evaporator), and 15 mL of methanol was added along with 2 drops of trifluoroacetic acid. The solution was stirred at room temperature for 30 min and concentrated in vacuo to give a yellow/orange and clear oil. The oil was purified by silica gel flash chromatography using gradient elution (0−30% ethyl acetate in petroleum ether) to provide analytically pure *E*-**10** as a colorless oil (1.38 g, 92% yield). Diastereomeric excess was determined after the RCM step (below). Analytical TLC: R_f 0.50 (33% ethyl acetate in petroleum ether). $[\alpha]^{22.5}_D$ +16.6 (c = 3.5, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.34 (t, J = 6.8 Hz, 2H), 7.30−7.25 (m, 3H), 5.73−5.62 (m, 3H), 5.18−5.11 (m, 2H), 4.75−4.68 (m, 1H), 4.26−4.18 (m, 7H), 3.94 (quintet, J = 6.8 Hz, 1H), 3.33 (dd, J = 13.7, 3.4 Hz, 1H), 2.80 (dd, J = 13.4, 9.3 Hz, 1H), 2.70−2.64 (m, 4H), 1.26 (t, J = 6.8 Hz, 6H), 1.17 (J = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 176.1, 170.6, 153.5, 134.9, 132.2, 129.5, 128.9, 127.6, 127.3, 119.3, 75.4, 66.1, 61.3, 57.3, 55.5, 43.2, 37.8, 35.2, 14.4, 14.1. FT-IR (thin film, cm^{-1}); 3513, 3386, 3059, 2977, 2924, 2867, 1779, 1726, 1448, 1391, 1293, 1211, 1100, 1027, 970, 920, 732, 700. High-resolution

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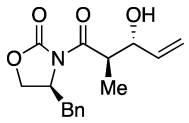
MS (EI$^+$, m/z): molecular ion calcd for $C_{27}H_{35}NO_8$ 501.2381, found 501.2370, error 2.1 ppm.

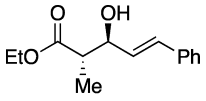


3

*(S)-4-Benzyl-3-((2R,3R)-3-hydroxy-2-methylpent-4-enoyl)-oxazolidin-2-one (**3**).* **Procedure A:** To an oven-dried 50 mL Schlenk tube was added **10** (125.4 mg, 0.25 mmol) followed by the addition of 2.5 mL of toluene. The reaction was purged with one balloon of ethylene, after which the Hoveyda−Blechert second-generation catalyst **6** (7.8 mg, 0.0125 mmol) was added. The reaction was kept under balloon atmosphere of ethylene for 12 h and then quenched with the addition of a methanolic solution of isocyanide KO_2CCH_2NC (8 mg, 0.063 mmol, 1 mL of MeOH). The reaction was concentrated in vacuo (rotary evaporator) and purified using silica gel flash column chromatography using a gradient elution (0−20% ethyl acetate in petroleum ether) to afford **3** as a clear oil which solidified to a white solid upon standing (60 mg, 83% yield).

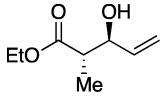
Procedure B. To an oven-dried pressure tube containing 50 mL of freshly distilled DCE was added the internal alkene **17** (366 mg, 1.0 mmol) followed by the addition of Hoveyda−Blechert second-generation catalyst **6** (31.3 mg, 0.05 mmol). The reaction was pressurized to 60 psi and vented (three cycles); after the final series, the reaction was pressurized to 60 psi and maintained at that pressure for the duration of the reaction. After 12 h, the reaction was judged complete by TLC, the pressure tube was vented, and the catalyst was quenched by the addition of a methanolic solution of KO_2CCH_2NC (31 mg, 0.25 mmol, 1 mL of MeOH). The reaction was concentrated in vacuo (rotary evaporator) and purified using silica gel flash column chromatography using a gradient elution (0−20% ethyl acetate in petroleum ether) to afford **3** as a white solid. Mp: 73−75 °C (263 mg, 91% yield). Analytical TLC: R_f 0.56 (33% ethyl acetate in petroleum ether). $[\alpha]^{22.5}_D$ +40.5 (c = 3.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.35 (t, J = 7.3 Hz, 2H), 7.31−7.25 (m, 3H), 5.99−5.93 (m, 1H), 5.37 (d, J = 17.1 Hz, 1H), 5.27 (d, J = 10.7 Hz, 1H), 4.74−4.69 (m, 1H), 4.30, (q, J = 6.8 Hz, 1H), 4.24−4.17 (m, 2H), 4.02 (quintet, J = 6.8 Hz, 1H), 3.31 (dd, J = 13.7, 3.42 Hz, 1H), 2.82−2.76 (m, 2H), 1.25 (d, J = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 176.3, 153.5, 138.4, 135.2, 129.5, 129.0, 127.4, 117.0, 75.8, 66.0, 55.5, 42.8, 37.8, 14.4. FT-IR (thin film, cm^{-1}); 3469, 3027, 2978, 2876, 1793, 1687, 1389, 1262, 1213, 115, 968. High-resolution MS (EI$^+$, m/z): molecular ion calcd for $C_{16}H_{19}O_4N$ 289.1308, found 289.1304, error 1.5 ppm.

Diastereomeric Excess Determination. After ring-closing metathesis cleavage of **10**, the diastereomeric excess of the *anti*-diastereomer **3** was determined by ^{1}H NMR spectroscopy. The diastereomeric excess of **3** (and indirectly of its progenitor **10**) could be determined by direct comparison to the *syn*-diastereomer, which we had previously synthesized.[3] Specifically, the major peak corresponding to the carbinol methine of the *anti*-diastereomer, δ 4.72 ppm was integrated as compared to the analogous proton in the *syn*-diastereomer, appearing at δ 4.57 ppm. The integrated ratio of the major (*anti*) to minor (*syn*) was 26.2:1.00, or >20:1 dr, >86% de. No other diastereomers were detected by ^{1}H NMR spectroscopy.



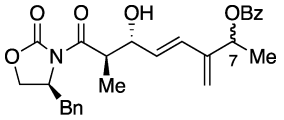
13

*(2S,3S,E)-Ethyl 3-Hydroxy-2-methyl-5-phenylpent-4-enoate (**13**).* The procedure described by Olivo et al.[14] afforded **13** as a clear and colorless oil in 87% yield. $[\alpha]^{22.5}_D$ −11.6 (c = 3.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.32 (d, J = 8.4 Hz, 2H), 7.26 (t, J = 7.6 Hz, 2H), 7.22−7.18 (m, 1H), 6.60 (d, J = 16.0 Hz, 1H), 6.21 (dd, J = 7.2, 16.0 Hz, 1H), 4.36 (quintet, J = 7.2 Hz, 1H), 4.14 (q, J = 7.2, 2H), 3.24 (br s, 1H), 2.63 (t, J = 7.2 Hz, 1H), 1.21 (t, J = 7.2, 3H), 1.17 (d, J = 7.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 175.2, 136.3, 131.8, 129.2, 128.3, 127.6, 126.3, 74.3, 60.5, 45.6, 13.9, 13.7. FT-IR (thin film, cm^{-1}) 3440, 2974, 1720, 1454, 1381, 1258, 1180, 1107, 1037. High-resolution MS (EI$^+$, m/z): molecular ion calcd for $C_{14}H_{18}O_3$ 234.1250, found 234.1239, error 4.2 ppm.



14

*(2S,3S,E)-Ethyl 3-Hydroxy-2-methyl-5-phenylpent-4-enoate (**14**).* Under argon, to an oven-dried pressure tube containing 50 mL of freshly distilled DCE was added internal alkene **13** (900 mg, 3.84 mmol) followed by the addition of Hoveyda−Blechert second-generation catalyst **6** (62.6 mg, 0.1 mmol). The reaction was pressurized to 60 psi and vented three times. After the final venting, the reaction was repressurized to 60 psi ethylene and maintained at that pressure for the duration of the reaction. After 12 h at room temperature, the reaction was judged complete by TLC analysis, and the pressure tube was carefully vented. The catalyst was quenched by the addition of a methanolic solution of KO_2CCH_2NC (62 mg, 0.5 mmol, 2 mL of MeOH) then subsequently concentrated in vacuo (rotary evaporator) and purified by silica gel flash column chromatography using gradient elution (0−20% ethyl acetate in petroleum ether) to afford **14** as a clear oil (474 mg, 78% yield). $[\alpha]^{22.5}_D$ −9.9 (c = 3.5, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 5.84 (m, 1H), 5.29 (d, J = 17.0 Hz, 1H), 5.20 (d, J = 10.5 Hz, 1H), 4.18 (q, J = 7.0 Hz, 2 H), 2.82 (d, J = 5.5 Hz, 1 H), 2.56 (quintet, J = 7.5 Hz, 1 H), 1.27 (t, J = 6.5 Hz, 3 H), 1.19 (d, J = 7.0 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 175.5, 138.1, 116.8, 74.7, 60.6, 45.1, 14.1, 13.9. FT-IR (thin film, cm^{-1}) 3424, 2978, 2929, 2880, 1728, 1462, 1377, 1254, 1197, 1037. High-resolution MS (EI$^+$, m/z): molecular ion calcd for $C_8H_{14}O_3$ 158.0937, found 158.0934, error 2.0 ppm.



16
(mixture of C7 epimers)

*(6R,7R,E)-8-((S)-4-Benzyl-2-oxooxazolidin-3-yl)-6-hydroxy-7-methyl-3-methylene-8-oxooct-4-en-2-yl benzoate (**16**).* Into an oven-dried 25 mL Schlenk tube equipped with a magnetic stir bar and purged with argon were added successively a solution of 35.1 mg of alkyne **15** (0.202 mmol, 1 equiv) dissolved in 1,2-dichloroethane, a solution of 70 mg of alkene **3** (0.242 mmol, 1.2 equiv) dissolved in 1,2 dichloroethane, and 4 mL of additional 1,2 dichloroethane to achieve a concentration of 0.04 M. To the solution was added 12.7 mg of Hoveyda−Blechert second-generation catalyst **6** (0.0202 mmol, 10 mol %). The solution was stirred at 45 °C for 14 h, and the reaction was judged to be complete by TLC analysis at that time. The reaction was quenched by addition of a methanolic solution of KO_2CCH_2NC (0.0606 mmol). The reaction was concentrated under reduced pressure and the crude product was purified by silica gel flash chromatography using gradient elution (0−30% ethyl acetate in petroleum ether). Analytically pure **16** was obtained as a clear oil (75 mg, 82% yield), containing all *E*-isomer and a 1:1 mixture of C7 epimers before and after purification. Analytical TLC: R_f 0.47 (33% ethyl acetate in petroleum ether). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 8.06−8.04 (m, 2H), 7.55 (t, J = 7.3 Hz, 1H), 7.43 (t, J = 7.8 Hz, 2H), 7.33−7.24 (m, 3H), 7.20 (t, J = 7.8 Hz, 2H), 6.34 (d, J = 16.1, 4.4 Hz, 1H), 6.00−5.93 (m, 1H), 5.80 (q, J = 6.4 Hz, 1H), 5.33 (s, 0.5H), 5.31 (s, 0.5H), 5.21 (s, 0.5H), 5.18 (s, 0.5H), 4.69−4.64 (m, 1H), 4.36 (sextet, J = 6.3 Hz, 1H), 4.19−4.16 (m, 2H), 4.13−4.07 (m, 0.5H), 4.01 (quintet, J = 7.3 Hz, 0.5H), 3.30−3.25 (m, 1H), 2.81 (d, J = 7.3 Hz, 0.5H), 2.77 (dd, J = 7.3 Hz, 0.5H), 2.70 (dt, J = 9.8, 13.2 Hz, 1H), 1.53 (d, J = 6.3 Hz, 3H), 1.21−1.19 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 176.1, 165.6, 165.5, 153.5, 153.4, 145.5, 145.4, 135.4, 135.3 132.9, 130.9, 130.6, 130.4, 130.3, 129.5, 129.4, 128.9, 128.8, 128.4, 127.3, 127.2, 115.6, 115.3, 75.5, 75.3, 70.5, 70.3, 66.0, 55.5, 43.2, 42.9, 37.7, 37.6, 20.5, 20.4, 14.5, 14.4. FT-IR (thin film, cm^{-1}): 3481,

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3072, 3027, 2974, 2925, 1781, 1704, 1450, 1389, 1274, 1209, 1111, 715. High-resolution MS (EI$^+$, m/z): molecular ion calcd for $C_{27}H_{29}NO_6$ 463.1989, found 463.1996, error 1.3 ppm.

■ ASSOCIATED CONTENT

Supporting Information

NMR spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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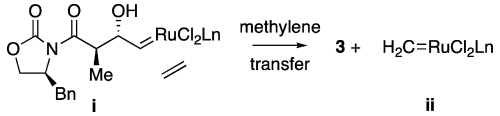
(7) (a) At the aldol stage, the minor diastereomers could not be unambiguously determined. The dr was therefore determined after the RCM step (see the Experimental Section). In this way, the dr was found to be >20:1 *anti*/*syn*. (b) As a comparison, Evans et al. report diastereoselectivities with α- or β-substituted acroleins in the range of 16−21:1 *anti*/(all others combined), see ref 2.

(8) A reviewer suggested that ethylene may directly cleave the $\Delta^{4,5}$ bond to release diethyl diallylmalonate. The RCM of **10** was run to partial conversion, quenched, and analyzed by GC. No diethyl diallylmalonate was found. This supports the conclusion that the relay RCM is initiating from the more reactive terminal alkene.

(9) For instance, ethylene helps speed up the slow step of an ene-yne metathesis catalytic cycle, see: Giessert, A. J.; Brazis, N. J.; Diver, S. T. *Org. Lett.* **2003**, *5*, 3819−3822.

(10) (a) The presence of ethylene is thought to assist catalysis and limit decomposition by speeding up turnover of the alkylidene **i** to product **3**. The methylene **ii** would serve as a chain carrier and can initiate with **10** to trigger ring-closing metathesis.



i **ii**

For decomposition of ruthenium carbenes due to allylic alcohols, see: (b) Hoye, T. R.; Zhao, H. *Org. Lett.* **1999**, *1*, 1123−1125.

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(12) The relay RCM using the thiazolidinethione also failed using the conditions of Table 2, entry 10.

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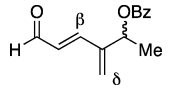
(15) An alternative is to conduct an ene−yne metathesis first and then an Evans catalytic aldol reaction. However, the dienes **iii** cannot be accessed by ene-yne metathesis directly and are expected to be unstable with respect to polymerization under Lewis acid conditions.



iii

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