Tetrahedron 67 (2011) 2197–2205

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Sequencing cross-metathesis and non-metathesis reactions to rapidly access building blocks for synthesis

Gopal Sirasani, Tapas Paul, Rodrigo B. Andrade *

Temple University, Department of Chemistry, Philadelphia, PA 19122, United States

ARTICLE INFO

Article history:
Received 10 December 2010
Received in revised form 25 January 2011
Accepted 26 January 2011
Available online 2 February 2011

Keywords:
One-pot
Tandem
Cross-metathesis
Olefination
2,4-Dienoates
trans Allylic alcohols
Evans aldol
Brown allylboration
Roush crotylboration

ABSTRACT

The olefin cross-metathesis reaction has been sequenced with four common organic transformations in a one- or two-pot manner to rapidly access useful building blocks. Those reactions are: (1) phosphorus-based olefination (e.g., Wittig and Horner–Wadsworth–Emmons); (2) hydride reduction; (3) Evans propionate aldol reaction; (4) Brown allyl- and Roush crotyl-boration. The products of these reactions include stereodefined 2,4-dienoates, *trans* allylic alcohols, *syn*-propionate aldols, and chiral non-racemic homoallylic alcohols, respectively. Many of these intermediates have been carried further to natural products, demonstrating the utility of the methodology.

1. Introduction

Current organic synthesis and synthetic methodology is largely driven by the goals of maximizing the *efficiency* (i.e., atom,[1] step,[2] redox economy[3]) and *selectivity* (e.g., chemo-, regio-, stereo-)[4] by which target molecules are prepared. Syntheses that employ tandem (sequential, ideally one-pot) operations[5] or domino (cascade) reactions[6] are aligned with this goal; herein, we report our studies on the former. Sequential (tandem) one-pot reactions by design streamline linear synthetic processes.[7] In addition, yields can often be increased due to minimization of intermediary purification steps and hence waste streams, which are time-consuming, expensive, and not environmentally friendly. Olefin cross-metathesis (CM)[8] has emerged as a powerful method for the stereoselective preparation of carbon–carbon double bonds in high yield, particularly when coupling terminal and electron-deficient olefins.[9] Terminal olefins are useful chemical handles (e.g., masked aldehydes) that tolerate a broad range of synthetic transformations, making them useful in complex molecule total synthesis. Moreover, there has been an appreciation of the facility by which CM reactions can be sequenced with non-CM reactions.[10] In the presence of commercially available Grubbs second-generation catalyst (Grubbs-II)[11] (**1**) or Hoveyda-Grubbs second-generation catalyst (HG-II) (**2**),[9,12] terminal and electron-deficient olefins (e.g., crotonaldehyde) can be coupled in high yield and with high *E*/*Z* selectivity (>20:1). The reaction is typically clean, producing an (*E*)-2-enal that can be subsequently reacted with various reagents in a one-pot fashion. Herein, we summarize and report the treatment of this intermediary enal with (1) Wittig and Horner–Wadsworth–Emmons reagents; (2) DIBAL-H; (3) *N*-propionyl oxazolidinones developed by Evans;[13] and (4) asymmetric Brown allylboration[14] and Roush crotylboration reagents (Scheme 1).[15]

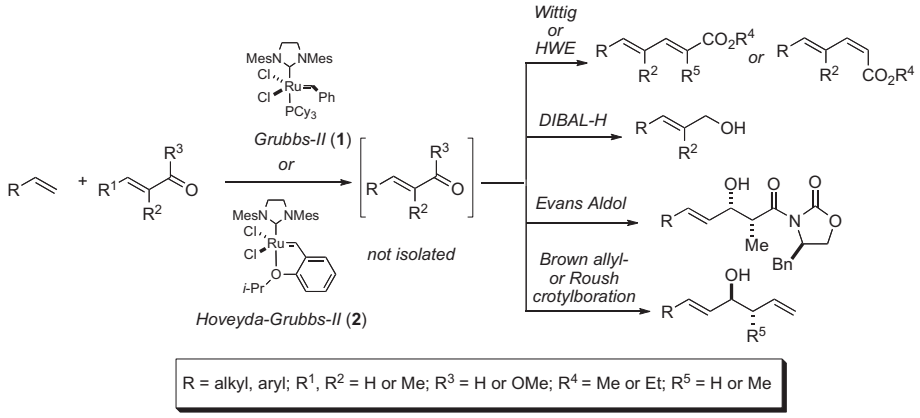
2. Results and discussion

2.1. Sequential CM/phosphorus-based olefination

The synthesis of stereodefined 2,4-dienoates generally involves the iterative olefination of aldehydes using stabilized Wittig[16] or Horner–Wadsworth–Emmons (HWE)[17] reactions, which often require inefficient redox manipulations to access key 2-enal intermediates between couplings. While vinylogous phosphonates[18] and the chemoselective CM reaction between terminal olefins and 2,4-dienoates[19,20] address synthetic inefficiency to a certain extent, these reagents must be prepared in a stepwise manner with intermediary purification. Herein we offer a convenient and efficient

* Corresponding author. Tel.: +1 215 204 7155; fax: +1 215 204 9851; e-mail address: randrade@temple.edu (R.B. Andrade).

0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.01.080



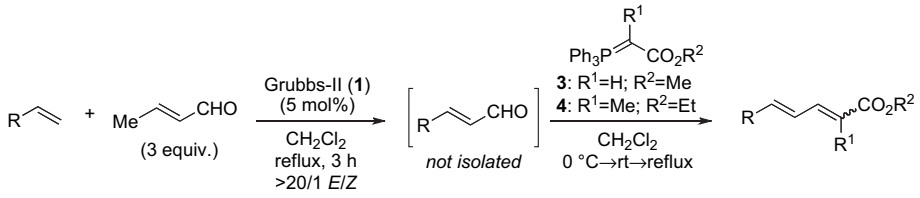
Scheme 1. Overview of sequential CM/non-CM method to access building blocks.

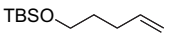
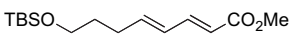
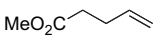
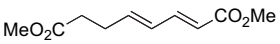
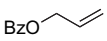
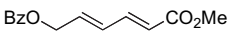
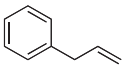
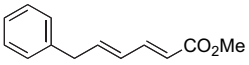
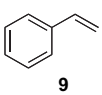
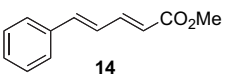
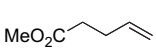
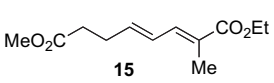
alternative that employs only commercially available reagents for the rapid assembly of either (2*E*,4*E*)- or (2*Z*,4*E*)-dienoates by modifying the second olefination step.

The one-pot CM/Wittig olefination sequence is summarized in Table 1. A variety of terminal olefins were prepared and subjected to 5 mol % Grubbs-II (**1**) and crotonaldehyde in refluxing dichloromethane to effect the first cross-metathesis step. It was determined that refluxing the olefin with an excess (3.0 equiv) of crotonaldehyde for 3 h was the optimal protocol.

The reaction mixture was then cooled to 0 °C, treated with a slight excess of phosphorane **3** and subsequently warmed to rt. While screening conditions for the second step, we discovered that equimolar phosphorane (3.0 equiv) did not result in higher product yields and that 1.2 equiv of either **3** or **4** would suffice. Our hypothesis that excess crotonaldehyde had decomposed over the course of the reaction was supported by the fact that very little methyl sorbate (the byproduct of the Wittig reaction and crotonaldehyde) was isolated from the reaction mixture when 3 equiv of **3** were employed. Yields as high as 77% (entry 1) were realized with this procedure, corresponding to an average of 88% per step. Upon adding phosphorane **3**, the solution was warmed to rt and stirred overnight (12 h). Entry 6 required reflux due to the hindered nature of phosphorane **4**.

Table 1
One-pot CM/Wittig olefination for the stereoselective synthesis of (2*E*,4*E*)-dienoates



Entry	Olefin	Phosphorane	Product	Yield[a,b] (ratio: 2*E*/2*Z*)[c]
1	 **5**	**3**	 **10**	77% (9:1)
2	 **6**	**3**	 **11**	57% (9:1)
3	 **7**	**3**	 **12**	60% (8:1)
4	 **8**	**3**	 **13**	73% (9:1)
5	 **9**	**3**	 **14**	48% (11:1)
6	 **6**	**4**	 **15**	50% (5:1)

[a] Yields refer to the average of two runs.
[b] Isolated yield of separable *E*/*Z* mixture.
[c] Ratio determined by ^{1}H NMR.

All reactions delivered good yields of dienoates **10**–**15** with entry 6 affording a trisubstituted (2*E*,4*E*)-dienoate. The *E*/*Z* geometric isomers were separable by chromatography. While it is known that stabilized phosphoranes are stereoselective for the *E* isomer in the Wittig reaction, we turned our attention to the Horner–Wadsworth–Emmons (HWE) reaction in order to (1) increase the stereoselectivity of the olefination step and (2) access the *Z*-enoate by recruiting the Still–Gennari[21] phosphonate **18** (vide infra). Toward this end, we repeated the CM sequence with the olefin substrates albeit in two pots as HWE reactions are performed in ethereal solvents (e.g., THF or diglyme). The results are summarized in Table 2.

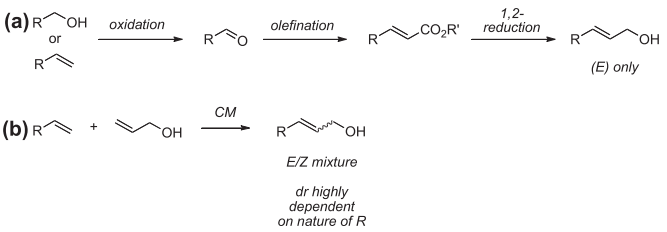
Operationally, the reaction mixtures were concentrated following the CM step and added to phosphonate anions corresponding to **16**–**18** at −78 °C. We were again pleased that yields ranged from 55% (entry 3) to 83% (entry 1), showing the synthetic viability of this tandem sequence. The Still–Gennari olefination with phosphonate **18** delivered (2*Z*,2*E*)-dienoate **21** in 63% yield with a good *Z*/*E* ratio (6.5:1).

In order to expand the scope of this methodology, we wanted to study what other α,β-unsaturated aldehydes could be used in the sequence. While (*E*)-2-methyl-2-butenal failed to react after 12 h under reflux, recourse to methacrolein (3 equiv) resulted in a favorable reaction (entry 2). Olefination with trimethyl phosphonoacetate (**16**) yielded 81% of dienoate **20** with excellent 2*E*,2*Z* selectivity (20:1). Finally, tandem CM/HWE with phosphonopropionate **17** afforded dienedioate **15** in 69% with good 2*E*,2*Z* selectivity (5:1), which was also prepared via one-pot CM/Wittig (see Table 1, entry 6) albeit in lower yield (50%).

2.2. Sequential CM/hydride reduction

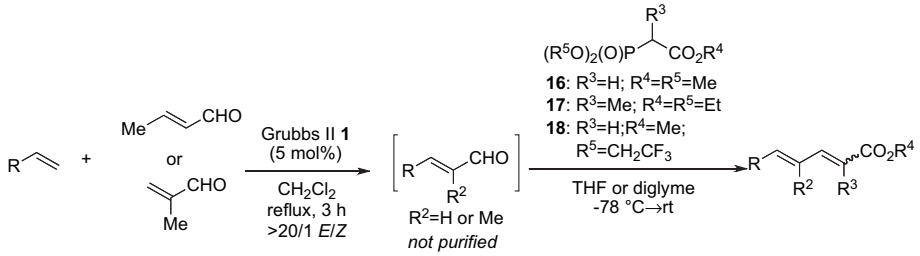
Primary (*E*)-allylic alcohols are excellent substrates for a variety of transformations, such as the Sharpless asymmetric epoxidation reaction,[22] which has been heavily utilized in the iterative synthesis of polyketide natural products.[23,24] These substrates are typically prepared in the three-step sequence due to the need for redox manipulation: (1) oxidation of a primary alcohol or terminal olefin to the aldehyde; (2) olefination of the resulting aldehyde with a phosphorus-based reagent (e.g., phosphorane, phosphonate); and (3) 1,2-reduction of the enoate to the primary (*E*)-allylic alcohol (Scheme 2a). A shorter alternative route features a CM between a terminal olefin and allyl alcohol (Scheme 2b). While this short route is attractive, the stereoselectivity of the transformation is highly dependent on the nature of 'R' such that an increase in steric bulk favors the (*E*) geometric isomer.[25,26]

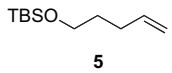
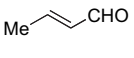
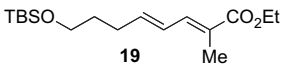
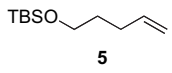
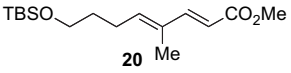
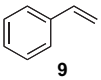
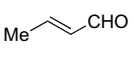
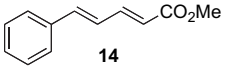
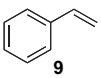
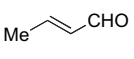
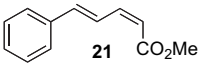
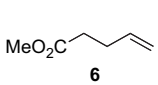
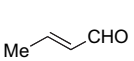
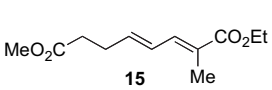
By sequencing (1) the highly (*E*)-selective CM reaction of an electron-rich terminal olefin and an electron-poor olefin



Scheme 2. Routes to primary (*E*)-allylic alcohols: (a) traditional; (b) CM.

Table 2
Tandem CM/HWE olefination for the stereoselective synthesis of (2*E*,4*E*)- or (2*Z*,4*E*)-dienoates



Entry	Olefin	Aldehyde (3 equiv)	Phosphonate	Product	Yield[a,b] (ratio: 2*E*/2*Z*)[c]
1	 **5**		**17**	 **19**	83% (20:1)
2	 **5**		**16**	 **20**	81% (20:1)
3	 **9**		**16**	 **14**	55% (18:1)
4	 **9**		**18**	 **21**	63% (1:6.5)
5	 **6**		**17**	 **15**	69% (5:1)

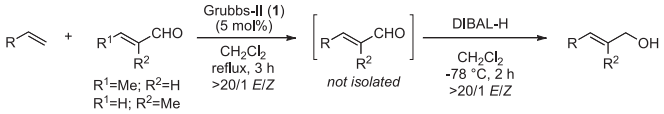
[a] Yields refer to the average of two runs.
[b] Isolated yield of separable *E*/*Z* mixture.
[c] Ratio determined by ^{1}H NMR.

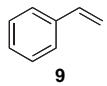
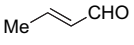
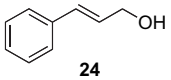
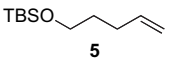
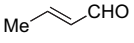
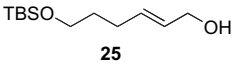
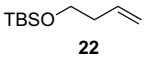
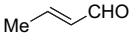
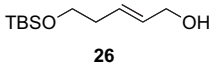
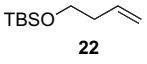
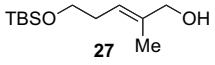
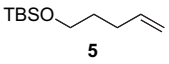
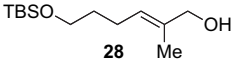
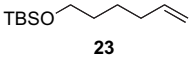
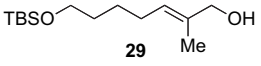
(i.e., acrolein, acrylate, etc.)[26] with (2) a hydride reduction step, the stereochemical fidelity of the product is preserved. Table 3 shows a variety of terminal olefins that were subjected to this one-pot method. Styrene (**9**) and a series of TBS-protected α,ω-alkenols were treated with 3 equiv of either crotonaldehyde or methacrolein and 5 mol % Grubbs-II (**1**) in refluxing CH_2Cl_2 for 3 h to afford intermediary α,β-enals in high yield and high dr (>20:1 *E*/*Z* by ^{1}H NMR).[27] As these reactions proceed cleanly and in high yield (a priori requirements for efficient one-pot procedures), the reaction mixtures were subsequently cooled to −78 °C and treated with excess DIBAL-H (commercially available solution in hexanes), affording exclusively primary (*E*)-allylic alcohols **24**–**29** in synthetically useful yields (59–74%). The temperature regime was necessary to avoid undesired 1,4-reduction. The substitution of the double bond is controlled by choice of either crotonaldehyde or methacrolein.

2.3. Sequential CM/Evans aldol reactions

The Evans aldol reaction is arguably the most powerful and versatile means of preparing propionate aldol subunits in a stoichiometric asymmetric manner.[13] The levels of diastereoselectivity enjoyed by the robust *N*-acyl oxazolidinones (in both single and double asymmetric synthesis) and facile nature of their manipulation have made the Evans aldol methodology popular in the synthesis of complex natural products, particularly polyketides.[13] As the products of CM reactions of terminal olefins and for 2 h. Of note are chemoselective CM entries 3 and 6, which afford alcohols **38** and **41** due to the bulky TBS protecting group that sterically shields the allylic site.[30] Synthetically useful yields (54–74%) were obtained for both allylated (entries 1–3) and crotylated (entries 4–6) substrates.

Table 3
One-pot sequential CM/hydride reduction method for the stereoselective synthesis of primary (*E*)-allylic alcohols with the Grubbs-II catalyst (**1**)



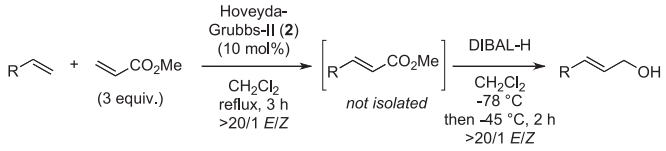
Entry	Olefin	Coupling partner (3 equiv)	Product	Yield[a] dr > 20:1 (*E*/*Z*)[b]
1	 **9**		 **24**	70%
2	 **5**		 **25**	74%
3	 **22**		 **26**	72%
4	 **22**		 **27**	56%
5	 **5**		 **28**	69%
6	 **23**		 **29**	59%

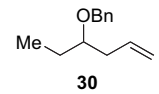
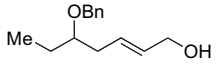
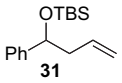
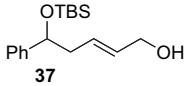
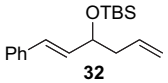
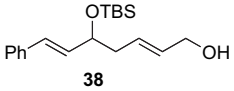
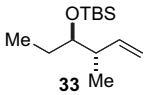
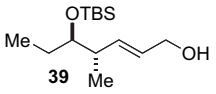
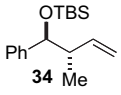
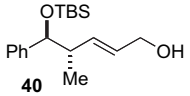
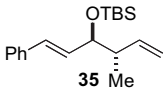
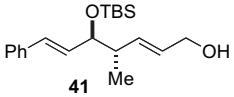
[a] Yields refer to the average of two runs.
[b] Ratio determined by ^{1}H NMR.

With these results in hand, we turned our attention to more synthetically useful terminal olefins **30**–**35** (Table 4). The allylation and crotylation reaction of aldehydes represents formidable alternatives to the acetate and propionate aldol reactions, respectively. These methodologies have been leveraged in the stereoselective total synthesis of natural products, particularly those of polyketide origin.[28] As the products of these reactions are terminal olefins, they represent excellent substrates for our methodology. Toward this goal, a variety of protected homoallylic alcohols **30**–**32** were prepared by the addition of allylmagnesium bromide to the corresponding aldehyde, whereas **33**–**35** were prepared in an asymmetric manner by the addition of Roush's tartrate-functionalized (*E*)-crotylboronate to the corresponding aldehyde.[15] For these substrates, we found that the combination of 10 mol % Hoveyda-Grubbs-II (**2**) catalyst and 3 equiv of methyl acrylate as coupling partner gave the best results.[29] Following the addition of DIBAL-H at −78 °C, the reaction mixture was warmed to −45 °C and stirred crotonaldehyde (or methacrolein) led to (*E*)-2-enals, which are substrates for the Evans aldol reaction, we investigated sequencing our method with the Evans propionate aldol reaction to rapidly access building blocks. To substantiate the utility in synthesis, we deliberately chose substrates that had been previously prepared in a stepwise manner and subsequently employed in total synthesis.

Table 5 shows four examples. Styrene (**9**) and a series of protected allyl ethers were treated with 3 equiv of crotonaldehyde and 5 mol % Hoveyda-Grubbs II (**2**) in refluxing CH_2Cl_2 for 12 h to afford intermediary α,β-enals in high yield and high dr (>20:1 *E*/*Z* by ^{1}H NMR).[31] In a separate reaction vessel, Evans propionimide **42** (or *ent*-**42** for entry 3) was enolized under standard reaction conditions (Bu_2BOTf, Et_3N or *i*-Pr_2NEt, CH_2Cl_2 at −78 °C). To this was added a solution of enal derived from the CM reaction, and the corresponding aldol products **46**–**49** were isolated in good yields (48–64%) with excellent diastereoselectivities (dr>20:1).[32]

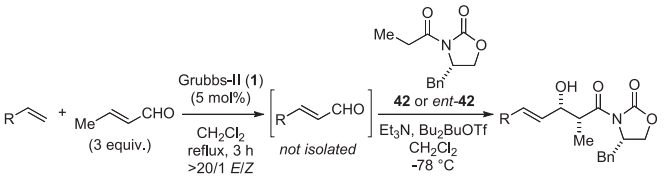
Table 4
One-pot sequential CM/hydride reduction method for the stereoselective synthesis of primary (*E*)-allylic alcohols with the Hoveyda-Grubbs-II catalyst (**2**)

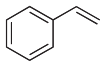
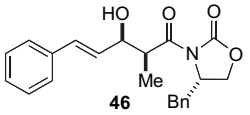
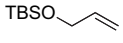
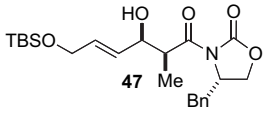
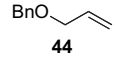
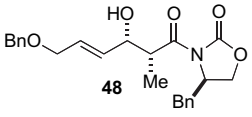
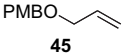
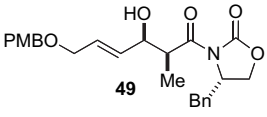


Entry	Olefin	Product	Yield[a] dr > 20:1 (*E*/*Z*)[b]
1	 **30**	 **36**	59%
2	 **31**	 **37**	56%
3	 **32**	 **38**	54%
4	 **33**	 **39**	64%
5	 **34**	 **40**	57%
6	 **35**	 **41**	74%

[a] Yields refer to the average of two runs.
[b] Ratio determined by ^{1}H NMR.

Table 5
Sequential CM/Evans aldol reaction for the asymmetric synthesis of unsaturated propionate aldols with 5 mol % Grubbs-II catalyst (**1**)



Entry	Olefin	Evans reagent	Product	Yield (dr > 20:1)[a,b]
1	 **9**	**42**	 **46**	60%
2	 **43**	**42**	 **47**	48%
3	 **44**	*ent*-**42**	 **48**	52%
4	 **45**	**42**	 **49**	64%

[a] Yields refer to the average of two runs.
[b] Aldol diastereoselectivity ratio (dr) determined by ^{1}H NMR.

2.4. Sequential CM/Roush allyl- and crotyl-boration reactions

The allyl- and crotyl-metalation of aldehydes represents powerful surrogates for the acetate and propionate aldol reactions, respectively.[33] Thus, they have found widespread use in the total synthesis of polyketides.[34] Brown and Roush have both developed some of most utilized stoichiometric allyl- and crotyl-boration methodologies.[15] As we had shown the utility of sequencing CM with the Evans aldol reaction (vide supra), we opted to employ Brown's Ipc-controlled allylboration and Roush's tartrate-derived crotylborates. Table 6 shows six examples of those products, which are known intermediates previously employed in natural product total syntheses.[35] Styrene (**9**) and a series of olefins (**53**–**55**) were subjected to the standard CM sequence. Following concentration and solvent exchange, the solution of enal was transferred to another reaction vessel containing Brown's allylborane **50** or Roush's (*E*)-crotylboronate **51** at −78 °C to afford allylated enantioenriched homoallylic alcohols **56**–**61** in high yields (71–82%) and good selectivities (67–88% ee).

3. Conclusion

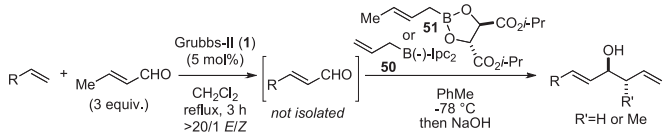
In conclusion, we have demonstrated the utility of sequencing olefin cross-metathesis with various non-metathesis reactions. The scope of this method now includes the Wittig and Horner–Wadsworth–Emmons olefination reactions to access stereodefined dienoates, hydride-mediated reduction to furnish *trans* allylic alcohols, the Evans aldol reaction to prepare diastereomerically pure *syn*-propionate aldols, and finally the Brown allyl- and Roush crotylboration reactions to furnish enantioenriched homoallylic alcohols. Most of the products of these reactions have been employed in total synthesis, thus validating the utility of this method in telescoping linear total synthesis and enabling greener, more efficient routes to complex targets (i.e., natural products).

4. Experimental section

4.1. General

All reactions containing moisture or air sensitive reagents were performed in oven-dried glassware under nitrogen or Argon. Diethyl ether, tetrahydrofuran, toluene, and dichloromethane were passed through two columns of neutral alumina. Diglyme, *i*-Pr_2NEt, and Et_3N were distilled from CaH_2 prior to use. Molecular sieves (4 Å) were activated by flame drying under vacuum prior to use. Crotonaldehyde and methacrolein were freshly distilled prior to use. Evans propionimides (**42**, *ent*-**42**) and Brown allylborane **50** and Roush crotylboronates **51** were prepared according to literature procedures, respectively.[13,15] All other reagents were purchased from commercial sources and used without further purification. All solvents for work-up procedures were used as received. Flash column chromatography was performed according to the procedure of Still[36] using ICN Silitech 32-63 D 60 Å silica gel with the indicated solvents. For all reactions involving cross-metathesis, CH_2Cl_2 was deaerated by bubbling Argon through the solution (1 min/mL). Enantiomeric excess (% ee) for Brown allylation and Roush crotylboration reactions was determined by the Mosher method.[37] Thin layer chromatography was performed on Analtech 60 F_{254}

Table 6
Sequential CM/Brown allyl- or Roush (*E*)-crotylation reactions for the asymmetric synthesis of homoallylic alcohols with 5 mol % Grubbs-II catalyst (**1**)



Entry	Olefin	Reagent	Product	Yield[a,b]
1	**9**	**50**	**56**	74% (83% ee)
2	**53**	**50**	**57**	75% (88% ee)
3	**54**	**50**	**58**	72% (82% ee)
4	**55**	**50**	**59**	71% (83% ee)
5	**9**	**51**	**60**	80% (dr > 20:1) (67% ee)
6	**53**	**51**	**61**	82% (dr > 20:1) (86% ee)

[a] Enantiomeric excess (% ee) determined by Mosher ester analysis.
[b] Crotylation *anti*/*syn* ratio (dr) determined by ^{1}H NMR.

silica gel plates. Detection was performed using UV light, $KMnO_4$ stain, PMA stain, and subsequent heating. ^{1}H and ^{13}C NMR spectra were recorded at the indicated field strength in $CDCl_3$ at rt. Chemical shifts are indicated in parts per million (ppm) downfield from tetramethylsilane (TMS, δ=0.00) and referenced to the $CDCl_3$. Splitting patterns are abbreviated as follows: s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet).

Spectral data (^{1}H and ^{13}C NMR) for the following known reaction products were consistent with literature values: Compound **9**: Spino, C.; Rezaei, H.; Dupont-Gaudet, K.; Belanger, F. *J. Am. Chem. Soc.* **2004**, *126*, 9926. Compound **10**: Xuan, J.X.; Fry, A.J. *Tetrahedron Lett.* **2001**, *42*, 3275. Compound **11**: Montserrat, C.; de March, P.; Figueredo, M.; Font, J.; Soria, A. *Tetrahedron* **1997**, *53*, 16,803. Compound **12**: Horsham, M.A.; Class, T.J.; Johnston, J.J.; Casida, J.E.J. *Agric. Food Chem.* **1989**, *37*, 777. Compound **25**: Takano, S.; Sekiguchi, Y.; Shimazaki, Y.; Ogasawara, K. *Heterocycles* **1992**, *33*, 713. Compound **16**: Yadav, J.S.; Rao, E. Sreenivasa. *Synth. Commun.* **1988**, *18*, 2315. Compound **17**: Hiebel, M.-A.; Pelotier, B.; Piva, O. *Tetrahedron* **2007**, *63*, 7874. Compound **19**: Masamune, S.; Kaiho, T.; Garvey, D.S. *J. Am. Chem. Soc.* **1982**, *104*, 5521. Compound **13**: Kim, D.D.; Lee, S.J.; Beak, P. *J. Org. Chem.*, **2005**, *70*, 5376. Compound **13**: Murelli, R.P.; Snapper, M.L. *Org. Lett.* **2007**, *9*, 1749. Compound **20**: Touchard, F.P. *Tetrahedron Lett.* **2004**, *45*, 5519. Compound **10**: Pospisil, J.; Marko, I.E. *Org. Lett.* **2006**, *8*, 5983. Compound **11**: Nicolaou, K.C.; Prasad, C.V.C.; Somers, P.K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5330. Compound **12**: Francesca, A.; Federico, C.; Paolo, C.; Cristina, G.; Granco, M.; Mauro, P. *Tetrahedron* **1995**, *51*, 10,601. Compound **13**: Wang, J.; Hsung, R.P.; Ghosh, S.K. *Org. Lett.* **2004**, *6*, 1939. Compound **14**: Nicolaou, K.C.; Prasad, C.V.C.; Hwang, C.-K.; Duggan, M.E.; Veale, C.A. *J. Am. Chem. Soc.* **1989**, *111*, 5321. Compound **15**: Hayashi, Y.; Kanayama, J.; Yamaguchi, J.; Shoji, M. *J. Org. Chem.* **2002**, *67*, 9443. Compound **46**: Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1998**, *110*, 2506. Compound **47**: Vanderwal, C. D.; Vosberg, D. A.; Sorensen, E. J. *Org. Lett.* **2001**, *3*, 4307. Compound **48**: Anderson, J. C.; McDermott, B. P.; Griffin, E. J. *Tetrahedron* **2000**, *56*, 8747. Compound **49**: Garcia-Fortanet, J.; Murga, J.; Carda, M.; Alberto Marco, J.; Matesanz, R.; Fernando Diaz, J.; Barasoain, I. *Chem. Eur. J.* **2007**, *13*, 5060. Compounds **56**, **58**, **59**: Fatima, A.D.; Kohn, L.K.; Carvalho, J.E.; Pilli, R.A.; *Bioorg. Med. Chem.* **2006**, *14*, 622. Compound **57**: Roush, W.R.; Hoong, L.K.; Palmer, M.A.J.; Park, J.C.; *J. Org. Chem.* **1990**, *55*, 4109.

Compounds **60**, **61**: Roush, W.R.; Ando, K.; Powers, D.B.; Palkowitz, A.D.; Halterman, R.L. *J. Am. Chem. Soc.*, **1990**, *112*, 6339.

4.2. General procedure for sequential one-pot CM/Wittig reactions (Table 1)

Crotonaldehyde (101 mg, 1.45 mmol) dissolved in deaerated CH_2Cl_2 (2.2 mL) was added to a solution of olefin (0.48 mmol) in deaerated CH_2Cl_2 (1.0 mL). Grubbs' second-generation catalyst **1** (20 mg, 5 mol %) was added, and the reaction mixture was heated to 40 °C under an Ar atmosphere for 3 h. The reaction mixture was cooled to 0 °C, and phosphorane **2** (194 mg, 0.58 mmol) was added. The reaction was stirred at rt for 15 h (for entries **2** and **6**, reaction was refluxed for 1 h), concentrated under reduced pressure, and purified by flash column chromatography eluting with 2–10% ethyl acetate/hexanes.

4.3. General procedure for sequential one-pot CM/HWE reactions (Table 2—entries 1, 2, and 5)

Sodium hydride (28 mg, 0.69 mmol) was added to a solution of phosphonate (0.69 mmol) in THF or diglyme (5.0 mL) at 0 °C. The reaction mixture was stirred for 30 min. The crude enal (0.48 mmol) derived from the cross-metathesis step (see above Experimental) was dissolved in THF or diglyme (3.0 mL) and added to the phosphonate solution. The reaction mixture was warmed to rt and stirred for 15 h. Diethyl ether (10 mL) was added, and the reaction was quenched with saturated aq NH_4Cl (5 mL). The aqueous phase was extracted with diethyl ether (2×20 mL). The combined organic layers were washed with water (2×10 mL), brine (2×10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with 2–10% EtOAc/hexanes.

4.4. General procedure for sequential one-pot CM/HWE reactions (Table 2—entries 3 and 4)

KHMDS (1.06 mL, 0.5 M in toluene, 0.53 mmol) was added to a solution of phosphonate (0.53 mmol) in THF (5.0 mL) at −78 °C. The reaction mixture was stirred for 30 min. The crude enal (0.48 mmol) derived from the cross-metathesis step (see above Experimental) was dissolved in THF (3.0 mL) and added to the phosphonate solution. The reaction mixture was stirred at −78 °C for 4 h. Et_2O (10 mL) was added, and the reaction was quenched with saturated aq NH_4Cl (5 mL). The aqueous phase was extracted with diethyl ether (2×20 mL). The combined organic layers were washed with water (2×10 mL), brine (2×10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with 2–10% ethyl acetate/hexanes.

4.5. General procedure for sequential one-pot CM/hydride reduction reactions (Tables 3 and 4)

To a solution of olefin (0.48 mmol) and α,β-unsaturated carbonyl partner (1.45 mmol) in deaerated CH_2Cl_2 (3.0 mL) was added catalyst **1** or **2** (5–10 mol %). The reaction mixture was heated to 40 °C under an Ar atmosphere and stirred for 3 h. The reaction mixture was cooled to −78 °C, and DIBAL-H (1 M in hexanes, 1.8 mL, 1.80 mmol) was added dropwise. The reaction mixture was stirred at −78 °C for 2 h and quenched by the slow addition of MeOH (1.8 mL) followed by a saturated solution of Rochelle's salt (1.8 mL). The reaction mixture was warmed to rt and filtered through a cotton plug. The residue was washed thoroughly with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with brine (2×10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with 20% EtOAc/hexanes.

4.6. Experimental procedures for sequential CM/Evans aldol reactions (Table 5)

*4.6.1. Aldol **46**.* Hoveyda-Grubbs II (**2**) (15 mg, 0.024 mmol) was added to a mixture of styrene (**9**) (50 mg, 0.480 mmol) and crotonaldehyde (67 mg, 0.96 mmol) in deaerated CH_2Cl_2 (3.2 mL). The reaction mixture was heated to 40 °C under an Ar atmosphere for 12 h and cooled to rt. The solvent was concentrated under reduced pressure and the residue was dried for 10 min. To propionimide **42** (112 mg, 0.481 mmol) in CH_2Cl_2 (2 mL) was added a 1.0 M solution of Bu_2BOTf (0.53 mL, 0.53 mmol) at 0 °C over 5 min followed by Et_3N (68 mg, 0.674 mmol) and stirred for 30 min. After cooling the reaction mixture to −78 °C, the metathesis product from the previous step in CH_2Cl_2 (2 mL) was added dropwise. The reaction mixture was stirred for 1 h, warmed to 0 °C, and stirred an additional hour. The reaction was quenched by dropwise addition of pH 7 phosphate buffer/MeOH (1 mL:1.5 mL) and MeOH/30% aq H_2O_2 (1 mL:0.5 mL). The reaction mixture was stirred for additional hour at 10 °C, extracted with CH_2Cl_2 (3×10 mL), washed with $NaHCO_3$ (10 mL), brine (10 mL), and dried over Na_2SO_4. The residue was purified by flash column chromatography eluting with EtOAc/hexanes (3:7) to give 105 mg (60%) of **46** as a colorless liquid. NMR spectra (^1H and ^{13}C) were identical with reported literature values.

*4.6.2. Aldol **47**.* Hoveyda-Grubbs II (**2**) (9 mg, 0.0145 mmol) was added to a mixture of TBS ether **43** (50 mg, 0.29 mmol) and crotonaldehyde (41 mg, 0.96 mmol) in deaerated CH_2Cl_2 (2 mL). The reaction mixture was heated to 40 °C under an Ar atmosphere for 12 h and cooled to rt. The solvent was concentrated under reduced pressure, and the residue was dried for 10 min under vacuum. To a solution of propionimide **42** (68 mg, 0.29 mmol) in CH_2Cl_2 (3 mL) was added a 1.0 M solution of Bu_2BOTf (0.34 mL, 0.34 mmol) at 0 °C over 5 min followed by freshly distilled *i*-Pr_2NEt (50 mg, 0.383 mmol) over 5 min and the reaction mixture was cooled to −78 °C. The above metathesis product dissolved in CH_2Cl_2 (2 mL) was added to the reaction mixture and stirred for 30 min after which the reaction vessel was transferred to a −20 °C freezer for 12 h. The solution was placed in an ice bath and quenched with pH 7 phosphate buffer (1 mL) followed by MeOH (3 mL). A mixture of MeOH (3 mL) and 30% H_2O_2 (1 mL) was added over 15 min and stirring was continued for 30 min at 0 °C. The mixture was extracted with CH_2Cl_2 (3×10 mL), washed with $NaHCO_3$ (10 mL), brine (10 mL), and dried over Na_2SO_4. After concentrating the organics, the residue was purified by flash column chromatography eluting with EtOAc/hexanes (3:7) to give 60 mg (48% yield) of **47** as a colorless liquid. NMR spectra (^1H and ^{13}C) were identical with reported literature values.

*4.6.3. Aldol **48**.* Hoveyda-Grubbs II (**2**) (11 mg, 0.017 mmol) was added to a mixture of benzyl ether **44** (50 mg, 0.337 mmol) and crotonaldehyde (47 mg, 0.674 mmol) in deaerated CH_2Cl_2 (2.2 mL). The reaction mixture was heated to 40 °C under an Ar atmosphere for 12 h and cooled to rt. The solvent was concentrated under reduced pressure and the residue was dried under vacuum for 10 min. To a solution of *ent*-**42** (79 mg, 0.337 mmol) in CH_2Cl_2 (2 mL) was added a 1.0 M solution of Bu_2BOTf (0.41 mL, 0.405 mmol) at −10 °C over 2 min followed by Et_3N (44 mg, 0.438 mmol) making sure that the internal temperature is below 0 °C and stirred for 30 min at 0 °C. The reaction mixture was cooled to −78 °C and the metathesis product was added slowly using CH_2Cl_2 (2 mL) and stirred for 45 min, warmed to 0 °C, and stirred for additional 3 h. The yellow orange solution was recooled to −10 °C and quenched by adding pH 7 buffer (2 mL), MeOH (2 mL), and a mixture of MeOH, 30% H_2O_2 (1+0.5 mL). The reaction mixture was extracted with CH_2Cl_2 (3×10 mL), washed with $NaHCO_3$ (10 mL), brine (10 mL), and dried over Na_2SO_4, purified by flash column chromatography eluting with EtOAc/hexanes (3:7) to give 71 mg (52.0%) of **48** as a colorless liquid. NMR spectra (^1H and ^{13}C) were identical with reported literature values.

*4.6.4. Aldol **49**.* Hoveyda-Grubbs II (**2**) (9 mg, 0.014 mmol) was added to a mixture of PMB ether **45** (50 mg, 0.281 mmol) and crotonaldehyde (40 mg, 0.562 mmol) in CH_2Cl_2 (2.0 mL) and deaerated for 5 min. The reaction mixture was heated to 40 °C under an Ar atmosphere for 12 h and cooled to rt, the solvent was concentrated under reduced pressure and the residue was dried for 10 min. To a solution of propionimide **42** (66 mg, 0.281 mmol) in CH_2Cl_2 (2 mL) was added 1.0 M solution of Bu_2BOTf (0.51 mL, 0.506 mmol) at 0 °C over 2 min followed by Et_3N (57 mg, 0.562 mmol) and stirred for 1 h at 0 °C and the metathesis product was added slowly using CH_2Cl_2 (2 mL) and cooled to −45 °C, stirred for 12 h and quenched by adding pH 7 buffer (2 mL), MeOH (2 mL), and a mixture of MeOH, 30% H_2O_2 (1+0.5 mL). The reaction was stirred for 30 min at rt and extracted with CH_2Cl_2 (3×10 mL), washed with $NaHCO_3$ (10 mL), brine (10 mL), and dried over Na_2SO_4, purified by flash column chromatography eluting with EtOAc/hexanes (3:7) to give 79 mg (64% yield) of **49** as a colorless liquid. NMR spectra (^1H and ^{13}C) were identical with reported literature values.

4.7. General procedure for sequential CM/Roush allylation reactions (Table 6)

Hoveyda-Grubbs II (**2**) (5 mol %) was added to a mixture of CM partner (1 equiv) and crotonaldehyde (2 equiv) in CH_2Cl_2 (0.15 M) and deaerated for 5 min. The reaction mixture was heated to 40 °C under an Ar atmosphere for 12 h and cooled to rt, the solvent was concentrated under reduced pressure, and the residue was filtered through a plug of silica eluting with Et_2O. The solvent was concentrated under reduced pressure and dried for 10 min. To a solution of (−)-DIPCl (2 equiv) in Et_2O (2 mL) at 0 °C was added a 1.0 M solution of allylmagnesium bromide in Et_2O (1.92 equiv). The reaction mixture was warmed to rt and stirred for 1 h. After cooling the reaction mixture to −78 °C, a solution of enal from the CM was slowly added over a period of 10 min using little ether (1 mL) and stirred for 70 min. The reaction was quenched by adding MeOH and allowed to rt, extracted with 1 N aq HCl solution. The combined organic layers were basified using 30% NaOH solution to a pH of 12–13 and extracted with CH_2Cl_2 (3×10 mL), washed with $NaHCO_3$ (10 mL), brine (10 mL), and dried over Na_2SO_4. Concentration of the organics and purification of the residue by flash column chromatography eluting with Et_2O/toluene (1:9) gave the corresponding

homoallylic alcohols, whose NMR spectra (^{1}H and ^{13}C) were identical with reported literature values. Mosher esters were prepared from the homoallylic alcohols to determine % ee.[37]

4.8. General procedure for sequential CM/Roush crotylation reactions (Table 6)

Hoveyda-Grubbs second-generation catalyst (5 mol %) was added to a mixture of the terminal olefin (1 equiv) and crotonaldehyde (2 equiv) in deaerated CH_2Cl_2 (0.15 M). The reaction mixture was heated to 40 °C under an Ar atmosphere for 12 h and cooled to rt. The solvent was concentrated under reduced pressure, and the residue was filtered through a plug of silica eluting with Et_2O. The solvent was concentrated under reduced pressure and dried for 10 min. To an oven-dried round-bottomed flask equipped with magnetic stirbar and 4 Å molecular sieves (100 mg per 1 mmol of the reagent) was added a 1.0 M solution of Roush's reagent **51** (1.5 equiv) in toluene. The mixture was cooled to −78 °C. The enal from the CM reaction was added to the reagent and rinsed with toluene (1 mL). The reaction mixture was stirred at −78 °C for 5 h. The reaction was quenched with dropwise addition of 2 N aq NaOH (1 mL), and the mixture was warmed to 0 °C. After stirring an additional 20 min at 0 °C, the mixture was extracted with Et_2O (3×10 mL), washed with brine (10 mL), and dried over K_2CO_3. Concentration of the organics and purification of the residue by flash column chromatography eluting with EtOAc/hexanes (1:4) gave the corresponding homoallylic alcohols, whose NMR spectra (^{1}H and ^{13}C) were identical with reported literature values. Mosher esters were prepared from the homoallylic alcohols to determine % ee.[37]

*4.8.1. Compound **15**.* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13 (d, J=11.2 Hz, 1H), 6.42–6.35 (m, 1H), 6.07–6.00 (m, 1H), 4.19 (q, J=7.2 Hz, 2H), 3.67 (s, 3H), 2.50 (t, J=6.4 Hz, 2H), 2.47–2.43 (m, 2H), 1.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0, 168.4, 139.7, 137.8, 127.0, 126.2, 60.4, 51.6, 33.3, 28.3, 14.2, 12.5; IR (neat): 2982, 2953, 1739, 1703 cm^{-1}; HRMS (FAB) calcd for $C_{12}H_{18}O_4$+H^+=227.1283, found 227.1277.

*4.8.2. Compound **19**.* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15 (d, J=11.2 Hz, 1H), 6.38–6.31 (m, 1H), 6.10–6.00 (m, 1H), 4.19 (q, J=7.2 Hz, 2H), 3.61 (t, J=6.0 Hz, 2H), 2.25 (q, J=7.2 Hz, 2H), 1.91 (s, 3H), 1.68–1.61 (m, 2H), 1.29 (t, J=7.2 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6, 142.4, 138.4, 126.3, 125.2, 62.2, 60.4, 32.0, 29.6, 25.9, 18.3, 14.3, 12.5, −5.3; IR (neat): 2953, 2930, 1706 cm^{-1}; HRMS (FAB) calcd for $C_{17}H_{32}O_3Si$+H^+=313.2199, found 313.2210.

*4.8.3. Compound **20**.* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (d, J=15.6 Hz, 1H), 5.89 (t, J=7.2 Hz, 1H), 5.78 (d, J=15.6 Hz, 1H), 3.73 (s, 3H), 3.58 (t, J=6.8 Hz, 2H), 2.26 (q, J=8.0 Hz, 2H), 1.76 (s, 3H), 1.65–1.58 (m, 3H), 0.88 (s, 9H), 0.34 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.0, 149.8, 141.8, 133.1, 115.1, 62.3, 51.4, 32.1, 25.9, 25.2, 18.3, 12.0, −5.3; IR (neat): 2952, 2930, 1726 cm^{-1}; HRMS (FAB) calcd for $C_{16}H_{30}O_3Si$+H^+=299.2043, found 299.2056.

*4.8.4. Compound **32**.* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46–7.44 (m, 2H), 7.40–7.37 (m, 2H), 7.32–7.29 (m, 1H), 6.61 (d, J=16.0 Hz, 1H), 6.31 (dd, J=16.0, 6.0 Hz, 1H), 5.99–5.89 (m, 1H), 5.20–5.13 (m, 2H), 4.44–4.39 (m, 1H), 2.51–2.37 (m, 2H), 1.03 (s, 9H), 0.19 (s, 3H), 0.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.1, 134.8, 132.8, 129.2, 128.5, 127.3, 126.4, 117.0, 73.3, 43.2, 25.9, 18.3, −4.3, −4.7; IR (neat): 2955, 2930, 2895, 2856, 1472, 1361, 1254, 1071, 966, 910 cm^{-1}; HRMS (FAB) calcd for $C_{18}H_{28}OSi-H^+$=287.1831, found 287.1826.

*4.8.5. Compound **34**.* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30–7.21 (m, 5H), 5.88–5.79 (m, 1H), 4.98–4.89 (m, 2H), 4.45 (d, J=6.0 Hz, 2H), 2.43–2.41 (m, 1H), 0.89 (s, 3H), 0.87 (s, 9H), −0.02 (s, 3H), −0.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.7, 141.1, 127.6, 126.9, 126.9, 114.4, 79.1, 46.4, 25.8, 18.2, 16.1, −4.6, −5.1; IR (neat): 2957, 2930, 2886, 2858, 1454, 1362, 1254, 1086, 1065, 910 cm^{-1}; HRMS (FAB) calcd for $C_{17}H_{28}OSi-H^+$=275.1831, found 275.1830.

*4.8.6. Compound **35**.* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53–7.51 (m, 2H), 7.47–7.43 (m, 2H), 7.38–7.34 (m, 1H), 6.66 (d, J=16.0 Hz, 1H), 6.33 (dd, J=16.0, 6.5, 16 Hz, 1H), 6.07–5.99 (m, 1H), 5.23–5.18 (m, 2H), 4.19 (t, J=5.2, 1.2 Hz, 1H), 2.53 (m, 1H), 1.20 (d, J=6.8 Hz, 1H), 1.11 (s, 9H), 0.24 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.8, 137.2, 131.4, 130.2, 128.5, 127.3, 126.4, 114.6, 45.1, 25.9, 18.3, 15.4, −4.1, −4.8; IR (neat): 2957, 2929, 2886, 2857, 1252, 1065, 967 cm^{-1}; HRMS (FAB) calcd for $C_{19}H_{30}OSi-H^+$=301.1989, found 301.1996.

*4.8.7. Compound **36**.* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.26 (m, 5H), 5.76–5.65 (m, 2H), 4.54, 4.52 (ABq, J=12.0 Hz, 2H), 4.08 (br s, 2H), 3.41–3.35 (m, 1H), 2.33–2.30 (m, 2H), 1.59–1.55 (m, 3H), 0.93 (t, J=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.9, 131.4, 129.0, 128.3 (2C), 127.7 (2C), 127.5, 79.8, 70.9, 63.6, 36.1, 26.4, 9.6; IR (neat): 3384, 2964, 2932, 2872, 1454, 1349, 1090, 1064, 1027, 1005, 972, 910 cm^{-1}; HRMS (FAB) calcd for $C_{14}H_{20}O_2$+Na=243.1361, found 243.1351.

*4.8.8. Compound **37**.* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.20 (m, 5H), 5.70–5.58 (m, 2H), 4.68 (dd, J=7.0, 5.0 Hz, 1H), 4.05–4.04 (m, 2H), 2.50–2.35 (m, 2H), 1.39 (br s, 1H), 0.88 (s, 9H), 0.02 (s, 3H), −0.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.9, 131.5, 129.4, 128.0 (2C), 127.0, 125.8 (2C), 74.9, 63.7, 43.8, 25.8, 18.2–4.7, −4.9; IR (neat): 3363, 2953, 2930, 2885, 2857, 1471, 1362, 1255, 1091, 1005, 909, 836 cm^{-1}; HRMS (FAB) calcd for $C_{17}H_{28}O_2Si$+Na=315.1756, found 315.1750.

*4.8.9. Compound **38**.* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39–7.30 (m, 4H), 7.26–7.23 (m, 1H), 6.52 (d, J=16.0 Hz, 1H), 6.20 (dd, J=16.0, 6.4 Hz, 1H), 5.74–5.71 (m, 2H), 4.36 (q, J=6.0 Hz, 1H), 4.16–4.12 (m, 2H), 2.38–2.35 (m, 2H), 1.50 (br s, 1H), 0.95 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.0, 132.7, 131.7, 129.3, 128.8, 128.5 (2C), 127.4, 126.4 (2C), 73.3, 63.6, 41.5, 25.9, 18.3, −4.3, −4.7; IR (neat): 3356 cm^{-1}; IR (neat): 3356, 2953, 2929, 2893, 2856, 1471, 1253, 1071, 968 cm^{-1}; HRMS (FAB) calcd for $C_{19}H_{30}O_2Si$+Na=341.1913, found 341.1904.

*4.8.10. Compound **40**.* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29–7.21 (m, 5H), 5.72–5.50 (m, 2H), 4.43 (d, J=6.0 Hz, 1H), 4.06 (br s, 2H), 2.45–2.40 (m, 1H), 1.16 (br s, 1H), 0.89 (d, J=3.6 Hz, 3H), 0.87 (s, 9H), 0.01 (s, 3H), −0.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.6, 135.3, 129.2, 127.6, 127.0, 126.9, 126.8, 79.1, 63.9, 45.1, 25.8, 18.2, 16.5, −4.6, −5.1; IR (neat): 3333, 2955, 2929, 2885, 2856, 1471, 1455, 1253, 1088, 1064 cm^{-1}; HRMS (FAB) calcd for $C_{18}H_{30}O_2Si$+Na=329.1913, found 329.1923.

*4.8.11. Compound **41**.* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42–7.34 (m, 4H), 7.30–7.26 (m, 1H), 6.53 (d, J=16.0 Hz, 1H), 6.19 (dd, J=16.0, 6.8 Hz, 1H), 5.80–5.68 (m, 2H), 4.19–4.16 (m, 3H), 2.44–2.38 (m, 1H), 1.43 (br s, 1H), 1.07 (d, J=6.8 Hz, 3H), 0.96 (s, 9H), 0.12 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.1, 135.0, 131.4, 130.3, 129.3, 128.5 (2C), 127.4, 126.4 (2C), 77.3, 63.8, 43.6, 25.9, 18.2, 15.8, −4.2, −4.8; IR (neat): 3357, 2956, 2929, 2884, 2856, 1471, 1461, 1362, 1253, 1070, 969, 909 cm^{-1}; HRMS (FAB) calcd for $C_{20}H_{32}O_2Si$+Na=355.2069, found 355.2079.

Acknowledgements

Financial support of this work by the Department of Chemistry at Temple University is gratefully acknowledged. We thank Dr.

Richard Pederson (Materia, Inc.) for a generous donation of Grubbs-II (**1**) and Hoveyda-Grubbs-II (**2**) catalysts.

References and notes

1. Trost, B. M. *Science* **1991**, *254*, 1471.
2. Wender, P. A.; Verma, V. A.; Paxton, T. J.; Pillow, T. H. *Acc. Chem. Res.* **2008**, *41*, 40.
3. Burns, N. Z.; Baran, P. S.; Hoffmann, R. W. *Angew. Chem., Int. Ed.* **2009**, *48*, 2854.
4. Trost, B. M. *Science* **1983**, *219*, 245.
5. Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131.
6. (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115; (b) Padwa, A.; Bur, S. K. *Tetrahedron* **2007**, *63*, 5341.
7. Ho, T.-L. *Tandem Organic Reactions*; Wiley: New York, NY, 1992.
8. For CM reviews see Ref. 12.
9. Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.
10. Dragutan, V.; Dragutan, I. *J. Organomet. Chem.* **2006**, *691*, 5129.
11. Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.
12. Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900 and references cited therein.
13. Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.
14. (a) Jadhav, P. K.; Bhat, K. S.; Perumal, T.; Brown, H. C. *J. Org. Chem.* **1986**, *51*, 432; (b) Ramachandran, P. V. *Aldrichimica Acta* **2002**, *35*, 23.
15. (a) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 293; (b) Roush, W. R.; Ando, K.; Powers, D. B.; Palkowitz, A. D.; Halterman, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 6339.
16. Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.
17. Wadsworth, W. S., Jr. *Org. React.* **1977**, *25*, 73.
18. (a) van den Tempel, P. J.; Huisman, H. O. *Tetrahedron* **1966**, *22*, 293; (b) Sato, K.; Mizuno, S.; Hirayama, M. *J. Org. Chem.* **1967**, *32*, 177.
19. (a) Funk, T. W.; Efskind, J.; Grubbs, R. H. *Org. Lett.* **2005**, *7*, 187; (b) Moura-Letts, G.; Curran, D. P. *Org. Lett.* **2007**, *9*, 5.
20. Andrade, R. B.; Martin, S. F. *Org. Lett.* **2005**, *7*, 5733.
21. Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.
22. For a review of the SAE, see Johnson, R. A.; Sharpless, K. B. *Catal. Asymmetric Synth. (2nd Ed.)* **2000**, 231.
23. Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873.
24. For examples see: Ref. 34.
25. Taber has reported an alternative CM approach using (Z)-2-butene-1,4-diol as olefin coupling partner Taber, D. F.; Frankowski, K. J. *J. Org. Chem.* **2003**, *68*, 6047.
26. Blackwell, H. E.; O'Leary, D. J.; Chatterjee, A. K.; Washenfelder, R. A.; Bussmann, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 58.
27. Enoate intermediates were isolated in separate experiments. Coupling constants obtained from the ^{1}H NMR (J=15.6–16.0 Hz) confirm a *trans* olefin geometry, which is retained in the subsequent reduction (DIBAL-H) step.
28. For a review see: (a) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 555; (b) Roush, W. R. In *Comprehensive Organic Synthesis*; Heathcock, C. H., Ed.; Pergamon: Oxford, 1991; Vol. 2, p 1.
29. Cossy, J.; BouzBouz, S.; Hoveyda, A. *J. Organomet. Chem.* **2001**, *624*, 327.
30. BouzBouz, S.; Simmons, R.; Cossy, J. *Org. Lett.* **2004**, *6*, 3465.
31. Enoate intermediates were isolated in separate experiments. Coupling constants obtained from the ^{1}H NMR (J=15.6–16.0 Hz) confirm a *trans* olefin geometry.
32. Compound 46 Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1998**, *110*, 2506; Compound 47 Vanderwal, C. D.; Vosberg, D. A.; Sorensen, E. J. *Org. Lett.* **2001**, *3*, 4307; Compound 48 Anderson, J. C.; McDermott, B. P.; Griffin, E. J. *Tetrahedron* **2000**, *56*, 8747; Compound 49 Garcia-Fortanet, J.; Murga, J.; Carda, M.; Alberto Marco, J.; Matesanz, R.; Fernando Diaz, J.; Barasoain, I. *Chem.—Eur. J.* **2007**, *13*, 5060.
33. Mulzer, J. In *Comprehensive Asymmetric Catalysis*; Jacobesen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Heidelberg, 1999; Vol. 1, pp 33–97.
34. Norcross, R. D.; Paterson, I. *Chem. Rev.* **1995**, *95*, 2041.
35. See Section 4.1 of the experimental for compound numbers and references.
36. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
37. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.