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]

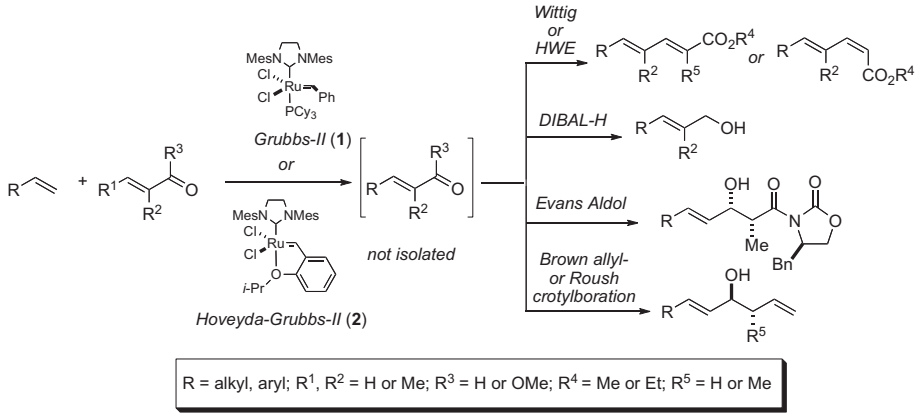
2. Results and discussion

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



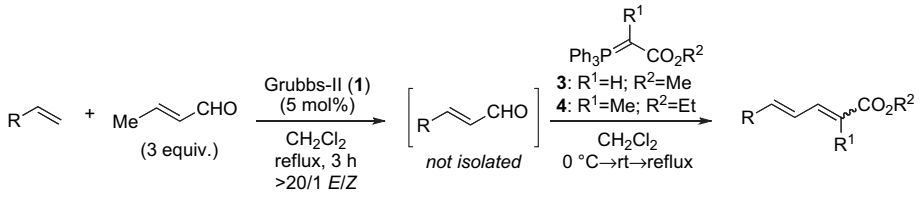
Scheme 1. Overview of sequential CM/non-CM method to access building blocks.

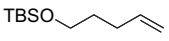
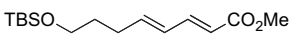
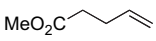
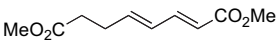
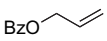
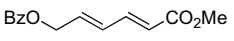
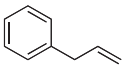
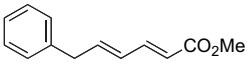
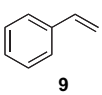
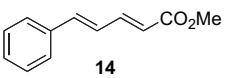
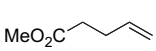
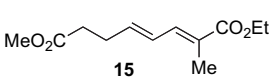
alternative that employs only commercially available reagents for the rapid assembly of either (2*E*,4*E*)- or (2*Z*,4*E*)-dienoates by modifying the second olefination step.

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.