August 2014

Relay Cross Metathesis Reactions of Vinylphosphonates

Raj Malla
University of Missouri–St. Louis

Jeremy Ridenour

Christopher Spilling
University of Missouri–St. Louis

BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Relay cross metathesis reactions of vinylphosphonates

Raj K. Malla, Jeremy N. Ridenour and Christopher D. Spilling*

Full Research Paper

Open Access

Address:
Department of Chemistry and Biochemistry, University of Missouri St. Louis, One University Boulevard, St. Louis, MO 63121, USA

Email:
Christopher D. Spilling* - cspill@umsl.edu

* Corresponding author

Keywords:
centrolobine; metathesis; organo phosphorus; relay; vinyl phosphonate

Beilstein J. Org. Chem. **2014,** *10,* 1933–1941.
doi:10.3762/bjoc.10.201

Received: 23 January 2014
Accepted: 14 July 2014
Published: 19 August 2014

This article is part of the Thematic Series "Organophosphorus chemistry".

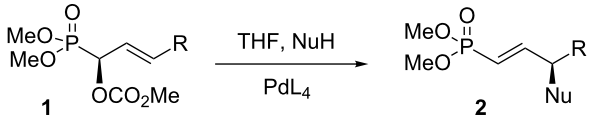
Guest Editor: P. R. Hanson

Abstract

Dimethyl (β-substituted) vinylphosphonates do not readily undergo cross metathesis reactions with Grubbs catalyst and terminal alkenes. However, the corresponding mono- or diallyl vinylphosphonate esters undergo facile cross metathesis reactions. The improved reactivity is attributed to a relay step in the cross metathesis reaction mechanism.

Introduction

Over the last two decades, we have developed reactions for the formation of chiral non-racemic γ-substituted vinylphosphonates [1-9]. In particular, carbonate derivatives **1** (phosphono allylic carbonates) of allylic hydroxy phosphonates undergo palladium-catalyzed addition of nucleophiles to give γ-substituted vinylphosphonates **2** in high yield (Scheme 1). The nucleophile adds exclusively to the 3-position, with migration of the double bond into "conjugation" with phosphoryl group. As expected, the reactions generally proceed with complete chirality transfer. Various carbon, nitrogen, and oxygen nucleophiles participate in the palladium-catalyzed substitution reactions of phosphono allylic carbonates **1**. Vinylphosphonates formed in this way, for example **2a–e** (Figure 1), have been used in the synthesis of the natural products turmerone [4] and enterolactone [5], the phosphonate derivatives of the natural product cyclophostin [6], the C18–C34 fragment of amphidinolide C [7], and the oxylipids from Australian brown algae [8].



Scheme 1: Palladium catalysed reaction of phosphono allylic carbonates.

The potential of vinylphosphonates as intermediates in organic synthesis is limited by their chemistry. Unlike the parent compound, vinylphosphonates substituted with an aryl or alkyl group on the alkene appear to have somewhat limited reactivity. This lack of reactivity is exemplified by the Grubbs cross metathesis reaction [10]. Grubbs and co-workers classified terminal vinylphosphonates as type III substrates [11]. Type III alkenes do not homodimerize, but will engage in alkene cross metathesis reactions. However, we have observed that β-substi-

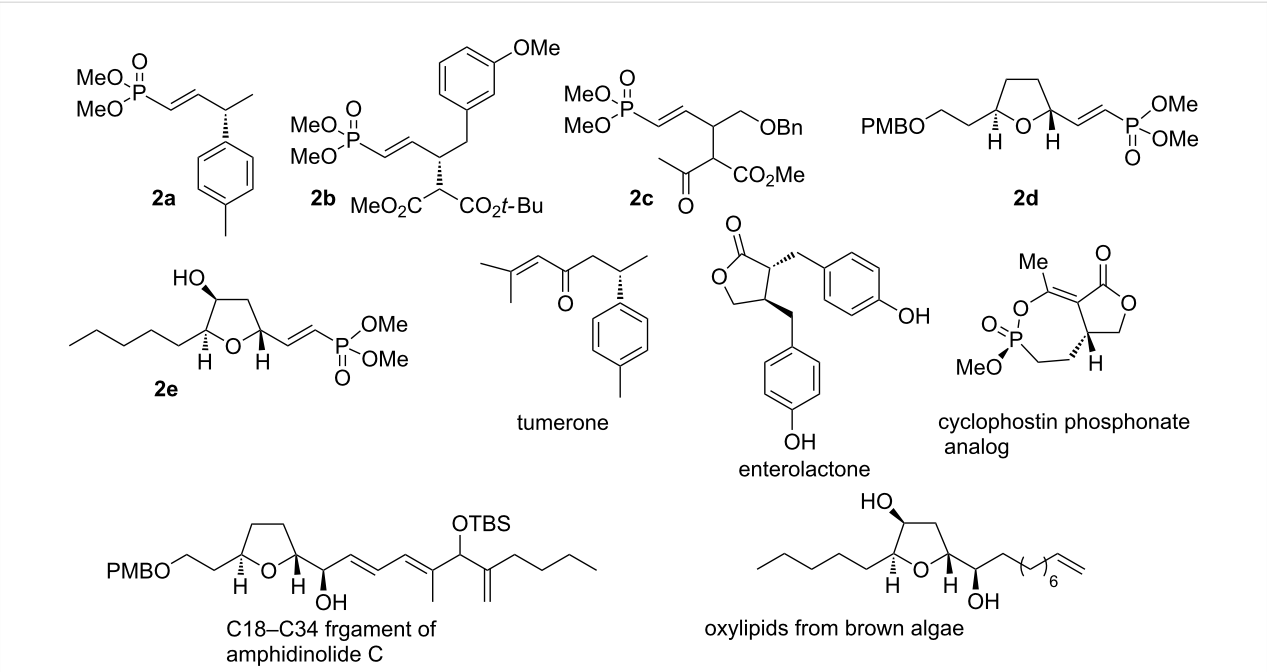
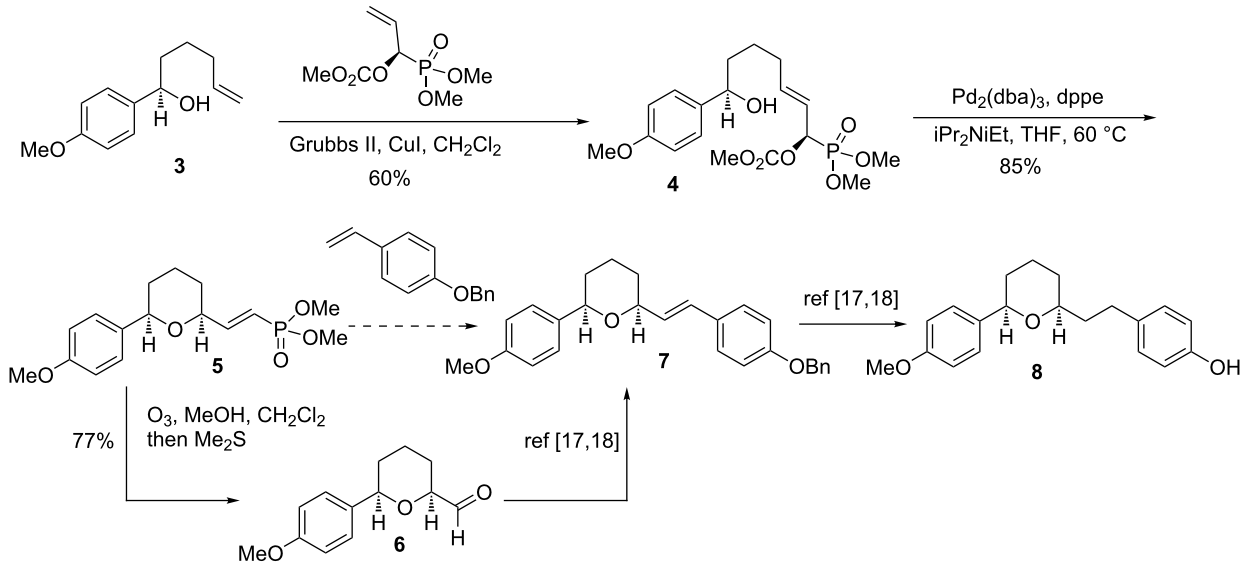


Figure 1: Natural products prepared using vinyl phosphonate intermediates.

tuted vinylphosphonates are unreactive towards cross metathesis and are therefore type IV substrates. Since alkene cross metathesis is a powerful method of combing organic fragments in natural product synthesis, the value of vinylphosphonates as synthetic intermediates would increase if their reactivity could be enhanced to a level where they would participate in cross metathesis reactions.

As an example, we recently described a method for the formal synthesis of centrolobine (**8**) [9], an antileishmananial compound isolated from the heartwood of various *Centrolobium* species [12-16] (Scheme 2). The *cis*-THP substituted vinylphosphonate **5**, formed by a stereospecific palladium-catalyzed cyclization of phosphono allylic carbonate **4**, was cleaved via ozonolysis to the aldehyde **6**, a known intermediate [17,18] on



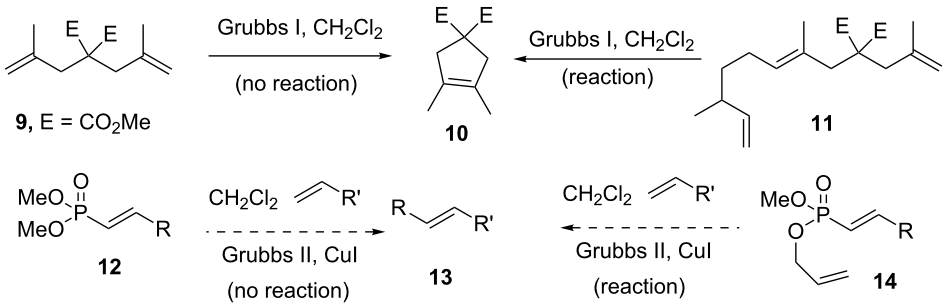
Scheme 2: Approaches to the synthesis of centrolobine.

route to (−)-centrolobine (**8**). An alternative approach could involve an alkene cross metathesis reaction between the vinylphosphonate and a styrene (**5** to **7**).

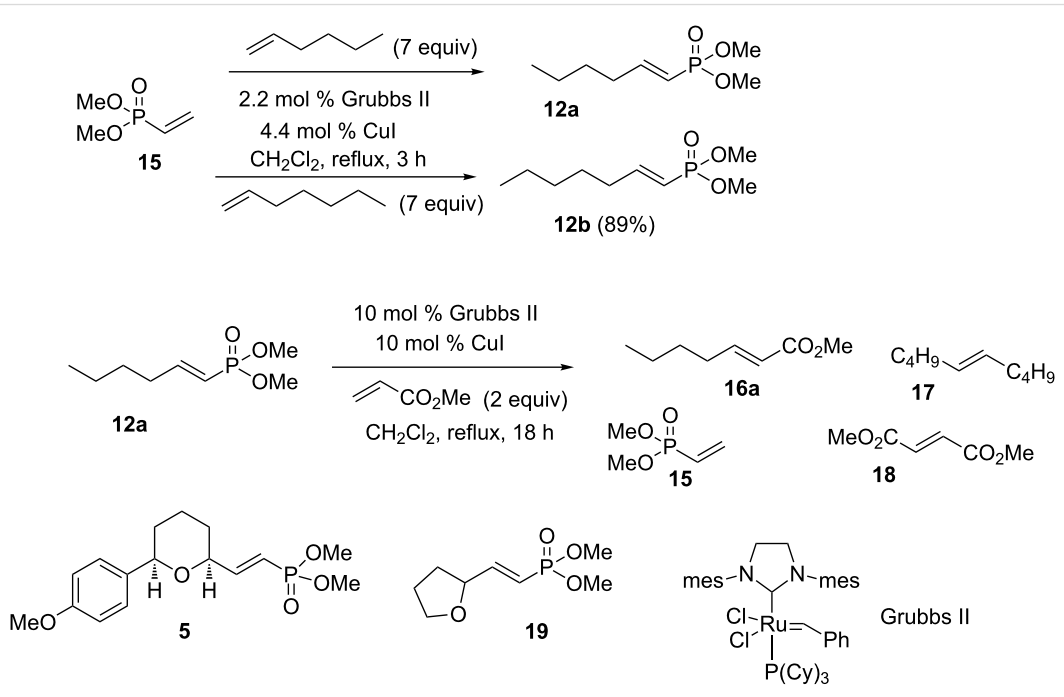
Since substituted vinylphosphonates are reluctant to participate in cross metathesis reactions (Scheme 3), this approach to the synthesis of cetrolobine appeared to have little merit. However, Hoye et al. reported the concept of "relay ring closing metathesis (RRCM)", wherein typically unreactive α,ω-dienes bearing 1,1-disubstituted ethylene moieties **9** would react via the intermediacy of an additional terminal alkene **11** (Scheme 3) [19-21]. Similarly, Hansen and Lee employed an allyl ether to activate enynes toward cross metathesis [22]. Furthermore, there are several examples of vinylphosphonates participating in ring closing metathesis (RCM) reactions [23-25]. Therefore, given the propensity for vinylphosphonates to undergo RCM, it was proposed that an allyl phosphonate ester **14** would act as an initial site of metathesis, which would lead to a relay cross metathesis and thus render vinylphosphonates reactive.

Results and Discussion

A series of cross metathesis reactions were performed to establish the baseline reactivity of vinylphosphonates (Scheme 4). Not surprisingly, the terminal vinylphosphonate **15** underwent smooth cross metathesis with either 1-hexene or 1-heptene using our standard conditions (2% Grubbs II, 4% CuI, CH_2Cl_2 reflux) [2,26,27] to give the substituted vinylphosphonates **12a** or **12b** in good yield. In contrast, when vinylphosphonate **12a** was subjected to a cross metathesis reaction with methyl acrylate, the cross metathesis product **16a** was formed in low yield



Scheme 3: Relay ring closing metathesis and relay cross metathesis.



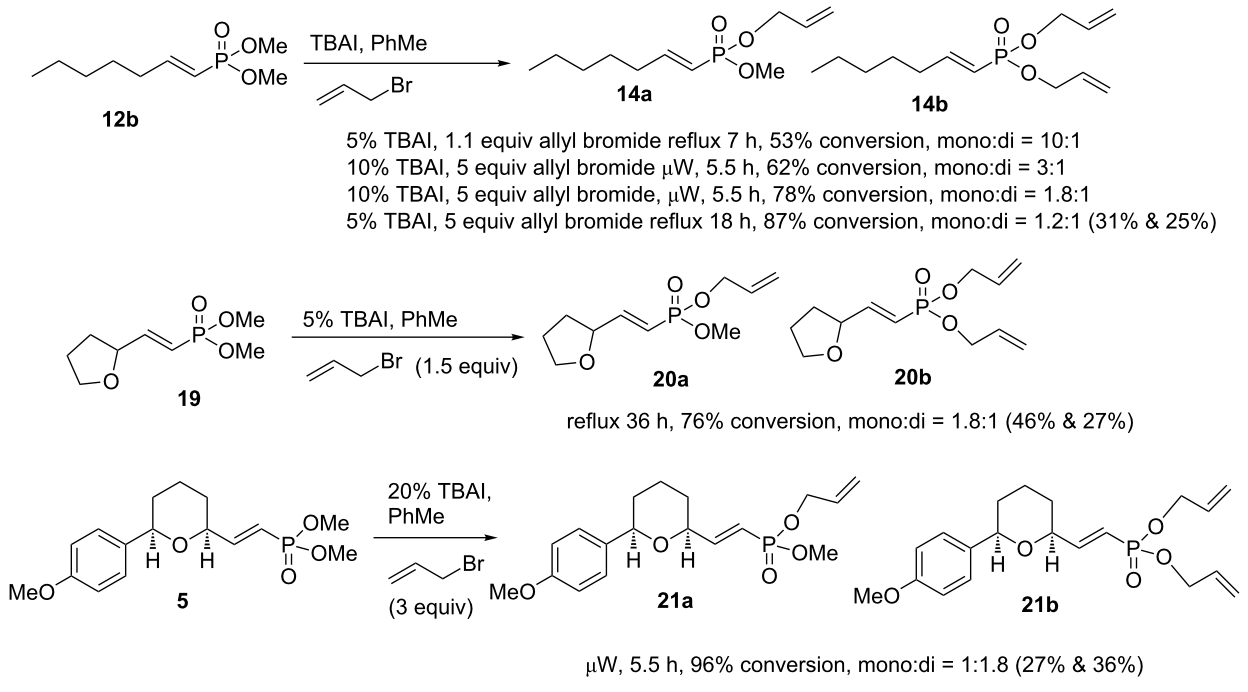
Scheme 4: Cross metathesis reactions of vinyl phosphonates.

(~11%) as part of a complex mixture. More highly substituted vinylphosphonates (**5** and **19**) failed to react at all with methyl acrylate under similar conditions, even with higher catalyst loading and extended reaction times.

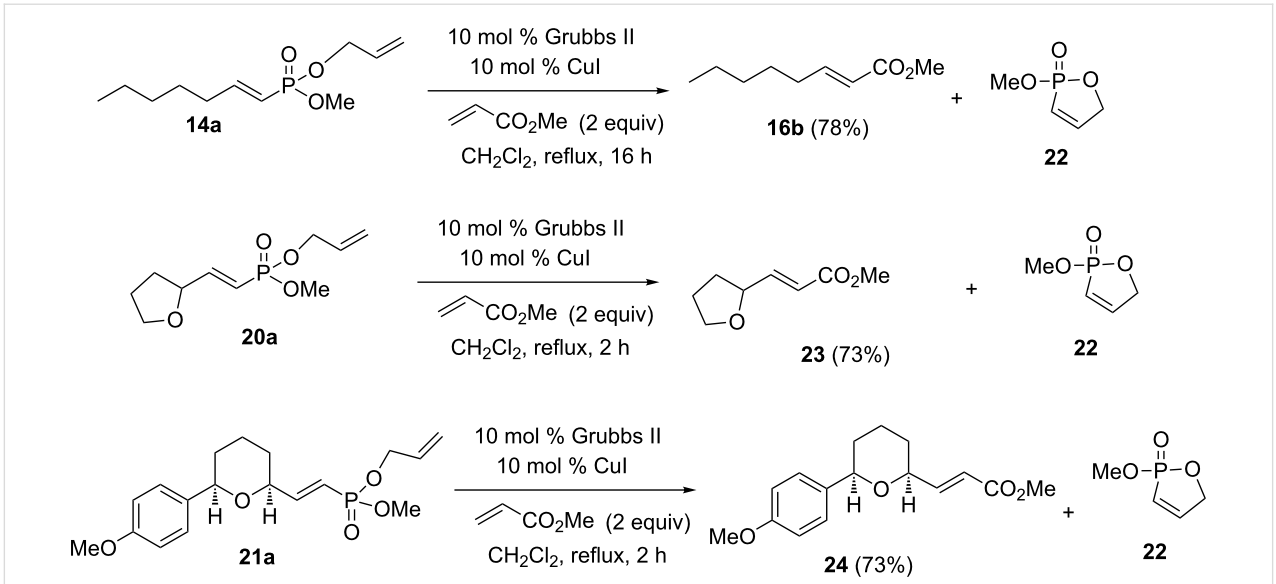
Initially, the synthesis of the allyl vinylphosphonate esters was achieved using a transesterification reaction catalysed by tetra *n*-butylammonium iodide (TBAI) (Scheme 5) [28]. A solution of the vinylphosphonate **12b**, 1.1 equivalents of allyl bromide and 5 mol % TBAI in toluene was heated at reflux for 7 hours to give a 53% conversion to both the mono- and diallyl vinylphosphonates **14a** and **14b** in a 10:1 ratio. The overall conversion could be improved with excess allyl bromide, increasing the amount of TBAI and prolonged heating times, either at reflux or in a microwave reactor. The ratio of di- to mono-allyl phosphonate esters increases with the duration of reaction. A subsequent reaction of vinylphosphonate **12b** employing 5 equivalents of allyl bromide, 5 mol % TBAI and 18 hours at reflux resulted in 87% conversion with 1.2:1 ratio of mono- to diallyl ester (**14a** and **14b**). The products were isolated by silica gel chromatography to give 31% yield of mono-allyl and 25% yield of diallyl phosphonate esters.

Similarly, THF-substituted vinylphosphonate **19** was treated with 5 equivalents of allyl bromide and 5 mol % TBAI in refluxing toluene for 36 hours to give a 76% conversion with 1.8:1 ratio of mono- to diallylated vinyl phosphonates **20a** and **20b** (Scheme 5). The products were isolated by silica gel chromatography to give 46% yield of mono-allyl and 27% yield of diallyl phosphonate esters. Finally, THP-vinylphosphonate **5** was subjected to transesterification by reaction with 20 mol % of TBAI and 5 equivalents of allyl bromide in toluene solution and heating in a microwave reactor for 5.5 hours. The reaction proceeded to 96% conversion and gave 1:1.8 ratio of mono- and diallyl vinylphosphonates **21a** and **21b**. The products were isolated by silica gel chromatography to give 27% yield of the mono-allyl and 36% yield of the diallyl phosphonate esters.

With the mono- and diallyl vinylphosphonates in hand, the cross metathesis reactions with methyl acrylate (a type II olefin) were examined (Scheme 6). The mono-allyl vinylphosphonate **14a** was treated with methyl acrylate, 10 mol % Grubbs catalyst and 10 mol % CuI in refluxing CH_2Cl_2. The unsaturated ester **16b** [29] was formed in 78% yield (estimated from NMR). However, ester **16b** is volatile and isolation by column chromatography resulted in some loss of material leading to an isolated yield of 45%. In addition, the ^{31}P NMR spectrum of the crude reaction mixture indicated the formation of a new phosphorus-containing product with a signal at 43 ppm, consistent with formation of the oxaphosphole **22** [25]. An impure sample of the oxaphosphole **22** was isolated by column chromatography, but it decomposed during attempts of further purification [23]. However, the ^{31}P NMR signal and the chemical shifts, multiplicities and coupling constants for the vinylic protons [Hα 7.16



Scheme 5: Transesterification of phosphonate esters.



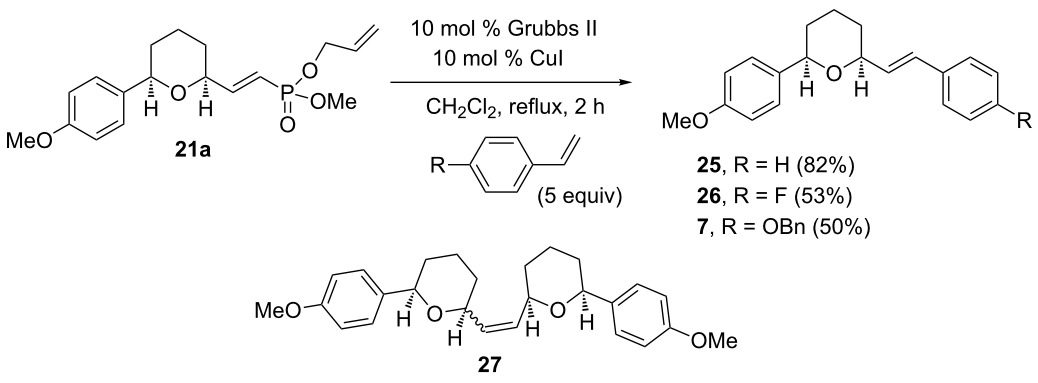
Scheme 6: Relay cross metathesis of mono-allyl vinylphosphonates with methyl acrylate.

(ddt, J_{HH} = 8.6, ~1 Hz, J_{Hp} = 46.9 Hz, 1H) and Hβ, 6.2 (ddt, J_{HH} = 8.6, 2.3 Hz, J_{HP} = 33.9 Hz, 1H] in the ^{1}H NMR spectrum were very similar to those reported for similar structures [25] giving confidence in the structural assignment. The THF-substituted allyl vinylphosphonate **20a** and THP-substituted allyl vinylphosphonate **21a** reacted under similar conditions to yield the unsaturated esters **23** [30] and **24**, respectively.

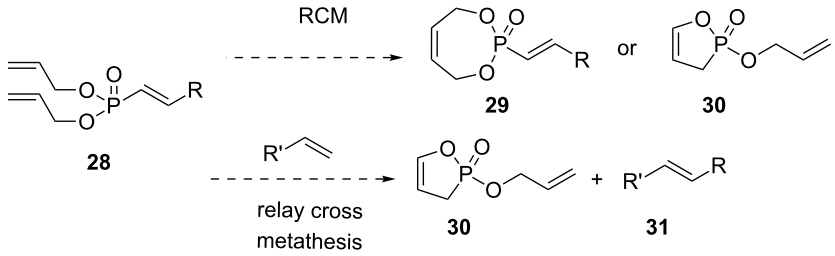
The proposed synthesis of centrolobine (and analogs) (Scheme 2) required the cross metathesis reaction of the THP-substituted allyl vinylphosphonate **21a** with substituted styrenes. *p*-Substituted styrenes are type I substrates and should readily engage in the metathesis reaction. Thus, reaction of the mono-allyl vinylphosphonate **21a** with 5 equivalents of styrene using 10 mol % Grubbs second generation catalyst and 10 mol % CuI in refluxing CH_2Cl_2 for two hours gave tetrahydropyran **25** in 82% isolated yield (Scheme 7). Similarly, reaction of vinylphosphonate **21a** with 4-fluorostyrene and 4-benzyloxystyrene gave the tetrahydropyrans **26** and **7**, respectively. Tetrahydropyran **7** is a known intermediate and can be converted to centrolobine by hydrogenation [17].

Surprisingly, the dimer **27** was isolated in small amounts (~20%) from the reaction of vinylphosphonate **21a** with styrenes. The dimeric product **27** was not observed during the cross metathesis of the vinylphosphonate **21a** with methyl acrylate.

Diallyl vinylphosphonates (**28**) are reported to undergo ring closing metathesis to give either 7-membered (**29**) or 5-membered (**30**) phosphorus heterocycles (Scheme 8) [23,24]. The mode of cyclization depends upon the geometry and substi-



Scheme 7: Relay cross metathesis of mono-allyl vinylphosphonates with styrenes.

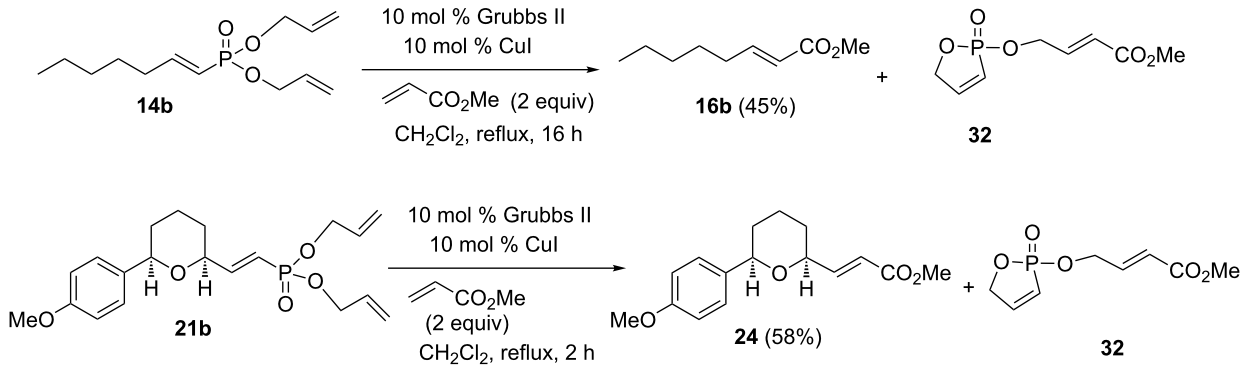


Scheme 8: Ring closing vs relay cross metathesis.

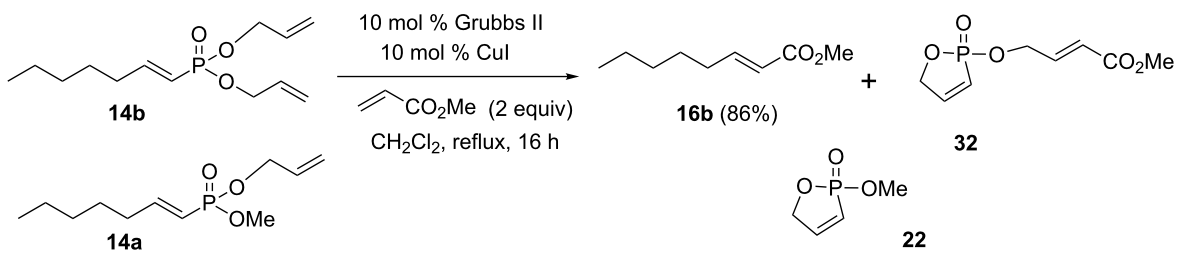
tution of the vinylphosphonate. It was proposed that (*E*) diallyl vinylphosphonates would prefer to form the 5-membered ring oxaphosphole **30** and therefore, like the corresponding mono-allyl phosphonates, should engage in relay cross metathesis reactions.

To test the hypothesis, the diallyl vinylphosphonate **14b** was subjected to cross metathesis with methyl acrylate using standard conditions (Scheme 9). The corresponding cross metathesis product, unstaurated ester **16b**, was obtained with 45% conversion. Again, isolation resulted in some loss of product. ^{31}P NMR measurements also confirmed the formation of the 5-membered phosphate heterocycle **32**. Similarly, diallyl phosphonate **21b** was reacted with methyl acrylate to give the corresponding unsaturated ester **24** in good yield along with the phosphonate heterocycle **32**. In general, reaction of either mono- allyl or diallyl vinylphosphonates with methyl acrylate proceeded with comparable yields.

The mono- and diallyl vinylphosphonates were first synthesized and then chromatographically separated before they were subjected to the cross metathesis reaction. In an ideal case, a single cross metathesis product would be formed from a crude mixture of mono-allyl and diallyl vinylphosphonates, avoiding the inefficiencies of chromatographic separation. A mixture of mono- and diallyl vinylphosphonates **14a** and **14b** was subjected to cross metathesis reaction with methyl acrylate (Scheme 10). The reaction progress was monitored by



Scheme 9: Relay cross metathesis of diallyl vinylphosphonates with methyl acrylate.



Scheme 10: A cross metathesis reaction of both mono- and diallyl vinylphosphonates with methyl acrylate.

^{31}P NMR spectroscopy. After the reaction was complete, the ^{31}P NMR spectrum showed the formation of the two oxaphospholes **22** and **32** in a ratio corresponding to the amount of vinylphosphonates **14a** and **14b** in the starting material. Chromatographic separation of the crude product gave the unsaturated ester **16b** in 86% isolated yield.

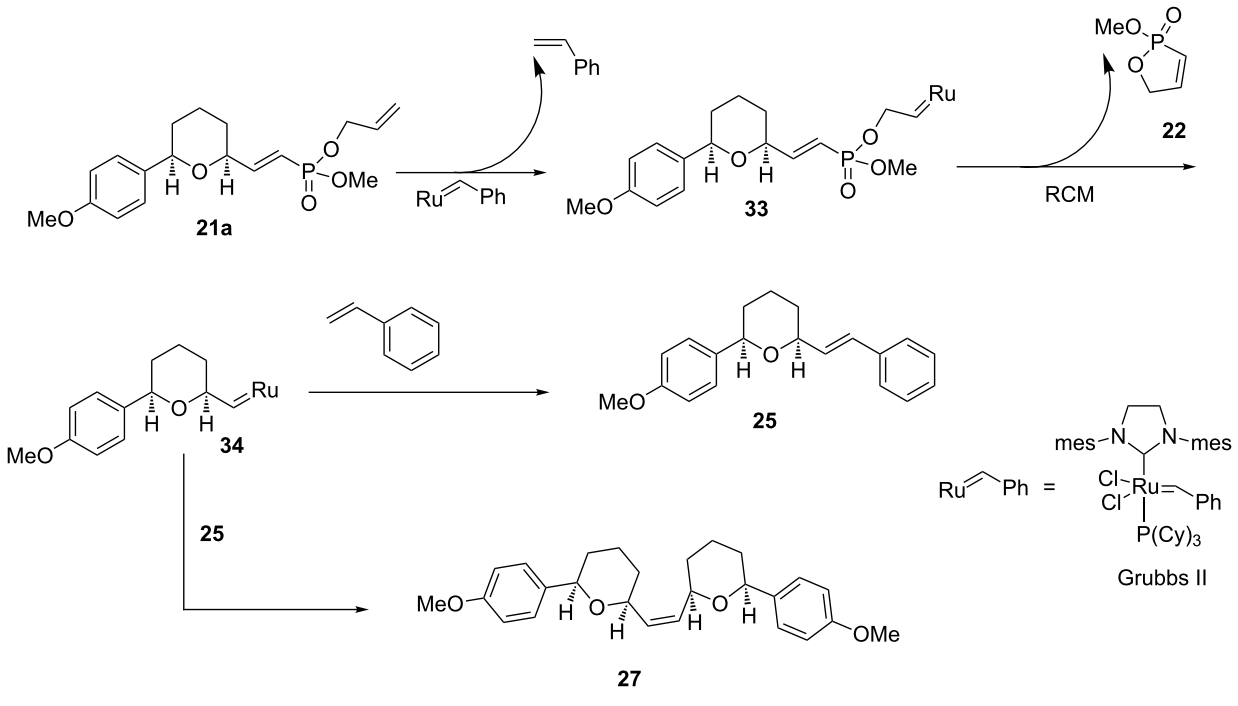
It is proposed that the Grubbs catalyst first reacts with the terminal alkene (Scheme 11) of the allyl phosphonate ester **21a** to give the metal alkylidene **33**. The metal alkylidene then reacts with the vinylphosphonate in a ring closing metathesis (RCM) to generate the oxaphosphole **22** and a new metal alkylidene **34**. The sequence is completed by reaction of the metal alkylidene **34** with the metathesis partner (styrene) to give the tetrahydropyran **25**. The formation of the dimeric product **27** is probably the result of a competitive cross metathesis reaction between the tetrahydropyran **25** and the metal alkylidene **34** [31].

Once the activation of vinylphosphonates toward cross metathesis was established, it became clear that the overall success of this method would depend on a selective, high yielding synthesis of mono-allyl phosphonates. The proposed mechanism of the TBAI catalyzed allylation (Scheme 12) involves cleavage of the Me–O bond to form a phosphonate anion **35**. The anion is re-alkylated with allyl bromide to produce the mono-allyl phosphonate **14a**. The major weakness of this approach is that the mono-allyl phosphonate can further react with iodide leading ultimately to the diallyl phosphonate **14b**. Early in the reaction, the mono-allyl phosphonate is the dominant product. However, attempts to force the reaction with longer reaction times, increased TBAI, or increased ally bromide, leads to an increase in diallyl phosphonate **14b**.

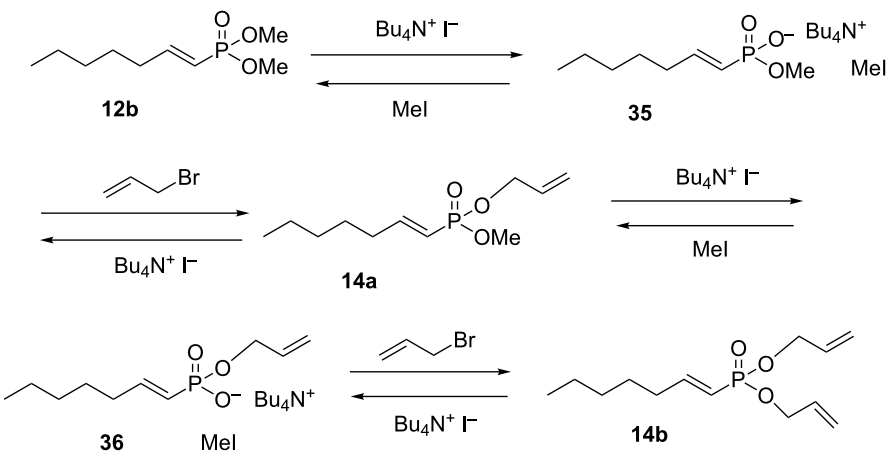
Analysis of the TBAI allylation mechanism suggested that a good approach to mono-allyl phosphonate **14a** would be a stoichiometric demethylation followed by a rapid allylation under ambient conditions. During the synthesis of phosphonate based ionic liquids, Sachnov et al. showed that ethylimidazole would reacted with dimethyl methylphosphonate to give ethylimidazolium methylphosphonate in quantitative yield [32]. We were pleased to observe [^{31}P NMR] that dimethyl vinylphosphonate **12b** reacted with neat methylimidazole at 100 °C to give the imidazolium salt **37** (Scheme 13). Treatment of the salt with 5 equivalents of allyl bromide at room temperature for two days gave the mono-allyl phosphonate in 71% isolated yield (two steps). It is probable that this transesterification reaction can be further optimized to both increase yields and decrease the reaction time.

Conclusion

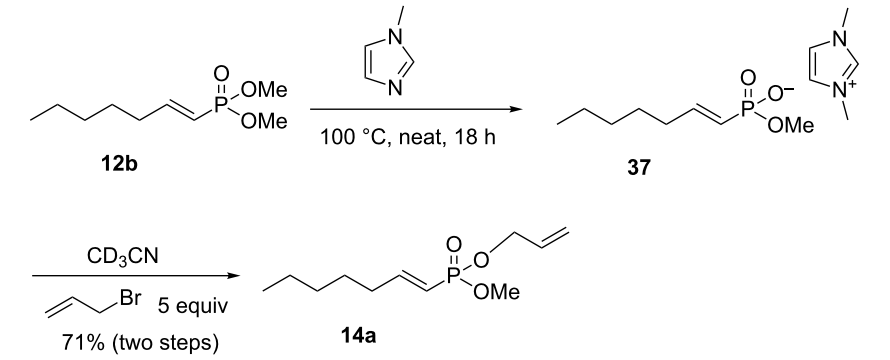
The experiments presented above have demonstrated that whereas the dimethyl esters of substituted vinylphosphonates are characterized as type IV substrates in alkene cross



Scheme 11: A proposed mechanism for the relay cross metathesis reaction of allyl vinylphosphonates.



Scheme 12: A proposed mechanism for the TBAI catalysed transesterification.



Scheme 13: A selective synthesis of mono-allyl phosphonates.

metathesis reactions and are unreactive, the corresponding allyl esters show significantly improved reactivity. The improved reactivity is attributed to relay step in the cross metathesis reaction mechanism.

Supporting Information

Supporting Information File 1

Experimental procedures, characterization data, ^{1}H and ^{13}C spectra for all new compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-10-201-S1.pdf]

References

1. Shabany, H.; Spilling, C. D. *Tetrahedron Lett.* **1998,** *39,* 1465–1468. doi:10.1016/S0040-4039(97)10837-1
2. De la Cruz, A.; He, A.; Thanavaro, A.; Yan, B.; Spilling, C. D.; Rath, N. P. *J. Organomet. Chem.* **2005,** *690,* 2577–2592. doi:10.1016/j.jorganchem.2004.11.019
3. Yan, B.; Spilling, C. D. *J. Org. Chem.* **2008,** *73,* 5385–5396. doi:10.1021/jo8004028
4. Rowe, B. J.; Spilling, C. D. *J. Org. Chem.* **2003,** *68,* 9502–9505. doi:10.1021/jo0351318
5. Yan, B.; Spilling, C. D. *J. Org. Chem.* **2004,** *69,* 2859–2862. doi:10.1021/jo035795h
6. Bandyopadhyay, S.; Dutta, S.; Spilling, C. D.; Dupureur, C. M.; Rath, N. P. *J. Org. Chem.* **2008,** *73,* 8386–8391. doi:10.1021/jo801453v
7. Roy, S.; Spilling, C. D. *Org. Lett.* **2010,** *12,* 5326–5329. doi:10.1021/ol102345v
8. Roy, S.; Spilling, C. D. *Org. Lett.* **2012,** *14,* 2230–2233. doi:10.1021/ol300597u
9. He, A.; Sutivisedsak, N.; Spilling, C. D. *Org. Lett.* **2009,** *11,* 3124–3127. doi:10.1021/ol900980s
10. Chatterjee, A. K.; Choi, T.-L.; Grubbs, R. H. *Synlett* **2001,** 1034–1037. doi:10.1055/s-2001-14654
11. Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003,** *125,* 11360–11370. doi:10.1021/ja0214882
12. De Albuquerque, I. L.; Galeffi, C.; Casinovi, C. G.; Marini-Bettolo, G. B. *Gazz. Chim. Ital.* **1964,** *94,* 287.
13. Galeffi, C.; Casinovi, C. G.; Marini-Bettolo, G. B. *Gazz. Chim. Ital.* **1965,** *95,* 95.

14. Craveiro, A. A.; da Costa Prado, A.; Gottlieb, O. R.; Welerson de Albuquerque, P. C. *Phytochemistry* **1970,** *9,* 1869–1875. doi:10.1016/S0031-9422(00)85606-X
15. Jurd, L.; Wong, R. Y. *Aust. J. Chem.* **1984,** *37,* 1127–1133. doi:10.1071/CH9841127
16. Sudarshan, K.; Aidhen, I. S. *Eur. J. Org. Chem.* **2013,** 2298–2302. doi:10.1002/ejoc.201300097
And references cited therein. See for the syntheses of (+) and (−)-centrolobine.
17. Colobert, F.; Des Mazery, R.; Solladié, G.; Carreño, M. C. *Org. Lett.* **2002,** *4,* 1723–1725. doi:10.1021/ol025778z
18. Prasad, K. R.; Anbarasan, P. *Tetrahedron* **2007,** *63,* 1089–1092. doi:10.1016/j.tet.2006.11.062
19. Hoye, T. R.; Jeffrey, C. S.; Tennakoon, M. A.; Wang, J.; Zhao, H. *J. Am. Chem. Soc.* **2004,** *126,* 10210–10211. doi:10.1021/ja046385t
20. Hoye, T. R.; Zhao, H. *Org. Lett.* **1999,** *1,* 1123–1125. doi:10.1021/ol990947+
21. Hoye, T. R.; Jeon, J. Metathesis Involving a Relay and Applications in Natural Product Synthesis. In *Metathesis in Natural Product Synthesis: Strategies, Substrates and Catalysts;* Cossy, J.; Arseniyadis, S.; Meyer, C., Eds.; Wiley VCH: Weinheim, Germany, 2010; pp 261–285.
22. Hansen, E. C.; Lee, D. *Org. Lett.* **2004,** *6,* 2035–2038. doi:10.1021/ol049378i
23. Hanson, P. R.; Stoianova, D. S. *Tetrahedron Lett.* **1998,** *39,* 3939–3942. doi:10.1016/S0040-4039(98)00728-X
24. Hanson, P. R.; Stoianova, D. R. *Tetrahedron Lett.* **1999,** *40,* 3297–3300. doi:10.1016/S0040-4039(99)00479-7
25. Timmer, M. S. M.; Ovaa, H.; Filippov, D. V.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron Lett.* **2000,** *41,* 8635–8638. doi:10.1016/S0040-4039(00)01511-2
26. Rivard, M.; Blechert, S. *Eur. J. Org. Chem.* **2003,** 2225–2228. doi:10.1002/ejoc.200300215
27. He, A.; Yan, B.; Thanavaro, A.; Spilling, C. D.; Rath, N. P. *J. Org. Chem.* **2004,** *69,* 8643–8651. doi:10.1021/jo0490090
28. Malla, R. K.; Bandyopadhyay, S.; Spilling, C. D.; Dutta, S.; Dupureur, C. M. *Org. Lett.* **2011,** *13,* 3094–3097. doi:10.1021/ol200991x
29. Trost, B. M.; Ball, Z. T.; Jöge, T. *J. Am. Chem. Soc.* **2002,** *124,* 7922–7923. doi:10.1021/ja026457l
30. Trost, B. M.; Li, C.-J. *J. Am. Chem. Soc.* **1994,** *116,* 10819–10820. doi:10.1021/ja00102a071
31. A reviewer suggested that perhaps dimer **27** is more efficiently formed from a sequence of unproductive cross metathesis (i.e., metal exchange) of ruthenium alkylidene **34** with either ethylene or allyl phosphonate **21a**, followed by homodimerization of the resulting vinyltetrahydropyran.
32. Sachnov, S. J.; Schulz, P. S.; Wasserscheid, P. *Chem. Commun.* **2011,** *47,* 11234–11236. doi:10.1039/c1cc14490a