ORGANIC LETTERS

2001
Vol. 3, No. 17
2765−2768

An Olefin Cross-Metathesis Approach to Vinylphosphonate-Linked Nucleic Acids

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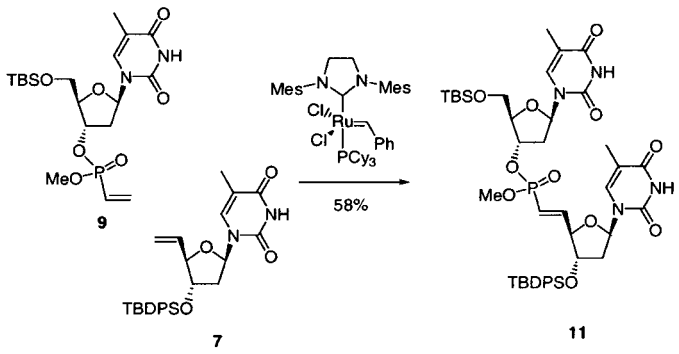
Received June 29, 2001

ABSTRACT



The synthesis of vinylphosphonate-linked nucleotide dimers has been achieved using an olefin cross-metathesis (CM) reaction as a key step. The 1,3-dimesityl-4,5-dihydroimidazol-2-ylidine-containing catalyst 5 (Grubbs' second-generation catalyst) was found to be the superior catalyst for this transformation. Both metathesis partners were readily available using known methodology, and the vinylphosphonate-linked dimer was produced with high levels of (*E*)-selectivity (>20:1) in 58% yield (70% based on recovered starting material).

As part of our ongoing research program examining the synthesis and biological applications of backbone-modified nucleic acids, we had reason to examine a novel approach to vinylphosphonate-linked nucleotide dimers. We have shown previously that these materials can be synthesized in good to excellent yields using a palladium-catalyzed coupling[1] to form the key phosphorus−carbon bond, and we wondered whether it would be possible to access this internucleotide linkage in a complementary manner using an olefin cross-metathesis reaction.

The development of readily available, stable, and well-defined metal-alkylidene catalysts has meant that olefin metathesis reactions have become a valuable tool in synthetic organic chemistry.[2] A large amount of recent work has focused upon the use of ring closing metathesis reactions (RCM) for the synthesis of a variety of medium to large carbo- and heterocyclic targets.[3] For many of these studies, the ruthenium-based catalysts **4** and **5**,[4] developed by Grubbs and co-workers, have been employed due to their excellent functional group tolerance and ease of use. In comparison, olefin cross-metathesis (CM)[5] has received much less synthetic attention even though it offers great potential for a range of intermolecular C═C bond constructions.

A number of excellent studies have recently appeared in the literature[6] which have shown that with the correct catalyst

(1) (a) Abbas, S.; Hayes, C. J. *Tetrahedron Lett.* **2000**, *41*, 4513. (b) Abbas, S.; Hayes, C. J. *Synlett* **1999**, 1124. (c) Lera, M.; Hayes, C. J. *Org. Lett.* **2000**, *2*, 3873.

(2) For general reviews, see: (a) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2076. (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (c) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371. (d) Furstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012 and references cited therein.

(3) For the synthesis of P-containing heterocycles, see: (a) Hetherington, L.; Greedy, B.; Gouverneur, V. *Tetrahedron* **2000**, *56*, 2053. (b) Bujard, M.; Gouverneur, V.; Mioskowski, C. *J. Org. Chem.* **1999**, *64*, 2119. (c) Hanson, P. R.; Stoianova, D. S. *Tetrahedron Lett.* **1998**, *39*, 3939.

(4) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

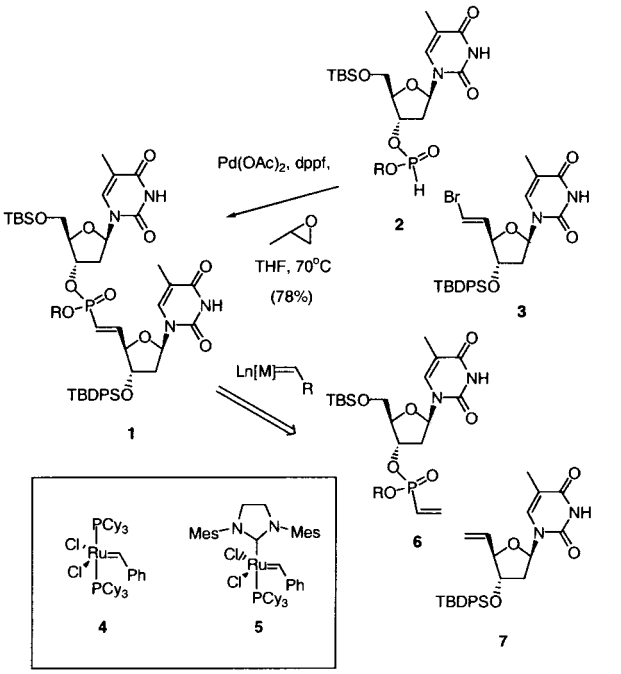
(5) (a) Crowe, W. E.; Goldberg, D. R. *J. Am. Chem. Soc.* **1995**, *117*, 5162. (b) Crowe, W. E.; Zhang, Z. J. *J. Am. Chem. Soc.* **1993**, *115*, 10998.

10.1021/ol016366d CCC: $20.00
Published on Web 08/02/2001

and reaction conditions CM can be used to access a variety of di- and trisubstituted[7] olefinic products in moderate to high yields with good *E*/*Z* ratios. Grubbs et al. have recently published a method for the synthesis of vinylphosphonates via an olefin cross-metathesis reaction,[8] and we now wish to report our own results in this area which have led to the formation of vinylphosphonate-linked nucleotide dimers.

Disconnection of the C=C bond of the vinylphosphonate **1** via a retro-cross-metathesis[9] reaction reveals the new vinylphosphonate **6** and the relatively simple alkene **7** as potential metathesis partners (Scheme 1). We anticipated that

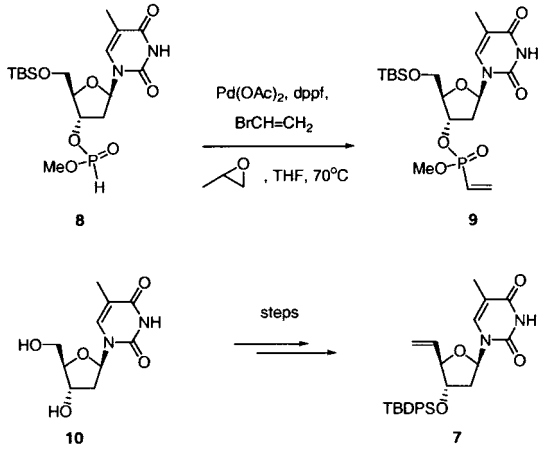
Scheme 1



6 could be synthesized from the corresponding *H*-phosphonate by coupling with vinyl bromide, using our previously developed palladium(0) chemistry and that the alkene **7** could be accessed using known methodology. The major advantage of this disconnection over the palladium-catalyzed cross-coupling approach is that we would now no longer need to worry about the alkene geometry (cf. **3**)[10] in either of our coupling partners, thus potentially simplifying their synthesis on large scale.

In a forward sense, the known *H*-phosphonate[11] **8** was reacted with commercially available vinyl bromide[12] utilizing a palladium(0)-catalyzed coupling reaction ($Pd(OAc)_2$ (0.10 equiv), Ph_3P (0.20 equiv), propylene oxide (17 equiv)) to afford the desired vinylphosphonate **9** in 64% yield (Scheme 2). Because of the volatility of both propylene oxide and

Scheme 2



vinyl bromide, the reaction was performed in a sealed, thick walled reaction vial at 70 °C (oil bath temperature) for 15 h. As the vinyl bromide was supplied as a solution in THF, no additional solvent was needed for this reaction. The remaining 1-alkene metathesis partner **7** was synthesized from thymidine **10** in five steps using previously reported procedures.[13]

With the two desired precursors in hand, we were now ready to study the key cross-metathesis reaction and we first examined the use of the catalyst **4** for this transformation. We found that when a solution of the 1-alkene **7** (1 equiv, 0.06 M in alkene), the vinylphosphonate **9** (1.25 equiv), and the catalyst **4** (20 mol %) in CH_2Cl_2 was heated at 35 °C for 16 h, none of the desired dimer **11** could be detected by TLC or ^1H NMR of the crude reaction mixture. Unreacted starting materials accounted for most of the mass balance of the reaction, and we were unable to find suitable conditions, using catalyst **4**, to achieve even modest conversion to the desired cross-metathesis product. This lack of reactivity may be associated with the formation of relatively stable chelate structures **A** → **C** (vide infra).[14]

(6) (a) Choi, T.-L.; Chatterjee, A. K.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 1277. (b) BouzBouz, Z.; Cossy, J. *Org. Lett.* **2001**, *3*, 1451. (c) 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. (d) Morgan, J. P.; Grubbs, R. H. *Org. Lett.* **2000**, *2*, 3153. (e) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783. (f) Verbicky, C. A.; Zercher, C. K. *Tetrahedron Lett.* **2000**, *41*, 8723.

(7) Chatterjee, A. K.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 1715.

(8) Chatterjee, A. K.; Choi, T.-L.; Grubbs, R. H. *Synlett* **2001**, 1034.

(9) For examples of the synthesis of vinylphosphonates via RCM, see: (a) Hanson, P. R.; Stoianova, D. S. *Tetrahedron Lett.* **1999**, *40*, 3297. (b) Timmer, M. S. M.; Ovaa, H.; Filippov, D. V.; van der Marel, G.; van Boom, J. H. *Tetrahedron Lett.* **2000**, *41*, 8635.

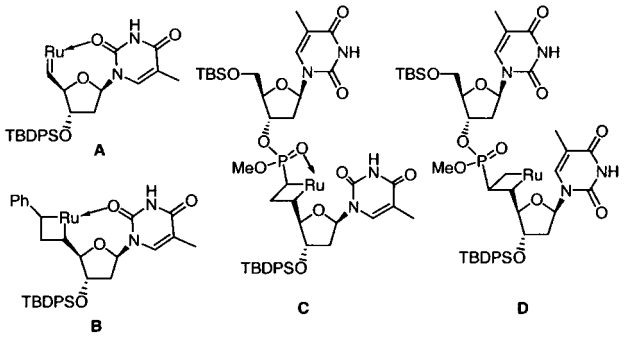
(10) On the basis of literature precedent, we would expect the proposed metathesis reaction to produce the (*E*)-vinylphosphonate, see ref 8.

(11) Used as a 1:1 mixture of diastereoisomers.

(12) Vinyl bromide is supplied as a 1.0 M solution in THF from the Aldrich Chemical Company.

(13) (a) von Matt, P.; Altmann, K.-H. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1553. (b) Fensholdt, J.; Wengel, J. *Acta Chem. Scand.* **1996**, *50*, 1157.

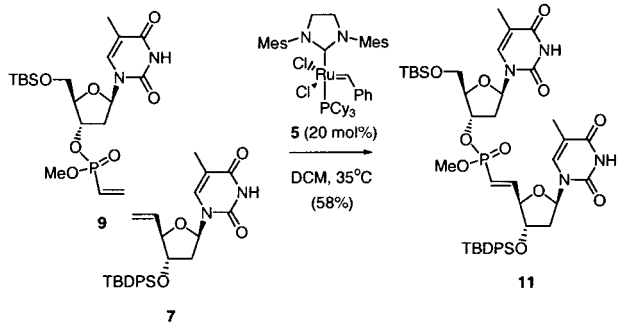
(14) For examples where chelation has been observed or proposed, see ref 6a and the following. (a) Feldman, J.; Murdzek, J. S.; Davis, W. M.; Schrock, R. R. *Organometallics* **1989**, *8*, 2260. (b) Furstner, A.; Langemann, K.. *J. Am. Chem. Soc.* **1997**, *119*, 9130. (c) Ghosh, A. K.; Cappiello, J.; Shin, D. *Tetrahedron Lett.* **1998**, *39*, 4651. (d) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J., Jr.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791.



Owing to this poor reactivity, we next decided to explore the use of the more electron rich 1,3-dimesityl-4,5-dihydroimidazol-2-ylidine-containing catalyst **5** for this process. It has been proposed that the more electron rich ruthenium center is less prone to chelate formation, and thus we would expect to see increased activity in comparison to catalyst **4**. Another advantage of having a more electron rich ruthenium center is that formation of the "productive" metallo-cyclobutane **D** (vide supra) should be relatively more facile, based upon electronic grounds, and once again, this should result in better catalyst turnover and increased yields of the desired cross-metathesis product.

Pleasingly, when a solution of the vinylphosphonate **9** (1.25 equiv), the 1-alkene **7** (1 equiv, 0.06 M in alkene), and the catalyst **5** (20 mol %) in CH_2Cl_2 was heated at 35 °C for 16 h, the desired cross-metathesis product **11** was formed in 58% isolated yield (70% based on recovered **7**), as a 1:1 mixture of diastereoisomers at phosphorus (Scheme 3). This product was identical in all respects to material that

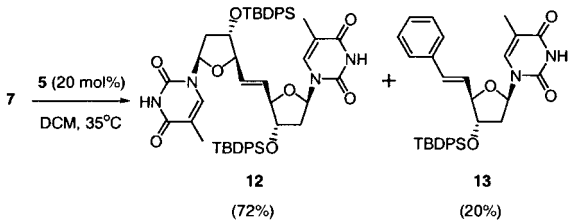
Scheme 3



we have prepared previously using a palladium(0)-catalyzed P−C═C cross-coupling reaction.[15] Analysis of the ^{1}H NMR clearly showed that the (*E*)-vinylphosphonate had been produced as the major compound, and we were unable to detect the corresponding (*Z*)-isomer. A number of other minor products were formed in this reaction which we believed were a combination of the products of benzylidene transfer from the catalyst **5** to **7** and **9** and the cross-metathesis of **7** with itself. To confirm these suspicions, we performed a series of control experiments examining the behavior of each of the cross-metathesis partners **7** and **9** to the reaction conditions.

First, we examined treatment of the 1-alkene **7** with the catalyst **5** (20 mol %) under conditions identical to those used for the successful cross-metathesis reaction (0.06 M in DCM, 35 °C, 14 h) and only two products were observed in the crude reaction mixture (Scheme 4). The major product

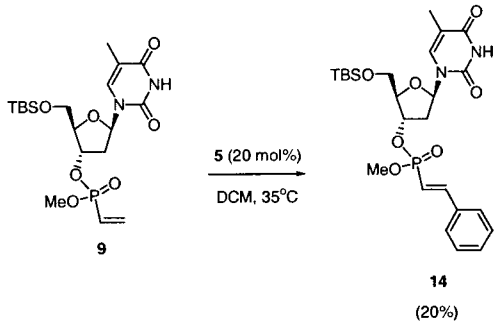
Scheme 4



was the homo-dimer **12** (5:1, *E*:*Z*), produced by cross-metathesis of **7** with itself in 72% yield.[16] The minor of the two products was the alkene **13** (20%) produced by transfer of the benzylidene group from the catalyst **5** to **7**. As we were using 20 mol % of catalyst, this latter product represents a quantitative transfer of the benzylidene moiety during catalyst activation.

We next exposed the vinylphosphonate **9** to the cross-metathesis conditions as described above (Scheme 5). In this

Scheme 5



case we saw no cross-metathesis of **9** with itself and instead observed formation of the new vinylphosphonate **14** as a 1:1 mixture of diastereoisomers at phosphorus in 20% isolated yield. The mass balance of the reaction was unreacted **9**. As seen earlier, the formation of **14** in 20% yield represents quantitative transfer of the benzylidene moiety during catalyst activation.

As a result of these reactions, we have been able to identify **12** (10%), **13** (15−20%), and **14** (<5%) as the minor products produced in the cross-metathesis of **7** and **9** (Scheme

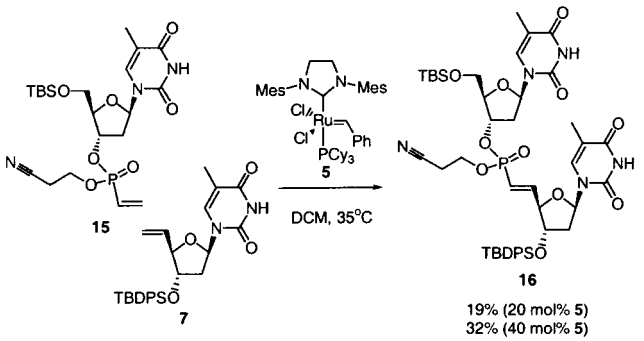
(15) See refs 1a and 1b for details.

(16) For another example of self-metathesis using nucleotide-derived alkenes, see: Batoux, N.; Benhaddou-Zerrouki, R.; Bressolier, P.; Granet, R.; Laumont, G.; Aubertin, A.-M.; Krausz, P. *Tetrahedron Lett.* **2001**, *42*, 1491.

3). On the basis of this, a number of potential ways of increasing the yield of the desired cross-metathesis product **11** can be envisaged. Perhaps the simplest is to use lower amounts of the benzylidene catalyst **5**, as this should inevitably reduce the amount of the phenyl-substituted alkene **13** being produced, thus leaving more of the alkene **7** to undergo productive metathesis. In practice, however, lower catalyst loadings (1−5 mol %) just resulted in very sluggish reactions and low conversions. A second way to improve the yield of **11** could be to use a larger excess (2−3 equiv) of either of the metathesis partners **7** or **9**. This approach has found application in a number of studies reported in the literature but is only practical when one of the alkenes is readily available in quantity. In our case, both alkenes are produced using multistep routes and in this situation it is desirable to use them in near equimolar amounts.

In anticipation of preparing building blocks suitable for solid-phase oligonucleotide synthesis, we carried out a preliminary study to assess the compatibility of the cyanoethyl-phosphate protecting group with the metathesis conditions. The required vinylphosphonate **15** was synthesized in a manner similar to that described for the methyl-protected analogue **9**. A solution of **7**, **15**, and the catalyst **5** (20 mol %) in CH_2Cl_2 was then heated at 35 °C, under conditions identical to those used previously for the successful cross-metathesis of **7** and **9** (Scheme 6). From this reaction we were able to isolate 19% of the desired cross-metathesis product **16**, with the mass balance consisting largely of unreacted starting materials and **13**. We suspected that the 19% yield represented just under one catalytic turnover, and in order to confirm this we performed the same reaction using 40 mol % of the catalyst **5**. Under these conditions we now obtained a 32% isolated yield, with the mass balance once again being unreacted starting materials and **13**. From these results, it appears that the introduction of the cyanoethyl group has adversely affected catalyst turnover. At present we are not sure about the nature of this effect, but it is tempting to speculate that the Lewis basic nitrile is involved in chelate formation, thus deactivating the catalyst.

Scheme 6



In conclusion, we have shown that an olefin cross-metathesis reaction can be used to access vinylphosphonate-linked nucleotide dimers. We have shown that the more electron-rich catalyst **5** is particularly well suited to this task, both in terms of activity and functional group compatibility. We are now examining the scope and limitations of this methodology for the synthesis of dimers containing the other heterocyclic nucleotide bases and alternative phosphonate protecting groups, and these results will be published in due course.

Acknowledgment. The authors thank the Nuffield Foundation (NUF-NAL), AstraZeneca, Pfizer Central Research, and the School of Chemistry, University of Nottingham, for financial support.

Supporting Information Available: Experimental procedures and characterization data for all new products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL016366D