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The Shortest Strategy for Generating Phosphonate Prodrugs by Olefin Cross-Metathesis – Application to Acyclonucleoside Phosphonates

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A short synthetic route to phosphonate prodrugs by olefin cross-metathesis, which uses either (acyloxymethyl) or (hexadecyloxypropyl) allylphosphonate building blocks is described. A study of eight ruthenium catalysts including the Ru–indenylidene catalyst, which bears the N-heterocyclic carbene 1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene, was undertaken. This method was applied to the synthesis of acyclonucleoside phosphonate prodrugs. This strategy is appealing for further uses in pharmaceutical and medicinal research.

Introduction

Phosphonates are present as pharmacophores in various classes of biologically important molecules. These biological agents include some antiviral[1] and anticancer nucleotides,[1b] inhibitors of the biosynthesis of cholesterol,[2] and bisphosphonates for the treatment of osteoporosis[3] or angiotensis-converting enzyme inhibitors.[4] However, of all the phosphonate molecules that are synthesized to be used as therapeutic agents, only a few have led to efficient drugs. One reason is a lack of activity due to the low bioavailability of the drugs, which are salts at physiological pH. Thus, medicinal chemists have designed a variety of biolabile promoieties to mask phosphonate groups by derivatization of the phosphorus-coupled oxygen atom(s) to form neutral ester(s), which significantly decrease the polarity of the compounds.[1,5] Once inside the targeted cell or tissue, the prodrug moiety is cleaved chemically or enzymatically to release the corresponding free-acid phosphonate and achieve a desirable biological effect. One of the most commonly used types of prodrug for phosphonates is the acyloxyalkyl ester, e.g. pivaloyloxymethyl (POM) ester or isopropyloxycarbonyloxymethyl (POC) ester.[6] This approach, pioneered by Farquhar et al.,[7] has been applied to numerous nucleotides. Two antiviral phosphonates are currently marketed by Gilead against hepatitis B (adefovir dipivoxil) and HIV (tenofovir disoproxil fumarate).[8a,8b] The bis(POM) nucleotide analogue LB-80380 is currently undergoing phase II clinical trials as a new agent for hepatitis B.[8c] More recently, a number of reports from Hostetler et al.[9] on lipid monoesters of nucleotide phosphonates, such as octadecyloxyethyl cidofovir (ODE-CDV) and the hexadecyloxypropyl (HDP) ester of HPMPA [HDP-(*S*)-HPMPA] (Figure 1), have been published.

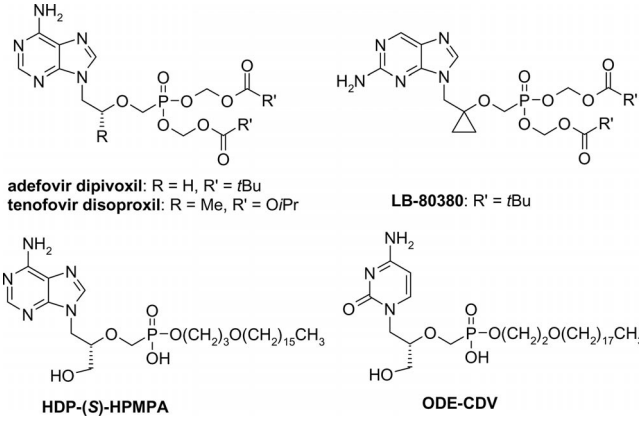

Figure 1. Some nucleoside phosphonate prodrugs.

Application of acyloxyalkyl ester prodrugs to non-nucleoside monophosphate or phosphonate esters led to the bis(POM) squalene synthase inhibitor BMS-188494,[10] which has been developed for hypercholesterolemia. The bisphosphonate tris(POM) prodrug ER-27856 (Figure 2) is a squalene synthase inhibitor[11] and the bis(POM) prodrug of FR900098 is has better oral bioavailability than the parent antimalarial agent.[12]

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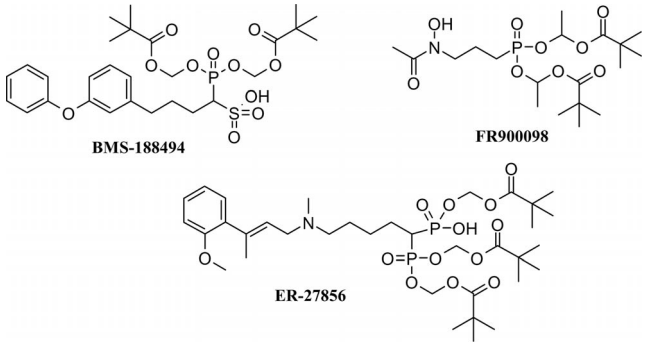


Figure 2. Various non-nucleoside prodrugs that bear an acyloxyalkyl ester.

However, the synthesis of these phosphonate prodrug derivatives is tedious and low yielding. Their synthesis commonly involves deprotection of the bis(alkyl)phosphonate with tetramethylsilyl bromide followed by conversion of the acid phosphonate by double alkylation. This procedure usually proceeds in very low (less than 10%) to moderate yields (up to 30%) depending on the substrate. Thus, given the increasing interest in generating masked phosphonate derivatives as biological tools and antiviral agents and in response to this challenge, we hypothesized that it may be possible to prepare and use hitherto unknown bis(acyloxyalkyl) allylphosphonate reagents [e.g. bis(POM), bis(POC), and (HDP/POC) allylphosphonates] to generate phosphonate prodrugs under olefin cross-metathesis conditions.

Over the past decade, ruthenium-mediated olefin metathesis, which includes polymerization reactions, cross-metathesis (CM), ring-closing metathesis, enyne metathesis, ring-rearrangement metathesis, and tandem processes, has been one of the most studied types of organic reaction.[13] Such expansion has been punctuated by the groundbreaking developments of various well-defined ruthenium–carbene complexes. Among them, benzylidene complexes **1**[14] and Hoveyda–Grubbs-type catalysts **2**[15] are the most widely used (Figure 3). Nevertheless, other types of catalysts have been found to exhibit comparably good catalytic activity, and one of the most important alternative classes of complexes includes the indenylidene-framework complexes **3**.[16]

Further improvements to these complexes was achieved by the introduction of *N*-heterocyclic carbenes (NHCs) as ligands in organometallic chemistry.[17] Thus, well-known 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene (IMes) and 1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene (SIMes) were introduced to the ruthenium center of both benzylidene and indenylidene catalysts, which led to **1b**,[18] **1c**,[19] and **3b**[20] (Figure 3).

Second-generation Ru complexes bearing NHC ligands resulted in an increased thermal stability of the 14-electron active species, which consequently led to improved catalyst activity, especially for sterically demanding substrates when elevated temperatures are required. As a result, various other NHC ligands have been appended to the Ru center, such as sterically hindered[21] 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (IPr) and 1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene (SIPr), which led to **1d**[22] and **1e**[23] in the benzylidene series, **3d** in the indenylidene series, and other NHC complexes.[24] Although differences of reactivity between the first- and second-generation catalysts are well established for both the benzylidene and indenylidene complexes, the influence of IMes, SIMes, IPr, and SIPr remain scarcely investigated for benzylidene and indenylidene complexes.[25,26]

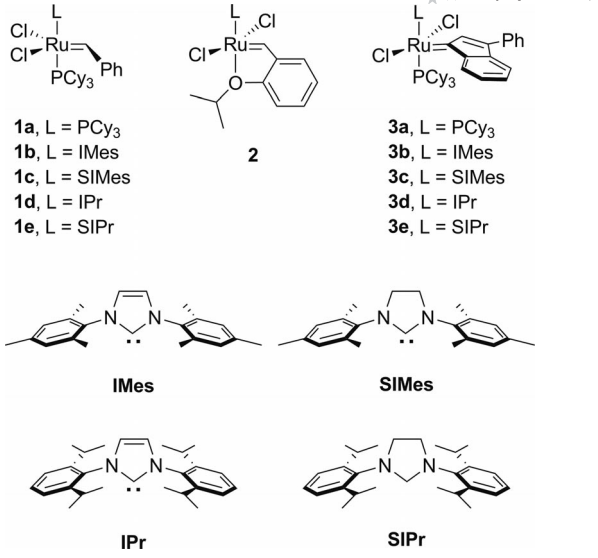


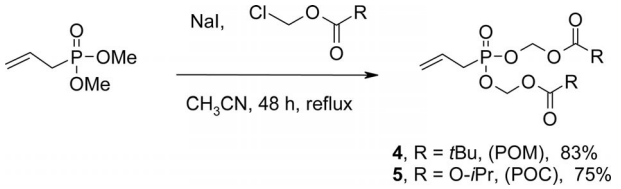
Figure 3. Some Ru-based metathesis catalysts.

To increasing interest[27] of the use of cross-coupling metathesis for one-step coupling of phosphonate moieties, we report the use of olefin cross-metathesis as the key step for the introduction of bis(POM)-, bis(POC), and (POC/HDP) groups to the phosphonate moiety in order to target new or improved biological activities. To the best of our knowledge, few examples have been reported that use allylphosphonates as precursors in cross-coupling metathesis.[28] Among these investigations, Grubbs et al. have disclosed an efficient CM reaction involving dihydrocarbyl allylphosphonate in the presence of **1c** and the use of nonbulky alkyl groups such as methyl or ethyl.[29] On the other hand, CM product yield is substrate dependant and the presence of bulky groups decreases CM reactivity and *trans* selectivity.[30] Furthermore, acyloxyalkyl ester phosphonates such as POC are unstable due to the possible nucleophilic attack of water at the carbonyl center and phosphorus atom at 37 °C and pH 7.[31] On the basis of these considerations, which could hamper CM efficiency, we hypothesized that CM reactions could be Ru-catalyst dependant. The evaluation of the catalytic efficiency of eight Ru catalysts (**1a**, **1b**, **1d**, and **3a**–**e**), including the Ru–indenylidene catalyst that bears SIPr (**3e**), for the CM reaction between our phosphonate synthons (**4**, **5**, and **13**) and N^1-crotylated-C^5-substituted uracils, which were chosen as representative of the class of therapeutic molecules.

Results and Discussion

The bis(POM) allylphosphonate **4** and bis(POC) derivative **5** were synthesized from dimethyl allylphosphonate by

reaction of chloromethyl pivalate (POM–Cl) and chloromethyl isopropyl carbonate in the presence of sodium iodide, in 83 and 75% yield, respectively (Scheme 1).[32] Although POM–Cl is commercially available, chloromethyl isopropyl carbonate was synthesized quantitatively by the reaction of isopropyl alcohol and chloromethyl chloroformate. This compound was used without purification and could be stored over molecular sieves.



Scheme 1. Synthesis of **4** and **5**.

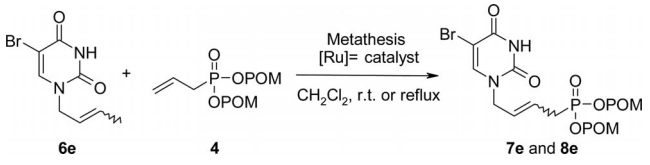
Following our previously reported synthesis of acid phosphonate derivatives by olefin cross-metathesis,[28e] in which N^1-crotylated 5-bromouracil **6e** was treated with **4** (1.5 equiv.) in the presence of 5 mol-% **1b** in dichloromethane from r.t. to 40 °C over 24 h, total degradation of the starting materials occurred. With these data in hand, we focused on catalyst screening of eight first- and second-generation catalysts that bear either a benzylidene (**1**) or an indenylidene (**3**) moiety. First-generation catalysts **1a** and **3a** bear two PCy_3 ligands, and second-generation **1b**, **1d**, and **3b**–**e** bear four different NHCs, which are unsaturated IMes (**1b** and **3b**) and IPr (**1d** and **3d**) and saturated SIMes (**3c**) and SIPr (**3e**). These eight catalysts were compared both at r.t. and 40 °C to determine the optimum reaction conditions. By closely examining these catalytic results, the complex efficiency can be compared to determine the influence of ligand (PCy_3 vs. NHC), alkylidene (benzylidene vs. indenylidene), NHC scaffold (imidazolylidene vs. imidazolinylidene), and nature of the substituent ancillary ligand (IMes vs. IPr).

Cross-Metathesis with 4

Catalyst screening of the CM reaction was first carried on **4** and **6e** at r.t. and 40 °C (Table 1). The importance of reaction time was crucial in leading to useful yields by finding the best compromise between formation of the product and its degradation.

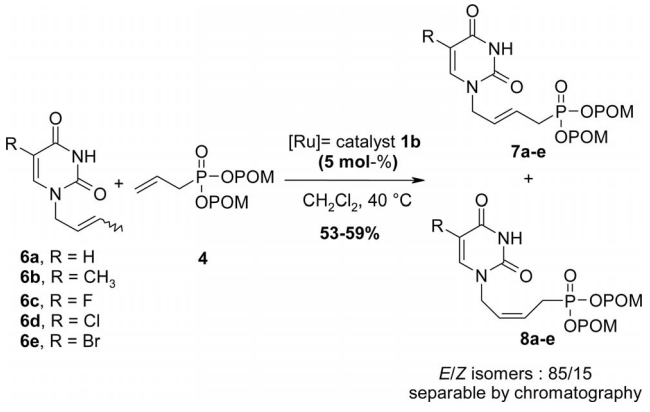
It appears from these data that: (1) **1a** and **3a** (Entries 1 and 2) do not afford the expected products at r.t. or 40 °C even after 24 h. The high catalyst generation instability is a possible cause for its inefficiency and (2) catalysts that bear a NHC substituent (having a strong σ donor effect) such as IMes (**1b**, **3b**) or SIMes (**3c**) resulted in trace product at r.t. but led to **7e** and **8e** in good yields (ca. 70%) at 40 °C (Entries 3–5). The catalysts that bear IPr (**1d** and **3d**) and SIPr (**3e**)[33] possess catalytic activity at r.t. (Entries 6–8), which affords moderate product yields (ca. 50%), whereas only low yields (Entry 8) were obtained at 40 °C, which is presumably due to an increase in catalyst decomposition. These results show that **1b**, **3b**, and **3c** are the most efficient

Table 1. Catalyst efficiency for CM reaction between **4** and **6e**.



Entry	Catalyst	Yield [%], (*t* [h]) at r.t.	at 40 °C
1	**1a**	no reaction	no reaction
2	**3a**	no reaction	no reaction
3	**1b**	low conversion	69, (0.3)
4	**3b**	trace	74, (4)
5	**3c**	trace	71, (3)
6	**1d**	50, (1)	–
7	**3d**	54, (1.5)	–
8	**3e**	47, (1)	36, (1)

for CM with **4** and provide similar yields. However, an important difference in reaction kinetics was observed as a function of the alkylidene moiety. Although benzylidene **1b** results in 69% yield in 20 min, indenylidene **3b** and **3c** require 4 and 3 h to give the products in 74 and 71% yield, respectively. The saturation or unsaturation of the NHC ligand does not appear to influence the catalyst efficiency or kinetics. Thus, optimized conditions using **1b** at 40 °C were employed for the synthesis of acyclonucleoside phosphonates **7a**–**e** and **8a**–**e**. The products were obtained in good yields (53–69%) in reaction times ranging from 30 min to 1 h (Scheme 2). This reaction led to the desired C^5-substituted uracil acyclonucleoside phosphonate bis(POM) prodrugs as separable mixtures of *E*/*Z* isomers with the more thermodynamically stable *E* isomer as the major product (ca. 4:1 *E*/*Z*). Due to the superposition of the olefinic proton signals in the ^{1}H NMR spectra, the *E*/*Z* stereochemistry at the double bond was assigned from the ^{13}C NMR spectra by observing the allylic carbon atom signals (NCH_2), which were at 49.4 ppm for the *E* isomer and 44.9 ppm for the *Z* isomer. This is in agreement with Goux et al.,[34] who reported a NCH_2 signal at 48 ppm for the *E* isomer, whereas the *Z* isomer signal moved upfield to 44 ppm in similar systems. Isomer separation was con-



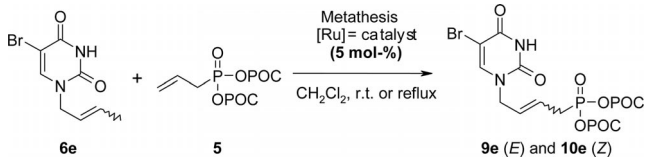
Scheme 2. Optimized CM of **4** with **6a**–**e**.

firmed by ^{1}H, ^{13}C, and, especially, ^{31}P NMR spectroscopy. The pure compounds exhibit only one signal compared with two signals for the isomer mixtures.

Cross-Metathesis with 5

The known instability of carbonates highlights the need for milder optimized reaction conditions; thus the catalyst screening was repeated with **6e** and **5** (Table 2). Only the second-generation catalysts found to be efficient in the reaction with **4** were further evaluated (Table 1).

Table 2. Catalyst efficiency for CM reaction between **5** and **6e**.



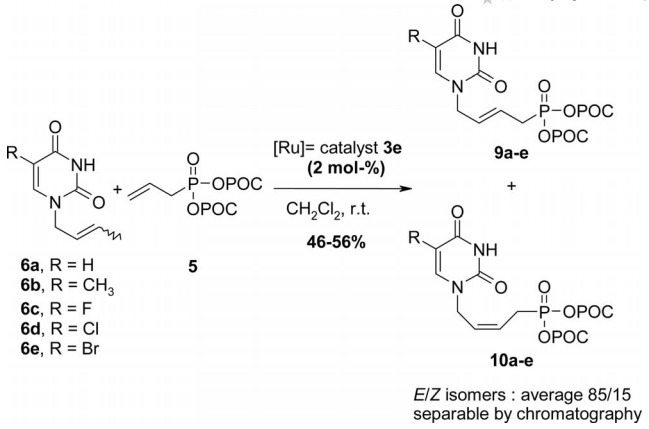
Entry	Catalyst	Yield [%], (*t* [h]) at r.t.	at 40 °C
1	**1b**	trace	36, (18)
2	**3b**	trace	59, (18)
3	**3c**	trace	29, (18)
4	**1d**	44, (0.5)	–
5	**3d**	46, (0.5)	–
6	**3e**	46, (0.5)	23, (18)

Benzenylidene **1b** and indenylidene **3b** and **3c** (Entries 1–3) were found to be inefficient at r.t. but gave the desired cross-metathesis product in low (29%) to good yield (59%) at 40 °C in 18 h (Entries 1–3). Catalysts **1d**, **3d**, and **3e** allowed the isolation of products **9e** and **10e** in moderate yields (ca. 45%) in a shorter reaction time (30 min) and at r.t. (Entries 4–6). The results in Table 2 highlight the thermal tolerance of **5** in the cross-metathesis reaction.

With the aim of minimizing reaction times and increasing the yields, we investigated the effects of **3e** loading from 5–3.5 mol-%. Whereas catalyst loadings of 2, 3.5, or 5 mol-% do not seem to affect the reaction kinetics, a 1 mol-% catalyst loading dramatically decreased the yield to 33% even after an extended reaction time (1 h). A 2 mol-% catalyst loading slightly increased the yield to 56%. Catalyst **3e** was selected to perform the reaction with a 2 mol-% catalyst loading at r.t. These conditions were used to obtain the bis(POC) prodrugs **9a**–**e** and **10a**–**e** in moderate yields (46–56%) at r.t. (Scheme 3). Catalysts **1d** and **3d** can also be used at r.t., and **3b** at 40 °C.

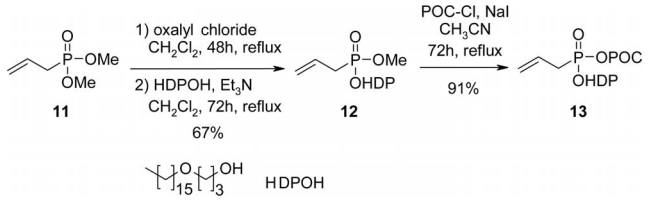
Cross-Metathesis with (HDP/POC) Allylphosphonate (13)

To complete and diversify our series, we were interested in the modification of the biolabile protecting group to deliver the first example of a mixed HDP/POC prodrug. Moreover, the POC group was found to be selectively cleavable to give HDP prodrugs. Thus, dimethyl allylphosphonate **11** was monochlorinated with oxalylchloride under classical conditions, and subsequent substitution of the



Scheme 3. Optimized CM of **5** with **6a**–**e**.

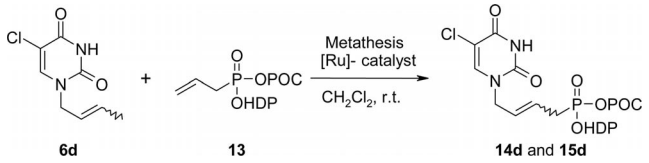
chlorinated phosphonate by HDP–OH[35] resulted in (methyl/HDP) allylphosphonate **12** in 67% yield. It was then possible to implement the high reactivity of the methyl group under NaI/POC–Cl conditions to introduce the POC group selectively, which led to (HDP/POC) allylphosphonate **13** in 91% yield (Scheme 4).



Scheme 4. Synthesis of **13**.

Based on the CM experiments with **5**, only the second-generation catalysts were screened at r.t. with **13** using a 5 mol-% catalyst loading. As seen previously, **1d** and **3d** (bearing IPr) and **3e** (with SIPr) efficiently gave the products in ca. 50% yield at r.t. A 2 mol-% catalyst loading of **1d**, **3d**, and **3e** led to a slight decrease in yields (Table 3).

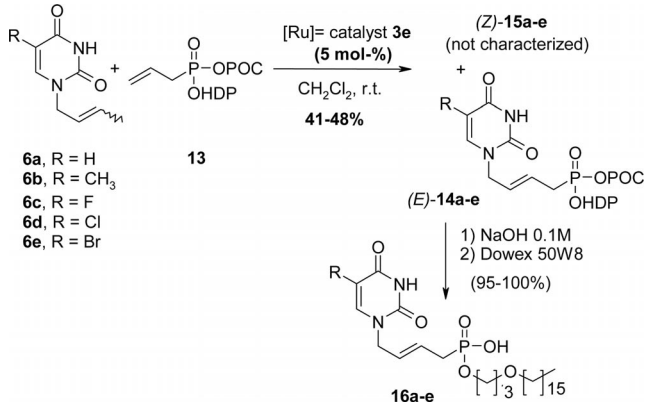
Table 3. Catalyst efficiency for CM reaction between **13** and **6d** at r.t.



Entry	Catalyst	Yield [%], (*t* [h])
1	**1b**	low conversion
2	**3b**	trace
3	**1d**	47, (0.5)
4	**3d**	50, (0.75)
5	**3e**	48, (0.5)

Thus, the optimized synthesis of 5′-substituted (HDP/POC)butenylacyclonucleoside phosphonates **14a**–**e** and **15a**–**e** was achieved by cross-metathesis in the presence of 5 mol-% **3e** in less than 1 h at r.t. (Scheme 5). These compounds were obtained in moderate yields (41–48%) as sepa-

rable *E*/*Z* mixtures (8:1). Unfortunately, the *Z*-isomers were always contaminated with **13**, which precluded their complete characterization.



Scheme 5. Optimized CM of **13** with **6a**–**e**.

Finally, the HDP/OH prodrugs **16a**–**e** were obtained from saponification of the POC protecting group of **14a**–**e** with a 0.1 M sodium hydroxide solution in ultrapure water for 4 h. The unstable carbonate anion underwent spontaneous chemical degradation, which resulted in the HDP phosphonate sodium salt, carbon dioxide, and formaldehyde. After neutralization with acidic ion exchange resin and evaporation of the volatile components, pure HDP/OH phosphonates **16a**–**e** were isolated in excellent yield (95–100%) without further purification. This procedure, which is based on the in situ degradation of POC moiety, allows the preparation of HDP/OH phosphonates in high yield and without further purification.

Conclusions

We report the first use of the cross-metathesis reaction of olefins that bear biolabile groups to convert therapeutic molecules into their prodrug forms. We believe that the use of either bis(POM)-, bis(POC)-, or (HDP/POC) allylphosphonates in the generation of phosphonate diester prodrugs under olefin cross-metathesis conditions represents a significant advance over previous approaches to bis(acyloxymethyl)-containing phosphonate compounds. We have performed a comparative study of Ru-based benzylidene and indenylidene bisphosphane, IMes, SIMes, IPr, and SIPr catalysts for this reaction. Their activities have been compared and we have underlined the important influence of NHC substitution on the catalyst operational conditions. We have shown the tolerance of biolabile groups to CM conditions, which could be a remarkable breakthrough for the conversion of prodrugs to molecules of therapeutic interest. The optimized reaction conditions for CM of **4** with crotylated nucleobases make use of IMes benzylidene catalyst **1b** at 40 °C; whereas the new SIPr indenylidene catalyst **3e** was used at r.t. to obtain bis(POC) phosphonate derivatives. Among the synthesized compounds, only *E* isomers exhibit significant antiviral properties against a variety of DNA viruses. For instance, **7b** showed pronounced antiviral activities against HSV-1, HSV-2, VZV TK$^+$, and VZV TK$^-$ with EC_{50} values of 3.1, 6.1, 0.41, and 0.19 μM, respectively.[36] Given the increasing interest in generating masked phosphonate derivatives as biological tools and antiviral agents, we are currently applying our cross-metathesis conditions with bis(acyloxymethyl) allylphosphonates to a wide range of important biological systems.

Experimental Section

General: All nonaqueous reactions were performed in oven-dried glassware under nitrogen. All commercial chemical reagents were used as supplied. The reactions were monitored by TLC, visualized by UV radiation (254 nm) or by spraying with 5% ethanolic H_2SO_4 in ethanolic solution and subsequent warming with a heat gun. Catalyst synthesis was performed in a glovebox containing dry argon and less than 1 ppm oxygen or under Schlenk conditions. Complexes **1b**,[14] **1d**,[15] and **3b**[16] were synthesized according to previously described procedures. 5-Substituted N^1-crotyluracils **6a**–**e**[36] were synthesized according to previously described procedures. Flash column chromatography was performed on silica gel 60 (230–400 mesh). The compounds were characterized by ^{1}H, ^{13}C, and ^{31}P NMR (Supporting Information). HRMS was conducted using the ESI technique.

Syntheses of Allylphosphonate-Bearing Acyloxyalkyl Esters or Ethers

Bis(POM) Allylphosphonate (4): To a CH_3CN (18 mL) solution of dimethyl allylphosphonate (2.6 g, 17.3 mmol) and anhydrous sodium iodide (5.2 g, 34.6 mmol) was added chloromethyl pivalate (6.58 g, 43.3 mmol). The solution was heated to reflux with stirring for 48 h under a positive pressure of dry Ar. After cooling, the solution was added to diethyl ether (170 mL) and washed with water (35 mL). The organic layer was dried with magnesium sulfate, evaporated, and purified by silica gel column chromatography (EtOAc/petroleum ether, 1:4) to give 5.02 g (14.6 mmol, 83%) of pure **4** as a slightly yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.74–5.57 (m, 5 H), 5.22–5.14 (m, 2 H), 2.64 (dd, J = 22.6, 7.3 Hz, 2 H), 1.16 (s, 18 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.6, 125.8, 125.7, 121.0, 120.9, 81.4, 81.3, 38.6, 32.7, 31.3, 26.7 ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 27.71 ppm. HRMS: calcd. for $C_{15}H_{27}O_7PNa$ [M + Na]$^+$ 373.1392; found 373.1402.

Bis(POC) Allylphosphonate (5): To a CH_3CN (23 mL) solution of dimethyl allylphosphonate (3.4 g, 22.6 mmo1) and anhydrous sodium iodide (6.8 g, 45.2 mmol) was added chloromethyl isopropyl carbonate (8.50 g, 56.7 mmol). The solution was heated to reflux with stirring for 48 h under a positive pressure of dry Ar. After cooling, the solution was added to diethyl ether (220 mL) and washed with water (45 mL). The organic layer was dried with magnesium sulfate, evaporated, and purified by silica gel column chromatography (EtOAc/petroleum ether, 1:4) to give 5.75 g (16.9 mmol, 75%) of pure **5** as a slightly yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.82–5.71 (m, 1 H), 5.68 (dd, J = 11.6, 5.4 Hz, 2 H), 5.65 (dd, J = 11.6, 5.4 Hz, 2 H), 5.30–5.22 (m, 2 H), 4.94 (m, J = 6.2 Hz, 2 H), 2.74 (tdd, J = 22.8, 7.4, 1.1 Hz, 2 H), 1.33 (d, J = 6.28 Hz, 12 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.2, 125.7, 125.6, 121.3, 121.2, 84.1, 84.0, 73.2, 32.9, 31.5, 21.6 ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 27.99 ppm. HRMS: calcd. for $C_{13}H_{23}O_9PNa$ [M + Na]$^+$ 377.0977; found 377.0990.

(HDP/POC) Allylphosphonate (13): To a CH_3CN (5 mL) solution of (Me/HDP) allylphosphonate **12** (2 g, 4.8 mmo1) and chlo-

romethyl isopropyl carbonate (1.10 g, 7.2 mmol) was added anhydrous sodium iodide (755 mg, 5.0 mmol). The solution was heated to reflux with stirring for 72 h under a positive pressure of dry Ar. After cooling, the solution was added to diethyl ether (100 mL) and washed with water (20 mL). The organic layer was dried with magnesium sulfate, evaporated, and purified by silica gel column chromatography (EtOAc/petroleum ether, 1:3) to give 2.27 g (4.4 mmol, 91%) of **13** as a slightly yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.82–5.68 (m, 1 H), 5.68–5.58 (m, 1 H), 5.26–5.17 (m, 2 H), 4.91 (m, J = 6.3 Hz, 2 H), 4.24–4.07 (m, 2 H), 3.47 (t, J = 6.2 Hz, 2 H), 3.37 (t, J = 6.7 Hz, 2 H), 2.67 (dd, J = 22.4, 7.4 Hz, 2 H), 1.91 (m, J = 6.3 Hz, 2 H), 1.57–1.49 (m, J = 6.9 Hz, 2 H), 1.33–1.20 (m, 32 H), 0.86 (t, J = 6. 7 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.2, 126.6, 126.5, 120.6, 120.5, 84.4, 84.3, 73.0, 71.2, 66.5, 63.3, 32.7, 31.9, 31.3, 30.7, 29.7, 29.6, 29.5, 29.3, 26.1, 22.7, 21.6, 14.1 ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 26.7 ppm. HRMS: calcd. for $C_{27}H_{53}O_7PNa$ $[M + Na]^+$ 543.3427; found 543.3435.

Typical Procedure for Cross-Metathesis with 4: To a CH_2Cl_2 (25 mL/mmol) solution of a 5-substituted N^1-crotyluracil **6a**–**e** (1 equiv.) and **4** (1.3 equiv.) was added **1b** (5 mol-%). The solution was heated to reflux gently under a positive pressure of dry Ar, and the reaction was monitored by TLC. After evaporation of all volatiles, the residue was purified by silica gel column chromatography (EtOAc in hexanes) and the desired compounds were isolated as (*E*)-**7a**–**e** and (*Z*)-**8a**–**e**.

General Procedure for Cross-Metathesis with 5: To a CH_2Cl_2 (25 mL/mmol) solution of **6a**–**e** (1 equiv.) and **5** (1.3 equiv.) was added **3e** (2 mol-%). The solution was stirred at r.t. under a positive pressure of dry Ar, and the reaction was monitored by TLC. After evaporation of all volatiles, the residue was purified by silica gel column chromatography (EtOAc in hexanes) and the desired compounds were isolated as (*E*)-**9a**–**e** and (*Z*)-**10a**–**e**.

General Procedure for Cross-Metathesis with 13: To a CH_2Cl_2 (8 mL) solution of **6a**–**e** (0.30 mmol) and **13** (0.39 mmol) was added **3e** (15.7 mg, 0.015 mmol). The solution was stirred at r.t. for 1 h under a positive pressure of dry Ar. After evaporation of all volatiles, the residue was purified by silica gel column chromatography (pure EtOAc) to obtain pure (*E*)-**14a**–**e** and the respective *Z* isomers.

General Procedure for Selective POC Deprotection of HDP/POC Nucleosides 14a–e: One of the (HDP/POC) acyclic nucleotide analog **14a**–**e** was added to a 0.1 M solution of sodium hydroxide in deionized water (70 mL/mmol). The solution was stirred vigorously at r.t. for 4 h. The basic solution was neutralized with acidic DOWEX resin 50W8 and washed twice with CH_2Cl_2 (20 mL/mmol). The desired pure products **16a**–**e** were directly obtained after evaporation of the volatiles.

Supporting Information (see footnote on the first page of this article): ^{1}H, ^{13}C, and ^{31}P NMR spectra of all new compounds.

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