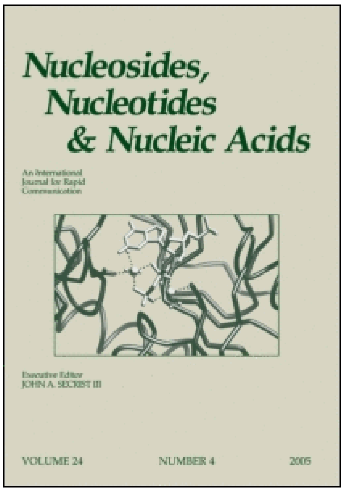

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Cross-Metathesis Mediated Synthesis of New Acyclic Nucleoside Phosphonates

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CROSS-METATHESIS MEDIATED SYNTHESIS OF NEW ACYCLIC NUCLEOSIDE PHOSPHONATES

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□ *With the commercial availability of well-defined ruthenium metathesis catalysts which combine high stability and broad functional group compatibility, olefin metathesis is now routinely integrated in various syntheses. We will report here the overwhelming power and scope of cross-metathesis in the area of new acyclic nucleoside phosphonates. Scope and limitations of this approach, and especially the E/Z stereocontrol, are discussed on selected examples from our drug discovery group.*

Keywords Acyclic nucleoside phosphonate; cidofovir; cross-metathesis

INTRODUCTION

The emergence of life threatened viral diseases has driven chemistry for the development of nucleosides. Acyclic nucleoside phosphonates—possessing the biologically stable carbon-phosphorus bond—are analogs of acyclic nucleotide monophosphates and do not require initial phosphorylation by kinase. Several acyclic nucleoside phosphonates show excellent therapeutic potential, such as PMEA, PMPA for the therapy of HSV, VZV,

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CMV, and AIDS, including thymidine-kinase deficient strains. The cidofovir recently was reported to be a potent antiviral agent with activity against several DNA viruses that cause coetaneous disease, including poxviruses. Nevertheless, cidofovir suffers from severe side effects and poor bioavailability. Thus, as part of an on-going program on smallpox, we will detail the synthesis and the biological data of several hitherto unknown acyclic nucleoside phosphonates related to cidofovir and analogs. Many variations, both on the heterocycle have been done through Pd(0) chemistry. The introduction of vinyl or allyl phosphonate moiety has been realized through an olefin cross-metathesis reaction.

RESULTS AND DISCUSSION

Over the past decade, olefin metathesis has become a powerful tool for advanced organic synthesis.[1] This mainly is due to the introduction of either the alkoxy imido molybdenum catalyst, [**Mo**], developed by Schrock[2] and various ruthenium carbene catalysts such as those developed by Grubbs,[3] [**Ru**]-**I**, [**Ru**]-**II**, the Hoveyda, [**Ru**]-**III**, the Hoveyda-ligand modified Grubbs catalyst, [**Ru**]-**IV**,[4] the ruthenium catalyst bearing an imidazolydidene developed by Nolan,[5] [**Ru**]-**V** (Figure 1).

Phosphorus containing compounds have gained considerable attention due to the diverse biological profile, such as the antiviral acyclic nucleoside phosphonates. The Michaelis-Arbuzov reaction between organic halides and trialkyl phosphates is used primarily for the synthesis of allylphosphonates. In this article, we propose to study a new way to synthesize quickly acyclophosphonate nucleosides using cross-coupling metathesis (CM). For this purpose, Nolan's catalyst **[Ru]-V** has been employed due to its excellent functional group tolerance and ease of use, between uracil analogues and vinylic or allylic phosphonates. During our first investigations, we observed the exclusive formation of homodimers issuing from the self-metathesis of *N1*-allylthymine and allylphosphonic acid dimethyl ester,[6] respectively. We hypothesized that the *N1*-crotyl phosphonate may be more reactive than the *N1*-allyl thymine in the CM reaction. Another hypothesis is based on the

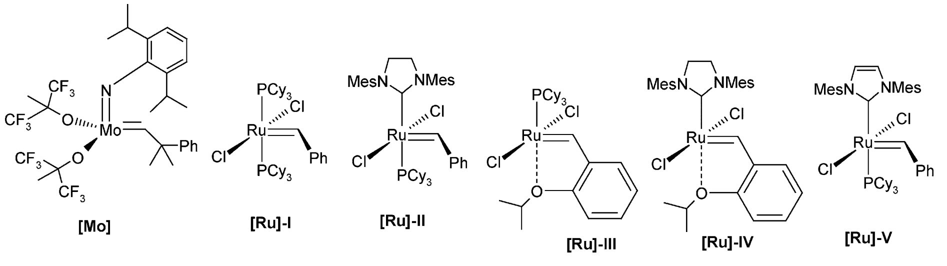
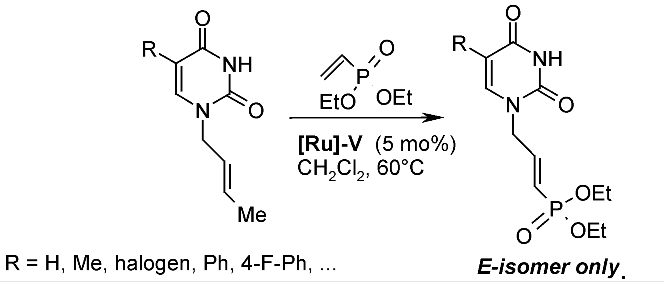


FIGURE 1 Main catalysts used in metathesis reactions.

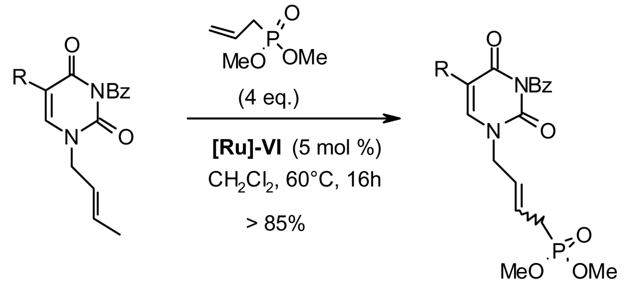
TABLE 1 Synthesis of vinylphosphonate nucleosides through CM



Entry	Vinyl phosphonate (eq.)	Time (h)	yield (%)
1	2	15	56 + homodimer (20%)
2	4	15	67 + homodimer (traces)
3	4	64	54
4	6	15	67

reversible nature of CM reaction which ensures the preferential formation of the most thermodynamically stable product. When reacting the more reactive *N1*-crotyl thymine (2.5 eq.) with the diethylvinyl phosphonate (6 eq.) in the presence of Nolan's catalyst **[Ru]-V** (5 mol%) in reflux CH_2Cl_2, the desired cross-coupling product was isolated as the only *E* isomer. An optimization of the reaction was necessary and best results were obtained using 4 or 6 equiv. of vinylic phosphonate (entries 3 and 4, respectively), Table 1.

This methodology was also successfully applied to the CM of various C5-substituted *N1*-crotyluracil. It is important to quote that the reaction proceeded without the protection at the *N3* position of the heterocycle. The C5-substituent has a direct incidence on the yield of the reaction; for instance, when substituted at the C5 by an alkyne, under those conditions, no reaction occurred. We next examined the cross-metathesis of various C5-substituted *N1*-crotyl uracil with dimethyl allyl phosphonate. Our preliminary results indicated that the expected cross-coupling products were isolated in only low yields (20–30%). We hypothesized that the active *N3*-proton of the



SCHEME 1 Synthesis of allylphosphonate nucleosides through CM.

pyrimidine would avoid for the proceedings of this metathesis reaction. Thus, after an *N3*-benzoylation, the CM reaction between pyrimidine derivatives and allylphosphoante gave the desired products, respectively, in >85%, as a mixture of *E* (major) and *Z* (minor) isomers, (Scheme 2). These results indicated that the allyl phosphonate would be more active metathesis partner than the vinyl analogue.

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