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A convenient approach to cyclic enol phosphates via ring-closing metathesis

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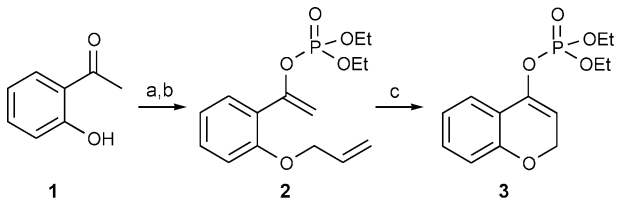
Abstract—A strategy employing the second generation Grubbs catalyst in order to facilitate the generation of a variety of cyclic enol phosphates, including 2*H*-chromen-4-yl, 1,2-dihydroquinolin-4-yl, 2*H*-thiochromen-4-yl, 2*H*-thiochromen-4-yl 1,1-dioxide, and benzofuran-2-yl enol phosphate scaffolds is described. This work represents the first case of an olefin metathesis reaction in which one of the groups participating in the metathesis event is an enol phosphate moiety.

Enol phosphates represent a versatile intermediate in the construction of complex organic molecules.[1] The ability to easily convert enol phosphates into a myriad of functional motifs of synthetic relevance is well known. In particular, this moiety has proved to be a robust and versatile precursor for a number of cross-coupling reactions facilitated by Pd(0) and Ni(0).[1] The ability of the enol phosphate to undergo these cross-coupling reactions in the presence of various heteroatoms, makes it an attractive functional group for the construction of various substituted heterocyclic systems. As a powerful extension to this chemistry, Nicolaou and co-workers developed lactone-derived ketene acetal phosphates as alternatives to the analogous ketene acetal triflates, which are often unstable and demonstrate low yields in both their formation and subsequent coupling reactions.[2] They were able to incorporate this strategy toward the total synthesis of the EFGH-core of brevotoxin A.[3] Other natural product syntheses, namely coumarin analogs[2] and the HIJK ring model of ciguatoxin,[4] have also utilized the enol phosphate and ketene acetal phosphate functional groups respectively. Our interest in the development of new transition metal-catalyzed processes to phosphorus-containing compounds leads us to report an RCM approach to enol phosphate and ketene acetal phosphate heterocyclic building blocks.

It is well known that the Grubbs ruthenium-based catalysts $[(PCy_3)_2(Cl)_2Ru{=}CHPh]$[5] and $[(ImesH_2)(PCy_3)(Cl)_2Ru{=}CHPh]$[6,7] are tolerant to a number of functional groups and facilitate RCM reactions with olefins bearing a wide array of functionality.[8] Recently Shibasaki and co-workers have carried out successful examples of RCM with enol silanes employing the second generation Grubbs catalyst.[9] Previous results by us and others have shown that RCM reactions catalyzed by either the first or second generation Grubbs catalysts are effective methods for the construction of a variety of *P*-heterocycles.[10] We herein report the first examples of RCM reactions on enol phosphate templates. These transformation are carried out exclusively with the second generation Grubbs catatyst to generate an array of heterocyclic enol phosphates.

We initially began our study with 2-hydroxyacetophenone **1** (Scheme 1). The uncyclized enol phosphate **2** was produced in good yield from a Mitsunobu allylation protocol using allyl alcohol followed by enol phosphate formation employing LDA and diethyl chlorophosphate. Subsequent RCM using 5 mol% $(ImesH_2)(PCy_3)(Cl)_2Ru{=}CHPh$[6,7] delivered the desired 2*H*-chromen-4-yl enol phosphate **3** in quantative yield (Scheme 1).



Scheme 1. *Reagents and conditions*: (a) Ph_3P, DEAD, allyl alcohol, 75%; (b) LDA, THF, $ClP(O)(OEt)_2$, 79%; (c) 5 mol% $(ImesH_2)(PCy_3)(Cl)_2Ru{=}CHPh$, CH_2Cl_2, 40°C, 99%.

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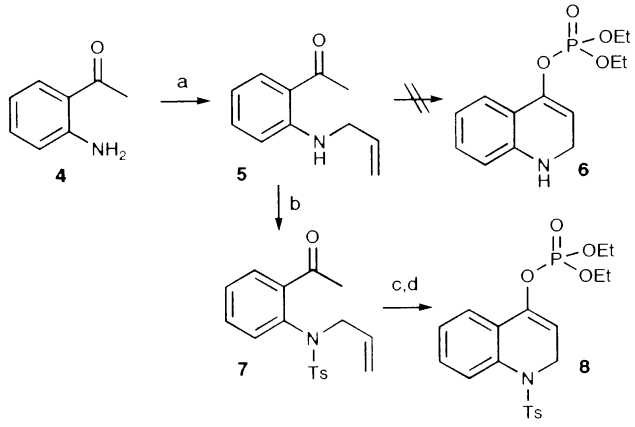
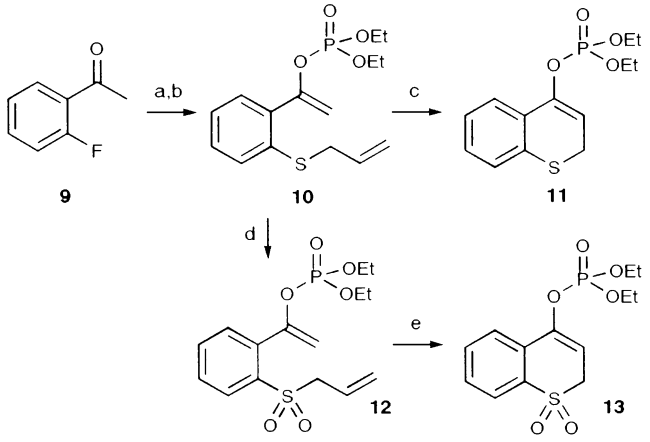
We next turned our attention toward the synthesis of the 1,2-dihydroquinolinyl enol phosphate system beginning with the allylation of 2-aminoacetophenone (**4**) generating *N*-allyl-2-aminoacetophenone (**5**) (Scheme 2). As anticipated, problems were encountered in our attempts to directly proceed to **6** utilizing an unprotected aniline moiety. Therefore, we opted for a tosylation step prior to these steps. This strategy proved to work well as the tosylated allylaniline **7** was converted to the 1,2-dihydroquinolin-4-yl enol phosphate **8** in good overall yield (Scheme 2).

A final example in this series to access 2*H*-thiochromenyl enol phosphates was carried out beginning with the nucleophilic aromatic substitution of sodium allylmercaptide with 2-fluoroacetophenone (**9**) (Scheme 3). Subsequent enol phosphate generation delivered metathesis precursor **10**. Subjection of this enol phosphate to RCM conditions was successful in producing the 2*H*-thiochromen-4-yl enol phosphates **11**, albeit in modest yield (48%). We then investigated the effect of the oxidation state of sulfur in the metathesis event. Oxidation of the sulfide using *m*-CPBA delivered the corresponding sulfone **12** in good yield. Subsequent RCM proceeded smoothly to afford the 2*H*-thiochromen-4-yl 1,1-dioxide **13** in excellent yield.

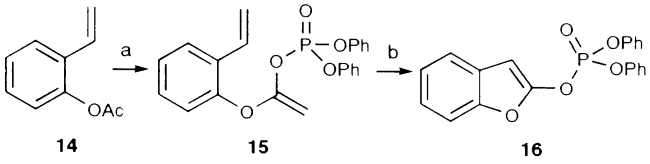
Following the success of these examples, we decided to investigate the scope of this method by probing its effectiveness on the more elaborate and more 'sensitive' ketene acetal phosphate example outlined below in Scheme 4. Beginning with the commerically available acetate derivative of 2-vinyl phenol **14**, enol phosphate formation was found to be most effectively carried out using KHMDS and $ClP(O)(OPh)_2$ as outlined by Nicolaou and co-workers[2] in place of the analogous LDA/diethyl chlorophosphate pair as previously used. These conditions afforded enol phosphate **15** in good yields (80%). The subsequent key RCM step proceeded without incident to produce the versatile benzofuran-2-yl enol phosphate **16** in quantitative yield.



Scheme 2. *Reagents and conditions*: (a) $CH_2{=}CH_2CH_2Br$, Cs_2CO_3, CH_3CN, 64%; (b) TsCl, CH_2Cl_2, Et_3N, 86%, (c) LDA, THF, $ClP(O)(OEt)_2$, 64%; (d) 5 mol% $(ImesH_2)(PCy_3)(Cl)_2Ru{=}CHPh$, CH_2Cl_2, 45°C, 75%.



Scheme 3. *Reagents and conditions*: (a) $CH_2{=}CH_2CH_2SH$, NaH, THF, 90%; (b) LDA, THF, $ClP(O)(OEt)_2$, 80%; (c) 10 mol% $(ImesH_2)(PCy_3)(Cl)_2Ru{=}CHPh$, CH_2Cl_2, 45°C, 48%; (d) *m*-CPBA, CH_2Cl_2, 82%; (e) 5 mol% $(ImesH_2)(PCy_3)(Cl)_2Ru{=}CHPh$, CH_2Cl_2, 45°C, 85%.



Scheme 4. *Reagents and conditions*: (a) LDA, THF, $ClP(O)(OPh)_2$, 80%; (b) 5 mol% $(ImesH_2)(PCy_3)(Cl)_2Ru{=}CHPh$, CH_2Cl_2, 40°C, 99%.

Conclusion

We have demonstrated that ring-closing metathesis is a viable method to effectively generate a variety of cyclic enol phosphates, including 2*H*-chromen-4-yl, 1,2-dihydroquinolin-4-yl, 2*H*-thiochromen-4-yl, and 2*H*-thiochromen-4-yl 1,1-dioxide enol phosphates. Furthermore, we have extended this chemistry to include a synthetically useful benzofuran-2-yl enol phosphate scaffold. To the best of our knowledge, this study represents the first examples of RCM reactions on substrates of this kind. Additional efforts in this area are underway and will be reported in due course.

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