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Cross-metathesis, a versatile synthetic methodology for the construction of alkenyl phosphine oxides and bis-phosphine oxides

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Abstract—Substituted vinyl and allyl phosphine oxides have been prepared by olefin cross-metathesis providing exclusive *E* olefin stereochemistry. The methodology has been successfully extended to the preparation of various bis-phosphine oxides.

1. Introduction

The development of strategies for the preparation of alkenyl phosphine oxides remains a very important area of research as these compounds are key intermediates for the preparation of numerous biologically active compounds and ligands for homogeneous catalysts.[1] A number of synthetic routes have been reported for this class of compounds with the metal-catalysed addition of P(V)–H bonds to alkynes providing one of the most elegant methodologies to access α,β-unsaturated phosphine oxides with good levels of regio- and stereocontrol.[2] Among the many transition metal catalysed C–C bond forming reactions, cross-metathesis (CM) has been neglected for the preparation of structurally diverse alkenyl phosphine oxides despite the fact that this reaction is now widely recognised as one of the most powerful synthetic tools in organic chemistry.[3] Two studies reported by the groups of Grubbs[4] and Hayes[5] have recently revealed that vinyl and allyl phosphonates are viable CM partners in metathesis reactions. In addition, one example of a CM reaction of a phosphine oxide has been previously reported in the literature.[6] As part of our ongoing research program studying the possibility of using metathesis for the preparation of new chiral phosphine ligands,[7] we had reason to investigate the scope and limitations of CM for the preparation of alkenyl phosphine oxides and selected bis-phosphine oxides.

2. Results and discussion

We set out to study first the reactivity of diphenyl vinyl phosphine oxide **2** with structurally diverse olefins (Table 1, entries 1–6).

The reactions were carried out in DCM with 2–6 mol% of catalyst **1**, one equivalent of **2** and three equivalents of the olefin. The highly reactive ruthenium catalyst **1** was chosen for this study as it is now well established that the presence of the non-labile sterically hindered NHC (*N*-heterocyclic carbene) ligand helps to stabilise the 14-electron ruthenium intermediates during metathesis resulting in enhanced activity.[8] All reactions proceeded in isolated chemical yields superior to 78% except for methyl vinyl ketone (MVK) which did not react. The lack of reactivity of MVK is hardly surprising as this latter reaction involves two electron-deficient alkenes.[9] All other reactions give the cross-products with excellent yield and exclusive *E* selectivity.[10] Under these conditions, no dimerisation of **2** could be detected, therefore allowing for high CM selectivity. In contrast to the metal-catalysed addition of P(V)–H bonds to alkynes, the cross-metathesis technology is not limited to the preparation of α,β-unsaturated alkenyl phosphine oxides. Indeed, diphenyl allyl phosphine oxide **3** was found to be a viable CM partner with both an electron-donating and an electron-withdrawing olefin (Table 1, entries 7 and 8). In the presence of 5-hexen-1-yl acetate, the desired cross-product was isolated in 70% yield but with a more modest stereoselectivity ($E/Z = 8/2$). We also found that **3** reacted with MVK albeit in diminished chemical yield (46%) but with exclusive *E* selectivity. No side-products resulting

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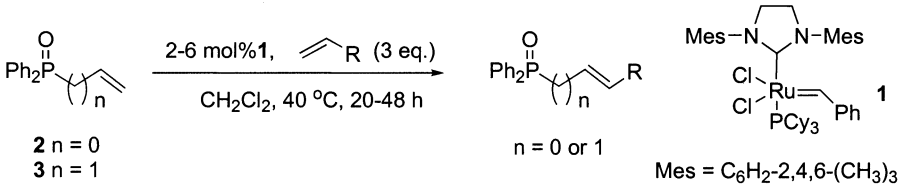
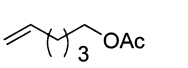
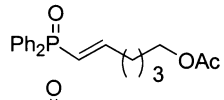
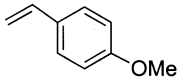
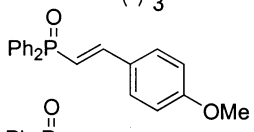
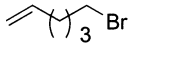
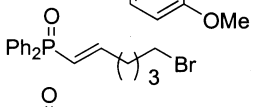
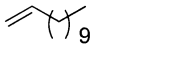
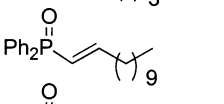
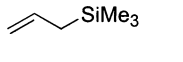
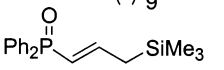
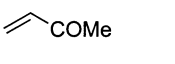
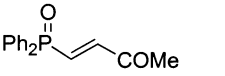
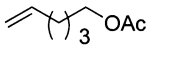
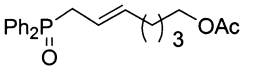
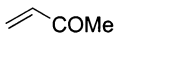
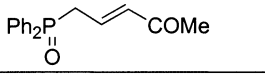
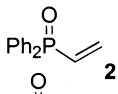
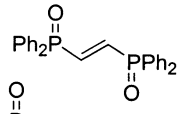
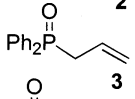
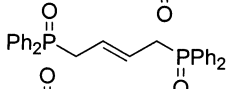
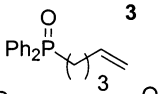
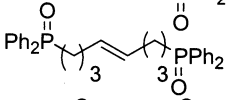
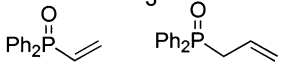
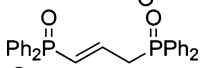
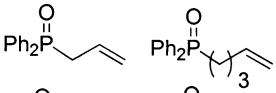
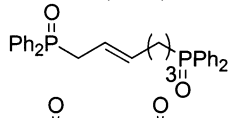
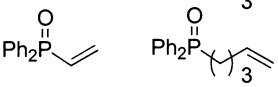
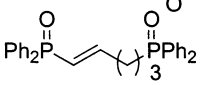
Table 1. Synthesis of vinyl and allyl phosphine oxides by olefin cross-metathesis



Entry	Phosphine oxide	CM Partner	Product	Isolated yield [a]
1	**2**			94%
2	**2**			78%
3	**2**			92%
4	**2**			100%
5	**2**			97%
6	**2**			0%
7	**3**			70% [b]
8	**3**			46%

a: *E* isomer only as determined by ^{1}H NMR.
b: An 8:2 ratio of *E*:*Z* isomers was formed.

Table 2. Synthesis of bis-phosphine oxides by olefin cross-metathesis

Entry	Reactants	mol% **1**	Product	Isolated yield [a]
1		6		0%
2		2		96%
3		4		95%
4		4		0%
5		4		94%
6		2		93%

a: *E* isomer only as determined by ^{1}H NMR

from olefin isomerisation could be detected in the crude reaction mixture. To probe further the synthetic scope of these reactions, we explored next the possibility of constructing various unsaturated bis-phosphine oxides (Table 2).

No dimerisation of the vinylphosphine oxide **2** was observed by ^{1}H NMR in the crude reaction mixture (entry 1). In contrast, the homodimerisation of the deconjugated allyl- and 4-penten-1-yl diphenyl phosphine oxides was feasible and afforded the homodimeric products in high yields and *E*-selectivity (entries 2 and 3). To access unsymmetrical bis-phosphine oxides, we attempted the CM of two different alkenyl phosphine oxides. No product of CM could be detected after 48 h upon treatment of one equivalent of **3** with three equivalents of **2** in the presence of 4 mol% of catalyst **1**, a lack of reactivity presumably due to steric factors (entry 4). This hypothesis is supported by the observation that **3** was found to react with the electron-deficient olefin, methyl vinyl ketone (Table 1, entry 8). However, by increasing the number of carbon units between the olefin and the phosphine oxide functional group, the reaction afforded excellent yields of the desired cross-products.[11] For example, cross-coupling of **3** (3 equiv.) with 4-penten-1-yl diphenyl phosphine oxide (1 equiv.) afforded the desired unsymmetrical bis-phosphine oxide with an isolated yield of 94% (entry 5). We also found that 4-penten-1-yl diphenyl phosphine oxide (1 equiv.) reacted with **2** (3 equiv.) to afford the unsymmetrical 1,5-bis-phosphine oxide in 93% yield (entry 6). Both bis-phosphines were produced with exclusive *E*-selectivity.

This study revealed that the CM technology gives easy access to various functionalised phosphine oxides in addition to unsaturated 1,4- 1,5-, 1,6- and 1,8-bis-phosphine oxides. The positioning of the double bond is simply programmed by a judicious choice of the reactants. So far, the technology could not be applied to 1,2- or 1,3-bis-phosphine oxides. Efforts to extend the use of the CM technology to access 1,2- and 1,3-bis-phosphines are currently underway in our laboratory. Applications of this technology are readily expected on the basis of the well-established synthetic utilities of these compounds.

Acknowledgements

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10. Typical $^3J_{P,H}=20$ Hz for *E* isomers, see: Williams, D. H.; Fleming, I. *Spectroscopic Methods in Organic Chemistry*, 5th Ed.; McGraw-Hill: London, 1995; p. 168.
11. For these reactions (entries 5 and 6, Table 2), one of the olefins is used in excess (3 equiv.).