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Synthesis of Substituted *P*-Stereogenic Vinylphosphine Oxides by Olefin Cross-Metathesis

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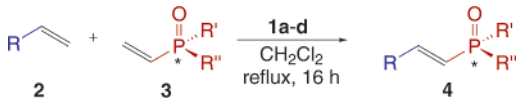
ABSTRACT



Substituted vinylphosphine oxides have been prepared in good yield and exclusive (*E*)-olefin selectivity via olefin cross-metathesis using Grubbs and Hoveyda-type ruthenium catalysts. In addition, metathesis of chiral vinylphosphine oxides proceeds without racemization of the phosphorus chirality center, providing easy access to functionalized chiral nonracemic (*E*)-alkenylphosphine oxides.

Achiral and chiral vinyl phosphine oxides have found wide use as versatile synthetic intermediates in the preparation of various mono- and diphosphorus systems.[1] Development of an easy access to their terminally substituted and functionalized homologues would greatly expand their synthetic utility.

Some examples have recently appeared in the literature which have shown that metathesis[2] can be used to access some phosphor-substituted olefins. Methods for the synthesis of vinylphosphonates via an olefin metathesis reaction have been recently published by Grubbs, Hanson, and Hayes.[3] Allylphosphonates and allylphosphoramides have been cyclized in ring-closing metathesis reaction (RCM) by Hanson et al.[4] Gouverneur and co-workers have demonstrated the intramolecular RCM of allylic phosphine oxides, phosphinates, and phosphine-boranes.[5] However, to the best of our knowledge, intermolecular cross-metathesis (CM) reactions of vinylphosphine oxides have not been previously reported.

In this communication, we report the single-step synthesis of β-functionalized α,β-unsaturated phosphine oxides catalyzed by the ruthenium metathesis catalysts.

Although the second-generation ruthenium complex **1a** possesses in general a very good application profile,[2] the phosphine-free catalyst **1b**, recently introduced by Hoveyda et al.,[6] displays even higher reactivity toward some electron-deficient substrates such as acrylonitrile,[7] fluorinated olefins,[8] and vinyl sulfones.[9] Excellent air stability, ease of storage and handling, and the possibility of catalyst reuse are

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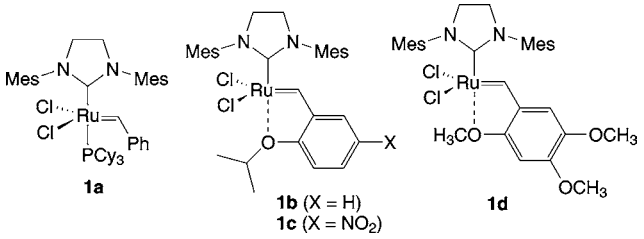
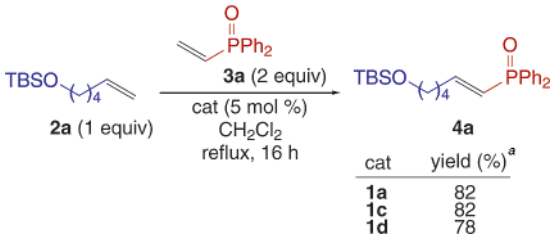
additional advantages of this system.[6] In this investigation, we decided to utilize two Hoveyda-type ruthenium complexes (**1c**,**d**) recently developed in our laboratory.[10,11] Catalyst **1d**, very stable and easy to prepare from inexpensive substrates, shows activity comparable to the parent Hoveyda carbene **1b**,[10] while the nitro-substituted catalyst **1c** possesses a dramatically enhanced reactivity, e.g., **1c** promotes metathesis even at 0 °C.[11]

Scheme 1. Grubbs **1a** and Hoveyda-type **1b**−**d** Second-Generation Ruthenium Olefin Metathesis Catalysts



Test reactions between olefin **2a** (1 equiv), diphenyl(vinyl)phosphine oxide **3a** (2 equiv), and complexes **1a** and **1c**,**d** (0.05 equiv) were performed under argon, at reflux temperature in dichloromethane (Procedure A). All the "second-generation" ruthenium complexes effect the formation of corresponding product **4a** in similarly good yields (78−82%) and exclusively as the (*E*)-isomer (Scheme 2).

Scheme 2. Screening of the Catalytic Activity of **1a**, **1c**, and **1d** in the Cross-Metathesis of **3a**



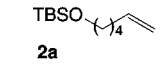
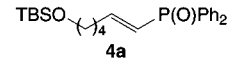
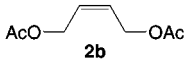
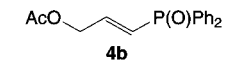
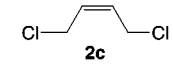
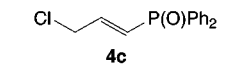
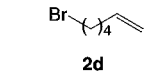
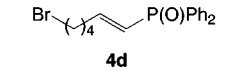
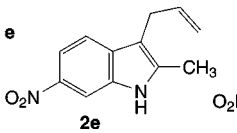
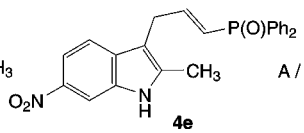
cat	yield (%)[a]
1a	82
1c	82
1d	78

[a] Isolated yields of analytically pure products.

These results indicate that, in this particular case, the Hoveyda-type carbenes are not superior to the Grubbs catalyst **1a**.

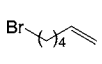
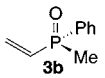
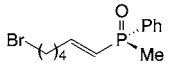
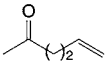
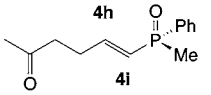
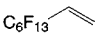
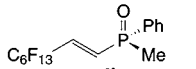
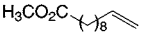
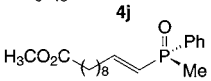
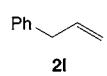
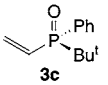
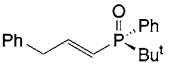
Having identified ruthenium complexes **1a**, **1c**, and **1d** as effective catalysts for this transformation, we decided to extend our investigation to a more diverse set of olefinic substrates. The results compiled in Tables 1 and 2 illustrate the scope and synthetic utility of this reaction. Thus, the olefinic substrates bearing various functionalities, including chloro- and bromoalkenes, carbonyl compounds, and NH-unprotected indole can be easily converted to the corresponding α,β-unsaturated phosphine oxides in good yields. In all reported cases, the (*E*)-isomer was the only phosphine oxide product detected by HPLC or NMR.

Table 1. Substituted Vinylphosphine Oxides **4** by Cross-Metathesis of Diphenyl(vinyl)phosphine Oxide **3a**

entry	alkene **2**	product **4**	procedure / cat yield (%)[a]
a	 **2a**	 **4a**	A / **1c** / 82
b	 **2b**	 **4b**	B / **1c** / 52[b]
c	 **2c**	 **4c**	B / **1d** / 65
d	 **2d**	 **4d**	B / **1d** / 99
e	 **2e**	 **4e**	A / **1c** / 76

[a] Isolated yields of analytically pure products. Procedure A: **2** (1 equiv), **3a** (2 equiv). Procedure B: **2** (2.5 equiv), **3a** (1 equiv). Reaction conditions: catalyst **1a**−**d** (5 mol %), dichloromethane, reflux, 16 h. [b] Yield based on NMR.

Table 2. Synthesis of *P*-Chiral Phosphine Oxides **4**[16]

entry	alkene **2**	phosphine oxide **3**[a]	product **4**	cat / yield (%)[b]
a	 **2d**	 **3b**	 **4h**	**1c** / 86
b	 **2i**	**3b**	 **4i**	**1d** / 85
c	 **2j**	**3b**	 **4j**	**1c** / 0[c]
d	 **2k**	**3b**	 **4k**	**1a** / 74
e	 **2l**	 **3c**	 **4l**	**1d** / 72

[a] Phosphine oxide **3b** (ref 17): $[\alpha]_D^{20}$ −80.5 (*c* 1, CH_2Cl_2), ee 98%, absolute configuration S_P. Phosphine oxide **3c** (ref 18): $[\alpha]_D^{20}$ −57.2 (*c* 1, CH_2Cl_2); ee 73%, absolute configuration R_P. [b] Isolated yields of analytically pure products. Reaction conditions: **2** (2.5 equiv), **3** (1 equiv), catalyst **1a**−**d** (5 mol %), dichloromethane, reflux, 16 h. [c] Homodimer **5** (85%) was isolated instead of the expected product **4j**.

(7) Randl, S.; Gessler, S.; Wakamatsu, H.; Blechert, S. *Synlett* **2001**, 430.

(8) Imhof, S.; Randl, S.; Blechert, S. *Chem. Commun.* **2001**, 1692.

(9) (a) For a CM reaction of phenyl vinyl sulfone catalyzed by **1a**, see: Grela, K.; Bieniek, M. *Tetrahedron Lett.* **2001**, *42*, 6425. (b) For screening of the catalytic performance of Ru- and Mo-based catalysts in this transformation, see: Grela, K.; Michrowska, A.; Bieniek, M.; Kim, M.; Klajn, R. *Tetrahedron* **2003**, *59*, 4525−4531.

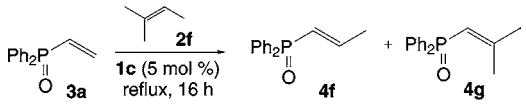
(10) Grela, K.; Kim, M. *Eur. J. Org. Chem.* **2003**, 963.

(11) (a) Grela, K.; Harutyunyan, S.; Michrowska, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4038. (b) For applications of **1c**, see ref 9b and: Ostrowski, S.; Mikus, A. *Mol. Divers.* Accepted for publication.

When the CM alkene partner **2** is inexpensive or easily available, it is reasonable to use it in excess, allowing the more economical utilization of vinylphosphine oxides **3a**−**c** (Procedure B). The excess of alkenes **2b**,**c** or their "dimerization" products can be easily removed by evaporation under vacuum or by flash chromatography.

It has been reported by Grubbs that CM of terminal olefins and 2-methyl-2-butene (**2f**) constitutes a very elegant method of an *allyl* to *prenyl* conversion.[12] However, when an electron-deficient substrate (such as acrylate) is used, another reaction pathway has been observed, leading to the preferential formation of methyl-substituted olefin.[12] Similarly, in the reaction of vinylphosphine oxide **3a** and neat 2-methyl-2-butene (bp 35−38 °C), we observed a highly chemo- and stereoselective formation of the (1*E*)-prop-1-enyl phosphine oxide **4f** (98% purity by NMR). It should be noted, however, that when the same reaction was performed in a 1:1 mixture of 2-methyl-2-butene:CH_2Cl_2, increased amounts of dimethyl-substituted product **4g** were formed (Scheme 3).

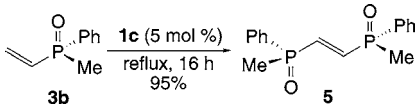
Scheme 3. Cross-Metathesis of Vinylphosphine Oxide **3a** and 2-Methyl-2-butene



In connection with our ongoing research program aimed at the preparation of new chiral phosphine ligands, we next decided to test the CM of *P*-stereogenic[13] vinylphosphine oxides **3b**,**c**. In recent years, resolved vinyl phosphine oxides have served as convenient precursors to *P*-stereogenic ligands[14] as well as chiral reagents for effecting P to C chirality transfer in stoichiometric addition, cycloaddition, and substitution processes.[15] The straightforward possibility of their metathetic conversions into functionalized terminally substituted analogues retaining the resolved *P*-stereogenic center, as well as the unsaturation functionality, would give a new impetus to the synthesis of novel elaborated *P*-stereogenic systems of diversified structures. Access to enantiopure vinyl phosphine oxides possessing substituents at the double bond has been so far very limited.[1b]

As summarized in Table 2,[16] various substituted chiral vinylphosphine oxides can be accessed by CM reaction of homochiral **3b** and **3c**. More electron-deficient alkene **2j** gave a somewhat unexpected result, as after column chromatography, an 85% yield of homodimer **5** was obtained instead of the expected cross-product **4j**. It should be noted that in previous reactions with **3a**−**c** (Procedure B), we have not observed formation of their homodimers.[19] The examples of homometathesis between two electron-deficient olefins are rare, and good yields have only been reported for homodimerization of acrylates[20] and for cross-metathesis of α,*β*-unsaturated substrates with styrenes.[21] To check if the presence of the fluoroolefin **2j** was necessary for the formation of **5**, we refluxed a CH_2Cl_2 solution of phosphine oxide **3b** in the presence of 5 mol % **1c**, and after the reaction, we isolated the product **5** in high yield and exclusively as the (*E*)-isomer (Scheme 4). This finding provides a potentially useful method for preparing chiral bidentate phosphine ligands.

Scheme 4. Homodimerization of **3b**



(12) Chatterjee, A. K.; Sanders, D. P.; Grubbs, R. H. *Org. Lett.* **2002**, *4*, 1939.

(13) Frequently, the terms "P-chiral" and "P-chirogenic" have been used to differentiate chiral phosphorus-containing compounds that bear a stereogenic phosphorus atom from those that do not. These terms are, however, incorret, and their use should be discouraged. We thank Prof. Scott E. Denmark for bringing this issue to our attention.

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(16) **General Procedure for Cross-Metathesis of Vinylphosphine Oxides. Procedure B.** To a mixture of vinylphosphine oxide **3** (0.5 mmol) and **2** (1.25 mmol) in CH_2Cl_2 (4 mL) was added a solution of catalyst **1** (0.025 mmol, 5 mol %) in CH_2Cl_2 (1 mL). The resulting mixture was stirred at 45 °C for 16 h. The solvent was removed under reduced pressure. The crude product **4** was purified by flash chromatography (hexane−acetone 4:1, then hexane−ethyl acetate−methanol 5:2:0.5). **(R_P)-(−)-*tert*-Butyl-(phenyl)[(1*E*)-3-phenylprop-1-enyl]phosphine oxide (4l):** pale gray crystals (72% of yield); $[\alpha]_D^{20}$ − 27.6 (*c* 1, CH_2Cl_2); mp 103−104 °C; IR (KBr, cm^{-1}) 2961, 1943, 1732, 1668, 1628, 1603, 1495, 1476, 1436, 1364, 1268, 1213, 1213, 1171, 1110, 997, 816, 776, 748, 699; ^{31}P NMR ($CDCl_3$, 202, MHz) δ = 38.8; ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.72−7.16 (m, 10 H, *Ph*), 7.07 (tt, *J* = 16.9, 6.3 Hz, 1 H, CH_2−C*H*), 6.23 (ddt, *J* = 26.9, 16.9, 1.7 Hz, 1 H, P(O)-C*H*), 3.63 (dt, *J* = 6.3, 1.9 Hz, 2 H, Ph-CH_2), 1.09 (d, *J* = 14.9 Hz, 9 H, C−(CH_3)3); ^{13}C NMR ($CDCl_3$, 126 MHz) δ = 151.7 (s, CH_2−*C*H), 137.8 (s, CH_2−*C*), 131.8 (d, *J* = 8 Hz, *o-C* in Ph−P(O)), 131.3 (d, *J* = 2.6 Hz, *p-C* in Ph−P(O)), 130.8 (d, *J* = 92.8 Hz, P(O)−*C*), 128.9 (s, *o-C* in Ph−CH_2), 128.6 (s, *m-C* in $PhCH_2$), 128.1 (d, *J* = 10.9 Hz, *m-C* in Ph−P(O)), 126.6 (s, *p-C* in Ph−CH_2), 119.1 (d, *J* = 91.5 Hz, *C*H−P(O)), 40.8 (d, *J* = 15.5 Hz, *C*H_2), 32.6 (d, *J* = 73.3 Hz, *C*$(CH_3)_3$), 24.2 (s, *C*$(CH_3)_3$); MS (ESI) *m*/*z* rel intensity) 299 (70) $[M + H]^+$, 321 (100) $[M + Na]^+$; HR-MS ($C_{19}H_{23}OPNa$): calcd 321.1379, found 321.1391.

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(18) Pietrusiewicz, K. M. *Phosphorus, Sulfur, Silicon* **1996**, *109*, 573. The optically pure oxide **3c** has been available, but for the sake of a more reliable comparison of enantiomeric purities of the substrate and the product by means of ^{1}NMR using chiral shift reagents, which in these cases gave only moderate line separations (ca. 4−5 Hz, refs 22 and 23), the enantiomeric purity of the starting **3b** was deliberately lowered to 73% by admixing of *rac*-**3b**.

To prove that the metathesis of *P*-stereogenic vinylphosphine oxides proceeds without racemization at the phosphorus chirality center, we subjected the resultant vinylphosphine oxides to ^{31}P and ^{1}H NMR experiments with Kagan's shift reagent.[22] Careful inspection of the NMR spectra revealed that no racemization takes place and that the ee values of substrates **3b**,**c** and of products **4h**,**l** are virtually identical.[23]

Similarly, in the case of homodimerization of **3b**, careful NMR inspection of the reaction mixture revealed that only one diastereoisomer of **5** was formed in this transformation.

In conclusion, we have shown that the substituted vinylphosphine oxides can be prepared in good yield and exclusive (*E*)-olefin selectivity via olefin cross-metathesis using Grubbs and Hoveyda-type ruthenium catalysts. The metathesis of *P*-stereogenic vinylphosphine oxides proceeds without racemization of a chiral phosphorus center, providing easy access to functionalized chiral nonracemic (*E*)-alkenylphosphine and bis(phosphine) oxides. These findings further expand the range of olefins that participate in CM reaction. Experiments to broaden the scope of this reaction for the preparation of phosphine ligands are under way.

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

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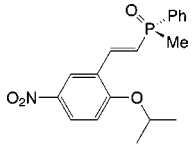
(19) In homodimerization reaction of **3b**, we have also isolated a theoretical yield (≈5%) of the phosphine oxide **6**, a product of CM between **3b** and catalyst **1c**.



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(23) Optical purities were calculated from the corresponding ^{31}P and ^{1}H NMR spectra registered in the presence of (*S*)-*N*-[1-(1-naphthyl)ethyl]-3,5-dinitrobenzamide (cf. Supporting Information). E.g., **4l**: ^{31}P NMR ($CDCl_3$, 202 MHz): δ (rel weight) = 39.30 (1.00), 39.25 (0.15); significant fragments of the ^{1}H NMR spectrum ($CDCl_3$, 500 MHz): δ (rel weight) = 6.29 (0.15), 6.27 (1.00); 6.26 (0.16), 6.24 (1.00); 6.20 (0.17), 6.19 (1.00); 1.10 (0.14), 1.08 (1.00); 1.07 (0.16), 1.05 (1.00). Calculated optical purity: 72 ± 4% ee.