

Homo- and Cross-Olefin Metathesis Coupling of Vinylphosphane Oxides and Electron-Poor Alkenes: Access to P-Stereogenic Dienophiles

Nikolai Vinokurov,^a Anna Michrowska,^b Anna Szmigielska,^c Zbigniew Drzazga,^c Grzegorz Wójciuk,^c Oleg M. Demchuk,^c Karol Grela,^{b,*} K. Michał Pietrusiewicz,^{b,c,*} Holger Butenschön^{a,*}

^a Institut für Organische Chemie, Universität Hannover, Schneiderberg 1B, 30167 Hannover, Germany
E-mail: holger.butenschoen@mbox.oci.uni-hannover.de

^b Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warsaw, Poland
Fax: (+48)-22-632-66-81, e-mail: grela@icho.edu.pl

^c Department of Organic Chemistry, Maria Curie-Skłodowska-University Lublin, ul. Gliniana 33, 20-614 Lublin, Poland
E-mail: michal@hermes.umcs.lublin.pl

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Abstract: Vinylphosphane oxides **6** undergo catalytic olefin homo-metathesis leading to achiral and P-stereogenic diphosphane dioxides **7** with exclusive (*E*)-selectivity. Similarly, EWG-substituted vinylphosphane oxides **11**, **12** could be prepared with complete (*E*)-olefin selectivity *via* olefin cross-metathesis with electron-deficient substrates, such as methyl acrylate and

2-fluorostyrene, using nitro-Hoveyda ruthenium pre-catalyst **III**. Cross- and homo-metathesis of chiral non-racemic vinylphosphane oxides proceeds without racemization of the phosphorus center of chirality.

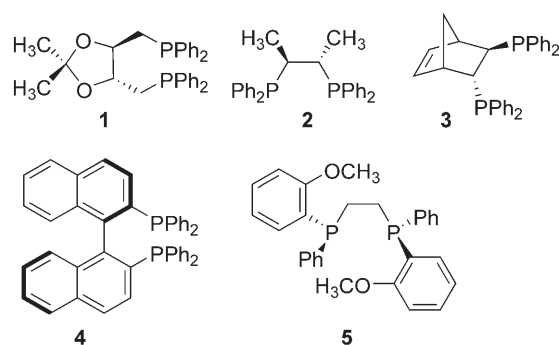
Keywords: catalysis; metathesis, P-stereogenic; ruthenium, vinylphosphane oxide

Introduction

Next to palladium-catalyzed coupling reactions, metathesis catalysis has proved to be the most valuable tool for the construction of specific organic frameworks in the last decade.^[1–6] Nowadays there are many kinds of alkene metathesis processes such as ring-opening metathesis polymerization (ROMP),^[1,7] ring-closing metathesis (RCM),^[8–10] enyne metathesis,^[11–14] cross metathesis,^[15–17] all of which are subject of current research and are frequently applied in the target-oriented synthesis of complicated organic compounds important for natural products synthesis, materials science and other fields. The development of this methodology has taken much advantage from the development of suitable precatalysts now making available catalysts tolerating a number of functional groups combined with high catalytic activity and stability allowing one to routinely handle them in an organic chemistry laboratory.^[18,19]

The importance of phosphanes as well as chelating diphosphanes as ligands in homogeneous transition metal catalysis^[20] has been known for decades and has gained particular importance by the introduction of chiral phosphane ligands, which have proved valuable in asymmetric catalysis.^[21] Historically, the first homogeneous enantioselective hydrogenation reaction of prochiral substrates by using a chiral rhodium metal complex was reported by Knowles and Horner independently.^[22] Common optically active phosphane ligands developed in the 1970s and 1980s in this context are DIOP **1**,^[23] CHIRAPHOS **2**,^[24] NORPHOS **3**,^[25] and BINAP **4**,^[26] which

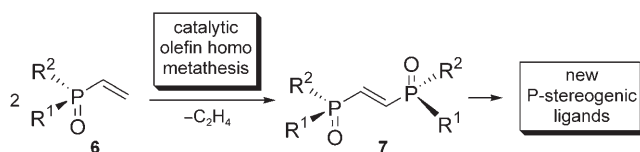
phane ligands, which have proved valuable in asymmetric catalysis.^[21] Historically, the first homogeneous enantioselective hydrogenation reaction of prochiral substrates by using a chiral rhodium metal complex was reported by Knowles and Horner independently.^[22] Common optically active phosphane ligands developed in the 1970s and 1980s in this context are DIOP **1**,^[23] CHIRAPHOS **2**,^[24] NORPHOS **3**,^[25] and BINAP **4**,^[26] which



Scheme 1. Selected chiral diphosphane ligands for asymmetric catalysis.

have widely been used in asymmetric catalysis. These diphosphanes and many other chiral diphosphanes have in common that they share the 1,2-diphosphanylene substructure and that the chiral information is located in the carbon backbone connecting the two phosphane fragments. This contrasts with P-stereogenic diphosphanes, the first of which was DIPAMP **5**, which had been introduced by Knowles et al. as early as 1975 and was applied in Monsanto's DOPA process.^[28] In contrast to most amines, phosphanes can show configurational stability.^[29]

As in complexes of P-stereogenic phosphane ligands the chiral information is located much closer to the metal atom than in complexes of phosphane ligands bearing the chiral information in the molecular backbone, asymmetric reactions taking place at the metal atom usually proceed with a high degree of enantioselectivity.^[30] Imamoto et al. have investigated this field using P-stereogenic phosphane-boranes as ligand precursors and found exceptionally high enantiomeric excesses in rhodium-catalyzed hydrogenation reactions.^[31,32] Enantiomerically pure vinylphosphane oxides are promising and versatile precursors to P-stereogenic ligands^[33–35] and can be used as sources of chirality in the P to C chirality transfer in conjugate addition reactions,^[36,37] Diels–Alder cycloadditions,^[38] [3 + 2] cycloadditions,^[39,40] and substitution reactions.^[41]



Scheme 2. Preparation of P-stereogenic 1,2-diphosphanylene dioxides **7** via homometathesis.

The availability of enantiomerically pure P-stereogenic vinylphosphane oxides **6**^[42] raises the question, in how far they may serve as substrates for catalytic homometathesis presumably leading to enantiomerically pure P-stereogenic 1,2-diphosphanylene oxides **7**.^[43] Subsequently, these might undergo hydrogenation^[44] or cycloaddition reactions and stereoselective reduction^[45] to give new P-stereogenic ligands for asymmetric catalysis (Scheme 2). *trans*-1,2-Bis(diphenylphosphanyl)ethene dioxide (**7**, $R^1 = R^2 = \text{Ph}$) was successfully used for the preparation of NORPHOS (**3**),^[25] a highly active ligand possessing chirality centers in the rigid carbocyclic skeleton. Recently, intermolecular olefin cross metathesis and intramolecular ring-closing metathesis were applied for preparation of functionalized phosphorus compounds including allyl and vinyl phosphonates,^[46] allylphosphane oxides,^[47] and allylphosphane-boranes.^[48]

Results and Discussion

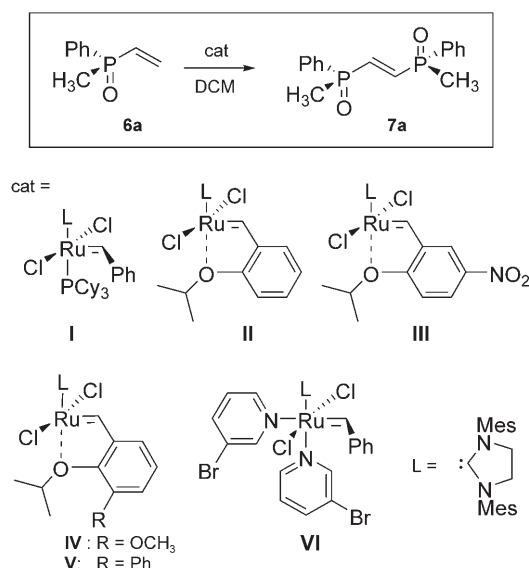
Catalytic Homometathesis of Vinylphosphane Oxides

According to a general classification published recently by Grubbs et al.,^[49] α,β -unsaturated substrates, such as acrylic acid derivatives, vinyl ketones or vinyl sulfones that undergo homodimerization at a significantly lower rate than unsubstituted olefins, if at all, shall be described as Type II or Type III substrates. One example of Type III substrates (no homodimerization) are vinyl phosphonates.^[46] Recently, Gouverneur et al. reported an unsuccessful attempt at the preparation of 1,2-bis(diphenylphosphanyl)ethene dioxide (**7**, $R^1 = R^2 = \text{Ph}$, Scheme 2) *via* homometathesis of the corresponding vinylphosphane oxide (**6**, $R^1 = R^2 = \text{Ph}$).^[50a]

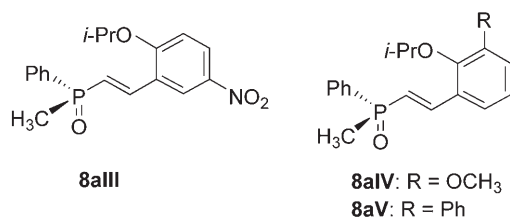
During our research aiming for the preparation of substituted P-stereogenic vinylphosphane oxides by olefin cross metathesis,^[51] we found the unprecedented homo-cross metathesis of enantiomerically pure (*S_P*)-methyl(phenyl)vinylphosphane oxide **6a** leading to homodimer **7a** as a single stereoisomer (Scheme 3).^[51] This serendipitous discovery prompted us to investigate the homometathesis of vinylphosphane oxides **6** and their cross-coupling with other electron-poor substrates in more detail.

The examples of homometathesis between two electron-deficient olefins of Type II are rare, and good yields have only been reported for homodimerization of acrylates and enones,^[52] and for the cross metathesis of α,β -unsaturated carbonyl and related substrates with styrenes.^[53] In such challenging cases, the proper choice of precatalysts and experimental conditions is of crucial importance. To probe this aspect, a series of homometathesis reactions of vinylphosphane oxide **6a**, catalyzed by a selection of modern ruthenium metathesis precatalysts^[54–58] **I–VI** (0.05 equivs.) was performed under argon at reflux temperature in dichloromethane (Scheme 3, Table 1).

As can be seen from Table 1, the homo-coupling reactions are visibly dependent on the chosen ruthenium precatalyst, with electronically^[56] and sterically^[57,58] activated Hoveyda–Grubbs^[55] type complexes **III–V** being the most effective ones. Therefore, we decided that the stable, industrially tested^[60] nitro-Hoveyda complex **III**, developed in our laboratories, is the most appropriate one from the practical point of view.^[61] In line with the previous observation,^[51] the CM of **6a** was in all cases highly stereoselective, as (*E*)-**7a** was the only isomer detected by ¹H and ³¹P NMR. Careful spectroscopic inspection of the reaction mixture reveals that no racemization takes place during the CM step as no trace of the respective *meso* CM product could be detected and the ee of the obtained **7a** (ee = 98 ± 2%)^[62] is found to be identical with that of the substrate (ee = 98 ± 2%).^[62]



Scheme 3. Screening of the catalytic activity of complexes **I–VI**^[54–58] in the homometathesis of (*S_P*)-**6a**. Cy = cyclohexyl; Mes = 2,4,6-trimethylphenyl.



Scheme 4.

This clearly attests to the mildness of the method in general terms.

In some homodimerization reactions catalyzed by Hoveyda–Grubbs complexes **III–V** we have also isolated phosphane oxides **8aIII**, **8aIV** and **8aV** (Scheme 4), products of CM between **6a** and the corresponding precatalyst. These by-products, formed in theoretical yields (ca. 5%), can be easily separated by flash chromatography because of their different polarity. The remainder of the mass balance was unreacted **6a**, which can be easily isolated by flash chromatography and recycled.

It is evident from the data compiled in Table 1, that the yield of **7a** is highly responsive to the concentration of substrate **6a**.^[63] For example, the reaction catalyzed by **III** at 0.020 M gave only 30% yield (entry 7), and a decrease of the concentration further decreased the yield (entry 6). However, an increase of the concentration increased the yield, and highest yields were obtained at 0.125–0.200 M (entries 8, 9). Because of the limited solubility of **6a** in DCM, we repeated this homodimerization at 0.4 M in chlorobenzene, however, without improving the conversion. The reaction of **6a** catalyzed by **III** was then further refined using other solvents, in-

Table 1. Optimization results of homometathesis of (*S_P*)-**6a**.^[a]

Entry	Precatalyst	Concentration of 6a [M]	Yield of 7a [%] ^[b]
1	I	0.020	(18)
2	I	0.125	(35)
3	I	0.200	(25)
4	II	0.125	(46)
5	II	0.200	(42)
6	III	0.005	(ca. 5)
7	III	0.020	(30)
8	III	0.125	76
9	III	0.200	80
10	IV	0.020	(30)
11	IV	0.125	75
12	IV	0.200	78
13	V	0.020	44
14	V	0.125	71
15	V	0.200	67
16	VI	0.200	(10)

^[a] Reagents and conditions: 5.0 mol % of precatalysts **I–VI**, DCM, 24 h, reflux.

^[b] Isolated yields of analytically pure products. In parentheses conversions determined by ³¹P NMR are given.

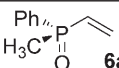
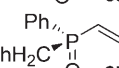
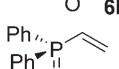
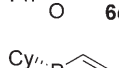
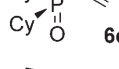
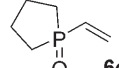
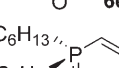
cluding 1,2-dichloroethane and benzene, showing that our initial choice of DCM was optimal.

In striking contrast to previously studied CM reactions of vinylphosphane oxides with olefins,^[51] the homometathesis of **6a** has been found to be very dependent not only on the substrate concentration but also on scale and subtle experimental set-up. For example, dimerization reactions conducted under optimized conditions (0.100–0.125 M in DCM, under reflux) in the scale of 0.5 mmol gave the expected product in the 88–95% range of yield (two runs),^[51] while in 1.0–1.5 mmol scale reproducibly lower yields of **7a** were obtained (63–80%, three runs).

Having identified ruthenium complex **III** as the effective precatalyst for this transformation, we decided to extend this investigation to a more diverse set of achiral and P-stereogenic substrates (Table 2). The behavior of differently substituted vinylphosphane oxides **6** as substrates for homometathesis was found to be more complex. While attempted homometathesis reactions of vinylphosphane oxides bearing either one aromatic (entry 3)^[50a] or sterically demanding substituents (entry 4) were in vain, the use of alkyl-aryl (entries 1, 2) or dialkyl (entries 6, 7) vinylphosphane oxides **6** resulted in moderate to good yields of the desired homocoupling products **7**. The rest of the mass balance consisted of unreacted substrates **6**, which could be easily recovered by chromatography and reused, rendering this method useful from the practical point of view.

It is well established that the cross metathesis of α,β -unsaturated substrates is very sensitive both to steric

Table 2. Homometathesis of representative vinylphosphane oxides **6** catalyzed by **III**.

$ \begin{array}{c} \text{R}^1 \\ \\ \text{R}^2 - \text{P} = \text{CH}_2 \\ \\ \text{O} \end{array} \xrightarrow[\text{DCM}]{\text{III}} \begin{array}{c} \text{R}^1 \\ \\ \text{R}^2 - \text{P} = \text{CH} - \text{CH} = \text{P} - \text{R}^2 \\ \quad \quad \\ \text{O} \quad \quad \text{O} \end{array} $			
Entry	Substrate 6	Concentration [M]	Yield [%] ^[a]
1	 6a	0.200	80 ^[b]
2	 6b	0.200	40 ^[c]
3	 6c	0.200	0 ^[d]
4	 6d	0.200	0
5	 6e	0.200	62
6	 6f	0.125	65
7	 6g	0.125	46

^[a] Reagents and conditions: 5.0 mol % of precatalysts **III**, DCM, 24 h, reflux. Reaction in the scale of 1.0–1.5 mmol. Isolated yields of analytically pure products. Only *E* isomers observed by ¹H NMR.

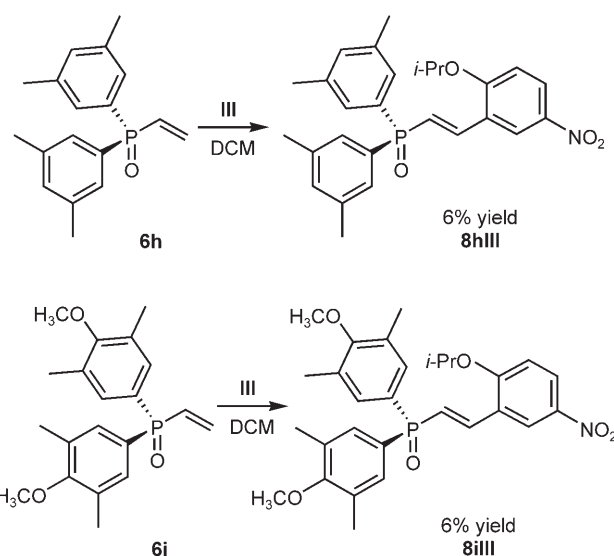
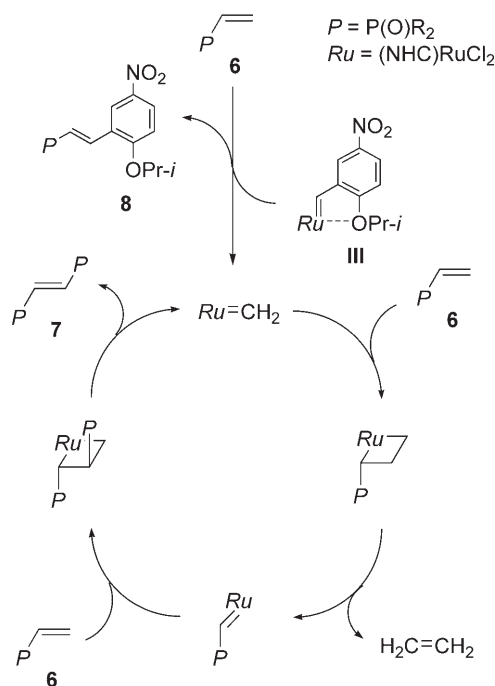
^[b] (*S_p*)-**6a** was used. When *rac*-**6a** was used, the corresponding *dl*- and *meso*-isomers were formed in a 1:1 ratio, as determined by ³¹P NMR.

^[c] *Rac*-**6b** was used; *dl*- and *meso*-isomers were formed in a ~3:1 ratio, as determined by ³¹P NMR.

^[d] Reaction with 10 mol % of **III**.

hindrance and electron density of the reacting C–C double bonds.^[16] One might therefore expect the ruthenium-catalyzed homometathesis of *more electron-rich* diarylvinylphosphane oxides, such as **6h** and **6i**, to proceed more readily than in the case of diphenylphosphane oxide **6c**. In order to learn about the influence of electronic factors we have attempted a homodimerization of **6h** and **6i** with 10 mol% of **III** (Scheme 5).

Disappointingly, no homometathesis was observed with these substrates. Instead, in addition to unreacted starting material (*ca.* 90% of mass balance) we isolated minute amounts of cross metathesis products **8hIII** and **8iIII** formed during the initiation step (Scheme 6).^[64] These results show that homodimerization of vinyl phosphanes bearing two aromatic substituents (**6c**, **6h**, **i**) is not possible even with highly active precatalyst **III**, and these substrates should therefore be classified as pure Type III olefins.^[50a]

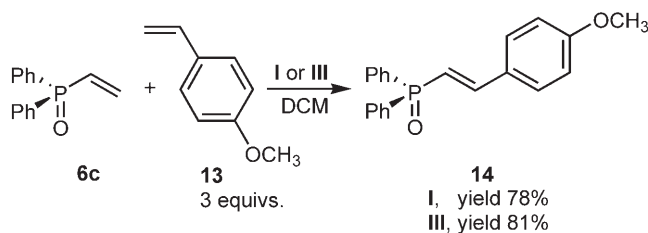
**Scheme 5.** Reagents and conditions:^[a] 10 mol % of precatalyst **III**, DCM, 24 h, reflux. Isolated yields of analytically pure products.**Scheme 6.** Plausible mechanism for the formation of products **7** and **8**. NHC = 1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene.

Catalytic Cross Metathesis of Vinylphosphane Oxides with Representative Olefins of Type II or III

To access other synthetically useful achiral and P-stereogenic phosphorus building blocks,^[65] we attempted cross-coupling reactions of vinylphosphane oxides **6** with selected Type II or Type III olefins. Cross metathe-

sis dimerization between electron-deficient or bulky substrates did not readily occur (Type II or Type III olefins) and thus is another challenging reaction. For example, it was observed that *ortho*-substituted styrenes bearing electron-withdrawing or bulky functionalities (Type III olefins) were poor CM substrates with acrylates (Type II substrates).^[16] Therefore we have chosen methyl acrylate **9** and 2-fluorostyrene **10** as challenging prototypical Type II and III substrates in our investigation.

Initial experiments of CM between **6a** and **9** revealed that under standard conditions (2 equivs. of **9**, 5 mol % **III**, DCM, reflux) selectivity was low and homometathesis product **7a** was formed in large amounts (12%). To optimize this reaction, a set of CM conditions was investigated. It was found that increasing the amount of methyl acrylate to 30 equivs. almost completely suppressed the undesired homometathesis of **6a** and allowed for



Scheme 7. Cross metathesis of **6b** with electron-rich Type I styrene **13**.

the formation of the desired cross metathesis product in 47% NMR yield. Utilizing 10 mol % of **III** increased the yield of **11a** to 64% (NMR; 62% isolated yield, Table 3, entry 1).

Varying amounts of dimethyl fumarate were detected in the crude reaction mixture by ¹H NMR. This by-product, formed in a homometathesis reaction of **9**,^[52a] could be easily separated by flash chromatography, while the excess of unreacted **9** could be removed under vacuum. In contrast to the above described homometathesis of vinylphosphane oxides **6**, changing the concentration of **6a** from 0.02 M to 0.200 M did not result in a further improvement of the conversion.

Interestingly, in the cross metathesis reaction of **6a** with methyl acrylate, no coupling product **8aIII** was isolated after the reaction, or even detected by ³¹P-NMR. This observation suggests that the acrylate **9** first reacts with Ru-carbene complexes to form Ru=CH-CO₂Me species, and that the vinylphosphane oxides **6** then enters the catalytic cycle.^[52a]

As can be seen from the results compiled in Table 3, under these optimized conditions, different vinylphosphane oxides, including diaryl ones (**6c** and **6j**), can be used as cross metathesis substrates for **9** and **10** to give products in 29–62% yield and excellent stereoselectivity.

Use of a 30-fold excess of an electron pure CM partner was unnecessary in the cases of hardly-dimerizing phosphanes **6c** and **6j**. The second generation Grubbs' precatalyst **I** could be used in this transformation as well, however, a slightly lower yield was obtained in that case (Table 3, entry 3).

It should be noted that CM of **6c** with the *more electron-rich* 4-methoxystyrene **13** proceeds readily to give the expected product **14**^[50a] with practically equal yields regardless if precatalyst **I** or **III** was used.

Conclusion

In conclusion, we have demonstrated that vinylphosphane oxides **6** could be successfully “dimerized” by catalytic olefin homometathesis leading to a series of new achiral and P-stereogenic diphosphane dioxides **7** with exclusive *E*-selectivity. This unprecedented strategy allows for direct access to these valuable compounds,

Table 3. Cross metathesis of vinylphosphane oxides **6** with methyl acrylate **9** or 2-fluorostyrene **10** catalyzed by **III**.

$\begin{array}{c} R^1 \\ \\ R^2-P=CH-CH_2 \\ \\ O \end{array} + \begin{array}{c} CH_2 \\ \\ CH-Z \end{array} \xrightarrow[DCM]{III} \begin{array}{c} R^1 \\ \\ R^2-P=CH-CH=CH-Z \\ \\ O \end{array}$			
6		9 : Z = CO ₂ CH ₃ 10 : Z = 2-F-C ₆ H ₄	11 : Z = CO ₂ CH ₃ 12 : Z = 2-F-C ₆ H ₄
Entry	Product 11 , 12	III [mol %]	Yield [%] ^[a]
1		10	62 ^[b,c]
2		5	34 ^[d]
3		5	32 ^[c]
4		5	54
5		5	29 ^[f]

^[a] Reagents and conditions: **6** (1 equiv.), **9** (30 equivs.) or **10** (3 equivs.), precatalysts **III** (5.0–10.0 mol %), DCM, 24 h, reflux. Isolated yields of analytically pure products. Homodimerization products of **9** and **10** were not shown.

^[b] (*S_p*)-**6a** was used.

^[c] In the reaction with 5 mol % of **III**, the conversion calculated from ³¹P NMR was 47%.

^[d] *rac*-**6b** was used.

^[e] With precatalyst **I** (5 mol %), the yield was 24%.

^[f] *rac*-**6j** was used.

sometimes hardly available by more traditional synthetic strategies. Cross metathesis of **6** with electron-poor substrates, such as methyl acrylate and 2-fluorostyrene was a second challenging reaction tested in this study. Further applications of this methodology are readily expected on the basis of the well-established synthetic utility of products **7**, **11** and **12**. The use of **7a** for the design of new P-chiral diphosphane ligands is currently under investigation.

Experimental Section

General

Unless otherwise noted, all reactions were carried out under argon in pre-dried glassware using Schlenk techniques. The solvents were dried by distillation over the following drying agents and were transferred under argon: THF (K/benzophenone), toluene (Na), *n*-pentane, *n*-hexane, CH₂Cl₂ (CaH₂), Et₂O (LiAlH₄). Flash column chromatography: Merck silica gel 60 (230–400 mesh). NMR (¹H, ¹³C, ³¹P) spectra were recorded on Bruker AVANCE 500, AVS 400 (400.1 MHz, 100.6; 162 MHz), Varian Gemini 200 and 400 spectrometers in CDCl₃; chemical shifts (δ) are given in ppm relative to TMS, coupling constants (*J*) in Hz. IR: Perkin-Elmer Spectrum 2000 and 1170 FT-IR, wavenumbers in cm⁻¹. MS (EI, LSI-MS): AMD 604 Intectra GmbH, MAT 112 and MAT 312 Finnigan 70 eV. MS (ESI): Mariner Perseptive Biosystems, Inc. HR-MS: Finnigan MAT 312, VG Autospec, peak matching with PFK. Optical rotations: Perkin-Elmer 341 Polarimeter with sodium lamp (589 nm); Melting points: Electrothermal IA 9200 SERIES Digital Melting Point Apparatus (uncorrected). Micro-analyses were provided by Institute of Organic Chemistry, PAS, Warsaw. Precatalysts **III**–**V**^[56–58] were prepared according to the literature procedures. Vinylphosphane oxides **6a**^[36], **6b**,^[67] **6c**,^[67] **6d**^[68] and **6j**^[69] were known compounds and were synthesized according to the literature procedures. Vinylphosphane oxides **6e**–**i** were prepared from the respective *sec*-phosphane oxides by the vinyl transfer methodology^[70] utilizing *rac*-phenyl vinyl sulfoxide as the vinyl donor and were available from another study.^[71] All other substrates were commercially available and were used as received.

General Procedure for Homometathesis of Vinylphosphane Oxides **7**^[72]

To a mixture of vinylphosphane oxide **6** (1.0 mmol) in CH₂Cl₂ (4–7 mL) was added a solution of precatalyst **I**–**VI** (0.05–0.10 mmol) in CH₂Cl₂ (1 mL). The resulting mixture was stirred at 45 °C for 24 h. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography.

General Procedure for Cross Metathesis of Vinylphosphane Oxides with Methyl Acrylate^[72]

To a mixture of vinylphosphane oxide **6** (0.250 mmol) and precatalyst **III** (16.80 mg, 0.025 mmol) in CH₂Cl₂ (12.5 mL) *via* sy-

ringe was added degassed methyl acrylate (0.675 mL, 7.5 mmol). The resulting mixture was stirred at 45 °C for 24 h. The solvent was removed under reduced pressure. The crude product **7** was purified by flash chromatography (ethyl acetate-methanol, 20:1) to afford **11**.

General Procedure for Cross Metathesis of Vinylphosphane Oxides with 2-Fluorostyrene^[72]

To a mixture of vinylphosphane oxide **6** (0.36 mmol) and precatalyst **III** (15.3 mg, 0.018 mmol) in CH₂Cl₂ (18 mL) *via* syringe was added 2-fluorostyrene **10** (0.146 mL, 1.08 mmol). The resulting mixture was stirred at 45 °C for 24 h. The solvent was removed under reduced pressure. The crude product **12** was purified by flash chromatography (ethyl acetate then ethyl acetate-methanol, 20:1).

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