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Graphical Abstract

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A Practical Method for N-Alkylation of Phosphinic (Thio)amides with Alcohols via Transfer Hydrogenation

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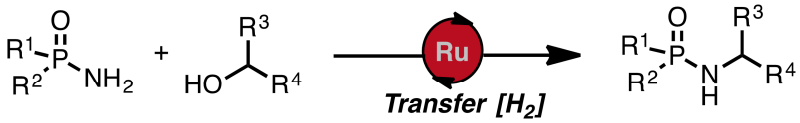

• low catalyst loading • H_2O as sole byproduct • redox-neutral

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A practical method for N-alkylation of phosphinic (thio)amides with alcohols via transfer hydrogenation

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ABSTRACT

This manuscript describes a modular method for preparing *N*-alkyl phosphinic amides from primary or secondary alcohols and primary phosphinic amide ($R^1R^2P{=}ONH_2$) nucleophiles via transfer hydrogenation. The transformation typically proceeds in excellent yields, employs conveniently available reagents, and produces water as the only byproduct.

1. Introduction

Phosphinic amides are a unique class of P(V) compounds that have been explored for diverse applications as medicines, agrochemicals, and materials, among others uses. (Fig. 1A).[1] Additionally *N*-alkyl phosphinic amides are commonly employed in organic synthesis as amine precursors by taking advantage of methods for reliable cleavage of the N–P bond.[2,3] These multifarious uses have motivated the development of several different methods for accessing structurally diverse phosphinic amides, including N-alkyl and N,N-dialkyl variants (Fig. 1B).[4] Strategies employing both P(III) and P(V) precursors have been pursued. P(III)-based methods inherently require an oxidation event at phosphorous, typically as a discrete step before or after P–N bond formation. In one example, a diorganophosphine chloride is coupled with an amine, followed by oxidation.[5] Alternatively, nucleophilic secondary phosphine oxides are first treated with an electrophilic halogenating reagent (or an electrophilic oxygenating agent followed activation with a reagent such as $SOCl_2$) to form the corresponding diorganophosphinic halide, which is then allowed to react with an amine.[6,7] While useful in their own right, P(III)-based methods have the disadvantage of generally employing air- or moisture-sensitive reagents and typically require two steps. Direct N-aryl/alkyation of P(V)–NH_2 phosphinic amides is an attractive alternative, as the starting materials in this case are air- and moisture-stable and the reaction requires only a single step.[8] N-Arylation of P(V)–NH_2 phosphinic amides has been described via Chan–Lam[9a] or Ullman coupling.[9b] Complementary N-alkylation can be achieved by several methods, including condensation with an aldehyde to form a (diorganophosphinoyl)imine, followed by 1,2-addition[2] or via an S_N2 reaction between an alkyl halide and an P(V)–NH_2 phosphinic amide nucleophile under phase-transfer conditions.[10] Given the widespread availability of

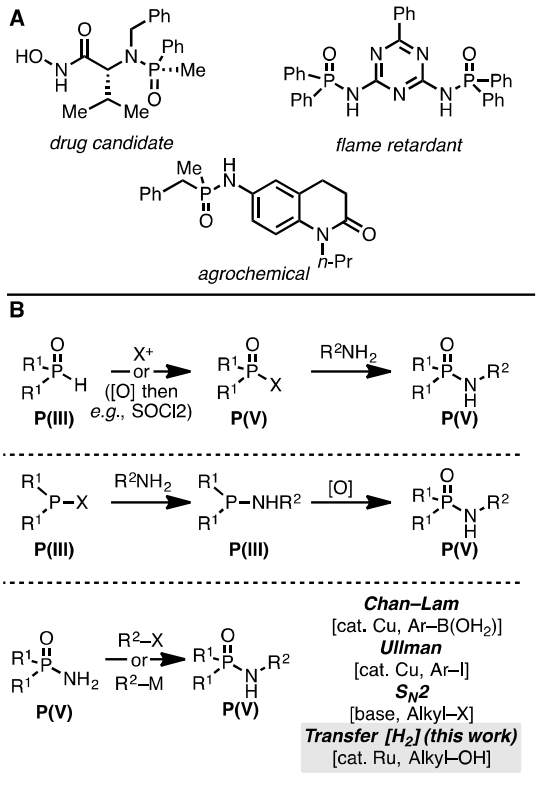


Fig. 1: (A) Representative examples of phosphinic amides with different applications. (B) Overview of synthetic methods for preparing phosphinic amides.

structurally diverse primary and secondary alcohols, direct coupling between a phosphinic amide nucleophile and an alcohol would represent an attractive alternative to the approaches described above. Seminal work during the past two decades has established that weak N–H nucleophiles,[11,12a] undergo N-alkylation with alcohols under transfer hydrogenation conditions. Additionally, electron rich primary aliphatic and aryl amines are known to give exclusive mono-methylation with methanol and Ru-MACHO (CAS no. 1295649-40-9; [RuHCl(CO)(HN($CH_2CH_2PPh_2$)$_2$)]).[12b,12c] To our knowledge, the strategy has been applied with P(V)–NH_2 phosphinic amides in two previous publications. In one case, Rámon and coworkers employed a copper catalyst at 150 °C for 10 days to couple benzyl alcohol and 1-hexanol with *P*,*P*-diphenylphosphinic amide, affording 35% and 17% of the desired products, respectively.[11a] In more recent work, Williams enlisted catalytic [Ru(p-cymene)Cl_2]$_2$ with PPh_3 as ligand to couple benzyl alcohol with *P*,*P*-diphenylphosphonic amide in 71% yield after 24 h at 150 °C.[11b] As part of our ongoing program in catalytic alkene functionalization via directed nucleometalation, we previously described Pd(II)-catalyzed hydrofunctionalization and difunctionalization reactions that employ weakly nucleophile nitrogen coupling partners, such as imides, amides, and sulfonamides.[13] We thus became interested in employing phosphinic amides to this type of reaction.[14] To this end, we sought access to a diverse collection of *N*-alkyl phosphinic amides, and thus required a robust and functional-group-tolerant method for their synthesis, which motivated the present study.

2. Results and Discussion

2.1. Reaction Design and Optimization

Based on the precedents above, we were attracted to the idea of preparing phosphinic amides via Ru(II)-catalyzed transfer hydrogenation[15], which we surmised would allow for atom-economical and modular coupling of P(V) N–H nucleophiles with alcohols. In terms of the proposed mechanism, we envisioned the following sequence of events. First, dehydrogenation of the alcohol would form the corresponding aldehyde or ketone, which would then be attacked by the weakly nucleophilic primary phosphinic amide. Loss of water would form the imine, and subsequent imine hydrogenation by the Ru(II) catalyst would turn over the catalyst and form the N-alkylated product. The commercial availability of a vast library of structurally diverse alcohols offered a convenient and inexpensive platform for building molecular complexity in a direct manner. After screening known (de)hydrogenative catalysts and bases, we identified Ru-MACHO[12,16] and KOH to give near quantitative yields for most primary alcohols and good yields for secondary alcohols, albeit at slightly higher temperatures. We also found a convenient base-free protocol using Ru-MACHO-BH[16b] **(**cas no. 1295649-41-0; [RuH(H-BH_3)(CO)(HN($CH_2CH_2PPh_2$)$_2$)]**)** for substrates with base-sensitive functional groups (**1x**). Ru-MACHO-BH was also a viable catalyst for the other substrates, but typically gave slightly lower yields (~5–10%) compared with Ru-MACHO in combination with KOH. We attribute the higher efficiency of the basic conditions to the ability of the base to deprotonate the alcohol and make coordination to the catalyst more favorable.

2.2. Transfer Hydrogenation Substrates

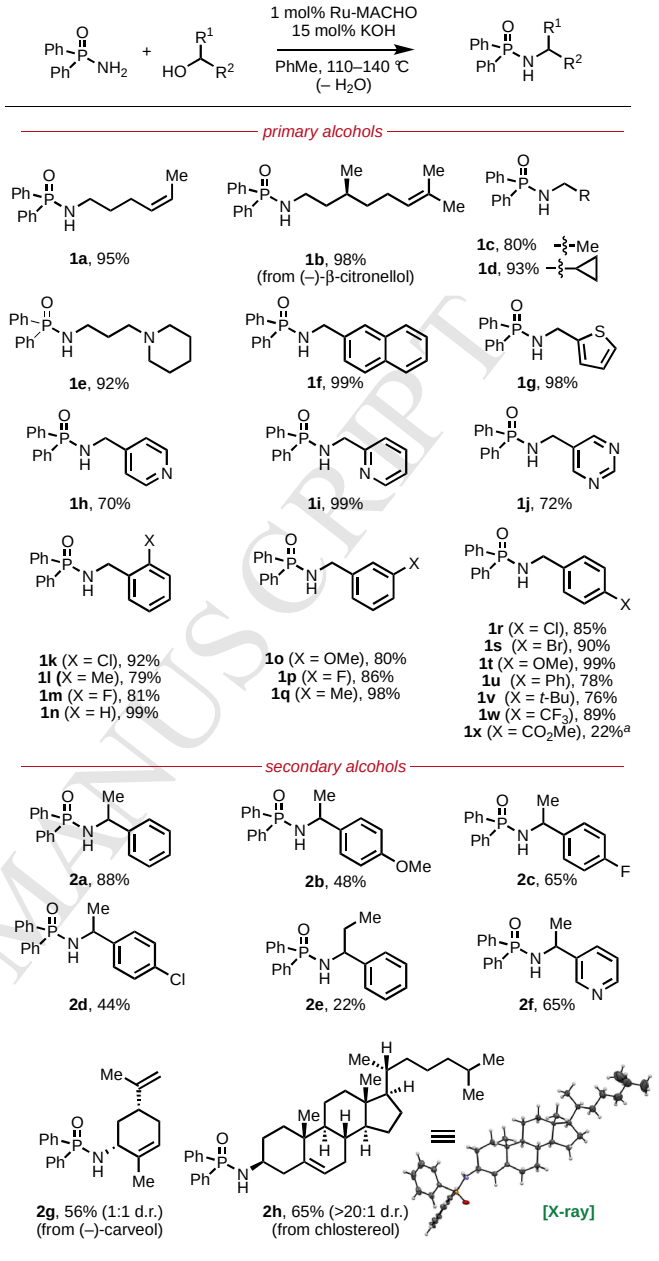


Table 1: Reaction condtions: phosphinic amide (0.2 mmol), alcohol (0.24 mmol), Ru-MACHO (0.002 mmol), KOH (0.030 mmol), toluene (0.7 mL), 110 ℃ (primary alcohols) or 140 ℃ (secondary alcohols), 16 h. Per centages represent isolated yields.
[a] Ru-MACHO-BH used as catalyst without addition of base.

Having identified an efficient catalyst system, we next moved on to examine the substrate scope (Table 1). The reaction was found to tolerate most common functional groups, giving excellent (in many cases quantitative) yields, provided that the alcohol is sterically unencumbered. Remarkably, disubstituted *Z*-alkenes (**1a**) were compatible, and no hydrogenation or isomerization of the alkene was observed—despite the fact that the reaction involves formation of a metal hydride intermediate at high temperature—showcasing the exquisite chemoselectivity of this catalyst. Additionally, a methyl ester (**1x**) was not hydrogenated under the reaction conditions, despite the fact that Ru-MACHO can be used as an ester hydrogenation catalyst under similar reaction conditions.[16a] The reaction also gave quantitative yields with heteroaryl-substituted alcohols that could coordinate in a bidentate fashion with the metal (**1d, 1f, 1h**). Other heterocycles similarly gave high yields (**1g, 1i, 2f**). A variety of electron-rich and neutral benzylic alcohols were superb electrophiles. In contrast the presence of strongly electron-withdrawing

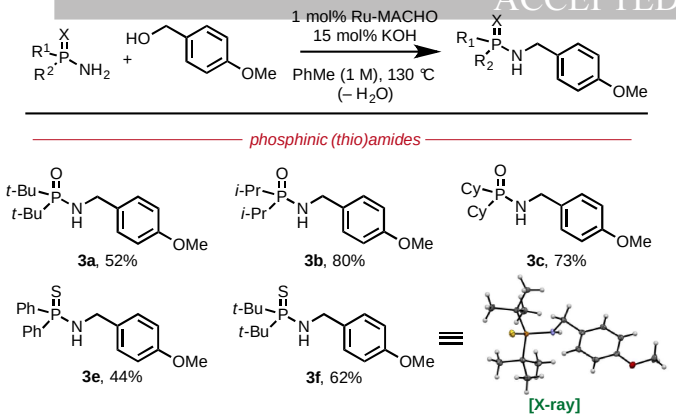
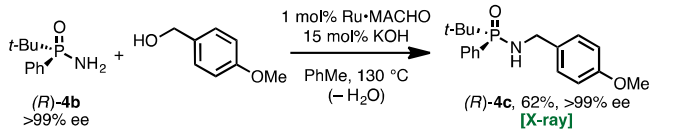


Table 2: Reaction condtions: phosphinic (thio)amide (0.2 mmol), alcohol (0.24 mmol), Ru-MACHO (0.002 mmol), KOH (0.030 mmol), toluene (0.7 mL), 130 ℃, 16 h. Percentages represent isolated yields.

groups or *ortho*-substituents led to diminished yields (**1k, 1l, 1x**). Aryl halides gave excellent yields and showed no evidence of decomposition under the reaction conditions (**1k, 1m, 1p, 1r, 1s**). Trifluoroethanol and methanol were both low-yielding (<5 %) under the standard reaction conditions. With methanol, slightly higher yield (13 %) could be obtained when 10 equiv MeOH was used. Some secondary alcohols were also amenable to this reaction, giving moderate to good yields depending on the properties of the alcohol coupling partner (**2a-2h**). In low-yielding cases, we attribute the decreased efficiency to the increased steric hindrance of these substrates and to the attenuated electrophilicity of the corresponding ketone intermediates compared to their aldehyde counterparts. We found that a number of naturally occurring terpenes such as cholesterol (**2h**), β-citronellol (**1b**) and carveol (**2g**) were viable substrates under the standard reaction conditions. Cholesterol reacted in good yield with high d.r. The major diastereomer was assigned by X-ray crystallography, and the stereochemical configuration of the C–N bond indicates that hydrogenation took place predominantly from the less hindered face. (–)-Carveol (used as a mixture of alcohol stereoisomers) was also reactive but generated a mixture of diastereomers, presumably due to the fact that the two faces of the putative imine intermediate were not significantly sterically differentiated. Given that the alcohol stereocenter is ablated during the initial dehydrogenation, the stereochemistry of the starting alcohol is not expected to affect the final d.r.

We next investigated the nucleophile scope and found different primary phosphinic amides performed well under the optimal reaction conditions (**3a–3f**, Table 2). Interestingly, benzamide (the carbon analog of *P*,*P*-diphenylphosphinic amide) was completely unreactive under standard conditions, illustrating that the presence of a heteroatom connected to the nucleophilic $–NH_2$ site is essential for reactivity. We also found that the much less explored sulfur analogs, thiophosphinic amides, were highly effective, providing similar yields.



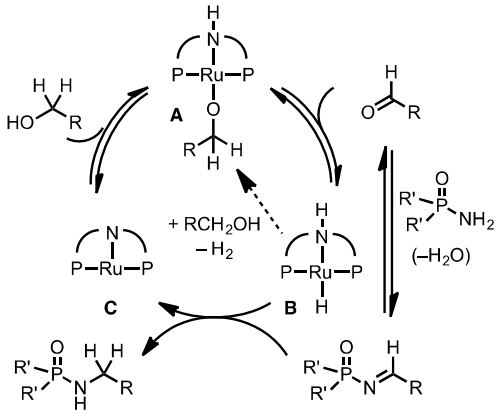
Scheme 1: Stereoretention of an enantioenriched chiral-at-P nucleophile under standard reaction conditions.

Next we sought to demonstrate that chiral-at-P phosphinic amides could be employed in this chemistry without erosion of optical purity (Scheme 1). The synthesis of optically pure P-chiral starting materials was accomplished by using phenyl *tert*-butylphosphine chloride and a commercially available enantiopure secondary benzyl amine, followed by mild oxidation to provide the P(V) intermediate. Separation of the two diastereomers by HPLC, followed by deprotection of the benzyl group afforded both enantiomers of *P*-*tert*-butyl,*P*-phenyl phosphinic amide (**4b**). When subjected to the catalytic *N*-alkylation conditions, (*R*)-(**4b**) gave similar yields to **3a** and **3f**, which have a similar steric environment about phosphorus, and the ee of the product was >99%, indicating that the P-stereocenter was configurationally stable under the reactions conditions.

Although the use of Ru-MACHO is typically limited to handling in a glovebox,[12] we found that our procedure can be carried out outside of the glovebox with nearly identical yields to those set up under strictly inert glovebox conditions. This finding simplifies the reaction operationally by allowing for alcohols to be used directly from the bottle without any degassing or drying.

2.3. Proposed Mechanism

The mechanism of this transformation likely follows a similar pathway to what has previously been described in the literature (Scheme 2).[12,17] Evidence for a stepwise dehydrogenation/hydrogenation pathway rather a concerted attack of the amine on a ruthenium bound alcohol/aldehyde is supported by the detection of the imine intermediate by LCMS when using 4-nitrobenzyl alcohol as the electrophile. Additionally, when synthesizing substrate **2e**, some unreacted ketone was also detected by LCMS. Based on these observations, it seems that the imine intermediate is highly reactive and cannot be trapped unless another suitable hydrogen acceptor such as a nitro group is present. Olefins (**1a, 1b, 2g, 2h**) do not appear to be competitive hydrogen acceptors in the presence of the imine intermediate. Although an acceptorless dehydrogenation of the alcohol where gaseous H_2 is generated followed by reactivation of H_2 by intermediate **C** is possible, the loss of H_2 from **B** is considered to be the rate limiting step with similar catalysts.[17] Therefore it is likely to be only a minor pathway, if operative at all. This reaction also appears to be completely selective for mono-*N*-alkylation; *N*,*N*-dialkylated products were never detected, even when using sterically unencumbered alcohols, such as ethanol, in large excess (10 equiv).



Scheme 2: Plausible catalytic cycle.

3. Conclusion

We have developed an efficient, high-yielding, and functional-group-tolerant route to access *N*-alkyl phosphinic amides from the corresponding P(V)–NH_2 nucleophiles and alcohols. This method allows rapid access to structurally diverse phosphinic amides from simple starting materials, and circumvents limitations associated with the use of P(III) precursors. We demonstrated enantioretentive N-alkylation with enantioenriched chiral-at-P phosphinic amides, allowing this family of bench-stable starting materials to serve as an entry point to more highly substituted chiral-at-P target molecules.

4. Experimental

4.1. General Procedures

Glovebox Procedure (General Procedure 1): Inside an argon-filled glovebox (O_2 levels between 35.0–55.0 ppm, H_2O levels unknown), to an oven dried 10-mL screw cap vial equipped with a Teflon-coated magnetic stir bar were added Ru-MACHO (1.2 mg, 2.00 μmol), KOH (1.7 mg, 30.0 μmol), and the appropriate phosphinic amide (0.200 mmol) in that order. Subsequently, toluene (0.7 mL) was added via micropipette, with care taken to ensure that solids on the wall were washed to the bottom of the vial. Next, the appropriate alcohol (0.240 mmol) was added either as a solid or via micropipette for liquid substrates. The reaction was sealed tightly with a non-puncturable cap and was further sealed by placing a piece of electrical tape around the cap and top of vial.

Schlenk Line Procedure (General Procedure 2): To a flame-dried vial were quickly added Ru-MACHO (1.2 mg, 2.00 μmol) and KOH (1.7 mg, 30.0 μmol) (stored under Ar) (addition time <1 min), and the reaction vial was left open under a steady flow of nitrogen (applied via a needle placed at the top of the vial). Next, the appropriate phosphinic amide (0.200 mmol) was added, followed by the addition of toluene (0.7 mL) from a standard Solvent Purification System (SPS). Lastly, the appropriate alcohol (0.240 mmol) was added either as a solid or via micropipette for liquid substrates. The nitrogen line was removed and the vial was then quickly and tightly sealed with a non-puncturable cap and further sealed by placing a piece of electrical tape around the cap and top of the vial. After the differing series of operations described above, General Procedures 1 and 2 then followed then same protocol. The reaction vessel was placed in a preheated oil bath at 110–140 °C with a stirring rate of 500 rpm. As the reaction was proceeding, the vessel was periodically visually monitored. If large amounts of solid were found to have accumulated on the wall, the vial was briefly removed from the oil bath and shaken to wash the solids back to the bottom of the vial. After 16 h, the vial was removed from the oil bath and allowed to cool to room temperature. Methanol (1 mL) was added to dissolve all solids, and the solvent removed *in vacuo*. The solid was redissolved in methanol (1 mL), and the solution was filtered through a 40-micron syringe filter. Samples were then purified by reverse-phase HPLC or recrystallized from hot benzene. In the case of HPLC purification, the fractions were combined, frozen in liquid N_2, and lyophilized to sublime the solvent.

The primary phosphinic amides used in the synthesis of compounds **3a–3f** were purchased from commercial sources or synthesized according to a known procedure.[19] Additional details can be found in the Supporting Information (page S-4).

4.2. Characterization of new compounds

(*Z*)-*N*-(hex-4-en-1-yl)-*P*,*P*-diphenylphosphinic amide (1a): The title compound was prepared from Ru•MACHO (1.2 mg, 0.002 mmol), KOH (1.7 mg, 0.030 mmol), *P*,*P*-diphenylphosphinic amide (43.4 mg, 0.20 mmol) and (*Z*)-hex-4-en-1-ol (24 mg, 0.24 mmol) according to General Procedure 1. Purification by reverse phase HPLC gave the product as a white solid (57 mg, 95% yield). **^{1}H NMR** (600 MHz, DMSO-d_6) δ 8.15–8.07 (m, 1H), 7.96–7.89 (m, 1H), 7.88–7.78 (m, 5H), 7.67 (d, *J* = 7.1 Hz, 1H), 7.57–7.41 (m, 9H), 5.94 (dt, *J* = 9.6, 7.2 Hz, 1H), 4.45 (dd, *J* = 9.4, 7.2 Hz, 2H). **^{13}C NMR** (150 MHz, DMSO-d_6) δ 134.06 (d, *J* = 126.0 Hz), 131.65 (dd, *J* = 9.2, 2.8 Hz), 131.31, 129.95, 128.37 (d, *J* = 12.0 Hz),123.82, 31.45 (d, *J* = 6.3 Hz) 23.84, 17.70, 12.61.**^{31}P NMR** (162 MHz, DMSO) δ 22.82. **HRMS** (FAB+) *m/z* Calcd for $C_{18}H_{23}NOP$ $[M]^+$ 300.1512, found 300.1511.

(*S*)-*N*-(3,7-dimethyloct-6-en-1-yl)-*P*,*P*-diphenylphosphinic amide (1b): The title compound was prepared from Ru-MACHO (1.2 mg, 0.002 mmol), KOH (1.7 mg, 0.030 mmol), *P*,*P*-diphenylphosphinic amide (43.4 mg, 0.20 mmol) and (–)-β-citronellol (34 mg, 0.22 mmol) according to General Procedure 1. Purification by reverse phase HPLC gave the product as a white solid (57 mg, 98% yield). **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.78 (dd, *J* = 11.6, 7.5 Hz, 4H), 7.59–7.41 (m, 6H), 5.22 (q, *J* = 7.3 Hz, 1H), 5.04 (t, *J* = 7.3 Hz, 1H), 2.74 (ddddt, *J* = 28.2, 12.3, 9.1, 6.0, 3.0 Hz, 2H), 1.89 (dq, *J* = 14.5, 7.2 Hz, 2H), 1.62 (s, 3H), 1.53 (s, 3H), 1.47 (m, 2H), 1.30 (ddt, *J* = 13.0, 7.8, 4.1 Hz, 1H), 1.19 (ddt, *J* = 12.3, 9.5, 6.0 Hz, 1H), 1.05 (ddt, *J* = 13.5, 9.1, 6.6 Hz, 1H), 0.75 (d, *J* = 6.5 Hz, 3H). **^{13}C NMR** (150 MHz, DMSO-d_6) δ 134.06 (d, *J* = 125.2 Hz), 131.64 (d, *J* = 9.2 Hz), 131.29, 130.40, 128.34 (d, *J* = 12.0 Hz) 124.61, δ 38.57 (d, *J* = 6.5 Hz) 37.98, 36.52, 29.31, 25.48, 24.81, 19.32, 17.49. **^{31}P NMR** (162 MHz, DMSO) δ 21.64. **HRMS** (FAB+) *m/z* Calcd for $C_{22}H_{31}NOP$ $[M]^+$ 356.2138, found 356.2139.

***N*-ethyl-*P*,*P*-diphenylphosphinic amide (1c):** The title compound was prepared from Ru-MACHO (1.2 mg, 0.002 mmol), KOH (1.7 mg, 0.030 mmol), *P*,*P*-diphenylphosphinic amide (43.4 mg, 0.20 mmol) and ethanol (58 μL, 1.0 mmol) according to General Procedure 1. Purification by reverse phase HPLC gave the product as a white solid (39 mg, 80% yield). ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.79 (ddt, *J* = 11.7, 6.8, 1.5 Hz, 4H), 7.58 – 7.40 (m, 6H), 5.30 (q, *J* = 7.3 Hz, 1H), 2.90 – 2.66 (m, 2H), 1.09 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 134.05 (d, *J* = 126.1 Hz), 131.64 (d, *J* = 9.3 Hz), 131.33 (d, *J* = 2.6 Hz), 128.39 (d, *J* = 12.0 Hz), 34.87 (d, *J* = 1.4 Hz), 17.42 (d, *J* = 6.9 Hz). ^{31}P NMR (162 MHz, DMSO) δ 21.61. **HRMS** (FAB+) *m/z* Calcd for $C_{14}H_{16}NOP$ $[M+H]^+$ 246.1042, found 246.1042.

***N*-(cyclopropylmethyl)-*P*,*P*-diphenylphosphinic amide (1d):** The title compound was prepared from Ru-MACHO (1.2 mg, 0.002 mmol), KOH (1.7 mg, 0.030 mmol), *P*,*P*-diphenylphosphinic amide (43.4 mg, 0.20 mmol) and cyclopropylmethanol (19 μL, 0.24 mmol) according to General Procedure 1. Purification by reverse phase HPLC gave the product as a white solid (58 mg, 93% yield). **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.84–7.77 (m, 4H), 7.55–7.49 (m, 2H), 7.48 (tdd, *J* = 6.5, 3.1, 1.7 Hz, 3H), 7.26 (dq, *J* = 4.5, 2.3 Hz, 1H), 5.41 (dt, *J* = 9.0, 7.0 Hz, 1H), 2.64 (dt, *J* = 10.5, 6.8 Hz, 2H), 0.93 (dddd, *J* = 11.5, 6.6, 4.0, 1.6 Hz, 1H), 0.40–0.32 (m, 2H), 0.12 (dt, *J* = 6.1, 4.3 Hz, 2H). **^{13}C NMR** (150

MHz, DMSO-d_6) δ 134.13 (d, J = 126.0 Hz), 131.67 (d, J = 9.3 Hz), 131.31, 128.34 (d, J = 12.1 Hz) 44.74, 12.80, 3.51. **^{31}P NMR** (162 MHz, DMSO) δ 21.57. **HRMS** (FAB+) *m/z* Calcd for $C_{24}H_{24}ClNOP$ $[M+H]^+$ 272.1199, found 272.1200.

***P,P*-diphenyl-*N*-(3-(piperidin-1-yl)propyl)phosphinic amide (1e):** The title compound was prepared from Ru-MACHO (1.2 mg, 0.002 mmol), KOH (1.7 mg, 0.030 mmol), *P,P*-diphenylphosphinic amide (43.4 mg, 0.20 mmol) and 3-(piperidin-1-yl)propan-1-ol (37 µL, 0.24 mmol) according to General Procedure 1. Purification by reverse phase HPLC gave the product as a viscous colorless oil (58 mg, 93% yield). This material was sparingly soluble in DMSO-d_6, MeOH-d_4, Acetone-d_6 or $CDCl_3$. The ^{13}C NMR spectrum showed extremely complex splitting in the aliphatic region, so peaks are listed without attempting to accurately calculate splitting values. **^{1}H NMR** (600 MHz, Acetone-d_6) δ 8.35 (s, 1H), 7.83 (ddd, J = 11.1, 7.3, 1.9 Hz, 5H), 7.30 (dt, J = 6.7, 3.7 Hz, 5H), 3.28 (dt, J = 22.2, 6.6 Hz, 1H), 2.98 (dt, J = 17.8, 6.7 Hz, 1H), 2.90–2.58 (m, 6H), 2.00–1.88 (m, 2H), 1.80–1.35 (m, 8H). **^{13}C NMR** (150 MHz, Acetone-d_6) δ 140.77 (d, J = 130.6 Hz), 130.86 (d, J = 9.2 Hz), 128.84 (d, J = 2.3 Hz), 127.14 (d, J = 11.6 Hz) 55.14, 52.82, 52.58, 52.47, 52.39, 52.33, 47.26, 37.54, 36.62, 25.15, 24.85, 23.81, 23.55, 23.41, 22.97, 22.45, 22.26, 22.10, 21.98..**^{31}P NMR** (162 MHz, Acetone) δ 16.51. **HRMS** (FAB+) *m/z* Calcd for $C_{20}H_{28}N_2OP$ $[M+H]^+$ 345.1934, found 345.1936.

***N*-(naphthalen-2-ylmethyl)-*P,P*-diphenylphosphinic amide (1f):** The title compound was prepared from Ru-MACHO (1.2 mg, 0.002 mmol), KOH (1.7 mg, 0.030 mmol), *P,P*-diphenylphosphinic amide (43.4 mg, 0.20 mmol) and naphthalen-2-ylmethanol (38.0 mg, 0.24 mmol) according to General Procedure 1. Purification by reverse phase HPLC gave the product as a white solid (72 mg, 99% yield). **^{1}H NMR** (600 MHz, DMSO-d_6) δ 8.13–8.08 (m, 1H), 7.95–7.90 (m, 1H), 7.87–7.79 (m, 5H), 7.67 (d, J = 7.1 Hz, 1H), 7.55–7.43 (m, 9H), 5.94 (dt, J = 9.6, 7.2 Hz, 1H), 4.45 (dd, J = 9.4, 7.2 Hz, 2H). **^{13}C NMR** (150 MHz, DMSO-d_6) δ 135.71 (d, J = 7.3 Hz), 134.24, 133.40, 133.12, 131.60 (d, J = 9.4 Hz), 131.48 (d, J = 2.4 Hz), 130.67, 128.59–128.24 (m), 127.33, 126.02, 125.63, 125.38, 125.23, 123.36, 41.12. **^{31}P NMR** (162 MHz, DMSO) δ 22.82. **HRMS** (FAB+) *m/z* Calcd for $C_{23}H_{21}NOP$ $[M+H]^+$ 358.1355, found 358.1356.

***P,P*-diphenyl-*N*-(thiophen-2-ylmethyl)phosphinic amide (1g):** The title compound was prepared from Ru-MACHO (1.2 mg, 0.002 mmol), KOH (1.7 mg, 0.030 mmol), *P,P*-diphenylphosphinic amide (43.4 mg, 0.20 mmol) and thiophen-2-ylmethanol (23 µL, 0.24 mmol) according to General Procedure 1. Purification by reverse phase HPLC gave the product as a white solid (77 mg, 98% yield). **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.83 (dd, J = 11.7, 7.4 Hz, 4H), 7.55 (t, J = 7.3 Hz, 2H), 7.50 (td, J = 7.6, 2.9 Hz, 4H), 7.40 (d, J = 5.0 Hz, 1H), 6.99 (d, J = 3.5 Hz, 1H), 6.95 (t, J = 4.3 Hz, 1H), 6.09 (q, J = 7.8 Hz, 1H), 4.14 (dd, J = 9.4, 7.3 Hz, 2H). **^{13}C NMR** (150 MHz, DMSO-d_6) δ 144.61 (d, J = 8.3 Hz), 133.60 (d, J = 126.3 Hz), 131.66 (d, J = 9.4 Hz), 131.56 (d, J = 2.6 Hz), 128.47 (d, J = 12.1 Hz), 126.72, 124.73 (d, J = 11.7 Hz), 38.78. **^{31}P NMR** (162 MHz, DMSO) δ 22.31. **HRMS** (FAB+) *m/z* Calcd for $C_{17}H_{17}NOPS$ $[M+H]^+$ 314.0763, found 377.0764.

***P,P*-diphenyl-*N*-(pyridin-4-ylmethyl)phosphinic amide (1h):** The title compound was prepared from Ru-MACHO (1.2 mg, 0.002 mmol), KOH (1.7 mg, 0.030 mmol), *P,P*-diphenylphosphinic amide (43.4 mg, 0.20 mmol) and pyridin-4-ylmethanol (26.2 mg, 0.24 mmol) according to General Procedure 1. Purification by reverse phase HPLC gave the product as a white solid (43 mg, 70% yield). **^{1}H NMR** (600 MHz, DMSO-d_6) δ 8.49 (d, J = 4.5 Hz, 2H), 7.83 (dd, J = 11.1, 7.8 Hz, 4H), 7.53 (d, J = 6.9 Hz, 2H), 7.51–7.45 (m, 4H), 7.42 (d, J = 4.5 Hz, 2H), 6.08 (q, J = 7.6 Hz, 1H), 4.07–3.96 (m, 2H). **^{13}C NMR** (150 MHz, DMSO-d_6) δ 149.73 (d, J = 5.8 Hz), 149.32, 133.46 (d, J = 126.6 Hz), 131.71 (d, J = 9.4 Hz), 131.64 (d, J = 2.7 Hz), 128.53 (d, J = 12.1 Hz), 122.35, 42.63. **^{31}P NMR** (162 MHz, DMSO) δ 22.85. **HRMS** (FAB+) *m/z* Calcd for $C_{18}H_{18}N_2OP$ $[M+H]^+$ 309.1151, found 309.1151.

***P,P*-diphenyl-*N*-(pyridin-2-ylmethyl)phosphinic amide (1l):** The title compound was prepared from Ru-MACHO (1.2 mg, 0.002 mmol), KOH (1.7 mg, 0.030 mmol), *P,P*-diphenylphosphinic amide (43.4 mg, 0.20 mmol) and pyridin-2-ylmethanol (23 µL, 0.24 mmol) according to General Procedure 1. Purification by reverse phase HPLC gave the product as a white solid (61 mg, 99% yield). **^{1}H NMR** (600 MHz, DMSO-d_6) δ 8.49–8.42 (m, 1H), 7.88–7.82 (m, 4H), 7.80 (td, J = 7.7, 1.9 Hz, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.54 (td, J = 7.3, 1.5 Hz, 2H), 7.49 (td, J = 7.4, 3.1 Hz, 4H), 7.25 (dd, J = 7.5, 4.8 Hz, 1H), 5.99 (dt, J = 9.4, 7.4 Hz, 1H), 4.08 (dd, J = 10.9, 7.3 Hz, 2H). **^{13}C NMR** (150 MHz, DMSO-d_6) δ 159.82 (d, J = 6.7 Hz), 148.47, 136.64, 133.56 (d, J = 126.5 Hz), 131.71 (d, J = 9.4 Hz), 131.58 (d, J = 2.6 Hz), 128.51 (d, J = 12.1 Hz), 122.02, 121.36, 45.43. **^{31}P NMR** (162 MHz, DMSO) δ 22.67. **HRMS** (FAB+) *m/z* Calcd for $C_{18}H_{18}N_2OP$ $[M+H]^+$ 309.1151, found 309.1152.

***P,P*-diphenyl-*N*-(pyrimidin-5-ylmethyl)phosphinic amide (1i):**
The title compound was prepared from Ru-MACHO (1.2 mg, 0.002 mmol), KOH (1.7 mg, 0.030 mmol), *P,P*-diphenylphosphinic amide (43.4 mg, 0.20 mmol) and pyrimid-5-ylmethanol (26 mg, 0.24 mmol) according to General Procedure 1. Purification by reverse phase HPLC gave the product as a white solid (45 mg, 72% yield). **^{1}H NMR** (600 MHz, DMSO-d_6) δ 9.05 (s, 1H), 8.78 (s, 2H), 7.82 (ddd, J = 11.8, 8.3, 1.5 Hz, 4H), 7.54 (td, J = 7.3, 1.5 Hz, 2H), 7.49 (ddd, J = 9.6, 5.3, 2.1 Hz, 4H), 6.12–6.00 (m, 1H), 4.03 (dd, J = 11.6, 7.3 Hz, 2H). **^{1}H NMR** (600 MHz, Methanol-d_4) δ 9.02 (s, 1H), 8.77 (s, 2H), 7.86 (dd, J = 12.3, 7.5 Hz, 5H), 7.57 (t, J = 7.5 Hz, 2H), 7.51 (td, J = 7.7, 3.2 Hz, 5H), 4.17 (d, J = 11.6 Hz, 2H). **^{13}C NMR** (151 MHz, Methanol-d_4) δ 157.90, 157.69133.55 (d, J = 2.8 Hz), 133.05 (d, J = 10.0 Hz), 132.74 (d, J = 9.9 Hz), 129.90 (d, J = 12.7 Hz), 129.56 (d, J = 12.7 Hz). 40.61. **^{31}P NMR** (162 MHz, MeOD) δ 28.03. **HRMS** (FAB+) *m/z* Calcd for $C_{17}H_{17}N_3OP$ $[M+H]^+$ 310.1105, found 310.1104.

***N*-(2-chlorobenzyl)-*P,P*-diphenylphosphinic amide (1k):** The title compound was prepared from Ru-MACHO (1.2 mg, 0.002 mmol), KOH (1.7 mg, 0.030 mmol), *P,P*-

diphenylphosphinic amide (43.4 mg, 0.20 mmol) and (2-chlorophenyl)methanol (34.3 mg, 0.24 mmol) according to General Procedures 1 or 2. Both yields are reported below. Purification by reverse phase HPLC gave the product as a white solid (GP1: 63 mg, 92% yield; GP2: 61 mg, 89% yield;). **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.84 (ddt, *J* = 11.8, 6.9, 1.5 Hz, 4H), 7.78 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.58–7.51 (m, 2H), 7.48 (ddd, *J* = 8.5, 6.6, 3.1 Hz, 4H), 7.42–7.34 (m, 2H), 7.27 (td, *J* = 7.7, 1.7 Hz, 1H), 6.00 (dt, *J* = 9.3, 7.5 Hz, 1H), 4.06 (dd, *J* = 10.6, 7.5 Hz, 2H). **^{13}C NMR** (150 MHz, DMSO-d_6) δ 137.60 (d, *J* = 6.6 Hz), 133.89, 133.05, 131.65 (d, *J* = 9.4 Hz), 131.59 (d, *J* = 2.8 Hz), 131.49, 128.90 (d, *J* = 51.2 Hz), 128.49 (d, *J* = 12.1 Hz)., 128.35, 127.09, 41.04. **^{31}P NMR** (162 MHz, Acetone) δ 22.94. **HRMS** (FAB+) *m/z* Calcd for $C_{19}H_{18}ClNOP$ $[M+H]^+$ 342.0809, found 342.0809.

***N*-(2-methylbenzyl)-*P*,*P*-diphenylphosphinic amide (1j):** The title compound was prepared from Ru-MACHO (1.2 mg, 0.002 mmol), KOH (1.7 mg, 0.030 mmol), *P*,*P*-diphenylphosphinic amide (43.4 mg, 0.20 mmol) and *o*-tolylmethanol (29 µL, 0.24 mmol) according to General Procedure 1. Purification by reverse phase HPLC gave the product as a white solid (58 mg, 79% yield). **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.88–7.75 (m, 3H), 7.58–7.42 (m, 7H), 7.22–7.03 (m, 3H), 5.79–5.65 (m, 1H), 3.94 (dd, *J* = 9.5, 7.2 Hz, 2H), 2.16 (s, 3H). **^{13}C NMR** (150 MHz, DMSO-d_6) δ 138.32 (d, *J* = 7.2 Hz), 135.11, 133.84 (d, *J* = 126.0 Hz), 131.63 (d, *J* = 9.4 Hz), 131.45 (d, *J* = 2.7 Hz), 129.62, 128.42 (d, *J* = 12.1 Hz) δ, 127.55, 126.58, 125.69, 40.95, 18.55. **^{31}P NMR** (162 MHz, DMSO) δ 22.66. **HRMS** (FAB+) *m/z* Calcd for $C_{20}H_{21}NOP$ $[M+H]^+$ 322.1355, found 322.1355.

***N*-(2-fluorobenzyl)-*P*,*P*-diphenylphosphinic amide (1m):** The title compound was prepared from Ru-MACHO (1.2 mg, 0.002 mmol), KOH (1.7 mg, 0.030 mmol), *P*,*P*-diphenylphosphinic amide (43.4 mg, 0.20 mmol) and (2-fluorophenyl)methanol (30.3 mg , 0.24 mmol) according to General Procedure 1. Purification by reverse phase HPLC gave the product as a white solid (53 mg, 81% yield). **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.88–7.78 (m, 4H), 7.59–7.45 (m, 6H), 7.21–7.13 (m, 3H), 7.03 (dt, *J* = 5.7, 2.3 Hz, 1H), 5.87 (dt, *J* = 9.5, 7.4 Hz, 1H), 3.93 (dd, *J* = 10.3, 7.4 Hz, 2H). **^{13}C NMR** (150 MHz, DMSO-d_6) δ 140.56 (d, *J* = 6.9 Hz), 131.69 (d, *J* = 9.3 Hz), 131.44 (d, *J* = 2.7 Hz), 128.42 (d, *J* = 12.1 Hz), 127.98 (d, *J* = 5.9 Hz). **^{19}F NMR** (376 MHz, DMSO) δ -119.85. **^{31}P NMR** (162 MHz, DMSO) δ 22.49. **HRMS** (FAB+) *m/z* Calcd for $C_{19}H_{18}FNOP$ $[M+H]^+$ 326.1105, found 326.1107.

***N*-benzyl-*P*,*P*-diphenylphosphinic amide (1n):** The title compound was prepared from Ru-MACHO (1.2 mg, 0.002 mmol), KOH (1.7 mg, 0.030 mmol), *P*,*P*-diphenylphosphinic amide (43.4 mg, 0.20 mmol) and benzyl alcohol (24 µL, 0.24 mmol) according to General Procedures 1 or 2, both giving identical yields. Purification by reverse phase HPLC gave the product as a colorless oil (61 mg, 99% yield). The NMR spectra match with reported spectra[9].

***N*-(3-methoxybenzyl)-*P*,*P*-diphenylphosphinic amide (1o):** The title compound was prepared from Ru-MACHO (1.2 mg, 0.002 mmol), KOH (1.7 mg, 0.030 mmol), *P*,*P*-diphenylphosphinic amide (43.4 mg, 0.20 mmol) and (3-methoxyphenyl)methanol (30 µL, 0.24 mmol) according to General Procedure 1. Purification by reverse phase HPLC gave the product as a white solid (54 mg, 80% yield). **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.88–7.77 (m, 4H), 7.56–7.51 (m, 2H), 7.48 (td, *J* = 7.5, 2.8 Hz, 4H), 7.21 (t, *J* = 7.8 Hz, 1H), 7.03–6.88 (m, 2H), 6.79 (dd, *J* = 8.1, 2.7 Hz, 1H), 5.91 (q, *J* = 7.9 Hz, 1H), 3.94 (dt, *J* = 11.3, 5.7 Hz, 2H), 3.72 (s, 3H). **^{13}C NMR** (150 MHz, DMSO) δ 159.19, 142.34, 133.78 (d, *J* = 126.5 Hz). 131.69 (d, *J* = 9.3 Hz), 131.47, 129.11, 128.44 (d, *J* = 12.1 Hz). 119.43, 112.93, 112.10, 54.93, 43.52. **^{31}P NMR** (162 MHz, DMSO) δ 22.48. **HRMS** (FAB+) *m/z* Calcd for $C_{20}H_{21}NO_2P$ $[M+H]^+$ 338.1304, found 338.1304.

***N*-(3-fluorobenzyl)-*P*,*P*-diphenylphosphinic amide (1p):** The title compound was prepared from Ru-MACHO (1.2 mg, 0.002 mmol), KOH (1.7 mg, 0.030 mmol), *P*,*P*-diphenylphosphinic amide (43.4 mg, 0.20 mmol) and (3-fluorophenyl)methanol (30.3 mg, 0.24 mmol) according to General Procedure 1. Purification by reverse phase HPLC gave the product as a white solid (56 mg, 86% yield). **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.82 (dd, *J* = 11.8, 7.4 Hz, 4H), 7.58–7.43 (m, 6H), 7.33 (td, *J* = 7.9, 6.0 Hz, 1H), 7.30–7.23 (m, 1H), 7.21 (d, *J* = 7.6 Hz, 1H), 7.04 (td, *J* = 8.6, 2.7 Hz, 1H), 6.01 (dt, *J* = 9.8, 7.4 Hz, 1H), 3.99 (dd, *J* = 11.1, 7.5 Hz, 2H). **^{13}C NMR** (150 MHz, DMSO-d_6) δ 162.20 (d, *J* = 243.0 Hz), 143.92 (t, *J* = 6.5 Hz), 133.62 (d, *J* = 126.5 Hz), 131.70 (d, *J* = 9.4 Hz), 131.56 (d, *J* = 2.6 Hz), 129.96 (d, *J* = 8.2 Hz), 128.49 (d, *J* = 12.1 Hz), 123.22 (d, *J* = 2.7 Hz), 114.00 (d, *J* = 21.7 Hz), 113.36 (d, *J* = 21.1 Hz) 43.14. **^{31}P NMR** (162 MHz, DMSO) δ 22.64. **^{19}F NMR** (376 MHz, DMSO) δ -114.14. **HRMS** (FAB+) *m/z* Calcd for $C_{19}H_{18}FNOP$ $[M+H]^+$ 326.1105, found 326.1104.

***N*-(3-methylbenzyl)-*P*,*P*-diphenylphosphinic amide (1q):** The title compound was prepared from Ru-MACHO (1.2 mg, 0.002 mmol), KOH (1.7 mg, 0.030 mmol), *P*,*P*-diphenylphosphinic amide (43.4 mg, 0.20 mmol) and m-tolylmethanol (29 µL, 0.24 mmol) according to General Procedure 1. Purification by reverse phase HPLC gave the product as a white solid (57 mg, 78% yield). **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.82 (dd, *J* = 11.6, 7.2 Hz, 4H), 7.52 (t, *J* = 7.2 Hz, 2H), 7.48 (td, *J* = 7.5, 2.8 Hz, 4H), 7.19 (d, *J* = 5.2 Hz, 2H), 7.15 (s, 1H), 5.87 (q, *J* = 7.9 Hz, 1H), 3.93 (dd, *J* = 10.3, 7.4 Hz, 2H), 2.27 (s, 3H). **^{13}C NMR** (150 MHz, DMSO-d_6) δ 140.58 (d, *J* = 6.6 Hz), 131.71 (d, *J* = 9.3 Hz), 137.06, 134.26, 133.43, 131.46 (d, *J* = 2.7 Hz), 128.44 (d, *J* = 11.9 Hz), 128.00 (d, *J* = 5.9 Hz), 127.28, 124.45, 43.52, 21.07. **^{31}P NMR** (162 MHz, DMSO) δ 22.45. **HRMS** (FAB+) *m/z* Calcd for $C_{20}H_{21}NOP$ $[M+H]^+$ 322.1355, found 322.1356.

***N*-(4-chlorobenzyl)-*P*,*P*-diphenylphosphinic amide (1r):** The title compound was prepared from Ru-MACHO (1.2 mg, 0.002 mmol), KOH (1.7 mg, 0.030 mmol), *P*,*P*-diphenylphosphinic amide (43.4 mg, 0.20 mmol) and (4-chlorophenyl)methanol (34.3 mg, 0.24 mmol) according to General Procedure 1. Purification by reverse phase HPLC gave the product as a white solid (58 mg, 85% yield). **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.86–7.77 (m, 4H), 7.55–7.50 (m, 2H), 7.48 (td, *J* = 7.5, 3.0 Hz, 4H), 7.42 (d, *J* = 8.3 Hz, 2H), 7.36 (d, *J* = 8.5 Hz, 2H), 5.98 (dt, *J* = 9.8, 7.4 Hz, 1H), 3.96 (dd, *J* = 10.8, 7.4 Hz, 2H). **^{13}C NMR** (150 MHz, DMSO-d_6) δ 139.83 (d, *J* = 6.1 Hz), 133.66 (d, *J* = 126.4 Hz), 131.70 (d, *J* = 9.3 Hz), 131.54 (d, *J* = 2.6 Hz), 131.19, 129.19, 128.48 (d, *J* = 12.1 Hz), 128.00, 42.93. **^{31}P NMR** (162 MHz, DMSO)

δ 22.58. **HRMS** (FAB+) *m/z* Calcd for $C_{19}H_{18}ClNOP$ $[M+H]^+$ 342.0809, found 342.0810.

***N*-(4-bromobenzyl)-*P,P*-diphenylphosphinic amide (1s):** The title compound was prepared from Ru-MACHO (1.2 mg, 0.002 mmol), KOH (1.7 mg, 0.030 mmol), *P,P*-diphenylphosphinic amide (43.4 mg, 0.20 mmol) and (4-bromophenyl) methanol (45 mg, 0.24 mmol) according to General Procedure 1. Purification by reverse phase HPLC gave the product as a white solid (57 mg, 90% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.69–7.64 (m, 2H), 7.42–7.38 (m, 2H), 7.31 (t, *J* = 7.9 Hz, 2H), 7.27–7.17 (m, 4H), 7.01 (s, 1H), 6.93 (d, *J* = 8.1 Hz, 1H), 6.83 (d, *J* = 8.1 Hz, 1H), 4.85 (s, 1H), 2.23 (s, 3H), 0.91 (s, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 156.36, 143.89, 140.38, 132.42, 130.52, 129.52, 129.20, 128.13, 127.62, 127.40, 127.32, 126.97, 125.73, 110.14, 95.95, 63.66, 51.00, 30.44, 21.06; **HRMS** (FAB+) *m/z* Calcd for $C_{19}H_{18}BrNOP$ $[M]^+$ 386.0304, found 386.0305.

***N*-(4-methoxybenzyl)-*P,P*-diphenylphosphinic amide (1t):** The title compound was prepared from Ru-MACHO (1.2 mg, 0.002 mmol), KOH (1.7 mg, 0.030 mmol), *P,P*-diphenylphosphinic amide (43.4 mg, 0.20 mmol) and (4-methoxyphenyl)methanol (30 µL, 0.24 mmol) according to General Procedure 1. Purification by reverse phase HPLC gave the product as a white solid (67 mg, 99% yield). **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.87–7.76 (m, 4H), 7.56–7.51 (m, 2H), 7.48 (td, *J* = 7.7, 2.5 Hz, 4H), 7.29 (d, *J* = 8.3 Hz, 2H), 6.89–6.84 (m, 2H), 5.82 (d, *J* = 8.5 Hz, 1H), 3.90 (dd, *J* = 10.1, 7.2 Hz, 2H), 3.73 (s, 3H). **^{13}C NMR** (150 MHz, DMSO-d_6) δ 158.13, 133.88 (d, *J* = 126.2 Hz), 132.66 (d, *J* = 6.9 Hz), 131.71 (d, *J* = 9.3 Hz), 131.44 (d, *J* = 2.6 Hz), 128.54, 128.43 (d, *J* = 12.0 Hz), 113.50, 55.05, 42.99. **^{31}P NMR** (162 MHz, DMSO) δ 22.33. **HRMS** (FAB+) *m/z* Calcd for $C_{20}H_{21}NO_2P$ $[M+H]^+$ 338.1304, found 338.1302.

***N*-([1,1'-biphenyl]-4-ylmethyl)-*P,P*-diphenylphosphinic amide (1u):** The title compound was prepared from Ru-MACHO (1.2 mg, 0.002 mmol), KOH (1.7 mg, 0.030 mmol), *P,P*-diphenylphosphinic amide (43.4 mg, 0.20 mmol) and [1,1'-biphenyl]-4-ylmethanol (44 mg, 0.24 mmol) according to General Procedure 1. Purification by reverse phase HPLC gave the product as a white solid (60 mg, 78% yield). **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.85 (dd, *J* = 11.7, 7.3 Hz, 4H), 7.65 (d, *J* = 7.7 Hz, 2H), 7.61 (d, *J* = 7.9 Hz, 2H), 7.53 (t, *J* = 7.2 Hz, 2H), 7.49 (t, *J* = 8.5 Hz, 6H), 7.45 (d, *J* = 7.6 Hz, 2H), 7.35 (t, *J* = 7.3 Hz, 1H), 5.96 (q, *J* = 7.5 Hz, 1H), 4.06–3.97 (m, 2H). **^{13}C NMR** (150 MHz, DMSO-d_6) δ 140.05, 140.00 (d, *J* = 6.6 Hz), 138.61, 134.22, 133.39, 131.74 (d, *J* = 9.3 Hz), 131.50 (d, *J* = 2.6 Hz), 128.92, 128.48 (d, *J* = 12.0 Hz), 127.96, 127.29, 126.50 (d, *J* = 23.0 Hz), 43.31. **^{31}P NMR** (162 MHz, DMSO) δ 22.52. **HRMS** (FAB+) *m/z* Calcd for $C_{25}H_{23}NOP$ $[M+H]^+$ 384.1512, found 384.1512.

***N*-(4-(*tert*-butyl)benzyl)-*P,P*-diphenylphosphinic amide (1r):** The title compound was prepared from Ru-MACHO (1.2 mg, 0.002 mmol), KOH (1.7 mg, 0.030 mmol), *P,P*-diphenylphosphinic amide (43.4 mg, 0.20 mmol) and (4-(tert-butyl)phenyl)methanol (39.4 mg, 0.24 mmol) according to General Procedure 1. Purification by reverse phase HPLC gave the product as a white solid (55 mg, 76% yield). **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.84–7.79 (m, 3H), 7.52 (dt, *J* = 7.4, 3.7 Hz, 2H), 7.47 (d, *J* = 2.9 Hz, 2H), 7.34–7.28 (m, 4H), 5.82 (q, *J* = 7.9 Hz, 1H), 3.92 (dd, *J* = 10.1, 7.3 Hz, 2H), 1.26 (s, 10H). **^{13}C NMR** (150 MHz, DMSO-d_6) δ 149.00, 137.61 (d, *J* = 6.9 Hz), 133.81 (d, *J* = 126.1 Hz), 131.69 (d, *J* = 9.3 Hz), 131.42 (d, *J* = 2.6 Hz), 128.41 (d, *J* = 12.1 Hz), 127.12, 124.80, 43.25, 34.13, 31.19. **^{31}P NMR** (162 MHz, DMSO) δ 22.30. **HRMS** (FAB+) *m/z* Calcd for $C_{20}H_{21}NOP$ $[M+H]^+$ 364.1825, found 364.1825.

***P,P*-diphenyl-*N*-(4-(trifluoromethyl)benzyl)phosphinic amide (1w):** The title compound was prepared from Ru-MACHO (1.2 mg, 0.002 mmol), KOH (1.7 mg, 0.030 mmol), *P,P*-diphenylphosphinic amide (43.4 mg, 0.20 mmol) and (4-(trifluoromethyl)phenyl)methanol (33 µL, 0.24 mmol) according to the General Procedure 1. Purification by reverse phase HPLC gave the product as a white solid (67 mg, 89% yield). **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.82 (ddt, *J* = 11.7, 6.9, 1.5 Hz, 4H), 7.67 (d, *J* = 8.2 Hz, 2H), 7.62 (d, *J* = 8.1 Hz, 2H), 7.56–7.51 (m, 2H), 7.48 (tdd, *J* = 6.5, 3.1, 1.5 Hz, 4H), 6.05 (dt, *J* = 9.6, 7.5 Hz, 1H), 4.06 (dd, *J* = 11.0, 7.4 Hz, 2H). . **^{13}C NMR** (150 MHz, DMSO-d_6) δ 159.66 (d, *J* = 243.8 Hz), 133.54 (d, *J* = 126.3 Hz), 131.67 (d, *J* = 9.3 Hz), 131.55 (d, *J* = 2.4 Hz), 129.83 (d, *J* = 4.3 Hz), 128.64 (d, *J* = 8.2 Hz), 128.46 (d, *J* = 12.0 Hz), 124.23 (d, *J* = 3.5 Hz), 114.73 (d, *J* = 21.1 Hz), 36.85 (d, *J* = 4.8 Hz).**^{31}P NMR** (162 MHz, DMSO) δ 22.65. **^{19}F NMR** (376 MHz, DMSO) δ -61.67. **HRMS** (FAB+) *m/z* Calcd for $C_{20}H_{18}F_3NOP$ $[M+H]^+$ 376.1073, found 376.1073.

methyl 4-(((diphenylphosphoryl)amino)methyl)benzoate (1x): The title compound was prepared from Ru-MACHO-BH (1.2 mg, 0.002 mmol), *P,P*-diphenylphosphinic amide (43.4 mg, 0.20 mmol) and methyl 4-(hydroxymethyl)benzoate (29 µL, 0.24 mmol) according to General Procedure 1. Purification by reverse phase HPLC gave the product as a white solid (16 mg, 22% yield). **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.90 (d, *J* = 7.9 Hz, 2H), 7.82 (dd, *J* = 11.7, 7.5 Hz, 4H), 7.53 (t, *J* = 7.8 Hz, 4H), 7.48 (td, *J* = 7.6, 3.0 Hz, 4H), 6.02 (q, *J* = 8.1 Hz, 1H), 4.04 (dd, *J* = 10.8, 7.4 Hz, 2H), 3.84 (s, 3H). **^{13}C NMR** (150 MHz, DMSO-d_6) δ 166.16, 134.01, 133.18, 131.68 (d, *J* = 9.4 Hz), 131.56 (d, *J* = 2.7 Hz), 129.01, 128.49 (d, *J* = 12.1 Hz). 128.01, 127.51, 52.05, 43.33. **^{31}P NMR** (162 MHz, DMSO) δ 22.78. **HRMS** (FAB+) *m/z* Calcd for $C_{21}H_{21}NO_3P$ $[M+H]^+$ 366.1254, found 366.1253.

***P,P*-diphenyl-*N*-(1-phenylethyl)phosphinic amide (2a):** The title compound was prepared from Ru-MACHO (1.2 mg, 0.002 mmol), KOH (1.7 mg, 0.030 mmol), *P,P*-diphenylphosphinic amide (43.4 mg, 0.20 mmol) and 1-phenylethan-1-ol (29 µL, 0.24 mmol) according to General Procedure 1. Purification by reverse phase HPLC gave the product as a white solid (57 mg, 88% yield). **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.87–7.79 (m, 2H), 7.74–7.68 (m, 2H), 7.57–7.45 (m, 4H), 7.40 (td, *J* = 7.7, 2.9 Hz, 2H), 7.37 (d, *J* = 7.6 Hz, 2H), 7.29 (t, *J* = 7.5 Hz, 2H), 7.20 (t, *J* = 7.3 Hz, 1H), 5.90 (t, *J* = 9.9 Hz, 1H), 4.15 (td, *J* = 10.7, 6.7 Hz, 1H), 1.44 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR** (150 MHz, DMSO-d_6) δ 146.11 (d, *J* = 5.6 Hz), 134.09 (dd, *J* = 126.8, 42.7 Hz), 131.77 (dd, *J* = 9.3, 2.0 Hz), 131.38 (dd, *J* = 14.2, 2.6 Hz), 128.33 (dd, *J* = 23.0, 12.1 Hz), 128.04, 126.36, 126.01, 50.22,

25.93. **^{31}P NMR** (162 MHz, DMSO) δ 20.60. **HRMS** (FAB+) *m/z* Calcd for $C_{20}H_{21}NOP$ $[M+H]^+$ 322.1355, found 322.1353.

***N*-(1-(4-methoxyphenyl)ethyl)-*P*,*P*-diphenylphosphinic amide (2b):** The title compound was prepared from Ru-MACHO (1.2 mg, 0.002 mmol), KOH (1.7 mg, 0.030 mmol), *P*,*P*-diphenylphosphinic amide (43.4 mg, 0.20 mmol) and 1-(4-methoxyphenyl)ethan-1-ol (34 µL, 0.24 mmol) according to General Procedure 1. Purification by reverse phase HPLC gave the product as a white solid (34 mg, 48% yield). **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.81 (ddd, *J* = 11.6, 8.2, 1.5 Hz, 2H), 7.74–7.63 (m, 2H), 7.56–7.42 (m, 4H), 7.40 (td, *J* = 7.7, 3.0 Hz, 2H), 7.26 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 5.79 (t, *J* = 9.9 Hz, 1H), 4.08 (td, *J* = 10.6, 5.8 Hz, 1H), 3.72 (s, 3H), 1.40 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR** (150 MHz, DMSO-d_6) δ 157.80, 138.20 (d, *J* = 5.9 Hz), 135.01–133.22 (m), 131.77 (dd, *J* = 9.3, 6.9 Hz), 131.35 (dd, *J* = 12.2, 2.7 Hz), 128.32 (dd, *J* = 19.9, 12.0 Hz), 127.10, 113.38, 55.02, 49.66, 25.98. **^{31}P NMR** (162 MHz, DMSO) δ 20.47. **HRMS** (FAB+) *m/z* Calcd for $C_{21}H_{23}NO_2P$ $[M+H]^+$ 352.1461, found 352.1462.

***N*-(1-(4-fluorophenyl)ethyl)-*P*,*P*-diphenylphosphinic amide (2c):** The title compound was prepared from Ru-MACHO (1.2 mg, 0.002 mmol), KOH (1.7 mg, 0.030 mmol), *P*,*P*-diphenylphosphinic amide (43.4 mg, 0.20 mmol) and 1-(4-fluorophenyl)ethan-1-ol (30 µL, 0.24 mmol) according to General Procedure 1. Purification by reverse phase HPLC gave the product as a white solid (44 mg, 65% yield). **^{1}H NMR** (500 MHz, DMSO-d_6) δ 7.82 (dd, *J* = 11.6, 7.4 Hz, 2H), 7.68 (dd, *J* = 11.7, 7.5 Hz, 2H), 7.50 (ddd, *J* = 18.5, 14.3, 7.4 Hz, 4H), 7.39 (td, *J* = 8.6, 4.1 Hz, 4H), 7.09 (t, *J* = 8.7 Hz, 2H), 5.90 (t, *J* = 10.0 Hz, 1H), 4.14 (td, *J* = 10.3, 5.6 Hz, 1H), 1.41 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR** (150 MHz, DMSO-d_6) δ 160.85 (d, *J* = 241.6 Hz), 142.33 (dd, *J* = 5.5, 2.8 Hz), 133.98 (dd, *J* = 126.8, 32.6 Hz), 131.75 (d, *J* = 8.9 Hz), 131.41 (dd, *J* = 16.3, 2.6 Hz), 128.35 (dd, *J* = 25.1, 12.1 Hz), 127.95 (d, *J* = 7.9 Hz), 114.63 (d, *J* = 21.0 Hz), 49.59, 25.85. **^{31}P NMR** (162 MHz, DMSO) δ 20.58. **^{19}F NMR** (376 MHz, DMSO) δ -117.40. **HRMS** (FAB+) *m/z* Calcd for $C_{20}H_{20}FNOP$ $[M+H]^+$ 340.1261, found 340.1263.

***N*-(1-(4-chlorophenyl)ethyl)-*P*,*P*-diphenylphosphinic amide (2d):** The title compound was prepared from Ru-MACHO (1.2 mg, 0.002 mmol), KOH (1.7 mg, 0.030 mmol), *P*,*P*-diphenylphosphinic amide (43.4 mg, 0.20 mmol) and 1-(4-chlorophenyl)ethan-1-ol (32 µL, 0.24 mmol) according to General Procedure 1. Purification by reverse phase HPLC gave the product as a white solid (31 mg, 44% yield). **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.82 (ddt, *J* = 11.7, 6.8, 1.5 Hz, 2H), 7.69 (ddt, *J* = 11.7, 6.8, 1.4 Hz, 2H), 7.58–7.46 (m, 4H), 7.44–7.36 (m, 4H), 7.35–7.32 (m, 2H), 5.93 (t, *J* = 9.9 Hz, 1H), 4.14 (tq, *J* = 10.7, 6.8 Hz, 1H), 1.42 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR** (150 MHz, DMSO-d_6) δ 145.14, 131.76 (d, *J* = 6.2 Hz), 131.70 (d, *J* = 6.4 Hz), 131.43 (d, *J* = 13.1 Hz), 130.88, 128.44 (d, *J* = 12.2 Hz), 128.28 (d, *J* = 12.1 Hz), 127.96 (d, *J* = 8.4 Hz). 49.65, 25.67.**^{31}P NMR** (162 MHz, DMSO) δ 20.62. **HRMS** (FAB+) *m/z* Calcd for $C_{20}H_{20}ClNOP$ $[M+H]^+$ 356.0966, found 356.0968.

***P*,*P*-diphenyl-*N*-(1-phenylpropyl)phosphinic amide (2e):** The title compound was prepared from Ru-MACHO (1.2 mg, 0.002 mmol), KOH (1.7 mg, 0.030 mmol), *P*,*P*-diphenylphosphinic amide (43.4 mg, 0.20 mmol) and 1-phenylpropan-1-ol (33 µL, 0.24 mmol) according to General Procedure 1. Purification by reverse phase HPLC gave the product as a white solid (15 mg, 22% yield). **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.81–7.74 (m, 2H), 7.63 (ddt, *J* = 11.7, 6.8, 1.4 Hz, 2H), 7.55–7.51 (m, 1H), 7.51–7.43 (m, 3H), 7.36 (td, *J* = 7.7, 3.2 Hz, 2H), 7.29–7.23 (m, 4H), 7.19 (ddt, *J* = 7.4, 5.9, 1.9 Hz, 1H), 5.87–5.81 (m, 1H), 3.84 (tt, *J* = 10.6, 7.1 Hz, 1H), 1.81 (dt, *J* = 13.5, 7.3 Hz, 1H), 1.68 (dp, *J* = 14.3, 7.2 Hz, 1H), 0.78 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (150 MHz, DMSO-d_6) δ 145.01 (d, *J* = 4.5 Hz), 134.82–133.49 (m), 131.80 (dd, *J* = 26.6, 9.3 Hz), 131.30 (dd, *J* = 18.6, 2.7 Hz), 128.33 (d, *J* = 12.1 Hz), 128.13 (d, *J* = 12.1 Hz), 127.96, 126.44 (d, *J* = 16.3 Hz), 56.61, 32.12 (d, *J* = 5.0 Hz), 11.10. **^{31}P NMR** (162 MHz, DMSO) δ 20.44. **HRMS** (FAB+) *m/z* Calcd for $C_{21}H_{23}NOP$ $[M+H]^+$ 336.1512, found 336.1512.

***P*,*P*-diphenyl-*N*-(1-(pyridin-3-yl)ethyl)phosphinic amide (2f):** The title compound was prepared from Ru-MACHO (1.2 mg, 0.002 mmol), KOH (1.7 mg, 0.030 mmol), *P*,*P*-diphenylphosphinic amide (43.4 mg, 0.20 mmol) and 1-(pyridin-3-yl)ethan-1-ol (29.6 mg, 0.24 mmol) according to General Procedure 1. Purification by reverse phase HPLC gave the product as a white solid (42 mg, 65% yield). **^{1}H NMR** (600 MHz, DMSO-d_6) δ 8.56 (s, 1H), 8.45 (d, *J* = 4.8 Hz, 1H), 7.89 (dt, *J* = 7.9, 2.0 Hz, 1H), 7.70 (ddd, *J* = 11.7, 8.2, 1.4 Hz, 2H), 7.55 (td, *J* = 7.3, 1.5 Hz, 1H), 7.50 (dddd, *J* = 13.2, 11.6, 6.6, 2.2 Hz, 3H), 7.40 (ddd, *J* = 15.7, 7.8, 3.9 Hz, 3H), 6.04 (t, *J* = 10.0 Hz, 1H), 4.23 (tq, *J* = 10.4, 6.8 Hz, 1H), 1.47 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR** (150 MHz, DMSO-d_6) δ 146.94 (d, *J* = 7.0 Hz), 141.69 (d, *J* = 4.7 Hz), 134.79, 133.70 (dd, *J* = 126.9, 11.1 Hz), 131.74 (dd, *J* = 17.7, 9.4 Hz), 131.54 (dd, *J* = 16.4, 2.6 Hz), 128.51 (d, *J* = 12.0 Hz), 128.34 (d, *J* = 12.1 Hz), 123.62, 48.15, 25.35. **^{31}P NMR** (162 MHz, DMSO) δ 20.84. **HRMS** (FAB+) *m/z* Calcd for $C_{19}H_{20}N_2OP$ $[M+H]^+$ 323.1308, found 340.1310.

***N*-((j,5*R*)-2-methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-yl)-*P*,*P*-diphenylphosphinic amide (2g):** The title compound was prepared from Ru-MACHO (1.2 mg, 0.002 mmol), KOH (1.7 mg, 0.030 mmol), *P*,*P*-diphenylphosphinic amide (43.4 mg, 0.20 mmol) and carveol (38 uL, 0.24 mmol) according to General Procedure 1. Purification by reverse phase HPLC gave the product as a white solid (39 mg, 56% yield). NMR assignments are given for the mixture of diastereomers. Attempts to assign the major and minor diastereomers were not made as the ratio was close to 1:1. The ^{13}C splitting combined with the mixture of the diastereomers made determining coupling very complicated, so peaks are reported without assigning multiplets and major/minor diastereomers. The ratio of diastereomers was determined by the integration of the ^{31}P NMR. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.11–7.79 (m, 4H), 7.50 (dtd, *J* = 28.9, 8.2, 7.5, 3.6 Hz, 6H), 5.59–5.49 (m, 1H), 4.86–4.58 (m, 3H), 4.04 (dt, *J* = 9.6, 5.0 Hz, 0H), 3.67 (s, 1H), 3.58 (s, 1H), 2.98 (dd, *J* = 10.5, 7.1 Hz, 1H), 2.79 (dd, *J* = 11.7, 6.3 Hz, 1H), 2.59 (t, *J* = 9.6 Hz, 1H), 2.47 (dd, *J* = 3.2, 1.6 Hz, 1H), 2.43–2.34 (m, 1H), 2.29 (q, *J* = 12.4, 12.0 Hz, 1H), 2.22–1.99 (m, 2H), 1.86 (d, *J* = 5.7 Hz, 3H), 1.78–1.62 (m, 7H), 1.61–1.34 (m, 1H), 1.09 (d, *J* = 7.3 Hz, 1H), 0.96 (d, *J* = 6.8 Hz, 1H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 148.98, 148.95, 148.14, 147.33, 135.34, 135.29, 134.71, 134.67,

132.57, 132.51, 132.39, 132.33, 132.24, 132.18, 131.95, 131.93, 128.65, 128.57, 128.54, 125.40, 125.29, 112.19, 109.97, 109.34, 109.31, 70.43, 52.35, 50.02, 49.69, 44.64, 41.89, 40.96, 39.95, 39.62, 39.38, 37.76, 37.34, 36.62, 36.61, 36.21, 35.47, 34.35, 30.94, 30.83, 28.01, 22.04, 21.44, 21.09, 21.01, 20.83, 18.73, 13.62, 12.94. **^{31}P NMR** (162 MHz, Acetone) δ 22.60 (minor), 22.23 (major).

***N*-((3*R*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl)-*P*,*P*-diphenylphosphinic amide (2h):** The title compound was prepared from Ru-MACHO (1.2 mg, 0.002 mmol), KOH (1.7 mg, 0.030 mmol), *P*,*P*-diphenylphosphinic amide (38.7 mg, 0.20 mmol) and cholesterol (93 mg, 0.24 mmol) according to General Procedure 1. After 16 hr the reaction was allowed to cool to room temperature, diluted with EtOAc and washed with aq. $NaHCO_3$. The aq. layer was then extracted with EtOAc (×3) and the combined organic layers were dried with $MgSO_4$ then concentrated to dryness by rotary evaporation. The crude white solid could easily be recrystallized from hot benzene to give crystals suitable for X-ray crystallography and afford the pure product as a white solid (76 mg, 65% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.92 (dd, *J* = 11.9, 7.6 Hz, 4H), 7.56–7.38 (m, 6H), 5.37 (q, *J* = 1.7 Hz, 1H), 3.57 (ddq, *J* = 10.9, 5.3, 2.7 Hz, 1H), 2.81 (dd, *J* = 11.4, 6.1 Hz, 1H), 2.18–1.87 (m, 6H), 1.86–1.74 (m, 1H), 1.72–1.60 (m, 3H), 1.59–1.49 (m, 3H), 1.42–1.26 (m, 5H), 1.26–1.01 (m, 7H), 0.99 (s, 3H), 0.91–0.82 (m, 12H), 0.65 (s, 3H). **^{13}C NMR (**150 MHz, $CDCl_3$) δ 147.32, 132.45 (dd, *J* = 129.7, 27.0 Hz), 131.71 (dd, *J* = 12.4, 9.2 Hz), 131.24, 128.01 (dd, *J* = 12.6, 9.9 Hz), 123.04 (d, *J* = 6.6 Hz),55.63, 53.92, 48.47, 41.98, 39.36, 39.05, 36.45, 32.54, 31.78, 29.92, 27.73, 27.54, 23.75, 23.35, 22.36, 22.10, 20.53, 18.56, 18.18, 11.50. **^{31}P NMR** (162 MHz, $CDCl_3$) δ 23.22. **HRMS** $C_{39}H_{56}NOP$ $[M+H]^+$ 586.4172, found 586.4172. **X-ray** (single-crystal) Single crystals suitable for X-ray diffraction were grown using the procedure described above (CCDC 1893911).[17]

***P*,*P*-ditertbutyl-*N*-(4-methoxybenzyl)phosphinic amide (3a):** The title compound was prepared from Ru-MACHO (1.2 mg, 0.002 mmol), KOH (1.7 mg, 0.030 mmol), *P*,*P*-ditertbutylphosphinic amide (35.4 mg, 0.20 mmol) and (4-methoxyphenyl)methanol (30 µL, 0.24 mmol) according to General Procedure 1. Purification by reverse phase HPLC gave the product as a white solid (31 mg, 52% yield). **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.33–7.19 (m, 2H), 6.93–6.77 (m, 2H), 4.34 (dt, *J* = 16.5, 7.2 Hz, 1H), 4.00 (t, *J* = 7.4 Hz, 2H), 3.73 (s, 3H), 1.13 (d, *J* = 13.4 Hz, 18H). **^{13}C NMR** (150 MHz, DMSO-d_6) δ 157.83, 134.60, 128.50, 113.36, 54.98, 42.93 (d, *J* = 2.1 Hz), 36.01 (d, *J* = 76.4 Hz), 26.37. **^{31}P NMR** (162 MHz, DMSO) δ 55.63. **HRMS** $C_{16}H_{26}NO_2P$ $[M+H]^+$ 298.1930, found 298.1932.

***P*,*P*-diisopropyl-*N*-(4-methoxybenzyl)phosphinic amide (3b**) The title compound was prepared from Ru-MACHO (1.2 mg, 0.002 mmol), KOH (1.7 mg, 0.030 mmol), *P*,*P*-diisopropylphosphinic amide (30.0 mg, 0.20 mmol) and (4-methoxyphenyl)methanol (30 µL, 0.24 mmol) according to General Procedure 1. Purification by reverse phase HPLC gave the product as a white solid (43 mg, 80% yield) **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.26 (d, *J* = 8.3 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 4.38 (dt, *J* = 14.6, 7.3 Hz, 1H), 3.96 (t, *J* = 7.8 Hz, 2H), 3.72 (s, 3H), 1.86 (dhept, *J* = 10.0, 7.1 Hz, 2H), 1.02 (ddd, *J* = 15.3, 7.1, 2.0 Hz, 12H). **^{13}C NMR** (150 MHz, DMSO-d_6) δ 157.92, 128.36, 134.30 (d, *J* = 4.1 Hz), 113.41, 55.00, 42.25.25.43 (d, *J* = 82.4 Hz), 15.67 (dd, *J* = 47.3, 3.1 Hz). **^{31}P NMR** (162 MHz, DMSO) δ 51.94. **HRMS** $C_{14}H_{25}NO_2P$ $[M+H]^+$ 270.1617, found 270.1615.

***P*,*P*-dicyclohexyl-*N*-(4-methoxybenzyl)phosphinic amide (3c):** The title compound was prepared from Ru-MACHO (1.2 mg, 0.002 mmol), KOH (1.7 mg, 0.030 mmol), *P*,*P*-dicyclohexylphosphinic amide (45.9 mg, 0.20 mmol) and (4-methoxyphenyl)methanol (30 µL, 0.24 mmol) according to General Procedure 1. Purification by reverse phase HPLC gave the product as a white solid (51 mg, 73% yield). **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.27–7.23 (m, 2H), 6.89–6.85 (m, 2H), 4.31 (dt, *J* = 14.5, 7.2 Hz, 1H), 3.93 (t, *J* = 7.8 Hz, 2H), 3.72 (s, 3H), 1.85–1.55 (m, 12H), 1.31–1.07 (m, 10H). **^{13}C NMR** (150 MHz, DMSO-d_6) δ 157.95, 134.32 (d, *J* = 4.4 Hz), 128.41, 113.42, 55.04, 42.26, 36.04, 35.49, 26.00 (dd, *J* = 13.0, 9.7 Hz), 25.80, 25.10 (dd, *J* = 31.8, 2.9 Hz). **^{31}P NMR** (162 MHz, DMSO) δ 46.66. **HRMS** $C_{20}H_{32}NO_2P$ $[M+H]^+$ 350.2243, found 350.2243.

***N*-(4-methoxybenzyl)-*P*,*P*-diphenylphosphinothioic amide (3e):** The title compound was prepared from Ru-MACHO (1.2 mg, 0.002 mmol), KOH (1.7 mg, 0.030 mmol), *P*,*P*-diphenylthiophosphinic amide (46.7 mg, 0.20 mmol) and (4-methoxyphenyl)methanol (30 µL, 0.24 mmol) according to General Procedure 1. Purification by reverse phase HPLC gave the product as a white solid (31 mg, 44% yield). **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.96–7.82 (m, 4H), 7.51 (dtd, *J* = 14.7, 7.2, 2.6 Hz, 6H), 7.33–7.24 (m, 2H), 6.92–6.84 (m, 2H), 5.74 (q, *J* = 7.0 Hz, 1H), 3.97 (dd, *J* = 10.6, 7.0 Hz, 2H), 2.51 (p, *J* = 1.9 Hz, 2H). **^{13}C NMR** (150 MHz, DMSO-d_6) δ 158.19, 135.15 (d, *J* = 100.8 Hz), 132.25 (d, *J* = 9.4 Hz), 131.39 (d, *J* = 2.8 Hz), 131.12 (d, *J* = 11.0 Hz), 128.87, 128.35 (d, *J* = 12.5 Hz), 113.53, 55.06, 43.27. **^{31}P NMR** (162 MHz, DMSO) δ 58.90. **HRMS** $C_{20}H_{20}NOPS$ $[M+H]^+$ 354.1076, found 354.1078.

***P*,*P*-di-*tert*-butyl-*N*-(4-methoxybenzyl)phosphinothioic amide (3f):** The title compound was prepared from Ru-MACHO (1.2 mg, 0.002 mmol), KOH (1.7 mg, 0.030 mmol), *P*,*P*-*tert*-butylthiophosphinic amide (38.7 mg, 0.20 mmol) and (4-methoxyphenyl)methanol (30 µL, 0.24 mmol) according to General Procedure 1. Purification by reverse phase HPLC gave the product as a white solid (39 mg, 62% yield). Recrystalization from hot benzene gave single crystals suitable for x-ray diffraction **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.26 (d, *J* = 8.3 Hz, 2H), 6.86 (d, *J* = 8.2 Hz, 2H), 4.59 (dt, *J* = 12.9, 6.8 Hz, 1H), 4.16 (dd, *J* = 9.8, 6.8 Hz, 2H), 3.72 (s, 3H), 1.23 (d, *J* = 15.1 Hz, 18H). **^{13}C NMR** (150 MHz, DMSO-d_6) δ 157.91, 134.44 (d, *J* = 5.4 Hz), 128.67, 113.37, 55.01, 44.38, 27.07, 27.06. **^{31}P NMR** (162 MHz, DMSO) δ 97.83. **HRMS** (FAB+) *m/z* Calcd for $C_{16}H_{29}NOPS$ $[M+H]^+$ 314.1702, found 314.1700. **X-ray** (single-crystal) Single crystals suitable for X-ray diffraction were grown using the procedure described above (CCDC 1893909).[17]

4.3. Preparation of Enantioenriched Chiral-at-P Starting Material

***P*-(*tert*-butyl)-*P*-phenyl-*N*-((*S*)-1-phenylethyl)phosphinic amide (4a):** A solution of phenyl tertbutylphosphine chloride (2.00 g, 9.97 mmol) in dichloromethane (20 mL) was added dropwise with stirring to a solution of triethylamine (1.51g,

15.0 mmol) and (*S*)-1-phenylethan-1-amine (1.81g, 15.0 mmol) in dichloromethane (30 mL) held at a temperature of –45 °C. The mixture was allowed to warm to room temperature and stir for 1 h, at which point it was filtered. The resulting filtrate was cooled to 0 °C and 30% hydrogen peroxide (3.4 mL) was added in a dropwise manner over a period of 1 h. Stirring was continued at room temperature for 1 h. Then, the organic layer was separated, washed with water (20 mL), and dried over $MgSO_4$. The solvent was removed *in vacuo* to give the crude product as a solid. This material was recrystallized from hot benzene to afford the product as a 1:1 mixture of diastereomers. The diastereomers were separated by reverse phase HPLC. Below analytical data is provided for both compounds. The two diastereomers are referred to by their P-stereochemistry, which was assigned based on X-ray crystallography of one of the final products.

(*R*-at-P)-diastereomer: **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.81–7.73 (m, 2H), 7.61–7.47 (m, 3H), 7.45–7.42 (m, 2H), 7.30 (t, *J* = 7.7 Hz, 2H), 7.21–7.14 (m, 1H), 5.17 (dd, *J* = 16.0, 10.6 Hz, 1H), 4.15 (dq, *J* = 15.8, 7.1 Hz, 1H), 1.32 (d, *J* = 6.9 Hz, 3H), 0.98 (d, *J* = 14.6 Hz, 9H). **^{13}C NMR** (150 MHz, DMSO-d_6) δ 146.86, 133.05 (d, *J* = 8.3 Hz), 132.12 (d, *J* = 111.1 Hz), 131.07, 127.83 (d, *J* = 11.0 Hz),127.82, 126.12, 126.07, 48.98, 31.69 (d, *J* = 90.8 Hz), 25.25 (d, *J* = 5.3 Hz), 24.29. **^{31}P NMR** (162 MHz, DMSO) δ 40.01. **HRMS** $C_{18}H_{25}NOP$ $[M+H]^+$ 302.1668, found 302.1669.

(*S*-at-P)-isomer: **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.53 (ddd, *J* = 10.3, 8.1, 1.4 Hz, 2H), 7.46–7.41 (m, 1H), 7.35–7.28 (m, 4H), 7.27–7.22 (m, 2H), 7.18–7.13 (m, 1H), 5.05 (dd, *J* = 12.6, 10.6 Hz, 1H), 4.11 (td, *J* = 10.1, 6.5 Hz, 1H), 1.43 (d, *J* = 6.9 Hz, 3H), 1.03 (d, *J* = 14.6 Hz, 9H). **^{13}C NMR** (150 MHz, DMSO-d_6) δ 146.27 (d, *J* = 6.2 Hz), 133.11 (d, *J* = 8.6 Hz), 130.96 (d, *J* = 2.7 Hz), 127.91, 127.56, 127.49, 126.19, 125.94, 49.75, 31.66 (d, *J* = 90.1 Hz). 26.26, 24.37. **^{31}P NMR** (162 MHz, DMSO) δ 41.15.

***P*-(*tert*-butyl)-*P*-phenylphosphinic amide (4b):** Anhydrous ammonia (aprox. 2 mL) was condensed into a 50 mL 2-neck flask and held at –45 °C (dry ice/acetonitrile bath). A few small shavings of solid sodium were added. The resulting blue solution was stirred for 10 min, and compound **4a** (0.400 g, 0.133 mmol) was added dropwise as a suspension in THF (2.0 mL) over a period of 5 min. The mixture was stirred for 10 min, whereupon solid NH_4C1 (0.11 g) was added. The ammonia was then allowed to evaporate off, and THF (2.00 mL) was added to the white slurry. After filtration and washing of the solids with an additional portion of THF (5 mL), the combined organic layers were concentrated to give a white solid. The white solid was re-dissolved in MeOH (1 mL) and purified by reverse phase HPLC to afford the title compound as a white solid (5 mg, 20% yield; >99% *ee*). **^{1}H NMR** (600 MHz, Acetone-d_6) δ 7.87 (ddd, *J* = 10.0, 8.0, 1.4 Hz, 2H), 7.55 (td, *J* = 7.4, 1.5 Hz, 1H), 7.49 (td, *J* = 7.6, 2.3 Hz, 2H), 3.89 (s, 2H), 1.10 (d, *J* = 14.6 Hz, 9H). **^{13}C NMR** (150 MHz, Acetone-d_6) δ 134.09, 128.60, 128.53 (d, *J* = 8.2 Hz), 131.98 (d, *J* = 2.7 Hz), 32.84 (d, *J* = 93.0 Hz), 25.09. **^{31}P NMR** (162 MHz, Acetone) δ 39.16. **HRMS** $C_{10}H_{17}NOP$ $[M+H]^+$ 198.1402, found 198.1404. **SFC** (chiral column). The enantiomeric excess or both compounds was determined by chiral SFC on a Daicel IG column (3 μm, 4.6Å×250 mm), 20% MeOH/CO_2, 4.0 mL/min, λ = 212 nm, t (*R* enantiomer) = 2.225 min, t (*S* enantiomer) = 1.654 min.

(*R*)-*P*-(*tert*-butyl)-*N*-(4-methoxybenzyl)-*P*-phenylphosphinic amide (4c): The title compound was prepared from Ru-MACHO (0.1 mg, 0.002 mmol), KOH (0.2 mg, 0.030 mmol), (*R*)-*P*-(*tert*-butyl)-*P*-phenylphosphinic amide (4.0 mg, 0.020 mmol) and (4-methoxyphenyl)methanol (3 μL, 0.024 mmol) according to General Procedure 1. Purification by reverse phase HPLC gave the product as a white solid (4 mg, 62% yield). Single crystals suitable for X-Ray diffraction could be grown by slow evaporation over one week of a dilute solution of the product in hot benzene. **^{1}H NMR** (600 MHz, Methanol-d_4) δ 7.84–7.76 (m, 2H), 7.63–7.57 (m, 1H), 7.52 (td, *J* = 7.7, 3.0 Hz, 2H), 7.28 (d, *J* = 8.3 Hz, 2H), 6.86 (d, *J* = 8.3 Hz, 2H), 5.12 (dt, *J* = 14.4, 7.2 Hz, 1H), 4.05–3.86 (m, 2H), 3.78 (s, 3H), 1.15 (d, *J* = 15.1 Hz, 9H). **^{13}C NMR** (150 MHz, Methanol-d_4) δ 158.87, 133.44 (d, *J* = 8.9 Hz), 132.41 (d, *J* = 5.6 Hz), 131.74 (d, *J* = 2.8 Hz), 129.27, 128.43, 127.96 (d, *J* = 11.7 Hz), 113.30, 54.26, 43.15 (d, *J* = 2.4 Hz), 31.49 (d, *J* = 90.3 Hz), 23.47. **^{31}P NMR (**162 MHz, MeOD) δ 47.17. **HRMS** $C_{18}H_{24}NO_2P$ $[M+H]^+$ 318.1617, found 318.1616. **SFC** (chiral column). The enantiomeric excess was determined by chiral SFC on a Daicel IG column (3 μm, 4.6Å×250 mm), 30% MeOH/CO_2, 4.0 mL/min, λ = 217 nm, t (*R* enantiomer) = 2.282 min, t (*S* enantiomer) = 1.921 min. **X-ray** (single-crystal) Single crystals suitable for X-ray diffraction were grown using the procedure described above (CCDC 1893910).[17]

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Supplementary Material

Supplementary material that may be helpful in the review process should be prepared and provided as a separate electronic file. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the appropriate editorial office.

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