CHEMISTRY
A EUROPEAN JOURNAL

ChemPubSoc Europe

DOI: 10.1002/chem.201204364

Cu-Catalyzed Asymmetric Allylic Alkylation of Phosphonates and Phosphine Oxides with Grignard Reagents

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Abstract: An efficient and highly enantioselective copper-catalyzed allylic alkylation of phosphonates and phosphine oxides with Grignard reagents and Taniaphos or phosphoramidites as chiral ligands is reported. Transformation of these products leads to a variety of new phosphorus-containing chiral intermediates.

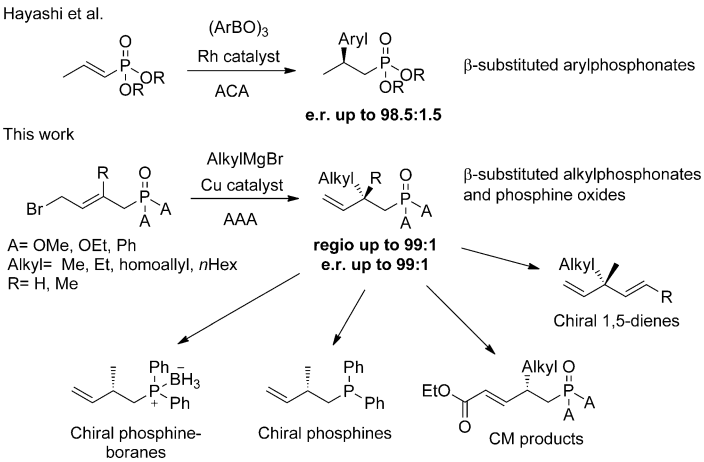
Keywords: alkylation · allylic compounds · chirality · copper · Grignard reagents · phosphanes

Introduction

Optically active organophosphorus compounds are frequently encountered in many areas of chemistry, in particular medicinal chemistry[1] and asymmetric catalysis.[2] Within this class of compounds, chiral phosphonic acid, phosphonate, and phosphine oxide derivatives have attracted interest because of their interesting biological properties[3] and synthetic versatility.[4] For example, phosphonates and phosphonic acids can act as isosteres of carboxylic esters and acids, which improves their activity or bioavailability; in addition, they have also been used as nonhydrolyzable phosphate mimics.[5] In addition, phosphine oxides are key components in Wittig-type reactions,[6] ligands or organocatalysts in asymmetric synthesis,[7] and stereogenic precursors to their corresponding phosphines.[8]

In view of their important role in stereoselective synthesis, the ability to generate stereogenic centers near the phosphorus atom in an enantioselective fashion is particularly attractive. Although several methods have been developed to obtain compounds with α-stereogenic centers,[9] catalytic asymmetric methodologies to obtain chiral β-substituted analogues are limited. Two complementary methods, reported by Jørgensen[10] and Alexakis,[11] for the organocatalyzed 1,4-addition of soft carbon nucleophiles to highly activated vinyl bis-phosphonates have been described, as well as an intramolecular Stetter reaction that employed N-heterocyclic carbenes as catalysts.[12] Recently, the organocatalyzed Michael addition of α-substituted nitrophosphonates to nitroolefins[13] and trimethylphosphonoacetate to α,β-unsaturated aldehydes[14] has been described. Chiral β-substituted alkylphosphonates have been prepared by using Rh-catalyzed asymmetric hydrogenation of the corresponding β-disubstituted α-β-unsaturated phosphonates[15] and through a Cu-catalyzed asymmetric conjugate reduction.[16]

From a synthetic perspective, a catalytic methodology based on a general substrate class would be particularly valuable. To the best of our knowledge, only one method is currently available; Hayashi and co-workers described the Rh-catalyzed asymmetric 1,4-addition of arylboroxines to 1-propenylphosphonates for the β-selective introduction of aryl groups.[17] The corresponding catalytic asymmetric conjugate addition to introduce alkyl groups remains a major challenge. We considered the catalytic asymmetric allylic alkylation (AAA) based on Cu-ferrocenyl or phosphoramidite chiral catalysts as a synthetically important alternative (Scheme 1).



Scheme 1. Catalytic asymmetric methodologies based on a general substrate class for the formation of β-substituted aryl- and alkylphosphonates and -phosphine oxides.

Copper-catalyzed AAA has proven to be a very powerful tool for the enantioselective construction of stereogenic centers.[18] This transformation offers the possibility of using nonstabilized organometallic nucleophiles, which thus enables the introduction of simple alkyl fragments. Moreover, a major advantage of this methodology is that it gives prod-

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201204364.

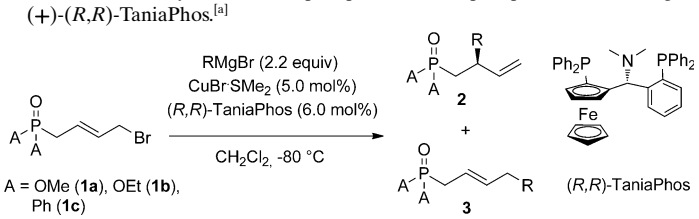
ucts with a terminal olefin, which can be further transformed into a broad range of functional groups.[19]

Herein, we report the copper-catalyzed AAA of 4-bromobut-2-en-1-ylphosphonates and phosphine oxides with Grignard reagents and (*R*,*R*)-TaniaPhos or phosphoramidites as chiral ligands, which provides an efficient route to chiral β-alkylsubstituted phosphonates with high yield and high regio- and enantioselectivity.

Results and Discussion

We started our study by using TaniaPhos[20] as the chiral ligand for copper-catalyzed AAA. Initially, a solution of Grignard reagent in CH_2Cl_2 was added (normal addition) over 2 h to a mixture of substrate and ligand–copper complex at −80 °C. However, the expected product was obtained but with low regio- and enantioselectivity (Table 1, entry 1). When the substrate was added slowly to a solution of EtMgBr and the catalyst (reverse addition), high regio- (S_N2'/S_N2 99:1) and enantioselectivity (98:2 e.r.) in the formation of β-ethylphosphonate **2a** was obtained (Table 1, entry 2). It should be noted that 2.2 equivalents of Grignard reagent were necessary to reach full conversion. This observation suggests that the Grignard reagent might also interact with the substrate either as a base that generates the corresponding phosphorus ylide in situ or by forming a complex prior to the Cu-catalyzed AAA reaction taking place (vide infra, Scheme 4 and Figure 2).

Table 1. Cu-catalyzed AAA of phosphonates and phosphine oxides using (+)-(*R*,*R*)-TaniaPhos.[a]



Entry	1	R	Add. *t* [h]	Yield [%][b]	**2**/**3**[c]	**2** (e.r.)[d]
1[e]	**1b**	Et	2	n.d.	88:12	**2a** (76:23)
2	**1b**	Et	2	96	99:1	**2a** (98:2)
3	**1b**	Me	2	97	99:1	**2b** (99:1)
4	**1a**	Et	2	95	99:1	**2c** (95:5)
5	**1a**	Me	2	92	99:1	**2d** (99:1)
6	**1c**	Et	2	89	93:7	**2e** (98:2)
7	**1c**	Me	2	94	99:1	**2f** (99:1)
8	**1b**	*n*Hex	2	89	83:17	**2k** (82:18)
9	**1b**	*n*Hex	5	92	85:15	**2k** (90:10)
10	**1b**	*n*Hex	8	n.d.	85:15	**2k** (91:09)
11	**1b**		5	n.d.	74:26	**2l** (90:10)
12	**1c**	*n*Hex	5	n.d.	70:30	**2g** (87:13)
13[e]	**1c**		5	n.d.	68:32	**2h** (59:41)
14[e]	**1b**	*n*Hex	5	n.d.	84:16	**2k** (57:43)

[a] Reactions were performed on a 0.2 mmol scale. A solution of the substrate was added slowly (reverse addition) by using a syringe pump. Full conversion was reached. [b] Isolated yield. [c] S_N2'/S_N2 ratio determined by ^{31}P and ^{1}H NMR spectroscopy. [d] Determined by chiral HPLC. [e] Normal addition.

The reaction of MeMgBr with phosphonate **1b** proved to be even more efficient, giving the corresponding β-methyl substituted compound **2b** in 97% yield (Table 1, entry 3) with near-perfect S_N2' selectivity (99:1) and enantioselectivity (99:1 e.r.). This transformation allows for the introduction of a methyl unit, which is the most common and valuable structural alkyl motif for biologically relevant systems.[21] The reaction was extended to the related methyl phosphonates (Table 1, entries 4, 5) and phosphine oxides (Table 1, entries 6, 7) by using both methyl and ethyl magnesium bromide. The results summarized in Table 1 show that the corresponding β-alkyl-substituted phosphorus compounds were obtained with excellent regio- and enantioselectivities in high yields. An important feature is the scalability of the reaction to 0.7 g (2.6 mmol) with similar results, as observed in the reaction of phosphonate **1b** and MeMgBr (see the Experimental Section, compound **2b** for details).

The regioselectivity and enantiomeric ratios were more moderate when Grignard reagents with a longer alkyl chain, for example, hexyl- or homoallyl magnesium bromide, were used with a (*R*,*R*)-Taniaphos-based copper catalyst (Table 1, entries 8–14). When the substrate was added over 5 h, the e.r. was improved (Table 1, entry 8 vs. entry 9), but slower addition did not lead to further improvement (Table 1, entry 9 vs. entry 10). As observed in Table 1, entry 1, the addition of the organometallic reagent to the reaction mixture (normal addition) decreased both the regio- and enantioselectivity (Table 1, entries 13, 14). To further improve the selectivity with longer or functionalized alkene Grignard reagents (e.g., hexyl- and homoallylmagnesium bromide), we turned our attention to other chiral ligands (Figure 1).

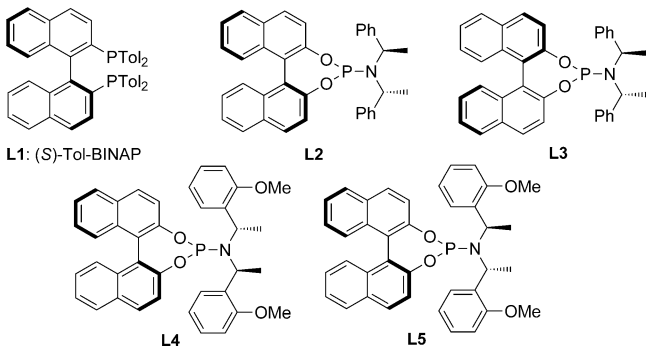
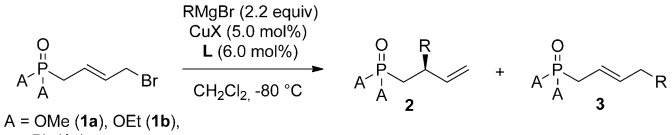


Figure 1. Chiral ligands used for the reaction screening.

We started the screening using (*S*)-Tol-BINAP (**L1**, 6 mol%; BINAP = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl) as an alternative bidentate chiral phosphine ligand but only modest regioselectivity and only 63:37 e.r were obtained. A dramatic improvement in selectivity was achieved by using the easily accessible monodentate phosphoramidite ligands.[22] Thus, the use of **L2** gave desired product **2** with a regioselectivity of 87:13 and high enantioselectivity (94:6 e.r., Table 2, entry 2). Use of methoxy-substituted phosphoramidite ligand **L4**[23a] improved the regiose-

Table 2. Optimization of ligands and conditions for the Cu-catalyzed AAA of hexyl and homoallyl magnesium bromide to phosphonate and phosphine oxide allylic bromides.[a]



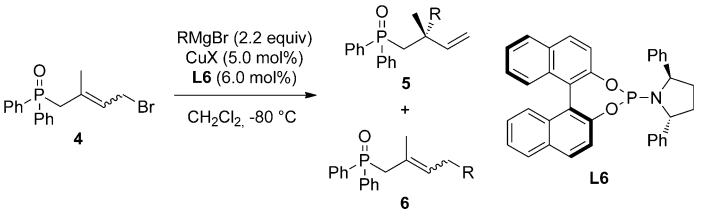
Entry	1	R	Cu salt	L	2/3[b]	2 (e.r.)[c]
1	**1c**	*n*Hex	CuBr·SMe$_2$	**L1**	66:34	**2g** (63:37)
2	**1c**	*n*Hex	CuBr·SMe$_2$	**L2**	87:13	**2g** (94:6)
3	**1c**	*n*Hex	CuBr·SMe$_2$	**L3**	80:20	**2g** (78:22)
4	**1c**	*n*Hex	CuBr·SMe$_2$	**L4**	92:8	**2g** (93:7)
5	**1c**	*n*Hex	CuBr·SMe$_2$	**L5**	84:16	**2g** (61:39)
6	**1c**	*n*Hex	CuTC	**L4**	92:8	**2g** (93:7)
7	**1c**	*n*Hex	CuTC	**L2**	87:13	**2g** (95:5)
8[d]	**1c**	*n*Hex	CuTC	**L2**	92:8	**2g** (95:5)
9[d]	**1c**		CuTC	**L2**	93:7	**2h** (96:4)
10[d]	**1a**	*n*Hex	CuTC	**L2**	95:5	**2i** (95:5)
11[d]	**1a**		CuTC	**L2**	97:3	**2j** (98:2)
12[d]	**1b**	Et	CuTC	**L2**	91:9	**2a** (96:4)
13[d]	**1b**	Me	CuTC	**L2**	78:22	**2b** (86:14)

[a] Reactions were performed on a 0.2 mmol scale. The substrate was added (reverse addition) over 5 h. Full conversion was reached in all cases. [b] S_N2'/S_N2 ratio determined by ^{31}P and ^1H NMR spectroscopy. [c] Determined by chiral HPLC. [d] Normal addition; representative isolated yield: **2g** (85%), **2h** (87%), **2i** (83%), **2j** (93%).

lectivity but did not enhance the e.r. (Table 2, entry 4). Consideration of the data in Table 2, entries 3 and 5 shows that **L3** and **L5** display a mismatch effect that gives lower e.r. and regioselectivity. We also observed that the use of CuTC (copper(I) thiophene-2-carboxylate)[23] as the copper salt in combination with optimized ligand **L2** provides **2g** with slightly higher e.r. than the one obtained with CuBr·SMe$_2$ (Table 2, entries 2 and 7). Finally, we could achieve an improvement in the regioselectivity when the Grignard reagent was added to the substrate (Table 2, entry 8), in contrast to the findings observed with Taniaphos as the chiral ligand (Table 1, entries 1, 13, and 14). Alkylation of **1c** with homoallylmagnesium bromide also proceeded with a high level of regio- and enantioselectivity (Table 2, entry 9). As a representative example, this protocol was extended to phosphonate **1a** by using hexyl- and homoallyl magnesium bromide to give compounds **2i**[24] and **2j** with excellent regioselectivity and e.r. (Table 2, entries 10 and 11). Notably, compound **2j** is an advanced intermediate in the synthesis of 2-(phosphonomethyl)pentanedioic acid (2-PMPA), the most potent known inhibitor of the enzyme GCP II.[25] The copper/phosphoramidite system also proved to be a good alternative for the addition of a shorter alkylmagnesium bromide, such as EtMgBr, which gave rise to slightly lower selectivity that that obtained with TaniaPhos (Table 2, entry 12). However, as shown in Table 2, entry 13, the use of MeMgBr led to a considerable decrease in the regio- and enantioselectivity, which demonstrates the complementarity of both catalytic systems.

The catalytic enantioselective construction of all-carbon quaternary centers in acyclic systems continues to be a highly challenging task in organic synthesis.[26] The screening of ligands for the addition of HexMgBr to *E*- and *Z*-trisubstituted allyl bromide phosphine oxides (Table 3) soon indicated **L6**[27] as the best ligand in terms of regio- and enantioselectivity (Table 3, entries 1–4). The effect of the double-bond geometry of allyl bromide **4** was studied (Table 3, entries 4 and 5). Although the nature of the double bond has an important effect in the regioselectivity of the reaction, both *E*- and *Z*-allyl bromides **4** gave rise to the same enantiomer of product **5a** with similar e.r. values. Remarkably, no isomerization of the olefin takes places during the reaction, as observed from the geometry of the resulting linear products **6a**. There was no substantial difference between the use of CuBr·SMe$_2$ or CuTC in terms of regio- or enantioselectivity (Table 3, entries 4 and 6). The addition of ethyl- and homoallylmagnesium bromide to *E*-trisubstituted allyl bromide phosphine oxide **4** afforded products **5b** and **5c**, respectively, in good yields and with similar selectivity to that obtained for **5a** (Table 3, entries 7 and 8).

Table 3. Enantioselective synthesis of compounds **5** with an all-carbon quaternary stereogenic center. For the conditions, see Table 2.[a]

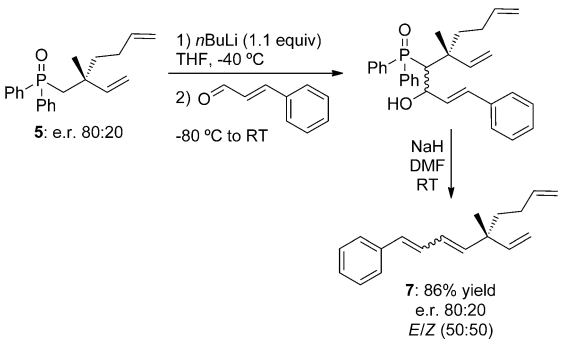


Entry	4; *E*/*Z*	R	Cu salt	L	5/6[b]	5 (e.r.)[c]
1	100:0	Hex	CuBr·SMe$_2$	**L2**	46:54	**5a** (71:29)
2	100:0	Hex	CuBr·SMe$_2$	**L4**	64:36	**5a** (66:34)
3	100:0	Hex	CuBr·SMe$_2$	**L5**	60:40	**5a** (51:49)
4	100:0	Hex	CuBr·SMe$_2$	**L6**	87:13[e]	**5a** (75:25)
5	0:100	Hex	CuBr·SMe$_2$	**L6**	69:31[f]	**5a** (78:22)
6[d]	100:0	Hex	CuTC	**L6**	87:13	**5a** (79:21)
7[d]	100:0		CuTC	**L6**	89:11	**5b** (80:20)
8[d]	100:0	Et	CuTC	**L6**	92:8	**5c** (78:22)

[a] Full conversion was reached in all cases. [b] S_N2'/S_N2 ratio determined by ^{31}P and ^1H NMR analysis. [c] Determined by chiral HPLC. [d] Compounds **5a** (68% yield), **5b** (73% yield), **5c** (85% yield). [e] Linear product **6a** was obtained as the pure *E* isomer. [f] Linear product **6a** was obtained as the pure *Z* isomer.

To further demonstrate the synthetic potential of this new methodology, phosphine oxide **5** was used as a chiral building block in a Horner–Wittig type reaction[6] for the synthesis of optically active polyunsaturated compound **7**, which has an all-carbon quaternary center (Scheme 2). Product **7**, formed by the reaction between **5** and cinnamaldehyde, features a similar substitution pattern at the quaternary center as the one present in bakuchiol[28] (an antimicrobial agent isolated from the seeds of *Psoralea corylifolia L.*). This olefination proceeds in high yield and without loss of enantiomeric purity.

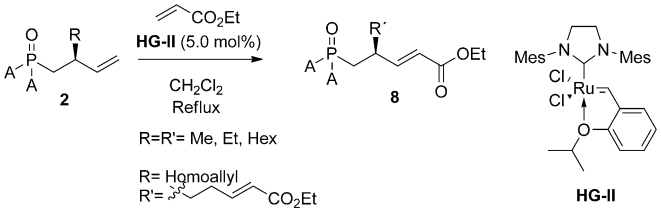
The new terminal olefin adjacent to the stereogenic center in AAA products **2** opens a wide array of possible



Scheme 2. Horner–Wittig reaction with phosphine oxide **5b**.

transformations. As an example, olefin cross metathesis[29] with ethyl acrylate was used to functionalize the terminal double bond in phosphonates **2a–d,i,j** to give the corresponding γ-alkyl unsaturated esters **8** with *E*/*Z* selectivities in excess of 10:1 to >20:1 and good yields without compromising the e.r. of the allylic stereocenter (Table 4).

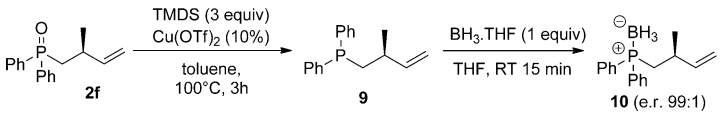
Table 4. Cross metathesis of phosphonates **2** with ethyl acrylate.[a]



Entry	**2**	R[b]	*t* [h]	Yield [%]	***E*/*Z***[b]	**8** (e.r.)[c]
1	**2a**	Et	8	75	15:1	**8a** (98:2)
2	**2b**	Me	8	83	11:1	**8b** (99:1)
3	**2c**	Et	8	80	14:1	**8c** (95:5)
4	**2d**	Me	8	78	>20:1	**8d** (99:1)
5	**2i**	Hex	8	62	>20:1	**8i** (95:5)
6	**2j**		24	60	10:1[d]	**8j** (98:2)

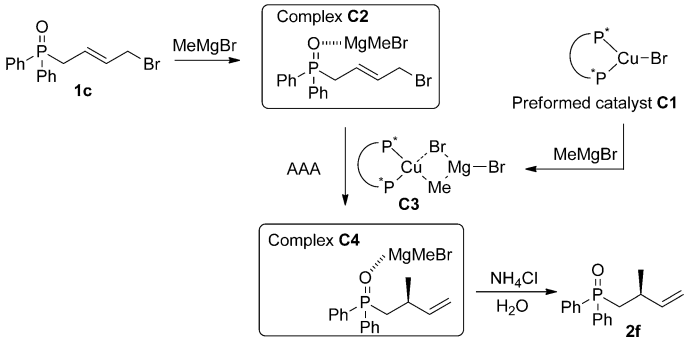
[a] Conditions: **2** (1 equiv), ethyl acrylate (3 equiv), CH_2Cl_2 (0.25 M in **2**). [b] *E*/*Z* ratio determined by ^{1}H NMR spectroscopy. [c] Determined by chiral HPLC. [d] (*E*,*E*) isomer/other isomers.

Finally, phosphine oxide **2f** was selectively reduced to the corresponding chiral phosphine **9** by using tetramethyldisiloxane (TMDS) in the presence $Cu(OTf)_2$, as recently described by Beller and co-workers (Scheme 3).[8] The corresponding phosphine–borane complex **10** was prepared by treating **9** with one equivalent of BH_3•THF (Scheme 3). Competing hydroboration of the alkene was not observed, as expected from the study of Vedejs and Shapland with homoallyldiphenylphosphine.[30]



Scheme 3. Reduction of phosphine oxide **2f** to phosphine **9** and further conversion to phosphine borane **10**.

As mentioned above, at least two equivalents of RMgBr were necessary for the copper-catalyzed AAA to reach completion. This suggests an interaction of the organometallic reagent with the substrate prior to alkylation. To elucidate the intermediates in this particular allylic alkylation, an NMR spectroscopy study was performed.[31] The ^{31}P NMR spectrum of a mixture of substrate **1c** (signal at $\delta = 29$ ppm) and a stoichiometric amount of preformed catalyst **C1**[32] (signal at $\delta = -18$ ppm[33]) at −80 °C in CD_2Cl_2 (t_0) is shown in Figure 2. After the addition of excess of MeMgBr (7.0 equiv; t_1), the ^{31}P NMR spectra were recorded at 5 min intervals (t_1–t_{14}; for details see the Supporting Information). Between t_0 and t_8 we observed the disappearance of the phosphorus resonance of the substrate ($\delta = 29$ ppm) and the appearance of a new signal at $\delta = 37$ ppm. We attributed this downfield shift to complex **C2** that formed between phosphine oxide **1c** and the first equivalent of Grignard reagent (Scheme 4). The expected deprotonation of phosphine oxide



Scheme 4. Proposed mechanistic pathway for the Cu-catalyzed AAA of phosphine oxide **1c** with MeMgBr.

1c by the organometallic reagent, which would lead to the corresponding ylide form, did not take place as confirmed by quenching the reaction with D_2O, CD_3OD, or DCl, which did not lead to deuterium incorporation at the α position. This observation was confirmed by repeating the same experiment with (2-methylbut-3-en-2-yl)diphenylphosphine oxide as a model phosphine oxide with two methyl groups in the α position. In this case, a similar downfield shift of the phosphorus resonance was observed (see the Supporting Information for details). Although complexes between magnesium salts and phosphine oxides are known,[34] there are no reports of the corresponding complex with Grignard reagents. At t_9, the phosphorus resonance at $\delta = 37$ ppm disappeared to reveal a new downfield singlet.[35] Interestingly, at the same time, two new different doublets at $\delta = -16$ and -19 ppm appeared. We attributed this to the formation of diphosphine Cu–Me chiral complex **C3** in accordance with our previous NMR spectroscopy studies.[32] When the reaction was allowed to go to completion,[36] the phosphine oxide ^{31}P resonance was split into two signals at $\delta = 39$ and 40 ppm. By using ^{1}H NMR spectroscopy at RT, we could identify the species associated with these two absorptions as

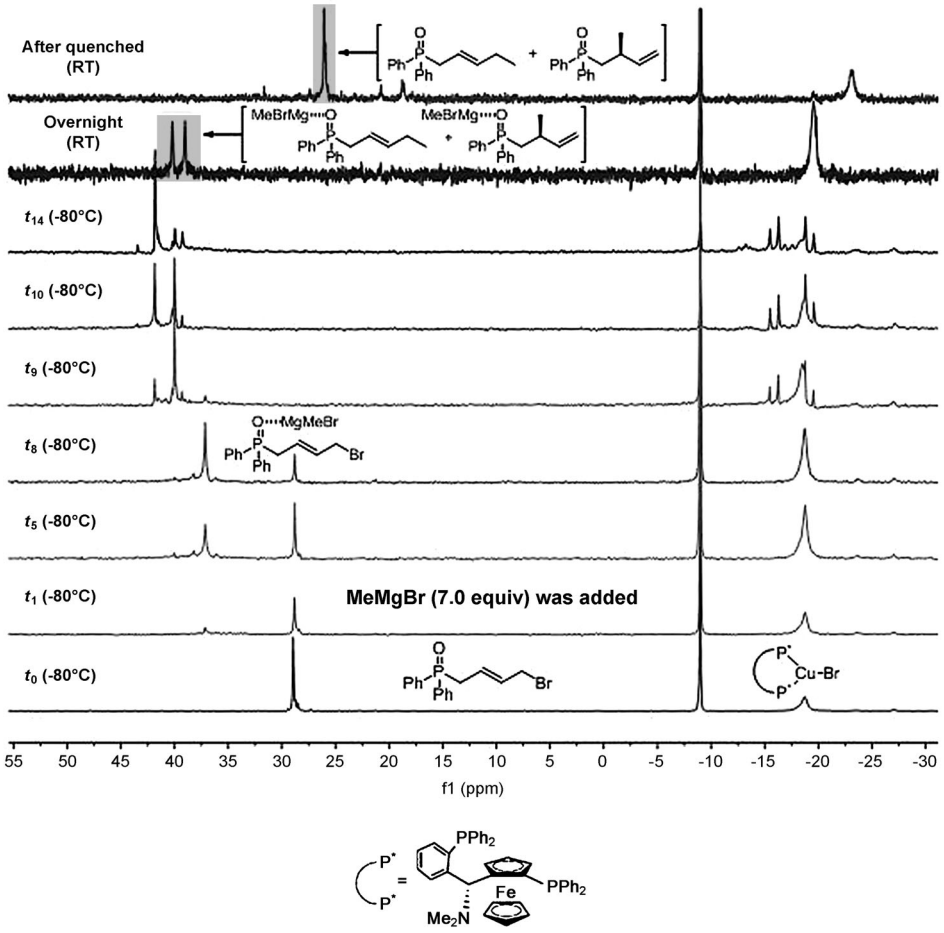


Figure 2. Representative ^{31}P NMR spectra upon treatment of phosphine oxide **2f** with MeMgBr at −80 °C in CD_2Cl_2. $t_n - t_{(n-1)} = 5$ min unless noted. PPh_3 ($\delta = -9$ ppm) was used as a reference.

the branched and linear[37] complexes **C4**. Quenching with aqueous NH_4Cl gave rise to a mixture of branched and linear products **2f** and **3f** in the same ratio as observed before quenching, with an e.r. of 99:1 for chiral S_N2' regioisomer **2f**.

Based on the combined data presented here and our recent study with organolithium reagents, we propose a mechanistic pathway for this allylic alkylation as shown in Scheme 4.

Conclusion

In summary, we have developed an efficient catalytic and highly enantioselective methodology for the asymmetric alkylation of phosphonate and phosphine oxide allylic bromides with Grignard reagents to form chiral β-alkylphosphonate and phosphine oxides in good yields. This protocol was optimized for methyl and ethyl magnesium bromide with CuBr·SMe_2 and (*R*,*R*)-TaniaPhos as ligand and for hexyl- and homoallyl magnesium bromide (functionalized alkene and long-chain nucleophiles) with CuTC and phosphoramidite **L2** as a chiral ligand. In addition, preliminary experiments show that this methodology can be applied to the enantioselective synthesis of quaternary carbon stereogenic centers in acyclic systems. Transformation of these products leads to important new optically active scaffolds with phosphine oxide and phosphonates that are not easily obtainable by other methods. Preliminary mechanistic studies indicate that the reaction takes place with a complex formed between the phosphorus compound and the Grignard reagent. Detailed mechanistic studies are ongoing and will be reported in due course.

Experimental Section

General remarks: Chromatography was performed on Merck silica gel type 9385 230–400 mesh and TLC was performed on Merck silica gel 60, 0.25 mm. Components were visualized by UV and potassium permanganate staining. Progress and conversion of the reactions were determined by GC-MS (GC, HP6890: MS HP5973) with an HP1 or HP5 column (Agilent Technologies, Palo Alto, CA). Mass spectra were recorded by using an AEI-MS-902 mass spectrometer (EI^+) or a LTQ Orbitrap XL (ESI^+). ^1H-, ^{13}C-, and ^{31}P NMR were recorded by using a Varian AMX400 or a Varian VXR300 spectrometer with $CDCl_3$ as the solvent. Chemical shift values are reported in ppm with the solvent resonance as the internal standard ($CHCl_3$: $\delta = 7.26$ for ^1H, $\delta = 7.0$ for ^{13}C). Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), and integration. Optical rotations were measured by using a Schmidt and Haensch polarimeter (Polartronic MH8) with a 10 cm cell (*c* given in g 100 mL^{-1}). Enantiomeric ratios were determined by HPLC analysis of both enantiomers for every compound by using a Shimadzu LC-10ADVP HPLC equipped with a Shimadzu SPD-M10AVP diode array detector. All reactions were carried out under a nitrogen atmosphere by using oven dried glassware and standard Schlenk techniques. Dichloromethane was dried and distilled over calcium hydride; toluene and THF were dried and distilled over sodium. All copper salts (CuTC and CuBr·SMe_2) were purchased from Aldrich and used without further purification. Allyl bromide **1b** was prepared by following a literature procedure.[38] MeMgBr (3.0 M in Et_2O), EtMgBr[39] (3.0 M in Et_2O), and *n*HexMgBr (2.0 M in Et_2O) were purchased from Aldrich and $CH_2CHCH_2CH_2MgBr$ was prepared as reported in the literature and titrated with *s*BuOH and catalytic amounts of 1,10-phenanthroline. Ligands (*R*,*R*)-TaniaPhos, (*S*,*S*)-TaniaPhos, and (*S*)-Tol-BINAP were purchased from Aldrich and phosphoramidite ligands (**L2**, **L3**),[40] (**L4**, **L5**),[41] and **L6**[42] were prepared as reported in the literature.

(*E*)-Dimethyl (4-bromobut-2-en-1-yl)phosphonate (1a): The same procedure as for **1b** was followed (80% yield). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.79$ (m, 2H), 3.94 (dd, $J = 6.8$, 3.4 Hz, 1H), 3.74 (d, $J = 11.0$ Hz, 6H), 2.62 ppm (dd, $J = 21.5$, 7.1 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta =$ 131.5 (d, $J = 15.2$ Hz), 124.2 (d, $J = 11.8$ Hz), 52.8 (d, $J = 6.6$ Hz, 2C), 31.8 (d, $J = 2.6$ Hz), 29.3 ppm (d, $J = 140.0$ Hz); ^{31}P NMR (161.9 MHz, $CDCl_3$): $\delta = 28.7$ ppm.

(*E*)-Diphenyl (4-bromobut-2-en-1-yl) phosphine oxide (1c): HG-II catalyst (0.62 mmol, 388 mg) was added to a solution of allyl diphenyl phosphine oxide (12.4 mmol, 3 g) and 1,4-dibromobutene (50 mmol, 10.6 g) in dry toluene (100 mL), and the mixture was heated at 80 °C for 10 h. The mixture was cooled down to RT and the solvent was removed under reduced pressure to give the crude product, which was purified by flash chromatography on silica gel with *n*-pentane/EtOAc 1:1 as the eluent (85% yield). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.69$ (m, 4H), 7.56 (m, 6H), 5.76 (m, 2H), 3.85 (m, 2H), 3.14 ppm (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta =$ 129.9–128.9 (m), 128.4 (d, $J = 9.2$ Hz, 4C), 126.1 (d, $J = 12.2$ Hz, 4C), 121.7 (d, $J = 9.2$ Hz), 32.0 (d, $J = 67.8$ Hz), 29.5 ppm (d, $J = 1.9$ Hz); ^{31}P NMR (161.9 MHz, $CDCl_3$): $\delta = 29.0$ ppm. EI MS: *m/z*: 334 [M^+] not observed, 254 (100%) [M−HBr].

General procedures for the copper-catalyzed allylic alkylation

Procedure A: In a dry Schlenk tube equipped with septum and stirring bar, CuBr·SMe_2 (0.01 mmol, 2.05 mg, 5.0 mol%) and (*R*,*R*)-Taniaphos (0.012 mmol, 8.25 mg, 6 mol%) were dissolved in CH_2Cl_2 (2.0 mL) and the mixture was stirred under a nitrogen atmosphere at RT for 20 min. The mixture was cooled to −80 °C and a solution of Grignard reagent (2.2 equiv) in Et_2O diluted with CH_2Cl_2 (combined volume: 1 mL) was added dropwise over 30 min through a syringe pump. Subsequently, a solution of the corresponding phosphonate or phosphine oxide allylic bromide **1** (0.2 mmol) in CH_2Cl_2 (1.0 mL) was added dropwise over 2 h through a syringe pump. Once the addition was complete, the resulting mixture was stirred at −80 °C for 16 h. Saturated aqueous NH_4Cl (2 mL) was added and the organic phase was separated. The aqueous phase was extracted with CH_2Cl_2 (3×10 mL), then the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure to give the crude product, which was purified by flash chromatography on silica gel with different mixtures of *n*-pentane/EtOAc as the eluent. **Note**: ^{31}P and ^{1}H NMR spectroscopic analyses were carried out to determine the branched/linear (b/l) ratio of a sample obtained after aqueous extraction with CH_2Cl_2.

Procedure B: In a Schlenk tube equipped with septum and stirring bar, CuTC (0.01 mmol, 1.9 mg, 5 mol%) and the appropriate phosphoramidite ligand (0.011 mmol, 5.5 mol%) were mixed. Dry CH_2Cl_2 (2 mL) was added and the solution was stirred under nitrogen at RT for 15 min, then the resulting solution was cooled to −80 °C. The corresponding phosphonate or phosphine oxide allylic bromide **1** (0.2 mmol) in CH_2Cl_2 (1 mL) was then added. In a separate Schlenk flask, the corresponding Grignard reagent (0.50 mmol, 2.5 equiv) was diluted with CH_2Cl_2 (combined volume of 1 mL) under nitrogen and added dropwise to the reaction mixture over 5 h by using a syringe pump. Once the addition was complete, the mixture was stirred at −80 °C for 16 h. The reaction was quenched with a saturated aqueous NH_4Cl solution (2 mL) and the mixture was warmed up to RT, diluted with CH_2Cl_2, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3×5 mL) and the combined organic layers were dried with anhydrous Na_2SO_4, filtered, and the solvent was evaporated in vacuo. The crude product was purified by flash chromatography on silica gel with different mixtures of *n*-pentane/EtOAc as the eluent. ^{31}P and ^{1}H NMR spectroscopic analyses were carried out to determine the b/l ratio of a sample obtained after aqueous extraction with CH_2Cl_2.

General protocol for cross-metathesis reaction: HG-II catalyst (0.01 mmol, 5 mol%) was added to a solution of the corresponding phosphonate **2** (0.2 mmol) and ethyl acrylate (0.6 mmol) in dry CH_2Cl_2 (2 mL) and the mixture was heated at reflux for the indicated time (8–24 h). The mixture was cooled down to RT and the solvent was removed under reduced pressure to give the crude product, which was purified by flash chromatography on silica gel with mixtures of *n*-pentane/EtOAc.

(+)-Diethyl (2-ethylbut-3-en-1-yl)phosphonate (2a): The title compound was prepared from **1b** by following general procedure A. Purification by column chromatography (SiO_2, eluent *n*-pentane/EtOAc 7:3) afforded **2a** (96% yield, 99:1 ratio (S_N2'/S_N2), 98:2 e.r.) as a colorless oil. The enantiomeric ratio was determined for cross-metathesis product **8a**. $[\alpha]_D^{20} = +2.0$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.60$ (m, 1H), 5.02 (m, 2H), 4.05 (m, 4H), 2.36 (m, 1H), 1.78 (m, 2H), 1.58 (m, 1H), 1.38 (m, 1H), 1.28 (dt, $J = 7.0$, 1.3 Hz, 6H), 0.84 ppm (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 141.3$ (d, $J = 10.7$ Hz), 114.8, 61.2 (m, 2C), 39.7 (d, $J = 4.0$ Hz), 31.4 (d, $J = 140.0$ Hz), 28.4 (d, $J = 14.0$ Hz), 16.4 (d, $J = 6.3$ Hz, 2C), 11.1 ppm; ^{31}P NMR (161.9 MHz, $CDCl_3$): $\delta = 31.1$ ppm; HRMS (ESI$^+$): *m/z* calcd for $C_{10}H_{22}O_3P$: 221.1307 [M+H$^+$]; found: 221.1301.

(−)-(*E*)-Ethyl 4-((diethoxyphosphoryl)methyl)hex-2-enoate (8a): The reaction was performed by using the cross-metathesis protocol, with a reaction time of 8 h. Purification by column chromatography (SiO_2, eluent *n*-pentane/EtOAc 1:1) gave **8a** as a colorless oil (75% yield, *E*/*Z* 15:1, 98:2 e.r.). $[\alpha]_D^{20} = -62.0$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.74$ (dd, $J = 15.2$, 8.7 Hz, 1H), 5.83 (d, $J = 15.9$ Hz, 1H), 4.16 (q, $J = 7.5$ Hz, 2H), 4.05 (m, 4H), 2.54 (m, 1H), 1.83 (m, 1H), 1.63 (m, 1H), 1.43 (m, 1H), 1.27 (m, 9H), 0.85 ppm (d, $J = 7.3$ Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 166.4$, 150.8 (d, $J = 8.8$ Hz), 121.7, 61.5 (m, 2C), 60.2, 38.4 (d, $J = 3.7$ Hz), 30.3(d, $J = 145.3$ Hz), 28.2 (d, $J = 12.1$ Hz), 16.4 (d, $J = 5.5$ Hz, 2C), 14.2, 11.2 ppm; ^{31}P NMR (161.9 MHz, $CDCl_3$): $\delta = 29.5$ ppm; HRMS (ESI$^+$): *m/z* calcd for $C_{13}H_{26}O_5P$: 293.1518 [M+H$^+$]; found: 293.1512; the enantiomeric ratio was determined by chiral HPLC analysis, Chiralpak AD-H column, *n*-heptane/*i*PrOH 97:3, 40 °C, retention times: 43.9 (minor) and 47.2 min (major).

(+)-Diethyl (2-methylbut-3-en-1-yl)phosphonate (2b): The title compound was prepared from **1b** (700 mg, 2.58 mmol) by following general procedure A. Purification by column chromatography (SiO_2, eluent *n*-pentane/EtOAc 7:3) gave **2b** as a colorless oil (97% yield, S_N2'/S_N2 99:1, 99:1 e.r.). The enantiomeric ratio was determined for cross-metathesis product **8b**. $[\alpha]_D^{20} = +2.4$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.80$ (m, 1H), 4.98 (m, 2H), 4.07 (m, 4H), 2.61 (m, 1H), 1.84 (m, 1H), 1.69 (m, 1H), 1.30 (t, $J = 7.0$ Hz, 6H), 1.13 ppm (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 143.6$ (d, $J = 12.5$ Hz), 113.0, 60.6 (m, 2C), 32.6 (d, $J = 140.0$ Hz), 32.4 (d, $J = 3.7$ Hz), 21.2 (d, $J = 9.2$ Hz), 16.6 ppm (d, $J = 5.9$ Hz, 2C); ^{31}P NMR (161.9 MHz, $CDCl_3$): $\delta =$ 30.6 ppm; HRMS (ESI$^+$): *m/z* calcd for $C_9H_{20}O_3P$: 207.1150 [M+H$^+$]; found: 207.1145.

(−)-(*E*)-Ethyl 5-(diethoxyphosphoryl)-4-methylpent-2-enoate (8b): The reaction was performed by using the cross-metathesis protocol, with a reaction time of 8 h. Purification by column chromatography (SiO_2, eluent *n*-pentane/EtOAc 1:1) gave **8b** as a colorless oil (83% yield, *E*/*Z* 11:1, 99:1 e.r.). $[\alpha]_D^{20} = -9.6$ ($c = 1.0$, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 6.89 (dd, $J = 15.5$, 7.7 Hz, 1H), 5.82 (dd, $J = 15.5$, 1.2 Hz, 1H), 4.18 (q, $J =$ 7.0 Hz, 2H), 4.07 (m, 4H), 2.78 (m, 1H), 1.82 (m, 1H), 1.34–1.24 (m, 9H), 1.19 ppm (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta =$ 166.5, 152.5, 120.0, 61.6 (m, 2C), 60.3, 31.9 (d, $J = 140.8$ Hz), 31.3 (d, $J =$ 3.7 Hz), 20.6 (d, $J = 10.7$ Hz), 16.3 (d, $J = 6.3$ Hz, 2C), 14.2 ppm; ^{31}P NMR (161.9 MHz, $CDCl_3$): $\delta = 29.4$ ppm; HRMS (ESI$^+$): *m/z* calcd for $C_{12}H_{24}O_5P$: 279.1361 [M+H$^+$]; found: 279.1356. The enantiomeric ratio was determined by chiral HPLC analysis, Chiralpak AD-H column, eluent *n*-heptane/*i*PrOH 97:3, 40 °C, retention times: 37.4 (minor) and 41.0 min (major).

(+)-Dimethyl (2-methylbut-3-en-1-yl)phosphonate (2c): The title compound was prepared from **1a** by following general procedure A. Purification by column chromatography (SiO_2, eluent *n*-pentane/EtOAc 1:1) afforded **2c** as a colorless oil (95% yield, S_N2'/S_N2 99:1, 95:5 e.r.). The enantiomeric ratio was determined for cross-metathesis product **8c**. $[\alpha]_D^{20} = +8.0$ ($c = 1.0$, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.60$ (m, 1H), 5.04 (m, 2H), 3.69 (d, $J = 11.0$ Hz, 6H), 2.35 (m, 1H), 1.80 (dt, $J =$ 18.3, 6.7 Hz, 2H), 1.55 (m, 1H), 1.33 (m, 1H), 0.85 ppm (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 141.1$ (d, $J = 9.2$ Hz), 115.0, 52.0 (m, 2C), 39.7 (d, $J = 3.7$ Hz), 30.0 (d, $J = 139.8$ Hz), 28.5 (d, $J = 11.1$ Hz), 11.2 ppm; ^{31}P NMR (161.9 MHz, $CDCl_3$): $\delta = 33.6$ ppm; HRMS (ESI$^+$): *m/z* calcd for $C_8H_{18}O_3P$: 193.0994 [M+H$^+$]; found: 193.0988.

(+)-(*E*)-Ethyl 5-(dimethoxyphosphoryl)-4-methylpent-2-enoate (8c): The reaction was performed by using the cross-metathesis protocol, with a reaction time of 8 h. Purification by column chromatography (SiO_2, eluent *n*-pentane/EtOAc 1:1) afforded **8c** as a colorless oil (80% yield, *E*/*Z* 14:1, 95:5 e.r.). $[\alpha]_D^{20} = -83$ ($c = 1.0$, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.73$ (dd, $J = 15.5$, 8.9 Hz, 1H), 5.84 (d, $J = 15.7$ Hz, 1H), 4.18 (q, $J = 7.3$ Hz, 2H), 3.69 (dd, $J = 10.8$, 3.3 Hz, 6H), 2.53 (m, 1H), 1.84 (m, 2H), 1.64 (m, 1H), 1.43 (m, 1H), 1.28 (t, $J = 7.1$ Hz, 3H), 0.86 ppm (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 166.4$, 150.6 (d, $J = 8.8$ Hz), 121.8, 60.3, 52.2 (m, 2C), 38.3 (d, $J = 3.3$ Hz), 29.3 (d, $J = 140.8$ Hz), 28.1 (d, $J = 11.8$ Hz), 14.2, 11.3 ppm; ^{31}P NMR (161.9 MHz, $CDCl_3$): $\delta = 32.3$ ppm; HRMS (ESI^+): *m*/*z* calcd for $C_{11}H_{21}NaO_5P$: 287.1024 [M+Na^+]; found: 287.1019. The enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel OD-H column, eluent *n*-heptane/*i*PrOH 95:5, 40 °C, retention times: 22.04 (minor) and 24.31 min (major).

(−)-Dimethyl (2-methylbut-3-en-1-yl)phosphonate (2d): The title compound was prepared from **1a** by following general procedure A. Purification by column chromatography (SiO_2, eluent *n*-pentane/EtOAc 1:1) afforded **2d** as a colorless oil (92% yield, S_N2'/S_N2 99:1, 99:1 e.r.). The enantiomeric ratio was determined for cross-metathesis product **8d**. $[\alpha]_D^{20} = -2.4$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.77$ (m, 1H), 4.99 (m, 2H), 3.69 (d, $J = 10.8$ Hz, 6H), 2.59 (m, 1H), 1.83 (ddd, $J = 18.4$, 15.4, 6.3 Hz, 1H), 1.69 (ddd, $J = 17.9$, 15.4, 7.6 Hz, 1H), 1.11 ppm (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 143.1$ (d, $J = 12.9$ Hz), 112.9, 52.0 (m, 2C), 32.3 (d, $J = 3.7$ Hz), 31.5 (d, $J = 140.0$ Hz), 21.1 ppm (d, $J = 9.6$ Hz); ^{31}P NMR (161.9 MHz, $CDCl_3$): $\delta = 33.4$ ppm; HRMS (ESI^+): *m*/*z* calcd for $C_7H_{16}O_3P$: 179.0837 [M+H^+]; found: 179.0832.

(+)-(*E*)-Ethyl 5-(dimethoxyphosphoryl)-4-methylpent-2-enoate (8d): The reaction was performed by using the cross-metathesis protocol, with a reaction time of 8 h. Purification by column chromatography (SiO_2, eluent *n*-pentane/EtOAc 1:1) afforded **8d** as a colorless oil (78% yield, *E*/*Z* >20:1, 99:1 e.r.). $[\alpha]_D^{20} = +47.0$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.87$ (dd, $J = 15.5$, 7.7 Hz, 1H), 5.81 (d, $J = 15.5$ Hz, 1H), 4.17 (q, $J = 7.0$ Hz, 2H), 3.71 (d, $J = 10.8$ Hz, 6H), 2.79 (m, 1H), 1.82 (m, 2H), 1.26 (t, $J = 7.0$ Hz, 3H), 1.19 ppm (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 166.5$, 152.1 (d, $J = 12.5$ Hz), 120.1, 60.3, 52.2 (m, 2C), 31.2 (d, $J = 3.7$ Hz), 30.9 (d, $J = 141$ Hz), 20.5 (d, $J = 9.2$ Hz), 14.2 ppm; ^{31}P NMR (161.9 MHz, $CDCl_3$): $\delta = 31.9$ ppm; HRMS (ESI^+): *m*/*z* calcd for $C_{10}H_{20}O_5P$: 251.1048 [M+H^+]; found: 251.1043. The enantiomeric ratio was determined by chiral HPLC analysis, Chiralpak AD-H column, eluent *n*-heptane/*i*PrOH 97:3, 40 °C, retention times: 41.5 (minor) and 45.5 min (major).

(+)-(2-Ethylbut-3-en-1-yl)diphenylphosphine oxide (2e): The title compound was prepared from **1c** by following general procedure A. Purification by column chromatography (SiO_2, eluent *n*-pentane/EtOAc 1:1) afforded **2e** as a colorless oil (89% yield, S_N2'/S_N2 93:7, 98:2 e.r.). $[\alpha]_D^{20} = +29.2$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.72$ (m, 4H), 7.43 (m, 6H), 5.52 (m, 1H), 4.83 (m, 2H), 2.46 (m, 1H), 2.31 (dd, $J = 11.4$, 6.6 Hz, 2H), 1.62 (m, 1H), 1.32 (m, 1H), 0.77 ppm (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 141.2$ (d, $J = 9.9$ Hz), 133.8 (m, 2C), 131.5 (m, 2C), 130.7 (m, 4C), 128.5 (m, 4C), 114.9, 39.5 (d, $J = 3.3$ Hz), 34.8 (d, $J = 73.7$ Hz), 28.8 (d, $J = 8.1$ Hz), 11.1 ppm; ^{31}P NMR (161.9 MHz, $CDCl_3$): $\delta = 30.8$ ppm; HRMS (ESI^+): *m*/*z* calcd for $C_{18}H_{22}OP$: 285.1408 [M+H^+]; found: 285.1403. The enantiomeric ratio was determined by chiral HPLC analysis, Chiralpak AS-H column, eluent *n*-heptane/*i*PrOH 98:2, 40 °C, retention times: 29.7 (minor) and 31.3 min (major).

(+)-(2-Methylbut-3-en-1-yl)diphenylphosphine oxide (2f): The title compound was prepared from **1c** by following general procedure A. Purification by column chromatography (SiO_2, eluent *n*-pentane/EtOAc 1:1) afforded **2f** as a colorless oil (94% yield, S_N2'/S_N2 99:1, 99:1 e.r.). $[\alpha]_D^{20} = +12.0$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.74$ (m, 4H), 7.46 (m, 6H), 5.76 (m, 1H), 4.87 (m, 2H), 2.71 (m, 1H), 2.39 (m, 1H), 2.24 (m, 1H), 1.11 ppm (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 143.5$ (d, $J = 10.3$ Hz), 133.7 (m, 2C), 131.5 (d, $J = 3.0$ Hz, 2C), 130.7 (m, 4H), 128.6 (m, 4H), 112.8, 36.2 (d, $J = 70.4$ Hz), 32.1 (d, $J = 3.3$ Hz), 21.4 ppm (d, $J = 6.6$ Hz); ^{31}P NMR (161.9 MHz, $CDCl_3$): $\delta = 30.8$ ppm; HRMS (ESI^+): *m*/*z* calcd for $C_{17}H_{20}OP$: 271.1252 [M+H^+]; found: 271.1246. The enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel OJ-H column, eluent *n*-heptane/*i*PrOH 98:2, 40 °C, retention times: 19.8 (major) and 20.5 min (minor).

(−)-(2-Vinyloctyl)diphenylphosphine oxide (2g): The title compound was prepared from **1c** by following general procedure B with (*R*,*S*,*S*)-**L2** as the ligand. Purification by column chromatography (SiO_2, eluent *n*-pentane/EtOAc 1:1) afforded **2g** as a colorless oil (85% yield, S_N2'/S_N2 92:8, 95:5 e.r.). $[\alpha]_D^{20} = -60.2$ ($c = 1.0$, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.73$ (m, 4H), 7.45 (m, 6H), 5.54 (m, 1H), 4.83 (m, 2H), 2.54 (m, 1H), 2.31 (dd, $J = 11.1$, 6.6 Hz, 2H), 1.54 (m, 1H), 1.22 (m, 9H), 0.83 ppm (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 141.6$ (d, $J = 7.7$ Hz), 133.9 (m, 2C), 131.5 (m, 2C), 130.9 (d, $J = 9.2$ Hz, 2C), 130.6 (d, $J = 9.2$ Hz, 2C), 128.5 (m, 4C), 114.7, 37.9 (d, $J = 3.3$ Hz), 36.1 (d, $J = 7.7$ Hz), 35.2 (d, $J = 70.8$ Hz), 31.7, 29.0, 26.7, 22.6, 14.0 ppm; ^{31}P NMR (161.9 MHz, $CDCl_3$): $\delta = 30.8$ ppm; HRMS (ESI^+): *m*/*z* calcd for $C_{22}H_{29}OP$: 363.1854 [M+H^+]; found: 363.1848. The enantiomeric ratio was determined by chiral HPLC analysis, Chiralpak AS-H column, eluent *n*-heptane/*i*PrOH 98:2, 40 °C, retention times: 19.0 (major) and 21.6 min (minor).

(−)-(2-Vinylhex-5-en-1-yl)diphenylphosphine oxide (2h): The title compound was prepared from **1c** by following general procedure B with (*R*,*S*,*S*)-**L2** as the ligand. Purification by column chromatography (SiO_2, eluent *n*-pentane/EtOAc 1:1) afforded **2h** as a colorless oil (87% yield, S_N2'/S_N2 93:7, 96:4 e.r.). $[\alpha]_D^{20} = -27.0$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.73$ (m, 4H), 7.46 (m, 6H), 5.67 (m, 1H), 5.54 (m, 1H), 4.87 (m, 4H), 2.58 (m, 1H), 2.33 (dd, $J = 11.1$, 6.5 Hz, 2H), 2.00 (m, 1H), 1.92 (m, 1H), 1.68 (m, 1H), 1.40 ppm (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 141.2$ (d, $J = 7.7$ Hz), 138.2, 134.2 (d, $J = 73.7$ Hz, 1C), 133.2 (d, $J = 73.7$ Hz, 1C), 131.5 (m, 2C), 130.9 (d, $J = 8.5$ Hz, 2C), 130.6 (d, $J = 8.5$ Hz, 2C), 128.5 (m, 4C), 115.2, 114.6, 37.5 (d, $J = 3.3$ Hz), 35.2 (d, $J = 70.8$ Hz), 35.1 (d, $J = 8.1$ Hz), 30.9 ppm; ^{31}P NMR (161.9 MHz, $CDCl_3$): $\delta = 30.5$ ppm; HRMS (ESI^+): *m*/*z* calcd for $C_{22}H_{29}OP$: 333.1384 [M+H^+]; found: 333.1379. The enantiomeric ratio was determined by chiral HPLC analysis, Chiralpak AS-H column, eluent *n*-heptane/*i*PrOH 98:2, 40 °C, retention times: 30.9 (major) and 34.6 min (minor).

(−)-Dimethyl (2-vinyloctyl)phosphonate (2i): The title compound was prepared from **1a** by following general procedure B with (*R*,*S*,*S*)-**L2** as the ligand. Purification by column chromatography (SiO_2, eluent *n*-pentane/EtOAc 7:3) afforded **2i** as a colorless oil (83% yield, S_N2'/S_N2 95:5, 95:5 e.r.). The enantiomeric ratio was determined for cross-metathesis product **8i**. $[\alpha]_D^{20} = -8.0$ ($c = 1.0$, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.60$ (m, 1H), 5.02 (m, 2H), 3.69 (d, $J = 10.8$ Hz, 6H), 2.43 (m, 1H), 1.79 (m, 2H), 1.49 (m, 1H), 1.24 (m, 9H), 0.85 ppm (t, $J = 6.3$ Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 141.5$ (d, $J = 8.8$ Hz), 114.8, 52.1 (m, 2C), 38.2 (d, $J = 3.7$ Hz), 35.8 (d, $J = 12.2$ Hz), 31.7, 30.5 (d, $J = 139.7$ Hz), 29.0, 26.7, 22.6, 14.0 ppm; ^{31}P NMR (161.9 MHz, $CDCl_3$): $\delta = 33.6$ ppm; HRMS (ESI^+): *m*/*z* calcd for $C_{12}H_{26}O_3P$: 249.1620 [M+H^+]; found: 249.1614.

(−)-(*E*)-Ethyl 4-((dimethoxyphosphoryl)methyl)dec-2-enoate (8i): The reaction was performed by using the cross-metathesis protocol, with a reaction time of 8 h. Purification by column chromatography (SiO_2, eluent *n*-pentane/EtOAc 1:1) afforded **8i** as a colorless oil (62% yield, *E*/*Z* >20:1, 95:5 e.r.). $[\alpha]_D^{20} = -153.0$ ($c = 1.0$, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.72$ (dd, $J = 15.8$, 9.2 Hz, 1H), 5.82 (d, $J = 15.8$ Hz, 1H), 4.16 (q, $J = 7.0$ Hz, 2H), 3.67 (dd, $J = 10.7$, 2.7 Hz, 6H), 2.58 (m, 1H), 1.82 (m, 2H), 1.55 (m, 1H), 1.38 (m, 1H), 1.23 (m, 11H), 0.84 ppm (t, $J = 6.3$ Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 166.4$, 150.9 (d, $J = 8.8$ Hz), 121.5, 60.3, 52.2 (m, 2C), 36.8 (d, $J = 4.0$ Hz), 35.3 (d, $J = 11.8$ Hz), 31.6, 29.8 (d, $J = 141.2$ Hz), 26.7, 22.5, 14.2, 14.0 ppm; ^{31}P NMR (161.9 MHz, $CDCl_3$): $\delta = 32.2$ ppm; HRMS (ESI^+): *m*/*z* calcd for $C_{15}H_{39}NaO_5P$: 343.1650 [M+Na^+]; found: 343.1545. The enantiomeric ratio was determined by chiral HPLC analysis, Chiralpak AD-H column, eluent *n*-heptane/*i*PrOH 97:3, 40 °C, retention times: 33.7 (major) and 37.8 min (minor).

(−)-Dimethyl (2-vinylhex-5-en-1-yl)phosphonate (2j): The title compound was prepared from **1a** by following general procedure B with (*R*,*S*,*S*)-**L2** as the ligand. Purification by column chromatography (SiO_2, eluent *n*-pentane/EtOAc 7:3) afforded **2j** as a colorless oil (93% yield, S_N2'/S_N2 97:3, 98:2 e.r.). The enantiomeric ratio was determined for cross-metathesis product **8j**. $[\alpha]_D^{20} = -6.0$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR (400 MHz,

$CDCl_3$): $\delta = 5.75$ (m, 1H), 5.60 (m, 1H), 4.99 (m, 4H), 3.68 (d, $J = 10.7$ Hz, 6H), 2.46 (m, 1H), 2.01 (m, 2H), 1.82 (m, 1H), 1.78 (m, 1H), 1.61 (m, 1H), 1.39 ppm (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 141.1$ (d, $J = 10.7$ Hz), 138.1, 115.3, 114.7, 52.1 (m, 2C), 37.7 (d, $J = 3.7$ Hz), 34.8 (d, $J = 11.8$ Hz), 30.9, 30.5 ppm (d, $J = 140.1$ Hz); ^{31}P NMR (161.9 MHz, $CDCl_3$): $\delta = 33.1$ ppm; HRMS (ESI$^+$): m/z calcd for $C_{12}H_{26}O_3P$: 219.1150 [M+H$^+$]; found: 219.1145.

(+)-((2*E*,7*E*)-Diethyl 4-((dimethoxyphosphoryl)methyl)nona-2,7-dienedioate (8j): The reaction was performed by using the cross-metathesis protocol, with a reaction time of 24 h. Purification by column chromatography (SiO_2, eluent *n*-pentane/EtOAc 3:7) afforded **8j** as a colorless oil (60% yield, all *E*/*Z* 10:1, 98:2 e.r.). $[\alpha]_D^{20} = +83.0$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.88$ (m, 1H), 6.71 (dd, $J = 15.6$, 9.2 Hz, 1H), 5.83 (dd, $J = 23.3$, 15.6 Hz, 2H), 4.18 (m, 4H), 3.72 (m, 6H), 2.65 (m, 1H), 2.15 (m, 2H), 1.87 (m, 2H), 1.80 (m, 1H), 1.56 (m, 1H), 1.27 ppm (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 166.4$, 166.1, 149.7 (d, $J = 9.9$ Hz), 147.4, 122.4, 122.0, 60.5, 60.2, 52.3 (m, 2C), 36.4 (d, $J = 3.7$ Hz) 33.2 (d, $J = 11.4$ Hz), 29.8 (d, $J = 141.5$ Hz), 29.4, 14.2 ppm (2C); ^{31}P NMR (161.9 MHz, $CDCl_3$): $\delta = 33.6$ ppm; HRMS (ESI$^+$): m/z calcd for $C_{16}H_{27}NaO_7P$: 385.1392 [M+Na$^+$]; found: 385.1387. The enantiomeric ratio was determined by chiral HPLC analysis, Chiralpak AD-H column, eluent *n*-heptane/*i*PrOH 92:8, 40°C, retention times: 35.7 (major) and 36.9 min (minor).

Synthesis of trisubstituted allyl halides 4: Allyl bromides (**4**) were synthesized from the corresponding (*E*)- and (*Z*)-(4-hydroxybut-2-en-1-yl)diphenylphosphine oxides[43] as described below.

(*E*)-(4-Bromo-2-methylbut-2-en-1-yl)diphenylphosphine oxide (4): PBr_3 (370 μL, 3.9 mmol) was added to a suspension of (*E*)-(4-hydroxybut-2-en-1-yl)diphenylphosphine oxide (930 mg, 3.25 mmol) in Et_2O (17 mL) at 0°C, and the mixture was stirred for 2 h at 25°C. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (3×5 mL) and the combined organic layers were washed with water and dried with anhydrous Na_2SO_4. The solvent was evaporated in vacuo to give the bromide as a pale yellow solid (90% yield). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.74$ (m, 4H), 7.49 (m, 6H), 5.42 (q, $J = 5.5$ Hz, 1H), 3.87 (dd, $J = 8.5$, 2.3 Hz, 2H), 3.14 (d, $J = 14.1$ Hz, 2H), 1.79 ppm (brs, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 133.9$ (d, $J = 10.7$ Hz), 132.2 (d, $J = 99.1$ Hz, 2C), 131.9 (d, $J = 2.6$ Hz, 2C), 131.0 (d, $J = 9.2$ Hz, 4C), 128.6 (d, $J = 11.4$ Hz, 4C), 126.0 (d, $J = 10.3$ Hz), 41.2 (d, $J = 67.1$ Hz), 28.2, 18.1 ppm; ^{31}P NMR (161.9 MHz, $CDCl_3$): $\delta = 29.8$ ppm; HRMS (ESI$^+$): m/z calcd for $C_{17}H_{19}BrOP$: 349.0357 [M+H$^+$]; found: 349.0351.

(*Z*)-Diphenyl (4-bromo-2-methylbut-2-enyl) phosphine oxide ((*Z*)-4): The title compound was prepared from (*Z*)-(4-hydroxybut-2-en-1-yl)diphenylphosphine oxide (540 mg, 1.89 mmol), and PBr_3 (215 μL, 2.26 mmol) in Et_2O (10 mL) by following the procedure described for (*E*)-**4** (93% yield). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.7$ (m, 4H), 7.5 (m, 6H), 5.7 (q, $J = 4.9$ Hz, 1H), 3.7 (d, $J = 8.5$ Hz, 2H), 3.2 (d, $J = 14.6$ Hz, 2H), 1.7 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 132.8$ (d, $J = 9.5$ Hz), 132.5 (d, $J = 98.4$ Hz, 2C), 132.0 (d, $J = 2.9$ Hz, 2C), 130.9 (d, $J = 9.2$ Hz, 4C), 128.7 (d, $J = 11.8$ Hz, 4C), 125.9 (d, $J = 9.6$ Hz), 34.9 (d, $J = 68.0$ Hz), 29.2, 25.7 ppm; ^{31}P NMR (161.9 MHz, CDCl3): $\delta = 27.5$ ppm; HRMS (ESI$^+$): m/z calcd for $C_{17}H_{19}BrOP$: 349.0357 [M+H$^+$]; found: 349.0351.

(+)-Diphenyl (2-methyl-2-vinyloctyl) phosphine oxide (5a): The title compound was prepared from (*E*)-**4** by following general procedure B with (*S*,*R*,*R*)-**L6** as the ligand. Purification by column chromatography (SiO_2, eluent *n*-pentane/EtOAc 1:1) afforded **5a** as a colorless oil (68% yield, S_N2'/S_N2 87:13, 79:21 e.r.). $[\alpha]_D^{20} = +19.2$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.76$ (m, 4H), 7.45 (m, 6H), 5.74 (dd, $J = 17.6$, 10.7 Hz, 1H), 4.85 (m, 2H), 2.39 (m, 2H), 1.48 (m, 2H), 1.30–1.00 (m, 8H), 1.12 (s, 3H), 0.83 ppm (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (101 MHz, CDCl3): $\delta = 146.5$ (d, $J = 7.7$ Hz), 135.3 (m, 2C), 131.2 (m, 2C), 130.6 (m, 4C), 128.4 (m, 4C), 111.5, 42.2 (d, $J = 7.0$ Hz), 40.5 (d, $J = 70.4$ Hz), 40.3 (d, $J = 4.3$ Hz), 31.7, 29.7, 24.3 (d, $J = 5.9$ Hz), 24.2, 22.6, 14.0 ppm; ^{31}P NMR (161.9 MHz, $CDCl_3$): $\delta = 27.5$ ppm; HRMS (ESI$^+$): m/z calcd for $C_{23}H_{31}NaOP$: 377.2010 [M+Na$^+$]; found: 377.2004. The enantiomeric ratio was determined by chiral HPLC analysis, Chiralpak AS-H column, eluent *n*-heptane/*i*PrOH 99:1, 40°C, retention times: 16.7 (minor) and 17.5 min (major).

(+)-(2-Methyl-2-vinylhex-5-en-1-yl)diphenylphosphine oxide (5b): The title compound was prepared from (*E*)-**4** by following general procedure B with (*S*,*R*,*R*)-**L6** as the ligand. Purification by column chromatography (SiO_2, eluent *n*-pentane/EtOAc 1:1) afforded **5b** as a colorless oil (73% yield, S_N2'/S_N2 89:11, 80:20 e.r.). $[\alpha]_D^{20} = +12.2$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.76$ (m, 4H), 7.44 (m, 6H), 5.71 (m, 2H), 4.85 (m, 4H), 2.41 (m, 2H), 1.90 (m, 2H), 1.61 (m, 2H), 1.19 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 145.9$ (d, $J = 7.7$ Hz), 138.7, 135.2 (m, 2C), 131.3 (m, 2C), 130.6 (m, 4C), 128.4 (m, 4C), 114.0, 112.0, 41.1 (d, $J = 7.0$ Hz), 40.6 (d, $J = 65.9$ Hz), 40.2, 28.6, 24.1 ppm (d, $J = 5.2$ Hz); ^{31}P NMR (161.9 MHz, $CDCl_3$): $\delta = 27.4$ ppm; HRMS (ESI$^+$): m/z calcd for $C_{21}H_{25}NaOP$: 347.1541 [M+Na$^+$]; found: 347.1535. The enantiomeric excess was determined by chiral HPLC analysis, Chiralpak AS-H column, eluent *n*-heptane/*i*PrOH 99:1, 40°C, retention times: 23.0 (minor) and 24.3 min (major).

(+)-Diphenyl (2-ethyl-2-methylbut-3-enyl) phosphine oxide (5c): The title compound was prepared from (*E*)-**4** by following general procedure B with (*S*,*R*,*R*)-**L6** as the ligand. Purification by column chromatography (SiO_2, eluent *n*-pentane/EtOAc 1:1) afforded **5c** as a colorless oil (85% yield, S_N2'/S_N2 92:8, 78:22 e.r.). $[\alpha]_D^{20} = +10.0$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.75$ (m, 4H), 7.50 (m, 6H), 5.71 (dd, $J = 17.4$, 10.8 Hz, 1H), 4.84 (m, 2H), 2.38 (d, $J = 10.7$ Hz, 2H), 1.57 (q, $J = 7.4$ Hz, 2H), 1.13 (s, 3H), 0.74 ppm (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 145.9$ (d, $J = 7.4$ Hz), 135.2 (m, 2C), 130.6 (m, 4C), 128.4 (m, 4C), 111.9, 40.5 (d, $J = 4.1$ Hz), 40.3 (d, $J = 70.4$ Hz), 34.5 (d, $J = 7.4$ Hz), 23.6 (d, $J = 5.5$ Hz), 8.6 ppm; ^{31}P NMR (161.9 MHz, $CDCl_3$): $\delta = 27.7$ ppm; HRMS (ESI$^+$): m/z calcd for $C_{19}H_{23}NaOP$: 321.1384 [M+Na$^+$]; found: 321.1379. The enantiomeric ratio was determined by chiral HPLC analysis, Chiralpak AS-H column, eluent *n*-heptane/*i*PrOH 99:1, 40°C, retention times: 22.0 (minor) and 23.2 min (major).

(5-Methyl-5-vinylnona-1,3,8-trienyl)benzene (7): *n*BuLi (0.09 mL, 0.22 mmol, 2.5 M) was added dropwise to a stirred solution of **5** (70 mg, 0.22 mmol) in dry THF (5 mL) under nitrogen at −20°C. After 15 min, the solution was cooled to −78°C and cinnamyl aldehyde (31 mg, 0.23 mmol) in THF (0.5 mL) was added dropwise. The mixture was allowed to warm rapidly to 0°C and saturated aqueous NH_4Cl (3 mL) was added. The aqueous layer was separated and extracted with AcOEt (3× 5 mL) and the combined organic layers were dried with anhydrous Na_2SO_4, filtered, and the solvent was evaporated in vacuo. The crude product was purified by flash chromatography on silica gel with *n*-pentane/EtOAc 1:1 as the eluent to give the corresponding alcohol as a pale yellow solid (yield 117 mg) This alcohol was dissolved in dry DMF (1 mL) and added to a stirred suspension of NaH (40 mg; 60% dispersion in mineral oil, previously washed with dry *n*-pentane) in DMF (3 mL) and the solution was stirred at 25°C for 2 h. Water (3 mL) was added, the mixture was extracted with Et_2O (3×5 mL), and the combined extracts were washed with brine (10 mL), dried with anhydrous Na_2SO_4, filtered, and the solvent was evaporated in vacuo. The crude product was purified by flash chromatography on silica gel with pentane as the eluent to give the product as a colorless oil (86% yield, *E*/*Z* 1:1, 80:20 e.r.).[44] ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.41$–7.19 (m, 10H), 6.80 (dd, $J = 15.7$, 10.3 Hz, 1H), 6.48 (dd, $J = 30.5$, 15.8 Hz, 2H), 6.22–6.02 (m, 3H), 5.85 (m, 4H), 5.46 (d, $J = 11.6$ Hz, 2H), 5.08 (m, 2H), 5.18–4.93 (m, 6H), 2.07 (m, 4H), 1.59 (m, 4H), 1.31 (s, 3H), 1.19 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 146.5$, 145.5, 142.3, 139.1, 138.7, 137.6, 132.9, 130.8, 129.5, 129.4, 128.6 (2C), 128.5 (2C), 128.1, 127.4, 127.2, 126.3 (2C), 126.2 (2C), 125.7, 114.2, 114.1, 122.1, 111.7, 42.8, 42.6, 42.2, 40.3, 28.9, 28.8, 26.1, 23.3 ppm; HRMS (ESI$^+$): m/z calcd for $C_{18}H_{23}$: 239.1800 [M+H$^+$]; found: 239.1794. The enantiomeric excess was determined by chiral HPLC analysis, Chiralcel OB-H column, eluent *n*-heptane/*i*PrOH 100:0, 40°C, retention times: 8.46 (minor) and 9.37 min (major).

(2-Methylbut-3-en-1-yl)diphenylphosphine (9): Compound **2f** (64.0 mg, 0.24 mmol) and $Cu(OTf)_2$ (13.0 mg, 0.025 mmol) were added to a 10 mL Schlenk tube at RT. Silane (90 μL, 0.5 mmol) and toluene (2 mL) were then added under an argon flow. The reaction mixture was stirred for 3 h at 100°C and the solvent was then removed under vacuum. The residue

was dissolved in degassed $CDCl_3$ and the conversion was determined by ^{31}P NMR spectroscopy, as described by Beller and co-workers[8] (89% conversion, 68% yield). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.43$ (m, 4H), 7.31 (m, 6H), 5.82 (m, 1H), 4.95 (m, 2H), 2.24 (m, 1H), 2.15 (m, 1H), 2.05 (m, 1H), 1.14 ppm (d, $J = 6.6$ Hz, 3H); ^{31}P NMR (161.9 MHz, $CDCl_3$): $\delta = -20.6$ ppm; EI MS: m/z (%): 253 [M^+], 239 (100) [$M-CH_3$]. This transformation proceeded without loss of enantiomeric purity, as confirmed by reoxidation to phosphine oxide **2f** under air followed by chiral HPLC analysis.

(+)-[(2-Methylbut-3-en-1-yl)diphenylphosphonio]trihydroborate (10): In an oven-dried Schlenk tube equipped with septum and stirring bar under a N_2 atmosphere, phosphine **9** (0.16 mmol, 45 mg) was dissolved in anhydrous THF (1.0 mL) and BH_3THF (1 M) in THF (0.16 mmol, 160 μL) was then added dropwise. The reaction mixture was stirred for 30 min, then the solvent was concentrated in vacuo. Flash column chromatography (SiO_2, eluent EtOAc/pentane 1:9) afforded **10** as a waxy solid (74% yield). $[\alpha]_D^{20} = +14$ ($c = 1.0$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.68$ (m, 4H), 7.44 (m, 6H), 5.66 (m, 1H), 4.85 (m, 2H), 2.70 (m, 1H), 2.36 (m, 1H), 2.20 (m, 1H), 1.58 (br s, 3H), 1.10 ppm (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 143.3$ (d, $J = 9.3$ Hz), 132.1 (m, 2C), 131.0 (m, 6C), 128.7 (m, 4C), 113.1, 32.9 (d, $J = 45.4$ Hz), 29.7, 21.7 ppm (d, $J = 6.6$ Hz); ^{31}P NMR (161.9 MHz, $CDCl_3$): $\delta = 14.4$ ppm; HRMS (ESI$^+$): m/z calcd for $C_{17}H_{22}BP$: 269.1625 [$M+H^+$]; found: 269.1625.

Mechanistic studies: ^{31}P NMR spectroscopy experiments were carried out in NMR tubes under a nitrogen atmosphere at −80 °C by adding MeMgBr (7.0 equiv, 3 M) in Et_2O to a mixture of phosphine oxide and preformed catalyst (1.0 equiv of copper bromide-(*R*,*R*)-Taniaphos) at −80 °C in CD_2Cl_2. The conversion was monitored by recording a spectrum every 5 min unless noted (Scheme 1). The sample was rapidly removed and inserted into an NMR spectrometer (keeping the temperature at −80 °C) before recording each spectrum to facilitate the stirring of the reaction mixture. PPh_3 in a sealed capillary tube was used as a reference. Allyl diphenyl phosphine oxide (**11**) or 2-methylbut-3-en-2-yl-diphenylphosphine oxide[45] (**12**; 15 mg) in CD_2Cl_2 (800 μL) were also treated with MeMgBr (100 μL) at RT in an NMR tube. As observed before for compound **2f**, in both cases the phosphorus resonance evolved rapidly to a new signal at low field ($\delta = 38.1$ (**11**) and 36.2 ppm (**12**)). After quenching the reaction of **11** with D_2O, CD_3OD, or DCl, deuterium incorporation in the α position was not observed (for details see the Supporting Information).

Acknowledgements

We thank the Netherlands Organization for Scientific Research (NWO-CW) and the National Research School Catalysis (NRSC-C) for financial support. V.H. thanks the Spanish Ministry of Science and Innovation (MICINN) for a postdoctoral fellowship. M.P. thanks the Xunta de Galicia for an Ángeles Alvariño contract.

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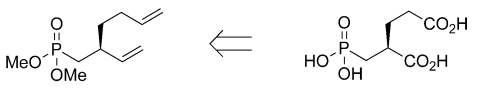

2j ⇐ **2-PMPA**

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Received: December 7, 2012
Published online: February 27, 2013

