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Enantioselective Synthesis of P-Stereogenic Phosphinates and Phosphine Oxides by Molybdenum-Catalyzed Asymmetric Ring-Closing Metathesis**

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Keywords

enantioselective synthesis; homogeneous catalysis; molybdenum; olefin metathesis; phosphorus

Chiral phosphines have found widespread use in chemical synthesis as ligands for transition metal catalysis.[1] Along with phosphine oxides and other derivatives, they have also become popular choices as catalysts in organic synthesis.[2] Organophosphorus-based catalysis will undoubtedly benefit from a more diverse range of P-stereogenic phosphines. In response to this demand, metal-catalyzed asymmetric syntheses of P-stereogenic phosphines and their derivatives have recently emerged, with key contributions including alkyne hydrophosphorylation,[3] the alkylation and arylation of secondary phosphines,[4] enantioselective deprotonation,[5] and rhodium-catalyzed [2+2+2] cycloaddition.[6] To date, these catalytic enantioselective routes remain largely outnumbered by well-established methods based on resolutions[7] or on the use of chiral auxiliaries.[8] In spite of recent advances in the area of olefin metathesis, the utility of asymmetric ring-closing metathesis (ARCM)[9] has not been applied to the preparation of P-stereogenic phosphine derivatives.[10] In light of literature precedents, which demonstrate that various P-containing dienes, trienes, and tetraenes are suitable substrates for olefin metathesis,[11] we reasoned that the ARCM of P-templates would be a strategically unique and valuable reaction for the preparation of P-stereogenic compounds. We opted for a catalytic enantioselective desymmetrization process of prochiral P-templates, as this approach offers the opportunity to explore ARCM with the chirality arising from the formation of a stereogenic center other than a carbon atom (Scheme 1). Moreover, the resulting products are structurally novel P-stereogenic scaffolds amenable to rich chemistry further downstream. Herein, we report the first examples of catalytic enantioselective olefin metathesis reactions of phosphinates and phosphine oxides,

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which lead to the formation of five-, six-, and seven-membered P-heterocycles in up to 98% *ee*. We also report an unprecedented case of complementary asymmetric induction in reactions promoted by a pair of chiral molybdenum-based complexes differing structurally in their achiral imido ligand.

For the purposes of this investigation, chiral molybdenum catalysts **1**–**4**[12] were selected based on their well-documented ability to promote asymmetric ring-closing metathesis in the context of kinetic resolution or enantioselective desymmetrization (Scheme 2).

To initiate our investigations, we examined the ARCM of prochiral phosphinate **6**. Catalyst **1b** was identified as the optimal catalyst for the ARCM and was established by screening studies involving molybdenum-based chiral complexes **1**–**4** (Table 1). This optimization study also involved varying the solvent. As indicated, subtle variations in the chiral catalyst impacted significantly on both the conversion and enantioselectivity. The biphenyl-based complex **1b** bearing the dimethyl-substituted phenylimido unit delivered **7** with the optimum combination of conversion (63% yield) and optical purity (60% *ee*) when the reaction was performed in CH_2Cl_2 (Table 1, entry 4).

On the basis of these preliminary results, we investigated the molybdenum-catalyzed ARCM of a range of structurally related phosphinates, all of which were synthesized according to literature procedures.[13] The results of these studies are summarized in Table 2. The catalytic ARCM of triene **8** failed to deliver the 5-membered ring-closed product **14** in the presence of all chiral molybdenum-catalysts screened (Table 2, entry 1).[14] The presence of one additional methylene group for the alkenoxy substituent was sufficient to restore reactivity, as demonstrated with the ring-closure of triene **6** and led to the six-membered phosphinate **7** in 60% *ee* (Table 1 and Table 2, entry 2). The replacement of the propenyl groups of triene **6** by unsubstituted vinyl groups had a beneficial impact. Indeed, the ARCM of triene **9** led to the ring-closed product **15** in higher optical purity (86% *ee*) and higher yield after purification (54%; Table 2, entry 3). Similarly, the ARCM of trienes **10** and **11** both led to seven-membered products; the vinyl-substituted triene **10** was a superior substrate and delivered **16** in higher yield and enantiomeric purity (73% *ee*;Table 2, entries 4 and 5). Substrates **12** and **13**, substituted with 2-methylallyl groups, were also subjected to ARCM. The ring-closure of phosphinate **12** was not successful, a result consistent with the lack of reactivity observed with **8**, which featured the same prop-2-enoxy group. In contrast, triene **13** cyclized efficiently and delivered **19** in 79% yield and 96% *ee*. The data indicate that the identity of the optimal molybdenum-based catalyst can change as a function of the structural features of the substrate. [10i]

The lack of reactivity for **8** and **12** is likely the result of catalyst sequestration and deactivation arising from the formation of an intramolecularly chelated metal-alkylidene complex (Scheme 3).[15] This hypothesis is consistent with the observation that increased distance between the terminal alkene and the Lewis basic phosphinate restores activity. To confirm this hypothesis, a mixture of achiral molybdenum-complex **5** and triene **8** was monitored by ^{1}H NMR spectroscopy (400 MHz). After 20 minutes, ^{1}H NMR analysis showed that initiation of the reaction had taken place and the presence of a molybdenum alkylidyne was observed, as characterized by a broad NH signal at δ = 8.1 ppm along with the absence of an alkylidene resonance.[14] When the reaction was carried out in the presence of a stoichiometric amount of **5**, the molybdenum alkylidyne carbon atom resonated at δ = 306.4 ppm as observed by 100 MHz ^{13}C NMR spectroscopy.[17] The above observation may be rationalized by a mechanistic scenario involving the formation of the chelated alkylidene complex **20** and subsequent tautomerization, thus leading to alkylidyne **21** (Scheme 3).

The second phase of our studies focused on molybdenum-catalyzed ARCM of phosphine oxides. The use of phosphine oxides as Lewis base catalysts highlights the need to expand the range of P-stereogenic phosphine oxides that are available for enantioselective catalysis.[2] We were well aware that, similar to phosphinates, the Lewis basicity of phosphine oxides may result in possible complications resulting from catalyst deactivation.[10i] Substrates **22**–**24** were subjected to olefin metathesis conditions and the results are summarized in Table 3. All prochiral triene derivatives underwent successful ring closure, including **22** and **23**, that could form five-or six-membered chelates between the Lewis basic phosphine oxide and the Lewis acidic molybdenum center—this might be the result of a weak and reversible chelation process. Similar to the ARCM of phosphinates, the identity of the optimal chiral molybdenum-based catalyst can vary.[16] The enantiomeric purities of **25**–**27** range from 71% to 91% *ee*. The studies required to optimize the ARCM of the prochiral P-templates examined revealed that the sense of the stereoinduction is reversed upon modulation of the substitution pattern of the catalyst (Table 4).

The pair of molybdenum-based catalysts **3b** and **4a**, bearing an identical achiral imido group but differently substituted diol, led to opposite enantiomers upon ARCM of trienes **13** (Table 4, entries 1 and 2). A similar trend was observed with triene **24** (Table 4, entries 3 and 4). For all four reactions, the products were formed in excellent optical purity with enantiomeric excess values ranging from 91% to 98%. In addition, we have established that complexes **1a** and **2** promote ARCM reactions with a complementary sense of asymmetric induction. The above molybdenum-based alkylidenes bear identical diolate ligands and are only distinguishable through their achiral imido ligand. The data show that, remarkably, the achiral imido ligand plays a critical role in the observed sense of stereoinduction. We found that the ARCM of **13** led to opposite enantiomers upon treatment with 10 mol% of either catalyst **1a** or **2**; both product enantiomers were formed in high optical purity (82% and 93% *ee*) (Table 4, entries 5 and 6). Triene **24** behaved similarly, and led, upon treatment with 10 mol% of **1a** or **2**, to the two enantiomers (+)-**27** and (−)-**27** in 96% and 73% *ee*, respectively (Table 4, entries 7 and 8). The reason why a reversal of stereoinduction is triggered by structural modification of the achiral imido group may be attributed to different reacting alkylidene isomers—possibly the *anti* isomer for catalyst **1a** based on steric repulsion between the alkylidene and the isopropyl groups and the *syn* isomer for catalyst **2**. Although a literature precedent exists, highlighting the disparate reactivity profile of these geometrical isomers,[12] the impact of the alkylidene geometry of chiral molybdenum-based catalysts on the formation of different enantiomers has not been previously observed (Scheme 4).

In summary, enantiomerically enriched P-stereogenic phosphinates and phosphine oxides have been prepared in up to 98% *ee* through molybdenum-catalyzed ARCM reactions. The investigations outlined here represent the first report of ARCM as a route to induce chirality arising from a stereogenic heteroatom, and highlight the importance of the structural features of the reactants on reactivity and of the catalyst on enantiocontrol. Cases where different enantiomers are generated through the use of chiral olefin metathesis catalysts that are structurally distinguishable (imido ligand) are also described. Ongoing efforts in our laboratories are aimed towards expanding the scope of catalytic ARCM of P-templates and investigation of the origin of the complementarity in the enantioselectivity of the aforementioned processes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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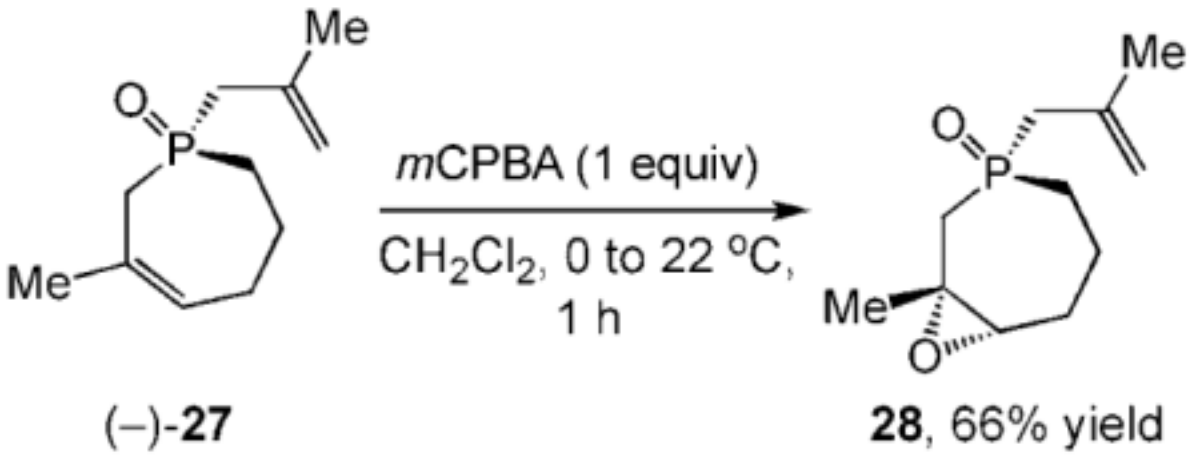
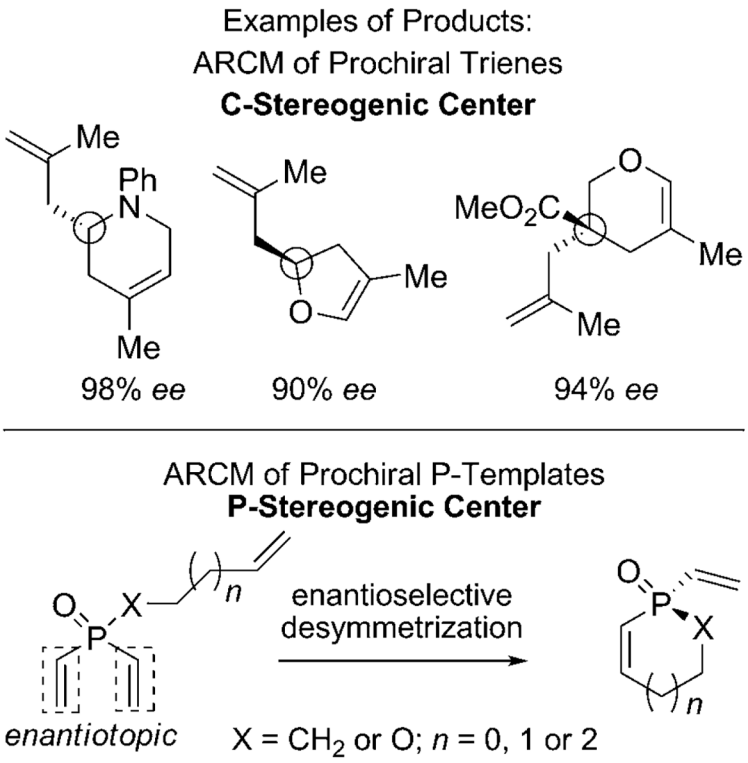
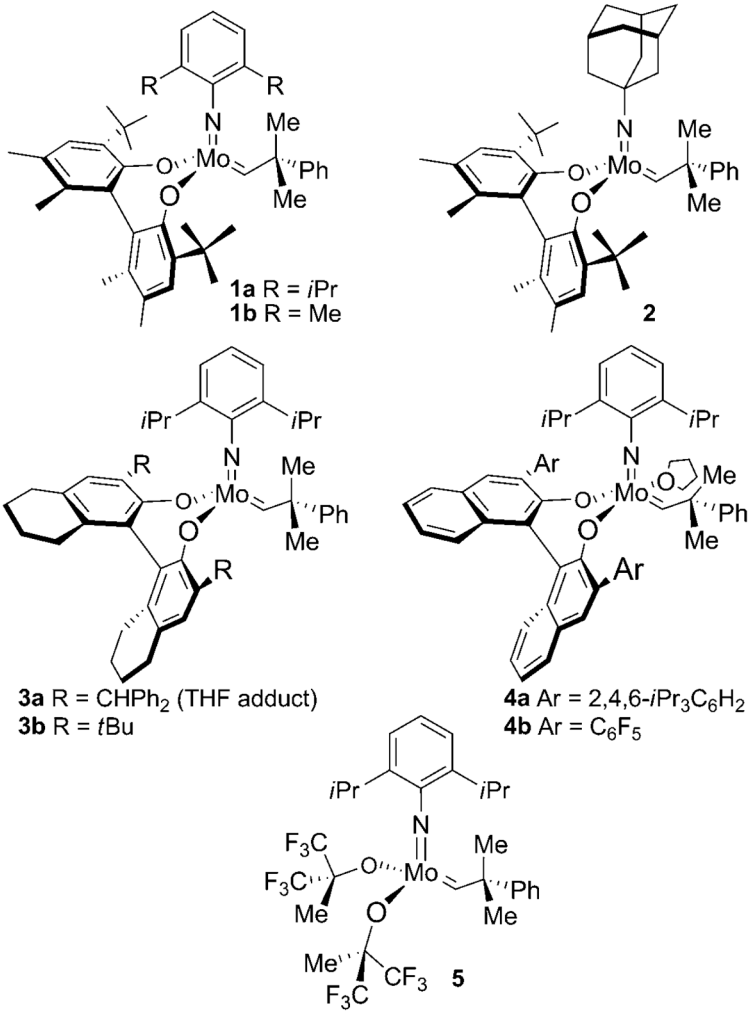
17. For the full optimization study see, the Supporting Information.
18. The absolute configuration of (−)-27 was determined by X-ray single crystal structure analysis of the corresponding epoxide 28; see the Supporting Information.



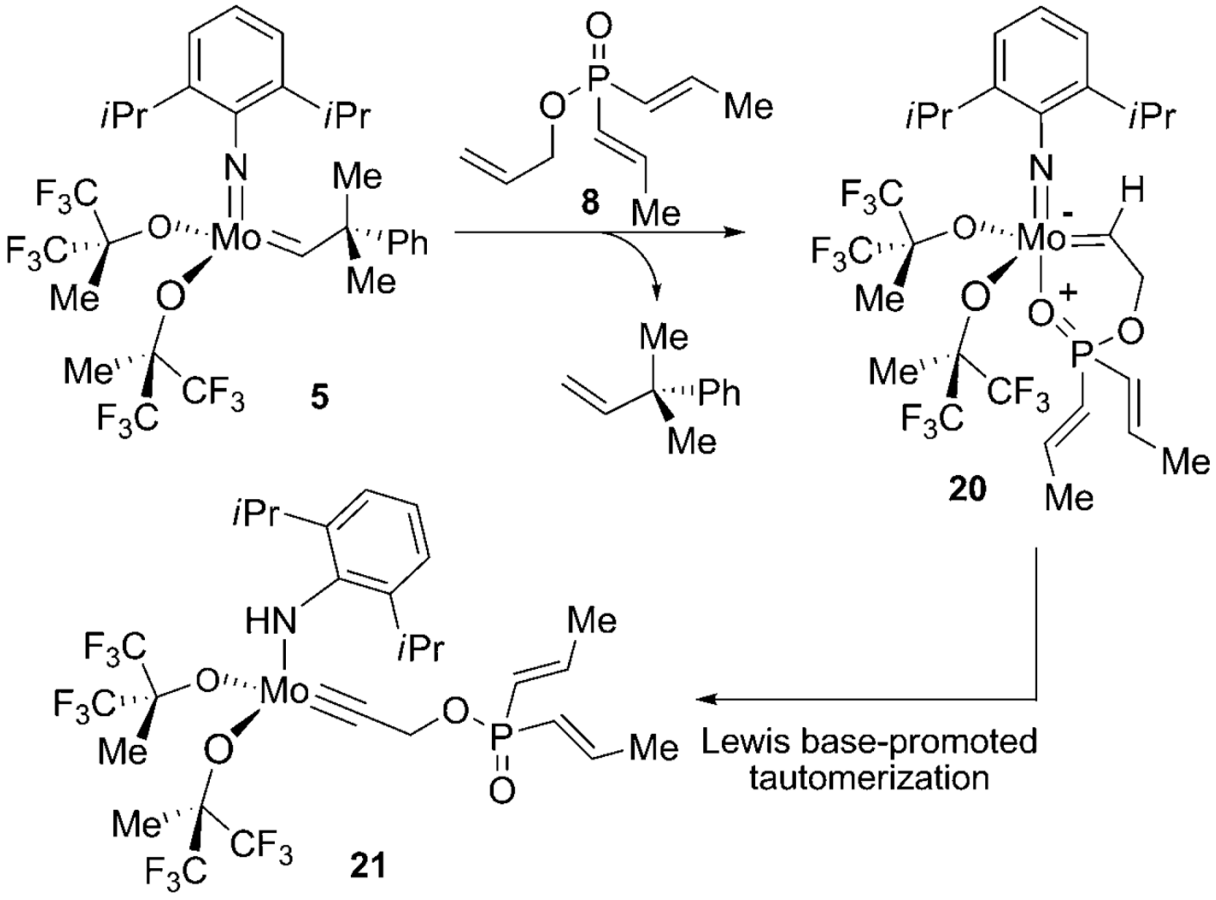
(–)-**27** **28**, 66% yield



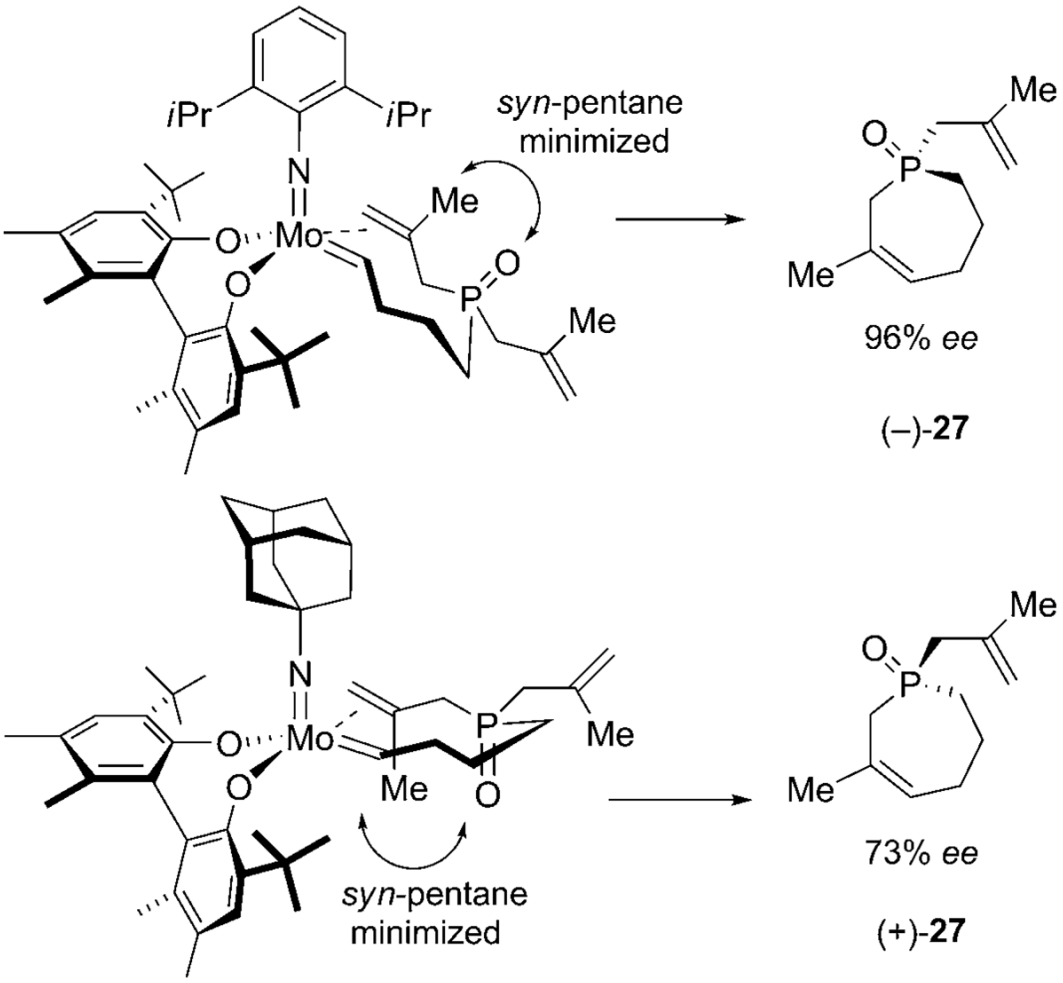
Scheme 1.
Catalytic ARCM for the generation of P-stereogenic centers.



Scheme 2.
Chiral and achiral molybdenum-based complexes used for ARCM and RCM reactions.



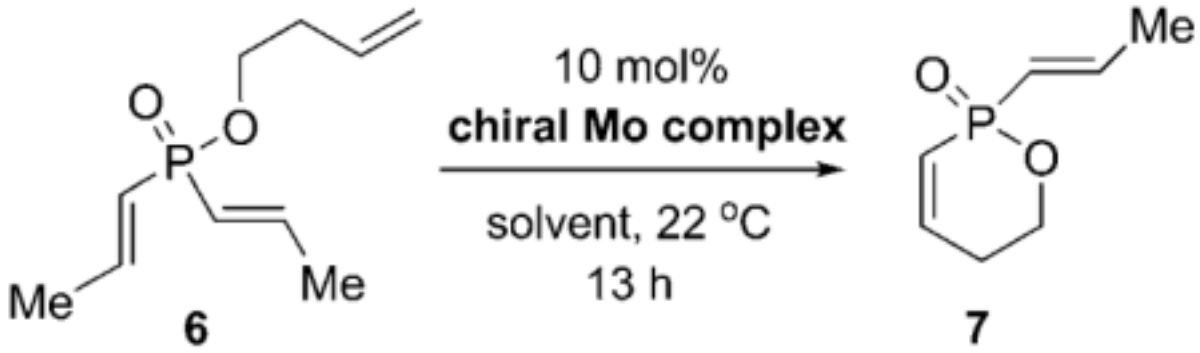
Scheme 3.
Formation of alkylidyne **21**.



Scheme 4.
Proposed model for molybdenum-catalyzed ARCM reactions of P-containing trienes, leading to the formation of (+) and (−) enantiomers.

Table 1

Initial catalyst screening for molybdenum-catalyzed ARCM reactions of **6.**[a]



Entry	Chiral Mo Complex	Solvent	Conv. [%][b]	*ee* [%][c]
1	**1 a**	C_6H_6	<2	–
2	**1 a**	CH_2Cl_2	<2	–
3	**1 b**	C_6H_6	45	51
4	**1 b**	**CH_2Cl_2**	**63**	**60**
5	**2**	C_6H_6	15	−22
6	**2**	CH_2Cl_2	49	11
7	**3 a**	C_6H_6	38	60
8	**3 a**	CH_2Cl_2	32	53
9	**3 b**	C_6H_6	<2	–
10	**3 b**	CH_2Cl_2	<2	–
11	**4 a**	C_6H_6	51	16
12	**4 a**	CH_2Cl_2	65	11

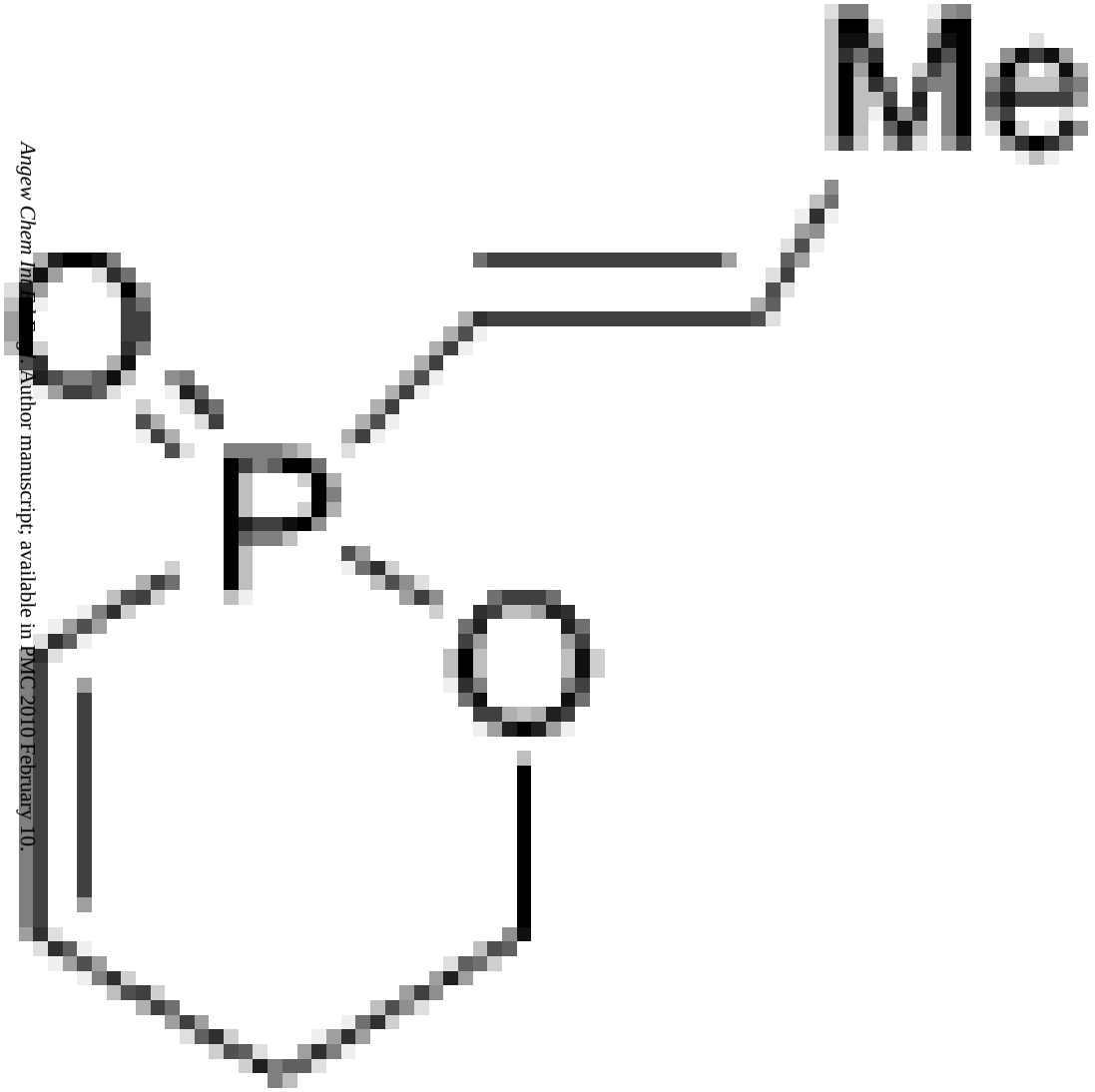
[a] All reactions performed under a nitrogen atmosphere.

[b] Conversion into the desired product was measured by ^{1}H NMR analysis (400 MHz) of the unpurified reaction mixture; traces of homodimer derived from reaction of terminal olefins were present.

[c] Determined by GLC analysis of the purified material; see the Supporting Information for details.

Table 2

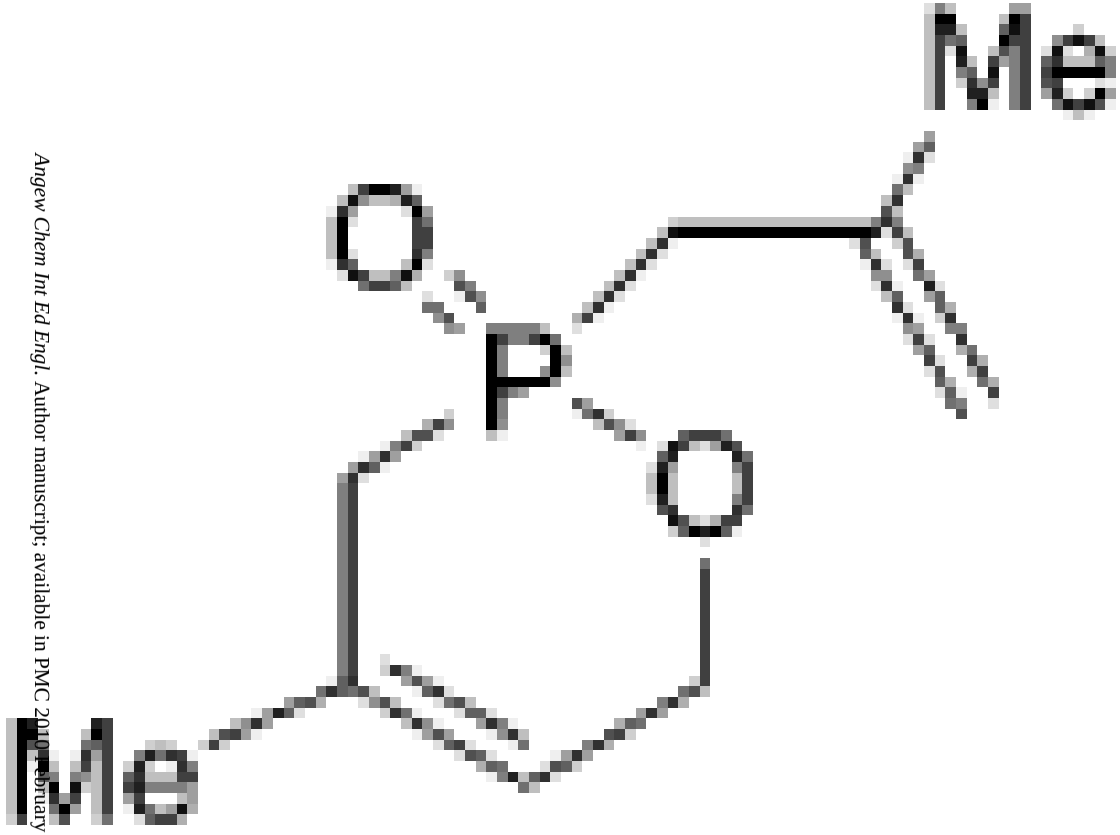
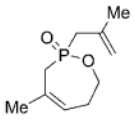
Chiral Mo Complex[b]	Solvent; *T* [°C]	Conv.[c]; Yield [%]	*ee* [%][d]	Product
1–4	CH_2Cl_2; 22–60	<2[e]	–	**14**

Product	Chiral Mo Complex[b]	Solvent; *T* [°C]	Conv.[c]; Yield [%]	*ee* [%][d]
	**1 b**	CH_2Cl_2; 22	63;43	60

Product	Chiral Mo Complex[b]	Solvent; *T* [°C]	Conv.[c]; Yield [%]	*ee* [%][d]
15	**1 a**	C_6H_6; 22	60;54	86

Product	Chiral Mo Complex[b]	Solvent; *T* [°C]	Conv.[c]; Yield [%]	*ee* [%][d]
16	**4 a**	C_6H_6; 22	48;42	73

Product	Chiral Mo Complex[b]	Solvent; *T* [°C]	Conv.[c]; Yield [%]	*ee* [%][d]
17	**1 b**	CH_2Cl_2; 22	32;30	27

Product	Chiral Mo Complex[b]	Solvent; *T* [°C]	Conv.[c]; Yield [%]	*ee* [%][d]
	1–4	C_6H_6; 22	<2[e]	–
 **18**				
 **19**	**4 a**	C_6D_6; 60	81;79	96

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[c] Conversion was measured by ^{1}H NMR analysis (400 MHz) of the unpurified reaction mixture; homodimer was also present (see the Supporting Information).

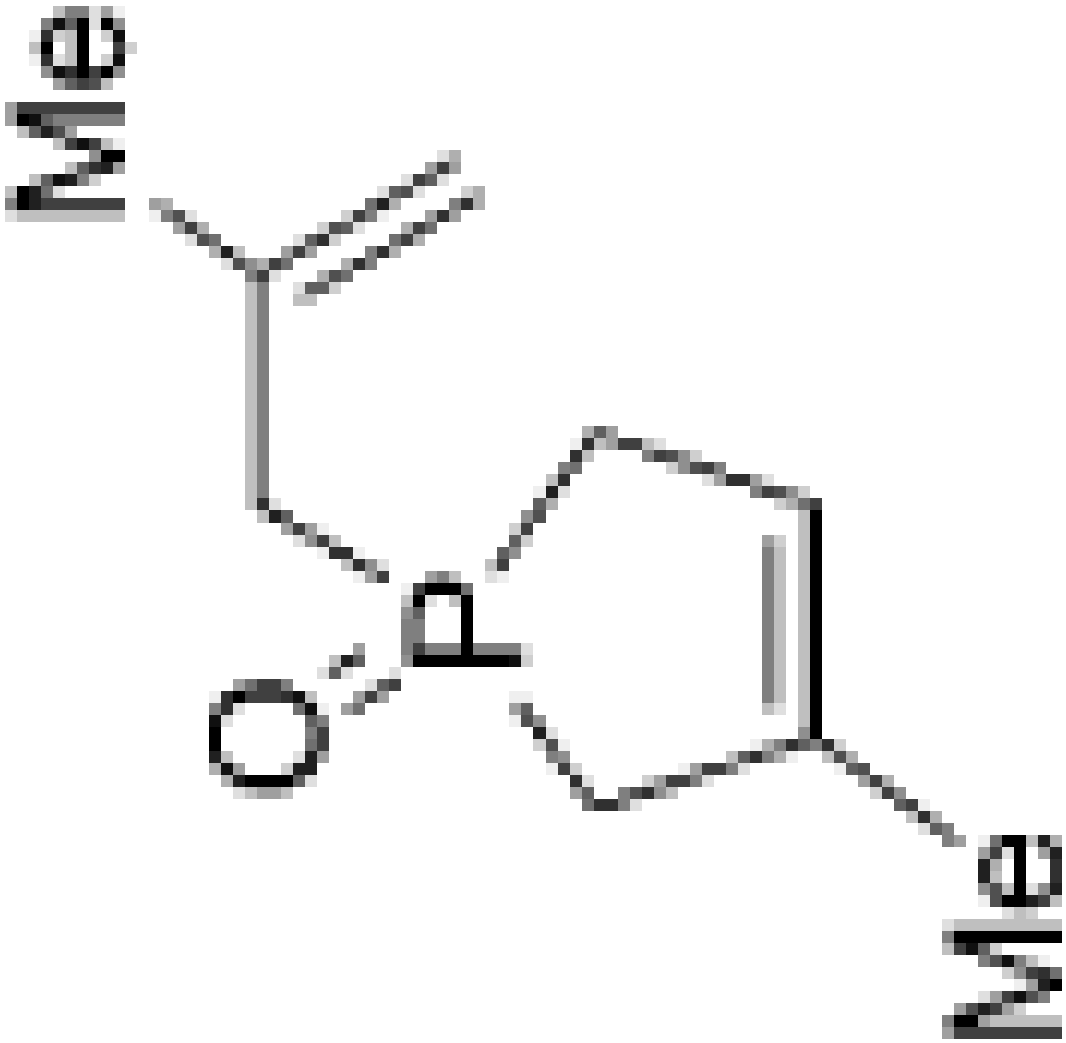
[d] Determined by GLC analysis of the purified material; see the Supporting Information for details.

[e] Recovered starting material.

Table 3

Chiral Mo Complex[b]	Solvent; *T* [°C]	Conv.[c]; Yield [%]	*ee* [%][d]
4 a	CH_2Cl_2; 60	96;88	71

Product



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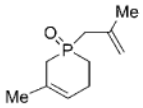
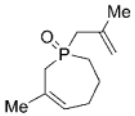
Product	Chiral Mo Complex[b]	Solvent; *T* [°C]	Conv.[c]; Yield [%]	*ee* [%][d]
 **26**	**3 b**	CH_2Cl_2; 22	84;80	74
 **27**	**3 b**	C_6H_6; 60	81;79	91

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Information).

Table 4

Formation of the (+) and (−) enantiomers by molybdenum-catalyzed ARCM reactions.[a]

Entry	Substrate	Chiral Mo Complex[b]	Product	Yield [%][c]	*ee* [%][d]
1	**13**	**4 a**	(−)-**19**	78	96
2	**13**	**3 b**	(+)-**19**	75	93
3	**24**	**4 a**	(−)-**27**	45	98
4	**24**	**3 b**	(+)-**27**	79	91
5	**13**	**1 a**	(−)-**19**[e]	65	82
6	**13**	**2**	(+)-**19**[e]	40	93
7	**24**	**1 a**	(+)-**27**[f]	61	96
8	**24**	**2**	(−)-**27**[f]	48	73

[a] All reactions performed under a nitrogen atmosphere.

[b] All reactions carried out with 10 mol% of catalyst.

[c] Yield of purified product.

[d] Determined by GLC analysis.

[e] Absolute configuration assigned by analogy to **27**.

[f] Absolute configuration determined by X-ray analysis of the epoxide derivative **28**, see Ref. [18].