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Asymmetric addition of P-H compounds to unsaturated carbonyl derivatives

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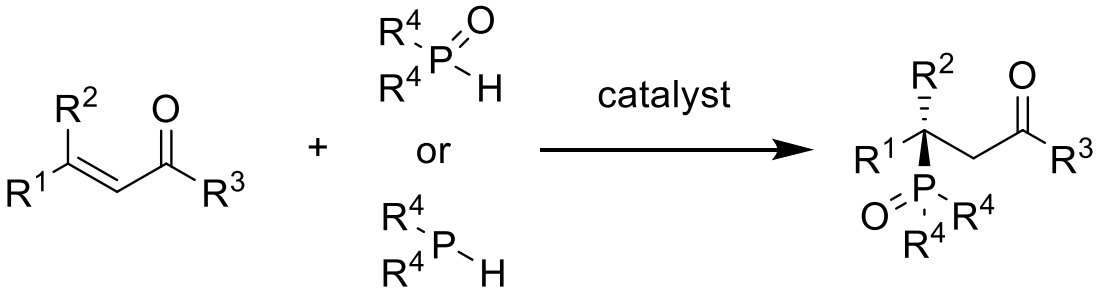
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Abstract

Michael addition of P-H compounds, such as phosphanes, phosphane oxides and phosphonates, is a practical tool to form P-C bonds. The stereochemistry of the newly formed compounds can be influenced either by using chiral starting materials or chiral catalysts. Since the former method is limited to the readily available optically-active derivatives, catalytic options are more common. Enantioenriched P-C compounds can have biological activity; therefore, they are pharmaceutically valuable molecules. In this paper, an overview is provided on the conjugate addition of P-H compounds according to the type of the phosphorus derivatives.



Keywords: P-H compounds, Michael addition, chiral catalysis, enantioselectivity, asymmetric induction

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1. Introduction

Optically-active phosphonates can be precursors of many biologically active compounds and pharmaceutically important molecules.[1] Direct addition of P-H compounds to electrophiles is one of the many methods for the preparation of such derivatives. Asymmetric conjugate addition of phosphanes to α,β-unsaturated carbonyl compounds is still challenging and has been much less developed. Products of addition can be converted to derivatives with various functional groups.

Enantioenriched organophosphorus compounds have an important role in organic chemistry since chiral phosphanes and phosphane oxides can be used as ligands or pre-ligands in metal-catalyzed reactions.[2,3] Phosphorus compounds have a wide structural diversity and various properties. Therefore, these derivatives cannot only be valuable building blocks, but also products with diverse biological activities. [1,4] The formation of a P-C bond can be straightforwardly carried out by a Michael addition of trivalent and pentavalent phosphorus species to an electron-deficient double bond.[5]

Chiral phosphanes are generally synthesized in racemic form and then the stereoisomers are separated by resolution, using chiral auxiliaries or enantiopure compounds.[6-8] Thus, the development of efficient enantioselective catalytic methods for the synthesis of enantiomerically-enriched compounds with a chiral carbon atom having a P-C bond is highly desired.[9-11] Chiral organophosphorus derivatives can have different biological activities. For this reason, they can be used as biophosphate mimics, antibiotics, antiviral agents, and antitumor agents.[12]

2. Asymmetric Induction Generated Without Chiral Catalysts

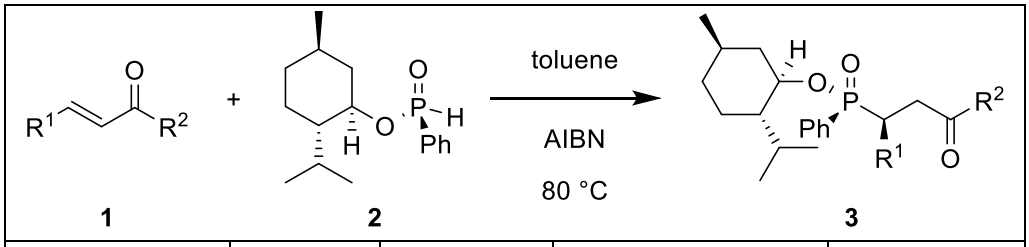
Selective addition of a P-H compound to an enone can be achieved by using a chiral P-compound or a chiral acceptor molecule. In the former case, the stereogenic center is closer to the active center in the catalyst. However, these methods are limited by the availability of P-stereogenic P-H compounds.

Chiral (−)-menthyl phenylphosphine oxide **2** showed configurational stability toward bases.[13] The (−)-menthyl group in compound **2** can stabilize the configuration of the phosphorus, is capable of inducing the asymmetric reaction, and be helpful in isolating the single stereoisomer of either the starting materials or the products. When chalcone (**1**, R^1 = Ph, R^2 = Ph) or benzylidene acetone (**1**, R^1 = Ph, R^2 = Me) were reacted with menthyl phenylphosphine oxide **2** by Wang *et al.*, excellent diastereomeric ratio (dr) was measured (99:1 in both

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cases, Table 1, entries 1-2). Interestingly, in the case of 5-methyl-1-phenylhex-2-en-1-one (**1**, R^1 = *i*Pr, R^2 = Ph), there was no reaction (the authors did not provide an explanation for this phenomenon). P-chirality remained unchanged during the reactions. This was also proven by Saga and co-workers, who reacted electron-deficient terminal olefins with compound **2**.[14]

Table 1. Michael addition of menthyl phenylphosphine oxide **2** to enones **1**



1 **2** **3**

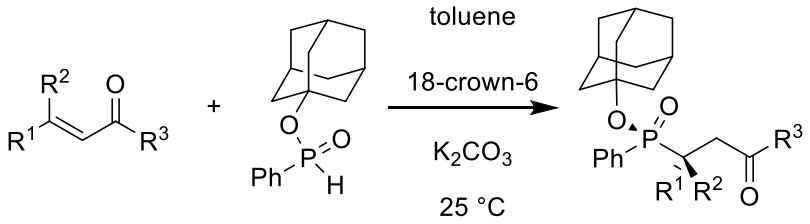
Entry	R^1	R^2	Yield[a], %	dr
1	Ph	Ph	71	99:1
2	Ph	Me	77	99:1
3	*i*Pr	Ph	0	-

[a]: 48 h reaction time

A mild phase-transfer diastereoselective phospha-Michael reaction was developed by Yadavalli and co-workers.[15] Adamantyl-based compound **5** was reacted with β,β-disubstituted alkenyl ketones **4** in a solid-liquid two-phase system. High diastereoselectivity was reached in the case of dipnone (**4**), **(**E)-1,3-diphenylbut-2-en-1-one, R^1 = Ph, R^2 = CH_3, R^3 = Ph), its isopropyl (**4**, R^1 = *iPr*, R^2 = Me, R^3 = Ph), and naphthyl (**4**, R^1 = naphthalen-2-yl, R^2 = Me, R^3 = Ph) derivatives (50:1, 100:0 and 10:0, respectively; Table 2, entries 1-3).

Reactions with β-substituted alkenyl ketones resulted in significantly lower diastereomeric ratios (Table 2, entry 4). Interestingly, when (−)-menthyl phenylphosphine oxide **2** was reacted with dipnone instead of the adamant derivative **5**, the diastereomeric ratio was 8:1; while, in the case of chalcone analogues, a 5:1 ratio was not exceeded.

Table 2. Michael addition of adamantyl phenylphosphine oxide **5** to enones **4**



4 **5** **6**

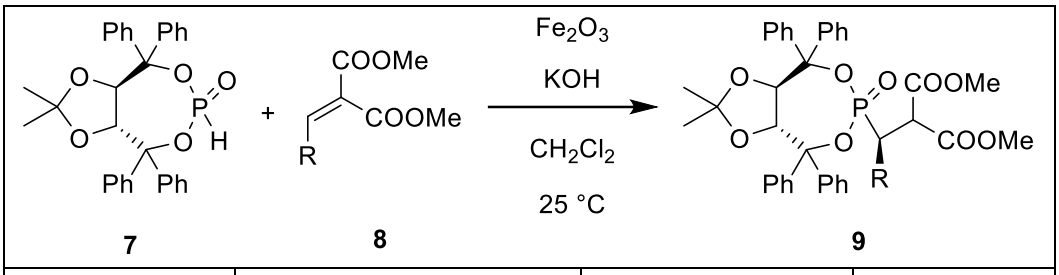
Entry	R^1	R^2	R^3	Yield[a], %	dr
1	Ph	Me	Ph	70	50:1
2	Naphthalen-2-yl	Me	Ph	80	100:0
3	*i*Pr	Me	Ph	51	100:0
4	Ph	H	Ph	72	5:1

[a]: 72-96 h reaction time

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TADDOL (α,α,α',α'-tetraaryl-2,2-disubstituted 1,3-dioxolane-4,5-dimethanol) - as is available in the chiral pool - was used to synthesize derivative **7**, which was reacted with arylidene malonates (**8**) in the presence of KOH and Fe_2O_3.[16,17] If a phenyl group was connected to the double bond in compound **8**, an 86% diasteomeric excess (de) was measured (Table 3, entry 1). It was shown that the use of derivatives bearing substituted aromatic rings do not significantly affect the diastereomeric ratio (Table 3, entries 2-3). Products **9** were converted to β-phosphono malonates without loss of chirality.

Table 3. Conjugate addition of TADDOL derivative **7** to arylidene malonates **8**



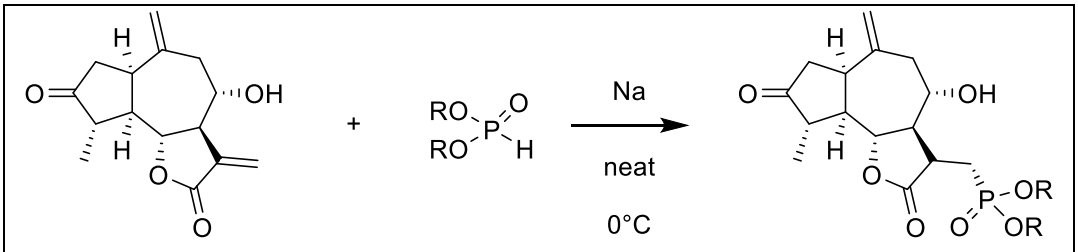
7 **8** **9**

Entry	R	Yield[a], %	de, %
1	Ph	64	86
2	piperonyl	67	91
3	biphenyl	63	94

[a]: 4-18 h reaction time

Grosshemin (**10**) was chosen as the chiral substrate for phospha-Michael addition by a Kazakh research group.[18] Products **12** were isolated in low yields (8-10%, Table 4, entries 1-3) after the reaction of compound **10** with diethyl, dipropyl and dibutyl phosphonate (**11**, R = Et, Pr and Bu, respectively). No data were reported on selectivity.

Table 4. Michael addition using grosshemin (**10**)



10 **11** **12**

Entry	R	Yield[a], %
1	Et	10
2	Pr	8
3	Bu	8

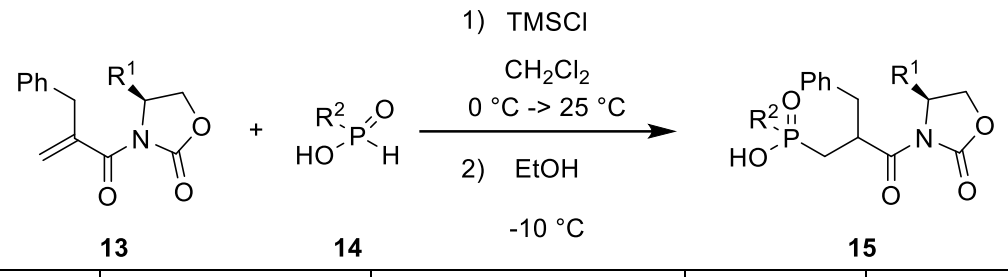
[a]: 40 min reaction time

In a similar way, diethyl oxophoshonates were synthesized from natural chiral acceptors, carvone, pinocarvone and 2-caren-4-one.[19] In the case of the latter, diastereoselectivity was observed using $(EtO)_2P(O)H$.

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The asymmetric Michael reaction of phosphinic or aminophosphinic acids **14** with acrylate derivatives of Evans oxazolidinone-type auxiliaries **13** was carried out by Liu *et al.* in order to synthesize peptidomimetic compounds.[20] The diastereomeric ratio was significantly higher if the chiral Michael acceptor **13** contained a diphenylmethyl moiety (Table 5, entries 2, 4 and 6) instead of a benzyl group (Table 5, entries 1, 3 and 5).

Table 5. Michael addition of phosphinic acids **14** to oxazolidinones **13**



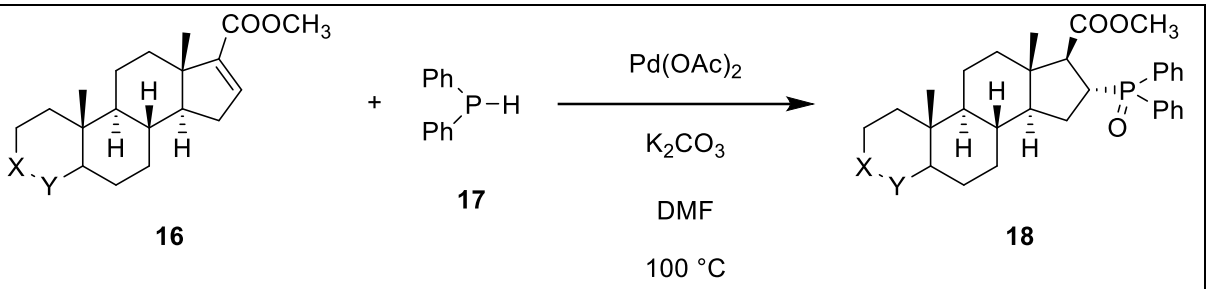
13 **14** **15**

Entry	R^1	R^2	Yield[a], %	dr
1	$PhCH_2$	$PhCH_2CH(NHAc)$	94	3:1
2	Ph_2CH	$PhCH_2CH(NHAc)$	90	86:1
3	$PhCH_2$	Naphthalen-2-yl	78	5:1
4	Ph_2CH	Naphthalen-2-yl	73	55:1
5	$PhCH_2$	$PhCH_2CH_2$	91	12:1
6	Ph_2CH	$PhCH_2CH_2$	90	54:1

[a]: 24 h reaction time

Steroidal α,β-unsaturated esters **16** underwent base-catalyzed addition with diphenyl phosphane **17** in the presence of palladium acetate (Table 6, entries 1-3).[21] Since the addition of diphenylphosphane oxide resulted in the formation of the same products **18** under the same conditions, it was assumed that an oxidation-addition sequence may be in the background. Other derivatives such as simple olefins or the amido (17-carboxamido-16-ene) analogue of **16** remained unreactive under similar reaction conditions.

Table 6. Michael reaction of diphenyl phosphane (**17**) and steroidal esters **16**



16 **17** **18**

Entry	X	Y	Yield[a], %	de, %
1	CH_2	CH_2	71	99
2	C=O	NH	85	99
3	C=O	NMe	81	99

[a]: 10h reaction time

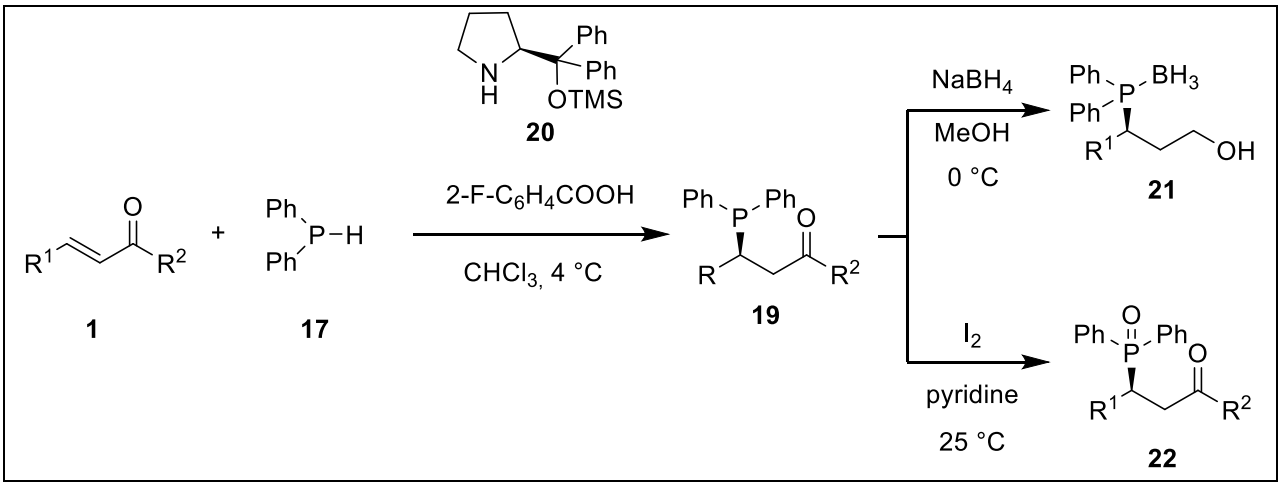
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When steroids with an exocyclic electron-deficient double bond were used, both diastereomers were formed, which were separated and identified.[22]

3. Asymmetric Addition of Phosphanes

Michael addition of trivalent P-H compounds is the most frequently investigated method for the synthesis of P-C chiral compounds. In the reaction of cinnamaldehyde (**1**, R^1 = Ph, R^2 = H) and diphenyl phosphane (**17**), several proline-based catalysts were tested by a Swedish group.[23,24] The direct product **19** was either reduced to the borane complex of the corresponding alcohol **21** or converted to its P-oxide **22** under mild conditions. Among the proline-based catalysts, compound **20** proved to be the most effective one, regardless of the transforming step (83% ee, Table 7, entries 1-2). Substituents of the aldehyde influenced the asymmetric induction positively, *e.g.,* 99% ee was measured when 4-nitrocinnamaldehyde (**1**, R^1 = 4-NO_2-C_6H_4, R^2 = H) was used (Table 7, entries 3-4).

Table 7. Conjugate addition of diphenyl phosphane (**17**) in the presence of organocatalyst **20**



Entry	R^1	R^2	Yield[a] of 21, %	Yield[a] of 22, %	ee of 21, %	ee of 22, %
1	Ph	H	99*	-	83	-
2	Ph	H		85		83
3	4-NO_2-C_6H_4	H	87		99	
4	4-NO_2-C_6H_4	H		87		99

*: conversion, not isolated yield

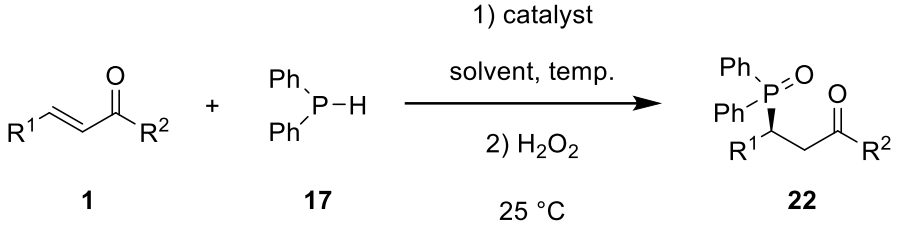
[a]: 20 min reaction time

Many attempts have been made to generate enantioselectivity by so-called pincer catalysts. Du *et al.* used cinnamic ester-type substrates and diphenyl phosphane (**17**) in the presence of catalyst **23**.[25] The trivalent P-containing product was oxidized to its pentavalent analogue, and product **22** was isolated. *Tert*-amylalcohol was found to be the best solvent for the reaction. The highest ee values were measured when trifluoroethyl (**1**, R^1 = Ph, R^2 = CF_3CH_2O), hexafluoroisopropyl (**1**, R^1 = Ph, R^2 = $(CF_3)CHO$) and phenyl (**1**, R^1 = Ph, R^2 = PhO) esters were used (91% ee, 95% ee, and 99% ee, respectively; Table 8, entries 1-3). Under optimized conditions, catalyst **23** tolerated most of the substituted Michael acceptor analogues, while the enantioselectivity remained high (96-99%).

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Similar results were achieved with catalyst **23** using chalcone (**1**, R^1 = Ph, R^2 = Ph) (99% ee, Table 8, entry 4) and its substituted derivatives. In all cases, the measured ee was in the range of 90-99%.[26] Addition of diphenyl phosphane (**17**) to (*E*)-3-phenyl-1-(1*H*-pyrrol-1-yl)prop-2-en-1-one (**1**, R^1 = Ph, R^2 = pyrrol-1-yl) in the presence of catalyst **23** resulted in the enantioselective formation of product **22** (R^1 = Ph, R^2 = pyrrol-1-yl) (99% ee, Table 8, entry 5).[27] High ee values were measured in the case of structurally similarly substituted *N*-acylpyrroles (**1**, R^1 = alkyl or aryl, R^2 = pyrrol-1-yl).

Table 8. Conjugate addition of diphenyl phosphane (**17**) in the presence of chiral metal complexes



Entry	R^1	R^2	catalyst	Solvent	Temp, °C	Yield, %	ee, %
1	Ph	CF_3CH_2O	**23**	*t*-amylalcohol	0	88[a]	91
2	Ph	$(CF_3)_2CHO$	**23**	*t*-amylalcohol	0	98[a]	95
3	Ph	PhO	**23**	*t*-amylalcohol	25	99[a]	99
4	Ph	Ph	**23**	CH_2Cl_2	25	93[a]	99
5	Ph	pyrrol-1-yl	**23**	THF	25	95[a]	99
6	6-Me-pyridin-2-yl	Ph	**23**	toluene	-60	96[b]	97
7	Ph-CH=CH	Ph	**24**	acetone	25	92[c]	99
8	Ph-CH=CH	pyridin-2-yl	**24**	acetone	0	86[c]	99
9	Ph	quinolin-2-yl	**24**	acetone	-40	99[d]	97
10	Ph	pyridin-2-yl	**24**	acetone	-40	99[d]	97
11	Ph	Ph	**25**[*]	toluene	0	84[b]	85
12	Ph	Ph	**26a**[*]	toluene	0	88[b]	82
13	Ph	Ph	**26b**[*]	toluene	0	99[b]	92
14	Ph	Ph	**26c**[*]	toluene	0	47[b]	30
15	Ph	pyridin-2-yl	**26d**[*]	acetone	25	99[b]	85
16	Ph	COO*i*Pr	**27**	$(MeOCH_2)_2$	-40	84[e]	66
17	imidazol-1-yl	Ph	**28**[#]	CH_2Cl_2	-78	92[f]	96
18	Ph	Ph	**29**	CH_2Cl_2	25	91[g]	56
19	Ph	NEt_2	**30**[¤]	THF	25	98[h]	96
20	Ph	Ph	**32**	THF	-20	99[e]	62
21	Ph	2-MeO-C_6H_4	**32**	THF	-20	96[e]	73

[*]: KOAc was used as additive; [#]:TMEDA was used as additive; [¤]:compound **31** was used as additive

[a]: 2h reaction time; [b]: 12h reaction time; [c]: 4-6h reaction time; [d]: 1-5h reaction time; [e]: 3h reaction time; [f]: 8h reaction time; [g]: 10h reaction time; [h]: 48h reaction time

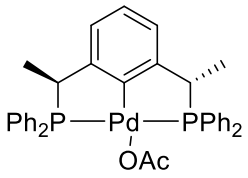
Good results were also achieved using catalyst **23** in the hydrophosphination of pyridine-containing substrates **1**.[28] In this case, sulfur was used instead of H_2O_2 to prepare the pentavalent air-stable compound (P=S analogue of **22**). In the reaction of **1** (R^1 = 6-Me-pyridyl-2-yl, R^2 = Ph) and diphenyl phosphane (**17**), 97% ee was

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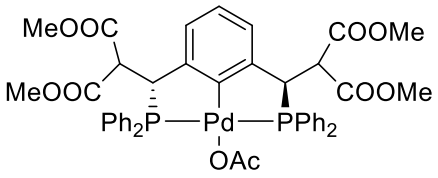
reached (Table 8, entry 6). A few analogous substrates were tested and, in all cases, an enantiomeric excess greater than 92% was measured.

The modification of Pincer catalyst **23** by introducing two benzoyl groups resulted in an ineffective derivative; only low enantiomeric excess could be reached in the reaction of **8** (R = Ph or Me) and diphenyl phosphane (**17**).[29]

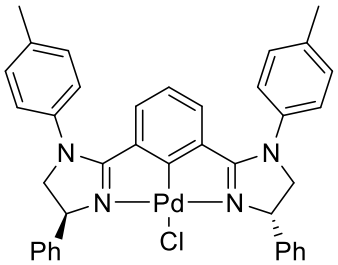
Pincer catalyst **24** was investigated in the Michael addition of diphenyl phosphane (**17**) to *N*-vinylimidazoles, however, it was ineffective. Meanwhile, under the same conditions, complex **28** generated significant asymmetric induction.[30] With acceptor **1** (R^1 = imidazole-1-yl, R^2 = Ph), 96% ee was measured in the presence of TMEDA (*N,N,N',N'*-tetramethylethylenediamine) (Table 8, entry 17). When substituents were introduced into the imidazole moiety, the enantioselectivity decreased.



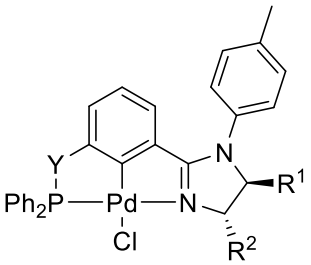
23



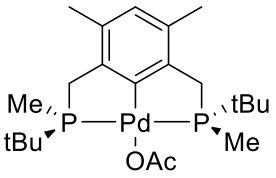
24



25



26a Y =NH, R^1 = H, R^2 = Ph
26b Y = O, R^1 = H, R^2 = Ph
26c Y = O, R^1 = H, R^2 = *t*Bu
26d Y =CH_2, R^1 = Ph, R^2 = Ph



27

Complex **24** was also used in the reaction of α,β,γ,δ-unsaturated ketones with diaryl phosphanes.[31] Under optimized conditions, only the 1,4 adducts were formed with ee up to 99% (with compound **17**, Table 8, entries 7-8). In the addition of diphenyl phosphane (**17**) to quinoline-based unsaturated compounds (*e.g.*, **1**, R^1 = quinoline-8-2-yl, R^2 = Ph), catalyst **24** proved to be superior to complex **28** and generated enantiomeric excess up to 97% (Table 8, entry 9).[32] In the second step of the reaction, sulfur, not hydrogen peroxide, was used to prepare air-stable pentavalent P-derivatives (P=S analogues of **22**). When the quinoline ring was replaced by a pyridine moiety (**1**, R^1 = pyridin-2-yl, R^2 = Ph), enantiomeric excess remained excellent (97% ee, Table 8, entry 10).

Using complex **24**, a self-breeding catalyst was developed when the product of the conjugate addition was transformed into a Pd complex, which was used in the same addition reaction as the catalyst. It was observed that enantioselectivity and yield were almost the same with the same substrate (93% ee).[33]

C_2-symmetric **23** and **25** and C_1-symmetric **26a** pincer complexes were compared in the hydrophosphination of chalcone **1** (R^1 = Ph, R^2 = Ph).[34] Catalyst **26a** gave a good result under optimized conditions (82% ee, Table 8, entry 12), while only a low enantiomeric excess could be reached with complex **26c** (30% ee, Table 8, entry 14). The enantioselectivity of C_2-symmetric complex **25** was similar to that of C_1-symmetric catalyst **26a** (85% ee, Table 8, entry 11). By testing a few substituted chalcones, it was found that the

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presence of an electron-donating substituent decreased the enantioselectivity generated by **26a**. Structures analogous to **25** were synthesized and compared to pincer catalysts **26a** and **26b**.[35] When Cl in compound **25** was replaced by Br, it generated comparable or better enantioselectivity than **26a,** while in most cases it was inferior to complex **26b**. C_2-symmetric pincer catalyst **27**, having a modified structure compared to **25**, was developed and tested in the hydrophosphination of β,γ-unsaturated-α-ketoesters.[36] A moderate ee value (66%) was measured in the case of ester **1** (R^1 = Ph, R^2 = COOiPr, Table 8, entry 16) using complex **27**. The enantioselectivity generated by **27** was strongly dependent on the structure of the substrate.

A series of chiral pincer Pd-complexes with aryl-based aminophosphine-imidazoline or phosphinite-imidazoline ligands were synthesized by Hao and co-workers.[37] The structural effect of the complex was investigated and asymmetric induction was found to be highly dependent on the substituents on the imidazole ring. The most effective structure was **26b**, which was tested in the hydrophosphination of chalcones. In the reaction of chalcone **1** (R^1 = Ph, R^2 = Ph), and diphenyl phosphane (**17**) 92% ee was measured (Table 8, entry 13). Substitution onthe aromatic rings in the acceptor only slightly influenced the enantioselectivity, although the *ortho*-substitution was strongly unfavorable.

A series of new chiral pincer Pd(II)-complexes bearing an imidazoline moiety were synthesized to study the structure-activity relationship.[38] Among these, **26d** showed the best result (85% ee) in the conjugate addition of **1** (R^1 = Ph, R^2 = pyridine-2-yl) and diphenyl phosphane (**17**) (Table 8, entry 15). Alteration of the structure of the substrate strongly affected the enantioselectivity of catalyst **26d.**

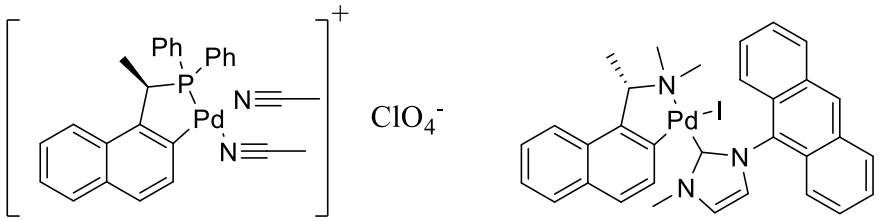
A comparative study was preformed by Yang *et al.* to gain information about the catalytic mechanism of complexes **24** and **28**.[39] It was found that the C_2-symmetric pincer catalyst **24** can direct the approach of the substrate by means of the prochiral P-Ph groups, while complex **28** allows the simultaneous coordination of both reagents to the Pd center. The differences shown in the mechanism may also be behind the phenomenon that, in the case of α,β,γ,δ-unsaturated carbonyl compounds, 1,4 addition takes place with palladacycles while 1,6 addition takes place with pincer catalysts.[29,40]

Catalyst **28** was used to form biologically-active chiral Pt complexes.[41] After it was used in the addition of diphenyl phosphane (**17**) to *N*-vinylbenzimidazoles, the adducts obtained were converted into new Pt complexes, the cytotoxicity of which toward cancer cell lines was investigated.

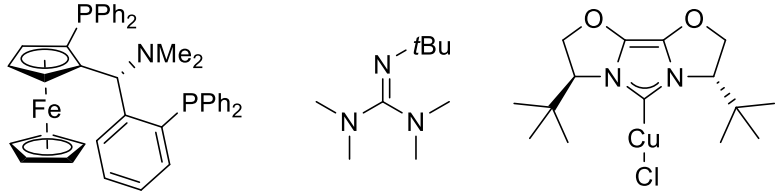
Chiral *N,N*-dimethylbenzylaminate palladacycles, which can be conveniently synthesized from commercially-available chiral tertiary amines, were investigated in the reaction of chalcone **1** (R^1 = Ph, R^2 = Ph) and diphenyl phosphane (**17**).[42] Among the synthesized complexes, compound **29** proved to be the most effective, however, the enantioselectivity was only moderate in the reaction of chalcone **1** (R^1 = Ph, R^2 = Ph) and diphenyl phosphane (**17**) (56% ee, Table 8, entry 18).

TANIAPHOS [(2*S*)-1-[(*R*)-(Dimethylamino)[2-(diphenylphosphino)phenyl]methyl]-2-(diphenylphosphino)ferrocene]-based catalytic system **30** proved to be effective in the hydrophosphination of unsaturated amides.[43] The enantioselective addition required the bidentate ligand **30**, a copper(I) complex and Barton's base (**31**). When the substrate was *N,N*-diethylcinnamide (**1**, R^1 = Ph, R^2 = NEt_2), product **22** was isolated with 96% ee (Table 8, entry 19). Different amides also gave excellent results; the lowest enantioselectivity was 84%.

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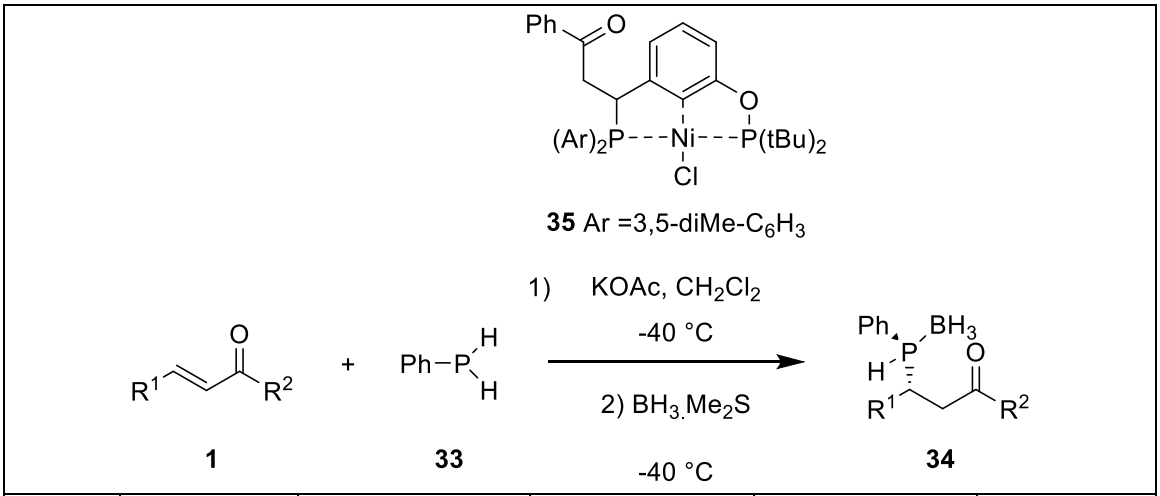
28 **29**



30 **31** **32**

The copper-containing catalyst **32** was investigated in the hydrophosphination of chalcones **1** (R^1 = aryl, R^2 = aryl).[44] Under optimized conditions, 62% ee was reached using chalcone **1** (R^1 = Ph, R^2 = Ph) as the substrate (Table 8, entry 20). Enantioselectivity was strongly dependent on the substituents of the aromatic rings of the chalcone. The best result was achieved using 2'-methoxychalcone (**1**, R^1 = Ph, R^2 = 2-$MeOC_6H_4$) (73% ee, Table 8, entry 21).

Table 9. Michael addition of phenyl phosphane (**33**) to chalcone derivatives **1**



35 Ar =3,5-diMe-C_6H_3

1) KOAc, CH_2Cl_2, -40 °C; 2) $BH_3.Me_2S$, -40 °C

1 **33** **34**

Entry	R^1	R^2	Yield[a], %	dr	ee %
1	Ph	Ph	82	13:1	94
2	4-Me-C_6H_4	Ph	87	20:1	94
3	*i*Pr	Ph	77	8:1	88
4	4-Me-C_6H_4	pyrrol-2-yl	86	20:1	99

[a]: 12h reaction time

Wang *et al.* developed a *C_1*-symmetric bisphosphine Ni-complex **35**.[45] Its efficiency was compared to compound **23** in the reaction of chalcone (**1**, R^1 = Ph, R^2 = Ph), and phenyl phosphane (**33**). In the second step, the trivalent P-containing product was converted into its borane complex (**34** R^1 = Ph, R^2 = Ph). While the

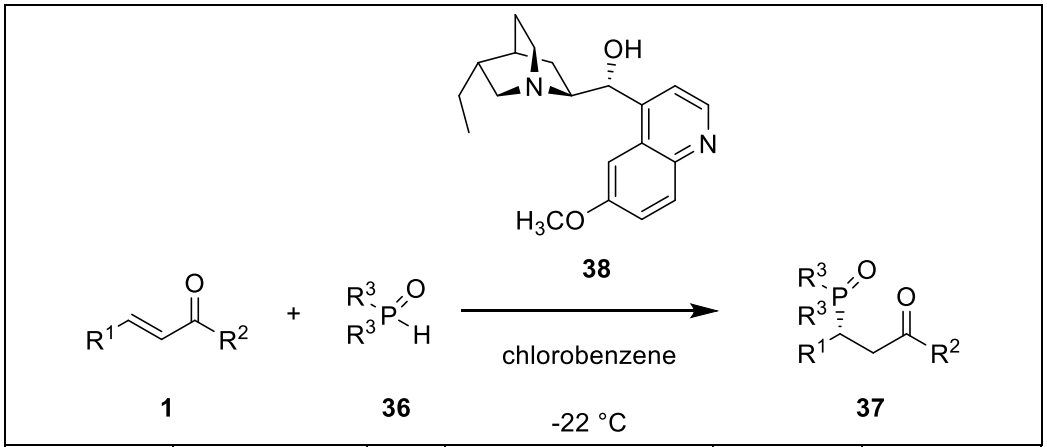
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enantioselectivity generated by **23** was very low, and the diasteromeric ratio was 1:1, catalyst **35** preferred the formation of one of the diastereomers with high ee (94%, Table 9, entry 1). The best dr value (20:1) was measured in the case of 4-methylchalcone (**1** R^1 = 4-Me-C_6H_4, R^2 = Ph), while the enantioselectivity was also high (94% ee, Table 9, entry 2). Selectivity was dropped in the case of 4-methyl-1-phenylpent-2-en-1-one (**1** R^1 = *i*Pr, R^2 = Ph) (88% ee, Table 9, entry 3). Excellent enantiomeric excess was reached, when a pyrrole unit was introduced into the substrate (**1** R^1 = Ph, R^2 = pyrrol-2-yl; 99% ee, Table 9, entry 4).

4. Asymmetric Addition of Phosphane Oxides

The first example of an enantioselective, asymmetric addition of diarylphosphane oxides to chalcones was reported by Lattanzi and Russo.[46] Chinona derivatives were used as catalysts and, under optimized conditions, compound **38** generated the highest ee value in the reaction of chalcone (**1**, R^1 = Ph, R^2 = Ph) and diphenyl phosphane oxide (**36**, R^3 = Ph) (80% ee, Table 10, entry 1). In the case of substituted chalcones, the substituents affected the outcome of the reaction. The best result was achieved with 2-methoxychalcone (**1**, R^1 = 2-$MeOC_6H_4$, R^2 = Ph) (89% ee, Table 10, entry 2). When using an analogue bearing a cyclohexane moiety (**1**, R^1 = cyclohexyl, R^2 = Ph), only a moderate enantiomeric excess (60% ee) and poor yield (30%) were obtained (Table 10, entry 3). It was found that the use of different phosphane oxides leads to changes in the asymmetric induction. While the addition of di(naphthalen-1-yl)phosphane oxide (**36**, R^3 = naphthalen-1-yl) gave the product **37** with 45% ee (Table 10, entry 4), using its napthhalen-2-yl analogue was more successful (75% ee, Table 10, entry 5).

Table 10. Michael reaction of diphenyl phosphane oxide (**36**, R^3= Ph) in the presence of organocatalyst **38**



Entry	R^1	R^2	R^3	Yield[a], %	ee %
1	Ph	Ph	Ph	99	80
2	2-MeO-C_6H_4	Ph	Ph	87	89
3	cyclohexyl	Ph	Ph	30	60
4	Ph	Ph	naphthalen-1-yl	99	45
5	Ph	Ph	naphthalen-2-yl	88	75

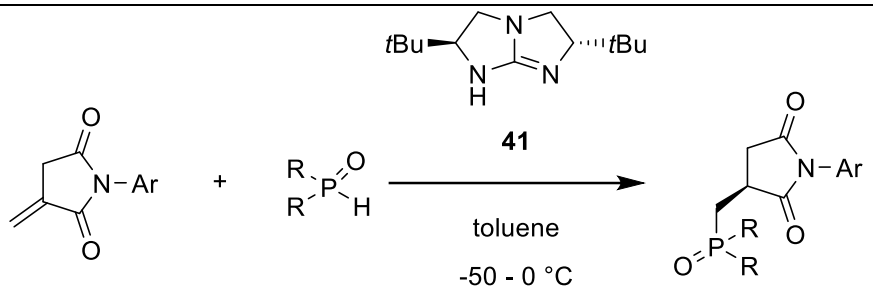
[a]: 75-160h reaction time

Tan's group used the bicyclic guanidine catalyst **41** in the reaction of itaconamides **39** and secondary phosphane oxides **36**.[47] The structure of **36** was investigated and it was found that the bulkiness and the

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electronic properties had little effect on the enantioselectivity, *e.g.*, in the case of trimethylphenyl derivative **39** (Ar = 2,4,6-triMe-C_6H_2) and di(naphthalen-1-yl)phosphane oxide (**36**, R = naphthalen-1-yl) or bis(2-trifluoromethylphenyl)phosphane oxide (**36**, R = 2-CF_3-C_6H_4), 98% and 96% ee was measured (Table 11, entries 1-2). When the aromatic ring on the nitrogen was unsymmetrically substituted (**39**, Ar = 2-*t*Bu-C_6H_4), diastereomers with high enantiomeric excess were formed (97% and 79% ee, Table 11, entry 3).

Table 11. Conjugate addition of itaconamides **39** and secondary phosphane oxides **36**

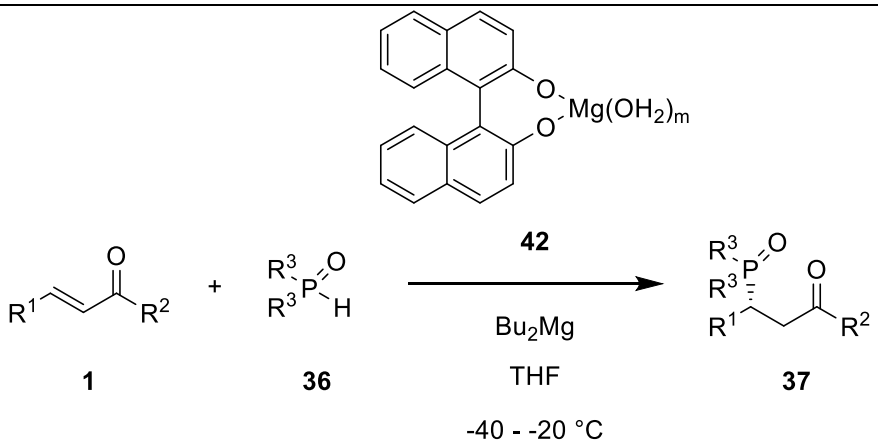


Entry	Ar	R	Yield[a], %	ee %	dr
1	2,4,6-triMe-C_6H_2	naphthalen-1-yl	95	98	-
2	2,4,6-triMe-C_6H_2	2-CF_3-C_6H_4	89	96	-
3	2-*t*Bu-C_6H_4	2-CF_3-C_6H_4	92	99 / 79	1:1

[a]: 2-10h reaction time

Binaphtholate catalyst **42** was developed to be a cooperative Brønsted/Lewis acid–base catalyst.[48] The addition of diphenyl phosphane oxide (**36**, R = Ph) to cinnamic esters (**1**, R^1 = Ph or substituted phenyl ring, R^2 = OMe or OEt) occured with good enantioselectivity. Michael adduct **37**, derived from methyl cinnamate (R^1 = Ph, R^2 = OMe, R^3 = Ph), was isolated with 95% ee (Table 12, entry 1). It was determined that changing R^1 had little effect on the enantioselectivity (Table 12, entries 2-3). It was also found that, when dialkyl phosphonates (**51**) were used instead of phosphane oxides, the addition involved the C=O group, not the double bond.

Table 12. Asymmetric Michael addition of diphenyl phosphane oxide (**36**, R^3 = Ph) in the presence of binaphtholate catalyst **42**



Entry	R^1	R^2	R^3	Yield[a], %	ee %

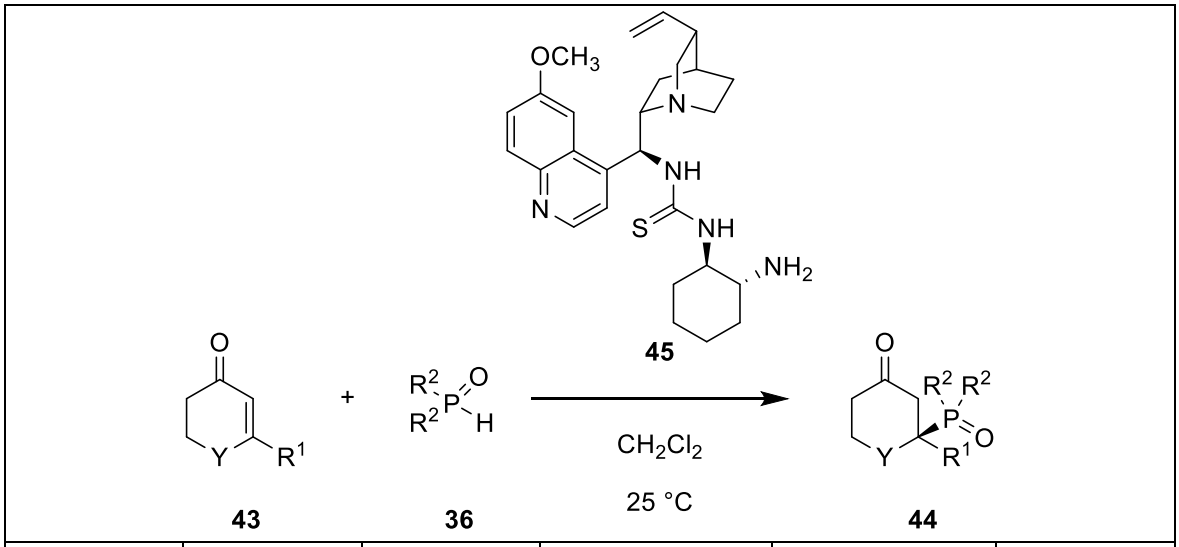
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1	Ph	OMe	Ph	91	95
2	cyclohexyl	OMe	Ph	86	95
3	furan-2-yl	Ph	Ph	89	90

[a]: 3-20h reaction time

Multifunctional organocatalysts derived from chincona alkaloids were tested in the addition of diphenyl phosphane oxide (**36**, R^3 = Ph) to cyclic enones **43**.[49] Catalyst **45** bearing a thiocarbamide and a cyclohexane-diamine unit proved to be highly effective. In the case of cyclohex-2-en-1-one (**43**, R^1 = H, Y = CH_2) and cyclohept-2-en-1-one (**43**, R^1 = H, Y = CH_2CH_2), 90% ee was generated in both cases by the multifunctional organocatalyst **45** (Table 13, entries 1-2). Using derivatives having additional alkyl group(s) (*e.g.*, **43**, R^1 = CH_3, Y = CH_2 or R^1 = H, Y = $C(CH_3)_2$) resulted in excellent enantiomeric excesses (98% ee, Table 13, entries 3-4).

Table 13. Conjugate addition of diphenyl phosphane oxide (**36**, R^2 = Ph) to cyclic enones **43**

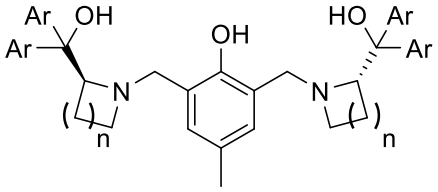


Entry	Y	R^1	R^2	Yield[a], %	ee %
1	CH_2	H	Ph	98	90
2	CH_2CH_2	H	Ph	87	90
3	CH_2	Me	Ph	96	98
4	$C(CH_3)_2$	H	Ph	95	98

[a]: 48-144h reaction time

The conjugate addition of dialkyl phoshane oxides **36** to dipnone in the presence of proline-based catalysts **47** was investigated by Zhao and co-workers.[50] Using **47a** resulted in low enantiomeric excess, while after some optimization, **47b** generated 94% ee, when diallyl phoshane oxide (**36**, R^4 = allyl) was applied (Table 14, entry 1). An excellent enantiomeric excess (99%) was also determined in the addition of dibutyl phoshane oxide (**36**, R^4 = butyl) (Table 14, entry 2). The structural modification of dipnone (**4**, R^1 = Ph, R^2 = CH_3, R^3 = Ph) had no significant effect on the enantioselectivity.

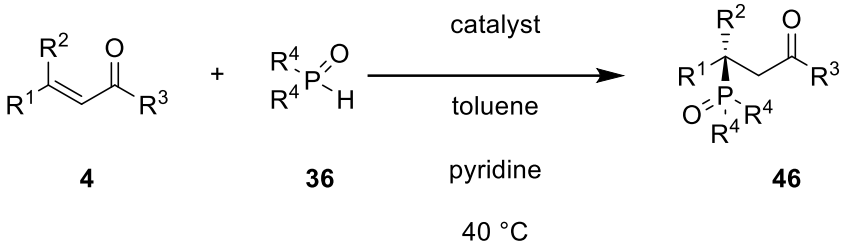
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47a n = 2, Ar = Ph
47b n = 2, Ar = thiophen-2-yl
47c n = 1, Ar = Ph
47d n = 2, Ar = 4-Cl-C_6H_4

Catalyst **47b** also proved to be effective in the reaction of chalcone (**1**, R^1 = Ph, R^2 = H, R^3 = Ph) (99% ee, Table 14, entry 3).[51] Enantioselectivity remained high when diethyl, dipropyl or dibutyl phoshane oxide (**38**, R^4 = Et, Pr, or Bu) was used. Furthermore, high ee values were measured with substituted chalcones.

Table 14. Michael addition of phosphane oxides **36** and enones **1**



4 **36** **46**

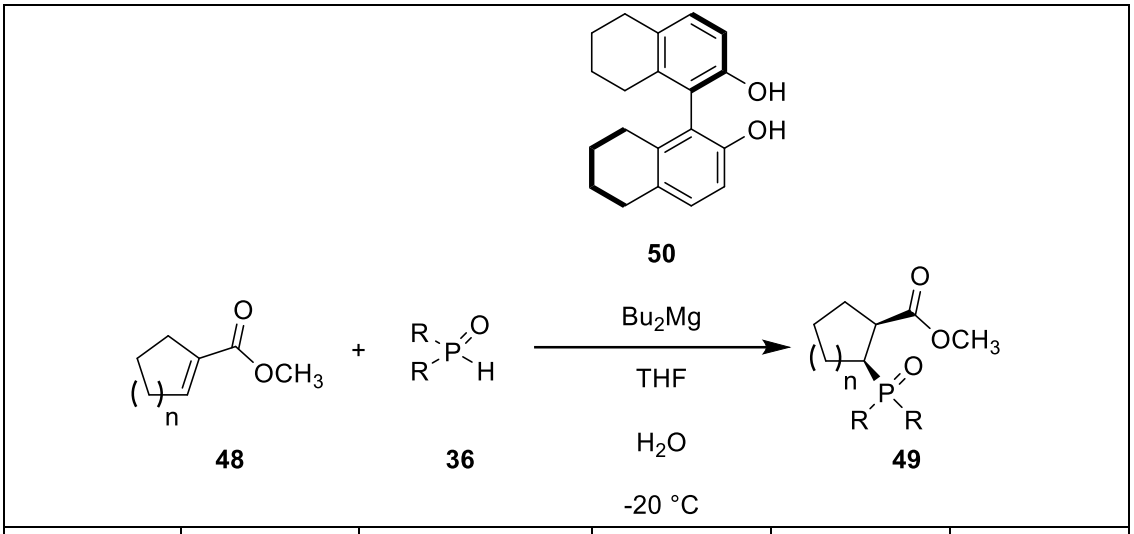
Entry	R^1	R^2	R^3	R^4	Catalyst	Yield[a], %	ee, %
1	Ph	Me	Ph	allyl	**47b**	85	94
2	Ph	Me	Ph	butyl	**47b**	90	99
3	Ph	H	Ph	allyl	**47b**	98	99

[a]: 12h reaction time

Cao and co-workers reported the reaction of unsaturated cyclic esters **48** with diaryl phosphane oxides **36** in the presence of H_8-BINOL **50**.[52] The ring size of substrate **48** affected the selectivity of the catalyst; the larger the ring, the greater the diastereomeric ratio and the enantioselectivity (see Table 15, entries 1,2 and 5). The addition of di-*p*-toluenephosphane oxide (**36**, R = 4-MeC_6H_4) followed the previously observed trend (Table 15, entry 4), however, in the case of di-*m*-toluenephosphane oxide (**36**, R = 3-Me-C_6H_4), the diastereomeric ratio was altered (0.7:1, Table 15, entry 3). It is worth mentioning that di-*o*-toluenephosphane oxide (**36**, R = 2-Me-C_6H_4) did not react at all, even at elevated temperature.

Table 15. Michael reaction of unsaturated cyclic esters **48** and phosphane oxides **36**

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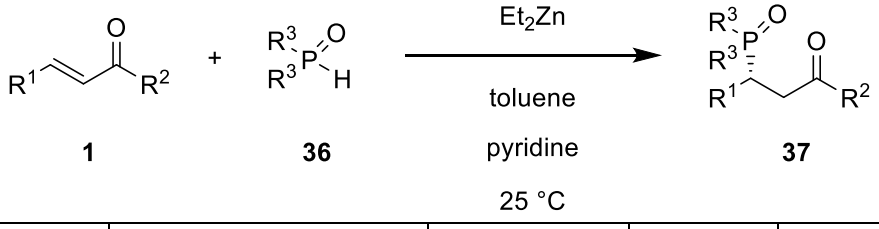
Entry	n	R	Yield[a], %	dr	ee, %
1	1	Ph	92	5.6:1	80
2	2	Ph	97	9.5:1	90
3	2	3-Me-C_6H_4	67	0.7:1	95
4	2	4-Me-C_6H_4	32	3.3:1	92
5	3	Ph	95	11.5:1	95

[a]: 48h reaction time

Zhao and co-workers tested catalyst **47a** in the reactions of *N*-acylpyrroles (**1**, R^1 = aryl or alkyl, R^2 = pyrrol-1-yl) with dialkyl phosphane oxides (**36**, R^3 = alkyl).[53] With unsubstituted substrate **1** (R^1 = Ph, R^2 = pyrrol-1-yl), the product was obtained with high enantioselectivity (96-98 % ee) with different alkyl phosphane oxides (Table 16, entries 1-3). Structural changes in compound **1** did not influence the effectiveness of catalyst **47a**.

Using *N*-acyl oxazolidin-2-ones (**1**, R^1 = aryl or alkyl, R^2 = oxazolidin-2-one-1-yl) and diphenyl phosphane oxide (**36**, R^3 = Ph), catalyst **47b** generated excellent enantioselectivity (99%, Table 16, entry 4).[54] Substitution on the phenyl ring (R^1) did not significantly affect the results. When di(4-methoxyphenyl) phosphane oxide (**36**, R^3 = 4-MeO-C_6H_4) or di(4-fluorophenyl) phosphane oxide (**36**, R^3 = 4-F-C_6H_4) was used, product **37** was formed in excellent enantiomeric excess (93% and 95%, respectively, Table 16, entries 5-6).

Table 16. Michael addition of heterocyclic enones **1** with phosphane oxides **36**



Entry	R^1	R^2	R^3	Catalyst	Yield, %	ee, %
1	Ph	pyrrol-1-yl	Et	**47a**	99[a]	97
2	Ph	pyrrol-1-yl	Pr	**47a**	96[a]	98
3	Ph	pyrrol-1-yl	allyl	**47a**	99[a]	96
4	Ph	oxazolidin-2-one-1-yl	Ph	**47b**	96[b]	99

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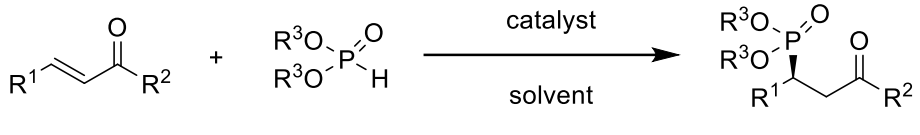
5	Ph	oxazolidin-2-one-1-yl	4-MeO-C_6H_4	**47b**	95[b]	93
6	Ph	oxazolidin-2-one-1-yl	4-F-C_6H_4	**47b**	99[b]	95

[a]: 12h reaction time; [b]: 10-90 min reaction time

5. Asymmetric Addition of Phosphonates

Zhao *et al.* applied *N*-acylpyrrol derivatives (**1**, R^2 = pyrrol-2-yl) as acceptors in the conjugate addition of phosphonates.[55] When diethyl phosphonate (**51**, R^3 = Et) was reacted with *N*-cinnamoyl pyrrol (**1**, R^1 = Ph, R^2=pyrrol-1-yl) in the presence of catalyst **47a**, excellent enantioselectivity was measured (99%, Table 17, entry 1). Asymmetric induction was slightly affected by the Michael donor applied, *e.g.*, using diisopropyl (**51**, R^3 = *i*Pr) or diphenyl phosphonate (**51**, R^3 = Ph) resulted in high enantiomeric excess (97% and 92%, respectively, Table 17, entries 2-3). Changing R^1 = Ph in the unsaturated compound **1** to a substituted aromatic ring or to another aromatic system or even to an alkyl group, had no effect on the enantioselectivity (98-99% ee in all cases).

Table 17. Conjugate addition of enones **1** and phosphonates **51**



1 **51** **52**

Entry	R^1	R^2	R^3	Catalyst	solvent	Temp, °C	Additive	Yield, %	ee, %
1	Ph	pyrrol-1-yl	Et	**47a**	toluene	25	Et_2Zn	99[a]	99
2	Ph	pyrrol-1-yl	*i*Pr	**47a**	toluene	25	Et_2Zn	95[a]	97
3	Ph	pyrrol-1-yl	Ph	**47a**	toluene	25	Et_2Zn	96[a]	92
4	Ph	Ph	Et	**47a**	toluene	25	Et_2Zn	90[a]	95
5	Ph	Ph	Et	**47c**	toluene	17	Et_2Zn	99[a]	99
6	Ph	pyrrol-1-yl	Et	**47c**	toluene	20	Et_2Zn	63[a]	96
7	Ph	Me	Ph	**53**	toluene	25	MS*	96[b]	92
8	Ph	Ph	Et	**54**	toluene	0	**55**	99[c]	99
9	Ph	Ph	*i*Pr	**54**	toluene	0	**55**	99[c]	99
10	*t*Bu	Ph	Et	**54**	toluene	0	**55**	97[c]	43
11	Ph	NHBn	Et	**56**	dioxane	20	**57**	99[c]	85
12	Ph	NH*i*Pr	Et	**56**	dioxane	20	**57**	83[c]	64
13	Ph	NHPh	Et	**56**	dioxane	20	**57**	98[c]	85
14	Ph	Ph	Et	**58**	toluene	0	**59**	94[d]	89

*: molecular sieve

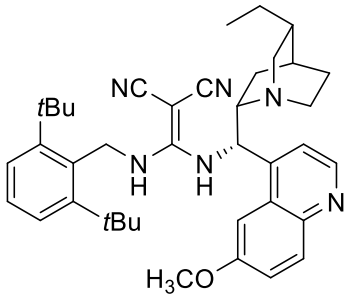
[a]: 12-24h reaction time; [b]: 62-71h reaction time; [c]: 12h reaction time; [c]: 24h reaction time

Using diethyl phosphonate (**51**, R^3 = Et), the scope of the substrate was extended to chalcone (**1**, R^1 = Ph, R^2 = Ph) using catalyst **47a**.[56] In this case, product **52** (R^1 = Ph, R^2 = Ph, R^3 = Et) was isolated also with good enantiomeric excess (95%, Table 17, entry 4). Again, changing R^1 = Ph in the unsaturated compound **1** to a substituted aromatic ring resulted in high enantioselectivity (93-99% ee). Complex **47c** was tested in a similar

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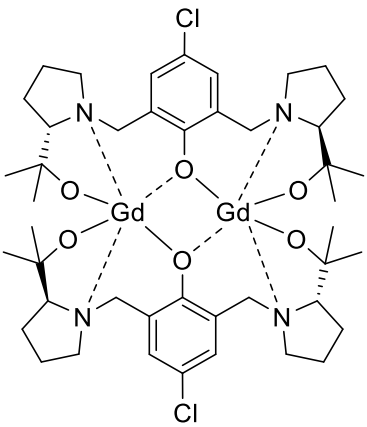
way to **47a**, and it showed excellent enantioselectivity, both in the reaction of chalcone (**1**, R^1 = Ph, R^2 = Ph) (99% ee, Table 17, entry 5), and in the conjugate addition to 3-phenyl-1-(pyrrol-1-yl)prop-2-ene-1-one (**1**, R^1 = Ph, R^2=pyrrol-1-yl) (96% ee, Table 17, entry 6).[57] Using substituted derivatives and analogues of the substrates also resulted in highly enantioselective reactions.

Organocatalyst **53** generated good enantioselectivity in the reaction of crotonophenone (**1**, R^1 = Me, R^2 = Ph) with diphenyl phosphonate (**51**, R^3 = Ph) in the presence of molecular sieves (92% ee, Table 17, entry 7).[58] Catalyst **53** could be reused 4 times without significant changes in the yield and enantiomeric excess. After the fifth cycle, the yield was lower. The catalytic system proved to be robust to substrates, e.g., changing R^2 to substituted aromatic rings did not affect the enantioselectivity.

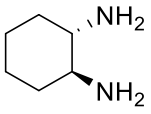


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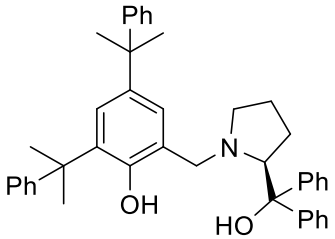
The rare-earth-metal complex **54**, bearing Trost ligands, was successfully applied in the asymmetric hydrophosphonylation of chalcones.[59] The reaction of chalcone (**1**, R^1 = Ph, R^2 = Ph) with diethyl phosphonate (**51**, R^3 = Et) resulted in the enantioselective formation of product **52** (R^1 = Ph, R^2 = Ph, R^3 = Et) when cyclohexane-1,2-diamine (**55**) was present in the reaction mixture (99% ee, Table 17, entry 8). Replacing diethyl phosphonate (**51**, R^3 = Et) with diisopropyl phosphonate (**51**, R^3 = *i*Pr) did not affect the enantioselectivity (99% ee, Table 17, entry 9). While using substituted chalcones and other aromatic analogues resulted in good enantioselectivity, introducing a *tert*-butyl moiety lowered the ee value significantly (43%, Table 17, entry 10).



54



55



56

$[(Me_3Si)_2N]_3Sc(\mu\text{-}Cl)Li(THF)_3$

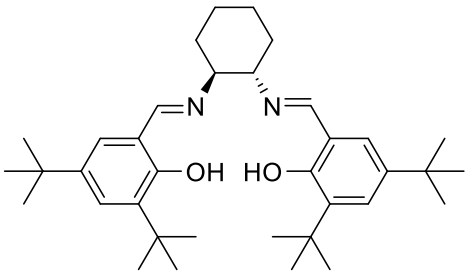
57

Asymmetric hydrophosphonylation of α,β-unsaturated amides was successfully catalyzed by combining the rare-earth metal amide **57** with phenoxy-functionalized chiral prolinol **56**.[60] 85% Ee was observed in the addition of diethyl phosphonate (**51**, R^3 = Et) to *N*-benzylcinnamide (**1**) (R^1 = Ph, R^2 = NHBn) (Table 17, entry 11). When the substituent of the amide was changed to *i*Pr (**1**) (R^1 = Ph, R^2 = NH*i*Pr), enantioselectivity dropped to

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64% (Table 17, entry 12). Using *N*-phenylcinnamide **1** (R^1 = Ph, R^2 = NHPh), the result of the reaction was similar to that of *N*-benzylcinnamide **1**, (R^1 = Ph, R^2 = NHBn) (85% ee, Table 17, entry 13).

Another rare-earth metal, ytterbium, was used (as complex **59**) together with chiral salen ligand **58** in the Michael addition of diethyl phosphonate (**51**, R^3 = Et) to chalcone (**1**, R^1 = Ph, R^2 = Ph).[61] Under optimized conditions, product **52** (R^1 = Ph, R^2 = Ph, R^3 = Et) was obtained with high enantioselectivity (89% ee, Table 17, entry 14). It was determined that the enantioselectivity was slightly affected by the substituents of the chalcones.



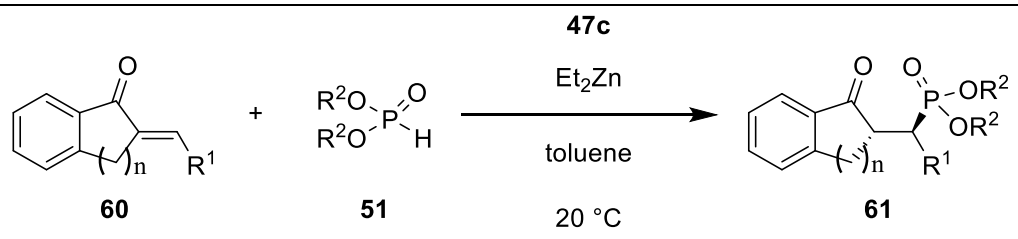
58

$[(Me_3Si)_2N]_3Yb(\mu\text{-}Cl)Li(THF)_3$

59

Later, catalyst **47c** was investigated in the reaction of cyclic enones.[62] It was found that both diastereomers of the products were formed, but both with excellent enantiomeric excess (99% in most cases). Using tetralones (**60**, n = 2, R^1 = Ph or 4-Br-C_6H_4), the diastereomeric ratio was 2.1:1 and 3.4:1 (Table 18, entries 1 and 2). If the phenyl group in the substrate was replaced by a furan ring, diastereomers were present in 1.1:1 ratio in the product (**61**, n = 2, R^1 = furan-2-yl, R^2 = Et) (Table 18, entry 3). In the case of indanones (**60**, n = 1, R^1 = Ph or 2,6-diMeO-C_6H_3), the diastereomeric ratio was changed to 1:2.2 and 1:6.6, respectively, while the enantioselectivity was maintained (99% in all cases, Table 18, entries 4 and 5). Substituents on the substrate had little effect on the enantioselectivity.

Table 18. Michael addition of cyclic enones **60** and phosphonates **51**



60 **51** **61**

Entry	n	R^1	R^2	Yield[a], %	dr	ee, %
1	2	Ph	Et	96	2.1:1	99/99
2	2	4-Br-C_6H_4	Et	91	3.4:1	99/99
3	2	furan-2-yl	Et	92	1.1:1	99/99
4	1	Ph	Et	95	1:2.2	99/99
5	1	2,6-diMeO-C_6H_3	Et	90	1:6.6	99/99

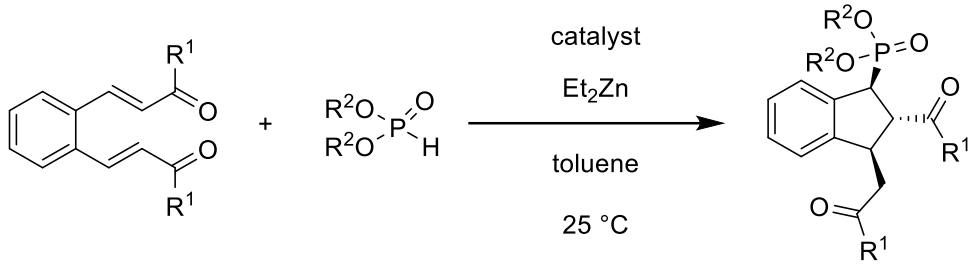
[a]: 20-24h reaction time

A new and efficient catalytic asymmetric phospha-Michael/Michael cascade reaction of *ortho*-dienones **62** and dialkyl phosphonates **51** using catalysts **47a-d** was reported by Tao *et al*.[63] The **63** indane derivatives bearing phosphoryl groups were obtained with excellent stereoselectivity (up to > 99% ee and >99 : 1 dr) under

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mild conditions. While catalyst **47a** and **47d** proved to be highly enantioselective (97% and 99% ee, Table 19, entries 1 and 4), analogue derivatives **47b** and **47c** generated moderate optical purity (76% and 74%, Table 19, entries 2 and 3). Interestingly, in compound **62**, when a methyl group was present next to the carbonyl functions (R^1 = Me), there was no reaction (Table 19, entry 5). The catalytic system with **47d** proved to be effective when other dialkyl phosphonates were used as well as when there was a substituent on the aromatic ring.

Table 19. Asymmetric phospha-Michael/Michael cascade reaction of *ortho*-dienones **62** and dialkyl phosphonates **51**



62 **51** **63**

Entry	R^1	R^2	Catalyst	Yield[a], %	dr	ee, %
1	Ph	Et	**47a**	87	99:1	97
2	Ph	Et	**47b**	63	99:1	76
3	Ph	Et	**47c**	40	99:1	74
4	Ph	Et	**47d**	92	99:1	99
5	Me	Et	**47d**	0	-	-

[c]: 16-72h reaction time

6. Conclusions

By Michael addition of P-H compounds, phosphorus-containing compounds with potential biological activity can be obtained. Enantioselective catalysis is a modern and green production method of P-C chiral derivatives as well, however, this requires chiral catalysts that are efficient, robust, and widely applicable. In order to be able to plan and carry out reactions resulting in the desired products, it is necessary to know the limitations and possibilities. In several cases presented in this review, the details of effect-structure relationships can be recognized which can be useful for further catalyst research and development. In addition, the possible routes presented, leading to the preparation of P-C chiral compounds with diverse structures, may inspire new methods and newer derivatives.

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István Orbán graduated from the Budapest University of Technology and Economics' Pharmaceutical Engineering M. Sc. course in 2018. During his studies he joined the research group of Dr. Péter Bakó and Dr. Zsolt Rapi, to conduct research on carbohydrate-based crown ethers. After graduation and two years of lab work in the synthetic industry he returned to the research group at BUTE in September 2020, to pursue a Ph.D. under the supervision of Dr. Zsolt Rapi. The research topic remained much the same – synthesis of carbohydrate-based aza-crown ethers and their application as catalysts in asymmetric reactions.

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