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An Unprecedented Rhodium-Catalyzed Asymmetric Intermolecular Hydroacylation Reaction with Salicylaldehydes

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Abstract: An unprecedented enantio- and diastereoselective rhodium-catalyzed intermolecular hydroacylation reaction of salicylaldehydes with norbornenes is reported in which the corresponding aryl ketones are obtained in high diastereomeric and moderate enantiomeric excesses. It was found that monodentate phosphoramidite ligands gave rise to *endo* products, while bidentate phosphine ligands catalyzed the reaction to form *exo* products predominantly.

Keywords: asymmetric catalysis; C–H activation; phosphane ligands; phosphites; phosphoramidites; rhodium

Introduction

The development of transition metal catalysts for carbon-carbon bond forming reactions by the C–H bond activation strategy still remains a significant challenge.[1] Along with ruthenium- and palladium-catalyzed C–C bond formation by means of C–H bond activation, rhodium-containing catalysts have been extensively studied.[2] The transition metal-catalyzed hydroacylation reaction involves the activation of the C–H bond of an aldehyde followed by insertion of an olefin to furnish a ketone function. The first example of an intramolecular hydroacylation reaction was reported by Sakai in 1972, who used Wilkinson's catalyst [$RhCl(PPh_3)_3$] for the cyclization of 4-pentenals into cyclopentanones.[3,4] A major drawback of this reaction is the competitive decarbonylation of the corresponding acyl-metal intermediates, forming reduced substrates. In order to avoid these competing steps, Miller described the use of a saturated ethylene solution,[5] and Bosnich applied a cationic rhodium(I) complex bearing a chelating diphosphine ligand.[6] The improvement of Bosnich's methodology over the use of Wilkinson's neutral catalyst was reasoned by the formation of a six-coordinate acyl-rhodium(III) intermediate with two available coordination sites after the oxidative addition, allowing the olefinic part of the substrate to coordinate in a chelating manner to the rhodium center (Figure 1). Additionally, it is known that carbonyl ligands are less stable when they are *trans* to phosphine ligands and when the complexes are cationic, thus suppressing decarbonylation processes.

The first attempt directed towards an asymmetric intramolecular hydroacylation was reported by James in 1983,[7] who used chiral bidentate phosphine ligands. Later this approach was extended by Sakai, Bosnich and Morehead, who achieved high enantioselectivities with other substrates.[8–10] Tanaka, Sakai and Suemune developed the asymmetric intramolecular hydroacylation reaction further into efficient desymmetrizations of symmetric dienals.[11]

The intermolecular hydroacylation reaction has been studied much less than its intramolecular counterpart. Due to the competitive rhodium-catalyzed decarbonylation, almost exclusively chelation-assisted intermolecular reactions have been developed.[2] Jun has elegantly shown that the addition of 2-amino-3-picoline as cocatalyst is effective in preventing the decarbonylation by chelation of the pyridyl nitrogen to the metal center.[12] Miura[13a,b] and Willis[13c–f] reported the applicability of chelating substrates such as salicylaldehyde and β-methylsulfanyl aldehyde, respectively,

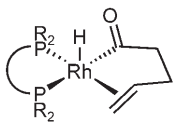
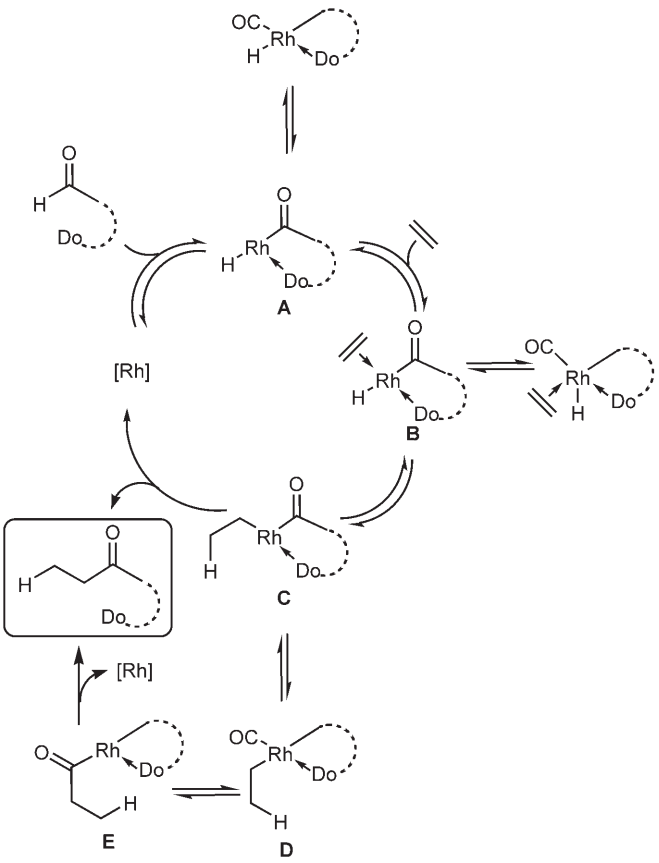


Figure 1. Acyl-rhodium intermediate after the oxidative addition of the aldehyde and coordination of the olefinic part of the substrate to the rhodium center.



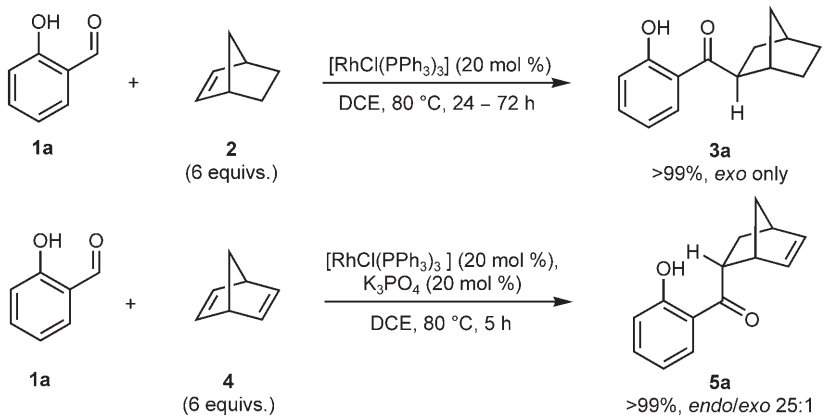
Scheme 1. Putative catalytic cycle of the intermolecular hydroacylation reaction.

in the intermolecular hydroacylation.[14] Additionally, a double-chelation assisted hydroacylation, in which both aldehyde and olefin coordinate to rhodium in a bidentate manner, was reported by Tanaka and Suemune in 2003.[15]

The assumed mechanism of the intermolecular hydroacylation reaction is commonly described as outlined in Scheme 1. Except for the final reductive elimination releasing the product, all of the other steps are reversible, but not at equilibrium.[16] As such, the enantioselection is controlled by a number of reversible steps involving reaction intermediates. Since none of these intermediates could be detected to date, the proposed mechanisms of intra- and intermolecular hydroacylations were inferred mainly from deuterium scrambling experiments.[15–17]

Oxidative addition of the aldehyde to the Rh(I) catalyst leads to the acyl-Rh(III) intermediate **A**. In the case of an *inter*molecular hydroacylation, the intermediate **A** is usually stabilized *intra*molecularly by chelation using a donor-atom on the aldehyde fragment (Do = SR, OH), whereas the stabilization of the intermediate in an *intra*molecular hydroacylation occurs by the chelating coordination of the olefin (Do = olefin), which is connected to the aldehyde fragment. Coordination of an olefin leads to intermediate **B**, followed by insertion of the olefin into the Rh–H bond to give intermediate **C**. Finally, the irreversible reductive elimination step releases the ketone and leads back to the Rh(I) catalyst. Each of the complexes **A**–**C** competitively reacts to decarbonylated intermediates, where the CO ligand can reinsert back to form complexes **A**–**C**. Intermediate **D** can also insert the CO ligand into the other Rh–C bond to give acyl-Rh(III) intermediate **E**, which can in turn release the product after reductive elimination. Although the proposed catalytic cycle is a plausible explanation, coordination of all the bidentate phosphine ligand, chelating aldehyde and olefin may afford a hepta-coordinated Rh-complex. Thus, the real intermediates may be μ^2-ligand-Rh-complexes or η^6-Ph-bi-Rh-complexes as suggested by Suemune.[15]

As a part of their study in the chelation-assisted hydroacylation, Suemune and Tanaka recently described the π-facial selective intermolecular hydroacylation between salicylaldehyde (**1a**) and norbornenes (Scheme 2).[17] With norbornene (**2**), the *exo*-product **3a** was obtained exclusively, whereas the use of nor-



Scheme 2. Hydroacylation reported by Suemune.[17]

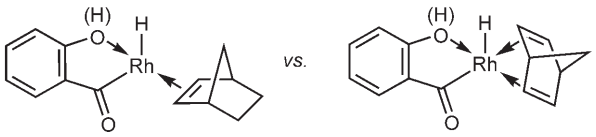


Figure 2. *Exo versus endo* coordination of nobornene and norbornadiene, respectively.

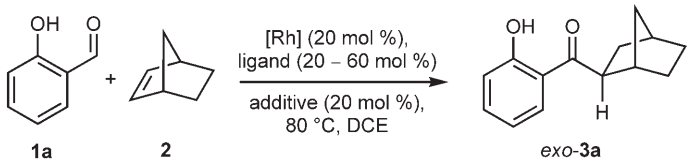
bornadiene (**4**) led to the *endo*-product **5a** preferentially.

Deuterium-labeling experiments suggest that the observed diastereoselectivity is a consequence of the different coordination modes of norbornene (**2**) and norbornadiene (**4**) (Figure 2). Norbornene coordinates with the least hindered face of the double bond (*exo*), while norbornadiene acts as a chelating ligand (*endo*).

Results and Discussion

The intermolecular hydroacylation between salicylaldehyde and norbornenes reported by Suemune and Tanaka prompted us to extend this reaction and develop an enantioselective protocol. First, we attempted to find a suitable catalyst precursor. Ideally, it should contain labile ligands coordinating to rhodium, which are exchangeable by phosphines. As test reactions we chose hydroacylations of norbornene (**2**) and norbornadiene (**4**) with salicylaldehyde (**1a**). The results are shown in Table 1 and Table 2, respectively.

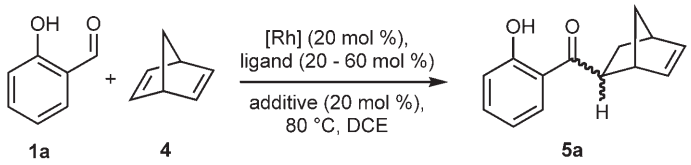
Table 1. Effect of rhodium sources and phosphine ligands in rhodium-catalyzed reactions between aldehyde **1a** and norbornene (**2**).



Entry	[Rh]	Ligand, amount [mol%]	Additive	*t* [h]	Conversion [%]	Yield [%]	*exo*/*endo*[a]
1[b]	$\{[RhCl(C_2H_4)_2]_2\}$	Ph_3P, 60	-	62	n.d.	40	98:2
2[b]	$\{[RhCl(C_2H_4)_2]_2\}$	dppf, 20	-	115	<5	n.d.	n.d.
3[b]	$\{[RhCl(C_2H_4)_2]_2\}$	dppf, 20	$AgClO_4$	115	22	n.d.	>95:5
4[b]	$\{[RhCl(C_2H_4)_2]_2\}$	*rac*-BINAP (**10**), 20	$AgClO_4$	37	<5	n.d.	n.d.
5	$[Rh(nbd)_2BF_4]$	Ph_3P, 60	-	115	100	95	97:3
6	$[Rh(nbd)_2BF_4]$	dppf, 20	-	115	15	n.d.	>95:5
7	$[Rh(acac)(C_2H_4)_2]$	dppf, 20	-	115	88	57	>99:1
8	$[Rh(acac)(C_2H_4)_2]$	S-Phos, 60	K_3PO_4	62	n.d.	34	>95:5

[a] Determined by ^1H NMR.
[b] Use of 10 mol% of $\{[RhCl(C_2H_4)_2]_2\}$.

Table 2. Effect of rhodium sources and phosphine ligands in rhodium-catalyzed reactions between aldehyde **1a** and norbornadiene (**4**).



Entry	[Rh]	Ligand, amount [mol%]	Additive	*t* [h]	Conversion [%]	Yield [%]	*exo*/*endo*[a]
1	$[Rh(nbd)_2BF_4]$	dppf, 20	K_3PO_4	70	100	65	77:23
2	$[Rh(acac)(C_2H_4)_2]$	dppf, 20	-	47	100	97	70:30
3	$[Rh(acac)(C_2H_4)_2]$	dppf, 20	K_3PO_4	70	100	50	85:15
4	$[Rh(acac)(C_2H_4)_2]$	PCy_3, 40	K_3PO_4	90	70	n.d.	50:50
5[b]	$[Rh(acac)(C_2H_4)_2]$	-	-	20	100	n.d.	54:46

[a] Determined by ^1H NMR.
[b] Use of 5 mol% of [Rh].

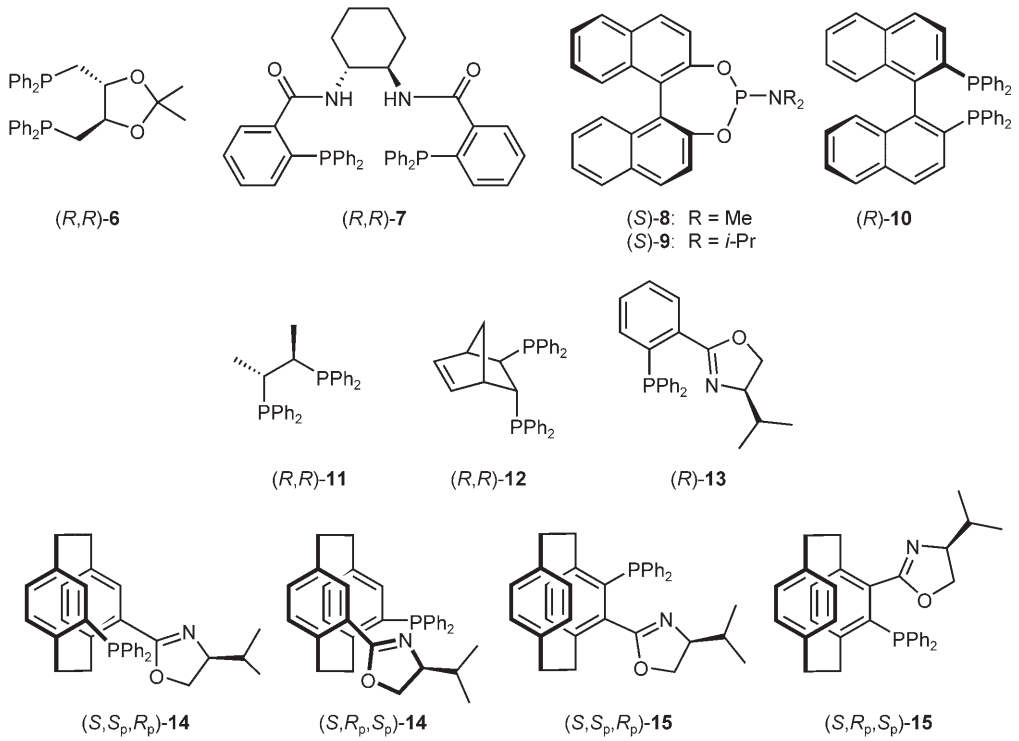


Figure 3. Chiral ligands for the asymmetric hydroacylation reaction.

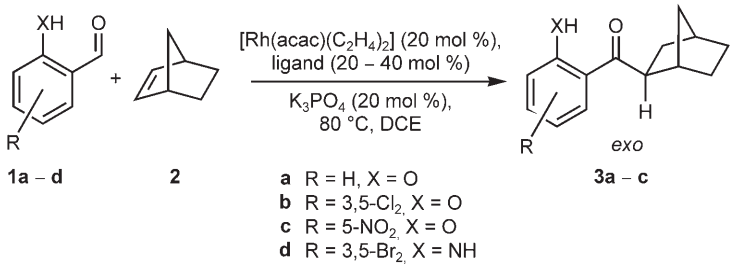
The rhodium catalyst (20 mol%), preformed from $\{[RhCl(C_2H_4)_2]_2\}$ and PPh_3, reacted well in 1,2-dichloroethane (DCE) at 80 °C to give norbornanyl ketone *exo*-**3a** with high diastereoselectivity in moderate yield (Table 1, entry 1). When a bidentate ligand such as 1,1′-bis-(diphenylphosphino)-ferrocene (dppf)[18] was used instead of PPh_3, the reaction did not proceed (entry 2), although the addition of $AgClO_4$ as an additive resulted in some conversion (entry 3).[19] *rac*-BINAP (**10**) inhibited the reaction completely, even in the presence of $AgClO_4$ (entry 4). $[Rh(nbd)_2BF_4]$ was also suitable as precatalyst in combination with PPh_3 (entry 5), but the bidentate ligand dppf inhibited the reaction (entry 6). In contrast, $[Rh(acac)(C_2H_4)_2]$ was quite effective in the presence of dppf, giving aryl norbornanyl ketone **3a** in good yield and with excellent diastereoselectivity (entry 7). Application of the monodentate, sterically demanding phosphine ligand S-Phos[20] was less effective (entry 8).

Suemune reported that the presence of inorganic bases accelerated the hydroacylation reaction, presumably as a result of a deprotonation of phenolic hydrogen.[15] Additionally, K_3PO_4 increased the *endo*-selectivity in the hydroacylation of norbornadiene.[17] Reaction of salicylaldehyde (**1a**) and norbornadiene (**4**) in the presence of K_3PO_4 (20 mol%) and the rhodium catalyst (20 mol%), formed *in situ* from $[Rh(nbd)_2BF_4]$ and dppf, furnished the corresponding ketone **5a** in good yield but as a 77:23 mixture of *exo*/*endo* diastereomers (Table 2, entry 1). $[Rh(acac)(C_2H_4)_2]$ and dppf were also effective, giving ketone **5a** in almost quantitative yield as a 70:30 mixture of diastereomers (entry 2). Performing the same reaction in the presence of K_3PO_4 led to a reduced yield but an increase in the diastereomeric ratio to 85:15 in favor of the *exo*-isomer, presumably due to an *exo*/*endo*-isomerization accelerated by the base (entry 3).[21] The use of an electron-rich monodentate phosphine, PCy_3, slowed down the reaction, which remained incomplete even after 90 h (entry 4). It is noteworthy that even the catalyst precursor $[Rh(acac)(C_2H_4)_2]$ (5 mol%) catalyzed the reaction very well in the absence of any phosphines and additives within 20 h, furnishing ketone **5a** as a 54:46 ratio of diastereomers (entry 5).

Altogether, $[Rh(acac)(C_2H_4)_2]$ has emerged as the most suitable rhodium source. Consequently, several catalyst systems, formed *in situ* from chiral phosphines and that rhodium source were tested for their ability to promote enantioselective intermolecular hydroacylation reactions (Figure 3).

With norbornene (**2**) as substrate, (+)-diop (**6**) was not a very effective ligand and product **3a** was isolated with only 11% *ee* and a 95:5 *dr* in 20% yield after 45 h (Table 3, entry 1). Trost's ligand **7** furnished the product in slightly higher yield and enantiomeric excess (34%, 20% *ee*), but the conversion was still low (entry 2). Application of the phosphoramidite ligand (*S*)-MonoPhos (**8**) gave *exo*-**3a** in higher yield

Table 3. Asymmetric intermolecular hydroacylation using norbornene (**2**) as substrate.



1a – d **2**

a R = H, X = O
b R = 3,5-Cl_2, X = O
c R = 5-NO_2, X = O
d R = 3,5-Br_2, X = NH

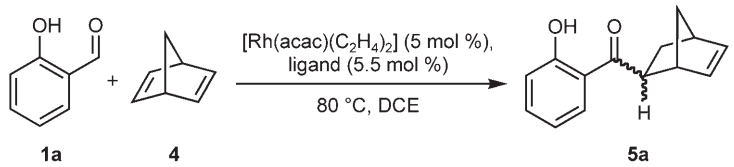
3a – c

Entry	Substrate	Ligand, amount [mol%]	*t* [h]	Conversion [%]	Yield [%]	*exo*/*endo*[a]	*ee* [%] (*exo*)[b]
1	**1a**	(*R*,*R*)-**6** (20)	45	n.d.	20	95:5	11 (−)
2	**1a**	(*R*,*R*)-**7** (20)	62	35	34	95:5	20 (−)
3	**1a**	(*S*)-**8** (40)	65	n.d.	50	98:2	18 (−)
4	**1a**	(*S*)-**9**, (40)	62	33	n.d.	98:2	3 (−)
5[c]	**1a**	(*S*)-**8** (40)	23	100	90	>99:1	0
6	**1b**	(*S*)-**8** (40)	23	100	70	>99:1	7 (−)
7	**1c**	(*S*)-**8** (40)	14	100	69	98:2	6 (−)
8	**1d**	(*S*)-**8** (40)	43	<5	n.d.	n.d.	n.d.

[a] Determined by ^{1}H NMR.
[b] The enantiomer ratios were determined by HPLC using a chiral stationary phase.
[c] $[Rh(cod)Cl]_2$ was used.

and with improved diastereoselectivity, but again with low enantioselectivity (entry 3). Surprisingly, the combination of $[Rh(acac)(C_2H_4)_2]$ and MonoPhos derivative (*S*)-**9** did not catalyze the reaction well (entry 4). The catalyst preformed from $[Rh(cod)Cl]_2$ and (*S*)-MonoPhos promoted the hydroacylation at a high rate, furnishing the product in 90% yield but as a racemate (entry 5). Reactions with aldehydes **1b–d** revealed the substrate scope of this catalyst system (Table 3, entries 6–8). Salicylaldehydes **1b** and **1c**

Table 4. Asymmeric intermolecular hydroacylation using norbornadiene (**4**) as substrate.



1a **4** **5a**

Entry	Ligand	Additive (20 mol%)	*t* [h]	Conversion [%]	Yield [%]	*exo*/*endo*[a]	*ee* [%] (*endo*)[b]
1	(*R*,*R*)-**7**	-	44	92	84	57:43	10 (+)
2	(*R*)-**10**	-	28	66	61	55:45	0
3	(*R*,*R*)-**11**	-	86	95	89	58:42	8 (+)
4	(*R*,*R*)-**12**	-	67	20	19	77:23	21 (+)
5[c,d]	(*R*)-**13**	K_3PO_4	19	100	77	46:54	19 (+)
6	(S,S_p,R_p)-**14**	-	17	100	98	54:46	7 (+)
7	(S,R_p,S_p)-**14**	-	19	100	99	56:44	9 (+)
8	(S,S_p,R_p)-**15**	-	47	31	31	38:62	15 (+)
9	(S,R_p,S_p)-**15**	-	46	58	54	50:50	6 (+)
10[c,e]	(*S*)-**8**	K_3PO_4	13	100	98	7:93	35 (+)
11[f]	(*S*)-**8**	K_3PO_4	17	100	93	5:95	37 (+)

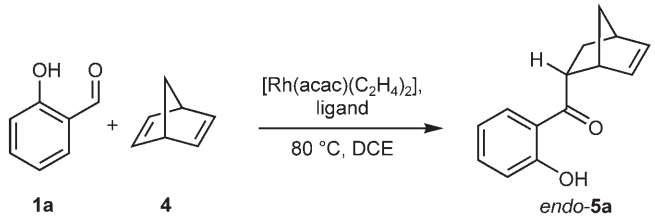
[a] Determined by ^{1}H NMR.
[b] The enantiomer ratios were determined by HPLC using a chiral stationary phase.
[c] Use of 20 mol% of $[Rh(acac)(C_2H_4)_2]$.
[d] Use of 20 mol% of the ligand.
[e] Use of 40 mol% of the ligand.
[f] $[Rh(nbd)_2BF_4]$ (20 mol%) and (*S*)-**8** (40 mol%) were used; reaction performed at room temperature.

were converted to the corresponding ketones with high diastereoselectivity, but the *ee* was low. Aminobenzaldehyde **1d** did not react under these conditions (entry 8).

Similarly, chiral phosphine ligands were tested in the reaction of norbornadiene (**4**) with salicylaldehyde (**1a**). In this case 5 mol% of the catalyst was sufficient to reach full conversion within 1–2 days in most cases. Complexes with Trost's ligand **7**, BINAP (**10**), Chiraphos (**11**), Norphos (**12**) and oxazolinylphosphine ligand **13** catalyzed the reaction well to furnish the hydroacylation product **5a** in ~1:1 ratios of *exo*/*endo* diastereomers (Table 4, entries 1–5). However, in some cases the conversion was still incomplete, even after 40 h. The [2.2]paracyclophane-based chiral ligands **14** and **15**[22] having a similar structure as **13**, were also applied. While both pseudo-*geminal* diastereomers (S,S_p,R_p)-**14** and (S,R_p,S_p)-**14** furnished the product in high yield (entries 6 and 7), both diastereomeric *ortho* ligands (S,S_p,R_p)-**15** and (S,R_p,R_p)-**15** slowed down the reaction, giving **5a** in lower yield (entries 8 and 9). Enantiomeric excesses remained low and below the *ee* obtained with **13**. When the monodentate phosphoramidite ligand (*S*)-**8** was used in the presence of K_3PO_4, *endo*-**5a** was obtained diastereoselectively and in high yield (98%, 7:93 *dr*) within 13 h (entry 10). Additionally, the enantiomeric excess of *endo*-**5a** was determined to be 35% *ee*. Use of 20 mol% of the catalyst formed *in situ* from [Rh(nbd)$_2$BF$_4$] and (*S*)-**8** at room temperature furnished ketone *endo*-**5a** with similar selectivities (5:95 *dr*, 37% *ee*, entry 11).

The screening result with chiral ligands **6**–**15** and in particular the promissing observations made in reactions with phosphoramidite **8** prompted us to examine the effect of monodentate phosphoramidite and phosphite ligands in more detail. With (*S*)-MonoPhos (**8**), the catalyst loading could be reduced to 1 mol% without significant loss of enantioselectivity. However, the diastereoselectivity dropped, presumably due to

Table 5. Hydroacylation reaction using monodentate phosphoramidite and phosphite ligands.



1a **4** *endo*-**5a**

Entry	[Rh] [mol%]	Ligand, amount [mol%]	Additive [20 mol%]	*t* [h]	Conversion [%]	Yield [%]	*exo*/*endo*[a]	*ee* [%] (*endo*)[b]
1	1	(*S*)-**8**, 2	K_3PO_4	18	100	95	35:65	33 (+)
2	1	(*S*)-**8**, 2	K_3PO_4	90	100	90	62:38	n.d.
3	5	(*S*)-**8**, 10	-	1	100	87	2:98	35 (+)
4[c]	20	(*S*)-**8**, 40	K_3PO_4	19	70	44	17:83	46 (+)
5	20	(S_a,R,R)-**16**, 40	K_3PO_4	20	100	81	57:43	6 (−)
6	20	(S_a,S,S)-**16**, 40	K_3PO_4	15	100	93	56:44	19 (+)
7	5	(*R*)-**21**, 10	-	2	100	99	3:97	13 (−)
8	5	(*R*)-**22**, 10	-	2	100	96	4:96	10 (+)
9	20	(*R*)-**17**, 40	K_3PO_4	5	100	96	45:55	32 (+)
10[d]	20	(*R*)-**17**, 40	K_3PO_4	19	95	73	14:86	41 (+)
11	5	(*R*)-**18**, 10	-	14	98	91	30:70	18 (+)
12	5	(*R*)-**19**, 10	-	39	66	59	26:74	10 (+)
13	5	(*R*)-**20**, 5.5	-	17	<5	n.d.	n.d.	n.d.
14	5	(*S*)-**27**, 10	-	0.5	100	96	5:95	39 (+)
15	5	(*S*)-**23**, 10	-	3.5	100	98	19:81	5 (+)
16	5	(*S,S*)-**24**, 10	-	1.2	100	99	3:97	13 (+)
17	5	(*S,R*)-**24**, 10	-	1.2	100	99	4:96	10 (−)
18	5	(*R,R*)-**25**, 10	-	4	95	95	48:52	13 (+) [34 (+)][e]
19	5	(*R,R*)-**26**, 10	-	1.5	96	93	1:99	44 (−)

[a] Determined by ^{1}H NMR.
[b] The enantiomer ratios were determined by HPLC using a chiral stationary phase.
[c] Reaction performed at room temperature.
[d] [Rh(nbd)$_2$BF$_4$] was used.
[e] *ee* of the *exo*-isomer, determined after hydrogenation to *exo*-**3a** by HPLC using a chiral stationary phase.

base-catalyzed isomerization, since the major product was *exo*-**5a** after 90 h under the same reaction conditions (Table 5, entries 1 and 2, see also Table 2, entries 2 and 3). Without K_3PO_4 the reaction was finished within less than 1 h using 5 mol% of catalyst, furnishing the *endo*-product in high yield with 35% *ee* and 98:2 *dr* (entry 3). Additionally, the reaction could be performed at room temperature producing the *endo*-isomer with 46% *ee* (entry 4). Consequently, several phosphoamidite and phosphite ligands with binaphthyl, taddol and tartrate backbones were synthesized and applied (Figure 4).[23]

Application of ligands (*S*,*R*,*R*)-**16** and (*S*,*S*,*S*)-**16**, which possess more steric bulk and additional stereocenters on the nitrogen substituents, catalyzed the reaction well but with low enantioinduction (Table 5, entries 5 and 6). Similar results were obtained using PipPhos [(*R*)-**21**] and MorfPhos [(*R*)-**22**] (entries 7 and 8). The effect of substituents in 3-position of the binaphthyl backbone was then studied. The 3,3′-dimethyl-substituted MonoPhos derivative (*R*)-**17** showed high activity, but the diastereoselectivity was low (entry 9). However, when the catalyst was derived from $[Rh(nbd)_2BF_4]$ and (*R*)-**17**, the diastereoselectivity was higher and *endo*-**3a** was isolated with 41% *ee* (entry 10). Although the opposite axial-chiral binaphthyl-backbone of (*R*)-**17** compared to (*S*)-**8** was used, the product was obtained with the same absolute configuration. A similar effect of reversed selectivity using BINAP and 3,3′-substituted BINAP derivatives was recently observed by Keay when these ligands were applied in Heck/Mizoroki reactions.[24] Phosphoramidites (*R*)-**18** and (*R*)-**19**, bearing aryl substituents on the binaphthyl backbone, were less active (entries 11 and 12), and (*R*)-**20**, bearing diphenylphosphines as additional coordination sites, was completely inactive (entry 13). Application of H_8-MonoPhos (*S*)-**27**, a partially hydrogenated derivative of **8**, in the hydroacylation reaction produced the ketone *endo*-**5a** within 30 min in high yield with 39% *ee* (entry 14), a slightly higher value than that obtained with MonoPhos (**8**). BINOL-derived phosphites **23** and **24** were also tested. They were as active and diastereoselective as their phosporamidite counterparts, but generated the product with lower enantioselectivity (5–13% *ee*, entries 15–17). In order to investigate the effect of the chiral backbone, ligands **25** and **26** were applied in the hydroacylation reaction. The TADDOL-derived phosphoramidite **25** was less active and non-selective, producing the product in a 1:1 ratio of diastereomers (entry 18). Interestingly, the *exo*-product was formed in higher *ee* than the *endo*-product (34% *vs.* 13% *ee*). Phosphoramidite **26**, however, furnished the product *endo*-**5a** in both excellent yield and diastereoselectivity with 44% *ee* (entry 19).

Next, several substituted salicylaldehydes were subjected to the hydroacylation reaction using (*S*)-MonoPhos [(*S*)-**8**] and $[Rh(acac)(C_2H_4)_2]$ as catalyst system (Table 6). Electron-poor salicylaldehydes **1b** und **1c** were transformed into the corresponding *endo*-ketones **5b** and **5c** within 30 min in high yields and diastereoselectivities, with moderate *ee*s (42% and 37% *ee*, respectively; entries 1 and 2). Interestingly, the minor *exo*-isomers were formed with significantly higher enantiomeric excesses, namely 72% and 74% *ee*, respectively. The reaction also proceeded at room temperature using $[Rh(nbd)_2BF_4]$, which produced *endo*-**5c** in high yield and with 40% *ee* (entry 3). In this case the minor isomer *exo*-**5c** was isolated with an excellent *ee* of 94%. Additionally, 2-aminobenzaldehyde **1d** could be used as substrate to furnish ketone *endo*-**5d** with 41% *ee* (entry 4). Electron-rich aromatic aldehydes **1e**–**1h** were diastereoselectively transformed into the corresponding *endo*-ketones **5e**–**5h** in high yields and moderate enantiomeric excesses of 11–54% (entries 5–8). 2-Pyridinecarboxaldehyde (**1i**) and 2-anisaldehyde (**1j**), however, did not react at all under these reaction conditions (entries 8 and 9).[25]

Besides norbornene (**2**) and norbornadiene (**4**), also 1,4-epoxy-1,4-dihydronaphthalene (**28**) reacted under these conditions to give the corresponding ketone **29**

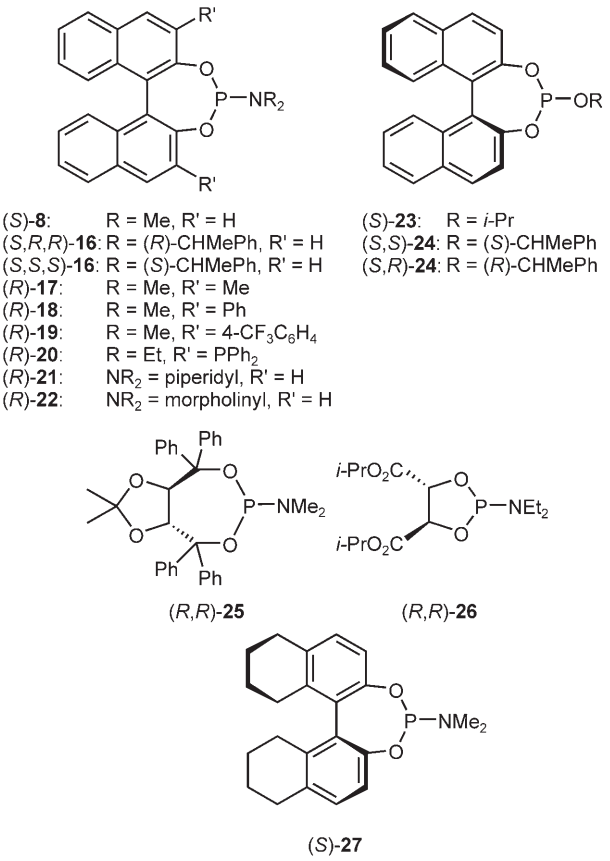
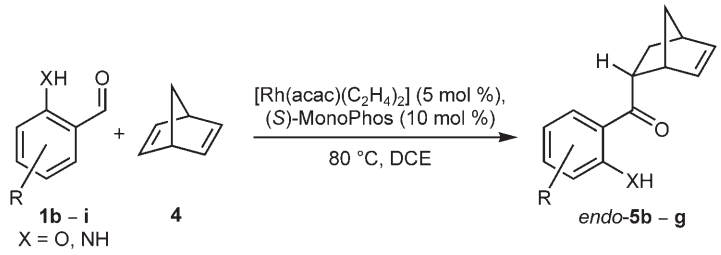
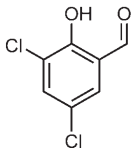
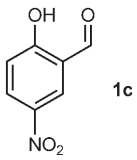
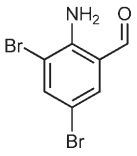
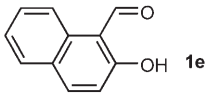
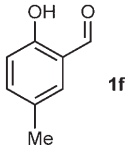
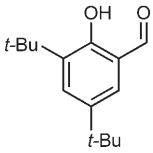
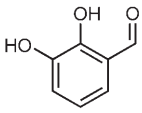
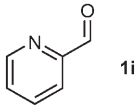
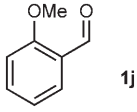


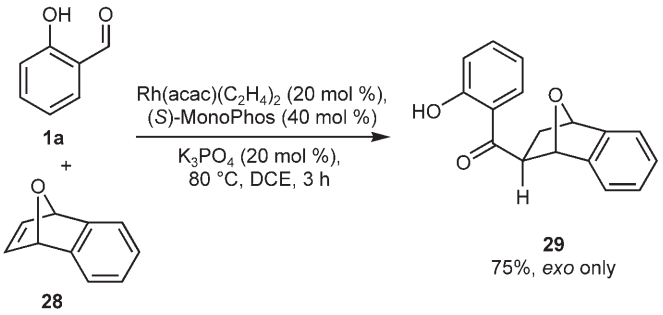
Figure 4. Monodentate phosphoramidite and phosphite ligands.

Table 6. Substrate scope of the *endo*-selective hydroacylation using (*S*)-MonoPhos [(*S*)-**8**].



Entry	Aldehyde	*t* [h]	Conversion [%]	Yield [%]	*exo*/*endo*[a]	*ee* [%] (*endo*)[b]	*ee* [%] (*exo*)[b]
1	 **1b**	0.5	100	97	9:91	42 (+)	72 (−)
2	 **1c**	0.5	100	81	5:95	37 (+)	74 (−)
3[c,d]	**1c**	13	100	97	9:91	40 (+)	94 (−)
4[d,e]	 **1d**	14	100	92	5:95	41 (+)	n.d.
5	 **1e**	0.7	100	99	3:97	32 (+)	n.d.
6	 **1f**	1	100	99	2:98	11 (+)	n.d.
7[f]	 **1g**	19	100	92	4:96	35 (+)	n.d.
8	 **1h**	1	100	98	5:95	54 (+)	n.d.
9[e]	 **1i**	39	< 5	n.d.	n.d.	n.d.	n.d.
10[e]	 **1j**	39	< 5	n.d.	n.d.	n.d.	n.d.

[a] Determined by ^{1}H NMR.
[b] The enantiomer ratios were determined by HPLC using a chiral stationary phase.
[c] [Rh(nbd)$_2$BF$_4$] (20 mol %) and (*S*)-MonoPhos (40 mol %) were used; reaction performed at room temperature.
[d] K_3PO_4 (20 mol %) added.
[e] Use of 20 mol % catalyst.
[f] [Rh(dpm)(cod)] (**30**, 5 mol %) was used.



Scheme 3. 4-Epoxy-1,4-dihydronaphthalene as substrate in the hydroacylation reaction.

in 75% yield. Unfortunately, in this case a racemate was obtained (Scheme 3).

Recently, Hayashi reported on a rhodium-catalyzed allylic alkylation, in which the enantioselectivity was greatly improved by modification of the acetylacetonato ligand of the precatalyst.[26] These results prompted us to investigate the effect of the β-diketonato ligand on the enantioselectivity (Table 7). Accordingly, the catalyst preformed from (*S*)-MonoPhos (**8**) and rhodium complex [Rh(dpm)(cod)] (**30**), bearing the bulky dipivaloylmethanato (dpm) ligand, furnished *endo*-**5a** in almost quantitative yield and enhanced the enantioselectivity [giving 47% *ee* compared to 35% *ee* using [Rh(acac)(C_2H_4)$_2$], entries 1 and 2]. The reaction proceeded even at room temperature. However, the enantioselectivity did not improve significantly (48% *ee*, entry 3). The complex [Rh(dbm)(cod)] (**31**), bearing a dibenzoylmethanato (dbm) ligand, was also effective in combination with (*S*)-**8**, furnishing *endo*-**5a** with 43% *ee* (entry 4). On the other hand, electron-withdrawing substituents on the acetylacetonato ligand as in [Rh(hfac)(cod)] (**32**, hfac = hexafluoroacetonato) slowed down the reaction and resulted in a reduced diastereomeric ratio as well as lower enantiomeric excess of the product *endo*-**5a** (entry 5).

Given that bidentate ligands led to ketone **5a** in favor of the *exo*-isomer (see Table 4) and the enantiomeric excesses of the *exo*-isomers are generally higher compared to the corresponding *endo*-isomers (see Table 5, entry 18 and Table 6, entries 1–3), the effect of bidentate phosphine ligands available from Solvias AG (shown in Figure 5) was examined. The Josiphos type ligands **33a–d** exhibited a low activity in the hydroacylation reaction of salicylaldehyde (**1a**) and norbornadiene (**4**), giving mixtures of diastereomers in low yields and with low enantiomeric excesses (Table 8, entries 1–4). Similarly, Solphos **34** was not able to induce good stereoselectivities, although ketone **5a** was isolated in high yield after 5 days (entry 5).

The application of Walphos ligands **35** in the hydroacylation reaction revealed a more active and highly *exo*-selective family of ligands. Thus, with **35a**, in which one coordinating phosphine is equipped with electron-withdrawing substituents, the *exo*-isomer of **5a** was formed almost exclusively in high yield and with 46% *ee* (entry 6). Hence the whole family of Walphos ligands was scrutinized (entries 7–13). Walphos **35b**, bearing two diphenylphosphino moieties, improved the enantioselectivity to 52% *ee* (entry 7), while the more electron-rich Walphos **35c** was less active and selective (entry 8). Application of the unsymmetrically substituted ligand **35d**, incorporating both an electron-rich and an electron-poor substituted phosphine, furnished *exo*-**5a** diastereoselectively with 35% *ee*. Although this catalyst system was also effective at room temperature, the enantioselectivity did not change significantly (32% *vs.* 35% *ee*, entries 9 and 10). Phosphine **35e** was somewhat less active and diastereoselective in the hydroacylation than **35a** and **35d**, but the *exo*-isomer was isolated with 63% *ee* (entry 11). Walphos **35f** and **35g** catalyzed the reaction with less selectivity and at a lower rate (entries 12 and 13). Interestingly, Walphos **35f** furnished *exo*-**5a** with 20% *ee* and opposite absolute configuration, presumably due to opposed electronic substitution on the phosphines (entry 12). Mandyphos ligands **36a** and **36b** showed only low activity and selectivity (entries 14 and 15), and Rophos **37** furnished both

Table 7. Dionato-olefin-rhodium complexes tested in the catalytic synthesis of ketone **5a** starting from aldehyde **1a** and diene **4**.[a]

Entry	[Rh]	*t* [h]	Conversion [%]	Yield [%]	*exo*/*endo*[b]	*ee* [%] (*endo*)[c]
1	[Rh(acac)(C_2H_4)$_2$]	1	100	87	2:98	35 (+)
2	[Rh(dpm)(cod)] (**30**)	1.5	100	99	<2:98	47 (+)
3[d]	[Rh(dpm)(cod)](**30**)	67	60	56	<2:98	48 (+)
4	[Rh(dbm)(cod)] (**31**)	1.5	100	99	2:98	43 (+)
5[d]	[Rh(hfac)(cod)](**32**)	22	57	54	7:93	29 (+)

[a] *Reaction conditions:* [Rh] (5 mol%), **8** (10 mol%), **4** (6.0 equivs.), **1a** (0.20 mmol, 1.0 equivs.), DCE, 80°C.
[b] Determined by ^{1}H NMR.
[c] The enantiomer ratios were determined by HPLC using a chiral stationary phase.
[d] Reaction performed at room temperature.

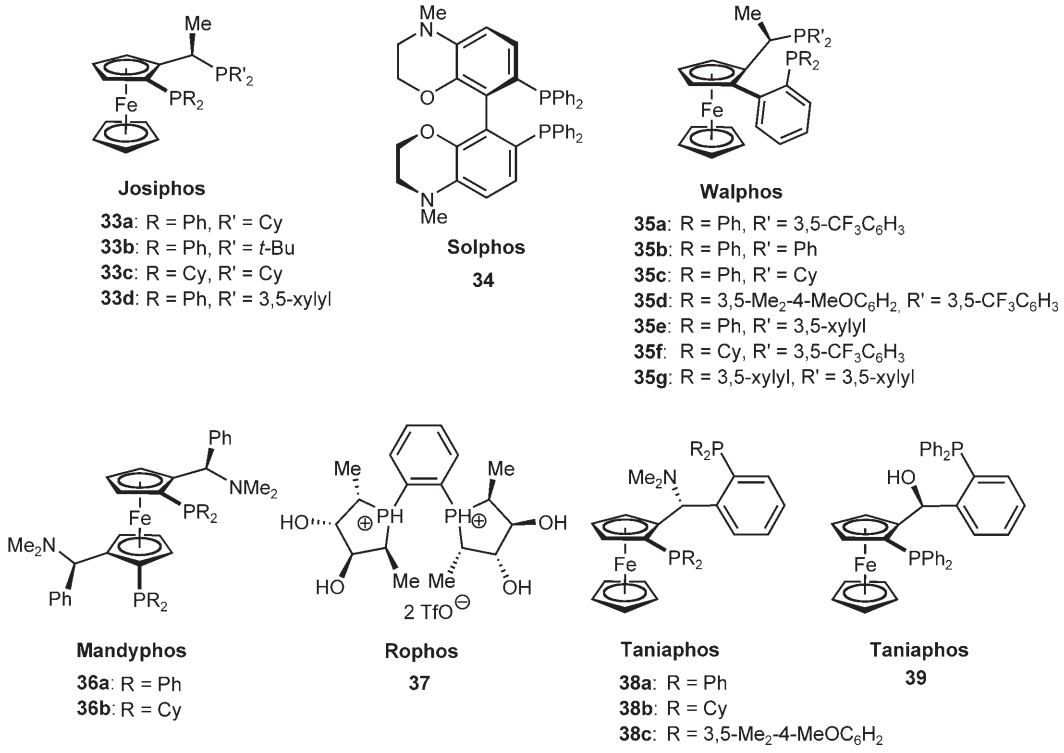


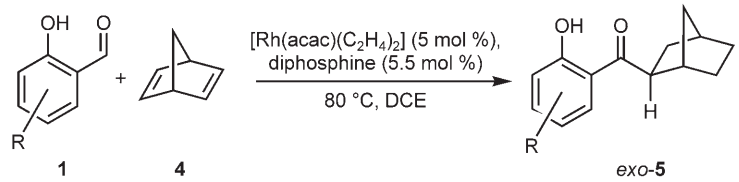
Figure 5. Solvias ligands applied in the hydroacylation reaction.

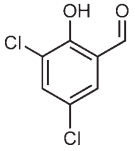
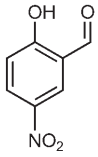
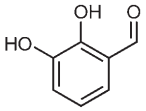
Table 8. Intermolecular hydroacylation reaction using Solvias ligands in the catalytic synthesis of ketone **5a** starting from aldehyde **1a** and diene **4**.[a]

Entry	Ligand	*t* [h]	Conversion [%]	Yield [%]	*exo*/*endo*[b]	*ee* [%] (*exo*)[c,d]	*ee* [%] (*endo*)[d]
1	**33**	14	39	22	58:42	3 (−)	4 (+)
2	**33**	14	24	23	60:40	n.d.	4 (+)
3	**33**	60	25	25	56:44	n.d.	4 (+)
4	**33**	60	29	29	59:41	n.d.	*rac*
5	**34**	116	100	93	66:34	n.d.	8 (+)
6	**35a**	22	100	90	>98:<2	46 (+)	n.d.
7	**35b**	21	82	77	94:6	52 (+)	25 (+)
8	**35c**	21	30	26	72:28	33 (+)	3 (−)
9	**35c**	1	100	99	98:2	35 (+)	n.d.
10[e]	**35d**	66	25	25	88:12	32 (+)	n.d.
11	**35e**	19	70	67	94:6	63 (+)	22 (+)
12	**35f**	43	44	35	70:30	20 (−)	8 (+)
13	**35g**	43	70	70	87:13	43 (+)	11 (+)
14	**36a**	43	39	33	87:13	18 (−)	9 (+)
15	**36b**	48	33	23	72:28	24 (−)	4 (+)
16[f]	**37**	24	25	23	57:43	*rac*	*rac*
17	**38a**	92	63	55	>98:<2	27 (−)	n.d.
18	**38b**	13	82	76	84:16	62 (−)	9 (+)
19	**38c**	18	100	99	98:2	48 (−)	n.d.
20	**39**	18	100	99	78:22	46 (−)	19 (+)

[a] *Reaction conditions:* [Rh(acac)(C_2H_4)$_2$], (5 mol%), ligand (5.5 mol%), **4** (6.0 equivs.), **1a** (0.20 mmol, 1.0 equiv), DCE, 80 °C.
[b] Determined by ^{1}H NMR.
[c] Ee determined after hydrogenation of *exo*-**5a** to *exo*-**3a** by HPLC using a chiral stationary phase.
[d] The enantiomer ratios were determined by HPLC using a chiral stationary phase.
[e] Reaction performed at room temperature.
[f] K_3PO_4 (20 mol%) was added.

Table 9. Substrate scope of the *exo*-selective hydroacylation reaction using Walphos and Taniaphos ligands.



Entry	Aldehyde	Ligand	*t* [h]	Yield [%]	*exo*/*endo*[a]	*ee* [%] (*exo*)[b]	*ee* [%] (*endo*)[b]
1	 **1b**	**35e**	5	78	59:41	*rac*	*rac*
2	**1b**	**38b**	0.7	92	59:41	*rac*	*rac*
3	**1b**	**35d**	0.5	94	96:4	80 (+)	9 (−)
4	 **1c**	**38b**	1.5	62	~50:50	11 (−)	7 (+)
5	**1c**	**35d**	0.5	95	>99:1	82 (+)	n.d.
6	 **1h**	**35e**	41	29	66:33	17 (+)	n.d.
7	**1h**	**35d**	1.0	99	99:1	55 (+)	n.d.

[a] Determined by ^{1}H NMR.
[b] The enantiomer ratios were determined by HPLC using a chiral stationary phase.

diastereomers of **5a** as racemates only (entry 16). Taniaphos ligands **38a–c** were similarly effective as the Walphos ligands. Thus, **38a** produced almost diastereomerically pure *exo*-**5** with 27% *ee*, but at a low rate (entry 17). Ligand **38b** provided the product with less diastereoselectivity, but with 62% *ee* of the *exo*-isomer (entry 18). Electron-rich Taniaphos **38c** was very active and selective, giving *exo*-**5a** almost diastereomerically pure with 48% *ee* (entry 19). Taniaphos **39**, containing an alcohol function with opposite configuration of the carbinol stereocenter compared to compounds **38a–c**, was as active as **38c** in the hydroacylation reaction, and the major *exo*-product was isolated with 46% *ee* and identical absolute configuration of the major enantiomer (entry 20).

In order to determine the generality of these findings, we decided to test substituted salicylaldehydes using Walphos **35e** and Taniaphos **38b**, respectively, as ligands, which induced the highest enantiomeric excess in the above screening. However, it turned out that in the reaction with 3,5-dichlorosalicylaldehyde (**1b**) the corresponding products were isolated as racemates (Table 9, entries 1 and 2). Similarly, the selectivities of both ligands **35e** and **38b** were low when 5-nitrosalicylaldehyde (**1c**) and 2,3-dihydroxybenzaldehyde (**1h**) were used as substrates (entries 4 and 6). On the other hand, when the most active Walphos ligand **35d** was applied using substituted salicylaldehydes the reaction was very fast and highly selective in all cases, giving the corresponding *exo*-**5b**, **5c**, **5h** with promising 55–82% *ee* (entries 3, 5 and 7).

Conclusions

We have developed two catalyst systems for the asymmetric intermolecular hydroacylation reaction of norbornenes with salicyladehydes, which both furnish the corresponding ketones with high diastereoselectivity. Use of 5 mol% of the catalyst was generally sufficient to give high yields of product within a few hours. Phophoramidite and phosphite ligands promoted the formation of *endo*-isomers with up to 54% *ee*. Noteworthy, the minor *exo*-isomers were formed with up to 94% *ee*. *Exo*-isomers with up to 82% *ee* were predominantly isolated when diphosphine ligands of the Walphos and Taniphos families were applied. Since the bidentate ligands occupy an additional coordination site in the coordination sphere of rhodium, we assume that norbornadiene is coordinated only with one double bond in the *exo*-like manner throughout the reaction, similar to the coordination of norbor-

nene depicted in Figure 2. Therefore, bidentate phosphine ligands favour the formation of *exo*-isomers in the hydroacylation reactions.[27] Further investigations to enhance the enantiomeric excess of both the *exo*- as well as the *endo*-isomer are currently subject of ongoing studies in our laboratories.

Experimental Section

Unless otherwise specified, all reagents were purchased from commercial suppliers and used without further purification. Toluene, diethyl ether and THF were distilled from sodium benzophenone ketyl radical and CH_2Cl_2 from CaH_2 under argon. All other solvents were reagent grade and used as received. All reactions were carried out under argon using standard Schlenk and vacuum line techniques. ^1H, ^{13}C, ^{31}P and ^{19}F NMR spectra were recorded on a Varian Mercury 300 spectrometer (300 MHz) and on a Varian Inova 400 spectrometer (400 MHz) in $CDCl_3$ using the solvent residual peak as internal standard and 85% H_3PO_4 or $CFCl_3$ as external standard, respectively. Chemical shifts are given in ppm and spin-spin coupling constants, *J*, are given in Hz. IR spectra were recorded on a Perkin–Elmer PE 1760 FT instrument as KBr pellets, neat or in $CHCl_3$ and are given in cm^{-1}. Mass spectra were recorded on a Varian MAT 212 or on a Finnigan MAT 95 spectrometer with EI ionization. Melting points were measured in open glass capillaries and are uncorrected. Optical rotations were determined on a Perkin–Elmer PE 241 polarimeter using HPLC-grade solvents. HPLC measurements were performed on a Gynkotek HPLC system (now Dionex) with autosampler Gina 50, UV-detector UVD 170S, degasser DG 503 and gradient pump M480G. Ligands **16**–**18** and **20**–**26** have been prepared using literature procedures.[23]

Representative Procedure (RP1) for the *endo*-Selective Hydroacylation Reaction

A 15-mL Schlenk tube was charged with $[Rh(acac)(C_2H_4)_2]$ (3.87 mg, 15.0 μmol, 5 mol%) and (*S*)-MonoPhos (**8**, 10.8 mg, 30.0 mmol, 10 mol%) in 1,2-dichloroethane (2 mL) and the solution was stirred for 40 min to give a pale yellow solution. Norbornadiene (**4**, 0.183 mL, 1.80 mmol, 6.0 equivs.) and salicylaldehyde (**1a**, 0.032 mL, 0.300 mmol, 1.0 equiv.) were added. The reaction vessel was sealed and heated to 80 °C for 60 min. The reaction mixture was allowed to cool to room temperature and the solvent was then removed under vacuum. The crude product (*dr* 98:2) was added to a silica gel column (1 × 15 cm) and was eluted with pentane/EtOAc 50:1, affording *endo*-**5a** as colourless oil, which crystallized on standing; yield: 57 mg (89%).

Representative Procedure (RP2) for the *exo*-Selective Hydroacylation Reaction

A Schlenk tube was charged with $[Rh(acac)(C_2H_4)_2]$ (2.58 mg, 10.0 μmol, 5 mol%) and Taniaphos **37b** (7.83 mg, 11.0 μmol, 5.5 mol%) in 1,2-dichloroethane (1 mL) and the solution was stirred for 30 min to give a pale brown solution. Norbornadiene (**4**, 0.122 mL, 1.20 mmol, 6.0 equivs.) and salicylaldehyde (21 μL, 0.20 mmol) were added. The reaction vessel was sealed and heated to 80 °C for 13 h. The reaction mixture was allowed to cool to room temperature and the solvent was then removed under vacuuzm. The crude product (*dr* 84:16) was added to a silica gel column and was eluted with pentane/EtOAc (100:1) to afford *exo*-**5a** as a colorless oil; yield: 33 mg (76%).

Representative Procedure (RP3) for the Hydrogenation of *exo*-5a to *exo*-3a

Ketone *exo*-**5a** (18 mg, 84 micromol, 1.0 equiv.) was charged into a vial and dissolved in MeOH (1 mL). Pd (5% on carbon, 1.79 mg, 0.840 micromol, 1 mol%) was added and the vial was purged with H_2 gas (3×) and pressurized with H_2 (1 bar). After stirring for 2 h at room temperature, the reaction mixture was filtered through a short plug of silica gel and eluted with MeOH (2 mL). The solvent was removed under vacuum to give analytically pure *exo*-**3a** as a colorless oil; yield: 18 mg (99%).

Representative Procedure (RP4) for the *exo*-Selective Hydroacylation Reaction using Norbonene

A 15-mL Schlenk tube was charged with $[Rh(acac)(C_2H_4)_2]$ (7.74 mg, 30.0 μmol, 20 mol%) and (*S*)-MonoPhos (**8**, 21.6 mg, 60 μmol, 40 mol%) in 1,2-dichloroethane (1 mL) and the solution was stirred for 30 min to give a pale yellow solution. Norbornene (**2**, 85 mg, 0.90 mmol, 6.0 equivs.) and salicylaldehyde (**1a**, 16 μL, 0.15 mmol, 1.0 equiv.) were added. The reaction vessel was sealed and heated to 80 °C for 65 h. The reaction mixture was allowed to cool to room temperature and the solvent was then removed under vacuum. The crude product (*dr* 98.2:1.8) was added to a silica gel column (1 × 15 cm) and was eluted with pentane/EtOAc 50:1, affording *exo*-**3a** as a colorless oil; yield: 16 mg (50%).

Three-Step Procedure for the Synthesis of (11b*R*)-*N*,*N*-Dimethyl-2,6-bis[4-(trifluoromethyl)phenyl]dinaphtho[2,1-*d*:1′,2′-*f*][1,3,2]dioxaphosphepin-4-amine [(*R*)-19]

*Step 1, (*R*)-2,2′-Bis(methoxymethoxy)-3,3′-bis(4-(trifluoromethyl)phenyl)-1,1′-binaphthyl* [(*R*)-**40**]: This compound was prepared by the procedure of Chong:[28] (*R*)-3,3′-dibromo-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl [600 mg, 1.13 mmol, 1.0 equiv.] and $[Pd(PPh_3)_4]$ (130 mg, 0.113 mmol, 10 mol%) were placed in a Schlenk tube and dissolved in DME (7.5 mL). *para*-(Trifluoromethyl)phenylboronic acid (749 mg, 3.95 mmol, 3.5 equivs.) and aqueous Na_2CO_3 solution (2 M, 2.93 mL, 5.86 mmol, 5.2 equivs.) were added. The resulting reaction mixture was stirred and heated to reflux for 10 h. The reaction mixture was allowed to cool to room temperature and the solvent was removed under vacuum. The residue was dissolved in CH_2Cl_2 (50 mL), washed with saturated aqueous NH_4Cl solution (30 mL), water (30 mL) and brine (30 mL). The organic layer was dried over $MgSO_4$ and concentrated. The crude product was subjected to column chromatography (silica gel, pentane/ethyl acetate 10:1), affording (*R*)-**40** as a colorless solid; yield: 639 mg (86%).

*Step 2, (*R*)-3,3′-Bis[4-(trifluoromethyl)phenyl]-1,1′-binaphthyl-2,2′-diol* [(*R*)-**41**]: This compound was prepared by the procedure of Chong:[28] (*R*)-2,2′-bis(methoxymethoxy)-3,3′-bis(4-(trifluoromethyl)phenyl)-1,1′-binaphthyl [(*R*)-**40**, 554 mg, 0.836 mmol, 1.0 equiv.] was dissolved in THF/MeOH (1:1 v/v, 20 mL). Amberlyst 15 resin (521 mg) was added and the reaction mixture was heated to reflux for 19 h, then cooled to room temperature. The resin was removed by filtration and washed with Et_2O (25 mL). The filtrate was concentrated under vacuum and the crude product was purified by column chromatography (silica gel, pentane/ethyl acetate 10:1), affording (*R*)-**41** as a colorless solid; yield: 493 mg (>99%).

*Step 3, (11b*R*)-N,N-Dimethyl-2,6-bis[4-(trifluoromethyl)-phenyl]dinaphtho[2,1-*d*:1′,2′-*f*][1,3,2]dioxaphosphepin-4-amine* [(*R*)-**19**]: Et_3N (0.340 mL, 247 mg, 2.44 mmol, 7.0 equivs.) and PCl_3 (30 μL, 48 mg, 0.348 mmol, 1.0 equiv.) were added to a Schlenk tube. At 0 °C, Me_2NH (2 M in THF, 0.174 mL, 0.348 mmol, 1.0 equiv.) was added and the suspension was stirred at room temperature for 3 h. A solution of (*R*)-3,3′-bis[4-(trifluoromethyl)phenyl]-1,1′-binaphthyl-2,2′-diol [(*R*)-**41**, 200 mg, 0.348 mmol, 1.0 equiv.] in THF (1 mL) was then added and the reaction mixture was stirred at room temperature for further 18 h. The ammonium salt was filtered off and washed with toluene. The filtrate was concentrated and the crude product was purified by column chromatography (neutral Al_2O_3, toluene), affording (*R*)-**19**; yield: 99 mg (44%).

Representative Procedure for the Synthesis of Catalyst Precursors 30–32

These compounds were prepared in analogy to the procedure for the preparation of [Rh(acac)(coe)$_2$] by Varshavsky.[29] To a solution of {[Rh(cod)Cl]$_2$} (200 mg, 0.509 mmol, 0.5 equivs.) in benzene (30 mL) was added sodium 2,2,6,6-tetramethyl-3,5-heptanedionate (210 mg, 1.02 mmol, 1.0 equiv.) and the reaction mixture was heated to reflux for 80 min. After cooling to room temperature, the solution was filtered and the filtrate was concentrated under vacuum. The residue was taken up in Et_2O (5 mL) and concentrated again to give (2,2,6,6-tetramethyl-3,5-heptanedionato)-(1,5-cyclooctadiene)rhodium(I) (**30**) as a yellow crystalline powder; yield: 358 mg (89%).

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