Letter

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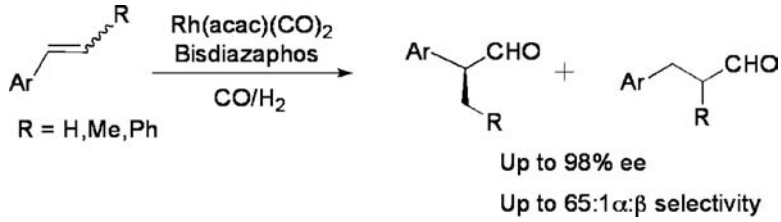

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Highly Enantioselective Hydroformylation of Aryl Alkenes with Diazaphospholane Ligands

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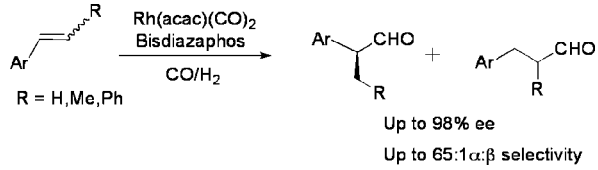
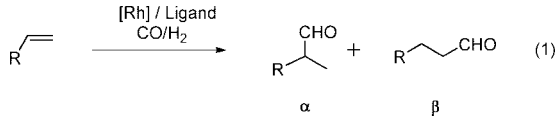
ABSTRACT



Asymmetric, rhodium-catalyzed hydroformylation of terminal and internal aryl alkenes with diazaphospholane ligands is reported. Under partially optimized reaction conditions, high enantioselectivity (>90% ee) and regioselectivities (up to 65:1 α:*β*) are obtained for most substrates. For terminal alkenes, both enantioselectivity and regioselectivity are proportional to the carbon monoxide partial pressure, but independent of hydrogen pressure. Hydroformylation of para-substituted styrene derivatives gives the highest regioselectivity for substrates bearing electron-withdrawing substituents. A Hammett analysis produces a positive linear correlation for regioselectivity.

Asymmetric hydroformylation (AHF) is an atom efficient method for synthesizing optically active aldehydes from simple alkenes[1] (eq 1). Such aldehydes are versatile intermediates for pharmaceuticals and agrochemicals.[2] Aryl alkenes are important substrates for AHF because oxidation of the resulting aldehyde to 2-arylpropionic



(1)

acids yields pharmacologically active, anti-inflammatory analgesics such as ibuprofen, ketoprofen, and naproxen. However, even for styrene, only a handful of catalyst systems are capable of producing useful enantioselectivities (>90% ee).[3]

Highly enantioselective styrene hydroformylation was first reported by Stille,[4] using platinum complexes of BPPM (**1**) as the catalyst (Figure 1). However, in situ conversion of the aldehydes to the corresponding acetals was required to achieve high enantioselectivity. Whiteker and co-workers at Union Carbide reported the first highly enantioselective hydroformylation under rhodium catalysis.[5] Using bisphosphite ligand (*R*,*R*)-Chiraphite, up to 90% ee was obtained for styrene. In a major breakthrough in enantioselective hydroformylation, Takaya and co-workers reported 94% ee for styrene using phosphine−phosphite ligand (*R*,*S*)-BINAPHOS (**2**).[6] Since then, only a handful of chiral ligands have been successfully applied to AHF. Among the most effective are (*S*,*S*)-Kelliphite[7] and (*S*,*S*)-ESPHOS,[8] which give high enantioselectivity for vinyl

(1) Claver, C.; van Leeuwen, P. W. N. M. *Rhodium Catalyzed Hydroformylation*; Kluwer Academic Publishers: Dordrecht, The Netherlands, 2000.

(2) Botteghi, C.; Paganelli, S.; Marchetti, M. *Chirality* **1991**, *3*, 355–369.

(3) Reviews: (a) Agbossou, F.; Carpentier, J.-F.; Mortreux, A. *Chem. Rev.* **1995**, *95*, 2485–2506. (b) Breit, B.; Seiche, W. *Synthesis* **2000**, 1–36. (c) Klosin, J.; Landis, C. R. *Acc. Chem. Res.* **2007**, *40*, 1251–1259.

(4) Stille, J. K.; Su, H.; Brechot, P.; Parrinello, G.; Hegedus, L. S. *Organometallics* **1991**, *10*, 1183–1189.

(5) Whiteker, G. T.; Babin, J. E., WO9393839, 1993.

(6) Sakai, N.; Mano, S.; Nozaki, K.; Takaya, H. *J. Am. Chem. Soc.* **1993**, *115*, 7033–7034.

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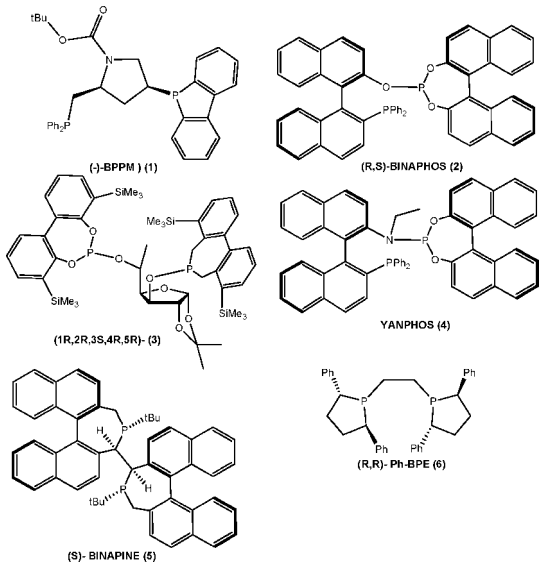

Figure 1. Prominent ligands for AHF of aryl alkenes.

acetate and allyl cyanide, respectively, the sugar-based bisphosphite ligand (**3**) developed by Claver and co-workers,[9] which yields 93% ee for styrene, and phosphine−phosphoramidite ligand YanPhos (**4**),[10] developed by Zhang and co-workers, which gives 98% ee for styrene. Despite the high enantioselectivity observed with these ligands, the regioselectivities are modest (<15:1 α:β), and the reactions are slow (20−50 catalytic turnovers per hour).

Recently, we[11] reported the first successful application of chiral bisphosphine ligands, diazaphospholanes, to AHF.[12] Of these ligands, (*S*,*S*,*S*)-bisdiazaphos (**7**) is particularly active and selective (87% ee for allyl cyanide, 89% ee for styrene, 97% ee for vinyl acetate, up to 9000 turnovers per hour with styrene). Subsequently, Klosin and co-workers[13] at Dow Chemical Company reported successful AHF using bisphosphine ligands (*R*,*R*)-Binaphine (**5**) and (*R*,*R*)-Ph-BPE (**6**), which both give excellent enantioselectivity (94% ee).

Although several chiral ligands produce high enantioselectivity in AHF of a few simple alkenes, there are few reports of successful AHF applied to more diverse alkenes. AHF of internal alkenes is particularly challenging due to their lower reactivity compared to terminal alkenes. To date, only BINAPHOS exhibits high enantioselectivity for the AHF of both terminal and internal alkenes.[14] However, poor regioselectivity and low catalyst activity limit the synthetic utility of this ligand. The high activity and selectivity obtained with 3,4-diazaphospholane ligands in AHF prompted us to examine these ligands in AHF of other challenging substrates. In this contribution, we report the application of three diazaphospholane ligands (Figure 2)[15] to the AHF of terminal and internal aryl alkenes.

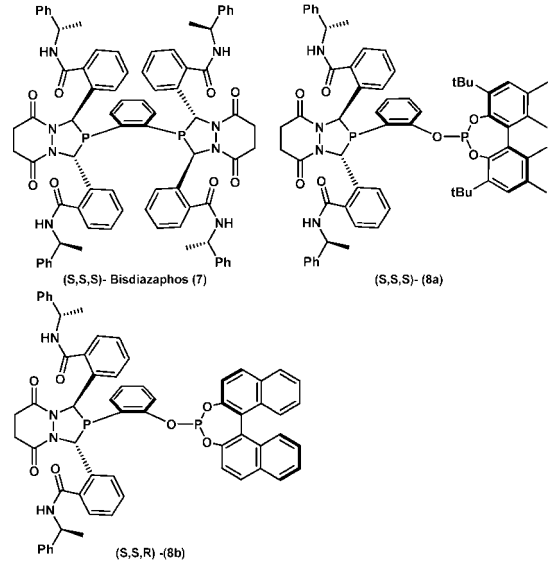

Figure 2. Chiral diazaphospholane ligands screened in this study.

An initial screen of chiral ligands **7**, **8a**, and **8b** in AHF under a standard set of conditions was performed (80 °C, substrate:catalyst 1:0.002 = 500, 150 psi of 1:1 CO:H_2 pressure, L:Rh = 1.2, toluene solvent) for a variety of aryl alkene substrates. In general, the chemoselectivities are excellent; no hydrogenation products were detected by ^{1}H NMR. For each alkene examined, the α aldehyde constitutes the major regioisomer. Hydroformylation of terminal alkenes generally is fast with complete conversion in most cases. AHF of internal alkenes is slower, but selectively produces internal aldehydes, only. Under screening conditions, bisphosphine ligand **7** provides good to excellent enantioselectivities (80−93% ee) and regioselectivity (4:1 to 20:1 α:β) for both terminal and internal alkenes (Table 1). Conversely, phosphine−phosphite ligands **8a** and **8b** give only modest enantio- and regioselectivities. (See the Supporting Information for complete screening results.)

Previously we observed[11] that AHF of styrene proceeded with improved enantioslectivity and regioselectivity at lower temperature and higher syngas pressure: at 60 °C and 500 psi (1:1 CO:H_2), selectivities up to 89% ee and 17:1 α:β are obtained. To optimize reaction conditions, we examined the independent effect of CO and H_2 pressures and found that

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(9) Dieguez, M.; Pamies, O.; Ruiz, A.; Claver, C. *New J. Chem.* **2002**, *26*, 827–833.
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(12) A selection of these ligands are available from Sigma Aldrich.
(13) Axtell, A. T.; Klosin, J.; Abboud, K. A. *Organometallics.* **2006**, *25*, 5003–5009.
(14) (a) Tanaka, R.; Nakano, K.; Nozaki, K. *J. Org. Chem.* **2007**, *72*, 8671–8676. (b) Sakai, N.; Nozaki, K.; Takaya, H. *J. Chem. Soc., Chem. Commun.* **1994**, 395–396. (c) Nozaki, K.; Li, W.; Horiuchi, T.; Takaya, H. *Tetrahedron Lett.* **1997**, *38*, 4611–4614. (d) Nanno, T.; Sakai, N.; Nozaki, K.; Takaya, H. *Tetrahedron: Asymmetry* **1995**, *6*, 57. (e) Horiuchi, T.; Ohta, T.; Shirakawa, E.; Nozaki, K.; Takaya, H. *Tetrahedron* **1997**, *53*, 7795–7804.
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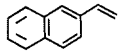
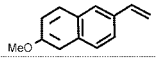
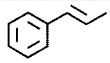
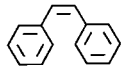
Table 1. Initial Screening Results for the Asymmetric Hydroformylation of Aryl Alkenes with Ligand **7**[e]

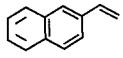
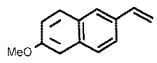
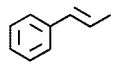
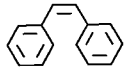
entry	alkene	Time (h)	TON[a]	α:β[a]	% ee
1[b]		4	500	6	81(R)
2[c]		4	500	12	93(R)
3[c]		4	500	6	83(R)
4[b,d]		12	287	20	18(R),67(nd)
5[b,d]		12	340	4	62(R),50(nd)
6[c]		12	450	---	84(R)
7[b]		12	383	20	81(R)

[a] Determined via ^{1}H NMR. [b] Determined via chiral GC. [c] Determined by converting the aldehdye to the corresponding alcohol with $NaBH_4$ followed by chiral SFC analysis. [d] Percent ee is shown as (% α,% β). Absolute stereochemistry was determined by comparing the sign of the optical rotation with the literature values. [e] All reactions run at 80 °C, 150 psia syngas, [alkene] = 1 M, [Rh] = 0.002 M,

hydroformylation of styrene at 40 °C with P_{CO} = 120 psi and P_{H_2} = 40 psi with ligand **7** resulted in 94% ee and 64:1 α:β ratio (Table 2 entry 1). Varying the hydrogen pressure had little effect on either percent ee or α:β. Apparently, hydroformylation selectivity is much more sensitive to CO partial pressure than H_2 partial pressure. Hydroformylation under these conditions effected increased selectivity with phosphine−phosphite ligands **8a** and **8b**: 90% ee is obtained for styrene with ligand **8b** (Table 2 entry 3). Nozaki and co-workers previously have reported modestly reduced enantio- and regioselectivity for styrene with BINAPHOS at 1 atm of syngas pressure.[16]

Application of optimized conditions to the hydroformylation of other terminal aryl alkenes results in significant selectivity gains. Notably, hydroformylation of 2-vinyl naphthalene with ligand **7** proceeds with *97% ee and no linear isomer*, as detected by ^{1}H NMR (Table 2 entry 5). Naproxen precursor 6-methoxy-2-vinyl naphthalene yields similar results: 96% ee and no detectable linear isomer (Table 2 entry 8). The optimized reaction conditions result in substantially increased enantioselectivity for AHF of other aryl alkenes with ligands **8a** and **8b**. Ligand **8a** provides nearly complete regioselectivity for both substituted and unsubstituted vinyl naphthalenes (Table 2 entries 7 and 10), while modest to good enantioselectivities (64−84% ee) were obtained with ligand **8b** (see the Supporting Information, Table 2).

Table 2. Optimized Results for the Asymmetric Hydroformylation of Vinyl Arenes with Ligands **7**, **8a**, and **8b**[g]

entry	alkene	ligand	% convn/TON	temp (°C)	P_{CO}/P_{H_2}[b]	time (h)	α:β[c]	% ee
1[c]		**7**	40/200	40	120/40	4	64	94(R)
2		**7**	96/480	40	120/40	8	55	93(R)
3		**8b**	20/100	40	120/40	4	20	90(S)
4		**8b**	40/200	40	120/40	8	21	87(S)
5		**7**	42/210	40	120/40	4	>51[a]	97(R)
6		**7**	100/500	40	120/40	8	51	94(R)
7		**8a**	2/11	40	120/40	4	>51[a]	64(R)
8[d]		**7**	45/225	40	120/40	4	>50[a]	96(R)
9		**7**	100/500	40	120/40	8	50	96(R)
10		**8a**	11/53	40	120/40	4	>50[a]	65(R)
11[c,f]		**8a**	7/35	40	75/75	12	14	86(R),55(nd)
12		**8a**	6/30	40	75/75	24	15	55(R),rac
13[e,f]		**7**	13/65	40	75/75	12	10	92(R),94(nd)
14		**7**	37/185	40	75/75	24	11	92(R),94(nd)
15[d]		**7**	20/100	40	35/35	12	---	93(R)
16		**7**	67/355	40	35/35	24	---	93(R)
16		**7**	22/112	40	75/75	12	20	83(R)

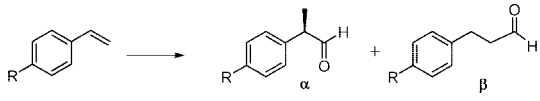
[a] No β-aldehyde was detected by ^{1}H NMR. [b] Pressure measured in psia. [c] Percent ee was determined via chiral GC. [d] Percent ee was determined by converting the aldehdye to the corresponding alcohol with $NaBH_4$ followed by chiral SFC analysis. [e] Determined via ^{1}H NMR. Absolute stereochemistry was determined by comparing the sign of the optical rotation with the literature values. [f] Percent ee is shown as (% α,% β). [g] Conditions: [alkene]= 1 M, [Rh]= 0.002 M, [ligand] = 0.0024 M..

In contrast with terminal aryl alkenes, the regio- and enantioselectivity for AHF of internal alkenes are largely independent of total syngas pressure. In some cases modest increases in enantioselectivity were achieved by lowering the reaction temperature, albeit with reduced regioselectivity. Hydroformylation of *trans*-β-methylstyrene with ligand **8a** at 40 °C gives the corresponding α-aldehyde, a precursor of antitussive butethamate,[2] in 86% ee and 14:1 α:β (Table 2, entry 11). For *cis*-β-methylstyrene, ligand **7** gives high ee (91%) and good regioselectivity (10:1 α:β). Excellent enantioselectivity (93% ee) was obtained for *cis*-stilbene with ligand **7**. In this case, reduced syngas pressure accelerates AHF relative to cis−trans isomerization of stilbene: *trans*-stilbene reacts slowly in AHF. Selectivities for AHF of indene were essentially identical at high and low temperatures.

Because α-aryl aldehydes are susceptible to racemization, we have examined the influence of extended reaction times for some ligand/substrate combinations which gives >90% ee. With ligand **7**, prolonged reactions do not result in significant erosion of percent ee (Table 2, entries 2, 6, 9, 14, and 16). As has been reported for phosphine−phosphite ligands such as BINAPHOS, ligands **8a** and **8b** at prolonged reaction times result in lowered ee values (Table 2, entries 4 and 12). In comparing diazaphospholanes with other ligands (see the Supporting Information, Table 3), we find that diazaphospholanes yield similar or superior selectivities to those previously reported for AHF of aryl alkenes.[16]

The influence of substrate electronics on selectivity was examined for AHF of para-substituted styrenes with ligand **7**. The results are shown in Table 3.

Table 3. Hydroformylation of Para-Substituted Styrenes with Ligand **7**[a]



entry	R	α:β	ee (%)[b]
1	OMe	20	70
2	Me	31	89
3	H	33	90
4	F	36	83
5	Cl	54	77
6	CF_3	65	80

[a] Reaction conditions; substrate:catalyst = 200:1, 4 0 °C, 150 psia 1:1 CO:H_2, 100% convn was achieved for each substrate in 3 h. [b] Determined by chiral GC.

In general, AHF of para-substituted styrenes provides good enantioselectivity (77% to 90% ee) and high regioselectivities (20−65:1). Branched isomer selectivity systematically increases with more electron-withdrawing substituents; the Hammett plot of log (α:β) vs σ_p (Figure 3) is linear with a

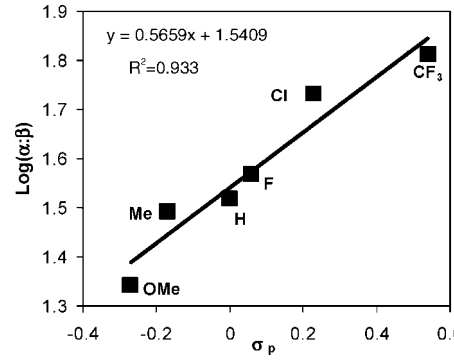


Figure 3. Hammett plot for the asymmetric hydroformylation of para-substituted styrenes with ligand **7**.

positive slope ($\rho = +0.56$, $R^2 = 0.93$). The positive slope indicates negative charge buildup in the regioselectivity-determining transition state. Stabilization of this charge via delocalization onto the aryl ring has previously been posed to explain the greater preference for branched aldehyde in the hydroformylation of styrene versus simple alkyl alkenes.[17] Interestingly, there is no obvious correlation of enantioselectivity with Hammett parameters.

In summary, we have demonstrated useful selectivity and activity for the AHF of both terminal and internal aryl alkenes using rhodium catalysts and diazaphospholane ligands. For terminal alkenes, strong correlation between carbon monoxide pressure and enantio- and regioselectivity is found, with higher CO pressure yielding higher selectivity. Applications of these diazaphospholane ligands to AHF of diverse, nonaryl alkenes are underway.

Acknowledgment. We would like to thank Jerzy Klosin, Susan Freed, and Greg Whiteker of Dow Chemical for their generous donation of $Rh(acac)(CO)_2$ and assistance in resolution of chiral ligands. We are also grateful Prof. Tehshik Yoon and co-workers for access to SCF instrumentation.

Supporting Information Available: Complete asymmetric hydroformylation results (optimized and nonoptimized) for each diazaphospholane ligand, detailed experimental procedures, and conditions for the determination of enantiomeric excess. This material is available free of charge via the Internet at http://pubs.acs.org.

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