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Highly Selective Asymmetric Rh-Catalyzed Hydroformylation of Heterocyclic Olefins

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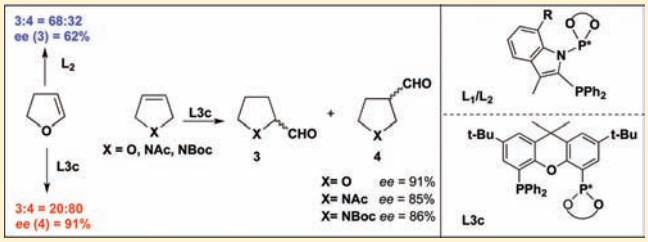
Supporting Information

ABSTRACT: A small family of new chiral hybrid, diphosphorus ligands, consisting of phosphine-phosphoramidites **L1** and **L2** and phosphine-phosphonites **L3a−c**, was synthesized for the application in Rh-catalyzed asymmetric hydroformylation of heterocyclic olefins. High-pressure (HP)-NMR and HP-IR spectroscopy under 5−10 bar of syngas has been employed to characterize the corresponding catalyst resting state with each ligand. Indole-based ligands **L1** and **L2** led to selective *ea* coordination, while the xanthene derived system **L3c** gave predominant *ee* coordination. Application of the small bite-angle ligands **L1** and **L2** in the highly selective asymmetric hydroformylation (AHF) of the challenging substrate 2,3-dihydrofuran (**1**) yielded the 2-carbaldehyde (**3**) as the major regioisomer in up to 68% yield (with ligand **L2**) along with good ee's of up to 62%. This is the first example in which the asymmetric hydroformylation of **1** is both regio- and enantioselective for isomer **3**. Interestingly, use of ligand **L3c** in the same reaction completely changed the regioselectivity to 3-carbaldehyde (**4**) with a remarkably high enantioselectivity of 91%. Ligand **L3c** also performs very well in the Rh-catalyzed asymmetric hydroformylation of other heterocyclic olefins. Highly enantioselective conversion of the notoriously difficult substrate 2,5-dihydrofuran (**2**) is achieved using the same catalyst, with up to 91% ee, concomitant with complete regioselectivity to the 3-carbaldehyde product (**4**) under mild reaction conditions. Interestingly, the Rh-catalyst derived from **L3c** is thus able to produce both enantiomers of 3-carbaldehyde **4**, simply by changing the substrate from **1** to **2**. Furthermore, 85% ee was obtained in the hydroformylation of *N*-acetyl-3-pyrroline (**5**) with exceptionally high regioselectivities for 3-carbaldehyde **8Ac** (>99%). Similarly, an ee of 86% for derivative **8Boc** was accomplished using the same catalyst system in the AHF of *N*-(*tert*-butoxycarbonyl)-3-pyrroline (**6**). These results represent the highest ee's reported to date in the AHF of dihydrofurans (**1**, **2**) and 3-pyrrolines (**5**, **6**).



INTRODUCTION

Asymmetric hydroformylation (AHF) is well-recognized as a powerful synthetic tool to construct a large variety of enantiomerically enriched compounds.[1−5] However, rather than chiral diphosphines,[4] diphosphonites,[6] or diphosphites,[7] the most promising ligands for asymmetric hydroformylation are hybrid systems, such as phosphine-phosphite,[8] phosphine-phosphinite,[9] and phosphine-phosphoramidite ligands.[10] To date, acyclic olefins and vinyl aromatics have been extensively explored in the AHF with both Rh[11] and Pt,[12] whereas heterocyclic olefins, such as dihydrofurans and pyrrolines, are scarcely reported, although the corresponding aldehydes are important building blocks in organic synthesis and medicinal chemistry.[13] The carbaldehydes of dihydrofuran and pyrrolines are known to be very important precursors for the syntheses of versatile pharmaceuticals, natural products, and amino-acids.[4,14] One example is the 4-formyl derivative of cholest-4-ene, which is a valuable intermediate of potent drugs for the treatment of prostatic cancer and other androgen-dependent diseases. A reliable methodology for the efficient asymmetric hydroformylation of highly functionalized and thus sterically hindered heterocyclic olefins requires a catalyst system with high functional group tolerance. Furthermore, the desired enantioselection should not jeopardize the required chemo- and regioselectivity, e.g., isomerization is a potential side reaction for these compounds,[15] which can have a profound influence on the overall reaction efficiency and in turn lead to detrimental loss of enantioselectivity (Scheme 1).

Suitable heterocyclic model substrates to establish activity and selectivity of specific catalyst systems are 2,3-dihydrofuran (**1**) and the corresponding 2,5-isomer (**2**). Under ideal nonisomerizing conditions the former may give a mixture of the 2- and 3-carbaldehyde products **3** and **4**, via the intermediacy of complexes **X1** and **X2**, respectively, whereas the 2,5-dihydrofuran (**2**) substrate should only generate product **4**. Formation of intermediate complex **X2** occurs under thermodynamic control, but CO insertion into the isomeric complex **X1** is faster than for **X2**.[15b] The group of van Leeuwen investigated the enantioselective hydroformylation of

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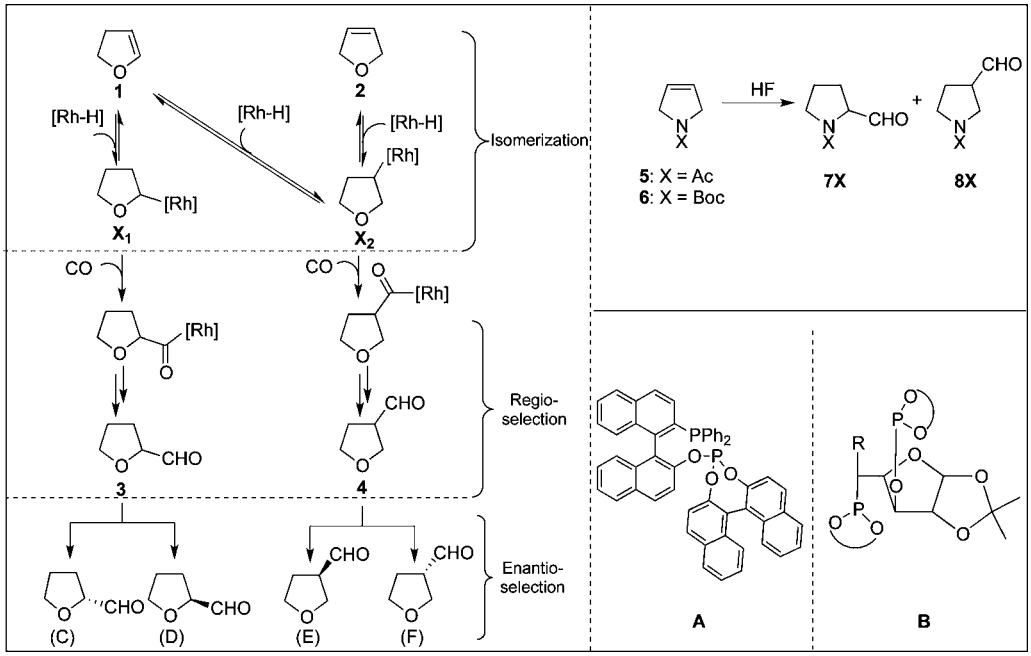
Scheme 1. Proposed Isomerization and Selectivity in the Hydroformylation of Dihydrofurans and Pyrrolines and (right below) Ligands A and B Previously Employed in the Asymmetric Hydroformylation of Substrates 1, 2, 5, and 6



substrate **2** using various chiral diphosphine ligands, but only 14% enantiomeric excess (ee) could be achieved for product **4**.[13] Application of phosphine-phosphite ligand **A** (Scheme 1) resulted in a mixture of regioisomers **3** (2-carbaldehyde) and **4** (3-carbaldehyde) from the AHF of substrate **1**, with up to 38% ee for isomer **4**, while substrate **2** mainly generated regioisomer **4** with a maximum ee of 68% (Table 1).[16] Better enantioselection in the conversion of **1** (ee up to 75%, *R*) and **2** (ee up to 74%, *S*) was achieved using sugar-based diphosphite ligands (see Table 1 for an overview).[17] Notably, selective asymmetric and highly regioselective hydroformylation to obtain regioisomer **3** has so far been elusive! The related nitrogen-substituted 3-pyrrolines **5** and **6**, generating the corresponding 2- and 3-carbaldehyde derivatives **7X** and **8X**, are equally ill-explored as substrates for asymmetric hydroformylation (Table 1).[18]

Table 1. Overview of Literature Reported Selectivities in the AHF of Heterocyclic Olefins

selectivity	ligand **A**	ligand **B**	substrate
4:**3**	50:50	76:24	**1**
4-ee%	38	75	
3-ee%	–	–	
4:**3**	97:3	99:1	**2**
4-ee%	68	74	
3-ee%	–	–	
8-ee%	66	71	**5**
8-ee%	73	–	**6**

A careful comparison of the various C_1-symmetric ligands applied in the hydroformylation of **1** revealed that large bite-angle ligands, such as **B**[19] (with bis-equatorial, ee, coordination), produced **4** as a major isomer, whereas the smaller bite-angle ligand **A** (ea coordination)[20] gave a regio-isomeric mixture (**3**:**4** = 50:50),[16] but none of the ligands meet all selectivity requirements. Therefore, the development of highly efficient catalytic systems that successfully addresses the multiple challenges (as depicted in Scheme 1) posed by the asymmetric hydroformylation of five-membered heterocyclic olefins would represent a significant advancement.

Since subtle changes in the ligand bite angle can significantly influence the overall catalytic performance,[21] we decided to tune the synthetically versatile indole and xanthene backbones to create both small (**L1**, **L2**) and wide (**L3a**–**c**) bite-angle hybrid ligands (see Scheme 2). It was anticipated that the distinctly different coordination modes of these hybrid ligands might infer hitherto inaccessible chemo-, regio-, and stereoselectivities in the AHF of these challenging heterocyclic olefins.

We herein describe the design and application of hybrid ligands in the rhodium catalyzed AHF of both dihydrofuran and pyrroline substrates, leading to unprecedented high levels of regio- and enantioselection. The structures of the catalytically active species under HF reaction conditions have been investigated using high-pressure NMR (HP-NMR) and IR (HP-IR) spectroscopy, and the correlation between the preferred coordination mode of the ligands and their catalytic performance is discussed. Finally, the practical applicability of selective asymmetric hydroformylation of small heterocyclic olefins is demonstrated by the asymmetric synthesis of the 3-carbaldehyde product derived from *N*-(*tert*-butoxycarbonyl)-3-pyrroline, which is subsequently transformed into the amino acid *β*-proline, furnishing the first catalytic protocol to generate this important chiral building block.

RESULTS AND DISCUSSION

Design and Synthesis of Hybrid Ligands. The hybrid, small bite-angle phosphine-phosphoramidite ligand **L1** was prepared in a straightforward two-step synthetic protocol, featuring the indole backbone that was recently introduced by us.[22] Treatment of octahydrobinol with excess PCl_3 under basic conditions produced the phosphorochloridite **9**, which was used without further purification.[23,24] Lithiation of indolylphos-

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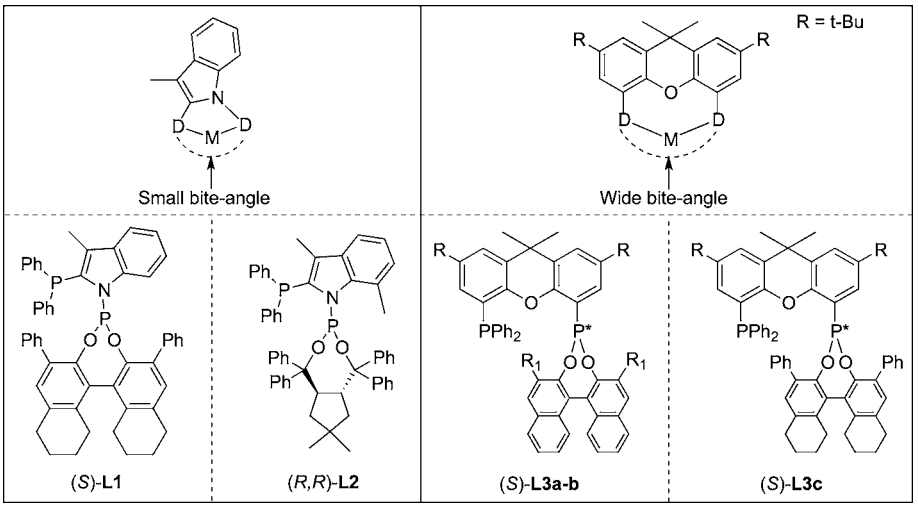
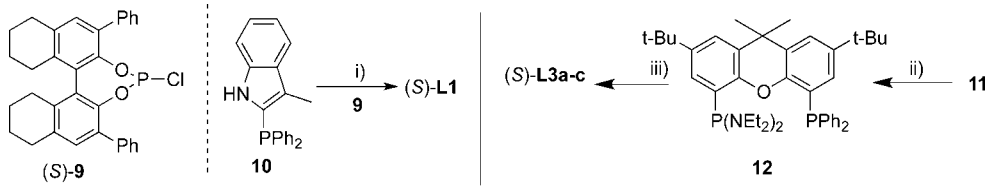
Scheme 2. Overview of Indole-Based Small Bite-Angle and Xanthene-Based Wide Bite-Angle Ligands

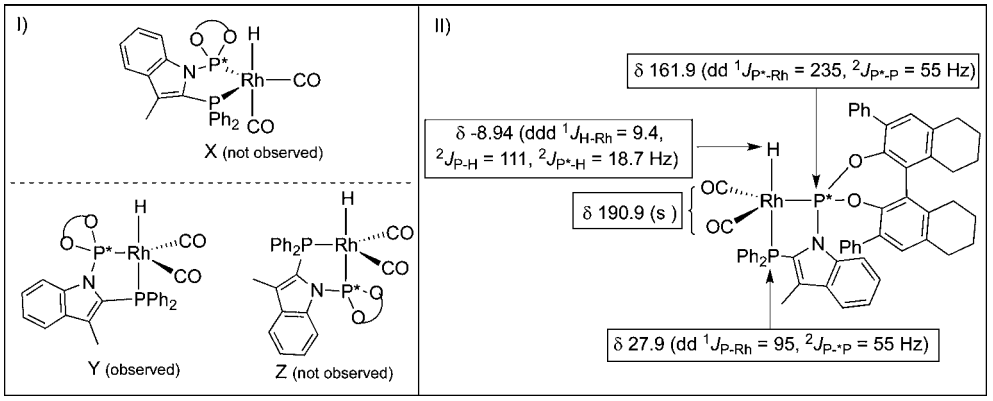


Scheme 3. Synthesis of Hybrid Ligands L1 and L3a–c[a]



[a](i) −78°C, 1 equiv n-BuLi, 1.5 equiv (*S*)-**9**; (ii) −78°C, 2 equiv *tert*-BuLi, 1.1 equiv $(NEt_2)_2PCl$; and (iii) 120°C, 1.1 equiv BINOL **a–c**.

Scheme 4. (I) Structure of the *ee* Species X (top left) and the Isomeric *ea* Species Y and Z (bottom left) and (II) HP-NMR Data of $Rh(H)(L1)(CO)_2$ Obtained at 298 K



phine **10**[10a,b] followed by addition of **9** at low temperature yielded ligand **L1** in 68% isolated yield. The related *α,α,α,α*-tetraaryl-1,3-dioxolane-4,5-dimethyl (TADDOL)-based ligand **L2** was readily prepared via base catalyzed salt elimination followed by a BuLi-mediated P–N coupling reaction.[10b]

In our pursuit to synthesize hybrid, wide bite-angle ligands with similar steric factors as in **L1**, ligands **L3a–c** were prepared (Scheme 3) via a straightforward three-step synthetic protocol from commercially available starting materials (Scheme 3).[25] The intermediate phosphine **11** was synthesized in high purity and good yield by a modified literature procedure.[26] Subsequent lithiation of **11** followed by addition of aminochlorophosphine led to intermediate **12**, which was reacted with the respective BINOL derivatives **a–c** to generate the desired hybrid ligands **L3**. The formation of **L3a** and **L3b** proceeded readily in refluxing toluene without additional reagents, whereas a catalytic amount of tetrazole was necessary to facilitate the formation of **L3c**.[27]

In situ HP-NMR and IR Spectroscopy: Phosphine-Phosphoramidite Ligands. The catalytic resting state in the generally accepted mechanism for hydroformylation (type I kinetics) is a five-coordinated complex $Rh(H)(CO)_2(PP)$, with the PP ligand coordinating in either a bis-equatorial (*ee*) or an equatorial-apical (*ea*) mode (Scheme 4).[28] It is also well-established that the ligand coordination mode strongly influences the regioselectivity during the hydroformylation and that this selectivity is severely hampered by ambiguous coordination (mixture of *ee* and *ea*) of the ligand to the metal center, especially also in asymmetric catalysis.[29,30] For a hybrid bidentate phosphorus ligand featuring two chemically inequi-

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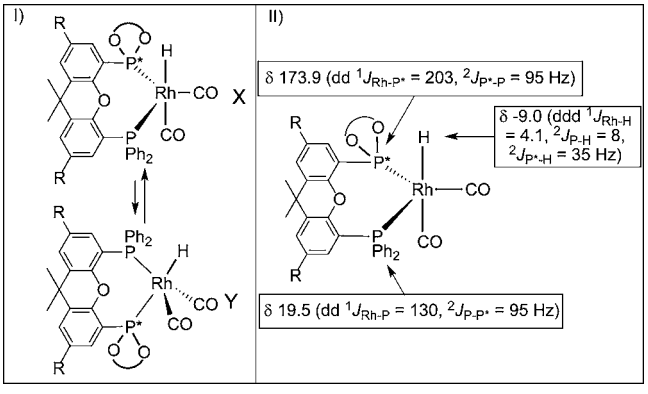
Table 2. HP-NMR and -IR Data of $Rh(H)(PP)(CO)_2$ (PP = L1, L2, or L3a−c) at 298 K

	phosphine			PO_2/ PO_2N				hydride		IR
ligand	δ (PPh_2), ppm	J_{PH}, Hz	J_{RhP}, Hz	δ (P*), ppm	J_{P*H}, Hz	$J_{Rh\ P*}$, Hz	J_{PP*}, Hz	δ(H), ppm	J_{RhH}, Hz	ν_{CO}, cm^{-1}
L1	27.92	111	94.6	161.87	18.7	235.3	54.7	−8.94	9.4	1976, 2021
L2	24.84	111	138.5	92.90	9.5	140	38.6	−8.86	2.3	–
L3c	19.5	8	130.6	173.9	35	203	95	−9.0	4.1	1950, 1985, 2041, 2128

valent P nuclei, three different isomers can be expected (Scheme 4(I), species **X**−**Z**). To generate the respective resting state species under reaction conditions, phosphine-phosphoramidite ligands **L1** and **L2** were treated with $Rh(acac)(CO)_2$ under 5 bar of syngas. Analysis by in situ HP-NMR spectroscopy revealed a characteristic doublet-of-doublets-of-doublets signal around δ −9 ppm in the ^1H HP-NMR spectrum (see Table 2). A very large J_{PH} coupling was observed for these systems, which hints at a mutual *trans* disposition of one of the phosphorus atoms and the hydride in a trigonal-bipyramidal rhodium complex, thus excluding *ee* coordination (species **X**).[31] The fairly small hydride-phosphoramidite coupling (19 Hz), a large hydride-phosphine (111 Hz) coupling, and the existence of only one set of signals observed by low-temperature HP-NMR spectroscopy established that the phosphine is positioned *trans* to the hydride, resulting in isomer **Y**.[24]

Accordingly, two distinct absorption bands at 1976 and 2021 cm^{-1} were detected by HP-IR spectroscopy, thereby demonstrating that ligand **L1** coordinates in a strictly *ea* fashion, generating isomer **Y**; similar observations were made with ligand **L2** (see Table 2). However, in the later case, variable temperature NMR spectroscopy indicated the presence of both isomers **Y** and **Z** at low temperature.[23,32] In contrast, the complex obtained by reaction of ligand **L3c** with $Rh(acac)(CO)_2$ under 5 bar of syngas showed two moderate J_{PH} coupling constants of 8 and 35 Hz, and the combined spectroscopic data (1D and 2D, ^1H and ^{31}P HP-NMR) suggest a strong preference for ee isomer **X** as a major species (Scheme 5). Selective correlation NMR measurements unveiled that the

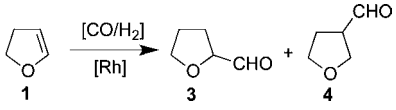
Scheme 5. (I) Structure of the *ee* Species X (top left) and the *ea* Species Y (bottom left) and (II) HP-NMR data of $Rh(H)(L3c)(CO)_2$ Obtained at 298 K



phosphonite fragment coordinates *trans* to the hydride in the minor *ea* complex. HP-infrared (HP-IR) spectroscopy confirmed the existence of both isomers under reaction conditions. Related xanthene-based diphosphonite ligands have been shown to also give mainly the *ee* isomer under applied reaction conditions.[33] We thus have two chiral, hybrid ligand systems in hand with similar steric properties but juxtaposing coordination behavior to Rh^I hydroformylation catalysts. This may infer unprecedented opportunities to tune and control the chemo-, regio-, and enantioselection of the asymmetric hydroformylation of heterocyclic olefins.

Rhodium Catalyzed Asymmetric Hydroformylation of 1. The 2-carbaldehyde **3** is typically obtained as a minor regioisomeric product from the hydroformylation of either **1** or **2**.[13,16,17] We anticipated that a chiral small bite-angle ligand, such as **L1**, could lead to the enantioselective formation of regioisomer **3**, as formation of intermediate **X1** should be favored (see Scheme 1). Initial screening experiments (Table 3)

Table 3. Rhodium Catalyzed AHF of 1 Using Ligands L1, L2, and L3a−c[a]



	Entry	Ligand/ L:M	Time [h]	Temp. [°C]	$p(CO/H_2)$ [bars]	Regio (3/4)[c]	Conv. [%][b]	ee 3 [%][c]	ee 4 [%][c]
Small bite-angle	1	**L1**/1.2	43	40	20	*61:39*	78	35	73
	2	**L1**/2	43	40	20	*60:40*	76	33	78
	3	**L1**/3	43	40	20	*59:41*	61	33	78
	4	**L1**/4	43	40	20	*59:41*	43	33	78
	5	**L1**/1.2	16	50	10	*61:39*	74	34	59
	6	**L1**/1.2	16	50	20	*63:37*	78	39	60
	7	**L1**/1.2	16	50	30	*65:35*	80	42	38
	8	**L1**/1.2	48	50	40	*65:35*	99	23	33
	9	**L1**/1.2	16	70	20	*63:37*	99	33	53
	10	**L2**/1.2	22	40	20	*75:25*	30	8	7
	11	**L2**/2	22	40	20	*68:32*	8	62	73(*R*)
	12	**L2**/2	16	50	10	*67:33*	13	45	69
	13	**L2**/2	16	50	30	*66:34*	9	49	71
	14	**L2**/2	16	60	20	*63:37*	20	19	22
Wide bite-angle	15[d]	**L3a**/2.1	18	60	20	*25:75*	34	6	19
	16[e]	**L3b**/2.4	16	40	20	*38:62*	ND	ND	17
	17[e]	**L3b**/4.7	16	40	20	*25:75*	5	2	46
	18[e]	**L3b**/4.7	16	40	40	*22:78*	ND	ND	53
	19[e]	**L3b**/4.7	18	40	55	*19:81*	3-7	19	55
	20[e]	**L3b**/4.7	18	10	80	*20:80*	1	21	58
	21[d]	**L3c**/4.7	60	10	40	*19:81*	1	38	89
	22[d]	**L3c**/4.7	18	35	40	*21:79*	ND	41	88(*R*)
	23	**L3c**/4.7	15	40	20	*21:79*	7	43	88(*R*)
	24	**L3c**/4.7	15	50	20	*25:75*	18	41	87(*R*)
	25[d]	**L3c**/4.7	20	25	15	*19:81*	ND	39	90(*R*)
	26[d]	**L3c**/4.7	40	25	25	*20:80*	5	43	91(*R*)
	27[d]	**L3c** /4.7	40	25	40	*20:80*	5-8	41	88(*R*)
	28[d]	**L3c**/4.7	20	25	50	*21:79*	5-8	29	83(*R*)
	29[e]	**L3c**/4.7	60	45	20	*23:77*	69	42	81(*R*)

[a] $Rh(acac)(CO)_2$ = 1.9×10^{-6} mol, sub/Rh = 200, toluene = 0.75 mL, no hydrogenation or isomerization product could be observed. [b] Total conversion determined by ^1H NMR. [c] Regio- and enantioselectivity measured by chiral GC (see Supporting Information). [d] sub/Rh = 400. [e] $Rh(acac)(CO)_2$ = 3.9×10^{-6} mol, sub/Rh = 400; ND: not determined or low conversion; L/M = Ligand to metal ratio.

with in situ prepared rhodium complex of **L1** revealed a optimal ligand to metal ratio of 1.2 and a syngas pressure of 30 bar, leading to a 65:35 (**3**:**4**) product mixture and ee's of up to 42% for **3** (entries 1−9). Thus, application of a rhodium catalyst with ligand **L1** in the AHF of **1** resulted in formation of **3** as the major isomer along with decent enantioselectivity, hinting at a ligand bite-angle controlled selection process. Gratifyingly, application of the related TADDOL-based hybrid phosphine-

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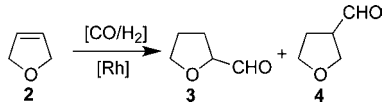
phosphoramidite ligand **L2** in the AHF of **1** led to the enhancement of both regio- and stereoselection,[34] albeit at the expense of somewhat lower activities. Using a **L2**:Rh ratio of 1.2 led to unprecedentedly high regioselectivity, with a ratio **3**:**4** of 75:25. Unfortunately the enantioselectivity was low (entry 10), indicating that a ligand-free rhodium complex might also be catalytically active under these conditions.[35] We therefore increased the L:M ratio to 2, which results in significantly higher enantioselectivities (**3**, 62%; **4**, 73%), without compromising the desired regioselectivity (ratio **3**:**4** is 68:32) (entry 11). To the best of our knowledge, this is the first example of AHF of **1** that efficiently produces the **3** as major product (up to 75%), with relatively high ee's (62% in **3**). Notably, no traces of hydrogenated, isomerized or oligomerized species were observed under these conditions.

To understand these results with respect to ligand geometry, we also evaluated the phosphine-phosphonite ligands **L3a–c** in the same reaction (Table 3). Contrary to the observations with **L1** and **L2**, application of wide bite-angle **L3a–c** in the AHF of **1** reversed the regioselectivity, with 3-carbaldehyde **4** obtained as a major isomer. Ligand **L3a** yielded a very poor catalyst with respect to enantioselection (run 15). Initial testing employing **L3b** indicated an optimal ligand to metal ratio of 4.7 with enhanced enantioselectivity (entry 16 vs 17). Evaluation of various reaction parameters revealed that reaction pressure and temperature have little influence on the regioselectivity (around 80:20 for **4**:**3**) (runs 16–20). Thus, after optimization of the reaction conditions, this ligand (**L3b**) led to a moderate ee of 55% at best for compound **4** (run 19) but with generally low activity. Markedly, **L3c** gave superior results, and further optimization was performed using this compound. The activity of rhodium complexes of **L3c** increased significantly upon raising the temperature from 10 to 50 °C, while the enantioselectivity remains higher than 80% in all cases (runs 21–24). At 25 bar, we reached an excellent enantioselection of 91% for 3-carbaldehyde **4** (run 26), which represents the first example of AHF of **1** with 91% ee to the best of our knowledge. Prolonged reaction at 45 °C led to improved conversion (up to 69%), although the enantioselectivity dropped slightly to 81%. The enantioselection in 2-carbaldehyde **3** (up to 43%) is moderate under these reaction parameters when employing wide bite-angle ligand **L3c**.

We are thus able for the first time and simply by changing the ligand system from **L2** to **L3c** to obtain either 2-carbaldehyde **3** or 3-carbaldehyde **4** as a major regioisomer with good to excellent enantioselection from the notoriously difficult substrate **1**.

Rhodium Catalyzed Asymmetric Hydroformylation of 2. The excellent selectivities displayed by the wide bite-angle ligands **L3a–c** in the AHF of **1** prompted us to also evaluate their performance in the AHF of **2**. Although direct functionalization of **2** should only lead to aldehyde **4**, this substrate is susceptible to isomerization under hydroformylation conditions to give the isomeric substrate **1** (Scheme 1), illustrating the need for highly selective catalysts to control the subtleties involving substrates **1** and **2** and the relative reactivity of species **X1** and **X2**. Using in situ prepared catalysts with hybrid ligands **L3a–c**, we examined the asymmetric hydroformylation of **2** under various conditions (Table 4). Interestingly, AHF of **2** essentially follows the same trends as the AHF of **1**, indicating that the ortho-substituent on the binol moiety of the phosphonite phosphorus atom plays a crucial role in controlling the selectivity. The catalyst based on the ligand

Table 4. Rhodium Catalyzed AHF of 2 Using Ligands L3a–c[a]



run	L/ time, h	L/M	$p(CO/H_2)$, bars	temp., °C	regio (4/3)	conv., %[b]	ee **4**, %[c]
1	**L3a**/ 18	2.1	20	60	85:15	60	4
2[d]	**L3b**/ 16	2.3	20	40	99:1	35	5
3[d]	**L3b**/ 16	4.7	40	40	99:1	ND	48
4	**L3b**/ 18	4.7	55	40	>99	20	47
5	**L3c**/ 15	2.0	20	25	>99	3–5	89(*S*)
6	**L3c**/ 15	3.0	20	25	>99	3–5	90(*S*)
7	**L3c**/ 15	4.7	20	25	>99	3–4	91(*S*)
8	**L3c**/ 15	4.7	20	40	>99	40	91(*S*)
9	**L3c**/ 48	5.5	20	45	>99	86	90(*S*)
10[e]	**L3c**/ 15	4.7	20	50	96:4	75	32(*S*)
11[f]	**L3c**/ 40	4.7	20	45	>99	90	91(*S*)
12	**L3c**/ 48	4.7	20	45	>99	97	90(*S*)
13	**L3c**/ 16	4.7	30	25	93:7	ND	90(*S*)

[a] $Rh(acac)(CO)_2 = 1.9 \times 10^{-6}$ mol, sub/Rh = 200, toluene = 0.75 mL, no hydrogenation or isomerization product could be observed. [b] Total conversion determined by ^1H NMR spectroscopy. [c] Regio- and enantioselectivity measured by chiral GC. [d] $Rh(acac)(CO)_2 = 3.9 \times 10^{-6}$ mol, sub/Rh = 400. [e] Isomerization to **1** was detected by NMR (15%). [f] Isomerization to **1** was detected by NMR (5%). ND: not determined.

L3a displayed good conversion but poor enantioselectivity (run 1), and good regioselectivities but only moderate ee's of up to 48% were obtained using ligand **L3b** (runs 2–4).

Use of the sterically more hindered ligand **L3c** resulted in excellent regioselectivity and a promising ee of 89% at room temperature for the 3-carbaldehyde product (run 5). There is a noteworthy reversal of enantioselection in product **4** going from substrate **1** (giving (*R*)-**4**) to **2** (leading to (*S*)-**4**). This explains why isomerization of **2** to **1** results in erosion of the enantiopurity for the 3-carbaldehyde. Optimization of the ligand to metal ratio (runs 5–8) led to a further increase in the enantioselection to 91%. Notably, higher reaction temperature (up to 45 °C) or longer reaction time (up to 48 h) substantially improved the overall conversion without affecting the regio- or enantioselectivity at all (runs 7 vs 9 and 12). A marked decrease in both regio- and enantioselection was observed when the reaction was performed at 50 °C, which is attributed to substantial levels of substrate isomerization and subsequent hydroformylation of in situ formed **1**, generating the opposite enantiomer of **4** (run 10). Attempts to suppress the isomerization side-reaction by using 30 bar of syngas led to lower regioselectivity (run 13). Overall, the 3-carbaldehyde **4** can thus be obtained under mild conditions in an unprecedented enantioselectivity of 91% with perfect regiose-

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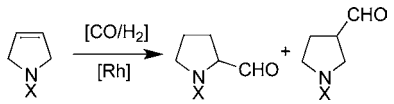
lectivity (4:3 >99%) and at 90% conversion of the substrate **2**,[36] which represent the highest selectivities in the AHF of **2** reported to date.

Rhodium Catalyzed AHF of 3-pyrrolines. Since only two ligand systems have so far been reported for the asymmetric hydroformylation of *N*-substituted 3-pyrrolines and given the excellent results obtained with our hybrid phosphine-phosphonite ligands in the AHF of related substrates **1** and **2**, this prompted us to use **L3c** in the asymmetric hydroformylation of *N*-acetyl-3-pyrroline **5** and *N*-(*tert*-butoxycarbonyl)-3-pyrroline **6**. Initial catalytic experiments on substrate **5** identified an optimal ligand to metal ratio of 3.3 (Table 5; run

Table 5. Rhodium Catalyzed AHF of 3-Pyrrolines 5 and 6 Using Ligand L3c To Afford 2-Carbaldehyde Species 7X and 3-Carbaldehyde 8X[a]



entry	L/M	sub/time, h	*p*(CO/H_2), bars	temp., °C	regio (**8X**/**7X**)	conv., %[b]	ee **8X**, %[b]
1	1.1	**5**/18	45	55	74:26	95	2
2	2.2	**5**/18	45	55	92:8	91	3
3	3.3	**5**/18	45	55	>99	16	81
4	3.3	**5**/19	30	35	>99	3	85
5	3.3	**5**/15	45	65	>99	37	78
6	3.3	**5**/90	45	45	>99	17	75
7	4.4	**5**/20	45	75	>99	80	78
8[c]	4.4	**5**/48	45	80	>99	>99	63
9	4.7	**6**/15	20	45	ND	8	84
10	4.7	**6**/60	30	45	ND	18	86(+)
11	4.7	**6**/60	55	45	ND	ND	84
12	4.7	**6**/19	30	35	ND	2	85
13	4.7	**6**/18	20	55	ND	18	82
14[d]	4.7	**6**/15	50	55	91:9	6	83
15	4.7	**6**/42	20	55	ND	41	83
16[d]	4.7	**6**/90	20	55	92:8	75	78(+)

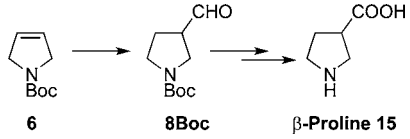
[a] $Rh(acac)(CO)_2$ = 1.9 × 10^{-6} mol, sub/Rh = 100, toluene = 0.75 mL, no hydrogenation or isomerization product could be observed. [b] Total conversion, regio- and enantioselectivity were measured by chiral-GC. [c] $Rh(acac)(CO)_2$ = 3.8 × 10^{-6} mol. The catalyst was preformed overnight at 60 °C under 45 bar of syngas. Initial reaction time after injection of substrate was 48 h at 60 °C (77% conversion, 72% ee) and then 24 h at 80 °C. [d] Regioselectivity determined by NMR. ND = not determined.

1−3) and an inverse relationship between reaction temperature and enantioselectivity (entries 4−6). Hence, at 35 °C we obtained 85% ee with excellent regioselectivity for 3-carbaldehyde **8Ac**. Furthermore, employing a higher L:M ratio of 4.4 in combination with a reaction temperature of 75 °C significantly enhanced the conversion (80%) while still providing very high regioselection (>99% for **8Ac**) as well as enantioselection with 78% ee for **8Ac** (entry 7). Similar results have also been obtained for substrate **6** after screening various reaction conditions (entry 9−15), with an unprecedented ee of 86% at 45 °C, albeit at a moderate conversion of 18%. We subsequently observed that at 55 °C, the enantioselection was still high at 78% ee with 92% regioselectivity for compound **8Boc** and at 75% conversion (entry 16). Furthermore, we managed to obtain full conversion for substrate **5** while retaining good enantioselection (63%) for **8Ac** using modified reaction conditions (entry 8, Table 5), i.e., a slightly higher catalyst loading of 2 mol % and a reaction temperature of 60−80 °C, which underlines the potential practical applicability of this methodology.

To our knowledge, the level of enantioselection obtained in the asymmetric hydroformylation of both *N*-acetyl-3-pyrroline (**5**, 85%) and *N*-(*tert*-butoxycarbonyl)-3-pyrroline (**6**, 86%) by employing hybrid ligand **L3c** (85%) is the highest ever reported for these substrates,[37] and the concomitant excellent regioselection for the respective desired 3-carbaldehyde products makes this a very powerful catalytic system.

Synthesis of β-Proline. β-Proline is a key structural element in peptides and proteins, and it has been extensively used for various applications.[38,39] However, there are only a handful of reports on the preparation of β-proline, and the cumbersome protocols, including many stoichiometric transformations, have limited synthetic access to this important building block.[40] Although highly desirable, no single catalytic protocol for the selective synthesis of β-proline has been reported to date. We anticipated that the asymmetric hydroformylation of pyrrolines, followed by subsequent transformation of the aldehyde into the free carboxylic acid (Scheme 6), would provide an atom-efficient, catalytic route for

Scheme 6. Projected General Two-Step Conversion of *N*-Protected 3-Pyrrolines into β-Proline



the synthesis of enantioenriched β-proline, with the added potential to perform selective, stereospecific isotope labeling of of β-proline.[41]

Having obtained considerable conversions and high enantioselectivities, we set out to synthesize β-proline using the asymmetric hydroformylation of *N*-Boc-pyrroline (**6**) as one of the intermediate reaction steps, which is unprecedented to the best of our knowledge. Using the optimized reaction conditions found in our screening study, the reaction mixture was purified by silica gel column chromatography. The pure 3-carbaldehyde product **8Boc** was subsequently oxidized to the corresponding acid using PDC (pyridinium dichromate) as an oxidant. The acidic proton could not be observed in the ^1H NMR spectrum, but the -COOH carbon was found at δ 178 ppm in the ^{13}C NMR spectrum. The *N*-protected 3-carboxylic acid was fully characterized by mass spectrometry and NMR spectroscopy. Finally, the enantioenriched β-proline was obtained via HCl deprotection of the *tert*-butoxycarbonyl (boc) fragment. Although we have not conducted a full investigation on the enantiopurity of the final product, the chosen reaction conditions typically go with retention of configuration and without erosion of enantiopurity. The unprecedented and facile catalytic transformation of readily available starting compounds into this highly valuable unnatural amino acid end product is expected to generate renewed interest in asymmetric hydroformylation as an efficient tool for organic synthesis.

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CONCLUSIONS

In summary, we have reported the synthesis of new and easily tunable, hybrid phosphorus ligands based on indole (**L1** and **L2**; small bite angle) or xanthene (**L3a–c**; large bite angle). Detailed in situ HP-NMR and -IR spectroscopic investigations revealed that the phosphine-phosphoramidite ligands **L1** and **L2** coordinate exclusively in an *ea* fashion in trigonal-bipyramidal $Rh(H)(CO)_2(PP)$, the catalytic resting state, while the phosphine-phosphonite ligand **L3c** predominantly coordinates in a *ee* mode. This distinction has marked effects on the regioselectivity achieved when applying these ligands in the asymmetric hydroformylation of 2,3-dihydrofuran (**1**), leading to a high degree of catalyst tunability. Application of the small bite-angle phosphine-phosphoramidite ligands produced 2-carbaldehyde **3** as the major regioisomer with up to 62% ee. We are not aware of any other catalyst system capable of regioselective asymmetric hydroformylation of **1** concomitantly with significant enantioselection. In contrast, the wide bite-angle ligand **L3c** afforded 3-carbaldehyde **4** as major regioisomer from the AHF of **1**, with an unprecedented high enantiomeric excess of 91% in **4**. Ligand **L3c** also clearly outperformed the other ligands reported for the AHF of **2**, with up to 91% ee concomitantly with complete regio-control and excellent conversions. In addition, it is important to note that both enantiomers of 3-carbaldehyde **4** are now accessible using the same ligand **L3c**, simply by switching between substrates **1** and **2**. Moreover, employing **L3c**, in the hydroformylation of *N*-acetyl-3-pyrroline (**5**) an excellent enantiomeric excess of 85% was obtained for pyrrolinyl-3-carbaldehyde-species **8Ac** along with exceptionally high regioselectivities. Similarly, in the AHF of *N*-(*tert*-butoxycarbonyl)-3-pyrroline (**6**) an unprecedented ee of 86% for **8Boc** was obtained using **L3c**. In addition, the synthetic utility of AHF in organic synthesis was demonstrated by transforming the carbaldehyde **8Boc** to *β*-proline. We are currently investigating the applications of hybrid ligands in other types of functionalized heterocyclic olefins, including bicyclic analogues as well as the possibilities to achieve the isotopic labeling of proline for biomarker applications using AHF methodologies.

EXPERIMENTAL SECTION

General Remarks. All manipulations involving moisture-sensitive compounds were carried out under an argon atmosphere using Schlenk techniques. Solvents were dried by standard procedures unless otherwise mentioned. With the exception of compounds given below, all chemicals were purchased from commercial suppliers and used without further purification. Toluene-d_8 was dried over sodium wire and distilled from sodium. The following compounds were prepared according to literature reported procedures: ligand **L2**, 3,7-dimethylindole,[42] protected 3-pyrroline **5**,[43] compound **9**,[22] and diphenyl(3-methyl-2-indolyl)phosphine (**10**).[10a] NMR spectra were recorded on a 400 MHz Bruker Avance, a 300 MHz Bruker, or a 300 MHz Varian instrument at 298 K unless mentioned otherwise; chemicals shifts are referenced to ext. TMS (^{1}H, ^{13}C) or 85% H_3PO_4 (Ξ = 40.480747 MHz, ^{31}P). Coupling constants are given as absolute values. Melting points were recorded on a Gallenkamp melting point apparatus in a 0.25 μm sealed capillary and are uncorrected. High-resolution fast atom bombardment mass spectrometry was carried out with a JEOL JMS SX/SX 102A spectrometer. Samples were loaded in a 3-nitrobenzyl alcohol matrix and bombarded with xenon atoms. Elemental analysis was performed at Mikroanalytisches Laboratorium KOLBE, Mülheim an der Ruhr, Germany. Chiral GC separations were recorded on an Interscience Trace-GC Ultra instrument with a Supelco BETA-DEX 225 column (internal diameter 0.25 mm, 10 m column, film thickness 0.25 μm) for the dihydrofurans. Chiral GC separations of 3-pyrrolines were conducted on an Interscience Focus-GC Ultra instrument with a Supelco BETA-DEX 225 column (internal diameter 0.25 mm, 30 m column).

Synthesis of 1-(2,6-Diphenyl-8,9,10,11,12,13,14,15-octahydrodinaphtho[2,1-*d*:1′,2′-*f*][1,3,2]dioxaphosphepin-4-yl)-2-(diphenylphosphino)-3-methyl-1*H*-indole (L1). To a THF solution (7 mL) of diphenyl(3-methyl-2-indolyl)phosphine (**10**) (313 mg; 1 mmol) was added dropwise 0.40 mL of *n*-BuLi (1 mmol, 2.5 M in hexanes) at −78 °C. The resulting reaction mixture was stirred for 40 min at −78 °C. Next, a solution of **9** (760 mg; 1.49 mmol in 10 mL of THF) was slowly added to the reaction mixture (at −78 °C) and stirred for an hour. Subsequently, the flask was warmed to room temperature over a period of 1 h and stirred overnight. The reaction mixture was filtered over a pad of Celite, and the filtrate dried in vacuum to produce a foamy residue. The crude was dissolved in eluent [few drops of dichloromethane (DCM) was added] and isolated as white solid after rapid silica gel chromatography on a chromatotron (10% triethylamine in hexane) in 68% yield (533 mg). Mp = 198 °C (dec.). ^{1}H NMR ($CDCl_3$, 300 MHz, 298 K): δ = 7.33–7.28(m, 4H), 7.26–7.17 (m, 8H), 7.16–7.13 (m, 3H), 7.08–7.02 (m, 2H), 7.01–6.93 (m, 2H), 6.88 (t, J = 10.5 Hz, 2H), 6.78 (m, 2H), 6.59 (s, 2H), 6.53 (m, 1H), 2.98–2.72 (m, 8H, CH_2-8H-BINOL), 2.02–1.78 (m, 8H, CH_2-8H-BINOL), 1.40 (s, 3H). ^{13}C NMR ($CDCl_3$, 300 MHz, 298 K): δ = 145.1, 144.2, 140.0, 136.1, 134.7, 134.5, 134.2, 133.6, 133.4, 132.9, 132.7, 132.5, 132.4, 131.9, 131.4, 131.0, 130.3, 129.6, 129.3, 129.2, 128.5, 127.9, 127.7, 127.3, 126.8, 126.2, 124.2, 122.6, 120.5, 117.5, 115.9, 29.22, 27.8, 23.0, 22.7, 9.71. ^{31}P NMR ($CDCl_3$, 300 MHz, 298 K): δ = 133 (d, $^3J_{PP}$ = 240 Hz, PN), −26.8 (d, $^3J_{PP}$ = 240 Hz, PPh_2). HR-MS (FAB$^+$) m/z calculated for [$C_{53}H_{45}NO_2P_2$ + H] = 790.0030 [MH]$^+$; obs.: 790.0012. Elemental analysis (%) calcd. for $C_{53}H_{45}NO_2P_2$ + 2THF + DCM: C, 73.08; H, 6.23; N, 1.37; found: C, 72.38; H, 6.25; N 1.19.

Synthesis of (5-Bromo-2,7-di-*tert*-butyl-9,9-dimethyl-9*H*-xanthen-4-yl)diphenylphosphine (11). This compound was prepared using a modified literature reported procedure.[26] The commercially available 4,5-dibromo-2,7-di-*tert*-butyl-9,9-dimethyl xanthene was dried by coevaporation with toluene prior to use. The complete procedure is described in the Supporting Information.

Synthesis of 1-(2,7-di-*tert*-butyl-5-(diphenylphosphino)-9,9-dimethyl-9H-xanthen-4-yl)-*N*,*N*,*N*′,*N*′-tetraethylphosphinediamine (12). To a diethyl ether (10 mL) solution of monophosphine **11** (730 mg, 1.246 mmol) was added *tert*-BuLi (1.56 mL of 1.6 M hexane solution, 2.492 mmol) dropwise at −78 °C, and the resulting yellow solution was allowed to warm to room temperature over 1 h. The reaction mixture was stirred for an additional 15 min before being cooled to −65 °C, and bis(diethylamino)chlorophosphine (0.32 mL, 1.495 mmol) was added. The reaction mixture was warmed to room temperature and stirred for another 2 h. The white precipitate was filtered over a pad of neutral alumina and washed with diethyl ether (3 × 10 mL). The solvent was evaporated in vacuo to obtain **12** in 85% isolated yield (720 mg). ^{1}H NMR (C_6D_6, 300 MHz, 298 K): δ = 7.7–7.4 (m, 7H, Ar), 7.3–7.0 (m, 6H, Ar), 6.97 (m, 1H, Ar), 3.40–3.10 (m, 8H, NCH_2), 1.71 (s, 6H, Me_2), 1.42 (s, 9H, *tert*-Bu), 1.19 (s, 9H, *tert*-Bu), 1.13 (t, $^2J_{H-H}$ = 7 Hz, 12H, NCH_3). ^{13}C NMR (C_6D_6, 300 MHz, 298 K): δ = 152.1(d, $^2J_{P-C}$ = 17.8 Hz, CO-Xant), 150.2 (d, $^2J_{P-C}$ = 16.6 Hz, CO-Xant), 145.5 (s, *C*-Xant), 144.9 (s, *C*-Xant), 138.7 (d, $^2J_{P-C}$ = 14.8 Hz, $CPPh_2$), 134.4 (d, $^1J_{P-C}$ = 19.9 Hz, $CPPh_2$), 130.6 (s, *C*-Xant), 130.3 (m, *C*-Xant), 130.1 (m, $CPPh_2$), 129.9 (s, *C*-Xant), 125.1 ($^1J_{P-C}$ = 18.9 Hz, *C*-Xant), 123.0 (s, *C*-Xant), 121.7 (s, $CPPh_2$), 43.6 (dd, $^2J_{P-C}$ = 19.0 Hz, $^1J_{C-C}$ = 2.1 Hz, PCH_2), 35.2 (t, *C*-Xant), 34.7 (s, Ct-Bu), 34.6 (s, Ct-Bu), 31.8 (s, $C(CH_3)_3$), 31.5 (s, $C(CH_3)_2$), 31.5 (s, $C(CH_3)_3$), 25.8 (s, $C(CH_3)_2$), 14.9 (d, $^3J_{P-C}$ = 2.9 Hz, $PN(CH_2CH_3)_2$). ^{31}P NMR (C_6D_6, 300 MHz, 298 K): δ = 92.4 (d, $^6J_{PP}$ = 17.1 Hz, PN_2), −15.1 (d, $^6J_{PP}$ = 17.1 Hz, PPh_2). HR-MS (FAB$^+$) m/z calculated for [$C_{43}H_{58}ON_2P_2$ + H] = 681.4103 [MH]$^+$; obs.: 681.4102.

Synthesis of 4-(2,7-di-*tert*-butyl-5-(diphenylphosphino)-9,9-dimethyl-9*H*-xanthen-4-yl)-2,6-diphenyl-8,9,10,11,12,13,14,15-octahydrodinaphtho[2,1-*d*: 1′, 2′-*f*]-[1,3,2]dioxaphosphepine (L3c). A solution of 3,3′-diphenyl-5,5′,6,6′,7,7′,8,8′-octahydro-[1,1′-binaphthalene]-2,2′-diol (*S*) (418 mg;

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0.936 mmol) in toluene (15 mL) was added to a solution of bisphosphine **12** (580 mg; 0.852 mmol) in toluene (15 mL). A catalytic amount of tetrazole (0.045 mmol) was added, and the mixture was refluxed at 120 °C for 60 h. The pale-yellow solution was cooled to room temperature, filtered through a glass frit, and concentrated to give **L3c** as a white solid. The crude powder was purified by chromatography (using a Chromatotron) using a 98:2 mixture of hexane and triethyl amine, which afforded pure **L3c** in 92% (767 mg, 0.784 mmol) yield. Mp = 198 °C (dec.). ^{1}H NMR (C_6D_6, 300 MHz, 298 K): δ = 7.86 (d, $^3J_{PH}$ = 8.1 Hz, 2H, PPh_2), 7.74 (m, 2H, PPh_2), 7.64 (m, 2H, Ar), 7.48 (s, 1H, Ar), 7.46 (s, 2H, Ar), 7.37 (m, 2H, Ar), 7.28−7.18 (m, 7H, Ar), 7.18−7.08 (m, 4H, Ar), 7.0−6.90 (m, 3H, Ar), 6.54 (t, $^3J_{H-H}$ = 7.4 Hz, 1H, Ar), 3.0−2.60 (m, 8H, CH_2-8H-BINOL), 1.9−1.7 (m, 8H, CH_2-8H-BINOL, 1.67 (s, 6H, Me_2), 1.33 (s, 9H, *tert*-Bu), 1.18 (s, 9H, *tert*-Bu). ^{13}C NMR (C_6D_6, 300 MHz, 298 K): δ = 152.8(d, $^2J_{PC}$ = 22.0 Hz, *C*O-Xant), 152.5 (s, *C*O-Xant), 150.28 (d, $^2J_{PC}$ = 15.8 Hz, *C*O-Xant) 150.26 (d, $^2J_{PC}$ = 15.5 Hz, *C*O-8H-BINOL), 150.24 (d, J_{PC} = 2.5 Hz, *C*-Xant), 150.22 (d, J_{PC} = 2.3 Hz, *C*-8H-BINOL), 150.17 (s, *C*-Xant), 146.7 (d, J_{PC} = 1.8 Hz, *C*-Xant), 145.4 (s, *C*-Xant), 144.7 (d, J_{PC} = 4.8 Hz, *C*-Xant), 144.1 (s, *C*-Xant), 138.8 (s, *C*-Xant), 138.2 (d, J_{PC} = 14.7 Hz, *C*PPh_2), 137.5−137.4 (m), 136.7 (s), 135.5 (s, *C*-8H-BINOL), 135.2 (s, *C*-8H-BINOL), 134.5 (d, J_{PC} = 1.7 Hz, *o*-*C*PPh_2), 134.3 (m, Ar), 134.2 (d, J_{PC} = 1.7 Hz, *o*-*C*PPh_2), 133.4 (s), 132.9 (d, J_{PC} = 2.6 Hz, *C*-Xant), 132.8 (s), 131.8 (s, *C*-Ar), 131.7 (s, *C*-Ar), 131.4(d, J_{PC} = 2.2 Hz, *C*-8H-BINOL), 130.2 (s, *C*-Ar), 130.1 (s, *C*-Ar), 129.9 (s, CH_2), 129.5 (d, J_{PC} = 0.8 Hz, *C*-Ar), 129.2 (m, *C*-Ar), 128.9 (s, *C*-Ar), 128.8 (s, *C*PPh_2), 126.9 (s, C−Ar), 126.7 (s, C−Ar), 126.5 (s, C−Ar), 125.6 (s, CH_2), 125.1 (s, CH_2), 124.6 (d, J_{PC} = 1.9 Hz, *C*-Xant), 124.5 (d, J_{PC} = 0.9 Hz, *C*-Xant), 123.9 (s, *C*-Xant), 121.7 (m, *C*-8H-BINOL), 35.1 (m, CH_3), 34.7 (s, *C*$[CH_3]_3$), 34.6 (m, CH_3), 34.5 (s, *C*$[CH_3]_3$), 31.5 (CH_2), 30.0 (CH_2), 29.5 (CH_2), 23.5−23.0 (m, CH_2). ^{31}P NMR (C_6D_6, 300 MHz, 298 K): δ = 167.7 (d, $^6J_{PP}$ = 34.3 Hz, PO_2), −13.8 (d, $^6J_{PP}$ = 34.3 Hz, PPh_2). HR-MS (FAB$^+$) *m*/*z* calculated for $[C_{67}H_{66}O_3P_2 + H]$ = 981.4565 $[MH]^+$; obs.: 981.4572 .

Preparation of the Hydride Complexes Rh(H)(CO)$_2$(PP) and HP-NMR Investigations. The ligand **L3c** (20 mg, 0.0202 mmol) and Rh(acac)(CO)$_2$ (5.212 mg, 0.0202 mmol) were dissolved in 1 mL of dry toluene-d_8 in a 2 mL glass vial under inert atmosphere. The vial was immediately transferred to a stainless steel autoclave which was purged three times with 30 bar of syngas pressure. Finally, the autoclave was pressurized to 20 bar and heated to 45 °C for 16 h with constant stirring. Next, the autoclave was slowly cooled to room temperature and depressurized to 1 bar. The vial content was transferred to a high pressure 5 mm sapphire NMR tube, and the tube was pressurized to 5 or 10 bar of syngas. The HP-NMR data were collected either on a 300 MHz Bruker or 300 MHz DRX instrument. Preparation of the respective rhodium complexes Rh(H)(CO)$_2$(**PP**) and the corresponding HP-NMR data is presented in the Supporting Information (see also Table 2).

HP-IR Spectroscopy. In a typical experiment a 50 mL HP-IR autoclave was filled with a solution of ligand in dichloromethane (DCM). The autoclave was purged three times with 30 bar of syngas, pressurized to 20 bar of CO/H_2, and heated to 40 °C with constant stirring, while a background spectrum was recorded. The DCM solution of Rh(acac)(CO)$_2$, previously charged into the autoclave reservoir, was added to the ligand solution via overpressure. The IR spectra were recorded overnight at 40 °C with constant stirring. A detailed description of the in situ generated rhodium species and the corresponding HP-IR data are supplied in the Supporting Information (see also Table 2).

General Procedure for Asymmetric Hydroformylation. In a typical hydroformylation experiment a stainless steel autoclave (150 mL) equipped with inserts suitable for five glass vials (2 mL) was employed. The vials were charged with appropriate amounts of solvent, substrate, metal precursor and ligand (see Tables 3−5) along with Teflon stirring bars. Before starting the catalytic reactions, the charged autoclave was purged three times with syngas (CO:H_2 = 1:1) and then pressurized to the desired pressure. After catalysis, the autoclave was cooled to 0 °C, and any excess gas removed, after which either the catalyst mixture was quenched (by the addition of tributyl phosphite) or the reaction solution was analyzed directly. The conversion and regioselectivity were determined either by ^{1}H NMR spectroscopy or by GC without evaporating the solvent. The chiral induction was determined by chiral GC. The determination of enantiomeric excess and the absolute configuration are described in the Supporting Information.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Synthesis of compounds **9**, **11**, **L3a**, **L3b**, NMR and HP-IR spectroscopic data, chiral GC chromatograms, synthesis of *β*-proline, and complete ref 14b. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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