JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Article
pubs.acs.org/JACS

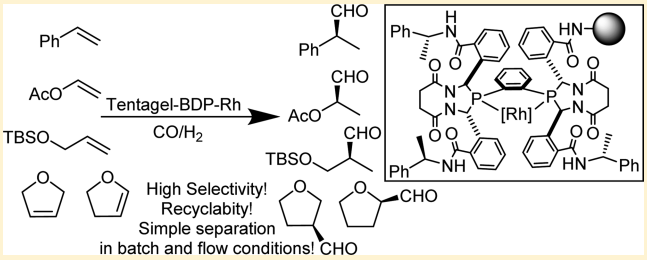
Immobilized Bisdiazaphospholane Catalysts for Asymmetric Hydroformylation

Tyler T. Adint and Clark R. Landis*

Department of Chemistry, University of Wisconsin-Madison, 1101 University Avenue, Madison Wisconsin 53706, United States

Supporting Information

ABSTRACT: Condensation reactions of enantiopure bis-3,4-diazaphospholanes (BDPs) that are functionalized with carboxylic acids enable covalent attachment to bead and silica supports. Exposure of tethered BDPs to the hydroformylation catalyst precursor, $Rh(acac)(CO)_2$, yields catalysts for immobilized asymmetric hydroformylation (iAHF) of prochiral alkenes. Compared with homogeneous catalysts, catalysts immobilized on Tentagel resins exhibit similarly high regioselectivity and enantioselectivity. When corrected for apparent catalyst loading, the activity of the immobilized catalysts approaches that of the homogeneous analogues. Excellent recyclability with trace levels of rhodium leaching are observed in batch and flow reactor conditions. Silica-bound catalysts exhibit poorer enantioselectivities.

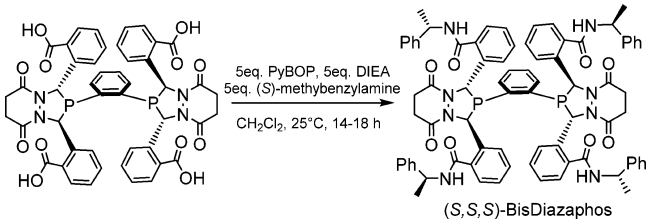


INTRODUCTION

Immobilization is an obvious, but not always successful, approach to retaining the high selectivity and activity of homogeneous catalysts while facilitating catalyst/product separation and catalyst recycling.[1,2] Immobilization of catalysts for linear selective alkene hydroformylation, one of the largest industrial processes that uses homogeneous, precious metals as catalysts, has been achieved, though apparently not implemented on an industrial scale.[3−5] Fewer reports detail the immobilization of *asymmetric* hydroformylation (AHF) catalysts, even though the generally higher costs of enantiopure catalysts and the need for high-purity pharmaceutical intermediates provide strong driving forces for the development of recyclable, heterogeneous AHF catalysts. To date, the report by Nozaki and co-workers of BINAPHOS-derivatives that are cross-linked with polystyrene constitute the most successful development of immobilized AHF catalysts.[6−9] While immobilized BINAPHOS ligands exhibit good selectivity relative to the homogeneous BINAPHOS catalysts, recycling studies using this catalyst are limited to relatively low TON (∼300) and require high syn gas pressures in flow (88−120 atm).[9] Application of immobilized AHF at both bench and production scales requires thorough understanding of catalyst activity, along with selectivity and catalyst leaching/recyclability, under practical conditions.

Bis-3,4-diazaphospholane (BDP) ligands reported by our group exhibit high selectivity and activity for a broad range of substrates, thus enabling efficient syntheses of chiral building blocks and complex structures.[10−14] Notable examples include the Burke group's synthesis of (+)-Patulolide C, for which the key step was the AHF of a *Z*-enolacetate, and Leighton's application of Rh(BDP)-catalyzed AHF for synthesis of two of the three fragments of Dictyostatin.[15,16] A key step in the synthesis of high-performing BDP ligands involves the coupling of the intermediate tetracarboxylic acid bisdiazaphospholane ((*S*,*S*)-tetraacid) (Scheme 1) with amines to form tetracarboxamide ligands. Generally speaking, the carboxamide resulting from coupling (*S*,*S*)-tetraacid with (*S*)-methylbenzylamine gives the most selective catalyst for a broad range of olefins.[17]

Scheme 1. Synthesis of (*S*,*S*,*S*)-BisDiazphos (previous work)



Carboxamide formation provides a simple route to BDP immobilization. Previously, we demonstrated immobilization of monodiazaphospholanes by coupling the carboxylic acid to an amine-functionalized polystyrene resin. Such immobilized ligands provided high enantioselectivity in Pd-catalyzed allylic alkylation reactions.[18] In this work we report the synthesis, characterization, and application of supported AHF catalysts based on immobilized BDP ligands. The overall plan of this paper begins with the synthesis of a small collection of resin-bound and silica-supported catalysts with different linkers and supports. Subsequent screening and recyclability study results are reported for shaker-style reactors. The section on resin-based catalysts concludes with NMR and rhodium-loading

Received: February 13, 2014
Published: April 17, 2014

   dx.doi.org/10.1021/ja501568k | *J. Am. Chem. Soc.* 2014, 136, 7943−7953

Scheme 2. Synthesis of Resin-Bound Bisdiazaphospholanes (L1−L3) and Rh Catalysts (C1−C3)

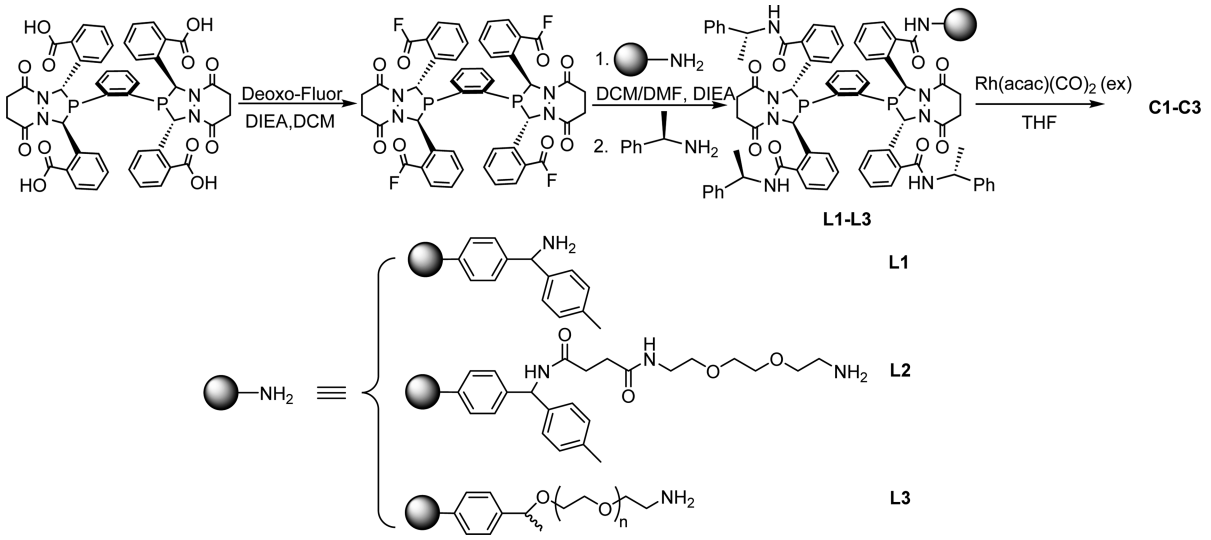
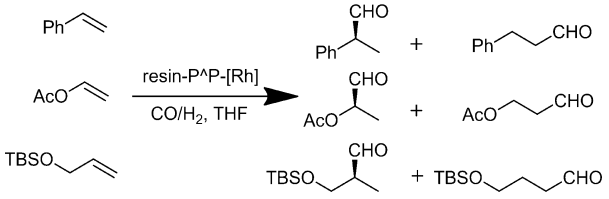


Table 1. Results for Simultaneous AHF of Three Substrates with Supported and Homogeneous Bisdiazaphospholane Ligands[a]



		styrene		vinyl acetate		allyloxy *tert*-butyldimethylsilane	
entry	catalyst	b:l ratio[b]	% ee[c]	b:l ratio[b]	% ee[c]	b:l ratio[b]	% ee[c]
1	C1	2.3:1	61	13:1	89	1.7:1	85
2	C2	4.7:1	77	48:1	92	1.2:1	88
3	C3	6.3:1	73	50:1	92	1.7:1	87
4	(*S*,*S*,*S*)-BisDiazphos-Rh(acac)$(CO)_2$ (1.2:1)	20:1	91	40:1	97	1.7:1	>95

[a]Conditions: 24 h, 60 °C, 150 psig H_2/CO (1:1), 0.2 M concentration of each substrate,1 mL total volume, 600:1 sub:cat, catalyst concentration estimated for C1−C3 from data in Chart 2, complete conversion of olefin to aldehyde. [b]Determined by ^{1}H NMR spectroscopy. [c]Determined by chiral GC analysis.

studies to better understand the effective active site count of the immobilized ligands. The paper concludes with application of the resin-bound catalysts in flow reactors.

RESULTS AND DISCUSSION

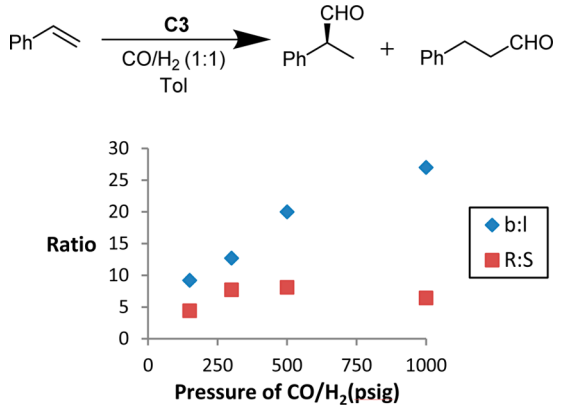
Tetraacid BDP was immobilized on three different amine resins using a three-step procedure to yield ligands **L1−L3** (Scheme 2). The first step involves conversion of the (*S*,*S*)-tetraacid BDP to the activated tetraacyl fluoride BDP as previously reported by our group.[17] Resins with different length PEG linkers were examined; previous studies have shown that PEG linkers yield more solution-like behavior for immobilized catalysts.[19,20] Overnight reaction of tetraacyl fluoride BDP with a substoichiometric amount of amine-terminated beads (in order to maximize the probability that just one carboxamide-linkage is formed between the ligand and the bead) presumably yields a ligand that is immobilized by one carboxamide attachment, with the three acyl fluoride groups remaining. This covalently linked BDP ligand is then reacted with (*S*)-methylbenzylamine (MBA) to generate asymmetrical tetracarboxamides. Note that the tetraacyl fluoride BDP comprises two pairs of diastereotopic acyl groups either of which may make the first linkage to the resin support. Thus, one expects two diastereomers of the final ligand to result from the immobilization procedure. Ligand synthesis is completed by capping with acetic anhydride any resin-based primary amine sites that were not functionalized with tetraacyl fluoride BDP. Free amine sites on the resin are undesirable because they could promote racemization of chiral aldehydes and provide a site for coordination to rhodium catalyst precursors. AHF catalysts (**C1−C3**) were formed by the gentle agitation of the catalyst precursor, Rh(acac)$(CO)_2$, with a suspension of BDP-containing beads for 2 h followed by several washings.

The immobilized catalysts **C1−C3** were screened for simultaneous rhodium-catalyzed iAHF of three substrates: styrene, vinyl acetate, and alloxy-*tert*-butyldimethylsilane (Table 1). Previously we have used this protocol to screen steric effects for homogeneous bisdiazaphospholane catalysts.[21−23]

The simultaneous screen results establish that the immobilized catalysts are active and selective. The activity of the catalyst will be discussed later in this manuscript. The data indicate that, although the regioselectivities and enantioselectivities obtained with the immobilized catalyst are respectably high, they are slightly lower than those obtained with the

dx.doi.org/10.1021/ja501568k | J. Am. Chem. Soc. 2014, 136, 7943−7953

Chart 1. AHF of Styrene at Increasing Syn Gas Pressure[a]



[a]Conditions: 23 h, 50 °C, 1.2 M styrene; 1600:1 sub:cat, changes in selectivity are assumed to be affected by p_{CO} and unaffected by p_{H2} based off previous studies.[12]

homogeneous catalyst. The observation of high enantioselectivity requires that the bulk, but not all, of product formation proceeds through BDP-ligated catalysts. Many factors could yield lower selectivity in the immobilized catalysts: diastereomeric environments created by immobilization of BDPs, variations in the amount of catalyst ligated by chiral phosphine, or mass transport limitations that yield different steady-state concentrations of reactants.

Because previous work by our group showed that both the regio- and enantioselectivities of styrene hydroformylation increase as the CO partial pressure is raised from 50 to 500 psig, we decided to examine pressure effects on styrene AHF using the Tentagel-S-NH_2-based catalyst, **C3** (Chart 1).[12] Interestingly, increased syn gas pressure dramatically increases the regioselectivity of styrene (>25:1) but has little influence on the enantiomeric ratio (~7:1). Such differences between immobilized and homogeneous catalysts suggest intrinsic selectivity differences between the catalysts rather than simply slower mass transport of gases to the immobilized catalyst active sites.

One motivation for catalyst immobilization is the recycling of expensive precious metals and chiral ligands. Using the protocol for simultaneous hydroformylation of three substrates in a shaker reactor, we examined the recyclability of Tentagel-linked **C3**. A single batch of immobilized catalyst was used for nine AHF cycles albeit with some variation of conditions between cycles 5–9 to examine different reaction conditions on the immobilized catalysts (Figure 1). After each cycle the reaction mixture was filtered, and beads were washed three times with clean solvent. Rhodium leaching was determined by ICP-OES analysis of the solution after each cycle following removal of the beads by filtration. At the end of the recycling experiments the total Rh content of the beads was determined by acid digestion of the beads followed by ICP-OES of the digest. Generally speaking, the regio- and enantioselectivities for each substrate were consistently high and similar to those of the initial run.

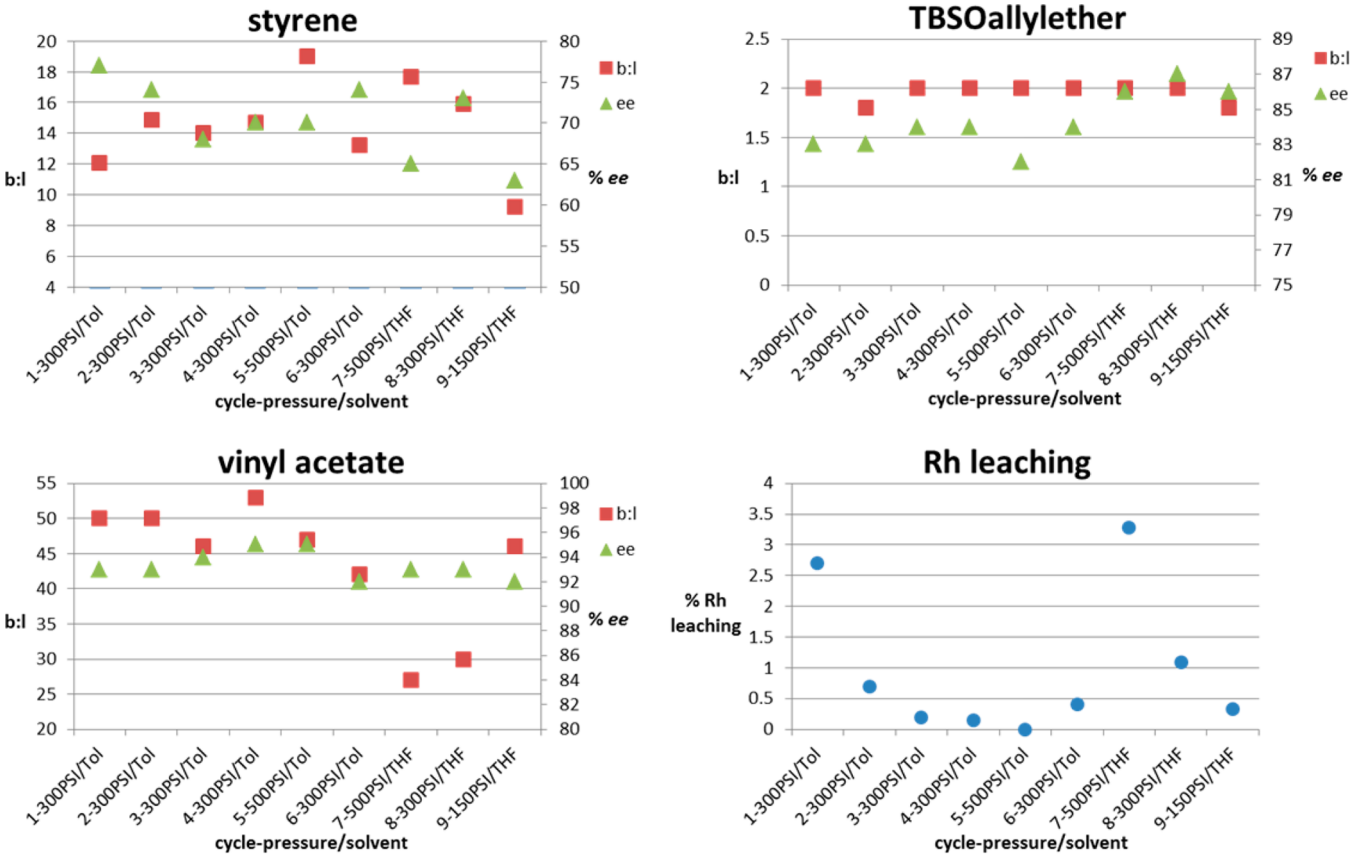
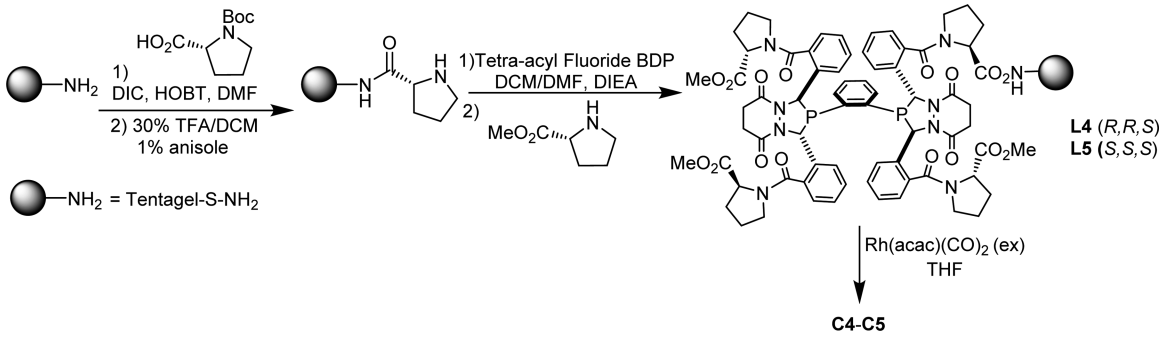


Figure 1. Recycling studies using 20 mg of **C3**. All reactions @ 60 °C, 1 mL total volume, 23 h. Beads washed three times with reaction solvent between cycles. All reactions went to complete conversion of olefin. Cycles 1–5, 0.4 M in each substrate = 1600:1 sub:cat. Cycles 6–9, 0.8 M in each substrate = 3200:1 sub:cat. Rh leaching determined by ICP analysis of Rh in product mixtures and decomposition of beads.

dx.doi.org/10.1021/ja501568k | J. Am. Chem. Soc. 2014, 136, 7943–7953

Scheme 3. Synthesis of Tentagel-proline-bisdiazaphospholanes L4(*R,R,S*) and L5(*S,S,S*) and Rh catalysts C4 and C5



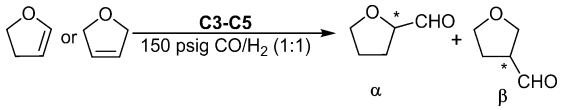
Furthermore, the Rh leaching was negligible (i.e., at the limits of detection) for most runs.[24] Two exceptions to these general features are seen: (1) higher styrene regioselectivity results when the CO pressure was increased (cycles 5, 7, and 9); (2) high Rh leaching occurs after the first run and after the seventh cycle when the solvent was changed from toluene to THF. Overall, such results demonstrate that immobilized rhodium AHF catalysts are robust and are capable of achieving reasonable catalyst recyclability and simple separation of catalyst from product. Using 20 mg of **C3** containing the equivalent of 1.3 mg of (*S,S,S*)-BisDiazphos, 2.1 g of combined aldehydes were produced over nine cycles, resulting in a TON of 20800.

Recently we examined a library of homogeneous bisdiazaphospholane catalysts that varied in the carboxamide substituent.[17] During this work we found that in the AHF of 2,3- and 2,5-dihydrofuran (DHF), bisdiazaphospholanes coupled with methyl prolinate instead of methylbenzylamine give higher selectivity and activity. We hypothesized that attachment of proline to a support followed by coupling the proline amine to the tetraacyl fluoride BDP would create an immobilized catalyst environment that was maximally similar to the analogous homogeneous catalyst (because all four carboxamides have prolines attached) while creating a practical catalyst for chiral furan building blocks that are useful in organic synthesis.[25] Proline-based immobilized bisdiazaphospholanes **L4** and **L5** were synthesized using the procedure outlined in Scheme 3.

Hydroformylation of the two substrates, 2,3- and 2,5-DHF were performed with catalysts containing immobilized ligands **C3**, **C4**, and **C5** (see Table 2). For the substrate, 2,3-DHF, the preferred regioisomer is the α-carboxaldehyde (2-formyl tetrahydrofuran). The proline-functionalized catalysts **C4** and **C5** yield significantly higher regioselectivity and activity than **C3**, with similar enantioselectivity (see entries 1−3).

Hydroformylation of 2,5-DHF is complicated due to competitive olefin isomerization to 2,3-DHF. Because AHF of 2,3-DHF is less selective and prefers the opposite antipode of the β-product (3-formyl tetrahydrofuran), isomerization of 2,5-DHF could result in substantially lower regio- and enantioselectivity of the major product.[17] However, 2,5-DHF commonly hydroformylates faster than 2,3-DHF, such that isomerization does not degrade selectivity at incomplete conversion.[17,26−28] Results for **C4** and **C5** were surprising because similar conversions were obtained starting from either 2,3- or 2,5-DHF. Also surprising was the finding that high selectivity is maintained during the AHF of 2,5-DHF, even though some isomerization to 2,3-DHF occurs and the apparent hydroformylation rates of 2,5- and 2,3-DHF seem similar. Starting with a mixture containing equal concentrations of both 2,5- and 2,3-DHF and running to low overall conversion (10%), nearly all of the consumed olefin is 2,5-DHF (Table 2 entry 7).[29] Thus, when both substrate isomers are present with immobilized catalysts, 2,5-DHF apparently *outcompetes* 2,3-DHF. Under competitive conditions, most of the 2,3-isomer formed by isomerization accumulates until the 2,5-isomer is consumed.

Table 2. Immobilized AHF of Dihydrofurans[a]



entry	catalyst	substrate	α:β ratio[b]	% CHO, % 2,3-DHF[b,c]	% ee α[c]	% ee β[c]
1	**C3**	2,3-DHF	1.3:1	32, 68	82(*S*)	42(*S*)
2	**C4**	2,3-DHF	3.7:1	73, 27	86(*S*)	54(*S*)
3	**C5**	2,3-DHF	4.0:1	61, 39	80(*S*)	40(*S*)
4	**C3**	2,5-DHF	1:100	58, 12	n.d.	84(*R*)
5	**C4**	2,5-DHF	1:50	69, 15	n.d.	91(*R*)
6	**C5**	2,5-DHF	1:50	70, 13	n.d.	88(*R*)
7[d]	**C4**	2,3/2,5 -DHF	1:14	10, 48	77(*S*)	88(*R*)

[a]Conditions: 0.8 M substrate, 1090:1 substrate:catalyst, 45 °C, 150 psig CO/H_2 (1:1), 21 h. [b]Determined by ^1H NMR spectroscopy. [c]2,3-DHF in entries 4−6 from isomerization of 2,5-DHF during reaction, remaining material is 2,5-DHF. [c]Determined by chiral GC analysis. [d]1.6 M in 2,3-DHF and 1.6 M in 2,5-DHF, 4000:1 substrate:catalyst, 40 °C, 21 h.

Determination of Effective Catalyst Loading. Active site counting and characterization is a ubiquitous problem in catalysis that is made more complicated with immobilized catalysts. For the immobilized catalysts used in this study, there are no guarantees that all amine sites in the support precursor are functionalized with ligand, that all ligand sites are bound to rhodium, that all immobilized rhodium is bound to chiral ligand, or that all rhodium sites are accessible to substrates.

As previously mentioned for the recycling studies, ICP-OES measurements provide a basis for quantitating the amount of rhodium that is retained in **C3** after synthesis and washing. Partial digestion of the beads by heating in aqua-regia greatly reduces the size of the beads, presumably by oxidation and cleavage of the PEG linker. After filtering to remove particulate PS, analysis of the filtrate solution by ICP-OES **C3** leads to an estimated loading of 36 μmol of rhodium per gram.[30] For comparison of Rh retention in nonphosphinated beads, excess $Rh(acac)(CO)_2$ (relative to amine linkers) was added directly to Tentagel-NH_2 beads, as well as Tentagel-NH_2 beads treated

dx.doi.org/10.1021/ja501568k | J. Am. Chem. Soc. 2014, 136, 7943−7953

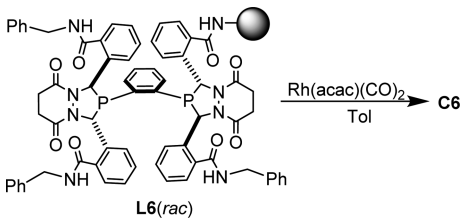
with acetic anhydride (Tentagel-NHAcyl). After washing both beads and acidic workup, the Tentagel-NH_2 beads retained 46 μmol Rh/g, while the Tentagel-NHAcyl beads retained just 6 μmol Rh/g. Both **C3** and Tentagel-NHAcyl beads show a negative ninhydrin test for free amines, suggesting that all the amine sites have been functionalized. The majority of the retained Rh on **C3** is, therefore, likely bound to a BDP since the synthesis of **C3** was followed by acylation of any remaining amine groups. It should be noted that the addition of BDP, Rh, and acetyl groups to **C3** corresponds to less than 10% of the original mass of the beads. Therefore, it is reasonable to normalize all values for rhodium loading to the mass of the bead.

Although we have measured the amount of Rh added to the beads and the amount of Rh recovered by acid workup and ICP analysis of the bead, these quantities do not indicate the number of phosphine sites that are attached to Rh *and* catalytically active. Comparison of reaction rates of homogeneous and immobilized catalysts gives a rough indication, only, of the active site count because of heterogeneity of the immobilized catalyst site activities arising from different steric environments and accessibility.

In order to assess the effective activity of immobilized catalysts while minimizing the consumption of precious enantiopure BDP, the ligand **L6**, a racemic analogue of **L3**, was prepared by first coupling racemic tetra acyl fluoride BDP with Tentagel-S-NH_2 followed by capping the remaining acyl fluorides with benzyl amine.

Equal masses of **L6** were mixed overnight with different amounts of a standardized Rh(acac)$(CO)_2$ solution and then were rinsed and filtered (Scheme 4). Beads exposed to different

Scheme 4. Racemic Tetrabenzyl Carboxamide BDP L6 and Rh Catalyst C6 for Activity Determination

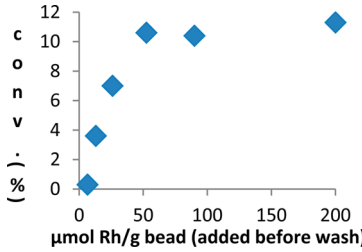


quantities of Rh were then used for the hydroformylation of vinyl acetate to determine if reactivity scales linearly with Rh loading, as seen for the homogeneous catalysts (Chart 2). If all BDP sites of **L6** have equal accessibility to Rh, one expects a plot of rate vs added rhodium to be linear until the all BDP sites are saturated with rhodium at which point there will be a breakpoint.

As shown in Chart 2, breakpoint behavior is observed with maximal rate observed at ~50 μmol Rh/g bead. This implies that exposure of **L6** to more than 50 μmol of rhodium per gram of bead does not lead to more active sites. While this value (~50 μmol/g) is slightly larger than the amount (~36 μmol/g) recovered by ICP analysis of the beads exposed to excess Rh(acac)$(CO)_2$, it is reasonable, considering possible error in weighing these materials and variability between different batches of immobilized phosphines. So far the data is consistent with the supposition that all of immobilized rhodium in the resin is effective for AHF.

A more direct method of characterizing immobilized ligands and catalysts is NMR spectroscopy. Attempts to obtain solid-

Chart 2. Hydroformylation Activity versus Rhodium Added[a]



[a]Conversion of 4.1 mmol of vinyl acetate vs the amount of Rh(acac)$(CO)_2$ added to 20 mg of **L6** followed by washing three times with 1 mL toluene. Conditions: 5 h, 4 M vinyl acetate in toluene, 150 psig CO/H_2, 44 °C.

state ^{31}P MAS NMR spectra of immobilized ligands were unsuccessful due to low signal-to-noise ratio. However, solution ^{31}P NMR of bead suspensions give spectra useful for characterization of the immobilized ligand. Tentagel beads were loaded into a Shigemi tube after reacting with a slight excess of tetraacyl fluoride BDP and washing three times with dichloromethane. Shigemi tubes concentrate the less dense beads in the detection region of the probe, allowing for integration versus an internal standard in solution. Although immobilized ligands yield broader spectra than the free BDP ligands, two clear doublets with a coupling constant of 185 Hz are seen in the ^{31}P NMR spectrum. This coupling value is consistent with $^3J_{PP}$ coupling of diastereotopic P atoms, the result of desymmetrization by attachment of the bisdiazaphospholane to the support through one amide bond (Figure 2).

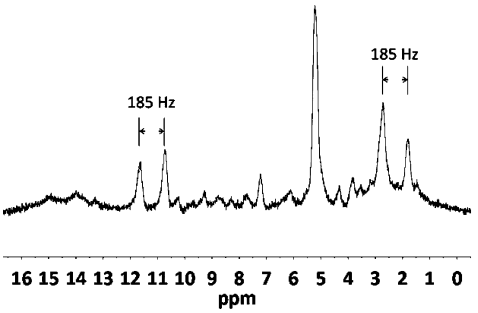


Figure 2. Solution-phase ^{31}P NMR of tetraacyl fluoride BDP reacted with Tentagel-S-NH_2, followed by washing with DCM.

The other major species at 5 ppm likely is noncovalently attached tetraacyl fluoride BDP, based on the chemical shift and lack of splitting. Fewer solvent washes were performed in the preparation of the samples for NMR analysis compared to the standard procedure in order to limit exposure to oxygen.[31] Multiple peaks corresponding to acyl fluorides are present in the ^{19}F NMR spectrum but cannot be assigned.

Unfortunately, addition of benzyl amine to form **L6** results in much broader NMR peaks that are less revealing (Figure 3). Crude integration of the broad **L6** peaks versus an internal standard (triphenylphosphine oxide) indicates loading of approximately 37 ($\pm$18) μmol bisdiazaphospholane/g bead. Finally, the addition of a solution of Rh(acac)$(CO)_2$ to the **L6**-functionalized beads in the NMR (50 μmol Rh/g bead) gives a ratio of metalated-to-free ligand around 3:1. Further addition of Rh(acac)$(CO)_2$ gives a negligible change to this ratio.

dx.doi.org/10.1021/ja501568k | J. Am. Chem. Soc. 2014, 136, 7943−7953

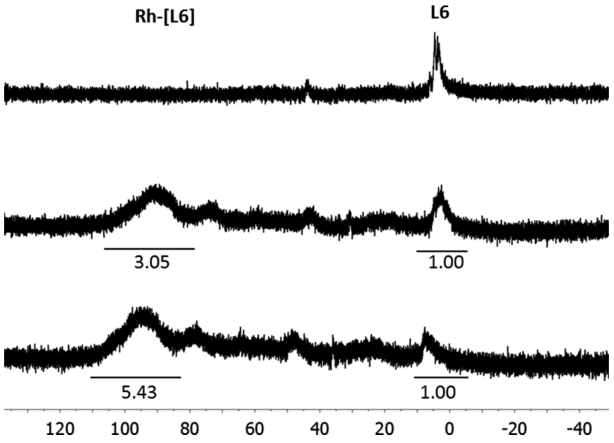


Figure 3. ^{31}P NMR of **L6** (top), addition of 2.44 μmol Rh(acac)$(CO)_2$ to 49 mg **L6** (50 μmol Rh/g bead) (middle), and addition of 4.88 μmol Rh(acac)$(CO)_2$ to 49 mg **L6** (100 μmol Rh/g bead) (bottom).Taken together, these data suggest that just 40−50 μmol/g of the nominal 290 μmol amine sites per gram Tentagel loading become functionalized with BDP ligand. Apparently, most of the BDP sites can be metalated with rhodium precursors. All of these numbers are somewhat crude, but it is clear that the nominal amine content of the bead far exceeds the active catalyst site count.

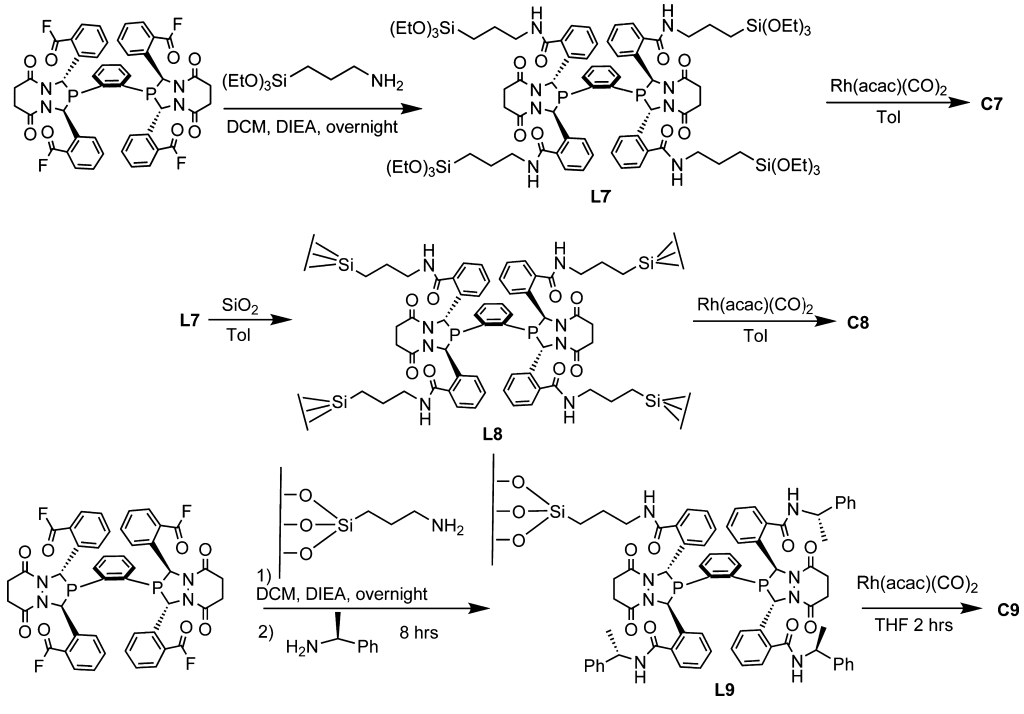
Now that we have a better understanding of the active site count of the immobilized catalysts, activity comparisons with the homogeneous catalysts can be made. Crude rate values taken between 10 and 30% total conversion show the immobilized catalyst to be 3−4 times slower than the corresponding homogeneous catalyst when normalized using the approximate active site counts. Using vinyl acetate, rates of 80 TOF h^{-1} were calculated for **C6**, compared to 280 TOF h^{-1} for the equivalent homogeneous catalyst (44 °C in shaker, 150 psig (1:1) CO/H_2, 4.1 M vinyl acetate, 4100:1 sub:cat). These rates are slower than those seen for homogeneous catalysts under *optimized* reaction conditions in well-stirred pressure bottles,[21] but provide a direct comparison of the homogeneous and immobilized catalysts under a single set of conditions. More detailed analysis of the rates of the immobilized catalysts is complicated by the inability to observe catalyst preactivation of the BDP−Rh(acac) complex with CO/H_2 to form the BDP−$RhH(CO)_2$ complex, which is the resting state for the AHF catalyst.

Overall the Tentagel-immobilized bisdiazaphospholane catalysts **C3**−**C6** perform AHF with high selectivity, exhibit 3.5-fold lower normalized activities than the homogeneous catalyst, and can be recycled. While developing these catalysts, we also pursued similar methods for immobilization on silica-based supports, due to their robustness and prevalence in the literature.[3,32−34]

Silica-Immobilized Catalysts. Rh−BDP complexes can be supported on silica either by covalent attachment of a metalated BDP complex to the support or by first attaching the BDP ligand to the silica followed by metalation. The former method involves coupling 3-aminopropyltriethoxysilane to the tetraacyl fluoride BDP precursor to give a tetracarboxamide BDP ligand with triethoxysilane groups (**L7**). Addition of a substoichiometric amount of Rh(acac)$(CO)_2$ followed by condensation on high-purity silica gel results in the immobilized catalyst **C8** (Scheme 5; middle). The latter method treats mesoporous silica SBA-15 with 3-aminopropyltriethoxysilane. Subsequent addition of tetraacyl fluoride BDP presumably forms at least one carboxamide linkage to the functionalized silica, followed by addition of methylbenzyl amine as in the synthesis of **L1**−**L3**. Washing and addition of Rh(acac)$(CO)_2$ gives the SBA-15 immobilized Rh-BDP catalyst **C9** (Scheme 5; bottom).

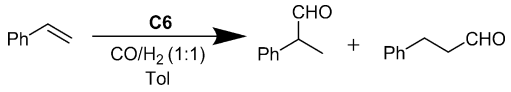
The silica-immobilized Rh−BDP catalysts **C8** and **C9**, along with homogeneous catalyst **C7**, were screened using the one-pot/multiolefin screen (styrene/vinyl acetate/allyloxy *tert*-butyldimethylsilane) used for bead-based catalysts. Unfortunately, these catalysts give decreased regio- and enantioselec-

Scheme 5. Synthesis of Silica-Bound Bisdiazaphospholanes



dx.doi.org/10.1021/ja501568k | J. Am. Chem. Soc. 2014, 136, 7943−7953

Table 3. Results of One-Pot AHF Screening of Silica-Immobilized Bisdiazaphospholanes and Homogeneous Precursor[a]



			styrene			vinyl acetate			allyloxy *tert*-butyldimethylsilane		
entry	catalyst	pressure	conv. (%)	b:l ratio[b]	% ee[c]	conv. (%)	b:l ratio[b]	% ee[c]	conv. (%)	b:l ratio[b]	% ee[c]
1	**C8**	150	15	6:1	63	25	30:1	78	34	1.2:1	82
2	**C9**	150	43	1.9:1	56	74	40:1	75	80	0.8:1	67
3	**C8**	300	57	4.6:1	62	79	30:1	81	88	1.3:1	70
4	**C9**	300	25	3.7:1	53	47	24:1	83	49	1.1:1	49
5[d]	**C7**	150	90	25:1	89	68	30:1	89	100	1.7:1	89
6[e]	(*S*,*S*,*S*)BisDiazphos−Rh(acac)$(CO)_2$ (1.2:1)	150	100	20:1	91	100	40:1	97	100	1.7:1	>95

[a]Conditions: 24 h, 50 °C, 0.6 M total substrate (equal concentrations of each ∼200:1 sub:cat (**C9**), ∼1000:1 sub:cat (**C8**). [b]Determined by ^{1}H NMR spectroscopy. [c]Determined by chiral GC analysis. [d]16 h, 4.3 M total substrate (equal concentrations of each), 1600:1 total substrate:cat. [e]60 °C, 600:1 sub:cat. Catalyst loadings for **C8** and **C9** are estimates based on loading of the materials assuming all Rh added forms a BDP catalyst.

tivities for all substrates examined compared to those of the homogeneous catalysts or Tentagel-supported catalyst **C3**. While previous experiments showed that increasing the CO pressure for **C3** improved the selectivity of styrene AHF, negligible changes in selectivity are observed for **C8**−**C9**. However, increasing syn gas pressure to 300 psig does improve the activity of **C8** (this effect has not been observed for the other immobilized or homogeneous BDP catalysts). This result may indicate that mass transport is limiting activity at 150 psig for **C8**. After filtering the solid catalyst away from aldehyde products, the product solution contains less than 1% of the rhodium loading as determined by ICP-OES.

Control experiments using **C7** under homogeneous reaction conditions show high regio- and enantioselectivities (Table 3, entry 5). Therefore, it is unlikely that the low selectivities for the silica-supported catalysts **C8** and C9 relative to the bead-supported catalysts **C3**-**C6** results from the different carboxamide groups used for support attachment. Reasonable enantioinduction is still observed for the AHF of vinyl acetate and allyloxy *t*-butyldimethylsilane and is the first example of an iAHF on silica supports with greater than 60% *ee* to the best of our knowledge. Unfortunately, the AHF product of styrene racemizes upon extended reaction times with the silica-based catalysts, while no change in the enantiomeric excess of the other two chiral aldehydes was observed after 24 h.

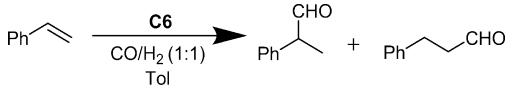
AHF in Flow. Recently the application of asymmetric catalysis in flow reactors has received considerable attention, but examples of AHF in flow reactors are uncommon.[35,36] Tentagel and other PS−PEG cografted beads have been used for immobilization of homogeneous catalysts and in flow reactors for hydrogenations, allylations, and other reactions.[2,37−39]

We set out to demonstrate the application of the more selective Tentagel-immobilized AHF catalysts in a plug flow reactor. Particularly for the bench-scale chemist, a packed column of recyclable catalyst would be easier to rinse, store, and set up as needed. Our goals for this setup were to demonstrate that these immobilized catalysts could be easily applied to a flow reactor and determine if syn gas concentration in solution could be maintained while passing through the catalyst bed.

Our primitive flow reactor consists of a glass pressure bottle and manifold, an HPLC pump with a max flow rate of 10 mL/min, and a 1/4 in. × 5.9 in. HPLC column packed with **C6**. Substrate solution is stirred under syn gas inside the pressure bottle, which acts as a reservoir while the gas-saturated solution is pumped through the column. Solution from the column then drips back into the pressure bottle, thus effecting recycle and gas-saturation of the substrate/product solution.

One limitation with this design is that dissolved syn gas is consumed as solution passes through the catalyst bed. This may lead to different syn gas concentrations at the beginning and end of the column. Previous work has demonstrated that the AHF selectivity for aryl alkenes such as styrene is particularly sensitive to the effective concentration of CO in solution.[12] To probe the effective gas concentration in the plug flow reactor we examined the effect of flow rate on the selectivity of styrene hydroformylation using the racemic, supported catalyst **C6**. One anticipates increased regioselectivity with increased flow rate if the reactor zone is significantly depleted in gas. This behavior is observed (Table 4). Increased flow rate yields

Table 4. Hydroformylation of styrene in plug flow reactor[a]



flow rate (mL/min)	conv. (%)	b:l[a]
1	19	1.3:1
2	11	2.2:1
5	25	9.0.:1
9	24	13:1

[a]Conditions: 3 h, 150 psig, 60 °C, 1.2 M styrene; 1000:1 sub:cat. 0.28g **C6** (≡ 14 μmol Rh based off batch reactor experiments).

increased regioselectivity with a plateau b:l ratio of about 13:1 reached at the highest flow rate examined (10 mL/min). This plateau corresponds to the regioselectivity observed in shaker-style batch reactors with the structurally similar catalyst **C3** at the same temperature and gas pressure (Chart 2). We conclude that the plug flow reactor using immobilized catalyst and sufficiently high flow rates mimics the behavior of immobilized catalysts in batch reactors.

Recycling studies were performed in which the **C6** catalyst effected the hydroformylation of eight separate batches of vinyl acetate in the plug flow reactor (Table 5). The Rh content of the product solutions was measured by ICP-OES after each batch. Catalyst was loaded onto the beads by placing phosphinated beads into the plug flow reactor and then circulating a solution of Rh(acac)$(CO)_2$ through the system

dx.doi.org/10.1021/ja501568k | *J. Am. Chem. Soc.* 2014, 136, 7943−7953

Table 5. Hydroformylation of Vinyl Acetate Using a Single Catalyst Loading in Plug Flow Reactor[a]

run	[substrate], time	conv.[b] (%)	b:l[c]	Rh leached (%)[d]
1	1 M, 15 h	100	58:1	6.1
2	1 M, 4 h	100	50:1	2.2
3	1 M, 4 h	100	54:1	0.7
4	1 M, 4 h	100	55:1	0.7
5	1 M, 4 h	100	56:1	0.7
6	1 M, 4 h	100	60:1	0.3
7	4.2 M, 4 h	48	46:1	0.4
8	4.2 M, 4 h	51	51:1	0.5

[a]Conditions. 50 °C, 150 psig 1:1 CO/H_2, 4 mL/min flow rate. 0.38 g **C6**, 19 μmol Rh based on Chart 2, 485:1 substrate:catalyst for 1 M runs. [b]Conversion percentages are estimates due to a leak in the HPLC pump, ∼20% (first run) to ∼50% (final run). Leaked solution was combined with reaction solution for analysis, but some vinyl acetate was lost due to its volatility. [c]Determined by ^{1}H NMR spectroscopy. [d]Determined by ICP analysis of rhodium in the product solution compared to beads following acid workup.

under N_2. Clean solvent was circulated through the system multiple times to remove any unbound Rh from the reactor.

As seen with beads in shaker reactors, immobilized catalyst in a plug flow reactor exhibits low catalyst leaching and stable activity and selectivity metrics. Recycling studies using the plug flow reactor show 6% of the total Rh loading leaches out in the first cycle, 2% in the second cycle, and ∼0.5% in the third and successive cycles. Initial turnover frequencies for the plug flow reactor are in the range of 100−200 TOF h^{-1}. This is comparable to the rates observed in batch reactor experiments. Over eight additions of fresh substrate solutions, nearly 5000 turnovers of the catalyst were achieved with no significant changes in apparent rates or selectivity.

Immobilized AHF reactions achieve high rates and selectivity in plug flow reactors. For substrates that are sensitive to gas partial pressures, the plug flow setup should be arranged such that equilibrium concentrations of dissolved gas in the catalytic reaction zone are maintained.

CONCLUSION

Ultimately, larger-scale application of catalysts containing precious metals and ligands requires recycling of the catalyst. We report a complete analysis of immobilized AHF that includes synthesis on both silica and resin supports, investigation of catalyst selectivity and activity, characterization of the often elusive "active site count", determination of catalyst leaching rates, and application to gram-scale synthesis in flow reactors. Ligand immobilization takes advantage of the versatile ligand precursor, tetraacyl fluoride BDP. Reaction of the acyl fluoride groups with amines enables covalent attachment of the ligand to supports and further elaboration of the BDP environment. Of the supports examined, immobilization on Tentagel-S-NH_2 beads yields the best combination of regio- and enantioselectivity in AHF reactions. In fact, the regio- and enantioselectivities obtained with immobilized catalysts approach the high bench-marks established by the homogeneous BDP catalyst.

Comparison of catalyst activities for immobilized and homogeneous catalysts depends critically on accurate determination of the active site counts. For the BDP-functionalized Tentagel-S-NH_2 beads, the active site counts are determined by breakpoint titration methods to be approximately 40−50 μmol per gram of bead. This is significantly lower than the nominal amine site count of 290 μmol per gram of native bead, demonstrating the importance of measuring, rather than assuming, active site counts in making comparisons between homogeneous and heterogeneous catalysts. On the basis of catalyst active site counts, the immobilized catalyst exhibits about 30% of the activity of the homogeneous catalyst. Like the homogeneous Rh(BDP) catalysts, the Tentagel immobilized catalysts demonstrate higher selectivity in styrene hydroformylation as the synthesis gas pressure is increased and faster conversion of 2,5-DHF than 2,3-DHF.

Tentagel-immobilized BDP ligands provide heterogeneous AHF catalysts that can be recycled with no loss of selectivity over nine cycles and applied in shaker-style batch reactors or plug flow reactors. Using only 20 mg of resin containing 1.3 mg of active catalyst, grams of aldehyde can be produced in high selectivity containing only trace amounts of precious metals. Flow reactors are a safe, scalable method of implementing reactions using dangerous gases such as CO and H_2 in general use facilities such as those in many pharmaceutical and fine-chemical companies. The work reported herein allows practical access to immobilized BDP ligands that are recyclable, active, and selective catalysts for AHF.

EXPERIMENTAL SECTION

General Considerations. All phosphines were prepared under N_2 using standard Schlenk line techniques. Rh(acac)-$(CO)_2$ was recrystallized (green needles) from toluene/hexanes prior to use. THF and toluene were distilled over Na/benzophenone under a nitrogen atmosphere. THF and toluene used for asymmetric hydroformylation reactions were further deoxygenated by at least three freeze−thaw cycles prior to use. Dichloromethane was distilled under nitrogen over P_2O_5. Routine NMR experiments (^{1}H, ^{13}C, ^{19}F, ^{31}P) were carried out on a Bruker AC-300, Varian Mercury-300, or a Varian Unity-500. Proton (^{1}H) and carbon (^{13}C) NMR spectra were referenced to TMS (0.00 ppm) and $CDCl_3$ (77.0 ppm) respectively. The fluorine (^{19}F) spectra were referenced to TMS in the ^{1}H spectra, using the Unified Scale. Phosphorus (^{31}P) chemical shifts were referenced to an external 85% phosphoric acid (H_3PO_4) sample. The percent conversion and regioisomer ratios were determined by ^{1}H NMR analysis of the crude reaction mixture. Gas chromatography (GC) was performed on a Varian 2010 using a β-DEX 225 column (30 m × 0.25 mm ID). Deoxo-Fluor, diisopropylethylamine, benzyl amine, (*S*)-methylbenzylamine, anhydrous grade dimethylformamide, diisopropylcarbodiimide, hydroxybenzotriazole hydrate, 3-aminopropyltriethoxysilane, and high-purity silica gel (Merck grade 7734, pore size 60 Å, 70−230 mesh) were purchased from Sigma-Aldrich and used without further purification. (*R*)- and (*S*)-Proline methyl esters were synthesized from (*R*)- and (*S*)-proline respectively, and recrystallized. Vinyl acetate, styrene, TBSO allyl ether, 2,5-dihydrofuran, and 2,3-dihydrofuran were all sparged with N_2 before use. Tentagel-S-NH_2 was purchased from Anaspec (0.29 mmol/g, 90 μm particle size). PS-MBHA resin was purchased from Polymer laboratories (1% cross-linking, loading 1.6 mmol/g). Synthesis of the EBES linker and attachment to the PS-MBHA resin was carried out following literature procedure.[18] SBA-15 treated with Ph_2SiCl_2 and 3-aminopropyltriethoxysilane to give an amine loading of 5.7 mmol/g was prepared by Daniel Resasco at University of Oklahoma. Synthesis of the tetraacid bisdiazaphospholane and tetraacyl

dx.doi.org/10.1021/ja501568k | J. Am. Chem. Soc. 2014, 136, 7943−7953

fluoride bisdiazaphospholane followed literature procedure.[10,17] The C_2 enantiomers of tetraacid bisdiazaphospholane are resolved by SFC using a Chiralpak IC-H column, (60% MeOH + 0.2% diethylamine)/CO_2, 2.4 mL/min, 100 bar, 40 °C. Reported substrate:catalyst ratios for **C3**−**C6** are based on the data for **C6** in Chart 2, corresponding to an estimated 50 μmol Rh/g bead. Substrate:catalyst ratios for the silica-based catalysts **C8**/**C9** are estimates based on the amount of Rh(acac)$(CO)_2$ added to the support.

General Asymmetric Hydroformylation Procedure. Reactions were performed in a multiwell Cat24 Parr reactor that was dried in the oven overnight. The supported catalysts were loaded into oven-dried glass tubes in a dinitrogen-filled glovebox; substrate and solvent were then added by 200 and 1000 μL Eppendorf pipettes. The reactor was sealed, removed from the glovebox, placed in a fume hood, purged three times with 150 psig of (1:1) synthesis gas to remove dinitrogen and filled to the appropriate synthesis gas pressure. The shaker speed used for all reactions was 300 rpm. Upon completion of the reaction, the reactor was allowed to cool to room temperature and was vented inside the fume hood down to a slight overpressure. The reactor was then brought back into a dinitrogen glovebox and disassembled. For recycling experiments, the supported catalyst was filtered and washed three times inside a glovebox with 1 mL of reaction solvent, followed by repeating the reaction setup. An aliquot of the reaction mixture was dissolved in d_8-toluene for ^{1}H NMR to determine percent conversion and regioselectivity. The enantiomeric excess of the branched hydroformylation product was determined by chiral GC.

Synthesis of Resin-Supported Bisdiazaphospholanes C1−C3. Two hundred mg of amine resin (MBHA/MBHA-EBES/Tentagel-S-NH_2) was loaded into a 6 mL SPE tube with a polypropylene frit. The tube was sealed with a septum on top and a two-way valve and needle on the bottom. The needle was then placed in a 250 mL Schlenk flask connected to Schlenk line to allow for draining reactant solution while maintaining a nitrogen atmosphere. The flask and SPE tube were pump-backfilled with N_2 three times. The beads were washed sequentially with 3 mL DMF, 1 mL DIEA, 3 mL DMF, and 3 mL DCM to remove any water inside the beads. The beads were then swollen in 1 mL DMF while being agitated by inserting a 22 gauge needle in the septum, allowing N_2 to slowly purge out. Two equivalents (relative to amine loading on the bead) of tetraacyl fluoride bisdiazaphospholane (*S*,*S*) was dissolved in 3 mL DCM and was added to the beads by syringe, followed by 10 equiv of DIEA. The solution was then mixed overnight, adding DMF as needed as solvent evaporates. The solution was then drained, followed by washing with 2 × 2 mL DMF, 2 × 2 mL MeOH, and 2 × 2 mL DCM. The beads were then suspended in 3 mL DMF, followed by addition of 10 equiv of (*S*)-methylbenzylamine and 10 equiv of DIEA. The beads were agitated overnight; solution was drained, followed by washing with 2 × 2 mL DMF, 2 × 2 mL MeOH, and 2 × 2 mL DCM. A solution of 0.3 mL acetic anhydride, 0.5 mL 2,6-lutidine, a grain of DMAP, and 2 mL THF was prepared and the solution was added to the beads, agitated for 20 min, drained, followed by washing of the beads with 2 × 2 mL DMF, 2 × 2 mL MeOH, and 2 × 2 mL DCM. 20 mg Rh(acac)$(CO)_2$ was dissolved in 4 mL toluene and added to the beads. The beads were agitated for 2 h, adding toluene as needed. The solution was drained followed by washing with 5 × 2 mL toluene; the beads were then dried in vacuo.

Synthesis of Resin-Supported Bisdiazaphospholanes C4−C5. One hundred and fifty mg of Tentagel-S-NH_2 resin was loaded into a 6 mL SPE tube with a PP frit. The tube was sealed with a septum and a two-way valve and needle on the bottom. The needle was then placed in a 250 mL Schlenk flask connected to Schlenk line to allow for draining reactant solution while maintaining a nitrogen atmosphere. The flask and SPE tube were pump-backfilled with N_2 three times. The beads were washed sequentially with 3 mL DMF, 1 mL DIEA, 3 mL DMF, and 3 mL DCM to remove any water inside the beads. The beads were then swollen in 1 mL DMF while being agitated by inserting a 22 gauge needle in the septum, allowing N_2 to slowly purge out. In 2 mL of DMF were dissolved 0.17 mmol of Boc-L-proline and 0.17 mmol of HOBT hydrate and added to beads, agitated for 10 min, followed by addition of 0.17 mmol of DIC. Beads were agitated overnight; solution was drained, and then washed with 2 × 2 mL DMF, 2 × 2 mL MeOH, and 2 × 2 mL DCM. Boc groups were cleaved by adding a mixture of 3 mL DCM, 1 mL TFA, and 0.05 mL anisole and agitating for 45 min. The solution was then drained and washed with 2 × 2 mL DMF, 2 × 2 mL MeOH, and 2 × 2 mL DCM. In 3 mL of DCM was dissolved 0.9 mmol of tetraacyl fluoride bisdiazaphospholane ((*R*,*R*)-**L4**/(*S*,*S*)-**L5**) and added to the bead by syringe. Added by syringe was 0.44 mmol of DIEA. The solution was mixed overnight, adding DMF as needed due to solvent evaporation. The solution was drained, followed by washing with 2 × 2 mL DMF, 2 × 2 mL MeOH, and 2 × 2 mL DCM. The remaining acyl fluorides on the immobilized bisdiazaphospholanes were then functionalized by suspending the beads in 3 mL DMF, followed by addition of 0.9 mmol of L-Pro-OMe and 0.9 mmol of DIEA. The beads were agitated overnight; the solution was drained, and then washed with 2 × 2 mL DMF, 2 × 2 mL MeOH, and 2 × 2 mL DCM. A solution of 0.3 mL acetic anhydride, 0.5 mL 2,6-lutidine, a grain of DMAP, and 2 mL THF was prepared and added to the beads; the beads were agitated for 20 min, drained, followed by washing of the beads with 2 × 2 mL DMF, 2 × 2 mL MeOH, and 2 × 2 mL DCM. Two mL of toluene was added to the beads, followed by a solution of 0.07 mmol of Rh(acac)$(CO)_2$ dissolved in 2 mL toluene. The beads were agitated for 1 h, adding toluene as needed. The solution was drained, followed by washing with 5 × 2 mL toluene; beads were then dried in vacuo.

Synthesis of Resin-Supported Bisdiazaphospholanes L6. Two hundred mg of Tentagel-S-NH_2 resin was loaded into a 6 mL SPE tube with a PP frit. The tube was sealed with a septum with a two-way valve and needle on the bottom. The needle was then placed in a 250 mL Schlenk flask connected to Schlenk line to allow for draining reactant solution, while maintaining a nitrogen atmosphere. The flask and SPE tube were pump-backfilled with N_2 three times. The beads were washed sequentially with 3 mL DMF, 1 mL DIEA, 3 mL DMF, and 3 mL DCM to remove any water inside the beads. The beads were then swollen in 1 mL DMF while being agitated by inserting a 22 gauge needle in the septum, allowing N_2 to slowly purge out. Dissolved in 3 mL DCM and added to the beads by syringe was 0.12 mmol of tetraacyl fluoride bisdiazaphospholane (RAC). Added by syringe was 0.6 mmol of DIEA. The solution was mixed overnight, adding DMF as needed as solvent evaporates. The solution was drained, followed by washing with 2 × 2 mL DMF, 2 × 2 mL MeOH, and 2 × 2 mL DCM. The beads were suspended in 3 mL DMF, followed by addition of 0.6 mmol of benzylamine and 0.6 mmol

dx.doi.org/10.1021/ja501568k | J. Am. Chem. Soc. 2014, 136, 7943−7953

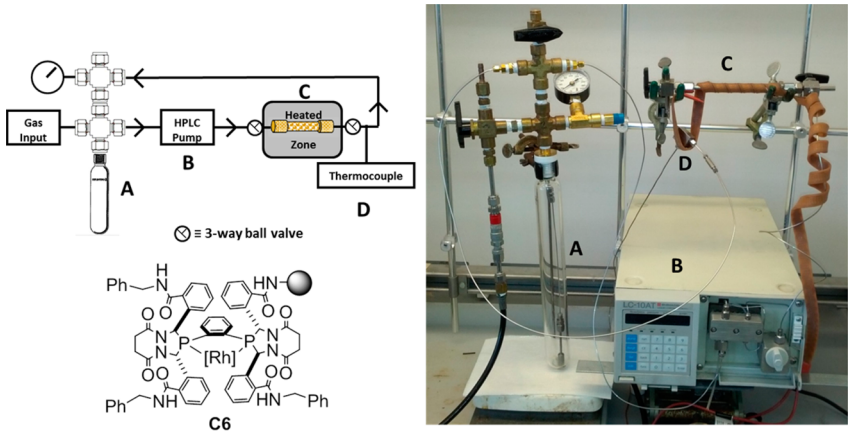


Figure 4. Diagram and photo of plug flow reactor.

of DIEA. The beads were agitated overnight; drained, and then washed with 2 × 2 mL DMF, 2 × 2 mL MeOH, and 2 × 2 mL DCM. A solution of 0.3 mL acetic anhydride, 0.5 mL 2,6-lutidine, a grain of DMAP, and 2 mL THF was prepared and added to the beads, agitated for 20 min, drained, followed by washing of the beads with 2 × 2 mL DMF, 2 × 2 mL MeOH, and 2 × 2 mL DCM. The beads were then dried in vacuo.

Synthesis of L7. In 100 mL DCM under N_2 was dissolved 0.18 mmol of tetraacyl fluoride bisdiazaphospholane (*S*,*S*). By syringe was added 1 mmol of DIEA, followed by 0.2 mL (1 mmol) 3-aminopropyltriethoxysilane. The reaction was stirred at room temperature overnight followed by aqueous extraction with sat. $NaHCO_3$, 1 M HCL, and brine. The organic layer was concentrated by rotovap to give **L7** in quantitative yield. ^{1}H NMR ($CDCl_3$, δ, ppm); 8.46 (t, J = 5.6 Hz, 2H) 7.63 (d, J = 7.5 Hz, 4H) 7.50 (m, 4H) 7.21 (m, 6H) 6.98 (m, 4H) 6.68 (t, J = 7.6 Hz, 2H) 6.23 (s, 2H) 6.16 (d, J = 8 Hz, 2H) 3.84 (m, 24H) 3.6−3.2 (m, 8H) 2.6−24 (m, 8H) 1.8−1.4 (m, 8H) 1.25 (m, 36H) 0.9−0.4 (m, 8H). ^{31}P{^{1}H} NMR ($CDCl_3$, δ, ppm) 7.25 (s).

Synthesis of Silica-Supported Bisdiazaphospholane C8. Three hundred mg (0.18 mmol) of **L7** was dissolved in 50 mL toluene, and added to a solution of 0.9 mmol of $Rh(acac)(CO)_2$ in 3 mL toluene, giving a 2:1 ligand:Rh ratio. The solution was stirred at room temperature for 1 h, and then added to 2 g of Merck 60 Å silica suspended in 50 mL toluene. The solution was stirred overnight at room temperature, followed by filtering the solution through Schlenk flask with a frit side arm. **C8** was then washed with 4 × 50 mL of toluene and dried in vacuo.

Synthesis of Silica-Supported Bisdiazaphospholane C9. One hundred mg of SBA-15 with an amine loading of 5.7 mmol/g was loaded into a 6 mL SPE tube with a PP frit. The tube was sealed with a septum and a two-way valve and needle on the bottom. The needle was then placed in a 250 mL Schlenk flask connected to Schlenk line to allow for draining reactant solution while maintaining a nitrogen atmosphere. The flask and SPE tube were pump-backfilled with N_2 three times. The silica was washed twice with DCM. Silica was suspended in 1 mL DMF while being agitated by inserting a 22 gauge needle in the septum, allowing N_2 to slowly purge out. Dissolved in 3 mL DCM and added by syringe was 1.2 mmol of tetraacyl fluoride BDP (*S*,*S*). Added by syringe was 5.7 mmol of DIEA. Suspension was mixed overnight, adding DMF as needed as solvent evaporates. Solution was drained, followed by washing with 2 × 2 mL DMF, 2 × 2 mL MeOH, and 2 × 2 mL DCM. Silica was suspended in 3 mL DMF, followed by addition of 5.7 mmol of (*S*)-methylbenzylamine and 5.7 mmol of DIEA. Silica was agitated overnight; the solution drained, followed by washing with 2 × 2 mL DMF, 2 × 2 mL MeOH, and 2 × 2 mL DCM. A solution of 0.3 mL acetic anhydride, 0.5 mL 2,6-lutidine, a grain of DMAP, and 2 mL THF was prepared and added to the silica, agitated for 20 min, drained, followed by washing with 2 × 2 mL DMF, 2 × 2 mL MeOH, and 2 × 2 mL DCM. Silica was suspended in 2 mL toluene, followed by addition of 0.8 mmol of $Rh(acac)(CO)_2$ dissolved in 2 mL toluene. Silica was agitated for 1 h, adding toluene as needed. Solution was drained followed by washing with 5 × 2 mL toluene; silica was then dried in vacuo.

Hydroformylation Procedure for a Plug Flow Reactor. A portion of 0.28 g of **L6** was loaded in a 1/4 in. × 5.9 in. HPLC column inside a glovebox, then connected to an HPLC pump and 200 mL glass pressure bottle (Figure 4). The pressure bottle was connected to a nitrogen source via quick-connect, purging the pressure bottle and pump by opening a three-way valve attached to the column, keeping the column closed off. Twelve mL of substrate solution was added to the pressure bottle via syringe, and the valves were then positioned to allow solution to circulate. Circulation and heating were maintained until a constant temperature was reached (~30 min) before pressurizing/venting the pressure bottle with synthesis gas three times to 150 psig. At the end of the desired reaction time the solution was drained through a three-way ball valve attached to the column for analysis. The apparatus was then rinsed with 3 × 10 mL toluene between recycles.

■ ASSOCIATED CONTENT

Supporting Information

Preparation of **L6** for rhodium titration, method for preparing ICP solutions, description of plug flow reactor part, homogeneous AHF data for **C7**, and GC conditions for chiral aldehydes. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

landis@chem.wisc.edu

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The assistance of Rob McClain for ICP instrumentation and a HPLC pump is greatly appreciated. We thank Daniel Resasco (University of Oklahoma) for a sample of SBA-15 treated with 3-aminopropyltriethoxysilane, the Dow Chemical Company for their generous donation of $Rh(acac)(CO)_2$, and Merck & Co. (Dr. Neil Strotman) for resolution of tetracarboxylic acid bisdiazaphospholane. We also acknowledge the NSF (CHE-9208463 and CHE-0342998) for funding the NMR facilities and some of the reactor equipment (CHE-0946901) and the NSF (CHE-1152989).

■ REFERENCES

(1) Baleizao, C.; Garcia, H. *Chem. Rev.* **2006**, *106*, 3987.
(2) Zhao, G.; Chai, Z. In *Recoverable and Recyclable Catalysts*; John Wiley & Sons, Ltd: New York, 2009; p 49.
(3) Marras, F.; Wang, J.; Coppens, M.-O.; Reek, J. N. H. *Chem. Commun.* **2010**, *46*, 6587.
(4) Lu, S.-M.; Alper, H. *J. Am. Chem. Soc.* **2003**, *125*, 13126.
(5) van Leeuwen, P. W. N. M.; Sandee, A. J.; Reek, J. N. H.; Kamer, P. C. J. *J. Mol. Catal. A: Chem.* **2002**, *182−183*, 107.
(6) Shibahara, F.; Nozaki, K.; Hiyama, T. *J. Am. Chem. Soc.* **2003**, *125*, 8555.
(7) Shibahara, F.; Nozaki, K.; Matsuo, T.; Hiyama, T. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1825.
(8) Nozaki, K.; Shibahara, F.; Hiyama, T. *Chem. Lett.* **2000**, *29*, 694.
(9) Nozaki, K.; Itoi, Y.; Shibahara, F.; Shirakawa, E.; Ohta, T.; Takaya, H.; Hiyama, T. *J. Am. Chem. Soc.* **1998**, *120*, 4051.
(10) Clark, T. P.; Landis, C. R.; Freed, S. L.; Klosin, J.; Abboud, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 5040.
(11) McDonald, R. I.; Wong, G. W.; Neupane, R. P.; Stahl, S. S.; Landis, C. R. *J. Am. Chem. Soc.* **2010**, *132*, 14027.
(12) Watkins, A. L.; Landis, C. R. *J. Am. Chem. Soc.* **2010**, *132*, 10306.
(13) Watkins, A. L.; Hashiguchi, B. G.; Landis, C. R. *Org. Lett.* **2008**, *10*, 4553.
(14) Wong, G. W.; Adint, T. T.; Landis, C. R. *Org. Synth.* **2012**, *89*, 243.
(15) Risi, R. M.; Burke, S. D. *Org. Lett.* **2012**, *14*, 1180.
(16) Ho, S.; Bucher, C.; Leighton, J. L. *Angew. Chem., Int. Ed.* **2013**, *52*, 6757.
(17) Adint, T. T.; Wong, G. W.; Landis, C. R. *J. Org. Chem.* **2013**, *78*, 4231.
(18) Landis, C. R.; Clark, T. P.; Halpern, J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5428.
(19) Bayer, E.; Albert, K.; Willisch, H.; Rapp, W.; Hemmasi, B. *Macromolecules* **1990**, *23*, 1937.
(20) Bayer, E. *Angew. Chem., Int. Ed.* **1991**, *30*, 113.
(21) Klosin, J.; Landis, C. R. *Acc. Chem. Res.* **2007**, *40*, 1251.
(22) Cobley, C. J.; Gardner, K.; Klosin, J.; Praquin, C.; Hill, C.; Whiteker, G. T.; Zanotti-Gerosa, A. *J. Org. Chem.* **2004**, *69*, 4031.
(23) Cobley, C. J.; Klosin, J.; Qin, C.; Whiteker, G. T. *Org. Lett.* **2004**, *6*, 3277.
(24) Cycles 3−5 are within error of 0 Rh g/mL.
(25) Stepan, A. F.; Karki, K.; McDonald, W. S.; Dorff, P. H.; Dutra, J. K.; DiRico, K. J.; Won, A.; Subramanyam, C.; Efremov, I. V.; O'Donnell, C. J.; Nolan, C. E.; Becker, S. L.; Pustilnik, L. R.; Sneed, B.; Sun, H.; Lu, Y.; Robshaw, A. E.; Riddell, D.; O'Sullivan, T. J.; Sibley, E.; Capetta, S.; Atchison, K.; Hallgren, A. J.; Miller, E.; Wood, A.; Obach, R. S. *J. Med. Chem.* **2011**, *54*, 7772.
(26) Chikkali, S. H.; Bellini, R.; de Bruin, B.; van, d. V.; Reek, J. N. H. *J. Am. Chem. Soc.* **2012**, *134*, 6607.
(27) Chikkali, S. H.; Bellini, R.; Berthon-Gelloz, G.; van der Vlugt, J. I.; de Bruin, B.; Reek, J. N. H. *Chem. Commun.* **2010**, *46*, 1244.
(28) Fernández-Pérez, H.; Benet-Buchholz, J.; Vidal-Ferran, A. *Org. Lett.* **2013**, *15*, 3634.
(29) Calculated from enantiomeric excess and branch to linear ratios of combined run to individual runs.
(30) Average of two runs that were within 1 μmol Rh/g.
(31) Standard procedure used is 2 × DMF, 2 × MeOH, and 2 × DCM washes to remove excess reagents, beads in Shigemi tube were only washed 2 × DCM.
(32) Merckle, C.; Blumel, J. *Top. Catal.* **2005**, *34*, 5.
(33) Lu, Z.-l.; Lindner, E.; Mayer, H. A. *Chem. Rev.* **2002**, *102*, 3543.
(34) Han, D.; Li, X.; Zhang, H.; Liu, Z.; Li, J.; Li, C. *J. Catal.* **2006**, *243*, 318.
(35) Tsubogo, T.; Ishiwata, T.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2013**, *52*, 6590.
(36) Webb, D.; Jamison, T. F. *Chem. Sci.* **2010**, *1*, 675.
(37) Bayston, D. J.; Travers, C. B.; Polywka, M. E. C. *Tetrahedron: Asymmetry* **1998**, *9*, 2015.
(38) Jee, J.-E.; Cheong, J. L.; Lim, J.; Chen, C.; Hong, S. H.; Lee, S. S. *J. Org. Chem.* **2013**, *78*, 3048.
(39) Nakano, H.; Takahashi, K.; Suzuki, Y.; Fujita, R. *Tetrahedron: Asymmetry* **2005**, *16*, 609.