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Self-Assembly of a Confined Rhodium Catalyst for Asymmetric Hydroformylation of Unfunctionalized Internal Alkenes

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Supporting Information

ABSTRACT: A chiral supramolecular ligand has been assembled and applied to the rhodium-catalyzed asymmetric hydroformylation of unfunctionalized internal alkenes. Spatial confinement of the metal center within a chiral pocket results in reversed regioselectivity and remarkable enantioselectivities.

In transition metal catalysis, the enantioselective transformation of unfunctionalized internal alkenes presents a daunting challenge.[1,2] Substrates of this class lack moieties for ancillary coordination to the metal center and so must rely on nonbonding interactions with the catalyst for the induction of chirality. To be selective, the catalyst should distinguish two linear alkyl groups whose electronics are nearly identical, and so must be capable of differentiating the alkyl groups' lengths. For the hydroformylation reaction in particular, these substrates pose the further complication that internal alkenes are much less reactive than terminal olefins, and substrate isomerization is a side reaction that needs to be suppressed as it compromises selectivity.[3,4] Elevated temperatures are often required to achieve adequate activities, which, however, also leads to lower selectivities. To circumvent these difficulties, efforts in the hydroformylation of internal olefins are generally focused on directing the migration of the π-bond to the chain terminus, followed by hydroformylation.[5−9] However, this strategy precludes the production of the more valuable chiral aldehydes, yielding achiral linear aldehydes preferentially. Thus, a major achievement in the hydroformylation of unfunctionalized internal alkenes would be the generation of a catalyst that hydroformylates the internal bond specifically with high enantioselectivity.[10−18] Supported by the evidence of myriad examples in the enzymatic world, we believed that such specific discrimination could be best achieved with the catalytically active metal located within a sterically restrictive pocket.[19,20] The encapsulation of transition metal catalysts in this manner has been shown to give rise to *substrate* selectivity in a variety of catalyzed reactions,[21] including epoxidation[22,23] and C−H activation.[24,25] In fewer examples, active-site confinement has led to enhanced *product* selectivities[26−28] or has altered product profiles altogether.[29] We previously reported an encapsulated catalyst for the selective hydroformylation of unfunctionalized internal alkenes.[30] This supramolecular catalyst exhibits unprecedented regioselectivity, with the ability to distinguish the C3 and C2 carbons of 2-octene with great precision, resulting in 9:1 selectivity. Based on this system, we anticipated that encapsulation would improve selectivity for the asymmetric variant of this reaction as well. We explored this possibility to modest success with a supramolecularly generated[31−35] monoligating capsule ligand, though the improved enantioselectivities were due to altered Rh^{I} coordination rather than active-site encapsulation.[36] We then postulated that, to generate a chiral system that would exhibit significant confinement effects, it was necessary to assemble a structurally robust ligand that would bind the metal center within a cavity in such a way that would minimize conformational freedom, thus enforcing the spatial preferences of the chiral pocket most effectively. To this end, we self-assembled a multivalently bound bidentate ligand that anchors a Rh^{I} catalytic center within a restricted chiral pocket. The remarkable enantioselectivities afforded by this ligand are reported herein.

We constructed a supramolecular "box" using bis-[Zn^{II}(salphen)] (**3**, Figure 1) as a template[37,38] and a chiral phosphorus-based ligand as the dipyridyl pillar. Boxes assembled from **3** and various dipyridyl linkers were previously shown to be extremely robust, forming spontaneously, with binding constants of at least 10^{20} M^{-3}. We conjectured that employing 3-pyridyl-substituted monodentate phosphoramidite ligands (**2**) as pillars of such a "box" would bring two phosphorus atoms into close proximity, affording a self-assembled chiral bidentate ligand (**1**, Figure 1). We foresaw that, once a Rh^{I} atom was bis-ligated and the active catalyst generated, the internal pocket of the "box" would be sterically crowded, as with our previously reported nonchiral capsule, decreasing the conformational freedom around the active site, as desired for good selectivity. A computational model of the active catalyst does indeed indicate that bis-ligation is feasible, with the metal center embedded within a chiral pocket (**1**-CORhH-octene, Figure 1).

A pure crystalline powder of **1** was obtained via slow evaporation of an equimolar solution of **3** and **2** in acetone. The ^{1}H NMR spectrum of dissolved **1** confirmed that **3** and **2** are present in a 1:1 ratio (see Supporting Information (SI) Figure S1). To ascertain whether **1** is a discrete architecture or a coordination polymer, **2** was titrated against **3**, monitored by circular dichroism spectroscopy. The titration curve (SI, Figure S3) had a single inflection point (1:1) with no further increase beyond this point, as would be expected for a discrete structure.[39] A diffusion NMR experiment was conducted to establish the number of molecules in the suprastructure (SI, Figure S4). The obtained diffusivity indicated a discrete assembly with a hydrodynamic radius of about 1 nm,

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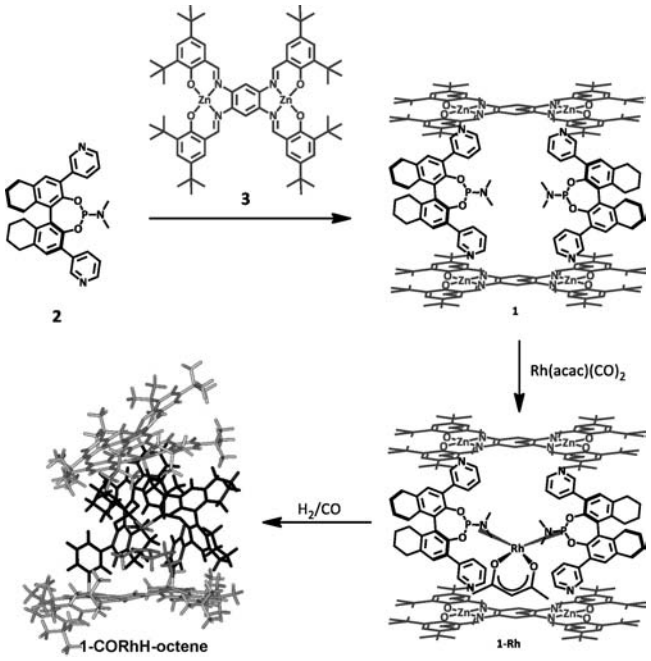


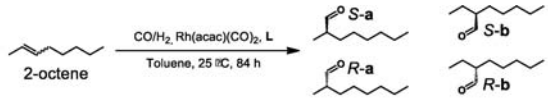
Figure 1. Construction of supramolecular ligand **1** from the assembly of 3-PyMonoPhos (**2**) with bis[Zn(salphen)] (**3**): metalation of **1** to **1**-Rh. Bottom left: Spartan PM3 calculated structure of the octene substrate coordinated to the active catalyst. Black, **2**; gray, **3**; teal, rhodium; green, *cis*-2-octene; red, oxygen.

corresponding most closely to a 2+2 assembly, as determined by the computational model.

The compound **1**-Rh was prepared by incubating **1** and $Rh(acac)(CO)_2$ (1:1) at 80 °C overnight. The major product, **1**-Rh, was characterized by ^{31}P NMR (SI, Figure S5), the sharper peaks of which (compared to those of **1**: SI, Figure S2) suggested a structure with less conformational freedom. The ^{31}P NMR spectrum has a single doublet (J_{P-Rh} = 290 Hz), indicating the formation of the bis-ligated square planar Rh^I complex. Electrospray ionization mass spectrometry corroborated the NMR evidence for bis-ligation, clearly showing a peak corresponding to the $[Rh(acac)(\mathbf{1})]^{2+}$ species (SI, Figure S6).

Satisfied that we had achieved our goal in terms of assembling a chiral encapsulating bidentate ligand, we explored its utility in the Rh-catalyzed asymmetric hydroformylation of both *cis*- and *trans*-2-octene. For comparison, the monodentate ligand **2** was also investigated. Using ligand **2**, both alkene isomers were converted to aldehyde **a** preferentially, as expected.[40] However, upon fixation of ligand **2** into box structure **1**, we observed a reversal of regioselectivity, resulting in a modest preference for aldehyde **b**. The more remarkable change, however, was in the increase in enantiomeric ratio (er): using ligand **1** in the hydroformylation of *trans*-2-octene resulted in an increase in the ratio of the *R* enantiomer of **b** from 61 to 86%. For *cis*-2-octene, we observed a more marked increase in enantioselectivity, from an er of 48:52 to a record-breaking 93:7. The significance of these results is apparent when compared to those of the commercially available (*R,R*)-Chiraphite and (*S,S*)-DIOP, as ligand **1** clearly outperforms both chiral bidentate ligands significantly. In the case of *cis*-2-octene, **1** affords *R*-**b** as 65% of all possible products, while the other ligands deliver about 20%. The activities observed with ligand **1**, however, are relatively low: 10% and 20% conversion for *trans*- and *cis*-2-octene, respectively. We performed the catalysis at slightly higher temperature and for a longer time (40 °C for 5 d) and found that we could increase the conversions to 36% and 79% respectively for the *trans* and *cis* substrates while retaining good selectivities (Table 1, entries 3 and 8).

Table 1. Evaluation of Ligands for the Hydroformylation of *trans*- and *cis*-2-Octene[a]



Entry	L	% conv[b]	rr (a:b)	er b (*R*:*S*)	% *R*-b
		trans-2-octene			
1	**2**	22	58:42	61:39	26
2	**1**	**10**	**40:60**	**86:14**	**52**
3	**1**[c]	36	43:57	79:21	45
4	*R,R*-Chiraphite	97	60:40	52:48	21
5	*S,S*-DIOP	23	65:35	51:49	18
		cis-2-octene			
6	**2**	35	61:39	48:52	19
7	**1**	**20**	**30:70**	**93:7**	**65**
8	**1**[c]	79	35:65	88:12	57
9	*R,R*-Chiraphite	93	61:39	52:48	20
10	*S,S*-DIOP	12	58:42	53:47	22

[a]All reactions were performed at 25 °C in toluene with 20 bar 1:1 CO/H_2, 0.5 mol % $Rh(acac)(CO)_2$, 2.5 mol % **L** (4.5 mol % **2**), and 84 h reaction time. [b]GC conversions (based on dodecane standard) are reported. [c]At 40 °C for 5 d.

The substrate scope of **1** was then evaluated using various unfunctionalized alkenes. Performing hydroformylation reactions on a series of *cis*- and *trans*-2-alkenes, using ligand **1**, we found that our selectivities were general for all 2-olefins: the innermost aldehyde was produced preferentially, with the *trans*-2-olefins affording 80% of the major enantiomer, and the *cis*-2-olefins 90% (Table 2, entries 1−6). For the symmetric 3-hexenes, both *cis* and *trans* substrates were converted with almost equal selectivity, i.e., 80% of the major enantiomer (Table 2, entries 7 and 8). For all substrates, **1** outshone ligand **2**, with the monodentate ligand performing exactly as it did in the case of the octenes (SI, Table S1). The performance of our ligand in the hydroformylation of terminal alkenes was also investigated. Ligand **1** was not particularly selective for 1-

Table 2. Evaluation of the Substrate Scope of Ligand 1[a]

entry	substrate	% conv[b]	% inner	er[c]
1	*trans*-2-nonene	13	48:52	81:19
2	*cis*-2-nonene	26	39:61	90:10
3	*trans*-2-octene	10	40:60	86:14
4	*cis*-2-octene	20	30:70	93:7
5	*trans*-2-heptene	9	45:55	83:17
6	*cis*-2-heptene	24	33:67	91:9
7	*trans*-3-hexene	19	na	19:81
8	*cis*-3-hexene	11	na	22:78
9	1-octene	77	56:44	nd
10	styrene	80	5:95	73:27[d]

[a]All reactions were performed at 25 °C in toluene with 20 bar 1:1 CO/H_2, 0.5 mol % $Rh(acac)(CO)_2$, 2.5 mol % **1**, and 84 h reaction time. [b]GC conversions (based on dodecane standard) are reported. [c]The er values were determined by chiral GC only for the innermost aldehyde. [d]*S*:*R*.

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octene; however, moderate selectivity was obtained for styrene, for which ligand **2** showed no enantioselectivity whatsoever.

Under hydroformylation conditions, an excess of ligand is required to suppress the formation of ligand-free rhodium, an active and nonselective catalyst that compromises the selectivity.[3] In line with this, we observed that a **1**:Rh ratio of 5:1 was necessary for optimal selectivity (see SI, Chart S1 for ligand ratio optimization). This excess ligand is not required to retain a stable box structure, and according to the large association constant involved in the formation of **1**, the excess ligand is present in solution as the metal-free box structure **1**. To confirm the stability of ligand **1**, we investigated its performance at elevated temperature. We performed the catalysis at 70 °C and determined selectivities after 1 h, as isomerization at higher conversions returned convoluted results (see SI, Table S2). Interestingly, despite a loss of the preference for product **b** due to substrate isomerization, the catalyst still displayed high enantiomeric ratios for the innermost aldehyde: 82:18 for *trans* and 88:12 for *cis*. Under the same conditions, ligand **2** gave essentially racemic mixtures. These results indicate that our design strategy was sound, i.e., that the multivalent binding of **1** results in a ligand robust enough to remain intact at elevated temperatures.

In conclusion, we have demonstrated that the confinement effects in the hydroformylation of unfunctionalized internal alkenes[30] can be extended to the asymmetric reaction. The supramolecularly generated chiral ligand has afforded extraordinary enantioselectivities for these difficult substrates, especially for the *cis*-2-olefins. Additionally, the design strategy calling for multiple points of attachment for each of the structural components has resulted in a robust architecture, allowing for continued selectivity at elevated temperatures.

■ ASSOCIATED CONTENT

Supporting Information

Synthetic protocols and characterization data for **1** and **1**-Rh; experimental procedures and results for all catalysis runs. 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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(39) The titration curve shape suggests that the dissociation constant (reciprocal binding constant) is orders of magnitude greater than the

host and guest concentrations, i.e., $K \gg 10^5$. This is much greater than expected for the coordination polymer and consistent with simultaneous binding within a discrete structure.

(40) For the ligand-free reaction, the regiomeric ratio **a**:**b** is 62:38.

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