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High-Precision Catalysts: Regioselective Hydroformylation of Internal Alkenes by Encapsulated Rhodium Complexes

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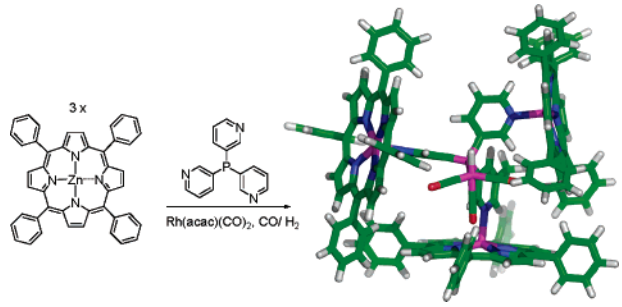
Enzymes are large biomolecules that are well suited for high-precision chemical transformations. A huge scientific effort has been devoted to understand and mimic enzymes, and it is well-established that the cavity around the active site plays an important role in the selectivity induced by enzymes. Therefore, synthetic spherical molecules that have a well-defined cavity are in demand[1] since (catalytic) transformations carried out within such a cavity can, in analogy to enzymes, change the activity and selectivity significantly compared to the bulk phase reaction.[2] The selectivity is generally steered by specific orientation of the substrates with respect to one another, enforced by the cavity. Most reactions carried out so far did not use an active site but were accelerated by just bringing two components together in a cavity. Indeed, for transition metal catalyzed transformations carried out within synthetic cavities, a similar effect of substrate orientation on the selectivity can be expected, hence, the importance of strategies that enable metal catalyst encapsulation.[3,4] Recently, we have introduced a general, templated approach for the encapsulation of transition metal complexes (Scheme 1).[4] In this contribution, we report that encapsulated rhodium complexes can be used as high-precision catalysts as they show unprecedented regioselectivity in the functionalization (hydroformylation) of internal alkenes.

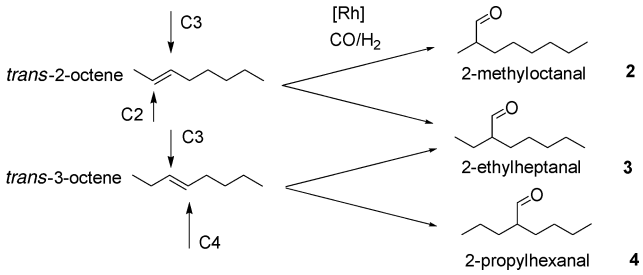
The reactivity of the double bond in *trans*-3-octene (or *trans*-2-octene) is very similar at the C3/C4 position (C2/C3 for 2-octene) because they are electronically identical and sterically similar (ethyl vs *n*-butyl). Consequently, to the best of our knowledge, there are neither catalysts nor stoichiometric reagents that can distinguish between these two positions in the molecule. Indeed, a high-precision catalyst is required, and the encapsulated rhodium complexes were evaluated as such, that is, in the rhodium-catalyzed hydroformylation of internal alkenes (Table 1). The encapsulated phosphorus-based rhodium catalysts (Scheme 1)[5] were already shown to be active in the rhodium-catalyzed hydroformylation of 1-octene, and more importantly, they provide unusual high selectivities for the branched product.[4] The hydroformylation of internal alkenes[6] to selectively produce one of the branched aldehydes (**2**−**4**, Scheme 2) is the ultimate challenge, also because internal alkenes are less reactive and isomerization often results in a large product distribution. In examples where the catalyst is sufficiently reactive and does not isomerize the substrate, the two products are always formed as a statistical mixture of the two possible isomers.[7,8]

The hydroformylation of *trans*-2-octene at room temperature using a (nonencapsulated) rhodium catalyst based on tris(*meta*-pyridyl)phosphine indeed provides the 2-methyloctanal **2** and 2-ethylheptanal **3** as the products in an almost 1:1 ratio, showing that there is no preference for either product (entry 1). In contrast, the encapsulated rhodium catalyst forms 2-ethylheptanal in an outstanding selectivity of 88% (entry 2). It is important to note that nonanal and 2-propylhexanal were only formed in trace amounts, indicating that under these conditions no isomerization

Scheme 1. The Formation of an Encapsulated Rhodium Catalyst by Self-Assembly of Tris(*meta*-pyridyl)phosphine and Zinc(II) Tetraphenylporphyrin (Zn-tpp)



Scheme 2. Hydroformylation of Internal Octenes Aiming for Selective Formation of One of the Aldehyde Products **2**−**4**



takes place. In addition to this astonishingly high selectivity, the conversion is roughly doubled, which was expected because monophosphine rhodium complexes are more reactive than the bisphosphine analogues.[4] Applying a reaction temperature of 40 °C (entries 3 and 4) resulted in a higher reaction rate for both the nonencapsulated and the encapsulated rhodium complexes. Interestingly, the regioselectivity induced by the encapsulated catalyst was still very high, producing 80% of 2-ethylheptanal. At 80 °C, all four possible aldehyde products are formed, indicating that isomerization processes occur (entries 5 and 6). The selectivity of the encapsulated catalyst is no longer retained because the isomerization reaction transforms the pure starting *trans*-2-octene in a mixture of alkenes.

The hydroformylation of *trans*-3-octene at room temperature using the (nonencapsulated) rhodium catalyst based on tris(*meta*-pyridyl)phosphine afforded the 2-ethylheptanal **3** and 2-propylhexanal **4** in exactly a 1:1 ratio (entry 7). The encapsulated catalyst provided an unprecedented selectivity for 2-propylhexanal **4** of 75% (entry 8). Again, the selectivity is largely retained at 40 °C, whereas at 80 °C, the isomerization side reaction prohibits the selective formation of aldehydes. Similar regioselectivities were obtained in the hydroformylation of *trans*-2-hexene, *trans*-2-nonene, and *trans*-3-nonene at 25 °C (see Supporting Information).

Using standard reaction conditions ($P = 20$ bar, $CO/H_2 = 1/1$), the encapsulated rhodium complexes gave, as previously reported,[4a,b]

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Table 1. Hydroformylation of Internal Alkenes and 1-Octene with Both Nonencapsulated and Encapsulated Catalyst Assemblies[a]

entry	olefin	template	P_{CO} (bar)	T (°C)	t (h)	conv (%)	iso (%)[b]	**1** (%)	**2** (%)	**3** (%)	**4** (%)
1	*trans*-2-octene	−	10	25	73	17	0.6	0	55.6	43.8	0
2	*trans*-2-octene	Zn-tpp	10	25	73	32	1.6	0.7	**9.4**	**87.8**	0.5
3	*trans*-2-octene	−	10	40	42	33	0.7	0.1	55.9	43.0	0.3
4	*trans*-2-octene	Zn-tpp	10	40	42	63	1.4	1.8	15.5	80.1	1.2
5	*trans*-2-octene	−	10	80	13	61	15.0	5.9	53.3	22.4	3.4
6	*trans*-2-octene	Zn-tpp	10	80	13	88	16.2	21.6	35.2	20.9	6.1
7	*trans*-3-octene	−	10	25	73	26	0.2	0	0	49.3	50.5
8	*trans*-3-octene	Zn-tpp	10	25	73	45	1.4	0	0	**23.3**	**75.4**
9	*trans*-3-octene	−	10	40	42	30	0.4	0.1	0.2	49.7	49.6
10	*trans*-3-octene	Zn-tpp	10	40	42	60	2.8	0	0.5	30.2	66.5
11	*trans*-3-octene	−	10	80	13	66	6.1	0.6	5.9	44.4	43.0
12	*trans*-3-octene	Zn-tpp	10	80	13	82	6.3	9.2	16.7	31.7	36.1
13	1-octene	−	10	25	24	5.9	2.9	72.1	25.0	0	0
14	1-octene	Zn-tpp	10	25	24	52	1.3	35.3	63.4	0	0
15	1-octene	−	5	25	24	27	1.3	73.5	25.2	0	0
16	1-octene	Zn-tpp	5	25	24	99	1.2	39.0	59.8	0	0
17	1-octene	−	15	25	48	18	1.9	71.7	26.4	0	0
18	1-octene	Zn-tpp	15	25	48	56	0.8	32.7	66.5	0	0

[a] [Rh(acac)(CO)$_2$] = 0.70 mmol/L in toluene, P_{H_2} = 10 bar, substrate/rhodium = 1052, [phosphorus] = 6.4 mmol/L. [b] Iso denotes the total amount of isomerization based on the total product distribution.

an increased conversion and a high selectivity for the formation of 2-methyloctanal in the hydroformylation of 1-octene (entries 13 and 14). Experiments using various partial CO pressures (entries 13−18) indicate a negative order in CO. Interestingly, the regioselectivity was retained, and the isomerization is low in all experiments. Control experiments in which the partial hydrogen pressure was varied showed that the reaction is zero order in hydrogen, and that the regioselectivity and chemoselectivity were preserved (Supporting Information).

These data suggest that, in line with literature,[9] the rate-determining step in the reaction mechanism of the hydroformylation is either alkene coordination or migratory insertion of the hydride to the rhodium−alkene. As the isomerization is suppressed at room temperature, this step is likely irreversible, which is commonly observed at low temperatures and high CO pressure.[9] Since after this point all steps are either fast or irreversible, the regioselectivity is determined early in the cycle. Since, after alkene coordination, still both isomers can be formed, we propose that the regioselectivity induced by the encapsulated catalysts is determined during the hydride migration step. During this migration, the substrate has to rotate,[10] and the steric restrictions of the metal−olefin complex imposed by the innerside of the capsule reduce rotational freedom.

In conclusion, we have shown that transition metal encapsulation using a straightforward templated ligand approach results in the formation of high-precision catalysts. In the current example, the catalyst shows unprecedented high selectivity in the rhodium-catalyzed hydroformylation of internal alkenes, forming predominantly one of the branched aldehydes. In analogy to enzymes, the cavity formed around the active site is of crucial importance. Likely, it reduces the rotation possibilities required for the hydride migration to the coordinated alkene. This is the first catalyst system that is able to discriminate between carbon atoms C3 and C4 in *trans*-3-octene, and the current findings can lead to new routes in organic synthesis. The next logical step we are exploring is the use of chiral capsules to produce the branched aldehydes in enantiopure form.

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Supporting Information Available: Experimental details and hydroformylation of other internal olefins. This material is available free of charge via the Internet at http://pubs.acs.org.

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