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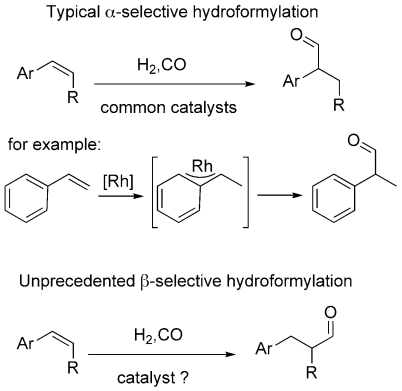
Supramolecular Control of Selectivity in Hydroformylation of Vinyl Arenes: Easy Access to Valuable β-Aldehyde Intermediates**

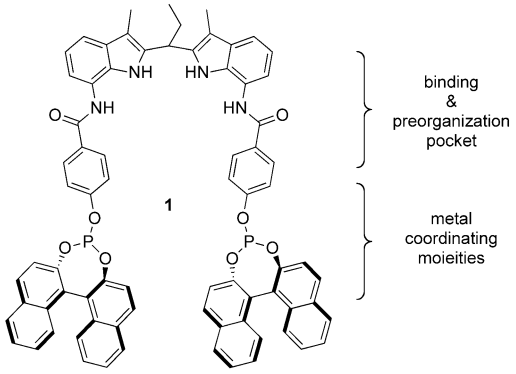
*Paweł Dydio and Joost N. H. Reek**

In the past decades numerous stoichiometric organic reactions have been replaced by catalytic transformations, thus resulting in more efficient synthetic and economic routes to create high-value chemicals.[1] To a large extent, the applicability of such catalytic reaction depends on the activity and the ability to control the selectivity, as well as the synthetic value of the functional group which has been introduced. The hydroformylation reaction,[2] which introduces a synthetically versatile aldehyde group to a C=C double bond with 100% atom economy, is a key example since a variety of cheap olefins can be converted into various valuable compounds, thus making this one of the most important industrial transformations involving a homogeneous catalyst.[3] Despite intensive research with a main focus on ligand design to control the activity and selectivity of the reaction, the regioselectivity of the hydroformylation can be controlled only to a limited extent.[2] Thus the applicability of this technology is still limited to certain classes of compounds and certain products. For instance, β-aryl aldehydes, common intermediates in the synthetic schemes of various important organic molecules, are prepared by rather sophisticated and tedious stochiometric reactions burdened with waste production, instead of applying clean hydroformylation processes.[4] In principle, hydroformylation of aryl vinyls could also provide this class of aldehydes, but typically only a small percent of the β-aldehyde product is formed alongside the main α-aldehyde product (Scheme 1).[2] The preference for the α-aldehyde is due to the formation of a stable rhodium α-arylalkyl intermediate, which is stabilized by π-benzyl interactions with the adjacent aromatic ring,[5] and there are no general catalytic systems that can effectively surpass this natural selectivity. There are remarkable exceptions of catalysts, reported by Peng and Bryant,[6] Beller and co-workers,[7] and Zhang and co-workers,[8] which form the β-aldehyde product with a good practical level of selectivity (ca. 90%), but only for the nonsubstituted benchmark substrate styrenes (R = H, Ar = Ph in Scheme 1). Directing the selectivity to the β-aldehyde is even more challenging for 1,2-disubstituted vinyl arenes (R ≠ H, in Scheme 1), as it involves an internal double bond with an inherently and significantly lower reactivity,[9] and possible isomerization side reactions.[2] Currently, there is no precedent in literature for the β-selective hydroformylation for this class of substrates, yet technology that can provide this unusual selectivity would be of high value given the potential broad application in bulk- or fine-chemicals synthesis. Herein we report a highly active [turnover frequency (TOF) > 6000 mol mol^{-1} h^{-1} and turnover number (TON) > 18000] and 100% chemo- and β-regioselective supramolecular catalyst for hydroformylation of vinyl 2-carboxyarenes.[10,11]



Scheme 1. Regioselectivity issues in hydroformylation of vinyl arenes.

On the basis of the previous studies on the regioselective hydroformylation of olefins with anionic groups,[10d] we devised a more active catalyst for the β-regioselective hydroformylation of vinyl arenes equipped with a carboxylic group, the products of which are common building blocks for valuable chemicals synthesis.[12] The designed catalyst contains the bidentate ligand **1**, which is functionalized with: 1) phosphite moieties for rhodium coordination to form



[*] P. Dydio, Prof. Dr. J. N. H. Reek
Van't Hoff Institute for Molecular Sciences
University of Amsterdam
Science Park 904, 1098 XH, Amsterdam (The Netherlands)
E-mail: j.n.h.reek@uva.nl
Homepage: http://www.science.uva.nl/research/imc/HomKat/

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sufficiently active catalysts for hydroformylation of internal alkenes;[2,9] and 2) the diamidodiindolylmethane pocket, which can strongly bind to the carboxylate group.[13] The rhodium ligand complex, [Rh(**1**)(acac)] (acac = acetylacetonate), which is the precursor to the active hydroformylation catalyst, was easily obtained by mixing a CD_2Cl_2 solution of **1** and [$Rh(CO)_2$(acac)]. NMR titration experiments for [Rh(**1**)(acac)] confirmed that the benzoate anion is strongly bound within the pocket of **1** ($K_a \gg 10^5\,M^{-1}$, in CD_2Cl_2). Molecular modeling (DFT, BP86, SV(P)) shows that, indeed, the active form of the catalyst, [Rh(**1**)(CO)(H)], can bind the model substrate deprotonated 2-vinylbenzoic acid (**2a**) in a ditopic fashion (Figure 1a) with the double bond coordinated to the metal center, while the carboxylate is held in the binding pocket.[14] The carboxylate interaction severely restricts the movement of the alkene moiety at the metal center, and consequently the double bond can rotate only in the direction of the hydride migration transition state ($\Delta G^{\neq}$ = 15.8 kJ mol^{-1}; Figure 1b) which leads to the β-phenylalkyl rhodium complex (Figure 1c).[15] The rotation towards the transition state which leads to the α-phenylalkyl rhodium complex is effectively blocked ($\Delta G^{\neq}$ = 71.6 kJ mol^{-1}),[16] and the usual stable π-benzyl intermediate cannot be formed while the carboxylate of the substrate is bound in the pocket. Therefore, this product can only be formed if either the carboxylate leaves the binding site, or a different conformer of the catalyst–substrate complex is formed. The complex having inverted positions of the carbonyl and hydride such that the formation of the α-aldehyde product is favored, is much higher in energy (ΔG = 15.1 kJ mol^{-1}), and also goes through a much higher energy transition state ($\Delta G^{\neq}$ = 40.2 kJ mol^{-1}).[16] Consequently, according to these calculations the bifunctional substrate binding effectively prevents the formation of the typical α-aldehyde product usually formed in the hydroformylation of vinyl arenes.

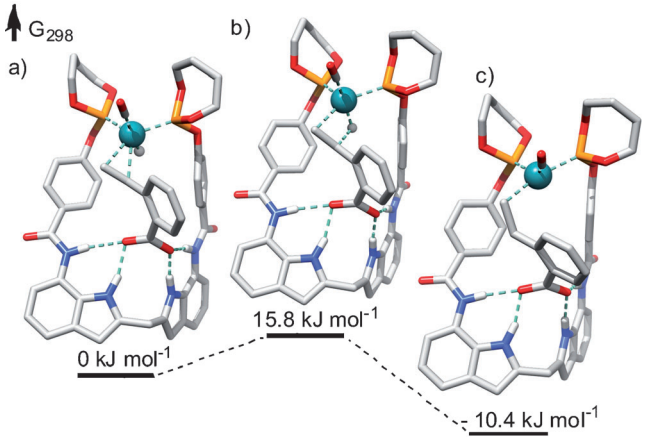
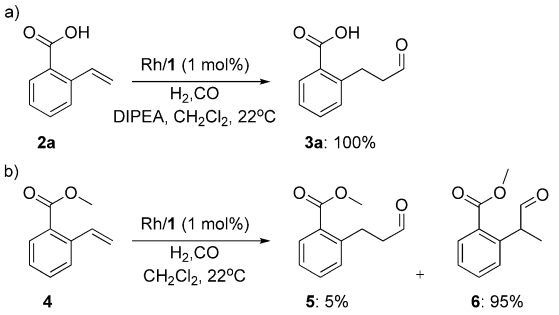


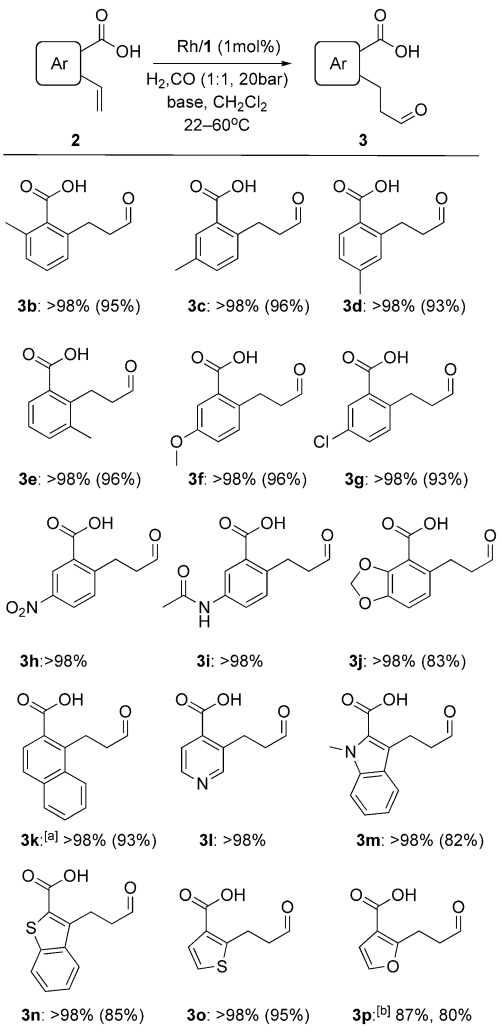
Figure 1. Calculated reaction pathway (DFT, BP86, SV(P)) of the regioselectivity-determining hydride-migration step in the hydroformylation of 2-vinylbenzoic acid (**2a**) by the Rh/**1** catalyst. The binol moieties are included in calculations but omitted in the picture for clarity. For full computational details, see the Supporting Information. binol = 1,1′-bi-2-naphthol.

As predicted by the model, hydroformylation of 2-vinylbenzoic acid (**2a**) by the Rh/**1** catalyst leads to exclusive formation of the β-aldehyde **3a**, 2-(3-oxopropane)-benzoic acid, and the reaction is 100% chemo- and regioselective (Scheme 2a). Moreover, the activity of the catalyst is high



Scheme 2. Hydroformylation of a) **2a** and b) **4** with the Rh/**1** catalyst. Product yields were determined by NMR spectroscopy and GC analysis. DIPEA = diisopropylethylamine.

(TOF = 57 h^{-1}) under mild reaction conditions (30 °C, 20 bar of CO/H_2, 1:1). To demonstrate that the supramolecular interactions between the substrate and the ligand are crucial to obtain the selectivity, a series of control experiments with substrates devoid of this functionality were carried out. Hydroformylation of various styrene derivatives, with electron-withdrawing and electron-donating groups which cannot bind in the pocket of the Rh/**1** catalyst, showed typical selectivity for α-aldehyde products, with only 3–10% of β-aldehydes formed (see Table S3 in the Supporting Information). The methyl ester of **2a** (**4**), which is the closest in terms of electronic effects but is unable to bind in the pocket, gives only 5% of the β-aldehyde **5** and 95% of the α-aldehyde **6** (Scheme 2b), a sharp contrast to the 100% selectivity for the β-aldehyde obtained for **2a**. Moreover, the ester **4** reacts more slowly than the acid analogue **2a** (TOF = 11.7 h^{-1} versus 57 h^{-1}) under the same reaction conditions. From the selectivity and activity of the reactions with **2a** and **4**, one can estimate the effect of substrate binding on relative reaction rates for formation of the α- and β-aldehyde products. Substrate preorganization accelerates the formation of the β-aldehyde by a factor of 60, while the rate of the α-aldehyde formation is slowed down by more than a factor 100. These experiments clearly confirm that the high activity and the unusual regioselectivity displayed by Rh/**1** are a result of substrate binding within the pocket of **1**. For comparison, hydroformylation of **2a** with typical hydroformylation catalysts, that is, rhodium complexes based on monodentate (PPh_3, $P(OPh)_3$) or bidentate [xantphos and dppp; (xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene, dppp = 1,3-bis(diphenylphosphino)propane)] ligands, under otherwise similar reation conditions, show no or only moderate activity (TOF < 9.5 h^{-1}) and typical regioselectivity for the α-aldehyde.[16] Furthermore, the rhodium catalyst containing a binol phosphite ligand without the covalently

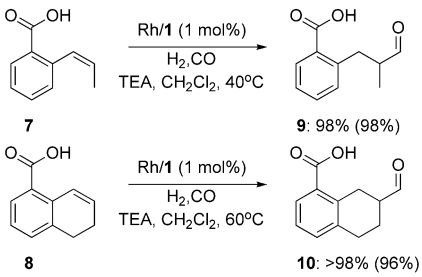


Scheme 3. Hydroformylation of vinyl 2-carboxyarenes **2** with the Rh/**1** catalyst. Product yield and selectivity determined by ^{1}H and ^{13}C NMR analysis of the reaction mixture. Value within parentheses indicates yield of isolated product for reactions conducted on a 0.3–0.8 mmol scale. Full conversion of the starting material in all cases (except where noted). Reagents and conditions: [**2**] = 0.2 M, base = DIPEA or TEA (0.5–1.5 equiv), [$Rh(CO)_2(acac)$] (1 mol%), ligand **1** (1.1 mol%), CO/H_2 = 1:1 (20 bar), 22-60 °C, 24-72 h. [a] 95% conversion. [b] Regioselectivity toward aldehyde **3p** and chemoselectivity towards aldehydes, respectively. For full experimental details see the Supporting Information. TEA = triethylamine.

attached anion binding pocket did not show any activity for hydroformylation of **2a** either in the presence or absence of the anion receptor.[16]

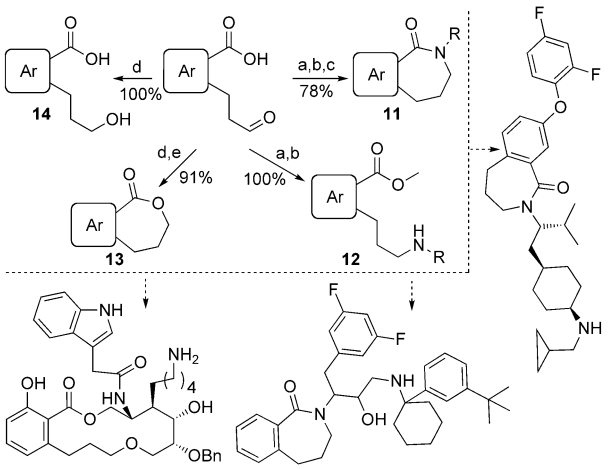
After demonstration of the operational mode of the supramolecular catalyst Rh/**1**, we next evaluated its substrate scope (Scheme 3). For all but one studied vinyl aryl derivatives we observed full selectivity for the β-aldehyde products. Most reactions went to completion at room temperature or slightly above, and only the naphthyl derivative **2k** required 60 °C to produce the product in high yield. In general, the catalytic system tolerates substitutions at every position of the aryl ring and a variety of functional groups, such as alkyl, alkoxy, chloride, nitro, and amide groups. Substrates with other aryl rings including heteroaromatics, such as naphthyl, pyridine, indole, and (benzo)thiophene rings are also smoothly converted. Only the furan derivative **2p** was not converted with full selectivity, but the β-aldehyde isomer **3p** was still formed in 70% yield and with 87% regioselectivity.

Next, we examined whether the system could convert even more challenging substrates, having an internal double bond, that is, β-substituted vinyl arene derivatives, in a selective manner. For this class of substrates the reactivity is lower and the preference for the β-position is further suppressed.[9] In addition, the double bond can in principle isomerize, which leads to a more complex mixture of products. The supramolecular catalyst Rh/**1** is the first catalyst that converts substrates **7** and **8** to form exclusively the β-aldehyde products, which are isolated in almost quantitative yield (Scheme 4).[17]



Scheme 4. Hydroformylation of β-substituted vinyl arenes **7** and **8** with the supramolecular catalyst Rh/**1**). Product yield determined by NMR analysis of the reaction mixture; no side products were observed. Value within parentheses indicates yield of isolated product for reactions conducted on a 0.5–0.8 mmol scale.

To further evaluate the potential of the Rh/**1** catalyst in applications, we investigated its operational properties in more detail. The catalyst can operate in various solvents, such as dichloromethane, toluene, tetrahydrofuran, and acetonitrile.[16] Interestingly, the activity is retained even under ambient pressure of syngas at room temperature, thus the reaction can be performed using common laboratory equipment (a Schlenk-type flask with a balloon).[16] We found that the activity of the Rh/**1** catalyst can be further increased by elevating the temperature without losing any selectivity, and even at 80 °C we obtained the product with full regioselectivity.[16] Importantly, we also demonstrate that even at very low catalyst loadings (0.005 mol%) the reaction still runs smoothly with the typical high activity and selectivity, TOF > 6000 mol mol^{-1} h^{-1} and TON > 18000, which is important in view of commercial applications. We also performed the reaction on a multigram scale (> 5 g), from which the analytically pure product **3a** was obtained with nearly quantitative yield (97%) by a simple acid/base extraction from the reaction mixture. The aldehyde product is a convenient intermediate for further synthesis. Indeed, **3a** is easily converted in three straightforward steps into the corresponding aryl ε-lactam **11** (78% overall yield in three steps), via the amino aryl ester **12**, which provides the basis for an efficient route to bioactive compounds such as a ghrelin receptor antagonist, a putative antiobesity pharmaceutical,[12g] and



Scheme 5. Transformation of the aldehydes **3** into other valuable building blocks (Ar = 1,2-C_6H_4, R = *n*-C_4H_9). Reaction conditions: a) CH_3I, $KHCO_3$; b) 1. RNH_2, 2) $NaBH_4$; c) $Al(CH_3)_3$; d) $NaBH_4$; e) *p*-$TolSO_3H$. For full experimental details see the Supporting Information.

aspartyl protease inhibitors for the treatment of Alzheimer's disease[12d] (Scheme 5). The aldehyde **3a** can also be converted in two steps into the hydroxyaryl acid **14**, which represents the basic skeleton for somatostatin mimetics,[12f] and into the aryl ε-lacton **13**. Thus, the obtained products represent important building blocks in the synthesis of several classes of aforementioned valuable compounds.[12]

Transition-metal catalysis is a powerful enabling technology for the sustainable preparation of chemical compounds, but only if the desired selectivity can be reached. Herein we report a supramolecular hydroformylation catalyst that was made by rational design and converts 2-vinylbenzoic acid and its analogues into the β-aldehyde in a regiospecific manner. As predicted by the model used in the design, the binding of the carboxylate moiety of the substrate in the pocket of the catalyst fixes the alkene coordination at the metal center such that it blocks the pathway to the undesired α-aldehyde. The preorganization of the substrate also resulted in very high activities (TOF > 6000 mol mol^{-1} h^{-1}) and the catalyst proved to be selective for a wide scope of substrates. This unprecedented selectivity opens new green routes to valuable intermediates, as demonstrated by a few examples in this report. In addition, clean catalytic technology to introduce vinyl groups onto aromatic substrates by aromatic C–H activation routes using carboxylic acid directing groups, amide or ester analogues,[18] as well as selective C–H alkylation of alkenes,[19] is already available and therefore these intermediates are accessible from benzoic acid using only green routes. As many transition-metal-catalyzed processes involve a migration in the selectivity determining step, related methodologies in the field of selective transformations in chemical catalysis, towards fully sustainable synthesis are anticipated.

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[1] M. Beller, *Chem. Soc. Rev.* **2011**, *40*, 4891 – 4892.
[2] a) P. W. N. M. van Leeuwen, C. Claver, *Rhodium Catalyzed Hydroformylation*, Kluwer Academic Publishers, Dordrecht, **2000**; b) R. Franke, D. Selent, A. Börner, *Chem. Rev.* **2012**, *112*, 5675 – 5732.
[3] *Applied Homogeneous Catalysis with Organometallic Compounds: A Comprehensive Handbook in Three Volumes*, 2nd ed. (Eds.: B. Cornils, W. A. Herrmann), Wiley-VCH, Weinheim, **2002**.
[4] a) A. S. Duerfeldt, G. E. L. Brandt, B. S. J. Blagg, *Org. Lett.* **2009**, *11*, 2353 – 2356; b) J. T. Spletstoser, J. M. White, A. Rao Tunoori, G. I. Georg, *J. Am. Chem. Soc.* **2007**, *129*, 3408 – 3419; c) P. Colbon, J. Ruan, M. Purdie, K. Mulholland, J. Xiao, *Org. Lett.* **2011**, *13*, 5456 – 5459.
[5] a) P. W. N. M. van Leeuwen, C. Claver, *Rhodium Catalyzed Hydroformylation*, Kluwer Academic Publishers, Dordrecht, **2000**, pp. 29 – 31; b) S. Yu, Y. Chie, Z. Guan, Y. Zou, W. Li, X. Zhang, *Org. Lett.* **2009**, *11*, 241 – 244.
[6] W.-J. Peng, D. R. Bryant, (UCC) PCT Int. Patent WO 03/78444, **2003**.
[7] R. Jennerjahn, I. Piras, R. Jackstell, R. Franke, K.-D. Wiese, M. Beller, *Chem. Eur. J.* **2009**, *15*, 6383 – 6388.
[8] C. Cai, S. Yu, B. Cao, X. Zhang, *Chem. Eur. J.* **2012**, *18*, 9992 – 9998.
[9] a) P. W. N. M. van Leeuwen, C. F. Roobeek, *J. Organomet. Chem.* **1983**, *258*, 343 – 350; b) P. W. N. M. van Leeuwen, C. Claver, *Rhodium Catalyzed Hydroformylation*, Kluwer Academic Publishers, Dordrecht, **2000**, pp. 55 – 59.
[10] For other examples of catalysts utilizing non-covalent substrate preorganization, see: a) S. Das, C. D. Incarvito, R. H. Crabtree, G. W. Brudvig, *Science* **2006**, *312*, 1941 – 1943; b) T. Šmejkal, B. Breit, *Angew. Chem.* **2008**, *120*, 317 – 321; *Angew. Chem. Int. Ed.* **2008**, *47*, 311 – 315; c) T. Šmejkal, D. Gribkov, J. Geier, M. Keller, B. Breit, *Chem. Eur. J.* **2010**, *16*, 2470 – 2478; d) P. Dydio, W. I. Dzik, M. Lutz, B. de Bruin, J. H. N. Reek, *Angew. Chem.* **2011**, *123*, 416 – 420; *Angew. Chem. Int. Ed.* **2011**, *50*, 396 – 400; e) P. Fackler, C. Berthold, F. Voss, T. Bach, *J. Am. Chem. Soc.* **2010**, *132*, 15911 – 15913; f) P. Fackler, S. M. Huber, T. Bach, *J. Am. Chem. Soc.* **2012**, *134*, 12869 – 12878.
[11] For an interesting alternative approach, developed by the groups of Grünanger and Breit, and Tan and co-workers, using reversible covalent bonding of catalytic ligandlike directing groups, see: C. U. Grünanger, B. Breit, *Angew. Chem.* **2008**, *120*, 7456 – 7459; *Angew. Chem. Int. Ed.* **2008**, *47*, 7346 – 7349; C. U. Grünanger, B. Breit, *Angew. Chem.* **2010**, *122*, 979 – 982; *Angew. Chem. Int. Ed.* **2010**, *49*, 967 – 970; T. E. Lightburn, M. T. Dombrowski, K. L. Tan, *J. Am. Chem. Soc.* **2008**, *130*, 9210 – 9211; X. Sun, K. Frimpong, K. L. Tan, *J. Am. Chem. Soc.* **2010**, *132*, 11841 – 11843; T. E. Lightburn, O. A. De Paolis, K. H. Cheng, K. L. Tan, *Org. Lett.* **2011**, *13*, 2686 – 2689. For a review on removable directing groups in organic synthesis and catalysis, see: G. Rousseau, B. Breit, *Angew. Chem.* **2011**, *123*, 2498 – 2543; *Angew. Chem. Int. Ed.* **2011**, *50*, 2450 – 2494, and references therein.
[12] a) Y. Hiraiwa, A. Morinaka, T. Fukushima, T. Kudo, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5162 – 5165; b) A. S. Duerfeldt, L. B. Peterson, J. C. Maynard, C. L. Ng, D. Eletto, O. Ostrovsky, H. E. Shinogle, D. S. Moore, Y. Argon, C. V. Nicchitta, B. S. J. Blagg, *J. Am. Chem. Soc.* **2012**, *134*, 9796 – 9804, and references therein; c) J. J. Deadman, E. D. Jones, T. G. Le, D. I. Rhodes, N. Thienthong, N. A. van de Graff, L. J. Winefield, PCT Int. Patent WO 2010/000031, **2010**; d) V. John, M. Maillard, J. Tucker, J. Aquino, B. Jagodzinska, L. Broglet, J. Tung, D. Bowers, D.

Dressen, G. Probst, N. Shah, PCT Int. Patent WO 2005/087751, **2005**; e) J. A. Pfefferkorn, C. Choi, Y. Song, B. K. Trivedi, S. D. Larsen, V. Askew, L. Dillon, J. C. Hanselman, Z. Lin, G. Lu, A. Robertson, C. Sekerke, B. Auerbach, A. Pavlovsky, M. S. Harris, G. Bainbridge, N. Caspers, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4531 – 4537; f) J. Zhou, M.-C. Matos, P. V. Murphy, *Org. Lett.* **2011**, *13*, 5716 – 5719, and references therein; g) J. T. Mihalic, Y.-J. Kim, M. Lizarzaburu, X. Chen, J. Deignan, M. Wanska, M. Yu, J. Fu, X. Chen, A. Zhang, R. Connors, L. Liang, M. Lindstrom, J. Ma, L. Tang, K. Dai, L. Li, *Bioorg. Med. Chem. Lett.* **2012**, *22*, 2046 – 2051, and references therein.

[13] P. Dydio, T. Zieliński, J. Jurczak, *Chem. Commun.* **2009**, 4560 – 4562; P. Dydio, T. Zieliński, J. Jurczak, *Org. Lett.* **2010**, *12*, 1076 – 1078; P. Dydio, D. Lichosyt, T. Zieliński, J. Jurczak, *Chem. Eur. J.* **2012**, *18*, 13686 – 13701. For review, see: P. Dydio, D. Lichosyt, J. Jurczak, *Chem. Soc. Rev.* **2011**, *40*, 2971 – 2985.

[14] This geometry represents the lowest energy conformer found among several possible structures of the catalyst–substrate complex.

[15] Studies by Lazzaroni et al., Nozaki et al. and Landis et al. demonstrated that in hydroformylation of styrene under mild reaction conditions (< 80 °C) and medium pressures of syngas (> 10 bar) the hydride migration step is irreversible. This is thus the selectivity determining step. Under lower pressures conditions (< 5 bar) and higher temperatures it can become reversible, hence the selectivity can be determined at a later stage in the catalytic cycle. The isotopic experiments with the Rh/**1** catalyst and substrates **2a** or **7**, under our standard reaction conditions (20 bar of D_2/CO, 1:1, 22–50 °C) showed that there is no deuterium scrambling within the substrate, thus indicating that the hydride migration step is indeed irreversible. This data confirms that under these reaction conditions it determines the selectivity. See: a) A. Raffaelli, S. Pucci, R. Settambolo, G. Uccello-Barretta, R. Lazzaroni, *Organometallics* **1991**, *10*, 3892 – 3898; b) G. Alagona, C. Ghio, R. Lazzaroni, R. Settambolo, *Organometallics* **2001**, *20*, 5394 – 5404; c) T. Horiuchi, E. Shirakawa, K. Nozaki, H. Takaya, *Organometallics* **1997**, *16*, 2981 – 2986; d) A. L. Watkins, C. R. Landis, *J. Am. Chem. Soc.* **2010**, *132*, 10306 – 10317.

[16] For details see the Supporting Information.

[17] Although, both **1** and the aldehyde products **9** and **10** are chiral, there was no enantioselectivity observed in these reactions.

[18] a) P. B. Arockiam, C. Bruneau, P. H. Dixneuf, *Chem. Rev.* **2012**, *112*, 5879 – 5918; b) G. Song, F. Wang, X. Li, *Chem. Soc. Rev.* **2012**, *41*, 3651 – 3678; c) S. Mochida, K. Hirano, T. Satoh, M. Miura, *J. Org. Chem.* **2011**, *76*, 3024 – 3033; d) F. W. Patureau, T. Besset, F. Glorius, *Angew. Chem.* **2011**, *123*, 1096 – 1099; *Angew. Chem. Int. Ed.* **2011**, *50*, 1064 – 1067.

[19] D.-H. Lee, K.-H. Kwon, C. S. Yi, *Science* **2011**, *333*, 1613 – 1616.

