Supramolecular control of selectivity in transition metal catalysis: Substrate preorganization & cofactor-steered catalysis

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Citation for published version (APA):
Supramolecular Control of Selectivity in Hydroformylation of Vinyl Arenes: Easy Access to Valuable β-Aldehyde Intermediates*

* Part of this work has been published: Dydio, P.; Reek, J. N. H. Angew. Chem., Int. Ed. 2013, 52, 3878-3882 (‘Very Important Paper’ and Back Cover Art Article, highlighted in Nat. Chem. 2013, 5, 250)
5.1 Introduction

In the past decades numerous stoichiometric organic reactions have been replaced by catalytic transformations, resulting in more efficient synthetic and economic routes to create high-value chemicals.\(^1\) To a large extent, the applicability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 that has been introduced. The hydroformylation reaction,\(^2\) which introduces a synthetically versatile aldehyde group into a C=C double bond with 100% atom economy, is a key example since a variety of cheap olefins can be converted towards various valuable compounds, 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.

\[\text{Typical } \alpha\text{-selective hydroformylation}\]

\[\text{Unprecedented } \beta\text{-selective hydroformylation}\]

\[\text{Scheme 1. Regioselectivity issues in hydroformylation of vinyl arenes.}\]

\(\beta\)-Aryl aldehydes, for instance, common intermediates in the synthetic schemes of various important organic molecules, are prepared by rather sophisticated and tedious stoichiometric reactions burdened with waste production, instead of applying clean hydroformylation processes.\(^4\) In principle, hydroformylation of abundant aryl vinyls could also provide this class of aldehydes, but typically only a few percent of the \(\beta\)-aldehyde product is formed, alongside the main \(\alpha\)-aldehyde product (Scheme 1).\(^2\) The preference for the \(\alpha\)-aldehyde is due to the formation of a stable rhodium \(\alpha\)-arylalkyl intermediate, which is stabilized via a \(\pi\)-benzyl-intermediate due to the adjacent aromatic ring,\(^5\) and there are no general catalytic systems that can effectively surmount this “natural” selectivity. There are remarkable exceptions, reported by Bryant,\(^6\) Beller,\(^7\) and Zhang,\(^8\) that form the \(\beta\)-aldehyde product with good practical level of selectivity (~90%), yet only for the non-substituted benchmark substrate styrenes (\(R=H, Ar=Ph\) in Scheme 1). Directing the selectivity to the \(\beta\)-aldehyde is even more challenging for 1,2-
disubstituted vinyl arenes (R≠H, in Scheme 1), as it involves an internal double bond with inherent significantly lower reactivity, and possible isomerization side reactions. 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/fine chemicals synthesis. Here, we report a highly active (TOF > 6,000 mol·mol⁻¹·h⁻¹ and TON > 18,000) and 100% chemo- and β-regioselective supramolecular catalyst for hydroformylation of vinyl 2-carboxyarenes. We extend the approach to related classes of substrates and we provide detailed mechanistic insight in Chapter 6, which presents the full account of this study (including the results presented in this chapter).

5.2 Results and discussion

On the basis of the previous studies on the regioselective hydroformylation of olefins with anionic groups (Chapters 2 and 3), 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. The designed catalyst contains bidentate ligand functionalized with i) phosphite moieties for rhodium coordination to form sufficiently active catalysts for hydroformylation of internal alkenes; and ii) the diamidodindolylmethane pocket that can strongly bind to the carboxylate group. The rhodium ligand complex, [Rh(1)(acac)], the precursor to the active hydroformylation catalyst, was easily obtained by mixing a CD₂Cl₂ solution of ligand 1 and [Rh(CO)₂(acac)]; acac=acetylacetonate. NMR titration experiments for [Rh(1)(acac)] confirmed that the benzoate anion is strongly bound in the pocket of 1 (Ka >> 10⁵ M⁻¹, in CD₂Cl₂). Molecular modeling (DFT, BP86, SV(P)) shows that, indeed, the active form of the catalyst, Rh(1)(CO)(H), can bind the model substrate 2-vinylbenzoate (2a) in a ditopic fashion (Figure 1) with the double bond coordinated to the metal center, while the carboxylate is held in the binding pocket. 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 (ΔG° = 15.8 kJ·mol⁻¹) that leads to the β-phenylalkyl Rh complex (Figure 1). The rotation towards the transition state that leads to the α-phenylalkyl Rh complex is effectively blocked (ΔG° = 71.6 kJ·mol⁻¹), and the usual stable π-allyl intermediate cannot be formed while the carboxylate of the substrate is bound in the pocket. Therefore, this product can only be formed if the carboxylate leaves the binding site, or from a different conformer of the catalyst-
substrate complex. The complex with inverted positions of carbonyl and hydride that favors the formation of the \( \alpha \)-aldehyde product is much higher in energy (\( \Delta G = 15.1 \text{ kJ mol}^{-1} \)), and goes also through a much higher transition state (\( \Delta G^\# = 40.2 \text{ kJ mol}^{-1} \)). Consequently, according to these calculations the bifunctional substrate binding effectively blocks the formation of the typical \( \alpha \)-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-vinylbenzoate (2a) by the Rh(I) catalyst; the binol moieties are included in calculations but omitted in the picture for clarity, binol=1,1’-bi-2-naphthol; for full computational details, see the experimental section.

**Scheme 2.** Hydroformylation of 2a and 4 with the Rh(I) catalyst. Products yields by NMR spectroscopy and GC analysis.

As predicted by the model, hydroformylation of 2-vinylbenzoic acid (2a) by the Rh(I) catalyst leads to exclusive formation of \( \beta \)-aldehyde 3a, 2-(3-oxopropane)-benzoic acid, and the reaction is 100% chemo- and regioselective (Scheme 2, equation 1). Moreover, the activity of the catalyst is high (TOF = 57 h\(^{-1}\)) already under mild 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 that cannot bind in the pocket of the Rh(I) catalyst, revealed typical selectivity for \( \alpha \)-aldehyde products, with only 3-10% of \( \beta \)-aldehydes formed.
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(see Table 4). 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 β-aldehyde 5 and 95% of α-aldehyde 6 (Scheme 2, equation 2), a sharp contrast to the 100% selectivity for the β-aldehyde obtained for 2a. Moreover, ester 4 reacts more slowly than acid analogue 2a (TOF = 11.7 h⁻¹ vs. 57 h⁻¹), under the same 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 with more than a factor 100. These experiments clearly confirm that the high activity and the unusual regioselectivity displayed by Rh(I) are a result of substrate binding in the pocket of 1. For comparison, hydroformylation of 2a with typical hydroformylation catalysts, i.e. Rh complexes based on monodentate PPh₃, P(OPh)₃ or with bidentate ligands xantphos and dppp ligands, (xantphos= 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene, dppp=1,3-bis(diphenylphosphino)propane), under otherwise the same conditions, show no or only moderate activity (TOF < 9.5 h⁻¹) and typical regioselectivity for the α-aldehyde. Furthermore, the Rh-catalyst containing a binol phosphate ligand without the covalently attached anion binding pocket did not show any activity for hydroformylation of 2a, in the presence or absence of the anion receptor.

After demonstration of the operational mode of the supramolecular catalyst Rh(I), 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 if the system can also convert in a selective manner even more challenging substrates with an internal double bond, i.e. β-substituted vinyl arene derivatives. For this class of substrates the reactivity is lower and the preference for the β-position is further suppressed. In addition, the double bond can in principle isomerize, which leads to a more complex mixture of products. The supramolecular catalyst Rh(I) 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).

To further evaluate the potential of the Rh(I) 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. Interestingly, the activity is retained even under ambient pressure of syngas at room temperature, thus the reaction can be performed using the common laboratory equipment (a Schlenk type flask with a balloon). We found that the activity of Rh(I) 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. 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 > 6,000 mol·mol⁻¹h⁻¹ and TON > 18,000, which is important in view of commercial
applications. We also performed the reaction on a multigram scale (> 5g) from which the analytically pure product 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 (78% overall yield in three steps), via the amino aryl ester 12, to the corresponding aryl ε-lactam 11, which provides the basis for an efficient route to bioactive compounds, such as a ghrelin receptor antagonist, a putative anti-obesity pharmaceutical,12g or aspartyl protease inhibitors for an Alzheimer’s disease treatment12d (Scheme 5). Aldehyde 3a can also be converted in two steps to the hydroxyaryl acid 14, which represents the basic skeleton for somatostatin mimetics,12f and to the aryl ε-lacton 13. Thus, the obtained products represent important building blocks in the synthesis of several classes of aforementioned valuable compounds.12

Scheme 3. Hydroformylation of vinyl 2-carboxyarenes 2 with the Rh(1) catalyst. Product yield and selectivity determined by 1H and 13C NMR analysis of the reaction mixture. Value in parentheses indicates yield after isolation for reactions conducted on 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; \(^95\%\) conversion; \(^95\%\) conversion; \(^95\%\) conversion; for full experimental details see the experimental section.

\(^95\%\) conversion; \(^95\%\) conversion; \(^95\%\) conversion; for full experimental details see the experimental section.
Scheme 4. Hydroformylation of β-substituted vinyl arenes 7 and 8 with the supramolecular catalyst Rh(I). Product yield by NMR analysis of the reaction mixture – no side products were observed. Value in parentheses indicates yield after isolation for reactions conducted on 0.5-0.8 mmol scale.

Scheme 5. Transformation of aldehydes 3 into other valuable building blocks; for Ar=1,2-Ph, R=n-C₄H₉: a) CH₃I, KHCO₃; b) 1. RNH₂, 2) NaBH₄; c) Al(CH₃)₃; d) NaBH₄; e) p-TolSO₃H; for full experimental details see the experimental section.

5.3 Conclusions

Transition metal catalysis is a powerful enabling technology for the sustainable preparation of chemical compounds, but only if the desired selectivity can be reached. Here we report a supramolecular hydroformylation catalyst that was made by rational design that converts 2-vinylbenzoic acid and its analogues to 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 > 6,000 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 is presented by a few examples in this report. In addition, clean catalytic technology to introduce vinyl-groups onto aromatic substrates via aromatic C-H activation routes using carboxylic acid directing groups, amide or ester analogues, as well as selective C-H alkylation of alkenes, 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.

5.4 Experimental section

General

All reactions were carried out under an argon atmosphere using standard Schlenk techniques. THF, pentane, hexane and diethyl ether were distilled from sodium benzophenone ketyl; CHCl₃, isopropanol and methanol were distilled from CaH₂ and toluene was distilled from sodium under nitrogen. NMR spectra were measured on a Bruker AMX 400 (400.1MHz, 100.6MHz and 162.0 for H, C and P respectively). Infrared spectra were recorded on a Thermo Nicolet NEXUS 670 FT-IR. Elemental analyses were carried out on a Carlo Erba NCSO-analyzer. High resolution mass spectra were recorded on a JEOL JMS SX/SX102A four sector mass spectrometer; for FAB-MS 3-nitrobenzyl alcohol was used as matrix. ESI-MS measurements were recorded on a Shimadzu LCMS-2010A liquid chromatography mass spectrometer by direct injection of the sample to the ESI probe. CDCl₃ and DIPEA were dried over molecular sieves (3Å) and degassed by 3 freeze-pump-thaw cycles. If not stated otherwise, syngas refers to a 1 : 1 mixture of H₂ and CO, and the pressure refers to a sum pressure of both.

Materials.

All reagents were purchased from commercial suppliers and used without further purification, with the exception of a ligand building block – 1,1-bis(-3-methyl-7-nitro-1H-indol-2-yl)-propane, 1,1-bis(-7-benzyloamino-3-methyl-1H-indol-2-yl)-propane (anion receptor R₁), 8-hydroxy-5,6,7,8-tetrahydrobenzaldehyde-1-carboxylic acid, 4-phenoxy-(R)-dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin (ligand L₂), which were synthesized according to the published procedures.

Synthesis of ligand and substrates

Synthesis of ligand 1

Bis-4-(4'-benzoxyl)benzoamide of 1,1-bis(-7-amino-3-methyl-1H-indol-2-yl)-propane (15): 1,1-Bis-(3-methyl-7-nitro-1H-indol-2-yl)propane (3.09g, 7.88mmol) was suspended in methanol (130 ml) and 10% palladium on charcoal was added (0.8g). The reaction mixture was flushed with hydrogen, and then vigorously stirred under a hydrogen atmosphere (balloon). The progress of the reaction was monitored by TLC, and after completion (~hour), the catalyst was filtered off over Celite®. The solvent was evaporated, and the crude diamine was immediately used in the subsequent reaction without further purification.

To the solution of crude diamine (7.88mmol) and triethylamine (8.85ml, 64mmol) in dichloromethane (100ml), the solution of 4-(benzoxyl)benzoyl chloride (4.86g, 19.7mmol) in dichloromethane (30ml) was slowly added while stirring, and the mixture was allowed to continue stirring overnight. The reaction mixture was washed with the saturated water solution of NaHCO₃ (2 • 100ml), water (100ml), then dried with MgSO₄ and evaporated. The solid residue was purified by column chromatography on silica gel (120g), with a DCM : hexane and diethyl ether were distilled from sodium benzophenone ketyl; CHCl₃, isolated pressure of both.

H NMR (400 MHz, DMSO-d₆): δ = 10.20 (bs, 2H), 9.95 (bs, 2H), 7.94 (d, J₁ = 8.7 Hz, 4H), 7.49 – 7.29 (m, 12H), 7.25 (d, J₁ = 7.8 Hz, 2H), 7.09 (d, J₁ = 8.7 Hz, 4H), 6.96 (t, J₁ = 7.7 Hz, 2H), 5.17 (t, J₁ = 2.6Hz, 4H, PhCH); 4.50 (t, J = 8.2 Hz, 1H, CHCH₂CH₃); 2.24 (s, 6H, ArCH₂); 2.20 (m, 2H, CHCH₂CH₃); 0.91 (t, J = 7.2 Hz, 3H, CH₂CH₃); C NMR (100MHz, DMSO-d₆): δ = 165.0, 160.8, 136.6, 135.7, 130.4, 129.8, 128.5, 127.9, 127.7, 127.4, 122.9, 118.3, 114.9, 114.6, 114.4, 106.4, 69.2, 35.9, 26.6, 12.2, 8.6.

HR MS (FAB): calcd. for C₃₂H₂₆N₄O₄ [M+H]⁺: 753.3441, found: 753.3447;
Bis-(4-(hydroxy)benzoamide) of 1,1-bis-(7-amino-3-methyl-1H-indol-2-yl)-propane (16): Diamide 15 (5.40g, 7.16mmol) was dissolved in a methanol: THF (1:3) mixture (120 ml) and 10% palladium on charcoal was added (1.68g). The reaction mixture was flushed with hydrogen, and then vigorously stirred under a hydrogen atmosphere (balloon) at 40°C. The progress of the reaction was monitored by TLC, and after completion (~12 hours), the catalyst was filtered off over Celite®. The solvent was evaporated, and the pure product was obtained by recrystallization. The solid was dissolved/suspended in dichloromethane (~10ml) and precipitated by the addition of hexane (~200ml), followed by the sonication (15min), and the powder was isolated by filtration of the solution, yielding 4.15g (100%) of 16.

1H NMR (400 MHz, DMSO-d6): δ = 10.26 (bs, 2H), 10.07 (bs, 2H), 9.84 (bs, 2H), 7.84 (d, J = 8.7 Hz, 4H), 7.35 (d, J = 7.7 Hz, 2H), 7.23 (d, J = 7.8 Hz, 2H), 6.95 (dd, J1 = J2 = 7.9 Hz, 2H), 6.85 (d, J = 8.7 Hz, 4H), 4.49 (t, J1 = 8.0 Hz, 1H, CHCH3), 2.22 (s, 6H, ArCH3), 2.19 (m, 2H, CH2CH3), 0.91 (t, J = 7.2 Hz, 3H, CH3CH2CH3);

13C NMR (100MHz, DMSO-d6): δ = 165.3, 160.5, 135.6, 130.4, 129.9, 128.3, 125.6, 123.1, 118.3, 114.9, 114.7, 114.4, 106.3, 36.0, 26.6, 12.2, 8.6.


Ligand 1 (bis-(4-(S)-1,1′-binaphthyl-2,2-diyi phosphorochloridate, (S)-binol-PCI): All glassware was oven-dried or flame-dried under vacuum. All solvents and reagents were dry and degassed. The solid was azeotropically dried prior to use, by co-evaporation with dry toluene. To a solution of TEA (1.1 ml, 8 mmol) in THF (20 mL) were added drop wise subsequently PCI3 (0.40 ml, 4.6 mmol) and a solution of (S)-binol (1.14 g, 4 mmol) in THF (20 ml) at -78°C. The reaction mixture was stirred for 5 minutes, then allowed to warm up to room temperature, and further stirred for 45 minutes at rt. Then, all volatiles were removed under vacuum, followed by addition of toluene (10 ml) and its evaporation. The solid residue, being a mixture of the desired (S)-binol-PCI and TEA·HCl salt, was dissolved/suspended in THF (30 ml) and used in the next step without further purification.

31P{1H} NMR (162MHz, THF-d8): δ = 177.9.

Synthesis of 2-methyl-6-vinylbenzoic acid (2b): Methyl 2-bromo-6-methylbenzoate: To a solution of 2-bromo-6-methylbenzoic acid (1.05 g, 4.9 mmol) in toluene (20 ml) and methanol (8 ml), a solution of trimethylsilyldiazomethane in diethyl ether (5 ml, 2 M, 10
mmol) was added dropwise while stirring, and stirring was continued for 2 hours. Upon removal of the volatiles under vacuum, the product was obtained in quantitative yield without further purification necessary.

**1H NMR (400 MHz, CDCl₃):** δ = 7.44 – 7.31 (m, 1H), 7.22 – 7.14 (m, 2H), 3.92 (s, 3H, OCH₃), 2.31 (s, 3H, ArCH₃);

**13C NMR (100MHz, CDCl₃):** δ = 168.6, 137.5, 136.4, 130.9, 130.2, 129.4, 119.2, 52.8, 19.8;

**HR MS (FAB):** calcd. for C₆H₆O₂Br [M+H]⁺: 228.9864, found: 228.9867.

**Methyl 2-methyl-6-vinylbenzoate: The synthesis was performed according to the published procedures for analogical reactions with small modifications.** A 50 ml sealable Schlenk tube (‘Schlenk bomb’) was charged with methyl 2-bromo-6-methylbenzoate (1.1 g, 4.8 mmol), potassium vinyltrifluoroborate (790 mg, 5.9 mmol), cesium carbonate (6 g), palladium (II) chloride (70 mg), triphenylphosphine (320 mg), THF (9 ml) and degassed water (1 ml), sealed with a Teflon screw cap and stirred at 85°C for ca. 40h. The **1H NMR analysis** of the crude reaction mixture showed ca. 30% of unreacted starting material, thus additional portions of potassium vinyltrifluoroborate (790 mg, 5.9 mmol), palladium (II) chloride (70 mg), triphenylphosphine (320 mg) were added and stirring at 85°C was continued for 3 days. Then, the reaction mixture was diluted with DCM (50 ml) and water (30 ml), filtered over Celite, the organic layer was separated, and the water phase was extracted with DCM (2×50 ml). The combined organic layers were dried over MgSO₄, and the solvent was removed under vacuum. The crude product was purified by column chromatography on silica gel, with a pentane : diethyl ether (95:5) mixture as an eluent. Fractions of the pure product were combined, and the solvent evaporated off, yielding 420 mg (50%) of product.

**2-Methyl-6-vinylbenzoic acid (2b): A round-bottom flask was charged with methyl 2-methyl-6-vinylbenzoate (400 mg, 2.3 mmol), lithium hydroxide (480 mg), a THF : methanol : water (4 : 1 : 1) mixture (10 ml), sealed and stirred at 70°C. The progress of the reaction was monitored by TLC, and after completion (4 days), the reaction mixture was diluted with water (20 ml), followed by evaporation of THF and methanol under reduced pressure (100 mbar, 40°C). Then, the water phase residue was washed with DCM (20 ml), dried over MgSO₄, acidified with 1M HCl to pH ~ 3, and extracted with DCM (3×40 ml). The combined organic layers were dried over MgSO₄, and the solvent was removed under vacuum. The solid residue was crystallized from a hot water : ethanol (10 : 3) mixture, yielding 350 mg (95%) of 2b.

**2-Benzylfuran-3-carboxylic acid (2c): To a solution of 2-bromo-5-methylbenzoic acid (0.9 g, 4.2 mmol) in toluene (20 ml) and methanol (8 ml), a solution of trimethylsilyldiazomethane in diethyl ether (2.7 ml, 2 M, 5.4 mmol) was added dropwise while stirring, and stirring was continued for 2 hours. Upon removal of the volatiles under vacuum, the product was obtained in quantitative yield without further purification necessary.

**1H NMR (400 MHz, CDCl₃):** δ = 7.59 (d, J₁ = 2.0 Hz, 1H), 7.53 (d, J₂ = 8.2 Hz, 1H), 7.16 (d, J₃ = 8.2 Hz, J₄ = 2.0 Hz, 1H), 3.89 (s, 3H, OCH₃), 2.33 (s, 3H, ArCH₃);

**13C NMR (100MHz, CDCl₃):** δ = 167.0, 138.0, 134.3, 133.8, 132.4, 132.1, 118.2, 52.7, 20.8;

**HR MS (FAB):** calcd. for C₆H₆O₂Br [M+H]⁺: 228.9864, found: 228.9852.

**Methyl 3-methyl-6-vinylbenzoate: A 50 ml sealable Schlenk tube (‘Schlenk bomb’) was charged with methyl 2-bromo-5-methylbenzoate (0.94 g, 4.1 mmol), potassium vinyltrifluoroborate (590 mg, 4.4 mmol), cesium carbonate (4.1 g), palladium (II) chloride (29 mg), triphenylphosphine (130 mg), THF (9 ml) and degassed water (1 ml), sealed with a Teflon screw cap and stirred at 85°C for ca. 40h. After cooling down, the reaction mixture was diluted with DCM (50 ml) and water (30 ml), filtered over Celite, the organic layer was separated, and the water phase was extracted with DCM (2×50 ml). The combined organic layers were dried over MgSO₄, and the solvent was removed under vacuum. The crude product was purified by column chromatography on silica gel, with a pentane : diethyl ether (95:5) mixture as an eluent. Fractions of the product were combined, and the solvent evaporated off, yielding 610 mg (84%) of product.
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3-Methyl-6-vinylbenzoic acid (2e): A round-bottom flask was charged with methyl 3-methyl-6-vinylbenzoate (600 mg, 3.4 mmol), lithium hydroxide (220 mg), a THF : methanol : water (4 : 1 : 1) mixture (18 ml), sealed and stirred at 70°C overnight. The next day, the reaction mixture was diluted with water (20 ml), followed by evaporation of THF and methanol under reduced pressure (100 mbar, 40°C). Then, the water phase residue was washed with DCM (20 ml), acidified with 1M HCl to pH ~ 3, and extracted with DCM (3×40 ml). The combined organic layers were dried over MgSO₄, and the solvent was removed under vacuum, yielding 470 mg (85%) of 2e.

1H NMR (400 Mhz, CDCl₃): δ = 7.77 (d, J = 7.9 Hz, 1H), 7.61 (s, 1H), 7.57 (d, J = 7.9 Hz, 1H), 7.38 (dd, J₁ = 17.6 Hz, J₂ = 11.0 Hz, 1H, CH₂), 7.34 (d, J = 8.1 Hz, 1H), 5.69 (dd, J₁ = 17.6 Hz, J₂ = 1.2 Hz, 1H, CH₂), 5.27 (dd, J₁ = 11.0 Hz, J₂ = 1.2 Hz, 1H, CH₂), 2.32 (s, 3H, ArCH₃).
13C NMR (100MHz, CDCl₃): δ = 166.7, 137.1, 135.2, 135.0, 130.2, 130.3, 129.6, 126.4, 115.5, 20.5;
Elemental analysis (%) calcd. for C₂₀H₁₆O₂: C 74.06, H 6.21, found: C 73.57, H 6.21.

Synthesis of 4-methyl-2-vinylbenzoic acid (2d)

Methyl 2-bromo-4-methylbenzoate: To a solution of 2-bromo-4-methylbenzoic acid (1.07 g, 5.0 mmol) in toluene (20 ml) and methyl alcohol (8 ml), a solution of trimethylsilyldiazomethane in diethyl ether (3.25 ml, 2 M, 6.2 mmol) was added dropwise while stirring, and stirring was continued for 2 hours. Upon removal of the volatiles under vacuum, the product was obtained in quantitative yield without further purification necessary.

1H NMR (400 Mhz, CDCl₃): δ = 7.70 (d, J = 7.9 Hz, 1H), 7.51 (s, 1H), 7.19 (d, J = 7.9 Hz, 1H), 3.88 (s, 3H, OCH₃), 2.36 (s, 3H, ArCH₃).
13C NMR (100MHz, CDCl₃): δ = 166.7, 144.3, 135.3, 134.7, 131.7, 129.4, 128.4, 52.6, 21.2;

Methyl 4-methyl-2-vinylbenzoate: A 50 ml sealable Schlenk tube (‘Schlenk bomb’) was charged with methyl 2-bromo-4-methylbenzoate (1.13 g, 4.9 mmol), potassium vinyltrifluoroborate (700 mg, 5.2 mmol), cesium carbonate (4.9 g), palladium (II) chloride (35 mg), triphenylphosphine (160 mg), THF (9 ml) and degassed water (1 ml), sealed with a Teflon screw cap and stirred at 85°C for ca. 40h. After cooling down, the reaction mixture was diluted with DCM (50 ml) and water (30 ml), filtered over Celite, the organic layer was separated, and the water phase was extracted with DCM (2×50 ml). The combined organic layers were dried over MgSO₄, and the solvent was removed under vacuum. The crude product was purified by column chromatography on silica gel, with a pentane : diethyl ether (95:5) mixture as an eluent. Fractions of the product were combined, and the solvent evaporated off, yielding 755 mg (87%) of product.

1H NMR (400 Mhz, CDCl₃): δ = 7.77 (d, J = 7.9 Hz, 1H), 7.47 (dd, J₁ = 17.5 Hz, J₂ = 11.0 Hz, 1H, CH₂), 7.42 (s, 1H), 7.15 (d, J = 7.9 Hz, 1H), 5.65 (dd, J₁ = 17.5 Hz, J₂ = 1.4 Hz, 1H, CH₂), 5.32 (dd, J₁ = 11.0 Hz, J₂ = 1.4 Hz, 1H, CH₂), 3.85 (s, 3H, OCH₃), 2.39 (s, 3H, ArCH₃);
13C NMR (100MHz, CDCl₃): δ = 168.0, 143.1, 139.8, 136.5, 130.8, 128.6, 128.1, 126.3, 116.1, 52.2, 21.6;

4-Methyl-2-vinylbenzoic acid (2d): A round-bottom flask was charged with methyl 4-methyl-2-vinylbenzoate (740 mg, 4.2 mmol), lithium hydroxide (300 mg), a THF : methanol : water (4 : 1 : 1) mixture (18 ml), sealed and stirred at 70°C overnight. The next day, the reaction mixture was diluted with water (20 ml), followed by evaporation of THF and methanol under reduced pressure (100 mbar, 40°C). Then, the water phase residue was washed with DCM (20 ml), acidified with 1M HCl to pH ~ 3, and extracted with DCM (3×40 ml). The combined organic layers were dried over MgSO₄, and the solvent was removed under vacuum, yielding 600 mg (88%) of 2d.

1H NMR (400 Mhz, DMSO-d₆): δ = 12.84 (bs, 1H, COOH), 7.72 (d, J = 8.0 Hz, 1H), 7.48 (s, 1H), 7.46 (dd, J₁ = 17.5 Hz, J₂ = 11.0 Hz, 1H, CH₂), 7.18 (d, J = 8.0 Hz, 1H), 5.72 (dd, J₁ = 17.5 Hz, J₂ = 1.4 Hz, 1H, CH₂), 5.30 (dd, J₁ = 11.0 Hz, J₂ = 1.4 Hz, 1H, CH₂), 2.36 (s, 3H, ArCH₃);
Elemental analysis (%) calcd. for C₁₀H₉O₂: C 74.06, H 6.21, found: C 73.54, H 6.30.
Chapter 5

Synthesis of 3-methyl-2-vinylbenzoic acid (2e)

Methyl 2-bromo-3-methylbenzoate: To a solution of 2-bromo-3-methylbenzoic acid (1.0 g, 4.65 mmol) in toluene (20 ml) and methanol (8 ml), a solution of trimethylsilyldiazomethane in diethyl ether (5.0 ml, 2 M, 10 mmol) was added dropwise while stirring, and stirring was continued for 2 hours. Upon removal of the volatiles under vacuum, the product was obtained in quantitative yield without further purification necessary.

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 7.44\) (d, \(J = 7.5\) Hz, 1H), 7.37 (d, \(J = 7.5\) Hz, 1H), 7.27 (dd, \(J_1 = J_2 = 7.5\) Hz, 1H), 3.90 (s, 3H, OCH\(_3\)), 2.45 (s, 3H, ArCH\(_2\)).

\(^{13}\)C NMR (100MHz, CDCl\(_3\)): \(\delta = 167.9, 140.2, 134.7, 133.4, 128.1, 127.3, 123.2, 52.8, 23.9\).

HR MS (FAB): calcd. for C\(_9\)H\(_8\)O\(_2\)Br [M+H]^+: 228.9864, found: 228.9876.

Methyl 3-methyl-2-vinylbenzoate: A 50 ml sealable Schlenk tube (‘Schlenk bomb’) was charged with methyl 2-bromo-3-methylbenzoate (1.05 g, 4.6 mmol), potassium vinyl trifluoroborate (935 mg, 7 mmol), cesium carbonate (6 g), palladium (II) chloride (105 mg), triphenylphosphine (480 mg), THF (9 ml) and degassed water (1 ml), sealed with a Teflon screw cap and stirred at 85°C for ca. 40h. The \(^1\)H NMR analysis of the crude reaction mixture showed ca. 40% of unreacted starting material, thus additional portions of potassium vinyl trifluoroborate (935 mg, 7 mmol), palladium (II) chloride (105 mg), triphenylphosphine (480 mg) were added and stirring at 85°C was continued for another 40h. After cooling down, the reaction mixture was diluted with DCM (50 ml) and water (30 ml), filtered over Celite, the organic layer was separated, and the water phase was extracted with DCM (2x50 ml). The combined organic layers were dried over MgSO\(_4\) and the solvent was removed under vacuum. The crude product was purified by column chromatography on silica gel, with a pentane : diethyl ether (95:5) mixture as an eluent. Fractions of the pure product were combined, and the solvent evaporated off, yielding 350 mg (43%) of product. (Alongside fractions containing the product the starting material were combined, and the solvent evaporated off, providing ~500 mg of a mixture product: starting material (~3:1 by \(^1\)H NMR analysis)).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 7.51\) (d, \(J = 7.8\) Hz, 1H), 7.33 (d, \(J = 7.5\) Hz, 1H), 7.21 (dd, \(J_1 = 7.8\) Hz, \(J_2 = 7.5\) Hz, 1H), 6.96 (dd, \(J_1 = 17.8\) Hz, \(J_2 = 11.4\) Hz, 1H, CHCH\(_3\)), 5.44 (dd, \(J_1 = 11.4\) Hz, \(J_2 = 1.6\) Hz, 1H, CHCH\(_3\)), 5.17 (dd, \(J_1 = 17.8\) Hz, \(J_2 = 1.6\) Hz, 1H, CHCH\(_3\)), 3.80 (s, 3H, OCH\(_3\)), 2.34 (s, 3H, ArCH\(_2\)).

\(^{13}\)C NMR (100MHz, CDCl\(_3\)): \(\delta = 169.5, 138.7, 137.2, 135.6, 133.4, 131.7, 127.1, 127.0, 118.9, 52.2, 20.8\).

HR MS (FAB): calcd. for C\(_9\)H\(_8\)O\(_2\) [M+H]^+: 177.0916, found: 177.0917.

3-Methyl-2-vinylbenzoic acid (2e): A round-bottom flask was charged with methyl 3-methyl-2-vinylbenzoate (300 mg, 1.7 mmol), lithium hydroxide (480 mg), a THF : methanol : water (4 : 1 : 1) mixture (10 ml), sealed and stirred at 50°C overnight. The next day, the reaction mixture was diluted with water (20 ml), followed by evaporation of THF and methanol under reduced pressure (100 mbar, 40°C). Then, the water phase residue was washed with DCM (20 ml), acidified with 1M HCl to pH ~ 3, and extracted with DCM (3x40 ml). The combined organic layers were dried over MgSO\(_4\), and the solvent was removed under vacuum, yielding 211 mg (76%) of 2e.

\(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta = 12.80\) (bs, 1H, COOH), 7.46 (d, \(J = 7.6\) Hz, 1H), 7.36 (d, \(J = 7.6\) Hz, 1H), 7.24 (dd, \(J_1 = J_2 = 7.6\) Hz, 1H), 6.96 (dd, \(J_1 = 17.8\) Hz, \(J_2 = 11.4\) Hz, 1H, CHCH\(_3\)), 5.43 (dd, \(J_1 = 11.4\) Hz, \(J_2 = 1.7\) Hz, 1H, CHCH\(_3\)), 5.21 (dd, \(J_1 = 17.8\) Hz, \(J_2 = 1.7\) Hz, 1H, CHCH\(_3\)), 2.30 (s, 3H, ArCH\(_2\)).

\(^{13}\)C NMR (100MHz, DMSO-\(d_6\)): \(\delta = 169.7, 137.1, 136.1, 135.1, 132.5, 132.4, 126.8, 126.3, 118.8, 20.4\).

HR MS (FAB): calcd. for C\(_9\)H\(_8\)O\(_2\) [M+H]^+: 163.0759, found: 163.0755.

Elemental analysis (%): calcd. for C\(_9\)H\(_8\)O\(_2\): C 74.06, H 6.21, found: C 72.22, H 6.31.

Synthesis of 5-methoxy-2-vinylbenzoic acid (2f)

Methyl 5-methoxy-2-vinylbenzoate: A 50 ml sealable Schlenk tube (‘Schlenk bomb’) was charged with methyl 2-bromo-5-methoxybenzoate (1.96 g, 8 mmol), potassium vinyl trifluoroborate (1.13 g, 8.4 mmol), cesium carbonate (7.8 g), palladium (II) chloride (30 mg), triphenylphosphine (130 mg), THF (18 ml) and degassed water (2 ml), sealed with a Teflon screw cap and stirred at 85°C for ca. 24h. After cooling down, the reaction mixture was diluted with DCM (100 ml) and water (30 ml), filtered over Celite, the organic layer was separated, and the water phase was extracted with DCM (2x50 ml). The combined organic layers were dried over MgSO\(_4\), and the solvent was removed under vacuum. The crude product was purified by column chromatography on silica gel, with a pentane : diethyl ether (95:5) mixture as an eluent. Fractions of the product were combined, and the solvent evaporated off, yielding 1.06 g (69%) of product.

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 7.55\) (d, \(J = 8.7\) Hz, 1H), 7.35 (d, \(J = 2.9\) Hz, 1H), 7.35 (dd, \(J_1 = 17.5\) Hz, \(J_2 = 11.0\) Hz, 1H, CHCH\(_3\)), 7.04 (dd, \(J_1 = 8.7\) Hz, \(J_2 = 2.9\) Hz, 1H), 5.57 (dd, \(J_1 = 17.5\) Hz, \(J_2 = 1.3\) Hz, 1H, CHCH\(_3\)), 5.24 (dd, \(J_1 = 11.0\) Hz, \(J_2 = 1.3\) Hz, 1H, CHCH\(_3\)), 3.87 (s, 3H), 3.83 (s, 3H).

\(^{13}\)C NMR (100MHz, CDCl\(_3\)): \(\delta = 167.9, 159.3, 135.5, 132.1, 130.3, 128.6, 118.7, 114.9, 114.7, 55.9, 52.4;\)

5-Methoxy-2-vinylbenzoic acid (2f): A round-bottom flask was charged with methyl 5-methoxy-2-vinylbenzoate (910 mg, 4.7 mmol), lithium hydroxide (300 mg), a THF : methanol : water (4 : 1 : 1) mixture (18 ml), sealed and stirred at 70°C overnight. The next day, the reaction mixture was diluted with water (20 ml), followed by evaporation of THF and methanol under reduced pressure (100 mbar, 40°C). Then, the water phase residue was washed with DCM (20 ml), acidified with 1M HCl to pH ~ 3, and extracted with DCM (3-40 ml). The combined organic layers were dried over MgSO₄, and the solvent was removed under vacuum. The solid residue was crystalized from hot water, yielding 700 mg (83%) of 2f.

\[^1\text{H}\text{ NMR}\ (400\text{ Mhz, DMSO-d}_{6}):\] δ = 13.08 (bs, 1H, COOH), 7.62 (d, J = 8.7 Hz, 1H), 7.32 (dd, Jₜ = 17.6 Hz, Jₛ = 11.0 Hz, 1H, CH₂Cl), 7.28 (d, Jₜ = 2.8 Hz, 1H), 7.11 (dd, Jₜ = 8.7 Hz, Jₛ = 2.8 Hz, 1H), 5.63 (dd, Jₜ = 17.6 Hz, Jₛ = 1.3 Hz, 1H, CH₂Cl), 5.21 (dd, Jₜ = 11.0 Hz, Jₛ = 1.3 Hz, 1H, CH₂Cl), 3.80 (s, 3H);

\[^{13}\text{C}\text{ NMR}\ (100\text{MHz, DMSO-d}_{6}):\] δ = 168.4, 158.4, 134.6, 131.0, 130.4, 127.9, 117.9, 114.4, 114.2, 55.4;

HR MS (FAB): calcd. for C₁₀H₁₁O₃ [M+H]⁺: 179.0708, found: 179.0710;

Elemental analysis (%) calcd. for C₁₀H₁₀O₃: C 67.41, H 5.66, found: C 66.39, H 5.42.

Synthesis of 5-chloro-2-vinylbenzoic acid (2g)

Methyl 2-bromo-5-chlorobenzoate: To a solution of 2-bromo-5-chlorobenzoic acid (1.88 g, 8.0 mmol) in toluene (20 ml) and methanol (8 ml), a solution of trimethylsilyldiazomethane in diethyl ether (5.2 ml, 2 M, 10.4 mmol) was added dropwise while stirring, and stirring was continued for 2 hours. Upon removal of the volatiles under vacuum, the product was obtained in quantitative yield without further purification necessary.

\[^{1}\text{H}\text{ NMR}\ (400\text{ Mhz, CDCl}_3):\] δ = 7.78 (d, Jₜ = 2.6 Hz, 1H), 7.61 (d, Jₜ = 8.6 Hz, 1H), 7.34 (dd, Jₜ = 8.6 Hz, Jₛ = 2.6 Hz, 1H), 3.91 (s, 3H);


Methyl 5-chloro-2-vinylbenzoate: A 50 ml sealed Schlenk tube (‘Schlenk bomb’) was charged with methyl 2-bromo-5-chlorobenzoate (1.98 g, 7.9 mmol), potassium vinyltrifluoroborate (1.13 g, 8.4 mmol), cesium carbonate (7.8 g), palladium (II) chloride (56 mg), triphenylphosphine (260 mg), THF (18 ml) and degassed water (2 ml), sealed with a Teflon screw cap and stirred at 85°C for ca. 40h. After cooling down, the reaction mixture was diluted with DCM (50 ml) and water (30 ml), filtered over Celite, the organic layer was separated, and the water phase was extracted with DCM (2-50 ml). The combined organic layers were dried over MgSO₄, and the solvent was removed under vacuum. The crude product was purified by column chromatography on silica gel, with a pentane : diethyl ether (95:5) mixture as an eluent. Fractions of the product were combined, and the solvent evaporated off, yielding 1.38 g (89%) of product.

\[^{1}\text{H}\text{ NMR}\ (400\text{ Mhz, CDCl}_3):\] δ = 7.85 (d, Jₜ = 2.3 Hz, 1H), 7.76 (d, Jₜ = 8.4 Hz, 1H), 7.45 (dd, Jₜ = 8.4 Hz, Jₛ = 2.3 Hz, 1H), 7.40 (dd, Jₜ = 17.4 Hz, Jₛ = 11.0 Hz, 1H, CH₂Cl), 5.67 (dd, Jₜ = 17.4 Hz, Jₛ = 1.2 Hz, 1H, CH₂Cl), 5.37 (dd, Jₜ = 11.0 Hz, Jₛ = 1.2 Hz, 1H, CH₂Cl₂), 3.88 (s, 3H);

HR MS (FAB): calcd. for C₁₀H₁₇O₃Cl [M+H]⁺: 197.0369, found: 197.0363.

5-chloro-2-vinylbenzoic acid (2g): A bottom-flask was charged with methyl 5-chloro-2-vinylbenzoate (1.36 g, 6.9 mmol), lithium hydroxide (440 mg), a THF : methanol : water (4 : 1 : 1) mixture (36 ml), sealed and stirred at 70°C overnight. The next day, the reaction mixture was diluted with water (20 ml), followed by evaporation of THF and methanol under reduced pressure (100 mbar, 40°C). Then, the water phase residue was washed with DCM (20 ml), acidified with 1M HCl to pH ~ 3, and extracted with DCM (3-40 ml). The combined organic layers were dried over MgSO₄, and the solvent was removed under vacuum, yielding 1.21 g (96%) of 2g.

\[^{1}\text{H}\text{ NMR}\ (400\text{ Mhz, DMSO-d}_{6}):\] δ = 13.38 (bs, 1H, COOH), 7.77 (d, Jₜ = 2.3 Hz, 1H), 7.71 (d, Jₜ = 8.4 Hz, 1H), 7.60 (dd, Jₜ = 8.4 Hz, Jₛ = 2.3 Hz, 1H), 7.36 (dd, Jₜ = 17.5 Hz, Jₛ = 11.0 Hz, 1H, CH₂Cl₂), 5.78 (dd, Jₜ = 17.5 Hz, Jₛ = 1.1 Hz, 1H, CH₂Cl₂), 5.38 (dd, Jₜ = 11.0 Hz, Jₛ = 1.1 Hz, 1H, CH₂Cl₂);

\[^{13}\text{C}\text{ NMR}\ (100\text{MHz, DMSO-d}_{6}):\] δ = 167.3, 136.7, 134.0, 132.1, 131.6, 131.4, 129.4, 128.5, 117.4;

HR MS (FAB): calcd. for C₂₆H₂₈O₂Cl [M+H]⁺: 383.1627, found: 383.1611;


Synthesis of 5-nitro-2-vinylbenzoic acid (2h)

Methyl 2-bromo-5-nitrobenzoate: To a solution of 2-bromo-5-nitrobenzoic acid (1.97 g, 8.0 mmol) in toluene (20 ml) and methanol (8 ml), a solution of trimethylsilyldiazomethane in diethyl ether (5.2 ml, 2 M, 10.4 mmol) was added dropwise while stirring, and stirring was continued for 2 hours. Upon removal of the volatiles under vacuum, the product was obtained in quantitative yield without further purification necessary.

\[^{1}\text{H}\text{ NMR}\ (400\text{ Mhz, CDCl}_3):\] δ = 8.63 (d, Jₜ = 2.8 Hz, 1H), 8.17 (dd, Jₜ = 8.8 Hz, Jₛ = 2.8 Hz, 1H), 7.89 (d, Jₜ = 8.8 Hz, 1H), 3.97 (s, 3H);
Methyl 5-nitro-2-vinylbenzoate: A 50 ml sealable Schlenk tube (‘Schlenk bomb’) was charged with methyl 2-bromo-5-nitrobenzoate (2.06 g, 7.9 mmol), potassium vinyltrifluoroborate (1.39 g, 10 mmol), cesium carbonate (9.8 g), palladium (II) chloride (70 mg), triphenylphosphine (320 mg), THF (18 ml) and degassed water (2 ml), sealed with a Teflon screw cap and stirred at 85°C for ca. 40h. After cooling down, the reaction mixture was diluted with DCM (50 ml) and water (30 ml), filtered over Celite, the organic layer was separated, and the water phase was extracted with DCM (2×50 ml). The combined organic layers were dried over MgSO₄, and the solvent was removed under vacuum. The crude product was purified by column chromatography on silica gel, with a pentane : ethyl ether (95:5) mixture as an eluent. Fractions of the product were combined, and the solvent evaporated off, yielding 1.22 g (74%) of product.

5-Nitro-2-vinylbenzoic acid (2h): A round-bottom flask was charged with methyl 5-nitro-2-vinylbenzoate (1.13 g, 5.5 mmol), lithium hydroxide (1.4 g), a THF : methanol : water (4 : 1 : 1) mixture (20 ml), sealed and stirred at rt overnight. The next day, the reaction mixture was diluted with water (20 ml), followed by evaporation of THF and methanol under reduced pressure (100 mbar, 40°C). Then, the water phase residue was washed with DCM (20 ml), acidified with 1M HCl to pH ~ 3, and extracted with DCM (3×40 ml). The combined organic layers were dried over MgSO₄ and the solvent was removed under vacuum, yielding 1.03 g (98%) of 2h.

5-Acetamido-2-bromobenzoic acid: Acetic anhydride (4 ml) was slowly added to a solution of 5-amino-2-bromobenzoic acid (4.27 g, 19.8 mmol) in acetic acid (30 ml), and the reaction mixture was stirred under reflux for several hours. Then, the volatiles were removed under vacuum, the solid residue was thoroughly washed with DCM and hexane, yielding 4.63 g (91%) of product.

5-Acetamido-2-bromobenzoic acid (5): Acetamido-2-bromobenzoic acid (2.06 g, 8 mmol) and Na₂CO₃ (4.26 g, 40 mmol) were dissolved in DMF (60 ml) and stirred for 30 min. Then, methyl iodide (2.5 ml, 40 mmol) was added to the reaction mixture, and the stirring was continued for 1h. Afterwards, all the volatiles were removed under vacuum, the solid residue was dissolved in ethyl acetate (100 ml), washed with saturated NH₄Cl(aq.) (2×50 ml), water (50 ml) and dried over MgSO₄. Upon removal of the solvent under vacuum, 1.95 g (90%) of product was obtained.

5-Acetamido-2-bromobenzoic acid (6): 5-Acetamido-2-bromobenzoic acid (2.06 g, 8 mmol) was stirred with methyl 5-acetamido-2-bromobenzene (1.88 g, 6.9 mmol), potassium vinyltrifluoroborate (1.39 g, 10 mmol), cesium carbonate (10 g), palladium (II) chloride (105 mg), triphenylphosphine (480 mg), THF (14 ml) and degassed water (1.5 ml), sealed with a Teflon screw cap and stirred at 85°C for ca. 40h. After cooling down, the reaction mixture was diluted with DCM (50 ml) and water (30 ml), filtered over Celite, the organic layer was separated, and the water phase was extracted with DCM (2×50 ml). The combined organic layers were dried over MgSO₄, and the solvent was removed under vacuum. The crude product was purified by column chromatography on silica gel, with a DCM : methanol (100:0 → 98:2) mixture as an eluent. Fractions of the product were combined, and the solvent evaporated off, yielding 1.22 g (74%) of product.

3H NMR (400 MHz, DMSO-d₆): δ = 13.17 (bs, 1H, COOH), 8.55 (dd, J = 8.7 Hz, 1H), 3.95 (dd, J = 11.7 Hz, 2H), 5.80 (dd, J = 16.0 Hz, 1H, CH₂), 6.50 (dd, J = 11.7 Hz, 1H, CH₂);

13C NMR (100MHz, CDCl₃): δ = 166.1, 164.9, 147.2, 135.8, 130.0, 128.7, 126.1, 120.6, 53.0;


Elemental analysis (%) calcd. for C₂₃H₂₂NO₃: C 54.96, H 3.65, N 7.25, found: C 55.99, H 3.88, N 7.12.
product was combined, the solvent evaporated off, and the solid was crystalized by hexane layering over its DCM solution, yielding 0.84 g (55%) of product.

1H NMR (400 MHz, DMSO-d6): δ = 10.16 (s, 1H), 8.07 (d, J = 2.2 Hz, 1H), 7.75 (dd, J1 = 8.6 Hz, J2 = 2.2 Hz, 1H), 7.66 (d, J = 8.6 Hz, 1H), 7.26 (dd, J1 = 17.5 Hz, J2 = 11.0 Hz, 1H, CHCH2), 5.69 (dd, J1 = 17.5 Hz, J2 = 1.3 Hz, 1H, CHCH2), 5.27 (dd, J1 = 11.0 Hz, J2 = 1.3 Hz, 1H, CHCH2), 3.83 (s, 3H, COOCH3), 2.05 (s, 3H, COCl).

13C NMR (100MHz, DMSO-d6): δ = 168.6, 167.1, 138.8, 134.3, 132.5, 128.8, 127.2, 122.4, 119.6, 115.6, 55.2, 24.0.


5-Acetamido-2-vinylbenzoic acid (2i): A round-bottom flask was charged with methyl 5-acetamido-2-vinylbenzoate (620 mg, 2.8 mmol), lithium hydroxide (480 mg), a THF : methanol : water (4 : 1 : 1) mixture (100 ml), sealed and stirred at rt overnight. The next day, the reaction mixture was diluted with water (20 ml), followed by evaporation of THF and methanol under reduced pressure (100 mbar, 40°C). Then, the water phase residue was washed with DCM (20 ml), acidified with 1M HCl to pH ~ 3, and extracted with ethyl acetate (40 ml). The crude product was dried over MgSO4, and the solvent was removed under vacuum, yielding 440 mg (76%) of 2i.

1H NMR (400 MHz, DMSO-d6): δ = 13.02 (s, 1H), 10.11 (s, 1H), 8.05 (d, J = 2.2 Hz, 1H), 7.74 (dd, J1 = 8.6 Hz, J2 = 2.2 Hz, 1H), 7.63 (d, J = 8.6 Hz, 1H), 7.35 (dd, J1 = 17.6 Hz, J2 = 11.1 Hz, 1H, CHCH2), 5.67 (dd, J1 = 17.6 Hz, J2 = 1.2 Hz, 1H, CHCH2), 5.24 (dd, J1 = 11.1 Hz, J2 = 1.2 Hz, 1H, CHCH2), 2.05 (s, 3H);

13C NMR (100MHz, DMSO-d6): δ = 168.6, 168.4, 138.7, 134.7, 132.5, 130.0, 127.0, 122.0, 119.9, 115.0, 24.0;


Elemental analysis (%) calcd. for C14H21NO3: C 64.38, H 5.40, N 6.83, found: C 64.17, H 5.27, N 6.45.

Synthesis of 5-vinyl-1,3-benzodioxole-4-carboxylic acid (2j)

Methyl ester of 5-bromo-1,3-benzodioxole-4-carboxylic acid: To a solution of 5-bromo-1,3-benzodioxole-4-carboxylic acid (1.08 g, 4.4 mmol) in toluene (20 ml) and methanol (8 ml), a solution of trimethylsilyldiazomethane in diethyl ether (5.8 ml, 2 M, 11.6 mmol) was added dropwise while stirring, and stirring was continued for 2 hours. Upon removal of the volatiles under vacuum, the product was obtained in quantitative yield without further purification necessary.

1H NMR (400 MHz, CD2Cl2): δ = 7.08 (d, J = 8.4 Hz, 1H), 6.76 (d, J = 8.4 Hz, 1H), 6.06 (s, 2H), 3.90 (s, 3H);

13C NMR (100MHz, CD2Cl2): δ = 164.5, 148.2, 148.1, 126.5, 116.7, 111.4, 111.2, 103.2, 52.9;


Methyl ester of 5-vinyl-1,3-benzodioxole-4-carboxylic acid: A 50 ml sealable Schlenk tube (‘Schlenk bomb’) was charged with methyl ester of 5-vinyl-1,3-benzodioxole-4-carboxylic acid (1.13 g, 4.4 mmol), potassium vinyltrifluoroborate (740 mg, 5.5 mmol), cesium carbonate (5.4 g), palladium (II) chloride (35 mg), triphenylphosphine (160 mg), THF (9 ml) and degassed water (1 ml), sealed with a Teflon screw cap and stirred at 85°C for ca. 40h. After cooling down, the reaction mixture was diluted with DCM (50 ml) and water (30 ml), filtered over Celite, the organic layer was separated, and the water phase was extracted with DCM (2×50 ml). The combined organic layers were dried over MgSO4, and the solvent was removed under vacuum. The crude product was purified by column chromatography on silica gel, with a pentane : diethyl ether (95:5 → 8:2) mixture as an eluant. Fractions of the product were combined, and the solvent evaporated off, yielding 500 mg (56%) of product.

1H NMR (400 MHz, CD2Cl2): δ = 7.08 (d, J = 8.2 Hz, 1H), 7.05 (dd, J1 = 17.3 Hz, J2 = 10.9 Hz, 1H, CHCH2), 6.89 (d, J = 8.2 Hz, 1H), 6.04 (s, 2H), 5.54 (dd, J1 = 17.3 Hz, J2 = 1.2 Hz, 1H, CHCH2), 5.21 (dd, J1 = 10.9 Hz, J2 = 1.2 Hz, 1H, CHCH2), 3.87 (s, 3H);

13C NMR (100MHz, CD2Cl2): δ = 165.8, 148.1, 135.1, 132.4, 120.4, 117.8, 115.1, 111.3, 111.1, 102.5, 52.4;

HR MS (FAB): calcd. for C14H15O2 [M+H]+: 207.0657, found: 207.0654.

5-Vinyl-1,3-benzodioxole-4-carboxylic acid (2j): A round-bottom flask was charged with methyl ester of 5-vinyl-1,3-benzodioxole-4-carboxylic acid (430 mg, 2.1 mmol), lithium hydroxide (480 mg), a THF : methanol : water (4 : 1 : 1) mixture (10 ml), sealed and stirred at rt overnight. The next day, the reaction mixture was diluted with water (20 ml), followed by evaporation of THF and methanol under reduced pressure (100 mbar, 40°C). Then, the water phase residue was washed with DCM (20 ml), acidified with 1M HCl to pH ~ 3, and extracted with DCM (3×40 ml). The combined organic layers were dried over MgSO4, and the solvent was removed under vacuum, yielding 400 mg (99%) of 2j.
Synthesis of 1-vinyl-2-naphthoic acid (2k)

Methyl 1-bromo-2-naphthoate: To a solution of 1-bromo-2-naphthoic acid (1.02 g, 4.0 mmol) in toluene (20 ml) and methanol (8 ml), a solution of trimethylsilyldiazomethane in diethyl ether (4 ml, 2 M, 8 mmol) was added dropwise while stirring, and stirring was continued for 2 hours. Upon removal of the volatiles under vacuum, the product was obtained in quantitative yield without further purification necessary.

\[ \text{HR MS (FAB): calcd. for C}_9\text{H}_8\text{O}_2\text{Br [M+H]}^+ : 264.9864, \text{found: 264.9862.} \]

Methyl 1-vinyl-2-naphthoate: A 50 ml sealable Schlenk tube (‘Schlenk bomb’) was charged with methyl 1-bromo-2-naphthoate (1.06 g, 4.0 mmol), potassium vinyltrifluoroborate (800 mg, 6 mmol), cesium carbonate (4.8 g), palladium (II) chloride (70 mg), triphenylphosphine (320 mg), THF (9 ml) and degassed water (1 ml), sealed with a Teflon screw cap and stirred at 85°C for ca. 40h. After cooling down, the reaction mixture was diluted with DCM (50 ml) and water (30 ml), filtered over Celite, the organic layer was separated, and the water phase was extracted with DCM (2x50 ml). The combined organic layers were dried over MgSO\(_4\), and the solvent was removed under vacuum. The crude product was purified by column chromatography on silica gel, with a pentane : diethyl ether (95:5) mixture as an eluent. Fractions of the product were combined, and the solvent evaporated off, yielding 665 mg (78%) of product.

\[ \text{HR MS (FAB): calcd. for C}_{13}\text{H}_{10}\text{O}_2\text{Br [M+H]}^+ : 213.0916, \text{found: 213.0912.} \]

2-L-Vinyl-2-naphthoic acid (2k): A round-bottom flask was charged with methyl 1-vinyl-2-naphthoate (647 mg, 3.0 mmol), lithium hydroxide (480 mg), a THF : methanol : water (4 : 1 : 1) mixture (10 ml), sealed and stirred at 50°C overnight. The next day, the reaction mixture was diluted with water (20 ml), followed by evaporation of THF and methanol under reduced pressure (100 mbar, 40°C). Then, the water phase residue was washed with DCM (20 ml), acidified with 1M HCl to pH ~ 3, and extracted with DCM (3x40 ml). The combined organic layers were dried over MgSO\(_4\), and the solvent was removed under vacuum, yielding 600 mg (99%) of 2k.

\[ \text{HR MS (FAB): calcd. for C}_{13}\text{H}_{10}\text{O}_2\text{Br [M+H]}^+ : 213.0916, \text{found: 213.0912.} \]

Synthesis of 3-vinyl-4-picolinic acid (2l)

Methyl 3-bromo-4-picolinate: To a solution of 3-bromo-4-picolinic acid (1.08 g, 5.3 mmol) in toluene (20 ml) and methanol (8 ml), a solution of trimethylsilyldiazomethane in diethyl ether (5 ml, 2 M, 10 mmol) was added dropwise while stirring, and stirring was continued for 2 hours. Upon removal of the volatiles under vacuum, the product was purified by column chromatography on silica gel, with a pentane : diethyl ether (1:1) mixture as an eluent. Fractions of the product were combined, and the solvent evaporated off, yielding 1.08 g (94%) of product.

\[ \text{HR MS (FAB): calcd. for C}_{13}\text{H}_{10}\text{O}_2\text{Br [M+H]}^+ : 213.0916, \text{found: 213.0912.} \]

Elemental analysis (%) calcd. for C\(_9\)H\(_8\)O\(_2\): C 78.77, H 5.09, found: C 78.32, H 4.82.
Ethyl 2-ous THF (90 ml). Then, the solid salt was filtered off, and the
mixture was

• 8.2 → 7.3

42

52.9, 32.5; 

1

J 8.2 Hz, 1H, CHC

1

→ 97:3

1

stirred

charged with methyl

Methyl 3-vinyl-4-picoline: A 50 ml sealable Schlenk tube (‘Schlenk bomb’) was charged with methyl 3-

bromo-4-picoline (1.07 g, 5.0 mmol), potassium vinyltrifluoroborate (1 g, 7.5 mmol), cesium carbonate (6 g),
palladium (II) chloride (105 mg), triphenylphosphine (480 mg), THF (9 ml) and degassed water (1 ml),
sealed with a Teflon screw cap and stirred at 85°C for ca. 40h. After cooling down, the reaction mixture was
diluted with DCM (50 ml) and water (30 ml), filtered over Celite, the organic layer was separated, and the
water phase was extracted with DCM (3×50 ml). The combined organic layers were dried over MgSO₄,
and the solvent was removed under vacuum. The crude product was purified by column chromatography on silica
gel, with a hexane : ethyl acetate (8.2 → 7.3) mixture as an eluent. Fractions of the product were combined,
and the solvent evaporated off, yielding 660 mg (81%) of product.

3-Vinyl-4-picoline (21): A round-bottom flask was charged with methyl 3-vinyl-4-picoline (326 mg, 2.0 mmol), sodium hydroxide (120 mg, 3 mmol), a THF : methanol : water (4 : 1 : 1) mixture (10 ml), sealed
and stirred at rt for 3h. Afterwards, the reaction mixture was neutralized with 1M HCl, evaporated to dryness,
followed by addition of anhydrous THF (90 ml). Then, the solid salt was filtered off, and the solvent
was removed under vacuum, yielding 270 mg (91%) of 21.

HR MS (FAB): calcd. for C₆H₁₀NO₂ [M+H]⁺: 164.0712, found: 164.0702.

Synthesis of 1-methyl-3-vinyl-1H-indole-2-carboxylic acid (2m)

Methyl 3-bromo-1-methyl-1H-indole-2-carboxylate: To a solution of 3-bromo-1-methyl-1H-indole-2-
carboxylic acid (1.2 g, 4.7 mmol) in toluene (20 ml) and methanol (8 ml), a solution of trimethylsilyldiazomethane in diethyl ether (5 ml, 2 M, 10 mmol) was added dropwise while stirring, and stirring
was continued for 2 hours. Upon removal of the volatiles under vacuum, the product was purified by
column chromatography on silica gel, with a hexane : ethyl acetate (9:1) mixture as an eluent. Fractions of the
product were combined, and the solvent evaporated off, yielding 1.07 g (85%) of product.

HR MS (FAB): calcd. for C₁₃H₁₉NO₂[Br⁺]: 266.9885, found: 266.9896.

Methyl 1-methyl-3-vinyl-1H-indole-2-carboxylate: A 50 ml sealable Schlenk tube (‘Schlenk bomb’) was
charged with methyl 3-bromo-1-methyl-1H-indole-2-carboxylate (1.03 g, 3.8 mmol), potassium
vinyltrifluoroborate (770 mg, 5.8 mmol), cesium carbonate (6 g), palladium (II) chloride (105 mg),
triphenylphosphine (480 mg), THF (9 ml) and degassed water (1 ml), sealed with a Teflon screw cap and
stirred at 85°C for ca. 40h. After cooling down, the reaction mixture was diluted with DCM (50 ml) and water
(30 ml), filtered over Celite, the organic layer was separated, and the water phase was extracted with DCM
(3×50 ml). The combined organic layers were dried over MgSO₄, and the solvent was removed under vacuum.
The crude product was purified by column chromatography on silica gel, with a pentane : diethyl ether (98.2 →
97.3) mixture as an eluent. Fractions of the pure product were combined, and the solvent evaporated off,
yielding 400 mg (48%) of product.

Chapter 5

1-Methyl-3-vinyl-1H-indole-2-carboxylic acid (2m): A round-bottom flask was charged with methyl 1-methyl-3-vinyl-1H-indole-2-carboxylate (230 mg, 1.1 mmol), lithium hydroxide (480 mg), a THF : methanol : water (4 : 1 : 1) mixture (10 ml), sealed and stirred at rt overnight. The next day, the reaction mixture was diluted with water (20 ml), followed by evaporation of THF and methanol under reduced pressure (100 mbar, 40°C). Then, the water phase residue was washed with DCM (20 ml), acidified with 1M HCl to pH ~ 3, and extracted with DCM (3×40 ml). The combined organic layers were dried over MgSO₄, and the solvent was removed under vacuum, yielding 180 mg (84%) of 2m.

³¹H NMR (400 MHz, DMSO-d₆): δ = 13.41 (bs, 1H, COOH), 7.98 (d, J = 8.2 Hz, 1H), 7.59 (d, J = 8.3 Hz, 1H), 7.41 (dd, J₁ = 18.1 Hz, J₂ = 1.7 Hz, 1H, CHCH₂), 7.37 (dd, J₁ = 17.7 Hz, 1H), 7.18 (dd, J₁ = J₂ = 7.7 Hz, 1H), 5.82 (dd, J₁ = 18.1 Hz, J₂ = 1.1 Hz, 1H, CHCH₂), 5.37 (dd, J₁ = 11.7 Hz, J₂ = 1.1 Hz, 1H, CHCH₂), 3.96 (s, 3H);

¹³C NMR (100MHz, DMSO-d₆): δ = 163.3, 138.5, 130.2, 126.8, 125.0, 121.1, 119.2, 115.2, 115.1, 32.0;


Synthesis of 3-vinylbenzothiophene-2-carboxylic acid (2n)

Methyl 3-bromobenzothiophene-2-carboxylate: To a solution of 3-bromobenzothiophene-2-carboxylic acid (1.0 g, 3.9 mmol) in toluene (20 ml) and methanol (8 ml), a solution of trimethylsilyldiazomethane in diethyl ether (4 ml, 2 M, 8 mmol) was added dropwise while stirring, and stirring was continued for 2 hours. Upon removal of the volatiles under vacuum, the product was obtained in quantitative yield without further purification necessary.

³¹H NMR (400 MHz, CD₂Cl₂): δ = 8.01 – 7.96 (m, 1H), 7.88 – 7.84 (m, 1H), 7.58 – 7.50 (m, 2H), 3.95 (s, 3H);

¹³C NMR (100MHz, CD₂Cl₂): δ = 162.0, 139.7, 139.0, 128.6, 127.9, 127.6, 126.1, 125.6, 123.1, 115.1, 52.9;


Methyl 3-vinylbenzothiophene-2-carboxylate: A 50 ml sealable Schlenk tube (‘Schlenk bomb’) was charged with methyl 3-bromobenzothiophene-2-carboxylate (1.04 g, 3.8 mmol), potassium vinyl trifluoroborate (800 mg, 6 mmol), cesium carbonate (5 g), palladium (II) chloride (105 mg), triphenylphosphine (480 mg), THF (9 ml) and degassed water (1 ml), sealed with a Teflon screw cap and stirred at 85°C for ca. 40h. After cooling down, the reaction mixture was diluted with DCM (50 ml) and water (30 ml), filtered over Celite, the organic layer was separated, and the water phase was extracted with DCM (3×50 ml). The combined organic layers were dried over MgSO₄, and the solvent was removed under vacuum. The crude product was purified by column chromatography on silica gel, with a pentane : diethyl ether (98:2 → 97:3) mixture as an eluent. Fractions of the pure product were combined, and the solvent evaporated off, yielding 670 mg (80%) of product.

³¹H NMR (400 MHz, CD₂Cl₂): δ = 8.03 (d, J₁ = 8.4 Hz, J₂ = 1.5 Hz, 1H), 7.78 (d, J₁ = 7.8 Hz, J₂ = 1.5 Hz, 1H), 7.44 – 7.32 (m, 3H), 5.73 (dd, J₁ = 18.2 Hz, J₂ = 1.5 Hz, 1H, CHCH₂), 5.64 (dd, J₁ = 11.7 Hz, J₂ = 1.5 Hz, 1H, CHCH₂), 3.82 (s, 3H);

¹³C NMR (100MHz, CD₂Cl₂): δ = 163.5, 141.3, 141.2, 138.2, 130.7, 127.9, 127.6, 125.5, 125.3, 123.1, 120.7, 52.9, 52.6;


3-Vinylbenzothiophene-2-carboxylic acid (2n): A round-bottom flask was charged with methyl 3-vinylbenzothiophene-2-carboxylate (470 mg, 2.2 mmol), lithium hydroxide (480 mg), a THF : methanol : water (4 : 1 : 1) mixture (20 ml), followed by evaporation of THF and methanol under reduced pressure (100 mbar, 40°C). Then, the water phase residue was washed with DCM (20 ml), acidified with 1M HCl to pH ~ 3, and extracted with DCM (3×40 ml). The combined organic layers were dried over MgSO₄, and the solvent was removed under vacuum, yielding 380 mg (86%) of 2n.

³¹H NMR (400 Mhz, DMSO-d₆): δ = 13.57 (bs, 1H, COOH), 8.13 (d, J₁ = 7.9 Hz, 1H), 8.04 (d, J₁ = 7.8 Hz, 1H), 7.58 – 7.40 (m, 3H), 5.84 (dd, J₁ = 18.2 Hz, J₂ = 1.2 Hz, 1H, CHCH₂), 5.71 (dd, J₁ = 11.7 Hz, J₂ = 1.2 Hz, 1H, CHCH₂);

¹³C NMR (100MHz, DMSO-d₆): δ = 163.8, 139.9, 139.2, 137.4, 130.0, 129.3, 127.3, 125.3, 124.8, 123.2, 120.5;

HR MS (FAB): calcld. for C₁₃H₁₁O₂S [M+H]⁺: 205.0323, found: 205.0327;

Elemental analysis (%): calcld. for C₁₃H₁₁O₂S: C 64.69, H 3.95, S 15.70, found: C 64.52, H 4.07, S 15.75.

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Synthesis of 2-vinyl-3-thiophenecarboxylic acid (2o)

Methyl 2-bromo-3-thiophenecarboxylate: To a solution of 2-bromo-3-thiophenecarboxylic acid (1.1 g, 5.3 mmol) in toluene (20 ml) and methanol (8 ml), a solution of trimethylsilyldiazomethane in diethyl ether (5.3 ml, 2 M, 10.6 mmol) was added dropwise while stirring, and stirring was continued for 2 hours. Upon removal of the volatiles under vacuum, the product was obtained in quantitative yield without further purification necessary.

\[ ^1H \text{NMR (400 MHz, CDCl}_3\): } \delta = 7.35 (d, J = 5.7 Hz, 1H), 7.27 (d, J = 5.7 Hz, 1H), 3.85 (s, 3H); \]

HR MS (FAB): calcd. for C\text{_{10}H}_{13}\text{O}_{2}S [M+H]^+: 222.9251, found: 222.9249.

Methyl 2-vinyl-3-thiophenecarboxylate: A 50 ml scaleable Schlenk tube (‘Schlenk bomb’) was charged with methyl 2-bromo-3-thiophenecarboxylate (1.07 g, 4.8 mmol), potassium vinyltrifluoroborate (1.06 g, 7.9 mmol), cesium carbonate (6.4 g), palladium (II) chloride (105 mg), triphenylphosphine (480 mg), THF (9 ml) and degassed water (1 ml), sealed with a Teflon screw cap and stirred at 85°C for ca. 40h. The crude product was purified by column chromatography on silica gel, with a pentane : diethyl ether (95:5) mixture as an eluent. Fractions of the pure product were combined, and the solvent evaporated off, yielding 590 mg (73%) of product.

\[ ^1H \text{NMR (400 MHz, CDCl}_3\): } \delta = 7.67 (dd, J = 17.6 Hz, J = 11.0 Hz, 1H, CHCH_2), 7.38 (d, J = 5.3 Hz, 1H), 7.11 (d, J = 5.3 Hz, 1H), 5.74 (d, J = 17.6 Hz, 1H, CHCH_2), 5.34 (d, J = 11.0 Hz, 1H, CHCH_2), 3.84 (s, 3H); \]


2-Vinyl-3-thiophenecarboxylic acid (2o): A round-bottom flask was charged with methyl 2-vinyl-3-thiophenecarboxylate (515 mg, 3.1 mmol), lithium hydroxide (480 mg), a THF : methanol : water (4 : 1 : 1) mixture (10 ml), sealed and stirred at rt overnight. The next day, the reaction mixture was diluted with water (20 ml), followed by evaporation of THF and methanol under reduced pressure (100 mbar, 40°C). Then, the water phase residue was washed with DCM (20 ml), acidified with 1M HCl to pH ~ 3, and extracted with DCM (3×40 ml). The combined organic layers were dried over MgSO\textsubscript{4}, and the solvent was removed under vacuum, yielding 350 mg (74%) of 2o.

\[ ^1H \text{NMR (400 MHz, DMSO-d_6): } \delta = 12.92 (bs, 1H, COOH), 7.63 (dd, J = 17.6 Hz, J = 11.0 Hz, 1H, CHCH_2), 7.44 (d, J = 5.3 Hz, 1H), 7.33 (d, J = 5.3 Hz, 1H), 5.70 (d, J = 17.6 Hz, 1H, CHCH_2), 5.35 (d, J = 11.0 Hz, 1H, CHCH_2); \]

HR MS (FAB): calcd. for C\text{_{10}H}_{13}\text{O}_{2}S [M+H]^+: 155.0167, found: 155.0165;

Elemental analysis (%: calcd. for C\text{_{10}H}_{13}\text{O}_{2}S: C 54.53, H 3.92, S 20.80, found: C 54.70, H 3.81, S 20.77.

Synthesis of 2-vinyl-3-furoic acid (2p)

Methyl 2-bromo-3-furoate: To a solution of 2-bromo-3-furoic acid (1.0 g, 5.3 mmol) in toluene (20 ml) and methanol (8 ml), a solution of trimethylsilyldiazomethane in diethyl ether (5.3 ml, 2 M, 10.6 mmol) was added dropwise while stirring, and stirring was continued for 2 hours. Upon removal of the volatiles under vacuum, the product was obtained in quantitative yield without further purification necessary.

\[ ^1H \text{NMR (400 MHz, CDCl}_3\): } \delta = 7.47 (d, J = 2.2 Hz, 1H), 6.76 (d, J = 2.2 Hz, 1H), 3.83 (s, 3H); \]

HR MS (FAB): calcd. for C\text{_{10}H}_{13}\text{O}_{2}S [M+H]^+: 204.9500, found: 204.9514.

Methyl 2-vinyl-3-furoate: A 50 ml scaleable Schlenk tube (‘Schlenk bomb’) was charged with methyl 2-bromo-3-furoate (1.08 g, 5.3 mmol), potassium vinyltrifluoroborate (1.06 g, 7.9 mmol), cesium carbonate (6.4 g), palladium (II) chloride (105 mg), triphenylphosphine (480 mg), THF (9 ml) and degassed water (1 ml), sealed with a Teflon screw cap and stirred at 85°C for ca. 40h. After cooling down, the reaction mixture was diluted with DCM (50 ml) and water (30 ml), filtered over Celite, the organic layer was separated, and the water phase was extracted with DCM (3×50 ml). The combined organic layers were dried over MgSO\textsubscript{4}, and the solvent was removed under vacuum. The crude product was purified by column chromatography on silica gel, with a pentane : diethyl ether (95:5) mixture as an eluent. Fractions of the pure product were combined, and the solvent evaporated off, yielding 580 mg (72%) of product.
2-Vinyl-3-furoic acid (2p): A round-bottom flask was charged with methyl 2-vinyl-3-furoate (440 mg, 2.9 mmol), lithium hydroxide (480 mg), a THF : methanol : water (4 : 1 : 1) mixture (10 ml), sealed and stirred at rt overnight. The next day, the reaction mixture was diluted with water (20 ml), followed by evaporation of THF and methanol under reduced pressure (100 mbar, 40°C). Then, the water phase residue was washed with DCM (20 ml), acidified with 1M HCl to pH ~ 3, and extracted with DCM (3×40 ml). The combined organic layers were dried over MgSO₄, and the solvent was removed under vacuum, yielding 340 mg (85%) of 2p.

3H NMR (400 MHz, DMSO-d₆): δ = 12.83 (bs, 1H, COOH), 7.70 (d, J = 1.8 Hz, 1H), 7.18 (dd, J = 17.8 Hz, J₂ = 11.3 Hz, 1H, CH₂), 6.73 (d, J = 1.8 Hz, 1H), 5.88 (dd, J₁ = 17.5 Hz, J₂ = 1.3 Hz, 1H, CH₂), 5.48 (dd, J₁ = 11.3 Hz, J₂ = 1.3 Hz, 1H, CH₂);

13C NMR (100MHz, DMSO-d₆): δ = 164.0, 157.0, 142.0, 124.5, 117.8, 114.6, 111.9, 51.8;


Synthesis of methyl 2-vinylbenzoate (4):
Methyl 2-vinylbenzoate (4): To a solution of 2-vinylbenzoic acid (750 mg, 5 mmol) in toluene (25 ml) and methanol (10 ml), a solution of trimethylsilyldiazomethane in diethyl ether (100 ml), 2, 3.3 m, 2.6 mmol) was added dropwise while stirring, and stirring was continued for 2 hours. Upon removal of the volatiles under vacuum, the product was obtained in quantitative yield without further purification necessary.

3H NMR (400 MHz, CDCl₃): δ = 7.88 (dd, J₁ = 7.8 Hz, J₂ = 1.5 Hz, 1H), 7.58 (d, J = 7.8 Hz, 1H), 7.51 – 7.43 (m, 2H), 7.32 (dd, J₁ = J₂ = 7.6 Hz, J = 1.1 Hz, 1H), 5.65 (dd, J₁ = 17.5 Hz, J₂ = 1.3 Hz, 1H, CH₂), 5.36 (dd, J₁ = 11.0 Hz, J₂ = 1.3 Hz, 1H, CH₂);

13C NMR (100MHz, CDCl₃): δ = 168.0, 139.7, 136.0, 132.2, 130.4, 128.7, 127.5, 127.3, 116.6, 52.2;

HR MS (FAB): calcd. for C₇H₁₀O₂ [M+H]+: 139.0395, found: 139.0401;

Elemental analysis (%): calcd. for C₇H₁₀O₂: C 60.87, H 4.38, found: C 60.86, H 4.25.

Synthesis of 2-[(1Z)-prop-1-en-1-yl]benzoic acid (7):
Methyl 2-[(1Z)-prop-1-en-1-yl]benzoate: A 50 ml sealable Schlenk tube ('Schlenk bomb') was charged with methyl 2-iodobenzoate (2.86 ml, 19.4 mmol), (1Z)-1-propenylboronic acid (2.5 g, 29 mmol), cesium carbonate (10 g), palladium (II) acetate (400 mg), triphenylphosphine (1.38 g), dimethoxymethane (25 ml) and degassed water (20 ml), sealed with a Teflon screw cap and stirred at 100°C for 3.5h. After cooling down, the reaction mixture was diluted with water (30 ml) and extracted with DCM (3×70 ml). The combined organic layers were dried over MgSO₄, and the solvent was removed under vacuum. The crude product was purified by column chromatography on silica gel, with a pentane : diethyl ether (98:2) mixture as an eluent. Fractions of the product were combined, and the solvent evaporated off, yielding 1.57 g (82%) of product.

3H NMR (400 MHz, CDCl₃): δ = 7.91 (d, J = 7.9 Hz, 1H), 7.44 (dd, J₁ = J₂ = 7.5 Hz, 1H), 7.31 – 7.25 (m, 2H), 6.86 (d, J = 12.0 Hz, 1H), 5.81 (dq, J₁ = 11.6 Hz, J₂ = 7.3 Hz, 1H, CH₂), 3.85 (s, 3H) 1.70 (dd, J₁ = 7.1 Hz, J₂ = 1.9 Hz, 1H, CH₂);

13C NMR (100MHz, CDCl₃): δ = 167.9, 138.9, 131.6, 131.0, 130.6, 129.7, 129.4, 126.7, 126.4, 52.1, 14.4;


2-[(1Z)-Prop-1-en-1-yl]benzoic acid (7): A round-bottom flask was charged with methyl 2-[(1Z)-prop-1-en-1-yl]benzoate (660 mg, 3.8 mmol), lithium hydroxide (480 mg), a THF : methanol : water (4 : 1 : 1) mixture (10 ml), sealed and stirred at 50°C for 8h. Afterwards, the reaction mixture was diluted with water (20 ml), followed by evaporation of THF and methanol under reduced pressure (100 mbar, 40°C). Then, the water phase residue was washed with DCM (20 ml), acidified with 1M HCl to pH ~ 3, and extracted with DCM (3×40 ml). The combined organic layers were dried over MgSO₄, and the solvent was removed under vacuum, yielding 610 mg (100%) of 7.

3H NMR (400 MHz, DMSO-d₆): δ = 12.85 (bs, 1H, COOH), 7.84 (d, J₁ = 7.8 Hz, 1H), 7.54 (dd, J₁ = J₂ = 7.5 Hz, 1H), 7.36 (dd, J₁ = J₂ = 7.5 Hz, 1H), 7.32 (d, J = 7.8 Hz, 1H), 7.84 (d, J₁ = 11.7 Hz, 1H), 5.76 (dd, J₁ = 11.7 Hz, J₂ = 7.0 Hz, 1H, CH₂), 1.70 (dd, J₁ = 7.0 Hz, J₂ = 1.7 Hz, 1H, CH₂);

13C NMR (100MHz, DMSO-d₆): δ = 168.4, 137.4, 131.2, 130.4, 130.3, 130.1, 129.5, 126.8, 125.7, 14.2;

HR MS (FAB): calcd. for C₁₃H₁₂O₂ [M+H]+: 163.0759, found: 163.0757;

Elemental analysis (%): calcd. for C₁₃H₁₂O₂: C 74.06, H 6.21, found: C 73.49, H 5.39.
Synthesis of 5,6-dihyronaphthalene-1-carboxylic acid (9)

A 50 ml Schlenk tube was charged with 8-hydroxy-5,6,7,8-tetrahydronaphthalene-1-carboxylic acid, (420 mg, 2.2 mmol), rhenum(VII) oxide (10.5 mg, 29 mmol) and toluene (20 ml), sealed and stirred at 100°C overnight. After cooling down, the product was extracted to the water layer with water solution of lithium hydroxide (30 ml). Then, the water phase was washed with DCM (20 ml), acidified with 1M HCl to pH ~ 3, and extracted with DCM (3×50 ml). The combined organic layers were dried over MgSO4, and the solvent was removed under vacuum, yielding 290 mg (77%) of 9.

\[ ^1H\text{ NMR} (400 \text{ MHz, DMSO-}d_6): \delta = 12.87 (s, 1H, COOH), 7.62 (d, J = 7.8 \text{ Hz}, 1H), 7.33 - 7.21 (m, 2H), 7.19 (dd, J1 = J2 = 7.6 \text{ Hz}, 1H), 6.20 (dt, J1 = 10.0 \text{ Hz}, J1 = 4.4 \text{ Hz}, 1H), 2.76 (t, J = 8.2 \text{ Hz}, 2H), 2.25 - 2.19 (m, 2H); \]

\[ ^{13}C\text{ NMR} (100\text{MHz, DMSO-}d_6): \delta = 168.8, 136.5, 133.3, 131.0, 128.2, 127.4, 126.3, 125.1, 27.5, 21.9; \]

HR MS (FAB): calcd. for C_{11}H_{10}O_2 [M+H]^+: 175.0759, found: 175.0753;

Elemental analysis (%) calcd. for C_{11}H_{10}O_2: C 75.84, H 5.79, found: C 75.61, H 5.62.

Coordination and titration studies

All manipulations were conducted under inert atmosphere (argon or nitrogen) using oven-dried or flame dried glassware and pre-dried CD2Cl2 as a solvent. Commercially available tetrabutylammonium (TBA) salt was used as the source of benzoate anions. The titration experiments were conducted with a constant concentration of host protocol. All NMR spectra were collected at 25°C.

An oven-dried vial equipped with a teflon stirring bar was charged with ligand I and with Rh(acac)(CO)2 (1:1 ratio), followed by addition of an appropriate amount of CD2Cl2 to obtain a 0.001 M solution of both of them. The solution was stirred for 15 minutes at room temperature. The \(^1\)H and \(^3\)P NMR experiments of the solution confirmed a quantitative formation of the [Rh(I)(acac)] complex.

In another oven-dried Schlenk flask a 0.012 M solution of tetrabutylammonium benzoate in the 0.001 M solution of the Rh(I) complex was prepared. Under inert atmosphere (glove-box), aliquots (0.6-0.4ml) of the Rh(I) complex solution were transferred to NMR tubes, followed by addition of aliquots (0.0018-0.2ml) of the tetrabutylammonium benzoate in the Rh(I) solution.

For the evaluation of the association constant of the [Rh(I)(acac)] complex with benzoate anion, the chemical shift of ligand protons upon addition of different amount of the anion was observed. The highest changes were observed for both NH-indole and NH-amide protons, as expected, since they take part in hydrogen bond formation. Due to slow anion/receptor complex formation on the NMR timescale, there are two sets of NH signals observed between 0 and 1 equivalent of anion (some of other signals are significantly broaden, however, they sharpen above 1 equivalent of the anion), and their ratio depends on the amount of anion added. When slightly more than a stoichiometric amount of anion is added (1.05 equiv.) all signals of the complex are sharpened, and further anion addition does not change the spectrum. At this point the anion binding pocket is saturated. Similar observations were taken at \(^3\)P NMR spectra. Taking into account the total complex concentration \(\left[C\text{[Rh(I)(acac)]}\right] = 0.001 \text{ M}\), the association constant can be easily estimated: \(K_a = [C][A]/([C][A]),\) with: \([A] = \text{the concentration of the anion-[Rh(I)(acac)] complex, [C] = the concentration of the free [Rh(I)(acac)], [A] = the concentration of the free anion. Based on analysis of the spectrum at 1.05 equivalents of anion: \([A] >> 0.95[C\text{[Rh(I)(acac)]}, [C] << 0.05[C\text{[Rh(I)(acac)]}, \) so then \([A] \sim 0.05[C\text{[Rh(I)(acac)]}, \) After rearrangement: \(K >> 380[C\text{[Rh(I)(acac)]}]^{-1},\) so then \(K_a >> 10^7 [\text{M}^{-1}]\).

Catalysis studies

General procedure for the hydroformylation experiments

A stock solution for the hydroformylation experiments was prepared by charging a flame-dried Schlenk flask with Rh(acac)(CO)2, ligand, base (if appropriate), internal standard (1,3,5-trimethoxybenzene) and appropriate solvent. The solution was stirred for 5 minutes and then transferred into 1.5ml reaction vessels equipped with mini teflon stir bars (under inert conditions), followed by substrate addition. The vessels were placed in a stainless steel autoclave (250 mL) charged with an insert suitable for 15 reaction vessels for conducting parallel reactions. Before starting the catalytic reactions, the charged autoclave was purged three times with 20 bar of syngas and then pressurized at 20 bar of syngas. The experiments at 1 bar of syngas were performed in an analogical maner but in a standard Schlenk flask equipped with a gas ballon. The reaction mixtures were stirred at the appropriate temperature for the required reaction time, after which the pressure was released and the regioselectivity and the conversion were determined by NMR and/or GC. Additionally, in selected cases, the reaction mixtures were analyzed by electrospray ionization mass spectrometry (ESI MS).

For \(^1\)H NMR analysis, small portions (75 μl) of each reaction mixture were taken, from which the solvent was evaporated. Then, the residues were diluted to 0.7ml with DMSO-d6 and \(^1\)H NMR spectra were recorded and compared with a \(^1\)H NMR spectrum of the initial reaction mixture (before hydroformylation). The \(^{13}\)C NMR
analysis was performed with analogic manner, but larger portions of (700 μl) of each reaction mixture were
taken. No by-products (hydrogenation, double bond isomerisation) were observed (except where noted).
For GC analysis of reaction mixtures with carboxylic acid substrates, small portions (100 μl) of each reaction
mixture were taken, from which the solvent was evaporated (100 mbar, 40 °C) and subsequently a pinch of
KHCO$_3$ and DMF (0.3 ml) were added, followed by stirring for 5 minutes. Then, CH$_3$I (0.1 ml) was added and
the stirring was continued for 1h. Then, samples were diluted with ethyl acetate (2ml) and water (1ml), the
organic layers were separated and filtered via a HPLC syringe filter, and GC spectra were recorded.

Table 1. Hydroformylation of 2-vinylbenzoic acid 2a with the Rh(I) – variation of reaction conditions.*

| Entry | [2a] (M) | base | Rh (mol%) | temp. (°C) | time (h) | Regioselectivity | Side products$^{b}$ | Conversion (%) |
|-------|---------|------|-----------|------------|----------|----------------|-------------------|-----------------
| 1     | 0.2     | DIPEA 1.5 equiv. | 1% | rt | 24 | >98 | 0 | - | 100% |
| 2     | 0.2     | DIPEA 1.5 equiv. | 0.25% | rt | 24 | >98 | 0 | - | 54% |
| 3     | 0.2     | DIPEA 1.5 equiv. | 1% | 40 | 24 | >98 | 0 | - | 100% |
| 4     | 0.2     | DIPEA 1.5 equiv. | 1% | 40 | 24 | >98 | 0 | - | 100% |
| 5     | 0.2     | DIPEA 1.5 equiv. | 0.25% | 40 | 24 | >98 | 0 | - | 100% |
| 6     | 0.2     | DIPEA 1.5 equiv. | 0.1% | 40 | 24 | >98 | 0 | - | 57% |
| 7     | 1       | DIPEA 1.5 equiv. | 0.2% | 40 | 24 | >98 | 0 | - | 76% |
| 8     | 1       | DIPEA 1.5 equiv. | 0.1% | 40 | 24 | >98 | 0 | - | 34% |
| 9     | 0.2     | DIPEA 1.5 equiv. | 1% | 60 | 24 | >98 | 0 | + | 100% |
| 10    | 0.2     | DIPEA 1.5 equiv. | 0.1% | 60 | 24 | >98 | 0 | + | 100% |
| 11    | 1       | DIPEA 1.5 equiv. | 0.1% | 60 | 24 | >98 | 0 | ++ | 100% |
| 12    | 0.2     | DIPEA 1.5 equiv. | 0.1% | 80 | 24 | >98 | 0 | ++ | 100% |
| 13    | 1       | DIPEA 1.5 equiv. | 0.1% | 80 | 24 | >98 | 0 | +++ | 100% |
| 14    | 0.2     | TEA 1.5 equiv. | 0.25% | 80 | 1 | >98 | 0 | + | 100% |
| 15    | 0.2     | TEA 1 equiv. | 0.25% | 80 | 1 | >98 | 0 | + | 100% |
| 16    | 0.2     | TEA 0.5 equiv. | 0.25% | 80 | 1 | >98 | 0 | - | 100% |
| 17    | 0.2     | TEA 0.5 equiv. | 0.05% | 80 | 1 | >98 | 0 | - | 100% |
| 18    | 0.2     | TEA 0.5 equiv. | 0.005% | 80 | 1 | >98 | 0 | - | 42% |
| 19    | 0.2     | TEA 0.5 equiv. | 0.05% | 100 | 1 | >98 | 0 | - | 100% |
| 20    | 0.2     | TEA 0.5 equiv. | 0.005% | 100 | 1 | >98 | 0 | - | 67% |
| 21    | 0.2     | TEA 0.5 equiv. | 0.002% | 100 | 1 | >98 | 0 | - | 10% |
| 22    | 0.2     | TEA 0.5 equiv. | 0.05% | 120 | 1 | >98 | 0 | + | 100% |

* Reagents and conditions: Rh(CO)$_2$(acac) as a rhodium source, Rh : ligand 1, 1/1.1, CO/H$_2$ = 1/1 (20bar),
CH$_2$Cl$_2$ as a solvent, regioselectivity and conversion were determined by 1H NMR analysis of the crude
reaction mixture; $^{b}$ The amount of side products, if present, was estimated by 1H NMR analysis of the crude
reaction mixture: (-) no (+) <5%, (+++) 5-15%, (++++) >15% of side products – ESI MS analysis reveals that
these are products of the aldol condensation of the hydroformylation aldehyde product.
Table 2. Hydroformylation of 2-vinylbenzoic acid 2a with the Rh(1) – variation of reaction conditions.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>solvent</th>
<th>CO/H(_2) pressure</th>
<th>temp. (°C)</th>
<th>Regioselectivity</th>
<th>Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH(_2)Cl</td>
<td>1 bar</td>
<td>rt</td>
<td>&gt;98</td>
<td>40%</td>
</tr>
<tr>
<td>2</td>
<td>toluene</td>
<td>20 bar</td>
<td>40</td>
<td>&gt;98</td>
<td>100%</td>
</tr>
<tr>
<td>3</td>
<td>tetrahydrofurane</td>
<td>20 bar</td>
<td>40</td>
<td>&gt;98</td>
<td>100%</td>
</tr>
<tr>
<td>4</td>
<td>acetonitrile</td>
<td>20 bar</td>
<td>40</td>
<td>&gt;98</td>
<td>84%</td>
</tr>
</tbody>
</table>

\(^a\)Reagents and conditions: Rh(CO\(_2\))(acac) as a rhodium source, [2a] = 0.2 M, Rh : ligand 1 : substrate 2a : TEA, 1/1.1/100/150, CO/H\(_2\) = 1/1, 24h, regioselectivity and conversion were determined by \(^1\)H NMR analysis of the crude reaction mixture.

Table 3. Hydroformylation of vinyl 2-carboxyarenes 2 with the Rh(1) – substrate scope.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Temp.</th>
<th>Selectivity</th>
<th>Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>rt</td>
<td>&gt;98%</td>
<td>70%</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td>&gt;98%</td>
<td>100%</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td>rt</td>
<td>&gt;98%</td>
<td>100%</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td>&gt;98%</td>
<td>26%</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td>&gt;98%</td>
<td>70%</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td>&gt;98%</td>
<td>94%</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td>&gt;98%</td>
<td>100%</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td>&gt;98%</td>
<td>100%</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td>&gt;98%</td>
<td>17%</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td>&gt;98%</td>
<td>80%</td>
</tr>
<tr>
<td>11</td>
<td></td>
<td></td>
<td></td>
<td>&gt;98%</td>
<td>2%</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
<td></td>
<td>&gt;98%</td>
<td>10%</td>
</tr>
</tbody>
</table>
he charged – 

12, 45 minutes at rt. Afterwards, water (25 ml) and 4, 4, 4
neutralized with 1M HCl and extracted with DCM (3·200ml).

H 3 (sat.) extracted with DCM (3 minutes at rt. Then, it was cool down to 0°C, followed by addition of NaBH 4 (Methyl 1.15 g, 6 mmol) was added, and stirring was continued overnight. The next day, water (60 ml) was

Isolation of 2-(3-oxopropane)-benzoic acid 3a (big scale) and its further derivatizations:

2-(3-oxopropane)-benzoic acid (3a): A stainless steel autoclave equipped with an oven-dried glass insert (250 ml) was charged with 2-vinyl benzoic acid (4.44 g, 30 mmol), dry triethylamine (4.17 ml, 30mmol), Rh(CO) 3(acac) (19 mg, 0.075 mmol), ligand 1 (104 mg, 0.083 mmol) and dry DCM (96ml). The charged autoclave was carefully purged three times with 20 bar of syngas and then pressurized at 20 bar of syngas, followed by stirring at 40°C for 16h. Afterwards the pressure was carefully released, the reaction mixture was

CH 2 = 7.5 Hz, 1H, CH 2 CHO); 2.74 (dt, J 1 = 7.5 Hz, J 2 = 1.3 Hz, 2H, CH 2 CHO).

13C NMR (100MHz, DMSO-d 6 ): δ = 201.6, 167.8, 142.8, 132.5, 131.4, 131.2, 129.4, 126.7, 52.2, 45.7, 27.4.

HR MS (FAB): calced. for C 19 H 19 O 3 [M+H] + : 279.0708, found: 279.0707;

Elemental analysis (%) calcd. for C 19 H 19 O 3: C 67.41, H 5.66, found: C 67.41, H 5.65.

Methyl 2-(3-oxopropane)-benzoate: In a Schlenk flask 2-(3-oxopropane)-benzoic acid 3a (1.07 g, 6 mmol) and KHCO 3 (720 mg, 7.2 mmol) was dissolved in DMF (10 ml) and stirred for 10 minutes. Then, methyl iodide (0.56ml, 9 mmol) was added, and stirring was continued overnight. The next day, water (60 ml) was added, the reaction mixture was extracted with ethyl acetate (3•70 ml). The combined organic layers were washed with NH 4 Cl (370 ml), dried over MgSO 4 , and the solvent was removed under vacuum, yielding 1.15 g (100%) of product.

Methyl 2-(3-oxopropan-1-yl)-benzoate (12): In a Schlenk flask methyl 2-(3-oxopropane)-benzoate (1.15 g, 6 mmol) and n-butyllamine (0.62 ml, 6.3 mmol) was dissolved in ethanol (30 ml) and stirred for 45 minutes at rt. Then, it was cool down to 0°C, followed by addition of NaBH 4 (238 mg, 6.3 mmol). The cooling bath was removed and the reaction mixture was stirred for 45 minutes at rt. Afterwards, water (25 ml) and DCM (25 ml) were added, followed by addition of 1M HCl to reach pH ~7. Then, the reaction mixture was extracted with DCM (3•70 ml). The combined organic layers were washed with NH 4 Cl (3•70 ml), dried over MgSO 4 , and the solvent was removed under vacuum, yielding 1.5 g (100%) of 12.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Temp.</th>
<th>Selectivity</th>
<th>Conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td></td>
<td></td>
<td>rt</td>
<td>&gt;98%</td>
<td>73%</td>
</tr>
<tr>
<td>14</td>
<td></td>
<td></td>
<td>rt</td>
<td>&gt;98%</td>
<td>100%</td>
</tr>
<tr>
<td>15</td>
<td></td>
<td></td>
<td>rt</td>
<td>87% (80%)</td>
<td>100%</td>
</tr>
<tr>
<td>16</td>
<td></td>
<td></td>
<td>40°C</td>
<td>&gt;98%</td>
<td>100%</td>
</tr>
<tr>
<td>17</td>
<td></td>
<td></td>
<td>40°C</td>
<td>&gt;98%</td>
<td>38%</td>
</tr>
</tbody>
</table>

Isolation of 2-(3-oxopropane)-benzoic acid 3a (big scale) and its further derivatizations:

To a solution of 2-(3-oxopropane)-benzoic acid 3a (3.44 g, 30 mmol), dry triethylamine (3.17 ml, 30mmol), Rh(CO) 3(acac) (19 mg, 0.075 mmol), and ligand 1 (104 mg, 0.083 mmol) in dry DCM (96 ml), the reaction mixture was

Table 3. Hydroformylation of vinyl 2-carboxyarennes 2 with the Rh(1) – substrate scope – continuation. 

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Temp.</th>
<th>Selectivity</th>
<th>Conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
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<td>15</td>
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<td></td>
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<tr>
<td>17</td>
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<td></td>
<td></td>
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</tr>
</tbody>
</table>

Reagents and conditions: Rh(CO) 3(acac) as a rhodium source, [2] = 0.2 M, Rh : ligand 1 : substrate 2 : DIPEA, 1/1/100/150, CO/H 2 = 1/1 (20bar), 24h, CH 2 Cl 2 ; as a solvent, regioselectivity and conversion was determined by 1H and 13C NMR analysis of the crude reaction mixture, no other isomers or side products were observed (except were noted), TEA can be used instead of DIPEA; acac = acetylacetonate, DIPEA = N,N-diisopropylethylamine, TEA = triethylamine; 72h reaction time; regioselectivity and chemoselectivity towards aldehydes, respectively; base : substrate 0.5/1.
2-Butyl-2,3,4,5-tetrahydro-1H-2-benzazepin-1-one (11): The synthesis was performed according to the published procedures for an analogous reaction. To a solution of methyl (N-buthyl-3-aminopropano)benzoate 12 (1.5 g, 6 mmol) in dry THF (20 ml), in a sealable Schlenk tube ("Schlenk bomb"), a solution of trimethylaluminium (30 ml, 2M, 60 mmol) in heptane was added dropwise at 0°C. Then the tube was sealed and stirred for 2 days at 70°C. Afterwards, the reaction mixture was carefully added into a cooled mixture of water and DCM. The organic layer was separated, the solid and the aqueous layer were extracted thoroughly with DCM. The combined organic layers were dried over MgSO4 and the solvent was removed under vacuum. The crude product was purified by column chromatography on silica gel, with a pentane: ethyl acetate (7:3) mixture as an eluent. Fractions of the product were combined, the solvent evaporated off, yielding 1.01 g (78%, 3 steps) of 11.

1H NMR (400 MHz, CDCl3): δ = 7.58 (dd, J1 = 7.5 Hz, J2 = 1.5 Hz, 1H), 7.36 (dd, J1 = J2 = 7.4 Hz, J3 = 1.5 Hz, 1H), 7.30 (ddd, J1 = J2 = 7.5 Hz, J3 = 1.4 Hz, 1H), 7.15 (dd, J4 = 7.6 Hz, 2H), 1.36 (t, J = 6.4 Hz, 2H), 2.77 (t, J = 7.2 Hz, 2H), 2.01 (s, J = J2 = J3 = J4 = 6.8 Hz, 2H), 1.66 – 1.57 (m, 2H), 1.40 (tq, J = 1.3 Hz, 1H), 1.05 (t, J = 7.4 Hz, 3H);

13C NMR (100MHz, CDCl3): δ = 170.8, 137.9, 137.3, 130.8, 128.7, 128.5, 128.1, 127.1, 47.4, 46.5, 31.5, 30.6, 30.4, 20.7, 14.1;

HR MS (FAB): calcd. for C14H20ON [M+H]+: 218.1545, found: 215.1544;

Elemental analysis (%) calcd. for C14H20ON: C 77.38, H 8.81, N 6.45, found: C 77.52, H 9.29, N 6.36.

2-(3-Hydroxypropeno)-benzoic acid (14): To a solution of 2-(3-oxopropane)-benzoic acid 3a (534 mg, 3 mmol) in ethanol (5ml) NaBH4 (227 mg, 6 mmol) was added at 0°C, and stirring was continued overnight at rt. The next day, water (15 ml) was added and ethanol was evaporated under reduced pressure. Then, the aqueous phase was washed with DCM (20 ml), followed by addition of 1M HCl (to pH ~ 6) and an extraction with DCM (3×30 ml). The combined organic layers were dried over MgSO4, and the solvent was removed under vacuum, yielding 540 mg (100%) of 14.

1H NMR (400 MHz, DMSO-d6): δ = 12.80 (s, 1H), 7.75 (dd, J1 = 7.7 Hz, J2 = 1.3 Hz, 1H), 7.44 (ddd, J1 = J2 = 7.5 Hz, J3 = 1.4 Hz, 1H), 7.31 – 7.24 (m, 2H), 4.43 (bs, 1H), 3.40 (t, J = 6.2 Hz, 2H), 2.91 (t, J = 7.7 Hz, 2H), 1.72 – 1.64 (m, 2H);

13C NMR (100MHz, DMSO-d6): δ = 168.9, 143.1, 131.5, 130.7, 130.6, 130.1, 125.8, 60.5, 34.6, 30.1;


Elemental analysis (%) calcd. for C9H10O2: C 74.06, H 6.21, found: C 73.92, H 6.21.

4.5-Dihydro-2-benzoxepin-1(3H)-one (13): A Schlenk flask was charged with 2-(3-hydroxypropeno)-benzoic acid 14 (1.15 g, 6 mmol), p-toluensulfonic acid (4 mg) and toluene (40 ml), sealed and stirred for 3h at 120°C. After cooling down, toluene was evaporated off and the product was purified by flash column chromatography on silica gel, with a pentane: ethyl acetate (7:3) mixture as an eluent. Fractions of the product were combined, the solvent evaporated off, yielding 148 mg (91%) of 13.

1H NMR (400 MHz, CDCl3): δ = 7.65 (dd, J1 = 7.6 Hz, J2 = 1.4 Hz, 1H), 7.48 (ddd, J1 = J2 = 7.6 Hz, J3 = 1.5 Hz, 1H), 7.36 (ddd, J1 = J3 = 7.6 Hz, J3 = 1.2 Hz, 1H), 7.23 (dm, J = 7.6 Hz, 1H), 4.11 (t, J = 6.3 Hz, 2H), 2.87 (t, J = 7.2 Hz, 2H), 2.13 – 2.06 (m, 2H);

13C NMR (100MHz, CDCl3): δ = 172.4, 138.1, 132.9, 132.2, 130.3, 129.0, 127.6, 66.9, 29.8, 28.1;

HR MS (FAB): calcd. for C16H13O2 [M+H]+: 163.0759, found: 163.0762;

Elemental analysis (%) calcd. for C16H13O2: C 74.06, H 6.21, found: C 73.92, H 6.02.

Isolation of other products (small scale):

General procedure: A stainless steel autoclave equipped with an oven-dried glass insert (15 mL) was charged with a solution of a substrate (0.2M), dry triethylamine (0.3M), Rh(CO)(acac) (0.002M), ligand 1 (0.0022M) in dry DCM. The charged autoclave was carefully purged three times with 20 bar of syngas and then pressurized at 20 bar of syngas, followed by stirring at appropriate temperature for desired time. Afterwards the pressure was carefully released, the reaction mixture was diluted with DCM or ethyl acetate to ~ 50 ml and
the product was extracted with aqueous NaHCO₃ (sat.) (3-15ml). The combined aqueous layers were subsequently washed with DCM or ethyl acetate, then neutralized with 1M HCl and extracted with DCM or ethyl acetate (3-50ml). The organic layers were combined, dried over MgSO₄ and the solvent evaporated off, yielding desired product 3.

6-Methyl-2-(3-oxopropane)-benzoic acid 3b:

The reaction was run at 40°C for 24h. 6-Methyl-2-vinylbenzoic acid 2b (49mg, 0.3mmol) was used as the starting material, yielding 55mg (95%) of product 3b.

1H NMR (400 Mhz, DMSO-d₆): δ = 13.21 (bs, 1H, COOH), 9.69 (t, J₁ = 0.9 Hz, 1H, CHO), 7.24 (dd, J₁ = J₂ = 7.6 Hz, 1H), 7.12 − 7.08 (m, 2H), 2.82 (t, J₁ = 7.5 Hz, 2H, CH₂CH₂CHO), 2.74 (t, J₁ = 7.5 Hz, 2H, CH₂CHO), 2.25 (s, 3H);
13C NMR (100MHz, DMSO-d₆): δ = 202.4, 170.7, 136.6, 135.3, 133.5, 128.8, 127.8, 126.4, 44.4, 25.5, 19.3;

5-Methyl-2-(3-oxopropane)-benzoic acid 3c:

The reaction was run at room temperature for 24h. 5-Methyl-2-vinylbenzoic acid 2c (130mg, 0.8mmol) was used as the starting material, yielding 148mg (96%) of product 3c.

1H NMR (400 Mhz, DMSO-d₆): δ = 12.85 (bs, 1H, COOH), 9.69 (t, J₁ = 1.2 Hz, 1H, CHO), 7.63 (s, 1H), 7.28 (d, J₁ = 7.8 Hz, 1H), 7.21 (d, J₁ = 7.9 Hz, 1H), 3.12 (t, J₁ = 7.6 Hz, 2H, CH₂CH₂CHO), 2.70 (td, J₁ = 7.6 Hz, J₂ = 1.2 Hz, 2H, CH₂CHO), 2.29 (s, 3H);
13C NMR (100MHz, DMSO-d₆): δ = 202.7, 168.6, 138.9, 135.5, 132.5, 130.81, 138.77, 130.0, 44.9, 26.0, 20.3;

4-Methyl-2-(3-oxopropane)-benzoic acid 3d:

The reaction was run at room temperature for 24h. 4-Methyl-2-vinylbenzoic acid 2d (130mg, 0.8mmol) was used as the starting material, yielding 148mg (96%) of product 3d.

1H NMR (400 Mhz, DMSO-d₆): δ = 12.74 (bs, 1H, COOH), 9.70 (t, J₁ = 1.3 Hz, 1H, CHO), 7.74 (d, J₁ = 7.9 Hz, 1H), 7.15 (s, 1H), 7.11 (d, J₁ = 7.9 Hz, 1H), 3.14 (t, J₁ = 7.6 Hz, 2H, CH₂CH₂CHO), 2.72 (td, J₁ = 7.6 Hz, J₂ = 1.3 Hz, 2H, CH₂CHO), 2.31 (s, 3H);
13C NMR (100MHz, DMSO-d₆): δ = 202.7, 168.4, 142.4, 142.0, 131.5, 130.8, 127.1, 126.9, 44.9, 26.5, 20.9;

3-Methyl-2-(3-oxopropane)-benzoic acid 3e:

The reaction was run at 50°C for 72h, using lower concentration of the base, [TEA] = 0.1M. 3-Methyl-2-vinylbenzoic acid 2e (65mg, 0.4mmol) was used as the starting material, yielding 74mg (96%) of product 3e.

1H NMR (400 Mhz, DMSO-d₆): δ = 12.85 (bs, 1H, COOH), 9.73 (s, 1H, CHO), 7.57 (d, J₁ = 7.7 Hz, 1H), 7.34 (d, J₁ = 7.5 Hz, 1H), 7.19 (dd, J₁ ≈ J₂ = 7.7 Hz, 1H), 3.08 (t, J₁ = 7.8 Hz, 2H, CH₂CH₂CHO), 2.68 (t, J₁ = 7.8 Hz, 2H, CH₂CHO), 2.31 (s, 3H);
13C NMR (100MHz, DMSO-d₆): δ = 202.4, 169.4, 139.4, 137.3, 133.4, 131.7, 127.7, 125.9, 43.5, 22.3, 19.2;

5-Methoxy-2-(3-oxopropane)-benzoic acid 3f:

The reaction was run at room temperature for 24h. 5-Methoxy-2-vinylbenzoic acid 2f (143mg, 0.8mmol) was used as the starting material, yielding 159mg (93%) of product 3f.

1H NMR (400 Mhz, DMSO-d₆): δ = 12.99 (bs, 1H, COOH), 9.69 (t, J₁ = 1.4 Hz, 1H, CHO), 7.31 (d, J₁ = 2.8 Hz, 1H), 7.25 (d, J₁ = 8.5 Hz, 1H), 7.06 (dd, J₁ ≈ J₂ = 2.8 Hz, 1H), 3.76 (s, 3H), 3.09 (t, J₁ = 7.6 Hz, 2H, CH₂CH₂CHO), 2.69 (td, J₁ = 7.6 Hz, J₂ = 1.4 Hz, 2H, CH₂CHO);
13C NMR (100MHz, DMSO-d₆): δ = 202.8, 168.4, 157.3, 133.8, 132.1, 131.2, 117.8, 115.1, 55.2, 45.1, 25.6;

5-Chloro-2-(3-oxopropane)-benzoic acid 3g:

The reaction was run at room temperature for 24h. 5-Chloro-2-vinylbenzoic acid 2g (146mg, 0.8mmol) was used as the starting material, yielding 158mg (93%) of product 3g.

1H NMR (400 Mhz, DMSO-d₆): δ = 13.34 (bs, 1H, COOH), 9.69 (t, J₁ < 1 Hz, 1H, CHO), 7.78 (d, J₁ = 2.4 Hz, 1H), 7.54 (dd, J₁ = 8.3 Hz, J₂ = 2.4 Hz, 1H), 7.38 (d, J₁ = 8.4 Hz, 1H), 3.14 (t, J₁ = 7.6 Hz, 2H, CH₂CH₂CHO), 2.74 (td, J₁ = 7.6 Hz, J₂ = 0.7 Hz, 2H, CH₂CHO);
The reaction was run at 40°C for 24h. 5-Vinyl-1,3-benzodioxole-4-carboxylic acid 2j (115mg, 0.6mmol) was used as the starting material, yielding 110mg (83%) of product 3j.

1H NMR (400 MHz, DMSO-d6); δ = 13.12 (bs, 1H, COOH), 9.79 (t, J = 1 Hz, 1H, CHO), 8.24 – 8.20 (m, 1H), 8.01 – 7.97 (M, 1H), 7.87 (d, J = 8.7 Hz, 1H), 7.79 (d, J = 8.7 Hz, 1H), 7.67 – 7.61 (m, 2H), 3.60 (t, J = 7.8 Hz, 2H, CH₂CH₂CHO), 2.83 (t, J = 7.8 Hz, 2H, CH₂CHO);

13C NMR (100MHz, DMSO-d6); δ = 128.5, 127.4, 124.8, 123.8, 123.0, 131.3, 128.9, 128.7, 127.4, 127.1, 126.7, 125.8, 124.8, 44.5, 21.6;


1-[(3-oxopropane)-2-naphthoic acid 3k:

The reaction was run at 60°C for 72h, using lower concentration of the base, [TEA] = 0.1M. 1-Vinyl-2-naphthoic acid 2k (79mg, 0.4mmol) was used as the starting material, yielding 85mg (93%) of product 3k, which contained 5% unreacted starting material, 1-vinyl-2-naphthoic acid 2k. Crystallization of this mixture by concentration of the hexane – dichloromethane solution provided pure product 3k.

1H NMR (400 MHz, DMSO-d6); δ = 13.12 (bs, 1H, COOH), 9.79 (t, J = 1 Hz, 1H, CHO), 8.24 – 8.20 (m, 1H), 8.01 – 7.97 (M, 1H), 7.87 (d, J = 8.7 Hz, 1H), 7.79 (d, J = 8.7 Hz, 1H), 7.67 – 7.61 (m, 2H), 3.60 (t, J = 7.8 Hz, 2H, CH₂CH₂CHO), 2.83 (t, J = 7.8 Hz, 2H, CH₂CHO);

13C NMR (100MHz, DMSO-d6); δ = 128.5, 127.4, 124.8, 123.8, 123.0, 131.3, 128.9, 128.7, 127.4, 127.1, 126.7, 125.8, 124.8, 44.5, 21.6;


1-Methyl-(3-oxopropane)-1H-indole-2-carboxylic acid 3m:

The reaction was run at 40°C for 24h. 1-Methyl-3-vinyl-1H-indole-2-carboxylic acid 2m (60mg, 0.3mmol) was used as the starting material, yielding 57mg (82%) of product 3m.

1H NMR (400 MHz, DMSO-d6); δ = 13.14 (bs, 1H, COOH), 9.72 (t, J = 1.6 Hz, 1H, CHO), 7.72 (d, J = 8.0 Hz, 1H), 7.52 (d, J = 8.4 Hz, 1H), 7.33 (dd, J = 7.2 Hz, 1H), 7.11 (dd, J = J₂ = 7.5 Hz, 1H), 3.95 (s, 3H), 3.30 (t, J = 7.5 Hz, 2H, CH₂CH₂CHO), 2.71 (td, J = 7.5 Hz, J₂ = 1.6 Hz, 2H, CH₂CHO);

13C NMR (100MHz, DMSO-d6); δ = 203.0, 163.4, 138.1, 125.7, 125.4, 125.0, 122.1, 120.3, 119.8, 110.7, 44.5, 31.9, 17.7;


3-(3-oxopropane)-benzo[b]thiophene-2-carboxylic acid 3n:

The reaction was run at 40°C for 24h. 3-Vinylbenzothiophene-2-carboxylic acid 2n (123mg, 0.6mmol) was used as the starting material, yielding 119mg (85%) of product 3n.

1H NMR (400 MHz, DMSO-d6); δ = 13.47 (bs, 1H, COOH), 9.74 (t, J = 1.2 Hz, 1H, CHO), 8.02 (d, J = 8.0 Hz, 1H), 8.01 (d, J = 8.0 Hz, 1H), 7.54 (dd, J = 7.2 Hz, 1H), 7.49 (dd, J = 7.2 Hz, 1H), 3.51 (t, J = 7.7 Hz, 2H, CH₂CH₂CHO), 2.76 (td, J = 7.7 Hz, J₂ = 1.0 Hz, 2H, CH₂CHO);

13C NMR (100MHz, DMSO-d6); δ = 202.3, 163.9, 142.8, 139.6, 139.0, 128.5, 127.4, 124.8, 123.8, 123.0, 43.2, 19.4;


2-(3-oxopropane)-3-thiophencarboxylic acid 3o:

The reaction was run at room temperature for 24h. 2-Vinyl-3-thiophencarboxylic acid 2o (123mg, 0.8mmol) was used as the starting material, yielding 140mg (95%) of product 3o.

1H NMR (400 MHz, DMSO-d6); δ = 12.73 (bs, 1H, COOH), 9.69 (t, J = 1.1 Hz, 1H, CHO), 7.34 (d, J = 5.4 Hz, 1H), 7.30 (d, J = 5.4 Hz, 1H), 3.38 (t, J = 7.4 Hz, 2H, CH₂CH₂CHO), 2.83 (td, J = 7.4 Hz, J₂ = 1.1 Hz, 2H, CH₂CHO);

13C NMR (100MHz, DMSO-d6); δ = 202.0, 164.2, 151.9, 129.3, 128.9, 122.7, 44.3, 21.5;


2-(2-Methyl-3-oxopropane)-benzoic acid 9:

The reaction was run at 40°C for 72h, using lower concentration of the base, [TEA] = 0.1M. 2-[(1Z)-Prop-1-en-1-yl]-benzoic acid 7 (130mg, 0.8mmol) was used as the starting material, yielding 151mg (98%) of product 9, which contains ~2% of 2-[(1E)-prop-1-en-1-yl]-benzoic acid.
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\( ^1 \)H NMR (400 MHz, DMSO-\( d_6 \)): \( \delta = 12.91 \) (bs, 1H, COOH), 9.63 (d, \( J = 1.5 \) Hz, 1H, CHO), 7.84 (d, \( J = 8.2 \) Hz, 1H), 7.48 (dd, \( J_1 = J_2 = 7.6 \) Hz, 1H), 7.35 – 7.30 (m, 2H), 3.43 (dd, \( J_1 = 13.1 \) Hz, \( J_2 = 6.4 \) Hz, 1H, CH\( _2 \)CHCHO), 2.86 (dd, \( J_1 = 13.1 \) Hz, \( J_2 = 7.9 \) Hz, 1H, CH\( _2 \)CHCHO), 2.73 – 2.63 (m, 1H, CHCHO), 0.96 (d, \( J = 7.0 \) Hz, 3H, CH\( _3 \)H).

**8-Formyl-5,6,7,8-tetrahydroxanthene-1-carboxylic acid 10:**

The reaction was run at 60°C for 72h, using lower concentration of the base, [TEA] = 0.1M. 5,6-Dihydranaphthalene-1-carboxylic acid 8 (87mg, 0.5mmol) was used as the starting material, yielding 98mg (96%) of product 10.

\( ^1 \)H NMR (400 MHz, DMSO-\( d_6 \)): \( \delta = 12.84 \) (bs, 1H, COOH), 9.72 (ps, 1H, CHO), 7.61 (d, \( J = 7.6 \) Hz, 1H), 7.27 (d, \( J = 7.6 \) Hz, 1H), 7.19 (dd, \( J_1 = J_2 = 7.6 \) Hz, 1H), 3.24 (dd, \( J_1 = 17.9 \) Hz, \( J_2 = 5.8 \) Hz, 1H, C(8)H\( _2 \)CHCHO), 3.07 (dd, \( J_1 = 17.9 \) Hz, \( J_2 = 9.1 \) Hz, 1H, C(8)H\( _2 \)CHCHO), 2.86 – 2.79 (m, 2H, C(5)H\( _2 \)), 2.78 – 2.69 (m, 1H, CHCHO), 2.13 – 2.05 (m, 1H, C(6)H\( _2 \)CHCHO), 1.75 – 1.64 (m, 1H, C(6)H\( _2 \)CHCHO);

\( ^13 \)C NMR (100MHz, DMSO-\( d_6 \)): \( \delta = 204.7, 169.0, 137.3, 135.4, 132.3, 131.2, 127.8, 125.4, 45.6, 28.1, 26.3, 21.6.

**HR MS (FAB):** calcd. for C\( _7 \)H\( _7 \)O\( _3 \) [M+H]\(^+\): 205.0865, found: 205.0861.

**Control experiments**

**Table 4.** Hydroformylation of styrene derivatives with the Rh(I) and Rh(PPh\(_3\)) catalysts – control experiments.\(^{a}\)

| Entry | Substrate | Ligand | Regioselectivity | Conversion (%)
|-------|-----------|--------|-----------------|----------------|
| 1     | 2-methylstyrene | I       | 5               | >99
| 2     | 2-methylstyrene | PPh\(_3\) | 7               | 93
| 3     | 3-methylstyrene | I       | 7               | 93
| 4     | 3-methylstyrene | PPh\(_3\) | 4               | 96
| 5     | 2-methoxystyrene | I       | 5               | 95
| 6     | 2-methoxystyrene | PPh\(_3\) | 9               | 81
| 7     | 3-methoxystyrene | I       | 6               | 94
| 8     | 3-methoxystyrene | PPh\(_3\) | 2               | 98
| 9     | styrene         | I       | 6               | 94
| 10    | styrene         | PPh\(_3\) | 5               | 95
| 11    | methyl 2-vinylbenzoate | I       | 5               | 95
| 12    | methyl 2-vinylbenzoate | PPh\(_3\) | 5               | 95
| 13    | methyl 3-vinylbenzoate | I       | 5               | 95
| 14    | methyl 3-vinylbenzoate | PPh\(_3\) | 2               | 98
| 15\(^b\) | 2-(trifluoromethyl)styrene | I       | 10              | 90
| 16    | 3-(trifluoromethyl)styrene | I       | 4               | 96
| 17    | 3-(trifluoromethyl)styrene | PPh\(_3\) | 1               | 99
| 18    | 4-(trifluoromethyl)styrene | I       | 3               | 97
| 19    | 4-(trifluoromethyl)styrene | PPh\(_3\) | 1               | 99

\(^a\) Reagents and conditions: [substrate]=0.2M, Rh(CO\(_3\))(acac) (1mol%), ligand 1 (1.1mol%) or PPh\(_3\) (6%), CO/H\(_2\) = 1/1 (20bar), CH\(_2\)Cl\(_2\), 24h, at room temp.; \(^b\) 24h reaction.
Table 5. Hydroformylation of 2-vinylbenzoic acid 2a – control experiments.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>TEA\textsuperscript{b}</th>
<th>anion receptor R1\textsuperscript{b}</th>
<th>Regioselectivity</th>
<th>Conversion (%)</th>
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\textsuperscript{a}Reagents and conditions: Rh(CO)\textsubscript{2}(acac) as a rhodium source, \([2a] = 0.2\) M, Rh : ligand L2 : receptor R1 : substrate 2a : TEA, 1/6/(2 or 0)/100/(150 or 0), CO/H\textsubscript{2} = 1/1 (20 bar), CH\textsubscript{2}Cl\textsubscript{2}, 24h, Conversion was determined by \(^1\)H NMR analysis of the crude reaction mixture; \textsuperscript{b}'+-' and '-.' denote if the component was added to the reaction mixture.

Gas uptake experiments

The experiments were carried out in the AMTEC SPR16 equipment\textsuperscript{23} consisting of 16 parallel reactors equipped with internal temperature and pressure sensors, and a mass flow controller. The apparatus is suited for monitoring gas uptake profiles during the catalytic reactions. Prior to catalytic experiments, the autoclaves were heated to 110°C and flushed with argon (22 bar) five times. Next the reactors were cooled to room temperature and flushed again with argon (22 bar) five times. Then, the autoclaves were charged with solutions of the rhodium precursor [Rh(acac)(CO)\textsubscript{2}], ligand, substrate, base (if necessary) and internal standard (1,3,5-trimethoxybenzene) in CH\textsubscript{2}Cl\textsubscript{2} (8ml). The reactors were pressurized with syngas (CO/H\textsubscript{2}, 1:1, 20bar) and heated up to appropriate temperature. The pressure was kept constant during the whole reaction, and the gas uptake was monitored and recorded for every reactor. After catalysis the pressure was reduced to 2.0 bar and samples were taken for further analysis (NMR and/or GC analysis, as described in the section above).

Conversions were determined by NMR analysis of the final reaction mixtures (in respect to the internal standard). All the measured data of the gas consumption in time were smoothed, to minimize the noise inherent in the integral measurements (to capture important patterns in the data, while leaving out noise),\textsuperscript{24} applying the Double Boltzmann model or the Boltzmann model with the Origin 8.0 software. The correctness of the model used was evaluated and confirmed by the analysis of the regular residuals of the fitting. The smoothed data were used for further analysis.

Isotope labeling studies - deuterioformylation

The deuterioformylation study was conducted analogously to the hydroformylation experiments, using a 1 : 1 mixture of D\textsubscript{2} and CO in place of H\textsubscript{2} and CO. The conversion was determined by the standard \(^1\)H NMR analysis. The reaction time was adjusted to reach a medial conversion, so that there is still a high substrate concentration, yet the reaction time allows for a significant level of, if possible, deuterium incorporation to the substrate molecules via the reversible hydride migration – beta-hydride elimination mechanism.\textsuperscript{15} The crude reaction mixture was investigated by \(^2\)H NMR spectroscopic analysis (no other solvents were added). No deuterium incorporation into neither of substrates 2a and 7 was observed.

Figure 2. \(^2\)H NMR spectrum of the substrate 2a deuterioformylation reaction mixture by the Rh(1) catalyst. Reagents and conditions: Rh(CO)\textsubscript{2}(acac) as a rhodium source, \([2a] = 0.2\) M, Rh : ligand 1 : substrate 2a : DIPEA, 1/1/100/150, CO/D\textsubscript{2} = 1/1 (20bar), 4h, 22°C, CH\textsubscript{2}Cl\textsubscript{2} as a solvent; acac = acetylacetonate, DIPEA = N,N-diisopropylethylamine. Conversion = 58%.
Figure 3. $^1$H NMR spectrum of the substrate 7 deuterioformylation reaction mixture by the Rh(I) catalyst. Reagents and conditions: Rh(CO)$_2$(acac) as a rhodium source, [substrate 7] = 0.2 M, Rh : ligand 1 : substrate 7 : DIPEA, 1/1.1/100/150, CO/D$_2$ = 1/1 (20bar), 24h, 50°C, CH$_2$Cl$_2$ as a solvent; acac = acetylacetonate, DIPEA = N,N-diisopropylethylamine. Conversion = 64%.

DFT calculations

The mechanism of the regioselectivity-determining hydrometalation step of 2-vinylbenzoate by Rh(I) was studied with DFT. A series of calculations on possible structures of the catalyst-substrate complex was performed, and the most important structures are reported. Structure A (Figure 2a) in the manuscript represents the lowest energy conformer found among several possible structures of the catalyst-substrate complex. The alkene insertion from conformer A toward the β-aldehyde product is represented by transition state B leading to alkyl complex C, which is energetically privileged over the route toward the alpha aldehyde product consisting of transition state D leading to alkyl complex E. Alternative conformer of the catalyst-substrate complex (structure F), which favors the formation of the alpha-aldehyde product is much higher in energy (ΔG = 15.1 kJ•mol$^{-1}$), and goes also through much higher transition state G (ΔG# = 40.2 kJ•mo l$^{-1}$), leading to alkyl complex H. According to this model, the bifunctional substrate binding effectively hinders the formation of the typical alpha-aldehyde product usually formed in the hydroformylation of vinyl arenes.

The geometry optimizations were carried out with the Turbomole program$^{25}$ coupled to the PQS Baker optimizer$^{26}$ at the ri-DFT level$^{27}$ using the BP86$^{28}$ functional and the resolution-of-identity (ri) method. We used the SV(P) basis set$^{29}$ for the geometry optimizations of all stationary points. All minima (no imaginary frequencies) and transition states (one imaginary frequency) were characterized by numerically calculating the Hessian matrix. ZPE and gas-phase thermal corrections (entropy and enthalpy, 298 K, 1 bar) from these analyses were calculated. The thus obtained energies in kJ mol$^{-1}$ are reported in Table 6 as well as in Figure 1 (the values are relative to structure A).

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<th>Structure</th>
<th>ΔE [kJ mol$^{-1}$]</th>
<th>ΔE$_{ZPE}$ [kJ mol$^{-1}$]</th>
<th>ΔG$_{298K}$ [kJ mol$^{-1}$]</th>
<th>ΔH$_{298K}$ [kJ mol$^{-1}$]</th>
<th>ΔS$_{298K}$ [J mol$^{-1}$ K$^{-1}$]</th>
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5.5 Acknowledgements

We kindly acknowledge the NRSC-Catalysis for financial support, Prof. Bas de Bruin and Dr. Jarl Ivar van der Vlugt for helpful discussions, and Dr. Remko J. Detz for assistance with gas-uptake experiments.

5.6 References

Chapter 5

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 conditions (< 80°C) and medium pressures of syngas (>10bar) the hydride migration step is irreversible. This is thus the selectivity determining step. Under lower pressures conditions (< 5bar) 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 conditions (20 bar of D₂/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 confirms that under these conditions it determines the selectivity. See: (a) Raffaelli, A.; Pucci, S.; Settambolo, R.; Uccello-Barretta, G.; Lazzaroni, R. Organometallics 1991, 10, 3892-3898. (b) Alagona, G.; Ghio, C.; Lazzaroni, R.; Settambolo, R. Organometallics 2001, 20, 5394–5404. (c) Horiuchi, T.; Shirakawa, E.; Nozaki, K.; Takaya, H. Organometallics 1997, 16, 2981-2986. (d) Watkins, A. L.; Landis, C. R.; J. Am. Chem. Soc. 2010, 132, 10306–10317.
16 For details see the experimental section.
18 Although, both ligand 1 and the aldehyde products 9 and 10 are chiral, there was no enantioselectivity observed in these reactions.
23 www.amtec-chemnitz.de