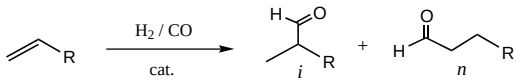
1998, *120*, 6661 – 6672; M. T. Didiuk, J. P. Morken, A. H. Hoveyda, *Tetrahedron*, **1998**, *54*, 1117 – 1130, and references therein.

[15] From seminal work by Bringmann[1d] it is appreciated that structural changes with such tetrahydroisoquinolines can alter the observed CD spectra, thereby leading to erroneous assignments. In the case of derivatives **16**, it is apparent that alterations at the C-3 methyl group do not impact, let alone overshadow, the significant bias imposed in each by the axially chiral, nonracemic, biaryl nuclei.

Isomerization of Aldehydes Catalyzed by Rhodium(I) Olefin Complexes**

Christian P. Lenges and Maurice Brookhart*

One of the earliest reported and most thoroughly investigated processes catalyzed by transition metals is the hydroformylation of olefins [Eq. (1)].[1–8] The oxidative addition of

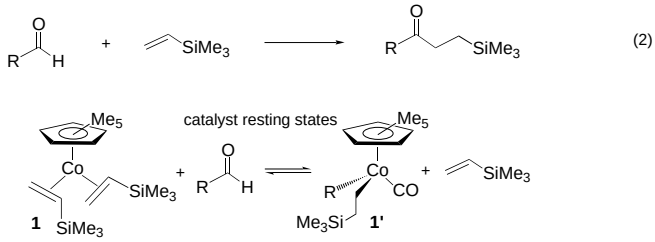


(1)

H_2 to a transition metal center is combined with reversible olefin and CO insertion processes to yield an acyl hydride complex. The final step in this catalytic process is generally accepted as the irreversible reductive elimination of the acyl hydride to generate the aldehyde products.[9–11] In most applications the linear product is desired, although branched products are becoming increasingly important as indicated by recent efforts directed at the asymmetric hydroformylation of olefins.[7b, c] An ongoing effort in this area of research is dedicated to altering the linear:branched isomer ratio by varying the ligand and catalyst structure.

We have recently reported that $[C_5Me_5Co(olefin)_2]$ complexes can be used to carry out intermolecular hydroacylation reactions of bulky olefins such as vinyltrimethylsilane. The resting state of the catalyst was established as a mixture of the Co^I bis-olefin complex and the Co^{III} dialkyl carbonyl complex whose ratio is dependent on the substrate structures and concentrations [Eq. (2)].[12, 13]

When *n*-butyraldehyde was used as the substrate traces of isobutyraldehyde were evident near complete conversion of aldehyde, which indicated some reversibility prior to the reductive elimination of ketone.[12] Reductive elimination



with the second row rhodium analogues should exhibit higher energy barriers than the cobalt complexes; thus rhodium analogues may exhibit more extensive reversibility and have the potential to isomerize aldehydes prior to ketone formation.[14, 15] Indeed, we report here that rhodium(I) olefin complexes of the type $[C_5Me_5Rh(C_2H_3R)_2]$ catalyze the interconversion of linear and branched aldehydes as well as transfer formylation reactions.[16]

Reduction of $[(C_5Me_5RhCl_2)_2]$ with zinc in the presence of propene results in the formation of $[C_5Me_5Rh(C_2H_3Me)_2]$ (**2**), which was isolated as an analytically pure yellow solid.[17, 18] Characterization of **2** by NMR spectroscopy indicates a mixture of isomers. Recrystallization from acetone generates the single isomer **2a**, which was characterized by X-ray crystallographic analysis (Figure 1). When complex **2a** is dissolved in $[D_6]$acetone a mixture of isomers **2a**, **2b**, and **2c**[19] is generated in minutes. These correspond to isomers generated by rotation around the Rh–olefin bond. Eventually a fourth isomer **2d** is observed, which is generated by olefin dissociation and rebinding (Scheme 1).

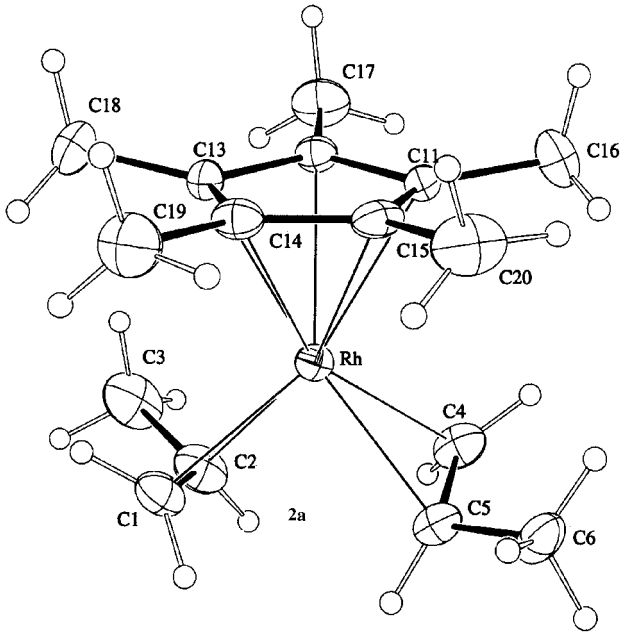


Figure 1. ORTEP diagram of complex **2a**; ellipsoids are drawn with 50% probability. Selected bond distances [Å] and angles [°]: Rh–C1 2.129(4), Rh–C2 2.129(5), Rh–C4 2.133(5), Rh–C5 2.134(4), C1–C2 1.404(6), C2–C3 1.493(7), C4–C5 1.416(6), C5–C6 1.517; C1-Rh-C2 38.51(18); C1-Rh-C4 108.61(19); C1-Rh-C5 87.38(18); C2-Rh-C4 85.15(20); C2-Rh-C5 87.00(20); C4-Rh-C5 38.77(16); C1-C2-C3 124.5(5); C4-C5-C6 120.4(4); C5-Rh-C1-C2 88.5(5); C4-Rh-C2-C1 128.4(6); C1-Rh-C4-C5 60.2(4); C2-Rh-C5-C4 86.0(5); C1-Rh-C2-C3 119.7(6); C2-Rh-C4-C5 91.2(5); C4-Rh-C5-C6 115.0(5); Rh-C1-C2-C3 110.1(7).

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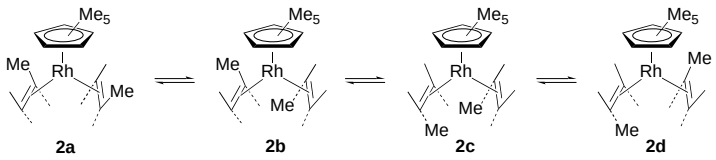
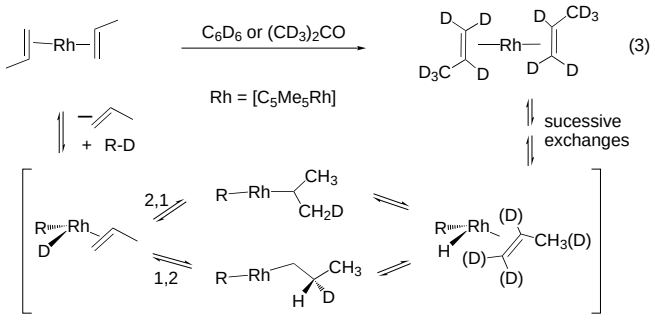


Scheme 1. Isomers of **2**.

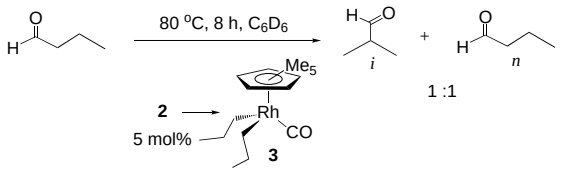
Propene readily dissociates from **2** to generate a 16-electron species of the type $[C_5Me_5Rh(C_2H_3Me)]$. Thermolysis of **2** in $[D_6]$benzene or $[D_6]$acetone results in H/D exchange reactions of the solvent with the coordinated olefin. After C–H(D) bond activation of the solvent, reversible 1,2- and 2,1-olefin insertions can take place to exchange the deuterium label into the methine, methylene, and methyl groups. All ^{1}H NMR resonances for coordinated propene have vanished in the spectrum after 5 h at 55 °C, with only singlets remaining in the C_5Me_5-resonance region for the isomers of **2** [Eq. (3)].



(3)

The reaction of **2** with aliphatic aldehydes was next investigated. The *n*- and *iso*-butanals were initially examined since the largest volume hydroformylation process involves these aldehydes. The reaction of **2** with ten equivalents of *n*-butanal in $[D_6]$benzene at 50 °C results in the disappearance of the series of C_5Me_5 resonances of **2** over 30 minutes to generate a single new rhodium species **3** with a C_5Me_5 resonance at $\delta = 1.74$ in the NMR spectrum. In addition, one equivalent of free propene is observed in the reaction mixture. Removal of all volatile material at this stage leaves a yellow oil corresponding to **3** which is pure by ^{1}H NMR spectroscopy and exhibits a series of multiplets in the alkyl region ($\delta = 1.21 - 1.48$) that integrates to 8 protons and a triplet at $\delta = 0.89$ (t, ^3J (H, H) = 8 Hz, 6H; CH_3) indicating the presence of two equivalent CH_3 groups. Analysis by ^{13}C NMR spectroscopy shows, in addition to methine and methyl signals for the C_5Me_5 moiety, three resonances in the alkyl region at $\delta = 24.2$ (d, J (Rh,C) = 25.8 Hz), 19.7 (d, J (Rh,C) = 2.6 Hz), and 29.4(s) and one resonance at $\delta = 196.0$ (d, J (Rh,C) = 83.2 Hz), which is characteristic of a CO group coordinated to a rhodium center. Correspondingly, IR analysis of the reaction mixture shows a strong Rh–CO band at $\tilde{\nu}_{CO} = 1979\ cm^{-1}$. Complex **3** is formulated as $[C_5Me_5Rh(CO)(CH_2CH_2CH_3)_2]$, which is the result of propene dissociation from **2** followed by oxidative addition of *n*-butanal, propene insertion into the Rh^{III} hydride, and CO deinsertion.[20] Decomposition of **3** occurs over 24 h in an inert atmosphere or in solution to generate carbonylated rhodium complexes, of which the major product is the blue dimer $[\{C_5Me_5Rh(CO)\}_2]$ (**4**) as indicated by IR analysis ($\tilde{\nu}_{CO} = 1732\ cm^{-1}$).[21, 22]

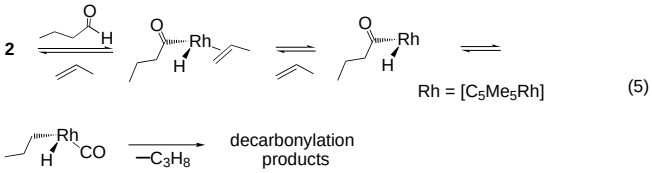
A reaction of **2** (0.01 g, 3.1×10^{-5} mol) with 20 equivalents *n*-butanal at 80 °C in $[D_6]$benzene was followed by NMR spectroscopy. Complex **3** was generated in a fast, initial reaction from **2**. After 8 h, *n*-butanal was isomerized to generate a 1:1 mixture of *n*-butanal and *iso*-butanal. The only rhodium species present in solution throughout this process is **3** [Eq. (4)] in addition to small amounts of free propene. This



(4)

reaction can be performed in a variety of solvents, such as acetone, toluene, or cyclohexane with similar results. The introduction of additional *n*-butanal to a reaction mixture generated in this fashion allows further isomerization, which indicates some active catalyst was still present. Higher reaction temperatures (exceeding 100 °C) favor the competing decarbonylation reaction and result in an initial fast isomerization followed by catalyst deactivation.

A reduced catalyst load (0.5 %) still results in initial isomerization; however, catalyst deactivation to generate carbonylated rhodium complexes (mainly **4**) is observed to be competitive with aldehyde isomerization. The hydroacylation of propene under the reaction conditions does not generate significant amounts of 4-heptanone.[23] Longer catalyst lifetimes were achieved by conducting the thermolysis in the presence of added propene (48 h at 100 °C, 3 mol % **2**, *n*-butanal, 50 equiv propene generates a 3:2 mixture of *n*:*iso*-butanals). Olefin loss from a Rh^{III} acyl hydride olefin complex generated from **2** after oxidative addition of aldehyde is thought to be a major deactivation route[12] since alkane loss from a Rh^{III} alkyl hydride carbonyl species is most likely irreversible under the reaction conditions. This pathway is minimized in the presence of excess olefin [Eq. (5)]. The formation of hexane by reductive elimination from **3** was not observed in the deactivation process.[12, 23]



(5)

The isomerization of *iso*-butanal to *n*-butanal is also observed using **2** as a catalyst precursor (5 mol % **2**, 80 °C, 24 h, 2:3 *n*:*iso*-butanals). Complex **3** is the only spectroscopically observed (^{1}H NMR) intermediate during this isomerization process. The possible resting state analogue $[C_5Me_5Rh(CO)(n\text{Pr})(i\text{Pr})]$ (**3′**) was not observed; IR analysis of a reaction mixture generated from the reaction of *iso*-butanal with **2** showed $\tilde{\nu}_{CO} = 1980\ cm^{-1}$, which is identical to **3**. These results indicate that aldehyde isomerization is observed starting from both isomeric aldehydes, but the thermody-

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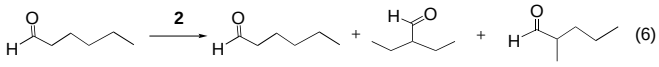
namic equilibrium for the isomeric aldehydes may not be reached in all cases because of catalyst decomposition.[24]

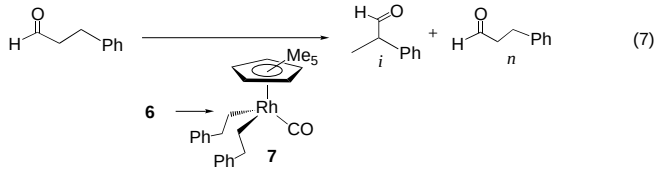
n-Hexanal was investigated as substrate by using complex **2** as a catalyst precursor. Complex **2** (0.01 g, 3.1×10^{-5} mol, 5 mol%) was heated to 80 °C in the presence of *n*-hexanal (20 equiv) and five equivalents of 1-pentene in benzene. Analysis of the reaction mixture by ^{1}H NMR spectroscopy indicated the formation of pentene isomers and the three isomeric hexanals (9.27, t; 9.33, d; 9.51, d).[25] Pentene isomerization is fast (30 min, 80 °C), while aldehyde isomerization occurs over 5 h. These results show that, as for butanals, aldehyde activation has occurred and is followed by insertion and deinsertion processes which distribute the formyl group throughout the pentyl chain [Eq. (6)].



(6)

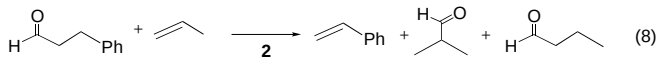
To increase the catalyst activity and to possibly extend catalysis to lower temperatures, a more electron-deficient rhodium olefin complex was investigated. The isomerization of *n*-butanal to a 1:1 mixture of *n* and *iso*-butanals with $[(C_5Me_4CF_3)Rh(C_2H_3SiMe_3)_2]$ (**5**, 0.011 g, 2.3×10^{-5} mol, 5 mol%)[26] was observed at 55 °C over 5 h. Small amounts of an additional aldehyde, assigned as $Me_3SiCH_2CH_2C(O)H$, are also observed during this process. A resting state species analogous to **3** is proposed for this system. This is suggested by the characteristic IR band at 2000 cm^{-1} that is indicative of a significant reduction in electron density at the rhodium center, which perhaps facilitates the conversion of the Rh^{III} resting state to Rh^{I} intermediates.[27]

The application of this isomerization process to substituted aldehydes was also investigated. The isomerization of 2-phenylpropanal was attempted using the bis-styrene complex $[C_5Me_5Rh(C_2H_3Ph)_2]$ (**6**) as the catalyst precursor. The rate of olefin dissociation from **6** is reduced relative to **2**. Heating a solution of **6** in [D$_6$]benzene for 24 h at 80 °C results in complete deuteration of the olefinic sites [see Eq. (3)]. Complete ring deuteration of coordinated styrene is observed after thermolysis for one week. Heating a solution of **6** (0.01 g, 2.2×10^{-5} mol, 5 mol%) in benzene to 120 °C with 2-phenylpropanal (20 equiv) generates a mixture of the two isomeric aldehydes in a 2:1 ratio (*n*:*iso*) after 12 h. The formation of an intermediate (**7**) analogous to **3** during aldehyde isomerization was observed and is assigned as the catalyst resting state ($\delta = 1.68$, C_5Me_5; $\tilde{\nu}_{CO} = 1983$ cm^{-1}) [Eq. (7)].[28]

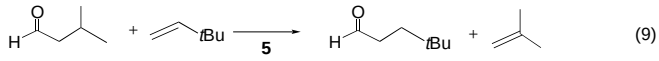


(7)

Formyl groups can be transferred between two different olefins using these rhodium catalysts. For example, thermolysis (110 °C, 24 h, [D$_8$]toluene) of 2-phenylpropanal (6×10^{-4} mol) with catalyst **2** (0.01 g, 3.1×10^{-5} mol, 5 mol%) in the presence of excess propene results in transfer formylation and exclusive generation of isomeric butanals and free styrene [Eq. (8)]. IR analysis of the working catalyst



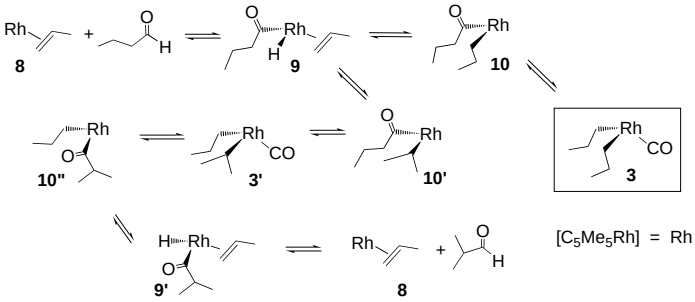
(8)



(9)

system shows a band at 1980 cm^{-1} in the spectrum and suggests a Rh^{III} dialkyl carbonyl resting state; however, the nature of the alkyl groups could not be identified by ^{1}H NMR spectroscopy because of low catalyst loading and the presence of multiple organic species at high concentrations. Analogously, transfer formylation from isovaleraldehyde to 3,3-dimethyl-1-butene (50 equiv) using complex **5** as catalyst generates the corresponding linear aldehyde exclusively together with 2-methylpropene (2 mol% **5**, 60 °C, 24 h, 85% conversion), [Eq. (9)].

Based on the information described herein and on prior studies detailing the reactivity of these types of rhodium complexes,[29] a mechanism is proposed for this catalytic aldehyde isomerization process (Scheme 2). Olefin dissociation from **2** generates a reactive 16-electron species **8** which



Scheme 2. Proposed mechanism for the catalytic isomerization of aldehydes.

oxidatively adds *n*-butanal to form an intermediate rhodium(III) acyl hydride olefin complex **9**. Olefin insertion can occur with either regiochemistry to generate an acyl alkyl rhodium(III) species, either **10** or **10′**. CO-deinsertion from **10** generates the observed resting state **3**. The branched intermediate (**3′**) generated from **10′** was not observed but must be formed to account for the aldehyde isomerization. Deinsertion of **3′** to generate **10″** followed by β-elimination gives **9′**, which forms *iso*-butyraldehyde on reductive elimination. This scheme, coupled with olefin exchange, also accounts for the observed transfer formylation reactions.

In summary, the reaction of alkyl aldehydes with $[C_5Me_5Rh(olefin)_2]$ complexes results in a catalytic isomerization process that generates a mixture of isomeric aldehydes. These initial results introduce a catalytic process that offers an indirect method for influencing the *n*:*iso* ratio of aldehydes formed in hydroformylation reactions. This procedure is a conceptually different approach for the preparation of a desired linear or branched aldehyde since olefin hydroformylation can be separated from an aldehyde isomerization

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process that avoids hydroformylation conditions. Catalyst deactivation pathways that result in decarbonylation products have been identified. In the presence of other olefins, transfer formylation was observed, which provides in principle a general method for the introduction of a formyl group into an olefinic substrate.

Experimental Section

All operations were carried out under an Ar atmosphere. All solvents used were degassed and purified following standard methods.

2: $[(C_5Me_5RhCl_2)_2]$ (0.2 g, 6.5×10^{-4} mol) was stirred with zinc (0.45 g, 6.5×10^{-3} mol) in THF (15 mL) for 24 h while a slow flow of propene was passed over the reaction mixture. The residual zinc was filtered from the homogeneous yellow mixture, which was evaporated, and extracted into pentane. Removal of the solvent generated a yellow solid. Recrystallization from acetone yielded complex **2a** as yellow crystalline material (one isomer) which was used for the structure determination (Figure 1). ^{1}H NMR (400 MHz, [D$_6$]acetone, 20 °C): $\delta = 1.51$, 1.56, 1.62 ($3\times$ s, $3\times$ 15 H, $3\times C_5Me_5$), 0.95, 1.41, 1.45, 1.59 ($4\times$ d, 4×3 H, Me), olefinic CH overlapping, the 4th C_5Me_5 resonance is obscured; ^{13}C{^{1}H} (100 MHz, [D$_6$]acetone, 20 °C): **2a**: $\delta = 9.40$, 97.0 (d, 3.8 Hz, C_5Me_5), 60.0, 45.7 (d, 5.6 Hz), 21.1 (Me); **2c**: 10.1, 97.5 (d, 3.8 Hz), 52.6, 47.8 (d, 14 Hz), 21.3 (Me); **2b** and **2d**: 9.3, 96.9 (d, C_5Me_5 and 8.7, 96.5 (d, C_5Me_5), 56.0, 54.5, 54.1, 52.2, 50.1, 47.4, 46.6, 44.6 (d), 21.8, 21.4, 19.5, 17.1 (Me). Elemental analysis: calcd: C 59.63, H 8.44; found: C 59.90, H 8.62.

Structural data for **2a**: crystals obtained from acetone; $C_{16}H_{27}Rh$, $M_r = 322.29$, monoclinic, space group $P2_1/n$, $Z = 4$, $a = 14.2482(7)$, $b = 7.1385(4)$, $c = 15.7584(8)$ Å, $\beta = 108.8420(10)°$, $V = 1516.91(14)$ Å^3, $\rho_{calcd} = 1.411$ g cm^{-1}, $T = -110$ °C, $2\theta_{max} = 50°$, $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å), 7807 reflections were measured; 2672 unique reflections were obtained, and 2100 of these with $I > 3.0\sigma(I)$ were used in the refinement, data were collected on a Siemens SMART diffractometer using the omega scan method. For significant reflections merging $R = 0.035$, residuals: $R_F = 0.044$, $R_w = 0.047$ (significant reflections), GOF: 2.54. – Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-136183. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

3: A solution of $[C_5Me_5Rh(C_2H_3Me)_2]$ (0.1 g, 3.1×10^{-4} mol) in benzene (10 mL) was treated with 10 equiv of *n*-butanal (0.22 g) and heated for one hour at 50 °C. All volatiles were removed and complex **3** was isolated as a yellow oil. Complex **3** decomposes as the oil or in solution over several hours at 20 °C; attempts to crystallize **3** from acetone were not successful. ^{1}H NMR (400 MHz, [D$_6$]acetone, 20 °C): $\delta = 1.74$ (s, 15 H, C_5Me_5), 0.89 (t, 7.8 Hz, 6 H, CH_3), 1.21 (m, 4 H, CH_2), 1.48 (m, 4 H, CH_2); ^{13}C{^{1}H} NMR (100 Mhz, [D$_6$]acetone, 20 °C): $\delta = 9.0$ ($C_5\mathit{Me}_5$), 101.9 (C_5Me_5), 24.2 (d, 25.8 Hz, $RhCH_2$), 19.7 (d, 2.6 Hz, CH_2), 29.4 (s, CH_3), 196.0 (d, 83.2 Hz, RhCO); IR (toluene): $\tilde{\nu}_{CO} = 1979$ cm^{-1}.

6: Complex **6** was prepared in an analogous manner to complex **2** and isolated as an orange solid after recrystallization from acetone. NMR analysis shows the formation of one major isomer (70 %) and two minor isomers based on olefin coordination as discussed for **2**. ^{1}H NMR (400 MHz, [D$_6$]benzene, 20 °C): $\delta = 1.43$ (s, 15 H, C_5Me_5), 2.10 (dd, 16.0, 2 Hz, 2 H), 2.55 (dd, 16.0, 2 Hz, 2 H), 3.83 (ddd, 16.0, 10, 2 Hz, 2 H), 6.38 (m, 2 H, Ar), 6.89 – 7.05 (m, 2 H, Ar), 7.02 – 7.23 (m, 6 H, Ar).

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[17] Complex **2** has been prepared previously by Müller and co-workers in a reaction of $[(C_5Me_5RhCl_2)_2]$ with *i*PrMgBr. J. Müller, H.-O. Stühler, W. Goll, *Chem. Ber.* **1975**, *108*, 1074.
[18] The analogous $[C_5H_5Rh]$ complex has been reported: L. P. Seiwell, *Inorg. Chem.* **1976**, *15*, 2560.
[19] The formation of isomers was also observed in analogous rhodium methylacrylate complexes. E. Hauptman, S. Sabo-Etienne, P. S. White, M. Brookhart, J. M. Garner, P. J. Fagan, J. C. Calabrese, *J. Am. Chem. Soc.* **1994**, *116*, 8038.
[20] Maitlis and co-workers have prepared similar complexes in a reaction of $[C_5Me_5Rh(dmso)Me_2]$ with aldehydes. The complex $[C_5Me_5Rh(CO)MeEt]$ ($\tilde{\nu}_{CO} = 1990$ cm^{-1}) was generated in a reaction with propionaldehyde, but was too unstable for isolation. P. M. Maitlis, G. J. Sunley, J. M. Kisenyi, M. Gomez, *J. Organomet. Chem.* **1985**, *296*, 197.
[21] Thermolysis of **3** in [D$_6$]benzene at 50 °C yields **4** (≈85 %) and other unassigned organometallic complexes in addition to *n*-butanal, propene, and propane.
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[23] a) Catalytic hydroacylation of aromatic aldehydes is observed using complexes of type **2** at 100 °C with 5 turnovers per hour; alkyl aldehydes are not converted under these conditions: C. P. Lenges, M. Brookhart, unpublished results; b) the presence of acid impurities in the reaction mixture can terminate catalysis and is more significant in reactions with reduced catalyst loading.
[24] a) Based on the heats of formation of *n*- and *iso*-butyraldehydes and calculated entropies of formation, the thermodynamic ratio of these aldehydes should be about 1:1. See K. B. Wiberg, L. S. Crocker, K. M. Morgan, *J. Am. Chem. Soc.* **1991**, *113*, 3447; b) during catalytic hydroacylation reactions using cobalt analogues only the formation of the Co-*n*-alkyl intermediates was observed in the reaction of the isomeric butanals, which is in line with the results observed here for **3** versus **3′**. The formation of the branched alkyl intermediate was suggested by labeling studies and the formation of isomeric product mixtures but not directly observed; see reference [12].
[25] In addition, propene, and the isomeric butanals are observed in the reaction mixture.
[26] The chloro-bridged complex $[(C_5Me_4CF_3)RhCl_2]_2$ was prepared as the precursor following the literature procedure. P. G. Gassman, J. W. Mickelson, J. R. Sowa, Jr., *J. Am. Chem. Soc.* **1992**, *114*, 6942. Using

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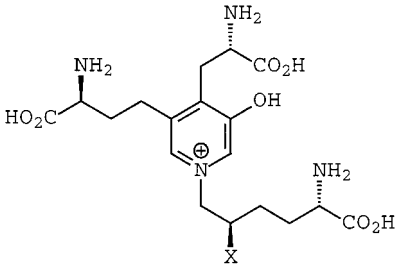
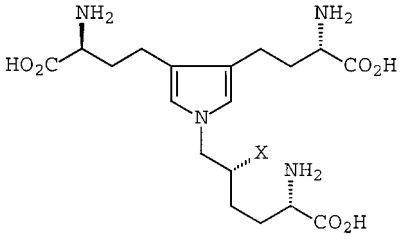
this dimer, complex **5** was prepared in a zinc reduction using an analogous procedure as described for **2**. Experimental details will be reported in a separate manuscript.
[27] A more electron-deficient rhodium center might also accelerate insertion reactions at Rh^{III} intermediates, which would result in increased activity.
[28] The formation of an intermediate with the same characteristics as **7** was also observed in a reaction of 1-phenylpropanal with **6**. At this point an alternative structure for **7** can not be excluded (for example, the branched isomer as in **3′**).
[29] C. P. Lenges, P. S. White, M. Brookhart, *J. Am. Chem. Soc.* **1999**, *121*, 4385.



(+)-**1**: X=OH, pyridinoline
(+)-**3**: X=H, deoxypyridinoline



2: X=OH, pyrrololine
(+)-**4**: X=H, deoxypyrrololine

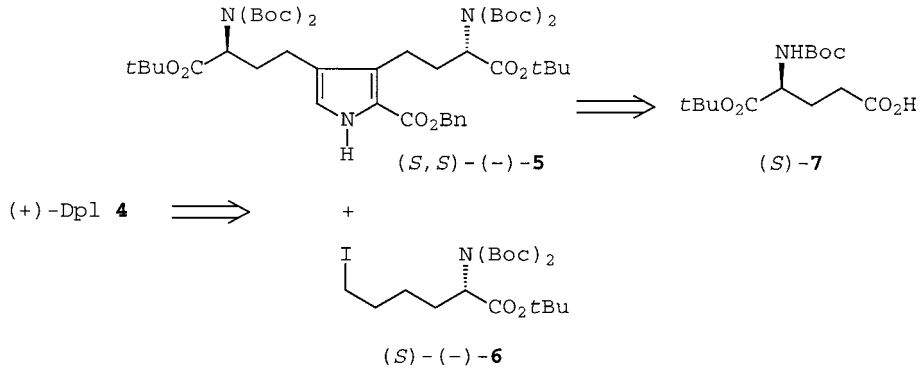
Total Synthesis of (+)-Deoxypyrrololine: A Potential Biochemical Marker for Diagnosis of Osteoporosis

Maciej Adamczyk,* Donald D. Johnson, and Rajarathnam E. Reddy

Osteoporosis is a crippling degenerative bone disease that affects the aged population, particularly postmenopausal women.[1] This metabolic disease is a consequence of an inbalance in the bone renewal process, which occurs when bone resorption exceeds bone formation. The current methods for diagnosis of osteoporosis involve analysis of bone based on histomorphometry and densitometric measurements.[2] The efforts for prevention of this bone disease, as well as to develop an effective antiresorptive therapy, have increased the search for reliable and noninvasive biochemical markers of bone resorption.[1c, 3] The traditional markers of bone resorption, for example urinary calcium[4] and hydroxyproline,[5] lack clinical sensitivity and specificity for diagnosis of osteoporosis.

In recent years, the pyridinium cross-links (+)-pyridinoline (Pyd, **1**)[6] and (+)-deoxypyridinoline (Dpd, **3**)[7] have gained much attention owing to their potential clinical utility in the diagnosis of osteoporosis and other bone diseases.[8–10] In 1981 Scott et al.[11] postulated the existence of pyrrole cross-links pyrrololine (Pyl, **2**) and deoxypyrrololine (Dpl, **4**)[12] in various tissues. Subsequent studies by several other groups have provided further convincing evidence for the existence of pyrrole cross-links.[13, 14] Unfortunately, the attempts to isolate cross-links **2** and **4** have not been successful so far.[3a,d] It was proposed that **2** and **4** are formed from natural (2*S*,5*R*)-hydroxylysine and (*S*)-lysine present in collagen by a lysyl oxidase mediated enzymatic process, in an analogous fashion to the pyridinium cross-links **1** and **3**.[3d, 13c,d,f] Here we report the first synthesis of the pyrrole cross-link (+)-deoxypyrrololine (Dpl, **4**) from (4*S*)-5-(*tert*-butoxy)-4-[(*tert*-butoxycarbonyl)amino]-5-oxo-pentanoic acid (**7**).

The synthesis of **4** involves alkylation of the pyrrole derivative (*S*,*S*)-(−)-**5** with iodide (*S*)-(−)-**6**, followed by hydrolysis of the protecting groups and removal of the 2-carboxybenzyl ester moiety (Scheme 1). It was envisioned that the key intermediate (*S*,*S*)-(−)-**5** could be prepared from the α-acetoxynitro compound **13** (see Scheme 2) and benzyl isocyanoacetate (**14**)[15, 16] by a base-promoted condensation and cyclization process. Compound **13** could be obtained from **7**.



Scheme 1. Retrosynthesis of (+)-deoxypyrrololine (Dpl, **4**). Bn = benzyl, Boc = *tert*-butyloxycarbonyl.

Accordingly, the commercially available (*S*)-**7** was converted into the aldehyde (*S*)-(−)-**8**,[17] which was then reduced

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