Crucial Role of β-Elimination in Determining Regio- and Chemoselectivity of the Rhodium-Catalyzed Hydroformylation of *N*-Allylpyrroles: A New Approach to 5,6-Dihydroindolizines

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Abstract: Rhodium-catalyzed hydroformylation of the chiral (*S*)-3-alkyl-3-pyrrol-1-ylprop-1-enes at 100 atmospheres total pressure and 25 °C led to the preferential formation of the branched 3-alkyl-2-methyl-3-pyrrol-1-ylpropanals. At 30 atmospheres and 125 °C, the linear 4-alkyl-4-pyrrol-1-ylbutanals were obtained: these aldehydes are not the final products, but evolve into more stable 5,6-dihydroindolizines, with the same optical purity as the starting olefins, via a domino cyclization–dehydration process. According to the generally accepted mechanism for rhodium-catalyzed hydroformylation, the regioselectivity, and then the final chemoselectivity, can be rationalized by taking into account that while at room temperature no β-elimination occurs, at high temperature the β-elimination involves the branched rhodium–alkyl intermediate only.

Key words: β-elimination, hydroformylations, rhodium–alkyl complexes, N-allylated pyrroles, indolizines

According to the generally accepted mechanism for the rhodium-catalyzed hydroformylation of olefins,[1] metal hydride addition to the double bond to give an isomeric metal–alkyl intermediates is a key step. This step can be reversible or nonreversible, depending on the substrate nature and the reaction conditions. Under mild conditions, i.e. at room temperature, the insertion is a nonreversible step; this is very important, because the regioselectivity for the formation of the branched **b** and the linear **l** rhodium–alkyl intermediates determines the regioselectivity for the formation of the final aldehydes **B** and **L**, respectively (Scheme 1). In contrast, if the alkyl formation is reversible, the selectivity-determining step will occur later, i.e. at the stage of the addition of carbon monoxide to the tricarbonyl species to give the tetracarbonyl species, as demonstrated by theoretical calculations in the case of hydroformylation of 1,1-diphenylethene at 100 °C.[2]

Both electronic and steric effects determine the regioselectivity of the formation of rhodium–alkyl complexes (Figure 1). Indeed, the hydroformylation under mild conditions of vinylaromatic substrates such as styrene,[3] vinylfurans,[4] vinylthiophenes,[5] vinylpyrroles,[6] and vinylpyridines[7] always provides a large predominance of the branched isomer over the linear one (**B/L** = 95:5 for styrene). As far as oxygen-containing substrates are concerned, vinyl ethers provide a regioisomeric ratio **B/L** of ≥ 80:20.[8] Under the same conditions, alkenes with α-hydrogens (i.e., linear alk-1-enes) give the two regioisomers in an almost 1:1 molar ratio.[9] An oxygen in the β-position to the vinyl group favors the formation of the branched isomers, as observed for allyl ethyl ether (**B/L** = 70:30) and similar substrates.[8] The linear isomers largely predominate over the branched ones in the hydroformylation of 3-alkyl-substituted alk-1-enes (e.g., 3-methylbut-1-ene).[10]

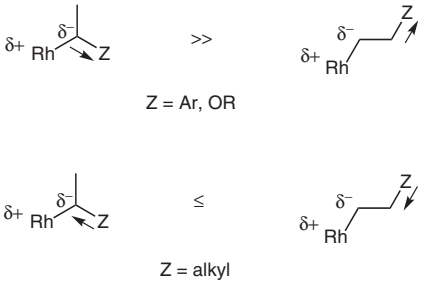
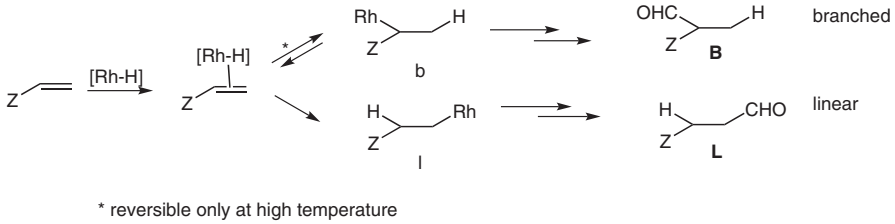


Figure 1

At higher reaction temperature (>90 °C) and reduced carbon monoxide and hydrogen partial pressure, the amount of linear aldehyde generally increases. Under these condi-



Scheme 1

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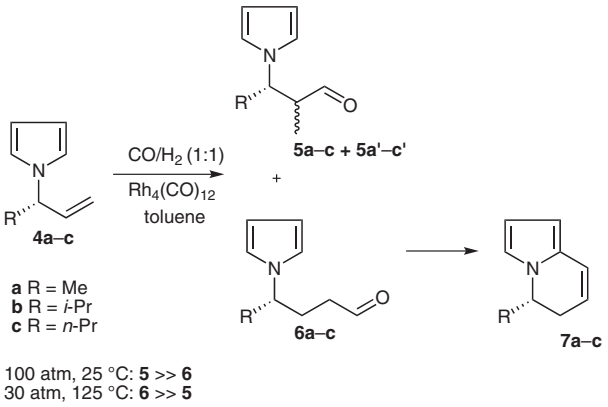
tions, the step resulting in the formation of the isomeric alkyl–rhodium intermediates becomes reversible via a β-elimination process involving mainly the branched species. Thus the whole process brings about a partial isomerization of the branched alkyl isomer into the linear one and hence determines an increase in the linear aldehyde content (Scheme 1). In the case of styrene, for instance, a strong increase in the linear aldehydic isomer (**B/L** = 98:2 at 20 °C to 64:36 at 130 °C) is observed.[11] For ethyl vinyl ether the above increase is lower, with the percentage of linear aldehyde ranging from 12% at 29 °C to 24% to 100 °C.[8] In the case of vinylidenic alkenes, the linear aldehyde isomer is obtained with complete selectivity at any temperature (80–130 °C).[12]

Direct experimental evidence for the formation of alkyl–rhodium intermediates is unavailable, because these species are present in a very low concentration in the reaction mixtures and very reactive under typical hydroformylation conditions. In the last decades deuterioformylation experiments were shown to be the best possible experimental probe to investigate the nature and fate of the intermediates involved in the reaction.[13] ^{2}H NMR investigations of crude deuterioformylation mixtures allowed the reversibility or nonreversibility of the alkyl–metal intermediate formation to be established via identification of the position of the incorporated deuterium atoms into unconverted substrates. In this way, the behavior of vinyl and allyl ethers,[8] vinyl- and vinylidenic olefins,[14] as well as styrene[15] and pyridines[7a] under rhodium-catalyzed hydroformylation conditions has been rationalized by our research group. In the last years, theoretical investigations have also contributed significantly to the clarification of the aforementioned aspects.[16–21] In particular, the regioselectivities and diastereoselectivities of a variety of unsaturated substrates in nonreversible rhodium-catalyzed hydroformylation have been elucidated by computational methods by examination of the stability of the relevant alkyl–rhodium transition states (TS).[19a] The theoretical results turned out to be in good agreement with the experimental results obtained under mild reaction conditions, i.e. the regioselectivities and diastereoselectivities determined for the final aldehyde products.

Within the framework of our investigations on rhodium-catalyzed hydroformylation of aromatic and heteroaromatic olefins, *N*-allylpyrroles proved to be special substrates. When the reaction was carried out on the chiral (*S*)-3-alkyl-3-pyrrol-1-ylprop-1-enes **4a–c** under high pressure and at low temperature, the branched aldehydes **5** formed preferentially (Scheme 2).[22]

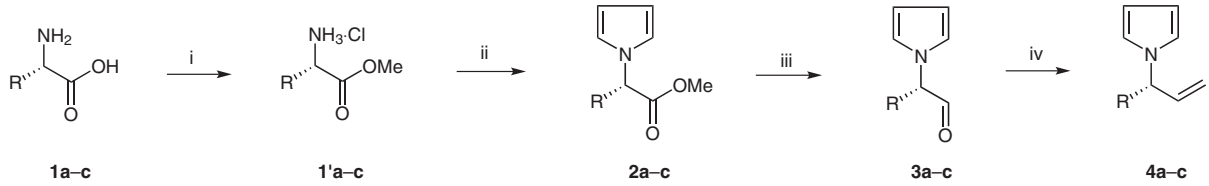
In contrast, at low pressure and high temperature an almost completely linear regioselectivity was observed (Scheme 2). Interestingly, the substituted pyrrolylbutanals **6** produced are not the final products, but evolve into the more stable 5,6-dihydroindolizines **7** via a domino cyclization/dehydration process.[23] These results can be rationalized by taking into account that while at room temperature no β-elimination occurs, at high temperature the β-elimination involves the branched alkyl intermediate only. In particular, the dihydroindolizines **7a–c** have the same optical purity as the starting material, thus indicating that the β-elimination process occurs without involving the methinic hydrogen α to the nitrogen atom.



Scheme 2

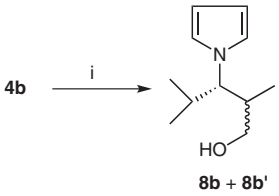
1-Allylpyrroles **4a–c** were prepared in 92% ee by a highly stereospecific multistep reaction sequence (Scheme 3) that uses L-α-amino acids as the source of chirality.[24] L-α-Amino acid methyl ester hydrochlorides **1a′–c′** were chosen to introduce both the stereogenic center and the useful ester functionality. L-Alanine and L-valine methyl ester hydrochlorides (**1a′** and **1b′**) were commercially available. L-Norvaline methyl ester hydrochloride (**1c′**) was prepared from the corresponding L-amino acid **1c** by treatment with gaseous hydrogen chloride in methanol (98% yield). Condensation of **1a′–c′** with 2,5-dimethoxytetrahydrofuran, according to a well-known procedure,[24] gave the corresponding 1*H*-pyrrole derivatives **2a–c** in good yield (70–92%) and excellent enantiomeric excess (99%). Esters **2a–c** were chemoselectively transformed into aldehydes **3a–c** by treatment with one molar diisobutylaluminum hydride in hexane (1.8 equiv) at –78 °C; the excess of the reducing agent was destroyed with methanol, and the resulting solution was hydrolyzed with Rochelle salt, at the same temperature. Under the adopted experimental conditions the substrate conversion was complete and neither overreduction to the respective alcohols nor significant racemization of the produced aldehydes was observed. The thus produced (2*S*)-2-pyrrol-1-ylpropanal (**3a**), (2*S*)-3-methyl-2-pyrrol-1-ylbutanal (**3b**), and (2*S*)-2-pyrrol-1-ylpentanal (**3c**) were obtained in high yield (>78%) and with almost complete retention of chiral integrity (>92% ee). The Wittig reaction was carried out with the Schlosser–Schaub instant ylide reagent at –30 °C in tetrahydrofuran. The olefins (3*S*)-3-pyrrol-1-ylbut-1-ene (**4a**), (3*S*)-4-methyl-3-pyrrol-1-ylpent-1-ene (**4b**), and (3*S*)-3-pyrrol-1-ylhex-1-ene (**4c**) were obtained in good yield (65–75%) and high ee (>92–98%). Under the experimental conditions described here, enolization of the aldehydes did not occur and the corresponding olefins were obtained with retention of optical integrity.

The hydroformylation reaction was carried out in toluene, in the presence of dodecacarbonyltetrarhodium as the cat-



Scheme 3 *Reagents and conditions*: (i) R = *n*-Pr: HCl(g), MeOH, reflux, 60 min, 98%; (ii) 2,5-dimethoxytetrahydrofuran, AcOH, NaOAc, 80 °C, 30–120 min; (iii) 1 M DIBAL-H in hexane (1.8 equiv), –78 °C, 15–40 min; (iv) Ph_3PMeBr, $NaNH_2$, THF, –30 °C, 30 min.

alyst precursor, at 25 °C and under a total pressure of 100 atmospheres (CO/H_2 = 1:1).[22] The crude reaction mixtures were analyzed by GLC and GLC-MS by using *n*-decane as internal standard. In all cases (**4a–c**) the reaction afforded 2-methyl-3-pyrrol-1-ylalkanals **5** (diastereomeric mixture) as main products (see Scheme 2). Compound **4a** gave 2-methyl-3-pyrrol-1-ylbutanals **5a** and **5a′** in a 77:23 regioisomeric ratio. A similar amount of the branched aldehyde **5c** and **5c′** was obtained by the hydroformylation of **4c**. When a branched alkyl group was linked to the carbon atom α to the double bond (in the case of **4b**), the regioisomeric ratio **5b**/**5b′** slightly decreased to 71:29 (Scheme 2). Traces of the alcohols coming from the branched aldehydes were also observed at complete substrate conversion. In particular, alcohols **8b** and **8b′** were obtained as almost exclusive products from **4b** under hydroformylation conditions at 80 °C, over long reaction times (24 h) (Scheme 4).



Scheme 4 *Reagents and conditions*: (i) $Rh_4(CO)_{12}$, CO/H_2 (1:1), 80 °C, toluene, 24 h; then alumina (hexane–EtOAc, 95:5).

When the reaction was carried out at high temperature and low pressure, an inversion of regioselectivity was observed.[23] In the case of **4a**, the conversion was 25% after 0.2 hours and the reaction mixture contained 5-methyl-5,6-dihydroindolizine (**7a**) and branched aldehydes **5a** and **5a′** in a 57:43 [**7a**/(**5a** + **5a′**)] molar ratio (Scheme 2). This value remained unchanged at total conversion (after 1.5 h, 59:41 regioisomeric ratio). The linear aldehyde **6a**, the precursor of **7a**, was present only in trace amounts in the reaction mixture both at partial and complete substrate conversion, the cyclization reaction being faster than hydroformylation. Under the same hydroformylation conditions **4b** gave 5-isopropyl-5,6-dihydroindolizine (**7b**); the regiosiomeric ratio **7b**/(**5b** + **5b′**) was 87:13. In a similar manner, 5-*n*-propyl-5,6-dihydroindolizine (**7c**) was obtained from **4c** [**7c**/(**5c** + **5c′**) = 84:16]. No traces of the linear aldehydes **6b** and **6c**, the precursors to **7b** and **7c**, were observed in the reaction mixture, both at partial and complete substrate conversion. Only by the use of a lower rhodium/substrate ratio (1:1000), at 10% conversion, a small amount of aldehyde **6a** could be detected in the reaction mixture, the indolizine formation still being a fast process compared to the oxo one.

Interestingly, **4a** showed, at all conversions, practically the same ee, that is, the starting ee value (98%). The same applied for dihydroindolizine **7a**, its ee value remaining the same as the corresponding olefin **4a** (98%) at all reaction times (Table 1).

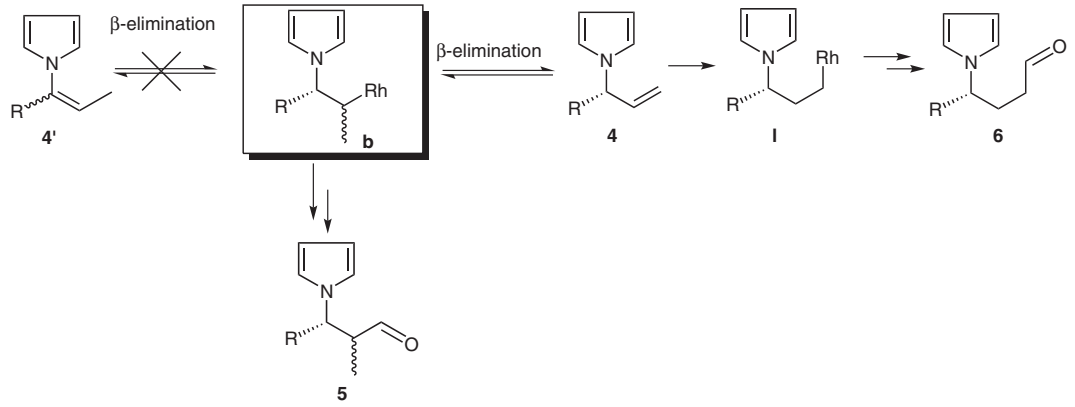
The regioselectivity values obtained at room temperature are very similar to the values obtained for styrene and derivatives.[11] The high α-regioselectivity of the reaction must be related to the regioselectivity of formation of the rhodium–alkyl intermediates (Scheme 1): the polarizable pyrrole ring directly bonded to the partially negative carbon atom favors the branched isomer **b** over the linear alkyl **l** (Figure 1), thus explaining the predominance of the branched aldehyde. The π-excessive nature of the pyrrole ring could account for the lower α-regioselectivity.

In contrast, at high temperature and low pressure, an interconversion of the alkyl intermediates takes place via a β-hydride elimination, generating the starting olefin again and hence promoting a successive increase of the linear aldehyde. Taking into account the generally accepted mechanism of hydroformylation,[25] we can affirm that, under the above conditions, the branched alkyl–rhodium intermediate **b** undergoes a β-hydride elimination process

Table 1 Hydroformylation of (3*S*)-3-Pyrrol-1-ylalk-1-enes **4a–c** in the Presence of Dodecacarbonyltetrarhodium[a]

4	R	ee[b] (%) of **4**	Conversion (%)	Ratio **7**/**5** (%)	Yield[c] (%) of **7**	ee[b] (%) of **7**
4a	Me	98	97	85:15	73	98
4b	*i*-Pr	92	99	87:13	70	92
4c	*n*-Pr	92	99	84:16	75	92

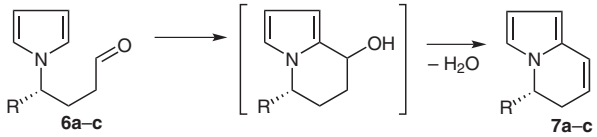
[a] Reaction conditions: **4**, $Rh_4(CO)_{12}$, toluene, <CO/H_2 (1:1), 125 °C, 30 atm, 0.5 h.
[b] Determined by GC [chiral capillary column CHIRALDEX G-TA (γ-cyclodextrin trifluoroacetyl, 50 m × 0.25 mm)].
[c] Yield of isolated pure product.



Scheme 5

not involving the stereogenic center, generating the olefin **4** again and not **4′** (Scheme 5). In fact, no traces of the internal olefin **4′** were observed in the crude reaction mixture at both partial or total conversion. Due to the influence of the electron-withdrawing heteroaromatic effect, the methinic hydrogen bonded to the carbon vicinal to the annular nitrogen in **b** probably does not have sufficient hydride character for β-hydride elimination (Scheme 5). This behavior of *N*-allylpyrroles is unusual compared to that of other aromatic or aliphatic allylolefins.[9b,26]

The six-membered nature of the newly formed ring, together with the observation that the sum of the linear aldehyde and the indolizine product gives a constant value with respect to the branched aldehyde suggest that the indolizine structure comes from the pyrrolylbutanal, possibly via an intramolecular nucleophilic attack of the pyrrole C2 carbon atom on the carbonyl group of the linear aldehyde. Then a bicyclic alcohol should form; it then undergoes water elimination very easily to give a double bond conjugated with the pyrrole ring (Scheme 6).



Scheme 6

The very high ee values obtained for **7** indicate that the hydroformylation conditions are perfectly compatible with the optically active pyrrolylolefins employed, allowing a complete configurational stability also under potentially isomerizing conditions (high temperature and low pressure).

In the light of these findings, it is clear that β-elimination plays a crucial role in the rhodium-catalyzed hydroformylation of *N*-allylpyrroles. Indeed, different products, dihydroindolizines and/or pyrrolylpropanals, were obtained when the temperature and pressure values of the reaction were changed. As the pyrrole ring is known to be a useful protecting group for primary amines,[27] the process at room temperature and high pressure can be considered to be a new access to optically active amino aldehydes, building blocks in biosynthesis and total synthesis of different alkaloids.[28] When the oxo process is applied at high temperature and low pressure, racemization is avoided and the regioselectivity is enhanced; this leads to a regioselective and stereospecific synthetic approach to optically active 5-alkyl-5,6-dihydroindolizine derivatives.[29] The unusual behavior of the *N*-allylpyrroles depicted here shows that the nature of the substrate is a crucial parameter for determining the selectivity of the rhodium-catalyzed hydroformylation reaction.

Reactions requiring an inert atmosphere were conducted under anhyd N_2, and the glassware was oven-dried (120 °C). Anhyd solvents were purified prior to use as follows: toluene was dried over molecular sieves and distilled under N_2 and THF was distilled from Na under N_2. All reagents were purchased in the highest quality available and were used without further purification. Schlosser–Schaub 'instant ylide' reagent (methyltriphenylphosphonium bromide + sodium amide) was purchased from Fluka. $Rh_4(CO)_{12}$ was from Strem Products. TLC analyses were performed on aluminum oxide 60 F_{254} neutral or silica gel 60 F_{254} plates from Merck. For preparative chromatography, Merck aluminum oxide 90 active neutral (70–230 mesh) or silica gel 60 (70–230 mesh) was used. Optical rotations were measured with a JASCO DIP-370 digital polarimeter at the given temperature. Microanalyses were performed at the Laboratorio di Microanalisi, Istituto di Chimica Organica, Facoltà di Farmacia, Università di Pisa. ^{1}H NMR spectra were recorded at 200 MHz, ^{13}C NMR spectra at 50 MHz on a Varian Gemini 200 spectrometer. Chemical shifts are given in δ (ppm) relative to $CDCl_3$. GC/MS analyses were performed on a Perkin-Elmer Q-Mass 910, equipped with an EI source, interfaced with a Perkin-Elmer 8500 chromatograph equipped with a 30 m × 0.25 mm apolar DB1 capillary column, using helium as a carrier.

(–)-(*S*)-Methyl 2-Pyrrol-1-ylpentanoate (2c); Typical Procedure

2,5-Dimethoxytetrahydrofuran (5.5 mL, 43 mmol) was added to a suspension of methyl (–)-(*S*)-2-aminopentanoate hydrochloride (**1c′**; 7.16 g, 43 mmol), AcOH (290 mL), and NaOAc (36.0 g), heated to 80 °C. After 30 min the reaction mixture was cooled to r.t. and hydrolyzed with 40% aq NaOH (40 mL). The two phases were separated, the aqueous layers were extracted with CH_2Cl_2 (3 × 150 mL), and the combined organic layers were washed with H_2O until the aqueous phase was neutralized. The organic layers were dried (Na_2SO_4), concentrated in vacuo, and purified by vacuum distillation (bp 80 °C/0.1 mmHg); this afforded **2c** as a colorless liquid.

Yield: 5.0 g (27.6 mmol, 65%, 99% ee); $[\alpha]_D^{26}$ –4.02 (*c* 2.3, MeOH); chiral GC (120 °C × 60 min): t_R (*R*) = 21.91 min, t_R (*S*) = 25.94 min.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.74 (t, *J* = 2.2 Hz, 2 H), 6.17 (t, *J* = 2.2 Hz, 2 H), 4.57 (dd, *J* = 6.4; 9.1 Hz, 1 H), 3.71 (s, 3 H), 2.04 (m, 2 H), 1.25 (m, 2 H), 0.92 (t, *J* = 9.0 Hz, 3 H).

MS: *m*/*z* (%) = 181 [M$^+$] (58), 139 (32), 122 (100), 107 (40), 94 (10), 80 (75), 68 (13).

(–)-(*S*)-2-Pyrrol-1-ylpentanal (3c); Typical Procedure

A 1 M soln of DIBAL-H (36 mL, 36 mmol) in hexane was added to a soln of **2c** (3.0 g, 17.0 mmol) in THF–hexane (1:7) cooled at –78 °C and stirring was continued at that temperature for 20 min. The reaction mixture was then quenched with MeOH (5 mL) at –78 °C and sat. aq mixed sodium–potassium tartrate (60 mL) was added, still at –78 °C. After warming to r.t., the two phases were separated, the aqueous phase was extracted with Et_2O (3 × 100 mL), and the combined organic layers were washed with H_2O (4 × 150 mL). The organic layers were dried (Na_2SO_4), concentrated in vacuo, and purified by vacuum distillation (bp 65 °C/0.02 mmHg); this gave **3c** as a colorless liquid.

Yield: 2.21 g (15.0 mmol, 88%, 95% ee); $[\alpha]_D^{26}$ –44.4 (*c* 1.05, benzene); chiral GC (100 °C × 60 min): t_R (*S*) = 30.10 min, t_R (*R*) = 35.80 min.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 9.63 (d, *J* = 1.0 Hz, 1 H), 6.67 (t, *J* = 2.1 Hz, 2 H), 6.26 (t, *J* = 2.1 Hz, 2 H), 4.42 (dd, *J* = 4.8, 9.5 Hz, 1 H), 1.96 (m, 2 H), 1.28 (m, 2 H), 0.95 (t, *J* = 7.0 Hz, 3 H).

MS: *m*/*z* (%) = 151 [M$^+$] (36), 122 (78), 84 (20), 80 (100), 68 (20).

(–)-(*S*)-2-Pyrrol-1-ylpropanal (3a)[24]

According to the procedure described above, (–)-(*S*)-methyl 2-pyrrol-1-ylpropanoate (**2a**; 4.9 g, 32.0 mmol) reacted with a 1 M hexane soln of DIBAL-H (64 mL, 64 mmol), affording **3a** as a colorless liquid.

Yield: 2.79 g (22.7 mmol, 80%, 98% ee); bp 78–81 °C/5 mmHg; $[\alpha]_D^{26}$ –70.8 (*c* 0.99, benzene).

(+)-(*S*)-3-Methyl-2-pyrrol-1-ylbutanal (3b)

According to the procedure described above, (–)-(*S*)-methyl 3-methyl-2-pyrrol-1-ylbutanoate (**2b**; 2.5 g, 14.0 mmol) reacted with a 1 M hexane soln of DIBAL-H (34 mL, 34 mmol), affording **3b** as a colorless liquid.

Yield: 1.62 g (11 mmol, 78%, 92% ee); bp 60 °C/0.01 mmHg; $[\alpha]_D^{26}$ +59.4 (*c* 1.1, benzene); chiral GC (120 °C × 60 min): t_R (*S*) = 12.24 min, t_R (*R*) = 13.51 min.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 9.75 (d, *J* = 1.8 Hz, 1 H), 6.70 (t, *J* = 2.2 Hz, 2 H), 6.27 (t, *J* = 2.2 Hz, 2 H), 4.13 (dd, *J* = 2.2, 8.8 Hz, 1 H), 2.46 (m, 1 H), 1.08 (d, *J* = 7.0 Hz, 3 H), 0.86 (d, *J* = 6.8 Hz, 3 H).

MS: *m*/*z* (%) = 151 [M$^+$] (49), 122 (100), 108 (32), 94 (18), 80 (70), 68 (32), 55 (50).

(+)-(*S*)-3-Pyrrol-1-ylhex-1-ene (4c); Typical Procedure

Schlosser–Schaub reagent (2 g, 4.8 mmol) in anhyd THF (14 mL) was stirred at r.t. for 1 h. A soln of **3c** (0.39 g, 2.6 mmol) in anhyd THF (6 mL) was added to the yellow suspension cooled at –30 °C. After 30 min the temperature was increased to r.t. and the mixture was hydrolyzed with 40% aq NaOH (12 mL). The aqueous phase was extracted with hexane (3 × 30 mL) and the combined organic layers were washed until neutrality. After drying (Na_2SO_4), the hexane soln was concentrated in vacuo, affording, after vacuum distillation, **4c** as a colorless liquid.

Yield: 0.21 g (1.6 mmol, 63%, 92% ee); bp 50 °C/0.02 mm Hg; $[\alpha]_D^{26}$ +58.5 (*c* 1.1, MeOH); chiral GC (100 °C × 60 min): t_R (*S*) = 16.09 min, t_R (*R*) = 16.55 min.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.69 (t, *J* = 2.1 Hz, 2 H), 6.16 (t, *J* = 2.1 Hz, 2 H), 5.97 (m, 1 H), 5.09 (m, 2 H), 4.43 (m, 1 H), 1.82 (m, 2 H), 1.26 (m, 2 H), 0.92 (t, *J* = 7.4 Hz, 3 H).

MS: *m*/*z* (%) = 149 [M$^+$] (60), 120 (8), 106 (100), 81 (24), 67 (52), 55 (20).

(+)-(*S*)-3-Pyrrol-1-ylbut-1-ene (4a)[24]

According to the procedure described above, the aldehyde **3a** (2.2 g, 18.0 mmol) reacted with the Schlosser–Schaub reagent (14 g, 28.8 mmol), affording **4a** as a colorless liquid.

Yield: 1.8 g (15 mmol, 85%, 98% ee); bp 70–74 °C/20 mmHg; $[\alpha]_D^{26}$ +62.5 (*c* 0.52, MeOH); chiral GC (80 °C × 60 min): t_R (*R*) = 14.97 min, t_R (*S*) = 16.35 min.

(+)-(*S*)-4-Methyl-3-pyrrol-1-ylpent-1-ene (4b)

According to the procedure described above, the aldehyde **3b** (0.4 g, 2.6 mmol) reacted with the Schlosser–Schaub reagent (2.0 g, 4.8 mmol), affording **4b** as a colorless liquid.

Yield: 0.2 g (1.3 mmol, 51%, 92% ee); bp 80 °C/0.05 mmHg; $[\alpha]_D^{26}$ +88.9 (*c* 1.5, MeOH); chiral GC (80 °C × 60 min): t_R (*R*) = 47.19 min, t_R (*S*) = 48.20 min.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.67 (t, *J* = 2.2 Hz, 2 H), 6.15 (t, *J* = 2.2 Hz, 2 H), 6.04 (m, 1 H), 5.16 (m, 2 H), 3.99 (t, *J* = 8.2 Hz, 1 H), 2.08 (m, 1 H), 0.97 (d, *J* = 6.6 Hz, 3 H), 0.78 (d, *J* = 6.6 Hz, 3 H).

MS: *m*/*z* (%) = 149 [M$^+$] (37), 106 (100), 79 (27), 67 (21), 55 (10).

Hydroformylation of 1-Allylpyrroles 4; Typical Procedure

A soln of the olefinic substrate **4** (5–6 mL) in toluene (5 mL) and $Rh_4(CO)_{12}$ (substrate/Rh = 100:1) was introduced by suction into an evacuated 25-mL stainless-steel autoclave. The autoclave was filled with CO up to the required pressure and heated to the required temperature. After 15 min, H_2 was introduced, giving the required final pressure (CO/H_2, 1:1). The autoclave was then rocked until complete conversion (GC monitoring) and allowed to cool to r.t. The residual reaction gases were evacuated and the crude reaction mixture was directly removed from the open autoclave for further manipulation.

(+)-(*S*)-5-Methyl-5,6-dihydroindolizine (7a)

From the reaction mixture obtained by the hydroformylation carried out at 30 atm total pressure and 125 °C, **7a** was obtained as an orange oil after column chromatography (silica gel, CH_2Cl_2–hexane, 1:7).

Yield: 0.33 g (2.5 mmol, 73%, 92% ee); $[\alpha]_D^{26}$ +107.5 (CH_2Cl_2, *c* = 1.18); chiral GC (in. temp: 100 °C; in. hold: 60 min): t_R (*R*) = 26.8 min, t_R (*S*) = 35.0 min.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.70 (m, 1 H, H3), 6.42 (d, *J* = 9.8 Hz, 1 H, H8), 6.14 (m, 1 H, H2), 6.03 (m, 1 H, H1), 5.65 (m, 1 H, H7), 4.10 (m, 1 H, H5), 2.53 (m, 1 H, H6), 2.20 (m, 1 H, H6′), 1.43 (d, *J* = 6.5 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.2, 32.2, 49.6, 106.2, 108.0, 117.9, 118.4, 120.1, 128.5.

MS: *m*/*z* (%) = 133 [M$^+$] (63), 132 (19), 118 (100), 117(44), 91 (23).

(+)-(*S*)-5-Isopropyl-5,6-dihydroindolizine (7b)

From the hydroformylation reaction mixture, **7b** was obtained as an orange oil after column chromatography (silica gel, CH_2Cl_2–hexane, 1:7).

Yield: 0.30 g (1.9 mmol, 70%, 92% ee); $[\alpha]_D^{26}$ +60.8 (*c* 1.08, CH_2Cl_2).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.66 (t, *J* = 2.2 Hz, 1 H), 6.41 (dd, *J* = 2.3, 9.6 Hz, 1 H), 6.12 (dd, *J* = 2.8, 3.4 Hz, 1 H), 6.03 (dd, *J* = 1.5, 3.7 Hz, 1 H), 5.64 (m, 1 H), 3.84 (m, 1 H), 2.65 (m, 1 H), 2.44 (m, 1 H), 2.22 (m, 1 H), 0.99 (d, *J* = 6.6 Hz, 3 H), 0.86 (d, *J* = 7.0 Hz, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.51, 19.4, 25.8, 31.4, 60.0, 105.5, 106.8, 117.9, 119.8, 121.0, 128.9.

MS: *m*/*z* (%) = 161 [M$^+$] (80), 146 (3), 132 (2), 118 (100), 91 (22), 63 (5), 39 (10).

(+)-(*S*)-5-Propyl-5,6-dihydroindolizine (7c)

From the hydroformylation reaction mixture, **7c** was obtained as an orange oil after column chromatography (silica gel, CH_2Cl_2–hexane, 1:7).

Yield: 0.405 g (2.5 mmol, 75%, 92% ee); $[\alpha]_D^{26}$ +43.5 (CH_2Cl_2, *c* = 0.86); chiral GC (in. temp: 120 °C; in. hold: 60 min): t_R (*R*) = 25.32 min, t_R (*S*) = 37.74 min.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.68 (t, *J* = 1.8 Hz, 1 H), 6.42 (d, *J* = 9.8 Hz, 1 H), 6.13 (t, *J* = 3.1 Hz, 1 H), 6.03 (br s, 1 H), 5.63 (m, 1 H), 4.04 (q, *J* = 6.5 Hz, 1 H), 2.68 (m, 1 H), 2.28 (m, 1 H), 1.85–1.25 (m, 4 H), 0.95 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.6, 18.9, 28.9, 36.2, 53.8, 105.6, 107.1, 117.2, 119.3, 119.6, 127.9.

MS: *m*/*z* (%) = 161 [M$^+$] (40), 132 (6), 118 (100), 91 (8).

Compounds 5a and 5a′

Compounds **5a** and **5a′** were characterized after being obtained from the **5a** + **5a′** + **7a** mixtures resulting from hydroformylation reaction carried out at 100 atm total pressure and 25 °C, after removing the solvent at reduced pressure and separation from the catalyst by pentane extraction.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.95 (d, *J* = 7.4 Hz, 3 H, $CH_{3\text{-}\mathbf{5a}}$), 1.17 (d, *J* = 7.4 Hz, 3 H, $CH_{3\text{-}\mathbf{5a'}}$), 1.55 (d, *J* = 7 Hz, 3 H, $CH_{3\text{-}\mathbf{5a'}}$), 1.57 (d, *J* = 6.6 Hz, 3 H, $CH_{3\text{-}\mathbf{5a}}$), 2.85 (m, 2 H, $CH^*_{\mathbf{5a+5a'}}$), 4.20 (m, 1 H, $CH^*_{\mathbf{5a'}}$), 4.40 (m, 1 H, $CH^*_{\mathbf{5a}}$), 6.20 (t, *J* = 2.2 Hz, 2 H, $pyr_{\mathbf{5a+5a'}}$), 6.66 (t, *J* = 1.8 Hz, 2 H, $pyr_{\mathbf{5a+5a'}}$), 6.72 (t, *J* = 2.2 Hz, 2 H, $pyr_{\mathbf{5a+5a'}}$), 6.75 (t, *J* = 1.8 Hz, 2 H, $pyr_{\mathbf{5a+5a'}}$), 9.49 (d, *J* = 1.8 Hz, 1 H, $CHO_{\mathbf{5a'}}$), 9.71 (d, *J* = 1.8 Hz, 1 H, $CHO_{\mathbf{5a}}$).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 10.8 (CH_3), 18.5 (CH_3), 20.1 (CH_3), 47.6 (CH*), 52.8 (CH*), 53.8 (CH*), 55.1 (CH*), 107.5–108.7 (pyr), 119.2 (pyr), 135.5 (CHO).

MS: *m*/*z* (**5a**) (%) = 151 [M$^+$] (3), 133 (63), 123 (100), 108 (16), 94 (72), 78 (22), 68 (68), 50 (18), 39 (33).

MS: *m*/*z* (**5a′**) (%) = 151 [M$^+$] (6), 123 (100), 108 (13), 94 (68), 78 (18), 68 (87), 41 (30).

Compounds 5c and 5c′

Compounds **5c** and **5c′** were characterized after being obtained from the **5c** + **5c′** + **7c** mixtures resulting from hydroformylation under analogous reaction conditions.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 7.5 Hz, 3 H, $CH_{3\text{-}\mathbf{5c}}$), 0.89 (t, *J* = 7.5 Hz, 3 H, $CH_{3\text{-}\mathbf{5c'}}$), 0.90 (d, *J* = 7.2 Hz, 3 H, $CH_{3\text{-}\mathbf{5c}}$), 1.15 (d, *J* = 6.9 Hz, 3 H, $CH_{3\text{-}\mathbf{5c'}}$), 1.19 (m, 4 H, $CH_{2\text{-}\mathbf{5c+5c'}}$), 1.75 (m, 4 H, $CH_{2\text{-}\mathbf{5c+5'c}}$), 2.72 (split q, *J* = 7.2, 2.4 Hz, 1 H, $CH^*_{\mathbf{5c'}}$), 2.73 (split q, *J* = 7.2, 2.1 Hz, 1 H, $CH^*_{\mathbf{5c}}$), 4.09 (split t, *J* = 6.3, 4.2 Hz, 1 H, $CH^*_{\mathbf{5c'}}$), 4.11 (split t, *J* = 10.5, 4.2 Hz, 1 H, $CH^*_{\mathbf{5c}}$), 6.15 (t, *J* = 2.1 Hz, 4 H, $pyr_{\mathbf{5c+5c'}}$), 6.63 (t, *J* = 1.8 Hz, 2 H, $pyr_{\mathbf{5c}}$), 6.66 (t, *J* = 1.8 Hz, 2 H, $pyr_{\mathbf{5c'}}$), 9.43 (d, *J* = 2.1 Hz, 1 H, $CHO_{\mathbf{5c'}}$), 9.68 (d, *J* = 2.1 Hz, 1 H, $CHO_{\mathbf{5c}}$).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 11.0 (CH_3), 13.7 (CH_3), 13.8 (CH_3), 19.5 (CH_2), 19.6 (CH_2), 35.0 (CH_2), 36.6 (CH_2), 52.0 (CH*), 52.9 (CH*), 59.9 (CH*), 108.3 (pyr), 108.6 (pyr), 119.6 (pyr) 119.7 (pyr), 140.7 (CHO).

MS: *m*/*z* (**5c**) (%) = 179 [M$^+$] (9), 151 (37), 122 (32), 108 (26), 95 (12), 80 (27), 68 (100), 55 (18), 41 (15), 29(5).

MS: *m*/*z* (**5c′**) (%) = 179 [M$^+$] (8), 151 (38), 122 (41), 108 (33), 95(15), 80 (36), 68 (100), 55 (20), 41 (18), 29(7).

Compounds 5b and 5b′

Compounds **5b** and **5b′** were characterized after being obtained from the **5b** + **5b′** + **7b** mixtures resulting from hydroformylation under analogous reaction conditions.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.87 (d, *J* = 6.4 Hz, 6 H, $CH_{3\text{-}\mathbf{5b+5b'}}$), 0.99 (d, *J* = 6.6 Hz, 3 H, $CH_{3\text{-}\mathbf{5b'}}$), 1.00 (d, *J* = 6.6 Hz, 3 H, $CH_{3\text{-}\mathbf{5b}}$), 1.06 (d, *J* = 7.2 Hz, 3 H, $CH_{3\text{-}\mathbf{5b'}}$), 1.15 (d, *J* = 7.0 Hz, 3 H, $CH_{3\text{-}\mathbf{5b}}$), 2.14 (sept, *J* = 6.6 Hz, 1 H, $CH_{iPr\text{-}\mathbf{5b'}}$), 2.28 (sept, *J* = 7.0 Hz, 1 H, $CH_{iPr\text{-}\mathbf{5b}}$), 2.95 (split q, *J* = 7.2, 2.2 Hz, 2 H, $CH^*_{\mathbf{5b+5b'}}$), 3.81 (dd, *J* = 7.8, 7.2 Hz, 1 H, $CH^*_{\mathbf{5b}}$), 4.06 (dd, *J* = 7.6, 7.4 Hz, 1 H, $CH^*_{\mathbf{5b'}}$), 6.16 (t, *J* = 2.2 Hz, 2 H, $pyr\text{-}_{\mathbf{5b'}}$), 6.17 (t, *J* = 2.2 Hz, 2 H, $pyr_{\mathbf{5b}}$), 6.63 (t, *J* = 2.2 Hz, 2 H, $pyr_{\mathbf{5b'}}$), 6.64 (t, *J* = 2.2 Hz, 2 H, $pyr_{\mathbf{5b}}$), 9.58 (d, *J* = 2.2 Hz, 1 H, $CHO_{\mathbf{5b}}$), 9.65 (d, *J* = 1.8 Hz, 1 H, $CHO_{\mathbf{5b'}}$).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 10.2 (CH_3), 12.1 (CH_3), 18.3 (CH_3), 20.4 (CH_3), 30.3 (CH), 31.3 (CH), 48.3 (CH*), 49.2 (CH*), 65.7 (CH*), 67.6 (CH*), 107.9 (pyr), 108.1 (pyr), 120.7 (pyr), 203.2 (CHO).

MS: *m*/*z* (**5b**) (%) = 179 [M$^+$] (10), 151 (40), 122 (13), 108 (67), 95 (27), 80 (18), 68 (100), 55 (13), 41 (19), 29 (5).

MS: *m*/*z* (**5b′**) (%) = 179 [M$^+$] (10), 151 (43), 122 (25), 108 (94), 95 (31), 80 (24), 68 (100), 55 (17), 41 (24), 29 (6).

Compounds 8b and 8b′

Colorless liquid mixture (column chromatography, alumina, hexane–EtOAc, 95:5); yield: 30%.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.85 (d, *J* = 6.4 Hz, 6 H, $CH_{3\text{-}\mathbf{8b+8b'}}$), 0.98 (d, *J* = 6.6 Hz, 3 H, $CH_{3\text{-}\mathbf{8b'}}$), 1.02 (d, *J* = 6.6 Hz, 3 H, $CH_{3\text{-}\mathbf{8b}}$), 1.06 (d, *J* = 7.2 Hz, 3 H, $CH_{3\text{-}\mathbf{8b'}}$), 1.08 (d, *J* = 7.0 Hz, 3 H, $CH_{3\text{-}\mathbf{8b}}$), 2.11 (sept, *J* = 6.6 Hz, 1 H, $CH_{iPr\text{-}\mathbf{8b'}}$), 2.22 (m, 2 H, $CH^*_{\mathbf{8b+8b'}}$) 2.28 (sept, *J* = 7.0 Hz, 1 H, $CH_{iPr\text{-}\mathbf{8b}}$),, 3.70 (dd, *J* = 7.8, 7.2 Hz, 1 H, $CH^*_{\mathbf{8b}}$), 3.98 (d, *J* = 7.0 Hz, 2 H, $CH_{2\text{-}\mathbf{8b+8b'}}$), 4.03 (dd, *J* = 7.6, 7.4 Hz, 1 H, $CH^*_{\mathbf{8b'}}$), 6.16 (t, *J* = 2.2 Hz, 2 H, $pyr\text{-}_{\mathbf{8b'}}$), 6.17 (t, *J* = 2.2 Hz, 2 H, $pyr_{\mathbf{8b}}$), 6.63 (t, *J* = 2.2 Hz, 2 H, $pyr_{\mathbf{8b'}}$), 6.64 (t, *J* = 2.2 Hz, 2 H, $pyr_{\mathbf{8b}}$).

MS: *m*/*z* (**8b**) (%) = 181 [M$^+$] (7), 179 (59), 161 (33), 146 (19), 136 (100), 118 (95), 94 (20), 41 (14).

MS: *m*/*z* (**8b′**) (%) = 181 [M$^+$] (7), 179 (57), 161 (33), 146 (16), 136 (90), 118 (100), 94 (24), 41 (16).

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