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Synthesis of New Water-Soluble Atropisomeric Ligands Derived from the MeOBIPHEP Skeleton: Applications for Asymmetric C–H Bond Formation and Mechanistic Studies

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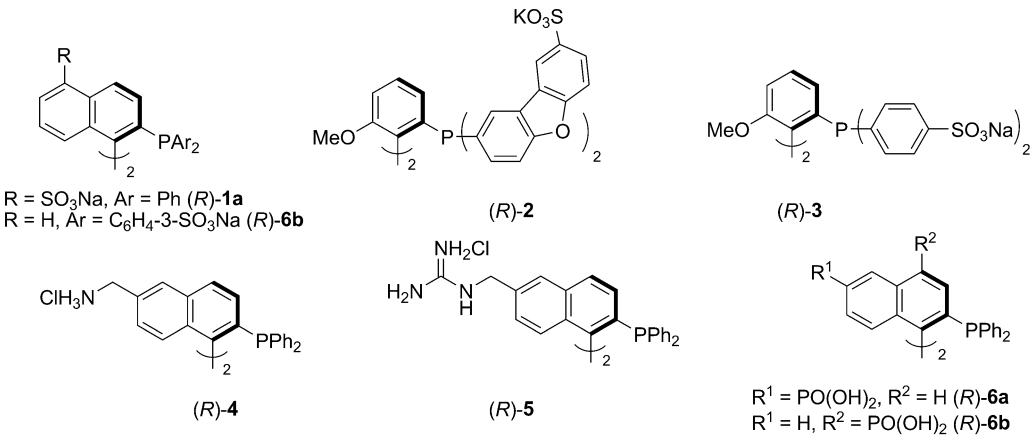
Abstract: We have extended the methodology developed for the preparation of atropisomeric chiral ligands derived from the MeOBIPHEP ligand to water-soluble ones. The hydrophilic ligands bearing sodium carboxylate and methylammonium chloride moieties were easily synthesized under mild conditions in a short sequence and in high yields. Their solubility and acid/base properties were also determined. The ruthenium(II) catalysts containing 4-CO_2Na- and 3,5-$(CO_2Na)_2$-substituted MeOBIPHEP analogues showed excellent activities and led to the desired hydrogenated products derived from dimethyl itaconate and 2-(4-fluorophenyl)-3-methylcrotonic acid in *ee*s $\geq$ 92%. An investigation of the asymmetric hydrogenation of the latter substrate in D_2O as solvent afforded an insight into the mechanism.

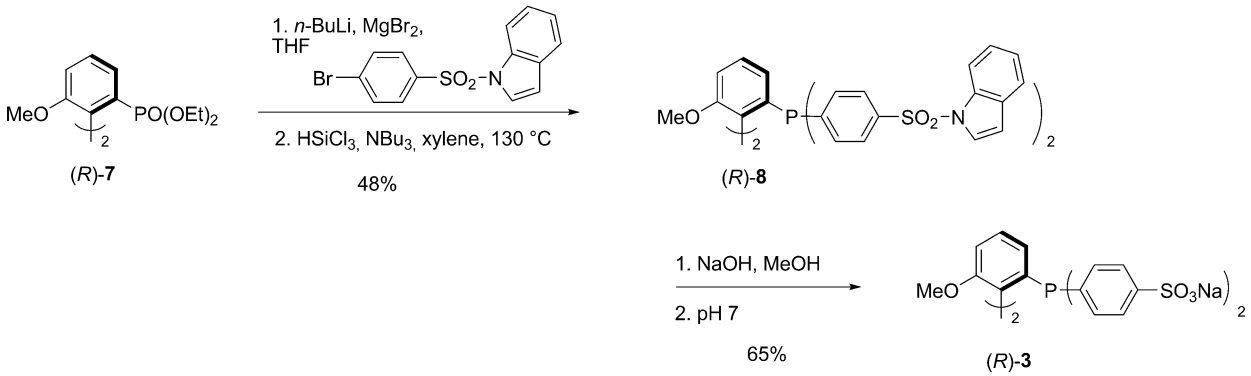
Keywords: asymmetric catalysis; atropisomeric ligands; bis-phosphanes; phosphorus; rhodium; ruthenium; water-soluble ligands

Transition metal-catalyzed reactions and specifically asymmetric homogeneous catalysis have given a considerable impetus to the progress in the areas of organometallic, organic and industrial chemistry.[1] Among them, carbon-hydrogen and carbon-carbon bond formation reactions using water-soluble organometallic catalysts are fundamentally important as they bear the potential to provide solutions to both environmental and economic concerns, for example, by facilitating the product/catalyst separation.[2] The last fifteen years therefore have witnessed tremendous growth in the synthesis of water-soluble ligands.[3] Whereas a flurry of achiral water-soluble ligands has been prepared by original strategies, the synthesis of chiral hydrophilic ligands has been more limited, which can be explained by the difficult and long sequences needed for their preparation.[4] Atropisomeric ligands bearing sulfonated water-soluble moieties are quite common due to the fact that their syntheses relied generally on the regioselective sulfonation of the "parent" ligand (Scheme 1). BINAP and MeOBIPHEP derivatives **1a**, **1b**[5] and **2**[6] have been prepared *via* sulfonation in the presence of an SO_3/H_2SO_4 mixture. Alternatively, Roche scientists have described in 1992 a sulfonated ligand **3**[7,8] according to a conceptually different 5-step strategy (52% isolated yield) and have studied various hydrogenation reactions under aqueous conditions[8] (Scheme 2). Moreover, starting from binaphthol, atropisomeric cationic ligands **4** and **5** have been described, respectively by Genêt's and Lemaire's groups.[9] Neutral phosphonic acid-substituted water-soluble ligands **6a** and **6b** were also prepared according to a similar strategy.[10,11] We recently described a novel synthesis of chiral atropisomeric ligands based on the MeOBIPHEP skeleton starting from chiral bisphosphonate **7**.[12] We envisioned that this methodology would offer a unique opportunity to easily prepare water-soluble ligands and more precisely to synthesize analogues of **3**. We wish therefore to describe our results concerning the synthesis of novel water-soluble ligands and our preliminary results in asymmetric C–H bond formation reactions.

Initially, we anticipated that alkoxycarbonyl-substituted ligands might be good precursors for anionic water-soluble MeOBIPHEP analogues. We recently described a Pd-catalyzed reaction of various alkoxy-



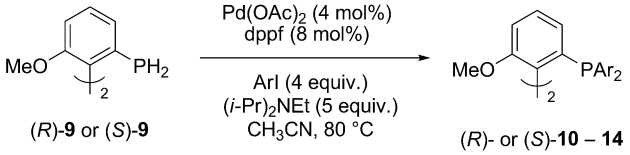
Scheme 1.



Scheme 2.

carbonyl-substituted iodides with bis-phosphane ligand (*R*)-**9** or (*S*)-**9** (prepared from **7**[13]) and the results are gathered in Table 1. Ligands bearing *tert*-butyl esters **10**, **11** and **13**, carboxylic acid **12** and a cyano group **14** were efficiently prepared in good to excellent yields and high enantiomeric purities.[12a]

Table 1. Pd-catalyzed P-C coupling of aryl iodides with bisphosphane ligand **9**.

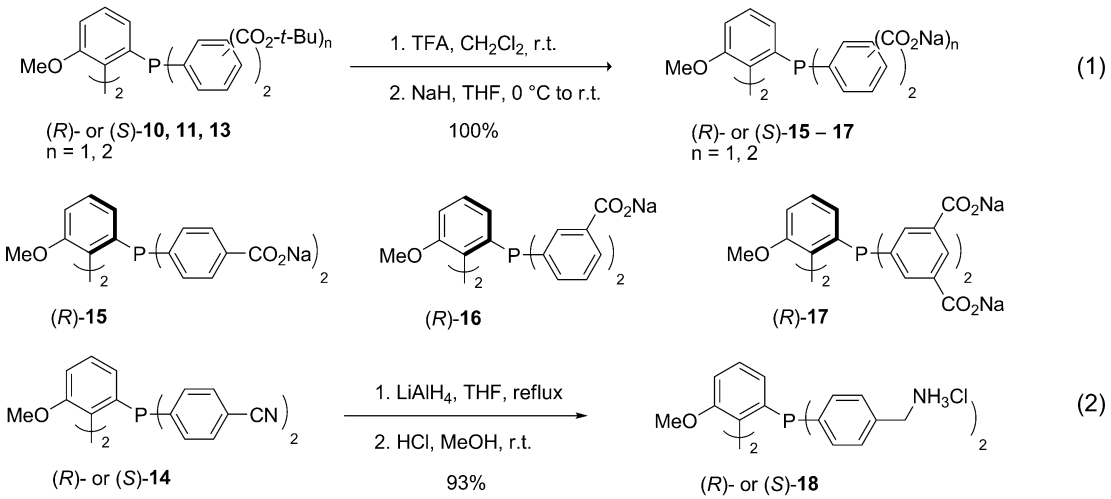


Entry	Ar	Ligand	Yield[a] [%]	*ee*[b] [%]
1	4-*t*-BuO_2C-C_6H_4	(*R*)-**10**	88	99
2	4-*t*-BuO_2C-C_6H_4	(*S*)-**10**	82	99
3	3-*t*-BuO_2C-C_6H_4	(*R*)-**11**	94	98
4	4-HO_2C-C_6H_4	(*R*)-**12**	70	99
5	3,5-(*t*-BuO_2C)$_2$-C_6H_3	(*R*)-**13**	76	>99
6	3,5-(*t*-BuO_2C)$_2$-C_6H_3	(*S*)-**13**	67	>99
7	4-NC-C_6H_4	(*R*)-**14**	89	>99
8	4-NC-C_6H_4	(*S*)-**14**	89	>99

[a] Isolated yield.
[b] Determined by HPLC analysis.

The *tert*-butyl esters were then converted to carboxylic acids in the presence of trifluoroacetic acid in dichloromethane in quantitative yields [Scheme 3, Eq. (1)]. Finally, the corresponding sodium salts were then prepared by addition of sodium hydride in tetrahydrofuran at 0 °C. With this procedure ligands **15**,[14] **16** and **17** were obtained in high overall yields. A cationic ligand was also synthesized using a 2-step synthesis involving the reduction of the cyano functionalities to methylamino groups followed by ammonium formation in the presence of hydrogen chloride. Accordingly, the tetra(methylammonium)-substituted ligand **18** was isolated in 93% yield over 2 steps [Scheme 3, Eq. (2)].

We further characterized the ligands by measuring their solubility in water; the results are collected in Table 2. The hydrophilic ligands **15**, **16**, **17** and **18** have similar solubilities ranging between $1.3{\cdot}10^2$ g/L and $3.85{\cdot}10^2$ g/L (for comparison, the water solubility of both triphenylphosphane analogues TPPTS[15,16] and *m*-TPPTC[17] are 1.1 kg/L, that of **3** is 3–3.5 g/L).



Scheme 3.

Table 2. Physical characterization of ligands.

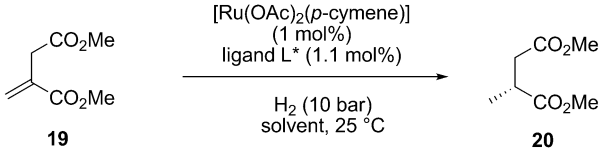
Entry	Ligand	Solubility[a] [10^2 g/L]	pK_a in H_2O[b]	pK_a in $MeOH_{aq}$[c]
1	**15**	1.75	3.5 and 7.5	3.9, 5.0, 5.2 and 5.8
2	**16**	1.30	3.7 and 7.8	3.3, 4.7, 5.3 and 6.1
3	**17**	3.85	3.4 and 8.0	<3, <3, 3.5, 4.5, 4.9, 5.5, 5.7 and 6.5
4	**18**	1.10	5.1 and 10.1	nd

[a] Determined in water.
[b] 15 mg of ligand were dissolved in 5 mL of H_2O and acidified except for **18**. The solution was dosed with aqueous sodium hydroxide (1×10^{-2} M).
[c] Determined in aqueous methanol solution (57%); nd: not determined

The acid/base behaviours of the polycarboxylic acid forms of ligands **15**, **16** and **17** were determined in water and in aqueous methanol.[18] In water, the tetracarboxylic acid moieties derived from ligands **15** and **16** present similar pK_a values for the corresponding first two acidities (3.5 and 3.7, respectively). The remaining two carboxylic groups (out of 4 present in the molecules) are less acidic and have measured pK_as equal to 7.5 and 7.8, respectively. In aqueous methanol, the four steps were independently determined and stayed in the same ranges for *para*- and *meta*-substituted ligands. In the case of the octasubstituted ligand **17**, four carboxylic groups have pK_a values close to 3.4, whereas the four others lie at *ca.* 8.0 in water. In aqueous methanol solution, the first two pK_a values of the acid moieties could not be measured whereas the six remaining were clearly determined. The tetra(methylammonium) substituted ligand **18** presents two pK_a values in water, one at 5.1 corresponding to one NH_3Cl/NH_2 function and one at 10.1 for the three remaining functions.

Having in hand these novel water-soluble ligands we chose to study the asymmetric hydrogenation reaction of a standard substrate such as dimethyl itaconate **19**[19] in water (Table 3). We selected the sodium salts-functionalized ligands **15**, **16**, **17** and the tetra-(methylammonium)-substituted ligand **18** to build up *in situ* the catalytic species. We were pleased to find

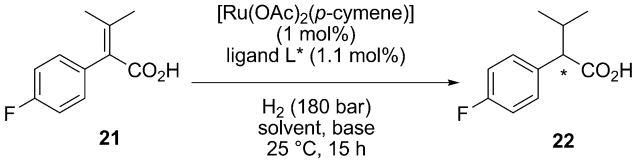
Table 3. Ru-catalyzed hydrogenation of dimethyl itaconate.



Entry	Ligand	Solvent	Conv.[a] [%]	*ee*[b] [%]
1	(*R*)-**15**	H_2O	100	92
2	(*R*)-**16**	H_2O	46	84
3	(*R*)-**17**	H_2O	100	89
4	(*R*)-**18**	H_2O	32	87
5	(*R*)-**3**	H_2O	100	95
6	(*R*)-**6b**	EtOH/H_2O/hexane (5/1/5)	99	79[11b]
7	(*R*)-**12**	MeOH	95	86
8	(*R*)-H_8-**17**	MeOH	27	91

[a] Determined by gas chromatography.
[b] Determined by HPLC analysis.

Table 4. Ru-catalyzed hydrogenation of 2-(4-fluorophenyl)-3-methyl-crotonic acid **21**.



Entry	Ligand	Solvent	Base (equiv.)	Conv.[a] [%] 2 h	Conv.[a] [%] 15 h	*ee*[b] [%] (configuration)
1	**(*R*)-12**	H_2O	Et_3N (0.6)	–	99	88 (*S*)
2	**(*R*)-15**	H_2O	Et_3N (0.6)	–	100	85 (*S*)
3	(*R*)-**16**	H_2O	Et_3N (0.6)	–	100	79 (*S*)
4	(*R*)-**17**	H_2O	Et_3N (0.6)	–	100	95 (*S*)
5	(*R*)-**3**	H_2O	Et_3N (0.6)	–	100	84 (*S*)
6	(*R*)-**12**	H_2O	DBU (0.6)	–	95	87 (*S*)
7	(*R*)-**12**	H_2O	NaOH (0.6)	–	99	88 (*S*)
8	(*R*)-**17**	H_2O	–	42	80	95 (*S*)
9	(*R*)-**17**	H_2O	NaOH (0.1)	85	100	95 (*S*)
10	(*R*)-**17**	H_2O	NaOH (0.6)	100	100	95 (*S*)
11	(*R*)-**17**	H_2O	NaOH (0.9)	46	100	95 (*S*)
12	(*R*)-**12**	MeOH	Et_3N (0.6)	–	100	88 (*S*)
13	(*R*)-H_4-**16**	MeOH	Et_3N (0.6)	–	100	88 (*S*)
14	(*S*)-H_8-**17**	MeOH	Et_3N (0.6)	–	100	85 (*R*)
15[c]	(*S*)-**12**	MeOH	Et_3N (0.6)	–	100	88 (*R*)

[a] Determined by gas chromatography.
[b] Determined by HPLC analysis, after 15 h.
[c] S/C = 1000.

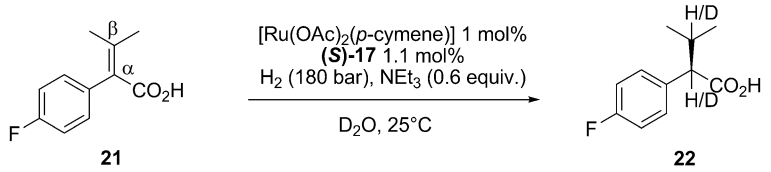
that with all tested catalysts the desired diester **20** was obtained within 20 h under 10 bar of dihydrogen in water. The presence of the sodium carboxylate moieties in *para* positions of the phenyl groups bound to phosphorus was crucial whereas lower conversion and enantiomeric excess were obtained in the presence of the *meta*-substituted ligand **16** (Table 3, entries 1 and 2). The catalyst containing the octasubstituted ligand **17** led to a total conversion and 89% enantiomeric excess (Table 3, entry 3). The presence of the cationic water-soluble functionality (ligand **18**) induced a low conversion but an enantiomeric excess of 87%, that is, comparable to that obtained with anionic ligands (Table 3, entry 4). With the *para*-substituted tetrasulfonate ligand **3** (Table 3, entry 5) similar results were obtained as with the ligand **15**, thus rendering **15** a convenient alternative to **3**. It's noteworthy that the results obtained with these new ligands compared favourably with the previously published results in the presence of phosphonic acid derivative **6b** (Table 3, entry 6).

We also compared the *para*- and di-*meta*-substituted ligands **12** and H_8-**17** (carboxylic acid form of ligand **17**) to the reaction conditions in methanol. In this solvent, a lower activity was observed compared to the reactions in water, but the *ee* values remained comparable (Table 3, entries 7 and 8).

We also tackled the preparation of (*S*)-2-(4-fluorophenyl)-3-methylbutanoic acid **22**, a key intermediate in the synthesis of Mibefradil, a calcium channel blocker developed by Roche for the treatment of hypertension and chronic angina pectoris.[20,21] The hydrogenation of 2(4-fluorophenyl)-3-methylcrotonic acid **21** was performed in water in the presence of the tetrasulfonated ligand **3** and led to the desired product **22** in 84% enantiomeric excess (Table 4, entry 5). With the catalysts containing the water-soluble ligands **12**, **15**, **16** and **17** excellent activities were observed in all cases (Table 4, entries 1–4). The enantioselectivities ranged from 79% to 95%, the best enantiomeric excess being obtained in the case of the 3,5-dicarboxylated ligand **17**.

Switching from triethylamine to DBU (Table 4, entry 6) or NaOH (Table 4, entry 7) had a minimal, if any, influence on the conversion or the enantioselectivity in the case of ligand **12**. The presence of lower or higher amounts of NaOH did not have an impact on the enantiomeric excess for ligand **17** (Table 4, entries 8–11), but influenced the conversion. The lower conversion at 0.9 equivalents of NaOH after 2 h might have various origins, a strong coordination of the base to the organometallic complex being a reasonable one. When the hydrogenation was conducted in MeOH, lower enantiomeric excesses were obtained (Table 4, entries 12–15). The catalyst loading could be reduced (S/C ratio = 1000) without erosion of either the conversion or the *ee* (Table 4, entry 15).

Table 5. Ru-catalyzed hydrogenation of 2-(4-fluorophenyl)-3-methylcrotonic acid **21** in D_2O.



21 **22**

Entry	Concentration (mol/L)	**22**-d_0	**22**-$d_{1\beta}$	**22**-$d_{1\alpha}$	**22**-d_2
1	1.55	24%	39%	13%	24%
2	0.7	40%	40%	10%	10%

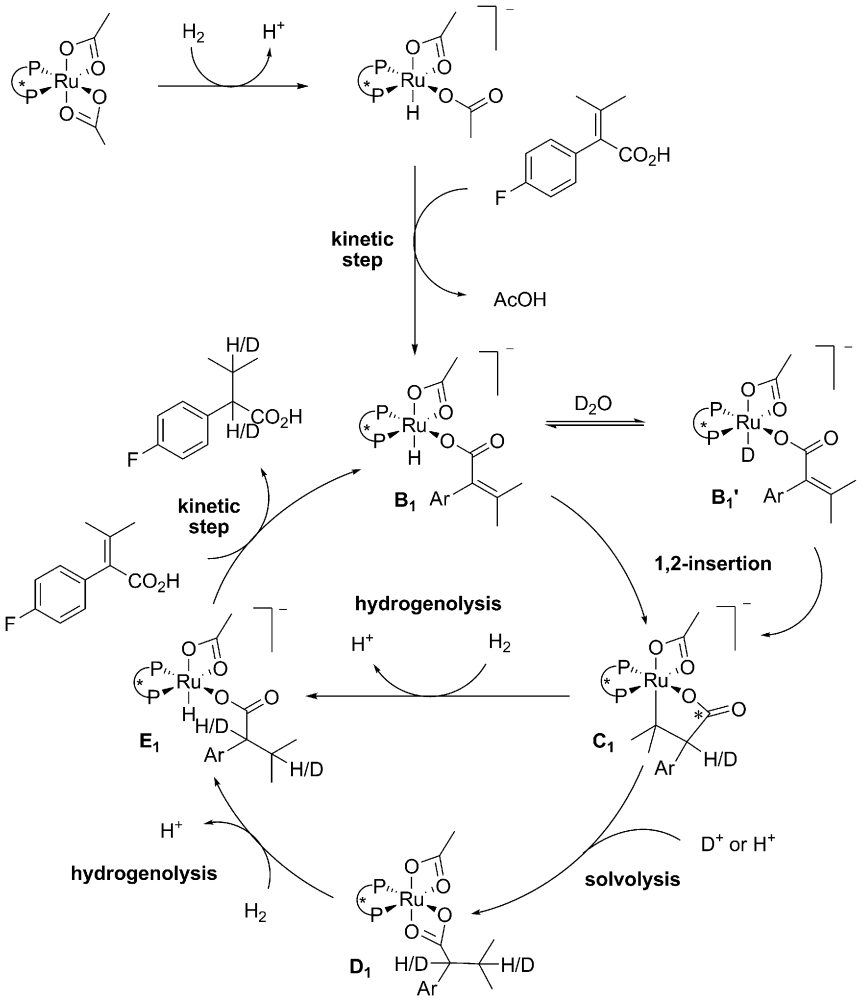
The mechanism of hydrogenation of α,β-unsaturated carboxylic acid has been described by Halpern,[22] Noyori,[23] Erkey[24] and recently Bergens[25] by studying the reduction of tiglic acid under H_2 or D_2 pressure in MeOH or MeOD as solvent. Depending on the dihydrogen pressure, the rate-limiting step is either the formation of the dicarboxylate ruthenium monohydride complex (*via* the heterolytic cleavage of H_2) or the reaction of the monohydride complex with the alkene (at high pressure). As part of the study of the hydrogenation reaction in water of 2-(4-fluorophenyl)-3-methylcrotonic acid, deuteration experiments were conducted in the presence of the catalyst containing ligand **17**. The reduction was carried out in D_2O in the presence of triethylamine at two concentrations in substrate. The various deuterated products and their proportions, as determined by ^{1}H NMR spectroscopy and mass spectrometry are collected in Table 5.

These observations and the results described in the literature[22–25] led us to postulate the mechanism described in Scheme 4 for the hydrogenation reaction of the acid 2-(4-fluorophenyl)-3-methylcrotonic **21** in water. From the *in situ* generated ruthenium bisacetate precursor, two steps involving the heterolytic cleavage of dihydrogen gas and ligand exchange between acetate and the substrate **21** would lead to ruthenium monohydride complex $\mathbf{B_1}$, which is in equilibrium with the species $\mathbf{B_{1'}}$. Monohydride complex $\mathbf{B_1}$ (or $\mathbf{B_{1'}}$) would then undergo a 1,2-insertion step of the double bond of the substrate leading to the five-membered heterometallacycle $\mathbf{C_1}$. Two ways are then possible for the evolution of $\mathbf{C_1}$ species, either the hydrogenolysis generating the monohydride species $\mathbf{E_1}$, or the solvolysis to form the biscarboxylate intermediate $\mathbf{D_1}$. Through a new cleavage of dihydrogen gas, the complex $\mathbf{D_1}$ would be converted to species $\mathbf{E_1}$.

In the final step ligand exchange between the substrate **21** and the product **22** would regenerate the intermediate $\mathbf{B_1}$. Accordingly, two steps would be rate-determining: one in an activation step of the catalyst leading to species $\mathbf{B_1}$ and the other in the catalytic cycle for the regeneration of the monohydride ruthenium complex $\mathbf{B_1}$. Based on this postulated mechanism, the formation of **22**-d_0 would come from 1,2-insertion in the Ru–H bond of intermediate $\mathbf{B_1}$ followed by hydrogenolysis of the five-membered heterometallacycle $\mathbf{C_1}$. The formation of **22**-$d_{1\beta}$ would be explained by the 1,2-insertion in the Ru–H bond of intermediate $\mathbf{B_1}$ followed by solvolysis of the five-membered heterometallacycle $\mathbf{C_1}$. The obtention of both **22**-$d_{1\alpha}$ and **22**-d_2 would arise from similar processes involving $\mathbf{B_{1'}}$ *in lieu* of $\mathbf{B_1}$.

Under the usual reaction conditions (C = 1.55 mol/L), the products resulting from the 1,2-insertion in the Ru–H bond (**22**-d_0 and **22**-$d_{1\beta}$) represent 63% of the total amount **22** (Table 5, entry 1). The equilibrium $\mathbf{B_1}/\mathbf{B_{1'}}$ would be in favour of $\mathbf{B_1}$,[28] the H/D exchange of the monohydride complexes $\mathbf{B_1}/\mathbf{B_{1'}}$ being similar as compared to what has been described in the literature for tiglic acid at high pressure in MeOD.[22,23,25] Furthermore, the hydrogenolysis (**22**-d_0 and **22**-$d_{1\alpha}$) would represent 37% of the cleavage of the five-membered heterometallacycle $\mathbf{C_1}$ affording $\mathbf{E_1}$. When the reaction was conducted in a volume twice as large, an enhancement of these phenomena (Table 5, entry 2) was observed. Indeed, considering that the volume of the autoclave was fixed assuming the validity of Henry's law, the amount of dissolved dihydrogen in water is two times larger in 2 mL than in 1 mL of D_2O. This leads to an increase in the proportion of products resulting from hydrogenolysis of the five-membered heterometallacycle $\mathbf{C_1}$ (**22**-d_0 + **22**-$d_{1\alpha}$: 50%) and a slowdown in the equilibrium of solvolysis between complexes $\mathbf{B_1}$ and $\mathbf{B_{1'}}$ (**22**-$d_{1\alpha}$ + **22**-d_2: 20%).

Given this work, the positive influence of the addition of a base on the reaction rate could be rationalized by considering the coordination of the substrate on the monohydride ruthenium complex as the rate-determining step under these conditions. The addition



Scheme 4. Mechanistic rationale.

of a base would accelerate this step *via* the formation of the carboxylate ion derived from **21**. It is noteworthy that a similar assumption on the effect of base addition was put forward by Ojima's group in a study of the hydrogenation reaction of α,β-unsaturated acids in the presence of rhodium complexes.[29] The acids and bases species being in equilibrium, the exchange of carboxylated ligands would thus be facilitated.

The successful development of asymmetric transformations in organo-aqueous medium depends on the ability to design inexpensive chiral ligands that are easy to prepare. We have extended the methodology developed for the preparation of MeOBIPHEP-based atropisomeric chiral ligands to congeners bearing carboxylate and methylammonium groups as water-soluble templates. These hydrophilic ligands were synthesized under mild conditions by a short sequence and in high yields; their solubility and acid/base properties were also determined. During the study of the asymmetric hydrogenation of dimethyl itaconate and 2-(4-fluorophenyl)-3-methylcrotonic acid in water, the ruthenium catalysts containing the 4-CO_2Na- and 3,5-$(CO_2Na)_2$-substituted MeOBIPHEP analogues showed high reactivities and enantioselectivities, leading to the desired products in $\geq 92\%$ *ee*.

Finally, the hydrogenation of 2-(4-fluorophenyl)-3-methylcrotonic acid in D_2O confirmed the simultaneous existence of a hydrogenolysis and a solvolysis variant of the mechanism and suggested an interpretation of the role of the added base.

These results pave the way for further applications in enantioselective C–H or C–C bond formation reactions in water. Current efforts are focused on expanding the scope of this methodology and to develop recyclable systems.

Experimental Section

General Remarks

All manipulations were carried out under argon. ^{1}H NMR, ^{13}C NMR and ^{31}P NMR were recorded on a Bruker AV 300 instrument. All signals were expressed as ppm (δ and inter-

nally referenced to residual protio solvent signals. Coupling constants (J) are reported in Hz and refer to apparent peak multiplicities. Mass spectroscopy and high resolution mass spectra were performed at Hoffmann-La Roche AG (Basel). Ligands **10**–**14** were prepared according to published procedures.[12a]

Synthesis of Sodium Salts 15, 16, 17

To a solution of *tert.*-butyl ester ligand (1 equiv.) in dry and degassed dichloromethane (0.5 M), trifluoroacetic acid (0.5 M in dichloromethane) was slowly added at 0 °C. The mixture was stirred at room temperature under argon during 2 h until completion, water was then added and the reaction mixture was extracted twice with EtOAc. The combined organic fractions were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The product was washed twice with 10 mL of dichloromethane and dried under vacuum and used directly in the next step without purification. After washing twice with pentane, sodium hydride (4 or 8 equiv, M = 24) was dried 30 min under vacuum. A solution of the acid ligand (1 equiv.) in dry and degassed THF (0.2 M) was carefully added to NaH at 0 °C under argon. The reaction mixture was degassed and stirred at room temperature during 5 h, then concentrated under vacuum.

(*R*)- or (*S*)-6,6′-Dimethoxy-*P*2,*P*2,*P*2′,*P*2′-tetrakis-[4-(carbonyloxy)phenyl]-biphenyl-2,2′-bisphosphine sodium salt (15): mp 250 °C (decomp.); ^{1}H NMR (D_2O, 300 MHz): δ = 3.06 (s, 6H), 6.78 (br. d, 2H, ^3J = 7.9 Hz), 6.91 (d, 2H, ^3J = 8.0 Hz), 7.08 (m, 4H), 7.21 (m, 4H), 7.34 (t, 2H, ^3J = 7.9 Hz), 7.66 (d, 4H, ^3J = 7.4 Hz), 7.73 (d, 4H, ^3J = 7.7 Hz); ^{13}C NMR (D_2O, 75 MHz): δ = 54.7 ($2CH_3$), 112.1 (2CH), 126.6 (2C), 128.8 (4CH), 130.0 (2CH), 131.9 (4CH) 132.9 (t, $^2J_{C,P}$ = 10.4 Hz, 4CH), 133.9 (t, $^2J_{C,P}$ = 10.4 Hz, 4CH), 136.5 (2C), 136.9 (2C), 137.0 (2C), 137.3 (2C), 138.7 (2C), 139.5 (2C), 155.7 (2C), 174.9 (2C), 175.1 (2C); ^{31}P NMR (D_2O, 121 MHz): δ = −16.3; ESI/MS: m/z = 781.3 $(M+3H-3Na)^+$; HR-MS: m/z = 781.1366, calcd. for $C_{42}H_{32}NaO_{10}P_2$: 781.1370; $[\alpha]_D^{25}$: + 14.2 (c 1.00, H_2O) (*R*).

(*R*)- or (*S*)-6,6′-Dimethoxy-*P*2,*P*2,*P*2′,*P*2′-tetrakis-[3-(carbonyloxy)phenyl]-biphenyl-2,2′-bisphosphine: mp 193 °C (decomp.); ^{1}H NMR (DMSO, 300 MHz): δ = 3.16 (s, 6H), 6.55 (br. d, ^3J = 7.6 Hz), 6.88 (d, 2H, ^3J = 8.2 Hz), 7.18 (m, 2H), 7.32 (m, 6H), 7.44 (t, 2H, ^3J = 7.6 Hz), 7.65 (m, 2H), 7.72 (m, 2H), 7.81 (d, 2H, ^3J = 7.8 Hz), 7.90 (d, 2H, ^3J = 7.7 Hz), 11.80 (br. s, 4H); ^{13}C NMR (CD_3OD, 75 MHz): δ = 55.3 ($2CH_3$), 112.3 (2CH), 127.0 (2CH), 129.4 (4CH), 130.3 (2CH), 130.6 (2CH), 131.0 (2CH), 131.9 (4C), 134.0 (2C), 135.3 (t, 2CH, $^2J_{C,P}$ = 9.8 Hz), 136.5 (t, 2CH, $^2J_{C,P}$ = 11.2 Hz), 138.8 (t, 2CH, $^2J_{C,P}$ = 11.2 Hz), 139.4 (t, 2CH, $^2J_{C,P}$ = 9.8 Hz), 137.8 (6C), 159.0 (2C), 169.6 (4C); ^{31}P NMR (DMSO, 121 MHz): δ = −14.9; ESI/MS: m/z = 759.5 $(M+H)^-$; HR-MS: m/z = 759.1537, calcd. for $C_{42}H_{33}O_{10}P_2$: 759.1543; $[\alpha]_D^{25}$: −12.0 (c 0.96, MeOH) (*R*).

(*R*)- or (*S*)-6,6′-Dimethoxy-*P*2,*P*2,*P*2′,*P*2′-tetrakis-[3-(carbonyloxy)phenyl]-biphenyl-2,2′-bisphosphine sodium salt (16): mp >260 °C; ^{1}H NMR (D_2O, 300 MHz): δ = 3.14 (s, 6H), 6.78 (br. d, 2H, ^3J = 7.4 Hz), 6.89 (d, 2H, ^3J = 8.2 Hz), 7.11 (m, 2H), 7.23 (m, 4H), 7.32 (t, 4H, ^3J = 8.3 Hz), 7.54 (br. s, 2H), 7.61 (br. s, 2H), 7.66 (d, 2H, ^3J = 8.0 Hz), 7.76 (d, 2H, ^3J = 7.7 Hz); ^{13}C NMR (D_2O, 75 MHz): δ = 54.8 ($2CH_3$), 112.1 (2CH), 126.6 (2CH), 128.5 (4CH), 129.3 (2CH), 129.6 (2CH), 130.0 (2CH, C_4, 4C), 130.6 (2C), 133.2 (br. s, 2CH), 134.3 (br. s, 2CH), 135.7 (br. s, 2CH), 136.4 (br. s, 2CH), 137.4 (6C), 156.7 (2C), 174.8 (2C), 175.0 (2C); ^{31}P NMR (D_2O, 121 MHz): δ = −15.9; ESI/MS: m/z = 781.1 $(M+3H-3Na)^+$; $[\alpha]_D^{25}$: +20.2 (c 1.00, H_2O) (*R*).

(*R*)- or (*S*)-6,6′-Dimethoxy-*P*2,*P*2,*P*2′,*P*2′-tetrakis-[3,5-di-(carbonyloxy)phenyl]-biphenyl-2,2′-bisphosphine: mp >260 °C; ^{1}H NMR (DMSO, 300 MHz): δ = 3.43 (s, 6H), 6.54 (d, 2H, ^3J = 7.8 Hz), 7.05 (d, 2H, ^3J = 8.4 Hz), 7.38 (t, 2H, ^3J = 8.0 Hz), 7.72 (m, 4H), 7.91 (m, 4H), 8.18 (s, 2H), 8.41 (s, 2H), 13.1 (br. s, 8H); ^{13}C NMR (DMSO, 75 MHz): δ = 54.9 ($2CH_3$), 112.2 (2CH), 125.9 (2C), 129.9 (4CH), 130.3 (2CH), 131.1 (4C), 131.4 (4C), 132.5 (2C), 132.8 (2C), 133.1 (2C), 136.0 (2C), 136.6 (t, $^2J_{C,P}$ = 10.9 Hz, 4CH), 137.4 (t, $^2J_{C,P}$ = 11.0 Hz, 4CH), 156.9 (2C), 165.8 (4C), 166.1 (4C); ^{31}P NMR (DMSO, 121 MHz): δ = −14.6; ESI/MS: m/z = 935.3 $(M+H)^+$; HR-MS: m/z = 957.0942, calcd. for $C_{46}H_{32}NaO_{18}P_2$: 957.0956; $[\alpha]_D^{25}$: +11.7 (c 0.99, MeOH) (*S*).

(*R*)- or (*S*)-6,6′-Dimethoxy-*P*2,*P*2,*P*2′,*P*2′-tetrakis-[3,5-di-(carbonyloxy)phenyl]-biphenyl-2,2′-bisphosphine sodium salt (17): mp 250 °C (decomp.); ^{1}H NMR (D_2O, 300 MHz): δ = 2.83 (s, 6H), 6.67 (d, 2H, ^3J = 8.0 Hz), 6.71 (br. d, 2H, ^3J = 7.6 Hz), 7.29 (t, 2H, ^3J = 8.0 Hz), 7.74 (m, 4H), 7.92 (m, 4H), 8.19 (s, 2H), 8.23 (s, 2H); ^{13}C NMR (D_2O, 75 MHz): δ = 54.5 ($2CH_3$), 111.7 (2CH), 125.5 (2CH), 129.6 (2CH, 2C), 130.2 (2CH), 130.4 (2CH), 134.8 (2C), 136.0 (t, $^2J_{C,P}$ = 10.5 Hz, 4CH), 136.3 (4C), 136.5 (4C), 136.8 (4C), 137.8 (t, $^2J_{C,P}$ = 11.2 Hz, 4CH), 157.0 (2C), 174.3 (4C), 174.6 (4C); ^{31}P NMR (D_2O, 121 MHz): δ = −12.3; ESI/MS: m/z = 957.4 $(M+8H-7Na)^+$; $[\alpha]_D^{25}$: +34.3 (c 0.99, H_2O) (*S*).

(*S*)-6,6′-Dimethoxy-*P*2,*P*2,*P*2′,*P*2′-tetrakis-[4-(methylamino)phenyl]-biphenyl-2,2′-bisphosphine Chloride Salt (18)

To a solution of 1 g of (*S*)-6,6′-dimethoxy-*P*2,*P*2,*P*2′,*P*2′-tetrakis-[4-(cyano)phenyl]-biphenyl-2,2′-bisphosphine (**14**) (1.466 mmol, 1 equiv., M = 682.64) in 15 mL of degassed and distilled THF, 334 mg of lithium aluminum hydride (8.796 mmol, 6 equiv., M = 38) were added in small portions. The reaction mixture was degassed and stirred at room temperature under argon during 4 h then treated at 0 °C by adding alternatively 1.5 mL of distilled and degassed water and 1.5 mL of 1 N NaOH. The resulting mixture was filtered through a short pad of celite [$(i\text{-Pr})_2O$] and concentrated under reduced pressure. (*S*)-6,6′-Dimethoxy-*P*2,*P*2,*P*2′,*P*2′-tetrakis-[4-(methylamino)phenyl]-biphenyl-2,2′-bisphosphine was obtained as an unstable pale brown solid and directly used for the next step; yield: 954 mg (93%).

A solution of 954 mg of (*S*)-6,6′-dimethoxy-*P*2,*P*2,*P*2′,*P*2′-tetrakis-[4-(methylamino)phenyl]-biphenyl-2,2′-bisphosphine (1.366 mmol, 1 equiv., M = 698.29) in 11 mL of HCl (5.5 mmol, 4 equiv., 0.5 M in methanol) was stirred under argon during 3 h. After concentration, (*S*)-6,6′-dimethoxy-*P*2,*P*2,*P*2′,*P*2′-tetrakis-[4-(methylamino)phenyl]-biphenyl-2,2′-bisphosphine chloride salt **18** was obtained as an orange solid; yield: 1.08 g (quantitative); mp >260 °C (decomp.). ^{1}H NMR (D_2O, 300 MHz): δ = 3.11 (s, 6H), 4.07 (s, 4H), 4.13 (s, 4H), 6.80 (dd, 2H, ^3J = 7.2 Hz, $^3J_{H,P}$ = 2.5 Hz), 6.95 (d, 2H, ^3J = 8.3 Hz), 7.10 (m, 4H), 7.27 (m, 8H, $H_{5'}$, H_6), 7.37 (m, 6H, H_3, $H_{6'}$); ^{13}C NMR (D_2O, 75 MHz): δ = 42.6

(2 CH_2), 54.8 (2 CH_3), 112.2 (2 CH), 126.5 (2 C), 128.9 (8 CH), 130.1 (2 CH), 131.6 (2 C), 133.1 (2 C), 133.6 (t, $^2J_{C,P}$ = 9.0 Hz, 4 CH), 134.6 (t, $^2J_{C,P}$ = 10.5 Hz, 4 CH), 136.3 (4 C), 137.1 (4 C), 156.8 (2 C). ^{31}P NMR (D_2O, 121 MHz): δ = −17.0; ESI/MS: m/z = 699.2 $(M-4HCl+H)^+$; $[\alpha]_D^{25}$: +19.1 (c 1.00, H_2O) (*S*).

Hydrogenation Reactions

In a glass tube and inside a glove box, ruthenium precursor (1 mol%) and diphosphine (1.1 mol%) were stirred in a dry and degassed solvent for 3 h under argon atmosphere before addition of the hydrogenation substrate. The reactor tube was put in an autoclave where hydrogen was introduced at the desired pressure. The reaction mixture was stirred at 25 °C and at the end of the reaction, dihydrogen was evacuated. If the reaction was carried out in water, the reaction mixture was extracted with *n*-hexane or ethyl acetate, dried over magnesium sulfate and concentrated under reduced pressure. If the reaction was carried out in MeOH, the reaction mixture was directly concentrated under reduced pressure. Crude materials were analyzed by ^{1}H NMR spectroscopy and chiral GC or HPLC.

Dimethyl methylsuccinate (20): ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.22 (d, ^3J = 7.2 Hz, 3 H), 2.41 (dd, ^3J = 6.0 Hz, ^2J = 24.8 Hz, 1 H), 2.76 (dd, ^3J = 8.0 Hz, ^2J = 24.8 Hz, 1 H), 2.92 (m, 1 H), 3.68 (s, 3 H), 3.70 (s, 3 H); Chiral GC (column BGB-176, T_0 = 60 °C, T_{30} = 150 °C): t_{r1} = 13.49 min, t_{r2} = 13.70 min, t_{rSM} = 15.21.

2-(4-Fluorophenyl)-3-methylbutanoic acid (22): ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.70 (d, ^3J = 6.8 Hz, 3 H), 1.07 (d, ^3J = 6.4 Hz, 3 H), 2.28 (app. h, ^3J = 6.4 Hz, 1 H), 3.13 (d, ^3J = 10.8 Hz, 1 H), 6.98 (d, ^3J = 8.8 Hz, 1 H), 7.00 (d, ^3J = 8.4 Hz, 1 H), 7.28 (d, ^3J = 8.4 Hz, 1 H), 7.30 (d, ^3J = 8.8 Hz, 1 H); Chiral HPLC [column Chiralpak IC, *n*-heptane/0.1% TFA in *n*-heptane/MTBE (75/5/20), flow: 1.0 mL min^{-1}, λ = 211 nm]: t_{r1} = 5.35 min, t_{r2} = 5.81 min, t_{rSM} = 7.83.

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