Homogeneous Catalysis

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Self-Assembled Bidentate Ligands for Ru-Catalyzed *anti*-Markovnikov Hydration of Terminal Alkynes**

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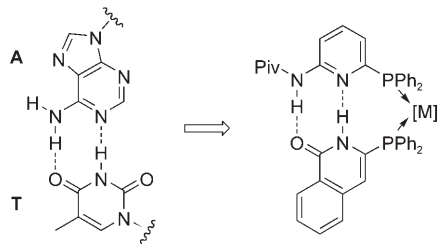
The regioselective functionalization of terminal alkynes is a fundamental process in organic synthesis since it allows the installation of a variety of important functional groups into an existing carbon skeleton.[1] Among these reactions, the addition of water across a triple bond generally follows the Markovnikov rule.[2] On the other hand, an *anti*-Markovnikov hydration of terminal alkynes could be a convenient way to the preparation of aldehydes, but so far only a few ruthenium complexes have been identified which allowed the catalysis of this unusual hydration mode.[3] The presence of bidentate phosphine ligands,[3b] the coordination of a water molecule stabilized by hydrogen bonding,[3e] and the use of phosphinopyridine ligands[3f] seem to be of major importance in these processes.

In the course of our investigation on the formation of bidentate ligands through hydrogen bonding,[4] we recently reported the construction of homodimeric[5] and heterodimeric[6] bidentate ligands by employing self-assembly.[7] In the latter case, an adenine/thymine base-pair analogous system was used: the aminopyridine/isoquinolone platform (Scheme 1).



Scheme 1. Self-assembly through hydrogen bonding of the adenine/thymine and aminopyridine/isoquinolone systems.

The first bidentate-phosphine ligand library for homogeneous metal-complex catalysis based on self-assembly through hydrogen bonding was realized, and these ligands furnished an active rhodium catalyst for the regioselective

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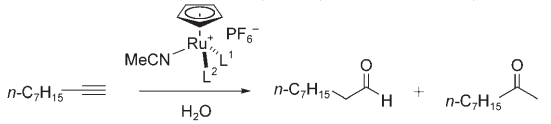
hydroformylation of terminal alkenes. Interestingly, these self-assembly systems incorporate a pyridinyl-functionalized phosphine ligand, emulate chelation, and contain a hydrogen-bonding network that may be suited to activating a molecule of water through further hydrogen bonding. Hence, the self-assembly ligand systems incorporate all the features that seem essential to allow a ruthenium-catalyzed *anti*-Markovnikov addition of water to a terminal alkyne.

In a first set of experiments, we studied the catalytic activity of a variety of half-sandwich ruthenium complexes bearing monodentate and bidentate phosphine ligands in the course of hydrating 1-nonyne as the test substrate. The ruthenium complexes used in this study were obtained in good yields (73–92%) by mixing one equivalent of each ligand in the presence of one equivalent of $[CpRu(CH_3CN)_3]PF_6$ (Cp = cyclopentadiene)[8] and subsequent precipitation with diethyl ether.

The results of the catalytic hydration are depicted in Table 1. Thus, triphenylphosphine, 2-diphenylphosphinopyridine and bis(diphenylphosphino)ethane (dppe) gave ruthenium complexes that performed with very low catalytic activity and selectivity. Using the 6-DPPon ligand, which should allow for self-dimerization based on hydrogen bonding between the pyridone form and its hydroxypyridine tautomer,[5] a similarly disappointing result was obtained. Conversely, on employing the self-assembled heterodimeric aminopyridine/isoquinolone bidentate ligands (entry 5; see also Scheme 1),[6] a catalyst was obtained that operated with outstanding activity and perfect regioselectivity. It is obvious from entries 6 and 7 that the self-assembled heterodimer is responsible for this interesting result. Thus, neither 6-DPPAP nor 3-DPICon ligands alone provided an active catalyst.

Table 1: Ruthenium complex-catalyzed hydration of 1-nonyne.



Entry	Cat.	L[1][a]	L[2][a]	*t* [h]	**a** [%][b]	**k** [%][b]
1	**1**	PPh_3	PPh_3	140	1.2	18
2	**2**[c]	dppy	dppy	168	4.0	2.4
3	**3**	dppe	–	168	2.1	20
4	**4**[c]	6-DPPon	6-DPPon	168	2.1	25
5	**5**	6-DPPAP	3-DPICon	26	94	0
6	**6**[c]	6-DPPAP	6-DPPAP	72	39	3.8
7	**7**	3-DPICon	3-DPICon	48	1.9	0

[a] dppy: 2-diphenylphosphinopyridine, dppe: 1,2-bis(diphenylphosphino)ethane, 6-DPPon: 6-diphenylphosphino-2-pyridone, 6-DPPAP: 6-diphenylphosphino-*N*-pivaloyl-2-aminopyridine, 3-DPICon: 3-diphenylphosphinoisoquinolone. [b] Yield calculated from GC response factors relative to hexadecane internal standard. a = aldehyde, k = ketone. [c] η^1-P,η^2-P,N coordination of the phosphinopyridine with replacement of the acetonitrile ligand.

Moreover, modifications of the aminopyridine and isoquinolone ligands with electron-donating and electron-withdrawing substituents furnished a 3×3 library of self-assembling ligands (Table 2). As no superior catalyst could be identified, we decided to focus on **5**.

Table 2: Ligand matrix (3×3) of aminopyridine/isoquinolone-derived self-assembled bidentate ligands in the Ru-catalyzed hydration of 1-nonyne.

	Aminopyridine[b]		
Isoquinolone[b]	6-DPPAP	6-D(*p*-MeO)PPAP	6-D(*p*-F)PPAP
3-DPICon	94:0[a]	77:0	84:1.8
3-D(*p*-MeO)PICon	60:0	60:1.2	66:1.8
3-D(*p*-F)PICon	78:1.0	71:2.2	70:4.9

[a] Yield of aldehyde/ketone products (%) determined by GC after 26 h. [b] 6-D(*p*-MeO)PPAP: 6-bis-(4-methoxyphenyl)-phosphino-2-(pivaloylamino)-pyridine, 6-D(*p*-F)PPAP: 6-bis(4-fluorophenyl)phosphino-2-(pivaloylamino)-pyridine, 3-D(*p*-MeO)PICon: 3-bis(4-methoxyphenyl)phosphinoisoquinolone, 3-D(*p*-F)PICon: 3-bis(4-fluorophenyl)phosphinoisoquinolone.

To get more structural information on the optimal catalyst **5**, the heterodimer-ligand formation based on self-assembly through hydrogen bonding was studied in solution by ^{31}P NMR spectroscopic analysis. Thus, a clean AB system with a ^2J(P-P) coupling constant of 35.9 Hz confirms the presence of two nonequivalent phosphine ligands coordinated at the same metal center (Figure 1).[9] Additionally, ^1H NMR experiments in $CDCl_3$ and [D$_6$]acetone show a substantial shift of the 6-DPPAP and 3-DPICon NH signals to low field after addition of $[CpRu(CH_3CN)_3]PF_6$, which is in agreement with hydrogen bonding. Furthermore NOE interactions observed in a solution of [D$_6$]acetone containing residual water confirm the existence of the hydrogen-bonding network under these conditions.

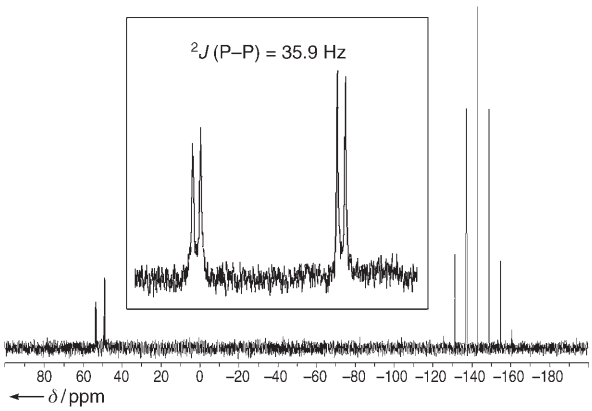


Figure 1. ^{31}P NMR spectrum of $[CpRu(CH_3CN)(6\text{-DPPAP})(3\text{-DPICon})]PF_6$ (**5**) in solution with $CDCl_3$.

Single crystals suitable for X-ray diffraction were obtained from slow diffusion of cyclohexane into a concentrated solution of **5** in dichloromethane.[10,11] As proposed, the aminopyridine and isoquinolone ligands form the expected hydrogen-bonding network reminiscent of the Watson–Crick base pairing of A and T in DNA (Figure 2).[12]

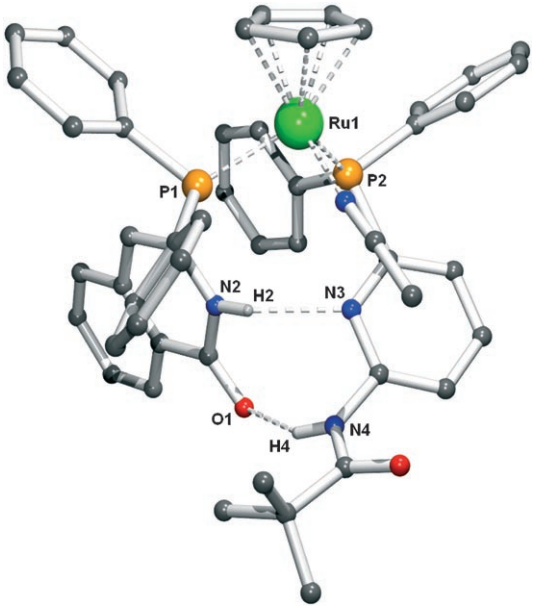
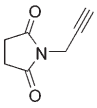
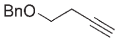
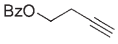
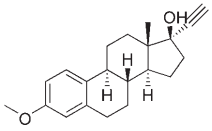


Figure 2. PLATON plot of **5** (H atoms bound to the carbon atoms and the PF_6^- counterion are omitted for clarity). Selected interatomic distances [Å] and angles [°]: Ru1-P1 2.3366(7), Ru1-P2 2.3193(8), H2···N3 2.811(3), O1···H4 2.846(3); P1-Ru1-P2 98.20(3), N2-H2···N3 135.35(3), O1···H4-N4 147.50(3).

The scope of the *anti*-Markovnikov hydration of various 1-alkynes was examined with **5** as the catalyst (Table 3). Reactions using 2–10 mol% of **5** gave the desired aldehydes in good yields. Linear terminal alkynes furnished the corresponding carbonyl products with complete regioselectivity, even if the catalyst seems to be partially inhibited by the presence of a nitrile group, which may act as a competing ligand for the ruthenium center (entries 1–3).[3b] 1,9-Decadiyne was converted into the corresponding dialdehyde in 78% yield, with only traces of the monoaldehyde (entry 4). The regioselectivity is excellent for a range of different functionalized substrates (entries 1–7, 9, and 10), with only one exception: a homopropargylic system bearing a benzoate function (entry 8). In this case, the regioselectivity is slightly diminished, which may be because of a chelation effect. Finally, a steroid ring system substituted by a propargylic alcohol reacted with water and gave the γ-hydroxy aldehyde selectively in 61% yield (entry 10). It should be noted that in this example the reaction was carried out at 70°C to avoid degradation of the product into an α,β-unsaturated aldehyde.[13]

In summary, the present study highlights the utility of bidentate ligands generated by the self-assembly of monodentate ligands through complementary hydrogen bonding for homogeneous catalysis. Thus, a new ruthenium catalyst was identified, which allows highly regioselective *anti*-Markovnikov hydration of terminal alkynes compatible with a wide range of functional groups. Although at this stage, the origin of the catalytic activity remains unknown, the hydrogen-bonding network may play an important role besides emulation of bidentate ligand binding.[14]

Table 3: Regioselective hydration of functionalized terminal alkynes with **5** as the catalyst.

Entry	Substrate	**5**[%]	*t* [h]	**a/k** [%][a]	Yield [%][b]
1	n-C_7H_{15}—	2	26	>99:1	89
2	Ph—	2	26	>99:1	73
3	N≡$(CH_2)_3$—	10	96	>99:1	78
4	—$(CH_2)_6$—	10	78	99:1[c]	82
5		5	70	>99:1	87
6		5	72	99:1	65
7		5	48	99:1	83
8		5	50	87:13	74
9		5	28	96:4	91
10[d]		10	124	>99:1	61

[a] Determined by GC analysis and ^{1}H NMR spectroscopy. a = aldehyde, k = ketone. [b] Yield of isolated product. [c] Ratio of decane-1,10-dial/9-oxodecanal. [d] Reaction performed at 70°C.

Experimental Section

Representative procedure: Freshly prepared **5** (21 mg, 2 mol%) was added to a solution of 1-nonyne (124 mg, 1.0 mmol) and water (90 mg, 5.0 mmol) in deoxygenated acetone (1.6 mL). The mixture was heated under Ar for 26 h at 120°C in a sealed tube and the reaction progress was monitored by GC. After cooling to room temperature, the solvent was removed in vacuo and the residue was extracted with diethyl ether. The solution was dried ($MgSO_4$), filtered through a plug of silica, and concentrated under reduced pressure to furnish nonanal (126 mg, 89%) as a colorless oil.

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[9] ^{31}P NMR spectra of complex **5** was measured in $CDCl_3$ and [D$_6$]acetone; in both cases, the AB-spin system, depicted in Figure 1, was observed with identical chemical shifts and coupling constants (the septet at $\delta = -141.6$ ppm (^1J(P-F) = 707.7 Hz) belongs to the PF_6 counterion).

[10] CCDC 289523 (**5**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[11] Crystal data for **5**: $C_{50}H_{47}F_6N_4O_2P_3Ru$; $M_r = 1043.90$; $T = 100(2)$ K; $\lambda = 0.71073$ Å; triclinic; space group $P\bar{1}$, $a = 11.1195(4)$, $b = 13.0414(4)$, $c = 18.2113(8)$ Å, $\alpha = 92.169(2)$, $\beta = 106.9106(17)$, $\gamma = 97.314(2)°$; $V = 2498.32(16)$ Å^3; $Z = 2$; $D_c = 1.388$ Mg m^{-3}; $\mu = 0.474$ mm^{-1}; $F(000) = 1068$; crystal size = $0.08 \times 0.08 \times 0.06$ mm; θ range for data collection: 1.58–27.52°, limiting indices: $-14 \le h \le 14$, $-16 \le k \le 16$, $-23 \le l \le 23$; 30814 reflections collected; 11483 reflections unique ($R_{int} = 0.0509$); completeness to $\theta = 25.00°$: 100.0%; absorption correction: semiempirical from equivalents; max. and min. transmission: 0.975 and 0.937; refinement method: full-matrix least-squares on F^2; data/restraints/parameters: 11483/0/599; GOF on F^2: 0.987; final R indices: ($I > 2\sigma(I)$): $R1 = 0.0438$, $wR2 = 0.0964$; R indices (all data): $R1 = 0.0718$, $wR2 = 0.1047$; largest diff. peak and hole: 0.533 and -0.585 e Å^{-3}.

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[14] A first confirmation for this assumption was obtained from the reaction of 6-DPPAP (1 equiv), 3-DPICon (1 equiv), and *cis*-[$PtCl_2$(cod)] (1 equiv; cod = cyclooctadiene) in toluene in the presence of water to give *cis*-[$PtCl_2$(6-DPPAP)(3-DPICon)-(H_2O)] quantitatively.

