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Highly Active in Situ Catalysts for Anti-Markovnikov Hydration of Terminal Alkynes

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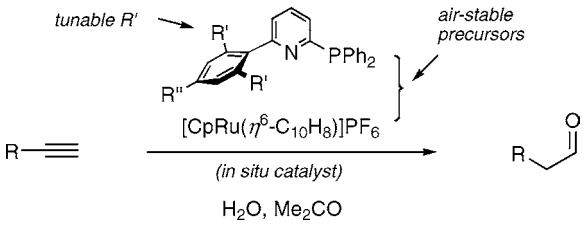
ABSTRACT



The anti-Markovnikov hydration of terminal alkynes to give aldehydes is catalyzed by complexes derived in situ from air-stable [CpRu(η^6-naphthalene)]PF_6 (C) and 6-aryl-2-diphenylphosphinopyridines (L). Ligands L are readily available from a modular synthesis. Increasing the size of the ligand C-6 aryl group in the order R = Ph < mesityl < 2,4,6-triisopropylphenyl < (2,4,6-triphenyl)phenyl gave hydration catalysts of highest known activity.

Alkynes have long been known to undergo synthetically useful metal-catalyzed hydrations to give carbonyl compounds, but only in 1998 did Tokunaga and Wakatsuki find a ruthenium catalyst that selectively produced aldehydes from terminal alkynes.[1] Complexes $[CpRu(PR_3)_2]X$ (**1**) (R = aryl, alkyl, bridging alkyl; Cp = η^5-cyclopentadienyl; X = Cl, PF_6) have since emerged as catalysts for anti-Markovnikov hydration with almost perfect regioselectivity.[2−4] A crucial ligand modification (PR_3 = **L1** = 6-*tert*-butyl-2-diphenylphosphanylpyridine)[5] by Grotjahn and Lev gave the complex $[CpRu(\mathbf{L1})_2(MeCN)]PF_6$ (**2**), which is 3 orders of magnitude more active than **1** and thus paved the way for synthetic applications under mild conditions.[4] Catalytic heterofunctionalization[6] reactions are promising tools for sustainable synthesis because they generate heterofunctionality with atom-economy.[7] We have been eager to incorporate the title reaction into synthetic sequences, but progress was initially hampered by the low activity of the first generation catalysts **1**, and later by availability of sufficient quantities of complex **2**.[8]

These hurdles in the way of a broader synthetic application of anti-Markovnikov hydration[9] of terminal alkynes have motivated us to search for more available and easy to handle catalysts. We can now present in situ catalysts for the title reaction that combine the advantages of ready availability and air-stability, and we also report on a surprising ligand effect that has allowed us to tune the catalyst to highest levels of activity.

(1) Tokunaga, M.; Wakatsuki, Y. *Angew. Chem., Int. Ed.* **1998**, *37*, 2867.
(2) (a) Suzuki, T.; Tokunaga, M.; Wakatsuki, Y. *Org. Lett.* **2001**, *3*, 735. (b) Tokunaga, M.; Suzuki, T.; Koga, N.; Fukushima, T.; Horiuchi, A.; Wakatsuki, Y. *J. Am. Chem. Soc.* **2001**, *123*, 11917.
(3) (a) Grotjahn, D. B.; Incarvito, C. D.; Rheingold, A. L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3884. (b) Chevallier, F.; Breit, B. *Angew. Chem., Int. Ed.* **2006**, *45*, 1599.
(4) (a) Grotjahn, D. B.; Lev, D. A. *J. Am. Chem. Soc.* **2004**, *126*, 12232. (b) Grotjahn, D. B. *Chem. Eur. J.* **2005**, *11*, 7146.
(5) Baur, J.; Jacobsen, H.; Burger, P.; Artus, G.; Berke, H.; Dahlenburg, L. *Eur. J. Inorg. Chem.* **2000**, 1411.
(6) (a) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079. (b) Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 3368. (c) *Catalytic Heterofunctionalization*; Togni, A., Grützmacher, H., Eds.; Wiley-VCH: Weinheim, Germany, 2001.
(7) Trost, B. M. *Science* **1991**, *254*, 1471.
(8) Availability of **2** is limited by the synthesis of **L1** (6 steps, low overall yield) and the use of an expensive precursor $[CpRu(MeCN)_3]PF_6$. Note, however, that **2** is now sold in research quantities by Strem Chemicals.
(9) We are not aware of applications of this methodology in synthesis.

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We initially discovered that the complex [CpRu(η^6-naphthalene)]PF_6 (**C**), when combined with **L1**, gave a highly active in situ catalyst for the anti-Markovnikov hydration of terminal alkynes (Figure 1). Complex **C** is an air-stable

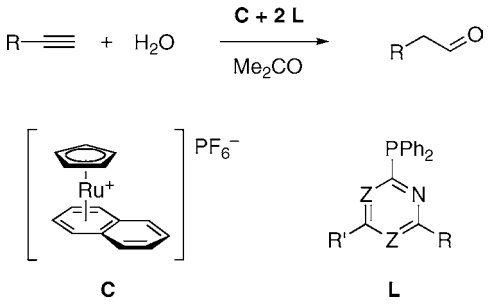


Figure 1. New in situ catalysts for anti-Markovnikov hydration of terminal alkynes (Z = CH or N; R = aryl, R′ = H or aryl).

material that is made in one step from ruthenocene.[10] Its use as a donor of the electrophilic $CpRu^+$-fragment is very practical since it replaces the complex [CpRu(MeCN)$_3$]PF_6, which is expensive and air-sensitive.[11] The ligand exchange was complete within an hour in acetonitrile at 50 °C and catalytic hydrations were then carried out efficiently in aqueous acetone[4a] (Table 1, entries 1 and 10−12). The components of the in situ catalyst could be handled in air, and the active catalyst was generated on demand. Unfortunately, this practical protocol still relied on the unique ligand **L1**, which is necessary for high rate acceleration,[4] but is not readily available.[5] According to Grotjahn, the peculiarity of **L1** is ascribed to steric shielding of the pyridine nitrogen by the bulky *tert*-butyl group; this prevents both η^2-P-N-chelation (Figure 2) and irreversible additions to alkyne substrates.[4b] In the hope to find ligands with sterically demanding R groups that would give rise to highly active catalysts we planned to synthesize 6-aryl-substituted pyridylphosphanes by a straightforward sequence involving selective cross-coupling reactions.[12,13]

A range of new 6-aryl-2-diphenylphosphinopyridines **L** was obtained in two steps from 2,6-dibromopyridine (**3**) (Table 2). Kumada couplings with bulky aryl Grignard reagents and PCy_3 as ligand for nickel[12a,14] selectively gave the monoarylated bromopyridines **P**. Nucleophilic phosphination of **P** resulted in ligands **L2**−**L8** as crystalline solids which could be handled in air. Complex **C** underwent complete ligand exchange with **L1** in MeCN to give [CpRu-

Table 1. Use of the New in Situ Catalysts in the Anti-Markovnikov Hydration of Selected Terminal Alkynes To Give Aldehydes[a]

entry	substrate	product	ligand[b]	[Ru] (mol % **C**)	temperature	time (h)	yield (%)
1	*n*-C_5H_{11}—	*n*-C_5H_{11}	**L1**	1	60 °C	14	78
2	"	"	**L6**	1	60 °C	6.5	91
3	*n*-C_6H_{13}—	*n*-C_6H_{13}	**L1**	5	60 °C	6	(95)[c]
4	"	"	**L5**	5	60 °C	3	(95)[c]
5	"	"	**L7**	5	60 °C	1	(95)[c]
6			**L7**	2	55 °C	3	94
7	"	"	**L6**	2	60 °C	12	90
8			**L6**	2	55 °C	6	73
9	"	"	**L5**	2	55 °C	6	69
10			**L1**	2	45 °C	18	69
11	OPiv, Ph	OPiv, Ph	**L1**	2	65 °C	20	83
12	CO_2t-Bu	CO_2t-Bu, CHO	**L1**	4	60 °C	8	98
13	"	"	**L6**	4	60 °C	8	95
14	MeO_2C, CO_2Me	MeO_2C, CO_2Me, CHO	**L6**	2	55 °C	6	95
15	"	"	**L5**	1	55 °C	4.5	72
16	"	"	**L7**	2	55 °C	1.5	99

[a] Conditions: The catalyst was generated from 2 equiv of **L** and 1 equiv of **C** in MeCN at 50−60 °C over 1 to 6 h, followed by evaporation. Hydration of the substrates (1 to 10 mmol, 0.5 *m*) was carried out in acetone with 5 equiv of water under argon. See the Supporting Information for a general procedure. [b] See Table 2 and text for ligand structures. [c] Time to 95% conversion was determined by GC, using an internal standard; $[octyne]_0 = 0.25$ *m*. Piv = pivaloyl.

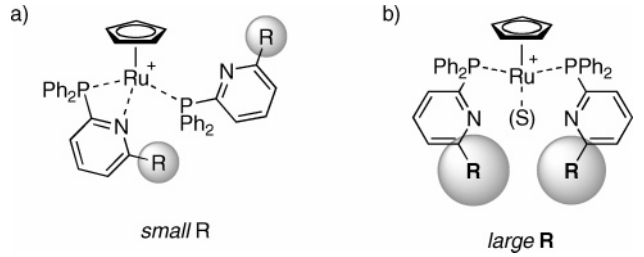
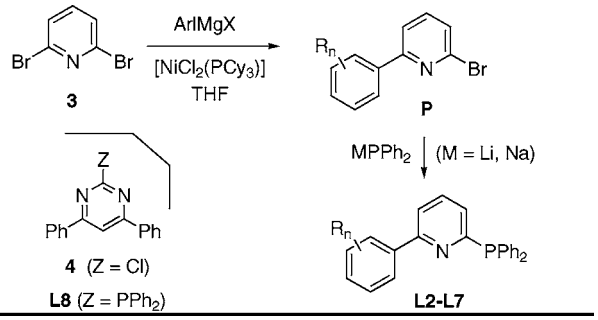


Figure 2. (a) Catalyst deactivation by PN-chelation with small R groups (H, Me). (b) Large substituents **R** prevent chelation. The substrate/solvent (S) at the free coordination site may interact with the pyridine nitrogen.[4b]

(**L1**)$_2$(MeCN)]$^+$ [15] within 1 h at 50 °C. The monophosphine complex cation [CpRu(η^1-**L1**)(MeCN)$_2$]$^+$ was detected as an intermediate.[16] Likewise, the phenyl-substituted pyridylphosphane **L2** reacted with **C** (MeCN, 2.5 h, 65 °C) to give [CpRu(**L2**)$_2$(MeCN)]$^+$,[17] with a fleeting appearance of [CpRu(**L2**)(MeCN)$_2$]$^+$ [18] after 1 h. Complex species incorporating a η^2-P-N chelate were not detected. The more hindered ligands **L6**[19] and **L7** (cf. Figure 3) required 6 h at 60 °C for complete ligand exchange. These experiments show that a phenyl group at the C-6-position of a 2-pyridylphosphane ligand **L** is already sufficient to prevent catalyst deactivation by P-N chelation (see Figure 2). Indeed, all of the in situ complexes prepared from **L2**−**L8** were catalysts for the anti-Markovnikov hydration, but their activities varied. Reaction progress curves for the hydration of 1-octyne were recorded (Figure 4) and fitted[20] to the rate law d*P*/dt = $k_{\mathbf{Ln}}$[Ru]$_0$[H$_2$O][octyne]. The values thus obtained for $k_{\mathbf{Ln}}$ were compared to the activity of the in situ catalyst from **L1** at 45 °C (Table 3). Since reaction progress did not

Table 2. Two-Step Synthesis of 6-Aryl-2-pyridylphosphanes[a]



entry	Arl substitution[b] (R_n)	P	yield (%)	ligand	yield (%)
1	H		*c*	**L2**	86
2	2,4,6-Me$_3$	**P3**	70	**L3**	79
3	2,6-(*i*-PrO)$_2$	**P4**	83	**L4**	74
4	2,6-*i*-Pr$_2$	**P5**	67	**L5**	71
5	2,4,6-*i*-Pr$_3$	**P6**	83	**L6**	75
6	2,4,6-Ph$_3$	**P7**	57	**L7**	78

[a] See the Supporting Information for reaction conditions. [b] Arl = aryl at C-6. [c] **L2** was synthesized by a different route, and compound **4** served as starting material for **L8**, see the Supporting Information.

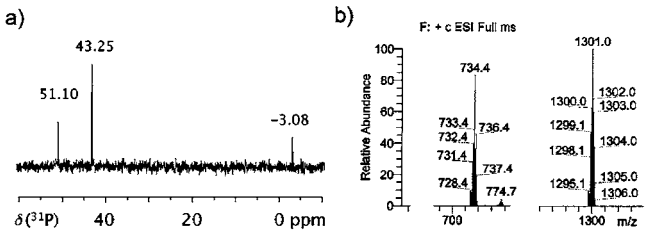


Figure 3. In situ complexation of **C** and **L7** in CD$_3$CN. (a) ^{31}P NMR spectrum after 2.5 h of ligand exchange at 60 °C: signals for **L7** (s, −3.1 ppm), [CpRu(**L7**)(MeCN)$_2$]$^+$ (s, 51.1 ppm), and [CpRu(**L7**)$_2$(MeCN)]$^+$ (s, 43.3 ppm). (b) ESI-MS of in situ formed [CpRu(**L7**)$_2$(MeCN)]PF$_6$ in MeCN: *m*/*z* 1301 ([CpRu(**L7**)$_2$]$^+$), fragments to *m*/*z* 734 ([CpRu(**L7**)]$^+$). A trace of the solvate [CpRu(**L7**)(MeCN)]$^+$ (*m*/*z* 775) is also visible.

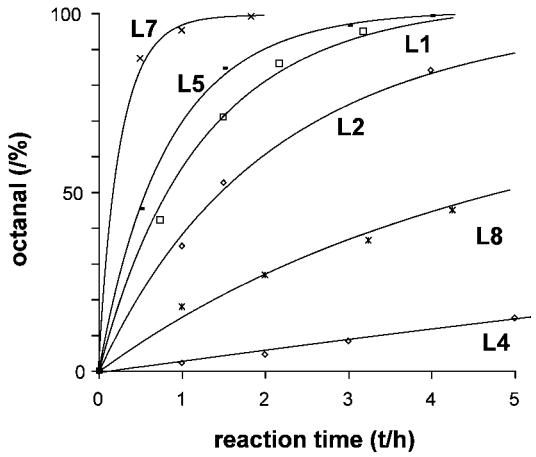
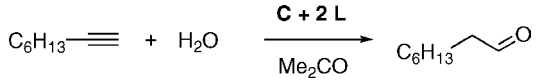


Figure 4. Hydration of 1-octyne to octanal at 60 °C (GC data points/idealized progress curves; cf. Table 3).

(10) Kündig, E. P.; Monnier, F. R. *Adv. Synth. Catal.* **2004**, *346*, 901.
(11) We believe that this replacement use is more general; e.g., reaction of **C** with 1,5-cyclooctadiene in MeCN yields [CpRu(η^4-COD)(MeCN)]PF$_6$; Hintermann, L., unpublished result.
(12) Selective monoarylation of dihalopyridines: (a) Scott, N. M.; Schareina, T.; Tok, O.; Kempe, R. *Eur. J. Inorg. Chem.* **2004**, 3297. (b) Loren, J. C.; Siegel, J. S. *Angew. Chem., Int. Ed.* **2001**, *40*, 754. (c) Alami, M.; Peyrat, J.; Belachmi, L.; Brion, J. *Eur. J. Org. Chem.* **2001**, 4207. (d) Zhang, H.; Tse, M. K.; Chan, K. S. *Synth. Commun.* **2001**, *31*, 1129.
(13) Conversely, reactions of bulky alkyl metals with dihalopyridines are usually not selective, cf.: Cui, X.; Brown, R. S. *J. Org. Chem.* **2000**, *65*, 5653.
(14) Modifications: [NiCl$_2$(PCy$_3$)$_2$] as catalyst, THF as solvent.
(15) δ(^{31}P) in CD$_3$CN = 42.7 ppm (s). ESI-MS (MeCN): *m*/*z* 805.4 ([CpRu(**L1**)$_2$]$^+$), 486.4 ([CpRu(**L1**)]$^+$).
(16) δ(^{31}P) in CD$_3$CN = 49.8 ppm (s). ESI-MS (CHCl$_3$/MeCN): *m*/*z* = 526.7 ([CpRu(**L1**)(MeCN)]$^+$), 486.3 ([CpRu(**L1**)]$^+$).

Table 3. Relative Catalytic Activities of in Situ Complexes (**C** + 2**L**) in the Hydration of 1-Octyne[a]



entry	ligand	R	RCA[b] 45 °C	RCA 60 °C
1	**L7**	2,4,6-$Ph_3C_6H_2$	2.9	16.6
2	**L6**	2,4,6-*i*-$Pr_3C_6H_2$	1.6	7.1
3	**L5**	2,6-*i*-$Pr_2C_6H_3$	1.2	5.0
4	**L1** (**2**)[c]	*t*-Bu	1.3	3.9
5	**L1**	*t*-Bu	1	3.5
6	**L3**	Mes	1.0	2.3
7	**L2**	Ph	0.4	1.6
8	**L8**	4,6-$Ph_2C_4N_2H$	n.d.	0.6
9	**L4**	2,6-(*i*-PrO)$_2C_6H_3$	n.d.	0.16

[a] Conditions: $[\text{octyne}]_0 = 0.25$ *m*, [Ru] = 5 mol %, $[H_2O]_0 = 1.25$ *m*, see the Supporting Information. [b] Relative catalytic activities, normalized: RCA (**Ln**) = $k_{\mathbf{Ln}}/k_{\mathbf{L1}@45°C}$. [c] Pure complex **2** was used as catalyst.

uniformly follow the above rate law over the full range of conversion, the results are approximate, but some conclusions can be drawn. The activity of the catalysts increases in the order R = Ph < Mes < *t*-Bu < *i*-$Pr_2C_6H_3$ < *i*-$Pr_3C_6H_2$ < $Ph_3C_6H_2$ and thus roughly correlates with the steric size of the ligand, which surprised us because it was not predicted by mechanistic models of this reaction.[2,4] The in situ catalysts from **L5**, **L6**, and **L7** surpassed the activity of either that from **L1** or that of the pure complex **2** and therefore are the most active catalysts for anti-Markovnikov hydration to date. On the other hand, introduction of heteroatoms into either the aza-arene nucleus (**L8**) or onto the aryl group R (**L4**) of the ligands gave less active catalysts. Catalyst activity at 60 °C was 2 to 5 times higher than that at 45 °C. The purified Grotjahn complex **2** was slightly more active than in situ catalysts from **L1**.

(17) $\delta(^{31}P)$ in CD_3CN = 43.2 ppm (s). ESI-MS (MeCN): *m/z* 845.1 ([CpRu(**L2**)$_2$]$^+$), 506.4 (−**L2**); 547 ([CpRu(**L2**)(MeCN)$^+$], weak).

(18) $\delta(^{31}P)$ in CD_3CN = 51.1 ppm (s).

(19) [CpRu(**L6**)$(MeCN)_2]^+$: $\delta(^{31}P)$ in CD_3CN = 50.1 ppm. [CpRu(**L6**)$_2$-(MeCN)]$^+$: $\delta(^{31}P)$ = 43.2 ppm.

(20) DYNAFIT program; Kuzmic, P. *Anal. Biochem.* **1996**, *237*, 260.

Some applications of the new in situ catalysts are presented in Table 1. The bulky arylpyridylphosphanes **L5**−**L7** performed very well and gave catalysts that were also more robust toward oxygen and substrate impurities than catalysts based on **L1**. This made them the preferred ligands for reactions at lower catalyst loadings (entries 1 and 2). In addition to the established functional group tolerance of Ru-catalyzed anti-Markovnikov-hydration[2−4] we find that β-ketoesters are tolerated even though they are potential ligands (entries 12 and 13). Regioisomeric ketone side products were not observed in any of the above reactions.

In conclusion, we have introduced a family of highly active in situ catalysts for the anti-Markovnikov hydration of terminal alkynes that is based on a combination of the metal precursor [CpRu(naphthalene)]PF_6 (**C**) and 6-aryl-2-diphenylphosphinopyridine ligands **L**. The reaction of **C** and **L** has been investigated in solution and the generation of active catalysts similar to Grotjahns complex **2** has been observed. The components of our in situ catalyst are readily available and easy to handle. The straightforward, modular two-step ligand synthesis renders the catalyst system tunable; this has by now led to a catalyst that is four times more active than the best previous one for anti-Markovnikov hydration. We are currently applying this fascinating reaction in multistep synthetic sequences, following a philosophy of sequential catalytic synthesis with high atom-economy. Progress along these lines will be reported in due course.

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Supporting Information Available: General experimental procedures, analytical data, and selected spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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