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# Mixed Phosphane $\eta^5$-CpRuCl$(PR_3)_2$ Complexes as Ambifunctional Catalysts for Anti-Markovnikov Hydration of Terminal Alkynes

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Supporting Information

**ABSTRACT:** The catalytic activity of $[CpRu(L)_2(MeCN)]PF_6$ (**L** = 2-diphenylphosphinopyridine with bulky groups at C-6) for anti-Markovnikov hydration of terminal alkynes to aldehydes is retained when one heterocyclic ligand **L** is replaced by **L′** = $PPh_3$. Equal amounts of $CpRuCl(PPh_3)_2$ (**1**) and phosphane **L** in acetone solution equilibrate to a mixture of **1**, $CpRuCl(L)(PPh_3)$ (**2**), and $CpRuCl(L)_2$ (**3**), which acts as highly active in situ catalyst for preparative anti-Markovnikov hydration of alkynes in water-rich media (2 mol % [Ru], 60 °C, 3−18 h in 4:1 (v/v) acetone/water). Reactions were completed in <15 min at 160 °C.

The catalytic anti-Markovnikov hydration of terminal alkynes to aldehydes is a relatively young[1−6] but synthetically powerful reaction[1a,5,7] that is catalyzed by selected $CpRuX(PR_3)_2$ complexes incorporating suitable phosphane ligands.[2b,3] Grotjahn has shown that the reaction profits from (am)bifunctional[3,8,9] acceleration in complexes **I** and **II**, which contain heterocyclic phosphane ligands that bind to the metal center via a P donor but are also capable of inner-sphere hydrogen bonding in catalytic intermediates via the nitrogen lone pair.[3,9,10] Grotjahn's complexes **I**[3a] and **IIa**[3b] and our in situ catalysts **IIb**[4a] incorporate the same *azaarylphos*phane (AZARYPHOS)[4b] ligand **L** twice at ruthenium, that is, they are homoleptic with respect to the $Ru(L)_2$ fragment (Figure 1).

Synthetic[5,7] and mechanistic[9,10] studies to date have used homoleptic catalyst complexes containing two bifunctional ligands. It is not known whether the cooperative assistance of the two ligands is required in critical mechanistic steps.[3a,9,10] We recently reported the synthesis of $[CpRu(MeCN)(L)(L')]PF_6$ complexes **C**, in which **L** is a heterocyclic AZARYPHOS[4b] ligand and **L′** is variable.[11] Here we present comparative kinetic analyses of catalytic hydrations with homoleptic and mixed phosphane complexes **C** and show that a *single* heterocyclic ligand **L** is sufficient to achieve maximal reaction rates in alkyne hydration catalysis. An immediate result of this finding is the introduction of a new, readily available, operationally simple, and synthetically powerful in situ mixed phosphane complex catalyst for anti-Markovnikov hydration of terminal alkynes.

The homoleptic complexes $[CpRu(L^n)_2(MeCN)]PF_6$ ($\mathbf{C^{nn}}$) were synthesized by ligand exchange from $[CpRu(\eta^6\text{-naphthalene})]PF_6$ (**A**) and 2 equiv of $L^n$ in acetonitrile (Scheme 1).[11] The heteroleptic complexes $[CpRu(L)(L')(MeCN)]PF_6$ ($\mathbf{C^{nn'}}$) were obtained by reaction of **A** with TRIPPYPHOS ($L^d$)[4] to give **B**[11] followed by substitution with either $L^a$,[3b,4b,12] $PPh_3$ ($L^e$), or $PBu_3$ ($L^f$).[11]

All of the complexes were amorphous or microcrystalline powders,[13] except for $C^{df}$, which gave crystals suitable for X-ray analysis (Figure 2).[14] The pyridine unit of its coordinated $L^d$ points away from the coordinated acetonitrile, the supposed site of the catalytic reaction after substitution of acetonitrile by the alkyne substrate.[15]

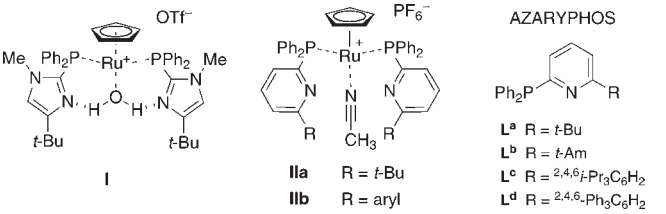
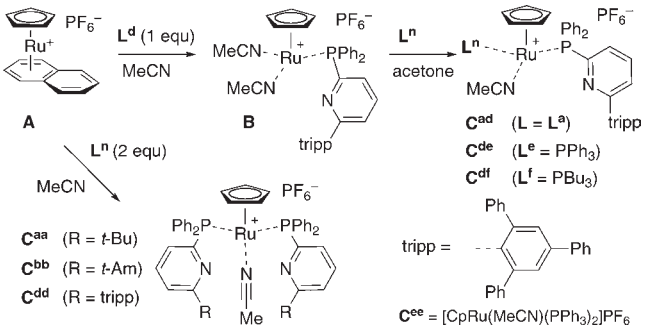



**Figure 1.** (left, center) Cationic $CpRu(PR_3)_2$ complexes **I**, **IIa**, and **IIb** displaying ambifunctional acceleration in catalytic anti-Markovnikov hydration of terminal alkynes. (right) AZARYPHOS ligands: $L^a$ = BUPYPHOS, $L^b$ = TAMPYPHOS, $L^c$ = ISIPHOS, $L^d$ = TRIPPYPHOS.

**Scheme 1. Synthesis of Homo- and Heteroleptic $[CpRu(L)_2(MeCN)]PF_6$ Complexes**




The hydration of 4-phenyl-1-butyne to 4-phenylbutanal was the reference reaction for recording reaction progress curves (Scheme 2). Catalytic runs with homoleptic complexes $C^{nn}$ at the 2 mol % level supported the earlier assumption[4a] of a ligand-size dependence of the rate of hydration, which increased as $C^{aa} \leq C^{bb} < C^{dd}$ (Figure 3, traces 4, 5, and 7). The binding of two phosphanes **L** to the $CpRu^+$ fragment was mandatory, since monophosphane complex **B** was hardly active (trace 2). In acetone, **B** exists as a P,N-chelate[11] in which the nitrogen lone pair is not accessible for ambifunctional interactions. Similarly, the complex $[CpRu(MeCN)(PPh_3)_2]PF_6$ ($C^{ee}$), which lacks a bifunctional ligand, was completely inactive (trace 1). We next

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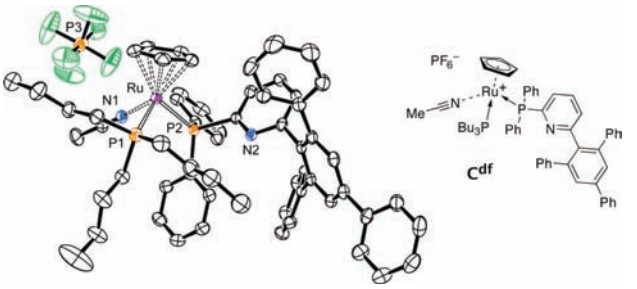
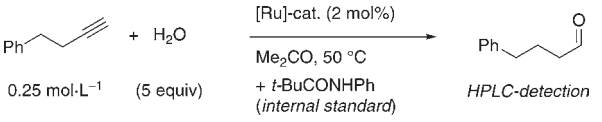



**Figure 2.** X-ray crystal structure of $\mathbf{C}^{\mathbf{df}}$: (left) thermal ellipsoid plot (50% probability; hydrogen atoms omitted) and (right) schematic drawing.

**Scheme 2. Reference Reaction for Hydration Kinetics**



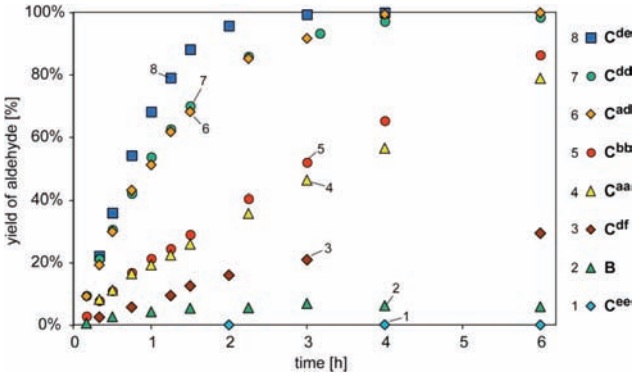
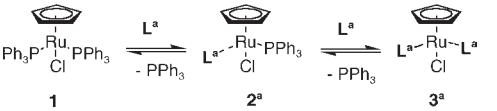




**Figure 3.** Catalytic anti-Markovnikov hydration of 4-phenyl-1-butyne to 4-phenylbutanal: HPLC reaction progress traces for catalyses with homoleptic ($\mathbf{C}^{\mathbf{nn}}$) and mixed ($\mathbf{C}^{\mathbf{nn}'}$) phosphane complexes.

investigated the catalytic activities of heteroleptic complexes with different AZARYPHOS ligands. Interestingly, the activity of $\mathbf{C}^{\mathbf{ad}}$ (trace 6), incorporating ligands $\mathbf{L}^{\mathbf{a}}$ and $\mathbf{L}^{\mathbf{d}}$, was *not* between those of $\mathbf{C}^{\mathbf{aa}}$ and $\mathbf{C}^{\mathbf{dd}}$ (traces 4 and 7) but closely matched that of the more active $\mathbf{C}^{\mathbf{dd}}$ (trace 7).

The stage was now set for the next, critical test of the catalytic activity of heteroleptic complexes $\mathbf{C}^{\mathbf{nn}'}$ in which one AZARYPHOS ligand was replaced by the nonfunctionalized phosphanes $PPh_3$ ($\mathbf{C}^{\mathbf{de}}$) and $PBu_3$ ($\mathbf{C}^{\mathbf{df}}$), which are devoid of functional groups for secondary interactions. Remarkably, both complexes retained catalytic activity, and whereas complex $\mathbf{C}^{\mathbf{df}}$ was a moderate catalyst (trace 3), the mixed complex $\mathbf{C}^{\mathbf{de}}$ containing $PPh_3$ was an excellent catalyst for anti-Markovnikov hydration of terminal alkynes (trace 8) whose activity slightly surpassed that of $\mathbf{C}^{\mathbf{dd}}$! Additional examples are shown in Figures S2 and S3 in the Supporting Information.[16] In parallel to the measurements presented in Figure 3, we also performed extended studies on the influence of various reaction parameters on the hydration kinetics of complex $\mathbf{C}^{\mathbf{dd}}$. The role of the *water concentration* is more complex than earlier assumed: previous experiments had employed 5 molar equiv of water in acetone solution.[3,4] This was

**Scheme 3. In Situ Complex Formation and Ligand Exchange**




an optimal choice because hydrations in the presence of 10 or 20 equiv of water proceeded at the same rate, indicating that saturation kinetics had been established. However, we found that the rate of hydration rose again when the water excess was increased to 37 or 56 equiv (Figure S4).[16] In the latter case, the reaction medium corresponded to a mixture of acetone and water in a 4:1 (v/v) ratio.[17] Another series of kinetic runs showed that *acetonitrile* is a competitive inhibitor of ruthenium-catalyzed alkyne hydration: the addition of merely 5 mol % MeCN decreased the reaction rate with catalyst $\mathbf{C}^{\mathbf{dd}}$ by a factor of 2.5 (Figure S5).[18] It is certainly unfortunate that the fragment $[CpRu(\mathbf{L})_2]^+$ in the catalyst precursor complexes **II** (= $\mathbf{C}^{\mathbf{nn}'}$) is bound to an inhibitor that diminishes its intrinsic catalytic activity. Finally, the effects of the counterion $X^-$ (added as 20 mol % $NBu_4X$) on the rate of hydration were determined: weakly coordinating ions such as $PF_6^-$ or tosylate ($TsO^-$) showed little effect, but the nucleophilic ions chloride and acetate inhibited the reaction (Figure S6). The observations from the kinetic measurements imply that a new and more powerful catalyst for anti-Markovnikov hydration of terminal alkynes should be obtained as follows: First, the catalyst complex should retain the $CpRu(PR_3)_2^+$ fragment but not include acetonitrile as coligand. Second, the catalyst may contain two AZARYPHOS ligands or a single AZARYPHOS ligand in combination with $PPh_3$ at ruthenium. Third, the catalyst should be cationic or readily ionize. Finally, the reaction medium should be rich in water. Most of those conditions were realized in a simple ligand exchange experiment in which equal amounts of $CpRuCl(PPh_3)_2$ (**1**) and $\mathbf{L}^{\mathbf{a}}$ were mixed in acetone-$d_6$: after 30 min at 60 °C, the solution gave rise to $^1H$ and $^{31}P$ NMR signals for **1** (28 mol %), $[CpRuCl(\mathbf{L}^{\mathbf{a}})(PPh_3)]$ (**2**$^{\mathbf{a}}$; 56 mol %), and $[CpRuCl(\mathbf{L}^{\mathbf{a}})_2]$ (**3**$^{\mathbf{a}}$; 16 mol %) (Scheme 3; also see Figure S8).[16]

Either species **2**$^{\mathbf{a}}$ or **3**$^{\mathbf{a}}$, which together account for 72 mol % of the ruthenium complex mixture (Table S1),[16] should be catalytically active, provided that dissociation of chloride occurs. In fact, our new in situ catalyst was obtained simply by mixing cocatalytic amounts of **1** and the ligand ISIPHOS ($\mathbf{L}^{\mathbf{c}}$)[19] in aqueous acetone at 60−70 °C prior to addition of the alkyne substrate. A halide-abstracting reagent was not necessary because the aqueous reaction medium aids in the dissociation of chloride.[20] Applications of the protocol are shown in Table 1.

The substrate scope is fairly broad: simple aliphatic (entry 1) and aromatic (entry 2) alkynes are readily transformed to corresponding aldehydes, as are substrates bearing alcoholic (entry 3) or acidic functions (entry 4). Carbonyl compounds (entry 5) or protected substrates with acid-sensitive (entries 6 and 8) or base-sensitive (entries 7 and 8) protecting groups are tolerated. Basic functionalities such as tertiary amines block the catalyst; however, catalytic hydration is still viable when the medium is buffered by addition of toluenesulfonic acid (entry 10). In several cases, we performed the reaction in a microwave reactor at 160 °C (entries 1b, 3b, 7b, and 8b); the reaction time was reduced to 2−15 min, and such conditions turned out to be beneficial for some substrates by minimizing the generation of byproduct in comparison with the regular reaction conditions


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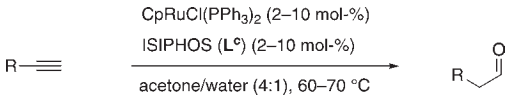
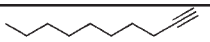
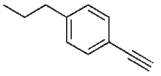
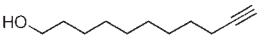
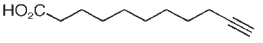
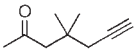
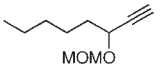
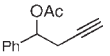
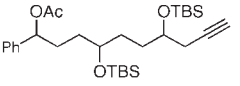
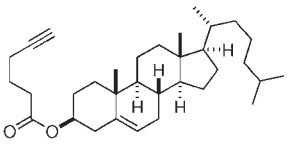
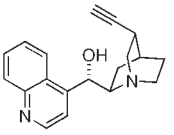
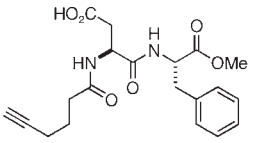
**Table 1. Substrate Scope of the $CpRuCl(PPh_3)_2$/ISIPHOS-Catalyzed Anti-Markovnikov Alkyne Hydration**[a]




| Entry | Substrate | Cat. [mol%] | Time [h] | Yield [%][b] |
|---|---|---|---|---|
| 1a |  | 2 | 18 | 99 |
| 1b[c] | | 2 | 0.25 | 93 |
| 2 |  | 2 | 17 | 87 |
| 3a |  | 2 | 3 | 94 |
| 3b[c] | | 2 | 0.25 | 96 |
| 4 |  | 2 | 3 | 97 |
| 5 |  | 4 | 4 | 96 |
| 6 |  | 5 | 20 | 55 |
| 7a |  | 2 | 4 | 92 |
| 7b[c] | | 2 | 0.03 | 99 |
| 8a[d] |  | 4 | 16 | 71 |
| 8b[c,e] | | 4 | 0.25 | 92 |
| 9[f] |  | 5 | 16 | 88 |
| 10[d,g] |  | 10 | 16 | 61 |
| 11 |  | 2 | 7 | 94[h] |

[a] Reactions (scale 0.25−2.0 mmol) were performed at 65 °C in 4:1 (v/v) acetone/water, concentration $c$ = 0.4 mol $L^{-1}$. [b] Yields of isolated products. [c] Reaction was performed at 160 °C (microwave heating). [d] $c$ = 0.2 mol $L^{-1}$. [e] $c$ = 0.1 mol $L^{-1}$. [f] $c$ = 0.025 mol $L^{-1}$. [g] With 1 equiv of *p*-TsOH as an additive. [h] The product was isolated as the 2,4-dinitrophenylhydrazone.

(entries 7b and 8b). Successful applications of the catalytic anti-Markovnikov hydration to structures of biological relevance (entries 9−11), including a peptidic substrate with a free carboxylic acid, two amide bonds, and an ester group (entry 11), underline the potential of this reaction for late-step transformations and as modification tool in bioorganic chemistry.

In conclusion, we have investigated the ruthenium-catalyzed anti-Markovnikov hydration of terminal alkynes by means of kinetic reaction progress curves and found that the mixed phosphane complexes $[CpRu(\mathbf{L})(\mathbf{L}')(MeCN)]PF_6$ ($\mathbf{C}^{\mathbf{nn}'}$), in which $\mathbf{L}^{\mathbf{n}}$ is a bifunctional heterocyclic phosphane and $\mathbf{L}'$ is a suitable nonfunctionalized placeholder phosphane ligand such as $PPh_3$, show high catalytic activity. This result implies that only *one* bifunctional ligand is involved in the postulated ambifunctional reaction mechanism[3,9,10] and that cooperative effects between the heterocyclic ligands **L** and $\mathbf{L}'$ in **C** are either not present or not kinetically relevant for the catalytic reaction. The hints obtained from the kinetic studies allowed us to the develop a new in situ mixed phosphane catalyst composed of cocatalytic amounts of the common precursor complex $CpRuCl(PPh_3)_2$ and an AZARYPHOS ligand such as ISIPHOS ($\mathbf{L}^{\mathbf{c}}$). The new in situ catalyst relies on readily available materials and displays high activity and functional group selectivity.

## ■ ASSOCIATED CONTENT

**Supporting Information.** Experimental procedures, spectral data for hydration products, additional examples and figures, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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## ■ ACKNOWLEDGMENT

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## ■ REFERENCES

(1) Reviews: (a) Hintermann, L.; Labonne, A. *Synthesis* **2007**, 1121. (b) Hintermann, L. *Top. Organomet. Chem.* **2010**, *31*, 123.

(2) (a) Tokunaga, M.; Wakatsuki, Y. *Angew. Chem., Int. Ed.* **1998**, *37*, 2867. (b) Suzuki, T.; Tokunaga, M.; Wakatsuki, Y. *Org. Lett.* **2001**, *3*, 735. (c) 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) Grotjahn, D. B.; Lev, D. A. *J. Am. Chem. Soc.* **2004**, *126*, 12232.

(4) (a) Labonne, A.; Kribber, T.; Hintermann, L. *Org. Lett.* **2006**, *8*, 5853. (b) Hintermann, L.; Dang, T. T.; Labonne, A.; Kribber, T.; Xiao, L.; Naumov, P. *Chem.—Eur. J.* **2009**, *15*, 7167.

(5) (a) Hintermann, L.; Kribber, T.; Labonne, A.; Paciok, E. *Synlett* **2009**, 2412. (b) Labonne, A.; Zani, L.; Hintermann, L.; Bolm, C. *J. Org. Chem.* **2007**, *72*, 5704. (c) Kribber, T.; Labonne, A.; Hintermann, L. *Synthesis* **2007**, 2809.

(6) Chevallier, F.; Breit, B. *Angew. Chem., Int. Ed.* **2006**, *45*, 1599.

(7) Nair, R. N.; Lee, P. J.; Rheingold, A. L.; Grotjahn, D. B. *Chem.—Eur. J.* **2010**, *16*, 7992.

(8) (a) Rowlands, G. J. *Tetrahedron* **2001**, *57*, 1865. (b) Muñiz, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 6622. (c) Ikariya, T.; Murata, K.; Noyori, R. *Org. Biomol. Chem.* **2006**, *4*, 393. (d) Natale, D.; Mareque-Rivas, J. C. *Chem. Commun.* **2008**, 425. (e) Grotjahn, D. B. *Dalton Trans.* **2008**, 6497. (f) Park, Y. J.; Park, J.-W.; Jun, C.-H. *Acc. Chem. Res.* **2008**, *41*, 222. (g) Kuwata, S.; Ikariya, T. *Chem.—Eur. J.* **2011**, *17*, 3542.

(9) Grotjahn, D. B. *Chem.—Eur. J.* **2005**, *11*, 7146.
(10) (a) Grotjahn, D. B. *Chem. Lett.* **2010**, *39*, 908. (b) Grotjahn, D. B.; Miranda-Soto, V.; Kragulj, E. J.; Lev, D. A.; Erdogan, G.; Zeng, X.; Cooksy, A. L. *J. Am. Chem. Soc.* **2008**, *130*, 20. (c) Grotjahn, D. B.; Kragulj, E. J.; Zeinalipour-Yazdi, C. D.; Miranda-Soto, V.; Lev, D. A.; Cooksy, A. L. *J. Am. Chem. Soc.* **2008**, *130*, 10860.
(11) Hintermann, L.; Xiao, L.; Labonne, A.; Englert, U. *Organometallics* **2009**, *28*, 5739.
(12) Hintermann, L.; Xiao, L.; Labonne, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 8246.
(13) All of the complexes $\mathbf{C}^{\mathbf{nn'}}$ were prepared in situ and characterized by $^{1}$H and $^{31}$P NMR spectroscopy and electrospray ionization mass spectrometry. Impurities due to homoleptic complexes amounted to less than 5% as determined by $^{31}$P NMR analysis.
(14) Coordinates have been submitted to the Cambridge Structural Database (CCDC 813354); also see the Supporting Information.
(15) The structure of $\mathbf{C}^{\mathbf{df}}$ provides no hints regarding potential secondary interactions between the ligand and a coordinated substrate; it probably does not correspond to a reactive conformation.
(16) See the Supporting Information for additional data.
(17) The acceleration is presumably due to a medium polarity effect that reduces the effects of ion pairing in the catalyst complex.
(18) Slow hydration of a cyanoalkyne has been ascribed to nitrile coordination (see ref 3b).
(19) ISIPHOS was preferred in the current study because it is readily prepared.[4b] Occasional reactions performed with ligands $\mathbf{L}^{\mathbf{a}}$ and $\mathbf{L}^{\mathbf{d}}$ (which are commercially available) were also successful.
(20) The chloro complex CpRuCl$(\mathbf{L}^{\mathbf{a}})_2$ was 10 times less active than the cationic complex $\mathbf{C}^{\mathbf{aa}}$ in acetone,[8e] but chloride inhibition was largely absent in the water-rich reaction medium used with our catalyst.