Homogeneous Catalysis **Hot Paper**

DOI: 10.1002/anie.201404320

Broad-Spectrum Catalysts for the Ambient Temperature Anti-Markovnikov Hydration of Alkynes**

*Le Li, Mingshuo Zeng, and Seth B. Herzon**

Abstract: *Anti-Markovnikov alkyne hydration provides a valuable route to aldehydes. Half-sandwich ruthenium complexes ligated by 5,5′-bis(trifluoromethyl)-2,2′-bipyridine are remarkably active for this transformation. In the presence of 2 mol % metal, a wide range of functionalized aliphatic and aromatic alkynes are hydrated in high yield at ambient temperature.*

The discovery of highly active catalysts for the anti-Markovnikov hydration of terminal alkynes (**1**→**2**, Figure 1), a powerful transformation that provides an atom-economical[1] and redox-neutral entry to aldehydes, is reported.[2] These reactions proceed by the addition of water to metal vinylidene intermediates.[3] The first catalysts developed for this reaction, discovered by Wakatsuki and Tokunaga, consisted of η^6-arene[4] or η^5-cyclopentadienyl[5] complexes of ruthenium ligated by electron-deficient mono- or bidentate phosphine ligands (see **3** and **4**). These complexes required elevated temperatures and up to 10% metal loadings to obtain useful reaction rates. Contemporaneous with the disclosure of **4**, Grotjahn reported that cationic complexes containing *P*, *N*-ligands, such as **5**[6] and **6**,[7] displayed increased activity at lower temperatures (45–70 °C) and broader scope. In a series of detailed mechanistic studies, it was established that the dramatic rate enhancements observed with **5** and **6** derive from the generation of a hydrogen-bonding network that facilitates vinylidene formation and nucleophilic addition.[8] Subsequently, Hintermann and co-workers showed that mixed phosphine catalysts such as **7** also displayed high hydration activity.[9] Breit and Chevallier reported that the catalyst **8**, which contains a self-assembled diphosphine ligand, displayed good substrate scope, but elevated temperatures were required to obtain high yields (120 °C).[10]

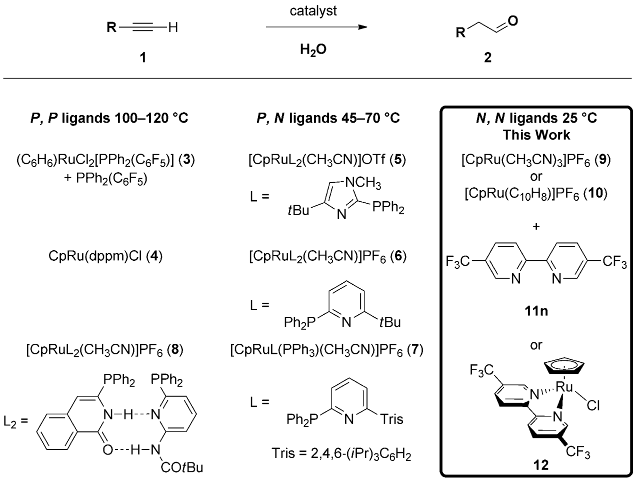


Figure 1. Prior catalysts for anti-Markovnikov alkyne hydration and the catalyst precursors and ligand employed herein.

The catalysts **6** and **7** efficiently hydrate unhindered aliphatic alkynes, but arylacetylenes and hindered aliphatic alkynes require extended heating to obtain high conversion. In addition, hydrations of propargylic alcohols and conjugated enynes are complicated by competitive rearrangement[11] or elimination, and the elevated reaction temperatures and Lewis acidity of the catalysts promote aldol addition reactions. We recently discovered[12] that a catalyst derived from (η^5-cyclopentadienyl) tris(acetonitrile)ruthenium hexafluorophosphate (**9**) or (η^5-cyclopentadienyl) (η^6-naphthalene)ruthenium hexafluorophosphate (**10**) and 2, 2′-bipyridine (bipy, **11a**) mediated the sequential hydration and hydrogenation of aliphatic and aromatic alkynes (reductive hydration), to provide linear alcohols, at 55–80 °C. The discovery that the hydration step could be promoted by this catalyst was surprising in light of the structures of **3**–**8**, which all contain phosphine-based ligands, and Grotjahn's comprehensive mechanistic model, which established the multifunctional role of the (2-heteroaryl)phosphine ligands in the most active catalysts **5**–**7**.[8] As many air-stable bipyridine ligands are commercially available or readily prepared, further study of our catalyst system seemed warranted. Herein we report that complexes formed in situ from **9** or **10** and 5,5′-bis(trifluoromethyl)-2,2′-bipyridine (**11n**) are remarkably active for anti-Markovnikov alkyne hydration. A broad range of aliphatic and aromatic alkynes are hydrated within 8–24 h at 25 °C and at 2 mol % metal loadings. The rate of hydration of aromatic alkynes is faster than aliphatic alkynes, which is in contrast to the trend observed with earlier catalysts. The catalyst can be employed at less than 1 mol % metal loadings on preparative scales, and an air-stable, single-component precursor (**12**) has been developed.

To assess the influence of ligand substituents on hydration activity, we evaluated catalysts formed in situ from **9** and a wide array of bidentate nitrogen ligands based on the bipy structure, using (2-fluorophenyl)acetylene (**1a**) as substrate at

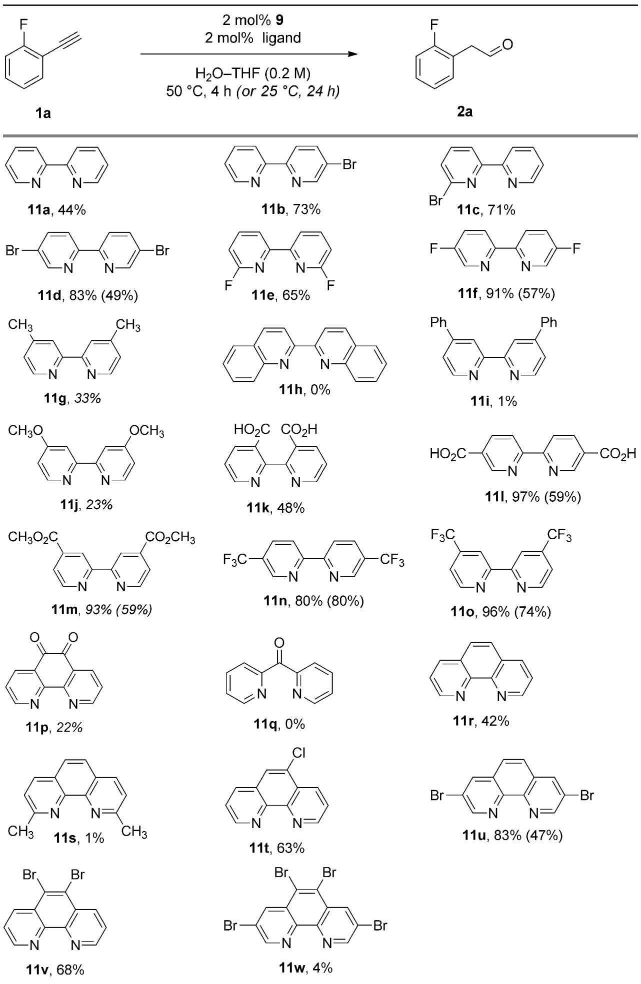
---

[*] Dr. L. Li, M. Zeng, Dr. S. B. Herzon
Department of Chemistry, Yale University
225 Prospect Street, New Haven, CT 06520-8107 (USA)
E-mail: seth.herzon@yale.du

[**] Financial support from the David and Lucile Packard Foundation is gratefully acknowledged. We thank Dr. Brandon Mercado for X-ray analysis of **12**.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201404320.

Table 1: Evaluation of bidentate nitrogen ligands in the hydration of **1a**.[a]



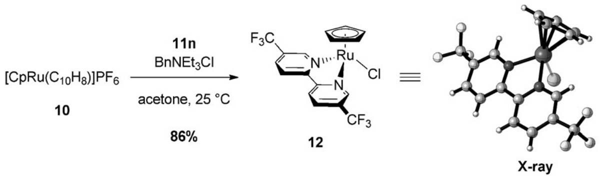
[a] All reactions were conducted on a 500 μmol scale. Yields in parentheses are after 24 h at 25 °C. Yields were determined by ^{1}H NMR analysis using mesitylene as an internal standard.

50 °C (Table 1). These experiments revealed a broad range of activities. Ligands with sterically demanding substituents near the nitrogen atoms, such as **11h** and **11s**, were inactive (≤ 1 % yield). This may be due to inefficient coordination of the substrate to the ruthenium center. Electron-rich ligands such as **11g** and **11j** also displayed poor activity (33 % and 23 % for **11g** and **11j**, respectively, versus 44 % for bipy, **11a**). Electron-deficient ligands displayed good to excellent activity, with the bromo-, fluoro- carboxy-, carbomethoxy-, and trifluoromethyl-substituted ligands **11d**, **11u**, **11f**, **11l**, **11m**, **11n**, and **11o** all providing good to excellent yields of **2a** (80–97 % yield). These latter ligands were further evaluated at 25 °C (yield in parentheses). This second set of experiments revealed complexes derived from 5,5′-bis(trifluoromethyl)-2,2′-bipyridine (**11n**) as the most active at 25 °C. Using 2 mol % of **9** and **11n**, an 80 % yield of (2-fluorophenyl)acetaldehyde (**2b**) was obtained after 24 h at 25 °C.

Additional experiments revealed a useful rate enhancement when tetrahydrofuran was replaced with *N*,*N*-dimethylformamide (DMF), *N*,*N*-dimethylacetamide (DMA), or *N*-methyl-2-pyrolidinone (NMP, see Table S1 in the Supporting Information). In the presence of 2 mol % each of **9** and **11n**, the yields of product **2a** were 93 %, 97 %, and 94 % in NMP, DMF, and DMA, respectively, after 6 h at 25 °C. The initial rates were also faster (72 %, 64 %, and 68 % yield of **2a** after 3 h for NMP, DMF, and DMA, respectively). The yields of product correlated with the solvent dielectric constant,[13] and may reflect an increase in the rate of vinylidene formation.[14]

A wide array of alkynes undergo hydration at ambient temperature using the combination of **9** and **11n** in aqueous NMP (Table 2). With the exception of **2n**, the yields of each product obtained by NMR spectroscopy and after purification (number in parentheses) are reported. High yields were obtained within 24 h using 2 mol % catalyst, and most arylacetylene substrates proceeded to full conversion within 8 h. *Ortho*-, *meta*-, and *para*-substituted arylacetylenes, which require elevated temperatures with existing catalysts, are efficiently converted to product at ambient temperature (**2a**–**2j**, 80–91 %). In addition, the unsubstituted aliphatic alkynes **2k**, **2l**, and **2m** also gave high yields of product (81–95 %) after 24 h. *tert*-Butylacetylene, which is a particularly challenging substrate for the hydration reaction,[5a] provided a 73 % yield of 3,3-dimethylbutanal (**2n**) after 48 h (90 % yield after 72 h). A range of functional groups are compatible with this catalyst, including alkyl chlorides (**2o**), imides (**2p**), alcohols (**2q**), amines (**2r**), ketones (**2s**), esters (**2t**), amides (**2u**, **2z**), and carboxylic acids (**2v**, 82–98 %). Aldehydes derived from enynes (**2w**–**2aa**), including a conjugated enyne (**2aa**), could be effectively prepared using this catalyst (80–96 %). Complexes related to **5** and **6** are remarkably active catalysts for the isomerization of terminal alkenes[15] whereas isomerization of the terminal alkene in **2w** is not observed using the catalyst derived from **9** and **11n**. In addition, the dial **2ab** is formed in 87 % yield from the corresponding diyne. It is also noteworthy that β-amino or β-hydroxy aldehydes could be prepared with this catalyst (**2ac**–**2af**, 76–96 %). Unsaturated aldehydes, which are major side products formed in reactions employing **6** and **7**,[16] were produced in only minor amounts (4 % for **2ae** and 15 % for **2af**).

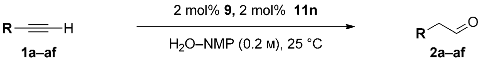
To increase the practical utility of this chemistry, we developed an air-stable, single component catalyst for this transformation [Eq. (1)].

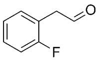
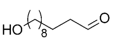
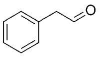
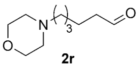
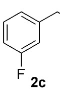
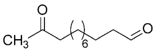
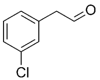
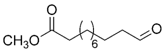
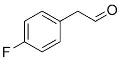
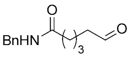
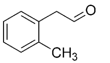
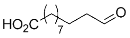
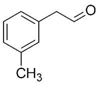
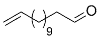
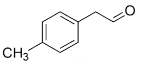
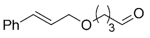
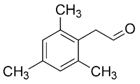
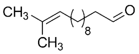
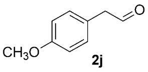
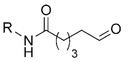
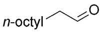
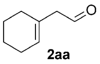
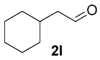
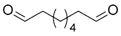
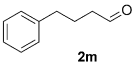
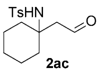
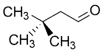
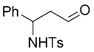
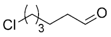
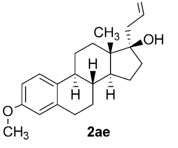
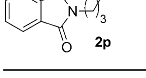
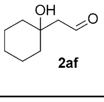


(1)

Stirring an equimolar mixture of **10**, **11n**, and benzyltriethylammonium chloride in acetone at 25 °C formed the ruthenium complex **12** in 86 % yield. The complex **12** was isolated by precipitation of benzyltriethylammonium hexafluorophosphate, followed by concentration of the mother liquor and washing of the solid residue obtained (hexanes) to remove naphthalene. Notably, all of these manipulations were conducted on the benchtop under air, using reagent-grade (non-deoxygenated) solvents. As shown below, the catalyst **12** also

Table 2: Substrate scope of the hydration reaction.[a]



Product	t [h]	Yield[b]	Product	t [h]	Yield[b]
 **2a**	8	86 % (82 %)	 **2q**	24	91 % (87 %)
 **2b**	8	80 % (76 %)	 **2r**	24	88 %[c,d] (82 %)
 **2c**	8	83 % (77 %)	 **2s**	24	96 % (90 %)
 **2d**	8	83 % (77 %)	 **2t**	24	98 % (91 %)
 **2e**	8	88 % (82 %)	 **2u**	24	82 %[c] (77 %)
 **2f**	8	91 % (85 %)	 **2v**	24	93 % (84 %)
 **2g**	8	88 % (82 %)	 **2w**	24	85 %[c] (80 %)
 **2h**	8	87 % (81 %)	 **2x**	24	80 %[c,e] (75 %)
 **2i**	24	87 % (80 %)	 **2y**	24	82 % (76 %)
 **2j**	8	89 % (84 %)	 **2z** (R=$C_{10}H_{17}$)	24	96 %[c] (86 %)
 **2k**	24	95 % (90 %)	 **2aa**	24	82 % (76 %)
 **2l**	24	81 % (77 %)	 **2ab**	24	87 %[c] (81 %)
 **2m**	24	94 % (90 %)	 **2ac**	24	96 %[c] (87 %)
 **2n**	48 72	73 % 90 %	 **2ad**	24	87 %[c] (81 %)
 **2o**	24	93 % (86 %)	 **2ae**	24	92 %[c] (80 %)
 **2p**	24	96 % (92 %)	 **2af**	24	76 %[c,e,f] (70 %)

[a] 500 µmol scale, H_2O–NMP (1:4 v/v). [b] NMR yield obtained using mesitylene as an internal standard. Isolated yield after purification by flash-column chromatography in parentheses. [c] Reactions conducted on a 250 µmol scale with 4.5 mol% catalyst. [d] 1 equiv PTSA was used. [e] Reactions were conducted in 0.4 M aqueous NMP. [f] **11 a** was used instead of **11 n**; 1.5 equiv acetic acid, with respect to **2af**, was employed.

displays high activity in the hydration reaction and constitutes a useful, air-stable precursor for this transformation.

The hydrations of (2-fluorophenyl)acetylene (**1a**) and 4-fluoro-dec-1-yne (**1ag**) were monitored continuously by ^{19}F NMR spectroscopy using the catalyst derived from **9** and **11n**, **6**, and **12** at 25 °C (Figure 2). In all cases 2 mol% of the metal precursor and ligand were employed. Using **9** and **11n**, the hydration of **1a** proceeded in > 99% yield after 7.6 h, and the hydration of **1a** employing **12** proceeded to 82% yield after 10 h. The activity of **12** was unchanged after storing under air for one week at 25 °C. By comparison, using catalyst **6** (in 4:1 acetone–water),[17] the hydration of **1a** proceeded to only 6% yield after 13 h. In the aliphatic series, the hydration of **1ag** proceeded to 88% yield after 13 h using **9** and **11n**, while the same reaction proceeded to 40% yield after 13 h using **6**. The hydration of **1ag** using **12** proceeded to only 50% yield after 13 h, indicating a lower reactivity of this preformed catalyst toward aliphatic alkynes.

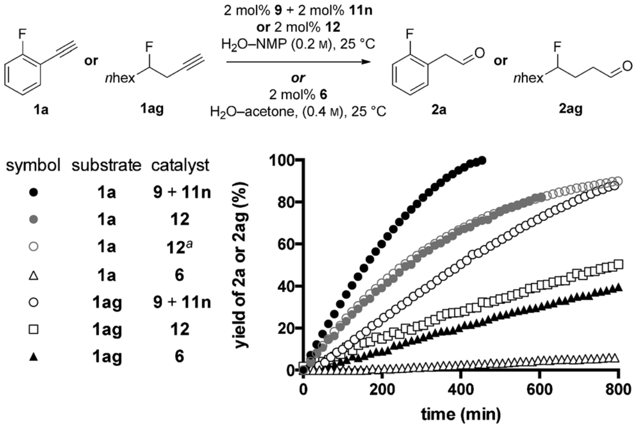
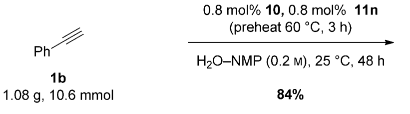


Figure 2. Comparison of the hydration activity of **9** + **11 n**, **6**, and **12.** Conditions: **1 a** or **1 ag** (300 µmol), **9** + **11 n** (6 µmol each), H_2O-NMP (1:4 v/v, 0.2 M), 25 °C; **1 a** or **1 ag** (300 µmol), **6** (6 µmol), H_2O–acetone (1:4 v/v, 0.4 M), 25 °C; **1 a** (300 µmol), **12** (6 µmol), H_2O–NMP (1:4 v/v, 0.2 M), 25 °C. [a] Employing catalyst that had been aged for one week under air at 25 °C.

Finally, we conducted the hydration of phenylacetylene (**1b**) using 0.8 mol% of the air-stable precursor **10** and 0.8 mol% of the ligand **11n** on a 10.6 mmol scale [Eq. (2)]. Employing **10** requires preheating of the ligand and the ruthenium precursor (60 °C, 3 h). In this experiment, an 84% yield of **2b** was obtained after 48 h at 25 °C.



(2)

In summary, we have described a comprehensive evaluation of the activities of catalysts derived from the (η^5-cyclopentadienyl)ruthenium fragment and bidentate nitrogen-based ligands for anti-Markovnikov alkyne hydration. These studies led to the identification of the electron-deficient bipyridine ligand **11n** as most effective. A broad array of aliphatic and aromatic alkynes are hydrated at 25 °C using 2 mol% of the ruthenium precursor **9** and ligand **11n**. For many substrates, the hydration is complete within 8 h. The rate of hydration of aromatic alkynes is faster than aliphatic alkynes using **9** and **11n**, which is opposite to the trend observed with earlier hydration catalysts. A single-component, air-stable catalyst precursor (**12**) has been developed, although the activity of this catalyst toward aliphatic substrates is lower than **9** + **11n**. Finally, the reaction may be conducted on preparative scales with low (0.8 mol%) catalyst loadings. These catalysts display the highest efficiencies and broadest scope of any reported to date, and the mild, practical conditions of the transformation should promote application of this chemistry.[18]

Experimental Section

Representative procedure for the hydration of **1a** employing **9** and **11n**: In a nitrogen-filled drybox, a 4 mL vial was charged sequentially with 5,5′-bis(trifluoromethyl)-2,2′-bipyridine (**11n**, 2.9 mg, 10 μmol, 0.020 equiv), tris(acetonitrile) (η^5-cyclopentadienyl)ruthenium hexafluorophosphate (**9**, 4.4 mg, 10 μmol, 0.020 equiv), a mixture of water-*N*-methyl-2-pyrrolidinone (1:4 v/v, 2.5 mL, deoxygenated by sparging with nitrogen for 30 min), and (2-fluorophenyl)acetylene (**1a**, 60.0 mg, 500 μmol, 1 equiv). The vial was sealed with a Teflon-lined cap and the sealed vial was removed from the drybox. The mixture was stirred for 8 h at 25 °C. The product mixture was transferred to a separatory funnel and diluted with ethyl acetate (20 mL). The organic layer was washed with brine (3 × 20 mL). Mesitylene (40.0 μL, 288 μmol) was added to the washed organic layer, and an aliquot of this mixture (1 mL) was removed and diluted with chloroform-*d* (2.0 mL). The diluted mixture was transferred to an NMR tube and analyzed by ^{1}H NMR spectroscopy, which indicated an 86% yield of **2a**. To obtain an isolated yield, the NMR sample was combined with the remaining ethyl acetate layer and the combined solution was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 1% ethyl acetate–hexanes initially, grading to 2% ethyl acetate-hexanes, one step) to provide (2-fluorophenyl)acetaldehyde (**2a**) as a clear, colorless oil (56.6 mg, 82%).

Representative procedure for the hydration of **1b** employing **10** and **11n**: A 100 mL round-bottomed flask fused to a Teflon-coated valve was charged sequentially with (η^5-cyclopentadienyl) (η^6-naphthalene)ruthenium hexafluorophosphate (**10**, 37.3 mg, 84.8 μmol, 0.008 equiv), 5,5′-bis(trifluoromethyl)-2,2′-bipyridine (**11n**, 24.8 mg, 84.8 μmol, 0.008 equiv), and a Teflon-coated stirbar. The headspace in the reaction vessel was purged with nitrogen for 15 min. *N*-Methyl-2-pyrrolidone (42 mL, deoxygenated by sparging with nitrogen for 30 min) and water (11 mL, deoxygenated by sparging with nitrogen for 30 min) were then added in sequence to the flask via syringe. The Teflon-coated valve was sealed, and the solution was stirred and heated for 3 h at 60 °C. The dark purple mixture that formed was cooled to 25 °C. Phenylacetylene (**1b**, 1.20 mL, 10.6 mmol, 1.00 equiv) was added via syringe, and the resulting mixture was stirred for 48 h at 25 °C. The product mixture was poured into a separatory funnel and diluted with saturated aqueous sodium chloride solution (100 mL). The diluted solution was extracted with ethyl acetate (3 × 50 mL). The organic layers were combined and the combined organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 30% ethyl acetate–hexanes initially, grading to 50% ethyl acetate–hexanes, two steps) to afford phenylacetaldehyde (**2b**) as a yellow oil (1.07 g, 84%).

Received: April 14, 2014

Keywords: alkynes · bipyridines · homogeneous catalysis · hydration · ruthenium

---

[1] B. M. Trost, *Science* **1991**, *254*, 1471.

[2] For reviews of metal-catalyzed addition of oxygen-based nucleophiles to alkenes and alkynes, see: a) M. Beller, J. Seayad, A. Tillack, H. Jiao, *Angew. Chem.* **2004**, *116*, 3448; *Angew. Chem. Int. Ed.* **2004**, *43*, 3368; b) L. Hintermann, A. Labonne, *Synthesis* **2007**, 1121; c) L. Hintermann, *Top. Organomet. Chem.* **2010**, *31*, 123.

[3] a) C. Bruneau, P. H. Dixneuf, *Acc. Chem. Res.* **1999**, *32*, 311; b) C. Fischmeister, C. Bruneau, P. H. Dixneuf in *Ruthenium in Organic Synthesis* Wiley-VCH, Weinheim, **2004**, p. 189; c) B. M. Trost, M. U. Frederiksen, M. T. Rudd, *Angew. Chem.* **2005**, *117*, 6788; *Angew. Chem. Int. Ed.* **2005**, *44*, 6630.

[4] M. Tokunaga, Y. Wakatsuki, *Angew. Chem.* **1998**, *110*, 3024; *Angew. Chem. Int. Ed.* **1998**, *37*, 2867.

[5] a) T. Suzuki, M. Tokunaga, Y. Wakatsuki, *Org. Lett.* **2001**, *3*, 735; b) M. Tokunaga, T. Suzuki, N. Koga, T. Fukushima, A. Horiuchi, Y. Wakatsuki, *J. Am. Chem. Soc.* **2001**, *123*, 11917.

[6] D. B. Grotjahn, C. D. Incarvito, A. L. Rheingold, *Angew. Chem.* **2001**, *113*, 4002; *Angew. Chem. Int. Ed.* **2001**, *40*, 3884.

[7] D. B. Grotjahn, D. A. Lev, *J. Am. Chem. Soc.* **2004**, *126*, 12232.

[8] a) D. B. Grotjahn, V. Miranda-Soto, E. J. Kragulj, D. A. Lev, G. Erdogan, X. Zeng, A. L. Cooksy, *J. Am. Chem. Soc.* **2008**, *130*, 20; b) D. B. Grotjahn, E. J. Kragulj, C. D. Zeinalipour-Yazdi, V. n. Miranda-Soto, D. A. Lev, A. L. Cooksy, *J. Am. Chem. Soc.* **2008**, *130*, 10860; For a review, see: c) D. B. Grotjahn, *Pure Appl. Chem.* **2010**, *82*, 635.

[9] a) A. L. Labonne, T. Kribber, L. Hintermann, *Org. Lett.* **2006**, *8*, 5853; b) L. Hintermann, T. T. Dang, A. Labonne, T. Kribber, L. Xiao, P. Naumov, *Chem. Eur. J.* **2009**, *15*, 7167; c) F. Boeck, T. Kribber, L. Xiao, L. Hintermann, *J. Am. Chem. Soc.* **2011**, *133*, 8138.

[10] F. Chevallier, B. Breit, *Angew. Chem.* **2006**, *118*, 1629; *Angew. Chem. Int. Ed.* **2006**, *45*, 1599.

[11] S. Swaminathan, K. V. Narayanan, *Chem. Rev.* **1971**, *71*, 429.

[12] L. Li, S. B. Herzon, *Nat. Chem.* **2014**, *6*, 22.

[13] J. A. Kerr in *CRC Handbook of Chemistry and Physics*, 79edth ed(Ed.: D. R. Lide), CRC, New York, **1998**, p. 8.120.

[14] a) R. M. Bullock, *J. Chem. Soc. Chem. Commun.* **1989**, 165; b) M. Jiménez-Tenorio, M. C. Puerta, P. Valerga, M. A. Ortuño, G. Ujaque, A. Lledós, *Inorg. Chem.* **2013**, *52*, 8919.

[15] D. B. Grotjahn, C. R. Larsen, J. L. Gustafson, R. Nair, A. Sharma, *J. Am. Chem. Soc.* **2007**, *129*, 9592.

[16] L. Hintermann, T. Kribber, A. Labonne, E. Paciok, *Synlett* **2009**, 2412.

[17] The catalyst **6** is inactive in aqueous NMP. A 4:1 ratio of acetone:water was employed to emulate the concentrations of water in experiments employing **9** + **11a** and **12**. An excess of water has been shown to increase the rate of hydration by catalysts related to **6**, see Ref. [9c].

[18] The ligand **11n** and the complex **12** will soon be commercially-available from Aldrich (catalog numbers L512346 and 794120, respectively).