Heterogeneous & Homogeneous & Bio- & Nano-

CHEMCATCHEM

CATALYSIS

Accepted Article

Title: Discovery and Comparison of Homogeneous Catalysts in a Standardized HOT-CAT Screen with Microwave-Heating and qNMR Analysis: Exploring Catalytic Hydration of Alkynes

Authors: Matthias Schreyer, Tobias M. Milzarek, Marcus Wegmann, Andreas Brunner, and Lukas Hintermann

To be cited as: *ChemCatChem* 10.1002/cctc.201900456

Link to VoR: http://dx.doi.org/10.1002/cctc.201900456

A Journal of

ChemPubSoc Europe

WILEY-VCH

www.chemcatchem.org

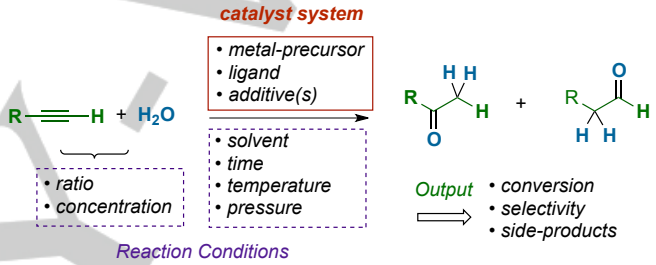
Discovery and Comparison of Homogeneous Catalysts in a Standardized HOT-CAT Screen with Microwave-Heating and qNMR Analysis: Exploring Catalytic Hydration of Alkynes

Matthias Schreyer,[a,b] Tobias M. Milzarek,[a] Marcus Wegmann,[a,b] Andreas Brunner[a] and Lukas Hintermann*[a,b]

Abstract: A HOT-CAT (*homogeneous thermal catalysis*) screen using microwave-heating and quantitative NMR (qNMR) analysis has been developed for identification and comparison of catalyst activity in homogeneous metal-based catalysis. The hydration of terminal alkynes to ketones or aldehydes served as a model reaction in this proof-of-concept study. Key aspects of the screen are the use of a high-temperature setting (e.g., 160 °C) at a fixed, short reaction time (e.g., 15 min) for all samples. Analysis of crude reaction mixtures by a standardized, quantitative ^{1}H NMR protocol gives a comprehensive picture of catalyst chemo- and regioselectivity, which permits broad comparisons and the discovery of non-target reactivity. For catalytic alkyne hydration, data for 105 runs involving 81 catalyst systems with 15 different metals is presented. The activity of all established catalyst systems was reproduced, and new catalyst systems with Markovnikov hydration selectivity were discovered and applied to preparative runs, namely Cu_2O–CSA (CSA = camphorsulfonic acid), $Co(OAc)_2$–tetraphenylporphyrin–CSA and [IrCl(COD)]–CSA.

Introduction

The identification of new catalysts for synthetic transformations is important for progress in synthetic organic chemistry.[1] Any new catalytic system that displays unique activity and selectivity patterns may help solving a specific synthetic problem. In searching new catalysts for an organic transformation one is first faced with choosing reaction conditions by defining relevant parameters for variables like temperature, pressure, solvent, reactant ratios, concentration and reaction time.[2] Limiting the discussion to homogeneous, metal-complex-catalyzed reactions, one will subsequently generate a potential catalyst by combining a metal precursor, steering ligand and various co-catalytic additives.[3] Such substance variables and their relative settings (ratios) define a catalyst system, whereas catalyst loading is rather a reaction condition.[4] Considering the large number of independent variables and parameter settings, the *de novo* search for a catalyzed reaction can be inherently complex, even for a predefined target transformation.[2a,5]



Scheme 1. General scheme of a catalyzed transformation (alkyne hydration). The reaction system is defined by setting parameters for general reaction conditions (variables), and for the subset of variables that make up the catalyst system. Each parameter setting affects the reaction output, measured as product composition and expressed in derived quantities.

Over the past years we have observed the development process for homogeneous catalytic hydration of alkynes to carbonyl compounds for application in organic synthesis.[6,7] In new research papers on alkyne hydration catalysts, there often is a common structure:[8] (I) A potential new catalyst system is proposed based on a mechanistic hypothesis or by analogy to established catalysts. (II) A screening with a suitable assay is performed, i.e. a suitable model reaction, whose product is readily detected, is performed in the presence of the potential catalyst. (III) Catalysis is confirmed through analysis or isolation of a target product in quantities exceeding those found in blank reactions. (IV) Key parameters of the single most promising catalyst system are optimized in a focused screen, until the model reaction reaches a satisfactory product yield. (V) The new catalyst system is applied to a selection of diversely co-functionalized substrates, with parameter settings optimized for the model substrate, and product yields are recorded as (exclusive) indicators of efficiency.

Certain aspects of this operation mode seem unsatisfactory: a) Restricting a study to a single type of catalyst system avoids recognizing interdependencies between chemically different, but related catalyst systems; b) optimizing a reaction to the maximal yield of a model target, while disregarding the nature and amount of side-products formed, ignores selectivity aspects and limits the predictive value of optimization data; c) the common

[a] Dr. M. Schreyer, T. M. Milzarek, Dr. M. Wegmann, Dr. A. Brunner, Prof. Dr. L. Hintermann
Technische Universität München, Department Chemie,
Lichtenbergstr. 4, 85748 Garching bei München, Germany

[b] Dr. M. Schreyer, Dr. M. Wegmann, Prof. Dr. L. Hintermann
TUM Catalysis Research Center, Ernst-Otto-Fischer-Str. 1, 85748 Garching bei München, Germany

E-mail: lukas.hintermann@tum.de
http://www.oca.ch.tum.de

Supporting information for this article is given via a link at the end of the document

approach to run a reaction to consumption of the starting material (at variable reaction times), or the failure to quantify unreacted starting material (at fixed reaction times), render comparisons among catalyst systems difficult, because the target yield intertwines activity and selectivity aspects (Figure 1).

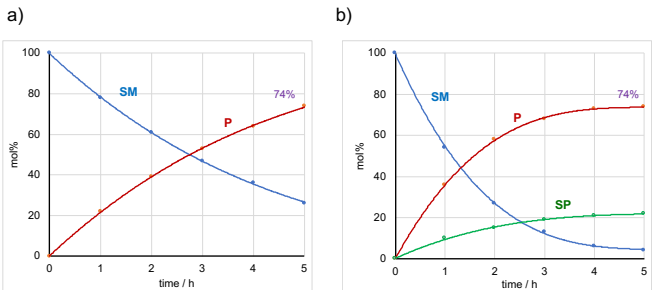


Figure 1. Two hypothetical, catalyzed reactions of starting material (**SM**) to product (**P**): a) Highly selective catalyst with low activity. b) More active, but less selective catalyst, generating side-product(s) (**SP**). The two cases are indistinguishable by a single-point yield determination of **P** after 5 h.

We now present a case-study in catalyst-screening that aims at collecting comprehensive information on catalyst activity and selectivity for a specific model reaction. Widely differing catalyst systems will be compared by activity and selectivity, based on a standardized experimental procedure. The kind of information we want to obtain is that usually found in a review article, where it is normally compiled from various individual studies and where direct comparisons are not possible, since all studies covered tend to use different model reactions and reaction conditions.

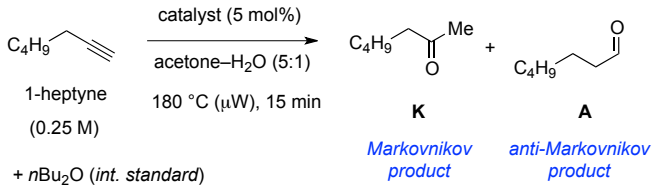
The reaction in case is catalytic hydration of terminal alkynes to aldehydes or ketones (Scheme 1).[6] This transformation is of synthetic interest, involves a fundamental selectivity (Markovnikov vs. anti-Markovnikov regioselectivity) and has already been catalyzed by a number of metal- and other element-based species. Our 2007 review listed catalytic activities for Brønsted acids, enzymes, Hg, other metals (Ce, W; Fe; Ru, Rh, Ir, Pd, Pt, Cu, Ag, Au, Zn, Cd, Tl) and a half-metal (Te). In total, hydration activity was listed for catalysts based on *ca.* 17 elements.[6] Over the past 12 years, alkyne hydration activity has been reported for additional elements (Ca,[9] Co,[10,11] Ga,[8c] In,[12] Tm,[8d] Yb,[8c] Sc,[8c] Bi,[8a] Y,[8a] Eu,[8a] La,[8a] Sn[8e]) while one reported activity has been refuted (W).[13] Many more new catalyst systems have been described for elements with previously established activity, the frequency of reports following the order Au >> Cu, Ag > Pt, Ru, Fe, Pd. We now wish to explore a generalized, systematic activity screening that can be applied to any type of potential alkyne hydration catalysts, and which will provide information on the relative activity and selectivity of each catalyst. As a secondary aim, we hope to find new and practically useful catalyst systems for alkyne hydration with either Markovnikov or anti-Markovnikov selectivity.

Results

Definition of the screening procedure and conditions. The reaction temperature in a comparative catalyst screening can be set to the lowest value for achieving notable, yet incomplete conversions. Relative catalyst activities are then derived by comparing the yield of target product after a fixed reaction time.[14] If a highly active catalyst emerges from the screening, the temperature setting may be lowered or the catalyst loading reduced for further optimization.[14,15] We have defined a different HOT-CAT (homogeneous thermal catalysis) approach for catalysis screening, where catalytic reactions are screened in a microwave reactor at deliberately high temperature settings.[16,17] Reaction times are fixed at short duration (15–30 min) to allow for serial experiments in a mono-mode reactor with auto-sampler. A boundary condition of our screen is that the desired catalytic activity will be scarce. Detecting the desired activity at all is a priority, no matter if it is high or low. An inherent assumption of our approach is that low activity catalysts will be easier to detect at a very high temperature setting. More active catalysts tend to show activity well above their usual temperature optimum and will therefore also be detected in the screen. *We propose that the HOT-CAT approach is most suited to detect catalytic activity with the least number of (e.g., a single) experiments*. The second key aspect of our approach is *quantification of all relevant reaction components to define catalyst selectivity*. For efficiency, analysis should be limited to a single measurement, which places restrictions on the model reaction and suitable analytical techniques.

In short, we wish to perform a fast, efficient screening for new catalytic reactivity under HOT-CAT conditions in a microwave-reactor, use a deliberately high reaction temperature at a fixed, short reaction time and gain comparative information on a large number of catalyst systems, their relative activity, chemo- and stereoselectivity, through quantitative product analysis. Questions to be answered are: is the HOT-CAT approach viable for new catalyst discovery? Does it reproduce known catalytic activity under screening conditions to validate the approach? Can we detect new catalysts for a defined model reaction? Will unexpected new catalytic activity towards unpredicted products be found?

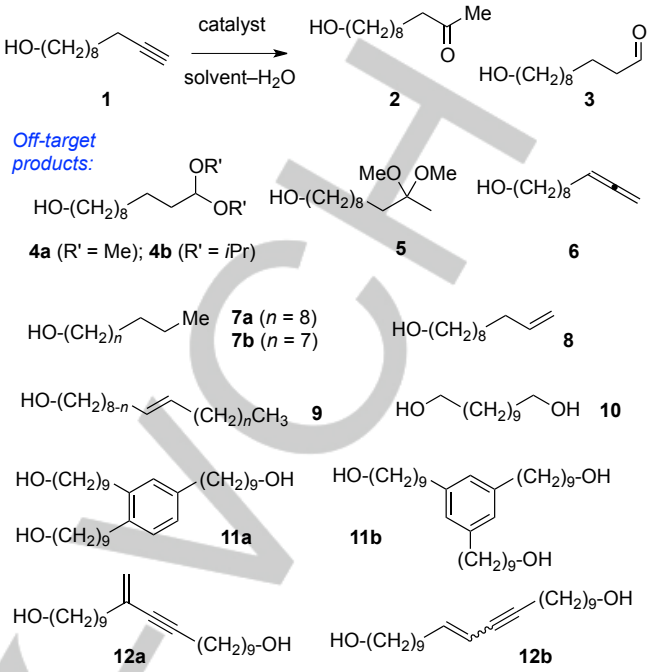
Screening System 1: Microwave heating–GC-MS analysis. Our first approach to catalyst screening centered on the hydration of 1-heptyne in aqueous acetone. As secondary substrate, 1-octene was added to the test mixture with the intention to concomitantly screen for catalytic alkene hydration.[17,18] This part of the project proved futile and will not be further discussed. Screening experiments were run under the conditions defined in Scheme 2. Di-*n*-butyl ether was added to the cooled reaction mixture as internal standard for GC–MS analysis.[19] Hydration products 2-heptanone, 1-heptanal and remaining 1-heptyne were quantified through calibration with reference samples.



Scheme 2. First reaction system for alkyne hydration catalyst screening. Conditions: 2 mL of test solution (0.25 M in 1-heptyne and 0.0625 M in 1-octene, see text).

This screening system detects catalytic hydration activity at a threshold of *ca.* 1 mol% of either Markovnikov- (2-heptanone) or anti-Markovnikov- (1-heptanal) product formation. The GC-MS-analysis was performed directly from the reaction mixture. Disadvantages of this approach, besides the not overly high sensitivity, were low substance recoveries, which implied that unknown reaction products had escaped detection. The screening was performed on a total of ca 60 potential metallic catalysts which were either tested as such, in combination with an ambifunctional pyridylphosphane ligand,[20,21] and other additives (CSA, AgOTf). The results from 159 runs thus performed are listed in the supporting information (Table S1) and will be referred to in the ensuing text where adequate. Eventually the first screening system was abandoned because of the difficulty of obtaining accurate quantitative data and satisfactory recoveries.

Screening System 2: Microwave heating–qNMR analysis. Undec-10-yn-1-ol (**1**) is commercially available as liquid alkyne that is easily purified by vacuum distillation and can be dosed by microliter syringe. The compound and its follow-up-products are little volatile, have low water solubility and are readily recovered by extractive workup. The hydration products ketone **2** (δ 2.12, 3 H) and aldehyde **3** (δ_H 9.77, 1 H) display characteristic, isolated peaks suitable for quantitative analysis by ^{1}H NMR spectroscopy. Unreacted **1** is detected through its acetylenic C–H (δ 1.94), while the R-CH$_2$OH signal (δ 3.64, 2 H) provides the total of products derived from **1** with intact alcohol end-groups. Multiple non-target products were also detected (Scheme 3; for qNMR diagnostics, see Table S2): acetals (**4**, **5**) result from acetalization of **2**/**3** and alcoholic solvent (MeOH, *i*PrOH), or via direct addition of the latter to alkyne. Allene **6** was an impurity in commercial **1**, but else was not significantly formed in the catalytic runs. Through hydride transfer and isomerization reactions, alkyne **1** is transformed into a hydrocarbon chain (**7**), a terminal alkene (**8**), or into isomeric internal (**9**) alkenes.[22] Transfer-hydrogenation of aldehyde **3** to diol **10** as secondary reaction was sometimes seen with *i*PrOH as solvent. Generation of **10** raises [CH$_2$OH] above 100 mol% relative to initial **1**, permitting an approximate quantification.[23] Alkyne trimerization[24] returns arenes **11a/b**, whereas alkyne dimerization[25] potentially generates (*E*/*Z*)-stereoisomers of regioisomers **12a**/**b**. *Recovery* is the sum of all individually detected components **1**–**12** in mol%. In case it amounts to less than [CH$_2$OH], there must be undetected components derived from **1** in the sample (*vide infra*). The difference is listed as *unknown* and serves as control for the integrity of analysis.



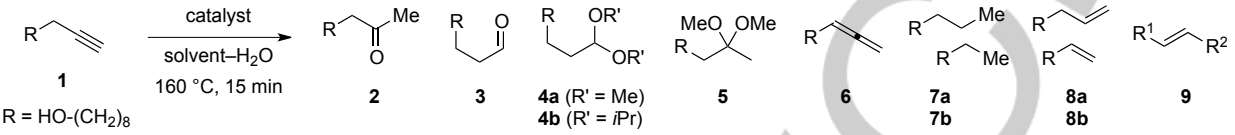
Scheme 3. On-target alkyne hydration of **1** to **2** and **3**, and side-products **4**–**12** from off-target-reactions that were identified in the course of the screen.

In practice, the screening procedure consisted in combining a potential catalyst with degassed solvent, water and **1** in a microwave tube, followed by heating to 160 °C for 15 minutes. After addition of internal standard and following a suitable workup-procedure, the sample was analyzed by quantitative ^{1}H NMR spectroscopy. Catalytic reactions were performed in one or several solvents (A: *i*PrOH, B: acetone, C: methanol, D: NMP) with water (4:1 (v/v)). Such comparatively water-rich, non-acidic media were deliberately chosen to reduce unspecific Brønsted acid catalysis as opposed to metal-specific reactivity.[26]

Validation of the screening approach with established alkyne hydration catalyst systems. Initial experiments focused on established catalyst systems for anti-Markovnikov hydration of terminal alkynes to check if their reported activities and selectivity are reproduced under HOT-CAT screening conditions (Table 1). Wakatsuki's catalyst CpRuCl(dppm)[27] (dppm = 1,2-bis-diphenylphosphino-methane) gave close to 90% aldehyde **3** at a regioselectivity of >200:1 (entry 1). The conversion was incomplete at lower catalyst loading, due to deactivation as confirmed by detection of 1-decanol, formed via R-CH$_2$-CH$_2$-CO-[Ru].[28] The reported activity (*"reactions using 2–10 mol% of catalyst in 2-propanol at 100 °C gave the desired aldehydes in good to excellent yields after 12 h"*) is well mirrored by the 15 min HOT-CAT experiment. A combination of CpRu$^+$-precursor complex [CpRu(C$_{10}$H$_8$)]PF$_6$[29] with dppm presented comparably high activity (entry 3), whereas the lower activity of a CpRu$^+$–dppe system (entry 4) mirrors Wakatsuki's findings with the latter ligand.[27] The choice of precursor is critical since CpRuCl(PPh$_3$)$_2$ with dppm is unreactive (entry 5); inactive [CpRu(η^2-dppm)-

$(PPh_3)]^+$ may have been formed (cf. Table S1, entry 93). The catalyst system $CpRuCl(PPh_3)_2$–ISIPHOS (ISIPHOS = 2-(diphenylphosphino)-6-(2,4,6-triisopropylphenyl)pyridine)[21,30] performs predictably well (entries 6, 7), with entry 6 mirroring our previously published HOT-CAT conditions.[30] Although entries 1–6 use optimal solvent mixtures for the respective catalyst systems, catalytic activity is also traced in a non-standard NMP–H_2O medium (entry 7). In practice, if novel but low activity was observed in one medium, we repeated the experiment in other media.

Table 1. HOT-CAT screen with some established anti-Markovnikov- or Markovnikov hydration catalysts.[a]



Entry	Catalyst (mol%)[b]	Solv.[c]	1	2	3	4[d]	6[e]	7a/b[f]	8	9	Rec.[g]	$[CH_2OH]$[h]	Unk.[i]
1	CpRuCl(dppm) (4)	A	0.6	0.4	89.3	0.8^{Pr}	0.5	4.0	0.5	0.8	96.1	98.8	2.7
2	CpRuCl(dppm) (2)	A	37.5	0.3	53.8	0.4^{Pr}	0.7	2.5	0.0	0.4	95.2	99.5	4.3
3	$[CpRu(C_{10}H_8)]PF_6$–dppm (4)	A	0.0	0.3	90.4	1.8^{Pr}	0.0	3.5	0.0	1.8	96.0	100.4	4.4
4	$[CpRu(C_{10}H_8)]PF_6$–dppe (4)	A	44.6	0.5	48.6	2.7^{Pr}	0.6	2.1	1.1	2.7	100.2	100.9	0.7
5	$CpRuCl(PPh_3)_2$–dppm (4)	A	95.4	0.1	0.6	0.0	0.8	1.2	0.0	0.0	98.1	99.6	1.5
6	$CpRuCl(PPh_3)_2$–ISIPHOS (2)	B	0.0	0.2	96.1	0.0	0.0	0.1	0.0	0.0	96.4	98.1	1.7
7	$CpRuCl(PPh_3)_2$–ISIPHOS (2)	C	79.2	0.0	13.2	0.0	0.6	3.2	0.8	0.0	97.0	100.4	3.4
8	$[CpRu(MeCN)_3]PF_6$–BTF-bipy (4)	C	0.0	0.9	94.4	0.0	0.0	2.8	0.5	0.4	99.0	99.0	0.0
9	$[CpRu(MeCN)_3]PF_6$–BTF-bipy (4)	B	0.0	2.0	91.9	0.0	0.5	2.9	0.6	0.2	98.1	98.5	0.4
10	$NaAuCl_4$ (2)	D	38.0	52.8	0.5	0.8	0.8	1.0	0.0	0.8	93.9	96.8	2.9
11	$AuCl(PPh_3)$ (2)	D	56.1	41.3	0.4	0.4	0.8	0.8	0.0	0.0	99.9	99.8	-0.1
12	(SPhos)AuOTf (2)	D	0.0	95.0	0.4	0.5	0.0	1.8	0.0	0.5	97.7	97.2	-0.5
13	AgOTf (2)	D	63.5	33.5	0.3	0.5	0.8	1.0	0.0	0.5	99.6	99.9	0.3
14	CSA (10)	D	98.2	0.4	0.0	0.14	0.9	0.4	0.0	0.0	100.0	100.5	0.5

[a] Conditions: **1** (50 μL, 0.26 mmol, 0.1 M), microwave heating (160 °C, 15 min). Product quantities in mol% by qNMR against internal standard. [b] Precatalyst and ligand quantity (mol%) in parantheses. [c] Solvent systems and volume ratios: A = 2-propanol–H_2O (10:3), B = acetone–H_2O (4:1); C = NMP–H_2O (4:1); D = MeOH–H_2O (4:1). [d] Methyl acetal **4a,** or *i*Pr-acetal **4b,** if denoted by a superscript Pr. [e] Allene **6** was an impurity (0.8 mol%) in **1**. [f] Sum of **7a/b**; for Ru-catalysts in particular, **7b** can be formed by decarbonylation. [g] Recovery, sum of analytically detected components from **1** in mol%; **10**–**12** were not detected. [h] Total hydroxymethylene (δ_H 3.64) in mol% of **1**. [i] Unidentified products, calculated as $[RCH_2OH]$ – [recovery], see text. BTF-bipy = 5,5'-bis-trifluoromethyl-2,2'-bipyridine; dppm = $CH_2(PPh_2)_2$, dppe = $Ph_2P(CH_2)_2PPh_2$; SPhos = 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl; CSA = camphorsulfonic acid; Tf = SO_2CF_3; $C_{10}H_8$ = naphthalene.

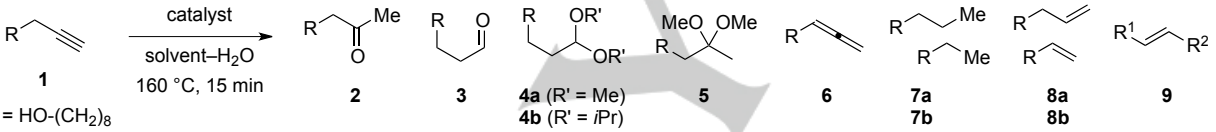
The recent catalyst by Herzon combining $CpRu^+$ with 5,5'-bis-trifluoromethyl-2,2'-bipyridine[31] worked well under HOT-CAT conditions, both in the original NMP–H_2O solvent (entry 8) or in acetone–H_2O (entry 9). Some runs were also performed with established Markovnikov hydration catalysts, including $NaAuCl_4$ in MeOH–H_2O (entry 10).[32] The moderate conversion of 62% might be caused by solvent-induced catalyst deactivation ($Au^I \rightarrow Au^0$). The original reaction conditions involve reflux at lower temperature (MeOH–H_2O 10:1; ca. 70 °C, 1 h).[32] Complex $AuCl(PPh_3)$ is not regarded as an alkyne hydration catalyst, but becomes active after ionization to $(Ph_3P)Au^+$,[33] which apparently takes place under HOT-CAT conditions in aqueous solvent, with no need for promotors (entry 11). Preformed cationic Au(SPhos)OTf predictably shows higher activity (entry 12).[34] We did not cover classical Hg(II) catalysts in a microwave setup due to toxicity.[35] Recent reports describe the catalytic alkyne hydration activity of simple silver salts with non-nucleophilic counter-ions.[36] This was supported by a positive screening result with AgOTf (entry 13). A blank experiment with camphorsulfonic acid (CSA)[37] confirmed the absence of background acid

catalysis in the hydration of **1** (entry 14). Complementary results from the initial HOT-CAT/GC-MS screen with 1-heptyne and either CSA or HOTf in acetone–H_2O at 180 °C (15 min) produced no more than 1 mol% of 2-heptanone (Table S1, entries 1, 2). The results of Table 1 confide that alkyne hydration catalysts are efficiently and reliably detected within a HOT-CAT-screen. The stage was set for a broader screen of alkyne hydration activity across the periodic table, emphasizing transition metal complexes.

Group 1–6 metals and lanthanides. Reported alkyne hydration activity among early transition metals (groups 3–5), the lanthanides[8,38] and main group metals[12b] is limited to acidic systems at low water content, conditions deliberately not reflected by our screening conditions. The preliminary screen (see Table S1, entries 3–17) indicated low activity for $Ce(OTf)_3$ (1% ketone), $Ce(SO_4)_2{\cdot}4\,H_2O$ (1%), $Al(OTf)_3$ (2%), $Bi(OTf)_3$ (≤1%), but none for $La(OTf)_3$, $Eu(hfc)_3$ or $Yb(OTf)_3$. The observed activities and ketone selectivity are consistent with acid-induced hydration. A screen of group 4 complexes Cp_2TiCl_2, $(RO)_2TiCl_2$ and Cp_2ZrCl_2 did not reveal activity (Table S1, entries 18–23). Neither would group VI complex $K_2[Cr(oxalate)_3]$ (Table S1, entries 24–26) or $Mo(CO)_6$ (Table 2, entry 1); the latter displayed minor activity for alkyne hydrogenation and -trimerization. We have recently disproven the earlier claimed acetylene hydration activity of tungsten(IV) complex $(NEt_4)_2[WO(mnt)_2]$ (mnt = maleonitrile dithiolate).[13,39] The complex was also inactive in the HOT-CAT screen with **1** (Table 2, entry 2).

Group 7 metals. Alkyne hydration activity is not documented in group 7, but analogies of Mn-vinylidenes[40] to those of ruthenium incited a search for anti-Markovnikov hydration catalysts with that element. Table 2 reveals that a focus screen with methylcyclopentadienyl-manganese-tricarbonyl either alone (entries 3, 4), together with co-ligands (entries 5, 6), or additionally with NMO as carbonyl-releasing reagent[41] (entry 6) induced no catalytic activity. A combination of Mn(III), tetraphenylporphyrin (TPP) and acid (cf. ref.[10]) was inactive (entry 7). Rhenium dodecacarbonyl showed little activity for Markovnikov hydration, besides alkyne trimerization (entry 8).

Table 2. HOT-CAT alkyne hydration screen with Mo, W, Mn, and Re compounds.[a]



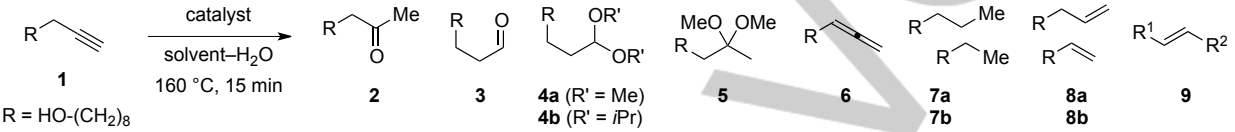
Entry	Catalyst (mol%)[b]	Solv.[c]	**1**	**2**	**3**	**4a**	**6**[d]	**7**	**8**	**9**	**11**[e]	Rec.[f]	$[CH_2OH]$[g]	Unk.[h]
1	$Mo(CO)_6$ (4)	D	87.0	0.0	0.0	0.0	0.6	1.8	0.0	0.0	2.2	91.6	96.9	5.3
2	$(NEt_4)_2[WO(mnt)_2]$ (20)	B	98.1	0.16	0.15	0.0	0.7	0.9	0.0	0.0	0.0	100.0	100.5	0.5
3	$Cp'Mn(CO)_3$ (4)	B	99.3	0.0	0.0	0.0	0.6	0.0	0.0	0.0	0.0	99.9	101.2	1.3
4	$Cp'Mn(CO)_3$ (4)	D	98.7	0.0	0.0	0.0	0.0	1.1	0.0	0.0	0.0	99.8	100.8	1.0
5	$Cp'Mn(CO)_3$–ISIPHOS (4)	D	96.1	0.0	0.0	0.0	0.0	0.9	0.0	0.0	0.0	97.0	100.9	3.9
6	$Cp'Mn(CO)_3$–dppe (4), NMO (114)	D	99.0	0.0	0.0	0.0	0.0	2.0	0.0	0.0	0.0	101.0	101.0	0.0
7	$Mn(OAc)_3$–TPP (4), CSA (10)	D	99.3	0.0	0.0	0.0	0.8	1.0	0.0	0.0	0.0	101.1	101.3	0.2
8	$Re_2(CO)_{10}$ (2)	D	91.2	1.1	0.2	0.1	0.8	0.8	0.0	0.0	1.2	95.4	97.4	2.0

[a] Conditions: **1** (50 μL, 0.26 mmol, 0.1 M), microwave heating (160 °C, 15 min). Product quantities by qNMR against internal standard in mol%. [b] Precatalyst and ligand quantity in parantheses. [c] Solvent systems and volume ratios: A = 2-propanol–H_2O (10:3), B = acetone–H_2O (4:1); C = NMP–H_2O (4:1); D = MeOH–H_2O (4:1). [d] Allene **6** was an impurity (0.8 mol%) in **1**. [e] Quantities of **11** (arenes; Scheme 3) are expressed in mol% of **1** incorporated; **12** (enyne, Scheme 3) was not reliably detected. [f] Recovery, sum of analytically detected components from **1** in mol%. [g] Total RCH_2OH (δ_H 3.64) in mol% of **1**. [h] Unidentified products, calculated as $[CH_2OH]$ – [recovery], see text. Cp' = methyl-cyclopentadienyl; CSA = camphorsulfonic acid; mnt = maleonitrile-dithiolate; TPP = tetraphenylporphyrine; NMO = *N*-methylmorpholine-*N*-oxide; ISIPHOS = 2-(diphenylphosphino)-6-(2,4,6-triisopropylphenyl)pyridine.

Group 8 metals. The known alkyne hydration activity of group 8 metals is focused on ruthenium.[6] In contrast, the reported activities of iron seem to fall into the category of Lewis-acid assisted Brønsted acid catalyses.[8f,42] Since such activation pathways are suppressed in water-rich reaction media and are less successful with aliphatic alkynes, the low Markovnikov hydration activity of $Fe(OTf)_3$, comparable to that of Brønsted acids, is expected (Table 3, entry 1; Table S1, entries 34, 35). The initial screen with $Fe(acac)_3$, $Fe(dbm)_3$, $FeCl_2(dppe)$, $[\{CpFe(CO)_2\}_2]$ and $CpFeI(CO)_2$ failed to show iron-specific

activity (Table S1, entries 36–47). Combining the CpFe-fragment with ambifunctional ligand via (attempted) oxidant-induced CO ligand release gave no hydration catalyst (entry 2). The low alkyne hydration activity seen with a water-soluble Fe–porphyrin complex[10] did not transform into a conclusive activity for the Fe–TPP–CSA system (entry 3), reflecting the blank experiment with CSA (Table 1, entry 14). Numerous ruthenium complexes were tested in the first screen (Scheme 1; Table S1, entries 48–98). Notable activity in the order of 5–10 mol% was found for RuO_2–ISIPHOS–CSA (8% **K**, 4% **A**; cf. Scheme 2), $RuCl_2$(COD) (9% **K**), (arene)$RuCl_2$ (8–15% **K**), [(η^3,η^3)-(2,7-dimethylocta-dienediyl)$RuCl_2$][43] (13% **K**, 5% **A**) and Cp*$RuCl_2$–ISIPHOS–2 AgOTf (7% **A**); the latter example is notable since Cp*Ru-fragments had shown a lack of activity, e.g. in the complex [Cp*RuCl(*t*BuPyPHOS)$_2$].[44] These ruthenium catalysts are not very chemoselective, with ≤20 mol% alkyne hydration products at ≥90% conversion. The first screen confirmed high anti-Markovnikov hydration activity of CpRuCl(dppm) in acetone besides *i*PrOH (72% **A**; cf. Table 1),[27] and for in situ catalyst [CpRu($C_{10}H_8$)]PF_6–ISIPHOS (84% **A**).[29] Additional runs with ruthenium were included in the qNMR-screen (Table 3).

Table 3. HOT-CAT alkyne hydration screen of iron, ruthenium and osmium-compounds.[a]



1 **2** **3** **4a** (R' = Me) **4b** (R' = *i*Pr) **5** **6** **7a** **7b** **8a** **8b** **9**

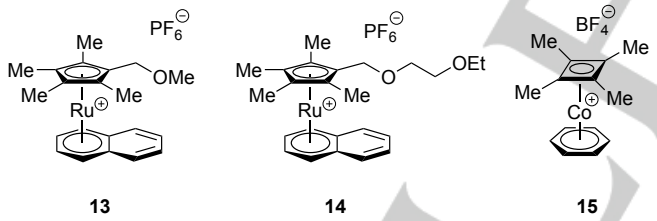
Entry	Catalyst (mol%)[b]	Solv.[c]	**1**	**2**	**3**	**4a**	**6**[d]	**7a/b**[e]	**8**	**9**	**11/12**[f]	Rec.[g]	[CH_2OH][h]	Unk.[i]
1	$Fe(OTf)_3$ (10)	B	97.0	1.4	0.0	0.0	1.0	1.5	0.0	0.0	n.d.	100.8	101.0	0.2
2	$CpFe(CO)_2I$–ISIPHOS (4), CSA (10), NMO (116)	D	97.9	0.0	0.0	0.1	0.7	0.3	0.0	0.0	0.0/0.0	99.0	99.0	0.0
3	FeCl(TPP) (2), CSA (10)	D	98.6	0.7	0.0	0.1	0.8	0.7	0.0	0.0	0.0/0.0	100.9	100.3	-0.6
4	$CpRuCl(PPh_3)_2$ (4)	A	82.7	0.6	2.6	–	0.3	5.1	1.4	1.2	0.0/0.0	98.9[j]	98.9	0.0
5	[CpRu($C_{10}H_8$)]PF_6–bipy (2)	B	67.1	4.5	20.2	0	4.0	3.4	0.0	0.0	0.0/0.0	99.2	100.9	1.7
6	[CpRu($C_{10}H_8$)]PF_6–Ph_2PyBOX (2),	B	74.2	0.2	20.6	0.4	0.2	1.9	0.8	0.0	0.7/0.0	99.0	100.1	1.1
7	CpRuCl(COD)–Ph_2PyBOX (2)	D	83.3	1.0	2.2	2.0	0.4	2.5	0.0	0.0	0.3/0.0	91.7	94.7	3.0
8	**13**–ISIPHOS (2)	B	87.4	0.0	0.8	0.0	0.4	2.1	1.3	1.2	0.0/1.0	94.1	101.9	7.8
9	**13**–dppm (2)	B	93.8	0.0	0.4	0.0	0.6	1.3	0.3	0.2	0.0/1.6	98.3	101.2	2.9
10	**14**–ISIPHOS (2)	B	85.2	0.0	0.9	0.0	0.5	1.8	1.5	1.5	0.0/0.8	92.3	100.9	8.6
11	**14**–dppm (2)	B	95.8	0.0	0.4	0.0	0.8	1.2	0.1	0.2	0.0/0.6	99.1	100.6	1.5
12	$(NH_4)_2[OsCl_6]$ (5)	A	0.0	6.2	1.1	–	0.0	5.9	39.2	29.4	2.5/0.0	84.3	99.2	14.9
13	$(NH_4)_2[OsCl_6]$ (5)	B	35.6	9.6	1.0	0.0	0.1	4.1	23.7	17.3	1.8/0.0	93.1	97.6	4.5
14	$(NH_4)_2[OsCl_6]$ (5)	C	47.7	4.9	2.1	0.0	0.1	5.9	13.5	12.7	1.7/0.0	88.6	96.9	8.4
15	$(NH_4)_2[OsCl_6]$ (5)	D	32.6	13.1	0.4	0.9	0.0	5.9	12.5	10.2	3.1/0.4	79.1	94.8	15.6

[a] Conditions: **1** (50 μL, 0.26 mmol, 0.1 M), microwave heating (160 °C, 15 min). Product quantities by qNMR against internal standard in mol%. [b] Precatalyst and ligand quantity in parentheses. [c] Solvent systems and volume ratios: A = 2-propanol–H_2O (10:3), B = acetone–H_2O (4:1); C = NMP–H_2O (4:1); D = MeOH–H_2O (4:1). [d] Allene **6** was an impurity (0.8 mol%) in **1**. [e] Sum of **7a**/**b**; for Ru-catalysts in particular, **7b** can be formed by decarbonylation. [f] Quantities of **11/12** (arenes/enynes, cf. Scheme 3) are expressed in mol% of **1** incorporated. [g] Recovery, sum of analytically detected components from **1** in mol%. [h] Total hydroxymethylene (δ_H 3.64) in mol% of **1**. [i] Unidentified products, calculated as [RCH_2OH] − [recovery], see text. [j] Includes 5.0 mol% **10**. bipy = 2,2'-bipyridine; Ph_2PyBOX = 2,6-bis((*S*)-4-phenyl-4,5-dihydrooxazol-2-yl)pyridine.

The lack of catalytic activity for $CpRuCl(PPh_3)_2$ (entry 4), in spite of its similarity to Wakatsuki's catalyst, was confirmed.[27,44,45] The side-product pattern confirms catalyst deactivation by hydro-de-carbonylation to $L_nRu(CO)$ with release of decanol **7b**.[28,46] Even before Herzon's fluorinated bipyridines (Table 1, entries 8, 9), Wakatsuki had noted the anti-Markovnikov hydration activity of diimine complexes [CpRuCl(N–N)] or $[CpRu(N–N)(NCMe)]PF_6$ with (N–N) = bipyridine (bipy), phenanthrolin (phen), and *i*Pr_2PyBOX (PyBOX = pyridine-2,6-bis-oxazoline) in a patent, although activity was lower than with CpRuCl(dppm).[47] Combining a $CpRu^+$-precursor with bipy or Ph_2PyBOX in the screen induced predominant anti-Markovnikov hydration at conversions of 25–30%. The regioselectivity was high with the more chemoselective PyBOX-system (entries 5, 6). The presence of chloride suppressed this activity (entry 7).

The $CpRu(II)^+$-fragment is to date retained in all anti-Markovnikov hydration catalyst systems, while Cp*Ru and η^3-indenylruthenium(II) were proven ineffective.[44,48] To evaluate further organometallic fragments, (tetramethyl-oxymethylene-cyclopentadienyl)ruthenium(II) complexes with naphthalene **13** and **14** (Figure 2) were obtained by courtesy of D. Perekalin[49] and combined with ISIPHOS or dppm as steering ligands in the screen (entries 8–11). Traces of aldehyde **3** were detected, but catalytic turnover for hydration was not realized.

For the first time, catalytic activity was detected with osmium complexes (entries 12–15).[6] Hydration with hexachloroosmate(IV) is Markovnikov-selective, and most notable in methanol (entry 15). The overall low chemoselectivity is due to a preference of transfer hydrogenation and alkene isomerization reactions of this catalyst. The large proportion of "unknowns" points to alkyne polymerization as other side-reaction (vide infra).



13 **14** **15**

Figure 2. Precursor complexes **13** (for $Cp^{*A}Ru^+$), **14** (for $Cp^{*B}Ru^+$) and **15** (for $(C_4Me_4)Co^+$ = $(TMB)Co^+$) used in the screening.

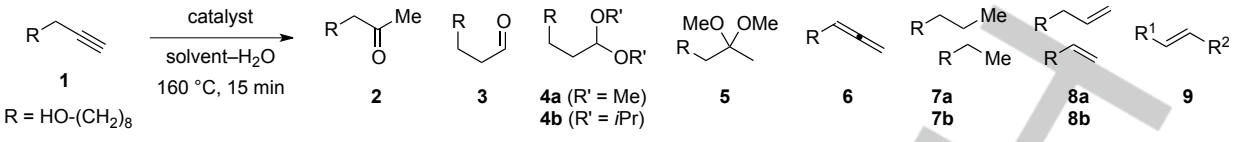
Group 9 metals. Naka found catalytic activity of water-soluble, sulfonated cobalt(III)porphyrins for Markovnikov hydration of terminal alkynes under relatively mild conditions ($MeOH–H_2O$, 80 °C, 6–16 h; neutral or slightly acidic).[10] Cationic cobalt(III)salen complexes were also found to hydrate arylalkynes in acidic media, but less so aliphatic alkynes.[11] The simple salts $CoCl_2$ and $Co(OAc)_2$ were inactive in the 1-heptyne screen (Table S1, entries 101–105). Cyanocobalamin (vitamin B_{12}) was included in both screens, but showed no catalytic activity, neither in presence of acid nor with iron(III)triflate as potential cyanide scavenger (Table S1, entries 106, 107; Table 4, entries 1–4). An in situ Co–porphyrin catalyst from cobalt(II) acetate and TPP (tetraphenylporphyrin) under argon displayed Markovnikov hydration activity after addition of CSA (entry 6); higher conversions were obtained in air (entry 7) and even more so with excess acid (entry 8). The active species in this system is likely similar to the Co(III)-porphyrin of Naka,[10] but is based on the accessible ligand TPP,[50] and thus was selected for preparative evaluation (vide infra). No activity was observed with Co(II)salen complexes – at least in the absence of Brønsted acid (entries 9, 10). Cobalt cyclobutadiene sandwich complex, $[(C_4Me_4)Co(C_6H_6)]BF_4$ (**15**)[49c] (Figure 2) was inactive either alone or with ambifunctional steering ligands (entries 11–13).

Catalytic alkyne hydration has been reported for aqueous Rh(III) ($RhCl_3$–HCl,[51a] $RhCl_4^-$[51b]), albeit with low chemoselectivity. Our initial screen with neutral $RhCl_3$ and $Rh_2(OAc)_4$ failed to show hydration products (Table S1, 108–111). Considering its well established vinylidene complex chemistry,[52] Rh(I) is a suitable candidate in the search for new anti-Markovnikov hydration catalysts. The first screen revealed some anti-Markovnikov hydration activity for ligandless $[RhCl(COD)]_2$ (4% **A**) or the generation of both regioisomers (7% **A**, 4% **K**) with ISIPHOS and CSA present, albeit at low chemoselectivity (Table S1, entries 112–115). The qNMR-screen confirms the anti-Markovnikov hydration selectivity of the ligandless system in acetone (Table 4, entry 14) and reveals important side-reactions including alkyne trimerization, transfer hydrogenation and alkene isomerization, which cause low chemoselectivity.

In methanol, the extent of hydration is even lower (entry 15–17). Ambifunctional steering ligands earlier used with the CpRu(II) fragment do not induce the anti-Markovnikov reaction mode with Rh(I) (entries 16, 17). Experiments with Rh(I) in MeOH display low analytical recoveries (50–66%) and $[CH_2OH]$ values (74–81%, entries 15–17). Some reaction components evidently escape analytical detection altogether, while others having the hydroxymethylene group remain unassigned for lack of diagnostic NMR signals ("unknowns"). The discrepancies are likely caused by alkyne oligomerizations, as known with Rh(I)-phosphane complexes (*vide infra*).[53,54] Complex (TRIPHOS)$RhCl_3$[55] revealed preference for Markovnikov hydration (4 turnovers; entry 18). Overall, rhodium shows alkyne hydration activity with a tendency for the anti-Markovnikov mode, but at low chemoselectivity due to alkyne oligomerization or polymerization.

For iridium, a Markovnikov hydration catalyst system $[Ir(COD)_2]BF_4$–$P(O{i}Pr)_3$–$ZrCl_4$ (70 °C, 15 h) was reported by Ishii[56] Our screen indicated notable hydration activity of $[Ir(COD)Cl]_2$ in various solvents (entries 19–22). The highest Markovnikov regioselectivity in $MeOH–H_2O$ was **2**:**3** = 26:1, although this ratio disregards the co-formation of methyl acetal. The chemoselectivity for hydration is higher than with rhodium, but generation of alkanol, alkenes and arenes is still notable.

Table 4. HOT-CAT alkyne hydration screen of cobalt, rhodium and iridium compounds.[a]



1 R = HO-$(CH_2)_8$ | **2** | **3** | **4a** (R' = Me) **4b** (R' = *i*Pr) | **5** | **6** | **7a** **7b** | **8a** **8b** | **9**

Entry	Catalyst (mol%)[b]	Solv.[c]	**1**	**2**	**3**	**4/5**[d]	**6**[e]	**7**	**8**	**9**	**11/12**[f]	Rec.[g]	[CH_2OH][h]	Unk.[i]
1[j]	vitamin B_{12} (2)	B	95.4	0.0	0.0	0.0	0.7	0.7	0.0	0.0	0.0/0.0	96.8	98.6	1.8
2[j]	vitamin B_{12} (2)	D	98.4	0.0	0.0	0.0	0.7	0.6	0.0	0.0	0.0/0.0	99.7	101.2	1.5
3[j]	vitamin B_{12} (2)–CSA (2)	D	94.9	0.0	0.0	0.0	0.7	0.8	0.0	0.0	0.0/0.0	96.4	98.0	1.6
4[j]	vitamin B_{12} (2)–$Fe(OTf)_3$ (10)	D	95.9	0.4	0.0	0.2	0.9	1.5	0.0	0.0	0.0/0.0	98.9	99.7	0.8
5[j]	$Co(OAc)_2$ (4)	D	98.2	0.0	0.1	0.0	0.8	1.6	0.0	0.0	0.0/0.0	100.7	100.8	0.1
6	$Co(OAc)_2$–TPP (4)–CSA (10)	D	77.0	18.3	0.0	0.2	0.9	1.2	0.0	0.0	0.0/0.0	97.6	98.1	0.5
7[j]	$Co(OAc)_2$–TPP (4)–CSA (10)	D	58.8	37.3	0.2	0.6/0.1	0.8	1.4	0.0	0.0	0.0/0.0	99.2	99.9	0.7
8[j]	$Co(OAc)_2$–TPP (4)–CSA (25)	D	0.0	89.6	0.7	2.2/0.14	1.1	1.6	0.0	0.0	0.0/0.0	95.4	97.1	1.7
9[j]	Co(salen) (4)	D	98.6	0.0	0.0	0.0	0.8	0.6	0.0	0.0	0.0/0.0	100.0	101.1	1.1
10[j]	Co(salen-J) (2)	D	98.4	0.0	0.0	0.0	0.8	1.0	0.0	0.0	0.0/0.0	100.2	100.8	0.6
11[j]	**15** (4)	D	90.4	0.0	0.3	0.0	0.1	1.6	0.6	0.2	2.2/0.0	95.4	100.5	5.1
12[j]	**15**–ISIPHOS (4)	D	78.9	0.0	0.3	0.0	0.4	1.2	0.4	0.0	4.0/0.0	85.3	100.2	14.9
13[j]	**15**–dppm (4)	D	90.5	0.0	0.3	0.0	0.5	0.4	0.6	0.0	3.5/0.0	95.8	101.1	5.3
14	$[RhCl(COD)]_2$ (2)	B	55.1	1.4	5.8	0.0	0.0	2.6	4.3	3.5	13.2/2.0	87.9	100.0	12.1
15	$[RhCl(COD)]_2$ (2)	D	41.4	1.9	1.3	1.2	0.0	2.0	1.3	0.0	5.2/3.4	57.7	76.5	18.8
16	$[RhCl(COD)]_2$–ISIPHOS (2)	D	25.9	0.0	0.3	0.0	0.0	0.9	2.5	0.0	3.1/17.7	50.4	73.8	23.4
17	$[RhCl(COD)]_2$–dppm (2)	D	56.8	1.9	0.1	0.2	0.0	1.0	0.9	0.0	2.6/2.8	66.3	81.0	14.7
18	$(TRIPHOS)RhCl_3$ (2)	D	61.1	8.1	1.0	0.6	0.0	1.2	1.4	0.0	2.7/2.0	78.1	87.7	9.6
19	$[IrCl(COD)]_2$ (2)	A	0.0	44.0	5.8	0.3^{Pr}	0.0	17.2	3.5	1.8	3.9/1.8	78.2	97.7	19.5
20	$[IrCl(COD)]_2$ (2)	B	2.6	41.7	7.1	0.0	0.0	18.1	3.8	1.9	3.2/3.0	81.4	96.3	14.9
21	$[IrCl(COD)]_2$ (2)	C	27.1	16.6	3.6	0.0	0.0	7.6	6.4	2.7	3.9/3.6	71.8[k]	93.2	21.4
22	$[IrCl(COD)]_2$ (2)	D	0.0	44.3	1.7	2.9/0.14	0.0	10.8	4.0	2.1	3.4/3.4	72.8	95.4	22.6

[a] Conditions: **1** (50 μL, 0.26 mmol, 0.1 M), microwave heating (160 °C, 15 min). Product quantities in mol% determined by qNMR against internal standard. [b] Precatalyst and ligand quantity in parantheses. [c] Solvent systems and volume ratios: A = 2-propanol–H_2O (10:3), B = acetone–H_2O (4:1); C = NMP–H_2O (4:1); D = MeOH–H_2O (4:1). [d] Methyl acetal **4a,** or *i*Pr-acetal **4b,** if denoted by a superscript Pr. If ketal **5** was detected, the quantity is given after a "/" separator. [e] Allene **6** was an impurity (0.8 mol%) of **1**. [f] Quantities of **11/12** (arenes/enynes, cf. Scheme 3) are expressed in mol% of **1** incorporated. [g] Recovery, sum of analytically detected components from **1** in mol%. [h] Total R-CH_2OH (δ_H 3.64) in mol% of **1**. [i] Unidentified products, calculated as [CH_2OH] – [recovery], see text. [j] Reaction performed in air. [k] Includes 0.25% unknown acetalic product. TRIPHOS = $MeC(CH_2PPh_2)_3$; COD = 1,5-cyclooctadiene; salen = bis(salicylidene)ethylenediamine; sal-J = Jacobsen's salen ligand;[57] TMB = tetramethyl-cyclobutadiene.

Component recoveries of 72–81 mol% at near complete [CH_2OH] recoveries mean that 15–23 mol% "unknowns" are present in the reaction mixtures. To identify those components, we performed an [IrCl(COD)]$_2$-catalyzed hydration of 1-octyne (0.6 M) under else identical conditions of Table 4, entry 22. The composition of crude product mirrored that obtained with **1**. Distillation of volatiles gave 2-octanone, some 1,1-dimethoxy-octane and 1,5-cyclooctadiene. The distillation residue consisted of poly-1-octyne (**16**), which was accompanied by 1,2,4- and 1,3,5-tri-*n*-hexylbenzene (**17a**/**b**) (Figure 3).

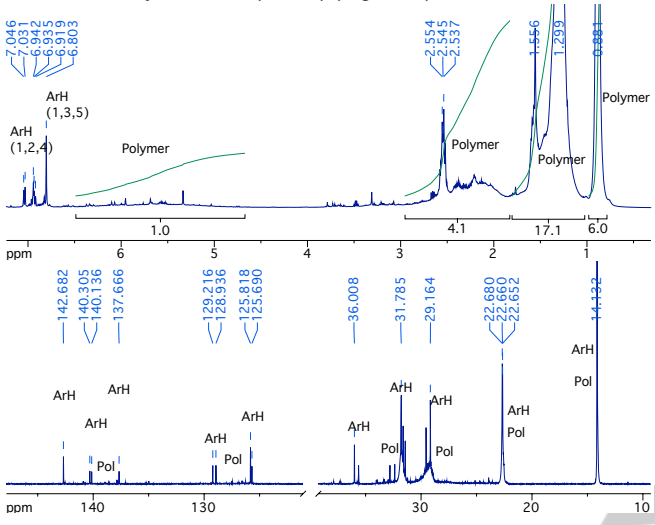
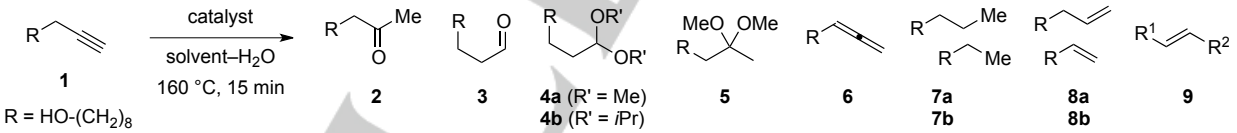


Figure 3. Analysis of the distillation residue of an iridium-catalyzed 1-octyne hydration reaction mixture, showing presence of arene trimerization products (ArH; 1,2,4- and 1,3,5-**17**) and poly-1-octyne ("Pol"; **16**) signals. Top: ^{1}H NMR spectrum (500 MHz, $CDCl_3$). Bottom: ^{13}C NMR spectrum (126 MHz, $CDCl_3$).

The ^{1}H and ^{13}C NMR spectra displayed broadened alkyl- (δ_H 0.7–3, δ_C 14–35) and olefinic signals (δ_H 5–6.5, δ_C 127 and 138) which fit reference data for poly-1-hexyne.[58] Cyclotrimerized arenes are common side-products in alkyne polymerization, and organorhodium- and -iridium compounds are established alkyne polymerization catalysts.[59] Oligomerization and polymerization satisfactorily explain unassigned materials listed in the column "unknown". Generation of *insoluble* polymers may also be responsible in case of low recoveries of the [CH_2OH] integral.

Group 10 (Ni, Pd, Pt). Nickel-based alkyne hydration catalysts are unknown.[6] The first screen covering Ni(acac)$_2$, $NiCl_2(PPh_3)_2$, $NiCl_2$(BINAP), and $NiCl_2(PCy_3)_2$ did not find hydration activity (Table S1, entries 128–135). Simple palladium salts only hydrate substrates that profit from anchimeric assistance.[6,60] $Pd(PPh_3)_4$–HCl hydrates aryl acetylenes with uneven results,[61] while $PdCl_2$(BOX) brings about hydration via hydroalkoxylation and in situ hydrolysis.[62] Our 1-heptyne screen of several palladium complexes (Table S1, entries 136–154) revealed notable Markovnikov hydration activity for $PdCl_2$(COD) (20% **K**) and $PdCl_2$ (11% **K**). For the former, Markovnikov hydration activity at low chemoselectivity was confirmed in the qNMR screen (Table 5, entry 1). Transfer hydrogenation and olefin isomerization are competing, but the high level of "unknowns" points to alkyne polymerization as major side-reaction. This was even more pronounced for an in situ cationic catalyst with a secondary phosphine oxide ligand[63] (Table 5, entry 2). The results clarify that palladium-catalyzed alkyne hydration without anchimeric assistance cannot usually compete with alkyne polymerization.

Table 5. HOT-CAT alkyne hydration screen of Ni, Pd and Pt compounds.[a]



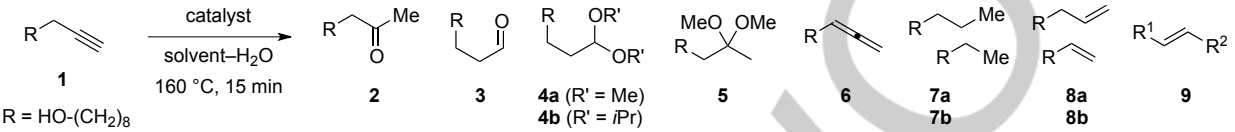
1 R = HO-(CH_2)$_8$ | **2** | **3** | **4a** (R' = Me) **4b** (R' = *i*Pr) | **5** | **6** | **7a** **7b** | **8a** **8b** | **9**

Entry	Catalyst (mol%)[b]	Solv.[c]	**1**	**2**	**3**	**4a**	**6**[d]	**7**	**8**	**9**	**11/12**[e]	Rec.[f]	[CH_2OH][g]	Unk.[h]
1	$PdCl_2$(COD) (2)	D	30.6	3.1	0.2	0.1	0.0	0.5	1.5	0.6	2.1/–	36.7	99.8	63.1
2	$Pd(OAc)_2$ (4)–Men_2POH (8)–CSA (8)	B	0.0	2.8	0.4	0.0	0.0	0.0	2.8	2.6	3.5/–	12.1	85.7	73.6
3	$PtCl_2$ (2)	D	41.8	18.5	0.6	0.8	0.0	1.8	2.1	0.3	2.6/3.2	71.7	94.4	22.7
4	(dppe)Pt(C_6F_5)$_2$ (2)–CSA (10)	D	84.2	12.1	0.0	0.4	0.5	0.6	1.1	0.0	0/0	98.9	101.0	2.1
5	(BINAP)PtCl(C_6F_5)–AgOTf (2)	D	62.6	18.5	0.3	0.3	0.6	1.0	1.0	0.3	0/0	84.6	98.0	13.4

[a] Conditions: **1** (50 µL, 0.26 mmol, 0.1 M), microwave heating (160 °C, 15 min). Product quantities by qNMR against internal standard in mol%. [b] Precatalyst and ligand quantity in parantheses. [c] Solvent systems and volume ratios: A = 2-propanol–H_2O (10:3), B = acetone–H_2O (4:1); C = NMP–H_2O (4:1); D = MeOH–H_2O (4:1). [d] Allene **6** was an impurity (0.8 mol%) in **1**. [e] Quantities of **11** (arenes, cf. Scheme 3) are expressed in mol% of **1** incorporated; **12** (enynes, cf. Scheme 3) was not reliably detected. [f] Recovery, sum of analytically detected components from **1** in mol%. [g] Total hydroxymethylene (δ_H 3.64) in mol% of **1**. [h] Unidentified products calculated as [CH_2OH] – [recovery], see text. Men_2POH = dimenthylphosphine-*P*-oxide;[63] BINAP = (*rac*)-2,2'-bis(diphenylphosphino)-1,1'-binaphthalene.

Catalytic Markovnikov hydration with $PtCl_2$ is established.[6,64] HOT-CAT screens confirm the activity (Table S1, entries 155–157), but the qNMR screen implies that polymerization may have been overlooked in earlier work (Table 4, entry 3).[64] In situ generated $[(P–P)Pt(C_6F_5)]^+$-cations[65] show comparable Markovnikov hydration activity, but higher chemoselectivity with less polymerization (Table 5, entries 4, 5).

Table 6. HOT-CAT alkyne hydration screen of copper, silver and gold compounds.[a]



Entry	Catalyst (mol%)[b]	Solv.[c]	1	2	3	4a/5[d]	6[e]	7	8	9	Rec.[f]	$[CH_2OH]$[g]	Unk.[h]
1	$[Cu(MeCN)_4]PF_6$ (4)	B	94.9	3.1	0.3	0.0	0.8	0.8	0.0	0.0	99.9	100.6	0.7
2	$[Cu(MeCN)_4]PF_6$ (4)	D	75.4	15.8	0.4	0.4/0.02	0.9	2.1	0.0	0.0	95.0	97.5	2.5
3	Cu-chlorophyllin (4)	D	95.1	0.0	0.1	0.2	0.8	1.6	0.0	0.0	97.8	98.6	0.8
4	[Cu(salen)] (4)	D	97.5	0.5	0.1	0.0	0.8	0.7	0.0	0.0	99.6	99.6	0.0
5	$Cu(OAc)_2$–TPP (4)–CSA (10)	D	88.8	9.6	0.1	0.3	0.9	1.0	0.0	0.0	100.7	100.6	-0.1
6	AuCl(*t*BuPyPPh$_2$) (2)	D	46.6	39.3	0.4	0.4	0.7	1.4	0.0	0.0	88.8	88.6	-0.2
7	AuCl(*t*BuPyPPh$_2$)–AgOTf (2)	D	0.0	91.6	0.6	1.0	0.7	1.2	0.0	0.0	95.1	96.1	1.0
8	AuCl(THT)–Men$_2$POH (4)	D	57.0	39.5	0.2	0.9/0.1	0.8	n.d.[i]	0.0	0.0	98.6	99.7	1.1

[a] Conditions: **1** (50 μL, 0.26 mmol, 0.1 M), microwave heating (160 °C, 15 min). Product quantities by qNMR against internal standard in mol%. [b] Precatalyst and ligand quantity in parantheses. [c] Solvent systems and volume ratios: A = 2-propanol–H_2O (10:3), B = acetone–H_2O (4:1); C = NMP–H_2O (4:1); D = MeOH–H_2O (4:1). [d] Methyl acetal **4a**. If methyl ketal **5** was detected, its content is given after a "/" separator. [e] Allene **6** was an impurity (0.8 mol%) in **1**. [f] Recovery, sum of analytically detected components from **1** in mol%. [g] Total hydroxymethylene (δ_H 3.64) in mol% of **1**. [h] Unidentified products, calculated as $[RCH_2OH]$ – [recovery], see text. [i] Not detected due to signal overlap. Arenes (**11**) or enynes (**12**; cf. Scheme 3) were not detected in any of the reactions from this table. *t*BuPyPPh$_2$ = 2-(*tert*-butyl)-6-(diphenylphosphino)pyridine;[21] THT = tetrahydrothiophene.

Group 11 transition metals. The initial screen failed to show hydration with $Cu(acac)_2$, $Cu(BH_4)(PPh_3)_2$, $CuCl(PPh_3)_3$, [CuCl(phen)(PPh_3)], Cu(salen), CuI(P*t*Bu$_3$), $Cu(OC_6H_4CHC{=}N\textit{i}Pr)_2$, Cu(salen-J) or $Cu(SC_6H_4Me)$, if applied as such or in combination with ISIPHOS, CSA and sometimes AgOTf (Table S1, entries 163–185). A little hydration (3% **K**) was seen with Cu(salen)–CSA, and considerable activity with $CuOTf{\cdot}(C_6H_6)_{0.5}$ (46% **K**; Table S1, entries 160–162). Cationic complex $[Cu(MeCN)_4]PF_6$ was then screened by qNMR, where it displayed promising activity in MeOH (Table 6, entries 1, 2). Neither Cu-chlorophyllin or Cu(salen) displayed notable activity, although the latter would probably have benefitted from an acid additive (Table 6, entries 3, 4). Distinct, if low activity was seen with Cu(II)–TPP–CSA (entry 5; cf. ref.[10]).

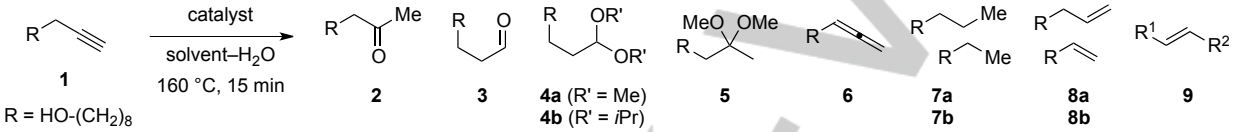
The Markovnikov hydration activity of silver and gold is well established and was not investigated much further (cf. Table 1, entries 10–13). The 1-heptyne screen found activity for AgOTf (18% **K**) and inactivity for AgOBz (Table S1, entries186–189; cf. ref.[36a]). Table 6 adds examples for Au(I)-complexes of *t*BuPyPPh$_2$ (2-*tert*-butyl-6-diphenylphosphino-pyridine),[21] whose activities are comparable to those of $AuCl(PPh_3)$ or Au(SPhos)OTf for the chloro and triflate forms, respectively (entries 6, 7; cf. Table 1, entries 11, 12). The ambifunctional ligand does not appear to play a specific role. An in situ gold(I)–SPO (secondary phosphine oxide)[66] catalyst was no more active than other AuCl-based complexes (Table 6, entry 8 vs 6 vs Table 1, entry 11).[67]

Group 12 transition metals. Alkyne hydration with zinc is characterized by high reaction temperatures and conditions point to an acid-induced mechanism, which render that element unattractive for our study.[6] We did not wish to reinvestigate the already well-known hydration activity of mercury.[6,35,68] Considering the toxicity of the latter and that of cadmium, group 12 was passed over in the present study.

Focus screening with cationic Cu(I). The promising screening results with $CuOTf(PhH)_{0.5}$ and $[Cu(MeCN)_4]PF_6$ pointed our attention to cationic copper(I). Copper-catalyzed alkyne

hydration has recently seen renewed[6] interest.[8a,69] Some catalyst systems used $Cu(OTf)_2$ in "dry" media (1–2 equiv. of H_2O),[8a,69c] i.e., under conditions that favor hidden Brønsted acid catalysis[70,71] and which may not be specific to copper.[72] A less acidic copper catalyst ($Cu(OAc)_2$) used trifluoroacetic acid as reaction medium and was limited to haloalkyne substrates.[69d] Still other systems with CuCl/CuBr included aniline as co-catalyst for hydroamination–hydrolysis of internal alkynes,[69a] or require irradiation with blue LED's over 12 h, and were limited to aryl-alkynes.[69b] Our focus screen centered on Cu_2O as cheap and easy to handle metal precursor. Combinations with nitrogen ligands like bipyridine, picolinic acid or nicotinic acid presented little or no activity (Table 7, entries 1–3). A binary combination with CSA gave Markovnikov hydration product with preference for methanol as cosolvent (entry 4 vs 5). The activity of this system was boosted by excess co-catalytic acid (entry 6). An increase of catalyst loading led to full conversion of starting material under screening conditions (entries 7, 8). The excess acidity (formally 5 mol%, since 10 mol% of Cu_2O will neutralize 20 mol% of CSA) is lower than in the blank experiment (Table 1, entry 14), excluding significant background activity of Brønsted-acid. The major side-product is dimethyl acetal **4b**, which could either arise via addition of MeOH across the alkyne, or by equilibrium acetalization of **3**. Preferential acetalization of **3** to **4b** might feign an overly high addition regioselectivity (**2**/**3** = 70:1).

Table 7. HOT-CAT alkyne hydration focus screen of Cu_2O derived catalyst systems.[a]



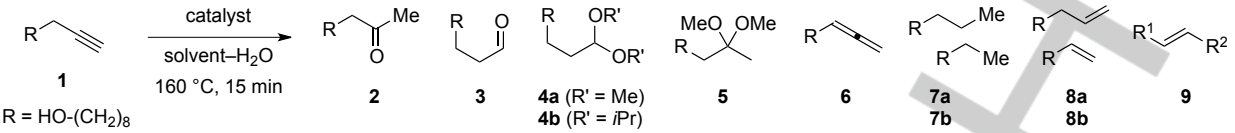
1 R = HO-$(CH_2)_8$ | **2** | **3** | **4a** (R' = Me) **4b** (R' = *i*Pr) | **5** | **6** | **7a** **7b** | **8a** **8b** | **9**

Entry	Catalyst (mol%)[b]	Solv.[c]	**1**	**2**	**3**	**4a/5**[d]	**6**[e]	**7**	**8**	**9**	Rec.[f]	[CH_2OH][g]	Unk.[h]
1	Cu_2O (4)–bipy (10)	D	97.6	0.0	0.1	0.0	0.8	1.4	0.0	0.0	99.9	99.9	0.0
2	Cu_2O (4)–Hpic (10)	D	95.9	1.5	0.3	0.2	0.9	2.2	0.0	0.0	101.0	100.9	-0.1
3	Cu_2O (4)–Hnic (10)	D	92.3	5.3	0.2	0.2	0.8	1.6	0.0	0.0	100.4	100.0	-0.4
4	Cu_2O (4)–CSA (4)	D	65.4	28.1	0.5	0.7/0.04	0.3	1.4	0.0	0.0	96.4	97.8	1.4
5	Cu_2O (4)–CSA (4)	B	91.2	4.1	0.2	0.0	0.7	1.8	0.0	0.0	98.0	99.6	1.6
6	Cu_2O (4)–CSA (10)	D	26.8	65.7	0.8	2.2	0.9	2.5	0.0	0.0	98.9	98.9	0.0
7	Cu_2O (10)–CSA (10)	D	37.3	53.8	0.8	1.5	0.8	1.5	0.0	0.0	95.8	96.9	1.1
8	Cu_2O (10)–CSA (25)	D	0.0	85.4	1.2	2.9/0.1	0.8	1.6	0.5	0.2	92.8	97.9	5.1

[a] Conditions: **1** (50 μL, 0.26 mmol, 0.1 M), microwave heating (160 °C, 15 min). Product quantities by qNMR against internal standard in mol%. [b] Precatalyst and ligand quantity in parantheses. [c] Solvent systems and volume ratios: A = 2-propanol–H_2O (10:3), B = acetone–H_2O (4:1); C = NMP–H_2O (4:1); D = MeOH–H_2O (4:1). [d] Methyl acetal **4a**; if **5** was observed, its quantity is given after a "/". [e] Allene **6** was an impurity (0.8 mol%) in **1**. [f] Recovery, sum of analytically detected components from **1** in mol%. [g] Total hydroxymethylene (δ_H 3.64) in mol% of **1**. [h] Unidentified products, calculated as [RCH_2OH] – [recovery], see text. Hnic = nicotinic acid; Hpic = picolinic acid.

Iridium focus screen. Another focus screen explored ligand effects on complex $[IrCl(COD)]_2$, which had shown a fair level of activity in MeOH, albeit at low chemoselectivity (Table 8, entry 1). The ligand dppm (entries 2, 3) or ambifunctional AZARYPHOS ligands[21] (entries 4, 5) did not accelerate hydration or invert regioselectivity. The level of polymerization remained high (cf. row "*unknowns*"). Chelating diphosphanes (entries 6, 7) or PPh_3 (entry 8) gave less active and selective hydration catalysts. Tributylphosphane induced high activity for alkyne (transfer) hydrogenation, alkene isomerization and alkyne polymerization, but not hydration (entry 9). Triisopropylphosphite (entries 10, 11) was supposed to give an approximation of Ishii's alkyne hydration catalyst,[56] but the system performed similar to $[IrCl(COD)]_2$ alone (entry 1), except showing higher levels of acetal **4a**. A PyBOX ligand suppressed most catalytic activity except polymerization (entry 12), whereas bipyridines restored the Markovnikov hydration and stimulated transfer hydrogenation (entries 13–14). Fluorinated bipyridine with silver triflate activation slightly increases Markovnikov hydration (entry 15). Brønsted acid activation of $[IrCl(COD)]_2$ also increased the hydration activity (entries 16–20), with the strong acid CSA and a high acid-to-metal ratio giving the best result (entry 18). The similarity of entries 18 and 20 indicate that iridium does not complex with TPP under reaction conditions.

Table 8. HOT-CAT alkyne hydration focus screen of iridium-COD catalyst systems.[a]



1 R = HO-$(CH_2)_8$ | **2** | **3** | **4a** (R' = Me) **4b** (R' = *i*Pr) | **5** | **6** | **7a** **7b** | **8a** **8b** | **9**

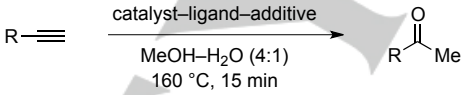
Entry	Catalyst (mol%)[b]	Solv.[c]	**1**	**2**	**3**	**4/5**[d]	**7**	**8**	**9**	**11/12**[e]	Rec.[f]	[CH_2OH][g]	Unk.[h]
1	[IrCl(COD)]$_2$ (2)	D	0.0	44.3	1.7	2.9/0.14	10.8	4.0	2.1	3.4/3.4	72.8	95.4	29.6
2	[IrCl(COD)]$_2$ (2)–dppm (2)	D	1.5	38.2	2.5	2.5/0.1	9.9	4.8	1.9	3.9/4.6	69.9	89.6	28.3
3	[IrCl(COD)]$_2$ (2)–dppm (4)	D	26.2	7.6	1.6	1.6	4.8	4.0	4.7	2.8/5.2	58.5	87.4	36.9
4	[IrCl(COD)]$_2$ (2)–ISIPHOS (2)	D	1.6	22.8	2.9	2.6/0.05	7.6	6.5	2.3	3.2/6.0	55.6	89.5	33.9
5	[IrCl(COD)]$_2$ (2)–*t*AmPyPPh$_2$ (8)	D	9.9	2.4	0.7	0.2	2.9	7.3	6.0	0/–	29.3	83.4	54.1
6	[IrCl(COD)]$_2$ (2)–dppe (4)	D	34.0	3.1	2.1	1.1/0.1	3.5	3.0	5.0	2.0/6.3	60.2	93.0	32.8
7	[IrCl(COD)]$_2$ (2) DPEPhos (4)	D	37.9	7.4	1.2	0.5	2.7	2.8	3.2	5.4/–	61.0	90.2	29.2
8	[IrCl(COD)]$_2$ (2)– PPh$_3$ (8)	D	20.0	3.0	0.6	0.2	2.7	7.7	3.8	2.5/–	40.4	81.6	41.2
9	[IrCl(COD)]$_2$ (2)–PBu$_3$ (8)	D	0.0	0.0	2.5	0.6	17.2	13.9	13.3	0/–	47.6	95.6	48.0
10	[IrCl(COD)]$_2$ (2)–P(O*i*Pr)$_3$ (8)	D	0.0	32.0	2.8	6.5/0.14	5.8	0.5	13.0	4.2/2.9	67.9	94.8	26.9
11	[IrCl(COD)]$_2$ (2)–P(O*i*Pr)$_3$ (2)–AgOTf (2)	D	0.0	38.5	1.7	4.3/0.1	9.2	1.5	5.8	4.6/2.6	68.3	94.5	26.2
12	[IrCl(COD)]$_2$ (2)–Ph$_2$PyBOX (4)	D	38.1	6.4	1.7	0.5	2.8	4.8	2.3	4.0/3.0	63.7	92.8	29.1
13	[IrCl(COD)]$_2$ (2)–bipy (4)	D	0.0	21.8	1.6	1.7/0.1	37.2	5.1	2.0	1.0/2.3	72.8	92.7	19.9
14	[IrCl(COD)]$_2$ (2)–BTF-bipy (4)	D	1.6	23.0	1.7	2.5/0.1	22.3	12.2	5.2	3.2/2.8	74.5	96.9	22.4
15	[IrCl(COD)]$_2$ (2)–BTF-bipy (2), AgOTf (2)	D	0.0	48.9	1.5	3.3/0.14	12.7	4.6	2.1	3.6/3.2	80.0	106.4[i]	26.4
16	[IrCl(COD)]$_2$ (2)–PivOH (10)	D	0.0	44.8	1.8	2.9/0.15	32.3	4.0	2.3	3.1/3.4	94.6	96.2	1.6
17	[IrCl(COD)]$_2$ (2)–TFA (10)	D	0.0	46.9	1.0	3.4/0.14	11.4	3.7	2.4	3.1/3.2	75.1	96.5	21.5
18	[IrCl(COD)]$_2$ (2)–CSA (10)	D	0.0	52.0	0.8	3.0/0.13	12.7	3.1	2.2	2.3/2.0	78.3	97.4	19.1
19[j]	[IrCl(COD)]$_2$ (2)–CSA (10)	D	30.8	26.4	0.6	1.7/0.1	2.9	2.1	1.1	2.0/2.6	70.2	91.3	21.1
20	[IrCl(COD)]$_2$ (4)–CSA (10)	D	0.0	35.7	1.6	4.7/0.1	14.4	3.5	4.3	5.1/2.7	72.1	96.1	24.0
21	[IrCl(COD)]$_2$ (2)–TPP (4)–CSA (10)	D	0.0	53.2	1.0	2.9/0.12	15.2	3.2	2.0	2.3/2.0	81.9	95.4	13.5
22	[Ir(OMe)(COD)]$_2$ (2)–CSA (10)	A	18.7	16.3	1.7	0.0	6.5	6.8	3.8	4.8/2.0	60.5	90.9	30.4
23	[Ir(OMe)(COD)]$_2$ (2)–CSA (10)	B	28.7	13.8	1.9	0.0	5.0	6.6	3.6	4.4/1.8	65.8	88.4	22.6
24	[Ir(OMe)(COD)]$_2$ (2)–CSA (10)	C	26.9	6.7	1.8	0.0	3.1	6.7	3.6	4.8/3.1	56.5	86.4	29.9
25	[Ir(OMe)(COD)]$_2$ (2)–CSA (10)	D	8.1	30.5	0.5	1.4/0.1	6.8	5.9	3.2	3.5/3.3	63.3	86.6	23.3

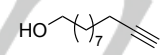
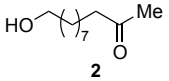
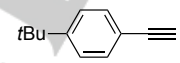
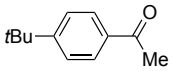
[a] Conditions: **1** (50 μL, 0.26 mmol, 0.1 M), microwave heating (160 °C, 15 min). Product quantities by qNMR against internal standard in mol%. [b] Precatalyst and ligand quantity in parantheses. [c] Solvent systems and volume ratios: A = 2-propanol–H_2O (10:3), B = acetone–H_2O (4:1); C = NMP–H_2O (4:1); D = MeOH–H_2O (4:1). [d] Methyl acetal **4a** and Ketal **5**, if present. [e] Quantities of **11** (arenes) and **12** (enynes; cf. Scheme 3) are expressed in mol% of **1** incorporated. [f] Recovery, sum of analytically detected components from **1** in mol%. [g] Total hydroxymethylene (δ_H 3.64) in mol% of **1**. [h] *Unknowns*, calculated as [CH_2OH] – [recovery], see text. [i] A high (>100%) recovery of [CH_2OH] points to generation of diol **10**. [j] Reaction with oil bath heating for 15 h at 60 °C. BTF-bipy = 5,5'-bis-trifluoromethyl-2,2'-bipyridine.

Halide-free reaction systems from $[Ir(OMe)(COD)]_2$ and CSA showed incomplete conversion and low hydration selectivity, irrespective of the solvent (entries 22–25). Generally, the focus screen revealed that $[IrCl(COD)]_2$-based catalyst systems slightly profit from co-catalytic Brønsted acid, while phosphane ligands have little or negative effects. Hydration activity levels remained limited (≤55%), since alkyne polymerization, hydrogenation and alkene isomerization remain important side-reactions. None of the steering ligands boosted alkyne hydration or affected its regioselectivity notably.

Preparative runs with new catalyst systems. The utility of reaction conditions found in HOT-CAT screens was validated by applying three promising catalyst systems in preparative hydration runs with each an aliphatic (**1**) and an aryl-substituted (4-*tert*-butylphenylacetylene; **18**) acetylene as substrate. The reaction conditions were as in the screening, except for working at higher concentration. The system $[IrCl(COD)]_2$–CSA (cf. Table 8, entry 18) had shown complete conversion and highest Markovnikov regioselectivity of the iridium catalysts. The preparative run with **1** closely reproduced the screening result, and the yield of chromatographically purified **2** was close to the analytical value. Aryl acetylene **18** was hydrated with low chemoselectivity, and the yield was mediocre (Table 9, entry 2). Alkyne polymerization is the major side-reaction. Another catalyst system is $Co(OAc)_2$–TPP–CSA in air, which is easy to set up and had shown favorable results in the screen (Table 4, entry 8). This was confirmed by the high isolated yields of **2** and **19**, both of which approached the analytical yields (Table 9, entries 3, 4). The third new catalyst tested is the simple Cu_2O–CSA system. It performed equally effective in the hydration of **1** and **18**, giving methyl ketones **2** and **19** in high yield. Chromatographic purification of the latter was complicated by the presence of methyl-acetal, thus **19** was isolated as crystalline dinitrophenylhydrazone (**20**).

Table 9. Preparative hydration with three selected new catalyst systems.[a]



Entry	Catalyst system (mol%)[b]	Solvent	Substrate	Product	Yield (spectr.)[c]	Yield (isol.)[d]
1	$[IrCl(COD)]_2$ (2) – CSA (10)	MeOH–H_2O (4:1)	 **1**	 **2**	57	54
2	$[IrCl(COD)]_2$ (2) – CSA (10)	MeOH–H_2O (4:1)	 **18**	 **19**	38	35
3	$Co(OAc)_2$ (4) – TPP (4) – CSA (25)	MeOH–H_2O (4:1)	**1**	**2**	83	82
4	$Co(OAc)_2$ (4) – TPP (4) – CSA (25)	MeOH–H_2O (4:1)	**18**	**19**	98	95
5	Cu_2O (10) – CSA (25)	MeOH–H_2O (4:1)	**1**	**2**	85	85
6	Cu_2O (10) – CSA (25)	MeOH–H_2O (4:1)	**18**	**19**	85	72[e]

[a] Conditions: **1** (200 μL, 1.04 mmol, 0.20 M); **18** (200 μL, 1.11 mmol, 0.21 M), MeOH (4.0 mL), H_2O (1.0 mL), microwave heating for 15 min at 160 °C. [b] Precatalyst and ligand quantity in parentheses. [c] qNMR yield in mol% of substrate, determined against internal standard. [d] Isolated yields. [e] Yield of 2,4-dinitrophenylhydrazone after precipitation and recrystallization from EtOAc.

Discussion

Newly detected catalyst systems from screening results. All of the established Markovnikov- and anti-Markovnikov-selective alkyne hydration catalysts tested in the HOT-CAT screen returned a positive result (Table 1; Table 2 for Ru; Table 5 for Pt; Table 6 for Au). This provides a benchmark by proving that the screen positively identifies active catalysts. The high reaction temperature and short reaction time did not prevent observation of catalytic activity with heat-sensitive systems (e.g., Ag(I), Au(I/III)) whose thermal deactivation is reflected by lower conversions.

The screens revealed many new findings, which can be divided into sub-categories based on activity and novelty, if compared to previously established catalyst systems:

1) Highly active catalysts with close analogy to established systems: High activity was detected for Co-TPP-CSA (90% **K**; highly chemoselective; Table 4, entry 8; also cf. Table 9, entries 3 and 4), $[IrCl(COD)]_2$ (44% **K**; low chemoselectivity; Table 8, entry 1) and Au(*t*BuPyPPh$_2$)OTf (92% **K**; Table 6, entry 7). Those are more or less obvious variations of reported catalyst systems (Co[10], Ir,[56] Au[34]). Yet there are novel aspects, such as the use of the simple TPP ligand with cobalt, as opposed to its water-soluble sulfonated version. The relatively high catalytic activity of $[IrCl(COD)]_2$ with acid (e.g., Table 8, entry 18), or of the complex alone (Table 8, entry 1), had not specifically been reported, although Ishii had devised the optimized system $[IrCl(COD)]_2$–P(O*i*Pr)$_3$–$ZrCl_4$ in MeOH as highly selective alkyne hydration catalyst.[56] Their screening data infer that both P(O*i*Pr)$_3$ and $ZrCl_4$ must be present to achieve high chemoselectivity.

2) Notable activity, moderate analogy to known systems: The activities of CuOTf·(PhH)$_{0.5}$ (Table S1, 160; 46% **K**) or $[Cu(MeCN)_4]PF_6$ (Table 6, entry 2; 16% **K**) from the screen were regarded as very promising, since simple cationic Cu(I) had not previously been reported for alkyne hydration. A focus screen identified the co-catalytic effect of Cu(I) and H^+ in the practical Cu_2O–CSA catalyst (Table 7; 85% **K**). The system is active in aqueous methanol at low acidity and is thus different from recently published Cu(OTf)$_2$-based systems, which work in acidic media with a preference for aryl-alkynes.[8c,69] An earlier Cu(II)-system of Meier and Marsella in alcoholic solution[60] may well have contained a similar active component formed by reaction of Cu(II) with alcohol.[71]

The complex cations $[(P–P)Pt(C_6F_5)^+]$ (18.5% **K** at 37% conversion with BINAP, 12% **K** at 16% conversion with dppe; Table 5, entries 4, 5) are chemically distinct from older platinum-systems based on $PtCl_2$ alone, or chloro complexes with alkene and phosphane steering ligands.[6,73] Those fluoroarylplatinum(II) cations were studied for alkene epoxidation catalysis by Strukul,[65,74] but now also appear as development candidates for catalytic alkyne hydration.

3) Low activity, at various degrees of analogy to existing systems: Significant alkyne hydration activity, although not at useful levels because of low chemoselectivity and turnover, was detected with $(NH_4)_2[OsCl_6]$ (13% **K**, 67% conversion; Table 3, entry 15) as novel type of central metal in catalytic alkyne hydration (for stoichiometric precedence, see ref.[75]). Transfer hydrogenation, isomerization and polymerization were major side-reactions. Further development is necessary to test if ligand effects can steer this activity further towards hydration.

A glimpse of anti-Markovnikov hydration activity was seen with $[RhCl(COD)]_2$ (5.8% **A**, 1.4% **K**; Table 4, entry 14), but only in acetone, and at low activity and chemoselectivity. anti-Markovnikov selectivity was also observed for Cp*$RuCl_2$–ISIPHOS in the 1-heptyne screen (Table S1, entries 68, 69), where the active species may have been related to known catalyst $[CpRu(ISIPHOS)_2]^+$.[30,44] Albeit low, it is the first demonstration of such activity for a Cp*Ru system.

Chemoselectivity was an issue with the moderately active systems $RhCl_3$(TRIPHOS) (8% **K**; Table 4, entry 18), $PdCl_2$(COD) (up to 20% **K**, Table S1, 144) and $PdCl_2$ (11% **K**, Table S1, 136 or 3% **K**, Table 5, entry 1). For the palladium-catalysts, alkyne polymerization is the major side-reaction, which explains the requirement for anchimeric assistance in successful Pd-catalyzed alkyne hydrations.[6]

Catalytic activity besides the target hydration. All reaction products are analyzed in our HOT-CAT screen, rather than focusing on a specific target. Ideally, this provides information about all important side-reactions. New or unexpected reactions may be found, and knowledge of side-reactions can give hints towards optimizing the target reaction. Our first screen with 1-heptyne and using GC-MS analysis was unsatisfactory in this regard, since the identification of "off-target" products in the complex hydrocarbon mixture (containing heptene isomers, heptyne dimers, -trimers, arenes etc.) was insecure, and quantification of each compound would have required reference samples. Consequently, the recoveries in that screen were often low. This situation was amended by the new HOT-CAT screen with alkyne **1** in combination with qNMR analysis. NMR signals provide structural information, and new compounds could be assigned based on literature data. Groups of similar compounds (e.g., **7a/b**, **8a/b**, **9**, total hydroxymethylene [CH_2OH]) are captured by area integration. Recoveries were typically in the 95–102% range (79 out of 105 runs), and outliers could be ascribed to polymer generation. Alkyne polymerization was the single most important side-reaction, most prominent for (% referring to mol% of **1**): $Pd(OAc)_2$–Men_2POH–CSA (74%),[76] $PdCl_2$(COD) (63%), $[IrCl(COD)]_2$–PR_3 (28–54%), $PtCl_2$ (23%), $[IrCl(COD)]_2$ (15–23%), $[RhCl(COD)]_2$ (19%, 23% with ISIPHOS, 15% with dppm).[54,77] Even though alkyne dimerization is a very common metal-catalyzed reaction of alkynes,[25] it was conspicuously absent from our screens, where dimers were found to notable extent only with $[RhCl(COD)]_2$–ISIPHOS (18%) and $[IrCl(COD)]_2$–(P–P) (4–6%; P–P = chelating diphosphine). Presumably, dimers formed in other reactions underwent polymerization under HOT-CAT reaction conditions.[78]

Alkyne trimerization to arenes was seen with $[RhCl(COD)]_2$ (13% in acetone), and generally with Rh- and Ir- complexes at levels up to 5% (referring to mol% of **1** incorporated). Some trimerization also occurred with $[(C_6H_6)Co(TMB)]^+$ (4%).

Transfer-hydrogenation, alkene isomerization. A family of metal-hydride induced reactions converts alkyne **1** to either

terminal alkene **8a** and/or alkane **7a** by transfer-hydrogenation, presumably involving solvent as hydride-donor. Once the alkene stage is reached, double-bond isomerization to internal alkenes **9** may occur. Alkyne-semihydrogenation/alkene isomerization activity was distinctive with $(NH_4)_2OsCl_6$, where such pathways (including alkene hydrogenation) accounted for a remarkable 75% in the solvent *i*PrOH (Table 3, entry 12).[79] Complex $[IrCl(COD)]_2$ apparently favors alkene hydrogenation of **1** to **7a** (Table 4), but since this was found alike in *i*PrOH (entry 19) and acetone (entry 20), an alternative explanation that **7a** was formed through a chain-walking redox-isomerization involving the $–CH_2OH$ unit may be considered.[80]

Reaction development experience gained in the HOT-CAT screen. The HOT-CAT screen keeps many reaction variables at fixed parameters and potentially deviates strongly from optimal or even satisfactory conditions. The development history of the practically applied catalyst systems (Table 9) provides critical case-studies: A first screen with cobalt was carried out in 2011,[81] prior to the report on water-soluble Co-porphyrin-catalyst systems by Naka.[10] Seven runs ($CoCl_2$, $Co(OAc)_2$, vitamin B_{12}; each alone and with ISIPHOS; $Co(OAc)_2$ additionally with ISIPHOS–CSA (Table S1, entries 101–107) displayed ≤10% conversion and no hydration product. The aim of the study at the time was to explore new alkyne hydration activity by harnessing potential accelerating effects of ambi-functional ligands, and the outcome for cobalt was negative. In this instance, the HOT-CAT screen failed to uncover a new type of activity, because a specific ligand (porphyrin type) was not considered for testing. More recently, and aware of Naka's results, we performed another screen (Table 4, entries 1–8) with cobalt. Vitamin B_{12} displayed no activity with co-catalytic acid or iron(III)triflate. The switch to $Co(OAc)_2$–TPP proved partially successful (Table 4, entry 6). The positive effects of oxygen and co-catalytic acid were then recognized in two additional experiments, providing the final catalyst system (Table 9).

With iridium, considerable activity was found with the simple metal precursor complex $[IrCl(COD)]_2$ in *i*PrOH–H_2O (Table 4, entry 19). Solvents were then varied (entries 20–22), and MeOH identified as best choice. The strategy to improve the low chemoselectivity through steering ligand effects in a focus screen failed (Table 8). Oligo- and polymerization were key distractors of this catalysis. The best conditions combine $[IrCl(COD)]_2$ with Brønsted acid, and this system was applied in two preparative runs, which still suffered from limited chemose-lectivity (Table 9).

The catalytic activity of cationic copper(I) was obvious in the initial screen with CuOTf (46% **K**; Table S1, entry 160). Lowering the catalyst loading and temperature with $[Cu(MeCN)_4]PF_6$ reduced the yield to 3%, whereas a solvent change to methanol increased it once again to 16%. In spite of the low yield, the chemoselectivity was high, which was taken as a hint to "intensify" the reaction conditions (e.g., increase reaction temperature, -time or acidity level). A Cu(I) focus screen with Cu_2O is a simple precursor for cationic Cu(I) with acids was performed ($Cu_2O + 2\ HX = 2\ Cu^+ + 2\ X^- + H_2O$; Table 7). The standard Brønsted acid additive of our screen, CSA[37] proved suitable, and, revealed a co-catalytic effect when used in excess (entries 4–8). The final catalyst system was suitable for preparative applications (Table 9).

Conclusions

We have proposed the HOT-CAT (*homogeneous thermal catalysis*; i.e. homogeneous catalysis at unusually high temperatures) screening approach as a tool to discover new catalysts systems for a predefined organic transformation. A peculiarity of this approach is that all test runs are performed at the same set of reaction parameters at a deliberately high temperature for a short reaction time. By fixing many reaction variables to constant values (temperature, time, concentration), and others to only few predefined settings (solvent type A–D, acid additive (yes/no)), the number of experiments in the screening of a variety of chemically distinct catalyst systems remains small. Concurrently, the short reaction time and standardized workup/analysis render the procedure efficient. The bottlenecks are sample preparation and -analysis which require a skilled operator.

Utility and limitations of the HOT-CAT screening approach. The HOT-CAT approach has proven suitable for broad-band screening across a large part of the periodic table. In spite of the elevated reaction temperature, there is neither extensive background reaction (e.g. by Brønsted acid) nor loss of starting material by non-productive decomposition. The screen is specific for catalytic activity by metal complexes and provides a wealth of information about the target reaction, accompanying side-reactions and about the catalyst systems tested. The number of side-reactions and side-products which were identified and analyzed for *all* individual catalyst systems in this study exceeds that which has been presented in published focused optimization studies for singular catalyst systems. Such data ensures comparability between diverse catalyst systems and will provide useful as reference in future searches for alkyne hydration catalysts.

At least two new promising catalyst systems of relevance for preparative application have emerged from the current work, namely Cu_2O–CSA and $Co(OAc)_2$–TPP–CSA in MeOH–H_2O (4:1), which both were run under the same microwave conditions (160 °C, 15 min) of the screening and provided 72–95% isolated yield of product in 4 runs with an aliphatic and an aryl acetylene.

One of the motivations behind the screen was the search for new (non $CpRu^+$-) types of anti-Markovnikov hydration catalysts. Notwithstanding indications of (low) anti-Markvonikov hydration activity with $[RhCl(COD)]_2$ (Table 4, entry 14), this search has not yet proven successful. The approach to invert regioselectivity by systematically combining ambifunctional pyridylphosphane ligands with metal precursor complexes was so far not effective.

Nevertheless, the HOT-CAT screen has allowed us to realize an unprecedentedly broad comparative overview of catalytic alkyne hydration and its accompanying reactions. We propose that as analytical tools progress, such generalized screens may be planned and performed as multi-reaction screens, in which the focus is no longer on a single target reaction, but as many

reactions as analytical tools allow (cf. the concept of an *undirected screen*, ref.[5]) In that sense, rather than screening for specific new *catalyst systems*, one will screen for *reaction systems* and optimize established reactions while searching for new ones.

Experimental Section

Unless otherwise specified, all reagents and solvents were obtained from commercial suppliers and used without further purification. Solvents used in catalytic reactions were purified by passing through a column of Al_2O_3 and kept under an argon atmosphere. Column chromatography (CC) was performed on silica gel 60 (35–70 μm particle size), usually as a flash chromatography with 0.2 bar positive air pressure. Thin layer chromatography was performed on glass plates coated with silica gel 60 F_{254} and visualized with UV light (254 nm) or Mostain (molybdenum stain with $Ce(SO_4)_2$ catalyst in H_2SO_4 aq). NMR spectra were recorded at ambient temperature (19–24 °C). ^{1}H NMR spectra were internally referenced to tetramethylsilane (TMS, δ 0.00) or residual solvent peaks ($CDCl_3$ δ 7.26; (D_6)-DMSO δ 2.50). Measurements for qNMR analysis used 16 scans and a pulse relaxation delay d1 of 20 seconds. ^{13}C NMR spectra were referenced to TMS (δ 0.00) or solvent peaks ($CDCl_3$ δ 77.16; (D_6)-DMSO δ 39.52).

General microwave–qNMR screening procedure with alkyne 1

Sample preparation: To a microwave glass vial containing a magnetic stirring bar, the metal precursor or -complex, the ligand, and/or any other additive were added. The glass vial was placed into a Schlenk vessel (29 mm diameter opening) and placed under argon by evacuating and filling with argon thrice. Solvent (2.0 mL), water (0.5 mL; 0.6 mL in case of solvent combination A with *i*PrOH) and 10-undecyn-1-ol (**1**; 50 μL, 0.26 mmol) were added to the vial in an argon counter-stream. The glass vial was closed with a corresponding standard cap and placed into the microwave reactor, where it was heated to 160 °C with a holding time of 15 minutes. The cooled reaction solution was transferred into a 10 mL headspace glass vial (for GC analysis), which contained the internal standard for qNMR analysis (e.g., 20–25 mg of 1,3-dinitrobenzene). Ethyl ether (3 x 2 mL) was used to complete the transfer. The content of the capped headspace vial was homogenized by intense shaking. A quantity of 0.5 mL of the resulting solution was removed into a 5 mL headspace vial, where it was diluted with ethyl ether (2 mL) and washed with water (2 x 2 mL) [5 drops of sat. aq. NaCl were added to speed up phase separation] and sat. aq. NaCl (2 x 2 mL) by intense shaking and removal of the lower water phase by a Pasteur pipette after phase separation. The organic phase was transferred into a 5 mL headspace vial (with stirring) containing $MgSO_4$ (300 mg) and a magnetic stirring bar. The vial was closed with a butyl rubber septum and sealed with an aluminum cap. The suspension was magnetically stirred (1200 rpm) while vacuum was applied by placing a hypodermic needle connected to a water aspiration pump into the septum. A low vacuum (ca 500 mbar, weak water flow in the pump) was initially applied to remove the majority of Et_2O, after which the solid contents of the vial showed a dry, powdery appearance. A stronger vacuum (full water flow, *ca.* 20 mbar) was then applied for another 2 minutes. The solid residue was extracted with $CDCl_3$ (0.6–0.8 mL) by magnetically stirring for 5 minutes, and the suspension was filtered through a cotton plug into an NMR tube for analysis.

Data analysis. ^{1}H NMR spectra were recorded with 16 scans using a relaxation delay (d1) of 20 seconds. After phase- and baseline-correction, the relevant signal integrals as detailed in Figure S1 and Table S3 were collected for evaluation.

Ir-catalyzed hydration of 1-octyne with product fractioning

[IrCl(COD)]$_2$-catalyzed hydration of 1-octyne: A 10 mL microwave vial with a PTFE stirring bar was loaded in air with [IrCl(COD)]$_2$ (40.9 mg, 60.7 μmol, 0.02 eq.). The vessel was placed under argon (3 cycles of evacuation and argon flooding). In an argon counter-stream, water (1.0 mL, 55.5 mmol, 18.2 eq.), degassed MeOH (4.0 mL) and 1-octyne (450 μL, 336 mg, 3.05 mmol, 1 eq.) were added. The vial was capped and placed into a microwave reactor for heating at 160 °C for 15 min (holding time at target temperature). The cooled reaction solution was diluted with Et_2O (10 mL) and completely transferred into a separatory funnel, the vessel being washed with additional Et_2O (2 × 5 mL). The organic phase was washed with H_2O (3 × 15 mL) and sat. aq. NaCl (10 mL). The combined aq. phase was washed with Et_2O (10 mL). The combined organic phases were dried ($MgSO_4$), filtered and evaporated (at 850 mbar, then shortly at 650 mbar). After addition of 1,1,2,2-tetrachloroethane (100 μL, 159 mg, 947 μmol), a sample (0.1 mL) was removed into an NMR tube and diluted with $CDCl_3$ (0.5 mL) for qNMR analysis. *Composition of the crude (mol%)*: 1-octyne (0.0%), octanal (0.6%), 2-octanone (42.3%), heptane (n.d.), 1-octene (2.2%), int. alkenes (2.5%), 1,1-dimethoxyoctane (2.5%), tri-*n*-hexylbenzene isomers (7.5%, in molar units of 1-octyne), enynes (*ca.* 2.6%, dito); component recovery: 60.2%; area integral for methyl end groups RCH_3: 89.6%; the difference 89.6–60.2 = 29.4% will approximately reflect poly-1-octyne.

Product fractioning: After combining the NMR sample with the crude product, solvent was removed and the residue was vacuum-distilled using a short-path distillation unit, initially up to 120 °C/35 mbar (fractions 1 and 2). The receiving vessels were changed and the distillation continued up to 140 °C/0.6 mbar (fraction 3, fraction 4 = residue). The fractions were analyzed by ^{1}H NMR spectroscopy: *fraction 1* (volatile, receiving vessel cooled), 274 mg, contains 2-octanone, 1,1-dimethoxy-octane, little 2,2-dimethoxyoctane, octanal, 1-octene; also contains 1,1,2,2-tetrachloroethane and 1,5-cyclooctadiene; *fraction 2* (volatile, receiving vessel not cooled), 86.7 mg, composition similar to fraction 1, but contains more 1,1-dimethoxy-octane; *fraction 3* (distillate): 19.2 mg, aldol condensation products, alkyne dimers; *fraction 4* (distillation residue): 151 mg, cyclotrimerization products (1,2,4- and 1,3,5-isomers), broad signals for poly-1-octyne.

NMR-Analysis of the distillation residue: ^{1}H NMR (500 MHz, $CDCl_3$): poly-1-octyne: δ 0.73–1.04 (m, CH_3), 1.07–1.75 (m, CH_2), 1.86–2.72 (m, CH_2), 4.94–6.45 (m, C=C*H*); 1,3,5-tri-*n*-hexylbenzene: δ 6.80 (s, 3 H, ArH); 1,2,4-tri-*n*-hexylbenzene: δ 6.91–6.97 (m, 2 H, ArH), 7.04 (d, J = 7.6 Hz, 1 H, ArH). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): poly-1-octyne;[58] δ 14.1 (br, CH_3), 22.7 (br, CH_2), 29.3 (br, CH_2), 31.8 (br, CH_2), 126.5–127.5 (*C*=CH), 138.7–139.3 (C=*C*H); 1,3,5- and 1,2,4-tri-*n*-hexylbenzene;[59] δ 14.2, 22.8, 29.3, 29.6, 31.5, 31.7, 31.7, 31.9, 32.5, 32.9, 35.7, 36.1, 125.8, 125.9, 129.0, 129.3, 137.8, 140.2, 140.4, 142.8.

Preparative hydration of alkynes with [IrCl(COD)]$_2$–CSA

11-Hydroxyundecan-2-one (2): A 10 mL microwave vial with a stirring bar was loaded in air with [IrCl(COD)]$_2$ (14.0 mg, 20.8 μmol, 0.02 eq.) and camphorsulfonic acid (24.2 mg, 104 μmol, 0.1 eq.). The vessel was evacuated and flooded with argon thrice. In an argon counter-stream, degassed H_2O (1.0 mL, 55.5 mmol, 52.9 eq.), degassed methanol (4.0 mL) and 10-undecyn-1-ol (**1**; 200 μL, 176 mg, 1.05 mmol, 1 eq.) were added to the contents. The vial was capped and placed into the microwave unit, where it was heated to 160 °C for 15 min (holding time at target temperature). The cooled reaction mixture was transferred into a separatory funnel and the vial washed with Et_2O (4 × 5 mL). The organic phase was washed with water (3 × 15 mL) and sat. aq. NaCl (10 mL), and the aq. phase was extracted with Et_2O (10 mL). The combined

organic phase was dried ($MgSO_4$), filtered and evaporated under reduced pressure. To the residue, 1,3-dinitrobenzene was added (41.2 mg, 245 μmol) and the materials were homogeneously dissolved in $CDCl_3$ (0.7 mL). An aliquot (0.2 mL) was removed and placed into an NMR tube with additional $CDCl_3$ (0.3 mL) for qNMR analysis. *Composition (mol%)*: starting material (0.0%), aldehyde (0.7%), ketone (56.9%), allene (0.0%), *n*-alkanols (9.1%), terminal alkene (2.3%), internal alkenes (2.1%), dimethyl acetal (2.3%), component recovery (73.4%), recovery of [CH_2OH] (98.9%). The NMR sample was combined with the remainder material and the solvent removed in vacuum. Purification by CC (SiO_2, EtOAc–hexanes 1:5→1:2) gave 11-hydroxyundecan-2-one (**2**; 104 mg, 54%) as colorless solid after drying in HV. R_f 0.40 (EtOAc–hexanes 1:1, Mostain). M.p. 42.1–42.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24–1.46 (m, 10 H, 5×CH_2), 1.43 (br s., 1 O*H*), 1.52–1.61 (m, 4 H, 2×CH_2), 2.13 (s, 3 H, CH_3), 2.42 (t, J = 7.5 Hz, 2 H, COCH_2), 3.64 (t, J = 6.6 Hz, 2 H, CH_2OH). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$: δ 23.83, 25.70, 29.13, 29.29, 29.33, 29.38, 29.84, 32.77, 43.79, 63.02, 209.36. Known compound, CAS-No. 35345-72-3.

4-*tert*-Butylacetophenone (19). A 10 mL microwave vial with a stirring bar was loaded in air with $[IrCl(COD)]_2$ (14.9 mg, 22.2 μmol, 0.02 eq.) and camphorsulfonic acid (25.7 mg, 111 μmol, 0.1 eq.). The vessel was evacuated and flooded with argon thrice. In an argon counter-stream, degassed H_2O (1.0 mL, 55.5 mmol, 50 eq.), degassed methanol (4.0 mL) and 4-*tert*-butylphenylacetylene (**18**; 200 μL, 176 mg, 1.11 mmol, 1 eq.) were added to the contents. The vial was capped and placed into the microwave unit, where it was heated to 160 °C for 15 min (holding time at target temperature). The cooled reaction mixture was transferred into a separatory funnel and the vial washed with Et_2O (4 × 5 mL). The organic phase was washed with water (3 × 15 mL) and sat. aq. NaCl (10 mL), and the combined aq. phase was extracted with Et_2O (10 mL). The combined organic phase was dried ($MgSO_4$), filtered and evaporated under reduced pressure. To the residue, 1,3-dinitrobenzene was added (41.1 mg, 245 μmol) and the materials were dissolved homogeneously in $CDCl_3$ (0.7 mL). An aliquot (0.2 mL) was removed and placed into an NMR tube with additional $CDCl_3$ (0.3 mL) for qNMR analysis. *Composition (mol%)*: starting material (0.0%), aldehyde (0.3%), ketone (38.0%), dimethyl acetal (1.0%), component recovery (39.3%). Broad signals (δ_H 6.5–7.5) indicate the presence of polymeric material. The NMR sample was combined with the remainder of material and the solvent was removed in vacuum. Purification by CC (SiO_2, EtOAc–hexanes 1:50→1:20) gave 92.6 mg of a yellowish oil. Shortpath-distillation (up to 75 °C/0.7 mbar) gave 4-*tert*-butylacetophenone (**19**; 68.9 mg, 35%) as colorless oil. R_f 0.63 (EtOAc–hexanes 1:5, UV). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.34 (s, 9 H, CMe_3), 2.58 (s, 3 H, COMe), 7.43–7.52 (m, 2 H, Ar-H), 7.86–7.94 (m, 2 H, Ar-H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 26.55, 31.09, 35.10, 125.49, 128.28, 134.62, 156.81, 197.84. Known compound, CAS-No. 943-27-1, data consistent with ref.[82]

Preparative hydration of alkynes with $Co(OAc)_2$–TPP–CSA

11-Hydroxyundecan-2-one (2): A 10 mL microwave vial with a stirring bar was loaded in air with $Co(OAc)_2$ (10.4 mg, 41.8 μmol, 0.04 eq.), tetraphenylporphyrin (25.6 mg, 41.6 μmol, 0.04 eq.) and camphorsulfonic acid (60.5 mg, 260 μmol, 0.25 eq.). H_2O (1.0 mL, 55.5 mmol, 53 eq.), methanol (4.0 mL) and 10-undecyn-1-ol (**1**; 200 μL, 175 mg, 1.04 mmol, 1 eq.) were added to the contents in air. The vial was capped and placed into the microwave unit, where it was heated to 160 °C for 15 min (holding time at target temperature). The cooled reaction mixture was transferred into a separatory funnel and the vial washed with Et_2O (4 × 5 mL). The organic phase was washed with water (3 × 15 mL) and sat. aq. NaCl (10 mL), and the aq. phase was extracted with Et_2O (10 mL). The combined organic phase was dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was dissolved in $CDCl_3$ (0.7 mL). An aliquot (0.2 mL) was removed and placed into an NMR tube with additional $CDCl_3$ (0.3 mL) for qNMR analysis. *Composition (mol%)*: starting material (9.4%), aldehyde (0.3%), ketone (83.2%), allene (0.7%), *n*-alkanols (0.0%), terminal alkene (0.2%), internal alkenes (0.0%), dimethyl acetal (0.8%), component recovery (94.6%); the quantities were referenced to the [CH_2OH]-signal (δ_H 3.60, 2 H) at 200%. The NMR sample was combined with the remaining material and the solvent removed in vacuum. The residue was distilled in vacuum (0.6 mbar/up to 120 °C) to give 180 mg of colorless solid, which was further purified by CC (SiO_2, EtOAc–hexanes 1:10→1:4) to give 11-hydroxyundecan-2-on (**2**; 160 mg, 82%) as colorless solid. See above for characterization data.

4-*tert*-Butylacetophenone (19): A 10 mL microwave vial with a stirring bar was loaded in air with $Co(OAc)_2$ (11.0 mg, 44.2 μmol, 0.04 eq.), tetraphenylporphyrin (27.3 mg, 44.4 μmol, 0.04 eq) and camphorsulfonic acid (64.4 mg, 277 μmol, 0.25 eq.). H_2O (1.0 mL, 55.5 mmol, 50 eq.), methanol (4.0 mL) and 4-*tert*-butylphenylacetylene (**18**; 200 μL, 176 mg, 1.11 mmol, 1 eq.) were added to the contents in air. The vial was capped and placed into the microwave unit, where it was heated to 160 °C for 15 min (holding time at target temperature). The cooled reaction mixture was transferred into a separatory funnel and the vial washed with Et_2O (4 × 5 mL). The organic phase was washed with water (3 × 15 mL) and sat. aq. NaCl (10 mL), and the combined aq. phase was extracted with Et_2O (10 mL). The combined organic phase was dried ($MgSO_4$), filtered and evaporated under reduced pressure. To the residue, 1,3-dinitrobenzene was added (40.2 mg, 239 μmol) and everything was dissolved in $CDCl_3$ (0.7 mL). An aliquot (0.2 mL) was removed and placed into an NMR tube with additional $CDCl_3$ (0.3 mL) for qNMR analysis. *Composition (mol%)*: starting material (0.0%), aldehyde (0.0%), ketone (98.4%), dimethyl acetal (0.0%), component recovery (98.4%). The NMR sample was combined with the remainder of material and the solvent removed in vacuum. Shortpath-distillation (up to 90 °C/0.7 mbar) removed the catalyst residues to give 221 mg of colorless oil, which was further purified by CC (SiO_2, EtOAc–hexanes 1:20) to give 4-*tert*-butylacetophenone (**19**; 187 mg, 95%) as colorless oil. See above for analytical data.

Preparative hydration of alkynes using the Cu_2O–CSA system

Hydration of 10-undecyn-1-ol (1) to 11-hydroxyundecan-2-one (2): A 10 mL microwave vial with a stirring bar was loaded in air with Cu_2O (14.9 mg, 104 μmol, 0.1 eq., 20 mol% [Cu]) and camphorsulfonic acid (60.4 mg, 260 μmol, 0.25 eq.). The vessel was evacuated and flooded with argon thrice. In a counter-stream of argon, water (1.0 mL, 55.5 mmol, 53 eq.), methanol (4.0 mL) and 10-undecyn-1-ol (**1**; 200 μL, 176 mg, 1.05 mmol, 1 eq.) were added to the contents. The vial was capped and placed into the microwave unit, where it was heated to 160 °C for 15 min (holding time at target temperature). The cooled reaction mixture was transferred into a separatory funnel and the vial washed with Et_2O (4 × 5 mL). The organic phase was washed with water (3 × 15 mL) and sat. aq. NaCl (15 mL), and the combined aq. washing phase was reextracted with Et_2O (10 mL). The combined organic phase was dried ($MgSO_4$), filtered and evaporated under reduced pressure. Purification by CC (SiO_2, EtOAc–hexanes 1:10→1:4) gave 11-hydroxyundecan-2-one (**2**; 166 mg, 85%) as colorless solid after drying in HV. Analytical data coincided with previous samples, see above.

4-*tert*-Butylacetophenone 2,4-dinitrophenylhydrazone (20): A 10 mL microwave vial with a stirring bar was loaded in air with Cu_2O (15.9 mg, 111 μmol, 0.1 eq., 20 mol% [Cu]) and camphorsulfonic acid (64.4 mg, 277 μmol, 0.25 eq.). The vessel was evacuated and flooded with argon thrice. In a counter-stream of argon, H_2O (1.0 mL, 55.5 mmol, 50 eq.), methanol (4.0 mL) and 4-*tert*-butylphenylacetylene (**18**; 200 μL, 176 mg, 1.11 mmol, 1 eq.) were added to the contents. The vial was capped and placed into the microwave unit, where it was heated to 160 °C for 15 min

(holding time at target temperature). The cooled reaction mixture was transferred into a separatory funnel and the vial washed with Et_2O (4 × 5 mL). The organic phase was washed with water (3 × 15 mL) and sat. aq. NaCl (15 mL), and the combined aq. phase was reextracted with Et_2O (10 mL). The combined organic phase was dried ($MgSO_4$), filtered and evaporated under reduced pressure. To the residue, 1,3-dinitrobenzene was added (40.4 mg, 240 μmol) and everything was dissolved homogeneously in $CDCl_3$ (0.7 mL). An aliquot (0.2 mL) was removed and placed into an NMR tube with additional $CDCl_3$ (0.3 mL) for qNMR analysis. *Composition (mol%)*: starting material (0.8%), aldehyde (1.8%), ketone (83.8%), dimethyl acetal (5.7%), component recovery (92.1%). The NMR sample was combined with the remainder of the material and the solvent was removed in vacuum. The residue was purified by CC (SiO_2, EtOAc–hexanes 1:20) to give crude product (165 mg, purity 93 mol%), which contained dimethylacetal (6 mol%) and aldehyde (1 mol%) as impurity. For purification, the material was derivatized by dissolving in MeOH (2.0 mL) and adding with stirring to a dinitrophenylhydrazine solution[83] (from 0.5 g of 2,4-dinitrophenylhydrazine {50% with water}, 2.5 mL of H_2SO_4 conc., 3.3 mL of H_2O and 12 mL of MeOH). After a short time, the precipitate formed was filtered through a glass filter and washed with water (2 x 20 mL) and 5% $NaHCO_3$ aq (2 x 20 mL). The solid was dried in high vacuum (337 mg, 84%) and recrystallized from EtOAc to give microcrystalline yellow solid (**20**; 286 mg, 72%). Data for 1-(1-(4-(*tert*-butyl)phenyl)ethylidene)-2-(2,4-dinitrophenyl)hydrazine (**20**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.36 (s, 9 H, CMe_3), 2.46 (s, 3 H, MeC=N), 7.46–7.51 (m, 2 H, Ar-H), 7.78–7.83 (m, 2 H, ArH), 8.13 (d, J = 9.6 Hz, 1 H, Ar-H), 8.35 (ddd, J = 9.6, 2.5, 0.6 Hz, 1 H, Ar-H), 9.16 (d, J = 2.5 Hz, 1 H, Ar-H), 11.36 (br. s, 1 H, NH). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 13.64, 31.19, 34.85, 116.75, 123.54, 125.67, 126.32, 129.59, 130.06, 134.47, 138.10, 145.02, 152.43, 153.68. Known compound, Reaxys-ID 964770. Analytical data consistent with ref.[84]

Acknowledgements

Funding of the microwave reactor was provided through Deutsche Forschungsgemeinschaft. We thank Dr. Li Xiao for the synthesis of gold(I) complexes.

Keywords: alkyne hydration • homogeneous catalysis • microwave reactions • transition metals • screening

[1] a) R. Bates, *Organic Synthesis Using Transition Metals*, 2nd ed, Wiley-VCH, Weinheim, **2012**. b) J. Tsuji, *Transition Metal Reagents and Catalysts*, John Wiley & Sons, **2002**.

[2] a) E. S. Isbrandt, R. J. Sullivan, S. G. Newman, *Angew. Chem. Int. Ed.* **2019**, *58*, 7180–7191; *Angew. Chem.* **2019**, *131*, 7254–7267; b) R. Carlson, J. E. Carlson, *Design and Optimization in Organic Synthesis*, 2nd ed, Elsevier, Amsterdam, **2005**; c) P. M. Murray, S. N. G. Tyler, J. D. Moseley, *Org. Process Res. Dev.* **2013**, *17*, 40–46.

[3] L. Hong, W. Sun, D. Yang, G. Li, R. Wang, *Chem. Rev.* **2015**, *116*, 4006–4123.

[4] We are not aware of a fixed terminology for catalyst systems or reaction variables and use the terms in an ad hoc sense; for some basic definitions, see: J. F. Hartwig, P. J. Walsh in *Organotransition Metal Chemistry* (Ed. J. F. Hartwig), University Science Books, **2010**; chapter 14.

[5] a) K. D. Collins, T. Gensch, F. Glorius, *Nature Chem.* **2014**, *6*, 859–871; b) L. J. Gooßen, *Inventing Reactions (Top. Organomet. Chem., Vol. 44)*, Springer, Berlin, **2013**. For examples of recently described innovative screening approaches, see: c) Y. Wang, S. Shaabani, M. Ahmadianmoghaddam, L. Gao, R. Xu, K. Kurpiewska, J. Kalinowska-Tluscik, J. Olechno, R. Ellson, M. Kossenjans, V. Helan, M. Groves, A. Dömling, *ACS Central Science* **2019**, *5*, 451–457; d) M. Teders, C. Henkel, L. Anhäuser, F. Strieth-Kalthoff, A. Gómez-Suárez, R. Kleinmans, A. Kahnt, A. Rentmeister, D. Guldi, F. Glorius, *Nature Chem.* **2018**, *10*, 981–988; e) M. N. Hopkinson, A. Gómez-Suárez, M. Teders, B. Sahoo, F. Glorius, *Angew. Chem. Int. Ed.* **2016**, *55*, 4361–4366; *Angew. Chem.* **2016**, *128*, 4173–4173; f) K. D. Collins, F. Glorius, *Nature Chem.* **2013**, *5*, 597–601; g) T. Gensch, F. Glorius, *Science* **2016**, *352*, 294–295; h) C. Lang, U. Gärtner, O. Trapp, *Chem. Commun.* **2011**, *47*, 391–393.

[6] L. Hintermann, A. Labonne, *Synthesis* **2007**, 1121–1150.

[7] L. Hintermann, *Top. Organomet. Chem.* **2010**, *31*, 123–155.

[8] This rather general statement may be illustrated by selected examples of catalysis development, where the general patterns are found: a) M. Jha, G. M. Shelke, K. Pericherla, A. Kumar, *Tetrahedron Lett.* **2014**, *55*, 4814–4816; b) H. Zou, J. Jiang, N. Yi, W. Fu, W. Deng, J. Xiang, *Chin. J. Chem.* **2016**, *34*, 1251–1254; c) S. Liang, G. B. Hammond, B. Xu, *Chem. Commun.* **2015**, *51*, 903–906; d) M.-Y. Chang, Y.-C. Cheng, *Synlett* **2016**, *27*, 1931–1935; e) D. Chen, D. Wang, W. Wu, L. Xiao, *Appl. Sciences* **2015**, *5*, 114–121; f) M. Bassetti, S. Ciceri, F. Lancia, C. Pasquini, *Tetrahedron Lett.* **2014**, *55*, 1608–1612.

[9] V. J. Meyer, L. Fu, F. Marquardt, M. Niggemann, *Adv. Synth. Catal.* **2013**, *355*, 1943–1947.

[10] T. Tachinami, T. Nishimura, R. Ushimaru, R. Noyori, H. Naka, *J. Am. Chem. Soc.* **2012**, *135*, 50–53.

[11] S. Wang, C. Miao, W. Wang, Z. Lei, W. Sun, *ChemCatChem* **2014**, *6*, 1612–1616; b) S. Wang, C. Miao, W. Wang, Z. Lei, W. Sun, *Chin. J. Catal.* **2014**, *35*, 1695–1700.

[12] Q. Gao, S. Li, Y. Pan, Y. Xu, H. Wang, *Tetrahedron* **2013**, *69*, 3775–3781; b) M. Zeng, R.-X. Huang, W.-Y. Li, X.-W. Liu, F.-L. He, Y.-Y. Zhang, F. Xiao, *Tetrahedron* **2016**, *72*, 3818–3822.

[13] M. Schreyer, L. Hintermann, *Beilstein J. Org. Chem.* **2017**, *13*, 2332–2339.

[14] The principle is seen in much of the previously cited methodological work. Alternatively, the time required to reach "full conversion" (starting material is no longer detected) of substrate can be compared, although this is theoretically less sound (the starting material might never be fully consumed), requires repeated monitoring and is subject to a large error margin.

[15] Comments on choices of typical reaction times: J. Yoshida, *Flash Chemistry: Fast Organic Synthesis in Microsystems*, John Wiley & Sons, **2008**, p. 1.

[16] Schlüter, M. Blazejak, F. Boeck, L. Hintermann, *Angew. Chem. Int. Ed.* **2015**, *54*, 4014–4017; *Angew. Chem.* **2015**, *127*, 4086–4089.

[17] For our previous applications of HOT-CAT-screening, see: a) S. Koller, M. Blazejak, L. Hintermann, *Eur. J. Org. Chem.* **2018**, 1624–1633; b) O. V. Maltsev, R. Rausch, Z.-J. Quan, L. Hintermann, *Eur. J. Org. Chem.* **2014**, 7426–7432; c) O. V. Maltsev, A. Pöthig, L. Hintermann, *Org. Lett.* **2014**, *16*, 1282–1285; d) J. Schlüter, M. Blazejak, L. Hintermann, *ChemCatChem* **2013**, *5*, 3309–3315.

[18] V. Resch, U. Hanefeld, *Catal. Sci. Technol.* **2015**, *5*, 1385–1399.

[19] Hydrocarbon standards such as tetradecane induced a phase-separation of the reaction mixture.

[20] a) G. J. Rowlands, *Tetrahedron* **2001**, *57*, 1865–1882; b) D. B. Grotjahn, *Chem. Eur. J.* **2005**, *11*, 7146–7153.

[21] L. Hintermann, T. T. Dang, A. Labonne, T. Kribber, L. Xiao, P. Naumov, *Chem. Eur. J.* **2009**, *15*, 7167–7179.

[22] Mechanistic studies of the ruthenium-catalyzed anti-Markonvikov hydration indicate decarbonylative chain-shortening of terminal alkyne (R'-$CH_2C{\equiv}CH$ + H_2O = R'-CH_2-CH_3 + CO; R-$CH_2C{\equiv}CH$ + H_2O = R-$CH{=}CH_2$ + CO + H_2) as potential, stoichiometric catalyst deactivation pathway. If lower homologs were formed through such processes, they would be quantified together with the higher homologs **7**, **8**, and **9**, respectively.

[23] Traces of **10** are difficult to detect by NMR due to signal overlap, but its presence in such mixtures was proven by TLC and GC-MS.
[24] M. Lautens, W. Klute, W. Tam, *Chem. Rev.* **1996**, *96*, 49–92.
[25] B. M. Trost, J. T. Masters, *Chem. Soc. Rev.* **2016**, *45*, 2212–2238.
[26] Lewis acid catalyzed alkyne hydrations in hot acetic acid have been reported (e.g., refs.[8c,e,f]). They may proceed through non-metal-specific additions of acetic acid to alkyne. It is of note that formic acid hydrates alkynes often cleanly at 100 °C: N. Menashe, D. Reshef, Y. Shvo, *J. Org. Chem.* **1991**, *56*, 2912–2914.
[27] T. Suzuki, M. Tokunaga, Y. Wakatsuki, *Org. Lett.* **2001**, *3*, 735–737.
[28] C. Bianchini, J. A. Casares, M. Peruzzini, A. Romerosa, F. Zanobini, *J. Am. Chem. Soc.* **1996**, *118*, 4585–4594.
[29] L. Hintermann, L. Xiao, A. Labonne, U. Englert, *Organometallics* **2009**, *28*, 5739–5748.
[30] F. Boeck, T. Kribber, L. Xiao, L. Hintermann, *J. Am. Chem. Soc.* **2011**, *133*, 8138–8141.
[31] L. Li, M. Zeng, S. B. Herzon, *Angew. Chem. Int. Ed.* **2014**, *53*, 7892–7895; *Angew. Chem.* **2014**, *126*, 8026–8029.
[32] Y. Fukuda, K. Utimoto, *J. Org. Chem.* **1991**, *56*, 3729–3731.
[33] a) J. H. Teles, S. Brode, M. Chabanas, *Angew. Chem. Int. Ed.* **1998**, 37, 1415–1418; *Angew. Chem.* **1998**, *110*, 1475–1478; b) E. Mizushima, K. Sato, T. Hayashi, M. Tanaka, *Angew. Chem. Int. Ed.* **2002**, *41*, 4563–4565; *Angew. Chem.* **2002**, *114*, 4745–4747.
[34] A. Leyva, A. Corma, *J. Org. Chem.* **2009**, *74*, 2067–2074.
[35] Microwave-heated samples occasionally break, which would release toxic mercury vapours and might contaminate the apparatus.
[36] a) M. B. T. Thuong, A. Mann, A. Wagner, *Chem. Commun.* **2012**, *48*, 434–436; b) R. Das, D. Chakraborty, *Appl. Organomet. Chem.* **2012**, *26*, 722–726; c) Z.-W. Chen, D.-N. Ye, Y.-P. Qian, M. Ye, L.-X. Liu, *Tetrahedron* **2013**, *69*, 6116–6120.
[37] Camphorsulfonic acid was chosen as standard acidic additive for the screen because of its availability and ease of handling. It is non-hygroscopic and easy to weigh out on a balance.
[38] W.-J. Liu, J.-H. Li, *Chin. J. Org. Chem.* **2006**, *26*, 1073–1078.
[39] J. Yadav, S. K. Das, S. Sarkar, *J. Am. Chem. Soc.* **1997**, *119*, 4315–4316.
[40] a) H. Sakurai, T. Fujii, K. Sakamoto, *Chem. Lett.* **1992**, *21*, 339–342; b) P. M. Treichel in *Comprehensive Organometallic Chemistry II, Vol. 6* (Eds. E W. Abel, F. G. A. Stone, G. Wilkinson), Elsevier, **1995**, pp 109–118; c) D. A. Valyaev, M. G. Peterleitner, L. I. Leont'eva, L. N. Novikova, O. V. Semeikin, V. N. Khrustalev, M. Y. Antipin, N. A. Ustynyuk, B. W. Skelton, A. H. White, *Organometallics* **2003**, *22*, 5491–5497.
[41] a) M. O. Albers, N. J. Coville, *Coord. Chem. Rev.* **1984**, 53*,* 227–259; T.-Y. Luh, *Coord. Chem. Rev.* **1984**, *60*, 255–276.
[42] a) X.-F. Wu, D. Bezier, C. Darcel, *Adv. Synth. Catal.* **2009**, 351, 367–370; b) J. R. Cabrero-Antonino, A. Leyva-Pérez, A. Corma, *Chem. Eur. J.* **2012**, *18*, 11107–11114; c) J. Park, J. Yeon, P. H. Lee, K. Lee, *Tetrahedron Lett.* **2013**, *54*, 4414–4417; d) G. Velegraki, M. Stratakis, *J. Org. Chem.* **2013**, *78*, 8880–8884.
[43] A. Bauer, U. Englert, S. Geyser, F. Podewils, A. Salzer, *Organometallics* **2000**, *19*, 5471–5476.
[44] D. B. Grotjahn, D. A. Lev, *J. Am. Chem. Soc.* **2004**, *126*, 12232–12233.
[45] M. Tokunaga, T. Suzuki, N. Koga, T. Fukushima, A. Horiuchi, Y. Wakatsuki, *J. Am. Chem. Soc.* **2011**, *123*, 11917–11924.
[46] The qNMR analysis does not differentiate **7a/b**, but we have independently studied the reaction of $CpRuCl(PPh_3)_2$ with **1** and water in the course of another project, where **7b** was unequivocally ascertained as major organic decomposition product. M. Schreyer, Ph. D. Thesis, TU Munich, 2018.
[47] T. Suzuki, Y. Wakatsuki, M. Tokunaga, Japanese Patent 2002114730 A2, **2002**.
[48] L. Hintermann, T. Kribber, A. Labonne, E. Paciok, *Synlett* **2009**, 2412–2416.
[49] a) A. I. Konovalov, E. E. Karslyan, D. S. Perekalin, Y. V. Nelyubina, P. V. Petrovskii, A. R. Kudinov, *Mendeleev Commun.* **2011**, *21*, 163–164; b) R.M. Fairchild, K.T. Holman, *Organometallics* **2008**, *27*, 1823–1833; c) E. V. Mutseneck, D. A. Loginov, D.S. Perekalin, Z. A. Starikova, D. G. Golovanov, P. V. Petrovskii, P. Zanello, M. Corsini, F. Laschi, A. R. Kudinov, *Organometallics* **2004**, *23*, 5944–5957.
[50] a) A. D. Adler, F. R. Longo, J. D. Finarelli, J. Goldmacher, J. Assour, L. Korsakoff, *J. Org. Chem.* **1967**, *32*, 476–476; b) D. F. Marsh, R. E. Falvo, L. M. Mink, *J. Chem. Educ.* **1999**, *76*, 237–237; c) P. Rothemund, *J. Am. Chem. Soc.* **1936**, *58*, 625–627.
[51] J. F. Larrow, E. N. Jacobsen, *Org. Synth.* **1998**, *75*, 1.
[52] a) B. R. James, G. L. Rempel, *J. Am. Chem. Soc.* **1969**, *91*, 863–865; b) J. Blum, H. Huminer, H. Alper, *J. Mol. Catal.* **1992**, *75*, 153–160.
[53] a) D. B. Grotjahn, X. Zeng, A. L. Cooksy, W. S. Kassel, A. G. DiPasquale, L. N. Zakharov, A. L. Rheingold, *Organometallics* **2007**, *26*, 3385–3402; b) M. J. Cowley, J. M. Lynam, J. M. Slattery, *Dalton Trans.* **2008**, *34*, 4552–4552; c) A. Höhn, H. Werner, *J. Organomet. Chem.* **1990**, *382*, 255–272; and cited literature.
[54] K.-S. Joo, S. Y. Kim, C. S. Chin, *Bull. Korean Chem. Soc.* **1997**, *18*, 1296–1301.
[55] M. Angoy, M. V. Jiménez, F. J. Modrego, L. A. Oro, V. Passarelli, J. J. Pérez-Torrente, *Organometallics* **2018**, *37*, 2778–2794.
[56] J. Ott, L. M. Venanzi, C. A. Ghilardi, S. Midollini, A. Orlandini, *J. Organomet. Chem.* **1985**, *291*, 89–100.
[57] T. Hirabayashi, Y. Okimoto, A. Saito, M. Morita, S. Sakaguchi, Y. Ishii, *Tetrahedron* **2006**, *62*, 2231–2234.
[58] a) N. Saragas, G. Floros, P. Paraskevopoulou, N. Psaroudakis, S. Koinis, M. Pitsikalis, K. Mertis, *J. Mol. Catal. A: Chem.* **2009**, *303*, 124–131; b) K. Yokota, M. Ohtubo, T. Hirabayashi, Y. Inai, *Polym. J.* **1993**, *25*, 1079–1086; c) A. Petit, S. Moulay, T. Aouak, *Eur. Polym. J.* **1999**, *35*, 953–963.
[59] a) N. Riache, A. Dery, E. Callens, A. Poater, M. Samantaray, R. Dey, J. Hong, K. Li, L. Cavallo, J.-M. Basset, *Organometallics* **2015**, *34*, 690–695; b) E. Farnetti, S. Filipuzzi, *Inorg. Chim. Acta* **2010**, *363*, 467–473; c) V. Cadierno, S. E. García-Garrido, J. Gimeno, *J. Am. Chem. Soc.* **2006**, *128*, 15094–15095; d) K. Tanaka, K. Toyoda, A. Wada, K. Shirasaka, M. Hirano, *Chem. Eur. J.* **2005**, *11*, 1145–1156; e) R. Nomura, J. Tabei, T. Masuda, *Macromolecules* **2002**, *35*, 2955–2961; f) M. Marigo, N. Marsich, E. Farnetti, *J. Mol. Catal. A: Chem.* **2002**, *187*, 169–177; g) M. Tabata, T. Sone, Y. Sadahiro, *Macromol. Chem. Phys.* **1999**, *200*, 265–282; h) K. Yokota, M. Ohtubo, T. Hirabayashi, Y. Inai, *Polym. J.* **1993**, *25*, 1079–1086.
[60] Attempts to hydrate 2-methyl-2-butyn-2-ol with $PdCl_2$ or $Pd(OAc)_2$ gave "higher-molecular-weight material": I. K. Meier, J. A. Marsella, *J. Mol. Catal.* **1993**, *78*, 31–42.
[61] C. Xu, W. Du, Y. Zeng, B. Dai, H. Guo, *Org. Lett.* **2014**, *16*, 948–951.
[62] T. Kusakabe, Y. Ito, M. Kamimura, T. Shirai, K. Takahashi, T. Mochida, K. Kato, *Asian J. Org. Chem.* **2017**, *6*, 1086–1090.
[63] For the ligand used (dimenthylphosphine oxide) see: S. Koller, J. Gatzka, K. M. Wong, P. J. Altmann, A. Pöthig, L. Hintermann, *J. Org. Chem.* **2018**, *83*, 15009–15028.
[64] a) W. Hiscox, P. W. Jennings, *Organometallics* **1990**, *9*, 1997–1999; b) P. W. Jennings, J. W. Hartman, W. C. Hiscox, *Inorg. Chim. Acta* **1994**, *222*, 317–322, c) J. W. Hartman, W. C. Hiscox, P. W. Jennings, *J. Org. Chem.* **1993**, *58*, 7613–7614.
[65] A. Scarso, M. Colladon, P. Sgarbossa, C. Santo, R. A. Michelin, G. Strukul, *Organometallics* **2010**, *29*, 1487–1497.
[66] Ambifunctionality of SPO-liands: a) T. Ghaffar, A. W. Parkins, *Tetrahedron Lett.* **1995**, *36*, 8657–8660; b) T. J. Ahmed, S. M. M. Knapp, D. R. Tyler, *Coord. Chem. Rev.* **2011**, *255*, 949–974.
[67] It is not clear if ligand Men_2POH coordinates to gold under such conditions; steric hindrance to complexation was noted with Cy_2POH and ruthenium precursors: E. Tomás-Mendivil, J. Francos, R. González-Fernández, P. J. González-Liste, J. Borge, V. Cadierno, *Dalton Trans.* **2016**, *45*, 13590–13603.

[68] For an analysis of reaction products in alkyne hydration with $Hg(OAc)_2$, see: M. Bassetti, B. Floris, *J. Chem. Soc., Perkin Trans. 2* **1988**, 227–233.

[69] a) Q. Mei, H. Liu, M. Hou, H. Liu, B. Han, *New J. Chem.* **2017**, *41*, 6290–6295; b) T. Niu, D. Jiang, S. Li, X. Shu, H. Li, A. Zhang, J. Xu, B. Ni, *Tetrahedron Lett.* **2017**, *58*, 1156–1159; c) M. Hassam, W.-S. Li, *Tetrahedron* **2015**, *71*, 2719–2723; d) H. Zou, W. He, Q. Dong, R. Wang, N. Yi, J. Jiang, D. Pen, W. He, Eur. *J. Org. Chem.* **2016**, 116–121; e) Y. Tokita, A. Okamoto, K. Nishiwaki, M. Kobayashi, E. Nakamura, *Bull. Chem. Soc. Japan* **2004**, *77*, 1395–1399.

[70] T. T. Dang, F. Boeck, L. Hintermann, *J. Org. Chem*. **2011**, *76*, 9353–9361.

[71] Hidden Brønsted acid catalysis has been proven in $Cu(OTf)_2$-catalyzed alkene hydroalkoxylation, where $Cu(OTf)_2$ was shown to be the source of both Cu(I) and HOTf: M. J.-L. Tschan, C. M. Thomas, H. Strub, J.-F. Carpentier, *Adv. Synth. Catal.* **2009**, *351*, 2496–2504.

[72] Ref. 8a mentions copper-catalysis in its title, yet the optimization results show that $Yb(OTf)_3$, $Sc(OTf)_3$, $In(OTf)_3$, $Bi(OTf)_3$, $Zn(OTf)_2$, $Eu(OTf)_3$ and $La(OTf)_3$ gave qualitatively and quantitatively similar results to $Cu(OTf)_2$ at the initial 5 mol% loading.

[73] For a cationic (P–P)Pt(II)-catalyst for methanol addition to alkyne, see: Y. Kataoka, O. Matsumoto, K. Tani, *Organometallics* **1996**, *15*, 5246–5249.

[74] M. Colladon, A. Scarso, P. Sgarbossa, R. A. Michelin, G. Strukul, *J. Am. Chem. Soc.* **2006**, *128*, 14006–14007.

[75] W. D. Harman, J. C. Dobson, H. Taube, *J. Am. Chem. Soc.* **1989**, *111*, 3061–3062.

[76] For reports on 1-alkyne dimerization catalyzed by Pd–SPO complexes: a) T. Chen, C. Guo, M. Goto, L.-B. Han, *Chem. Commun.* **2013**, *49*, 7498–7500; b) R. E. Islas, J. Cárdenas, R. Gaviño, E. García-Ríos, L. Lomas-Romero, J. A. Morales-Serna, *RSC Advances* **2017**, *7*, 9780–9789.

[77] M. Falcon, E. Farnetti, N. Marsich, *J. Organomet. Chem.* **2001**, *629*, 187–193.

[78] Ref.[76a] mentions the ease of polymerization of terminal alkyne dimers from aryl acetylenes.

[79] Overview of Osmium-catalyzed hydrogenations: R. H. Morris, *Ruthenium and Osmium* in *The Handbook of Homogeneous Hydrogenation* (Eds. J. G. de Vries, C. J. Elsevier), Wiley-VCH, **2008**; chapter 3.

[80] For iridium-catalyzed redox-isomerization over many bonds in alkenols: D. B. Grotjahn, C. R. Larsen, J. L. Gustafson, R. Nair, A. Sharma, *J. Am. Chem. Soc.* **2007**, *129*, 9592–9593.

[81] M. Wegmann, Research report, TU München, **2011**. The screening results of this report are included in the supporting information.

[82] K. Moriyama, M. Takemura, H. Togo, *Org. Lett.* **2012**, *14*, 2414–2417.

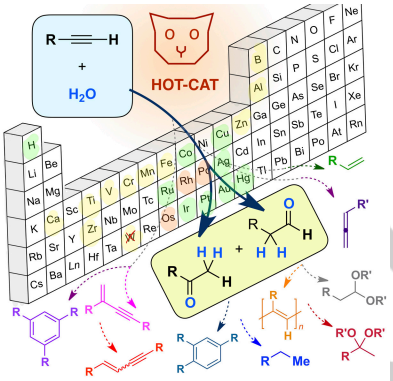
[83] K. Schwetlick, *Organikum: Organisch-chemisches Grundpraktikum 21. Auflage*, Wiley-VCH, Weinheim, Germany, **2001**, p. 466.

[84] P. Teo, Z. K. Wickens, G. Dong, R. H. Grubbs, *Org. Lett.* **2012**, *14*, 3237–3239.

Entry for the Table of Contents

FULL PAPER

Using alkyne hydration as example, the work suggests an efficient screening procedure to find homogeneous catalytic activity covering a vast field of diverse potential catalysts, using a low number of experiments. The key idea is combining homogeneous thermal conditions (HOT-CAT) in a microwave-unit with accurate quantitative NMR analysis.



*Matthias Schreyer, Tobias M. Milzarek, Marcus Wegmann, Andreas Brunner, Lukas Hintermann**

Page No. – Page No.

Discovery and Comparison of Homogeneous Catalysts in a Standardized HOT-CAT Screen with Microwave-Heating and qNMR Analysis: Exploring Catalytic Hydration of Alkynes