Novel Aza-Arylphosphane Ligands For Ruthenium-Catalyzed Anti-MARKOVNIKOV Hydration of Terminal Alkynes

Von der Fakultät für Mathematik, Informatik und Naturwissenschaften der Rheinisch-Westfälischen Technischen Hochschule Aachen zur Erlangung des akademischen Grades einer Doktorin der Naturwissenschaften genehmigte Dissertation

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Parts of this work have already been published:

1) A. Labonne, T. Kribber, L. Hintermann
"Highly Active in Situ Catalysts for anti-Markovnikov Hydration of Terminal Alkynes"
Org. Lett. **2006**, *8*, 5853-5856.

2) L. Hintermann, A. Labonne
"Catalytic Hydration of Alkynes and its Aplication in Synthesis"
Synthesis **2007**, 1121-1150.

3) T. Kribber, A. Labonne, L. Hintermann
"Iterative Synthesis of Oligo-1,4-Diols via Catalytic anti-Markovnikov Hydration of Terminal Alkynes"
Synthesis **2007**, *in press*.

4) A. Labonne, L. Zani, L. Hintermann, C. Bolm
"Redox-neutral Synthesis of β-Amino Aldehydes from Imines by an Alkynylation/Hydration Sequence"
J. Org. Chem. **2007**, *72*, 5704-5708.

« Nothing in life is to be feared, it is only to be understood »

Marie Sklodowska-Curie

« Que serais-je sans toi qui vins à ma rencontre
Que serais-je sans toi qu'un coeur au bois dormant
Que cette heure arrêtée au cadran de la montre
Que serais-je sans toi que ce balbutiement… »

Louis Aragon, poem « Que serais-je sans toi »

1. Introduction

The demand for new transformations in synthetic chemistry has increased considerably in recent years. This demand has arisen from the need for a wide range of functional group transformations and the desirability of having more processes to provide direct access to polyfunctionalized compounds. Therefore, a great challenge for contemporary chemists is the development of efficient synthetic methodologies.

Nature is a vast source of readily available and effective catalysts for several selective processes (biocatalysis), but nature's catalysts still present limitations, one example for enantioselective enzymatic processes being the possibility to access only one of the two enantiomeres of a desired product in a direct manner.[1] Therefore, chemists need to expand their horizons in a broader field of chemical sciences in order to make progress toward solving such complex synthetic problems and to find creative solutions matching or even surpassing the efficiency of enzymes and nature's other catalysts.

Over the last decades intensive research has been carried out in the field of organometallic chemistry in order to develop transition-metal complexes able to effect highly selective transformations with sometimes formerly unknown reactivity.[2] In the 1970's recognition of organometallic chemistry as a distinct subfield culminated in the award of the Nobel Prize in chemistry to FISCHER and WILKINSON in 1973 for their work on "sandwich" complexes (metallocenes).[3] Further major advances have been achieved by KNOWLES,[4] who performed the first enantioselective hydrogenation of a prochiral olefin in the presence of a rhodium-phosphine catalyst. The latter process was rapidly commercialized (*Monsanto*-process) and subsequently applied in the large scale-synthesis of the amino acid L-DOPA (anti-PARKINSON drug). In recognition of his achievements in organometallic chemistry, KNOWLES shared the Nobel Prize in 2001 with NOYORI for enantioselective hydrogenation and SHARPLESS for

[1] a) *Enzyme Catalyst in Organic Synthesis*; Eds.: K. Drauz, H. Waldmann, Wiley-VCH, Weinheim, 1995.
[2] a) M. E. O'Neill, K. Wade in *Comprehensive Organometallic Chemistry*, Vol. 1, p. 2; Eds: G. Wilkinson, F. G. A. Stone, E. W. Abel; Pergamon, New York; 1982. b) *Transition Metals for Organic Synthesis*, 2nd Ed.; Eds.: M. Beller, C. Bolm; Wiley-VCH, Weinheim, 2004. For many useful synthetic procedures, see: c) *Organometallics in Synthesis*, 2nd Ed.; Ed. M. Schlosser; John Wiley & Sons, Chichester, 2002. d) R. H. Crabtree *The Organometallic Chemistry of the Transition Metals,* 4th Ed., John Wiley & Sons, Hoboken, 2005.
[3] For the Nobel lectures, see a) G. Wilkinson *Angew. Chem*. **1974**, *86*, 664. b) E. O. Fischer *Angew. Chem*. **1974**, *86*, 651.
[4] W. S. Knowles, M. J. Sabacky *J. Chem. Soc., Chem. Commun*. **1968**, 1445. For a review see, b) W. S. Knowles *Acc. Chem. Res.* **1983**, *80*, 1034.

enantioselective oxidation catalysis.[5] Most of these processes have found industrial applications in the synthesis of chiral drugs and building blocks for asymmetric synthesis.[6]

From organometallic chemistry emerged a countless number of transition metal complexes, and particularly ruthenium complexes, are the object of increased investigations because many of these complexes are catalysts for transformations which were not accessible before.[7] Thus, Ru-catalyzed activation of unsaturated bonds can lead to the formation of polyfunctionalized compounds via carbon-carbon bond forming reactions. For example, stereo- and regiocontrolled catalytic dimerization of alkynes gives access to butenynes or butatrienes[8] and Pauson-Khand-type reactions afford cyclopentenones.[9] Ru-catalyzed addition of alkenes to alkynes provides an atom economical approach for selective C-C bond formation.[10] Likewise, introduction of functionality can be performed by regioselective addition of heteronucleophiles to alkynes and alkenes, as for example of carboxylic acids or amides to terminal alkynes resulting in the formation of vinyl esters or enamides, respectively.[11,12] Ruthenium-complexes are also catalysts for the activation of O-H and C-H bonds.[7,13]

[5] a) P. Ahlberg *Advanced Information on the Nobel Prize in Chemistry 2001*, Kungl. Vetenskapakademien; The Royal Swedish Academy of Science, 2001. For the Nobel lectures, see: b) W. S. Knowles *Angew. Chem.* **2002**, *114*, 2097; *Angew. Chem. Int. Ed.* **2002**, *41*, 1998. c) R. Noyori *Angew. Chem.* **2002**, *114*, 2109; *Angew. Chem Int. Ed.* **2002**, *41*, 2008. d) K. B. Sharpless *Angew. Chem.* **2002**, *114*, 2126; *Angew. Chem. Int. Ed.* **2002**, *41*, 2024.

[6] a) R. Noyori *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, 1994. b) *Comprehensive Asymmetric Catalysis*; Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto; Springer, Berlin, 1999.

[7] For an overview of the non metathesis C-C bond formation catalyzed by ruthenium, see: B. M. Trost, F. D. Toste, A. B. Pinkerton *Chem. Rev*. **2001**, *101*, 2067.

[8] For the synthesis of butenynes, see: a) M. Daniels, R. U. Kirss *J. Organomet. Chem*. **2007**, *692*, 1716. b) V. Cadierno, S. E. Garcia-Garrido, J. Gimeno *J. Am. Chem. Soc.* **2006**, *128*, 15094. c) M. Bassetti, S. Marini, F. Tortorella, V. Cadierno, J. Diez, M. P. Gamasa, J. Gimeno *J. Organomet. Chem*. **2000**, 593. d) C. S. Yi, N. Liu *Synlett* **1999**, *3*, 281. e) C. Bianchini, M. Peruzzini, F. Zanobini, P. Frediani, A. Albinati *J. Am. Chem. Soc.* **1991**, *113*, 5453. f) H. Matsuzaka, Y. Takagi, Y. Ishii, M. Nishio, M. Hidai *Organometallics* **1995**, *14*, 2153. For the synthesis of butatrienes, see: g) C. S. Yi, N. Liu *Organometallics* **1996**, *15*, 3968. h) C. Shegvoc, K. Mereiter, E. Zobetz, R. Schmid, K. Kirchner *Organometallic* **1996**, *15*, 5275. i) Y. Wakatsuki, H. Yamazaki, N. Kumegawa, T. Satoh, J. Y. Satoh *J. Am. Chem. Soc.* **1991**, *113*, 9604.

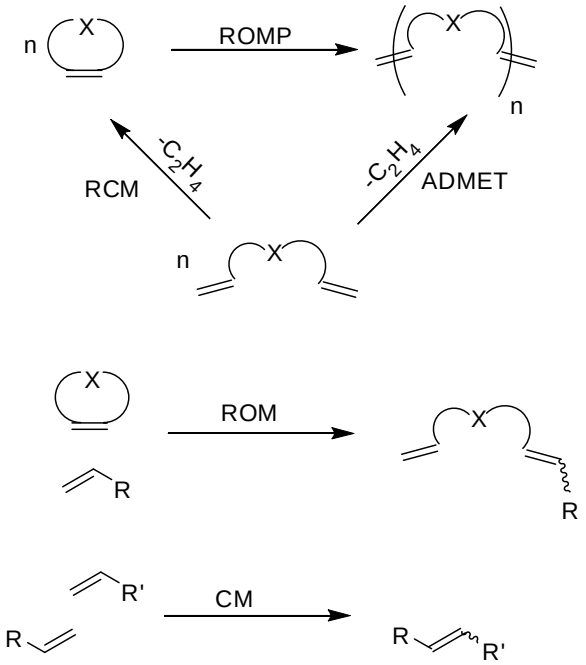
[9] a) K. Itami, K. Mitsudo, K. Fujita, Y. Ohashi, J. Yoshida *J. Am. Chem. Soc.* **2004**, *126*, 11058. b) T. Kondo, A. Nakamura, T. Okada, N. Suzuki, K. Wada, T. Mitsudo *J. Am. Chem. Soc.* **2000**, *122*, 6319. c) T. Morimoto, N. Chatani, S. Murai *J. Am. Chem. Soc.* **1999**, *121*, 1758. d) N. Chatani, M. Tobisu, T. Asaumi, Y. Fukumoto, S. Murai *J. Am. Chem. Soc.* **1999**, *121*, 7160. e) N. Suzuki, T. Kondo, T. Mitsudo *Organometallics* **1998**, *17*, 766.

[10] a) Y. Yamamoto, R. Ogawa, K. Itoh *Chem. Commun*. **2000**, 549. b) B. M. Trost *Angew. Chem.* **1995**, *107*, 285; *Angew. Chem. Int. Ed.* **1995**, *34*, 259. c) B. M. Trost, A. F. Indolese, T. J. J. Müller, B. Treptow *J. Am. Chem. Soc.* **1995**, *117*, 615.

[11] a) F. Alonso, I. P. Beletskaya, M. Yus *Chem. Rev.* **2004**, *104*, 3079. b) M. Beller, J. Seayad, A. Tillack, H. Jiao *Angew. Chem. Int. Ed.* **2004**, *43*, 3368.

[12] a) L. J. Goossen, M. Blanchot, C. Brinkmann, K. Goossen, R. Karch, A. Rivas-Nass *J. Org. Chem*. **2006**, *71*, 9506. b) L. J. Goossen, J. E. Rauhaus, G. Deng *Angew. Chem. Int. Ed.* **2005**, *44*, 4042. c) L. J. Goossen, J. Paetzold, D. Koley *Chem. Commun*. **2003**, 706. d) K. Melis, P. Samulkiewicz, J. Rynkowski, F. Verpoort *Tetrahedron Lett*. **2002**, *43*, 2713. e) J. Le Paih, D. Cuervo Rodriguez, S. Dérien, P. H. Dixneuf *Synlett* **2000**, 95.

Finally, the recent development of versatile Ru-catalysts for olefin metathesis has led to a broad array of new type of olefin metathesis reactions and widely applied in organic chemistry. Illustrated examples are depicted in Scheme 1 and include ring opening metathesis polymerisation of strained alkenes (ROMP), ring closing metathesis (RCM), acyclic diene metathesis polymerisation (ADMET), ring opening metathesis (ROM) and cross metathesis (CM).[14] In addition, transition-metal catalysed alkyne- and enyne metathesis has been developed.[15]



Scheme 1. Olefin metathesis reactions.

Again in 2005, the achievements in this metal-mediated reaction were recognized in the award of the Nobel Prize in chemistry to CHAUVIN, GRUBBS and SCHROCK for their work on

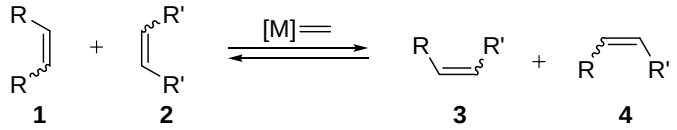
f) J. Le Paih, S. Dérien, P. H. Dixneuf *Chem. Commun*. **1999**, 1437. g) M. Rotem, Y. Shvo *J. Organomet. Chem*. **1993**, *448*, 189. h) Y. Sasaki, P. H. Dixneuf *J. Chem. Soc., Chem. Commun.* **1986**, 790. i) R. Mahé, P. H. Dixneuf, S. Lécolier *Tetrahedron Lett.* **1986**, *27*, 6333.

[13] a) K. Tani, Y. Kataoka In *Catalytic Heterofunctionalization*; Eds.: A. Togni, H. Grützmacher; Wiley-VCH: Weinheim, 2001, 171. b) N. Chatani, Y. Le, F. Kakiuchi, S. Murai *J. Org. Chem*. **1997**, *62*, 2604. b) E. J. Moore, W. R. Pretzer, T. J. O'Connell, J. Harris, L. LaBounty, L. Chou, S. S. Grimmer *J. Am. Chem. Soc.* **1992**, *114*, 5888.

[14] a) *Handbook of Metathesis*; Ed.: R. H. Grubbs; Wiley-VCH, Weinheim, 2003. b) M. R. Buchmeiser *Chem. Rev.* **2000**, *100*, 1565. c) K. C. Nicolaou, S. A. Snyder *Classics in Total Synthesis II*, Wiley-VCH, Weinheim, 2003, pp. 163-172. d) J. J. Van Veldhuizen, S. B. Garber, J. S. Kingsbury, A. H. Hoveyda *J. Am. Chem. Soc.* **2002**, *124*, 4954.

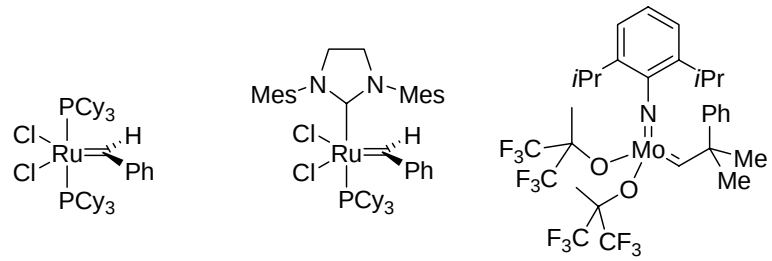
[15] a) H. Villar, M. Frings, C. Bolm *Chem. Soc. Rev*. **2007**, *36*, 55. b) S. T. Diver *Coord. Chem. Rev*. **2007**, *251*, 671.

olefin metathesis.[14a,16] This reaction involves redistribution of carbon-carbon double bonds. Thus, after cleavage of the double bonds in the alkenes **1** and **2** in the presence of a metallocarbene, two new compounds **3** and **4** are formed (Scheme 2).



Scheme 2. Carbon-carbon double bonds redistribution in the olefin metathesis.

The recent applications of this reaction have been made possible by the availability of new and effective homogeneous catalysts, such as those shown in Figure 1. Besides Ru-complexes, molybdenum- and tungsten-complexes show also remarkable reactivity in metathesis reactions.[17]



5, GRUBBS (1st generation) **6**, GRUBBS (2nd generation) **7**, SCHROCK

Figure 1. Catalysts for olefin metathesis.

Thus, selective catalysis is often connected to metal-complex catalyzed reactions and much work in this area has focused on the design and synthesis of organometallic complexes which are able to induce selectivity in catalytic reactions.

What are the issues that need to be resolved as one looks towards inventing/developing new reactions? According to TROST a key factor in synthesis is efficiency.[18] He formalized his thinking around the themes of selectivity and atom economy.[19,10b]

[16] a) J.-L. Hérisson, Y. Chauvin *Makromol. Chem.* **1971**, *141*, 161. b) J.-P. Soufflet, D. Commereuc, Y. Chauvin *C. R. Acad. Sci. Sér. C* **1972**, *276*, 169.
[17] a) S. L. Aeilts, D. R. Cefalo, P. J. Bonetatebus Jr., J. H. Houser, A. H. Hoveyda, R. R. Schrock *Angew. Chem* **2001**, *113*, 1500; *Angew. Chem. Int. Ed.* **2001**, *40*, 1452. b) X. Teng, D. R. Cefalo, R. R. Schrock, A. H. Hoveyda *J. Am. Chem. Soc.* **2002**, *124*, 10779. For a review on enantioselective olefin-metathesis reactions, see: c) R. R. Schrock, A. H. Hoveyda *Angew. Chem.* **2003**, *115*, 4741; *Angew. Chem. Int. Ed.* **2003**, *42*, 4592.
[18] B. M. Trost *Science* **1983**, *219*, 245.
[19] a) B. M. Trost *Science* **1991**, *254*, 1471.

First and foremost, reactions must be capable of differentiating among various bond types - not only between two different kinds of bonds such as C–O and C=C (chemoselectivity) but, also desirably between two identical bonds (such as two C=O bonds) within a different chemical environment in the same molecule- a type of selectivity termed regioselectivity. The third aspect deals with controlling stereochemistry either in a relative fashion (diastereoselectivity) or an absolute fashion (enantioselectivity). Very often the synthetic challenge is delivered by finding solutions to control theses issues of selectivity. However, a major issue of immense importance is being ignored and even sacrificed in order to solve problems of selectivity: the issue relates to the question of atom economy.

Atom economy describes the conversion efficiency of a chemical process in terms of all atoms involved. Reactions of the general form A + B → C + D (Figure 2a) generate a waste product (if C is the desired product, D is an obligatory waste product).

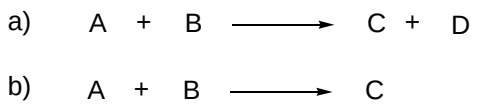
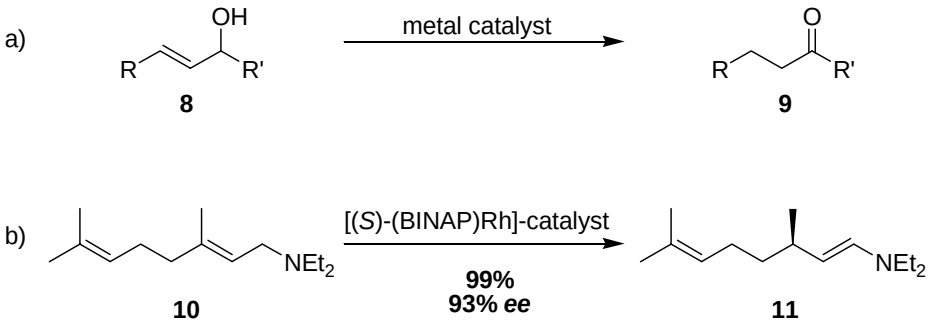


Figure 2. Atom economy in chemical processes.

In an ideal chemical process the amount of reactants equals the amount of all products generated and no atom is wasted. Therefore, the amount of D should be as small and innocuous as possible with the ideal being the vanishment of D which reduces the reaction to a simple addition (Figure 2b). On the other hand, formation of carbon-carbon bonds in a synthetically efficient and selective manner forms the backbone of organic chemistry. In addition to selectivity as a requirement for efficiency, increasing emphasis is placed upon atom economy in order to utilize raw materials more effectively by minimising waste production.

A nice example for an atom-economical reaction is the conversion of allylic alcohols **8** into saturated carbonyl compounds **9** (Scheme 3a).[20] This internal process is catalysed by several transition metal catalysts. Because it is a fully atom-economical process it avoids the use of costly and/or toxic redox-chemistry reagents. Another prominent example is the isomerisation of *N*,*N*-diethylgeranylamine **10** with chiral Rh-complexes to produce chiral enamine **11** as a key step in the industrial synthesis of α-tocopherol and menthol (Scheme 3b).[19]

[20] R. Uma, C. Crévisy, R. Grée *Chem. Rev*. **2003**, *103*, 27.



Scheme 3. Examples of reactions with complete atom-economy.

Recent developments like mounting cost of raw materials (such as petrochemicals) and increased sensitivity to environmental concerns have made atom economical approaches more popular. Atom economy is therefore an important concept in "green chemistry".[19b]

Another key question in green chemistry is how to judge the environmental impact of new processes. Sheldon's E-factor[21] -defined as the weight of waste per unit weight of product- has been used widely by chemists. This metric is simple to apply industrially, as a production facility can measure how much material enters the site and how much leaves as product and waste, thereby directly giving an accurate global E-factor for the site. However, establishing the true environmental impact of a new technology requires full life-cycle assessments as well as toxicological testing of any materials involved, such as reagents or solvents.

Table 1. Environmental acceptability as measured by the E-factor.

Industry	Product tons per year	Waste/ product ratio by weight
Oil refining	10^6–10^8	~0.1
Bulk chemicals	10^4–10^6	<1-5
Fine Chemicals	10^2–10^4	5-50
Pharmaceuticals	10^0–10^3	25>100

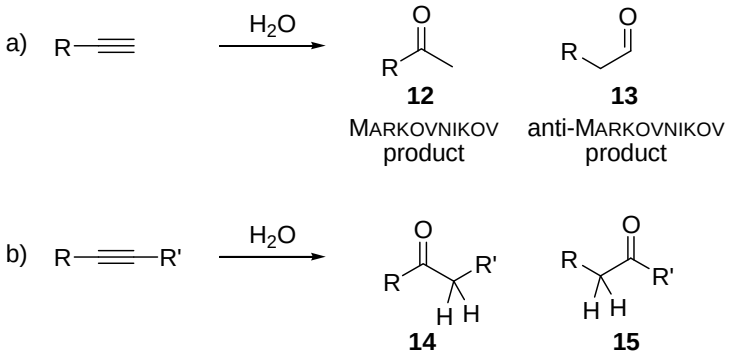
Despite its simplicity, SHELDON's E-factor is useful in highlighting the fine chemicals and pharmaceutical industries (Table 1) as the areas in which green chemistry is likely to have its most immediate impact. Fine chemical companies tend to produce a wide range of chemicals on a small scale (500 to 5000 tons per year). They therefore offer more diverse opportunities for introducing new technology than the bulk chemicals sector, and the scale-up from laboratory to plant is less daunting.

[21] R. A. Sheldon *ChemTech* 1994, p. 38.

2. Catalytic Hydration of Alkynes[22]

The catalytic addition of water to alkynes (hydration) generates valuable carbonyl compounds from unsaturated hydrocarbon precursors. Unlike many other syntheses of carbonyl compounds, the catalytic hydration of alkynes can generate products in a fully atom-economic[19] way from unsaturated hydrocarbon feedstocks and water without the use of energy-intensive redox-chemistry and presents therefore a great potential for synthesis.

The hydration of terminal alkynes gives either a methyl ketone **12** (MARKOVNIKOV addition; Scheme 4a) or an aldehyde **13** (anti-MARKOVNIKOV[23] addition; Scheme 4a), whereas non-symmetrical internal alkynes can give two regioisomeric ketones **14** and **15** (Scheme 4b). The reaction is exergonic: hydration of acetylene (*g*) to acetaldehyde (*g*) is characterized by Δ_rG = –105.8 kJ/mol and Δ_rH = –111.2 kJ/mol,[24] and hydrations of higher alkynes are slightly more exergonic, *eg.* propyne (*g*) → acetone (*g*): Δ_rH = –118 kJ/mol and 1-butyne (*g*) → 2-butanone (*g*): Δ_rH = –117 kJ/mol.[24]



Scheme 4. Hydration of terminal (a) and internal (b) alkynes.

BERTHELOT discovered acetylene in 1860 and described its hydration in sulfuric acid to give a product believed to be vinyl alcohol,[25] but later identified as a mixture of acetaldehyde and crotonaldehyde.[26] Meanwhile, propyne had been hydrated to acetone by means of sulfuric acid and water.[27] The concept of alkyne hydration was thus known when KUCHEROV

[22] This chapter is based in part on our review article: L. Hintermann, A. Labonne *Synthesis* **2007**, 1121.
[23] Here, "anti" is not in italic-form because it refers to the selectivity of the reaction (following the MARKOVNIKOV's rules) rather than the stereochemistry of the relative molecules.
[24] Thermodynamic values calculated with data from: http://webbook.nist.gov/ chemistry/; accessed January 2007. Note that phase-changes will affect Δ_rG/Δ_rH.
[25] M. Berthelot *Ann. Chim. Phys.* **1863**, *67*, 52.
[26] H. Lagermarck, A. Eltekoff *Chem. Ber.* **1877**, *10*, 637.
[27] R. Fittig, A. Schrohe *Chem. Ber.* **1875**, *8*, 367.

described the mercury(II) catalyzed hydration of alkynes in 1881.[28] The reaction is one of the earliest examples of homogeneous metal-complex catalysis.[29] Starting from 1916, acetic acid was produced in Germany on an industrial scale from acetylene *via* hydration to acetaldehyde followed by Manganese-catalyzed air-oxidation.[30] Initially, acetylene was prepared from water and calcium carbide, but by the 1940s, thermal cracking of methane started to supersede the energy-intensive carbide process as source for acetylene.[31] Based on the hydration of acetylene, a variety of industrial chemicals have been produced on a large scale over many years.

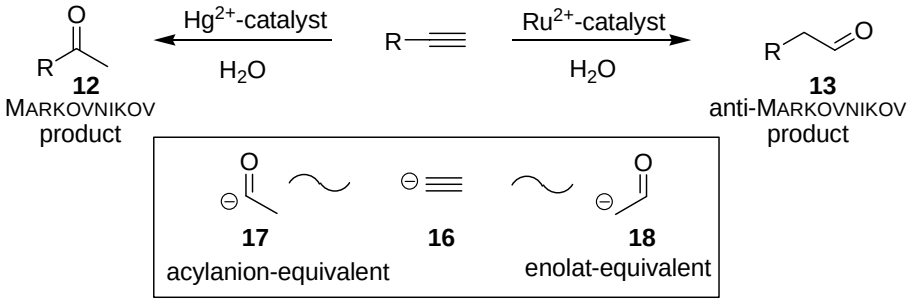
Catalytic hydration of higher alkynes was rarely used in synthetic research, and procedures for hydration of terminal alkynes in organic media were not published until 1938.[32] Partly as a consequence of REPPE-chemistry,[33] many alkynes had become readily available from 1940 onwards, and research on alkyne chemistry flourished, including studies on the hydration of higher alkynes, which continued into the late 1960s. Until the 1970s, acetylene remained a cheap primary organic raw material, but ethylene and propylene have now surpassed it in importance; still, acetylene is used in the production of vinyl derivatives, acrylates and acetylenic chemicals.[31] After the introduction of the WACKER process (ethylene + O_2 $\rightarrow$ acetaldehyde) and acetic acid syntheses based on carbonylation of methanol, industrial acetylene hydration became obsolete.[34] Pollution by toxic mercury waste had always been an inherent problem of the process. A steady development of alternative alkyne hydration catalysts has taken place over the past 30 years, nurtured by the desire to replace mercury salts by less toxic and more active metal catalysts, the most promising being based on Au(I), Au(III), Pt(II) and Pd(II) (see Section 2.1.2). Moreover, applied alkyne chemistry has experienced a revival with the advent of catalytic cross-coupling methodology and its application in synthetic and supramolecular chemistry as well as material sciences.[35]

Another focus of research emerges from the recent fascinating discovery of anti-MARKOVNIKOV-selective hydration of terminal alkynes to give aldehydes. The first catalyst

[28] a) M. Kutscheroff *Chem. Ber.* **1881**, *14*, 1540. b) M. Kutscheroff *Chem. Ber.* **1884**, *17*, 13.
[29] I. I. Moiseev *Kinet. Catal.* **2001**, *42*, 1.
[30] B. Neumann, H. Schneider *Angew. Chem.* **1920**, *33*, 189.
[31] *Ullmann's Encyclopedia of Industrial Chemistry*, 7th ed.; Wiley-VCH: Weinheim, 2006, *Acetylene.*
[32] R. J. Thomas, K. N. Campbell, G. F. Hennion *J. Am. Chem. Soc.* **1938**, *60*, 718.
[33] a) W. Reppe *Liebigs Ann. Chem.* **1948**, *560*, 1. b) W. Reppe *Liebigs Ann. Chem.* **1953**, *582*, 1. c) W. Reppe *Liebigs Ann. Chem.* **1955**, *596*, 1. d) W. Reppe *Liebigs Ann. Chem.* **1955**, *596*, 25. e) W. Reppe *Liebigs Ann. Chem.* **1955**, *596*, 38. f) W. Reppe *Liebigs Ann. Chem.* **1956**, *601*, 81.
[34] *Ullmann's Encyclopedia of Industrial Chemistry*, 7th ed.; Wiley-VCH: Weinheim, 2006, *Acetaldehyde.*
[35] a). *Acetylene Chemistry*; Eds.: F. Diederich, P. J. Stang, R. R. Tykwinski; Wiley-VCH: Weinheim, 2005. b) *Modern Acetylene Chemistry*; Eds.: F. Diederich, P. J. Stang; Wiley-VCH: Weinheim, 1995.

was found only in 1998, and the methodology has already seen an impressive development (see Section 2.2).

The hydration opens a direct door between alkyne and carbonyl chemistry, thus its potential in organic synthesis is enormous, provided the transformation can be carried out selectively under mild conditions. The chemical union of apolar hydrocarbons with water is against their 'affinities'. For this reason, a hydration catalyst is required, the role of which is to polarize the alkyne unit to facilitate attack of water.



Scheme 5. The acetylide anion as acylanion- or enolat-equivalent.

The ability to perform a regioselective hydration of terminal alkyne reveals that the acetylide-anion **16**, which serves as a reagent in many syntheses of acetylenic compounds, can now be regarded as a reagent for two different synthons. By the classical MARKOVNIKOV-type hydration with mercury salts it stands for an acylanion equivalent **17** (which is an *umpoled*-carbonyl-equivalent). New catalyst development led to the possibility of the acetylide being also an enolat-equivalent **18** by anti-MARKOVNIKOV selective hydration (Scheme 5). Consequently, a terminal alkyne can be now regarded either as a masked methyl ketone or a masked aldehyde. This is a synthetic advantage for introducing heterofunctionality at a late stage of a synthesis without the need of protecting groups, taking into account the reactivity and the instability of carbonyl compounds, particularly aldehydes.

2.1 Markovnikov Hydration of Alkynes

2.1.1. Mercury, BRØNSTED-Acid and -Base Catalysts

2.1.1.1. Mercury Catalysts

The mercury(II) salt catalyzed hydration of alkynes is the classic method that continues to be used because of its reliability. In 1881, KUCHEROV reported that Hg(II) salts mediate the hydration of acetylene to acetaldehyde, and of higher terminal alkynes to methyl ketones.[28a,36] Even though the quantity of mercury salt was not specified, its catalytic nature was recognized and likened to that of an enzyme.[28b] Various salts of mercury(II) are catalytically active in aqueous or biphasic solution: $HgBr_2$,[28a] $HgCl_2$, $HgSO_4$,[28b,32] $Hg(OAc)_2$[36] or $Hg(ClO_4)_2/HClO_4$.[37] Other reagent combinations include $Hg(OAc)_2$/*p*-TsOH in MeOH,[38] $Hg(OAc)_2$ in HOAc,[30] $Hg(OAc)_2$/HOAc in MeOH,[39] and $Hg(OTf)_2$ + 2 TMU in $CH_3CN/CH_2Cl_2/H_2O$ (Table 2).[40]

Table 2. Mercury catalysts for alkyne hydration.

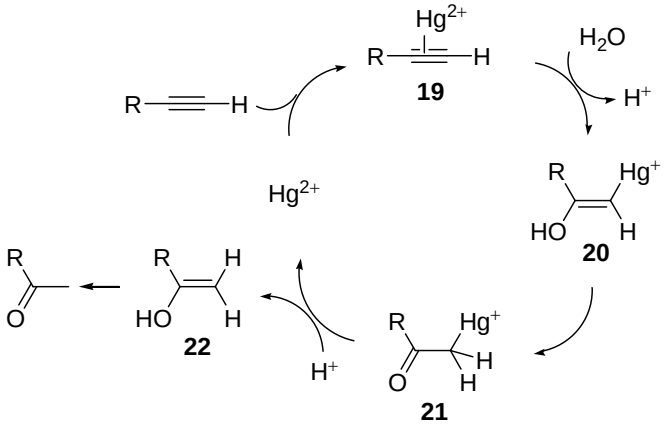
catalyst	mol-%	conditions	substrates[a]	lit.
$HgO–H_2SO_4$	0.5–100	H_2O rt→100 °C	RC≡CH RC≡CR	28b, 41
$HgO–H_2SO_4$	0.7	ROH (Me_2CO; HOAc)–H_2O 60–80°C, 4 h	RC≡CH RC≡CR	32
$Hg(OTf)_2$–2TMU	1–5	$MeCN/CH_2Cl_2$ rt, 6–48 h	RC≡CH	40
Hg(II)–IER[b]	-	HOAc(EtOH)–H_2O rt→100 °C	AlkC≡CH RC≡CR	42
$HgO–BF_3$	1–4	Cl_3CCO_2H MeOH/ROH[c] rt→60 °C	RC≡CH RC≡CR	51

a) AlkC≡CH = aliphatic alkynes; RC≡CH includes aryl and alkyl; RC≡CR = internal alkynes (aryl and alkyl). b) IER = ion exchange resin. c) Generates acetals, which are hydrolyzed during acidic workup.

[36] M. Kutscheroff *Chem. Ber.* **1909**, *42*, 2759.
[37] W. L. Budde, R. E. Dessy *J. Am. Chem. Soc.* **1963**, *85*, 3964.
[38] M. Bassetti, B. Floris *Gazz. Chim. Ital.* **1986**, *116*, 595.
[39] a) M. Bassetti, B. Floris, G. Illuminati *Organometallics* **1985**, *4*, 617. b) M. Bassetti, B. Floris *J. Org. Chem.* **1986**, *51*, 4140. c) M. Bassetti, B. Floris *J. Chem. Soc., Perkin Trans. II* **1988**, 227.
[40] M. Nishizawa, M. Skwarczynski, H. Imagawa, T. Sugihara *Chem. Lett.* **2002**, 12.
[41] G. W. Stacy, R. A. Mikulec *Org. Synth. Coll. Vol. IV* **1963**, 13.
[42] a) M. S. Newman *J. Am. Chem. Soc.* **1953**, *75*, 4740. b) G. A. Olah, D. Meidar *Synthesis* **1978**, 671.

The most popular catalyst is an acidic solution of mercury(II) sulfate, often obtained by dissolution of mercury(II) oxide (HgO) in aqueous sulfuric acid, that is diluted in organic solvents such as alcohols, acetone, acetic acid,[32] formic acid, THF, dioxane, acetonitrile, or dichloromethane and chloroform (in mixtures with other solvents).

Mercury(II) oxide exists in both yellow and red varieties, but the materials differ only in particle size, and both can be used. The addition of Fe(III)sulfate prolongs catalyst lifetime through reoxidation of Hg(0) to the active Hg(II).[31] As already noted in the development of technical hydrations of acetylene, the presence of an excess of acid (sulphuric acid, phosphoric acid, sulfonic acid, acetic acid) accelerates the reaction.[30] If a strongly acidic reaction medium is not desirable, pyridinium *p*-toluenesulfonate (PPTS) may be used,[43] or the acid may be simply omitted.[44] Alternatively, stoichiometric methods are applied.
The currently proposed mechanism of the Hg(II)-catalyzed hydration of alkynes is relatively simple, but several aspects are not known in detail.[45,37-39,46,47,48]



Scheme 6. Mechanism of the KUTCHEROV hydration.

At least a single free coordination site on the mercury cation is needed in order to form a short-lived π-complex with the substrate (Scheme 6, **19**). The MARKOVNIKOV selectivity observed in most alkyne hydrations is explained by steric and electronic arguments; the better

[43] a) I. Paterson, M. Tudge *Tetrahedron* **2003**, *59*, 6833. b) I. Paterson, M. Tudge *Angew. Chem.* **2003**, *115*, 357; *Angew. Chem. Int. Ed.* **2003**, *42*, 343.
[44] G. G. Cox, C. J. Moody, D. J. Austin, A. Padwa *Tetrahedron* **1993**, *49*, 5109.
[45] P. F. Hudrlik, A. M. Hudrlik; In *The Chemistry of the Carbon-Carbon Triple Bond*; Ed.: S. Patai; John Wiley & Sons: Chichester, 1978, 240.
[46] S. C. Wang, M. D. Person, W. H. Johnson, C. P. Whitman *Biochemistry* **2003**, *42*, 8762.
[47] J. Barluenga, F. Aznar, R. Liz, R. Rodes *J. Chem. Soc., Perkin Trans. 1* **1983**, 1087.
[48] a) S. Uemura, H. Miyoshi, M. Okano *J. Chem. Soc., Perkin. Trans. 1* **1980**, 1098. b) R. D. Bach, R. A. Woodard, T. J. Anderson, M. D. Glick *J. Org. Chem.* **1982**, *47*, 3707. c) M. Bassetti, M. P. Trovato, G. Bocelli, *Organometallics* **1990**, *9*, 2292.

stabilization of a partial positive charge at the internal alkyne carbon (larger σ-donor effect of R *vs* H) as well as the steric repulsion between metal ion and alkyl group R favor an attack at the inner alkyne carbon atom.[11] Water then attacks the triple bond to form, presumably, a β-hydroxyethenyl-mercury species (**20**). Judging from related acetoxy-mercurations, where organo-mercury addition products can be isolated, the addition step is often *anti*-stereoselective, though *syn*-adducts have sometimes been obtained.[48] In case of hydration, compounds **20** have neither been isolated nor characterized spectroscopically. The acid-mediated protodemercuration of the intermediate **20** affording the product **22** (maybe *via* intermediate **21**) might be the rate-determining step.[49] Curiously, α-mercuriated carbonyl compounds **21**, which are well characterized and for which even X-ray structures exist,[50] have received little consideration in mechanistic discussions. It is assumed that the reaction product is initially released as an enol (**22**), before tautomerizing to the final product, though enols have not been directly observed.

The counterion of the mercury salt has an influence on reaction rate; non-nucleophilic counter-ions give faster reactions, but their solutions tend to be less stable towards precipitation of elemental mercury. An important catalyst in this respect is the one developed by HENNION and NIEUWLAND,[51] which is prepared by dissolution of HgO in MeOH by addition of boron trifluoride-diethyletherate ($BF_3{\cdot}OEt_2$).[51a,b] Even better results are obtained by addition of co-catalytic trichloroacetic acid (0.3 equivalents relative to HgO).[51c,d] These preparations may contain non-coordinating fluoroborate counterions.[51a] The HENNION-NIEUWLAND-catalyst mediates the addition of alcohols (and carboxylic acids) to triple bonds, but an acidic workup of the acetals (dioxolanes) resulting from MeOH (or ethylene glycol) addition gives ketones.[52] Another kind of non-nucleophilic counterion is provided by ion-exchange resins as solid supports for mercury(II).[42] Sulfonated polystyrene resins or the perfluoroalkylsulfonic acid based Nafion® polymer are suitable. Here, the simple handling and work-up (by filtration) are advantageous.

[49] A. F. Rekasheva, I. P. Samchenko *Dokl. Akad. Nauk SSSR* **1960**, *133*, 1340.
[50] L. A. Paquette, D. G. Bolin, M. Stepanian, B. M. Branan, U. V. Mallavadhani, J. Tae, S. W. E. Eisenberg, R. D. Rogers *J. Am. Chem. Soc.* **1998**, *120*, 11603.
[51] a) J. A. Nieuwland, R. R. Vogt, W. L. Foohey *J. Am. Chem. Soc.* **1930**, *52*, 1018. b) G. F. Hennion, D. B. Killian, T. H. Vaughn, J. A. Nieuwland *J. Am. Chem. Soc.* **1934**, *56*, 1130. c) D. B. Killian, G. F. Hennion, J. A. Nieuwland *J. Am. Chem. Soc.* **1934**, *56*, 1786. d) D. B. Killian, G. F. Hennion, J. A. Nieuwland *J. Am. Chem. Soc.* **1936**, *58*, 80.
[52] a) A. M. Islam, R. A. Raphael *J. Chem. Soc.* **1952**, 4086. b) J. C. Hamlet, H. B. Henbest, E. R. H. Jones *J. Chem. Soc.* **1951**, 2652. c) H. Monti, M. Bertrand *Tetrahedron* **1973**, *29*, 2821.

Both the KUCHEROV and HENNION-NIEUWLAND catalysts are powerful tools that have seen many applications over the years, with minor variations. Reaction temperatures range from –20 °C to reflux temperature of the organic solvent.[53] Reaction times vary from minutes to a day and catalyst loadings from 0.1 mol-% to excess (≥250 mol-%), though the range of 2–10 mol-% is more usual. Little improvement of the basic methodology has occurred except for the introduction by NISHIZAWA of $Hg(OTf)_2 \cdot 2TMU$ in $MeCN/CH_2Cl_2$ as efficient catalyst at room temperature.[40]

2.1.1.1. BRØNSTED-Acid and -Base Catalysts

Acetylene and terminal alkynes have been hydrated to MARKOVNIKOV products in pure water at elevated temperatures (200–350 °C).[54–56] Microwave irradiation has been the procedure of choice in recent reports.[55,56] While electron-rich aryl-alkynes react readily, aliphatic substrates do so with more difficulty. Addition of $AuBr_3$ accelerates this reaction, presumably by acid catalysis.[56] Even in pure water, the hydrations are probably catalyzed by H_3O^+, and the addition of protic acids certainly increases reaction rate. Alkynes are hydrated to ketones in dilute H_2SO_4 at 280 °C.[57] The hydration of activated π-donor-(hetero)aryl-substituted alkynes is readily mediated by *para*-toluenesulfonic acid in alcohols at reflux[58] or with microwave heating.[55]

As shown in Scheme 7, acid-catalyzed hydration proceeds by protonation of the carbon-carbon triple bond of **23**, followed by fast nucleophilic addition of water to generate an enol **26**.[59-61] The strong kinetic dependence on the cation-stabilizing ability of alkyl or aryl substituents connected to the triple bond, together with a kinetic isotope effect (H_2SO_4/D_2SO_4) of ≈ 2 is taken as indication of rate-determining protonation of the alkyne to generate a vinyl cation intermediate **25**.[60,61]

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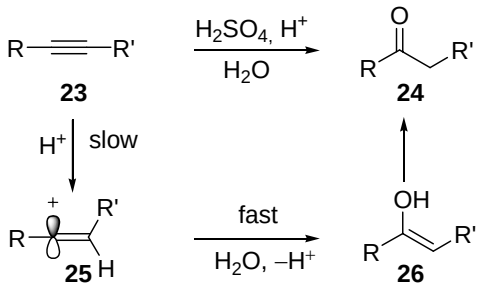
[53] H. Schick, B. Roatsch, S. Schramm, H. Gilsing, M. Ramm, E. Gründemann *J. Org. Chem.* **1996**, *61*, 5788.
[54] A. Desgrez *Ann. Chim.* **1894**, *3*, 209.
[55] J. M. Kremser, C. O. Kappe *Eur. J. Org. Chem.* **2005**, 3672.
[56] A. Vasudevan, M. K. Verzal *Synlett* **2004**, 631.
[57] G. An, L. Bagnell, T. Cablewski, C. R. Strauss, R. W. Trainor *J. Org. Chem.* **1997**, *62*, 2505.
[58] N. Olivi, E. Thomas, J. Peyrat, M. Alami, J. Brion *Synlett* **2004**, 2175.
[59] G. H. Schmid; In *Chemistry of the Carbon-Carbon Triple Bond*; Ed.: S. Patai; John Wiley: Chichester, 1978, 275.
[60] a) A. D. Allen, Y. Chiang, J. A. Kresge, T. T. Tidwell *J. Org. Chem.* **1982**, *47*, 775. b) D. S. Noyce, M. D. Schiavelli *J. Am. Chem. Soc.* **1968**, *90*, 1020. c) D. S. Noyce, M. A. Matesich, P. E. Peterson *J. Am. Chem. Soc.* **1967**, *89*, 6225.
[61] V. Lucchini, G. Modenan *J. Am. Chem. Soc.* **1990**, *112*, 6291.

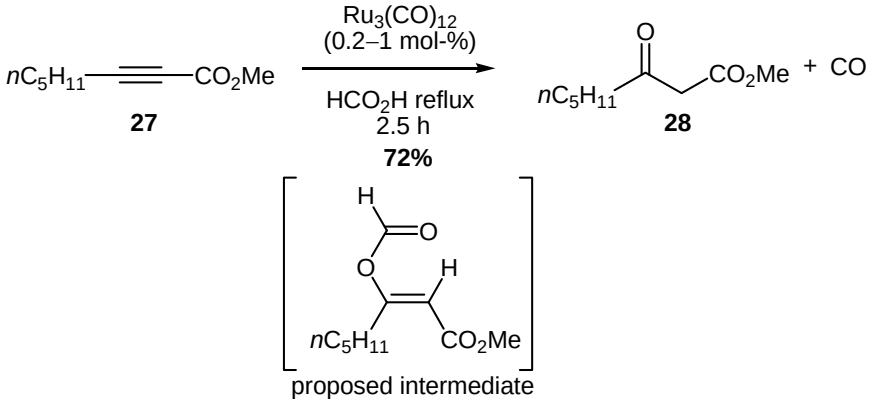


Scheme 7. Mechanism proposed for acid-catalyzed hydration.

Under conditions of photoexcitation (UV-light, λ = 254 nm), hydration of arylalkynes in dilute acid at room temperature proceeds smoothly, because the excited states are of greater basicity than the ground state, which facilitates vinyl cation formation.[62]

Activated heteroaryl-alkynes are also hydrated by stoichiometric Na_2S-HCl aq. in MeOH.[63] Catalytic amounts of trifluoromethanesulfonic acid (TfOH) or Tf_2NH hydrate alkynes in hot dioxane,[64] and acidic ion-exchange resins mediate the reaction in water at reflux.[65] Many other procedures use stoichiometric or excess amounts of acid: π-acceptor-alkynes are hydrated by dissolution in cold, concentrated sulfuric acid, followed by dilution with water.[66] A mixture of H_3PO_4 and BF_3 hydrates alkynes in benzene/MeCN (1 h; 60–70 °C; 54–73%).[67] Activated aryl- or heteroaryl-alkynes react in trifluoroacetic acid containing a small amount of water at room temperature.[68] Many alkynes are hydrated in refluxing formic acid; notably, formic acid catalyzes its own addition to the alkyne, and the intermediary enol formate suffers decarbonylation. With less activated alkynes, a catalytic amount of $Ru_3(CO)_{12}$ is added to facilitate the reaction.[69] For example, 2-octynoate (**27**) reacted with refluxing formic acid to yield methyl 3-oxooctanoate (**28**) (Scheme 8).[69b]

[62] a) Y. Chiang, A. J. Kresge, M. Capponi, J. Wirz *Helv. Chim. Acta* **1986**, *69*, 1331. b) P. Wan, S. Culshaw, K. J. Yates *J. Am. Chem. Soc.* **1982**, *104*, 2509. c) T. Wooldridge, T. D. Roberts *Tetrahedron Lett.* **1973**, *41*, 4007.
[63] M. J. Chapdelaine, P. J. Warwick, A Shaw *J. Org. Chem.* **1989**, *54*, 1218.
[64] T. Tsuchimoto, T. Joya, E. Shirakawa, Y. Kawakami *Synlett* **2000**, 1777.
[65] a) S. Iimura, K. Manabe, S. Kobayashi *Org. Biomol. Chem.* **2003**, *1*, 2416. b) B. S. Kupin *Zh. Org. Khim.* **1965**, *1*, 1206.
[66] A. Baeyer, W. H. Perkin *Chem. Ber.* **1883**, *16*, 2128.
[67] A. Pourzal, P. Bonnet *Monatsh. Chem.* **1983**, *114*, 809.
[68] a) B. Meseguer, D. Alonso-Díaz, N. Griebenow, T. Herget, H. Waldmann *Angew. Chem. Int. Ed.* **1999**, *38*, 2902. b) S. Duclos, H. Stoeckli-Evans, T. R. Ward *Helv. Chim. Acta* **2001**, *84*, 3148.
[69] a) N. Menashe, D. Reshef, Y. Shvo *J. Org. Chem.* **1991**, *56*, 2912. b) N. Menashe, Y. Shvo *J. Org. Chem.* **1993**, *58*, 7434.



Scheme 8. Hydration in refluxing formic acid by SHVO.

Alkynes have also been hydrated over H_3PO_4 on solid support at 150–350 °C in the vapor phase.[70] There is an extensive literature on hydration over solid metal oxides or -phosphates in connection with mercury-free production of acetaldehyde; mixed cadmium phosphomolybdates are the most active catalysts.[71,72,73]

Base-catalysed hydrations of alkynes are less common, since carbonyl compounds are not stable under the reaction conditions. π-Acceptor-substituted alkynes react by conjugate hydroxide-addition to give stable enolates of β-keto-compounds; therefore, stoichiometric amounts of base are required for full conversions.[74] The base-catalyzed addition of alcohols to alkynes results in vinyl ethers or acetals, which can be hydrolysed in a separate step.[33f]

The most common way of hydrating π-acceptor alkynes is the method developed by MOUREU which proceeds by stoichiometric conjugate addition of primary or secondary amines, followed by an acid-mediated hydrolysis.[75,76,77]

The BRØNSTED acids and bases used for alkyne hydration are listed in Table 3.

[70] R. E. Schaad, V. N. Ipatieff *J. Am. Chem. Soc.* **1940**, *62*, 178.
[71] V. Jäger, H. G. Viehe; *Houben-Weyl*, 4th Ed., Vol. V/2a; Ed.: E. Müller; Thieme: Stuttgart, 1977, 726.
[72] T. F. Rutledge; *Acetylenes and Allenes*; Reinhold Book Corporation: New York, 1969**.**
[73] a) Y. Izumi *Catalysis Today* **1997**, *33*, 371. b) P. Moggi, G. Albanesi *React. Kinet. Catal. Lett.* **1991**, *44*, 375. c) Y. A. Gorin, L. P. Bogdanova *Zh. Obshch. Khim.* **1958**, *28*, 1144.
[74] C. Moureu, R. Delange *C. R. Hebd. Acad. Sci.* **1903**, *136*, 753.
[75] For the hydration of esters, see: a) C. Moureu, I. Lazennec *Bull. Soc. Chim. Fr.* **1906**, *35*, 1190. For the hydration of nitriles, see: b) C. Moureu, I. Lazennec *Bull. Soc. Chim. Fr.* **1906**, *35*, 1179. c) C. Moureu, I. Lazennec *Bull. Soc. Chim. Fr.* **1907**, *1*, 1062. For the hydration of amides: d) C. Moureu, I. Lazennec *Bull. Soc. Chim. Fr.* **1907**, *1*, 1066.
[76] For recent applications, see: a) M. S. Chattha, A. M. Aguiar *J. Org. Chem.* **1973**, *38*, 2908. b) H. J. Bestmann, C. Geismann, R. Zimmermann *Chem. Ber.* **1994**, *127*, 1501. c) S. Abel, D. Faber, O. Hüter, B. Giese *Synthesis* **1999**, 188.
[77] M. Suzuki, M. Kambe, H. Tokuyama, T. Fukuyama *J. Org. Chem.* **2004**, *69*, 2831.

Table 3. BRØNSTED acids and bases for alkyne hydration.

catalyst/ reagent	mol-%	conditions	substrates[a]	lit.
H_2O	-	H_2O, 200–350 °C 0.5–3 h	RC≡CH RC≡CR	54-56
H_2SO_4		H_2O, 280 °C 1 h	RC≡CH	57
p-TsOH	20	ROH–H_2O 80–170 °C 6–144 h	ArlC≡CH HetarlC≡CH RC≡CR	55,58
Na_2S–HCl	>100	H_2O, MeOH rt	HetarlC≡CH[b] ArlC≡CH[b] ArlC≡CR[b]	63
HOTf	10-20	dioxane, H_2O 100 °C, 50 h	RC≡CH RC≡CR	64
HCO_2H	≥100	100 °C 0.5–10 h	RC≡CH RC≡CR	69
CF_3CO_2H	>100	H_2O r.t.–60 °C	HetarlC≡CH[b] ArlC≡CH[b]	68
R_2NH	100	THF/EtOH heating, H^+, H_2O	RC≡CZ[c]	75–77

a) AlkC≡CH = aliphatic alkynes; ArlC≡CH = aromatic alkynes; HeteralC≡CH = heteroaromatic alkynes; RC≡CH includes aryl and alkyl; RC≡CR = internal alkynes (aryl and alkyl).b) Only π-donor-activated aryls. c) Z = π-acceptor group.

2.1.2. Non-Mercurial Catalysts for Alkyne Hydration

2.1.2.1. Zinc, Cadmium, Tellurium, Thallium

In addition to mercury(II) catalysts in alkyne hydration, zinc and cadmium salts have also been studied. In 1909, KUCHEROV reported that aqueous solutions of zinc- or cadmium-salts mediate the hydration of 3-methyl-1-butyne within 3 h at 150 °C, and that hydration with acetylene was sluggish.[36] In a more recent patent, the reaction with acetylene was carried out under a pressure of 22 atm at 140 °C within 4 h, in solutions of zinc sulfate.[78]

p-Methoxytellurinic acid anhydride was shown to hydrate terminal alkynes, selectively in the presence of internal ones in refluxing acetic acid.[79]

[78] M. Ban, F. Ida U.S. Patent 2791614, **1957**.
[79] N. X. Hu, Y. Aso, T. Otsubo, F. Ogura *Tetrahedron Lett.* **1986**, *27*, 6099.

Thallium(III) salts such as the chloride, acetate and sulfate catalyze the hydration of phenylacetylene in hot acetic acid.[80] The reaction is relatively slow and more of academic interest, if one considers the toxicity of thallium compounds.

2.1.2.2. Groups 1 Through 7 and Lanthanides

There are very few alkyne hydration catalysts in the left third of the periodic table. A single report of cerium(IV)-sulfate catalyzed alkyne hydration has appeared.[81]

In the late 1990s, an acetylene hydratase (a tungsten iron-sulfur protein) was isolated from the bacterium *Pelobacter acetylenicus* which feeds anaerobically on acetylene as the sole carbon source. In a model study aimed at reproducing the enzymatic alkyne hydration activity of tungsten iron-sulfur enzymes, the tungsten(IV)-complex $(Et_4N)_2[W(O)(mnt)_2]$ was identified as a catalyst for hydration of acetylene to acetaldehyde in a strongly reducing environment.[82] Unfortunately, the reaction mechanism is presently unknown.[83]

2.1.2.3. Iron, Ruthenium and Osmium (Group 8)

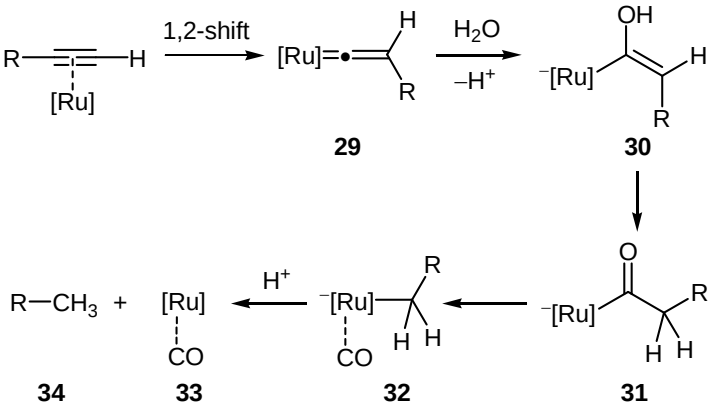
There are no iron-catalysts for alkyne hydration, but the stoichiometric hydration of phenylacetylene to acetophenone is mediated by the combined action of $FeCl_3/3\ H_2O$. α-Chlorostyrene was an intermediate in the reaction, which appears to be a BRØNSTED-acid-mediated (HCl) addition of H_2O to the alkyne. Acetophenone was also generated from phenyl acetylene with $FeCl_3$ and either acetic acid or camphor sulfonic acid.[84]

Ruthenium is one of the prominent elements in research on alkyne hydration. In the early 1960's, JAMES and co-workers demonstrated that ruthenium(III) chloride was a catalyst for the MARKOVNIKOV hydration of simple alkynes and phenyl propiolic acid.[85] The catalytically less efficient complex $[Ru^{II}Cl_4(CO)(H_2O)]^{2-}$ and eventually inactive $[Ru^{II}Cl_4(CO)_2]^{2-}$ were

[80] S. Uemura, H. Miyoshi, M. Okano, K. Ichikawa *J. Chem. Soc., Perkin Trans. 1* **1981**, 991. b) S. Uemura, R. Kitoh, K. Fujita, K. Ichikawa. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 1499.
[81] W. Liu, J. Li *Chinese J. Org. Chem.* **2006**, *26*, 1073.
[82] a) B. M. Rosner, B. Schink *J. Bacteriol.* **1995**, *177*, 5767. b) R. U. Meckenstock, R. Krieger, S. Ensign, P. M. H. Kroneck, B. Schink *Eur. J. Biochem.* **1999**, *264*, 176.
[83] M. Boll, B. Schink, A. Messerschmidt, P. M. H. Kroneck *Biol. Chem.* **2005**, *386*, 999.
[84] J. P. Damiano, M. Postel *J. Organomet. Chem.* **1996**, *522*, 303. b) P. O. Miranda, D. D. Díaz, J. I. Padrón, M. A. Ramírez, V. S. Martín *J. Org. Chem.* **2005**, *70*, 57.
[85] a) J. Halpern, B. R. James, A. L. W. Kemp *J. Am. Chem. Soc.* **1961**, *83*, 4097. b) J. Halpern, B. R. James, A. L. W. Kemp *J. Am. Chem. Soc.* **1966**, *88*, 5142.

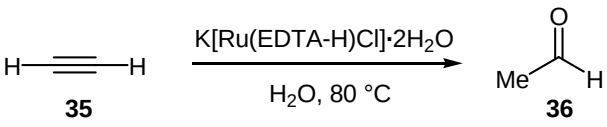
formed in the course of the reaction, and catalysis stopped before full conversion. Deactivation was faster for higher alkynes.

A mechanistic study by BIANCHINI shed light on possible pathways for catalyst-deactivation (Scheme 9).[86] Whereas Ru(II) is known to readily form vinylidene complexes **29** that add water to give Ru-acyl species **31**, the latter decarbonylate with release of alkane **34**, rather than the expected aldehyde.



Scheme 9. Mechanism for alkyne splitting by water by BIANCHINI.

In 1990, TAQUI KHAN reported the hydration of acetylene (**35**) to acetaldehyde (**36**) catalyzed by a water-soluble ruthenium(III)-complex (Scheme 10).[87] Ru(III)-loaded Nafion ion-exchange resin was found to hydrate 3-methyl-1-butyn-3-ol to the hydroxyketone.[88]

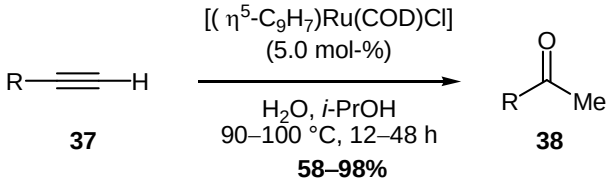


Scheme 10. Hydration of acetylene by TAQUI KHAN.

In the course of studies on anti-MARKOVNIKOV hydration (see Section 2.2), WAKATSUKI identified complex $[RuCl_2(\eta^6\text{-}C_6H_6)(PPh_3)]$ as a catalyst for terminal alkyne hydration with predominant MARKOVNIKOV selectivity (≥8:1).[89]

[86] C. Bianchini, J. A. Casares, M. Peruzzini, A. Romerosa, F. Zanobini *J. Am. Chem. Soc.* **1996**, *118*, 4585.
[87] M. M. Taqui Khan, S. B. Halligudi, S. Shukla *J. Mol. Catal.* **1990**, *58*, 299.
[88] I. K. Meier, J. A. Marsella *J. Mol. Catal.* **1993**, *78*, 31.
[89] M. Tokunaga, Y. Wakatsuki *Angew. Chem.* **1998**, *110*, 3024; *Angew. Chem. Int. Ed.* **1998**, *37*, 2867.

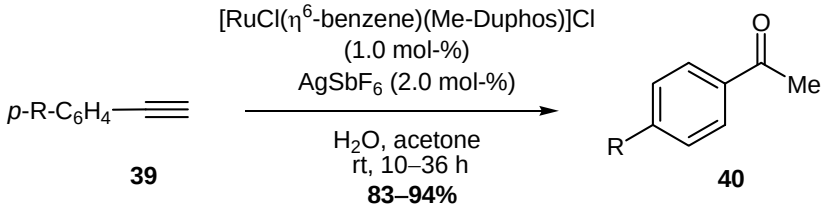
In 2001, BASSETI and GIMENO reported the regioselective hydration of phenyl acetylene into acetophenone (98%) using the complex [Ru(η^5-indenyl)Cl(η^4-COD)]. In addition, several aliphatic terminal alkynes **37** underwent the addition of water to give the corresponding methyl ketones **38** in high selectivity (92–98%) and moderate to high yield (58–98%) as presented in Scheme 11.[90]



R = Ph, *n*-C_5H_{11}, *n*-C_6H_{13}, 1-hydroxycyclohexyl

Scheme 11. Hydration of aliphatic terminal alkynes by BASSETI and GIMENO.

Related complexes [$RuCl_2$(η^6-arene)(PR_3)] or [RuCl(η^6-arene)(PR_3)$_2$]Cl with variations in the arene and phosphane ligands also catalyze the hydration of phenyl acetylene.[91] Recently, PREGOSIN and co-workers introduced cationic complexes [RuCl(P–P)(arene)]Cl (arene = η^6-benzene and η^6-*p*-cymene; P–P = diphosphane or 2 Bu_3P) that catalyzed the hydration of terminal aryl acetylenes **39** with MARKOVNIKOV selectivity after chloride abstraction with $AgSbF_6$, as shown in Scheme 12.[92] The *in situ* generated species hydrates aryl alkynes (electron-rich substrates react faster) at room temperature, but alkyl acetylenes do not react; a large excess of water stops the reaction.



R = H, OMe, Cl

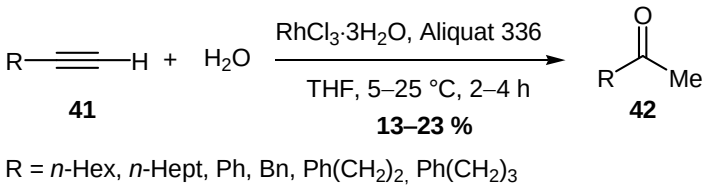
Scheme 12. Aryl-alkyne hydration by PREGOSIN.

[90] P. Alvarez, J. Gimeno, E. Lastra, S. García-Granda, J. F. Van der Maelen, M. Bassetti *Organometallics* **2001**, *20*, 3762.
[91] a) H. D. Hansen, J. H. Nelson *Organometallics* **2000**, *19*, 4740. b) K. Y. Ghebreyessus, J. H. Nelson *Inorg. Chim. Acta* **2003**, *350*, 12. c) V. Cadierno, P. Crochet, S. E. García-Garrido, J. Gimeno *Dalton Trans.* **2004**, 3635.
[92] Y. Chen, M. Valentini, P. S. Pregosin, A. Albinati *Inorg. Chim. Acta* **2002**, *327*, 4.

2.1.2.4. Rhodium and Iridium (Group 9)

In the late 1960s, JAMES and REMPEL described the catalytic hydration of alkynes under mild conditions,[93] employing acidic solutions of rhodium(III) chloride aqua-complexes of the type $[Rh(H_2O)_{6-n}Cl_n]^{(n-3)-}$. The species with n= 0 or n= 6 were found to be completely inactive, whereas the activity increased between n= 1 to n= 5. Related kinetic and mechanistic studies imply the importance of a coordinated water molecule on the metal ion, and have underscored the similarities between this system and the reactivity of the corresponding ruthenium(III) chloride. In the case of acetylene, which was converted to acetaldehyde at 1 atm pressure and 60 °C, these rhodium(III)-catalyzed systems were about three times more active than the corresponding system involving ruthenium(III), but deactivation was also a problem for the Rh-system.

In 1992, BLUM reported the use of catalysts composed of $RhCl_3 \bullet 3H_2O$ and quaternary ammonium salts Aliquat 336 (Scheme 13). Their system provided MARKOVNIKOV products from terminal alkynes and regioisomeric mixtures from internal ones, both at reasonable rates though in low yield.[94]



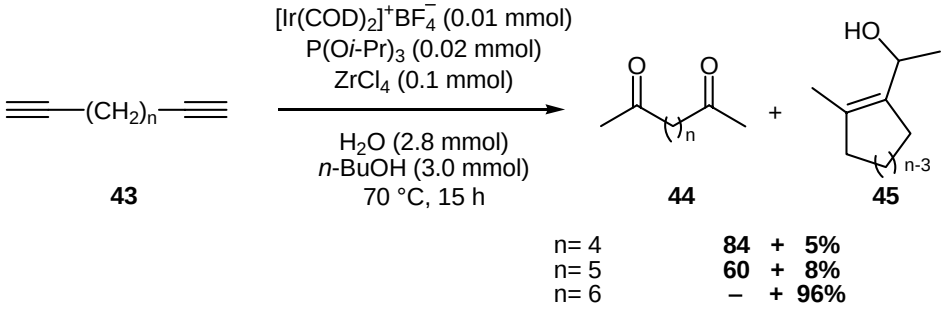
Scheme 13. Rhodium-catalyzed hydration of terminal alkynes by BLUM.

Later work showed that a polystyrene-supported complex, resulting from $RhCl_3$ and the Dowex-1 ion exchanger, promoted the hydration of aromatic terminal alkynes affording the ketones selectively in good to high yields (64–97 %), together with variable amounts of oligomerization products (5–20 %).[95] The catalytic activity of $IrCl_3$ in combination with a quarternary ammonium salt was also noted.

[93] B. R. James, G. L. Rempel *J. Am. Chem. Soc.* **1969**, *91*, 863.
[94] J. Blum, H. Huminer, H. Alper *J. Mol. Catal.* **1992**, *75*, 153.
[95] M. Setty-Fichman, Y. Sasson, J. Blum *J. Mol. Catal.* **1997**, *126*, 27.

The hydration of alkynes with water-soluble metal complexes of sulfonated tertiary phosphines was studied in detail by CHIN.[96] Hydration of acetylene and terminal alkynes was achieved with the water-soluble iridium(I) complex $[IrCl(TPPST)_2(CO)]$ at room temperature with moderate to excellent yield (900 turnovers), whereas internal alkynes such as diphenylacetylene did not react. Notably, pure water was much less efficient as solvent than organic media containing 10% of water; presumably, competitive coordination of substrate and water at the metal center plays a role. MeOH also added to alkynes, to give acetals, but at a lower rate.

The precursor complex $[Ir(COD)_2]BF_4$ in combination with tri-isopropyl phosphite and $ZrCl_4$ (or other chloride-containing LEWIS acids) hydrates terminal alkynes **43** at low catalyst loadings to afford mehtyl ketones **44** in good to excellent yields (Scheme 14).[97]



Scheme 14. Iridium-catalyzed hydration of terminal diynes by ISHII.

With some changes, namely with $P(OEt)_3$ as co-ligand and $AlCl_3$ as Lewis acid, this catalyst also generated acetals by addition of MeOH or higher alcohols to terminal alkynes. The iridium(III) complex $[Ir(Me)(OTf)(CO)(H_2O)(PPh_3)_2]OTf$ catalyzed acetalizations of terminal alkynes by several α,ω-diols; the cyclic acetals have been hydrolyzed separately to methyl ketones, whereas direct catalytic hydration was not possible.[97b]

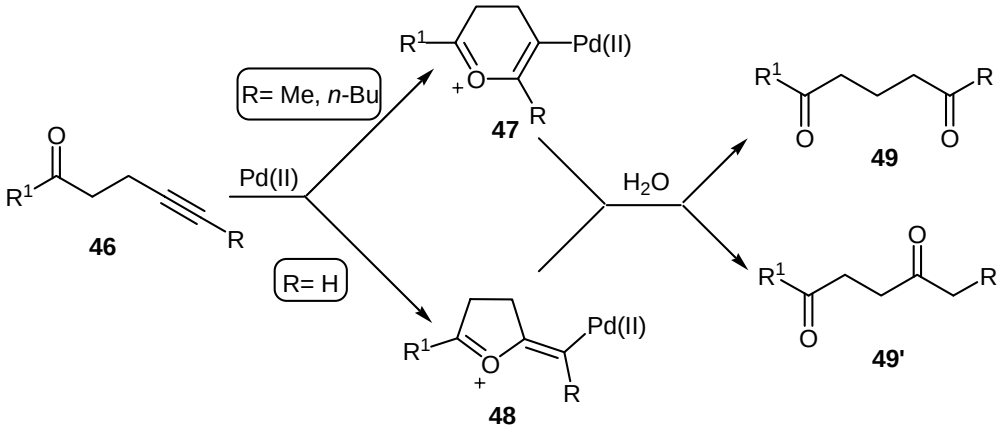
In the early 2000s, FUKUZUMI reported the pH-selective synthesis of alkynyl, acyl, and ketonyl complexes in the hydration of a terminal alkyne, with a water-soluble iridium(III) aqua complex of the type $[Cp^*Ir(III)(bpy)(H_2O)]^{2+}$.[98] The interaction of the iridium(III) aqua complex with phenylacetylene was investigated in aqueous solution at 70 °C. Either metal-

[96] C. S. Chin, W.-T. Chang, S. Yang, K.-S. Joo *Bull. Korean Chem. Soc.* **1997**, *18*, 324.
[97] a) T. Hirabayashi, Y. Okimoto, A. Saito, M. Morita, S. Sakaguchi, Y. Ishii *Tetrahedron Lett.* **2006**, *62*, 2231. b) S. Y. Kim, C. S. Chin, M. S. Eum *J. Mol. Cat.* **2006**, *253*, 245.
[98] S. Ogo, K. Uehara, T. Abura, Y. Watanabe, S. Fukuzumi *J. Am. Chem. Soc.* **2004**, *126*, 16520.

acyl or metal-2-oxoalkyl (ketonyl) species were formed depending on the pH of the medium, but only 3 turnovers to acetophenone were observed at 80 °C and pH 1 in a catalytic reaction.

2.1.2.5. Palladium, Platinum (Group 10)

A cationic species generated from *cis*-[$Pd(PPhMe_2)_2Cl_2$] and $AgBF_4$ catalyzes the addition of water to dimethyl acetylene dicarboxylate in refluxing acetone.[99] Extensive studies by UTIMOTO on the use of $PdCl_2$ (or solvates like [$PdCl_2(RCN)_2$] with R= Me, Ph) as catalysts for cycloisomerizations of alkynols or alkynyl ketones to oxygen heterocycles also resulted in protocols for the hydration of the same substrates.[100] The $PdCl_2$ catalyst is highly specific for hydrations assisted by *anchimeric assistance* (neighbouring group participation), and simple alkylacetylenes do not usually undergo hydration. In the late 1980s, UTIMOTO also performed the palladium(II)-catalyzed hydration of alkynyl ketones **46** that under mild conditions allowed the preparation of a series of diketones (**49,49'**) in good to excellent yields (Scheme 15).[101] The observed regioselectivity resulted from the carbonyl group participation and depended on the steric effect of the substituents on the alkynes.



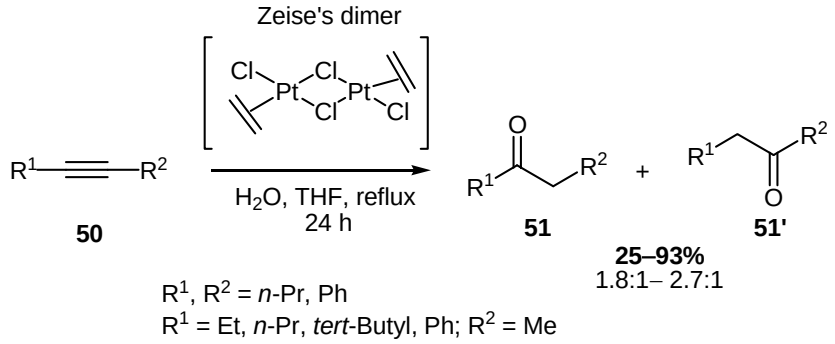
Scheme 15. Hydrations assisted by *anchimeric assistance* by UTIMOTO.

In addition, LIU and coworkers reported recently an intermolecular Pd(II)-mediated alkyne-alkene cyclisation reaction that generates a macrocyclic α,β-unsaturated ketone.[102]

[99] a) A. Avshu, R. D. O'Sullivan, A. W. Parkins, N. W. Alcock, R. M. Countryman *J. Chem. Soc., Dalton Trans.* **1983**, 1619. b) Y. Kataoka, O. Matsumoto, M. Ohashi, T. Yamagata, K. Tani *Chem. Lett.* **1994**, 1283.
[100] K. Utimoto *Pure and Appl. Chem.* **1983**, *55*, 1845.
[101] K. Imi, K. Imai, K. Utimoto, *Tetrahedron Lett.* **1987**, *28*, 3127.
[102] N. Nomiyama, M. W. Kanan, D. R Liu *J. Am. Chem. Soc.* **2007**, *129*, 2230.

Modified conditions use NBu_4Cl as phase-transfer-catalyst in a two-phase CH_2Cl_2/HCl_{aq} system.[103] Among other Pd(II)-compounds, a Nafion/Pd(II) resin hydrated a propargylic alcohol.[88]

While being engaged in their studies concerning the preparation of alkyne-platinum(II) complexes, CHATT reported in 1961 that ethanolic $Na_2PtCl_4 \cdot 4\ H_2O$ converts alkyne to methyl ketones.[104]
Later, JENNINGS established that ZEISE's dimer [$\{PtCl_2(C_2H_4)\}_2$], or simply $PtCl_2$ and other platinum halides, are catalysts for the hydration of internal alkynes at rather low catalyst loading (Scheme 16).[105] The regioselectivity of the catalyst for hydration of internal alkynes was comparable to mercury catalysis.[105c]



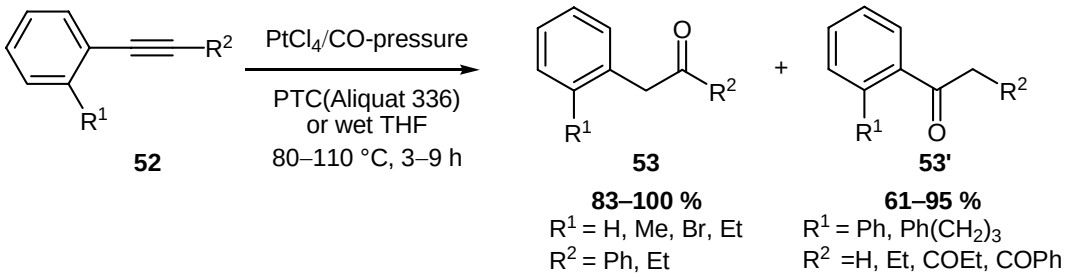
Scheme 16. ZEISE's dimer as catalyst for the hydration of alkynes by JENNING.

The Pt(II) catalysts hydrate selectively in the presence of a large excess of alcohol, but upon addition of co-catalytic non-nucleophilic base (Na_2SO_4, $MgSO_4$, 2,6-di-*tert*-butylpyridine) alcohols also add to the alkyne producing acetals.[105d] No added base was necessary to cyclize alkynols to acetals or spiro-acetals with ZEISE's dimer.[81]

$PtCl_4$ catalyzes the hydration of alkynones **52** in aqueous THF or under phase-transfer conditions, but a superior catalyst is generated *in situ* from $PtCl_4$ and CO (14 bar), followed

[103] A. Arcadi, S. Cacchi, F. Marinelli *Tetrahedron* **1993**, *49*, 4955.
[104] J. Chatt, R. G. Guy, L. A. Duncanson *J. Chem. Soc.* **1961**, 827.
[105] a) W. Hiscox, P. W. Jennings *Organometallics* **1990**, *9*, 1997. b) J. W. Hartman, W. C. Hiscox, P. W. Jennings *J. Org. Chem.* **1993**, *58*, 7613. c) P. W. Jennings, J. W. Hartman, W. C. Hiscox *Inorg. Chim. Acta* **1994**, *222*, 317. d) J. W. Hartman, L. Sperry *Tetrahedron Lett.* **2004**, *45*, 3787.

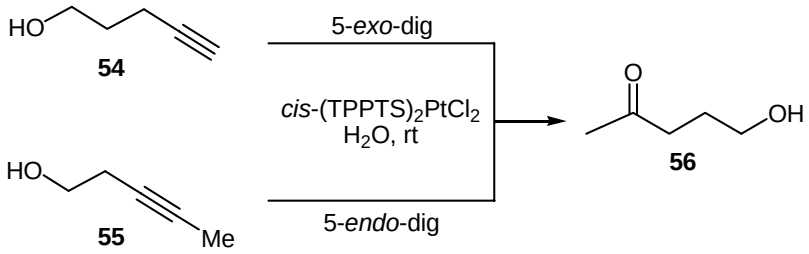
by reaction under CO (1.4 bar).[106] Reactions are either performed in homogeneous THF solution or a two phase system with quaternary ammonium chloride (Scheme 17).



Scheme 17. Platinum(IV)-catalyzed hydration of alkynes by BLUM.

High yields (>90%) were initially reported for alkyl-, aryl- and internal alkynes, but later problems of reproducibility were mentioned and considerably lower yields were only achieved.[106c] The active species is presumably [PtH(CO)Cl(L)] (L = CO, H_2O, THF), which is in equilibrium with green-colored clusters $[Pt_3(CO)_3(\mu^2\text{-}CO)_3]_n^{2-}$ (n = 5,6) and HCl.[106]

The water-soluble complex *cis*-$(TPPTS)_2PtCl_2$ [TPPTS = (m-$NaOSO_2C_6H_4)_3P$] catalyzes regioselective hydrations of both 4-pentyn-1-ol **54** and 3-pentyn-1-ol **55** to the common product 5-hydroxy-2-pentanone **56**, as expected from a mechanism with anchimeric group assistance.[107] This indicated that the reaction occurred through 5-*exo*-dig and 5-*endo*-dig cyclization steps, as shown in Scheme 18.



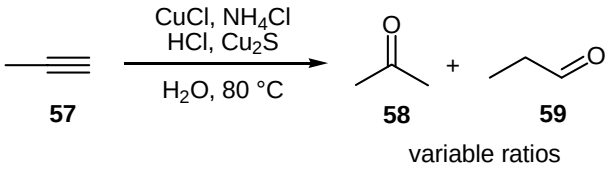
Scheme 18. Platinum-catalyzed hydration of pentyl-1-ol to 5-hydroxy-2-pentanone.

A sulfonated version of the chelating ligand dppe, dppets ({m-$NaO_3SC_6H_4$}$_2$$PCH_2CH_2P${$m$-$C_6H_4SO_3Na$}$_2$) is also catalytically active in the same model reactions,[108] but hydrations of other alkynes have not been reported.

[106] a) Y. Badrieh, A. Kayyal, J. Blum, *J. Mol. Catal.* **1992**, *75*, 161. b) W. Baidossi, M. Lahav, J. Blum *J. Org. Chem.* **1997**, *62*, 669. c) O. Israelsohn, K. P. C. Vollhardt, J. Blum *J. Mol. Catal.* **2002**, *184*, 1.
[107] L. W. Francisco, D. A. Moreno, J. D. Atwood *Organometallics* **2001**, *20*, 4237.
[108] D. W. Lucey, J. D. Atwood *Organometallics* **2002**, *21*, 2481.

2.1.2.6. Copper, Silver, Gold (Group 11)

Copper catalysts have been investigated as replacements for mercury catalysts in industrial scale hydration of acetylene or propyne. In 1961, VARTANYAN developed a catalyst composed of CuCl (28–34%), NH_4Cl (14–18%), mineral acids (*eg.* HCl, 1–3%) and a sulfide additive, either inorganic (H_2S, Na_2S, or heavy metal sulfides; 0.4–3%) or organic (*n*-$C_8H_{17}SH$, mercaptobenzoic acid, thioglycol) for the catalytic hydration of acetylene at 80–85 °C.[109] The hydration of propyne **57** with this catalyst led to mixtures of acetone **58** and propanal **59** (MARKOVNIKOV and anti-MARKOVNIKOV products) in variable ratios (Scheme 19).[110] Organic thiol additives had similar effects, however their steric size affected the regioselectivity of the reaction.[111] The generation of aldehydes was explained by intermediacy of a vinyl sulfide and its hydrolysis. CuCl-Clusters were proposed to be the active catalysts in presence of thiol additives.[111d]

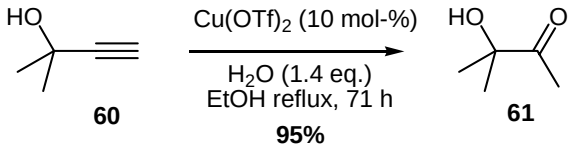


Scheme 19. Copper-catalyzed hydration of alkyne in presence of sulfide additives.

The kinetics of Cu(I) catalyzed hydration of acetylene has been determined in the course of a study on the dimerization of acetylene to vinylacetylene, where hydration is a side-reaction.[112] In 1993, MARSELLA reported that copper(II)-cations in conjunction with non-coordinating anion-environments catalyze the hydration of a range of functionalized and nonfunctionalized alkynes.[88] The catalytic system was mild enough to allow hydration of propargyl alcohols with complete MARKOVNIKOV regioselectivity and without any trace of dehydration. Under homogeneous conditions, copper(II)-triflate and -tetrafluoroborate are catalysts for the hydration of 2-methyl-3-butyn-2-ol **60** into 3-hydroxy-3-methyl-2-butanone **61** in high yield (Scheme 20). Non-coordinating counter-ions are important for the catalytic activity. Copper (II) acetate is not active in the hydration of simple alkynes, though it can mediate the

[109] S. A. Vartanyan, S. K. Pirenyan, N. G. Manasyan *Zh. Obshch. Khim.* **1961**, *31*, 2436.
[110] G. K. Shestakov, N. Y. Vsesvyatskaya, A. M. Stepanov, O. N. Temkin *Kinet. Catal.* **1976**, *17*, 815.
[111] a) G. K. Shestakov, O. N. Temkin, N. Y. Vsesvyatskaya, A. M. Stepanov *Zh. Org. Khim.* **1979**, *15*, 248. b) N. Y. Vsesvyatskaya, G. K. Shestakov, O. N. Temkin *Kinet. Catal.* **1986**, *27*, 1330. c) N. Y. Vsesvyatskaya, D. V. Tsyganov, A. M. Bykov, G. K. Shestakov, O. N. Temkin *Zh. Org. Khim.* **1985**, *21*, 2041. d) N. Y. Vsesvyatskaya, G. K. Shestakov, O. N. Temkin *Kinet. Catal.* **1988**, *29*, 965.
[112] Y. Tokita, A. Okamoto, K. Nishiwaki, M. Kobayashi, E. Nakamura *Bull. Chem. Soc. Jpn.* **2004**, *77*, 1395.

hydration of *N*-propargylamides with anchimeric assistance.[113] Nafion-Cu(II) resin catalyst hydrates several alkynes rather slowly.[88]

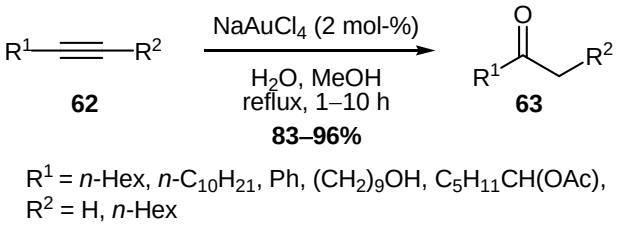


Scheme 20. Copper(II)-catalyzed hydration of α-hydroxy-1-alkynes by MARSELLA.

Cationic sources of silver (AgOTf, $AgPF_6$) can activate alkynes towards attack of oxygen nucleophiles mostly in cyclization reactions.[114] Intermolecular reactions are less common for non-activated alkynes. The hydration of 2-methyl-3-butyn-2-ol **60** was difficult with AgOTf,[88] whereas this salt catalyzes the addition of alcohols to π-acceptor alkynes more readily.[115] Moreover, with silver nitrate as catalyst hydration of N-propargylamides is realized with anchimeric assistance.[116]

The first catalytic hydration of alkynes with a gold catalyst ($HAuCl_4$) was observed in 1976.[117] Later, UTIMOTO and co-workers discovered a synthetically useful protocol with $NaAuCl_4$ as catalyst under weak acidic conditions (pH 5).[101] Thus, the hydration of a range of internal and terminal alkynes **62** performed under gold(III) catalysis in refluxing aqueous methanol, yielded exclusively ketones **63** in excellent yields (Scheme 21).[118] Alkynes bearing a remote hydroxyl group were smoothly hydrated under the above reaction conditions, but propargylic alcohols do not react. Access to dimethoxyacetals by addition of 2 equivalents of anhydrous methanol was also reported with very high regioselectivity and yields. The failure of $K[Au(CN)_2]$ to act as a catalyst was taken as evidence for an Au(III) rather than an Au(I) species as the active catalyst, but the cyanide complex is probably not a good model for the kind of Au(I) species that forms under reaction conditions. $NaAuCl_4$ catalyzes the MEYER-SCHUSTER rearrangement of internal propargyl ethers to α,β-unsaturated ketones, whereas a terminal propargyl ether gave the regular hydration product.

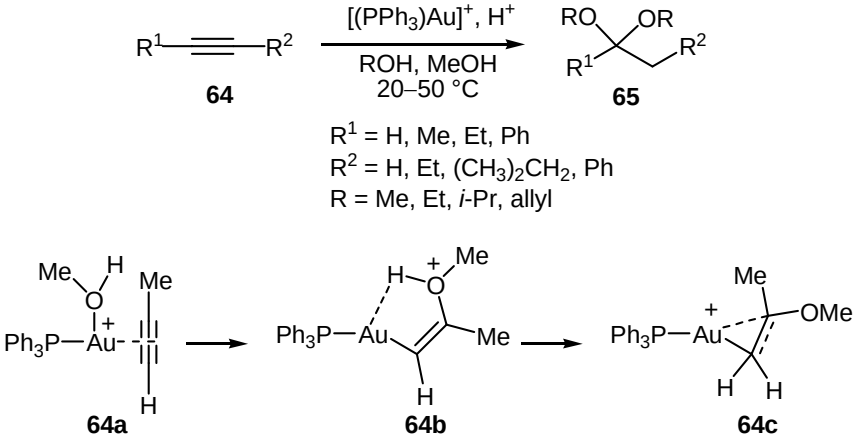
[113] N. R. Easton, D. R. Cassady, R. D. Dillard *J. Org. Chem.* **1965**, *30*, 3084.
[114] P. Pale, J. Chuche *Eur. J. Org. Chem.* **2000**, 1019.
[115] Y. Kataoka, O. Matsumoto, K. Tani *Chem. Lett.* **1996**, 727.
[116] N. R. Easton, D. R. Cassady, R. D. Dillard *J. Org. Chem.* **1965**, *30*, 3084.
[117] R. O. C. Norman, W. J. E. Parr, C. B. Thomas *J. Chem. Soc.* **1976**, 1983.
[118] a) Y. Fukuda, K. Utimoto *J. Org. Chem.* **1991**, *56*, 3729. b) Y. Fukuda, K. Utimoto *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2013.



Scheme 21. Gold(III)-catalyzed hydration of internal and terminal alkynes by UTIMOTO.

A variety of Au(III)-organometallic compounds, containing Au-C_6F_5 or Au-Mes units and chloro ligands are catalyst precursors for the hydration of phenylacetylene and 1-heptyne under neutral or acidic conditions (HOTf, H_2SO_4).[119] Best results were obtained with mononuclear complexes bearing electronegative ligands such as $NBu_4[Au(C_6F_5)_2Cl_2]$ or $PR_4[Au(Aryl)Cl_3]$, that had similar activity to that of $NaAuCl_4$. Higher turnover numbers are achieved in acidic media.

In 1998, TELES reported on additions of alcohols to alkynes **64** catalyzed by cationic gold(I) complexes of the type [L-Au$^+$] (where L is a phosphine, a phosphite or an arsine), to afford acetals **65** (Scheme 22).[120]



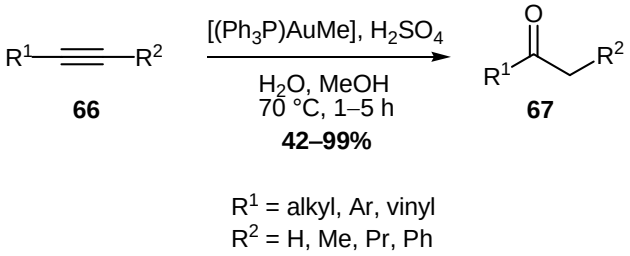
Scheme 22. Gold(I) catalyzed acetization of alkynes by TELES.

The reaction took place under mild conditions (20–50 °C) in the presence of an acid as co-catalyst (*eg.* $MeSO_3H$), with a turnover frequency (TOF) of up to 5400 h^{-1}. The catalysts were generated from (a) $[AuX(PPh_3)]$ (X = Cl, CF_3CO_2, $MeSO_3$, NO_3) and BF_3, or from (b) $[AuCl(PPh_3)]$ and AgY (Y = non-nucleophilic counterion), or from (c) $[AuMe(PPh_3)]$ by protonolysis of the gold–carbon bond with a strong acid with a non-nucleophilic counterion

[119] R. Casado, M. Contel, M. Laguna, P. Romero, S. Sanz *J. Am. Chem. Soc.* **2003**, *125*, 11925.
[120] a) J. H. Teles, S. Brode, M. Chabanas *Angew. Chem.* **1998**, *110*, 1475; *Angew. Chem. Int. Ed.* **1998**, *37*, 1415. b) M. Schulz, J. H. Teles U.S. Patent 6037482, **2000.**

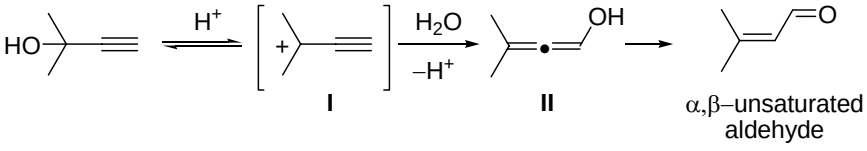
(H_2SO_4, HBF_4, $MeSO_3H$). The reactivity of alkynes **64** increased with higher electron density on the triple bond, and decreased with increased steric hindrance of the substituents R^1 and R^2. Primary alcohols are about ten times more reactive than secondary alcohols, but tertiary alcohols and phenols do not react. For the Au(I) catalyzed addition of MeOH to alkynes, a *syn*-addition mode involving activation of both MeOH and the alkyne by LAu^+ has been proposed (Scheme 22, **64a**).

More recently, TANAKA extended the use of the gold(I)-acid catalytic system to the hydration reaction in aqueous methanol (Scheme 23).[121]



Scheme 23. Gold(I)-acid catalytic system for hydration of alkynes by TANAKA.

Aliphatic and aromatic terminal alkynes **66** including those bearing functional groups such as cyano, chloro, alkoxy and olefinic moieties, underwent hydration with good to excellent yields at low catalyst loading and formed exclusively MARKOVNIKOV products **67**. Tertiary propargylic alcohols gave a mixture of ketoalcohols and rearranged α,β-unsaturated aldehydes (MEYER-SCHUSTER rearrangement, Scheme 24). The (LEWIS)-acid mediated generation of a propargyl cation (**I**) is followed by addition of water to give an allenol **II** that tautomerizes to the MEYER-SCHUSTER product, an α,β-unsaturated aldehyde (from terminal alkynes).



Scheme 24. The MEYER-SCHUSTER rearrangement.

[121] a) E. Mizushima, K. Sato, T. Hayashi, M. Tanaka *Angew. Chem.* **2002**, *114*, 4745; *Angew. Chem. Int. Ed.* **2002**, *41*, 4563. b) E. Mizushima, D. Cui, D. C. D. Nath, T. Hayashi, M. Tanaka *Org. Synth.* **2006**, *83*, 55.

Internal alkynes react slowly, presumably because of steric hindrance. Catalyst stability and activity could be both increased with triphenyl phosphite as additive or in the presence of carbon monoxide (1 atm) (TOF to 15600 h^{-1} at 70 °C with 0.005 mol-% of the gold(I)-catalyst). A practical laboratory procedure for the hydration of terminal alkynes with this procedure has appeared in 2006.[121b]

Moreover, the complexes $[Au(PPh_3)(RCO_2)]$ or $[Au(PPh_3)(RSO_3)]$ in combination with $BF_3{\cdot}Et_2O$ have been used as catalyst precursors for hydration of terminal and internal alkynes.[122] The complex $[(Ph_3P)Au(C_2F_5CO_2)]$ was the most active catalyst of those investigated (TOF up to 3900 h^{-1} for hydration of 3-hexyne in MeOH at 70 °C). Recently, the catalytic hydration of phenylacetylene by a porphyrin complex [Au(TPP)Cl] was noted.[123]

Finally, it is first worth noting that the mechanism of MARKOVNIKOV hydration of alkynes with metal-catalysts is superficially similar to that with mercury (see Scheme 6), though details of the mechanistic pathway are not fully understood. However, subtle differences due to the relative stabilities of the catalytic intermediates should be emphasized. For example, transition metal ions with a partially filled *d*-electron shell form stable π-complexes with alkynes; the attack of H_2O to the coordinated substrate then becomes rate-determining.[94,105]

2.2 Anti-MARKOVNIKOV Hydration of Terminal Alkynes

It took more than a century from KUCHEROV's demonstration of metal-catalyzed MARKOVNIKOV-selective alkyne hydration to the discovery of suitable catalysts displaying the anti-MARKOVNIKOV selectivity.[110] In the meantime, the best synthetic approach for realizing the latter conversion was a hydroboration/oxidation sequence.[124]

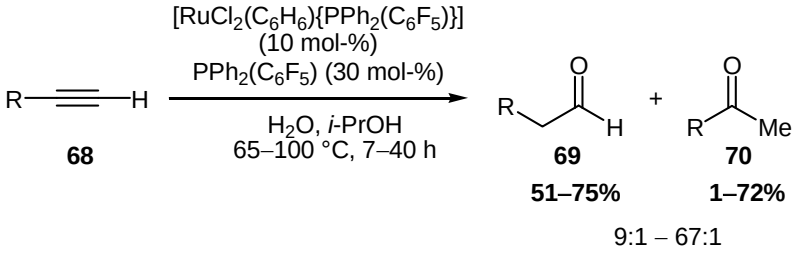
2.2.1. Ruthenium-catalyzed Anti-MARKOVNIKOV Hydration

In the late 1980s, DIXNEUF demonstrated that certain donor-stabilized Ru(II)-complexes were able to catalyze anti-MARKOVNIKOV additions of carbamates to terminal alkynes,[11h,i] as a consequence of a reaction mechanism that proceeds by an alkyne/vinylidene tautomerization

[122] P. Roembke, H. Schmidbaur, S. Cronje, H. Raubenheimer *J. Mol. Catal.* **2004**, *212*, 35.
[123] C. Zhou, P. W. H. Chan, C. Che *Org. Lett.* **2006**, *8*, 325.
[124] G. Zweifel, H. C. Brown *Org. React.* **1963**, *13*, 1.

pathway.[125] This chemistry was successfully extended to ligand-controlled regioselective additions of carboxylic acids and other nucleophiles,[7] but anti-MARKOVNIKOV hydration of terminal alkynes could not have been considered a straightforward extension of the reaction principle since a mechanistic study had implied that hydration of alkynes by the vinylidene pathway would stop at the stage of Ru(II)-carbonyl complexes and thereby poisoning of the catalyst (as discussed in section 2.1.2.3, Scheme 9).[79]

In 1998, WAKATSUKI described the first anti-MARKOVNIKOV hydration of terminal alkynes catalyzed by Ru(II)-complexes, which in the presence of auxiliary phosphane ligands yield predominantly aldehydes.[89,126] Generally, the reactions were carried out in the presence of 10 mol-% of $[RuCl_2(C_6H_6)\{PPh_2(C_6F_5)\}]$ and 30 mol-% of $PPh_2(C_6F_5)$ (catalyst **75**, Figure 3), in aqueous *iso*-propanol, at a temperature between 65 °C and 100 °C. As shown in Scheme 25, aliphatic alkynes **68** give aldehydes with selectivities (aldehyde **69**/methyl ketone **70**) from 9:1 to 67:1, whereas aromatic alkynes showed very low conversion and no regioselectivity (< 2% conversion, selectivity 1:1).

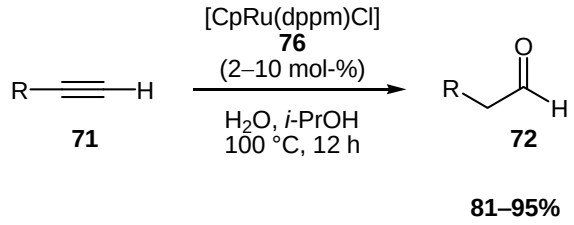


R = *n*-Bu, *n*-Hex, *n*-Dec, Bn, $(CH_2)_3Cl$, $(CH_2)_2OBn$

Scheme 25. Use of catalyst **75** in the hydration of terminal alkynes by WAKATSUKI.

A few years later, a remarkable increase in the reaction rate and the selectivity has been achieved by use of cyclopentadienylruthenium(II)-complexes bearing monodentate or bidentate phosphine ligands.[127] Typically, reactions were carried out with 2-10 mol-% of [CpRuCl(dppm)] (catalyst **76**, Figure 3) in *iso*-propanol-H_2O (3:1) at 100 °C and gave the desired aldehydes in good to excellent yields after 12 h (Scheme 26).

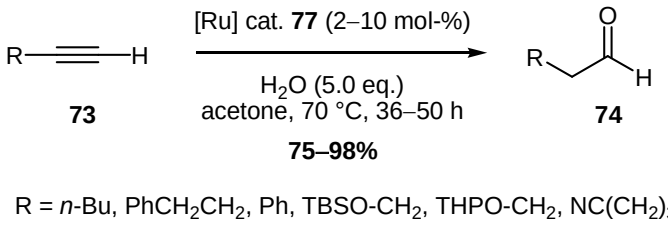
[125] C. Bruneau, P. H. Dixneuf *Angew. Chem.* **2006**, *118*, 2232; *Angew. Chem. Int. Ed.* **2006**, *45*, 2176.
[126] M. Tokunaga, Y. Wakatsuki Jap. Patent 11319576 A2, **1999.**
[127] a) T. Suzuki, M. Tokunaga, Y. Wakatsuki *Org. Lett.* **2001**, *3*, 735. b) T. Suzuki, Y. Wakatsuki, M. Tokunaga Jap. Patent 2002114730 A2, **2002**.



Scheme 26. Use of catalyst **76** in the hydration of terminal alkynes by WAKATSUKI.

The new catalyst has an extended substrate scope: phenylacetylene and *tert*-butylacetylene gave phenylacetaldehyde and 3,3-dimethylbutyraldehyde in high yields (90% and 81%, respectively). Generally, regioselectivity of the addition was very high and no traces of methyl ketone could be detected.

In 2001, GROTJAHN reported on the application of the principle of cooperative catalysis by the metal center and functional groups in the ligand sphere to anti-MARKOVNIKOV hydration.[128] A $[CpRu(PR_3)_2]^+$-fragment incorporating a sterically demanding phosphino-imidazole ligand was found to lead to a more active catalysts. The catalytic hydration of several terminal alkynes with complex **77** (2–10 mol-%) afforded the anti-MARKOVNIKOV products **74** with good to high yields and in a regioselectivity of usually ≥100:1 for aldehydes (Scheme 27). X-ray crystal structure of aqua-complex **77** showed two hydrogen bonds from coordinated water to the nitrogen lone-pairs of the imidazolyl-subunit (Figure 3, **77**) and invited therefore to speculations about the nucleophile-activating role of the ligand.



Scheme 27. Use of catalyst **77** in the hydration of terminal alkynes by GROTJAHN.

A breakthrough came with the next catalyst generation, where the imidazolyl group was replaced by a pyridine ring.[129] A cyclopentadienylruthenium(II) complex bearing two C-6 subtituted pyridylphosphane ligands (**78**, Figure 3) was found to be 1000 times more active in

[128] D. B. Grotjahn, C. D. Incarvito, A. L. Rheingold *Angew. Chem.* **2001**, *113*, 4002; *Angew. Chem. Int. Ed.* **2001**, *40*, 3884.
[129] D. B. Grotjahn, D. A. Lev *J. Am. Chem. Soc.* **2004**, *126*, 12232.

anti-MARKOVNIKOV hydration of terminal alkynes than the catalyst **76**, and present the advantage to also underwent the hydration at room temperature (1-nonyne; **78** 5 mol-% , 48 h, 99% conversion). This enormous rate difference was held as a strong argument for the occurrence of cooperative catalysis (see section 2.2.2).

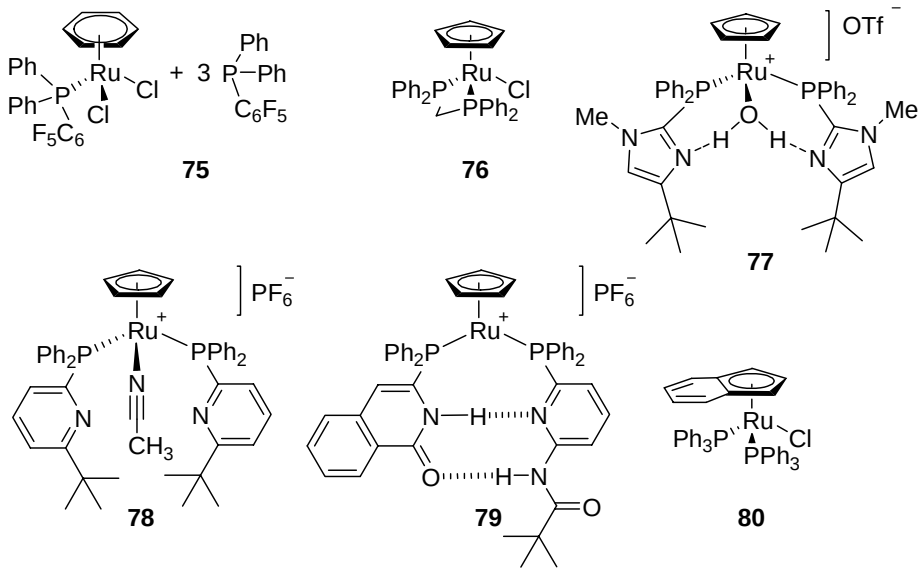


Figure 3. Catalysts for anti-MARKOVNIKOV hydration of alkynes.

Recently, BREIT investigated the self-assembly through hydrogen-bonding association of monodentate subunits to imitate a bidentate ligand at the CpRu-fragment.[130] On mixing the catalyst precursor $[CpRu(MeCN)_3]PF_6$ with 1:1-combinations of each one of three phosphino-isoquinolones with each one of three phosphino-aminopyridines (9 pairs), complex **79** (Figure 3) emerged as most active and selective catalyst for anti-MARKOVNIKOV hydration of terminal alkynes. Typical reaction conditions used 2–10 mol-% of **79** in aqueous acetone at 120 °C. Good to high yields were obtained within 26–124 h. In many cases, the regioselectivity was greater than 99:1, although a few substrates capable of anchimeric assistance produced some ketone (≤ 13%).

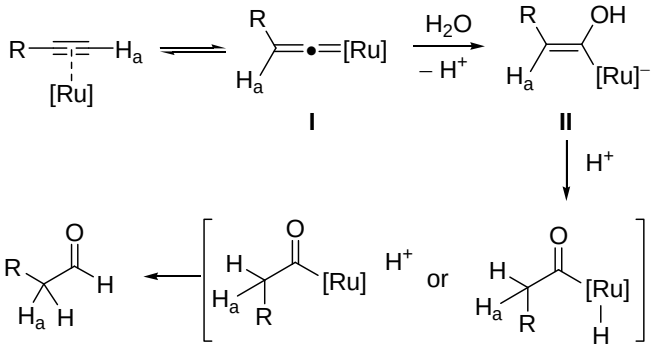
Next to the above cyclopentadienylruthenium(II)-based systems, GIMENO and BASSETTI reported the use of complex $[(Ind)RuCl(PPh_3)_2]$ (**80**, Figure 3) as catalyst for alkyne hydration.[131] Under optimized conditions (*i*-PrOH–H_2O = 4:1, 90 °C, 48 h), alkynes gave mixtures of aldehyde and ketone in ratios of 3:1 to 4:1, but in a miscellar solution of sodium dodecyl sulfate (or related tensides), aldehydes were formed with higher selectivity at 60 °C

[130] F. Chevallier, B. Breit *Angew. Chem.* **2006**, *118*, 1629; *Angew. Chem. Int. Ed.* **2006**, *45*, 1599.
[131] P. Alvarez, M. Bassetti, J. Gimeno, G. Mancini *Tetrahedron Lett.* **2001**, *42*, 8467.

(8:1–80:1). Unprotected propargyl alcohols are claimed to give aldols, but neither isolated yields nor characterization data for these rather unstable compounds have been given.

2.2.2. Mechanism of Ruthenium-catalyzed Anti-MARKOVNIKOV Hydration of Terminal Alkynes

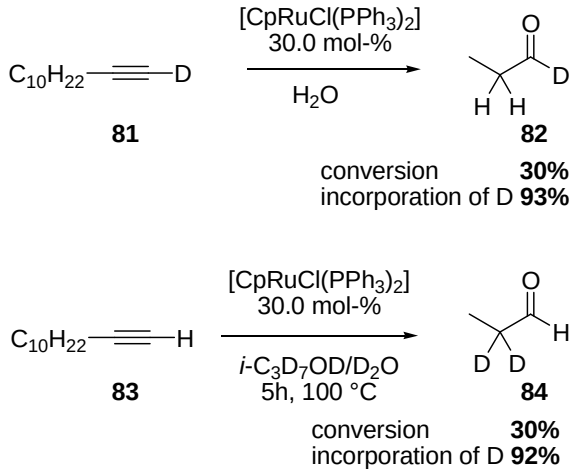
Anti-MARKOVNIKOV products cannot be obtained by a simple electrophilic activation pathway as discussed for mercury and other metals, so these products must emerge from a competing and fundamentally different mechanism. In analogy to the mechanism for alkyne splitting by water, a first mechanistic proposal for anti-MARKOVNIKOV hydration of alkynes assumed addition of water to a vinylidene intermediate **I**, generating a metal-acyl species **II**, which would undergo protonolysis of a carbon-ruthenium bond or reductive elimination of aldehyde (Scheme 28).[89]



Scheme 28. First mechanistic proposal for Ru-catalyzed anti-MARKOVNIKOV hydration of alkynes by WAKATSUKI.

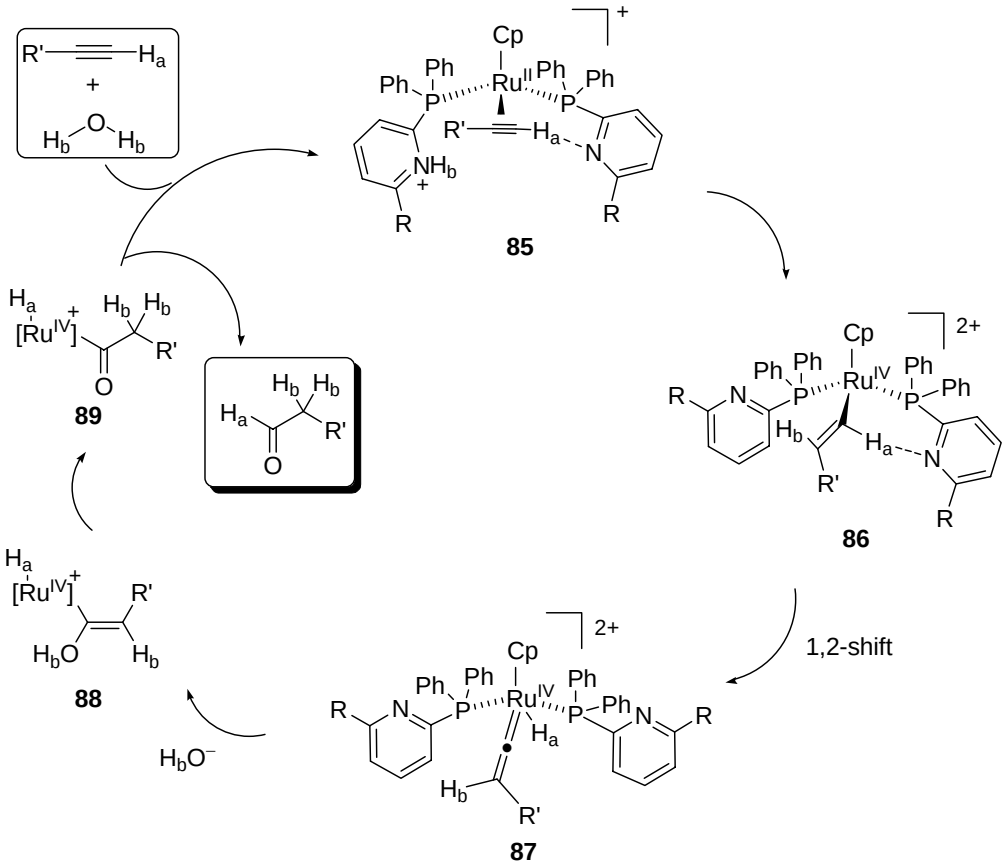
This mechanism incorporating well-documented Ru-vinylidene species[132] satisfactorily explained the generation of aldehydes, but failed to correctly predict the result of deuterium marker experiments disclosed by WAKATSUKI in 2001.[133] Thus, the use of a substrate with acetylenic deuterium **81** led to almost exclusive deuterium incorporation at the carbon of the carbonyl group **82**. In contrast, use of D_2O lead exclusively to products with deuterium only at the α-position of the carbonyl group **84** (Scheme 29).

[132] C. Bruneau, P. H. Dixneuf *Acc. Chem. Res*. **1999**, *32*, 311.
[133] M. Tokunaga, T. Suzuki, N. Koga, T. Fukushima, A. Horiuchi, Y. Wakatsuki *J. Am. Chem. Soc.* **2001**, *123*, 11917.



Scheme 29. Deuterium marker experiments by WAKATSUKI.

These results backed up by DFT calculations and isolation of organic and organometallic by-products resulted in the formulation of a new mechanistic proposal (Scheme 30).



Scheme 30. Current mechanistic picture for Ru^{II}-catalyzed hydration of terminal alkynes, including the proposal by WAKATSUKI and extensions by GROTJAHN.

It was anticipated that the first step is a protonation of the alkyne π-complex **85** to give a doubly charged Ru(IV)-vinyl-species **86**.[133] This process must be faster under the reaction

conditions than the alkyne-vinylidene-tautomerization. The Ru-vinyl complex then undergoes a 1,2-hydrogen shift to a Ru(IV)-hydride-vinylidene intermediate **87**. Subsequently, the electrophilic carbon next to the metal center is attacked by water or hydroxide anion. Then, the α-hydroxyvinyl-Ru-complex **88** isomerizes to Ru-acyl-tautomer **89**, and reductive elimination regenerates a Ru(II)-species by releases of the aldehyde product.

The recent introduction by GROTJAHN of bifunctional catalysts with their spectacularly accelerated reaction kinetics provides an important test-case for the mechanistic hypothesis, since any mechanistic scheme should also be capable of explaining the accelerations induced by the pyridylphosphane ligands.[128-129,134] It was found that pyridylphosphanes with large substituents in position C-6 of the pyridine are required for anti-MARKOVNIKOV hydration catalysis, whereas small pyridyl groups block the catalyst by a P-N coordination mode (Figure 4a), and the simple pyridylphosphine (R = H) undergoes irreversible addition to Ru-coordinated alkyne (Figure 4b).

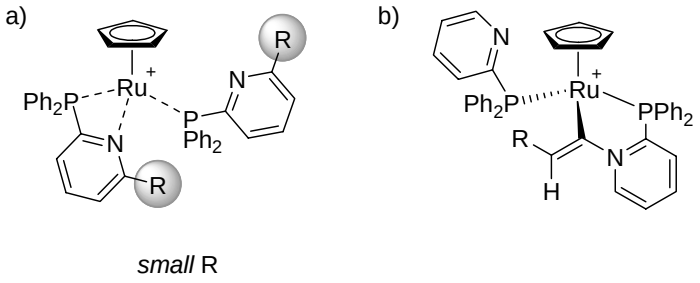


Figure 4. Catalyst deactivation by PN-chelation with small R groups or irreversible addition of alkyne by GROTJAHN.

With regard to the higher activity of pyridylphosphanes compared to other phosphane ligands, bifunctional catalysis was considered to play a key role in this process.[129] Here, the basic pyridine nitrogen may assist in the proton transfer from water to the Ru-alkyne complex **85** and by activating the nucleophile in close proximity of the reaction center (Scheme 30). Furthermore, a stabilizing hydrogen bond between the pyridine and the Ru-vinyl intermediate can be assumed (as indicated in structure **86**) to facilitate the 1,2-hydrogen shift.
Reports on the catalytic H/D-exchange with $[CpRu(phosphinopyridine)_2]^+$ fragments also hint at a specific role of the pyridine lone pairs in activating weakly acidic substrates.[135]

[134] D. B. Grotjahn *Chem. Eur. J.* **2005**, *11*, 7146.
[135] F. A. Jalón, B. R. Manzano, A. Caballero, M. C. Carrión, L. Santos, G. Espino, M. Moreno *J. Am. Chem. Soc.* **2005**, *127*, 15364.

2.2.3. Substrate Range of Anti-MARKOVNIKOV Hydration of Terminal Alkynes

An overview of the substrate scope of anti-MARKOVNIKOV hydration of terminal alkynes is presented in Figure 5. Aliphatic terminal alkynes **90** are hydrated by all ruthenium-catalysts presented in Figure 3 and diynes **93** are hydrated with catalysts **76**, **78**, **79**. Slow reactions occur with bulky substrates as is evident with *tert*-butylacetylene **91**.[89,128] Hydration of aromatic alkynes **92** proceeds generally more slowly and good results are only obtained with catalyst **78**. The functional group tolerance is broad (Figure 5).

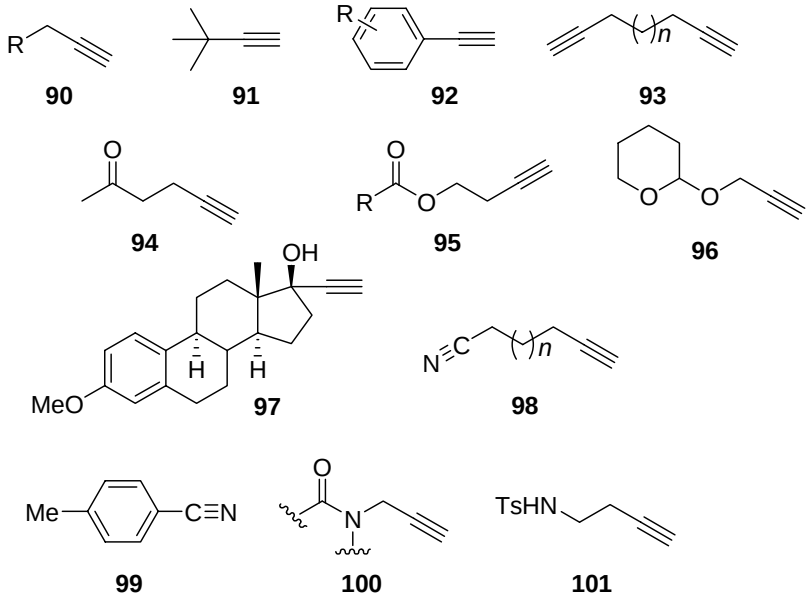


Figure 5. Substrate scope for ruthenium-catalyzed anti-MARKOVNIKOV hydration catalysis.

Typical oxygen functionality like ketones **94** or esters **95** are compatible with catalysts **75**, and **76** or **79**, respectively. As a result of the mild reaction conditions with catalysts **78**, even THP-acetals (**96**) are tolerated in a substrate.[128,129] The hydration of a steroidal tertiary propargyl alcohol **97** proceeded without elimination to an aldol using Ru(II)-catalyst **77**.[130] A nitrile group (**98**) may slow down catalysis by competitive binding.[127a,129] 4-Methylbenzonitrile (**99**) was recently hydrated into the corresponding amide with catalyst **79**.[136] Moreover, although basic nitrogen (*eg.* tertiary amines) is not tolerated, amides **100**, imides and sulfonamides **101** are tolerated with catalysts **79** and **78**, respectively. [129,130] An application of considerable synthetic relevance would be the hydration of propargyl alcohols to aldols,[129,131] but propargyl alcohols are often found to undergo MEYER-SCHUSTER rearrangements with anti-MARKOVNIKOV hydration catalysts.[127,137]

[136] T. Smejkal, B. Breit *Organometallics* **2007**, *26*, 2461.
[137] T. Suzuki, M. Tokunaga, Y. Wakatsuki *Tetrahedron Lett.* **2002**, *43*, 7531.

3. Aims of the Project

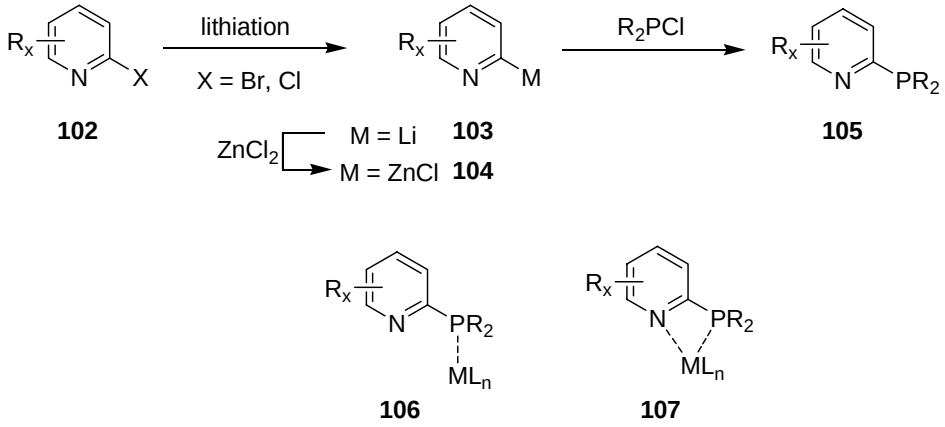
The development of new catalytic carbon-heteroatom and carbon-carbon bond forming reactions from simple starting materials is an ongoing field of interest, especially with regard of an efficient synthesis of complex target molecules. In order to minimize waste, energy, and the unnecessary consumption of raw materials, the aspect of atom economy of a reaction should be addressed in a more sustained fashion.

The transition metal-catalyzed addition of water to alkynes displays a paradigm, since it generates valuable carbonyl compounds in a fully atom-economic way. This carbon-oxygen bond forming reaction generates products without the use of energy-intensive redox-chemistry, having therefore a great potential for synthesis. A considerable part of the research in the field of the ruthenium(II)-catalyzed anti-MARKOVNIKOV hydration of terminal alkynes has been concentrated on the design and preparation of new and more powerful phosphane ligands. Despite the fact that high yields and high regioselectivities had already been achieved in the reaction, at the outset of this study the development of new efficient catalyst which are more easily accessible appeared yet desirable. The number of known ligands able to promote the anti-MARKOVNIKOV hydration was still rather limited. Amongst them, pyridyl- and imidazoyl phosphanes constitute a formidable target for new catalyst development. While being highly active, their synthesis was tedious and therefore only few different catalysts of this class have been reported.

First aim of this thesis was to develop new and highly efficient synthetic pathways towards C-6-substituted pyridylphosphanes. These should allow easy modification of the ligand structure in order to investigate stereoelectronic effects of the reaction with the ultimate aim to find more active catalysts. Moreover, the substrate scope of these newly prepared catalysts should be explored in the anti-MARKOVNIKOV functionalization of more complex substrates and thereby demonstrating the power of this method to access various functionalized aldehydes.

4. Synthesis of Aza-Arylphosphanes

Pyridylphosphanes are ubiquitous in transition metal chemistry and have been successfully used as ligands affording extremely reactive and versatile homogeneous catalysts.[129,138]



Scheme 31. General approach for pyridylphosphanes.

The most common approach reported for synthesizing this class of compounds (**105**) is constituted by electrophilic trapping of a metallated pyridine with a chlorophosphane species (Scheme 31).[138] This metallation can be achieved by simple lithiation of a 2-halogenated pyridine **102**. The use of organo-zinc species like **104** has also been reported which can be prepared by transmetallation of 2-lithio-pyridine **103** with $ZnCl_2$.[139]

In transition-metal complexes, pyridylphosphanes can act as a monodentate two-electron ligand (**106**) or as a bidentate ligand with four electrons (**107**). The monodentate coordination with the non-coordinated pyridine nitrogen would open the possibility for these compounds to act as a bifunctional catalyst by activating a reactant via metal center and the nucleophilic nitrogen as discussed for some of the structures.[134]

[138] G. R. Newkome *Chem. Rev*. **1993**, *93*, 2067.
[139] P. H. M. Budzelaar, J. H. G. Frijns, A. G. Orpen *Organometallics* **1990**, *9*, 1222.

4.1. Preparation of 2-Pyridylphosphanes via a WITTIG-Olefination/Cyclization Strategy

One of these pyridylphosphanes, the 2-*tert*-butyl-6-(diphenylphosphino)pyridine (**108**, Figure 6) was recently employed as a ligand for the ruthenium-catalyzed anti-MARKOVNIKOV hydration of terminal alkynes giving high selectivity and yield, as described in Sections 2.2.1. Taking into account the reaction sequence previously employed to access 2-*tert*-butyl-6-(diphenylphosphino)pyridine (**108**), the first objective of the presented work was to investigate a more efficient synthetic approach to this pyridylphosphane and subsequently to attempt the preparation of new 2-pyridylphosphanes by varying the carbon substituent on the pyridine ring.

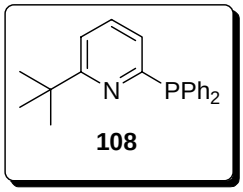
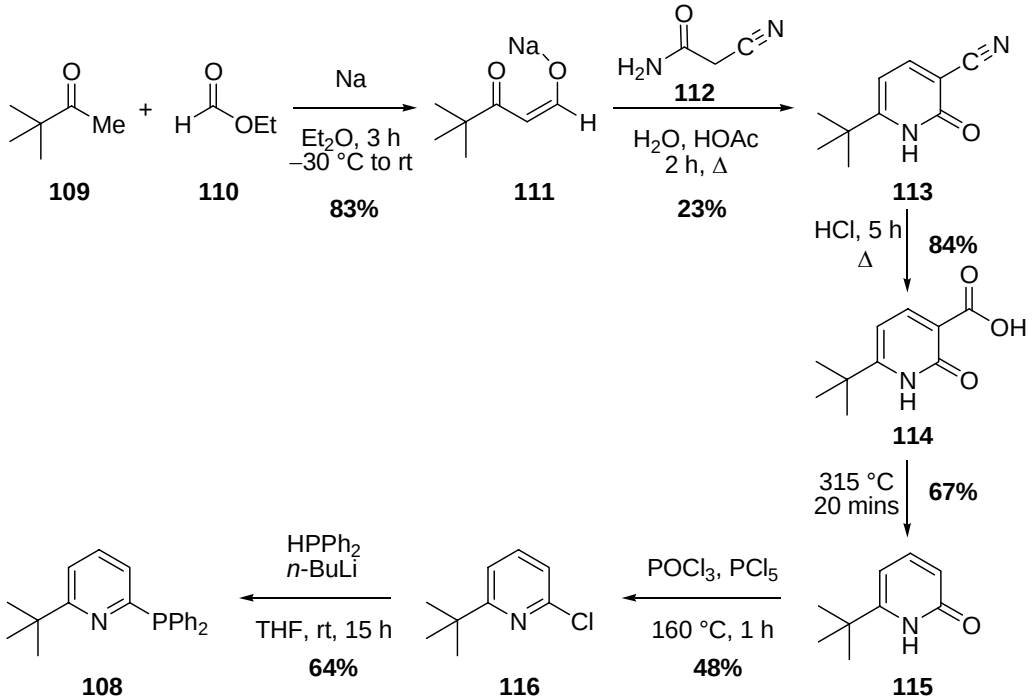


Figure 6. 2-*tert*-Butyl-6-(diphenylphosphino)pyridine.

The known procedure used to prepare 2-*tert*-butyl-6-(diphenylphosphino)pyridine (**108**) is presented in Scheme 32.[140]

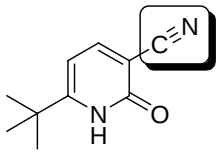


Scheme 32. Preparation of 2-*tert*-butyl-6-(diphenylphosphino)pyridine (**108**) by BERKE.

[140] a) J. Baur, H. Jacobsen, P. Burger, G. Artus, H. Berke, L. Dahlenburg *J. Inorg. Chem.* **2000**, 1411. b) R. P. Mariella *J. Am. Chem. Soc*. **1947**, *69*, 2670.

The synthesis required six steps and gave an overall yield of 3.3% starting from *tert*-butyl-methyl ketone (**109**) and ethyl formate (**110**)**.** The stepwise condensation of ethyl formate with ketone **109** and cyanoacetamide (**112**) provided 3-cyano-pyridinone **113** in a moderate 19% yield. Complete saponification of the nitrile to the pyridine-carboxylic acid was achieved by heating to reflux in concentrated hydrochloric acid during 5 h followed by thermal decarboxylation. 6-*tert*-Butyl-2-pyridine-2(1*H*)-one (**115**) could be isolated in 67% yield. Chlorination with a mixture of $POCl_3/PCl_5$ generated chloropyridine **116** in 48% yield and final phosphination with lithium diphenylphosphide gave the desired 2-*tert*-butyl-6-(diphenylphosphino)pyridine (**108**) in 64% yield.

In light of the possible use of 2-pyridylphosphanes as ligands for the above mentioned Ru-catalyzed hydration of alkynes, the existing synthetic route suffered from major drawbacks. Firstly, the harsh reaction conditions employed for the nitrile saponification and subsequent decarboxylation raised doubts about its generality for synthesizing various pyridylphosphanes with different substituents at the C_2-position. Secondly, the low overall yield of the route would limit significantly the amount of material made available for large-scale applications.



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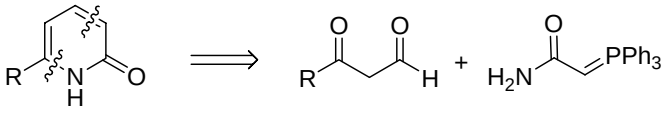
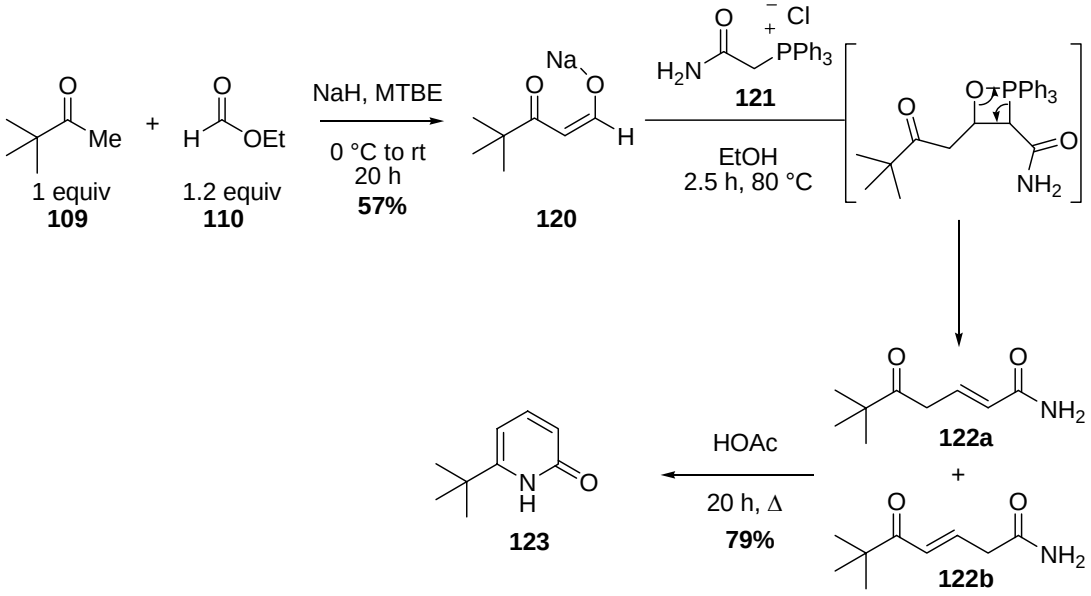


117 **118** **119**

Scheme 33. Retrosynthetic approach of 2-substituted pyridine-2(1*H*)-ones **117**.

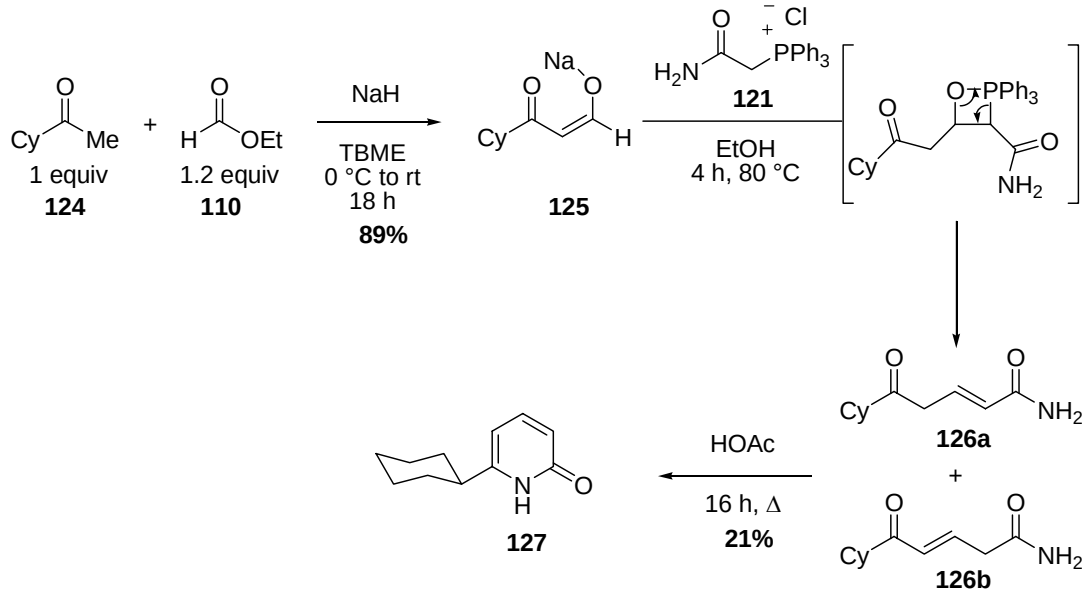
Consequently, a direct carbon-carbon coupling reaction without the use of activating groups, such as nitrile, would be desirable (Scheme 33). On reconsideration of the synthetic approach to **108**, a different route towards pyridinone **117** was envisaged based on a WITTIG-olefination/cyclization strategy starting from diketones **118** and ylide **119**.

Thus, it was found that 6-*tert*-butylpyridin-2(1*H*)-one (**123**) could be synthesized in fewer steps and higher overall yield using a one pot WITTIG-olefination reaction using the ready available phosphonium salts **121** followed by an acid-catalyzed cyclisation (Scheme 34).



Scheme 34. Synthesis of 6-*tert*-butylpyridine-2(1*H*)-ones **123** via a one pot "WITTIG-olefination/cyclization" reaction.

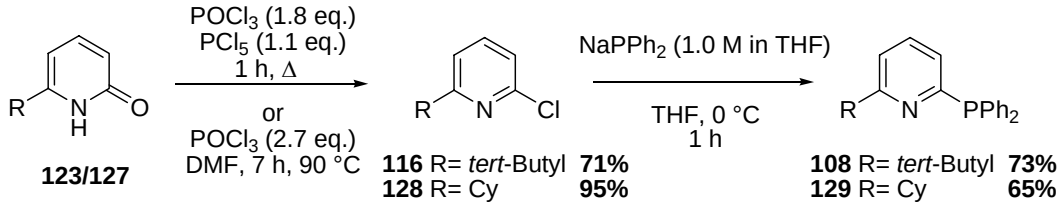
First, condensation of ethyl formate with either *tert*-butyl-methyl ketone (**109**) afforded the sodium salts **120** with a yield of 57%. In the following step, addition of 2-triphenylphosphonium acetamide-chloride (**121**)[141] to sodium enolate **120** led to the formation of a mixture of α,β-unsaturated amide **122a** and enone **122b**. Upon heating under acidic conditions this mixture underwent a ring closure to give pyridinone **123** in 79% yield over two steps. In a similar fashion, 6-cyclohexylpyridin-2(1*H*)-one (**127**) was synthesized in a moderate overall yield of 19% (Scheme 35).



Scheme 35. Synthesis of 6-cylohexylpyridine-2(1*H*)-ones **127** via a one pot "WITTIG-olefination/cyclization" reaction.

[141] Compound **121** is formed by reaction of 2-chloroacetamide with triphenylphosphine in acetonitrile (12 h, 80 °C) in high yields (90%).

Subsequent chlorination of pyridinones **123** and **127** was effected using either $POCl_3$ in DMF or a mixture of $POCl_3/PCl_5$, to afford the corresponding 2-chloro-6-substituted-pyridines **116** and **128** in 71% and 95% yield, respectively. Finally, reaction of compounds **116** and **128** with sodium diphenylphosphide as a solution in THF at rt provided analytically pure 2-pyridylphosphanes **108** and **129** in good yields after recrystallization (Scheme 36).



Scheme 36. Synthesis of pyridilphosphanes **108** and **129** starting from pyridine-2(1*H*)-ones.

As a result, the synthesis of 2-*tert*-butyl-6-(diphenylphosphino)pyridine (**108**) was achieved on a multigram-scale in five steps with a significantly improved overall yield of 24%.[142] Moreover, this new synthetic approach also allowed for the preparation of novel pyridylphosphane **129** in an overall yield of 12%.

Although this new synthetic approach to 2-pyridylphosphane compounds presented the advantage to improve the yields over the previous strategy, still a more versatile route was desirable and thus an alternative sequence based on cross-coupling reactions was developed.

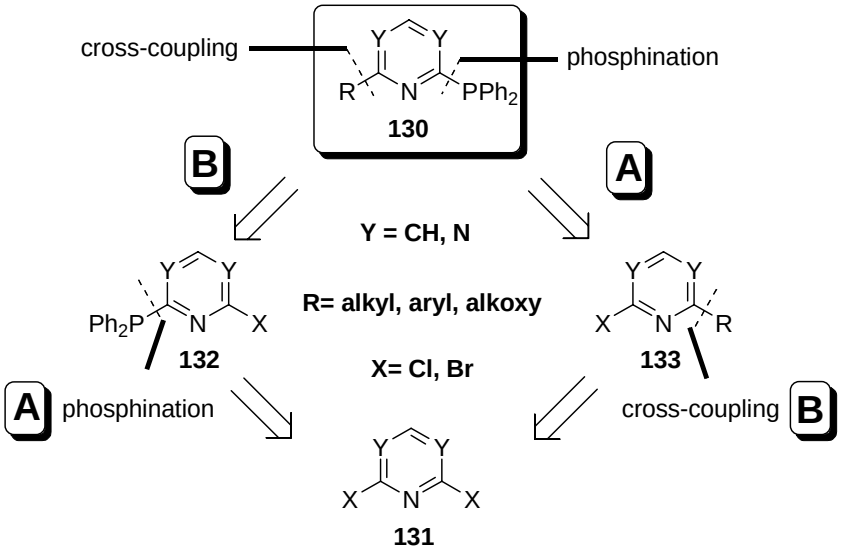
4.2. Preparation of 2-Substituted Aza-Arylphosphanes via Cross-Coupling/Nucleophilic Substitution Strategy

The role of the bulky *tert*-butyl-substituent in 2-position on the pyridine ring of the pyridylphosphane ligand in the Ru-catalyzed hydration of alkynes as reported by GROTJAHN[129] was supposedly to avoid the deactivation of the catalytic turnover by shielding the nitrogen atom, whose presence is necessary for the activation of the nucleophile. Thus, it was hypothesized that analogous aza-arylphosphanes **130**, with different bulky substituents at C-6, could also be employed as ligands for the same reaction. As a consequence, a more flexible route toward the synthesis of new 2-substituted pyridylphosphanes **130** was required.

[142] The optimization of this synthetic route for the preparation of **108** was done in collaboration with THOMAS KRIBBER, Staatsprüfung für das Lehramt, RWTH Aachen, **2005**.

Despite the improvement in the overall yield of 2-*tert*-butyl-6-(diphenylphosphino)pyridine, the new synthetic method presented above was still suffering from two major drawbacks. First, it still comprised of five steps and while each step was efficient for the preparation of *tert*-butyl-compound **108**, the cyclohexyl-analogue **129** was already obtained in a much lower overall yield. As a consequence, the general applicability of this route towards a broad range of different pyridylphosphanes was in doubt at this stage. A second, more important drawback was related to the strategy itself. In the route presented above, the whole sequence had to be repeated for every new compound prepared, since the substituent at the C-2 of the final product was introduced already in the very first step of the sequence. Therefore, a more convergent and modular synthesis was highly desirable.

As a consequence, it was necessary to look for a new synthetic strategy able to provide easier access to a large array of 2-substituted pyridylphosphanes **130**. Moreover, the possibility to use heterocycles other than pyridine to build a larger library of analogues was envisaged.



Scheme 37. Retrosynthetic analysis of aza-arylphosphanes **130**.

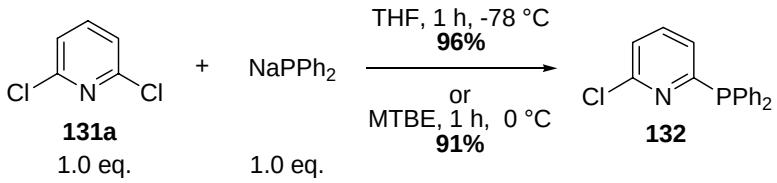
Analysis of the possible disconnections of the target structure **130** revealed that cleavage of the C-C (or C-O for R = alkoxy) and C-P bonds at the C-2 and C-6 positions of the aza-aryl ring would allow for a rapid and modular introduction of different groups at these positions. The corresponding two step sequence would involve a cross-coupling reaction in order to introduce different alkyl- or aryl-groups (**B** in Scheme 37), followed by a nucleophilic phosphination reaction (**A** in Scheme 37) to install the phopsphane moiety. This approach presented the advantage of starting the synthesis from commercially available 2-dihalo-aza-

aryl compounds **131**. Moreover, this strategy would be also beneficial with regard to a parallel ligand screening. Since the order of steps **A** and **B** in the reaction sequence could in principle be inverted, the synthesis of a large number of analogues having different substituents in one position, e.g. in 2-position, while keeping the substituent at C-6 fixed (or *vice versa*) might be easily achieved from a common precursor **132** (or **133**) without the need of repeating the whole synthetic sequence for every new compound.

4.2.1 Synthesis of 2-Substituted Aza-Arylphosphanes: A→B-Sequence

4.2.1.1 Phosphination of 2,6-Dichloropyridine

Concerning the phosphination of halogenated pyridines, a literature precedent was found in which lithium-diphenylphosphide, formed by deprotonation of diphenylphosphine with *n*-butyllithium in THF, was added to 2,6-dichloropyridine at −78 °C to selectively afford the 2-chloro-6-(diphenylphosphino)pyridine (**132**) in 63% yield.[143]



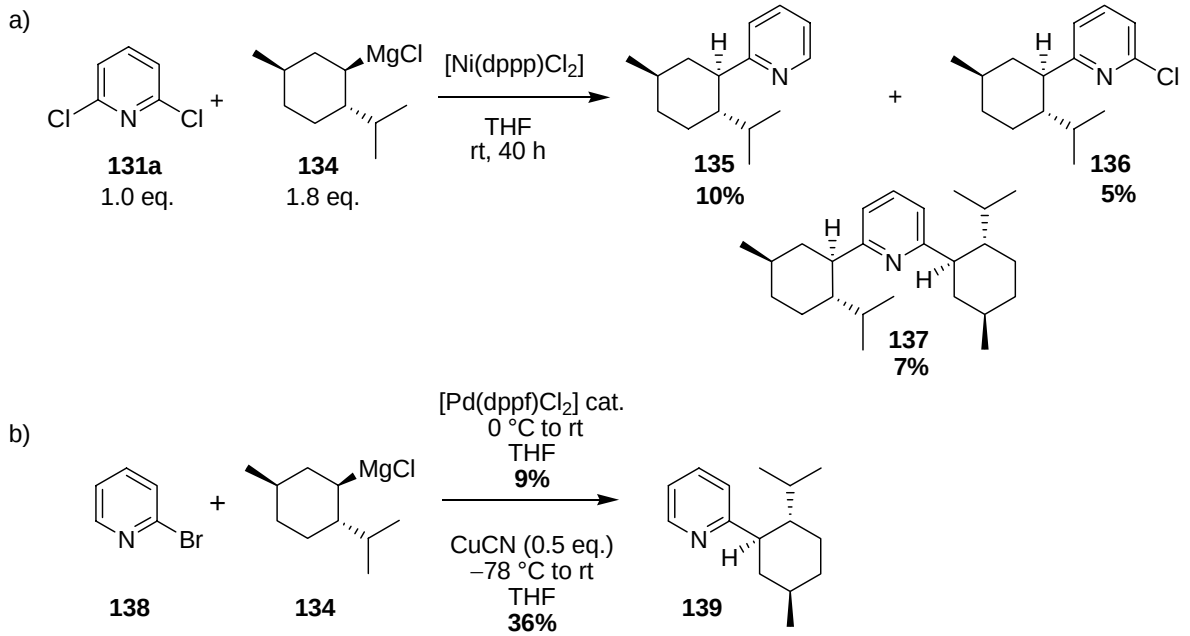
Scheme 38. Nucleophilic mono-phosphination of 2,6-dichloropyridine.

In our hands, a similar nucleophilic phosphination was successfully effected by addition of one equivalent of sodium diphenylphosphide, as a solution in THF (1.0 M, solution prepared from Na, NH_3 and PPh_3[144]), to 2,6-dichloropyridine in either THF at −78 °C or MTBE at 0 °C to give 2-chloro-6-(diphenylphosphino)pyridine (**132**) in 96% or 91% yield, respectively (Scheme 38).

[143] S.-M. Kuang, Z.-Z. Zhang, Q.-G. Wang, T. C. W. Mak *J. Chem. Soc., Dalton Trans*., **1998**, 2927.
[144] W. Hewertson, H. R. Watson *J. Chem. Soc*. **1962**, 1490.

4.2.1.2 Cross-Coupling Reactions of 2-Chloro-6-(diphenylphosphino)pyridine with Alkyl Sources

As the second step of the sequence, alkylation of heteroaryl halides with different alkyl-GRIGNARD-reagents was investigated.



Scheme 39. Alkylation of heteroaryl halide by BROWN and by BRUNNER.

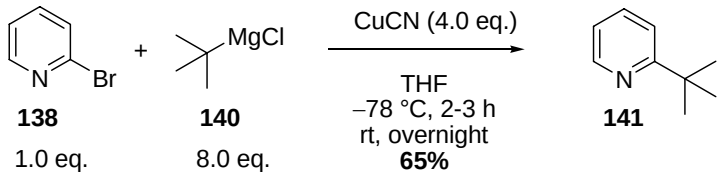
Although, Ni- or Pd-catalyzed KUMADA-type reactions remain the methods of choice for cross-coupling reactions involving GRIGNARD-reagents and aryl halides, neither high selectivity nor satisfactory yields have been reported so far in the literature with bulky secondary or with tertiary alkyl-GRIGNARD-reagents.

For example, BROWN obtained a mixture of products in the reaction of 2,6-dichloropyridine (**131a**) with an excess of (1*R*)-(−)-menthyl-magnesium chloride (**134**) in the presence of a Ni-catalyst (Scheme 39a). Besides the low overall yield, side products from reductive dehalogenation (**135**) and bis-coupling (**137**) were observed.[145a]

Moreover, also the Pd- or Cu-catalysed coupling of 2-bromo-pyridine (**138**) with the GRIGNARD-reagent **134** gave only unsatisfying yields of the desired product **139** (Scheme 39b).

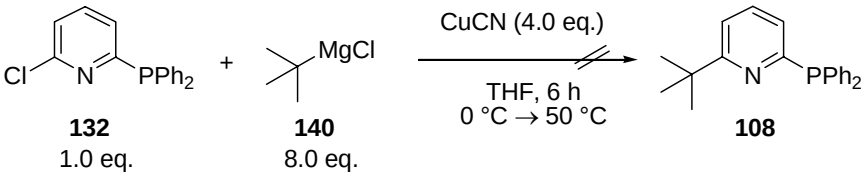
[145] a) X. L. Cui, R. S. Brown, *J. Org. Chem*. **2000**, *65*, 5653. b) H. Brunner, R. Stôriko, B. Nuber *Tetrahedron: Asymmetry* **1998**, *9*, 407.

A brief survey of the literature revealed a possible solution to the problem. BELL reported the alkylation of 2-bromopyridine with a large excess of *tert*-butyl-magnesium chloride **140** (8.0 eq.), in the presence of an excess of copper cyanide (4.0 eq.), resulting in the formation of 2-*tert*-butylpyridine (**141**) in 65% yield as shown in Scheme 40.[146]



Scheme 40: Alkylation of heteroaryl halide by BELL.

Hence, a copper-mediated alkylation of compound **132** was attempted by addition of 8.0 eq. of *t*BuMgCl at 0 °C in THF in the presence of 4.0 eq. of CuCN. The reaction mixture was then stirred at 50 °C for six hours (Scheme 41).



Scheme 41. Attempted cross-coupling reaction to access **108**.

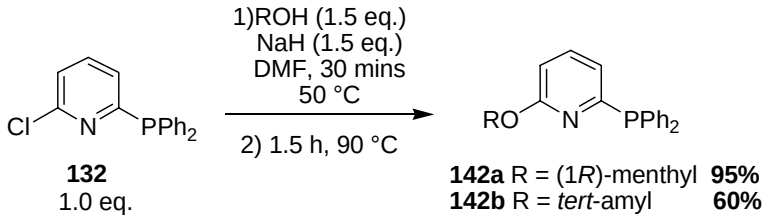
Unfortunately, the cross-coupling reaction failed to afford the desired product **108**, although the starting material **132** was completely consumed according to GC-MS analysis. A possible explanation involves the coordination of the copper-reagent in excess with the phosphorus moiety of the starting material, thus renders the cross-coupling reaction impossible. To circumvent this problem, it was decided to introduce the alkyl group on the heteroaryl ring before the phosphine moiety as it will be described in Section 4.2.2.

4.2.1.3. Nucleophilic Substitution with Alcoholates

With the 2-chloro-6-(diphenylphosphino)pyridine (**116**) in hand (Section 4.3.1.1), the synthesis of alkyloxy-subtituted pyridylphosphanes **142** by aromatic nucleophilic substitution reaction with various alcohols was attempted. 6-Alkoxy-substituted pyridylposphanes are of great interest as ligands, since they possess a more electron rich pyridine ring in comparison

[146] T. W. Bell, L.-Y. Hu, S. V. Patel *J. Org. Chem*. **1987**, *52*, 3847.

with their analogues bearing simple alkyl groups. As a consequence, they have more basic nitrogen and phosphorous atoms, which can affect their ability to activate the nucleophile and/or to coordinate the transition-metal (see Section 5) when employed in the Ru-catalyzed hydration reaction.



Scheme 42. Synthesis of 6-alkyloxy-substituted pyridylphosphanes **142a/b**.

First, sodium salts of (1*R*)-(−)-menthol and *tert*-amyl alcohol were formed by deprotonation of the alcohols with sodium hydride at 50 °C in DMF. Addition of **132** to a suspension of the salts in DMF, followed by stirring for 1.5 h at 90 °C, produced the desired (1*R*)-2-(diphenylphosphino)-6-menthyloxypyridine **142a** and 2-(diphenylphosphino)-6-(*tert*-amyloxy)pyridine **142b** in 95% and 60% yield, respectively (Scheme 42).

4.2.2 Synthesis of 6-Substituted Aza-Arylphosphanes: B→A-Sequence

4.2.2.1 Cross-Coupling of 2,6-Dichloro-Aza-Aryls with Alkyl Grignard-Reagents

As mentioned in section *4.2.1.2*, it was considered possible to generate the desired pyridylphosphanes **130** also by employing a synthetic route featuring the phosphination and cross-coupling reaction steps in inverse order.

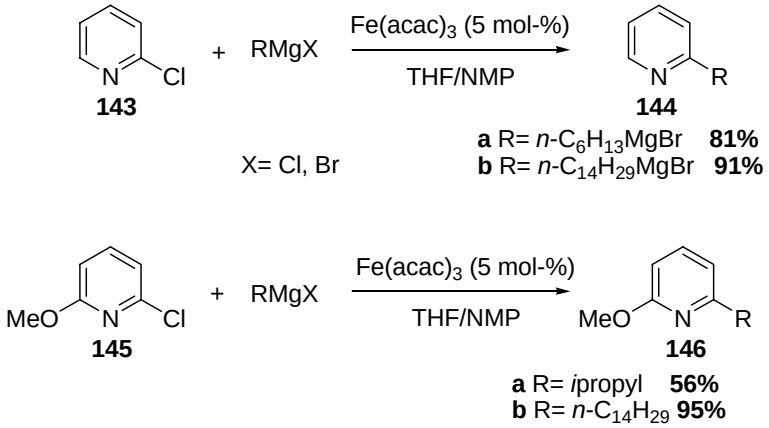
Surprisingly, a survey of the literature revealed that none of the so far reported catalytic cross-coupling reactions with aza-arene halides was ever conducted with tertiary alkyl GRIGNARD-reagents.[147,148,149] Recently, FÜRSTNER has reported a very efficient iron-catalyzed cross-

[147] a) E. D. Thorsett, F. R. Stermitz *J. Heterocycl. Chem*. **1973**, *10*, 243. b) L. N. Prindgen *J. Heterocycl. Chem.* **1975**, *12*, 443. c) F. Babudri, S. Florio, L. Ronzini, M. Aresta *Tetrahedron* **1983**, *39*, 1515. d) H. Andersson, F. Almqvist, R. Olsson *Org. Lett*. **2007**, *9*, 1335.

[148] a) M. R. Netherton, G. C. Fu *Adv. Synth. Catal*. **2004**, *36*,1525. b) A. C. Frisch, M. Beller *Angew. Chem.* **2005**, *117*, 680; *Angew. Chem. Int. Ed*. **2005**, *44*, 674. c) For a recent review showing the importance of alkyl-aryl cross-coupling chemistry, see: S. R. Chemler, D. Trauner, S. J. Danishefsky *Angew. Chem.* **2001**, *113*, 4676;

coupling reaction of primary alkyl GRIGNARD-reagents with various halogenated-heterocycles, such as 2-chloropyridine (**143**) which afforded within 10 min **144a** and **144b** in 81% and 91% yield, respectively (Scheme 43).[150]

On the other hand, this catalytic alkylation was less efficient with a secondary alkyl GRIGNARD-reagent, as can be seen by a significantly decreased yield in the coupling of 2-chloro-6-methoxypyridine (**145**) with *iso*-propylmagnesium bromide (compared to the 95% yield with *n*-tetradecylmagnesium bromide).



Scheme 43. Cross-coupling reactions of alkyl GRIGNARD-reagents with heteroaryl chlorides by FÜRSTNER.

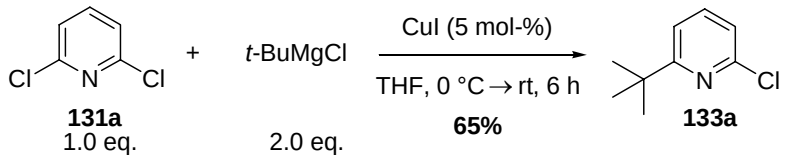
In light of these results, Fe-catalyzed addition of *t*BuMgCl to 2,6-dichloropyridine was also attempted in this work following the procedure developed by FÜRSTNER. Unfortunately, the starting material **115a** was recovered unchanged, even after prolonged reaction time. This result was thought to be due to β-elimination of the GRIGNARD-reagent coordinating the Fe-catalyst. Since this attempt to synthesize 2-*tert*-butyl-6-chloropyridine using the Fe-mediated cross-coupling methodology failed to afford the desired product, attention was focused on an alternative Cu-mediated process (Scheme 44).

Angew. Chem. Int. Ed. **2001**, *40*, 4544. d) K. Tamao in *Comprehensive Organic Synthesis*; Eds.: B. M. Trost, I. Fleming; Pergamon: Oxford, U.K., 1991; Vol. 3, p 435.

[149] Selected references for the KUMADA cross-coupling, see: a) M. Nakamura, K. Matsuo, S. Ito, E. Nakamura *J. Am. Chem. Soc.* **2004**, *126*, 3686. b) A. C. Frisch, N. Shaikh, A. Zaph, M. Beller *Angew. Chem.* **2002**, *114*, 4218; *Angew. Chem. Int. Ed*. **2002**, *41*, 4056. c) J. Terao, H. Watanabe, A. Ikumi, H. Kuniyasu, N. Kambe *J. Am. Chem. Soc.* **2002**, *124*, 4222. For the SUZUKI cross-coupling, see: d) J. Zhou, C. G. Fu *J. Am. Chem. Soc.* **2004**, *126*, 1340. e) J. S. Dickschat, H. Reichenbach, I. Wagner-Doebler, S. Schulz *Eur. J. Org. Chem*. **2005**, *19*, 4141. f) T. Ishiyama, S. Abe, N. Miyaura, A. Suzuki *Chem. Lett*. **1992**, 691. For the NEGISHI cross-coupling, see: g) H. Takahashi, S. Inagaki, Y. Nishihara, T. Shibata, K. Takagi *Org. Lett*. **2006**, 8, 3037. h) R. Giovannini, T. Stüdemann, G. Dussin, P. Knochel *Angew. Chem.* **1998**, *110*, 2512; *Angew. Chem., Int. Ed*. **1998**, 37, 2387. i) P. Knochel *Angew. Chem.* **1995**, *107*, 134; *Angew. Chem., Int. Ed*. **1995**, *34*, 2723.

[150] a) R. Martin, A. Fürstner *Angew. Chem.* **2004**, *116*, 4045; *Angew. Chem. Int. Ed*. **2004**, *43*, 3955. b) A. Fürstner, A. Leitner *Angew. Chem.* **2002**, *114*, 632; *Angew. Chem. Int. Ed*. **2002**, *41*, 609. c) A. Fürstner, A. Leitner, M. Méndez, H. Krause *J. Am. Chem. Soc.* **2002**, *124*, 13856. d) J. Quintin, X. Franck, R. Hocquemiller, B. Figadère *Tetrahedron Lett*. **2002**, *43*, 3547.

Thus, an excess of *t*BuMgCl was added to a mixture of 2,6-dichloropyridine (**131a**) and CuI (5 mol-%) in THF at 0 °C. After stirring at room temperature for six hours formation of the 2-*tert*-butyl-6-chloropyridine (**133a**) was observed and interestingly, no traces of disubstituted product could be detected with GC-MS analysis.



Scheme 44. Cu-catalyzed selective mono-alkylation of 2,6-dichloropyridine **133a**.

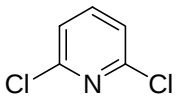
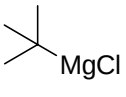
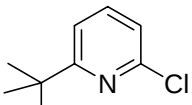
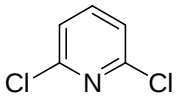
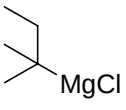
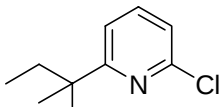
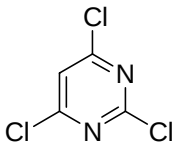
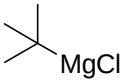
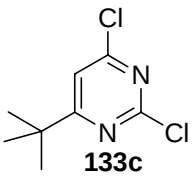
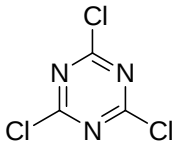
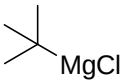
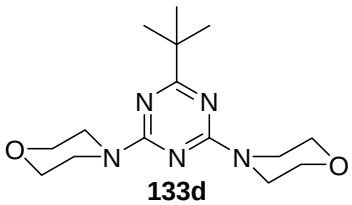
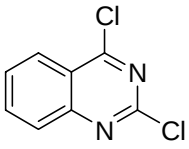
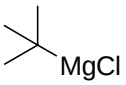
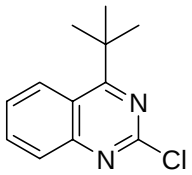
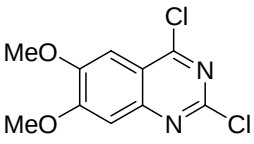
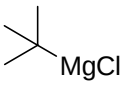
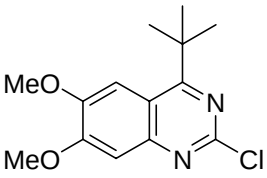
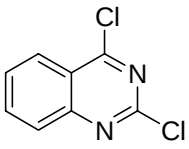
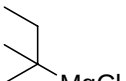
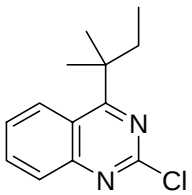
The outcome of the reaction in the presence of copper-iodide was surprising. The yield of product **133a** was highly satisfactory in view of the previous syntheses (65%), and the high level of selectivity was unexpected. The reaction carried out with *tert*-amylmagnesium chloride gave very similar results in terms of selectivity (Table 4, entry 2). Though, a longer reaction time was necessary. To ascertain the need for the copper catalyst in the reaction, the two last experiments were run again in the absence of CuI. Under these conditions, no traces of the product could be detected and the starting material was recovered unchanged.

This transformation represents the first example of a selective catalytic cross-coupling reaction of a halogenated aza-heterocycle with a tertiary alkyl GRIGNARD-reagent, and allows the preparation of 6-alkylated 2-chloropyridines by using readily available and inexpensive starting materials.[151]

Having identified a reliable catalytic reaction for the coupling of tertiary alkyl GRIGNARD-reagent with 2,6-dichloropyridine, further variations in both the architecture of the heterocycle and the GRIGNARD-reagent were examined in order to test the scope of the reaction. As can be seen from the results compiled in Table 4, the pyridine-core could be replaced with other di- or tri-chlorinated aza-aromatic rings, and such as pyrimidine **131b**, triazine **131c**, and quinazoline **135d**, **131e** were substrates for the Cu-catalyzed cross-coupling reaction.

[151] Current price for 100 g of 2,6-dichloropyridine (97%) taken from Alfa Aesar/Lancaster/Avocado 2006-2007 catalogue (Germany) is 20.20 €.

Table 4. Selective Cu-catalyzed mono-alkylation of di- or tri-halogenated aza-arenes.[a]

entry	aza-aryl halide	R-MgCl (eq.)	product	time	yield (%)
1	 **131a**	 (2.0)	 **133a**	6 h	65
2	 **131a**	 (2.0)	 **133b**	48 h	74
3	 **131b**	 (1.0)	 **133c**	1.5 h	98
4	 **131c**	 (1.7)	 **133d**	15 min.	43[b]
5	 **131d**	 (1.5)	 **133e**	10 min.	78
6	 **131e**	 (2.5)	 **133f**	15 min.	63
7	 **131d**	 (1.5)	 **133g**	10 min.	68

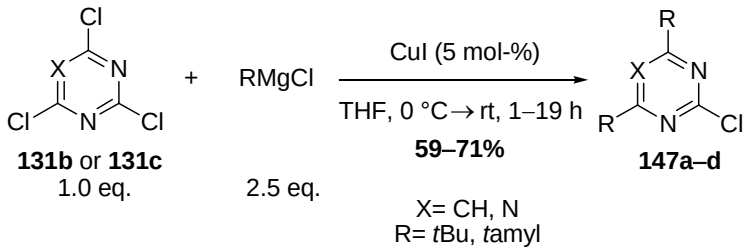
a) Reaction conditions: aza-aryl halide (1.0 mmol), CuI (5 mol-%), R-MgCl (1.0-2.5 mmol), THF (1 mL), 0 °C to rt. b) Due to the instability of the intermediate, the latter was converted to **133d** by addition of 2.0 eq. morpholine (for details, see experimental section **8**); isolated yield over two steps.

In all cases, the monoalkylation products were formed in good to excellent yields (63-98%).

Selective mono-alkylation in the 4-position of 2,4,6-trichloropyrimidine (**131b**) was achieved by cross-coupling reaction with 1.0 equivalent of Grignard-reagent (entry 3). 2,4,6-Trichlorotriazine (**131c**) could be selectively mono-alkylated in the presence of 1.7 equivalents of GRIGNARD-reagent. This mono-alkylated product proved to be unstable to purification via chromatography on silica. Therefore it has been directly converted into the bis-morpholino derivative **133d** by double substitution of the remaining chlorides with morpholine (entry 4).[152] 2,4-Dichloroquinazoline derivatives reacted selectively in the 4-position. These substrates showed much higher reactivity and full conversions were observed within 30 minutes (entries 5,6,7). For the reaction of the more electron rich 2,4-dichloroquinazoline **131e**, a larger excess of *tert*-butylmagnesium chloride had to be used to get a acceptable yield (entry 6). Still, in no case was over-alkylation detected.
All the reactions were also done in parallel without addition of the copper-catalyst, and all resulted in intractable mixtures of decomposition product, and mono- and disubstituted aza-arenes.

In the next set of experiments, it was investigated if the selectivity could be changed towards the double alkylation using 2,4,6-trichloro-pyrimidine (**131b**) and 2,4,6-trichloro-triazine (**131c**) as substrates. The resulting products **147** would still bear one chlorine atom in order to be phosphinated in a consecutive step (Scheme 45).

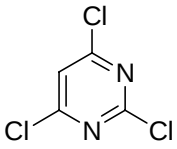
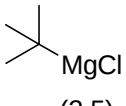
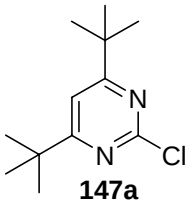
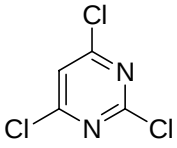
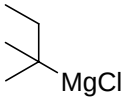
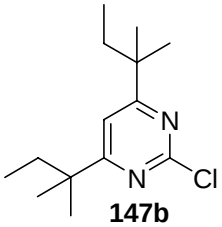
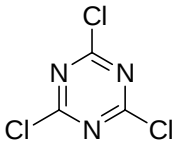
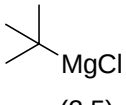
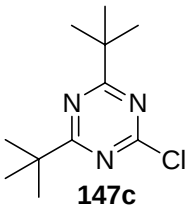
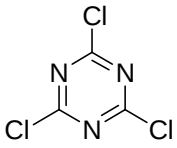
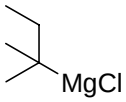
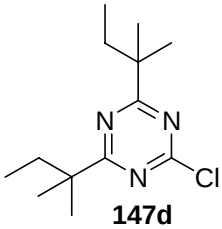
The results of these investigations are reported in Table 5.



Scheme 45. Selective Cu-catalyzed di-alkylation of 2,4,6-trichloro-pyrimidine **131b** and triazine **131c**.

[152] R. Menicagli, S. Samaritani, V. Zucchelli *Tetrahedron* **2000**, *56*, 9705.

Table 5. Selective Cu-catalyzed di-alkylation of poly-halogenated aza-arenes.[a]

entry	aza-aryl halide	R-MgCl (eq.)	product	time (h)	yield (%)
1	 **131b**	 (2.5)	 **147a**	3	71
2	 **131b**	 (2.5)	 **147b**	19	60
3	 **131c**	 (2.5)	 **147c**	1	59
4	 **131c**	 (2.5)	 **147d**	12	68

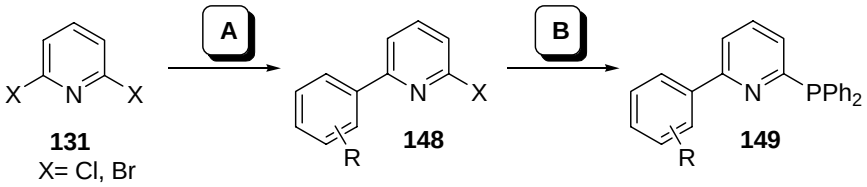
a) Reaction conditions: aza-aryl halide (1.0 mmol), CuI (5 mol-%), R-MgCl (2.3-2.5 mmol), THF (1 mL), 0 °C to rt.

The selective dialkylation of the trichloro-pyrimidine and triazine proceeded smoothly in the presence of 2.5 equivalents of GRIGNARD-reagents. Thus, 2,4,6-trichloropyrimidine (**131b**) could be selectively di-alkylated in positions 4 and 6 (entries 1-2). Likewise selective dialkylation in the positions 2 and 4 of 2,4,6-trichlorotriazine (**131c**) was achieved by cross-coupling reaction (entries 3-4). As already seen in the mono-alkylation reactions, the coupling with the *tert*-amyl-GRIGNARD-reagent required generally significantly longer reaction times to go to completion (entries 2,4).

The above examples illustrate the exceptional efficiency of this new methodology which gives practical and selective access to functionalized alkyl-substituted aza-arenes.

4.2.2.2 Cross-Coupling of 2,6-Dichloro-Aza-Aryls with Aryl Grignards-Reagents

One of the objectives of the present work was to extend the family of pyridylphosphanes to be used as ligands in the Ru-catalyzed hydration of alkynes by varying the substituent at the C-2 position. In this section attention will be focused on the preparation of pyridylphosphanes bearing a 2-aryl substituent **149**.



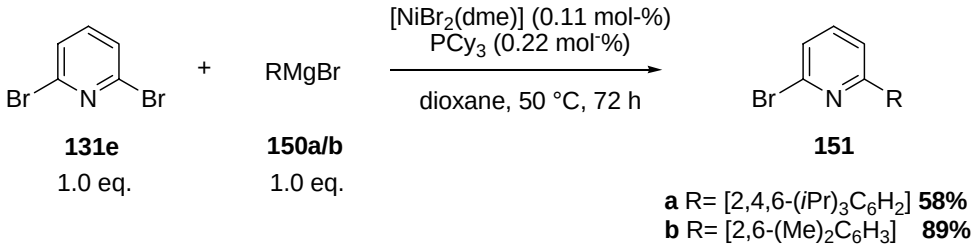
Scheme 46. Two step synthesis of 6-aryl-2-pyridylphosphanes **149**.

In analogy to the synthetic strategy towards 2-alkyl-aza-aryl phosphanes described above (paragraph 4.2.2.1 Scheme 44), it was envisaged that access to 2-aryl-substituted pyridylphosphanes **149** could again be achieved through a two-step sequence starting from a 2,6-dihalogenated pyridine **131** involving a mono-selective cross-coupling reaction with a suitable aryl-source organometallic reagent (**A** Scheme 46) and a nucleophilic phosphination (**B** Scheme 46).

Among the protocols available for the selective mono-arylation of poly-halogenated heterocycles,[153,154,155] KEMPE developed a Ni-catalyzed cross-coupling reaction, in which aryl GRIGNARD-reagents were added to 2,6-dibromopyridine to give mono-acylated bromopyridines using PCy_3 as a ligand.[156] Coupling of 2,4,6-(triisopropylphenyl)MgBr (**150a**) or 2,6-(dimethylphenyl)MgBr (**150b**) with 2,6-dibromopyridine (**131e**) in the presence of 0.11 mol-% of the *in situ* generated Ni-phosphine catalyst in a nonpolar solvent led to formation of

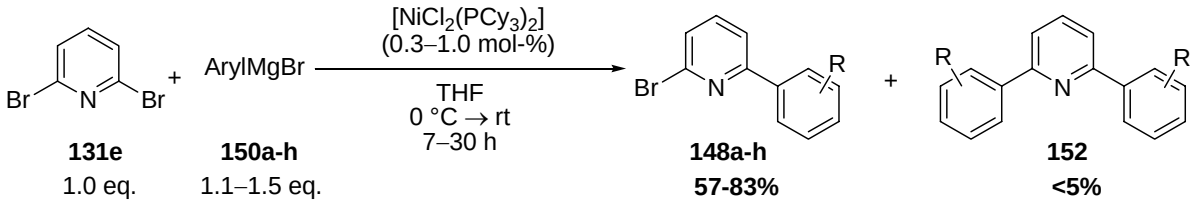
[153] S. Schröter, C. Stock, T. Bach *Tetrahedron* **2005**, *61*, 2245.
[154] Selected references: a) Y. Uozumi, M. Kikuchi *Synlett* **2005**, 1775. b) R.-Z. Jin, Z. Bian, C.-Q. Kang, H.-Q. Guo, L.-X. Gao *Synth. Commun*. **2005**, *35*, 1897. c) S. Orlandi, R. Annunziata, M. Benaglia, F. Cozzi, L. Manzoni *Tetrahedron* **2005**, *61*, 10048. d) A. Petitjean, R. G. Khony, N. Kyritsakas, J. M. Lehn *J. Am. Chem. Soc*. **2004**, *126*, 6637. e) A. Bouillon, J.-C. Lancelot, J. Sopkova-de Oliveira Santos, V. Collot, P. Bovy, S. Rault *Tetrahedron* **2003**, *59*, 10043. f) F. Berthiol, I. Kondolff, H. Doucet, M. Santelli *J. Organomet. Chem*. **2004**, *689*, 2786. g) T. Bunlaksananusorn, K. Polborn, P. Knochel *Angew. Chem.* **2003**, *115*, 4071; *Angew. Chem. Int. Ed*. **2003**, 42, 3941. h) A. Puglisi, M. Benaglia, G. Roncan *Eur. J. Org. Chem*. **2003**, *8*, 1552. i) J. C. Loren, J. S. Siegel *Angew. Chem.* **2001**, *113*, 776; *Angew. Chem. Int. Ed*. **2001**, 40, 754.
[155] a) V. Bonnet, F. Mongin, F. Trécourt, G. Quéguiner, P. Knochel *Tetrahedron* **2002**, *58*, 4429. b) C. Wolf, R. Lerebours *J. Org. Chem.* **2003**, *68*, 7077. c) V. P. W. Böhm, T. Weskamp, C. K. W. Gstöttmayr, W. A. Herrmann *Angew. Chem.* **2000**, *112*, 3500; *Angew. Chem. Int. Ed*. **2000**, *39*, 1602. d) D. E. Bergstrom, P. A. Reddy *Tetrahedron Lett*. **1982**, *23*, 4191.
[156] N. M. Scott, T. Schareina, O. Tok, R. Kempe *Eur. J. Inorg. Chem*. **2004**, 3297.

2-bromo-6-(2,4,6-triisopropylphenyl)pyridine (**151a**) or 2-bromo-6-(2,6-dimethylphenyl)pyridine (**151b**) in 58% and 89% yields, respectively (Scheme 47).



Scheme 47. KUMADA-coupling employed by KEMPE for the preparation of the 2-bromo-6-aryl-pyridine **151a/b**.

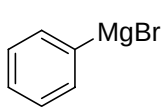
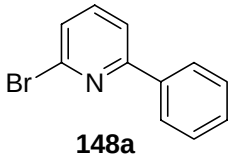
By using similar conditions, a range of new 2-bromo-6-arylpyridines **148a-h** could be generate starting from a variety of bulky aryl GRIGNARD-reagents (Scheme 48). The cross-coupling reactions were carried out in THF at room temperature instead of dioxane at 70 °C, using the complex $[NiCl_2(PCy_3)_2]$ as a catalyst, and an excess of GRIGNARD-reagent (1.1 to 1.5 eq. depending on the steric size of the substituents).

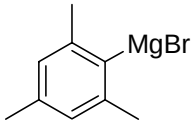
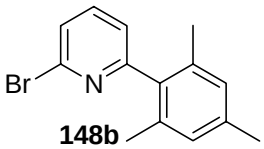
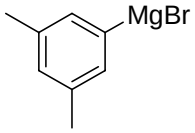
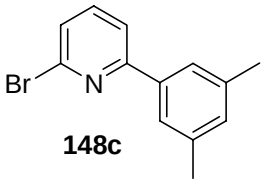
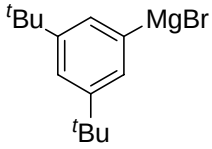
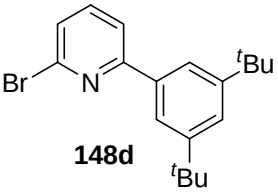
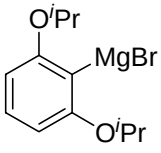
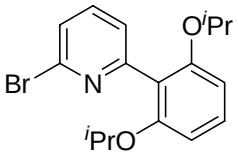
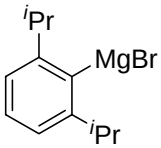
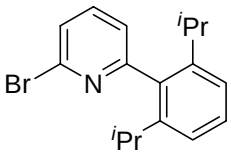
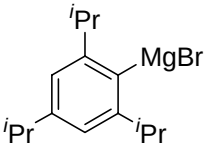
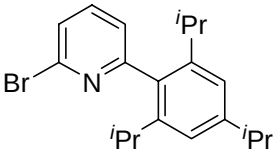
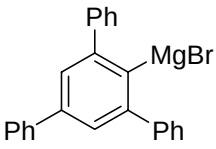
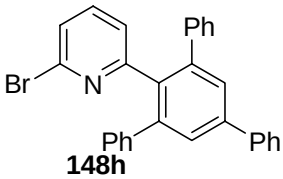


Scheme 48. Synthesis of 2-bromo-6-arylpyridine **Xa-h**.

Under these conditions, mono-arylated bromopyridines **148** were formed with very good selectivity (<5% of the di-substitution product **152** was usually observed). The results obtained in this Ni-catalyzed cross coupling reaction are summarized in Table 6.

Table 6. Mono-selective Ni-catalyzed cross-coupling reaction of arylmagnesium bromides **150** and 2,6-dibromopyridine **131e**.[a]

entry	Ar-MgBr (eq.)	product	[Ni] cat (mol-%)	time (h)	yield (%)
1	 **150a** (1.1)	 **148a**	0.3	3	-[b]

entry	Ar-MgBr (eq.)	product	[Ni] cat (mol-%)	time (h)	yield (%)
2	 **150b** (1.1)	 **148b**	0.3	7	70
3	 **150c** (1.1)	 **148c**	0.3	12	-[c]
4	 **150d** (1.1)	 **148d**	0.3	16	61
5	 **150e** (1.2)	 **148e**	0.6	15	83
6	 **150f** (1.1)	 **148f**	0.3	15	67
7	 **150g** (1.1)	 **148g**	0.3	30	83
8	 **150h** (1.5)	 **148h**	1.0	192[d]	57

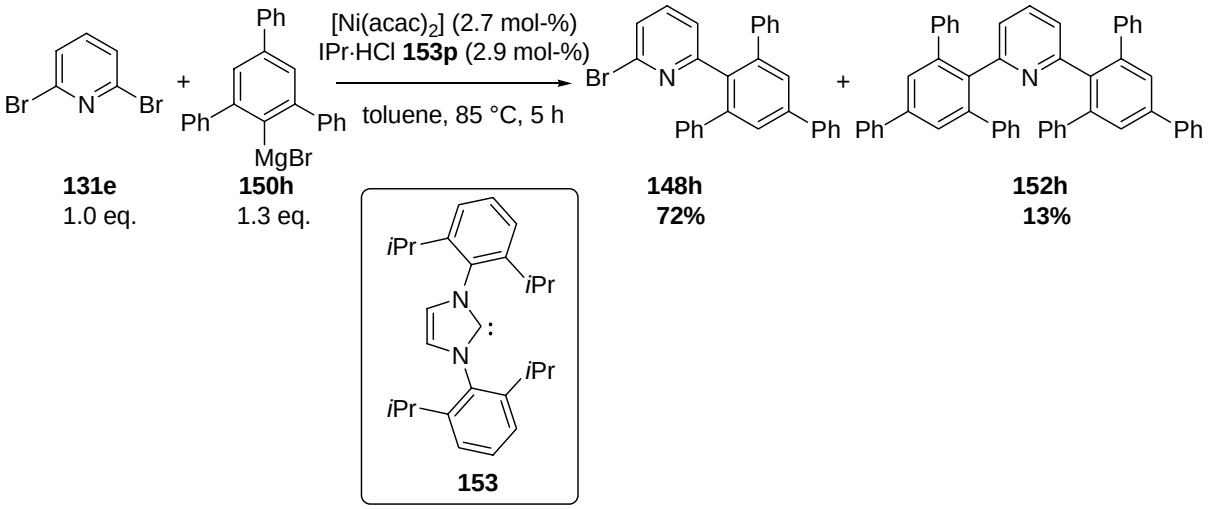
a) Reaction conditions: 2,6-dibromopyridine **131e** (1.0 mmol), [$NiCl_2(PCy_3)_2$] (0.3 mol-%), R-MgBr **150** (1.1-1.5 mmol), THF (1 mL), rt. b) Product **148a** was not isolated due to the formation of an inseparable mixture; NMR ratios of the crude mixture: **148a**/**152a** ≈1:2. c) Product **148c** was not isolated due to the formation of an inseparable mixture; NMR ratios of the crude mixture: **148c**/**152c** 45/55. d) Modification of the method by heating the reaction 4 days at 75 °C and additional 4 days at 85 °C.

Surprisingly, the outcome of the cross-coupling reaction depended on the steric size of the aryl group. The reaction with phenylmagnesium bromide (**150a**) was sluggish resulting in an intractable mixture of mono- and di-substituted products (entry 1). In the case of meta-substituted aryl GRIGNARD-reagents, the selectivity of the cross-coupling reaction was drastically affected by the steric size of the substituents. Indeed, the reaction with 3,5-dimethylphenylmagnesium bromide afforded an inseparable mixture of mono- and di-substituted products, whereas the bulkier 3,5-*tert*-butylphenylmagnesium bromide (**150d**) gave compound **148d** in 61% yield (entries 3-4). Ortho-substituted arylmagnesium bromides gave better selectivity and prevented the formation of disubstituted products. Here, mono-selective arylation of 2,6-dibromopyridine was observed even with a reagent having two relatively small methyl substituents (entry 2).

Thus, the following trend regarding the efficiency of this catalytic reaction could be extrapolated: the higher the steric hindrance of the GRIGNARD-reagent (in the order **150a,c** < **150b** < **150g**), the higher the yield of compounds **148** (less than 40% < 70% < 83%, respectively). Similarly, considering the electronic factors, the higher the substitution of GRIGNARD-reagent with electrodonating alkyl-group (in the order **150f** < **150g**), the higher the yield of compounds **148** (67% < 83%, entry 6 *vs*. entry 7). However, in the case of the cross-coupling with 2,6-diisopropylphenylmagnesium bromide **150e** the product **148e** was afforded in a very good yield of 83%, which can be explained by a possible coordination of the oxygen moiety with the Ni-catalyst (entry 5).

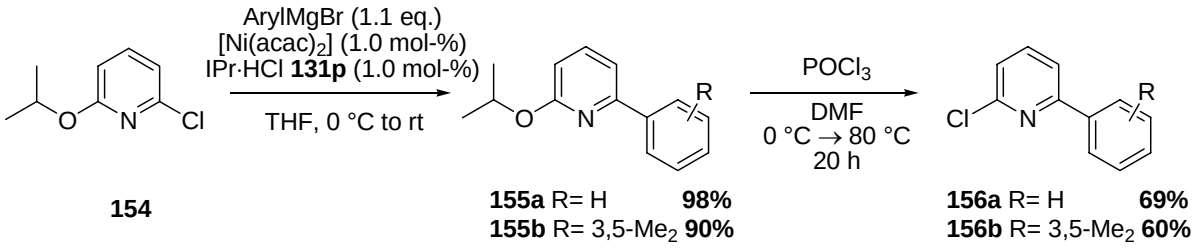
In addition, it was observed that the solubility of the products **148** in most common organic solvents dropped with the increased size of the C-2-aryl substituents. In the case of GRIGNARD-reagent **150h** (Entry 8) it was necessary to heat the reaction to 75 °C and 85 °C, respectively in order to get a faster conversion. But still, only 57% yield was obtained with this substrate which was attributed to the bulkyness of the GRIGNARD-reagent.

However, a novel procedure, reported by HERMANN et al.,[155c] was employed for the synthesis of compound **148h** on a multigram scale, which involved the use of the complex [$Ni(acac)_2$] (2.7 mol-%) in combination with a carbene ligand **153** (2.9 mol-%) which is generated *in situ* by deprotonation of the prercursor IPr·HCl **153p** by the GRIGNARD-reagent acting as a base, in toluene (Scheme 49). This led to a higher reaction rate and the desired mono-arylated product **148h** could be isolated within five hours at 85 °C and in 72% yield. Unfortunately the selectivity was lower in this reaction as the by-product from double arylation, bis-2,6-(2,4,6-triphenylphenyl)pyridine (**152h**)**,** was also formed and isolated in 13% yield.



Scheme 49. Gram scale synthesis of 2-bromo-6-(2,4,6-triphenylphenyl)pyridine **148h**.

A reconsideration of the synthetic approach towards less sterically hindered compounds **148a** and **148c** by Ni-catalyzed cross-coupling reaction led to the identification of 2-*iso*-propyloxy-6-chloropyridine (**154**), reported by BREIT and co-workers,[157] as another suitable precursor.



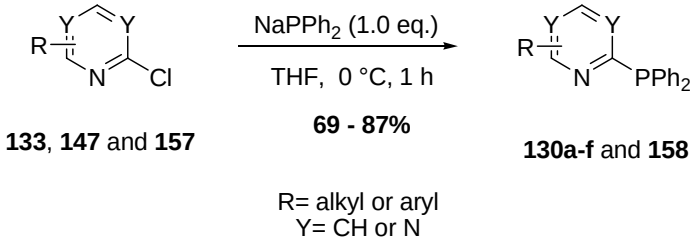
Scheme 50. Synthesis of 2-chloro-6-arylpryridine **156a/b**.

As shown in Scheme 50, the cross-coupling reaction using the complex [Ni(acac)$_2$] and the precursor **153p** of the carben ligand proceeded smoothly at room temperature to give the products **133a** and **133b** in 98% and 90% yield, respectively. Subsequent chlorination was effected using phosphorous oxychloride in DMF to afford the corresponding 2-chloro-6-phenylpyridine **156a** in 69% yield and 2-chloro-6-(3,5-dimethylphenyl)pyridine **156b** in 60% yield.

[157] B. Breit, W. Seiche *J. Am. Chem. Soc*. **2003**, *125*, 6608.

4.2.2.3 Phosphination of 2-Substituted 6-Chloro-Aza-Aryl Compounds

In order to access the desired 2-substituted aza-arylphosphanes **130**, the 6-halogenated aza-arenes prepared as described above were then subjected to nucleophilic phosphination by reaction of the remaining halogen with sodium diphenylphosphide.

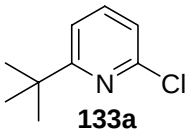
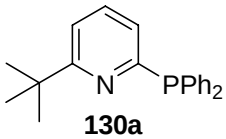
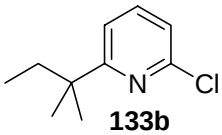
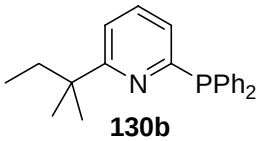
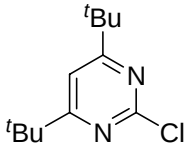
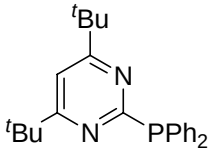
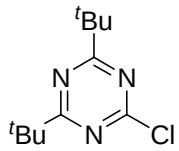
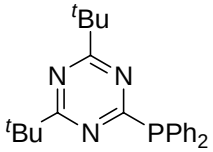
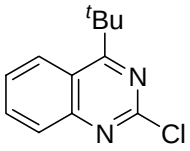
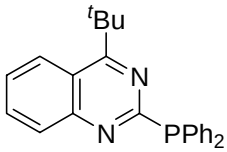
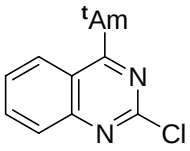
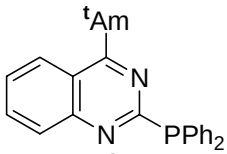


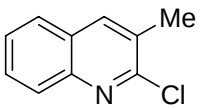
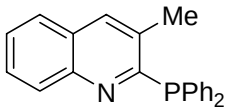
Scheme 51. Nucleophilic phosphination of the alkyl-substituted arene-chloride derivatives **133**, **147** and **157**.

The addition of one equivalent of sodium diphenylphosphide as a solution in THF to compounds **133**, **147** and **157** afforded the alkyl-substituted aza-arylphosphanes **130a-f** and **158** in 69-87% yields within one hour at 0 °C, as depicted in Scheme 51 and Table 7.
The phosphination of the 2-*tert*-butyl-6-chloropyridine (**133a)** gave the corresponding phosphane **130a** in 73% yield (entry 1). The present synthetic route to this compound, comprising a cross-coupling and a phosphination step, is superior to the previous WITTIG-olefination/cyclisation-route. The new synthetic sequence requires only two steps giving an overall yield of 48%, whereas the WITTIG-olefination/cyclisation-route needed five steps affording the product in an overall yield of 24%, and the BERKE's original synthesis required 6 steps with an overall yield of 3%.

In all cases, the nucleophilic phosphination proceeded smoothly and afforded the corresponding phosphanes in good yields (69-87%, entries 2-6). In addition, the reaction was performed with commercially available 2-chloro-3-methylquinoline (**157**) with the aim of preparing an additional candidate ligand with different structural properties (entry 7).

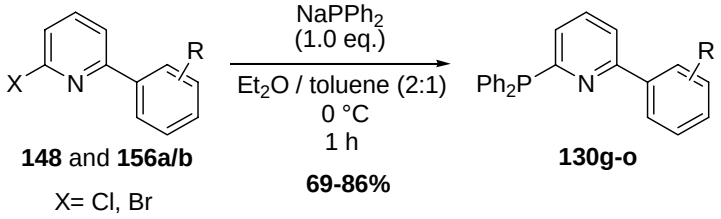
Table 7. Alkyl-substituted aza-arylphosphanes prepared by phosphination of the corresponding aza-arene chloride.[a]

entry	aza-aryl halide	aza-arylphosphanes	yield (%)
1	 **133a**	 **130a**	73
2	 **133b**	 **130b**	69
3	 **147a**	 **130c**	87
4	 **147c**	 **130d**	82
5	 **133e**	 **130e**	75
6	 **133g**	 **130f**	79

7	 **157**	 **158**	80

a) Reaction conditions: aza-arene chloride (1.0 mmol), $NaPPh_2$ (1.0 mmol, 1.0 M solution in THF), THF (1 mL), 0 °C, 1.0 h.

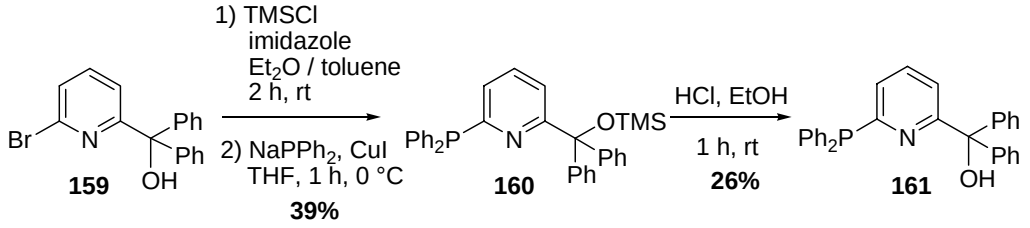
For the synthesis of 2-aryl-substituted aza-arylphosphanes **130g-o**, all reactions had to be performed in a solvent mixture of diethylether and toluene (2:1) in order to obtain an homogeneous reaction mixture (Scheme 52). The results obtained in the phosphination reaction are listed in Table 8. The nucleophilic phosphination reaction proceeded smoothly and gave the various potential ligands **130g-o** in good yields. These compounds could all be purified by either flash column chromatography on silica under argon or recrystallization.



Scheme 52. Phosphination of 6-aryl-substituted pyridines **148** and **156a/b**.

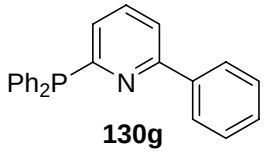
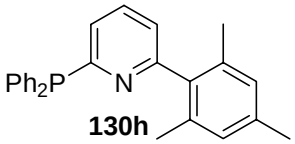
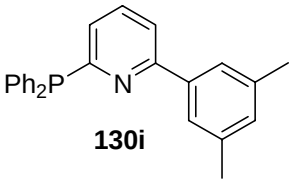
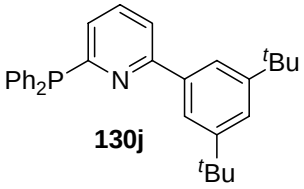
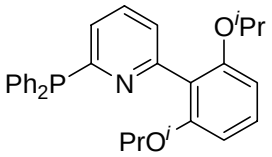
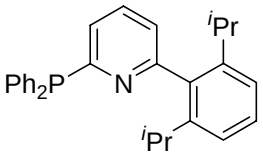
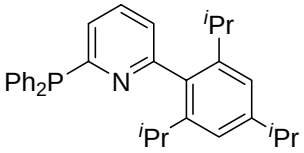
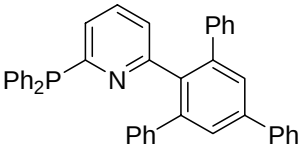
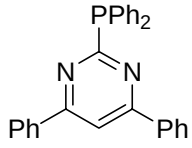
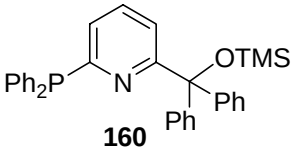
The phosphination was also performed with 2-chloro-4,6-diphenylpyrimidine and [6-(2-bromopyridyl)]diphenylmethanol (**159**), both prepared according to literature procedures.[158,159] As depicted in Scheme 53, the synthesis of (6-(diphenylphosphino)pyridin-2-yl)diphenylmethanol (**161**) required three steps, namely a TMS protection of the hydroxyl group, a copper-catalyzed nucleophilic phosphination and finally the removal of the silyl protecting group. In the case of the 2-bromo-6-[diphenyl(trimethylsilyloxy)methyl]pyridine, a catalytic amount of copper iodide was used in order to enhance the reaction rate.[160]At this stage, it was considered of interest to synthesize both the phosphanes **160** and **161**, with protected and unprotected hydroxyl group, to evaluate the possible hydrogen-bonding effect of the potential ligand **161** (see Section 5).

[158] J. Nasielski, A. Standeart, R. Nasielski-Hinkens *Synth. Commun.* **1991**, *21*, 901.
[159] M. A. Peterson, J. R. Mitchell *J. Org. Chem.* **1997**, *62*, 8237.
[160] C. Meyer, H. Grützmacher, H. Pritzkow *Angew. Chem.* **1997**, *109*, 2576; *Angew. Chem. Int. Ed*. **1997**, *36*, 2471.



Scheme 53. Synthesis of (6-(diphenylphosphino)pyridin-2-yl)diphenylmethanol **161**.

Table 8. Aza-arylphosphanes **130g-o** prepared in this study.[a]

entry	aza-arylphosphanes	yield (%)	entry	aza-arylphosphanes	yield (%)
1	 **130g**	86	2	 **130h**	79
3	 **130i**	76	4	 **130j**	69
5	 **130k**	74	6	 **130l**	71
7	 **130m**	75	8	 **130n**	78
9	 **130o**	69	10	 **160**	39[b]

a) Reaction conditions: aza-arene halide (1.0 mmol), $NaPPh_2$ (1.0 mmol, 1.0 M solution in THF), Et_2O/toluene (2:1 mL), 0 °C, 1 h. b) over 2 steps yield (sylilation/phosphination).

After purification, all compounds **130** could be handled in air, thus simplifying subsequent manipulations. However, storage under an inert atmosphere is still recommended since triarylphosphines are prone to oxidation.

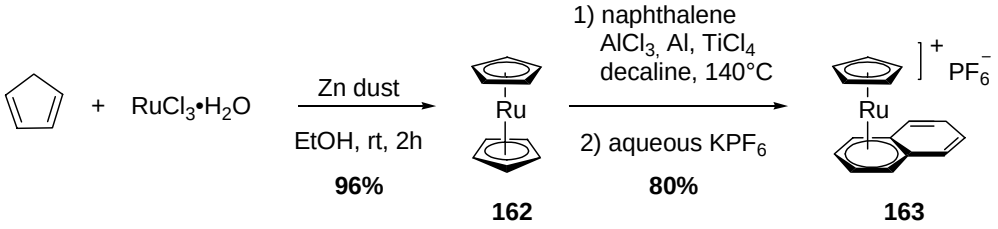
5. [CpRu(L)$_2$CH$_3$CN]PF$_6$ Complexes

5.1. Preparation of Complexes [CpRu(L)$_2$CH$_3$CN]PF$_6$

With a selection of aza-arylphosphanes **130** described above (see Section 4) in hand, the second part of the present work, aimed at finding more readily available and easily handled catalysts for the Ru-catalyzed hydration of terminal alkynes, was initiated.

Among the various ruthenium-based catalysts available for the hydration reaction of alkynes (see Section 1),[127-131] the CpRu$^+$-fragment bearing mono- or bidentate phosphine ligand has recently attracted much attention, as a catalyst of the *anti*-MARKOVNIKOV hydration of terminal alkynes with high selectivity. A common approach to the synthesis of new cyclopentadienyl-ruthenium complexes is based on the substitution of labile CH$_3$CN ligands in the complex [CpRu(CH$_3$CN)$_3$]PF$_6$.[161] However, this catalyst precursor has the drawbacks of being air-sensitive and expensive.[162]

A brief survey of the literature revealed a possible alternative to the use of the latter compound. As shown in Scheme 54, it was found that the complex [CpRu(η^6-naphthalene)]PF$_6$ (**163**) could be prepared in a single step from ruthenocene **162** following a procedure reported by KÜNDIG and co-workers.[161c]



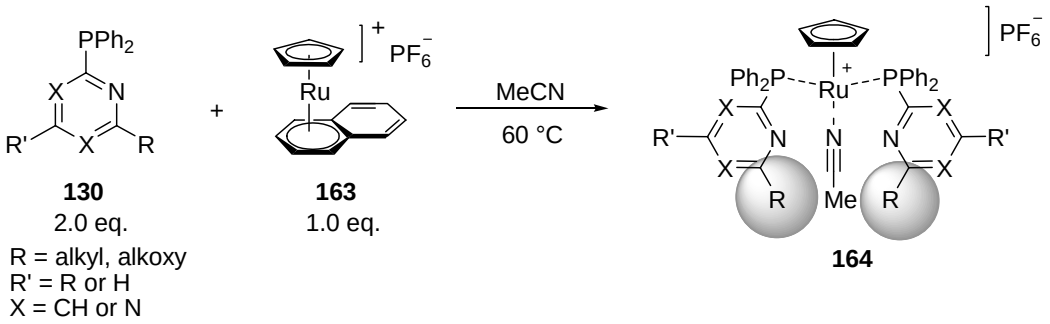
Scheme 54. Synthesis of the Ruthenium complex precursor **163**.

Complex **163** is air-stable and easy to handle and can be prepared in multi-gram amounts, which rendered its use as a source of the cationic CpRu$^+$ fragment very practical. Consequently, it was envisaged that the complex [CpRu(η^6-naphthalene)]PF$_6$ (**163**) could

[161]a) C. Slugovc, E. Rüba, R. Schmid, K. Kirchner, K. Mereiter *Monatsh. Chem*. **2000**, *131*, 1241. b) B. M. Trost, C. M. Older *Organometallics* **2002**, *12*, 2544. c) E. P. Kündig, F. R. Monnier *Adv. Synth. Catal.* **2004**, *346*, 901.

[162] Current price for 1 g of [CpRu(CH$_3$CN)$_3$]PF$_6$ taken from Strem 2006-2008 catalogue is 354 €.

serve as a starting material for the formation in solution of complexes of the type $[CpRu(L)_2(CH_3CN)]PF_6$ **164**, which could be obtained by the exchange of the 6-electron donor naphthalene by three 2-electron donors such as two monodentate aza-arylphosphane ligands **130** and one solvent molecule.



Scheme 55. Ligand exchange in acetonitrile.

Thus, compounds of the type **164** were easily generated by mixing precursor complex **163** (1.0 eq.) and phosphane ligands **130** (2.0 eq.) in acetonitrile at 60 °C (Scheme 55). The ligand exchange required from 0.5 to 6 hours, depending on the solubility of the ligands in acetonitrile.

First, the ligand exchange was performed in the presence of two equivalents of 2-*tert*-butyl-6-(diphenylphosphino)pyridine (**130a**), and the course of the reaction was monitored by means of ^{31}P-NMR spectroscopy (Figure 7).

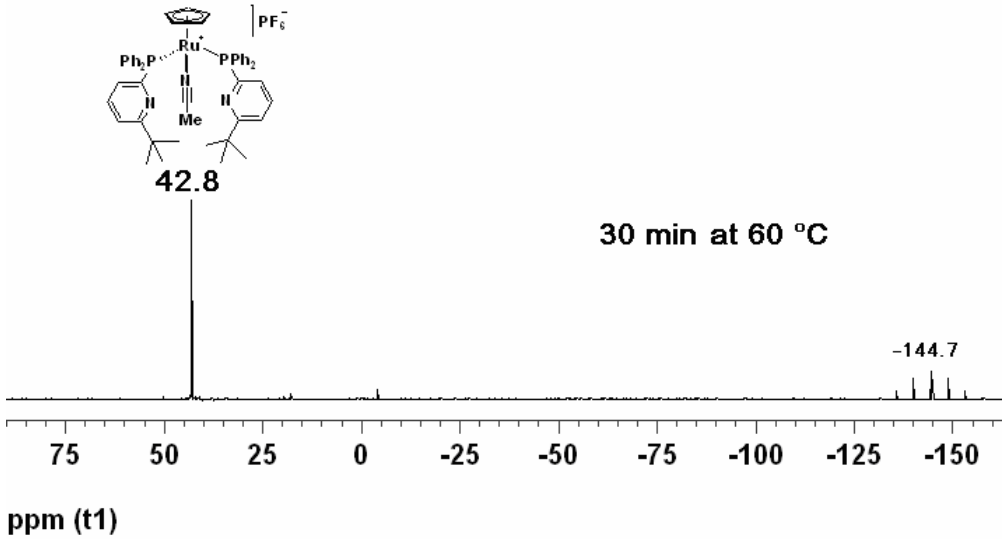


Figure 7. Ligand exchange experiment with **163** + 2.05 eq. **130a**: ^{31}P-NMR (CD_3CN) spectrum of the reaction solution.

After 30 minutes, the signal corresponding to the free ligand **130a** (δ = −4.4 ppm) had almost completely disappeared. In contrast, a sharp signal at 42.8 ppm appeared which was assigned to the expected complex **164a,** along with the signal of the PF_6-counteranion (δ = −144.7 ppm).

Surprisingly, the ^{31}P-NMR chemical shift corresponding to the phosphorous of the *in situ* generated complex **164a** was not in agreement with the value of 49.3 ppm reported by GROTJAHN.[129] A possible explanation for the observed upfield shift was thought to be the use of deuterated acetonitrile as the solvent instead of deuterated chloroform used by GROTJAHN. To check this hypothesis, the NMR experiments were repeated using chloroform. However, the NMR-spectrum recorded in $CDCl_3$ showed a single peak at 43.6 ppm, which was again attributed to complex **164a**. To identify the structure of the complex unambiguously, it was attempted to grow crystals for an X-ray structure determination but all efforts at crystallization under a variety of conditions always produced orange crystals of a tris-phosphine complex. Difficulties in obtaining crystals from this complex had already been noticed by GROTJAHN.[129]

Finally, ESI-MS spectral analysis confirmed the formation of the cation $[CpRu(\mathbf{130a})_2]^+$ giving a signal at *m/z* 805 along with another signal at *m/z* 486 with significant lower intensity, corresponding to trace amounts of the fragment $[CpRu(\mathbf{130a})]^+$ (Figure 8).

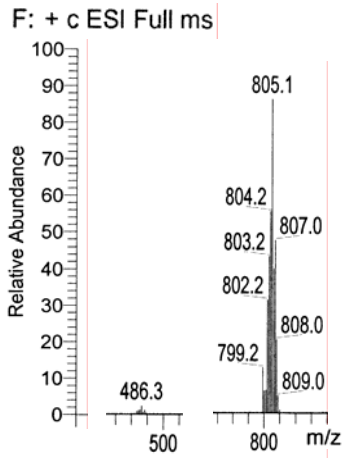


Figure 8. Ligand exchange experiment with **163** + 2.05 eq. **130a**: ESI-MS spectrum of the reaction solution.

In order to verify the correct assignment of complex **164a** in the ^{31}P-NMR spectrum, the ligand exchange was carried out once more in the presence of only one equivalent of ligand

130a in acetonitrile. Under these conditions, the mono-phosphine complex **165a** [CpRu(**130a**)(CH$_3$CN)$_2$]PF$_6$ was expected as the major product along with a smaller amount of the diphosphine complex **164a** [CpRu(**130a**)$_2$(CH$_3$CN)]PF$_6$.

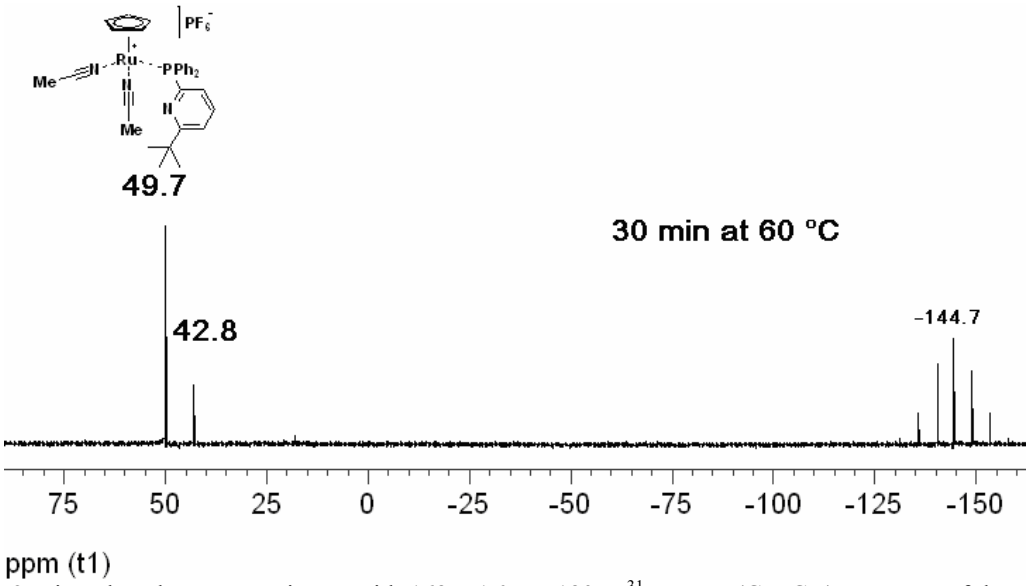


Figure 9. Ligand exchange experiment with **163** + 1.0 eq. **130a**: ^{31}P-NMR (CD$_3$CN) spectrum of the reaction solution.

The resulting ^{31}P-NMR spectrum in CD$_3$CN showed no traces of the free ligand, a minor peak at 42.8 ppm and a major peak at 49.7 ppm, as shown in Figure 9. To help assess these results, ^{31}P-NMR analysis of a parallel experiment in deuterated chloroform was found to give signals with similar chemical shifts (δ_{minor} = 43.6 and δ_{major} = 50.0 ppm) and intensities. Furthermore, ESI-MS spectral analysis of the latter experiment showed the presence of the cation [CpRu(**130a**)]$^+$ *m/z* = 486 as the major component along with a small amount of the cation [CpRu(**130a**)$_2$]$^+$ *m/z* 805 (Figure 10).

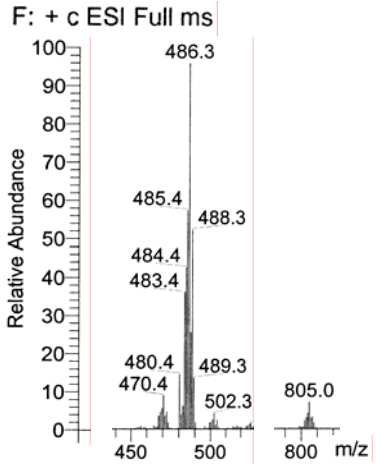


Figure 10. Ligand exchange experiment with **163** + 1.0 eq. **130a**: ESI-MS spectrum of the reaction solution.

Based on these experiments, the assignment of the ^{31}P-NMR signals in deuterated acetonitrile is as follows: the signal at δ = 49.7 ppm stems from monophosphine complex [CpRu(**130a**)(CH$_3$CN)$_2$]PF$_6$ (**165a**) and the signal at δ = 42.8 ppm corresponds to the diphosphine complex [CpRu(**130a**)$_2$(CH$_3$CN)]PF$_6$ (**164a**). Thus, it seems that the value reported by GROTJAHN (δ = 49.3 ppm for the diphosphine complex) is an error.

Next, the ligand exchange was performed with 2-(diphenylphosphino)-6-*tert*-amylpyridine **130b** (2.05 equiv) as the ligand because its structure resembles that of the previously reported pyridylphosphane **130a** and may exhibit similar properties. *In situ* formation of the complex **164b** [CpRu(**130b**)$_2$(CH$_3$CN)]PF$_6$ proceeded smoothly over 30 minutes at 60 °C.

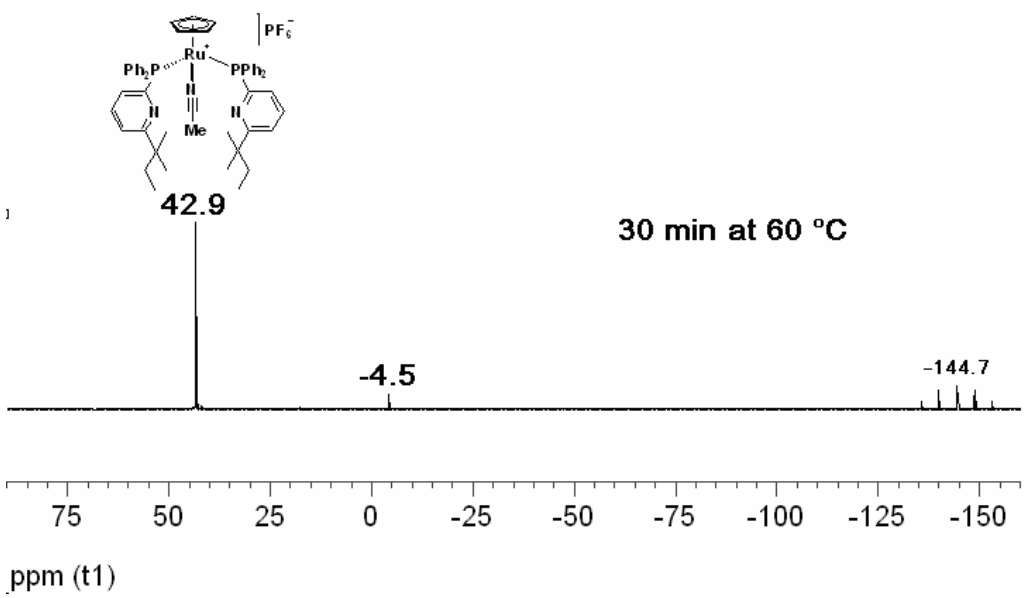


Figure 11. Ligand exchange experiment with **163** + 2.05 eq. **130b**: ^{31}P-NMR (CD$_3$CN) spectrum of the reaction solution.

As presented in Figure 11 and Figure 12, a peak at 42.9 ppm in the ^{31}P-NMR spectrum and signal for the cation [CpRu(**130b**)$_2$]$^+$ (*m/z* = 833) in the ESI-MS spectrum indicated again the generation of a biphosphine complex **164b**.

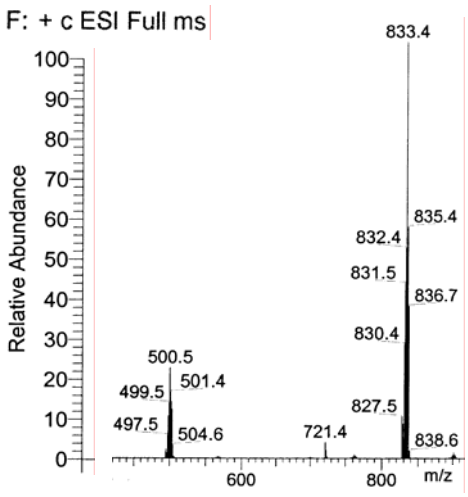


Figure 12. Ligand exchange experiment with **163** + 2.05 eq. **130b**: ESI-MS spectrum of the reaction solution.

Considering the modular approach developed for the preparation of the aza-arylphosphanes **130** and the facile *in situ* generation of the corresponding complexes [CpRu(L)$_2$(CH$_3$CN)]$^+$ (**164**) from the readily available Ru-precursor **163**, the possibility to apply the latter as *in situ* catalysts for a variety of metal-mediated reactions appears very attractive.

With the intention of investigating the influence of the substituents in 2-position of the aza-aryl ring on the ligand exchange, additional experiments were also performed with the 6-aryl-2-(diphenylphosphino)pyridines (**130g-o**). Because of the lower solubility of those pyridylphosphanes in acetonitrile, complete ligand exchange with 2-(diphenylphosphino)-6-(2,4,6-triisopropylphenyl)pyridine **130m** (2.05 equiv) was only achieved after prolonged reaction times at 60 °C.

In Figure 13, the course of the exchange reaction between **163** and 2.05 equivalents of ligand **130m** is illustrated by ^{31}P-NMR spectra of the reaction solution at different time intervalls. After one hour at 60 °C, the mono-substituted complex **165m** [CpRu(**130m**)(CH$_3$CN)$_2$]PF$_6$ (δ = 50.2 ppm) was observed as the major component of the reaction mixture. At this stage, free ligand **130m** (δ = −3.8 ppm) could be still detected alongside with some of the bisphopshine complex (δ = 43.3 ppm). Additional heating for 5 h led to disappearance of the signals of both the free ligand **130m** and monophosphine complex **165m**, the latter having been transformed completely into the bisphosphine complex **164m**.

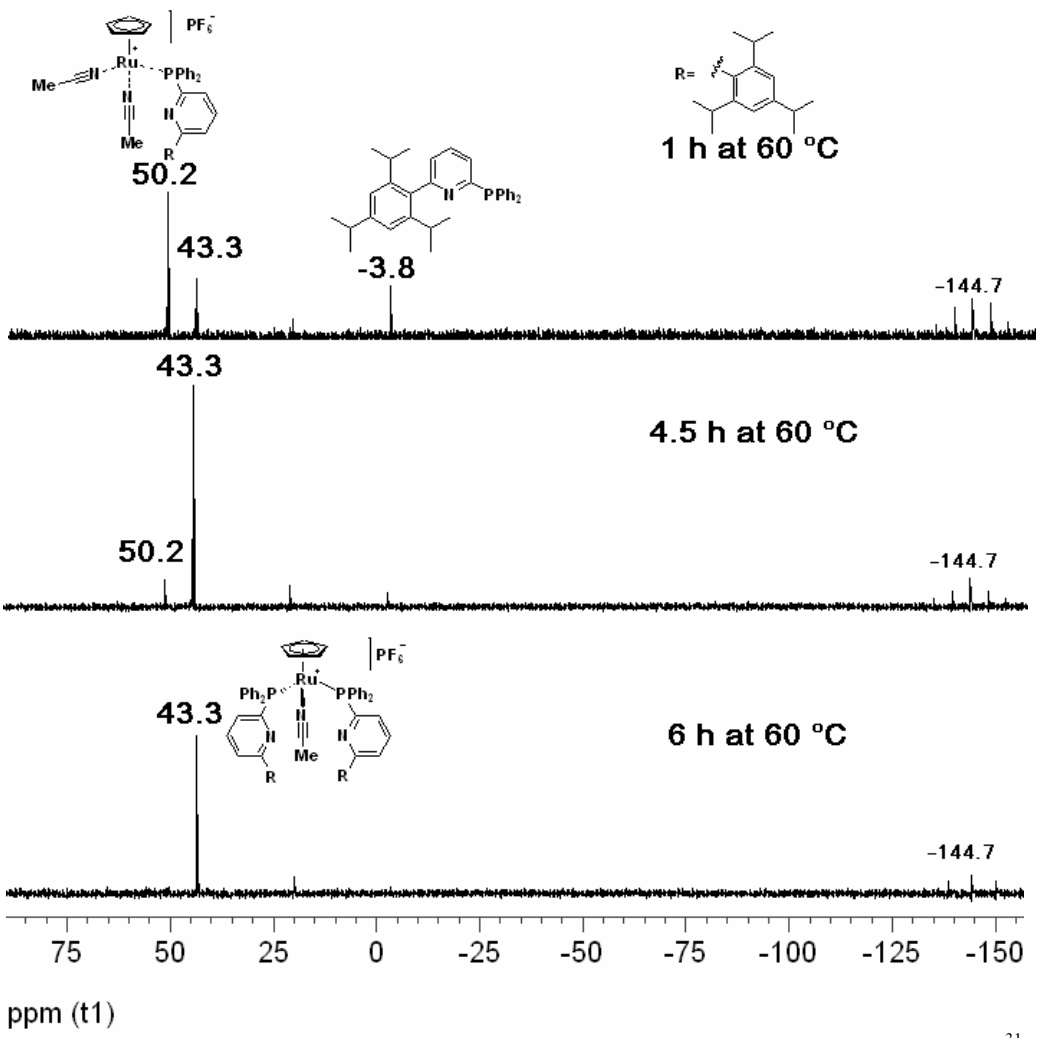


Figure 13. Time course of the ligand exchange of **163** with 2.05 equivalents of **130m**, illustrated by ^{31}P-NMR (CD_3CN) spectra.

Likewise, the ligand exchange took place with the extremely bulky 2-(diphenylphosphino)-6-(2,4,6-triphenylphenyl)pyridine **130n** (δ = –3.1 ppm); the corresponding bisphosphine complex **164n** (δ = 43.2 ppm) was quantitatively formed after stirring for 6 h at 60 °C (Figure 14).

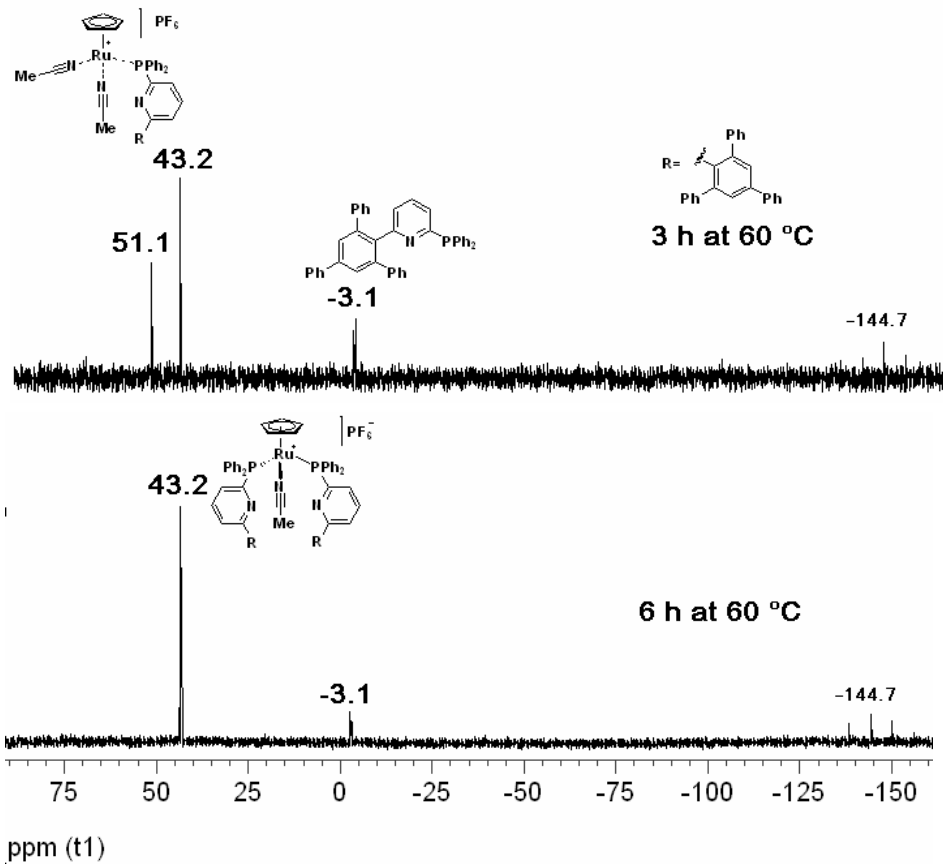


Figure 14. Time course of the ligand exchange of **163** with 2.05 equivalents of **130n**, illustrated by ^{31}P-NMR (CD_3CN) spectra.

In a similar manner as described above, ESI-MS spectral analysis of the reaction solution confirmed the formation of the cation $[CpRu(\mathbf{130n})_2]^+$ *m/z* 1301, and the fragment $[CpRu(\mathbf{130n})]^+$ *m/z* 734 (Figure 15).

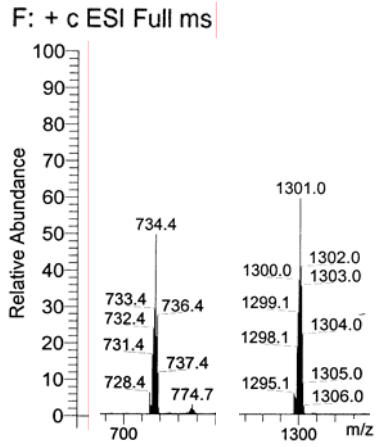


Figure 15. Ligand exchange experiment with **163** + 2.05 eq. **130n**: ESI-MS spectrum of the reaction solution.

Interestingly, in case of the exchange with sterically very demanding ligands such as **130n**, the ligand exchange process can also be followed in ^{1}H-NMR (Figure 16). The chemical shift

of the cyclopentadienyl group in the monophosphine complex **165n** (δ = 4.33 ppm) differs significantly compared to signal in the bisphosphine complex **164n** (δ = 3.93 ppm) and complete ligand exchange can be unambiguously identified by ^{1}H-NMR.

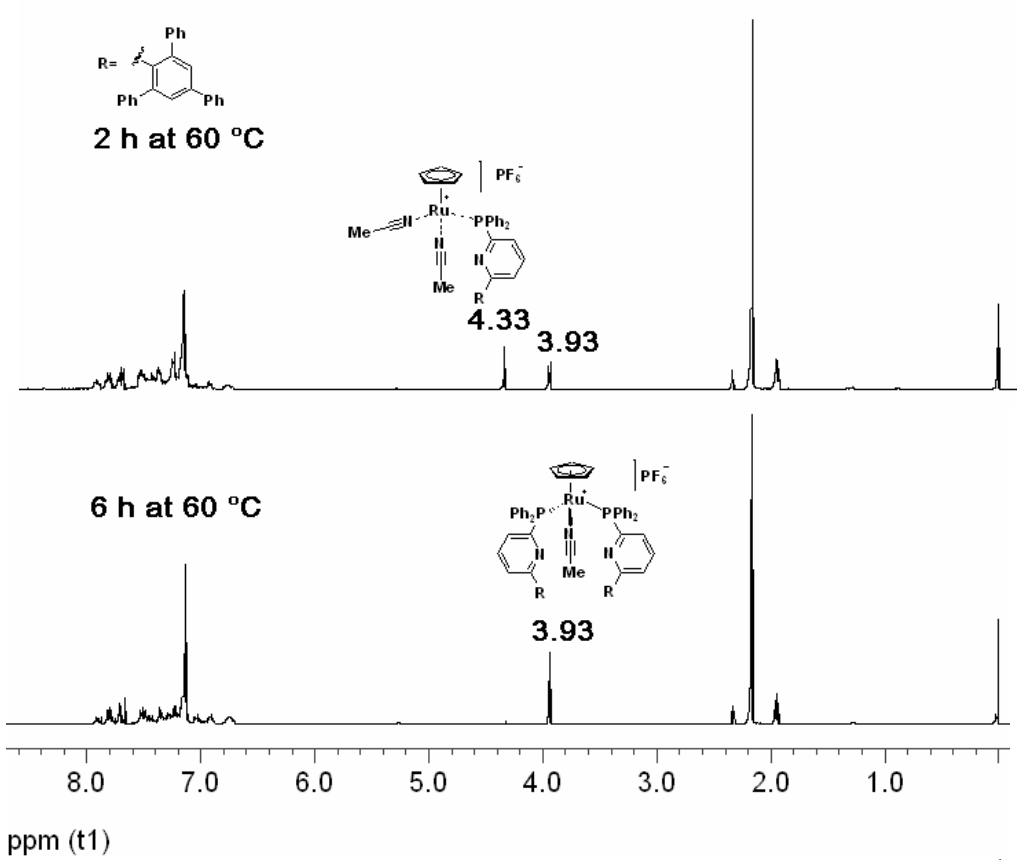
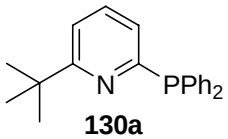
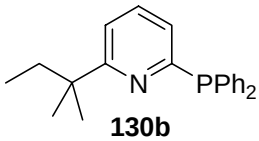
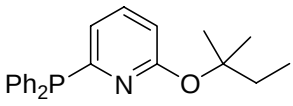
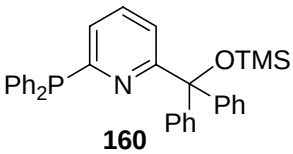
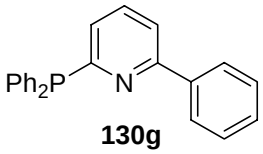
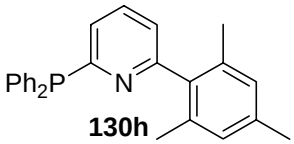
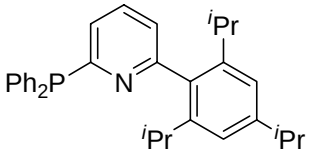
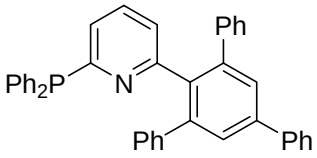
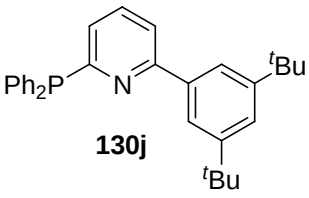


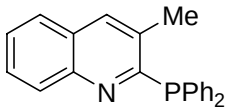
Figure 16. Time course of the ligand exchange of **163** with 2.05 equivalents of **130n**, illustrated by ^{1}H-NMR (CD_3CN) spectra.

By applying this methodology to a variety of aza-arylphosphane ligands **130** and **158**, it was possible to generate a range of new complexes 164 in solution.

Selected parameters of the ligand exchange experiments, followed by ^{31}P-NMR spectroscopy, are summarized in Table 9.

Table 9. Summary of key parameters from ligand (**130**, **158** and **160**) exchange with **163** in CD_3CN at 60 °C.[a]

entry	ligand	δ (^{31}P) L (ppm)	δ (^{31}P) 165 (ppm)	δ (^{31}P) 164 (ppm)	time (h)
1	 **130a**	−4.4	49.7	42.8	0.5
2	 **130b**	−4.5	49.7	42.8	0.5
3	 **142b**	−2.9	51.4	45.4	12.0
4	 **160**	−4.6	50.5	44.4	4.0
5	 **130g**	−3.9	51.0	43.1	2.5
6	 **130h**	−4.0	50.7	43.2	2.5
7	 **130m**	−3.8	50.2	43.3	6.0
8	 **130n**	−3.1	51.1	43.2	6.0
9	 **130j**	−0.7	52.1	46.6	5.0

10	 **158**	−7.5	51.9/52.1[b]	43.9	>100[c]

a) Reaction conditions: [CpRu(η^6-naphthalene)]PF$_6$ **163** (0.012 mmol), aza-arylphosphane ligand (0.024 mmol), degassed CD$_3$CN (650 µL). b) A rapid interconversion of the ligand binding mode could be an explanation for the two peaks observed. For a discussion, see text c) After > 100 h at 60 °C, less than 20% of the complex [CpRu(**158**)$_2$CH$_3$CN]PF$_6$ was formed.

In the case of the ligand exchange with quinolylphosphane **158**, the precursor proved reluctant to undergo complete exchange with two molecules of ligand and gave a mixture of monophosphine (**166**) and bisphosphine (**167**) complexes (entry 10). Even after a prolonged reaction time, only a small amount of the complex [CpRu(**158**)$_2$(CH$_3$CN)]PF$_6$ (**167**) was observed in the ^{31}P-NMR spectrum (δ = 43.9 ppm) (Figure 17) and in the ESI-MS spectrum (*m/z* = 820 for [CpRu(**158**)$_2$]$^+$) (Figure 17).

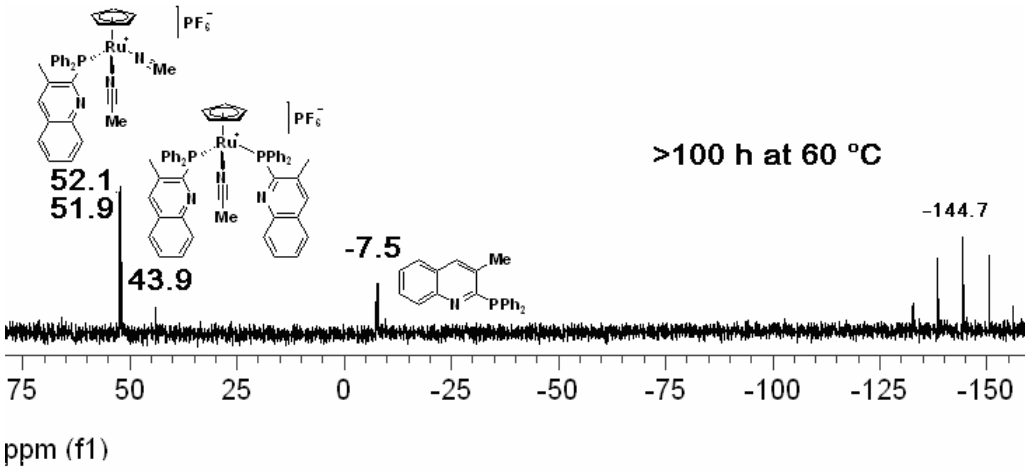


Figure 17. Ligand exchange experiment with **163** + 2.05 eq. **158**: ^{31}P-NMR (CD$_3$CN) spectrum of the reaction solution.

The major product gave rise to two peaks at 51.9 and 52.1 ppm in the ^{31}P-NMR spectrum and a single peak at *m/z* = 494, corresponding to the cation [CpRu(**158**)]$^+$ in the ESI-MS spectrum (Figure 18).

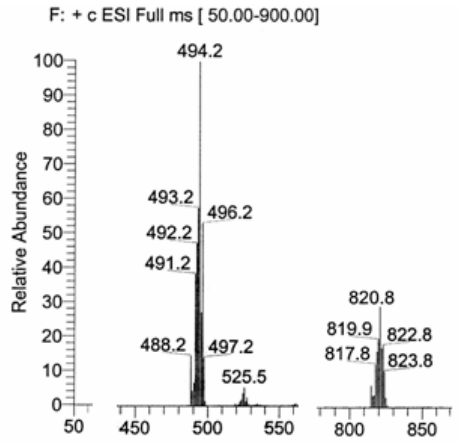


Figure 18. Ligand exchange experiment with **163** + 2.05 eq. **158**: ESI-MS spectrum of the reaction solution.

An explanation for the occurence of two distinct signals in the ^{31}P-NMR spectrum involves the presence of two rotational isomers as represented in Figure 19.

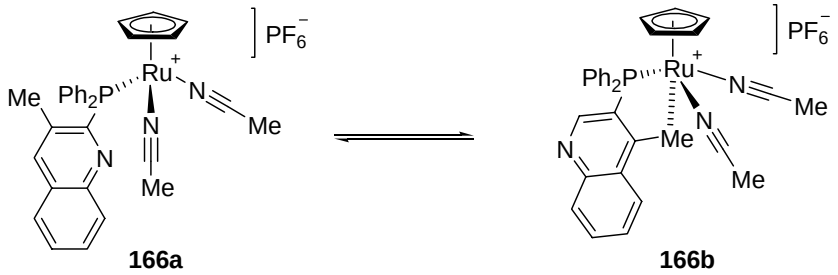


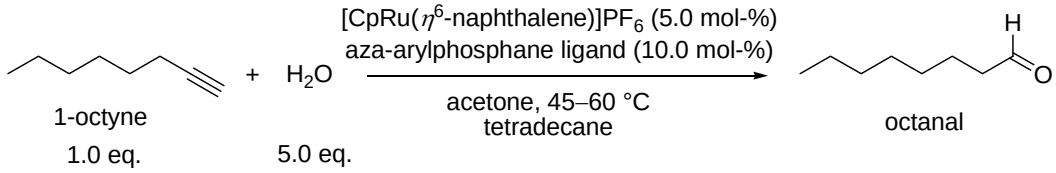
Figure 19. Representation of the potential rotationel isomers of complex **166**.

In conclusion, a straightforward *in situ* generation of complexes **164** via *in situ* exchange of naphthalene with different aza-arylphosphane ligands **130** starting from the readily available complex [CpRu(η^6-naphthalene)]PF$_6$ **163**, has been developed.

5.2. Ligand Effect on the Ru-Catalysed Hydration Reaction of Terminal Alkynes

In order to compare the ability of the newly prepared phosphanes **130** to serve as ligands in the title reaction with that of the known 2-*tert*-butyl-6-(diphenylphosphino)pyridine **130a**, kinetic studies on the hydration reaction of 1-octyne were carried out. The catalysts were

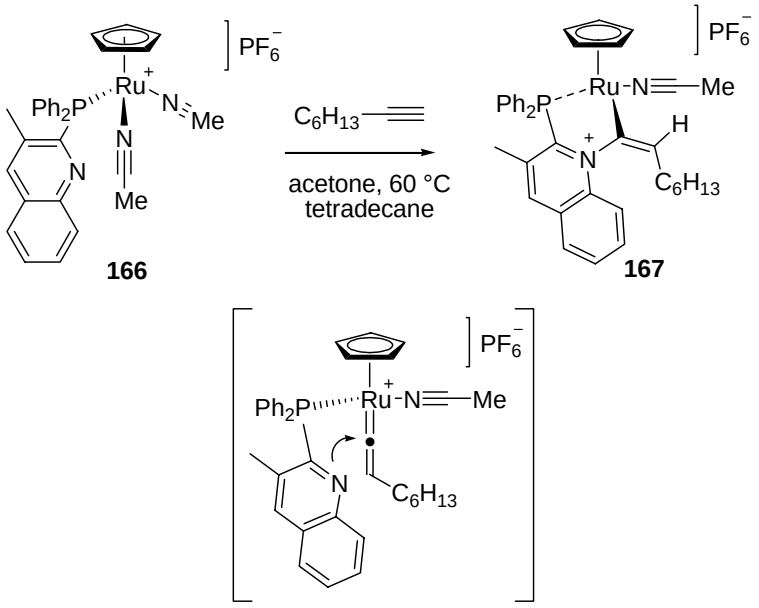
prepared *in situ* from Ru-precursor **163** and 2.05 equivalents of the aza-arylphosphane ligand in acetonitrile. Then, for the catalytic hydration the solvent had to be replaced with acetone.



Scheme 56. Hydration of 1-octyne employing *in situ* catalysts **164**.

As depicted in Scheme 56, the hydration of 1-octyne with the new *in situ* catalysts **164** proceeded indeed with high anti-MARKOVNIKOV selectivity by using 5.0 mol-% of the *in situ* generated catalyst and 5.0 equivalents of water.

In initial attempts with complexes **164** and **166**, two observations were immediately made. Based on GROTJAHN's reports,[129,134] catalyst deactivation by η^2-P-N chelation was a possible explanation for the unsuccessfull hydration of 1-octyne when the reaction was performed with complex **166**.



Scheme 57. Trapping of vinylidene by heterocycle .

As shown in Scheme 57, it was hypothesized that the heterocyclic nitrogen atom can add to the terminal carbon of 1-octyne in α-position of the ruthenium, presumably at the stage of the vinylidene complex, to afford the specie **167** as a result of an irreversible addition of the 1-

octyne (hypothese based on the studies reported by GROTJAHN related to the behaviour of C-6-substituted pyridylphosphanes bearing small substituents).[134]
In contrast, the complexes **164** prepared from ligands **130** were all active hydration catalysts with perfect anti-MARKOVNIKOV regioselectivity, although their catalytic efficiency varied. No formation of 2-octanone, stemming from the MARKOVNIKOV hydration, was observed in any case.

In a first set of experiments, the activity of the catalysts derived from ligands having different aza-aryl backbones was evaluated (Figure 20).

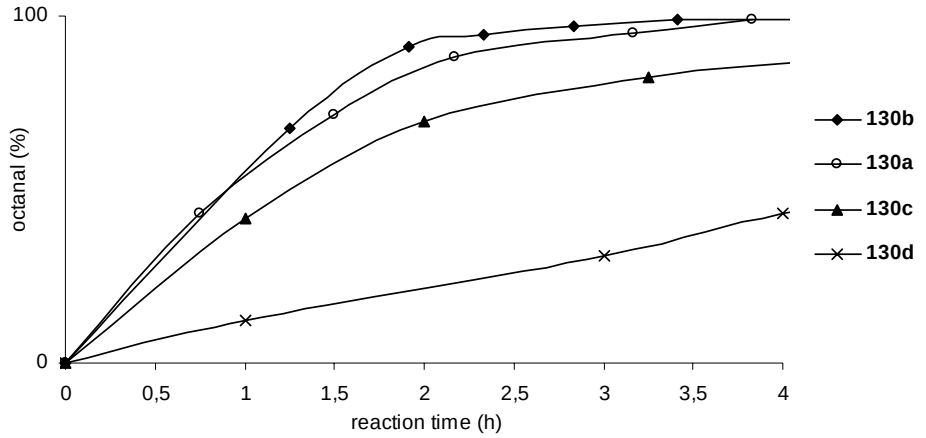


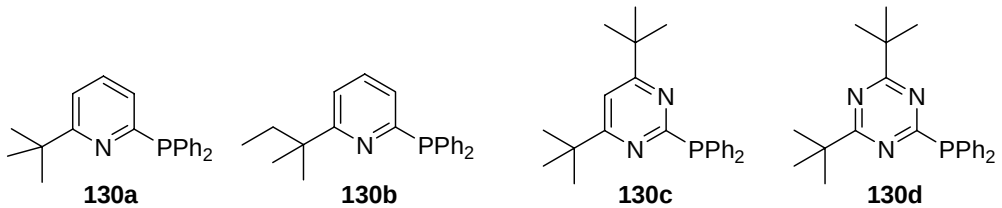
Figure 20. Hydration of 1-octyne at 60 °C using alkyl-substituted aza-arylphosphane ligands **130a-d** (GC data points).

To monitor the progress of the reaction quantitatively, a GC-FID technique, using tetradecane as internal standard, was employed to measure the formation of 1-octanal. The curves were recorded and fitted[163] to the rate law $d[octanal]/dt = k_X[Ru]_0[H_2O][octyne]$. The values thus obtained for k_X were compared to the activity of the catalyst generated *in situ* from ligand **130a**. Since reaction progress did not follow the above rate law uniformly over the full range of conversion, the results are approximate, but some conclusions can still be drawn.

While the *in situ* generated catalysts **164c** and **164d**, derived from 4,6-di-*tert*-butyl-2-(diphenylphosphino)pyrimidine **130c** and 2,4-di-*tert*-butyl-6-(diphenylphosphino)-1,3,5-triazine **130d**, showed lower catalytic activity, compared to the reference hydration catalyst **130a**, with relative catalytic activities (RCA (Ln) = k_{Ln}/k_{L1}) of 0.64 and 0.16, respectively. A

[163] DYNAFIT program; P. Kuzmic *Anal. Biochem*. **1996**, *237*, 260.

slightly higher activity was observed with 2-(diphenylphosphino)-6-*tert*-amylpyridine (**130b**) as the ligand, with an RCA of 1.3 (Figure 21).



	130a	**130b**	**130c**	**130d**
RCA @ 60°C	1.0	1.3	0.64	0.16

Figure 21. Relative Catalytic Activities of aza-arylphosphane ligands **130a-d** at 60 °C.

These results indicated that introduction of further heteroatoms into the aza-arene nucleus of the ligand gave less active catalysts and that a bulky group at the C_6 position of the pyridine ring was required to obtain at least similar catalytic activity as with ligand **130a**. The lower activity of the ligands **130c** and **130d** may be related either to a lower binding affinity of the less basic phosphorous atom to the metal center or to a weaker nucleophilic activation resulting from the lower basicity of the pyrimidine or triazine nitrogen atom respectively.

Next, the C-6-aryl substituted pyridylphosphane ligands **130g-n** were tested in this reaction.

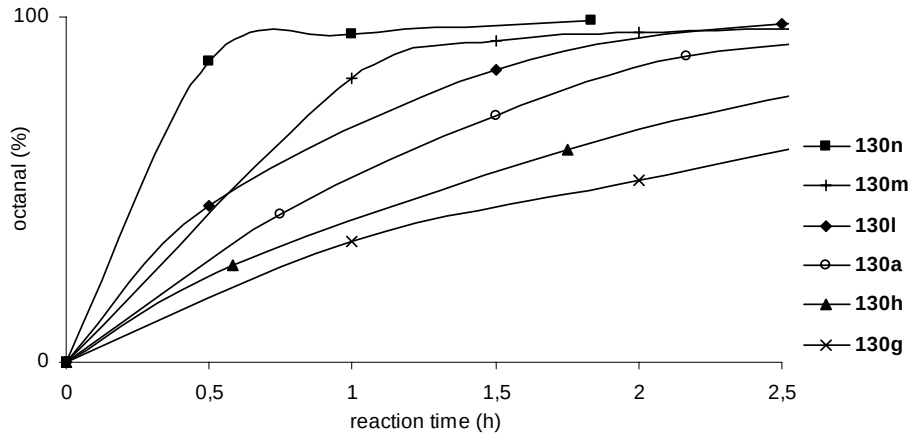


Figure 22. Hydration of 1-octyne at 60 °C using 6-aryl-pyridylphosphane ligands **130g-n** (GC data points).

Reaction progress curves of the 1-octyne hydration at 60 °C employing *in situ* catalysts made from ligands **130g-n** are presented in Figure 22. The activity of the catalysts increased in the order R (substituent at the C_6 position of the pyridine ring) = Ph < Mesityl < *t*-Bu < 2,4-(*i*-Pr$_2$)C$_6$H$_3$ < 2,4,6-(*i*-Pr$_3$)C$_6$H$_2$ < 2,4,6-(Ph$_3$)C$_6$H$_2$ and thus roughly correlated with the steric size of the ligand. Moreover, ligands **130l**, **130m** and **130n** displayed a higher activity

compared to 6-alkyl-aza-aryl phosphanes. Hence, the hydrations, under the same conditions, were repeated at 45 °C, to allow better analysis of the curves (Figure 23).

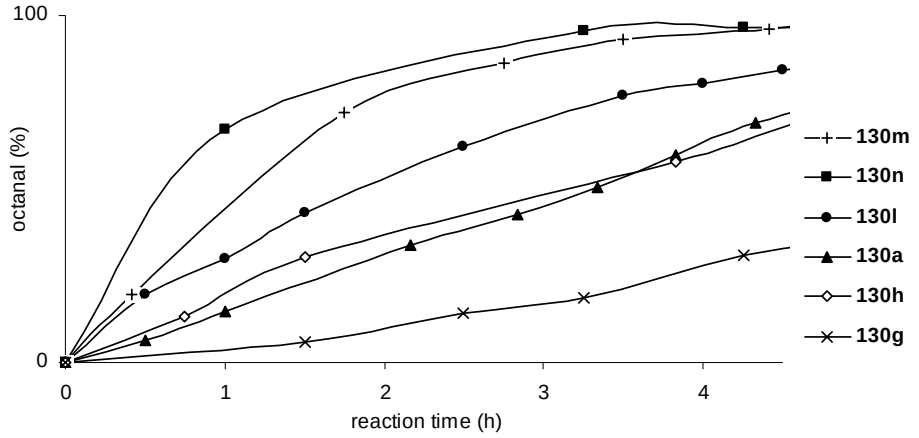
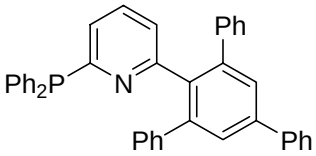
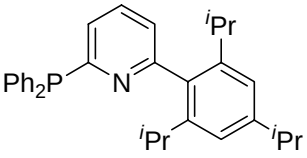
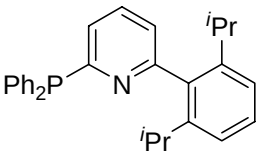
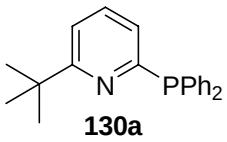
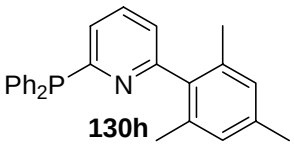
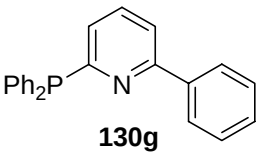


Figure 23. Hydration of 1-octyne at 45 °C using 6-aryl-pyridylphosphane ligands **130g-n** (GC data points).

The values thus obtained for k_L at both 60 °C and 45 °C were compared to the activity of the ligand **130a** (Table 10).

Table 10. Relative catalytic activities of aza-arylphosphane ligands in the hydration of 1-octene at 45 °C and 60 °C.

entry	ligand	RCA 45 °C[a]	RCA 60 °C
1	 **130n**	2.9	16.6
2	 **130m**	1.6	7.1
3	 **130l**	1.2	5.0
4	**78**[b]	1.3	3.9

5	 **130a**	1.0	3.5
6	 **130h**	1.0	2.3
7	 **130g**	0.4	1.6

a) Relative Catalytic Activities, normalized: RCA (**Ln**) = $k_{\mathbf{Ln}}/K_{\mathbf{L130a}@45\ °C}$. b) Pure complex **78**, purchased from Strem Chemicals, was used as catalyst.

These experiments revealed some interesting information about the catalysts. First, catalyst activity at 60 °C was two to five times higher than at 45 °C. Secondly, whereas, the pure complex **78** was slightly more active than the corresponding *in situ* generated catalyst from **164a** (entry 4), ligands **130l**, **130m** and **130n** surpassed the activity of both **130a** and the purified complex **78** (entries 1-3). The best result of all was obtained with 2-(diphenylphosphino)-6-(2,4,6-triphenylphenyl)pyridine **130n** as a ligand showing remarkable RCA's of 2.9 at 45 °C and 16.6 at 60 °C (entry 1). This confirms the assumption made in the previous section that an increase of the steric size at the C-6 position of pyridylphosphanes would increase the activity of the catalyst **164** for anti-MARKOVNIKOV hydration of alkynes.
Thus, a larger group in 2-position led to a higher reaction rate. This observation provided insights into a possible reaction pathway. As already discussed in section 2.2.2, bifunctional catalysis was considered to play a key role in the hydration process. Here, the hypothesis that the basic pyridine nitrogen may assist in the proton transfer from water to the Ru-alkyne complex or activate the nucleophile in close proximity of the reaction center is supported by the observations above, considering that ligands with less basic nitrogen are leading to less active catalysts.

Next, catalysts were generated *in situ* from the other aza-arylphosphane ligands prepared as described in Section 3 and kinetic studies of the hydration of 1-octyne, performed at 60 °C, with these catalysts were made (Figure 24).

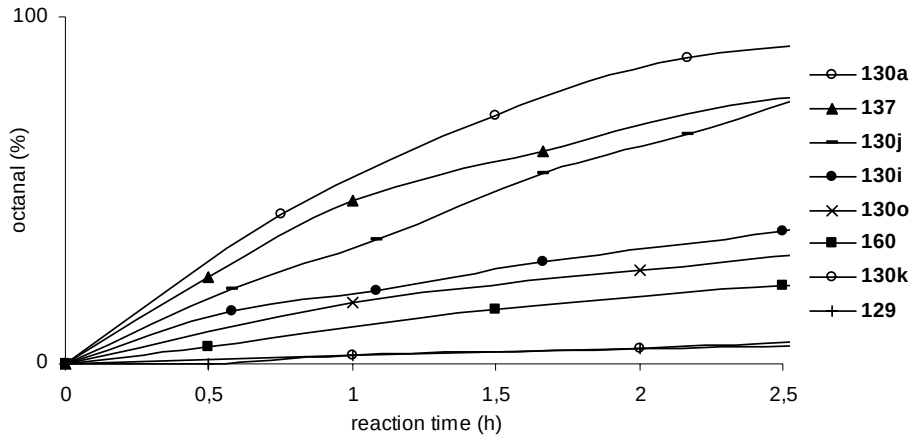


Figure 24. Hydration of 1-octyne at 60 °C using aza-arylphosphane ligands (GC data points).

As can be seen in Figure 24, none of these catalysts showed a higher activity than **130a**. The complexes with the ether-pyridylphosphane derivatives **142a** and **142b** showed a very low activity and their relative RCA could not be determined.

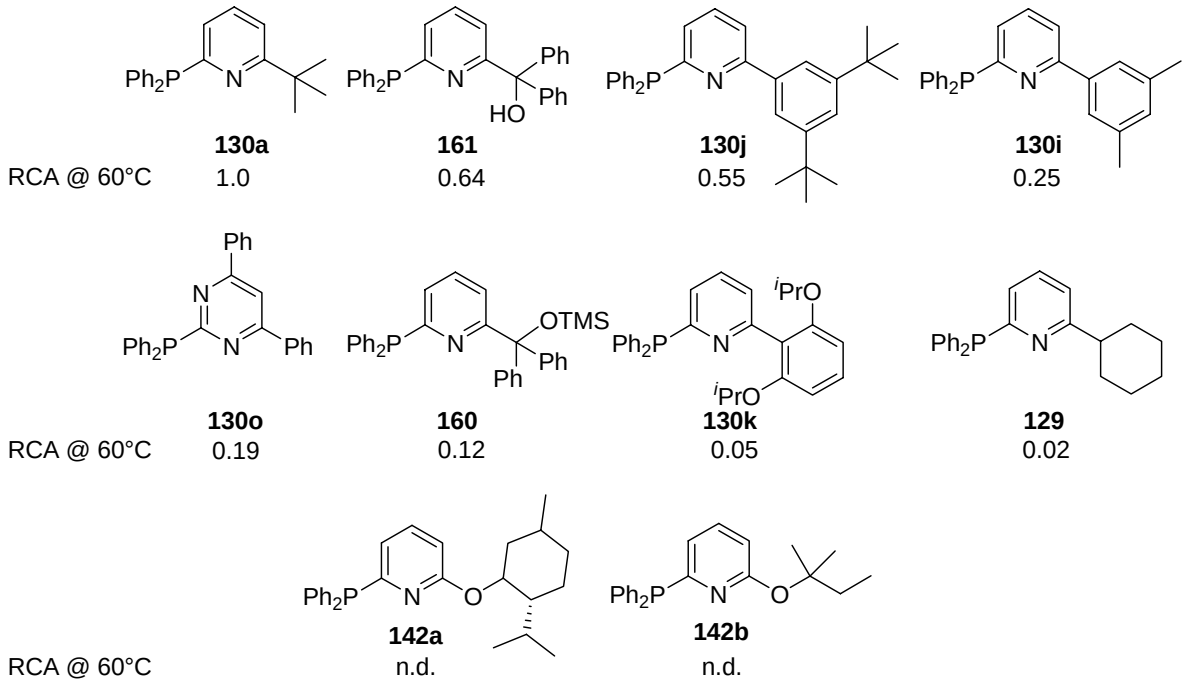


Figure 25. Relative Catalytic Activities of aza-arylphosphane ligands at 60 °C.

In addition, the introduction of heteroatoms into either the aza-arene nucleus or onto the aryl ring again gave less active catalysts **130o** and **130k**. Ligands with meta-substituted aryl groups **130i** and **130j** led to less active catalyst compared to their ortho-substituted counterparts. Surprisingly, although ligand **129** presents some steric hindrance with their cyclohexyl group, the relative catalytic activity of the resulting catalyst was very poor.

Interestingly, the hydration catalyzed by the catalyst from **161** gave a good RCA of 0.64 wich may be attributed to the formation of an additional hydrogen bond between the nucleophile and the hydroxyl group in the side chain of the ligand, favorising the protonation of the alkyne π-complex (see the mechanistic proposal Scheme 30). In accordance with this, the TMS-protected analogue showed almost no catalytic activity.

Subsequent studies involved investigations of the effect of the counterion and catalyst loading (Figure 26).

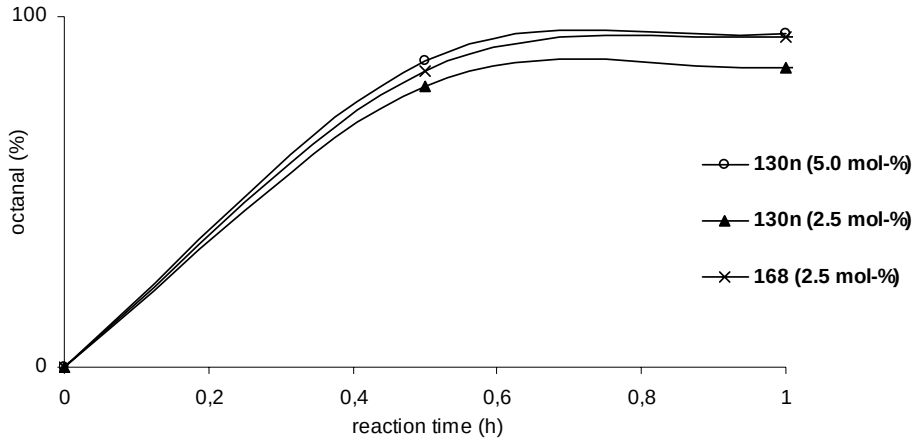


Figure 26. Catalyst loading and counterion effect on hydration of 1-octyne at 60 °C (GC data points).

The catalyst loading could be lowered to 2.5 mol-% of the Ru-catalyst **164n** when performing the reaction at 60 °C. A slight improvement in the activity was obtained with catalysts **168** by replacing the hexafluorophosphate anion with the trisphate anion. However, the limited accuracy of the GC data points of these two experiments only permitted a rough estimation of the influence of the counterion on the reaction.

Finally, it was found that the catalyst formation can be more conveniently performed under the conditions of the hydration reaction. So, a one-pot procedure for the catalyst preparation and the hydration of alkynes was developed. Mixing 1-octyne (1.0 eq.), the complex **163** [CpRu(η^6-naphthalene)]PF$_6$ (0.05 eq.) and aza-arylphosphine ligands **130** (0.1 eq.) in acetone/water at 60 °C led to a catalytically active system.[164]

[164] This procedure was discovered by EVA PACIOK, Forschungsarbeit, 2006. Further applications of this protocol to the iterative synthesis of oligo-1,4-diols are currently being conducted by THOMAS KRIBBER and will be reported in due course.

As shown in the Figure 27, the one pot process displayed longer overall reaction times due to an induction period in which the active catalyst is formed. None the less, this method provides a practical improvement for the hydration of alkynes since the solvent switch from acetonitrile to acetone can be avoided.

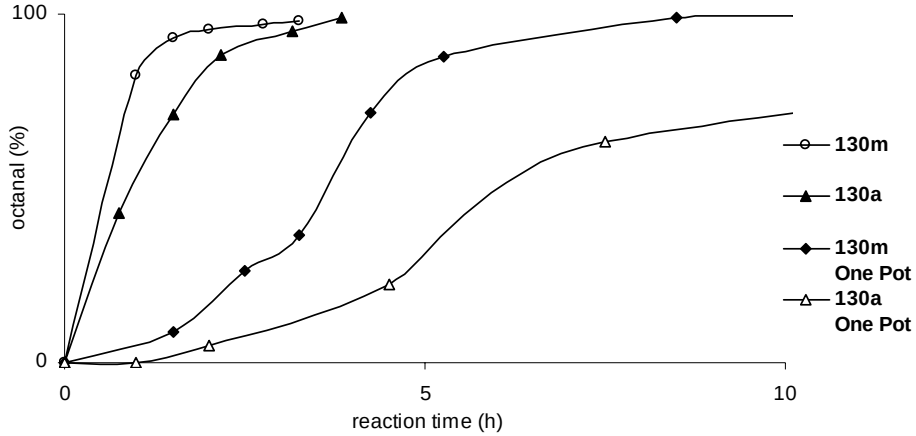


Figure 27. One-pot process of *in situ* catalyst formation and hydration of 1-octyne (GC data points).

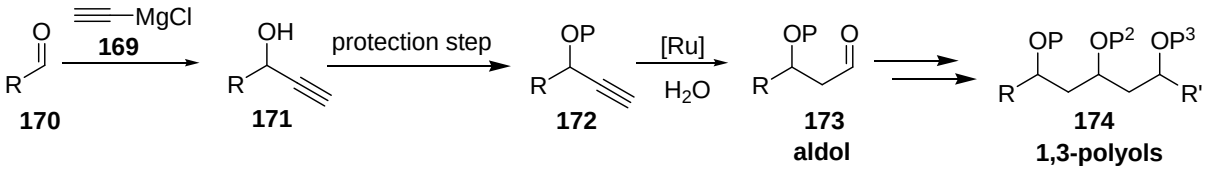
In summary, new catalysts **164** for the *anti*-MARKOVNIKOV hydration of terminal alkynes derived from readily available and easy to prepare components have been generated *in situ*. Furthermore, a screening of various aza-arylphosphanes as ligands allowed for tuning the catalyst to high levels of activity with perfect regioselectivity. Ultimately, this led to the identification of catalyst **164n** which is more than 4 four times more active than the best system known so far for the *anti*-MARKOVNIKOV hydration of terminal alkynes.

6. Ruthenium-catalyzed Hydration of Terminal Alkynes

6.1. Hydration of Propargylalcohols

The second part of this work was dedicated to the application of aza-arylphopsphanes **130** in the Ru-catalyzed anti-MARKOVNIKOV hydration of terminal alkynes.

First, the synthesis of β-hydroxy aldehydes via an alkynylation/hydration sequence starting from simple aldehydes was investigated. As presented in Scheme 58, it was envisaged that addition of ethynylmagnesium chloride **169** to aldehydes **170** would afford propargylic alcohol **171**. The latter might then be hydrated after protection of the hydroxyl group. Therefore, this sequence would constitute an elegant alternative to access aldol-type products **173** which are notoriously difficult to synthesise, such as β-hydroxy aldehydes from a crossed aldol reactions of two enolisable aldehydes.[165] The application of an iterative sequence of alkynylation/hydration reactions would lead to 1,3-polyols **174**, which are found in countless natural products.



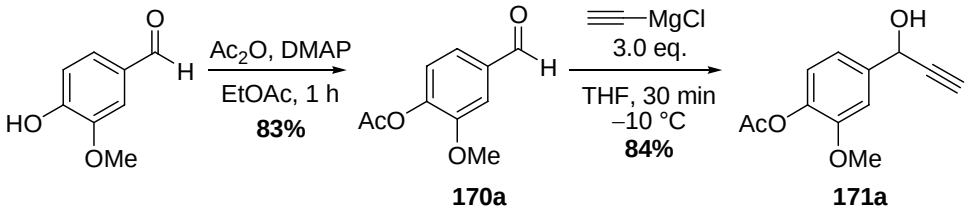
Scheme 58. Synthetic sequence envisaged to access protected 3-hydroxy aldehydes and 1,3-polyols.

Ethynylmagnesium chloride **169** was synthesized, according to a procedure reported by HOLMES, by passing gaseous acetylene through THF and subsequently adding a solution of butylmagnesium chloride in THF at -10 °C.[166] The resulting GRIGNARD-solution was stored at −20 °C under an inert atmosphere.

Alkynylation of the vanilline-derivative **170a** gave the corresponding propargylalcohol **171a** in 84% yield after stirring for 30 min at −10 °C (Scheme 59).

[165] For examples of organocatalytic aldehyde-aldehyde cross-aldol coupling, see: a) A. B. Northrup, D. W. C. MacMillan *Science* **2004**, *305*, 1752. b) A. B. Northrup, I. K. Mangion, F. Hettche, D. W. C. MacMillan *Angew. Chem.* **2004**, *116*, 2204; *Angew. Chem. Int. Ed.* **2004**, *43*, 2152.

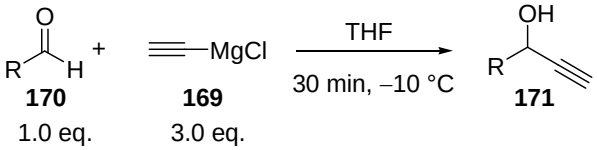
[166] B. Holmes, C. N. Heathcock *Org. Syn. Coll*. **1993**, *8*, 606.

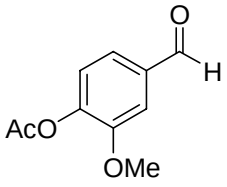
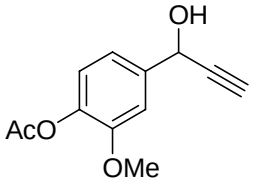
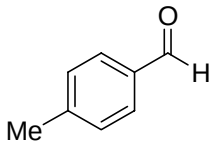
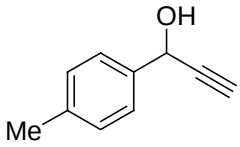
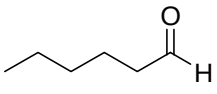
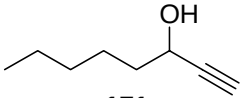


Scheme 59. Synthesis of the propargylic alcohol **171a**

The alkynylation of a range of substrates **170** with ethynylmagnesium chloride **169** required three equivalents of the GRIGNARD-reagent and occurred within 30 minutes at −10 °C in THF (Table 11). By this, various propargylalcohols **171** were prepared with high yields (84-98%).

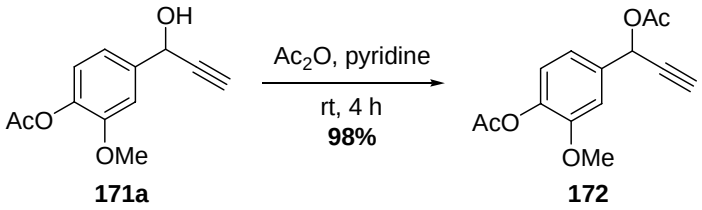
Table 11. Alkynylation of aldehydes **170** to yield propargylic alcohols **171**.



entry	substrate	product	yield (%)
1	 **170a**	 **171a**	84
2	 **170b**	 **171b**	85
3	 **170c**	 **171c**	98

Before carrying out the hydration reaction protection of the propargylic alcohols was necessary since these compounds are known to undergo MEYER-SCHUSTER rearrangement with anti-MARKOVNIKOV hydration catalysts, affording α,β-unsaturated aldehyde instead of the desired aldol product.[129,137]

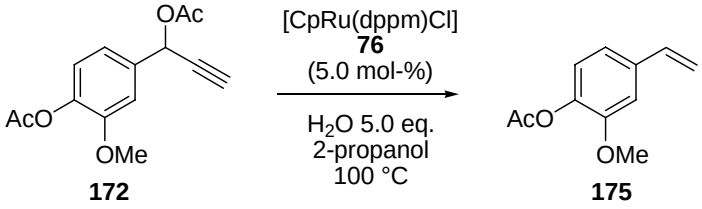
As presented in Scheme 60, acetic anhydride reacted smoothly with the propargylic alcohol **171a** to give compound **172** in 98% yield.



171a **172**

Scheme 60. Acetylation of the hydroxyl group of propargylalcohol **171a**.

Next, hydration of the *O*-acetyl propargylic alcohol **172** (Scheme 61) was attempted under the conditions reported by WAKATSUKI,[127] using 5.0 mol-% of complex [CpRu(dppm)Cl] (**76**) as catalyst in 2-propanol at 100 °C.

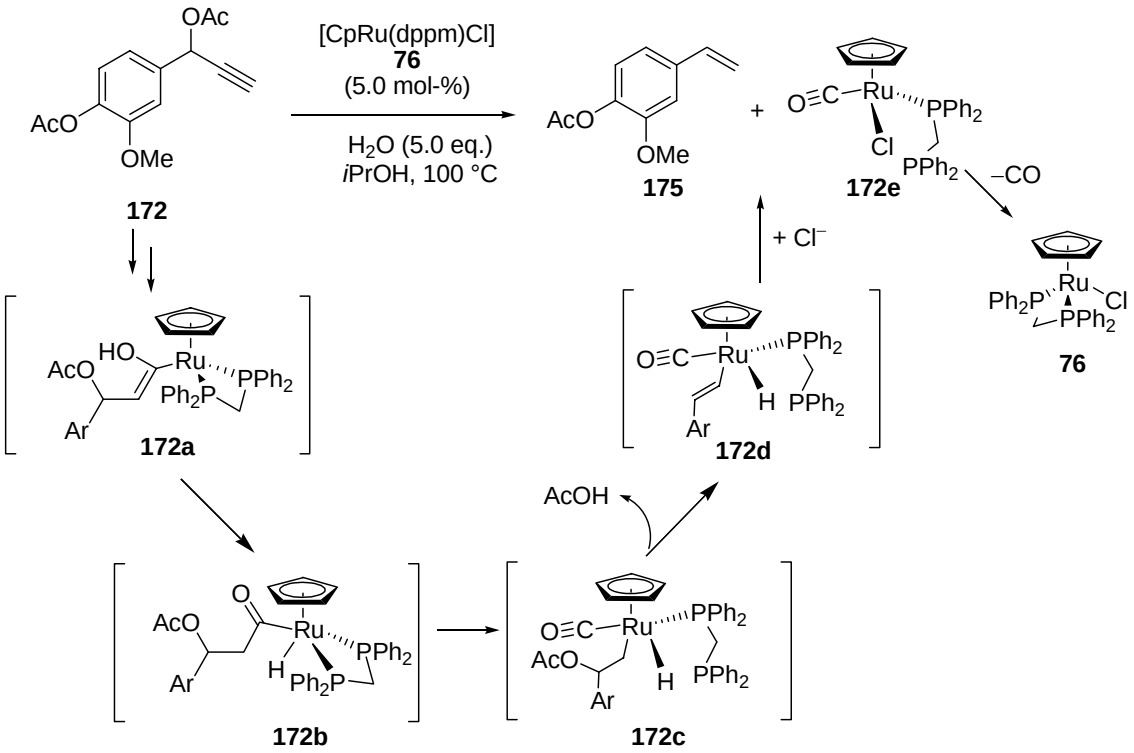


172 **175**

Scheme 61. Ru-catalyzed hydration of *O*-acetyl propargylalcohol **172**.

Surprisingly, this Ru-catalyzed hydration did not furnish the desired β-acetoxy-aldehyde, instead the styrene derivative **172** was isolated.

It is hypothesized that the harsh reaction conditions still necessary for the reaction to occur using [CpRu(dppm)Cl] (**76**) as the catalyst led to an undesired rearrangement, whose proposed mechanism is shown in Scheme 62. After formation of the enol-species **172a** and its tautomerisation to the acyl-Ru-species **172b**, CO-migration leads to the labile Ru-alkyl-complex. By elimination of acetic acid, a more favourable vinyl-Ru-hydride species is formed. Then, reductive elimination releases the observed styrene **175**. Stable complex such as **172e** was observed and isolated by GROTJAHN in similar reactions.[134]



Scheme 62. Proposed mechanism for the formation of the styrene derivative **175**.

It was anticipated that changing the solvent, thus allowing lower reaction temperatures, may help to minimize the risk of elimination processes.

Table 12. Solvent screening for the Ru-catalyzed hydration of *O*-acetyl propargylalcohol **172**.

entry	solvent	temp. (°C)	time (h)	yield of 175 (%)
1	2-propanol	100	20	15
2	toluene	90	125	58
3	acetonitrile	90	72	69
4	dichloroethane	90	72	22
5	2-methyl-2-butanol	95	48	-
6	2,4-dimethyl-3-pentanone	110	90	75
7	acetone	70	40	83

However, as it can be seen from Table 12, the hydration of the alkyne **172** with different solvents gave, in all cases, the unexpected product **175**. Therefore, under these conditions, the elimination of acetic acid seems favourable and affords the styrene derivative as the exclusive

product of the reaction. Compound **175** was generally obtained in only moderate yields, except in the last case when acetone was used as the solvent (entry 7).

Following these results, no further efforts to hydrate propargylic alcohols were pursued in this work, although the use of other protecting groups such as silyl ethers,[167] which should not suffer from facile elimination, was thought to be a possible alternative to avoid the aforementioned side reaction. Instead, attention was focused on developing new catalytic systems (see Section 5).

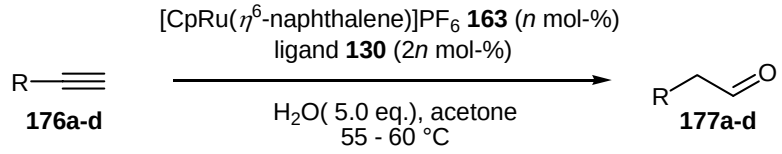
6.2. Use of Catalysts $[CpRu(L)_2CH_3CN]PF_6$ in the Hydration of Terminal Alkynes

Having identified a reliable procedure for the generation in solution of Ru-aza-arylphosphane complexes (Chapter 5), an investigation was launched into the substrate scope of these catalysts in the anti-MARKOVNIKOV hydration of different terminal alkynes.
As already described in section 5.2., kinetic studies demonstrated that the efficiency of the reaction was enhanced by using aza-arylphosphanes with a sterically demanding substituent in position C-6 of the heterocycle.

First, the procedure was applied to two aliphatic, nonfunctionalized terminal alkynes **176a/b** which afforded the corresponding aldehydes **177a/b** in good yields (78-95%) within short reaction times (Table 13). Again, no traces of the corresponding methyl ketones stemming from the reaction proceeding with MARKOVNIKOV selectivity were observed. Furthermore, the hydration of aromatic alkynes **176c** and **176d** proceeded smoothly using the bulky arylpyridylphosphanes **130l-n** at low catalyst loading (1.0-2.0 mol-% of catalyst, entries 11-14).

[167] Several silyl ethers are currently used as protecting groups in combination with the application of the *in situ* generated catalysts **164** with the ligands **130b**, **130m** and **130n** in the iterative synthesis of oligo-1,4-diols. These investigations are part of the Ph.D. work of THOMAS KRIBBER. A comprehensive account on the outcome of these experiments will be reported in due course.

Table 13. Use of the *in situ* catalysts in the anti-MARKOVNIKOV hydration of nonfunctionalized terminal alkynes.[a]



entry	substrate	product	ligand	[Ru] (mol-%)	temp. (°C)	time (h)	yield (%)
1	*n*-C_6H_{13} **176a**	*n*-C_6H_{13} **177a**	**130a**	5	60	3.2	95[b]
2	"	"	**130d**	5	60	22	95[b]
3	"	"	**130b**	5	60	3.0	95[b]
4	"	"	**130c**	5	60	5.5	95[b]
5	"	"	**130g**	5	60	6.0	95[b]
6	"	"	**130l**	5	60	2.0	95[b]
7	"	"	**130m**	5	60	2.0	95[b]
8	"	"	**118n**	5	60	1.0	95[b]
9	*n*-C_5H_{11} **176b**	*n*-C_5H_{11} **177b**	**130a**	1	60	14	78
10	"	"	**130n**	1	60	6.5	91
11	C_6H_5 **176c**	C_6H_5 **177c**	**130m**	2	60	12	90
12	"	"	**130n**	2	55	3	94
13	*p*-tBu-C_6H_5 **176d**	*p*-tBu-C_6H_5 **177d**	**130l**	2	55	6	69
14	"	"	**130n**	2	55	6	73

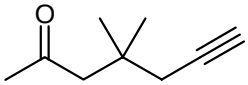
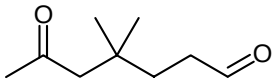
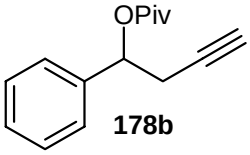
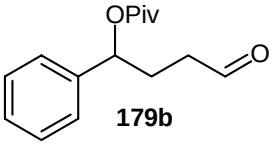
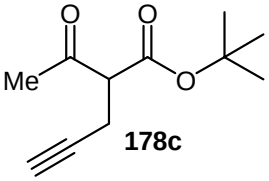
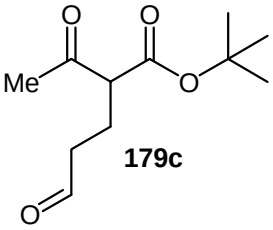
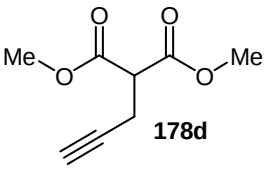
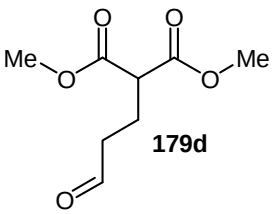
a) Reaction conditions for [Ru]-catalyst formation: [CpRu(η^6-naphthalene)]PF_6 (**163**) (1.0 eq.), ligand **130** (2.0 eq.), CH_3CN (0.025 *m*), 60 °C, 1-6 h; hydration conditions: alkynes (1.0 mmol), acetone (4 mL), H_2O (5.0 mmol), 55-60 °C. b) Time to 95% conversion was determined by GC, using tetradecane as internal standard.

Given these encouraging results, the title reaction was applied also to functionalized alkynes **178** which revealed the functional group tolerance to be broad. As presented in Table 14, functional groups such as ketones or esters were compatible with the reaction conditions and the corresponding functionalized aldehydes could be prepared in good to excellent yields (69-99%).

The ketone **178a** and the protected homo-propargylic alcohol **178b** were converted into 1,6-keto-aldehyde **179a** and γ-hydroxy-aldehyde **179b** in 69% and 83% yield, respectively (entries 1-2). No side products from elimination were observed (entry 2). The hydration of alkyne **178c**, bearing a β-ketoester group proceeded also with high yields (entries 3-4) even though it is a potential ligand for ruthenium.

The best results were obtained with the malonate **178d** (entries 5-7), in particular when the bulkier ligand **130n** was employed. Almost quantitative yields (99%) were obtained within 1.5 h in acetone at 55 °C. Again these results indicate the importance of the steric hindrance of the substituents in 6-position on the pyridine ring of the ligand for activating high activity of the catalyst.

Table 14. Use of the *in situ* catalysts **164** in the anti-MARKOVNIKOV hydration of functionalized terminal alkynes.[a]

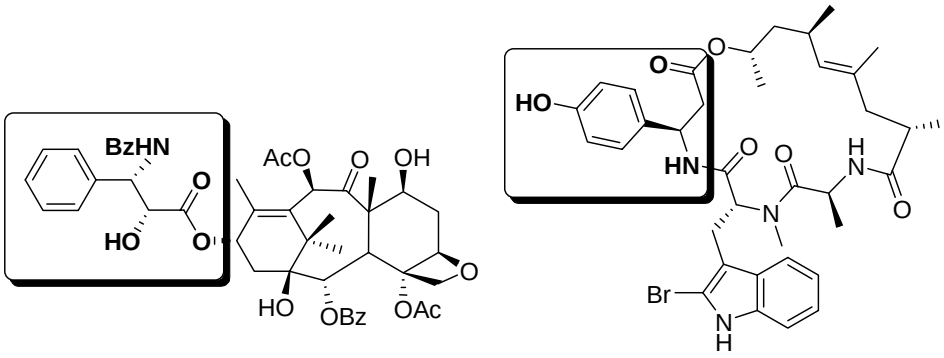
entry	substrate	product	ligand	[Ru] (mol-%)	temp. (°C)	time (h)	yield (%)
1	 **178a**	 **179a**	**130a**	2	45	18	69
2	 **178b**	 **179b**	**130a**	2	65	20	83
3	 **178c**	 **179c**	**130a**	4	60	8	98
4	"	"	**130m**	4	60	8	95
5	 **178d**	 **179d**	**130m**	2	55	6	95
6	"	"	**130l**	1	55	4.5	72
7	"	"	**130n**	2	55	1.5	99

a) Reaction conditions for [Ru]-catalyst formation: [CpRu(η^6-naphthalene)]PF_6 (**163**) (1.0 eq.), ligand **130** (2.0 eq.), CH_3CN (0.025 *m*), 60 °C, 1-6 h; hydration conditions: alkynes (1.0 to 10.0 mmol), acetone (0.5 *m*), H_2O (5.0 eq.), 45-65 °C.

6.3. Synthesis of β-Amino Aldehydes

The synthesis of β-amino carbonyl compounds is of considerable interest due to their potential applications as building blocks for the preparation of biologically active compounds.[168] β-Amino carbonyl compounds can be used as precursors to important classes of substances, such as β-amino acids, 1,3-amino alcohols or 1,3-diamines.[169,170]

For example, β-amino acids are found in several natural products such as Paclitaxel (**180**, Figure 28), one of the most active antitumor agents, which contains (L)-phenyl-isoserine in its side chain, or Jasplakinolide (**181**, Figure 28), a sponge metabolite with potent insecticidal, antifungal, and antihelminthic properties which contains (L)-β-tyrosine.



Paclitaxel **180** Jasplakinolide **181**

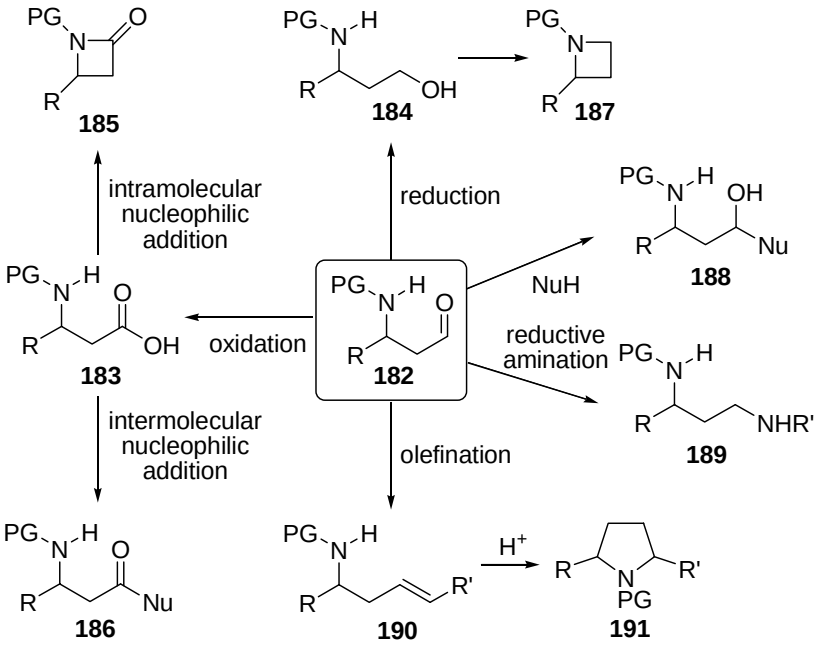
Figure 28. Paclitaxel (**180**) and Jasplakinolide (**181**) containing β-amino acids.

Although several synthetic approaches to these families of compounds have been reported, many of the conventional syntheses involve energy-intensive redox-processes and generate byproducts. In the present study, attention was focused on the preparation of β-amino carbonyls by using redox-neutral Ru-catalyzed hydration of propargylic amines.

[168] E. F., Kleinman *In Comprehensive Organic Synthesis*; Heathcock, C. H., Eds.; Pergamon Press: Oxford, UK, 1991; Vol. 2, Chapter 4, pp 893. b) M. Arend, B. Westermann, N. Risch *Angew. Chem.* **1998**, *110*, 1096; *Angew. Chem. Int. Ed*. **1998**, *37*, 1044.
[169] For reviews, see: a) E. Juaristi *Enantioselective Synthesis of β-Amino Acids*; Wiley-VCH: New York, 1997. b) M. Liu, M. P. Sibi *Tetrahedron* **2002**, *58*, 7991.
[170] For a review, see: R. W. Bates, K. Sa-Ei *Tetrahedron* **2002**, *58*, 5957.

6.3.1. Synthesis of β-Amino Aldehydes

As presented in Scheme 63, β-amino aldehydes **182** are particularly valuable because of the versatility of the carbonyl group, which can for example be easily oxidized to give β-amino acids **183,** or reduced to yield β-amino alcohols **184**. Subsequent intra- or intermolecular addition of a nucleophile to β-amino acids **183** afford lactams **185** or **186** derivatives, respectively. On the other hand, β-amino alcohols **184** can be further transformed into *N*-protected azetidines **187**.[171] Furthermore β-amino aldehydes represent very attractive substrates for the reaction with nucleophiles, giving 1,3-amino alcohols **188**, and they can also undergo reductive amination to provide 1,3-diamine **189**. The use of the carbonyl group in an olefination reaction will lead to homo-allylic amines **190** that can react under acidic conditions to afford proline analogues **191**.[172]



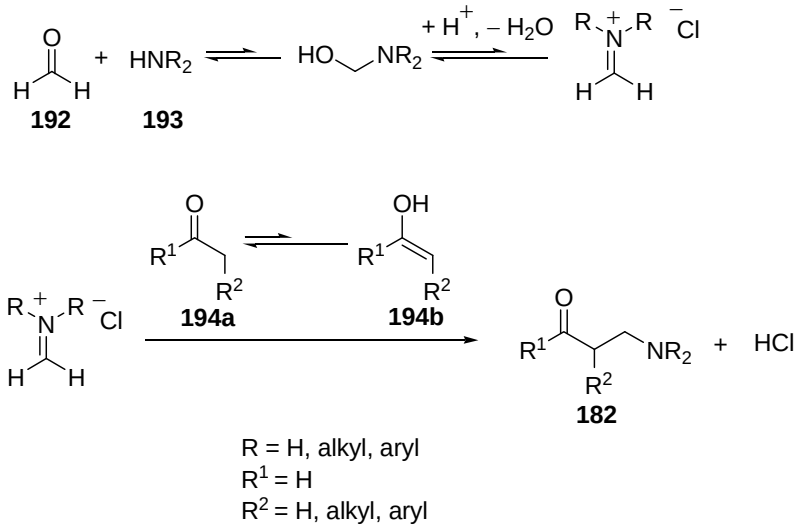
Scheme 63. Overview of the versatility of the formyl group of β-amino aldehydes **182**.

Despite this plethora of potential applications, β-amino aldehydes **182** have found limited use in synthesis unlike α-amino aldehydes whose use in synthesis is widespread and for which several reliable methods of synthesis are available.[173] This is mostly due to the lack of general methods for their preparation and to their reported instability. For example, problems in

[171] M. K. Ghorai, K. Das, A. Kumar *Terahedron Lett*. **2007**, *48*, 2471.
[172] S. R. Angle, D. S. Belanger *J. Org. Chem*. **2004**, *69*, 4361 and references cited therein.
[173] J. Jurczak, A. Golebiowski *Chem. Rev*. **1989**, *89*, 149.

synthesizing and using β-amino aldehydes include their tendency to undergo polymerization, self-condensation or elimination of the β-amino group.[174] Therefore, in both α- and β-amino aldehydes *N*-protection seems to be essential if extensive self condensation is to be avoided. However, the synthesis of remarkably stable unprotected amino aldehydes has been recently reported by YUDIN using unprotected aziridines as source of secondary amines.[175]

To date, the most common approach used for the synthesis of β-amino aldehydes is based on a MANNICH reaction.[168b,176] As shown in Scheme 64, this multi-component condensation of a nonenolizable aldehyde **192**, a primary or secondary amine **193** and an enolizable carbonyl compound **194** affords β-amino aldehyde **182**.



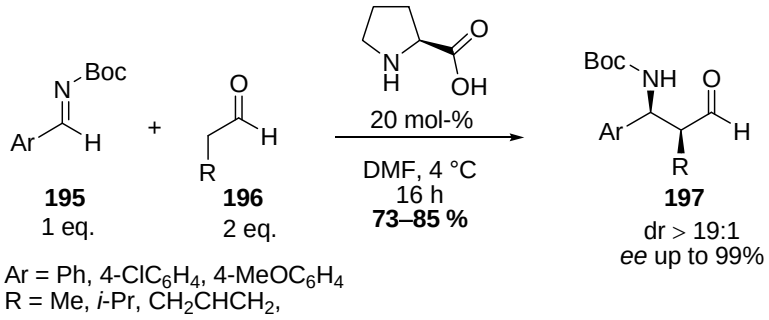
Scheme 64. MANNICH reaction between an imine **193** and an enol **194** to afford β-amino aldehyde **182**.

Later, extension of the MANNICH reaction to imines and esters, followed by reduction of the carboxylic groups (often carried out after conversion to the corresponding WEINREB-amide[177]) to the aldehydes provided a new way to access β-amino aldehydes.[178]

[174] For reports on this behavior, in the context of different synthetic approaches, see: a) A. Chesney, I. E. Markó *Synth. Commun.* **1990**, *20*, 3167. b) I. E. Markó, A. Chesney *Synlett* **1992**, 275. c) J.-L. Toujas, E. Jost, M. Vaultier *Bull. Chim. Soc. Fr.* **1997**, *134*, 713. d) A. J. Burke, S. G. Davies, A. C. Garner, T. D. McCarthy, P. M. Roberts, A. D. Smith, H. Rodriguez-Solla, R. J. Vickers *Org. Biomol. Chem*. **2004**, *2*, 1387.
[175] R. Hili, A. K. Yudin *J. Am. Chem. Soc*. **2006**, *128*, 14772.
[176] For pioneering studies, see: a) C. Mannich, W. Krosche *Arch. Pharm. (Weinheim, Ger.)* **1912**, *250*, 647. b) C. Mannich, B. Lesser, F. Silten *Chem. Ber*. **1932**, *65*, 378.
[177] a) F. A. Davis, M. B. Nolt, Y. Wu, K. R. Prasad, D. Li, B. Yang, K. Bowen, S. H. Lee, J. H. Eardley *J. Org. Chem.* **2005**, *70*, 2184. b) F. A. Davis, M. Song, A. Augustine *J. Org. Chem.* **2006**, *71*, 2779.
[178] See for example: a) F. A. Davis, J. M. Szewczyk *Terahedron Lett*. **1998**, *39*, 5951. For a synthesis based on an aza-Mannich reaction, see: b) X.-L. Hou, Y.-M. Luo, K. Yuan, L.-X. Dai, *J. Chem. Soc., Perkin Trans. 1* **2002**, 1487.

Recently, the first organocatalytic enantioselective MANNICH reactions between imines and unmodified aldehydes have been developed which afforded β-amino aldehydes with high enantiomeric excesses in a single step[179-180]

For example, CÓRDOVA reported the proline-catalyzed asymmetric MANNICH-reaction between *N*-protected imines **195** and unmodified aldehydes **196**.[179g] The reaction proceeded with excellent chemo- and enantioselectivities affording the corresponding *N*-Boc-protected β-amino aldehydes **197** in high yield with up to 99% ee (Scheme 65).

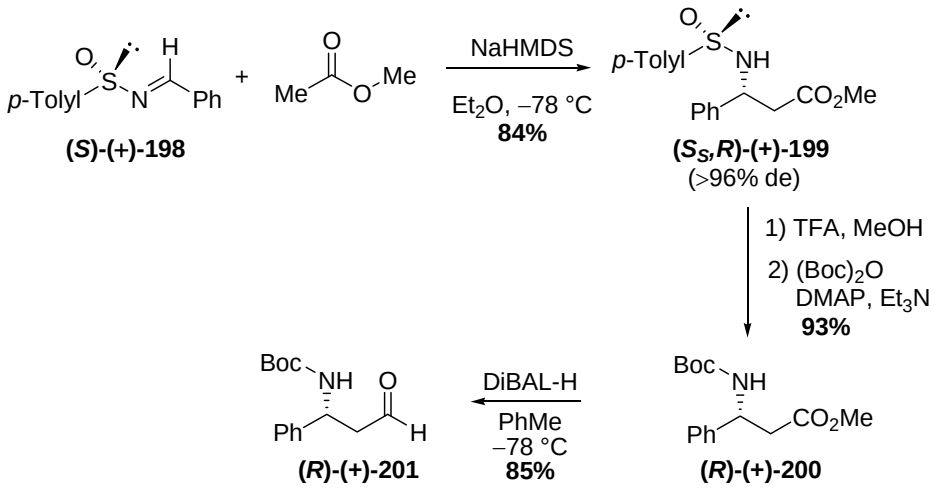


Scheme 65. Direct organocatalytic asymmetric MANNICH reactions between *N*-Boc protected imines **195** and aldehydes **196** by CÓRDOVA.

Moreover, DAVIS reported in 1998 the asymmetric synthesis of *N*-protected β-amino aldehydes **201** from sulfinimines **198**, by addition of the sodium enolate of methyl acetate (Scheme 66). Removal of the sulfinyl group of the resulting sulfinamide **199** and Boc-protection of the amine group afforded *N*-protected β-amino ester **200** in 93% yield**.** Finally, *N*-Boc β-amino aldehyde **201** was prepared by DIBAL-H reduction of **200** in toluene at –78 °C in 85% yield.[177a]

[179] a) A. Córdova, S. Watanabe, F. Tanaka, W. Notz, C. F. Barbas III *J. Am. Chem. Soc*. **2002**, *124*, 1866. b) A. Córdova, C. F. Barbas III *Tetrahedron Lett*. **2002**, *43*, 7749. c) Y. Hayashi, W. Tsuboi, I. Ashimine, T. Urushima, M. Shoji, K. Sakai *Angew. Chem.* **2003**, *115*, 3805; *Angew. Chem. Int. Ed.* **2003**, *42*, 3677. d) T. Kano, Y. Yamaguchi, O. Tokuda, K. Maruoka *J. Am. Chem. Soc.* **2005**, *127*, 16048. e) I. Ibrahem, A. Córdova *Chem. Comun*. **2006**, 1760. f) Y. Chi, S. H. Gellman *J. Am. Chem. Soc*. **2006**, *128*, 6804. g) J. Vesely, R. Rios, I. Ibrahem, A. Córdova *Tetrahedron Lett*. **2007**, *48*, 421. h) For a comprehensive review on the direct catalytic asymmetric Mannich reaction, see: A. Córdova *Acc. Chem. Res.* **2004**, *37*, 102.

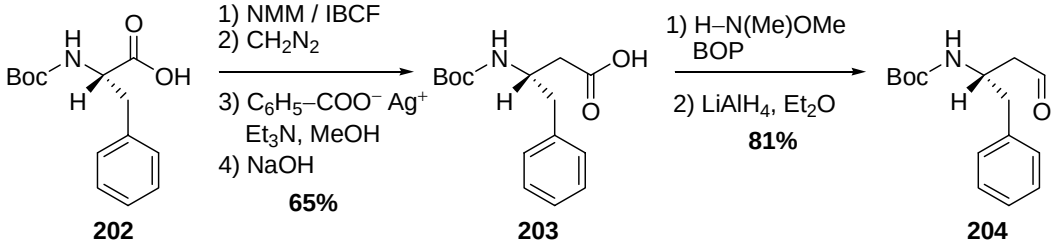
[180] For organocatalytic enantioselective conjugate additions of nitrogen nucleophiles to α,β-unsaturated aldehydes, see: a) Y. K. Chen, M. Yoshida, D. W. C. MacMillan *J. Am. Chem. Soc*. **2006**, *128*, 9328. b) I. Ibrahem, R. Rios, J. Vesely, G.-L. Zhao, A. Córdova *Chem. Commun*. **2007**, 849. c) P. Dinér, M. Nielsen, M. Marigo, K. A. Jørgensen *Angew. Chem.* **2007**, *119*, 2029; *Angew. Chem. Int. Ed*. **2007**, *46*,1983. d) J. Vesely, I. Ibrahem, R. Rios, G.-L. Zhao, Y. Xu, A. Córdova *Tetrahedron Lett*. **2007**, *48*, 2193.



Scheme 66. Synthesis of β-amino aldehydes **201** based on asymmetric MANNICH reaction by DAVIS.

N-Protected β-amino aldehydes have also been obtained from the corresponding α-amino acids, either through an ARNDT-EISTERT homologation/reduction sequence or by a chain elongation via nitrile addition and subsequent partial reduction.[174a,c,181] As shown in Scheme 67, an example of this homologation was reported by MARTINEZ in 1990. (L)-*N*-Boc-Phenylalanine **202** reacted under the classical ARNDT-EISTERT procedure to afford *N*-Boc-β–homo-L-Phe-OH **203** in 65% yield, which was then further converted into the corresponding WEINREB amide. $LiAlH_4$ reduction of the latter afforded the corresponding β-amino aldehyde **204** in 81% yield.[181a]

Furthermore, synthetic routes have been described which feature the conjugate addition of nitrogen nucleophiles to α,β-unsaturated aldehydes or amides as the key step.[182,183]



Scheme 67. Synthesis of the *N*-Boc-protected β-amino aldehyde **204** through an homologation step by MARTINEZ.

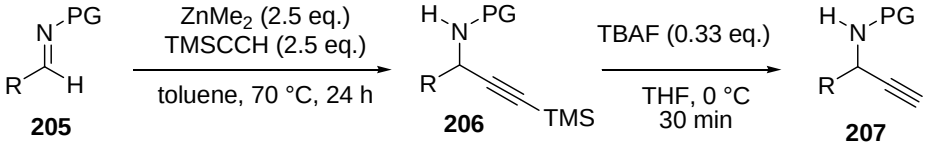
[181] a) M. Rodriguez, A. Aumelas, J. Martinez *Tetrahedron Lett*. **1990**, *31*, 5153. b) M. Rodriguez, A. Heitz, J. Martinez *Tetrahedron Lett.* **1990**, *31*, 7319. c) S. B. Davies, M. A. McKervey *Tetrahedron Lett.* **1999**, *40*, 1229. d) J.-L. Toujas, L. Toupet, M. Vaultier *Tetrahedron* **2000**, *56*, 2665.
[182] S. G. Davies, T. D. McCarthy *Synlett* **1995**, 700.
[183] For syntheses based on alternative approaches, see: a) L. Birkofer, L. Erlenbach *Chem. Ber.* **1958**, *91*, 2383. b) L. Birkofer, E. Frankus *Chem. Ber.* **1961**, *94*, 216. c) R. W. M. Aben, R. Smit, J. W. Scheeren *J. Org. Chem.* **1987**, *52*, 365. d) D. L. J. Clive, M. Yu, Z. Li *Chem. Commun.* **2005**, 906.

6.3.1.1. Hydration of N-Protected Propargylic Amines

As already mentioned above, this part of the present research work was dedicated to the application of the novel *in situ* generated catalysts **164** to the Ru-catalyzed hydration of propargylic amines, in order to gain direct access β-amino aldehydes **182**. Here, the idea behind applying hydration as catalytic heterofunctionalization reaction is to increase the atom-economy and efficiency of the synthetic route to β-amino aldehydes by reducing the number of energy- and waste-intensive redox steps.

The starting point for this research was provided by the recent findings by BOLM and co-workers, who reported the first $ZnMe_2$-mediated alkynylation of imines, providing access to a large array of *N*-protected propargylic amines.[184,185] It was anticipated that addition of TMS-acetylene to *N*-protected imines **205**, followed by removal of the silyl group, could be used to generate racemic terminal propargylic amines **207.** The results obtained are presented in Scheme 68 and in Table 15.[186]

Various *N*-protected imines **205a-i** were reacted with TMS-acetylene in the presence of $ZnMe_2$ in toluene at 70 °C. The alkynylation of aromatic *N*-sulfonyl and *N*-phosphinoyl aldimines **205a-g** proceeded smoothly (entries 1-7), affording the *N*-protected amines **206a-g** in 61-81% yield. Noteworthy, imines **205h-i** bearing α-branched alkyl groups such as cyclohexyl or *tert*-butyl were also good substrates for the reaction (entries 8-9).



Scheme 68. Synthetic approach to *N*-protected propargylic amines **207**.

Then, desilylation was achieved in high yields upon treatment of alkynes **206** with a substoichiometric quantity of tetrabutylammonium fluoride in THF at 0 °C. Only compounds **207b** and **207f** furnished the corresponding products in diminished yields of 55% and 41%, respectively (entries 2 and 6).

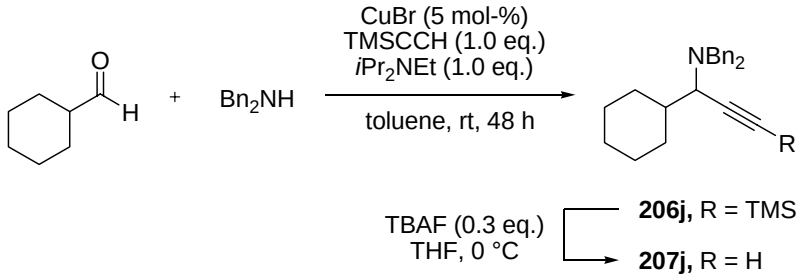
[184] a) L. Zani, S. Alesi, P. G. Cozzi, C. Bolm *J. Org. Chem.* **2006**, *71*, 1558. b) L. Zani, T. Eichhorn, C. Bolm *Chem. Eur. J.* **2007**, *13*, 2587. c) L. Zani *Dissertation*, RWTH, Aachen, **2006**.
[185] For a review on the metal-mediated alkynylation of imines, see: L. Zani, C.Bolm. *Chem. Commun.* **2006**, 4267.
[186] All the experiments reported in Table 15 were performed by Dr. LORENZO ZANI.

Table 15. $ZnMe_2$-mediated alkynylation of imines and subsequent desilylation to afford *rac*-propargylic amines **207**.

entry	substrate	R	PG	yield of **206**[a] (%)	yield of **207**[b] (%)
1	**205a**	Ph	Ts	60	85
2	**205b**	Ph	$P(O)Ph_2$	78	55
3	**205c**	4-MePh	Ts	81	90
4	**205d**	4-MeOPh	Ts	76	79
5	**205e**	2-BrPh	Ts	77	94
6	**205f**	2-Naph	Ts	70	41
7	**205g**	2-Furyl	Ts	61	85
8	**205h**	Cy	Ts	74	90
9	**205i**	*t*-Bu	Ts	81	99

a) Reaction conditions: imine **205** (2.0 mmol), trimethylsilylethine (5.0 mmol), dimethylzinc (5.0 mmol, 2.0 M in toluene), toluene (17.5 mL), 70 °C, 24 h. b) Reaction conditions: 1-trimethylsilyl propargylic amine **206** (1.00-1.56 mmol), TBAF (0.33-0.52 mmol, 1.0 M in THF), dry THF (5.0-7.8 mL), 0 °C, 30 min.

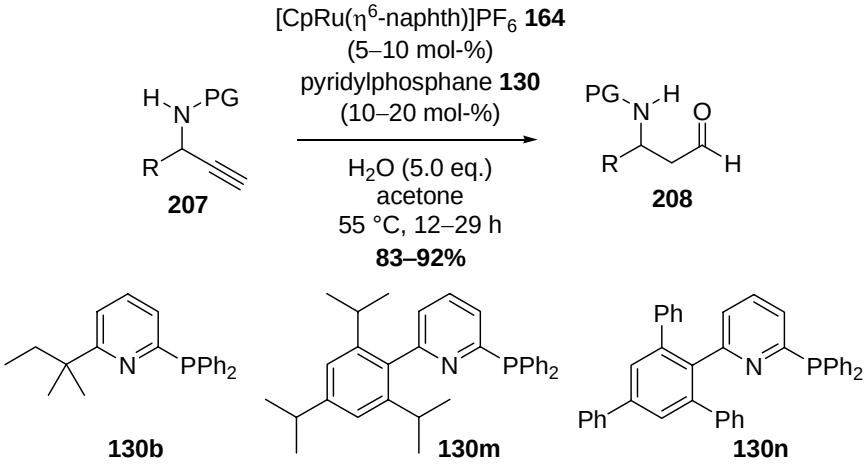
In addition, in order to assess the applicability of a substrate bearing a more basic nitrogen atom in the following hydration reaction, the known terminal propargylamine **207j**, having two benzyl groups on the nitrogen atom, was prepared according to a procedure reported by KNOCHEL (Scheme 69).[187]



Scheme 69. Preparation of compound **207j** according to KNOCHEL.

[187] N. Gommermann, P. Knochel *Tetrahedron* **2005**, *61*, 11418.

These propargylic amines were then used as substrates for the Ru-catalyzed hydration reaction (Scheme 70).



Scheme 70. Ruthenium-catalyzed anti-MARKOVNIKOV hydration of propargylic amines **207**.

In the first set of experiments, the three 6-substituted pyridylphosphanes **130a**, **130m** and **130n,** which showed the highest activity in the previous kinetic studies (see chapter 5.2) were chosen as ligands. The reactions were performed with 5.0 eq. of water at 55 °C.

The results of the ruthenium-catalyzed hydration of propargylic amines **207** are summarized in Table 16.

All substrates bearing *N*-tosyl groups reacted smoothly under the influence of the ruthenium catalyst (entries 1, 3-10) affording the corresponding terminal aldehydes in high yields (83-92%). Unfortunately, alkyne **207b** carrying the diphenylphosphinoyl-protecting group was completely decomposed under standard reaction conditions (entry 2). Also, N,N-dibenzyl propargylamine **207j** did not react, but was recovered unchanged even after more than five days (entry 11).

Interestingly, use of only 3.0 and 5.0 mol-% of the *in situ* generated ruthenium catalyst still gave protected β-amino aldehydes in moderate to good yields (36-78%, entries 12-16). However, a substantial increase in the reaction time was required (≥ 40 h) and none of the reactions showed full consumption of the starting material.

Table 16. Ruthenium-catalyzed anti-MARKOVNIKOV hydration of propargylic amines **207** into β-amino aldehydes **208**.[a]

entry	alkyne	R	ligand	[Ru] (mol-%)	time (h)	aldehyde (%) [conv.][b]
1	**207a**	Ph	**130m**	10	17	83 [100]
2	**207b**	Ph	**130b/m**	10	>130	n.d.
3	**207c**	4-MePh	**130m**	10	29	83 [100]
4	**207d**	4-MeOPh	**130m**	10	15	83 [100]
5	**207e**	2-BrPh	**130m**	10	17	84 [100]
6	**207f**	2-Naph	**130n**	10	19	85 [100]
7	**207g**	2-Furyl	**130b**	10	22	90 [100]
8	**207h**	Cy	**130b**	10	15	91 [100]
9	**207i**	*t*-Bu	**130m**	10	20	85 [100]
10	**207i**	*t*-Bu	**130n**	10	12	92 [100]
11	**207j**	Cy	**130b/m**	10	>130	0
12	**207a**	Ph	**130m**	5	60	48 [55]
13	**207d**	4-MeOPh	**130m**	3	60	36 [40]
14	**207e**	2-BrPh	**130m**	5	40	78 [90]
15	**207g**	2-Furyl	**130b**	3	60	48 [53]
16	**207i**	*t*-Bu	**130m**	5	90	77 [90]

a) Reation conditions: propargylic amine **207** (0.10 mmol), $[CpRu(\mathbf{130})_2(CH_3CN)]PF_6$ (5-10 mol-%), H_2O (0.50 mmol), acetone (0.7 mL), 55 °C. b) Yields of isolated products; conversion determined by NMR analysis.

It should be noted that all product aldehydes were solids amenable to purification by standard flash column chromatography on silica gel. Moreover, they could be stored for several weeks at room temperature without decomposition. This observation is in sharp contrast with the previously reported instability of various other *β*-amino aldehydes.

6.3.1.2. Hydration of N-Protected Propargylic Amines under Microwave Irradiation

Microwaves (MW) are constituted by an electromagnetic radiation, occurring at frequencies between 0.3 - 300 GHz. The domestic microwave ovens, as well as the laboratory microwave

reactors function at 2.45 GHz (wavelength of 12.24 cm). At this frequency, the energy of a microwave photon is 0.0016 eV which is too low to break chemical bonds. From this follows, that in contrast to UV radiation and radiation of the visible spectrum, microwaves cannot induce chemical reactions by direct absorption of energy.[188]

Microwave chemistry generally relies on the ability of the reaction mixture to efficiently absorb energy, taking advantage of "microwave dielectric heating" phenomena such as dipolar polarization or ionic conduction mechanisms. Through microwave irradiation, the ions or dipoles in a sample align themselves according to the electromagnetic field. This field oscillates and the dipoles or ions try to reorient themselves along the oscillating field. This in turn releases heat through molecular friction and dielectric loss. In most cases this means that the solvent used for a particular transformation must be microwave absorbing. The ability of a specific solvent to convert microwave energy into heat at a given frequency and temperature is determined by the so-called loss tangent (tan δ), expressed as the quotient, tan $\delta = \varepsilon'' / \varepsilon'$, where ε'' is the dielectric loss, indicative of the efficiency with which electromagnetic radiation is converted into heat, and ε' is the dielectric constant, describing the ability of molecules to be polarized by the electric field. A reaction medium with a high tan δ at the standard operating frequency of a microwave synthesis reactor (2.45 GHz) is required for good absorption and, consequently, efficient heating.

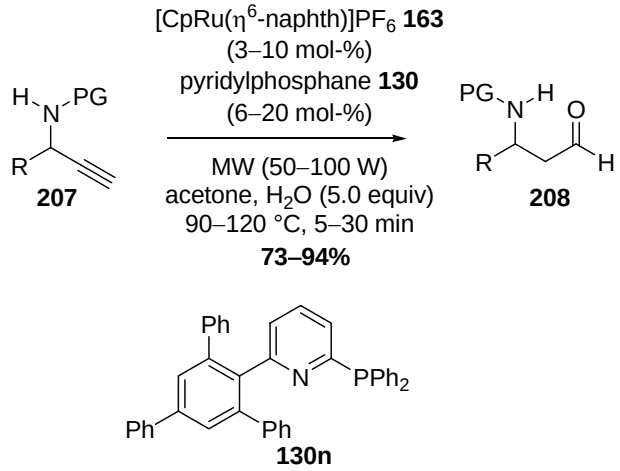
In general, solvents used for microwave synthesis can be classified as high (tan $\delta > 0.5$), medium (tan δ 0.1-0.5), and low microwave-absorbing (tan $\delta < 0.1$). Microwave synthesis in low-absorbing or microwave-transparent solvents is often not feasible unless either the substrates or some of the reagents/catalysts are strongly polar and therefore microwave-absorbing, raising the overall dielectric properties of the reaction medium to a level that allows sufficient heating by microwaves. Water can be considered only as a medium microwave-absorbing solvent with a loss tan δ of 0.123.

Microwaves are known to accelerate various organic reactions, such as metal-catalyzed cross-coupling processes, nucleophilic aromatic substitutions, cycloadditions.[188]188[b,c] Microwave heating has already been utilised in some total syntheses of natural products, such as the synthesis of (+)-Plicamine by LEY in 2002 which combined polymer-supported reagents with

[188] a) A. Loupy *Microwaves in Organic Synthesis* Eds.: Wiley-VCH: Weinheim, 2002. b) P. Lidström *Microwave-Assisted Organic Synthesis* Eds.: J. P. Tierney, Blackwell, Oxford, 2004. c) C. O. Kappe, A. Stadler *Microwaves in Organic and Medicinal Chemistry* Eds.: Wiley-VCH: Weinheim, 2005.

microwave heating.[189] Recently, BOLM has shown that organocatalytic processes can also benefit from microwave irradiation.[190]

According to the criteria of acceleration of chemical reactions through microwave irradiation, the Ru-catalyzed hydration of alkynes seemed to be an ideal candidate since it required activation of water. Although the thermally induced catalytic hydration of propargylic amines **207** reported above allowed in most cases to prepare the desired β-amino aldehydes **208** in high yield, it still required heating of the reaction mixture at 55 °C for a prolonged time, generally longer than 15 hours. Microwave heating has been demonstrated to be a useful tool for drastically shortening the duration of thermally induced reactions by simply achieving high reaction temperatures in closed vessels under pressure. Thus, its effect on the Ru-catalyzed anti-MARKOVNIKOV alkyne hydration, employing complex [CpRu(η^6-naphthalene)]PF_6 **163** as the metal precursor and **130n** as the ligand was examined (Scheme 71).



Scheme 71. Ruthenium-catalyzed hydration of alkynes **207** under microwave irradiation.

All the experiments were carried out in a microwave oven designed for laboratory use with rigorous control of temperature, pressure and reaction time and with simultaneous cooling of the reaction mixture to sub-ambient temperatures, as shown in Figure 29.

[189] a) I. R. Baxendale, S. V. Ley, C. Piutti *Angew. Chem.* **2002**, *114*, 2298; *Angew. Chem. Int. Ed.* **2002**, *41*, 2194. b) I. R. Baxendale, S. V. Ley, M. Nessi, C. Piutti *Tetrahedron* **2002**, *58*, 6285.
[190] B. Rodriguez, C. Bolm *J. Org. Chem.* **2006**, *71*, 2888.

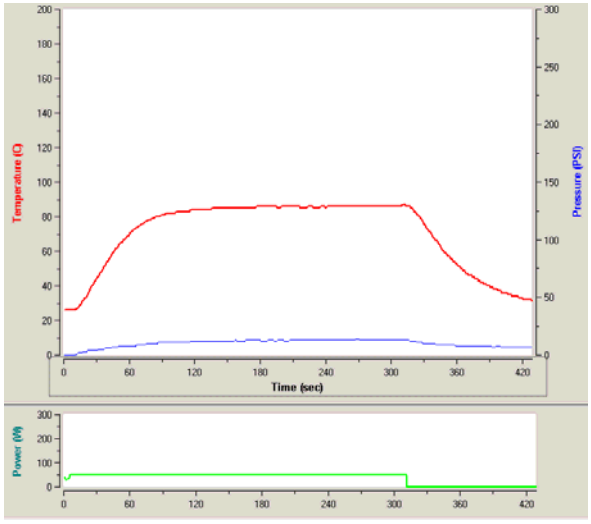


Figure 29. Ru-catalyzed hydration of **207** under MW irradiation. Upper curve: temperature in the reaction vessel; lower curve: power of irradiation.

In an initial set of experiments, optimization of the reaction conditions was established with the alkyne **207c** as the substrate (Table 17, entries 1-5). Then, the scope of the *N*-protected propargylic amine **207** as substrates for the hydration under microwave irradiation was examined.

Table 17. Ruthenium-catalyzed hydration of propargylic amines **207** under MW irradiation

entry	alkyne	R	P (W) / T (°C)	[Ru] (mol-%)	time (min)	aldehyde (%)[conv.][b]
1	**207c**	4-MePh	75 / 120	-	120	0
2	**207c**	4-MePh	50 / 90	10	5	92 [100]
3	**207c**	4-MePh	50 / 90	5	30	94 [100]
4	**207c**	4-MePh	100 / 120	3	120	31 [67]
5	**207c**	4-MePh	75 / 120	2.5	120	Traces
6	**207e**	2-BrPh	75 / 100	5	15	79 [100]
7	**207f**	2-Naph	75 / 115	5	20	76 [100]
8	**207g**	2-Furyl	50 / 90	10	30	88 [100]
9	**207h**	Cy	75 / 100	5	15	92 [100]
10	**207h**	Cy	75 / 115	3	20	80 [100]
11	**207i**	*t*-Bu	75 / 100	5	15	73 [100]

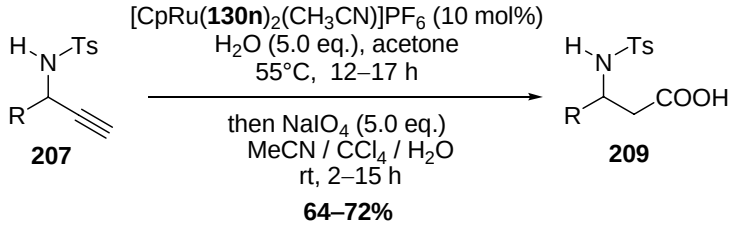
a) Reaction conditions: *N*-tosyl propargylic amines **176** (0.10 mmol), [CpRu(**118o**)$_2$(CH$_3$CN)]PF$_6$ (2.5-10 mol-%), H$_2$O (0.50 mmol), acetone (0.7 mL), temperature (90-120 °C), constant microwave irradiation of 50-75 W, simultaneous air cooling (1.4-4.0 bar, 10 psi), 5-30 min. b) Yields of isolated products; conversion determined by NMR analysis.

First, the test reaction was conducted in the absence of catalyst and product formation was not observed. This result demonstrated that metal catalysis was necessary for the hydration to occur and that the reaction could not be induced by simple microwave irradiation. With 10 mol-% of catalyst, the reaction was found to give 92% yield of the product after only 5 minutes (entry 2). In the presence of only 5.0 mol-% of catalyst roughly the same yield of **208c** was obtained after 30 min, but further reduction of the catalyst loading was not possible without significant decrease of the yields (entries 3-5), even after application of longer reaction times (up to 2 h), higher temperatures (up to 120 °C) and higher power of the MW (up to 100 W).

Various *N*-tosyl propargylamines afforded the corresponding aldehydes **208** in good to high yields (73-92%), often requiring a smaller amount of catalyst in comparison with the thermal reaction and in every case with no reaction time exceeding 30 min (entries 6-11).

6.3.2. Synthesis of rac-β-Amino Acids

In this study, the possibility of directly converting the amines **207** into *rac*-β-amino acids **209** by means of a Ru-catalyzed one-pot hydration/oxidation procedure was envisaged as a new straightforward route to such compounds. This transformation was inspired by various protocols for the oxidation of aldehydes into carboxylic acids using $RuCl_3$ as a catalyst in the presence of a stoichiometric oxidant.[191]

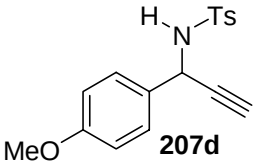
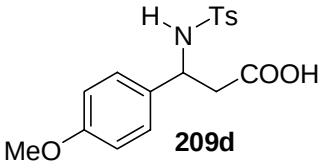
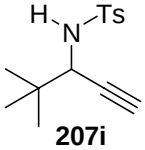
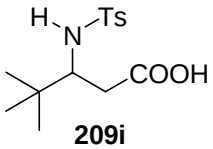


Scheme 72. Preparation of *rac*-β-amino acids **209** from *N*-tosyl amines **207** by a one-pot hydration/oxidation procedure.

[191] a) J. N. Desrosiers, A. Coté, A. B. Charrette *Tetrahedron* **2005**, *61*, 6186. b) A. Y. Koposov, R. R. Karimov, A. A. Pronin, T. Skrupsakaya, M. S. Yusubov, V. V. Zhdankin *J. Org. Chem.* **2006**, *71*, 9912. c) S. Roth, C. B. W. Stark *Angew. Chem.* **2006**, *118*, 6364; *Angew. Chem. Int. Ed.* **2006**, 45, 6218. d) B. Plietker, M. Niggemann *J. Org. Chem.* **2005**, *70*, 2402. e) G. Palmisano, I. Dosi, D. Monti, R. Pellegata *J. Chem. Soc., Perkins Trans. 1* **1990**, 1875.

Indeed, hydration of propargylamines **207** with the *in situ* generated Ru-catalyst **164n** under standard conditions, followed by removal of acetone and replacement with the typical MeCN / CCl_4 / H_2O solvent mixture and addition of sodium periodate ultimately led to formation of β-amino acids **209** in good yields over two steps (Scheme 72). The results of the one-pot hydration/oxidation procedure to yield *rac*-β-amino acids **209** are summarized in Table 18.

Table 18. Preparation of a *rac*-β-amino acids **209** from *N*-tosyl amines **207** by a one-pot hydration/oxidation procedure.[a]

entry	substrate	$time_{HYD}$ (h)	$time_{OX}$ (h)	product	yield (%)
1	 **207d**	12	2	 **209d**	64
2	 **207i**	17	15	 **209i**	72

a) Reaction conditions for the hydration: *N*-tosyl amines **207** (0.10 mmol), [CpRu(**130n**)$_2$(CH_3CN)]PF_6 (10 mol-%), H_2O (0.50 mmol), acetone (0.7 mL), 55 °C; reaction conditions for the oxidation: evaporation of acetone followed by addition of CH_3CN / CCl_4 / H_2O (1:1:1.3 mL)), $NaIO_4$ 99% (0.4 mmol), rt.

The oxidation of the *in situ* formed aldehyde **208d** was finished within two hours (TLC control) at room temperature, and afforded β-amino acid **209**n 64% yield over two steps (entry 1). In the case of aldehyde **208** (entry 2), however, stirring overnight was required to give β-amino acid **209i** in 72% yield over the two steps.

6.3.3. Synthesis of *rac*-1,3-Amino Alcohols

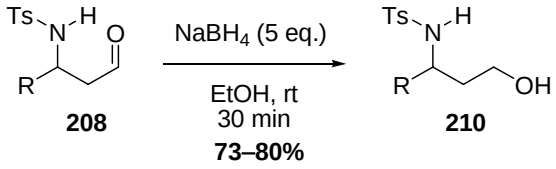
Aminoalcohols have a rich history in asymmetric organic synthesis.[170,192] While frequently overlooked in favour of the more common 1,2-aminoalcohols, in the last decades, a wide variety of 1,3-aminoalcohols has been extensively used to achieve asymmetric induction in organic synthesis, both as chiral ligands and auxiliaries. The principal advantage of these

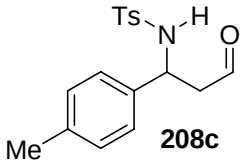
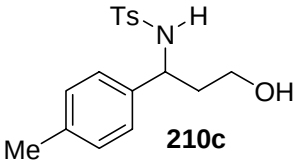
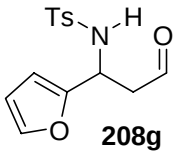
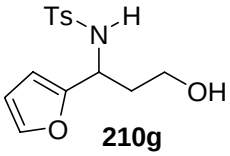
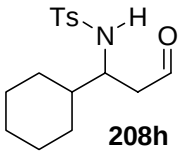
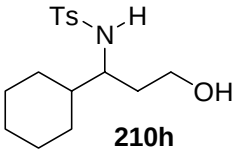
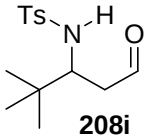
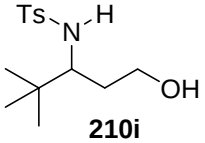
[192] For reviews, see: a) S. M. Lait, D. A. Rankic, B. A. Keay *Chem. Rev*. **2007**, *107*, 767.

compounds is their great flexibility due to the presence of two heteroatoms; one or both can be bound to a transition metal, Lewis acid or prochiral starting material. Some 1,3-aminoalcohols are derived from natural products such as camphor, menthol, and sugars while others are entirely synthetic in nature. Consequently, they range from small linear compounds to multicyclic structures and heterocyclic derivatives.

With the various *rac*-β-amino aldehydes **208** in hand, the possibility of directly converting amines **207** into 1,3-aminolacohols was envisaged. Guided by classical protocols for the reduction of carbonyl compounds into primary alcohols using an excess of $NaBH_4$, the synthesis of *rac*-1,3-aminoalcohols **210** was achieved within 30 min in ethanol at room temperature. As shown in Table 19, the reaction of various aldehydes **208** bearing either alkyl, furyl, cyclohexyl, or aryl groups at the C_1 position furnished the corresponding aminoalcohols **210** in good yields (73-80%).

Table 19. Preparation of a *rac*-1,3-aminoalcohols **210** by $NaBH_4$ reduction of β-amino aldehydes **208**.[a]



entry	substrate 208	time (min)	product 210	yield of 210 (%)
1	 **208c**	30	 **210c**	74
2	 **208g**	30	 **210g**	80
3	 **208h**	30	 **210h**	80
4	 **208i**	30	 **210i**	73

a) Reaction conditions for reduction: β-amino aldehydes **208** (0.15 mmol), $NaBH_4$ (0.75 mmol), EtOH (4 mL), rt, 30 min.

7. Summary and Outlook

In the present work, the development of new catalysts for anti-MARKOVNIKOV hydration of terminal alkynes and application of the latter reaction in atom-economic organic synthesis was inestigated. First, new aza-pyridylphosphanes **130** to be used as ligands in the anti-MARKOVNIKOV hydration of terminal alkynes were synthesized (Figure 30).

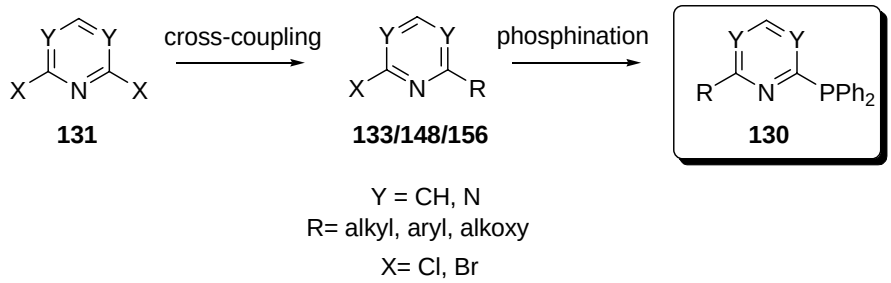
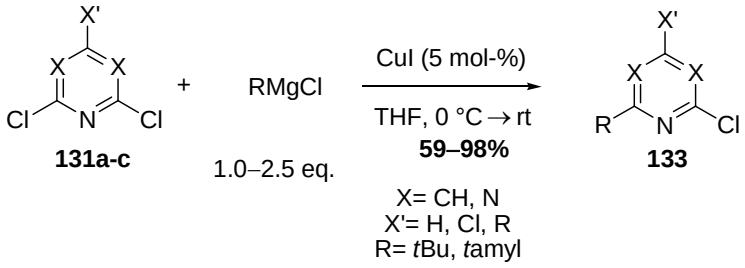


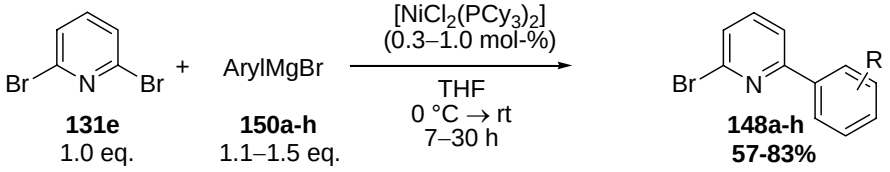
Figure 30. Synthetic approach of aza-pyridylphosphanes **130**.

A new route to bulky alkyl-substituted aza-aryl chlorides **133** has been developed using a selective copper-catalyzed cross coupling reaction of aza-aryl halides **131a-c** with tertiary alkyl GRIGNARD-reagents (Scheme 73). Depending on the reaction conditions, selective mono- or dialkylation can be achieved with poly-halogenated pyrimidines, triazines or quinolines. The remaining carbon-chlorine bond of products **133** is then still available for further functionalization, like transition metal catalyzed cross-coupling reactions or nucleophilic substitution with heteronucleophiles.



Scheme 73. Copper-catalyzed alkylation of aza-arenes **133a-c**.

Furthermore, a Ni-catalyzed mono-selective cross-coupling reaction of 2,6-dibromopyridine **131e** with aryl GRIGNARD-reagents was used to prepare mono-substituted pyridine derivatives **148a-h** (Scheme 74).



Scheme 74. Nickel-catalyzed arylation of 2,6-dibromopyridine **131e**.

Thus, a high degree of structural diversity could be introduced in a single synthetic step starting from readily available precursors. The use of appropriate GRIGNARD-reagents allowed several different substituents to be introduced at the C-2-position of the pyridine unit.

In order to access the desired aza-arylphosphanes **130**, the 6-halogenated aza-aryls **133** and **148** prepared as described above were then subjected to nucleophilic phosphination by reaction of the remaining halogen with sodium diphenylphosphide.

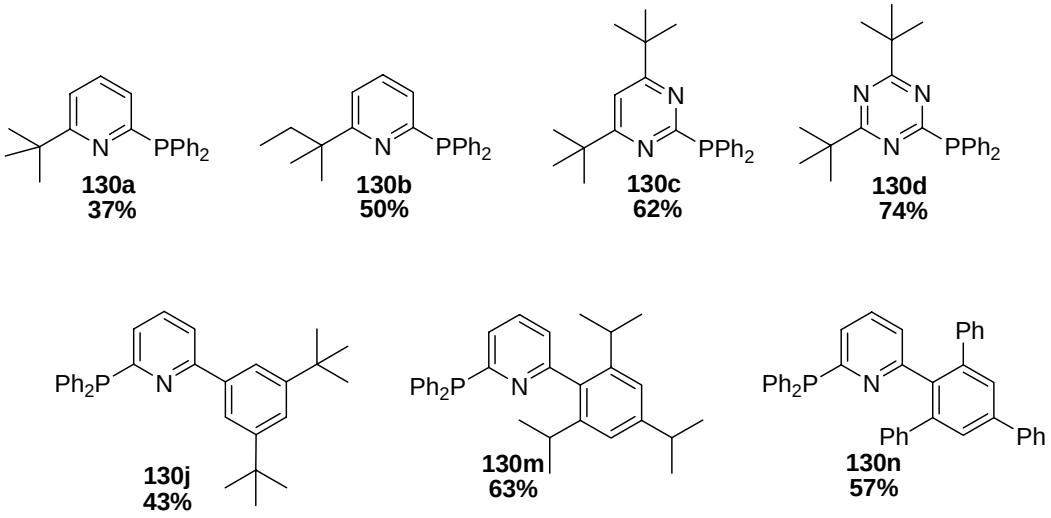


Figure 31. Aza-pyridylphosphanes **130** (over two steps yields).

A straightforward and modular approach comprising only two synthetic steps was developed for the synthesis of various aza-arylphosphanes **130a-o**, allowing the easy preparation of a library of sterically and electronically variable compounds (Figure 31). Additionally this new synthetic sequence afforded good to excellent overall yields. Starting from commercially available precursors **131**, the desired target compounds are readily available in gram amounts, the only precautions needed being the use of anhydrous solvents and an inert atmosphere. In view of the importance of aza-arenes phosphane as ligands for metal-catalyzed catalysis, the main goal in the future, with regard to the results presented in the present work, is to extend this ligand class to aza-arylphosphanes bearing different diarylphosphanes or even more basic

dialkylphosphanes. These compounds should be accessible via the synthetic pathway presented in this work by nucleophilic addition with different R_2PNa (with R = alkyl, aryl).
The compounds **130** were subsequently employed as ligands in the Ru-catalyzed hydration of terminal alkynes (Sections 5 and 6). However, it is expected that extensive screening of such a library of compounds will identify further applications for aza-arylphosphanes as ligands in metal-catalysed reactions.
The reaction of [CpRu(η^6-naphthalene)]PF_6 (**163**) and aza-arylphosphane ligands **130** has been investigated in solution, and the products have been analyzed by NMR-spectroscopy and mass spectromety. In the presence of two equivalents of an aza-arylphosphane, complexes of general formula [CpRu$(L)_2(CH_3CN)]PF_6$ **164** were formed (Figure 32).

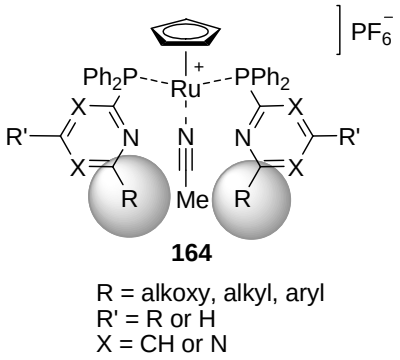
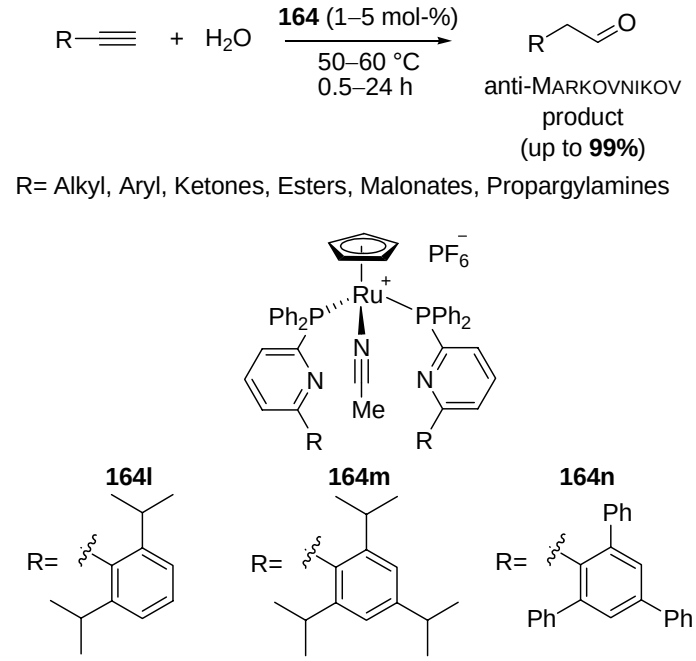


Figure 32. Formation in solution of complexes **164**.

These *in situ* generated complexes can be used as catalysts for the anti-MARKOVNIKOV hydration of terminal alkynes. The short time necessary for the exchange reaction render this methodology convenient to screen a wide range of these complexes in catalytic applications. Kinetic studies (Section 5.2) revealed the importance of the steric size at the C-6 position of the aza-aryl ring. Ultimately, this led to the identification of catalyst **164n** as the most active catalyst currently known for the anti-MARKOVNIKOV hydration of terminal alkynes.

The use of *in situ* generated catalysts **164** for the anti-MARKOVNIKOV hydration of various terminal alkynes has been successfully developed (Scheme 75). In comparison with the previous methodology, the new procedure is straightforward and allows tuning of the catalyst. Thus, the bulky 6-aryl-pyridylphosphane ligands **130l-n** performed very well in the hydration even with a low catalyst loading, and gave catalysts that were more robust towards oxygen than catalysts based on ligands **130a/b**. In addition, the substrate scope of alkyne hydration has been extended including functional groups such as ketones, esters and malonates.



Scheme 75. Ru-catalyzed anti-MARKOVNIKOV hydration of terminal alkynes with catalysts **164l-n**.

In addition, straightforward routes to β-amino carbonyl compounds have been developed by means of easy access to *N*-protected propargylic amines **207** followed by a redox-neutral Ru-catalyzed anti-MARKOVNIKOV hydration of the terminal alkyne. The operational simplicity, practicability and mild conditions of the hydration render this an attractive approach for the generation of different β-amino aldehydes **208** and their derivatives. In contrast with previously reported syntheses of β-amino aldehydes, which all used a reduction/oxidation sequence, the use of the alkynylation/hydration methodology is an elegant redox-neutral alternative. In addition, the first Ru-catalyzed anti-MARKOVNIKOV hydration of terminal alkynes under conditions of microwave (MW) irradiation has been described. Microwave heating reduced the reaction times from several hours of the thermal reaction to minutes.

Finally a novel one-pot hydration/oxidation process has been developed, which provides direct access to *rac*-β-amino acids **209** from propargylamines **207** in good overall yields.

In view of the importance of enantiopure β-amino carbonyls as intermediates and building blocks for organic synthesis, the main goal in the future, with regard to the results presented in the present work, is to carry out such processes starting from enantiomerically pure compounds and to ensure that no racemisation takes place during the hydration reaction.

8. Experimental Section

8.1. General Remarks

All the synthetic operations including reactions, work-ups and chromatographic separations were carried out in a well ventilated hood according to the current safety dispositions.
All reactions involving air- or moisture-sensitive compounds were carried out under argon using standard Schlenk and vacuum line techniques.[193] The glassware employed for those manipulations was oven-dried, and then cooled under argon. Reagents and solvents were transferred under argon using cannulae or syringes. Labile chemicals were kept in a Glovebox or refrigerator, and stored under argon.

8.1.1. Solvents

Solvents for anhydrous reactions were dried and purified according to standard techniques.[194]

- Dichloromethane: Simple distillation followed by distillation from CaH_2 under argon.
- Diethyl ether: Predried over KOH, filtered through Al_2O_3 and distilled from sodium-benzophenone ketyl radical under argon.
- Tetrahydrofuran: Predried on over KOH, filtered through Al_2O_3 and distilled from sodium-benzophenone ketyl radical under argon.
- Toluene: Distillation from sodium-benzophenone ketyl radical under argon.

Ethyl acetate (EtOAc), diethyl ether (Et_2O), petroleum ether, *n*-hexane (Hex), *n*-pentane and *tert*-butylmethylether (MTBE) for flash column chromatography were distilled before use. N,N-Dimethylformamid (*Merck*) and *n*-hexane were dried over molecular sieves 4Å before use. Acetone (*Acros*), MeOH (*Merck, Riedel-de Häen*), 1,2-dichloroethane (*Riedel-de Häen*), DMSO (*Merck*) and acetonitrile (*Roth*, *Promochem*) were HPLC- or reagent grade and were used as received.

[193] D. F. Shriver, M. D. Drezdzon *The Manipulation of Air-Sensitive Compounds*, Wiley, Chichester, 1986.
[194] W. L. F. Armarego, D. D. Perrin *Purification of Laboratory Chemicals*, Butterworth-Heinemann, Oxford, 1996.

8.1.2. Chemicals

All the reagents employed were purchased from commercial suppliers (*Acros, Sigma-Aldrich, Fluka, Lancaster, Merck, Riedel-de Häen* and *Strem*) and were used as received without further purification. $RuCl_3$ was kindly donated by *Umicore*.

8.1.3. Analytics Methods

❖ *NMR-Spectroscopy*

The coupling constants *J* are given in Hertz, and the following abbreviations are used to describe the signals observed: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, se = sextet, hept = heptuplet, m = multiplet, br = broad signal, vt = virtual triplet.

^{1}H-NMR-Spectroscopy: ^{1}H-NMR spectra were recorded at room temperature on a *Varian Gemini 300* spectrometer (300 MHz) or *Varian Inova 400* spectrometer (400 MHz). The chemical shifts are given in ppm relative to tetramethylsilane (TMS, δ = 0.00 ppm) as internal standard, or referenced to residual solvent signals (acetone: δ = 2.09 ppm; acetonitrile: δ = 1.94; benzene: δ = 7.18 ppm; chloroform: δ = 7.26 ppm; methanol: δ = 3.34 ppm).

^{13}C-NMR-Spectroscopy: ^{13}C-NMR spectra were recorded either on a *Varian Gemini 300* spectrometer (75 MHz) on a *Varian Inova 400* spectrometer (100 MHz). The chemical shifts are given in ppm using tetramethylsilane (TMS, δ = 0.00 ppm) as internal standard, or relative to deuterated solvent signals (acetone: δ = 29.8/206.2 ppm; acetonitrile: δ = 1.32/118.2 ppm; benzene: δ = 127.6 ppm; chloroform: δ = 77.0 ppm).

^{31}P-NMR-Spectroscopy: ^{31}P-NMR spectra were recorded either on a *Varian Gemini 300* spectrometer (121 MHz) on a *Varian Inova 400* spectrometer (160 MHz). The chemical shifts are given in ppm relative to H_3PO_4 as external standard.

❖ *IR Spectroscopy*

IR spectra were measured on a *Perkin-Elmer* PE 1760 FT spectrometer as KBr pellets or neat (in case of liquid compounds). Only characteristic absorption bands are reported. Absorptions are given in wavenumbers (cm^{-1}). The following abbreviations are used to describe the relative intensities of the signals observed: w = weak, m = medium, s = strong.

❖ *Mass Spectrometry*

Mass spectra were recorded on a *Varian* MAT 212 or on a *Finnigan* MAT 95 spectrometer with either EI (electronic impact) or CI (chemical impact) ionization, at a 70 eV ionization potential. Peaks are listed according to their *m/z* value. High resolution mass spectra (HRMS) were recorded on a *Finnigan* MAT 95 spectrometer.

❖ *Gas Chromatography (GC)*

Gas chromatographic analyses were performed on a Hewlett-Packard 5890 Series II gas chromatograph equipped with a split mode injection system, a FID detector with mechanical pressure control and a G2913A autoinjector. The stationary phase was an Ultra 2 column from Hewlett-Packard. Pre-columns were FS-Phenyl-Sil columns (*Chromatographie Service GmbH*).

❖ *GC-MS*

GC-MS measurements were conducted with the following instrument: GC (HP 6890 Series), MSD 5973. Column: HP-5 MS (30 m × 0.25 mm × 0.25 μm). Carrier gas: He, constant flow 200 °C.

❖ *Elemental Analysis*

Elemental analyses were performed on a *Heraeus* CHN-O-Rapid instrument. All values are given as mass percentages.

❖ Melting Point

Melting Points were measured in open glass capillaries with a *Gallenkamp* apparatus, equipped with a metal-block heating and a digital thermometer.

8.1.4. Chromatography

❖ *Preparative Column Chromatograpy*

Purifications by Flash Column Chromatography were carried out in glass columns (10 mm-10 cm diameter) according to STILL,[195] using *Merck* silica gel 60, particle size 0.040-0.063 mm (230-400 mesh).

❖ *Thin Layer Chromatography (TLC)*

Support: TLC aluminum sheets silica gel 60 F_{254} (*Merck*) with a fluorescent indicator.

Detection: 1) exposition to UV-light (λ = 254 nm).

2) treatment with an acidic aqueous solution of ammonium molibdate tetrahydrate $[(NH_4)_6Mo_7O_{24}]\cdot 4H_2O$ and cerium sulfate tetrahydrate $[Ce(SO_4)]\cdot 4H_2O$ (Mostain).

3) treatment with a basic aqueous solution of potassium permanganate ($KMnO_4$+Na_2CO_3).

8.1.5. Compounds Prepared Following Literature Procedures

The following substances were prepared according to literature procedures: 2-tert-butoxy-6-chloropyridine (**154**),[157] 2-chloro-4,6-diphenylpyrimidine,[158] [6-(2-bromopyridyl)]diphenylmethanol (**159**),[159] [Cp_2Ru] (**162**) and [CpRu(η^6-naphthalene)]PF_6 (**163**).[161c] The solution of $NaPPh_2$ (1.0 M in THF) was prepared by the Na / NH_3 / PPh_3 method[196] followed by evaporation of liquid NH_3 excess and careful dissolution of the resulting residue in THF.

8.1.6. Microwave-assisted Reactions

The microwave-assisted reactions were conducted using a focused microwave unit (Discover® LabMate™ Reactor from CEM Corporation). The instrument consists of a continuous focused microwave power delivery system with operator-selectable power output of 0-300 W.

[195] W. C. Still, M. Kahn, A. Mitra *J. Org. Chem.* **1978**, *43, 2923.*
[196] W. Hewertson, H. R. Watson *J. Chem. Soc*. **1962**, 1490.

In all experiments the microwave power was held constant throughout the reaction. The specified reaction time corresponds to the total irradiation time. The temperature was monitored by an infrared temperature sensor positioned below the reaction vessel; the indicated temperature corresponds to the maximal temperature reached during each experiment.

8.2. General Synthetic Procedures

General procedure for the preparation of aza-alkoxyphosphanes 142a-b (GP-1). In a dried round-bottom Schlenk flask under an inert atmosphere of argon the appropriate alcohol (1.5 mmol) was dissolved in anhydrous DMF (1.5 mL). A suspension of NaH 60% (1.5 mmol) in anhydrous DMF (1.5 mL) was then carefully added, and the resulting mixture was stirred for 30 min at 50 °C. Subsequently, 2-chloro-6-(diphenylphosphino)pyridine **132** (1.0 mmol) was added in one portion and the resulting orange solution was stirred for an additional 1.5 h at 90 °C. The reaction was quenched with H_2O (2 mL) and Et_2O (4 mL). The organic phase was washed with H_2O (3×3 mL), and the combined organic layers were dried over Na_2SO_4. Evaporation of the solvent under reduced pressure furnished crude **142a** or **142b** typically as a solid, which was purified by flash column chromatography under atmosphere of argon.

General procedure for Cu-catalyzed cross-coupling of tertiary-alkyl Grignard reagents and aza-aryl derivatives (GP-2). In a dried round-bottom Schlenk flask under an inert atmosphere of argon, anhydrous THF (1 mL) was added to the aza-aryl halide derivative (1.0 mmol) and CuI (5 mol-%). The mixture was cooled to 0 °C and stirred for 20 min. A solution of the appropriate alkyl-Grignard reagent (1.0-2.5 mmol) in THF was added slowly, and the mixture stirred at room temperature until GC showed completion of the reaction (10 mins to 48 h, see Table 4). The reaction was quenched by careful addition of saturated aqueous NH_4Cl (3 mL) and the aqueous phase was then extracted with MTBE (3 mL). The organic phase was washed with saturated aqueous NH_4Cl (3×3 mL), H_2O (3 mL) and finally dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded crude products **133a-g**, which were purified by crystallization, distillation or flash column chromatography.

General procedure for Cu-catalyzed cross-coupling of tertiary-alkyl Grignard reagents and 2,4,6-trichloro- pyrimidine and triazine (GP-3). In a dried round-bottom Schlenk flask under an inert atmosphere of argon, anhydrous THF (1 mL) was added to 2,4,6-trichloropyrimidine or 2,4,6-trichlorotriazine (1.0 mmol) and CuI (5 mol-%). The mixture was cooled to 0 °C and stirred for 20 min. A solution of the appropriate alkyl-Grignard reagent (2.3-2.5 mmol) in THF was added slowly, and the resulting mixture stirred at room temperature until TLC showed completion of the reaction (1-19 h, see Table 5). The reaction was quenched by careful addition of saturated aqueous NH_4Cl (4 mL). The aqueous phase was extracted with MTBE (4 mL). The organic phase was washed with saturated aqueous NH_4Cl (3×4 mL), H_2O (4 mL) and finally dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded crude products **147a-d**, which were purified by either distillation or flash column chromatography.

General procedure for Ni-catalyzed cross-coupling of aryl Grignard reagents and 2,6-dibromopyridine (GP-4). In a dried round-bottom Schlenk flask under an inert atmosphere of argon, 2,6-dibromopyridine (1.0 mmol) and $[NiCl_2(PCy_3)_2]$ (0.3 mol-%) were dissolved in anhydrous THF (1 mL). A solution of the appropriate aryl-Grignard reagent (1.1-1.5 mmol) in THF was added slowly, and the resulting mixture stirred at room temperature for 7-30 h (see Table 6). The reaction was quenched by careful addition of saturated aqueous NH_4Cl (3 mL). The aqueous phase was extracted with MTBE (3 mL) or DCM (3 mL). The organic layer was washed with H_2O (6 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded crude products **148a-h**, which were purified either by crystallization or flash column chromatography.

General procedure for Ni-catalyzed cross-coupling of aryl Grignard reagents and 2-*tert*-butoxy-6-chloropyridine (GP-5). In a dried round-bottom Schlenk flask under an inert atmosphere of argon, *t*BuOPyCl **X** (1.00 mmol) was dissolved in anhydrous THF (1.5 mL). Then, $[Ni(acac)_2]$ (1 mol-%) and the imidazolium salts IPr·HCl **131p** (1 mol-%) were added and the mixture was cooled to 0 °C. A solution of the appropriate aryl-Grignard reagent in THF (1.13 mmol) was added dropwise, and the resulting mixture was stirred at 0 °C until it became a thick dark-green/brown suspension. It was then stirred overnight at room temperature, whereupon it turned into a solid mass. The reaction was quenched with either MTBE (4 mL) or EtOAc (4 mL), H_2O (5 mL) and a large amount of saturated aqueous NH_4Cl in order to dissolve inorganics. The aqueous phase was extracted with either MTBE (6 mL) or

EtOAc (6 mL). The organic phase was washed with H_2O (5 mL), aqueous Seignette-salt (5 mL), and finally H_2O (3×5 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded crude products **155a/b**, which were purified by Kugelrohr distillation.

General procedure for the chlorination of the 2-aryl-6-*tert*-butoxy-pyridine 155a/b (GP-6).[197] In a round-bottom Schlenk flask, the appropriate 6-aryl-2-*tert*-butoxy-pyridine **155a/b** (1.0 mmol) was dissolved in DMF (0.7 mL) and cooled to 0°C. $POCl_3$ (2.2 mmol) was added dropwise and the resulting mixture was warmed to room temperature, then heated at 80 °C for 30 h. The solution was allowed to cool to room temperature, and poured onto a mixture of H_2O (7 mL) and MTBE (5 mL). The resulting two-phase mixture was carefully basified by addition of aqueous NH_3 25%. The aqueous phase was extracted with EtOAc (2×7 mL) and the combined organic phases washed with H_2O (5 mL) and aqueous solution of NaOH (0.1 M). The organic layer was washed with H_2O (4×4 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded pure products **156a/b**.

General procedure for the preparation of aza-alkylphosphanes 130a-f and 158 (GP-7). In a dried round-bottom Schlenk flask under an inert atmosphere of argon, the appropriate aza-arene chloride **133/147/157** (1.0 mmol) was dissolved in anhydrous THF (1 mL) and cooled to 0 °C. A solution of $NaPPh_2$ (1.0 mmol, 1.0 M solution in THF) was added dropwise with stirring. The orange reaction mixture was stirred at 0 °C for 1.0 h. The reaction was allowed to warm to room temperature, then quenched with saturated aqueous NH_4Cl (5 mL) and extracted with MTBE (2×5 mL). The combined organic layers were washed with H_2O (5 mL) and dried over Na_2SO_4. The Removal of the solvent under reduced pressure afforded crude products **130a-f** and **158**, which were purified by either crystallization or flash column chromatography under argon.

General procedure for the preparation of aza-arylphosphanes 130g-o (GP-8). In a dried, round-bottom Schlenk flask under an inert atmosphere of argon, the appropriate 2-bromo-6-arylpyridine **148/156** (1.0 mmol) was dissolved in anhydrous ether / toluene (2:1 mL) and cooled to 0 °C. A solution of $NaPPh_2$ (1.0 mmol, 1.0 M solution in THF) was added dropwise to the resulting mixture. The orange-yellow reaction mixture was stirred at 0 °C for 1.0 h then warmed to room temperature, quenched with DCM (3 mL) and the suspension was filtered

[197] M.-J. Shiao, K.-J. Tarng *Heterocycles* **1990**, *31*, 637.

through a short pad of Celite®. The Removal of the solvent under reduced pressure afforded crude products **130g-o**, which were directly purified by flash column chromatography under atmosphere of argon.

General procedure for the ligand exchange in the preparation of the *in situ* catalyst 164 (GP-9). Under an inert atmosphere of argon, a dried NMR tube was charged with the complex **163** [CpRu(η^6-naphthalene)]PF_6 (0.012 mmol), an aza-arylphosphane ligand **130** (0.024 mmol) and degassed CD_3CN (650 µL). The resulting mixture was heated to 60 °C until complete ligand exchange had occurred (0.5-6 h, NMR control, see Table 9) to afford a solution of the complex **164** [CpRu(**130**)$_2CH_3CN$]PF_6.

General procedure for the *in situ* formation of the catalyst 164 (GP-10). Under an inert atmosphere of argon, a dried round-bottom Schlenk flask was charged with the ruthenium precursor **163** [CpRu(η^6-naphthalene)]PF_6 (0.050 mmol.) and an aza-arylphosphane ligand **130** (0.102 mmol). Subsequently, degassed CH_3CN (2 mL) was added, and the resulting mixture was heated to 60 °C for 0.5-6 h. After completion of the ligand exchange (^{31}P-NMR control), the solvent is evaporated under high vacuum, to afford the complex [CpRu(**130**)$_2$(CH_3CN)]PF_6 **164**.

General procedure for the synthesis of the propargylalcohols 171a-c (GP-11). In a dried round-bottom Schlenk flask under an inert atmosphere of argon, ethynylmagnesium chloride (3.0 mmol, 0.72 M solution in THF) was added dropwise to a solution of the appropriate aldehyde **170a-c** (1.0 mmol) in anhydrous THF (1.5 mL) at -10 °C with stirring. The resulting mixture was stirred for 30 min and was then quenched with saturated aqueous NH_4Cl (2 mL) and extracted with MTBE (2×3 mL). The combined organic layers were washed with H_2O (4 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded crude products **171a-c**, which were purified by flash column chromatography.

General procedure for the hydration of terminal alkynes (GP-12). To a dried round-bottom Schlenk flask containing the catalyst **164** (1-5 mol-%) prepared *in situ* under an inert atmosphere of argon according to GP-10, was added the chosen alkyne (1.0 mmol), H_2O (5.0 mmol) and acetone (4 mL). The resulting solution was heated to 45-60 °C for 1-22 h (see Table 13 and 14). After completion of the reaction (GC-MS control), the solution was allowed to cool to room temperature. Removal of the solvent under reduced pressure afforded the

crude aldehyde wich was purified either by Kugelrohr distillation or flash column chromatography.

General procedure for determination of reaction kinetics at 60 °C and 45 °C (GP-13). To a dried, round-bottom Schlenk flask containing catalyst **164** (5 mol-%) prepared *in situ* under an inert atmosphere of argon according to GP-10, was added 1-octyne (1.0 mmol), H_2O (5.0 mmol), acetone (4 mL) and tetradecane as an internal standard. The resulting mixture was heated to either 60 °C or 45 °C for 1-48 h (see, Table 9). Aliquots (approximately 100 µL) were removed at certain intervals, diluted with 1.5 mL of dry acetone and 1 µL portion injected into a GC-FID to determine the yield. Yields were calculated from response factors relative to internal tetradecane standard.

General procedure for the *anti*-MARKOVNIKOV hydration of propargylic amides 207a-j (GP-14). To a dried, round-bottom Schlenk flask containing catalyst **164** (5-10 mol-%, prepared *in situ* according to GP-10) under an inert atmosphere of argon was added a solution of the appropriate propargylic amide **207** (0.1 mmol) and H_2O (0.5 mmol) in acetone (0.7 mL). The resulting mixture was heated at 55 °C. After completion of the reaction (11-90 h, according to TLC), the solution was allowed to cool to room temperature and MTBE (10 mL) was added. The organic layer was washed with H_2O (10 mL) and brine (10 mL), and dried over Na_2SO_4. The solvent was then removed *in vacuo* to afford the crude aldehydes **208a-i**, which were purified by flash column chromatography.

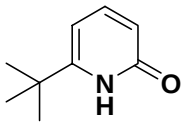
General procedure for the *anti*-MARKOVNIKOV hydration of propargylic amides 207a-j under conditions of microwave irradiations (GP-15). Under an inert atmosphere of argon, a dried vial was placed in a Schlenk flask and charged with the catalyst **164n** (5-10 mol-%, prepared *in situ* according to GP-X). A solution of the appropriate propargylic amide **207** (0.1 mmol) and H_2O (0.5 mmol) in acetone (0.7 mL) was subsequently added. The vial was sealed with a septum, removed from the Schlenk flask and placed in the cavity of the microwave reactor and locked with the pressure device. The microwave source was then turned on. Temperature (90-120 °C), constant microwave irradiation of 50-75 W as well as simultaneous air cooling (1.4-4.0 bar, 10 psi) were used during the entire reaction time (5-30 min). After cooling to room temperature, the product was isolated as described above for the thermal reaction.

General procedure for the preparation of β-aminoacids 209a/b via the "One Pot" anti-Markovnikov hydration/oxidation of propargylic amides 207d/i (GP-16). Under an inert atmosphere of argon, a dried round-bottom Schlenk flask was charged with the catalyst **164n** (10 mol-%, prepared *in situ* according to GP-11). A solution of the appropriate propargylic amine **207d/i** (0.1 mmol) and water (0.5 mmol) in acetone (0.7 mL) was subsequently added and the resulting mixture was stirred at 55 °C. The reaction was monitored by TLC. After completion (11-22 h), the reaction allowed to cool to room temperature. Evaporation of the solvent under reduced pressure furnished the crude aldehydes **208d/i**, which were dissolved in a mixture of CH_3CN / CCl_4 / H_2O (1:1:1.3 mL) without further purification. $NaIO_4$ 99% (0.4 mmol) was then added in one portion, and the resulting solution was stirred for 2-15 h (see Table 18) at room temperature. The solvent was evaporated and the residue taken up in H_2O (5 mL). After acidification to pH 2 with an aqueous solution of HCl (2 M), the aqueous layer was extracted with Et_2O (2×5 mL). The combined organic layers were washed with brine (10 mL) and dried over Na_2SO_4. The solvent was removed under vacuum to afford the crude β-aminoacids **209d/i**, which were purified by flash column chromatography.

General procedure for the reduction of *N*-tosyl-protected β-aminoaldehydes 210 (GP-17). In a dried round-bottom Schlenk flask under an inert atmosphere of argon, the appropriate *N*-tosyl-β-aminoaldehyde **208** (0.1 mmol) was dissolved in anhydrous EtOH (1.5 mL). A solution of $NaBH_4$ (0.5 mmol) in EtOH (1.5 mL) was added dropwise, and the mixture stirred at room temperature for 30 min. After evaporation of the solvent under reduced pressure, DCM (10 mL) and H_2O (10 mL) were added. The organic phase was washed with water (2×5 mL) and dried over Na_2SO_4. The solvent was removed under vacuum to afford the crude β-aminoalcohols **210**, which were purified by flash column chromatography.

8.3. Synthesis of Pyridin-2(1*H*)-one Derivatives

8.3.1. 6-*tert*-Butylpyridin-2(1*H*)-one (123)



$C_9H_{13}NO$. MW = 151.21 g mol^{-1}

To a suspension of NaH (0.89 mol, 35.7 g, 60%) in MTBE (500 mL) cooled at 0 °C was added dropwise a mixture of pinacoline (101.90 mmol, 82.0 mL) and ethyl formate (84.85 mmol, 85.00 g). After complete addition, the reaction mixture was allowed to warm to room temperature and stirred for 18 h. The resulting suspension was diluted with *n*-pentan (250 mL) and stirred for additional 2 h. The resulting sodium salt was filtered, washed with *n*-pentan (250 mL) and dried in vaccuo. To a solution of the sodium salt (0.14 mol, 48 g) in EtOH (500 mL) was slowly added triphenylphosphonium acetamide chloride **121** (0.32 mol, 114.00 g). The resulting yellow mixture was heated to 80 °C for 2.5 h. AcOH (200 mL) was then added and the reaction mixture was stirred at 110 °C for 20 h. After cooling to room temperature and concentration of the solvent *in vacuo*, the crude product was taken up in DCM and silica gel was added. Concentration of the solvent *in vacuo* left the product mixture suspended on the silica ready for purification by flash column chromatography EtOAc/Hexan/HOAc 1:2:0.5%). The fractions containing the product (TLC control) were washed with Na_2CO_3 until pH>8. The combined aqueous layers were then extracted with EtOAc (500 mL). The organic layer was washed with H_2O (2×200 mL) and dried over Na_2SO_4. Removal of the solvent under reduced pressure, followed by purification by crystallization from *n*-pentane afforded pure **123** (0.25 mol, 38.14 g, 79% yield) as a slightly yellow solid;

^{1}H-NMR (300 MHz, $CDCl_3$)

δ = 1.35 (s, 9 H; CH_3), 6.11 (d, *J* = 6.7 Hz, 1 H; Ar-H), 6.40 (d, *J* = 8.9 Hz, 1 H; Ar-H), 7.38 (dd, *J* = 8.8 Hz, 6.7 Hz, 1 H; Ar-H), 11.53 (br s, 1 H; NH) ppm;

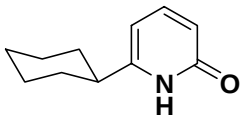
^{13}C-NMR (75 MHz, $CDCl_3$)

δ = 29.2, 36.3, 101.7, 117.3, 141.5, 156.8, 164.6 ppm;

Analytical data are in agreement with those reported in the literature.[198]

[198] J. Baur, H. Jacobsen, P. Burger, G. Artus, H. Berke, L. Dahlenburg *Eur. J. Inorg. Chem*. **2000**, 1411.

8.3.2. 6-Cyclohexylpyridin-2(1*H*)-one (127)



$C_{11}H_{15}NO$. MW = 177.24 g mol^{-1}

To a suspension of NaH 0.52 mol, 20.7 g) in MTBE (650 mL) cooled at 0 °C was added dropwise a mixture of cyclohexylmethylketone (0.52 mol, 65.51 g) and ethyl formate (0.62 mol, 45.83 g). After complete addition (within 2 h), the reaction mixture was allowed to warm to room temperature and stirred for 16 h. The resulting suspension was diluted with petroleum ether (200 mL), stirred for additional 2 h and quenched with H_2O (200 mL). The aqueous phase was washed with MTBE (200 mL), DCM (2×200 mL), then acidified with an aqueous solution of concentred HCl (50 mL in 30 mL H_2O) and finally extracted with DCM (200 mL) and MTBE (200 mL). The combined organic layers were washed with brine (2×250 mL) and evaporated under reduced pressure to give pure sodium salt **125**. To a solution of the sodium salt **125** in EtOH (100 mL) cooled at 0 °C was added a solution of NaOH in EtOH (300 mL). Then triphenylphosphonium acetamide chloride (0.46 mol, 165.10 g) was added to the reaction mixture previously allowed to warm to room temperature. The resulting yellow mixture was heated 4h to 80 °C until it became red-orange. AcOH (160 mL) was then added and the reaction mixture was stirred at reflux overnight. After cooling to room temperature and concentration of the solvent *in vacuo*, the crude product was taken up in MTBE (500 mL) and silica gel was added. Concentration of the solvent *in vacuo* left the product mixture suspended on the silica ready for purification by flash column chromatography (EtOAc/Petrolether/HOAc 1:4:1%). The fractions containing the product (TLC control) were washed with Na_2CO_3 until pH>8. The combined aqueous layers were then extracted with DCM (400 mL). The organic layer was washed with H_2O (2×300 mL) and dried over Na_2SO_4. Removal of the solvent under reduced pressure followed by purification by crystallisation from *n*-hexane afforded pure **127** (96.95 mmol, 17.16 g, 21% yield) as a light yellow solid;

Mp: 234-235 °C;

^{1}H-NMR (400 MHz, $CDCl_3$)

δ = 1.19-1.37 (m, 1 H; CH_2), 1.32-1.49 (m, 4 H; CH_2), 1.71-1.78 (m, 1 H; CH_2), 1.81-1.86 (m, 2 H; CH_2), 1.92-1.98 (m, 2 H; CH_2), 2.49-2.57 (m, 1 H; CH), 6.05 (d, J = 6.8 Hz, 1 H; Ar-H), 6.40 (dd, J = 9.1, 1.1 Hz, 1 H. Ar-H), 7.38 (dd, J = 9.1, 6.8 Hz, 1 H; Ar-H), 12.6 (br s, 1 H; NH) ppm;

^{13}C-NMR (100 MHz, $CDCl_3$)

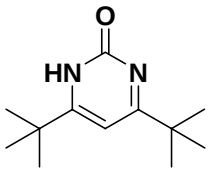
25.8, 26.2, 32.1, 42.0, 102.8, 116.9, 141.7, 154.7, 165.4 ppm;

IR (KBr): ν = 30125 (w), 2926 (s), 2847 (s), 2766 (m), 1640 (s), 1547 (m), 1462 (m), 990 (m), 791 (m), 533 (m) cm^{-1};

MS (EI, 70 eV): m/z (%) = 178.2 (5)$[M+1]^+$, 148.1 (22), 122.1 (100), 109.1 (63);

Elemental Analysis for $C_{11}H_{15}NO$: Calcd.: C 74.54; H 8.53; N 7.90;
Found: C 74.14; H 8.52; N 7.77.

8.3.3. 4,6-Di-*tert*-butylpyrimidin-2(1*H*)-one.



$C_{12}H_{20}N_2O$. MW = 208.3 g mol^{-1}

Dipivaloylmethane (61.70 mmol, 12.37 g) and urea (100.00 mmol, 6.06 g) were stirred in 25 mL of HOAc at 110 °C for 10 h. Subsequently, another portion of urea (90.00 mmol, 5.40 g) was added, and the reaction mixture was stirred for an additional 8 h at 140 °C. After addition of a third portion of urea (87.00 mmol, 5.20 g), the resulting solution was stirred for additional 40 h. After this time, the reaction mixture was cooled to room temperature, quenched with H_2O (10 mL) and diluted with EtOAc (10 mL). The aqueous phase was basified with aqueous KOH and extracted with DCM (4x100 mL). Evaporation of the solvent under vacuum afforded a sligthy yellow powder, which was directly added to an aqueous solution of HCl 2.4 N (15 mL) and stirred for one day. The reaction mixture was then basified with aqueous NH_3 25% and extracted with DCM (300 mL). Purification by crystallization from *n*-hexane afforded pure 4,6-di-*tert*-butylpyrimidin-2(1*H*)-one (11.70 mmol, 2.42 g, 19% yield) as a colorless powder;

^{1}H-NMR (300 MHz, $CDCl_3$)

δ = 1.34 (br s, 9 H; CH3), 1.40 (br s, 9 H; CH3), 6.32 (s, 1 H; CH), 12.34 (s, 1 H; NH) ppm;

^{13}C-NMR (75 MHz, $CDCl_3$)

δ = 28.8, 29.2, 96.8, 159.8, 187.6 ppm;

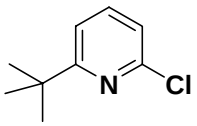
IR (KBr): ν = 2967 (m), 1646 (s), 1611 (s), 1442 (m), 1132 (w), 937 (w) cm^{-1};

MS (EI, 70 eV): m/z (%) = 208 (30)$[M^+]$, 193 (100), 178 (7), 166 (30);

Elemental Analysis for $C_{12}H_{20}N_2O$: Calcd.: C 69.19; H 9.68; N 13.45;
Found: C 68.93; H 9.72; N 13.34.

8.4. Synthesis of Chloro-substituted Aza-aryl Derivatives

8.4.1. 2-*tert*-Butyl-6-chloropyridine (116)



$C_9H_{12}ClN$. MW = 169.07 g mol^{-1}

A solution of 6-*tert*-butylpyridin-2(1*H*)-one **123** (59.50 mmol, 9.00 g) in $POCl_3$ (109.00 mmol, 10.00 mL) was refluxed at 120 °C until changement of the mixture coloration from orange into black. The solution was allowed to cool to rt and PCl_5 (66.30 mmol, 13.80 g) was added in portions over 10 min. The resulting solution was heated to reflux and stirred for an additional 1 h. After this time, the reaction mixture was cooled to room temperature. After removing excess of $POCl_3$ under high vacuum, the solution was poured over ice (100 g), diluted with H_2O (50 mL) and extracted with EtOAc (100 mL). The organic layer was washed with aqueous $NaHCO_3$ (50 mL), dried over $MgSO_4$ and concentrated. Purification by Kugelrohr distillation (ca. 15 mbar, 120 °C) afforded pure **116** (42.30 mmol, 7.15 g, 71% yield) as a colorless liquid;

^{1}H-NMR (300 MHz, $CDCl_3$)

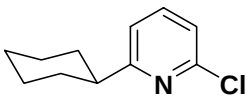
δ = 1.35 (s, 9 H; CH_3), 7.10 (d, *J* = 7.9 Hz, 1 H; Ar-H), 7.23 (d, *J* = 7.6 Hz, 1 H; Ar-H), 7.39 (dd, *J* = 7.9 Hz, 7.6 Hz, 1 H; Ar-H) ppm;

^{13}C-NMR (75 MHz, $CDCl_3$)

δ = 29.9, 37.5, 117.4, 121.1, 138.7, 150.2, 170.6 ppm;

Analytical data are in agreement with those reported in the literature.[140a]

8.4.2. 2-Chloro-6-cyclohexylpyridine (128)



$C_{11}H_{14}ClN$. MW = 195.69 g mol^{-1}

To the suspended 6-cyclohexylpyridin-2(1*H*)-one **127** (56.40 mmol, 10.00 g) in DMF (30 mL), $POCl_3$ (150.00 mmol, 14.00 mL) was slowly added dropwise over 30 min with stirring. After completion of the addition, the mixtured was heated to 90 °C and stirred for 7 h. The cooled reaction mixture was poured over ice (100 g) and H_2O (50 mL), carefully neutralized

with aqueous NH_3 25% and then extracted with MTBE (100 mL). The organic phase was washed with aqueous solution of NaOH 2 M (3×50 mL) and dried over $MgSO_4$. The solvent was then removed under vacuum. Purifiation by Kugelrohr distillation (0.1 mbar, 150 °C) afforded pure **128** (0.54 mol, 10.54 g, 95% yield) as slightly yellow oil;

^{1}H-NMR (500 MHz, $CDCl_3$)

δ = 1.20–2.02 (m, 10 H; CH_2), 2.68 (tt, *J* = 11.8, 3.5 Hz, 1 H; CH), 7.06 (d, *J* = 7.6 Hz, 1 H; Ar-H), 7.12 (d, *J* = 8.0 Hz, 1 H; Ar-H), 7.55 (t, *J* = 7.8 Hz, 1 H; Ar-H) ppm;

^{13}C-NMR (125 MHz, $CDCl_3$)

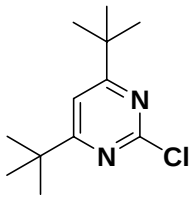
δ = 25.9, 26.4, 32.7, 46.2, 119.2, 121.4, 138.9, 150.5, 167.7 ppm;

IR (film): 2927 (s), 2854 (s), 1581 (s), 1441 (s), 1158 (m), 793 (m);

MS (EI, 70 eV): m/z (%) = 195/197 (40)[M^+], 166 (45), 154 (25), 140 (100), 127 (60);

Elemental Analysis for $C_{11}H_{14}ClN$: Calcd.: C 67.51; H 7.21; N 7.16;
Found: C 67.67; H 7.26; N 7.51.

8.4.3. 4,6-Di-*tert*-butyl-2-chloropyrimidine



$C_{12}H_{19}ClN_2$. MW = 226.75 g mol^{-1}

A solution of 4,6-di-*tert*-butylpyrimidin-2(1*H*)-one (11.32 mmol, 2.36 g) in $POCl_3$ (54.00 mmol, 5.00 ml) was refluxed at 120 °C for 25 h. The reaction mixture was allowed to cool to room temperature and subsequently poured onto water (300 mL) and MTBE (100 mL). The aqueous phase was carefully neutralized with K_2CO_3 and extracted with MTBE (100 mL). The combined organic layers were washed with aqueous $NaHCO_3$ (200 mL), then H_2O (200 mL) and dried over $MgSO_4$. The solvent was then removed under vacuum. Purifiation by crystallization from *n*-pentane afforded pure 4,6-di-*tert*-butyl-2-chloropyrimidine (10.78 mmol, 2.45 g, 95% yield) as colorless solid;

Mp: 82-83 °C;

^{1}H-NMR (400 MHz, $CDCl_3$)

δ = 1.34 (s, 18 H; CH_3), 7.22 (s, 1 H; CH) ppm;

^{13}C-NMR (100 MHz, $CDCl_3$)

δ = 29.5, 38.0, 110.1, 160.1, 181.3 ppm;

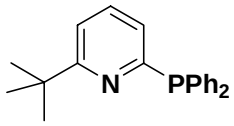
IR (KBr): ν = 2970 (s), 1569 (m), 1263 (s), 1165 (m), 1101 (s), 1061 (m) cm^{-1};

MS (EI, 70 eV): m/z (%) = 226/228 (15)[M^+], 225/227 (16), 211 (100), 196 (15), 184 (43), 169 (6);

Elemental Analysis for $C_{12}H_{19}ClN_2$: Calcd.: C 63.56; H 8.45; N 12.35;
Found: C 63.85; H 8.53; N 12.38.

8.5. Synthesis of Pyridylphosphane Derivatives

8.5.1. 2-*tert*-Butyl-6-(diphenylphosphino)pyridine (108)



$C_{21}H_{22}NP$. MW = 319.38 g mol^{-1}

Prepared according to GP-7, starting from 2-chloro-6-*tert*-butylpyridine **116** (2.0 mmol, 350.0 mg) and a solution of $NaPPh_2$ (2.0 mmol, 1.0 M in THF). Purification by flash column chromatography under argon (*n*-pentane/DCM 3:1) afforded pure **108** (1.5 mmol, 480 mg, 73% yield) as a white solid;

^{1}H-NMR (300 MHz, C_6D_6)

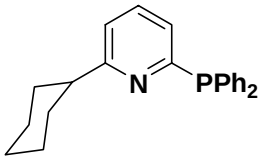
δ = 1.28 (s, 9 H; CH_3), 6.82-6.86 (ddd, *J* = 6.3, 2.5, 0.9 Hz, 1 H; Ar-H), 6.94-7.03 (m, 3 H; Ar-H), 7.06-7.13 (m, 5 H; Ar-H), 7.51-7.58 (m, 4 H; Ar-H) ppm;

^{13}C-NMR (75 MHz, C_6D_6)

δ = 30.3, 38.5, 117.3, 125.3 (d, $J_{C\text{-}P}$ = 19.4 Hz), 128.5 (d, $J_{C\text{-}P}$ = 7.7 Hz), 128.9, 134.5 (d, $J_{C\text{-}P}$ = 19.8 Hz), 135.7 (d, $J_{C\text{-}P}$ = 4.3 Hz), 137.5 (d, $J_{C\text{-}P}$ = 4.6 Hz), 161.4 (d, $J_{C\text{-}P}$ = 5.4 Hz), 169.4 (d, $J_{C\text{-}P}$ = 10.3 Hz) ppm;

Analytical data are in agreement with those reported in the literature.[140a]

8.5.2. 6-Cyclohexyl-2-(diphenylphosphino)pyridine (129).



$C_{23}H_{24}NP$. MW = 345.42 g mol^{-1}

Prepared according to GP-7, starting from 2-chloro-6-cyclohexyl-pyridine **128** (51.00 mmol, 9.96 g) and a solution of $NaPPh_2$ (51.0 mmol, 1.0 M in THF). Purification by filtration through Al_2O_3 under argon and crystallization from MeOH afforded pure **129** (32.57 mmol, 11.24 g, 65% yield) as a white solid;

Mp: 88 °C;

^{1}H-NMR (400 MHz, C_6D_6)

δ = 0.99-1.27 (m, 3 H; CH_2), 1.45-1.59 (m, 3 H; CH_2), 1.60-1.69 (m, 2 H; CH_2), 1.82-1.92 (m, 2 H; CH_2), 2.61 (tt, *J* = 11.8, 3.5 Hz, 1 H; CH), 6.63 (d, *J* = 7.7 Hz, 1 H; Ar-H), 6.90 (dt, *J* = 7.6, 6.2 Hz, 1 H; Ar-H), 6.96 (td, *J* = 7.6, 2.2 Hz, 1 H; Ar-H), 7.00-7.09 (m, 6 H; Ar-H), 7.47-7.54 (m, 4 H; Ar-H) ppm;

^{13}C-NMR (100 MHz, C_6D_6)

δ = 26.5, 27.0, 33.2, 46.8, 119.7, 125.6 (d, $J_{C\text{-}P}$ = 18.6 Hz), 128.7 (d, $J_{C\text{-}P}$ = 7.0 Hz), 129.0, 134.7 (d, $J_{C\text{-}P}$ = 19.7 Hz), 135.9 (d, $J_{C\text{-}P}$ = 3.0 Hz), 138.0 (d, $J_{C\text{-}P}$ = 12.0 Hz), 163.5 (d, $J_{C\text{-}P}$ = 4.0 Hz), 166.9 (d, $J_{C\text{-}P}$ = 11.5 Hz) ppm;

^{31}P-NMR (160 MHz, C_6D_6)

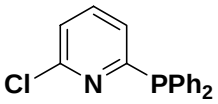
δ = –4.1 ppm;

IR (KBr): ν = 3050 (m), 2925 (s), 2853 (s), 1555 (s), 1436 (s), 1164 (m), 800 (m), 744 (s), 694 (s) cm^{-1};

MS (EI, 70 eV): m/z (%) = 345 (100)$[M+H]^+$,, 290 (68), 277 (42), 212 (25), 183 (17);

Elemental Analysis for $C_{23}H_{24}NP$: Calcd.: C 79.97; H 7.00; N 4.06;
Found: C 79.66; H 7.12; N 4.00.

8.5.3. 2-Chloro-6-(diphenylphosphino)pyridine (132).



$C_{17}H_{13}ClNP$. MW = 297.72 g mol^{-1}

Prepared according to GP-7, starting from 2,6-dichloropyridine (5.00 mmol, 755 mg, 98% purity) and a solution of $NaPPh_2$ (5.00 mmol, 1.0 M in THF). Purification by recrystallization from *n*-hexane afforded pure **132** (3.1 mmol, 920 mg, 62% yield) as a white solid;

Mp: 81-82 °C;

^{1}H-NMR (400 MHz, $CDCl_3$)

δ = 6.95 (dd, *J* = 7.4, 0.8 Hz, 1 H; Ar-H), 7.19 (dd, *J* = 8.0, 0.8 Hz, 1 H; Ar-H), 7.35-7.41 (m, 10 H; Ar-H), 7.49 (td, *J* = 7.7, 1.4 Hz, 1 H; Ar-H) ppm;

^{13}C-NMR (100 MHz, $CDCl_3$)

δ = 122.9, 126.2 (d, $J_{C\text{-}P}$ = 12.9 Hz), 128.6 (d, $J_{C\text{-}P}$ = 7.5 Hz), 129.2, 134.1 (d, $J_{C\text{-}P}$ = 19.7 Hz), 135.5 (d, $J_{C\text{-}P}$ = 10.2 Hz), 138.1, 151.7 (d, $J_{C\text{-}P}$ = 12.1 Hz), 165.3 ppm;

^{31}P-NMR (160 MHz, $CDCl_3$)

δ = –3.3 ppm;

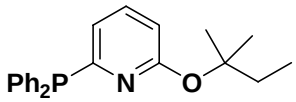
IR (KBr): ν = 3067 (m), 1546 (s), 1476 (s), 1412 (s), 1165 (m), 1119 (s), 784 (s), 746 (s), 694 (s) cm^{-1};

MS (EI, 70 eV): m/z (%) = 297 (100)[M^+], 262 (6), 220 (13), 183 (30), 152 (3);

Elemental Analysis for $C_{17}H_{13}ClNP$: Calcd.: C 68.58; H 4.40; N 4.70;
Found: C 68.25; H 4.70; N 4.62.

8.6. Synthesis of Aza-alkoxyphosphanes 142a/b

8.6.1. 2-(Diphenylphosphino)-6-(*tert*-amyloxy)pyridine (142a).



$C_{22}H_{24}NOP$. MW = 349.41 g mol^{-1}

Prepared according to GP-1, starting from *tert*-amylalcohol (30.0 mmol, 3.31 mL) and 2-chloro-6-(diphenylphosphino)pyridine **132** (7.5 mmol, 2.235 g). Purification by flash column chromatography under argon (Hex/MTBE 25:1) afforded pure **XXX** (4.4 mmol, 1.55 g, 60% yield) as a white solid;

Mp: 67 °C;

^{1}H-NMR (300 MHz, $CDCl_3$)

δ = 0.77 (t, J = 7.4 Hz, 3 H; CH_3), 1.29 (s, 6 H; CH_3), 1.70 (q, J = 7.4 Hz, 2 H; CH_2), 6.52 (dd, J = 8.2, 0.75 Hz, 1 H; Ar-H), 6.76-6.82 (m, 1 H; Ar-H), 7.29-7.44 (m, 11 H; Ar-H) ppm;

^{13}C-NMR (75 MHz, $CDCl_3$)

δ = 8.3, 25.9, 33.3, 82.0, 112.0, 121.3 (d, $J_{C\text{-}P}$ = 26.9 Hz), 128.3 (d, $J_{C\text{-}P}$ = 6.5 Hz), 128.7, 134.2 (d, $J_{C\text{-}P}$ = 19.7 Hz), 136.8 (d, $J_{C\text{-}P}$ = 10.1 Hz), 137.8 (d, $J_{C\text{-}P}$ = 6.5 Hz), 159.6 (d, $J_{C\text{-}P}$ = 2.3 Hz), 163.5 (d, $J_{C\text{-}P}$ = 9.5 Hz) ppm;

^{31}P-NMR (121 MHz, $CDCl_3$)

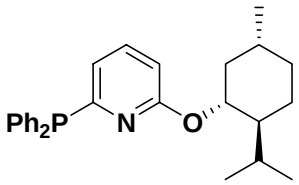
δ = –2.6 ppm;

IR (KBr): ν = 2924 (s), 2852 (s), 1576 (s), 1432 (s), 1306 (s), 1160 (s), 950 (m), 798 (m), 742 (s), 696 (s) cm^{-1};

MS (EI, 70 eV): m/z (%) = 350 (14) $[M+H]^+$, 349 (54) $[M]^+$, 296 (5), 279 (100), 200 (13), 183 (14), 108 (7);

Elemental Analysis for $C_{22}H_{24}NOP$: Calcd.: C 75.62; H 6.92; N 4.01;
Found: C 76.01; H 6.96; N 3.89.

8.6.2. 2-(Diphenylphosphino)-6-[(2*R*)-2-isopropyl-5-methylcyclohexyloxy]pyridine (142b).



$C_{27}H_{32}NOP$. MW = 417.52 g mol^{-1}

Prepared according to GP-1, starting from (1*R*)-menthol (2.25 mmol, 351 mg) and 2-chloro-6-(diphenylphosphino)pyridine **132** (1.50 mmol, 446 mg). Purification by flash column chromatography under argon (Hex/MTBE 20:1) afforded pure **142b** (1.40 mmol, 592 mg, 95% yield) as a white solid;

Mp: 50-51 °C;

^{1}H-NMR (300 MHz, $CDCl_3$)

δ = 0.61 (d, *J* = 6.9 Hz, 3 H; CH_3), 0.90-1.68 (m, 7 H; CH, CH_2), 1.86-2.04 (m, 2 H; CH_2), 4.87 (td, *J* = 10.6, 4.4 Hz, 1 H; CH), 6.53 (dd, *J* = 8.4, 0.7 Hz, 1 H; Ar-H), 6.85 (dq, *J* = 3.7, 0.75 Hz, 1 H; Ar-H), 7.29-7.35 (m, 6 H; Ar-H), 7.39-7.47 (m, 5 H; Ar-H) ppm;

^{13}C-NMR (75 MHz, $CDCl_3$)

δ = 15.5, 19.6, 21.1, 22.6, 25.2, 30.1, 33.4, 39.5, 46.3, 73.3, 109.5, 120.8 (d, $J_{C\text{-}P}$ = 28.6 Hz), 127.1 (d, $J_{C\text{-}P}$ = 26.6 Hz), 127.6, 133.2 (d, $J_{C\text{-}P}$ = 19.4 Hz), 135.9 (d, $J_{C\text{-}P}$ = 7.5 Hz), 137.0 (d, $J_{C\text{-}P}$ = 6.5 Hz), 158.5, 162.1 (d, $J_{C\text{-}P}$ = 6.9 Hz) ppm;

^{31}P-NMR (121 MHz, $CDCl_3$)

δ = –3.3 ppm;

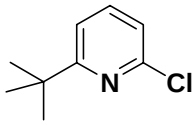
IR (KBr): ν = 3967 (m), 3913 (m), 3866 (m), 3049 (m), 2946 (s), 2859 (s), 1577 (s), 1432 (s), 1294 (s), 1249 (m), 1160 (m), 985 (s), 800 (m), 744 (s), 694 (s), 496 (s) cm^{-1};

MS (EI, 70 eV): m/z (%) = 417 (65) $[M^+]$, 389 (1), 374 (6), 304 (2), 279 (100), 202 (10), 183 (9), 108 (4);

Elemental Analysis for $C_{27}H_{32}NOP$: Calcd.: C 77.67; H 7.73; N 3.35;
Found: C 77.73; H 7.40; N 3.03.

8.7. Synthesis of Alkyl-substituted Aza-aryl Derivatives

8.7.1. 2-*tert*-Butyl-6-chloropyridine (133a)



$C_9H_{12}ClN$. MW = 169.07 g mol^{-1}

Prepared according to GP-2, starting from 2,6-dichloropyridine (0.10 mol, 14.80 g, 98% purity), CuI (5 mol-%) and *t*-BuMgCl (0.20 mmol, 1.0 M in THF). Purification by distillation in vacuo (ca. 15 mbar, 90 °C) afforded pure **133a** (65.60 mmol, 11.10 g, 65% yield) as a colorless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$)

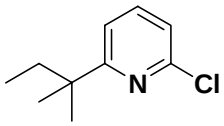
δ = 1.35 (s, 9 H; CH_3), 7.11 (d, *J* = 7.9 Hz, 1 H; Ar-H), 7.23 (d, *J* = 7.6 Hz, 1 H; Ar-H), 7.38 (dd, *J* = 7.9 Hz, 7.6 Hz, 1 H; Ar-H) ppm;

^{13}C-NMR (75 MHz, $CDCl_3$)

δ = 29.9, 37.5, 117.4, 121.1, 138.7, 150.2, 170.6 ppm;

Analytical data are in agreement with those reported in the literature.[198]

8.7.2. 2-Chloro-6-*tert*-pentylpyridine (133b)



$C_{10}H_{14}ClN$. MW = 183.08 g mol^{-1}

Prepared according to GP-2, starting from 2,6-dichloropyridine (33.80 mmol, 5.00 g, 98% purity), CuI (5 mol-%) and *t*-AmMgCl (67.60 mmol, 0.7 M in THF). Purification by flash column chromatography (*n*-pentane/DCM 5:1) afforded pure **133b** (24.90 mmol, 4.56 g, 74% yield) as a colorless liquid;

^{1}H-NMR (400 MHz, $CDCl_3$)

δ = 0.69 (t, *J* = 7.5 Hz, 3 H; CH_3), 1.30 (s, 6 H; CH_3), 1.73 (q, *J* = 7.4 Hz, 2 H; CH_2), 7.09 (d, *J* = 7.7 Hz, 1 H; Ar-H), 7.18 (d, *J* = 7.7 Hz, 1 H; Ar-H), 7.54 (t, *J* = 7.8 Hz, 1 H; Ar-H) ppm;

^{13}C-NMR (100 MHz, $CDCl_3$)

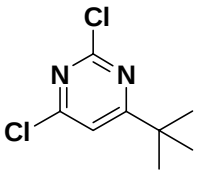
δ = 9.1, 27.2, 35.6, 40.8, 118.4, 120.9, 138.4, 150.2, 169.5 ppm;

IR (neat): ν = 2965 (m), 2878 (s), 1562 (s), 1433 (s), 1401 (s), 1131 (s), 795 (s) cm^{-1};

MS (EI, 70 eV): m/z (%) = 184 (1)[M^+], 168 (77), 155 (100), 139 (16), 127 (15), 117 (16);

Elemental Analysis for $C_{10}H_{14}ClN$: Calcd.: C 65.39; H 7.68; N 7.63;
Found: C 65.59; H 7.95; N 7.68.

8.7.3. 4-*tert*-Butyl-2,6-dichloropyrimidine (133c)



$C_8H_{10}Cl_2N_2$. MW = 205.08 g mol^{-1}

Prepared according to GP-2, starting from 2,4,6-trichloro-pyrimidine (2.69 mmol, 500 mg, 99% purity), CuI (5 mol-%) and *t*-BuMgCl (2.69 mmol, 1.0 M in THF). Purification by flash column chromatography (*n*-pentane/DCM 2:1) afforded pure **133c** (2.64 mmol, 540 mg, 98% yield) as a light yellow solid;

Mp: 61-62 °C;

^{1}H-NMR (300 MHz, $CDCl_3$)

δ = 1.35 (s, 9 H; CH_3), 7.28 (s, 1 H; Ar-H) ppm;

^{13}C-NMR (75 MHz, $CDCl_3$)

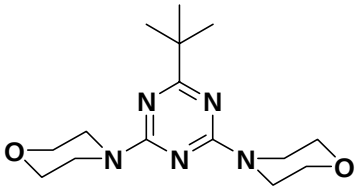
δ = 29.0, 38.2, 115.6, 160.2, 162.5, 183.0 ppm;

IR (KBr): ν = 2966 (s), 2870 (w), 1559 (s), 1520 (s), 1479 (m), 1455 (m), 1364 (m), 1303 (s), 1260 (s), 1101 (s), 1023 (s), 882 (s), 824 (s) cm^{-1};

MS (EI, 70 eV): m/z (%) = 205/207 (10)[M^+], 204/206 (10), 189/191 (100), 161/163 (9), 153 (5), 126/128 (4), 118 (17), 90/92 (3), 65/67 (4);

Elemental Analysis for $C_8H_{10}Cl_2N_2$**:** Calcd.: C 46.85; H 4.91; N 13.66;
Found: C 46.91; H 4.98; N 13.43.

8.7.4. 2-*tert*-Butyl-4,6-dimorpholino-1,3,5-triazine (133d)



$C_{15}H_{25}N_5O_2$. MW = 307.39 g mol^{-1}

Prepared according to GP-2, starting from 2,4,6-trichloro-triazine (2.7 mmol, 500 mg, 99% purity), CuI (5 mol-%) and *t*-BuMgCl (4.85 mmol, 1.0 M in THF) with the following derivatisation,[152] after complete conversion into 2-*t*-butyl-4,6-dichloro-1,3,5-triazine (GC-MS

control) achieved in 15 min at room temperature. Subsequently, a solution of morpholine (8.0 mmol, 698 mg) in 1,4-dioxan (3.5 mL) and Et_3N (8.0 mmol, 1.1 mL) was slowly added to the stirred solution of the 1,3,5-triazine intermediate. The resulting reaction mixture was stirred at room temperature for 20 h. The solvent were removed at reduced pressure and the residue was triturated and hydrolyzed with aqueous solution of HCl 0.6 M (2 mL), then extracted with DCM (3x20 mL) and dried over Na_2SO_4. The solvent was then removed under vacuum to afford the crude, which was purified by flash column chromatography (Hex/EtOAc 8:2) afforded pure **133d** (1.1 mmol, 350 mg, 43% over 2 steps yield) as a brown-orange solid;

Mp: 148-149 °C;

^{1}H-NMR (300 MHz, $CDCl_3$)

δ = 1.25 (s, 9 H; CH_3), 3.71 (t, *J* = 4.7 Hz, 8 H; CH_2), 3.80 (br s, 8 H; CH_2) ppm;

^{13}C-NMR (75 MHz, $CDCl_3$)

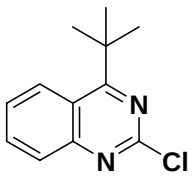
δ = 28.9, 39.0, 43.5, 66.8, 165.1, 184.1 ppm;

IR (KBr): ν = 3462 (w), 2967 (s), 2896 (m), 2855 (m), 1540 (s), 1478 (s), 1441 (s), 1260 (s), 1223 (s), 1116 (m), 996 (m), 704 (m) cm^{-1};

MS (EI, 70 eV): m/z (%) = 307 (100)[M^+], 292 (26), 277 (88), 262 (36), 250 (58), 232 (14), 220 (14), 207 (6), 193 (4), 176 (4), 164 (3), 138 (6), 113 (13), 94 (5), 81 (5), 69 (11);

Elemental Analysis for $C_{15}H_{25}N_5O_2$**:** Calcd.: C 58.61; H 8.20; N 22.78;
Found: C 58.29; H 8.14; N 21.81.

8.7.5. 4-*tert*-Butyl-2-chloroquinazoline (133e)



$C_{12}H_{13}ClN_2$. MW = 220.7 g mol^{-1}

Prepared according to GP-2, starting from 2,4-dichloroquinazoline (1.00 mmol, 199 mg), CuI (5 mol-%) and *t*-BuMgCl (1.50 mmol, 1.0 M in THF). Purification by flash column chromatography (*n*-pentane/DCM 3:1) afforded pure **133e** (0.77 mmol, 170 mg, 78% yield) as a light brown solid;

Mp: 86-87 °C;

^{1}H-NMR (400 MHz, $CDCl_3$)

δ = 1.57 (s, 9 H; CH_3), 7.52 (ddd, *J* = 8.5, 6.9, 1.4 Hz, 1 H; Ar-H), 7.77 (ddd, *J* = 8.4, 7.0, 1.4 Hz, 1 H; Ar-H), 7.92 (d, *J* = 8.5 Hz, 1 H; Ar-H), 8.38 (d, *J* = 8.8 Hz, 1 H; Ar-H) ppm;

^{13}C-NMR (100 MHz, $CDCl_3$)

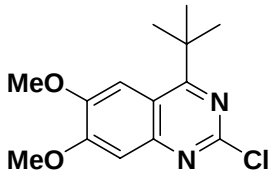
δ = 29.4, 39.3, 120.3, 125.3, 125.5, 127.9, 132.3, 151.6, 155.1, 179.5 ppm;

IR (KBr): ν = 2972 (m), 1529 (m), 1365 (s), 1275 (s), 1103 (s), 895 (s), 763 (s) cm^{-1};

MS (EI, 70 eV): m/z (%) = 220 (30)[M^+], 205 (100), 178 (43), 129 (32), 102 (23);

Elemental Analysis for $C_{12}H_{13}ClN_2$**:** Calcd.: C 65.31; H 5.94; N 12.69;
Found: C 65.16; H 5.95; N 12.49.

8.7.6. 4-*tert*-Butyl-2-chloro-6,7-dimethoxyquinazoline (133f)



$C_{12}H_{11}ClN_2$. MW = 218.68 g mol^{-1}

Prepared according to GP-2 with a reaction time of 10 minutes, starting from 2,4-dichloro-7,8-dimethoxy-quinazoline (1.50 mmol, 400 mg, 97% purity), CuI (5 mol-%) and *t*-BuMgCl (3.70 mmol, 1.25 M in THF). Purification by flash column chromatography (*n*-pentane/EtOAc 5:4) afforded pure **133f** (1.66 mmol, 362 mg, 63% yield) as a light orange solid;

Mp: 103-105 °C;

^{1}H-NMR (300 MHz, $CDCl_3$)

δ = 1.64 (s, 9 H; CH_3), 4.04 (s, 6 H; CH_3O), 7.29 (s, 1 H; Ar-H), 7.62 (s, 1 H; Ar-H) ppm;

^{13}C-NMR (75 MHz, $CDCl_3$)

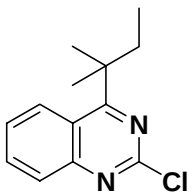
δ = 30.2, 39.8, 56.1, 56.3, 102.7, 104.5, 107.2, 116.8, 148.8, 151.2, 155.3, 177.1 ppm;

IR (KBr): ν = 2973 (s), 2932 (s), 2870 (m), 1620 (s), 1571 (m), 1504 (s), 1466 (s), 1415 (s), 1239 (s), 1202 (s), 1159 (s), 1138 (s), 1029 (m), 1010 (m), 987 (m), 900 5s), 845 (s) cm^{-1};

MS (EI, 70 eV): m/z (%) = 218 (3)[M^+], 206 (6), 189 (21), 132 (4), 117(3);

Elemental Analysis for $C_{12}H_{11}ClN_2$**:** Calcd.: C 59.89; H 6.10; N 9.98;
Found: C 59.49; H 6.17; N 9.71.

8.7.7. 4-*tert*-Pentyl-2-chloroquinazoline (133g)



$C_{13}H_{15}ClN_2$. MW = 234.72 g mol^{-1}

Prepared according to GP-2, starting from 2,4-dichloroquinazoline (1.00 mmol, 199 mg), CuI (5 mol-%) and *t*-AmMgCl (1.50 mmol, 0.85 M in THF). Purification by flash column chromatography (*n*-pentane/DCM 3:1) afforded pure **133g** (0.68 mmol, 159 mg, 68% yield) as a light brown solid;

Mp: 94 °C;

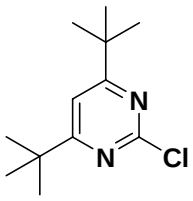
^{1}H-NMR (400 MHz, $CDCl_3$)

δ = 0.63 (t, *J* =7.6 Hz, 3 H; CH_3), 1.50 (s, 6 H; CH_3), 2.03 (q, *J* = 7.4 Hz, 2 H; CH_2), 7.49 (ddd, *J* = 8.7, 6.8, 1.4 Hz, 1 H; Ar-H), 7.76 (ddd, *J* = 8.3, 6.9, 1.4 Hz, 1 H; Ar-H), 7.90 (dd, *J* = 8.5, 0.6 Hz, 1 H; Ar-H), 8.36 (dd, *J* = 8.7, 0.6 Hz, 1 H; Ar-H) ppm;

^{13}C-NMR (100 MHz, $CDCl_3$)

δ = 9.4, 28.5, 35.6, 44.4, 121.9, 126.2, 126.6, 129.1, 133.5, 152.7, 156.2, 180.1 ppm;

8.7.8. 4,6-Di-*tert*-butyl-2-chloropyrimidine (147a)



$C_{12}H_{19}ClN_2$. MW = 226.75 g mol^{-1}

Prepared according to GP-3, starting from 2,4,6-trichloro-pyrimidine (2.4 mmol, 452 mg, 99% purity), CuI (5 mol-%) and *t*-BuMgCl (6.0 mmol, 1.0 M in THF). Purification by flash column chromatography (*n*-pentane/DCM 3:1) afforded pure **147a** (2.1 mmol, 481 mg, 71% yield) as a white solid;

Mp: 82-83 °C;

^{1}H-NMR (400 MHz, $CDCl_3$)

δ = 1.34 (s, 18 H; CH_3), 7.22 (s, 1 H; CH) ppm;

^{13}C-NMR (100 MHz, $CDCl_3$)

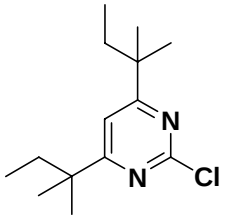
δ = 29.5, 38.0, 110.1, 160.1, 181.3 ppm;

IR (KBr): ν = 2970 (s), 1569 (m), 1263 (s), 1165 (m), 1101 (s), 1061 (m) cm^{-1};

MS (EI, 70 eV): m/z (%) = 226/228 (15)[M^+], 225/227 (16), 211 (100), 196 (15), 184 (43), 169 (6);

Elemental Analysis for $C_{12}H_{19}ClN_2$**:** Calcd.: C 63.56; H 8.45; N 12.35;
Found: C 63.85; H 8.53; N 12.38.

8.7.9. 2-Chloro-4,6-di-*tert*-pentylpyrimidine (147b)



$C_{14}H_{23}ClN_2$. MW = 254.8 g mol^{-1}

Prepared according to GP-3, starting from 2,4,6-trichloro-pyrimidine (2.6 mmol, 500 mg, 99% purity), CuI (5 mol-%) and *t*-AmMgCl (5.9 mmol, 0.5 M in THF). Purification by flash column chromatography (*n*-pentane/DCM 2:1) afforded pure **147b** (1.6 mmol, 410 mg, 60% yield) as a yellow liquid;

^{1}H-NMR (400 MHz, $CDCl_3$)

δ = 0.71 (t, *J* =7.7 Hz, 6 H; CH_3), 1.30 (s, 12 H; CH_3), 1.73 (q, *J* = 7.4 Hz, 4 H; CH_2), 7.13 (s, 1 H; CH) ppm;

^{13}C-NMR (100 MHz, $CDCl_3$)

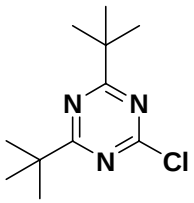
δ = 9.0, 26.6, 35.1, 41.2, 112.1, 160.5, 180.2 ppm;

IR (neat): ν = 2967 (s), 2878 (s), 1568 (s), 1514 (s), 1463 (m), 1288 (m), 1255 (s), 868 (m), 794 (m) cm^{-1};

MS (CI, CH_4, 70 eV): m/z (%) = 255/257 (100)$[M+H]^+$, 239/241(7), 226 (21), 219 (71), 211 (1), 198 (1);

Elemental Analysis for $C_{14}H_{23}ClN_2$**:** Calcd.: C 65.99; H 9.10; N 10.99;
Found: C 65.24; H 8.79; N 11.40.

8.7.10. 2-Chloro-4,6-di-*tert*-butyl-1,3,5-triazine (147c)



$C_{11}H_{18}ClN_3$. MW = 227.73 g mol^{-1}

Prepared according to GP-3, starting from 2,4,6-trichloro-triazine (1.50 mmol, 280 mg, 99% purity), CuI (5 mol-%) and *t*-BuMgCl (3.75 mmol, 1.0 M in THF). Purification by flash column chromatography (*n*-pentane/DCM 30:1) afforded pure **147c** (0.90 mmol, 200 mg, 59% yield) as a white solid;

Mp: 65-66 °C;

^{1}H-NMR (300 MHz, $CDCl_3$)

δ = 1.39 (s, 18 H; CH_3) ppm;

^{13}C-NMR (75 MHz, $CDCl_3$)

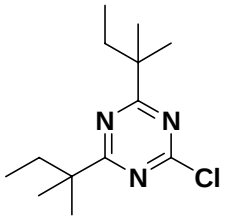
δ = 29.7, 39.7, 171.8, 187.6 ppm;

IR (KBr): ν = 2969 (s), 2932 (s), 2871 (s), 1547 (s), 1497 (s), 1365 (s), 1271 (s), 1234 (s), 1208 (s), 904 (s), 871 (s), 841 (m), 800 (s) cm^{-1};

MS (CI, CH_4, 70 eV): m/z (%) = 228 (100)$[M+H]^+$, 225/227 (12), 210/212 (20), 207/209 (44), 192 (45), 187 (7), 83/85 (35);

Elemental Analysis for $C_{11}H_{18}ClN_3$**:** Calcd.: C 58.01; H 7.97; N 18.45;
Found: C 58.04; H 7.85; N 18.33.

8.7.11. 2-Chloro-4,6-di-*tert*-pentyl-1,3,5-triazine (147d)



$C_{13}H_{22}ClN_3$. MW = 255.79 g mol^{-1}

Prepared according to GP-3, starting from 2,4,6-trichloro-triazine (2.0 mmol, 372 mg, 99% purity), CuI (5 mol-%) and *t*-AmMgCl (5.0 mmol, 0.5 M in THF). Purification by flash column chromatography (*n*-pentane/DCM 5:1) afforded pure **147d** (1.3 mmol, 343 mg, 68% yield) as a colorless liquid;

^{1}H-NMR (300 MHz, $CDCl_3$)

δ = 0.75 (t, *J* =7.6 Hz, 6 H; CH_3), 1.56 (s, 12 H; CH_3), 1.80 (q, *J* = 7.4 Hz, 4 H; CH_2) ppm;

^{13}C-NMR (75 MHz, $CDCl_3$)

δ = 9.0, 25.9, 34.6, 43.1, 171.0, 186.9 ppm;

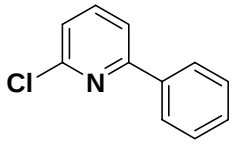
IR (neat): ν = 2969 (s), 2879 (m), 1540 (s), 1499 (s), 1371 (m), 1274 (s), 1204 (w), 868 (m), 797 (w) cm^{-1};

MS (CI, CH_4, 70 eV): m/z (%) = 256/258 (100)$[M+H]^+$, 240 (11), 227 (22), 220 (37), 192 (5), 123 (10), 98 (2), 83/85 (6);

Elemental Analysis for $C_{13}H_{22}ClN_3$**:** Calcd.: C 61.04; H 8.67; N 16.43;
Found: C 60.89; H 8.37; N 16.53.

8.8. Synthesis of 2-Halo-6-arylpyridines

8.8.1. 2-Chloro-6-phenylpyridine (156a)



$C_{11}H_8ClN$. MW = 189.64 g mol^{-1}

Prepared according to GP-6, starting from 2-*tert*-butoxy-6-phenylpyridine **155a** (22.00 mmol, 5.00 g) and $POCl_3$ (48.40 mmol, 4.51 mL). Purification by flash column chromatography (MTBE/Hex 1:30) afforded pure **156a** (14.90 mmol, 2.89 g, 69% yield) as colorless oil;

^{1}H-NMR (400 MHz, $CDCl_3$)

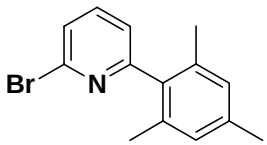
δ = 7.21 (dd, *J* = 7.4, 0.8 Hz, 1 H; Ar-H), 7.38-7.47 (m, 3 H; Ar-H), 7.60 (dd, *J* = 8.0, 1.1 Hz, 1 H; Ar-H), 7.65 (t, *J* = 7.5 Hz, 1 H; Ar-H), 7.95-7.99 (m, 2 H; Ar-H) ppm;

^{13}C-NMR (100 MHz, $CDCl_3$)

δ = 118.7, 122.5, 127.0, 128.8, 129.6, 127.7, 129.3, 151.3, 158.0 ppm;

Analytical data are in agreement with those reported in the literature.[157]

8.8.2. 2-Bromo-6-mesitylpyridine (148b)



$C_{14}H_{14}BrN$. MW = 276.17 g mol^{-1}

Prepared according to GP-4, starting from 2,6-dibromopyridine (12.70 mmol, 3.00 g, 98% purity) and mesitylMgBr (13.90 mmol, 1.36 M in THF). Purification by flash column chromatography (*n*-pentane/EtOAc 15:1) afforded **148b** (8.9 mmol, 2.45 g, 70% yield) as a colorless oil;

^{1}H-NMR (300 MHz, $CDCl_3$)

δ = 2.03 (s, 6 H; CH_3), 2.30 (s, 3 H; CH_3), 6.91 (br s, 2 H; Ar-H), 7.17 (d, *J* = 7.6 Hz, 1 H; Ar-H), 7.43 (d, *J* = 7.5, 1 H; Ar-H), 7.5 (t, *J* = 7.5 Hz, 1 H; Ar-H) ppm;

^{13}C-NMR (75 MHz, $CDCl_3$)

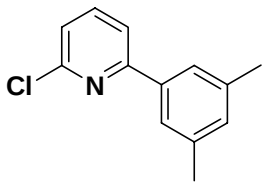
δ = 20.2, 21.1, 123.7, 126.0, 128.4, 135.6, 136.3, 137.9, 138.5, 141.8, 161.2 ppm;

IR (KBr): ν = 3008 (m), 2960 (m), 1730 (m), 1610 (s), 1572 (s), 1440 (s), 1382 (s), 1277 (m), 1159 (s), 1121 (s), 1034 (s), 849 (s), 794 (s), 745 (s) cm-1;

MS (EI, 70 eV): m/z (%) = 275/277 (51)[M^+], 274/276 (100)[M-H]$^+$, 196 (32), 181 (18), 90 (19);

HRMS for $C_{14}H_{14}BrN$: Calcd.: 275.030972;
Found: 275.030934.

8.8.3. 2-Chloro-6-(3,5-dimethylphenyl)pyridine (156b)



$C_{13}H_{12}ClN$. MW = 217.69 g mol^{-1}

Prepared according to GP-6, starting from 2-*tert*-butoxy-6-(3,5-dimethylphenyl)pyridine **155b** (21.40 mmol, 5.50 g) and $POCl_3$ (47.08 mmol, 4.4 mL). Purification by flash column chromatography (MTBE/Hex 1:30) afforded pure **156b** (11.4 mmol, 2.50 g, 60% yield) as a white solid;

Mp: 52 °C;

^{1}H-NMR (400 MHz, $CDCl_3$)

δ = 2.38 (s, 6 H; CH_3), 7.06 (s, 1 H; Ar-H), 7.22 (dd, *J* = 7.7, 0.8 Hz, 1 H; Ar-H), 7.59 (br s, 2 H; Ar-H), 7.61 (dd, *J* = 7.7, 0.8 Hz, 1 H; Ar-H), 7.66 (t, *J* = 7.7 Hz, 1 H; Ar-H) ppm;

^{13}C-NMR (100 MHz, $CDCl_3$)

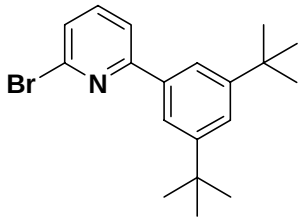
δ = 21.5, 118.7, 122.2, 124.8, 131.2, 137.6, 138.3, 139.1, 151.1, 158.4 ppm;

IR (KBr): ν = 3012 (w), 2918 (m), 1604 (m), 1578 (s), 1557 (s), 1436 (s), 1387 (m), 1158 (s), 1136 (s), 1098 (m), 854 (m), 795 (s), 731 (s), 745 (s) cm^{-1};

MS (EI, 70 eV): m/z (%) = 218/220 (35)[M^+], 217 (100), 214/216 (49), 201/203 (10), 180 (7), 166 (6), 152 (3);

Elemental Analysis for $C_{13}H_{12}ClN$: Calcd.: C 71.72; H 5.56; N 6.43;
Found: C 71.87; H 5.34; N 6.13.

8.8.4. 2-Bromo-6-(3,5-di-*tert*-butylphenyl)pyridine (148d)



$C_{19}H_{24}BrN$. MW = 346.3 g mol^{-1}

Prepared according to GP-4, starting from 2,6-dibromopyridine (3.2 mmol, 787 mg, 98% purity) and 3,5-di-*t*BuPhMgBr (3.5 mmol, 0.5 M in THF). Purification by flash column chromatography (*n*-pentane/DCM 2:1) afforded pure **148d** (2.3 mmol, 819 mg, 61% yield) as a white solid;

Mp: 108-109 °C;

^{1}H-NMR (400 MHz, $CDCl_3$)

δ = 1.38 (s, 18 H; CH_3), 7.426 (s, 1 H; Ar-H), 7.45 (br s, 2 H; Ar-H), 7.47 (d, *J* = 1.2 Hz, 1 H; Ar-H), 7.57 (t, *J* = 7.7 Hz, 1 H; Ar-H), 7.66 (dd, *J* = 7.1, 0.7 Hz, 1 H; Ar-H) ppm;

^{13}C-NMR (100 MHz, $CDCl_3$)

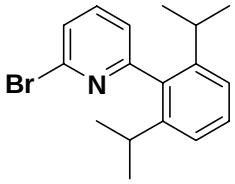
δ = 31.6, 35.1, 119.4, 121.4, 123.8, 125.9, 138.7, 140.8, 141.9, 151.1, 159.8 ppm;

IR (KBr): ν = 3425 (m), 2926 (s), 2861 (s), 1573 (s), 1545 (s), 1461 (s), 1413 (s), 1247 (s), 1162 (m), 1128 (s), 1087 (s), 797 (s), 739 (s), 704 (s) cm^{-1};

MS (EI, 70 eV): m/z (%) = 345/347 (49)[M^+], 330 (100), 304 (6), 273/275 (15), 257/259 (2), 143 (6), 103 (4);

HRMS for $C_{19}H_{24}BrN$: Calcd.: 345.109223;
Found: 345.109183.

8.8.5. 2-Bromo-6-(2,6-diisopropylphenyl)pyridine (148f)



$C_{17}H_{20}BrN$. MW = 318.25 g mol^{-1}

Prepared according to GP-4, starting from 2,6-dibromopyridine (17.00 mmol, 4.13 g, 98% purity) and 2,6-di-*i*PrPhMgBr (20.50 mmol, 0.71 M in THF). Purification by flash column chromatography (*n*-pentane/DCM 1:1) afforded pure **148f** (11.38 mmol, 3.62 g, 67% yield) as a white solid;

Mp: 176-177 °C;

^{1}H-NMR (400 MHz, $CDCl_3$)

δ = 1.09 (d, *J* = 6.9 Hz, 6 H; CH_3), 1.14 (d, *J* = 6.9 Hz, 6 H; CH_3), 2.47 (hept, *J* = 6.9 Hz, 2 H; CH), 7.19 (s, 1 H; Ar-H), 7.21 (s, 1 H; Ar-H), 7.23 (dd, *J* = 7.4, 0.8 Hz, 1 H; Ar-H), 7.36 (t, *J* = 7.7 Hz, 1 H; Ar-H), 7.48 (dd, *J* = 8.0, 0.8 Hz, 1 H; Ar-H), 7.60 (t, *J* = 7.4 Hz, 1 H; Ar-H) ppm;

^{13}C-NMR (100 MHz, $CDCl_3$)

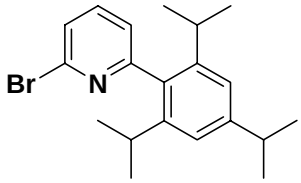
δ = 22.7, 23.0, 29.3, 121.5, 122.6, 124.8, 127.7, 135.9, 136.7, 140.3, 145.1, 159.7 ppm;

IR (KBr): ν = 3028 (s), 2956 (m), 1569 (s), 1431 (s), 1113 (s), 1039 (s), 804 (s) cm^{-1};

MS (EI, 70 eV): m/z (%) = 318 (100)[M^+], 302 (13), 287 (5), 273 (3), 260 (5), 238 (23), 196 (21), 180 (10);

HRMS for $C_{17}H_{20}BrN$: Calcd.: 317.077923;
Found: 317.077795.

8.8.6. 2-Bromo-6-(2,4,6-triisopropylphenyl)pyridine (148g)



$C_{20}H_{26}BrN$. MW = 360.33 g mol^{-1}

Prepared according to GP-4, starting from 2,6-dibromopyridine (2.00 mmol, 500 mg, 98% purity) and 2,4,6-*i*$Pr_3C_6H_2MgBr$ (2.28 mmol, 0.82 M in THF). Purification by flash column chromatography (*n*-pentane/DCM 2:1) afforded pure **148g** (1.65 mmol, 595 mg, 83% yield) as a white solid;

Mp: 241 °C;

^{1}H-NMR (300 MHz, $CDCl_3$)

δ = 1.09 (d, *J* = 6.9 Hz, 6 H; CH_3), 1.14 (d, *J* = 6.9 Hz, 6 H; CH_3), 1.26 (d, *J* = 6.9 Hz, 6 H; CH_3), 2.47 (hept, *J* = 6.9 Hz, 2 H; CH), 2.91 (hept, *J* = 6.9 Hz, 1 H; CH), 7.05 (s, 2 H; Ar-H), 7.23 (d, *J* = 1.0 Hz, 1 H; Ar-H), 7.46 (dd, *J* = 7.9, 1.0 Hz, 1 H; Ar-H), 7.59 (t, *J* = 7.4 Hz, 1 H; Ar-H) ppm;

^{13}C-NMR (75 MHz, $CDCl_3$)

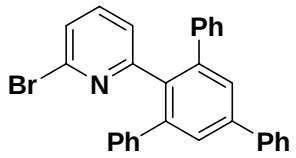
δ = 23.8, 24.0, 24.1, 30.4, 34.4, 120.8, 123.9, 125.9, 134.9, 137.9, 141.5, 146.1, 149.3, 161.3 ppm;

IR (KBr): ν = 2961 (m), 2868 (m), 1574 (s), 1544 (s), 1432 (s), 1127 (s) cm^{-1};

MS (EI, 70 eV): m/z (%) = 361 (53)[M^+], 360 (100), 359 (59), 344 (8);

HRMS for $C_{20}H_{26}BrN$: Calcd.: 359.12487;
Found: 359.12486.

8.8.7. 2-Bromo-6-(2,4,6-triphenylphenyl)pyridine (148h)



$C_{29}H_{20}BrN$. MW = 462.38 g mol^{-1}

Prepared according to GP-4, starting from 2,6-dibromopyridine (8.40 mmol, 2.00 g, 98% purity) and 2,4,6-tris-PhPhMgBr (12.60 mmol, 0.4 M in THF) with the following modifications: 1 mol-% of $[NiCl_2(PCy_3)_2]$ as catalyst, the reaction was stirred for 4 days at 75 °C and for additional 4 days at 85 °C. Purification by flash column chromatography (Hex/toluene 3:2-1:1) afforded pure **148h** (4.82 mmol, 2.23 g, 57% yield) as a white solid;

Mp: 243-244 °C;

^{1}H-NMR (400 MHz, $CDCl_3$)

δ = 6.82 (d, *J* = 7.3 Hz, 1 H; Ar-H), 7.12 (t, *J* = 7.0 Hz, 1 H; Ar-H), 7.15-7.28 (m, 11 H; Ar-H), 7.38 (t, *J* = 7.3 Hz, 1 H; Ar-H), 7.46 (t, *J* = 7.5 Hz, 2 H; Ar-H), 7.65-7.72 (m, 4 H; Ar-H) ppm;

^{13}C-NMR (100 MHz, $CDCl_3$)

δ = 125.1, 125.3, 126.5, 127.1, 127.5, 127.6, 128.0, 128.7, 129.5, 135.7, 137.0, 140.1, 140.3, 140.9, 142.3, 159.5 ppm;

IR (KBr): ν = 3031 (w), 1699 (m), 1651 (m), 1575 (m), 1558 (s), 1542 (s),1506 (m), 1420 (m), 1129(m), 767 (s), 698 (s) cm^{-1};

MS (EI, 70 eV): m/z (%) = 461/463 (60)[M^+], 460/462 (50), 383 (28), 382 (100), 354 (14), 341 (11), 183 (7);

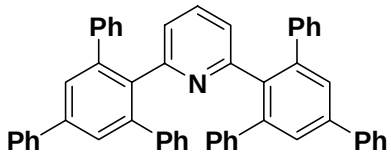
Elemental Analysis for $C_{29}H_{20}BrN$: Calcd.: C 75.33; H 4.36; N 3.03;
Found: C 75.64; H 4.60; N 3.01.

❖ *Gram scale synthesis of 2-bromo-6-(2,4,6-triphenylphenyl)pyridine (**148h**)*

A Grignard solution was prepared from bromo-2,4,6-triphenylbenzene (82.30 mmol, 31.72 g) and Mg (100.00 mmol, 2.50 g) in THF (200 mL); after complete addition of the bromoarene, the reaction mixture was stirred for 2 h at 70 °C. The resulting suspension was then transferred via teflon-canula and under an inert atmosphere of argon, to a well-stirred mixture of 2,6-dibromopyridine (62.00 mmol, 14.69 g, 98% purity), $[Ni(acac)_2]$ (1.65 mmol, 424 mg, 2.7 mol-%) and *i*PrHCl (1.82 mmol, 774 mg, 2.9 mol-%) in toluene (50 mL). The volume of

the solution was reduced in vacuum to 200 mL, and slowly heated to 85 °C. The reaction mixture turned from dark-red to a green-yellow suspension and was stirred for 5 h at 85 °C. After cooling to room temperature, the reaction was quenched with H_2O (150 mL), saturated aqueous NH_4Cl (150 mL) and toluene (200 mL). EtOH was used to transfer the slurry into a round-bottomed flask, where it was shaken until obtaining homogeneous mixture. This slurry was then filtered to leave a solid, which was washed with H_2O (100 mL), EtOH (100 mL) and plenty of toluene and afforded as a by-product of the reaction the pure bis-2,6-(2,4,6-triphenylphenyl)pyridine **152h** (7.8 mmol, 5.41 g, 13% yield) as a white powder. The organic layer resulting from the combined filtrates was washed with H_2O (150 mL), evaporated to a volume of 100 mL and filtered to leave a solid, which was washed with MTBE (2×70 mL) and afforded a first crop of product. The filtrates were evaporated to dryness, slurried up with acetone (30 mL), filtered and washed with acetone (2×20 mL) to leave a second crop of product. The combined products were dried in an oven (100 °C) to afford pure **148h** (44.37 mmol, 20.50 g, 72% yield) as a white powder.

8.8.8. Bis-2,6-(2,4,6-triphenylphenyl)pyridine (152h)



$C_{53}H_{37}N$. MW = 687.87 g mol^{-1}

Obtained as by-product in the large scale synthesis of **148h**, see above;

^{1}H-NMR (400 MHz, $CDCl_3$)

δ = 6.36 (d, *J* = 7.8, 2 H), 6.72 (t, *J* = 7.8, 1 H), 6.84-6.90 (m, 8 H), 7.09-7.16 (m, 12 H), 7.33-7.40 (m, 2 H), 7.42-7.49 (m, 4 H), 7.57 (s, 4 H), 7.69-7.72 (m, 4 H) ppm;

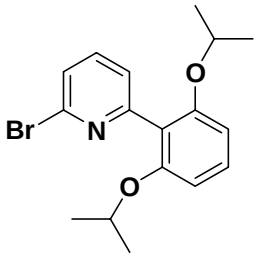
Solubility of **X** too low to get ^{13}C-NMR spectra;

IR (KBr): ν = 3042 (m), 1588 (m), 1492 (m), 1434 (m), 762 (s), 698 (s);

MS (ESI): m/z = 688.5 $[M+H]^+$;

Elemental Analysis for $C_{53}H_{37}N$ + 0.5 H_2O: Calcd.: C 91.35; H 5.50; N 2.01;
Found: C 91.32; H 5.42; N 2.14.

8.8.9. 2-Bromo-6-(2,6-diisopropoxyphenyl)pyridine (148e)



$C_{17}H_{20}BrNO_2$. MW = 350.25 g mol^{-1}

<u>*2,6-diisopropylphenyllithium*</u>: A solution of *n*-BuLi (55.00 mmol, 35.0 mL, 16% in *n*-hexane) was added to neat 2,6-diisopropoxy-benzene (55.00 mmol, 10.69 g) and the mixture was heated 14 h at 50 °C, resulting in a suspension of a colorless powder of 2,6-diisopropylphenyllithium;

<u>*Magnesium dibromide:*</u> a solution of $MgBr_2$ was prepared from the addition of 1,2-dibromoethane (50.00 mmol, 4.3 mL) to Mg (50.00 mmol, 1.22 g) in THF (50 mL) with few crystals of iodine. After initialization of the reaction, the remaining 1,2-dibromoethane was added dropwise and the resulting mixture was stirred 1 h at 55 °C;

<u>*2,6-diisopropylphenylmagnesiumbromide:*</u> the suspension of the aryllithium compound was transferred via teflon-tubing under argon to the $MgBr_2$-solution, resulting in a clear solution, which was evaporated in vacuum (to ca. 20 mL), then redissolved in 60 mL of THF;

To the solution of 2,6-diisopropylphenylmagnesiumbromide were slowly added 2,6-dibromopyridine (50.00 mmol, 11.84 g, 98% purity) and [$NiCl_2(PCy_3)_2$] (0.29 mmol, 200 mg, 0.58 mol-%) and the reaction mixture was stirred for 15 h in a water bath at room temperature (exothermal reaction). The solidified mixture was quenched by addition of aqueous NH_4Cl (200 mL) and MTBE (150 mL). The organic phase was washed with H_2O (3×100 mL), then the solvent was removed under reduced pressure. Purification by flash column chromatography (Hex/MTBE 20:1), followed by recrystallization afforded pure **148e** (2.30 mmol, 14.54 g, 83% yield) as colorless crystals;

Mp: 77-78 °C;

^{1}H-NMR (300 MHz, $CDCl_3$)

δ = 1.18 (d, *J* = 6.1 Hz, 12 H; CH_3), 4.42 (hept, *J* = 6.1 Hz, 2 H; CH), 6.59 (d, *J* = 8.4 Hz, 2 H; Ar-H), 7.22 (d, *J* = 7.5 Hz, 1 H; Ar-H), 7.27 (d, *J* = 7.5 Hz, 1 H; Ar-H), 7.37 (d, *J* = 7.8 Hz, 1 H; Ar-H), 7.53 (t, *J* = 7.7 Hz, 1 H; Ar-H) ppm;

^{13}C-NMR (75 MHz, $CDCl_3$)

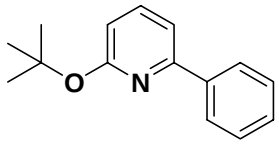
δ = 22.1, 71.4, 107.5, 120.9, 125.3, 125.4, 129.7, 137.5, 140.5, 156.2, 156.9 ppm;

IR (KBr): ν = 2976 (m), 2921 (m), 1592 (s), 1545 (m), 1459 (s), 1381 (m), 1249 (s), 1118 (s), 1062(s), 785 (m) cm^{-1};

MS (EI, 70 eV): m/z (%) = 349/351 (33)[M^+], 334/336 (11), 265/267 (100), 249/251 (25), 186 (14);

Elemental Analysis for $C_{17}H_{20}BrNO_2$: Calcd.: C 58.30; H 5.76; N 4.00;
Found: C 58.43; H 5.82; N 4.11.

8.8.10. 2-*tert*-Butoxy-6-phenylpyridine (155a).



$C_{15}H_{17}NO$. MW = 227.3 g mol^{-1}

Prepared according to GP-5, starting from 2-*tert*-butoxy-6-chloropyridine (43.00 mmol, 8.00 g) and a solution of PhMgCl (48.6 mmol, 1.8 M in THF). Purification by Kugelrohr distillation (ca. 0.1 mbar; 130 °C) afforded pure **155a** (41.9 mmol, 9.53 g, 98% yield) as colorless oil;

^{1}H-NMR (300 MHz, $CDCl_3$)

δ = 1.67 (s, 9 H), 6.60 (d, *J* = 8.2, 1 H), 7.27 (d, *J* = 7.4, 1 H), 7.31-7.48 (m, 3 H), 7.54 (dd, *J* = 8.2, 7.4, 1 H), 7.97-8.04 (m, 2 H) ppm;

^{13}C-NMR (75 MHz, $CDCl_3$)

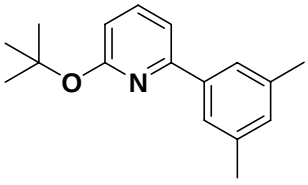
δ = 28.4, 78.9, 111.2, 111.7, 126.2, 128.1, 128.1, 138.4, 139.0, 153.8, 163.1 ppm;

IR (film): ν = 3059 (w), 2975 (s), 1575 (s), 1441 (s), 1332 (m), 1174 (s), 946 (m) cm^{-1};

MS (EI, 70 eV): m/z (%) = 227 (4)[M^+], 171 (100), 143 (45), 115 (15), 104 (3);

Elemental Analysis for $C_{15}H_{17}NO$: Calcd.: C 79.26; H 7.54; N 6.16;
Found: C 79.36; H 7.56; N 6.58.

8.8.11. 2-*tert*-Butoxy-6-(3,5-dimethylphenyl)pyridine (155b).



$C_{17}H_{21}NO$. MW = 255.35 g mol^{-1}

Prepared according to GP-5, starting from 2-*tert*-butoxy-6-chloropyridine (27.00 mmol, 5.00 g) and a solution of 3,5-$Me_2C_6H_3MgCl$ (30.5 mmol, 1.1 M in THF). Purification by Kugelrohr distillation (ca 0.1 mbar; 140 °C) afforded pure **155b** (24.11 mmol, 6.15 g, 90% yield) as colorless oil;

^{1}H-NMR (300 MHz, $CDCl_3$)

δ = 1.67 (s, 9 H; CH_3), 2.39 (s, 6 H; CH_3), 6.58 (dd, *J* = 8.1, 0.7 Hz, 1 H; Ar-H), 7.05 (br s, 1 H; Ar-H), 7.26 (dd, *J* = 7.5, 0.6 Hz, 1 H; Ar-H), 7.54 (t, *J* = 7.5 Hz, 1 H; Ar-H), 7.60 (s, 2 H; Ar-H) ppm;

^{13}C-NMR (75 MHz, $CDCl_3$)

δ = 21.5, 28.8, 79.3, 111.4, 112.4, 124.6, 130.2, 138.0, 138.7, 139.5, 154.6, 163.4 ppm;

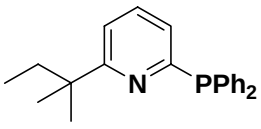
IR (KBr): ν = 2973 (s), 2923 (s), 1580 (s), 1442 (s), 1282 (m), 1173 (s), 802 (s) cm^{-1};

MS (EI, 70 eV): m/z (%) = 255 (11)[M^+], 199 (100), 184 (3), 171 (26), 156 (4), 128 (3), 82 (3);

Elemental Analysis for $C_{17}H_{21}NO$: Calcd.: C 79.96; H 8.29; N 5.49;
Found: C 80.32; H 8.10; N 5.84.

8.9. Synthesis of Aza-alkylphosphanes 130a-f, 158

8.9.1. 2-(Diphenylphosphino)-6-*tert*-pentylpyridine (130b)



$C_{22}H_{24}NP$. MW = 333.41 g mol^{-1}

Prepared according to GP-7, starting from 2-chloro-6-*tert*-amylpyridine **133b** (12.0 mmol, 2.197 g) and a solution of $NaPPh_2$ (12.0 mmol, 1.0 M in THF). Purification by flash column chromatography under argon (*n*-pentane/DCM 3:1) afforded pure **130b** (8.3 mmol, 2.746 g, 69% yield) as a white solid;

Mp: 75-76 °C ;

^{1}H-NMR (300 MHz, C_6D_6)

δ = 0.64 (t, *J* = 7.4 Hz, 3 H; CH_3), 1.24 (s, 6 H; CH_3), 1.69 (q, *J* = 7.4 Hz, 2 H; CH_2), 6.82 (dt, *J* = 7.3, 1.2 Hz, 1 H; Ar-H), 6.95 (dt, *J* = 7.9, 1.6 Hz, 1 H; Ar-H), 6.99 (dd, *J* = 7.3, 2.5 Hz, 1 H; Ar-H), 7.02-7.13 (m, 6 H; Ar-H), 7.48-7.55 (m, 4 H; Ar-H) ppm;

^{13}C-NMR (75 MHz, C_6D_6)

δ = 9.3, 27.4, 35.8, 41.1, 118.3, 125.2 (d, $J_{C\text{-}P}$ =22.6 Hz), 128.5 (d, $J_{C\text{-}P}$ = 6.8 Hz), 128.8, 134.6 (d, $J_{C\text{-}P}$ = 19.6 Hz), 135.5 (d, $J_{C\text{-}P}$ = 3.7 Hz), 137.9 (d, $J_{C\text{-}P}$ = 12.0 Hz), 162.7 (d, $J_{C\text{-}P}$ = 3.0 Hz), 168.3 (d, $J_{C\text{-}P}$ = 9.8 Hz) ppm;

^{31}P-NMR (121 MHz, C_6D_6)

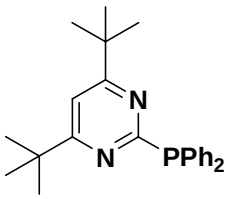
δ = –3.7 ppm;

IR (KBr): ν = 3449 (w), 3062 (m), 2957 (s), 2869 (s), 1556 (s), 1431 (s), 1380 (s), 806 (s), 744 (s), 695 (s) cm^{-1};

MS (EI, 70 eV): m/z (%) = 333 (74)[M^+], 318 (41), 305 (100);

Elemental Analysis for $C_{22}H_{24}NP$: Calcd.: C 79.25; H 7.26; N 4.20;
Found: C 79.17; H 7.41; N 4.14.

8.9.2. 4,6-Di-*tert*-butyl-2-(diphenylphosphino)pyrimidine (130c)



$C_{24}H_{29}N_2P$. MW = 376.47 g mol^{-1}

Prepared according to GP-7 starting from 2-chloro-4-di-*tert*-butylpyrimidine **147a** (2.0 mmol, 452 mg) and a solution of $NaPPh_2$ (2.0 mmol, 1.0 M in THF). Purification by flash column chromatography under argon (*n*-pentane/DCM 2.5:1) afforded pure **130c** (1.7 mmol, 650 mg, 87% yield) as a white solid;

Mp: 70-71 °C ;

^{1}H-NMR (400 MHz, C_6D_6)

δ = 0.88 (s, 18 H; CH_3), 6.73 (s, 1H; Ar-H), 6.80-6.88 (m, 6 H; Ar-H), 7.42-7.48 (m, 4 H; Ar-H) ppm;

^{13}C-NMR (100 MHz, C_6D_6)

δ = 29.0, 37.5, 108.2, 127.5, 127.8 (d, $J_{C\text{-}P}$ = 7.1 Hz), 128.4, 134.8 (d, $J_{C\text{-}P}$ = 19.1 Hz), 137.0 (d, $J_{C\text{-}P}$ = 8.9 Hz), 176.6 (d, $J_{C\text{-}P}$ = 6.5 Hz) ppm;

^{31}P-NMR (160 MHz, C_6D_6)

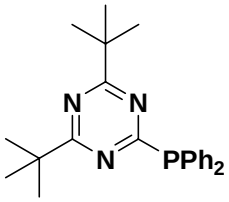
δ = 1.2 ppm;

IR (KBr): ν = 3058 (m), 2955 (s), 1564 (s), 1510 (s), 1436 (m), 1279 (s), 880 (m), 740 (s), 687 (s), 504 (m) cm^{-1};

MS (EI, 70 eV): m/z (%) = 376 (100)[M^+], 361 (19), 334 (11), 299 (8), 283 (7), 267 (4), 253 (3), 193 (10), 183 (17);

Elemental Analysis for $C_{24}H_{29}N_2P$**:** Calcd.: C 76.57; H 7.76; N 7.44;
Found: C 76.60; H 7.94; N 7.24.

8.9.3. 2,4-Di-*tert*-butyl-6-(diphenylphosphino)-1,3,5-triazine (130d)



$C_{23}H_{28}N_3P$. MW = 377.46 g mol^{-1}

Prepared according to GP-7, starting from 2-chloro-4,6-di-*tert*-butyl-triazine **147c** (1.0 mmol, 227 mg) and a solution of $NaPPh_2$ (1.0 mmol, 1.0 M in THF). Purification by flash column chromatography under argon (Hex/MTBE 30:1) afforded pure **130d** (0.8 mmol, 307 mg, 82% yield) as a white solid;

Mp: 66-67 °C;

^{1}H-NMR (400 MHz, C_6D_6)

δ = 1.02 (s, 18 H; CH_3), 6.80-6.87 (m, 6 H; Ar-H), 7.35-7.41 (m, 4 H; Ar-H) ppm;

^{13}C-NMR (100 MHz, C_6D_6)

δ = 28.6, 39.5, 127.0, 128.0 (d, $J_{C\text{-}P}$ = 7.6 Hz), 128.9, 132.2 (d, $J_{C\text{-}P}$ = 9.8 Hz), 134.8 (d, $J_{C\text{-}P}$ = 19.8 Hz), 182.9 ppm;

^{31}P-NMR (160 MHz, C_6D_6)

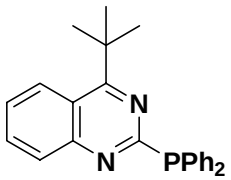
δ = 0.4 ppm;

IR (KBr): ν = 3926 (s), 3400 (w), 3055 (m), 2959 (s), 2927 (s), 1512 (s), 1434 (m), 1361 (m), 1289 (s), 741 (s), 694 (s) cm^{-1};

MS (EI, 70 eV): m/z (%) = 378 (26)[M^+], 377 (100), 376 (13), 362 (16), 335 (3), 320 (5), 211 (13), 183 (24);

Elemental Analysis for $C_{12}H_{13}ClN_2$**:** Calcd.: C 73.19; H 7.48; N 11.13;
Found: C 73.45; H 7.28; N 10.74.

8.9.4. 4-*tert*-Butyl-2-(diphenylphosphino)quinazoline (130e)



$C_{24}H_{23}N_2P$. MW = 370.43 g mol^{-1}

Prepared according to GP-7, starting from 2-chloro-4-*tert*-butyl-quinazoline **133e** (0.42 mmol, 93 mg) and a solution of $NaPPh_2$ (0.42 mmol, 1.0 M in THF). Purification by flash column chromatography under argon (*n*-pentane/DCM 2:1) afforded pure **130e** (0.31 mmol, 115 mg, 75% yield) as a light pink solid;

Mp: 111 °C;

^{1}H-NMR (400 MHz, C_6D_6)

δ = 1.33 (s, 9 H; CH_3), 7.02 (dt, *J* = 6.8, 1.3 Hz, 1 H; Ar-H), 7.09-7.19 (m, 6 H; Ar-H), 7.24 (dt, *J* = 8.2, 1.5 Hz, 1 H; Ar-H), 7.79 (td, *J* = 8.2, 1.5 Hz, 4 H; Ar-H), 7.93 (d, *J* = 8.3 Hz, 1 H; Ar-H), 8.02 (d, *J* = 8.4 Hz, 1 H; Ar-H) ppm;

^{13}C-NMR (100 MHz, C_6D_6)

δ = 30.4, 40.3, 121.1, 125.8, 126.2, 128.1 (d, $J_{C\text{-}P}$ = 7.6 Hz), 128.7, 130.3, 132.0, 135.0 (d, $J_{C\text{-}P}$ = 19.8 Hz), 137.0 (d, $J_{C\text{-}P}$ = 9.1 Hz), 151.5 (d, $J_{C\text{-}P}$ = 6.8 Hz), 170.8 (d, $J_{C\text{-}P}$ = 14.4 Hz), 174.4 (d, $J_{C\text{-}P}$ = 6.8 Hz);

^{31}P-NMR (160 MHz, C_6D_6)

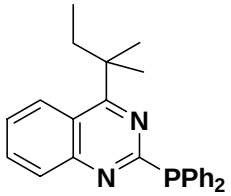
δ = 1.6 ppm;

IR (KBr): ν = 3056 (m), 2973 (s), 2929 (s), 2870 (m), 1608 (w), 1558 (s), 1518 (m), 1481 (s), 1432 (s), 1362 (m), 1279 (s), 1214 (s), 1172 (m), 1101 (m), 768 (s), 743 (s), 696 (s) cm^{-1};

MS (EI, 70 eV): m/z (%) = 370 (100)[M^+], 355 (33), 327 (18), 312 (3), 291 (3), 277 (10), 183 (29), 108 (7);

Elemental Analysis for $C_{24}H_{23}N_2P$**:** Calcd.: C 77.82; H 6.26; N 7.56;
Found: C 77.15; H 6.32; N 7.34.

8.9.5. 4-*tert*-Pentyl-2-(diphenylphosphino)quinazoline (130f)



$C_{25}H_{25}N_2P$. MW = 384.45 g mol^{-1}

Prepared according to GP-7, starting from 2-chloro-4-*tert*-amyl-quinazoline **133g** (0.47 mmol, 110 mg) and a solution of $NaPPh_2$ (0.47 mmol, 1.0 M in THF). Purification by flash column chromatography under argon (*n*-pentane/DCM 1.5:1) afforded pure **130f** (0.37 mmol, 142 mg, 79% yield) as a light brown solid;

Mp: 121 °C;

^{1}H-NMR (300 MHz, C_6D_6)

δ = 0.50 (t, *J* =7.7 Hz, 3 H; CH_3), 1.30 (s, 6 H; CH_3), 1.81 (q, *J* = 7.6 Hz , 2 H; CH_2), 7.00-7.27 (m, 8 H; Ar-H), 7.73-7.80 (m, 3 H; Ar-H), 7.91-8.08 (m, 2 H; Ar-H), 8.16-8.24 (m, 1 H; Ar-H) ppm;

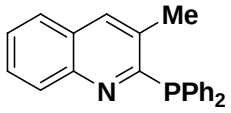
^{13}C-NMR (75 MHz, C_6D_6)

δ = 9.7, 28.8, 35.9, 44.6, 122.1, 126.4 (d, $J_{C\text{-}P}$ = 12.0 Hz), 128.7, 129.2, 130.9, 132.6, 133.1 (d, $J_{C\text{-}P}$ = 8.9 Hz), 135.5 (d, $J_{C\text{-}P}$ = 19.7 Hz), 137.6 (d, $J_{C\text{-}P}$ = 8.9 Hz), 152.0 (d, $J_{C\text{-}P}$ = 7.5 Hz), 171.4 (d, $J_{C\text{-}P}$ = 15.1 Hz), 174.2 (d, $J_{C\text{-}P}$ = 7.5 Hz) ppm;

^{31}P-NMR (121 MHz, C_6D_6)

δ = 1.3 ppm;

8.9.6. 2-(Diphenylphosphino)-3-methylquinoline (158)



$C_{22}H_{18}NP$. MW = 327.36 g mol^{-1}

Prepared according to GP-7, starting from 2-chloro-3-methylquinoline **157** (2.5 mmol, 450 mg, 98% purity) and a solution of $NaPPh_2$ (2.5 mmol, 1.0 M in THF). Purification by flash column chromatography under argon (*n*-pentane/DCM 15:1) afforded pure **158** (1.9 mmol, 650 mg, 80% yield) as a crystalline powder;

Mp: 143-144 °C;

^{1}H-NMR (400 MHz, C_6D_6)

δ = 2.01 (s, 3 H; CH_3), 6.77-6.86 (m, 7 H; Ar-H), 6.90 (ddd, *J* = 1.6, 1.4, 0.4 Hz, 1 H; Ar-H), 6.95 (d, *J* = 5.2 Hz, 1 H; Ar-H), 7.05 (d, *J* = 8.0 Hz, 1 H; Ar-H), 7.23-7.28 (m, 4 H; Ar-H), 7.70 (d, *J* = 8.5 Hz, 1 H; Ar-H) ppm;

^{13}C-NMR (100 MHz, C_6D_6)

δ = 19.7 (d, $J_{C\text{-}P}$ = 16.0 Hz), 126.3, 126.5, 127.8, 128.1 (d, $J_{C\text{-}P}$ = 7.5 Hz), 128.6, 129.9, 134.2, 134.4 (d, $J_{C\text{-}P}$ = 4.6 Hz), 134.5, 134.8 (d, $J_{C\text{-}P}$ = 19.9 Hz), 136.0 (d, $J_{C\text{-}P}$ = 7.6 Hz), 147.2 (d, $J_{C\text{-}P}$ = 4.5 Hz), 163.5 (d, $J_{C\text{-}P}$ = 7.6 Hz), 186.5 ppm;

^{31}P-NMR (160 MHz, C_6D_6)

δ = –4.0 ppm;

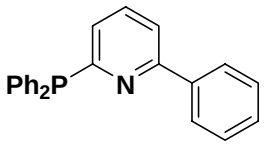
IR (KBr): ν = 2971 (w), 1586 (s), 1548 (m), 1480 (s), 1433 (s), 1306 (m), 1131 (m), 1033 (s), 1004 (s), 746 (s), 695 (s) cm^{-1};

MS (EI, 70 eV): m/z (%) = 327 (100)[M^+], 312 (5), 248 (28), 235 (4), 218 (7), 183 (11);

Elemental Analysis for $C_{22}H_{18}NP$**:** Calcd.: C 80.72; H 5.54; N 4.28;
Found: C 80.39; H 5.70; N 4.23.

8.10. Synthesis of Aza-arylphosphanes 130g-o

8.10.1. 2-(Diphenylphosphino)-6-phenylpyridine (130g)



$C_{23}H_{18}NP$. MW = 339.37 g mol^{-1}

Prepared according to GP-8, starting from 2-chloro-6-phenylpyridine **156a** (10.54 mmol, 2.00 g) and a solution of $NaPPh_2$ (10.54 mmol, 1.0 M in THF). Purification by flash column chromatography under argon (*n*-pentane/DCM 2:1) afforded pure **130g** (9.07 mmol, 3.08 g, 86% yield) as a white solid;

Mp: 122 °C;

^{1}H-NMR (400 MHz, C_6D_6)

δ = 6.99 (dd, *J* = 5.2, 1.9 Hz, 2 H; Ar-H), 7.04-7.21 (m, 10 H; Ar-H), 7.52-7.58 (m, 4 H; Ar-H), 8.01 (dt, *J* = 6.9, 1.60 Hz, 2 H; Ar-H) ppm;

^{13}C-NMR (100 MHz, C_6D_6)

δ = 118.5, 126.6 (d, $J_{C\text{-}P}$ = 20.1 Hz), 127.3, 127.5, 128.7, 128.8 (d, $J_{C\text{-}P}$ = 4.0 Hz), 129.0, 129.2, 134.7 (d, $J_{C\text{-}P}$ = 19.1 Hz), 136.3 (d, $J_{C\text{-}P}$ = 3.0 Hz), 137.6 (d, $J_{C\text{-}P}$ = 12.0 Hz) ,139.3, 157.3 (d, $J_{C\text{-}P}$ = 11.0 Hz), 164.1 (d, $J_{C\text{-}P}$ = 3.0 Hz);

^{31}P-NMR (160 MHz, C_6D_6)

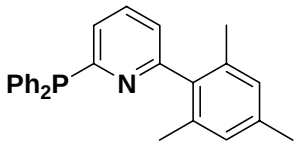
δ = –3.3 ppm;

IR (KBr): ν = 3050 (s), 1551 (s), 1425 (s), 1169 (s), 748 (s), 685 (s) cm^{-1};

MS (EI, 70 eV): m/z (%) = 338 (100)[M^+], 262 (21), 183 (16), 152 (3);

Analytical data are in agreement with those reported in the literature.[157]

8.10.2. 2-(Diphenylphosphino)-6-mesitylpyridine (130h)



$C_{26}H_{24}NP$. MW = 381.45 g mol^{-1}

Prepared according to GP-8, starting from 2-bromo-6-mesitylpyridine **148b** (4.12 mmol, 1.14 g) and a solution of $NaPPh_2$ (4.12 mmol, 1.0 M in THF). Purification by flash column chromatography under argon (Hex/MTBE 10:1) afforded pure **130h** (3.19 mmol, 1.22 g, 79% yield) as a white solid;

Mp: 118 °C;

^{1}H-NMR (300 MHz, $CDCl_3$)

δ = 1.96 (s, 6 H; CH_3), 2.28 (s, 3 H; CH_3), 6.87 (s, 2 H; Ar-H), 6.97 (dt, *J* = 7.7, 0.5 Hz, 1 H; Ar-H), 7.09 (dt, *J* = 7.7, 1.0 Hz, 1 H; Ar-H), 7.31-7.43 (m, 10 H; Ar-H), 7.59 (td, *J* = 6.9, 2.0 Hz, 1 H; Ar-H) ppm;

^{13}C-NMR (75 MHz, $CDCl_3$)

δ = 20.2, 21.0, 123.3, 125.4 (d, $J_{C\text{-}P}$ = 14.0 Hz), 128.2, 128.4 (d, $J_{C\text{-}P}$ = 7.5 Hz), 128.9, 134.3 (d, $J_{C\text{-}P}$ = 20.2 Hz), 135.7, 135.8, 136.5 (d, $J_{C\text{-}P}$ = 10.5 Hz), 137.4, 137.8, 160.6 (d, $J_{C\text{-}P}$ = 13 Hz), 164.0 (d, $J_{C\text{-}P}$ = 5.0 Hz) ppm;

^{31}P-NMR (121 MHz, $CDCl_3$)

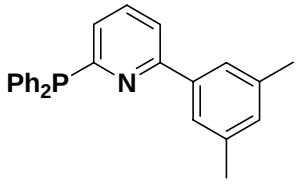
δ = –4.7 ppm;

IR (KBr): ν = 3466 (m), 2917 (m), 1569 (s), 1549 (s), 1440 (s), 853 (s), 757 (s), 695 (s) cm^{-1};

MS (EI, 70 eV): m/z (%) = 381 (100)[M^+], 302 (28), 287 (5), 195 (9), 183 (6);

Elemental Analysis for $C_{26}H_{24}NP$: Calcd.: C 81.87; H 6.34; N 3.67;
Found: C 82.06; H 6.03; N 3.66.

8.10.3. 2-(3,5-Dimethylphenyl)-6-(diphenylphosphino)pyridine (130i)



$C_{25}H_{22}NP$. MW = 367.42 g mol^{-1}

Prepared according to GP-8, starting from 2-chloro-6-(3,5-dimethylphenyl)pyridine **156b** (2.75 mmol, 720 mg) and a solution of $NaPPh_2$ (2.75 mmol, 1.0 M in THF). Purification by

flash column chromatography under argon (*n*-pentane/DCM 2:1) afforded pure **130i** (2.09 mmol, 768 mg, 76% yield) as a white solid;

Mp: 123 °C;

^{1}H-NMR (400 MHz, C_6D_6)

δ = 2.13 (s, 6 H; CH_3), 6.82 (s, 1 H; Ar-H), 7.0-7.03 (m, 2 H; Ar-H), 7.05-7.10 (m, 7 H; Ar-H), 7.21-7.25 (m, 1 H; Ar-H), 7.53-7.59 (m, 3 H; Ar-H), 7.73 (s, 2 H; Ar-H) ppm;

^{13}C-NMR (100 MHz, C_6D_6)

δ = 21.3, 118.4, 125.2, 126.3 (d, $J_{C\text{-}P}$ = 20.6 Hz), 128.5 (d, $J_{C\text{-}P}$ = 6.8 Hz), 128.7, 130.8, 134.5 (d, $J_{C\text{-}P}$ = 19.8 Hz), 135.9 (d, $J_{C\text{-}P}$ = 3.8 Hz), 137.5 (d, $J_{C\text{-}P}$ = 12.1 Hz), 137.8, 139.1, 157.6 (d, $J_{C\text{-}P}$ = 10.6 Hz), 163.6 (d, $J_{C\text{-}P}$ = 3.1 Hz) ppm;

^{31}P-NMR (160 MHz, C_6D_6)

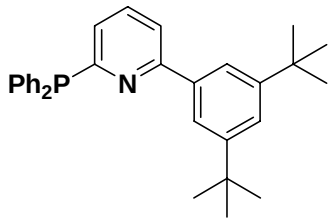
δ = –3.6 ppm;

IR (KBr): ν = 3057 (m), 2906 (m), 1555 (s), 1430 (s), 803 (s), 742 (s), 694 (s), 500 (s) cm^{-1};

MS (EI, 70 eV): m/z (%) = 367 (79)[M^+], 366 (100), 290 (14), 274 (1), 262 (8), 183 (11);

Elemental Analysis for $C_{25}H_{22}NP$: Calcd.: C 81.72; H 6.04; N 3.81;
Found: C 81.78; H 5.84; N 3.69.

8.10.4. 2-(3,5-Di-*tert*-butylphenyl)-6-(diphenylphosphino)pyridine (130j)



$C_{31}H_{34}NP$. MW = 451.58 g mol^{-1}

Prepared according to GP-8, starting from 2-bromo-6-(3,5-di-*tert*-butylphenyl)pyridine **148d** (1.45 mmol, 500 mg) and a solution of $NaPPh_2$ (1.45 mmol, 1.0 M in THF). Purification by flash column chromatography under argon (*n*-pentane/DCM 2:1) afforded pure **130j** (0.99 mmol, 450 mg, 69% yield) as a white solid;

Mp: 92-93 °C;

^{1}H-NMR (300 MHz, C_6D_6)

δ = 1.31 (s, 18 H; CH_3), 7.0-7.13 (m, 7 H; Ar-H), 7.16 (br s, 2 H; Ar-H), 7.36 (dt, *J* = 7.9, 1.0 Hz, 1 H; Ar-H), 7.57-7.66 (m, 4 H; Ar-H), 8.03 (d, *J* = 1.8 Hz, 2 H; Ar-H) ppm;

^{13}C-NMR (75 MHz, C_6D_6)

δ = 31.6, 35.0, 118.9, 122.0, 123.2, 126.8 (d, J_{C-P} = 26.3 Hz), 128.6 (d, J_{C-P} = 7.2 Hz), 128.9, 134.8 (d, J_{C-P} = 19.7 Hz), 136.1 (d, J_{C-P} = 4.8 Hz), 137.7 (d, J_{C-P} = 11.4 Hz), 139.3, 151.2, 158.6 (d, J_{C-P} = 8.9 Hz), 163.8 (d, J_{C-P} = 1.3 Hz) ppm;

^{31}P-NMR (121 MHz, C_6D_6)

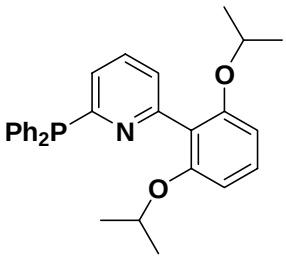
δ = –2.4 ppm;

IR (KBr): ν = 3050 (m), 2955 (s), 2863 (s), 1594 (s), 1554 (s), 1436 (s), 1364 (s), 1248 (s), 1089 (s), 880 (m), 807 (s), 744 (s), 695 (s) cm-1;

MS (EI, 70 eV): m/z (%) = 452 (30)[M^+], 451 (100), 450 (86), 434 (6), 394 (4), 374 (14);

Elemental Analysis for $C_{31}H_{34}NP$: Calcd.: C 82.45; H 7.59; N 3.10;
Found: C 82.31; H 7.40; N 2.96.

8.10.5. 2-(2,6-Diisopropoxyphenyl)-6-(diphenylphosphino)pyridine (130k)



$C_{29}H_{30}NO_2P$. MW = 455.53 g mol^{-1}

Prepared according to GP-8, starting from 2-bromo-6-(2,6-diisopropoxyphenyl)pyridine **148e** (2.86 mmol, 1.00 g) and a solution of $NaPPh_2$ (2.86 mmol, 1.0 M in THF). Purification by flash column chromatography under argon (*n*-pentane/DCM 2:3) afforded pure **130k** (1.97 mmol, 0.90 g, 70% yield) as a white solid;

Mp: 112 °C.

^{1}H-NMR (400 MHz, C_6D_6)

δ = 0.96 (d, *J* = 6.0 Hz, 12 H; CH_3), 4.16 (hept, *J* = 6.0 Hz, 2 H; CH), 6.55 (d, *J* = 8.5 Hz, 2 H; Ar-H), 6.99 (dt, *J* = 7.5, 1.2 Hz, 1 H; Ar-H), 7.02-7.16 (m, 9 H; Ar-H), 7.52 (td, *J* = 7.6, 1.6 Hz, 4 H; Ar-H) ppm;

^{13}C-NMR (100 MHz, C_6D_6)

δ = 22.0, 71.2, 108.1, 123.8, 125.0, 125.7 (d, J_{C-P} = 17.1 Hz), 128.3, 128.4 (d, J_{C-P} = 3.8 Hz), 129.0, 134.5 (d, J_{C-P} = 19.9 Hz), 134.6 (d, J_{C-P} = 3.1 Hz), 138.0 (d, J_{C-P} = 13.0 Hz), 156.3 (d, J_{C-P} = 14.0 Hz), 157.2, 162.5 (d, J_{C-P} = 5.3 Hz) ppm;

^{31}P-NMR (160 MHz, C_6D_6)

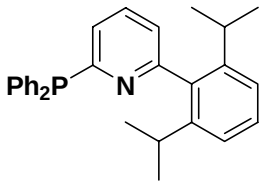
δ = –4.8 ppm;

IR (KBr): ν = 2971 (m), 1583 (s), 1451 (s), 1373 (s), 1238 (s), 1114 (s), 1047 (s), 742 (s), 695 (m) cm^{-1};

MS (EI, 70 eV): m/z (%) = 455 (100)[M^+], 440 (49), 412 (16), 396 (13), 382 (19), 370 (41), 354 (28), 338 (30), 292 (22), 254 (32);

Elemental Analysis for $C_{29}H_{30}NO_2P$: Calcd.: C 76.46; H 6.64; N 3.07;
Found: C 76.03; H 6.70; N 3.05.

8.10.6. 2-(2,6-Diisopropylphenyl)-6-(diphenylphosphino)pyridine (130l)



$C_{29}H_{30}NP$. MW = 423.53 g mol^{-1}

Prepared according to GP-8, starting from 2-bromo-6-(2,6-isopropylphenyl)pyridine **148f** (3.29 mmol, 1.05 g) and a solution of $NaPPh_2$ (3.29 mmol, 1.0 M in THF). Purification by flash column chromatography under argon (*n*-pentane/DCM 2:1) afforded pure **130l** (2.31 mmol, 0.98 g, 71% yield) as a white solid;

Mp: 143-144 °C;

^{1}H-NMR (400 MHz, C_6D_6)

δ = 1.03 (d, *J* = 6.8 Hz, 6 H; CH_3), 1.09 (d, *J* = 6.8 Hz, 6 H; CH_3), 2.66 (hept, *J* = 6.9 Hz, 2 H; CH), 6.86 (dt, *J* = 7.4, 0.9 Hz, 1 H; Ar-H), 6.99 (td, *J* = 7.7, 2.2 Hz, 1 H; Ar-H), 7.03-7.10 (m, 8 H; Ar-H), 7.15 (d, 1 H; Ar-H), 7.29 (t, *J* = 7.7 Hz, 1 H; Ar-H), 7.51 (td, *J* = 7.7, 1.6 Hz, 4 H; Ar-H) ppm;

^{13}C-NMR (100 MHz, C_6D_6)

δ = 23.9, 24.3, 30.7, 122.7, 123.2, 125.9 (d, $J_{C\text{-}P}$ = 20.0 Hz), 128.4 (d, $J_{C\text{-}P}$ = 6.8 Hz), 128.7, 128.8, 134.4 (d, $J_{C\text{-}P}$ = 19.9 Hz), 135.0 (d, $J_{C\text{-}P}$ = 3.8 Hz), 137.2 (d, $J_{C\text{-}P}$ = 11.4 Hz), 139.0, 146.4, 160.8 (d, $J_{C\text{-}P}$ = 11.5 Hz), 163.9 (d, $J_{C\text{-}P}$ = 1.4 Hz) ppm;

^{31}P-NMR (160 MHz, C_6D_6)

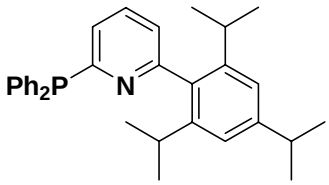
δ = –4.3 ppm;

IR (KBr): ν = 3055 (s), 2957 (s), 2865 (s), 1554 (s), 1433 (s), 744 (s), 693 (s) cm^{-1};

MS (EI, 70 eV): m/z (%) = 423 (100)[M^+], 408 (5), 344 (11), 328 (6), 236 (20), 222 (38), 211 (6);

HRMS for $C_{29}H_{30}BrN$: Calcd.: 423.211589;
Found: 423.211409.

8.10.7. 2-(Diphenylphosphino)-6-(2,4,6-triisopropylphenyl)pyridine (130m)



$C_{32}H_{36}NP$. MW = 465.61 g mol^{-1}

Prepared according to GP-8, starting from 2-bromo-6-(2,4,6-triisopropylphenyl)pyridine **148g** (2.0 mmol, 718 mg) and a solution of $NaPPh_2$ (2.0 mmol, 1.0 M in THF). Purification by flash column chromatography under argon (*n*-pentane/DCM 3:1) afforded pure **130m** (1.5 mmol, 700 mg, 75% yield) as a white solid;

Mp: 198 °C;

^{1}H-NMR (400 MHz, C_6D_6)

δ = 1.10 (d, *J* = 6.9 Hz, 6 H; CH_3), 1.17 (d, *J* = 6.9 Hz, 6 H; CH_3), 1.28 (d, *J* = 6.9 Hz, 6 H; CH_3), 2.73 (hept, *J* = 6.9 Hz, 2 H; CH), 2.86 (hept, *J* = 6.9 Hz, 1 H; CH), 6.91 (dt, *J* = 7.4, 1.2 Hz, 2 H; Ar-H), 6.99 (td, *J* = 7.7, 2.2 Hz, 1 H; Ar-H), 7.03-7.10 (m, 6 H; Ar-H), 7.19 (s, 2 H; Ar-H), 7.50-7.57 (m, 4 H; Ar-H) ppm;

^{13}C-NMR (100 MHz, C_6D_6)

δ = 23.9, 24.1, 24.2, 30.6, 34.6, 120.4, 123.3, 125.7 (d, $J_{C\text{-}P}$ = 20.1 Hz), 128.3 (d, $J_{C\text{-}P}$ = 7.6 Hz), 128.5, 134.2 (d, $J_{C\text{-}P}$ = 19.1 Hz), 134.8 (d, $J_{C\text{-}P}$ = 3.8 Hz), 136.8 137.1 (d, $J_{C\text{-}P}$ = 11.4 Hz), 146.3, 148.6, 160.9 (d, $J_{C\text{-}P}$ = 12.1 Hz), 163.6 (d, $J_{C\text{-}P}$ = 2.0 Hz) ppm;

^{31}P-NMR (160 MHz, C_6D_6)

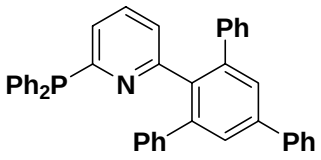
δ = –4.3 ppm;

IR (KBr): ν = 3437 (m), 2959 (s), 2868 (s), 1565 (s), 1435 (s), 745 (s) cm^{-1};

MS (EI, 70 eV): m/z (%) = 466 (25)[M^+], 465 (89), 464 (100), 386 (7);

Elemental Analysis for $C_{32}H_{36}NP$: Calcd.: C 82.55; H 7.79; N 3.01;
Found: C 82.20; H 7.79; N 2.91.

8.10.8. 2-(Diphenylphosphino)-6-(2,4,6-triphenylphenyl)pyridine (130n)



$C_{41}H_{30}NP$. MW = 567.66 g mol^{-1}

Prepared according to GP-8, starting from 2-bromo-6-(2,4,6-triphenylphenyl)pyridine **148h** (2.16 mmol, 1.00 g) and a solution of $NaPPh_2$ (2.16 mmol, 1.0 M in THF). Purification by flash column chromatography under argon (*n*-pentane/DCM 1:1) afforded pure **130n** (1.56 mmol, 0.89 g, 78% yield) as a white solid;

Mp: 197-198 °C;

^{1}H-NMR (400 MHz, C_6D_6)

δ = 6.57-6.65 (m, 2 H; Ar-H), 6.82 (ddd, *J* = 6.6, 2.7, 1.9 Hz, 1 H; Ar-H), 6.96-7.10 (m, 13 H; Ar-H), 7.19-7.24 (m, 6 H; Ar-H), 7.38 (td, *J* = 7.7, 2.0 Hz, 4 H; Ar-H), 7.45 (dt, *J* = 6.8, 1.6 Hz, 2 H; Ar-H), 7.63 (s, 2 H; Ar-H) ppm;

^{13}C-NMR (75 MHz, C_6D_6)

δ = 125.5, 126.0 (d, $J_{C\text{-}P}$ = 26.0 Hz), 126.7, 127.6, 127.7, 128.0, 128.5, 128.7 (d, $J_{C\text{-}P}$ = 6.8 Hz), 128.8, 129.1, 130.3, 134.6 (d, $J_{C\text{-}P}$ = 5.0 Hz), 134.7 (d, $J_{C\text{-}P}$ = 20.0 Hz), 137.7 (d, $J_{C\text{-}P}$ = 11.3 Hz), 138.4, 140.9, 141.4, 142.1, 142.9, 160.0 (d, $J_{C\text{-}P}$ = 9.8 Hz), 162.4 ppm;

^{31}P-NMR (160 MHz, C_6D_6)

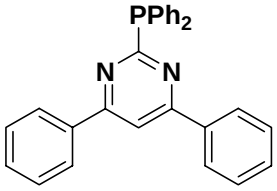
δ = –3.1 ppm;

IR (KBr): ν = 3437 (m), 3050 (s), 1688 (s), 1557 (s), 1420 (m), 1150 (s), 693 (m) cm^{-1};

MS (EI, 70 eV): m/z (%) = 567 (100)[M^+], 490 (25), 412 (4), 283 (45);

HRMS for $C_{41}H_{30}NP$: Calcd.: 567.211589;
Found: 567.211506.

8.10.9. 2-(Diphenylphosphino)-4,6-diphenylpyrimidine (130o)



$C_{28}H_{21}N_2P$. MW = 416.45 g mol^{-1}

Prepared according to GP-8, starting from 2-chloro-4,6-diphenylpyrimidine (2.49 mmol, 666 mg) and a solution of $NaPPh_2$ (2.49 mmol, 1.0 M in THF). Purification by flash column

chromatography under argon (Hex/MTBE 30:1) afforded pure **130o** (1.72 mmol, 716 mg, 69% yield) as a white solid;

Mp: 104-105 °C;

^{1}H-NMR (300 MHz, $CDCl_3$)

δ = 7.30-7.34 (m, 6 H; Ar-H), 7.35-7.41 (m, 7 H; Ar-H), 7.54-7.60 (m, 3 H; Ar-H), 7.87 (d, *J* = 1.4 Hz, 1 H; CH), 7.95-7.99 (m, 4 H; Ar-H) ppm;

^{13}C-NMR (75 MHz, $CDCl_3$)

δ = 109.6, 127.1, 128.1(d, $J_{C\text{-}P}$ = 7.6 Hz), 128.8, 128.9, 130.7, 134.6 (d, $J_{C\text{-}P}$ = 19.8 Hz), 136.0 (d, $J_{C\text{-}P}$ = 7.0 Hz), 136.9, 160.8, 163.4 (d, $J_{C\text{-}P}$ = 6.8 Hz) ppm;

^{31}P-NMR (121 MHz, $CDCl_3$):

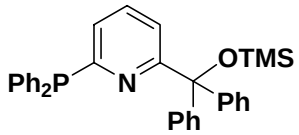
δ = 1.4 ppm;

IR (KBr): ν = 3473 (m), 3057 (m), 1565 (s), 1510 (s), 1432 (s), 749 (s), 688 (s) cm-1;

MS (EI, 70 eV): m/z (%) = 416 (100)[M^+], 339 (31), 233 (14), 183 (13);

Elemental Analysis for $C_{28}H_{21}N_2P$: Calcd.: C 80.75; H 5.08; N 6.73;
Found: C 80.67; H 5.28; N 6.72.

8.10.10. 2-[Diphenyl(trimethylsilyloxy)methyl]-6-(diphenylphosphino)pyridine (160).[160]



$C_{33}H_{32}NOPSi$. MW = 517.67 g mol^{-1}

To a mixture of [6-(2-bromopyridyl)]diphenylmethanol (7.50 mmol, 2.55 g) and imidazol (11.95 mmol, 0.82 g) in DCM/toluene (8/10 mL) was added dropwise TMSCl (9.20 mmol, 1.16 mL, 1.00 g). The reaction mixture was stirred at room temperature for 2 h, then quenched by addition of saturated aqueous NH_4Cl (20 mL). The aqueous phase was extracted with MTBE (20 mL). The organic layer was washed with H_2O (2×20 mL), then with citric acid 5% and again with H_2O (3×15 mL). The Removal of the solvent under reduced pressure afforded crude product, which was then direcly use following to GP-7 with an additional use of CuI (0.26 mmol, 53 mg). Purification by flash column chromatography under argon (Hex/MTBE 25:1) followed by recrystallization from petroleum ether afforded pure **160** (2.89 mmol, 1.50 g, 39% over 2 steps yield) as a white solid;

Mp: 108-109 °C;

^{1}H-NMR (400 MHz, C_6D_6)

δ = 0.00 (s, 9 H; CH_3), 6.98-7.07 (m, 14 H; Ar-H), 7.35-7.40 (m, 4 H; Ar-H), 7.46-7.50 (m, 4 H; Ar-H), 7.62-7.65 (m, 1 H; Ar-H) ppm;

^{13}C-NMR (75 MHz, C_6D_6)

δ = 1.7, 85.1, 119.6, 125.8, 126.1, 126.8, 128.2 (d, J_{C-P} = 7.5 Hz), 128.4, 129.1, 134.4 (d, J_{C-P} = 19.7 Hz), 135.5 (d, J_{C-P} = 5.3 Hz), 137.0 (d, J_{C-P} = 10.5 Hz), 146.3, 162.3, 166.4 (d, J_{C-P} = 9.0 Hz) ppm;

^{31}P-NMR (160 MHz, C_6D_6)

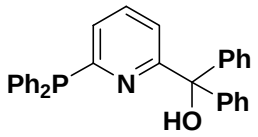
δ = –3.8 ppm;

IR (KBr): ν = 3438 (s), 3059 (s), 3023 (m), 2951 (s), 2893 (m), 1559 (s), 1482 (m), 1434 (s), 1383 (m), 1244 (s), 1180 (s), 1097 (s), 878 (s), 840 (s), 744 (s), 695 (s) cm^{-1};

MS (EI, 70 eV): m/z (%) = 518 (42) $[M+H]^+$, 517 (100)$[M^+]$, 502 (30), 426 (16), 349 (4), 334 (7), 255 (32), 73 (18);

Elemental Analysis for $C_{33}H_{32}NOPSi$: Calcd.: C 76.56; H 6.23; N 2.71;
Found: C 76.25; H 5.90; N 2.47.

8.10.11. [6-(Diphenylphosphino)pyridin-2-yl]diphenylmethanol (161).



$C_{30}H_{24}NOP$. MW = 445.49 g mol^{-1}

In a dried round-bottom Schlenk flask under an inert atmosphere of argon 2-[diphenyl(trimethylsilyloxy)methyl]-6-(diphenylphosphino)pyridine **160** (8.85 mmol, 4.57 g) was dissolved in degassed EtOH (25 mL). An aqueous solution of HCl 2.4 N (4 mL) was added and the resulting solution was stirred for 1 h at room temperature. Then, the reaction mixture was basified by addition of aqueous NH_3 25%. The Removal of the solvent under reduced pressure afforded crude product, which was then purified by flash column chromatography under argon (Hex/MTBE 15:1), followed by recrystallization from Hex/MTBE afforded within 6 days at 4 °C pure **161** (2.28 mmol, 1.02 g, 26% yield) as a white solid;

Mp: 98-99 °C;

^{1}H-NMR (400 MHz, C_6D_6)

δ = 6.05 (br s, 1 H; OH), 6.76 (ddd, *J* = 7.2, 1.8, 1.4 Hz, 1 H; Ar-H), 6.81 (ddd, *J* = 7.2, 1.8, 1.4 Hz, 1 H; Ar-H) 6.92 (ddd, *J* = 7.2, 1.8, 1.4 Hz, 1 H; Ar-H), 7.00-7.13 (m, 12 H; Ar-H), 7.37-7.45 (m, 8 H; Ar-H) ppm;

^{13}C-NMR (75 MHz, C_6D_6)

δ = 81.0, 121.0, 126.4 (d, $J_{C\text{-}P}$ = 21.8 Hz), 126.9, 127.6, 128.3, 128.3 (d, $J_{C\text{-}P}$ = 6.9 Hz), 128.8, 134.1 (d, $J_{C\text{-}P}$ = 19.7 Hz), 135.6 (d, $J_{C\text{-}P}$ = 3.8 Hz), 136.3 (d, $J_{C\text{-}P}$ = 11.4 Hz), 146.5, 162.0 (d, $J_{C\text{-}P}$ = 3.0 Hz), 163.9 (d, $J_{C\text{-}P}$ = 7.6 Hz) ppm;

^{31}P-NMR (160 MHz, C_6D_6)

δ = –3.4 ppm;

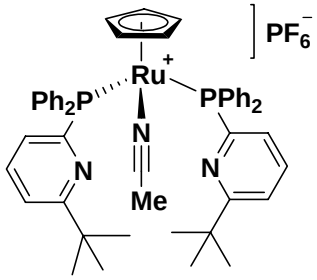
IR (KBr): ν = 3418 (br s), 302 (m), 2858 (w), 1559 (m), 1434 (m), 1359 (s), 1165 (m), 1034 (m), 745 (s), 693 (s), 495 (s) cm^{-1};

MS (EI, 70 eV): m/z (%) = 445 (100)[M^+], 426 (26), 368 (30), 290 (16), 262 (11), 183 (10), 105 (15) ;

Elemental Analysis for $C_{30}H_{24}NOP$: Calcd.: C 80.88; H 5.43; N 3.14;
Found: C 80.48; H 5.56; N 3.10.

8.11. Synthesis of [η^5-cyclopentadienylruthenium(II) bis-aza-arylphosphane(acetonitrile)][Counterion]

8.11.1. [η^5-Cyclopentadienylruthenium(II) bis-(2-*tert*-butyl-6-(diphenylphosphino)pyridine)(acetonitrile)] hexafluorophospate (164a).



$C_{49}H_{52}F_6N_3P_3Ru$. MW = 990.94 g mol^{-1}

Prepared according to GP-9, starting from the ruthenium precursor **163** [CpRuNaphth]PF_6 (0.02 mmol, 11.0 mg) and the aza-arylphosphane **130a** (0.05 mmol, 16.0 mg) lead in 30 min to the complex **164a** as a yellow powder in an equimolar mixture with naphthalene;

^{1}H-NMR (300 MHz, CD_3CN)

δ = 1.32 (s, 18 H; CH_3), 2.24 (br s, 3 H; CH_3), 4.42 (s, 5 H; Cp), 6.94 (dt, *J* = 7.6, 1.0 Hz, 2 H; Ar-H), 7.11-7.21 (m, 8 H; Ar-H), 7.21-7.29 (m, 4 H; Ar-H), 7.33-7.52 (m, 16 H; Ar-H, Naphth), 7.84-7.93 (m, 4 H; Naphth) ppm;

^{13}C-NMR (75 MHz, CD_3CN)

δ = 30.3, 38.6, 83.7, 120.1, 125.9 (vt, *J* = 10.6 Hz), 126.7, 127.9, 128.6 (m), 129.2 (d, *J* = 7.6 Hz), 129.7, 130.3, 130.8, 134.2 (vt, *J* = 4.6 Hz), 134.7, 134.8, 135.5 (vt, *J* = 5.3 Hz), 137.0 (vt, *J* = 3.8 Hz), 160.7, 170.0 (d, *J* = 5.0 Hz) ppm;

^{31}P-NMR (121 MHz, CD_3CN)

δ = 42.8 (s, PPh_2), –144.6 (hept, *J* = 704.4 Hz, PF_6) ppm;

^{1}H-NMR (400 MHz, $CDCl_3$)

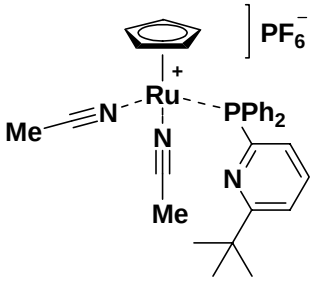
δ = 1.31 (s, 18 H; CH_3), 2.21 (br s, 3 H; CH_3), 4.44 (s, 5 H; Cp), 6.68 (d, *J* = 7.4 Hz, 2 H; Ar-H), 7.14-7.20 (m, 8 H; Ar-H), 7.23-7.27 (m, 4 H; Ar-H), 7.28-7.45 (m, 12 H; Ar-H), 7.48 (dd, *J* = 6.6, 3.6 Hz, 4 H; Naphth), 7.84 (dd, *J* = 6.1, 3.3 Hz, 4 H; Naphth) ppm;

^{31}P-NMR (160 MHz, $CDCl_3$)

δ = 43.6 (s, PPh_2), –144.3 (hept, *J* = 712.6 Hz, PF_6) ppm;

ESI-MS of [CpRu(130a)$_2$(MeCN)]PF_6 in (MeCN): m/z = 805 ($[CpRu(130a)_2]^+$), 486 ($[CpRu(130a)]^+$).

8.11.2. [η^5-Cyclopentadienylruthenium(II) bis(acetonitrile)-2-(diphenylphosphino)-6-*tert*-butylpyridine] hexafluorophospate (164'b).



$C_{30}H_{33}F_6N_3P_2Ru$. MW = 712.61 g mol^{-1}

Prepared according to the modified GP-9, starting from the ruthenium precursor **163** [CpRuNaphth]PF_6 (0.02 mmol, 11.0 mg), the addition of one equivalent of the ligand aza-arylphosphane **130b** (0.02 mmol, 7.8 mg) lead in 30 min to the complex **164'b** as a yellow powder in an equimolar mixture with naphthalene;

^{1}H-NMR (400 MHz, $CDCl_3$)

δ = 1.30 (s, 9 H; CH_3), 2.15 (d, *J* = 1.3 Hz, 6 H; CH_3), 4.39 (s, 5 H; Cp), 6.97 (ddd, *J* = 7.7, 4.1, 0.8 Hz, 1 H; Ar-H), 7.31 (ddd, *J* = 8.3, 2.5, 0.9 Hz, 1 H; Ar-H), 7.41-7.51 (m, 14 H; Ar-H, Naphth), 7.63 (ddd, *J* = 7.9, 7.7, 3.5 Hz, 1 H; Ar-H), 7.83-7.86 (m, 4 H; Naphth) ppm;

^{31}P NMR (160 MHz, $CDCl_3$)

δ = 50.0 (s, PPh_2), –144.3 (hept, *J* = 712.6 Hz, PF_6) ppm;

^{1}H-NMR (400 MHz, CD_3CN)

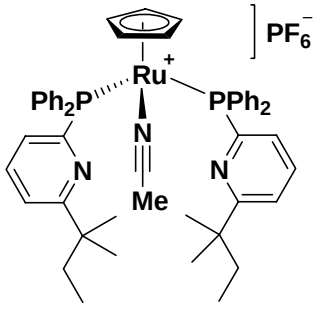
δ = 1.28 (s, 9 H; CH_3), 2.20 (br s, 6 H; CH_3), 4.43 (s, 5 H; Cp), 7.10 (ddd, *J* = 7.4, 4.0, 0.8 Hz, 1 H; Ar-H), 7.39-7.52 (m, 15 H; Naphth), 7.68 (ddd, *J* = 7.9, 7.7, 3.9 Hz, 1 H; Ar-H), 7.89 (dd, *J* = 6.3, 3.6 Hz 4 H; Naphth) ppm;

^{31}P-NMR (160 MHz, CD_3CN)

δ = 49.7 (s, PPh_2), –144.6 (hept, *J* = 704.4 Hz, PF_6) ppm;

ESI-MS of [CpRu(130b)$(MeCN)_2$]PF_6 in ($CHCl_3$): m/z = 486 ([CpRu(130b)]$^+$) and traces of 805 ([CpRu(130b)$_2$]$^+$).

8.11.3. [η^5-Cyclopentadienylruthenium(II) bis-(2-(diphenylphosphino)-6-*tert*-amylpyridine)(acetonitrile)] hexafluorophospate (164b).



$C_{51}H_{56}F_6N_3P_3Ru$. MW = 1018.99 g mol^{-1}

Prepared according to GP-9, starting from the ruthenium precursor **163** [CpRuNaphth]PF_6 (0.007 mmol, 3.0 mg) and the aza-arylphosphane **130b** (0.014 mmol, 4.8 mg) lead in 30 min to the complex **164b** as a yellow powder in an equimolar mixture with naphthalene;

^{1}H-NMR (400 MHz, CD_3CN)

δ = 0.63 (t, *J* = 7.4 Hz, 6 H; CH_3), 1.27 (d, *J* = 9.6 Hz, 12 H; CH_3), 1.65-1.72 (m, 4 H; CH_2), 2.19 (br s, 3 H; CH_3), 4.42 (s, 5 H; Cp), 6.74 (d, *J* = 7.7 Hz, 2 H; Ar-H), 7.12-7.27 (m, 12 H; Ar-H), 7.32-7.40 (m, 10 H; Ar-H), 7.42-7.50 (m, 6 H; Ar-H, Naphth), 7.89 (dd, *J* = 6.2, 3.2 Hz, 4 H; Naphth) ppm;

^{13}C-NMR (100 MHz, CD_3CN)

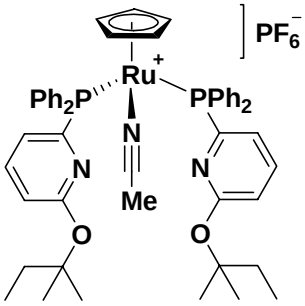
δ = 9.5, 27.5, 27.7, 36.3, 41.9, 83.6, 119.6, 121.0, 125.9 (t, *J* = 11.4 Hz), 126.7, 128.6 (m), 129.2 (d, *J* = 6.0 Hz), 129.7, 130.3, 130.8, 134.3 (vt, *J* = 4.5 Hz), 134.8 (d, *J* = 19.7 Hz), 135.4 (vt, *J* = 5.3 Hz), 136.8 (vt, *J* = 3.8 Hz), 169.0 (d, *J* = 6.7 Hz) ppm;

^{31}P-NMR (160 MHz, CD_3CN)

δ = 42.9 (s, PPh_2), –144.6 (hept, *J* = 704.4 Hz, PF_6) ppm;

ESI-MS of [CpRu(130b)$_2$(MeCN)]PF_6 in ($CHCl_3$): m/z = 833 ($[CpRu(130b)_2]^+$), 500 ($[CpRu(130b)]^+$).

8.11.4. [η^5-Cyclopentadienylruthenium(II) bis-(2-diphenylphosphinyl-6-(*tert*-amyloxy)pyridine)(acetonitrile)] hexafluorophospate (164alkox).



$C_{40}H_{49}F_6N_3O_2P_3Ru$. MW = 1018.99 g mol^{-1}

Prepared according to GP-9, starting from the ruthenium precursor **163** [CpRuNaphth]PF_6 (0.007 mmol, 3.0 mg) and the aza-arylphosphane **142a** (0.014 mmol, 4.9 mg) lead in 12 h to the complex **164alkox** as a yellow powder in an equimolar mixture with naphthalene;

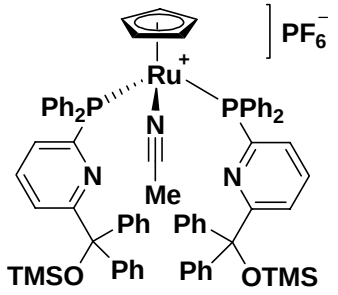
^{1}H-NMR (400 MHz, CD_3CN)

δ = 0.75 (t, *J* = 7.5 Hz, 6 H; CH_3), 1.27 (s, 12 H; CH_3), 1.69 (q, *J* = 7.5 Hz, 4 H; CH_2), 2.14 (s, 3 H; CH_3), 4.44 (s, 5 H; Cp), 6.76 (ddd, *J* = 7.1, 3.3, 0.9 Hz, 2 H; Ar-H), 7.13-7.19 (m, 4 H; Ar-H), 7.20-7.30 (m, 8 H; Ar-H), 7.32-7.510 (m, 16 H; Ar-H, Naphth), 7.89 (dd, *J* = 6.3, 3.3 Hz, 4 H; Naphth) ppm;

^{31}P-NMR (160 MHz, CD_3CN)

δ = 43.2 (s, PPh_2), –144.6 (hept, *J* = 704.4 Hz, PF_6) ppm.

8.11.5. [η^5-Cyclopentadienylruthenium(II) bis-(2-(diphenyl(trimethylsilyloxy)methyl)-6-(diphenylphosphino)pyridine)(acetonitrile)] hexafluorophospate (164ol).



$C_{73}H_{72}F_6N_3O_2P_3RuSi_2$. MW = 1387.52 g mol^{-1}

Prepared according to GP-9, starting from the ruthenium precursor **163** [CpRuNaphth]PF_6 (0.012 mmol, 5.5 mg) and the aza-arylphosphane **160** (0.024 mmol, 12.8 mg) lead in 4 h to the complex **164ol** as a yellow powder in an equimolar mixture with naphthalene;

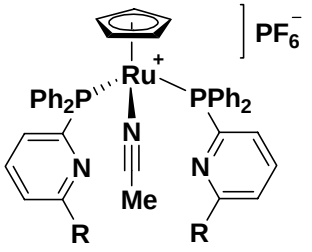
^{1}H-NMR (400 MHz, CD_3CN)

δ = 0.00 (s, 18 H; CH_3), 2.15 (br s, 3 H; CH_3), 3.9 (s, 5 H; Cp), 6.74 (dt, *J* = 7.4, 1.6 Hz, 2 H; Ar-H), 7.01-7.06 (m, 4 H; Ar-H), 7.13-7.19 (m, 12 H; Ar-H), 7.30-7.35 (m, 6 H; Ar-H), 7.36-7.47 (m, 22 H; Ar-H), 7.66-7.70 (m, 4 H; Naphth), 8.07 (dd, *J* = 6.2, 3.2 Hz, 4 H; Naphth) ppm;

^{31}P-NMR (160 MHz, CD_3CN)

δ = 44.4 (s, PPh_2), –144.6 (hept, *J* = 704.4 Hz, PF_6) ppm.

8.11.6. [η^5-Cyclopentadienylruthenium(II) bis-(2-(diphenylphosphino)-6-phenylpyridine)(acetonitrile)] hexafluorophospate (164g).



R= Ph

$C_{53}H_{44}F_6N_3P_3Ru$. MW = 1030.92 g mol^{-1}

Prepared according to GP-9, starting from the ruthenium precursor **163** [CpRuNaphth]PF_6 (0.011 mmol, 5.0 mg) and the aza-arylphosphane **130g** (0.022 mmol, 7.6 mg) lead in 2.5 h to the complex **164g** as a yellow powder in an equimolar mixture with naphthalene;

^{1}H-NMR (400 MHz, CD_3CN)

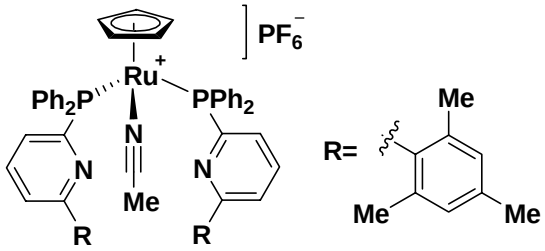
δ = 2.18 (br s, 3 H; CH_3), 4.48 (s, 5 H; Cp), 6.78 (dm, *J* = 7.9 Hz, 2 H; Ar-H), 7.20-7.26 (m, 8 H; Ar-H), 7.28-7.40 (m, 12 H; Ar-H), 7.46-7.54 (m, 12 H; Ar-H), 7.69-7.74 (m, 2 H; Ar-H), 7.84-7.88 (m, 4 H; Naphth), 7.90 (dd, *J* = 6.2, 3.2 Hz, 4 H; Naphth) ppm;

^{31}P-NMR (160 MHz, CD_3CN)

δ = 43.1 (s, PPh_2), –144.6 (hept, *J* = 704.4 Hz, PF_6) ppm;

ESI-MS of $[CpRu(130g)_2(MeCN)]PF_6$ in (CH_3CN): m/z = 845 ($[CpRu(130g)_2]^+$), 506 ($[CpRu(130g)]^+$).

8.11.7. [η^5-Cyclopentadienylruthenium(II) bis-(2-(diphenylphosphino)-6-(2,4,6-triisopropylphenyl)pyridine)(acetonitrile)] hexafluorophospate (164h).



$C_{59}H_{56}F_6N_3P_3Ru$. MW = 1115.08 g mol^{-1}

Prepared according to GP-9, starting from the ruthenium precursor **163** $[CpRuNaphth]PF_6$ (0.007 mmol, 3.0 mg) and the aza-arylphosphane **130h** (0.014 mmol, 5.3 mg) lead in 2.5 h to the complex **164h** as a yellow powder in an equimolar mixture with naphthalene;

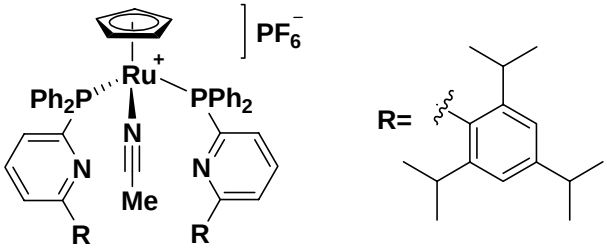
^{1}H-NMR (300 MHz, CD_3CN)

δ = 2.01 (s, 3 H; CH_3), 2.15 (br s, 12 H; CH_3), 2.34 (s, 6 H; CH_3), 4.40 (s, 5 H; Cp), 6.68-7.06 (m, 8 H; Ar-H), 7.18-7.34 (m, 12 H; Ar-H), 7.36-7.4 (m, 4 H; Ar-H), 7.46-7.62 (m, 10 H; Ar-H, Naphth), 7.90 (dd, *J* = 6.2, 3.2 Hz, 4 H; Naphth) ppm;

^{31}P-NMR (121 MHz, CD_3CN)

δ = 43.2 (s, PPh_2), –144.6 (hept, *J* = 704.4 Hz, PF_6) ppm.

8.11.8. [η^5-Cyclopentadienylruthenium(II) bis-(2-(diphenylphosphino)-6-(2,4,6-triisopropylphenyl)pyridine)(acetonitrile)] hexafluorophospate (164m).



$C_{71}H_{80}F_6N_3P_3Ru$. MW = 1283.4 g mol^{-1}

Prepared according to GP-9, starting from the ruthenium precursor **163** [CpRuNaphth]PF_6 (0.007 mmol, 3.0 mg) and the aza-arylphosphane **130m** (0.014 mmol, 6.8 mg) lead in 6 h to the complex **164m** as a yellow powder in an equimolar mixture with naphthalene;

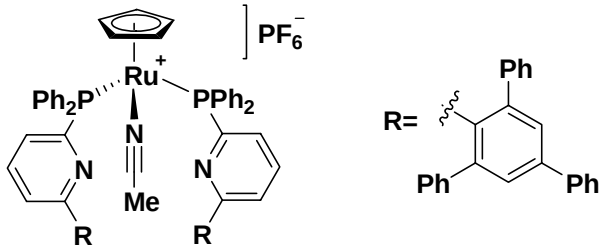
^{1}H-NMR (300 MHz, CD_3CN)

δ = 0.93-1.15 (m, 24 H; CH_3), 1.31 (d, *J* = 6.7 Hz, 12 H; CH_3), 2.16 (s, 3 H; CH_3), 2.40 (m, 4 H; CH), 2.97 (hept, *J* = 6.9 Hz, 2 H; CH), 4.37 (s, 5 H; Cp), 6.93 (t, *J* = 7.6 Hz, 4 H; Ar-H), 6.98-7.04 (m, 1 H; Ar-H), 7.08 (d, *J* = 2.5 Hz, 1 H; Ar-H), 7.16-7.34 (m, 20 H; Ar-H), 7.35-7.55 (m, 8 H; Ar-H, Naphth), 7.90 (dd, *J* = 6.2, 3.2 Hz, 4 H; Naphth) ppm;

^{31}P-NMR (121 MHz, CD_3CN)

δ = 43.1 (s, PPh_2), –144.6 (hept, *J* = 704.4 Hz, PF_6) ppm.

8.11.9. [η^5-Cyclopentadienylruthenium(II) bis-(2-(diphenylphosphino)-6-(2,4,6-triphenylphenyl)pyridine)(acetonitrile)] hexafluorophospate (164n).



$C_{89}H_{68}F_6N_3P_3Ru$. MW = 1487.49 g mol^{-1}

Prepared according to GP-9, starting from the ruthenium precursor **163** [CpRuNaphth]PF_6 (0.008 mmol, 4.0 mg) and the aza-arylphosphane **130n** (0.018 mmol, 10.2 mg) lead in 6 h to the complex **164n** as a yellow powder in an equimolar mixture with naphthalene;

^{1}H-NMR (300 MHz, CD_3CN)

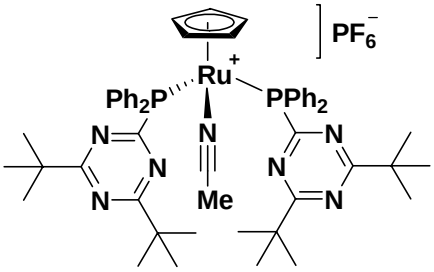
δ = 2.33 (br s, 3 H; CH_3), 3.93 (s, 5 H; Cp), 6.74 (m, 4 H; Ar-H), 6.86-6.94 (m, 2 H; Ar-H), 6.98-7.06 (m, 2 H; Ar-H), 7.11-7.45 (m, 46 H; Ar-H), 7.46-7.52 (m, 4 H; Naphth), 7.65-7.71 (m, 2 H; Ar-H), 7.75-7.82 (m, 4 H; Ar-H), 7.89 (dd, *J* = 6.2, 3.2 Hz, 4 H; Naphth) ppm;

^{31}P-NMR (121 MHz, CD_3CN)

δ = 43.2 (s, PPh_2), –144.6 (hept, *J* = 704.4 Hz, PF_6) ppm;

ESI-MS of [CpRu(130n)$_2$(MeCN)]PF_6 in (CH_3CN): m/z = 1301 ([CpRu(130n)$_2$]$^+$), 734 ([CpRu(130n)]$^+$).

8.11.10. [η^5-Cyclopentadienylruthenium(II) bis-(2-(diphenylphosphino)-6-(2,4-di-*tert*-butyl-l,3,5-triazine)pyridine)(acetonitrile)] hexafluorophospate (164d).



$C_{63}H_{70}F_6N_9P_3Ru$. MW = 1261.27 g mol^{-1}

Prepared according to GP-9, starting from the ruthenium precursor **163** [CpRuNaphth]PF_6 (0.007 mmol, 3.0 mg) and the aza-arylphosphane **130d** (0.014 mmol, 5.3 mg) lead in 4 h to the complex **164d** as a yellow powder in an equimolar mixture with naphthalene;

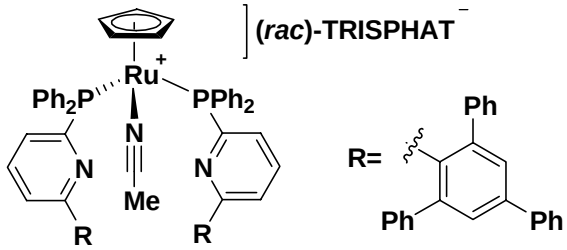
^{1}H-NMR (300 MHz, CD_3CN)

δ = 1.25 (br s, 36 H; CH_3), 2.15 (br s, 3 H; CH_3), 4.57 (s, 5 H; Cp), 7.10-7.60 (m, 30 H; Ar-H, Naphth), 7.91 (dd, *J* = 6.2, 3.2 Hz, 4 H; Naphth) ppm;

^{31}P-NMR (121 MHz, CD_3CN)

δ = 46.6 (s, PPh_2), –144.6 (hept, *J* = 704.4 Hz, PF_6) ppm.

8.11.11. [η^5-Cyclopentadienylruthenium(II) bis-(2-(diphenylphosphino)-6-(2,4,6-triphenylphenyl)pyridine)(acetonitrile)] (*rac*)-TRISPHAT.



$C_{107}H_{68}Cl_{12}N_3O_6P_3Ru$. MW = 2111.13 g mol^{-1}

The complex **164n** (0.299 mmol, 444 mg) and ($HNBu_3$)(*rac*)-TRISPHAT (0.303 mmol, 290 mg) were stirred in DCM (10 mL) for 30 min to give a yellow solution, which was then concentrated to a volume of 2-3 mL and purified by flash column chromatography under argon (Hex / DCM 4:6-0:1). The yellow product fractions (TLC control) were combined and the solvent was removed under vacuum. The resulting residue was dissolved in DCM (2 mL) and MeCN (1 mL) and evaporated under high vaccum to afford pur complex (0.270 mmol, 568 mg, 90% yield) as a colorless powder.

^{1}H-NMR (300 MHz, C_6D_6)

δ = 1.30 (br s, 3 H; CH_3), 3.88 (s, 5 H; Cp), 6.50-6.70 (m, 8 H; Ar-H), 6.84-7.04 (m, 34 H; Ar-H), 7.06 (s, 6 H; Ar-H), 7.09-7.19 (m, 8 H; Ar-H, Naphth), 7.40 (dt, *J* = 6.9, 1.4 Hz, 4 H; Ar-H), 7.53 (dd, *J* = 6.2, 3.2 Hz, 4 H; Naphth), 7.61 (d, *J* = 1.0 Hz, 4 H; Ar-H) ppm;

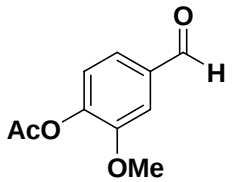
^{31}P-NMR (121 MHz, C_6D_6)

δ = 44.1 (s, PPh_2), –80.0 (s, $P(O)_{TRISPHAT}$) ppm;

ESI-MS of [CpRu(130n)$_2$(MeCN)](*rac*)-TRISPHAT in (CH_3Cl): m/z = 1301 ($[CpRu(130n)_2]^+$), 735 ($[CpRu(130n)]^+$).

8.12. Synthesis of Propargylalcohols 171 and Derivatives

8.12.1. 4-Formyl-2-methoxyphenyl acetate.



$C_{10}H_{10}O_4$. MW = 194.18 g mol^{-1}

In a dried round-bottom flask, vanillin (2.0 mmol, 305 mg), Ac_2O (3.4 mmol, 348 mg) and DMAP (0.4 mmol, 49 mg, 99% purity) were stirred in EtOAc (3 mL) at room temperature for 1 h. After completion (TLC control), the reaction was quenched with MTBE (5 mL) and H_2O (3 mL). The organic phase was washed with water (5 mL), then with an aqueous solution of HCl 2 N (3 mL), and with saturated aqueous $NaHCO_3$ (5 mL). The organic layer was dried

over $MgSO_4$. Removal of the solvent under reduced pressure afforded the product (1.65 mmol, 320 mg, 83% yield) as white crystals;

Mp: 85-86 °C;

^{1}H-NMR (300 MHz, $CDCl_3$)

δ = 1.19 (s, 3 H; CH_3), 2.34 (s, 3 H; CH_3), 7.23 (d, *J* = 7.6 Hz, 1 H; Ar-H), 7.48 (d, *J* = 9.6 Hz, 1 H; Ar-H), 9.94 (s, 1 H; C(O)H) ppm;

^{13}C-NMR (75 MHz, $CDCl_3$)

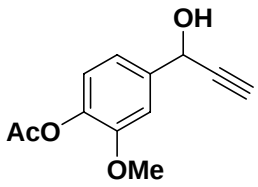
δ = 20.6, 56.0, 110.8, 123.4, 124.6, 135.2, 144.9, 151.9, 168.3, 191.0 ppm;

IR (KBr): ν = 2967 (w), 2944 (w), 2846 (m), 1754 (s), 1689 (s), 1597 (s), 1508 (s), 1394 (s), 1378 (s), 1280 (s), 1211 (s), 1152 (s), 737 (s) cm^{-1};

MS (EI, 70 eV): m/z (%) = 194 (6)[M^+], 177 (4), 152 (100), 136 (3), 123 (6), 108 (7), 91 (90);

Elemental Analysis for $C_{10}H_{10}O_4$: Calcd.: C 61.85; H 5.19;
Found: C 61.69; H 5.29.

8.12.2. 4-(1-Hydroxyprop-2-ynyl)-2-methoxyphenyl acetate (171a).



$C_{12}H_{12}O_4$. MW = 220.22 g mol^{-1}

Prepared according to GP-11, starting from 4-formyl-2-methoxyphenylacetate (10.00 mmol, 1.94 g) and ethynylmagnesiumchloride (30.0 mmol, 0.72 M in THF). Purification by flash column chromatography (MTBE/Hex 1:4) afforded pure **171a** (8.36 mmol, 1.84 mg, 84% yield) as a slighty yellow oil;

^{1}H-NMR (300 MHz, $CDCl_3$)

δ = 2.33 (s, 3 H; CH_3), 2.70 (d, *J* = 2.3 Hz, 1 H; CH), 3.28 (br s, 1 H; OH), 3.84 (s, 3 H; CH_3), 5.41 (br s, 1 H; CH), 6.99 (d, *J* = 8.2 Hz, 1 H; Ar-H), 7.12 (dd, *J* = 8.9, 2.7 Hz, 1 H; Ar-H), 7.19 (d, *J* = 1.9 Hz, 1 H; Ar-H) ppm;

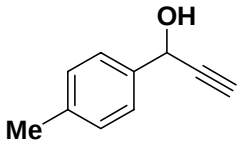
^{13}C-NMR (75 MHz, $CDCl_3$)

δ = 20.7, 26.9, 55.9, 63.8, 74.9, 83.4, 110.8, 118.9, 122.7, 139.2, 151.1, 169.4 ppm;

IR (KBr): ν = 3771 (w), 3282 (s), 3013 (s), 2942 (s), 2879 (m), 1762 (s), 1509 (s), 1420 (s), 1373 (s), 1150 (s), 1029 (s), 863 (s), 673 (s) cm^{-1};

MS (EI, 70 eV): m/z (%) = 220 (14)[M^+], 178 (100), 161 (21), 146 (25), 135 (4), 125 (11), 118 (5), 107 (3), 93 (3).

8.12.3. 1-*p*-Tolylprop-2-yn-1-ol (171b).



$C_{10}H_{10}O$. MW = 146.19 g mol^{-1}

Prepared according to GP-11, starting from 4-methylbenzaldehyde (10.00 mmol, 1.94 g) and ethynylmagnesiumchloride (30.0 mmol, 0.72 M in THF). Purification by flash column chromatography (MTBE/Hex 1:4) afforded pure **171b** (8.47 mmol, 1.24 g, 85% yield) as a colorless oil;

^{1}H-NMR (300 MHz, $CDCl_3$)

δ = 2.32 (s, 3 H; CH_3), 2.59 (d, *J* = 2.2 Hz, 1 H; CH), 3.09 (br s, 1 H; OH), 5.33 (br s, 1 H; CH), 7.13 (d, *J* = 7.9 Hz, 2 H; Ar-H), 7.37 (d, *J* = 7.9 Hz, 2 H; Ar-H) ppm;

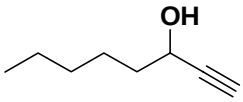
^{13}C-NMR (75 MHz, $CDCl_3$)

δ = 21.2, 64.1, 74.7, 83.9, 126.7, 129.3, 137.3, 138.2 ppm;

MS (EI, 70 eV): m/z (%) = 146 (63)[M^+], 131 (100), 128 (13), 115 (17), 103 (13), 91 (21), 77 (9), 53 (39);

Elemental Analysis for $C_{10}H_{10}O$: Calcd.: C 82.16; H 6.89;
Found: C 82.10; H 7.24.

8.12.4. Oct-1-yn-3-ol (171c).



$C_8H_{14}O$. MW = 126.2 g mol^{-1}

Prepared according to GP-11, starting from hexanal **X** (2.00 mmol, 200 mg, 97% purity) and ethynylmagnesiumchloride (6.0 mmol, 0.72 M in THF). Purification by flash column chromatography (MTBE/Hex 1:4) afforded pure **171c** (1.95 mmol, 247 mg, 98% yield) as a colorless oil;

^{1}H-NMR (300 MHz, $CDCl_3$)

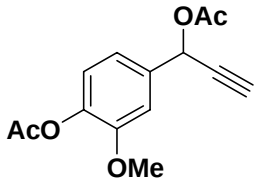
δ = 0.83 (t, *J* = 7.1 Hz, 3 H; CH_3), 1.19-1.27 (m, 4 H; CH_2), 1.33-1.44 (m, 2 H; CH_2), 1.58-1.67 (m, 2 H; CH_2), 2.37 (d, *J* = 1.9 Hz, 1 H; CH), 3.23 (br s, 1 H; OH), 4.27 (td, *J* = 6.9, 2.2 Hz, 1 H; CH) ppm;

^{13}C-NMR (75 MHz, $CDCl_3$)

δ = 13.8, 22.4, 24.6, 25.4, 31.3, 61.8, 67.7, 85.3 ppm.

Analytical data are in agreement with those reported in the literature.[199]

8.12.5. 4-[1-(Acetoxy)prop-2-ynyl]-2-methoxyphenyl acetate (172).



$C_{14}H_{14}O_5$. MW = 262.26 g mol^{-1}

In a dried round-bottom flask, 4-(1-hydroxyprop-2-ynyl)-2-methoxyphenyl acetate **171a** (1.0 mmol, 220 mg), Ac_2O (1.85 mmol, 189 mg) and pyridine (0.3 mL) were stirred in EtOAc (1.5 mL) at room temperature for 4 h. After completion (TLC control), the reaction was quenched with MTBE (5 mL) and H_2O (3 mL). The organic phase was washed with water (5 mL), then with an aqueous solution of HCl 2 N (3 mL), and with saturated aqueous $NaHCO_3$ (5 mL). The organic layer was dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded the product **172** (0.98 mmol, 255 mg, 98% yield) as light brown solid;

Mp: 92-93 °C;

^{1}H-NMR (400 MHz, $CDCl_3$)

δ = 2.11 (s, 3 H; CH_3), 2.31 (s, 3 H; CH_3), 2.67 (d, *J* = 2.7 Hz, 1 H; CH), 3.86 (s, 3 H; CH_3), 6.44 (d, *J* = 2.2 Hz, 1 H; CH), 7.03 (d, *J* = 8.0 Hz, 1 H; Ar-H), 7.10-7.15 (m, 2 H; Ar-H) ppm;

^{13}C-NMR (100 MHz, $CDCl_3$)

δ = 20.6, 20.9, 55.8, 64.8, 75.4, 79.9, 111.8, 120.1, 122.7, 134.9, 140.0, 150.9, 168.5, 169.3 ppm;

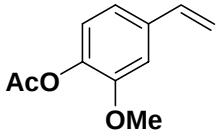
IR (KBr): ν = 3448 (w), 3232 (s), 2943 (m), 2120 (w), 1735 (s), 1606 (m), 1514 (m), 1369 (s), 1291 (s), 1233 (s), 1156 (s), 1014 (s), 779 (s) cm^{-1};

MS (EI, 70 eV): m/z (%) = 262 (16)[M^+], 220 (67), 178 (30), 160 (100), 146 (8), 118 (3), 89 (4);

[199] J. Fried, C. H. Mehra, P. Dalven *Ann. N. Y. Acad. Sci*. **1971**, *180*, 38.

Elemental Analysis for $C_{14}H_{14}O_5$: Calcd.: C 64.12; H 5.38;
Found: C 63.97; H 5.40.

8.12.6. 2-methoxy-4-vinylphenyl acetate (175).



$C_{11}H_{11}O_3$. MW = 192.21 g mol^{-1}

To a dried round-bottom Schlenk flask charged with complex **76** [CpRu(dppm)Cl] (5 mol-%) under an inert atmosphere of argon was added alkyne **172** (0.5 mmol, 131 mg), H_2O (0.4 mL) and acetone (1.5 mL). The resulting mixture was heated to 70 °C for 36 h. After completion (TLC control), the solution was allowed to cool to room temperature and was quenched with MTBE (2 mL) and H_2O (2 mL). The organic layer was washed with water (2 mL), brine (3 mL), and was dried over $MgSO_4$. Removal of the solvent under reduced pressure gave crude product wich was purified by flash column chromatography (MTBE/Hex 1:4) to afford pure **175** (0.41 mmol, 79 mg, 83% yield) as a slighty brown solid;

^{1}H-NMR (300 MHz, $CDCl_3$)

δ = 2.30 (s, 3 H; CH_3), 3.83 (s, 3 H; CH_3), 5.23 (dd, *J* = 10.8, 0.8 Hz, 1 H; CH_2), 5.68 (dd, *J* = 7.7, 1.0 Hz, 1 H; CH_2), 6.67 (dd, *J* = 17.6, 10.9 Hz, 1 H; CH), 6.98 (d, *J* = 7.2 Hz, 3 H; Ar-H) ppm;

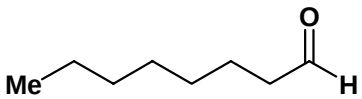
^{13}C-NMR (75 MHz, $CDCl_3$)

δ = 20.7, 55.8, 109.9, 114.1, 118.9, 122.8, 136.3, 136.7, 139.4, 151.1, 169.1 ppm;

IR (KBr): ν = 3448 (w), 3232 (s), 2943 (m), 2120 (w), 1735 (s), 1606 (m), 1514 (m), 1369 (s), 1291 (s), 1233 (s), 1156 (s), 1014 (s), 779 (s) cm^{-1};

8.13. Synthesis of Aldehydes 177/179

8.13.1. Octanal (177a).



$C_8H_{16}O$. MW = 128.21 g mol^{-1}

Prepared according to GP-12, starting from 1-octyne (1.0 mmol, 113 mg, 97% purity). Purification by Kugelrohr distillation afforded pure **177a** (0.9 mmol, 122 mg, 95% yield) as a colorless liquid;

^{1}H-NMR (400 MHz, $CDCl_3$)

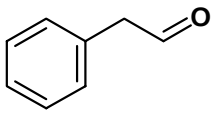
δ = 0.87 (t, *J* = 8.9 Hz, 3 H; CH_3), 1.21-1.39 (m, 8 H; CH_2), 1.59-1.68 (m, 2 H; CH_2), 2.38-2.44 (m, 2 H; CH_2), 9.79 (t, *J* = 1.1 Hz, 1 H; C(O)H) ppm;

^{13}C-NMR (100 MHz, $CDCl_3$)

δ = 14.1, 22.1, 22.6, 29.0, 29.2, 31.6, 43.9, 202.6 ppm;

Analytical data are in agreement with those reported in the literature.

8.13.2. Phenyacetaldehyde (177c).



C_8H_8O. MW = 120.15 g mol^{-1}

Prepared according to GP-12, starting from phenylacetylene (1.4 mmol, 153 mg, 164 µL, 98% purity) and the *in situ* catalyst [CpRu(130n)$_2$(MeCN)]PF_6 (2 mol-%) at 55 °C in 3 h. Purification by Kugelrohr distillation afforded pure **177c** (1.37 mmol, 165 mg, 94% yield) as a colorless liquid;

^{1}H-NMR (400 MHz, $CDCl_3$)

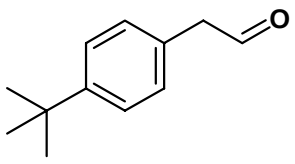
δ = 3.60 (s, 2 H; CH_2), 7.19 (d, *J* = 7.8 Hz, 2 H; Ar-H), 7.22-7.30 (m, 1 H; Ar-H), 7.30-7.38 (m, 2 H; Ar-H), 9.65 (t, *J* = 1.4 Hz, 1 H; C(O)H) ppm;

^{13}C-NMR (100 MHz, $CDCl_3$)

δ = 50.6, 127.3, 128.9, 129.6, 131.9, 199.3 ppm;

Analytical data are in agreement with those reported in the literature.[200]

8.13.3. 4-*tert*-Butylphenyl-acetaldehyde (177d).



$C_{12}H_{16}O$. MW = 176.25 g mol^{-1}

[200] N. M. Scott, T. Schareina, O. Tok, R. Kempe *J. Inorg. Chem.* **2004**, 3297.

Prepared according to GP-12, starting from 4-*tert*-butylphenyl-acetylene (2.0 mmol, 329 mg, 96% purity) and the *in situ* catalyst [CpRu(130m)$_2$(MeCN)]PF$_6$ (2 mol-%) at 55 °C in 6 h. Purification by Kugelrohr distillation afforded pure **177d** (1.4 mmol, 256 mg, 73% yield) as a colorless liquid;

^{1}H-NMR (500 MHz, CDCl$_3$)

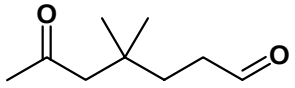
δ = 1.34 (s, 9 H; CH$_3$), 3.63 (s, 2 H; CH$_2$), 7.18 (d, *J* = 8.0 Hz, 2 H; Ar-H), 7.40 (d, *J* = 8.2 Hz, 2 H; Ar-H), 9.78 (t, *J* = 1.2 Hz, 1 H; C(O)H) ppm;

^{13}C-NMR (175 MHz, CDCl$_3$)

δ = 31.3, 50.0, 125.9, 128.9, 129.3, 150.4, 199.7 ppm;

Analytical data are in agreement with those reported in the literature.[200]

8.13.4. 4,4-Dimethyl-6-oxo-heptanal (179a).



C$_9$H$_{16}$O$_2$. MW = 156.22 g mol^{-1}

Prepared according to GP-12, starting from 4,4-dimethyl-6-oxo-heptyne (3.4 mmol, 470 mg) and the *in situ* catalyst [CpRu(130a)$_2$(MeCN)]PF$_6$ (2 mol-%) at 45 °C in 18 h. Purification by flash column chromatography (MTBE/Hex 1:4) afforded pure **179a** (2.3 mmol, 366 mg, 69% yield) as a colorless liquid;

^{1}H-NMR (400 MHz, CDCl$_3$)

δ = 1.01 (s, 6 H; CH$_3$), 1.65-1.73 (m, 2 H; CH$_2$), 2.14 (s, 3 H; CH$_3$), 2.35 (s, 2 H; CH$_2$), 2.38-2.44 (m, 2 H; CH$_2$), 9.77 (t, *J* = 1.8 Hz, 1 H; C(O)H) ppm;

^{13}C-NMR (100 MHz, CDCl$_3$)

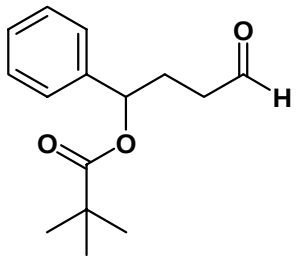
δ = 27.1, 32.5, 33.0, 33.4, 39.4, 53.5, 202.4, 208.3 ppm;

IR (neat): ν = 2984 (m), 1684 (s), 1651 (m), 1559 (m), 1457 (m), 1266 (m), 754 (m), 668 (m) cm^{-1};

MS (EI, 70 eV): m/z (%) = 156 (1)[M$^+$], 138 (12), 123 (12), 113 (55), 81 (48), 69 (40), 43 (100);

Elemental Analysis for C$_9$H$_{16}$O$_2$ + O: Calcd.: C 62.77; H 9.36;
Found: C 62.88; H 9.51.

8.13.5. 4-Phenyl-4-pivaloyloxy-butanal (179b).



$C_{15}H_{20}O_3$. MW = 248.32 g mol^{-1}

Prepared according to GP-12, starting from 4-phenyl-4-pivaloyloxy-butyne (4.3 mmol, 990 mg) and the *in situ* catalyst [CpRu(130a)$_2$(MeCN)]PF_6 (2 mol-%) at 65 °C in 20 h. Purification by flash column chromatography (MTBE/Hex 1:6) afforded pure **179b** (3.5 mmol, 883 mg, 83% yield) as a colorless oil;

^{1}H-NMR (300 MHz, $CDCl_3$)

δ = 1.21 (s, 9 H; CH_3), 2.07-2.28 (m, 2 H; CH_2), 2.47 (t, *J* = 7.5 Hz, 2 H; CH_2), 5.74 (dd, *J* = 7.2, 6.1 Hz, 1 H; CH), 7.24-7.40 (m, 5 H; Ar-H), 9.73 (t, *J* = 1.3 Hz, 1 H; C(O)H) ppm;

^{13}C-NMR (75 MHz, $CDCl_3$)

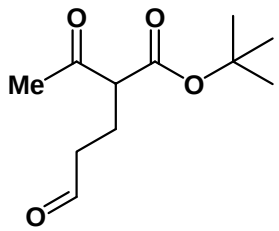
δ = 27.1, 29.0, 38.8, 39.9, 74.6, 126.0, 128.0, 128.6, 140.2, 177.5, 201.0 ppm;

IR (film): ν = 3022 (w), 2976 (w), 1718 (s), 1216 (m), 1157 (s), 760 (s) cm^{-1};

MS (EI, 70 eV): m/z (%) = 248 (1)[M^+], 204 (40), 163 (100), 147 (67), 129 (50), 117 (85), 91 (90);

Elemental Analysis for $C_{15}H_{20}O_3$ (+0.1 O): Calcd.: C 72.55; H 8.04;
Found: C 72.09; H 8.07.

8.13.6. t*ert*-Butyl 2-(3-oxo-propyl)-3-oxobutanoate (179c).



$C_{11}H_{18}O_4$. MW = 214.26 g mol^{-1}

Prepared according to GP-12, starting from *tert*-butyl 2-(3-propyne)-3-oxobutanoate (1.5 mmol, 294 mg) and the *in situ* catalyst [CpRu(130m)$_2$(MeCN)]PF_6 (4 mol-%) at 60 °C in 8 h. Purification by flash column chromatography (MTBE/Hex 25:1) afforded pure **179c** (1.4 mmol, 305 mg, 95% yield) as colorless oil;

^{1}H-NMR (400 MHz, $CDCl_3$)

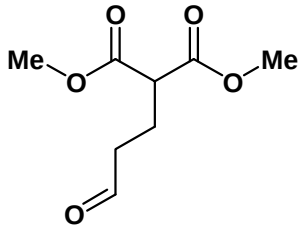
δ = 1.38 (s, 9 H; CH_3), 1.99-2.11 (m, 2 H; CH_2), 2.23 (s, 3 H; CH_3), 2.41-2.50 (m, 2 H; CH_2), 3.39 (dd, *J* = 7.6, 5.8 Hz, 1 H; CH), 9.72 (t, *J* = 1.4 Hz, 1 H; C(O)H) ppm;

^{13}C-NMR (100 MHz, $CDCl_3$)

δ = 20.1, 27.9, 29.1, 41.1, 59.2, 82.3, 168.2, 200.8, 202.6 ppm;

Analytical data are in agreement with those reported in the literature.[201]

8.13.7. Dimethyl 2-(3-oxopropyl)malonate (179d).



$C_8H_{12}O_5$. MW = 188.18 g mol^{-1}

Prepared according to GP-12, starting from dimethyl 2-(2-prop-ynyl)-malonate (2.0 mmol, 340 mg, 307 µL) and the *in situ* catalyst $[CpRu(130n)_2(MeCN)]PF_6$ (2 mol-%) at 55 °C in 1.5 h. Purification by flash column chromatography (MTBE/Hex 30:1) afforded pure **179d** (1.9 mmol, 372 mg, 99% yield) as a light orange solid;

^{1}H-NMR (500 MHz, $CDCl_3$)

δ = 2.19-2.24 (m, 2 H; CH_2), 2.59 (t, *J* = 6.9 Hz, 2 H; CH_2), 3.44 (dd, *J* = 7.2, 5.3 Hz, 1 H; CH), 3.78 (s, 6 H; CH_3), 9.78 (t, *J* = 0.9 Hz, 1 H; C(O)H) ppm;

^{13}C-NMR (175 MHz, $CDCl_3$)

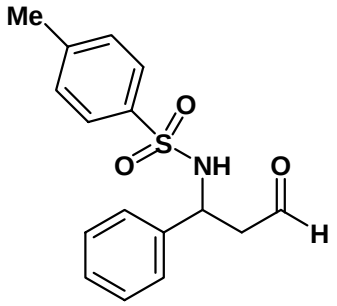
δ = 21.0, 40.9, 50.2, 52.6, 169.3, 200.5 ppm;

Analytical data are in agreement with those reported in the literature.[202]

[201] G. Bartoli, M. Bosco, M. C. Bellucci, E. Marcantoni, L. Sambri, E. Torregiani *Eur. J. Org. Chem*. **1999**, 617.
[202] G. Fournet, G. Balme, J. J. Barieux, J. Gore *Tetrahedron* **1988**, *44*, 5821.

8.14. Synthesis of *N*-Tosyl-1-amino-1-propanal Derivatives 208a-i

8.14.1. *N*-Tosyl-1-amino-1-phenylpropanal (208a).



$C_{16}H_{17}NO_3S$. MW = 303.09 g mol^{-1}

Prepared according to GP-14, starting from propargylic amine **207a** (0.421 mmol, 120 mg) and *in situ* catalyst $[CpRu(130m)_2(MeCN)]PF_6$ (10 mol-%). Purification by flash column chromatography (*n*-pentane/EtOAc 2:1) afforded pure **208a** (0.247 mmol, 75 mg, 83% yield) as a light orange solid;

Mp: 88-89 °C;

^{1}H-NMR ($CDCl_3$, 400 MHz)

δ = 2.37 (s, 3 H; CH_3), 2.88-2.97 (m, 1 H; CH_2), 3.00-3.09 (m, 1 H; CH_2), 4.80 (q, *J* = 6.9 Hz, 1 H; CH), 5.47 (br s, 1 H; NH), 7.04-7.11 (m, 2 H; Ar-H), 7.14-7.21 (m, 5 H; Ar-H), 7.56-7.62 (m, 2 H; Ar-H), 9.63 (br s, 1 H; C(O)H) ppm;

^{13}C-NMR ($CDCl_3$, 100 MHz)

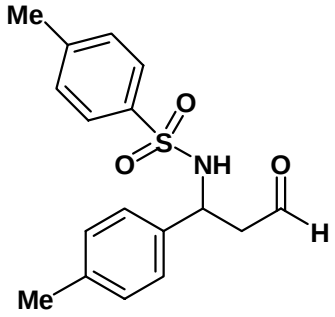
δ = 21.5, 50.1, 53.2, 126.4, 127.0, 127.8, 128.6, 129.4, 136.9, 139.1, 143.3, 199.4 ppm;

IR (KBr): 3520 (m), 3254 (s), 3051 (w), 2823 (m), 1727 (s), 1598 (m), 1455 (s), 1315 (s), 1159 (s), 1082 (m), 674 (s), 550 (s) cm^{-1};

MS (CI, CH_4, 70 eV): *m/z* = 304 (25)$[M+H]^+$, 260 (76), 200 (5), 172 (25), 155 (7), 148 (12), 133 (100), 104 (11), 91 (4);

Elemental Analysis for $C_{16}H_{17}NO_3S$: Calcd.: C 63.34; H 5.65; N 4.62;
Found: C 63.42; H 5.83; N 4.62.

8.14.2. *N*-Tosyl-1-amino-1-(4-methylphenyl)propanal (208c).



$C_{17}H_{18}NO_3S$. MW = 317.1 g mol^{-1}

Prepared according to GP-14 or GP-15, starting from propargylic amine **207c** (0.336 mmol, 100 mg) and *in situ* catalyst $[CpRu(130m)_2(MeCN)]PF_6$ (10 mol-%). Purification by flash column chromatography (*n*-pentane/EtOAc 2:1) afforded pure **208c** (0.277 mmol, 88 mg, 83% yield) as a yellow solid;

Mp: 109-110 °C;

^{1}H-NMR ($CDCl_3$, 300 MHz)

δ = 2.27 (s, 3 H; CH_3), 2.39 (s, 3 H; CH_3), 2.84-2.97 (m, 1 H; CH_2), 2.99-3.11 (m, 1 H; CH_2), 4.74 (q, *J* = 6.8 Hz, 1 H; CH), 5.26 (br s, 1 H; NH), 6.91-7.04 (m, 4 H; Ar-H), 7.14-7.21 (m, 2 H; Ar-H), 7.57-7.64 (m, 2 H; Ar-H), 9.62 (t, *J* = 1.4 Hz, 1 H; C(O)H) ppm;

^{13}C-NMR ($CDCl_3$, 75 MHz)

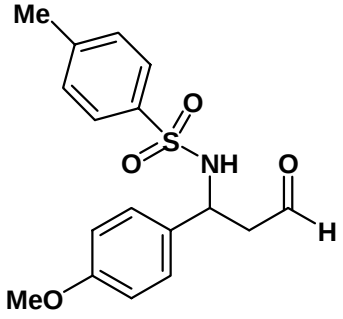
δ = 21.0, 21.5, 50.1, 53.0, 126.4, 127.2, 129.4, 129.5, 136.3, 137.1, 137.8, 143.4, 199.7 ppm;

IR (KBr): 3491 (w), 3436 (w), 3248 (s), 2715 (m), 1729 (s), 1451 (s), 1320 (s), 1161 (s), 1075 (s), 678 (s) cm^{-1};

MS (CI, CH_4, 70 eV): *m/z* = 318 (4)$[M+H]^+$, 274 (48), 226 (2), 200 (9), 172 (17), 162 (13), 155 (7), 147 (100), 119 (9), 91 (4);

Elemental Analysis for $C_{17}H_{19}NO_3S$: Calcd.: C 64.33; H 6.03; N 4.41;
Found: C 64.13; H 6.04; N 4.48.

8.14.3. *N*-Tosyl-1-amino-1-(4-methoxyphenyl)propanal (208d).



$C_{17}H_{19}NO_4S$. MW = 333.14 g mol^{-1}

Prepared according to GP-14, starting from propargylic amine **207d** (0.316 mmol, 100 mg) and *in situ* catalyst [CpRu(130m)$_2$(MeCN)]PF$_6$ (10 mol-%). Purification by flash column chromatography (*n*-pentane/EtOAc 4:3) afforded pure **208d** (0.261 mmol, 87 mg, 83% yield) as a light brown solid;

Mp: 133-134 °C;

^{1}H-NMR ($CDCl_3$, 400 MHz)

δ = 2.38 (s, 3 H; CH_3), 2.85-2.94 (m, 1 H; CH_2), 2.98-3.07 (m, 1 H; CH_2), 3.74 (s, 3 H; CH_3), 4.75 (q, *J* = 6.9 Hz, 1 H; CH), 5.44 (d, *J* = 7.4 Hz, 1 H; NH), 6.67-6.72 (m, 2 H; Ar-H), 6.95-7.01 (m, 2 H; Ar-H), 7.15-7.21 (m, 2 H; Ar-H), 7.55-7.61 (m, 2 H; Ar-H), 9.62 (t, *J* = 1.4 Hz, 1 H; C(O)H) ppm;

^{13}C-NMR ($CDCl_3$, 100 MHz)

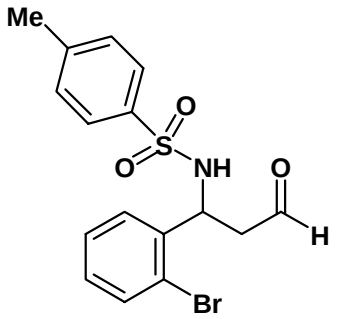
δ = 21.5, 50.2, 52.7, 55.2, 113.9, 127.0, 127.6, 129.4, 131.2, 137.0, 143.2, 159.0, 199.5 ppm;

IR (KBr): 3423 (w), 3236 (s), 2959 (w), 2849 (m), 1722 (s), 1606 (m), 1511 (s), 1453 (s), 1406 (m), 1318 (s), 1253 (s), 1152 (s), 1070 (s), 674 (s) cm^{-1};

MS (EI, 70 eV): *m/z* = 333 (6)[M$^+$], 290 (83), 178 (55), 162 (8), 155 (47), 134 (56), 107 (9), 91 (100), 65 (30);

Elemental Analysis for $C_{17}H_{19}NO_4S$: Calcd.: C 61.24; H 5.74; N 4.20;
Found: C 61.14; H 6.01; N 4.16.

8.14.4. *N*-Tosyl-1-amino-1-(2-bromophenyl)propanal (208e).



$C_{16}H_{16}BrNO_3S$. MW = 381.1 g mol^{-1}

Prepared according to GP-14, starting from propargylic amine **207e** (0.275 mmol, 100 mg) and *in situ* catalyst [CpRu(130b)$_2$(MeCN)]PF$_6$ (10 mol-%). Purification by flash column chromatography (*n*-pentane/EtOAc 2:1) afforded pure **208e** (0.228 mmol, 87 mg, 84% yield) as a white solid;

Mp: 105-106 °C;

^{1}H-NMR ($CDCl_3$, 400 MHz)

δ = 2.33 (s, 3 H; CH_3), 2.89-2.97 (m, 1 H; CH_2), 2.97-3.06 (m, 1 H; CH_2), 5.15-5.24 (m, 1 H; CH), 5.84 (d, *J* = 8.8 Hz, 1 H; NH), 7.02 (td, *J* = 7.7, 1.7 Hz, 1 H; Ar-H), 7.09-7.14 (m, 3 H; Ar-H), 7.23 (dd, *J* = 7.8, 1.8 Hz, 1 H; Ar-H), 7.39 (dd, *J* = 8.0, 1.4 Hz, 1 H; Ar-H), 7.55-7.61 (m, 2 H; Ar-H), 9.62 (dd, *J* = 1.6, 0.8 Hz, 1 H; C(O)H) ppm;

^{13}C-NMR ($CDCl_3$, 100 MHz)

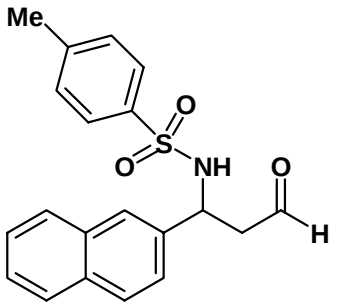
δ = 21.5, 48.4, 52.8, 121.9, 127.0, 127.5, 128.8, 129.0, 129.3, 132.9, 136.6, 137.8, 143.3, 199.2 ppm;

IR (KBr): 3487 (w), 3242 (s), 2919 (w), 2836 (m), 2745 (w), 1721 (s), 1446 (s), 1337 (s), 1165 (s), 1085 (s), 668 (s) cm^{-1};

MS (CI, CH_4, 70 eV): *m/z* = 382-384 (8)$[M+H]^+$, 338-340 (19), 302 (1), 239-241 (6), 211-213 (100), 172 (68), 155 (10), 131 (25), 91 (4);

Elemental analysis for $C_{16}H_{16}BrNO_3S$: Calcd.: C 50.27; H 4.22; N 3.66;
Found: C 50.19; H 4.59; N 3.61.

8.14.5. *N*-Tosyl-1-amino-1-(2-naphthyl)propanal (208f).



$C_{20}H_{19}NO_3S$. MW = 353.1 g mol^{-1}

Prepared according to GP-14 starting from propargylic amine **207f** (0.143 mmol, 48 mg) and *in situ* catalyst $[CpRu(130m)_2(MeCN)]PF_6$ (10 mol-%). Purification by flash column chromatography (*n*-pentane/EtOAc 1:1) afforded pure **208f** (0.119 mmol, 42 mg, 85% yield) as a light brown solid;

Mp: 104-105 °C;

^{1}H-NMR ($CDCl_3$, 400 MHz)

δ = 2.20 (s, 3 H; CH_3), 2.94-3.05 (m, 1 H; CH_2), 3.07-3.17 (m, 1 H; CH_2), 4.97 (q, *J* = 6.9 Hz, 1 H; CH), 5.63 (d, *J* = 7.7 Hz, 1 H; NH), 7.00 (d, *J* = 8.0 Hz, 2 H; Ar-H), 7.17 (dd, *J* = 8.5, 1.6 Hz, 1 H; Ar-H), 7.40-7.48 (m, 3H; Ar-H), 7.53 (d, *J* = 8.2 Hz, 2 H; Ar-H), 7.60-7.68 (m, 2 H; Ar-H), 7.70-7.77 (m, 1 H; Ar-H), 9.66 (br s, 1 H; C(O)H) ppm;

^{13}C-NMR ($CDCl_3$, 100 MHz)

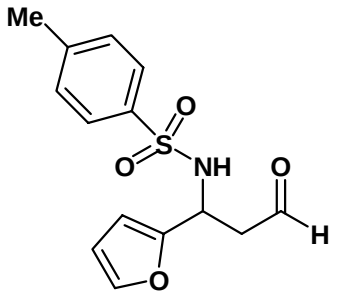
δ = 21.4, 50.0, 53.4, 123.9, 125.8, 126.2, 126.3, 127.0, 127.4, 127.8, 128.6, 129.2, 132.6, 132.8, 136.1, 136.9, 143.3, 199.4 ppm;

IR (KBr): 3421 (m), 3216 (s), 2851 (m), 1722 (s), 1595 (w), 1449 (m), 1328 (s), 1159 (s), 1071 (m), 667 (s) cm^{-1};

MS (EI, 70 eV): *m/z* = 310 (2)$[M-C_2H_3O]^+$, 211(5), 183 (100)$[M-C_7H_8NO_2S]^+$, 172, 155, 128, 107, 91;

Elemental Analysis for $C_{20}H_{19}NO_3S$: Calcd.: C 67.97; H 5.42; N 3.96;
Found: C 67.70; H 5.36; N 3.90.

8.14.6. *N*-Tosyl-1-amino-1-(2-furyl)propanal (208g).



$C_{14}H_{15}NO_4S$. MW = 293.07 g mol^{-1}

Prepared according to GP-14 or GP-15, starting from propargylic amine **207g** (0.327 mmol, 90 mg) and *in situ* catalyst $[CpRu(130b)_2(MeCN)]PF_6$ (10 mol-%). Purification by flash column chromatography (*n*-pentane/EtOAc 2:1) afforded pure **208g** (0.297 mmol, 87 mg, 90% yield) as a light yellow solid;

Mp: 81-82 °C;

^{1}H-NMR ($CDCl_3$, 400 MHz)

δ = 2.39 (s, 3 H; CH_3), 2.90-2.99 (m, 1 H; CH_2), 3.00-3.09 (m, 1 H; CH_2), 4.90 (dt, *J* = 8.5, 6.2 Hz, 1 H; CH), 5.43 (d, *J* = 8.8 Hz, 1 H; NH), 5.97 (d, *J* = 3.3 Hz, 1 H; Ar-H), 6.15 (dd, *J* = 3.3, 1.7 Hz, 1 H; Ar-H), 7.16 (dd, *J* =1.9, 0.8 Hz, 1 H; Ar-H), 7.21-7.27 (m, 2 H; Ar-H), 7.63-7.69 (m, 2 H; Ar-H), 9.68 (t, *J* = 1.2 Hz, 1 H; C(O)H) ppm;

^{13}C-NMR ($CDCl_3$, 100 MHz)

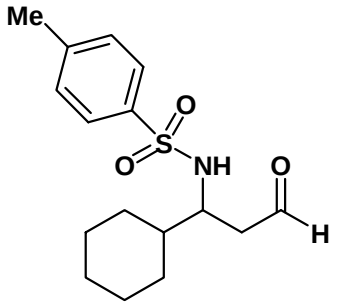
δ = 21.6, 47.0, 47.4, 107.3, 110.3, 126.9, 129.5, 137.1, 142.1, 143.4, 151.3, 198.9 ppm;

IR (KBr): 3446 (w), 3239 (s), 2918 (w), 2818 (w), 2716 (m), 1727 (s), 1598 (m), 1451 (s), 1324 (s), 1163 (s), 1075 (s), 675 (s) cm^{-1};

MS (EI, 70 eV): *m/z* = 295 (1)$[M+H]^+$, 279 (4), 250 (20), 226 (12), 171 (39), 155 (67), 149 (22), 138 (76), 122 (30), 109 (31), 91 (100);

Elemental Analysis for $C_{14}H_{15}NO_4S$: Calcd.: C 57.32; H 5.15; N 4.77;
Found: C 57.26; H 5.35; N 4.76.

8.14.7. *N*-tosyl-1-amino-1-(2-cyclohexyl)propanal (208h).



$C_{16}H_{23}NO_3S$. MW = 309.14 g mol^{-1}

Prepared according to GP-14 or GP-15, starting from propargylic amine **207h** (0.276 mmol, 80 mg) and *in situ* catalyst $[CpRu(130n)_2(MeCN)]PF_6$ (10 mol-%). Purification by flash column chromatography (*n*-pentane/EtOAc 2:1) afforded pure **208h** (0.243 mmol, 75 mg, 91% yield) as a light yellow solid;

Mp: 92-93 °C;

^{1}H-NMR ($CDCl_3$, 300 MHz)

δ = 0.67-0.95 (m, 2 H; CH_2), 0.99-1.22 (m, 3 H; CH_2, CH), 1.36-1.52 (m, 2 H; CH_2), 1.55-1.76 (m, 4 H; CH_2), 2.43 (s, 3 H; CH_3), 2.52-2.60 (m, 2 H; CH_2), 3.47 (dq, *J* = 9.0, 5.7 Hz, 1 H; CH), 4.94 (d, *J* = 8.9 Hz, 1 H; NH), 7.27-7.34 (m, 2 H; Ar-H), 7.70-7.77 (m, 2 H; Ar-H), 9.58 (t, *J* = 1.4 Hz, 1 H; C(O)H) ppm;

^{13}C-NMR ($CDCl_3$, 75 MHz)

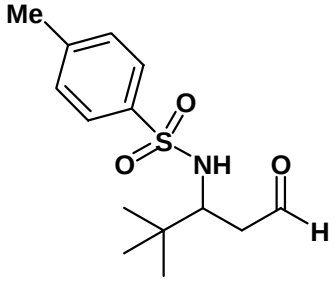
δ = 21.5, 25.8, 25.9, 26.0, 28.9, 29.3, 41.4, 45.7, 54.2, 127.1, 129.7, 137.8, 143.5, 200.7 ppm;

IR (KBr): 3456 (s), 3279 (s), 2928 (s), 2849 (s), 1729 (s), 1597 (m), 1448 (s), 1418 (s), 1320 (s), 1159 (s), 1090 (s), 668 (s), 551 (s) cm^{-1};

MS (EI, 70 eV): *m/z* = 310 (1)$[M+H]^+$, 266 (5), 226 (100), 198 (10), 184 (5), 155 (66), 139 (3), 110 (21), 91 (43);

Elemental Analysis for $C_{16}H_{23}NO_3S$: Calcd.: C 62.11; H 7.49; N 4.53;
Found: C 61.95; H 7.69; N 4.45.

8.14.8. *N*-Tosyl-1-amino-1-(2-*tert*-butyl)propanal (208i).



$C_{14}H_{21}NO_3S$. MW = 283.12 g mol^{-1}

Prepared according to GP-14 or GP-15, starting from propargylic amine **207i** (0.377 mmol, 100 mg) and *in situ* catalyst [CpRu(130n)$_2$(MeCN)]PF_6 (10 mol-%). Purification by flash column chromatography (*n*-pentane/EtOAc 2:1) afforded pure **208i** (0.311 mmol, 88 mg, 85% yield) as a yellow solid;

Mp: 107-108 °C;

^{1}H-NMR ($CDCl_3$, 300 MHz)

δ = 0.82 (s, 9 H; CH_3), 2.41 (s, 3 H; CH_3), 2.41-2.63 (m, 2 H; CH_2), 3.56 (dt, *J* = 9.2, 5.7 Hz, 1 H; CH), 5.01 (d, *J* = 9.2 Hz, 1 H; NH), 7.26-7.34 (m, 2 H; Ar-H), 7.70-7.77 (m, 2 H; Ar-H), 9.57 (dd, *J* = 2.2, 1.5 Hz, 1 H; C(O)H) ppm;

^{13}C-NMR ($CDCl_3$, 75 MHz)

δ = 21.5, 26.3, 34.9, 45.9, 57.3, 127.1, 129.7, 137.6, 143.5, 200.4 ppm;

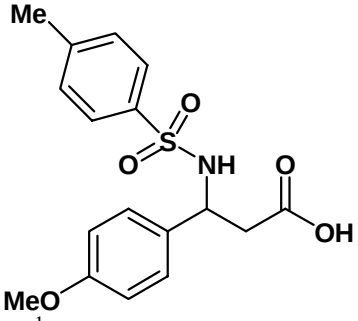
IR (KBr): 3270 (s), 2965 (s), 2823 (m), 1722 (s), 1599 (m), 1457 (s), 1319 (s), 1157 (s), 1089 (s), 670 (s), 577 (s) cm^{-1};

MS (EI, 70 eV): *m/z* = 284 (1)[M+H]$^+$, 240 (5), 226 (100), 198 (12), 155 (72), 113 (6), 91 (51), 57 (14);

Elemental Analysis for $C_{14}H_{21}NO_3S$: Calcd.: C 59.34; H 7.47; N 4.94;
Found: C 59.24; H 7.62; N 4.97.

8.15. Synthesis of *N*-Tosyl-β-amino-acid Derivatives

8.15.1. *N*-Tosyl-1-amino-1-(4-methoxyphenyl)propanoic acid (209d).



$C_{17}H_{19}NO_5S$. MW = 349.4 g mol^{-1}

Prepared according to GP-16, starting from propargylic amine **207d** (0.14 mmol, 45 mg) and *in situ* catalyst $[CpRu(130n)_2(MeCN)]PF_6$ (10 mol-%). Purification by flash column chromatography (*n*-pentane/EtOAc/HOAc 80:20:1) afforded pure **209d** (0.088 mmol, 31 mg, 64% yield over two steps) as a white solid;

Mp: 180-181 °C;

^{1}H-NMR ($CDCl_3$, 300 MHz)

δ = 2.10 (s, 3 H; CH_3), 2.75-2.84 (dd, *J* = 16.3, 6.4 Hz 1 H; CH_2), 2.88-2.98 (dd, *J* = 16.3, 6.1 Hz 1 H; CH_2), 3.76 (s, 3 H; CH_3), 4.68 (dd, *J* = 13.1, 6.4 Hz, 1 H; CH), 5.62 (d, *J* = 7.7 Hz, 1 H; NH), 6.74 (d, *J* = 8.6 Hz, 2 H; Ar-H), 7.03 (d, *J* = 8.8 Hz, 2 H; Ar-H), 7.19 (d, *J* = 7.9 Hz, 2 H; Ar-H), 7.61 (d, *J* = 8.4 Hz, 2 H; Ar-H) ppm;

^{13}C-NMR ($CDCl_3$, 75 MHz)

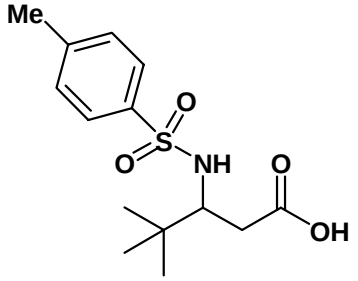
δ = 21.5, 40.6, 53.5, 55.2, 113.9, 127.1, 127.7, 129.4, 131.0, 137.2, 143.3, 159.1, 174.0 ppm;

IR (KBr): 3260 (m), 1712 (s), 1515 (s), 1449 (m), 1412 (m), 1320 (s), 1258 (m), 1159 (s), 947 (m), 811 (m), 673 (s), 576 (m) cm^{-1};

MS (EI, 70 eV): *m/z* = 349 (3)[M^+], 332 (2), 242 (3), 290 (9), 219 (2), 200 (6), 179 (100), 172 (20), 155 (6), 135 (4), 91 (2);

Elemental Analysis for $C_{17}H_{19}NO_5S$: Calcd.: C 58.44; H 5.48; N 4.01;
Found: C 58.65; H 5.28; N 3.57.

8.15.2. *N*-tosyl-1-amino-1-(2-*tert*-butyl)propanoic acid (209i).



$C_{14}H_{21}NO_4S$. MW = 299.39 g mol^{-1}

Prepared according to GP-16, starting from propargylic amine **207i** (0.150 mmol, 40 mg) and *in situ* catalyst $[CpRu(130n)_2(MeCN)]PF_6$ (10 mol-%). Purification by flash column chromatography (EtOAc/*n*-pentane/HOAc 80:20:1) afforded pure **209i** (0.107 mmol, 32 mg, 72% yield over two steps) as a white solid;

Mp: 169 °C;

^{1}H-NMR ($CDCl_3$, 300 MHz)

δ = 0.86 (s, 9 H; CH_3), 2.35-2.39 (m, 2 H; CH_2), 2.41 (s, 3 H; CH_3), 3.43 (dt, *J* = 9.6, 5.4 Hz, 1 H; CH), 5.26 (d, *J* = 9.4 Hz, 1 H; NH), 7.26-7.32 (m, 2 H; Ar-H), 7.73-7.79 (m, 2 H; Ar-H) ppm;

^{13}C-NMR ($CDCl_3$, 75 MHz)

δ = 21.5, 26.4, 35.3, 58.9, 127.1, 127.6, 129.6, 137.7, 143.4, 177.0 ppm;

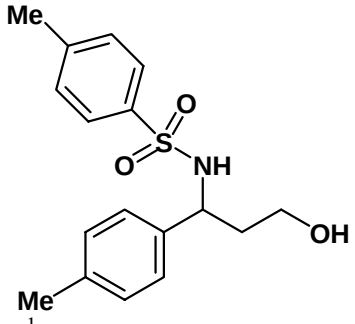
IR (KBr): 3276 (s), 2971 (s), 1716 (s), 1447 (s), 1314 (s), 1150 (s), 1087 (s) cm^{-1};

MS (EI, 70 eV): *m/z* = 300 (1)[M^+], 242 (100), 224 (7), 172 (6), 155 (32), 91 (22);

Elemental Analysis for $C_{14}H_{21}NO_4S$: Calcd.: C 56.16; H 7.07; N 4.68;
Found: C 56.09; H 7.17; N 4.60.

8.16. Synthesis of *N*-Tosyl-β-amino-alcohol Derivatives

8.16.1. *N*-Tosyl-1-amino-1-(4-methylphenyl)propanol (210c).



$C_{17}H_{21}NO_3S$. MW = 319.42 g mol^{-1}

Prepared according to GP-17, starting from β-amino aldehyde **208c** (0.126 mmol, 40 mg) and $NaBH_4$ (0.63 mmol, 24 mg). Purification by flash column chromatography (*n*-pentane/EtOAc 1:1) afforded pure **210c** (0.090 mmol, 29 mg, 71% yield) as a white solid;

Mp: 140-141 °C;

^{1}H-NMR ($CDCl_3$, 400 MHz)

δ = 1.89-1.95 (m, 2 H; CH_2), 2.08 (br s, 1 H; OH), 2.28 (s, 3 H; CH_3), 2.38 (s, 3 H; CH_3), 3.60-3.67 (m, 1 H, A part of an AB system; CH_2), 3.78-3.85 (m, 1 H, B part of an AB system; CH_2), 4.47 (dt, *J* = 7.4, 6.3 Hz, 1 H; CH), 5.50 (d, *J* = 7.4 Hz, 1 H; NH), 6.90 (d, *J* = 7.9 Hz, 2 H; Ar-H), 6.97 (d, *J* = 7.9 Hz, 2 H; Ar-H), 7.16 (d, *J* = 8.2 Hz, 2 H; Ar-H), 7.59 (d, *J* = 8.2 Hz, 2 H; Ar-H) ppm;

^{13}C-NMR ($CDCl_3$, 100 MHz)

δ = 20.9, 21.4, 39.2, 55.5, 59.2, 126.0, 126.9, 128.9, 129.1, 136.9, 137.4, 142.8, 186.3 ppm;

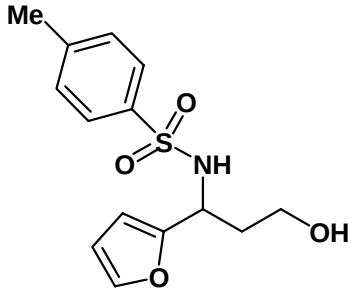
IR (KBr): 3548 (s), 3247 (s), 2959 (m), 2921 (s), 2869 (m), 1453 (m), 1305 (s), 1157 (s), 1055 (s), 993 (s), 914 (m), 805 (s), 722 (m), 676 (s), 536 (s) cm^{-1};

MS (EI, 70 eV): *m/z* = 320 (2)$[M+H]^+$, 302 (1), 274 (33), 260 (2), 200 (9), 172 (6), 149 (100), 131 (6), 119 (6);

Elemental Analysis for $C_{17}H_{21}NO_3S$: Calcd.: C 63.92; H 6.63; N 4.39;
Found: C 63.27; H 6.37; N 4.44;

HRMS for $C_{17}H_{21}NO_3S$-C_2H_5O: Calcd.: 274.090176;
Found: 274.090188.

8.16.2. *N*-Tosyl-1-amino-1-(2-furyl)propanol (210g).



$C_{14}H_{17}NO_4S$. MW = 295.35 g mol^{-1}

Prepared according to GP-17, starting from β-amino aldehyde **208g** (0.136 mmol, 40 mg) and $NaBH_4$ (0.68 mmol, 26 mg). Purification by flash column chromatography (*n*-pentane/EtOAc 1:1) afforded pure **210g** (0.108 mmol, 32 mg, 80% yield) as a white solid;

Mp: 96-97 °C;

^{1}H-NMR ($CDCl_3$, 400 MHz)

δ = 1.89-2.06 (m, 3 H; CH_2, OH), 2.40 (s, 3 H; CH_3), 3.65-3.71 (m, 1 H, A part of an AB system; CH_2), 3.84-3.91 (m, 1 H, B part of an AB system; CH_2), 4.63 (td, *J* = 8.8, 5.2 Hz, 1 H; CH), 5.24 (d, *J* = 8.8 Hz, 1 H; NH), 5.87 (d, *J* = 3.3 Hz, 1 H; Ar-H), 6.13 (dd, *J* = 3.0, 1.9 Hz, 1 H; Ar-H), 7.15 (d, *J* = 1.7 Hz, 1 H; Ar-H), 7.34 (d, *J* = 8.0 Hz, 2 H; Ar-H), 7.67 (d, *J* = 8.2 Hz, 2 H; Ar-H) ppm;

^{13}C-NMR ($CDCl_3$, 100 MHz)

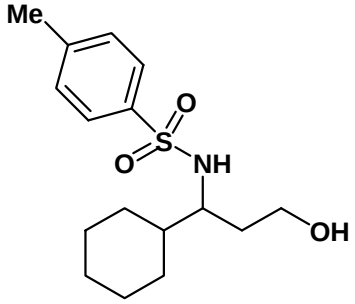
δ = 21.6, 36.8, 49.0, 58.7, 106.6, 110.1, 127.0, 129.4, 137.2, 141.9, 143.2, 152.8 ppm;

IR (KBr): 3507 (s), 3153 (m), 2949 (m), 2896 (m), 1599 (m), 1459 (m), 1316 (s), 1153 (s), 1047 (s), 926 (s), 810 (m), 739 (s), 703 (s), 662 (s), 567 (s), 502 (m) cm^{-1};

MS (EI, 70 eV): *m/z* = 296 (2)$[M+H]^+$, 250 (5), 200 (3), 172 (51), 154 (9), 140 (15), 125 (100), 107 (5), 91 (3);

Elemental Analysis for $C_{14}H_{17}NO_4S$: Calcd.: C 56.93; H 5.80; N 4.74;
Found: C 56.60; H 5.74; N 4.71.

8.16.3. *N*-Tosyl-1-amino-1-(2-cyclohexyl)propanol (210h).



$C_{16}H_{25}NO_3S$. MW = 311.44 g mol^{-1}

Prepared according to GP-17, starting from β-amino aldehyde **208h** (0.146 mmol, 45 mg) and $NaBH_4$ (0.73 mmol, 28 mg). Purification by flash column chromatography (*n*-pentane/EtOAc 1:1) afforded pure **210h** (0.115 mmol, 36 mg, 80% yield) as a white solid;

Mp: 120-121 °C;

^{1}H-NMR ($CDCl_3$, 300 MHz)

δ = 0.70-0.86 (m, 2 H; CH_2), 0.96-1.14 (m, 3 H; CH_2), 1.18-1.31 (m, 1 H; CH_2), 1.37-1.48 (m, 2 H; CH_2), 1.49-1.77 (m, 5 H; CH, CH_2), 2.22 (br s, 1 H; OH), 2.43 (s, 3 H; CH_3), 3.28 (br s, 1 H; CH), 3.56-3.65 (m, 1 H, A part of an AB system; CH_2), 3.73-3.84 (m, 1 H, B part of an AB system; CH_2), 4.84 (d, *J* = 6.9 Hz, 1 H; NH), 7.31 (d, *J* = 7.9 Hz, 2 H; Ar-H), 7.75 (d, *J* = 7.9 Hz, 2 H; Ar-H) ppm;

^{13}C-NMR ($CDCl_3$, 75 MHz)

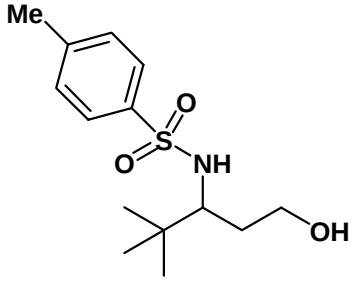
δ = 21.5, 26.1, 26.2, 26.3, 28.7, 28.8, 34.1, 42.1, 55.9, 59.0, 127.0, 129.5, 138.1, 143.3 ppm;

IR (KBr): 3458 (s), 3182 (s), 2928 (s), 2854 (s), 1469 (m), 1446 (s), 1321 (s), 1301 (s), 1159 (s), 1055 (s), 1016 (m), 819 (m), 587 (m), 551 (s) cm^{-1};

MS (EI, 70 eV): *m/z* = 312 (100)$[M+H]^+$, 294 (3), 266 (4), 228 (32), 198 (4), 172 (6), 155 (4), 141 (35), 123 (18);

Elemental Analysis for $C_{16}H_{25}NO_3S$: Calcd.: C 61.70; H 8.09; N 4.50;
Found: C 61.08; H 8.04; N 4.31.

8.16.4. *N*-Tosyl-1-amino-1-(2-*tert*-butyl)propanol (210i).



$C_{14}H_{23}NO_3S$. MW = 285.4 g mol^{-1}

Prepared according to GP-17, starting from β-amino aldehyde **208i** (0.106 mmol, 30 mg) and $NaBH_4$ (0.53 mmol, 20 mg). Purification by flash column chromatography (*n*-pentane/EtOAc 1:1) afforded pure **210i** (0.077 mmol, 22 mg, 73% yield) as a white solid;

Mp: 109-110 °C;

^{1}H-NMR ($CDCl_3$, 400 MHz)

δ = 0.70 (s, 9 H; CH_3), 1.29-1.38 (m, 1 H, A part of an AB system; CH_2), 1.89-1.98 (m, 1 H, B part of an AB system; CH_2), 2.42 (s, 3 H; CH_3), 2.50 (br s, 1 H; OH), 3.20-3.28 (m, 1 H, A part of an AB system; CH_2), 3.64-3.71 (m, 1 H; CH), 3.81-3.89 (m, 1 H, B part of an AB system; CH_2), 4.64 (d, *J* = 9.9 Hz, 1 H; NH), 7.29 (d, *J* = 7.9 Hz, 2 H; Ar-H), 7.76 (d, *J* = 8.4 Hz, 2 H; Ar-H) ppm;

^{13}C-NMR ($CDCl_3$, 100 MHz)

δ = 21.6, 26.7, 33.9, 34.7, 58.7, 59.7, 127.0, 129.5, 138.2, 143.2 ppm;

IR (KBr): 3451 (s), 3140 (s), 2962 (s), 2881 (s), 1473 (m), 1321 (s), 1150 (s), 1088 (m), 1025 (s), 900 (s), 812 (s), 711 (m), 668 (s), 586 (s), 529 (s) cm^{-1};

MS (EI, 70 eV): *m/z* = 286 (100)$[M+H]^+$, 268 (6), 228 (24), 198 (4), 186 (3), 172 (4), 155 (4), 115 (32), 97 (21);

Elemental Analysis for $C_{14}H_{23}NO_3S$: Calcd.: C 58.92; H 8.12; N 4.91;
Found: C 58.56; H 8.01; N 4.70.

9. Appendix

9.1. List of Abbreviations

Å	Ångstrom
[α]	specific optical rotation
Ac	acetyl
acac	acetylacetonate
Ac_2O	acetic anhydride
*t*Am	*tert*-amyl
aq.	aqueous (solution)
Ar	aromatic substituent
Bn	benzyl
Bu	butyl
*n*BuLi	*n*-butyllithium
*t*Bu	*tert*-butyl
Cp	cyclopentadienyl
Cy	cyclohexyl
δ	chemical shift
DCM	dichloromethane
DFT	density function theory
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
dppe	1,2-bis-diphenylphosphinoethane
dppm	diphenylphosphinomethane
ee	enantiomeric excess
EI	electronic impact (in mass spectroscopy)
ESI-MS	electrospray impact-mass spectrometry
Et	ethyl
EtOAc	ethyl acetate
EtOH	ethanol
eV	electronvolt

GC	gas chromatography
Hex	hexane
HOAc	acetic acid
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
IR	infrared spectroscopy
J	coupling constant (in NMR spectroscopy)
L	ligand
M	molar
Me	methyl
Mes	2,4,6-trimethylphenyl (mesityl)
mol	mole
Mp	melting point
Ms	methanesulfonyl (mesyl)
MS	mass spectroscopy
MTBE	methyl-*tert*-butylether
MW	microwaves
ν	wave number
NME	*N*-methylephedrine
NMR	nuclear magnetic resonance (spectroscopy)
Ns	*p*-nitrobenzenesulfonyl (nosyl)
Piv	pivaloate ester
PMP	*p*-methoxyphenyl
ppm	parts per milion
*i*Pr	*iso*-propyl
*n*Pr	*n*-propyl
PG	protecting group
PyBOX	pyridine-bisoxazoline
rac	racemic
rt	room temperature
TBAF	tertabutylammonium fluoride
TBS	tertbutyldimethylsilyl
THF	tetrahydrofurane
TMEDA	tetramethylethylendiamine
TMS	trimethylsilyl

TMSCCH	trimethylsilylethyne
TMSCl	trimethylsilylchloride
tert	tertiary
TO	Turnover
TOF	Turnover frequency
Ts	*p*-toluenesulfonyl (tosyl)
TPP	tetraphenylporphyrine
TPPTS	tris(sodium *m*-benzenesulfonate)phosphine

9.2. List of Publications, Poster and Oral Communications

Publication on Journals:

1) J. Quancart, A. Labonne, Y. Jacquot, G. Chassaing, S. Lavielle, P. Karoyan.
"Asymmetric Synthesis of 3-Substituted Proline Chimeras Bearing Polar Side Chains of Proteinogenic Amino Acids"
J. Org. Chem., **2004**, *69*, 7940-7948.

2) A. Labonne, T. Kribber, L. Hintermann
"Highly Active in Situ Catalysts for anti-Markovnikov Hydration of Terminal Alkynes"
Org. Lett. **2006**, *8*, 5853-5856.

3) L. Hintermann, A. Labonne
"Catalytic Hydration of Alkynes and its Aplication in Synthesis"
Synthesis **2007**, 1121-1150.

4) T. Kribber, A. Labonne, L. Hintermann
"Iterative Synthesis of Oligo-1,4-Diols via Catalytic anti-Markovnikov Hydration of Terminal Alkynes"
Synthesis **2007**, *in press*.

5) A. Labonne, L. Zani, L. Hintermann, C. Bolm
"Redox-neutral Synthesis of β-Amino Aldehydes from Imines by an Alkynylation/Hydration Sequence"
J. Org. Chem. **2007**, *72*, 5704-5708.

6) A. Labonne, L. Hintermann *manuscript in preparation*
"Copper-Catalyzed Cross-Coupling of Tertiary Grignard Reagents: Regioselective Synthesis of Aza-heterocyclic Building Blocks"

Poster and Oral Communications:

02/2007 KAIST, RWTH Aachen, Germany;
Oral presentation: «Synthesis of new Pyridylphosphane Ligands and their Applications in the Ru-catalyzed anti-MARKOVNIKOV hydration of alkynes".

12/2006	9th Nikolaus-Symposium, RWTH Aachen, Germany; Oral presentation: «Synthesis of new Pyridylphosphane Ligands and their Applications in the Ru-catalyzed anti-MARKOVNIKOV hydration of alkynes".
09/2006	15Th Nachwuchswissenschaftler-Symposium Bioorganische Chemie, Berlin, Germany.
09/2006	Poster **prize in ORCHEM 2006**, Bad Nauheim, Germany; Poster: "Applications of New Aza-Arylphosphane Ligands In Ru-catalyzed anti-MARKOVNIKOV Hydration of Alkynes".
07/2006	22th International Conference on Organometallic Chemistry (ICOMC 2006), Zaragoza, Spain; Poster: "Novel Aza-Arylphosphane Ligands for Ru-catalyzed anti-MARKOVNIKOV Hydration of Alkynes".
12/2005	8thNikolaus-Symposium, RWTH Aachen, Germany; Poster
11/2005	4th Symposium "Hochschule trifft Industrie", Wermelskirchen, Germany; Oral presentation: „In situ Catalysts for anti-MARKOVNIKOV Hydrolysis of Alkynes".
10/2005	9th International SFB Symposium, Aachen, Germany; Poster: "*In Situ* Catalysts for anti-MARKOVNIKOV Hydrolysis of Alkynes". CRC International Symposium in Aachen on "Cross-Coupling & Organometallics", Aachen, Germany.
12/2004	7thNikolaus-Symposium, RWTH Aachen, Germany; Poster
	11/2004 2004 Lilly European Distinguished Lectureship, Namur, Belgian; Poster: "Synthetic Application of new Ru-catalyzed Alkyne Hydrolysis".
10/2004	8th International SFB Symposium, Forschungszentrum Jülich, Germany; Poster: "Synthetic Application of new Ru-catalyzed Alkyne Hydrolysis".

9.3. Curriculum Vitae

Personal Informations

Name:	Aurélie Labonne
Date of birth	25 July 1979
Place of birth	Paris
Nationality	French
Marital Status	Single
Current Affiliation	Institute of Organic Chemistry, RWTH Aachen University
	Landoltweg 1, D-52074 Aachen

Education

09/1985-06/1990	Primary school, Paris
09/1990-06/1994	Secondary school, Paris
09/1994-06/1997	High-school, Paris
06/1997	Baccalaureat

Academic qualifications

1997-2003	Course of studies in biochemistry and chemistry at the University of Pierre & Marie Curie, Paris, France.
07-2003	Graduation examination. Degree of Master of Science in the field of Organic and Bioorganic Chemistry.
2004-2007	PhD work at the institute of Organic Chemistry, RWTH Aachen University, Germany, under the supervision of Dr. Lukas Hintermann.

9.4. Acknowledgements

There are many people to whom I am very grateful for their help and encouragement during this unforgettable time which has been my PhD work at the IOC RWTH Aachen. For this support and the amazing memories along these three years: MERCI!

First I would like to thank my supervisor, Dr. Lukas Hintermann, for giving me the opportunity to work in his research group and to become his first PhD student. With his unbelievable knowledges, he helped me to become a better chemist, and stronger over the months, sometimes stressful, that I needed to complete the work presented in this thesis.

Then I would like to specially thank Prof. Dr. Carsten Bolm for his constant support and enthusiasm, as well as the fruitful collaboration. It was such a great time in "Ak Bolm": It has been a pleasure to know so many interesting people; it was such an exciting melting pot! In addition to the rich scientific aspect, it was an unforgettable life's experience.

I would like to express my gratitude to all co-workers of the "AK Hintermann": Claudia Dittmer, Jens Ackerstaff, Tanja Schimmel, Thomas Kribber and Marco Schmitz.

Futhermore I would like to thank the administrative and technical personnel of the Organic Chemistry Institute of the RWTH Aachen for their most appreciated help during my work. In particular, I sincerely thank Ingrid Voss for resolving all the bureaucratic problems and for our entertaining conversations ("ast Du gutt geschlaffen?").

Special Thanks to the Laborantinnen Nicole Brendgen ("Starfisch- or Sulfoximin-Göttin") and Susi Grünebaum ("Viva Colognііia!") for the synthesis of various "stinky-stinky" phosphanes and their inestimable help and warm support along these years.

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