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The AZARYPHOS Family of Ligands for Ambifunctional Catalysis: Syntheses and Use in Ruthenium-Catalyzed anti-Markovnikov Hydration of Terminal Alkynes**

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Abstract: The family of AZARYPHOS (aza–aryl–phosphane) phosphane ligands, containing a phosphine unit and sterically shielded nitrogen lone pairs in the ligand periphery, is introduced as a tool for developing ambifunctional catalysis by the metal center and nitrogen lone pairs in the ligand sphere. General synthetic strategies have been developed to synthesize over 25 examples of structurally diverse (6-aryl-2-pyridyl)phosphanes (ARPYPHOS), (6-alkyl-2-pyridyl)phosphanes (ALPYPHOS), 4,6-disubsituted 1,3-diazin-2-ylphosphanes or 1,3,5-triazin-2-ylphosphanes, quinazolinylphosphanes, quinolinylphosphanes, and others. The scalable syntheses proceed in a few steps. The incorporation of AZARYPHOS ligands (**L**) into complexes $[RuCp(\mathbf{L})_2(MeCN)][PF_6]$ (Cp = cyclopentadienyl) gives catalysts for the anti-Markovnikov hydration of terminal alkynes of the highest known activities. Electronic and steric ligand effects modulate the reaction kinetics over a range of two orders of magnitude. These results highlight the importance of using structurally diverse ligand families in the process of developing cooperative ambifunctional catalysis by a metal and its ligand.

Keywords: alkynes · catalysis · phosphane ligands · ruthenium · synthetic methods

Introduction

Ligand steering effects are crucial for tuning catalyst performance, and extended ligand screens are now primary tools in the search for new catalysts.[1] The concept of (cooperative) ambifunctional catalysis (or bifunctional/multifunctional catalysis) proposes that a ligand, modulating the catalytically active metal center, additionally interacts with metal-bound substrates in a specific and directed manner by means of an appropriately placed functional group within the ligand structure.[2,3] If this secondary interaction assists in accelerating the slowest step of a catalytic reaction, the overall reaction rate may dramatically increase. Several examples involving pyridylphosphane ligands imply that cooperative ambifunctional catalysis may be a generally useful concept in developing or optimizing catalytic reactions (Scheme 1): Drent and co-workers found that the palladium-catalyzed methoxycarbonylation of propyne is faster and more regioselective with pyridylphosphanes[4] instead of triphenylphosphane as the ligand.[5,6] The protonated pyridine unit may act as a general acid in an assisted hydrodemetalation.[5a,b] Alternatively, a proton transfer from pyridinium to the metal-bound alkyne could facilitate the generation of a vinyl-palladium(II) species (Scheme 1a).[7] Notably, the placement of a methyl group in the 6-position of the pyridyl unit further increased the regioselectivity of the catalytic reaction.[5]

Berke and co-workers synthesized 6-*tert*-butyl-2-diphenylphosphinopyridine to explore the steric shielding of a nitrogen lone pair in pyridylphosphanes as a tool for preventing P–N chelation.[8] When studying heterocyclic phosphanes as ligands in bifunctional catalysis,[3] Grotjahn and co-workers

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[**] AZARYPHOS = aza–aryl–phosphane.

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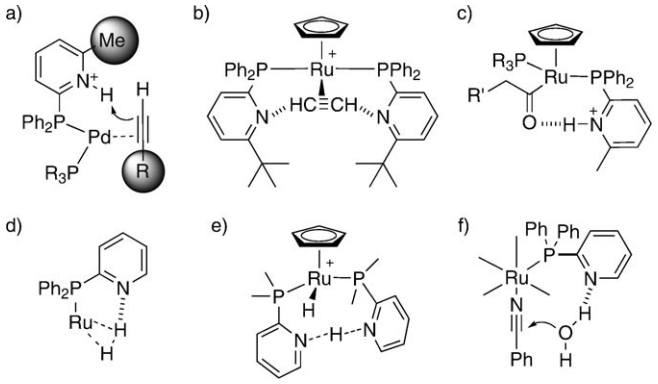
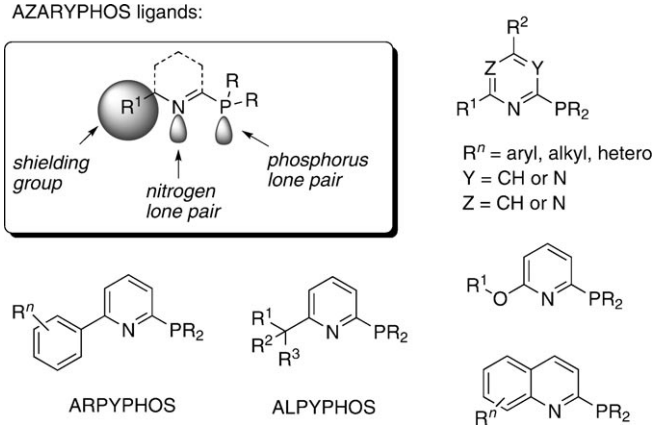


Scheme 1. Metal-bound pyridylphosphanes involved in (presumed) ambifunctional interactions with catalysis substrates: a) selectivity- and rate-enhancement in alkyne methoxycarbonylation, according to Drent[5] and Matteoli;[7] b) hydrogen bridges to acetylene C–H bonds;[10a] c) a reaction intermediate of catalytic anti-Markovnikov alkyne hydration;[10b] d) heterolytic splitting of H_2 at ruthenium;[13] e) a presumed catalytic intermediate in a H_2/D_2 exchange reaction;[13b] f) acceleration of ruthenium-catalyzed nitrile hydration through inner-sphere general base activation of water.[14]

found that the same ligand impressively accelerates ruthenium-catalyzed anti-Markovnikov hydration of terminal alkynes.[9] The pyridine lone pairs are hydrogen-bond acceptors towards C–H bonds of coordinated acetylene (Scheme 1b).[10a] In a reaction intermediate of catalytic alkyne hydration, a protonated pyridine unit acts as hydrogen-bond donor to a metal acyl species (Scheme 1c).[10b] Considering these findings, an active involvement of the pyridyl group as a proton shuttle in catalysis is very probable. Grotjahn also found that heterocyclic phosphane ligands speed up the prototropic equilibrium between π-alkyne and metal vinylidene complexes of rhodium[11] or ruthenium,[10a] and observed an impressive acceleration of ruthenium-catalyzed olefin isomerization by means of ionic 1,3-hydrogen shifts.[12] Catalytic H_2/D_2-exchange reactions may benefit from ambifunctional activation of the heterolytic split of coordinated molecular hydrogen by a pyridylphosphane ligand (Scheme 1d).[13] It was proposed that the resulting hydride complex stores a bridging proton between two pyridyl groups (Scheme 1e).[13b] Finally, the acceleration of ruthenium-catalyzed hydration of nitriles by 2-diphenylphosphinopyridine has been ascribed to general base activation of water by a pyridine lone pair.[14] Other ligand classes have been applied in ambifunctional catalysis,[2,3,15] but many examples and much substantial mechanistic evidence involve the pyridylphosphane fragment. Although the parent 2-diphenylphosphinopyridine (**L1**) has found several applications in catalysis,[4b,16] the above precedence implies that shielded pyridylphosphanes are particularly valuable ligands. Of those, only 6-methyl-2-diphenylphosphinopyridine (**L2**) is commercially available. In the absence of general synthetic routes to 6-substituted pyridylphosphanes,[17] the ligand screening approach in bifunctional catalysis development is limited. We now define the family of AZARYPHOS (aza–aryl–phosphane) ligands for application in ambifunctional catalysis, which lend themselves to ligand screening and structural optimization (Scheme 2). Single representatives of the ligand family have previously been prepared.[17] In the present work, we describe straightforward synthetic approaches to AZARYPHOS ligands bearing all kinds of sub-



Scheme 2. General structure definition of AZARYPHOS ligands and pertinent sub classes, for which syntheses are described in the present work.

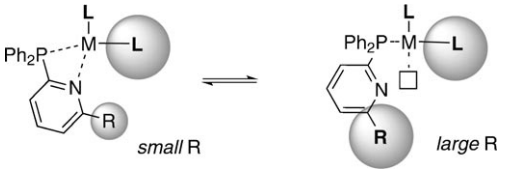
stituents.[18] An evaluation of the ligand class in ruthenium-catalyzed anti-Markovnikov hydration of terminal alkynes reveals that the new AZARYPHOS ligands cover a wider range of catalytic activities, depending on steric and electronic ligand properties. This proves that the concept of fine-tuning of ligand steering effects extends to ambifunctional catalysis.

Results and Discussion

Definition of the AZARYPHOS ligand structure: In a most convincing demonstration of ambifunctional acceleration in catalysis, Grotjahn and co-workers[3,9] included *t*BuPyPPh$_2$ (**L7**; Py = pyridine-2,6-yl)[8] into the cationic fragment $[RuCp(\mathbf{L7})_2]^+$ (Cp = cyclopentadienyl) to obtain a catalyst for anti-Markovnikov hydration of terminal alkynes to aldehydes[9,19–24] with a roughly 1000 times higher activity than [RuClCp(dppm)] (dppm = 1,1-bis(diphenylphosphino)methane).[9] Through working on applications of alkyne hydration in synthetic sequences,[24] we were immediately drawn to the Grotjahn catalyst. However, the involved synthesis of **L7**[8] presented an obstacle in the way of further studies of the new catalyst. Furthermore, ligand **L7** was singular in its peculiar ability to accelerate catalysis and did not lend itself easily to ligand variation studies. We wished to develop new tunable and readily available classes of ligands for bifunctional catalysis. In 2006, we introduced 6-aryl-2-diphenylphosphinopyridines as highly efficient ligands for ruthenium-catalyzed anti-Markovnikov hydration of terminal alkynes.[23] Later, our discovery of the catalytic cross-coupling of tertiary alkyl nucleophiles opened a straightforward synthetic route to 6-*tert*-alkylpyridylphosphanes including **L7**.[25] Now, we generalize and extend our studies by defining the class of AZARYPHOS (aza–aryl–phosphane) ligands

(Scheme 2), which share the properties of a 1,2,3-arrangement in a 6-membered heterocyclic core of a phosphorus donor, a nitrogen lone pair, and an R substituent of varying size (Scheme 2). In terms of applications in ambifunctional catalysis, the phosphorus donor will bind to a metal, the nitrogen lone pair will undergo secondary interactions with substrates, and the additional substituent R will serve as a steric shield of the nitrogen lone pair (see below).

In the following we present general synthetic routes to (6-alkyl-2-pyridyl)phosphanes (ALPYPHOS) bearing primary, secondary, or tertiary alkyl groups, to (6-aryl-2-pyridyl)phosphanes (ARPYPHOS), and to other aza–aryl phosphanes (AZARYPHOS) including pyrimidine, 1,3,5-triazine, quinoline, quinazoline, and 6-alkoxypyridine derivatives. A key structural element is the steric shielding of the nitrogen lone pair by an *ortho* substituent; the size of this group R (Scheme 3) will determine the stability difference between

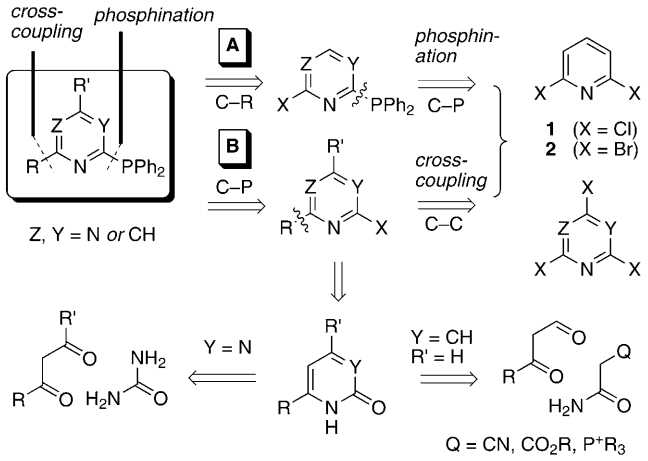


Scheme 3. Role of the shielding group R in suppressing chelation and opening up of a coordination site for the catalysis substrate in proximity to the ligand nitrogen lone pair.

the chelate and the open coordination mode through destabilizing steric interactions with additional steering ligands (**L**) at the metal (Scheme 3). Larger R substituents will help to liberate a free site of coordination for a substrate at the metal center.

Syntheses of AZARYPHOS ligands

Retrosynthetic analysis: The synthesis of pyridylphosphanes has been reviewed.[4a] Initial preparations relied on the reaction of metalated pyridines (M = Li, Mg, Zn[26]) with chlorophosphanes.[4a] Substitutions (S_NAr) of halopyridines with alkali phosphanides[27,28] ($LiPPh_2$, $NaPPh_2$, or $KPPh_2$) have since emerged as the more general method. The problem of accessing a certain aza–aryl phosphane is usually reduced to accessing the corresponding halogenated heterocycle. Only simple starting materials like 2-chloropyridine, 2-bromopyridine, or 6-methyl-2-chloropyridine are commercially available. There is no single general route to 6-substituted 2-halopyridines.[17] Our retrosynthetic analysis of the AZARYPHOS ligand structure (Scheme 4) starts with the disconnection of C–R/R′ (path **A**) or C–P bonds[29] (path **B**) to halogenated precursors. By experiment, we found that path **A** is viable for S_NAr reactions with, for example, alkoxides, but not successful for catalytic cross-coupling reactions of phosphorus-bearing precursors. Path **B**, which leads to substituted halogenated azacycles, is more general. The latter are further disconnected by C–C cleavage to give multiply halogenated precursors, or by C–X cleavage to give heterocyclic

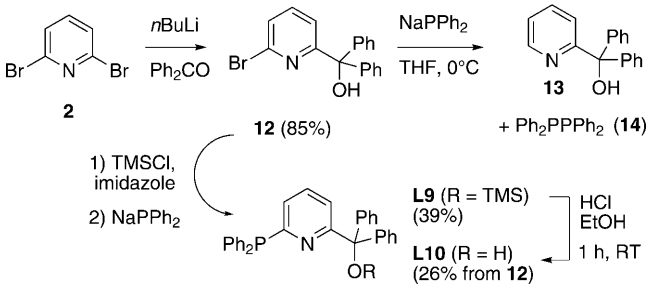


Scheme 4. Retrosynthetic disconnection strategies for some AZARYPHOS ligands.

carbonyl precursors such as pyrimidones or pyridones (Scheme 4).

Synthesis of ALPYPHOS ligands from halogenated precursors: All aza–aryl–phosphanes in this study have been obtained by means of nucleophilic phosphination from halogenated precursors. ALPYPHOS (alkyl–pyridyl–phosphane) ligands with either primary, secondary, or tertiary alkyl groups in the 6′-position of the pyridine nucleus have been prepared (Table 1).

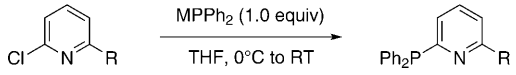
The commercially available compounds 2-diphenylphosphinopyridine (**L1**), also readily prepared from 2-chloropyridine (entry 1), and 6-methylpyrid-2-yl-diphenylphosphane (**L2**) from **4** (entries 2 and 3), are included for completeness. The phosphinations proceeded uneventfully. The synthesis of 1′-hydroxy-1,1-diphenylmethylpyridylphosphane **L10** deserves special mention, since this ligand contains a hydroxy group as added functionality (Scheme 5).

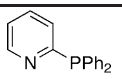
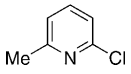
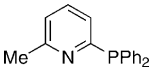
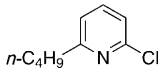
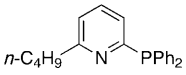
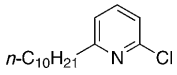
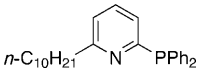
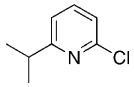
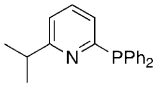
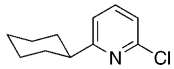
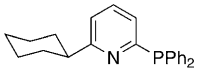
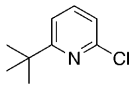
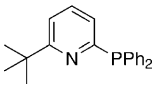
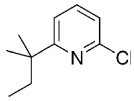
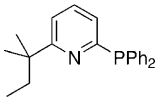
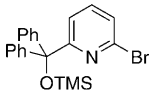
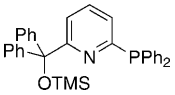
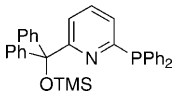
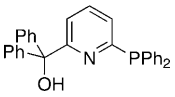


Scheme 5. Synthesis of a hydroxyalkyl pyridylphosphane by means of temporary silyl protection.

Selective lithiation of 2,6-dibromopyridine (**2**)[30,31] and reaction with benzophenone[32] gave hydroxyalkylpyridine **12** (Scheme 5). Reaction of the latter with $NaPPh_2$ gave dehalogenated alcohol **13** and presumably a phosphine coupling product **14** instead of the desired **L10** (Scheme 5). Apparently, the presence of a proton donor induces this redox reaction. Thus, alcohol **12** was first silylated and the trimethylsilane (TMS)-protected phosphine **L9** obtained successfully

Table 1. Synthesis of ALPYPHOS ligands from halogenated precursors.[a]



Entry	Substrate	M	Product	Yield [%]
1	 **3**	K	 **L1**	69
2	 **4**	Li	 **L2**	77[b]
3	**4**	Li	**L2**	89[c]
4	 **5**	K	 **L3**	61
5	 **6**	K	 **L4**	70
6	 **7**	K	 **L5**	57
7	 **8**	Na	 **L6**	65
8	 **9**	Na	 **L7**	73
9	 **10**	Na	 **L8**	69
10	**10**	Li	**L8**	79[d]
11	 **11**	Na	 **L9**	39
12	 **L9**	–	 **L10**	26[e]

[a] See the Supporting Information for experimental details. [b] Ref. [8], compare with ref. [28]. [c] Ref. [9]. [d] Large-scale reaction (0.18 mol). [e] 26% in two steps from **12** without isolation of **L9**.

in a nonoptimized yield of 39%.[33] Trifunctional ligand **L10** was then liberated by acidic hydrolysis of **L9** in a nonoptimized yield of 26% over 3 steps.

Synthesis of ARPYPHOS ligands from halogenated precursors: The nucleophilic phosphination of 2-aryl-6-halopyridines in THF or in solvent mixtures composed of either diethyl ether or THF and toluene (added for solubility reasons) gave the target (6-aryl-2-pyridyl)phosphanes (ARPYPHOS) (Table 2). They were either purified by flash chromatography on silica gel under argon, or by recrystallization, which was more convenient on a large scale. Selective crystallization by seeding of cooled (−40°C) supersaturated methanol solutions was advantageous.

Synthesis of other AZARYPHOS ligands: Heterocyclic phosphanes were also obtained from chlorinated diazine and triazine precursors, chloroquinolines, or chloroquinazolines (Table 3). These phosphinations proceeded uneventfully. Both mono-[34] and bis-phosphination[35] of dihalopyridines have been reported. We achieved monosubstitution of 2,6-dichloropyridine (**1**) with $NaPPh_2$. An attempted alkylation of **L25** with 4 equiv of a *t*BuMgCl/CuCN (2:1) reagent[36] gave a reaction mixture from which the desired **L7** could not be isolated. On the other hand, the chlorine in **L25** is readily substituted with sodium alkoxides in dimethyl formamide to give alkoxypyridylphosphanes **L26** and **L27** (Table 4).

Properties of AZARYPHOS ligands: Aza–aryl–phosphanes are colorless crystalline solids, which crystallize from methanol (exceptions: **L5** is low-melting, **L3** and **L4** were obtained as oils). They are stable to air as solids, but oxidize to phosphane oxides in solution. The recording of NMR spectra in $CDCl_3$ occasionally gave erratic results, presumably due to reactions with solvent impurities. Consistent spectral data were obtained for samples in degassed deuterobenzene. Large colorless crystals of **L8** crystallized from methanol at −20°C. The structure as determined by X-ray crystallography is shown in Figure 1.[37] The arrangement of the diphenylphosphino group (with one N-C-P-C_{aryl} dihedral angle at roughly 180°) has also been found in other pyridylphosphanes and is often retained in metal complexes.[38]

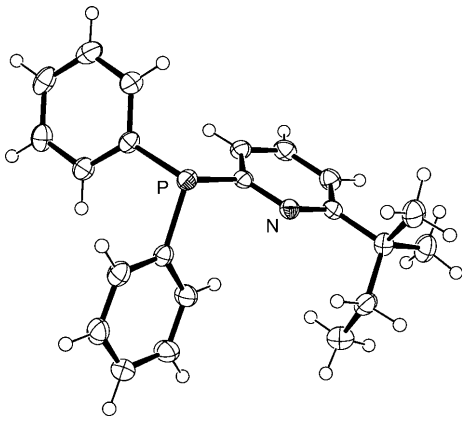
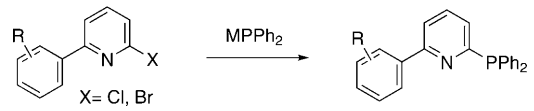


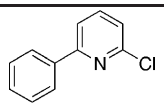
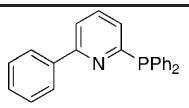
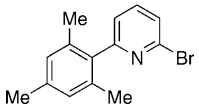
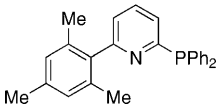
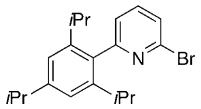
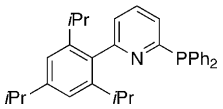
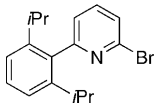
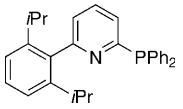
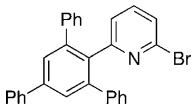
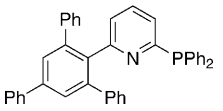
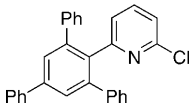
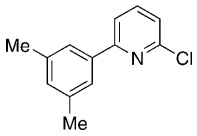
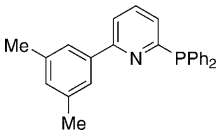
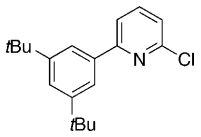
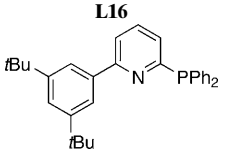
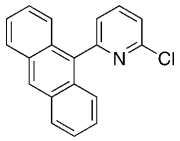
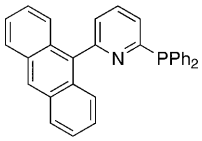
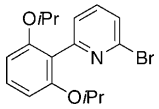
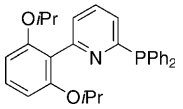
Figure 1. X-ray crystal-structure determination of **L8**;[37] ORTEP view.

Synthesis of halogenated precursors

6-Alkyl-2-halopyridines by means of a new Wittig synthesis of pyridones: Berke et al. had obtained 6-*tert*-butyl-2-chloropyridine (**9**) via pyridone **30** from pinacoline.[8] The lengthy procedure gave an overall yield of 6% over 5 steps,[39] limit-

Table 2. Synthesis of ARPYPHOS ligands.[a]



Entry	Substrate	M	Product	Yield [%]
1	 **15**	Na	 **L11**	86
2	 **16**	Na	 **L12**	79
3	 **17**	Na	 **L13**	75
4	 **18**	Na	 **L14**	71
5	 **19**	Na	 **L15**	78
6	 **20**	K	**L15**	69
7	 **21**	Na	 **L16**	76
8	 **22**	Na	 **L17**	69
9	 **23**	K	 **L18**	58
10	 **24**	Na	 **L19**	70

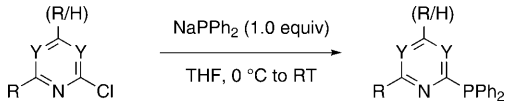
[a] Typical conditions: 1 equiv of $MPPh_2$ in THF, reaction in Et_2O/toluene or THF at 0°C to RT. Reaction time: 1 to 8 h. See the Supporting Information for details.

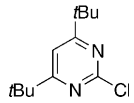
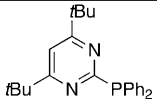
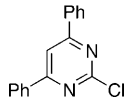
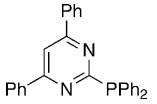
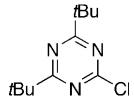
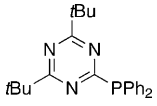
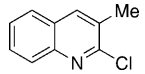
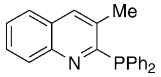
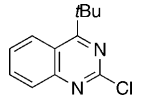
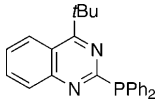
ing access to the material. We devised a shorter synthesis of 6-pyridones by retrosynthetic disconnection to a β-ketoaldehyde and ylide **31**, the latter derived from phosphonium salt **32** and base (Scheme 6a). Alternatively, the mixing of a sodium β-ketoaldehyde enolate (**33**: R = *t*Bu) and **32** should give an ion pair **34** in an acid/base equilibrium with β-ketoaldehyde and ylide. Eventually, both routes should lead to pyridones (Scheme 6b).

Indeed, mixing of enolate **33** and **32**[40] gave Wittig coupling products that cyclized to **30** after acidification. Pyridone **30** was produced in 79% yield (>30 g scale) in a one-pot reaction (Scheme 7a). This new pyridone synthesis is more general, but not always high yielding. In another application example, 6-cyclohexylpyridin-2(1*H*)-one (**35**) was obtained from ketoaldehyde **36**, phosphonium salt **32**, and a base in moderate overall yield (Scheme 7b). Side products included triketone **37** (by trimerization of **33**) and 2,6-dicyclohexylpyridine (**38**).

The intermediacy of open-chain unsaturated amides in this synthesis was evident in the reaction of hydroxymethylene camphor (**39**)[41] with excess **32** and triethylamine in ethanol (Scheme 8). The resulting amide mixture (*E*/*Z*)-**40** cyclized to pyridone **41** under forcing conditions in an ammonium acetate/acetic acid melt (Scheme 8). The intermediates (*E*)-**40** (major product) and (*Z*)-**40** (minor product) could also be isolated. Pure (*E*)-**40** in EtOH with acid (*p*-toluene sulfonic acid (*p*TsOH)) under reflux conditions gave an equilibrium mixture of (*E*)-**40** and (*Z*)-**40**. The *E*/*Z* isomerization is a prerequisite to cyclization, however, pyridone **41** was not formed

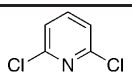
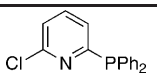
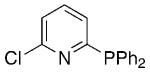
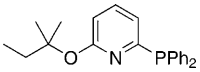
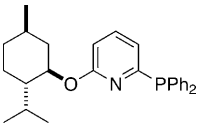
Table 3. Synthesis of pyrimidyl, triazinyl, and annelated ligands.[a]



Entry	Substrate	Product	Yield [%]
1	 **25**	 **L20**	87
2	 **26**	 **L21**	69
3	 **27**	 **L22**	82
4	 **28**	 **L23**	80
5	 **29**	 **L24**	75

[a] See the Supporting Information for experimental details.

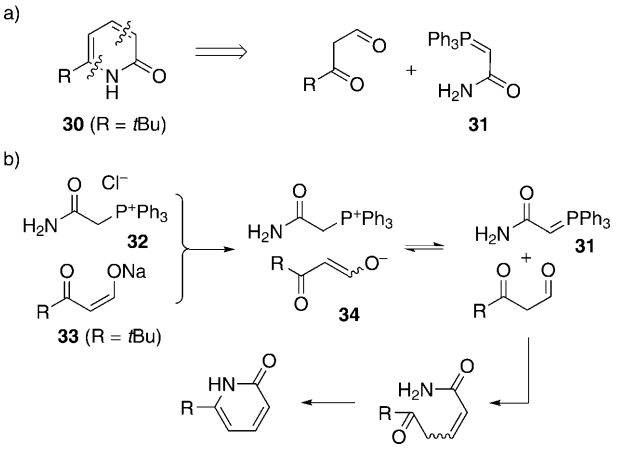
Table 4. Synthesis of ALPYPHOS ligands from halogenated precursors.[a]

Entry	Substrate	Reagent[b]	T [°C]	t [h]	Product	Yield [%]
1	 **1**	$NaPPh_2$ (1.0), THF	0	1.0	 **L25**	62
2	**1**	$NaPPh_2$ (1.0), *t*BuOMe	0	1.0	**L25**	91
3	 **L25**	*t*AmOH (1.5), NaH (1.5), DMF	90	1.5	 **L26**	60
	L25	(1*R*)-menthol (1.5), NaH (1.5), DMF	90	1.5	 **L27**	95

[a] See the Supporting Information for experimental details. [b] *t*AmOH = *tert*-amyl alcohol.

under these milder conditions, possibly reflecting ring strain in the tricyclic product.

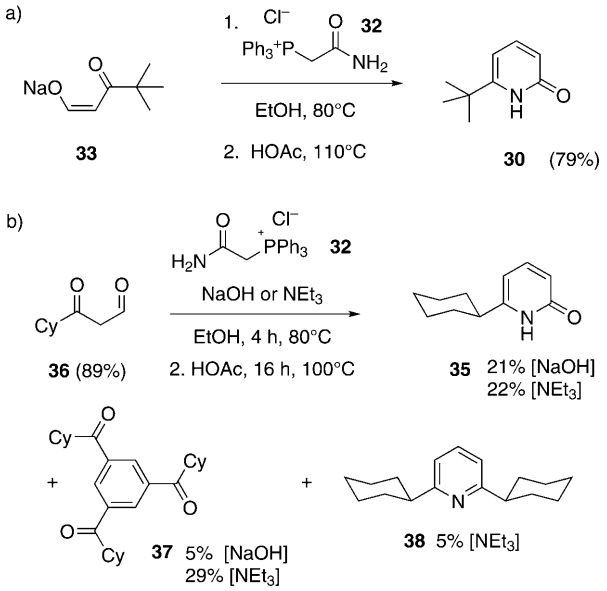
Pyridones **30** and **35** were chlorinated either by $POCl_3$ alone, PCl_5 in $POCl_3$, or $POCl_3$ in DMF. The mixed reagents are more reactive. Pyridone **30** reacted only partially in $POCl_3$, but was fully consumed by $POCl_3/PCl_5$ (Scheme 9).[8,9] The chloropyridines were then phosphinated as described in Table 1. The new Wittig synthesis of pyridones provides scalable access to ligands **L7** (33% over 4 steps from pinacolone) and **L6** (12% over 4 steps), but the pyridone syntheses require laborious purification procedures. Therefore, for synthesizing **L6** and **L7** we now prefer the cross-coupling approaches described below for 6-ar/alkyl-2-chloropyridines and the copper-catalyzed *tert*-alkylation of multiply chlorinated azacycles. The new pyridone synthesis will still be valuable for accessing targets that cannot be obtained by cross-coupling approaches, like tricyclic pyridone **41** (Scheme 8).



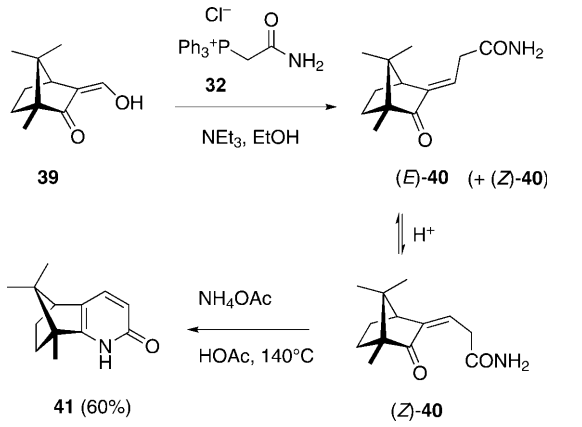
Scheme 6. Projected one-pot synthesis of 2-(1*H*)pyridones by means of Wittig condensation.

2-Bromo-6-arylpyridines by monoarylation of 2,6-dibromopyridine (2): Cross-coupling of 2,6-dihalopyridines (**1**: Cl; **2**: Br) are usually performed as double substitutions. Precedence implies that monosubstitutions,[42] though seldom performed with $C(sp^3)$ nucleophiles,[43] should proceed selectively with 2,6-dibromopyridine (**2**) and hindered aryl metals.[44] Bulky aryl Grignard reagents were coupled with **2** and a $[NiBr_2(DME)]/PCy_3$ (DME = dimethoxyethane, Cy = cyclohexyl) catalyst in dioxane at extended reaction times of 72 h by Kempe and co-workers.[45] We used a mixed THF/toluene solvent and air-stable complex $[NiCl_2(PCy_3)_2]$[46] as the catalyst instead, and reliably obtained 2-bromo-6-arylpyridines in only a few hours (Table 5).

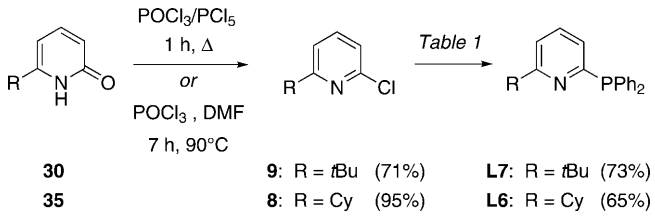
This approach was less successful for small aryl groups, where the resulting mixtures of mono- and diarylation products with starting material were difficult to separate (entries 1–4). The solubility of the reaction products dropped with increasing size of the C-6 aryl substituent. Steric limits of the reaction were evident in the case of the 2,4,6-triphenylphenyl derivative (entry 8). A reaction time of several days and a higher catalyst loading was required. Remarkably, the coupling catalyst developed by Herrmann and co-



Scheme 7. Application examples of the new 2-pyridone synthesis.



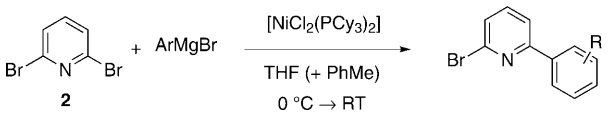
Scheme 8. Open-chain intermediates in the synthesis of a camphor-derived pyridone.

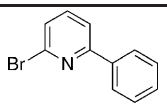
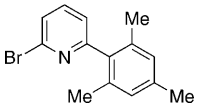
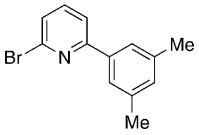
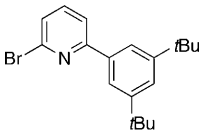
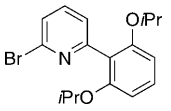
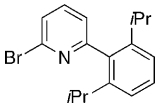
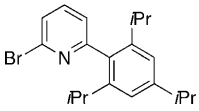
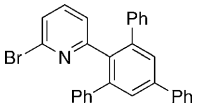


Scheme 9. Conversion of 2-pyridones to 2-chloropyridines and ALPYPHOS ligands.

workers,[47] consisting of [Ni(acac)$_2$] (acac = acetylacetonate) and the imidazolium salt IPr·HCl (**43**),[48] precursor to a N-heterocyclic carbene ligand,[49] gave **19** within a few hours at 85 °C (Table 6)![50] Even diarylpyridine **44** formed under these conditions; its amount depended on the excess of Grignard reagent used (Table 6).

Table 5. Synthesis of ARPYPHOS ligands from halogenated precursors.[a]

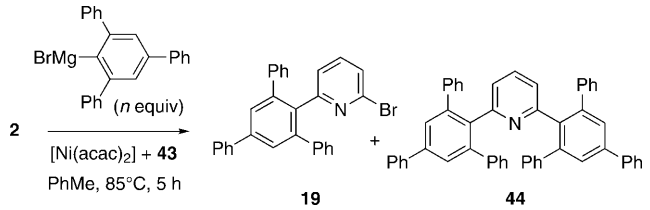


Entry	ArMgBr [equiv]	[Ni] [%]	t [h]	Product	Yield
1	1.1	0.3	3	 **42**	–[b]
2	1.1	0.3	7	 **16**	< 70[c]
3	1.1	0.3	12	 **21**-Br	–[b]
4	1.1	0.3	16	 **22**	< 61[c]
5	1.2	0.6	15	 **24**	83
6	1.1	0.3	15	 **18**	67
7	1.1	0.3	30	 **17**	83
8	1.5	1.0	192	 **19**	57[d]

[a] See the Supporting Information for experimental details. [b] The product could not be separated from impurities. [c] The products contained a little diarylpyridine impurity. [d] Modification: heating for 4 d at 75 °C and for 4 d at 85 °C.

*A general two-step synthesis of 6-ar/alkyl-2-chloropyridines from 2-*tert*-butoxy-6-chloropyridine (**45**)*: Since the direct arylation approach described above failed for small aryl Grignard reagents, an indirect synthesis of 2-halo-6-arylpyridines was needed. Starting from cheap 2,6-dichloropyridine,

Table 6. Large scale cross-coupling synthesis of **19**.[a]



19 44

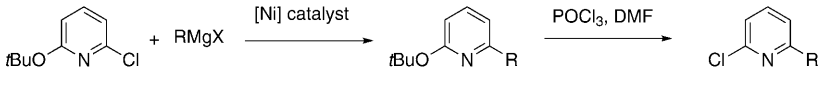
Entry	Scale [mmol]	ArlMgBr [equiv]	[Ni][b] [mol%]	Yield of **19**[c] [%]	Yield of **44** [%]
1	125	1.50	2.0	50	28
2	62	1.33	2.7	72	13
3	254	1.08	2.0	74	6

[a] See the Supporting Information for experimental details. [b] [Ni(acac)$_2$] was combined with 1.1 equiv of IPr·HCl (**43**) as ligand precursor.

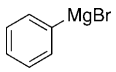
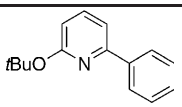
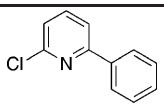
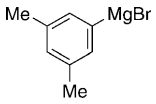
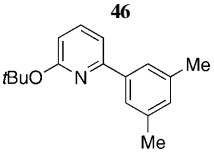
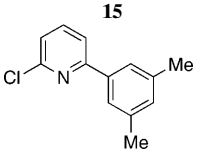
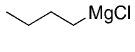
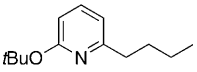
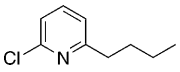
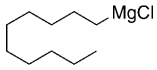
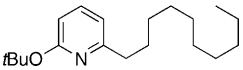
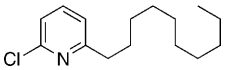
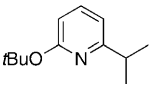
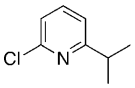
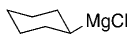
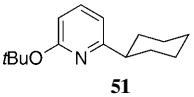
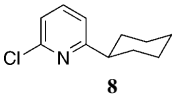
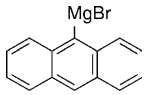
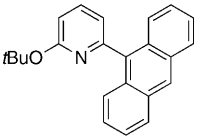
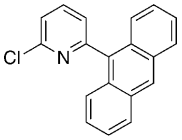
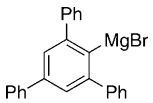
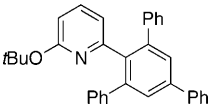
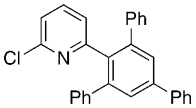
a strategy was devised, in which a bulky "dummy" nucleophile desymmetrizes the starting material to leave a single halogen for cross-coupling.[51] In a final step, the "dummy" group is transformed back to a halogen. According to Breit and Seiche, 2,6-dichloropyridine (**1**) reacts with potassium *tert*-butoxide to give monoether **45** in high yield.[52] The latter is readily cross-coupled according to Kumada et al.[53] with a range of Grignard nucleophiles (Table 7).

The nickel/carbene catalyst reported by Herrmann and co-workers gave best results with small aryl nucleophiles,[47] whereas primary and secondary alkyl-Grignard reagents were coupled under the conditions reported by Kumada et al.;[53] 1,3-bis(diphenylphosphino)propane (dppp) was the preferred ligand for couplings of primary, and 1,2-bis(diphe-

Table 7. Nickel-catalyzed cross-coupling of 2-*tert*-butoxy-6-chloropyridine (**45**) with Grignard reagents, and chlorodealkoxylation to 2-chloro-6-ar/alkylpyridines.[a]



45 A B

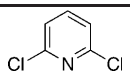
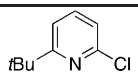
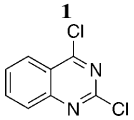
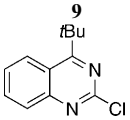
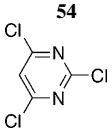
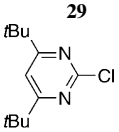
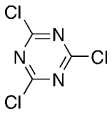
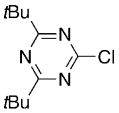
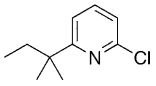
Entry	RMgX[b]	[equiv]	Ni[c] [%]	Ligand[d]	*T* [°C]	*t* [h]	Product **A**	Yield **A** [%]	Product **B**	Yield **B** [%]
1		1.1	1	IPr	RT	15	 **46**	98	 **15**	69
2		1.1	1	IPr	RT	5	 **47**	90	 **21**	60
3		1.5	0.3	dppp	RT	4	 **48**	89	 **5**	75
4		1.4	0.3	dppp	RT	4	 **49**	97	 **6**	79
5		1.5	0.3	dppe	RT	4	 **50**	92	 **7**	77
6		1.3	0.3	dppe	RT	4	 **51**	96	 **8**	94
7		1.5	3	PBu_3	60	10	 **52**	53	 **23**	66
8		1.25	2	IPr	60	8	 **53**	67	 **20**	89

[a] See the Supporting Information for experimental details. [b] Grignard reagents as solutions in THF. [c] The nickel precursor in combination with IPr is [Ni(acac)$_2$]; in all other cases, the complexes [$NiCl_2(PR_3)_2$] were used; quantity in mol%. [d] Ligands: IPr = 1,3-bis(2,6-diisopropylphenyl)imidazolylidene carbene, derived from imidazolium salt **43**.

nylphosphino)ethane (dppe) for secondary alkyl groups (Table 7, **45** → **A**). The 9-anthracenyl Grignard reagent gave unsatisfactory results with carbene ligands, but coupled well with $[NiCl_2(PBu_3)_2]$ as the catalyst (entry 7). The contrary was true for the 2,4,6-triphenylphenyl Grignard reagent (entry 8). Reaction of the 2-*tert*-butoxy-6-ar/alkylpyridines with Vilsmeyer reagent gave chloropyridines in good yields (Table 7, **A**→**B**).[54] This approach of synthesizing 6-ar/alkyl-2-halopyridines from 2,6-dichloropyridine (**1**) via 2-*tert*-butoxy-6-chloropyridine is very general and extends to primary or secondary alkyl, and small or hindered aryl groups, giving pyridylphosphane ligands in only 3 steps from the storable precursor **45**. So far, it only fails for tertiary alkyl groups, for which catalytic cross-coupling reactions with chloroarenes are hardly known.

Copper-catalyzed tert-*alkylation of multiply chlorinated azacycles*: The difficulties originally encountered in the synthesis of 6-*tert*-butyl-2-chloropyridine (**9**) translate to the lack of suitable cross-coupling methodology for tertiary alkyl nucleophiles and the nonsymmetric nature of the target, which asked for an lengthy de novo synthesis.[8] We have recently found a general copper-catalyzed cross-coupling reaction of tertiary alkyl Grignard reagents with multiply chlorinated azacycles that solves this problem: dichlorinated azacycles **1** or **54** are selectively monoalkylated, whereas 2,4,6-trichloropyrimidine (**55**) and trichlorotriazine (**56**) are selectively disubstituted (Table 8). Details of this transformation have already been reported.[25]

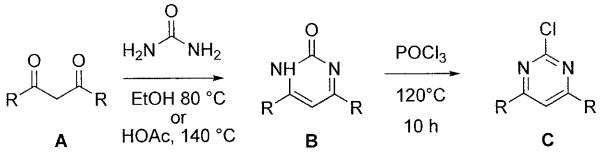
Table 8. Cu-catalyzed selective monoalkylation of multiply chlorinated azacycles.[a]

Entry	Substrate	RMgX [equiv]	CuI [%]	Product	Yield [%]
1	 **1**	1.5	5	 **9**	85
2	 **54**	1.05	5	 **29**	92
3	 **55**	2.5	10	 **25**	83
4	 **56**	2.4	3.5	 **27**	90
5	**1**	2.0	5	 **10**	74

[a] See the Supporting Information for experimental details.

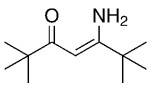
Chlorodiazines from 1,3-diketones and urea: Generally, 1,3-diketones condense with urea in acidic solution,[55,56] but the reaction turned out to be very slow with the bulky dipivaloylmethane (**57**): hydrolytic decomposition of urea competed with heterocyclization to **58**, and enamine **59** was the major reaction product (56%) in hot acetic acid (Table 9).

Table 9. 2-Chloropyrimidines from 1,3-diketones via pyrimidones.[a]



Entry	R	Substrate **A**	Product **B**	Yield [%]	Product **C**	Yield [%]
1	*t*Bu	**56**	**58**	19	**25**	95
2	Ph	**60**	**61**	64	**26**	75

[a] See the Supporting Information for experimental details.


59

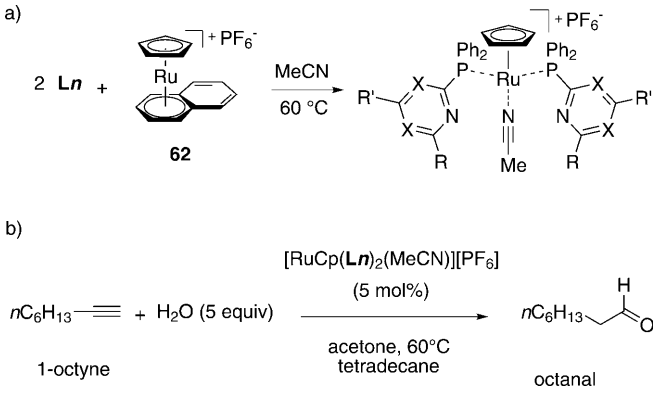
The pyrimidones gave 2-chloropyrimidines by reaction with $POCl_3$ (Table 9), which were readily converted to the symmetric pyrimidylphosphanes as previously shown in Table 3.

Ligand structure–activity relationships in ruthenium-catalyzed anti-Markovnikov hydration of terminal alkynes: The anti-Markovnikov hydration of terminal alkynes to aldehydes serves as the first test reaction to study ligand structure–activity relationships. The Grotjahn group found that complex $[RuCp(\mathbf{L}n)_2(MeCN)][PF_6]$ catalyzes the reaction with unprecedented rates when using the bulky ligand **L7**, but that incorporation of the smaller **L1** or **L2** led to either inactive or very weakly active catalysts.[9] In our communication[23] we had established that bulky ARPYPHOS ligands also give highly active in situ catalysts for anti-Markovnikov hydration of terminal alkynes. Here we generalize our study of structure–activity relationships of AZARYPHOS ligands. The hydration catalysts were generated in situ by ligand exchange from $[RuCp(\eta^6\text{-naphthalene})][PF_6]$ (**62**)[57] with the AZARYPHOS ligands, followed by evaporation to dryness (Scheme 10a).[23]

The catalytic hydration of 1-octyne to octanal was chosen as the standard reaction for kinetic comparisons (Scheme 10b). Reaction progress was determined from the time-dependent octanal concentration by means of gas chromatography with tetradecane as the internal standard. Reaction-progress curves were fitted[58] to the rate law shown in Equation (1):

$$d[\text{octanal}]/dt = k_{\mathbf{L}n}[Ru]_0[H_2O][\text{octyne}] \quad (1)$$

The rate constants for individual ligands ($k_{\mathbf{L}n}$) were divided by the rate constant of the catalyst derived from **L7** ($k_{\mathbf{L7}}$) at 60°C to obtain a relative catalytic activity (RCA). As evi-

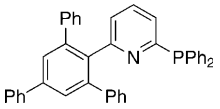
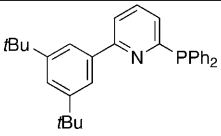
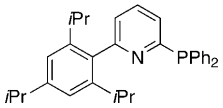
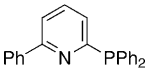
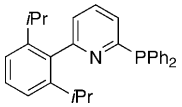
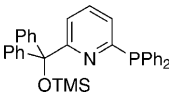
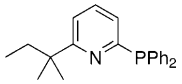
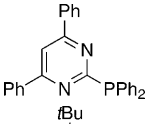
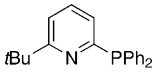
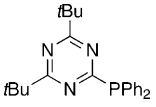
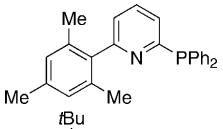
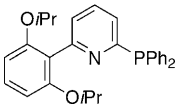
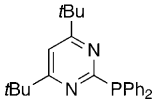
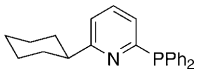
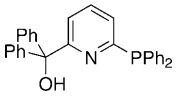
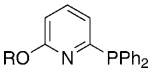


Scheme 10. a) General scheme of ligand exchange of **62** with AZARYPHOS (**L*n***) in acetonitrile. b) Model reaction for the kinetic comparison of ligand performance.

dent from Table 10, many in situ complexes were catalytically active, but their efficiency varied over two orders of magnitude. The regioisomeric byproduct 2-octanone was not detected in any of these reactions, implying a mechanism-based regiospecificity of the reaction.[3,20c]

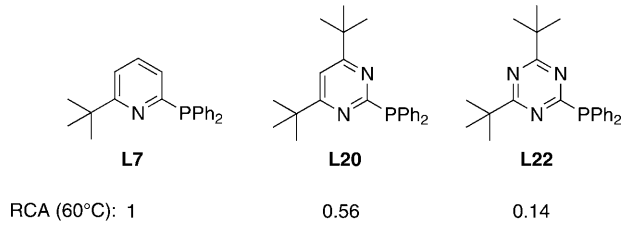
Steric ligand effects on catalyst performance are crucial in the ARPYPHOS series. The activity of the catalysts increased in the order R (R = aryl group at pyridine C-6) = Ph (**L11**) < mesityl (**L12**) < 2,4-*i*Pr$_2$C$_6$H$_3$ (**L14**) < 2,4,6-*i*Pr$_3$C$_6$H$_2$ (**L13**) < 2,4,6-Ph$_3$C$_6$H$_2$ (**L15**). This roughly correlates with the size of the aryl group. Substitutions in the aryl group were most effective in the *ortho* positions. Exceptionally, the diisopropoxy derivative **L19** gave a less-active catalyst than **L11** (phenyl) or **L12** (mesityl), which indicates that the oxygen functionality actively interferes with the catalysis. Substitution in the *meta* position had little effect, since the catalyst derived from **L17** was only slightly more active than that of **L11** (entry 9 vs. 10). In the ALPYPHOS series, the inactivity of 2-diphenylphosphinopyridine (**L1**) and the low catalytic activity of **L2** (RCA ca. 0.01) had earlier been noted.[9] We find that replacing methyl (in **L2**) by a secondary alkyl group (**L6**) increases catalytic activity (entry 15), but only substitution by a tertiary alkyl group (**L7**; entry 5) causes a large jump of catalyst activity (0.02→1.0). Within a series of tertiary ALPYPHOS ligands, **L8** is slightly more effective than **L7** (entries 4 vs. 5),[59] but **L9** and **L10** with functionalized 1,1-diphenylmethyl groups gave less-active catalysts (entries 8 vs. 11). Even though **L10** is less bulky than

Table 10. Relative catalytic activity induced by ligands in the hydration of 1-octyne.[a]

Entry	Ligand	**L*n***	RCA[b] [45 °C]	RCA[b] [60 °C]	Entry	Ligand	**L*n***	RCA[b] [45 °C]	RCA[b] [60 °C]
1		**L15**	0.73	4.2	9		**L17**	–[d]	0.48
2		**L13**	0.41	1.8	10		**L11**	0.09	0.41
3		**L14**	0.32	1.3	11		**L9**	–[d]	0.28
4		**L8**	0.35	1.1	12		**L21**	–[d]	0.16
5		**L7**	0.34	1[c]	13		**L22**	–[d]	0.14
6		**L12**	0.25	0.59	14		**L19**	–[d]	0.04
7		**L20**	–[d]	0.56	15		**L6**	–[d]	0.02
8		**L10**	–[d]	0.56	16		**L26/L27**	–[d]	0[e]

[a] See Scheme 10b for the test reaction. Conditions: [1-octyne] = 0.25 M, [Ru] = 5 mol %, 5 equiv H_2O. [b] Relative catalytic activities in the test reaction, see text. [c] Reference value. [d] Not determined. [e] No catalytic activity observed.

L9, it generated a slightly more active catalyst. It is tempting to assume involvement of the hydroxy group of **L10** in the reaction, which could be considered a case of "trifunctional" catalysis. The effect is quite small and far-reaching conclusions are premature, but future investigations of even more functionalized ligands are certainly justified. Compared with the reference hydration catalyst derived from **L7**, in situ catalysts derived from pyrimidine **L20** and triazine **L22** were less active (Scheme 11). The additional 4-*tert*-butyl groups in **L20** and **L22** are presumably not sterically active, because they will point away from the active site if phosphorus binds to ruthenium.



Scheme 11. Relative catalytic activities (RCA) of pyridyl, pyrimidyl, and triazinyl ligands.

The lower activity of catalysts derived from the nitrogen-rich ligands is probably a consequence of the lower basicity of these heterocycles,[60] with a concomitant weaker interaction of their nitrogen lone pairs with the substrate. Additionally, the σ-acceptor effect of the heterocycles will reduce electron density at ruthenium, with an as yet unclear influence on the alkyne/vinylidene interconversion[61] or other steps within the overall mechanism of the reaction. Future studies should address this issue by modulating the electron density through variation of the non-heterocyclic aryl groups at phosphorus. For some AZARYPHOS ligands, the derived species $[RuCp(\mathbf{L})_2]^+$ was not catalytically active: these include alkoxy-substituted pyridyl ligands **L26** and **L27**, and the quinoline-derived ligand **L23**. For the latter, a chelating species $[RuCp(\eta^2\text{-}\mathbf{L23})(\eta^1\text{-}\mathbf{L23})][PF_6]$ was formed in $[D_3]$MeCN (doublets at $\delta[^{31}P] = 50.6$ ppm and -7.8 ppm, $J(P,P) = 37.7$ Hz). As Grotjahn had previously found, chelation is a cause of catalytic inactivity with sterically insufficiently demanding ligands.[3b] In agreement with earlier work, we found no catalytic activity for the complexes $[RuCp(MeCN)(PPh_3)_2][PF_6]$ or $[RuClCp(PPh_3)_2]$.[9,16,62]

Conclusion

The AZARYPHOS class of heterocyclic phosphanes has been defined as a useful and promising ligand family for application in ambifunctional catalysis. Prior to our work, only a few members of this ligand family had been described in the literature and no general synthetic methodology was available. We have developed synthetic strategies to efficiently access almost any desired member of this ligand class in a few steps with a scalable methodology. Syntheses often require as little as two steps from readily available starting materials. General routes to 6-aryl-2-phosphinopyridines, 6-alkyl-2-phosphinopyridines (alkyl = primary, secondary, and tertiary), or other AZARYPHOS ligands like diazinylphosphanes, triazinylphosphanes, or 6-alkoxy-2-phosphinopyridines have been elaborated. ARPYPHOS (6-aryl-2-phosphinopyridines) ligands have been applied in catalysis for the first time and were found to be highly efficient in the ruthenium-catalyzed anti-Markovnikov hydration of terminal alkynes. Ambifunctional catalysis by a metal and a functional group within the steering ligand is a promising concept for developing new reaction chemistry. Our study of the ruthenium-catalyzed anti-Markovnikov hydration of terminal alkynes implies that steric and electronic ligand variation is an essential element also in ambifunctional catalysis reaction development. The readily available AZARYPHOS ligands open a door to systematically explore the potential of ambifunctional catalysis chemistry by means of ligand screening approaches.

Experimental Section

All experimental data and copies of ^1H and ^{13}C NMR spectra of new compounds have been given in the Supporting Information.

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