Homogeneous Catalysis

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Halogen-Bridged Methylnaphthyl Palladium Dimers as Versatile Catalyst Precursors in Coupling Reactions

*Nardana Sivendran[+,++], Nico Pirkl[+,++], Zhiyong Hu, Angelino Doppiu, and Lukas J. Gooßen**

Abstract: *Halogen-bridged methylnaphthyl (MeNAP) palladium dimers are presented as multipurpose Pd-precursors, ideally suited for catalytic method development and preparative organic synthesis. By simply mixing with phosphine or carbene ligands, they are in situ converted into well-defined monoligated complexes. Their catalytic performance was benchmarked against state-of-the-art systems in challenging Buchwald–Hartwig, Heck, Suzuki and Negishi couplings, and ketone arylations. Their use enabled record-setting activities, beyond those achievable by optimization of the ligand alone. The MeNAP catalysts permit syntheses of tetra-ortho-substituted arenes and bulky anilines in near-quantitative yields at room temperature, allow mono-arylations of small ketones, and enable so far elusive cross-couplings of secondary alkyl boronic acids with aryl chlorides.*

Introduction

Pd-mediated cross-coupling reactions have developed into indispensable synthetic methods, widely used in the preparation of pharmaceuticals, agrochemicals, and functional materials on laboratory and industrial scales.[1] The use of electron-rich ligands, such as phosphines bearing *tert*-butyl,[2] neopentyl,[3] adamantyl,[4] ferrocenyl,[5] or biaryl substituents,[6] N-heterocyclic[7] (IPr, IMes), cyclic alkyl amino carbenes (CAAC)[8] and ylide-based phosphines (YPhos),[9] has dramatically improved the scope and efficiency of catalytic couplings.[10] However, it is well documented that the Pd precursor also influences not only the activation process and thereby the initial reaction rate,[11] but also the catalyst selectivity and longevity.[12] Challenging substrate combinations close to the performance limit of a synthetic methodology only allow for a very narrow window of suitable conditions. Especially in such cases, the use of a highly efficient, broadly applicable Pd-source can make a decisive difference.

Figure 1 gives an overview of precursors used in Pd catalysis. One common approach is to employ pre-formed Pd^0 complexes bearing excess steering ligands as precatalysts (Figure 1 a).[13] However, excess ligands continuously compete with the substrates for the coordination site at the Pd center.[14] Moreover, homoleptic PdL_2 complexes tend to be rather air-sensitive.[14]

Alternatively, the catalyst is generated in situ from Pd^{II} or Pd^0 precursors and phosphine or carbene ligands (Figure 1 b). However, incomplete reduction of Pd^{II} precursors to Pd^0 can

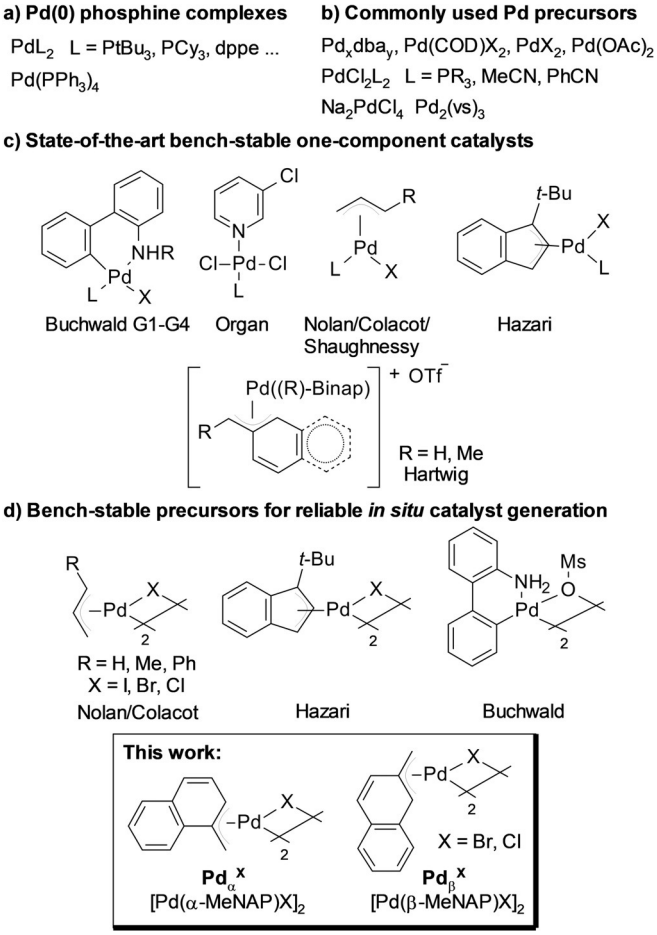

Figure 1. Classes of Pd precursors used for the generation of monoligated Pd^0 catalysts.

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affect the reaction outcome,[15] while for Pd^0 precursors, competition between the substrates and excess ligands may prevail. Moreover, the soluble Pd content of commercially available precursors fluctuates, resulting in variable catalyst performance.[16] For Pd_xdba_y complexes, the yields can range between 10 and 95% depending on the batch of starting material under otherwise identical conditions.[17] Similar issues were observed for $Pd(OAc)_2$.[18] Other common precursors are one-component Pd precatalysts bearing hemilabile auxiliary ligands (Figure 1c). Examples include Pd complexes bearing pyridines (Organ's PEPPSI™),[19] allyl groups (Nolan, Shaughnessy, Colacot),[20] or *tert*-butylindene (Hazari's Yale catalyst)[21] as well as amine-containing palladacycles (Buchwald).[22] The discovery of π-allyl palladium dimers dates back to the early 1960s.[23] Their utility as Pd-precatalysts for cross-couplings has extensively been explored by Nolan for halide-bridged η^3-allyl, η^3-crotyl, or η^3-cinnamyl complexes bearing NHC ligands[20a–e] and by Colacot and Shaughnessy for phosphine analogues.[20f,g] Nolan and co-workers established a correlation between the length of the longest $Pd-C_{allyl}$ bond and the activity of the catalytic system. Thus, the longest $Pd-C_{allyl}$ bond length, and with it also the catalytic activity, increases from allyl (R = H) to crotyl (R = Me) to cinnamyl (R = Ph) and from I to Br to Cl, which matches the literature data.[20a–c] The groups of Verkade and Shaughnessy demonstrated the use of highly electron-rich and sterically demanding phosphines in combination with η^3-allyl-type ligands as precatalyst while observing the same correlation.[20f,24]

Catalyst activation is proposed to proceed via solvent-assisted activation, transmetalation, or nucleophilic attack depending on the reaction conditions.[20e,21,25] Hartwig et al. have comparatively evaluated stoichiometric reactions of cationic Pd-BINAP complexes bearing allyl, benzyl, and 2-methylnaphthyl ligands with excess aniline. They found that the 2-methylnaphthyl complexes react particularly fast with release of the corresponding allyl amines upon nucleophilic attack.[11] The catalytic efficiency of allyl–Pd^{II} precatalysts mainly depends on their rate of activation and their tendency to comproportionate with active Pd^0 species to unreactive Pd^I.[21,26] The latter deactivation pathway has been studied in detail by Hazari and resulted in the development of chloride-bridged Pd catalysts bearing η^3-1-*tert*-butylindenyl ligands, specifically suppressing Pd^I dimer formation.[21]

A drawback common to all these one-component precatalysts is that one defined steering ligand is introduced already during catalyst preparation. However, for rapid ligand screening, a generation of the actual catalysts from defined Pd^{II} complexes and equimolar amounts of phosphines and NHC ligands under in situ conditions is more convenient (Figure 1d).

Examples of effective Pd sources include Pd–halide dimers bearing allyl, cinnamyl, crotyl, *tert*-butylindenyl, or chelating *N*,*N*-diaryldiazabutadiene substituents, as well as 2-aminobiphenyl palladacycles.[20,21,22b,27,28] However, these precursors still have individual limitations with regard to synthetic accessibility, stability, or scope of application.

Thus, there still is a need for Pd-sources that a) are accessible in one step from abundant precursors, b) are easy to store and handle, c) reliably form monoligated Pd species upon mixing with various ligands, and d) have an efficiency that matches or exceeds that of state-of-the art systems across a wide range of catalytic applications. Following the rationale by Nolan and Hazari, we reasoned that dimeric 1- or 2-methylnaphthyl palladium halide complexes should ideally fulfil these requirements (Figure 2, left). They should be

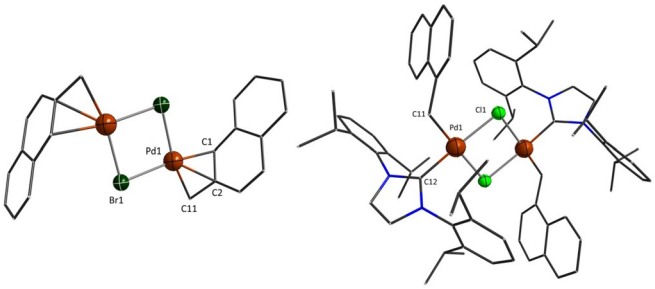

Figure 2. X-ray structure of $\mathbf{Pd_\beta^{Br}}$ (left) and $\mathbf{Pd3_{\alpha\text{-dim}}^{Cl}}$ (right).[59] Selected bond lengths (Å) and bond angles (°) for $\mathbf{Pd_\beta^{Br}}$: Pd1–C1 2.179(8), Pd1–C2 2.143(8), Pd1–C11 2.127(10); Br1-Pd1-Br1 90.73(4).

accessible from methylnaphthyl bromides and chlorides, which are commercially available at low cost. Related to allyl–Pd dimers, we envisioned them to react smoothly with various phosphine and carbene ligands to give well-defined complexes. This however, requires the anticipated η^3-coordination of the methylnaphthyl moiety which is expected to reduce the aromatic resonance within the naphthyl system. Thus, the displacement of this ancillary ligand by substrate molecules under the conditions of a catalytic reaction may be facilitated. The steric strain induced by the bulky naphthyl moiety should further contribute to its ease of dissociation, potentially resulting in a leap forward in activity of such complexes in catalytic cross-coupling reactions.

Results and Discussion

Synthesis of Methylnaphthyl Complexes

The first challenging step was to discover an expedient synthesis of the targeted methylnaphthyl complexes. After evaluating various synthetic strategies, we found that in a 1,3-divinyl-1,1,3,3-tetramethyldisiloxanepalladium (Pd(vs)) solution[29] upon treatment with 1- or 2-(bromomethyl)naphthalene or 1- or 2-(chloromethyl)naphthalene, respectively, the corresponding 1- or 2-methylnaphthalene complexes ($[Pd(\alpha\text{-}/\beta\text{-MeNAP})X]_2$) form within minutes and precipitate out of the reaction medium in high purity as yellow powders (Scheme 1, for experimental details see S1.2). In order to ensure a high purity of the catalysts, we used only the first crop of the precipitate, usually around 50% yield. For $\mathbf{Pd_\alpha^{Br}}$, the reaction was scaled up to 7.2 mmol, which increased the yield to 83%. The methylnaphthyl complexes can alternatively be obtained by reaction of Pd_2dba_3 with the methylnaphthyl halides.

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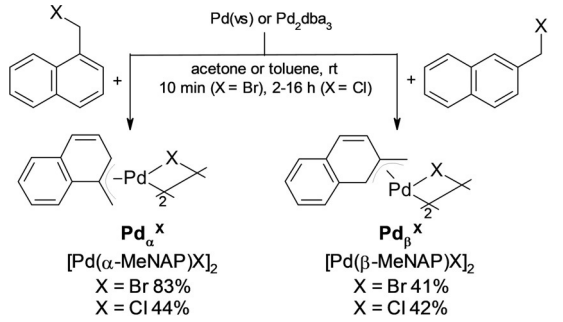


Scheme 1. Synthesis of Pd–methylnaphthyl halide complexes: Addition of Pd(vs) or Pd_2dba_3 to a toluene or acetone solution of 1.2 equiv of 1 or 2-(bromo-/chloromethyl)naphthalene. Precipitation of the respective product occurs within 10 min for X = Br and within 16 h for X = Cl. The products were obtained in high purity after washing with acetone.

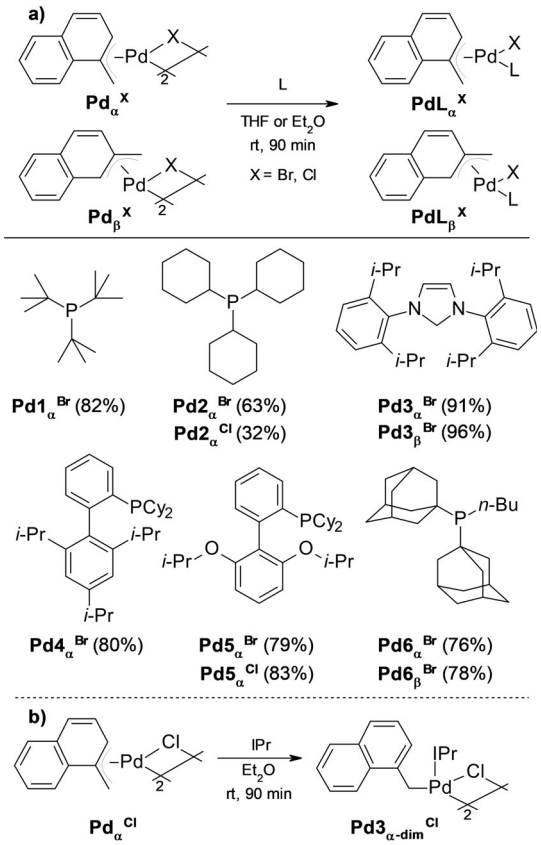
The products are easily isolated by filtration and washing with acetone to remove residual vinyl siloxane. Exclusion of air and moisture is not required. The structure of one of the Pd dimers (**Pd_β^{Br}**) was elucidated by X-ray crystallography (Figure 2). The analysis confirms the desired η^3-coordination of the MeNAP moiety. The bond between C1 and C2 is clearly elongated (1.41 Å vs. 1.38 Å in naphthalene)[30] giving evidence of the anticipated reduction of the aromatic resonance within the naphthyl moiety. The solid-state structure revealed a particularly long Pd–C bond in **Pd_β^{Br}** compared to [Pd(allyl)Cl]$_2$ (Pd1–C2 2.143(8) Å vs. 2.108(9) Å),[31] which should result in a rapid catalyst activation.

All four complexes were found to be sufficiently stable to allow their preparation and handling under non-inert conditions. They were stored under ambient conditions over months without visible decomposition or decrease of catalytic activity. Overall, MeNAP palladium halide dimers fulfil all prerequisites of user-friendly catalyst precursors with regard to cost and availability of reagents, stability, and ease of handling.

We next investigated the reactivity of Pd–MeNAP complexes towards phosphine and carbene ligands. All four complexes reacted within minutes with various ligands in THF or diethyl ether solution to form complexes of the type η^3-(MeNAP)(X)–Pd–L (Scheme 2). The products precipitate after partial evaporation of the solvent and addition of pentane and can easily be isolated.

This straightforward method was successfully applied to the synthesis of various monoligated Pd–MeNAP complexes in yields up to 96%. Some of the products were recrystallized at −20 °C and investigated by X-ray crystallography. In almost all reactions with NHC or phosphine ligands, both the bromide- and the chloride-substituted complexes yield products of the type η^3-(MeNAP)(X)–Pd–L (Figure 3). In contrast, the reaction of **Pd_α^{Cl}** with IPr gave the η^1-coordinated dimeric complex **$Pd3_{\alpha\text{-dim}}^{Cl}$** as shown by X-ray crystallography (Figure 2).

The structures of the crystallized complexes are similar to related allyl–Pd complexes (Figure 3). **$Pd3_\alpha^{Br}$** and **$Pd3_\beta^{Br}$** have a significantly longer maximum Pd–C bond in comparison to analogous cinnamyl complexes (**$Pd3_\alpha^{Br}$** 2.299 Å vs. [Pd(cinnamyl)(IPr)Cl] 2.284 Å).[20c] Among the RuPhos complexes, the methylnaphthyl bromide complex **$Pd5_\alpha^{Br}$** also bears the longest Pd–C bond with 2.388 Å. The maximum Pd–C bond lengths of selected α- and β-methylnaphthyl compounds in comparison to other allyl complexes are compiled in Table S1. These findings raised high expectations concerning the catalytic activity of the MeNAP complexes and differentiate them from classical allyl systems.



Scheme 2. a) Synthesis of NHC and phosphine complexes. b) Deviating structure of **$Pd3_{\alpha\text{-dim}}^{Cl}$**.

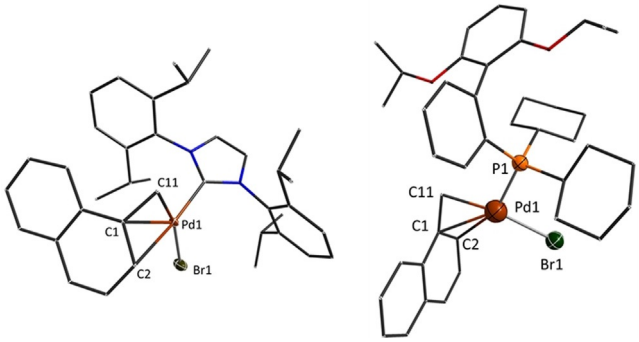


Figure 3. X-ray structure of **$Pd3_\alpha^{Br}$** (left) and **$Pd5_\alpha^{Br}$** (right).[59]

Catalytic Studies

In order to probe whether elongation of the Pd–C bonds indeed translates to increased catalytic activity, we inves-

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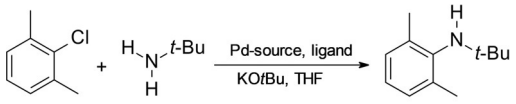
tigated the complexes in various catalytic reactions and compared them with other allyl precursors. A Pd-to-ligand ratio of 1:1 was consistently used in all test reactions to ensure that preformed catalysts are comparable to those generated in situ. Moreover, stoichiometric catalyst experiments have been conducted to shed light on the activation pathway (see Section S4). We started the comparative study with the Pd-catalyzed Buchwald–Hartwig amination, which has become a standard transformation in organic synthesis.[32] Continuous catalyst development has made this reaction extremely efficient. Still, only few systems rapidly couple aryl chlorides at low temperature.[20c,33]

In a comparative kinetic study of the reaction of 4-chlorotoluene with morpholine at 30 °C, the MeNAP precursors were benchmarked against state-of-the-art precatalysts (Scheme S1). The results show that $[Pd(\alpha\text{-MeNAP})Br]_2$ and $[Pd(\beta\text{-MeNAP})Br]_2$ even outperform the best known allyl chloride catalysts such as Hazari's *tert*-butylindenyl complexes or Nolan's cinnamyl systems. Both systems gave full conversion with > 99 % yield of the desired product **3aa** after 4 h. The chloride-substituted complexes were somewhat less active but still performed very well.

In a stoichiometric reaction of $[Pd(\alpha\text{-MeNAP})Br]_2$ with ligand, base, and excess morpholine, the naphthylmethyl amine is formed, which suggests that the catalyst is activated by amination of the ligand (see S4.1).[11] In the amination of 4-chlorotoluene with morpholine, a TON of 2650 was reached for 0.025 mol % $[Pd(\beta\text{-MeNAP})Br]_2$, which confirms the longevity of the MeNAP catalysts.[34]

We next chose some of the most difficult substrate combinations to elucidate the effect of the Pd–MeNAP precursors on Buchwald–Hartwig aminations. Aminations of sterically demanding aryl chlorides with *tert*-butylamine are known to pose substantial challenges.[35] Even with the specialized ligand 9-[2-(dicyclohexylphosphino)phenyl]-2-ethoxy-9*H*-carbazole (dppec), a temperature of 110 °C was required to get a moderate yield of 68 % (Table 1, entry 1).[35c]

Table 1: Buchwald–Hartwig amination with alkylamines.[a]



1b **2b** **3bb**

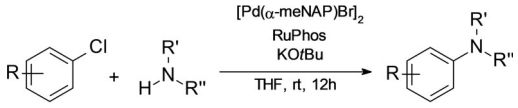
Entry	Pd-source	Ligand	**3bb** [%]
1	$Pd(OAc)_2$	dppec	68[b]
2	"	RuPhos	traces
3	Pd_2dba_3	"	21
4	$[Pd(allyl)Cl]_2$	"	6
5	$[Pd(cinnamyl)Cl]_2$	"	13
6	$[Pd(t\text{-Bu-indenyl})Cl]_2$	"	93
7	$[Pd(\alpha\text{-MeNAP})Cl]_2$	"	> 99
8	$[Pd(\alpha\text{-MeNAP})Br]_2$	"	> 99
9	$[Pd(\beta\text{-MeNAP})Cl]_2$	"	88
10	$[Pd(\beta\text{-MeNAP})Br]_2$	"	82

[a] Conditions: 0.5 mmol of **1b**, 1.1 equiv **2b**, 1 mol % [Pd], 1 mol % ligand, 1.5 equiv KO*t*Bu, 2 mL THF, rt, 12 h. Yields determined via GC-analysis using *n*-undecane as internal standard. [b] Literature yield obtained at 110 °C for 24 h.[35c]

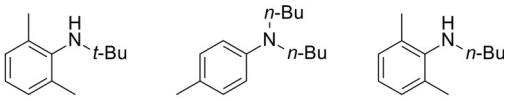
When performing this reaction at room temperature in the presence of $Pd(OAc)_2$, Pd_2dba_3 or Pd–allyl complexes, and commercially available RuPhos ligand, only low yields were obtained. Solely Hazari's indenyl precatalyst proved to be effective (Table 1). However, we were pleased to find that the α-MeNAP complexes gave near quantitative yields. This is the best result ever reported for this challenging substrate combination in a room temperature coupling. The β-MeNAP complexes were somewhat less effective. Thus, the longer allylic Pd–C bonds indeed seem to translate into higher catalytic activities. Other state-of-the-art catalysts were tested as well but did not give satisfactory yields (Table S4).

We went on to investigate a set of similarly challenging substrate combinations, for example, with long-chain aliphatic amines prone to undergo β-hydride eliminations (Table 2). In all cases, excellent yields were reached. These examples illustrate how α-MeNAP complexes as Pd-sources can take catalytic aminations beyond the level that is achievable with simple Pd-precursors.[32b] We found it is safe to assume that the catalyst will be at least as effective for simpler substrate combinations and directly turned our attention to other catalytic cross-couplings.

Table 2: Buchwald–Hartwig amination with alkylamines.[a]



1 **2** **3**



3bb 97% **3ac** 98% **3ad** 97%

[a] Conditions: 0.5 mmol of **1**, 1.1 equiv **2**, 0.5 mol % $[Pd(\alpha\text{-MeNAP})Br]_2$, 1 mol % RuPhos, 1.5 equiv KO*t*Bu, 2 mL THF, rt, 12 h, isolated yields.

The Heck reaction is another widely used Pd-catalyzed transformation, and of enormous importance for the synthesis of vinyl arenes and dienes.[36] The reaction is well developed, but the conversion of sterically demanding, deactivated aryl chlorides still seems challenging.[10b,37]

We chose the reaction of 2-chloroquinoline with bulky *tert*-butyl acrylate as our model system. We had experienced this substrate combination to be extremely challenging, and to the best of our knowledge, there is no literature report of their successful coupling.[38] We started with conditions that Zhou et al.[39] had reported to be effective in the coupling of 1-chlorobenzaldehyde, namely a $Pd(OAc)_2$/DavePhos catalyst system combined with $n\text{-Bu}_4NOAc$ as the base (Table 3, entry 1). However, low yields were obtained even at 120 °C. A screening of commercial ligands revealed that $t\text{-Bu}_3P$ and in particular $PAd_2n\text{-Bu}$[35b] gave satisfactory yields (Table 3, entries 1–3,).[40] However, the reaction could be brought to full conversion only by optimizing the Pd-source. With Pd_2dba_3 or Pd–allyl complexes as Pd-precursors, a step-up in the yields was observed (Table 3, entries 4–8). However, the best results were once again achieved with [Pd(α-Me-

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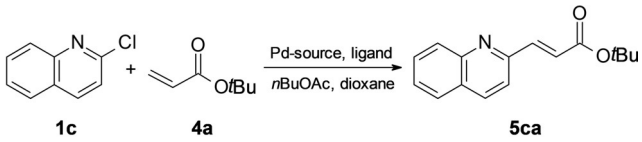
Table 3: Heck vinylation with acrylates.[a]



Entry	Pd-source	Ligand	**5ca** [%]
1	$Pd(OAc)_2$	DavePhos	13
2	"	P*t*-Bu_3	46
3	"	PAd_2*n*-Bu	64
4	Pd_2dba_3	"	82
5	$[Pd(allyl)Cl]_2$	"	85
6	$[Pd(2\text{-Me-allyl})Cl]_2$	"	88
7	$[Pd(cinnamyl)Cl]_2$	"	96
8	$[Pd(t\text{-Bu-indenyl})Cl]_2$	"	95
9	$[Pd(\alpha\text{-MeNAP})Cl]_2$	"	92
10	$[Pd(\alpha\text{-MeNAP})Br]_2$	"	98
11	$[Pd(\beta\text{-MeNAP})Cl]_2$	"	84
12	$[Pd(\beta\text{-MeNAP})Br]_2$	"	98

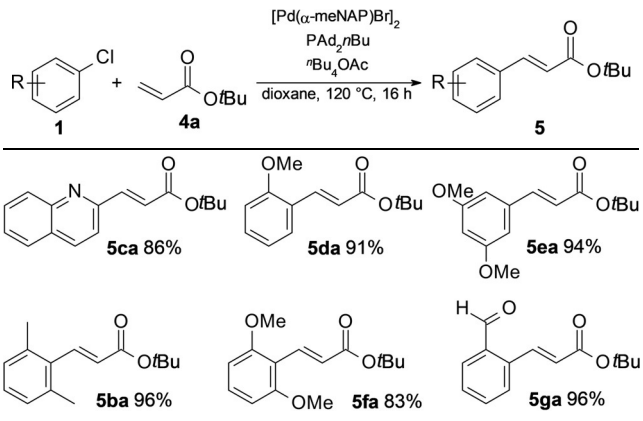
[a] Conditions: 0.5 mmol of **1c**, 1.1 equiv **4a**, 2 mol% [Pd], 2 mol% ligand, 2.5 equiv *n*-Bu_4OAc, 1.5 mL dioxane, 120°C, 16 h. Yields determined via GC-analysis using *n*-undecane as internal standard.

NAP)Br]$_2$ and [Pd(β-MeNAP)Br]$_2$, which both gave near quantitative yields. The other MeNAP complexes were also superior to $Pd(OAc)_2$ and Pd_2dba_3.

We conducted a brief study to probe the efficiency of the new precatalyst for other challenging Heck reactions. As can be seen from the examples in Table 4, various aryl chlorides were smoothly converted, including substrates with methyl, methoxy, and even the problematic formyl group in their *ortho*-positions. Most of the products had never before been synthesized from chloroarenes (**5ca**–**5ga**), others only in lower yields (**5ha**).[41] These results underline the advantages of MeNAP complexes as catalyst precursors also for Heck reactions.

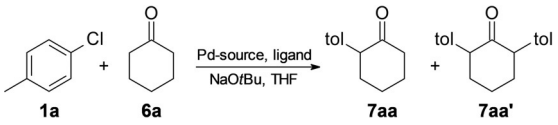
The α-arylation of ketones is another synthetically useful, widely used Pd-catalyzed C–C bond-forming process.[42] One of the few remaining challenges is the selective monoarylation of unsubstituted alkyl ketones with aryl chlorides. The main side reaction is the formation of polyarylated products.[43] Only few ligands including Beller's PAd_2*n*-Bu[44] and Gessner's YPhos[9] allow the selective monoarylation of cyclohexanones with aryl chlorides. This is why we chose the reaction of 4-chlorotoluene with cyclohexanone as the model reaction for our comparative experiments (Table 5).

Table 4: Heck vinylation with acrylates.[a]



[a] Conditions: 0.5 mmol of **1**, 1.1 equiv **4**, 1 mol% [Pd(α-MeNAP)Br]$_2$, 2 mol% PAd_2*n*-Bu, 2.5 equiv *n*-Bu_4OAc, 1.5 mL dioxane, 120°C, 16 h, isolated yields.

Table 5: α-arylation of unhindered ketones.[a]



Entry	Pd-source	Ligand	**7aa** [%]	**7aa′** [%]
1	$Pd(COD)Cl_2$	keYPhos	68	0
2	"	RuPhos	61	5
3	$[Pd(allyl)Cl]_2$	"	74	0
4	$[Pd(cinnamyl)Cl]_2$	"	77	0
5	$[Pd(t\text{-Bu-indenyl})Cl]_2$	"	75	0
7	$[Pd(\alpha\text{-MeNAP})Cl]_2$	"	87	0
8	$[Pd(\alpha\text{-MeNAP})Br]_2$	"	60	0
9	$[Pd(\beta\text{-MeNAP})Cl]_2$	"	83	0
10	$[Pd(\beta\text{-MeNAP})Br]_2$	"	77	0

[a] Conditions: 0.5 mmol of **1a**, 2.0 equiv **6a**, 2 mol% [Pd], 2 mol% ligand, 1.5 equiv NaO*t*Bu, 2 mL THF, 60°C, 16 h. Yields determined via GC-analysis using *n*-tetradecane as internal standard.

The ylide-functionalized phosphine ligand $Y_{Me}PCy_2$ (keYPhos) under the reported conditions[45] led to reasonable yield and a near-complete selectivity. However, comparative experiments with commercially available ligands gave unsatisfactory results under these conditions, including even high-performance ligands such as PAd_2*n*-Bu. The best yields were finally obtained with RuPhos, but in combination with $Pd(COD)Cl_2$, it gave only a moderate selectivity for monoarylation.

As the identity of the precatalyst does not only affect catalyst performance, but also markedly improved the selectivity when using allyl complexes, it is conceivable that byproducts derived from the allyl systems during the activation process play a role in the catalytic reaction. This aspect has not been investigated yet. Once again, the MeNAP systems were found to compare favorably with the other palladium precursors tested. With [Pd(α-MeNAP)Cl]$_2$, a yield of 87% was obtained, with unwanted diarylation byproduct not even detected in traces. The chloride complexes were found to be superior to the bromide complexes, and α-MeNAP was more efficient than β-MeNAP.

A brief screening of common ketone substrates reveals that the [Pd(α-MeNAP)Cl]$_2$/RuPhos system is generally applicable to ketone arylations. Unwanted diarylation products were not detected, confirming that the MeNAP markedly increases the selectivity towards monoarylation (Table 6).

We next moved our attention to Pd-catalyzed Negishi couplings, another widely used tool for the construction of C–C bonds.[1b,46] State-of-the-art ligands include Buchwald's and Knochel's dialkylbiaryl phosphines,[47] Gessner's Yphos,[48] and Organ's IPent ligand.[19,49] We chose the coupling of

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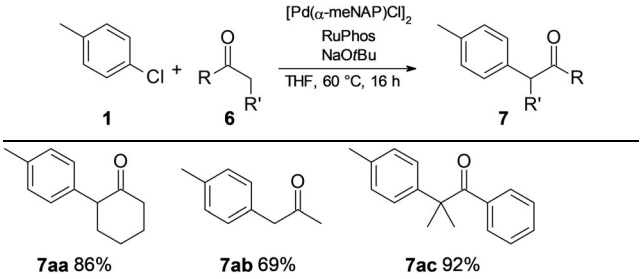
Table 6: α-Arylation of unhindered ketones.[a]

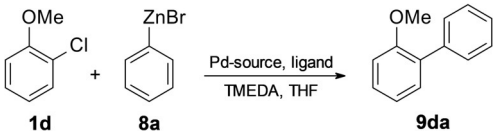


[a] Conditions: 0.5 mmol of **1** 2.0 equiv **6**, 1 mol% [Pd(α-MeNAP)Cl]$_2$, 2 mol% RuPhos,1.5 equiv NaO*t*Bu, 2 mL THF, 60°C, 16 h, isolated yields.

electron-rich, sterically hindered 2-chloroanisole (**1d**) with phenyl zinc bromide (**8a**) as the model reaction. Such *ortho*-methoxy-substituted products are rare in the scope tables of state-of-the-art Pd systems. At best a 25% yield of **9da** had been achieved at 70°C using a Pd_2dba_3/RuPhos system described in literature (Table 7, entry 1).[47b] At room temperature, this ligand was ineffective with Pd_2dba_3 and gave low yields with $Pd(OAc)_2$ as precursors, even when activating the zinc reagent with TMEDA[48] (Table 7, entries 1 and 2). Comparative experiments at 8 h reaction time revealed that allyl–Pd complexes, in particular [Pd(cinnamyl)Cl]$_2$, are effective catalyst precursors, but the best results were obtained with [Pd(α-MeNAP)Cl]$_2$. When extending the reaction time to 16 hours quantitative yields were obtained with all MeNAP complexes (Table 7, entries 8–11). After 16 h, $Pd(OAc)_2$ still gave unsatisfactory results, whereas the indenyl system was highly effective.

We next probed [Pd(α-MeNAP)Br]$_2$ for other challenging substrate combinations, and to our delight, various sterically demanding biaryls, even **9fa** bearing two methoxy groups in *ortho*-position, were successfully coupled (Table 8). This

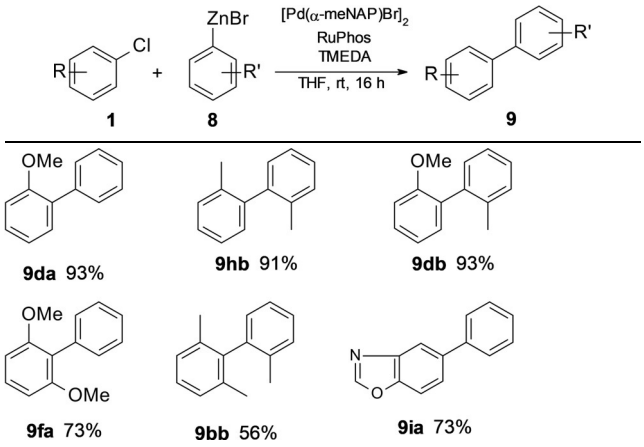
Table 7: Negishi coupling of aryl zinc bromides.[a]



Entry	Pd-source	Additive	Ligand	**9da** [%]
1	Pd_2dba_3	–	RuPhos	25[b]
2	″	TMEDA	RuPhos	0
3	$Pd(OAc)_2$			25 (36)
4	[Pd(allyl)Cl]$_2$		″	19
5	[Pd(2-Me-allyl)Cl]$_2$		″	35
6	[Pd(cinnamyl)Cl]$_2$		″	37
7	[Pd(*t*-Bu-indenyl)Cl]$_2$		″	31 (99)
8	[Pd(α-MeNAP)Cl]$_2$		″	42 (>99)
9	[Pd(α-MeNAP)Br]$_2$		″	36 (>99)
10	[Pd(β-MeNAP)Cl]$_2$		″	35 (>99)
11	[Pd(β-MeNAP)Br]$_2$		″	7 (>99)

[a] Conditions: 0.5 mmol of **1d**, 1.5 equiv **8a**, 2 mol% [Pd], 2 mol% ligand, 2.0 equiv TMEDA, 1.5 mL THF, rt, 8 h; value for 16 h in brackets. Yields determined via GC-analysis using *n*-undecane as internal standard. [b] At 70°C.

Table 8: Negishi coupling of aryl zinc bromides.[a]



[a] Conditions: 0.5 mmol of **1**, 1.5 equiv **8**, 1 mol% [Pd(α-MeNAP)Br]$_2$, 2 mol% RuPhos, 2.0 equiv TMEDA, 1.5 mL THF, rt, 16 h, isolated yields. Substituents arising from the aryl chloride are placed on the left-hand side.

result shows that optimization of catalytic reactions using MeNAP complexes can take them to efficiencies substantially beyond those reachable using standard precursors.

The Suzuki–Miyaura reaction is commonly used for the synthesis of biaryl compounds.[10b,50] The few remaining challenges include couplings of alkyl compounds as well as room-temperature couplings of aryl chlorides leading to the formation of sterically extremely shielded, tetra-*ortho*-substituted compounds.[51] Nolan's protocol based on electron-rich, sterically high demanding NHC-ligand IPr^{*OMe} in combination with [Pd(cinnamyl)Cl]$_2$ has set records in this context.[20a,52] In order to evaluate if even this highly developed system would benefit from the use of the MeNAP–Pd sources, we chose the coupling of 2-chloro-*m*-xylene with 2,4,6-trimethylphenylboronic acid as the model reaction and evaluated various Pd-sources under the conditions reported in the literature (Table 9).[20a] The only adjustment made was the use of THF rather than DME as the solvent. This was necessary due to the low solubility of the methylnaphthyl dimers in DME.

As can be seen from Table 9, cinnamyl Pd precursors were confirmed to be most effective among the known systems. Neither simple Pd_2dba_3 nor other allyl–Pd complexes gave satisfactory results. However, all four MeNAP complexes compared favorably to the other complexes tested as catalyst precursors. The desired product **11ba** was formed in quantitative yields within 12 hours at room temperature in all cases.

Further investigations on the scope of the catalyst system are summarized in Table 10. We were pleased to find that the [Pd(α-MeNAP)Br]$_2$/IPr^{*OMe} catalyst promotes even the extremely challenging coupling of electron-rich, sterically hindered *ortho,ortho*-dimethoxy-substituted aryl chloride with 2,4,6-trimethylphenylboronic acid in near quantitative yield (**11fa**).

In a stoichiometric reaction of [Pd(α-MeNAP)Br]$_2$ with ligand, base, and the phenylboronic acid, the phenylated product was formed, which supports an activation process via arylation of the methylnaphthyl substituent (see S4.2).

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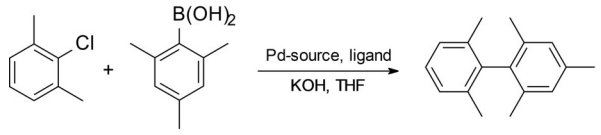
Table 9: Suzuki–Miyaura coupling of sterically hindered substrates.[a]

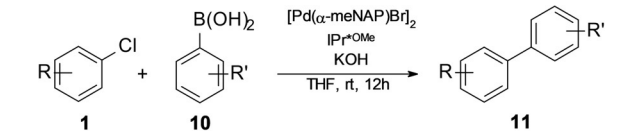


1b **10a** **11ba**

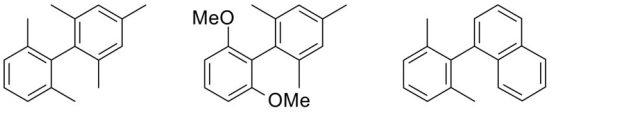
Entry	Pd-source	Ligand	**11ba** [%]
1	$[Pd(cinnamyl)Cl]_2$	IPr^{*OMe}	95[b]
2	Pd_2dba_3	"	5
3	$[Pd(allyl)Cl]_2$	"	9
4	$[Pd(cinnamyl)Cl]_2$	"	51
5	$[Pd(t\text{-Bu-indenyl})Cl]_2$	"	23
6	$[Pd(\alpha\text{-MeNAP})Cl]_2$	"	>99
7	$[Pd(\alpha\text{-MeNAP})Br]_2$	"	>99
8	$[Pd(\beta\text{-MeNAP})Cl]_2$	"	>99
9	$[Pd(\beta\text{-MeNAP})Br]_2$	"	>99

[a] Conditions: 0.5 mmol of **1b**, 1.5 equiv **10a**, 2 mol% [Pd], 2 mol% ligand, 2.0 equiv KOH, 2 mL THF, rt, 12 h. Yields determined via GC-analysis using *n*-tetradecane as internal standard. [b] Reaction performed in DME for 22 h.

Table 10: Suzuki–Miyaura coupling of sterically hindered substrates.[a]



1 **10** **11**



11ba 95% **11fa** 97% **11bb** 98%

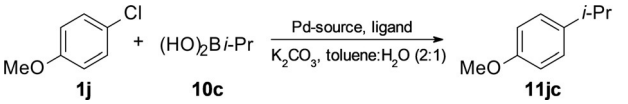
[a] Conditions: 0.5 mmol of **1**, 1.5 equiv **10**, 1 mol% $[Pd(\alpha\text{-MeNAP})Br]_2$, 2 mol% IPr^{*OMe}, 2.0 equiv KOH, 2 mL THF, rt, 12 h, isolated yields. Substituents arising from the aryl chloride are placed on the left-hand side.

We went on to address one of the remaining challenges in Suzuki reactions, namely the coupling of branched secondary alkyl boronic acids with aryl chlorides. Only a few examples of such couplings have been reported, none of them with a full scope.[5,53] Alkyl boronic acids are prone to autooxidation, form boroxines upon dehydration and undergo protodeborylation at elevated temperatures.[54] These side reactions take place since the transmetalation to the palladium center is slower for boronic acids than that of other organometallic reagents.[55] Moreover, the alkyl palladium species resulting from this transmetalation step tend to undergo β-hydride elimination/reinsertion sequences resulting in the formation of alkenes or constitutional isomers of the desired products.[56]

Faster transmetalation can be achieved by using trifluoroborates as demonstrated by Molander, Dreher and van Hoogenband using Buchwald or ferrocene ligands with Pd_2dba_3 or $Pd(OAc)_2$,[57] which are less subject to protodeboronation but have to be synthesized in an additional reaction step from other alkylboron compounds.

The use of free boronic acids has only been demonstrated exemplarily, for example, by Biscoe using a P*t*-Bu_3-ligated palladacyle,[58] Carrow a PAd_3-ligated palladacyle,[4b] and Hazari using the P*t*-Bu_3-Yale precatalyst.[21] Isomerization could only be fully suppressed using the well-defined one-component catalysts, but not when starting from in situ generated complexes.[27,57] We chose the model reaction of 4-chloroanisole and isopropylboronic acid to evaluate the role of the precatalyst.[21] Selected results in Table 11 show that,

Table 11: Suzuki–Miyaura coupling of alkyl boronic acids.[a]



1j **10c** **11jc**

Entry	Pd-source	Ligand	**11jc** [%]
1	$Pd(OAc)_2$	P*t*-Bu_3·HBF_4	0
2	Pd_2dba_3	"	55
3	$[Pd(allyl)Cl]_2$	"	28
4	$[Pd(cinnamyl)Cl]_2$	"	68
5	$[Pd(t\text{-Bu-indenyl})Cl]_2$	"	60
6	$[Pd(\alpha\text{-MeNAP})Cl]_2$	"	88
7	$[Pd(\alpha\text{-MeNAP})Br]_2$	"	89
8	$[Pd(\beta\text{-MeNAP})Cl]_2$	"	61
9	$[Pd(\beta\text{-MeNAP})Br]_2$	"	65

[a] Conditions: 0.25 mmol of **1j**, 1.5 equiv **10c**, 2 mol% [Pd], 4 mol% ligand, 3.0 equiv, K_2CO_3, 0.75 mL toluene:H_2O (2:1), 80°C, 11 h. Yields determined by GC-analysis using *n*-tetradecane as the internal standard.

regardless of the Pd/ligand ratio, palladium acetate is ineffective whereas moderate yield is obtained with Pd_2dba_3 in combination with tris-*tert*-butyl phosphine. The use of allyl–Pd precursors led to a step-up in the yield. By far the best results were obtained with α-MeNAP complexes. The product was formed in high yield (89%) without detectable isomerization of the isopropyl residue. The activity of the β-MeNAP complexes was, once again, significantly lower than that of α-MeNAP catalysts but still in the same range as state-of-the-art allyl complexes.

We further probed the catalytic activity of the α-MeNAP complexes in the coupling of aliphatic boronic acids by evaluating a wide range of substrate combinations (Table 12). Both electron-rich and electron-deficient aryl chlorides give high yields in the coupling with isopropylboronic acid. Common functional groups, including nitro, ester, and amino groups, are tolerated. The successful coupling of *ortho,ortho*-dimethylphenyl chloride exemplifies the high efficiency of the catalyst with regard to steric hindrance. Various alkyl boronic acids were successfully coupled with 4-chloroanisole, including linear, branched, and cyclic substrates. In none of the cases, more than trace quantities of side products arising from isomerization, deboronation, or dehalogenation were obtained.

The new catalyst precursor is thus not only able to further improve known reactions, but can be an enabling factor in the development of new methods. The direct coupling of alkylboronic acids without activation step is a significant extension of Suzuki couplings with potential applications ranging from natural product synthesis to drug discovery.

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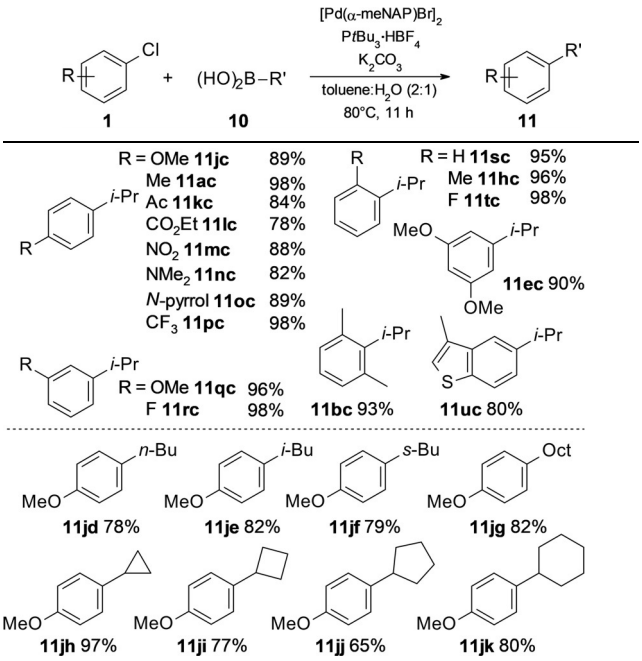
Table 12: Suzuki–Miyaura coupling of alkyl boronic acids: scope of aryl chlorides (top), boronic acids (bottom).[a]



[a] Conditions: 0.5 mmol of **1**, 1.5 equiv **10**, 1 mol% [Pd(α-MeNAP)Br]$_2$, 4 mol% P*t*-Bu$_3$*HBF$_4$, 3.0 equiv K_2CO_3, 1.5 mL toluene:H_2O (2:1), 80°C, 11 h, isolated yields. **11jc** was prepared on a 1 mmol scale. Substituents arising from the aryl chloride are placed on the left-hand side.

Conclusion

Methylnaphthyl palladium complexes were shown to be bench-stable, easy-to-use catalyst precursors with excellent performance. They are easily accessible in one step from commercial precursors and react smoothly with various ligands to give defined complexes. This allows to reliably access highly active monoligated catalysts. The versatile applicability of the new palladium sources was demonstrated in Buchwald–Hartwig amination, Heck vinylation, α-arylation as well as Negishi and Suzuki–Miyaura coupling. In the case of Buchwald–Hartwig amination, and Suzuki–Miyaura coupling, the effect of the methylnaphthyl precursor on the catalyst activity was particularly profound. In the case of Suzuki–Miyaura coupling, it even allowed the extension of the reaction to a new substrate class. The structures generated from 1-methylnaphthyl halides are recommended as the first choice. With regard to the halide, the situation is less clear. In most cases, the bromide complex Pd(α-MeNAP)Br]$_2$ was most efficient, but in ketone arylation, the chloride complex Pd(α-MeNAP)Cl]$_2$ gave best results.

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Conflict of Interest

Results are part of a patent filed by Umicore AG & Co. KG in 2021.

Keywords: allyl ligands · C–C coupling · cross coupling · homogeneous catalysis · palladium

[1] a) C. Torborg, M. Beller, *Adv. Synth. Catal.* **2009**, *351*, 3027–3043; b) A. de Meijere, F. Diederich, *Metal-Catalyzed Cross-Coupling Reactions*, Wiley-VCH, Weinheim, **2004**; c) C. C. C. Johansson Seechurn, M. O. Kitching, T. J. Colacot, V. Snieckus, *Angew. Chem. Int. Ed.* **2012**, *51*, 5062–5085; *Angew. Chem.* **2012**, *124*, 5150–5174.
[2] J. Brunel, *Mini-Rev. Org. Chem.* **2004**, *1*, 249–277.
[3] a) K. Ogawa, K. R. Radke, S. D. Rothstein, S. C. Rasmussen, *J. Org. Chem.* **2001**, *66*, 9067–9070; b) L. L. Hill, L. R. Moore, R. Huang, R. Craciun, A. J. Vincent, D. A. Dixon, J. Chou, C. J. Woltermann, K. H. Shaughnessy, *J. Org. Chem.* **2006**, *71*, 5117–5125.
[4] a) A. G. Sergeev, A. Zapf, A. Spannenberg, M. Beller, *Organometallics* **2008**, *27*, 297–300; b) L. Chen, P. Ren, B. P. Carrow, *J. Am. Chem. Soc.* **2016**, *138*, 6392–6395.
[5] N. Kataoka, Q. Shelby, J. P. Stambuli, J. F. Hartwig, *J. Org. Chem.* **2002**, *67*, 5553–5566.
[6] D. S. Surry, S. L. Buchwald, *Chem. Sci.* **2011**, *2*, 27–50.
[7] a) M. N. Hopkinson, C. Richter, M. Schedler, F. Glorius, *Nature* **2014**, *510*, 485–496; b) W. A. Herrmann, C. Köcher, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2162–2187; *Angew. Chem.* **1997**, *109*, 2256–2282; c) S. Díez-González, N. Marion, S. P. Nolan, *Chem. Rev.* **2009**, *109*, 3612–3676.
[8] a) V. Lavallo, Y. Canac, C. Präsang, B. Donnadieu, G. Bertrand, *Angew. Chem. Int. Ed.* **2005**, *44*, 5705–5709; *Angew. Chem.* **2005**, *117*, 5851–5855; b) M. Melaimi, R. Jazzar, M. Soleilhavoup, G. Bertrand, *Angew. Chem. Int. Ed.* **2017**, *56*, 10046–10068; *Angew. Chem.* **2017**, *129*, 10180–10203.
[9] T. Scherpf, C. Schwarz, L. T. Scharf, J.-A. Zur, A. Helbig, V. H. Gessner, *Angew. Chem. Int. Ed.* **2018**, *57*, 12859–12864; *Angew. Chem.* **2018**, *130*, 13041–13046.
[10] a) J. F. Hartwig, *Organotransition Metal Chemistry: From Bonding to Catalysis*, University Science Books, Sausalito, Calif, **2010**; b) A. F. Littke, G. C. Fu, *Angew. Chem. Int. Ed.* **2002**, *41*, 4176–4211; *Angew. Chem.* **2002**, *114*, 4350–4386; c) S. Noyori, Y. Nishihara, in *Applied Cross-Coupling Reactions* (Ed.: Y. Nishihara), Springer, Berlin, Heidelberg, **2013**, pp. 177–202.
[11] A. M. Johns, J. W. Tye, J. F. Hartwig, *J. Am. Chem. Soc.* **2006**, *128*, 16010–16011.
[12] a) M. Prashad, X. Y. Mak, Y. Liu, O. Repič, *J. Org. Chem.* **2003**, *68*, 1163–1164; b) T. Hama, J. F. Hartwig, *Org. Lett.* **2008**, *10*, 1549–1552.
[13] T. J. Colacot, *Platinum Met. Rev.* **2012**, *56*, 110–116.
[14] K. H. Shaughnessy, *Isr. J. Chem.* **2020**, *60*, 180–194.
[15] a) C. Amatore, E. Carre, A. Jutand, M. A. M'Barki, *Organometallics* **1995**, *14*, 1818–1826; b) C. S. Wei, G. H. M. Davies, O. Soltani, J. Albrecht, Q. Gao, C. Pathirana, Y. Hsiao, S. Tummala,

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M. D. Eastgate, *Angew. Chem. Int. Ed.* **2013**, *52*, 5822 – 5826; *Angew. Chem.* **2013**, *125*, 5934 – 5938.
[16] S. S. Zalesskiy, V. P. Ananikov, *Organometallics* **2012**, *31*, 2302 – 2309.
[17] P. Weber, A. Biafora, A. Doppiu, H.-J. Bongard, H. Kelm, L. J. Gooßen, *Org. Process Res. Dev.* **2019**, *23*, 1462 – 1470.
[18] a) W. A. Carole, J. Bradley, M. Sarwar, T. J. Colacot, *Org. Lett.* **2015**, *17*, 5472 – 5475; b) W. A. Carole, T. J. Colacot, *Chem. Eur. J.* **2016**, *22*, 7686 – 7695.
[19] M. G. Organ, S. Avola, I. Dubovyk, N. Hadei, E. A. B. Kantchev, C. J. O'Brien, C. Valente, *Chem. Eur. J.* **2006**, *12*, 4749 – 4755.
[20] a) A. Chartoire, M. Lesieur, L. Falivene, A. M. Z. Slawin, L. Cavallo, C. S. J. Cazin, S. P. Nolan, *Chem. Eur. J.* **2012**, *18*, 4517 – 4521; b) A. Chartoire, M. Lesieur, A. M. Z. Slawin, S. P. Nolan, C. S. J. Cazin, *Organometallics* **2011**, *30*, 4432 – 4436; c) N. Marion, O. Navarro, J. Mei, E. D. Stevens, N. M. Scott, S. P. Nolan, *J. Am. Chem. Soc.* **2006**, *128*, 4101 – 4111; d) O. Navarro, H. Kaur, P. Mahjoor, S. P. Nolan, *J. Org. Chem.* **2004**, *69*, 3173 – 3180; e) M. S. Viciu, R. F. Germaneau, O. Navarro-Fernandez, E. D. Stevens, S. P. Nolan, *Organometallics* **2002**, *21*, 5470 – 5472; f) L. L. Hill, J. L. Crowell, S. L. Tutwiler, N. L. Massie, C. C. Hines, S. T. Griffin, R. D. Rogers, K. H. Shaughnessy, G. A. Grasa, C. C. C. Johansson Seechurn, H. Li, T. J. Colacot, J. Chou, C. J. Woltermann, *J. Org. Chem.* **2010**, *75*, 6477 – 6488; g) C. C. C. Johansson Seechurn, S. L. Parisel, T. J. Colacot, *J. Org. Chem.* **2011**, *76*, 7918 – 7932; h) M. S. Viciu, R. M. Kissling, E. D. Stevens, S. P. Nolan, *Org. Lett.* **2002**, *4*, 2229 – 2231.
[21] P. R. Melvin, A. Nova, D. Balcells, W. Dai, N. Hazari, D. P. Hruszkewycz, H. P. Shah, M. T. Tudge, *ACS Catal.* **2015**, *5*, 3680 – 3688.
[22] a) A. Bruneau, M. Roche, M. Alami, S. Messaoudi, *ACS Catal.* **2015**, *5*, 1386 – 1396; b) N. C. Bruno, M. T. Tudge, S. L. Buchwald, *Chem. Sci.* **2013**, *4*, 916 – 920.
[23] a) J. Smidt, W. Hafner, *Angew. Chem.* **1959**, *71*, 284; b) H. C. Dehm, J. C. W. Chien, *J. Am. Chem. Soc.* **1960**, *82*, 4429 – 4430; c) E. O. Fischer, G. Buerger, *Z. Naturforsch. B* **1961**, 702 – 703; d) S. P. Gubin, A. Z. Rubezhov, B. L. Winch, A. N. Nesmeyanov, *Tetrahedron Lett.* **1964**, *5*, 2881 – 2887.
[24] C. V. Reddy, J. V. Kingston, J. G. Verkade, *J. Org. Chem.* **2008**, *73*, 3047 – 3062.
[25] D. Ortiz, M. Blug, X.-F. Le Goff, P. Le Floch, N. Mézailles, P. Maître, *Organometallics* **2012**, *31*, 5975 – 5978.
[26] a) D. P. Hruszkewycz, D. Balcells, L. M. Guard, N. Hazari, M. Tilset, *J. Am. Chem. Soc.* **2014**, *136*, 7300 – 7316; b) D. P. Hruszkewycz, L. M. Guard, D. Balcells, N. Feldman, N. Hazari, M. Tilset, *Organometallics* **2015**, *34*, 381 – 394.
[27] M. R. Espinosa, A. Doppiu, N. Hazari, *Adv. Synth. Catal.* **2020**, *362*, 5062 – 5078.
[28] J. Huang, M. Isaac, R. Watt, J. Becica, E. Dennis, M. I. Saidaminov, W. A. Sabbers, D. C. Leitch, *ACS Catal.* **2021**, *11*, 5636 – 5646.
[29] J. Krause, G. Cestaric, K.-J. Haack, K. Seevogel, W. Storm, K.-R. Pörschke, *J. Am. Chem. Soc.* **1999**, *121*, 9807 – 9823.
[30] H. Sellers, J. E. Boggs, *J. Mol. Struct.* **1981**, *74*, 137 – 142.
[31] A. E. Smith, *Acta Crystallogr.* **1965**, *18*, 331 – 340.
[32] a) J. F. Hartwig, in *Handbook of Organopalladium Chemistry for Organic Synthesis* (Ed.: E. Negishi), Wiley, New York, **2002**, pp. 1051 – 1096; b) R. Dorel, C. P. Grugel, A. M. Haydl, *Angew. Chem. Int. Ed.* **2019**, *58*, 17118 – 17129; *Angew. Chem.* **2019**, *131*, 17276 – 17287.
[33] a) J. P. Stambuli, R. Kuwano, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2002**, *41*, 4746 – 4748; *Angew. Chem.* **2002**, *114*, 4940 – 4942; b) Q. Shen, S. Shekhar, J. P. Stambuli, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2005**, *44*, 1371 – 1375; *Angew. Chem.* **2005**, *117*, 1395 – 1399; c) C. A. Wheaton, J.-P. J. Bow, M. Stradiotto, *Organometallics* **2013**, *32*, 6148 – 6161; d) J. F. Hartwig, M. Kawatsura, S. I. Hauck, K. H. Shaughnessy, L. M. Alcazar-Roman, *J. Org. Chem.* **1999**, *64*, 5575 – 5580.
[34] S. R. Stauffer, S. Lee, J. P. Stambuli, S. I. Hauck, J. F. Hartwig, *Org. Lett.* **2000**, *2*, 1423 – 1426.
[35] a) J. Tappen, I. Rodstein, K. McGuire, A. Großjohann, J. Löffler, T. Scherpf, V. H. Gessner, *Chem. Eur. J.* **2020**, *26*, 4281 – 4288; b) A. Ehrentraut, A. Zapf, M. Beller, *J. Mol. Catal. A* **2002**, *182 – 183*, 515 – 523; c) W. I. Lai, M. P. Leung, P. Y. Choy, F. Y. Kwong, *Synthesis* **2019**, *51*, 2678 – 2686.
[36] a) I. P. Beletskaya, A. V. Cheprakov, *Chem. Rev.* **2000**, *100*, 3009 – 3066; b) S. Jagtap, *Catalysts* **2017**, *7*, 267.
[37] a) G. C. Fu, *Acc. Chem. Res.* **2008**, *41*, 1555 – 1564; b) A. F. Littke, G. C. Fu, *J. Am. Chem. Soc.* **2001**, *123*, 6989 – 7000.
[38] The product has only been accessed via reductive olefination of *N*-oxides: H. Xia, Y. Liu, P. Zhao, S. Gou, J. Wang, *Org. Lett.* **2016**, *18*, 1796 – 1799.
[39] H.-J. Xu, Y.-Q. Zhao, X.-F. Zhou, *J. Org. Chem.* **2011**, *76*, 8036 – 8041.
[40] T. Schareina, A. Zapf, A. Cotté, M. Gotta, M. Beller, *Adv. Synth. Catal.* **2010**, *352*, 1205 – 1209.
[41] S. Mohanty, D. Suresh, M. S. Balakrishna, J. T. Mague, *Tetrahedron* **2008**, *64*, 240 – 247.
[42] a) G. A. Grasa, T. J. Colacot, *Org. Process Res. Dev.* **2008**, *12*, 522 – 529; b) F. Bellina, R. Rossi, *Chem. Rev.* **2010**, *110*, 1082 – 1146; c) D. Prim, S. Marque, A. Gaucher, J.-M. Campagne, in *Organic Reactions*, Wiley, Hoboken, **2011**, pp. 49 – 280.
[43] J. M. Fox, X. Huang, A. Chieffi, S. L. Buchwald, *J. Am. Chem. Soc.* **2000**, *122*, 1360 – 1370.
[44] A. Ehrentraut, A. Zapf, M. Beller, *Adv. Synth. Catal.* **2002**, *344*, 209 – 217.
[45] X.-Q. Hu, D. Lichte, I. Rodstein, P. Weber, A.-K. Seitz, T. Scherpf, V. H. Gessner, L. J. Gooßen, *Org. Lett.* **2019**, *21*, 7558 – 7562.
[46] a) *Handbook of Organopalladium Chemistry for Organic Synthesis* (Ed.: E. Negishi), Wiley, New York, **2002**; b) C. Dai, G. C. Fu, *J. Am. Chem. Soc.* **2001**, *123*, 2719 – 2724.
[47] a) G. Manolikakes, M. A. Schade, C. M. Hernandez, H. Mayr, P. Knochel, *Org. Lett.* **2008**, *10*, 2765 – 2768; b) J. E. Milne, S. L. Buchwald, *J. Am. Chem. Soc.* **2004**, *126*, 13028 – 13032.
[48] Z. Hu, X.-J. Wei, J. Handelmann, I. Rodstein, V. H. Gessner, *Angew. Chem. Int. Ed.* **2021**, *60*, 6778 – 6783; *Angew. Chem.* **2021**, *133*, 6852 – 6858.
[49] a) C. Valente, M. E. Belowich, N. Hadei, M. G. Organ, *Eur. J. Org. Chem.* **2010**, 4343 – 4354; b) C. Valente, S. Çalimsiz, K. H. Hoi, D. Mallik, M. Sayah, M. G. Organ, *Angew. Chem. Int. Ed.* **2012**, *51*, 3314 – 3332; *Angew. Chem.* **2012**, *124*, 3370 – 3388.
[50] a) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457 – 2483; b) A. Suzuki, *Angew. Chem. Int. Ed.* **2011**, *50*, 6722 – 6737; *Angew. Chem.* **2011**, *123*, 6854 – 6869.
[51] a) L. Ackermann, H. K. Potukuchi, A. Althammer, R. Born, P. Mayer, *Org. Lett.* **2010**, *12*, 1004 – 1007; b) T. Hoshi, T. Nakazawa, I. Saitoh, A. Mori, T. Suzuki, J. Sakai, H. Hagiwara, *Org. Lett.* **2008**, *10*, 2063 – 2066; c) C. M. So, W. K. Chow, P. Y. Choy, C. P. Lau, F. Y. Kwong, *Chem. Eur. J.* **2010**, *16*, 7996 – 8001; d) M. G. Organ, S. Çalimsiz, M. Sayah, K. H. Hoi, A. J. Lough, *Angew. Chem. Int. Ed.* **2009**, *48*, 2383 – 2387; *Angew. Chem.* **2009**, *121*, 2419 – 2423.
[52] a) G. Bastug, S. P. Nolan, *Organometallics* **2014**, *33*, 1253 – 1258.
[53] a) S.-M. Zhou, M.-Z. Deng, L.-J. Xia, M.-H. Tang, *Angew. Chem. Int. Ed.* **1998**, *37*, 2845 – 2847; *Angew. Chem.* **1998**, *110*, 3061 – 3063; b) D. J. Wallace, C. Chen, *Tetrahedron Lett.* **2002**, *43*, 6987 – 6990.
[54] a) *Boronic Acids: Preparation and Applications in Organic Synthesis and Medicine* (Ed.: D. G. Hall), Wiley-VCH, Weinheim, **2006**; b) D. G. Hall, in *Boronic Acids* (Ed.: D. G. Hall), Wiley-VCH, Weinheim, **2006**, pp. 1 – 99; c) P. A. Cox, A. G.

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Leach, A. D. Campbell, G. C. Lloyd-Jones, *J. Am. Chem. Soc.* **2016**, *138*, 9145 – 9157.

[55] a) N. Miyaura, T. Ishiyama, H. Sasaki, M. Ishikawa, M. Sato, A. Suzuki, *J. Am. Chem. Soc.* **1989**, *111*, 314 – 321; b) A. J. J. Lennox, G. C. Lloyd-Jones, *Chem. Soc. Rev.* **2014**, *43*, 412 – 443.

[56] R. Jana, T. P. Pathak, M. S. Sigman, *Chem. Rev.* **2011**, *111*, 1417 – 1492.

[57] a) S. D. Dreher, P. G. Dormer, D. L. Sandrock, G. A. Molander, *J. Am. Chem. Soc.* **2008**, *130*, 9257 – 9259; b) G. A. Molander, P. E. Gormisky, *J. Org. Chem.* **2008**, *73*, 7481 – 7485; c) A. van den Hoogenband, J. H. M. Lange, J. W. Terpstra, M. Koch, G. M. Visser, M. Visser, T. J. Korstanje, J. T. B. H. Jastrzebski, *Tetrahedron Lett.* **2008**, *49*, 4122 – 4124.

[58] L. Li, S. Zhao, A. Joshi-Pangu, M. Diane, M. R. Biscoe, *J. Am. Chem. Soc.* **2014**, *136*, 14027 – 14030.

[59] Deposition Numbers 2101202 ($\mathbf{Pd}_{\beta}^{\mathbf{Br}}$), 2101198 ($\mathbf{Pd3}_{\alpha\text{-dim}}^{\mathbf{Cl}}$), 2101197 ($\mathbf{Pd3}_{\alpha}^{\mathbf{Br}}$), and 2101200 ($\mathbf{Pd5}_{\alpha}^{\mathbf{Br}}$) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

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