# ACCOUNTS
## of chemical research

# Surveying Sterically Demanding N-Heterocyclic Carbene Ligands with Restricted Flexibility for Palladium-catalyzed Cross-Coupling Reactions

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## CONSPECTUS

**N**-Heterocyclic carbenes (NHCs), especially monodentate ones, have become the ligand of choice for many transition-metal-catalyzed transformations. They generally form highly stable complexes, have strong $\sigma$-donor character, and have a unique shape that can be used to generate sterically demanding ligands.

In this Account, we survey recent developments in the design and synthesis of some sterically demanding NHCs with a particularly strong influence on the metal's coordination sphere. We show the successful and insightful application of these ligands in transition-metal catalysis. First, we discuss methods for determining and classifying the electronic and steric properties of NHCs. In addition, we present data on the most important NHC ligands.



catalytically active monoligated palladium species

**NHC**
flexible
electron-rich
sterically demanding
hemilabile binding possible
(agostic, anagostic, π-complex)

The selective variation of either electronic or steric parameters of NHCs, and therefore of the catalyst, allows for the optimization of the reaction. Thus, we prepared several series of differentially substituted NHC derivatives. However, because the substituents varied were not directly connected to the carbene carbon, it was difficult to induce a large electronic variation. In contrast, an independent variation of the ligands' steric properties was more straightforward. We highlight three different classes of very sterically demanding NHCs that allow this kind of a steric variation: imidazo[1,5-*a*]pyridine-3-ylidenes, bioxazoline-derived carbenes (IBiox), and cyclic (alkyl)(amino)carbenes (CAAC).

These latter NHC ligands can facilitate a number of challenging cross-coupling reactions. Successful transformations often require a monoligated palladium complex as the catalytically active species, and the sterically demanding NHC ligand favors this monoligated complex. In addition, the electron-rich NHC facilitates difficult oxidative addition steps. Moreover, the conformational flexibility of the ligands can facilitate the formation of catalytically active species and hemilabile interactions, such as agostic or anagostic bonds, as well as stabilize coordinatively unsaturated catalyst species. The increasing level of understanding of the role of NHC ligands in transition-metal catalysis will soon allow the design of even more sophisticated ligand systems.
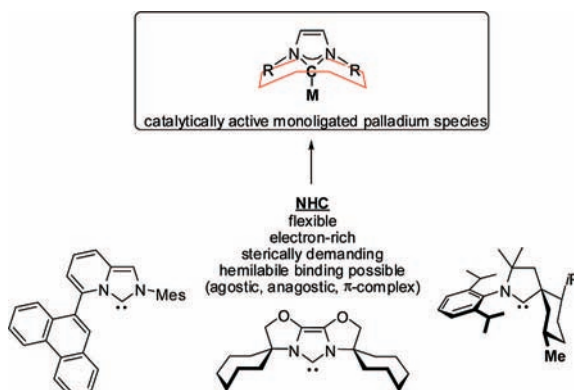
## Introduction

Since the first use of N-heterocyclic carbene (NHC) ligands in transition-metal catalysis by Herrmann et al. in 1995,[1] NHCs have become the ligands of choice for many transformations,[2] imidazolium and 4,5-dihydroimidazolium salt derived NHCs arguably being the most frequently used carbene ligands for transition-metal catalysis (Figure 1). In this context, the measurement and variation of the electronic and steric properties of NHCs has been important for understanding and influencing the carbene's catalytic properties.[3]

## Electronic Properties

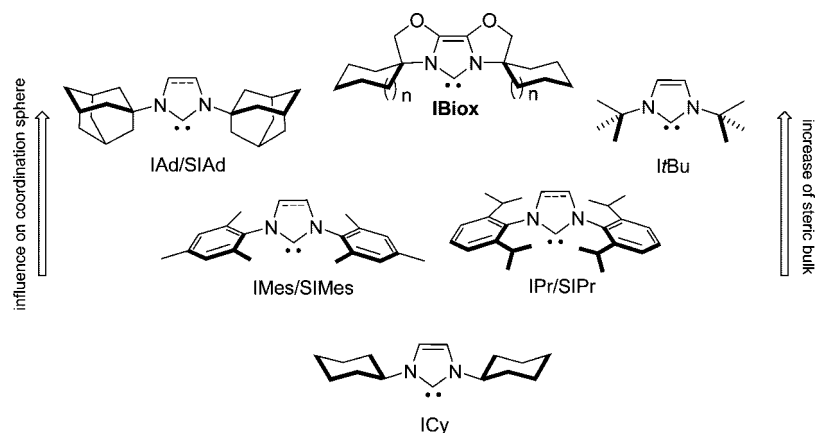NHCs are stronger $\sigma$-donors than even trialkyl phosphines and, thus, bind more strongly to many

**FIGURE 1.** Some sterically demanding, symmetrical, and monodentate NHCs.

transition metals than phosphine ligands do.[4] In addition, $\pi$-acceptor[5] and even $\pi$-donor properties[6] of NHC ligands have recently been reported in some transition-metal complexes. Many different methods for the determination of the electronic properties of ligands in transition-metal complexes have been applied. The basicity of NHCs, available from measurement or calculation of the $pK_a$ values of the corresponding azolium salts, can provide a rough estimate for their $\sigma$-donor characteristics.[7] A more sophisticated method relies on the relationship between the metal−ligand bond strength and the ligand's electronic properties. Thus, Nolan et al. determined the bond dissociation energies of various ruthenium NHC bonds by calorimetric measurements.[8]

The most widely accepted methodology for the determination of a ligand's electronic properties, however, is the IR-spectroscopic analysis of the CO-stretching frequencies of $(L)Ni(CO)_3$, $(L)Rh(CO)_2Cl$, $(L)Ir(CO)_2Cl$, and related complexes.[9] $\sigma$-Donor ligands (L) lead to an increased electron density on the metal center that causes stronger back-bonding from the transition metal to the $\pi^*$ of the CO ligands and, thus, a weakening of the C-O bond detectable by IR-spectroscopy. However, care has to be taken, since not only different transition metals but also different vibrational frequencies (frequency of the trans-CO ligand vs averaged frequency of all CO ligands) have been employed.

Tolman developed methods for the classification of steric and electronic properties of phosphine ligands.[10a] Whereas the cone angle ($\theta$) was found to be a suitable descriptor for the steric demand, the electronic properties were determined by IR-spectroscopic analysis of the CO-stretching frequency $A_1$ of $(L)Ni(CO)_3$ complexes. Nickel was chosen as the metal because of its square planar geometry reducing the impact of steric effects. However, the sterically very demanding I*t*Bu and IAd ligands do not give the desired tricarbonyl complexes but react with $Ni(CO)_4$ to the corresponding $(NHC)Ni(CO)_2$

**TABLE 1.** Comparison of the Donor Properties of Phosphine and Various NHC ligands: Average Stretching Frequencies of $(L)Ir(CO)_2Cl$ and TEP Values of $(L)Ni(CO)_3$ Complexes

| entry | ligand | $\nu_{av}(CO)$ | measured TEP in $cm^{-1}$ | calculated[a] TEP in $cm^{-1}$ |
|---|---|---|---|---|
| 1 | $PPh_3$ | 2044 | 2068.9 | |
| 2 | $PCy_3$ | 2028 | 2056.4 | |
| 3 | SIPr | 2024.9 | 2052.2 | |
| 4 | SIMes | 2024.6 | 2051.5 | |
| 5 | IPr | 2023.9 | 2051.5 | |
| 6 | IMes | 2023.1 | 2050.7 | 2049.6 |
| 7 | ICy | 2023.0 | 2049.6 | |
| 8 | IBiox6 | 2023.5 | | 2049.9 |
| 9 | IBiox8 | 2022.5 | | 2049.1 |
| 10 | IBiox12 | 2022.0 | | 2048.6 |
| 11 | IAd | 2021.6 | | 2048.3 |
| 12 | CAAC c | 2013 | | 2041 |

[a] Values calculated by using the linear regression (TEP = 0.847[$\nu_{av}(CO)$] + 336 $cm^{-1}$).[11]

complexes.[3c] However, the major drawback of this methodology is the extreme toxicity of $Ni(CO)_4$. Recently, Crabtree reported a linear correlation between the average CO-stretching frequencies of $(L)Ir(CO)_2Cl$ complexes and the CO-stretching frequencies $A_1$ of Tolman's phosphine−nickel complexes.[10b] Very recently, Nolan and co-workers determined the TEP values for different $(NHC)Ni(CO)_3$ complexes and, in addition, correlated these results with the average CO-stretching frequencies of $(NHC)Ir(CO)_2Cl$ complexes. These results allow a direct correlation of the different values of nickel and iridium complexes, and an improved regression line for the determination of TEP values of NHC ligands has been calculated.[11] Table 1 shows the electronic properties of some phosphine and NHC ligands, some TEP values being calculated by Nolan's improved regression line.[11]

It can be seen that NHCs are more electron-rich than even very electron-rich trialkyl phosphines and, furthermore, that alkyl-substituted imidazolydene ligands are more electron-rich than their aryl-substituted counterparts (Table 1). The electronic properties of the bioxazoline-derived IBiox12 (Figure 2)
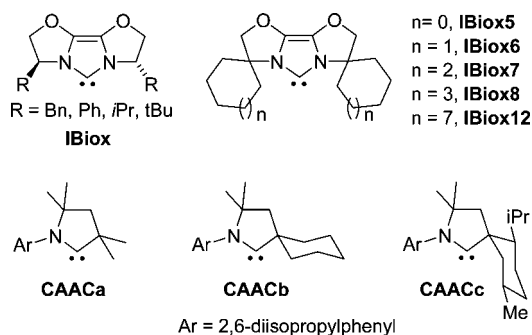
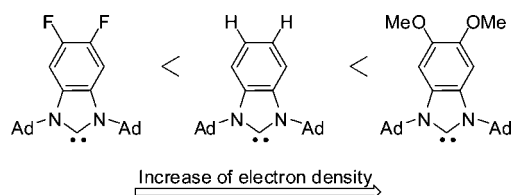**FIGURE 2.** Chiral and achiral bioxazoline-derived carbenes (IBiox) and cyclic (alkyl)(amino)carbenes (CAAC).



**FIGURE 3.** Tuning of electronic properties.



**FIGURE 4.** NHCs with tunable electronic properties by Bertrand and Plenio.



**FIGURE 5.** Modulation of donor properties by "through-space" interaction.

are comparable to the electron-rich adamantyl-substituted imidazolydene IAd, whereas IBiox6 and IBiox8 are slightly less donating and more comparable to IMes or IPr.[12c] However, it is remarkable that the TEP values of the different IBiox ligands are hardly affected by the substituents on the quaternary carbon. As a result of a quaternary carbon placed next to the carbene carbon, Bertrand's cyclic (alkyl)(amino)carbenes (CAACs) (Figure 2 and Table 1, entry 12) are more electron-donating than most other five-membered ring NHCs (Table 1, entry 12).

To synthesize tailor-made catalysts, it is helpful to be able to tune the electronic and steric properties of the metal center independently of each other. Several approaches have been reported to generate families of NHC ligands with similar steric though different electronic character by modification of substituents. However, since these substituents are not directly linked to the carbene carbon, this strategy has mostly resulted in small electronic variations only. A series of differently substituted benzimidazole-derived carbene ligands with similar steric demand has been prepared (Figure 3).[13] These ligands were compared in the palladium-catalyzed Suzuki–Miyaura cross-coupling of chloroarenes with arylboronic acids and, as expected, the highest yields were obtained by employing the palladium complex with the most electron-rich ligand. But even the least electron-donating difluoro-substituted ligand gave satisfying results. Thus, it can be concluded that after reaching a certain level of electron-richness required for oxidative addition, modification of the steric demand becomes more important than modulation of the ligand's electronic parameters.[13]

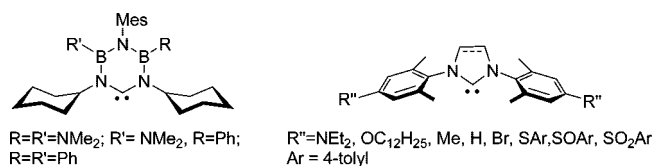Similarly, Bertrand et al. reported on boron-containing cyclic six-membered NHCs whose electronic properties can be modified by introducing different groups at the boron atom with quasi-constant steric bulk of the ligands over quite a wide range.[14] In another recent work, Plenio et al. prepared aryl-substituted imidazolydenes, only differing in the aryl's *para*-substituents (Figure 4).[15] The donor abilities of these tunable NHCs were determined by CO stretching frequencies of the corresponding [(NHC)IrCl(CO)$_2$] and by cyclic voltammetry of [(NHC)IrCl(cod)] complexes. Electron-withdrawing SO$_2$Ar substituents render the donor ability comparable to PCy$_3$, while electron-donor substituents (NEt$_2$) lead to NHCs electronically comparable to 1,3-dialkyl-substituted imidazolydenes.
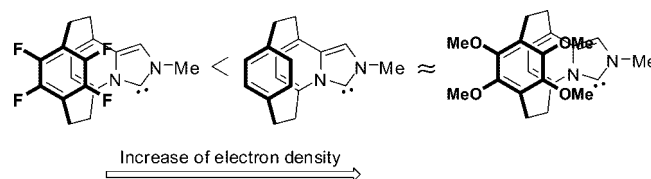
An inspiring concept of modulating the electronic properties of pyridine-derived imidazolydenes was reported by Fürstner et al. (Figure 5). The substituents on an annulated cyclophane affect the donor properties of the carbene by "through-space" interaction.[9] Interestingly, while the tetrafluoro-substituted cyclophane gave the least electron-rich ligand, the unsubstituted and the tetramethoxy-substituted ligands were of comparable electron-richness. Still, this modification allowed the electronic variation over a remarkably wide range, giving vibrational CO frequencies for the trans-CO ligand of 1989 cm$^{-1}$ for the unsubstituted ligand and 2004 cm$^{-1}$ for the tetrafluoro-substituted one for the corresponding (L)Rh(CO)$_2$Cl complexes.

## Steric Properties

The shape of NHCs significantly differs from that of phosphine ligands. In the case of transition-metal phosphine complexes, the phosphine substituents point away from the metal center, forming a cone. In transition-metal NHC complexes, however, the substituents bound to the carbene's nitrogen atoms point toward the metal center and thereby surround the metal (Figure 6).

Thus, Tolman's cone angle descriptor for phosphine ligands can not be applied to NHCs. In order to define the steric bulk of the highly asymmetric NHC ligands, a new model was
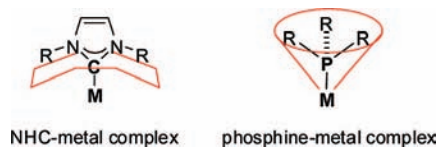
**FIGURE 6.** Different shape of NHC ligands compared with phosphine ligands.

**TABLE 2.** "Buried Volume" (%$V_{Bur}$) of Some NHC and Phosphine Ligands[17]

| entry | ligand | %$V_{Bur}$ |
|---|---|---|
| 1 | I$^t$Bu | 37 |
| 2 | IAd | 37 |
| 3 | PCy$_3$ | 32 |
| 4 | SIPr | 30 |
| 5 | IPr | 29 |
| 6 | SIMes | 27 |
| 7 | PPh$_3$ | 27 |
| 8 | IMes | 26 |
| 9 | ICy | 23[a] |

[a] Reference 3a.

defined.[3a,16,17] The concept of the so-called "buried volume" defines the occupied space of a ligand bound to a metal in its coordination sphere with a radius of 3 Å. This concept enables the comparison between the steric bulk of both NHC and phosphine ligands. Of course the value depends on the bond length of the carbene carbon to the transition metal. One approach for a simple evaluation is to define the metal—ligand bond length as 2 Å (Table 2). According to this measure, the NHC ligands IAd and I$t$Bu are the most sterically demanding ligands (entries 1 and 2).

Increasing the steric bulk of the NHCs leads to a decrease of the bond energy of the NHC—metal bond in the Cp*Ru(NHC)Cl complexes.[17] In Nolan's examination of buried volumes and bond dissociation energies of (L)Ni(CO)$_x$ complexes, similar trends compared with the Cp*Ru(NHC)Cl system are observed, but the dependence on steric bulk of the ligands and their electronic nature is less pronounced.[3a,16] These results show that the strength of a NHC—transition-metal bond depends on the availability of the carbene lone pair, which is a function of steric and electronic factors. ICy is a prime example for an electron-rich carbene with a small sterical bulk forming one of the strongest metal—carbene bonds.[18]

In addition to electronic and steric factors of the NHC ligands, access to the catalytically active metal complex is crucial for high levels of reactivity. For this purpose, many palladium precatalysts have been developed that contain at least one ligand that can easily dissociate from the palladium center,[2] for example, IPr- and IMes-derived palladium(0) complexes with *p*-naphthoquinone or divinyldisiloxan ligands (dvds) (Figure 7).[19] Palladium(II) complexes can be stabilized by the finely tuned 3-chloropyridine ligand, which after in situ

reduction of the precatalyst to Pd(0) can easily dissociate to generate the catalytically active species (Figure 7).[20] Similarly, allyl ligands form stable palladium(II) complexes and can easily be removed by the attack of suitable nucleophiles onto the allyl ligand. Thus, a change of the precatalyst results in the formation of catalysts with a reactivity increased by several orders of magnitude allowing the rapid cross-coupling of challenging substrates under mild reaction conditions.[21]

Three different classes of very sterically demanding, monodentate NHCs with restricted flexibility and their applications in palladium catalysis will be highlighted: imidazo[1,5-*a*]pyridine-3-ylidenes, bioxazoline-derived carbenes (IBiox), and cyclic (alkyl)(amino)carbenes (CAAC). Since results are influenced by many factors (vide supra) care has to be taken in the explanation of the observed reactivity.

**Imidazo[1,5-*a*]pyridine-3-ylidenes.** Glorius[22] and Lassaletta[23] developed independently a novel class of imidazo[1,5-*a*]pyridine-3-ylidenes that enables an efficient manipulation of the metal's coordination sphere (Figure 8). Due to the unique geometry of the bicyclic structure of this carbene, the substituent R can play several roles like shielding of the metal or formation of a chelate by an additional hemilabile bond to the complexed metal.

Several differently substituted ligand precursors **2** can readily be synthesized (Scheme 1). Starting from 6-bromopicolinaldehyde, it is possible to synthesize a bromide-functionalized imidazolium salt (**2e**) that can be further modified by a Suzuki—Miyaura coupling to generate a variety of different ligand precursors. Of the ligands displayed in Scheme 1, **2g** and **2h** have shown the best reactivity in Suzuki—Miyaura couplings of aryl halides.[22]

**IBiox and CAAC.** The facile formation of imidazolium salts from bioxazolines (Scheme 2) creates a rigid tricyclic backbone that allows for the design of carbene ligands (IBiox) with different properties.[12] Rigid, chiral ligands derived from chiral 1,2-amino alcohols or achiral ligands with flexible steric bulk derived from cycloalkyl-substituted amino alcohols with markedly different properties can be formed (Figure 2). The latter class has successfully been employed in a number of challenging cross-couplings of sterically hindered substrates (vide infra).

The restricted flexibility of the latter is a result of the ringflip of the cyclohexyl chair of IBiox6 providing several cycloalkyl conformations (Figure 2). A low-temperature NMR study (CD$_2$Cl$_2$, −80 °C) showed two sets of signals corresponding to the coexisting conformers **x** and **y** in a ratio of 2.4:1, respectively. With a coalescence temperature around −55 °C, these conformers rapidly interconvert at room temperature. This flexibility seems to be important in a number of challenging cross-coupling reac-
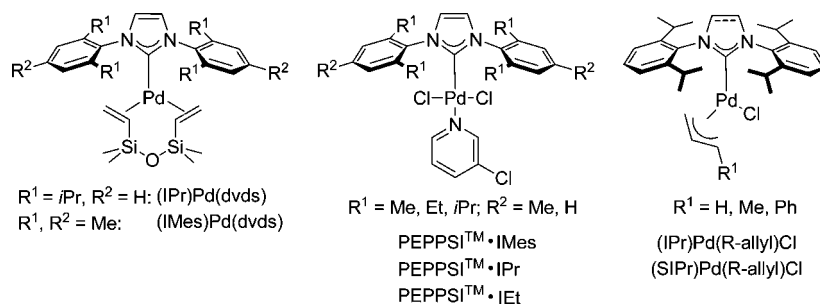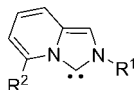
**FIGURE 7.** Imidazolydene—Pd-derived precatalysts.



**FIGURE 8.** Imidazo[1,5-*a*]pyridine-3-ylidene ligand.

**SCHEME 1.** Synthesis of Various Pyridine-Derived Imidazolium Bromides as Ligand Precursors



**2a**, R = H: 53%, **2b**, R = Me: 52%
**2c**, R = Ph: 47%, **2d**, R = OMe: 22%
**2e**, R = Br: 54%



**SCHEME 2.** Facile Synthesis of Bioxazoline-Derived Imidazolium Salts



tions, for example, in the synthesis of sterically demanding tetra-*ortho*-substituted biaryls in the palladium–IBiox-catalyzed Suzuki–Miyaura cross-coupling (vide infra).

Single crystals of the IBiox triflate salts were grown for X-ray structural analysis (Figure 11), providing an indication for the steric demand and some of the conformations accessible. However, it is important to note that whereas the cycloalkyl rings are constrained close to the IBiox ligand core, further away they can exist in several favorable conformations.
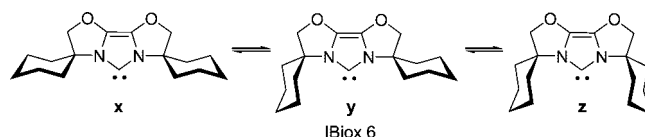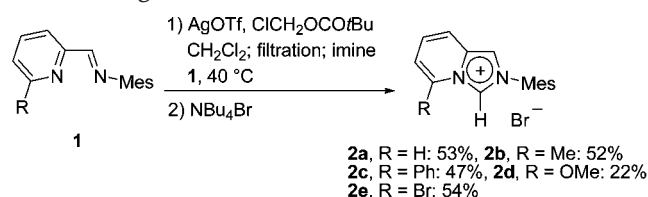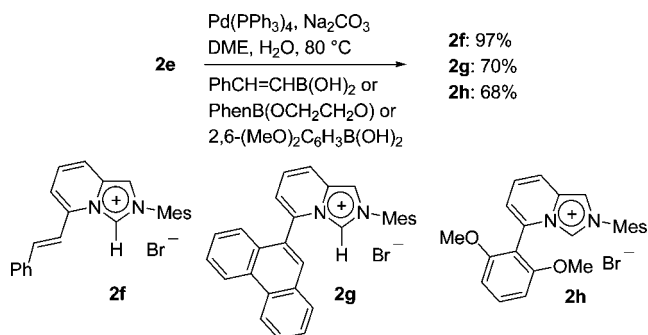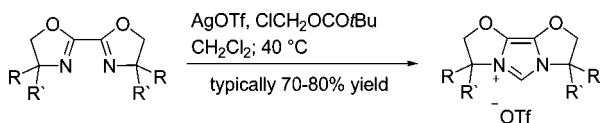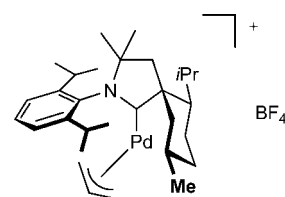


**FIGURE 9.** Different conformations of IBiox6 and CAAC ligand bearing cyclohexyl groups.



**FIGURE 10.** Stable cationic 14 e⁻ palladium complex.

The concept of sterically flexible ligands has also been recognized by Bertrand et al. in the development of a novel class of cyclic (alkyl)(amino) carbenes (CAACs, Figure 9).[24] These carbenes are based on a pyrrolidine ring bearing two quaternary carbon centers, thus rendering these carbenes more electron-rich than most other NHCs. Moreover, whereas IBiox6 and CAAC b can adopt different conformations, the introduction of substituents on the cyclohexyl ring in CAAC c results in a locking of the more sterically demanding conformation (shown in Figure 9) in order to avoid unfavorable 1,3-diaxial interactions. As a result of a "wall of protection", a unique coordinatively and electronically unsaturated 14-electron palladium species was obtained using CAAC c (Figure 10). The steric demand of the ligand prevents dimerization of the unsaturated palladium species, and agostic/anagostic interactions[25] stabilize the cationic metal center electronically.[26]

## Application of NHC Ligands in Catalysis

### Suzuki–Miyaura Cross-Coupling of Sterically Demanding Substrates.

NHC ligands with certain flexibility of their steric bulk and coordination mode can provide several advantages in

**TABLE 3.** Suzuki–Miyaura Cross-Coupling of a Sterically Hindered Aryl Chlorides Resulting in Tri-*ortho*-Substituted Biaryl **3**[a]
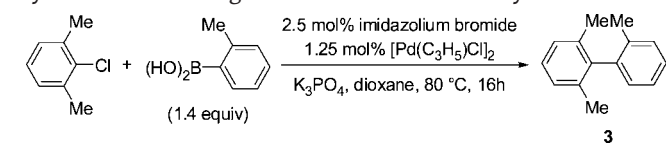
| entry | ligand | yield of **3**[a] |
|-------|--------|-------------------|
| 1 | **2a** | <10 |
| 2 | **2b** | 30 (28) |
| 3 | **2c** | (27) |
| 4 | **2d** | (<10) |
| 5 | **2f** | (<10) |
| 6 | **2g** | 78 |
| 7 | **2h** | 67 (69) |

[a] Yield of isolated product; GC yield in parentheses.

the conversion of sterically demanding substrates. Sterically very demanding NHCs may facilitate the formation of a catalytically active species,[27] as well as enhance the reductive elimination step.[28] On the other hand, oxidative addition or transmetalation steps might be slowed by steric demand.

Using the pyridine-derived imidazolium salts **2** as ligand precursors, we investigated the Suzuki–Miyaura cross-coupling of sterically demanding aryl chlorides with aryl boronic acids to give di- and tri-*ortho*-substituted biaryls (Table 3). Substantial differences were found between the different ligands. For example, employing 2.5 mol % catalyst, most ligand/palladium combinations produced only low amounts of the desired product **3** (Table 3). In contrast, ligands **2g** and **2h** lead to the formation of di- and tri-*ortho*-substituted biaryls in respectable yields of up to 78% isolated yield. In these cases, steric shielding or hemilabile binding might be beneficial for the stability of a monoligated Pd catalyst. Ligands derived from **2g** (R = phenanthryl) and **2h** (R = 2,6-dimethoxyphenyl)[29] are especially suited for this kind of σ-interaction, since they exhibit reduced aromaticity and increased electron-richness.

The preformed (IAd)₂Pd complex dissociates in solution to give a monoligated palladium complex being one of the most active catalysts for the Suzuki–Miyaura coupling of nonactivated aryl chlorides at room temperature.[30] However, sterically demanding substrates containing *o*-substituents were not tolerated under these mild reaction conditions. Intriguingly, the structurally rather similar IBiox6 ligand could successfully be applied to these otherwise difficult cases. The corresponding in situ formed palladium–IBiox6 complex catalyzes the coupling of sterically demanding aryl chlorides with arylboronic acids efficiently to generate di- and tri-*ortho*-sustituted biaryls at room temperature (Table 4).

Encouraged by these results, a family of IBiox ligands with varying cycloalkyl ring sizes was prepared, ranging from the
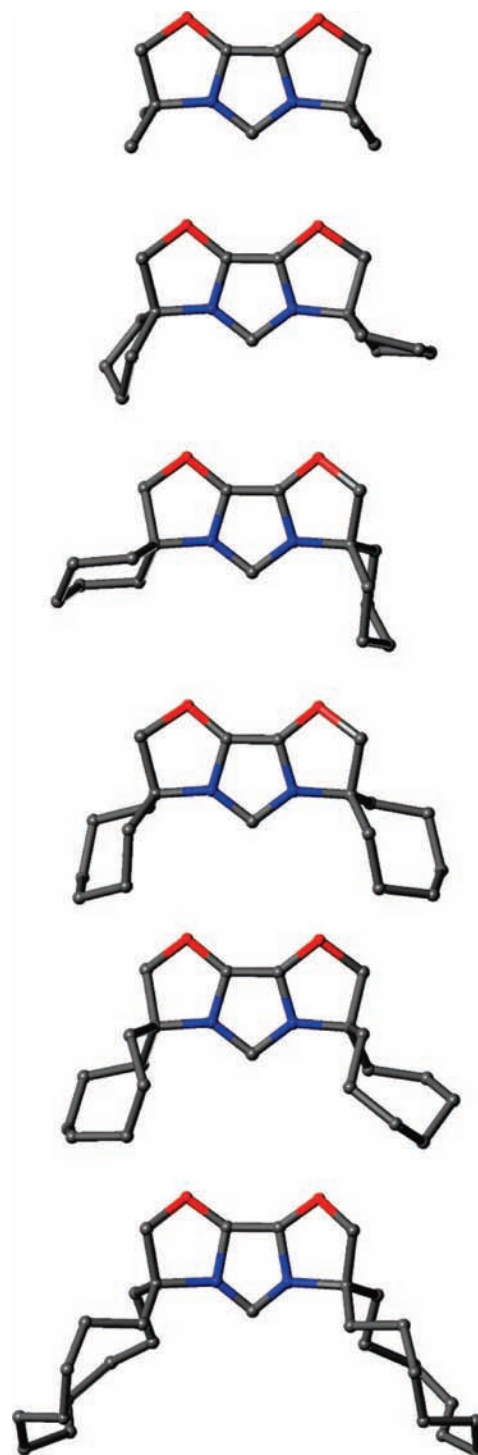


**FIGURE 11.** X-ray structures of the IBiox·HOTf salts of IBioxMe₄, IBiox5, IBiox6, IBiox7, IBiox8, and IBiox12. Hydrogen atoms and triflate anions are omitted for clarity.

five-membered cyclopentyl-substituted IBiox5 to the sterically more demanding cyclododecyl-substituted IBiox12 (see Figure 2).[12] The open-chain tetramethyl-substituted IBioxMe₄ was synthesized for comparison. This represents a series of related ligands with similar electronic character and different steric demand, ideal for a systematic optimization of a reaction. Con-

**TABLE 4.** Suzuki−Miyaura Cross-Coupling of Sterically Demanding Aryl Chlorides and Boronic Acids
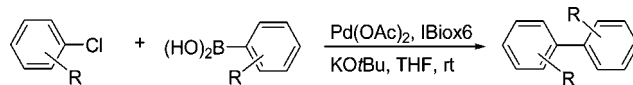


| Entry | Aryl chloride | Boronic acid | product | Yield [%] |
|---|---|---|---|---|
| 1 | | | | 94 |
| 2 | | | | 87 |
| 3 | | | | 70 |
| 4 | | | | 95 |
| 5 | | | | 76 |
| 6 | | | | 66[a] |

[a] Reaction conducted at 60 °C.
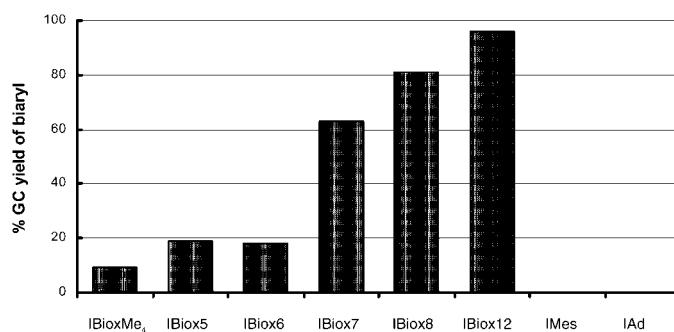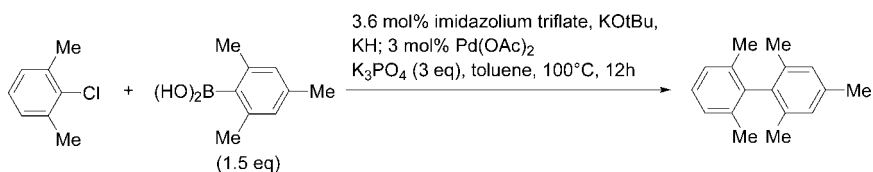




**FIGURE 12.** Screening of ligands for Suzuki−Miyaura cross-coupling of sterically hindered substrates.

sequently, these ligands were found to be useful for the difficult formation of tetra-*ortho*-substituted biaryls starting from aryl chlorides by Suzuki−Miyaura reactions. The results of an initial screening are shown in Figure 12.

Preliminary experiments of the Suzuki−Miyaura coupling of 1-chloro-2,6-dimethylbenzene and 2,4,6-trimethylbenzeneboronic acid identified toluene and $K_3PO_4$ as optimal solvent/base combination. Using the toluene/$K_3PO_4$ system and
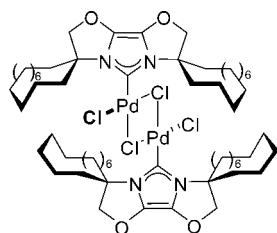
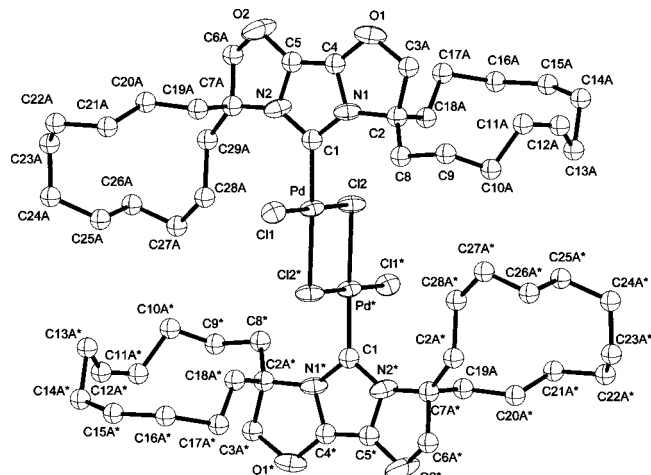**FIGURE 13.** Palladium(II) precatalyst [(IBiox12)PdCl$_2$]$_2$.



**FIGURE 14.** X-ray structure of [(IBiox12)PdCl$_2$]$_2$, showing one of the conformations of the disordered cyclododecyl rings. Selected distances (Å) and angles (deg): Pd−C1 1.944(5); Pd−Cl1 2.285(1); Pd−Cl2 2.337(1); Pd−Cl2* 2.415(1); C8···Pd 3.627(6); plane(Pd, C1, Cl1, Cl2, Cl2*)/plane(Pd, C1, N1, N2, C4, C5) 85(3).

an excess of the aryl boronic acid (1.5 equiv), a combination of Pd(OAc)$_2$ and IBioxMe$_4$·HOTf, IBiox5·HOTf, or IBiox6·HOTf gave only small amounts of the desired cross-coupled product (Figure 12). In these cases, the main product was 2,4,6-trimethylbenzene formed by proto-deboronation, which is a well-known side reaction of sterically demanding substrates.[31] Use of IBiox7·HOTf and IBiox8·HOTf resulted in significantly increased product formation. Gratifyingly, still more product was formed by using the IBiox12 ligand (96%). It is important to note that under the same conditions IMes·HOTf and IAd·HOTf failed to provide substantial amounts of product (Figure 12).

In order to demonstrate the efficacy and generality of this catalytic system, several biaryl derivatives were prepared from sterically hindered aryl chlorides and aryl boronic acids.[12c] In all cases, around 3% homocoupling of the boronic acid was obtained, presumably originating from the reduction of the Pd(II) precatalyst. Whereas water was tolerated and sometimes even beneficial in the synthesis of di- and tri-*ortho*-substituted biaryls at ambient temperature,[12b] the use of strictly anhydrous conditions was found optimal for tetra-*ortho*-substituted biaryls since it minimized the competing proto-deboronation of the aryl boronic acid.[32] Thus, the use of dry reagents like

**TABLE 5.** Suzuki−Miyaura Couplings of Aryl Chlorides Resulting in Tetra-*ortho*-Substituted Biaryls$^a$

| entry | ArX | Ar'B(OH)$_2$ | Product | Yield |
|---|---|---|---|---|
| 1 | | | | 91 |
| 2 | | | | 96 |
| 3 | | | | 71$^b$ |
| 4 | | | | 87$^{c,d}$ |
| 5 | | | | 75 |
| 6 | | | | 78 |
| 7 | | | | 89 |
| 8 | | | | 82 |
| 9 | | | | 83 |
| 10 | | | | 87 |
| 11 | | | | 65$^d$ |
| 12 | | | | 69 |
| 13 | | | | 70 |
| 14 | | | | 47 |

$^a$ Reaction conditions: 1.0 mmol of ArX, 1.5 mmol of Ar'B(OH)$_2$, 3 mmol of K$_3$PO$_4$, 3.6 mol % IBiox12 (from IBiox12·HOTf, KH, cat. KOtBu), 3 mol % Pd(OAc)$_2$ in THF (0.5 mL), toluene (2.5 mL), 110 °C, 16 h; yield of isolated products. $^b$ 3 mol % of complex [(IBiox7)PdCl$_2$]$_2$. $^c$ 3 mol % of complex [(IBiox12)PdCl$_2$]$_2$. $^d$ 0.5 mmol scale.

finely ground, flame-dried K$_3$PO$_4$ gave best results. As shown in Table 5, IBiox12 proved to be an excellent ligand for the

**TABLE 6.** Ligand Screening in the Intermolecular α-Arylation of Aryl Chlorides with Phenylethylketone
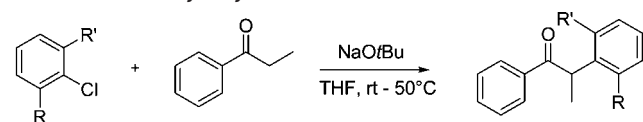


R = H, R' = H
R = Me, R '= Me

| Entry | Ligand | R | R' | Yield [%] |
|-------|--------|---|----|-----------|
| 1 | | H | H | 22 |
| 2 | Ar—N (CAAC **a**) | H | Me | 0 |
| 3 | | Me | Me | 0 |
| 4 | | H | H | 29 |
| 5 | Ar—N (CAAC **b**) | H | Me | 10 |
| 6 | | Me | Me | 81[a)] |
| 7 | | H | H | 100 |
| 8 | Ar—N *iPr* | H | Me | 82 |
| 9 | Me (CAAC **c**) | Me | Me | 0 |

*a* 50 °C, 20 h. Yield = 61%, rt, 16 h.

synthesis of tetra-*ortho*-substituted biaryls in good yields. Many different *ortho*-substituents, including methyl, ethyl, fluorine, and methoxy, can be accommodated. These results represent the first Suzuki−Miyaura cross-coupling of aryl chlorides to give tetra-*ortho*-substituted biaryls with *ortho*-substituents that are methyl or larger.

Heating IBiox12·HOTf with Pd(OAc)$_2$ in the presence of LiCl and Cs$_2$CO$_3$ with dioxane as solvent results in the formation of [(IBiox12)PdCl$_2$]$_2$, an efficient precatalyst (Figures 13 and 14).[12b] It is interesting to note that a relatively short Pd···C contact (3.6 Å) between a carbon atom of the cyclododecyl ring (C8 in Figure 14) and the metal can be found in this complex, indicative of a weak C−H···Pd interaction. This kind of stabilizing agostic or anagostic interaction should become even more important for the stabilization of unsaturated palladium catalysts formed in the course of a catalytic transformation. This might be one important mode of action of these IBiox ligands, allowing longer catalyst lifetime and generating a larger amount of catalytically active species.

**The Alkyl Sonogashira Cross-Coupling.** For a long time the application of nonactivated *alkyl* halides, especially secondary and tertiary ones, in cross-coupling reactions remained elusive, due to a difficult oxidative addition step and possible side reactions like β-hydride elimination. Recently, catalyst systems have been developed that can oxidatively add to

alkyl halides and suppress side reactions and thereby allow the cross-coupling of these substrates.[33,34] The Sonogashira coupling[35] of alkynes with organic halides is an efficient method for the synthesis of differently substituted alkynes, versatile synthetic intermediates and also important motifs of biologically active compounds. Generally, aromatic halides have been used as the alkyne coupling partner. Fu et al. developed the first examples of a palladium-catalyzed cross-coupling of *primary* alkyl bromides and iodides with terminal alkynes.[36] In comparison, *secondary* alkyl halides possess an increased steric bulk and electronic richness that lowers their tendency for oxidative addition. Again the IBiox−palladium complexes serve as efficient catalysts; best results were obtained with the preformed [(IBiox)7PdCl$_2$]$_2$ complex.[37] Because of the mild reaction conditions various functional groups on the alkyl bromides are well tolerated, for example, esters and epoxides (Figure 15). However, the intolerance of functional groups on the alkyne cross-coupling partner still represents a significant limitation.

**The Palladium-Catalyzed α-Arylation of Ketones: Effects of Ligand Flexibility.** The reactivity of several (CAAC)Pd(allyl)Cl complexes was examined in the challenging intermolecular α-arylation of arylchlorides with phenylethylketone (Table 6).[24] This type of reaction was developed in 1997 independently by the groups of Buchwald,[38] Hartwig,[39] and Miura.[40] However, no catalyst has been able so far to catalyze this coupling with aryl chlorides at room temperature.

Three different aryl chloride substrates with different levels of steric hindrance were employed. CAAC a, the least sterically demanding ligand was found to provide low yields at best. On the other hand, the most sterically demanding CAAC c ligand is very effective in the α-arylation of the unsubstituted chlorobenzene. After 1 h at room temperature the reaction was finished and quantitative yields were obtained (Table 6, entry 7). However, increasing the steric hindrance of the aryl chloride deteriorates the yield (Table 6, entries 8 and 9). Interestingly, whereas the cyclohexyl-substituted CAAC b exhibiting flexible steric bulk gave rather low yields with the less sterically demanding aryl chlorides, it gave a good yield with the 2,6-dimethyl chlorobenzene (entries 4−6). Thus, ligands CAAC b and CAAC c are complementary in their substrate scope. These results by Bertrand et al. are an additional example of the advantages of sterically flexible ligands in the cross-coupling of sterically demanding substrates.
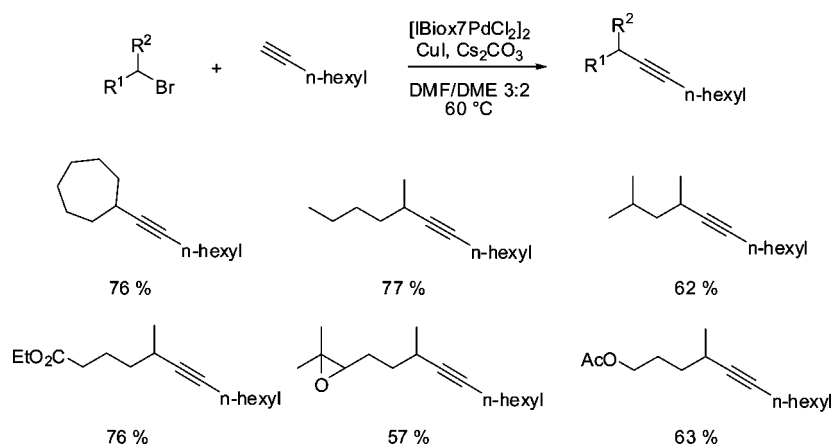
**FIGURE 15.** Representative examples for the Sonogashira reaction of secondary alkyl bromides using the $[(IBiox7)PdCl_2]_2$ catalyst.

## Conclusion

In the last couple of years, NHCs have transformed from laboratory curiosities to standard ligands for many catalytic transformations. Sterically demanding NHCs have been found to be especially valuable, and in many cases, the unique impact on the metal's coordination sphere has been key to success. Some aspects like the formation of unsaturated metal complexes, stabilization of labile intermediates, or dynamic behavior of the ligands have been highlighted in this Account. The design of NHC ligand families whose electronic and steric properties can be independently varied has been another major improvement. In addition, the understanding of the electronic, steric, and dynamic properties of NHCs will allow the design of more sophisticated ligand systems for numerous novel applications.

### BIOGRAPHICAL INFORMATION

**Sebastian Würtz** was born 1977 and raised in Eschenburg, Germany. He received his diploma degree in organic chemistry in 2005 at the Philipps-Universität Marburg. At present, he is a Ph.D. student in the research group of Professor F. Glorius at the Westfälische Wilhelms-Universität Münster. His research interests are focused on the synthesis and application of novel N-heterocyclic carbenes and the development of new methodologies in field of transition-metal-catalyzed C—H activation.

**Frank Glorius** studied chemistry at the Universität Hannover, Stanford University (Prof. Paul A. Wender), the Max-Planck-Institut für Kohlenforschung and Universität Basel (Prof. Andreas Pfaltz), and Harvard University (Prof. David A. Evans). In 2001, he began his independent research career at the Max-Planck-Institut für Kohlenforschung in Germany (Prof. Alois Fürstner) and in 2004 was promoted to Associate Professor for Organic Chemistry at the Philipps-Universität Marburg. Since 2007, he has been Full Professor at the Westfälische Wilhelms-Universität Münster. His research focuses on the development of new concepts for catalysis and their implementation in organic synthesis.

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