Wege zur Synthese ungewöhnlich substituierter Polyaromaten

Synthetic Routes towards Unusually Substituted Polyaromatic Compounds

Dissertation zur Erlangung des Doktorgrades

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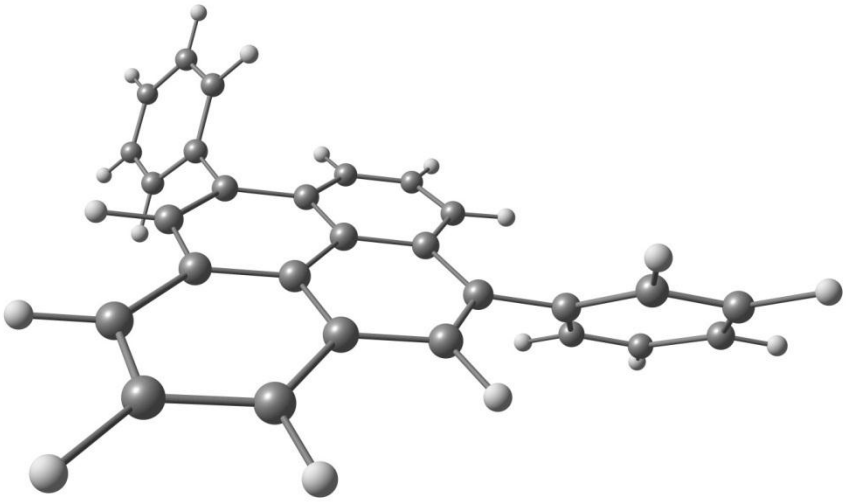

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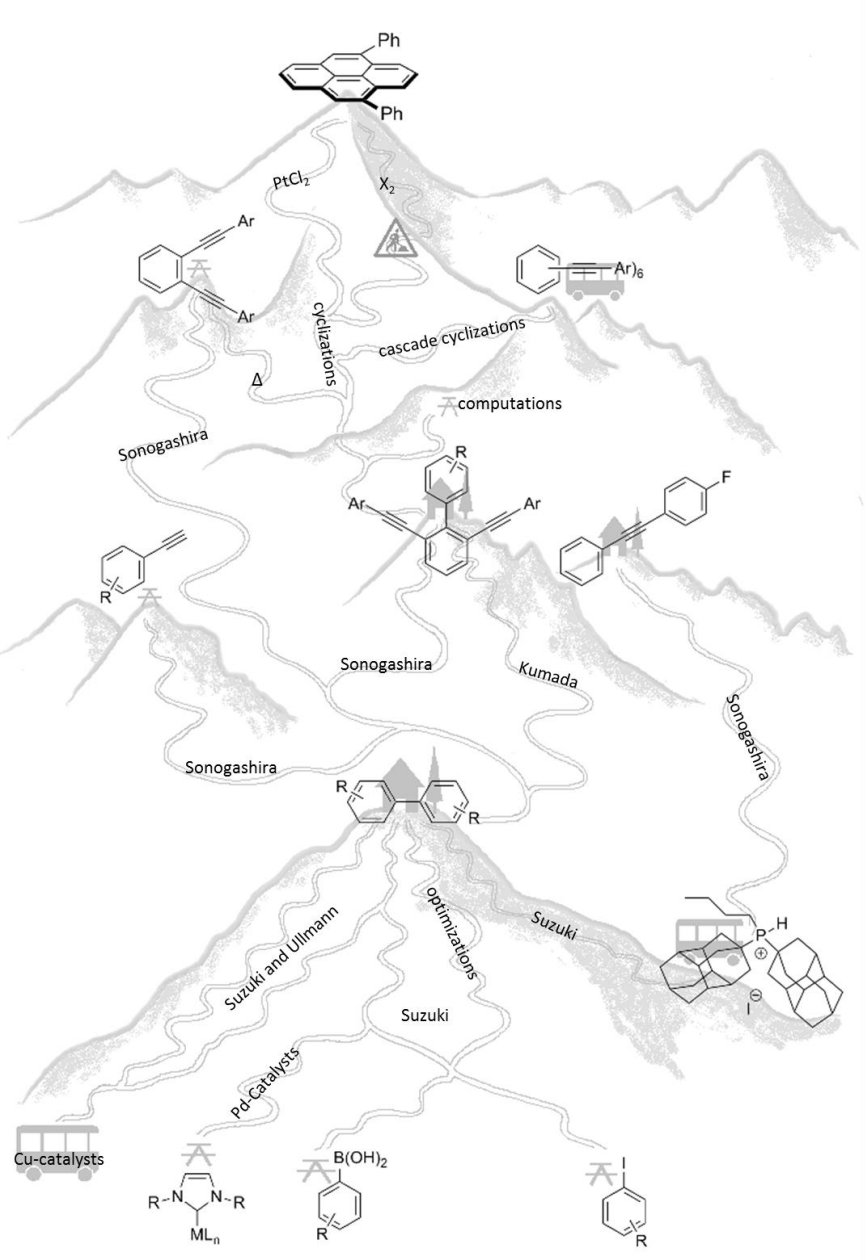
Friedrich von Schiller

Motivation

It is no longer possible to imagine everyday life without LEDs (acronym for Light Emitting Diodes). We often come across them for example in smartphones, tablet computers and flat screens. In some cases these LEDs or LCDs (liquid crystal displays) are already being replaced by OLEDs (Organic LEDs). The goal of this thesis is to develop an elegant path to obtain pyrene-based materials suitable for OLEDs not by employing the toxic basic pyrene scaffold, but rather using cross couplings and, as a final step, a cyclization reaction to obtain these pyrene derivatives with unusual substitution patterns.



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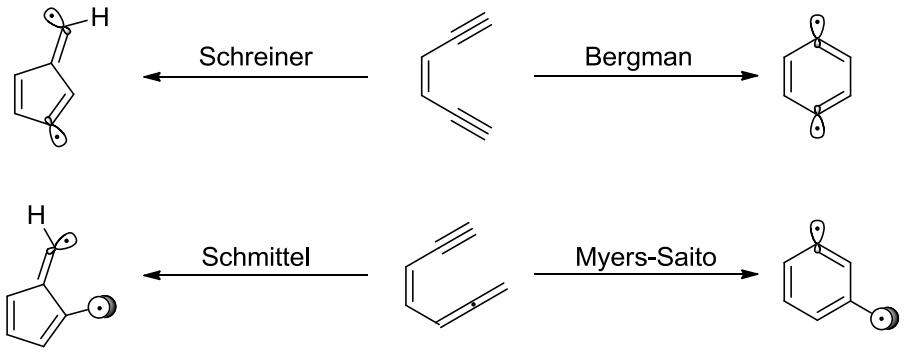
1 Introduction

1.1 Cyclizations

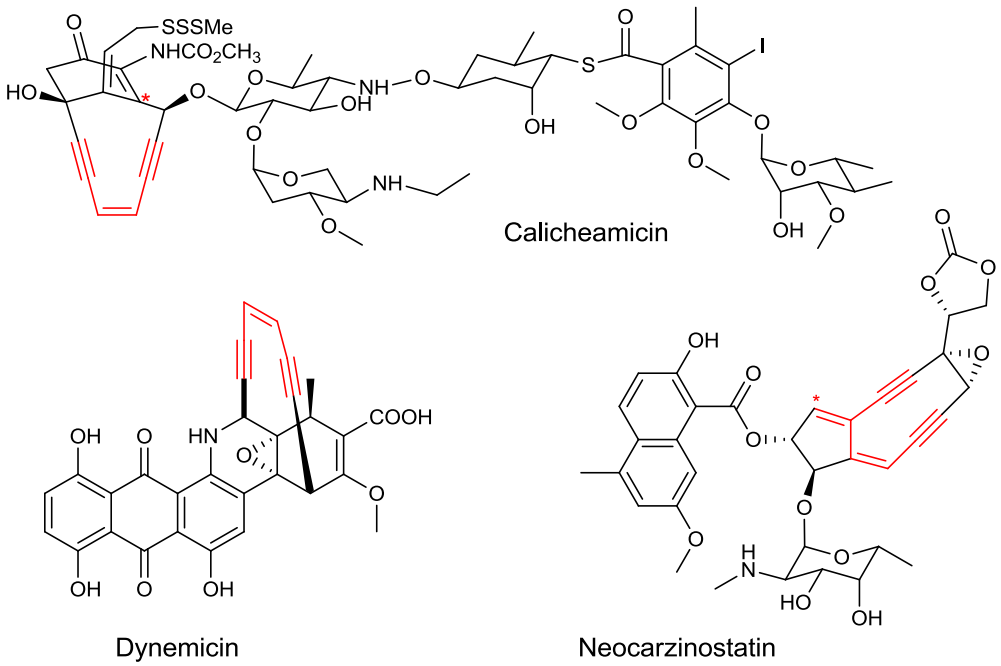
Cyclization reactions are an elegant path to obtain rings especially aromatic or even polyaromatic ring systems. Chemists distinguish between the different ways of initiations (electrophilic, thermic and photochemical), the course of the reactions (*via* radical or cationic intermediates) and also the connectivity of the ensuing cyclic structures.[1]



Scheme 1 Cyclizations passing through diradicaloid intermediates.[2]

C^1–C^6 cycloaromatizations (Bergman-type) of enediynes and also C^2-C^7 (Myers-Saito-type) and C^2–C^6 cycloannulations (Schmittel-type) of enyne-allenes could be the mode of action of naturally occurring antitumor compounds because of their diradical intermediates (Scheme 1).[3] Already in 1995, Schmittel *et al.* observed the cleavage of DNA *in vitro* due to an alternative C^2–C^6 cyclization of enyne allenes, which leads to fulvene diradical intermediates and subsequent H-abstraction from DNA, which entails the cutting feature.[4]

Owing to the formation of these diradical intermediates, such systems can act as anti-cancer drugs. H-abstraction from DNA occurs, resulting in scission of the double helix and, ultimately, cell death. Prototypical compounds for such efficient “cell killers” are Calicheamicin, Neocarzinostatin and Dynemicin (Scheme 2).[5]

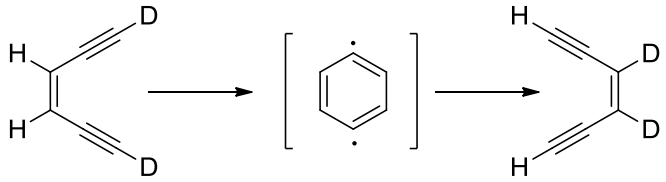


Scheme 2 Natural anti-tumor agents

These natural compounds remain a challenge both for pharmaceutical and synthetic researchers because they need to be able to induce cyclization under physiological conditions and require a selective trigger mechanism to initiate the cyclization process, which generates the cytotoxic diradical intermediates. For Calicheamicin and Neocarzinostatin the cyclization is initiated by conjugate addition of a thiolate nucleophile (Michael addition, see asterisk in Scheme 2) and resulting increased ring strain. In Dynemicin reduction followed by epoxide ring opening causes spontaneous cyclization of the enediyne moiety. However, these miscellaneous natural anti-tumor agents are not very selective as their cyclization reactions cannot be controlled yet. Favorably, the trigger should launch the cyclization *via* diradical formation only when the drug is in proximity to DNA molecules of transformed cells.[3,5a,6]

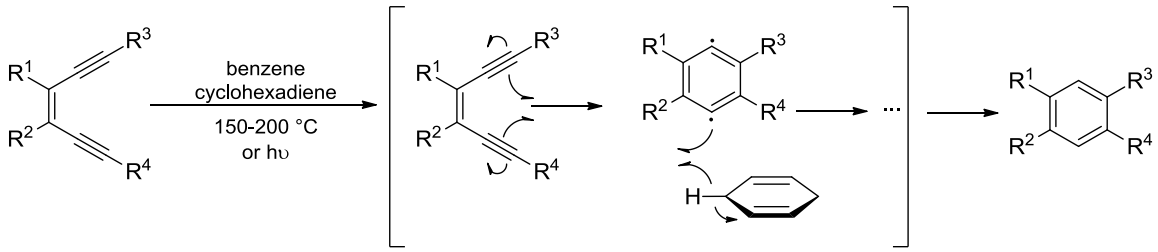
The Myers-Saito products are formed preferentially from sterically undemanding enyne allenes or those precursors carrying substituents that do not stabilize radical formation, whereas the Schmittel-type C^2–C^6-cyclization occurs preferably under kinetically controlled conditions and by stabilization of the fulvene biradicals by its substituents. The Bergman cyclization is a thermal pericyclic reaction, which proceeds in a concerted fashion and as usual in pericyclic reactions two (or more) bonds form (and/or break). Mechanistic proof for the thermal Bergman cyclization and rearrangement proceeding concertedly *via* an intermediate biradical has been reported by Bergman *et al.* by

deuterium labeling experiments.[3,7] The 1,4-didehydrobenzene diradical forms as the reactive intermediate before cycloaromatization takes place. If the radical scavenger is missing, the diradical intermediate again forms an enediyne as depicted in Scheme 3.



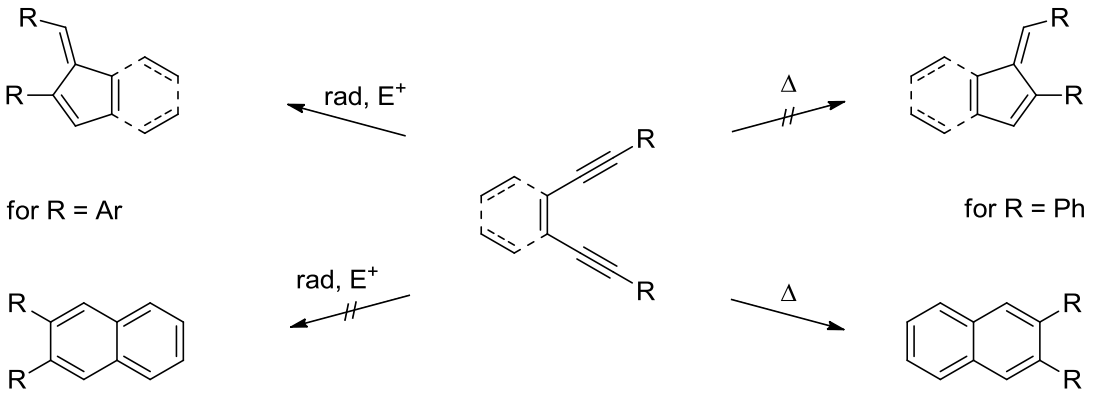
Scheme 3 Deuterium labeled Bergman cyclization

The ring closure towards the non-conjugated σ,σ-diradical is an endothermic process and requires high temperatures (Scheme 4). It is caused by the formation of two new C–H-bonds due to addition of two H-atoms provided by an H-donor. The reaction is irreversible.[8] Computations of thermally induced diradical cyclizations (BLYP/6-31G(*d*) level of theory) indicate that π-acceptors do not increase the thermal reactivity of enediynes.[9]



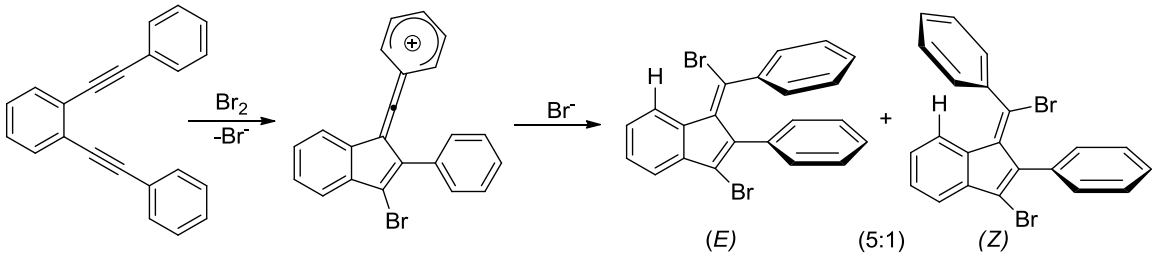
Scheme 4 Thermally induced Bergman cyclization

Comparing the two different types of cyclization precursors incorporating alkyne moieties, the basic structural element save either an enediyne system carrying aryl substituents or phenylethynylbiphenyls (note: these structures incorporate enyne motifs only). As mentioned above, under thermal cyclization conditions, enediynes usually give the aromatic Bergman products while radical or cationic initiation gives fulvenyl derivatives (Scheme 5).



Scheme 5 Cyclization of enediynes

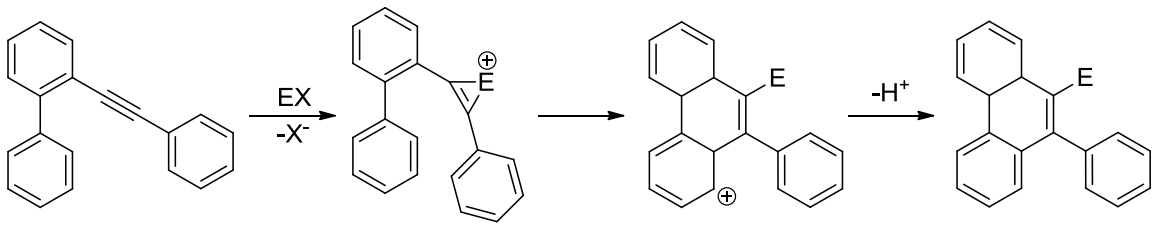
Schreiner *et al.* found much higher barriers for the thermally induced cyclization of the enediyne moieties of C^1–C^5 diradicalic cyclizations than for the formation of the C^1–C^6 diradicalioid Bergman intermediate (41 kcal mol^{-1} *vs.* 25.5 kcal mol^{-1}) at the (UBS)-BLYP/6-31G(*d*) level of theory.[10] But Pascal *et al.* found a thermally induced C^1–C^5-annulation of 1,2-bis(2,4,6-trichlorophenyl)ethynylbenzene and argue that steric effects are responsible for the formation of five-membered rings.[11] In this thesis, it will be investigated if this C^1–C^5-cyclization is really caused by steric effects or by stabilization of the diradical intermediate, which could be proven by replacing the trichlorophenyl-group by mesityl- and 4-nitrophenyl-groups as substituents. The kinetically favored C^1–C^5 product always forms by triggering the annulation with radicals or electrophiles. An electrophilically induced cyclization, *i.e.*, with Br_2, leads to fulvene derivatives *via* a cationic intermediate (Scheme 6).[12] This electrophilically induced, regioselective 1,5-cyclization was reported by Schreiner *et al.* and built on work by Whitlock from 1966.[13] The observation of *E*- and *Z*-products led to the deduction of a mechanism proceeding *via* a resonance-stabilized vinyl cation.[13] Usually an electrophilic attack of bromine at C–C double bonds at first gives a bromonium ion (electrophilic addition for alkenyl substrates and electrophilic substitution of aryls). The crystal structure of the majority *E*-product and the excess of *E*- over *Z*- product was explained based upon steric congestion: coplanar orientation of the peripheral phenyl rings in the *E*-products was found while in the *Z*-products, a perpendicular arrangement of these phenyl groups is found, reducing overall resonance stabilization of the benzofulvene moiety.[12]



Scheme 6 Electrophilically induced cyclization of enediynes.

In the present work, we take advantage of these electrophilically induced cyclizations to obtain the desired pyrene derivatives starting from enyne systems. As described above, this is successfully applied to the enediyne starting materials, however, in this section we focus on enynes, *i.e.*, ethynyl-1,1-biphenyl-systems, with researchers such as Larock and Fürstner as the leading experts for their preparation.[1b,14]

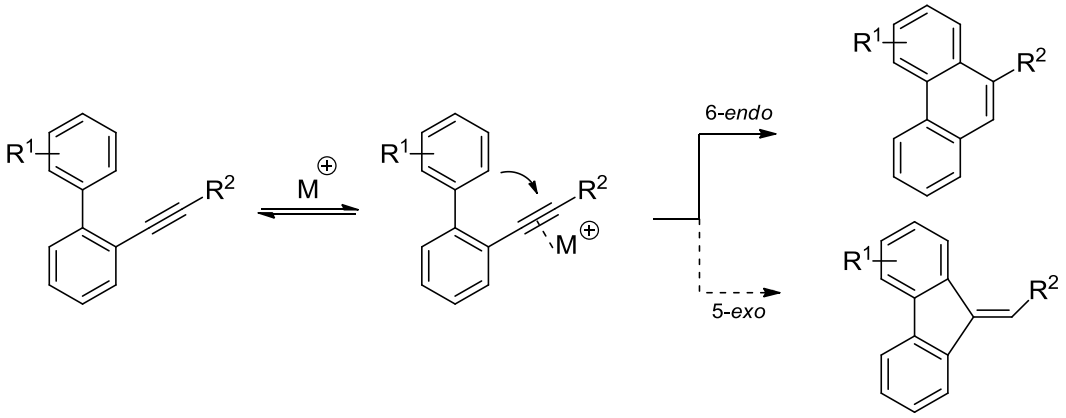
Electrophilically induced phenylethynylbiphenyl systems (enynes) cyclize intramolecularly to phenanthrene derivatives. The scope of this thesis is using regioselective twofold coupling of 2,6-(phenylethinyl)biphenyls to obtain pyrene derivatives. Larock's and Swager's carbo-cyclization is initiated by (halogenium-) cations to produce such rigid polycyclic aromatics (Scheme 7).[1a]



Scheme 7 Larock's scheme for an electrophilically induced cyclization, E^+ = I, Br, *p*-$O_2NC_6H_4S$

This electrophilic annulation was also demonstrated by Fürstner *et al.* as a versatile route to substituted phenanthrene derivatives using transition metal catalysts. Starting with enynes, in accordance with the Baldwin rules two various possible products were expected. Baldwin's rules rationalize how the ring closure takes place with respect to the orbitals involved, including a classification of the number of atoms in the newly formed ring.[10] For a cationic ring closure the Baldwin rules classify the prospective ring size. For the structures described herein, this means formation of a carbon-carbon bond and the position of the bond cleaved during ring closure. This can be described by "*exo*" and "*endo*", referring to the arrangement of the group where the bond has been cleaved to the outside of the new ring or incorportaed into the new ring, respectively (Scheme 8). The last classification is the hybridization of the "electrophilic" carbon. "Dig" indicates *sp*

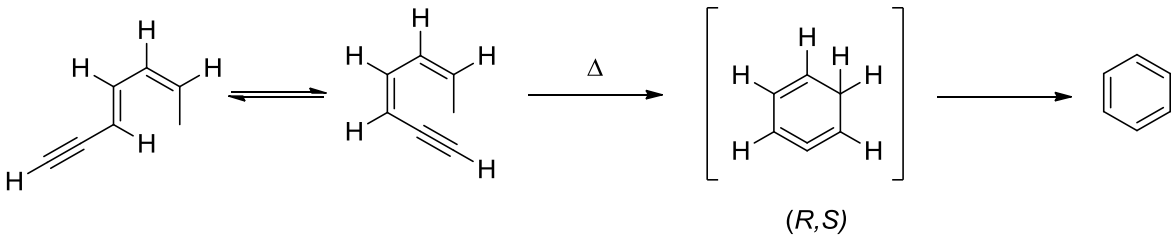
hybridization, "trig" sp^2 and "tet" sp^3 hybridization, respectively. Scheme 8 shows two "dig" cyclization paths.



Scheme 8 Fürstner's mechanism for dig-annulations[14]

Fürstner reiterated the concept of Larock and Swager, but instead of adding an electrophile to a biphenyl also bearing an alkyne unit in *ortho*-position, Fürstner used metal catalysts (*i.e.*, $PtCl_2$, $AuCl_3$, $GaCl_3$, $InCl_3$), which coordinate to the triple bond thereby triggering a 6-*endo*-dig cyclization to give the phenanthrene derivative. This conversion is initiated through π-coordination of the metal species to give a η^2-metal species at the triple bond that is subsequently attacked nucleophilically by the adjacent aryl ring. Fürstner described two alternative courses of this cycloisomerization.[1c,14]

For the sake of completeness, another type of cyclization has to be mentioned, which involves acetylenic derivatives, known as Hopf cyclization of hexa-1,4-dien-5-ynes to benzene (Scheme 9).[15]



Scheme 9 Hopf cyclization

These concepts are analyzed and extended in the present thesis. The cyclizations described above enabled the preparation of a number of novel pyrene derivatives, as has recently been shown by Davis *et al.* as well as Schreiner *et al.* These operations are covered in Chapter 3.[16]

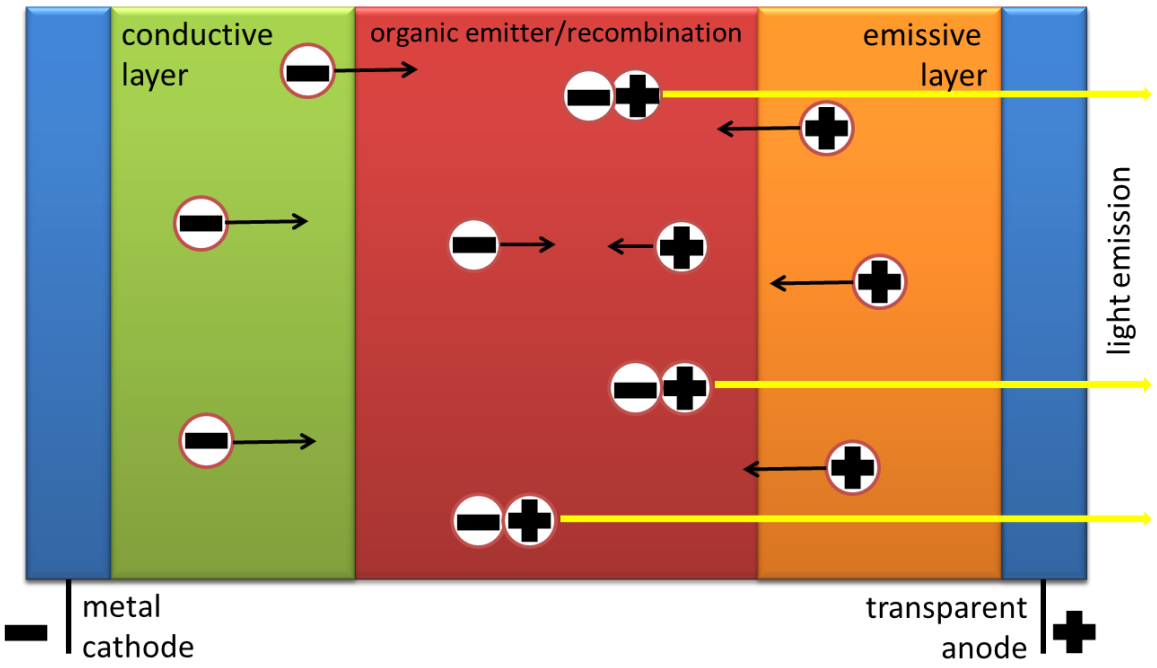
1.2 Pyrenes and OLEDs

Pyrenes belong to the family of polycyclic aromatic hydrocarbons (PAHs), which are molecules consisting of multiply fused benzene rings. Parent pyrene contains four condensed phenyl rings and this "darling of the photochemists" is named after the Greek word for fire.[17] The discovery of pyrene was reported in 1837 by Laurent, who found it in the residue of distillation of coal tar. Galletly characterized pyrene in 1864.[18] In 1871, Gräbe succeeded in the extraction of pyrene out of the residue of destructive distillated coal tar with CS_2 and further purified pyrene by crystallization with picric acid.[18] He also reported functionalizations, *e.g.*, with bromine, but suggested an incorrect structure.[18] The first synthesis of pyrene was accomplished by Weitzenböck in 1913.[19] In the 1950s, other synthetic methods to synthesize pyrene and its derivatives were discovered.[17] Pyrene's optoelectronic activity was reported for the first time by Kasper and Förster in 1954.[20]

Nowadays, pyrenes are associated with attractive electronic and optoelectronic properties for use as building blocks for organic electronics. They are already used in organic light emitting diodes (OLEDs), organic field-effect transistors (OFETs), and organic photovoltaic devices (OPVs).[21] Organic pyrene-based materials are of interest for electroluminescent devices because of their high fluorescene quantum efficiency including the blue region of the visible spectrum and the possibility for fine tuning of solubility, stability, electron affinity, molecular packing, and the control of intermolecular interactions. This fine tuning is feasible because of the flexibility in varying the molecular architecture of the pyrene core structure through selection and variation of different substituents at dissimilar positions, thereby tuning the electronic properties of the material.

The success of OLEDs commenced in 1987 with the introduction of double layer OLEDs using TAPC (1,1-bis[(di-4-tolylamino)phenyl]cyclohexane) in combination with the emitter material 8-hydroxyquinoline aluminum (Alq_3) and indium tin oxide (ITO) as the anode.[21h] OLEDs are commonly built of an anode followed by an emissive (hole transport) layer, emitter layer (often Alq_3 and the organic material) and finally a metal or alloy layer as the cathode (Scheme 10). The negative potential at the cathode induces a current of negative charges, which recombine with the "electron holes" provided by the anode. Recombination of negative charges and holes is an exothermic process and forms

excitons. The excitons' deactivation through fluorescence or phosphorescence is measured as electroluminescence.[17]



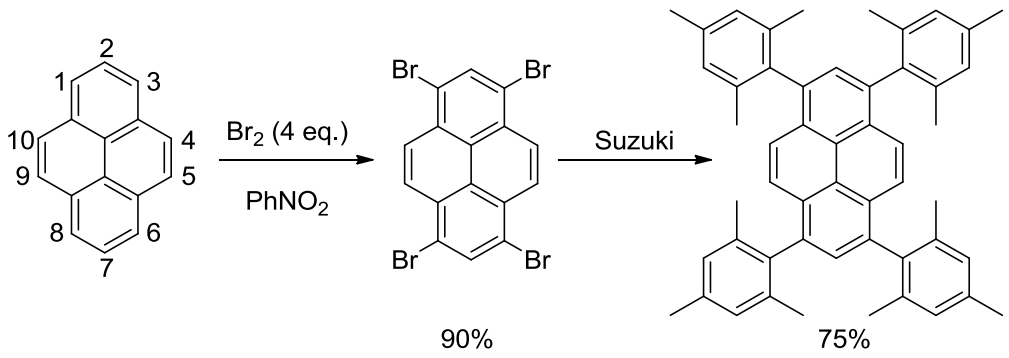
Scheme 10 Operating mode of an OLED

The efficiency of an OLED is characterized by three measures: the quantum efficiency, which is composed of the internal and external quantum efficiency (number of emitted photons divided by number of injected charges); the current efficiency (η_L, in units of cd A^{-1}), and luminous efficiency (η_p, in lm W^{-1}). In general the brightness of LEDs is given in cd m^{-2} and OLED devices reach values of about 75 cd m^{-2}.[22] For comparison: A common flat screen TV today reaches values between 1600 cd m^{-2}.[23]

A special property of pyrenes is their blue emission fluorescence when substituents are placed in such a way to avoid undesirable face-to-face π-π stacking interactions.[21c] Parent unsubstituted pyrene leads to a red shift in emission spectra. Pyrene derivatives that are designed to emit blue light have large band gaps and emit specific wavelengths.

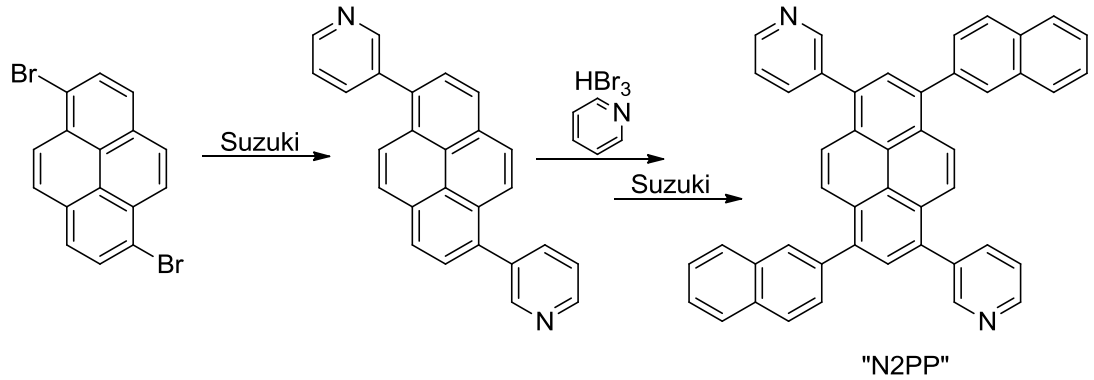
Traditional synthetic pathways to substituted pyrenes typically involve electrophilic halogenation of the parent pyrene and the most popular derivatives are the fine-tuned 1,3,6,8-tetrasubstituted pyrenes, which are prepared by halogenation and subsequent cross-couplings or Diels-Alder reactions.[17] The example depicted in Scheme 11 shows the preparation of 1,3,6,8-tetramesitylpyrene *via* Suzuki-Miyaura cross-coupling after tetrabromination as reported by Moorthy *et al.*[21c] This pyrene is a suitable blue emitter in

OLEDs and has a band gap of 3.19 eV. In solution, it emits blue light of 411 nm wavelength.



Scheme 11 Preparation of a 1,3,6,8-tetrasubstituted pyrene[21c,24]

It is well-known that pyrenes can be synthesized with substituents in nearly all positions, however, mostly not with various substituents.[17,25] Many examples exist for the modification in the 1-position, *e.g.*, ethynylpyrenes and pyrenecaroxyaldehydes.[24,26] Plenty of these pyrenens were synthesized recently.[17] A special representative is depicted in Scheme 12. The pyrene is an organic semiconductor in blue OLED devices with a bandgap of 2.94 eV and an absorption maximum at 386 nm.



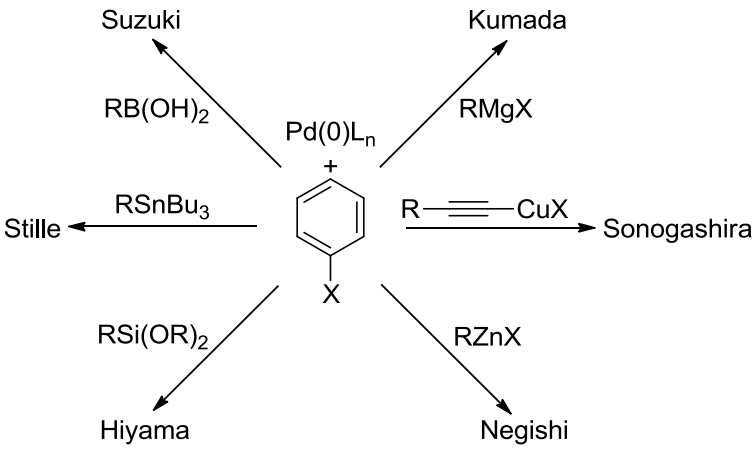
Scheme 12 Preparation of 1,6,-di(pyridine-3-yl)-3,8-di(naphthalene-2-yl)pyrene (N2PP)[27]

Furthermore, there are pyrenes disubstituted in 1,3-, 1,6-, 1,8- and 2,7-position, tetrasubstituted in 4,5,9,10- and hexasubstituted in 2,4,5,7,9,10-position. Substituted pyrenes are partly suitable for liquid crystals or to construct dendritic structures.[17]

1.3 Cross-Coupling Reactions

2,6-Dibromobiphenyl moieties are the core building block for our favored pyrenes. These biphenyls were prepared by Suzuki-Miyaura cross-coupling, a reaction belonging to the 2nd generation of palladium catalyzed cross-couplings. This "2nd generation" involves the

utilization of silicon, stannous, and boronic organyls. Originally discovered in 1982, this reaction earned Suzuki the 2010 Nobel Prize in chemistry. The subsequent step of our synthetic strategy is the phenylethynylation of these biphenyls *via* Sonogashira-Hagihara or Kumada-Tamao-Corriu cross-couplings, respectively. Both belong to the first generation of palladium catalyzed cross-coupling reactions, which are characterized by the utilization of electropositive metals such as copper, magnesium, aluminum, and zinc.[28] Strikingly, all these "1st generation" Pd-catalyzed cross-coupling reactions have been developed almost simultaneously in the mid-1970s. Cross-couplings are the most straightforward and general methods to form C–C-bonds. The Heck reaction preceded these achievements, however it does not involve organometallic substrates and is adhering to the general formula of consequently not considered part of the cross-coupling family, which is defined as $R^1M+R^2X \rightarrow R^1R^2+MX$ (Scheme 13).[28] This definition has later been expanded to also tolerate N, O and (semi)metals such as B, Si and Sn as coupling partners. These are summarized under the term '2nd-generation cross-couplings'. The most important members of this family are the Kumada-Tamao-Corriu reaction (1972),[29] Negishi and Sonogashira-Hagihara cross-couplings (1975/76),[30] and later Stille and Suzuki cross-couplings (1979-1982).[31]

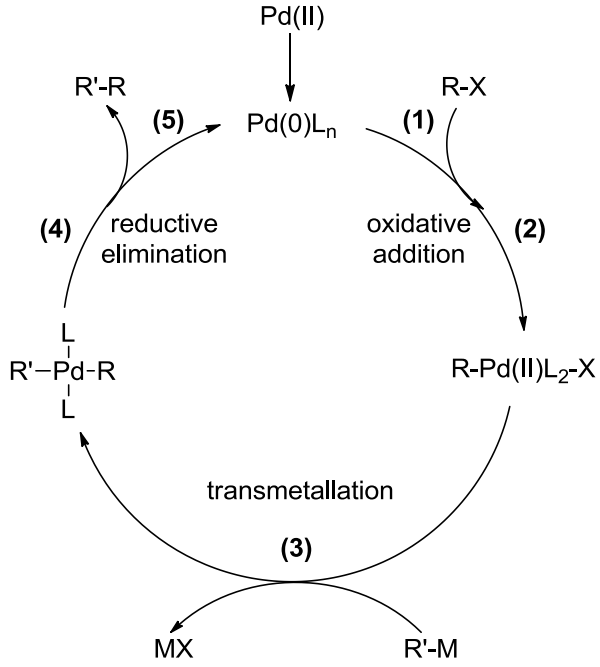


Scheme 13 Different Pd(0) catalyzed cross-coupling reactions using halo-benzenes

The role of the organometallic reagents is to transfer the organic moiety to the organopalladium intermediate. The first transition metal-catalyzed reactions, *i.e.*, Ni catalyzed, utilized Mg and Li organyls, led to unfavorable side reactions such as α- and β-eliminations, R^1-R^1 and R^2-R^2 homo-couplings, non-selective halogen-metal exchange, and low chemoselectivity. The evolution of the first generation cross-couplings focused on the central transition metal moving from Ni to Pd central atoms, as the latter species

are much less problematic with regard to side reactions such as stereoisomerization, regioisomerization, and other undesirable reactions of the substrates. With regard to the organometallic substrates, the evolution proceeded from RMgX, over $RAlX_2$, RZnX, RZrX to RBX_3. Within this series of organometallics, the reactivity of the organic moiety varied and the electrophilic character of these nucleophile substances enhanced and these are so more susceptible for nucleophilic attacks.[28]

The whole family of Pd catalyzed cross-coupling reactions proceeds *via* a similar mechanism, which can be illustrated by a catalytic cycle (Scheme 14). The Pd(II) precursor forms a Pd(0) complex *in situ* by losing one or two of four ligands, generating an electron-deficient complex. The catalytic cycle commences with step (1) – the activation of RX *via* oxidative addition.[32] The Pd(0)-complex possesses a fully occupied outer electron shell (d^{10}) and a tetrahedral configuration whereas the Pd(II)-complexes generated in the catalytic cycle have a square planar geometry, their electron shell being "understaffed" with only eight outer electrons (d^8). We will discuss the catalytic cycle individually for the cross-couplings of interest in the following.



Scheme 14 General catalytic cycle for cross-coupling reactions

This general catalytic cycle involves branching in the oxidative addition (2), transmetalation (3) and reductive elimination step (4), respectively. Oxidative addition affords stable *trans*-σ-Pd(II) complexes.[33] For alkenyl halides the reaction proceeds under retention of configuration whereas inversion of configuration takes place in case of

benzylic and allylic halides. The oxidative addition is in most cases the rate-determining step; with the rate presumably depending on the metal's abiliy to support five fold coordination states and as well as the nature of the ligands and leaving groups for this S_N2-type mechanism.

There is a wide range of possible Pd-catalysts and co-catalysts for the use in cross-coupling reactions. The most common are $Pd(PPh_3)_4$ and $Pd(OAc)_2$ plus PPh_3 and other phosphine ligands. In general, palladium(0) complexes with bulky or less than four ligands are highly reactive for oxidative addition because they resemble "coordinatively unsatured" palladium species.[34] Regeneration of the Pd(0)-complex takes place after the reductive elimination and prelimary *trans-cis* isomerization. For this step, dissociative and nondissociative-nonassociative mechanisms have been proposed.[35]

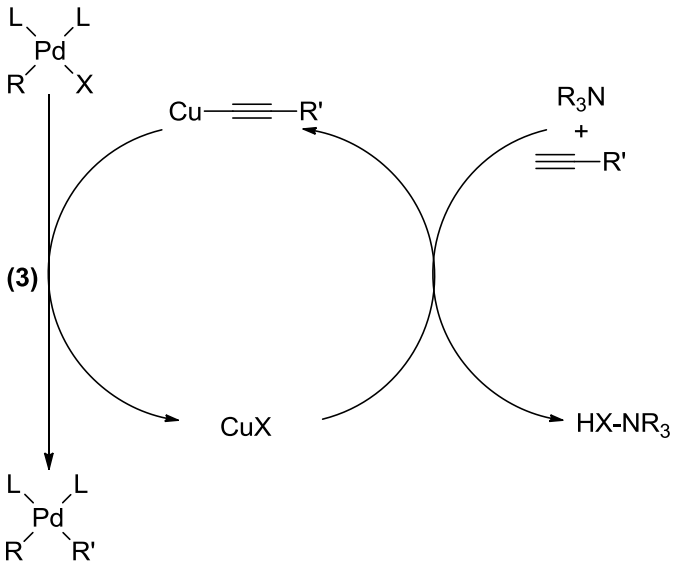
1.3.1 Sonogashira-Hagihara Cross-Coupling

Sonogashira-Hagihara cross-coupling can be designated as the alkyne version of Heck reaction, additionally using Cu(I) salts to generate the organometallic species.[30b,36] Closely related with the Sonogashira-Hagihara coupling are the Cacci,[37] Glaser,[38] Cadiot-Chodkiewicz,[39] and Stevens-Castro couplings,[40] all of which are employed to couple terminal alkyne moieties under participation of copper organyls. Historically the first of these copper-mediated couplings, the Glaser coupling has been introduced as early as 1869 and was subsequently applied by Baeyer for the synthesis of Indigo.[41] The connatural Cadiot-Chodkiwiecz reaction employs a catalytic amount of Cu(I)-salts and an aliphatic amine, providing unsymmetrically substituted diynes.[41a] Stevens-Castro coupling affords products similar to those obtained using the Sonogashira-Hagihara method, but without employing Pd catalysts. It is for this reason that the Stephens-Castro reaction requires harsh conditions and additionally uses explosive Cu-acetylides in stoichiometric amounts.[42]

The Sonogashira-Hagihara reaction couples vinyl-/aryl-(sp^2)halides to *sp*-carbons, *i.e.* terminal alkynes, it is performed with a Pd-catalyst and, Cu(I) as co-catalyst and an amine as the base. The protocol relies on Cu(I) catalyzed transmetalation of amines, which represents a second reaction cycle running in parallel [Scheme 14, Step (3)].

The catalytic cycle of the Sonogashira-Haghiara cross-coupling is entered with the usual formation of the catalytically active 14-electron-Pd(0) complex. Subsequently, the catalytic cycle is initiated by an oxidative addition, which is considered to be the rate

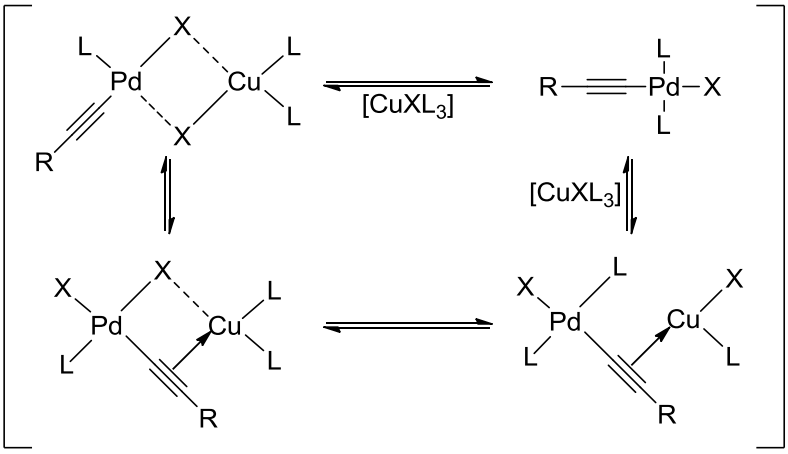
determing step[43] [*vide supra*, Scheme 14; steps (1), (2)], which can also be described as end-on ligation of the halogen and therefore as electron donation step. At this point, it must be dealt with the finding that a high HOMO of the substrate (electron donor groups) generates a more stable complex, consequently rising the rate determing activation barriers for the following steps. The opposite holds true for a low HOMO of the substrate participating in the oxidative addition step.[43a,44] The transmetallation step (3) is more sophisticated in case of the Sonogashira-Hagihara cross-coupling with the second catalytic cycle branching as depicted in Scheme 15. Formation of the copper acteylide takes place while the amine acts as base to deprotonate the terminal alkyne. The ammonium salt precipitated here contains the copper counter ion. The role of copper is to mediate the formation of the transition-metal acetylide as well as to collect the halogen, which leaves the palladium complex during the transmetallation step. All these steps proceed *in situ*.



Scheme 15 Second and simueltanous catatalytic cycle of Sonogashira-Hagihara cross-coupling

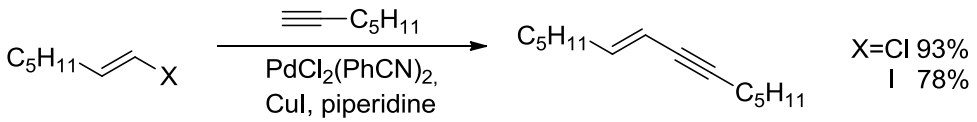
This second catalytic cycle running simultaneously is poorly understood. It is assumed that the π-alkyne copper complex assists in the formation of the copper actetylides *via* enhancing the acidity.[43a] After *cis-trans* isomerization reductive elimination (4) forms a π-complex and dissociation step (5) follows.

Vasella *et al.*, however, proposed a mechanism, which proceeds in a completely different way. In their mechanistical proposal palladium forms a complex with the halo-alkynes involving bimetallic complexes (Scheme 16).[45]



Scheme 16 Alternative mechanism for Sonogashira-Hagihara cross-coupling[45]

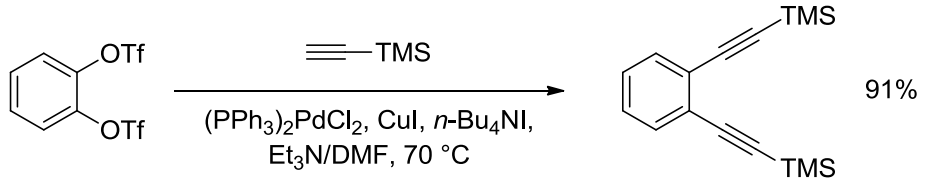
Substrate reactivities in the Sonogashira-Hagihara cross-coupling generally follow the order vinyl iodide = vinyl bromide > aryl iodide > vinyl chloride >> aryl bromide.[46] As depicted in Scheme 17, the yields of these reactions depend on the reactivity of the halide as well of the catalyst, the amine base used, and the alkyne moiety.



Scheme 17 Comparison of two alkenyl halides to prove that the chemoselectivity depends on the reaction conditions and not exclusively on the reacitivity of the halide-substituents.

The good result of the coupling of a chloride depicted in Scheme 17 shows that the combination of coupling reagents is crucial to achieve good turnovers and, hence, also influence the chemoselectivities.[46-47] Sonogashira-Hagihara cross-coupling proceeds stereospecifically for vinylic substrates, maintaining the *E/Z*-configuration.[48]

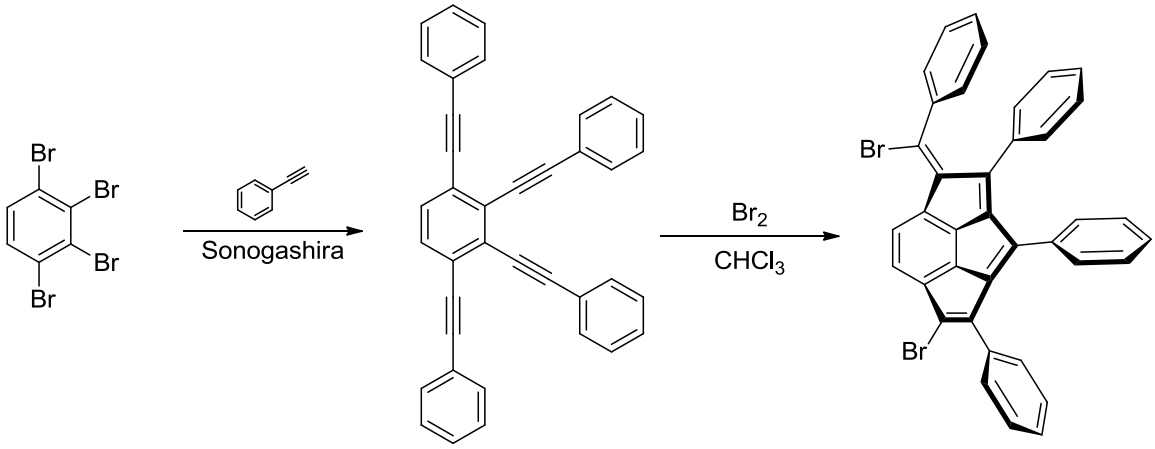
Using the general protocol of the Sonogshira-Hagihara cross-coupling, but replacing the halide with a triflate, the cross-coupling variant is known as Cacchi coupling (Scheme 18).[37,49]



Scheme 18 Chacci cross-coupling

Oligoynes are also accessible using the Sonogashira-Hagihara methology. Such oligoynes are crucial precursors for electrophilically induced tandem cyclizations that can be

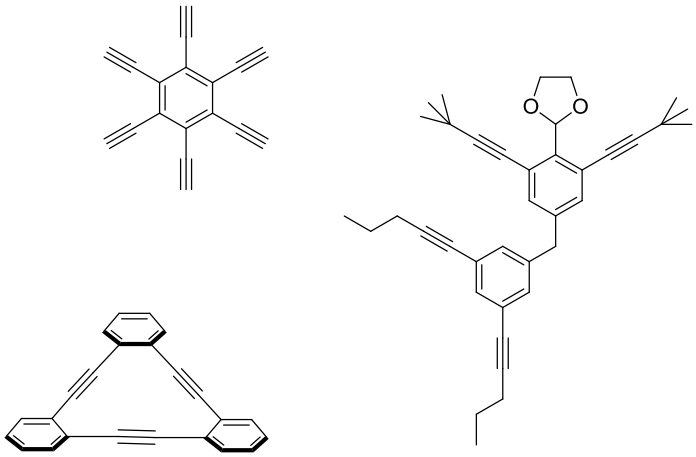
utilized to provide bowl-shaped structures (Scheme 19), which will be covered in Chapter 3 of the present thesis.



Scheme 19 Synthesis of a *555*-half bowl compound[12,50]

The half-bowl shaped product depicted in Scheme 19 (and related structures) belong to the family of the polyaromatic hydrocarbons (PAHs). This exemplifies a generally applicable and important use of arylalkyne-containing scaffolds as key precursor in their synthesis.[51] These starting materials enable the annulation of five- and six membered rings to form such nonplanar hydrocarbons, similar principles are also applied in the design and synthesis of fullerenes and carbon nanotubes.[51]

Sonogashira-Hagihara cross-coupling is also most suitable for the construction of molecules with a handsome appearance such as dendrimeric structures of Tour's "Nano Putians" (Scheme 20).[52] The core structure of graphyne is also depicted in Scheme 20 (top left), whose long range order consists of iteratively arranged phenyl- and ethynyl moieties. These carbon networks were synthesized by Haley *et al.* and have been utilized as carbon-rich materials investigated in material science due to their stability, electricals and further characteristics of these materials.[53] Linear polyyne structures or functionalized pentacenes have been designed and synthesized by Tykwinski *et al.*[54]



Scheme 20 Sonogashira-Hagihara cross-coupling products[48b,52,55]

These acetylenic molecular architectures enable the synthesis of made-to-order molecules for use in material science (*i.e.*, chromophores, 4*n*+2 annulenes),[41a,56] and, as mentioned before, in the synthesis and screening of enediyne antitumor agents in pharmaceutical research.

Recent developements of Sonogashira-Hagihara cross-coupling present copper free variants. However, strictly speaking these reactions do not belong to the cross-coupling family and consequently are not described properly as Sonogashira-Hagihara type cross-couplings.[43a]

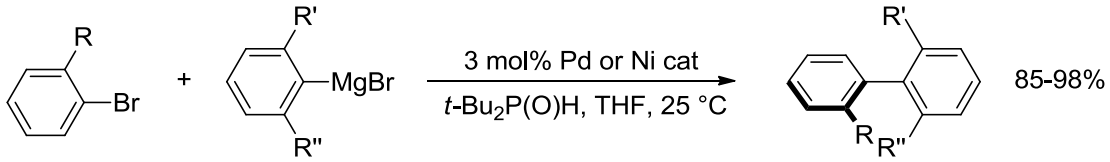
1.3.2 Kumada-Tamao-Corriu Cross-Coupling

In 1972, Kumada and Corriu independently reported the cross-coupling reaction of Grignard reagents catalyzed by Ni- and Ni-phosphine-complexes.[29,57] The Kumada-Tamao-Corriu reaction can be described as the birth of the transition metal-catalyzed cross-coupling reactions.

In 1975, Murahashi reported the first catalytic use of palladium in Kumada-Tamao-Corriu reactions.[58] The mechanism of this cross-coupling also follows the catalytic cycle discussed above (Scheme 14) and can be summarized briefly as follows: (1) Ar-X enters into the coordination sphere of Pd(0) as π-ligand and subsequently the C(sp^2)-X is cleaved *via* formal insertion of Pd(0) [step (2)] simultaneously, the oxidation state of the central atom changes formally from Pd(0) to Pd(II). The transmetallation step (3) and *cis-trans* isomerization follows, whereupon MgX_2 is being formed. Subsequently the ethynyl-Grignard adduct forms an ethynyl-Pd-complex. After reductive elimination (4), the cross-coupling product remains within the coordination sphere of the Pd(0) central atom as a π-

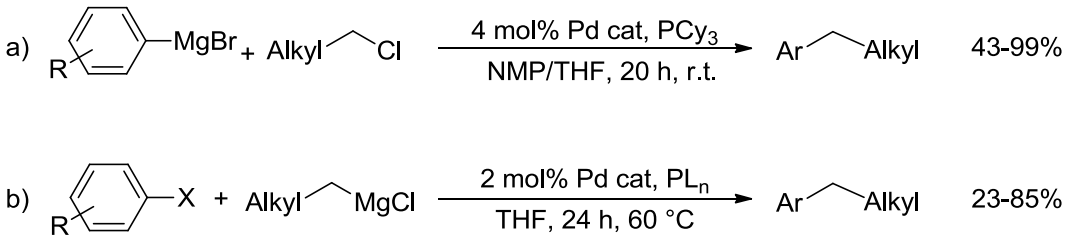
complex. Dissociation of this species (5) regenerates the Pd(0) species for the next catalytic turnover.

A further developement of this reaction is a Kumada-Tamao-Corriou biaryl synthesis reported by Wolf *et al.*[59] These authors used *in situ* generated metal-phosphinous acid in the transition metal-catalyzed cross-coupling of aryl halides and aryl Grignard compounds as depicted in Scheme 21.



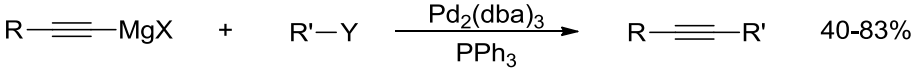
Scheme 21 Kumada-Tamao-Corriou biphenyl synthesis by Wolf *et al.*

Chloride substrates (*e.g.*, alkyl chlorides) are attractive materials for industrial processes because they are mostly inexpensive and readily available. The reactions depicted in Scheme 22 proceed with the alkyl chlorides acting as electrophiles[60] a) and in return organomagnesium chlorides acting as nucleophilic species b).[61] In case of reaction a) phosphines/secondary phosphine oxides act as co-ligand and in case of reaction b) the best results have been achieved using PCy_3 as co-ligand.



Scheme 22 Kumada-Tamao-Corriou with chlorides

Luh *et al.* reported another cross-coupling based of alkynyl nucleophiles and with alkyl halides. These findings have inspired us to deploy our starting materials in a Kumada-Tamao-Corriu cross-coupling reaction using Pd-catalysts (Scheme 23).[62]



Scheme 23 Kumada-Tamao-Corriou cross-coupling with R = TMS, Ph and Y = I, Br in THF

Negishi speculated that the high intrinsic reactivity of an electropositive metal such as Mg, Li, and Na could poison and hence inactivate the catalyst.[28,63] Another reason for the infrequent use of Kumada-Tamao-Corriu reactions is that Grignard reagents do not

tolerate common functional groups such as carbonyl- or nitro-groups in contrast to organo boranes, which tolerate such functionalities. Additionally Grignard precursors generally possess low chemoselectivity. Another inconvenience of the Kumada-Tamao-Corriu cross-coupling is the necessity to prepare the Grignard additive first, thus requiring an additional reaction step whereas these transformations occur *in situ* employing the other cross-coupling reactions decribed above.

1.3.3 Suzuki-Miyaura Cross-Coupling

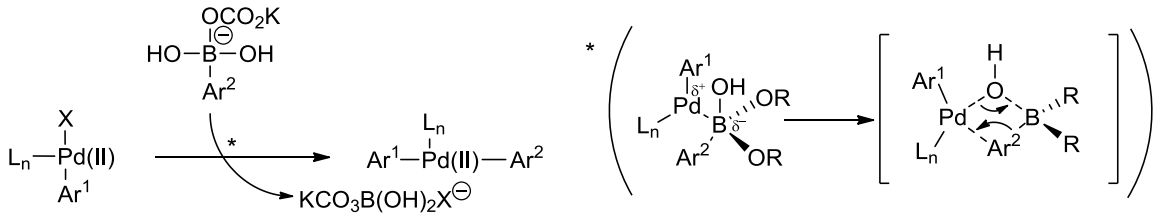
Pd-catalyzed coupling of aryl or vinyl boronic acids with aryl or vinyl halides or triflates yields in conjugated olefins, stryrenes, and biphenyls. Generally applicable and efficient methods to construct C(sp^2)-C(sp^2) bonds have been developed using this methology, that has in recent years also been extended to couple C(sp^3)–B with C(sp^3) by Fu *et al.* and C(*sp*)–B with C(sp^2) by Fürstner and Soderquist.[64] The first Suzuki-Miyaura cross-coupling was described as a stereoselective synthesis of arylated (*E*)-alkenes in 1979.[65] The major advantage of this cross-couplings reaction compared to the other metal-catalyzed cross-couplings described hitherto is the tolerance of water. One explanation for this behavior is that hydroxide ions will substitute the halogens on the palladium catalyst in the presence of water and base. Boron-organyls suitable for the Suzuki-Miyaura cross-coupling include alkenylboronic-acids and -esters, arylboronic acids and -esters, 9-BBN-derivatives, and trifluoroborates.[66]

Suitable substrates are alkenyl- and aryl-triflates, iodides, bromides and chlorides. The reactivity of these substrates correlates with the quality of the leaving groups in the series $I^- > TfO^- > Br^- >> Cl^-$.[33]

Suitable are common palladium species such as $Pd(PPh_3)_4$, $Pd(OAc)_2$ with bulky, electron-rich phosphines as ligands or co-ligands, resepectively. The use of NHC-ligands in these catalysts (such as PEPPSI-IPr) is a valuable alternative to the phosphines and allows for the utilization of aryl chlorides as coupling partners.[67]

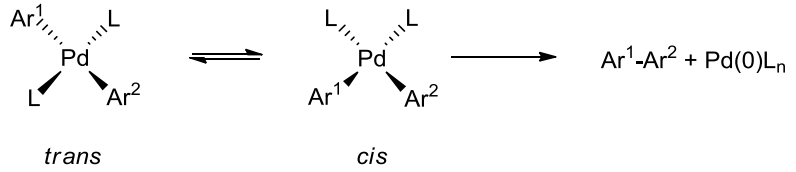
The catalytic cycle of the Suzuki-Miyaura cross-coupling is entered by formation of the Pd(0) complex and starts with the formation of a π-complex (1) of the Pd(0) complex thus formed *in situ* with the aryl substrate as a ligand (Scheme 14). Subsequently, an oxidative addition step takes place (2), whereupon Pd(0) inserts into the C(sp^2)-X bond, yielding a Pd(II)-complex. Therefore, inversion of configuration is observed for aryl halides. As mentioned above, oxidative addition has been described as the rate-determing step in the

literature,[32-33] the transmetallation step follows (3). In case of Suzuki-Miyaura cross-coupling with organoboron compounds, the reaction requires assistance of bases (Scheme 24), the careful selection of which is essential (note that the bases may also act as ligands). It was discovered that, depending on the pH, "quaternization" to a $ArB(OR)_3^-$ (or "ate"-complex) of the boronic species takes place, enhancing the electrophilic character of the organic residue. Comparative measurements show that at pH 7-8.5, the formation of $PhB(OH)_3^-$ is slower than at pH 9.5-11. Hence, the pH of a reaction has to be higher than the pK_A of the boronic acid (for example: pK_A (phenylboronic acid) = 8.8).



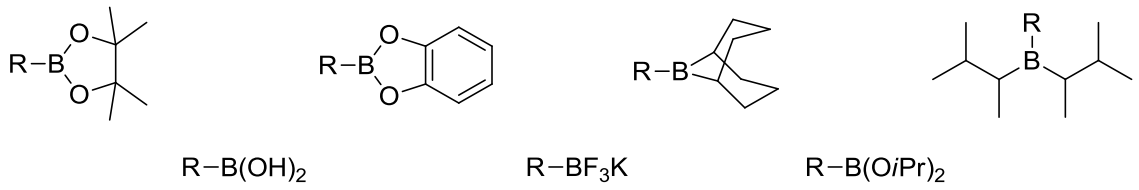
Scheme 24 Transmetallation step; postulated mechanism

Reductive elimination [Scheme 14, step (4)] takes place by combination of the aryl moieties that are bound to the Pd(II) centralion *via* σ-bonds. The cross-coupling product remains in the coordination sphere as a π-ligand (5). The oxidation number of Pd formally decreases back to Pd(0) (Scheme 25). There is no doubt about the presence of the *cis* and *trans* intermediates, which also have been characterized spectroscopically.[68]



Scheme 25 Reductive elimination including isomerization [Scheme 14; (4) and (5)]

Dissociation of this Pd(0)-π-complex regenerates the active Pd(0)-complex (5), which is readily available for the next turnover. The Suzuki-Miyaura cross-coupling is operationally friendly as the precipitated inorganic salts can simply be removed by aqueous work-up. As already mentioned, a variety of organoboron compounds is suited for Suzuki-Miyaura cross-couplings (Scheme 26).

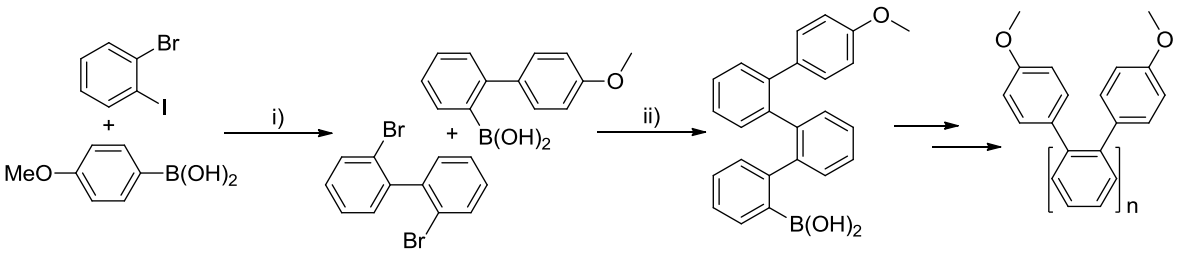


Scheme 26 Organoboron compounds suited for Suzuki-Miyaura cross-coupling

The classical and efficient methods to prepare alkyl-, aryl- and 1-alkenylboronic acids or the corresponding esters utlize Grignard- or organolithium reagents in excess. The most successful variant utilizes organolithium and trialkylborates followed by acidic treatment to give the desired boronic acids in good yields.[69]

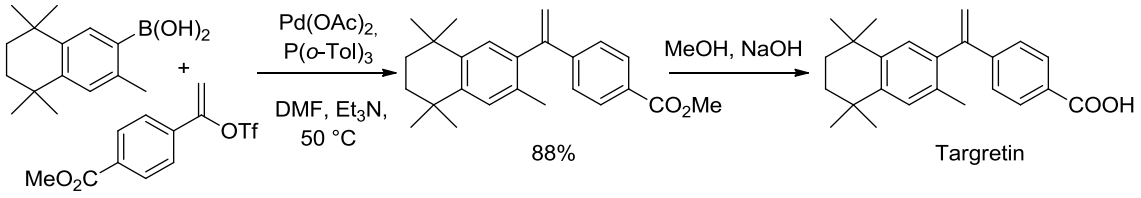
Hydroboration with dialkylboranes results in *syn* anti-Markownikow addition and yields the corresponding alkyl-dialkylborane derivatives. These reagents are useful for the transfer of primary alkyl groups. Hydroboration is particularly useful for synthesis of stereodefined and functionalized alkenylboronic acids and esters. Alkenylboronates were prepared by hydroboration of 1-haloalkynes *via* an S_N2-like internal displacement of the halogen with $KHB(OiPr)_3$.[70] A further synthesis of the boron-derived cross-coupling partners is the haloboration of terminal alkynes. 2,2-Diorgano-1-alkenylboronates were prepared by bromoboration to the β-bromo-1-alkenylboronic ester and subsequent displacement of the β-halogen with organozinc reagents.[71] Aryltrifluoroborates are prepared by treatment of the corresponding boronic acid with KHF_2. These trifluoroborates should be less susceptible to protodeboronation compared with the corresponding acids.[66a]

Sequential Suzuki-Miyaura cross-couplings can be favorably utilized to prepare helical *ortho*-phenylene oligomers using *p*-methylphenylboronic acid and dihaloarenes or 2,2′-dibromobenzene as the precursors (Scheme 27).[72]



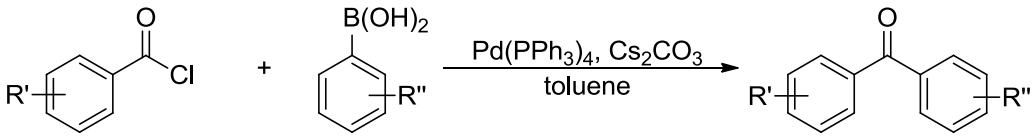
Scheme 27 Synthesis of helical *ortho*-phenylene; i) 3% Pd catalyst, DME, H_2O, $Ba(OH)_2$, reflux; ii) *n*-BuLi, $B(OiPr)_3$, THF, −78 °C, n = 1-7

Targretin is a retinoid used as anti-skin cancer drug.[73] The penultimate step of its synthesis utilizing Suzuki-Miyaura cross-coupling as reported by Faul *et al.* is depicted in Scheme 28.



Scheme 28 Synthesis of a retinoid precursor

Suzuki-Miyaura cross-coupling is widely applied for the coupling of biphenyls and related structures in drug design. Further applications of these cross-coupling concepts are total syntheses of natural products, dendrimeric structures, and unusual amino acids and peptides, porphyrines, thiophene derivatives and diaryl ketones *via* a carbonylative Suzuki-Miyaura cross-coupling. One example for this latter methodology is the reaction of arylboronic acids with acyl chlorides under anhydrous conditions, such as the reaction depicted in Scheme 29.[74]



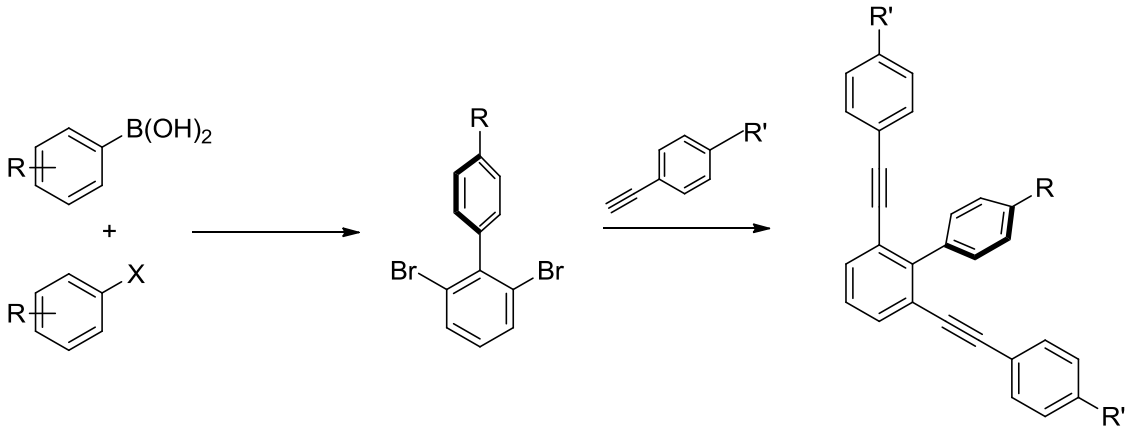
Scheme 29 Cross-coupling of acid chlorides with arylboronic acids

The Stille cross-coupling can be considered as the competitive reaction to the Suzuki-Miyaura cross-coupling as it is of similar versatility with respect to the possible combinations of starting materials with stannanes, yielding a wide range of diverse cross-coupling products. The Suzuki-Miyaura type cross-coupling, however, offers a similar array of products using suitable boronic acids as coupling partners, thereby avoiding the toxic stannanes. In addition, the reaction of primary organoboranes is possible in Suzuki-Miyaura cross-couplings, while typically primary organostannanes are not employed in Stille couplings. Still, some highly sensitive compounds do not tolerate the basic conditions present in the Suzuki-Miyaura cross-coupling.[75]

Lastly, the catalysts themselves and, in particular, the ligands and co-ligands utilized, are crucial for optimal results in all of the Pd-catalyzed cross-couplings described above. As mentioned, *N*-heterocyclic carbenes[76] have successfully been utilized as ligands for palladium based catalysts, such as PEPPSI-IPr and related catalysts, giving impressive

cross-coupling results.[77] Careful choice of the phosphonium salts frequently used as co-catalysts in cross-coupling reactions also has significant influence in optimizing a given cross-coupling protocol.[78] Bulky phosphorous ligands such as adamantane- and diamantane-derived groups have likewise been successfully utilized in cross-couplings.[79] The choice of the ligands in some cases changes the course of the reaction.[77,80]

2 Preparation of Starting Materials *via* Transition Metal-Catalyzed Cross-Coupling Reactions



Scheme 30 Synthetic steps towards pyrene precursors

The topic of this chapter is the synthesis of the precursors, which are suitable for cyclization to pyrene derivatives (Scheme 30). Secondly the preparation of 1,2-bis(mesitylethynyl)benzene as enediyne-precursor for thermal induced cyclization reactions is described.

2.1 Biphenyls

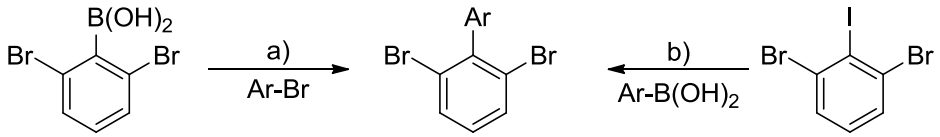
The archetypal biphenyl was used as a chemical preservative (E 230) in food and also as pesticide due to his fungicidal nature for a long time.[81] Due to its carcinogenic properties, its use has been prohibited since 2005. The biphenyl scaffold is the building block of the first liquid crystals, pharmaceutical products and polychlorinated biphenyls (PCBs). Historically PCBs had a broad field of applications, for example as thermal insulation material and electrical equipment due to their non-flammability, electrical insulating properties, chemical stability and high boiling points.[81] However, PCBs were also banned owing to their toxicity in 2001.[82]

Scientific researchers nowadays generally synthesize biphenyls *via* Suzuki-Miyaura and Ullmann coupling reactions. The Ullmann reaction respresents the symmetric synthesis path[83], whereas Suzuki-Miyaura cross-coupling stands for the unsymmetric version to obtain biphenyls. One of the leadoff unsymmetrical biphenyl syntheses was pointed out by Gilmann *et al.* in the 1950s.[84] They prepared 2,2′-dibromobiphenyl by treating 1,2-dibromobenzene with *n*-butyllithium, followed by the addition of 1,2-dibromobenzene. They postulated an aryne mechanism, which was picked up by Leroux and Schlosser in

2002, who described this coupling as a "metallation, elimination and addition sequence".[85] Currently, the Pd-catalyzed Suzuki-Miyaura cross-coupling is the most important biphenyl synthesis.

2.1.1 2,6-Dibromobiphenyls

For the preparation of sterically demanding 2,6-dibromobiphenyls, the protocol of Suzuki-Miyaura cross-coupling was selected in the present work. Phenylboronic acids and the corresponding aryl halides are coupling partners. There are two possible pathways a) and b) (Scheme 31) to obtain the desired product. Starting with 2,6-dibromoboronic acid [path a)] displays the convenience that generation of *o*-terphenyls as coupling side products is hardly possible. A further advantage of this approach is that the previous preparation of different phenylboronic acids is not necessary and the required aryl bromides as starting materials are more easily available. The second path b) necessitates in most cases the preparation of 2,6-dibromoaryl iodides and the arylboronic acids. Yet, they are effortlessly available unlike the sterically demanding 2,6-dibromoboronic acid [path a)]. The second route could only be followed by taking advantage of the chemoselectivity of these reactions, as in this case iodide is the preferred leaving group.

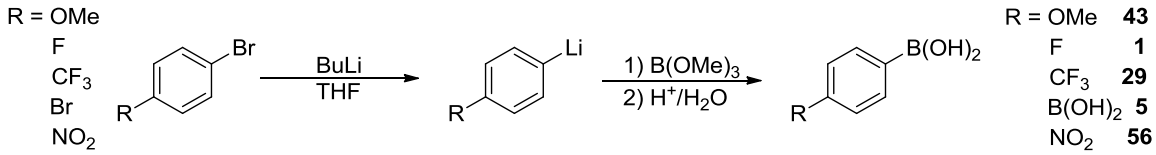


Scheme 31 Potential synthesis routes for 2,6-dibromobiphenyl derivatives

2.1.1.1 Starting Materials

2.1.1.1.1 Phenylboronic Acids

Classical synthesis of boronic acids proceeds by preparation of aryl-magnesium halides and their treatment with boronic esters.[86] However, we used a revised protocol starting from aryl bromides employing halogen-metal exchange with *n*-butyllithium and subsequent reaction with boronic esters; aqueous work-up and recrystallization or digeration provided the aryl-boronic acids.[87] These operations take place as low temperature reactions, which starting at –78 °C and, upon acid hydrolysis, the reaction mixture is allowed to warm to ambient temperature (Scheme 32).



Scheme 32 Preparation of aryl boronic acids

In nearly all cases, we obtained a colorless powder after recrystallation from water or treatment with *n*-hexane, which owns the characteristic smell of boronic acids (Table 1).

Table 1 Results of the phenylboronic acid syntheses

Entry	R	Hydrolysis	Yield (%)	Product
1	OMe	NH_4Cl	78	**43**
2	F	HCl (2N)	65	**1**
3	CF_3	NH_4Cl	67	**29**
4	$B(OH)_2$	HCl (2N)	22	**5**
5	NO_2	HCl (2N)	-	**56**

2,6-Dibromoboronic acid was prepared by using the *in situ* metallation-borylation procedure, which employs LDA as base. Due to the fact that LDA tolerates bromine as substituent, this approach was very convenient (Scheme 33).[88]

Scheme 33 Preparation of 2,6-dibromoboronic acid

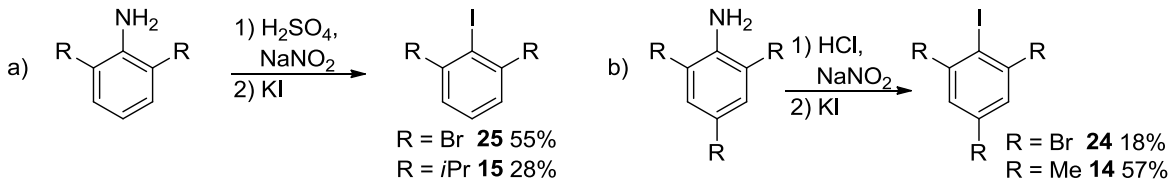
To 1,3-dibromobenzene, diisopropylamine and *n*-butyllithium were added successively at –78 °C. After several hours of stirring at –20 °C, trimethylborate subsequently was added again at –78 °C and the reaction mixture was allowed to warm to ambient temperature overnight. The following acidic hydrolysis and purification resulted in 2,6-dibromo-phenylboronic acid as colorless powder in a yield of 65%.

Another idea was preparation of 4-nitrophenylboronic acid **56** and thereby modifying the electronic properties of the biphenyls. The second idea was to prepare phenyl-1,4-diboronic acid **5** to sythesize 2,2",6,6"-tetrabromo-1,1',4',1"-terphenyl and couple this product *via* Sonogashira-Hagihara cross-coupling, employing phenylacetylene derivatives. The products obtained by the cross-couplings subsequently were subjected to

various cyclization reactions. The attempted preparation of the 4-nitrophenylboronic acid and the phenyl-1,4-diboronic acid gave, however, only impure products and several purification attempts were to no avail. The spectra of this crude diboronic acid show dimers or trimers. A treatment with pinacol ester could be an alternative solution to prevent this dimerization or trimerization and to obtain several isolated diboronic ester molecules.[89]

2.1.1.1.2 Iodides

As mentioned, our biphenyls were prepared by the coupling of arylboronic acids with the appropriate aryl iodide. We also transformed iodides in Sonogashira-Hagihara cross-couplings for the preparation of enediynes. These products acted as starting materials for thermal cyclizations attempts. It is known that iodine is a most suitable substituent in cross-coupling reactions. We carried out various procedures to obtain iodides. The first tartgeted product was 2,6-dibromoiodobenzene **25** (Scheme 34). We started with the diazotation-halogenation procedure (Sandmeyer reaction) following a protocol published by Coe *et al.* (Scheme 34, a).[90] 2,6-Dibromoaniline and H_2SO_4 were placed in a flask at 0 °C and $NaNO_2$ was added. After cessation of N_2 evolution, a KI-solution was added and the mixture was subjected to aqueous workup. Colorless crystals were obtained after digeration with hexane in a yield of 55%. We also performed a procedure inspired by Schlosser *et al.* by using LDA in THF/hexane for transmetallation in *ortho* position between the bromines as described before in the case of the similar 2,6-boronic acid **6** (Scheme 33), but instead of boronic ester, iodine was added subsequently.[85] Yet, the yield of the crude product was so low that we decided to stick to the first procedure. For mesityliodide **14,** the Sandmeyer-reaction was employed (Scheme 34, b). However, the procedure using H_2SO_4 was to no avail. As a result, we replaced sulfuric acid by HCl and obtained the product as a yellow oil, which was purified by Kugelrohr distillation in a yield of 57%.[91]

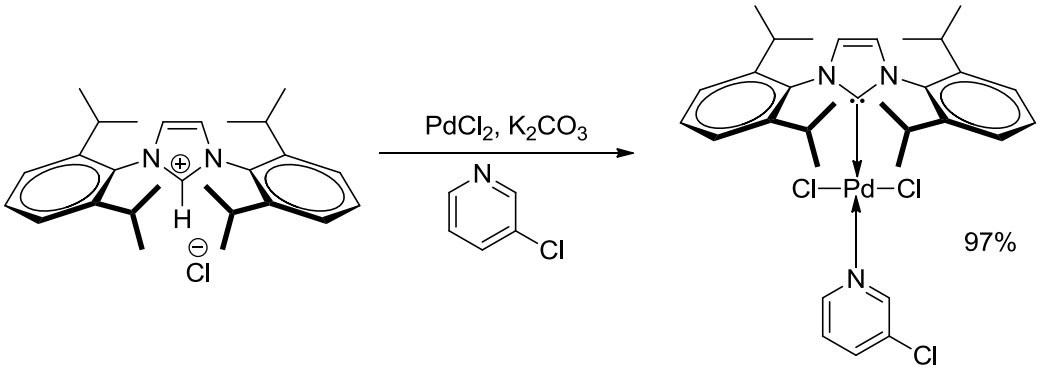


Scheme 34 Synthesis routes towards different iodides

2-Iodo-1,3-diisopropylbenzene **15** was prepared according to the procedure for 2,6-dibromoiodobenzene in a yield of 28% as a yellow oil after purification by distillation. Iodide **15** was used for preparation of 1,5-cyclization/annulation precursors (Section 3.2). For the investigation and optimization of these biphenyl coupling reactions, 3,5-dibromo-4-iodotoluene **92a** (Scheme 48) was required, which was prepared analogously to compound **25** as depicted in Scheme 34. For the sake of completeness, we have to mention the fourth aryl iodide we prepared, namely 2,4,6-tribromoiodobenzene **24**. For this product, the starting material 1,3,5-tribromobenzene undergoes a metallation respectively deprotonation with LDA as primarily described for 2,6-dibromoiodobenzene and also as step 1 for the 2,6-dibromoboronic acid **6** (Scheme 33). The second reagent was replaced by I_2 in THF, which afforded the metal-halogen exchange. We obtained a light brown solid in 18% yield. However, **24** was not employed in any further reaction.

2.1.1.1.3 Catalyst PEPPSI-IPr

We choose Organ's PEPPSI-IPr as catalyst because of the convincing results in Suzuki-Miyaura reactions.[78a] This palladium catalyst consists of an imidazolium-2-ylidene salt, which belongs to the family of NHC-ligands. PEPPSI is an acronym for Pyridine Enhanced Precatalyst Preparation Stabilization Initiation and the shorthand symbol IPr for the isopropyl substituents.[78a] Conversion of the imidazolium chloride with $PdCl_2$ and 3-chloropyridine *in situ* gives the catalyst-complex (Scheme 35). It is not necessary to isolate the carbene.[78,92] A detailed description of this synthesis can be found in Chapter 4.

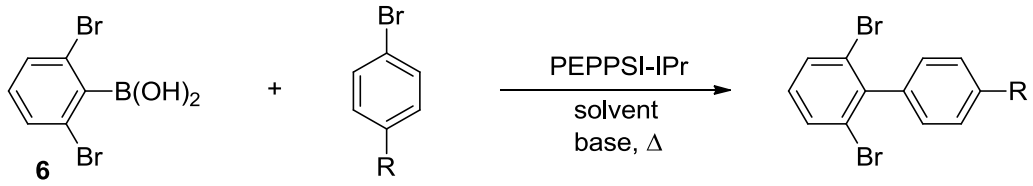


Scheme 35 Preparation of PEPPSI-IPr

2.1.1.2 Preparation of 2,6-Dibromobiphenyls

The 2,6-dibromobiphenyls are known, but have not been yet fully characterized in literature. First of all, we tried to implement path a) (Scheme 31) and started some test

reactions.[93] We carried out the following couplings with bromobenzene and 4-fluoro-bromobenzene as the aryl halide and 2,6-dibromophenylboronic acid (Scheme 36, Table 2).



Scheme 36 Synthesis route [path a), Scheme 31] towards 2,6-dibromobiphenyl derivatives

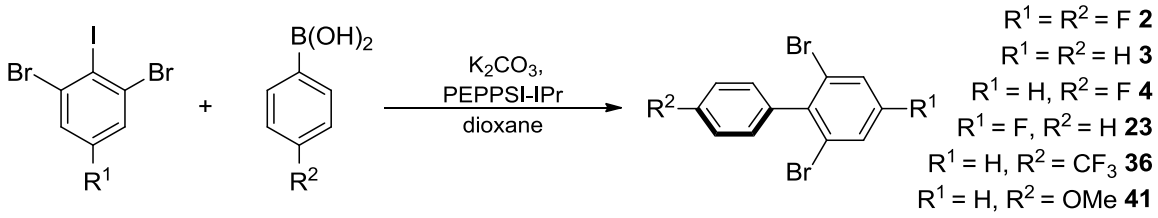
Table 2 Synthesis of 2,6-dibromobiphenyls based on 2,6-dibromophenylboronic acid using various bases and solvents.

Entry	R	Solvent	Base	Yield
1	F	1,4-Dioxane	K_2CO_3	-
2	F	1,4-Dioxane	Cs_2CO_3	-
3	F	*i*-PrOH	*t*-BuOK	-
4	H	1,4-Dioxane	K_2CO_3	-
5	H	1,4-Dioxane	Cs_2CO_3	-
6	H	*i*-PrOH	*t*-BuOK	-

The reactions were performed under inert conditions at 60 °C with 0.5 mmol 2,6-dibromoboronic acid and, accordingly, 0.5 mmol arylbromide, 3 eq. of base and 5 mol% PEPPSI-IPr in 2 mL solvent. After 21 h reaction time, a sample was taken for GC/MS analysis and after 120 h, another sample was taken. In neither case, conversion to product was detected, and the starting material exclusively was recovered. A further attempt was carried out analogously to entry 4, yet with increased catalyst loading of 10 mol% PEPPSI-IPr. For heating, an ultra sound bath was used for 4 h at 45–60 °C. Another experiment was performed using DBU (1,8-diazabicyclo[5.4.0]undec-7-en) as base and DMF as the solvent. Likewise we could not detect any product. However, in the corresponding GC/MS spectra, we discovered the M^+-signal of 1,3-dibromobenzene, which indicates a protodeboronation as competitive simultaneous reaction. These findings could represent an unusual protodeboronation of the aromatic C–B bond under non-hydrolytic conditions. Presumably, this deboronation proceeded before complexation with the metallic species.[93] On the other hand, this deboronation could proceed as the commonly known hydrolytic variant and hence react with residual water among the

reaction components. Suzuki himself described this phenomenon for 2,6-substituted, sterically hindered arylboronic acids. Electron withdrawing groups as substituents at arylboronic acids additionally accelerate this decomposition process. Suzuki *et al.* suggested a speedup of the coupling rate by using stronger bases, which could prevent this undesirable side reaction, as the amount of deboronated products increase slowly during reaction progress.[94]

After unsuccessfully pursuing path a), we followed path b) (Scheme 31) and took advantage of the chemoselectivity of Suzuki-Miyaura cross-couplings. These reactions were carried out under oxygen-free and dry conditions. We charged the flasks with 1,4-dioxane, 5 mol% PEPPSI-IPr, 3 eq. K_2CO_3 and the appropriate aryl iodide (Scheme 37). We found that we could realize higher yields when we stirred the solution for 1 h and then added the boronic acid.

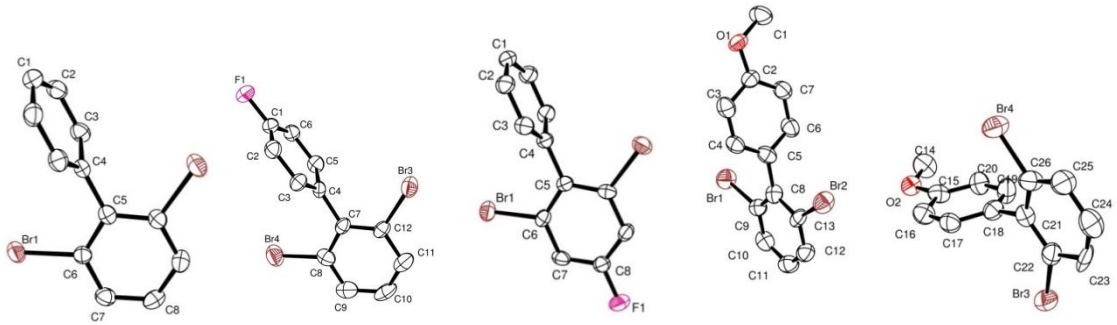


Scheme 37 2,6-Dibromobiphenyl derivatives

After 36 h at 60 °C aqueous $NaHCO_3$ solution was added and the crude product was extracted with CH_2Cl_2 for GC/MS analysis. In case of **2** (Table 3, Entry 1), we found one-, two-, and threefold coupling and also homocoupling products. Yet, we were unable to separate them. In other cases, especially for **3**, **4**, and **36**, we observed the terphenyl derivatives. For **3** and **4**, we were able to isolate the desired products *via* column chromatography, albeit in very low yield. Substance **36** could not be purified by column chromatography and required purification by preparative GC. The products **3**, **4**, **23**, and **42** were purified by column chromatography. These products as well as **36** were obtained as colorless crystals. The crystalline biphenyls were characterized spectroscopically. Compounds **3**, **4**, **23** and **41** also by x-ray analyses, as shown in Figure 1.

Table 3 Results of the Suzuki-Miyaura coupling of 2,6-dibromobiphenyl derivatives

Entry	R^1	R^2	Purification	Yield (%)	Product
1	F	F	-	-	**2**
2	H	H	Chromatography	62	**3**
3	H	F	Chromatography	45	**4**
4	F	H	Chromatography	58	**23**
5	H	CF_3	Preparative GC	18	**36**
6	H	OMe	Chromatography	49	**41**



3 **4** **23** **41**

Figure 1 X-ray structures of **3**, **4**, **23** and **41** (last two)

These structures were also utilized for validation of the optimized computed geometries at the M06-2X/6-31G(*d*,*p*) level of theory, for which we found that the experimentally determined bond lengths and angles are being reproduced well. In Figure 2, the X-ray structure of **3** is depicted with its elementary cell and selected bond lengths are compared with the computed values.

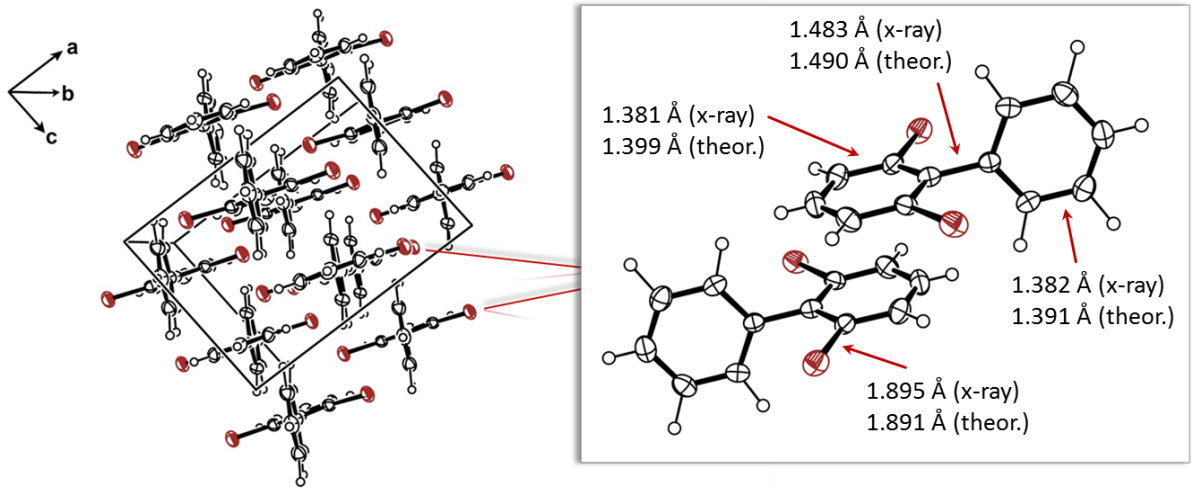


Figure 2 X-ray structure of **3** with elementary cell (see text for details); theoretical values computed at the M06-2X/6-31G(*d*,*p*) level of theory

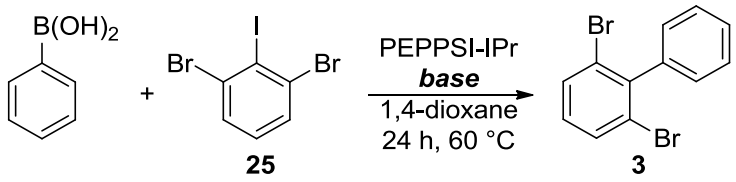
Figure 2 above shows structure **3** within its elementary cell and an enlarged detail portrait of two biphenyls, which reveal that the bromine substituted phenyl rings lie on top of each other, but in reversed orientation. Consequently, the second aryl ring is oriented almost perpendicular to the others. In case of **41** we found an arrangement, which is twisted by approximately 90° with regard to the bromine substituted phenyl ring.[16b]

2.1.2 Optimization of the Preparation of 2,6-Dibromobiphenyl Derivatives

Reiterating the results of synthesis of our biphenyls described above, the question arose why the Suzuki-Miyaura cross-couplings have such abnormally low yields of around 50%. The next step was to improve the efficiency of this coupling reaction. We had to consider whether steric hinderance in 2,6-dibromoiodobenzene, the electron withdrawing nature of the bromides or their ability to enter side reactions are an issue. Additionally, we have to mention that the boronic acid could take part in a hydrolytic deboronation. Hence we would have lost the boronic acid before the reaction starts. As variables, we have to consider on the one hand the conditions and reagents, which includes the nature of the base, solvent, heating (conventional or using microwave irradiation) and also the temperature, type of ligands of the palladium catalyst and reaction time. On the other hand, we also have to consider the reactants, in particular the halogen substituents of the aryl rings and with that, possible electronic effects.

2.1.2.1 Bases

It is known that organoboron reagents take part in transmetallation reactions only in the presence of base.[33] Carbonates (such as Na_2CO_3, K_2CO_3 and Cs_2CO_3) work best in biphenyl coupling reactions. There are also examples with KO*t*Bu and $Ba(OH)_2$.[95] For a series of test reactions in which we investigated, which base gives the best results, we chose similar conditions as we published for the simple coupling to 2,6-dibromobiphenyl **3** (Scheme 38).[16b]



Scheme 38 Test reaction for identification of the optimal base.

On a 0.5 mmol scale, we carried out three similar reactions using PEPPSI-IPr (5 mol%), 1,4-dioxane and in each case base (3 eq.). The reaction time was 24 h at 60 °C. During

the first three reactions, we figured out that this reaction is insensitive to water, so subsequently we used water as a co-solvent. The results are presented in Table 4. The conversion of all screenings in Section 2.1.2 was determined by GC. Calculations of the peak areas are as follows:

$$\left(\frac{[\text{product}]}{[\text{product}]+[\text{starting material}]+[\text{by product}]}\right)\times 100\% \qquad (1)$$

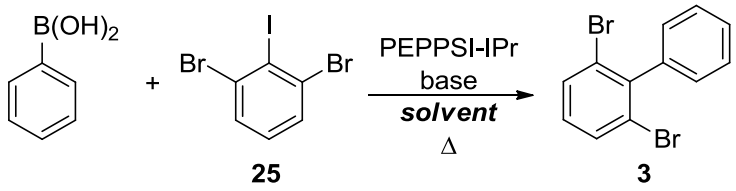
Table 4 Base screening

Entry	Base	Solvent	Catalyst	Time (h)	Conversion (%)
1	K_2CO_3	1,4-Dioxane	PEPPSI-IPr	24	64
2	Cs_2CO_3	1,4-Dioxane	PEPPSI-IPr	24	61
3	KO*t*Bu	1,4-Dioxane	PEPPSI-IPr	24	-
4	$Ba(OH)_2$	1,4-Dioxane /H_2O	$Pd(OAC)_2/PPh_3$	18	75
5	KOH	1,4-Dioxane	PEPPSI-IPr	24	-

Due to the finding that the yields are in the same range (except for entry 4), we carried out the following optimization steps using potassium carbonate as we did in the first place. Note that for entry 4 we used (for solubility reasons) degassed water as co-solvent (9:1, solvent/water). Solvent effects are the subject of the following section.

2.1.2.2 Solvents

Toluene, DMF, 1,4-dioxane, THF, and benzene are some of the solvents which have been commonly used in Suzuki-Miyaura cross-couplings. The choice of solvent as crucial as the reaction itself. Suzuki and Miyaura carried out their primary enantioselective reaction in benzene. Biaryl couplings found in the literature mostly report 1,4-dioxane as the solvent. Water can be used as a co-solvent, but at first, we investigated the main solvents to subsequently examine the effects of water to this reaction. Suzuki reactions usually perform better in polar solvents. We are dealing with sterically hindered substrates, which require higher reaction temperatures. This has to be taken into consideration during the selection of the solvent. We already knew that the system is stable against protic solvents, so were able to use 2-propanol, which was successfully used by Organ *et al.*, employing PEPPSI-IPr as catalyst.[78a] We tested polar aprotic and protic solvents to investigate their influence on their ratio and selectivity in our system.



Scheme 39 Test reactions to determine a suitable solvent

We chose the same starting materials as in the base screening, using two different bases and the PEPPSI-IPr catalyst. The experiments were designed around the solvent used in literature examples.[95] The results are presented in Table 5.

Table 5 Solvent investigation (Scheme 39)

Entry	Solvent	Temperature (°C)	Time (h)	Base	Catalyst	Conversion (%)
1	2-Propanol	r.t.	24	KO*t*Bu	PEPPSI-IPr	-
2	2-Propanol	70	24	KO*t*Bu	PEPPSI-IPr	-
3	DMSO	60	24	K_2CO_3	PEPPSI-IPr	10
4	THF	60	48	K_2CO_3	PEPPSI-IPr	67
5	1,4-Dioxane	60	48	K_2CO_3	PEPPSI-IPr	66

In the case of 2-propanol and DMSO, the reactions were entirely fruitless. Methanol was tested using aryltrifluoroborates, but it was found not to be suitable because of its low reflux temperature. We figured out that cyclic ethers, in our case THF and 1,4-dioxane provided the highest GC-determined yields in accordance with our published procedures.[16b] The next step was to continue with these solvents and test water as co-solvent. Conveniently, 1,4-dioxane is miscible with water.[96] Suzuki and Miyaura carried out couplings of phenylboronic acid with aqueous base and obtained better yields than under dry conditions. They used NaOH/H_2O, NaOAc/H_2O and Na_2CO_3/H_2O in coupling reactions.[65a] An explanation for this behavior is the possibility that water promotes the formation of Pd(0) in the catalytic cycle in the presence of phosphine ligands by removing the oxidized phosphonium during the reduction of Pd(II).[96b] Another explanation might be the formation of highly active Pd-hydroxy-complexes.[96a]

To investigate the influence of water in this coupling, we carried out eight experiments with varying amounts of water ranging from 0 to 25%. For this reaction, we used 0.5 mmol 2,6-dibromoiodobenzene and the same amount of phenylboronic acid, 5 mol%

PEPPSI-IPr, and 3 eq. K_2CO_3 in 1,4-dioxane. The reaction was performed in a Schlenk tube under oxygen free conditions and a total amount of 2 mL solvent was added. The composite solvent was thoroughly mixed and deoxygenated before use. The reactions were stirred at 60 °C for 4 days and subsequently analyzed by GC (Table 6).

Table 6 Results of Suzuki-Miyaura couplings with varying amounts of water as the co-solvent.

Entry	Vol% water	Conversion (%)
1	0.0	66
2	1.3	75
3	2.5	75
4	4.0	75
5	5.0	73
6	7.5	75
7	10.0	75
8	25.0	75

A benefit of the addition of water was that both catalyst and base dissolve entirely. We observed (Table 6) that the yield increases with the amounts of water up to 10 Vol% where the yield reached its maximum of approximately 75%. We observed no further beneficial effect by adding more than 10 Vol% of water. To be absolutely sure that water was causing the increased yields, we carried out two test reactions in THF and obtained the following results (Table 7).

Table 7 Suzuki-Miyaura test-reaction in THF with and without water as co-solvent.

Entry	Vol%	Conversion (%)
1	0.0	67
2	1.0	77

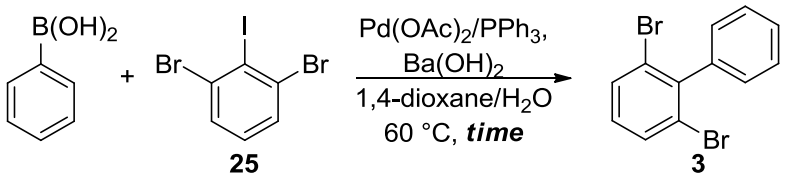
From that, we conclude that a small amount of water as co-solvent increases the yield. Hence, we kept the 1,4-dioxane/water solvent system constant and decided to vary the other reaction parameters instead.

2.1.2.3 Reaction Time

We usually heated the reaction mixture to 60 °C, which is the optimum reaction temperature found for most substrates catalyzed with PEPPSI-IPr,[78a] and stirred for four

days to ensure completeness of the reaction. The next step was to figure out precisely how long the reaction needed to be stirred at 60 °C until it reached completion. For our purpose, the long reaction times turned out to be a disadvantage. For biphenyl systems, Suzuki couplings went to completeness within one hour to three days.[64b] As an additional benefit shorter reaction times would also make the optimization screening process more convenient.

As a test reaction we chose 0.5 mmol 2,6-dibromoiodobenzene in conjunction with 1 eq. of phenyl boronic acid combined with the 1,4-dioxane/water mixture, 3 eq. $Ba(OH)_2$ as base and 5 mol% $Pd(OAc)_2$, 10 mol% PPh_3 as catalyst and co-catalyst system (Scheme 40). The reaction temperature was maintained at 60 °C. The GC analysis revealed the following results (Table 8).



Scheme 40 Optimization of the reaction time

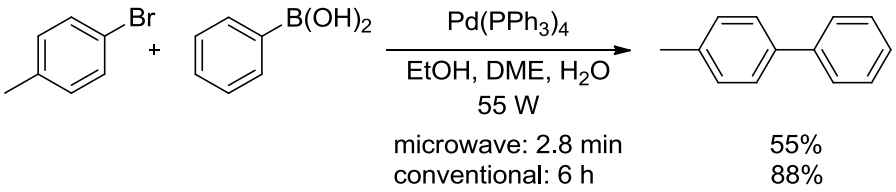
Table 8 Evaluation of the optimal reaction time for our Suzuki-Miyaura reaction

Entry	Time (h)	Conversion (%)
1	21	72
2	45	74
3	90	74

The table shows that the yield did not change between 45 h and 90 h. These results let us shorten the reaction time to two days. Using microwave irradiation was envisaged as another possible way to further shorten the reaction time (*vide infra*).

2.1.2.4 Microwave Enhanced Synthesis

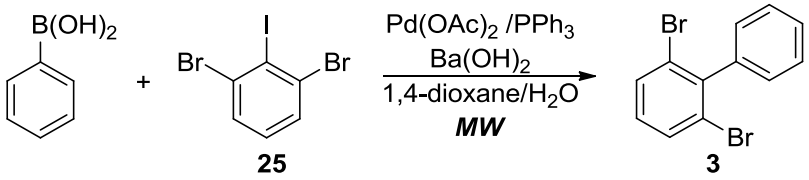
The use of microwaves as an energy source for the Suzuki reaction can speed up reactions by several orders of magnitude: microwave irradiation can reduce reaction time from days to minutes (Scheme 41).



Scheme 41 Conventional *vs.* microwave-assisted Suzuki-Miyaura cross-coupling of Hallberg *et al.*[97]

Microwave-assisted reactions, contrary to conventionally heated reactions, proceed faster because of a more efficient heat transfer to the reaction mixture, a procedure which is also known as homogenous heating. Due to the ability to seal the vessel, it is also possible to work under elevated pressure. Under conventional conditions, there is a temperature gradient and the resulting heat distribution is inhomogeneous. Moreover, the source of energy is different (microwave excitation cause molecular rotation). As described above, we had already found that water is a suitable co-solvent in our system. Water is also particulary well suited for microwave heating, as solvents with dipole moments are required to efficiently absorb microwaves.

The important questions are whether our cross-coupling system is suitable for microwave-assisted reactions and if the reaction time could be reduced further. An additional challenge would be whether we would be able to work out an applicative protocol for our system because previous experiments pointed out that the coupling occurs both at the iodine-substituted C-atom as well as the bromine-substituted C-atoms. As a result, we obtain a mixture of all possible coupling products. Hence, for this reaction we replaced the PEPPSI-IPr catalyst with the considerably less active $Pd(OAc)_2/PPh_3$ catalyst system (Scheme 42).



Scheme 42 Microwave-assisted Suzuki-Miyaura cross-coupling

The reported Suzuki reactions were performed under atmospheric conditions without deoxygenated reactants. We decided to test our system under atmospheric and inert conditions. We carried out three reactions on a 0.5 mmol scale with 5 mol% $Pd(OAc)_2$, 10 mol% PPh_3 and 3 eq. $Ba(OH)_2$ in 1,4-dioxane/water. The conditions and yields are summarized in Table 9.

Table 9 Results of the microwave-assisted Suzuki-Miyaura cross-coupling of **3** at 1 bar

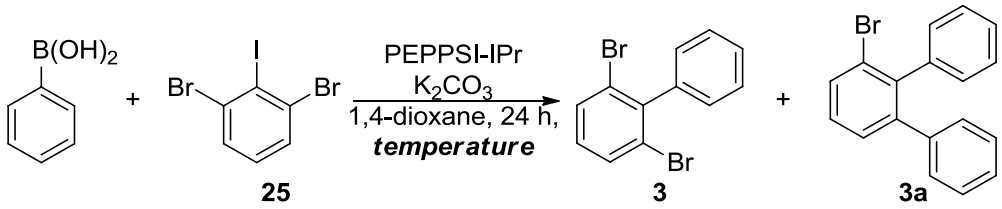
Entry	Max. Power (W)	Temperature (°C)	Time (h)	Conversion (%)
1	100	60	0.3	-
2	200	40	1.6	17
3	20	50	10.0	35

For the first reaction, we used the common sealed vessel and we observed a black precipitate after 20 min. No product was detected in GC analysis. The experiment was again carried out in a round bottom flask with a condenser and bubble counter and, hence, under ambient pressure and argon atmosphere. In this case, we observed a light green solution after 100 min and some coupling product in GC analysis, but not as much as under conventional conditions. The third reaction was also carried out in a flask, but we increased temperature, reaction time and decreased the maximum power to 20 W to ensure a careful heating. Despite of the 10 h reaction time we obtained only a twofold yield compared to the second reaction.

The comparably poor results of these microwave-enhanced couplings could be due to the poorly absorbing 1,4-dioxane as solvent. Apparently, the 10% amount of water as a microwave absorbant was not sufficient. Consulting the literature with regard to sterically hindered coupling partners our results confirm that the yields with the conventional procedure are still higher.[98] In order to achieve a successful microwave synthesis for our system, we will have to vary all parameters individually to develop a suitable synthetic protocol.

2.1.2.5 Reaction Temperature

As mentioned before, the PEPPSI-IPr catalyst reacts optimally at 60 °C for most substrates.[78a] Suzuki *et al.* have already shown in the early 1980s that reactions with sterically encumbered substrates require elevated reaction temperatures compared with reactions of unhindered substrates.[65a] The difficulty of our system is the reduced chemoselectivity with increasing temperature, which means that we have to establish an optimal temperature.



Scheme 43 Temperature optimization reaction

The optimization conditions are based on our previous biphenyl couplings. At the different temperatures we used phenylboronic acid, 2,6-dibromoiodobenzene, 3 eq. of K_2CO_3, 5 mol% PEPPSI-IPr and 1,4-dioxane stirred at the noted temperature for 24 h. A sample was taken and analyzed by GC (Table 10). Besides the desired biphenyl **3**, we also observed bis-coupled 1-bromo-2,3-bisphenylbenzene (*o*-terphenyl derivative) **3a** in each reaction. The next goal was to determine how the chemoselectivity depends on the reaction temperature.

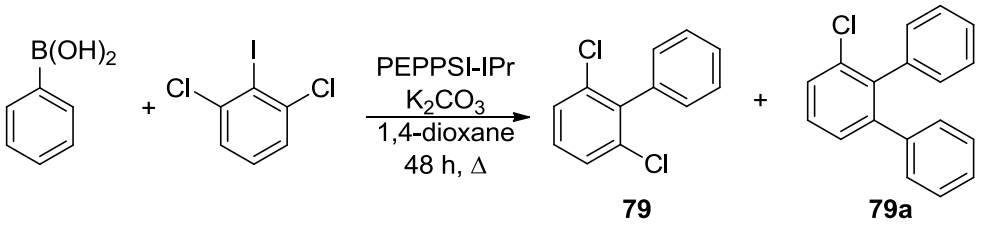
Table 10 Optimization of the reaction temperature

Entry	Temperature (°C)	Conversion 3[a] (%)	Converision 3a[b] (%)
1	ambient	-	-
2	60	64	8
3	90	70	9
4	reflux	65	10

[a] 2,6-dibromobiphenyl; [b] 1-bromo-6-phenylbiphenyl

At first glance, it seems that the optimal reaction temperature should be 90 °C, but we have to consider the formation of 1-bromo-6-phenylbiphenyl as a side product and this relative amount increases marginally proportional to the oil bath temperature. In all optimization experiments, we observed the twofold coupling product in an 8:1 ratio of **3** to **3a**. It remained at this ratio during all our experiments and we were not able to increase this ratio.

As a control experiment we carried out a similar cross-coupling, but replaced the 2,6-dibromoiodobenzene with its dichloro analogue (Scheme 44).

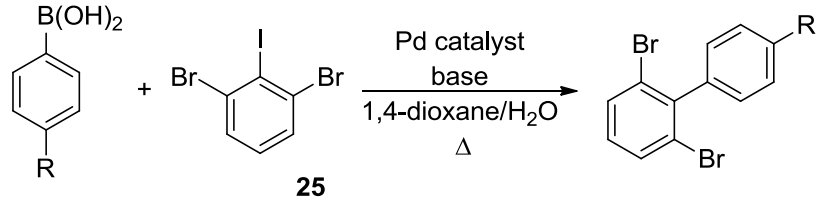


Scheme 44 Control reaction for detection of potentially formed side products

GC/MS analysis of this reaction gave a ratio of peak areas of product **79** to by-product **79a** of 30:1 and the yield of **79** was 96%. We observed no remaining starting material. The *ortho*-bromides are detrimental to the chemoselectivity of this coupling reaction and cause the formation of *o*-terphenyl side-products. Consequently, the mediocre results are not a consequence of a faulty protocol. The bromo-substitueted biphenyls were retained for the subsequent Sonogashira-Hagihara cross-coupling, which is the next step towards functionalized pyrenes. The best performance of our biphenyl coupling was found at 90 °C, including lightly decreasing chemoselectivity and therefore 30 °C higher than the temperature hitherto used. However, we should now use the increased reaction temperature in combination with the other varied parameters to determine if this combinated system would be still stable at temperatures higher than 60 °C.

2.1.2.6 Substituted Arylboronic Acids and Substituted Aryliodides

Another issue on the synthetic path to functionalized pyrenes is to control the substitution in the *para*-(4′)-position of the biaryl and consequently to control and influence the electronic properties of these systems, which could be important for the HOMO-LUMO band gap of pyrenes. Another feature is to expand the catalogue of the available pyrenes, because the biphenyls are the basic building blocks for their preparation. Just as the coupling reaction of the phenyl boronic acid were optimized, the change of the substituent on the aryl boronic acid required also an optimization process. Consequently, we wanted to investigate the reactivity of different arylboronic acids (Scheme 45, Table 11).



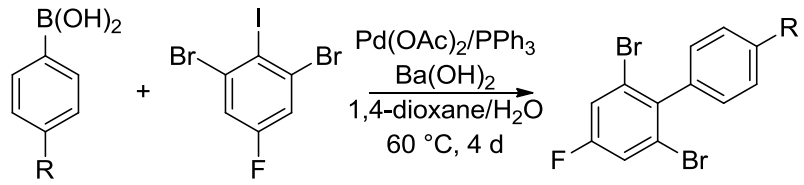
Scheme 45 Suzuki-Miyaura cross-coupling with various phenylboronic acids

Table 11 Cross-coupling with various boronic acids

Entry	R	Base	Catalyst	Solvent	Temp. (°C)	Time (d)	Conv. (%)*	Prod.
1	H	K_2CO_3	$Pd(OAc)_2$/ PPh_3	1,4-Dioxane/ H_2O	60	3	82	**3**
2	H	$Ba(OH)_2$	$Pd(OAc)_2$/ PPh_3	1,4-Dioxane/ H_2O	60	4	*66*	**3**
3	F	$Ba(OH)_2$	$Pd(OAc)_2$/ PPh_3	1,4-Dioxane/ H_2O	60	4	*60*	**4**
4	CF_3	$Ba(OH)_2$	$Pd(OAc)_2$/ PPh_3	1,4-Dioxane/ H_2O	60	4	58	**36**
5	*n*-Bu	$Ba(OH)_2$	$Pd(OAc)_2$/ PPh_3	1,4-Dioxane/ H_2O	60	4	75	**90**
6	*n*-Oct	$Ba(OH)_2$	$Pd(OAc)_2$/ PPh_3	1,4-Dioxane/ H_2O	60	4	65	**89**
7	3-F	$Ba(OH)_2$	$Pd(OAc)_2$/ PPh_3	1,4-Dioxane/ H_2O	60	3	47	**91**
8	OMe	K_2CO_3	PEPPSI-IPr	1,4-Dioxane	40	3	*55*	**41**

*yields of isolated products are shown in *italics*

The purification of these biaryls proceeds *via* column chromatography; the purified products were characterized by NMR. The biphenyls **89**, **90**, and **91** (entries 6, 5 and 7) are hitherto unknown. To modify the second *para*-substitution of the biaryl *para*-substituted dibromoiodobenzene was used. We carried out the Suzuki-Miyaura cross-coupling using 2,6-dibromo-4-fluoroiodobenzene and three different boronic acids (Scheme 46, Table 12)



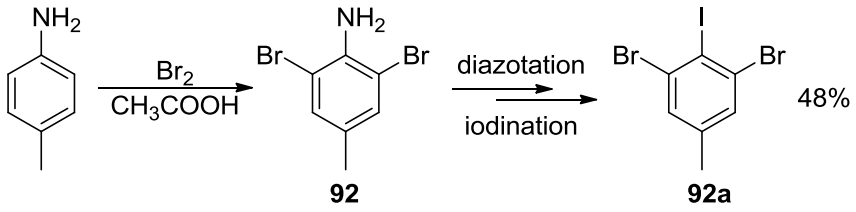
Scheme 46 Suzuki-Miyaura cross-coupling reactions with 4-fluoro-2,6-dibromoiodobenzene

Table 12 Suzuki-Miyaura cross-coupling using as halide 2,6-dibromo-4-fluoroiodobenzene

Entry	R	Conversion (%)*	Product
1	H	57/*54*	**23**
2	F	53/*42*	**2**
3	OMe	*47*/*31*	**95**

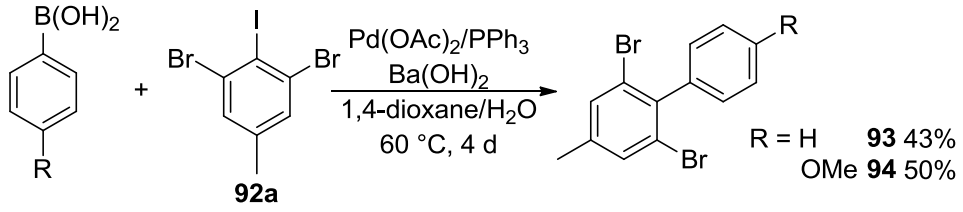
*yields of isolated products are shown in *italics*

These products were isolated by column chromatography and the yields show that these are candidates for further conversions to finally obtain functionalized pyrenes. Encouraged by these results, we decided to modify further the *para*-position of the 2,6-dibromoiodobenzene and replace the fluoro substituents with a methyl group to obtain 3,5-dibromo-4-iodotoluene **92a** (Scheme 47). For this substance, we had to choose another preparation procedure. As starting material, we employed *para*-toluidine and this substitution reaction is influenced by the *ortho*-directing nature of the amino group and the weakly *ortho*-directing nature of the methyl group. As described in the literature, we used acetic acid as solvent and slowly added an excess of bromine, which was also dissolved in acetic acid.[99] After adding a small amount of water, we obtained colorless product **92**. Recrystallization gave colorless crystals, which were subsequently employed in the diazotation and, in following, an iodide substitution reaction analogous to the preparation of **25** (Scheme 34).



Scheme 47 Preparation 3,5-dibromo-4-iodotoluene **92a**

We carried out two coupling reactions with two boronic acids. The first experiments employed common phenyl boronic acid and the second experiments utilized 4-methoxyphenylboronic acid. We chose the same conditions that were also utilized for the fluoro-substituted analogue (*cf.* Scheme 46, Table 12).



Scheme 48 Synthesis of 2,6-dibromo-4-methyl-4′-substituted biphenyl (Table 13)

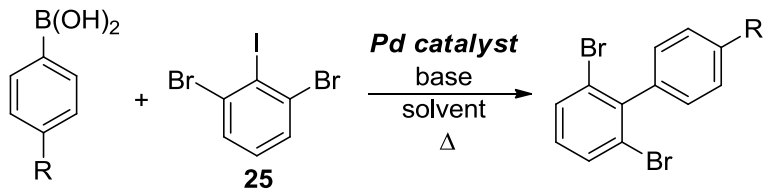
Table 13 Synthesis of 4′-substituted biphenyls

Entry	R	Conversion (%)	Product
1	H	43	**93**
2	OMe	50	**94**

Summarizing these reactions with 2,6-dibomoiodobenzenes, it turned out that the unsubstituted performs best. We reasoned that a further substituent could have influence on the yield in the biaryl coupling reaction because it could be able to affect the oxidative addition step directly due to +I- and +M-effect of the methyl group. In this case these effects likely stabilize the C-halogen bond and hence impede the Pd-insertion. Hence, we conclude that a methyl substituent in the *para*-position reduces the yield compared to fluoro- or unsubstituted analogues.

2.1.2.7 Palladium Catalyst

A crucial point is the choice of the palladium species. The classical Suzuki-Miyaura couplings were performed using $(PPh_3)_4Pd$, commonly using the $Pd(OAc)_2/PPh_3$-catalyst system. For a number of years, Organ's PEPPSI-IPr is reportedly a reliable catalyst system for Suzuki-Miyaura cross-couplings. We carried out several experiments to compare the capability and activity of PEPPSI-IPr with the catalyst system $Pd(OAc)_2/PPh_3$ for our biphenyl coupling reactions. Accounts in the literature show that PEPPSI-IPr works well with carbonate bases and in return PPh_3-systems work well using barium hydroxide as base.[78b,94]



Scheme 49 Comparison of various Pd-catalysts (Table 14)

Table 14 Comparison of various Pd-catalyst systems

Entry	R	Catalyst	Temp. (°C)	Solvent	Time (days)	Conv. (%)*	Product
1	H	PEPPSI-IPr	60	1,4-Dioxane /H_2O	4	75	**3**
2	H	$Pd(OAc)_2$ /PPh_3	60	1,4-Dioxane /H_2O	2	74	**3**
3	H	$Pd(OAc)_2$ /PPh_3	60	1,4-Dioxane /H_2O	2	*60*	**3**
4	OMe	$Pd(OAc)_2$ /PPh_3	60	1,4-Dioxane /H_2O	2	*60*	**41**
5	OMe	PEPPSI-IPr	50	1,4-Dioxane	3	*56*	**41**

*yields of isolated products are shown in *italics*

Reactions and reaction conditions of entries **2** and **3** are identical and give an impression of the relation between GC-conversion and isolated yield. Results in Table 14 show no significant difference between both catalyst systems as we obtained similar yields. The outcome suggested that the difference of the steric bulk is not yet sufficient to influence the speed of the oxidative addition step in one or the other direction. Probably, these should be tested again with smaller co-ligands or with an enhanced size of the side groups on the PEPPSI-NHC ligand.

In addition to the investigations of this section, a different boron-species should be selected in future experiments. Inspired by a talk of Gary Molander (OMCOS 2009) the idea emerged to use trifluoroborates. These aryltrifluoroborates were prepared by conversion of boronic acid with potassiumtrifluoride and promise easy handling and good results without hydroboronation or other undesirable side reactions of trivalent organoboronic species.[66,70a,100] In combination with Organ's PEPPSI-IPr catalyst, we envision enhanced results in the synthesis of our biphenyl-systems.

2.2 Acetylene Couplings

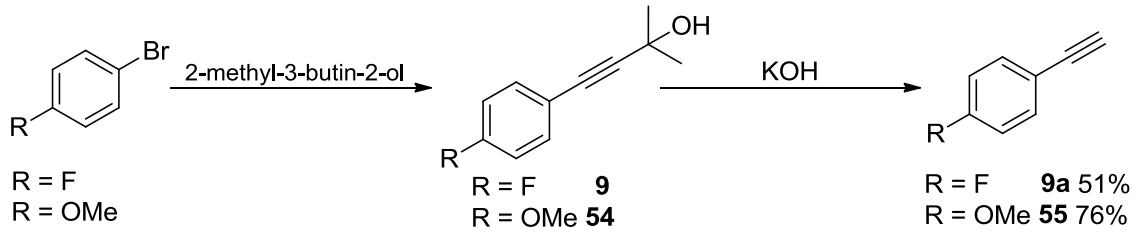
To provide the precursors for the cyclization towards the desired functionalized pyrenes, it is necessary to insert a phenylethynyl moiety in 2- and 6-position of the prepared biphenyls. The first step is to synthesize the substituted phenylacetylenes and

subsequently prepare the phenylethynylbiphenyls for the key cyclization towards the desired pyrenes.

In addition to using ethynyl precursors for the cyclizations to pyrenes, they are valuable building blocks for a unique family of compounds. Structures consisting of a combination of aryl units and acetylenic moieties are known for the aesthetic appearance.[53b] This is due to their capability to build fascinating "nano figures",[52] and additionally, this family of compounds has various applications, *e.g.*, in liquid crystal engineering and drug design.[101]

2.2.1 Synthesis of Phenylacetylenes

We used the corresponding aryl bromides as starting materials to install the ethynyl moiety. There are two different routes to obtain these terminal alkynes. Both of them proceed *via* Sonogashira-Haghiara cross-coupling. One route uses trimethylsilylacetylene to transfer the alkyne moiety (Scheme 51) and the other route employs methylbutinol (Scheme 50). Elimination of the trimethylsilyl and acetone protecting groups in a basic medium and subsequent distillation results in the arylethynyl. We employed different procedures using various aryl halides to detect the most suitable protocol for each substrate.

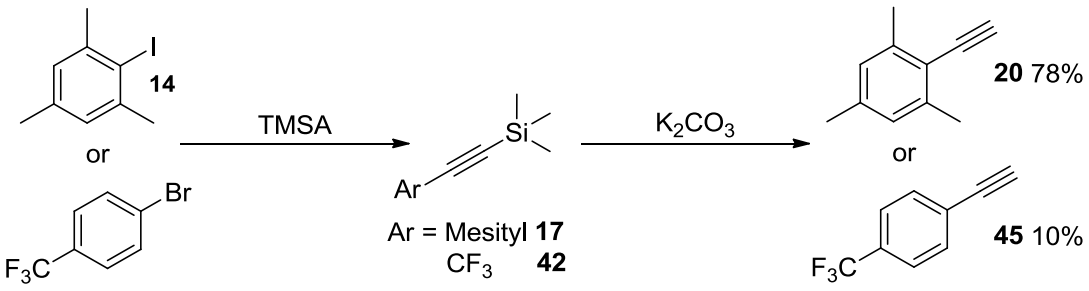


Scheme 50 Preparation of aryl acetylenes

The synthesis of the first stage products **9** and **54** from 2-methyl-3-butin-2-ol proceeds *via* the classical Sonogashira-Hagihrara cross-coupling protocol, using CuI and PPh_3 as co-catalysts, triethylamine as base and $(PPh_3)_2PdCl_2$ as catalyst, which was prepared beforehand according to the literature procedure (Scheme 50).[102] Crude product **9** was obtained in a yield of 96% and a similar amount of **54** was available for further processing. After treatment with KOH in paraffin and distillation of the products, we obtained colorless oils that solidified spontaneously, yielding **9a** in 51% and **55** in 76%.

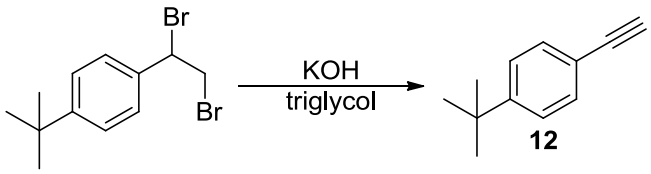
The second procedure also proceeds *via* Sonogashira-Hagihara cross-coupling, but the inserting aryl moiety was changed to trimethylsilylacetylene from 4-bromo-

trifluoromethylbenzene (Scheme 51). We obtained compounds **20** and **45** in yields of 78% and 10%, respectively.



Scheme 51 Preparation of aryl acetylenes

Another third procedure is feasible, which involves a simple 1,2-elimination of the respective dibromostyrene (Scheme 52). The obtained product was a colorless oil in a yield of 36%.



Scheme 52 1,2-Elimination of 1-(*tert*-butyl)-4-(1,2-dibromoethyl)benzene

2.2.2 2,6-Bis(arylethynyl)biphenyls

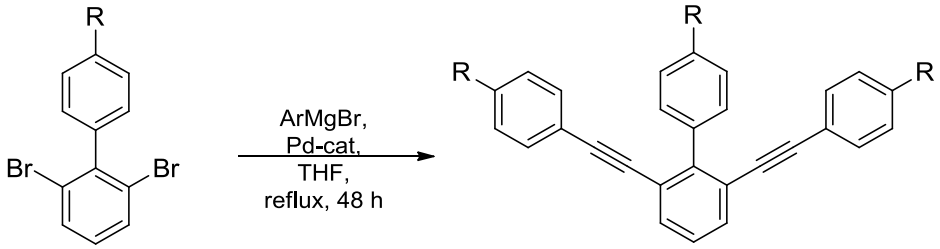
Armed with our 2,6-dibromobiphenyl derivatives and the various synthesized arylethynyls in addition to the available phenylacetylene (which was distilled prior to use), we started the last synthetic step in the development of our targeted pyrenes with Sonogashira-Haghiara cross-coupling. These coupling steps were all carried out under oxygen-free conditions using degassed solvents. After adding the appropriate phenylacetylene, the reactions were refluxed for 20 to 36 h. Generally, we employed the 2,6-dibrombiphenyl derivative, 2.2 eq. of the corresponding phenylacetylene, $(PPh_3)_2PdCl_2$ and CuI (5 mol% each), and 10 mol% PPh_3 in TEA, which acts both as the solvent and a base. We combined different biphenyls with phenylacetylenes and obtained low yields of the twofold coupling product or the mono-phenylethynylated product exclusively (Scheme 53). In some cases, we observed no conversion at all (Scheme 54).

We also employed microwave irradiation for the synthesis of products **19** and **26**. We charged the reaction vessel with the 2,6-biphenyl derivative, 4 eq. of the appropriate

phenyl acetylene, 5 mol% $(PPh_3)_2PdCl_2$, 10 mol% PPh_3, 5 mol% CuI, and 5 mL TEA. The mixture was degassed, the vessel was sealed and flushed with argon. These experiments were performed with 140 W microwave irradiation for 10 min at 17 mbar and 170 °C. However, GC/MS analysis exclusively showed the starting materials.

Inspired by Luh *et al.*, we envisaged another possibility to obtain our cyclization precursors using Kumada-Tamao-Corriu coupling with magnesium organyls.[62] They could successfully be coupled as described in the introducing chapter with alkynyl nucleophiles and with alkyl halides (Scheme 23).

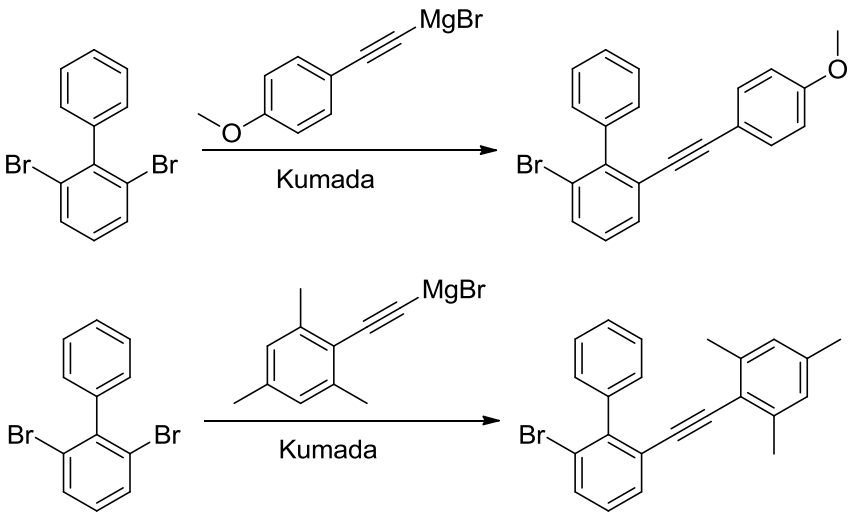
These reactions require previous synthesis of custom-made Grignard reagents to be implemented in Kumada-Tamao-Corriou cross-couplings. We prepared the organomagnesium precursor by a Grignard reaction between ethylbromide and Mg-splinters in dry THF. This precursor was required for the subsequent conversion with the alkyne moiety to the phenylethynylmagesium species. The concentration of the ethylmagnesiumbromides was determined by titration using diphenylacetic acid as the indicator. The enhanced acidity of terminal alkynes leads to metal exchange with this Gringnard reagent. The obtained magnesium organyl in THF was instantaneously added to the previously prepared coupling mixture. First experiments yielded mono-alkynylated product, but reducing the amount of solvent led to the desired products. With this, we repeated the Sonogashira-Hagihara cross-coupling with a smaller amount of solvent, but still, these efforts were fruitless. We obtained the starting material and, until now, undefined black residues of decomposition or polymerization.



Scheme 53 General synthesis route towards 2,6-bis(arylethynyl)-biphenyls

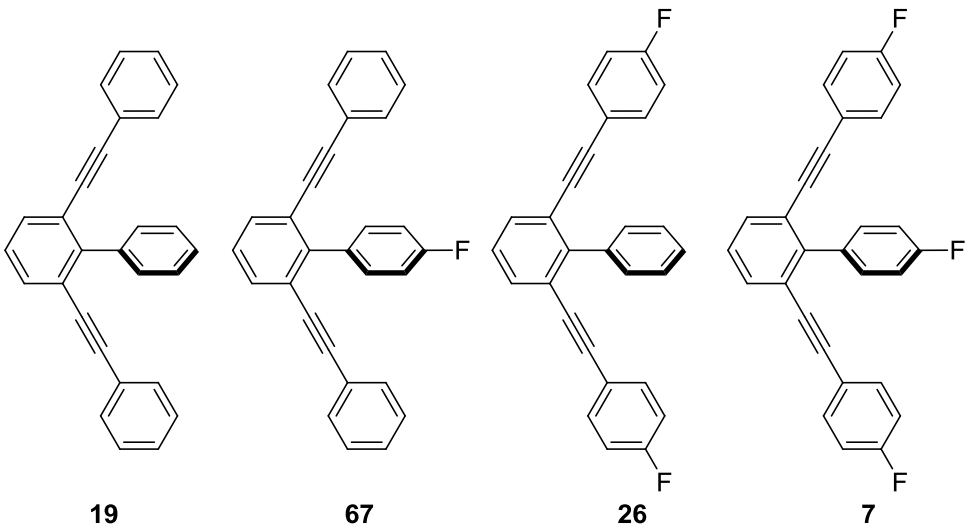
The Kumada-Tamao-Corriu cross-coupling started with preparation of the arylethynylmagnesiumbromide. At –40 °C ethylmagnesiumbromide was added to the respective arylacetylene and the mixture was stirred at this temperature. The solution (6 eq.) was added to the oxygen-free mixture of 2,6-dibromobiphenyl and the Pd-catalyst (10 mol%) in THF and refluxed for 48 h. NH_4Cl was added and the crude product was

extracted with DCM. We tried to couple eleven different combinations of biphenyls and phenylacetylene derivatives. However, GC/MS analysis showed no product for five of these experiments (*cf.* Experimental Section) and only mono-coupling products in two cases (Scheme 54). In some experiments also were found homocoupling products of the arylethynyls.



Scheme 54 Kumada-Tamao-Corriu cross-coupling experiments resulting in mono-coupling product

We obtained 2,6-[bis(phenylethynyl)]biphenyls in four cases (Scheme 55). Products **7**, **26** and **67** were purified by silica gel flash chromatography using hexane/DCM and **19** was purified by preparative HPLC. During the syntheses, we also changed the catalyst and tested the reactions by employing $Pd_2(dba)_3$. For product **26** we reached better yields using the alternative Pd species.



Scheme 55 Synthesized 2,6-bis(arylethynyl)biphenyls

Table 15 Results of the synthesis of 2,6-bis(arylethynyl)biphenyl derivatives.

Entry	Catalyst	Yield (%)	Product
1	$(PPh_3)PdCl_2$	53	**19**
2	$(PPh_3)PdCl_2$	almost complete conversion	**7**
3	$Pd_2(dba)_3$	15	**26**
4	$(PPh_3)PdCl_2$	40	**67**

With regard to all the promising combinations of cross-coupling partners, all of which would impose various electronic and steric properties, which are useful to modify the characteristics of the substituted pyrenes, and consequently of the photoelectronic properties of the ultimate products, it would still be important to devolop reaction protocols adjusted to the already exsisting properties. It would be necessary to determine what prevents them to react under the same conditions like the four performed bis(arlyethynyl)biphenyls (Scheme 55). These four are similar and combined out of two 2,6-dibromobiphenyls and two various arylacetylenes. In order to expand the scope of the different arylethynylbiphenyls, it is necessary to investigate the reaction conditions and refine to develop further to the present experiments. For example, one possibility would be to employ different catalyst/co-catalyst systems, choosing more reactive sytems or replacing them by less active species to prevent the acetylene moieties from homocoupling to tolane derivatives. Other variables are - as in Suzuki-Miyaura cross-couplings - solvents, temperature, concentration, reaction time, and the choice of base. These optimizations remain a challenge for the future.

UV/Vis spectra of aromatic and acetylenic species are abundant. The spectra of **7** and **19** show strong absorbance between 280 and 300 nm (acetylenic $\pi \rightarrow \pi^*$ transition) and also at 310 nm in the case of fluoro-substituted **7** ($n \rightarrow \pi^*$ transition). These spectra also display the characteristic three-peak pattern of the diphenylacetylene-chromophore, which occurs at ca. 280, 290 and 300 nm for the parent diphenylacetylene.[103] For compound **19** we observe a similar pattern. Yet, for compound **7** we observe a bathochromic shift (+10 nm) and a distinctable three peak pattern at 280, 290 and 310 nm (Figure 3).

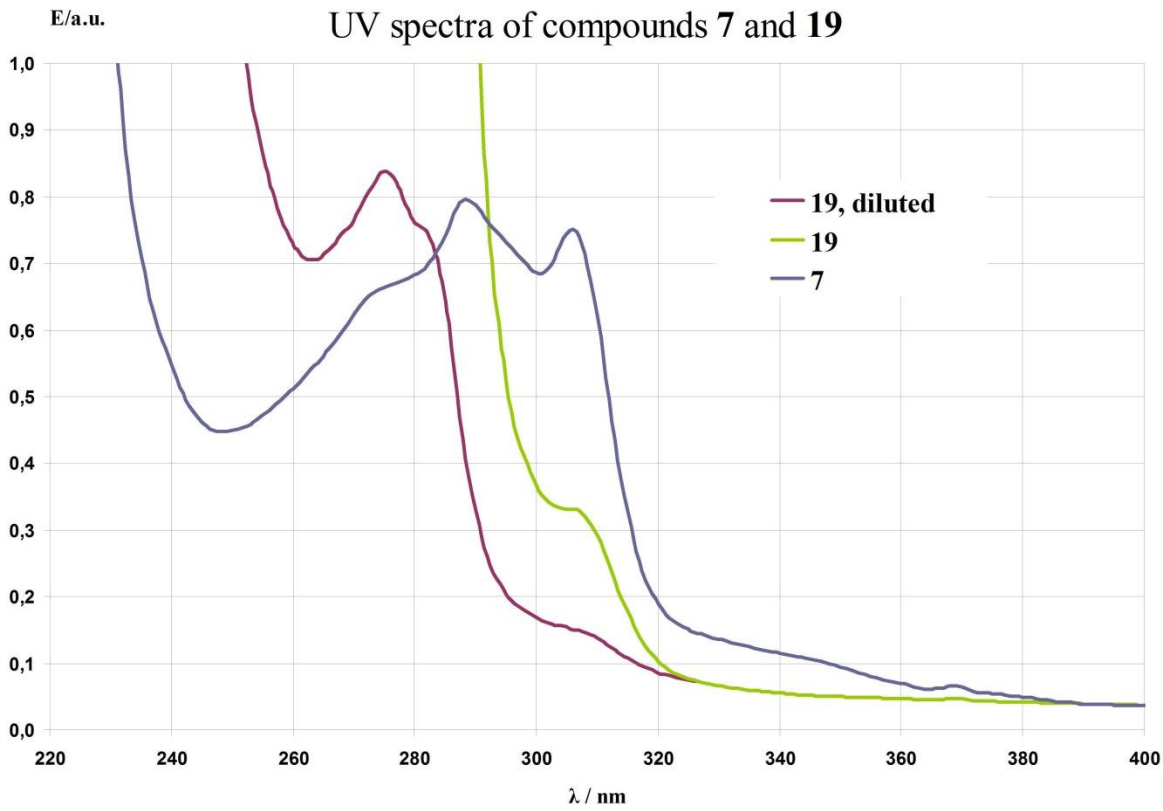
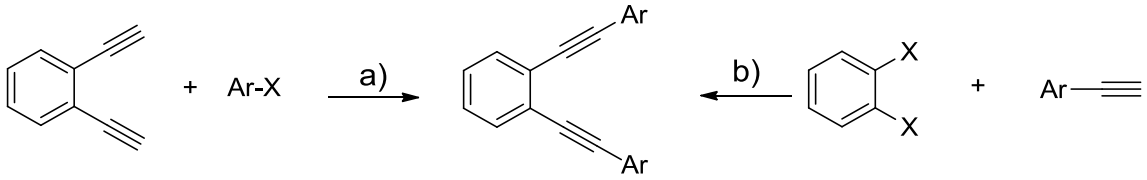


Figure 3 UV/Vis spectra of compounds **7** and **19**

In conclusion, we have to mention that the Sonogashira-Hagihara cross-coupling may have pushed generally the Kumada-Tamao-Corriu reaction into a marginal role, but in our case the Kumada-Tamao-Corriu reaction provided good results.

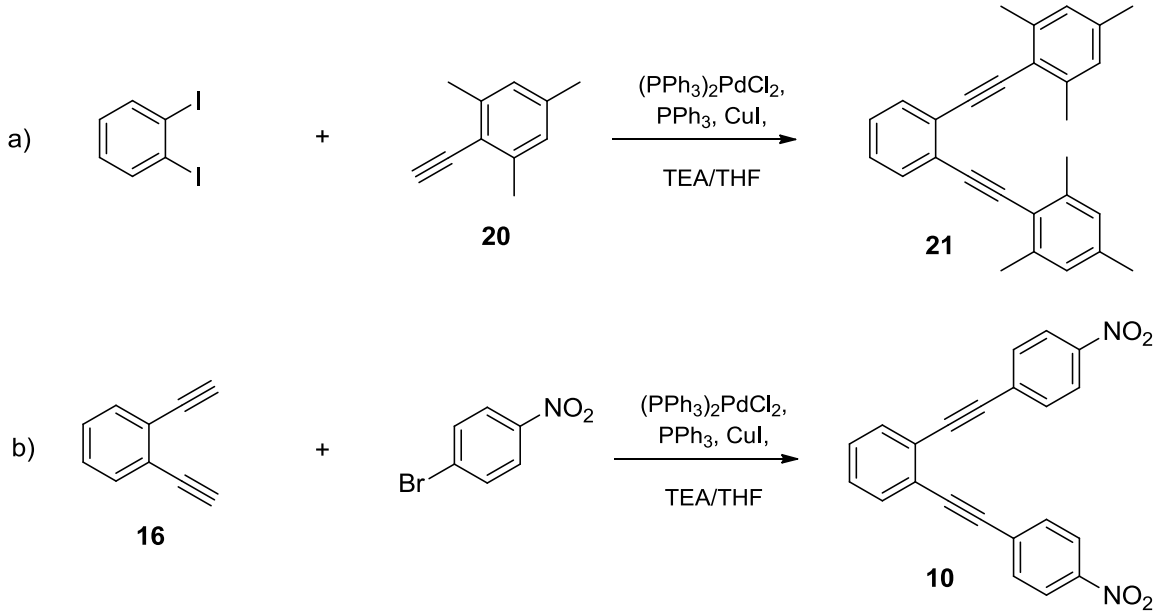
2.2.3 Preparation of 1,2-Bis(phenylethynyl)benzenes (Enediynes)

To investigate the effects of substituents in thermally induced cyclizations of enediynes and to examine the results of Pascal *et al.*, we had to prepare substituted 1,2-bis-(phenylethynyl)benzenes as the enediyne moiety. For preparation of the starting materials we had two choices (Scheme 56). Version a) implements 1,2-bis(ethinyl)benzene with the corresponding aryl halide. Version b) uses 1,2-dihalobenzenes to be cross-coupled with appropriate aryl acetylenes.



Scheme 56 Possible synthesis routes to prepare 1,2-bis(arylethynyl)benzene derivatives

We decided to start with the preparation of the appropriate phenylacetylene derivatives, which requires two steps in case of 4-nitrophenylactylene. 4-Nitrobromobenzene was treated with an acetylenic precursor and was subsequently deprotected. For mesitylacetylene, we had to prepare the iodide **14** first (*cf*. Section 2.1.1.1.2, Scheme 34), subsequent Sonogashira-Hagihara cross-coupling and also deprotection in basic milieu offers the product (as described in section before). These phenylacetylene derivatives could subsequently be subjected to Sonogashira-Hagihara cross-coupled with 1,2-diiodobenzene [Scheme 56, path a)]. Another possibility to generate these enediyne moieties is to implement the enediyne moiety as diethynylbenzene **16**. For this 1,2-dibromobenzene was treated with 3,3-dimethylbut-1-yne in a Sonogashira-Hagihara cross-coupling followed by a deprotecion reaction and subsequent Sonogashira-Hagihara cross-coupling for insertion of the aryl-moitey. Preparation of **21** proceeds well *via* the initially described synthesis route [Scheme 57, path a)] and **10** on the other hand *via* the second depicted route [Scheme 57, path b)].

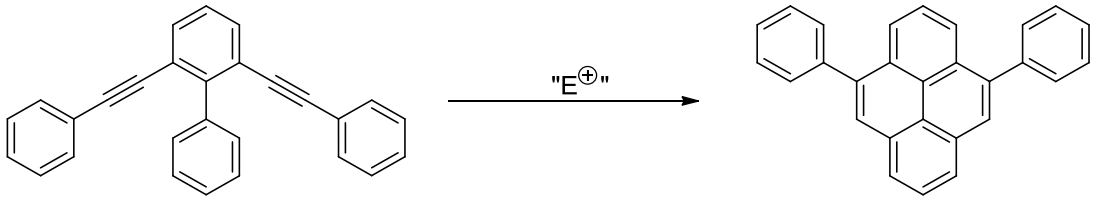


Scheme 57 Synthesis of 1,2-bis(phenylethynyl)benzene derivatives

Compound **21** was purified by column chromatography and was obtained as a pale yellow oil in a yield of about 92%, but NMR-analysis showed impurities of monophenylethynylated product. For the nitro compound **10,** the fine yellow needles were recrystallized from toluene to obtain the pure product in a yield of 47%.

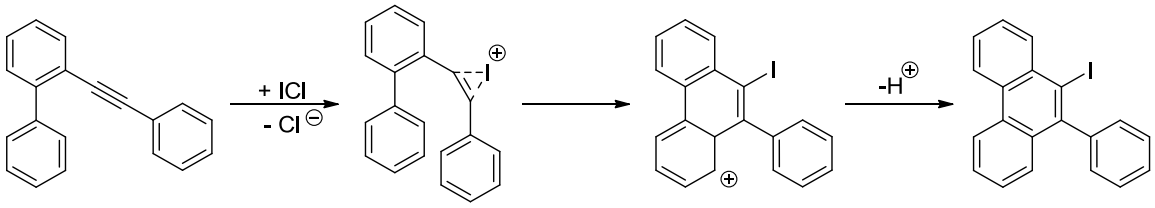
3 Cyclizations

3.1 Twofold Electrocyclization towards Pyrene Derivatives



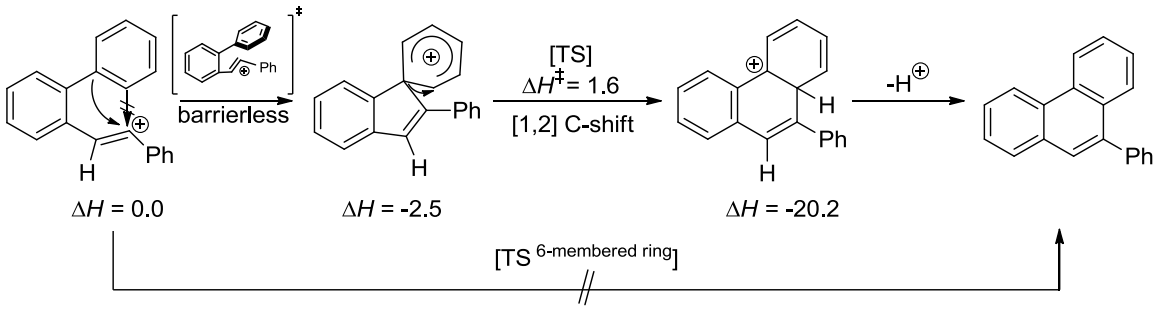
Scheme 58 Goal: electrophilically induced cyclization to pyrene-derivatives

In order to obtain pyrenes in an elegant and novel manner, the key idea was to cyclize our phenylethynylbiphenyls *via* electrophilically induced cyclization to pyrenes (Scheme 58), inspired by the work of Larock *et al*., who cyclized enynes to phenanthrene derivatives (Scheme 59).[1b,104]



Scheme 59 Larock's cyclization and postulated mechanism

We took a closer look at this mechanism by employing DFT methods (at the M06-2X/6-31G(*d*,*p*) level of theory).[105] Contrary to expectations based on the results of Larock *et al.*, a transition state leading directly to the product could not be found (Scheme 59).[1a,104] Instead, this cyclization occurs *via* a five membered ring as transition state as revealed by the computational results (Scheme 60). Subsequently, the product is formed from the five-membered ring intermediate *via* the depicted Wagner-Meerwein rearrangement.



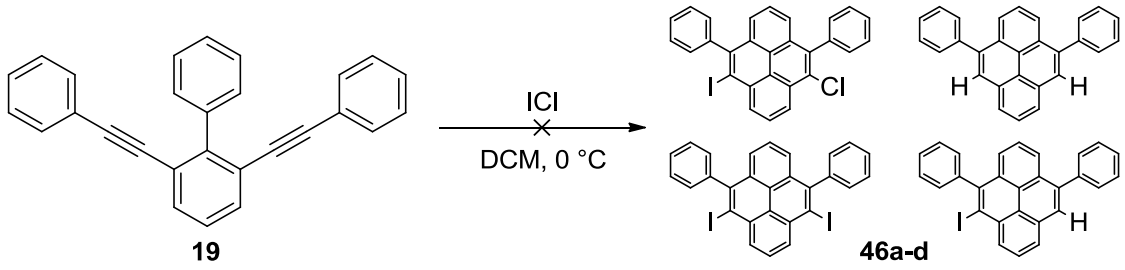
Scheme 60 Postulated mechanism; computationally supported (M06-2X/6-31G(*d*,*p*) level of theory); Δ*H* values in kcal mol^{-1}

Larock *et al.* used ICl to induce the intramolecular electrophilic acetylene cyclization and, hence, generated molecules which can be further functionalized by cross-couplings. In this way, iterative cyclization steps towards PAHs can be induced. This attractive

synthesis, which opens up substitution patterns with different substituents in either 10 and 4 or 9 and 5 position, was hitherto unknown.

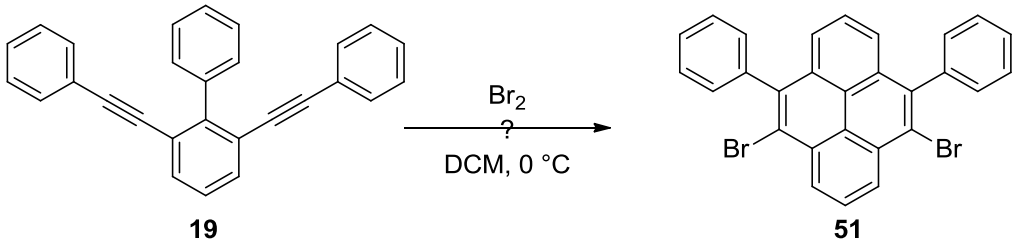
Further work of Schreiner *et al.* likewise showed an electrophilically induced cyclization using enediynes to form fulvenes. This cyclization occurs by a similar mechanism and has been extended to domino and tandem cyclizations (*cf.* Section 3.3).[12] Our idea was to use the concept of Larock *et al.*, but to expand the basic scaffold with an additional phenylacetylenic moiety to form pyrenes with diverse and complementary substitution patterns.

The first attempt employed ICl as cyclization initiation reagent. To a solution of **19** in DCM under oxygen-free and dry conditions at 0 °C, ICl (5 eq. in DCM) was added dropwise (Scheme 61). The mixture turned clear and we continued the dropwise addition until the discoloration stopped and the solution remained dark brown. Work-up and purification (*e.g.*, by preparative TLC) provided a dark brown viscous oil. NMR- and mass spectra only show the starting material and unidentified impurities and gave no evidence of possibly formed products.



Scheme 61 Cyclization with ICl with a range of possibly formed cyclization products.

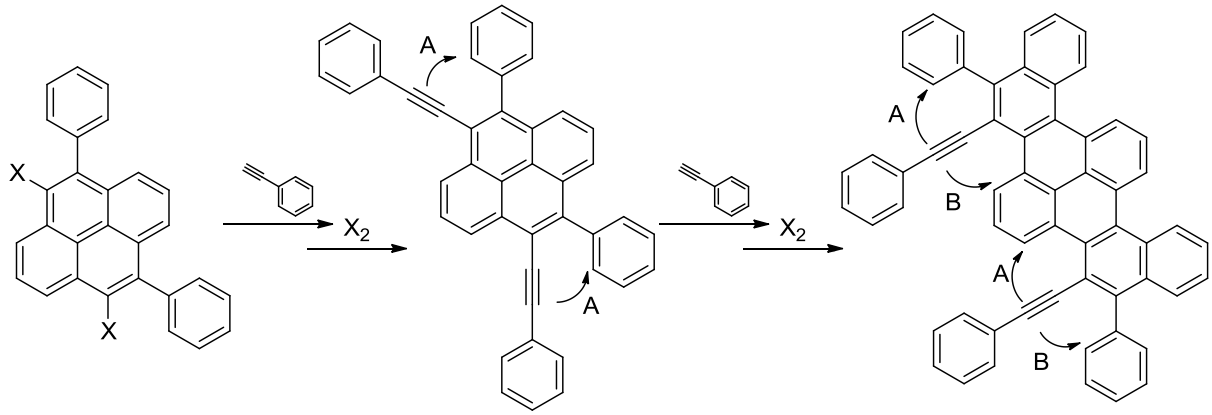
The second attempt was carried out under same conditions, but instead of ICl, Br_2 (5 eq.) was used as cyclization initiation halogen (Scheme 62). A brown oil was obtained, but all purification attempts lead to no success. Comparison of the NMR spectra of the starting material with these of the crude product apparently show that we obtained more signals in case of the crude product mixture (‘a mountain like appearance’ of the NMR spectra, metaphorically speaking) with a chemical shift around 130 ppm (^{13}C-NMR). These are characteristic shifts in polyaromatic systems. In conclusion, a cyclization has probably occurred, but we could not precisely eludicate the outcome of the reaction.



19 **51**

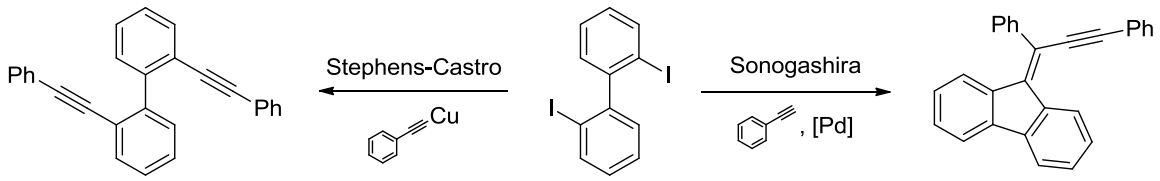
Scheme 62 Cyclization attempt using Br_2 as initiating reagent

Concluding, it is necessary to investigate and optimize the cyclization protocols, because the development of halogen-substituted pyrene derivatives enables further substitutions in positions 5 and 9. This strategy allows affecting the specific electronic properties of the pyrene system and therefore its optoelectronic properties. Another possibility is to substitute this system in these positions with phenylethynyl moieties and cyclize them. An iterative progress of this sequence would lead to polyaromatic systems (Scheme 63).



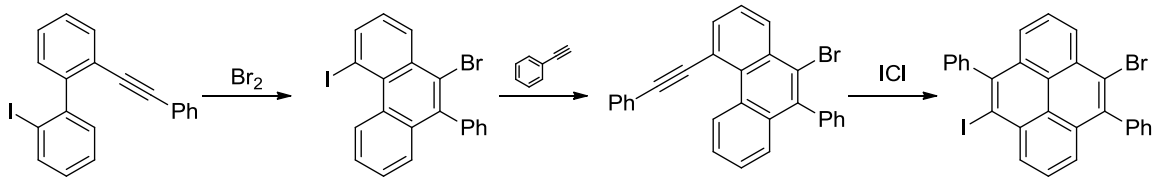
Scheme 63 Possible iterative progress of the electrophilically induced cyclization

Two cyclization pathways (Scheme 63, A and B) with two spatial arrangements are possible, resulting in either a helical structure or a bowl shaped molecule, respectively. Expanding these ideas to biphenyls, which carry diagonally arranged phenylethynyl moieties, affords yet another substitution pattern after cyclization. However, the precursors had to be prepared employing Stephens-Castro coupling, because Sonogashira-Hagihara cross-coupling would lead to fluorenyl-type species (Scheme 64).



Scheme 64 Proposed synthesis of additional cyclization educts, which make further pyrene substitution patters possible.

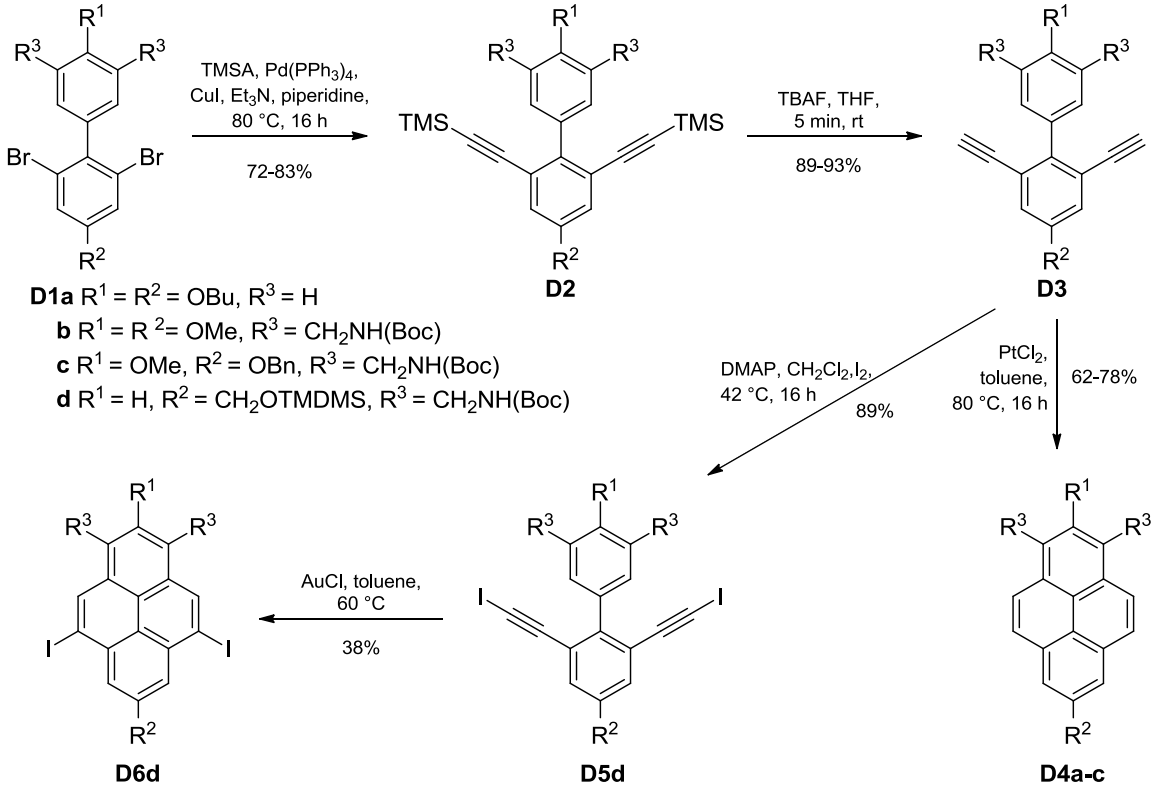
This synthesis route yields pyrenes carrying substituents in 4-, 5-, 9- and 10-position after the cyclization step, each pair of substituents positioned 'diagonally' being equal. Another extended methology of this concept would be stopping the Stephens-Castro coupling after onefold coupling, subsequent cyclization and further coupling with a phenylethynyl substituent, followed by another cyclization step (Scheme 65).



Scheme 65 Proposal for development of further substitution patterns of pyrene derivatives

This could lead to various halogen-substituents (4,9-dihalopyrenes) and consequently to two different reactivies, which could be exploited for further functionalizations. But before doing that, it would be necessary to optimize the cyclization reaction initiated by halides. We have to consider several variables such as temperature, solvents, and dilution factor. For example, Larock's ICl- and Br_2-induced cyclizations proceed at –78 °C or r.t.[1b,104] Perhaps, our twofold coupling systems require a customized temperature protocol with gradual heating or cooling sections. Also, other solvents and concentrations as well as different rates of addition have to be investigated. The subsequent challenge is the purification of these products and hence their separation from the wide range of possibly formed side products. Yet, these are plans for the future work.

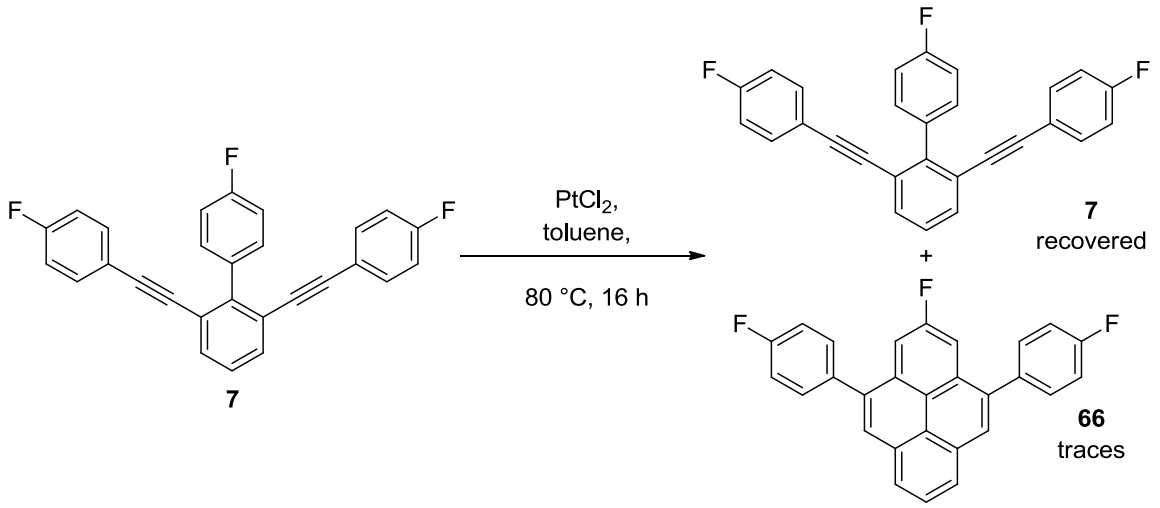
Electrophilic cyclizations not only can be initiated by halogen-cations, but also by metal salts like $PtCl_2$, $AuCl_3$, $GaCl_3$, and $InCl_3$. Davis *et al.* reported cyclizations of similar substrates using a protocol of Fürstner *et al.*[14,16a] The difference was that Davis induced the twofold intramolecular acetylene cyclization with $PtCl_2$ and AuCl and not by the addition of an electrophile (Scheme 66).



Scheme 66 Davis' pyrene synthesis[16a]

Davis'[16a] and previous work of Schreiner *et al.*[12] utilizing electrophically induced ring closures[1a,1c,14] enables the introduction of substituents in positions 4 and 10 of the pyrene taget without substitution in positions 5 and 9.[16b] Furthermore, the use of electrophilic cyclizations is a viable approach to achieve these highly functionalized pyrene derivatives without employing toxic pyrene as starting material. We achieved an extension of Davis'/Fürstner's strategy to prepare functionalized pyrenes form 2,6-bis-(phenylethynyl)biphenyls anticipating that these can also be conveniently employed for cyclization reactions.[1c,106]

We started with **7** (and identically with **19**) under inert and dry conditions at 80 °C with 5 mol% $PtCl_2$ in toluene. After 24 h, we mostly regained the starting material and the pyrene, respectively, as in very low yields (Scheme 67). We obtain the same result using AuCl. We experienced that various cyclization attempts utilizing established procedures of Fürstner *et al.* were to partial success only.[1a,107]



Scheme 67 Cyclization attempt of **7** employing Fürstner's protocol

We also addressed the question which factors might prevent such systems to give pyrenes. In order to elucidate this unexpected behavior, we compared our systems with those of Larock *et al.* (Figure 4) and employed density functional theory (DFT) computations to gain insight into the geometric constraints of the cyclization precursors.[16b]

Computations at the M06-2X/6-31G(*d,p*)[105,108] level indicate that **19** is twisted, with the phenyl substituent in 1-position being almost perpendicular (~90°) to the plane of the other aryl moieties. The twisted structure lies 14.7 kcal mol^{-1} below a hypothetical planar arrangement, which is not a stationary point on the potential energy hypersurface. In contrast, the corresponding energy difference of the rotational profile of Larock's phenylethynylbiphenyl system is only about 7.2 kcal mol^{-1}.[104,109] Between the C–atoms that eventually form the new C–C bond and the enyl-attached C–atom of the biphenyl element in **19**, we observe an angle of 79° and a C–C distance of 3.85 Å, while Larock's precursor has a critical angle of 73° and a distance of 3.40 Å. Hence, the steric arrangement of structure **19** is rather unfavorable for the desired 1,6-cyclization (Figure 4).

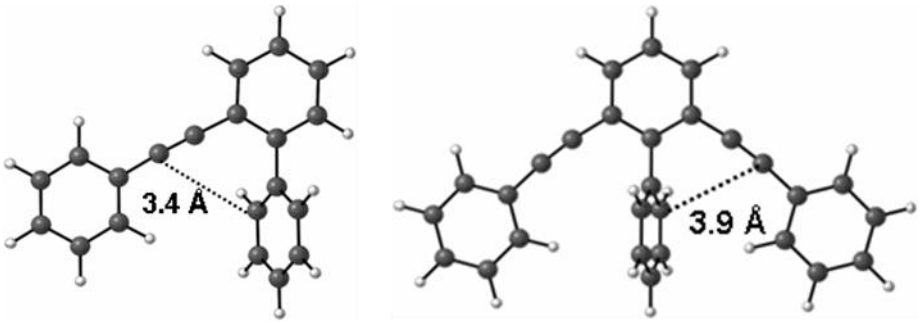
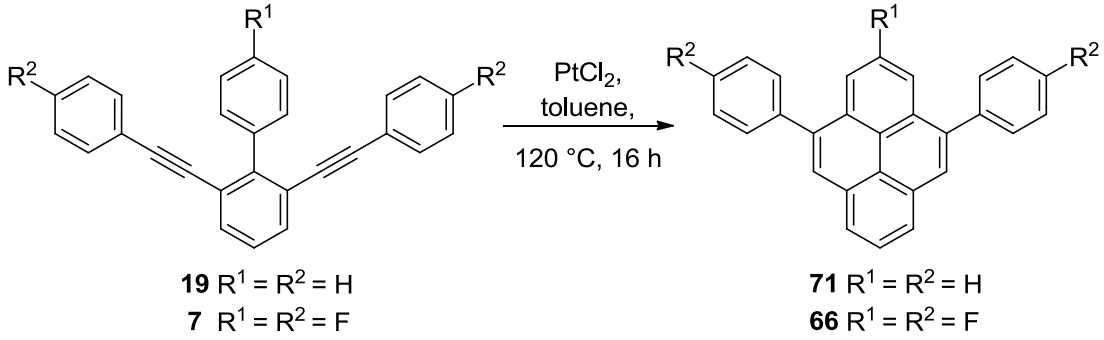


Figure 4 Optimized structures (M06-2X/6-31G(*d,p*) level of theory). Distance marked are between C-atoms that form the new bond. Larock's structure is depicted on the left and **19** on the right.

These findings suggest that our system requires higher reaction temperatures. Hence, we performed the reaction under reflux. We obtained the pyrenes **66** and **71** (Scheme 68). Both were purified by HPLC and subsequent sublimation in UHV (10^{-6} mbar). For **71** we could obtain an NMR-spectrum, but for **66** too many signals appeared due to the fluorine interconnections and non-analyzable side products prohibited the interpretation of the spectra. Yet, we found evidence of the product when we compared the mass traces of the HRMS spectra of product and starting material.



Scheme 68 Cyclization to 4,10-aryl-substituted pyrene derivatives

The optimized geometry of pyrene **71** obtained by DFT computations also shows twisted (almost perpendicular) phenyl substituents, which supports the spectroscopic finding that **71** shows pronounced blue fluorescence and therefore does not display undesirable π-π stacking. The main quality for potential use of these pyrene derivatives in optic devices is their fluorescence capability. Hence, we measured fluorescence- and UV/Vis spectra of **71** (Figure 5).

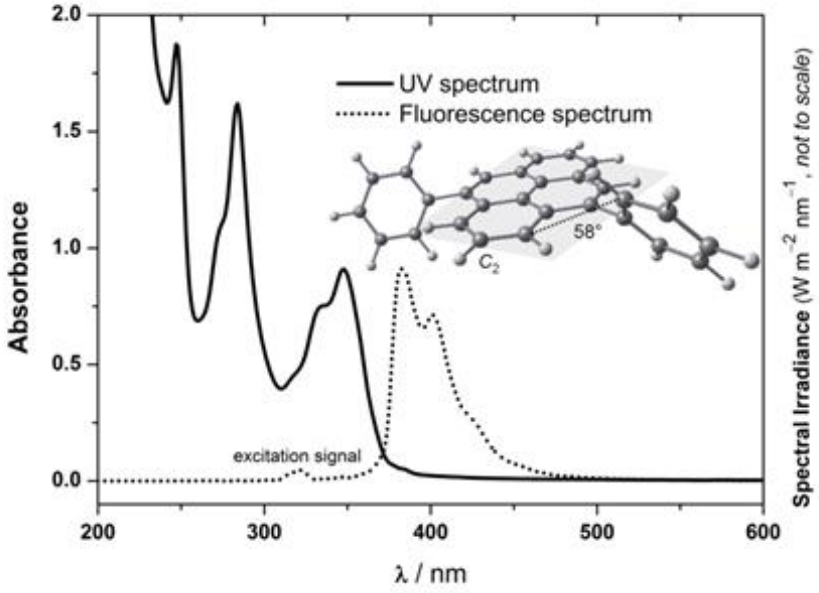


Figure 5 UV/Vis- and fluorescence-spectra of **71**

We recorded a blue shift (–20 nm) of the absorption bands compared to parent pyrene (338 nm). Pyrene derivatives with alkyl substituents show a hypsochromic effect.[110] The emission spectrum (Figure 5) shows a maximum at about 380 nm and nicely mirrors the UV/Vis spectrum. The Stokes shift was determined to be around 50 nm. We measured the long-wavelength absorption of pyrene **71** at 310 nm as a $\pi \rightarrow \pi^*$ transition, which mainly involves the HOMO-LUMO transition of the S_0 (^{1}B) ground state to the open-shell singlet state S_1 (^{1}A).

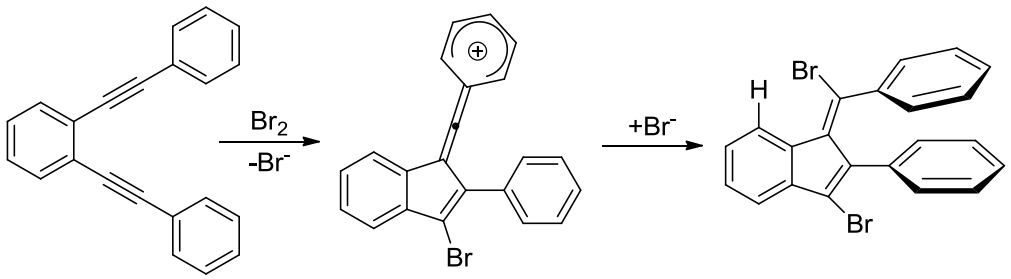
In summary, we were able to cyclize the resulting phenylethynyl biphenyls to pyrene derivatives, with a substitution pattern that is not readily available utilizing common approaches to pyrenes. It is necessary to expand the substrate scope for the cyclization towards pyrenes and also to optimize the cyclization conditions. Furthermore, it is necessary to develop a successful purification protocol for pyrene derviatives, which is unavoidable for the application in OLEDs.

3.2 Cascade Cyclization of Polyethynylarylbenzenes

By expanding the approach of electrophilically induced cationic cyclization of enediynes, which leads to pentafulvene derivatives, to cascade cyclization of polyethynylarylbenzenes, bowl-shaped polyaromatic hydrocarbons should be formed in a single step. In 2001, Schreiner *et al.* demonstrated an electrophilic domino-cyclization of benzene-1,2,3,4-tetrayltetrakis(ethyne-2,1-diyl)tetrabenzene **VL-4** (Figure 6), resulting in

a half-bowl shaped compound. The reaction proceeds *via* a *555*-cyclization mode and gives an inseparable mixture of products.[12] These nonplanar scaffolds include, next to the unfavorable six-membered rings, also five-membered rings. The strategy should allow the formation of both ring sizes. The cyclization of 1,2-bisethynylbenzene to the benzopentafulvene derivative using bromine as initiator has already been demonstrated experimentally.[12]

The ultimate goal of this research is obviously to understand the mechanism of these cyclizations at the molecular level which implies studies which intermediate cations are formed. Computations on the parent system at the B3LYP/6-31G(*d*) level of theory show the formation of a stabilized phenyl/allenyl-cation to be feasible.[12]



Scheme 69 Electrophilic domino cyclization[12]

In addition to the computational results of the mechanistic progress we have designed experiments to validate and supplement the computed results. The system shown in Scheme 69 was expanded with further phenylethynyl moieties to yield phenylethynylarylbenzenes (Figure 6). These experiments should also result in the formation of bowl shaped PAHs *via* electrophilic initiation of the cyclization. The experimental confirmation of the postulated mechanism of this kinetically controlled reaction by cyclization of the parent enediyne moieties as depicted in Scheme 70 is performed by trapping the *in situ* formed allenyl cations using iododipyridinumtetrafluroborate. These results are proven by the x-ray structures depicted in Figure 6.

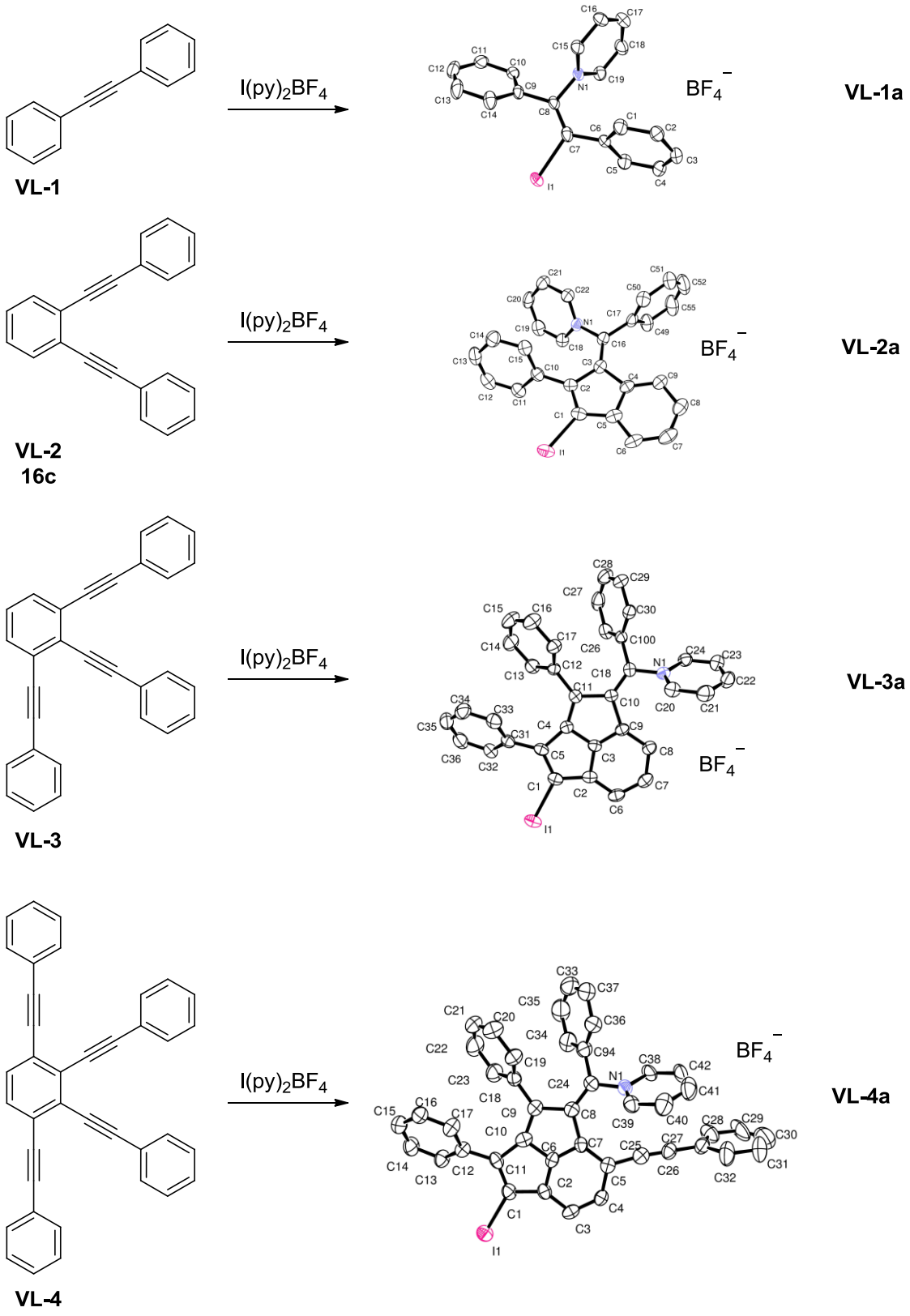
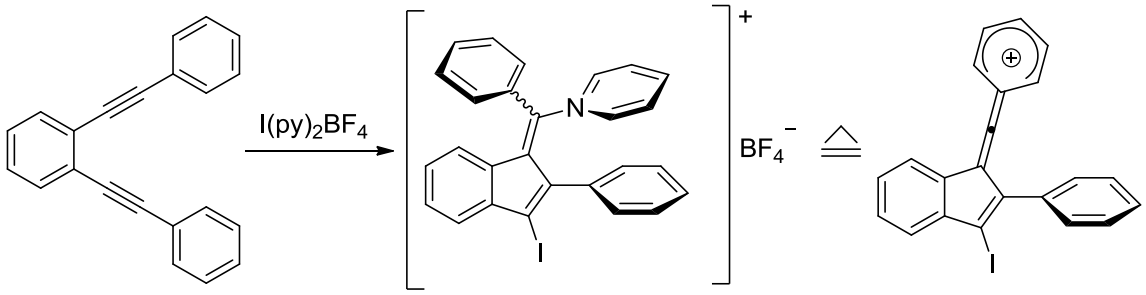
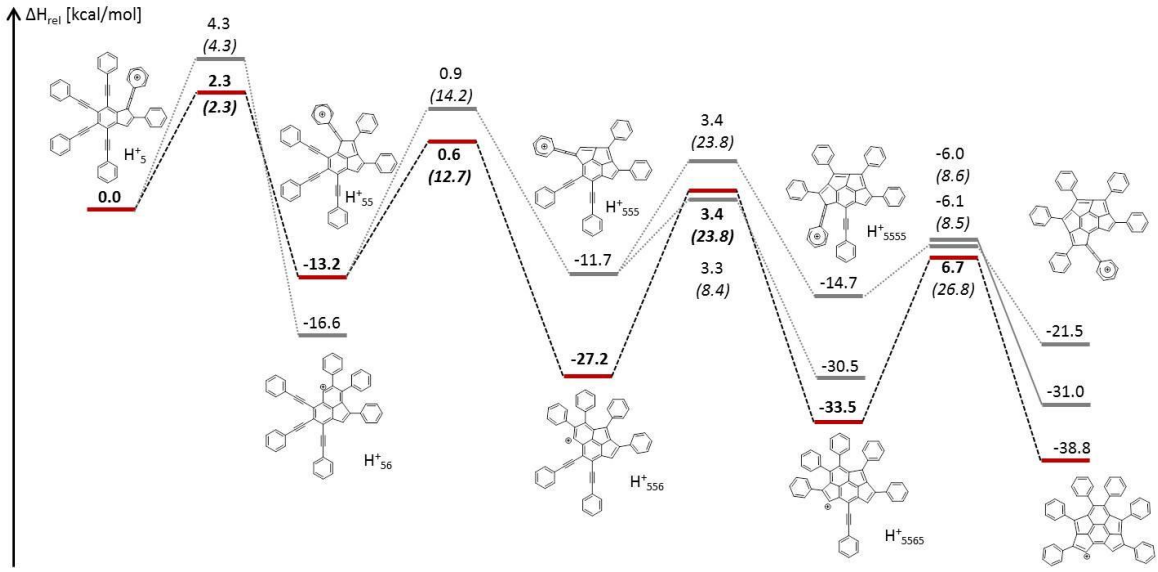


Figure 6 x-ray structures of the trapped pyridinum salts[111]



Scheme 70 Trapped intermediary formed allenyl cation as pyridinum salt for **VL-2a**

The pyridinum salts obtained by this method differ from the optimal linear geometry caused by the stabilization of the pyridinium-nitrogen.[111] Schreiner *et al.* explored the scope of these "cascade cyclization" to curved systems with respect to the cationic intermediates. These appear upon formation of five- and six-membered rings. Investigation of ring closure selectivity, also with regard to the ring strain energy was studied computationally. The computations of this stepwise electrophilically induced cascade cyclization are shown in Scheme 71, which depicts pathways forming intermediary quasi-allenyl cations. The energies are shown graphically as potential energy surface, showing the most favorable ring closures and thermodynamically pathway based on structure **48** (for structure see Scheme 72).[111]

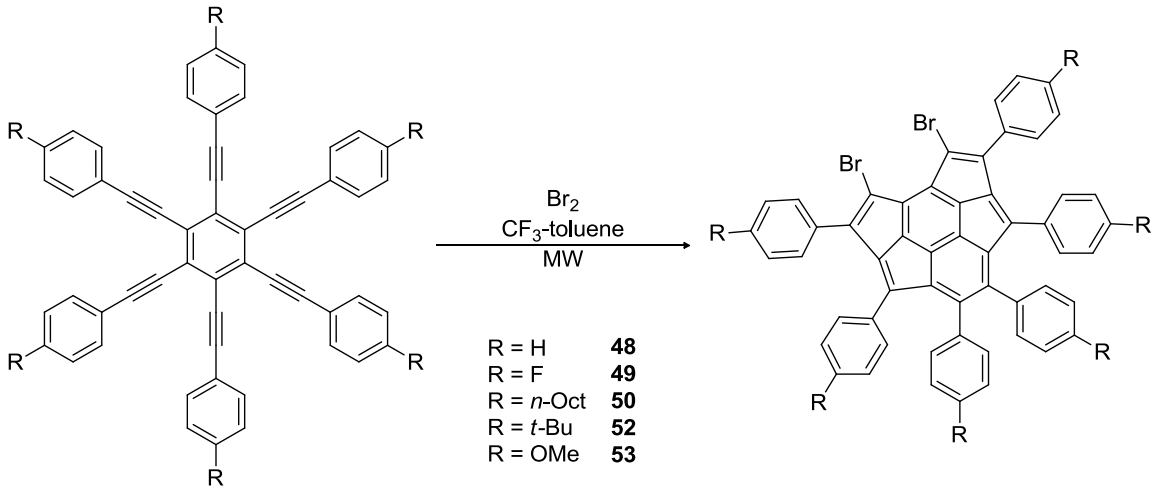


Scheme 71 PES (computed at the B3PW91/6-31G(*d*) level of theory) of iterative electrophically-induced cascade cyclization of 1,2,3,4,5,6-hexa-(1-ethynyl-2-phenyl)benzene **48**. Indices of the intermediates characterize the type of ring formation. The thermodynamically most favorable pathway is marked as broad line and red steps. Alternative formations are shown as grey lines. Relative activation barriers are shown in *italics* in parenthesis.[111] Δ*H* values given in kcal mol^{-1}.

This stepwise, electrophically induced cascade cyclization was computed at the B3PW91/6-31G(*d*) level of theory. This level was choosen because it reveals the lowest systematic error due to an improper treatment of dispersion interactions of the relative energies for large hydrocarbon molecules.[112] The **48**-H^+-monocyclized species was used as the starting structure. "Br^+" was replaced by "H^+" for the computations because of bromine's triplet state and the possible problems, which could arise from an alteration of the systems' multiplicity during the computations. The intramolecular cascade cyclization was treated also computationally in a stepwise fashion. The computations for the first three annulations of the ethynyl moieties predict products featuring five-membered rings because of a low activation barrier. The fourth ring closure leads to the six-membered ring computationally, whereas the last two are five-membered cyclization products again. Overall, the reaction is thermodynamically controlled and gives the bowl-shaped *55655*-product (Scheme 71).

For the experimental analysis of a sixfold cascade cyclization we started with 1,2,3,4,5,6-hexa-(1-ethynyl-2-phenyl)benzene derivatives and used Br_2 as the initiating reagent while treating the reaction mixtures with microwave irradiation. As already mentioned, the use of microwave irradiation provides homogenous and fast heating of the reaction mixture and moreover leads to high pressure in a sealed vessel.

The first two experiments were carried out in a 10 mL sealed vessel using 0.1 mmol of the starting material (**48** - **51**), and 0.5 mmol Br_2 in dichloromethane (Scheme 72). We chose a reaction temperature of 150 °C, 150 W power, and a reaction time of 2 h under maximum pressure. The reaction temperature could not be reached with these settings and the pressure exceeded the maximum because of the low boiling point of dichloromethane and, consequently, excessive vapor pressure (in one case, the vessel's cap even burst due to the inner pressure). Therefore, we changed the solvent to trifluorotoluene, because of its similar dipole moment compared to dichloromethane, but with at significantly higher boiling point (102 °C) and hence lower vapor pressure.

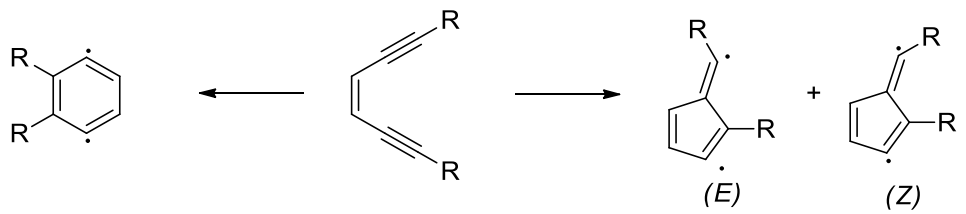


Scheme 72 Sixfold cascade cyclization; starting materials were prepared using Sonogashira-Hagihara cross-coupling.

The reactions in trifluorotoluene using **48**, **52** and **53** as starting material were carried out under same conditions in the microwave apparatus. In all cases, we obtained a dark brown, inseparable mixture of undefined products. However, ^{13}C-NMR-spectra show an accumulation of signals with a chemical shift in the aromatic range and the signals of the actylenic carbons vanished. It is certainly necessary to optimize these reaction protocols and purification methods for these complex structures. Conceivably, performing a low temperature reaction with long running time or a revised microwave operating protocol will lead to less complex product mixtures of these cascade cyclization reactions. To conclude, certainly more experience has to be accumulated from a higher number of experiments.

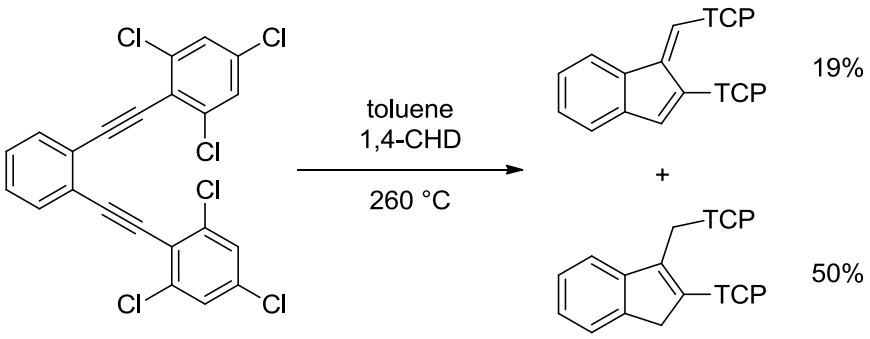
3.3 Thermal 1,5- *vs.* Thermal 1,6-Annulation

The subject is a 1,5-cyclization of "Bergman starting materials", *i.e.*, enediynes, which are usually triggered by photoinduced electron transfer,[1d] electrophiles,[12-13] radicals[113] or metals,[14,114] but not by thermal induction.[1d,113] Commonly, a 1,5-cyclization passes by an fulvenoid-biradicalic intermediate, which can occur as two isomers as depicted in Scheme 73.



Scheme 73 Biradicaloid intermediates formed out of enediynes

These intermediates possess an enhanced biradicaloid character compared with the classical Bergman intermediates and bulky substituents should support the cyclization towards fulvene derivatives.[50] Pascal *et al.* found a thermally induced 1,5-cyclization[11] and postulated that the thermal 1,5-cyclization of 1,2-bis[(2,4,6-trichlorophenyl)-ethynyl]benzene proceeds in that manner, because of the steric bulk of the chlorine-substituents. The driving force of ring closure or the ring size, respectively, is only caused by steric effects and not by electronic influence of the substituents according to the results of Pascal *et al.* (Scheme 74).

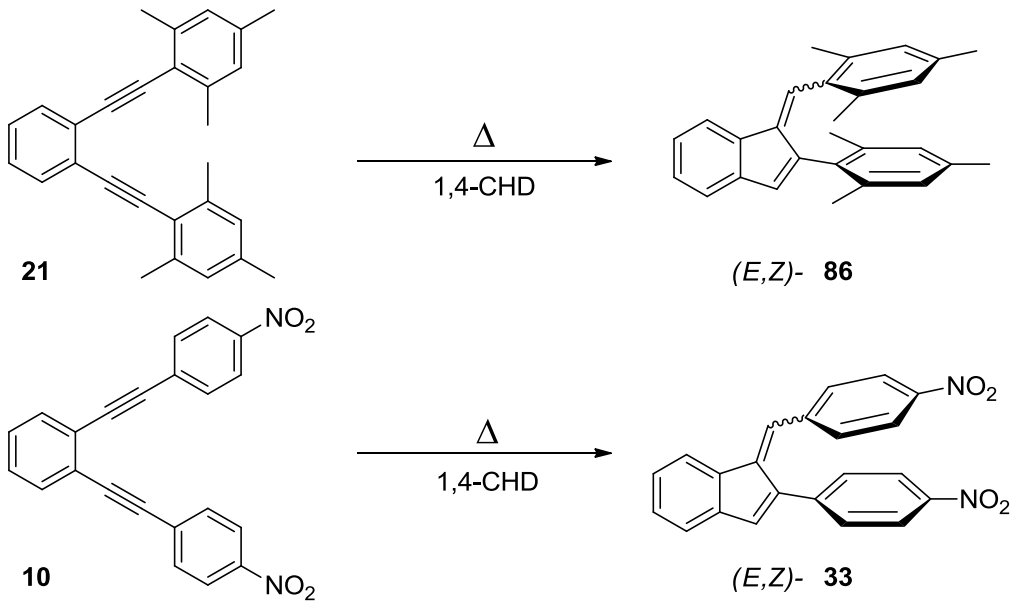


Scheme 74 Thermally induced 1,5-cyclization published by Pascal *et al.*[11]

Previous computational findings of Schreiner *et al.* deduce that the driving force towards the annulation of five-membered rings should be caused by mesomeric and, hence, electronic effects are responsible for the stabilization of the biradicaloid intermediate.[2,10,115] Herein, we investigated whether the results of Pascal *et al.* are really due to steric effects. We studied thermal cyclization attempts of mesityl- and 4-nitrophenyl enedyine derivatives to determine the radicaloid stabilization of the 1,5-biradicaloid intermediate. It could be also that a steric effect of bulky groups is pushing the cyclization towards the 1,5-product. Sterically demanding groups at the terminal alkyne position support a reaction that leads to fulvene derivatives as the product of thermally initiated cyclizations *via* a diradical.

However, our results support the formation of 1,5-cyclization products in both cases. According to Pascal *et al.*, only 1,2-bis(mesitylethynyl)benzene **21** should cyclize *via* the C^1-C^5 cyclization pathway because of the comparable size of the methyl and chlorine substituents. This finding would support, but not ultimately verify the results of Pascal *et al.* Therefore, we set out the other experiment, employing 4-nitrophenyl enediyne **10** to provide further evidence on how these diradicalioid cyclizations proceed. The replaced mesityl substituent by a 4-nitrophenyl substituent should also stabilize the radicaloid

intermediate. If the cyclizations are dominated by steric effects, for enediyne **10** we should obtain the C^1–C^6-product, but if there are other effects of electronic nature (mesomeric effects) the 1,5-product should be observed.



Scheme 75 Possible thermal 1,5-cyclizations

First cyclization attemps were started as microwave enhanced synthesis with different operating parameters, but all these test-reactions were to no avail. TLC control of these experiments only showed the starting materials.

Thermally initiated cyclizations usually proceed at high temperature and, hence, at high pressure, caused by the high vapor pressure of the solvent in the closed system of the microwave synthesis vessel. We reproduced the reaction protocol of Pascal *et al.* using toluene as solvent, cyclohexadiene as proton source (one attempt using **10** as starting material, also with using didehydroanthracene as H-donor gave similar results) and the enediyne sealed in a glass ampoule under vacuum. The autoclave containing the ampoule was heated up to 300 °C in the furnace. In both cases we obtained a dark, waxy mixture of various, unidentified products. TLC control showed an additionally spot beneath the starting materials **10**. The ^{13}C-NMR-spectrum of the cyclization attempt with substance showed no signals in range of 80 to 100 ppm, which indicates that the acetylenic moieties had vanished. If a 1,5-cyclization had taken place, we would expect a signal of the fluorenyl proton (position 3, in place of the double bond) in ^{1}H-NMR spectrum in a range about 7 ppm, as well as an additionally signal in the aromatic range. This aromatic signal could give a hint to the ring-size compared to the ^{1}H-NMR spectrum of the starting

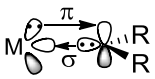
material. The additional expected signals in case of the Bergman cyclization should show a shift in the aromatic region caused by the formed naphthalene moiety. Yet, these were not identifiable. We interpret the findings in the crude spectra of the unseparated reaction mixture as evidence for a 1,5-cyclization, which could have taken place due to the ability of the aryl moiety (and also in this case the nitro substituent) to stabilize the radicaloid intermediate. With this findings, we assume that a 1,5-cyclization to **33** took place. However, it is necessary to optimize purification and to isolate the product.

Cyclization of **21** follows the same protocol using cyclohexadiene as hydrogen source. The reaction was carried out in a sealed glass ampoule at 300 °C in an autoclave overnight. We obtained a dark, waxy mixture of various, unidentified products. NMR-spectra of the partly purified product was measured and interpreted as follows. The ^{13}C-NMR spectra show starting material as well as a number of additional signals in the aromatic range. The ^{1}H-spectra show, apart from small signals of starting material no signals in a range from 7.3 ppm to 8.5 ppm, in which the ^{1}H-signals of the naphthalene ring are expected. This is a hint that a 1,5-cyclization has taken place. All other signals agree with this finding. Hence, we assume that we obtained the 1,5-cyclization product **86** (Scheme 75) but as mentioned above, it is necessary to optimize the purification and to isolate the pure product to ascertain these findings.

4 Additives for Optimizations of Metal-Catalyzed Couplings

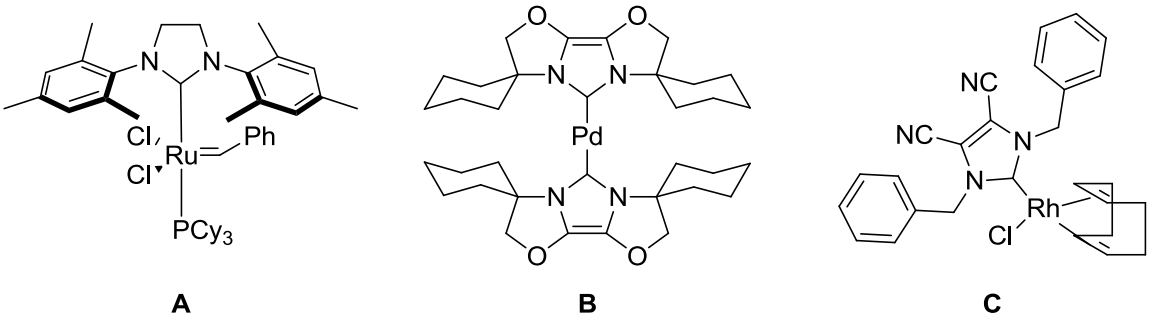
4.1 *N*-Heterocyclic Carbenes

N-heterocyclic carbenes (NHCs) and their complexes are widely used in organic synthesis. The first stable, characterized N-hetereocyclic carbene is associated with Arduengo by most chemists.[116] However, already 1962 Wanzlick depicted the first of these species as a dimer ("das doppelte Lottchen").[117] Bertrand *et al.* succeeded in the preparation of the λ^3-phosphinocarbene in solution in 1988.[118] The first stable imidazolium-2-yliden bearing adamantyl (IAd) substituents was first isolated by Arduengo *et al.* in 1991.[116b] Carbenes are usually reactive specied bearing a bivalent carbon with an electron sextet. In NHCs, the carbene carbon bearing the two "free" electrons is part of a heterocycle and flanked by at least one nitrogen atom. The pronounced stability of NHCs is a result of the mesomeric interaction of the nitrogen lone pair(s) with the empty p-orbital of the sp^2-hybridisized carbene carbon. The steric shielding by bulky substituents is also advantageous because of the kinetic stabilization.[76] NHCs are nucleophilic, in contrast to conventional carbenes, such as methylene. The C–N-bonds to the carbene center are longer and the N*C*N-valence angle in carbenes is smaller than in the corresponding imidazolium salts, leading to the assumption that they possess enhanced σ-bond character.[119] NHCs are popular in coordination chemistry because of their formation of (dative-) bonds with a wide range of metals and also their stabilizing and activating features onto metal centers.[120] In recent years, a NHC family with different electronic properties was discovered and it is possible to modify the electronic behavior by specifically chosen heterocycles.[121] In case of transition metal complexes carbenes are distinguished into "Fischer carbenes", which are electrophilic and include heteroatoms, and "Schrock carbenes", which possess nucleophilic character.[122] These metal complexes possess relatively long carbon-metal bond of around 210 nm (2.1 Å). A shortening of these bonds may be caused by π-back donation (double bond, Scheme 77).[122]



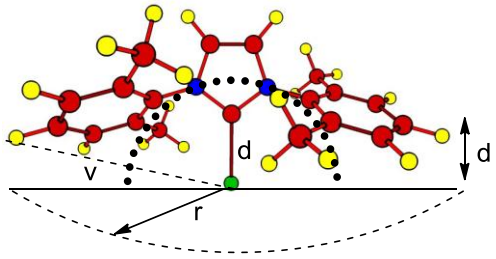
Scheme 76 NHC-metal complexes in general

Bulky NHC-metal complexes, especially these with palladium atoms as the center, are fruitful catalysts in cross-couplings reactions,[77,123] transesterifications,[124] and aryl aminations.[120] NHCs have become universal ligands employed in a large number of bond forming reactions.[125] For instance, when using Ru as central atom, NHC-complexes are useful for olefin metathesis reactions (Grubbs' metathesis catalysts, Scheme 78). Using NHCs as ligands usually gives better results compared to phosphine ligands in homogenous catalysis.[120] NHCs are now widespread employed in cross-coupling chemistry.[126] NHCs are stronger σ-bond donors than phosphine ligands and the electron richness of these ligands can be determined by IR-spectroscopical measurement with in $M(CO)_3L$-complexes (M = Ni, Ir, Rh).[76] In these complexes, the ligands push their electron density not only towards the metal but also into the π*-orbital of the CO-ligand, resulting in a shift of CO-stretching vibration to lower values. This is described by the Tolman electronic parameter (TEP).[127]



Scheme 77 NHC-metal complexes: **A**) 2nd generation Grubbs' metathesis catalyst;[128] **B**) Glorius' catalyst with flexible steric bulk applied in cross-couplings;[129] **C**) Herrmann's Rh complex[130]

As also described for phosphines,[131] the steric properties of these ligands in organometallic chemistry are described as percent buried volume (an advancement of the concept of cone angles), which represents the coordination sphere of the ligands assigned to a hypothetical bowl and its radius (Scheme 79).[132] The cone angel θ is defined as perimeter of the cone of the outer sphere of the ligands (v) and the metal atom serves as the vertex. But these models only depict a snapshot of these structures and neglect their dynamics.[76,129,133]



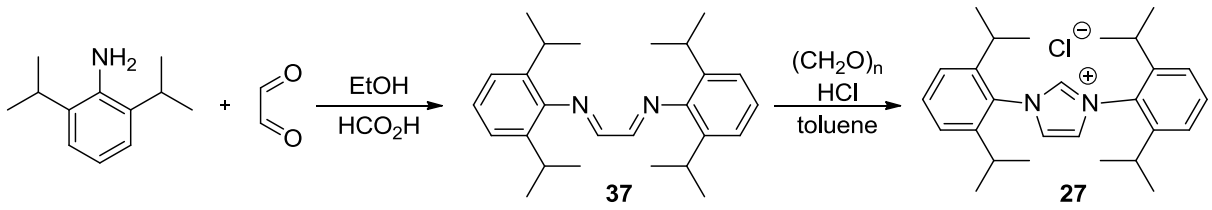
Scheme 78 Definition of cone angels (v and d) and buried volume (bold dotted bow)

Free NHCs can be generated by different methods. The most common method is deprotonation of imidazolium salts by bases. Other rarely employed *in situ* methods are desulfurization of thioureas by melted potassium,[76] vacuum pyrolysis of imidazolum salts based on alcohols[76] or corresponding aldehydes.[124] Further methods are the employment of NHC-CO_2 or metal-carrying starting materials for pyrolysis as used in polyurethane syntheses, and by treatment of chloroamidinum- and 2-chloroazoliumsalts with bis(trimethylsilyl)mercury.[76]

4.1.1 Synthesis of PEPPSI-IPr and Precursors

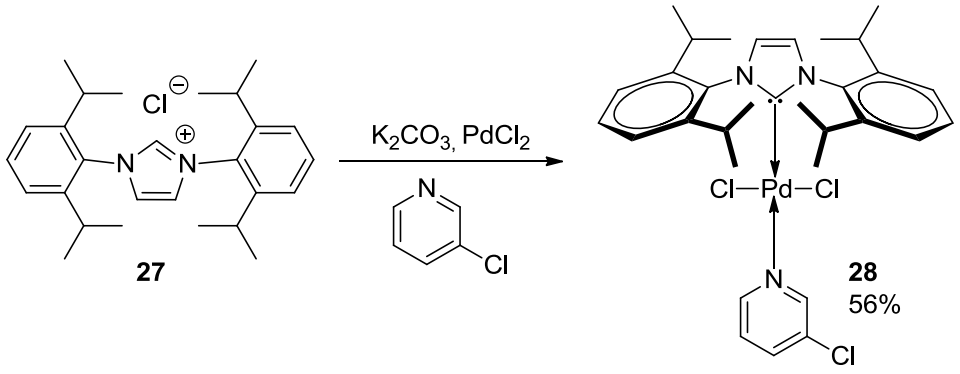
The imidazolium salts used in this work were mostly prepared in two steps as described in the following for Nolans IPr-ligand (Scheme 80). Other, similar methods, for example, preparation of unsymmetrically substituted *N*-derivatives effort as first step in additional to prepare the primary amine, ammoniumchloride and a subsequent alkylation or arylation by reactive halide species. There are further routes employing orthoformiate and thiophosgene for the ring closure.[120]

In recent years, Organ's PEPPSI-IPr catalyst provided good results when applied as a catalyst in cross-coupling reactions. The imidazolium salt precursor was prepared by a protocol of Nolan *et al.* (Scheme 80).[92] The first step was the formation of the Schiff base **37** by condensation of glyoxal with 2,6-diisopropylaniline in a ratio of 1:2 catalyzed by a small amount of formic acid. From the Schiff base **37**, diaryl amidazolium chloride was prepared by nucleophilic addition to *p*-formaldehyde and subsequent treatment with HCl afforded the imidazolium chloride **27**.



Scheme 79 Synthetic route *via* the Schiff base towards the imidazolium chloride

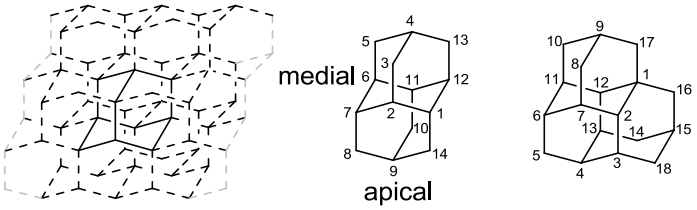
The final step is the coordination of the monodentate PEPPSI-IPr-ligand to palladium dichloride and 3-chloropyrindine (Scheme 81). This proceeds *via* insertion of Pd into the imidazolium moiety in the presence of 3-chloropyridine. A flask was charged with $PdCl_2$, K_2CO_3 and **27** in a ratio of about 1:10:2 using 3-chloropyridine as solvent. The mixture was heated to 80 °C and, after work up and recrystallization, yellow crystals were obtained in a yield of 56%.



Scheme 80 Preparation of PEPPSI-IPr

4.1.2 Preparation of Arduengo-type Carbene Complexes and Related Compounds

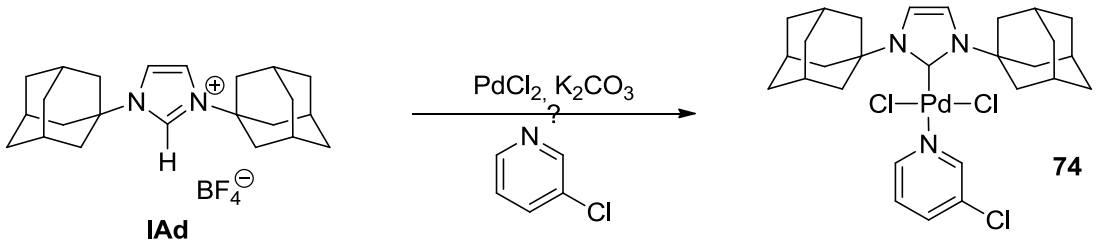
Diamantane (Scheme 82, middle structure) consists of two condensed adamantane units and belongs to the family of the so-called diamondoids or nanodiamonds.[134] The task in the context of the present thesis was their use in sterically demanding ligands for *N*-heterocyclic carbenes and their potentional use as NHC-transition metal catalyst complexes for the application in organometal-catalyzed cross-coupling reactions. Based on the model of Herrmann *et al.*,[135] which includes the corresponding adamantyl carbene known as the Arduengo carbene,[116b] the diamantane derivative should be a promising catalyst for these kinds of reactions.



Scheme 81 Structure of nanodiamonds.

There are also NHC-catalyst systems reported in literature, which utlize Arduengo's carbene as a ligand. Hence, it is obvious to replace the adamantyl substituents with diamantyl substituents in such NHC-ligands. Herrmann *et al.* synthetisized Ardengo-NHC-complexes and successfully employed them in Suzuki-Miyaura cross-coupling.[135]

Before implementing diamantyl-imidazolium salts, we tested the respective reactions with the corresponding adamantyl salt. This imidazolium salt was prepared in our group. At first, we carried out Organ's protocol that is successful for the preparation of the PEPPSI catalyst family. The IAdBF$_4$ salt, PdCl$_2$, K$_2$CO$_3$ and 3-chloropyridine were heated overnight to 100 °C oil bath temperature. The color changed from brown to yellow and a solid precipitated.

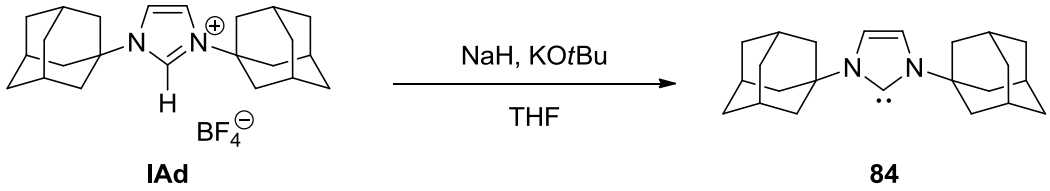


Scheme 82 Preparation of a NHC-Pd complex

The crude product was diluted with CH_2Cl_2 and filtered over celite. The solvents were removed and an NMR spectrum was measured. Compared with the NMR signals of PEPPSI catalyst derivatives, we obtained similar signals, but we cannot unambiguously define, which signals belongs to the expected complex and, which to the 4-chloro-pyridine. Compared with the ^{13}C-NMR-spectra of the IAdBF$_4$ salt, the N*C*N-signal at about 130 ppm vanished and the adamantyl signals doubled. These findings allow the assumption that something complex-like is formed, in spite of the fact that the HRMS-spectrum showed no molecular ion peak corresponding to the complex.

Our following test reactions were inspired by the homoleptic Pd-IAd complexes of Hermann *et al.*[135] First, we deprotonated the imidazolium salt to get the free carbene (Scheme 84). We adhered to the procedure of Arduengo *et al.*[116a] A dry and with argon-

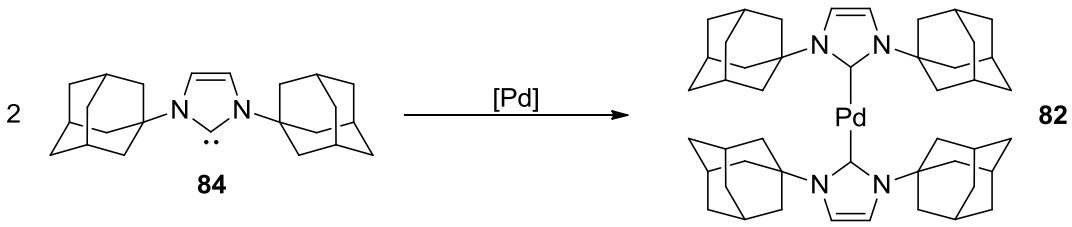
flushed flask was charged with the $IAdBF_4$ salt, NaH, THF and subsequently KO*t*Bu dissolved in THF. We observed the evolution of hydrogen with a bubble counter and stirred continously for 4 h. The residue was filtered over a celite pad using standard Schlenk techniques. The solvent was removed *in vacuo*.



Scheme 83 Preparation of the free carbene

A colorless residue remained and NMR spectra were recorded. We observed no signal at around 200 ppm (which would have been characteristic for the carbene carbon). The reason for the missing signal, although hydrogen evolution was detected, may be that the NMR sample was not handled under perfectly inert conditions. Hence, the carbene could have been re-protonated or oxygenated.

Despite the uncertainty if any carbene was generated at all, we proceeded with the preparation of the Pd-NHC complex (Scheme 85) first by dissolving bis-(tri-*tert*-butylphosphine) palladium in *n*-hexane and adding the IAd-carbene in hexane solution. The mixture was stirred at ambient temperature for two days and a yellow solid precipitated. However, the obtained NMR data were not in accord with those in the literature.[135]



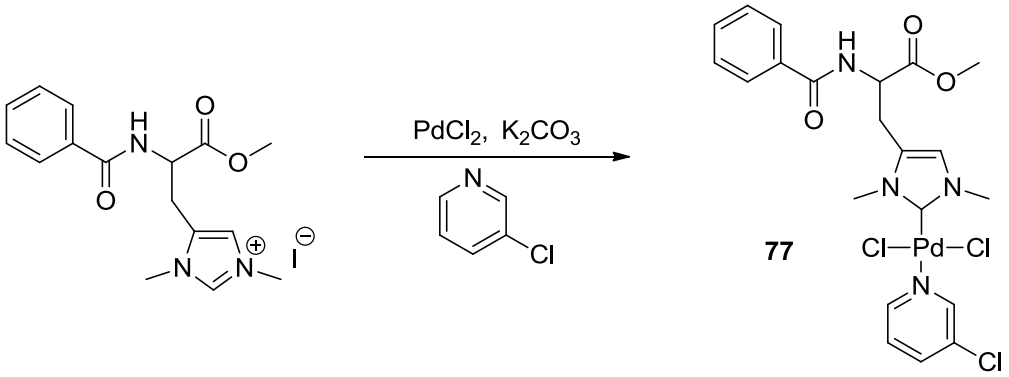
Scheme 84 Herrmanns homoleptic IAd-Pd-complex

As a second approach, we carried out the reaction in the same flask, in which the carbene had been prepared in order to prohibit contact with air or moisture. Hence, we added to the solution of the assumed carbene in reversed order the Pd-salt solution. Nevertheless, also with these operations we obtained no conformity with the NMR shifts reported in literature. For the third attempt, we chose another protocol that requires sodium dimethyl malonate, which we prepared using NaH and dimethyl malonate in THF.[136] Sodium

dimethyl malonat and $[(C_3H_5)PdCl_2]_2$ (allylpalladiumdichloride) were deoxygenated and the IAd carbene (dissolved in toluene) was added. The solution turned light green and was kept at 110 °C (oil bath) overnight. The mixture was worked-up and crystallization at –50 °C was attempted as described in in the orginal protocol; however we only obtained a light yellow powder that showed inconclusice NMR signals. We identified the signals of the adamtane-substituents and the two C-Hs of the imidazolium-ring and a ^{13}C-NMR-shift around 70 ppm, which could be due to the protonated carbene carbon.

Our failure to synthesize these complexes probably could be tracked back to the preparation of the carbene. Possibly our handling of moisture-sensitive compounds *via* standard Schlenk techniques was not rigorous enough, lacking a glove-box for handling of reagents and solvents. Indeed, Arduengo *et al.* handled their carbenes in a glove box, while Herrmann *et al.* do not give details of their procedure. Likewise, our batch of KO*t*Bu could, in addition to being dried and deoxygenated *via* standard procedure, also require sublimation. In conclusion, the perfectly dry operations obviously required during the preparation of these sensitive *N*-heterocyclic carbenes and their complexes were not achieved at the time the syntheses were tried. Again, additional experience and possibly glove-box conditions are inevitable for renewed attemptes to synthesize the NHC-complexes.

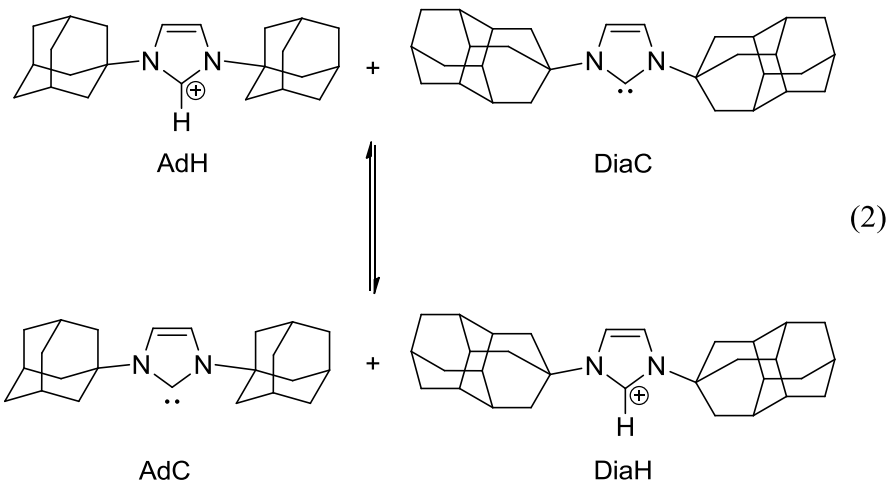
Another strategy we followed to synthesize an NHC-complex was to use an amino acid containing imidazoliumiodide as a precursor again following the protocol of Organ *et al.* (Scheme 86). In this case, we also obtained a pale yellow powder and were not able to interpret the NMR-signals, as also was described for the Arduengo-carbene-complex above. Compared with the NMR signals of the PEPPSI catalyst derivatives, we obtained similar signals, but we can not unambiguouly define, which signals belongs to the expected complex and which to the 4-chloropyridine. Compared with the ^{13}C-NMR-spectrum of the precursory iodine-salt, the N*C*N-signal at about 130 ppm vanished. As described above, the presumed carbene carbon is protonated probably.



Scheme 85 Preparation of a peptide-based NHC-Pd-catalyst system

4.1.3 Proton Affinity of Adamantyl- and Diamantyl-NHCs

One main area of research in our group are the functionalizations and the reactions of diamantane and higher "diamondoids".[134] It is obvious to replace (just like in case of phosphine ligands) the adamantyl substituent with the diamantane moiety. The corresponding imidazolium salt was prepared in our group and the design of an applicable catalyst is within reach. In order to estimate the behavior and reactivity of these carbene species compared to the adamantyl analogue, suitable computations were performed. The nucleophilic character of the resulting NHC-carbene was addressed with isodesmic equation (2).

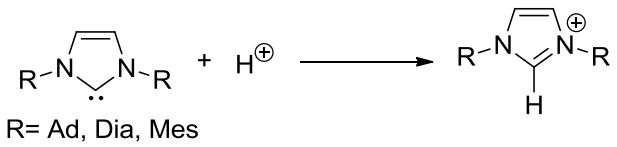


(2)

To that end, the structures were optimized at the M06-2X/6-31G(*d,p*) level of theory. ΔH and ΔH_0 values were obtained. An isodesmic relationship is provided if the number and the nature of the bonds are constant on both sides of the equation.[137] The reaction enthalpies [ΔH_R = (sum of products) – (sum of educts)] gives an indication which of these NHCs are more nucleophilic. We computed for ΔH_R (298 K) = –1.6 kcal mol^{-1} and for

ΔH_R (0 K) = –0.9 kcal mol^{-1}. Since these values are negative, the reaction favors the product, demonstrating that 1,3-bis(4-diamantyl)imidazole-2-ylidene is only slightly more nucleophilic than the 1,3-bis(adamantly)imidazole-2-ylidene. Hence, with a negligible difference, both species are equally nucleophilic.

The proton affinities (PA = $-\Delta H_R$) of the three NHC moieties were evaluated *via* equation (3). For comparison, a di-mesityl imidazole species is included.



(3)

Table 16 Evaluation of the proton affinity at the M06-2X/6-31G(*d,p*) level of theory

	PA (kcal mol^{-1})
AdH–AdC	275
DiaH–DiaC	275
MesH–MesC	271

These findings confirm the results of the isodesmic evaluation of nucleophilicities. From the values in Table 16, we deduce that the PA of the adamantyl and diamantyl species are enhanced compared to the PA of the mesityl-carrying NHC, but that all three are able to stabilize the cationic NHC-species. Yet, it should be kept in mind that the computed energies are rather similar.

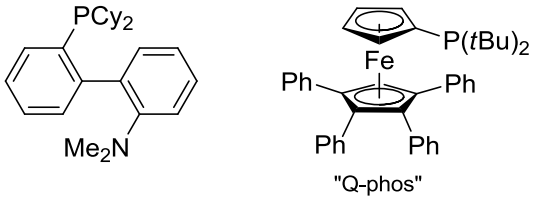
4.2 A Diamondoid Phosphonium Salt as Co-Ligand in Sonogashira and Suzuki Cross-Coupling Reactions

For optimal (cross-)coupling results, (transition) metal catalysts require bulky ligands or co-ligands such as phosphines. Most prominent representatives are P(*t*Bu$_3$) and PPh$_3$.[138] Another important motivation for development of such phosphine co-ligands is the aim of improving industrial processes and the resulting use of inherently cheaper and less reactive starting materials, such as aryl chlorides.[139]

Trisubstituted phosphines with sterically demanding ligands can be fine-tuned. There are examples reported in literature that utilize secondary phosphine oxides.[140] Phosphines possess beneficial properties for the stabilization of zero-valent palladium due to their

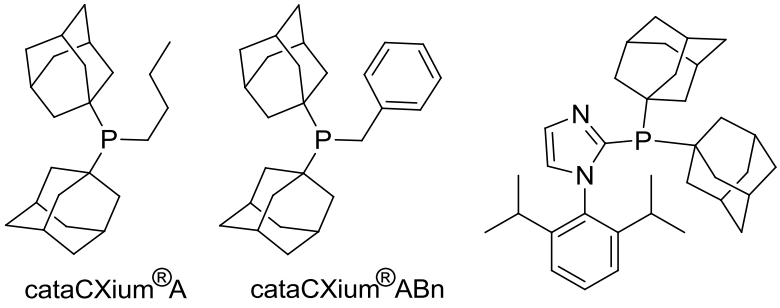
steric shielding and electron-richness as well as their highly electron-donating character.[131,138] These are essential properties of highly active catalysts.[141] These different ligand capabilities also allow the tuning of the metal catalysts for a given coupling reaction.[138] Already in 1978 Heck reported that bulkier triarylphosophines lead to higher catalytic activity than the parent PPh_3 ligand.[141b] An explanation based on comparisons of several phosphines and their influence on catalytic activity was given by Osborn.[142] For high catalytic activities, phosphines have to be strongly basic and the cone angle θ has to average at about 160°.[142] The new generation of bulky phosphines having been synthetisized over the last ten years are able to activate nearly inert subtrates, such as arylchlorides, tosylates, and mesylates, and provide hitherto unknown results in cross-coupling reactions (Scheme 87). Additionally, the newly tailored ligands increased the turnover numbers in some cases and decreased the required palladium concentration.[143] Little is known about the role of the phosphines in the transmetallation step of the catalytic circle. Of course, there are also transition metal catalysts bearing phosphine ligands,[144] but this is not the main subject of this chapter.

Important properties of these phosphines are the presence of one or two tertiary carbons bonded to phosphorus. These ligands are necessary for the steric bulk and also for electron donation. However, three tertiary carbons would complicate the modification of the periphery of the ligands.



Scheme 86 Selected phosphines of Buchwald and Hartwig, deployed in the Suzuki-Miyaura cross-coupling of aryl chlorides.[143,145]

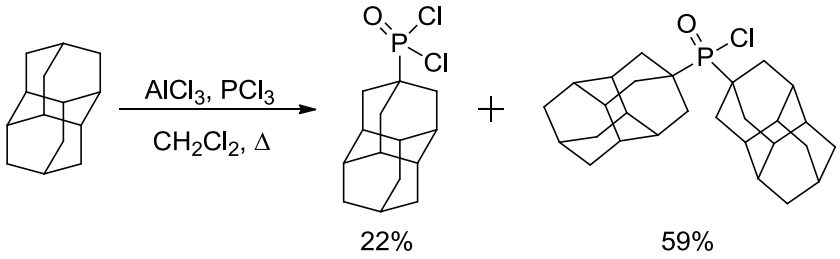
A very important group of potent phosphine ligands for cross-coupling reactions are the diadamantylalkylphosphines introduced by Beller *et al.* since 2000 (Scheme 88).[139] These ligands are characterized by a higher sterical demand than that of the related *tert*-butyl group, and they possess a larger volume and an overall more rigid structure. Some of them are commercially available, air stable and versatile in Suzuki-Miyaura cross-couplings with aryl-chlorides, Buchwald-Hartwig aminations, α-arylations, hydroformylation, carbonylations, cyanations and Sonogashira-Haghiara couplings.[146]



Scheme 87 Ad_2PR ligands of Beller *et al.*[139,147]

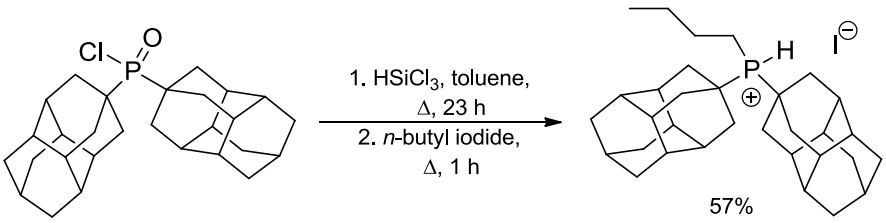
The heavier homologue of these adamantane-based scaffolds is diamantane and we approached the challenge to reproduce and test some of these catalytic transformations with the larger and more bulky diamantane phosphine ligands.[79a]

Based on the apical dichlorophosphorylation with PCl_3, $AlCl_3$ and CH_2Cl_2 reported by Olah *et al.*[148] (and not, as described earlier, for medially substituted derivatives) substituted di-1-diamantanylphosphonic acid dichloride was obtained in 60% yield. Reducing the amount of PCl_3 to one half results in 4-diamantylphosphinic acid dichloride (22%) and di-4-diamantylphosphinic acid chloride (59%) (Scheme 89). These results are corroborated by the result that the formation of apically substituted diamandoid derivatives is observed upon the use of Lewis acids.[149]



Scheme 88 Phosphorylation of diamantane

The next step was to obtain the corresponding phosphine. Refluxing di-4-diamantyl-phosphonic acid chloride in toluene with $HSiCl_3$ leads to the di-4-diamantylphosphine, which oxidizes rapidly (in solution and in the solid state). To obtain this specific oxide, we treated di-4-diamantylphosphine with H_2O_2 (30%) *in situ* at r.t. An alternative path to obtain a stable phosphonium salt instead of the phosphine was inspired by a similar implementation by the complementary di-1-adamantylphosphine of Tewari *et al.*[79b] This experiment revealed that di-4-diamantylphosphine reacts with *n*-butyl iodide.[79b]

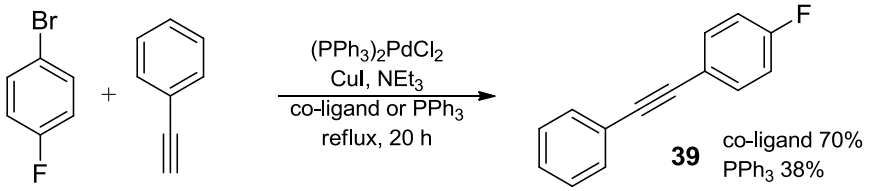


Scheme 89 Preparation of di-4-diamantyl-*n*-butylphosphonium iodide

The product was an air- and moisture-stable salt. For the sake of completeness, it should be mentioned that the deprotonation according to the existing protocol with NEt_3 in CH_2Cl_2 failed. Hence, di-4-diamantyl-*n*-butylphosphonium iodide was oxidized directly using H_2O_2 to obtain the tertiary phosphine oxide.

4.2.1 Application of Di-4-diamantyl-*n*-butylphosphinum Iodide as Co-Ligand in Cross-Coupling Reactions

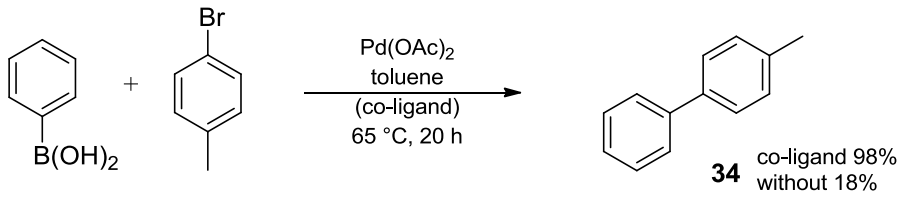
It is generally known that phosphines, phosphonium oxides and their salts act as co-catalysts in metal-catalyzed cross-coupling reactions. Hence, we examined the catalytic potential of di-4-diamantyl-*n*-butylphosphinum iodide. The first test reaction was a Sonogashira-Hagihara cross-coupling of 4-bromofluorobenzene with phenylactylene using 10 mol% of the di-4-diamantyl-*n*-butylphosphinum iodide in combination with 5 mol% $(PPh_3)_2PdCl_2$ and CuI in NEt_3. Addtionally, we ran the same reaction with the standard co-ligand PPh_3, instead of di-4-diamantyl-*n*-butylphosphinum iodide. After 20 h, we isolated 1-fluoro-4-(phenylethynyl) benzene **39** with a yield of 70% with the diamandoid co-ligand, while only 38% of the product was isolated using a conventional catalyst such as $(PPh_3)_2PdCl_2$.



Scheme 90 Sonogashira-Hagihara cross-coupling as test reaction

The second test-reaction using the diamantyl catalyst was the Suzuki-Miyaura biphenyl coupling. At first, we tried to couple the relatively unreactive chlorotoluene with phenylboronic acid. We started the reaction both with and without any co-ligand. Both showed no conversion in GC/MS analysis. Additional test reactions were carried out in a microwave apparatus, likewise giving no conversion for both catalyst systems. After a few further reaction attempts, we decided to replace the chloro substituent with a more

reactive bromine species. Hence, we coupled the more active 4-bromotoluene with phenylboronic acid, adding 1.5 mol% di-4-diamantyl-*n*-butylphosphinum iodide and using 1.5 mol% $Pd(OAc)_2$ as catalyst and K_3CO_3 in toluene (Scheme 92). After 20 h, we isolated 4-phenyltoluene in nearly quantitative yield. The same reaction was carried out without any co-ligand. In the latter case, the product and traces of biphenyl were obtained after 20 h. Biphenyl usually forms as the result of a homocoupling reaction of the boronic acid if the palladium catalyst is not sterically demanding.[150] We isolated the product **34** in 18% yield after preparative GC.



Scheme 91 Suzuki-Miyaura cross-coupling test reaction with and without the co-ligand di-4-diamantyl-*n*-butylphosphinum iodide

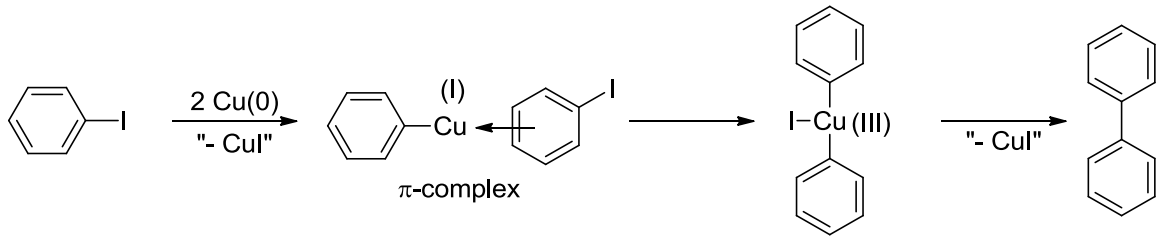
The question arises why these co-ligands work so well, but are yet not as active as cataCXium® A introduced by Beller *et al.* (Scheme 88) in the catalysis of cross-coupling reactions.[79b] These latter derivatives are able to couple the less reactive aryl chlorides. Upon consideration of the results of our cross-coupling reactions, the question arises what the practical upper limit of steric bulk of phosphines in C–C bond forming reactions may be.

One concept uses the cone angle, which is defined between the metal (metal-phosphorus bond 228 pm) and the vector to the van der Waals radius of the outermost atom of the ligand (Scheme 79).[127,131] This value should be around 160° to warrant good catalytic activity. The determination of this value could give a first clue why the catalytic activity of our diamandoid salt is not as good as that of adamantane analogues. We calculated the buried volume of cataCXium® A (the adamantane analog) and of di-4-diamantyl-*n*-butylphosphine using a software, which is normally configured for NHC-ligands and reportedly does not give overly precise values for phosphines.[133] The Samb*V*ca-program (acronym for Salerno at the MoLNaC Buried Volume Calculation) is based on a set of radii derived from a number of DFT computations.[151] The buried volume (%V_Bur) for cataCXium® A is 32.4% and for the corresponding diamantyl salt 33.7%. (using 2.1 Å as distance sphere from the coordinated metal). These values are quite close to one another so that very similar catalytic activities should be expected. This could not be proven

experimentally because we used the iodine salt instead of the “free” phosphines (due to the difficulties in preparation of the free phosphines, *vide supra*): presumabely the catalytic activity decreases just for this reason.

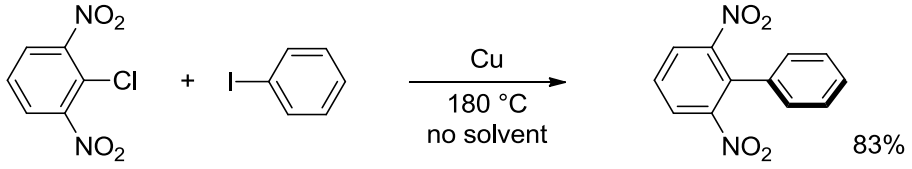
4.3 Ullmann and Suzuki-Miyaura Test Reactions with Copper(I/II)-Complexes as Catalysts

When studying copper-complexes with regard to their catalytic activity, at first it is worth considering different coupling reactions such as Glaser-,[38] Ullmann-,[152] Cadiot-Chodkiewz-[39] and Stephens-Castro[40] reactions, respectively, and recently the Suzuki-Miyaura cross-couplings, in which cooper-complexes were also applied.[153] The classic Ullmann reaction leads to symmetrical biphenyls using elemental Cu(0) and aryl halides, belonging to transition-metal mediated C–C coupling and nucleophilic aromatic substitution reactions. The coupling proceeds at temperatures around 200 °C and the active species is the copper(I)-aryl compound formed *in situ*, which subsequently generates the biaryl by a reductive elimination step (Scheme 93).[154]



Scheme 92 Ullmann coupling reaction

Ullmann reactions proceed with good yields when using electron acceptor-substituted aryls.[83,155] Biphenyls with various substituted aryl moieties are available and can be generated by using an aryl halide diffrent from ones used initially. This “crossing step” of these Ullmann coupling takes place after the oxidative addition step. After formation of the active copper(I)-complex with the first coupling partner, the second coupling partner is added. The mechnism progressed as described above (Scheme 93).



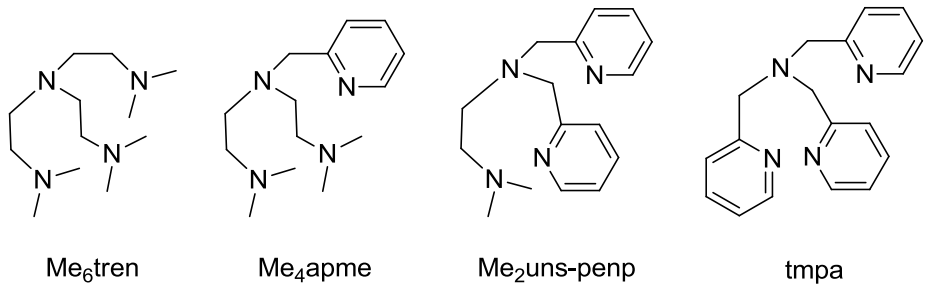
Scheme 93 “Crossed” Ullmann synthesis[156]

Using Cu(I) or Cu(II) salts allows comparatively moderate reaction conditions, but nevertheless gives good coupling yields. As in numerous other reactions (*vide supra*), the nature of solvent and base affect the results.[157]

We decided to study the Ullmann coupling as a test reaction, which provides symmetric biphenyl with equally substitued aryl building blocks. The Suzuki-Miyaura cross-coupling gives biphenyls with varying substituents at the aryl moities. The Ullmann reaction impresses with its simple implementation. Also, the biphenyls are detectable with GC/MS analysis and are usually easily purified. The convenience of the Suzuki-Miyaura biphenyls is that it is effortless to couple various substituted biphenyls. The coupling to these products proceeds at lower temperatures, but makes higher demands to activity and selectivity of the catalyst. The high selectivity is necessary to prevent homocoupling of the boronic acid as well as an Ullmann-type reaction as a "side reaction".

4.3.1 Experiments for the Detection of the Catalytic Activity of Cu(I/II)-Complexes

Our Suzuki-Miyaura cross-coupling as well as the Ullmann coupling were carried out under dry and oxygen-free conditions. Both Cu(I)-complex families were provided by Würtele *et al.* These complexes are extremely sensitive and, when subjected to ambient conditions, quickly oxidize to Cu(II). Several of the investigated copper(I)-complexes contain tripodal tren ligands (Scheme 95).[158]

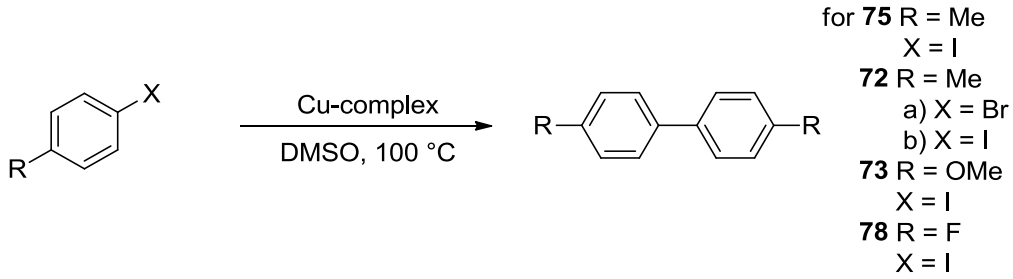


Scheme 94 Family of tripodal tren-skeletons

Me_6tren [tris(2-dimethylaminoethylamine] was prepared by conversion of aqueous formaldehyde with tris(2-aminoethyl)amine to form an imine (Schiff base) and subsequent reduction of the double bonds using $NaBH_4$. Me_4apme [bis(2-dimethyl-aminoethyl)(2-pyridylmethyl)amine] was prepared by conversion of pyridine-2-carboxaldehyde with bis[2-(dimethylamino)ethyl]amine to the immonium salt and subsequent reduction using NaH. Me_2uns-penp [(2-dimethyl-aminoethyl)bis(2-

pyridylmethyl)-amine] was prepared by treatment of *N*,*N*-dimethylethylenediamine with 2-pyridinecarboxyaldehyde. The last ligand, tmpa [tris(2-pyridylmethyl)amine] was generated by conversion with 2 eq. of pyridine-2-carboxaldehyde and 2-aminopyridine.[158b,159]

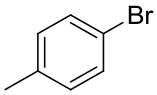
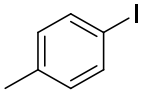
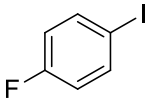
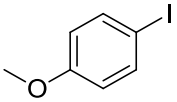
These tetradentate tripodal ligands were transformed into the copper complexes $[Cu(L)]BPh_4$ by ligand exchange reaction starting with $[Cu(CH_3CN)_4]PF_6$. A subsequent treatment with $NaBPh_4$ allowed the introduction of the BPh_4^- counterion.



Scheme 95 Ullmann test reaction

For the Ullmann coupling, we selected at first bromotoluene as the aryl halide, but the GC/MS spectra showed no conversion to the biphenyl. Hence, we replaced the aryl bromides by the corresponding iodides. The reactions were carried out under oxygen-free conditions with 2 mmol halide, 2 mmol KF and 0.2 mmol copper catalyst in deoxygenated and dried DMSO. The mixture was warmed to ca. 100 °C. After 20 h a sample was taken for GC/MS analysis. A second sample was taken after two days. The results are summarized in Table 17.

Table 17 Ullmann reaction

Halide	Complex	Counter anion	Result
	[Cu(I)me_2uns-penp]	BPh_4^-	Traces
	[Cu(I)me_6tren]	BPh_4^-	-
	[Cu(I)me_2uns-penp]	BPh_4^-	Traces
	[Cu(I)me_6tren]	BPh_4^-	Traces
	[Cu(I)me_4apme]	BPh_4^-	Traces
	[Cu(I)tmpa]	BPh_4^-	Traces 11.6 mg, 1.6%*
	[Cu(I)me_6tren]	PF_6^-	Traces
	[Cu(I)me_2uns-penp]	PF_6^-	-
	[Cu(I)tmpa]	PF_6^-	-
	Tet B	SBF_4^-	-
	[Cu(I)me_6tren]	PF_6^-	Traces

* Purification by column chromatography, hexane/DCM, 99:1

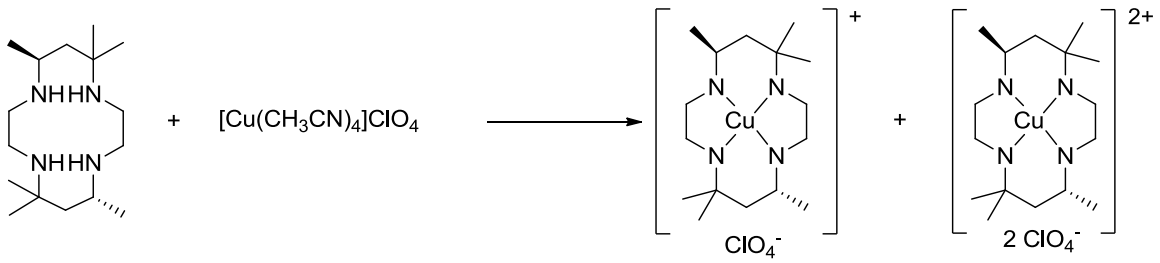
By choosing various substituted aryl halides, we modified the electronic properties of the system to investigate the catalytic activity of the copper complexes. It is already known that electron-accepting substituents at the aryl halide lead to good results but also starting materials bearing deactivating groups in *meta*- or *para*-position increase the reactivity of the halide.[160]

The other regulating screw were the Tet-complexes, which are classified into Tet A and Tet B skeletons. The macrocyclic ligands Tet A and B were prepared by the reaction of 1,2-diaminoethane with the Michael acceptor after aldol condensation of acetone. The resulting macrocyclic Schiff base was reduced with $NaBH_4$. The first fraction of the crystallization gave the isomer Tet A, the second Tet B.

Tet A Tet B

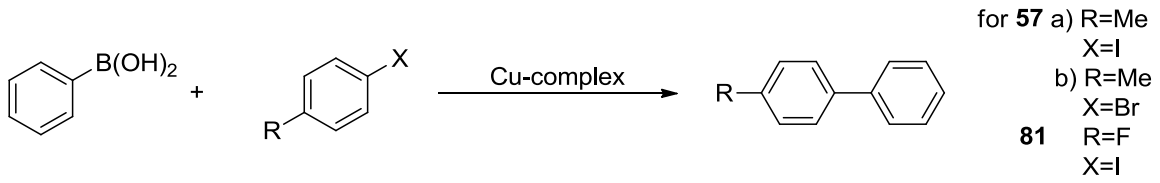
Scheme 96 Macrocyclic ligands

The copper complex incoperating these ligands was syntheszed by dropwise addition of a solution of [Cu Tet A/B]X (with X = SbF_6^-, BF_4^-, ClO_4^-) in CH_3CN to a solution of the ligand Tet A/B in CH_3CN (equimolar) (Scheme 98). This gives a violet solution and a small amount of colloidal copper. The solution was filtered and the solvent was removed under reduced pressure. It is well known that the copper(I)-complexes of these macrocyclic ligands undergo disproportionation. Likewise, we also observed that this synthesis results in a mixture of both the copper(I)- and copper(II)-species.[161]



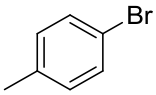
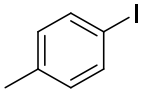
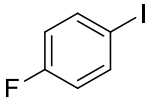
Scheme 97 Preparation copper Tet A complex

As a second test-reaction, Suzuki-Miyaura cross-coupling was carried out.[153a] Similar halides were employed and the classical cross-coupling procedure was chosen as the protocol. Phenylboronic acid (3 mmol), 4-bromotoluene (2 mmol), K_2CO_3 (7 mmol) and 0.03 mmol of the copper-complex were placed in a nitrogen-flask under dry and oxygen-free conditions (Scheme 99, Table 18).



Scheme 98 Suzuki-Miyaura cross-coupling as test reaction

Table 18 Suzuki-Miyaura cross-coupling

Halide	Complex	Counter ion	Result
	Tet B	SBF_6^-	Traces
	Tet B	BF_4^-	-
	Tet B	$CF_3SO_3^-$	-
	[Cu(I)me_2uns-penp]	BPh_4^-	Traces
	[Cu(I)me_6tren]	BPh_4^-	Homocoupling
	[Cu(I)me_4apme]	BPh_4^-	-
	[Cu(I)tmpa]	BPh_4^-	Homocoupling
	[Cu(I)tmpa]	PF_6^-	Traces
	Tet B	SBF_6^-	-
	Tet B	ClO_4^-	Traces
	Tet A	ClO_4^-	Traces
	Tet B	SBF_6^-	-

We carried out both Ullmann coupling reactions and Suzuki-Miyaura cross-coupling reactions. Whereas the Ullmann reaction in nearly all cases showed a trace of coupling product, the Suzuki-Miyaura reaction hardly ever showed product. If we received traces of the expected coupling product, then only along with homocoupling product of phenyl boronic acids. We tested in both cases aromatic starting materials with various substituents and hence different electronic properties. For the Ullmann coupling, we observed no effect in the outcome of these experiments, which points out the influence of these diverse electronic properties of the starting materials. In the literature, preferably electron-accepting substituents in *ortho*-position of the aryl halide are described as reaction partners.[83] The next step in this project would be employing such functionalities and also varying the other parameters such as solvents, temperature, and base. For Suzuki-Miyaura reactions active catalysts with bulky ligands are required, typically co-catalysts and/or co-ligands.

5 Summary

This work established the basis for the selective synthesis of a family of pyrene derivatives with uncommon substitution patterns that are accessible *via* electrophilically induced cyclization reactions. The construction of these molecules with desirable optoelectronic properties was started by coupling of two phenyl-moieties *via* Suzuki-Miyaura cross-coupling to give sterically demanding 2,6-dibromobiphenyls. Through this step, we gained access to a group of these biphenyls. After characterization, we optimized some of the parameters of this synthetic step. Using arylethynyls in Kumada-Tamao-Corriu cross-coupling gave 2,6-phenylethynylbiphenyls that act as pyrene cyclization precursors. Subsequent cyclization lead to 4,10-aryl substituted pyrene derivatives, which display blue shifts in UV/Vis spectra and mirros these in fluorescence spectra.

Beside these synthetic steps, we successfully tested a diamantyl-salt (di-4-diamantyl-*n*-butylphosphonium iodide) prepared in our group in Suzuki-Miyaura and Sonogashira-Haghiara cross-coupling reactions, respectively. We also synthesized bis(arylethynyl)benzenes (enediynes) as precursors for thermally induced 1,6- and 1,5-cyclizations, and performed several test reactions in order to determine the influence of the substituents of the aryl moieties of these enediynes on the progress of these annulations and their ring size. In these first experiments, we found that these cyclization proceed in the 1,5-Schreiner-pathway, if the substrate carries radical-stabilizing substituents and that this reaction-pathway is not caused by steric effects as postulated by Pascal *et al.*[11] Other experiments include an electrophilically induced casacade cyclization of such enediyne- and related enhanced systems and mechanistic studies that have been supplemented by computations.

Several computations were carried out to compare Arduengo-type carbenes as ligands with their NHC-diamantyl-analogue for potential use of NHCs as palladium-catalysts. The computations reveal that the PA of these adamantyl and diamantyl derived systems are in the same range as computed for the mesityl substituted anlogues; first experiments were realized, but until now without noteworthy results.

Furthermore we started a series of catalyst screenings for the potential use of copper-catalysts in Suzuki-Miyaura and Ullmann reactions in cooperation with Würtele *et al.* In a

couple of test-reactions, we obtained traces of coupling product and consequently, these salts evince catalytic activity. However, better results have not been achieved yet.

6 Zusammenfassung

In dieser Arbeit wurde die Basis für die Synthese einer weiteren Familie von Pyrenderivaten gelegt, die aufgrund ihrer photochemischen Eigenschaften von Bedeutung sind. Diese Pyrene eröffnen ein weiteres Substitutionsmuster und wurden durch elektrophil-induzierte Cylclisierungsreaktionen hergestellt. Zugänglich sind die Edukte dieser Substanzgruppe durch aufeinanderfolgende Kreuzkupplungsreaktionen. Zunächst wurden mit Hilfe der Suzuki-Miyaura Kreuzkupplung 2,6-Dibrombiphenyle hergestellt. Einige dieser sterisch anspruchsvollen 2,6-Dibrombiphenyl-Derivate wurden charakterisiert und Reaktionsparameter dieses Syntheseschrittes optimiert und untersucht. Unter Anwendung der Kumada-Tamao-Corriu-Kupplung wurden die beschriebenen Biphenyle mit Arylacetylenen zu 2,6-Bis(phenylethinyl)biphenylen umgesetzt, die als Cyclisierungsvorläufer dienten. Anschließend wurde eine elektrophil induzierte 1,6-Anellierung durchgeführt und 4,10-Aryl-substituierte Pyrene erhalten, die eine Blau-Verschiebung im Absorptionsspektrum zeigen. Diese sind als Spiegelbild im Emissionsspektrum wiedergegeben.

Des Weiteren wurde ein in dieser Arbeitsgruppe synthetisiertes Diamantyl-Salz (Di-4-diamantyl-*n*-butylphosphonium Iodid) erfolgreich auf seine katalytische Aktivität in zwei Kreuzkupplungsreaktionen untersucht. Ebenfalls wurden 2,6-Bis(arylethinyl)benzole (Endiine) als Vorläuferverbindungen für die Untersuchung von thermisch induzierten 1,5- und 1,6-Cyclisierungen dargestellt. Bei diesen Cyclisierungen wurde der Einfluss verschiedener Substituenten auf den Cyclisierungsverlauf bzw. die Ringgröße untersucht. Das erste Ergebnis dieser Experimente unterstützt die Theorie, daß Substituenten, die in der Lage sind einen radikalischen Übergangszustand zu stabilisieren die Reaktion hin zum 1,5-Produkt, dem sogenannten Schreiner-Produkt beeinflussen und nicht wie von Pascal *et al.* postuliert, der 1,5-Cyclisierungsschritt aus sterischen Gründen abläuft.[11] Andere Experimente zeigen wie eine elektrophil induzierte Kaskadencyclisierung von Endiinen und erweiterten verwandten Systemen verläuft. Diese Ergebnisse wurden computerchemisch nachvollzogen.

Computerchemische und erste experimentelle Untersuchungen wurden zum Vergleich von Arduengo-Carbenen mit ihrem Diamantyl-Gegenstück durchgeführt. Gegenstand dieser Untersuchungen war die potenzielle Eignung für den Einsatz als Liganden in

Übergangsmetallkatalysatoren. Beispielsweise besitzen Adamantyl-, Diamantyl- und Mesityl-substituierte NHCs eine ähnliche Protonenaffinität und eignen sich gleichermaßen für ihren Einsatz als Liganden. Ebenfalls wurden erste Experimente zu NHC-Metallkomplexbildungen durchgeführt, allerdings bisher ohne nennenswerte Ergebnisse.

Zusätzlich wurden in Kooperation mit Würtele *et al.* Testreaktionen zur Eignung einiger Kupfer-Komplexe als Katalysatoren in Suzuki-Miyaura- und Ullmann-Kupplungen durchgeführt. Für einige Substratkombinationen wurden Spuren von Kupplungsprodukt erhalten, was auf eine katalytische Aktivität der Komplexe hinweist, jedoch wurden noch keine verwertbaren Ergebnisse erzielt.

7 Outlook

Organic light emitting diodes, OLEDs, have already been commercialized in, *e.g.*, flat screen panels for computer screens or television sets. At the same time, research aiming at more advantageous materials to be used in the OLEDs is actively pursued in many laboratories, both in academia and industry. This thesis provides contributions for improved synthetic methods for one important class of OLED materials: substituted pyrenes. The electronic and, consequently, photoelectronic properties of pyrenes are depending on the substitution patterns of the parent pyrene scaffold, so for fine-tuning of pyrenes as OLEDs the syntheses reported in Chapter 3 of this thesis are of significance. While already the synthetic route *via* twofold electrophilic induced cyclization reactions allows, in principle, the syntheses of substituted pyrenes with substitution patterns that are difficult to obtain using established methods. One strategy to develop this methodology further is the sequential electrocyclization strategy depicted in Scheme 65: Such an "alkynylation-cyclization-alkynylation-cyclization" sequence would enable the selective synthesis of libraries of pyrene derivatives incorporating up to four different substituents, all of which introduced in a regioselective fashion. Development of such a synthetic route, however, will require careful optimization of both the alkynylation reactions and the cyclization conditions - conversions for which significant basic studies have been disclosed herein. These flexible OLED devices could be utilized in devices as different as furnitures, clothing or flexible OLED displays. The optoelectronic properties of OLEDs using pyrenes would benefit from fine-tuning using such pyrene libraries, in particular with regards to brilliance of colors, the durability of the OLED, and a further reduction in overall energy consumption, including the production process. Upon elaborating synthetic routes for the selective synthesis of pyrenes, the methodologies to synthesize the cyclization precursors that yield pyrenes upon electrophilically induced cyclizations also allow for studies on cascade cyclizations towards polyethynylarylbenzenes. The ultimate goal of a bowl-shaped molecule representing a part of the C_{60} fullerene structure - prepared in a *selective* fashion - appears feasible and attractive not only for aesthetic reasons, but also to generate new lubricants or cavitands.[51,162] The synthetic pathways towards these bowl-shaped structures *via* cyclizations, the ones reported in this thesis and alternatives in the literature,[163] can also be utilized to give hemispherical polyarenes, but remain a challenge for the synthetic chemist. However, these hemispherical polyarenes are attractive building blocks for nanotubes with defined rim structures, diameter, and

conductivity to be utilized in the rational design of, *e.g.*, single-walled carbon nanotubes.[164]

The methodologies to generate the cyclization precursors, that is, transition-metal-catalyzed carbon-carbon couplings, have, likewise, pushed further in this thesis. As holds true for probably any experimentally oriented thesis, further optimizations of both catalytic metal complexes and the reaction conditions they have been used at is warranted. Higher-yielding coupling reactions and, therefore, simpler work-up of reaction mixtures (*cf.* Chapter 2) will be the result.

8 Experimental Section

8.1 General Information

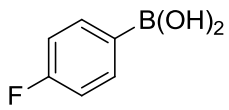
Chemicals were purchased from Alfa Aesar, Acros Organics, Applichem, Acros, Merck, Fluorochem, Fluka TCI, Janssen Chimica, and Lancanster and used without further purification. Solvents used for filtrations, column chromatography, extractions, and recrystallizations were distilled with a rotary evaporator. Solvents and liquids employed in cross-coupling reactions were dried, deoxygenated or purified according to established literature procedures and the dry solvents stored under argon and over activated molecular sieve (3 Å or 4 Å). Column chromatography was carried out exclusively by using flash silica gel. TLC was performed using pre-coated Machery-Nagel plastic sheets Polygram SiO_2 G/UV_{254}, employing UV light for visualization. Reaction progress and products were monitored by GC/MS analysis with a Quadropol-MS HP MSD 5971 (EI, GC-column, 30 m x 0.250 mm) and a HP 5890 (EI, GC-column, 10 m x 0.250 mm). The GC-columns were equipped with silica as 0.25 micron DB-5MS stationary phase 5% phenyl and 95% methyl silicone. Helium was used as carrier gas and the temperature programs act in a range of 60 °C to 250 °C with molecule or reaction customized heating rates; injector and transfer-line were kept at 250 °C. Microwave synthesis was performed in a CEM-Discover S apparatus, operating at a frequency of 2.54 GHz.

All ^{1}H NMR spectra were recorded at 400 MHz or 600 MHz respectively on Bruker AV 400 or AV 600 spectrometers. ^{13}C-NMR spectra were taken at 100 MHz and 151 MHz. Chemical shifts are reported in ppm (δ scale) using either TMS or the residual solvent signal as a standard. Structural assignments were made by 2D NMR spectra (HSQC) and DEPT 135 NMR spectra. UV/Vis spectra were measured with a HP 8423 spectrometer equipped with a mercury lamp. Emissions spectra were measured with an Ocean Optics SD 200 spectrometer (lamp: Beckmann Xe 1045, monochromatic illuminator: Beckmann GM 1139). Preparative GC was carried out using an OV17 Mesh column and a temperature program working at 100 °C to 250 °C with 4 °C/min per minute ramping. Preparative HPLC was carried out using a Knauer HPLC Pump 64 with a RP18 column. Melting points are not corrected and were measured with a Büchi *Dr. Tottoli Typ S* or with the melting point meter *KSP I N* by Krüss. HRMS were recorded using a Finnigan *MAT 95* with the electron impact ionization method (EI).

X-ray crystal structures were obtained using a STOE IPDS-diffractometer equipped with a low temperature system (Karlsruher Glastechnisches Werk). Mo-K_α radiation (λ= 0.71069 Å) and a graphite monochromator were used. No absorption corrections were applied.

8.2 Boronic Acids and Iodides

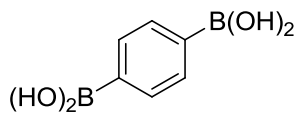
4-Fluorophenylboronic acid (1)



Chemical Formula: $C_6H_6BFO_2$
Molecular Weight: 139.92

A solution of 4-fluorobromobenzene (40 mmol, 7.04 g, 4.4 mL) in 80 mL THF was cooled to –78 °C. *n*-BuLi (1.1 eq.) was added and was stirred for 0.5 h, warmed to –20 °C. After stirring for 2 h at this temperature trimethylborate (60 mmol, 6.23 g, 6.8 mL) was added and the reaction mixture cooled to –78 °C. The mixture was stirred overnight and allowed slowly warm to room temperature. HCl (2 N, 100 mL) was added and the mixture stirred vigorously for 3 d. The mixture was extracted with THF/pentane (70:30) and the aqueous and organic phases were separated. The solvents were removed and the colorless solid was treated with pentane and dried overnight in the desiccator. Yield 3.6 g (26 mmol, 65%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ = 2.51 (s, 2 H, 2 OH), 7.15 (t, ^3J = 9.1 Hz, 2 H, 2 CH), 7.85 (t, ^3J = 7.6 Hz, 2 H, 2 CH); ^{13}C-NMR (100 MHz, DMSO-d_6) δ = 114.2 (d, ^3J(CF) = 9.9 Hz, 2 *C*H), 130.3 (*C*q), 135.5 (d, ^2J(CF) = 8.0 Hz, 2 *C*H), 163.7 (d, ^1J(CF) = 245.0 Hz, *C*F); IR-spectrum (KBr, cm^{-1}) $\tilde{\nu}$ = 3215 m (ν OH), 3051 w (ν aryl-H), 1599, 1590 s (ν C=C), 835 s (δ aryl-H, 1,4-disubstitution).

1,4-Phenyl-diboronic acid (5)

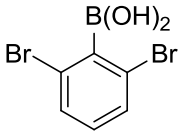


Chemical Formula: $C_6H_8B_2O_4$
Molecular Weight: 165.75

In a 100 mL nitrogen-flask a solution of 1,4-dibromo-benzene (15 mmol, 3.54 g) in 30 mL THF was cooled to –78 °C. *n*-BuLi (2.2 eq.) was added after 0.5 h, stirred and allowed to warm to –20 °C. The mixture was stirring for 2 h at this temperature and cooled again to –78 °C. Trimethylborate (33 mmol, 3.2 mL) was added, the mixture stirred overnight and then warmed to ambient temperature. HCl (2 N, 100 mL) was added and stirred vigorous overnight. The aqueous and organic phases were separated, the solvent was removed and the colorless solid treated with pentane and dried overnight in a desiccator. Yield approx. 22% (2.6 mmol, 431 mg). No pure spectra were

obtained, likely due to dimerization or trimerisation of the boronic acid taking place. The following signals could be assigned: ^{1}H-NMR (400 MHz, DMSO-d_6) δ = 7.56 (d, ^{3}J = 8.0 Hz, 2 H, 2 CH), 7.8 (d, ^{3}J = 8.0 Hz, 2 H, 2 CH); ^{13}C-NMR (100 MHz, DMSO-d_6) δ = 135.6 (4 *C*H); 123.4 (*C*B(OH)$_2$).

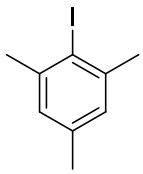
2,6-Dibromophenylboronic acid (6)



Chemical Formula: $C_6H_5BBr_2O_2$
Molecular Weight: 279.72

In a 250 mL nitrogen-flask THF (100 mL) and 1,3-dibromobenzene (50 mmol, 6 mL) were mixed and cooled to –78 °C. Diisopropylamine (50 mmol, 7 mL) and *n*-BuLi (1 eq.) were added and the mixture was warmed to –20 °C and stirred for 3 h at this temperature. After cooling again to –78 °C, trimethylborate (100 mmol, 11.3 mL) was added and once more warmed to ambient temperature overnight. HCl (2 N, 100 mL) was added and the mixture stirred for one more day. After addition of THF/hexane the phases were separated, dried over $MgSO_4$ and the solvents removed. A colorless solid was obtained. Yield 9.1 g (32.5 mmol, 65%); ^{1}H-NMR (400 MHz, DMSO-d_6) δ = 7.52 (d, ^{3}J = 8.4 Hz, 1 H, CH), 6.99 (t, ^{3}J = 8 Hz, 2 H, CH); ^{13}C-NMR (100 MHz, DMSO-d_6) δ = 129.7 (2 *C*Br), 129.1 (2 *C*H), 124.4 (*C*H).

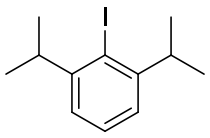
2-Iodo-1,3,5-trimethylbenzene (14)



Chemical Formula: $C_9H_{11}I$
Molecular Weight: 246.09

To a suspension of conc. HCl (25 mL) and 15 g ice 2,4,6-trimethylanilin (7.44 g, 55 mmol)was added. A solution of $NaNO_2$ (4.14 g, 60 mmol) in H_2O (20 mL) was added dropwise over 40 min at 0 °C. The solution was stirred for 30 min at the same temperature. Subsequently a solution of KI (12.45 g, 75 mmol) was added slowly and the mixture was warmed to ambient temperature. The reaction was exothermic with gas evolution. Afterwards the red solution was stirred overnight. The mixture was extracted with ethylacetate. The organic layer was washed with saturated Na_2SO_3-solution and dried over $MgSO_4$. After removal of the solvent, the red-colored raw product was filtrated with hexane over silica-gel and the resulting product was destilled using kugelrohr destillation. Yield 7.75 g (31.5 mmol, 57%) as yellow oil ^{1}H-NMR ($CDCl_3$, 400 MHz) δ = 2.11 (s, 3 H), 2.30 (s, 6 H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ = 20.6 (2 *C*H$_3$), 29.4 (*C*H$_3$), 104.2 (*C*I), 127.7 (2 *C*H), 137.4 (*C*q), 141.0 (2 *C*q).

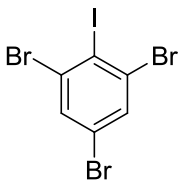
2-Iodo-1,3-diisopropylbenzene (15)



Chemical Formula: $C_{12}H_{17}I$
Molecular Weight: 288.17

In a 250 mL three-necked flask H_2SO_4 (conc. 40 mL) was placed at 0 °C and 2,6-diisopropylanilin (7.09 g, 40 mmol) was added. The white suspension was stirred until a homogenous solution was obtained. Afterwards, $NaNO_3$ (6.07 g, 88 mmol) was added slowly and the dark red solution stirred for 3 h at 0 °C. The crude product was carefully poured into 750 mL ice water and stirred. When the gas evolution finished the mixture was added to KI (dissolved in 1 L ice water). The dark brown solution was extracted three times with ethylacetate. The organic layer was washed with satured $NaHSO_3$-solution, water and brine and dried over $MgSO_4$. The solvent was removed and the crude product distilled at 110 °C in rotary vane pump vacuum. A yellow oil resulted with a yield of 3.26 g (11.3 mmol, 27.5%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ = 1.40 (t , ^3J = 6.05 Hz, 12 H), 3.58-3.64 (m, 2 H), 7,24 (s, 2 H), 7.39 (s, 1 H) ^{13}C-NMR ($CDCl_3$, 100 MHz) δ = 23.4 (4 *C*H_3), 39.4 (2 *C*H), 109.2 (*C*I), 123.8 (2 *C*H), 128.32 (*C*H), 151.01 (2 *C*q).

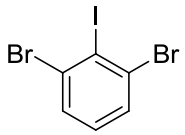
1,3,5-Tribromo-2-iodobenzene (24)



Chemical Formula: $C_6H_2Br_3I$
Molecular Weight: 440.70

A solution of *n*-BuLi (1.6 M, 25 mmol, 15.6 mL) in hexane/THF (40 mL/15 mL) was cooled to –78 °C. Diisopropylamin (25 mmol, 3.51 mL) and 1,3,5-tribromobenzene (25 mmol, 7.9 g) were added and the mixture was stirred for 2 h at –78 °C. Iodine (25 mmol, 6.34 g) was dissolved in THF (15 mL), added dropwise and the reaction mixture was allowed to warm to ambient temperature overnight. The residue was washed with satured $Na_2S_2O_3$-solution, dried over $MgSO_4$ and the solvents were removed. Yield: 2 g (4.5 mmol, 18%). ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.63 (s, 2 H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 133.6 (2 *C*Br), 131.8 (2 *C*H), 123.0 (*C*Br), 108.0 (*C*I).

2,6-Dibromoiodobenzene (25)

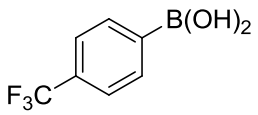


Chemical Formula: $C_6H_3Br_2I$
Molecular Weight: 361.80

a) H_2SO_4 (40 mL) and 2,6-dibromoaniline (40 mmol, 10 g) was placed in a 500 mL three-necked flask were placed and cooled in an ice bath. After stirring for 10 min, $NaNO_2$ (80 mmol, 6 g) was added slowly and the solution was stirred for another 3 h. The color changed from yellow to green. The solution was added carefully into a beaker together with KI (240 mmol, 40 g) in 500 mL ice water. The color turned to reddish brown and a N_2 evolution was visible. When the gas evolution ceased, the crude mixture was stirred for 5 min at ambient temperature and extracted with ethylacetate. The organic layer was washed with satured $NaHSO_3$ solution, brine, and water, and subsequently dried over $MgSO_4$ and concentrated. The orange solid was treated with hexane and colorless crystals were obtained. Yield 7.9 g (22 mmol, 55%). Identical spectroscopic data as reported in literature were obtained.[90]

b) *n*-BuLi (1.6 M, 25 mmol, 15.6 mL) in hexane/THF (40 mL/15 mL) was cooled to –78 °C and diisopropylamin (25 mmol, 3.51 mL) was added. 1,3-Dibromobenzene (25 mmol, 5.9 g) was added and the solution was stirred for 2 h at –75 °C. Iodine (25 mmol, 6.35 g) was dissolved in THF (15 mL) and added dropwise. The solution was allowed to warm to ambient temperature overnight. The residue was washed with satured $Na_2S_2O_3$-solution and dried over $MgSO_4$. Removal of the solvents gave the crude product in a worse yield compared to procedure a) Hence, we abstained from purification.

4-Trifluoromethylphenylboronic acid (29)

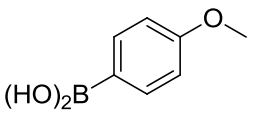


Chemical Formula: $C_7H_6BF_3O_2$
Molecular Weight: 189.93

A solution of 4-trifluoromethylbromobenzene (40 mmol, 9.0 g, 5.6 mL) in 80 mL THF was cooled to –78 °C. *n*-BuLi (44 mmol, 28 mL) was added and the solution was stirred for 1 h. Trimethylborate (44 mmol, 4.6 g, 5.1 mL) was added dropwise and stirred for another 2 h. Satured NH_4Cl solution (50 mL) with a trace of HCl (2 N) was added and the mixture was allowed to warm to ambient temperature overnight while stirring. The color of the solution turned to red. Water was added (100 mL) and the solution was extracted three times with diethyl ether (100 mL). The extract was washed with aqueous satured $NaHCO_3$ solution (200 mL) and satured brine (200 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure.

Treatment with hexane yielded a colorless solid (5.1 g, 27 mmol, 67%). Identical spectroscopic data as reported in literature.[87] HRMS: m/z calcd. for $C_7H_6BF_3O_2$: 190.041, found 190.042.

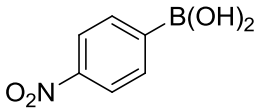
4-Methoxyphenylboronic acid (43)



Chemical Formula: $C_7H_9BO_3$
Molecular Weight: 151.96

A solution of 4-trifluoromethylbromobenzene (40 mmol, 9.0 g, 5.6 mL) in 80 mL THF was cooled to −78 °C. *n*-BuLi (44 mmol, 28 mL) was added and the solution was stirred for 1 h. Trimethylborate (80 mmol, 8.3 g, 9.1 mL) was added dropwise and the mixture was stirred for another 2 h. Satured NH_4Cl solution [50 mL with traces of HCl (2 N)] was added and the stirred solution was allowed to warm to room temperature overnight. The color of the solution turned to pink. Water was added (100 mL) and the solution was extracted for three times with diethyl ether (100 mL). The extract was washed with aqueous satured $NaHCO_3$-solution (200 mL) and saturated brine (200 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Treatment with hexane gave colorless solid (4.7 g, 31 mmol, 78%). Mp: decomposition at approx. 180 °C. Identical spectroscopic data as reported in literature.[165]

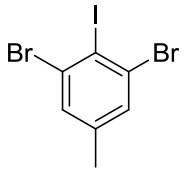
4-(Nitrophenyl)boronic acid (56)



Chemical Formula: $C_6H_6BNO_4$
Molecular Weight: 166.93

A solution of 4-nitrobromotoluene (40 mmol, 8.1 g) in 30 mL THF was cooled to –78 °C. *n*-BuLi (44 mmol, 35 mL) was added and the solution was stirred for 1 h. Trimethylborate (44 mmol, 4.6 g, 5.1 mL) was added dropwise and stirred for another 2 h. Satured NH_4Cl solution [50 mL with traces of HCl (2 N)] was added and the solution was allowed to warm to ambient temperature overnight while stirred. The color of the solution had turned to brown. Water was added (100 mL) and the solution was extracted three times with diethyl ether (100 mL). The extract was washed with aqueous saturated $NaHCO_3$ solution (200 mL) and saturated brine (200 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Digestion with hexane gave a light brown sludge. Different attempts of purification were to no avail.

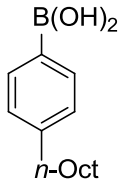
3,5-Dibromo-4-iodotoluene (92a)



Chemical Formula: $C_7H_5Br_2I$
Molecular Weight: 375.83

A 500 mL three-necked flask was charged with H_2SO_4 (15 mL) and 2,6-dibromo-4-methylaniline **92** (15 mmol, 4 g) and cooled with an ice bath. After stirring for 10 minutes $NaNO_2$ (30 mmol, 2.25 g) was added slowly and the solution was stirred for another 3 h. The color changed from yellow to green. The solution was carefully added into a beaker with KI (90 mmol, 15 g) dissolved in 200 mL ice water. The color turned to reddish brown and gas evolution was noticeable. When the gas evolution ceased, the solution was stirred for 5 min at ambient temperature and extracted with ca. 500 mL ethylacetate. The organic layer was washed with satured $NaHSO_3$ solution, brine and water, dried over $MgSO_4$ and concentrated. The resulting orange solid was treated with hexane and colorless crystals were obtained. Yield: 2.7 g (22 mmol, 48%), Mp 67-68 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39 (s, 2 H), 2.25 (s, 3 H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 141.2 (*C*q), 132.1 (2 *C*Br), 130.1 (*C*I), 105.0 (2 *C*H), 20.6 (*C*H_3).

4-*n*-Octylphenylboronic acid (88)

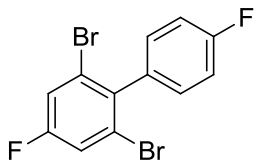


Chemical Formula: $C_{14}H_{23}BO_2$
Molecular Weight: 234.14

THF (80 mL) and 4-*n*-octylbromobenzene (8.08 g, 30 mmol) were placed in a 250 mL flask at –78 °C under argon atmosphere. *n*-BuLi (1.55 M, 21.3 mL, 33 mmol) was added slowly and afterwards, the solution was allowed to warm to –20 °C and stirred overnight. Then the reaction mixture again was cooled to –78 °C and trimethylborate (60 mmol, 7 mL) was added. Then the mixture was allowed to warm to ambient temperature. 2 N HCl (ca. 100 mL) was added and the mixture was stirred at ambient temperature. Extraction with pentane/THF and removing of the solvents provided a colorless waxy solid. NMR spectra show impurities and the following signals, which could be assingend: ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 0.88 (t, ^3J = 6.8 Hz, 3 H, CH_3), 1.27 (s, 2H, CH_2), 1.65 (t, ^3J = 7.5 Hz; 12 H, 6 CH_2), 2.7 (d, ^3J = 7.9 Hz, 2 H, OH), 7.29 (d, ^3J = 7.5 Hz, 2 H, 2 CH), 8.22 (d, ^3J = 7.6 Hz, 2H, 2 CH) ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 14.2 (*C*H_3), 22.7-36.4 (7 aliphatic *C*), 128.2 (2 *C*H), 128.3 (*C*q), 133.6 (2 *C*H), 135.7 (*C*q).

8.3 2,6-Dibromobiphenyl Derivatives

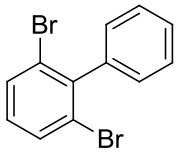
2,6-Dibromo-4,4'-difluorobiphenyl (2)



Chemical Formula: $C_{12}H_6Br_2F_2$
Molecular Weight: 347.98

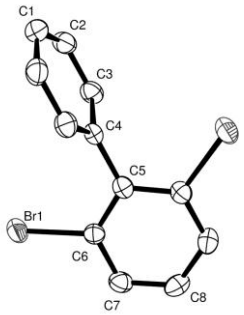
A 100 mL nitrogen-flask equipped with condenser and bubble counter was charged with 4-fluoroboronic acid (3 mmol, 0.42 g), 2,6-dibromo-4-fluoroiodobenzene (3 mmol, 1.14 g), PEPPSI-IPr (0.015 mmol, 0.1 g) and K_2CO_3 (1.24 g, 9 mmol). The solids were deoxygenated and 1,4-dioxane (10 mL) was added. The mixture was heated to 80 °C (oilbath) for 70 h. The crude product was diluted with pentane/DCM, filtrated and dried over Na_2SO_4. Different purification attempts were without success. Starting material, product and twofold as well as treefold coupling products were detected by GC/MS analysis. No pure product was isolated.

2,6-Dibromobiphenyl (3)

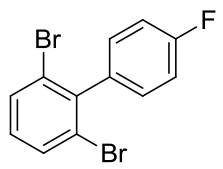


Chemical Formula: $C_{12}H_8Br_2$
Molecular Weight: 312.00

A 100 mL nitrogen-flask was charged with 2,6-dibromoiodobenzene (5 mmol, 1.8 g), PEPPSI-IPr (0.2 g, 0.25 mmol, 5 mol%), K_2CO_3 (18 mmol, 2.48 g) and 1,4-dioxane under argon and dry conditions. After 1 h of stirring at ambient temperature, phenylboronic acid (5 mmol, 0.6 g) was added and the solution was refluxed for 36 h. Saturated aqueous $NaHCO_3$ was added and the crude product extracted with CH_2Cl_2. The mixture was dried over $MgSO_4$ and subsequently purified by column chromatography (pentane/CH_2Cl_2, 99:1, R_f: 0.32). Evaporation of the eluent provided colorless crystals with a yield of 0.97 g (3.1 mmol, 62%); Mp 71 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.05 (t, ^3J = 8.00 Hz, 1 H), 7.2 (d, ^3J = 7.20 Hz, 2 H), 7.4-7.5 (m, 3 H), 7.62 (d, ^3J = 8.01 Hz, 2 H), ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 124.6 (2 *C*Br), 128.1 (*C*H), 128.2 (2 Ar*C*H), 129.1 (2 Ar*C*H), 129.8 (2 Ar*C*H), 131,8 (Ar*C*H), 141.1 (Ar*C*q), 143.0 (Ar*C*q); HRMS: m/z calcd. for $C_{12}H_8Br_2$: 309.899, found: 309.897. X-ray structure depicted on the right.[16b]

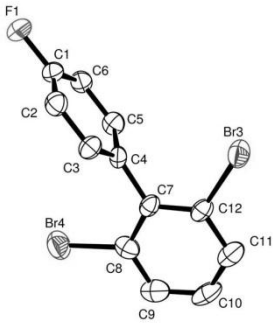


2,6-Dibromo-4'-fluorobiphenyl (4)

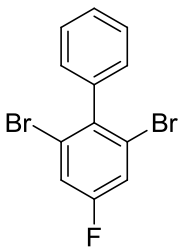


Chemical Formula: $C_{12}H_7Br_2F$
Molecular Weight: 329.99

Into a 100 mL nitrogen-flask were placed 2,6-dibromoiodobenzene (5 mmol, 1,8 g), PEPPSI-IPr (0.25 mmol, 0.2 g, 5 mol%), K_2CO_3 (18 mmol, 2.48 g) and 1,4-dioxane under argon and dry conditions. After 1 h of stirring at ambient temperature, 4-fluorophenylboronic acid (5 mmol, 0.7 g) was added and the solution was refluxed for 36 h. Subsequently saturated aqueous $NaHCO_3$ was added and the crude product was extracted with CH_2Cl_2. The mixture was dried over $MgSO_4$ and purified by column chromatography (pentane/CH_2Cl_2, 99:1; R_f: 0.26). This afforded colorless crystals in a yield of 0.74 g (2.24 mmol, 45%); Mp 56 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.04–7.18 (m, 5 H), 7.61 (d, ^3J = 8.9 Hz, 2 H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 115.3 (d, ^2J(CF) = 22.0 Hz, 2 Ar*C*H), 124.7 (2 *C*Br), 130.0 (2 Ar*C*H), 131.0 (d, ^3J(CF) = 8.2 Hz, 2 Ar*C*H),; 131.9 (*C*H), 137.0 (*C*q), 142.0 (*C*q), 162.8 (d, ^1J(CF) = 243.0 Hz, *C*F); HRMS: m/z calcd. for $C_{12}H_7Br_2F$: 327.889, found: 327.890. X-ray structure depicted on the right.

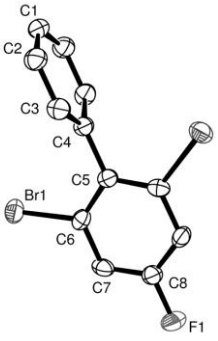


2,6-Dibromo-4-fluorobiphenyl (23)



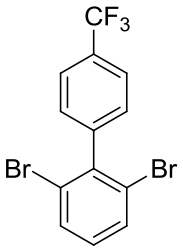
Chemical Formula: $C_{12}H_7Br_2F$
Molecular Weight: 329.99

A 100 mL nitrogen-flask was charged with 4-fluoro-2,6-dibromiodobenzene (5 mmol, 1.9 g), PEPPSI-iPr (0.25 mmol, 0.17 g, 5 mol%) K_2CO_3 (15 mmol, 2.1 g) and 1,4-dioxane (25 mL) under argon and dry conditions. After 1 h of stirring at room temperature phenylboronic acid (5 mmol, 0.6 g) was added and the solution was refluxed for 36 h. Saturated aqueous $NaHCO_3$ was added and the crude product extracted with CH_2Cl_2 (60 mL). The mixture was dried over $MgSO_4$ and subsequently purified by column chromatography (hexane/CH_2Cl_2, 9:1, R_f = 0.35). This afforded colorless crystals in a yield of 0.96 g, (2.9 mmol, 58%); Mp 110 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.18 (d, ^3J = 7.3 Hz, 2 H), 7.4-7.5 (m, 5H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 119.4 (^2J(CF) = 23 Hz, Ar*C*H), 124.4 (2 *C*Br), 128.3 (3 Ar*C*H); 129.4



(2 CH), 139.4 (^4J(C,F) = 4 Hz, Ar*C*q), 140.3 (Ar*C*q), 161.1 (^1J(CF) = 254 Hz, Ar*C*F); HRMS: m/z calcd. for $C_{12}H_7Br_2F$: 327.889, found: 327.890. X-ray structure depicted on the left. [16b]

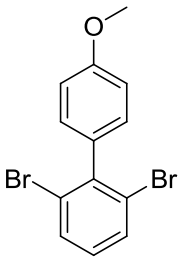
2,6-Dibromo-4'-(trifluoromethyl)biphenyl (36)



Chemical Formula: $C_{13}H_7Br_2F_3$
Molecular Weight: 379.99

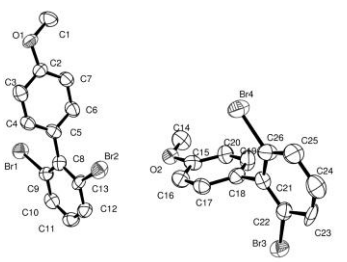
In a 100 mL nitrogen-flask were placed 2,6-dibromiodobenzene (1 mmol, 0.362 g), PEPPSI-IPr (0.15 mmol, 0.1 g, 15 mol%), K_2CO_3 (3 mmol, 0.42 g) and 1,4-dioxane (10 mL) under argon and dry conditions. After 1 h stirring at room temperature, 4-trifluoromethylphenylboronic acid (1 mmol, 0.19 g) was added and the solution was heated to reflux for 36 h. Saturated aqueous $NaHCO_3$ was added and the crude product was extracted with CH_2Cl_2 (60 mL). The mixture was dried over $MgSO_4$ and subsequently purified by preparative GC/MS. This afforded colorless crystals in a yield of 0.07 g (0.18 mmol, 18%); Mp 46 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.09 (t, ^3J = 8.1 Hz, 1 H), 7.33 (d, ^3J = 8 Hz, 2 H), 7.63 (d, ^3J = 8.1 Hz, 2 H), 7.71 (d, ^3J = 8 Hz, 2 H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 122.75 (^1J(CF) = 273 Hz, *C*F_3), 124.04 (2 *C*Br), 125.3 (*C*q , ^3J(CF) = 4 Hz, 2 ArCH), 129.8 (2 Ar*C*H), 130.1 (^2J(CF) = 32 Hz, Ar*C*q), 131.1 (2 Ar*C*H), 131.9 (Ar*C*H), 141.7 (Ar*C*q), 144.5 (Ar*C*q); HRMS: m/z calcd. for $C_{13}H_7Br_2F_3$: 377.886, found: 377.885.

2,6-Dibromo-4'-methoxybiphenyl (41)



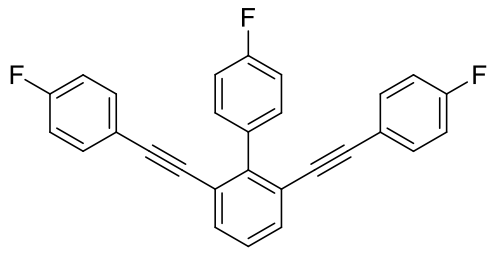
Chemical Formula: $C_{13}H_{10}Br_2O$
Molecular Weight: 342.03

In a 100 mL nitrogen-flask 2,6-dibromoiodobenzene (1,8 g, 5 mmol), PEPPSI-IPr (0.17 g, 0.25 mmol, 5 mol%) K_2CO_3 (2.48 g, 18 mmol) and 1,4-dioxane were placed under argon and dry conditions. After 1 h of stirring at room temperature 4-methoxyphenylboronic acid (0.76 g, 5 mmol) was added and the solution was refluxed for 36 h. Saturated aqueous $NaHCO_3$ was added and the crude product was extracted with CH_2Cl_2. The mixture was dried over $MgSO_4$ and subsequently purified by column chromatography



(hexane/CH_2Cl_2, 95:5, R_f = 0.1). This afforded colorless crystals with a yield of 0.83 g (2.43 mmol, 49%); mp 60 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 3.85 (s, 3 H), 6.97 (d, ^3J = 8.7 Hz, 2 H), 7.03 (t, ^3J = 8.1 Hz, H), 7.13 (d, ^3J = 8.4 Hz, 2 H), 7.60 (d, ^3J = 7.9 Hz, 2 H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 55.2 (O*C*H$_3$), 113.5 (2 Ar*C*H), 125.2 (2 *C*Br), 129.7 (*C*q), 130.4 (2 *C*H), 131.8 (2 Ar*C*H), 133.7 (Ar*C*H), 142.7 (Ar*C*q), 159.2 (*C*O); HRMS: m/z calcd. for $C_{13}H_{10}Br_2O$: 339.909, found: 339.911. X-ray structure depicted on previous page. [16b]

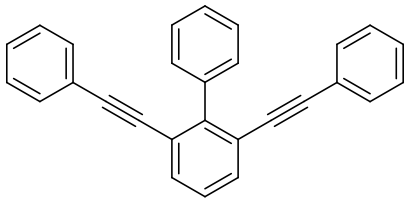
6-Bis(4-fluorophenylethynyl)-4'-fluorobiphenyl (7)



Chemical Formula: $C_{28}H_{15}F_3$
Molecular Weight: 408.41

To a stirred mixture of 2,6-dibromo-4'-fluorobiphenyl **4** (1 mmol, 0.330 g), $(PPh_3)_2PdCl_2$ (0.15 mmol, 0.105 g) was added 4-fluorophenyl ethynyl magnesiumbromide under argon atmosphere and dry conditions in THF (15 mL). Phenylethynylmagnesiumbromide was prepared beforehand from ethynylmagnesiumbromide (1 eq.) and 4-fluorophenylacetylene (6 mmol) by transmetallation at –40 °C. The solution was refluxed for 48 h. Then NH_4Cl (50 mL) was added to the dark brown solution and extracted with CH_2Cl_2 (150 mL). The crude product was purified by column chromatography using flash silica gel (hexane/CH_2Cl_2, 95:5, R_f: 0.18). A pale yellow solid was obtained. The conversion was almost complete (Probably spectroscopically invisible impurity); Mp 82 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 6.96 (t, ^3J = 8.6 Hz, 4 H), 7.1-7.2 (m, 6 H), 7.34 (t, ^3J = 7.5 Hz, H), 7.5 (m, 4 H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 88.2 (2 *C*CAr), 92.1 (2 C*C*Ar), 114.3 (^2J(CF) = 21 Hz, 2 Ar*C*H), 115.6 (^2J(C,F) = 22 Hz, 4 Ar*C*H), 119.05 (^4J(C,F) = 3 Hz, 2 Ar*C*H), 123.3 (2 Ar*C*q), 127.4 (Ar*C*H), 131.3 (Ar*C*q), 132.1 (2 Ar*C*H), 133.2 (^3J(CF) = 8 Hz, 2 Ar*C*H), 135.0 (2 Ar*C*H), 145.0 (Ar*C*q), 161.3 (^1J(CF) = 245 Hz, 2 Ar*C*F), 163.8 (^1J(CF) = 248 Hz, Ar*C*F); HRMS: m/z calcd. for $C_{28}H_{15}F_3$: 408.113, found: 408.112.

2,6-Bis(phenylethynyl)biphenyl (19)

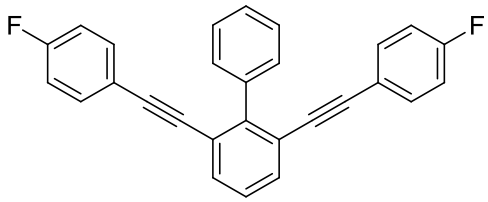


Chemical Formula: $C_{28}H_{18}$
Molecular Weight: 354.44

a) To a stirred mixture of 2,6-dibromobiphenyl **3** (1 mmol, 0.312 g), $(PPh_3)_2PdCl_2$ (0.15 mmol, 0.105 g) was added phenylethinylmagnesiumbromide under argon atmosphere and dry conditions in THF (15 mL). Phenylethynylmagnesiumbromide was prepared beforehand from ethynylmagnesiumbromide (1 eq.) and phenylacetylene (6 mmol) by transmetallation reaction at –40 °C. The solution was refluxed for 48 h. Then NH_4Cl (50 mL) was added to the dark brown solution and the solution was extracted with CH_2Cl_2 (150 mL). The crude product was purified with preparative HPLC (CH_3CN/H_2O, 80:20, 3 mL/min, 220 nm). This afforded a pale yellow viscous solid in a yield of 0.19 g (0.53 mmol, 53%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.1-7.2 (m, 10 H), 7.24 (t, ^3J = 8 Hz, 1 H), 7.34-7.43 (m, 3 H), 7.52-7.55 (m, 4 H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 88.9 (2 *C*CAr), 92.9 (2 C*C*Ar), 123.2 (2 Ar*C*q), 123.3 (2 Ar*C*q), 127.1 (Ar*C*H), 127.4 (Ar*C*H), 127.7 (2 Ar*C*H), 128.2 (6 Ar*C*H), 130.4 (2 Ar*C*H), 131.4 (4 Ar*C*H), 132.1 (2 Ar*C*H), 139.1 (Ar*C*q), 146.4 (Ar*C*q); HRMS: m/z calcd. for $C_{28}H_{18}$: 354.140, found: 354.139.

b) The same reaction was tested under similar conditions with $Pd_2(dba)_3$ but the GC/MS analysis already showed little product. Beforehand the reaction was carried out as Sonogashira-Hagihara cross-coupling with 5 mol% CuI and 5 mol% $(PPh_3)_2PdCl_2$ and 10 mol% PPh_3 in triethylamine. Only mono-coupling product was obtained.

2,6-Bis[(4-fluorophenyl)ethynyl]biphenyl (26)



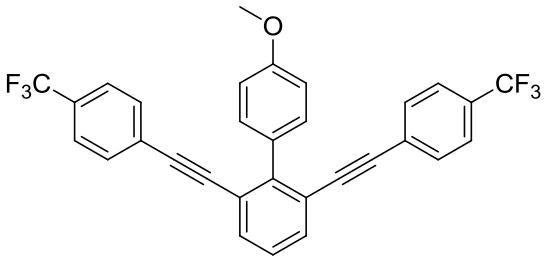
Chemical Formula: $C_{28}H_{16}F_2$
Molecular Weight: 390.42

a) To a stirred mixture of 2,6-dibromobiphenyl **3** (1 mmol, 0.312 g), $Pd_2(dba)_3$ (0.15 mmol, 0.137 g) was added 4-fluorophenylethynyl-magnesiumbromide under argon atmosphere and dry conditions in THF (10 mL). Phenylethynylmagnesiumbromide was prepared beforehand from ethynylmagnesiumbromide (1 eq.) and 4-fluorophenylacetylene (6 mmol) by transmetallation at –40 °C. The solution was refluxed for 48 h. In the following, NH_4Cl (50 mL) were added to the dark brown solution and the solution was extracted with 150 mL CH_2Cl_2. The crude product was purified by column

chromatography with flash silica gel (cyclohexane/CH_2Cl_2; 95:5; R_f: 0.36). A pale yellow viscous oil was obtained in a yield of 0.057g (0.15 mmol, 15%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 6.93 (t, ^3J = 8.8 Hz, 4 H), 7.12-7.16 (m, 4 H), 7.30 (t, H, ^3J = 8.8 Hz), 7.4-7.5 (m, 3 H), 7.56-7.58 (m, 4 H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 88.5 (2 *C*CAr), 91.9 (2 C*C*Ar), 115.5 (^2J(CF) = 21 Hz, 4 Ar*C*H), 119.2 (^4J(CF) = 4 Hz, 2 Ar*C*q), 123.1 (2 Ar*C*q), 127.1 (Ar*C*H), 127.4 (Ar*C*H), 127.7 (2 Ar*C*H), 130.3 (2 Ar*C*H), 132.0 (2 Ar*C*H), 133.3 (^3J(CF) = 8.5 Hz,4 Ar*C*H), 139.1 (Ar*C*q), 146.4 (Ar*C*q), 163.7 (Ar*C*F, ^1J(CF) = 250 Hz); HRMS: m/z calcd. for $C_{28}H_{16}F_2$: 390.122, found: 390.121.

b) The reaction was also carried out as Sonogashira cross-coupling, using 2,6-dibromobiphenyl (2.4 mmol, 0.74 g), 4-fluorophenylactylene (7 mmol, 0.84 g), PPh_3PdCl_2 (0.15 mmol, 0.1 g), CuI (0.15 mmol, 0.03 g), PPh_3 (0.3 mmol, 0.08 g) in 20 mL TEA. After 24 h at about 100 °C, GC/MS analysis showed only one fold coupling product.

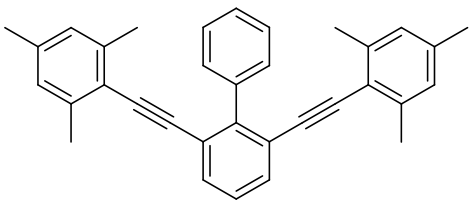
2,6-Dibromo-4'-(trifluoromethyl)biphenyl (38)



Chemical Formula: $C_{31}H_{18}F_6O$
Molecular Weight: 520.46

To a stirred mixture of 2,6-dibromo-4'-methoxybiphenyl **41** (1 mmol, 0.34 g), $(PPh_3)_2PdCl_2$ (0.15 mmol, 0.11 g) was added 4-trifluoromethylphenylethinylmagnesium-bromide under argon atmosphere and dry conditions in THF (15 mL). The solution was refluxed for 2 days. After 24 h and 48 h, samples were taken and subjected to GC/MS analysis. Only starting material **41** was identified.

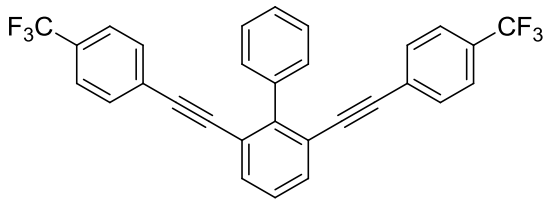
2,6-Bis(mesitylethynyl)-1,1'-biphenyl (58)



Chemical Formula: $C_{34}H_{30}$
Molecular Weight: 438.60

To a stirred mixture of 2,6-dibromobiphenyl **3** (1 mmol, 0.312 g), $(PPh_3)_2PdCl_2$ (0.15 mmol, 0.105 g) was added 2,4,6-trimethylphenylethinyl-magnesiumbromide under argon atmosphere and dry conditions in THF (10 mL). The solution was refluxed for 24 h at 100 °C. GC/MS analysis only showed the monoethynylation product.

2,6-Bis{[4-(trifluoromethyl)phenyl]ethynyl}-1,1'-biphenyl (60)

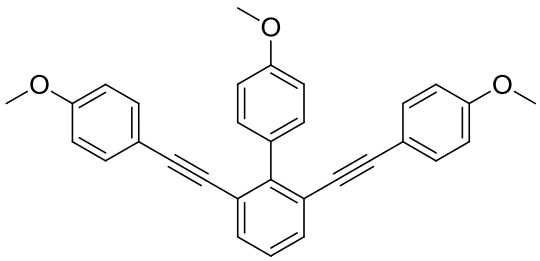


Chemical Formula: $C_{30}H_{16}F_6$
Molecular Weight: 490.44

a) 2,6-Dibromobiphenyl **3** (1.5 mmol, 0.468 g), CuI (0.075 mmol, 14 mg), $(PPh_3)_2PdCl_2$ (0.075 mmol, 53 mg), PPh_3 and TEA (15 mL) were placed in a 25 mL nitrogen-flask and degassed. After 1 h of stirring at ambient temperature trifluoromethyl-phenylaceylene was added and the mixture was stirred for 24 h at 50 °C. GC/MS analysis after 24 h and 48 h, respectively, only showed the monoethynylation product.

b) To a stirred mixture of 2,6-dibrombiphenyl **3** (1 mmol, 0.312 g), $Pd(dba)_3$ (0.15 mmol, 137 mg) was added 4-trifluoromethylphenylethinylmagnesiumbromide (6 mmol) under argon atmosphere and dry conditions in THF (10 mL). The solution was refluxed for 24 h at 60 °C. GC/MS analysis showed no product, solely starting materials.

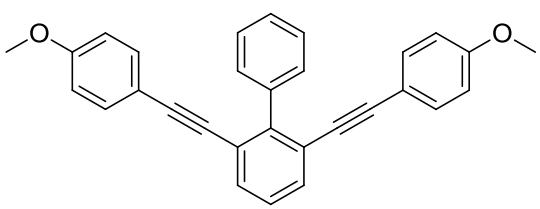
4'-Methoxy-2,6-bis[(4-methoxyphenyl)ethynyl]-1,1'-biphenyl (62)



Chemical Formula: $C_{31}H_{24}O_3$
Molecular Weight: 444.52

To a stirred mixture of 2,6-dibromo-4'-methoxybiphenyl **41** (1 mmol, 0.34 g), $(PPh_3)_2PdCl_2$ (0.15 mmol, 0.105 g) under argon atmosphere and dry conditions in THF (10 mL) was added 4-methoxyphenyl-ethinylmagnesiumbromide. The solution was refluxed for 24 h at 100 °C. GC/MS analysis showed no product, only starting materials.

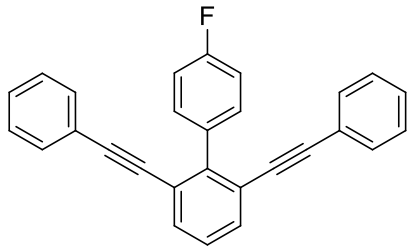
2,6-Bis[(4-methoxyphenyl)ethynyl]-1,1'-biphenyl (64)



Chemical Formula: $C_{30}H_{22}O_2$
Molecular Weight: 414.49

To a stirred mixture of 2,6-dibrombiphenyl (**3**) (0.5 mmol, 0.156 g), $Pd(dba)_3$ (0.15 mmol, 0.13 mg) was added 4-methoxy phenylethinylmagnesiumbromide under argon atmosphere and dry conditions in THF (10 mL). The solution was refluxed for 24 h at 60 °C. GC/MS analysis only showed mono ethynylated product.

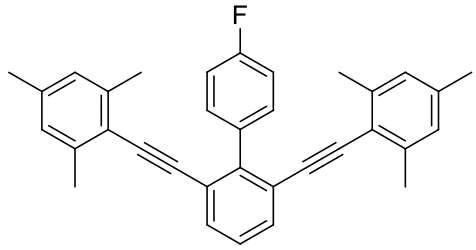
4-'Fluoro-2,6-bis(phenylethynyl)biphenyl (67)



Chemical Formula: $C_{28}H_{17}F$
Molecular Weight: 372.43

To a stirred mixture of 2,6-dibromo-4'-fluorobiphenyl (1 mmol, 0.330 g), $(PPh_3)_2PdCl_2$ (0.15 mmol, 0.105 g) phenylethynylmagnesiumbromide was added under argon atmosphere and dry conditions in THF (10 mL). Phenylethynylmagnesiumbromide was prepared beforehand from ethynylmagnesiumbromide (1 eq.) and phenylacetylene (6 mmol) at –40 °C by transmetallation. The solution was refluxed for 48 h. Subsequently, NH_4Cl (50 mL) was added to the dark brown solution and the solution was extracted with CH_2Cl_2 (150 mL). The crude product was purified by flash chromatography (hexane/CH_2Cl_2, 95:5; R_f: 0.17) A pale yellow viscous oil was obtained in a yield of 0.148 g (0.4 mmol, 40%); the following signals could be assigned: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.1-7.3 (m, 5 H), 7.5-7.6 (m, 12 H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 88.6 (2 *C*CAr), 93.1 (2 C*C*Ar), 114.5 (^2J(CF) = 21 Hz, 2 Ar*C*H) 123.0 (2 Ar*C*q), 123.4 (2 Ar*C*q), 127.2 (2 Ar*C*H), 128.3 (^3J(CF) = 3 Hz, 2 Ar*C*H), 129.4 (4 Ar*C*H), 131.4 (4 Ar*C*H), 132.1 (2 Ar*C*H), 135.0 (Ar*C*q), 145.1 (Ar*C*q), 163.7 (^1J(CF) = 243 Hz, Ar*C*F); HRMS: m/z calcd. for $C_{28}H_{17}F$: 372.131, found: 372.130.

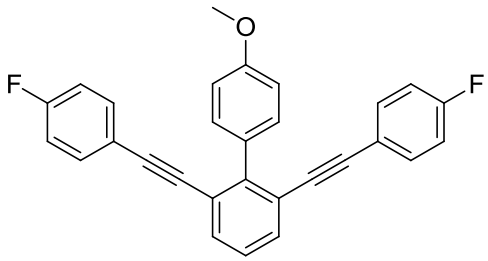
4'-Fluoro-2,6-bis(mesitylethynyl)-1,1'-biphenyl (68)



Chemical Formula: $C_{34}H_{29}F$
Molecular Weight: 456.59

To a stirred mixture of 2,6-dibromo-4'-fluorobiphenyl **4** (0.5 mmol, 0.165 g), $(PPh_3)_2PdCl_2$ (0.15 mmol, 0.105 g) was added 4-methoxyphenylethinylmagnesiumbromide) under argon atmosphere and dry conditions in THF (10 mL). The solution was refluxed for 24 h at 60 °C. GC/MS analysis showed no product, only starting materials.

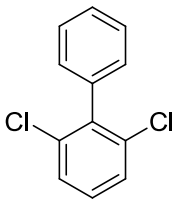
4'-Fluoro-2,6-bis[(4-methoxyphenyl)ethynyl]-1,1'-biphenyl (70)



Chemical Formula: $C_{29}H_{18}F_2O$
Molecular Weight: 420.45

To a stirred mixture of 2,6-dibromo-4'-methoxybiphenyl (**41**) (1 mmol, 0.330 g), $(PPh_3)_2PdCl_2$ (0.15 mmol, 0.105 g) phenylethynylmagnesiumbromide was added under argon atmosphere and dry conditions in THF (10 mL). 4-fluorophenylethynyl-magnesiumbromide was prepared beforehand from ethynylmagnesiumbromide (1 eq.) and phenylacetylene (6 mmol) by transmetallation. The solution was refluxed for 48 h. GC/MS analysis showed no product.

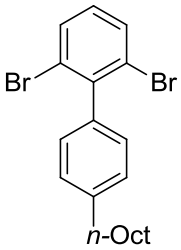
2,6-Dicholorobiphenyl (79)



Chemical Formula: $C_{12}H_8Cl_2$
Molecular Weight: 223.10

In a 100 mL nitrogen-flask were placed 2,6-dichloroiodobenzene (1 mmol, 272 mg), PEPPSI-iPr (0.05 mmol, 34 mg), K_2CO_3 (3 mmol, 414 mg) and 2 mL 1,4-dioxane under argon and dry conditions. After 1 h of stirring at room temperature, phenylboronic acid (1 mmol, 122 mg) was added and the solution was refluxed for 36 h. Saturated aqueous $NaHCO_3$ was added and the crude product extracted with CH_2Cl_2. GC/MS analysis showed a product distribution of 30:1 product to side product 3'-chloro-1,1',2',1''-terphenyl.

2,6-Dibromo-4'-*n*-octyl biphenyl (89)

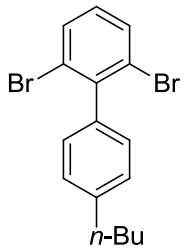


Chemical Formula: $C_{20}H_{24}Br_2$
Molecular Weight: 424.21

A Schlenk tube was charged with 4-*n*-octylphenyltrihydroxyborate (1 mmol, 247 mg **88**, treated with NaOH-solution), 2,6-dibromoiodobenzene (1.5 mmol, 543 mg), palladium acetate (0.05 mmol, 11.2 mg), triphenylphosphine (0.1 mmol, 26.2 mg), 5% deoxygenated water as solvent in 1,4-dioxane and then flushed with argon. The reaction mixture was stirred for 2 days at 60 °C. A small fraction could be isolated and purified by column chromatography on silica gel using hexane R_f: 0.45. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.63 (d, ^3J = 8.0 Hz, 2 H), 7.28 (d, ^3J = 8.2 Hz, 2 H), 7.05 (t, ^3J = 8.0 Hz, 1 H), 2.69 (t, ^3J = 7.8 Hz, 2 H), 1.69 (q, ^3J = 7.6

Hz, 2 H), 1.36-1.29 (m, 10 H), 0.90 (t, 3 H, ^{3}J = 7.0 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 143.2, 142.8, 138.5, 131.8, 129.0, 128.2, 124.8, 35.9, 31.9, 31.2, 29.5, 29.3, 22.7, 14.2.

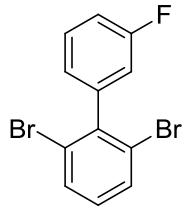
2,6-Dibromo-4'-*n*-butyl biphenyl (90)



Chemical Formula: $C_{17}H_{18}Br_2$
Molecular Weight: 382.13

A nitrogen-flask was charged with argon and 2,6-dibromoiodobenzene (1.5 mmol, 543 mg), *n*-butylphenylboronic acid (1 mmol, 178 mg) $Ba(OH)_2$ (3 mmol, 514 mg), $Pd(OAc)_2$ (0.05 mmol, 11 mg), PPh_3 (0.1 mmol, 26.2 mg) and deoxygenated 1,4-dioxane/water (4 mL, 10% water) as solvent. The reaction mixture was stirred for 2 days at 60 °C. A small amount of product was purified by column chromatography using *n*-hexane. R_f: 0.28. Isolated product was a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.59 (d, ^{3}J = 7.6 Hz, 2 H), 7.23 (d, ^{3}J = 7.3 Hz, 2 H), 7.1-7.69 (m, 3 H), 2.66 (t, ^{3}J = 7.7 Hz, 2 H), 1.6-1.3 (m, 4 H), 0.92 (t, 3 H, ^{3}J = 7.1 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 143.1, 142.7, 138.4, 131.8, 129.6, 128.9, 128.1, 124.8, 35.5, 33.4, 22.5, 14.9.

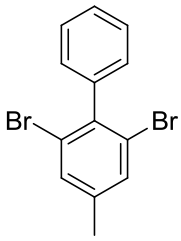
2,6-Dibromo-3'-fluorobiphenyl (91)



Chemical Formula: $C_{12}H_7Br_2F$
Molecular Weight: 329.99

A nitrogen-flask was charged with argon and 2,6-dibromoiodobenzene **25** (1.5 mmol, 543 mg), 3-fluorophenylboronic acid (1 mmol, 178 mg) $Ba(OH)_2$ (3 mmol, 514 mg), $Pd(OAc)_2$ (0.05 mmol, 11 mg), PPh_3 (0.1 mmol, 26.2 mg) and deoxygenated 1,4-dioxane/water (10% water) as solvent. The reaction mixture was stirred for 3 days. The crude product was purified by column chromatography (*n*-hexane/DCM, 99:1; R_f: 0.35). A colorless solid was obtained in a yield of 120 mg (0.36 mmol, 36%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.64 (d, 2 H, ^{3}J = 8.0 Hz), 7.42 (m, 1 H), 7.13 (m, 1 H), 7.1 (t, 1 H, ^{3}J = 8 Hz), 7.0 (m, 1 H), 6.95 (m, 1 H), 6.95 (m, 1 H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 162.5 (d, ^{1}J(CF) = 247 Hz), 143.0 (d, ^{3}J(CF) = 8.2 Hz), 141.9 (d, ^{4}J(CF) = 1.9 Hz), 132.0, 130.3, 130.0 (d, ^{3}J(CF) = 8.4 Hz), 125.2 (d, ^{4}J(CF) = 3 Hz), 124.4, 116.6 (d, ^{2}J(CF) = 22 Hz), 115.2 (d, ^{2}J(CF) = 21 Hz).

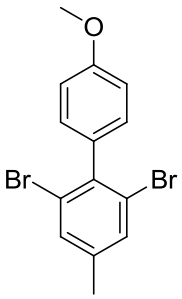
2,6-Dibromo-4-methylbiphenyl (93)



Chemical Formula: $C_{13}H_{10}Br_2$
Molecular Weight: 326.03

A nitrogen-flask was charged under argon with 3,5-dibromo-4-iodotoluene **92a** (0.5 mmol, 188 mg), phenylboronic acid (0.5 mmol, 61 mg) $Ba(OH)_2$ (1.5 mmol, 267 mg), $Pd(OAc)_2$ (0.025 mmol, 6 mg), PPh_3 (0.5 mmol, 13 mg) and deoxygenated 1,4-dioxane/water (10% water) as solvent. The reaction mixture was stirred for 4 days. The crude product was purified by column chromatography (*n*-hexane; R_f: 0.19). A colorless solid was obtained in a yield of 71 mg (0.22 mmol, 43%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.47-7.40 (m, 5 H), 7.21 (d, 2 H, ^3J = 6.8 Hz), 2.36 (s, 3 H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 141.1, 140.3, 140.0, 132.4, 129.4, 128.1, 128.0, 124.1, 20.5.

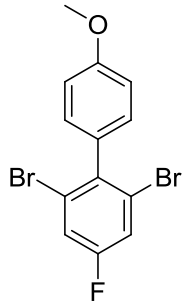
2,6-Dibromo-4-methyl-4'-methoxybiphenyl (94)



Chemical Formula: $C_{14}H_{12}Br_2O$
Molecular Weight: 356.05

A nitrogen-flask was charged with 3,5-dibromo-4-iodotoluene **92a** (0.5 mmol, 188 mg), 4-methoxy-phenylboronic acid (0.5 mmol, 76 mg) $Ba(OH)_2$ (1.5 mmol, 267 mg), $Pd(OAc)_2$ (0.025 mmol, 6 mg), PPh_3 (0.05 mmol, 13 mg) and deoxygenated 1,4-dioxane/water (10% water). The reaction was stirred for 4 days. The crude product was purified by column chromatography (*n*-hexane/DCM, 7:3; R_f: 0.19). A colorless solid was obtained in a yield of 88 mg (0.25 mmol, 50%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.46 (s, 2 H), 7.14 (m, 2 H), 6.98 (m, 2 H), 3.87 (s, 3 H), 2.35 (s, 3 H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 159.1, 140.1, 139.6, 133.5, 132.3, 130.6, 124.6, 113.4, 55.13, 20.4.

2,6-Dibromo-4-fluoro-4′-methoxybiphenyl (95)

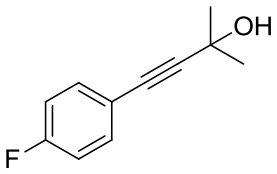


Chemical Formula: $C_{13}H_9Br_2FO$
Molecular Weight: 360.02

A two-necked Schlenk-tube was baked out, flushed with argon and charged with 2,6-dibromo-4-fluoro-iodobenzene (1.5 mmol, 570 mg), $Ba(OH)_2$ (3 mmol, 514 mg), $Pd(OAc)_2$ (0.05 mmol, 11 mg), PPh_3 (0.1 mmol, 26 mg) 4-methoxyphenylboronic acid **43** (1 mmol, 152 mg) and deoxygenated 1,4-dioxane/water (4 mL, 10% water). The reaction was stirred for 2 days at 60 °C, worked-up with brine, extracted with DCM and purified by column chromatography (pentane/DCM, 4:1; R_f: 0.25). The product was obtained in a yield of 113 mg (0.3 mmol, 31%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.40 (d, ^3J =7.8 Hz, 2 H), 7.11 (d, ^3J = 8.9 Hz, 2 H), 6.98 (d, ^3J = 8.9 Hz, 2 H), 3.87 (s, 3 H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 160.8 (d, ^1J(CF) = 253 Hz), 159.3, 139.1 (d, ^4J = 4.2 Hz), 132.7, 130.6, 124.9 (d ^3J(CF) = 10.3 Hz), 119.2 (d ^2J(CF) = 24.1 Hz), 113.6, 55.2.

8.4 Phenylacetylenes and Precursors

4'-Fluororphenyl-2-methyl-3-butin-2ol (9)

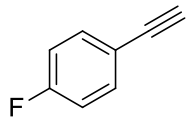


Chemical Formula: $C_{11}H_{11}FO$
Molecular Weight: 178.20

In a 250 mL nitrogen-flask with a condenser CuI (1.5 mmol, 286 mg), $(PPh_3)_2PdCl_2$ (1.5 mmol, 1.05 g), PPh_3 (3 mmol, 786.9 mg) were dissolved in triethylamine (200 mL) under oxygen free conditions. 4-Bromo-fluorobenzene (100 mmol, 17.5 g) wasν added and stirred for 1 h. Subsequently 2-methyl-3-butin-2-ol (120 mmol, 10.1 g) was added. The mixture was slowly warmed to 60 °C (oil bath) and stirred for 4 days at this temperature. After cooling to ambient temperature the crude product was diluted with diethyl ether, the ammonium salt was filtered off and the solvents were removed. The product was immediately employed in the subsequent deshielding reaction. Yield (crude product) 96% (192 mmol, 34.2 g). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 1.53 (s, 6 H, 2 CH_3), 2.3 (s, OH); 6.9 (t, ^3J = 8.8 Hz, 2 CH), 7.3 (m, 2 CH) ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 31.4 (2 CH_3), 65.5 (*C*OH), 81.03 (*C*q), 93.4 (*C*q), 115.5 (d, ^2J(CF) = 22.5 Hz, 2 *C*H), 118.6 (d, ^4J(CF) = 3.7 Hz, *C*q), 133.5 (d, ^3J(CF) = 8.1 Hz, 2 *C*H), 162.4 (d, ^1J(CF) = 250 Hz, *C*F); IR-spectrum (KBr, cm^{-1}) $\tilde{\nu}$ = 3278 s (ν O-H), 3050 m (ν aryl-H), 2976, 2931, 2866 (ν C-H),

2250 w (C≡C), 1602 s (ν C-C), 1506 s (δ C-H), 1362 m (δ CH_3), 1225, 1155 s (Aryl-F), 835 s (δ Aryl-H, 1,4-disubstitution).

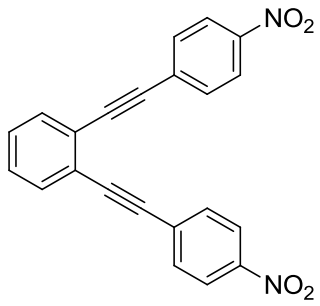
4-Fluorophenylacetylene (9a)



Chemical Formula: C_8H_5F
Molecular Weight: 120.12

A 100 mL one necked flask was charged with 15 mL paraffin and powdered KOH (90 mmol, 5.2 g). 4-(4'-fluorophenyl)-2-methyl-3-butin-2-ol (228 mmol, 40.5 g) was added and destillation apparatus combined with a 20 cm Vigreux column and a cooled receiver flask (T = –78 °C) was put on. The destillation occured at temperatures ranging from 90 to 110 °C (mpv, ~50 mbar residual pressure). A colorless oil was obtained, which quickly solidified. The product was obtained in a yield of 14 g (117 mmol, 51%). Mp: body temperature; ^{1}H-NMR (200 MHz, $CDCl_3$) δ = 3.03 (1 H, CH), 6.99 (t, ^{3}J =, 5.84 Hz, 2 H, 2 CH), 7.46 (m, 2 H, 2 CH); ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 77.5 (CH), 82.6 (Cq), 115.7 (d, ^{2}J(CF) = 22.5 Hz, 2 CH), 118.2 (d, ^{4}J(CF) = 3.6 Hz, Cq), 134.11 (d, ^{3}J(CF) = 9.6 Hz; 2 CH), 162.8 (d, ^{1}J(CF) = 250 Hz, CF); IR-spectrum (ATR; cm^{-1}) $\tilde{\nu}$= 3263 s (ν C≡C-H), 1635 (ν C=C aromatic), 1260 (ν aryl-halogen), 799 (δ-aryl-H, 1,4-disubstitution).

1,2-Bis[2-(4-nitrophenyl)ethinyl]benzene (10)

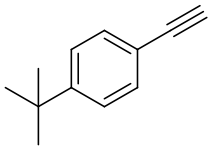


Chemical Formula: $C_{22}H_{12}N_2O_4$
Molecular Weight: 368.34

A mixture of dry THF/TEA (5 mL:15 mL) PPh_3 (105 mg, 0.4 mmol), $(PPh_3)_2PdCl_2$ (140 mg, 0.2 mmol), CuI (76 mg, 0.4 mmol), and 4-nitrobromobenzene (830 mg, 4 mmol) was placed in a 100 mL flask with an equipped condenser under inert conditions. After stirring for 10 min 1,2-diethynylbenzol (250 mg, 2 mmol) was added and the solution was heated to 50 °C for 3 h. Satured NH_4Cl-solution was added and the mixture was diluted with DCM, washed with saturated brine and water and dried over $MgSO_4$. The solvents were removed by evaporation and the product was purified by silica gel flash chromatography (pentane/DCM 2:3, R_f: 0.44). Recrystallization from toluene gave yellow crystals in a yield of 348 mg (0.94 mmol, 47%). Mp 205 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.2 (d, ^{3}J = 8.9 Hz, 4 H), 7.6 (d, ^{3}J = 8.9 Hz, 4 H), 7.57-7.54 (q, ^{3}J = 3.1 Hz, 2 H), 7.37-7.34 (q, ^{3}J = 3.1 Hz, 2 H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 147.4 (*C*NO_2), 132.3

(Ar*C*H), 129.9 (Ar*C*H), 129.2 (Ar*C*H), 125.1 (Ar*C*H), 123.8 (Ar*C*H), 92.9 (*C*C), 91.7 (C*C*).

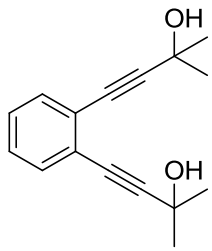
1-*tert*-Butyl-4-ethynylbenzene (12) [166]



Chemical Formula: $C_{12}H_{14}$
Molecular Weight: 158.24

To a solution of powdered KOH (500 mmol, 28 g) in triglycol (120 mL) was added 1,2-dibromo-2-(4'-*tert*-butylphenyl)-ethane (200 mmol, 64 g). The crude product was distilled off in membrane pump vacuum. Two layers were obtained. The mixture of triglycol and product was separated and the organic layer was dried over Na_2SO_4 and subsequently subjected by precision distillation (mpv, 78 °C head temperature). A colorless oil was obtained in a yield of 11.5 g (73 mmol, 36.5%). Identical spectroscopic data as reported in literature. [167]

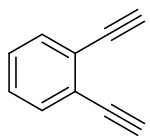
1,2-Di-(2-methylbut-3-yn-2-ol)benzene (16a)



Chemical Formula: $C_{16}H_{18}O_2$
Molecular Weight: 242.31

$(PPh_3)_2PdCl_2$ (2.25 mmol, 1.6 g), CuI (2.25 mmol, 0.43 g) and PPh_3 (4.6 mmol, 1.18 g) were placed in a nitrogen-flask with equipped condenser and degassed. 150 mL TEA and 1,2-dibromobenzene (75 mmol, 9.07 mL) were added subsequently. The mixture was stirred for 10 min at ambient temperature. Then, 2-methyl-3-butin-2-ol (165 mmol, 19.5 mL) was added and the solution stirred at 60 °C for 2 days. The crude product was filtered over silica gel (pentane/DCM, 1:1) and after removing the eluent orange crystals were obtained in a yield of 86% (15.6 g, 64.3 mmol). ^{1}H-NMR (200 MHz, $CDCl_3$) δ = 7.3 (m, 2 H, 2 CH) 7.15 (m, 2 H, 2 CH), 3.27 (2 H, 2 OH), 1.56 (s, 12 H, 4 CH_3); ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 131.2 (2 *C*H), 127.8 (2 *C*H), 125.5 (2 *C*q), 98.1 (2 *C*q), 80.8 (2 *C*q) 65.7 (*C*OH), 31.4 (4 *C*H_3).

1,2-Bisethynylbenzene (16b)

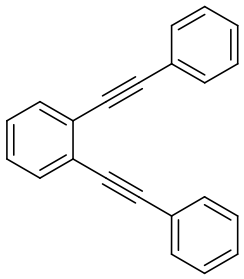


Chemical Formula: $C_{10}H_6$
Molecular Weight: 126.15

1,2-Di-(2-methylbut-3-yn-2-ol)benzene **16a** (64 mmol, 15.5 g) was added to a mixture of powdered KOH (64 mmol, 3.6 g) in paraffin (10 mL) in a 100 mL round-bottom flask with a Vigreux column and an equipped distillation apparatus. The mixture was slowly heated up to 130 °C under reduced pressure (oilbath). Destillation (65 °C head temperature) gave a colorless oil in a yield of

3.16 g (25 mmol, 39%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ = 7.41 (q, ^{3}J = 3.1 Hz, 2 H), 7.19 (q, ^{3}J = 3.1 Hz, 2 H), 3.25 (s, 2 H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 132.56 (2 *C*H), 128.42 (2 *C*H), 124.96 (2 *C*q), 81.18 (2 *C*H).

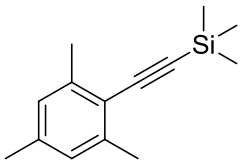
1,2-Bis-(2-phenylethynyl)benzene (16c)



Chemical Formula: $C_{22}H_{14}$
Molecular Weight: 278.35

$(PPh_3)_2PdCl_2$ (0.72 mmol, 505 mg), CuI (0.72 mmol, 140 mg) and PPh_3 (1.4 mmol, 378 mg) were placed in a 100 mL round-bottom-flask and degassed. Then triethylamine (25 mL) and 1,2-dibromobenzene (10 mmol, 3.3 g) were added. The mixture was stirred for 1 h and then phenylacetylene (24 mmol, 2.45 g) was added. The solution was stirred for 13 h at 60 °C. The color turned from yellow to brown and ammonium salts precipitated. The solvent was evaporated and the residue was diluted with diethyl ether, filtrated and the solvent was evaporated again. Purification proceeded by column chromatography (pentane/TBME, 99:1, R_f: 0.68); Mp 54 °C. ^{1} H-NMR (200 MHz, $CDCl_3$) δ = 7.51-7.45 (m, 6 H, CH), 7.26-7.12 (m, 8 H, CH) ^{13}C-NMR (200 MHz, $CDCl_3$) δ = 131.8 (4 *C*H), 131.6 (2 *C*H), 128.4 (2 *C*H), 128.35 (4 *C*H), 127.8 (2 *C*H), 125.8 (2 *C*q), 123.3 (2 *C*q), 93.6 (2 *C*C), 88.3 (2 *C*C).

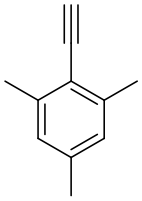
(Mesitylethynyl)trimethylsilane (17)



Chemical Formula: $C_{14}H_{20}Si$
Molecular Weight: 216.39

In a nitrogen-flask were placed iodomesitylene (10 mmol, 2.46 g) in triethylamine (20 mL) and the mixture was degassed. $(PPh_3)_2PdCl_2$ (0.33 mmol, 0.23 g) and CuI (0.5 mmol, 0.095 g) were added and the mixture was cooled to –40°C and degassed again. Trimethylsilylacetylene was added through a septum and the solution was allowed to warm to ambient temperature under stirring overnight. The dark mixture was diluted with diethylether and filtered. The solvents were removed and the crude product was purified by column chromatography with *n*-hexane (R_f: 0.27). The product obtained was a yellow oil in a yield of 0.78 g (3.6 mmol, 36%). Identical spectral data as reported in literature.[91]

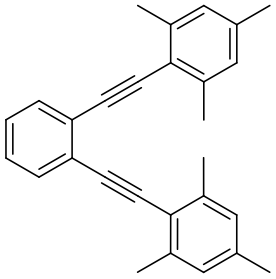
Mesitylacetylene (20)



Chemical Formula: $C_{11}H_{12}$
Molecular Weight: 144.21

(Mesitylethynyl)trimethylsilane **17** (10 mmol, 2.17 g) and K_2CO_3 (10 mmol, 1.38 g) were added to a solution of methanol (30 mL) and THF (30 mL) at ambient temperature and stirred overnight. The mixture was filtered, washed with diethylether and dried over $MgSO_4$. After removing the eluents, the crude product was purified by column chromathography (*n*-hexane, R_f: 0.36) and a yellow oil was obtained in a yield of 1.12 g (7.8 mmol, 78%). Identical spectroscopic data as reported in literature.[91]

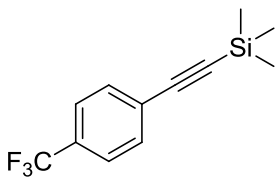
1,2-Bis(mesitylethynyl)benzene (21)



Chemical Formula: $C_{28}H_{26}$
Molecular Weight: 362.51

A mixture of dry THF (5 mL)/TEA (15 mL), PPh_3 (63 mg, 0.24 mmol), $(PPh_3)_2PdCl_2$ (0.12 mmol, 84 mg), CuI (0.12 mmol, 23 mg) and 1,2-diodobenzene (2.5 mmol, 0.82 g, 0.33 mL) were placed in a 100 mL flask equipped with condenser. After stirring this solution for 10 min mesitylacetylene (5 mmol, 700 mg) was added. The mixture was heated up to 50 °C for 2 d. The mixture then was diluted with DCM/pentane. After removing the solvents, the crude product was purified by silica gel flash chromatography (pentane, R_f: 0.16). A yellow oil was obtained in a yield 100 mg (28 mmol, 92%). The NMR-spectrum showed also mono-phenylethynylated product as an impurity. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 2.23, (s, 6 H), 2.4 (s, 12 H), 6.85 (s, 4 H), 7.29 (d, 2 H, ^3J = 8 Hz), 7.48 (d, 2 H, ^3J = 8 Hz).

Trimethyl{[4-(trifluoromethyl)phenyl]ethynyl}silane (42)

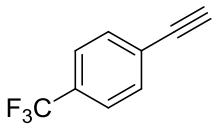


Chemical Formula: $C_{12}H_{13}F_3Si$
Molecular Weight: 242.3123

In a 100 mL nitrogen-flask sealed with a septum CuI (0.75 mmol, 0,143 g), $(PPh_3)_2PdCl_2$ (0.75 mmol, 0.53 g) and PPh_3 (1.5 mmol, 0.39 g) were placed and TEA (40 mL) and 1-bromo-4-(trifluoromethyl)benzene (50 mmol, 7.03 mL) were added. The mixture was degassed and trimethylsilylacetylene (70 mmol, 10 mL) was slowly added. The mixture was stirred overnight. The ammonium salt was filtered off and the residue diluted with diethylether. Subsequently the organic layer was washed with

water and brine, the solvents were removed and the crude product was destilled (headtemperature 82 °C, mpv). A colorless oil was obtained in a yield of 6.3 g (26 mmol, 52%). Identical spectroscopic data as reported in literature.[168]

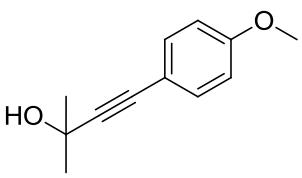
1-Ethynyl-4-(trifluoromethyl)benzene (45)



Chemical Formula: $C_9H_5F_3$
Molecular Weight: 170.1312

In a 250 ml nitrogen-flask trimethyl{[4-(trifluoromethyl)phenyl]ethynyl}silane **42** (35 mmol, 5.1 g), K_2CO_3 (35 mmol, 5.1 g), methanol (80 mL) and THF (80 mL) were placed under argon and dry conditions. The mixture was stirred at ambient temperature overnight. Water was added and the solution was extracted with diethylether, concentrated and destilled (oil pump vacuum, 60 °C head temperature). A yellow oil in a yield of approx. 0.6 g (3.5 mmol, 10%) was obtained. Identical spectroscopic data as reported in literature.[169]

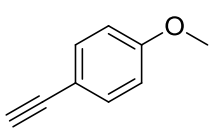
4-(4-Methoxyphenyl)-2-methylbut-3-yn-2-ol (54)



Chemical Formula: $C_{12}H_{14}O_2$
Molecular Weight: 190.24

4-Bromoanisole (18.7 g, 12.5 mL, 100 mmol), CuI (286 mg, 1.5 mmol), $(PPh_3)_2PdCl_2$ (530 mg), and PPh_3 (3 mmol, 790 mg) were placed in a 250 mL nitrogen-flask equipped with condenser and dissolved in 120 mL triethylamine. The mixture was heated to 60 °C and 2-methyl-3-butinol (120 mmol, 10.1 g, 11.7 mL) was added and the solution was refluxed overnight. NH_4Cl was added, the mixture was extracted with diethylether and filtrated over celite. In a preliminary NMR spectra of the crude product, the expected shifts could be recognized. Without further purification was continued with the next reaction step.

4-Methoxyphenylacetylene (55)



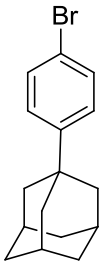
Chemical Formula: C_9H_8O
Molecular Weight: 132.16

4-(4-Methoxyphenyl)-2-methylbut-3-yn-2-ol **54**, paraffin (15 mL) and powdered KOH (2.6 g, 45 mmol) were placed in a flask with a micro distillery under oil pump vacuum and the receiver flask was cooled by an ice bath. The reaction mixture was heated (160 °C oil bath temperature, 65 °C head temperature) and colorless crystals were obtained in a yield of 11.6 g (76%, 88 mmol); Mp ambient temperature. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 2.9 (s, 1 H), 3.73 (s, 3 H), 6.76

(d, 2 H, ^{3}J = 8.9 Hz); ^{13}C-NMR (151 MHz, $CDCl_3$) δ = 55.3 (*C*H_3), 75.8 (*C*H), 83.7 (*C*CH), 113.9 (Ar*C*H), 114.2 (Cq), 133.6 (Ar*C*H), 159.9 (*C*q).

8.5 Catalysts and Materials Appendix

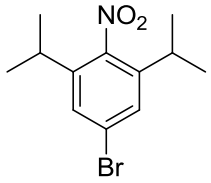
1-(4-Bromophenyl)-adamantane (8)



Chemical Formula: $C_{16}H_{19}Br$
Molecular Weight: 291.23

1-Bromoadamantane (4.3 g, 20 mmol), bromobenzene (15.7 g, 100 mmol) and $FeCl_3$ (0.32 g, 2 mmol) were gently refluxed until the hydrogen bromide evolution ceased. The crude product was worked up with water and purified by column chromatography using hexane as the eluent. GC/MS analysis showed the 1- and 4-substituted product. The search for a more suitable eluent to separate the two products came to no success.

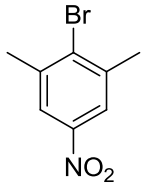
5-Bromo-1,3-diisopropyl-2-nitrobenzene (11)



Chemical Formula: $C_{12}H_{16}BrNO_2$
Molecular Weight: 286.16

A solution of $KMnO_4$ (20 mmol, 3.16 g) in H_2O (15 mL) was added dropwise to 4-bromo-2,6-diisopropylaniline (5 mmol, 1.3 g) at ambient temperature. The mixture was stirred for 5 h at 55 °C. The solution was filtered over celite and washed with acetone. Then diethylether was added, the organic layers were combined and washed with water, brine and dried over Na_2SO_4. A wax-like solid was obtained. NMR showed no identifiable signals. Attempts to purify the crude product by column chromatography (hexane/Et_2O, 95:5) were to no avail.

2-Bromo-1,3-dimethylnitrobenzene (13)

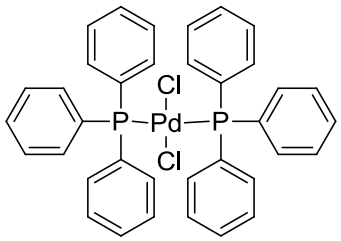


Chemical Formula: $C_8H_8BrNO_2$
Molecular Weight: 230.06

To a solution of 2-bromo-1,3-dimethylbenzene (50 mmol, 9.3 g, 6.7 mL) in a three-necked flask equipped with an internal thermometer, dropping funnel, magnetic stirrer and an ice bath nitric acid was added (HNO_3/H_2SO_4, 5 mL/6 mL) through the dropping funnel while maintaining an inner temperature of 0 °C. Subsequently, the solution was warmed to ambient temperature and stirred for 2.5 h. The mixture was

slowly added to ice water (100 mL), extracted with diethylether, washed with satured $NaHCO_3$-solution and water and dried over Na_2SO_4. GC/MS analysis exclusively showed starting material. Repeating the reaction at lower temperature was unsuccessful as well.

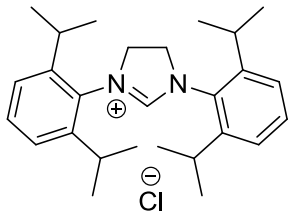
Bis(triphenylphosphin)palladium(II)chlorid (18)[102]



Chemical Formula: $C_{36}H_{30}Cl_2P_2Pd$
Molecular Weight: 701.90

A 100 mL nitrogen-flask equipped with condenser and bubble-counter was charged with $PdCl_2$ (5.64 mmol, 1 g) and PPh_3 under intert gas conditions. Benzonitrile (30 mL) was added and the mixture heated up to 180 °C and maintained at this temperature for 20 min. Cooling to ambient temperature overnight provided crystals of crude product. The solvent was removed and the crude product was washed with diethylether. The catalyst was obtained as yellow crystals in a yield of 3.83 g (5.45 mmol, 97%). Discoloration was found to occur at 260 °C.

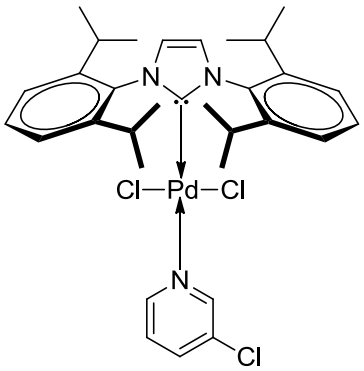
1,3-Bis(2,6-diisopropylphenyl)-4,5-dihydro-1*H*-imidazol-3-ium chloride (27)



Chemical Formula: $C_{27}H_{39}ClN_2$
Molecular Weight: 427.06

To a mixture of 1,4-bis-(2,6-diisopropyl)diazabutadien (33 mmol, 12.43 g) and toluene (250 mL) paraformaldehyde (33 mmol, 1 g) was added. The mixture was heated to 100 °C to dissolve paraformaldehyde and then cooled to 40 °C before adding HCl in 1,4-dioxane (33 mmol). The solution was stirred for 2 d and a colorless solid precipitated. The crude solid was filtered, washed with THF. The product was obtained in a yield of 4.94 g, (11.6 mmol, 35%). Identical spectroscopic data as reported in literature.[92]

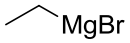
PEPPSI-IPr-complex (28)



Chemical Formula: $C_{32}H_{40}Cl_3N_3Pd^{2\bullet}$
Molecular Weight: 679.46

A flask was charged with $PdCl_2$ (1.7 mmol, 1.15 g), K_2CO_3 (15 mmol, 2.1 g) and diisopropylphenylimidazoliumchloride (3.3 mmol, 1.4 g). 3-Chloropyridine was added and the solution was heated to 80 °C overnight. After cooling to ambient temperature, the mixture was diluted with CH_2Cl_2 and filtrated through a glass frit equipped with a layer of celite. Celite was eluted with CH_2Cl_2 untill the product was completely recovered. CH_2Cl_2 was removed and 3-chloropyridine was removed under reduced pressure and stored for reuse. The crude product was treated with pentane and a yellow solid was obtainedin a yield of 1.13 g (1.7 mmol, 56%) Identical spectroscopic data as reported in literature.[78a]

Ethylmagnesiumbromide (30)



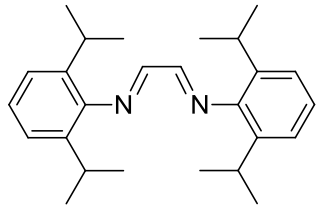
Chemical Formula: C_2H_5BrMg
Molecular Weight: 133.27

A three-necked flask equipped with condenser was charged with a small amount of absolute THF (ca. 5 mL) to Mg turnings (250 mmol, 6.1 g, previously dried). After initiation of the Grignard reaction, bromoethane (250 mmol, 40.86 g) in THF (ca. 250 mL) was added slowly. Afterwards, the mixture was heated to reflux for 30 min. Further THF was added to prevent precipitation. The product concentration rate was 0.88 mol/L as determined by titration with diphenylhydrazine.

Arylethynylmagnesiumbromides (31/32/40/59/61/63)

Ethylmagnesiumbromide (6 mmol) was cooled to –30 °C in a nitrogen-flask under continous argon flow. Using a syringe arylacetylene (6 mmol) was added and the solution was stirred for 1 h at this temperature. The solution was moved into a syringe and then transferred to the corresponding reaction mixture.

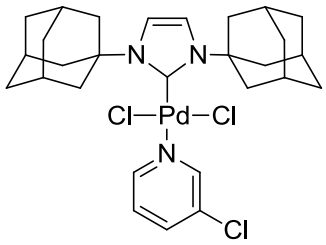
1,4-Bis(2,6-diisopropylphenyl)diazabutadien (37)



Chemical Formula: $C_{26}H_{36}N_2$
Molecular Weight: 376.58

A 250 mL flask was charged with 2,6-diisopropylaniline (140 mmol, 24.8 g, 26.4 mL), glyoxal (40% in H_2O, 70 mmol, 4.1 g, 10 mL) in (absolute) ethanol (ca. 200 mL) and a few drops of formic acid were added as catalyst. The solution was stirred for 2 days and in course of time the color turned to dark red and a precipitate formed. A light red solid was collected by filtration and washed out with cold methanol. The product was obtained in a yield of 14.87 g (39.4 mmol, 56%). Identical spectroscopic data as reported in literature.[92]

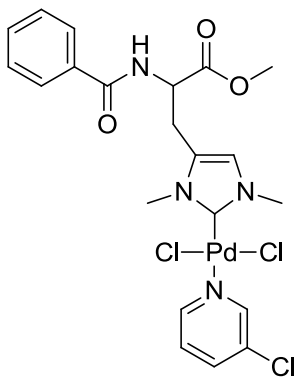
Diadamantyl-NHC-$PdCl_2$-pyridine complex (74) [78a]



Chemical Formula: $C_{28}H_{37}Cl_3N_3Pd$
Molecular Weight: 628.39

A flask was charged with $PdCl_2$ (0.1 mmol, 17 mg), $IAdBF_4$ (0.11 mmol, 0.05 g), 0.5 mmol K_2CO_3 (0.5 mmol) and 3-chloropyridine (0.4 mL). The mixture was heated to 80 °C and stirred overnight. The crude product was passed through a layer of silica gel and celite. A yellow slurry was obtained. Treatment with pentane and hexane, oil pump vacuum and several filtrations did not yield a solid. NMR signals were not explicitily assigned for Pd-NCN. HRMS showed no complex.

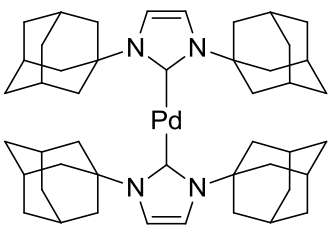
Peptide-based-NHC-pyridine-palladium complex (77)



Chemical Formula:
$C_{21}H_{24}Cl_3N_4O_3Pd$
Molecular Weight: 593,22

NHC-peptide-salt (0.55 mmol, 236 mg) was placed in a nitrogen-flask equipped with a condenser and a bubble counter under oxygen-free and dry conditions. $PdCl_2$ (0.5 mmol, 89 mg), K_2CO_3 (2.5 mmol, 345 mg) and 3-chloropyridine (2 mL) were added and the mixture was heated up to reflux (120 °C oil bath temperature). The color changed from dark brown to orange and a precipitate formed. NMR analysis showed no identifiable product.

Homoleptic Arduengo-NHC Pd(0) complex (82)[135]

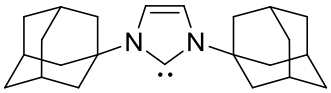


Chemical Formula: $C_{46}H_{66}N_4Pd$
Molecular Weight: 781.46

a) Compound **84** (1 mmol, 300 mg) was placed in a nitrogen-flask under oxygen-free conditions and dissolved in dry degassed *n*-hexane (15 mL). Bis-tri-*tert*-butylphosphinepalladium (0.43 mmol, 160 mg) was added and the mixture was stirred for 2 days at ambient temperature. The solvent was removed and the light yellow solid recrystallized from diethylether. NMR spectra could not be clearly interpreted.

b) A 100 mL nitrogen-flask was charged with allylpalladiumchloride (0.254 mmol, 100 mg), sodiumdimethylmalonat (0.5 mmol, 80 mg) **84** (ca. 1 mmol) dissolved in toluene (2 mL) was added. The mixture was warmed to 115 °C oil bath temperature overnight. Subsequently was filtrated over a celite layer using standard Schlenk techniques, the solvent was removed and the product was recrystallized at –50 °C from toluene. NMR spectra could not be clearly interpreted.

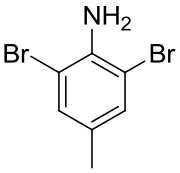
Arduengo Carbene – 1,3-bis(adamantly)imidazole-2-ylidene (84)[116a]



Chemical Formula: $C_{23}H_{32}N_2$
Molecular Weight: 336.51

A 25 mL round bottom nitrogen-flask was baked out, flushed with argon and charged with 1,3-bis(adamantly)imidazoliumtetrafluoroborat (1 mmol, 420 mg), 1.5 mL THF and the flask was capped with a septum. The suspension was stirred at room temperature and KO*t*Bu (solved in 0.5 mL THF) was added *via* a syringe. Gas evolution was monitored by a bubble counter. After 5 h, the mixture was filtrated through a celite pad using Schlenk techniques. The filtercake was washed with THF and the filtrate was concentrated. A light yellow solid was obtained, which was stored under argon. NMR spectra could not be clearly interpreted.

2,6-Dibromo-4-methylaniline (92)[99]



Chemical Formula: $C_7H_7Br_2N$
Molecular Weight: 264.94

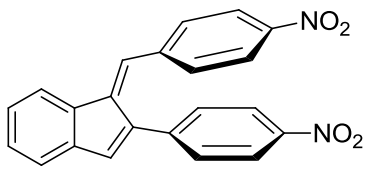
p-Toluidine (19 mmol, 5 g) and 20 mL acetic acid were placed in a three-necked round bottom flask equipped with a condenser and a bromine solution (0.16 mol, 4 mL in 50 mL acetic acid) was added dropwise. A colorless precipitate formed and yellow-brown slurry was obtained. After addition, the solution was stirred for 30 min and water (5 mL) was added. This afforded a sudden loss of color. The solid was filtered off and washed with water. A fraction of the crude product was recrystallized from ethanol and colorless needle-like crystals were obtained. Mp 73 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.2 (d, 2 H, ^3J = 0.5 Hz), 4.28 (s 2 H, NH_2), 2.2 (s, 3 H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 139.7 (*C*N), 132.3 (2 *C*H), 129.5 (*C*q), 108.9 (2 *C*Br), 20.0 (CH_3).

Dipalladiumtri(dibenzalaceton) $Pd_2(dba)_3$ (87)[170]

A nitrogen-flask equipped with a condenser and a bubble counter was charged with NaCl (5.6 mmol; 328 mg) and $PdCl_2$ (2.8 mmol; 500 mg). The solids were flushed with argon, 15 mL methanol was added and stirred for 24 h at ambient temperature. The crude mixture was filtered over cotton wool and the solvent was removed *in vacuo*. After adding a small amount of sodiumacetate, the solution was warmed for 15 min to 60 °C. Afterwards, the mixture was stirred for 2 h at ambient temperature and the black precipitate was filtered off. After washing with methanol, water and acetone, we obtained a dark red solid, which decomposes beween 125 and 130 °C. IR spectra (CH_2Cl_2, cm^{-1}) $\tilde{\nu}$ = 1648 w (ν C=O), 1611 s (ν C=C); 1575 m (ν C=C, aromatic); 982 m (ν CH, trans).

8.6 Cyclizations

Thermal Cyclization of 1,2-bis[2-(4-nitrophenyl)ethinyl]benzene 10 (33)



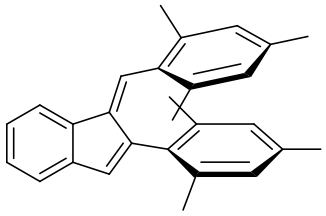
Chemical Formula: $C_{22}H_{14}N_2O_4$
Molecular Weight: 370.36

a) Microwave-assisted attempts: **aa)** A 10 mL vessel was charged with 1,2-bis[2-(4-nitrophenyl)ethynyl]benzene (0.14 mmol, 52 mg), 9,10-dihydroanthracene (0.5 mmol, 90 mg) and naphthalin (8 mmol, 1 g). The vessel was sealed and the microwave was configured at temperature of 200 °C, maximum power of 300 W, maximum pressure of 17 bar and hold time of 2 h. The obtained crude product was a brown slime

and TLC (hexane/DCM 1:1, silica gel) showed only the starting materials. **ab)** A 10 mL vessel was charged with 1,2-bis[2-(4-nitrophenyl)ethynyl]benzene (0.07 mmol, 25 mg) and 9,10-dihydroanthracene (0.17 mmol, 30 mg) in toluene (1.5 mL). The vessel was sealed and the microwave configured at 300 °C, 300 W power, maximum pressure of 18 bar and hold time of 2 h. The obtained product was dark brown and TLC (hexane/DCM, 1:1, silica gel) showed only the starting materials.

b) high pressure attempts in an ampoule and autoclave: A baked out ampoule was charged with **10** (0.1 mmol, 37 mg), 9,10-dihydroanthracene (1 mmol, 180 mg) and toluene (5 mL). The mixture was degassed and the ampoule was closed under vacuum with freezed starting materials. The sealed ampoule was placed in an autoclave and put into an oven for 12 h at 300 °C. The ampoule was cracked and a TLC of the dark brown product was carried out. The same procedure was repeated by replacing 9,10-didehydroanthracene with cyclohexadiene (1 mmol, 0.1 mL). The latter reaction mixture showed additional spots beneath the starting materials. Purification attempts by preparative TLC were to no avail. NMR-spectra of the pure product could not be obtained (*cf.* Chapter 3.3)

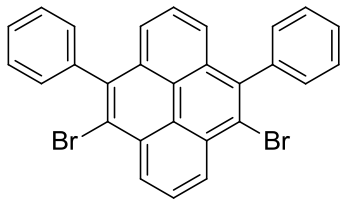
2-Mesityl-1-(2,4,6-trimethylbenzylidene)-1*H*-indene (86)



Chemical Formula: $C_{28}H_{28}$
Molecular Weight: 364.52

High pressure attempts carried out in ampoule and autoclave: A baked out ampoule was charged with **21** (0.28 mmol, 100 mg), cyclohexadiene (3 mmol, 0.3 mL) and 5 mL toluene. The mixture was degassed and the ampoule was closed under vacuum. The sealed ampoule was placed in an autoclave and put into an oven for 12 h at 300 °C. The ampoule was cracked and the TLC of the dark brown product was carried out. Purification attempts were to no avail. NMR-spectra of the pure products could not be obtained (*cf.* Chapter 3.3).

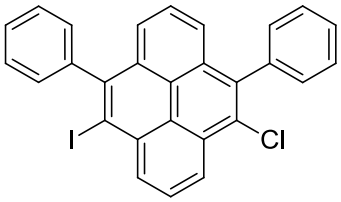
4,10-Diphenylpyrene (51) using Br_2



Chemical Formula: $C_{28}H_{16}Br_2$
Molecular Weight: 512.23

In a 20 mL Schlenk flask 2,6-bis(phenylethynyl)biphenyl (0.6 mmol, 210 mg) was placed under argon and dry conditons at 0 °C. Br_2 (0.048 g, 0.015 mL) in dichloromethane (0.2 mL) was added. The solution was allowed to come to ambient temperature and only the evaporation of bromine was observed. NMR spectra showed just the precursor.

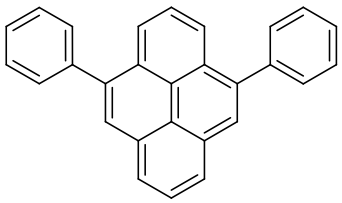
4,10-Diphenylpyrene (46) using ICl



Chemical Formula: $C_{28}H_{16}ClI$
Molecular Weight: 514.78

A solution of **19** (0.4 mmol, 130 mg) in DCM (2 mL) was cooled to 0 °C and ICl in DCM (1.85 mmol, 1.9 mL) was added dropwise. Initially, the solution discolored. At ambient temperature, Na_2SO_4 was added and the crude product was extracted with DCM and subsequently dried over $MgSO_4$. TLC gave no indication of product. HRMS spectra gave no evidence of one of the possible annulation products. NMR spectra showed an increasing number of signals with an aromatic shift. Purification attempts, *i.e.*, by recrystalization and preparative TLC, were to no avail.

4,10-Diphenylpyrene (71)

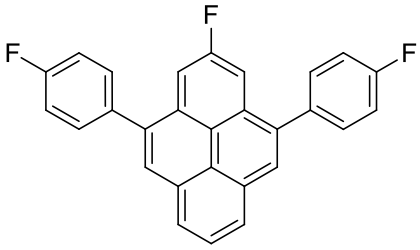


Chemical Formula: $C_{28}H_{18}$
Molecular Weight: 354.44

2,6-Bis(phenylethynyl)biphenyl (0.6 mmol, 118 mg) and $PtCl_2$ (0.06 mmol, 40 mg) were placed in a nitrogen-flask and purged with argon. Anhydrous toluene (3 mL) was added and the oilbath was heated to 130 °C for 20 h. The reaction mixture was filtered through celite and the dark brown solid was purified by preparative HPLC (CH_3CN/H_2O, 80:20, 3 mL/min, 220 nm) sublimed in UHV (10^{-6} mbar) by careful heating. This afforded a pale yellow solid in a yield of 28 mg (0.08 mmol, 13%). The following signals could be assigned: ^{1}H-NMR (600 MHz, $CDCl_3$) δ = 7.47-7.58 (8 H, 8 ArH), 7.65-7.70 (4 H, 4 pyrene-CH), 8.03-8.05 (2 H, 2 pyrene-CH), 8.18-8.24 (4 H, 2 pyrene-CH, 2 ArH). ^{13}C-NMR (151 MHz, $CDCl_3$) δ = 124.1 (*C*H), 125.0 (Ar*C*H), 127.5

(Ar*C*H), 128.7 (Ar*C*H), 130.1 (*C*H), 130.6 (*C*q), 131.8 (*C*q), 139.7 (*C*q), 140.9 (*C*q). HRMS: m/z calcd. for $C_{28}H_{18}$: 354.141, found: 354.142.

2-Fluoro-4,10-bis(4-fluorophenyl)pyrene (66)



Chemical Formula: $C_{28}H_{15}F_3$
Molecular Weight: 408.41

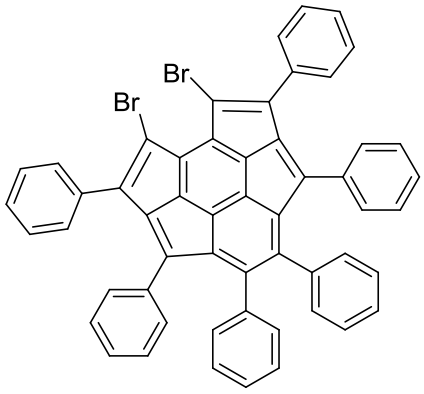
Compound **7** (0.3 mmol, 122 mg) and $PtCl_2$ (0.03 mmol, 8 mg) were placed in a nitrogen-flask and purged with argon. Anhydrous toluene (1.5 mL) was added and the oil bath was heated to 130 °C for 20 h. The reaction mixture was filtered through celite and the dark brown solid was purified by preparative HPLC and subsequently sublimed. NMR spectra were not analyzable because of further unidentified side-products. HRMS: m/z calcd. for $C_{28}H_{15}F_3$: 408.112, found: 408.112 (fragmentation pattern of mass spectra unambiguously shows that we have **66**).

2-Fluoro-4,10-bis(4-fluorophenyl)pyrene (69)

To a solution of **7** (0.3 mmol, 122 mg) in anhydrous toluene (7 mL) was added AuCl (0.4 eq., 28 mg, 0.12 mmol) and the mixture was refluxed overnight and the color turned into dark brown. TLC showed only precursor **7**.

Approaches on sixfold cascade cyclization

3,4-Dibromo-1,2,5,6,7,8-hexaphenylcyclopenta[bc]pentaleno[6,1,2-efg]-acenaphthylene (48)



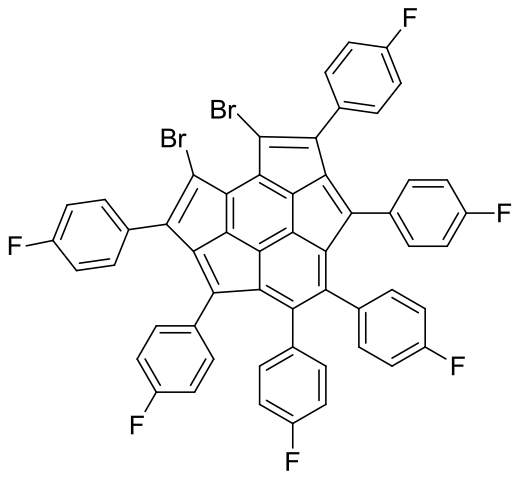
Chemical Formula: $C_{54}H_{30}Br_2$
Molecular Weight: 838.62

a) 1,2,3,4,5,6-Hexakis(phenylethynyl)benzene (0.1 mmol, 67 mg), Br_2 (0.5 mmol, 0.05 mL), and dicholoromethane (2 mL) were placed in a 10 mL vessel, which was sealed with a cap. The microwave program was configured to a temperature of 80 °C, a time of 1 h, a maximum pressure of 17 bar and a power of 150 W. During the experiment, the pressure was sloped down from 3 bar to 1.7 bar and the temperature remained constant at 81 °C. The starting material is not soluble in dichloromethane. A second

experiment was conducted with the same amount of starting material and 0.07 mL Br_2. The reaction parameters were set to temperature: 150 °C, time: 1.5 h, pressure: 17 bar, and power: 150 W. The operation proceeded in the microwave at a maximum of 141 °C and 9 bar. In both cases, only the yellow starting material recrystallized after cooling.

b) 1,2,3,4,5,6-Hexakis(phenylethynyl)benzene (0.1 mmol, 70 mg) and trifluorotoluene (7 mL) were placed in a 25 mL two necked flask equipped with a condenser and heated (oil bath temperature 130 °C). Br_2 (ca. 0.5 mL) was added dropwise until no more discoloration was visible. The mixture was stirred for 3 h at this temperature. Satured $NaHSO_3$ was added to the brown slurry and the mixture was extracted with dichloromethane, filtrated over celite and dried over $MgSO_4$. The NMR spectra showed signals (appearance like a rising ground) at low field in aromatic range.

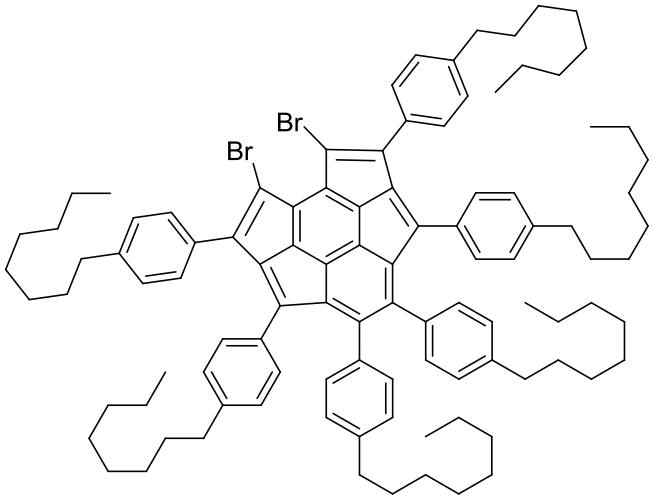
3,4-Dibromo-1,2,5,6,7,8-hexakis(4-fluorophenyl)cyclopenta[bc]pentaleno[6,1,2-efg]acenaphthylene (49)



Chemical Formula: $C_{54}H_{24}Br_2F_6$
Molecular Weight: 946.57

1,2,3,4,5,6-hexakis-[(4-fluorophenyl)ethynyl] benzene (0.1 mmol, 0.08 g) and dichloromethane (4 mL) were placed in an 10 mL vessel, which was sealed with a cap. The microwave run was configured to temperature: 120 °C, time: 1.5 h, maximum pressure: 17 bar, power: 150 W (actual operating parameters were 121 °C and 5 bar). For the second run-through, the mode was configured to temperature: 150 °C, time: 2 h, maximum pressure: 17 bar and power: 150 W (actual operating parameters were 131 °C and 8 bar) and Br_2 (0.05 mmol, 0.05 mL) was added. Yellow starting material recrystallized after cooling.

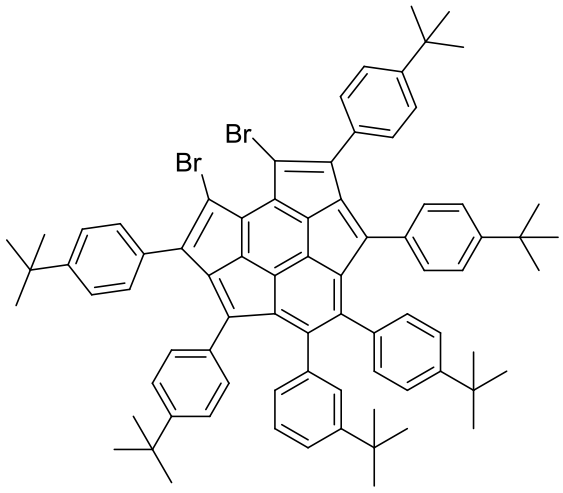
3,4-Dibromo-1,2,5,6,7,8-hexakis(4-octylphenyl)cyclopenta[bc]pentaleno[6,1,2-efg]acenaphthylene (50)



Chemical Formula: $C_{102}H_{126}Br_2$
Molecular Weight: 1511.90

1,2,3,4,5,6-hexakis[(4-*n*-octylphenyl)ethynyl]-benzene (0.135 g, 0.1 mmol) and dichloromethane (4 mL) were placed in a 10 mL vessel and sealed with a vessel cap. The first microwave run was configured at temperature: 120 °C, time: 1.5 h, maximum pressure: 17 bar and power: 150 W (actual operating parameters were 121 °C and 8 bar). In this case, the precursor dissolved instantly. The second microwave run was started with a clear orange solution and added Br_2 (0.5 mmol, 0.05 mL). After microwave treatment a viscous dark brown product was obtained. Satured $NaHSO_3$ was added to the brown slurry and the mixture was extracted with dichloromethane, filtrated over celite and dried over $MgSO_4$. NMR spectra were taken. The NMR spectra showed signals (appearance like a rising ground) at low field in aromatic range.

3,4-Dibromo-1,2,5,6,7,8-hexakis[4-(*tert*-butyl)phenyl]cyclopenta[*bc*]pentaleno[6,1,2-*efg*]acenaphthylene (52)

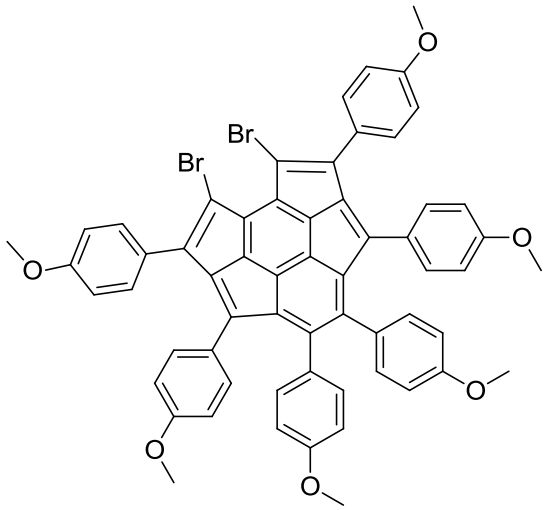


Chemical Formula: $C_{78}H_{78}Br_2$
Molecular Weight: 1175.26

1,2,3,4,5,6-hexakis((4-(*tert*-butyl)phenyl)-ethynyl)benzene (0.1 mmol, 0.102 g) was placed in a two-necked flask equipped with a condenser. The mixture was heated (120 °C oil bath temperature) and Br_2 (0.5 mmol, 0.05 mL) was added dropwise until discoloration of the solution stopped and the solution was held at this temperature. Satured $NaHSO_3$ was added to the brown slurry and the mixture was extracted with dichloromethane, filtrated

over celite and dried over $MgSO_4$. The NMR-spectra showed signals (appearance like a rising ground) at low field in aromatic range.

3,4-Dibromo-1,2,5,6,7,8-hexakis(4-methoxyphenyl)cyclopenta[*bc*]pentaleno[6,1,2-*efg*]acenaphthylene (53)



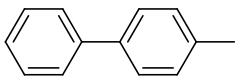
Chemical Formula: $C_{60}H_{42}Br_2O_6$
Molecular Weight: 1018.78

1,2,3,4,5,6-hexakis-[(4-methoxyphenyl)-ethynyl]benzene (0.1 mmol, 0.086 g) and trifluorotoluene (8 mL) were placed in a two-necked flask equipped with a condenser. The solution was heated up (120 °C oil bath temperature) and Br_2 (0.5 mmol, 0.05 mL) was added dropwise until discoloration of the solution ceased. The mixture was held at this temperature for 1 h. Satured $NaHSO_3$ was added to the brown slurry and the mixture was extracted with dichloromethane, filtrated over celite and dried over $MgSO_4$. The NMR-spectra showed signals (appearance like a rising ground) at low field in aromatic range.

8.7 Test Reactions

Studies to the quality of diamantyl-phosphonium salts as co-catalysts for Suzuki-Miyaura and Sonogashira-Haghiara cross-couplings

4-Phenyltoluene (34)



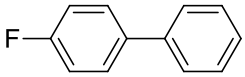
Chemical Formula: $C_{13}H_{12}$
Molecular Weight: 168.23

aa) Phenylboronic acid (4 mmol, 490 mg), 4-chlorotoluene (4 mmol, 500 mg), $Pd(OAc)_2$ (0.04 mmol, 0.9 mg), K_3PO_4 (8 mmol, 1.7 g), and **aa)** diamantyl-*n*-butylphosphinumiodide (0.04 mmol, 4.7 mg) or **ab)** no co-ligand were mixed with toluene (10 mL) under dry and inert conditions. The solution was stirred for 20 h at 65 °C. GC/MS analysis after 20 h showed no conversion. Hence, we decided to replace chorotoluene with the bromine analog.

ba) Phenylboronic acid (3 mmol, 366 mg), 4-bromotoluene (2 mmol, 342 mg), $Pd(OAc)_2$ (0.03 mmol, 7 mg), K_2CO_3 (7 mmol, 1 g), and **a)** diamantyl-*n*-butylphosphinumiodide

(16 mg, 0.03 mmol) or **bb)** no co-ligand were mixed with toluene (10 mL) under dry and inert conditions. The solution was stirred for 20 h at 65 °C. After cooling to r.t. the mixture was diluted with CH_2Cl_2 (80 mL), washed with sat. $NaHCO_3$ solution (3 × 50 mL) and dried over $MgSO_4$. The solvents were removed. The crude product was purified by filtration over silicagel (pentane/CH_2Cl_2, 95:5). The isolated yield for **ba)** was 331 mg (1.97 mmol, 98%) and for **bb)** after preparative GC 60 mg (0.36 mmol, 18%). Identical spectral data as reported in literature.[171]

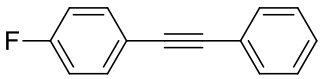
4-Fluoro-1,1'-biphenyl (35)



Chemical Formula: $C_{12}H_9F$
Molecular Weight: 172.20

Phenylboronic acid (4 mmol, 490 mg), 4-bromofluorobenzene (440 mg, 4 mmol), K_3PO_4 (8 mmol 1.7 g,) in toluene (8 mL) and **a)** $Pd(OAC)_2$ (0.004 mmol, 0.9 mg) and diamantyl-*n*-butylphosphinumiodide (0.008 mmol, 4.7 mg) or **b)** without co-ligand and **c)** with PEPPSI-IPr (0.04 mmol, 27 mg) were mixed and stirred at 65°C for 20 h. GC/MS showed product formation for **a),** product and homocoupling product for **b)** and **c).** There were no further investigations.

1-Fluoro-4-(phenylethynyl)benzene (39)



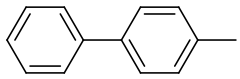
Chemical Formula: $C_{14}H_9F$
Molecular Weight: 196.22

To a stirred mixture of 4-bromo-fluorobenzene (1 mmol, 0.175 g), $(PPh_3)_2PdCl_2$ (0.05 mmol, 0.035 g) CuI (0.05 mmol, 0.01 g,) and **a)** di-4-diamantyl-*n*-butylphosphinumiodid (0.1 mmol, 0.059 g,) or **b)** PPh_3 (0.1 mmol, 0.026 g) under argon and dry conditions in NEt_3 (10 mL) phenylacetylene (1.2 mmol, 0.123 g) was added. The solution was refluxed for 20 h. During this time the color turned from bright yellow to dark brown and a grey precipitate was formed. Aqueous NH_4Cl-solution (70 mL) was added, the crude product was extracted with diethylether (3 × 50 mL) and subsequently purified by colum chromatography on silica gel (hexane/CH_2Cl_2 9:1, R_f: 0.36). Yield for **a)** 136 mg (0.70 mmol, 70%) and for **b)** 75 mg (0.38 mmol, 38%). Identical spectral data as reported in literature.[172]

Testreactions using Copper-Complexes as Catalysts in Ullmann and Suzuki-Miyaura Couplings (Cooperation with Würtele *et al*.)

General procedures:

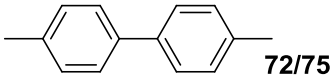
4-Methylbiphenyl (57) (Suzuki-Miyaura cross-coupling)



Chemical Formula: $C_{13}H_{12}$
Molecular Weight: 168.23

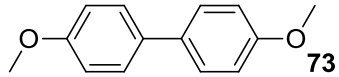
In a 100 mL nitrogen-flask 4-bromotoluene (2 mmol, 342 mg), copper complex (0.03 mmol), K_2CO_3 (7 mmol, 1 g), phenylboronic acid (3 mmol, 366 mg) and 1,4-dioxane (12 mL) were placed under dry and inert conditions. The solution was refluxed. After 20 h and 40 h, GC/MS analysis was carried out.

4,4'-Dimethyl-1,1'-biphenyl (72/73/75) (Ullmann coupling)



72/75

Chemical Formula: $C_{14}H_{14}$
Molecular Weight: 182,2610

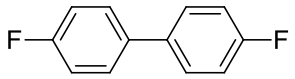


73

Chemical Formula: $C_{14}H_{14}O_2$
Molecular Weight: 214,2598

A dried nitrogen-flask equipped with condenser and bubble counter was charged with Cu-complex (0.2 mmol), KF (2 mmol, 116 mg), arylhalogenide (**72** = bromotoluene 0.2 mmol, 0.342 g, 0.25 mL) or (**73** = iodanisol, 2 mmol, 0.47 g) or (**75** = iodotoluene, 2 mmol, 0.44 g, 0.2 mL) and degassed DMSO (4 mL). The mixture was refluxed at 120 °C. After 20 h and 40 h, GC/MS analysis was carried out.

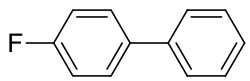
4,4'-Difluoro-1,1'-biphenyl (78) (Ullmann coupling)



Chemical Formula: $C_{12}H_8F_2$
Molecular Weight: 190.19

A dried nitrogen-flask with condenser and bubble counter was charged with Cu-Complex (0.2 mmol), KF (2 mmol, 116 mg), fluoro-4-iodobenzene (2 mmol, 444 mg, 0.23 mL) and degassed DMSO (4 mL). The mixture was refluxed at 120 °C. After 20 h and 40 h GC/MS analysis was carried out.

4-Fluoro-1,1'-biphenyl (81) (Suzuki-Miyaura cross-coupling)



Chemical Formula: $C_{12}H_9F$
Molecular Weight: 172.20

Phenylboronic acid (3 mmol, 366 g), 4-iodofluorobenzene (2 mmol, 444 mg, 0.23 mL), K_2CO_3 (1.7 g, 8 mmol) in 1,4-dioxane (5 mL) and Cu-complex (0.2 mmol) were mixed and stirred at 110 °C for 20 h. After 20 h and 40 h, GC/MS analysis was carried out.

8.8 Crystallographic Data

Crystal data and structure refinement for 4

Identification code	shre220p
Empirical formula	$C_{12}H_7Br_2F$
Formula weight	330.00 g mol^{-1}
Temperature	193(2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, P2(1)/c
Unit cell dimensions	a = 11.519(2) Å alpha = 90 deg.
	b = 8.7751(18) Å beta = 103.39(3) deg.
	c = 22.852(5) Å gamma = 90 deg.
Volume	2247.0(8) $Å^3$
Z, Calculated density	8, 1.951 Mg/m^3
Absorption coefficient	7.190 mm^{-1}
F(000)	1264
Crystal size	0.32 x 0.24 x 0.08 mm
Theta range for data collection	2.50 to 27.02 deg.
Limiting indices	-14<=h<=14, -11<=k<=11, -29<=l<=28
Reflections collected / unique	17452 / 4853 [R(int) = 0.1499]
Completeness to theta = 27.02	98.6%
Absorption correction	None
Max. and min. transmission	0.5970 and 0.2069
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4853 / 0 / 327
Goodness-of-fit on F^2	0.857
Final R indices [I>2sigma(I)]	R1 = 0.0450, wR2 = 0.0979
R indices (all data)	R1 = 0.1008, wR2 = 0.1158
Largest diff. peak and hole	0.980 and –0.839 e. $Å^{-3}$

Crystal data and structure refinement for VL-1a

Identification code	shre193p
Empirical formula	$C_{19}H_{15}BF_4IN$
Formula weight	471.03 g mol^{-1}
Temperature	193(2) K
Wavelength	0.71073 Å
Crystal system, space group	Triclinic, P–1
Unit cell dimensions	a = 8.7220(17) Å alpha = 103.29(3) deg.
	b = 9.967(2) Å beta = 90.14(3) deg.
	c = 11.581(2) Å gamma = 113.47(3) deg.
Volume	893.7(3) $Å^3$
Z, Calculated density	2, 1.750 Mg/m^3
Absorption coefficient	1.833 mm^{-1}
F(000)	460
Crystal size	0.56 x 0.40 x 0.32 mm
Theta range for data collection	3.03 to 28.10 deg.
Limiting indices	-11<=h<=11, -13<=k<=13, -15<=l<=14
Reflections collected / unique	8109 / 3955 [R(int) = 0.0617]
Completeness to theta = 28.10	90.5 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3955 / 0 / 235
Goodness-of-fit on F^2	1.194
Final R indices [I>2sigma(I)]	R1 = 0.0549, wR2 = 0.1713
R indices (all data)	R1 = 0.0583, wR2 = 0.1761
Largest diff. peak and hole	2.133 and –4.212 e. $Å^{-3}$

Crystal data and structure refinement for VL-2a

Identification code	shre089p

Empirical formula	$C_{28}H_{21}BCl_2F_4IN$
Formula weight	656.07 g mol^{-1}
Temperature	193(2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, P2(1)/c
Unit cell dimensions	a = 16.178(3) Å alpha = 90 deg.
	b = 16.278(3) Å beta = 107.89(3) deg.
	c = 21.433(4) Å gamma = 90 deg.
Volume	5371.3(19) $Å^3$
Z, Calculated density	8, 1.623 Mg/m^3
Absorption coefficient	1.438 mm^{-1}
F(000)	2592
Crystal size	0.40 x 0.20 x 0.16 mm
Theta range for data collection	2.26 to 26.03 deg.
Limiting indices	-19<=h<=19, -19<=k<=20, -26<=l<=26
Reflections collected / unique	38756 / 10217 [R(int) = 0.0503]
Completeness to theta = 26.03	96.5 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	10217 / 0 / 733
Goodness-of-fit on F^2	0.986
Final R indices [I>2sigma(I)]	R1 = 0.0353, wR2 = 0.0913
R indices (all data)	R1 = 0.0501, wR2 = 0.0979
Largest diff. peak and hole	0.595 and –0.838 e. $Å^{-3}$

Crystal data and structure refinement for structure VL-3a

Identification code	shre092p
Empirical formula	$C_{36}H_{25}BCl_2F_4IN$
Formula weight	756.18 g mol^{-1}

Temperature	193(2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, P2(1)/n
Unit cell dimensions	a = 8.4160(17) Å alpha = 90 deg.
	b = 25.853(5) Å beta = 94.35(3) deg.
	c = 14.703(3) Å gamma = 90 deg.
Volume	3189.8(11) $Å^3$
Z, Calculated density	4, 1.575 Mg/m^3
Absorption coefficient	1.222 mm^{-1}
F(000)	1504
Crystal size	0.48 x 0.32 x 0.20 mm
Theta range for data collection	2.10 to 24.12 deg.
Limiting indices	-9<=h<=9, -28<=k<=28, -15<=l<=16
Reflections collected / unique	18877 / 4964 [R(int) = 0.0718]
Completeness to theta = 24.12	97.7 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4964 / 0 / 406
Goodness-of-fit on F^2	1.065
Final R indices [I>2sigma(I)]	R1 = 0.0402, wR2 = 0.1064
R indices (all data)	R1 = 0.0465, wR2 = 0.1092
Largest diff. peak and hole	0.574 and –0.579 e. $Å^{-3}$

Crystal data and structure refinement for structure VL-4a

Identification code	shre122p
Empirical formula	$C_{43.50}H_{28}BClF_4IN$
Formula weight	813.83 g mol^{-1}
Temperature	193(2) K
Wavelength	0.71073 Å

Crystal system, space group	Triclinic, P–1
Unit cell dimensions	a = 8.5469(17) Å alpha = 107.67(3) deg.
	b = 13.810(3) Å beta = 96.33(3) deg.
	c = 16.043(3) Å gamma = 92.72(3) deg.
Volume	1786.7(6) A^3
Z, Calculated density	2, 1.513 Mg/m^3
Absorption coefficient	1.025 mm^{-1}
F(000)	814
Crystal size	0.28 x 0.16 x 0.08 mm
Theta range for data collection	2.60 to 28.08 deg.
Limiting indices	-11<=h<=11, -18<=k<=16, -21<=l<=21
Reflections collected / unique	16231 / 7949 [R(int) = 0.0901]
Completeness to theta = 28.08	91.5 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	7949 / 0 / 470
Goodness-of-fit on F^2	0.909
Final R indices [I>2sigma(I)]	R1 = 0.0679, wR2 = 0.1524
R indices (all data)	R1 = 0.1414, wR2 = 0.1903
Largest diff. peak and hole	1.047 and –1.449 e. $Å^{-3}$

9 Theoretical section

9.1 General Information

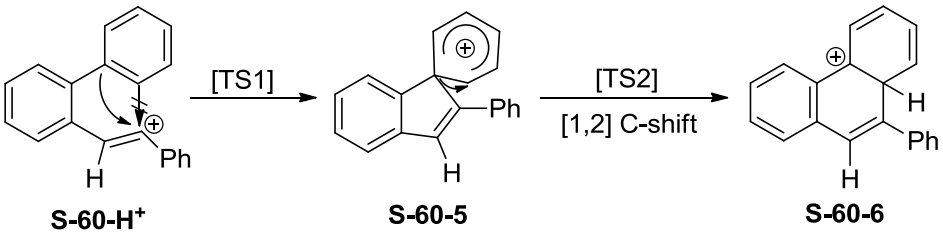
For all DFT computations, the Gaussian09 software package was used. All structures are results of gas-phase computations. The economical M06-2X was chosen as method because this DFT-method has proven to be well suitable for the computations of PAs and thermochemical parameters, such as enthalpies and reaction barriers.[105] B3LYP was chosen for reasons of comparability with existing data.[112c] B3PW91 was chosen because it suffers from the least systematic error due to the neglect of dispersion for hydrocarbons among uncorrected DFT functionals.[112a] As a basis set, we employed 6-31G(*d,p*), which includes polarization functions.

9.1.1 Chapter 2, Figure 2

M06-2X/6-31G(*d,p*) level of theory.

The structures of 2,6-dibromobiphenyls **3**, **4**, **23** and **41** were fully optimized and computed bond lengths were compared with the measured values from x-ray analysis. The bond lengths are reproduced well for all compounds. These results have already been published.[16b]

9.1.2 Chapter 3, Scheme 60



Scheme 99 Computed structures of the mechanism postulated in Scheme 60; values in Table 19

Table 19 Computed values; M06-2X/6-31G(*d,p*) level of theory

	S-60-H$^+$	**TS1**	**S-60-5**	**TS2**	**S-60-6**
ΔH_0 (hartree)	−770.26611	−770.26233	–770.27003	−770.26749	−770.29828
ΔE (kcal mol^{-1})	0.0	−0.1	–2.5	–0.9	–20.2

9.1.3 Chapter 3, Figure 4

M06-2X/6-31G(*d,p*) level of theory.

2-(Phenylethynyl)-1,1'-biphenyl (Larock's starting material) and **19** were optimized. Additionally, the hypothetical planar arrangement of these structures was computed to

compare the energies and angles of the twisted phenyl ring in 1-position of these structures in order to find out why compound **19** requires higher reaction temperatures for cyclization. These results have already been published.[16b]

9.1.4 Chapter 4, Equation 2 and 3

Computed values for determination of nucleophilicity and proton affinity of the depicted structures in Equations 2 and 3. Computed values (M06-2X/6-31G(*d,p*) level of theory) of structrures depicted in Equation 2.

Table 20 Computed values for structures depicted in Equation 2

	AdH	**AdC**	**DiaH**	**DiaC**	**MesH**	**MesC**
ΔH*	–1004.73925	–1004.32092	–1314.18993	–1313.75114	-	-
ΔH_0**	–1004.75850	–1004.32127	–1314.21279	–1313.77390	–923.82642	–923.39442

All values in hartrees; 1 hartree = 627.51 kcal mol^{-1}; * Δ*H* at 298 K, sum of electronic and thermal energies; **ΔH_0 at 0 K sum of electronic and zero-point vibrational energies.

We also obtained reaction enthalpies by subtracting Δ*H*(product)–Δ*H*(reactant) and obtained for ΔH_R (298 K) = –1.6 kcal mol^{-1} and for ΔH_R (0 K) = –0.9 kcal mol^{-1}. The PA (PA = –ΔH_R) in Equation 3 were evaluated at the M06-2X/6-31G(*d,p*) level of theory. Results are given in Table 21.

Table 21 Computed results for PA depicted in Equation 3 [level of theory: M06-2X/6-31G(*d,p*)].

	PA (hartrees)	**PA(kcal mol^{-1})**
AdH–AdC	–0.43757	274.6
DiaH–DiaC	–0.43889	275.4
MesH–MesC	-0.43200	271.1

9.1.5 Gaussian 09, Revision B.01

M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R.

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10 Abbreviations

Ad	adamantyl
approx.	approximately
aq	aqueous
Ar	aryl
Asymm	asymmetric
Bu	butyl
BuLi	*n*-butyllithium
calcd.	calculated
cat.	catalyst
CHD	cyclohexadiene
conc.	concentration
conv.	conversion
COSY	correlation spectroscopy
Cp	cyclopentadiene
d	dublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DFT	Density Functional Theory
Dia	diamantantyl
DMF	dimethyl formamide
DMSO	dimethylsulfoxide
eq.	equivalent
GC/MS	gas chromatography/mass spectrometry
ΔG	Gibbs enthalpy
ΔH	enthalpy
HOMO	highest occupied molecular orbital

HPLC	high performance liquid chromatography
i	*iso*
*i*Pr	*iso*-propyl
IR	infrared
LCD	liquid crystal display
LDA	lithiumdiisopropylamid
LED	light emitting diode
LUMO	lowest unoccupied molecule orbital
M	molarity (mol/L)
m	multiplet
m	*meta*
min	minutes
Me	methyl
Mes	mesityl
Mp	melting point
mpv	membrane pump vacuum
MS	molecular sieve, mass spectrometry
MW	microwave
n-Oct	*n*-octyl
n-Bu	*n*-butyl
NHC	*N*-heterocyclic carbene
NMR	nuclear magnetic resonance
Nuc	nucleophile
o	*ortho*
OMe	methoxy
p	*para*
PA	proton affinity

PAH	polyaromatic hydrocarbons
PCB	polychlorinated biphenyls
PEPPSI	Pyridine Enhanced Precatalyst Preparation Stabilization Inititation
Ph	phenyl
ppm	parts per million
Pr	propyl
prep. GC	preparative gaschromatography
prod.	product
q	quartet
r.t.	room temperature
s	singulet
t	triplet
TCP	2,4,6-trichlorophenyl
TBME	*tert*-butyl methylether
TEA	triethylamine
*t*Bu	*tert*-butyl
tert	tertiary
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TMSA	trimethylsilylacetylene
UV/Vis	ultraviolet visible

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12 Literature

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