The Palladium Way to N-Heteroacenes

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Abstract: Novel synthetic methodologies access known organic materials effectively and/or allow the preparation of species otherwise inaccessible. Pd-catalyzed coupling of aromatic dihalides to ortho-diaminoarenes furnishes embedded stable N,N'-dihydropyrazines in expeditiously and in often excellent yields. The embedded N,N'-dihydropyrazines are oxidized by MnO₂ into substituted azatracenes, azapentacenes, azahexacenes and azahexatracenes, soluble, processible and stable. This powerful Pd-methodology allows the preparation of diaza-, tetraaza- and hexazacenes. Azacenes are now accessible using this powerful tool. We find that Buchwald-type biarylphosphines in combination with a suitable Pd-precursor gives excellent results. Activated dihalides such as 2,3-dihaloquinazolines couple easily under simplified conditions, while 2,3-dibromoacenes need more stringent conditions and advanced catalyst precursors. Pd-catalysis assembles azacenes with otherwise difficult to obtain substitution patterns; high yields and flexibility make this method most attractive.

Introduction

The development of new synthetic methodologies is critical in organic materials science, as they allow efficient access to known key-compounds, and enable preparation of new classes of materials, with both issues being important. We have tackled this task for the synthesis of larger azacenes, developing Pd-catalyzed coupling reactions of aromatic ortho-dihalides to aromatic ortho-diamines.

N-Heteroacenes: Acenes massively impact organic electronics, particularly as charge transport layers in organic thin film transistors. Pentacene and its stabilized and substituted derivatives are heavily deployed in this field. And since Anthony’s TIPSpen [2] is commercially available, both vacuum processed but also solution processed OFETs of this material are easily prepared. Pentacene (3) and its derivatives are hole transporters, as the oxidation of the pentacene nucleus is much easier than its reduction, necessary for the generation of negative charge carriers in the organic semiconductor material. Problems with water, oxygen and trap states render pentacenes difficult for electron transport.[5]

Charge transport is, in a simplified way, proportional to the rate of degenerate charge transfer between two identical neighboring molecules (Figure 1). The charge transfer rate is dependent upon the transfer integral t, which denotes the electronic overlap[3] of two neighboring molecules and the reorganization energy λ, defined as the energy gain of a radical anion or a radical cation upon structural relaxation from the equilibrium structure in the uncharged state to the equilibrium structure in its charged state. As seen from eq. 1, t should be maximized, while λ should be minimized. Generally, both factors can be favorable in the larger acenes; particularly the rigid structure but also the size of the acenes minimizes λ.

Figure 1. Schematic view of an organic thin film transistor with simplified charge (electron) transport in the film.

\[ \mu \sim k_{GT} \sim \frac{1}{\sqrt{T}} e^{\frac{-\lambda}{4kT}} \] (eq 1)

Here \( \mu \) = charge carrier mobility, \( k_{GT} \) = charge transfer rate constant, \( T \) = temperature, \( k \) = Boltzmann constant, \( t \) = transfer integral and \( \lambda \) = reorganization energy.

As the “normal” pentacenes are poor electron transport materials one has to modify their structure. Lowering the energetic cost of electron injection and uptake, i.e. increasing electron affinities, yet still retaining the superb properties of pentacenes would be desirable. A number of groups has exploited the attachment of halogen atoms to pentacene.[6] The alternative is the introduction of electron-attractive atoms directly into the perimeter of the acenes. Doing this, results in the N-heteroacenes such as 1; 1 packs most similarly in the solid state as TIPSpen 2 does.

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Classic Syntheses of Azaacenes

Azaacenes have been known for a long time and to understand the issues in the synthesis of large N-heterocycles we examine the conventional way of preparation. As an aside, for most of the direct condensation methods that will be discussed, azatetracenes form directly in their oxidized form, while azapentacenes (with some exceptions) and azahexacenes are produced in their N,N'-dihydro forms. Breaking of the azapentacene into two aromatic naphthalene-type subsystems plus one large 4n-pi-system commences; according to calculations[11] two Clar sextets are energetically much more favorable than the presence of one large aromatic system. For the azatetracenes the equilibrium is on the side of the large aromatic species, the oxidized form is more stable than the N,N'-dihydro-compound, which in air spontaneously oxidizes back into the azaacene. N,N'-dihydro azapentacenes are more stable. They are oxidized slowly under the influence strong bases and heat. This cannot be found for higher N,N'-dihydroazaacenes.

Winkler and Houk[8] calculated several N-heteropentacenes to display small reorganization energies and frontier orbital positions that should make them useful as electron transporting materials. Several years later, compound 1 was prepared.[9] Miao reported spectacular electron transporting properties of 1 with mobilities of up to 3.3 cm$^2$V$^{-1}$s$^{-1}$.[8] 1 (Figure 1) is now a state of the art electron transporting material.

Hartwig-Buchwald amination for cyclizing C-N-bond formation: The Pd-catalyzed formation of C-N-bonds is an established and important reaction that forms sp$^2$-C-N-bonds through a variety of different catalysts and Pd-precurors.[9,10] The coupling was developed in many different variants. Five-membered rings of the indole etc. type are described and the Pd-catalyzed synthesis of acridines is reported,[10] but the synthesis of other six-membered N-heterocycles using Pd-catalysis is a much less explored area. The Pd-catalyzed synthesis of N,N'-dihydropyrazines was unexplored, before we started to investigate this area.

In the oldest syntheses (Scheme 1) one melts together dihydroxarenes such as 4, dichloroquinazoline 9a, or dicyanoquinazoline 7 with ortho-phenylenediamine 5 or -naphthalenediamine 10. These fire and sword methods furnish unsubstituted azaacenes, often in good to excellent yields. If pentacenes or hexacenes are produced, they form as their N,N'-dihydro-compounds, such as 11 or 8. A similar reaction that works in solution phase is the reaction of ortho-quinones with diamines. While more reactive than the dihydroxy-compounds, ortho-quinones often (not always) are more sensitive and therefore hard to synthesize but also more reactive and can lead to azaacenes and various extendedazaarenes.[11] Mastalerz et al. assembled up to 11 six-membered rings using this condensation strategy.[11] The direct formation of azatetracenes deploying ortho-quinones works well, while for azapentacenes yields are variable[14] Very recently Zhang and co-workers synthesized hexaazaazapentacenes by the condensation of teraaminophenazine with various diketones.[15]
Scheme 2. Synthesis of a partially fluorinated tetraazapentacene 14 using an addition-elimination route.


Scheme 4. Synthesis of kinked azaarennes 23a-c by condensation of the diamines 20-22 with 1,2-naphthalenedione.

Scheme 5. Synthesis of compound 1 using Anthony’s alkylation strategy.

A variant of this condensation (Scheme 2) is the nucleophilic reaction of the diamine 12 in the presence of sodium amide with hexafluorobenzene to give the tautomerized N,N’-dihydro compound 13 in 24% yield.\[^{[16]}\] 13 is oxidized in good yields into the tetraazaacene 14. Extension of this concept (Scheme 3) generates the N,N’-dihydro compounds 17 and 18 in reasonable yields. For 18 oxidation is not possible anymore, due to their deep HOMO, while for 17 only the dimer 19 is observed upon oxidation with MnO\(_2\), probably through the intermediacy of the fleeting tetrafluorotetraazahexacene. Harnessing quinones, we reacted the aromatic diamines 20-22 with naphthalene-1,2-dione. 1,2-Naphthoquinone is stable and condenses in high yields to give bent, phenanthrene-like azaarennes 23a-c (Scheme 4) in good to excellent yields.\[^{[17]}\] A critical way to introduce substituents into azaarennes is the alkylation of para-quinone structures such as 24 (Scheme 5). This works well for 1, if one uses a magnesium acetylide and then deoxygenates with tin chloride. Oxidation of the intermediate furnishes 1.\[^{[6]}\] This approach should be suitable for all heterocyclic quinones, which are obtained by aggressive oxidation of N,N'-dihydroyazaarennes.

Yet the arsenal of established methods can fail in the synthesis of substituted azaarennes. The harsh conditions do not allow the coupling of the alkylnylated diamines 20-22 to
dichloroquinoxaline 9a or towards dihydroxy arenes. 20-22 are great starting materials; it was an important challenge to find synthetic methods transforming them into azacenes. Pd-catalyzed coupling reactions were an attractive proposition.

Coupling of Activated Halides to 20-22. The Simple Pd-Protocol

In our first experiments we reacted the diaminonaphthalene 21 with dichloroquinoxaline 9a in the presence of \((\text{Ph}_3\text{P})_2\text{PdCl}_2\) in boiling Hünig’s base \((N,N\text{-di-iso-propylethylamine})\). Traces of the desired product 25a formed. Upon changing the catalyst system into \(\text{Pd}_2(\text{dba})_3\) as a Pd source and RuPhos as ligand, we obtained the coupling product 25a in good yields (>75 %, Scheme 6). We also tested other Buchwald-type ligands, most of which worked also satisfactorily. In an extension of this concept, we also reacted substituted dichloroquinoxalines 9b,c to 21, to give substituted, stable tetraazapentacenes 26b,c in good yields after coupling and oxidation as stable compounds.

We observe that the coupling of 21 works with the tetrachloride 9b, in which only two of the four chloride substituents partake, i.e. only the activated ones react. 5-Nitro-2,3-dichloroquinoxaline 9c also couples easily with the diamine 21. The coupling reactions proceed smoothly in Hünig’s base \((14\text{-}18\text{ h})\) at its boiling temperature. In all cases 5 mol% of catalyst were used. The isolated \(N,N’\)-dihydro tetraazapentacenes are all easily oxidized by MnO\(_2\).

This approach (Scheme 7) accesses tetraazatetracenes. While the Pd-catalyzed coupling of 5 to dichloropyrazines works only in traces, the diaminobenzene 20, obtained through reduction of diethylbenzenothiadiazole (27) couples to dichloroquinoloxalines 9a-d to give the \(N,N\text{-dihydrotetraazatetracenes 28a-d}\); one of the few cases where \(N,N\text{-dihydroazatetracenes are isolated. MnO}_2\) then oxidizes 28a-d into the tetraazatetracenes 29a-d.

This reaction cascade extends to the synthesis of the first azahexacenes (Scheme 8). Both tetraaza- as well as hexaaza-hexacenes were obtained by the Pd-catalyzed coupling of the substituted diaminoanthracene (22) or -phenazine (12), employing the activated dichloroquinoloxalines 9a-c (Scheme 8). While all of the possible six \(N,N’\)-dihydroazahexacenes 30a-f are obtained in high yield, only the derivatives 30a-d, leading to 31a-d could be oxidized by MnO\(_2\). The other two dihydro-derivatives (30e,f) display HOMOs that were energetically too deep; they could not be oxidized into azahexacenes 31.

The Problem of Coupling De-Activated Dihalides\(^{19}\)
The Pd-catalyzed coupling of 20-22 to activated ortho-dihalides is facile and furnishes the coupling products in good to excellent yields. The coupling to un-activated aromatic halides such as 2,3-dibromonaphthalene (34) or 2,3-dibromoanthracene (43) was not yet possible. Therefore, we carefully optimized the reaction to find conditions under which we could couple the non-activated ortho-dihalides.

Scheme 9. Coupling of dichlorobenzene with diamine 12.

Conditions: Pd(db)₃₂, RuPhos, Hung base. 120 °C, 16 h.

Screening

PdRuPhos (5 mol%) a) Cs₂CO₃ (4 equiv.), dioxane, µW, 120 °C, 16 h.

b) NaOtBu (4 equiv.), toluene, µW, 150 °C, 4 h.

Scheme 10. Developing reaction conditions for the coupling of non-activated aromatic dihalides to aromatic diamines.

While the choice of the phosphane ligand was relatively clear, as the Buchwald ligands are by far the best systems we had tested, and most Buchwald-type ligands worked. The Pd source Pd₂dba₃ was not ideal (Scheme 9). In a first experiment, coupling of 12 to 32 under modified standard conditions furnished (Scheme 9) the monoarylated species 33 in 63% yield, without any ring-closed products. A cyclometalated Pd-complex with a RuPhos ligand was the most suitable system (Scheme 10). Good results were achieved with 5 mol% of pre-catalyst. Less than 5 mol% of PdRuPhos loading led to decreased yield. 10 mol% of the pre-catalyst increased the yield only slightly. As base/solvent combination we could either employ Cs₂CO₃ in dioxane or toluene in the presence of NaOtBu, both under microwave irradiation at temperatures between 120-150°C.

There are limits to this approach. We were never able to couple 12 with dichloro- (32) or dibromobenzene (37) to the cyclic product. In the best case mono-arylated product were isolated. If strong bases were used, catalyst decomposition was observed, while weak bases did not give any reaction. Bidentate and sterically encumbered phosphine ligands worked best but only gave low conversion with dihalides. Ortho-dichlorobenzene worked best with a highest 63% of the monoarylated open product. We assumed the superiority of chlorides is due a steric effect indicating the reaction leads through sterically crowded intermediate. Consecutive optimizations to ring-close 33 were not very successful either, as sterically encumbered ligands provide stability but suppress ring closure.

Azapentacenes

The diamine 21 reacted with dibromonaphthalene 34 into the formation of 35 in 53% yield if the optimized reaction conditions (Scheme 11) were used. The choice of base and temperature is critical for the formation of dihydro azapentacenes. When strong bases and temperatures over 120°C were applied, catalyst...
degradation was observed due to catalyst poisoning. We are convinced that oxidation of the formed dihydro azaacene 35 caused the poisoning. Strong bases increase this tendency by deprotonation of 35, forming an even stronger reductant at these high temperatures. Oxidation of 35 with MnO₂ gave the azaacene 36 in 92% yield. An X-ray crystal structure of 36 was obtained (Figure 3). In the same way (Scheme 12) dibromobenzene 37 couples to the diamino-anthracene 22 to furnish 39 in 53% yield. However, there was always some monoarylated product present, even if benzoquinone was employed to re-oxidize the Pd-catalyst. These modified conditions are powerful to make azapentacenes that are otherwise available only with difficulty. This Pd-catalyzed coupling has also been employed by Müllen et al. to prepare some attractive bisanthraceno-thiadiazoles.⁴²

Azahexacenes and Azaheptacenes

Could one make diazahexacenes and possibly diazahexacenes using Pd-catalyzed coupling sequences (vide supra). While the tetraaza and hexaza-hexacenes had been prepared by us, diazahexacenes and diazahexacenes were unknown at the beginning of our synthetic endeavor. With the experience from the synthesis of the diazapentacenes we coupled 22 to 34 and obtained the N,N'-dihydrodiazahexacene 40 in 49% yield (Scheme 13). More forcing conditions were applied in this case, as N,N'-dihydrodiazahexacenes are more resistant towards oxidation in contrast to N,N'-dihydrodiazapentacenes (see above) during Hartwig-Buchwald cyclization step. Oxidation of 40 with MnO₂ gave the diazahexacene 41 in 81% yield (Scheme 13). The diazahexacene 41 is stable in solution, but attempts to obtain a single crystal X-ray structure of 41 failed, and we isolated the butterfly dimer 42, the structure of which was solved and is analog to that of the dimerization products formed from Anthony’s hexacenes (Figure 4).⁴³

Employing the same strategy (Scheme 14) we coupled 2,3-dibromoanthracene 43 to the diamine 22. The N,N'-dihydrodiazahexacene 44 forms in 74% (Scheme 14), however, oxidation of 44 by MnO₂ only produced the butterfly dimer 46. The preceding diazahexacene 45 was elusive, even using UV-vis spectroscopy of the reaction solution. The diazahexacene 45 apparently is too reactive and immediately dimerized. We could though ascertain the structure of the butterfly dimer 46 by a single crystal X-ray structure (Figure 5). It features the same
topology, the analogous hydrocarbon-based heptacenes incur, when they dimerize, as reported by Anthony et al.\textsuperscript{[21]}

Figure 5. Single crystal X-ray structure of the butterfly dimer 46.

What would be the solution to the problem of dimerization of the azaheptacenes?\textsuperscript{[22]} The introduction of a second set of TIPS-ethynyl groups might stabilize an azaheptacene sufficiently to allow its isolation. The two positions that participate in the cycloadditions (Scheme 15) are the positions closest to the central pyrazine ring. Blocking these sites in 41 or 45 should result in stabilization of such a large diazaacene. Retro-synthetic analysis suggests 48 and 49 as coupling partners, but neither of these two building blocks were known.

Reduction of the anthracenothiadiazole 50a-c (Scheme 16), obtained from their respective quinones, furnished the diamines 48a-c. The best yields are obtained for \( R = \text{iso-Pr} \), with 64%. For the sterically more encumbered derivatives, the yields are lower. In the case of the dibromides 49 the yield is variable but less afflicted by steric bulk. Surprising is the decreased stability of the anthracenothiadiazoles 50 and their reduced diamines 48a-c, when compared to the much higher stability of isomeric 22.

Coupling of 48 to 49 under optimized Pd-catalysis conditions rendered the \( N,N' \)-dihydridiazaheptacenes 52a-d in yields ranging from traces to 63% (Scheme 17). The higher the steric burden on the starting materials, the lesser the yield of the coupling. For \( R \) and \( R' = \text{sec-Bu} \) practically acceptable coupling yields are still obtained. The formed \( N,N' \)-dihydridiazahptacenes 52 are easily oxidized by \( \text{MnO}_2 \) to give the diazaheptacenes in less than a minute (!) reaction time. Only the diazaheptacene 53 is reasonably stable and persists in solution for some time. For smaller substituents, the diazaheptacenes dimerize quickly into structures 54 and 55.

Scheme 15. Retrosynthetic scheme for the identification of the target diazaheptacene 47 and the necessary building blocks 48 and 49.

Scheme 16. Synthesis of the diaminanthracene 51a-c and the substituted dibromoanthracenes 52a-c.

Scheme 17. Synthesis of the diazaheptacene 53.
The situation is entirely different if one introduces biphenyl etc. units that enforce electronic separation of the aromatic units through the presence of more than one Clar-sextet. Under such conditions, one can make considerably larger N-heteroacenes,[23] however, these materials then do not show the extremely red-shifted absorption bands so prominent in the "real" azaacenes. If one allows N,N'-dihydropyrazine rings embedded into the system, the size limitation of seven rings is also not an issue. Interestingly enough, there is no knowledge, if band structures containing N,N'-dihydropyrazine units at certain intervals, would present stable and persistable materials.[24]

Figure 8. Separation of aromatic units according to Clar in heteroarenes (left) and heteroacenes (right). The heteroacenes do only have one Clar sextet, while heteroarenes have more than one Clar sextet.

Conclusions

N-Heteroacenes have come a long way from the backwaters of organic chemistry to well-performing materials for organic electronics. The substitution of an electron accepting nitrogen group into the acene framework leads to changes both with respect to their synthesis but also with respect to their properties. We and others have mostly concentrated on the introduction of pyrazine units into azaacenes. Pyrazines are - from a retrosynthetic point of view - modularized into azaacenes, as they can be quickly built up by the combination of an aromatic ortho-diamine with an aromatic ortho-dielectrophile. When employing aromatic ortho-dihalides as electrophiles, Pd-catalyzed coupling with ortho-diamines is a powerful new method to build up such N,N'-dihydroazaacenes. The accessibility of different aromatic ortho-dihalides, coupled with the modules 12 and 20-22, makes series of different azaacenes easily available in a construction-set type approach.

Recently Koert et al.[25] have employed 2,3-diaminonaphthalene as coupling partner for different dibromonaphthalenes, giving rise to interesting diazapentacenes, including the dicyano-diazapentacene 56 and other, fluorinate azaacenes. These elegant coupling reactions were successful, as the authors employed RuPhos-G2 as the active catalyst precursor.

Questions for the synthesis of larger heteroacenes remain, and it is for example not clear if long-term stable azaheptacenes and stable azaoctacenes can be prepared. It might be useful to look at targets with at least four nitrogen atoms, as they apparently
are less prone towards Diels-Alder dimerization. An important issue is the relative sensitivity of the Pd-catalyzed couplings towards steric pressure, an issue that will have to be addressed by the use of more advanced phosphine ligands, as recently demonstrated by Koert et al.[5]

Over all, the Pd-catalyzed formation of the dihydropyrazines is a major progress in the preparation of novel diaza- and tetraazapentacenes–heptacenes. This powerful methodology has accessed molecular topologies that simply can otherwise not be achieved.

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