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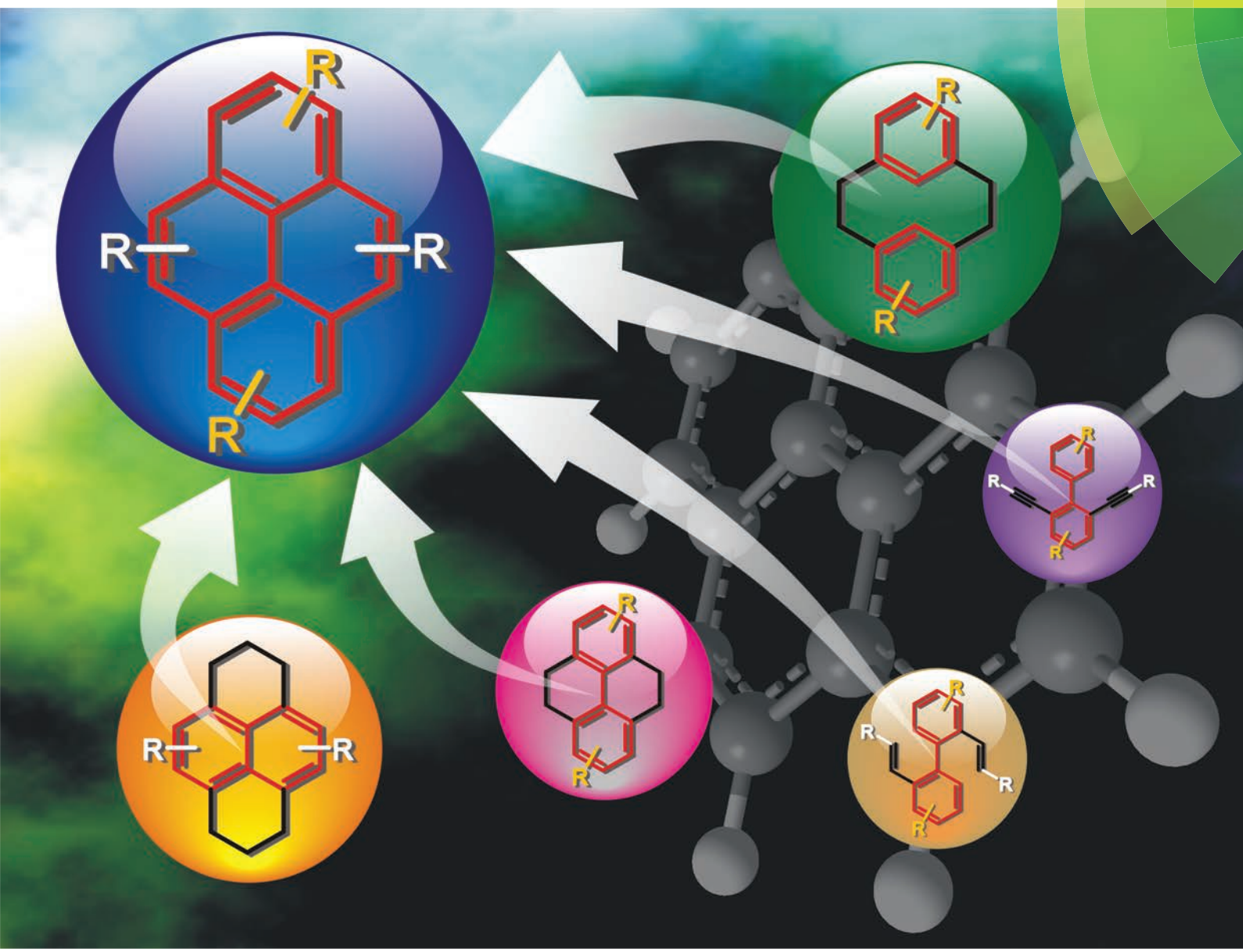

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REVIEW

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Synthesis of substituted pyrenes by indirect methods

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The pyrene nucleus is a valuable component for materials, supramolecular and biological chemistry, due to its photophysical/electronic properties and extended rigid structure. However, its exploitation is hindered by the limited range of methods and outcomes for the direct substitution of pyrene itself. In response to this problem, a variety of indirect methods have been developed for preparing pyrenes with less usual substitution patterns. Herein we review these approaches, covering methods which involve reduced pyrenes, transannular ring closures and cyclisations of biphenyl intermediates. We also showcase the diverse range of substituted pyrenes which have been reported in the literature, and can serve as building blocks for new molecular architectures.

1. Introduction

The pyrene nucleus is a compact polycyclic aromatic unit which is widely exploited for its electronic and photophysical properties, and for its ability to take part in non-covalent interactions. It serves as a key component in organic electronics[1–4] where it has been used, for example, to make field-effect transistors[5] and OLEDs.[1] It is also widely utilised in supramolecular photosensors.[6] It possesses an exceptionally long fluorescence lifetime, and the vibronic band structure of its emission shows a strong dependence on solvent polarity (Ham effect).[7,8] Furthermore, the wavelength of the bright fluorescence of pyrene is dependent on whether it is a present as a monomer or excimer. As a result, there have been many supramolecular sensors reported in which the sensing mechanism is based on a simple monomer–excimer interconversion, triggered by the presence or absence of the guest. In other cases signalling results from guest-induced perturbation of more complicated processes such as photoinduced electron (PET) and charge (PCT) transfers, fluorescence resonance energy transfer (FRET) and chelation-enhanced fluorescence (CHEF).

The pyrene unit is also valued for its binding properties. As a large aromatic surface, it is capable of taking part in π-stacking and CH–π interactions which, in water, can be reinforced by the hydrophobic effect.[9,10] This has been much exploited in the noncovalent functionalisation of extended planar

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Joshua Howgego grew up in Ipswich, UK, and completed his first degree in chemistry at the University of Reading. From there he moved to the University of Bristol to study for a PhD focussing on the design and synthesis of biomimetic receptors for carbohydrates, under the supervision of Professor Anthony Davis. Upon completion of his PhD Joshua entered the field of science journalism and in 2013 was appointed deputy news and opinions editor at SciDev.Net, a website that provides news and analysis of science as practised and applied in the developing world.

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π-systems such as carbon nanotubes[11–14] and graphene.[15–17] For example, poly(pyrenebutyric acid) has been used as a non-covalent stabilising unit for single-walled carbon nanotubes, preventing formation of bundles and enabling dispersion in solvents.[18] Pyrene has also found use in biological chemistry, especially in systems for binding nucleic acids,[19–22] and in the design of synthetic receptors for aromatic[23,24] and carbohydrate[25] substrates.

Although pyrene is already used extensively, its potential appears to be under-realised. The main limitation is a lack of well-known methodology for the construction of pyrenes with diverse substitution patterns. Thus, while pyrene is easily appended to a system, the generation of architectures with pyrenyl cores is much less straightforward. This is especially relevant to supramolecular chemistry, where polysubstituted pyrenes could serve as components for a variety of structures with well-defined cavities.

The obvious starting material for substituted pyrenes is pyrene itself, which is readily accessible and inexpensive. However, as discussed in the following section, possibilities for the direct functionalisation of the parent hydrocarbon are rather limited. For this reason a range of alternatives have been developed in which groups are introduced to non-pyrene precursors, and the full aromatic system is only generated at a late stage of the synthesis. Herein we provide a survey of such "indirect" methods. We hope this review will increase awareness of the range of pyrenes which can be made, and facilitate the use of this valuable unit in supramolecular, materials and biological chemistry.

2. The direct functionalisation of pyrene – problems and limitations

To place the later sections in context, we begin with a brief account of the direct functionalisation of pyrene, *i.e.* those methods which involve reactions on pre-existing pyrene units. More details can be found in the recent review by Figueira-Duarte and Müllen,[1] and Vollmann's classical investigations into pyrene reactivity provide a useful foundation.[26] As shown in Fig. 1, pyrene **1** is most activated for electrophilic aromatic substitution at the 1, 3, 6 and 8 positions. These are the most

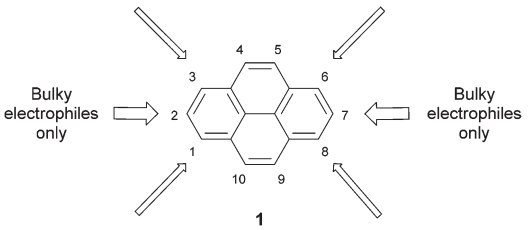

Fig. 1 Pyrene **1** is activated towards electrophilic aromatic substitution at the 1, 3, 6 and 8 positions only. Some bulky electrophiles are forced by steric hindrance to react at the 2 and 7 positions.

electron-rich centres, and are predicted to be the most reactive by calculations on Wheland intermediates.[27]

The synthesis of simple (tetra) 1,3,6,8-halogenated and -cyanated pyrenes was originally reported by Ogino.[28] Monosubstitution has also been achieved. Further elaboration of the compounds (*e.g.* by Heck coupling of the bromides with styrenes)[29] has been demonstrated. However, if two or three equivalents of an electrophile are used, the substitution pattern obtained is a statistical distribution of regioisomers. It is therefore difficult to prepare anything other than 1-substituted pyrenes or 1,3,6,8-tetrasubstituted pyrenes by direct electrophilic substitution. Further difficulties are caused by the fact that tetrasubstituted pyrenes are often highly insoluble. This means that purification methods are rather limited. The compounds prepared by Ogino, for example, were purified by high-temperature sublimation.

The 2 and 7 positions of pyrene are activated towards electrophilic aromatic substitution to a lesser extent than the 1, 3, 6 and 8 positions, but they can react selectively if a very bulky electrophile is employed, *e.g. tert*-butyl chloride.[30] In a recent development, Marder has reported that the 2- and 2,7-borylated pyrenes **2** and **3** may be prepared in excellent yields *via* reaction with bulky iridium-boryl complexes (Scheme 1).[31] Since aryl C–B bonds are useful for Suzuki–Miyaura coupling reactions as well as other transformations, this promises to be a very useful methodology. These borylated pyrenes have been used as precursors for other derivatives including alcohols, ethers, triflates, bromides and oxidative coupling products.[32–36] When positions 2 and 7 are already occupied, Marder's borylation takes place at position 4.[37]

The synthesis of 2-substituted pyrenes has also been reported from the pyrene-chromium tricarbonyl (CTC) complex **4** in relatively high yields.[38] The complexes can be made from native pyrene by reacting with $(NH_3)_3Cr(CO)_3$ and $BF_3{\cdot}Et_2O$ in fair yields. The highly electron-withdrawing CTC group increases the acidity of the aromatic protons, so that treatment with a strong base (in this case LiTMP) results in deprotonation. Addition of ethyl chloroformate, $B(OBu)_3$ (followed by oxidation) or trimethylsilyl chloride then lead to derivatives **5–7** as shown in Scheme 2. Selectivity for position 2 was generally good; only the ethoxycarbonylation gave a second product (the 1,2-disubstituted derivative). However, to our knowledge there are no examples of the procedure being

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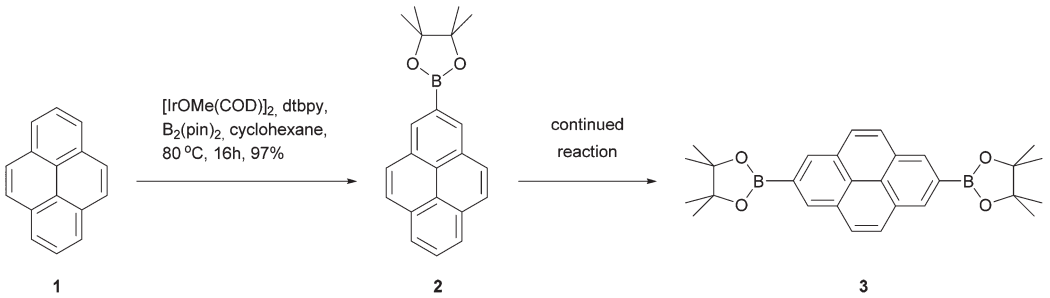
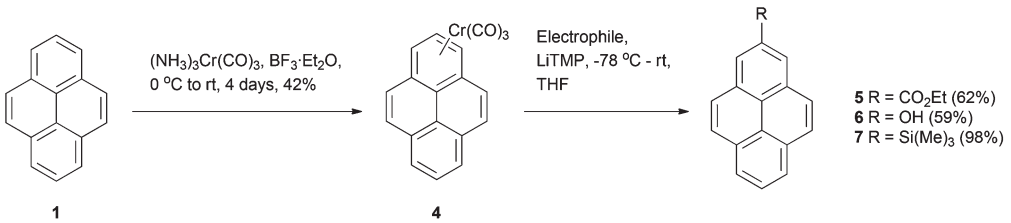
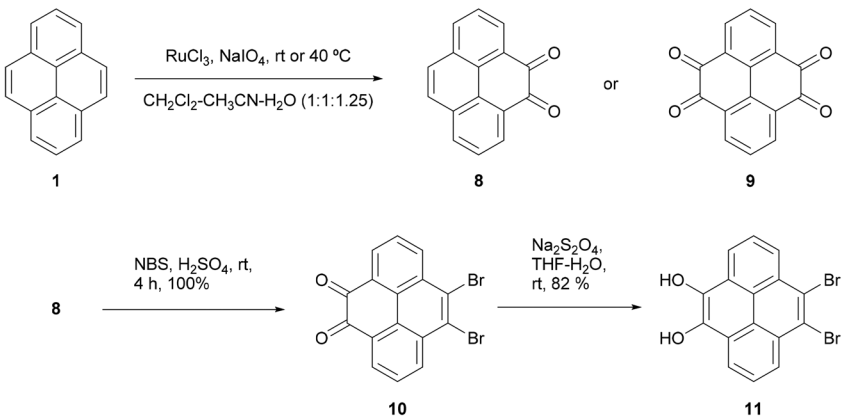


Scheme 1 Marder's iridium-catalysed 2-borylation of pyrene.



Scheme 2 Uses of pyrene-chromium tricarbonyl (CTC) complexes.

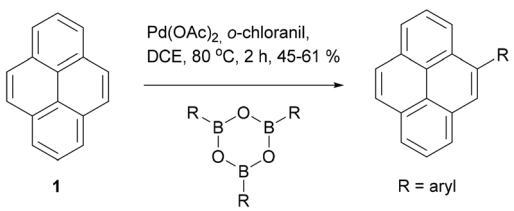


Scheme 3 Müllen's direct 4,5-substitutions *via* ruthenium trichloride catalysis.

used aside from the original report, which may be due to the toxicity of the chromium reagent.

K-region[39] (4,5,9,10-) substituted pyrenes are not accessible *via* Friedel–Crafts type reactions unless the 2 and 7 positions have been substituted with bulky *tert*-butyl groups which block the electronically favoured 1, 3, 6 and 8 positions. However, it is possible to prepare the tetrahydropyrene-4,5,9,10-tetraone **9** *via* oxidation of pyrene in the presence of a ruthenium salt catalyst (Scheme 3).[40,41] The 4,5-dione **8** can be prepared in fair yield (45%) under mild conditions and can be further oxidised to the tetraone **9** by increasing the concentration of oxidising agent and heating to 40 °C. Dione **8** turned out to be useful for the synthesis of desymmetrised pyrenes as it reacted selectively with bromine at the K-region to give **10** in quantitative yield,[42] an important result given the difficulty in accessing these positions. Presumably the electronic effects of the carbonyl groups reduce electron density at the usually active positions and render the 9,10 positions the most electron rich in dione **8**. It was also possible to reduce the carbonyls to alcohols and produce fully aromatic desymmetrised pyrene **11**.

One final example of direct modification of pyrene is worth mentioning. Itami and coworkers reported that palladium catalysed arylation of pyrene with boroximes in the presence of *o*-chloranil takes place exclusively at the K-region (Scheme 4).[43]



Scheme 4 Itami's 4-arylation of pyrene *via* palladium catalysis.

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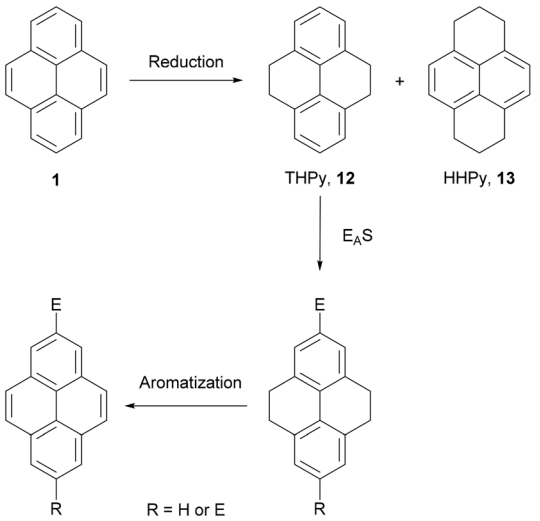
The mechanism of this transformation is unclear but seems to be quite specific, given that alternative oxidants (such as *p*-chloranil) completely shut down the reaction. Several examples of aryl groups were presented and the yields of 4-arylpyrenes were fair to good (45–61%). When further equivalents of the aryl boroxime reagent were employed diarylation also took place, but there was essentially no regioselectivity; the 4,9-diarylpyrene and 4,10-diaryl pyrenes were produced in ~1 : 1 ratio. Although the mechanism of the reaction is not known, the authors suggest that complexation of a Pd(II) species by the pyrene K-region may be a first step. If this is the case, further research could open up a range of other reactions making use of the C–Pd interaction as a handle for reactivity.

The above summary shows that is possible to substitute pyrenes at each of its positions by direct methods. However, the methodology is not always satisfactory. Control over the degree of substitution is poor in some cases, and the range of functionality that can be introduced is often limited. Moreover the positioning of multiple substituents in specific relation to each other is often impossible. Where direct substitution cannot solve the problem, alternatives may be provided by indirect methods as described in the following sections.

3. The tetrahydropyrene (THPy) method

The first indirect method of pyrene synthesis we will consider is the tetrahydropyrene (THPy) approach. The main purpose of this strategy is to allow, effectively, the performance of electrophilic aromatic substitutions (E_AS) at positions 2 and 7 on pyrene. As already described, these positions on native pyrene are accessible to only a very limited group of reagents. The THPy approach involves the reduction of pyrene to 4,5,9,10-tetrahydropyrene **12**, the reactivity of which is displaced to positions 2 and 7 under E_AS conditions. Subsequent re-aromatisation gives pyrene derivatives carrying substituents in either one or both extreme positions (Scheme 5).



Scheme 5 Synthesis of 2,7-substituted pyrenes *via* the THPy method.

THPy was first identified as a minor product (*ca.* 10% yield) from hydrogenation of pyrene under vigorous conditions (100 bar, 400 °C) using a molybdenum–sulphur–carbon catalyst.[44] However, later studies indicated that hydrogenation can be limited to the K-region by tuning conditions of the reaction.[45,46] Currently there are several methods reported for the preparative synthesis of THPy using H_2/Pd/C in EtOAc (Table 1).[47–54] Some authors have reported that hydrogenation does not take place unless the commercial pyrene starting material is purified by column chromatography[47] or desulphurisation with RANEY® nickel[50,53,54] prior to the reaction. The latter method introduces traces of water (*ca.* 0.5%) to the reaction mixtures which are reported to help restrict over-reduction. The quality of the catalyst is also a significant factor and different commercial sources have been compared.[47] In many cases hydrogenation does not go to completion in a single reaction cycle. Common steps to increase the extent of reaction are addition of a very large amount of catalyst[48,54] and performing several hydrogenation cycles with fresh catalyst.[49,51] More recently, higher pressures and temperatures have been applied, reducing reaction times and the amounts of impurities found in the crude products.[52,53] In general, the main impurity is 1,2,3,6,7,8-hexahydropyrene (HHPy) **13**, which can be removed by column chromatography on Florisil,[47] silica[49,51,54] or alumina,[53] or by diacetylation of the crude product followed by fractional precipitation of the impurity.[50]

Very pure THPy can be prepared on a small scale by photochemical reduction of pyrene in the presence of triphenyltin hydride. This reaction takes only 1 h and no products other than THPy are formed.[55] Birch conditions with lithium reductant have also been used by some workers.[56–58] Again, purification of commercial pyrene prior to the reaction seems to be essential for the reaction to be successful. The Birch reduction does not give directly the desired compound but the intermediate 4,5-dihydropyrene (DHPy), which can be subsequently hydrogenated in the presence of Pd/C to yield the desired THPy in good yields. Alternatively, the second reduction can be accomplished by applying Birch conditions again, but extremely short reaction times (2 min) must be used to avoid over-reduction. This method usually gives mixtures of DHPy and THPy which are then separated by charge-transfer chromatography (10% caffeine on silica gel).[57] If sodium is employed instead of lithium, initial reduction takes place in positions 1 and 9, after which treatment with acid is required for the isomerisation to 4,5-dihydropyrene. A second reduction with sodium in xylene–ethanol yields a mixture of THPy and HHPy, from which THPy may be isolated after selective nitration of the latter.[58] It is also possible to synthesise THPy *via* ring closure of [2,2]metacyclophane or photo-chemical cyclisation of 2,2′-divinylbiphenyl. These approaches are discussed further in sections 5 and 6.

Re-aromatisation of THPy derivatives to give the final substituted pyrenes can be achieved with a variety of conditions.[59] The most popular method is the reaction with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ).[49,51,53–56,60–65] Catalytic

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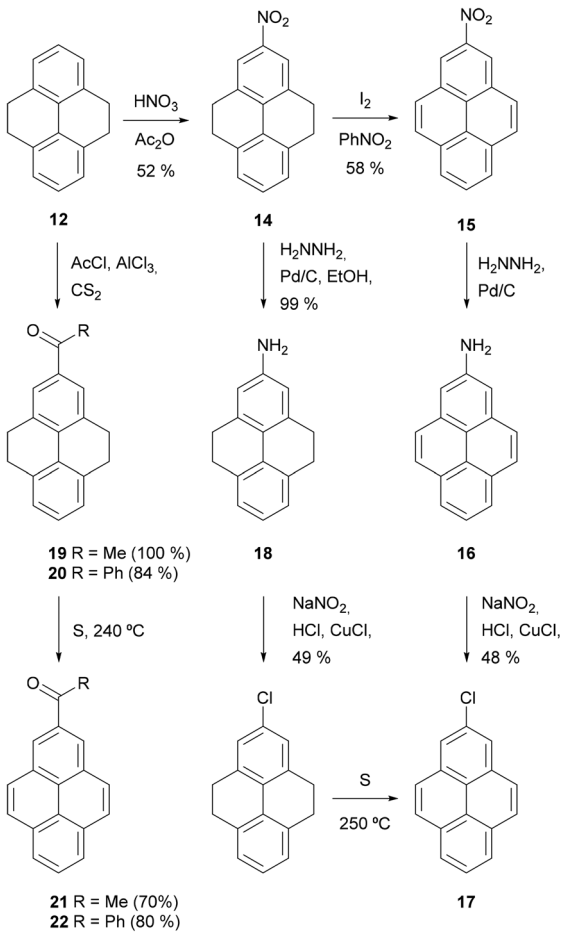
Table 1 Reported preparative syntheses of THPy by catalytic hydrogenation of commercial pyrene with Pd/C in EtOAc

Entry	H_2 pressure (bar)	T (°C)	Time (h)	Purification	Yield (%)	Ref.
1[a]	3.4	rt	96	Chromatography on Florisil	95	47
2	4.1	rt	192	—[c]	—[d]	48
3	3.4	rt	24 (×3)	Chromatography on silica	50	49
4[b]	3.4	rt	65	Acetylation and selective solubilisation	53[e]	50
5	3.8	rt	24 (×3)	Chromatography on silica	86	51
6	140	90	7	—[c]	96	52
7[a,b]	160	60	24	Chromatography on alumina	76	53
8[b]	3.4	rt	72	Chromatography on silica	—[d]	54

[a] Pyrene purified using Florisil column prior to reaction. [b] Pyrene desulphurised with RANEY® nickel prior to reaction. [c] No purification described. [d] No yield given. [e] Obtained as 2,7-diacetyl-THPy.

dehydrogenation with Pd/C[47,60,66] and treatment with halogens[50,52,57,67,68] have also been used. There are also examples employing selenium,[44] sulphur[68] and *o*-chloranil.[48,69]

The utility of THPy as a source of 2-substituted pyrenes was first described by R. Bolton in 1964, who prepared 2-nitro- **15**, 2-acetyl- **21** and 2-benzoylpyrene **22** for the first time in moderate to good yields after two steps by using this strategy (Scheme 6). Nitro derivative **15** was then used as the starting material for the synthesis of 2-aminopyrene **16** and 2-chloropyrene **17**.[68]



Scheme 6 Bolton's first application of the THPy method.[68]

The syntheses of many of these compounds have been revisited and improved by later authors. For example, 2-nitroTHPy **14** has also been prepared by treatment of THPy with dinitrogen tetraoxide,[62] or with nitrate salts in acetic or trifluoroacetic anhydride.[49,51,54,55,58] The early work of Bolton had a large impact on subsequent synthetic work with pyrene, since some of the compounds initially described by this author have served as intermediates for a variety of subsequent pyrene derivatives (Schemes 7–10).

Thus, application of the Willgerodt–Kindler method to 2-acetylTHPy **19** has allowed the preparation of 2-(formylmethyl)pyrene **23** and the butanoate derivative **24** (Scheme 7).[61] 2-MethoxyTHPy **25** has also been prepared from compound **19** by using Baeyer–Villiger oxidation conditions,[47] or from 2-aminoTHPy **18** *via* a diazonium salt.[58] Haloform oxidation of **19** leads to the corresponding acid **26**, which can be transformed into 7-amino-2-pyrenylcarboxylic acid **27** after five steps.[57] Compound **19** has also been nitrated in position 7 to yield 2-acetyl-7-nitroTHPy.[70]

2-Acetylpyrene **21** can be reduced to the alcohol **29**, dehydrated to 2-vinylpyrene **31** then transformed to the corresponding epoxide **33** (Scheme 8). A similar sequence has been performed for 2,7-disubstituted analogues (**28** → **30** → **32** → **34**).[56] Compound **21** has also been transformed into 2-ethynyl derivative **35** using Vilsmeier–Haack–Arnold methodology followed by Bodendorf fragmentation.[53] The synthesis of **35** has also been reported *via* other routes starting from bromopyrene derivatives (see below).

Acetylation of 2-amino-THPy **18** gives acetamide **36** (Scheme 9), which provides a point of entry to rare 1,2- and 2,6-substituted pyrenes (*e.g.* 2-acetyl-6-bromopyrene **38** and 1,2-dinitropyrene **41**). The presence of the acetylamino group in position 2 activates the vicinal *ortho* position 1, which competes with position 7 depending on the electrophile. Thus, bromination of **36** takes place exclusively in position 1 to give **37**, while nitration gives a mixture of 1- and 7-derivatives, **39** and **40** respectively.[63]

Bolton's synthetic strategy for 2-nitropyrene **15** and 2-aminopyrene **16** has been exploited for the preparation of more elaborate 2-substituted pyrenes (Scheme 10). For example,

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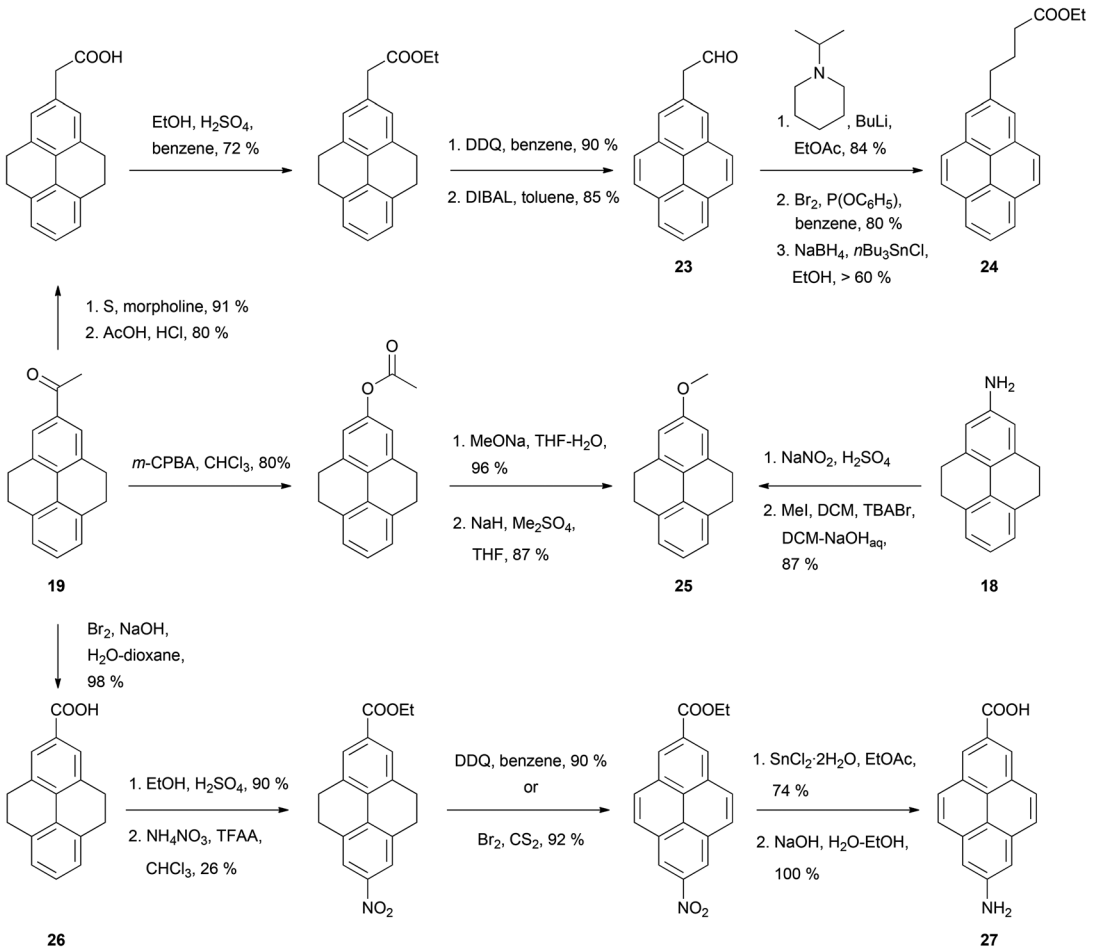
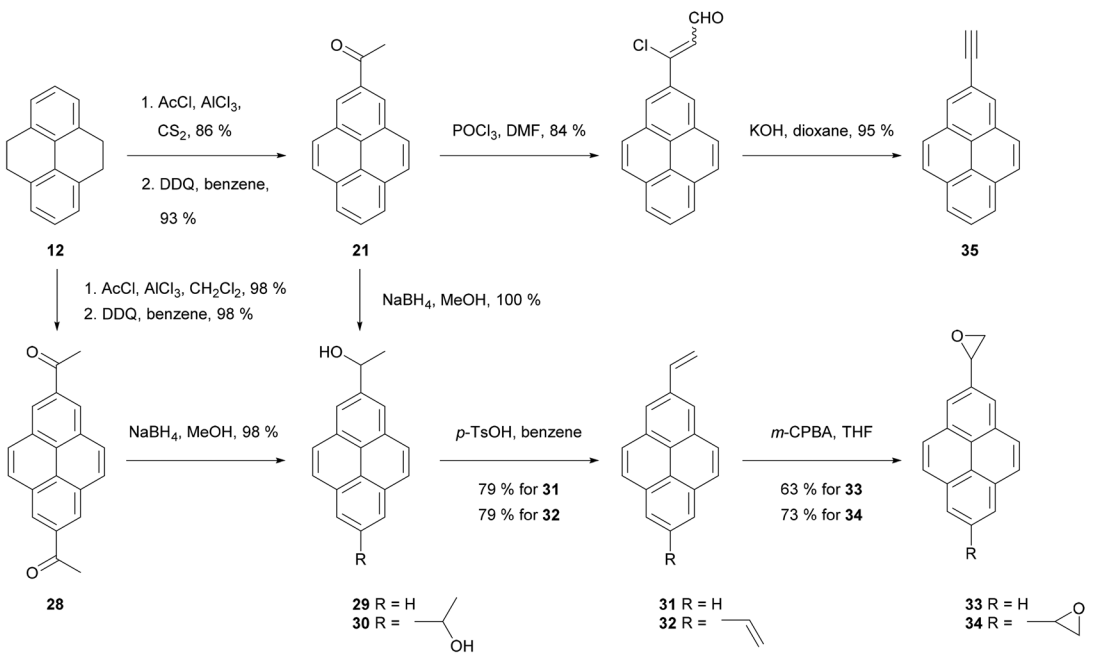


Scheme 7 Further transformations from amine **18** and ketone **19**.



Scheme 8 Transformations *via* 2-acetylpyrene **21** and 2,7-diacetylpyrene **28**.

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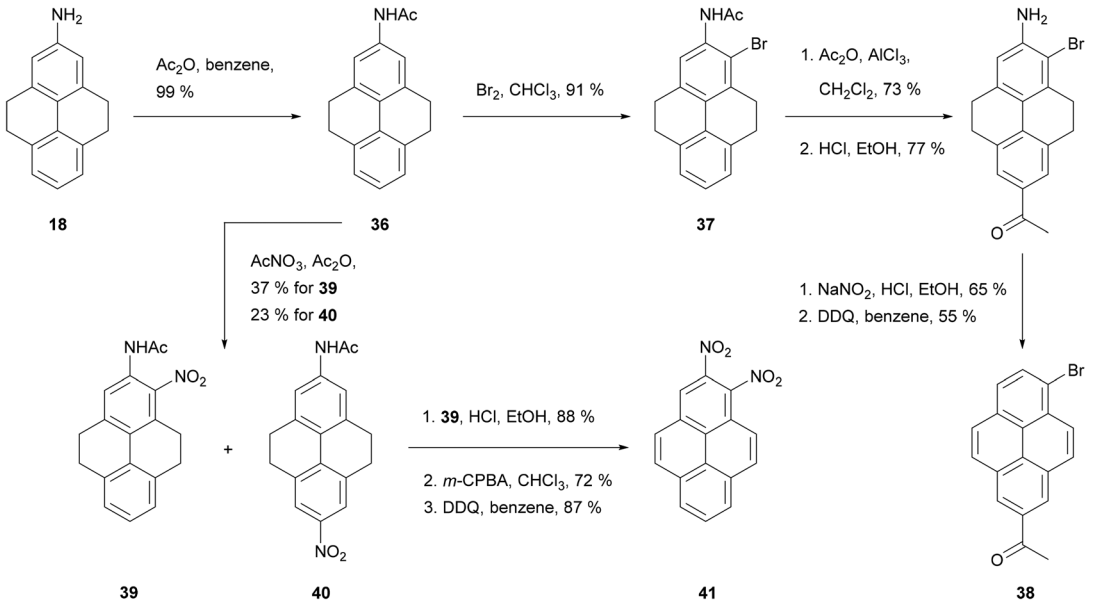
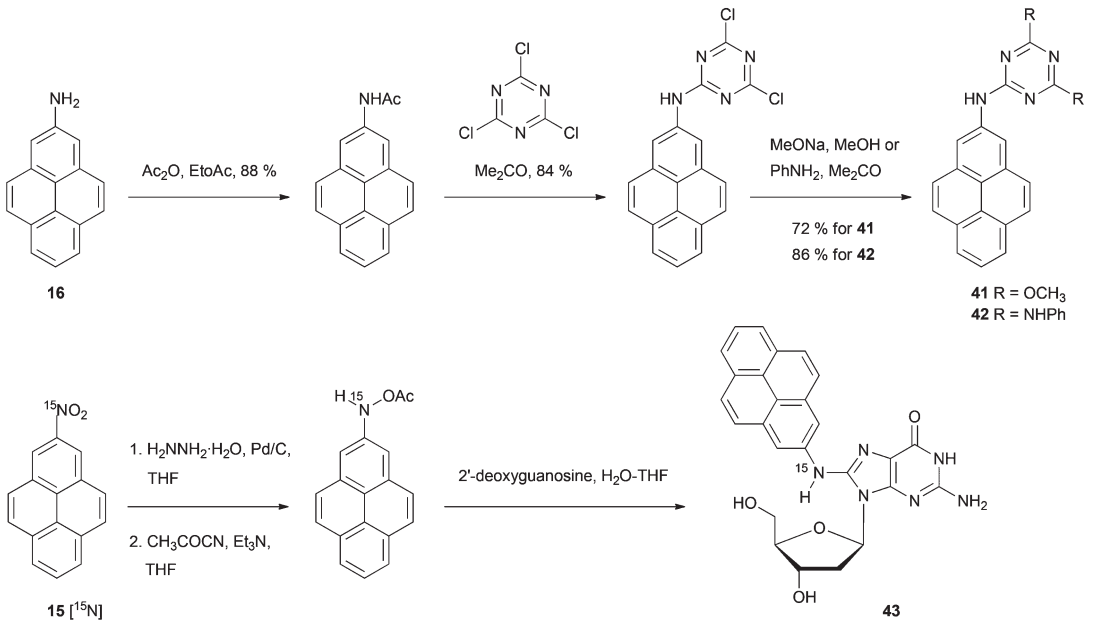


Scheme 9 Preparation of 1,2- and 2,6-disubstituted pyrenes *via* 2-amino-THPy **18**.



Scheme 10 Synthesis of pyrenyltriazine derivatives **41** and **42**, and pyrenyl nucleoside **43**.

2-aminopyrene **16** has been transformed into dimethoxy- and bis-anilino-triazines **41** and **42** in three steps.[52] Zhou and Cho synthesised the ^{15}N-labeled analogue of **15** as the starting material for the exotic nucleoside [^{15}N](2′-deoxyguanosin-8-yl)-2-aminopyrene **43**.[49]

THPy overreaction to give 2,7-disubstituted derivatives can be a problem, and conditions need to be tuned in order to avoid it. Disubstitution is sometimes a major outcome even when only one reagent equivalent is used, yielding complex mixtures which can be difficult to separate. This is the case for acetylation (Scheme 11). Harvey *et al.* have reported that the reaction can be controlled by the solvent: CS_2 leads to mono-acetylation while CH_2Cl_2 gives diacetylation,[56] although temperature and reagent amount must be carefully controlled in the former case.[57] 2,7-Diacetyl-THPy **44** has been oxidised to THPy-2,7-dicarboxylic acid using I_2 in pyridine or NaOBr in water, and subsequently esterified.[50] The resulting ester **45** has been reduced to diol **46** and reacted with PBr_3 to give the bis-(bromomethyl) derivative **47**. The latter has been conjugated with an immobilised cyclic peptide scaffold, creating a synthetic carbohydrate receptor effective in MeCN–water mixtures.[25] 2,7-Diacetyl-THPy **44** can also be dehydrogenated to

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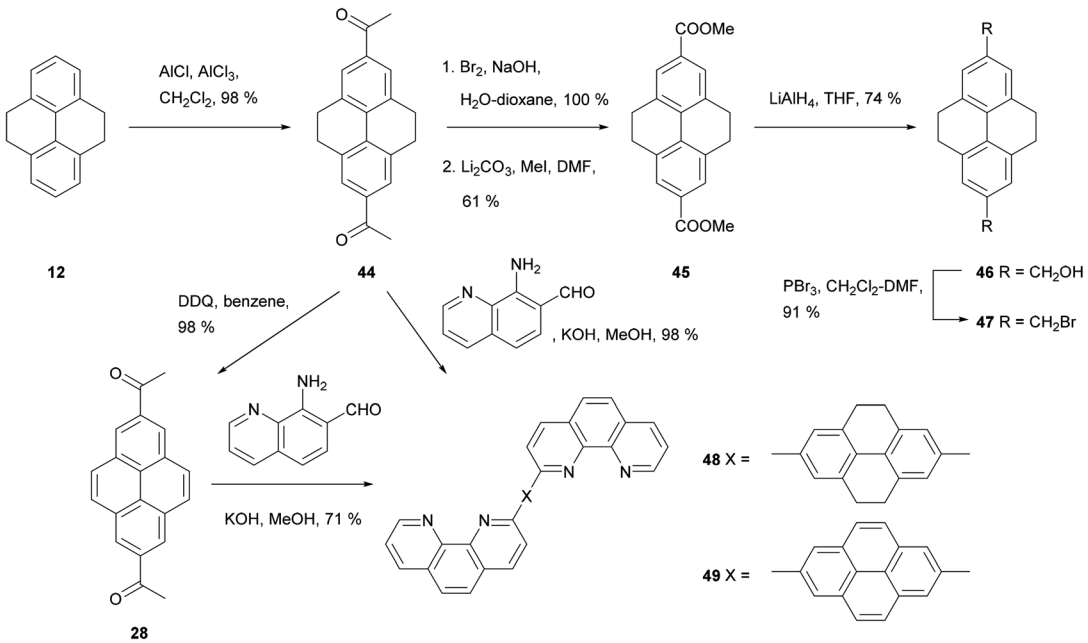
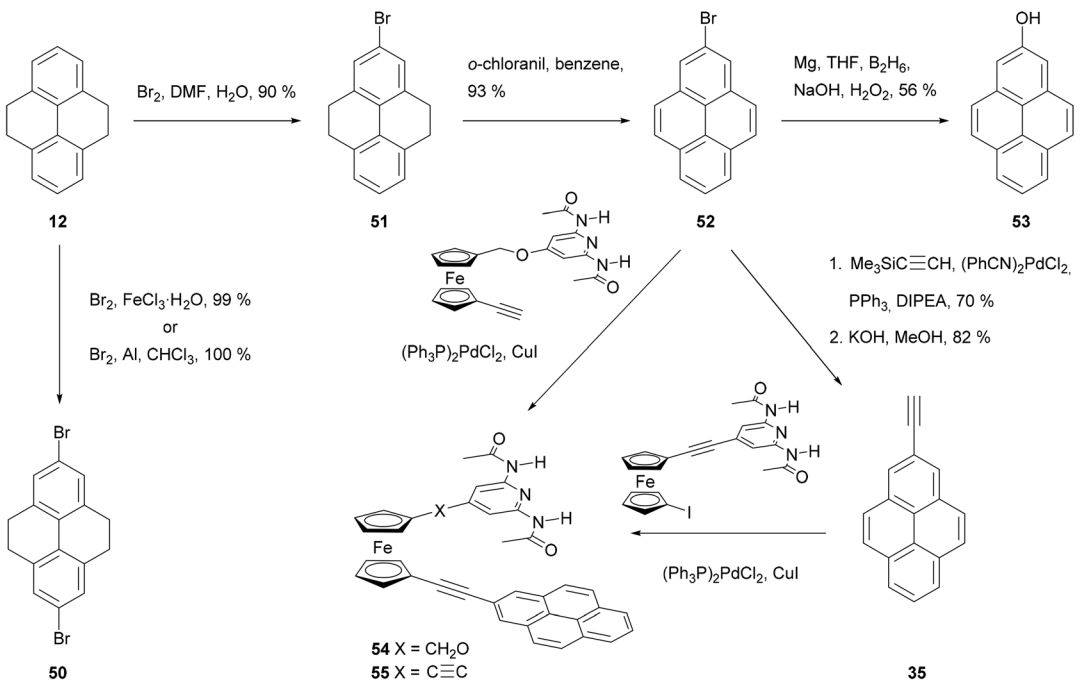


Scheme 11 Preparation of 2,7-dibromomethyl-THPy **47** and phenanthroline derivatives **48** and **49**.

yield 2,7-diacetylpyrene **28**. Both **44** and **28** have been condensed with 8-amino-7-quinolinecarbaldehyde under Friedländer conditions to prepare the corresponding conjugates **48** and **49** carrying phenanthroline moieties.[66]

Disubstitution is also an issue in the case of bromination (Schemes 12 and 13). Treating THPy with bromine in the presence of $FeCl_3$ in an aqueous medium[67] or Al powder in chloroform,[71] leads mainly to 2,7-dibromo derivative **50**, while the monobromo analogue **51** can be formed by reaction of THPy with bromine in DMF for 6 h and then in water overnight. After dehydrogenation of compound **51**, the resulting 2-bromopyrene **52** can also be transformed into the phenol **53** by reacting the corresponding Grignard reagent with diborane and alkaline peroxide,[69] or into 2-ethynylpyrene **35** with trimethylsilylacetylene followed by desilylation with KOH[48] or with 3-methyl-1-butyn-3-ol followed by deprotection with NaH.[72]



Scheme 12 Bromination of THPy **11**, and further transformations on mono-bromo derivative **51**.

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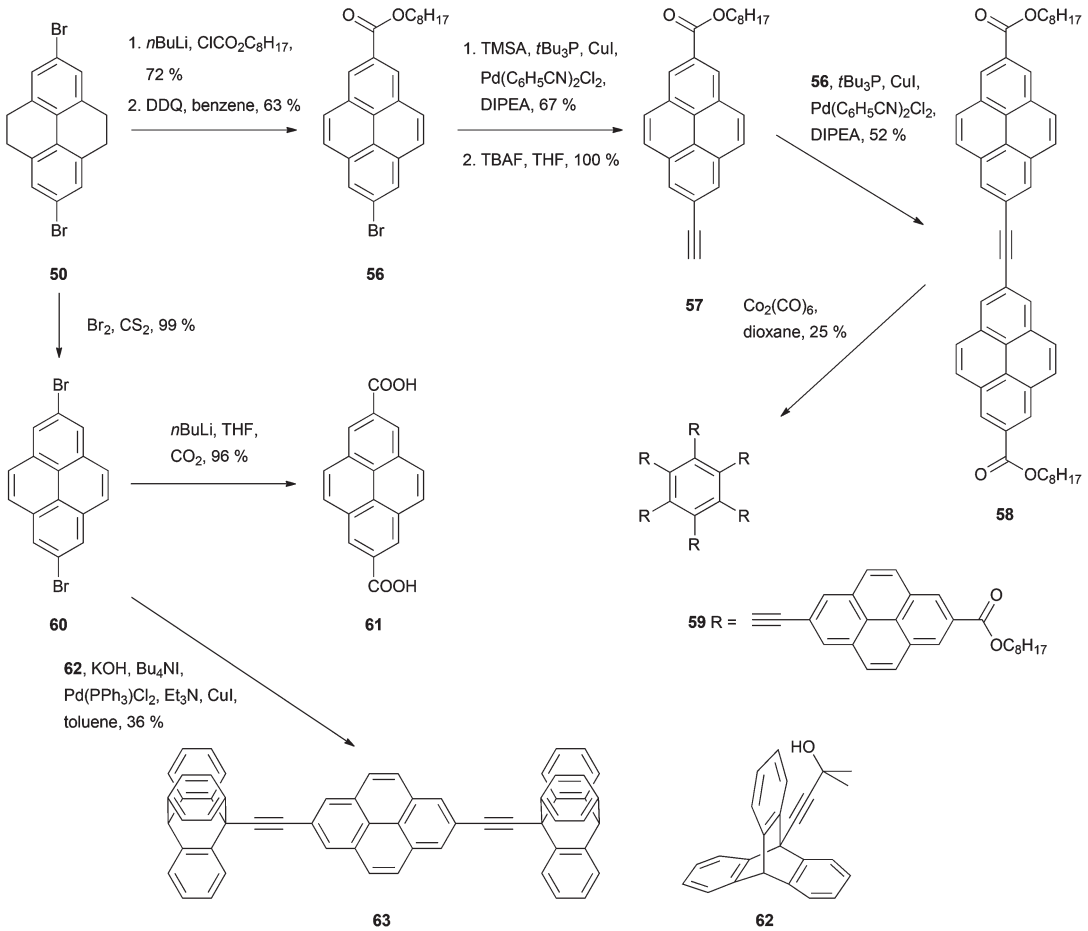

Scheme 13 Further transformations of 2,7-dibromoTHPy **50**.

Both 2-bromopyrene **52** and 2-ethynylpyrene **35** have been conjugated with diamidopyridinyl ferrocene derivatives by Pd-catalysed coupling to prepare novel artificial nucleobase receptors **54** and **55**.[72] More examples of Sonogashira type reactions on bromopyrene derivatives can be found in Scheme 13. Thus, asymmetric modification of the dibromide **50** yielded bromoester **56** and thence alkynylester **57**. This was transformed into the symmetric tolan **58** through a second coupling. Cyclotrimerisation of the latter in the presence of $Co_2(CO)_8$ finally gave the hexapyrenylbenzene **59**.[65] A Pd-catalysed coupling reaction was also used to transform 2,7-dibromopyrene **60** into the molecular rotor **63**, with two axially positioned ethynyltriptycenes as paddles.[73] Compound **60** may also be lithiated through reaction with *n*-BuLi. Subsequent reaction with CO_2 gas gives the corresponding 2,7-dicarboxylic acid derivative **61** in very good yield.[71]

Routes to some fluoro- and deutero-pyrenes are shown in Scheme 14. Direct fluorination of THPy to give **64** (and thence **65**) was possible only in very low yield.[74] Instead, better results were obtained when 2-amino-THPy **18** was transformed into the corresponding diazonium salt and treated with $NaBF_4$ (Scheme 14).[58] This reaction has also been performed on the aromatised analogue 2-aminopyrene **16** under Balz–Schiemann conditions using *t*-BuONO and $Et_2O{\cdot}BF_3$.[51] A number of deuterated pyrenes were made *via* treatment of THPy **12** with P_2O_5 in D_2O to give **66**. Aromatisation–bromination–reduction then gave dideuteropyrene **67**, while bromination–reduction–aromatisation gave tetradeuteriopyrene **68**.[64]

The THPy strategy also allows the preparation of pyrene derivatives containing a new fused ring involving position 2 (Scheme 15). One approach starts with the direct modification of native pyrene on the reactive position 1. An appendage is introduced which includes a group capable of subsequent electrophilic aromatic substitution, such as an ester or an acid. This derivative is then hydrogenated to the equivalent THPy analogue in order to direct the following cyclisation to the position 2. Finally, re-aromatisation of the molecule yields the desired compound. Depending on the groups present in the new ring after the cyclisation, a careful selection of the dehydrogenation treatment may be needed.[59] Lee and Harvey have employed this strategy for the preparation of 4,5,8,9,10,11-hexahydro-7-oxo-7*H*-cyclopenta[*a*]pyrene **69**, where a 5-membered aliphatic ring is fused to pyrene on positions 1 and 2. Further reactions were later performed to yield 7*H*- and 9*H*-cyclopenta[*a*]pyrenes.[60] A second strategy involves attachment of a functionalised chain to position 2 on a THPy derivative. Cyclisation either before or after dehydrogenating the THPy gives a new ring fused to positions 1 and 2. Thus, cyclisation of ethyl

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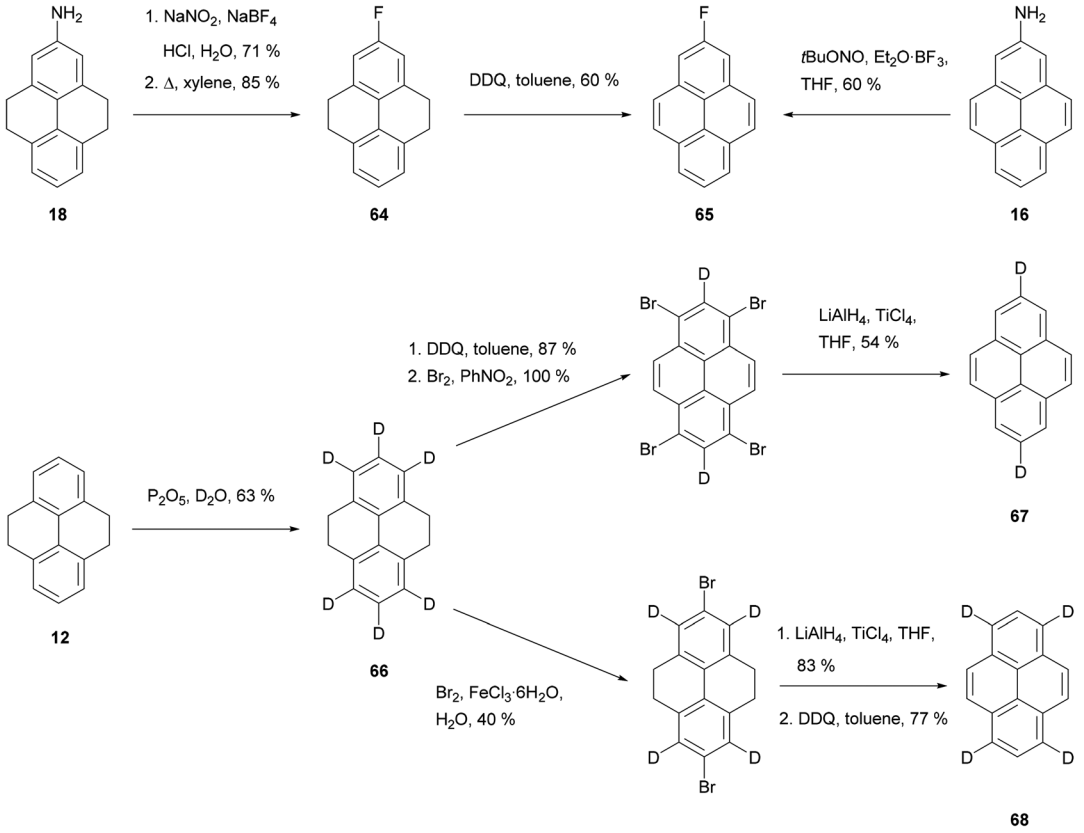

Scheme 14 Routes to 2-fluoropyrene **65** and regioselectively deuterated pyrenes.

4-(pyren-2-yl)butanoate **24**, prepared from 2-acetyl-THPy **19** as shown in Scheme 7, was accomplished with HF. After reduction, dehydration and dehydrogenation of the new ring, benzo[*a*]pyrene **70** was obtained.[61] Benzo[*a*]pyrene derivatives are compounds of particular interest because they undergo metabolic epoxidation *in vivo* which transforms them into highly tumorigenic agents capable of covalent conjugation with purine bases. 2-Hydroxybenzo[*a*]pyrene **71** was prepared in a similar way to that described for **70**, although in this case cyclisation was performed before rearomatisation of the THPy core.[47] Benzo[*a*]pyrene derivatives can also be obtained if a four-carbon alkyne chain is attached to positions 6 or 8 on a suitable pyrene derivative. Thus, 2-fluoropyrene **65**, obtained from 2-aminopyrene **16** as outlined in Scheme 14, was succinoylated on position 6, after which ketone reduction with HI/P, cyclisation with HF, reduction and dehydration were also performed to yield compound **72**. Further transformations yielded epoxydiols **73** and **74**, which were studied as electrophiles towards water and dGMP.[51]

4. The hexahydropyrene (HHPy) method

As discussed in the previous section, the hydrogenation of pyrene **1** gives mainly two compounds, 4,5,9,10-tetrahydropyrene (THPy) **12** and 1,2,3,6,7,8-hexahydropyrene (HHPy) **13**. The composition of the reaction mixture depends on the reduction conditions. When using Na in 1-pentanol or isoamyl alcohol the main product of the reduction is HHPy **13**, which can be isolated in very pure form by a simple crystallisation from EtOH.[44,55,75]

The reactivity of **13** towards E_AS reactions is straightforward, as only one position is available for the first substitution.[26] This allows the preparation of pyrene derivatives substituted on their K-region if a subsequent re-aromatisation step with *o*-chloranil or DDQ is applied (Scheme 16). Thus, 4-bromo-**75**,[76,77] 4-acetyl-**76**,[78] and 4-nitropyrene[55] **77** have been prepared in good yields following this synthetic route (Scheme 17). These compounds act as starting materials for further transformations. For example, 4-bromopyrene **75** can be treated with *n*-BuLi followed by CH_3I or ethylene oxide to yield the corresponding 4-alkylpyrenes **78** and **79**.[77,79,80] Similarly, 4-acetylpyrene **76** has been converted into 4-ethynylpyrene **80** by successive Vilsmeier–Haack–Arnold reaction and Bodendorf fragmentation.[53]

The HHPy method has been extended to the preparation of pyrene derivatives bearing fused aromatic rings, which are of interest due to their carcinogenic nature and their presence in polluting fumes such as automobile exhausts. For instance, 1,2,3,6,7,8-hexahydro-γ-oxo-4-pyrenebutanoic acid **81**, obtained by the direct Friedel–Crafts alkylation of HHPy, can undergo a Wolff–Kishner decarboxylation followed by cyclisation and oxidation to yield benzo[*e*]pyrene **82** (Scheme 18).[75] Alternatively,

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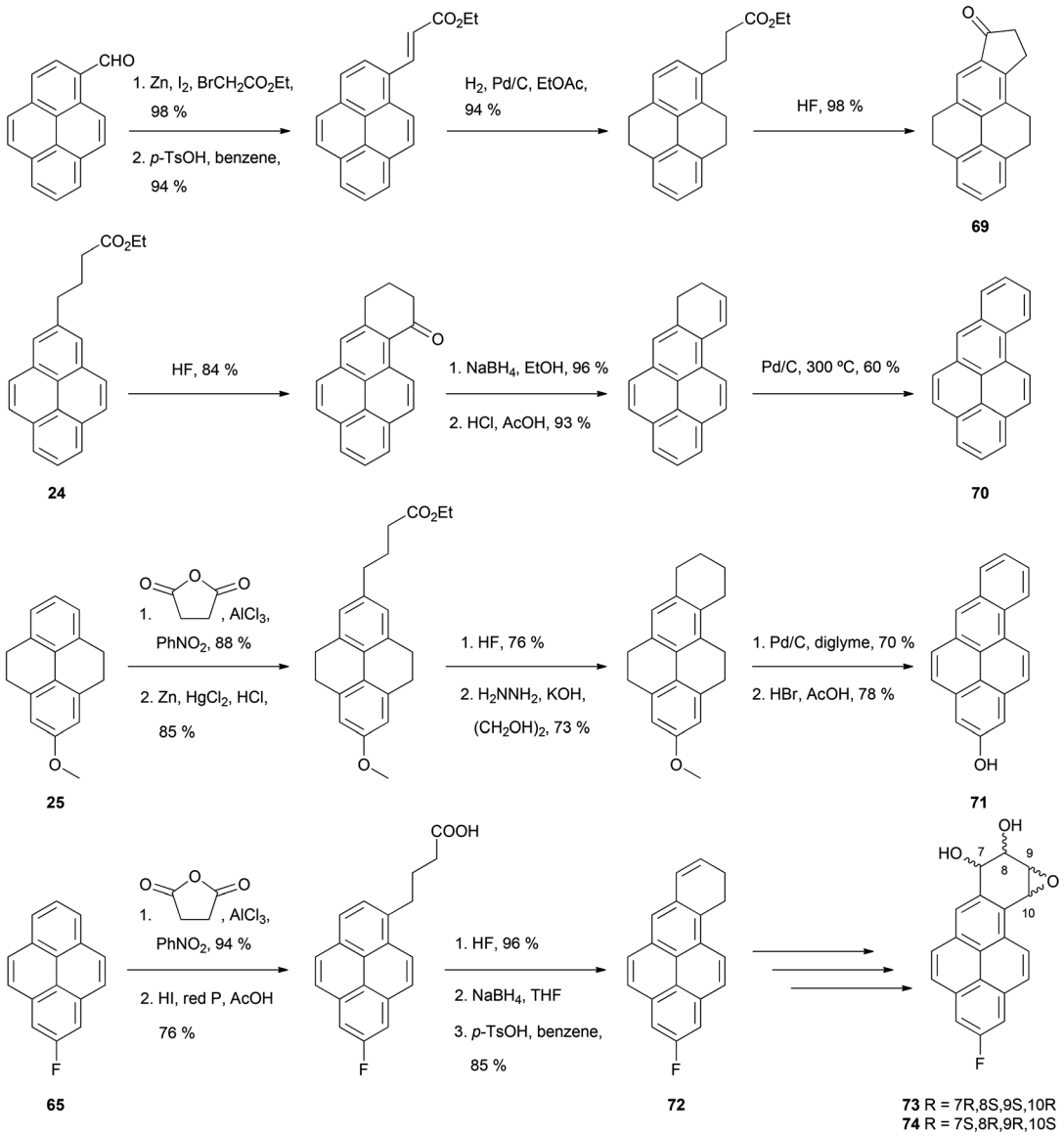
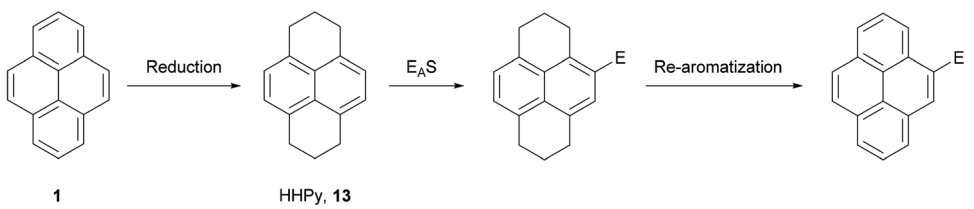


Scheme 15 Preparation of cyclopenta[*a*]pyrene precursor **69** and benzo[*a*]pyrene derivatives **70–74**.



Scheme 16 Synthesis of 4-substituted pyrenes *via* the HHPy method.

compound **81** can be esterified, re-aromatised and converted into diacid **83**, the double cyclisation and subsequent oxidation of which gives the methylene-bridged analogue **84**.[81] Extended heterocyclic pyrene derivatives **85–89**, containing thiophene,[82] furan[83] and pyrrole[84] rings fused in positions 4 and 5, have also been prepared starting from 4-bromopyrene **75** and 4-nitropyrene **77**, respectively.

Among the fused aromatic ring pyrene analogues reported, cyclopenta[*c*,*d*]pyrene (CPP) **90** is probably the one whose synthesis has received the most attention. The key compound for this synthesis is 4-pyrenylacetic acid **91**, which has been prepared in several ways starting from HHPy or its derivatives (Scheme 19). For example, HHPy was reacted with methyl (methylsulfinyl)acetate to give **92**, rearomatised to **93** then

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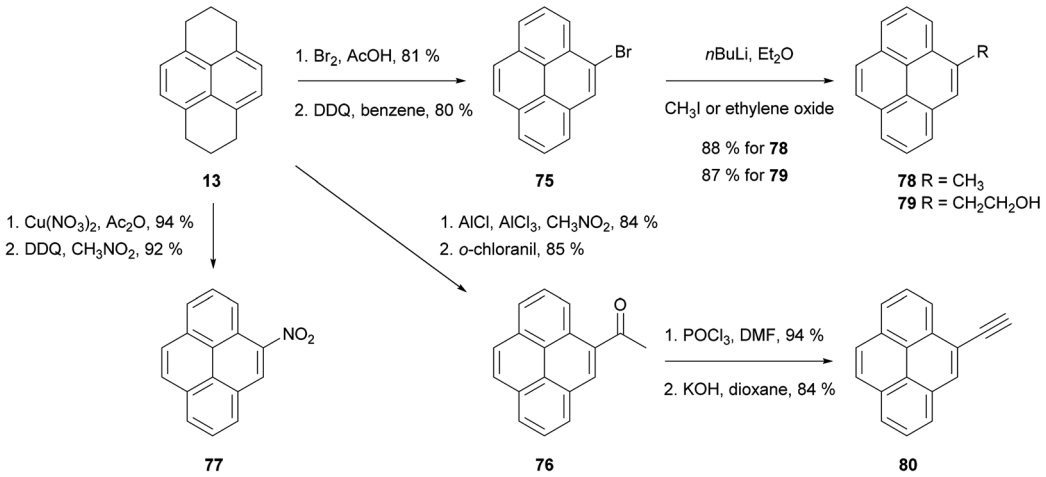
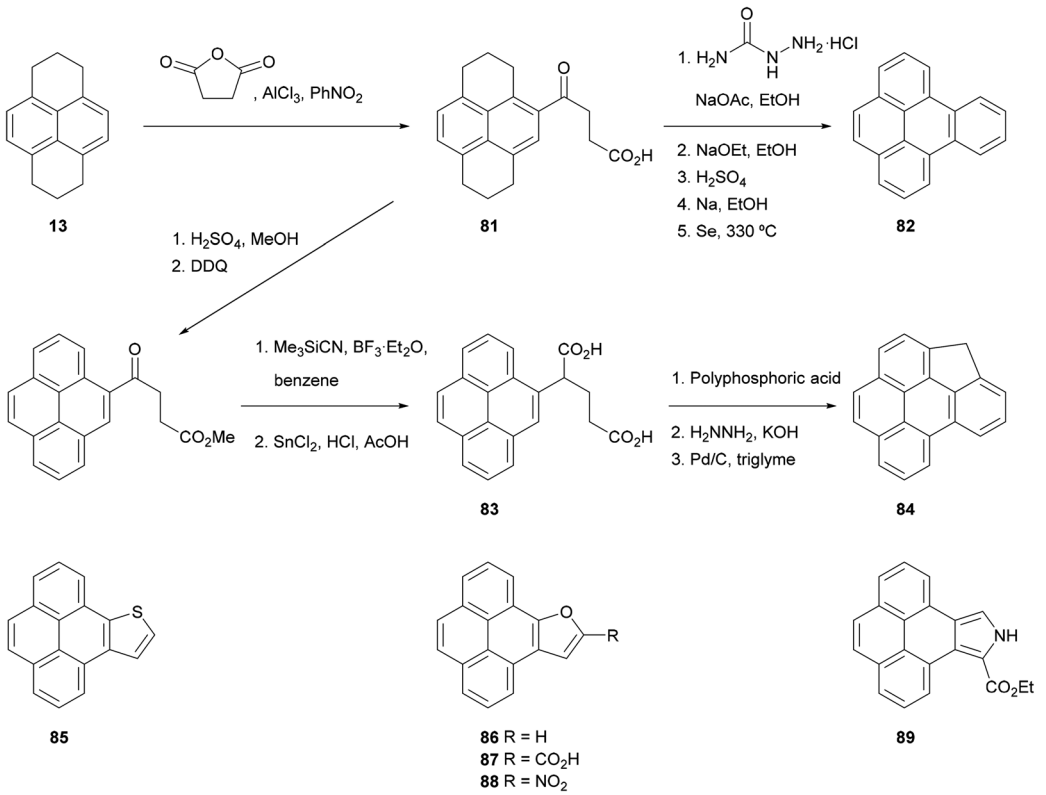


Scheme 17 Preparation and further transformations of 4-bromo-, 4-acetyl- and 4-nitropyrene.



Scheme 18 Benzo[*e*]pyrenes and analogous heterocycles prepared *via* the HHPy strategy.

desulfurised with zinc–copper.[85] Alternatively, two routes used 4-acetylpyrene **76** as starting material: (i) Willgerodt oxidation to 4-pyrenylthioacetamide, followed by treatment with HCl–AcOH,[78] and (ii) oxidation with thallium trinitrate.[86] As a further option, 4-methylpyrene **78** was brominated to give **94** and cyanated to give **95** before obtaining the desired acid by simple hydrolysis.[79] Finally, 2-(4-pyrenyl)ethanol **79** was oxidised in two steps employing the *N*-chlorosuccinimide/Me_2S method followed by Ag_2O.[80] CPP **90** has also been prepared following a slightly different strategy by oxidizing HHPy at position 1 and condensing the ketone with the Wittig reagent triethyl phosphonoacetate. The resulting product was subsequently hydrogenated, cyclised, decarboxylated and finally rearomatised (Scheme 20).[87]

HHPy may also be dibrominated to give selectively the 4,9-dibromide **96**. Recently, this has been used to synthesise the

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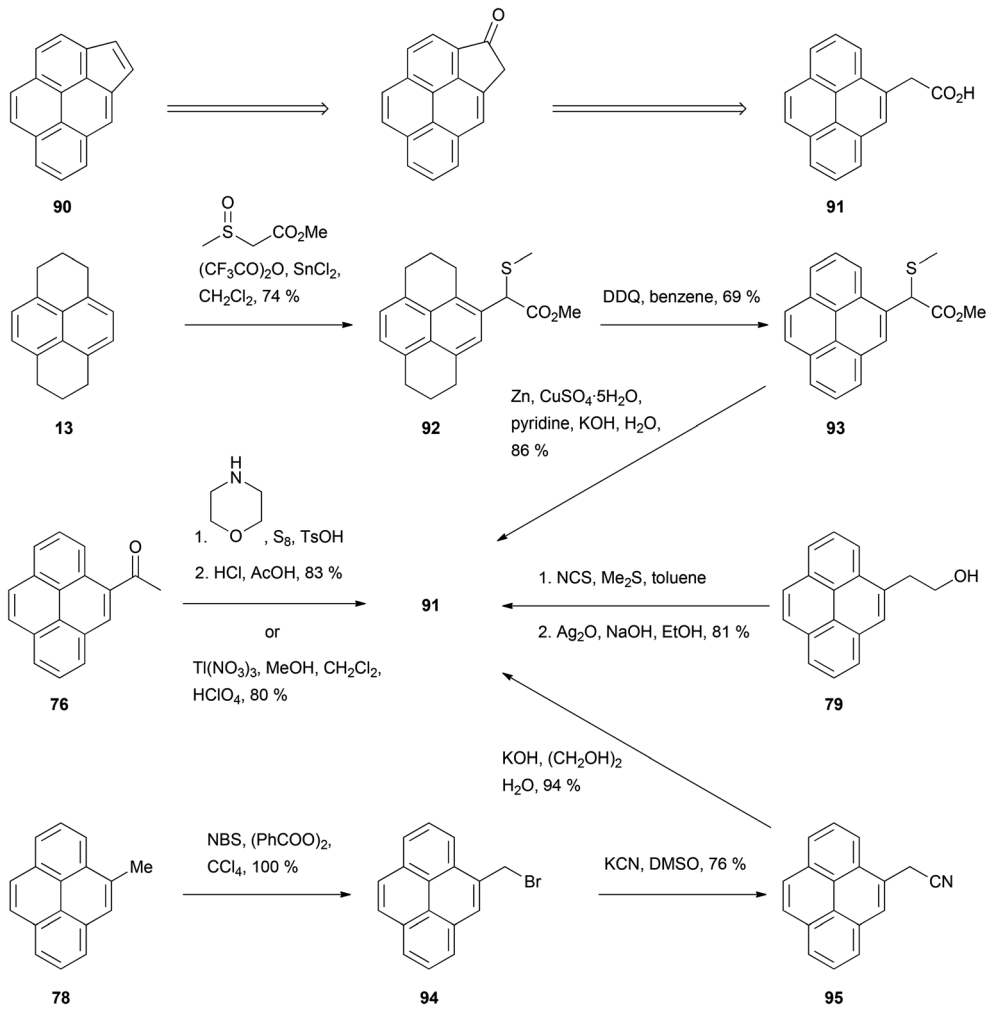
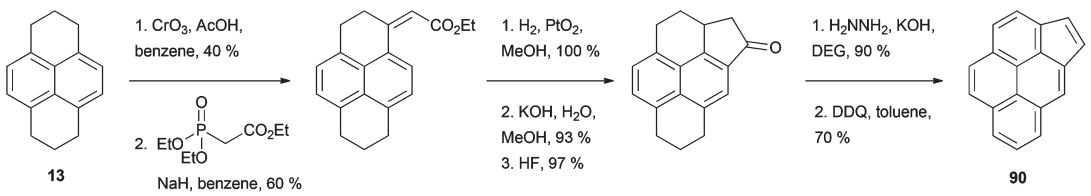


Scheme 19 Methods for the preparation of 4-pyrenylacetic acid **91**, en route to cyclopenta[*c,d*]pyrene **90**.



Scheme 20 Alternative route to cyclopenta[*c,d*]pyrene **90**.

phosphoramidite ligand **97**, employed in a gold(I)-catalysed enantioselective cyclisation of allenenes (Scheme 21).[88]

5. Transannular ring closure of [2,2]metacyclophanes

It is well known that [2,2]metacyclophanes such as **98** can undergo transannular ring closure to yield products with the 4,5,9,10-tetrahydropyrene (THPy) skeleton (*e.g.* **12**),[89] which may then be dehydrogenated to pyrenes as discussed in section 3 (Scheme 22). The transannular ring closing reaction can be triggered by the presence of an electrophilic reagent which can also be incorporated into the THPy product. If there is no substituent present on the starting [2,2]metacyclophane derivative, this electrophile is generally incorporated at position 5 (position 2 of the THPy product; for cyclophane numbering, see Scheme 22). Otherwise, other positions can be attacked. For example, when [2,2]metacyclophane **98** is treated with dilute HNO_3 in AcOH, 2-nitro-THPy **14** is obtained in 83% (Scheme 23). On the other hand, the 5,13-dimethyl analogue **99** leads to the THPy derivative **100** nitrated in position 1.[89] Bromine also effects the cycloisomerisation of **98**. Depending on the amount of halogen added, the final

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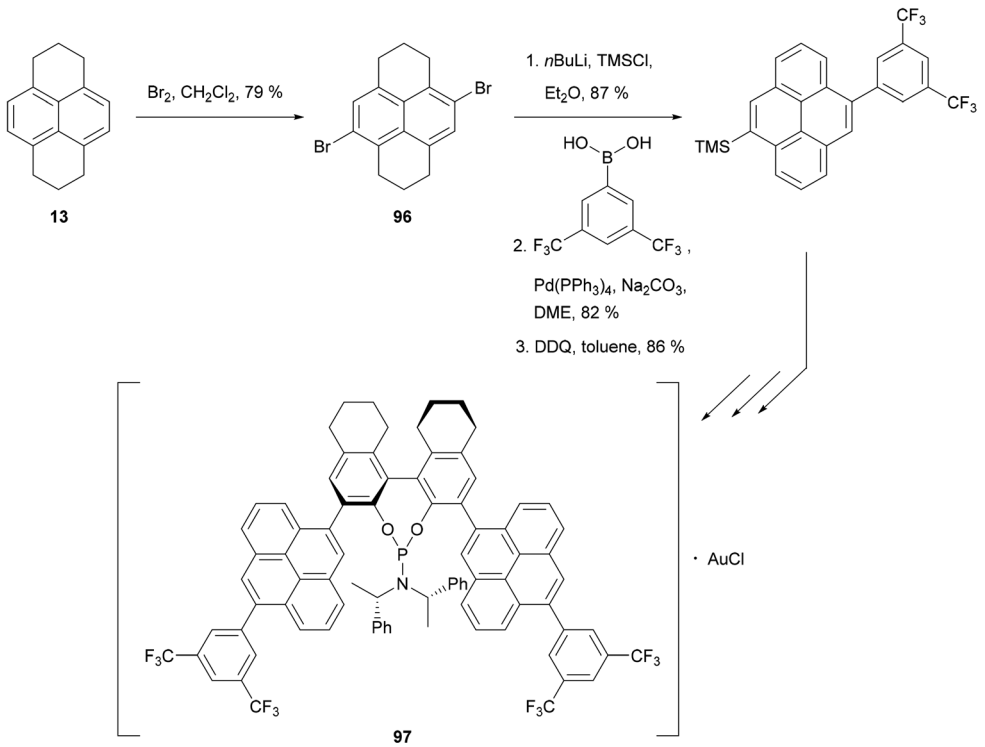
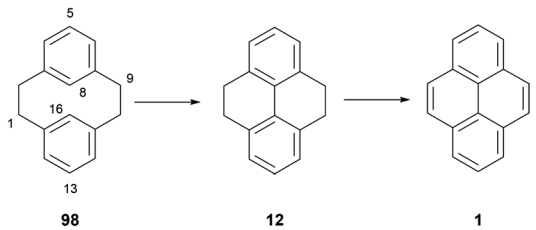


Scheme 21 A ligand for gold catalysis incorporating 4,9-disubstituted pyrene units.



Scheme 22 Transannular ring closure of [2,2]metacyclophane to THPy and pyrene.

product can be 2-bromo-THPy **51** or dibromide **101**.[90] Interestingly, when the latter reaction is carried out in the presence of iron, no bromination of the final THPy is observed. Pyridinium hydrobromide perbromide (Py·HBr_3) also gives the same result.[91] Transannular ring closure of **98** to **12**, without incorporating a substituent, can be achieved under ultraviolet irradiation in the presence of I_2. However this method is not general, and only a low yield (26%) can be achieved for the "dimethyl-analogue" **99** → **102**.[92] An improved method for the latter transformation employed $FeCl_3$ as oxidant, giving **102** in 98% yield.[93] Electrochemical oxidation has also been proposed as a cyclisation method, effective for **98** and **99** as well as the variously substituted derivatives **103–107** (giving **108–112** respectively).[94] DDQ was employed for the transannular ring closure of diamino-[2,2]metacyclophanes **113** and **114**, giving **115** and **116** respectively.[95]

Transannular ring closing reactions can be achieved even in the presence of substituent groups at carbons 8 and 16 of the [2,2]metacyclophane skeleton (Scheme 24; for numbering see Scheme 22). For instance, when alkyl groups are placed at those positions (as in **117**), Br_2–Fe or $FeBr_3$ promote THPy formation with alkyl migration to give 2,7-disubstituted products such as **118** and **119**. Bromination of some other positions is also observed when using the former reagent.[96] Cyclisation can also take place when the group in position 8 is methoxy, although in this case the MeO group is generally lost (*e.g.* **120** → **121**, **122** → **123**; see Scheme 24).[97,98]

A process closely related to the transannular ring closure of [2,2]metacyclophanes is the valence isomerisation undergone by [2,2]metacyclophane-1,9-dienes such as **124** (Scheme 25). This reaction, which may be thermal or photochemical, transforms the starting material into *trans*-15,16-dihydropyrenes such as **127**. The latter compound is readily converted to pyrene through exposure to UV light or oxygen.[99] Halogenated analogues such as **125** and **126** undergo similar ring closures, to **128** and **129** respectively. In these cases aromatisation occurs thermally with migration of a halogen atom to position 1, giving **131** and **132** respectively.[100]

Although attractive in some respects, these cyclisation methods are limited by the requirement to synthesize the starting macrocycles. Methods for preparing [2,2]metacyclophane and [2,2]metacyclophane-1,9-diene derivatives are not especially convenient. Typically, *m*-di(bromomethyl)- and *m*-di(mercaptomethyl)benzenes are combined under high dilution to give dithiamacrocycles, which are then desulfurised by oxidation/pyrolysis[94,97,98] or *S*-methylation/rearrangement/elimination[99,100] (Scheme 26). Reagents and conditions tend to be

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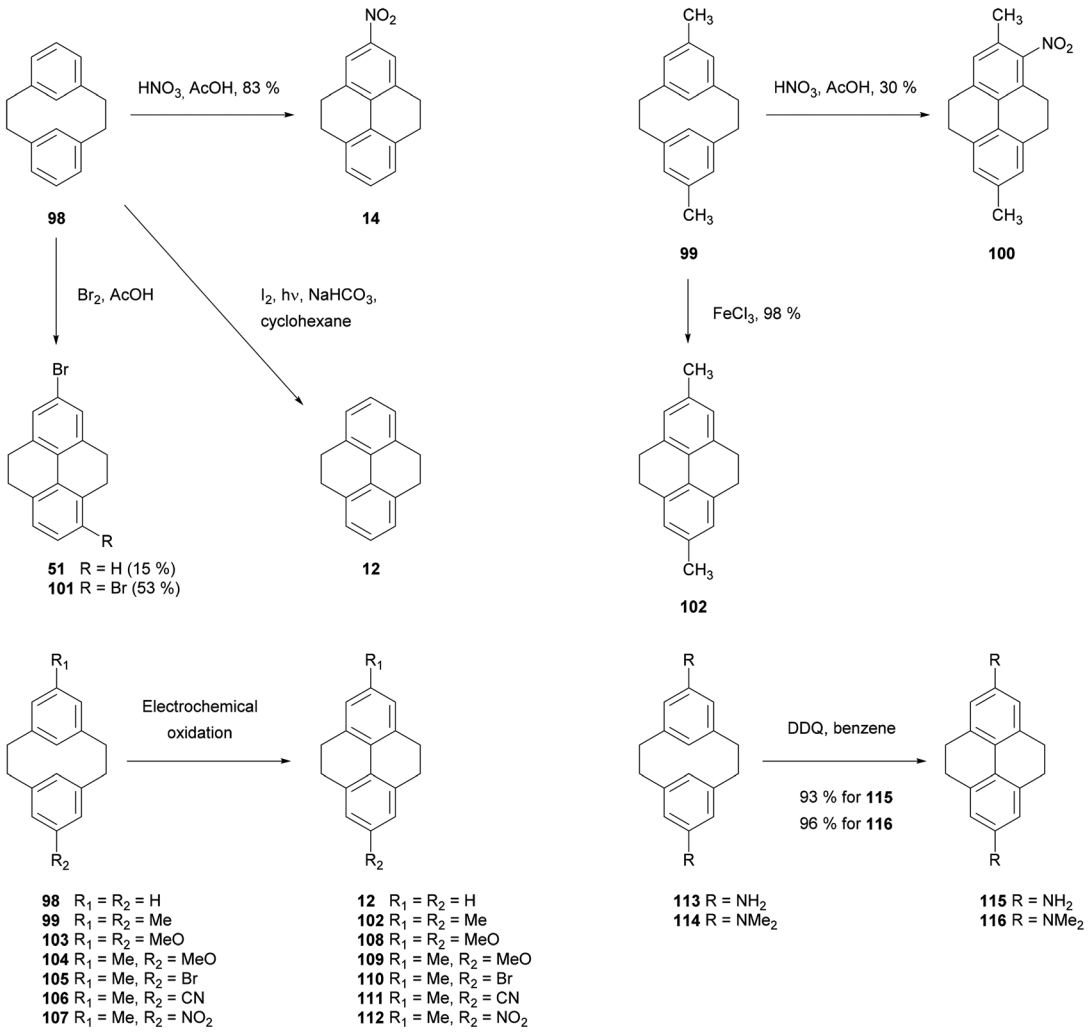
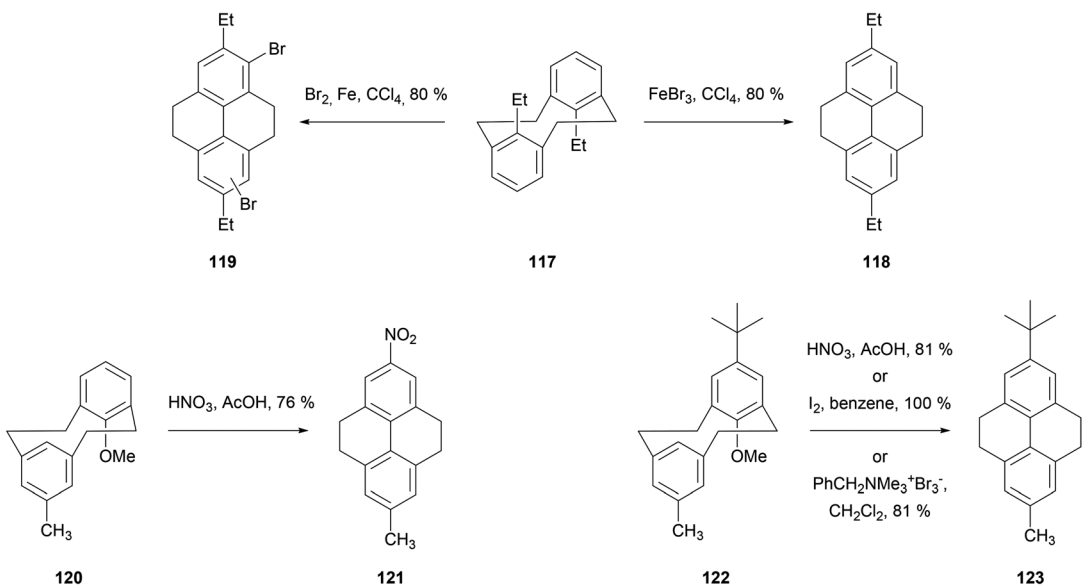


Scheme 23 THPy syntheses *via* [2,2]metacyclophane transannular ring closure.



Scheme 24 Transannular ring closures of 8,16-disubstituted [2,2]metacyclophanes.

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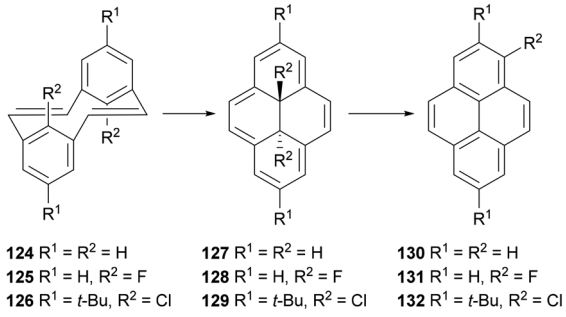
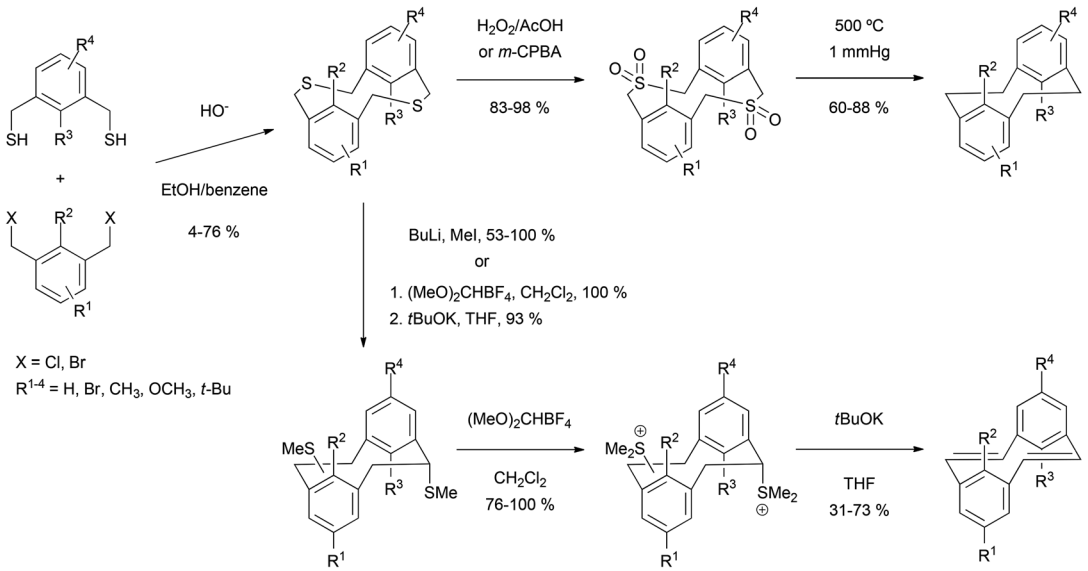
vigorous, and overall yields are often low. Furthermore, in the case of the [2,2]metacyclophane route, the conditions for the transannular ring closure do not seem to be general and require careful selection depending on substitution pattern. In addition, hydropyrenes other than THPy can be formed as by-products, and may even be obtained as the major products under certain conditions.[101,102]

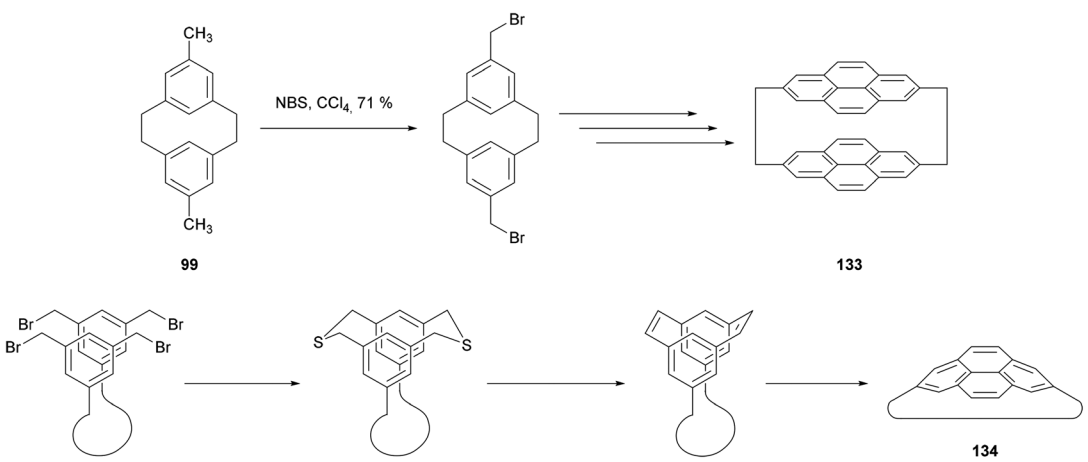


Scheme 25 Isomerisation of [2,2]metacyclophane-1,9-dienes to pyrene derivatives.

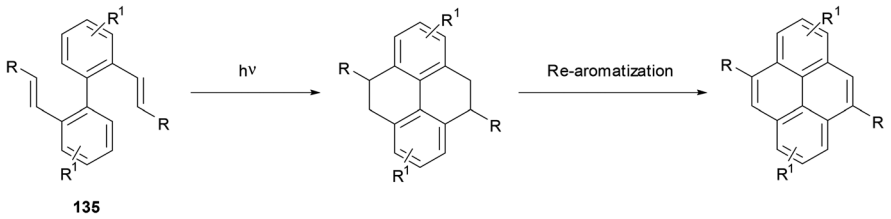
The cycloisomerisation of [2,2]metacyclophanes has found its main synthetic applications in the preparation of [2,2]pyrenophanes such as **133** (Scheme 27).[103–105] Meanwhile, the valence isomerisation/dehydrogenation of [2,2]metacyclophane-1,9-dienes has proved especially useful for the synthesis of pyrenophanes containing strained pyrene moieties, of general form **134**. As shown in Scheme 27 the method allows the framework of the pyrenophane to be constructed *via* unstrained macrocyclic precursors. The aromatisation is delayed until the final step, where it compensates for the strain generated. The method has been used quite extensively; pyrenophanes incorporating a range of tethers including alkyl, ether, phenyl and polyphenyl chains have been reported in the last decade.[106–109]



Scheme 26 Routes to [2,2]metacyclophane and [2,2]metacyclophane-1,9-diene derivatives.



Scheme 27 Synthesis of pyrenophanes *via* [2,2]metacyclophanes.



Scheme 28 Synthesis of 4,10-disubstituted pyrenes *via* photocyclisation of divinylbiphenyls.

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6. Biphenyl annulations

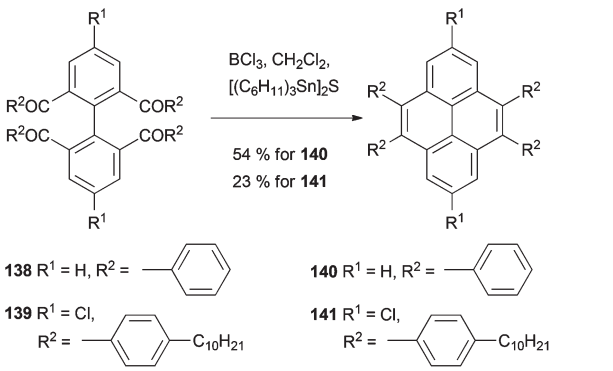
The construction of pyrenes from biphenyl cores is an attractive option, given that the starting materials are readily available through modern coupling methodology. One possibility is the photocyclisation of 2,2′-divinyl biphenyls **135** as shown in Scheme 28. The method was first demonstrated by Laarhoven for the case of styrenyl biphenyls (where R = Ph).[110] Later, the strategy was successfully applied to the synthesis of several 4,9-disubstituted THPy derivatives (Table 2).[111,112] The efficiency of the cyclisation was found to be dependent on the substituent on the vinyl group and the conditions used (particularly λ). In particular, it is important to take account of a competing [2 + 2] intramolecular cycloaddition reaction, which can be reversed by using λ = 300 nm or lower.[111] A mixture of stereoisomers results at the THPy stage, but if the objective is a pyrene derivative then oxidation of all the products leads to the same aromatic product. Müllen has extended this reaction to the preparation of 4,9-dialkylTHPy derivatives with *n*-octyl or *n*-pentyl substituents, yields for which were 80 and 85%, respectively.[113,114] The long chain 4,9-dialkylpyrenes obtained by oxidising these products were found to be highly soluble. Although the method has not been used very widely, it seems to be versatile and fairly general, and could probably be extended beyond the simple systems that have been reported so far.

A second method employing biphenyl starting materials involves the expulsion of sulphur from *ortho*-thiocarbonyl substituents. The transformation was originally demonstrated in a phenanthrene synthesis due to Wang and Zhang.[115] As shown in Scheme 29, biphenyl-based polymeric ketones **136** were treated with thionating agents (either Lawesson's reagent or boron sulfide, formed *in situ* from $[(C_6H_{11})Sn]_2S$ and BCl_3) which converted the ketones to the corresponding thiones. Refluxing in trichloroethane was required to effect this transformation, and once the thiones were formed they immediately decomposed with expulsion of molecular sulphur to give phenanthrenes, possibly *via* four-membered cyclic disulphide units as in **137**.

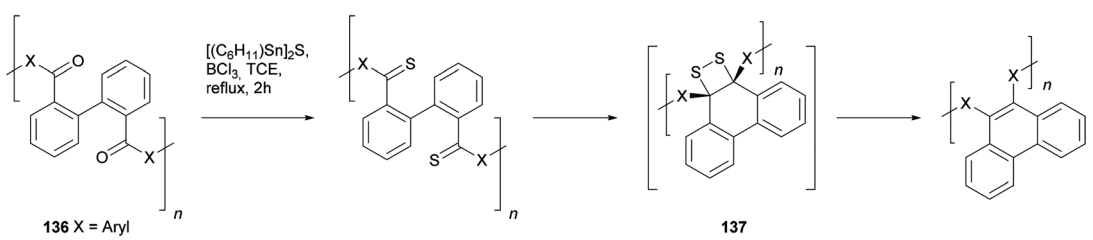
Clearly there was scope for extending this strategy to pyrene synthesis, as recognised by Müllen, Baumgarten and co-workers (Scheme 30). After constructing the tetraketone

Table 2 Photocyclisations of 2,2′-divinylbiphenyls **135**

Entry	R=	Yield of THPy derivative/%	Ref.
1	H	90	111
2	CN	71	112
3	CO_2Me	60	112
4	Ph	70	111
5	β-Naphthyl	60	111
6	*p*-MeOPh	20	111
7	*n*-Pentyl	80	113
8	*n*-Octyl	85	114



Scheme 30 Müllen's synthesis of 4,5,9,10-tetraarylpyrenes by thermal annulation of tetrathiones.



Scheme 29 Wang and Zhang's polymeric phenanthrene synthesis *via* spontaneous thermal annulation of dithione units and subsequent molecular sulphur extrusion.

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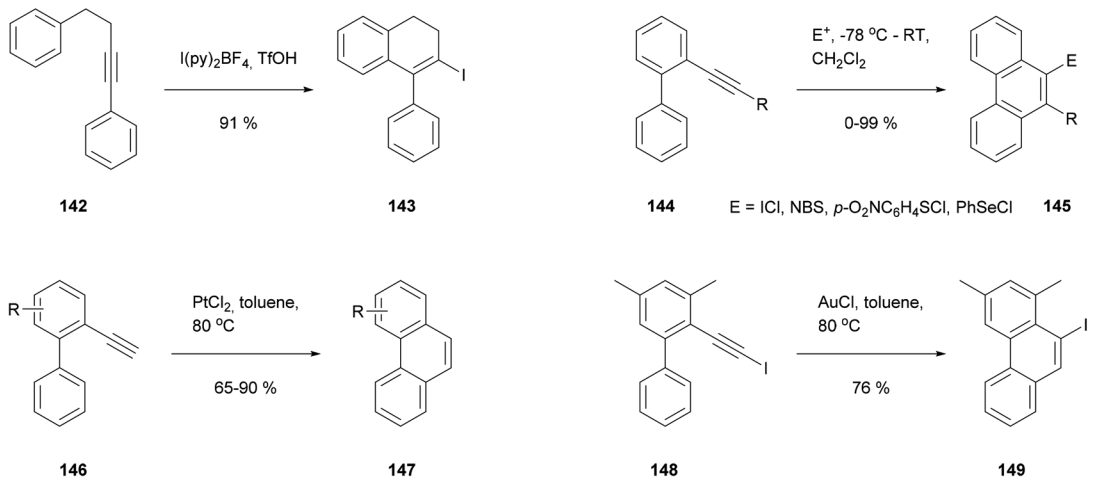


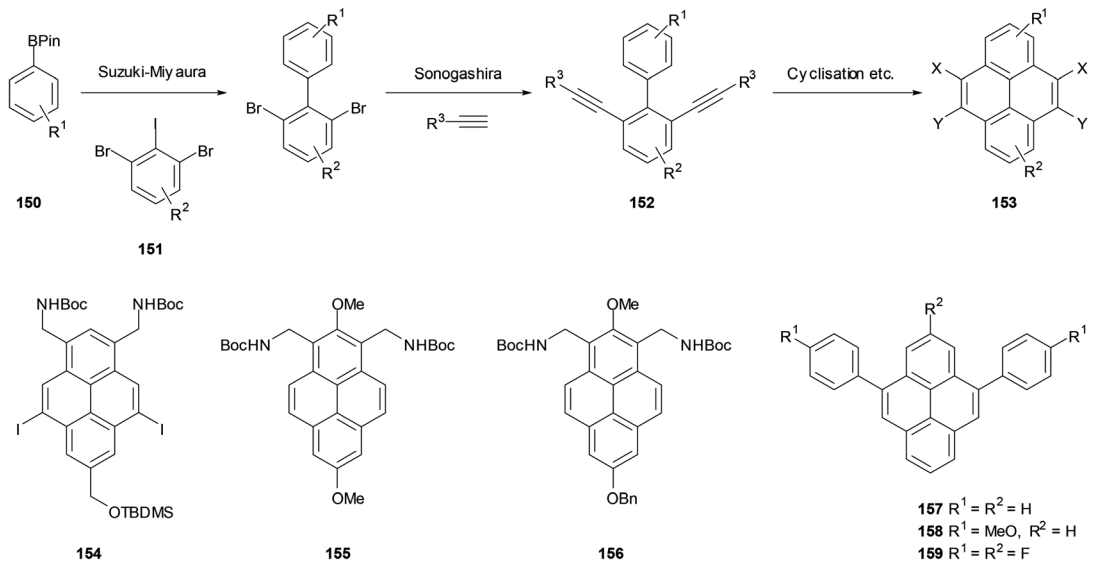
142 143 144 145 146 147 148 149

Scheme 31 Alkyne cyclisations applied to the synthesis of polycyclic aromatics.

precursor **138** these workers applied similar thionating conditions but at room temperature in CH_2Cl_2. 4,5,9,10-tetraphenylpyrene **140** was formed directly, in 54% yield. This methodology also allowed the preparation of the more complicated derivative **141**, which was subsequently polymerised.[116]

A third annulation approach is based on the cyclisation of alkynyl substituents. This type of reaction has been known for some time as a method for appending rings to aromatic nuclei (Scheme 31). An early example due to Barluenga employed $I(py)_2^+$ as an electrophilic initiator (**142** → **143**),[117] and this approach was later extended by Swager[118] and Larock[119] to make a variety of phenanthrenes (*e.g.* **144** → **145**). Meanwhile Fürstner showed that cyclisation could also occur under less acidic conditions, induced by transition metal salts.[120] $PtCl_2$ was effective for simple alkynes (**146** → **147**), while AuCl was employed for iodoalkynes (**148** → **149**). Surprisingly the latter reaction entailed a 1,2-iodine migration, away from the carbon involved in ring closure.

Our group in Bristol saw the opportunity to extend these methods to prepare a wide range of pyrenes. As shown in Scheme 32, the starting materials could be prepared from boronates **150** and iododibromides **151**, followed by Sonogashira coupling to give bis-alkynes **152**. Bis-cyclisation and further transformations could then give pyrenes **153**. In common with other biphenyl-based approaches, the versatility of the initial Suzuki coupling would allow various options for substitution outside the K-region (*i.e.* R^1/R^2 in **150–153**). The sequence was followed for a number of cases, employing Fürstner's two cyclisation protocols (**146** → **147**, **148** → **149**) for the final steps. Compounds **154–156** serve as examples of highly-substituted pyrenes prepared by this approach.[121] Similar methodology has subsequently been employed by other workers to prepare



Scheme 32 Top: synthesis of pyrenes *via* cyclisation of bis-alkynylbiphenyls. Bottom: examples of targets prepared using this strategy.

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157–159.[122,123] The electrophile-initiated cyclisations (**142** → **143**, **144** → **145**) could probably be used to extend the scope of this approach even further, but as far as we know this has not yet been attempted.[124]

7. Summary and outlook

The indirect methods described in this article provide access to a range of substituted pyrenes which would be difficult or impossible to prepare *via* direct substitutions. We hope that this compilation will facilitate the use of these methods, and thus encourage the design of new systems which exploit the optical, electronic and structural properties of the pyrene nucleus. There is clearly scope for further methodology development, and we believe the approach of "biphenyl annulation" is especially promising. As progress continues, one may hope that pyrene can play an increasingly important role as both a functional component and scaffold in materials, supramolecular and biological chemistry.

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