

Modular Synthesis of Tetracyclic Heteroarenes via Platinum-Catalyzed Cyclization of Ethynylbiaryl Precursors

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Polycyclic heteroarenes that contain internal thiophene, furan and pyrrole rings are well-documented materials due to their presence in fossil fuels and their importance in organic optoelectronic applications. Accordingly, a variety of methods are available for their synthesis. In this report we prepared naphthannulated 4-membered heteroarene isomers through the PtCl₂-catalyzed 6-*endo* cyclization of ethynylbiaryls. Isomers were accessible from two structurally different precursors that contained the ethynyl subunit in different positions. We synthesized two pairs of thiophene-based ethynylbiaryls where each pair would lead to the same tetracyclic isomer and explored their reactivity in the Pt-catalyzed transformation. The

formation of a detectable amount of inseparable side-product was observed when the alkyne was introduced onto the benzene ring of the biaryls. This is suggested to be an *exo*-methylene group containing derivative that forms via a 5-*exo* cyclization pathway. Similarly, naphthannulated benzofuran isomers were prepared following the same strategy and an *exo*-methylene-containing side product was observed when the alkyne unit was on the benzene ring of the biaryl. Finally, novel synthesis methods were described for benzo-fused carbazoles from ethynylbiaryls containing an alkyne either on the heterocyclic ring or on the phenyl substituent attached to the indole ring. No side-product formation was detected in this case.

Introduction

Interest in polycyclic heteroarenes with an internal thiophene, furan or pyrrole ring spans the fields of geochemistry, petrochemistry, environmental science and advanced organic materials. These structures are present in nature as components of fossil fuels and also form through combustion processes of these carbon-based energy sources. In geochemistry they are interesting as markers of geothermal evolution processes and to track oil migration.^[1–4] As model compounds to study the composition and aggregation of asphaltenes^[5] in crude petroleum they are of petrochemical interest. In the atmosphere they are monitored as environmental pollutants^[6] and potential source of health hazards.^[7,8] Furthermore, they can be used as chromophores in organic optoelectronics,^[9–13] hence, access to pure samples of these materials is of wide interest.

Synthetic methods reported for the preparation of naphthannulated benzoheteroarenes mainly focus on derivatives having a terminal thiophene ring, while the synthetic routes

resulting in an internal thiophene, furan and pyrrole moieties are comparably limited. Isomeric naphthannulated 4-membered heteroarenes can be prepared via different methods,^[14–27] among which the metal catalyzed 6-*endo*-dig cyclization of ethynylbiaryl type structures provides a straightforward and atom-economic option.^[22,28,29] The use of π acids such as PtCl₂, AuCl₃, InCl₃ as catalysts renders the process safe and operationally simple. Synthesis of [2,1-*d*]naphthannulated benzothiophene and benzofuran (Figure 1) was reported using PtCl₂ catalyst for cyclization of the precursor alkynyl derivatives.^[9] Nonetheless, reports on the use of this catalyst in the synthesis of polycyclic heteroarene derivatives from ethynylbiaryls are uncommon or in the case of fused carbazoles is even unprecedented.^[9,30–32] Preparation of heteroarylethynyl derivatives in a cyclization/direct alkynylation domino reaction was reported by PtCl₂ and AuCl₃ catalysis using ethynylbenziodoxole hypervalent iodine compounds as stoichiometric reagents.^[9] A considerable drawback of this elegant chemistry is the multi-step synthesis of the active ethynylbenziodoxole reagent, which is accessed in five steps with roughly 10% overall yield. Therefore, synthesis of heteroarylethynyl intermediates by catalytic cross-coupling of the respective aryl halides with acetylenes seems a more feasible alternative, which only requires preformed halides.

Our objective was to synthesize various rigid naphthannulated heteroarenes via heteroaryl-phenyl intermediates having terminal alkyne substituent either at position 2 or 3 of the heteroaromatic ring or at position 5 of the phenyl group, and to use platinum(II) chloride to perform 6-*endo*-dig electrocyclization (Figure 1). The terminal alkyne could be attached either to the benzene unit or to the heteroarene unit of the biaryl system without, formally, affecting the outcome of the reaction. Notably, Pt-catalyzed cyclization of such precursors with differ-

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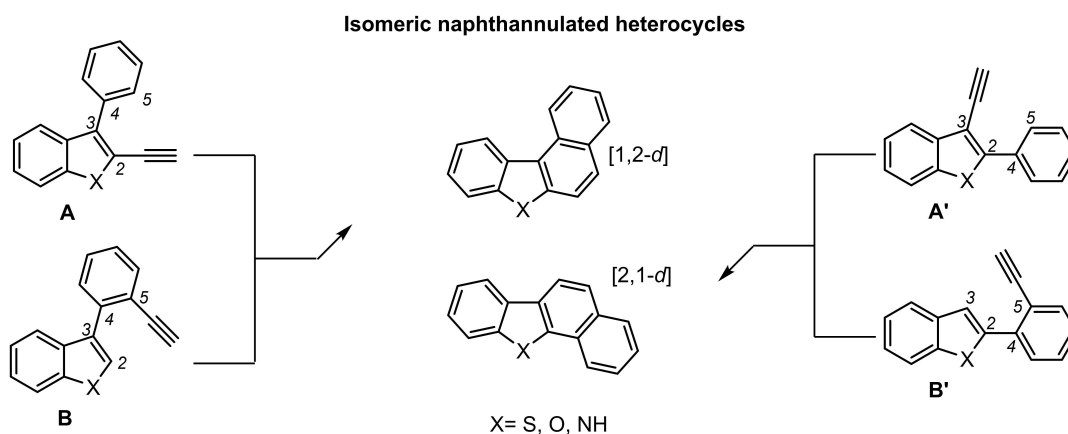


Figure 1. Synthesis of isomeric naphthannulated heterocycles from various ethynylbiaryls.

ent structures could lead to the same target molecules (Figure 1), thus widening the range of potential starting materials and ultimately aiding modularity in the synthesis of these structures. The availability of alternative synthetic routes is especially useful when functional group tolerance is important. Moreover, synthetic routes that involve intermediates with different reactivities could facilitate functionalization at different stages of the synthesis. Herein, we explore the effect of the different functional group patterns in the biarylacetylene precursors on the outcome of the cyclization reaction.

Results and Discussion

In the following, we first present the synthesis of thiophene containing ethynylbiaryls of type **A**, **B**, **A'** and **B'** (Figure 1) and the results of their $PtCl_2$ -catalyzed cyclizations to access isomeric heteroarenes **7** and **18** (Scheme 1 and 4). We then systematically extend the synthesis to furan and pyrrole analogues.

Synthesis of Naphthannulated Benzothiophenes **7** and **18**

To probe the effect of the alkyne position on the formation of naphthannulated benzothiophene **7** we prepared both alkynyl aryl precursors **6** and **9**, where the alkyne is attached to both the thiophene ring and the benzene ring, respectively (Scheme 1). The synthesis of compound **6** was started from benzothiophene, which was brominated at position 3 of the heterocycle with NBS in a mixture of $CHCl_3$ and glacial acetic acid. Subsequently, Suzuki coupling of the resulting 3-bromobenzothiophene (**2**) yielded the 3-phenyl derivative (**3**), which was brominated with NBS in DMF to access compound **4**. The silyl-protected acetylene functionality was introduced through a Sonogashira reaction (**5**) which, upon deprotection, yielded terminal acetylene **6**. Acetylene **6** was subjected to a $PtCl_2$ -catalyzed intramolecular cyclization^[28,30] in toluene at 100 °C to yield the target benzo[*b*]naphtho[1,2-*d*]thiophene **7**. The overall yield of this synthetic route was 47%.

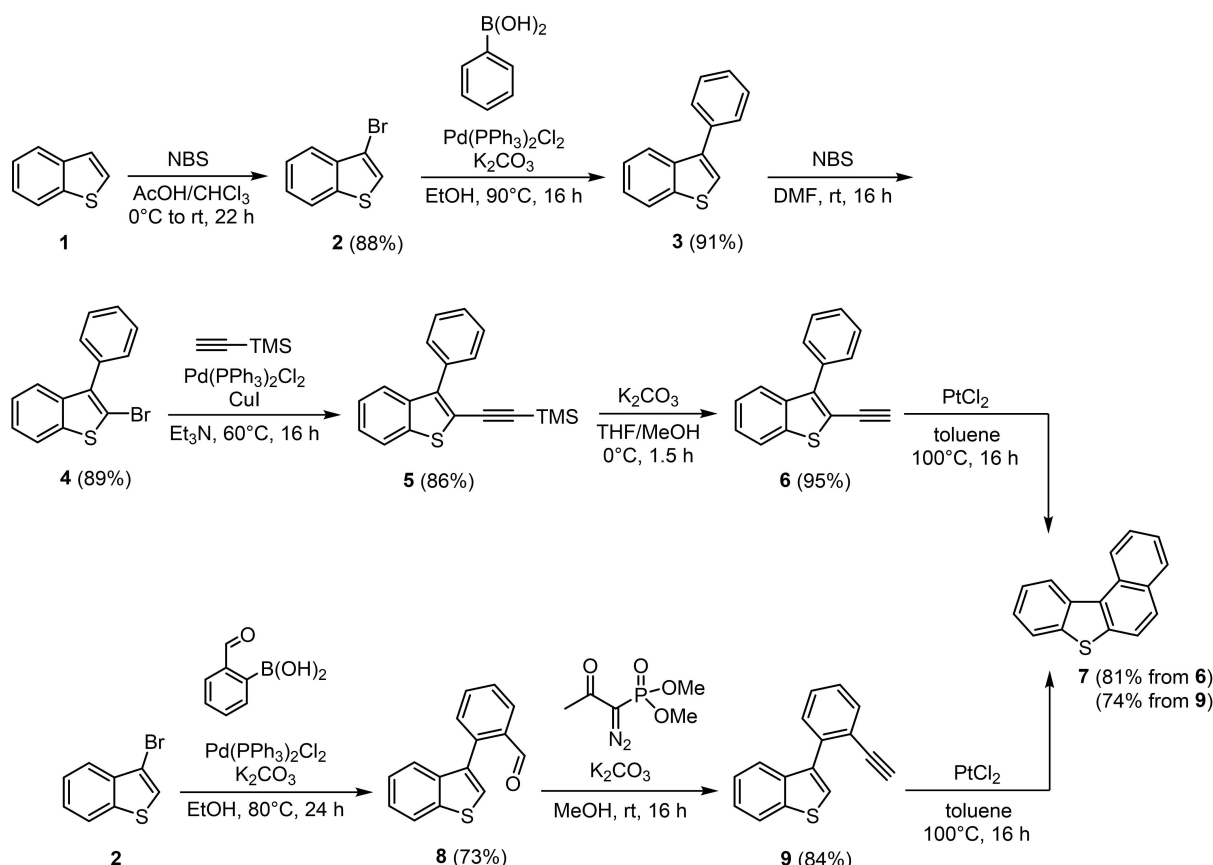
Compound **9**, having the acetylene on the benzene ring, was synthesized from 3-bromobenzothiophene **2** (Scheme 1). In the first step **2** was reacted with 2-formyl-phenylboronic acid in a Suzuki coupling reaction leading to **8**. In the next step, the aldehyde functionality of **8** was converted to an acetylene group through a Gilbert-Seifert homologation using the Bestmann-Ohira reagent to provide alkyne **9**.

$PtCl_2$ -promoted cyclization of **9** furnished the expected naphthannulated benzothiophene **7**, however, in this case, an inseparable mixture of two products (99:1) was detected in the 1H NMR spectrum (see Figure S12 in the Supporting Information). Based on literature comparison,^[33] the minor product is suggested to be the *exo*-methylene derivative *exo*-**7** (Scheme 2), which forms via the 5-*exo* cyclization pathway from compound **9**.^[28,32,34] Notably, this side-product was not detected when the cyclization was carried out from **6**, where the acetylene group is attached to the thiophene ring.

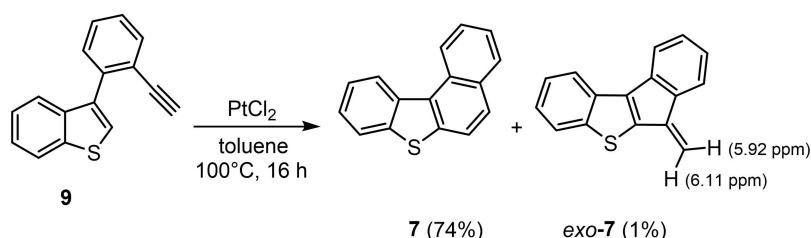
To our knowledge, $PtCl_2$ -catalyzed 5-*exo*-dig cycloisomerization of heterocyclic 2-ethynylbiaryls to 9-methylidene fluorene (*exo*-**7**) type derivatives has not been reported yet. Unexpected ring-expansion cycloisomerization was detected during $PtCl_2$ -catalyzed reaction of 2-(*o*-ethynylphenyl) thiophene derivatives, while 6-*endo* cyclization occurred when these compounds were heated at 180 °C with DBU in NMP. On the other hand, 5-*exo*-dig cyclization was dominant in the presence of $Pd(OAc)_2$ and 1,1'-bis(*di*-*i*-propylphosphino)ferrocene as catalyst and ligand.^[34] A palladium-catalyzed cycloisomerization of 2-ethynylbiaryls was also reported *via* successive hydropalladation and aromatic C–H activation in the presence of weak acid to produce 9-methylidene fluorenes and 6-methylene-6*H*-benzo[*b*]indeno[1,2-*d*]thiophene.^[35]

In the synthesis of the isomeric naphthannulated benzothiophene **18** (Scheme 3 and Scheme 4) a similar strategy was applied to that we used for the preparation of compound **7**. Like in the previous case, acetylene precursors of type **A'** and **B'** (Figure 1) were prepared.

Initially, commercial 2-bromobenzothiophene **10** was converted to its phenylated derivative **11** via a Suzuki coupling reaction, which was subsequently brominated with NBS yielding compound **12** (Scheme 3). In the following step, however,



Scheme 1. Synthesis of compound 7 from ethynylbiaryls 6 and 9.

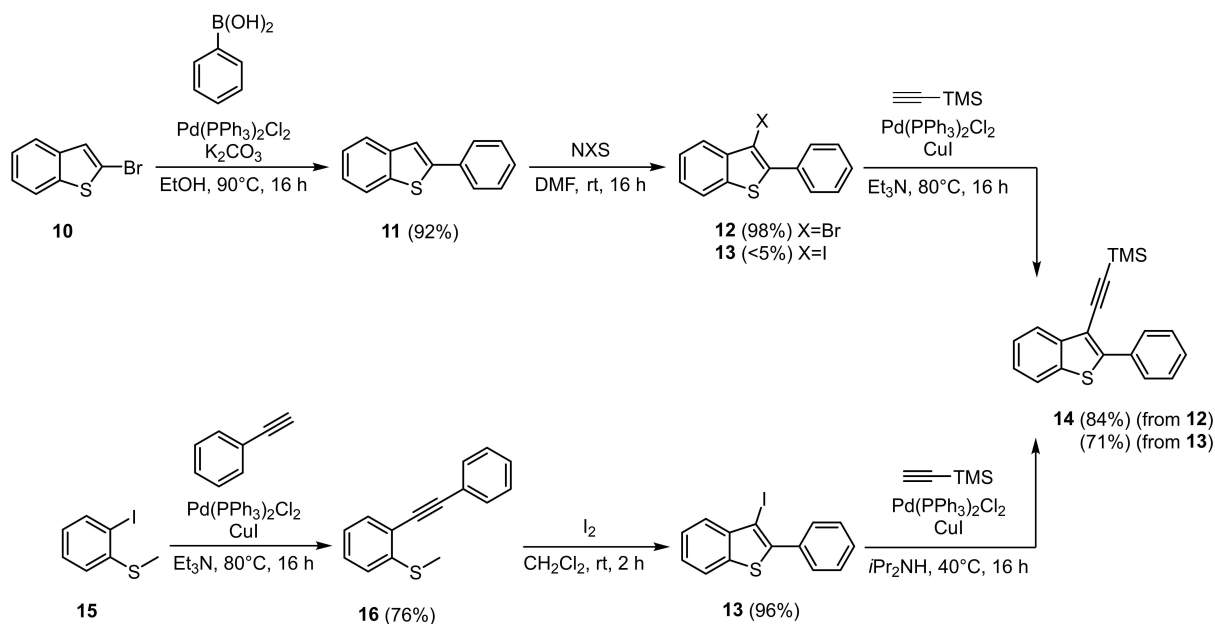


Scheme 2. Products of the cyclization of 9.

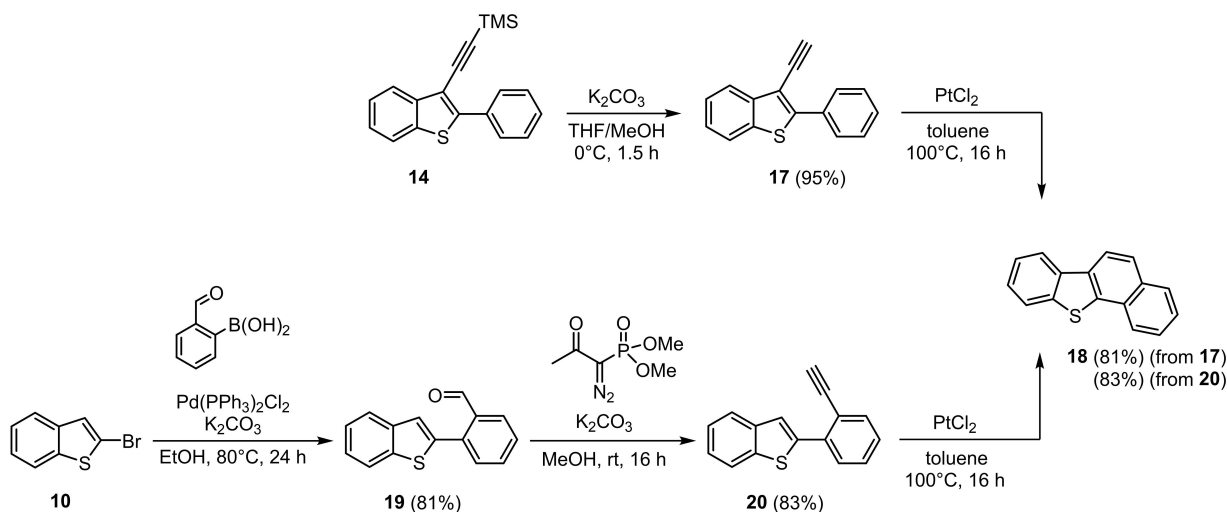
trimethylsilylacetylene reacted very sluggishly in the Sonogashira coupling with **12**. Even after prolonged reaction times (up to 2 weeks) 30% of the heteroaryl bromide remained unreacted. To prepare the expectedly more reactive 3-iodo derivative **13**, we attempted the iodination of compound **11** with NIS in DMF. However, no iodinated product formed, hence we turned to an alternative route to access **13**. Our modified synthetic strategy was based on the electrophilic cyclization of 2-(phenylethynyl) thioanisole **16** with I_2 ,^[36] which proved to be an efficient method to access **13**. Compound **16** was prepared from **15** in a Sonogashira reaction with phenylacetylene. Using iodide **13** for the synthesis of acetylene **14** improved the isolated yield moderately compared to what was obtained from bromide **12**. Notably, the synthesis of the TIPS-protected analogue of compound **14** has been reported via a domino cyclization-alkynylation sequence from **16** using a hypervalent

iodine reagent.^[9] As the synthesis of the active hypervalent iodine reagent required five steps, we judged the two-step I_2 promoted cyclization/Sonogashira coupling process operationally simpler. The TMS-group of **14** was deprotected to access alkyne **17** for the final Pt-catalyzed cyclization, which proceeded well and delivered naphthannulated benzothiophene **18** in a good yield (Scheme 4).

Compound **20**, having the alkyne on the benzene ring, was prepared from bromide **10** through a Suzuki coupling with 2-formyl-phenylboronic acid as the first step. The aldehyde group of the resulting compound **19** was again converted to an alkyne through the Gilbert-Seifert homologation using the Bestmann-Ohira reagent. This alkyne (**20**) could be converted to naphthannulated benzothiophene **18** with similar efficiency as compound **17**. However, like in the cyclization of compound **9** that contained the acetylene group on the benzene ring, a



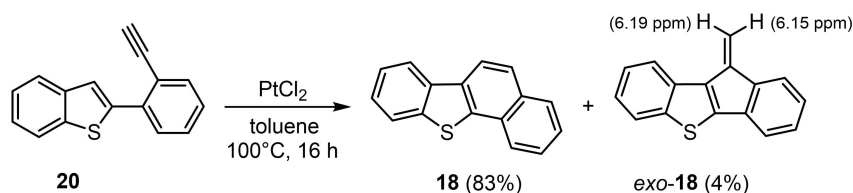
Scheme 3. Approaches to the synthesis of 14.



Scheme 4. Synthesis of compound 18 from ethynylbiaryls 17 and 20.

small, but detectable amount of the 5-*exo* cyclization product *exo*-18 was formed (Scheme 5) (see also Figure S33 in the Supporting Information). Notably, in a literature report, no *exo*-methylene product was observed from 20 when the cycloisomerisation took place in the presence of η^6 -(*p*-

cymene)RuCl₂(PR₃) and two equivalents of AgPF₆ in chlorobenzene at 120°C over 20 h.^[22] We suspect the difference in reactivity between 17 and 20 (also 6 and 9) that leads to the *exo* side-products may be a result of electronic difference of the corresponding terminal acetylene moieties (reflected also by



Scheme 5. Products of the cyclization of 20.

their ^1H NMR chemical shifts; see Supporting Information). However, more detailed explanation for the competing pathway requires further mechanistic studies.

Due to the observed differences in the reactivity of isomeric ethynylthiophenes, we explored the transformation of **B** and **A'** type (Figure 1) furan and pyrrole analogues.^[9,22,28]

Synthesis of Naphthannulated Benzofurans **31** and **36**

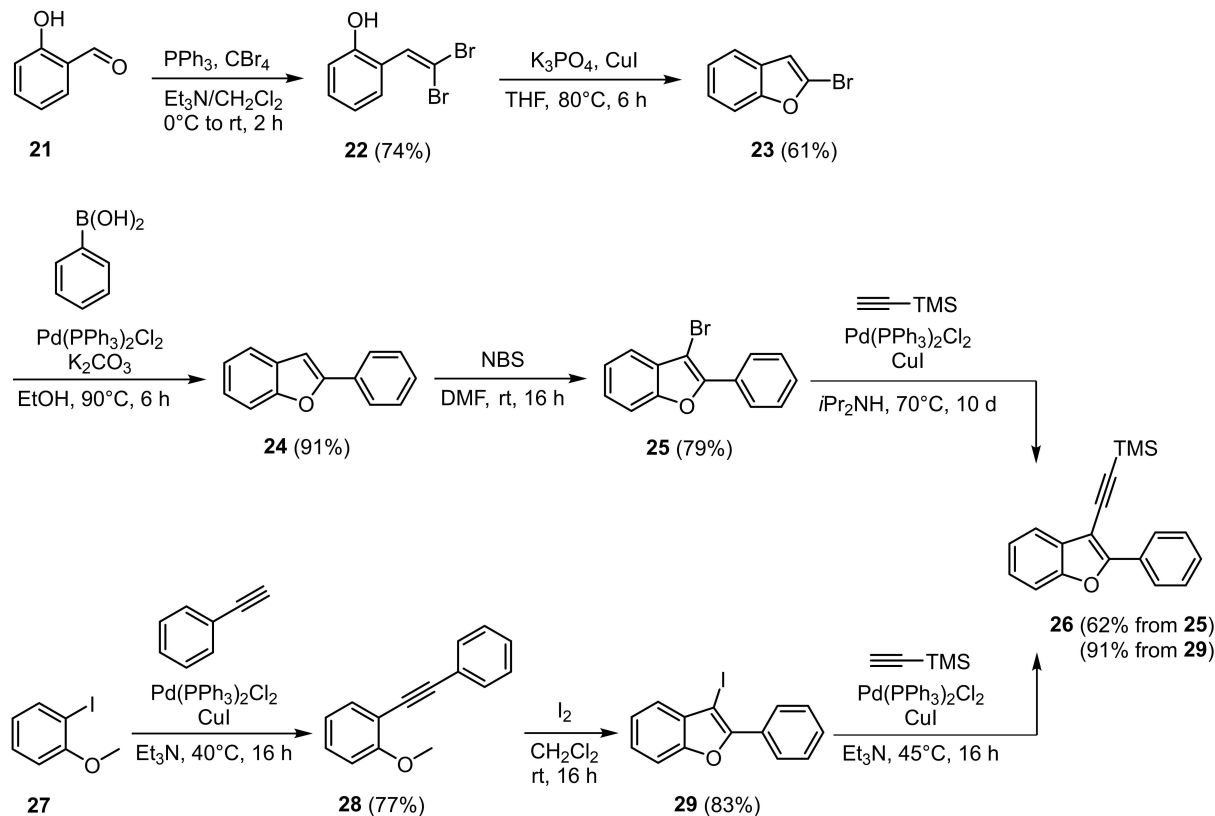
Initially, the ethynylbenzofuran (**26**) precursor was synthesized from salicylaldehyde **21** that was converted to the corresponding *gem*-dibromoolefin **22** (Scheme 6). Subsequently, a Cu-catalyzed intramolecular cross-coupling of **22** yielded 2-bromobenzofuran **23**,^[37] which was arylated with phenylboronic acid in a Suzuki coupling reaction. Arylbenzofuran **24** was brominated with NBS, and the corresponding heteroaryl bromide **25** was submitted to a Sonogashira coupling with TMS-acetylene to furnish compound **26**. Similarly to what was observed in the Sonogashira coupling of the thiophene analogue of **25**, this reaction was incomplete even after 10 days.

As an attempt to improve the yield of the Sonogashira reaction, the iodinated derivative (**29**)^[38] was synthesized from 2-(phenylethynyl) anisole through the I_2 promoted cyclization reaction^[39] that was successfully used in the synthesis of the thiophene analogue **13**. In addition to **29**, a byproduct, unreported 1-(1,2-diiodo-2-phenylvinyl)-2-methoxybenzene (6%), was also isolated and identified as an iodo adduct of

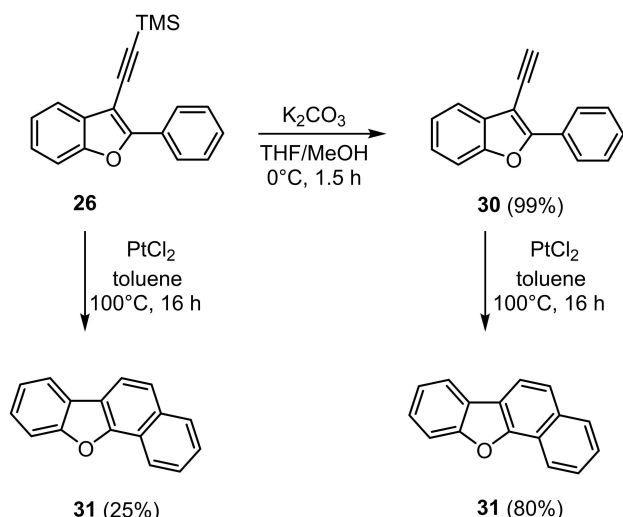
acetylene **28** (see structure S1 in the Supporting Information). The Pd-catalyzed coupling of iodide **29** with TMS-acetylene was more efficient for the synthesis of **26**. Alternatively, compound **29** was also prepared from 2-iodophenol through a Sonogashira reaction^[40]/PtCl₂ catalyzed cyclization sequence to access **24**, which was iodinated using NIS^[41] (See Scheme S1 in the Supporting Information).

To access naphthannulated benzofuran **31**, first the TMS-protecting group in **26** was removed, then the free acetylene **30** was submitted to the conditions of the Pt-catalyzed cyclization (Scheme 7). To our experience, acetylene **30** was unstable, hence, we used this compound in the cyclization reaction immediately after deprotection, without further purification. The moderate yield that was obtained prompted us to test the stable TMS-protected acetylene **26** in the cyclization reaction. Notably, TMS-protected **26** could be converted to the corresponding naphthannulated benzofuran **31** in lower yield (25%), which was inseparable from unreacted **26** (9%). Importantly, no *exo*-methylene-type side-product was detected in the Pt-catalyzed cyclizations of **26** and **30**.

Synthetic methods^[42,43] have been reported for the preparation of naphtho[2,1-*b*]benzofuran **36** using less common intermediates and catalytic conditions that yield isomeric mixtures of products. In our synthesis (Scheme 8), 3-bromobenzofuran **33** was prepared from benzofuran **32** in two steps,^[44] which was transformed into benzofuran-linked *o*-phenylaldehyde **34** via a Suzuki reaction similarly to the synthesis of **8** and **19**. Subsequent homologation using the



Scheme 6. Approaches to the synthesis of **26**.



Scheme 7. Synthesis of compound **31** from ethynylbiaryls **26** and **30**.

Bestmann–Ohira reagent yielded the alkynyl derivative **35** from which PtCl_2 -catalyzed ring closure provided the required naphthannulated benzofuran product **36** containing traces of *exo*-methylene byproduct **37**.

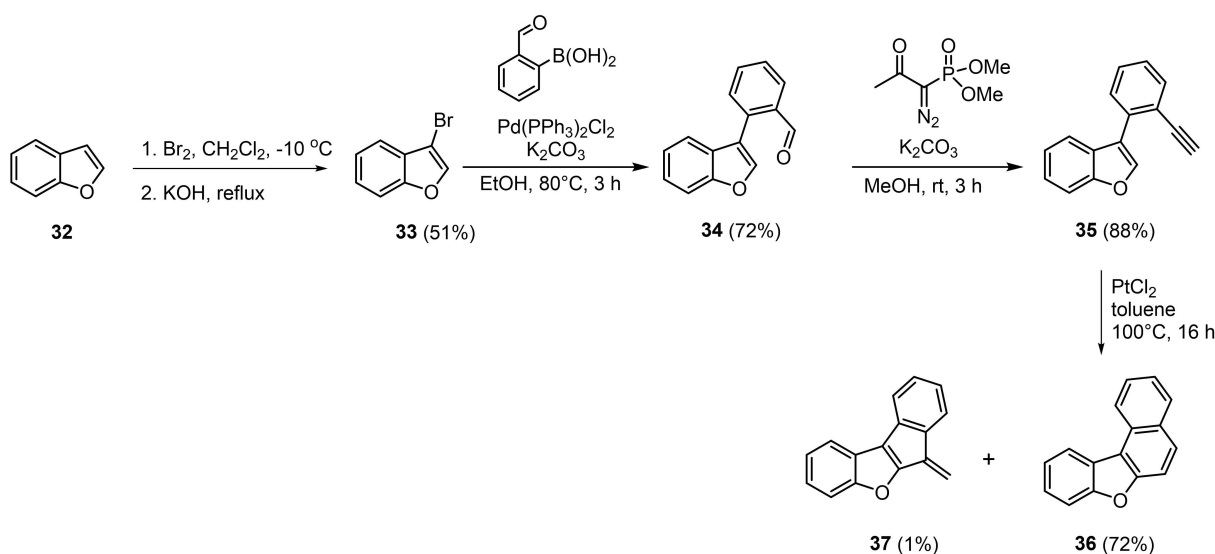
Synthesis of Benzo-Fused Carbazoles **46** and **52**

The synthesis of benzo-fused carbazole **46** was performed starting from iodoaniline **38** to avoid the lower-yielding and slower Sonogashira coupling (Scheme 9), which was found through the bromide-derivative in the synthesis of the *S*- and *O* analogues above. To access **41**, first 2-(phenylethynyl)aniline **39** was converted into 2-phenylindole **40** using a PtCl_2 -catalyzed cyclization.^[45] A one-step synthesis of **40** was reported from *o*-iodoaniline via a Sonogashira coupling/annulation sequence^[46]

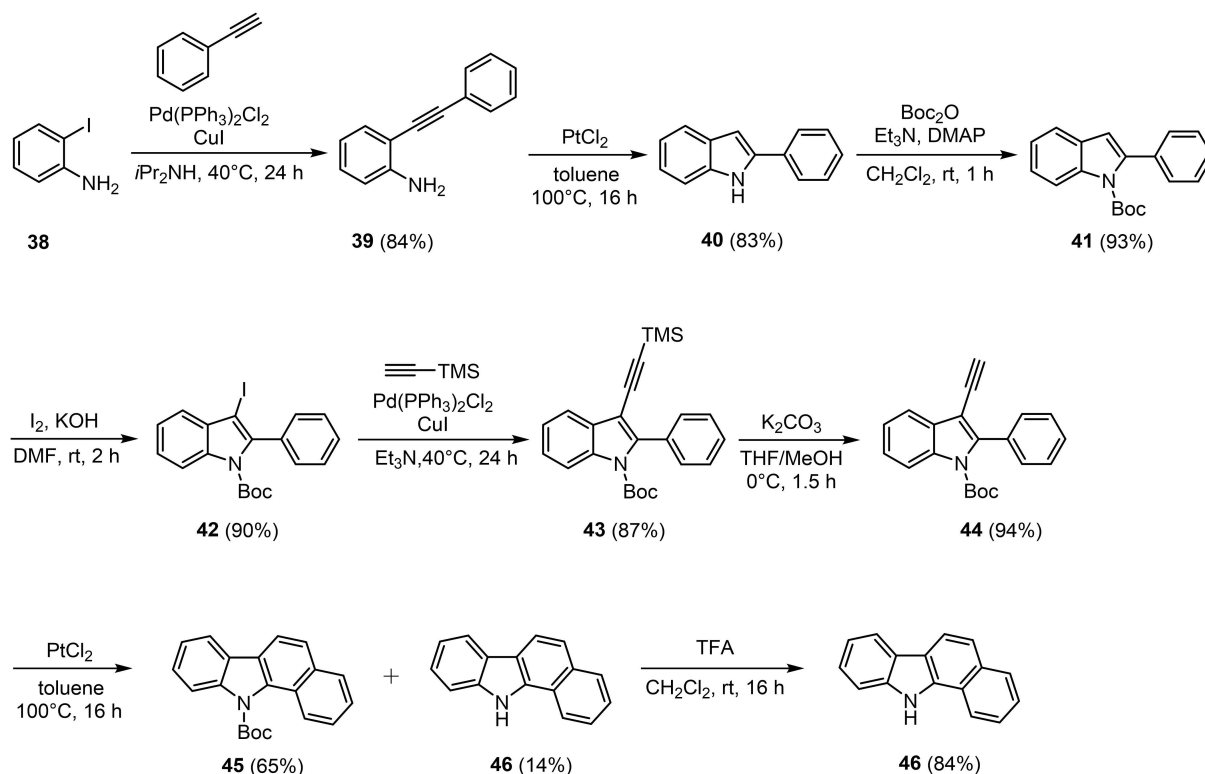
using PdCl_2 catalyst and PPh_3 ligand. Unfortunately, we were unsuccessful reproducing the literature method and the isolated product was assigned as **39**. The protection of the indole NH-group in **40** was necessary before iodination as the unprotected 3-iodoindole derivative was prone to degradation. Iodination of **41** using I_2/KOH in DMF^[47] provided **42**, which was coupled with TMS-acetylene under Sonogashira conditions. Deprotection of the TMS-acetylene in **43** and the following PtCl_2 -catalyzed cyclization of **44** yielded both *N*-Boc-protected **45** (65%) and target 11*H*-benzo[*a*]carbazole **46** (14%), which formed by the loss of the Boc group sensitive to the mildly acidic platinum salt and the elevated temperature. Deprotection of Boc-protected **45** with TFA also resulted in the formation of **46**. No *exo*-methylene-type side-product was detected after the PtCl_2 -catalyzed cyclization step.

Preparation of **46** via the intermediate in which an *o*-alkynyl substituted phenyl ring was attached to the indole moiety at position 2 was not attempted since cyclization was reported to yield isomeric mixture of indolo[2,1-*a*]isoquinoline and 11*H*-benzo[*a*]carbazole **46** (11% and 75%, respectively).^[28]

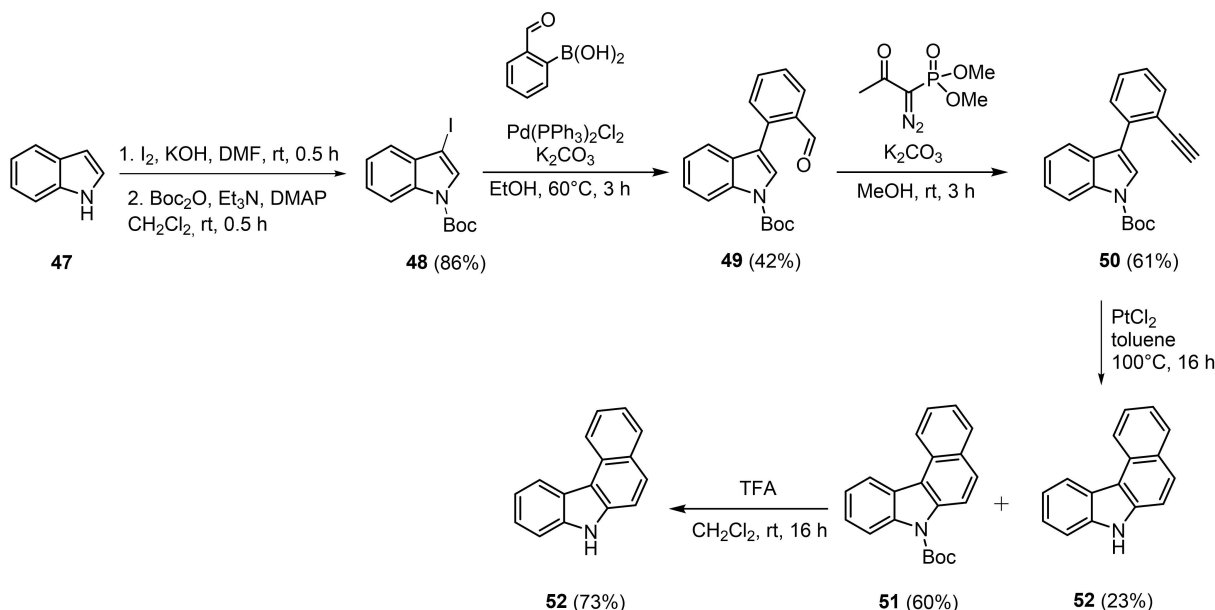
For the preparation of benzannulated carbazole **52** (Scheme 10) the alkynylphenyl moiety was introduced to position 3 of the indole. Synthesis of **52** started from indole (**47**), which was iodinated, and then protected with a Boc group to provide **48**.^[47] Suzuki coupling of this intermediate with 2-formyl-phenylboronic acid yielded aldehyde **49** in moderate yield, which was converted to alkynyl derivative **50** in a Gilbert–Seifert homologation reaction. During cyclization with PtCl_2 catalyst at 100°C , in addition to the formation of Boc-protected **51**, unprotected target molecule **52** was also isolated indicating that the Boc group is labile under these conditions. Finally, 7*H*-benzo[*c*]carbazole **52** was obtained after acidic cleavage of the Boc group from **51**.



Scheme 8. Synthesis of compound **36**.



Scheme 9. Synthesis of compound 46.



Scheme 10. Synthesis of compound 52.

Conclusions

We studied the synthesis of isomeric naphthannulated 4-membered heteroarenes from structurally different ethynylbiaryl precursors using the PtCl_2 -catalyzed 6-*endo* cyclization reaction. Ethynylbiaryls that contained the ethynyl unit either on the attached phenyl group or on the heteroaromatic ring of

the biaryls were prepared. While the cyclizations were found to be efficient in general, a side-reaction was observed for S- and O-heteroarenes in the cases where the alkyne moiety was attached to the benzene unit of the biaryls. The undesired side product is suggested to be the product of a competing 5-*exo* cyclization pathway. The side-products containing exomethylene groups accounted for only minor quantities (1–5%),

but their separation from the heteroring-fused major products proved to be challenging. Hence, care must be taken when choosing starting materials and methodologies for the synthesis of polycyclic S- and O-heteroarenes. In the synthesis of benzo-fused carbazoles prepared from 3-alkynyl-heteroaryl precursor no 5-exo cyclization pathway was detected.

Supporting Information

Detailed synthetic procedures, characterization data and copies of ^1H NMR and ^{13}C NMR spectra.

Additional references cited within the Supporting Information.^[48–69]

Acknowledgements

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

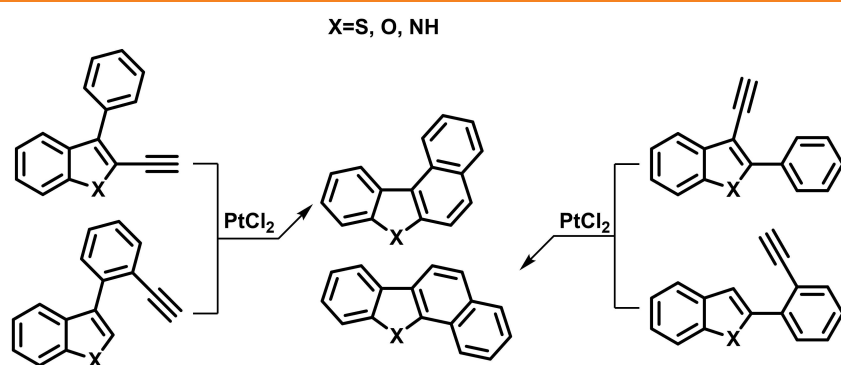
Keywords: acetylene · cyclization · heteroarenes · platinum · synthesis

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The synthesis of naphthannulated S-, O-, and N-heteroaryl compounds from isomeric ethynylbiaryl starting

materials using a $PtCl_2$ -catalyzed cyclization reaction is reported.

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Modular Synthesis of Tetracyclic Heteroarenes via Platinum-Catalyzed Cyclization of Ethynylbiaryl Precursors

