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Iodine/Palladium Approaches to the Synthesis of Polyheterocyclic Compounds

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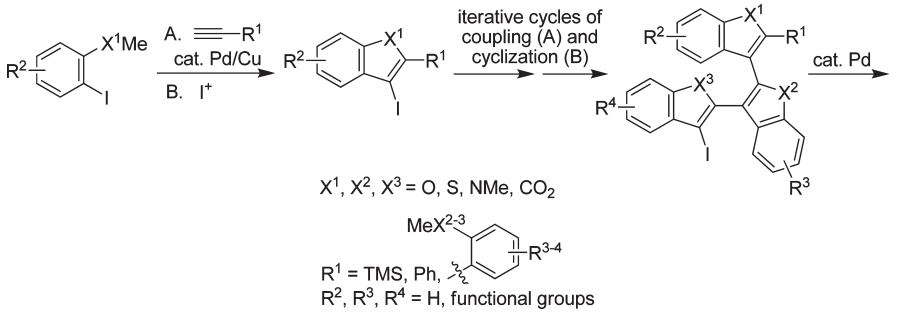

A simple, straightforward strategy for the synthesis of polyheterocyclic compounds (PHCs) is reported, which involves iterative cycles of palladium-catalyzed Sonogashira coupling, followed by iodocyclization using I_2 or ICl. A variety of heterocyclic units, including benzofurans, benzothiophenes, indoles, and isocoumarins, can be efficiently incorporated under mild reaction conditions. In addition, variations of this strategy afford a variety of linked and fused PHCs.

Introduction

The iodocyclization of alkynes has emerged as an efficient tool for the synthesis of important heterocycles and carbocycles.[1] We and others have utilized this methodology (Scheme 1) for the synthesis of benzofurans,[2] furans,[3] benzothiophenes,[4] thiophenes,[5] benzopyrans,[6] benzoselenophenes,[7] selenophenes,[8] naphthols,[9] indoles,[10] quinolines,[11] isoquinolines,[12] α-pyrones,[13] isocoumarins,[13] naphthalenes[14] and polycyclic aromatics,[15] isoxazoles,[16]

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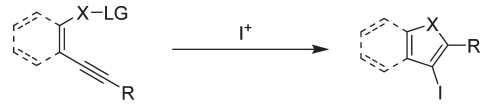
SCHEME 1. Iodocyclization Reaction



LG = leaving group
X = O, NMe, S, CO_2, CONHR, C=N *etc.*
R = alkyl, aryl, vinylic, TMS

chromones,[17] bicyclic β-lactams,[18] cyclic carbonates,[19] pyrroles,[20] furopyridines,[21] spiro[4.5]trienones,[22] coumestrol and coumestans,[23] furanones,[24] benzothiazine 1,1-dioxides,[25] isochromenes,[26] etc.[27]

In general, iodocyclization is a very efficient reaction, proceeds under very mild reaction conditions, and exhibits a very broad scope in terms of the functional group/substituent compatibility. As iodine is known to be an excellent handle for further elaboration through transition-metal-catalyzed cross-couplings, especially palladium-catalyzed transformations,[28] the iodocyclization products are ideal substrates for further functionalization and a rapid increase in molecular diversity. These features prompted us to test the applicability of this strategy for building more complex systems containing multiple heterocyclic units. Polyheterocyclic compounds (PHCs) of this type have found applications in biological[29] as well as materials chemistry.[30] We here present several versatile synthetic strategies involving iodocyclization and subsequent palladium-catalyzed transformations for the synthesis of PHCs.

Results and Discussion

The general scheme employed by us for polyheterocycle synthesis involves the Sonogashira coupling[31] of a functionally substituted haloarene with a functionalized alkyne (Scheme 2). The alkyne is then subjected to iodocyclization, and the resulting 3-iodoheterocycle is generally isolated in good to excellent yields as reported previously. The resulting iodine-containing heterocycle is then used as the starting material for further iterative cycles of Sonogashira coupling and iodocyclization to generate the desired polyheterocyclic molecule.

Repetitive cycles of Sonogashira coupling, followed by iodocyclization, have proven quite efficient and lead to PHCs bearing two or three linked heterocycles in moderate to good yields. Representative heterocycles and the corresponding intermediates prepared by this general strategy are listed in Scheme 2. For preparation of the intermediate alkynes, the usual Sonogashira coupling conditions have been somewhat modified, as they have generally been performed in DMF (see the Supporting Information). The intermediate alkynes have generally been prepared in good to excellent yields (Scheme 2). The iodocyclization reactions have been performed using our previously published procedures for the corresponding heterocycles.

Various 5- and 6-membered ring heterocycles linked through different positions have been conveniently synthesized by this general strategy. We believe that this basic methodology can be extended to all other functional groups and substituents that have previously been shown to undergo facile iodocyclization.[1−27] An interesting feature of this approach is the fact that after starting the reaction sequence using an *o*-haloarene, only one other type of building block, namely a readily available functionalized terminal alkyne **5**, is required for polyheterocycle generation, and different heterocyclic units can be successfully inserted at the desired positions in the PHC by simply changing the sequence of functionalized alkyne building blocks. The iterative nature

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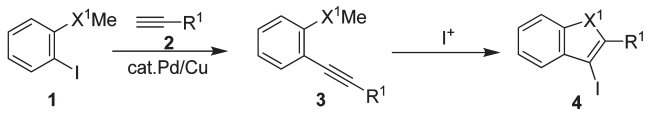
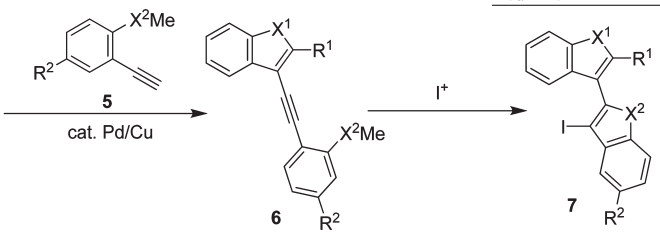
SCHEME 2. Generation of Polyheterocyclic Compounds by the General Strategy[a]



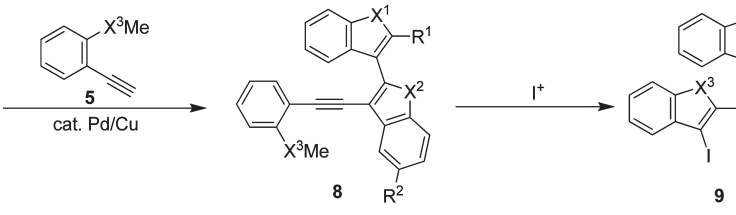
	X^1	R^1	yield (%)
3a	O	Ph	72
3b	S	Ph	100
3c	S	TMS	97

	X^1	R^1	yield (%)
4a	O	Ph	81
4b	S	Ph	99
4c	S	TMS	99
4d	S	H	95[b]



	X^1	R^1	X^2	R^2	yield (%)
6a	O	Ph	CO_2	H	98
6b	O	Ph	S	H	84
6c	O	Ph	NMe	H	81
6d	S	Ph	O	H	65
6e	S	H	O	OMe	95
6f	S	TMS	CO_2	H	79

	X^1	R^1	X^2	R^2	yield (%)
7a	O	Ph	CO_2	H	91
7b	O	Ph	S	H	98
7c	O	Ph	NMe	H	96
7d	S	Ph	O	H	67
7e	S	H	O	OMe	66



	X^1	R^1	X^2	R^2	X^3	yield (%)
8a	O	Ph	CO_2	H	NMe	79
8b	O	Ph	CO_2	H	O	75
8c	O	Ph	CO_2	H	S	55
8d	O	Ph	S	H	CO_2	89
8e	S	H	O	OMe	CO_2	81

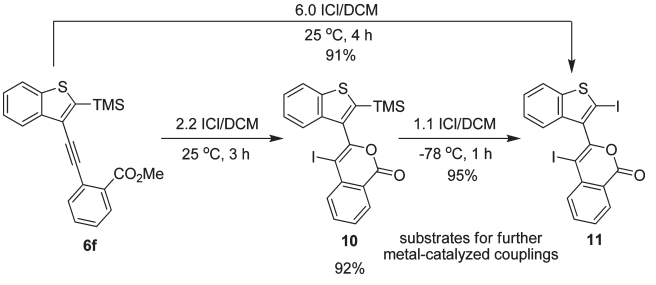
	X^1	R^1	X^2	R^2	X^3	yield (%)
9a	O	Ph	CO_2	H	NMe	91
9b	O	Ph	CO_2	H	O	70
9c	O	Ph	CO_2	H	S	96
9d	O	Ph	S	H	CO_2	63
9e	S	H	O	OMe	CO_2	71

[a]Conditions: All Sonogashira reactions were carried out on a 0.25−5.0 mmol scale, and the iodocyclization reactions were carried out on a 0.10−4.0 mmol scale using I_2 or ICl (see the Supporting Information).[b]This compound was prepared from **4c** by desilylation.

of this approach to linked PHCs lends itself well to the automated synthesis of large heterocyclic sequences of varying complexity.[32] The solubility issues in larger heterocyclic systems should be resolved by adjusting the polarity of the individual alkyne building blocks.

After successful implementation of this general strategy for the efficient synthesis of PHCs, several variations in the approach have been explored that further highlight the versatility and scope of this methodology. First, iodocyclization can be carried out quite selectively affording a variety of intermediates, which should prove quite versatile for further elaboration (Scheme 3). For example, 2-silyl-3-alkynylbenzothiophene derivative **6f** can be converted to the benzothiophene−isocoumarin diheterocycle **11** in one step in excellent

SCHEME 3. Simultaneous and Stepwise Diiodination

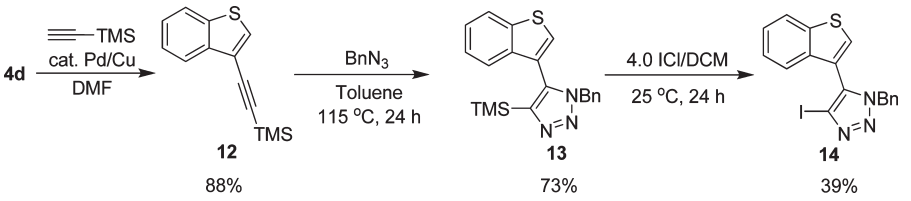


yield or **6f** can be very efficiently cyclized to the corresponding silicon-containing iodoisocoumarin **10**, allowing for further selective functionalization and/or iodocyclization.

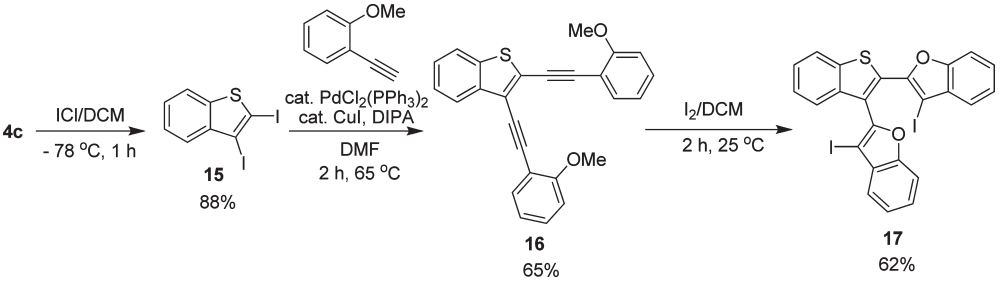
As noted previously, a variety of heterocyclic units are readily accessible by this iodocyclization strategy. This approach can be combined with other efficient transformations to broaden the scope of the methodology and allow easy access to heterocycles that are not presently accessible by

(32) Preliminary studies were performed to develop a one-pot procedure for this Sonogashira/iodocyclization sequence. DCE, DCM, and DMF were examined as the reaction solvents (single solvent or in combinations), and the reactions were found to be relatively cleaner when performed in DCE. However, at present additional work is necessary in order to find appropriate reaction conditions for this potentially useful one-pot Sonogashira/iodocyclization sequence.

SCHEME 4. Click Chemistry Followed by Iodo-desilylation



SCHEME 5. Double Sonogashira Coupling, Followed by Double Iodocyclization

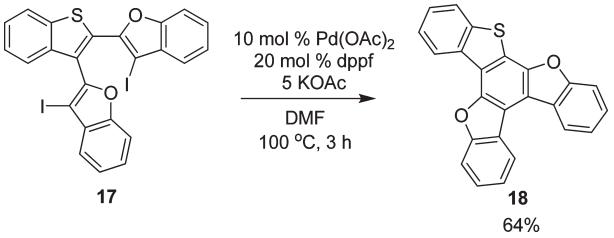


iodocyclization. For example, alkyne **12** has been subjected to well-known click chemistry using benzyl azide, and the desired triazole **13** was obtained in good yield (Scheme 4).[33] Upon iodo-desilylation, the iodotriazole **14** was obtained, providing avenues for the further introduction of heterocycles using our Sonogashira coupling/iodocyclization methodology or other coupling reactions, such as Suzuki–Miyaura couplings.[34]

In an effort to synthesize fused polyheterocyclic compounds, the benzothiophene derivative **4c** was subjected to silyl-iodine exchange (Scheme 5). The resulting 2,3-diiodobenzothiophene (**15**) on double Sonogashira coupling with an appropriate *o*-functionalized terminal alkyne, followed by double cyclization, quickly leads to a compound **17**, having three linked heterocyclic units and two iodine handles.

The diiodo compound **17** was then subjected to a palladium-catalyzed Ullmann reaction leading to the formation of fused heterocycle **18** (Scheme 6).[35] Similar fused heterocyclic systems have been shown to exhibit interesting electronic and luminescent properties.[36] This approach can be conveniently extended to the synthesis of symmetrical fused heterocycles as well. PHCs such as these should prove useful as ligands in coordination and organometallic chemistry.

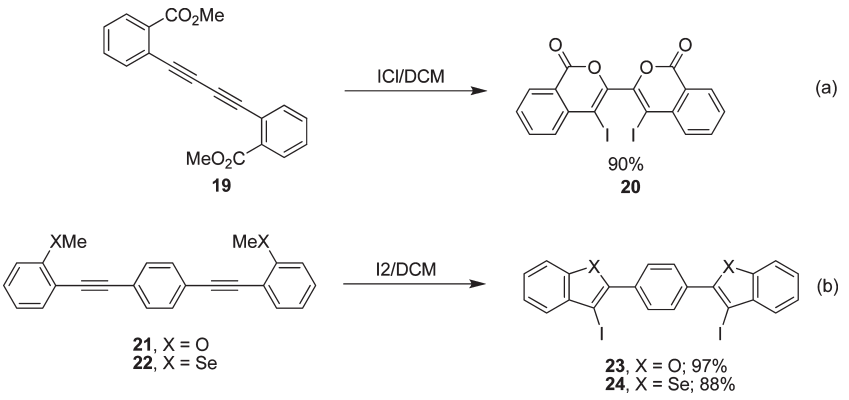
SCHEME 6. Palladium-Catalyzed Ullmann Reaction



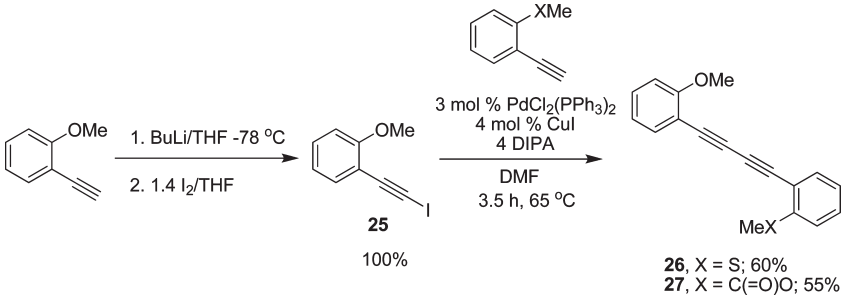
The above variations in our basic strategy (Schemes 4 and 6) highlight the ability to couple our methodology with other efficient methodologies to synthesize molecules with diverse functionalities quickly and efficiently. In another variation, the cyclization of 1,3-diynes has been explored. Efficient examples of homo-1,3-diyne cyclization have been reported (Scheme 7) previously by us and others.[2b,3h,7a,13,37]

In an effort to cover other functional groups and heteroatom-containing diynes, several additional 1,3-diynes have been synthesized using our optimized Sonogashira conditions (Scheme 8). The hetero-1,3-diynes were obtained in only moderate yields as the cross-coupling suffers from formation of homocoupling byproduct. Nonetheless, the homo- and hetero-1,3-diynes were subjected to iodocyclization, and

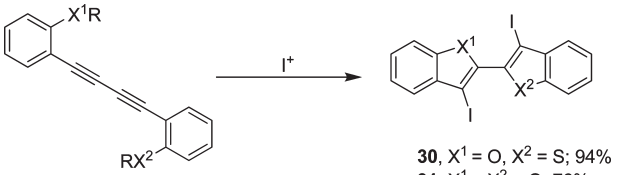
SCHEME 7. Previously Reported Examples of 1,3-Diyne Cyclization



SCHEME 8. Preparation of 1,3-Diynes



SCHEME 9. Iodocyclization of Homo- and Hetero-1,3-diynes



26, X^1R = OMe, X^2R = SMe
28, $X^1R = X^2R$ = OMe
29, $X^1R = X^2R$ = SMe

30, X^1 = O, X^2 = S; 94%
31, $X^1 = X^2$ = O; 76%
32, $X^1 = X^2$ = S; 98%

the double-cyclized products **30**−**32** were obtained in good to excellent yields (Scheme 9). Furthermore, in the case of hetero-1,3-diyne **27**, the reaction conditions were tuned to achieve single or double cyclization (Scheme 10). Thus, symmetrical, as well as unsymmetrical, bisheterocyclic units with dihalide functionality are readily accessible using our methodology. Recently, similar dihalo compounds have been used as precursors for the synthesis of more complex fused heterocycles exhibiting potential applications as organic field effect transistors (OFETs).[38]

As observed in all of the processes outlined above, the end products contain iodine, an important handle for further modifications. Thus, these heterocyclic iodides can either be subjected to reductive hydrodehalogenation[39] or they can be used to introduce further diversity and polarity into the molecules using conventional palladium-catalyzed transformations (Scheme 11), for example, Suzuki−Miyaura couplings (Scheme 11, eqs 1 and 2) and Sonogashira alkynylation (Scheme 11, eq 3).

Finally, palladium-catalyzed annulations have been examined in order to extend the scope of this methodology for the generation of complex fused PHCs. For example, in an attempt to perform the cyclocarbonylation reaction, bisheterocyclic compound **7b** was subjected to our previously published conditions (Scheme 12).[40] However, neither of the two expected regioisomeric annulated products was formed presumably due to the ring strain. Instead, the reaction led to the corresponding carboxylic acid **38**, whose structure was confirmed by single crystal X-ray analysis, in 59% yield. Carboxylic acid formation probably happens because of nucleophilic attack by the pivalate anion on the initially formed acylpalladium intermediate, which leads to the corresponding anhydride, followed by hydrolysis during aqueous workup of the reaction mixture (Scheme 12).

On the other hand, the alkyne annulation of polyheterocyclic compound **7b** affords the fused ring heterocycle **39** in 52% yield (Scheme 13).[41] The regioisomeric assignment is based on X-ray crystallographic data. Such annulation processes provide considerable scope in terms of the types of heterocycles that can be included in different positions, the ring size, etc., allowing one to introduce a wide variety of heterocycles in desired positions.

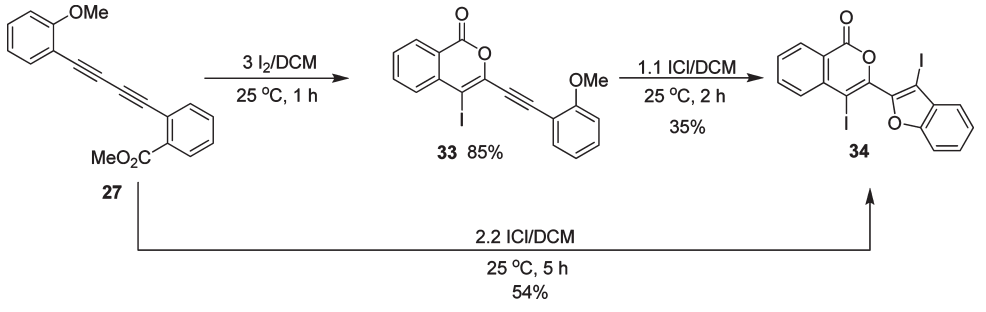
Conclusions

Several iodocyclization/palladium-catalyzed approaches have been reported for the generation of linked and fused polyheterocyclic compounds. The ability to quickly put together multiple heterocyclic rings and accommodate various other subsequent transformations adds to the synthetic utility and scope of the methodology, making this a very practical approach for PHC synthesis. In some cases, the potential exists for combinatorial automated synthesis. Considering the broad scope and considerable flexibility of this methodology and the widespread potential applications of the resulting products, rapid advances in this area of research are anticipated.

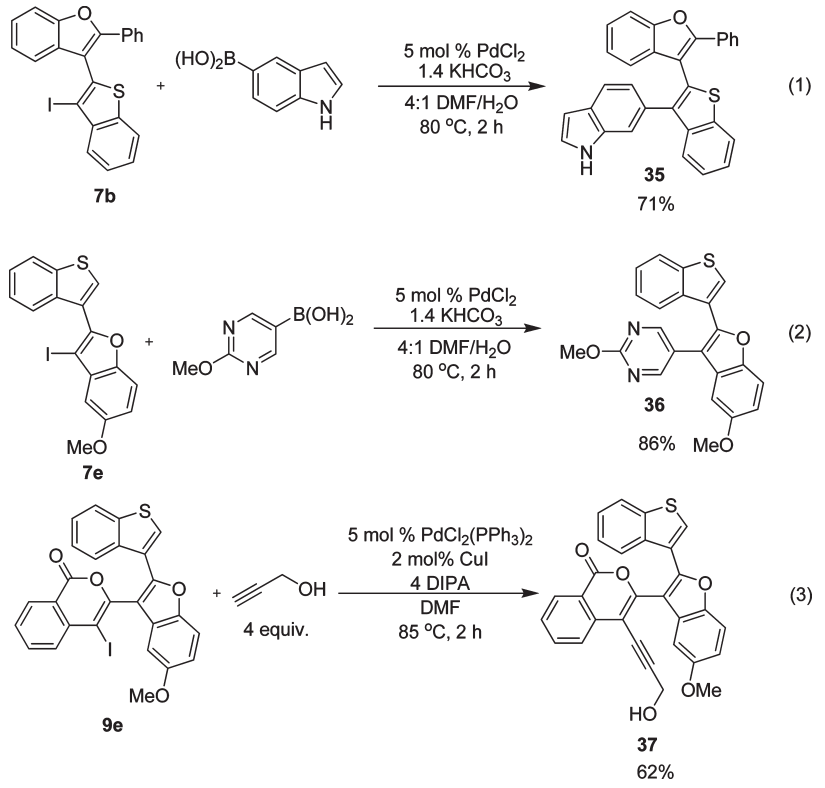
Experimental Section

General Methods. The ^{1}H NMR and ^{13}C NMR spectra were recorded at 25 °C at 300 or 400 MHz and 75 or 100 MHz,

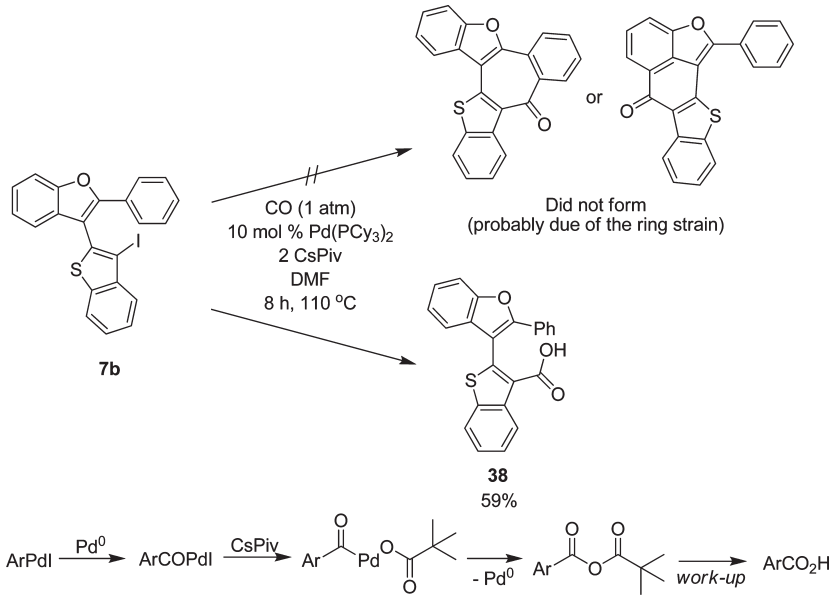
SCHEME 10. Tuning of Reaction Conditions for Single or Double Cyclization



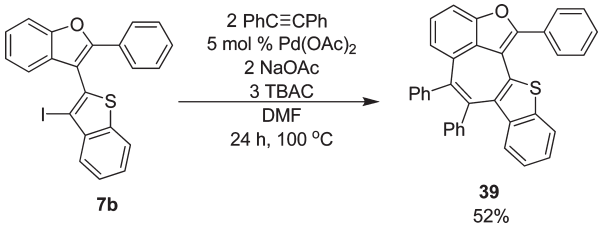
SCHEME 11. Elaboration of the Iodine-Containing Products



SCHEME 12. Cyclocarbonylation Attempt



SCHEME 13. Alkyne Annulation Reaction Leading to a Fused PHC



respectively, with Me_4Si as an internal standard. The chemical shifts (δ) and coupling constants (J) are given in ppm and Hz, respectively. Thin-layer chromatography was performed using commercially prepared 60-mesh silica gel plates and visualization was effected with short wavelength UV light (254 nm). Purification of the compounds has been performed by column chromatography and/or recrystallization. All melting points are uncorrected. HRMS data: the electron impact ionization experiments were performed on a triple quadrupole mass spectrometer fitted with a EI/CI ion source. The samples were introduced to the mass spectrometer using a solids probe. The probe was

heated gradually from 100 to 400 °C. The instrument was used as a single quadrupole and scanned from 50 to 1000 Da. Accurate mass measurements were conducted using a manual peak matching technique with the double focusing mass spectrometer. DCM was distilled over CaH_2. Anhydrous MeCN and DMF were used as received. All reagents were used directly as obtained commercially unless otherwise noted.

General Procedure Used for the Sonogashira Coupling. To a solution of haloarene starting material in DMF were added 3 mol % of $PdCl_2(PPh_3)_2$ and 4 mol % of CuI. The reaction vial was then sealed and flushed with argon. After the solution was stirred for 5 min at room temperature, 4 equiv of DIPA was added by syringe. The reaction mixture was then heated to 65 °C, a solution of the alkyne (1.2 equiv) in DMF (1 mL) was added dropwise over 5−10 min, and the mixture was allowed to stir at 65−80 °C for 2−3 h. After cooling, the reaction mixture was diluted with EtOAc and washed with satd aq NH_4Cl, water, and brine. The combined organic extracts were dried over $MgSO_4$ and concentrated under vacuum to give the crude product, which was purified by column chromatography on silica gel using hexane−EtOAc as eluent.

General Procedure for Iodocyclization. To a solution of the starting alkyne in DCM was added gradually the I_2/ICl solution (0.25 M) in DCM. The reaction mixture was allowed to stir at 25 °C, and the reaction was monitored by TLC for completion. The excess I_2 or ICl was removed by washing with satd aq $Na_2S_2O_3$. The mixture was then extracted by EtOAc or diethyl ether. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under vacuum to yield the crude product, which was purified by flash chromatography on silica gel using hexane−EtOAc as the eluent or by recrystallization.

3-(2-(Benzo[*b*]thiophen-3-yl)-5-methoxybenzofuran-3-yl)-4-iodo-1*H*-isocoumarin (9e). The product was obtained (yield = 71%) as a yellow solid: mp 148−151 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.91 (s, 3H), 6.98 (d, J = 8.4 Hz, 1H), 7.18 (s, 1H), 7.38−7.47 (m, 3H), 7.61 (t, J = 7.2 Hz, 1H), 7.70 (s, 1H), 7.76−7.83 (m, 2H), 7.87 (d, J = 7.6 Hz, 1H), 8.31−8.33 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.0, 81.4, 96.2, 113.0, 113.6, 120.6, 120.7, 121.0, 122.9, 124.1, 125.1, 125.2, 126.3, 127.7, 129.9, 130.1, 131.5, 135.9, 136.9, 138.0, 140.2, 149.6, 150.8, 155.0, 158.9, 161.9; HRMS calcd for $C_{26}H_{15}IO_4S$ 549.97359, found 549.97467.

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Supporting Information Available: General experimental methods, reaction procedures, characterization data, copies of ^{1}H and ^{13}C NMR spectra for previously unreported compounds and X-ray crystallographic data for compounds **38** and **39**. This material is available free of charge via the Internet at http://pubs.acs.org.

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