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# Regioselective *5-endo-dig* Electrophilic Iodocyclization of Enediynes: A Convenient Route to Iodo-substituted Indenes and Cyclopenta Fused Arenes

Rakesh K. Saunthwal, Abhinandan K. Danodia, Monika Patel, Sushil Kumar and Akhilesh K. Verma*

**Abstract:** An efficient iodine-mediated regioselective tandem approach for the synthesis of symmetric **4a−g** and asymmetric **5a−f** iodo-substituted indenes and stereoselective cyclopenta [*b*]pyridine/thiophene **6a−h** from easily accessible enediynes **3a−u** via *in situ* formation of iodonium intermediate followed by regioselective *5-endo-dig* cyclization has been described. The intramolecular electrophilic iodocyclization was selectively triggered by the distribution of electronic density along the alkyne bond. Subsequently, the iodo-substituted indenes have been diversified by employing palladium-catalyzed cross-coupling reactions and the coupled products were further confirmed by the X-ray crystallographic studies.

The carbo- and heterocyclic compounds,[1] constitutes an important class due to their presence in a large number of drug molecules which acquire a remarkable pharmaceutical activity.[2,3] For instance, indene skeleton with an *exo*-alkylidene moiety is embedded in Sulindac (**1**) which is a non-steroidal anti-inflammatory drug,[4] Dimethindene (**2**) an oral anti-histamine agent and Donepezil (**3**) [5] an anti-Alzheimer drug (Figure 1).[6,7] In addition to these commercial medicines, indenes are the structural constituent of group IV metallocene bound catalyst which are used for olefin polymerization.[8]

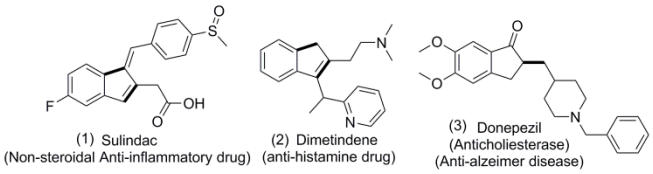
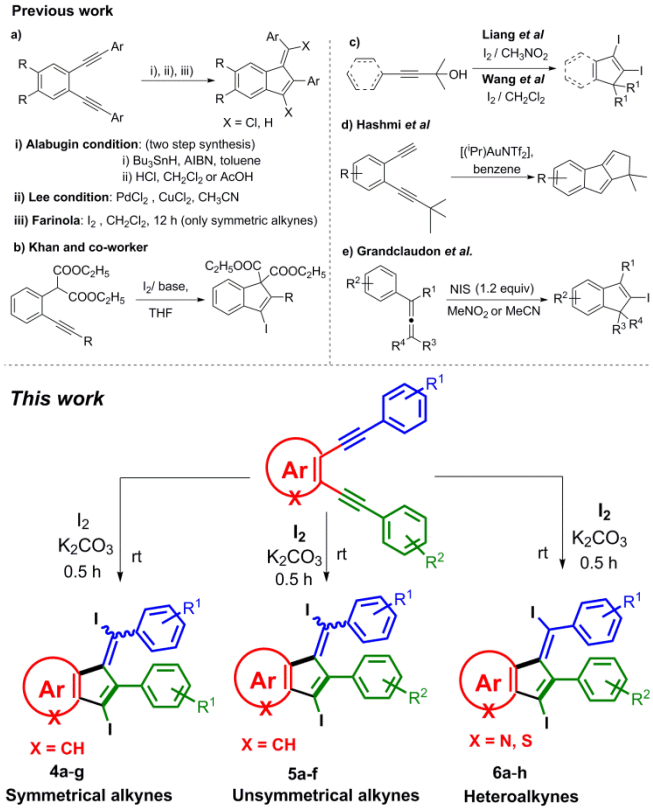



**Figure 1** Biological significance of indenes

Due to immense biological activity, a number of synthetic methodologies have been developed for the construction of indene moiety such as the ring enlargement of substituted cyclopropenes,[9] the Lewis acid mediated ring closure of substituted 1,3-butadienes [10] and the reduction or dehydration of indanones.[11] During the past decade, a rapid interest has been developed in the area of electrophilic iodocyclization and it emerge as an extremely active and original field for heterocyclic synthesis.[12-13] The halide functionality introduced through electrophilic iodocylization provide a useful avenue for structure elaboration to generate complex molecules.[14] The electrophilic iodocyclization of alkynes and allene bound substrate are an alternative powerful tool for the construction of diversely functionalized carbocycles and heterocycles having a mono-iodo substituent. However, a number of methods are available in the literature for the synthesis of monoiodonated indenes by electrophilic cyclization.[15] On introducing an electron-rich alkyne moiety into the domino transformations via cross-coupling chemistry leads to the rapid production of polycyclic frameworks.




**Scheme 1.** Approach for the synthesis of indene derivatives.

In last few years, Takai,[16a] Larock,[16b,c] Kondo [1] and Tian [16d] groups have demonstrated the transition metal C-H functionalization of alkynes followed by electrophilic annulation to generate indene. Alabugin and co-workers [17a] have developed a two-step strategy for the synthesis of benzofulvene via $Bu_3SnH$ mediated 5-*exo-dig* radical cyclization of diaryl enediyne. Subsequently, Lee et. al [17b] have explored the synthesis of benzofulvenes via Bergman cyclization using Pd/Cu-catalyst. Farinola group[17c] demonstrated the application

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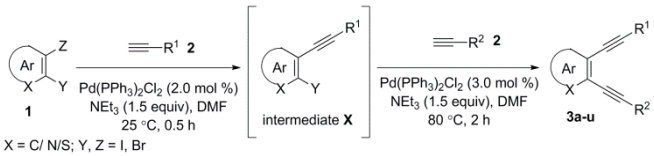
of symmetric benzofulvene intermediate for the *5-exo-dig* cyclization of macro conjugated molecules with limited substrate scope (Scheme 1a). In 2009, Khan[18a] and fellow workers reported the iodine-mediated electrophilic cyclization of substituted ethenylmalonates for the construction of 3-iodo-1*H*-indene derivatives by 5-*endo-dig* carbocyclization (Scheme 1b). The synthesis of iodinated indenes via electrophilic carbocyclizations of propargylic alcohol in nitromethane have been described by Liang group [18b] in 2011 (Scheme 1c). Later, Wang and co-workers[18c] synthesized substituted 2,3-diiodoindenes in dichloromethane (Scheme 1c). They extended the chemistry for the synthesis of 13*H*-indeno[1,2-*l*]phenanthrenes from synthesized 2,3-diiodoindene through Suzuki and Scholl oxidative coupling reaction. In 2012, Hashmi and co-workers,[19a] described gold-catalyzed synthesis of benzofluvene, via dual activation of substrate (Scheme 1d). During our manuscript preparation, an iodonium-induced cyclization of arylallenes has been demonstrated by Grandclaudon et al. for the synthesis of 2-iodoindenes (Scheme 1e). [19b]

Owing to the broad biological importance of indenes and limitations in the previous reported strategies, such as use of expensive metal catalysts, limited scope or availability of starting materials and requirement of multistep procedures. Due to the above drawbacks and presence of indenes in many natural products, this motivated us for designing an efficient route to synthesize iodo-substituted indenes and heterocycles. Encouraged by our laboratory results for the synthesis of pyrano[4,3-*b*]quinoline via iodine-mediated electrophilic cyclization,[20] herein we report the electrophilic iodocyclization chemistry for the synthesis of diiodoindenes from dialkynyl aromatic/heteroaromatic through sequential Sonogashira/ Sonogashira coupling reaction followed by 5-*endo-dig* cyclization.

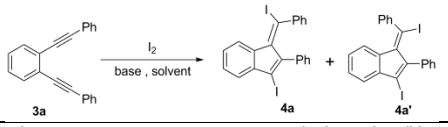
Our approach towards the synthesis of diiodoindene involves two steps: (i) preparation of dialkynyl aromatic/heteroaromatic (**3**) from 1-bromo-2-iodo-benzene (**1)** by sequential Sonogashira/Sonogashira coupling reaction and (ii) electrophilic iodocyclization of dialkynyl aromatic/heteroaromatic. The coupling products **3** were obtained in 76-85% yield in the presence of 2.0 + 3.0 mol % of $Pd(PPh_3)_2Cl_2$ by coupling of **1** with terminal alkyne **2**.[21] The coupling reaction accommodates a wide variety of functional groups (Scheme 2).




**Scheme 2.** Sonogashira Reaction of Hindered Aromatic/Heteroaromatic Dihalide with Alkynes

To identify the optimal reaction conditions for the reaction, we examined the reaction of 1,2-bis(phenylethynyl)benzene (**3a)** with 1.2 equiv of $I_2$, and 2.0 equiv of $K_2CO_3$, in 2.0 mL of $CH_2Cl_2$ at 25 °C for 0.5 h, the corresponding cyclized product was obtained in 37% yield in a mixture of E and Z (*E*:*Z*::75:25) isomers (Table 1, entry 1). Increasing the amount of $I_2$ from 1.2 equiv to 1.5 equiv and reaction time from 0.5 h to 1 h, the desired product **4a/4a'** was observed in 47% yield (entry 2). Further increasing of the amount of molecular $I_2$ from 1.5 equiv to 2.0 and then to 2.4 equiv afforded the mixture of isomers **4a/4a'** in 74 and 88% yields respectively (entries 3 and 4). When the reaction was monitored at short interval of time with 2.4 equiv of molecular iodine, the yield of the corresponding iodocyclized product **4a/4a'** remain unchanged (entry 5). Inferior results were obtained with $K_3PO_4$, NaOH, and $CsCO_3$ (entries 6–9), while no iodocyclized product was detected with $Et_3N$ (entry 10). Although $CH_2Cl_2$ is an inadequate solvent for $K_2CO_3$ however; $K_2CO_3$ provides a mild basic condition which is essential for a clean and high yielding reaction. $K_2CO_3$ is presumed to avoid the by-product of the reaction which can degrade the desired product.[22] In the absence of base, no progress in the reaction was observed (entry 11). The electrophilic cyclization of **3a** using $ClCH_2CH_2Cl$ solvent at 25 °C and 60°C successfully provided the desired product **4a/4a'** in 72 and 85% yields respectively with 60:40 stereoisomeric ratio (entries 12 and 13). However, other solvents like THF, DMF, MeCN failed to provide the iodocyclized product (entries 14–16).

**Table 1.** Optimization of iodocyclization of dialkynylbenzene[a]

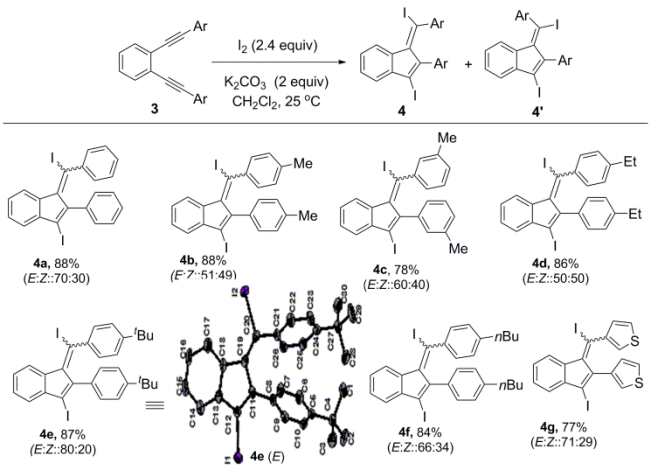



| Entry | Solvent | Base | $I_2$ reagent (equiv) | *T*(°C) | Time(h) | Yield(%)[b] **4a/4a'** (*E*:*Z*)[c] |
|---|---|---|---|---|---|---|
| 1 | $CH_2Cl_2$ | $K_2CO_3$ | 1.2 | 25 | 0.5 | 37(75:25) |
| 2 | $CH_2Cl_2$ | $K_2CO_3$ | 1.5 | 25 | 1 | 47(70:30) |
| 3 | $CH_2Cl_2$ | $K_2CO_3$ | 2.0 | 25 | 1 | 74(70:30) |
| 4 | $CH_2Cl_2$ | $K_2CO_3$ | 2.4 | 25 | 1 | 88(70:30) |
| **5** | **$CH_2Cl_2$** | **$K_2CO_3$** | **2.4** | **25** | **0.5** | **88(70:30)** |
| 6 | $CH_2Cl_2$ | $K_3PO_4$ | 2.4 | 25 | 0.5 | 66(68:32) |
| 7 | $CH_2Cl_2$ | $K_3PO_4$ | 2.4 | 25 | 1 | 78(68:32) |
| 8 | $CH_2Cl_2$ | NaOH | 2.4 | 25 | 1 | 40(70:30) |
| 9 | $CH_2Cl_2$ | $CsCO_3$ | 2.4 | 25 | 1 | 61(70:30) |
| 10 | $CH_2Cl_2$ | $Et_3N$ | 2.4 | 25 | 1 | N. R[d] |
| 11 | $CH_2Cl_2$ | - | 2.4 | 25 | 1 | N. R[d] |
| 12 | $ClCH_2CH_2Cl$ | $K_2CO_3$ | 2.4 | 25 | 1 | 72(60:40) |
| 13 | $ClCH_2CH_2Cl$ | $K_2CO_3$ | 2.4 | 60 | 1 | 85(60:40) |
| 14 | THF | $K_2CO_3$ | 2.4 | 60 | 1 | N. R[d] |
| 15 | DMF | $K_2CO_3$ | 2.4 | 60 | 1 | N. R[d] |
| 16 | MeCN | $K_2CO_3$ | 2.4 | 60 | 1 | N. R[d] |

[a] Reaction were performed using 1,2-bis(phenylethynyl)benzene **3a** (0.5 mmol), $I_2$, and base (2.0 equiv) and 1.5 mL of solvent unless otherwise noted.[b]Total isolated yield of two isomers. [c] Stereoisomeric ratio. [d] no reaction.

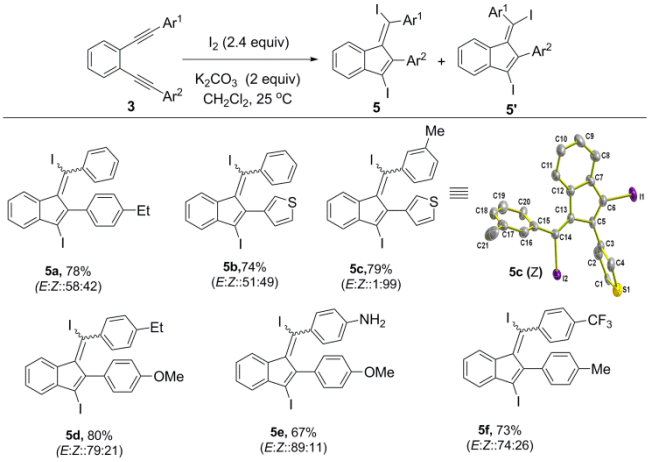
After establishing the optimal reaction conditions, we explored the substrate scope of electrophilic iodocyclization chemistry by employing various symmetrical **3a–g** and unsymmetrical dialkyne **3h–m** in the presence of molecular iodine and afforded the corresponding mixture of *E* and *Z* isomers in 67–88% yields. Substrate **3a** bearing phenyl substituent at $R^1$ and $R^2$ provided a mixture of *E* and *Z* (70:30) isomer in 88% yield. Alkynes **3b–g** bearing electron-rich substituents at $R^1$ and $R^2$ on reaction with iodine afforded the *E*:*Z* mixture of correponding products in 77–88% yields. Substrates **3c**, bearing methyl substitution at the *meta* position of the phenyl ring afforded the desired product **4c** along with **4c'** in comparatively lower yield. Reaction of 1,2-bis((4-ethylphenyl) ethynyl)benzene **3d** provided the mixture of stereoisomers *E*:*Z* in equal ratio. Substrates **3e–f** bearing a *tert*-

butyl, and *n*-butyl were found suitable for the reaction and provided the mixture of desired products (**4+4') e–f** in 87 and 84% yield respectively (entries 5 and 6). The structure of **4e** (*E*-isomer) was confirmed by the X-ray crystallographic studies. The electron-rich thiophene alkyne **3g** afforded the iodocyclized product in 77% yield (Scheme 3).




**Scheme 3.** Scope of symmetrical dialkyne [a] The reactions were performed using dialkynylbenzene **3** (0.50 mmol), 2.4 equiv of $I_2$ and 2.0 equiv of $K_2CO_3$ in 2.0 mL of $CH_2Cl_2$ at 25 °C for 0.5 h. [b] Isolated yields. Data CCDC number of **4e** is 845040 .

The reaction of unsymmetrical alkyne, 1,2-bis((4-(alkyl)phenyl) ethynyl)benzene containing different substituent at the end of triple bond have also been investigated. Under similar condition the various substrates **3h–m** bearing different alkyl coupling partner were found successful for the reaction and provided the mixture of *E* and *Z* isomers **5a–f** in 67−80% yields. The structure of **5c** (*Z*-isomer) was confirmed by the X-ray crystallographic studies. Interestingly, when substrates **3j** were used for iodocyclization, the formation of *Z*-isomer was predominated; the possible reason could be due to the spatial arrangement of intermediate during the course of reaction. It is noteworthy that alkynes **3m** bearing a electron-withdrawing trifluoromethyl group at 4-position of the phenyl ring was found successful for the reaction and provided the desired product (**5+5')f** in *E*:*Z* ::74:26 stereoisomeric ratio in 73% yield (Scheme 4).




**Scheme 4.** Scope of unsymmetrical dialkyne. [a] The reactions were performed using dialkynylbenzene **3** (0.50 mmol), 2.4 equiv of $I_2$ and 2.0 equiv of $K_2CO_3$ in 2.0 mL of $CH_2Cl_2$ at 25 °C for 0.5 h. [b] Isolated yields. CCDC number of **5c** is 978613 .

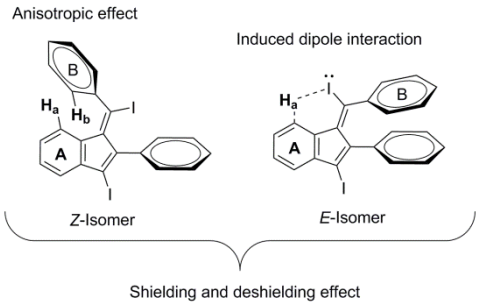
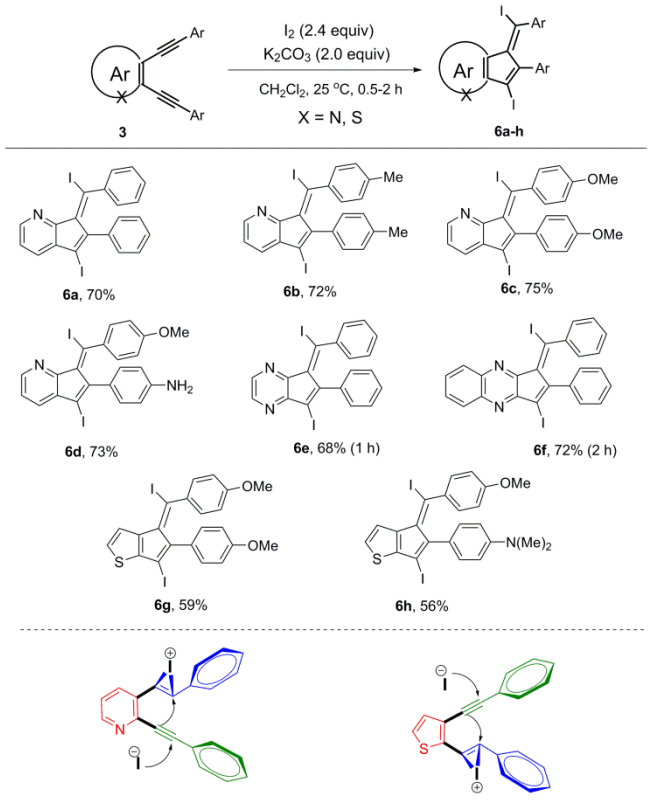



**Figure 2.** Anisotropic effect

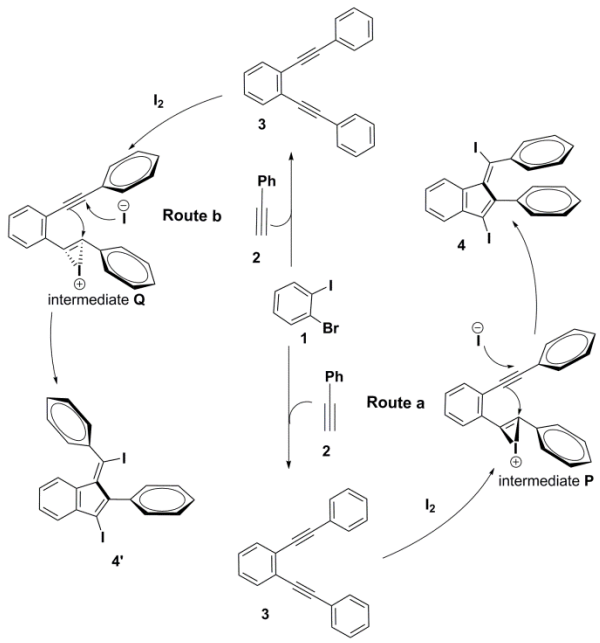
Encourage by the result from X-ray crystallography, NOESY and NMR spectroscopy, we ascertained the mixture of *E* and *Z* isomer. In *Z*-isomer, possibly the π orbital of phenyl ring **A** and **B** are in same plane. When an external magnetic field is applied, then **Ha** (*δ* 5.85-6.00 ppm) and **Hb** proton comes in same region, therefore **Ha** proton comes perpendicular to applied magnetic field and showed the shielding of **Ha** (*δ* 5.85-6.00 ppm) proton (Figure 2). In *E*-isomer no anisotropic effect occurred between phenyl ring **A** and **B** (as shown in Figure 2). We presumed that the deshielding of **Ha** (*δ* 8.85-9.01 ppm) proton might be due to induced dipole interaction. This anisotropic effect also supports the formation of mixture of stereoisomers in case of 1,2-bis((4-(alkyl)phenyl)ethynyl)benzenes (**3**).




**Scheme 5.** Synthesis of cyclopenta fused arenes via electrophilic iodocyclization

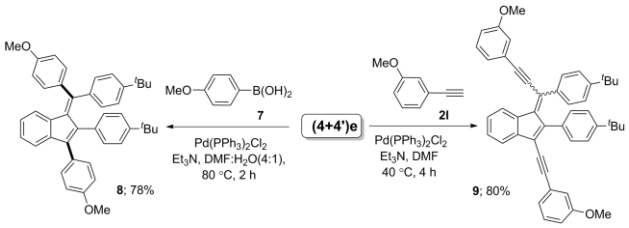
We further extended the scope of the developed chemistry for

the synthesis of an important class of heterocyclic scaffold. In contrast to the phenyl dialkyne, introduction of heteroatom in the phenyl ring helped in controlling the stereoselectivity of product (Scheme 5). When we performed the reaction using electron-deficient pyridyl substrates containing symmetrical alkynes bearing –Ph (**3n**),–p-tolyl (**3o**) and 4-methoxyphenyl (**3p**) groups with iodine, we observed exclusive *Z* isomer of **6a**, **6b** and **6c** in 70%, 72% and 75% yields, respectively. Unsymmetrical alkyne(**3q**) were also successful in providing the iodocyclized product **6d** in 73% yield. Interestingly, 2,3-bis (phenylethynyl) pyrazine (**3r**) and 2,3-bis(phenylethynyl)quinoxaline (**3s**) were also capable in providing the intriguing iodocyclized products **6e–f** in 68–72% yields with excellent stereoselectivity. The synthesis of (*E*)-6-iodo-4-(iodo(4-methoxyphenyl)methylene)-5-(4-methoxy phenyl) -4H-cyclopenta[b]thiophene (**6g**) and (*E*)-4-(6-iodo-4-(iodo(4-methoxyphenyl) methylene)-4H-cyclopenta[b] thiophen-5-yl)-N,N-dimethylaniline (**6h**) were carried out in good yields with high stereoselectivity using dialkynylthiophene **3t** and **3u** using optimized reaction conditions. It is noteworthy, that the reaction of heterocyclic dialkyne provided a single stereoisomer probably due to the electronic effect of the heterocyclic moiety.




**Scheme 6.** Plausible mechanism

On the basis of the above observations, a plausible reaction mechanism for 5-*endo-dig* iodocylization has been described in Scheme 6. Presumably the electrophile ($I_2$) and the enediynes **3** would generate the cyclic iodonium intermediate **P** and **Q** upon electrophilic attack of the $I_2$ on the electron deficient carbon of alkyne. Subsequent attack of nucleophile provides the mixture of *E* and *Z* isomers via 5-endo-dig cyclization. The formation of *E* and *Z* isomer depends upon the attack of the iodine nucleophile on to alkyne carbon via route a or b. The present strategy depicts the dual role of $I_2$ as an electrophile as well as nucleophile.




**Scheme 7.** Synthetic elaboration using Pd-catalyzed cross-coupling reactions

We further investigated the structural elaboration of iodo-substituted indene via palladium-catalyzed cross-coupling reactions. To this end, mixture of (**4**+**4'**)**e** was functionalized by applying palladium-catalyzed Suzuki and Sonogashira coupling reactions and the corresponding coupling products **8** and **9** were obtained in 78% and 80% yields, respectively (Scheme 7). The structure of Sonogashira coupled product was further confirmed by X-ray crystallographic data (Figure 3).

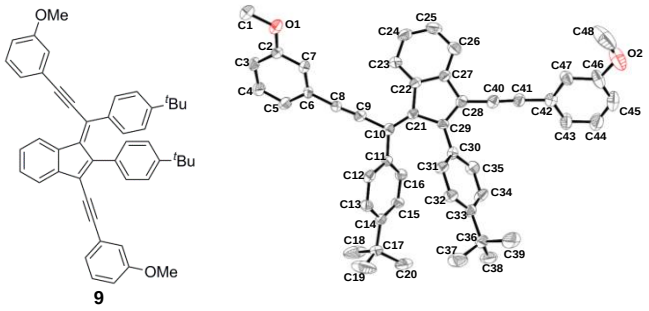



**Figure 3**. X-ray crystallographic ORTEP drawing of compound **9** drawn at the 50% probability level . CCDC number of **9** is 978612

In summary, we have described the iodine-mediated 5-endo-dig cyclization for the regio- and stereoselective synthesis of diiodo-substituted indenes, cyclopenta[b]pyridine/thiophene from easily accessible enediynes via in situ formation of iodonium intermediate. It is noteworthy, that the reaction of heterocyclic arenes provided the single stereoisomers in good yields. Iodo-cyclization method leads to the synthesis of halogen containing indene derivatives which thereafter elaborated using palladium catalyzed coupling reactions, such as Suzuki-Miyaura and Sonogashira coupling reactions. The X-ray crystallographic studies confirmed the stereochemistry of the reaction products. Due to the immense diversity in the substitution pattern, this developed chemistry can be used for the synthesis of various heterocyclic systems.

## Experimental Section

### General Information Method

Nuclear magnetic resonance spectra were recorded in $CDCl_3$, $^1H$ NMR (400 MHz) and $^{13}C$ NMR (100 MHz), at ambient temperature. Chemical shifts (δ) for all protons are reported in parts per million (ppm) and were measured relative to the residual $CHCl_3$ resonance as an internal reference in the deuterated solvent. Chemical shifts were reported as parts per million (δ in ppm) using tetramethylsilane (TMS) as internal standard or by reference to proton resonances resulting from incomplete deuteration of the NMR solvent. The following abbreviations were used to

describe the multiplicities: when appropriate (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet, td = triplet of doublet). Reactions were monitored using thin-layer chromatography on commercially prepared silica gel plates and visualized by either UV irradiation or by staining with $I_2$. Chemical yields are referred to the pure isolated substances. Chromatographic purification of the compounds was accomplished by column chromatography using 100− 200 mesh size silica gels.

**General Procedure for the Synthesis of Diiodoindene 4+4'**

To a vial dialkynyl aromatic/heteroaromatic **3** (0.50 mmol) and 2.4 equiv of $I_2$ and 2.0 equiv of $K_2CO_3$ was added in $CH_2Cl_2$. The reaction vial was then sealed and stirred at room temperature until TLC revealed complete conversion of the starting material. The solution was washed with saturated solution of $Na_2S_2O_3$ and then extracted with EtOAc(3X10 mL).The combined organic layers were dried over $Na_2SO_4$, concentrated under vacuum, and purified by column chromatography using 100− 200 mesh size silica gels (hexane) to afford the corresponding product **3**

## Acknowledgements

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**Keywords** Regioselective • *5-endo-dig* • Electrophilic Iodocyclization • Indenes • Enediynes

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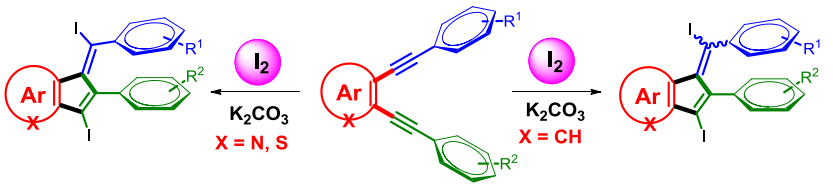
# COMMUNICATION




An efficient iodine-mediated regioselective tandem approach for the synthesis of symmetric **4a−g** and asymmetric **5a−f** iodo-substituted indenes and stereoselective cyclopenta [*b*]pyridine/thiophene **6a−h** from easily accessible enediynes **3a−u** via *in situ* formation of iodonium intermediate followed by regioselective *5-endo-dig* cyclization has been described. The intramolecular electrophilic iodocyclization was selectively triggered by the distribution of electronic density along the alkyne bond. Subsequently, the iodo-substituted indenes have been diversified by employing palladium-catalyzed cross-coupling reactions and the coupled products were further confirmed by the X-ray crystallographic studies.

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**Regioselective *5-endo-dig* Electrophilic Iodocyclization of Enediynes: A Convenient Route to Iodo-substituted Indenes and Cyclopenta Fused Arenes**