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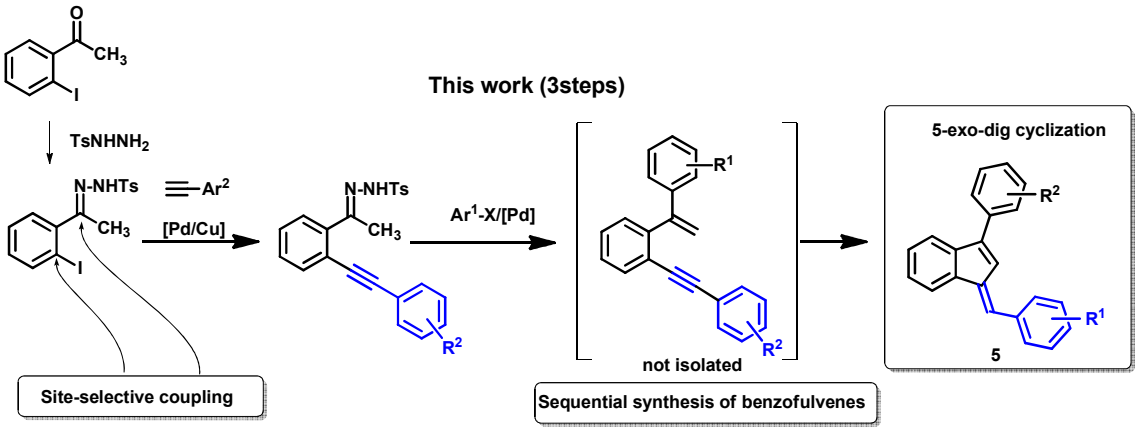

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ARTICLE

Synthesis of Benzofulvenes through Chemoselective Sonogashira, Barluenga Couplings of *ortho* Ethynyl-*N*-Tosylhydrazones and Cycloisomerization

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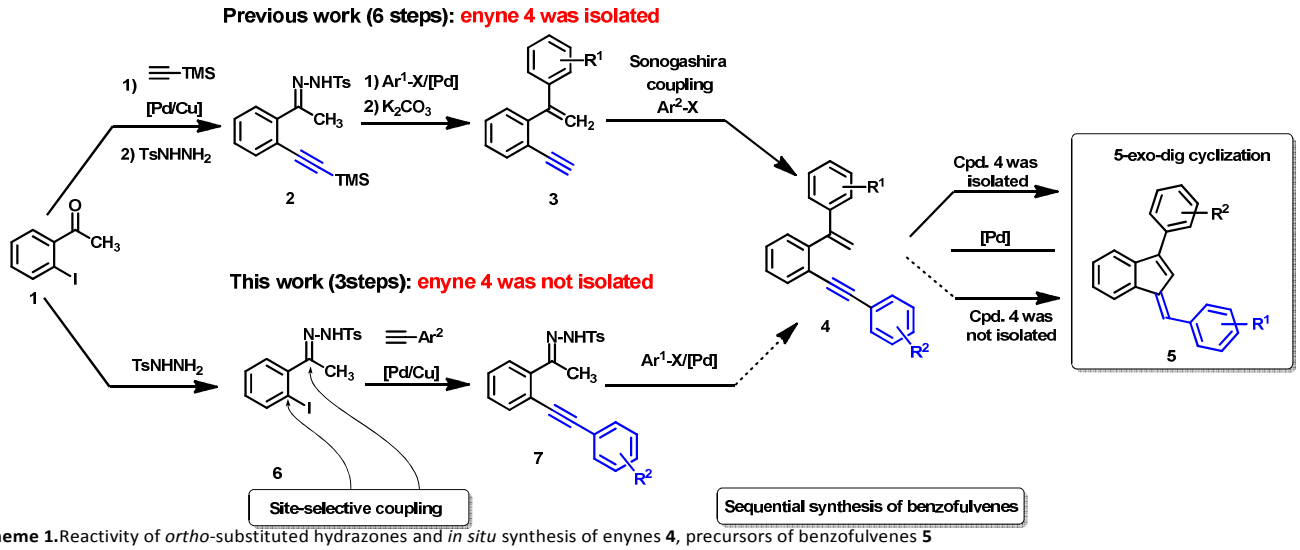
Chemoselective synthesis of *ortho* ethynylhydrazones **7**, derived from 2-iodoacetophenone *via* a Sonogashira coupling is reported for the first time. In this challenging transformation, a site-selective coupling in the presence of a hydrazone function was developed. These compounds represent useful intermediates for the synthesis of benzofulvenes through a sequence of palladium-catalyzed cross-coupling and palladium-catalyzed 5-*exo-dig* cyclization.

Introduction

Multi-functionalized building blocks have become an appealing tool in organic synthesis. In fact, they can be involved in cascade reactions, which became highly recommended for chemists due to their simple, inexpensive and time-saving character along with facile addition of complexity to the final structures. Among these new scaffolds, *N*-tosylhydrazones have emerged as precursors for the *in-situ* generation of non-stabilized diazo compounds.[1] When these compounds are properly functionalized, multiple C–C and C–heteroatom bonds are created in a one-pot fashion.[2]

One of the major research topics of our laboratory includes developing synthetic methods using *N*-tosylhydrazones as readily available starting materials for the C–C[3] and C–N[4] bonds formation. Recently, we disclosed an excellent approach to the synthesis of benzofulvenes **5** through a selective palladium-catalyzed 5-*exo-dig* cyclization of aromatic 1,5-enynes **4**.[5] These latter were prepared from 2-iodoacetophenone **1** in a six steps sequence using as intermediate *N*-tosylhydrazone **2** having a trimethylsilylethynyl group at the C2 position (Scheme 1).



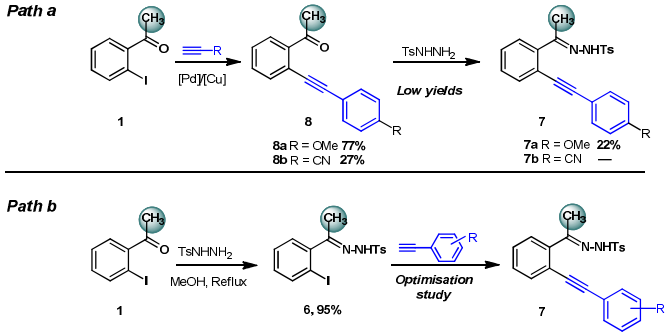
Scheme 1. Reactivity of *ortho*-substituted hydrazones and *in situ* synthesis of enynes **4**, precursors of benzofulvenes **5**

In our continuing attempts to discover new reactivity of *N*-tosylhydrazones, and to increase the interest of our synthetic approach in the formation of benzofulvenes **5**, we decided to improve two aspects of this sequence. First, we sought to shorten the synthetic scheme exploring the unprecedented site selective Sonogashira coupling of 2-iodo-*N*-tosylhydrazone **6**

with terminal aromatic alkynes while maintaining intact the hydrazone function.[6] Second, because the Barluenga coupling of **7** and the 5-*exo*-*dig* cyclization of **4** both required the presence of a palladium catalyst and a base under heating, we tried to explore the ability of *N*-tosylhydrazone intermediates **7** to achieve the sequential Barluenga coupling and the aromatic 1,5-enynes cycloisomerization without prior isolation of compound **4**. Each of these goals was met with success; herein we wish to disclose our full results that extended the scope of our earlier work.[5] This strategy provides a convenient challenging and site selective approach to a variety of benzofulvenes, which are not readily available by other methods.

Results and discussion

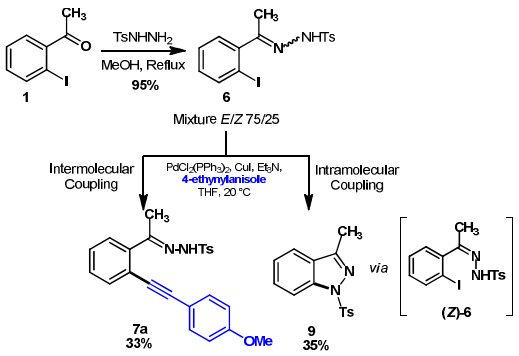
As outlined in Scheme 2, 2-ethynylhydrazones **7** can be obtained according two routes starting from readily available 2-iodoacetophenone **1**. The first one will involve a Sonogashira coupling with a terminal aryl alkyne, followed by the *N*-tosylhydrazones formation (compound **7,** *path a*). The second one, more challenging, will consist in tosylhydrazone **6** formation from **1** and then its site selective Sonogashira coupling with an aryl alkyne under palladium-copper catalysis while keeping intact the hydrazine function (*path b*). In order to achieve this transformation selectively, fine-tuning of the palladium catalyst, the ligand and the base employed will be necessary to assure high reaction selectivity, thus avoiding the formation of indazole by-products as has been reported by Inamoto *et al.*[7]



Scheme 2. Synthesis of*N*'-(2-alkynylbenzilidene)hydrazides **7**, derived from acetophenones.

According to *path a*, the Sonogashira coupling of 2-iodoacetephenone **1** under standard conditions ($PdCl_2(PPh_3)_2$ (10 mol%), CuI (20 mol%), Et_3N (2equiv), THF, rt) took place with a good yield for the electron-rich alkyne (**8a**: R = *p*-OMe) but with a low yield for the electron-poor alkyne (**6b**: R = *p*-CN). The major drawback of this *path* is the condensation step with *p*-toluenesulfonylhydrazide because very low yields were obtained for hydrazone **7a** formation, and we never succeeded in isolating the hydrazone **7b** despite the use of many protocols by changing the solvent (MeOH, EtOH), the temperature (rt or reflux) and additives ($MgSO_4$, PTSA). In all cases, the ^1H NMR of the crude mixture was very complicated and separation was tedious. For these reasons, we turned our attention to the alternative synthetic route *path b* (Scheme 2). The first step consisting in the condensation of **1** with sulfonylhydrazide worked well, providing the *N*-tosylhydrazone **6** in an excellent yield (95%) as a mixture of *E*- and *Z*-isomers in a 75/25 ratio.[8] The next step consists in installing an ethynyl group at position 2 by a Sonogashira reaction. To our knowledge, this site-selective coupling has never been described in the presence of a hydrazone function.

Initially, *N*-tosylhydrazone **6** and 4-ethynylanisole were chosen as coupling partners to optimize the Sonogashira reaction. When conventional Sonogashira reaction conditions were applied ($PdCl_2(PPh_3)_2$ (10 mol%), CuI (20 mol%), Et_3N (2equiv),THF, rt), the desired coupling product **7a** was formed with only a 33% isolated yield (Scheme 3).



Scheme 3. Chemoselectivity issue during the coupling of *N*-tosylhydrazone **6**

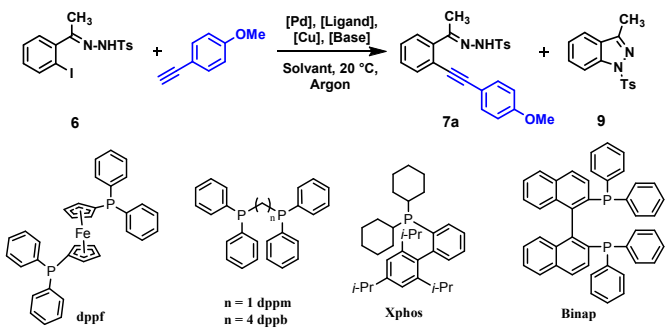
As expected from Inamoto report,[7] another product was formed simultaneously, the 3-methyl-1-tosyl-1*H*-indazole **9** in a 35% yield through an intramolecular Buchwald-Hartwig coupling of the hydrazone(*Z*)-**6** isomer.[7, 9] It should be noticed that a possible *E*/*Z* isomerisation of hydrazone **6** can occur during storage or under the reaction conditions of the coupling; which explains the yield of indazole **9**.

As a consequence, the main challenge of this work is to determine chemoselective coupling conditions preserving the *N*-tosylhydrazone function, and favoring the intermolecular Sonogashira reaction over the intramolecular Buchwald-Hartwig coupling. The optimization assays for the Sonogashira coupling between *N*-tosylhydrazone **6** and 4-ethynylanisole are depicted in Table 1.[10]

We started screening different bases (entries 1-3), diisopropylamine gave the best result with a complete conversion of the hydrazone **6** and the formation of the desired product **7a** in a 45% yield (entry 3). Several solvents were also tested (entries 3-6) and dimethylsulfoxide permitted a full conversion of the starting material in just 8 hours, furnishing **7a** in a 55% yield (entry 6). It should be noticed that all the assays were conducted at room temperature. At higher temperatures, decomposition of the *N*-tosylhydrazone **6** occurred leading to the Bamford-Stevens product.[11]Then, we turned our attention to the catalytic system. Different copper catalysts were tested (entries 6-9), however, no significant increase in the yield of **7a** was observed. Copper (I) iodide was maintained as the copper

source in this coupling. Changing the palladium source enabled the reduction of the reaction time to 3 hours (entries 10-12).

Table 1. Optimization assays for the Sonogashira coupling between *N*-tosylhydrazone **6** and 4-ethynylanisole[a]



Entry	Pd	Ligand	Cu	Base	Solvent	Yield[b]	
						7a	9
1[c,d]	$PdCl_2(PPh_3)_2$	-	CuI	Et_3N	THF	33	35
2[c,d]	$PdCl_2(PPh_3)_2$	-	CuI	Piperidine	THF	31	26
3[c]	$PdCl_2(PPh_3)_2$	-	CuI	iPr_2NH	THF	45	32
4[c]	$PdCl_2(PPh_3)_2$	-	CuI	iPr_2NH	Toluene	40	31
5[d]	$PdCl_2(PPh_3)_2$	-	CuI	iPr_2NH	MeCN	42	32
6[c]	$PdCl_2(PPh_3)_2$	-	CuI	iPr_2NH	DMSO	55	37
7[c]	$PdCl_2(PPh_3)_2$	-	CuBr	iPr_2NH	DMSO	54	40
8[c]	$PdCl_2(PPh_3)_2$	-	$CuCl_2$	iPr_2NH	DMSO	46	36
9[c]	$PdCl_2(PPh_3)_2$	-	CuTc	iPr_2NH	DMSO	51	36
10	$Pd(OAc)_2$	-	CuI	iPr_2NH	DMSO	55	39
11	$Pd(acac)_2$	-	CuI	iPr_2NH	DMSO	44	42
12	$Pd(PPh_3)_4$	-	CuI	iPr_2NH	DMSO	55	44
13	$Pd(OAc)_2$	Dppf	CuI	iPr_2NH	DMSO	55	44
14	$Pd(OAc)_2$	Dppm	CuI	iPr_2NH	DMSO	63	37
15	$Pd(OAc)_2$	Dppb	CuI	iPr_2NH	DMSO	45	50
16	$Pd(OAc)_2$	XPhos	CuI	iPr_2NH	DMSO	58	41
17	**$Pd(OAc)_2$**	**Rac-Binap**	**CuI**	**iPr_2NH**	**DMSO**	**76**	**19**

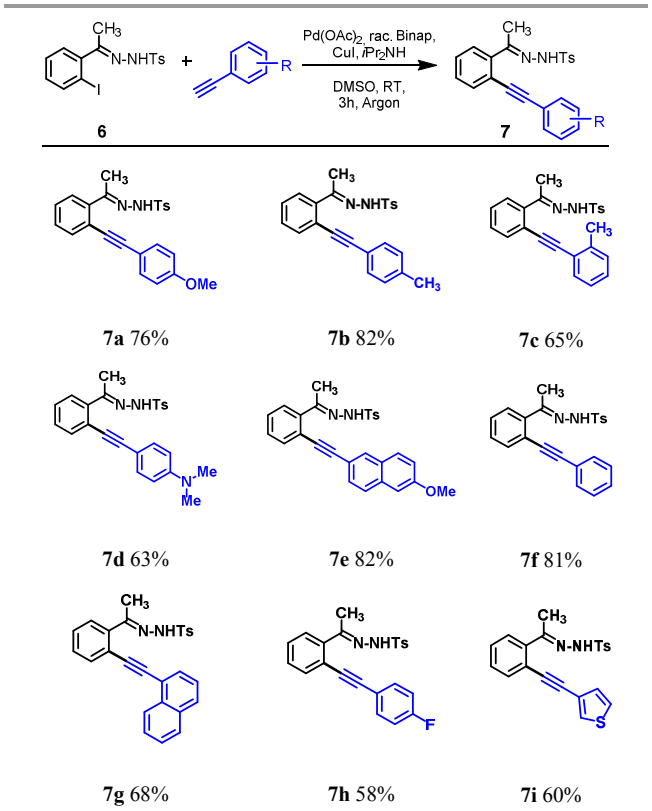
[a] Unless otherwise noted, reaction conditions: *N*-tosylhydrazone**6** (0.48 mmol), 4-ethynylanisole (2 eq), Pd (10 mol%), Ligand (20 mol%), CuI (20 mol%), Base (3 equiv), Solvent (3 mL) at 20 °C for 3 hours, under argon inlet. [b] Yields of isolated product. [c]Reaction time = 6-24h. [d] 10-15% of **6** was recovered.

Among several palladium source examined, $Pd(OAc)_2$ afforded **7a** in the highest yield of 55% (entry 10). Finally, the ligands had the most notable effect on the yield of **7a** (entries 10 and 13-17). The chemoselectivity for the Sonogashira coupling was enhanced in the presence of a bidendate phosphine ligand (rac-Binap, entry 17), affording the desired product **7a** in a 76% yield and limiting the formation of indazole **9** to 19%.

Once the optimized conditions were established, the scope for the Sonogashira coupling between hydrazone **6** and different terminal alkynes was examined (Table 2). Electron-enriched alkynes allow the coupling to proceed with good isolated yields ranging from 63 to 82% (compounds **7a-f**). *O*-tolylacetylene gave also the desired coupling product **7c** with a good yield, indicating that there no influence of steric hindrance of the alkyne partner on the coupling.

This new protocol worked also well with electron-neutral alkynes, giving the desired products **7f** and **7g** in good yields. Electron-deficient alkynes were also effective, albeit affording the coupling product **7h** with a slightly diminished yield.

Table 2. Synthesis of **7** from *N*-tosylhydrazone **6** and terminal arylalkynes[a]



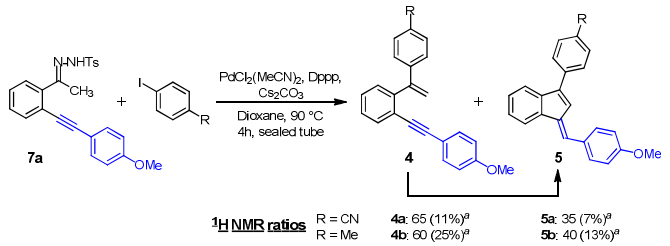
[a]Reaction conditions: *N*-tosylhydrazone**6** (0.48 mmol), alkyne (2 equiv), $Pd(OAc)_2$ (10 mol%), rac. Binap (20 mol%), CuI (20 mol%), iPr_2NH (3 equiv), DMSO (3 mL) at 20 °C for 3 hours, under argon inlet.

We were pleased to find that heterocyclic 3-thienylthiophene was successfully coupled with hydrazone **6** to access compound **7i** in a 60% yield. Unfortunately, our conditions were not compatible with aryl alkynes having electron-withdrawing substituents (CN, NO_2) on the aromatic nucleus as no coupling products were isolated. It should be noticed that all hydrazones **7** were obtained as a single (*E*)-isomer as determined by NOESY experiment.[12] This diastereoselectivity is in accordance with the above statement that only the *Z* isomer of hydrazone **6** gives indazole **9** *via* intramolecular amination while the *E* isomer reacts with the terminal alkyne and gives hydrazones **7,** with retention of the configuration, *via* a Sonogashira coupling.

Next, we tested the formation of enynes **4** through a palladium-catalyzed cross-coupling reaction between *ortho*-ethynylhydrazones **7a** and aryl halides (Scheme 4). Thus, when using the following conditions: $PdCl_2(MeCN)_2$, dppp, Cs_2CO_3, dioxane 90 °C, 4 h in a sealed tube,[13] we noticed the formation of benzofulvenes **5a** and **5b** *via in situ* 5-*exo*-*dig* cyclisation alongside the expected enynes **4a** and **4b**. Enynes **4** and

benzofulvenes **5** were obtained as a mixture in a ratio of about 60/40 determined by ^{1}H NMR (Scheme 4).

In order to avoid any tedious separation of compounds **4** and **5**, these results prompted us to consider the sequential synthesis of benzofulvenes **5** starting from *ortho*-ethynylhydrazones **7** and without prior isolation of **4**.

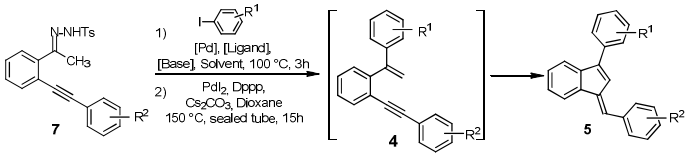


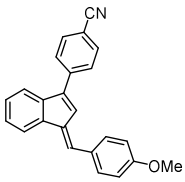
Scheme 4. Synthesis of enynes **4** from *N*-tosylhydrazones **7a.**
Reaction conditions: *N*-tosylhydrazone **7a** (0.24 mmol), aryle iodide (1 equiv), $PdCl_2(MeCN)_2$ (10 mol%), Dppp (20 mol%), Cs_2CO_3 (3 equiv), Dioxane (3 mL) at 90 °C for 4 hours in a sealed tube. [a] Values between brackets refers to isolated yields.

Indeed, enynes **4**, formed *in situ* by a palladium-catalyzed coupling between hydrazones **7** and aryl iodides,[3b, 3c] were then subjected, without prior isolation, to a 5-*exo-dig* cyclization giving rise to benzofulvene derivatives **5**.

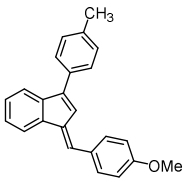
Table 3 shows unoptimized results for the sequential two steps synthesis of benzofulvenes **5**.[10] We succeeded preparing a variety of benzofulvenes with electron-poor (**5a**) and electron-rich substituents (compounds **5b** and **5c**). Likewise, the reaction conditions were compatible with the thiophene moiety and benzofulvene **5e** was formed in a 40% yield. Despite the moderate yields observed, this method represents a short approach for the synthesis of a variety of benzofulvene derivatives **5**.

Table 3. Sequential synthesis of benzofulvenes **5.**

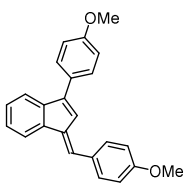




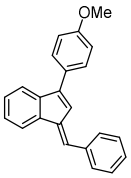
5a 45%[a]



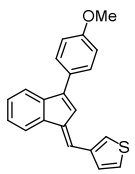
5b 62%[a]



5c 55%[b]



5d 60%[b]



5e 40%[b]

[a] Reaction conditions for the palladium-catalyzed cross-coupling reaction: *N*-tosylhydrazone **7** (0.48 mmol), aryl iodide (0.80 eq), $PdCl_2(MeCN)_2$(10 mol%), XPhos (20 mol%), NaO*t*Bu (3 eq), PhF (3 ml) at 100 °C for 3 hours, sealed tube. [b]*N*-tosylhydrazone **7** (0.48 mmol), aryl iodide (0.80 eq), $PdCl_2(MeCN)_2$(10 mol%), Dppp (20 mol%), Cs_2CO_3 (3 eq), dioxane (3 ml) at 100 °C for 3 hours, sealed tube.

Conclusions

In summary, a site-selective Sonogashira coupling was successfully performed on a *N*-tosylhydrazone **6** derived from 2-iodoacetophenone, leading to a variety of *ortho*-ethynylhydrazones **7**. These compounds were further used for the formation of aromatic 1,5-enynes and their *in situ* cyclisation to provide benzofulvene derivatives. This represents an original and practical synthetic method of benzofulvenes starting from functionalized *N*-tosylhydrazones.

Experimental section

General method

Melting points (mp) were recorded on a Büchi B-450 apparatus and were uncorrected. NMR spectra were performed on a Bruker AMX 200 (^{1}H, 200 MHz; ^{13}C, 50 MHz), Bruker AVANCE 300 or Bruker AVANCE 400 (^{1}H, 400 MHz; ^{13}C, 100 MHz). Solvent peaks were used as reference values: $CDCl_3$ at 7.26 ppm for ^{1}H NMR and 77.16 ppm for ^{13}C NMR; DMSO at 2.50 ppm for ^{1}H NMR and 39.52 ppm for ^{13}C NMR; Acetone at 2.05 ppm for ^{1}H NMR and 29.84 ppm for ^{13}C NMR; MeOD at 3.31 ppm for ^{1}H NMR and 49.00 ppm for ^{13}C NMR. Chemical shifts δ are given in ppm, and the following abbreviations are used: singlet (s), doublet (d), doublet of doublet (dd), triplet (t), quadruplet (q), multiplet (m) and broad singlet (bs). Infrared spectra (IR) were measured on a Bruker Vector 22 spectrophotometer and were recorded neat (neat, cm^{-1}). High resolution mass spectra were recorded on a MicrotofQBrukerDaltonics. Reaction courses and product mixtures were routinely monitored by TLC on silica gel (precoated F254 Merck plates), and compounds were visualized under a UVP Mineralight UVGL-58 lamp (254 nm) and with phosphomolybdic acid/Δ. Flash chromatography was performed using silica gel 60 (40–63 mm, 230–400 mesh ASTM) at medium pressure (200 mbar). Dimethylsulfoxide was used as received, dioxane, cyclohexane and tetrahydrofuran were dried using the procedures described in D. Perrin Purification of Laboratory Chemicals.[14]*N*-Tosylhydrazones were prepared according to literature procedure described by Creary, X. et al.[15] All products reported showed ^{1}H and ^{13}C NMR spectra in agreement with the assigned structures.

Experimental procedure for the preparation of *N*-tosylhydrazone 6

To a rapidly stirred suspension of *p*-toluenesulfonylhydrazide (5.5 mmol) in dry methanol (10 mL) was added the carbonyl substrate (5 mmol) in portion wise. The reaction mixture was refluxed for 12 hours. The mixture was allowed to cool to room temperature and the tosylhydrazone began to precipitate. After approximately 30 min, the mixture was cooled to 0 °C and the product removed by filtration, washed with a small quantity of methanol and then dried under vacuum.

***N*'-(1-(2-iodophenyl)ethylidene)-4-methylbenzene-sulfonohydrazide 6**. Hydrazone (**6**) precipitated as a white solid (yield 95%) as a mixture of *E* and Z isomers (75/25); M = 414.26 g.mol^{-1}; m.p.: 146-148 °C; R_f = 0.46 (Cyclohexane/EtOAc 70/30); IR (film, cm^{-1}): 3444, 3426, 3376, 3302, 3264, 3245, 3190, 3169, 3123, 3086, 3040, 3014, 2961, 2835, 2723, 2666, 2535, 2364, 2340, 2263, 2212, 2160, 2142, 2107, 1995, 1970, 1698, 1424, 1339, 1291, 1244, 1167, 1091, 1032, 1010; Major isomer: (*E*)-: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.45 (s, 1H), 7.87 (d, *J* = 8.7 Hz, 2H), 7.74 (dd, *J* = 8.2, 1 Hz, 1H), 7.29 (d, *J* = 8.7 Hz, 2H), 7.27 (td, *J* = 8.2, 1 Hz, 1H), 7.07 (dd, *J* = 8.2, 1.7 Hz, 1H), 6.97 (td, *J* = 8.2, 1.7 Hz, 1H), 2.40 (s, 3H), 2.14 (s, 3H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 156.5 (C), 144.2 (C), 144.1 (C), 139.4 (CH), 135.7 (C), 130.0 (CH), 129.7 (2CH), 129.3 (CH), 128.2 (2CH), 128.1 (CH), 95.2 (C), 21.7 (CH_3), 18.1 (CH_3); Minor isomer: (*Z*)-: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.84 (d, *J* = 8.7 Hz, 2H), 7.79 (dd, *J* = 8.2, 1 Hz, 1H), 7.38 (td, *J* = 8.2, 1 Hz, 1H), 7.33 (s, 1H), 7.31 (d, *J* = 8.7, 2H), 7.05 (td, *J* = 8.2, 1.7 Hz, 1H), 6.92 (dd, *J* = 8.2, 1.7 Hz, 1H), 2.41 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 155.6 (C), 144.1 (C), 139.9 (CH), 139.6 (C), 135.5 (C), 131.2 (CH), 129.6 (2CH), 129.5 (CH), 128.1 (2CH), 127.7 (CH), 93.2 (C), 24.0 (CH_3), 21.7 (CH_3); HRMS (ESI) (M + H)$^+$ calculated for $C_{15}H_{16}IN_2O_2S$ 414.9959 found 414.9972.

Typical procedure for the Sonogashira coupling between hydrazone 6 and terminal alkynes

To 1 equivalent of *N*-tosylhydrazone (0.48 mmol) in 3 ml of anhydrous DMSO under argon inlet, 0.1 eq of $Pd(OAc)_2$ (0.048 mmol), 0.2 eq of rac-BINAP (0.097 mmol) and 0.2 eq of CuI (0.097 mmol) were respectively added. The reaction mixture was stirred at room temperature for 3 minutes. Then, 3 equivalents of the distilled base *i*Pr_2NH (1.45 mmol) were slowly added and the mixture stirred for about 1 minute before adding 2 equivalents of the terminal alkyne (0.97 mmol). The reaction mixture was stirred for 3 hours at 20 °C, than quenched with a saturated solution of NH_4Cl and washed with ethyl acetate. The organic layers were washed with a saturated solution of NaCl, dried with Na_2SO_4 and concentrated under pressure. Column chromatography (Cyclohexane/EtOAc 90/10) afforded the final products.

(*E*)-N'-(1-(2-((4-methoxyphenyl)ethynyl)phenyl)ethylidene)-4-methylbenzenesulfono- hydrazide 7a. Brown solid; Yield 76%; M = 418.14 g.mol^{-1}; m.p.: 141-144 °C; R_f = 0.36 (Cyclohexane/EtOAc 70/30); IR (film, cm-1): 2214, 2168, 1605, 1511, 1340, 1307, 1288, 1248, 1165, 1080, 1051, 1030, 906; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.02 (s, 1H), 7.90 (d, *J* = 8.3 Hz, 2H), 7.53 – 7.45 (m, 1H), 7.39 – 7.21 (m, 7H), 6.85 (d, *J* = 8.9 Hz, 2H), 3.81 (s, 3H), 2.37 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (75 MHz, CDCl3) δ 160.0 (C), 155.4 (C), 144.2 (C), 141.2 (C), 135.6 (C), 133.0 (2CH), 132.8 (CH), 129.7 (2CH), 128.8 (CH), 128.7 (CH), 128.2 (2CH), 128.1 (CH), 121.8 (C), 115.1 (C), 114.2 (2CH), 94.6 (C), 86.9 (C), 55.5 (OCH_3), 21.7 (CH_3), 17.3 (CH_3); HRMS (ESI) (M + H)$^+$ calculated for $C_{24}H_{23}N_2O_3S$ 419.1418 found 419.1424.

(*E*)-4-methyl-*N*'-(1-(*p*-tolylethynyl)phenyl)ethylidene)-benzenesulfonohydrazide 7b. Grey solid; Yield 82%; M= 402.14 g.mol^{-1}; m.p.: 142-144 ^{o}C; R_f = 0.33 (Cyclohexane/EtOAc 80/20); IR (film, cm^{-1}): 3459, 2214, 2040, 2006, 1971, 1950, 1597, 1511, 1405, 1341, 1309, 1166, 1081, 1052, 1019, 912; ^{1}H NMR (400 MHz, $CDCl_3$,) δ (ppm) 7.89 (d, *J* = 8.2 Hz, 2H), 7.82 (s, 1H), 7.51 (d, *J* = 7.3 Hz, 1H), 7.29 (m, 7H), 7.13 (d, *J* = 7.9 Hz, 2H), 2.37 (s, 3H), 2.37 (d, 3H), 2.32 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 155.1 (C), 144.2 (C), 141.3 (C), 139.0 (C), 135.6 (C), 133.0 (CH), 131.4 (2CH), 129.7 (2CH), 129.3 (2CH), 128.9 (CH), 128.8 (CH), 128.3 (CH), 128.2 (2CH), 121.7 (C), 120.0 (C), 94.7 (C), 87.6 (C), 21.7 (CH_3), 21.7 (CH_3), 17.2 (CH_3); HRMS (ESI) (M + H)$^+$ calculated for $C_{24}H_{23}N_2O_2S$ 403.1464 found 403.1475.

(*E*)-4-methyl- *N*'-(1-(*o*-tolylethynyl)phenyl)ethylidene)-benzenesulfonohydrazide 7c. Green solid; Yield 65%; M = 402.14 g.mol^{-1}; m.p.: 78-80 ^{o}C; R_f = 0.33 (Cyclohexane/EtOAc 80/20); IR (film, cm^{-1}): 3060, 2212, 2196, 2155, 2118, 2045, 2001, 1597, 1492, 1455, 1403, 1381, 1341, 1308, 1266, 1166, 1081, 1049, 920, 913, 814; ^{1}H NMR (300 MHz, DMSO) δ (ppm) 10.63 (s, 1H), 7.75 (d, *J* = 8.2 Hz, 2H), 7.59 – 7.54 (m, 1H), 7.42 (d, *J* = 6.8 Hz, 2H), 7.40 – 7.37 (m, 1H), 7.28 (d, *J* = 8.2 Hz, 4H), 7.23 (dd, *J* = 6.8, 2.3 Hz, 2H), 2.35 (s, 3H), 2.31 (s, 3H), 2.28 (s, 3H);^{13}C NMR (75 MHz, DMSO) δ 155.2 (C), 143.2 (C), 141.6 (C), 139.6 (C), 136.3 (C), 132.6 (CH), 131.6 (CH), 129.6 (CH), 129.3 (2CH), 128.9 (CH), 128.7 (CH), 128.7 (CH), 128.1 (CH), 127.3 (2CH), 125.8 (CH), 121.9 (C), 120.5 (C), 92.5 (C), 91.6 (C), 20.9 (CH_3), 20.2 (CH_3), 18.4 (CH_3); HRMS (ESI) (M + H)$^+$ calculated for $C_{24}H_{23}N_2O_2S$ 403.1468 found 403.1475.

(*E*)-*N*'-(1-(2-((4-(dimethylamino)phenyl)ethynyl)phenyl)-ethylidene)-4-methylbenzene- sulfonehydrazide 7d. Green solid; Yield 63%; M = 431.17 g.mol^{-1}; m.p.: 148-150 ^{o}C; R_f = 0.19 (Cyclohexane/EtOAc 80/20); IR (film, cm^{-1}): 3259, 3235, 2855, 2206, 2192, 2158, 2098, 2044, 2011, 1987, 1913, 1605, 1524, 1444, 1402, 1365, 1340, 1309, 1265, 1166, 1084, 1052; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.95 (s, 1H), 7.91 (d, *J* = 8.3 Hz, 2H), 7.47 (d, *J* = 7.7 Hz, 1H), 7.36 – 7.17 (m, 7H), 6.62 (d, *J* = 8.9 Hz, 2H), 2.98 (s, 6H), 2.37 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (75 MHz, DMSO) δ (ppm) 155.9 (C), 150.3 (C), 143.2 (C), 141.2 (C), 136.3 (C), 132.3 (2CH), 131.9 (CH), 129.4 (2CH), 128.7 (CH), 128.1 (CH), 127.7 (CH), 127.4 (2CH), 121.3 (C), 111.8 (2CH), 108.2 (C), 95.6 (C), 85.9 (C), 39.7 (2CH_3), 21.0 (CH_3), 18.2 (CH_3); HRMS (ESI) (M + H)$^+$ calculated for $C_{25}H_{26}N_3O_2S$ 432.1732 found 432.1740.

(*E*)-*N*'-(1-(2-((6-methoxynaphtalen-2-yl)ethynyl)phenyl)-ethylidene)-4-methylbenzene- sulfonohydrazide 7e.
Brown solid; Yield 82%; M = 468.15 g.mol^{-1}; m.p.: 152-154 ^{o}C; R_f = 0.17 (Cyclohexane/EtOAc 80/20); IR (film, cm^{-1}): 3368, 2214, 2199, 2038, 2017, 1985, 1627, 1601, 1499, 1477, 1437, 1390, 1339, 1309, 1261, 1211, 1165, 1121, 1094, 1080, 1052, 1030, 968, 909, 856, 814, 763, 733; ^{1}H NMR (300 MHz, DMSO) δ (ppm) 10.60 (s, 1H), 7.99 (s, 1H), 7.85 (d, *J* = 8.2 Hz, 2H), 7.76 (d, *J* = 8.2 Hz, 2H), 7.62 – 7.55 (m, 1H), 7.50 – 7.34 (m, 4H), 7.24 (dd, *J* = 12.2, 5.6 Hz, 4H), 3.90 (s, 3H), 2.36 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (75 MHz, DMSO) δ (ppm) 158.2 (C), 155.6 (C), 143.1 (C), 141.7 (C), 136.3 (C), 134.1 (C), 132.4 (CH), 130.9 (CH), 129.3 (3CH), 128.8 (CH), 128.6 (CH), 128.3 (CH), 128.1 (CH), 127.9 (C), 127.3 (2CH), 127.1 (CH), 120.5 (C), 119.4 (CH), 116.9 (C), 106.1 (CH), 94.3 (C), 87.5 (C), 55.3 (OCH_3), 20.9 (CH_3), 18.3 (CH_3); HRMS (ESI) (M + H)$^+$ calculated for $C_{28}H_{25}N_2O_3S$ 469.1567 found 469.1580.
(*E*)-4-methyl- *N*'-(1-(2-phenylethynyl)phenyl)ethylidene)-benzenesulfonohydrazide 7f. Green solid; Yield 81%; M= 388.12 g.mol^{-1};m.p.: 80-82 ^{o}C; R_f = 0.33 (Cyclohexane/EtOAc 80/20); IR (film, cm^{-1}): 3057, 2245, 2190, 2085, 2038, 2022, 1597, 1492, 1456, 1437, 1399, 1341, 1308, 1266, 1166, 1120, 1081, 1050, 1017, 916; ^{1}H NMR (300 MHz, MeOD) δ (ppm) 7.82 (d, *J* = 8.2 Hz, 2H), 7.54 – 7.45 (m, 1H), 7.33 (m, 7H), 7.25 (d, *J* = 8.0 Hz, 3H), 2.30 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (75 MHz, MeOD)δ (ppm) 157.5 (C), 145.2 (C), 143.4 (C), 137.5 (C), 133.6 (2CH), 132.4 (2CH), 130.4 (2CH), 129.7 (2CH), 129.5 (2CH), 129.3 (CH), 129.0 (2CH), 124.2 (C), 122.5 (C), 94.8 (C), 88.7 (C), 21.5 (CH_3), 18.3 (CH_3);HRMS (ESI) (M + H)$^+$ calculated for $C_{23}H_{21}N_2O_2S$ 389.1306 found 389.1318.

(*E*)-4-methyl- *N*'-(1-(2-(naphtalen-1-ylethynyl)phenyl)-ethylidene)benzenesulfonohydrazide 7g.
Grey solid; Yield 68%; M = 438.14 g.mol^{-1}; m.p.: 134-136 ^{o}C; R_f = 0.33 (Cyclohexane/EtOAc 80/20); IR (film, cm^{-1}): 2836, 1603, 1583, 1498, 1484, 1466, 1453, 1414, 1394, 1336, 1311, 1225, 1204, 1161, 1124, 1081, 1051, 1037, 1007, 950; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.26 (d, *J* = 8.3 Hz, 1H), 8.18 (s, 1H), 7.89 (d, *J* = 8.3 Hz, 2H), 7.83 (d, *J* = 6.5 Hz, 1H), 7.68 – 7.59 (m, 3H), 7.57 – 7.53 (m, 1H), 7.53 – 7.48 (m, 1H), 7.44 (d, *J* = 7.3 Hz, 1H), 7.39 (dd, *J* = 4.8, 3.0 Hz, 1H), 7.35 (d, *J* = 1.0 Hz, 2H), 7.17 (d, *J* = 8.1 Hz, 2H), 2.39 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (75 MHz, MeOD)δ (ppm)157.2 (C), 145.0 (C), 143.4 (C), 137.4 (C), 134.6 (C), 134.2 (C), 133.7 (CH), 131.4 (CH), 130.3 (2CH), 130.1 (CH), 129.8 (CH), 129.6 (CH), 129.4 (CH), 129.3 (CH), 128.9 (2CH), 128.2 (CH), 127.6 (CH), 126.8 (CH), 126.3 (CH), 122.5 (C), 121.5 (C), 93.6 (C), 92.9 (C), 21.4 (CH_3), 18.6 (CH_3); HRMS (ESI) (M + H)$^+$ calculated for $C_{27}H_{23}N_2O_2S$ 439.1459 found 439.1475.
(*E*)-*N*'-(1-(2-((4-fluorophenyl)ethynyl)phenyl)ethylidene)-4-methylbenzenesulfono- hydrazide 7h. Green solid; Yield 58%; M = 406.11 g.mol^{-1}; m.p.: 134-136 ^{o}C; R_f = 0.32 (Cyclohexane/EtOAc 80/20); IR (film, cm^{-1}): 3470, 3380, 3364, 3196, 3130, 3100, 3071, 2209,2158, 2108, 2045, 1987, 1958, 1599, 1508, 1405, 1342, 1308, 1229, 1168, 1093, 1048, 920; ^{1}H NMR (300 MHz, DMSO) δ (ppm) 10.59 (s, 1H), 7.75 (d, *J* = 8.3 Hz, 2H), 7.59 – 7.46 (m, 3H), 7.44 – 7.34 (m, 2H), 7.34 – 7.15 (m, 5H), 2.30 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (75 MHz, DMSO) δ (ppm) 162.1 (C, $^{1}J_{C-F}$ = 234.0 Hz), 155.4 (C), 143.2 (C), 141.8 (C), 136.3 (C), 133.6 (2CH, $^{3}J_{C-F}$ = 8.6.0 Hz), 132.5 (CH), 129.4 (2CH), 128.7 (2CH), 128.1 (CH), 127.4 (2CH), 120.2 (C), 118.6 (C, $^{4}J_{C-F}$ = 3.0 Hz), 115.9 (2CH, $^{2}J_{C-F}$ = 22.2 Hz), 92.4 (C), 87.6 (C), 20.9 (CH_3), 18.2 (CH_3); ^{19}F NMR (188 MHz, DMSO) δ (ppm) -108.42; HRMS (ESI) (M + H)$^+$ calculated for $C_{23}H_{20}FN_2O_2S$ 407.1230 found 407.1216.
(*E*)-*N*'-(1-(2-(thiophen-3-ylethynyl)phenyl)ethylidene)-4-methylbenzenesulfonohydrazide 7i. yellow oil; Yield 60%; M = 394.51 g.mol^{-1}; R_f = 0.29 (Cyclohexane/EtOAc 80/20); IR (film, cm^{-1}): 3215, 1597, 1439, 1401, 1385, 1339, 1309, 1246, 1187, 1165, 1080, 1050, 1018; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)8.29 (bs, 1H), 7.89 (d, *J* = 8.3 Hz, 2H), 7.52 – 7.44 (m, 1H), 7.42 (dd, *J* = 3.0, 1.1 Hz, 1H), 7.25 (dd, *J* = 8.3, 6.3 Hz, 6H), 7.08 (dd, *J* = 5.0, 1.1 Hz, 1H), 2.35 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)155.3 (C), 144.2 (C), 141.4 (C), 135.5 (C), 132.8 (CH), 129.7 (3CH), 128.9 (CH), 128.7 (CH), 128.7 (CH), 128.3 (CH), 128.1 (2CH), 125.6 (CH), 122.0 (C), 121.4 (C), 89.6 (C), 87.7 (C), 21.7 (CH_3), 17.34 (CH_3); HRMS (ESI) (M + H)$^+$ calculated for $C_{21}H_{19}N_2O_2S_2$ 395.0888 found 395.0888.

General procedure for the sequential synthesis of benzofulvenes 5

Condition A: In a sealed tube, *N*'-(2-alkynylbenzilidene)hydrazide (**7**) (0.48 mmol), $PdCl_2(MeCN)_2$ (0.05 mmol, 10 mol%), 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (XPhos) (0.1 mmol, 20 mol %), and 3 mL of fluorobenzene (PhF) were mixed under argon for 5 minutes at rt. NaO*t*Bu (1.44 mmol, 3 eq) was then added, the reaction mixture is stirred for 1 minute and aryl halide (0.38 mmol, 0.80 eq) is added. The reaction vessel was then capped with a pressure screw cap and the reaction mixture was stirred at 100 °C for 3 h. After cooling to room temperature, EtOAc was added to the mixture, which was filtered through celite. The solvents were evaporated under reduced pressure. The crude residue was transferred in a sealed tube, where under argon inlet, PdI_2 (0.05 mmol, 10 mol%), 1,3-Bis(diphenylphosphino)propane (Dppp) (0.1 mmol, 20 mol%) and Cs_2CO_3 (0.48 mmol, 1 eq) were mixed in 3 mL of dioxane. The reaction vessel was then capped with a pressure screw cap and the reaction mixture was stirred at 150 °C for 12 hours. The crude reaction mixture was allowed to cool to room temperature. EtOAc was added to the mixture, which was filtered through celite. The solvents were evaporated under reduced pressure and the crude residue purified by flash chromatography on silica gel.
Condition B: In a sealed tube, *N*'-(2-alkynylbenzilidene)hydrazide (**7**) (0.48 mmol), $PdCl_2(MeCN)_2$ (0.05 mmol, 10 mol%), 1,3-Bis(diphenylphosphino)propane (Dppp) (0.1 mmol, 20 mol%) and 3 mL of dioxane were mixed under argon for 5 minutes at rt. Cs_2CO_3 (1.44 mmol, 3 eq) was

then added, the reaction mixture is stirred for 1 minute and aryl halide (0.38 mmol, 0.80 eq) is added. The reaction vessel was then capped with a pressure screw cap and the reaction mixture was stirred at 100 °C for 3 h. After cooling to room temperature, EtOAc was added to the mixture, which was filtered through celite. The solvents were evaporated under reduced pressure. The crude residue was transferred in a sealed tube, where under argon inlet, PdI_2 (0.05 mmol, 10 mol%), 1,3-Bis(diphenylphosphino)propane (Dppp) (0.1 mmol, 20 mol%) and Cs_2CO_3 (0.48 mmol, 1 eq) were mixed in 3 mL of dioxane. The reaction vessel was then capped with a pressure screw cap and the reaction mixture was stirred at 150 °C for 15 hours. The crude reaction mixture was allowed to cool to room temperature. EtOAc was added to the mixture, which was filtered through celite. The solvents were evaporated under reduced pressure and the crude residue purified by flash chromatography on silica gel.

(*E*)-4-(1-(4-methoxybenzylidene)-1*H*-inden-3-yl)benzonitrile 5a.

Conditions A. For a complete description, see reference 5.

(*E*)-1-(4-methoxybenzylidene)-3-(*p*-tolyl)-1*H*-indene 5b.

Condition A: Yellow oil; Yield 62%; M = 324.42 g.mol^{-1}; R_f = 0.85 (Cyclohexane/EtOAc 70/30); IR (film, cm^{-1}): 3068, 2957, 2923, 2854, 2835, 1730, 1601, 1569, 1510, 1464, 1446, 1377, 1342, 1303, 1256, 1174, 1141, 1112, 1052; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.80 – 7.75 (m, 1H), 7.64 (m, 5H), 7.47 (s, 1H), 7.35 – 7.26 (m, 4H), 7.15 (s, 1H), 6.99 (d, *J* = 8.8 Hz, 2H), 3.87 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 160.1 (C), 146.9 (C), 140.7 (C), 139.3 (C), 138.1 (C), 137.5 (C), 133.2 (C), 131.9 (2CH), 130.1 (C), 129.5 (2CH), 127.9 (CH), 127.7 (2CH), 127.1 (CH), 125.4 (CH), 122.7 (CH), 120.4 (CH), 119.2 (CH), 114.5 (2CH), 55.5 (OCH_3), 21.5 (CH_3); HRMS (ESI) $(M + H)^+$ calculated for $C_{24}H_{21}O$ 325.1592 found 325.1596.

(*E*)-1-(4-methoxybenzylidene)-3-(4-methoxyphenyl)-1*H*-indene 5c.

Condition B: Yellow oil; Yield 55%; M = 340.41 g.mol^{-1}; R_f = 0.8 (Cyclohexane/EtOAc 70/30); IR (film, cm^{-1}): 3000, 2958, 2835, 1731, 1599, 1569, 1510, 1498, 1462, 1441, 1418, 1378, 1342, 1302, 1284, 1246, 1172, 1111, 1052, 1028; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.81 – 7.73 (m, 1H), 7.70 – 7.57 (m, 5H), 7.45 (s, 1H), 7.33 – 7.27 (m, 2H), 7.11 (s, 1H), 7.00 (dd, *J* = 9.9, 8.9 Hz, 4H), 3.88 (s, 3H), 3.87 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 160.0 (C), 159.7 (C), 146.5 (C), 140.7 (C), 139.4 (C), 137.5 (C), 131.9 (2CH), 130.1 (C), 129.0 (2CH), 128.6 (C), 127.6 (CH), 127.1 (CH), 125.4 (CH), 122.1 (CH), 120.4 (CH), 119.2 (CH), 114.5 (2CH), 114.2 (2CH), 55.5 ($2OCH_3$); HRMS (ESI) $(M + H)^+$ calculated for $C_{24}H_{21}O_2$ 341.1542 found 341.1537.

(*E*)-1-benzylidene-3-(4-methoxyphenyl)-1*H*-indene 5d.

Condition B: Yellow oil; Yield 60%; M = 310.39 g.mol^{-1}; R_f = 0.67 (Cyclohexane/EtOAc 80/20); IR (film, cm^{-1}): 2956, 2923, 2852, 1732, 1606, 1502, 1465, 1453, 1438, 1343, 1303, 1286, 1249, 1177, 1157; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.82 – 7.74 (m, 1H), 7.71 – 7.64 (m, 4H), 7.63 – 7.57 (m, 1H), 7.47 (dd, *J* = 14.7, 7.5 Hz, 3H), 7.37 (dd, *J* = 5.0, 3.7 Hz, 1H), 7.35 – 7.29 (m, 2H), 7.10 (s, 1H), 7.05 – 6.98 (m, 2H), 3.88 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 159.8 (C), 147.2 (C), 141.1 (C), 139.4 (C), 137.4 (C), 136.0 (C), 130.3 (2CH), 129.0 (2CH), 128.9 (2CH), 128.4 (C), 128.3 (CH), 127.60 (CH), 125.6 (CH), 124.9 (CH), 122.2 (CH), 120.5 (CH), 119.4 (CH), 114.2 (2CH), 55.5 (OCH_3); HRMS (ESI) $(M + H)^+$ calculated for $C_{23}H_{19}O$ 311.1436 found 311.1432.

(*E*)-3-((3-(4-methoxyphenyl)-1H-inden-1-ylidene)methyl)-thiophene 5e.

Condition B: Yellow oil; Yield 40%; M = 316.42 g.mol^{-1}; R_f = 0.67 (Cyclohexane/EtOAc 80/20); IR (film, cm^{-1}): 2958, 2927, 2834, 1621, 1606, 1501, 1448, 1415, 1361, 1330, 1303, 1286, 1250, 1177, 1033; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)7.78 – 7.70 (m, 1H), 7.67 (d, *J* = 8.8 Hz, 2H), 7.62 – 7.55 (m, 2H), 7.49 (dd, *J* = 5.0, 1.2 Hz, 1H), 7.43 (s, 1H), 7.41 (dd, *J* = 5.0, 2.9 Hz, 1H), 7.32 – 7.27 (m, 2H), 7.09 (s, 1H), 7.02 (d, *J* = 8.8 Hz, 2H), 3.88 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm)159.8 (C), 146.6 (C), 141.0 (C), 139.3 (C), 139.1 (C), 138.0 (C), 129.0 (2CH), 128.7 (CH), 128.4 (C), 127.2 (CH), 127.0 (CH), 126.6 (CH), 125.5 (CH), 122.0 (CH), 121.2 (CH), 120.6 (CH), 119.3 (CH), 114.3 (2CH), 55.5 (OCH_3); HRMS (ESI) $(M + H)^+$ calculated for $C_{21}H_{17}OS$ 317.1000 found 317.1002.

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Notes and references

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