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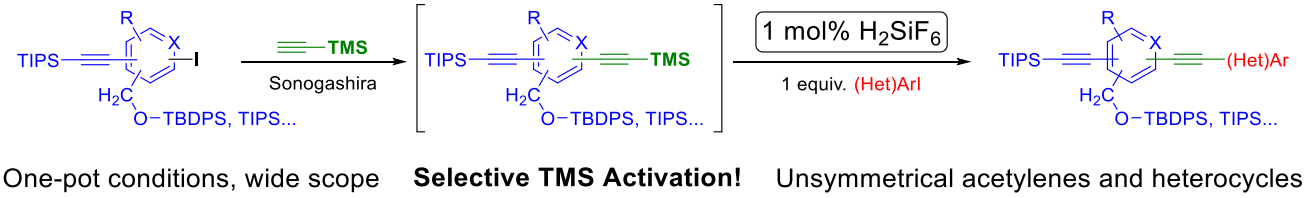
Catalytic Activation of Trimethylsilylacetylenes: A "One –Pot" Route to Unsymmetrical Acetylenes and Heterocycles

Dániel Lasányi,[a] Ádám Mészáros,[a] Zoltán Novák,[a,*] Gergely L. Tolnai[a,*]

[a] Institute of Chemistry, Eötvös University, Pázmány P. stny 1/a, H1117, Budapest, Hungary

novakz@elte.hu; web: http://zng.elte.hu, tolnai@chem.elte.hu, web: http://tolnai.chem.elte.hu



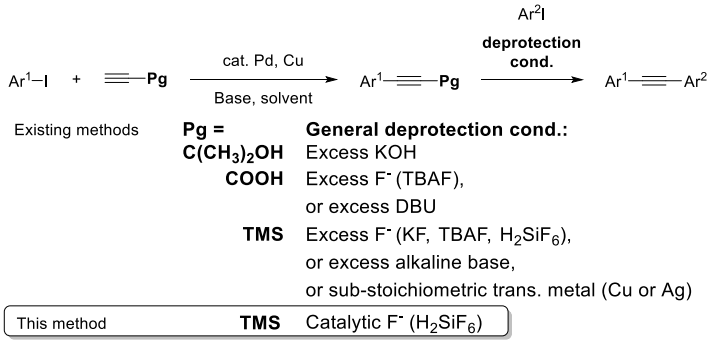
ABSTRACT: For the synthesis of unsymmetrical acetylenes, a Sonogashira coupling-deprotection-Sonogashira coupling reaction sequence is often used. Removal of protecting groups requires harsh conditions or an excess of difficult to handle and expensive reagents. Herein we disclose a novel catalytic method for the selective deprotection of trimethylsilylacetylenes in Sonogashira reaction. The reagent hexafluorosilicic acid, an inexpensive non-toxic compound was used to promote the selective desilylation. This method enables the efficient synthesis of unsymmetric acetylenes with other silylated functional groups present. Further possibilities of the method was explored by synthesis of heterocycles.

INTRODUCTION

Diaryl acetylenes are widely used compounds not only because of their synthetic utility, but their unique optical and electronic properties.[1] In the art of molecular engineering diaryl acetylenes are often used as linear building blocks.[2] Their synthesis therefore is a useful conquest of organic chemistry and has different solutions. The first synthesis of diaryl acetylenes consists of elimination and/or rearrangement strate-

gies, usually requires strong bases and harsh reaction conditions.[3] The synthesis strategies for aryl acetylenes has changed with the Sonogashira reaction[4] that is one of the most efficient sp-sp^2 carbon-carbon bond forming reactions. The modern synthesis of unsymmetrical acetylenes preliminary use tandem Sonogashira reactions.[5]

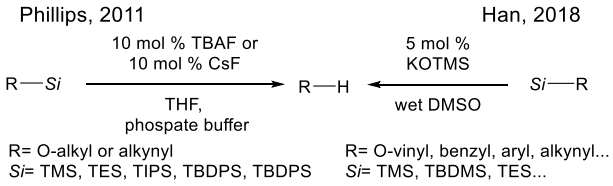
Despite their obvious drawbacks, the use of protecting groups has an inevitable positive impact on organic synthesis. For the efficient synthesis of the unsymmetrical acetylenes, the choice of the right C2 source is crucial. Carbinols are one of the cheapest acetylene sources,[5-6] however the deprotection requires harsh alkaline conditions in the Sonogashira coupling. (Scheme 1) Propiolic acid can also be used as the alkyne source.[7] The alkynylcarboxilyc acid can be activated by excess tetrabutylammoniumfluoride (TBAF) or DBU. The most extensively used acetylene source in tandem Sonogashira reaction is trimethylsilylacetylene[8,9] due to the ease of deprotection with excess of KOH, or fluoride source, preliminary TBAF. This hygroscopic and expensive fluoride source disables the feasibility of the synthesis of complex substrates, as other silyl groups, or base-sensitive functionalities cannot be present elsewhere on the molecule. Established methods for Sonogashira couplings directly from alkynylsilanes require the addition of sub-stoichiometric amount of silver or copper metal, or the addition of equivalent fluoride source.[10] These conditions often result in side-products,[11] as well as desilylation of other protected functionalities. Another general drawback of these methods are the high temperature and high Pd-loading.



Scheme 1. Tandem Sonogashira Protocols

There is an interesting, yet very specialized method of using catalytic TBAF for the desilylation of TMS-acetylenes in the synthesis of steroidal oral contraceptives. The deprotection only happens in the very basic conditions of carbonyl addition, and took advantage of the nearby alkoxide, that –according to the authors– was able to regenerate the fluoride ion from TMSF.[12]

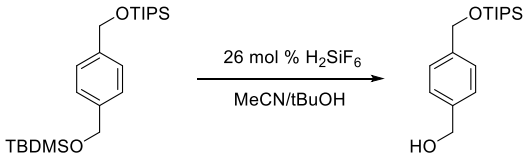
A general mild catalytic desilylation method was published by Philipps, using buffer solutions (Scheme 2, left).[13] The method utilizes TBAF or CsF as a fluoride source. An elegant fluoride ion free alternative has been shown by Han and coworkers (Scheme 2, right).[14] With catalytic amount of KOTMS, wide variety of alkynylsilanes could be deprotected. Both methods are effectively removing TES, TBDMS, TIPS protecting groups from oxygen and alkynes.



Scheme 2. Catalytic Protodesilylation Strategies

However, these methods serve a useful way to gain terminal acetylenes, those type of compounds are rarely the goal of synthesis. Terminal acetylenes are usually serve as building block for internal acetylenes or heterocycles.[15]

DeShong's studies on deprotection of O benzyl-silyl ethers showed, that hexafluorosilicic acid is a very potent compound in cleavage of Si-O bonds.[16] Later studies (Scheme 3) proved, that using H_2SiF_6 in a sub-stoichiometric manner provide selective removal of TBDMS over TIPS from benzyl-ethers.[17]



Scheme 3. Selective Deprotection of O-Si Bond with H_2SiF_6

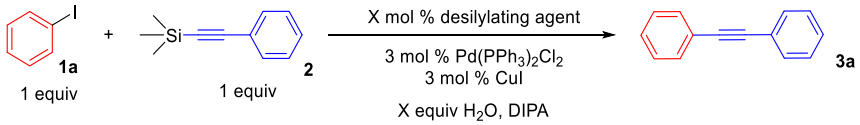
RESULTS AND DISCUSSION

These results and our experience on desilylation of alkynylacetamides[18] inspired us to find a general selective catalytic desilylation method in tandem Sonogashira reactions. H_2SiF_6 is a very cheap[19] industrial starting material available as an aqueous solution, used in water fluorination of drinking water.[20] The fact, that the compound is able to remove the silyl group in a sub-equivalent fashion, encouraged us to further improve its efficiency to establish a general tandem Sonogashira reaction that is able to generate unsymmetrical acetylenes with a wide scope.

To elucidate the frontiers of the desilylating agent in the Sonogashira conditions, iodobenzene (**1a**) and TMS-phenylacetylene (**2**) were applied as model substrates, and the coupling reactions were performed in the presence of common 3 mol% $Pd(PPh_3)_2Cl_2$, and CuI catalyst system. To our delight 1.0 and 0.5 equivalent of the addition of hexafuorosilicic acid resulted in complete conversion by GC under the Sonogashira conditions (Table 1, entries 1-2). The addition of 1 % of this compound resulted in 28 % conversion (entry 3). As the H_2SiF_6 is in a 34 % aqueous solution, we assumed, that the lack of nucleophile could have led to the loss of activity in our case. Thus, adding 10 equivalents of water increased the yield to 60 % in 24 h and to 100% in 48 h (entries 4 and 6), but only in the presence of hexafluorosilicic acid (entry 5). Other hexafluorosilicates (entries 7-9) had were less asctive, as 10, 18 and 37 % conversions with potassium-, sodium- and ammonium-hexafluorosilicates were observed in the same conditions at 20% catalyst loadings. This might be the result of the low solubility of these compounds in the media. However, the reaction resulted in full conversion in 48 h, it was found, that increasing the temperature sped up the reaction without noticeable side effects. The reaction led to 91 % conversion in 24 h on 60 °C (entry 11) with only 1% of desilylating agent. As the presence of water turned out to be an important factor, different amounts of water was added over the aqueous solution (entries 12-14). No loss of activity was observed down to 5 equivalents of H_2O, but either increasing to 20 equivalents, or decreasing to 1 equivalent was inferior to 5 or 10 equivalents in these conditions. With 1% HCl, from a 36 % aqueous

solution and 10 equivalents of water, the conversion was 5 % (entry 15). A control experiment omitting hexafluorosilicic acid resulted in only 7% yield in our condition (entry 16). The low efficiency of "sila" Sonogashira coupling under these mild conditions predicts the good efficiency of tandem reaction, as the homocoupling could be suppressed, without a further manipulation with catalysts or temperature. The conditions of entry 11 gave no coupled product with chlorobenzene, and led to a 55% conversion with bromobenzene.

Table 1. Optimization of Reaction Conditions



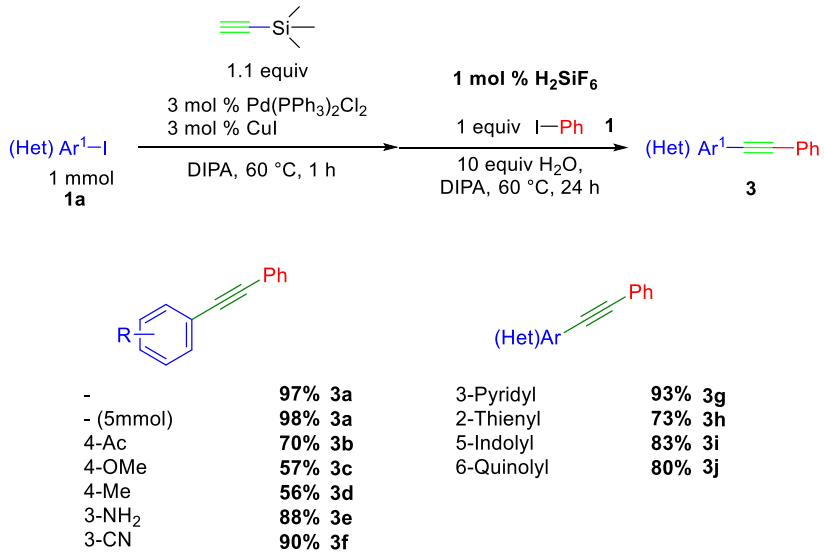
Entry	Desilylating agent	mol%	H_2O added (equiv)	Time (h)	T (°C)	Yield[a] (%)
1	H_2SiF_6	100		24	25	98
2	H_2SiF_6	50		24	25	98
3	H_2SiF_6	1	-	24	25	28
4	H_2SiF_6	1	10	24	25	60
5	-	0	10	24	25	traces
6	H_2SiF_6	1	10	48	25	100
7	K_2SiF_6	20	10	48	25	10
8	Na_2SiF_6	20	10	48	25	18
9	$(NH_4)_2SiF_6$	20	10	48	25	37
10	H_2SiF_6	0.5	10	24	60	50
11	H_2SiF_6	**1**	**10**	24	**60**	**91**
12	H_2SiF_6	1	5	24	60	87
13	H_2SiF_6	1	20	24	60	61
14	H_2SiF_6	1	1	24	60	39
15	HCl	1	10	24	60	5
16	-	0	10	24	60	7

[a] As determined by GC-FID, on 0.5 mmol scale

With the optimized reaction condition in hand, we turned our attention to establish conditions for a tandem coupling reaction. As predicted by the preliminary results, the deprotection of the acetylene was

not likely to occur without the H_2SiF_6. Indeed, the first Sonogashira coupling proceeded to complete conversion, enabling a one-pot procedure for the coupling. To establish the synthetic utility of the method, we examined the scope of this reaction with 1 mmol of the starting aryl halides, in the presence of only 1 mol% of the desilylating agent.

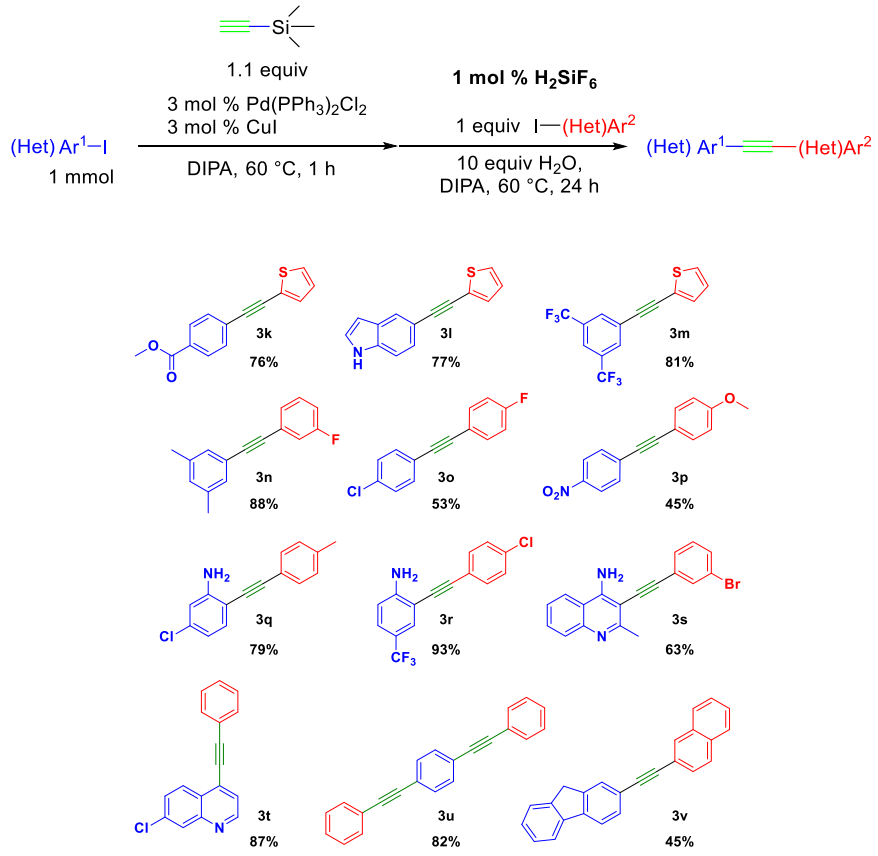
First, we ran a series of experiments with different monofunctionalized aryl iodides, TMS-acetylene and iodobenzene. As expected, diaryl acetylenes (Scheme 4, **3a-f**) were obtained with different functionalities, including electron donating and electron withdrawing in medium to excellent yields. For medicinal chemistry applications, the use of heterocyclic compounds is very important. Our one pot method proved to be excellent in this field, as iodo- pyridine, indole, thiophene and quinoline (**3g-j**) provided the corresponding internal acetylenes in very good to excellent yields.



Scheme 4. Synthesis of Unsymmetric Acetylenes (I)

Acetylenic thiophenes are present in material science as conducting polymers and nonlinear optical materials.[21] Using the developed conditions, series of unsymmetrical thienyl acetylenes (Scheme 5, **3k-m**) were synthesized in good yields. Continuing the exploration of the substrate scope of acetylene products, series of acetylenes with different aryl groups (**3n-t**) were synthesized.

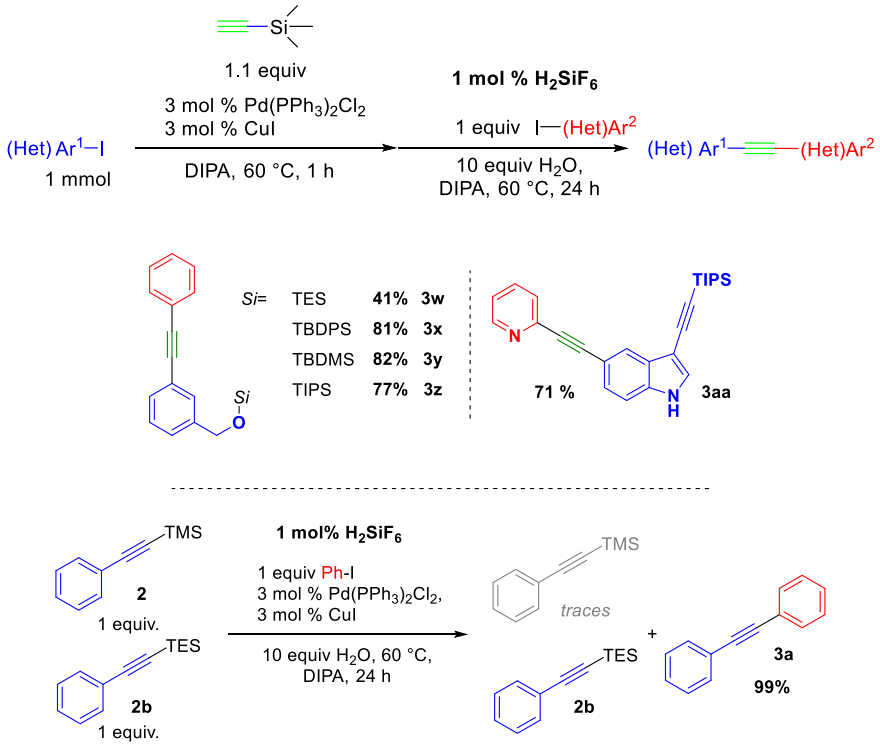
Multicyclic hydrocarbons **3u-v**, with extended conjugation were also synthesized with good efficiency. Synthesis of the molecular rod **3u** provided 82 % yield, with 2.2 equivalent TMSA and 0.5 % H_2SiF_6 respectively to the TMS.



Scheme 5. Synthesis of Unsymmetric Acetylenes (II)

To further challenge our synthetic methodology, we aimed to explore the stability of different silyl groups. Primary silyl ethers are the most labile silyl ethers due to the lack of steric hindrance. 3-Iodobenzyl alcohol was protected with different silyl protecting groups. As a first example, coupling and selective TMS-acetylene activation was demonstrated with the TES, TBDPS, TBDMS and TIPS groups (Scheme 6, **3w-z**). All of these aryl-iodides provided the unsymmetrical diaryl acetylene. Competing deprotection in a ratio of 1:9 was only observed in the case of O-TES, indicating that the low yield might only be a

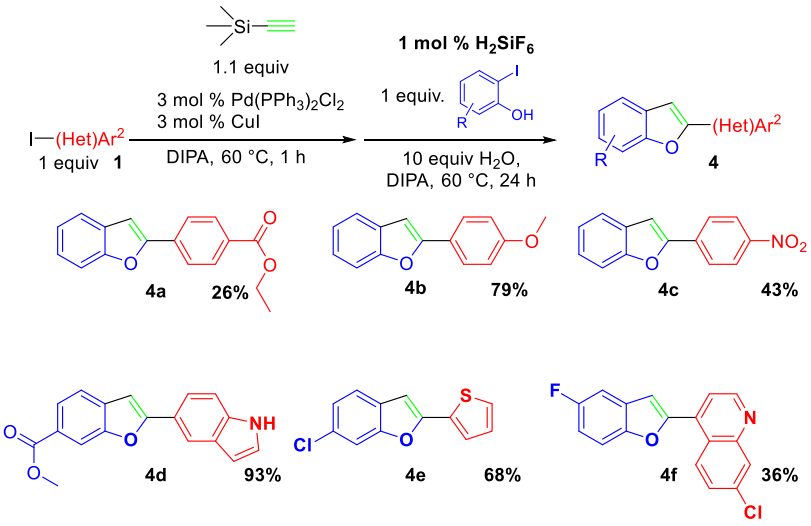
problem with the workup. Iodoindole, with a TIPS-protected acetylene at position 3 was coupled with TMS-acetylene, and one pot coupled with iodopyridine, by the aid of 1% H_2SiF_6. To our delight the expected product **3aa** was isolated in 71% yield, and no sign of TIPS-deprotection was observed. In a further control experiment (Scheme 6, down), the mixture the 1 equivalent of iodobenzene was reacted in our optimized conditions with equimolar TES- and TMS-phenylacetylenes. As a result, full conversion of PhI and only ~1% of TMS-phenylacetylene was detected after 24 h. The TES-protected acetylene remained intact.



Scheme 6. Synthesis of Internal Acetylenes with Various Silyl Protecting Groups Present

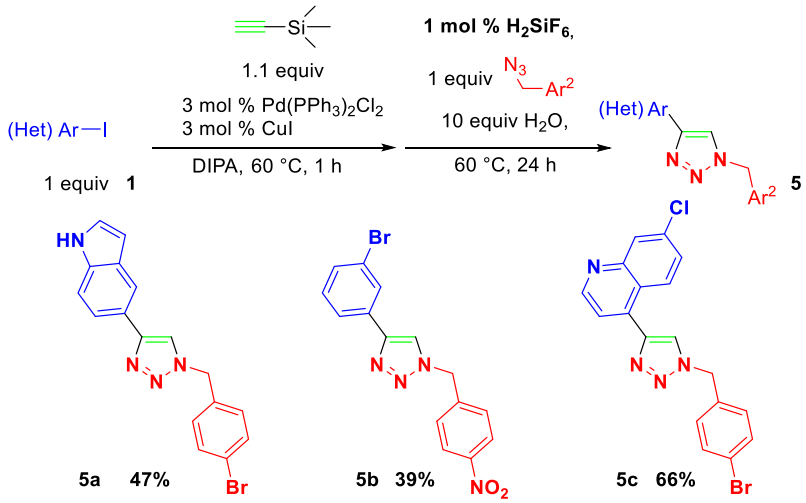
One of the preliminary uses of aromatic acetylenes in organic synthesis is applying them as building blocks for the construction of heterocycles. Utilizing the exact same conditions, a 4 step one-pot synthesis of benzofurans was performed, where the Sonogashira coupling, the deprotection and the second coupling followed by ring closing takes place. A series of complex heterocycles were produced (Scheme 7, **4a-f**). This procedure affects the formation of 3 new C-C or C-O bonds. However the conditions are unoptimized

and this lead to some degree of (presumably) polymerized side-products in the case of **4a** and **f**, the yields are ranging up to 93% (**4b-e**)



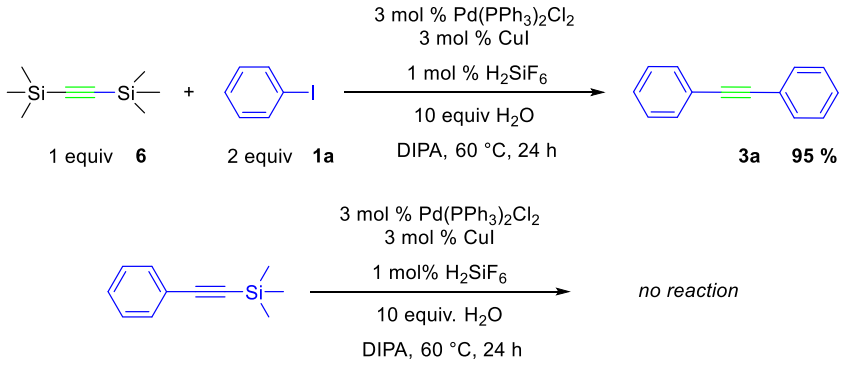
Scheme 7. Synthesis of Benzofurans

An other general use of acetylenes are synthesizing triazoles, therefor the general conditions were challenged to examine to scope of a tandem reaction of this kind. Same condition has been applied to generate a small set of triazoles (Scheme 8, **5a-c**) via CuAAC type of ring construction. To our delight the catalytic coupling-desilylation protocol was useful in synthesizing this class of compounds in one-pot. Importantly, **5a-c**, along with other compounds like **3r-t** and **4f,** could be further modified by other cross-coupling methods.



Scheme 8. Synthesis of Triazoles

The mechanistic aspects of this reaction are not clear at the moment. Generally observed side products of this reaction were silyl ethers. The need of water for the efficient synthesis could suggest the preliminary formation of a terminal acetylene. Control experiment on coupling with bis(trimethylsilyl)acetylene (Scheme 9, **6**) with 2 equivalents of **1a** led to high yield of **3a** (95%), instead of generating ethyn. This could be due to the direct transmetalation from Si to Cu or Pd or the immediate Sonogashira reaction in this condition therefore avoiding the formation of HCCH.



Scheme 9. Investigation on Mechanism

These results were examined more in depth: in a control experiment iodobenzene was omitted from the coupling of TMS-phenylacetylene (Scheme 9). Surprisingly, instead of protodesilylation, no change was observed on the starting materials after 24 h. One pathway would be the formation of $^{-}$OTMS, from water and the protecting group in situ. This version does not seem likely, as Han's method[14] is a general desilylation process, and there is a high TMS selectivity in our case. As a plausible reaction scheme, hexafluorosilicic acid is first hydrolyzed. The transmetalation to the transition metal can be accelerated by the coordination of the SiF_x as a Lewis acid. Transmetalation from Si to Cu is suggested in the literature.[22]

CONCLUSIONS

In conclusion, a new catalyst, the cheap and easy to handle H_2SiF_6 was introduced for the selective desilylation of TMS alkynes in tandem Sonogashira cross-coupling reaction. With the optimized protocol a tandem Sonogashira condition was developed, where great variety of unsymmetrical acetylenes were synthetized, with very low catalyst loading. The new selective trimethylsilane activating agent enabled the coupling of substrates with the generally used Si-O and Si-acetylene protecting groups present. Moreover, the synthetic utility was demonstrated in the synthesis of benzofuran and triazole heterocycles.

EXPERIMENTAL SECTION

Unless otherwise indicated, all starting materials were obtained from commercial suppliers, and were used without further purifcation. Analytical thin-layer chromatography (TLC) was performed on Merck DC precoated TLC plates with 0.25 mm Kieselgel 60 F_{254}. Visualization was performed with a 254 nm UV lamp. The ^1H (250 MHz), ^{13}C (63 MHz) and ^{19}F (235 MHz) NMR spectra were recorded on a Bruker Avance-250 spectrometer and in $CDCl_3$, and DMSO-d_6, at room temperature. Chemical shifts are expressed in parts per million (δ) using residual solvent protons as internal standards (δ 7.26 for ^1H, δ 77.0 for ^{13}C) for $CDCl_3$ and (δ 2.50 for ^1H, δ 39.5 for ^{13}C) for DMSO-d_6. Coupling constants (*J*) are reported in Hertz (Hz). Splitting patterns are designated as *s* (singlet), *d* (doublet), *t* (triplet), *q* (quartet), *m* (multiplet). Combination gas chromatography and low resolution mass spectrometry was obtained on an Agilent 6890N Gas Chromatograph (30 m x 0.25 mm column with 0.25 μm HP-5MS coating, He carrier gas) and Agilent 5973 Mass Spectrometer (Ion source: EI+, 70eV, 230 °C; interface: 300 °C). IR spectra were obtained on a Bruker IFS55 spectrometer on a single-reaction diamond ATR unit. All melting points were measured on Büchi 501 apparatus and are uncorrected. High-resolution mass spectra were acquired on an Agilent 6230 time-of-flight mass spectrometer equipped with a Jet Stream electrospray ion source in positive ion mode. Injections of 0.1-0.3 μl were directed to the mass spectrometer at a flow rate of 0.5 ml/min (70% acetonitrile-water mixture, 0.1 % formic acid), using an Agilent 1260 Infinity HPLC system. Jet:

drying gas (N_2) flow and temperature: 10.0 l/min and 325 °C, respectively; nebulizer gas (Stream parameters N_2) pressure: 10 psi; capillary voltage: 4000 V; sheath gas flow and temperature: 325 °C and 7.5 l/min; TOFMS parameters: fragmentor voltage: 120 V; skimmer potential: 120 V; OCT 1 RF Vpp:750 V. Full-scan mass spectra were acquired over the m/z range 100-2500 at an acquisition rate of 250 ms/spectrum and processed by Agilent MassHunter B.03.01 software.

Synthesis of Starting Materials

Triethyl((3-iodobenzyl)oxy)silane 1w

Chlorotriethylsilane (301.4 mg, 2.0 mmol, 1.0 equiv) was added to a stirring solution of imidazole (163.4 mg, 2.4 mmol, 1.2 equiv) and 3-iodo-benzylalcohol (468.1 mg, 2.0 mmol, 1.0 equiv) in CH_2Cl_2 (8 mL). The reaction was sealed and stirred at room temperature for overnight. CH_2Cl_2 (15 mL) was added, the organic layer was washed twice with H_2O (30 mL). The aqueous layers were combined and extracted with CH_2Cl_2 (30 mL). The organic layers were combined, washed with brine (50 mL), dried over $MgSO_4$ and concentrated under reduced pressure.

Colorless oil (578 mg, yield 83%), R_f.: 0.23 (in hexanes: EtOAc 100:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ = 7.61 (s, 1H), 7.49 (d, *J* = 7.8 Hz, 1H), 7.21 (d, *J* = 7.7 Hz, 1H), 6.98 (t, *J* = 7.7 Hz, 1H), 4.60 (s, 2H), 0.90 (t, *J* = 7.9 Hz, 9H), 0.57 (q, *J* = 8.1 Hz, 6H) ppm. ^{13}C{^{1}H}NMR (63 MHz, $CDCl_3$) δ = 144.1, 136.3, 135.5, 130.4, 125.7, 94.7, 64.2, 7.2, 4.8 ppm. IR (thin film, ATR) ν_{max} 2952, 2876, 1693, 1567 cm^{-1}. MS (EI, 70 eV) *m/z* (%): 348(1), 319(100, [M+]), 289(21), 217(34), 163(19), 90(23). HRMS calcd for $C_{13}H_{21}IOSi$ $[M]^+$ 348.0406 found 348.03969

tert-Butyl((3-iodobenzyl)oxy)diphenylsilane 1x

tert-Butyldiphenylchlorosilane (549.7 mg, 2.0 mmol, 1.0 equiv) was added to a stirring solution of imidazole (163.4 mg, 2.4 mmol, 1.2 equiv) and 3-iodo-benzylalcohol (468.1 mg, 2.0 mmol, 1.0 equiv) in CH_2Cl_2 (8 mL). The reaction was sealed and stirred at room temperature for overnight. CH_2Cl_2 (15 mL) was added, the organic layer was washed twice with H_2O (30 mL). The aqueous layers were combined

and extracted with CH_2Cl_2 (30 mL). The organic layers were combined, washed with brine (50 mL), dried over $MgSO_4$ and concentrated under reduced pressure.

Colorless oil (583.4 mg, yield 62%), R_f.: 0.25 (in hexanes: EtOAc 100:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ = 7.70 (dt, *J* = 6.4, 1.8 Hz, 5H), 7.60 (d, *J* = 7.7 Hz, 1H), 7.50 – 7.29 (m, 7H), 7.08 (t, *J* = 7.7 Hz, 1H), 4.72 (s, 2H), 1.12 (s, 9H) ppm. ^{13}C{^{1}H}NMR (63 MHz, $CDCl_3$) δ = 143.8, 136.3, 135.9, 135.5, 133.6, 130.4, 130.2, 128.2, 125.6, 94.6, 65.1, 27.2, 19.7 ppm. IR (thin film, ATR) ν_{max} 2961, 2931, 2892, 2856, 1592, 1567 cm^{-1}. MS (EI, 70 eV) *m/z* (%): 415(100, [M+]), 385(15), 337(15), 217(35), 211(25), 183(36), 90(27). HRMS calcd for $C_{19}H_{16}IOSi$ $[M-C_4H_9]^+$ 415.0015 found 415.0000

tert-Butyl((3-iodobenzyl)oxy)dimethylsilane[23] 1y

tert-Butyldimethylchlorosilane (302 mg, 2.0 mmol, 1.0 equiv) was added to a stirring solution of imidazole (163.4 mg, 2.4 mmol, 1.2 equiv) and 3-iodo-benzylalcohol (468 mg, 2.0 mmol, 1.0 equiv) in CH_2Cl_2 (8 mL). The reaction was sealed and stirred at room temperature for overnight. CH_2Cl_2 (15 mL) was added, the organic layer was washed twice with H_2O (30 mL). The aqueous layers were combined and extracted with CH_2Cl_2 (30 mL). The organic layers were combined, washed with brine (50 mL), dried over $MgSO_4$ and concentrated under reduced pressure.

Colorless oil (486.2 mg, yield 70%), R_f.: 0.24 (in hexanes: EtOAc 100:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ = 7.57 (s, 1H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.18 (d, *J* = 7.8 Hz, 1H), 6.96 (t, *J* = 7.7 Hz, 1H), 4.58 (s, 2H), 0.84 (s, 9H), 0.00 (s, 6H) ppm. ^{13}C{^{1}H}NMR (63 MHz, $CDCl_3$) δ = 144.2, 136.3, 135.4, 130.4, 125.5, 94.7, 64.5, 26.3, 18.8, -4.9 ppm. IR (thin film, ATR) ν_{max} 2958, 2933, 2885, 2858, 1567 cm^{-1}. MS (EI, 70 eV) *m/z* (%): 291(100, [M+]), 261(40), 217(41), 149(19), 90(21).

((3-Iodobenzyl)oxy)triisopropylsilane 1z

Triisopropylchlorosilane (386 mg, 2.0 mmol, 1.0 equiv) was added to a stirring solution of imidazole (163.4 mg, 2.4 mmol, 1.2 equiv) and 3-iodo-benzylalcohol (468 mg, 2.0 mmol, 1.0 equiv) in CH_2Cl_2 (8 mL). The reaction was sealed and stirred at room temperature for overnight. CH_2Cl_2 (15 mL) was added,

the organic layer was washed twice with H_2O (30 mL). The aqueous layers were combined and extracted with CH_2Cl_2 (30 mL). The organic layers were combined, washed with brine (50 mL), dried over $MgSO_4$ and concentrated under reduced pressure.

Colorless oil (706 mg, yield 90%), R_f.: 0.38 (in hexanes). ^{1}H NMR (250 MHz, $CDCl_3$) δ = 7.72 (s, 1H), 7.58 (d, *J* = 7.7 Hz, 1H), 7.33 (d, *J* = 7.6 Hz, 1H), 7.08 (t, *J* = 7.7 Hz, 1H), 4.79 (s, 2H), 1.11 (app. s, 21H) ppm. ^{13}C{^{1}H}NMR (63 MHz, $CDCl_3$) δ = 144.5, 136.1, 135.1, 130.4, 125.2, 94.6, 64.5, 18.4, 12.4 ppm. IR (thin film, ATR) ν_{max} 2943, 2867, 1592, 1567 cm^{-1}. MS (EI, 70 eV) *m/z* (%): 364(2), 347(100, [M+]), 319(20), 217(32), 91(17). HRMS calcd for $C_{24}H_{33}OSi$ $[M+H]^+$ 365.2301 found 365.2299

5-Iodo-3-((triisopropylsilyl)ethynyl)-1H-indole[24] 1aa

1-[(Triiso-propylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (1027 mg, 2.40 mmol, 1.2 equiv) was added to a stirring solution of AuCl (4.6 mg, 0.020 mmol, 0.01 equiv) and 5-iodoindole (2.0 mmol, 1.0 equiv) in Et_2O (40 mL). The reaction was sealed and stirred at room temperature overnight. Et_2O (50 mL) was added, the organic layer was washed twice with NaOH 0.1 M (75 mL). The aqueous layers were combined and extracted with Et_2O (100 mL). The organic layers were combined, washed with saturated $NaHCO_3$ (100 mL), brine (100 mL), dried over $MgSO_4$ and concentrated under reduced pressure.

Brown solid (767.3 mg, yield 91%) Mp.= 75- 77 °C (Ref.: 75-77 °C), R_f.: 0.20 (in hexanes: Et_2O 7:3). ^{1}H NMR (250 MHz, $CDCl_3$) δ = 8.14 (s, 1H), 7.96 (dd, *J* = 1.6, 0.8 Hz, 1H), 7.41 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.29 (d, *J* = 2.7 Hz, 1H), 7.06 (dd, *J* = 8.5, 0.6 Hz, 1H), 1.09 (app. s, 21H) ppm. ^{13}C{^{1}H}NMR (63 MHz, $CDCl_3$) δ = 134.5, 131.6, 129.5, 129.2, 113.6, 99.6, 99.3, 92.9, 84.8, 19.2, 11.8 ppm. IR (^{thin} film, ATR) ν_{max} 2943, 2865, 2144, 1451, 1410 cm^{-1}. MS (EI, 70 eV) *m/z* (%): 423(43), 381(23), 380(100, [M+]), 310(50), 210(65), 168(75), 142(23), 59(11).

General procedure for the one-pot synthesis

Into a 7 mL screw cap vial CuI (5.7 mg, 0.03 mmol, 0.03 equiv.) and $Pd(PPh_3)_2Cl_2$ (21.1 mg, 0.03 mmol, 0.03 equiv.) was and the starting aryl halide (1 mmol, 1 equiv.) if a solid, was filled. The vial was closed,

and the atmosphere was changed 3 times to Ar. DIPA (4 mL) was added, and the starting aryl halide (1 mmol, 1 equiv.) if a liquid. Trimethylsilylacetylene (154 μL, 1.1 mmol, 1.1 equiv.) was added via a syringe and the mixture was stirred at 60 °C for 1 h. The completion of the first coupling was verified by TLC, then the second aryl halide (1 mmol, 1 equiv.) was added. Hexafluorosilicic acid (34 % in aqueous solution, 3 μL, 0.01 mmol, 0.01 equiv.) and water (180 μL) was added via Hamilton syringes. The mixture was stirred for 24 h at 60 °C. The mixture was diluted with EtOAc (15 mL) and water (15 mL), the pH of the aqueous phase was adjusted to neutral. The layers were separated, then the aqueous phase was extracted with EtOAc (2 x15 mL). The combined organic layers were dried over $MgSO_4$. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography.

1,2-Diphenylethyne[25] 3a

The general procedure was followed. White solid (175.5 mg, yield 98%), Mp.: 54-55 °C (Ref.: 54-55 °C), R_f.: 0.53 (in hexanes:EtOAc 25:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ = 7.70 – 7.51 (m, 4H), 7.48 – 7.30 (m, 6H) ppm. $^{13}C\{^1H\}$NMR (63 MHz, $CDCl_3$) δ = 132.1, 128.8, 128.7, 123.7, 89.8 ppm. IR (thin film, ATR) ν_{max} 1599, 1571, 1492, 1441 cm^{-1}. MS (EI, 70 eV) *m/z* (%): 178 (100, [M$^+$]), 152 (20), 126 (10), 76 (15).

5 mmol Scale Experiment

Into a 50 mL round bottomed flask CuI (28.6 mg, 0.15 mmol, 0.03 equiv.) and $Pd(PPh_3)_2Cl_2$ (105.3 mg, 0.15 mmol, 0.03 equiv.) was and the starting aryl halide (5 mmol, 1 equiv.) if a solid, was filled. The flask was closed, and the atmosphere was changed 3 times to Ar. DIPA (20 mL) was added, and the starting aryl halide (5 mmol, 1 equiv.) if a liquid. Trimethylsilylacetylene (780 μL, 5.5 mmol, 1.1 equiv.) was added via a syringe and the mixture was stirred at 60 °C for 1 h. The completion of the first coupling was verified by TLC, then the second aryl halide or azide (1 mmol, 1 equiv.) was added. Hexafluorosilicic acid (34 % in aqueous solution, 15.2 μL, 0.01 mmol, 0.01 equiv.) and water (900 μL) was added via Hamilton syringes. The mixture was stirred for 24 h at 60 °C. The mixture was diluted with EtOAc (75

mL) and water (75 mL), the pH of the aqueous phase was adjusted to neutral. The layers were separated, then the aqueous phase was extracted with EtOAc (2 x50 mL). The combined organic layers were dried over $MgSO_4$. The solvent was removed under vacuum, and the crude was purified by column chromatography. White crystals. (868.6 mg, 98 %) Analytical data is the same as at 1 mmol scale.

1-(4-(Phenylethynyl)phenyl)ethan-1-one[25] 3b

The general procedure was followed. White solid (154.2 mg, yield 70%) Mp.= 96-97 °C (Ref.: 95-96 °C), R_f.: 0.23 (in hexanes: EtOAc 10:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ = 7.86 (d, *J* = 8.5 Hz, 2H), 7.57 – 7.41 (m, 4H), 7.34 – 7.23 (m, 3H), 2.53 (s, 3H) ppm. $^{13}C\{^1H\}$NMR (63 MHz, $CDCl_3$) δ = 197.7, 136.6, 132.1, 132.1, 129.2, 128.8, 128.7, 128.6, 123.0, 93.1, 89.0, 27.0 ppm. IR (thin film, ATR) ν_{max} 2222, 1680, 1603, 1486 cm^{-1}. MS (EI, 70 eV) *m/z* (%): 220(75), 205(100, [M+]), 176(70), 151(32).

1-Methoxy-4-(phenylethynyl)benzene[25] 3c

The general procedure was followed. White solid (119.2 mg, yield 57%) Mp.= 58-59 °C (Ref.: 59-60 °C), R_f.: 0.29 (in hexanes: EtOAc 10:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ = 7.60 – 7.41 (m, 4H), 7.39 – 7.29 (m, 3H), 6.97 – 6.83 (m, 2H), 3.84 (s, 3H) ppm. $^{13}C\{^1H\}$NMR (63 MHz, $CDCl_3$) δ = 160.0, 133.4, 131.8, 128.7, 128.3, 124.0, 115.8, 114.4, 89.8, 88.5, 55.7 ppm. IR (thin film, ATR) ν_{max} 2212, 2162, 1604, 1592, 1266, 1506, 1457 cm^{-1}. MS (EI, 70 eV) *m/z* (%): 208 (100, [M^+]), 193 (46), 165 (40), 139 (12), 104 (5). The sample contains 5 % of ((4-methoxyphenyl)ethynyl)trimethylsilane. Yield is corrected with purity.

1-Methyl-4-(phenylethynyl)benzene[25] 3d

The general procedure was followed. White solid (107.0 mg, yield 56%) Mp.= 70-72 °C (Ref.: 70-72 °C), R_f.: 0.60 (in hexanes). ^{1}H NMR (250 MHz, $CDCl_3$) δ = 7.47 – 7.36 (m, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 7.27 – 7.17 (m, 3H), 7.04 (d, *J* = 7.9 Hz, 2H), 2.25 (s, 3H) ppm. $^{13}C\{^1H\}$NMR (63 MHz, $CDCl_3$) δ = 138.6, 131.9, 131.9, 129.5, 128.7, 128.5, 123.6, 120.4, 90.1, 89.0, 21.7 ppm. IR (thin film, ATR) ν_{max} 2923, 2138, 1593, 1508, 1483 cm^{-1}. MS (EI, 70 eV) *m/z* (%): 192 (100, [M^+]), 191 (50), 165 (20), 152 (5), 115 (5).

3-(Phenylethynyl)aniline[26] 3e

The general procedure was followed. Brown solid (170.1 mg, yield 88%) Mp.= 46-48 °C, R_f.: 0.25 (in hexanes: EtOAc 5:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ = 7.51 – 7.35 (m, 2H), 7.32-7.19 (m, 3H), 7.05 (t, *J* = 7.8 Hz, 1H), 6.95 – 6.82 (m, 1H), 6.78 (t, *J* = 1.9 Hz, 1H), 6.64 – 6.50 (m, 1H), 3.60 (s, 2H) ppm. ^{13}C{^{1}H}NMR (63 MHz, $CDCl_3$) δ = 146.52, 132.0, 129.7, 128.7, 128.6, 124.3, 123.7, 122.6, 118.3, 115.8, 90.0, 89.2 ppm. IR (thin film, ATR) ν_{max} 2216, 1678, 1599, 1494, 1445 cm^{-1}. MS (EI, 70 eV) *m/z* (%): 263(100, [M+]), 227(35), 200(40), 131(10).

3-(Phenylethynyl)benzonitrile[27] 3f

The general procedure was followed. Yellow oil (140.8 mg, yield 90%) R_f.: 0.48 (in hexanes:EtOAc 5:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ = 7.87 – 7.78 (m, 1H), 7.73 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.60 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.57 – 7.31 (m, 6H) ppm. ^{13}C{^{1}H}NMR (63 MHz, $CDCl_3$) δ = 136.0, 135.3, 132.1, 131.7, 129.7, 129.4, 128.9, 125.4, 122.7, 118.5, 113.3, 92.2, 87.3 ppm. IR (thin film, ATR) ν_{max} 2233, 2213, 1601, 1574, 1493 cm^{-1}. MS (EI, 70 eV) *m/z* (%): 203 (100, [M$^+$]), 176 (15), 151 (10), 101 (10).

3-(Phenylethynyl)pyridine[28] 3g

The general procedure was followed. White solid (168.2 mg, yield 93%) Mp.= 50-51°C (Ref.: 49-51 °C), R_f.: 0.29 (in hexanes: EtOAc 20:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ = 8.72 (s, 1H), 8.50 (dd, *J* = 4.9, 1.7 Hz, 1H), 7.76 (dt, *J* = 7.9, 2.0 Hz, 1H), 7.41-7.58 (m, 2H), 7.39 – 7.13 (m, 4H) ppm. ^{13}C{^{1}H}NMR (63 MHz, $CDCl_3$) δ = 152.5, 148.8, 138.9, 132.1, 129.2, 128.8, 123.5, 122.9, 120.9, 93.1, 86.3 ppm. IR (thin film, ATR) ν_{max} 2224, 1559, 1488, 1472, 1413 cm^{-1}. MS (EI, 70 eV) *m/z* (%): 179(100, [M+]), 151(20), 126(30), 100(15).

2-(Phenylethynyl)thiophene[29] 3h

The general procedure was followed. Pale rose crystals (134.8 mg, yield 73%) Mp.= 52-54 °C, R_f.: 0.58 (in hexanes). ^{1}H NMR (250 MHz, $CDCl_3$) δ = 7.60 – 7.46 (m, 2H), 7.44 – 7.25 (m, 5H), 7.03 (dd, *J* = 5.0,

3.8 Hz, 1H) ppm. $^{13}C\{^{1}H\}$NMR (63 MHz, $CDCl_3$) δ = 132.3, 131.8, 128.8, 128.8, 127.6, 127.51, 123.7, 123.3, 93.4, 83.0 ppm. IR (thin film, ATR) ν_{max} 2209, 1594, 1516, 1484 cm^{-1}. MS (EI, 70 eV) *m/z* (%): 184(100, [M+]), 152(21), 139(33).

5-(Phenylethynyl)-1*H*-indole[30] 3i

The general procedure was followed. Yellow solid (179.1 mg, yield 83%) Mp.= 126-128 °C (Ref.: 124-128 °C), R_f.: 0.27 (in hexanes:EtOAc 10:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ = 8.20 (s, 1H), 7.91 (s, 1H), 7.58 (m, *J* = 4.7, 2.7 Hz, 2H), 7.47 – 7.28 (m, 5H), 7.23 (t, *J* = 2.8 Hz, 1H), 6.58 (t, *J* = 2.6 Hz, 1H) ppm. $^{13}C\{^{1}H\}$NMR (63 MHz, $CDCl_3$) δ = 135.8, 131.9, 128.7, 128.2, 128.2, 126.1, 125.51, 125.1, 124.34, 114.8, 111.56, 103.3, 91.5, 87.5 ppm. IR (thin film, ATR) ν_{max} 2208, 1595, 1490, 1467 cm^{-1}. MS (EI, 70 eV) *m/z* (%): 217(100, [M+]), 189(30), 108(15).

6-(Phenylethynyl)quinoline[31] 3j

The general procedure was followed. Yellow solid (201.1 mg, yield 88%) Mp.= 94-96 °C, R_f.: 0.35 (in hexanes: EtOAc 1:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ = 8.89 (d, *J* = 4.3 Hz, 1H), 8.21 – 7.91 (m, 3H), 7.81 (d, *J* = 8.7 Hz, 1H), 7.58 (dd, *J* = 6.8, 3.0 Hz, 2H), 7.44 – 7.28 (m, 4H) ppm. $^{13}C\{^{1}H\}$NMR (63 MHz, $CDCl_3$) δ = 151.25, 147.96, 136.16, 132.58, 132.10, 131.47, 129.94, 128.98, 128.83, 128.40, 123.30, 122.12, 122.00, 91.10, 89.38 ppm. IR (thin film, ATR) ν_{max} 1590, 1567, 1496, 1441, 1372, 1333, 1129, 1071, 1027, 920, 889, 839, 800, 759, 692 cm^{-1}. MS (EI, 70 eV) *m/z* (%): 229(100, [M+]), 228(20), 200(10), 114(6).

Methyl 4-(thiophen-2-ylethynyl)benzoate[32] 3k

The general procedure was followed. Yellow crystals (185 mg, yield 76%) Mp.= 107-109 °C (Ref.: 104-105 °C), R_f.: 0.23 (in hexanes: EtOAc 10:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ = 7.92 (d, *J* = 8.3 Hz, 2H), 7.47 (d, *J* = 8.2 Hz, 2H), 7.27 – 7.15 (m, 2H), 6.93 (dd, *J* = 4.9, 3.9 Hz, 1H), 3.82 (s, 3H) ppm. $^{13}C\{^{1}H\}$NMR (63 MHz, DMSO) δ 136.1, 132.0, 128.2, 128.0, 127.1, 124.5, 124.1, 123.3, 112.3, 112.2, 101.8, 95.5, 80.2 ppm. IR (thin film, ATR) ν_{max} 2209, 1711, 1603, 1439, 1408 cm^{-1}. MS (EI, 70 eV) *m/z*

(%): 243(16), 242(100, [M+]), 211(95), 183(20), 139(67), 91(10). HRMS calcd for $C_{14}H_{11}O_2S$ $[M+H]^+$ 243.0480 found 243.0471.

5-(Thiophen-2-ylethynyl)-1*H*-indole 3l:

The general procedure was followed. Brown solid (135 mg, yield 60%) Mp.= 154-156 °C, R_f.: 0.20 (in hexanes: EtOAc 5:1). ^{1}H NMR (250 MHz, DMSO-d6) δ 11.35 (s, 1H), 7.77 (s, 1H), 7.58 (m, 1H), 7.47 – 7.30 (m, 3H), 7.23 (dd, J = 8.4, 1.6 Hz, 1H), 7.09 (dd, J = 5.2, 3.6 Hz, 1H), 6.46 (t, J = 2.5 Hz, 1H). ^{1}H NMR (250 MHz, $CDCl_3$) δ = 8.16 (s, 1H), 7.80 (s, 1H), 7.30 (m, 2H), 7.23 – 7.08 (m, 3H), 6.95 (dd, *J* = 5.2, 3.6 Hz, 1H), 6.50 (t, *J* = 2.6 Hz, 1H) ppm. ^{13}C{^{1}H}NMR (63 MHz, $CDCl_3$) δ = 133.4, 129.1, 125.6, 124.9, 124.4, 123.3, 123.0, 122.4, 122.0, 111.8, 109.1, 100.8, 92.6, 78.1 ppm. IR (thin film, ATR) ν_{max} 2931, 2207, 1612, 1590, 1469 cm^{-1}. MS (EI, 70 eV) *m/z* (%): 224(16), 223(100, [M+]), 195(12), 152(10), 111(5). HRMS calcd for $C_{14}H_{10}NS$ $[M+H]^+$ 224.0534 found 224.0535.

2-((3,5-*bis*(Trifluoromethyl)phenyl)ethynyl)thiophene 3m:

The general procedure was followed. White crystals (260 mg, yield 81%), Mp.: 43-45 °C R_f.: 0.31 (in hexanes). ^{1}H NMR (250 MHz, $CDCl_3$)) δ = 7.94 (s, 2H), 7.82 (s, 1H), 7.43 – 7.32 (m, 2H), 7.06 (dd, *J* = 5.0, 3.8 Hz, 1H) ppm. ^{13}C{^{1}H}NMR (63 MHz, $CDCl_3$) δ = 133.6, 132.4 (q, *J* = 34.2 Hz), 131.5 (m), 129.0, 127.7, 125.6, 123.3 (d, *J* = 273.3 Hz), 122.1, 121.9 (p, *J* = 3.8 Hz), 90.4, 86.6 ppm. ^{19}F NMR (235 MHz, $CDCl_3$) δ = -63.21 ppm. IR (thin film, ATR) ν_{max} 2214, 1383, 1349, 1277 cm^{-1}. MS (EI, 70 eV) *m/z* (%): 320(100, [M$^+$]), 301(20), 251(10), 206(10), 160(5), 69(10). HRMS calcd for $C_{14}H_6F_6S$ $[M+H]^+$ 320.0094 found 320.00843.

1-((3-Fluorophenyl)ethynyl)-3,5-dimethylbenzene 3n

The general procedure was followed. White crystals (198 mg, yield 88%), Mp.: 38-40 °C R_f.: 0.37 (in hexanes). ^{1}H NMR (250 MHz, $CDCl_3$) δ = 7.33 – 7.14 (m, 5H), 7.10 – 6.90 (m, 2H), 2.33 (s, 6H) ppm. ^{13}C{^{1}H}NMR (63 MHz, $CDCl_3$) δ = 162.8 (d, *J* = 245.6 Hz), 138.4, 130.9, 130.3 (d, *J* = 8.4 Hz), 129.7, 127.8 (d, *J* = 3.0 Hz), 125.7 (d, *J* = 8.6 Hz), 122.8, 118.7 (d, *J* = 23.8 Hz), 115.8 (d, *J* = 23.8 Hz), 91.1,

87.8, 21.5 ppm. ^{19}F NMR (235 MHz, $CDCl_3$) δ = -113.07 ppm. IR (thin film, ATR) ν_{max} 2920, 2863, 2219, 1610, 1580, 1489, 1436, 1379, 1335, 1304 cm^{-1}. MS (EI, 70 eV) *m/z* (%): 295(100, [M+]), 276(10), 233(30), 190(20), 163(15), 138(10), 108(5), 75(10). HRMS calcd for $C_{16}H_{13}F$ $[M+H]^+$ 224.1001 found 224.09905.

1-Chloro-4-((4-fluorophenyl)ethynyl)benzene[33] 3o

The general procedure was followed. White solid (121 mg, yield 53%), Mp.: 112-113 °C, (Ref.: 113 °C) R_f.: 0.26 (in hexanes). ^{1}H NMR (250 MHz, $CDCl_3$) δ = 7.57 – 7.40 (m, 4H), 7.38 – 7.26 (m, 2H), 7.15 – 6.96 (m, 2H) ppm. $^{13}C\{^1H\}$NMR (63 MHz, $CDCl_3$) δ = 163.0 (d, *J* = 250.0 Hz), 134.7, 133.9 (d, *J* = 8.5 Hz), 133.2, 129.1, 122.0, 119.4 (d, *J* = 3.5 Hz), 116.1 (d, *J* = 22.9 Hz), 89.6, 88.3 ppm. ^{19}F NMR (235 MHz, $CDCl_3$) δ = -110.48 ppm. IR (thin film, ATR) ν_{max} 2021, 1601, 1506, 1400, 1226 cm^{-1}. MS (EI, 70 eV) *m/z* (%): 230(100, $[M^+]$), 194(32), 175(15), 144(5), 115(5), 97(5).

1-Methoxy-4-((4-nitrophenyl)ethynyl)benzene[34] 3p

The general procedure was followed. Yellow solid (114 mg, yield 45%), Mp.: 122- 124 °C (Ref.: 122-124 °C), R_f.: 0.25 (in hexanes: EtOAc 10:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ = 8.09 (d, *J* = 8.9 Hz, 2H), 7.52 (d, *J* = 8.9 Hz, 2H), 7.40 (d, *J* = 8.9 Hz, 2H), 6.81 (d, *J* = 8.9 Hz, 2H), 3.75 (s, 3H) ppm. $^{13}C\{^1H\}$NMR (63 MHz, $CDCl_3$) δ = 160.8, 147.0, 133.8, 132.4, 131.1, 124.0, 114.6, 95.6, 87.0, 78.0, 55.7 ppm. IR (thin film, ATR) ν_{max} 2211, 1589, 1511, 1464 cm^{-1}. MS (EI, 70 eV) *m/z* (%): 253(100, $[M^+]$), 223(20), 207(20), 163(80), 152(15), 87(10).

5-Chloro-2-(p-tolylethynyl)aniline[35] 3q

The general procedure was followed. Off-white solid. (177 mg, yield 79%) Mp.= 135 - 137 °C (Ref.: not given), R_f (Hex.-EtOAc = 5:1) = 0.50; ^{1}H NMR (250 MHz, $CDCl_3$) δ = 7.28 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 8.3 Hz, 1H), 7.00 (d, *J* = 8.1 Hz, 2H), 6.68 – 6.45 (m, 2H), 4.46 (s, 2H), 2.22 (s, 3H) ppm. $^{13}C\{^1H\}$NMR (63 MHz, $CDCl_3$) δ = 148.0, 138.8, 135.2, 133.1, 131.5, 129.3, 119.9, 118.7, 114.6, 107.3,

95.9, 84.2, 21.7 ppm. IR (thin film, ATR): 1614, 1558, 1486 cm^{-1}. MS (EI, 70 eV) m/z (% relative intensity, ion): 243(32, [M+]), 241(100, [M+]), 204(23), 178(14), 164(6), 120(7), 105(15), 89(16), 76(6).

2-((4-Chlorophenyl)ethynyl)-4-(trifluoromethyl)aniline 3r

The general procedure was followed. Brown crystals (260 mg, yield 81%), Mp.: 61-63 °C R_f.: 0.21 (in hexanes:EtOAc 5:1). ^1H NMR (250 MHz, $CDCl_3$) δ = 7.62 (s, 1H), 7.51 – 7.41 (m, 2H), 7.40 – 7.31 (m, 3H), 6.74 (d, *J* = 8.5 Hz, 1H), 4.57 (s, 2H) ppm. $^{13}C\{^1H\}$NMR (63 MHz, $CDCl_3$) δ = 150.6, 135.1, 133.1, 130.0 (q, *J* = 3.6 Hz), 129.2, 127.2 (q, *J* = 3.6 Hz), 124.7 (q, *J* = 270.9 Hz), 121.5, 120.3 (q, *J* = 33.1 Hz), 114.2, 107.5, 94.8, 85.8 ppm. ^{19}F NMR (235 MHz, $CDCl_3$) δ = -61.46 ppm. IR (thin film, ATR) ν_{max} 2021, 1623, 1490 cm^{-1}. MS (EI, 70 eV) *m/z* (%): 295(100, [M+]), 276(10), 233(30), 190(20), 163(15), 138(10), 108(5), 75(10). HRMS calcd for $C_{15}H_{10}ClF_3N$ $[M+H]^+$ 296.0454 found 296.0458.

3-((3-Bromophenyl)ethynyl)-2-methylquinolin-4-amine 3s

The general procedure was followed. Light brown solid (211 mg, yield 63%). Mp.= 177 - 179 °C. R_f (EtOAc) = 0.53; ^1H NMR (250 MHz, DMSO-d_6) δ = 8.27 (d, *J* = 8.2 Hz, 1H), 7.98 (t, *J* = 1.6 Hz, 1H), 7.74 – 7.53 (m, 5H), 7.43 – 7.32 (m, 2H), 7.13 (s, 2H), 2.64 (s, 3H) ppm. $^{13}C\{^1H\}$NMR (63 MHz, DMSO-d_6) δ = 158.9, 152.5, 146.7, 133.3, 130.9, 130.5, 130.0, 129.9, 128.4, 125.5, 123.9, 122.5, 121.6, 116.0, 97.7, 95.0, 86.7, 24.5 ppm. MS (EI, 70 eV) m/z (% relative intensity, ion): 338(92, [M+]), 336(100, [M+]), 281(15), 256 (55), 207 (61), 193(20), 147(24), 128(41), 114(14), 94(13), 73(59). IR (thin film, ATR): 2200, 1642, 1614, 1570 cm^{-1}. HRMS *m/z* $[M+H]^+$ calculated for $C_{18}H_{14}N_2Br^+$: 337.0340; found: 337.0339.

7-Chloro-4-(phenylethynyl)quinolone 3t

The general procedure was followed. Brown solid (154 mg, yield 70%) Mp.= 95-96 °C, R_f.: 0.28 (in hexanes: EtOAc 10:1). ^1H NMR (250 MHz, $CDCl_3$) δ = 8.89 (d, *J* = 4.5 Hz, 1H), 8.29 (d, *J* = 8.9 Hz, 1H), 8.13 (d, *J* = 2.2 Hz, 1H), 7.74 – 7.50 (m, 4H), 7.49 – 7.32 (m, 3H) ppm. $^{13}C\{^1H\}$NMR (63 MHz, $CDCl_3$) δ = 151.0, 148.6, 136.4, 132.4, 130.5, 130.0, 129.0, 129.0, 128.6, 127.8, 126.6, 124.0, 122.3, 99.8, 84.9

ppm. IR (thin film, ATR) ν_{max} 2217, 1608, 1574, 1496 cm^{-1}. MS (EI, 70 eV) *m/z* (%): 263(100, $[M^+]$), 227(35), 200(40), 131(10). HRMS calcd for $C_{17}H_{11}ClN$ $[M+H]^+$ 264.0580 found 264.0582.

1,4-*bis*(Phenylethynyl)benzene[36] 3u

The general procedure was modified. (1,4-iiodobenzene (1 mmol, 330 mg), trimethylsilylacetylene (2.2 equiv., 2.2 mmol) and iodobenzene (2.0 equiv., 2 mmol) were used) Yellow crystals (228 mg, yield 82%) mp.= 175-176 °C (Ref.: 178-179 °C), R_f.: 0.25 (in hexanes). ^1H NMR (250 MHz, $CDCl_3$) δ = 7.55 (dd, *J* = 6.7, 3.1 Hz, 4H), 7.53 (s, 4H), 7.37 (dd, *J* = 5.0, 1.7 Hz, 6H) ppm. $^{13}C\{^1H\}$NMR (63 MHz, $CDCl_3$) δ = 132.0, 131.9, 128.9, 128.8, 123.5, 123.5, 91.6, 89.5 ppm. IR (thin film, ATR) ν_{max} 1594, 1514, 1441, 1070, 839, 752, 690 cm^{-1}. MS (EI, 70 eV) *m/z* (%): 278(100, [M+]), 276(15), 139(18).

2-(Naphthalen-2-ylethynyl)-9*H*-fluorene 3v

The general procedure was followed. Orange solid (283 mg, yield 45%), R_f.: 0.20 (in hexanes: EtOAc 100:1). Mp.: 137-139 °C ^1H NMR (250 MHz, $CDCl_3$) δ = 8.40 (d, *J* = 8.2 Hz, 1H), 7.93 – 6.94 (m, 13H), 3.82 (d, *J* = 7.6 Hz, 2H) ppm. $^{13}C\{^1H\}$NMR (63 MHz, $CDCl_3$) δ = 144.0, 143.7, 142.4, 141.5, 133.7, 133.6, 131.0, 130.7, 129.0, 128.7, 128.6, 127.6, 127.4, 127.2, 126.8, 126.7, 125.7, 125.5, 121.8, 121.5, 120.6, 120.3, 95.6, 88.0, 37.2 ppm. IR (thin film, ATR) ν_{max} 2964, 2897, 2829, 2205, 1585 cm^{-1}. MS (EI, 70 eV) *m/z* (%): 316 (100, $[M^+]$), 156(35), 143(10), 73(5).

Triethyl((3-(phenylethynyl)benzyl)oxy)silane 3w

The general procedure was followed. Yellow oil (131 mg, yield 41%), R_f.: 0.25 (in hexanes: EtOAc 100:1). ^1H NMR (250 MHz, $CDCl_3$) δ = 7.57 – 7.38 (m, 3H), 7.37 – 7.18 (m, 6H), 4.64 (s, 2H), 0.90 (t, *J* = 7.8 Hz, 9H), 0.58 (q, *J* = 7.9 Hz, 6H) ppm. $^{13}C\{^1H\}$NMR (63 MHz, $CDCl_3$) δ = 142.0, 132.0, 130.6, 129.7, 128.7, 128.7, 128.6, 126.6, 123.7, 123.5, 90.0, 89.6, 64.7, 7.2, 4.9 ppm. IR (thin film, ATR) ν_{max} 2958, 2912, 2878, 1604, 1493, 1459, 1413, 1368, 1239, 1201, 1101, 1078, 1005, 974, 915, 889, 817, 784, 754, 728, 689 cm^{-1}. MS (EI, 70 eV) *m/z* (%): 322(15), 293(95), 263(33), 235(20), 206(20), 191(100, $[M^+]$), 165(30), 95(15), 59(10). HRMS calcd for $C_{21}H_{26}OSiNa$ $[M+Na]^+$ 345.1651 found 345.1650.

tert-Butyldiphenyl((3-(phenylethynyl)benzyl)oxy)silane 3x

The general procedure was followed. Yellow oil (382 mg, yield 86%), R_f.: 0.27 (in hexanes: EtOAc 100:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ = 7.68 – 7.57 (m, 4H), 7.54 – 7.15 (m, 15H), 4.67 (s, 2H), 1.02 (s, 9H) ppm. $^{13}C\{^1H\}$NMR (63 MHz, $CDCl_3$) δ = 141.7, 136.0, 133.7, 132.1, 130.6, 130.2, 129.6, 128.8, 128.7, 128.7, 128.2, 126.5, 123.7, 123.5, 90.0, 89.6, 65.6, 27.3, 19.8 ppm. IR (thin film, ATR) ν_{max} 2960, 2933, 2856, 1603, 1493 cm^{-1}. MS (EI, 70 eV) *m/z* (%): 389(90), 311(83), 189(100, [M$^+$]), 165(45), 105(15), 77(10). HRMS calcd for $C_{31}H_{31}OSi$ [M+H]$^+$ 447.2144 found 447.2143.

tert-Butyldimethyl((3-(phenylethynyl)benzyl)oxy)silane 3y

The general procedure was followed. Yellow oil (261 mg, yield 82%), R_f.: 0.25 (in hexanes: EtOAc 100:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ = 7.50 – 7.34 (m, 3H), 7.33 – 7.14 (m, 6H), 4.62 (s, 2H), 0.84 (s, 9H), 0.00 (s, 6H) ppm. $^{13}C\{^1H\}$NMR (63 MHz, $CDCl_3$) δ = 142.1, 132.0, 130.6, 129.5, 128.7, 128.7, 128.6, 126.5, 123.7, 123.5, 89.9, 89.5, 65.0, 26.4, 18.9, -4.8 ppm. IR (thin film, ATR) ν_{max} 2958, 2934, 2883, 2857, 1604, 1493 cm^{-1}. MS (EI, 70 eV) *m/z* (%): 322(2), 265(100, [M+]), 235(55), 191(90), 165(20), 75(5). HRMS calcd for $C_{21}H_{26}OSiNa$ [M+Na]$^+$ 345.1651 found 345.1656.

Triisopropyl((3-(phenylethynyl)benzyl)oxy)silane 3z

The general procedure was followed. Colorless oil (281 mg, yield 77%), R_f.: 0.23 (in hexanes: EtOAc 100:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ = 7.73 – 7.50 (m, 3H), 7.48 – 7.31 (m, 6H), 4.86 (s, 2H), 1.13 (app. s, 21H) ppm. $^{13}C\{^1H\}$NMR (63 MHz, $CDCl_3$) δ = 142.3, 132.0, 130.5, 129.3, 128.7, 128.7, 128.6, 126.2, 123.8, 123.4, 90.0, 89.5, 65.0, 18.5, 12.4 ppm. IR (thin film, ATR) ν_{max} 2942, 2894, 2886, 1604, 1493, 1462 cm^{-1}. MS (EI, 70 eV) *m/z* (%): 364(2), 321(100, [M$^+$]), 293(10), 249(15), 206(25), 191(90), 165(24), 133(10), 95(10), 59(10). HRMS calcd for $C_{24}H_{33}OSi$ [M+H]$^+$ 365.2301 found 365.2299.

5-(Pyridin-2-ylethynyl)-3-((triisopropylsilyl)ethynyl)-1*H*-indole 3aa

The general procedure was followed. Green solid (284 mg, yield 71%). Mp.= 168-170 °C, R_f.: 0.21 (in hexanes: EtOAc 2:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ = 9.34 (s, 1H), 8.72 (s, 1H), 8.43 (dd, *J* = 4.8, 1.4 Hz, 1H), 7.85 (s, 1H), 7.78 (dt, *J* = 7.9, 1.8 Hz, 1H), 7.37 (d, *J* = 2.6 Hz, 1H), 7.34 – 7.18 (m, 3H), 1.09 (app. s, 21H) ppm. ^{13}C{^{1}H}NMR (63 MHz, $CDCl_3$) δ = 152.2, 148.0, 139.1, 135.6, 130.1, 129.2, 126.9, 124.4, 123.7, 121.8, 114.7, 112.2, 100.0, 99.8, 95.0, 92.8, 84.4, 19.2, 11.8 ppm. IR (thin film, ATR) ν_{max} 2944, 2865, 2725, 2211, 2150, 1589 cm^{-1}. MS (EI, 70 eV) *m/z* (%): 398(32), 355(100, [M+]), 313(43), 285(50), 149(37), 135(27), 59(10). HRMS calcd for $C_{26}H_{31}N_2Si$ $[M+H]^+$ 399.2257 found 399.2249.

Ethyl 4-(benzofuran-2-yl)benzoate[18] 4a

The general procedure was followed. Light yellow solid (0.067 g, 26%). Mp.= 109 - 111 °C (Ref.: 109 - 111 °C), R_f (Hex.-EtOAc = 5:1) = 0.55; ^{1}H NMR (250 MHz, $CDCl_3$) δ = 7.98 (dt, *J* = 8.5, 1.6 Hz, 2H), 7.77 (dt, *J* = 8.5, 1.6 Hz, 2H), 7.46 (dd, *J* = 7.3, 1.5 Hz, 1H), 7.40 (d, *J* = 8.2 Hz, 1H), 7.23 – 7.05 (m, 2H), 6.99 (s, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 1.28 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C{^{1}H}NMR (63 MHz, $CDCl_3$) δ = 166.3, 155.3, 154.8, 134.5, 130.2, 130.2, 129.0, 125.1, 124.7, 123.3, 121.4, 111.5, 103.5, 61.2, 14.5. MS (EI, 70 eV) m/z (% relative intensity, ion): 266(100, [M^+]), 238 (55), 221(63), 193(13), 165(62), 163(22), 139(11), 110(10), 82(13). IR (thin film, ATR): 1708, 1614, 1454, 1411 cm^{-1}.

2-(4-Methoxyphenyl)benzofuran[5] 4b

The general procedure was followed. White crystals (0.177 g, 79%). Mp.= 140 – 141 °C (Ref.: 143 – 144 °C), R_f (Hex.-EtOAc = 5:1) = 0.60; ^{1}H NMR (250 MHz, $CDCl_3$) δ = 7.70 (td, J = 10, 2.5 Hz, 2H), 7.49 – 7.37 (m, 3H), 7.21 – 7.06 (m, 2H), 6.88 (td, J = 32, 2.0 Hz, 2H), 6.78 (d, *J* = 0.8 Hz, 1H), 3.75 (s, 3H) ppm. ^{13}C{^{1}H}NMR (63 MHz, $CDCl_3$) δ = 160.1, 156.2, 154.8, 129.6, 126.5, 123.9, 123.5, 123.0, 120.7, 114.4, 111.1, 99.8, 55.5 ppm. MS (EI, 70 eV) m/z (% relative intensity, ion): 224(100, [M+]), 209(78), 181(53), 152(37), 126(8), 112(10), 63(7). IR (thin film, ATR): 1611, 1506, 1456 cm^{-1}.

2-(4-Nitrophenyl)benzofuran[37] 4c

The general procedure was followed a second column chromatographic purification was needed. Orange solid (0.103 g, 43%). Mp.= 169 – 171 °C (Ref.: 181 - 183 °C), Rf (Hex.-EtOAc = 5:1) = 0.55; ^{1}H NMR (250 MHz, $CDCl_3$) δ = 8.16 (d, *J* = 8.6 Hz, 2H), 7.84 (d, *J* = 8.6 Hz, 2H), 7.50 (d, *J* = 7.5 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.23 (t, *J* = 7.5 Hz, 1H), 7.14 (t, *J* = 7.5 Hz, 1H), 7.09 (s, 1H) ppm. ^{13}C{^{1}H}NMR (62.5 MHz, $CDCl_3$) δ = 155.5, 153.4, 147.3, 136.4, 128.8, 126.0, 125.3, 124.4, 123.7, 121.8, 111.6, 105.2 ppm. MS (EI, 70 eV) m/z (% relative intensity, ion): 239(100, [M^+]), 209(25), 181(25), 165(98), 163(35), 152(11), 115(10), 63(10). IR (thin film, ATR): 1601, 1573, 1519, 1452, 1346 cm^{-1}.

Methyl 2-(1*H*-indol-5-yl)benzofuran-6-carboxylate 4d

The general procedure was followed. Light brown solid (0.271 g, 93%). Mp.= 134 - 136 °C, R_f (Hex.-EtOAc = 5:1) = 0.23; δ = ^{1}H NMR (250 MHz, DMSO-d_6) δ = 11.30 (s, 1H), 8.12 (s, 1H), 8.05 (s, 1H), 7.78 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.63 (m, 2H), 7.45 (d, *J* = 8.5 Hz, 1H), 7.37 (m, 1H), 7.29 (s, 1H), 6.49 (s, 1H), 3.80 (s, 3H) ppm. ^{13}C{^{1}H}NMR (63 MHz, DMSO-d_6) δ = 166.4, 160.7, 153.4, 136.6, 134.1, 127.9, 126.8, 124.6, 124.1, 120.3, 120.2, 118.8, 117.5, 112.2, 111.6, 102.0, 99.6, 52.1 ppm. MS (EI, 70 eV) m/z (% relative intensity, ion): 291(37, [M^+]), IR (thin film, ATR): 1700, 1614, 1577 cm^{-1}. HRMS *m/z* [M+H]$^+$ calculated for $C_{18}H_{14}NO_3^+$: 292.0974; found: 292.0975.

6-Chloro-2-(thiophen-2-yl)benzofuran 4e

The general procedure was followed. White powder (0.159 g, 68%). Mp.= 142 - 143 °C, R_f (Hex.-EtOAc = 5:1) = 0.68; ^{1}H NMR (250 MHz, $CDCl_3$) δ = 7.49 (m, 2H), 7.43 – 7.33 (m, 2H), 7.22 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.11 (t, *J* = 1 Hz, 1H), 6.79 (s, 1H) ppm. ^{13}C{^{1}H}NMR (63 MHz, $CDCl_3$) δ = 153.3, 153.1, 133.1, 130.9, 129.1, 128.4, 126.8, 125.5, 124.8, 120.6, 112.4, 100.9 ppm. MS (EI, 70 eV) m/z (% relative intensity, ion): 236(37, [M^+]), 234(100, [M+]), 205(6), 171(44), 145(6), 126(7), 117(8), 85(8). IR (thin film, ATR): 1586, 1448 cm^{-1}. HRMS *m/z* [M]$^+$ calculated for $C_{12}H_7ClOS^+$: 233.9901; found: 233.9903.

7-Chloro-4-(5-fluorobenzofuran-2-yl)quinoline 4f

The general procedure was followed. Yellow solid (0.105 g, 36%). Mp.= 208 - 210 °C, R_f (Hex.-EtOAc = 1:1) = 0.55; ^{1}H NMR (250 MHz, $CDCl_3$) δ = 8.97 (d, *J* = 4.6 Hz, 1H), 8.47 (d, *J* = 9.1 Hz, 1H), 8.20 (d, *J* = 2.1 Hz, 1H), 7.74 (d, *J* = 4.6 Hz, 1H), 7.63 – 7.49 (m, 2H), 7.34 (dd, *J* = 8.3, 2.6 Hz, 1H), 7.26 (s, 1H), 7.13 (td, *J* = 9.0, 2.6 Hz, 1H) ppm. ^{13}C{^{1}H}NMR (63 MHz, $CDCl_3$) δ = 161.8(d, *J* = 242 Hz), 158.0, 154.4, 152.0, 150.9, 149.4, 136.3, 136.1, 129.4 (d, *J* = 10.9 Hz), 129.2, 128.0 (d, *J* = 110.4 Hz), 123.4, 120.2, 114.2 (d, *J* = 26.6 Hz), 112.7 (d, *J* = 9.6 Hz), 109.3 (d, *J* = 3.8 Hz), 107.6, 107.2 ppm. ^{19}F NMR (235 MHz, $CDCl_3$) δ -119.5. MS (EI, 70 eV) m/z (% relative intensity, ion): 299(37, [M+]), 297(100, [M+]), 270(6), 262(20), 234(13), 207(17), 148(4), 135(6), 117(6), 103(8). IR (thin film, ATR): 1596, 1577, 1497 cm^{-1}. HRMS *m*/*z* $[M+H]^+$ calculated for $C_{17}H_{10}NOClF^+$: 298.0435; found: 298.0428.

5-(1-(4-Bromobenzyl)-1*H*-1,2,3-triazol-4-yl)-1*H*-indole 5a

The general procedure was followed. Pale yellow solid (0.165 g, 47%). Mp.= 173 - 176 °C, R_f (Hex.-EtOAc = 1:1) = 0.30; ^{1}H NMR (250 MHz, DMSO-d_6) δ = 11.18 (s, 1H), 8.51 (s, 1H), 8.03 (s, 1H), 7.60 (d, *J* = 8.4 Hz, 3H), 7.44 (d, *J* = 8.4 Hz, 1H), 7.38 – 7.28 (m, 3H), 6.47 (s, 1H), 5.62 (s, 2H) ppm. ^{13}C{^{1}H}NMR (63 MHz, DMSO-d_6) δ = 148.3, 135.7, 135.6, 131.7, 130.2, 127.9, 126.1, 121.6, 121.4, 120.3, 119.0, 116.9, 111.7, 101.4, 52.2 ppm. MS (EI, 70 eV) m/z (% relative intensity, ion): 354(9, [M+]), 352(10, [M+]), 325(33), 281(7), 245(15), 218(16), 207(25), 171(18), 169(39), 155(100), 141 (10), 128(44), 122(11), 101(18), 90(24), 77(11), 73(24), 63(10). IR (thin film, ATR): 1491, 1439, 1417, 1350, cm^{-1}. HRMS *m*/*z* $[M+H]^+$ calculated for $C_{17}H_{14}BrN_4^+$: 353.0402; found: 353.0399.

4-(3-Bromophenyl)-1-(4-nitrobenzyl)-1*H*-1,2,3-triazole[18] 5b

The general procedure was followed. Yellow powder (0.138 g, 39%). Mp.= 88 - 90 °C (Ref.: 90 – 93 °C), R_f (Hex.-EtOAc = 1:1) = 0.43; ^{1}H NMR (250 MHz, DMSO-d_6) δ = 8.79 (s, 1H), 8.25 (d, *J* = 8.6 Hz, 2H), 8.05 (s, 1H), 7.88 (d, *J* = 7.7 Hz, 1H), 7.58 (d, *J* = 8.6 Hz, 2H), 7.53 (d, *J* = 8.9 Hz, 3H), 7.41 (t, *J* = 7.8 Hz, 1H), 5.85 (s, 2H) ppm. ^{13}C{^{1}H}NMR (63 MHz, DMSO-d_6) δ = 147.3, 145.3, 143.2, 132.8, 131.1,

130.7, 129.1, 127.7, 124.1, 124.0, 122.7, 122.3, 52.2 ppm. MS (EI, 70 eV) m/z (% relative intensity, ion): 360(5, [M^+]), 358(6, [M^+]),281(7), 207(24), 196(98), 194(100), 169(13), 167(14), 147(10), 136(15), 121(36), 120(28), 115(26), 106(18), 102(12), 90(30), 89(44), 88(24), 78(40), 73(30), 63(17), 51(10). IR (thin film, ATR): 1607, 1568, 1519, 1346 cm^{-1}.

4-(1-(4-Bromobenzyl)-1*H*-1,2,3-triazol-4-yl)-7-chloroquinoline 5c

The general procedure was followed. Brown solid (0.264 g, 66%). Mp.= 128 - 130 °C, R_f (EtOAc) = 0.55; ^{1}H NMR (250 MHz, DMSO-d_6) δ = 9.00 (s, 1H), 8.97 (d, *J* = 4.6 Hz, 1H), 8.86 (d, *J* = 9.1 Hz, 1H), 8.13 (d, *J* = 2.2 Hz, 1H), 7.83 (d, *J* = 4.6 Hz, 1H), 7.71 (dd, *J* = 9.1, 2.3 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 5.75 (s, 2H) ppm. ^{13}C{^{1}H}NMR (63 MHz, DMSO-d_6) δ = 151.6, 149.0, 143.8, 135.6, 135.1, 134.2, 131.8, 130.4, 128.2, 128.1, 127.7, 125.9, 123.2, 121.6, 120.4, 52.5 ppm. MS (EI, 70 eV) m/z (% relative intensity, ion): 400(10, [M^+]), 398(7, [M^+]), 371(9), 369(7), 291(10), 281(8), 203(29), 201(100), 182(11), 171(69), 169(80), 166(17), 147(17), 90(54), 89(39), 75(10), 73(24). IR (thin film, ATR): 1590, 1491 cm^{-1}. HRMS *m/z* $[M+H]^+$ calculated for $C_{17}H_{14}N_4Br^+$: 353.0402; found: 353.0397.

ASSOCIATED CONTENT

AUTHOR INFORMATION

Corresponding Author

* novakz@elte.hu, *tolnai@chem.elte.hu

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Supporting Information

NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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