Journal of the Mexican Chemical Society
ISSN: 1870-249X
editor.jmcs@gmail.com
Sociedad Química de México
México

Flores-Jarillo, Mariana; Ayala-Mata, Francisco; Zepeda-Vallejo, Gerardo; Vázquez-García, Rosa Ángeles; Ramos-Ortiz, Gabriel; Méndez-Rojas, Miguel Ángel; Suárez-Castillo, Oscar Rodolfo; Alvarez-Hernández, Alejandro

Synthesis of Fluorescent oligo(p-phenyleneethynylene) (OPE3) via Sonogashira Reactions

Journal of the Mexican Chemical Society, vol. 59, núm. 2, abril-junio, 2015, pp. 151-160
Sociedad Química de México
Distrito Federal, México

Article

J. Mex. Chem. Soc. **2015**, *59(2)*, 151-160

ISSN 1870-249X

Synthesis of Fluorescent oligo(*p*-phenyleneethynylene) (OPE3) via Sonogashira Reactions

Mariana Flores-Jarillo,[1] Francisco Ayala-Mata,[2] Gerardo Zepeda-Vallejo,[2] Rosa Ángeles Vázquez-García,[3] Gabriel Ramos-Ortiz,[4] Miguel Ángel Méndez-Rojas,[5] Oscar Rodolfo Suárez-Castillo,[1] and Alejandro Alvarez-Hernández[1]*

[1] Área Académica de Química, Universidad Autónoma del Estado de Hidalgo, Carr. Pachuca Tulancingo Km 4.5, Pachuca, Hidalgo 42184, México
[2] Departamento de Química Orgánica, Escuela Nacional de Ciencias Biológicas, Instituto Politécnico Nacional, Prol. Carpio y Plan de Ayala s/n, 11340 México, D.F., México
[3] Área Académica de Ciencias de la Tierra y Materiales, Universidad Autónoma del Estado de Hidalgo, Carr. Pachuca Tulancingo km 4.5, Pachuca, Hidalgo 42184, México
[4] Centro de Investigaciones en Óptica. A.P. 1-948, León, México
[5] Departamento de Química y Biología, Universidad de las Américas-Puebla, Ex-Hda de Sta. Catarina Mártir, A. P. 100, Cholula 72820, Puebla, México
* Corresponding author: Alejandro Alvarez-Hernández, email: alvarez@uaeh.edu.mx, alalvareher@yahoo.com

Received February 16th, 2015; Accepted May 28th, 2015

Abstract. Sonogashira reactions of 4-(2,5-diiodobenzoyl)morpholine and 4-(5-bromo-2-iodobenzoyl)morpholine with arylacetylenes catalyzed by $Pd_2(dba)_3$ in DMSO allowed preparation of fluorescent oligo(*p*-phenyleneethynylene)s (OPE3) with fluorescence quantum yields up to 0.87. DMSO proved to be very efficient for this double Sonogashira coupling in which other solvents failed.
Key words: Sonogashira coupling, oligo(*p*-phenyleneethynylene)s, OPE3, fluorescence

Resumen. Las reacciones de Sonogashira de la 4-(2,5-diiodobenzoil) morfolina y la 4-(5-bromo-2-iodobenzoil)morfolina con arilacetilenos catalizadas por $Pd_2(dba)_3$ en DMSO permitieron preparar oligo(*p*-fenilenetinilenos) (OPE3) fluorescentes con rendimientos cuánticos de hasta 0.87. El DMSO demostró ser muy eficiente para este doble acoplamiento de Sonogashira en el cual otros disolventes no fueron adecuados.
Palabras clave: Acoplamiento de Sonogashira, oligo(*p*-fenilenetinilenos), (OPE3), fluorescencia

Introduction

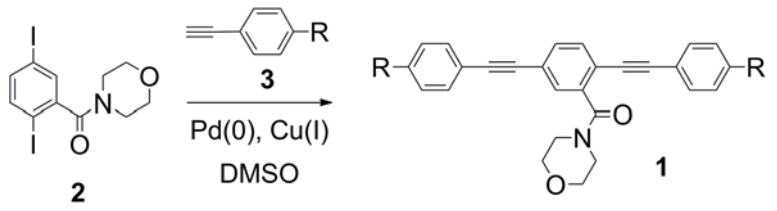
The Sonogashira [1] coupling reaction and its variants [2] have found widespread use in the synthesis of oligomeric aryleneethynylene materials [3] These conjugated materials incorporate aryl, heteroaryl [4] and organometallic [5] units joined by acetylene links and display remarkable electronic and optical properties [6], such as semiconduction and fluorescence, for which they have been used to construct molecular wires [7], chemosensors [8], imaging materials [9] and the emitting layer in light emitting devices [10]. Short oligomers [11] and small molecules [12] of precise structure can retain some of the electronic and optical properties of their polymeric counterparts and are more easily manipulated and prepared. Thus, in this work a series of oligo(*p*-phenyleneethynylene)s OPE3s (Fig. 1) was prepared in search for highly fluorescent molecules of low molecular weight for future adaptation and application as biological probes. Herewith the synthesis of these compounds by double Sonogashira couplings in DMSO and their optical properties are described.

At the onset of this work, OPE3 compounds of type **1** were designed as low molecular weight models of fluorescent polyphenylenethynylenes [13]. Substituents on the terminal aryl groups allow tuning of the optical properties and the morpholine amide group at the central aryl unit was designed to confer solubility to phenyleneethynylenes in organic solvents. The synthesis of pseudo symmetrical compounds was envisaged as a double Sonogashira coupling of diiodoamide **2** with two equivalents of an arylacetylene **3**. (Scheme 1)

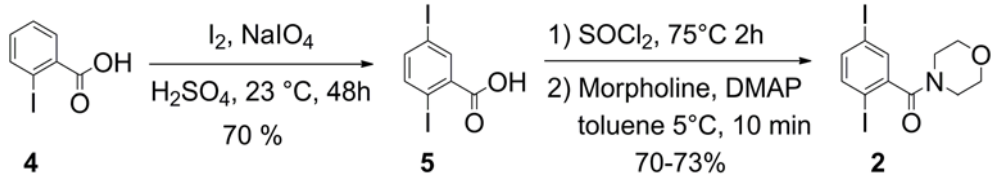
Thus, synthesis of the required diiodoarene **2** started with iodination of commercial 2-iodobenzoic acid **4** with iodine/$NaIO_4$ [14] in sulfuric acid that led to diiodo acid **5**, which was converted to **2** by reaction with thionyl chloride followed by addition of morpholine and catalytic DMAP (Scheme 2).

Coupling of diiodoarene **2** with two equivalents of 4-ethynylanisole (**3a**) to produce **1a** was chosen as model reaction to establish a protocol for preparation of a set of related OPE3s **1**.

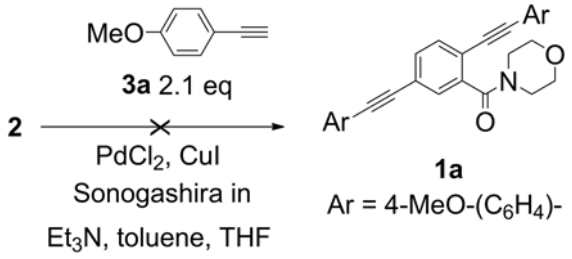
Fig. 1. Structure of oligo(p-phenyleneethynylene)s (OPE3)



Scheme 1



Scheme 2



Scheme 3

Unexpectedly, the reaction proved to be problematic under standard Sonogashira conditions ($PdCl_2$, CuI and triphenylphosphine) in toluene, THF and triethylamine (Scheme 3).

Thus, it was decided to study the possible effect of other solvents in this Sonogashira coupling. Thus, coupling of **2** and **3a** was carried out using several organic solvents of different polarity [15] (Scheme 4) and $Pd_2(dba)_3$ [16] was used as the source of catalyst. Results are summarized in Table 1. Reaction in Et_3N (entry 1) gave a mixture of OPE3 **1a** and monoalkyne **6a,** whose structure was elucidated by HMBC and X-ray diffraction studies. Reactions in toluene (entry 2) and THF (entry 3) were sluggish. Coupling in anhydrous DMF (entry 4) gave products **1a** (double coupling) and **6a** (monocoupling) in almost equal yields. Remarkably, reaction in anhydrous DMSO (entry 5) proceeded in 1 h and gave exclusively the desired double-coupled product **1a** in good yield. Couplings in acetonitrile (entry 6) and nitromethane (entry 7) yielded mixtures of mono (minor) and double coupling (major) products. Ulven and coworkers [17] have reported the beneficial effect of addition of water to TMEDA used as solvent in a case of a problematic Sonogashira coupling. Accordingly, the use of a 9:1 TMEDA-water mixture was tested (entry 8). However, this reaction gave a mixture of coupling products **1a**, **6a** and **7a** in low yield. Thus, of the solvents studied only DMSO was effective for the model double Sonogashira coupling.

It was explored if adventitious water in DMSO represented any problem in these Sonogashira couplings since this sol-

Table 1. Effect of the solvent in the model Sonogashira coupling of diiodoarene **2** and **3a** according to Scheme 4.

Entry	Solvent[a]	Polarity[b]	**1**[a](%)	**6a**(%)	**7a**(%)	**2**(%)
1	TEA	32.1	56	24	0	0
2	dry toluene	33.9	0	0	0	[d]
3	dry THF	37.4	[d]	[d]	0	[d]
4	DMF	43.2	48	34	0	0
5	DMSO	45.1	81	0	0	0
6	CH_3CN	45.6	73	8	0	0
7	CH_3NO_2	46.3	52	21	0	0
8	9:1 TMEDA-H_2O	--	48	(14)[e]	[e]	25

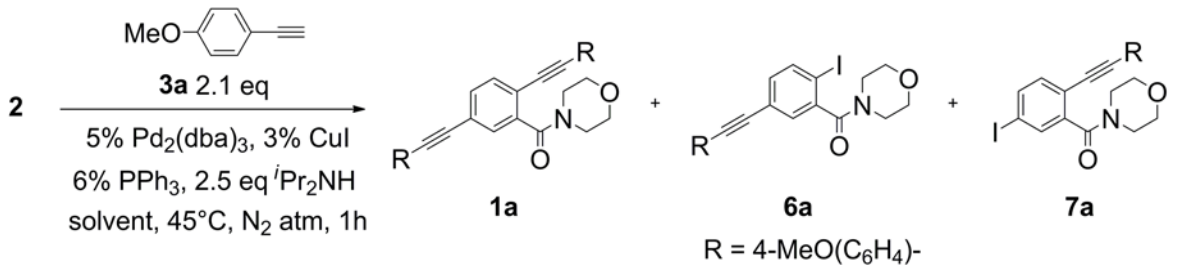
[a] Anhydrous solvents (DMF 0.150% H_2O; DMSO 0.013% H_2O, by Karl Fisher determination) were used as received. TEA, THF and toluene were dried according to standard procedures.

[b] Polarity values of solvents is based in $E_T(30)$ scale. Ref. 15.

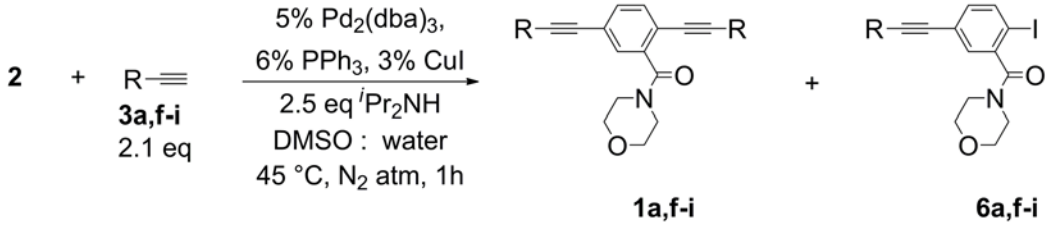
[c] Yields refer to isolated products. Identity of the coupling product **6a** is supported by HMBC and X-ray diffraction.

[d] Compound detected by TLC

[e] Inseparable 2:1 mixture (NMR) of isomers **6a** and **7a** isolated in 14% yield.



Scheme 4



Scheme 5

vent is hygroscopic and also known for remarkable changes of its properties in the presence of water [18]. Consequently, model experiments in DMSO containing 5, 33 and 67% of water were carried out (Scheme 5) and their results are shown in Table 2. While coupling of **2** and **3a** in commercial "anhydrous DMSO" (0.013% H_2O) gave 81% of **1a** (Table 2**,** entry 1) the same reaction in DMSO containing 5% water led to a 10% improved yield (entry 2; both coupling reactions in dry and wet DMSO were repeated at least three times). The reaction in DMSO containing 33% water led to a significant decrease in yield of **1a** and formation of monocoupled **6a** as the major product (entry 3). Reaction in 33% DMSO - 67% H_2O (entry 4) led to reactant solubility problems and gave almost equal amounts of mono (**6a**) and double (**1a**) coupled products. In addition, Sonogashira couplings with other arylacetylenes were tested in 5:95 water-DMSO (entries 5-10). The results show that couplings using arylacetylenes substituted with electron donating groups OCH_3 (entry 1 *vs.* entry 2) and Me_2N (entry 5 *vs.* entry 6) improved their chemical yield by about 10% in 5% water-DMSO *vs.* reaction in dry DMSO. However, water had little effect in chemical yield of coupling reactions with arylacetylenes substituted with electron withdrawing groups such as CN (entries 7 and 8), NO_2 (entries 9 and 10) and methylketone (entries 11 and 12).

The observed solvent effect in these coupling reactions could be due to coordination of DMSO with Pd. The coordinating ability of DMSO towards Pd is known [19] and it has been associated to keep catalytically active Pd° in solution, thus avoiding formation of black palladium which is inactive as catalyst. Other examples of Pd catalyzed alkynylation reactions in

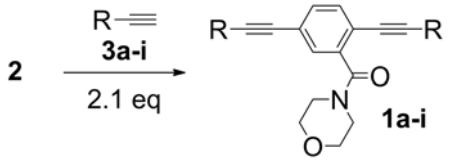
Table 2. Effect of DMSO containing different amounts of water in the Sonogashira reactions of **2** and arylalkynes according to Scheme 5.

Entry	Alkyne	**R**	**Water** [%]	**1**	[%]	**6**	[%]	**Total yield** [%]
1	**3a**	4-MeO-C_6H_4	0*	**1a**	81	**6a**	0	81
2	**3a**	4-MeO-C_6H_4	5	**1a**	91	**6a**	0	91
3	**3a**	4-MeO-C_6H_4	33	**1a**	24	**6a**	64	88
4	**3a**	4-MeO-C_6H_4	67	**1a**	47	**6a**	42	89
5	**3f**	4-Me_2N-C_6H_4	0	**1f**	83	**6f**	0	83
6	**3f**	4-Me_2N-C_6H_4	5	**1f**	94	**6f**	0	94
7	**3g**	4-NC-C_6H_4	0	**1g**	80	**6g**	0	80
8	**3g**	4-NC-C_6H_4	5	**1g**	79	**6g**	0	79
9	**3h**	4-O_2N-C_6H_4	0	**1h**	80	**6h**	0	80
10	**3h**	4-O_2N-C_6H_4	5	**1h**	78	**6h**	0	78
11	**3i**	4-MeC(O)-C_6H_4	0	**1i**	71	**6i**	0	71
12	**3i**	4-MeC(O)-C_6H_4	5	**1i**	67	**6i**	0	67

* "Dry" DMSO contained 0.013% water, as determined by Karl-Fischer titration.

DMSO are known [20] Studies of some other reactions involving the use of Pd and DMSO show the active role of this solvent in catalysis [21]. Studies of solvent dependence in cases of problematic Sonogashira couplings are rather limited [2d, 22] as compared to the more common practice of an exhaustive ligand/catalyst search, in spite of a more practical change of solvent.

With reaction conditions established, a series of OPE3 products **1a-i** were prepared in good yields (Scheme 6, Table 3). Despite the known acceleration of Sonogashira cross-couplings with alkynes substituted with electron withdrawing groups [23] couplings in DMSO worked equally well within 1 h with aryl acetylenes substituted either with strong electron donating (entry 5), electron withdrawing groups (entries 6-8) or heterocyclic acetylenes (entries 3 and 4). Compounds **1a-i** were soluble in common organic solvents. ^{1}H NMR spectra of all these compounds indicated high mobility of the morpholine moiety in solution.



Scheme 6

Table 3. Synthesis of OPE3s **1** by Sonogashira couplings in dry DMSO via Scheme 6.

Entry	Alkyne	R	Product	**Yield [%]**
1	**3a**	4-MeO(C_6H_4)	**1a**	81
2	**3b**	C_6H_5	**1b**	60
3	**3c**	3-Piridyl	**1c**	86
4	**3d**	3-Thiophenyl	**1d**	90
5	**3e**	4-Me(C_6H_4)	**1e**	70
6	**3f**	4-Me_2N(C_6H_4)	**1f**	83
7	**3g**	4-NC(C_6H_4)	**1g**	80
8	**3h**	4-O_2N(C_6H_4)	**1h**	80
9	**3i**	4-MeC(O)(C_6H_4)	**1i**	71

Reaction conditions: 5% $Pd_2(dba)_3$, 6% PPh_3, 3% CuI, $^iPr_2NH$ 2.5 eq, DMSO, 45°C, N_2 atm, 1h.

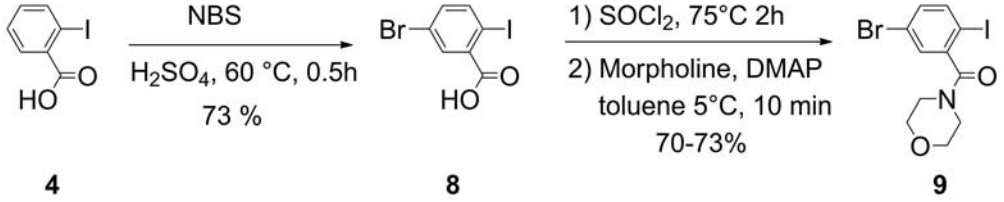
At this stage it was decided to prepare OPE3s substituted with both electron donating groups and electron withdrawing groups in a push-pull electronic architecture, a common feature found in optoelectronic materials [3-5]. Thus, it was required to sequentially install different arylacetylene groups in dihaloarene **9** by means of a regioselective Sonogashira coupling at the more reactive C-I bond [1, 2d, 24]. The required dihaloarene **9** was in turn prepared by bromination [25] of acid **4** followed by treatment with thionyl chloride and morpholine (Scheme 7).

Sonogashira reactions of **9** in DMSO with aryl acetylenes **3a,f-h** were carried out for preparation of mono coupled products **10a,f-h**. (Scheme 8, Table 4). These reactions produced the desired mono coupled products **10a,f-h** along with minor amounts of the undesired double coupled product **1a,f-h**. Sonogashira coupling of **9** with arylacetylenes substituted with electron donating groups OCH_3 (**3a**, entry 1) and NMe_2 (**3f**, entry 2) clearly gave better results in terms of yield and selectivity than those observed using arylacetylenes bearing electron withdrawing groups CN (**3g**, entry 3) and NO_2 (**3h**, entry 4).

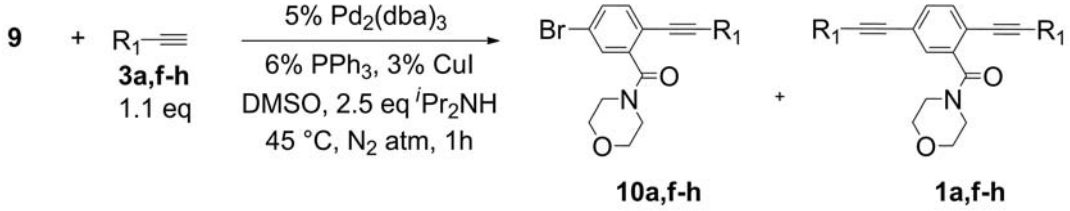
Installation of the second arylacetylene group at the C-Br bond of compounds **10a,f-h** proved more difficult than expected, but eventually was accomplished using reaction conditions reported by Buchwald [26] to afford compounds **1j-p**. (Scheme 9)

Table 4. Regioselective Sonogashira cross coupling at the C-I bond in compound **10** via Scheme 8.

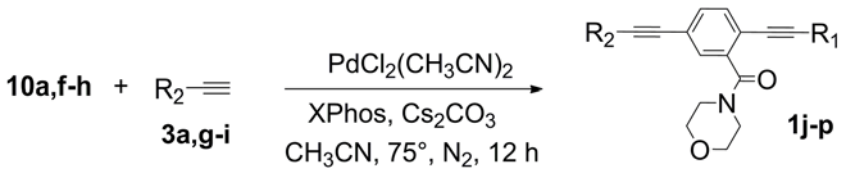
Entry	Alkyne	R_1	**9**(%)	**10**	%	**1**	%
1	**3a**	4-MeO-C_6H_4	0	10a	73	1a	15
2	**3f**	4-Me_2N-C_6H_4	0	**10f**	72	1f	10
3	**3g**	4-NC-C_6H_4	20	10g	43	1g	22
4	**3h**	4-O_2N-C_6H_4	16	10h	42	1h	20



Scheme 7



Scheme 8



Scheme 9

The low reactivity of substrates **10a** and **10f** (see Table 5) can be explained by the enhanced electron density at the C-Br bond due to the strong electron donating groups (OMe and NMe_2) on the arylacetylene unit which likely made worse the Pd(0) oxidative addition step of the coupling reaction [1]. By contrast, bromoarene **10h** bearing a nitro substituted arylacetylene (entry 7) gave compound **1p** in higher yield.

With compounds **1a-p** at hand, their photoluminescence properties were studied and results are shown in Table 6. Several compounds including the parent phenyleneethynylene **1b**, methyl substituted **1e**, and heterocyclic 3-pyridyl **1c** and 3-thiophenyl analogs **1d** display almost identical UV maxima absorbance. The rest of the compounds show bathochromic (red) shifts. All compounds are UV active and their ε values indicate intense absorption bands due to π-π* transitions. Compounds **1h, n, p** containing one or two NO_2 groups and the diketone compound **1i** did not show fluorescence. All other compounds emit fluorescence in the 352-505 nm (violet to green) range. Compounds **1l** and **1o**, substituted with the electron withdrawing keto group, show modest fluorescence (entries 11 and 14).

Compounds with equal terminal aryl groups are listed in entries 1 through 9. Among them, compounds **1f** with electron donating NMe_2 substituents (entry 6) and **1g** with electron withdrawing CN substituents (entry 7) displayed high quantum fluorescence yields, which were measured by Brouwer´s method [27] On the other hand, compounds with push-pull architecture (entries 10-15) show intramolecular charge transfer, as evidenced by large Stokes shifts which are associated to fluorescence quenching [28] However, cyano substituted compounds **1g** (entry 7), **1k** (entry 10) and **1m** (entry 12) show high quantum fluorescence yields; the cyano group is a common feature of molecular wires [13b]. Similar OPE3s with high quantum yields are known [29]

In summary, we have prepared a series of soluble, fluorescent oligo phenyleneethynylenes OPE3, some of which display high quantum yields. Additionally, it was found that Sonogashira couplings proceeded much better in DMSO without need for other additives, the chemical yields were good and reactions took place within 1 h at 40-45°C. Couplings in DMSO containing 5% water gave a small increment of the yield of reactions of **2** with arylacetylenes substituted with electron donating groups.

Acknowledgments

Financial support from Conacyt-México (grants 61247 and 221360 and a predoctoral fellowship to MFJ) is gratefully acknowledged.

Experimental

General

Commercial reagents were used without further purification. Toluene was distilled from Na and stored over activated 4 Å molecular sieves under N_2. THF was refluxed in the presence of triphenylphosphine then distilled and stored over activated 4-Å molecular sieves under N_2. Reactions were monitored by TLC on Merck silica gel F_{254} plates and spots were visualized by a UV lamp at 254 and 365 nm. Column flash chromatography was performed using Whatman silica gel 60 (230-400 mesh). ^1H and ^{13}C NMR spectra were recorded on a Varian VNMR System 400 MHz spectrometer using tetramethylsilane (TMS δ=0.0 ppm) and $CDCl_3$ (δ = 77.16 ppm) as internal standards; bs means broad signal, app d means apparent doublet in ^1H NMR spectra. Infrared spectra were measured on a Perkin-Elmer FT-IR Spectrum GX spectrometer. High resolution mass spectra were recorded in a Jeol Gcmate mass spectrometer using EI (70 eV) as ionization mode. UV spectra were recorded on a Perkin-Elmer Lambda XLS spectrometer using quartz cells. For UV and fluorescence determinations spectros-

Table 5. Preparation of push-pull OPE3s **1j-p** via Scheme 9.

Entry	Arene 10	R_1	Alkyne 3	R_2	Product	Yield [%]
1	**10a**	4-MeO-C_6H_4	**3g**	4-NC-C_6H_4	**1j**	80
2	**10a**	4-MeO-C_6H_4	**3h**	4-O_2N-C_6H_4	**1k**	0
3	**10a**	4-MeO-C_6H_4	**3i**	4-MeC(O)-C_6H_4	**1l**	55
4	**10f**	4-Me_2N-C_6H_4	**3g**	4-NC-C_6H_4	**1m**	36
5	**10f**	4-Me_2N-C_6H_4	**3h**	4-O_2N-C_6H_4	**1n**	35
6	**10f**	4-Me_2N-C_6H_4	**3i**	4-MeC(O)-C_6H_4	**1o**	35
7	**10h**	4-O_2N-C_6H_4	**3a**	4-MeO-C_6H_4	**1p**	65

Table 6. Optical characterization of OPE3 compounds **1a-o** depicted in Schemes 6 and 9.

Entry data	OPE3	R_2	R_1	λ_{max}[a] (nm)	$\varepsilon(10^4)$ cm^{-1} M^{-1}	λ_{mx}[b] (nm)	Stokes Shift (nm)	Φ[c]
1	**1a**	MeO	MeO	338	5.50	389	51	0.475
2	**1b**	H	H	325	5.56	375	50	0.103
3	**1c**	3-pyr[d]	3-pyr	326	5.57	352	26	0.121
4	**1d**	3-thioph[e]	3-thioph	326	4.54	380	54	0.077
5	**1e**	Me	Me	330	6.93	380	50	0.178
6	**1f**	Me_2N	Me_2N	385	6.58	441	56	0.792
7	**1g**	CN	CN	338	6.71	369	31	0.708
8	**1h**	NO_2	NO_2	359	5.30	[nd]	-	0
9	**1i**	MeC(O)	MeC(O)	344	6.99	[nd]	-	0
10	**1j**	CN	OMe	341	5.52	406	65	0.874
11	**1l**	COMe	OMe	345	5.19	416	71	0.130
12	**1m**	CN	NMe_2	388	4.65	495	157	0.786
13	**1n**	NO_2	NMe_2	328	3.09	[nd]	-	0
14	**1o**	COMe	NMe_2	384	3.48	505	121	0.494
15	**1p**	OMe	NO_2	364	4.63	[nd]	-	0

[a] UV absorption (10^{-6} M solution in $CHCl_3$).
[b] Fluorescence emission (10^{-6} M solution in $CHCl_3$) with UV excitation at 10 nm below each maximum absorption.
[c] Quantum fluorescence yield determined using quinine sulfate / H_2SO_4 as standard. Ref. 27
[d] 3-piridyl
[e] 3-thiophenyl
[nd] No fluorescence emission was detected.

copy quality $CHCl_3$ was used. Fluorescence spectra were recorded at room temperature on a Perkin Elmer LS 55 spectrofluorometer. Fluorescence quantum yields ϕ in $CHCl_3$ are relative to quinine sulfate 1N in H_2SO_4 [27]. Melting points were measured using a Büchi Melting Point B-540 apparatus and are uncorrected.

4-(2,5-Diiodobenzoyl)morpholine (2) Iodination of commercial 2-iodobenzoic acid **4** leading to 2,5-diiodobenzoic acid (**5**) was carried out according to a reported method [14]. Thus, in a 100 mL round bottom flask containing 30 mL of concentrated sulfuric acid were added 1.20 g of iodine and 0.34 g of $NaIO_4$ at room temperature under vigorous magnetic stirring. When the solids dissolved it was added 2.48 g of 2-iodobenzoic acid **4** and the mixture was left stirring at room temperature (23°C) for 48 h. Then, the crude reaction mixture was poured on ice and the pink solid was filtered off. The solid was dissolved in ethyl acetate and washed with a saturated sodium thiosulfate solution. The organic layer was separated and dried with anhydrous sodium sulfate, filtered and concentrated *in vacuo* to afford 2.62 g (70%) of **5** as a white powder. Then, 1.68 g (4.5 mmol) of carboxylic acid **5** was suspended in 8 mL of thionyl chloride and heated to reflux for 2 h under N_2 and allowed to cool to room temperature. Excess of thionyl chloride was removed *in vacuo* and the reaction mixture was diluted with 10 mL of anhydrous toluene. Catalytic DMAP and morpholine (1.6 mL, 18.0 mmol) were added under stirring at room temperature. After completion of the reaction (15 min), indicated by TLC analysis, the mixture was washed with 3% HCl solution, then with saturated $NaHCO_3$ solution and extracted with ethyl acetate. The organic layer was dried with anhydrous Na_2SO_4 and concentrated to yield a yellow syrup that precipitated upon addition of hexane. Recrystallization from toluene-hexane afforded 1.40 g of **2** (70%) as an off-white powder, mp 145-146 °C; IR (KBr): λ 1600 ($\nu_{N-C=O}$), 1700 ($\nu_{C=O}$) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, *J*= 8.34, 1H), 7.50 (d, *J*= 1.99, 1H), 7.39 (dd, *J*=8.33, *J*=2.04, 1H), 3.9-3.1 (bs, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.8, 143.8, 140.9, 139.5, 135.9, 94.2, 91.8, 66.8, 66.6, 47.4, 42.1; HRMS (EI) *m/z* calcd. for $C_{11}H_{11}I_2NO_2$: 442.8880, found: 442.8886.

General procedure for double Sonogashira cross-coupling reactions of 4-(2,5-diiodobenzoyl)morpholine 2 with arylacetylenes 3a-i in DMSO

A mixture of 4-(2,5-diiodobenzoyl)morpholine **2** (177.2 mg, 0.40 mmol), alkynes **3a-i** (0.84 mmol), $Pd_2(dba)_3$ (10.4 mg, 10 μmol), CuI (2.3 mg, 12 μmol), triphenylphosphine (6.3 mg, 24 μmol) and dry DMSO (5 mL) under N_2, was degassed. ^{i}Pr$_2$NH (140 μL, 1 mmol) was added and then the mixture was heated at 45 °C (temperature of the external bath) under vigorous stirring. TLC analysis showed completion of the reaction after 1 h. After aqueous work-up and extraction with ethyl acetate the residue was adsorbed on silica gel and purified by flash chromatography (elution with hexane/EtOAc gradient).

Evaporation of solvent gave a solid residue which was triturated with hexane/acetone to afford the desired pure product **1a-i**.

The same procedure was followed for those reactions carried out in DMSO containing 5%, 33% and 67% of water (v/v) shown in Table 3.

2,5-Bis((4-ethoxyphenyl)ethynyl)morpholinebenzamide (**1a**) Obtained in 81% yield from the reaction of 2,5-diiodo-*N*-morpholinebenzamide (**2)** with 4-ethynylanisole (**3a**) as a white powder, mp 149-151 °C. IR (KBr,): λ 1604 ($\nu_{N-C=O}$), 1633 ($\nu_{C=O}$), 2213 ($\nu_{Csp-Csp}$) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.50-7.41 (m, 7H), 6.89 (app d, 4H), 3.90-3.25 (bs, m, 8H), 3.84 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 160.2, 160.1, 138.5, 133.32, 133.26, 132.0, 131.8, 129.6, 124.0, 119.9, 114.9, 114.7, 114.3, 114.2, 95.0, 92.4, 87.3, 85.6, 67.1, 67.0, 55.50, 55.48, 47.5, 42.3; HRMS (EI) *m/z* calcd. for $C_{29}H_{25}NO_4$: 451.1784, found: 451.1765.

2,5-Bis(phenylethynyl)morpholinebenzamide (**1b**) Prepared in 60% yield by the reaction of 2,5-diiodo-*N*-morpholinebenzamide (**2)** with phenylacetylene (**3b**) as yellow syrup that solidifies upon standing. IR (film): λ 1599 ($\nu_{N-C=O}$), 1639 ($\nu_{C=O}$), 2216 ($\nu_{Csp-Csp}$) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.55-7.47 (m, 7H), 7.38-7.34 (m, 6H), 3.95-3.20 (bs, m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.0, 138.7, 132.2, 132.0, 131.8, 131.7, 129.7, 129.1, 128.9, 128.6, 128.5, 124.0, 122.7, 122.5, 119.8, 94.9, 92.4, 88.3, 86.6, 67.0, 66.9, 47.5, 42.2; HRMS (EI) *m/z* calcd. for $C_{27}H_{21}NO_2$: 391.1572, found: 391.1589.

2,5-Bis(3-pyridinylethynyl)morpholinebenzamide (1c) Prepared in 86% yield by the reaction 2,5-diiodo-*N*-morpholinebenzamide (**2)** with 3-ethynylpyridine (**3c**) as an off-white powder, mp 157.7-158.2 °C. IR (KBr): λ 1613 ($\nu_{C=O}$), 2211 ($\nu_{Csp-Csp}$) cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$): δ 8.70 (bs, app d, 2H), 7.80 (app t, 3H), 7.61-7.51 (m, 4H), 7.33 (bs, s, 2H), 3.90-3.25 (bs, m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6, 152.4, 152.3, 149.4, 149.2, 139.0, 138.6, 138.5, 132.5, 132.1, 129.8, 123.8, 119.7, 123.25, 123.34, 91.5, 91.3, 89.6, 89.2, 67.0, 66.9, 47.5, 42.3; HRMS (EI) *m/z* calcd. for $C_{25}H_{19}N_3O_2$: 393.1477, found: 393.1482.

2,5-Bis(3-thiophenylethynyl)morpholinebenzamide (**1d**) Prepared in 90% yield by the reaction 2,5-diiodo-*N*-morpholinebenzamide (**2)** with 3-ethynylthiophene (**3d**) as a brown powder, mp 156.0-156.5 °C. IR (KBr): λ 1633 ($\nu_{C=O}$), 2207 ($\nu_{Csp-Csp}$) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.55 (dd, *J*=2.97 Hz, *J*= 1.18 Hz, 1H), 7.53 (dd, *J*=2.98 Hz, *J*= 1.17 Hz, 1H), 7.51-7.49 (m, 2H), 7.49-7.48 (app d, 1H), 7.33 (t, *J*= 2.93, 1H), 7.32 (*t*, J= 2.93, 1H) , 7.19 (dd, *J*=5.02 Hz, *J*= 1.18 Hz, 1H), 7.16 (dd, *J*=4.97 Hz, *J*= 1.18 Hz, 1H), 3.90-3.25 (bs, m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.9, 138.5, 132.0, 131.8, 129.7, 129.6, 129.53, 129.46, 129.3, 125.6, 123.8, 121.7, 121.5, 119.6, 89.9, 87.8, 87.5, 86.0, 66.9, 66.8, 47.3, 42.1; HRMS (EI) *m/z* calcd. for $C_{23}H_{17}NO_2S_2$: 403.0701, found: 403.0706.

2,5-Bis(*p*-tolylethynyl)morpholinebenzamide (**1e**) Prepared in 70% yield by the reaction 2,5-diiodo-*N*-morpholinebenzamide (**2)** with 4-methylphenylacetylene (**3e**) as a white powder, mp 179.9-180.8 °C. IR (KBr): λ 1630 ($\nu_{C=O}$), 2213 ($\nu_{Csp-Csp}$) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.52-7.48 (m, 3H), 7.42 (app d, 2H), 7.38 (app d, 2H), 7.17 (app d, 4H), 3.95-3.20 (bs, m, 8H), 2.38 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.0, 139.2, 139.0, 138.5, 132.0, 131.8, 131.5, 131.5, 129.6, 129.3, 129.2, 123.9, 119.7, 119.5, 119.3, 95.0, 92.5, 87.7, 85.9, 66.9, 66.8, 47.3, 42.1; HRMS (EI) *m/z* calcd. for $C_{29}H_{25}NO_2$: 419.1885, found: 419.1890.

2,5-Bis((4-(dimethylamino)phenyl)ethynyl)morpholinebenzamide (**1f**) Prepared in 83% yield by the reaction 2,5-diiodo-*N*-morpholinebenzamide (**2)** with 4-ethynyl-*N*,*N*-dimethylaniline (**3f**) as a yellow powder, mp 209.4-210.2 °C. IR (KBr): λ 1607($n_{N-C=O}$), 1630 ($\nu_{C=O}$), 2204 ($\nu_{Csp-Csp}$) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.45 (s, 3H), 7.41-7.34 (m, 4H), 6.68-6.62 (m, 4H), 3.92-3.20 (bs, m, 8H), 3.00 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6, 150.5, 150.4, 138.1, 133.0, 132.9, 131.7, 131.6, 129.4, 124.0, 119.9, 111.91, 111.89, 109.5, 109.2, 96.3, 93.6, 86.9, 85.2, 67.1, 67.0, 47.5, 42.2, 40.33, 40.31; HRMS (EI) *m/z* calcd. for $C_{31}H_{31}N_3O_2$: 477.2416, found: 477.2432.

2,5-Bis((4-cyanophenyl)ethynyl)morpholinebenzamide (**1g**) Prepared in 80% by the reaction 2,5-diiodo-*N*-morpholinebenzamide (**2)** with 4-ethynylbenzonitrile (**3g**) as a yellow powder, mp 228.0-230.0 °C (dec.) IR (KBr): λ 1602 ($n_{N-C=O}$), 1640 ($\nu_{C=O}$), 2217 ($\nu_{Csp-Csp}$), 2227 (ν_{Csp-N}) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.68 (app dd, 4H), 7.64-7.54 (m, 7H), 3.9-3.25 (bs, m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.3, 139.1, 132.5, 132.3, 132.3, 132.2, 132.1, 129.9, 127.3, 127.0, 123.7, 119.6, 118.3, 118.2, 112.4, 112.1, 93.1, 92.0, 90.9, 90.2, 66.9, 66.8, 47.4, 42.2; HRMS (EI) *m/z* calcd. for $C_{29}H_{19}N_3O_2$: 441.1477, found: 441.1488.

2,5-Bis((4-nitrophenyl)ethynyl)morpholinebenzamide (**1h**) Prepared in 80% yield by the reaction 2,5-diiodo-*N*-morpholinebenzamide (**2)** with 1-ethynyl-4-nitrobenzene (**3h**) as a yellow powder, mp 204.8-205.7 °C. IR (KBr): λ 1347 and 1519 (ν_{NO2}), 1593 ($\nu_{N-C=O}$), 1638 ($\nu_{C=O}$), 2218 ($\nu_{Csp-Csp}$), cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.26 (app d, 4H), 7.71-7.55 (m, 7H), 3.90-3.25 (bs, m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.4, 147.6, 147.4, 139.3, 132.7, 132.6, 132.5, 132.3, 130.0, 129.4, 129.0, 124.0, 123.8, 119.7, 93.0, 92.9, 91.1, 90.8, 67.0, 66.9, 47.5, 42.3; HRMS (EI) *m/z* calcd. for $C_{27}H_{19}N_3O_6$: 481.1274, found: 481.1280.

2,5-Bis((4-acetophenyl)ethynyl)morpholinebenzamide (**1i**) Prepared in 71% yield by the reaction 2,5-diiodo-*N*-morpholinebenzamide (**2)** with 4-ethynylacetophenone (**3i**) as a green-yellow powder, mp 194.1-196.0 °C. IR (KBr): 1600 ($\nu_{N-C=O}$), 1630 ($\nu_{C=O}$), 1677 ($\nu_{C=O}$), 1690 ($\nu_{C=O}$), 2208 ($\nu_{Csp-Csp}$) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.95 (app d, 4H), 7.63-7.52 (m, 7H), 3.90-3.25 (bs, m, 8H), 2.61 (s, 6H); ^{13}C NNMR (100 MHz, $CDCl_3$): δ 197.4, 197.3, 167.7139.1, 136.9, 136.7, 132.5, 132.2, 131.9, 131.9, 129.9, 128.6, 128.5, 127.4, 127.1, 123.8, 119.8, 94.2, 91.8, 91.2, 89.5, 67.0, 66.9, 47.5, 42.3, 26.8; HRMS (EI) *m/z* calcd. for $C_{31}H_{25}NO_4$: 475.1784, found: 475.1800.

4-(5-Bromo-2-iodobenzoyl)morpholine (9) Bromination of commercial 2-iodobenzoic acid **4** leading to 5-bromo-2-iodobenzoic acid (**8**) was carried out according to a reported method [25] Thus, in a 100 mL round bottom flask containing 30 mL of concentrated sulfuric acid at 60 °C, was

added 2-iodobenzoic acid **4** (3.72 g, 15 mmol), then maintaining this temperature three portions of solid NBS (6 mmol) were added every 15 min, for a total of 3.2 g (18 mmol) of NBS. After the last addition, the mixture was left stirring for 1 h at 60°C, then left to cool to room temperature and poured over crushed ice. The pink solid was filtered off and dissolved in ethyl acetate and washed with a concentrated solution of sodium thiosulfate. The organic portion was dried with anhydrous Na_2CO_3, filtered and concentrated *in vacuo* to afford 3.58 g (73%) of the carboxylic acid **8** as a white solid. Then, 1.471 g (4.5 mmol) of carboxylic acid **8** was suspended in 8 mL of thionyl chloride and heated to reflux for 2 h under N_2 and allowed to cool to room temperature. Excess of thionyl chloride was removed *in vacuo* and the reaction mixture was diluted with 10 mL of anhydrous toluene. Catalytic DMAP and morpholine (1.6 mL, 18.0 mmol) were added under stirring at room temperature. After completion of the reaction (15 min), indicated by TLC analysis, the mixture was washed with 3% HCl solution, then with saturated $NaHCO_3$ and extracted with ethyl acetate. The organic layer was dried with anhydrous Na_2SO_4 and concentrated to yield a yellow syrup that precipitated upon addition of hexane. Recrystallization from toluene-hexane afforded 1.301 g of **10** (73%) as a white powder, mp 148 °C; IR (KBr) λ 1620 ($\nu_{N\text{-}C=O}$) cm^{-1}, ^1H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, *J*= 8.44, 1H), 7.34 (d, *J*= 2.31, 1H), 7.22 (dd, *J*=8.43, *J*=2.35, 1H), 3.9-3.1 (bs, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ167.92, 143.60, 140.76, 133.67, 130.15, 123.09, 90.55, 66.76, 66.62, 47.31, 42.12; HRMS (EI) *m/z* calcd. for $C_{11}H_{11}BrINO_2$: 394.9018, found: 394.9020

General procedure for C-I regioselective Sonogashira cross-coupling reactions of 9 with arylacetylenes. A mixture of **9** (158.4 mg, 0.40 mmol), alkynes **3a,f-h** (0.44 mmol), $Pd_2(dba)_3$ (10.4 mg, 10 μmol), CuI (2.3 mg, 12 μmol), triphenylphosphine (6.3 mg, 24 mmol) and DMSO (5 mL) under N_2, was degassed. $^iPr_2NH$ (140 μL, 1 mmol) was added and then the mixture was heated at 45 °C (temperature of external bath) under vigorous stirring for 1 h as TLC analysis indicated completion of the reaction. Aqueous work-up and extraction gave the crude reaction mixture which was adsorbed on silica gel and after flash chromatography (elution with hexane/EtOAc gradient) the solid residue was washed with hexane/acetone to afford the desired pure products **10a, f-h**.

5-Bromo-2-((4-methoxyphenyl)ethynyl)morpholinebenzamide (**10a**) Prepared in 73% yield by the reaction of 5-bromo-2-iodo-*N*-morpholinebenzamide (**9**) with 4-ethynylanisole (**6a**) as a yellow powder, mp 138-139 °C. IR (KBr): λ 1600 ($\nu_{N\text{-}C=O}$), 1692 ($\nu_{C=O}$), 2212 ($\nu_{Csp\text{-}Csp}$) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.52-7.47 (m, 2H), 7.44-7.37 (m, 3H), 6.88 (app d, 2H), 3.90-3.25 (bs, m, 8H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.2, 160.1, 139.7, 133.2, 133.1, 132.2, 129.7, 122.5, 119.5, 114.24, 114.19, 94.4, 84.6, 66.8, 66.7, 55.4, 47.3, 42.1; HRMS (EI) *m/z* calcd. for $C_{20}H_{18}BrNO_3$: 399.0470, found: 399.0472.

5-Bromo-2-((4-(dimethylamino)phenyl)ethynyl)morpholinebenzamide (**10f**) Prepared in 72% yield by the reaction of 5-bromo-2-iodo-*N*-morpholinebenzamide (**9**) with 4-ethynyl-*N*,*N*-dimethylaniline (**3f**) as a yellow powder, mp 123-124 °C. IR (KBr): λ 1604 ($\nu_{N\text{-}C=O}$), 1688($\nu_{C=O}$), 2204 ($\nu_{Csp\text{-}Csp}$) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.49-7.45 (m, 2H), 7.38-7.32 (m, 3H), 6.64 (app d, 2H), 3.90-3.25 (bs, m, 8H), 3.00 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): d167.4, 150.4, 139.4, 133.0, 132.8, 132.1, 129.7, 121.7, 120.1, 111.7, 108.6, 96.0, 84.0, 66.8, 66.7, 47.3, 42.1, 40.1; HRMS (EI) *m/z* calcd. for $C_{21}H_{21}BrN_2O_2$: 412.0786, found: 412.0770.

5-Bromo-2-((4-cyanophenyl)ethynyl)morpholinebenzamide (**10g**) Prepared in 43% yield by the reaction of 5-bromo-2-iodo-*N*-morpholinebenzamide (**9**) and 4-ethynylbenzonitrile (**3g**) as a yellow powder, mp 237-238 °C (dec). IR (KBr): λ 1602 ($\nu_{N\text{-}C=O}$), 1687 ($\nu_{C=O}$), 2224 ($\nu_{Csp\text{-}N}$) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.66 (app d, 2H), 7.58-7.54 (m, 3H), 7.51 (app d, 1H), 7.44(dd, *J*=8.2 Hz *J*= 0.26 Hz, 1H), 3.90-3.25 (bs, m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9, 140.4, 133.8, 132.6, 132.4, 132.2, 130.0, 127.2, 124.2, 118.4, 118.3, 112.5, 92.2, 89.9, 67.0, 66.9, 47.5, 42.3; HRMS (EI) *m/z* calcd. for $C_{20}H_{15}BrN_2O_2$: 394.0317, found: 394.0306.

5-Bromo-2-((4-nitrophenyl)ethynyl)morpholinebenzamide (**10h**) Prepared in 42% yield by the reaction of 5-bromo-2-iodo-*N*-morpholinebenzamide (**9**) with 1-ethynyl-4-nitrobenzene (**3h**) as a yellow powder, mp 229-230 °C (dec). IR (KBr): λ 1347 and 1528 (ν_{NO2}), 1600 ($\nu_{N\text{-}C=O}$), 1691 ($\nu_{C=O}$), 2217 ($\nu_{Csp\text{-}Csp}$) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.23 (app d, 2H), 7.62 (app d, 2H), 7.56 (dd, *J*=8.30 Hz *J*= 2.01 Hz, 1H), 7.52 (d, *J*= 1.97 Hz, 1H), 7.45 (d, *J*= 8.27 Hz, 1H), 3.90-3.25 (bs, m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7, 147.4, 140.3, 133.7, 132.5, 132.3, 129.8, 129.0, 124.2, 123.8, 118.0, 91.8, 90.6, 66.8, 66.8, 47.4, 42.2; HRMS (EI) *m/z* calcd. for $C_{19}H_{15}BrN_2O_4$: 414.0215, found: 414.0227.

General procedure for Sonogashira cross-coupling reactions used to prepare 1j-p. Compounds **10a**, **10f** and **10h** were subjected to Sonogashira couplings at the C-Br bond with arylacetylenes following conditions reported by Buchwald.[26] Thus, a mixture of the bromoarene **10a,f-h** (0.40 mmol, 1.0 equiv), arylalkynes **3a,g-1** (0.44 mmol, 1.1 equiv), $PdCl_2(CH_3CN)_2$ (3.1 mg, 0.03 equiv, 12 mmol), XPhos (11.4 mg, 24 mmol, 0.06 equiv), Cs_2CO_3 (338.9 mg, 1.04 mmol, 2.6 equiv) and CH_3CN (6 mL) under N_2, was degassed. Then, the mixture was heated at 75 °C (temperature of external bath) under vigorous stirring for 12 h. After this time, TLC analysis of the reaction mixture indicated completion of the reaction. Aqueous work-up and extraction with ethyl acetate (3 × 15 mL) gave the crude reaction mixture which was dried over anhydrous Na_2CO_3, filtered, and finally adsorbed on silica gel. After flash chromatography (elution with hexane/EtOAc gradient) the solid residue was washed with hexane/acetone to afford the desired pure products **1j-p**.

5-((4-Cyanophenyl)ethynyl)-2-((4-methoxyphenyl)ethynyl)morpholinebenzamide (**1j**) Prepared in 80% yield by the reaction of **10a** with 4-ethynylbenzonitrile (**3g**) as a yellow powder, mp 188.4-188.8 °C (dec). IR (KBr): λ 1605 ($\nu_{N\text{-}C=O}$), 1625 ($\nu_{C=O}$), 2205 ($\nu_{Csp\text{-}Csp}$), 2225 ($\nu_{Csp\text{-}N}$) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.66 (app d, 2H), 7.60 (app d, 2H), 7.54-7.52 (m, 3H), 7.44 (app d, 2H), 6.90 (app d, 2H), 3.90-3.25 (bs, m, 8H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.8, 160.2, 138.5, 133.2, 132.1, 131.98, 132.02, 132.0, 129.9,

127.6, 122.3, 121.1, 118.4, 114.2, 114.2, 111.9, 95.7, 92.4, 90.2, 85.2, 66.9, 66.8, 55.4, 47.3, 42.1; HRMS (EI) *m/z* calcd. for $C_{29}H_{22}N_2O_3$: 446.1631, found: 446.1627.

5-((4-Acetophenyl)ethynyl)-2((4-methoxyphenyl) ethynyl)morpholinebenzamide (**1l**) Prepared in 55% yield from the reaction of **10a** with 4-ethynylacetophenone (**3i**) as a yellow powder, mp 182.0-182.5 °C. IR (KBr): λ 1605 ($\nu_{N-C=O}$), 1627 ($\nu_{C=O}$), 1677 ($\nu_{C=O}$), 2208 ($\nu_{Csp-Csp}$) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.96 (app d, 2H), 7.60 (app d, 2H), 7.53 (s, 3H), 7.44 (app d, 2H), 6.90 (app d, 2H), 3.90-3.25 (bs, m, 8H), 3.85 (s, 3H), 2.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.2, 167.9, 160.2, 138.5, 136.4, 133.2, 132.0, 131.9, 131.7, 129.8, 128.3, 127.5, 122.8, 120.8, 114.3, 114.2, 95.5, 91.4, 91.2, 85.3, 66.9, 66.8, 55.3, 47.3, 42.1, 26.7; HRMS (EI) *m/z* calcd. for $C_{30}H_{25}NO_4$: 463.1784, found: 463.1804.

5-((4-Cyanophenyl)ethynyl)-2-((4-(dimethylamino) phenyl)ethynyl)morpholine benzamide (**1m**) Prepared in 36% yield by the reaction of **10f** with 4-ethynylbenzonitrile (**3g**) as a yellow powder, mp 210.7-212.1 °C. IR (KBr): λ 1593 ($\nu_{N-C=O}$), 1633 ($\nu_{C=O}$), 2213 ($\nu_{Csp-Csp}$), 2223 (ν_{Csp-N}) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.65 (app d, 2H), 7.59 (app d, 2H), 7.50 (s, 3H), 7.36 (d app, 2H), 6.65 (app d, 2H), 3.95-3.20 (bs, m, 8H), 3.01 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.0, 150.5, 138.1, 132.9, 132.09, 132.07, 132.0, 131.7, 130.0, 127.7, 121.8, 121.6, 118.5, 111.7, 111.7h, 108.5, 97.5, 92.7, 89.9, 84.8, 66.9, 66.8, 47.3, 42.1, 40.1; HRMS (EI) *m/z* calcd. for $C_{30}H_{25}N_3O_2$: 459.1947, found: 459.1968.

2-((4-(Dimethylamino)phenyl)ethynyl)-5-((4-nitrophenyl)ethynyl)morpholine benzamide (**1n**) Prepared in 35% yield by the reaction of **10f** with 1-ethynyl-4-nitro benzene (**3h**) as a red powder, mp 227.3 - 227.9 °C. IR (KBr): λ 1339 and 1512 (ν_{NO2}), 1589 ($\nu_{N-C=O}$), 1624 ($\nu_{C=O}$), 2205 ($\nu_{Csp-Csp}$) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.21 (app d, 2H), 7.64 (app d, 2H), 7.53-7.49 (m, 3H), 7.36 (app d, 2H), 6.64 (app d, 2H), 3.95-3.20 (bs, m, 8H), 3.00 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.9, 150.5, 147.1, 138.2, 132.9, 132.3, 132.0, 131.7, 130.0, 129.7, 123.7, 122.0, 121.4, 111.7, 108.5, 97.6, 93.6, 89.7, 84.8, 66.9, 66.8, 47.4, 42.1, 40.1; HRMS (EI) *m/z* calcd. for $C_{29}H_{25}N_3O_4$: 479.1845, found: 479.1832.

5-((4-Acetophenyl)ethynyl)-2-((4-(dimethylamino) phenyl)ethynyl)morpholine benzamide (**1o**) Prepared in 35% yield by the reaction of **10f** with 4-ethynylacetophenone (**3i**) as a yellow powder, mp 214.8-215.3 °C. IR (KBr): λ 1592 ($\nu_{N-C=O}$), 1641 ($\nu_{C=O}$), 1677 ($\nu_{C=O}$), 2199 ($\nu_{Csp-Csp}$) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.94 (app d, 2H), 7.59 (app d, 2H), 7.52-7.47 (m, 3H), 7.35 (app d, 2H), 6.64 (app d, 2H), 3.95-3.20 (bs, m, 8H), 2.99 (s, 6H), 2.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.3, 168.0, 150.5, 138.1, 136.4, 132.9, 131.9, 131.7, 131.6, 129.9, 128.3, 127.6, 122.0, 121.4, 111.7, 108.6, 97.2, 91.7, 90.9, 84.8, 66.9, 66.8, 47.3, 42.1, 40.1, 26.7; HRMS (EI) *m/z* calcd. for $C_{31}H_{28}N_2O_3$: 476.2100, found: 476.2130.

5-((4-Methoxyphenyl)ethynyl)-2-((4-nitrophenyl) ethynyl)morpholinebenzamide (**1p**) Prepared in 65% yield by the reaction of **10h** and 4-ethynylanisole (**3a**) as a yellow powder, mp 194.3-194.5 °C. IR (KBr): λ 1340 y 1513 (ν_{NO2}), 1590 ($\nu_{N-C=O}$), 1636 ($\nu_{C=O}$), 2209 ($\nu_{Csp-Csp}$), cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.24 (app d, 2H), 7.63 (app d, 2H), 7.58-7.50 (m, 3H), 7.47 (app d, 2H), 6.90 (app d, 2H), 3.90-3.25 (bs, m, 8H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.8, 160.3, 147.4, 139.1, 133.4, 132.6, 132.4, 131.9, 129.5, 129.4, 125.6, 124.0, 118.2, 114.5, 114.3, 93.5, 92.4, 91.7, 87.0, 67.1, 67.0, 55.5, 47.5, 42.3; HRMS (EI) *m/z* calcd. for $C_{28}H_{22}N_2O_5$: 466.1529, found: 466.1512.

References

1. a) Sonogashira, K. *J. Organomet. Chem*. **2002**, *653*, 46-49. b) Chinchilla, R.; Nájera, C. *Chem. Soc. Rev.*, **2011**, *40*, 5084-5121. c) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007**, *107*, 874-922.
2. a) Cassar L. *J. Organomet. Chem*. **1975**, *93*, 253-257. b) Dieck, H. A.; Heck, F. R. *J. Organomet. Chem*. **1975**, *93*, 259-263. c) Alami, M.; Ferri, F.; Linstrumelle, G. *Tetrahedron Lett.* **1993**, *34*, 6403-6406. d) Doucet, H.; Hierso, J. C. *Angew. Chem. Int. Ed.* **2007**, *46*, 834-871. e) Tykwinski, R. R. *Angew. Chem. Int. Ed*. **2003**, *42*, 1566-1568. f) Plenio, H. *Angew. Chem. Int. Ed.* **2008,** *47***,** 6954-6956**.**
3. a) Bunz, U. H. F. *Chem. Rev*. **2000**, *100*, 1605-1644. b) Bunz, U. H. F. *Adv. Poly. Sci.* **2005**, *177*, 1-52.
4. Yamamoto, T.; Yamaguchi, I.; Yasuda, T. *Adv. Polym. Sci*. **2005**, *177*, 181-208.
5. Klemm, E.; Pautzsch, T.; Blankenburg, L. *Adv. Polym. Sci*. **2005**, *177*, 53-90.
6. a) Tour J. M. *Acc. Chem. Res*. **2000,** *33*, 791-804. b) Voskerician, G.; Weder, C. *Adv. Poly. Sci.* **2005**, *177*, 209-248. c) Liu, J.; Lam, J. W. Y.; Tang, B. Z. *Chem. Rev.* **2009,** *109*, 5799-5867. d) Swager, T. M.; Gil, C. J.; Wrighton M. S. *J. Phys. Chem.* **1995**, *99*, 4886-4893. Vokataand, T.; Moon J. H. *Macromolecules*, **2013**, *46*, 1253-1259.
7. James, D. K.; Tour, J. M. *Top. Curr. Chem.* **2005**, *257*, 33-62.
8. a) Swager, T. M.; Zheng, J. *Adv. Polym. Sci*. **2005**, *177*, 151-179. b) Swager, T. M. *Acc. Chem. Res*. **1998**, *31*, 201-207. c) McQuade, D. T.; Pullen, A. E.; Swager T. M**.** *Chem. Rev.*, **2000**, *100*, 2537-2574.
9. a) Miranda, O. R.; You, C. C.; Phillips, R.; Kim, I. B.; Ghosh, P. S.; Bunz, U. H.; Rotello, V. M. *J. Am. Chem. Soc*. **2007**, *129*, 9856-9857. b) You, C. C.; Miranda, O. R.; Gider, B.; Ghosh, P. S.; Kim, I. B.; Erdogan, B.; Krovi, S. A.; Bunz, U. H.; Rotello, V. M. *Nat. Nanotechnol.* **2007**, *2*, 318-323. c) Bajaj, A.; Miranda, O. R.; Kim, I. B.; Phillips, R. L.; Jerry, D. J.; Bunz, U. H.; Rotello, V. M. *Proc. Natl. Acad. Sci. U.S.A.* **2009**, *106*, 10912-10916. d) Zhu, C.; Liu, L.; Yang, Q.; Lv, F.; Wang, S. *Chem. Rev*. **2012**, *112*, 4687-4735. e) Vendrell, M.; Zhai, D.; Er, J. C.; Chang, Y. T. *Chem. Rev*. **2012**, *112*, 4391-4420.
10. Voskerician, G.; Weder, C. *Adv. Polym. Sci*. **2005**, *177*, 209-248.
11. a) Tour, J. M. *Chem. Rev.* **1996**, *96*, 537-554. b) Xue, C.; Luo, F. T. *Tetrahedron*, **2004**, *60*, 6285–6294. c) Wang, C.; Batsanov, A. S.; Bryce, M. R.; Sage, I. *Org. Lett*. **2004**, *6*, 2181-2184. d) Wang, C.; Batsanov, A. S.; Bryce, M. R. *J. Org. Chem.* **2006**, *71*, 108-116. e) Mayr, A.; Srisailas, M.; Zhao, Q.; Gao, Y.; Hsieh, H.; Hoshmand-Kochi, M.; St. Fleur, N. *Tetrahedron*, **2007**, *63*, 8206-8217. f) Wang, L. G.; Zhan, T. G.; Zhao, X.; Jiang, X. K.; Li, Z. T. *Tetrahedron*, **2012**, *68*, 5303-5310. g) Bai, X.; Chen, X.; Barnes, C.; Dias, J. R.; Sandreczki, T. C. *Tetrahedron*, **2013**, *69*, 1105-1111.
12. a) Dirk, S. M.; Tour, J. M. *Tetrahedron*, **2003**, *59*, 287-293. b) Price, D. W.; Tour, J. M. *Tetrahedron*, **2003**, *59*, 3131-3156. c)

Price, D. W.; Dirk, S. M.; Maya, F.; Tour, J. M. *Tetrahedron*, **2003**, *59*, 2497-2518. d) Neto, B. A. D.; Lopes, A. S.; Ebeling, G.; Goncalves, R. S.; Costa, V. E. U.; Quinab, F. H.; Dupont, J. *Tetrahedron*, **2005**, *61*, 10975-10982. e) Stuhr-Hansen, N.; Sørensen, J. K.; Moth-Poulsen, K.; Christensen, J. B.; Bjørnholm, T.; Nielsen, M. B. *Tetrahedron* **2005**, *61*, 12288-12295. f) Dixon, S.; Whitby, R. J. *Tetrahedron Letters*, **2006**, *47*, 8147-8150. g) Chandra, K. L.; Zhang, S.; Gorman, C. B. *Tetrahedron*, **2007**, *63*, 7120-7132. h) Ryhding, T.; Kirketerp, M. B. S.; Kadhane, U.; Lykkegaard, M. K.; Panja, S.; Nielsen, S. B.; Nielsen, M. B. *Tetrahedron*, **2008**, *64*, 11475-11479.

13. a) Beeby, A.; Findlay, K.; Low, P. J.; Marder, T, B. *J. Am. Chem. Soc***. 2002**, *124*, 8280-8284. b) Dirk, S. M.; Tour, J. M. *Tetrahedron* **2003**, *59*, 287-293.
14. a) Kraszkiewicz, L.; Sosnowski, M.; Skulski L. *Tetrahedron* **2004**, *60*, 9113-9119. b) Kraszkiewicz, L.; Sosnowski, M.; Skulski L. *Synthesis* **2006**, 1195-1199.
15. a) Reichardt, C. *Chem. Rev.* **1994**, *94*, 2319-2358. b) Reichardt, C.; Schäfer, G. *Liebigs Ann.* **1995**, 1579-1582. c) Eberhardt, R.; Löbbecke, S.; Neidhardt, B.; Reichardt, C. *Liebigs Ann./Recueil.* **1997**, 1195-1199. d) Reichardt, C. *Green Chem.* **2005**, *7*, 339-351.
16. Wagner, R. W.; Johnson, T. E.; Li, F.; Lindsey, J. S. *J. Org. Chem*. **1995**, *60*, 5266-5273.
17. Christiansen, E.; Due-Hansen, M. E.; Ulven, T. *J. Org. Chem.* **2010**, *75*, 1301-1304.
18. Catalán, J.; Díaz, C.; García-Blanco, F. *J. Org. Chem.* **2001**, *66*, 5846-5852.
19. Diao, T.; White, P.; Guzei, I.; Stahl, S. *Inorg. Chem*. **2012**, *51*, 11898-11909.
20. a) Lee, H. B.; Huh, D. H.; Oh, J. S.; Min, G. H.; Kim, B. H.; Lee, D. H.; Hwang, J. K.; Kim, Y. G. *Tetrahedron*. **2001**, *57*, 8283-8290. b) Köllhofer A.; Plenio H. *Chem. Eur. J*. **2003**, *9*, 1416-1425. c) Remmele, H.; Köllhofer, A.; Plenio, H. *Organometallics* **2003**, *22,* 4098-4103. d) Shirakawa, E.; Kitabata, T.; Otsuka, H.; Tsuchimoto, T. *Tetrahedron* **2005**, *61*, 9878-9885. e) Yi C.; Hua R. *J. Org. Chem.* **2006**, *71*, 2535-2537. f) Huang M.; Feng Y.; Wu, Y. *Tetrahedron* **2012**, *68*, 376-381. g) Gallop, C. W. D.; Chen, M. T.; Navarro, O. *Org. Lett.* **2014**, *16*, 3724-3727.
21. a) Grennberg, H.; Gogoll, A.; Bäckvall, J. E. *J. Org. Chem.* **1991**, *56*, 5808-5811. b) Steinhoff, B. A.; Stahl, S. S. *J. Am. Chem. Soc.* **2006**, *128*, 4348-4355. c) Vasseur, A.; Harakat D.; Muzart, J.; Le Bras, J. *J. Org. Chem.* **2012**, *77*, 5751-5758. d) Qi, C. Z.; Sun, X. D.; Lu, C. Y; Yang, J. Z.; Du, Y. J.; Wu, H. J.; Zhang, X. M. *J. Organomet. Chem.* **2009**, *694*, 2912-2916. e) Zierkiewicz, W.; Privalov, T. *Organometallics.* **2005**, *24*, 6019-6028.
22. Ljungdahl, T.; Pettersson, K.; Albinsson, B., Mårtensson, J. *J. Org. Chem.* **2006**, *71*, 1677-1687.
23. Schilz, M.; Plenio, H. *J. Org. Chem.* **2012**, *77*, 2798-2807.
24. Mphahlele M. J.; Lesenyeho L. G.; Makelane H. R. *Tetrahedron*, **2010**, *66*, 6040-6046.
25. Rajesh, K.; Somasundaram, M.; Saiganesh, R.; Balasubramanian, K. K. *J. Org. Chem*. **2007**, *72*, 5867-5869.
26. Gelman, D.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2003**, *42*, 5993-5996.
27. Brouwer, A. M. *Pure Appl. Chem*. **2011**, *83*, 2213-2228.
28. Tonzola, C. J.; Alam, M. M.; Kaminsky, W.; Jenekhe, S. A. *J. Am. Chem. Soc*. **2003**, *125*, 13548-13558.
29. a) Bai, X.; Chen, X.; Dias, J. R.; Sandreczki T. C. *Tetrahedron Lett.* **2013**, *54*, 1711-1713. b) Fang, J. K.; An, D. L.; Wakamatsu, K.; Ishikawa, T.; Iwanaga, T.; Toyota, S.; Akita, S.; Matsuo, D.; Orita, A.; Otera, J. *Tetrahedron.* **2010**, *66*, 5479-5485.