Microwave-Assisted Aqueous Suzuki Cross-Coupling Reactions

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The poly(ethylene glycol) ester of bromo-, iodo-, and triflate-para-substituted benzoates are smoothly cross-coupled with aryl boronic acids (Suzuki reaction) under "ligandless" palladium acetate catalysis in water. The reaction proceeds without organic cosolvent under conventional thermal conditions (70 °C, 2 h) and under microwave irradiation (75 W, 2−4 min). The polymeric support remains stable under both reaction conditions. Whereas conventional thermal conditions induced ester cleavage (up to 45%), this side reaction is suppressed when microwave conditions are employed. Aryl nonaflates give fair yields under these conditions. Non-polymer-bound aryl halides form biaryls in good to excellent yields in water/poly(ethylene glycol) mixtures under microwave irradiation (4 min, 75 W).

Introduction

The palladium-catalyzed cross-coupling reaction of organoboron compounds with aromatic organic electrophiles in the presence of base (Suzuki reaction) provides a mild method for the synthesis of various functionalized biaryls[1] and tolerates water as a cosolvent.[2] The biaryl subunit is of interest as an important pharmacophore in a variety of biologically active compounds[3] as well as for intriguing physical properties (e.g., chiroptical).[4] Iodobenzoates and iodophenols are known to cross-couple in water without organic cosolvent in the absence of phosphine ligands.[5] Aqueous reaction conditions offer a safe, economic, and environmentally benign alternative in organic synthesis, but are often limited by sparse solubility of reactants in water. Recently, less water soluble aryl halides were efficiently cross-coupled in the presence of equimolar amounts of tetrabutylammonium bromide[6] under "ligandless" palladium acetate-catalyzed conditions,[7] thus avoiding phosphine-related side reactions.[8]

We have observed that no additional phase-transfer catalyst (PTC) is needed when poly(ethylene glycol) (PEG) bound formal electrophiles (ArX with X = I, Br, OTf, ONf) are coupled with representative boronic acids in water. PEG and poly(ethylene glycol) monomethyl ethers (mPEG) have been investigated as thermally stable, recoverable, inexpensive, and nontoxic PTC, presumably operating by the same mechanism as crown ethers.[9] PEG and mPEG have been applied as soluble polymeric supports for the synthesis of peptides, nucleotides, oligosaccharides, and small molecules as an alternative to the solid-phase synthesis.[10] The soluble polymer-supported liquid phase strategy has recently been demonstrated in combinatorial and parallel synthesis.[11] Only very recently, the combined use of PEG as polymeric support and PTC was reported.[12]

The rapid parallel synthesis (RPS) of PEG-esterified biaryls via the Suzuki reaction can be achieved in water. The reactions utilize the intrinsic solubilizing and phase transfer catalytic properties of the polymer support. PEG-supported aryl halides and sulfonates were cross-coupled with representative boronic acids under "ligandless" palladium acetate-catalyzed conditions. We compared conventional thermal heating to rapid reactions under microwave irradiation and found that quantitative conversion of polymer-bound iodides, bromides, and triflates can be obtained in 2−4 min under microwave conditions. The influence of the concentration of water during the reaction was investigated. The results of the extension of this protocol to aryl nonaflates is described. The phase transfer catalytic properties of underivatized PEG in the

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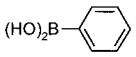
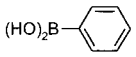
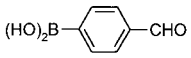
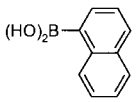
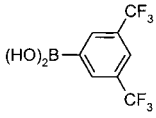
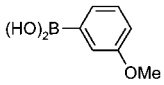
Table 1. Suzuki Couplings of PEG-Bound Aryl Halides with Boronic Acids in Water without Additional Phase Transfer Catalyst

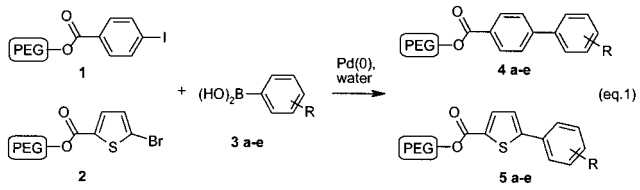
Entry	PEG-Aryl halide	Boronic acid **3a-e**	Product	Cleavage from the Polymer [%][b]	Purity [%][c]
1	**1**		**4a**	-	>95
2	**2**		**5a**	3	>95
3	**2**		**5b**	3	>95
4	**2**		**5c**	6	>95
5	**2**		**5d**	45	70
6	**2**		**5e**	5	>95

[a] 1 g of PEG 6000-bound aryl halide was coupled at 70 °C in 5 mL water for 2 h in the presence of 10 mol % $Pd(OAc)_2$ and 2.5 equiv of K_2CO_3 with 1.2 equiv of boronic acid under argon. [b] Estimated by ^{1}H NMR in d_6-DMSO by comparison with the PEG-OH signal at 4.56 ppm. [c] The purity of the products was estimated by ^{1}H NMR.

Suzuki reaction of non-polymer-bound aryl iodides in water is also reported.

Results and Discussion

Aryl Halide Coupling with Conventional Heating. Initially, the application of PEG as polymeric support and PTC in "ligandless" Suzuki cross-coupling reactions under conventional thermal conditions was examined. Disubstituted PEG 6000 offers an acceptable loading capacity of 0.33 mequiv/g and easy workup via the crystallization method[13,9] and was therefore employed as the polymeric support. The electron-withdrawing ester group activates the aryl halides in cross-coupling reactions.[14] The PEG-diesters **1** and **2** were synthesized following literature procedures[15] and coupled with five representative boronic acids **3a**−**e** in water (eq 1).



All reactions were carried out at 70 °C for 2 h on 1 g of polymer-bound starting material **1** and **2** in 5 mL of water with 1.2 equiv of **3a**−**e** and 2.5 equiv of K_2CO_3 in the presence of 10 mol % $Pd(OAc)_2$ (Table 1). Aryl iodides were recently reported to give incomplete conversion in water with tetrabutylammonium bromide as PTC.[6] Due to the intrinsic autocatalytic activity of the polymeric support, the aryl iodide **1** (entry 1) and the aryl bromide **2** (entries 2−4, 6) were converted quantitatively into pure products, except **5d** (entry 5). The main side reaction in most reactions (entries 2−6) was cleavage of the ester bond off the polymeric support, as estimated by ^{1}H NMR in d_6-DMSO.[16] The reaction of **2** with electron deficient boronic acid **3d** resulted in 45% loss of the ester, and the polymer-bound product **5d** was only 70% pure.

Nevertheless, the liquid phase parallel synthesis of PEG-bound biaryls in water described here requires lower temperatures and shorter reaction times for the quantitative conversion of **1** as compared to the analogous reaction in organic solvents reported earlier.[17]

Microwave-Assisted Aryl Halide Coupling. We assumed that cleavage of the ester bond could be minimized by more rapid reaction conditions. Microwaves are known to accelerate some organic reactions in polar solvents[18] and microwave-assisted palladium-catalyzed reactions were recently reported.[19] Furthermore, the reaction can easily be performed in parallel fashion. Irradiation (75 W) of 0.2 g of PEG-bound aryl halide in 1 mL of water with 1.2 equiv of benzene boronic acid resulted in quantitative cross-coupling of **1** in 2 min (Table 2; entry 3) and of **2** in 1 min (entry 9). For parallel synthesis the reaction time was prolonged to 4 min, and **1** was quantitatively coupled with all five boronic acids to form **4a**−**e** (entries 4−8). The aryl bromide **2** was smoothly converted into **5a**−**c** and **5e** in 2 min (entry 10−12, 14). Even at high irradiation energy level (900 W, 10 min) the polymer support as well as the ester remained stable as determined by ^{1}H NMR in d_6-DMSO[16] and MALDI TOF MS. The reaction of electron poor boronic acid **3d** with **2** gave only 73% of **5d** and 8% of the ester bond was hydrolyzed (entry 13).

The workup procedure involved precipitation of the polymer-bound product from a suitable organic solvent with ether.[9] Water and insoluble impurities needed to be removed prior to the precipitation process to ensure high recovery of the products. For convenient workup, the minimal amount of water necessary for quantitative conversion of 0.2 g of polymer-bound aryl iodide **1** was estimated. High energy irradiation (400 to 900 W) was required for melting the starting materials under solvent-free conditions, but resulted in incomplete conversion of **1** (60% at 400 W; 71% at 900 W; 5 min, entries 1, 2). However, apart from the starting materials no side products could be detected. Homogeneity of the reaction mixture was supposed to be crucial for the quantitative conversion of **1** under microwave irradiation and should also be ensured for safety reasons.[20] A minimal amount

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(20) **Caution!!** The palladium catalyst must be well distributed in the reaction mixture otherwise extreme local overheating can occur resulting in the destruction of the reaction tube! Reaction vessels must not be closed!

Table 2. Effect of the Amount of Water on the Conversion Rate of the Microwave-Assisted Cross-Coupling Reactions[a]

						Conversion (%)[b,c] in water (μL)					
entry	aryl halide	boronic acid	reaction time (min)	energy (W)	product	0	100	100[d]	200	400	1000
1	**1**	3d	5	400	**4d**	60	–	–	–	–	–
2	**1**	3d	5	900	**4d**	71	–	–	–	–	–
3	**1**	3a	2	75	**4a**	–	–	–	–	–	>95
4	**1**	3a	4	75	**4a**	–	67	80	–	>95	>95
5	**1**	3b	4	75	**4b**	–	>95	47	–	>95	>95
6	**1**	3c	4	75	**4c**	–	58	>95	90	>95	>95
7	**1**	3d	4	75	**4d**	–	75	85	>95	>95	>95
8	**1**	3e	4	75	**4e**	–	71	53	93	>95	>95
9	**2**	3a	1	75	**5a**	–	–	–	–	–	>95
10	**2**	3a	2	75	**5a**	–	–	–	–	–	>95
11	**2**	3b	2	75	**5b**	–	–	–	–	–	>95
12	**2**	3c	2	75	**5c**	–	–	–	–	–	>95
13	**2**	3d	2	75	**5d**	–	–	–	–	–	73[e]
14	**2**	3e	2	75	**5e**	–	–	–	–	–	>95

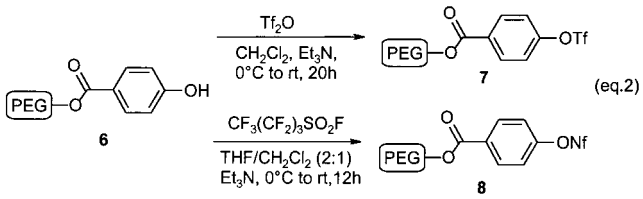
[a] All microwave-assisted couplings were carried out in 20-mL screw-cap culture tubes equipped with punctured silicon septa under argon. PEG 6000-bound aryl halides **1** and **2** were coupled in water with 1.2 equiv of boronic acid in the presence of 5−10 mol % $Pd(OAc)_2$ and 2.5 equiv of K_2CO_3. [b] Percent conversion into the PEG-bound biaryls is defined as (biaryl/[biaryl+aryl halide]) × 100 and was estimated by ^{1}H NMR. [c] The purity of the products was estimated by ^{1}H NMR to be at least 90% unless stated otherwise. [d] 200 μL of CH_2Cl_2 was added and evaporated prior to the microwave heating. [e] The PEG-bound product was impure, and 8% of the ester bond was cleaved as determined by ^{1}H NMR in d_6-DMSO.

of 400 μL water was found to be necessary for reproducibly transforming 0.2 g of starting polymer **1** in quantitative yield at 75 W microwave irradiation (Table 2). The recovery of the polymer-bound products was generally higher than 90%, and the procedure was suitable for parallel synthesis.

Although originally not designed for up-scaling, the microwave-assisted cross-coupling reaction was safely performed[33] on a 10-fold larger scale: 2 g of **1** in 4 mL of water was reacted with **3b** and **3d** forming the corresponding biaryls **5b** and **5d** quantitatively within 4 min at 75 W.

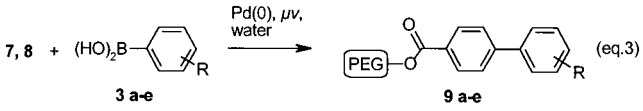
Microwave-Assisted Aryl Sulfonate Coupling. Aryl triflates have been extensively reported in palladium-catalyzed cross-coupling reactions with organoboronic acids.[21] Under anhydrous conditions, the order of reactivity usually is I > Br > OTf.[22] Nonaflates were reported to display a slightly higher reactivity in Suzuki reactions than triflates,[23] whereas activated aryl mesylates and *p*-fluorobenzenesulfonates gave only poor yields.[24]

We synthesized the PEG 6000-supported ester **6** with DCC and the sulfonates **7** and **8** following variations of literature procedures[21,23] (eq 2).



(eq.2)

The cross-coupling reactions were carried out under microwave irradiation on 0.2 g of **7** and **8** in 400 μL water with 1.2 equiv of boronic acid **3a**−**e** (eq 3).



(eq.3)

The PEG-bound triflate **7** was smoothly converted with the boronic acids **3a**−**e** into the corresponding biaryls **9a**−**e** in 4 min at 75 W (Table 3, entries 1−5). Potassium carbonate was used as a base for the "ligandless" cross-coupling conditions. The yield of the reaction decreased considerably when potassium phosphate was employed as a base (entry 6, **9d**). Conversion of the nonaflate **8** in **9a**−**e** proceeded in fair yields (entries 7−11), but the polymer-bound products were not pure.

Microwave-Assisted Aryl Iodide Coupling with Underivatized PEG. Since PEG 6000 could easily be removed from the reaction mixture by precipitation[9] or aqueous extraction from benzene,[25] we explored the general utility of this method. 4-Iodobenzoic acid methyl ester **10** was coupled with the boronic acids **3a**−**e** (Table 4) under otherwise identical conditions employing un-

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(32) Depending on the anionic polymerization conditions, the polydispersity of the polymer varies, making elemental analysis or melting points of the polymer-bound compounds inadequate for characterization.
(33) Microwave-assisted reactions for up to 2 g of polymer in 4 mL of water were carried out under argon in 20 mL screw-cap culture tubes equipped with a silicon septum in which little holes had been punched for release of pressure. The reaction volume filled not more than 1/3 of the volume of the tube allowing headspace for pressure build-up during the microwave treatment. The reaction mixtures were vortexed prior to the irradiation to ensure a well distribution of the reagents. During the microwave treatment, the mixtures were not stirred, since heavy agitation usually occurred.

Table 3. PEG-Bound Sulfonates as Substrates for Microwave-Assisted Cross-Coupling Reactions[a]

entry	PEG-aryl sulfonate	boronic acid	reaction time (min)	energy (W)	product	conversion (%)[b]	purity (%)[d]
1	**7**	3a	4	75	**9a**	>95	91[d]
2	**7**	3b	4	75	**9b**	>95	83[d]
3	**7**	3c	4	75	**9c**	>95	88[d]
4	**7**	3d	4	75	**9d**	>95	77[d]
5	**7**	3e	4	75	**9e**	>95	>95[d]
6	**7**	3d	4	75	**9d**	26[c]	>95
7	**8**	3d	1	75	**9d**	28	86
8	**8**	3d	2	75	**9d**	87	70
9	**8**	3d	4	75	**9d**	92	65
10	**8**	3b	4	75	**9b**	88	70
11	**8**	3c	4	75	**9c**	>95	83

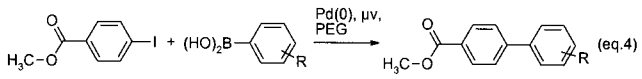
[a] All microwave-assisted couplings were carried out on 0.2 g of polymer in 400 μL of water following the same protocol as in Table 2. [b] Percent conversion is defined in Table 2. [c] K_3PO_4 (2.5 equiv) was used as the base. [d] The purity of the PEG-bound products was estimated by ^{1}H NMR integration.

Table 4. Microwave-Assisted Cross-Coupling Reaction with Underivatized PEG 6000[a]

entry	aryl halide	boronic acid	reaction time (min)	energy (W)	product	water (mL)	conversion (%)[b]	isolated yield (%)[c]
1	**10**	3a	4	70	**11a**	1.5	86	78
2	**10**	3b	4	70	**11b**	1.5	72	66
3	**10**	3c	4	70	**11c**	1.5	88	80
4	**10**	3d	4	70	**11d**	1.5	67	59
5	**10**	3e	4	70	**11e**	1.5	91	86
6	**10**	3c	4	100	**11c**	1.0	86	72
7	**10**	3c	8	200	**11c**	2.0	98	76

[a] All microwave-assisted couplings were carried out in a 20-mL screw cap culture tube equipped with a punctured silicon septum under argon. **10** (0.33 mmol) was coupled with 1.2 equiv of boronic acid in the presence of 2.5 equiv of K_2CO_3 and 8 mol % $Pd(OAc)_2$. PEG 6000 (1 g, 0.17 mmol) was added as PTC. [b] Percent conversion refers to the crude reaction mixtures and was determined by HPLC (biaryl/[biaryl+**10**]·100). [c] Yield of analytically pure compounds.

derivatized PEG 6000 (MW distribution approximately 5600−7000 g/mol, 0.5 equiv) as PCT.



As expected, steric hindrance had little effect on the Suzuki reaction[26] (entry 3) but lower yields were obtained with electron poor boronic acids (**3b** and **3d**, entry 2, 4). The yields of the PEG-bound products were superior to those of the non-PEG-bound transformations; however, nearly quantitative conversion of **10** was achieved by irradiation with 200 W in 2 mL of water in 8 min (entry 7).

The proposed mechanistic sequence for the palladium-catalyzed cross-coupling pathway involves sequential oxidative addition of the organic halide to the stabilized Pd(0) species, transmetalation of the stabilized Ar−Pd−OH or Ar−Pd−X with $Ar'B(OH)_3-M^+$ and reductive elimination to give Ar−Ar′.[27] Although known reducing agents such as tertiary phosphines[28] are not present under "ligandless" conditions, $Pd(OAc)_2$ has been described to be reduced to Pd(0) by solvents other than alcohols.[29,7,6] All reaction mixtures darkened, and palladium metal began to deposit soon after the addition of the catalyst and immediately upon heating. This indicates that Pd(II) was readily reduced by some other constituent in the mixture. Pd(0) is not known to exist in solutions in absence of strong donor or acceptor ligands.[30] PEG has been described as PTC presumably operating by the same mechanism as crown ethers.[9] It seems to be likely that PEG is able to stabilize the Pd(0) species. In addition, water-miscible, polar, weakly coordinating cosolvents such as THF and DME were reported to accelerate the yield of cross-coupling reactions under "ligandless" conditions in water.[7] However, the "ligandless" cross-coupling reactions with PEG as PTC could also proceed under heterogeneous processes on palladium metal.[31]

In summary, we have demonstrated the liquid phase "ligandless" palladium acetate-catalyzed Suzuki cross-coupling in water with PEG as soluble support and PTC without organic cosolvent. Compared to classical heating, microwave irradiation shortened the reaction time with representative boronic acids from 2 h to 2−4 min, and the linkage to the polymer and the polymer itself remained stable. The reaction proceeded well on PEG-bound aryl iodides, bromides, triflates, and nonaflates and on nonpolymer-bound aryl iodide on various scales.

Experimental Section

General. All reagents were obtained from either Aldrich Chemical Co. or Fisher Scientific Co. and are used without further purification. Coupling reactions and ester cleavage reactions were carried out in 20 mL screw-cap culture tubes. Microwave-assisted reactions were carried out in 20 mL screw-cap culture tubes equipped with silicon septa in which little holes had been punched for release of pressure. All reactions were carried out under argon. Microwave-assisted reactions were performed in a domestic microwave (Moulinex, Model Optimo, 2450 MHz). For HPLC purification a Grom-Sil 120 ODS-4 HE, 11 μm, 250 × 20 mm column with a acetonitrile/water gradient was applied. Parallel evaporation of solvent was performed with a RapidVapTM Evaporation System (Model 79000) from Labconco (Missouri). Elemental analysis were performed at the University of Hamburg, Germany. MALDI-MS spectra were obtained at the Beiersdorf AG in Hamburg, Germany. ^{1}H NMR spectra were recorded at the Beiersdorf AG in Hamburg, Germany, at 500 MHz using $CDCl_3$ or d_6-DMSO as both solvent and reference. ^{13}C NMR spectra were obtained at corresponding frequencies. Melting points are uncorrected.

Representative Cross-Coupling Reaction of PEG 6000-Bound Aryl Halides (Table 1, entry 6). In a typical reaction an argon-flushed 20-mL screw-cap culture tube was charged

with 1.0 g of **2** (approximately 0.31 mmol aryl halide) and 5 mL of water. 3-Methoxy phenyl boronic acid (57 mg, 0.37 mmol), 7 mg (10 mol %) of $Pd(OAc)_2$, and 107 mg of (0.78 mmol) K_2CO_3 were added. The reaction mixture was argon flushed and stirred for 2 h at 70 °C. The solvent was coevaporated with 400 μL toluene at 60 °C under reduced pressure. toluene (15 mL) was added and the mixture centrifuged. The clear supernatant was precipitated with 60 mL of cold (−18 °C) *tert*-butyl methyl ether and centrifuged, and the precipitate was dissolved in CH_2Cl_2. This procedure was repeated twice, and the product was dried under vacuum until no signal of residual solvent could be detected (m = 921 mg, 92%).[32]

Representative Microwave-Assisted Cross-Coupling Reaction on PEG 6000-Bound Aryl Halides and Aryl Sulfonates[33] (Table 2, entry 7 [400 μL]). A 20-mL screw-cap culture tube was charged with 0.2 g of PEG 6000-bound aryl iodide (approximately 0.062 mmol end groups) and 400 μL water. 3,5-Bis(trifluoromethyl) phenyl boronic acid (19 mg, 0.37 mmol), 1.4 mg (10 mol %) of $Pd(OAc)_2$, and 21 mg (0.16 mmol) of K_2CO_3 were added under argon. The reaction mixture was vortexed (some samples were warmed to approximately 45 °C to give a homogeneous mixture) and then irradiated for 4 min at 75 W. After cooling to room temperature, the remaining solvent was coevaporated with 400 μL toluene at 80 °C in a parallel evaporation system under reduced pressure for 4 h. The residue was dissolved in 8 mL of toluene and centrifuged. The clear supernatant was transferred into 80-mL centrifugation vessels and precipitated with 60 mL of ice cold *tert*-butyl methyl ether (−18 °C). The crystalline precipitate was centrifuged and dissolved in 2 mL of CH_2Cl_2. The precipitation process was repeated once and the purified PEG-bound product dried under vacuum (m = 182 mg, 94%).[32]

Representative Microwave-Assisted Cross-Coupling Reaction of Aryl Iodides[33] (Table 4, entry 3). A 20-mL screw-cap culture tube was flushed with argon and charged with 87 mg (0.33 mmol) of 4-iodobenzoic acid methyl ester, 69 mg (0.4 mmol) of 1-naphthaleneboronic acid, 3.7 mg (5 mol %) of $Pd(OAc)_2$, 114 mg (0.825 mmol) of K_2CO_3, 1.0 g (0.17 mmol) of PEG 6000, and 1.5 mL of water. The reaction mixture was vortexed (some samples were warmed to approximately 45 °C to give a homogeneous mixture) and then irradiated for 4 min at 70 W. After cooling to room temperature, 200 μL toluene was added and the volume of the mixture was reduced in a parallel evaporation system under vacuum for 1 h. The residue was dissolved in 8 mL of toluene and centrifuged. The clear supernatant was transferred into 80-mL centrifugation vessels and precipitated with 70 mL of ice cold (−18 °C) *tert*-butyl methyl ether. The crystalline precipitate was centrifuged and the residue dissolved in 5 mL of CH_2Cl_2. This procedure was repeated three times, and the combined solvents were filtered through 1 g of silica gel. The volume of the filtered solvent was reduced under vacuum and the crude product purified by HPLC (conversion 88%, isolated yield m = 70 mg, 80%).

Representative Transesterification Reaction, 5-(4-Formylphenyl)thiophene-2-carboxylic Acid Methyl Ester (Table 1, entry 3). To 0.5 g (approximately 0.155 mmol end groups) of dry PEG 6000-bound biaryl was added 15 mL of dry 20% TEA/MeOH and the mixture stirred in a 20-mL screw-cap culture tube under argon at 85 °C for 3 d. The progress of the transesterification was followed by TLC (CH_2Cl_2/EtOH 95:5). The mixture was precipitated with 60 mL of ice cold *tert*-butyl methyl ether (−18 °C) and centrifuged and the residue dissolved in 4 mL of CH_2Cl_2. The precipitation procedure was repeated three times, and the volume of the combined solvents was reduced under vacuum. The crude product was purified by HPLC (m = 36.8 mg, 96%).

Biphenyl-4-carboxylic Acid PEG Ester (**4a**, Table 2, entry 4). White crystals; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.05 (d, J = 8.16 Hz, 2H), 7.84 (d, J = 8.22 Hz, 2H), 7.74 (d, J = 7.58 Hz, 2H), 7.51 (t, J = 7.60 Hz, 2H), 7.44 (t, J = 7.31 Hz, 1H), 4.42 (t, J = 4.47 Hz, 2H), 3.65−3.41 (m, PEG).

4′-Formylbiphenyl-4-carboxylic Acid PEG Ester (**4b**, Table 2, entry 5). White crystals; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.09 (s, 1H), 8.09 (d, J = 8.20 Hz, 2H), 8.04 (d, J = 8.15 Hz, 2H), 7.99 (d, J = 8.15 Hz, 2H), 7.94 (d, J = 8.20 Hz, 2H), 4.43 (t, J = 4.65 Hz, 2H), 3.65−3.41 (m, PEG).

4-Naphthalene-1-ylbenzoic Acid PEG Ester (**4c**, Table 2, entry 6). White crystals; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.13 (d, J = 8.16 Hz, 2H), 8.03 (m, 2H), 7.78 (d, J = 8.36 Hz, 1H), 7.66 (d, J = 8.21 Hz, 2H), 7.64−7.48 (m, 4H), 4.46 (t, J = 4.65 Hz, 2H), 3.66−3.40 (m, PEG).

3′,5′-Bis(trifluoromethyl)biphenyl-4-carboxylic Acid PEG Ester (**4d**, Table 2, entry 7). White crystals; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.42 (s, 2H), 8.17 (s, 1H), 8.09 (d, J = 8.45 Hz, 2H), 8.06 (d, J = 8.40 Hz, 2H), 4.44 (t, J = 4.75 Hz, 2H), 3.78−3.37 (m, PEG).

3′-Methoxybiphenyl-4-carboxylic Acid PEG Ester (**4e**, Table 2, entry 8). White crystals; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.05 (d, J = 8.19 Hz, 2H), 7.85 (d, J = 8.21 Hz, 2H), 7.43 (t, J = 7.93 Hz, 1H), 7.31 (d, J = 7.62 Hz, 1H), 7.27 (s, 1H), 7.01 (d, 8.20 Hz, 1H), 4.42 (t, J = 4.62 Hz, 2H), 3.84 (s, 3H), 3.60−3.41 (m, PEG).

5-Phenylthiophene-2-carboxylic Acid PEG Ester (**5a**, Table 1, entry 2). White crystals; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.81 (d, J = 3.77 Hz, 1H), 7.77 (d, J = 7.46 Hz, 2H), 7.63 (d, J = 3.74 Hz, 1H), 7.48 (t, J = 7.42 Hz, 2H), 7.43 (d, J = 7.16 Hz, 1H), 4.39 (t, J = 4.55 Hz, 2H), 3.65−3.42 (m, PEG).

5-(4-Formylphenyl)thiophene-2-carboxylic Acid PEG Ester (**5b**, Table 1, entry 3). White crystals; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.04 (s, 1H), 8.01 (d, J = 8.35 Hz, 2H), 7.98 (d, J = 8.35 Hz, 2H), 7.86 (d, J = 4.00 Hz, 1H), 7.82 (d, J = 3.90 Hz, 1H), 4.41 (t, J = 4.55 Hz, 2H), 3.65−3.41 (m, PEG).

5-Naphthalene-1-ylthiophene-2-carboxylic Acid PEG Ester (**5c**, Table 1, entry 4). White crystals; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.12 (d, J = 3.35 Hz, 1H), 8.05 (d, 7.70 Hz, 2H), 7.92 (d, J = 3.7 Hz, 1H), 7.66 (d, J = 6.7 Hz, 1H), 7.62 (m, 3H), 7.44 (d, J = 6.7 Hz, 1H), 4.55 (t, J = 5.45 Hz, 2H), 3.65−3.41 (m, PEG).

5-(3,5-Bis(trifluoromethyl)phenyl)-thiophene-2-carboxylic Acid PEG Ester (**5d**, Table 1, entry 5). White crystals; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.41 (s, 2H), 8.14 (s, 1H), 8.09 (d, J = 3.91 Hz, 1H), 7.88 (d, J = 3.90 Hz, 1H), 4.40 (t, J = 4.60 Hz, 2H), 3.65−3.41 (m, PEG).

5-(3-Methoxyphenyl)thiophene-2-carboxylic Acid PEG Ester (**5e**, Table 1, entry 6). White crystals; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.80 (d, J = 3.76 Hz, 1H), 7.65 (d, J = 3.82 Hz, 1H), 7.38 (t, J = 7.88 Hz, 1H), 7.32 (d, J = 7.63 Hz, 1H), 7.28 (s, 1H), 6.99 (d, J = 6.70 Hz, 1H), 4.38 (s, 2H), 3.83 (s, 3H), 3.65−3.41 (m, PEG).

4-Hydroxybenzoic Acid PEG Ester (**6**). White crystals; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.97 (d, J = 8.4 Hz, 2H), 7.76 (d, J = 8.0 Hz, 2H), 7.49 (d, J = 8.2 Hz, 2H), 7.20 (d, J = 8.4 Hz, 2H) 3.66−3.36 (m, PEG)

4-(Trifluoromethanesulfonyloxy)benzoic Acid PEG Ester (**7**). White crystals; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.14 (d, J = 8.8 Hz, 2H), 7.68 (d, J = 8.8 Hz, 2H), 4.42 (t, J = 4.6 Hz, 3H), 3.66−3.36 (m, PEG).

4-(1,1,2,2,3,3,4,4,4-Nonafluorobutane-1-sulfonyloxy)-benzoic Acid PEG ester (**8**). White crystals; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.14 (d, J = 8.8 Hz, 2H), 7.69 (d, J = 8.6 Hz, 2H), 4.42 (t, J = 4.7 Hz, 2H), 3.66−3.33 (m, PEG).

5-Phenylthiophene-2-carboxylic Acid Methyl Ester (Table 1, entry 2). White crystals; mp 97 °C (lit.[34] 98 °C).

5-(4-Formylphenyl)thiophene-2-carboxylic Acid Methyl Ester (Table 1, entry 3). White crystals; mp 125.5−127 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.21 (s, 1H), 7.93 (d, J = 8.19 Hz, 2H), 7.80 (d, J = 7.92, 2H), 7.80 (d, J = 4.44 Hz, 1H), 7.43 (d, J = 3.92 Hz, 1H), 3.93 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 191.66, 162.76, 149.48, 139.36, 136.48, 134.82, 134.38, 130.91, 126.94, 125.71, 52.76; MS (EI) 246 (100), 215 (91), 143 (28). Anal. Calcd for $C_{13}H_{10}O_3S$: C, 63.39; H, 4.09. Found: C, 63.66; H, 4.28.

5-Naphthalene-1-ylthiophene-2-carboxylic Acid Methyl Ester (Table 1, entry 4). White crystals; ^{1}H NMR (500 MHz,

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$CDCl_3$) δ 8.17 (d, J = 7.98 Hz, 1H), 7.92−7.89 (m, 2H), 7.87 (d, J = 3.77 Hz, 1H), 7.57 (d, J = 6.86 Hz, 1H), 7.53−7.50 (m, 3H), 7.23 (d, J = 3.77, 1H), 3.93 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.14, 149.58, 134.25, 134.09, 133.54, 131.85, 131.77, 129.75, 128.89, 128.71, 128.53, 127.29, 126.69, 125.72, 125.62, 52.62; MS (EI): 268 (100), 237 (48), 208 (23), 165 (25); HRMS: calcd for $C_{16}H_{12}O_2S$, 268.0552; found, 268.0558.

5-(3,5-Bis(trifluoromethyl)phenyl)thiophene-2-carboxylic Acid Methyl Ester (Table 1, entry 5). White crystals; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (s, 2H), 7.85 (s, 1H), 7.82 (d, J = 3.91 Hz, 1H), 7.43 (d, J = 3.86 Hz, 1H), 3.93 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.50, 147.35, 135.94, 134.82, 133.20, 132.94, 126.44, 126.02, 124.50, 122.33, 52.85; MS (EI): 354 (53), 323 (100), 251 (48); HRMS: calcd for $C_{14}H_8F_6SO_2 - CH_3O$, 322.9986; found, 322.9986.

5-(3-Methoxyphenyl)thiophene-2-carboxylic Acid Methyl Ester (Table 1, entry 6). White crystals; mp 41−42 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, J = 3.85 Hz, 1H), 7.32 (t, J = 7.98 Hz, 1H), 7.28 (d, J = 3.95 Hz, 1H), 7.22 (d, J = 7.66 Hz, 1H), 7.16 (t, J = 1.99 Hz, 1H), 6.91 (dd, J = 8.21 Hz, 2.15 Hz, 1H), 3.90 (s, 3H), 3.86 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.07, 160.47, 151.53, 135.12, 134.72, 132.48, 130.55, 124.21, 119.18, 114.76, 112.26, 55.77, 52.57; MS (EI) 248 (100), 217 (89), 145 (26), 99 (67). Anal. Calcd for $C_{13}H_{12}O_2S$: C, 62.89; H, 4.87. Found: C, 62.92; H, 5.07.

Biphenyl-4-carboxylic Acid Methyl Ester (Table 2, entry 4). White crystals; mp 115.5−116.5 (lit.[24,35] 117−118 °C).

4′-Formylbiphenyl-4-carboxylic Acid Methyl Ester (Table 4, entry 2). White crystals; mp 107−108 °C (lit.[36] 108 °C).

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4-Naphthalene-1-ylbenzoic Acid Methyl Ester (Table 4, entry 3). White crystals; mp 65.5−66.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, J = 8.20 Hz, 2H), 7.93−7.88 (m, 2H), 7.83 (d, J = 8.46 Hz, 1H), 7.58 (d, J = 8.16 Hz, 2H), 7.55−7.51 (m, 2H), 7.44−7.40 (m, 2H), 3.97 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.47, 146.00, 139.55, 134.20, 131.65, 130.54, 130.00, 129.47, 128.81, 128.69, 127.34, 126.76, 126.38, 126.02, 125.74, 52.59; MS (EI) 262 (100), 231 (36), 202 (83), 100 (21). Anal. Calcd for $C_{18}H_{14}O_2$: C, 82.42; H, 5.38. Found: C, 82.23; H, 5.45.

3′,5′-Bis(trifluouromethyl)biphenyl-4-carboxylic Acid Methyl Ester (Table 2, entry 7). White crystals; mp 103−104.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (d, J = 8.28 Hz, 2H), 8.04 (s, 2H), 7.91 (s, 1H), 7.68 (d, J = 8.36 Hz, 2H), 3.96 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.88, 143.00, 142.78, 132.91, 132.64, 130.91, 127.76, 124.73, 122.56, 122.12, 52.71; MS (EI) 348 (64), 317 (100), 269 (55), 220 (20). Anal. Calcd for $C_{16}H_{10}F_6O_2$: C, 55.19; H, 2.90. Found: C, 55.02; H, 2.94.

3′-Methoxybiphenyl-4-carboxylic Acid Methyl Ester (Table 2, entry 8). White crystals; mp 55 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, J = 8.28 Hz, 2H), 7.63 (d, J = 8.26 Hz, 2H), 7.36 (t, J = 7.92 Hz, 1H), 7.19 (d, J = 7.66 Hz, 1H), 7.13 (t, J = 1.66 Hz, 1H), 6.94−6.92 (dd, 8.21 Hz, 2.11 Hz, 1H), 3.92 (s, 3H), 3.85 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.37, 160.46, 145.91, 141.92, 130.48, 130.36, 130.12, 129.62, 127.72, 127.51, 120.17, 113.92, 113.46, 55.76, 52.53; MS (EI) 242 (100), 211 (75). Anal. Calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82. Found: C, 74.29; H, 5.94.

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