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Synthesis of novel poly(ethylene glycol) supported benzazepines: the crucial role of PEG on the selectivity of an intramolecular Heck reaction

Patrice Ribière,[a] Valérie Declerck,[a] Yannig Nédellec,[b] Neerja Yadav-Bhatnagar,[c] Jean Martinez[a] and Frédéric Lamaty[a,*]

[a]*Laboratoire des Aminoacides, Peptides et Protéines (LAPP), CNRS-Universités Montpellier 1 et 2, Place Eugène Bataillon, 34095 Montpellier Cedex 5, France*
[b]*Laboratoire des Agrégats Moléculaires et Matériaux Inorganiques (LAMMI), CNRS-Université Montpellier 2, Place Eugène Bataillon, 34095 Montpellier Cedex 5, France*
[c]*Aventis Pharma, 102 route de Noisy, 93325 Romainville Cedex, France*

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Abstract—Poly(ethylene glycol) (PEG 3400) was used as a soluble polymeric support for the synthesis of a series of novel benzazepines. The key step for the preparation of these heterocycles was a phosphine-free palladium-catalyzed Heck reaction. Palladium nanoparticles formed during the course of the reaction were characterized. The presence of PEG 3400 influenced the outcome of the reaction in terms of selectivity.

1. Introduction

For economical, environmental, and practical reasons, organic synthesis relies more and more on catalysis.[1] Organometallic catalysis has proven to be a major field in carbon–carbon and carbon–heteroatom bond formations, key to the efficient building of more complex molecules. Major breakthrough has been performed in the field of homogeneous catalysis by the design and preparation of new ligands leading to efficient catalytic systems.[2] A complementary approach was the discovery that finely divided and stabilized metallic particles are also active in catalytic transformations.[3–6] Nanoparticles are generally generated in the presence of a protector providing either an electrostatic or steric stabilization.[3] Several types of macromolecules have been described for their ability of stabilizing metallic particles by steric shielding (polymers, cyclodextrins, surfactants…)[4] including poly(ethylene glycol) (PEG), a polymer widely used for biomedical applications[7] and in supported synthesis.[8] Among the different metals employed in catalysis, palladium has found a special place due to the number of transformations, which can be mediated by this metal.[9]

We now report that a soluble PEG 3400 polymer supporting a substrate involved in a Pd-catalyzed Heck cyclization acts also as stabilizer for in situ generated nanoparticles. To the best of our knowledge, this is the first reaction performed on the end group of a PEG polymer with simultaneous formation of nanoparticles, which have been unambiguously characterized by Transmission Electronic Microscopy and Light Scattering experiments. Furthermore, the efficiency and selectivity induced by the presence of PEG 3400 were demonstrated when using PEG 3400-OH as a solvent in a non-supported version of the reaction. Interestingly smaller liquid PEGs such as PEG 300 do not exert the same influence. This reaction was applied to the synthesis of a series of original benzazepines.

2. Results and discussion

Bifunctional poly(ethylene glycol) with an average molecular weight of 3400 was used as a polymeric support for the preparation of α-methylene β-aminoesters **1a–g** by an aza-Baylis–Hillman reaction involving PEG-SES-NH_2, an aldehyde, and methyl acrylate in the presence of DABCO (Scheme 1).[10–12] Compound **2a**, obtained by alkylation of **1a** with 2-bromobenzyl bromide, was subjected to different Heck reaction conditions using $Pd(OAc)_2$ as catalyst in the presence of a base in DMF. After 12 h at 80 °C, **2a** was fully converted to the cyclized benzazepine **3a** using either K_2CO_3 or Oct_3N as a base. The reaction time was shortened to 6 h in the absence of solvent. The reaction was very selective since only **3a** was obtained among the different products, which could be formed during the reaction.[13] Since

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* Corresponding author. Tel.: +33 4 67 14 38 47; fax: +33 4 67 14 48 66; e-mail: frederic.lamaty@univ-montp2.fr

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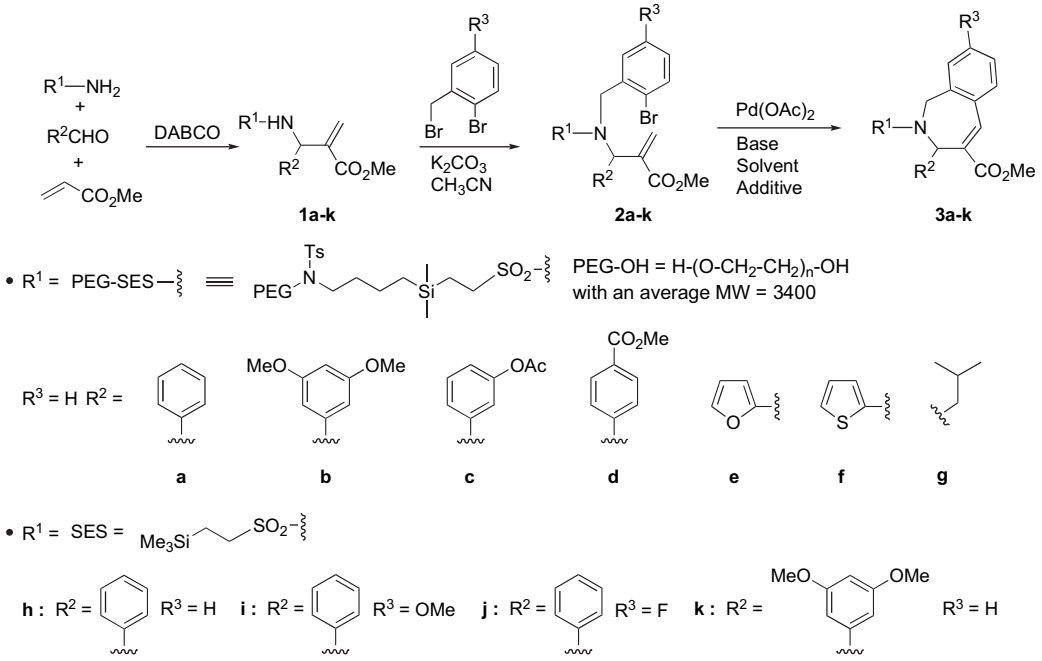
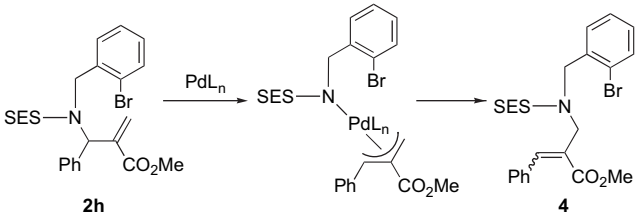


Scheme 1.

the reaction product was isolated by precipitation in Et_2O and filtration, the use of lipophilic Oct_3N was preferred because it was readily eliminated during this operation.[14]

In a non-supported version of the reaction,[12] substrate **2h**, which is not linked to PEG, was reacted in the Pd-catalyzed cyclization using similar conditions as for the transformation of **2a** in **3a** (Table 1). In sharp contrast with the results previously obtained, we could not reach the same results in terms of rate, selectivity, and reproducibility using 'classical' Heck reaction conditions.

Using Et_3N, the reaction was slower and a side product **4** arising from a competing Tsuji–Trost rearrangement was formed (entry 1 and Eq. 1).[15–17] Using Oct_3N, the reaction was complete but the formation of side product **4** increased (entry 2). Jeffery's conditions[18] were tried but resulted in a slower reaction and the exclusive formation of **4** (obtained in this case as an *E*/*Z* mixture with a 4/1 diastereomeric ratio) (entry 3). Since the presence of PEG seemed to be of prime significance in the catalytic system, we explored the improvement of the results by adding PEG 3400-OH to the reaction mixture, in the same weight amount as in the case of the polymer supported substrate. The reaction was not complete within 12 h but only formation of the cyclized product **3h** was observed (entry 4). Finally, PEG 3400-OH, solid at room temperature but liquid at 80 °C, was used as the solvent (entry 5). In this case, excellent results were obtained, similar to those obtained in the supported reaction, with exclusive formation of **3h**. Interestingly, replacing solid PEG 3400-OH by liquid PEG 300-OH with either Oct_3N or K_2CO_3 yielded only a sluggish mixture of products. Furthermore, the presence of the hydroxyl groups on PEG is necessary, since the use of PEG 3400-OMe instead of PEG-OH as a solvent did not give the cyclized product (entry 6).



(1)

Various substrates were used in the reaction described within this study. Structures and the corresponding yield of the alkylated aminoesters **2a**–**k** are presented in Figure 1. Aminoesters **2a**–**k** were cyclized to benzazepines **3a**–**k**, which are presented in Figure 2. In all cases, complete conversion of the starting material to the expected product was obtained.

Table 1. Conversion of **2h** under Pd catalysis[a]

Entry	Base	Solvent	Additive	Reaction time (h)	**2h** (%)	**3h** (%)	**4** (%)
1	Et_3N	DMF		36	10	68	22
2	Oct_3N	DMF		12	0	50	50
3	K_2CO_3	DMF	*n*-Bu_4NCl	48	0	0	100
4	K_2CO_3	DMF	PEG 3400-OH	12	54	46	0
5	K_2CO_3	PEG 3400-OH		12	0	100	0
6	K_2CO_3	PEG 3400-OMe		12	100	0	0

[a] Reaction conditions: **2h** (1 equiv), $Pd(OAc)_2$ (0.1 equiv), K_2CO_3 (3 equiv), and PEG 3400-OH (100 mg/mg of $Pd(OAc)_2$) were stirred during the indicated time at 80 °C.

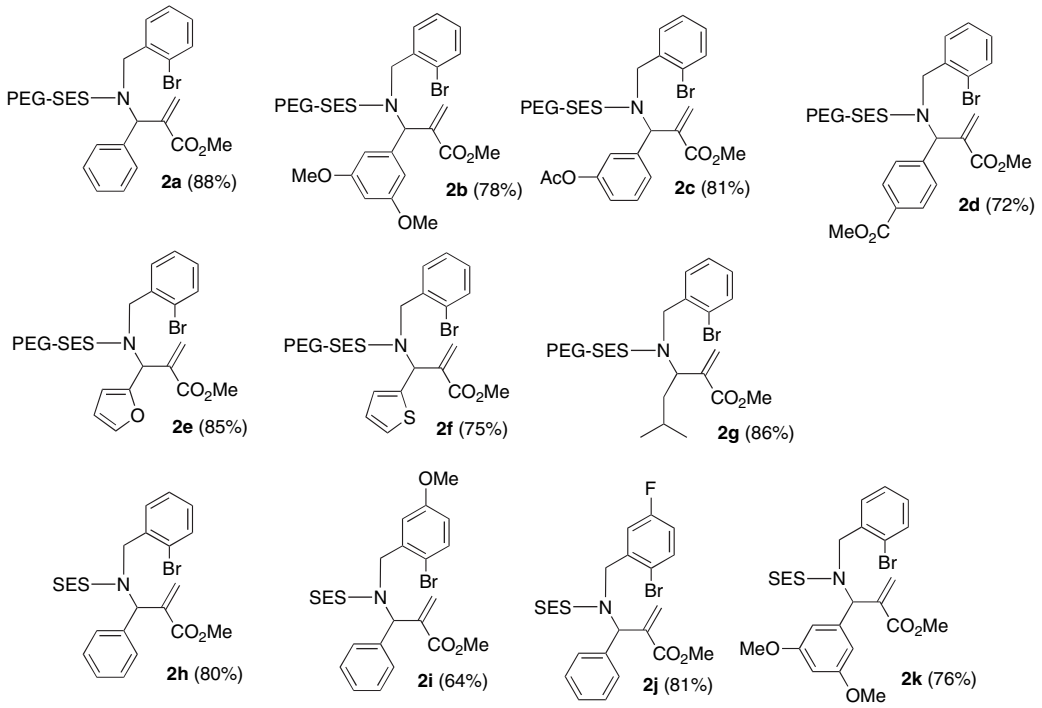


Figure 1.

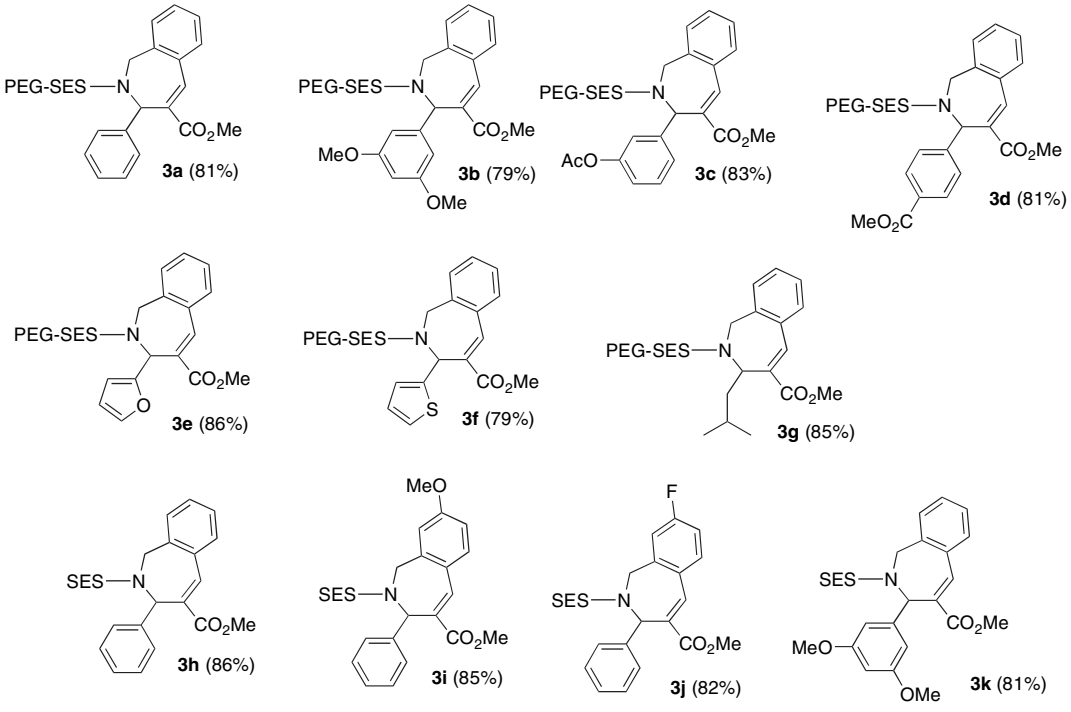


Figure 2.

Purity of the PEG-supported molecule was further ascertained by ^{1}H NMR and HPLC.[19] The diversity of cyclic structures in the supported version of the reaction originated from the aldehydes employed in the aza-Baylis–Hillman reaction (Scheme 1 and Fig. 1). In the case of the non-supported synthesis of benzazepines, we have shown that further diversity could be obtained by adding a substituent on the aromatic ring of the alkylating agent (Scheme 1 and Fig. 2).

The catalytic systems described above for the supported and non-supported reactions are quite simple. No phosphine was necessary to achieve good conversion and selectivity and the presence of ammonium salts did not improve the results. Furthermore, direct observation of a mixture of $Pd(OAc)_2$, Oct_3N, and DMF in the presence of PEG 3400-OH showed a dramatic difference in the homogeneity of the mixture (Fig. 3).

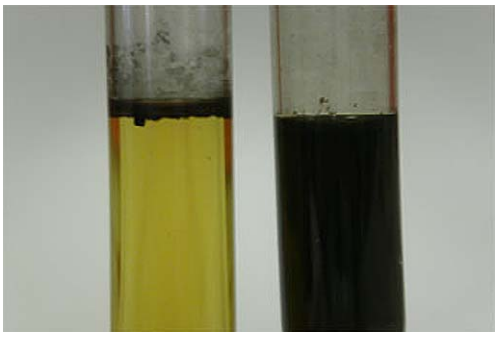


Figure 3. Left: mixture of $Pd(OAc)_2$, Oct_3N, DMF; right: mixture of $Pd(OAc)_2$, Oct_3N, DMF, PEG 3400-OH.

Since PEG has been recently described as nanoparticle stabilizer,[20–22] we investigated the possible presence of nanoparticles by analyzing the reaction mixture after 12 h of **2a** with $Pd(OAc)_2$ and Oct_3N in DMF, by Transmission Electronic Microscopy (TEM) either directly after evaporation of the solvent or through a layer of carbon. The images resulting from both techniques revealed the presence of homogeneously dispersed nanoparticles of palladium of 5–10 nm diameter (Fig. 4). This was further confirmed by light scattering experiments. Nanoparticles were also obtained when a mixture of PEG 3400-OH, $Pd(OAc)_2$, and K_2CO_3 was heated at 80 °C.

The most striking results were obtained when larger PEGs were used as solvent for unsupported reactions. The use of PEG as the sole solvent has a strong influence on the outcome of the reaction in terms of stereo- and regioselectivity. The use of co-solvents generated the formation of side products or slowed down the reaction. One plausible hypothesis is that the presence of palladium species stabilized by PEG may play a role on the kinetics of the different steps of the reaction and orients the outcome of the process to one pathway (mainly Heck cyclization) versus another (mainly Tsuji–Trost allylation). It has indeed been shown in the literature that ionic liquid-stabilized nanoparticles can accelerate such steps.[23] Furthermore, smaller PEGs, liquids at room temperature, have also been used as solvent in conjunction with palladium catalysts providing an easy medium for catalyst recycling.[24–26] However, a larger polymer is more prone to stabilize nanoparticles[20] while in the case of smaller PEGs additional stabilizers[26] are needed to induce these nanostructures. As we have shown in this study, the absence of selectivity with smaller PEGs is indeed not comparable with the results obtained with larger PEGs. Additionally, it has been reported that stabilization by ammonium salts (Jeffery's conditions) can also yield nanoparticles that differ in size and probably in structure, explaining the discrepancy with the results presented herein.[27] The importance of the size effect of larger PEGs in stabilizing nanoparticles can be correlated to similar adsorption effects, which have been reported either on proteins,[28] on silica particles,[29] or on surfaces.[30,31] Nevertheless, the question of the actual catalytic species is still pending, since some literature data advocate that nanoparticles may serve as a reservoir for small quantities of leaching active palladium species.[32–35] In the present case, PEG 3400 would then influence the nature of this reservoir.

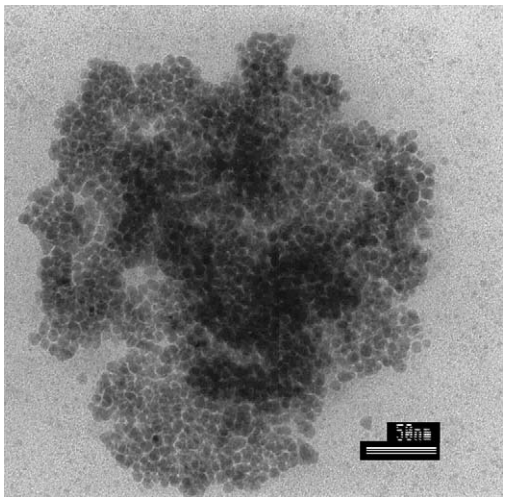


Figure 4. TEM of reaction mixture of **2a** with $Pd(OAc)_2$ and $OctN_3$ in DMF deposited on a copper-grid.

Modified PEGs were previously used as support for Pd catalysts.[36–39] These PEGs are usually terminated by a ligand such as a phosphine to generate a soluble supported complex of palladium that have been in some cases characterized by solution NMR. Nonetheless, one cannot rule out in these examples the additional stabilizing effect exerted by the polymer on the metallic centers and probably the concomitant existence of two forms of palladium. Most probably, the involvement of in situ generated Pd nanoparticles must be also considered in these cases.[40]

3. Conclusion

In conclusion, we have shown that a PEG polymer supporting an organic substrate can also stabilize a Pd catalyst. This phenomenon leads to a very efficient and selective Heck cyclization of the supported organic molecule for the preparation of novel heterocyclic structures. These results seem to be general in PEG-supported chemistry since our group[41,42] and others[43] have reported few years ago the positive effect of larger PEG polymeric support on a Heck reaction. Additionally, following the recent results concerning the use of larger PEG/Pd as catalytic medium for intermolecular Heck reaction,[20,22,44] we have shown herein that this system could be used in its intramolecular version to elaborate more complex and heterocyclic structures. Further studies to assess recycling of this catalytic system and to broaden its scope to other Pd-catalyzed reactions are underway in our laboratories.

4. Experimental

4.1. General remarks

All reagents were purchased from Aldrich Chemical Co. and used without further purification. ^1H and ^{13}C NMR analyses were performed with a Bruker AM 300 MHz spectrometer, and calibrated using residual undeuterated solvents as an internal reference. Mass spectra (electrospray ionization mode, ESIMS) were recorded on a Platform II (Micromass,

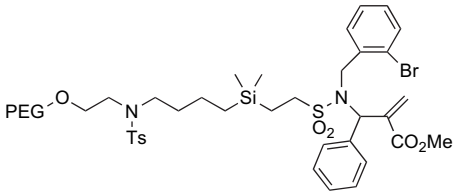
Manchester, U.K.) quadrupole mass spectrometer fitted with an electrospray interface. The mass spectrometer was calibrated in the positive- and negative-ion ESI mode. The sample was dissolved in H_2O/CH_3CN (50/50 v/v). FAB mass spectra and HRMS (High-Resolution Mass Spectrum) were recorded on a JEOL JMS DX300-SX 102 in positive mode using NBA (3-nitrobenzylalcohol) as matrix.

The preparation of unsaturated β-aminoesters **1a–g** and **1k** has been previously described.[10–12]

4.2. General procedure for the alkylation of PEG 3400-supported β-aminoesters

A mixture of PEG 3400-supported sulfonamide (1 equiv), 2-bromobenzyl bromide (8 equiv), and K_2CO_3 (10 equiv) in CH_3CN (5 mL/100 mg de PEG) was heated to reflux for 6 h. After concentration, the residue was diluted in CH_2Cl_2, filtered over Celite, and precipitated in ether. After filtration, the solid was dried in vacuo to yield the corresponding *N*-2-bromobenzyl-β-aminoester.

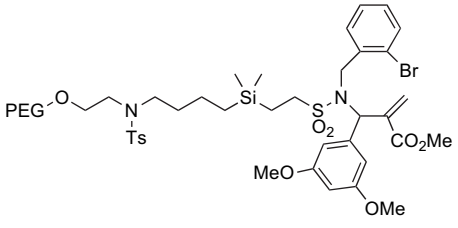
4.2.1. Methyl 2-(*N*-2-bromobenzyl-(PEG 3400-SES-amido)(phenyl)methyl)acrylate (2a).



Prepared according to the general procedure with **1a** (900 mg, 0.20 mmol), 2-bromobenzyl bromide (800 mg, 3.2 mmol), and K_2CO_3 (550 mg, 4 mmol) to afford 850 mg (88%) of the title compound.

^{1}H NMR ($CDCl_3$, Me_4Si) δ −0.17 (s, 6H), 0.32–0.42 (m, 2H), 0.86–0.94 (m, 2H), 1.06–1.22 (m, 2H), 1.44–1.55 (m, 2H), 2.37 (s, 3H), 2.49–2.65 (m, 2H), 3.08 (t, *J*=7.0 Hz, 2H), 3.20–3.27 (m, 2H), 3.50–3.70 (large s, 154H), 3.53 (s, 3H), 4.71 (s, 2H), 5.82 (s, 1H), 6.10 (s, 1H), 6.39 (s, 1H), 6.98 (dt, *J*=1.5, 7.7 Hz, 1H), 7.09–7.37 (m, 10H), 7.65 (d, *J*=8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ −3.18, 9.11, 14.78, 21.02, 21.89, 32.67, 47.96, 49.40, 50.51, 50.86, 52.47, 62.28, 70.37–70.86, 122.96, 127.45, 127.50, 128.60, 128.98, 129.05, 129.09, 129.88, 130.03, 132.74, 136.68, 137.18, 137.70, 139.28, 143.52, 166.42.

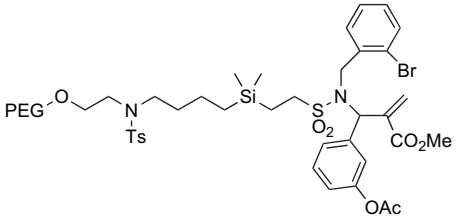
4.2.2. Methyl 2-(*N*-2-bromobenzyl-(PEG 3400-SES-amido)(3,5-dimethoxyphenyl)methyl)acrylate (2b).



Prepared according to the general procedure with **1b** (900 mg, 0.20 mmol) to afford 750 mg (78%) of the title compound.

^{1}H NMR ($CDCl_3$, Me_4Si) δ −0.08 (s, 6H), 0.41–0.49 (m, 2H), 0.96–1.05 (m, 2H), 1.14–1.30 (m, 2H), 1.50–1.64 (m, 2H), 2.44 (s, 3H), 2.65–2.82 (m, 2H), 3.14 (t, *J*=7.0 Hz, 2H), 3.30 (t, *J*=7.0 Hz, 2H), 3.50–3.70 (large s, 154H), 3.61 (s, 3H), 3.75 (s, 6H), 4.76 (s, 2H), 5.89 (s, 1H), 6.12 (s, 1H), 6.30 (s, 1H), 6.43 (s, 1H), 6.49 (s, 2H), 7.01–7.08 (m, 1H), 7.11–7.34 (m, 3H), 7.41 (d, *J*=8.9 Hz, 1H), 7.47 (d, *J*=8.0 Hz), 7.71 (d, *J*=7.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ −3.77, 8.84, 14.41, 20.65, 21.47, 32.31, 47.57, 49.00, 50.02, 50.37, 52.10, 55.32, 61.56, 70.08–70.47, 99.90, 106.72, 122.46, 122.46, 126.96, 127.12, 128.61, 129.40, 129.62, 130.17, 132.25, 136.37, 136.85, 138.76, 139.60, 143.10, 160.85, 165.98.

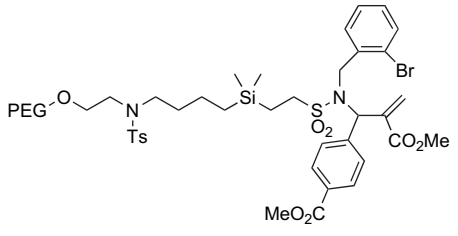
4.2.3. Methyl 2-(*N*-2-bromobenzyl-(PEG 3400-SES-amido)(3-acyloxyphenyl)methyl)acrylate (2c).



Prepared according to the general procedure with **1c** (600 mg, 0.13 mmol) to afford 520 mg (81%) of the title compound.

^{1}H NMR ($CDCl_3$, Me_4Si) δ −0.12 (s, 6H), 0.36–0.48 (m, 2H), 0.90–0.99 (m, 2H), 1.10–1.25 (m, 2H), 1.46–1.58 (m, 2H), 2.26 (s, 3H), 2.39 (s, 3H), 2.55–2.78 (m, 2H), 3.10 (t, *J*=7.5 Hz, 2H), 3.26 (t, *J*=7.5 Hz, 2H), 3.50–3.70 (large s, 154H), 3.57 (s, 3H), 4.72 (s, 2H), 5.87 (s, 2H), 6.11 (s, 1H), 6.44 (s, 1H), 6.93–7.20 (m, 5H), 7.24–7.42 (m, 5H), 7.66 (d, *J*=8.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ −3.77, 8.73, 14.36, 20.64, 21.13, 21.48, 32.30, 47.55, 49.01, 50.29, 52.14, 61.61, 70.06–71.00, 121.30, 122.10, 122.62, 125.65, 127.11, 127.20, 128.78, 129.56, 129.63, 129.91, 130.18, 132.43, 136.05, 136.29, 136.81, 138.53, 138.83, 139.09, 143.03, 150.80, 165.96, 168.93.

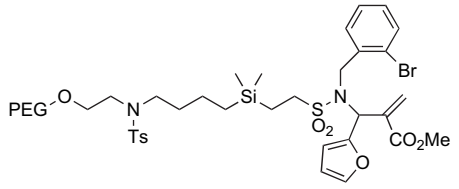
4.2.4. Methyl 2-(*N*-2-bromobenzyl-(PEG 3400-SES-amido)(4-methyloxycarbonyl-phenyl)methyl)acrylate (2d).



Prepared according to the general procedure with **1d** (900 mg, 0.20 mmol) to afford 700 mg (72%) of the title compound.

^{1}H NMR ($CDCl_3$, Me_4Si) δ −0.11 (s, 6H), 0.34–0.54 (m, 2H), 0.89–1.04 (m, 2H), 1.10–1.26 (m, 2H), 1.42–1.64 (m, 2H), 2.40 (s, 3H), 2.62–2.82 (m, 2H), 3.11 (t, J=7.7 Hz, 2H), 3.22–3.33 (m, 2H), 3.50–3.75 (large s, 154H), 3.87 (s, 3H), 4.73 (s, 2H), 5.84 (s, 1H), 6.16 (s, 1H), 6.48 (s, 1H), 7.00 (dt, J=1.7, 7.5 Hz, 1H), 7.15 (dt, J=1.3, 7.4 Hz, 1H), 7.23–7.53 (m, 6H), 7.67 (d, J=8.2 Hz, 2H), 7.91 (d, J=8.2 Hz, 2H).

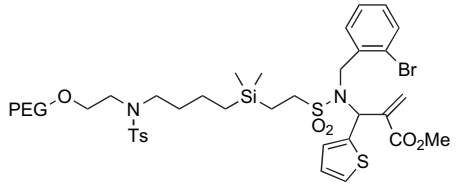
4.2.5. Methyl 2-(*N*-2-bromobenzyl-(PEG 3400-SES-amido)(furan-2-yl)methyl)acrylate (2e).



Prepared according to the general procedure with **1e** (500 mg, 0.11 mmol) to afford 460 mg (85%) of the title compound.

^{1}H NMR ($CDCl_3$, Me_4Si) δ −0.10 (s, 6H), 0.39–0.49 (m, 2H), 0.86–1.01 (m, 2H), 1.12–1.28 (m, 2H), 1.48–1.60 (m, 2H), 2.41 (s, 3H), 2.62–2.79 (m, 2H), 3.12 (t, J=7.0 Hz, 2H), 3.23–3.30 (m, 2H), 3.50–3.75 (large s, 154H), 3.57 (s, 3H), 4.58 (d, J=17.2 Hz, 1H), 4.86 (d, J=17.2 Hz, 1H), 5.86 (s, 1H), 6.20 (s, 1H), 6.26 (s, 1H), 6.33–6.38 (m, 2H), 7.06 (dt, J=1.5, 7.4 Hz, 1H), 7.20–7.56 (m, 6H), 7.68 (d, J=8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ −3.82, 8.38, 14.42, 20.65, 21.47, 32.33, 47.59, 48.45, 49.04, 49.49, 52.09, 54.91, 70.10–70.47, 109.84, 110.78, 122.43, 127.07, 128.61, 129.63, 129.75, 130.04, 130.12, 132.32, 136.71, 136.81, 136.94, 142.83, 143.12, 151.12, 165.31.

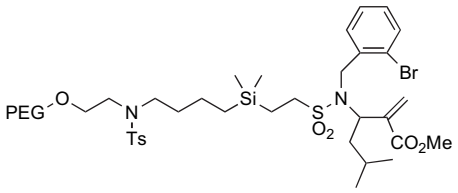
4.2.6. Methyl 2-(*N*-2-bromobenzyl-(PEG 3400-SES-amido)(thiofuran-2-yl)methyl)acrylate (2f).



Prepared according to the general procedure with **1f** (900 mg, 0.20 mmol) to afford 730 mg (75%) of the title compound.

^{1}H NMR ($CDCl_3$, Me_4Si) δ −0.16 (s, 6H), 0.31–0.49 (m, 2H), 0.83–0.95 (m, 2H), 1.06–1.26 (m, 2H), 1.42–1.60 (m, 2H), 2.39 (s, 3H), 2.47–2.73 (m, 2H), 3.04–3.14 (m, 2H), 3.21–3.29 (m, 2H), 3.50–3.75 (large s, 154H), 3.54 (s, 3H), 4.61 (d, J=17.5 Hz, 1H), 4.74 (d, J=17.5 Hz, 1H), 5.94 (s, 1H), 6.28 (s, 1H), 6.26 (s, 1H), 6.42 (s, 2H), 6.93–7.54 (m, 9H), 7.66 (d, J=8.2 Hz, 2H).

4.2.7. Methyl 2-(*N*-2-bromobenzyl-(PEG 3400-SES-amido)(2-isobutyl)methyl)acrylate (2g).



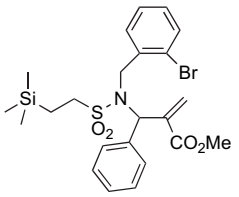
Prepared according to the general procedure with **1g** (900 mg, 0.21 mmol) to afford 830 mg (86%) of the title compound.

^{1}H NMR ($CDCl_3$, Me_4Si) δ 0.00 (s, 3H), 0.01 (s, 3H), 0.42–0.57 (m, 2H), 0.76 (d, J=6.1 Hz, 3H), 0.84 (d, J=6.1 Hz, 3H), 0.88–1.07 (m, 2H), 1.15–1.34 (m, 4H), 1.39–1.80 (m, 3H), 2.43 (s, 3H), 2.72–3.04 (m, 2H), 3.15 (t, J=7.4 Hz, 2H), 3.25–3.35 (m, 2H), 3.50–3.80 (large s, 154H), 3.79 (s, 3H), 4.47–4.65 (m, 3H), 4.89–4.99 (m, 1H), 5.83 (s, 1H), 6.52 (s, 1H), 7.13 (dt, J=1.7, 7.4 Hz, 1H), 7.27–7.37 (m, 3H), 7.50 (dd, J=1.3, 8.0 Hz, 1H), 7.63–7.74 (m, 3H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ −3.79, 8.79, 14.51, 20.70, 21.37, 21.46, 23.17, 24.92, 32.32, 41.12, 47.54, 49.00, 49.36, 52.23, 55.43, 70.07–70.44, 122.55, 127.09, 127.33, 128.85, 129.45, 129.61, 130.78, 132.49, 136.84, 137.07, 137.13, 143.08, 166.99.

4.3. General procedure for the alkylation of non-supported β-aminoesters

A mixture of sulfonamide (1 equiv), 2-bromobenzyl bromide or a related reagent (1.2 equiv), and K_2CO_3 (10 equiv) in CH_3CN was heated to reflux for 6 h. After concentration, the residue was diluted in ether, washed successively with a solution of 5% $KHSO_4$ and brine, dried over $MgSO_4$, and evaporated. Purification by silica gel chromatography (hexane/Et_2O) afforded the corresponding *N*-2-bromobenzyl-β-aminoester.

4.3.1. Methyl 2-((*N*-2-bromobenzyl-2-(trimethylsilyl)-ethan-3-ylsulfonamido)(phenyl)methyl)acrylate (2h).

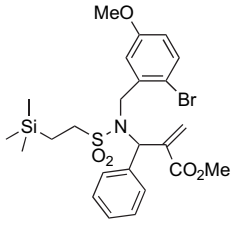


Prepared according to the general procedure with **1h** (100 mg, 0.28 mmol), 2-bromobenzyl bromide (85 mg, 0.34 mmol), and K_2CO_3 (390 mg, 2.83 mmol) to afford 118 mg (80%) of the title compound after silica gel chromatography (hexane/Et_2O, 8/2).

^{1}H NMR ($CDCl_3$, Me_4Si) δ −0.05 (s, 9H), 0.95–1.05 (m, 2H), 2.55–2.77 (m, 2H), 3.61 (s, 3H), 4.78 (s, 2H), 5.90 (d,

J=1.48 Hz, 1H), 6.17 (s, 1H), 6.46 (s, 1H), 7.04 (dt, J=1.48, 7.6 Hz, 1H), 7.16–7.45 (m, 7H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ −2.05, 10.20, 50.35, 50.62, 52.04, 62.07, 122.63, 127.08, 128.19, 128.64, 128.68, 129.33, 130.29, 132.38, 136.34, 137.34, 139.02, 166.08; HPLC t_R=14.50 min; ESIMS m/z 524.2 $(M+H)^+$ (monoisotopic); HRMS calcd for $C_{23}H_{31}BrNO_4SSi$ 524.0926 (monoisotopic), found 524.0952; R_f (hexane/Et_2O, 8/2) 0.31.

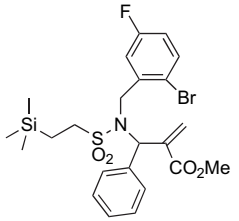
4.3.2. Methyl 2-((*N*-2-bromo-5-methoxy-benzyl-2-(trimethylsilyl)ethan-3-ylsulfonamido)(phenyl)methyl)acrylate (2i).



Prepared according to the general procedure with **1i** (75 mg, 0.21 mmol) and 5-methoxy-2-bromobenzyl bromide (71 mg, 0.25 mmol) to afford 75 mg (64%) of the title compound after silica gel chromatography (hexane/Et_2O, 85/15).

^{1}H NMR ($CDCl_3$, Me_4Si) δ −0.05 (s, 9H), 0.96–1.04 (m, 2H), 2.56–2.80 (m, 2H), 3.61 (s, 3H), 3.75 (s, 3H), 4.74 (s, 2H), 5.87 (d, J=1.5 Hz, 1H), 6.19 (s, 1H), 6.45 (s, 1H), 6.61 (dd, J=3.0, 8.9 Hz, 1H), 6.97 (d, J=3.0 Hz, 1H), 7.25–7.40 (m, 6H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ −1.98, 10.18, 50.29, 50.47, 52.04, 55.38, 61.98, 112.17, 115.02, 115.38, 128.22, 128.57, 128.72, 129.58, 132.91, 137.32, 137.53, 139.03, 158.81, 166.14; HPLC t_R=14.56 min; ESIMS m/z 554.3 $(M+H)^+$ (monoisotopic); HRMS calcd for $C_{24}H_{33}BrNO_5SSi$ 554.1032 (monoisotopic), found 554.1039; R_f (hexane/Et_2O, 7/3) 0.33.

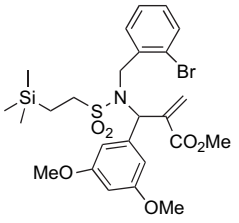
4.3.3. Methyl 2-((*N*-2-bromo-5-fluoro-benzyl-2-(trimethylsilyl)ethan-3-ylsulfonamido)(phenyl)methyl)acrylate (2j).



Prepared according to the general procedure with **1j** (75 mg, 0.21 mmol) and 5-fluoro-2-bromobenzyl bromide (68 mg, 0.25 mmol) to afford 93 mg (81%) of the title compound after silica gel chromatography (hexane/Et_2O, 85/15).

^{1}H NMR ($CDCl_3$, Me_4Si) δ −0.03 (s, 9H), 0.98–1.06 (m, 2H), 2.61–2.86 (m, 2H), 3.65 (s, 3H), 4.74 (s, 2H), 5.83 (d, J=1.5 Hz, 1H), 6.22 (s, 1H), 6.46 (s, 1H), 6.75 (dt, J=3.0, 7.7 Hz, 1H), 7.13 (dd, J=3.0, 7.7 Hz, 1H), 7.21–7.39 (m, 6H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ −2.06, 10.22, 50.23, 52.18, 61.75, 115.79 (J=22.8 Hz), 116.07 (J=3.1 Hz), 116.98 (J=24.8 Hz), 128.34, 128.42, 128.78, 129.39, 133.40 (J=7.9 Hz), 138.95 (J=7.4 Hz), 139.10, 161.85 (J=246.6 Hz), 166.00; HPLC t_R=14.58 min; ESIMS m/z 541.9 $(M+H)^+$ (monoisotopic); HRMS calcd for $C_{23}H_{30}BrFNO_4SSi$ 542.0832 (monoisotopic), found 542.0825; R_f (hexane/Et_2O, 8/2) 0.39.

4.3.4. Methyl 2-((*N*-2-bromobenzyl-2-(trimethylsilyl)ethan-3-ylsulfonamido)(3,5-dimethoxyphenyl)methyl)acrylate (2k).



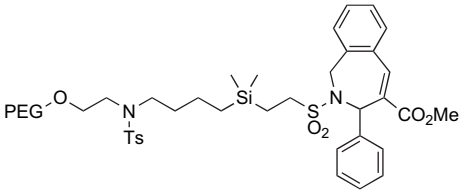
Prepared according to the general procedure with **1k** (75 mg, 0.18 mmol) and 2-bromobenzyl bromide (55 mg, 0.22 mmol) to afford 80 mg (76%) of the title compound after silica gel chromatography (hexane/Et_2O, 8/2).

^{1}H NMR ($CDCl_3$, Me_4Si) δ −0.04 (s, 9H), 0.98–1.08 (m, 2H), 2.64–2.85 (m, 2H), 3.61 (s, 3H), 3.75 (s, 6H), 4.77 (s, 2H), 5.90 (s, 1H), 6.12 (s, 1H), 6.30 (t, J=2.2 Hz, 1H), 6.43 (s, 1H), 6.50 (d, J=2.2 Hz, 2H), 7.04 (dt, J=1.5, 8.0 Hz, 1H), 7.21 (t, J=7.7 Hz, 1H), 7.41 (d, J=8.0 Hz, 1H), 7.48 (d, J=8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ −2.10, 10.29, 50.19, 50.46, 52.11, 55.32, 61.61, 99.92, 106.92, 122.49, 127.00, 128.62, 129.38, 130.22, 132.27, 136.40, 138.81, 139.65, 160.87, 166.00; HPLC t_R=14.39 min; ESIMS m/z 584.1 $(M+H)^+$ (monoisotopic); HRMS calcd for $C_{25}H_{34}BrNO_6SSi$ 583.1059 (monoisotopic), found 583.1066; R_f (hexane/Et_2O, 7/3) 0.22.

4.4. General procedure for the Heck reaction on PEG 3400-supported substrate

To a mixture of PEG 3400-supported *N*-2-bromobenzyl-β-aminoester (1 equiv) and $Pd(OAc)_2$ (0.1 equiv) in DMF (1 mL/50 mg de PEG) was added $(n\text{-octyl})_3N$ (3 equiv). The solution was stirred at room temperature for few minutes under nitrogen. The mixture was then heated at 80 °C for 6 h, filtered over Celite, and precipitated in ether. After filtration, the solid was dried in vacuo to yield the corresponding benzazepine.

4.4.1. 2-(PEG 3400-SES)-3-phenyl-2,3-dihydro-1*H*-benzo[*c*]azepine-4-carboxylic acid methyl ester (3a).

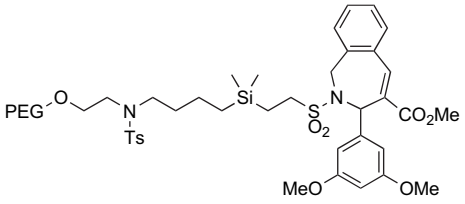


Prepared according to the general procedure with **2a** (500 mg, 0.10 mmol), $Pd(OAc)_2$ (5 mg, 0.022 mmol), and

(n-octyl)$_3$N (222 mg, 0.63 mmol) to afford 410 mg (81%) of the title compound.

^{1}H NMR ($CDCl_3$, Me_4Si) δ −0.26 (s, 3H), −0.25 (s, 3H), 0.24–0.32 (m, 2H), 0.68–0.76 (m, 2H), 1.00–1.14 (m, 2H), 1.46–1.58 (m, 2H), 2.44 (s, 3H), 2.27–2.56 (m, 2H), 3.11 (t, J=7.9 Hz, 2H), 3.27–3.33 (m, 2H), 3.55–3.75 (large s, 154H), 3.70 (s, 3H), 4.14 (d, J=16.8 Hz, 1H), 4.46 (d, J=16.8 Hz, 1H), 6.43 (s, 1H), 7.22–7.44 (m, 10H), 7.54–7.60 (m, 1H), 7.72 (d, J=8.3 Hz, 2H), 8.02 (s, 1H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ −4.07, 8.35, 14.32, 20.59, 21.50, 32.27, 47.37, 47.56, 49.06, 49.83, 52.57, 61.02, 70.09–71.03, 127.12, 128.04, 128.29, 128.63, 128.69, 129.64, 130.30, 132.02, 132.05, 135.27, 136.81, 140.40, 140.67, 140.83, 143.12, 167.26.

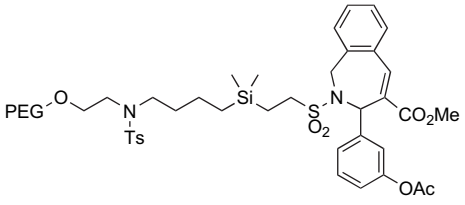
4.4.2. 2-(PEG 3400-SES)-3-(3,5-dimethoxyphenyl)-2,3-dihydro-1*H*-benzo[*c*]azepine-4-carboxylic acid methyl ester (3b).



Prepared according to the general procedure with **2b** (500 mg, 0.10 mmol) to afford 380 mg (79%) of the title compound.

^{1}H NMR ($CDCl_3$, Me_4Si) δ −0.29 (s, 3H), −0.28 (s, 3H), 0.21–0.29 (m, 2H), 0.64–0.74 (m, 2H), 0.97–1.09 (m, 2H), 1.43–1.61 (m, 2H), 2.23–2.40 (m, 2H), 2.44 (s, 3H), 3.05–3.13 (m, 2H), 3.25–3.31 (m, 2H), 3.55–3.75 (large s, 154H), 3.71 (s, 3H), 3.71 (s, 6H), 4.20 (d, J=17.4 Hz, 1H), 4.45 (d, J=17.4 Hz, 1H), 6.32 (s, 1H), 6.38 (t, J=2 Hz, 1H), 6.53 (d, J=2.0 Hz, 2H), 7.19–7.56 (m, 6H), 7.69 (d, J=8.0 Hz, 2H), 7.95 (s, 1H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ −4.09, 8.36, 14.33, 20.60, 21.49, 32.36, 47.45, 47.57, 49.07, 49.83, 52.61, 55.37, 60.96, 70.10–71.07, 99.81, 106.97, 127.14, 128.25, 128.65, 129.58, 129.65, 130.31, 131.85, 132.05, 135.27, 136.86, 140.39, 140.55, 143.14, 160.89, 167.24.

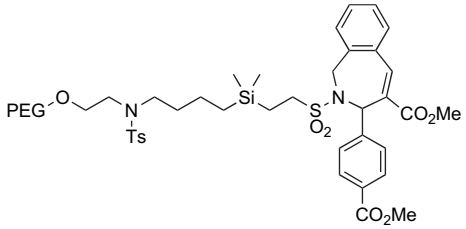
4.4.3. 2-(PEG 3400-SES)-3-(3-acyloxyphenyl)-2,3-dihydro-1*H*-benzo[*c*]azepine-4-carboxylic acid methyl ester (3c).



Prepared according to the general procedure with **2c** (500 mg, 0.10 mmol) to afford 400 mg (83%) of the title compound.

^{1}H NMR ($CDCl_3$, Me_4Si) δ −0.27 (s, 3H), −0.26 (s, 3H), 0.24–0.40 (m, 2H), 0.68–0.77 (m, 2H), 0.96–1.14 (m, 2H), 1.43–1.60 (m, 2H), 2.29 (s, 3H), 2.44 (s, 3H), 2.27–2.56 (m, 2H), 3.10–3.22 (m, 2H), 3.25–3.35 (m, 2H), 3.55–3.75 (large s, 154H), 4.12 (d, J=17.4 Hz, 1H), 4.47 (d, J=17.4 Hz, 1H), 6.41 (s, 1H), 7.05–7.55 (m, 10H), 7.71 (d, J=8.2 Hz, 2H), 8.02 (s, 1H).

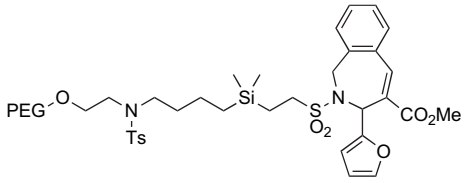
4.4.4. 2-(PEG 3400-SES)-3-(4-methyloxycarbonylphenyl)-2,3-dihydro-1*H*-benzo[*c*]azepine-4-carboxylic acid methyl ester (3d).



Prepared according to the general procedure with **2d** (500 mg, 0.10 mmol) to afford 370 mg (81%) of the title compound.

^{1}H NMR ($CDCl_3$, Me_4Si) δ −0.30 (s, 6H), 0.19–0.29 (m, 2H), 0.62–0.76 (m, 2H), 0.94–1.12 (m, 2H), 1.40–1.58 (m, 2H), 2.39 (s, 3H), 2.24–2.51 (m, 2H), 3.01–3.15 (m, 2H), 3.21–3.29 (m, 2H), 3.50–3.80 (large s, 154H), 3.88 (s, 3H), 4.03 (d, J=17.4 Hz, 1H), 4.41 (d, J=17.4 Hz, 1H), 6.40 (s, 1H), 7.16–7.59 (m, 8H), 7.66 (d, J=7.4 Hz, 2H), 7.96–8.04 (m, 3H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ −3.77, 8.34, 14.27, 20.55, 21.47, 32.30, 46.91, 47.44, 47.55, 49.01, 49.90, 52.18, 52.61, 60.73, 70.05–70.98, 127.10, 128.46, 128.59, 128.73, 129.63, 129.81, 129.96, 130.53, 131.31, 135.27, 136.82, 140.05, 141.21, 143.12, 145.76, 166.59, 166.98.

4.4.5. 2-(PEG 3400-SES)-3-furan-2-yl-2,3-dihydro-1*H*-benzo[*c*]azepine-4-carboxylic acid methyl ester (3e).

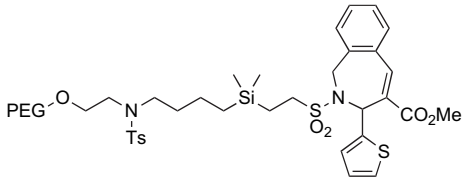


Prepared according to the general procedure with **2e** (300 mg, 0.063 mmol) to afford 250 mg (86%) of the title compound.

^{1}H NMR ($CDCl_3$, Me_4Si) δ −0.15 (s, 3H), −0.14 (s, 3H), 0.30–0.53 (m, 2H), 0.80–0.96 (m, 2H), 1.10–1.30 (m, 2H), 1.46–1.60 (m, 2H), 2.44 (s, 3H), 2.65–2.80 (m, 2H), 3.10–3.30 (m, 4H), 3.27–3.33 (m, 2H), 3.50–3.80 (large s, 154H), 3.76 (s, 3H), 4.28 (d, J=16.7 Hz, 1H), 4.57 (d, J=16.7 Hz, 1H), 6.22 (d, J=4.2 Hz, 1H), 6.34–6.40 (m, 2H), 7.25–7.60 (m, 7H), 7.72 (d, J=8.3 Hz, 2H), 7.91 (s, 1H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ −3.94, 8.56, 14.38, 20.61, 21.47, 32.24, 47.02, 47.58, 49.03, 49.84, 52.55, 55.74, 70.08–71.00, 110.53, 110.88, 127.11, 128.09,

128.23, 129.63, 129.75, 130.34, 131.60, 135.37, 136.83, 140.47, 140.72, 143.12, 152.56, 166.97.

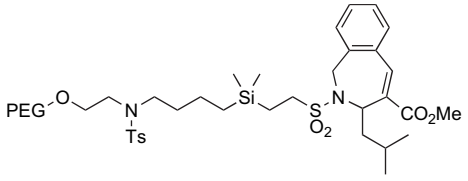
4.4.6. 2-(PEG 3400-SES)-3-thiofuran-2-yl-2,3-dihydro-1*H*-benzo[*c*]azepine-4-carboxylic acid methyl ester (3f).



Prepared according to the general procedure with **2f** (500 mg, 0.10 mmol) to afford 380 mg (79%) of the title compound.

^{1}H NMR ($CDCl_3$, Me_4Si) δ −0.24 (s, 6H), 0.19–0.29 (m, 2H), 0.62–0.76 (m, 2H), 0.94–1.12 (m, 2H), 1.40–1.58 (m, 2H), 2.42 (s, 3H), 2.43–2.57 (m, 2H), 3.01–3.15 (m, 2H), 3.21–3.29 (m, 2H), 3.50–3.80 (large s, 154H), 3.88 (s, 3H), 4.32 (d, J=17.2 Hz, 1H), 4.52 (d, J=17.2 Hz, 1H), 6.56 (s, 1H), 6.87–6.97 (m, 2H), 7.18–7.54 (m, 7H), 7.68 (d, J=7.5 Hz, 2H), 7.89 (s, 1H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ −4.17, 8.30, 14.18, 20.44, 21.33, 32.16, 47.34, 47.42, 48.88, 49.89, 52.48, 56.64, 69.92–70.32, 126.59, 126.64, 126.96, 127.82, 128.04, 128.30, 129.49, 130.23, 131.61, 131.81, 135.18, 136.67, 142.98, 144.11, 166.96.

4.4.7. 2-(PEG 3400-SES)-3-(2-isobutyl)-2,3-dihydro-1*H*-benzo[*c*]azepine-4-carboxylic acid methyl ester (3g).



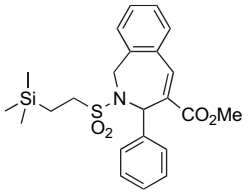
Prepared according to the general procedure with **2g** (500 mg, 0.10 mmol) to afford 410 mg (85%) of the title compound.

^{1}H NMR ($CDCl_3$, Me_4Si) δ −0.31 (s, 3H), −0.29 (s, 3H), 0.20–0.27 (m, 2H), 0.64–0.76 (m, 2H), 0.95 (d, J=6.5 Hz, 3H), 1.06 (d, J=6.5 Hz, 3H), 1.13–1.30 (m, 2H), 1.40–1.72 (m, 4H), 2.09–2.23 (m, 1H), 2.42 (s, 3H), 2.25–2.47 (m, 2H), 3.06–3.20 (m, 2H), 3.24–3.32 (m, 2H), 3.50–3.75 (large s, 154H), 3.84 (s, 3H), 4.45 (d, J=17.0 Hz, 1H), 4.69 (d, J=17.0 Hz, 1H), 5.16–5.22 (m, 1H), 7.10–7.56 (m, 6H), 7.64 (s, 1H), 7.69 (d, J=8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ −4.09, 8.22, 14.31, 20.59, 21.48, 23.61, 23.77, 32.34, 43.79, 46.56, 47.55, 49.05, 49.22, 52.44, 56.28, 70.09–71.04, 127.13, 128.29, 128.62, 128.69, 129.64, 130.08, 132.52, 134.75, 135.35, 136.85, 138.08, 139.61, 143.12, 167.55.

4.5. General procedure for the Heck reaction with PEG as solvent

To *N*-2-bromobenzyl-β-aminoester (1 equiv) and $Pd(OAc)_2$ (0.1 equiv) was added a mixture of PEG 3400-OH (100 mg/mg de $Pd(OAc)_2$) and finely powdered K_2CO_3 (3 equiv). The resulting mixture was heated at 80 °C with strong stirring for 12 h. After cooling, the crude is solubilized in CH_2Cl_2 and precipitated in ether. After filtration, the filtrate was concentrated to yield the corresponding benzazepine.

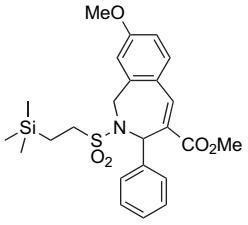
4.5.1. 3-Phenyl-2-(2-(trimethylsilanyl)ethylsulfonyl)-2,3-dihydro-1*H*-benzo[*c*]azepine-4-carboxylic acid methyl ester (3h).



Prepared according to the general procedure with **2h** (29 mg, 0.055 mmol), $Pd(OAc)_2$ (1.2 mg, 5.5 μmol), PEG-OH (120 mg), and K_2CO_3 (25 mg, 0.18 mmol) to afford 21 mg (86%) of the title compound.

^{1}H NMR ($CDCl_3$, Me_4Si) δ −0.20 (s, 9H), 0.70–0.80 (m, 2H), 2.32–2.58 (m, 2H), 3.71 (s, 3H), 4.15 (d, J=17.0 Hz, 1H), 4.45 (dd, J=17.0, 1.5 Hz, 1H), 6.45 (s, 1H), 7.23–7.44 (m, 8H), 7.55–7.59 (m, 1H), 8.02 (s, 1H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ −2.97, 9.07, 46.70, 49.32, 51.88, 60.35, 127.35, 127.53, 127.97, 128.00, 131.37, 131.41, 134.54, 139.80, 140.02, 140.20, 166.66; HPLC t_R=13.92 min; ESIMS m/z 444.2 $(M+H)^+$, 887.5 $(2M+H)^+$; HRMS calcd for $C_{23}H_{30}NO_4SSi$ 444.1665, found 444.1677.

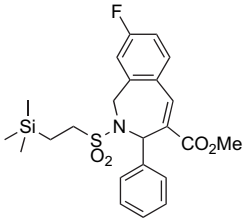
4.5.2. 8-Methoxy-3-phenyl-2-(2-(trimethylsilanyl)ethylsulfonyl)-2,3-dihydro-1*H*-benzo[*c*]azepine-4-carboxylic acid methyl ester (3i).



Prepared according to the general procedure with **2i** (40 mg, 0.072 mmol) to afford 29 mg (85%) of the title compound.

^{1}H NMR ($CDCl_3$, Me_4Si) δ −0.16 (s, 9H), 0.71–0.85 (m, 2H), 2.35–2.70 (m, 2H), 3.70 (s, 3H), 3.85 (s, 3H), 4.09 (d, J=17.3 Hz, 1H), 4.41 (dd, J=17.3, 1.7 Hz, 1H), 6.43 (s, 1H), 6.77 (d, J=2.6 Hz, 1H), 6.90 (dd, J=2.6, 8.3 Hz, 1H), 7.27–7.44 (m, 5H), 7.50 (d, J=8.5 Hz, 1H), 7.99 (s, 1H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ −2.25, 9.83, 47.54, 50.01, 52.39, 55.53, 60.92, 113.14, 114.36, 124.88, 127.99, 128.67, 128.72, 137.31, 140.54, 140.87, 142.53, 161.13, 167.54; HPLC t_R=13.53 min; ESIMS m/z 474.1 $(M+H)^+$, 947.6 $(2M+H)^+$; HRMS calcd for $C_{24}H_{32}NO_5SSi$ 474.1770, found 474.1757.

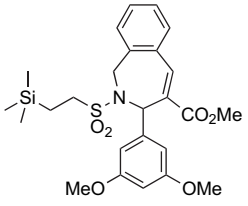
4.5.3. 8-Fluoro-3-phenyl-2-(2-(trimethylsilanyl)ethylsulfonyl)-2,3-dihydro-1*H*-benzo[*c*]azepine-4-carboxylic acid methyl ester (3j).



Prepared according to the general procedure with **2j** (20 mg, 0.036 mmol) to afford 14 mg (82%) of the title compound.

^{1}H NMR ($CDCl_3$, Me_4Si) δ −0.15 (s, 9H), 0.70–0.88 (m, 2H), 2.41–2.67 (m, 2H), 3.71 (s, 3H), 4.11 (d, J=17.2 Hz, 1H), 4.42 (dd, J=17.2, 1.8 Hz, 1H), 6.42 (s, 1H), 6.98 (dd, J=2.7, 8.6 Hz, 1H), 7.08 (dt, J=2.7, 8.0 Hz, 1H), 7.28–7.41 (m, 5H), 7.55 (dd, J=5.6, 8.6 Hz, 1H), 7.98 (s, 1H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ −2.24, 9.90, 47.15, 50.13, 52.59, 61.05, 115.03 (d, J=21.5 Hz), 115.89 (d, J=22.2 Hz), 128.20, 128.48 (d, J=3.6 Hz), 128.62, 128.79, 131.35, 131.33 (d, J=2.9 Hz), 137.39 (d, J=8.7 Hz), 139.53, 140.53, 143.45 (d, J=7.3 Hz), 163.27 (d, J=255.1 Hz), 167.20; HPLC t_R=14.08 min; ESIMS m/z 462.2 $(M+H)^+$; HRMS calcd for $C_{23}H_{29}FNO_4SSi$ 462.1571, found 462.1611.

4.5.4. 3-(3,5-Dimethoxy-phenyl)-2-(2-(trimethylsilanyl)-ethylsulfonyl)-2,3-dihydro-1*H*-benzo[*c*]azepine-4-carboxylic acid methyl ester (3k).



Prepared according to the general procedure with **2k** (20 mg, 0.034 mmol) to afford 14 mg (81%) of the title compound.

^{1}H NMR ($CDCl_3$, Me_4Si) δ −0.20 (s, 9H), 0.67–0.80 (m, 2H), 2.25–2.59 (m, 2H), 3.74 (s, 3H), 3.80 (s, 6H), 4.23 (d, J=17.0 Hz, 1H), 4.49 (dd, J=1.7, 17.0 Hz, 1H), 6.34 (s, 1H), 6.41 (t, J=2.2 Hz, 1H), 6.56 (d, J=2.2 Hz, 2H), 7.22–7.46 (m, 3H), 7.51–7.59 (m, 1H), 7.99 (s, 1H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ −2.29, 9.77, 47.46, 50.00, 52.59, 55.38, 60.98, 99.85, 106.99, 128.18, 128.66, 130.25, 131.90, 132.09, 135.22, 140.47, 140.57, 143.21, 160.91, 167.29; HPLC t_R=13.56 min; ESIMS m/z 504.2 $(M+H)^+$; HRMS calcd for $C_{25}H_{34}NO_6SSi$ 504.1876, found 504.1855.

4.6. General procedure for the Heck reaction with liquid PEG as solvent

To a mixture of *N*-2-bromobenzyl-β-aminoester **2h** (1 equiv) and $Pd(OAc)_2$ (0.1 equiv) in PEG 300-OH (100 mg/mg de $Pd(OAc)_2$) was added a base (K_2CO_3 or Oct_3N (3 equiv)). The resulting mixture was heated at 80 °C with strong stirring for 12 h. The mixture was diluted with AcOEt, and the organic layer was washed with water and brine, dried over $MgSO_4$, filtered, and evaporated to give the crude product, which was then analyzed by ^{1}H NMR.

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