

Task Specific Onium Salts and Ionic Liquids as Soluble Supports in *Grieco's* Multicomponent Synthesis of Tetrahydroquinolines

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Summary. In this work was presented an application of the use of task specific onium salts (TSOSs) as soluble supports in *Grieco's* multicomponent synthesis of tetrahydroquinolines. These soluble supports are of wide applicability and combine advantages of solid phase synthesis without its limitations with those of solution phase chemistry. After a simple washing step, products were cleaved from the supports and obtained in pure form and good yields.

Keywords. Heterocycles; Solution phase synthesis; Multicomponent reactions; Acid catalysis; Functionalized ammonium salts.

Introduction

In the last decades solid phase organic synthesis (SPOS) has undoubtedly been the method of choice for rapidly preparing ensembles of small molecules. By supporting a reagent on a resin or a polymer, purification was shortened to simple filtrations; diversity was enhanced by split and mix methods and high throughput parallel synthesis could be realized [1, 2]. However, some limitations were remaining, inherent to the heterogeneous nature of mixtures. In addition to high prices and low loading capacities, resins were inducing slow and non-linear kinetics due to poor diffusion and difficulties to access active sites. Often, analysis happened to be tricky and necessitated special technology such as HR MAS NMR. To circumvent these problems, soluble sup-

ports have been developed based on dendrimeric alcohols [3], polyethylene glycols (*PEGs*), or soluble polystyrenes (*JandaJels*) to mention the most important ones [4–6]. They allowed for recovering liquid phase properties by fine tuning of solvent conditions and linker structures. *PEGs* have for example been used successfully in the synthesis of peptides [7], oligosaccharides [8], oligonucleotides [9], and small molecules. However, once again, low loading capacity, water solubility, and impurities co-precipitation during the purification have narrowed their applicability.

Recently, a valuable alternative to these supports has been proposed based on specificities of room temperature ionic liquids (RTILs) [10]. Introducing a specific functionality into RTILs led to the so-called task specific ionic liquids (TSILs), which could serve as reagents, reactants, catalysts, or soluble supports for organic synthesis [11–14]. Task specific onium salts were an extension of the above concept to salts having a melting point over 100°C [15]. We and others have used them successfully for peptide synthesis [16], transition metal catalyzed reactions [17] and multi component reactions (MCR) (Fig. 1) [18, 19]. Non-supported versions of multicomponent reactions were often handicapped by side reactions leading to separation difficulties. Indeed, by supporting one reactant and therefore getting supported products, purification and removal of traces of impurities would be largely improved, but examples were scarce due to kinetic limitations in heterogeneous medium [20–22].

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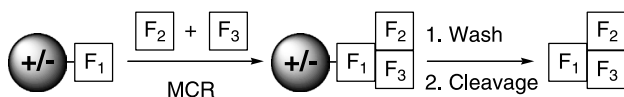


Fig. 1. Onium salts supported synthesis (OSSS) applied to multicomponent reactions

Here, we report our results concerning multicomponent reactions involving a task specific onium salts synthesis strategy. After design and preparation of task specific onium salts with suitable functionality, they were separately engaged in a *Grieco* reaction with two other partners. An easy purification by simple washings followed by cleavage from support provided *Grieco* quinolines in excellent yields.

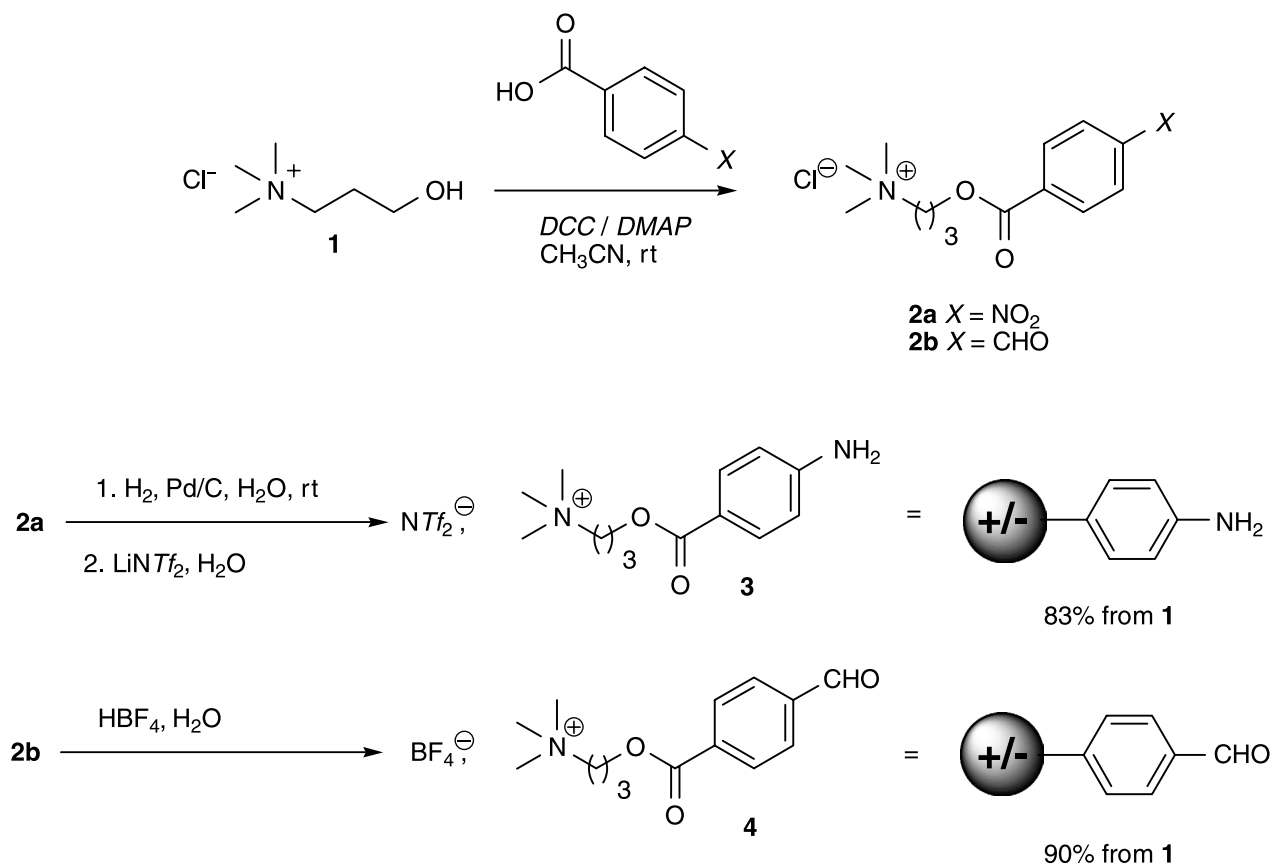
Results and Discussion

Substrates Synthesis

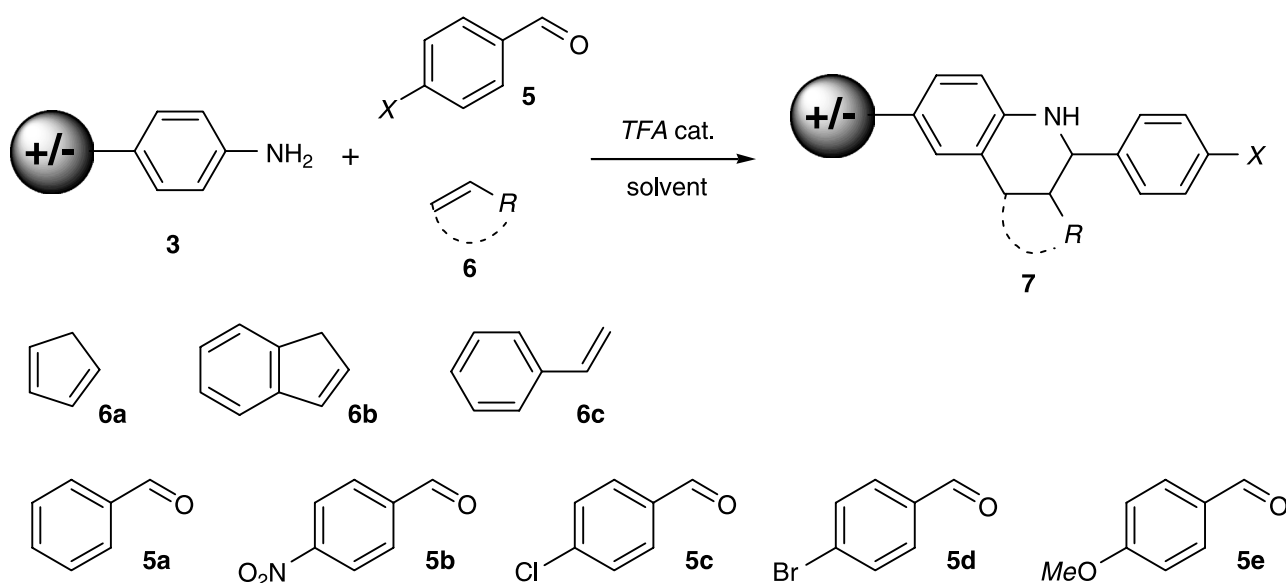
Grieco synthesis is a single pot multicomponent reaction between anilines, aldehydes, and electron-rich alkenes providing tetrahydroquinolines in high

yields [23]. Mild catalytic conditions (often using lanthanide triflates) [24], could be used and were compatible with a wide range of aldehydes and anilines, therefore easily providing tetrahydroquinolines with large diversity.

In our case, we decided to support on onium salts two of the three possible partners, namely the aniline and the benzaldehyde. Starting from trimethyl-3-hydroxypropylammonium chloride (**1**) both supported reagents were prepared in few high yielding steps. Supported aniline was synthesized by coupling 4-nitrobenzoic acid with alcohol **1** followed by hydrogenative reduction of **2a** into the aniline. If necessary, preparation of the triflimide onium salts was achieved by ion metathesis with lithium triflimide in water providing aniline **3** in 83% overall yield (3 steps). Similarly, aldehyde **2b** was prepared by simply coupling of 4-formylbenzoic acid with alcohol **1** under standard conditions. Tetrafluoroborate salt **4** was subsequently obtained by simple treatment with aqueous tetrafluoroboric acid in 90% yield after 2 steps.



Scheme 1



Scheme 2

Table 1. Grieco's reaction using onium salt supported aniline

Entry	X	Olefin	Solvent	Time/h	Product	Conv/% ^a (Yield/%) ^b
1	H 5a	6a	[<i>tmba</i>][NTf ₂]	0.5	7aa	100 (77) ^c
2	H 5a	6a	[HO(CH ₂) ₃ NMe ₃][NTf ₂]	0.5	7aa	100
3	H 5a	6a	CH ₃ CN	0.4	7aa	100 (70)
4	NO ₂ 5b	6a	[<i>tmba</i>][NTf ₂]	0.5	7ba	100 (90) ^c
5	Cl 5c	6a	[<i>tmba</i>][NTf ₂]	0.5	7ca	100
6	Br 5d	6a	[<i>tmba</i>][NTf ₂]	0.5	7da	100 (88) ^c
7	OMe 5e	6a	[<i>tmba</i>][NTf ₂]	0.5	7ea	100
8	NO ₂ 5b	6a	CH ₃ CN	0.4	7ba	100 (93)
9	Cl 5c	6a	CH ₃ CN	0.4	7ca	100 (89)
10	Br 5d	6a	CH ₃ CN	0.4	7da	100 (90)
11	OMe 5e	6a	CH ₃ CN	1.25	7ea	100 (67)
12	NO ₂ 5b	6b	CH ₃ CN	0.5	7bb	100 (85)
13	Br 5d	6b	CH ₃ CN	0.5	7db	100 (83)
14	NO ₂ 5b	6c	CH ₃ CN	0.75	7bc	100 (79)
15	Br 5d	6c	CH ₃ CN	0.75	7dc	100 (86)

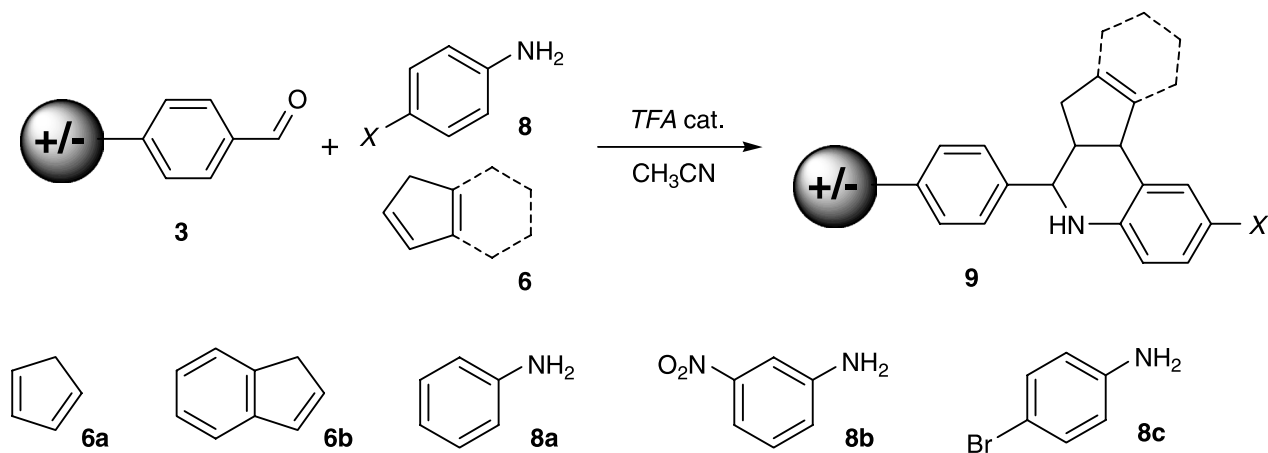
^a Measured by ¹H NMR ^b isolated yield after purification ^c isolated after cleavage from support

Use of Supported Aniline in the Grieco Reaction

We decided next to tackle the core of the project by engaging supported aniline in the *Grieco* reaction with an aldehyde and an electron-rich olefin. Several solvents were investigated in the presence of a catalytic amount of trifluoroacetic acid. The reaction was found to be efficient in both molecular solvents like acetonitrile and ionic liquids, such as [*tmba*][NTf₂] (trimethylbutylammonium triflimide) (Table 1, entries 1–3).

Reaction applicability was investigated simultaneously in [*tmba*][NTf₂] (entries 4–7) and acetonitrile

(entries 8–15). To our delight, most benzaldehydes (entries 4–6) were highly reactive (100% conversion after 30 min) with cyclopentadiene **6a** and supported aniline. For example, condensation with 4-nitrobenzaldehyde (entry 4), 4-bromobenzaldehyde (entry 5), and 4-chlorobenzaldehyde (entry 6) proceeds smoothly affording supported tetrahydroquinolines in 30 min. Reaction was slightly slower using benzaldehyde bearing electron-donating groups, although 82% conversion was obtained after 75 min in the case of 4-methoxybenzaldehyde (entry 7). In acetonitrile, similarly to [*tmba*][NTf₂] most reactions



Scheme 3

appeared to be quantitative after a short 20 min reaction time. With 4-nitro (entry 8), 4-chloro (entry 9), and 4-bromobenzaldehyde (entry 10), the reaction was efficiently leading to expected products in good to excellent yields. Using electron rich 4-methoxybenzaldehyde (entry 11), like previously mentioned, reaction was slower albeit affording the expected product in a good 67% yield after 75 min. Other olefins were used, such as indene (**6b**) or styrene (**6c**). With respects to the olefin, tetrahydroquinolines were equally obtained in less than an hour in good yields (entries 12–15). In all cases, the products were purified by filtration followed by washing with Et_2O , which eliminates unreacted reagents and eventual non-supported side products. This procedure simplifies to a large extent previously reported methodologies for multicomponent reactions in homogeneous phase as no complicated purification was needed. Moreover, reactions could be easily monitored by ^1H NMR unlike the solid phase synthesis.

Use of Supported Benzaldehyde in Grieco Reaction

Similarly, supported benzaldehyde **4** was engaged under the same reaction conditions. After 2 h, quan-

titative conversions were obtained using both cyclopentadiene (**6a**) (entry 1) and indene (**6b**) (entry 4). Various anilines **8** were tested, bearing nitro (entry 2) or bromide (entry 3) substituents affording tetrahydroquinolines in good yields.

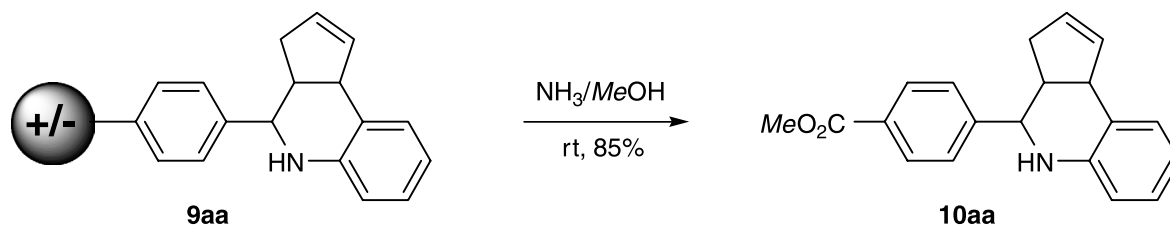
Like previously mentioned, products **9** were purified after reaction by simple filtration followed by washing with Et_2O . Concerning cleavage from the support, simple treatment by NH_3 in methanol afforded methyl ester **10aa** in good yield.

Onium salts supported organic synthesis turned out to be particularly suitable in the *Grieco* multicomponent reaction. A wide variety of tetrahydroquinolines were obtained with quantitative conversion in a short

Table 2. *Grieco's* reaction using onium salt supported benzaldehyde

Entry	Aniline	Olefin	Time/ h	Product	Conv/ % ^a	Yield/ % ^b
1	8a	6a	2	9aa	100	77
2	8b	6a	2	9ba	100	90
3	8c	6a	2	9ca	100	88
4	8c	6b	2	9cb	100	92

^a Measured by NMR ^1H ^b isolated yield after purification



Scheme 4

period of time. We showed that supporting both anilines and aldehydes could be envisioned in this strategy. Both supports synthesis turned out to be high yielding, and only simple workup (filtration and wash) was needed to obtain a good purity. Furthermore, unlike traditional solid phase supported versions of this reaction, kinetics were increased and no large excess of reagent was needed to drive the reaction to completion.

Experimental

General Methods

All reactions were carried out using standard *Schlenk* techniques under argon. Acetonitrile and ether were carefully dried and distilled prior to use. All other standard chemicals were purchased from ACROS Chimica or Aldrich Chemical Co., and used without further purification. Reactions were monitored by gas chromatography (GC-MS) (GC system: HP 6890 series, mass selective detector HP 5973) using a capillary column DB-5MS. Column chromatography purifications were performed on silica gel Si 60 (40–63 μm , 230–400 mesh, Merck). Melting points were determined on an electrothermal IA9300 digital melting point instrument. NMR spectra were recorded on a Bruker ARX 200 (^1H : 200.13 MHz, ^{13}C : 50.32 MHz) or AC 300 (^1H : 300.13 MHz), ^1H chemical shifts (δ) are given in ppm relative to TMS as internal standard, J values in Hz; ^{13}C chemical shifts are given relative to the central signal of CDCl_3 at 77.0 ppm. High resolution mass spectra measurements were performed at the Centre Regional de Mesures Physiques de l'Ouest (C. R. M. P. O., University of Rennes 1) using a Micromass ZABSpec TOF with EBE OA TOF geometry with LSIMS Ionization (Liquid Secondary Ion Mass Spectrometry) at 8 kV with Cs^+ gun in *m*-nitrobenzyl alcohol (*mNBA*).

[3-(4-Aminobenzoyloxy)propyl]trimethylammonium bistrifluoromethanesulfonamide (**3**, $\text{C}_{28}\text{H}_{42}\text{F}_6\text{N}_5\text{O}_8\text{S}_2$)

To a mixture of 5.00 g alcohol **1** (32.57 mmol) in 100 cm^3 dry acetonitrile were added DCC (48.5 mmol, 1.5 equ.), 4-nitrobenzoic acid (48.5 mmol, 1.5 equ.), and DMAP (6.52 mmol, 0.2 equ.). After 4 h at room temperature, solvents were removed under vacuum and product was extracted with $3 \times 30 \text{ cm}^3 \text{ Et}_2\text{O}$ to afford an oil used without further purification in the next step. ^1H NMR (200 MHz, D_2O): δ = 2.18–2.43 (m, 2H), 3.15 (s, 9H), 3.38–3.60 (m, 2H), 4.43 (t, 2H, J = 5.8 Hz), 8.02 (dd, 2H, J_1 = 1.9 Hz, J_2 = 7.1 Hz), 8.18 (dd, 2H, J_1 = 2.1 Hz, J_2 = 6.9 Hz) ppm; ^{13}C NMR (50 MHz, D_2O): δ = 22.6, 53.5 (t, $J_{\text{C-N}}$ = 4.0 Hz), 63.4, 64.1, 123.8, 130.9, 134.94, 150.3, 166.0 ppm. A solution of **2a** (8.5 g) in 100 cm^3 water with Pd/C (1%, 5% on C) was stirred under hydrogen atmosphere (5 bar) for 48 h. After filtration and concentration under reduced pressure, 6.95 g of a white solid were obtained (90% yield, two steps) corresponding to *N,N,N*-trimethyl-*N*-3-(4-nitrobenzoyloxypropyl)ammonium chloride as shown by ^1H and ^{13}C NMR. Mp 120–122°C; ^1H NMR

(200 MHz, D_2O): δ = 2.10–2.25 (m, 2H), 3.09 (s, 9H), 3.32–3.45 (m, 2H), 4.48 (t, 2H, J = 6.1 Hz), 6.75 (d, 2H, J = 7.8 Hz), 7.72 (d, 2H, J = 7.8 Hz) ppm; ^{13}C NMR (50 MHz, D_2O): δ = 22.6, 53.47 (t, $J_{\text{C-N}}$ = 4.1 Hz), 61.9, 64.2, 114.9, 118.2, 132.0, 153.0, 168.8 ppm; HRMS (FAB) $\text{C}_{13}\text{H}_{21}\text{N}_2\text{O}_2$: calcd. 237.1603, found 237.1603. To an aqueous solution (300 cm^3) of this solid (6.95 g) was added an aqueous solution of lithium bistrifluoromethanesulfonamide (1.1 equ.) in 300 cm^3 . After 2 h at room temperature, the mixture was extracted with $3 \times 200 \text{ cm}^3 \text{ CH}_2\text{Cl}_2$. Organic phases were assembled, dried over Na_2SO_4 , and after filtration and concentration under reduced pressure, 20.5 g of a white powder were obtained. Yield 93%; mp 109–110°C; ^1H NMR (200 MHz, Acetone- d_6): δ = 2.35–2.51 (m, 2H), 3.41 (s, 9H), 3.78–3.92 (m, 2H), 4.50 (t, 2H, J = 6.1 Hz), 5.51 (br, 2H), 6.58 (d, 2H, J = 7.9 Hz), 7.84 (d, 2H, J = 7.7 Hz) ppm; ^{13}C NMR (50 MHz, Acetone- d_6): δ = 24.2, 54.1 (t, $J_{\text{C-N}}$ = 4.1 Hz), 61.7, 65.6, 114.2, 118.3, 121.2 (q, $J_{\text{C-F}}$ = 320 Hz), 132.7, 154.7, 167.1 ppm; HRMS (FAB) $\text{C}_{28}\text{H}_{42}\text{F}_6\text{N}_5\text{O}_8\text{S}_2$: calcd. 754.2379, found 754.2379.

[3-(4-Formylbenzoyloxy)propyl]trimethylammonium tetrafluoroborate (**4**, $\text{C}_{14}\text{H}_{20}\text{NO}_3\text{BF}_4$)

To a solution of 2 g **1** (13 mmol) in 100 $\text{cm}^3 \text{ CH}_3\text{CN}$ were added DCC (19.5 mmol, 1.5 equ.), 4-formylbenzoic acid (19.5 mmol, 1.5 equ.) and DMAP (2.6 mmol, 0.2 equ.). After 2 h at room temperature, solvent was removed and the residue was extracted with $3 \times 30 \text{ cm}^3 \text{ H}_2\text{O}$. To this solution was added a 50% aqueous solution of HBF_4 (19.5 mmol, 1.5 equ.) and after 2 h at room temperature, a yellow precipitate formed. The suspension was filtered and yellow crystals were washed with 20 $\text{cm}^3 \text{ H}_2\text{O}$ then $2 \times 20 \text{ cm}^3 \text{ Et}_2\text{O}$ to afford 2.92 g of a pale yellow solid. Yield 90%; mp 146–148°C; ^1H NMR (200 MHz, CD_3CN): δ = 2.10–2.33 (m, 2H), 3.05 (s, 9H), 3.36–3.55 (m, 2H), 4.45 (t, 2H, J = 5.8 Hz), 8.00 (dd, 2H, J = 1.6, 6.6 Hz), 8.13 (dd, 2H, J = 1.4, 8.3 Hz), 10.10 (s, 1H) ppm; ^{13}C NMR (50 MHz, CD_3CN): δ = 22.1, 52.7 (t, J = 3.8 Hz), 61.5, 63.5 (t, J = 3.0 Hz), 129.1, 129.8, 134.4, 139.3, 164.9, 192.0 ppm; MS (APCI) m/z = 250.3 (C^+).

General Procedure for Grieco Condensation with Supported Aniline **3** (Procedure A)

To a solution of amine **3** (100 mg) in 2 $\text{cm}^3 \text{ CH}_3\text{CN}$ were successively added aldehyde (1.1 equ.), olefin (10 equ.), and TFA (1.2 equ.). After 2 h at room temperature, volatiles were removed under reduced pressure. Upon addition of Et_2O , the residue crystallized. Crystals were filtered off and washed with $3 \times 2 \text{ cm}^3 \text{ Et}_2\text{O}$ to afford product in pure form.

General Procedure for Grieco Condensation with Supported benzaldehyde **4** (Procedure B)

To a solution of aldehyde **4** (100 mg) in 2 $\text{cm}^3 \text{ CH}_3\text{CN}$ were successively added aniline (1.1 equ.), olefin (10 equ.), and TFA (1.2 equ.). After 2 h at room temperature, solvent was removed under reduced pressure. Upon addition of Et_2O , the residue crystallized. Crystals were filtered off and washed with $3 \times 2 \text{ cm}^3 \text{ Et}_2\text{O}$ to afford product in pure form.

[3-[4-Phenyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]-quinoline-8-carbonyloxy]propyl]trimethylammonium bistrifluoromethanesulfonamide (7aa, C₂₉H₃₅F₆N₃O₆S₂)

Following procedure A using benzaldehyde **5a** and cyclopentadiene **6a** provided expected product **7aa** as a solid in 70% yield; mp 118–120°C; ¹H NMR (300 MHz, acetone-*d*₆): δ = 1.65–1.84 (m, 1H), 2.38–2.64 (m, 3H), 2.96–3.15 (m, 1H), 3.45 (s, 9H), 3.73–3.90 (m, 2H), 4.10–4.22 (m, 1H), 4.42 (t, 2H, *J* = 5.8 Hz), 4.70–4.80 (m, 1H), 5.58–5.65 (m, 1H), 5.70–5.80 (m, 1H), 5.93–6.05 (m, 1H), 6.85 (d, 1H, *J* = 8.4 Hz), 7.25–7.75 (m, 7H) ppm; ¹³C NMR (50 MHz, acetone-*d*₆): δ = 24.2, 32.7, 46.8, 47.2, 54.2 (t, *J*_{C–N} = 3.9 Hz), 58.1, 61.9, 65.6, 116.4, 120.2, 121.4 (q, *J*_{C–F} = 321 Hz), 126.0, 127.8, 128.4, 129.4, 129.6, 131.2, 132.3, 135.6, 143.5, 152.5, 167.1 ppm; MS (APCI): *m/z* = 391.4 (C+).

[3-[4-(Nitrophenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]-quinoline-8-carbonyloxy]propyl]trimethylammonium bistrifluoromethanesulfonamide (7ba, C₂₉H₃₄F₆N₄O₈S₂)

Following procedure A using 4-nitrobenzaldehyde **5b** and cyclopentadiene **6a** provided expected product **7ba** as a solid in 93% yield; mp 132–134°C; ¹H NMR (300 MHz, acetone-*d*₆): δ = 1.55–1.80 (m, 1H), 2.35–2.58 (m, 3H), 3.01–3.20 (m, 1H), 3.40 (s, 9H), 3.70–3.90 (m, 2H), 4.10–4.22 (m, 1H), 4.42 (t, 2H, *J* = 5.8 Hz), 4.90–5.00 (m, 1H), 5.58–5.65 (m, 1H), 5.70–5.80 (m, 1H), 5.93–6.05 (m, 1H), 6.90 (d, 1H, *J* = 8.6 Hz), 7.60–7.95 (m, 4H), 8.28 (d, 2H, *J* = 8.6 Hz) ppm; ¹³C NMR (50 MHz, acetone-*d*₆): δ = 24.2, 32.5, 46.6, 46.7, 54.2 (t, *J*_{C–N} = 4.0 Hz), 57.7, 62.0, 65.4, 116.7, 120.1 (q, *J*_{C–F} = 321 Hz), 120.7, 124.7, 126.0, 129.0, 129.4, 131.0, 132.3, 135.5, 148.5, 151.4, 151.8, 167.0 ppm; MS (APCI): *m/z* = 436.1 (C+).

[3-[4-(Chlorophenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]-quinoline-8-carbonyloxy]propyl]trimethylammonium bistrifluoromethanesulfonamide (7ca, C₂₉H₃₄ClF₆N₃O₆S₂)

Following procedure A using 4-chlorobenzaldehyde **5c** and cyclopentadiene **6a** provided expected product **7ca** as a solid in 89% yield; mp 202–204°C; ¹H NMR (300 MHz, acetone-*d*₆): δ = 1.60–1.80 (m, 1H), 2.35–2.58 (m, 3H), 3.01–3.20 (m, 1H), 3.40 (s, 9H), 3.70–3.90 (m, 2H), 4.10–4.22 (m, 1H), 4.42 (t, 2H, *J* = 5.8 Hz), 4.90–5.00 (m, 1H), 5.58–5.65 (m, 1H), 5.70–5.80 (m, 1H), 5.93–6.05 (m, 1H), 6.85 (d, 1H, *J* = 8.4 Hz), 7.30–7.70 (m, 6H) ppm; ¹³C NMR (50 MHz, acetone-*d*₆): δ = 24.2, 32.6, 46.7, 47.0, 54.2 (t, *J*_{C–N} = 4.0 Hz), 57.5, 61.9, 65.5, 116.5, 120.4, 121.4 (q, *J*_{C–F} = 321 Hz), 125.9, 129.4, 129.5, 129.6, 131.1, 132.3, 133.6, 135.6, 142.6, 152.2, 167.1 ppm; MS (APCI): *m/z* = 425.3 (C+).

[3-[4-(Bromophenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]-quinoline-8-carbonyloxy]propyl]trimethylammonium bistrifluoromethanesulfonamide (7da, C₂₉H₃₄BrF₆N₃O₆S₂)

Following procedure A using 4-bromobenzaldehyde **5d** and cyclopentadiene **6a** provided expected product **7da** as a solid in 90% yield; mp 122–124°C; ¹H NMR (300 MHz, acetone-*d*₆): δ = 1.60–1.80 (m, 1H), 2.35–2.58 (m, 3H), 3.01–3.20 (m, 1H), 3.40 (s, 9H), 3.70–3.90 (m, 2H), 4.10–4.22 (m, 1H),

4.42 (t, 2H, *J* = 5.8 Hz), 4.90–5.00 (m, 1H), 5.58–5.65 (m, 1H), 5.70–5.80 (m, 1H), 5.93–6.05 (m, 1H), 6.85 (d, 1H, *J* = 8.4 Hz), 7.30–7.70 (m, 6H) ppm; ¹³C NMR (50 MHz, acetone-*d*₆): δ = 24.2, 32.6, 46.7, 46.9, 54.2 (t, *J*_{C–N} = 4.0 Hz), 57.5, 61.9, 65.5, 116.5, 120.4, 121.4 (q, *J*_{C–F} = 321 Hz), 121.6, 125.9, 129.4, 129.9, 131.1, 132.3, 132.6, 135.6, 143.0, 152.2, 167.1 ppm; MS (APCI): *m/z* = 470.1 (C+).

[3-[4-(Methoxyphenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]-quinoline-8-carbonyloxy]propyl]trimethylammonium bistrifluoromethanesulfonamide (7ea, C₃₀H₃₇F₆N₃O₇S₂)

Following procedure A using 4-methoxybenzaldehyde **5e** and cyclopentadiene **6a** provided expected product **7ea** as a yellowish solid in 67% yield. ¹H NMR (300 MHz, acetone-*d*₆): δ = 1.60–1.78 (m, 1H), 2.32–2.54 (m, 3H), 2.93–3.14 (m, 1H), 3.38 (s, 9H), 3.64–3.74 (m, 2H), 3.85 (s, 3H), 4.01–4.11 (m, 1H), 4.17 (t, 2H, *J* = 5.8 Hz), 4.58 (s, 1H), 5.51–5.61 (m, 1H), 5.69–5.77 (m, 1H), 5.82–5.88 (m, 1H), 6.87 (d, 1H, *J* = 8.3 Hz), 7.42 (d, 2H, *J* = 8.5 Hz), 7.51 (d, 2H, *J* = 8.5 Hz), 7.63 (dd, 1H, *J*₁ = 1.4 Hz, *J*₂ = 8.3 Hz), 7.73 (s, 1H) ppm; ¹³C NMR (300 MHz, acetone-*d*₆): δ = 22.1, 38.3, 45.3, 45.8, 53.1 (t, *J*_{C–N} = 4 Hz), 55.0, 56.3, 61.7, 63.7, 114.8, 118.3, 121.2, 121.4 (q, *J*_{C–F} = 321 Hz), 124.5, 127.8, 128.0, 128.1, 129.6, 130.8, 132.4, 133.9, 148.9, 158.1, 165.5 ppm; MS (APCI): *m/z* = 421.2 (C+).

[3-[6-(4-Nitrophenyl)-5,6a,7,11b-tetrahydro-6H-indeno[2,1-c]quinoline-2-carbonyloxy]propyl]trimethylammonium bistrifluoromethanesulfonamide (7bb, C₃₃H₃₆F₆N₄O₈S₂)

Following procedure A using 4-nitrobenzaldehyde **5b** and indene **6b** provided expected product **7bb** as a solid in 85% yield; mp 122–124°C; ¹H NMR (300 MHz, acetone-*d*₆): δ = 2.23–2.38 (m, 1H), 2.40–2.54 (m, 2H), 3.05–3.38 (m, 2H), 3.45 (s, 9H), 3.78–3.90 (m, 2H), 4.30–4.54 (m, 2H), 4.60 (d, 1H, *J* = 7.5 Hz), 5.04–5.12 (m, 1H), 6.15–6.20 (m, 1H), 6.83 (d, 1H, *J* = 8.3 Hz), 7.02–7.13 (m, 3H), 7.60–7.70 (m, 2H), 7.85 (d, 2H, *J* = 9.1 Hz), 7.95–8.01 (m, 1H), 8.30 (d, 2H, *J* = 9.1 Hz) ppm; ¹³C NMR (50 MHz, acetone-*d*₆): δ = 24.2, 32.1, 46.7, 48.5, 54.2 (t, *J*_{C–N} = 3.9 Hz), 57.1, 57.2, 61.9, 65.5, 116.2, 120.2, 121.4 (q, *J*_{C–F} = 321 Hz), 123.3, 124.7, 126.1, 126.3, 127.8, 128.4, 129.1, 129.5, 129.8, 133.1, 143.4, 147.4, 148.6, 151.2, 151.3, 167.0 ppm; MS (APCI): *m/z* = 486.6 (C+).

[3-[6-(4-Bromophenyl)-5,6a,7,11b-tetrahydro-6H-indeno[2,1-c]quinoline-2-carbonyloxy]propyl]trimethylammonium bistrifluoromethanesulfonamide (7db, C₃₃H₃₆BrF₆N₃O₆S₂)

Following procedure A using 4-bromobenzaldehyde **5d** and indene **6b** provided expected product **7db** as a yellow solid in 83% yield. ¹H NMR (300 MHz, acetone-*d*₆): δ = 2.15–2.36 (m, 2H), 2.98–3.05 (m, 2H), 3.37 (s, 9H), 3.38–3.44 (m, 2H), 4.17 (t, 2H, *J* = 5.6 Hz), 4.34 (m, 1H), 4.73 (bl, 1H), 6.24 (d, 1H, *J* = 8.3 Hz), 6.94 (m, 1H), 7.01–7.21 (m, 3H), 7.27 (s, 1H), 7.46–7.74 (m, 2H), 8.05 (d, 2H, *J* = 8.3 Hz) ppm; ¹³C NMR (75 MHz, acetone-*d*₆): δ = 22.1, 38.2, 45.1, 45.7, 53.1 (t, *J*_{C–N} = 4 Hz), 54.9, 61.7, 63.8, 114.0, 121.4 (q, *J*_{C–F} = 321 Hz), 121.5, 123.8, 125.2, 125.8, 126.5, 127.3, 127.4, 127.6,

129.0, 129.9, 137.3, 142.0, 145.9, 146.3, 150.1, 165.9 ppm; MS (APCI): $m/z = 519.1$ (C+).

{3-[2-(4-Nitrophenyl)-4-phenyl-1,2,3,4-tetrahydroquinoline-6-carbonyloxy]propyl}trimethylammonium bistrifluoromethanesulfonamide (7bc, C₃₂H₃₆F₆N₄O₈S₂)

Following procedure A using 4-nitrobenzaldehyde **5b** and styrene **6c** provided expected product **7bc** as a yellow solid in 79% yield; mp 128–130°C; ¹H NMR (300 MHz, acetone-*d*₆): $\delta = 2.10$ – 2.28 (m, 1H), 2.30 – 2.43 (m, 3H), 3.38 (s, 9H), 3.42 – 3.48 (m, 1H), 3.62 – 3.75 (m, 2H), 4.28 (t, 2H, $J = 5.7$ Hz), 4.32 – 4.42 (m, 1H), 4.90 – 5.01 (m, 1H), 6.80 (d, 1H, $J = 8.7$ Hz), 7.23 – 7.44 (m, 6H), 7.60 – 7.70 (m, 1H), 7.82 (d, 2H, $J = 8.7$ Hz), 8.25 (d, 2H, $J = 9.1$ Hz) ppm; ¹³C NMR (50 MHz, acetone-*d*₆): $\delta = 24.1$, 42.0 , 45.2 , 54.2 (t, $J_{C-N} = 4.0$ Hz), 57.2 , 65.4 (t, $J_{C-N} = 3.2$ Hz), 114.8 , 118.7 , 121.4 (q, $J_{C-F} = 321$ Hz), 124.9 , 124.9 , 125.2 , 128.1 , 129.1 , 130.0 , 130.0 , 130.3 , 130.5 , 132.4 , 145.7 , 148.8 , 151.3 , 152.6 , 167.0 ppm; MS (APCI): $m/z = 474.3$ (C+).

{3-[2-(4-Bromophenyl)-4-phenyl-1,2,3,4-tetrahydroquinoline-6-carbonyloxy]propyl}trimethylammonium bistrifluoromethanesulfonamide (7dc, C₃₂H₃₆BrF₆N₃O₆S₂)

Following procedure A using 4-bromobenzaldehyde **5d** and styrene **6c** provided expected product **7dc** as a solid in 86% yield. ¹H NMR (300 MHz, acetone-*d*₆): $\delta = 2.09$ – 2.18 (m, 1H), 2.40 – 2.52 (m, 3H), 3.37 (s, 9H), 3.40 – 3.45 (m, 1H), 3.62 – 3.75 (m, 2H), 4.20 (t, 2H, $J = 5.7$ Hz), 4.28 – 4.39 (m, 1H), 4.90 – 5.01 (bl, 1H), 6.85 (d, 1H, $J = 8.7$ Hz), 7.18 – 7.23 (m, 9H), 7.60 – 7.65 (m, 1H), 7.82 (s, 1H) ppm; ¹³C NMR (75 MHz, acetone-*d*₆): $\delta = 24.1$, 38.2 , 42.0 , 46.1 , 54.2 (t, $J_{C-N} = 4.0$ Hz), 59.9 , 65.1 (t, $J_{C-N} = 3.2$ Hz), 114.8 , 118.7 , 121.4 (q, $J_{C-F} = 321$ Hz), 124.9 , 125.1 , 125.9 , 128.1 , 129.14 , 129.8 , 130.5 , 130.7 , 131.0 , 132.4 , 145.7 , 148.8 , 151.4 , 152.6 , 165.6 ppm.

{3-[4-(3a,4,5,9b-Tetrahydro-3H-cyclopenta[c]quinolin-4-yl)benzoyloxy]propyl}trimethylammonium tetrafluoroborate (9aa, C₂₇H₃₁F₆N₃O₆S₂)

Following procedure B using aniline **8a** and cyclopentadiene **6a** provided expected product **9aa** as a solid in 77% yield; mp 186–188°C; ¹H NMR (300 MHz, acetone-*d*₆): $\delta = 1.58$ – 1.75 (m, 1H), 2.40 – 2.64 (m, 3H), 2.77 – 2.98 (br, 1H), 3.00 – 3.15 (m, 1H), 3.40 (s, 9H), 3.77 – 3.92 (m, 2H), 4.03 – 4.15 (m, 1H), 4.46 (t, 2H, $J = 5.9$ Hz), 4.68 – 4.76 (m, 1H), 5.55 – 5.62 (m, 1H), 5.81 – 5.92 (m, 1H), 6.58 – 7.13 (m, 4H), 7.60 (d, 2H, $J = 8.3$ Hz), 8.05 (d, 2H, $J = 8.4$ Hz) ppm; ¹³C NMR (50 MHz, acetone-*d*₆): $\delta = 23.6$, 32.2 , 46.7 , 47.1 , 53.7 (t, $J_{C-N} = 3.8$ Hz), 58.2 , 62.4 , 64.8 , 117.0 , 119.5 , 126.5 , 126.9 , 127.6 , 129.5 , 129.6 , 130.2 , 130.4 , 135.4 , 146.9 , 149.8 , 166.6 ppm; MS (APCI): $m/z = 391.4$ (C+).

{3-[4-(9-Nitro-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)benzoyloxy]propyl}trimethylammonium tetrafluoroborate (9ba, C₂₇H₃₀F₆N₄O₈S₂)

Following procedure B using 3-nitroaniline **8b** and cyclopentadiene **6a** provided expected product **9ba** as a solid in 90%

yield; mp 186–188°C; ¹H NMR (300 MHz, acetone-*d*₆): $\delta = 1.58$ – 1.80 (m, 1H), 2.40 – 2.64 (m, 3H), 3.14 – 3.28 (m, 1H), 3.42 (s, 9H), 3.73 – 3.92 (m, 2H), 4.15 – 4.30 (m, 1H), 4.48 (t, 2H, $J = 6.0$ Hz), 4.65 – 4.78 (m, 1H), 5.48 – 5.60 (m, 1H), 5.63 – 5.78 (m, 1H), 5.85 – 6.00 (m, 1H), 7.03 – 7.25 (m, 2H), 7.58 – 7.76 (m, 3H), 7.98 – 8.12 (m, 2H) ppm; ¹³C NMR (50 MHz, acetone-*d*₆): $\delta = 23.6$, 32.3 , 44.2 , 46.2 , 46.5 , 47.0 , 53.7 , 57.2 , 57.6 , 62.4 , 64.9 , 64.9 , 111.0 , 113.5 , 115.0 , 119.5 , 121.4 , 127.7 , 129.8 , 130.5 , 131.9 , 132.8 , 148.8 , 166.5 ppm; MS (APCI): $m/z = 436.1$ (C+).

{3-[4-(8-Bromo-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)benzoyloxy]propyl}trimethylammonium tetrafluoroborate (9ca, C₂₇H₃₀BrF₆N₃O₆S₂)

Following procedure B using 4-bromoaniline **8c** and cyclopentadiene **6a** provided expected product **9ca** as a brownish solid in 88% yield; mp 190–192°C; ¹H NMR (300 MHz, acetone-*d*₆): $\delta = 1.54$ – 1.80 (m, 1H), 2.40 – 2.60 (m, 2H), 2.88 – 3.20 (m, 2H), 3.40 (s, 9H), 3.75 – 3.95 (m, 2H), 4.02 – 4.20 (m, 1H), 4.55 (t, 2H, $J = 5.9$ Hz), 4.72 – 4.80 (m, 1H), 5.58 – 5.75 (m, 1H), 5.7 – 5.8 (m, 1H), 5.93 – 6.05 (m, 1H), 6.70 – 6.81 (m, 1H), 7.01 – 7.30 (m, 2H), 7.65 (d, 2H, $J = 8.2$ Hz), 8.05 (d, 2H, $J = 8.3$ Hz) ppm; ¹³C NMR (50 MHz, acetone-*d*₆): $\delta = 22.5$, 31.2 , 45.1 , 45.8 , 53.0 (t, $J_{C-N} = 4.0$ Hz), 57.0 , 61.3 , 63.9 , 109.7 , 117.8 , 126.7 , 128.3 , 128.7 , 128.8 , 129.5 , 130.2 , 131.3 , 133.9 , 145.3 , 148.4 , 167.1 ppm; MS (APCI): $m/z = 470.1$ (C+).

{3-[4-(2-Bromo-5,6a,7,11b-tetrahydro-6H-indeno[2,1-c]quinolin-6-yl)benzoyloxy]propyl}trimethylammonium tetrafluoroborate (9cb, C₃₁H₃₂BrF₆N₃O₆S₂)

Following procedure B using 4-bromoaniline **8c** and indene **6b** provided expected product **9cb** as a yellow solid in 92% yield; mp 210–212°C; ¹H NMR (300 MHz, CD₃CN): $\delta = 2.15$ – 2.35 (m, 1H), 2.40 – 2.58 (m, 3H), 3.15 – 3.22 (m, 2H), 3.40 (s, 9H), 3.75 – 4.05 (m, 2H), 4.43 – 4.68 (m, 3H), 4.80 – 4.95 (m, 1H), 6.75 (d, 1H, $J = 8.6$ Hz), 6.95 – 7.22 (m, 3H), 7.40 – 7.75 (m, 4H), 7.92 – 8.85 (m, 3H) ppm; ¹³C NMR (75 MHz, CD₃CN): $\delta = 22.1$, 37.1 , 45.0 , 46.7 , 53.2 (t, $J_{C-N} = 4$ Hz), 55.6 , 61.7 , 62.7 , 114.9 , 121.6 , 123.8 , 125.2 , 125.4 , 126.5 , 127.2 , 127.4 , 127.6 , 129.0 , 129.9 , 137.3 , 142.0 , 145.9 , 147.3 , 152.6 , 166.0 ppm; MS (APCI): $m/z = 520.0$ (C+).

Methyl 4-(8-bromo-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl)benzoate CAS [347362-64-5] (10aa, C₂₀H₁₉NO₂)

To a solution of compound **9aa** (1 mmol) in methanol (2 cm³) was added commercial 7 N NH₃ solution in methanol (10 cm³). After vigorous stirring at 25°C for 18 h, the solvent was eliminated under reduced pressure. After extraction from residue using 3 × 30 cm³ Et₂O, combined organic fractions were concentrated under vacuum and subsequently purified by flash chromatography on silica gel 60F 254 (Merck) using CH₂Cl₂ as eluent. Concentration under reduced pressure afforded **10aa** in 85% yield as a white powder. ¹H NMR (200 MHz, CDCl₃): $\delta = 2.19$ – 2.25 (m, 1H), 2.40 – 2.52 (m, 1H), 3.15 – 3.24 (m, 1H), 3.96 (s, 3H), 4.02 – 4.12 (m, 1H), 4.54 (bl, 1H), 4.62

(m, 1H), 5.57–5.60 (m, 1H), 5.62–5.65 (m, 1H), 6.53–6.71 (m, 2H), 6.96–7.12 (m, 2H), 7.31 (d, 2H, $J = 8.7$ Hz), 7.82 (d, 2H, $J = 8.7$ Hz) ppm; APCI-MS: m/z MS (APCI): $m/z = 306.1$.

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