Metal-Free Addition of Benzyl Halides to Aldehydes Using Super Electron Donors: Access to 3,4-Dihydroisocoumarins and 1,2-Diarylethanols

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Metal-Free Addition of Benzyl Halides to Aldehydes Using Super Electron Donors: Access to 3,4-Dihydroisocoumarins and 1,2-Diarylethanols.

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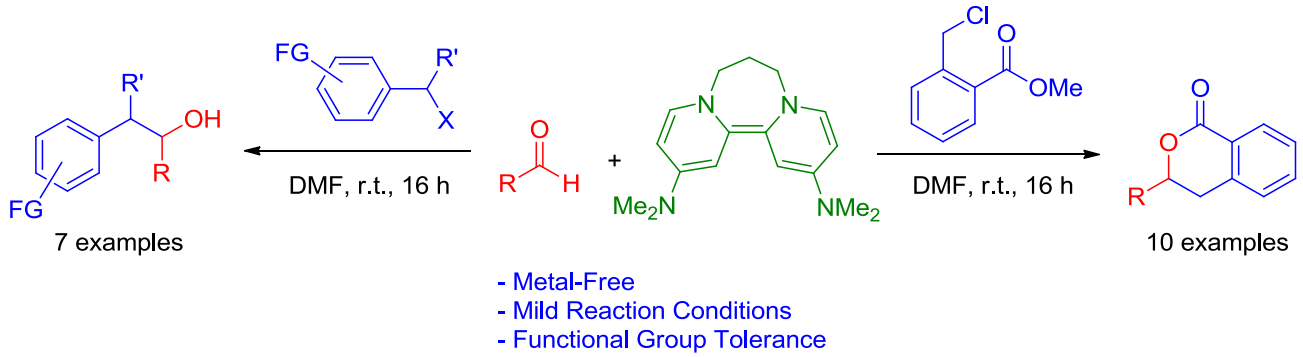


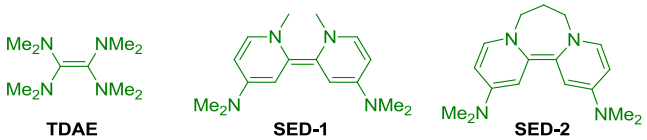
ABSTRACT: We report here the intermolecular metal-free addition reaction of functionalized benzyl halides to aldehydes using a super electron donor (SED). The metal-free and mild conditions allowed the formation of 3,4-dihydroisocoumarins and 1,2-diarylethanols with unprecedented functional group tolerance.

The 3,4-dihydroisocoumarin scaffold is found in several natural products and is known for its antimalarial, antituberculous, antifungal and antiproliferative properties.[1] The spatially related 1,2-diarylethanols are also structural motifs in natural products and biologically important molecules.[2] Thus, numerous strategies have been investigated to allow the construction of these skeletons.[3] Recently, the synthesis of a 3,4-dihydroisocoumarin was allowed by a metal-free intramolecular direct oxidative lactonization of carboxylic acids using iodine and a photoredox catalyst.[4] However, most of methodologies synthesizing 3,4-dihydroisocoumarins or 1,2-diarylethanols still need the use of strong bases or organometallics. One major limitation of these bases and these reactive organometallics of Mg, Li, Zn, Mn and Ti is their poor functional group tolerance.

Tetrakis(dimethylamino)ethylene (TDAE) is an organic reducing agent, which reacts with halogenated derivatives to generate a carbanion under mild conditions.[5] It was for a long period the most used organic electron donor (OED) thanks to its commercial availability. A comprehensive study of the reducing reactivity of TDAE revealed that a strong electron-withdrawing group (e.g. NO_2 or CN) is required on the benzylic substrate to reductively cleave the carbon-halogen bond. This constitutes the major drawback of this strategy. Since 2005, Murphy and co-workers developed new reducing agents with neutral organic structures and exceptionally negative redox potentials[6] (Figure 1). More recently, Dyker and co-workers, with a tetra(iminophosphorano)-substituted bispyridinylidene,[7] and Wenger and co-workers, using photoexcitation of TDAE,[8] improved even more the reduction potential of organic electron donors.

These "super electron donors" (SEDs) are capable of spontaneous Single Electron Transfer (SET) and Double Electron Transfer (DET) affording the formation of radicals or anions from non-activated benzyl halides, aryl halides, sulfones, triflate esters and triflamides.[9] They operate under mild conditions and are selective and tolerant to functional groups (nitro, carbonyl, ester, cyano …) compared to metallic reducers. Furthermore, the use of expensive metal derivatives that cause environmental and economic problems can be avoided. This approach resulted in excellent reducing agents that could be used for organic transformations. However, despite this important gain in reduction power, the reactivity of SEDs has been scarcely studied for carbon-carbon bond-forming reactions. SEDs have been recently used as initiators of base-induced homolytic aromatic substitution (BHAS) for the carbon-carbon coupling of haloarenes and arenes.[10] However, in the role of reducer for the generation of key active species for addition reactions to electrophiles, only intramolecular reactions have been hitherto described.[6,11]

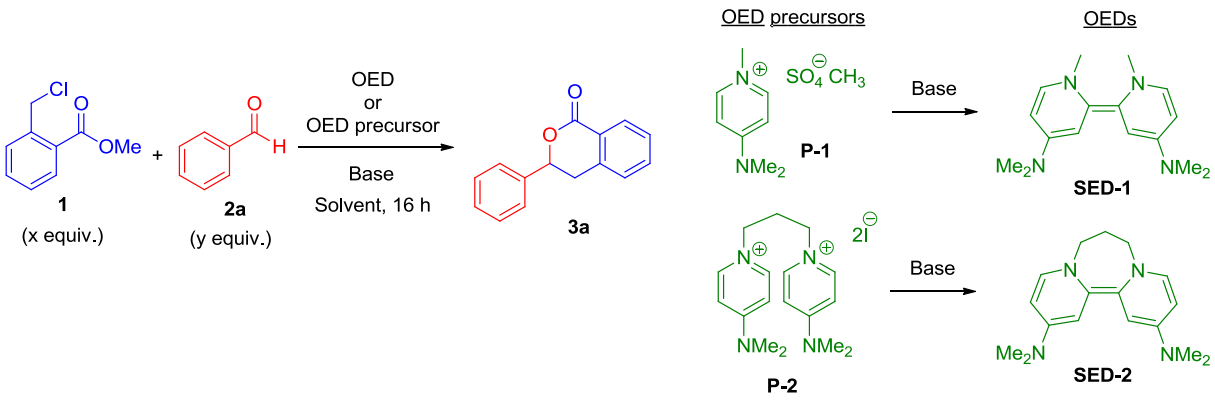
Figure 1. Example of Organic Electron Donors



Our aim was to determine if these SEDs could allow intermolecular addition reactions of diversely functionalized benzyl halides to aldehydes under metal-free and mild conditions.

The reaction between methyl 2-(chloromethyl)benzoate **1** and benzaldehyde **2a** in presence of an OED was selected as a benchmark reaction (Table 1). As expected, the commercially available TDAE was not powerful enough to reduce the benzyl chloride derivative **1** (Table 1, entry 1). The low reactivity of methyl 2-(chloromethyl)benzoate **1** to TDAE compared to nitro or cyano benzyl halides can be explained by the lower electron-withdrawing effect of ester compared to NO_2 or CN. This renders the methyl 2-(chloromethyl)benzoate **1** more difficult to reduce compared to nitro or cyano benzyl halides. Interestingly, the more powerful **SED-1**, *in situ* generated from pyridinium precursor salt **P-1** and a strong base like KHMDS, allowed the reduction of the methyl 2-(chloromethyl)benzoate **1** in DMF. The nucleophilic addition of the benzylic anion to benzaldehyde **2a**, followed by intramolecular cyclisation of the alcoholate on the ester gave the 3,4-dihydroisocoumarin **3a** in 39% yield (entry 2). This nucleophilic addition on an aldehyde moiety of the reduced benzylic species confirms the generation of an anion by DET rather than a benzyl radical. Indeed, radical addition to carbonyls is a reversible process due to the formation of a thermodynamically unfavorable alkoxy radical.[12] We next investigated the effect of the solvent and only traces of product were obtained in acetonitrile and tetrahydrofuran (entries 3–4). Using more equivalents (entry 5) or less equivalents (entry 6) of **P-1** and KHMDS were detrimental to the reaction. Using methyl 2-(chloromethyl)benzoate **1** in excess compared to benzaldehyde **2a** was not beneficial (entry 7). The amount of solvent slightly influenced the reaction (entry 2 *vs* entry 8). Changing the temperature of the reaction (entries 9–10) showed that room temperature advantageously remains the best choice. No significant influence of the base was observed using either KHMDS or NaH (entry 8 *vs* entry 11). **SED-2**, *in situ* generated from pyridinium precursor salt **P-2** and KHMDS, was also tested in the reaction and a slightly better yield was obtained (45%, entry 12). Finally, directly using the isolated **SED-2** gave an improved yield of 64% (entry 13).

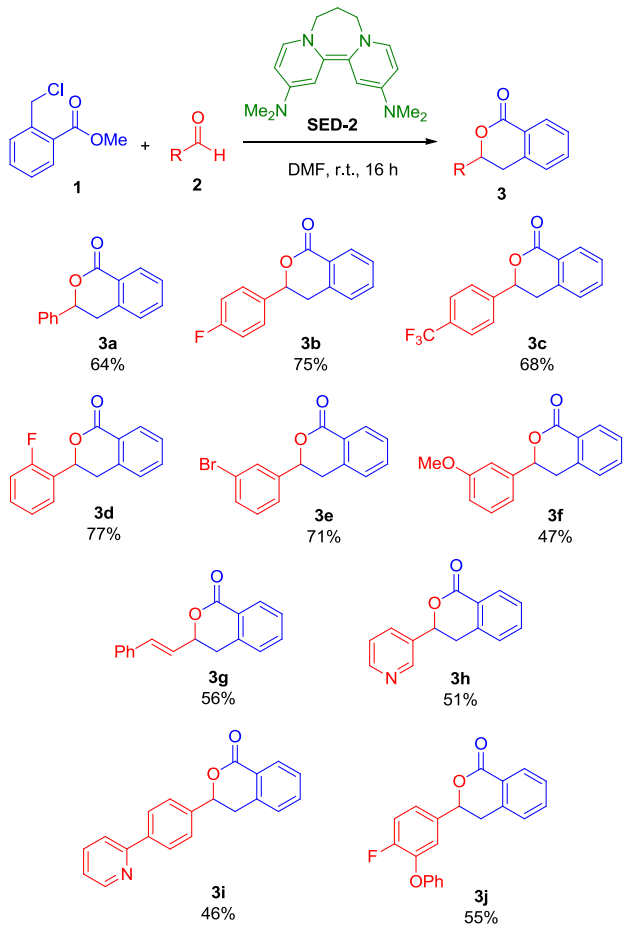
Table 1. Optimization of Reaction Conditions



Entry	x equiv.	y equiv.	OED or OED precursor (equiv.)	Base (equiv.)	Solvent [M]	T(°C)	Yield (%)
1	1	3	TDAE (3)	-	DMF [0.04]	rt	0
2	1	3	**P-1** (3)	KHMDS (3)	DMF [0.04]	rt	39
3	1	3	**P-1** (3)	KHMDS (3)	MeCN [0.04]	rt	traces
4	1	3	**P-1** (3)	KHMDS (3)	THF [0.04]	rt	traces
5	1	3	**P-1** (10)	KHMDS (10)	DMF [0.04]	rt	20
6	1	3	**P-1** (2)	KHMDS (2)	DMF [0.04]	rt	11
7	2	1	**P-1** (4)	KHMDS (4)	DMF [0.04]	rt	12
8	1	3	**P-1** (3)	KHMDS (3)	DMF [0.2]	rt	42
9	1	3	**P-1** (3)	KHMDS (3)	DMF [0.2]	0	18
10	1	3	**P-1** (3)	KHMDS (3)	DMF [0.2]	40 °C	traces
11	1	3	**P-1** (3)	NaH (3)	DMF [0.2]	rt	40
12	1	3	**P-2** (1.5)	KHMDS (3)	DMF [0.2]	rt	45
13	1	3	**SED-2** (1.5)	-	DMF [0.2]	rt	64

With the optimized conditions in hand, we next investigated the generality and scope of this reaction with a series of aldehydes **2a–j** (Scheme 1). To our delight, moderate to good yields of 3,4-dihydroisocoumarins were obtained with both electron-poor (**3b–e**) and electron-rich substituents (**3f**). The position of the substituent seemed to have little effect on the reaction. The use of cinnamaldehyde allowed the formation of the 3,4-dihydroisocoumarin **3g** resulting from a regioselective 1,2-addition, no 1,4-addition was observed. Interestingly, the reaction conditions are tolerant with the formation of isocoumarins **3h** and **3i** respectively from heteroaromatic aldehydes **2h** and **2i**. Finally, a disubstituted aldehyde **2j** allowed the formation of the 3,4-dihydroisocoumarin **3j** with a 55% yield. Thus, we showed that our reaction conditions are compatible with an ester moiety on the benzyl chloride derivative and diversely functionalized aldehydes. The intermolecular addition of the metal-free generated benzylic anion, followed by a cyclisation, allowed the synthesis of ten 3,4-dihydroisocoumarins in one-step.

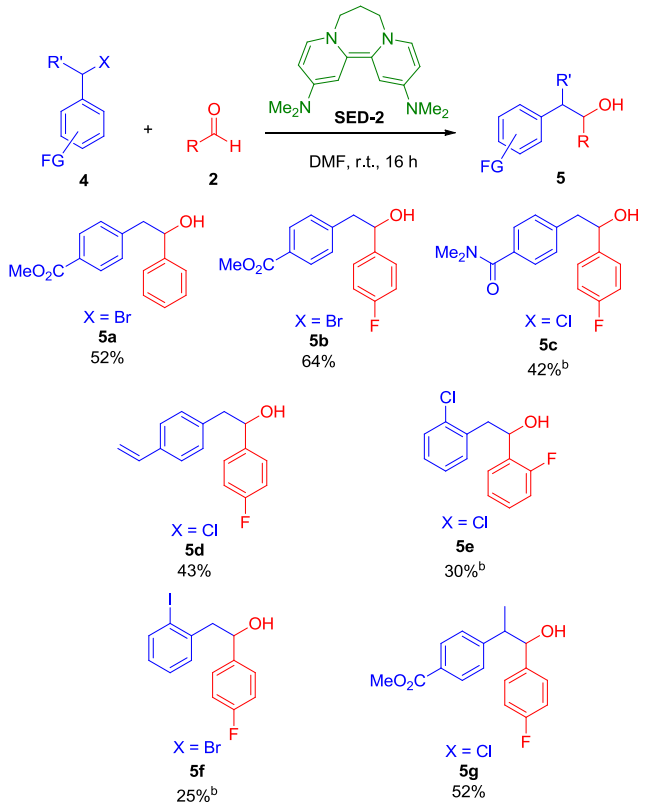
Scheme 1. Scope With Diverse Aldehyde Derivatives.[a]



[a] Reaction Conditions: **1** (0.2 mmol), **2** (0.6 mmol) and **SED-2** (0.3 mmol) in DMF (1 mL) were stirred at rt for 16 h under an inert atmosphere.

To further outline the utility of this method, we next examined the scope of the reaction with diversely functionalized benzyl halide derivatives (Scheme 2). Shifting the ester moiety from *ortho* to *para* position allowed the synthesis of alcohol **5a** (52% yield) from benzaldehyde **2a** and alcohol **5b** (64% yield) from 4-fluorobenzaldehyde **2b**. Contrary to our previous observations with methyl 2-(chloromethyl)benzoate **1**, the intramolecular cyclization of the alcoholate on the ester was not observed with methyl 4-(bromomethyl)benzoate because, as expected, the alcoholate was too far to attack on the ester. To our delight, an amide moiety was well tolerated and allowed the synthesis of alcohol **5c** in 42% yield. To the best of our knowledge, the addition of a benzyl halide derivative, possessing an amide function, on an aldehyde was never described. Interestingly**,** the super electron donor **SED-2** was very selective as it only reduced the chlorine atom of the 4-vinylbenzyl chloride to give alcohol **5d** in 43% yield. Addition on the double bond was not observed so it confirmed that DET was rapid and that the benzyl radical lifetime is short. The challenging 2-chlorobenzyl chloride was also compatible with our metal-free reaction conditions as the benzylic chlorine atom was preferentially reduced to allow the synthesis of alcohol **5e** in 30% yield. The even more challenging 2-iodobenzyl bromide, as it was described that SDEs can reduce iodoaryl derivatives,[6a] allowed the alcohol **5f** in a modest 25% yield. Interestingly, a secondary benzylic halide was compatible with our strategy and alcohol **5g** was obtained with a 52% yield. Here, we showed that diversely functionalized benzyl halide reagents can be selectively reduced by a super electron donor to form the corresponding benzylic carbanion under mild conditions. This anion can then be added to aldehydes to give the corresponding 1,2-diarylethanols.

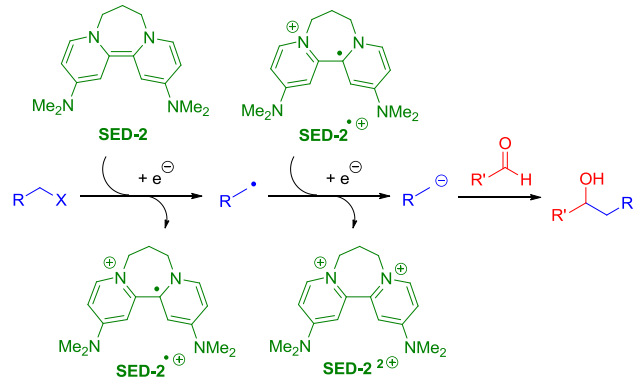
Scheme 2. Scope With Diverse Benzyl Halide Derivatives.[a]



[a] Reaction Conditions: **4** (0.2 mmol), **2** (0.6 mmol) and **SED-2** (0.3 mmol) in DMF (1 mL) were stirred at rt for 16 h under an inert atmosphere. [b] 10 equivalents of aldehyde were used.

To support a two consecutive electron transfer mechanism (Scheme 3), the reaction between methyl 2-(chloromethyl)benzoate **1**, 4-fluorobenzaldehyde and **SED-2** was carried out in the presence of TEMPO. The isocoumarin **3b** was obtained in only 17% yield which confirms the intermediacy of a benzyl radical. Furthermore, the second electron transfer to form the anion was supposed to be fast as no complete inhibition was observed with TEMPO and no addition on the double bond was observed during the synthesis of alcohol **5d**.

Scheme 3. Proposed DET Reaction Mechanism



In conclusion, the intermolecular addition of functionalized benzyl halides to aldehydes using a super electron donor **SED-2** is documented. Thus, a range of 3,4-dihydroisocoumarins and 1,2-diarylethanols was obtained with unprecedented functional group tolerance using metal-free and mild conditions.

EXPERIMENTAL SECTION

General Information. All reactions were carried out under an argon atmosphere using an oven-dried glassware. All solvents and chemicals were used as purchased without further purification. Melting points were determined on a Büchi melting point B-540 apparatus and are uncorrected. HRMS analyses were performed on a Synapt G2 HDMS (Waters) with a TOF mass analyzer type at the spectropole of Aix-Marseille University. Both ^{1}H- and ^{13}C-NMR spectra were determined on a Bruker Avance NEO 400 MHz Nanobay spectrometer and on a Bruker AC 250 spectrometer at the Service de RMN de la Faculté de Pharmacie de Marseille of the Aix-Marseille University. The ^{1}H and the ^{13}C chemical shifts are reported from $CDCl_3$ peaks: ^{1}H (7.26 ppm) and ^{13}C (77.16 ppm). Multiplicities are represented by the following notations: s, singlet; d, doublet; t, triplet; q, quartet; m, a more complex multiplet or overlapping multiplets. The following adsorbents were used for column chromatography: Silica gel 60 (particle size 0.063–0.200 mm, 70–230 mesh ASTM). TLC was performed on 5 x 10 cm aluminum plates coated with silica gel 60 F254 in an appropriate solvent.

Preparation of P-1. To a solution of DMAP (1.22 g, 10 mmol) in toluene (10 mL), dimethylsulfate (0.95 mL, 10 mmol) was added dropwise and the reaction mixture was stirred at 100 °C for 3 h. After being cooled, the product was filtered, washed with toluene (20 mL), and dried in vacuo to give a white solid (2.21 g, 89%). Mp 242–244 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 7.8 Hz, 2H), 6.90 (d, *J* = 7.8 Hz, 2H), 4.01 (s, 3H), 3.68 (s, 3H), 3.21 (s, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 156.2, 143.3, 108.2, 54.6, 45.0, 40.3; HRMS (ESI) : *m/z* $[2C^{+}+A^{-}]^{+}$ calcd for $[C_{17}H_{29}N_4O_4S]^{+}$: 385.1904; found : 385.1901.

Preparation of SED-2. The procedure, previously reported for the synthesis of **SED-2**,[11] was slightly modified: in the glovebox, sodium hydride (1.1 g, 46 mmol, 5 equiv.) was added to a solution of the precursor bis-pyridinium salt[11] in extra dry *N,N*-dimethylformamide (20 mL). After 2 h stirring at room temperature, the reaction mixture was filtrated to remove excess sodium hydride. The grey residue was washed with diethyl ether and solvents were removed under vacuum. Diethyl ether was then added in several fractions to re-dissolve the dark purple bispyridinylidene **SED-2**. The mixture was filtrated to remove excess sodium iodide. Evaporation of the filtrate afforded **SED-2** as a well-defined dark purple solid (2.42 g, 92%). **SED-2** was stable under inert atmosphere and stored in a glovebox. Spectral data match those previously reported.[11]

General Procedures for the Synthesis of isocoumarins 3a–j or alcohols 5a–g.

General Procedure A when the benzyl halide derivative is liquid: in a glove-box, to **SED-2** (85 mg, 0.3 mmol, 1.5 equiv.) was added dry DMF (1 mL). The previous solution was put out from the glove-box and the aldehyde (0.6 mmol, 3 equiv.) was added followed by the benzyl halide (0.2 mmol, 1 equiv.) under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 16 h. Water was added (5 mL) and a 1M solution of HCl was added until pH = 1. The aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layer was dried over Na_2SO_4. Evaporation of the solvent furnished the crude product. Purification by silica gel chromatography afforded pure isocoumarin**s 3a–j** or alcohols **5d–e**.

General Procedure B when the benzyl halide derivative is solid: in a glove-box, to **SED-2** (85 mg, 0.3 mmol, 1.5 equiv.) was added dry DMF (0.5 mL) and 0.5 mL of dry DMF was put in another vial. The solid benzyl halide (0.2 mmol, 1 equiv.) was weight in a Schlenk and solubilized with the previous 0.5 mL of dry DMF under nitrogen atmosphere. The vial containing **SED-2** in DMF was put out from the glove-box and the aldehyde (0.6 mmol, 3 equiv.) was added followed by the benzyl halide solution. The reaction mixture was stirred at room temperature for 16 h. Water was added (5 mL) and a 1M solution of HCl was added until pH = 1. The aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layer was dried over Na_2SO_4. Evaporation of the solvent furnished the crude product. Purification by silica gel chromatography afforded pure alcohols **5a–c** and **5f–g**.

*3-Phenyl-3,4-dihydroisocoumarin **(3a)***. Following the general procedure A with 2-(chloromethyl)benzoate and benzaldehyde, **3a** was purified by PE/EtOAc (90/10). 28.8mg, yield: 64%; white solid; mp 87–89 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.16 (d, *J* = 7.5 Hz, 1H), 7.61–7.31 (m, 8H), 5.57 (dd, *J* = 11.9, 3.2 Hz, 1H), 3.36 (dd, *J* = 16.4, 12.0 Hz, 1H), 3.14 (dd, *J* = 16.5, 3.2 Hz, 1H). Spectral data match those previously reported.[13]

*3-(4-fluorophenyl)-3,4-dihydroisocoumarin **(3b)***. Following the general procedure A with 2-(chloromethyl)benzoate and 4-fluorobenzaldehyde, **3b** was purified by PE/EtOAc (90/10). 36.2 mg, yield: 75%; pale-yellow solid; mp 84–86 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.15 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.58 (td, *J* = 7.5, 1.4 Hz, 1H), 7.52–7.39 (m, 3H), 7.29 (d, *J* = 7.6 Hz, 1H), 7.18–7.05 (m, 2H), 5.54 (dd, *J* = 12.1, 3.2 Hz, 1H), 3.32 (dd, *J* = 16.5, 12.1 Hz, 1H), 3.11 (dd, *J* = 16.4, 3.2 Hz, 1H) Spectral data match those previously reported.[14]

*3-(4-(trifluoromethyl)phenyl)-3,4-dihydroisocoumarin **(3c)***. Following the general procedure A with 2-(chloromethyl)benzoate and 4-(trifluoromethyl)benzaldehyde, **3c** was purified by PE/EtOAc (90/10). 39.7 mg, yield: 68%; white solid; mp 106–108 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.69 (d, *J* = 8.3 Hz, 2H), 7.62 (d, *J* = 8.2 Hz, 2H), 7.59 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 1H), 7.30 (d, *J* = 7.6 Hz, 1H), 5.63 (dd, *J* = 11.9, 3.3 Hz, 1H), 3.31 (dd, *J* = 16.4, 11.9 Hz, 1H), 3.17 (dd, *J* = 16.4, 3.3 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) *δ* 165.0, 142.6, 138.5, 134.3, 131.4 (C-F_3, ^{2}JC-F = 33.3 Hz), 131.1 (C-F_3, ^{2}JC-F = 33.3 Hz), 130.8 (C-F_3, ^{2}JC-F = 33.3 Hz), 130.7, 130.5 (C-F_3, ^{2}JC-F = 33.3 Hz), 128.3, 128.1 (C-F_3, ^{1}JC-F = 272.7 Hz), 127.5, 126.5, 125.92 (C-F_3, ^{3}JC-F = 3.37 Hz), 125.89 (C-F_3, ^{3}JC-F = 3.37 Hz) 125.85 (C-F_3, ^{3}JC-F = 3.37 Hz), 125.81 (C-F_3, ^{3}JC-F = 3.37 Hz), 125.4 (C-F_3, ^{1}JC-F = 272.7 Hz), 125.1, 122.7 (C-F_3, ^{1}JC-F = 272.7 Hz), 120.0 (C-F_3, ^{1}JC-F = 272.7

Hz), 79.1, 35.7; HRMS (ESI) : *m/z* $[M+H]^+$ calcd for $[C_{16}H_{12}O_2F_3]^+$: 293.0784; found : 293.0782.

*3-(2-fluorophenyl)-3,4-dihydroisocoumarin (**3d**).* Following the general procedure A with 2-(chloromethyl)benzoate and 2-fluorobenzaldehyde, **3d** was purified by PE/EtOAc (90/10). 37.4 mg, yield: 77%; pale-yellow solid; mp 85–87 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.16 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.69–7.54 (m, 2H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.38–7.32 (m, 1H), 7.29 (d, *J* = 7.7 Hz, 1H), 7.25–7.20 (m, 1H), 7.13–7.05 (m, 1H), 5.87 (dd, *J* = 11.6, 3.6 Hz, 1H), 3.31 (dd, *J* = 16.4, 11.6 Hz, 1H), 3.17 (dd, *J* = 16.4, 3.6 Hz, 1H); ^{13}C{^{1}H} NMR (63 MHz, $CDCl_3$) δ 165.3, 161.2 (C-F, ^{1}JC-F = 219.9 Hz), 157.7 (C-F, ^{1}JC-F = 219.9 Hz), 139.0, 134.1, 130.6, 130.3 (C-F, ^{3}JC-F = 8.2 Hz), 130.2 (C-F, ^{3}JC-F = 8.2 Hz), 128.1, 127.73 (C-F, ^{4}JC-F = 3.2 Hz), 127.68 (C-F, ^{4}JC-F = 3.2 Hz), 127.5, 126.2 (C-F, ^{2}JC-F = 12.6 Hz), 126.0 (C-F, ^{2}JC-F = 12.6 Hz), 125.1, 124.71 (C-F, ^{3}JC-F = 3.5 Hz), 124.65 (C-F, ^{3}JC-F = 3.5 Hz), 115.8 (C-F, ^{2}JC-F = 21.4 Hz), 115.5 (C-F, ^{2}JC-F = 21.4 Hz), 74.27 (C-F, ^{4}JC-F = 3.4 Hz), 74.21 (C-F, ^{3}JC-F = 3.4 Hz), 34.7 (C-F, ^{4}JC-F = 1.4 Hz); HRMS (ESI) : *m/z* $[M+H]^+$ calcd for $[C_{15}H_{12}O_2F]^+$: 243.0816; found : 243.0815.

*3-(3-bromophenyl)-3,4-dihydroisocoumarin (**3e**).* Following the general procedure A with 2-(chloromethyl)benzoate and 3-bromobenzaldehyde, **3e** was purified by PE/EtOAc (90/10). 42.8 mg, yield: 71%; white solid; mp 113–115 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.15 (d, *J* = 7.6 Hz, 1H), 7.66–7.55 (m, 2H), 7.52–7.39 (m, 3H), 7.32–7.27 (m, 2H), 5.52 (dd, *J* = 11.8, 3.4 Hz, 1H), 3.30 (dd, *J* = 16.4, 11.8 Hz, 1H), 3.13 (dd, *J* = 16.4, 3.4 Hz, 1H). Spectral data match those previously reported.[3d]

*3-(3-methoxyphenyl)-3,4-dihydroisocoumarin (**3f**).* Following the general procedure A with 2-(chloromethyl)benzoate and 3-methoxybenzaldehyde, **3f** was purified by PE/EtOAc (90/10). 24.1 mg, yield: 47%; white solid; mp 98–99 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.57 (td, *J* = 7.5, 1.4 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.32 (t, *J* = 8.1 Hz, 1H), 7.29 (d, *J* = 7.6 Hz, 1H), 7.05–7.03 (m, 2H), 6.91 (ddd, *J* = 8.3, 2.5, 0.9 Hz, 1H), 5.54 (dd, *J* = 12.0, 3.2 Hz, 1H), 3.84 (s, 3H), 3.34 (dd, *J* = 16.4, 12.0 Hz, 1H), 3.14 (dd, *J* = 16.4, 3.2 Hz, 1H). Spectral data match those previously reported.[15]

*3-styryl-3,4-dihydroisocoumarin (**3g**).* Following the general procedure A with 2-(chloromethyl)benzoate and cinnamaldehyde, **3g** was purified by PE/EtOAc (90/10). 28.2 mg, yield: 56%; white solid; mp 73–75 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 7.6 Hz, 1H), 7.56 (td, *J* = 7.5, 1.0 Hz, 1H), 7.46–7.27 (m, 7H), 6.79 (d, *J* = 16.0 Hz, 1H), 6.34 (dd, *J* = 16.0, 6.4 Hz, 1H), 5.21 (td, *J* = 9.4, 4.7 Hz, 1H), 3.19 (dd, *J* = 16.3, 10.3 Hz, 1H), 3.11 (dd, *J* = 16.3, 4.0 Hz, 1H). Spectral data match those previously reported.[13]

*3-(pyridin-3-yl)-3,4-dihydroisocoumarin (**3h**).* Following the general procedure A with 2-(chloromethyl)benzoate and 3-pyridinecarboxaldehyde, **3h** was purified by PE/EtOAc (from 50/50 to 20/80). 22.9 mg, yield: 51%; white solid; mp 80–82 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.74–8.60 (m, 2H), 8.14 (d, *J* = 7.7 Hz, 1H), 7.87 (d, *J* = 7.9 Hz, 1H), 7.65–7.53 (m, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.42–7.34 (m, 1H), 7.30 (d, *J* = 7.5 Hz, 1H), 5.61 (dd, *J* = 11.9, 3.3 Hz, 1H), 3.35 (dd, *J* = 16.3, 12.0 Hz, 1H), 3.16 (dd, *J* = 16.4, 3.3 Hz, 1H); ^{13}C{^{1}H} NMR (63 MHz, $CDCl_3$) *δ* 164.9, 150.2, 147.8, 138.4, 134.34, 134.29, 134.1, 130.7, 128.3, 127.5, 125.0, 123.8, 77.8, 35.4; HRMS (ESI) : *m/z* $[M+H]^+$ calcd for $[C_{14}H_{12}NO_2]^+$: 226.0863; found : 226.0862.

*3-(4-(pyridin-2-yl)phenyl)-3,4-dihydroisocoumarin (**3i**).* Following the general procedure A with 2-(chloromethyl)benzoate and 4-(pyridin-2-yl)benzaldehyde, **3i** was purified by PE/EtOAc (from 90/10 to 80/20). 27.5 mg, yield: 46%; white solid; mp 107–109 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (d, *J* = 4.6 Hz, 1H), 8.17 (d, *J* = 8.0 Hz, 1H), 8.06 (d, *J* = 8.4 Hz, 2H), 7.82–7.75 (m, 2H), 7.62–7.56 (m, 3H), 7.44 (t, *J* = 7.6 Hz, 1H), 7.32–7.27 (m, 2H), 5.64 (dd, *J* = 11.8, 3.2 Hz, 1H), 3.37 (dd, *J* = 16.4, 11.9 Hz, 1H), 3.19 (dd, *J* = 16.5, 3.2 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 165.4, 156.8, 149.7, 139.6, 139.5, 139.0, 137.2, 134.1, 130.6, 128.1, 127.5, 127.4, 126.6, 125.3, 122.6, 120.9, 79.7, 35.7; HRMS (ESI) : *m/z* $[M+H]^+$ calcd for $[C_{20}H_{16}NO_2]^+$: 302.1176; found : 302.1172.

*3-(4-fluoro-3-phenoxyphenyl)-3,4-dihydroisocoumarin (**3j**).* Following the general procedure A with 2-(chloromethyl)benzoate and 4-fluoro-3-phenoxybenzaldehyde, **3j** was purified by PE/EtOAc (90/10). 36.6 mg, yield: 55%; white solid; mp 88–90 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 7.7 Hz, 1H), 7.55 (t, *J* = 7.2 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.32 (t, *J* = 7.9 Hz, 2H), 7.28–7.14 (m, 4H), 7.10 (t, *J* = 7.4 Hz, 1H), 6.97 (d, *J* = 8.0 Hz, 2H), 5.46 (dd, *J* = 12.0, 2.9 Hz, 1H), 3.27 (dd, *J* = 16.3, 12.1 Hz, 1H), 3.08 (dd, *J* = 16.4, 3.0 Hz, 1H) ; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 165.1, 157.1, 155.6 (C-F, ^{1}JC-F = 251.5 Hz), 153.1 (C-F, ^{1}JC-F = 251.5 Hz), 144.2 (C-F, ^{2}JC-F = 11.7 Hz), 144.1 (C-F, ^{2}JC-F = 11.7 Hz), 138.7, 135.60 (C-F, ^{3}JC-F = 3.7 Hz), 135.57 (C-F, ^{3}JC-F = 3.7 Hz), 134.2, 130.6, 130.0, 128.1, 127.5, 125.0, 123.6, 122.7 (C-F, ^{3}JC-F = 7.2 Hz), 122.6 (C-F, ^{3}JC-F = 7.2 Hz), 119.83 (C-F, ^{4}JC-F = 1.2 Hz), 119.82 (C-F, ^{4}JC-F = 1.2 Hz), 117.6, 117.6 (C-F, ^{2}JC-F = 20.1 Hz), 117.4 (C-F, ^{2}JC-F = 20.1 Hz), 79.1, 35.6; HRMS (ESI) : *m/z* $[M+H]^+$ calcd for $[C_{21}H_{16}O_3F]^+$: 335.1078; found : 335.1074.

*Methyl 4-(2-hydroxy-2-phenylethyl)benzoate (**5a**).* Following the general procedure B with methyl 4-(bromomethyl)benzoate and benzaldehyde, **5a** was purified by PE/EtOAc (from 90/10 to 80/20). 26.7 mg, yield: 52%; yellow solid; mp 75–77 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.1 Hz, 2H), 7.38–7.29 (m, 5H), 7.25 (d, *J* = 8.1 Hz, 2H), 4.96 (m, 1H), 3.94 (s, 3H), 3.17–3.06 (m, 2H), 2.15 (*br*-s, 1H). Spectral data match those previously reported.[16]

*Methyl 4-(2-(4-fluorophenyl)-2-hydroxyethyl)benzoate (**5b**).* Following the general procedure B with methyl 4-(bromomethyl)benzoate and 4-fluorobenzaldehyde, **5b** was purified by PE/EtOAc (from 90/10 to 80/20). 35.0 mg, yield: 64%; white solid; mp 114–116 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.2 Hz, 2H), 7.30–7.19 (m, 4H), 7.07–6.97 (m, 2H), 4.94–4.89 (m, 1H), 3.90 (s, 6H), 3.08–3.04 (m, 2H), 2.01 (s, 1H). Spectral data match those previously reported.[17]

*4-(2-(4-fluorophenyl)-2-hydroxyethyl)-N,N-dimethylbenzamide (**5c**).* Following the general procedure B with 4-(chloromethyl)-*N*,*N*-dimethylbenzamide and 4-fluorobenzaldehyde (10 equiv.), **5c** was purified by PE/EtOAc (from 50/50 to 30/70). 24.2 mg, yield: 42%; white solid; mp 96–98 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.1 Hz, 2H), 7.31–7.27 (m, 2H), 7.18 (d, *J* = 8.1 Hz, 2H), 7.03–6.99 (m, 2H), 4.90–4.86 (m, 1H), 3.15–2.95 (m, 8H), 1.87 (*br*-s, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 171.7, 163.6 (C-F, ^{1}JC-F = 246.4 Hz), 161.2 (C-F, ^{1}JC-F = 246.4 Hz), 139.6, 139.49 (C-F, ^{4}JC-F = 3.0 Hz), 139.46 (C-F, ^{4}JC-F = 3.0 Hz), 134.7, 129.6, 127.74 (C-F, ^{3}JC-F = 8.1 Hz), 127.66 (C-F, ^{3}JC-F = 8.1 Hz), 127.5, 115.5 (C-F, ^{2}JC-F = 21.2 Hz), 115.3 (C-F, ^{2}JC-F = 21.2 Hz), 74.7, 46.0, 39.7, 35.5; HRMS (ESI) : *m/z* $[M+Na]^+$ calcd for $[C_{17}H_{18}NO_2FNa]^+$: 310.1214; found : 310.1208.

*1-(4-fluorophenyl)-2-(4-vinylphenyl)ethanol (**5d**).* Following the general procedure A with 4-vinylbenzyl chloride and 4-fluorobenzaldehyde, **5d** was purified by PE/EtOAc (from 95/5 to 85/15). 20.7 mg, yield: 43%; yellow solid; mp 59–61 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.29 (m, 4H), 7.12 (d, *J* = 8.1 Hz, 2H), 7.05–7.00 (m, 2H), 6.70 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.72 (dd, *J* = 17.6, 0.9 Hz, 1H), 5.23 (dd, *J* = 10.9, 0.8 Hz, 1H), 4.88 (dd, *J* = 7.7, 5.6 Hz, 1H), 3.00–2.97 (m, 2H), 1.95 (*br*-s, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 163.6 (C-F, ^{1}JC-F = 246.4 Hz), 161.1 (C-F, ^{1}JC-F = 246.4 Hz), 139.59 (C-F, ^{4}JC-F = 3.0 Hz), 139.56 (C-F, ^{4}JC-F = 3.0 Hz), 137.4, 136.6, 136.3, 129.8, 127.74 (C-F, ^{3}JC-F = 8.1 Hz), 127.66 (C-F, ^{3}JC-F = 8.1 Hz), 126.5, 115.5 (C-F, ^{2}JC-F = 22.2 Hz), 115.3 (C-F, ^{2}JC-F = 22.2 Hz), 113.7, 74.8, 46.0; HRMS (ESI) : *m/z* $[M+Na]^+$ calcd for $[C_{16}H_{15}OFNa]^+$: 265.0999; found : 265.0996.

*2-(2-chlorophenyl)-1-(2-fluorophenyl)ethanol (**5e**).* Following the general procedure A with 2-chlorobenzyl chloride and 2-fluorobenzaldehyde (10 equiv.), **5e** was purified by PE/EtOAc (90/10). 15.1 mg, yield: 30%; white solid; mp 48–50 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (td, *J* = 7.6, 1.6 Hz, 1H), 7.42–7.34 (m, 1H), 7.30–7.25 (m, 1H), 7.24–7.14 (m, 4H), 7.05–7.00 (m, 1H), 5.34

(dd, J = 8.7, 4.5 Hz, 1H), 3.27 (dd, J = 13.7, 4.5 Hz, 1H), 3.14 (dd, J = 13.7, 8.8 Hz, 1H), 1.63 (*br*-s, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 161.2 (C-F, ^{1}JC-F = 247.5 Hz), 158.8 (C-F, ^{1}JC-F = 247.5 Hz), 135.7, 134.7, 132.1, 130.9 (C-F, ^{2}JC-F = 13.1 Hz), 130.8 (C-F, ^{2}JC-F = 13.1 Hz), 129.8, 129.25 (C-F, ^{3}JC-F = 8.1 Hz), 129.17 (C-F, ^{3}JC-F = 8.1 Hz), 128.3, 127.52 (C-F, ^{3}JC-F = 4.5 Hz), 127.48 (C-F, ^{3}JC-F = 4.5 Hz), 126.9, 124.45 (C-F, ^{4}JC-F = 3.5 Hz), 124.41 (C-F, ^{4}JC-F = 3.5 Hz), 115.6 (C-F, ^{2}JC-F = 22.2 Hz), 115.4 (C-F, ^{2}JC-F = 22.2 Hz), 68.18 (C-F, ^{3}JC-F = 2.1 Hz), 68.15 (C-F, ^{3}JC-F = 2.1 Hz), 42.3; HRMS (ESI) : *m/z* $[M+Na]^+$ calcd for $[C_{14}H_{12}OFClNa]^+$: 273.0453; found : 273.0452.

1-(4-fluorophenyl)-2-(2-iodophenyl)ethanol **(5f).** Following the general procedure B with 2-iodobenzyl bromide and 4-fluorobenzaldehyde (10 equiv.), **5f** was purified by PE/EtOAc (90/10). 16.8 mg, yield: 25%; white solid; mp 69–71 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (dd, J = 7.9, 1.1 Hz, 1H), 7.41–7.37 (m, 2H), 7.29–7.25 (m, 1H), 7.16 (dd, J = 7.6, 1.7 Hz, 1H), 7.06–7.02 (m, 2H), 6.94 (td, J = 7.7, 1.7 Hz, 1H), 5.01 (dd, J = 8.4, 4.9 Hz, 1H), 3.16–3.05 (m, 2H), 1.60 (*br*-s, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 163.7 (C-F, ^{1}JC-F = 246.4 Hz), 161.2 (C-F, ^{1}JC-F = 246.4 Hz), 140.7, 139.9, 139.56 (C-F, ^{4}JC-F = 3.0 Hz), 139.53 (C-F, ^{4}JC-F = 3.0 Hz), 131.4, 128.8, 128.4, 127.6 (C-F, ^{3}JC-F = 8.1 Hz), 127.5 (C-F, ^{3}JC-F = 8.1 Hz), 115.5 (C-F, ^{2}JC-F = 21.2 Hz), 115.3 (C-F, ^{2}JC-F = 21.2 Hz), 101.2, 73.1, 50.7; HRMS (ESI) : *m/z* $[M+Na]^+$ calcd for $[C_{14}H_{12}OFINa]^+$: 364.9809; found : 364.9808.

*Methyl 4-(1-(4-fluorophenyl)-1-hydroxypropan-2-yl)benzoate (**5g**).* Following the general procedure B with methyl 4-(1-bromoethyl)benzoate and 4-fluorobenzaldehyde, **5g** was purified by PE/EtOAc (from 95/5 to 90/10) as a 1:1 ratio of diastereoisomers. 29.9 mg, yield: 52%; white solid; mp 157–159 °C; ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of diastereoisomers) δ 8.00 (d, J = 8.3 Hz, 2H), 7.89 (d, J = 8.3 Hz, 2H), 7.32 (d, J = 8.3 Hz, 2H), 7.29–7.25 (m, 2H), 7.14 (d, J = 8.3 Hz, 2H), 7.12–7.08 (m, 2H), 7.05–7.00 (m, 2H), 6.93–6.89 (m, 2H), 4.76 (d, J = 6.5 Hz, 1H), 4.71 (d, J = 8.2 Hz, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 3.13–3.04 (m, 2H), 1.79 (*br*-s, 2H), 1.36 (d, J = 7.0 Hz, 3H), 1.11 (d, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) (mixture of diastereoisomers) δ 167.17, 167.14, 163.8 (C-F, ^{1}JC-F = 246.4 Hz), 163.4 (C-F, ^{1}JC-F = 246.4 Hz), 161.3 (C-F, ^{1}JC-F = 246.4 Hz), 160.1 (C-F, ^{1}JC-F = 246.4 Hz), 148.8, 138.43 (C-F, ^{4}JC-F = 3.0 Hz), 138.40 (C-F, ^{4}JC-F = 3.0 Hz), 138.22 (C-F, ^{4}JC-F = 3.0 Hz), 138.19 (C-F, ^{4}JC-F = 3.0 Hz), 130.0, 129.6, 128.9, 128.57 (C-F, ^{3}JC-F = 8.1 Hz), 128.54, 128.49 (C-F, ^{3}JC-F = 8.1 Hz), 128.3, 128.09 (C-F, ^{3}JC-F = 7.1 Hz), 128.02 (C-F, ^{3}JC-F = 7.1 Hz), 115.5 (C-F, ^{2}JC-F = 21.2 Hz), 115.24 (C-F, ^{2}JC-F = 21.2 Hz), 115.15 (C-F, ^{2}JC-F = 22.2 Hz), 114.9 (C-F, ^{2}JC-F = 22.2 Hz), 78.8, 78.3, 52.22, 52.17, 48.2, 47.7, 18.1, 15.8 (two aromatic carbons are missing due to overlap); HRMS (ESI) : *m/z* $[M+Na]^+$ calcd for $[C_{17}H_{17}O_3FNa]^+$: 311.1054; found : 311.1052.

Larger scale synthesis of 3d. Following the general procedure A with 2-(chloromethyl)benzoate (155 µL, 1 mmol), 2-fluorobenzaldehyde (316 µL, 3 mmol) and **SED-2** (427 mg, 1.5 mmol) in DMF (5 mL), **3d** was purified by PE/EtOAc (90/10). 167 mg, yield: 69%.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

^{1}H NMR spectra for known compounds and ^{1}H and ^{13}C NMR spectra for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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