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Convergent routes to substituted naphthylamides†‡

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Practical, convergent routes to variously substituted 1- and 2-naphthylamides have been developed. They exploit the ability of xanthates to undergo both intermolecular radical additions to vinyl pivalate and intramolecular radical cyclisations to aromatic rings. In the case of 1-naphthylamides, the existence of an intramolecular hydrogen bond was used to facilitate the cyclisation step.

Introduction

Even though naphthalenes have been known for a long time, these classical aromatic compounds have found their importance growing over the years. Indeed, numerous applications of naphthalenes have been reported in many different fields such as organic synthesis, medicinal chemistry and materials science.[1] It is not surprising, therefore, that a plethora of methods to access these structures have been developed.[2] However, the preparation of the naphthylamine subfamily remains a significant challenge, despite its importance in the manufacture of dyes, rubber stabilisers, agrochemicals, pharmaceuticals, *etc.*

For example, naphthionic acid (1-naphthylamine-4-sulphonic acid) **I** is an important dye intermediate for Congo Red, Fast Dye A and azo dyes in general; *N*-phenyl-1-naphthylamine **II** is used as an antioxidant for rubber;[3a] *N*-1-naphthylphthalamic acid **III** (Naptalam) is a selective herbicide used for soybean, peanut, and vine crops; compound **IV** is a potent binder of the chemokine receptor CCR8;[3b] and rifampicin **V** is a semisynthetic antibiotic of the ansa family that is in clinical use (Fig. 1).[3c]

Generally, naphthylamine derivatives are prepared by nitration of naphthalene, followed by reduction of the nitro group. The relatively harsh reaction conditions do not allow easy control of regioselectivity. Thus, no simple method for the regioselective synthesis of substituted naphthylamines has been reported so far. We recently described a convenient approach to synthesise substituted naphthalenes using a xanthate radical addition–cyclisation sequence under mild conditions.[4] We have now exploited this chemistry for the synthesis of both α- and β-naphthylamides.

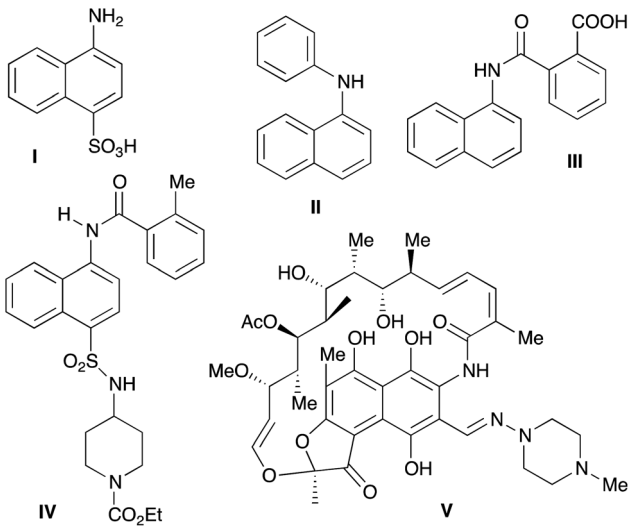

Fig. 1 Examples of important naphthylamines.

Synthesis of substituted 2-naphthylamides

Our initial synthesis of naphthalenes, depicted in the top part of Scheme 1, hinges on the possibility of addition of a phenacyl type radical to vinyl pivalate and cyclisation onto the aromatic ring followed by aromatisation of the tetralone through acid-induced elimination of pivalic acid.[4a] Introduction of a protected amino group in the position adjacent to the carbonyl group in the xanthate partner would allow a simple extension of this approach to the synthesis of 2-naphthylamides, as outlined in the lower part of Scheme 1.

The main general synthetic scheme we adopted to access the requisite tetralones **6** is depicted in Scheme 2. The readily available α-bromoacetophenone precursors **1** were first treated with potassium phthalimide in DMF at room temperature to

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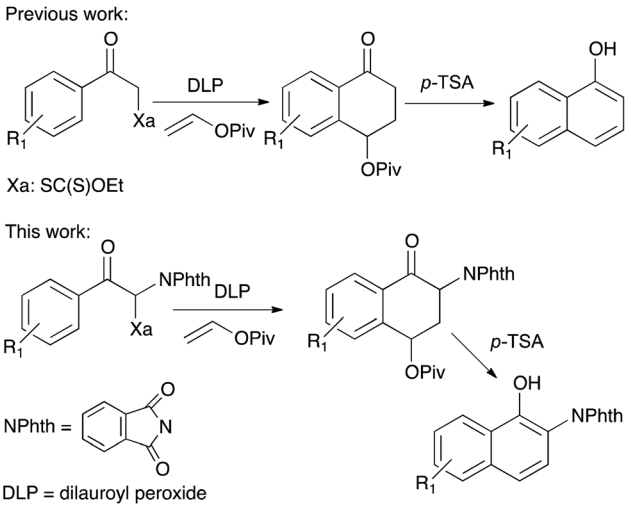
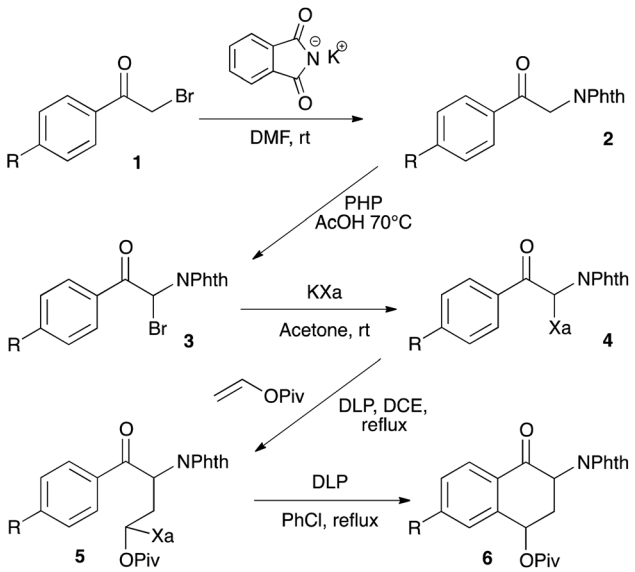
†This article is dedicated to Professor Richard J. K. Taylor on the occasion of his 65th birthday.

‡Electronic supplementary information (ESI) available: NMR spectra of all new compounds. See DOI: 10.1039/c4ob00339j



Scheme 1 Proposed route to 2-naphthylamides.



Scheme 2 Synthesis of key tetralones.

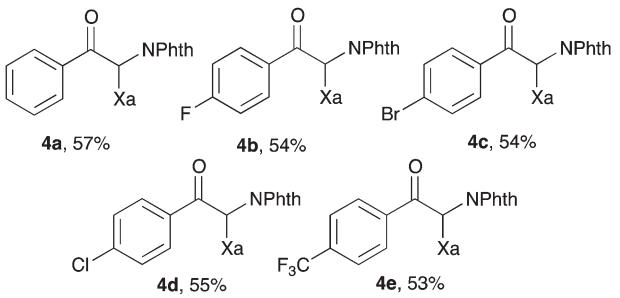
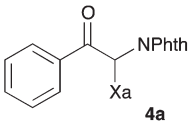
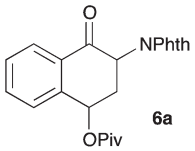
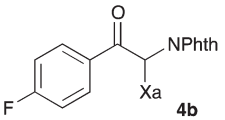
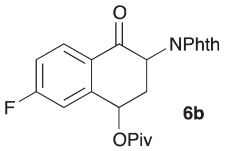
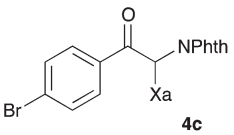
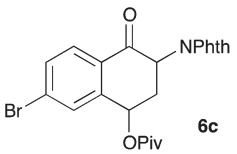
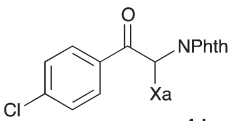
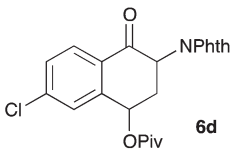
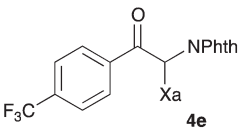
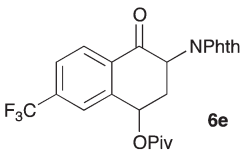


Fig. 2 Examples of xanthates 4.

Table 1 Radical addition–cyclisation of xanthates 4

Xanthates 4	Tetralones 6	Yield (%)
 4a	 6a	42
 4b	 6b	45
 4c	 6c	40
 4d	 6d	37
 4e	 6e	41

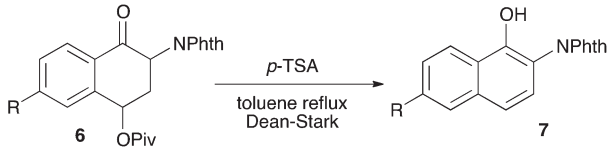
furnish compounds 2, which were brominated with pyridinium hydrobromide perbromide (PHP) in acetic acid at 70 °C.[5] The α-bromine in compounds 3 thus obtained was easily substituted by the salt of potassium *O*-ethyl xanthate to provide the starting xanthates 4 (Xa in all the schemes and tables corresponds to EtOC(=S)S–). In this manner, xanthates **4a–4e** displayed in Fig. 2 were readily prepared.

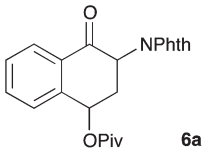
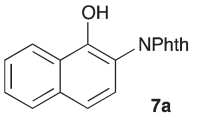
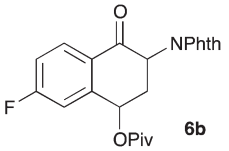
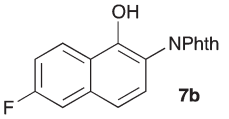
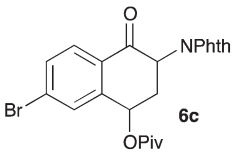
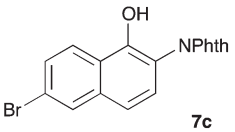
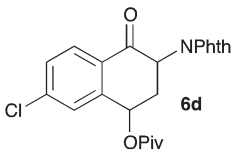
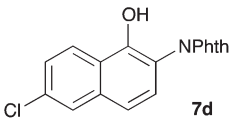
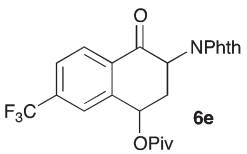
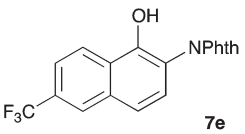
With the starting xanthates 4 in hand, the addition–cyclisation sequence could be tested. The radical addition of xanthates 4 and vinyl pivalate to give adducts 5, precursors for the next cyclisation step, was accomplished using 25–30 mol% of dilauroyl peroxide (DLP) as the initiator and 1,2-dichloroethane (DCE) as the solvent. Once the starting xanthate was consumed, the solvent and excess vinyl pivalate were evaporated and the residue taken up in chlorobenzene and treated with a stoichiometric amount of DLP to induce cyclisation onto the aromatic ring. In this manner, the desired tetralones 6 were obtained successfully in a one-pot procedure in an overall yield varying from 37% to 45% (Table 1).

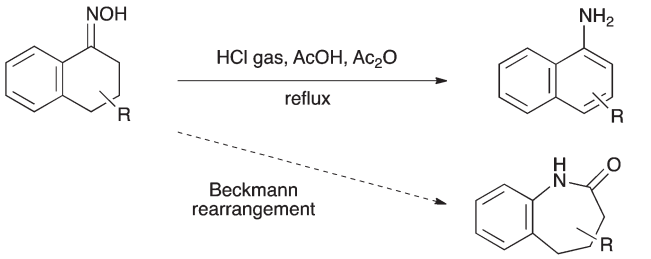
These moderate yields are mostly due to the difficult cyclisation step. In any case, both the intermolecular addition to vinyl pivalate and the ring-closure onto the aromatic ring are not trivial processes and cannot be easily achieved by more conventional radical methods.

For the aromatisation step, numerous methods such as oxidation with DDQ or Pd/C at high temperature[6] or heating under acidic conditions[4a] have been reported. As in our previous study,[4a] tetralones 6 were treated with *p*-toluenesulfonic

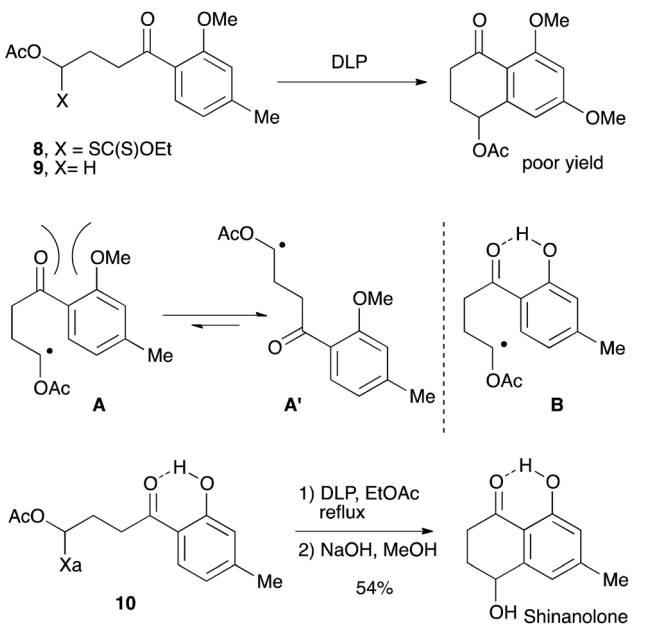
Table 2 Aromatisation of tetralones **6** into aminonaphthols **7**



Tetralones **6**	2-Naphthylamide **7**	Yield (%)
 **6a**	 **7a**	83
 **6b**	 **7b**	78
 **6c**	 **7c**	72
 **6d**	 **7d**	80
 **6e**	 **7e**	79



Scheme 3 The Semmler–Wolff/Schroeter reaction.



Scheme 4 Ring closure of unprotected phenol derivatives.

acid in refluxing toluene using a Dean–Stark apparatus for 3 hours. After workup, the residue was easily purified by simply washing with pentane or dichloromethane and provided the final products as crystalline solids. This efficient aromatisation (up to 83% yield) completed the sequence leading to 2-naphthylamides **7a–e** (Table 2).

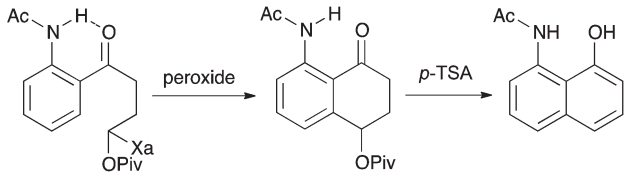
No attempt was made to remove the phthalimide group because of the reputed carcinogenicity of 2-naphthylamines in general. It is interesting to note that the 2-amino-1-naphthol motif is found at the core of the important rifamycin ansa family of antibiotics (*cf.* rifampicin in Fig. 1 above). Furthermore, with the exception of the parent 2-amino-1-naphthol corresponding to phthalimide **7a**, none of the substituted 2-amino-1-naphthols corresponding to **7b–e** has been described in the open literature.

Synthesis of substituted 1-naphthylamides

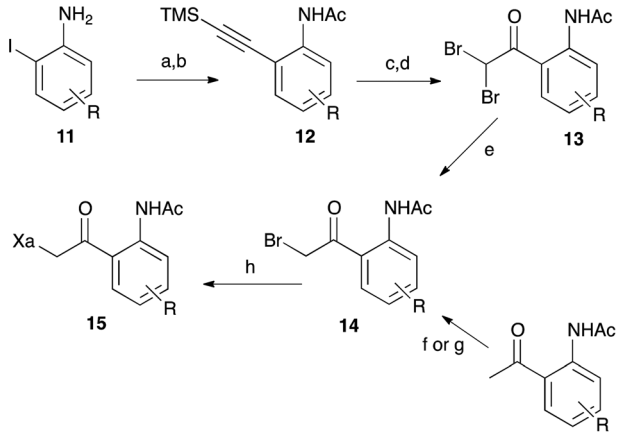
Apart from nitration and reduction, a classical method to prepare 1-naphthylamines is the Semmler–Wolff/Schroeter aromatisation, which involves dehydration of the α-tetralone-derived oxime under acidic conditions using anhydrous HCl gas in refluxing $AcOH/Ac_2O$. Yet, this method has rarely been used because of the limited availability of substituted α-tetralones and the harsh conditions that often lead to the Beckmann rearrangement lactam as a significant side product (Scheme 3).[7]

Recently, the Stahl group developed the use of Pd as the catalyst to improve the efficiency of this process.[8] Even though the transformation of tetralone to naphthylamine can now be accomplished in high yield, a limitation of this approach appeared with substrates bearing a bromide substituent because of the competing oxidative addition of the bromoarenes to the palladium complex.

From our earlier experience with the synthesis of tetralones,[9] we had noted that the presence of a substituent *ortho*- to the acyl chain, and especially a methoxy group, is quite detrimental to the cyclisation step. Thus, xanthate **8** furnishes mostly prematurely reduced material **9** and only a very poor yield of the corresponding tetralone. This is almost certainly due to a combination of steric and dipole–dipole repulsions favouring conformation **A′** over **A** (Scheme 4). A simple and effective solution to this synthetic problem was to work with

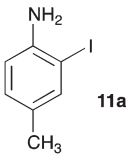
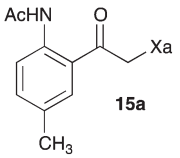
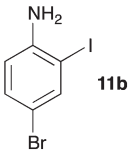
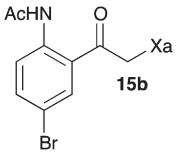
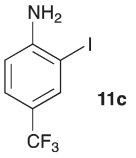
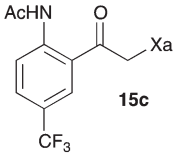
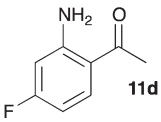
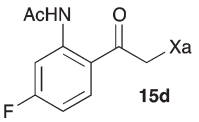
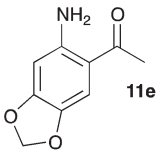
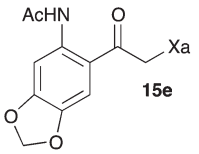


Scheme 5 Strategy for the synthesis of 1-naphthylamines.



Scheme 6 Synthesis of xanthate precursors **15**. (a) $PdCl_2(PPh_3)_2$ 2 mol%, CuI 1 mol%, TMSCCH, Et_3N, THF, rt; (b) Ac_2O, DCM, rt; (c) K_2CO_3, MeOH, rt; (d) NBS, $FeCl_3$ 5 mol%, H_2O : THF (1 : 1) reflux; (e) $(EtO)_2POH$, Et_3N, THF, rt; (f) PHP, AcOH 50 °C; (g) $CuBr_2$, CH_3COOEt : $CHCl_3$ (1 : 1) reflux; (h) KXa, acetone, rt.

Table 3 Formation of xanthates **15**

Precursors **11**	Xanthate **15**	Yield (%)
 **11a**	 **15a**	49
 **11b**	 **15b**	53
 **11c**	 **15c**	48
 **11d**	 **15d**	63
 **11e**	 **15e**	40

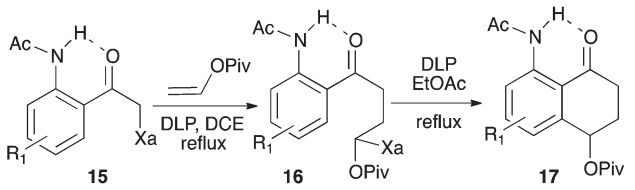
the naked phenol, which is able to form a strong hydrogen bond with the ketone oxygen.[9] This hydrogen bond freezes the structure in the correct conformation **B** for cyclisation and, at the same time, slows down considerately the rate of hydrogen abstraction from the phenol.[10] Indeed both the addition and cyclisation steps could be accomplished on the unprotected phenol, as illustrated by the conversion of xanthate **10** into shinanolone by radical cyclisation followed by saponification of the acetate group in a two-step one-pot process.

We decided therefore to incorporate this feature into our synthesis of 1-naphthylamide derivatives. Thus, in the same fashion, an *N*-acetyl group *ortho* to the ketone bearing side-chain should exhibit a hydrogen bonding encouraging similarly the desired cyclisation and leading to a convenient synthesis of *N*-acetyl naphthylamides (Scheme 5).

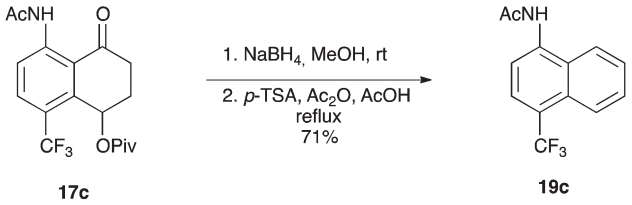
For the preparation of the requisite substituted xanthate precursors **15**, we applied the Sonogashira reaction on 2-iodoanilines, as pictured in Scheme 6.[11] Acetylation with acetic anhydride furnished acetanilides **12** in overall yields in excess of 90%. The trimethylsilyl group was first cleaved off by potassium carbonate in methanol at room temperature, followed by heating with *N*-bromosuccinimide in the presence of the iron trichloride catalyst in a refluxing mixture of water and tetrahydrofuran to provide the intermediate α-dibromo derivatives **13**.[12] This two-step sequence took place in around 60% yield. Intermediates **13** were easily reduced into the α-bromo derivatives **14** by diethyl phosphite $(EtO)_2POH$ and triethylamine in tetrahydrofuran at room temperature,[13] which were then converted into xanthates **15** by substitution of the bromine with potassium *O*-ethyl xanthate in almost quantitative yield for the two steps (Table 3). In cases where the 2-acetyl acetanilide was available, a simple bromination delivered the desired α-bromoacetyl precursor **14**. With xanthates **15** in hand, the synthesis of tetralones **17** could be accomplished as outlined in Scheme 7.

In this case, the additional products were obtained fairly cleanly after the addition of only 10 mol% of DLP. We observed that tetralones **17a** and **17b** started appearing after the consumption of around 40% of starting xanthates **15a** and **15b** respectively. This behaviour indicated that the corresponding intermediates **16a** and **16b** began to cyclise during the intermolecular addition process. As a result, we decided to add a stoichiometric amount of DLP to the mixture of xanthate **15** with vinyl pivalate in 10 mol% portions every hour to generate directly tetralones **17a** and **17b**. This indicated that the cyclisation of these compounds proceeded smoothly under mild conditions.

In the case of the other xanthates, **17c**, **17d** and **17e**, the addition–cyclisation procedure was the same as that for the synthesis of 2-naphthylamides. The overall yield for these one-pot reactions was generally higher than that for the substituted 2-naphthylamides discussed above and varied from 48% to 65% (Table 4). These results are in accord with our hypothesis

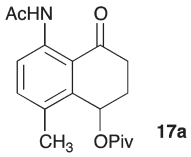
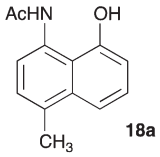
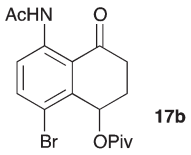
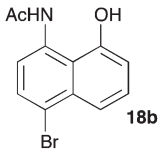
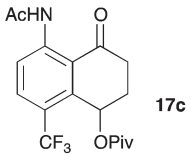
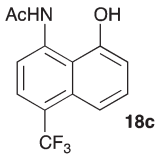
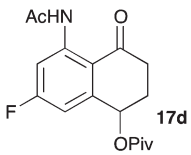
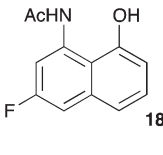
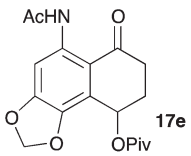
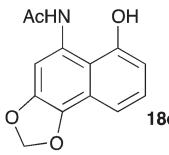


Scheme 7 Radical addition–cyclisation sequence.



Scheme 8 Synthetic variant leading to a naphthylamide.

Table 4 Cyclisation–aromatisation of xanthates **15**

Tetralones **17**	Yield (%)	1-Naphthylamide **18**	Yield (%)
 **17a**	48	 **18a**	74
 **17b**	51	 **18b**	72
 **17c**	60	 **18c**	74
 **17d**	65	 **18d**	60
 **17e**	57	 **18e**	70

regarding the crucial role of the intermolecular hydrogen bond in promoting the closure of the intermediate radical onto the aromatic ring.

Tetralones **17** could also be converted into *N*-acetylnaphthylamines by first reducing the ketone with $NaBH_4$,[14] followed by acid mediated aromatisation. A mixture of acetic acid and acetic anhydride was used as the solvent instead of toluene to prevent the deacetylation. In this manner, tetralone **17c** was transformed into *N*-acetyl-4-trifluoromethyl-1-naphthylamine (Scheme 8).

Substituted 1- and 2-naphthylamides with the halogen substituents are important because they can easily undergo transition metal catalysed coupling reactions and can act as a source of benzynes useful in Diels–Alder reactions.[15] Most of the naphthalene derivatives described herein are not readily accessible by other approaches.

Conclusion

In summary, we have presented a practical, convergent approach to protected 1- and 2-naphthylamides. Both electron withdrawing and electron donating substituents appear to be tolerated, reflecting the broad tolerance of radical processes in general. Numerous naphthylamines with a defined substitution pattern can now be obtained by simply varying the substitution of the starting xanthates or by modifying the tetralones prior to the aromatisation step. In the case of substituents in the *meta* position in starting xanthates **4**, the radical cyclisation leads normally to a mixture of two regioisomeric tetralones.[4] This regioselectivity issue can be resolved in principle blocking temporarily the undesired position, for example with a halogen atom that could be removed later, or by sterically hindering the unwanted cyclisation mode by placing a bulky protecting group on a neighbouring position.

Experimental

All reactions were carried out under dry, oxygen free nitrogen. Flash chromatography was performed on silica gel (SDS, 60 Å C.C. 40–63 mm) as the stationary phase. Thin Layer Chromatography (TLC) was performed on alumina plates pre-coated with silica gel (Merck silica gel, 60 F254), which were visualized by the quenching of UV fluorescence when applicable (λ_{max} = 254 nm and/or 366 nm) and/or by staining with vanillin or anisaldehyde in acidic ethanol followed by heating. Infrared spectra were recorded as solutions in CH_2Cl_2 using NaCl cells, on a Perkin-Elmer FT 2000. Absorption maxima (nmax) are reported in wavenumbers (cm^{-1}) and only selected peaks are reported. Magnetic resonance spectra were recorded at rt on a Bruker Avance DPX 400 instrument. Proton magnetic resonance spectra (^{1}H NMR) were recorded at 400 MHz and coupling constants (J) are reported to ±0.5 Hz. The following abbreviations were utilized to describe peak patterns where appropriate: br = broad, s = singlet, d = doublet, t = triplet, bs = broad singlet, bd = broad doublet, bt = broad triplet, q = quartet. Carbon magnetic resonance spectra (^{13}C NMR) were recorded in the same instrument at 100.6 MHz. Chemical shifts (δH, δC) are quoted in parts per million (ppm) and are referenced to TMS (0 ppm). Low-resolution mass spectra (m/z) were recorded by chemical ionization (CI/NH_3) on a Hewlett-Packard HP 5989B and only report molecular species ($[M + H]^+$, $[M + NH_4]^+$) and other major fragments.

High-resolution mass spectra were recorded by positive electron impact ionization (EI+) at 70 eV on a JEOL JMS-GCmate II mass spectrometer. The quoted masses are accurate to ±5 ppm. The names of the molecules that appear in the following pages were generated using either Beilstein AutoNom 2000 (CAS) or ChemBioDraw Ultra 10.0.

General procedure I for the formation of xanthates (4)

Step 1: Bromination of substituted acetophenones **2**: A solution of the 2-phthalimido-acetophenone (**2**) (5 mmol) in acetic acid (15 mL) at rt was added pyridinium hydrobromide perbromide (880 mg, 5.5 mmol). The reaction mixture was heated at 70 °C for 4 hours, cooled and diluted with dichloromethane (15 mL). The resulting solution was then washed with water, then with a saturated aqueous solution of $NaHCO_3$ (2 times) and then with brine. The organic phase was dried with $MgSO_4$ and evaporated to dryness under reduced pressure. The crude residue contained the mixture of the desired product (around 60% by NMR) and the starting material. Step 2: Formation of xanthate (**4**): To a stirred solution of the crude product of step 1 in acetone (10 mL) at rt was added portion-wise potassium *O*-ethyl xanthate (885 mg, 5.5 mmol). The reaction was stirred until the complete consumption of the starting material. The acetone was evaporated and the reaction mixture was diluted with ethyl acetate. The organic phase was washed with water and brine, dried over $MgSO_4$, filtered and evaporated to dryness under reduced pressure. The residue was purified by silica gel column chromatography or recrystallised to afford the desired xanthate.

***S*-1-(1,3-Dioxoisoindolin-2-yl)-2-oxo-2-phenylethyl *O*-ethyl carbonodithioate (4a).** Following general procedure I, after workup, the residue was washed with hot ethanol several times to eliminate the starting un-brominated acetophenone (**2a**) and afford the desired xanthate (**4a**) as a white solid (1.1 g, 57%). Mp: 149–150 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.95 (d, J = 8.0 Hz, 2H), 7.89 (m, 2H), 7.86 (s, 1H), 7.58 (t, 7.4 Hz, 1H), 7.75 (m, 2H), 7.45 (t, J = 7.4 Hz, 2H), 4.72 (m, 2H), 1.46 (t, J = 7.1 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 210.2 (CS), 189.4 (CO), 166.4 (2CO), 134.5 (2CH), 133.9 (2CH), 133.6 (Cq), 131.7 (2Cq), 128.8 (2CH), 128.6 (2CH), 123.9 (2CH), 71.8 (CH), 62.0 (CH_2), 13.8 (CH_3). IR (ν, cm^{-1}): 1704, 1653, 1558, 1231, 1113, 1053. HRMS (EI) Calcd for $C_{19}H_{15}NO_4S_2$: 385.0442. Found: 385.0442.

***S*-1-(1,3-Dioxoisoindolin-2-yl)-2-(4-fluorophenyl)-2-oxoethyl *O*-ethyl carbonodithioate (4b).** Following general procedure I, after workup, the residue was purified by silica gel column chromatography with a gradient of dichloromethane in petroleum ether (30 : 70 to 50 : 50) to afford xanthate (**4b**) (1.09 g, 54%) as a white solid. Mp: 131–132 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.99 (m, 2H), 7.89 (m, 2H), 7.83 (m, 1H), 7.75 (m, 2H), 7.13 (t, J = 8.6 Hz, 2H), 4.72 (m, 2H), 1.44 (t, J = 7.1 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 210.2 (CS), 187.9 (CO), 166.4 (2CO), 166.2 (d, J = 256 Hz, Cq), 134.6 (2CH), 131.7 (2Cq), 131.5 (d, J = 9 Hz, CH), 129.9 (d, J = 3 Hz, Cq), 123.9 (2CH), 116.1 (d, J = 22 Hz, 2CH), 71.9 (CH), 62.0 (CH_2), 13.8 (CH_3). IR (ν, cm^{-1}): 1777, 1731, 1703, 1601, 1377, 1240, 1103, 1048. HRMS (EI) Calcd for $C_{19}H_{14}FNO_4S_2$: 403.0348. Found: 403.0350.

***S*-2-(4-Bromophenyl)-1-(1,3-dioxoisoindolin-2-yl)-2-oxoethyl *O*-ethyl carbonodithioate (4c).** Following general procedure I, after workup, the residue was purified by silica gel column chromatography with a gradient of dichloromethane in petroleum ether (30 : 70 to 50 : 50) to afford xanthate (**4c**) (1.25 g, 54%) as a white solid. Mp: 102–103 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.90 (m, 2H), 7.81 (m, 3H), 7.76 (m, 2H), 7.60 (m, 2H), 4.73 (m, 2H), 1.44 (t, J = 7.1 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 210.2 (CS), 188.6 (CO), 166.4 (2CO), 134.6 (2CH), 132.4 (Cq), 132.2 (2CH), 131.7 (2Cq), 130.0(2CH), 129.3 (Cq), 124.0 (2CH), 72.0 (CH), 62.0 (CH_2), 13.8 (CH_3). IR (ν, cm^{-1}): 1731, 1703, 1588, 1377, 1242, 1048. HRMS (EI) Calcd for $C_{19}H_{14}BrNO_4S_2$: 462.9548. Found: 462.9548.

***S*-2-(4-Chlorophenyl)-1-(1,3-dioxoisoindolin-2-yl)-2-oxoethyl *O*-ethyl carbonodithioate (4d).** Following general procedure I, after workup, the residue was purified by silica gel column chromatography with a gradient of dichloromethane in toluene (30 : 70 to 50 : 50) to afford xanthate (**4d**) (1.15 g, 55%) as a light yellow solid. Mp: 84–85 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.90 (m, 4H), 7.83 (s, 1H), 7.76 (m, 2H), 7.43 (m, 2H), 4.72 (m, 2H), 1.45 (t, J = 7.1 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 210.2 (CS), 188.4 (CO), 166.4 (2CO), 140.5 (Cq), 134.6 (2CH), 131.9 (Cq), 131.7 (2Cq), 130.0 (2CH), 129.2 (2CH), 123.9 (2CH), 72.0 (CH), 62.0 (CH_2), 13.8 (CH_3). IR (ν, cm^{-1}) 1731, 1703, 1596, 1376, 1243, 1094, 1048. HRMS (EI) Calcd for $C_{19}H_{14}ClNO_4S_2$: 419.0053. Found: 419.0045.

***S*-1-(1,3-Dioxoisoindolin-2-yl)-2-oxo-2-(4-(trifluoromethyl)-phenyl)-ethyl *O*-ethyl carbonodithioate (4e).** Following general procedure I, after workup, the residue was purified by silica gel column chromatography with a gradient of ethyl acetate in petroleum ether (5 : 95 to 15 : 85) to afford xanthate (**4e**) (1.2 g, 53%) as a light yellow solid. Mp: 57–58 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.05 (m, 2H), 7.87 (m, 3H), 7.70–7.76 (m, 4H), 4.73 (m, 2H), 1.42 (t, J = 7.1 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 210.0 (CS), 188.9 (CO), 166.3 (2CO), 136.7 (Cq), 135.0 (q, J = 33 Hz, Cq), 134.7 (2CH), 131.6 (2Cq), 128.9 (2CH), 125.9 (2CH), 124.0 (2CH), 123.4 (q, J = 272 Hz, CF_3), 72.2 (CH), 62.2 (CH_2), 13.8 (CH_3). IR (ν, cm^{-1}): 1777, 1731, 1708, 1615, 1410, 1376, 1324, 1242, 1175, 1140, 1048. HRMS (EI) Calcd for $C_{20}H_{14}F_3NO_4S_2$: 453.0316. Found: 453.0321.

General procedure II for the synthesis of tetralones (6) by radical addition and cyclisation

A magnetically stirred solution of xanthate (1 mmol) and olefin (2.5 mmol) in 1,2-dichloroethane (1 mL) was refluxed for 15 min under a nitrogen flow. Dilauroyl peroxide (DLP) (5 mol%) was then added and additional DLP (2.5 mol%) was added every 60 min until total consumption of the starting material or until no evolution could be detected by TLC analysis. The reaction mixture was then cooled to 20 °C and evaporated to dryness under reduced pressure. The residue was then dissolved in 10 mL ethyl acetate or chlorobenzene. The mixture was refluxed for 15 min under a nitrogen flow. Dilauroyl peroxide (DLP) (20 mol%) was then added and

additional DLP (20 mol%) was added every 60 min until total consumption of the starting material or until no evolution could be detected by TLC analysis. The reaction mixture was then cooled to 20 °C and evaporated to dryness under reduced pressure. The residue was purified by silica gel column chromatography to yield the desired compounds.

3-(1,3-Dioxoisoindolin-2-yl)-4-oxo-1,2,3,4-tetrahydronaphthalen-1-yl pivalate (6a). Following general procedure II, the reaction was carried out using xanthate (**4a**) (385 mg, 1 mmol, 1 equiv.) and vinyl pivalate (0.37 mL, 2.5 mmol, 2.5 equiv.) in refluxing 1,2-dichloroethane (1 mL); it needed 25 mol% DLP to go to completion. After the reaction mixture was evaporated to dryness under reduced pressure, the residue was dissolved in chlorobenzene (10 mL), heated to reflux and treated with 1.2 equiv. of DLP. After evaporation, the residue was purified by silica gel column chromatography using a gradient of dichloromethane in petroleum ether (30 : 70 to 50 : 50) to afford 187 mg mixture of (**6a**) contaminated with (**2a**) ((**6a**) : (**2a**) = 1 : 0.2) as a yellow oil. The calculated NMR yield of (**6a**) is 42%. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.16 (m, 1H), 7.90 (m, 2H), 7.78 (m, 2H), 7.69 (m, 1H), (7.41–7.57, m, 2H), 6.35 (dd, J = 11.5 Hz, J = 5.0 Hz, 1H maj), 6.25 (m, 1H min), 5.54 (dd, J = 13.3 Hz, J = 4.8 Hz, 1H min), 5.18 (dd, J = 14.2 Hz, J = 4.6 Hz, 1H maj), 3.28 (dt, J = 13.3 Hz, J = 2.9 Hz, 1H min), 3.11 (td, J = 14.2 Hz, J = 11.6 Hz, 1H maj), 2.66 (td, J = 11.6 Hz, J = 4.6 Hz, 1H maj), 2.54 (m, 1H min), 1.31 (s, 9H maj), 1.22 (s, 9H min). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 191.1 (CO min), 190.3 (CO maj), 177.8 (CO maj + min), 167.7 (2CO maj), 167.6 (2CO min), 142.4 (Cq maj), 139.2 (Cq min), 134.7 (CH min), 134.5 (CH maj), 134.3 (2CH maj + min), 132.9 (2Cq maj), 132.0 (2Cq min), 131.4 (Cq min), 130.3 (Cq maj), 130.1 (CH maj), 129.8 (CH min), 128.5 (CH min), 128.2 (CH maj), 128.1 (CH min), 125.6 (CH maj), 123.6 (2CH maj + min), 68.6 (CH maj), 68.3 (CH min), 53.1 (CH maj), 50.7 (CH min), 39.1 (Cq maj + min), 33.8 (CH_2 maj), 32.9 (CH_2 min), 27.2 ($3CH_3$ maj), 27.1 ($3CH_3$ min). IR (ν, cm^{-1}): 2974, 2909, 1725, 1605, 1390, 1230, 1145, 1003. HRMS (EI) Calcd for $C_{23}H_{20}BrNO_5$: 391.1420. Found: 391.1436.

3-(1,3-Dioxoisoindolin-2-yl)-7-fluoro-4-oxo-1,2,3,4-tetrahydronaphthalen-1-yl pivalate (6b). Following general procedure II, the reaction was carried out using xanthate (**4b**) (403 mg, 1 mmol, 1 equiv.) and vinyl pivalate (0.37 mL, 2.5 mmol, 2.5 equiv.) in refluxing 1,2-dichloroethane (1 mL); it needed 25 mol% DLP to go to completion. The reaction mixture was then evaporated to dryness under reduced pressure and the residue was dissolved in chlorobenzene (10 mL), heated to reflux and treated with 1.2 equiv. DLP. After evaporation, the residue was purified by silica gel column chromatography with a gradient of dichloromethane in petroleum ether (30 : 70 to 50 : 50) to afford (**6b**) (184 mg, 45%) as a yellow oil. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.16 (m, 1H), 7.85 (m, 2H), 7.73 (m, 2H), 7.03–7.23 (m, 2H), 6.28 (dd, J = 11.6 Hz, J = 5.0 Hz, 1H maj), 6.19 (m, 1H min), 5.50 (dd, J = 13.2 Hz, J = 4.8 Hz, 1H min), 5.17 (dd, J = 14.2 Hz, J = 4.6 Hz, 1H maj), 3.26 (dt, J = 13.6 Hz, J = 2.9 Hz, 1H min), 3.08 (m, 1H maj), 2.65 (td, J = 11.5 Hz, J = 4.8 Hz, 1H maj), 2.48 (m, 1H min), 1.30 (s, 9H maj), 1.22 (s, 9H min). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 189.7 (CO min), 189.0 (CO maj), 177.6 (CO maj), 177.5 (CO min), 167.7 (2CO maj), 167.5 (2CO min), 166.6 (d, J = 256 Hz, Cq maj), 166.2 (d, J = 256 Hz, Cq min), 145.7 (d, J = 9 Hz, Cq maj), 142.2 (d, J = 9 Hz, Cq min), 134.3 (d, J = 3 Hz, 2CH maj + min), 132.0 (2Cq maj + min), 131.6 (d, J = 10 Hz, CH maj), 131.4 (d, J = 10 Hz, CH min), 128.1 (d, J = 3 Hz, Cq min), 126.9 (d, J = 3 Hz, Cq maj), 123.6 (2CH maj + min), 117.5 (d, J = 22 Hz, CH min), 116.8 (d, J = 22 Hz, CH min), 116.3 (d, J = 22 Hz, CH maj), 112.6 (d, J = 23 Hz, CH maj), 68.0 (CH maj), 67.9 (CH min), 52.9 (CH maj), 50.4 (CH min), 39.0 (Cq maj + min), 33.8 (CH_2 maj), 32.8 (CH_2 min), 27.1 ($3CH_3$ maj + min). IR (ν, cm^{-1}): 3412, 1783, 1724, 1612, 1551, 1389, 1264, 1142. HRMS (EI) Calcd for $C_{23}H_{20}FNO_5$: 409.1326. Found: 409.1327.

7-Bromo-3-(1,3-dioxoisoindolin-2-yl)-4-oxo-1,2,3,4-tetrahydronaphthalen-1-yl pivalate (6c). Following general procedure II, the reaction was carried out using xanthate (**4c**) (464 mg, 1 mmol, 1 equiv.) and vinyl pivalate (0.37 mL, 2.5 mmol, 2.5 equiv.) in refluxing 1,2-dichloroethane (1 mL); it needed 25 mol% DLP to go to completion. The reaction mixture was then evaporated to dryness under reduced pressure, and the residue was dissolved in chlorobenzene (10 mL), heated to reflux and treated with 1.2 equiv. of DLP. After evaporation, the residue was purified by silica gel column chromatography with a gradient of dichloromethane in petroleum ether (30 : 70 to 50 : 50) to afford **6c** (187 mg, 40%) as a yellow oil. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.79 (m, 1H), 7.86 (m, 2H), 7.52–7.75 (m, 4H), 6.29 (dd, J = 11.6 Hz, J = 5.0 Hz, 1H maj), 6.17 (m, 1H min), 5.49 (dd, J = 13.3 Hz, J = 4.8 Hz, 1H min), 5.16 (dd, J = 14.2 Hz, J = 4.6 Hz, 1H maj), 3.23 (dt, J = 2.9 Hz, J = 13.6 Hz, 1H min), 3.07 (td, J = 11.6 Hz, J = 14.2 Hz, 1H maj), 2.64 (td, J = 4.8 Hz, J = 11.6 Hz, 1H maj), 2.48 (m, 1H min), 1.31 (s, 9H maj), 1.22 (s, 9H min). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 190.4 (CO min), 189.6 (CO maj), 177.6 (CO maj), 177.5 (CO min), 167.6 (2CO maj), 167.5 (2CO min), 144.0 (Cq maj), 140.7 (Cq min), 134.3 (2CH maj + min), 133.3 (CH min), 133.0 (CH min), 132.0 (CH maj), 131.9 (2Cq maj), 131.8 (2Cq min), 130.1 (Cq maj + min), 130.0 (Cq min), 129.9 (CH maj), 129.8 (CH min), 129.1 (Cq maj), 129.0 (CH maj), 123.7 (2CH maj + min), 67.9 (CH min), 67.7 (CH maj), 52.9 (CH maj), 50.5 (CH min), 39.0 (Cq maj + min), 33.7 (CH_2 maj), 32.8 (CH_2 min), 27.2 ($3CH_3$ maj), 27.1 ($3CH_3$ min). IR (ν, cm^{-1}): 3481, 1726, 171à, 1589, 1470, 1389, 1142. HRMS (EI) Calcd for $C_{23}H_{20}BrNO_5$: 469.0525. Found: 469.0520.

7-Chloro-3-(1,3-dioxoisoindolin-2-yl)-4-oxo-1,2,3,4-tetrahydronaphthalen-1-yl pivalate (6d). Following general procedure II, the reaction was carried out using xanthate (**4d**) (420 mg, 1 mmol, 1 equiv.) and vinyl pivalate (0.37 mL, 2.5 mmol, 2.5 equiv.) in refluxing 1,2-dichloroethane (1 mL); it needed 30 mol% DLP to go to completion. The reaction mixture was evaporated to dryness under reduced pressure and the residue was dissolved in chlorobenzene (10 mL), heated to reflux and treated with 1.2 equiv. of DLP. After evaporation, the residue was purified by silica gel column chromatography with a gradient of dichloromethane in petroleum ether (30 : 70 to 50 : 50) to afford **6d** (157 mg, 37%) as a yellow oil. ^{1}H-NMR ($CDCl_3$,

400 MHz) δ 8.07 (m, 1H), 7.87 (m, 2H), 7.75 (m, 2H), 7.36–7.54 (m, 2H), 6.28 (dd, J = 11.6 Hz, J = 4.9 Hz, 1H maj), 6.16 (m, 1H min), 5.50 (dd, J = 13.2 Hz, J = 4.8 Hz, 1H min), 5.16 (dd, J = 14.2 Hz, J = 4.7 Hz, 1H maj), 3.24 (dt, J = 13.7 Hz, J = 2.9 Hz, 1H min), 3.08 (m, 1H maj), 2.65 (m, 1H maj), 2.49 (m, 1H min), 1.31 (s, 9H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 190.2 (CO min), 189.4 (CO maj), 177.6 (CO maj + min), 167.6 (2CO maj), 167.5 (2CO min), 144.0 (Cq maj), 141.3 (Cq maj), 141.1 (Cq min), 140.7 (Cq min), 134.3 (2CH maj + min), 132.0 (2Cq min), 131.9 (2Cq maj), 130.3 (CH min), 130.0 (CH min), 129.9 (CH maj), 129.8 (CH min), 129.1 (CH maj), 128.7 (Cq maj + min), 125.8 (CH maj), 123.6 (2CH maj + min), 68.0 (CH min), 67.8 (CH maj), 52.9 (CH maj), 50.5 (CH min), 39.0 (Cq maj + min), 33.7 (CH_2 maj), 33.5 (CH_2 min), 27.1 ($3CH_3$). IR (ν, cm^{-1}): 3486, 1782, 1727, 1595, 1470, 1389, 1230, 1142. HRMS (EI) Calcd for $C_{23}H_{20}ClNO_5$: 425.1030. Found: 425.1036.

3-(1,3-Dioxoisoindolin-2-yl)-4-oxo-7-(trifluoromethyl)-1,2,3,4-tetrahydronaphthalen-1-yl pivalate (6e). Following general procedure II, the reaction was carried out using xanthate (**4e**) (455 mg, 1 mmol, 1 equiv.) and vinyl pivalate (0.37 mL, 2.5 mmol, 2.5 equiv.) in refluxing 1,2-dichloroethane (1 mL); it needed 25 mol% DLP to go to completion. The reaction mixture was evaporated to dryness under reduced pressure and the residue was dissolved in chlorobenzene (10 mL), heated to reflux and treated with 1.2 equiv. DLP. After evaporation, the residue was purified by silica gel column chromatography with a gradient of dichloromethane in petroleum ether (30 : 70 to 50 : 50) to afford (**6e**) (188 mg, 41%) as a white solid. The product consisted of a 33 : 67 mixture of two diastereoisomers of (**6e**) and a pure sample of the major diastereoisomer could be obtained by chromatography. Mp: 185–186 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.25 (d, J = 8.1 Hz, 1H), 7.67–7.89 (m, 6H), 6.36 (dd, J = 11.4 Hz, J = 4.9 Hz, 1H), 5.22 (dd, J = 14.2 Hz, J = 4.7 Hz, 1H), 3.11 (m, 1H), 2.70 (m, 1H), 1.33 (s, 9H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 189.5 (CO), 177.6 (CO), 167.4 (2CO), 143.2 (Cq), 135.8 (q, J = 33 Hz, Cq), 134.4 (2CH), 132.7 (Cq), 131.9 (2Cq), 129.1 (CH), 125.3 (q, J = 3.5 Hz, CH), 123.7 (2CH), 123.3 (q, J = 272 Hz, CF_3), 123.0 (q, J = 3.9 Hz, CH), 67.8 (CH), 53.0 (CH), 39.1 (Cq), 33.7 (CH_2), 27.1 ($3CH_3$). IR (ν, cm^{-1}): 3615, 1726, 1549, 1389, 1142. HRMS (EI) Calcd for $C_{24}H_{20}F_3NO_5$: 459.1294. Found: 459.1283.

General procedure III for the aromatisation into naphthylamine derivatives (7)

To a solution of tetralone (**6**) (1 mmol) in toluene (3 mL), *p*-toluenesulfonic acid (PTSA; 3 mmol) was added and the reaction mixture was heated to reflux using a Dean–Stark apparatus for 3 h. The reaction mixture was allowed to cool to rt, diluted with saturated sodium carbonate solution, and extracted with ethyl acetate. The combined organic layers were dried and concentrated. The residue was washed with pentane or dichloromethane, and then filtered to afford the desired product.

2-(1-Hydroxynaphthalen-2-yl)isoindoline-1,3-dione (7a). Following general procedure III, the reaction was carried out using (**6a**) (78 mg, 0.2 mmol, 1 equiv.) and PTSA (105 mg, 0.6 mmol, 3 equiv.) in refluxing toluene (3 mL). The residue was washed with dichloromethane to afford (**7a**) (48 mg, 83%). Mp: 287–288 °C. ^{1}H-NMR (DMSO-D_6, 400 MHz) δ 10.20 (bs, 1H), 8.23 (d, J = 8.0 Hz, 1H), 7.90–7.99 (m, 5H), 7.55 (m, 2H), 7.45 (d, J = 8.6 Hz, 1H), 7.33 (d, J = 8.6 Hz, 1H). ^{13}C-NMR (DMSO-D6, 100 MHz) δ 167.6 (2CO), 150.1 (Cq), 134.3 (2CH), 132.5 (2Cq), 132.4 (Cq), 127.5 (CH), 127.4 (CH), 127.1 (CH), 125.3 (CH), 125.2 (Cq), 123.2 (2CH), 122.5 (CH), 118.7 (CH), 112.4 (Cq). IR (ν, cm^{-1}): 3377, 1696, 1541, 1399, 1229, 1083. HRMS (EI) Calcd for $C_{18}H_{11}NO_3$: 289.0739. Found: 289.0737.

2-(6-Fluoro-1-hydroxynaphthalen-2-yl)isoindoline-1,3-dione (7b). Following general procedure III, the reaction was carried out using (**6b**) (82 mg, 0.2 mmol, 1 equiv.) and PTSA (105 mg, 0.6 mmol, 3 equiv.) in refluxing toluene (3 mL). The residue was washed with dichloromethane to afford (**7b**) as a yellow solid (48 mg, 78%). Mp: 265–267 °C. ^{1}H-NMR (DMSO-D_6, 400 MHz) δ 10.32 (bs, 1H), 8.30 (dd, J = 9.2 Hz, J = 5.9 Hz, 1H), 7.90–7.99 (m, 4H), 7.70 (dd, J = 10.4 Hz, J = 2.6 Hz, 1H), 7.37–7.46 (m, 3H). ^{13}C-NMR (DMSO-D_6, 100 MHz) δ 167.6 (2CO), 160.9 (d, J = 245 Hz, Cq), 150.4 (Cq), 135.4 (d, J = 10 Hz, Cq), 134.3 (2CH), 132.5 (2Cq), 128.9 (CH), 125.8 (d, J = 9 Hz, CH), 123.2 (2CH), 122.4 (Cq), 118.2 (d, J = 5 Hz, CH), 115.2 (d, J = 25 Hz, CH), 112.1 (d, J = 2 Hz, Cq), 110.6 (d, J = 21 Hz, Cq). IR (ν, cm^{-1}): 3313, 1721, 1551, 1398, 1244. HRMS (EI) Calcd for $C_{18}H_{10}FNO_3$: 307.0645. Found: 307.0644.

2-(6-Bromo-1-hydroxynaphthalen-2-yl)isoindoline-1,3-dione (7c). Following general procedure III, the reaction was carried out using (**6c**) (95 mg, 0.2 mmol, 1 equiv.) and PTSA (105 mg, 0.6 mmol, 3 equiv.) in refluxing toluene (3 mL). The residue was washed with dichloromethane to afford a yellow solid (**7c**) (53 mg, 72%). Mp: 294–295 °C. ^{1}H-NMR (DMSO-D_6, 400 MHz) δ 10.40 (bs, 1H), 8.18 (m, 2H), 7.97–7.99 (m, 4H), 7.66 (m, 1H), 7.43 (m, 2H). ^{13}C-NMR (DMSO-D_6, 100 MHz) δ 167.5 (2CO), 150.4 (Cq), 135.5 (Cq), 134.3 (2CH), 132.5 (2Cq), 129.3 (CH), 128.9 (CH), 128.2 (CH), 125.0 (CH), 123.8 (Cq), 123.2 (2CH), 120.6 (Cq), 117.9 (CH), 113.0 (Cq). IR (ν, cm^{-1}): 3301, 1701, 1550, 1398, 1103. HRMS (EI) Calcd for $C_{18}H_{10}BrNO_3$: 366.9844. Found: 366.9845.

2-(6-Chloro-1-hydroxynaphthalen-2-yl)isoindoline-1,3-dione (7d). Following general procedure III, the reaction was carried out using (**6d**) (85 mg, 0.2 mmol, 1 equiv.) and PTSA (105 mg, 0.6 mmol, 3 equiv.) in refluxing toluene (3 mL). The residue was washed with dichloromethane to afford a yellow solid (**7d**) (52 mg, 80%). Mp: 283–284 °C. ^{1}H-NMR (DMSO-D_6, 400 MHz) δ 10.40 (bs, 1H), 8.25 (m, 2H), 7.91–8.05 (m, 4H), 7.40–7.56 (m, 3H).^{13}C-NMR (DMSO-D_6, 100 MHz) δ 167.5 (2CO), 150.4 (Cq), 135.5 (Cq), 134.3 (2CH), 132.5 (2Cq), 131.9 (CH), 128.9 (Cq), 126.1 (Cq), 125.7 (CH), 125.0 (CH), 123.7 (2CH), 123.2 (Cq), 118.0 (CH), 113.0 (Cq). IR (ν, cm^{-1}): 3302, 1708, 1152, 1396, 1265, 1082. HRMS (EI) Calcd for $C_{18}H_{10}ClNO_3$: 323.0349. Found: 323.0349.

2-(1-Hydroxy-6-(trifluoromethyl)naphthalen-2-yl)isoindoline-1,3-dione (7e). Following general procedure III, the reaction was carried out using (**6e**) (92 mg, 0.2 mmol, 1 equiv.) and PTSA (105 mg, 0.6 mmol, 3 equiv.) in refluxing toluene (3 mL).

The residue was washed with dichloromethane to afford (**7e**) as a yellow solid (56 mg, 79%). Mp: 307–309 °C. ^{1}H-NMR (DMSO-D_6, 400 MHz) δ 10.58 (bs, 1H), 8.43 (m, 2H), 7.91–8.00 (m, 4H), 7.78 (d, J = 8.9 Hz, 1H), 7.69 (d, J = 8.7 Hz, 1H), 7.52 (d, J = 8.7 Hz, 1H). ^{13}C-NMR (DMSO-D_6, 100 MHz) δ 167.4 (2CO), 150.2 (Cq), 134.4 (2CH), 133.1 (Cq), 132.4 (2Cq), 129.1 (CH), 127.3 (q, J = 32 Hz, Cq), 126.7 (Cq), 125.4 (q, J = 5 Hz, CH), 124.4 (q, J = 272 Hz, CF_3), 124.3 (CH), 123.3 (2CH), 120.5 (d, J = 3 Hz, CH), 119.7 (CH), 114.7 (Cq). IR (ν, cm^{-1}): 3333, 1713, 1554, 1264, 1102. HRMS (EI) Calcd for $C_{19}H_{10}F_3NO_3$: 357.0613. Found: 357.0615.

General procedure IV for the Sonogashira reaction

A suspension of 2-iodoaniline (1.0 mmol), $PdCl_2(PPh_3)_2$ (14.0 mg, 0.02 mmol, 2.0 mol%) and CuI (2.0 mg, 0.01 mmol, 1.0 mol%) in 2 mL triethylamine and 2 mL THF was degassed with argon and evacuated/backfilled with argon (3 cycles). The reaction mixture was stirred at rt for 10 minutes. After addition of the alkyne (1.2 mmol) the suspension was stirred for 24 hours at rt under an argon atmosphere. The reaction mixture was evaporated to dryness under reduced pressure, then diluted with 2.0 mL water and extracted with EtOAc (2 × 2.0 mL). The combined organic phases were washed with brine and dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded the desired product. To a solution of the Sonogashira product (1 mmol) in dichloromethane (2 mL) was added Ac_2O (1.25 mmol) and the resulting solution was stirred at rt until complete consumption of the starting material. It was then diluted with dichloromethane, extracted with saturated solution of $NaHCO_3$, brine, dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by silica gel column chromatography with a gradient of ethyl acetate in petroleum ether (5/95 to 35/65) to afford the product as a solid.

***N*-(4-Methyl-2-((trimethylsilyl)ethynyl)phenyl)acetamide (12a).** Following general procedure IV, to a solution of 2-iodo-4-methylaniline (20 mmol, 4.66 g, 1.0 equiv.), $PdCl_2(PPh_3)_2$ (280 mg, 0.4 mmol, 2.0 mol%) and CuI (40 mg, 0.2 mmol, 1.0 mol%) in 40 mL triethylamine in 40 mL THF, trimethylsilylacetylene (24 mmol, 3.42 mL, 1.2 equiv.) was added. After workup, the product was dissolved in DCM (40 mL) and then Ac_2O (25 mmol, 2.36 mL, 1.25 equiv.) was added. Upon complete acetylation, the residue was purified by silica gel column chromatography with a gradient of ethyl acetate in petroleum ether (5/95 to 25/75) to afford the product (**12a**) as a pinkish solid (4.6 g, 95%). Mp: 82–83 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.25 (d, J = 8.4 Hz, 1H), 7.90 (bs, 1H), 7.22 (d, J = 1.3 Hz, 1H), 7.13 (dd, J = 8.4 Hz, J = 1.3 Hz, 1H), 2.27 (s, 3H), 2.09 (s, 3H), 0.00 (s, 9H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 167.9 (CO), 137.2 (Cq), 132.8 (Cq), 131.7 (CH), 130.8 (CH), 118.9 (CH), 111.5 (Cq), 101.8 (C≡C), 100.6 (C≡C), 24.8 (CH_3), 20.7 (CH_3), 0.0 ($3CH_3$). IR (ν, cm^{-1}): 3334, 2956, 2155, 1669, 1507, 1121. HRMS (EI) Calcd for $C_{14}H_{19}NOSi$: 245.1236. Found: 245.1240.

***N*-(4-Bromo-2-((trimethylsilyl)ethynyl)phenyl)acetamide (12b).** Following general procedure IV, to a solution of 2-iodo-4-bromoaniline (20 mmol, 5.96 g), $PdCl_2(PPh_3)_2$ (280 mg, 0.4 mmol, 2.0 mol%) and CuI (40 mg, 0.2 mmol, 1.0 mol%) in 40 mL triethylamine in 40 mL THF, trimethylsilylacetylene (24 mmol, 3.42 mL, 1.2 equiv.) was added. After workup, the product was dissolved in DCM (40 mL) and Ac_2O (25 mmol, 2.36 mL, 1.25 equiv.) was added. Upon complete acetylation, the residue was purified by silica gel column chromatography with a gradient of ethyl acetate in petroleum ether (5/95 to 25/75) to afford the product (**12b**) as a white solid (5.90 g, 92%). Mp: 88–100 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.31 (d, J = 8.9 Hz, 1H), 7.92 (bs, 1H), 7.53 (d, J = 2.3 Hz, 1H), 7.42 (dd, J = 8.9 Hz, J = 2.3 Hz, 1H), 2.20 (s, 3H), 0.00 (s, 9H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 168.2 (CO), 138.7 (Cq), 134.0 (CH), 133.0 (CH), 120.5 (CH), 115.4 (Cq), 113.6 (Cq), 104.0 (CH), 98.8 (CH), 25.0 (CH_3), 0.0 ($3CH_3$). IR (ν, cm^{-1}): 3304, 2925, 2162, 1673, 1519, 1393, 1297. HRMS (EI) Calcd for $C_{13}H_{16}BrNOSi$: 309.0185. Found: 309.0185.

***N*-(4-(Trifluoromethyl)-2-((trimethylsilyl)ethynyl)-phenyl)-acetamide (12c).** Following general procedure IV, the reaction was carried out with a solution of 2-iodo-4-methylaniline (20 mmol, 5.74 g), $PdCl_2(PPh_3)_2$ (280 mg, 0.4 mmol, 2.0 mol%) and CuI (40 mg, 0.2 mmol, 1.0 mol%) in 40 mL triethylamine in 40 mL THF, to which trimethylsilylacetylene (24 mmol, 3.42 mL, 1.2 equiv.) was added. After workup, the product was dissolved in DCM (40 mL) and then Ac_2O (25 mmol, 2.36 mL, 1.25 equiv.) was added. Upon complete acetylation, the residue was purified by silica gel column chromatography with a gradient of ethyl acetate in petroleum ether (5/95 to 35/65) to afford the product (**12c**) as a rose solid (5.45 g, 91%). Mp: 65–66 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.55 (d, J = 8.7 Hz, 1H), 8.10 (bs, 1H), 7.67 (d, J = 1.9 Hz, 1H), 7.55 (dd, J = 8.7 Hz, J = 1.9 Hz, 1H), 2.29 (s, 3H), 0.00 (s, 9H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 168.5 (CO), 142.0 (Cq), 128.7 (q, J = 4 Hz, CH), 127.0 (q, J = 4 Hz, CH), 125.3 (q, J = 33 Hz, Cq), 123.8 (q, J = 272 Hz, CF_3), 118.9 (CH), 112.0 (Cq), 104.3 (C≡C), 98.8 (C≡C), 25.1 (CH_3), 0.0 ($3CH_3$). IR (ν, cm^{-1}): 3307, 2972, 2161, 1681, 1520, 1416, 1331. HRMS (EI) Calcd for $C_{14}H_{16}F_3NOSi$: 299.0953. Found: 299.0955.

General procedure V for the preparation of dibromoacetylphenylacetamides (13)

To a solution of phenylacetamide (**12**) (1 mmol) in methanol (2.5 mL), potassium carbonate was added (5 mol%). After 30 minutes, the solvent was evaporated and to the residue, *N*-bromosuccinimide (2 mmol), $FeCl_3{\cdot}6H_2O$ (0.05 mmol), water (2.0 mL) and tetrahydrofuran (2.0 mL) were added under nitrogen at rt. The reaction temperature was raised to 80 °C for several hours. After the complete consumption of the starting material, the reaction mixture was cooled to rt and quenched with 2.0 mL of saturated $NaHCO_3$ and then extracted with 3 × 15 mL of ether. The combined extracts were dried over $MgSO_4$ and the solvent was evaporated *in vacuo* to afford the crude product, which was purified by silica gel column chromatography with a gradient of ethyl acetate in toluene (0/100 to 8/92) to afford the product as a solid.

***N*-(2-(2,2-Dibromoacetyl)-4-methylphenyl)acetamide (13a).** Following general procedure V, the reaction was carried

out with a solution of compound (**12a**) (2.45 g, 10 mmol) in MeOH (25 mL) and potassium carbonate (70 mg). After removing the methanol, *N*-bromosuccinimide (20 mmol, 3.56 g), $FeCl_3{\cdot}6H_2O$ (0.5 mmol, 135 mg), water (20 mL) and tetrahydrofuran (20 mL) were added under nitrogen at rt. The reaction temperature was raised to 80 °C and kept for 3 h. After workup, the crude product was purified by silica gel column chromatography with a gradient of ethyl acetate in toluene (0/100 to 8/92) to afford the product (**13a**) as a brown solid (1.98 g, 57%). Mp: 144–146 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 11.00 (bs, 1H), 8.67 (d, J = 8.7 Hz, 1H), 7.67 (s, 1H), 7.45 (d, J = 8.7 Hz, 1H), 6.92 (s, 1H), 2.37 (s, 3H), 2.24 (s, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 189.4 (CO), 169.3 (CO), 140.5 (Cq), 137.7 (CH), 132.1 (Cq), 130.5 (CH), 121.6 (CH), 116.0 (Cq), 40.1 (CH), 25.6 (CH_3), 20.9 (CH_3). IR (ν, cm^{-1}): 3371, 1678, 1579, 1505, 1462, 1249 HRMS (EI) Calcd for $C_{11}H_{11}Br_2NO_2$: 346.9157. Found: 346.9162.

***N*-(4-Bromo-2-(2,2-dibromoacetyl)phenyl)acetamide (13b).** Following general procedure V, the reaction was carried out with a solution of compound (**12b**) (3.1 g, 10 mmol) in MeOH (25 mL) and potassium carbonate (70 mg). After removing the methanol, *N*-bromosuccinimide (20 mmol, 3.56 g), $FeCl_3{\cdot}6H_2O$ (0.5 mmol, 135 mg), water (20 mL) and tetrahydrofuran (20 mL) were added under nitrogen at rt. The reaction temperature was raised to 80 °C and kept for 3 h. After workup, the crude product was purified by silica gel column chromatography with a gradient of ethyl acetate in toluene (0/100 to 8/92) to afford the product (**13b**) as a brown solid (2.69 g, 65%). Mp 140–141 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 11.00 (bs, 1H), 8.74 (d, J = 9.1 Hz, 1H), 8.03 (d, J = 2.3 Hz, 1H), 7.72 (d, J = 9.1 Hz, J = 2.3 Hz, 1H), 6.80 (s, 1H), 2.27 (s, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 194.3 (CO), 169.5 (CO), 140.9 (Cq), 138.8 (CH), 133.6 (CH), 122.9 (CH), 120.2 (Cq), 114.7 (Cq), 32.0 (CH), 25.6 (CH_3). IR (ν, cm^{-1}): 3330, 1682, 1564, 1495, 1393, 1295, 1195. HRMS (EI): Calcd for $C_{10}H_8Br_3NO_2$: 410.8105. Found: 410.8105.

***N*-(2-(2,2-Dibromoacetyl)-4-(trifluoromethyl)-phenyl)acetamide (13c).** Following general procedure V, the reaction was carried out with a solution of compound (**12c**) (3 g, 10 mmol, 3.0 g, 1 equiv.) in MeOH (25 mL) and potassium carbonate (0.5 mmol, 70 mg, 5 mol%). After removing the methanol, *N*-bromosuccinimide (20 mmol, 3.56 g, 2 equiv.), $FeCl_3{\cdot}6H_2O$ (0.5 mmol, 135 mg, 5 mol%), water (20 mL) and tetrahydrofuran (20 mL) were added under nitrogen at rt. The reaction temperature was raised to 80 °C and kept for 3 h. After workup, the crude product was purified by silica gel column chromatography with a gradient of ethyl acetate in toluene (0/100 to 8/92) to afford the product (**13c**) as a brown solid (2.40 g, 60%). Mp: 133–134 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 11.26 (bs, 1H), 8.98 (d, J = 9.0 Hz, 1H), 8.22 (d, J = 1.4 Hz, 1H), 7.85 (dd, J = 9.0 Hz, J = 1.4 Hz, 1H), 6.85 (s, 1H), 2.31 (s, 3H).^{13}C-NMR ($CDCl_3$, 100 MHz) δ 187.8 (CO), 168.7 (CO), 144.3 (Cq), 131.9 (q, J = 4 Hz, CH), 126.9 (q, J = 4 Hz, CH), 123.18 (q, J = 33.8 Hz, Cq), 122.2 (q, J = 272.0 Hz, CF_3), 120.7 (CH), 114.2 (Cq), 38.4 (CH), 24.7 (CH_3). IR (ν, cm^{-1}): 3296, 1693, 1586, 1515, 1421, 1299, 1131. HRMS (EI) Calcd for $C_{11}H_{11}Br_2NO_2$: 400.8874. Found: 400.8883.

General procedure VI for the preparation of monobromoketones (14)

To a mixture of dibromoketone (**13**) (1 mmol) and Et_3N (1.05 mmol) in THF (4 mL), $(EtO)_2POH$ (1.05 mmol) was added at rt. After 30 min, the resulting reaction solution was quenched with 2 mL of saturated $NaHCO_3$ and extracted with 3 × 15 mL of ethyl acetate. The combined extracts were dried over $MgSO_4$ and the solvent was evaporated *in vacuo* to afford the crude bromoketone (**14**), which was sufficiently pure for the next step.

***N*-(2-(2-Bromoacetyl)-4-methylphenyl)acetamide (14a).** Following general procedure VI, the reaction was carried out with a solution of compound (**13a**) (1.74 g, 5 mmol, 1 equiv.), Et_3N (0.73 mL, 5.25 mmol, 1.05 equiv.) and $(EtO)_2POH$ (0.67 mL, 5.25 mmol, 1.05 equiv.) in THF (20 mL) at rt. The product (**14a**) was obtained as a white solid (1.27 g, 95%). Mp: 139–141 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 11.25 (bs, 1H), 8.65 (d, J = 8.7 Hz, 1H), 7.64 (s, 1H), 7.41 (d, J = 8.7 Hz, 1H), 4.53 (s, 2H), 2.37 (s, 3H), 2.22 (s, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 195.1 (CO), 169.4 (CO), 139.6 (Cq), 137.0 (CH), 132.0 (Cq), 131.2 (CH), 121.2 (CH), 118.9 (Cq), 32.6 (CH_2), 25.6 (CH_3), 20.9 (CH_3). IR (ν, cm^{-1}): 3244, 1682, 1659, 1597, 1506, 1366, 1300, 1173. HRMS (EI): Calcd for $C_{11}H_{12}BrNO_2$: 269.0051. Found: 269.0056.

***N*-(4-Bromo-2-(2-bromoacetyl)phenyl)acetamide (14b).** Following general procedure VI, the reaction was carried out with a solution of compound (**13b**) (2.07 g, 5 mmol, 1 equiv.), Et_3N (0.73 mL, 5.25 mmol, 1.05 equiv.) and $(EtO)_2POH$ (0.67 mL, 5.25 mmol, 1.05 equiv.) in THF (20 mL) at rt. The product (**14b**) was obtained as a white solid (1.6 g, 96%). Mp: 188–190 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 11.26 (bs, 1H), 8.72 (d, J = 9.1 Hz, 1H), 7.97 (d, J = 2.3 Hz, 1H), 7.68 (dd, J = 9.1 Hz, J = 2.3 Hz, 1H), 4.49 (s, 2H), 2.24 (s, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 194.3 (CO), 169.5 (CO), 140.9 (Cq), 138.8 (CH), 133.6 (CH), 123.0 (CH), 120.3 (Cq), 114.7 (Cq), 32.6 (CH_2), 25.6 (CH_3). IR (ν, cm^{-1}): 3234, 1668, 1599, 1580, 1505, 1372, 1290, 1178. HRMS (EI): Calcd for $C_{10}H_9Br_2NO_2$: 332.9000. Found: 332.8994.

***N*-(2-(2-Bromoacetyl)-4-(trifluoromethyl)phenyl)acetamide (14c).** Following general procedure VI, the reaction was carried out with a solution of compound (**13c**) (2.0 g, 5 mmol, 1 equiv.), Et_3N (0.73 mL, 5.25 mmol, 1.05 equiv.) and $(EtO)_2POH$ (0.67 mL, 5.25 mmol, 1.05 equiv.) in THF (20 mL) at rt. The product (**14c**) was obtained as a white solid (1.55 g, 96%). Mp: 110–112 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 11.50 (bs, 1H), 8.96 (d, J = 8.9 Hz, 1H), 8.12 (d, J = 2.0 Hz, 1H), 7.82 (dd, J = 8.9 Hz, J = 2.0 Hz, 1H), 4.54 (s, 2H), 2.29 (s, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 194.7 (CO), 169.7 (CO), 144.6 (Cq), 132.5 (q, J = 4 Hz, CH), 128.3 (q, J = 4 Hz, CH), 124.2 (q, J = 33 Hz, Cq), 123.4 (q, J = 272 Hz, CF_3), 121.4 (CH), 118.2 (Cq), 31.8 (CH_2), 25.7 (CH_3). IR (ν, cm^{-1}): 3282, 1719, 1660, 1590, 1525, 1292, 1135. HRMS (EI): Calcd for $C_{11}H_9BrF_3NO_2$: 322.9769. Found: 322.9764.

General procedure VII for the formation of xanthates (15)

To a stirred solution of 2-bromoacetylphenylacetamide (**14**) (1 mmol) in acetone (2 mL) at rt was added portion-wise potassium ethyl xanthate (1.1 mmol). The reaction was stirred until complete consumption of the starting material. The solvent was evaporated, and the residue was diluted with ethyl acetate. The organic phase was washed with brine, and the organic layer was washed with water, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was recrystallised from ethanol to afford the desired xanthate (**15**).

***S*-2-(2-Acetamido-5-methylphenyl)-2-oxoethyl *O*-ethyl carbonodithioate (15a).** Following general procedure VII, the reaction was carried out with a solution of compound (**14a**) (1.08 g, 4 mmol, 1 equiv.) in acetone (8 mL) and potassium ethyl xanthate (705 mg, 4.4 mmol, 1.1 equiv.) at rt for 1 h. Xanthate (**15a**) was obtained as a white solid (1.18 g, 95%). Mp: 149–150 °C (from EtOH). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 11.22 (bs, 1H), 8.65 (d, J = 8.7 Hz, 1H), 7.79 (s, 1H), 7.42 (d, J = 8.7 Hz, 1H), 4.74 (s, 2H), 4.66 (q, J = 7.1 Hz, 2H), 2.40 (s, 3H), 2.20 (s, 3H), 1.42 (t, J = 7.1 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 213.1 (CS), 196.1 (CO), 169.4 (CO), 138.9 (Cq), 136.7 (CH), 132.1 (Cq), 130.8 (CH), 121.1 (Cq), 120.8 (CH), 71.0 (CH_2), 45.0 (CH_2), 25.6 (CH), 20.9 (CH_3), 13.8 (CH_3). IR (ν, cm^{-1}): 2989, 1698, 1667, 1587, 1505, 1356, 1295, 1234, 1111, 1049. HRMS (EI): Calcd for $C_{14}H_{17}NO_3S_2$: 311.0650. Found: 311.0653.

***S*-2-(2-Acetamido-5-bromophenyl)-2-oxoethyl *O*-ethyl carbonodithioate (15b).** Following general procedure VII, the reaction was carried out with a solution of compound (**14b**) (1.34 g, 4 mmol, 1 equiv.) in acetone (8 mL) and potassium ethyl xanthate (705 mg, 4.4 mmol, 1 equiv.) at rt for 1 h. Xanthate (**15b**) was obtained as a pinkish solid (1.4 g, 93%). Mp: 144–145 °C (from EtOH). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 11.20 (bs, 1H), 8.68 (d, J = 9.1 Hz, 1H), 8.10 (d, J = 2.3 Hz, 1H), 7.66 (dd, J = 9.1 Hz, J = 2.3 Hz, 1H), 4.67 (s, 2H), 4.64 (q, J = 7.1 Hz, 2H), 2.19 (s, 3H), 1.41 (t, J = 7.1 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 212.8 (CS), 195.3 (CO), 169.5 (CO), 140.2 (Cq), 138.4 (CH), 133.1 (CH), 122.8 (CH), 122.3 (Cq), 114.8 (Cq), 71.2 (CH_2), 44.7 (CH_2), 25.6 (CH), 13.8 (CH_3). IR (ν, cm^{-1}): 3290, 1673, 1574, 1496, 1394, 1288, 1229, 1113, 1048. HRMS (EI): Calcd for $C_{13}H_{14}BrNO_3S_2$: 374.9598. Found: 374.9600.

***S*-2-(2-Acetamido-5-(trifluoromethyl)phenyl)-2-oxoethyl *O*-ethyl carbonodithioate (15c).** Following general procedure VII, the reaction was carried out with a solution of compound (**14c**) (1.30 g, 4 mmol, 1 equiv.) in acetone (8 mL) and potassium ethyl xanthate (705 mg, 4.4 mmol, 1.1 equiv.) at rt. The reaction finished in one hour. Xanthate (**15c**) was obtained as a pinkish solid (1.34 g, 92%). Mp: 85–86 °C (from EtOH). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 11.50 (bs, 1H), 8.94 (d, J = 8.9 Hz, 1H), 8.25 (m, 1H), 7.82 (dd, J = 9.0 Hz, J = 1.9 Hz, 1H), 4.74 (s, 2H), 4.66 (q, J = 7.1 Hz, 2H), 2.25 (s, 3H), 1.42 (t, J = 7.1 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 212.7 (CS), 195.8 (CO), 169.8 (CO), 143.9 (Cq), 132.2 (q, J = 3 Hz, CH), 127.7 (q, J = 4 Hz, CH), 124.4 (q, J = 33 Hz, Cq), 123.5 (q, J = 272 Hz, CF_3), 121.4 (CH), 120.3 (Cq), 71.3 (CH_2), 44.5 (CH_2), 25.7 (CH), 13.8 (CH_3). IR (ν, cm^{-1}) 3279, 1714, 1660, 1591, 1524, 1419, 1340, 1293, 1230, 1134, 1053. HRMS (EI): Calcd for $C_{14}H_{14}F_3NO_3S_2$: 365.0367. Found: 365.0369.

***S*-2-(2-Acetamido-4-fluorophenyl)-2-oxoethyl *O*-ethyl carbonodithioate (15d).** Starting with *N*-(2-acetyl-5-fluorophenyl)-acetamide (**11d**) (976 mg, 5 mmol) and pyridinium hydrobromide perbromide (880 g, 5.5 mmol) in 15 mL acetic acid at rt, general procedure I was followed, but the reaction mixture was heated to only 50 °C in the first step. After the substitution of bromine by potassium *O*-ethyl xanthate, the residue was purified by silica gel column chromatography with a gradient of ethyl acetate in toluene (0 : 100 to 5 : 95) to afford xanthate (**15d**) (995 g, 63%) as a white solid. Mp: 98–100 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 11.57 (bs, 1H), 8.59 (dd, J = 2.6 Hz, J = 12.0 Hz, 1H), 8.04 (dd, J = 9.0 Hz, J = 6.2 Hz, 1H), 6.84 (ddd, J = 9.1 Hz, J = 7.3 Hz, J = 2.6 Hz, 1H), 4.69 (s, 2H), 4.66 (q, J = 7.1 Hz, 2H), 2.21 (s, 3H), 1.41 (t, J = 7.1 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 213.0 (CS), 195.1 (CO), 169.7 (CO), 166.8 (d, J = 256 Hz, Cq), 144.1 (d, J = 13 Hz, Cq), 133.3 (d, J = 11 Hz, CH), 117.2 (d, J = 3 Hz, Cq), 109.9 (d, J = 23 Hz, CH), 108.0 (d, J = 28 Hz, CH), 71.0 (CH_2), 44.8 (CH_2), 25.6 (CH_3), 13.8 (CH_3). IR (ν, cm^{-1}): 3271, 1711, 1652, 1592, 1554, 1431, 1234, 1113, 1052. HRMS (EI): Calcd for $C_{20}H_{14}F_3NO_4S_2$: 315.0399. Found: 315.0413.

***S*-2-(6-Acetamidobenzo[*d*][1,3]dioxol-5-yl)-2-oxoethyl *O*-ethyl carbonodithioate (15e).** To a refluxing solution of $CuBr_2$ (2.25 g, 10.1 mmol, 2.01 equiv.) in 11 mL AcOEt was added dropwise a solution of *N*-(6-acetylbenzo[*d*][1,3]dioxol-5-yl)acetamide (**11e**) (1.1 g, 5 mmol, 1 equiv.) in 11 mL $CHCl_3$. Reflux was continued for 8 hours (or until a white precipitate was formed). Then, the solvent was evaporated and the remaining solid was boiled in the 1 : 1 mixture of ethanol and chloroform and filtered off while hot. The filtrate was left to cool down and the resulting solid was collected. The crude solid was dissolved in acetone (10 mL) and potassium *O*-ethyl xanthate (805 mg, 5 mmol) was added at rt. After completion of the reaction, the acetone was evaporated and the mixture was diluted with ethyl acetate. The organic layer was washed with water, brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography with a gradient of dichloromethane in petroleum ether (50/50 to 90/10) to afford the desired xanthate (**15e**) as a white solid (684 mg, 40%). Mp: 132 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 11.57 (bs, 1H), 8.41 (s, 1H), 7.39 (s, 1H), 6.06 (s, 2H), 4.66 (q, J = 7.1 Hz, 2H), 4.63 (s, 2H), 2.20 (s, 3H), 1.42 (t, J = 7.1 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 213.0 (CS), 193.9 (CO), 169.5 (CO), 153.7 (Cq), 142.7 (Cq), 140.9 (Cq), 113.9 (Cq), 108.6 (CH), 102.4 (CH), 101.8 (CH_2), 71.0 (CH_2), 44.9 (CH_2), 25.6 (CH_3), 13.8 (CH_3). IR (ν, cm^{-1}): 3124, 1704, 1614, 1541, 1435, 1354, 1274, 1051. HRMS (EI): Calcd for $C_{14}H_{15}NO_5S_2$: 341.0392. Found: 341.0395.

General procedure VIII for the synthesis of tetralones (17) by radical addition and cyclisation

A magnetically stirred solution of xanthate (1 mmol) and vinyl pivalate (2.5 mmol) in 1,2-dichloroethane (2 mL) was refluxed

for 15 min under a slightly positive nitrogen pressure. Dilauroyl peroxide (DLP) (10 mol%) was then added and additional DLP (10 mol%) was added every 60 min until total consumption of the starting material or until no evolution could be detected by TLC analysis. The reaction mixture was then cooled to 20 °C and evaporated to dryness under reduced pressure. The residue was purified by silica gel column chromatography to yield the desired compound.

5-Acetamido-8-methyl-4-oxo-1,2,3,4-tetrahydronaphthalen-1-yl pivalate (17a). Following general procedure VIII, the reaction was carried out using xanthate (**15a**) (310 mg, 1 mmol, 1 equiv.) with vinyl pivalate (0.37 mL, 2.5 mmol, 2.5 equiv.) in refluxing dichloroethane and needed 1.2 equiv. of DLP (478 mg) to go to completion (7 h). The residue after evaporation of the solvent was purified by silica gel column chromatography with a gradient of ethyl acetate in petroleum ether (5 : 95 to 15 : 85) to afford (**17a**) (152 mg, 48%) as a white solid. Mp: 104–105 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 12.03 (bs, 1H), 8.68 (d, J = 8.7 Hz, 1H), 7.41 (d, J = 8.7 Hz, 1H), 6.18 (m, 1H), 2.92 (m, 1H), 2.61 (m, 1H), 2.37 (m, 1H), 2.31 (s, 3H), 2.23 (s + m, 4H), 1.18 (s, 9H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 203.1 (CO), 177.8 (CO), 169.6 (CO), 140.0 (Cq), 138.3 (Cq), 137.9 (CH), 131.5 (Cq), 121.1 (CH), 118.2 (Cq), 66.2 (CH_2), 39.2 (Cq), 34.4 (CH_2), 27.2 ($3CH_3$), 26.7 (CH_2), 25.7 (CH_3), 18.6 (CH_3). IR (ν, cm^{-1}): 3228, 1730, 1703, 1655, 1541, 1256, 1143. HRMS (EI) Calcd for $C_{18}H_{23}NO_4$: 317.1627. Found: 317.1627.

5-Acetamido-8-bromo-4-oxo-1,2,3,4-tetrahydronaphthalen-1-yl pivalate (17b). Following general procedure VIII, the reaction was carried out using xanthate (**15b**) (375 mg, 1 mmol, 1 equiv.) and vinyl pivalate (0.37 mL, 2.5 mmol, 2.5 equiv.) in refluxing dichloroethane and needed 1.1 equiv. of DLP (438 mg) to go to completion (6 h). After evaporation of the solvent, the residue was purified by silica gel column chromatography with dichloromethane to afford (**17b**) (195 mg, 51%) as a white solid. Mp: 202–203 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 12.08 (bs, 1H), 8.74 (d, J = 9.1 Hz, 1H), 7.77 (d, J = 9.2 Hz, 1H), 6.27 (m, 1H), 2.94 (m, 1H), 2.65 (m, 1H), 2.43 (m, 1H), 2.31 (s + m, 4H), 1.21 (s, 9H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 202.3 (CO), 177.3 (CO), 169.7 (CO), 141.3 (Cq), 139.7 (CH), 139.2 (Cq), 122.6 (CH), 119.6 (Cq), 118.1 (Cq), 68.9 (CH_2), 39.2 (Cq), 34.3 (CH_2), 27.2 ($3CH_3$), 26.3 (CH_2), 25.7 (CH_3). IR (ν, cm^{-1}): 3227, 1734, 1709, 1660, 1541, 1507, 1138, 1037. HRMS (EI) Calcd for $C_{17}H_{20}BrNO_4$: 381.0576. Found: 381.0595.

5-Acetamido-4-oxo-8-(trifluoromethyl)-1,2,3,4-tetrahydronaphthalen-1-yl pivalate (17c). Following general procedure II, the reaction was carried out using xanthate (**15c**) (365 mg, 1 mmol, 1 equiv.) and vinyl pivalate (0.37 mL, 2.5 mmol, 2.5 equiv.) in refluxing dichloromethane (1 mL) and needed 10 mol% DLP to go to completion. Then the reaction mixture was evaporated to dryness under reduced pressure. The residue was dissolved in ethyl acetate (10 mL), heated to reflux, and needed 1 equiv. DLP to go to completion. After evaporation, the residue was purified by silica gel column chromatography with a gradient of petroleum ether in dichloromethane (40 : 60 to 100 : 0) to afford (**17c**) (222 mg, 60%) as a white solid. Mp: 150–151 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 12.28 (bs, 1H), 8.94 (d, J = 9.1 Hz, 1H), 7.87 (d, J = 9.1 Hz, 1H), 6.35 (m, 1H), 2.934 (m, 1H), 2.70 (m, 1H), 2.54 (m, 1H), 2.28 (s, 3H), 2.21 (m, 1H), 1.15 (s, 9H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 202.3 (CO), 177.0 (CO), 170.0 (CO), 144.7 (Cq), 139.8 (Cq), 132.8 (q, J = 5.7 Hz, CH), 123.5 (q, J = 272 Hz, CF_3), 122.8 (q, J = 31.2 Hz, Cq), 121.0 (CH), 118.7 (Cq), 64.9 (CH_2), 39.0 (Cq), 33.7 (CH_2), 27.0 ($3CH_3$), 26.1 (CH_2), 25.8 (CH_3). IR (ν, cm^{-1}): 3215, 1737, 1713, 1662, 1595, 1398, 1286, 1135. HRMS (EI) Calcd for $C_{17}H_{20}F_3NO_4$: 371.1344. Found: 371.1339.

5-Acetamido-7-fluoro-4-oxo-1,2,3,4-tetrahydronaphthalen-1-yl pivalate (17d). Following general procedure II, the reaction was carried out using xanthate (**15d**) (315 mg, 1 mmol, 1 equiv.) and vinyl pivalate (0.37 mL, 2.5 mmol, 2.5 equiv.) in refluxing dichloromethane (1 mL) and needed 10 mol% DLP to go to completion. The reaction mixture was evaporated to dryness under reduced pressure and the residue was dissolved in ethyl acetate (10 mL), heated to reflux and treated with 1.0 equiv. DLP. After evaporation, the residue was purified by silica gel column chromatography with a gradient of ethyl acetate in petroleum ether (5 : 95 to 15 : 85) to afford (**17d**) (208 mg, 65%) as a white solid. Mp: 119–120 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 12.24 (bs, 1H), 8.55 (dd, J = 11.8 Hz, J = 2.5 Hz, 1H), 6.78 (dd, J = 8.4 Hz, J = 2.5 Hz, 1H), 5.99 (dd, J = 7.0 Hz, J = 3.7 Hz, 1H), 2.91 (m, 1H), 2.70 (m, 1H), 2.33 (m, 1H), 2.19 (s + m, 4H), 1.12 (s, 9H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 200.5 (CO), 177.5 (CO), 169.8 (CO), 166.4 (d, J = 256 Hz, Cq), 145.5 (d, J = 10 Hz, Cq), 144.7 (d, J = 14 Hz, Cq), 113.9 (d, J = 3 Hz, Cq), 109.3 (d, J = 23 Hz, CH), 107.4 (d, J = 28 Hz, CH), 69.1 (CH_2), 39.0 (Cq), 35.8 (CH_2), 27.7 (CH_2), 27.1 ($3CH_3$), 25.6 (CH_3). IR (ν, cm^{-1}): 3217, 1734, 1654, 1542, 1445, 1142. HRMS (EI) Calcd for $C_{17}H_{20}FNO_4$: 321.1376. Found: 321.1374.

5-Acetamido-6-oxo-6,7,8,9-tetrahydronaphtho[2,1-*d*][1,3]-dioxol-9-yl pivalate (17e). Following general procedure II, the reaction was carried out using xanthate (**15e**) (341 mg, 1 mmol, 1 equiv.) and vinyl pivalate (0.37 mL, 2.5 mmol, 2.5 equiv.) in refluxing dichloromethane (1 mL) and needed 10 mol% DLP to go to completion. The reaction mixture was evaporated to dryness under reduced pressure and the residue was dissolved in ethyl acetate (10 mL), heated to reflux and treated with 1.0 equiv. DLP to go to completion. After evaporation, the residue was purified by silica gel column chromatography with a gradient of ethyl acetate in petroleum ether (5 : 95 to 30 : 70) to afford (**17e**) (198 mg, 57%) as a white solid. Mp: 120–121 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 12.36 (bs, 1H), 8.39 (s, 1H), 6.19 (s, 1H), 6.02 (d, J = 8.4 Hz, 2H) 2.85 (m, 1H), 2.57 (m, 1H), 2.20 (s + m, 5H), 1.17 (s, 9H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 200.0 (CO), 177.5 (CO), 169.7 (CO), 153.2 (Cq), 140.6 (Cq), 140.1 (Cq), 120.0 (CH), 111.1 (Cq), 102.5 (CH_2), 101.5 (CH), 63.8 (CH), 39.0 (Cq), 34.8 (CH_2), 27.1 ($3CH_3$ + CH_2), 25.6 (CH_3). IR (ν, cm^{-1}): 3124, 1733, 1703, 1653, 1625, 1503, 1503, 1470, 1367, 1257, 1142. HRMS (EI) Calcd for $C_{17}H_{21}FNO_4$: 347.1369. Found: 347.1373.

***N*-(8-Hydroxy-4-methylnaphthalen-1-yl)acetamide (18a).** Following general procedure III, the reaction was carried out using (**17a**) (64 mg, 0.2 mmol, 1 equiv.) and PTSA (105 mg,

0.6 mmol, 3 equiv.) in refluxing toluene (3 mL) and needed 3 hours to go to completion. The product was recrystallised from dichloromethane to afford a pinkish solid (**18a**) (32 mg, 74%). Mp: 143–145 °C. ^{1}H-NMR (acetone-D_6, 400 MHz) δ 10.93 (bs, 1H), 10.09 (bs, 1H), 8.43 (d, J = 7.9 Hz, 1H), 7.42 (dd, J = 1.0 Hz, J = 8.5 Hz, 1H), 7.25 (m, 1H), 7.16 (d, J = 7.9 Hz, 1H), 6.91 (dd, J = 7.6 Hz, J = 1.0 Hz, 1H), 2.46 (s, 3H), 2.05 (s, 3H). ^{13}C-NMR (acetone-D_6, 100 MHz) δ 168.2 (CO), 154.4 (Cq), 136.3 (Cq), 135.5 (Cq), 129.1 (Cq), 127.9 (CH), 126.8 (CH), 117.7 (CH), 116.3 (Cq), 115.6 (CH), 111.2 (CH), 25.6 (CH_3), 20.0 (CH_3). IR (ν, cm^{-1}): 3733, 2359, 1542. HRMS (EI) Calcd for $C_{13}H_{13}NO_2$: 215.0946. Found: 215.0947.

***N*-(4-Bromo-8-hydroxynaphthalen-1-yl)acetamide (18b).** Following general procedure III, the reaction was carried out using (**17b**) (77 mg, 0.2 mmol, 1 equiv.) and PTSA (105 mg, 0.6 mmol, 3 equiv.) in refluxing toluene (3 mL) and needed 3 hours to go to completion. The product was washed with dichloromethane to afford a greyish solid (**18b**) (40.2 mg, 72%). Mp: 149–150 °C. ^{1}H-NMR (acetone-D_6, 400 MHz) δ 11.01 (bs, 1H), 10.38 (bs, 1H), 8.45 (d, J = 8.5 Hz, 1H), 7.64 (m, 2H), 7.34 (m, 1H), 6.97 (dd, J = 0.6 Hz, 7.6 Hz, 1H), 2.05 (s, 3H). ^{13}C-NMR (acetone-D_6, 100 MHz) δ 168.5 (CO), 154.5 (Cq), 137.5 (Cq), 135.0 (Cq), 131.4 (CH), 128.5 (CH), 120.6 (CH), 117.4 (Cq), 116.1 (Cq), 116.0 (CH), 112.3 (CH), 25.6 (CH_3). IR (ν, cm^{-1}): 2360, 1542, 1258. HRMS (EI) Calcd for $C_{12}H_{10}BrNO_2$: 278.9895. Found: 278.9899.

***N*-(8-Hydroxy-4-(trifluoromethyl)naphthalen-1-yl)acetamide (18c).** Following general procedure III, the reaction was carried out using (**17c**) (74 mg, 0.2 mmol, 1 equiv.) and PTSA (105 mg, 0.6 mmol, 3 equiv.) in refluxing toluene (3 mL) and needed 3 hours to go to completion. The product was washed with pentane to afford a light pinkish solid (**18c**) (40 mg, 74%). Mp: 177–178 °C. ^{1}H-NMR (acetone-D_6, 400 MHz) δ 11.22 (bs, 1H), 10.42 (bs, 1H), 8.59 (d, J = 8.5 Hz, 1H), 7.71 (d, J = 8.5 Hz, 1H), 7.51 (m, 1H), 7.35 (m, 1H), 6.97 (d, J = 7.6 Hz, 1H), 1.89 (s, 3H). ^{13}C-NMR (Acetone-D_6, 100 MHz) δ 168.9 (CO), 154.7 (Cq), 141.5 (Cq), 133.0 (Cq), 129.0 (CH), 127.1 (q, J = 6 Hz, CH), 126.1 (q, J = 272 Hz, CF_3), 120.0 (q, J = 30 Hz, Cq), 117.3 (q, J = 3 Hz, CH), 116.3 (Cq), 113.2 (CH), 112.2 (CH), 25.7 (CH_3). IR (ν, cm^{-1}): 2592, 1549, 1291. HRMS (EI) Calcd for $C_{13}H_{10}F_3NO_2$–H_2O = 251.0558. Found: 251.0555.

***N*-(3-Fluoro-8-hydroxynaphthalen-1-yl)acetamide (18d).** Following general procedure III, the reaction was carried out using (**17d**) (65 mg, 0.2 mmol, 1 equiv.) and PTSA (105 mg, 0.6 mmol, 3 equiv.) in refluxing toluene (3 mL) and needed 3 hours to go to completion. After evaporation of the solvent, the residue was purified by silica gel column chromatography with a gradient of ethyl acetate in toluene (10 : 90 to 30 : 70) to afford (**18d**) as a pinkish solid (26.5 mg, 60%). Mp: 193–194 °C. ^{1}H-NMR (DMSO-D_6, 400 MHz) δ 11.49 (bs, 1H), 11.31 (bs, 1H), 8.37 (dd, J = 12.2 Hz, J = 2.7 Hz, 1H), 7.32 (m, 1H), 7.31 (m, 1H), 7.27 (dd, J = 9.6 Hz, J = 2.7 Hz, 1H), 6.86 (m, 1H), 2.18 (s, 3H). ^{13}C-NMR (DMSO-D_6, 100 MHz) δ 168.2 (CO), 159.5 (d, J = 240 Hz, Cq), 153.6 (Cq), 138.0 (d, J = 13 Hz, Cq), 136.5 (d, J = 11 Hz, Cq), 127.5 (CH), 119.5 (d, J = 5 Hz, CH), 112.1 (Cq), 109.6 (d, J = 2 Hz, CH), 105.3 (d, J = 21 Hz, CH), 103.6 (d, J = 31 Hz, CH), 25.3 (s, CH_3). IR (ν, cm^{-1}): 2500, 1545, 1360. HRMS (EI) Calcd for $C_{12}H_{10}FNO_2$–H_2O = 201.0590. Found: 201.0589.

***N*-(6-Hydroxynaphtho[2,1-*d*][1,3]dioxol-5-yl)acetamide (18e).** Following general procedure III, the reaction was carried out using (**17e**) (70 mg, 0.2 mmol, 1 equiv.) and PTSA (105 mg, 0.6 mmol, 3 equiv.) in refluxing toluene (3 mL) and needed 3 hours to go to completion. The residue was washed with pentane to afford a white solid (**18e**) (34.3 mg, 70%). Mp: 189–190 °C. ^{1}H-NMR (DMSO-D_6, 400 MHz) δ 11.3 (bs, 2H), 8.26 (s, 1H), 7.27 (m, 1H), 7.13 (d, J = 8.3 Hz, 1H), 6.74 (d, J = 7.5 Hz, 1H), 6.14 (s, 2H), 2.12 (s, 3H). ^{13}C-NMR (DMSO-D_6, 100 MHz) δ 167.0 (CO), 154.6 (Cq), 142.2 (CH), 136.0 (Cq), 131.1 (Cq), 127.2 (CH), 121.2 (CH), 11.1 (Cq), 110.4 (Cq), 108.1 (CH), 101.3 (CH_2), 100.1 (Cq), 25.1 (CH_3). IR (ν, cm^{-1}): 2918, 1550, 1264. HRMS (EI) Calcd for $C_{13}H_{11}NO_4$: 245.0688. Found: 245.0688.

***N*-(4-(Trifluoromethyl)naphthalen-1-yl)acetamide (19c).** To a solution of (**17c**) (74 mg, 0.2 mmol, 1 equiv.) in methanol (3 mL), $NaBH_4$ (12 mg, 0.3 mmol, 1.5 equiv.) was added and the mixture was stirred for 1 hour at rt. A saturated solution of NH_4Cl was added to the reaction and the mixture was extracted with ethyl acetate. The organic layer was washed twice with H_2O, brine, dried with $MgSO_4$ and then filtered. The solvent was removed under reduced pressure to provide a brown residue. Following general procedure III, the second step was carried out with the residue and PTSA (105 mg, 0.6 mmol, 3 equiv.) in refluxing Ac_2O–AcOH (1 mL/2 mL) and needed 3 hours to go to completion. The product was washed with pentane to afford a light pink solid (**19c**) (36 mg, 71%). Mp: 185–186 °C. ^{1}H-NMR (acetone-D_6, 400 MHz) δ 9.20 (bs, 1H), 8.09 (d, J = 8.2 Hz, 1H), 7.93 (m, 2H), 7.70 (d, J = 8.1 Hz, 1H), 7.48 (ddd, J = 8.2 Hz, J = 6.9 Hz, J = 1.3 Hz, 1H), 7.41 (ddd, J = 8.1 Hz, J = 6.9 Hz, J = 1.3 Hz, 1H), 2.57 (s, 3H). ^{13}C-NMR (acetone-D_6, 100 MHz) δ 169.8 (CO), 139.3 (Cq), 130.4 (Cq), 128.7 (CH), 128.0 (Cq), 127.4 (CH), 126.1 (q, J = 6 Hz, CH), 125.0 (q, J = 2 Hz, CH), 126.0 (q, J = 272 Hz, CF_3), 123.6 (CH), 122.1 (q, J = 30 Hz, Cq), 118 (CH), 24.2 (CH_3). IR (ν, cm^{-1}): 3464, 1714, 1558, 1338, 1125. HRMS (EI) Calcd for $C_{13}H_{10}F_3NO_2$: 253.0714. Found: 253.0713.

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