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Alkylidene malonates and α,β-unsaturated α′-hydroxyketones as practical substrates for vinylogous Friedel–Crafts alkylations in water catalysed by scandium(III) triflate/SDS†

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Alkylidene malonates and α,β-unsaturated α′-hydroxyketones are demonstrated to be efficient classes of electrophiles for the scandium(III) triflate/sodium dodecyl sulphate (SDS) catalysed vinylogous Friedel–Crafts alkylation of indoles and pyrroles in water. These substrates contain an easily removable auxiliary group that increases affinity for the catalytic metal ion in such a way that they can compete with water for binding to the catalytic metal ion. Thus, alkylidene malonates and α,β-unsaturated α′-hydroxyketones are attractive substitutes for, *e.g.*, α,β-unsaturated carboxylic acids and -esters, which in aqueous media are not reactive enough in these reactions. The combination of Lewis acid and SDS in catalysis results in considerable acceleration of the reaction in water compared to organic solvents. The method presented is attractive because the reactions are fast, experimentally straightforward and give rise to high yields of products.

Introduction

The 3-substituted indole motif is common in many natural products and biologically and pharmacologically active compounds.[1] Taking advantage of the π-nucleophilic character of indoles, a range of 3-substituted indoles are accessible by Friedel–Crafts type alkylation. A plethora of catalytic methods involving organo- and Lewis acid catalysts is available to achieve these transformations in organic solvents.[2]

The current emphasis on more sustainable approaches to chemical synthesis has, among others, fuelled the development of catalytic synthesis in water.[3,4] Indeed, a number of Lewis acid catalysts have been reported for the Friedel–Crafts alkylation reaction in water or aqueous mixtures.[5,6] Of particular interest for this reaction is the development of Lewis acid surfactant combined catalysts (LASCs).[7] This involves Lewis acid catalysis for activation of the electrophile, *e.g.* an enone-type substrate, in combination with micellar catalysis. The latter entails the use of surfactants that above the critical micelle concentration form aggregates in water in which hydrophobic substrates preferably localize. For some reactions, the resulting high effective molarity causes significant rate accelerations.[4,8] The LASC concept was pioneered by two research groups. Kobayashi and co-workers reported that the scandium triflate ($Sc(OTf)_3$) catalysed aldol reaction between silyl enol ethers and aldehydes is significantly more efficient in the presence of anionic surfactants such as sodium dodecyl sulphate (SDS).[9] The scandium dodecyl sulphate ($Sc(DS)_3$) catalyst was then also applied successfully to other reactions including allylations[10] Michael additions[11] and hydroxymethylations.[12] The vinylogous Friedel–Crafts alkylation reactions of indoles with reactive electron deficient olefins, such as methyl vinyl ketone were also catalysed successfully in water using a combination of Lewis acids and surfactants.[13] For α,β-unsaturated ketones containing a substituent at the β position, the reactions were considerably slower and moderate yields were obtained. Moreover, no reaction was achieved using α,β-unsaturated esters or carboxylic acids, reflecting the less electrophilic character of these substrates compared to enones.

Almost simultaneously with the first report on $Sc(OTf)_3$/SDS as catalyst, Engberts and co-workers reported the Diels–Alder reaction between azachalchone and cyclopentadiene using a cupric dodecyl sulphate ($Cu(DS)_2$) catalyst.[14] A million-fold rate acceleration compared to the uncatalysed reaction was found; most of this was due to the presence of the Lewis acidic Cu^{2+} ion while the effect of the presence of micelles contributed an additional order of magnitude to the observed rate enhancement. Later, we have successfully applied the combination of $Cu(NO_3)_2$ with SDS to the Friedel–Crafts alkylation of indoles, using α,β-unsaturated 2-acyl-1-methylimidazoles as substrate.[15] Rate accelerations of up to 9000 fold were observed compared

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to the reactions catalysed by $Cu(NO_3)_2$ alone, in the absence of surfactant. Recently, also $Cu(OTf)_2$/SDS catalysed conjugate addition of indoles to vinylidenebisphosphonate esters was reported.[16]

The low reactivity of α,β-unsaturated carboxylic acids and -esters in the Friedel–Crafts alkylation reactions in water make it necessary to use a more reactive α,β-unsaturated carbonyl substrate and subsequently convert this into the desired carboxylic ester or carboxylic acid. A key requirement is that these carbonyl substrates bind efficiently to the Lewis acid, *i.e.* that they can compete with water for binding to the Lewis acid. This is best achieved by using an auxiliary group that, in combination with the carbonyl oxygen, provides a bidentate chelation. Subsequently, this auxiliary group should be easily removable, introducing the desired carboxylic acid or -ester functionality in the product. One such a class of substrates are the α,β-unsaturated 2-acyl-1-methyl imidazoles The corresponding Friedel–Crafts alkylation products have been converted to carboxylic esters by methylation of the imidazole moiety followed by treatment with methanol.[17] However, this involves conditions that are not compatible with many products.

Alkylidene malonates are a class of compounds that combine several advantages, which makes them attractive as substrates for Lewis acid catalysis in water. Many alkylidene malonates are commercially available or readily synthesized by Knoevenagel condensations. They provide a bidentate coordination to a Lewis acid catalyst through two carbonyl groups and are thus activated for conjugate addition reactions. These features have been combined for the synthesis of 3-indole derivatives in a Cu^{2+} catalysed three component reaction in water, albeit that elevated temperatures were needed.[18] Finally, the product of the reaction is readily decarboxylated, resulting in the product of a formal conjugate addition to an α,β-unsaturated carboxylic acid or -ester.

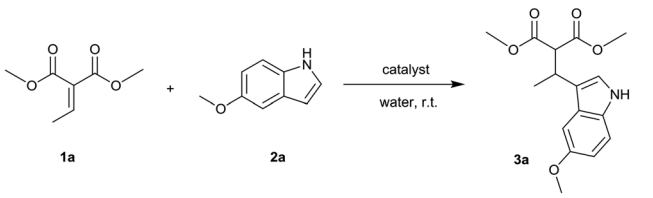
Another interesting class of substrates is the α,β-unsaturated α′-hydroxy ketones.[19] These substrates can also chelate Lewis acids by coordination between the carbonyl and α′-hydroxy oxygen atoms. Moreover, the auxiliary moiety is easily removed by oxidative cleavage of the C–C bond between the carbonyl- and the α′-carbon, resulting in the corresponding carboxylic acids.

Here, we present an experimentally simple and high yielding procedure for the combined Sc^{3+}/SDS catalysed vinylogous Friedel–Crafts alkylation reaction in water, using alkylidene and benzylidene malonates and α,β-unsaturated α′-hydroxy ketones as electrophiles. Moreover, it is shown that both classes of electrophiles are complementary to each other with regard to the substituents on the β-position of the alkene.

Results and discussion

Based on the literature[13,14] and previous research in our group,[15] $Cu(OTf)_2$ and $Sc(OTf)_3$ in combination with 5 mM SDS were evaluated as catalysts in the Friedel–Crafts alkylation

Table 1 Screening of catalysts for the Friedel–Crafts alkylation of indoles with alkylidene malonates[a]



Entry	Catalyst	Time (h)	Conversion[b] (%)
1	10 mol% $Cu(OTf)_2$	24	11
2	10 mol% $Sc(OTf)_3$	24	19
3	10 mM SDS	24	13
4	10 mol% $Cu(OTf)_2$, 5 mM SDS	2	24
5	10 mol% $Sc(OTf)_3$, 5 mM SDS	2	Full

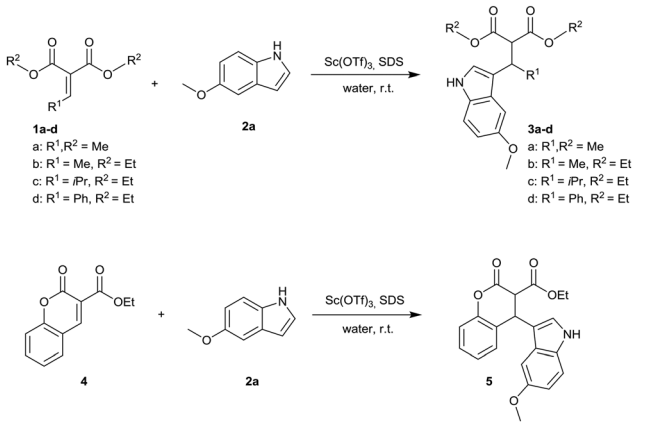
[a] Conditions used: 0.075 mmol **1a**, 0.15 mmol **2a** and indicated concentrations of metal salt and SDS, in 15 ml H_2O (1.5% v/v EtOAc) at room temperature for the indicated time. [b] Conversion analysed by ^1H NMR, averaged over two experiments, reproducibility within ±3%.

of 5-methoxy indole (**2a**) with dimethyl 2-ethylidenemalonate (**1a**) (Table 1). Using 10 mol% $Cu(OTf)_2$ or $Sc(OTf)_3$, without SDS, the reaction was slow with 13 and 19% conversion, respectively, after 24 hours (entries 1 and 2). A similar conversion was obtained using 10 mM SDS, without Cu^{2+} or Sc^{3+} present. (Table 1, entry 3). The combination of $Cu(OTf)_2$ and 5 mM of SDS gave rise to 24% conversion already after 2 hours, suggesting a significant benefit from using the Cu^{2+} catalysts in combination with SDS. However, the best results were achieved using 10 mol% $Sc(OTf)_3$ in combination with 5 mM of SDS: already after 2 h full conversion was obtained (Table 1, entry 5). Therefore, the $Sc(OTf)_3$/SDS combination was selected as the catalytic system of choice for this reaction.

The scope of the catalysed vinylogous Friedel–Crafts reaction was investigated at a preparative scale, using 1.5 mmol of alkylidene malonate and 2.25 mmol of the π nucleophile, 10 mol% $Sc(OTf)_3$ and 5 mM SDS in 300 ml of water at room temperature. The Friedel–Crafts alkylation of **2a** was used to establish the scope of malonate substrates (Table 2).

Using dimethyl 2-ethylidenemalonate **1a**, the corresponding product **3a** was isolated after 4 hours in 85% of yield. Using the diethyl ester **1b**, similar results were obtained (entry 2). Expanding the size of the alkyl group of the alkylidene moiety resulted in in 89% isolated yield of **3c** (entry 3). With the substrate diethyl 2-benzylidenemalonate (**1d**) that bears a phenyl ring conjugated with the double bond, the reaction proceeded much slower giving rise to only 44% isolated yield after 24 hours. Using 20 mol% $Sc(OTf_3)$ and 5 mM SDS, ethyl 2-oxo-2*H*-chromene-3-carboxylate (**4**) reacted with **2a** to give 66% conversion after 24 h, with an isolated yield of 43% of the *trans* product, which was assigned based on the coupling constant of 7 Hz between the α and β protons. In this case, the formation of some unidentified side products was observed. Substrates containing aromatic moieties are more efficiently converted in case of α,β-unsaturated α′-hydroxy ketones as substrate (*vide infra*).

Table 2 Scope of malonate substrates in the $Sc(OTf)_3$/SDS catalysed Friedel–Crafts alkylation of **2a**[a]



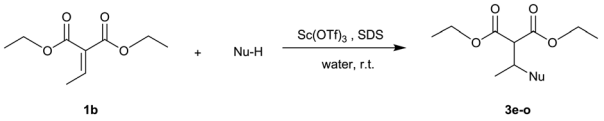
Entry	Substrate	Product	Yield[b] (%)
1	**1a**	**3a**	85
2	**1b**	**3b**	93
3	**1c**	**3c**	89
4[c]	**1d**	**3d**	44
5[d]	**4**	**5**	43 (66%)[e]

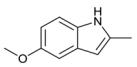
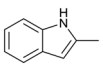
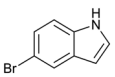
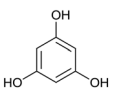
[a] Conditions used: 1.50 mmol **1a–d**, 2.25 mmol **2a**, 0.15 mmol (10 mol%) $Sc(OTf)_3$ in 300 ml H_2O (1.5% v/v EtOAc), 5 mM SDS, at room temperature for 4 hours. [b] Isolated yield after column chromatography averaged over two experiments, reproducibility within ±4%. [c] For 24 hours. [d] With 0.30 mmol (20 mol%) $Sc(OTf)_3$ for 24 hours. [e] Conversion of **4**, determined by ^{1}H-NMR.

Next, the π-nucleophile scope was investigated in the reaction with **2a** (Table 3). Using several indoles containing a variable substitution pattern in all cases gave rise to good yields of products in 4 hours reaction (entries 1–5). Also pyrroles were found to react, albeit that the results were strongly dependent on the substitution. In case of pyrrole itself, **3k** resulting from double alkylation was obtained as the main product in 71% yield based on the alkylidene malonate (entry 6). In contrast, 2,4-dimethyl-1*H*-pyrrole reacted considerably faster with the alkylidene malonate to give full conversion already after 2 hours and provided **3j** in 83% isolated yield (entry 7). Benzofuran and benzo[b]thiophene did not react under these conditions (entries 8 and 9), while 3-methoxythiophene and benzene-1,3,5-triol gave rise to unselective reactions (entries 10 and 11). The products of the Friedel–Crafts reaction can be decarboxylated to give the corresponding ester derivatives. This was demonstrated for **3e**. One ester group was removed in a Krapcho decarboxylation procedure, resulting in the monoester product **6** in 64% isolated yield (Scheme 1).[20]

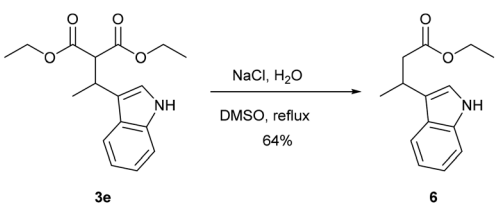
Since benzylidene malonates, *i.e.* substrates containing an aromatic moiety at the β position of the double bond, reacted much slower and gave rise to lower yields compared to alkylidene malonates, (*vide supra*) α,β-unsaturated α′-hydroxy ketones[19,20] were investigated as an alternative class of substrates (Table 4). The reaction between (*E*)-4-hydroxy-4-methyl-1-phenylpent-1-en-3-one (**7a**) and 1*H*-indole in presence of $Sc(OTf)_3$ or SDS alone resulted in only 14 and 16% conversion,

Table 3 Nucleophile scope of the $Sc(OTf_3)_2$/SDS catalysed Friedel–Crafts alkylation reaction[a]



Entry	Nu-H	Time (h)	Product	Yield[b] (%)
1		4	**3e**	85
2		4	**3f**	80
3		4	**3g**	80
4		4	**3h**	92
5		4	**3i**	63
6		22	**3j**	71[c]
7		2	**3k**	83
8		24	**3l**	n.r.[d]
9		24	**3m**	n.r.[d]
10		24	**3n**	n.d.[e]
11		24	**3o**	n.d.[e]

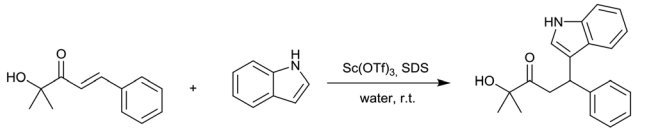
[a] Conditions used: 1.50 mmol **1b**, 2.25 mmol nucleophile, 0.15 mmol (10 mol%) $Sc(OTf)_3$ in 300 ml H_2O (1.5% v/v EtOAc), 5 mM SDS, at room temperature for the indicated time. [b] Isolated yield after column chromatography averaged over two experiments, reproducibility within ±7%. [c] Of the double alkylation product. [d] n.r. = no reaction. [e] n.d. = not determined; complex mixture of products.



Scheme 1 Krapcho decarboxylation of **3e**.

respectively, after 7 days (168 h) (entries 2 and 4). Full conversion after 7 days was obtained using 1 mol% $Sc(OTf)_3$ in combination with 5 mM SDS. Increasing the loading of $Sc(OTf)_3$ to

Table 4 Screening of catalysts for the Friedel–Crafts alkylation of indoles with α,β-unsaturated α′-hydroxy ketones[a]



7a 8a

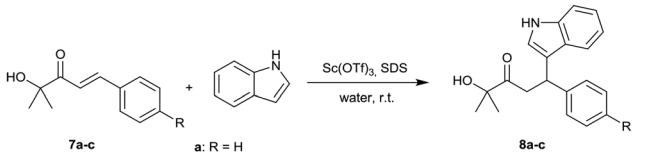
Entry	Catalyst	Time (h)	Conversion[b] (%)
1	10 mol% $Sc(OTf)_3$	6	5
2	10 mol% $Sc(OTf)_3$	168	14
3	5 mM SDS	6	3
4	5 mM SDS	168	16
6	1 mol% $Sc(OTf)_3$, 5 mM SDS	168	Full
7	10 mol% $Sc(OTf)_3$, 5 mM SDS	8	80
8	10 mol% $Sc(OTf)_3$, 5 mM SDS	16	Full
9[c]	10 mol% $Sc(OTf)_3$	8	6
10[d]	10 mol% $Sc(OTf)_3$	8	6

[a] Conditions used: 0.075 mmol **7a**, 0.113 mmol 1*H*-indole and indicated concentrations of metal salt and SDS, in 15 ml H_2O (1.5% v/v EtOAc) at room temperature for the indicated time. [b] Conversion analysed by ^{1}H NMR, averaged over two experiments, reproducibility within ±4%. [c] Reaction in DCM. [d] Reaction in EtOAc.

10 mol% resulted in 80% conversion already after 8 hours and after 16 hours full conversion was reached (entries 7 and 8). Interestingly, when the same reaction was performed in organic solvents, such as ethyl acetate or dichloromethane, using 10 mol% $Sc(OTf)_3$, only 6% conversion was obtained after 8 hours (entries 9 and 10).

The reactions were performed on a preparative scale with 3 different α,β-unsaturated α′-hydroxy ketones, which differ in the substituent on the aromatic ring (Table 5). Product **8a** was isolated in 91% yield after 16 hours (entry 1). The reaction with the *p*-nitro substituted substrate **7b** proceeded faster and after 6 hours the product **8b** was isolated in 82% yield (entry 2). Using *p*-methoxy substituted substrate **7c**, the reaction was found to be much slower and after 22 hours only 30% of **8c** (38% conversion) was isolated (entry 3).

Table 5 Scope of α,β-unsaturated α′-hydroxy ketone substrates in the $Sc(OTf)_3$/SDS catalysed Friedel–Crafts alkylation of 1*H*-indole[a]



7a-c a: R = H b: R = NO_2 c: R = OMe 8a-c

Entry	Substrate	Product	Time (h)	Yield[b] (%)
1	**7a**	**8a**	16	91
2	**7b**	**8b**	6	82
3[c]	**7c**	**8c**	22	30[d] (38)

[a] Conditions used: 1.5 mmol **7a–b**, 2.25 mmol 1*H*-indole, 0.15 mmol (10 mol%) $Sc(OTf)_3$ in 300 ml H_2O (1.5% v/v EtOAc), 5 mM SDS, at room temperature for the indicated time. [b] Isolated yield, averaged over two experiments, reproducibility within ±4%. [c] Conditions used: 0.5 mmol **7c**, 0.75 mmol 1*H*-indole, 0.05 mmol (10 mol%) $Sc(OTf)_3$ in 100 ml H_2O (1.5% v/v EtOAc), 5 mM SDS, at room temperature for the indicated time. [d] Conversion analysed by ^{1}H NMR.

Conclusions

Here, it was demonstrated that alkylidene and benzylidene malonates are convenient substrates for the vinylogous Friedel–Crafts alkylation of indoles and pyrroles, using Lewis acid surfactant combined catalysis. In those cases where the Friedel–Crafts reaction is slower, *i.e.* with benzylidene malonates, it was demonstrated that α,β-unsaturated-α′-hydroxy ketones are viable alternatives.

The auxiliary groups, which are required to achieve efficient catalysis in water, are readily removable, as was demonstrated in case of the malonate derived products. Thus, the procedure presented here gives convenient access to the products of a formal Friedel–Crafts alkylation with α,β-unsaturated carboxylic esters and acids, which are not reactive enough as electrophiles by themselves. Moreover, the results presented here provide yet another demonstration of the potential of Lewis acid in combination with SDS in organic synthesis.

Experimental

General remarks

Diethyl 2-(2-methylpropylidene)malonate was obtained from Merck. All other chemicals were purchased from Sigma Aldrich and used without further purifications. α-hydroxy ketones **7a–c** were synthesized following published procedures.[21,22] ^{1}H-NMR, and ^{13}C-NMR spectra were recorded on a Varian 400 (400 and 100 MHz). Chemical shifts (δ) are denoted in ppm using residual solvent peaks as internal standard (δ_H = 7.26 and δ_C = 77.0 for $CDCl_3$). Melting points were measured on a Mettler FP-2 melting point apparatus equipped with a Mettler FP-21 microscope and are uncorrected. High resolution mass spectra (HRMS) were recorded on an Orbitrap XL (Thermo Fisher Scientific; ESI pos. mode). Flash chromatography was performed using silica gel 60 Å (Merck, 200–400 mesh) or a Grace Reveleris® Flash System (40 μm silica column).

Representative procedure for the catalytic vinylogous Friedel–Crafts alkylations in water

In a 500 ml flask SDS (433 mg, 1.50 mmol) was added to distilled H_2O (300 ml). Then, $Sc(OTf)_3$ (73.8 mg, 0.15 mmol, dissolved in 1.5 ml EtOAc) was added to form a milky suspension that became a clear solution upon addition of the substrate (1.5 mmol, dissolved in 1.5 ml EtOAc). After 5 min. the nucleophile (2.25 mmol, dissolved in 1.5 ml EtOAc) was added. The aqueous solution was stirred under ambient atmosphere at room temperature for the indicated time. Products **3a–c** were extracted with diethyl ether (3 × 250 ml) and products **3d**, **5** and **7a–c** were extracted with ethyl acetate (3 × 250 ml). In cases of slow separation of the phases during extraction, NaCl

was added to force separation. The combined organic phases were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure.

Dimethyl 2-(1-(5-methoxy-1*H*-indol-3-yl)ethyl)malonate (3a). Synthesized using the representative procedure starting from **1a** (237 mg, 1.5 mmol). Purified by flash column chromatography (EtOAc–pentane; gradient), to afford **3a** as colourless oil. Yield: 406 mg (1.33 mmol, 89%) (average yield: 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.95 (br, 1H), 7.22 (d, J = 8.8, 1H), 7.08 (d, J = 2.3, 1H), 7.02 (d, J = 2.3, 1H), 6.84 (dd, J = 8.8, 2.4, 1H), 3.87 (s, 3H), 3.92–3.82 (m, 1H), 3.79 (d, J = 9.8, 1H), 3.75 (s, 3H), 3.48 (s, 3H), 1.44 (d, J = 6.9, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 169.3, 169.0, 153.9, 131.3, 126.6, 122.0, 117.7, 112.3, 111.9, 101.0, 58.4, 56.0, 52.4, 52.3, 31.5, 19.5. HRMS calcd for $C_{16}H_{19}NNaO_5^+$ $[M + Na]^+$: 328.116; found 328.116.

Diethyl 2-(1-(5-methoxy-1*H*-indol-3-yl)ethyl)malonate (3b). Synthesized using the representative procedure starting from **1b** (279 mg, 1.5 mmol). Purified by flash column chromatography (EtOAc–pentane; gradient), to afford **3b** as white solid. Yield: 470 mg (1.41 mmol, 94%) (average yield: 93%) mp = 91–92 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.94 (br, 1H), 7.21 (d, J = 8.8, 1H), 7.10 (d, J = 2.3, 1H), 7.02 (d, J = 2.3, 1H), 6.83 (dd, J = 8.8, 2.4, 1H), 4.23 (q, J = 7.1, 2H), 3.92 (q, J = 7.1, 2H), 3.87 (s, 3H), 3.89–3.81 (m, 1H), 3.76 (d, J = 9.9, 1H), 1.44 (d, J = 6.9, 3H), 1.27 (t, J = 7.1, 3H), 0.94 (t, J = 7.1, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 168.7168.5, 153.8, 131.3, 126.7, 122.1, 117.8, 112.1, 111.8, 101.1, 61.3, 61.1, 58.7, 55.9, 31.5, 19.7, 14.1, 13.6. HRMS calcd for $C_{18}H_{23}NO_5Na^+$ $[M + Na]^+$: 356.147; found 356.147.

Diethyl 2-(1-(5-methoxy-1*H*-indol-3-yl)-2-methylpropyl)malonate (3c). Synthesized using the representative procedure starting from **1c** (321 mg, 1.5 mmol). Purified by flash column chromatography (SiO_2, EtOAc–pentane gradient), to afford **3c** as white solid. Yield: 494 mg (1.37 mmol, 91%) (average yield: 89%). mp = 117–119 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.09 (br, 1H), 7.18 (d, J = 8.8, 1H), 7.10 (d, J = 2.2, 1H), 6.96 (d, J = 2.5, 1H), 6.81 (dd, J = 8.7, 2.4, 1H), 4.27–4.17 (m, 2H), 3.93 (d, J = 11.3, 1H), 3.85 (s, 3H), 3.85–3.75 (m, 3H), 2.16–1.98 (m, 1H), 1.26 (t, J = 7.1, 3H), 0.87 (m, 6H), 0.77 (t, J = 7.1, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 169.0, 168.3, 153.8, 130.7, 129.1, 123.5, 112.8, 112.0, 111.4, 101.4, 61.4, 61.0, 56.6, 55.9, 42.0, 30.5, 21.9, 17.7, 14.0, 13.5. HRMS calcd for $C_{20}H_{27}NO_5Na^+$ $[M + Na]^+$: 384.178; found 384.178.

Diethyl 2-((5-methoxy-1*H*-indol-3-yl)(phenyl)methyl)malonate (3d). Synthesized using the representative procedure starting from **1d** (372 mg, 1.5 mmol). Purified by flash column chromatography (SiO_2, EtOAc–pentane gradient), to afford **3d** as white solid. Yield: 260 mg (0.657 mmol, 44%) (average yield: 44%). mp = 145–147 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.12 (br, 1H), 7.36 (d, J = 7.5, 2H), 7.23 (dd, J = 14.0, 6.6, 2H), 7.18–7.09 (m, 3H), 6.96 (d, J = 2.3, 1H), 6.77 (dd, J = 8.8, 2.4, 1H), 5.02 (d, J = 11.8, 1H), 4.26 (d, J = 11.8, 1H), 4.05–3.93 (m, 4H), 3.77 (s, 3H), 1.04–0.95 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 168.1, 167.9, 153.8, 141.3, 131.4, 128.3, 128.1, 127.1, 126.7, 121.6, 116.6, 112.4, 111.7, 101.1, 61.5, 61.4, 58.4, 55.8, 42.9, 18.4, 13.7. HRMS calcd for $C_{23}H_{25}NO_5Na^+$ $[M + Na]^+$: 418.163; found 418.162.

Ethyl 4-(5-methoxy-1*H*-indol-3-yl)-2-oxochroman-3-carboxylate (5). Synthesized using the representative procedure with $Sc(OTf)_3$ (20 mol%, 0.3 mmol), starting from **4** (327 mg, 1.5 mmol). Purified by flash column chromatography (SiO_2, EtOAc–pentane gradient), to afford **5** as white solid. Yield: 236 mg (0.645 mmol, 43%) (average yield: 43%). mp = 59–61 °C. ^{1}H NMR (400 MHz, cdcl$_3$) δ = 8.30 (br, 1H), 7.31 (td, J = 8.2, 1.7, 1H), 7.25 (d, J = 8.8, 1H), 7.15 (d, J = 8.1, 2H), 7.08 (t, J = 9.6, 1H), 6.92 (d, J = 2.3, 1H), 6.87 (dd, J = 8.8, 2.4, 1H), 6.75 (d, J = 2.5, 1H), 5.00 (d, J = 7.0, 1H), 4.19 (d, J = 7.0, 1H), 4.17–4.02 (m, 2H), 3.81 (s, 3H), 1.05 (t, J = 7.1, 3H). ^{13}C NMR (101 MHz, cdcl$_3$) δ = 167.2, 164.9, 154.2, 150.9, 131.9, 129.0, 128.7, 125.9, 125.1, 123.9, 123.8, 116.9, 112.6, 112.5, 112.4, 100.7, 62.1, 55.9, 53.1, 36.6, 13.8. HRMS calcd for $C_{21}H_{20}NO_5^+$ $[M + H]^+$: 366.134, found 366.132.

Diethyl 2-(1-(1*H*-indol-3-yl)ethyl)malonate (3e). Synthesized using the representative procedure starting from **1b** (279 mg, 1.5 mmol). Purified by flash column chromatography (SiO_2, EtOAc–pentane gradient), to afford **3e** as white solid. Yield: 413 mg (1.36 mmol, 91%) (average yield: 85%). mp = 62–64 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.06 (br, 1H), 7.68 (d, J = 7.9, 1H), 7.33 (d, J = 8.0, 1H), 7.18 (t, J = 7.5, 1H), 7.11 (t, J = 7.5, 1H), 7.04 (d, J = 2.2, 1H), 4.23 (q, J = 7.1, 2H), 3.95–3.87 (m, 3H), 3.80 (d, J = 9.9, 1H), 1.46 (d, J = 6.9, 3H), 1.27 (t, J = 7.1, 3H), 0.93 (t, J = 7.1, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 168.7, 168.5, 136.9, 126.3, 121.9, 1214, 119.3, 119.3, 118.0, 111.1, 61.3, 61.0, 58.7, 31.6, 19.6, 14.1, 13.6. HRMS calcd for $C_{17}H_{21}NO_4Na^+$ $[M + Na]^+$: 326.136, found 326.137.

Diethyl 2-(1-(1-methyl-1*H*-indol-3-yl)ethyl)malonate (3f). Synthesized using the representative procedure starting from **1b** (279 mg, 1.5 mmol). Purified by flash column chromatography (SiO_2, EtOAc–pentane gradient), to afford **3f** as colourless oil. Yield: 374 mg (1.18 mmol, 79%) (average yield: 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.67 (d, J = 7.9, 1H), 7.27 (d, J = 8.0, 1H), 7.21 (t, J = 7.5, 1H), 7.11 (t, J = 7.4, 1H), 6.92 (s, 1H), 4.23 (q, J = 7.1, 2H), 3.97–3.85 (m, 3H), 3.78 (d, J = 9.8, 1H), 3.73 (s, 3H), 1.46 (d, J = 6.9, 3H), 1.28 (t, J = 7.1, 3H), 0.95 (t, J = 7.1, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 168.6, 168.4, 136.9, 126.7, 126.2, 121.5, 119.4, 118.71, 116.5, 109.1, 61.2, 611.0, 58.8, 32.6, 31.5, 19.8, 14.1, 13.6. HRMS calcd for $C_{18}H_{23}NO_4Na^+$ $[M + Na]^+$: 340.152, found 340.152.

Diethyl 2-(1-(5-methoxy-2-methyl-1*H*-indol-3-yl)ethyl)malonate (3g). Synthesized using the representative procedure starting from **1b** (279 mg, 1.5 mmol). Purified by flash column chromatography (SiO_2, EtOAc–pentane gradient), to afford **3g** as colourless oil. Yield: 424 mg (1.22 mmol, 81%) (average yield: 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.69 (br, 1H), 7.11 (d, J = 8.7, 1H), 7.07 (d, J = 2.3, 1H), 6.74 (dd, J = 8.7, 2.4, 1H), 4.27 (q, J = 7.1, 2H), 3.96 (d, J = 11.3, 1H), 3.87 (s, 3H), 3.85–3.75 (m, 3H), 2.38 (s, 3H), 1.44 (d, J = 7.0, 3H), 1.32 (t, J = 7.1, 3H), 0.81 (t, J = 7.1, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 169.0, 168.4, 153.5, 132.5, 130.5, 127.6, 112.2, 110.8, 109.9, 102.1, 61.4, 60.8, 57.6, 56.1, 31.5, 18.6, 14.1, 13.5, 12.2. HRMS calcd for $C_{19}H_{25}NO_5Na^+$ $[M + Na^+]$: 370.163, found 370.163.

Diethyl 2-(1-(2-methyl-1*H*-indol-3-yl)ethyl)malonate (3h). Synthesized using the representative procedure starting from **1b** (279 mg, 1.5 mmol). Purified by flash column chromatography (SiO_2, EtOAc–pentane gradient), to afford **3h** as white solid. Yield: 412 mg (1.30 mmol, 87%) (average yield: 92%). mp = 55–56 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.75 (br, 1H), 7.61 (dd, J = 6.8, 2.0, 1H), 7.27–7.21 (m, 1H), 7.11–7.03 (m, 2H), 4.32–4.24 (m, 2H), 3.99 (d, J = 11.3, 1H), 3.86–3.75 (m, 3H), 2.41 (s, 3H), 1.46 (d, J = 7.1, 3H), 1.33 (t, J = 7.1, 3H), 0.79 (t, J = 7.1, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 169.0, 168.4, 135.3, 131.5, 127.0, 120.7, 119.1, 119.0, 112.4, 110.3, 61.4, 60.8, 57.8, 31.6, 18.8, 14.2, 13.5, 12.1. HRMS calcd for $C_{18}H_{23}NO_4Na^+$ [M + Na^+]: 340.152, found 340.152.

Diethyl 2-(1-(5-bromo-1*H*-indol-3-yl)ethyl)malonate (3i). Synthesized using representative procedure starting from **1b** (279 mg, 1.5 mmol). Purified by flash column chromatography (SiO_2, EtOAc–pentane gradient), to afford **3i** as white solid. Yield: 374 mg (0.978 mmol, 65%) (average yield: 63%). mp = 100–101 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.32 (br, 1H), 7.78 (d, J = 1.7, 1H), 7.23 (dd, J = 8.6, 1.8, 1H), 7.17 (d, J = 8.6, 1H), 7.01 (d, J = 2.4, 1H), 4.23 (q, J = 7.1, 2H), 3.97–3.87 (m, 2H), 3.87–3.78 (m, 1H), 3.74 (d, J = 9.9, 1H), 1.43 (d, J = 6.9, 3H), 1.27 (t, J = 7.1, 3H), 0.97 (t, J = 7.1, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 168.5, 168.4, 134.7, 128.0, 124.7, 122.8, 121.7, 117.5, 112.7, 112.5, 61.4, 61.2, 58.8, 31.4, 19.7, 14.1, 13.6. HRMS calcd for $C_{17}H_{20}BrNO_4Na^+$ [M + Na^+]: 404.047, found 404.047.

Tetraethyl 2,2′-((1*H*-pyrrole-2,5-diyl)bis(ethane-1,1-diyl))-dimalonate (3j). Synthesized using the representative procedure starting from **1b** (279 mg, 1.5 mmol). Purified by flash column chromatography (SiO_2, EtOAc–pentane gradient), to afford **3j** as colourless oil. Mixture of diastereomers. Yield: 238 mg (0.542 mmol, 72%) (average yield: 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.81 (br, 1H), 5.77 (d, J = 2.6, 2H), 4.19 (q, J = 7.1, 4H), 4.14–4.02 (m, 4H), 3.58–3.47 (m, 2H), 3.45 (dd, J = 8.2, 3.1, 2H), 1.32 (d, J = 7.0, 6H), 1.25 (t, J = 7.1, 6H), 1.15 (t, J = 7.1, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 168.7, 168.7, 168.6, 168.6, 132.1, 132.1, 104.5, 61.4, 61.3, 61.3, 58.9, 58.9, 32.5, 32.5, 18.2, 18.1, 14.0, 13.9. HRMS calcd for $C_{22}H_{33}NO_8Na^+$ [M + Na^+]: 462.210, found 462.209.

Diethyl 2-(1-(3,5-dimethyl-1*H*-pyrrol-2-yl)ethyl)malonate (3k). Synthesized using the representative procedure starting from **1b** (279 mg, 1.5 mmol). Purified by flash column chromatography (SiO_2, EtOAc–pentane gradient), to afford **3k** as colourless oil. Yield: 358 mg (1.27 mmol, 85%) (average yield: 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.31 (br, 1H), 5.56 (d, J = 2.3, 1H), 4.26–4.01 (m, 4H), 3.66–3.51 (m, 2H), 2.18 (s, 3H), 1.98 (s, 3H), 1.34 (d, J = 6.8, 3H), 1.20 (t, J = 7.1, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 169.0, 168.7, 126.3, 125.8, 114.5, 107.4, 61.3, 61.3, 57.4, 31.1, 18.6, 13.9, 13.9, 12.9, 10.9. HRMS calcd for $C_{15}H_{24}NO_4^+$ [M + H]$^+$: 282.170, found 282.170.

Ethyl 3-(1*H*-indol-3-yl)butanoate (6). Synthesized using a modified literature procedure. **3e** (1.007 g, 3.320 mmol) was added to a vigorously stirred mixture of sodium chloride (409 mg, 6.81 mmol), anhydrous DMF (21 mL) and H_2O (260 μL, 14.4 mmol). The resulting mixture was heated under reflux for 26 hours and afterwards stirred for 16 hours at 75 °C. The dark brown reaction mixture was allowed to cool to room temperature and water (50 mL) was added. The aqueous solution was extracted with dichloromethane (3 × 25 mL) and the combined organic layers were washed with brine (3 × 75 mL), dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by column chromatography (SiO_2, EtOAc–pentane : 1/4) to afford **6** as yellow oil. Yield: 509 mg (2.20 mmol, 66%) (average yield: 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.01 (br, 1H), 7.69 (d, J = 7.9, 1H), 7.35 (d, J = 8.1, 1H), 7.20 (t, J = 7.6, 1H), 7.14 (t, J = 7.5, 1H), 6.98 (d, J = 2.0, 1H), 4.13 (q, J = 7.1, 2H), 3.69–3.58 (m, 1H), 2.84 (dd, J = 14.9, 6.2, 1H), 2.59 (dd, J = 14.9, 8.7, 1H), 1.44 (d, J = 6.9, 3H), 1.22 (t, J = 7.1, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.9, 136.4, 126.3, 121.9, 120.8, 112.0, 119.2, 119.1, 111.2, 60.2, 42.5, 28.0, 21.0, 14.2. HRMS calcd for $C_{14}H_{18}NO_2^+$ [M + H]$^+$: 232.133, found 232.132.

4-Hydroxy-1-(1*H*-indol-3-yl)-4-methyl-1-phenylpentan-3-one (8a). Synthesized using the representative procedure starting from **7a** (285 mg, 1.5 mmol). Purified by flash column chromatography (SiO_2, EtOAc–pentane gradient), to afford **8a** as white solid. Yield: 437 mg (1.42 mmol, 95%) (average yield: 91%). mp = 130–131 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.02 (br, 1H), 7.44 (d, J = 8.0, 1H), 7.35–7.30 (m, 3H), 7.26 (dd, J = 8.9, 6.1, 2H), 7.21–7.13 (m, 2H), 7.07–7.00 (m, 1H), 6.98 (d, J = 1.9, 1H), 4.96 (t, J = 7.3, 1H), 3.63 (br, 1H), 3.36 (d, J = 7.3, 2H), 1.26 (s, 3H), 1.15 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 212.5, 143.6, 136.5, 128.4, 127.8, 126.5, 126.4, 122.3, 121.1, 119.5, 119.4, 118.9, 111.1, 76.3, 42.4, 37.8, 26.0, 25.9. HRMS calcd for $C_{20}H_{21}NO_2Na^+$ [M + Na]$^+$: 330.147, found 330.146.

4-Hydroxy-1-(1*H*-indol-3-yl)-4-methyl-1-(4-nitrophenyl)pentan-3-one (8b). Synthesized using the representative procedure starting from **7b** (353 mg, 1.5 mmol). Purified by flash column chromatography (SiO_2, EtOAc–pentane gradient), to afford **8b** as yellow solid. Yield: 446 mg (1.27 mmol, 84%) (average yield: 82%). mp = 175–176 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.13 (d, J = 8.8, 2H), 8.09 (br, 1H), 7.49 (d, J = 8.6, 2H), 7.36 (t, J = 7.0, 2H), 7.19 (t, J = 7.6, 1H), 7.05 (t, J = 7.9, 2H), 5.05 (dd, J = 8.1, 6.5, 1H), 3.49–3.33 (m, 3H), 1.28 (s, 3H), 1.20 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 211.9, 151.6, 146.5, 136.5, 128.7, 126.0, 123.7, 122.6, 121.2, 119.8, 118.9, 117.4, 111.4, 76.4, 41.9, 37.5, 26.1. HRMS calcd for $C_{20}H_{20}N_2O_4Na^+$ [M + Na]$^+$: 375.132, found 375.131.

4-Hydroxy-1-(1*H*-indol-3-yl)-1-(4-methoxyphenyl)-4-methylpentan-3-one (8c). Synthesized using the representative procedure with $Sc(OTf)_3$ (0.05 mmol), 1*H*-indole (0.075 mmol) and 5 mM SDS in 100 ml water starting from **7c** (110 mg, 0.5 mmol). Purified by flash column chromatography (SiO_2, EtOAc–pentane gradient), to afford **8c** as white solid. Yield: 54 mg (0.160 mmol, 32%) (average yield: 30%). mp = 171–173 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.14 (br, 1H), 7.44 (d, J = 8.0, 1H), 7.31 (d, J = 8.1, 1H), 7.24 (d, J = 8.6, 2H), 7.17 (t, J = 7.6, 1H), 7.05 (t, J = 7.5, 1H), 6.94 (d, J = 2.0, 1H), 6.82 (d, J = 8.6, 2H), 4.92 (t, J = 7.3, 1H), 3.76 (s, 3H), 3.70 (br, 1H), 3.37–3.31 (m, 2H), 1.28 (s, 3H), 1.16 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 212.7, 158.0, 136.5, 135.7, 128.7, 126.3, 122.1, 121.1, 119.4, 119.3, 119.1, 113.7, 111.1, 76.4, 55.1, 42.5,

37.0, 26.0, 25.9. HRMS calcd for $C_{21}H_{24}N_1O_3^+$ $[M + H]^+$: 338.175, found 338.174.

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