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Synthesis of fluorinated 2-oxindoles via intramolecular dehydrogenative coupling†

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An expedient synthesis of fluorinated 2-oxindoles bearing an all carbon quaternary center at the pseudobenzylic position is envisioned under "*transition metal free*" intramolecular dehydrogenative coupling (IDC) pathway. This method has been applied to a wide range of substrate affording fluorinated 2-oxindoles in moderate to good yields in a facile one-pot C-alkylation concomitant with oxidative coupling strategy. There are several advantages of our methodology, namely, (i) *transition metal-free process* and simple oxidants are used and (ii) wide substrate scope. The control experiment using radical scavenger suggesting that reaction goes via radical pathway. Further works on the biological potential of these fluorinated 2-oxindoles are currently under active investigation.

Keywords: 2-Oxindoles, intramolecular dehydrogenative coupling (IDC), fluorine, drugs, KO^{t}Bu.

1. Introduction

Natural products contain privileged molecular structures with inherent biological properties, and therefore, these fulfill specific biological functions within the context of signaling pathways and protein interaction[1]. The structural modification of secondary metabolites isolated from Nature plays crucial rule in the invention of new drug entities. Since, a small change in structure alters its activity, the medicinal chemists often use this tool as the fundamental strategies when inventing new drugs[2].

On the other hand, the excellent therapeutic profile of pharmaceutical drugs featuring fluorine atom(s) stimulates research for new discovery in medicinal chemistry. It has been universally appreciated that the presence of fluorine atom in a bioactive molecule profoundly modifies its physico-chemical and biological properties[3]. As per reports, it is probably through concomitant alteration of its steric, electronic, lipophilic, and metabolic characteristics[3]. Due to these properties introduction of fluorine into molecules or drugs can increase their metabolic stability, bioavailability and blood-brain barrier (BBB) penetration[4]. Approximately 20–30% of pharmaceuticals and agrochemicals contain fluorine atoms as their integral part either on aliphatic chain or linked with aromatic rings.

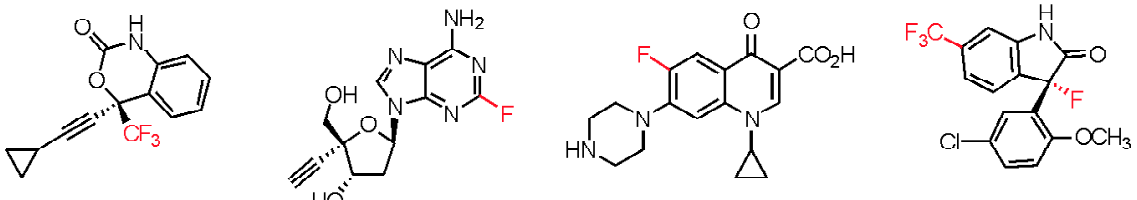


Fig. 1. Biologically active fluorinated compounds.

†**Invited Lecture.**

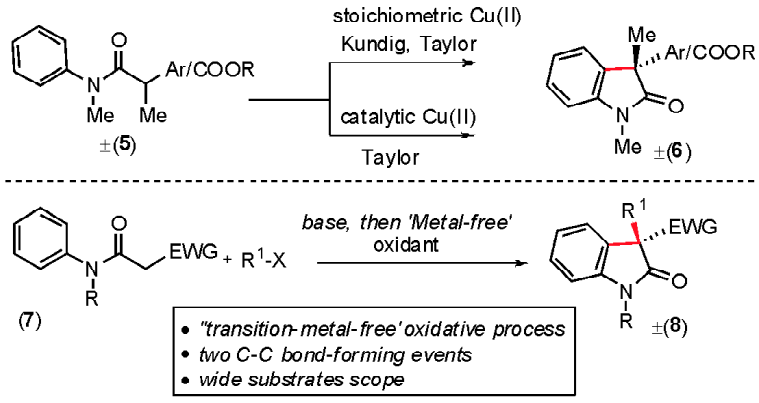
Because of the less abundance of fluoride ion compared to another halide ion in Nature, there are very few naturally occurring secondary metabolites that contain fluorine[4]. Efavirenz (**1**), sharing a trifluoromethyl group in the aliphatic side chain, is a non-nucleoside reverse transcriptase inhibitor that shows high potency against a variety of HIV-1 mutant strains[5]. Islatravir (**2**) is a first-in-class inhibitor of reverse transcriptase translocation (NRTTI)[6] that has shown great promise in preclinical studies for the treatment of HIV[7]. Ciprofloxacin (**3**), sharing a fluoro group in the aromatic ring, is an antibiotic used to treat a number of bacterial infections, including bone and joint infections and intra-abdominal infections[8]. BMS 204352 (**4**), sharing a trifluoromethyl group in the aromatic ring and fluorine at the pseudobenzylic position of 2-oxindole, is a potent and effective opener of two important subtypes of neuronal potassium channels developed for the treatment of stroke[9].

Further, establishment of efficient methodologies to forge an all-carbon quaternary stereocenter of 2-oxindoles remains an active area in the realm of exploratory synthetic research. Towards this, one of the direct approaches to 2-oxindoles could be a one electron oxidation of an amide enolate. While working on the asymmetric construction of 3,3-disubstituted-2-oxindoles via a Pd-catalyzed (chiral *N*-heterocyclic carbene as ligands) intramolecular α-arylation of amide[10], Kundig and co-workers have discovered a novel, efficient and atom-economic route to access 3,3-disubstituted 2-oxindoles (Scheme 1)[11]. Independently, Taylor and co-workers reported the synthesis of 2-oxindoles in the presence of $Cu(OAc)_2.H_2O$ as an oxidant (Scheme 1)[12]. Mechanistically, these reactions proved to be a free-radical process. The α-carbonyl alkyl radicals were generated by the Cu(II)-mediated oxidation of the corresponding enolate precursors. In 2010, Hu and co-workers have reported synthesis of 3-acetyloxindoles via Ag_2O-mediated intramolecular oxidative coupling[13].

In this direction, our group have reported an 'intramolecular-dehydrogenative-coupling' (IDC) strategy to these 2-oxindole motifs that involves a C-alkylation step concomitant with an oxidative construction of the C-C bond via tandem activation of two C-H bonds (Scheme 1) under '*transition-metal-free*' conditions[14]. Herein, we disclose the synthesis of fluorinated 2-oxindoles via 'intramolecular-dehydrogenative-coupling' (IDC) of Csp^2-H and Csp^3-H mediated by iodine and/or *N*-halosuccinimide (NXS) as oxidants.

Results and discussions

2-Oxindole is the core structure in a variety of natural products and drugs. Also, fluorine is an important tool in the drug designing process because of its properties. Considering the significance of these two facts, we have undertaken in developing a methodology where the easy incorporation of fluorine to the 2-oxindole moiety is possible. These fluorinated products might be a great synthetic platform for many therapeutically active products. One of the primary research areas of our group is the synthesis of 2-oxindoles sharing all-carbon quaternary stereocenters via oxidative coupling reactions mediated by simple oxidants such as iodine[14a] and 2,3-dichloro-4,5-dicyano *p*-benzoquinone (DDQ)[14b]. A wide range of 2-oxindoles has been prepared using this methodology[15]. *N*-Halosuccinimides (NXS) having well-established precedence in its use as an oxidant in organic chemistry[16].



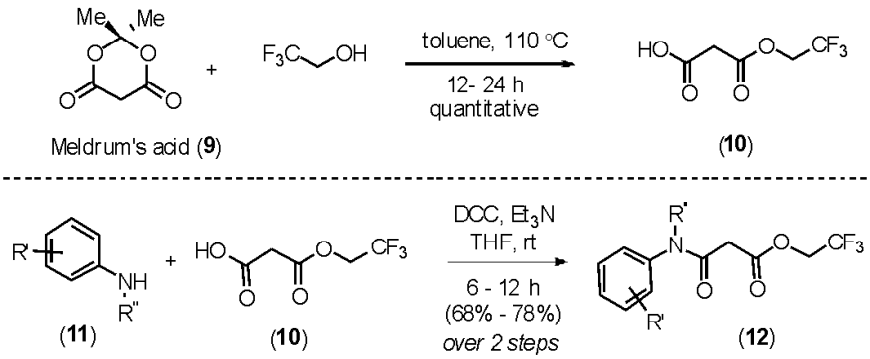
Scheme 1. Synthesis of 2-oxindoles via oxidative processes.

Therefore, we thought of using it as the oxidant for the synthesis of 2-oxindoles. Towards this, a few fluorinated β-*N*-arylamido esters **12** were synthesized from 2-trifluoro ethyl alcohol from Meldrum's acid in two steps, as per Scheme 2. Meldrum's acid (**9**) was desymmetrized with 2-trifluoro ethyl alcohol in toluene at elevated temperature to get carboxylic acid **10**, which was then directly reacted with *N*-methylanilines (**11**) to afford β-*N*-arylamido esters **12** in 68–78% overall yields in 2 steps (Scheme 2).

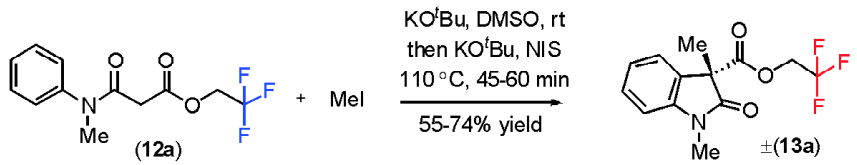
Initially, to establish a standard reaction protocol, we selected β-*N*-arylamido ester (**12a**) and methyl iodide as the substrate and electrophile, respectively (Scheme 3) and *N*-iodosuccinimide (NIS) as the oxidant. The reaction was carried out on a 0.25 mmol of **12a** with 0.275 mmol of methyl iodide in presence of 0.30 mmol of base in 1 mL of dimethyl sulfoxide (DMSO) at 25°C for 15 min for complete alkylation followed by addition of 0.275 mmol of *N*-iodosuccinimide (NIS) in presence of 0.30 mmol of base under heating at 110°C for oxidative coupling steps, unless noted otherwise. Among the different bases employed in this reaction, KO^{t}Bu was found to be superior over NaH, NaOMe, K_2CO_3, Cs_2CO_3, and NaO^{t}Bu. Optimization studies in search of suitable solvent revealed that the desired product could be obtained in good yield in dimethylsulfoxide (DMSO). Various *N*-halosuccinimide were tested. It was found that iodine, *N*-iodosuccinimide (NIS), and *N*-bromosuccinimide (NBS) afforded 2-oxindole **13a** in 74%, 70%, and 55% yields, respectively (Scheme 3).

Next, the substrate scope of the reaction was explored and shown in Scheme 4. Under optimized condition, various β-*N*-arylamido esters (**12**) were subjected to a one-pot alkylation using 1.2 equivalents of KO^{t}Bu to produce C-alkylated intermediate **14** followed by oxidative coupling using 1.2 equivalents of iodine (condition **A**) or 1.2 equivalents of *N*-iodosuccinimide (NIS) (condition **B**). As can be seen, a variety of fluorinated β-*N*-arylamido ester (**12a-c**)underwent alkylation with different alkyl halides followed by intramolecular-dehydrogenative-coupling (IDC) to afford 2-oxindole products **13a-c** in good yields (52–74%) via the intermediacy of **14a-c** (Scheme 4).

Later, we have used fluorinated β-*N*-arylamido ester (**12d-j**) as starting material for the synthesis of 2-oxindoles **13d-j** where fluorine is linked with aliphatic as well as aromatic

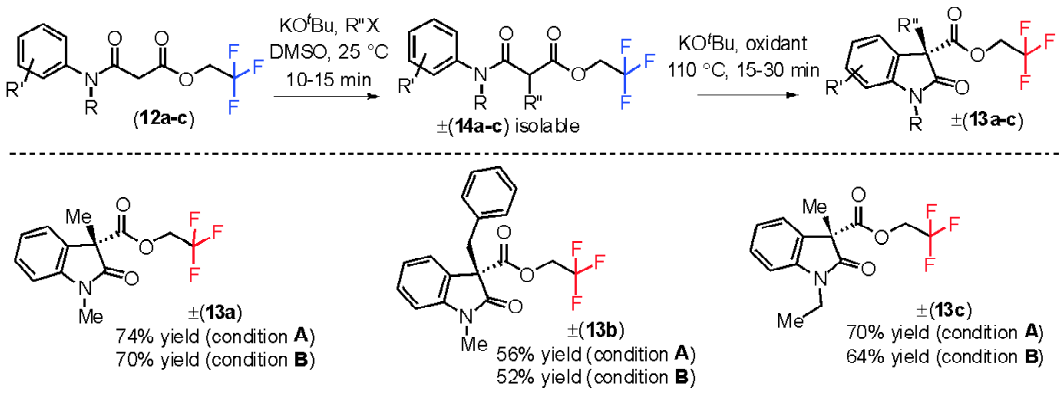


Scheme 2. Synthesis of fluorinated β-*N*-arylamido esters**12** from Meldrum's acid.



Oxidants	Yield (13a)	Time (min)
Iodine	74%	45 min
NIS	70%	60 min
NCS	55%	60 min

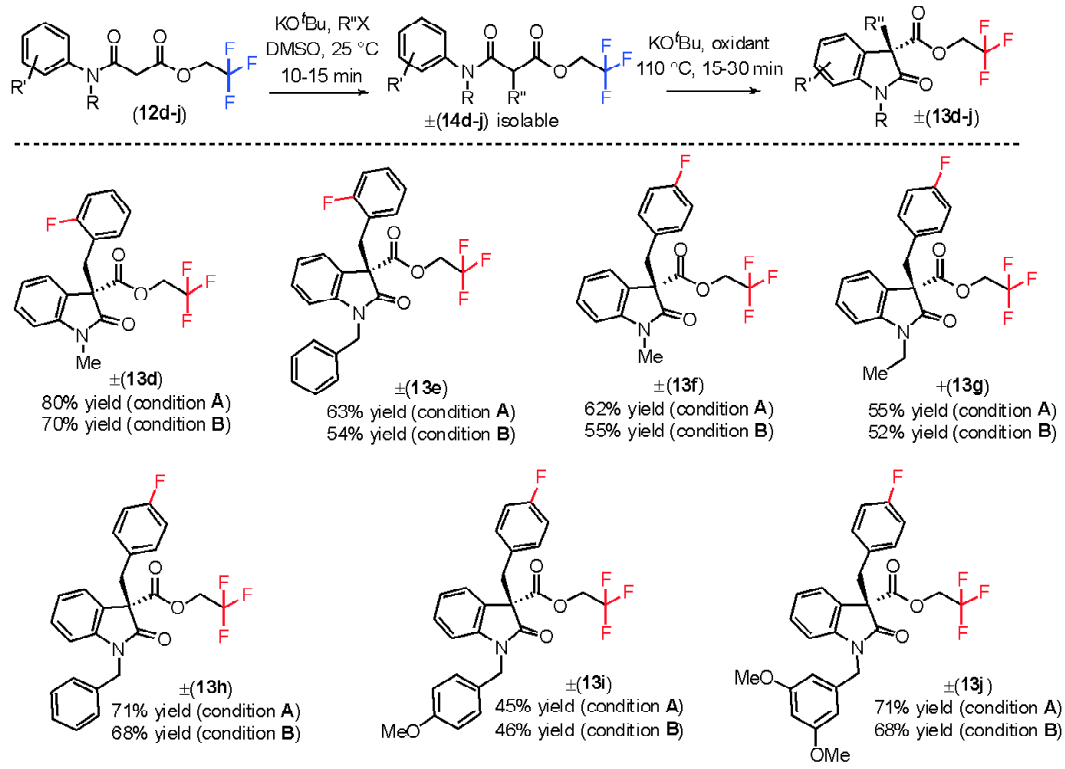
Scheme 3. Optimization of 'intramolecular-dehydrogenative-coupling' (IDC).



Condition **A**: KO^{t}Bu, Iodine; condition **B**: KO^{t}Bu, NIS

Scheme 4. Synthesis of fluorinated 2-oxindoles **13a-c** under *'transition metal-free'* IDC.

ring and the results are show in Scheme 5. The reactions were further carried out in two different conditions (conditions **A** and **B**) by taking two oxidants such as iodine (condition **A**) and *N*-iodosuccinimide (NIS) (condition **B**). Gratifyingly, it was found that β-*N*-arylamido esters **12d-j** underwent IDC process to furnish a wide range of 2-oxindoles such as **13d-j** having an all-carbon-quaternary center in synthetically useful yields through the intermediate *N*-alkylated β-*N*-arylamido esters (**14d-j**) (Scheme 5). In case of *N*-*p*-methoxybenzyl protected β-*N*-arylamido ester **12i**, we could isolate only 45–46% yields of 2-oxindole **13i**. This is probably due to the presence of *N*-*p*-methoxybenzyl group, which is known to be cleaved under the oxidative condition. However, when it is *N*-3,5-dimethoxybenzyl protected β-*N*-arylamido ester **12j**, we could isolate 68–71% isolated yield (Scheme 5).

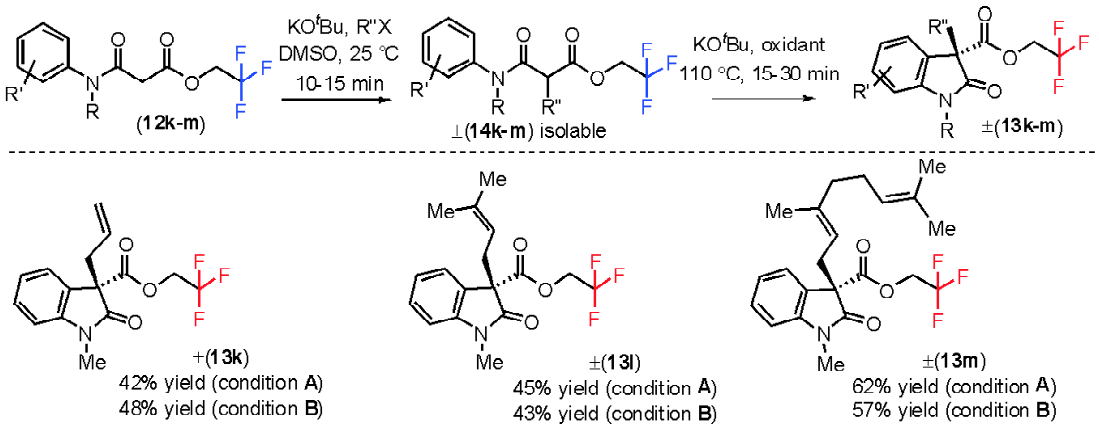


Condition **A**: KO^{t}Bu, Iodine; condition **B**: KO^{t}Bu, NIS

Scheme 5. Synthesis of fluorinated 2-oxindoles **13d-j** under *'transition metal-free'* IDC.

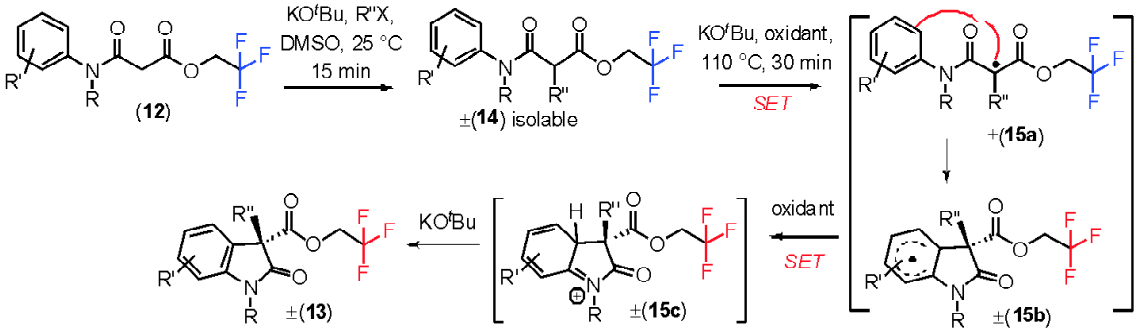
Later, few more β-*N*-arylamido esters (**12k-m**) were alkylated with allyl bromide, 3,3-dimethylallyl bromide and geranyl bromide to generate *N*-alkylated β-*N*-arylamido esters (**14k-m**), which upon treatment with oxidants such as iodine (condition **A**) and *N*-iodosuccinimide (NIS) (condition **B**) afforded fluorinated 2-oxindoles **13k-m** in moderate good yields (Scheme 6). The oxidation of *N*-alkylated β-*N*-arylamido esters (**14k-m**) are challenging because of their inherent reactivity towards oxidants at the allylic position. Gratifyingly, we could perform 'intramolecular-dehydrogenative-coupling' (IDC) onto these substrates to obtain products 2-oxindoles **13k-m** (Scheme 6).

A probable mechanism of the 'intramolecular-dehydrogenative-coupling' (IDC) promoted by potassium *tert*-butoxide and an oxidant is shown in Scheme 7. It has been seen that the IDC is feasible when the reaction was carried out with substrates having substitution at carbon atom β- to the amides such as **12**, therefore clearly indicating a three-degree radical might be the probable pathway where a single electron transfer (SET) mechanism might be operating. After C-alkylation of β-*N*-arylamido ester **12**, the reaction can adopt a SET mechanism leading to the intermediates **15a**, which in turn can form an intermediate aryl radical **15b**. The aryl radical could transfer one electron to the oxidant to form intermediate aryl carbocation **15c** (stabilized by amide nitrogen). Finally, re-aromatization of **15c** in the presence of base could afford oxidative coupling products **13a-m** (Schemes 4-6).

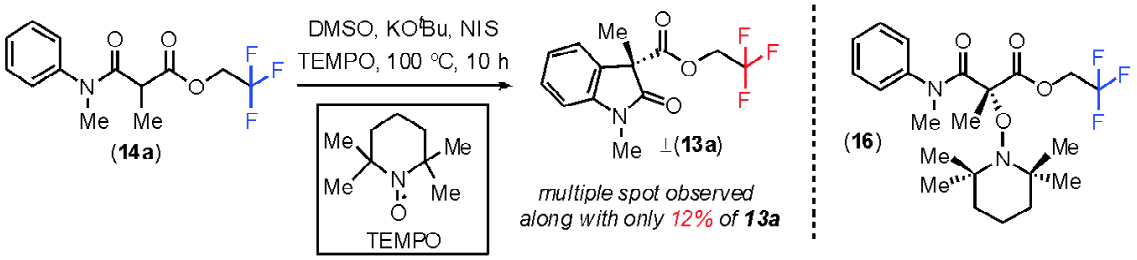


Condition **A**: KO^{t}Bu, Iodine; condition **B**: KO^{t}Bu, NIS

Scheme 6. Synthesis of fluorinated 2-oxindoles **13k-m** under *'transition metal-free'* IDC.



Scheme 7. Plausible mechanism of *'transition metal-free'* IDC.



Scheme 8. Control experiment using stoichiometric TEMPO.

Further proof of the radical nature of our reaction mechanism was shown via control experiments (Scheme 8). It is well known that the radical quencher such as 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO) reacts with the radical and inhibits the progress of the reaction. Therefore, intramolecular oxidation reaction of *N*-methylated β-*N*-arylamido esters **14a** was performed in DMSO with 1 equivalent of *N*-iodosuccinimide (NIS) in the presence of 1 equivalent of KO^{t}Bu and 1 equivalent of TEMPO (condition **B**). It has been found that the reaction led to a mixture of products in addition to only 12% of 2-oxindole **13a** (Scheme 8). This result gives an indirect support of radical pathway of our oxidative process.

Conclusions

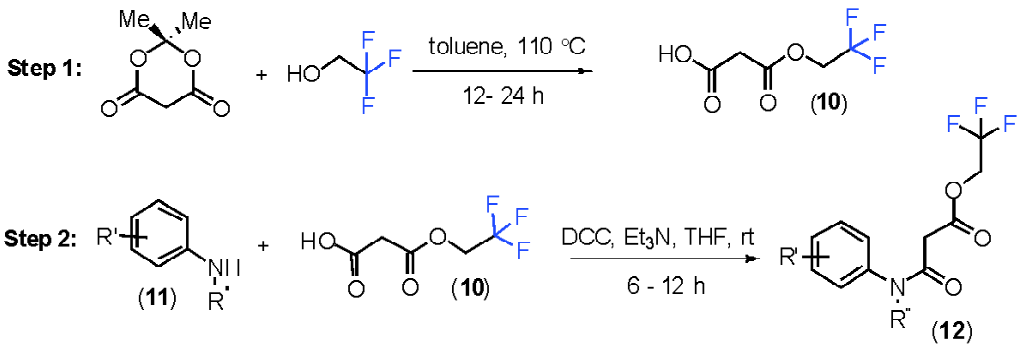
In summary, we have demonstrated intramolecular dehydrogenative coupling (IDC) strategy for the synthesis of fluorinated 2-oxindole bearing an all carbon quaternary center at the pseudobenzylic position. This method has been applied to a wide range of substrate affording fluorinated 2-oxindoles in good yields in a facile one-pot C-alkylation concomitant with oxidative coupling strategy. This methodology has many advantages: (i) *transition metal-free* process and simple oxidants are used and (ii) wide substrate scope. So, incorporating fluorine to the 2-oxindole moiety will give an easy and powerful methodology for the synthesis of fluorinated products which might be having different biological properties. Control experiment suggesting that reaction goes via radical pathway and that supports our proposed mechanism. Further works on the biological potential of these fluorinated 2-oxindoles are currently under active investigation.

Experimental section

Materials and methods:

Unless otherwise stated, reactions were performed in oven-dried glassware fitted with rubber septa under an inert atmosphere and were stirred with Teflon-coated magnetic stirring bars. Liquid reagents and solvents were transferred via syringe using standard Schlenk techniques. Tetrahydrofuran (THF) was distilled over sodium/benzophenone ketyl. Toluene was distilled over calcium hydride. All other solvents and reagents were used as received unless otherwise noted. Reaction temperatures above 23°C refer to oil bath temperature. Thin layer chromatography was performed using silicagel 60 F-254 precoated plates (0.25 mm) and visualized by UV irradiation, anisaldehyde stain, and other stains. Silica gel of particle size 100–200 mesh was used for flash chromatography. Melting points were recorded on a digital melting point apparatus from Jyoti Scientific (AN ISO 9001:2000) and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded 400, 500 MHz spectrometers with ^{13}C operating frequencies of 100, 125 MHz respectively. Chemical shifts (δ) are reported in ppm relative to the residual solvent ($CDCl_3$) signal (δ = 7.24 for ^{1}H NMR and δ = 77.0 for ^{13}C NMR). Data for ^{1}H NMR spectra are reported as follows: chemical shift (multiplicity, coupling constants, number of hydrogen). Abbreviations are as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). IR spectra were recorded on a FT-IR system (Spectrum BX) and are reported in frequency of absorption (cm^{-1}). Only selected IR absorbencies are reported. High-Resolution Mass Spectrometry (HRMS) and Low-Resolution Mass Spectrometry (LRMS) data were recorded on MicrOTOF-Q-II mass spectrometer using methanol as solvent.

General procedure for the synthesis of the β-N-arylamido esters

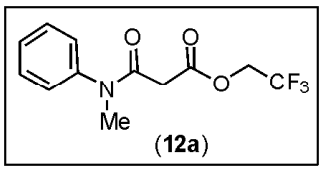


Scheme 9. Synthesis of β-*N*-arylamido esters **12**.

Step 1: A flame-dried round-bottom flask was charged with Meldrum's acid [1.0 equiv. (generally in 10 g scale)] and required alcohol (1.5–5.0 equiv. case to case). The reaction mixture was heated under refluxed at 110°C for indicated time. Upon completion of the reaction (as judged by TLC), the reaction mixture was cooled to room temperature. Most of the volatile components were evaporated under reduced pressure, without work up. The crude malonic acid monoesters were directly used for coupling reaction without purification.

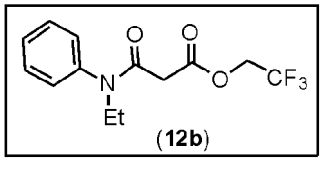
Step 2: In a flame-dried round-bottom flask, crude malonic acid monoester (1.0 mmol) was taken in THF (5 mL/mmol) and cooled to 0°C on an ice-bath. To this reaction mixture was added triethylamine (3 mmol) via a syringe, followed by DCC (1.2 mmol). After 5 min of stirring at same temperature, a THF solution of *N*-methylaniline derivatives (1.0 mmol) was added dropwise to the reaction mixture and slowly allowed to warm to rt (over 10 min). The stirring was continued till TLC showed complete consumption of starting materials. The reaction mixture was diluted with dichloromethane (approx. 40 mL for 5 mmol scale of a reaction) and then successively washed with water (20 mL), 2(N)-HCl (20 mL), saturated $NaHCO_3$ (20 mL) and finally with brine (20 mL). The organic extracts were dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by flash chromatography (4:1 hexanes/EtOAc) to afford β-*N*-arylamido esters.

*2,2,2-Trifluoroethyl-3-(methyl(phenyl)amino)-3-oxopropanoate (**12a**):* The compound was obtained as yellow oil (7.97 g, 60% yield), R_f = 0.32 (20% EtOAc in hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.39 (m, 2H), 7.37–7.33 (m, 1H), 7.21–7.19 (m, 2H), 4.43 (q, *J* 8.5 Hz, 2H), 3.29 (s, 3H), 3.28 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 165.0, 143.2, 130.1, 128.5, 127.2, 126.9–118.6 (q, *J* 276 Hz), 60.8 (q, *J* 37.0 Hz), 40.9, 37.5; IR (film) υ_{max} 3025, 2921, 1600, 1492, 1451, 1180, 1068, 1028, 966, 907, 757, 703 cm^{-1}; HRMS (ESI) *m/z* 276.0833 [(M+H)$^+$; calculated for [$C_{12}H_{12}NO_3F_3$ + H]$^+$: 276.0842].



(**12a**)

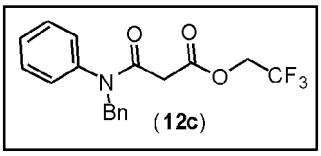
*2,2,2-Trifluoroethyl-3-(ethyl(phenyl)amino)-3-oxopropanoate (**12b**):* The compound was obtained as yellow oil (8.0 g, 70% yield), R_f = 0.34 (20% EtOAc in hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.34 (m, 3H), 7.18–7.16 (m, 2H), 4.42 (q, *J* 8.4 Hz, 2H), 3.75 (q, *J* 7.19 Hz, 2H), 3.22 (s, 2H), 1.11 (t, *J* 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 164.4, 141.5, 130.0, 128.6, 128.3, 126.9–118.6 (q, *J* 276.8 Hz), 60.7 (q, *J* 37.0 Hz), 44.4, 41.2,



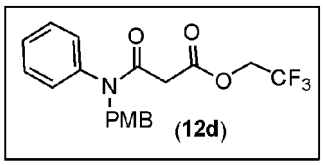
(**12b**)

12.8; IR (film) υ_{max} 3025, 2923, 1942, 1771, 1653, 1600, 1492, 1451, 1180, 1068, 1028, 965, 907, 841, 757, 703 cm^{-1}; HRMS (ESI) *m/z* 290.0982 $[(M+H)^+$; calculated for $[C_{13}H_{14}NO_3F_3 + H]^+$: 290.0999].

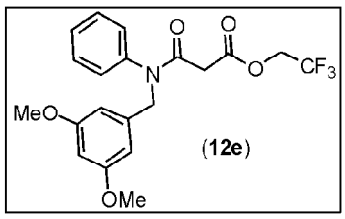
*2,2,2-Trifluoroethyl-3-(benzyl(phenyl)amino)-3-oxopropanoate (**12c**):* The compound was obtained as brown oil (7.97 g, 55% yield), R_f = 0.48 (20% EtOAc in hexane). ^1H NMR (400 MHz, $CDCl_3$) δ 7.32–7.29 (m, 3H), 7.26–7.23 (m, 3H), 7.19–7.18 (m, 2H), 7.00–6.97 (m, 2H), 4.90 (s, 2H), 4.44 (q, *J* 8.3 Hz, 2H), 3.29 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 165.0, 141.4, 136.7, 129.9, 128.8, 128.7, 128.5, 128.3, 127.6, 126.9–118.6 (q, *J* 268.3 Hz), 60.8 (q, *J* 36.5 Hz), 53.2, 41.1; IR (film) υ_{max} 3028, 2922, 1769, 1653, 1600, 1492, 1451, 1307, 1179, 1151, 1065, 1029, 979, 908, 842, 754, 703 cm^{-1}; HRMS (ESI) *m/z* 352.1155 $[(M+H)^+$; calculated for $[C_{18}H_{16}NO_3F_3 + H]^+$: 352.1155].



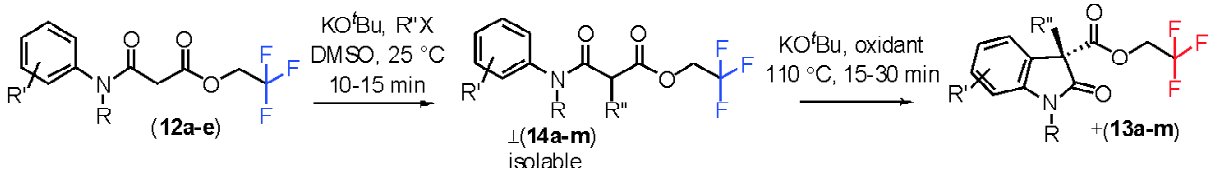
*2,2,2-Trifluoroethyl-3-((4-methoxybenzyl)(phenyl)amino)-3-oxopropanoate (**12d**):* The compound was obtained as yellow oil (7.49 g, 64% yield), R_f = 0.28 (10% EtOAc in hexane). ^1H NMR (400 MHz, $CDCl_3$) δ 7.32–7.30 (m, 3H), 7.09 (d, *J* 8.6 Hz, 2H), 6.96 (q, *J* 3.5 Hz, 2H), 6.77 (d, *J* 8.6 Hz, 2H), 4.82 (s, 2H), 4.43 (q, *J* 9.0 Hz, 2H), 3.76 (s, 3H), 3.26 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 164.9, 159.1, 141.4, 130.2, 129.8, 128.8, 128.6, 128.4, 124.1 (q, *J* 277 Hz), 113.8, 60.8 (q, *J* 36.3 Hz), 55.2, 52.6, 41.2; IR (film) υ_{max} 3024, 2925, 2847, 1762, 1652, 1600, 1512, 1493, 1450, 1408, 1246, 1179, 1061, 1030, 980, 906, 840, 757, 703 cm^{-1}; HRMS (ESI) *m/z* 382.1253 $[(M+H)^+$; calculated for $[C_{19}H_{18}NO_4F_3 + H]^+$: 382.1261].



*2,2,2-Trifluoroethyl-3-((3,5-dimethoxybenzyl)(phenyl)amino)-3-oxopropanoate (**12e**):* The compound was obtained as brown oil (4.0 g, 47% yield), R_f = 0.25 (10% EtOAc in hexane). ^1H NMR (400 MHz, $CDCl_3$) δ 7.34–7.30 (m, 3H), 7.04–7.01(m, 2H), 6.36–6.33 (m, 3H), 4.82 (s, 2H), 4.43 (q, *J* 8.5 Hz, 2H), 3.71 (s, 6H), 3.30 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 166.0, 160.8, 141.5, 138.9, 129.9, 128.7, 128.2, 124.1 (q, *J* 280 Hz), 106.6, 99.8, 60.8 (q, *J* 37.3 Hz), 55.3, 53.3, 41.1; IR (film) υ_{max} 3023, 2924, 2845, 1770, 1651, 1600, 1491, 1451, 1311, 1177, 1151, 1068, 1027, 980, 906, 840, 757, 703 cm^{-1}.

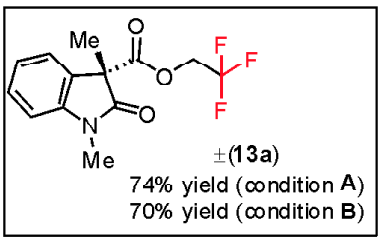


General procedure for the synthesis of 3-subsituted 2-oxindoles



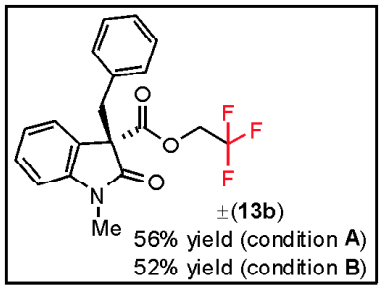
Representative experimental procedure for intramolecular-dehydrogenative-coupling (IDC) promoted by N-iodosuccinimide (NIS): In a flame-dried round-bottom flask, β-amidoester (1.0 mmol) was taken in DMSO (8 mL) at room temperature. To this reaction mixture, KO^{t}Bu (1.05 mmol) was added in one portion. After 5 min of stirring at the same temperature, 1.0 mmol of alkyl halide was added to the reaction mixture. After 5–10 min of stirring at the same temperature, KO^{t}Bu (1.2 mmol) was added in one portion followed by 1.2 mmol of NIS. Immediately afterwards, the reaction mixture was placed in oil bath maintaining temperature 110°C for 15–30 min. Upon completion of the reaction (judged by TLC analysis), the reaction mixture was cooled to room temperature and diluted with 10 mL of EtOAc and quenched with 10 mL saturated sodium thiosulfate solution. The organic layer was separated and successively washed with water (10 mL), and brine (10 mL). The organic extracts were dried over anhydrous $MgSO_4$ and concentrated under vacuum. The crude product was purified by flash chromatography (hexane and EtOAc as eluents) to afford 2-oxindoles derivatives.

*(±)-2,2,2-Trifluoroethyl-1,3-dimethyl-2-oxoindoline-3-carboxylateethyl (**13a**):* The compound was obtained as brown gel, R_f = 0.45 (20% EtOAc in hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (td, *J* 7.9, 0.9 Hz, 1H), 7.22 (d, *J* 7.6 Hz, 1H), 7.06 (t, *J* 7.22 Hz, 1H), 6.86 (d, *J* 7.9 Hz, 1H), 4.54–4.33 (m, 2H), 3.24 (s, 3H), 1.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 168.3, 143.6, 129.4, 129.3, 129.0, 126.6–118.3 (q, *J* 276 Hz), 123.1, 108.6, 60.8 (q, *J* 37.0 Hz), 54.8, 26.6, 19.9; IR (film) υ_{max} 3026, 2923, 1973, 1732, 1601, 1492, 1452, 1374, 1288, 1180, 1106, 1029, 977, 907, 840, 757 cm^{-1}; HRMS (ESI) *m/z* 288.0853 [(M+H)$^+$; calculated for [$C_{13}H_{13}NO_3F_3$ + H]$^+$: 288.0842].



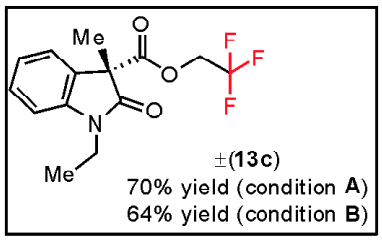
±(**13a**)
74% yield (condition **A**)
70% yield (condition **B**)

*(±)-2,2,2-Trifluoroethyl-3-benzyl-1-methyl-2-oxoindoline-3-carboxylate (**13b**):* The compound was obtained as colorless solid, R_f = 0.33 (10% EtOAc in hexane). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (dd, *J* 7.4, 0.7 Hz, 1H), 7.26 (dd, *J* 7.8, 1.3 Hz, 1H), 6.98 (m, 4H), 6.86 (m, 2H), 6.62 (d, *J* 7.8 Hz, 1H), 4.67–4.39 (m, 2H), 3.60 (m, 2H), 2.97 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 167.8, 144.0, 133.7, 130.0, 129.5, 127.6, 127.0, 126.3, 125.8–119.2 (q, *J* 220.7 Hz), 124.0, 122.7, 108.4, 61.0 (q, *J* 29.5 Hz), 60.6, 39.9, 26.2; IR (film) υ_{max} 3026, 2923, 1942, 1717, 1601, 1492, 1452, 1373, 1180, 1028, 965, 907, 757, 703 cm^{-1}; m.p. = 86–89°C; HRMS (ESI) *m/z* 364.1155 [(M+H)$^+$; calculated for [$C_{19}H_{16}NO_3F_3$ + H]$^+$: 364.1155].



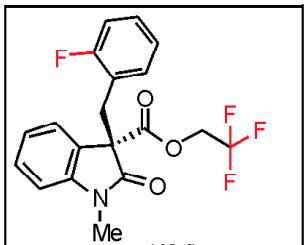
±(**13b**)
56% yield (condition **A**)
52% yield (condition **B**)

*(±)-2,2,2-Trifluoroethyl-1-ethyl-3-methyl-2-oxoindoline-3-carboxylate (**13c**):* The compound was obtained as yellow gel, R_f = 0.35 (20% EtOAc in hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (td, *J* 7.9, 0.9 Hz, 1H), 7.22 (d, *J* 7.4 Hz, 1H), 7.05 (t, *J* 7.8 Hz, 1H), 6.88 (d, *J* 7.9 Hz, 1H), 4.49–4.34 (m, 2H), 3.90–3.64 (m, 2H), 1.68 (s, 3H), 1.26 (t, *J* 7.2 Hz, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 173.8, 168.5, 142.7, 129.4, 129.3, 124.9–120.1 (q, *J* 275.8 Hz), 123.2, 122.9, 108.8, 61.1 (q, *J* 36.8 Hz), 54.8, 35.1, 19.6, 12.3; IR (film) υ_{max} 3020, 2924, 1755, 1716, 1602, 1490, 1451, 1376, 1358, 1286, 1180, 1107, 1027, 976, 907, 839, 756, 703 cm^{-1}; HRMS (ESI) *m/z* 324.0827 [(M+Na)$^+$; calculated for [$C_{14}H_{14}NO_3F_3$ + Na]$^+$: 324.0818].



±(**13c**)
70% yield (condition **A**)
64% yield (condition **B**)

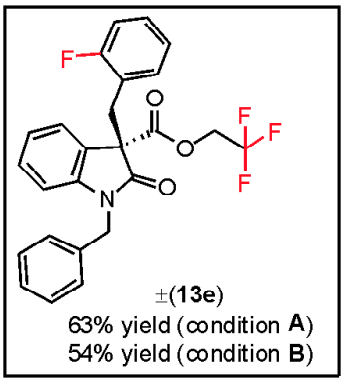
*(±)-2,2,2-Trifluoroethyl-3-(2-fluorobenzyl)-1-methyl-2-oxoindoline-3-carboxylate (**13d**):* The compound was obtained as yellow gel, pale yellowish gel, R_f = 0.35 (20% EtOAc in hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* 7.6 Hz, 1H), 7.23 (m, 1H), 7.02 (m, 3H), 6.86 (t, *J* 8.0 Hz, 1H), 6.72 (t, *J* 8.9 Hz, 1H), 6.60 (d, *J* 7.8 Hz, 1H), 4.62–4.34 (m, 2H), 3.82 (d, *J* 13.7, 1H), 3.46 (d, *J* 13.6 Hz, 1H), 3.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 167.7, 162.1–159.7 (d, *J* 245.5 Hz), 143.8, 131.5–131.4 (d, *J* 3.8 Hz), 129.5, 129.0–128.9 (d, *J* 8.3 Hz), 126.6 118.3 (q, *J* 275.9



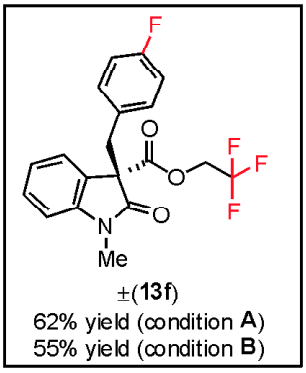
±(**13d**)
80% yield (condition **A**)
70% yield (condition **B**)

Hz), 125.8, 124.5–124.4 (d, *J* 2.8 Hz), 123.5–123.4 (d, *J* 3.6 Hz), 122.7, 121.5–121.3 (d, *J* 15.1 Hz), 115.1–114.9 (d, *J* 22.7 Hz), 108.1, 61.1 (q, *J* 36.8 Hz), 60.0, 31.8–31.7 (d, *J* 2.0 Hz), 26.4; IR (film) υ_{max} 3025, 2925, 1717, 1601, 1492, 1452, 1373, 1181, 1070, 1028, 907, 841, 757, 703 cm^{-1}; HRMS (ESI) *m/z* 382.1040 $[(M+H)^+$; calculated for $[C_{19}H_{15}NO_3F_4 + H]^+$: 382.1061.

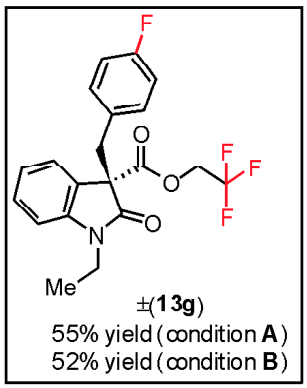
*(±)-2,2,2-Trifluoroethyl-1-benzyl-3-(2-fluorobenzyl)-2-oxoindoline-3-carboxylate (**13e**):* The compound was obtained as colorless solid, R_f = 0.44 (20% EtOAc in hexane). ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* 7.46 Hz, 1H), 7.19–7.16 (m, 3H), 7.11–7.06 (m, 3H), 7.02–6.98 (m, 1H), 6.92 (dd, *J* 7.4, 1.7 Hz, 2H), 6.87–6.83 (m, 1H), 6.77 (t, *J* 9.8 Hz, 1H), 6.44 (d, *J* 7.8 Hz, 1H), 4.79 (q, *J* 16.0 Hz, 2H), 4.60–4.42 (m, 2H), 3.88 (d, *J* 14.0 Hz, 1H), 3.60 (d, *J* 13.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 167.8, 162.2–159.8 (d, *J* 245.9 Hz), 143.1, 134.9, 132.0–131.9 (d, *J* 3.8 Hz), 129.5, 129.0–128.9 (d, *J* 8.2 Hz), 128.7, 127.5, 126.8, 126.6–118.4 (q, *J* 275.9 Hz), 125.8, 124.4–124.3 (d, *J* 2.9 Hz), 123.8–123.7 (d, *J* 3.6 Hz), 122.8, 121.5–121.3 (d, *J* 15.3 Hz), 115.3–115.0 (d, *J* 22.8 Hz), 109.4, 61.2 (q, *J* 36.8 Hz), 60.1, 43.8, 31.4; IR (film) υ_{max} 3026, 2923, 2846, 1755, 1732, 1652, 1602, 1488, 1452, 1365, 1281, 1179, 1104, 1075, 1029, 981, 907, 844, 754, 703 cm^{-1}; HRMS (ESI) *m/z* 458.1376 $[(M+H)^+$; calculated for $[C_{25}H_{19}NO_3F_4 + H]^+$: 458.1374; m.p. = 80–83°C.



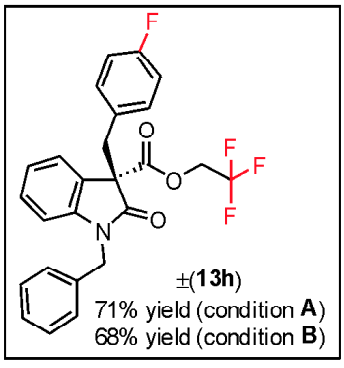
*(±)-2,2,2-Trifluoroethyl-3-(4-fluorobenzyl)-1-methyl-2-oxoindoline-3-carboxylate (**13f**):* The compound was obtained as brown gel, R_f = 0.30 (20% EtOAc in hexane). ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* 7.7 Hz, 1H), 7.23 (d, *J* 6.7 Hz, 1H), 7.07 (t, *J* 7.5 Hz, 1H), 6.76–6.80 (m, 2H), 6.68 (t, *J* 8.6 Hz, 2H), 6.60 (d, *J* 8.0 Hz, 1H), 4.36–4.62 (m, 2H), 3.56–3.42 (m, 2H), 2.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 167.7, 163.1–160.7 (d, *J* 244.0 Hz), 144.0, 131.6–131.5 (d, *J* 7.9 Hz), 129.6, 129.5–129.4 (d, *J* 3.2 Hz), 126.6–118.3 (q, *J* 275.8 Hz), 126.1, 123.8, 122.8, 114.6–114.4 (d, *J* 21.1 Hz), 108.5, 61.0 (q, *J* 36.8 Hz), 60.5, 38.9, 26.2; IR (film) υ_{max} 3025, 2919, 1717, 1601, 1493, 1451, 1374, 1180, 1070, 1028, 907, 840 cm^{-1}; HRMS (ESI) *m/z* 382.1032 $[(M+H)^+$; calculated for $[C_{19}H_{15}NO_3F_4 + H]^+$: 382.1061.



*(±)-2,2,2-Trifluoroethyl-1-ethyl-3-(4-fluorobenzyl)-2-oxoindoline-3-carboxylate (**13g**):* The compound was obtained as yellow gel, R_f = 0.38 (20% EtOAc in hexane). ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* 7.2 Hz, 1H), 7.24 (t, *J* 3.8 Hz, 1H), 7.07 (t, *J* 7.8 Hz, 1H), 6.78 (td, *J* 5.6, 1.9 Hz, 2H), 6.68 (t, *J* 8.7 Hz, 2H), 6.63 (d, *J* 7.8 Hz, 1H), 4.59–4.37 (m, 2H), 3.92–3.66 (m, 4H), 0.84 (t, *J* 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 167.8, 163.2–160.7 (d, *J* 243.9 Hz), 143.2, 131.7–131.6 (d, *J* 7.9 Hz), 129.6, 129.5–129.4 (d, *J* 3.3 Hz), 126.7–118.3 (q, *J* 276.0 Hz), 126.5, 123.9, 122.6, 114.6–114.4 (d, *J* 21.1 Hz), 108.7, 61.0 (q, *J* 36.7 Hz), 60.3 (d, *J* 1.3 Hz), 38.7, 34.7, 11.8; IR (film) υ_{max} 3026, 2922, 1716, 1601, 1492, 1451, 1373, 1287, 1180, 1071, 1028, 964, 907, 841, 756, 703 cm^{-1}; HRMS (ESI) *m/z* 396.1189 $[(M+H)^+$; calculated for $[C_{20}H_{17}NO_3F_4 + H]^+$: 396.1217.

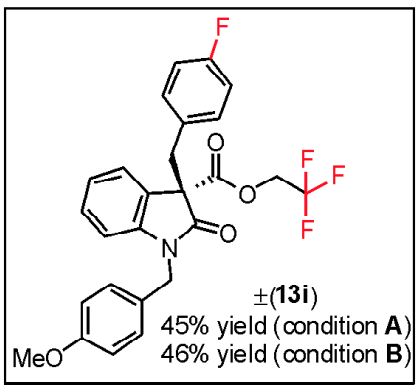


*(±)-2,2,2-Trifluoroethyl-1-benzyl-3-(4-fluorobenzyl)-2-oxoindoline-3-carboxylate (**13h**):* The compound was obtained as colorless solid, R_f = 0.45 (20% EtOAc in hexane). ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* 7.4 Hz, 1H), 7.21–7.11 (m, 4H), 7.06 (t, *J* 7.5 Hz, 1H), 6.84–6.81 (m, 2H), 6.73–6.68 (m, 4H), 6.44 (d, *J* 7.8 Hz, 1H), 4.71 (dd, *J* 47.1, 16.5 Hz, 2H), 4.60–4.42 (m, 2H), 3.60 (q, *J* 13.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 167.8, 163.3–160.9 (d, *J* 244 Hz), 143.4, 134.6, 131.9–131.8 (d, *J* 7.9 Hz), 129.7, 129.6–129.5 (d, *J* 3.2 Hz), 128.6, 127.5, 126.6–118.2 (q, *J* 275.8 Hz), 126.6,

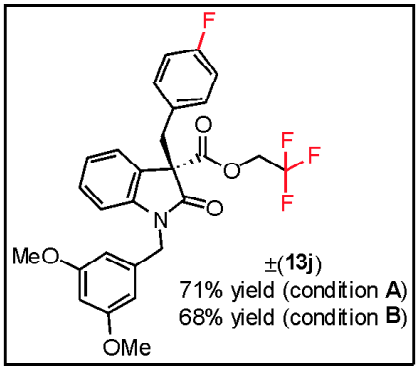


126.1, 123.7, 122.9, 115.0–114.8 (d, *J* 21.1 Hz), 109.9, 61.2 (q, *J* 36.8 Hz), 60.6–60.5 (d, *J* 1.1 Hz), 43.7, 38.4; IR (film) υ_{max} 3025, 2923, 2850, 1750, 1716, 1601, 1491, 1452, 1363, 1286, 1220, 1180, 1029, 981, 907, 840, 756, 703 cm^{-1}; HRMS (ESI) *m/z* 458.1397 $[(M+H)^+$; calculated for $[C_{18}H_{17}NO_3$ + $H]^+$: 458.1374; m.p. = 113–116°C.

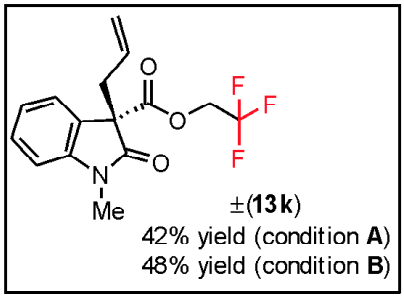
*(±)-2,2,2-Trifluoroethyl-3-(4-fluorobenzyl)-1-(4-methoxybenzyl)-2-oxoindoline-3-carboxylate (**13i**):* The compound was obtained as colorless gel, R_f = 0.42 (20% EtOAc in hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* 6.79 Hz, 1H), 7.14 (td, *J* 7.7, 1.1 Hz, 1H), 7.07–7.04 (m, 1H), 6.83–6.80 (m, 2H), 6.73–6.65 (m, 6H), 6.47 (d, *J* 7.7 Hz, 1H), 4.74 (d, *J* 15.7 Hz, 1H), 4.61–4.38 (m, 3H), 3.73 (s, 3H), 3.59 (q, *J* 13.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 167.8, 163.3–160.8 (d, *J* 243.8 Hz), 158.9, 143.4, 131.9–131.8 (d, *J* 8.0 Hz), 129.7, 129.6–129.5 (d, *J* 3.1 Hz), 127.9, 126.7–118.4 (q, *J* 276.0 Hz), 126.7, 126.1, 123.7, 122.8, 114.9–114.7 (d, *J* 21.0 Hz), 113.9, 109.9, 61.1 (q, *J* 36.8 Hz), 60.50–60.49 (d, *J* 1.1 Hz), 55.2, 43.2, 38.4; IR (film) υ_{max} 3025, 2926, 2845, 1746, 1716, 1601, 1491, 1451, 1362, 1286, 1180, 1072, 1029, 981, 906, 839, 756, 703 cm^{-1}; HRMS (ESI) *m/z* 488.1451 $[(M+H)^+$; calculated for $[C_{26}H_{21}NO_4F_4$ + $H]^+$: 488.1479.



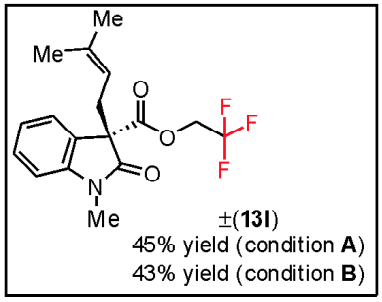
*(±)-2,2,2-Trifluoroethyl-1-(3,5-dimethoxybenzyl)-3-(4-fluorobenzyl)-2-oxoindoline-3-carboxylate (**13j**):* The compound was obtained as colorless gel, R_f = 0.34 (20% EtOAc in hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* 7.3 Hz, 1H), 7.2–7.1 (m, 1H), 7.06 (t, *J* 7.6 Hz, 1H), 6.82 (dd, *J* 8.5, 3.0 Hz, 2H), 6.68 (t, *J* 8.8 Hz, 2H), 6.53 (d, *J* 7.8 Hz, 1H), 6.28 (t, *J* 1.9 Hz, 1H), 6.09 (d, *J* 2.1 Hz, 2H), 4.73–4.42 (m, 4H), 3.69 (s, 6H), 3.65–3.53 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 167.8, 163.3–160.7 (d, *J* 262.9 Hz), 161.1, 143.4, 137.2, 131.6–131.5 (d, *J* 8.0 Hz), 129.7, 129.34–129.30 (d, *J* 3.3 Hz), 126.6–118.3 (q, *J* 276.0 Hz), 126.0, 123.8, 122.9, 114.9–114.7 (d, *J* 21.1 Hz), 109.8, 105.2, 98.7, 61.2 (q, *J* 36.7 Hz), 60.57–60.56 (brs), 55.2, 43.9, 38.4; IR (film) υ_{max} 3025, 2920, 2847, 1758, 1717, 1600, 1492, 1452, 1362, 1286, 1204, 1177, 1156, 1069, 1028, 977, 964, 907, 839, 757, 703 cm^{-1}; HRMS (ESI) *m/z* 518.1617 $[(M+H)^+$; calculated for $[C_{27}H_{23}NO_5F_4$ + $H]^+$: 518.1585.



*(±)-2,2,2-Trifluoroethyl-3-allyl-1-methyl-2-oxoindoline-3-carboxylate (**13k**):* The compound was obtained as brown gel, R_f = 0.31 (10% EtOAc in hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (td, *J* 7.7, 0.8 Hz, 1H), 7.24 (d, *J* 7.4 Hz, 1H), 7.06 (t, *J* 7.5 Hz, 1H), 6.84 (d, *J* 7.8 Hz, 1H), 5.41–5.34 (m, 1H), 5.60–4.95 (m, 2H), 4.56–4.33 (m, 2H), 3.21 (s, 3H), 3.02–2.91 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 167.5, 144.0, 130.4, 129.5, 126.6–118.4 (q, *J* 275.8 Hz), 126.5, 123.8, 123.0, 120.3, 108.5, 61.0 (q, *J* 36.7 Hz), 58.9, 38.2, 26.5; IR (film) υ_{max} 3025, 2923, 1750, 1600, 1492, 1451, 1180, 1071, 1028, 965, 907, 841, 757, 703 cm^{-1}; HRMS (ESI) *m/z* 314.0971 $[(M+H)^+$; calculated for $[C_{15}H_{14}NO_3F_4$ + $H]^+$: 314.0999.

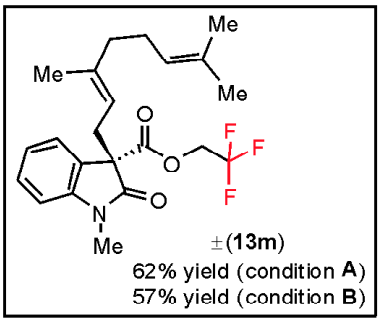


*(±)-2,2,2-Trifluoroethyl-1-methyl-3-(3-methylbut-2-en-1-yl)-2-oxoindoline-3-carboxylate (**13l**):* The compound was obtained as brown gel, R_f = 0.35 (10% EtOAc in hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (td, *J* 7.7, 0.9 Hz, 1H), 7.23 (d, *J* 7.0 Hz, 1H), 7.04 (t, *J* 7.5 Hz, 1H), 6.82 (d, *J* 7.8 Hz, 1H), 4.73 (td, *J* 7.4, 1.2 Hz, 1H), 4.56–4.33 (m, 2H), 3.20 (s, 3H), 2.92 (d, *J* 7.2 Hz, 2H), 1.51 (s, 3H), 1.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 167.8, 144.1, 136.9, 129.3, 127.0, 126.7–



118.4 (q, *J* 275.9 Hz), 123.8, 122.8, 115.8, 108.3, 60.9 (q, *J* 36.7 Hz), 59.0, 32.9, 26.5, 25.8, 18.0; IR (film) υ_{max} 3026, 2920, 1733, 1601, 1492, 1451, 1373, 1307, 1180, 1072, 1028, 976, 906, 840 cm^{-1}; HRMS (ESI) *m/z* 342.1292 $[(M+H)^+$; calculated for $[C_{17}H_{18}NO_3F_3 + H]^+$: 342.1312.

*(±)-(E)-2,2,2-Trifluoroethyl-3-(3,7-dimethylocta-2,6-dien-1-yl)-1-methyl-2-oxoindoline-3-carboxylate (**13m**):* The compound was obtained as brown gel, R_f = 0.45 (20% EtOAc in hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (td, *J* 7.7, 1.2 Hz, 1H), 7.24 (d, *J* 7.3 Hz, 1H), 7.04 (t, *J* 7.5 Hz, 1H), 6.81 (d, *J* 7.8 Hz, 1H), 4.88–4.87 (m, 1H), 4.73 (t, *J* 7.3 Hz, 1H), 4.55–4.35 (m, 2H), 3.20 (s, 3H), 2.94 (t, *J* 6.1 Hz, 2H), 1.79 (m, 4H), 1.60 (s, 3H), 1.49 (s, 3H), 1.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 167.9, 144.1, 140.7, 131.4, 129.3, 127.0, 126.7–118.4 (q, *J* 275.8 Hz), 123.9, 123.8, 122.8, 115.7, 108.3, 60.9 (q, *J* 36.7 Hz), 59.1, 39.7, 32.8, 26.7, 26.4, 25.6, 17.6, 16.4; IR (film) υ_{max} 3025, 2924, 1733, 1601, 1493, 1452, 1374, 1181, 1070, 1028, 907, 751, 703, cm^{-1}; HRMS (ESI) m/z 410.1944 $[(M+H)^+$; calculated for $[C_{21}H_{23}NO_3 + H]^+$: 410.1938.



Associated content

Copies of ^{1}H, ^{13}C NMR spectra, HRMS data for new compounds. The supporting information is available free of charge via the Internet at www.indianchemicalsociety.com.

Acknowledgements

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