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ARTICLE

Catalyst-Free and Selective Trifluoromethylative Cyclizations of Acryloanilides Using $PhICF_3Cl$

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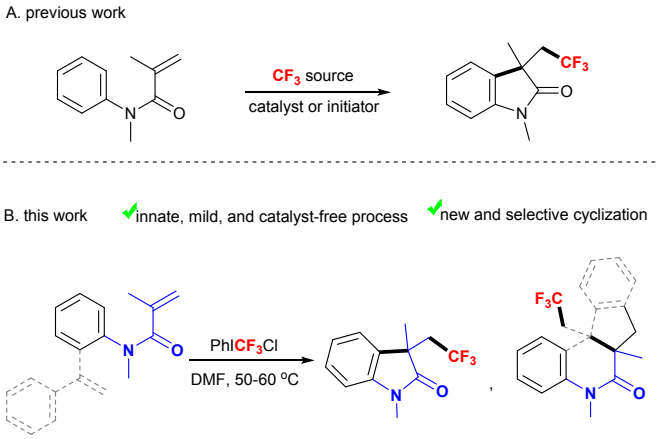
Trifluoromethylation-triggered cyclization of alkenes provides a useful route to CF_3-containing cyclic compounds. Current approaches to generate CF_3-based initiator from a CF_3 source require a catalyst or an activator. This work describes a catalyst-free protocol to innately produce electrophilic CF_3 species from $PhICF_3Cl$ for trifluoromethylative cyclizations of acryloanilides. A new domino biscyclization of dienes has been developed leading to trifluoroethylated tetrahydroindenoquinolinones in chemo- and stereo-selectivity.

Trifluoromethyl group is a privileged structure in pharmaceuticals, agrochemicals, and specialty materials.[1] Contrastingly, it is extremely absent in nature. The rich and profound impact aroused by the presence of CF_3 fragment have inspired persistent and intensive efforts to artificially synthesize CF_3-containing molecules.[2] In fact, the efficient introduction of CF_3 group into organic frameworks still challenges this field though a large number of catalytic trifluoromethylation reactions have been developed. In view of the practicability, mild and catalyst-free trifluoromethylation methods would be a synthetically enabling strategy that would dramatically simplify access to trifluoromethylated compounds.

Trifluoromethylation-triggered cyclization of alkenes[2d-g,3,4] is a very valuable transformation for accessing CF_3-containing cyclic compounds, which have potential use in developing new drug candidates and biological probes. Many kinds of trifluoromethylating reagents have been well utilized for such cyclizations,[3,4] among which trifluoromethylative cyclization of acryloanilides is an important representative (Scheme 1A). Togni's reagents[3] is the most widely used CF_3 source, which is generally reduced by a Cu catalyst or a photocatalyst to produce a CF_3 radical for the reaction.[2b,2f-g,3a-n] Comparatively, the ionic pathway has been seldom reported, while it has also been proposed to release an electrophilic CF_3 species by the activation of copper salt or nBu$_4$NI for the cyclizations of alkenes.[3o-r]



Scheme 1. Trifluoromethylation-triggered cyclization of acryloanilides.

In the field of fluorine chemistry, the extreme challenges in the preparation of unstable aryltrifluoromethyl λ^3 -iodanes ($ArICF_3X$) have hindered their applications as trifluoromethylating agents.[5a-d] Recently, we prepared $PhICF_3Cl$ by a direct ligand exchange reaction of $PhI(OCOCF_3)_2$, $TMSCF_3$, and NaCl for the first time[6a] since 1978 when such kinds of compounds were defined as fundamentally electrophilic perfluoroalkylating reagents.[5a] Compared with neutral and intramolecularly coordinated CF_3-hypervalent iodanes, which have been developed by Togni' group afterwards,[2b,5e-g] noncyclic $PhICF_3Cl$ has been proved to have an iodonium-like character, which results in an enhanced CF_3-transfer ability in a range of trifluoromethylation reactions.[6,7] Taking into consideration of unique electrophilicity of $PhICF_3Cl$, and of the important applications of electrophilic cyclizations in cyclofunctionalizations of alkenes,[8] we envisioned an innate trifluoromethylation-carbocyclization of alkenes by using $PhICF_3Cl$ as the electrophile (Scheme 1B). Herein, we report a set of catalyst-free trifluoromethylation-cyclizations, in which all tested acryloanilides are compatible with the catalyst-free conditions to furnish cyclic compounds bearing a trifluoroethyl group efficiently. It is noteworthy that a novel bicyclization

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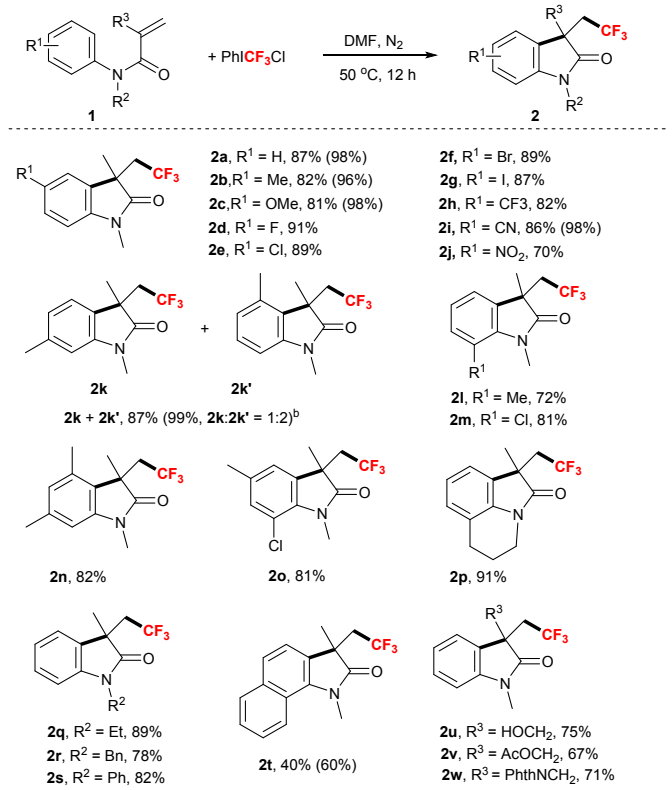
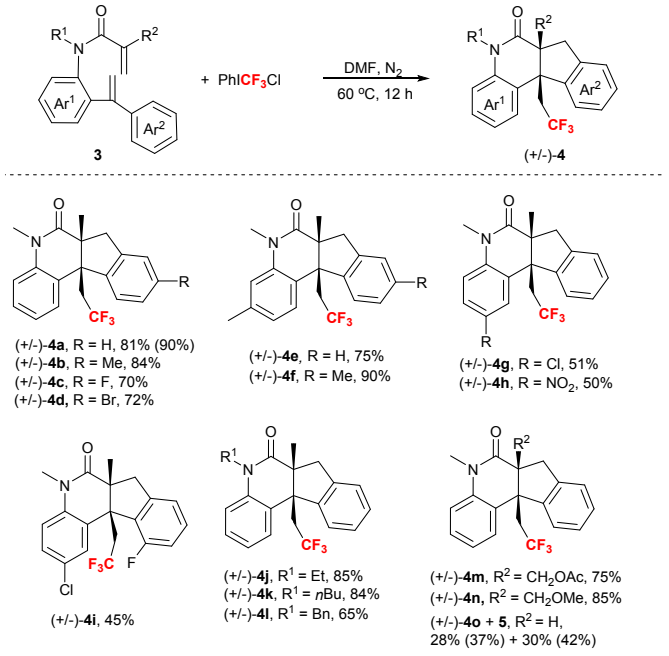
reaction has been found to afford trifluoroethylated hydroindenoquinolinone derivatives in high chemo- and stereo-selectivity when using diene substrates. Obviously, it is the use of powerful trifluoromethylating agent that allows efficient and mild trifluoromethylation-triggered cascades.



Scheme 2. Catalyst-free trifluoromethylation-acryloanilides. **1** (0.3 mmol), $PhICF_3Cl$ (0.45 mmol), DMF (3 mL). Isolated yields. Yields in brackets are ^{19}F NMR yields using $PhCF_3$ as an internal standard. [b]The ratio of **2k** to **2k'** was determined by ^{19}F NMR spectroscopy.

At first, we examined the electrophilic cyclization of *N*-methyl-*N*-phenylmethacrylamide (**1a**) using $PhICF_3Cl$ as the electrophile (For screening of reaction conditions, see SI). As presented in Scheme 2, the desired cyclization product **2a** was finally isolated in 87% yield using DMF as the solvent at 50 °C under N_2. Indeed, the process indicates a very facile route to CF_3-substituted oxindoles, which are important in natural products and biologically active compounds.[9] Thus, we documented the scope of acryloanilide substrates. It was found that all tested **1** bearing alkyl, alkoxy, halo, trifluoromethyl, cyano, and nitro at the different positions of the arene ring performed well in this intramelocularly catalyst-free trifluoromethylation-arylation (**2b**–**o**). Among them, **1k** afforded an isomeric mixture of **2k** and **2k'** as the products. By comparison, **1j** with a strong electron-withdrawing nitro substituent gave **2j** in a relatively lower yield. When **1p**–**s** with different *N*-substituent were tested, **2p**–**s** were also obtained in high yields. However, the reaction of acryloanilide with free NH did not give the desired product and the substrate was recovered in ~90% yield after 12 h. Additionally, we found that this cyclization could also tolerate other R^3 substituent, including phenyl, hydroxymethyl, acetoxymethyl, and phthalimidomethyl group. **2u**–**w** were obtained in relatively lower yields likely due to the steric hindrance of large R^3. By comparison, our method could not be applied to acryloanilide with no R^3 substituent.

As described above, a catalyst-free intramolecular aryltrifluoromethylation of acryloanilides has been developed for the first time by using $PhICF_3Cl$ as the CF_3 reagent. Encouraged by the easy achievements in trifluoromethylative cyclization process, we further tested diene substrates **3** with the aim of making comparison of the reactivity of two olefinic bonds toward the electrophilic activation of $PhICF_3Cl$. Thus, **3a** was first treated with $PhICF_3Cl$ in DMF at 60 °C (Scheme 3). Interestingly, the reaction worked well and a biscyclization product, tetrahydroindenoquinolin-6-one **4a**, which was resulted from the preferential activation of styrene olefin bond by $PhICF_3Cl$ at the beginning of the biscyclization, was isolated in 81% yield. By comparison, the reaction of **3a** with Togni II in DMF at 60 °C gave no any product after 12 h. Notably, **4a** was identified by the X-ray analysis as the *syn*-6a,11b-disusbtituted isomer (Figure 1).[10]



Scheme 3. Catalyst-free trifluoromethylation-biscyclizations of dienes. **3** (0.3 mmol), $PhICF_3Cl$ (0.45 mmol), DMF (3 mL). Isolated yields. Yields in brackets are ^{19}F NMR yields using $PhCF_3$ as an internal standard.

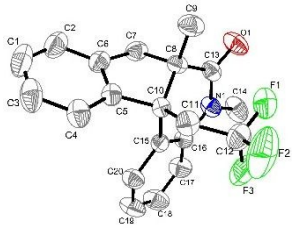
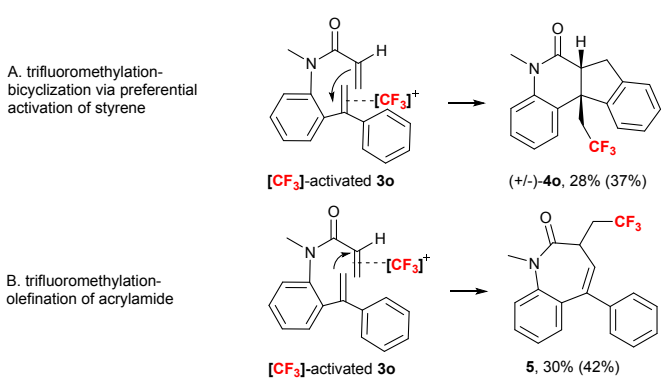


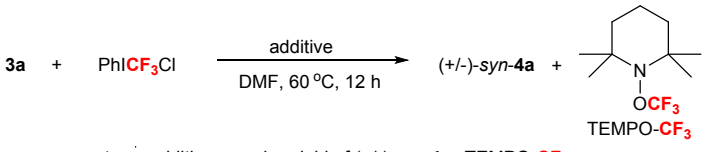
Figure 1. X-ray structure of (+/-)-*syn*-**4a**.

Evoked by this fascinating serendipity, we expanded the scope of such chemo- and stereo-selective domino cyclization for facile constructions of interesting CF_3-containing tetracyclic compounds.[11b] Thus, a series of *N*-(2-vinylphenyl)acrylamides **3** were synthesized toward the catalyst-free condition. As shown in Scheme 3, most tested reactions were complete in 12 h affording (+/-)-*syn*-**4a**–**n** in good yields with well control of both chemoselectivity and stereoselectivity. The electronic properties and steric effect of the substituents on the aromatic rings of **3** have effects on the transformations. **3** with different *N*-R^1 were suitable substrates to provide the corresponding (+/-)-*syn*-**4j**–**l** in comparably good results. It should be pointed out that the R^2 was not confined to the methyl group, and the acetoxymethyl and methoxymethyl group could also be tolerated to give (+/-)-*syn*-**4m** and (+/-)-*syn*-**4n** respectively. However, when amide **3** with phenyl as the R^2 substituent was treated with $PhICF_3Cl$, large amide substrate was recovered along with a small amount of unidentified mixture. Comparatively, when **3o** without R^2 substituent was tested, the reaction afforded two products in almost equal amounts. One was the desired cyclization product (+/-)-*syn*-**4o** (Scheme 4A) and the other was trifluoroethylated dihydrobenzoaze-2-pinone **5**, likely resulted from the preferential activation of the acrylamide moiety by $PhICF_3Cl$ (Scheme 4B). Finally, the gram-scale synthesis of (+/-)-*syn*-**4j** with 75% isolated yield under the optimal reaction conditions demonstrates the practicality of the transformations.



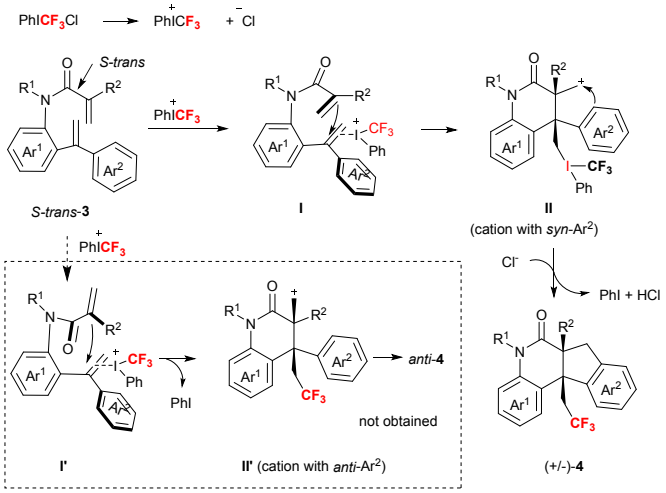
Scheme 4. Trifluoromethylative Cyclization of **3o.**

To elucidate the reaction mechanism, control experiments were performed (Scheme 5 and SI). The reactions of **1a**/**3a** and $PhICF_3Cl$ in the presence of 1.5 equivalents of BHT were conducted. By the analysis of ^{19}F NMR spectroscopies, **2a**/(+/-)-*syn*-**4a** could be obtained, in yields almost comparable to those obtained under the standard conditions. Comparatively, the addition of 1.5 equivalents of TEMPO into the reaction mixtures could not completely suppress the desired reaction and products **2a**/(+/-)-*syn*-**4a** was obtained in 41% and 57% yield, respectively. The corresponding TEMPO-CF_3 adduct could not be detected in this case. The decrease of the reaction yield may be due to the consumption of oxidative $PhICF_3Cl$ for the formation of oxoammonium salt and hydroxylamine from TEMPO.[12] Although the exact mechanism requires further investigation and a radical cation pathway (see SI) can't be ruled out at this time, based on current experimental results and reference,[13] we prefer an ionic process including the activation of the olefin bond by $PhICF_3Cl$ and the exo-cyclization *via* an attack of the aryl substituent (see SI).



entry	additive	equiv	yield of (+/-)-*syn*-**4a**	TEMPO-CF_3
1	--	--	90%	--
2	BHT	1.5	90%	--
3	TEMPO	1.5	57%	0

Scheme 5. Mechanism studies with radical scavenger. **3a** (0.2 mmol), $PhICF_3Cl$ (0.3 mmol), DMF (2 mL). ^{19}F NMR yields using $PhCF_3$ as an internal standard.



Scheme 6. Trifluoromethylative Rationale for the Observed *syn*/*anti* Stereoselectivity in Products **4**.

When dienes **3** were used, both the chemoselectivity in the initial activation of the olefin double bond and the stereoselectivity in biscyclization products could be observed. As described in Scheme 5,[14] $[PhICF_3]^+$ prefers to activate more electron-rich styrene olefin bond of *S-trans*-**3** and a following trap of the acryloyl substituent furnishes carbocation **II** or **II'**. It is found that the carbocation center in **II** happens to have a *syn*-Ar^2 group for easy trap along with the elimination of PhI. As a result, *syn*-disubstituted **4** are delivered as the main products. Comparatively, we did not isolate *anti*-**4** from the reaction mixture in all cases. Besides having a suitable *syn*-position between cation center and Ar^2 group in intermediate **II**, the other factor for the observed high *syn*/*anti* stereoselectivity in **4** is likely because better π-π stack of two olefinic bonds in intermediate **I** leads to its preferential formation.

In conclusion, we report herein a concise trifluoromethylative cyclization of a range of acryloanilides. The use of readily prepared $PhICF_3Cl$ as powerful trifluoromethylating agent enables a catalyst-free process for constructing trifluoroethylated cycles for the first time. Control experiments

support the suggested ionic mechanism. Significantly, the efficiency of this protocol was highlighted by the new biscyclization of dienes. Broad substrate scope, mild reaction conditions, and easy operation make the method well-suited for wide applications in organic synthesis and drug design. Further mechanistic study and synthetic applications of this catalyst-free process are currently ongoing in our laboratory.

Experimental

Typical procedures for catalyst-free intramolecular trifluoromethylation biscyclization of dienes (taking **3a** as an example): To a dried polytetrafluoroethene (PTFE) sealed pressure tube was added **3a** (83.2 mg, 0.3 mmol), $PhICF_3Cl$ (138.6 mg, 4.5 mmol) and anhydrous DMF (3.0 mL) in sequence under N_2. After the reaction mixture was stirred at 60 °C for 12 h, $PhCF_3$ was added as the internal standard and the NMR yield of **4a** was calculated from ^{19}F-NMR integrals. Then the mixture was washed with water and brine, extracted by CH_2Cl_2. The combined organic phase was dried over anhydrous $MgSO_4$ and concentrated under reduce pressure. Residues were purified by silica column chromatography (eluent: petroleum ether/EtOAc = 15/1 to 10/1, v/v) to give **4a** as a white solid. Characterization data for Supporting information.

Characterization data for new products:

(+/-)-*Syn*-5,6a-dimethyl-11b-(2,2,2-trifluoroethyl)-5,6a,7,11b-tetrahydro-6H-indeno[2,1-c]quinolin-6-one (4a).
83.9 mg, 81% yield. White solid. mp: 143-144 °C. **^{1}H-NMR** (600 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 7.8 Hz, 1H), 7.33 (d, *J* = 7.2 Hz, 1H), 7.19 - 7.24 (m, 3H), 7.04 (dd, *J* = 7.8 Hz, 1.2Hz, 1H), 6.99 (d, *J* = 9.0 Hz, 1H), 6.93 (t, *J* = 7.2 Hz, 1H), 3.45 (s, 3H), 3.19 (d, *J* = 15.0 Hz, 1H), 2.93 - 3.02 (m, 1H), 2.78 (d, *J* = 15.0 Hz, 1H), 2.66 - 2.77 (m, 1H), 1.35 (s, 3H). **^{13}C-NMR** (151 MHz, $CDCl_3$): δ = 172.2, 146.5, 140.8, 139.5, 129.3, 128.2, 127.5, 126.8, 126.2 (q, *J* = 276.5 Hz), 125.4, 124.6, 123.4, 123.1, 114.5, 52.7, 52.6 (q, *J* = 1.4 Hz), 44.4, 39.3 (q, *J* = 27.3 Hz), 30.1, 18.7. **^{19}F-NMR** (565 MHz, $CDCl_3$): δ = -60.8 (t, *J* = 10.7 Hz). HRMS (ESI): Calcd for $[C_{20}H_{18}F_3NO, M+Na]^+$: 368.1233, measured: 368.1241.

(+/-)-*Syn*-5,6a,9-trimethyl-11b-(2,2,2-trifluoroethyl)-5,6a,7,11b-tetrahydro-6H-indeno[2,1-c]quinolin-6-one (4b).
90.5 mg, 84% yield. Red solid. mp: 175-176 °C. **^{1}H-NMR** (600 MHz, $CDCl_3$): δ = 7.31 (d, *J* = 7.8 Hz, 1H), 7.20 (t, *J* = 7.8 Hz, 1H), 7.13 (d, *J* = 7.8 Hz, 1H), 7.05 (dd, *J* = 7.8 Hz, 1.2Hz, 1H), 7.02 (s, 1H), 6.97 (d, *J* = 8.4 Hz, 1H), 6.93 (t, *J* = 7.8 Hz, 1H), 3.44 (s, 3H), 3.05 (d, *J* = 15.0 Hz, 1H), 2.90 - 2.95 (m, 1H), 2.73 (d, *J* = 15.0 Hz, 1H), 2.63 - 2.71(m, 1H), 2.33 (s, 3H), 1.35 (s, 3H). **^{13}C-NMR** (151 MHz, $CDCl_3$): δ = 172.3, 143.7, 140.8, 139.4, 137.4, 129.3, 128.1, 127.4, 126.2 (q, *J* = 276.6 Hz), 126.2, 124.9, 123.1, 123.1, 114.5, 52.7, 52.2 (q, *J* = 1.5 Hz), 44.3, 39.4 (q, *J* = 27.3 Hz), 30.1, 21.2, 18.7. **^{19}F-NMR** (565 MHz, $CDCl_3$): δ = -60.9 (t, *J* = 10.7 Hz). HRMS (ESI): Calcd for $[C_{21}H_{20}F_3NO, M+Na]^+$: 382.1389, measured: 382.1399.

(+/-)-*Syn*-9-fluoro-5,6a-dimethyl-11b-(2,2,2-trifluoroethyl)-5,6a,7,11b-tetrahydro-6H-indeno[2,1-c] quinolin-6-one (4c).
76.3 mg, 70% yield. Yellow solid. mp: 152-153 °C. **^{1}H-NMR** (600 MHz, $CDCl_3$): δ = 7.37 (dd, *J* = 7.8 Hz, 4.8 Hz, 1H), 7.22 - 7.24 (m, 1H), 6.99 - 7.03 (m, 3H), 6.95 (t, *J* = 7.8 Hz, 1H), 6.91 (d, *J* = 7.8 Hz, 1H), 3.44 (s, 3H), 3.07 (d, *J* = 15.6 Hz, 1H), 2.88 - 2.96 (m, 1H), 2.76 (d, *J* = 15.6 Hz, 1H), 2.64 - 2.72 (m, 1H), 1.36 (s, 3H). **^{13}C-NMR** (151 MHz, $CDCl_3$): δ = 171.7, 162.4 (d, *J* = 246.4 Hz), 143.2 (d, *J* = 8.5 Hz), 142.2, 139.4, 129.2, 128.4, 126.0 (q, *J* = 278.4 Hz), 124.4, 124.3, 123.1, 114.7, 113.5 (d, *J* = 22.7 Hz), 113.0 (d, *J* = 22.8 Hz), 53.0, 52.0 (q, *J* = 1.4 Hz), 44.3, 39.4 (q, *J* = 27.6 Hz), 30.2, 18.7. **^{19}F-NMR** (470 MHz, $CDCl_3$): δ = -60.9 (t, *J* = 10.7 Hz, 3F), -114.8 - -114.7 (m, 1F). HRMS (ESI): Calcd for $[C_{20}H_{17}F_4NO, M+Na]^+$: 386.1138, measured: 386.1145.

(+/-)-*Syn*-9-bromo-5,6a-dimethyl-11b-(2,2,2-trifluoroethyl)-5,6a,7,11b-tetrahydro-6H-indeno[2,1-c] quinolin-6-one (4d).
91.4 mg, 72% yield. White solid. mp: 112-113 °C. **^{1}H-NMR** (600 MHz, $CDCl_3$): δ = 7.47 (d, *J* = 8.4 Hz, 1H), 7.35 (s, 1H), 7.31 (d, *J* = 7.8 Hz, 1H), 7.23 (t, *J* = 7.8 Hz, 1H), 6.99 (t, *J* = 8.4 Hz, 2H), 6.94 (t, *J* = 7.8 Hz, 1H), 3.44 (s, 3H), 3.07 (d, *J* = 15.0 Hz, 1H), 2.88 - 2.97 (m, 1H), 2.76 (d, *J* = 15.6 Hz, 1H), 2.64 - 2.71 (m, 1H), 1.35 (s, 3H). **^{13}C-NMR** (151 MHz, $CDCl_3$): δ = 171.5, 145.7, 143.2, 139.4, 129.9, 129.1, 128.7, 128.5, 125.9 (q, J = 278.4 Hz), 124.8, 123.9, 123.2, 121.4, 114.7, 52.8, 52.4 (q, J = 1.4 Hz), 44.0, 39.1 (q, J = 27.6 Hz), 30.2, 18.6. **^{19}F-NMR** (565 MHz, $CDCl_3$): δ = -60.8 (t, J= 10.7 Hz). HRMS (ESI): Calcd for $[C_{20}H_{17}BrF_3NO, M+Na]^+$: 446.0338, measured: 446.0336.

(+/-)-*Syn*-3,5,6a-trimethyl-11b-(2,2,2-trifluoroethyl)-5,6a,7,11b-tetrahydro-6H-indeno[2,1-c]quinolin-6-one (4e).
80.8 mg, 75% yield. White solid. mp: 192-193 °C. **^{1}H-NMR** (600 MHz, $CDCl_3$): δ = 7.41 (d, *J* = 7.8 Hz, 1H), 7.32 (t, *J* = 7.2 Hz, 1H), 7.21 (td, *J* = 7.2 Hz, J = 0.6 Hz, 1H), 7.18 (d, *J* = 7.2 Hz, 1H), 6.90 (d, *J* = 7.8 Hz, 1H), 6.79 (s, 1H), 6.74 (d, *J* = 7.8 Hz, 1H), 3.44 (s, 3H), 3.07 (d, *J* = 15.6 Hz, 1H), 2.91 - 2.99 (m, 1H), 2.77 (d, *J* = 15.0 Hz, 1H), 2.64 - 2.71 (m, 1H), 2.30 (s, 3H), 1.34 (s, 3H). **^{13}C-NMR** (151 MHz, $CDCl_3$): δ = 172.4, 146.7, 140.8, 139.3, 138.1, 129.2, 127.4, 126.7, 126.2 (q, *J* = 278.4 Hz), 125.3, 123.9, 123.3, 121.6, 115.3, 52.7, 52.3 (q, *J* = 1.7 Hz), 44.4, 39.2 (q, *J* = 27.5 Hz), 30.1, 21.4, 18.7. **^{19}F-NMR** (565 MHz, $CDCl_3$): δ = -60.8 (t, *J* = 10.7 Hz). HRMS (ESI): Calcd for $[C_{21}H_{20}F_3NO, M+Na]^+$: 382.1389, measured: 382.1402.

(+/-)-*Syn*-3,5,6a,9-tetramethyl-11b-(2,2,2-trifluoroethyl)-5,6a,7,11b-tetrahydro-6H-indeno[2,1-c] quinolin-6-one (4f).
100.6 mg, 90% yield. White solid. mp: 173-174 ºC. **^{1}H-NMR** (600 MHz, $CDCl_3$): δ = 7.29 (d, *J* = 7.8 Hz, 1H), 7.11 (d, *J* = 7.2 Hz, 1H), 7.00 (s, 1H), 6.90 (d, *J* = 8.4 Hz, 1H), 6.78 (s, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 3.43 (s, 3H), 3.03 (d, *J* = 15.0 Hz, 1H), 2.88 - 2.96 (m, 1H), 2.71 (d, *J* = 15.0 Hz, 1H), 2.61 - 2.69 (m, 1H), 2.32 (s, 3H), 2.30 (s, 3H), 1.33 (s, 3H). **^{13}C-NMR** (151 MHz, $CDCl_3$): δ = 172.5, 143.9, 140.8, 139.2, 138.0, 137.3, 129.1, 127.3, 126.2 (q, *J* = 276.6 Hz), 126.1, 123.9, 123.0, 122.1, 115.2, 52.7, 51.9 (q, *J* = 1.4 Hz), 44.4, 39.3 (q, *J* = 27.6 Hz), 30.1, 21.4, 21.2, 18.7. **^{19}F-NMR** (565 MHz, $CDCl_3$): δ = -60.8 (t, *J* = 10.7 Hz). HRMS (ESI): Calcd for $[C_{22}H_{22}F_3NO, M+Na]^+$: 396.1546, measured: 396.1556.

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(+/-)-*Syn*-2-chloro-5,6a-dimethyl-11b-(2,2,2-trifluoroethyl)-5, 6a,7, 11b-tetrahydro-6H-indeno[2,1-c] quinolin-6-one (4g).
58.0 mg, 51% yield. White solid. mp: 235-236 °C. **^{1}H-NMR** (600 MHz, $CDCl_3$): δ = 7.42 (d, *J* = 7.2 Hz, 1H), 7.36 (t, *J* = 7.2 Hz, 1H), 7.26 (t, *J* = 7.2 Hz, 1H), 7.22 (d, *J* = 7.8 Hz, 1H), 7.17 (dd, *J* = 9.0 Hz, 2.4Hz, 1H), 6.98 (d, *J* = 1.8 Hz, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 3.42 (s, 3H), 3.07 (d, *J* = 15.0 Hz, 1H), 2.92 - 3.00 (m, 1H), 2.79 (d, *J* = 15.0 Hz, 1H), 2.66 - 2.73 (m, 1H), 1.34 (s, 3H). **^{13}C-NMR** (151 MHz, $CDCl_3$): δ = 171.9, 145.8, 140.6, 138.3, 129.2, 128.3, 128.2, 127.9, 127.2, 126.6, 126.0 (q, *J* = 278.4 Hz), 125.5, 123.3, 115.9, 52.6, 52.5 (q, *J* = 1.5 Hz), 44.3, 39.2 (q, *J* = 27.4 Hz), 30.3, 18.7. **^{19}F-NMR** (565 MHz, $CDCl_3$): δ = -60.9 (t, *J* = 10.7 Hz). HRMS (ESI): Calcd for $[C_{20}H_{17}ClF_3NO, M+Na]^+$: 402.0842, measured: 402.0855.

(+/-)-*Syn*-5,6a-dimethyl-2-nitro-11b-(2,2,2-trifluoroethyl)-5,6a, 7, 11b-tetrahydro-6H-indeno[2,1-c] quinolin-6-one (4h).
58.8 mg, 50% yield. Yellow solid. mp 152-153 °C. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 8.11 (dd, *J* = 8.8 Hz, 2.4 Hz, 1H), 7.95 (d, *J* = 2.4 Hz, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.23 - 7.31 (m, 3H), 7.09 (d, *J* = 9.2 Hz, 1H), 3.50 (s, 3H), 2.97 - 3.09 (m, 2H), 2.99 - 3.03 (m, 1H), 2.85 (d, *J* = 15.6 Hz, 1H), 2.70 - 2.82 (m, 1H), 1.39 (s, 3H). **^{13}C-NMR** (151 MHz, $CDCl_3$): δ = 172.2, 145.1, 144.8, 142.9, 140.2, 128.3, 127.7, 126.1, 125.9 (q, *J* = 278.3 Hz), 125.6, 125.3, 124.3, 123.3, 114.8, 52.5 (q, *J* = 1.5 Hz), 52.5, 44.6, 39.3 (q, *J* = 27.8 Hz), 30.6, 18.7. **^{19}F-NMR** (470 MHz, $CDCl_3$): δ = -60.9 (t, *J* = 10.3 Hz). HRMS (ESI): Calcd for $[C_{20}H_{17}F_3N_2O_3, M+Na]^+$: 415.1164, measured: 415.1173.

(+/-)-*Syn*-3-chloro-11-fluoro-5,6a-dimethyl-11b-(2,2,2-tri fluoroethyl)-5,6a,7,11b-tetrahydro-6H-indeno[2,1-c]quinolin-6-one (4i).
53.6 mg, 45% yield. White solid. mp 142-143 °C. **^{1}H-NMR** (600 MHz, $CDCl_3$): δ = 7.19 - 7.25 (m, 3H), 7.03 - 7.06 (m, 1H), 7.01 (d, *J* = 1.2 Hz, 1H), 6.92 (d, *J* = 9.0 Hz, 1H), 3.49 - 3.57 (m, 1H), 3.41 (s, 3H), 3.08 (d, *J* = 15.6 Hz, 1H), 2,79 - 2.87 (m, 2H), 1.40 (s, 3H). **^{13}C-NMR** (151 MHz, $CDCl_3$): δ = 170.2, 159.0 (d, *J* = 246,0 Hz), 142.9 (d, *J* = 5.2 Hz), 136.8, 128.9 (d, *J* = 8.2 Hz), 128.0 (d, *J* = 3.8 Hz), 127.7, 127.6 (q, *J* = 277.8 Hz), 127.5, 125.9 (d, *J* = 1.5 Hz), 120.4 (d, *J* = 3.0 Hz), 114.9, 114.4, 114.2, 53.4, 51.5, 44.2, 37.6 (q, *J* = 19.9 Hz), 29.3, 17.9. **^{19}F-NMR** (565 MHz, $CDCl_3$): δ = -61.0 (t, *J* = 10.7 Hz, 3F), -119.5 (dd, *J* = 11.3 Hz, *J* = 4.5 Hz, 1F). HRMS (ESI): Calcd for $[C_{20}H_{16}ClF_4NO, M+Na]^+$: 420.0749, measured: 420.0749.

(+/-)-*Syn*-5-ethyl-6a-methyl-11b-(2,2,2-trifluoroethyl)-5,6a,7, 11b-tetrahydro-6H-indeno[2,1-c]-quinolin-6-one (4j).
100.0 mg, 85% yield. White solid. mp: 125-126 °C. Large scale test gave the product **4j** (1.0635 g , 75%). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 7.8 Hz, 1H), 7.33 (t, *J* = 7.2 Hz, 1H), 7.19 - 7.23 (m, 3H), 7.06 (d, *J* = 7.8 Hz, 1H), 7.01 (d, *J* = 8.4 Hz, 1H), 6.91 (d, *J* = 7.2 Hz, 1H), 4.15 - 4.20 (m, 1H), 4.00 - 4.06 (m, 1H), 3.10 (d, *J* = 15.0 Hz, 1H), 2.93 - 3.01 (m, 1H), 2.79 (d, *J* = 15.6 Hz, 1H), 2.65 - 2.72 (m, 1H), 1.34 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H). **^{13}C-NMR** (151 MHz, $CDCl_3$): δ = 171.7, 146.7, 140.8, 138.1, 129.7, 128.2, 127.5, 126.8, 126.2 (q, *J* = 276.6 Hz), 125.3, 124.7, 123.4, 122.9, 114.4, 52.6 (q, *J* = 1.1 Hz), 52.5, 44.7, 39.3 (q, *J* = 27.3 Hz), 37.2, 18.6, 12.1. **^{19}F-NMR** (565 MHz, $CDCl_3$): δ = -60.6 (t, *J* = 10.7 Hz). HRMS (ESI): Calcd for $[C_{21}H_{20}F_3NO, M+Na]^+$: 382.1389, measured: 382.1392.

(+/-)-*Syn*-5-butyl-6a-methyl-11b-(2,2,2-trifluoroethyl)-5,6a,7, 11b-tetrahydro-6H-indeno[2,1-c]-quinol-in-6-one (4k).
97.6 mg, 84% yield. White solid. mp: 113-114 °C. **^{1}H-NMR** (600 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 7.8 Hz, 1H), 7.32 (t, *J* = 7.2 Hz, 1H), 7.18 - 7.23 (m, 3H), 7.06 (d, *J* = 7.8 Hz, 1H), 6.98 (d, *J* = 8.4 Hz, 1H), 6.91 (d, *J* = 7.8 Hz, 1H), 3.95 - 4.04 (m, 2H), 3.11 (d, *J* = 15.0 Hz, 1H), 2.94 - 3.02 (m, 1H), 2.79 (d, *J* = 15.6 Hz, 1H), 2.65 - 2.72 (m, 1H), 1.67 - 1.73 (m, 1H), 1.57 - 1.63 (m, 1H), 1.42 - 1.48 (m, 2H), 1.34 (s, 3H), 1.00 (t, *J* = 7.2 Hz, 3H). **^{13}C-NMR** (151 MHz, $CDCl_3$): δ = 171.9, 146.7, 140.9, 138.5, 129.7, 128.2, 127.5, 126.8, 126.2 (q, *J* = 276.6 Hz), 125.3, 124.6, 123.4, 122.8, 114.5, 52.7 (q, *J* = 1.1 Hz), 52.5, 44.7, 42.5, 39.3 (q, *J* = 27.2 Hz), 28.9, 20.4, 18.6, 13.9. **^{19}F-NMR** (565 MHz, $CDCl_3$): δ = -60.6 (t, *J* = 10.7 Hz). HRMS (ESI): Calcd for $[C_{23}H_{24}F_3NO, M+Na]^+$: 410.1702, measured: 410.1707.

(+/-)-*Syn*-5-benzyl-6a-methyl-11b-(2,2,2-trifluoroethyl)-5,6a,7, 11b-tetrahydro-6H-indeno[2,1-c]-quinol-in-6-one (4l).
82.1 mg, 65% yield. White solid. mp: 137-138 °C. **^{1}H-NMR** (600 MHz, $CDCl_3$): δ = 7.45 (d, *J* = 7.8 Hz, 1H), 7.34 (t, *J* = 7.8 Hz, 3H), 7.25 - 7.27 (m, 3H), 7.23 - 7.24 (m, 2H), 7.04 - 7.07 (m, 2H), 6.90 (t, *J* = 7.8 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 5.75 (d, *J* = 16.2 Hz, 1H), 4.69 (d, *J* = 16.2 Hz, 1H), 3.29 (d, *J* = 15.0 Hz, 1H), 2.99 - 3.07 (m, 1H), 2.93 (d, *J* = 15.0 Hz, 1H), 2.71 - 2.78 (m, 1H), 1.40 (s, 3H). **^{13}C-NMR** (151 MHz, $CDCl_3$): δ = 172.5, 146.6, 140.6, 139.0, 137.4, 129.4, 128.8 (2C), 128.2 (2C), 127.6, 127.1, 126.9, 126.2, 126.2 (q, *J* = 276.6 Hz), 125.4, 124.4, 123.4, 123.2, 115.4, 52.8, 47.3, 44.8 (2C), 39.3 (q, *J* = 27.5 Hz), 18.6. **^{19}F-NMR** (565 MHz, $CDCl_3$): δ = -60.5 (t, *J* = 10.7 Hz). HRMS (ESI): Calcd for $[C_{26}H_{22}F_3NO, M+Na]^+$: 444.1546, measured: 444.1554.

(+/-)-*Syn*-(5-methyl-6-oxo-11b-(2,2,2-trifluoroethyl)-5,6,7,11b-tetrahydro-6aH-indeno[2,1-c]-quinolin-6a-yl)methyl acetate (4m).
90.7 mg, 75% yield. White solid. mp: 146-147 °C. **^{1}H-NMR** (600 MHz, $CDCl_3$): δ = 7.41 (d, *J* = 7.8 Hz, 1H), 7.32 (t, *J* = 7.8 Hz, 1H), 7.20 - 7.25 (m, 2H), 7.16 (d, *J* = 7.2 Hz, 1H), 7.08 (d, *J* = 7.8 Hz, 1H), 7.01 (d, *J* = 8.4 Hz, 1H), 6.97 (d, *J* = 7.2 Hz, 1H), 4.69 (d, *J* = 12.0 Hz, 1H), 4.45 (d, *J* = 12.0 Hz, 1H), 3.44 (s, 3H), 3.03 - 3.14 (m, 3H), 2.88 - 2.95 (m, 1H), 1.70 (s, 3H). **^{13}C-NMR** (151 MHz, $CDCl_3$): δ = 170.4, 169.5, 146.3, 139.8, 138.8, 129.1, 128.4, 127.8, 127.0, 126.1 (q, *J* = 276.5 Hz), 124.8, 124.4, 123.4, 122.8, 114.7, 64.7, 55.9, 52.0 (q, *J* = 5.4 Hz), 40.4, 39.7 (q, *J* = 27.8 Hz), 30.0, 20.3. **^{19}F-NMR** (565 MHz, $CDCl_3$): δ = -59.8 (t, J= 10.2 Hz). HRMS (ESI): Calcd for $[C_{22}H_{20}F_3NO_3, M+Na]^+$: 426.1287, measured: 426.1296.

(+/-)-*Syn*-6a-(methoxymethyl)-5-methyl-11b-(2,2,2-trifluoro ethyl)-5,6a,7,11b-tetrahydro-6H-indeno[2,1-c]-quinolin-6-one (4n).
95.6 mg, 85% yield. White solid. mp: 181-182 °C. **^{1}H-NMR** (600 MHz, $CDCl_3$): δ = 7.34 (d, *J* = 7.8 Hz, 1H), 7.23 (t, *J* = 7.8 Hz, 1H),

7.12 - 7.15 (m, 2H), 7.08 (d, *J* = 7.8 Hz, 1H), 7.01 (d, *J* = 7.8 Hz, 1H), 6.91 (d, *J* = 8.4 Hz, 1H), 6.87 (t, *J* = 7.2 Hz, 1H), 3.74 (d, *J* = 10.2 Hz, 1H), 3.58 (d, *J* = 9.6 Hz, 1H), 3.36 (s, 3H), 3.17 (s, 3H), 2.88 - 2.98 (m, 4H). **^{13}C-NMR** (151 MHz, $CDCl_3$): δ = 169.5, 145.5, 139.4, 137.9, 128.2, 127.1, 126.5, 125.7, 125.3 (q, *J* = 278.3 Hz), 123.8, 123.6, 122.0, 122.0, 113.5, 72.8, 58.3, 55.7, 51.1, 39.2, 38.5 (q, *J* = 27.9 Hz), 29.0. **^{19}F-NMR** (565 MHz, $CDCl_3$): δ = -59.6 (t, *J* = 11.3 Hz). HRMS (ESI): Calcd for $[C_{21}H_{20}F_3NO_2$, M+Na] $^+$: 398.1338, measured: 398,1349.

(+/-)-*Syn*-5-Methyl-11b-(2,2,2-trifluoroethyl)-5,6a,7,11b-tetrahydro-6H-indeno[2,1-c]-quinolin-6-one (4o).

26.1 mg, 28% yield. Red solid. mp: 167-168 °C. **^{1}H-NMR** (600 MHz, $CDCl_3$): δ = 7.49 (d, *J* = 7.8 Hz, 1H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.25 (d, *J* = 9.6 Hz, 3H), 7.17 (d, *J* = 7.8 Hz, 1H), 7.01 (d, *J* = 8.4 Hz, 1H), 6.98 (t, *J* = 7.8 Hz, 1H), 3.51 (dd, *J* = 15.6 Hz, 7.8 Hz, 1H), 3.44 (s, 3H), 3.33 (q, *J* = 7.8 Hz, 1H), 2.95 - 3.03 (m, 1H), 2.88 - 2.92 (m, 1H), 2.61 - 2.69 (m, 1H). **^{13}C-NMR** (151 MHz, $CDCl_3$): δ = 169.6, 146.1, 140.7, 139.2, 128.7, 128.4, 127.8, 127.0, 125.8 (q, *J* = 277.1 Hz), 124.9, 124.6, 123.7, 123.4, 114.9, 51.6, 49.0 (q, *J* = 1.5 Hz), 43.5 (q, *J* = 27.0 Hz), 35.8, 29.6. **^{19}F-NMR** (565 MHz, $CDCl_3$): δ = -60.8 (t, *J* = 10.7 Hz). HRMS (ESI): Calcd for $[C_{19}H_{16}F_3NO$, M+H]$^+$: 332.1269, measured: 332.1278.

1-Methyl-5-phenyl-3-(2,2,2-trifluoroethyl)-1,3-dihydro-2H-benzo[b]azepin-2-one (5).

29.8 mg, 30% yield. Red oil. **^{1}H-NMR** (600 MHz, $CDCl_3$): δ = 7.41 - 7.44 (m, 1H), 7.38 (dd, *J* = 8.4 Hz, 1.2 Hz, 1H), 7.33 - 7.36 (m, 3H), 7.26 - 7.27 (m, 2H), 7.23 (dd, *J* = 8.4 Hz, 1.8 Hz, 1H), 7.15 - 7.17 (m, 1H), 5,95 (d, *J* = 7.2 Hz, 1H), 3.46 (s, 3H), 2.96 - 3.05 (m, 1H), 2.91 - 2.94 (m, 1H), 2.66 - 2.76 (m, 1H). **^{13}C-NMR** (151 MHz, $CDCl_3$): δ = 170.5, 142.3, 140.7, 140.0, 132.6, 130.4, 129.0, 128.7 (2C), 128.4 (2C), 128.1, 128.1, 126.9 (q, *J* = 275.0 Hz), 124.7, 122.6, 38.5 (q, *J* = 2.6 Hz), 36.8, 34.1 (q, *J* = 28.5 Hz). **^{19}F-NMR** (565 MHz, $CDCl_3$): δ = -64.2 (t, *J* = 10.7 Hz). HRMS (ESI): Calcd for $[C_{19}H_{16}F_3NO$, M+Na]$^+$: 354.1076, measured: 354.1072.

Conflicts of interest

There are no conflicts to declare.

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14 The bis-cyclization of *S-cis*-**3** also furnished *syn*-**4** as main products. For details, see the Supporting Information.

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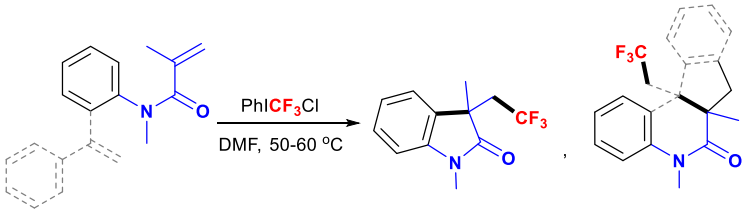

✔innate, mild, and catalyst-free process ✔new and selective cyclization