Copper-Catalyzed Annulation–Cyanotrifluoromethylation of 1,6-Enynes Toward 1-Indanones via a Radical Process

Tian-Shu Zhang¹, Wen-Juan Hao², Pei-Jun Cai¹*, Guigen Li³,⁴, Shu-Jiang Tu² and Bo Jiang²*

¹ School of Chemical Engineering & Technology, China University of Mining and Technology, Xuzhou, China, ² Jiangsu Key Laboratory of Green Synthetic Chemistry for Functional Materials, School of Chemistry & Materials Science, Jiangsu Normal University, Xuzhou, China, ³ Collaborative Innovation Center of Chemistry for Life Sciences, Institute of Chemistry and BioMedical Sciences, Nanjing University, Nanjing, China, ⁴ Department of Chemistry and Biochemistry, Texas Tech University, Lubbock, TX, United States

A new Cu(II)-catalyzed annulation–cyanotrifluoromethylation of 1,6-enynes with Togni’s reagent and trimethylsilyl cyanide (TMSCN) has been established, enabling the direct construction of trifluoromethylated 1-indanones with an all-carbon quaternary center in good yields. This reaction was performed by using low-cost Cu(OTf)₂ as the catalyst and Togni’s reagent as both the radical initiator and a CF₃ source, providing an efficient protocol for building up an 1-indane framework with wide functional group compatibility. The reaction mechanism was proposed through a radical triggered addition/5-exo-dig cyclization/oxidation/nucleophilic cascade.

Keywords: Cu(II) catalysis, annulation–difunctionalization, cyanotrifluoromethylation, 1,6-enynes, 1-indanones

INTRODUCTION

Trifluoromethylation of organic molecular skeletons has attracted considerable attention in pharmaceutical chemistry, agrochemicals, and functional materials, owing to the fact that incorporation of the trifluoromethyl group into organic molecules can modulate their abilities including lipophilicity, bioavailability, and metabolic stability (Umemoto, 1996; Müller et al., 2007; Hagmann, 2008; Studer, 2012; Yang et al., 2015). Therefore, many efforts have been done in the past few decades, which mainly depended on transition-metal-catalyzed trifluoromethylation reactions. Such reactions enable direct construction of the C–CF₃ bond in an atom-economic manner and provide efficient and practical methods for the collection of trifluoromethyl-containing compounds, such as catalytic trifluoromethylation of alkane (Pan et al., 2011; Fu et al., 2012; Kuninobu et al., 2015; Wang et al., 2015; Xiao et al., 2019), alkenes (Chu and Qing, 2012; Shimizu et al., 2012; Zhu and Buchwald, 2013; Lin et al., 2016; He et al., 2018), and alkyynes (Ge et al., 2014; Iqbal et al., 2014; Tomita et al., 2015; Wu et al., 2017; Huang et al., 2018). Among them, a vast majority of reports focused on the difunctionalization of alkenes or enynes (He et al., 2014a,b), such as hydrotrifluoromethylation (Wilger et al., 2013; Wu et al., 2013), carbotrifluoromethylation (Chen et al., 2013; Egami et al., 2013; Liu et al., 2013), and oxytrifluoromethylation (Egami et al., 2012; Janson et al., 2012; Li and Studer, 2012; Zhu and Buchwald, 2012) for their high utilization by incorporating trifluoromethyl groups into target molecules across the unsaturated π system. On the other hand, 1-indanones are privileged structural motifs commonly present...
A new Cu(II)-catalyzed annulation-cyanotrifluoromethylation of 1,6-enynes with Togni’s reagent and TMSCN has been established, enabling the direct construction of trifluoromethylated 1-indanones with an all-carbon quaternary center in good yields. This reaction was performed by using low-cost Cu(OTf)$_2$ as the catalyst and Togni’s reagent as both the radical initiator and a CF$_3$ source, providing an efficient protocol for building up 1-indanone framework with wide functional group compatibility. The reaction mechanism was proposed through a radical triggered addition/5-exo-dig cyclization/oxidation/nucleophilic cascade. This protocol enables a radical-induced three-component cascade to access trifluoromethylated 1-indanones with generally good yields with generally good yields.}

**Graphical Abstract**

In many bioactive molecules and natural products such as Pterosin B and C (Nagle et al., 2000; Wessig and Teubner, 2006), pauciflorol F (Dai et al., 1998; Nitta et al., 2002; Ito et al., 2004), and (+)-indacrinone (Desolms et al., 1978) (Figure 1). Consequently, many chemists made their contributions to establish numerous elegant protocols for their synthesis including Friedel–Crafts acylation (Koelsch, 1932; Frank et al., 1944), Grignard reactions (Bergmann, 1956; Manning et al., 1981), and transition metal-catalyzed annulation of arylalkynes (Shintani et al., 2007; Chernyak et al., 2011; He et al., 2018; Song et al., 2019), radical addition–cyclization of 1,6-enynes (Shen et al., 2018a,b, 2019), and other methods (Zhu et al., 2017, 2018a,b; Shi et al., 2019a). To the best of our knowledge, introduction of a trifluoromethyl group into the 1-indanone framework via a radical-triggered annulation–difunctionalization strategy remains elusive.

Multicomponent reactions (MCRs) represent an attractive and powerful tool for building complex molecular architectures under usually mild conditions (Hao et al., 2016; Wang et al., 2016a,b; Ji et al., 2019; Liu et al., 2019; Qin et al., 2019; Shi et al., 2019b). Radical-triggered annulation–difunctionalization cascades, standing at the intersection of both radical and multicomponent transformations, constitute a unique reaction category, which enables direct assembly of difunctionalized cyclic systems containing both isocyclic and heterocyclic skeletons which are not available from other methods. As a result, lots of unsaturated compounds endowed with alkene and/or alkyne units are devised and prepared as radical acceptors to capture the various radical species (Chen et al., 2008; Liu et al., 2014; Kong et al., 2015; Wang F. et al., 2016; Zhang et al., 2019). Generally, the success of the radical annulation–difunctionalization relies on the radical continuous transfer across the unsaturated systems through a synergistic orientation process. Over the years, our group has been heavily involved in the development of new annulation–difunctionalization cascades for multiple ring formations. For example, we reported a copper-catalyzed annulation–haloalkylation of 1,6-enynes, leading to the atom-economic and highly stereoselective protocol toward functionalized 1-indenones (Scheme 1, path a) (Shen et al., 2019). To continue our interest in this project, we approach a radical addition–cyclization strategy to install both trifluoromethyl and cyano moieties into the 1-indenone framework, due to the behaviors of trifluoromethyl and cyano groups in the wide application potentiality in assigning and discovering new biological lead compounds. An extensive literature survey revealed that the radical-triggered annulation–cyanotrifluoromethylation of 1,6-enynes toward 1-indanones remains unreported to date. For this reason, the copper-catalyzed annulation–cyanotrifluoromethylation of 1,6-enynes 1 with Togni’s reagent 2a and trimethylsilyl cyanide (TMSCN) was carried out by 1,10-phenanthroline (phen) as the ligand, enabling a radical-induced three-component cascade to access trifluoromethylated 1-indanones 3 with generally good yields (Scheme 1, path b). Remarkably, some cases showed complete stereoselectivity, and only E-selectivity was observed. Herein, we report this copper-catalyzed radical transformation.

**Scheme 1** Profiles for annulation–difunctionalization of 1,6-enynes.
RESULTS AND DISCUSSION

At the outset of our studies, we chose the preformed 1,6-eneyne 1a, Togni’s reagent 2a, and TMSCN as the model substrate (Table 1). To our delight, the reaction of 1a with 2a and TMSCN in a 1:2:2 mol ratio catalyzed by 10 mol% Cu(OAc)₂ proceeded smoothly in acetonitrile at 50°C by using 1,10-phenanthroline (phen, L₁) as a ligand, and the target product 3a as a sole (E)-stereoisomer was obtained in 36% yield. The following screening of solvents showed that the use of DMSO and DMF led to a slightly decreased yield of 3a compared with acetonitrile (entries 2 and 3 vs. entry 1), whereas both 1,4-dioxane and THF completely suppressed the formation of 3a (entries 4 and 5). Thus, acetonitrile was the best solvent for the reaction. An employment of NaOAc as the base facilitated the reaction process, delivering 40% yield of the desired product 3a (entry 6). After that, we conducted the screening of a variety of copper salts, such as Cu(CH₂CN)₂PF₆, CuCN, CuI, and Cu(OTf)₂, that are often utilized in catalytic transformations, for this addition–cyclization cascade by using acetonitrile as the reaction medium. All these catalysts could promote the conversion of 1a into 3a (entries 7–10), and the latter one showed the best catalytic performance in the current reaction, generating product 3a in 55% yield (entry 10). As the next optimization step, several ligands, such as 1,10-phenanthroline-5,6-dione (L₂), 2,2’,6’,2”-terpyridine (L₄), were investigated and anticipated to enhance the yield of product 3a. Disappointingly, ligands L₂–L₄ showed slightly weaker performance on the conversion of 1a into 3a as compared with L₁ (entries 11–13). Using Togni’s reagent 2b to replace 2a resulted in a lower conversion (42%, entry 14 vs. entry 10). Different bases such as potassium phosphate tribasic (K₂PO₄), trimethylamine (Et₃N), and cesium carbonate (Cs₂CO₃) were then screened. The results indicated that K₂PO₄ could improve the reaction, providing product 3a in 64% yield. After careful optimizations, we found that fine-tuning the substrate ratio 1a/2a/TMSCN to 1:3:2 delivered product 3a in a higher 87% yield (entry 18).

With the optimized conditions in hand (Table 1, entry 18), the substrate scope of this radical-triggered annulation–cyanotrifluoromethylation of 1,6-eneynes was investigated. The results were presented in Scheme 2. Upon repeating the reaction with 2a and TMSCN, substrate 1 with diverse substituents such as fluoro (1b), chloro (1c and 1d), and bromo (1e) groups on the arylalkynyl moiety all work well, giving the corresponding functionalized (E)-1-indanones 3b–3e in 45–78% yields. Notably, substrates 1c–1e could completely orient the E-selectivity to the target products 3c–3e. Alternatively, both cyclopropyl 1f and n-butyl 1g counterparts were proven to be favorable, enabling radical-induced cyclization reactions.
to offer the corresponding (E)-1-indanones 3f and 3g with complete stereoselectivities, albeit with low yields. Due to the pharmacological significance of fluorine-containing molecules compared to their non-fluorinated analogs, we decided to prepare 1,6-enynes 1h–1j containing the fluoro group residing in the 5-position of the internal arene ring and employed them to react with 2a and TMSCN. The reaction worked well, accessing the corresponding polyfluoro products 3h–3j in 42–64% yields and 5:3 to 5:2 E/Z ratios. Other substituents including chloro (1k–1o, 1r, and 1s), methyl (1p and 1t–1x), and methoxy (1q) located at the C4- or C5-position on the internal arene ring did not hamper this copper-catalyzed reaction, and a range of new substituted 1-indanones 3k–3x can be isolated in synthetically useful yields, in which a complete diastereoselectivity was also observed in the cases of 3k, 3l, 3p, 3q, 3r, and 3t. However, unsatisfactory E/Z ratios were detected for the other products. Either electronically neutral (H), poor (fluoro, chloro, and bromo), or rich [methyl, ethyl, t-butyl, and methoxy (PMP = p-methoxyphenyl)] groups at the para-position of the arylalkynyl moiety (R1) are well-tolerated with the catalytic conditions. Unfortunately, 1,6-enyne 1y carrying a 2-thienyl group was an ineffective reaction partner in this transformation. The structures of these resulting 1-indanones were fully characterized by NMR spectroscopy and HRMS data (Data Sheet 1).

To gain mechanistic insight into this transformation, radical trapping experiments were performed. When 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) as a radical scavenger was subjected to the reaction conditions, the generation of 3a was completely suppressed (Scheme 3a). Similarly, BHT could inhibit the formation of 3a. These results showed that the reaction may include a radical process. Moreover, the developed transformation could be valorized through post-functionalization of indanone 3q (Scheme 3b). The combination of NaBH₄ and I₂ was found to be effective to reduce 3q to give 2,3-dihydro-1H-inden-1-ol 4 (51% yield) (He et al., 2015; Chen et al., 2018).
According to these results and related literature (Kamigata et al., 1990; Liu et al., 2012; Pair et al., 2013; Yasu et al., 2013; He et al., 2014b; Shen et al., 2019), a plausible mechanism was proposed (Scheme 4). The copper(II) catalyst activates Togni’s reagent 2a to give the activated complex A, which releases a Cu(III) species and the trifluoromethyl radical. The latter rapidly adds to 1,6-enyne 1a to give the radical intermediate B. In the presence of ligands and TMSCN, Cu(III) species activates an alkyne unit of intermediate B to drive 5-exo-dig cyclization, giving favorable anti-Cu(III) species C (Shen et al., 2019), some of which is converted into syn-Cu(III) species C’, together with trimethylsilyl 2-iodobenzoate D. Finally, anti-Cu(III) species C undergoes reductive elimination to give the desired (E)-product 3a as a major isomer and regenerate a Cu(II) complex to complete a catalytic cycle through the release of ligands (He et al., 2014b), whereas syn-Cu(III) species C’ undergoes the same reductive elimination to access minor (Z)-product 3a.

CONCLUSION

In summary, we have established a copper-catalyzed annulation-cyanotrifluoromethylation of 1,6-enynes with easily available Togni’s reagent and TMSCN, by which a wide range of 1-indanones with a quaternary carbon center were stereoselectively synthesized in generally good yields. Notably, a complete stereoselectivity could be detected in most cases. This approach is efficiently induced by Togni’s reagent as a radical donor and ultimately terminated by TMSCN as the nucleophilic reagent. The transformation offered a new entry to prepare the CF$_3$ containing 1-indanone skeleton via a complex radical addition-cyclization cascade. Further investigations into the mechanism and its application will be conducted in due course.

MATERIALS AND METHODS

General

$^1$H NMR ($^{13}$C NMR, $^{19}$F NMR) spectra were measured on a Bruker DPX 400-MHz spectrometer in CDCl$_3$ (DMSO-d$_6$) with chemical shift (δ) given in ppm relative to TMS as internal standard [s = singlet, d = doublet, t = triplet, brs = broad singlet, m = multiplet], coupling constant (Hz)]. HRMS (ESI) was done by using a micrOTOF-Q II HRMS/MS instrument (Bruker).

General Procedure for the Synthesis of 3

Example for the Synthesis of 3a

Under Ar conditions, a mixture of Togni’s reagent 2 (0.6 mmol), Cu(OTf)$_2$ (0.02 mmol), K$_2$PO$_4$ (0.4 mmol), and ligand L1 (0.04 mmol) was added in a Schlenk tube. Acetonitrile was added into the tube. Then, 2-methyl-1-[2-(phenylethynyl)phenyl]prop-2-en-1-one 1a (0.2 mmol) and TMSCN (0.4 mmol) were put in the system, stirred for 3 h at 50°C until thin-layer chromatography (TLC) revealed that conversion of the starting material 1a was complete. Next, the reaction mixture was concentrated in vacuum, and the resulting residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 25:1, v/v) to afford the desired product 3a.

General Procedure for the Synthesis of 4

Under Ar conditions, 3q (0.05 mmol), NaBH$_4$ (3.0 equiv), and I$_2$ (1.0 equiv) were added in a Schlenk tube. THF was added, and the reaction mixture was stirred at room temperature for 10 h. The solution was treated with water and extracted with dichloromethane. The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, concentrated in vacuum, and purified by preparative TLC (petroleum ether/ethyl acetate = 2/1) to afford product 4 (He et al., 2015; Chen et al., 2018).

(E)-2-[2-Methyl-3-oxo-2-(2,2,2-trifluoroethyl)-2,3-dihydro-1H-inden-1-ylidene]-2-phenylacetonitrile (3a)

Light yellow solid, 59 mg, 87% yield; mp 105.2–106.1°C. $^1$H NMR (400 MHz, CDCl$_3$; δ, ppm): 8.96 (d, $J = 8.0$ Hz, 1H), 7.94 (d, $J = 7.6$ Hz, 1H), 7.90–7.85 (m, 1H), 7.73–7.67 (m, 1H), 7.54–7.49 (m, 1H), 7.46–7.41 (m, 1H), 7.24–7.17 (m, 1H), 7.19 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$; δ, ppm): 202.3, 153.2, 144.5, 136.3, 135.5, 133.0, 132.4, 129.9, 129.5, 129.2, 125.0 (q, $J = 85.1$ Hz, CF$_3$), 118.9, 109.1, 49.8, 40.4 (q, $J = 27.6$ Hz, CH$_2$CF$_3$), 25.1. $^{19}$F NMR (376 MHz, CDCl$_3$; δ, ppm): −61.29 (s, 3F). IR
(E)-2-(4-Fluorophenyl)-2-[2-methyl-3-oxo-2-(2,2,2-trifluoroethyl)-2,3-dihydro-1H-inden-1-ylidene]acetocarbonyl (3b, Major)

Light yellow solid, 56 mg, 78% yield; mp 148.9–150.9°C. 1H NMR (400 MHz, CDCl₃; δ, ppm): 8.94 (d, J = 8.0 Hz, 1H), 7.96 (d, J = 7.6 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.73–7.67 (m, 1H), 7.46–7.42 (m, 2H), 7.27–7.22 (m, 2H), 2.67–2.58 (m, 1H), 2.18–2.09 (m, 1H), 1.20 (s, 3H). 13C NMR (100 MHz, CDCl₃; δ, ppm): 202.0, 163.3 (d, J = 247.0 Hz, CF), 153.9, 144.3, 136.3, 135.3, 132.6, 131.6 (d, J = 83.8 Hz, CF), 128.9 (d, J = 3.7 Hz, CF), 126.6, 125.0 (q, J = 80.7 Hz, CF), 117.4, 117.4, 116.4 (d, J = 21.8 Hz, CF), 108.0, 49.8, 40.3 (q, J = 27.8 Hz, CH₂CF₂), 25.2. 19F NMR (376 MHz, CDCl₃; δ, ppm): −61.31 (s, 3F), −109.82 (s, 1F). IR (KBr, ν, cm⁻¹): 2,202, 1,724, 1,599, 1,509, 1,361, 1,257, 1,142, 1,070, 776. HRMS (ESI; m/z): calcd for C₂₀H₁₃F₂NONa [M + Na]+ 382.0825, found 382.0874.

(E)-2-(3-Chlorophenyl)-2-[2-Methyl-3-oxo-2-(2,2,2-Trifluoroethyl)-2,3-Dihydro-1H-Inden-1-Ylidene]acetocarbonyl (3c)

Light yellow solid, 34 mg, 45% yield; mp 174.6–177.1°C. 1H NMR (400 MHz, CDCl₃; δ, ppm): 8.94 (d, J = 8.0 Hz, 1H), 7.96 (d, J = 7.6 Hz, 1H), 7.91–8.16 (m, 1H), 7.75–7.69 (m, 1H), 7.52–7.42 (m, 2H), 7.34 (d, J = 7.2 Hz, 1H), 2.69–2.61 (m, 1H), 2.21–2.12 (m, 1H), 1.21 (s, 3H). 13C NMR (100 MHz, CDCl₃; δ, ppm): 201.9, 154.0, 144.2, 136.4, 135.6, 135.2, 134.6, 132.7, 130.5, 130.2, 129.8, 127.7, 125.1 (q, J = 78.5 Hz, CF₃), 118.5, 107.6, 49.8, 40.2 (q, J = 55.5 Hz, CH₂CF₂), 25.2. 19F NMR (376 MHz, CDCl₃; δ, ppm): −61.31 (s, 3F). IR (KBr, ν, cm⁻¹): 2,204, 1,728, 1,595, 1,260, 1,140, 1,069, 776. HRMS (ESI; m/z): calcd for C₂₀H₁₃ClF₂NONa [M + Na]+ 398.0529, found 398.0520.

(E)-2-(4-Chlorophenyl)-2-[2-Methyl-3-oxo-2-(2,2,2-Trifluoroethyl)-2,3-Dihydro-1H-Inden-1-Ylidene]acetocarbonyl (3d)

Light yellow solid, 53 mg, 70% yield; mp 154.5–155.3°C. 1H NMR (400 MHz, CDCl₃; δ, ppm): 8.94 (d, J = 8.0 Hz, 1H), 7.95 (d, J = 7.6 Hz, 1H), 7.91–7.85 (m, 1H), 7.75–7.69 (m, 1H), 7.50 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.4 Hz, 2H), 2.69–2.59 (m, 1H), 2.20–2.11 (m, 1H), 1.20 (s, 3H). 13C NMR (100 MHz, CDCl₃; δ, ppm): 201.9, 153.9, 144.2, 136.4, 136.3, 135.6, 132.7, 131.4, 130.1, 129.6, 125.1 (q, J = 78.5 Hz, CF₃), 118.6, 107.8, 49.8, 40.7 (q, J = 27.7 Hz, CH₂CF₂), 25.2. 19F NMR (376 MHz, CDCl₃; δ, ppm): −61.28 (s, 3F). IR (KBr, ν, cm⁻¹): 2,204, 1,729, 1,593, 1,491, 1,360, 1,256, 1,143, 1,072, 835, 776. HRMS (ESI; m/z): calcd for C₂₀H₁₃ClF₂NONa [M + Na]+ 398.0529, found 398.0569.

(E)-2-(4-Bromophenyl)-2-[2-Methyl-3-oxo-2-(2,2,2-Trifluoroethyl)-2,3-Dihydro-1H-Inden-1-Ylidene]acetocarbonyl (3e)

Light yellow solid, 53 mg, 63% yield; mp 103.9–104.7°C. 1H NMR (400 MHz, CDCl₃; δ, ppm): 8.93 (d, J = 8.0 Hz, 1H), 7.95 (d, J = 7.6 Hz, 1H), 7.91–7.85 (m, 1H), 7.74–7.68 (m, 1H), 7.66 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 2.71–2.59 (m, 1H), 2.21–2.11 (m, 1H), 1.20 (s, 3H). 13C NMR (100 MHz, CDCl₃; δ, ppm): 201.9, 153.9, 144.2, 136.4, 135.6, 132.7, 132.5, 131.9, 131.2, 125.1 (q, J = 77.7 Hz, CF₃), 124.5, 118.5, 107.8, 49.8, 40.4 (q, J = 27.8 Hz, CH₂CF₂), 25.2. 19F NMR (376 MHz, CDCl₃; δ, ppm): −61.27 (s, 3F). IR (KBr, ν, cm⁻¹): 2,205, 1,728, 1,585, 1,486, 1,360, 1,255, 1,142, 1,069, 1,011, 986, 832, 723. HRMS (ESI; m/z): calcd for C₂₀H₁₂BrF₂NONa [M + Na]+ 442.0024, found 442.0020.

(Zhang et al. Annulation-Cyanotrifluoromethylation 2011)
(E)-2-[4-(tert-Butyl)phenyl]-2-[5-fluoro-2-methyl-3-oxo-2-(2,2,2-trifluoroethyl)-2,3-dihydro-1H-inden-1-ylidene]acetonitrile (3j, Major)

Light yellow oil, 53 mg, 64% yield. 1H NMR (400 MHz, CDCl3; δ, ppm): 8.89–8.82 (m, 1 H), 7.89 (d, J = 2.0 Hz, 1H), 7.54–7.48 (m, 3H), 7.25–7.19 (m, 2H), 4.61–4.51 (m, 1H), 2.20–2.12 (m, 1H), 1.36 (s, 3H), 0.94 (s, 3F). IR (KBr, v cm⁻¹): 2,205, 1,732, 1,589, 1,507, 1,475, 1,362, 1,258, 1,187, 1,141, 0.97, 948, 833. HRMS (ESI, m/z): calcd for C21H17ClF3Na [M + Na]+ 426.0843, found 426.0824.

(E)-2-[5-Chloro-2-methyl-3-oxo-2-(2,2,2-trifluoroethyl)-2,3-dihydro-1H-inden-1-ylidene]-2-(4-ethylphenyl)acetonitrile (3m, Major)

Light yellow solid, 25 mg, 66% yield; mp 157.1–158.8°C. 1H NMR (400 MHz, CDCl3; δ, ppm): 8.84 (d, J = 8.8 Hz, 1H), 7.81 (d, J = 2.0 Hz, 1H), 7.53–7.47 (m, 3H), 7.24–7.18 (m, 2H), 4.58–4.50 (m, 1H), 2.24–2.14 (m, 1H), 1.29 (s, 3H). 13C NMR (100 MHz, CDCl3; δ, ppm): 204.0, 155.0, 142.5, 139.4, 130.6, 126.7, 126.4, 118.7, 110.6, 50.2, 40.5 (q, J = 27.8 Hz, CH2CF3), 25.1. 19F NMR (376 MHz, CDCl3; δ, ppm): −61.25 (s, 3F). IR (KBr, v cm⁻¹): 2,206, 1,724, 1,597, 1,487, 1,362, 1,258, 1,187, 1,141, 0.97, 948, 833. HRMS (ESI, m/z): calcd for C20H13ClF3Na [M + Na]+ 438.0530, found 438.0491.

(E)-2-[5-Chloro-2-methyl-3-oxo-2-(2,2,2-trifluoroethyl)-2,3-dihydro-1H-inden-1-ylidene]-2-(4-fluorophenyl)acetonitrile (3k, Major)

Light yellow oil, 43 mg, 69% yield; mp 169.7–171.0°C. 1H NMR (400 MHz, CDCl3; δ, ppm): 8.87 (d, J = 8.8 Hz, 1H), 7.82 (d, J = 2.0 Hz, 1H), 7.79–7.73 (m, 2H), 7.23–7.19 (m, 2H), 4.59–4.51 (m, 1H), 2.20–2.12 (m, 1H), 1.30 (s, 3H). 13C NMR (100 MHz, CDCl3; δ, ppm): 204.1, 156.9, 142.7, 139.1, 137.0, 136.3, 132.7, 130.1, 129.4, 126.7, 124.4, 118.7, 109.6, 50.2, 40.5 (q, J = 27.8 Hz, CH2CF3), 25.1. 19F NMR (376 MHz, CDCl3; δ, ppm): −61.25 (s, 3F). IR (KBr, v cm⁻¹): 2,205, 1,724, 1,597, 1,487, 1,362, 1,258, 1,187, 1,141, 0.97, 948, 833. HRMS (ESI, m/z): calcd for C20H13ClF3Na [M + Na]+ 438.0530, found 438.0491.
(E)-2-(4-Chlorophenyl)-2-[5-methoxy-2-methyl-3-oxo-2-(2,2,2-trifluoroethyl)-2,3-dihydro-1H-inden-1-ylidene]acetoniitrile (3q)

Light yellow solid, 52 mg, 64% yield; mp 130.5–131.2°C. ^1H NMR (400 MHz, CDCl₃; δ, ppm): 8.83 (d, J = 8.8 Hz, 1H), 7.48 (d, J = 8.4 Hz, 2H), 7.40 (d, J = 6.4 Hz, 1H), 7.39–7.35 (m, 2H), 7.32 (d, J = 2.4 Hz, 1H), 3.94 (s, 3H), 2.68–2.56 (m, 1H), 2.20–2.08 (m, 1H), 1.19 (s, 3H). ^13C NMR (100 MHz, CDCl₃; δ, ppm): 201.9, 163.3, 153.5, 137.8, 137.5, 136.1, 131.6, 131.2, 129.5, 126.0 (q, J = 160.5 Hz, CF₃), 119.0, 105.8, 105.0, 56.0, 50.3, 40.3 (q, J = 27.7 Hz, CH₂CF₃), 25.2. ^19F NMR (376 MHz, CDCl₃; δ, ppm): −61.38 (s, 3F). IR (KBr, ν, cm⁻¹): 2,202, 1,727, 1,595, 1,488, 1,364, 1,295, 1,143, 1,019, 845. HRMS (ESI, m/z): calcld for C₂₁H₁₅F₂Cl₃Na [M + Na]^+ 428.0636, found 428.0616.

(E)-2-[6-Chloro-2-methyl-3-oxo-2-(2,2,2-trifluoroethyl)-2,3-dihydro-1H-inden-1-ylidene]-2-phenylacetonitrile (3r)

Light yellow solid, 53 mg, 71% yield; mp 161.6–163.8°C. ^1H NMR (400 MHz, CDCl₃; δ, ppm): 8.94 (d, J = 1.2 Hz, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.69–7.64 (m, 1H), 7.54–7.50 (m, 3H), 7.45–7.39 (m, 2H), 6.26–2.54 (m, 1H), 2.22–2.13 (m, 1H), 1.19 (s, 3H). ^13C NMR (100 MHz, CDCl₃; δ, ppm): 201.0, 151.9, 145.7, 143.3, 133.8, 133.0, 132.6, 130.1, 129.4, 129.5, 125.6, 125.5, 118.4, 110.5, 50.0, 40.4 (q, J = 27.7 Hz, CH₂CF₃), 25.2. ^19F NMR (376 MHz, CDCl₃; δ, ppm): −61.25 (s, 3F). IR (KBr, ν, cm⁻¹): 2,202, 1,724, 1,589, 1,489, 1,361, 1,271, 1,139, 1,072, 835, 712. HRMS (ESI, m/z): calcld for C₂₃H₁₇F₂Cl₃Na [M + Na]^+ 398.0530, found 398.0566.

(E)-2-[6-Chloro-2-methyl-3-oxo-2-(2,2,2-trifluoroethyl)-2,3-dihydro-1H-inden-1-ylidene]-2-p-tolylacetonitrile (3s, Major)

Light yellow solid, 48 mg, 62% yield; mp 121.5–123.1°C. ^1H NMR (400 MHz, CDCl₃; δ, ppm): 8.92 (s, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.36 (d, J = 7.6 Hz, 1H), 7.30 (s, 3H), 6.26–2.52 (m, 2H), 2.43 (s, 3H), 2.26–2.17 (m, 1H), 1.19 (s, 3H). ^13C NMR (100 MHz, CDCl₃; δ, ppm): 201.1, 151.7, 145.8, 143.2, 140.3, 133.8, 132.9, 130.8, 129.9, 126.8, 125.6, 118.5, 110.7, 50.1, 40.4 (q, J = 27.7 Hz, CH₂CF₃), 25.2, 21.4. ^19F NMR (376 MHz, CDCl₃; δ, ppm): −61.24 (s, 3F). IR (KBr, ν, cm⁻¹): 2,205, 1,731, 1,588, 1,509, 1,456, 1,362, 1,255, 1,145, 1,072, 825. HRMS (ESI, m/z): calcld for C₂₃H₁₅BrF₂Cl₃Na [M + Br]^+ 456.0181, found 456.0137.

(E)-2-[2,6-Dimethyl-3-oxo-2-(2,2,2-trifluoroethyl)-2,3-dihydro-1H-inden-1-ylidene]-2-p-tolylacetonitrile (3t, Major)

Light yellow solid, 54 mg, 73% yield; mp 127.8–129.9°C. ^1H NMR (400 MHz, CDCl₃; δ, ppm): 8.73 (s, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.30 (s, 4H), 2.61–2.53 (m, 4H), 2.43 (s, 3H), 2.24–2.17 (m, 1H), 1.18 (s, 3H). ^13C NMR (100 MHz, CDCl₃; δ, ppm): 201.9, 153.2, 147.8, 144.9, 140.0, 133.6, 133.3, 130.5, 129.8, 129.4, 127.1, 125.4 (q, J = 114.4 Hz, CF₃), 119.1, 108.9, 50.0, 40.3 (q, J = 27.7 Hz, CH₂CF₃), 25.2, 22.6. ^19F NMR (376 MHz, CDCl₃; δ, ppm): −61.32 (s, 3F). IR (KBr, ν, cm⁻¹): 2,204, 1,719, 1,609, 1,590, 1,456, 1,362, 1,255, 1,141, 1,070, 1,011, 831. HRMS (ESI, m/z): calcld for C₂₁H₁₈F₂Br₂Na [M + Na]^+ 392.1233, found 392.1223.

(Z)-2-[2,6-Dimethyl-3-oxo-2-(2,2,2-trifluoroethyl)-2,3-dihydro-1H-inden-1-ylidene]-2-(4-methoxyphenyl)acetonitrile (3x, Major)

Light yellow solid, 63 mg, 82% yield; mp 120.8–122.4°C. ^1H NMR (400 MHz, CDCl₃; δ, ppm): 8.72 (s, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.61, 1.489, 1.455, 1.360, 1.253, 1.136, 1.072, 831, 767. HRMS (ESI, m/z): calcld for C₂₁H₁₈F₂Br₂Na [M + Na]^+ 378.1076, found 378.1054.
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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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