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Efficient synthesis of trifluoromethylated dihydrochalcones, aryl vinyl ketones and indanones by superelectrophilic activation of 4,4,4-trifluoro/3-(trifluoromethyl)crotonic acids

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Acylation/cyclialkylation
Ab initio theory

ABSTRACT

Superacid catalyzed electrophilic substitution of arenes using 4,4,4,-trifluoro/3-trifluoromethylcrotonic acids has been investigated. The direct synthesis of various trifluoromethylated dihydrochalcones, aryl vinyl ketones and indanones has been achieved by this methodology. It has been found that the position of the trifluoromethyl group has a profound effect on the nature of the reaction and the products. In the pharmaceutical industry, many fluoroorganics are shown to possess significant biological and therapeutic activities. Therefore, these novel compounds can be considered key intermediates for the preparation of potential biologically active molecules.

1. Introduction

The formation of a carbon–carbon bond (C–C) is the fundamental process for the construction of a molecular framework in organic synthesis. Friedel–Crafts reactions are the most widely used procedure for (C–C) bond formation by directly introducing carbon substituent into an aromatic ring [1]. The two major aromatic electrophilic substitution reactions – alkylation and acylation, often provide a variety of highly important aromatic substances under mild conditions [2]. On the other hand, synthesis of the compounds containing trifluoromethyl group continues to be an important area in the fields of agricultural, medicinal and synthetic organic chemistry due to the unique properties incurred by the presence of fluorine atom [3]. Preparation of trifluoromethylated compounds have been often achieved by two different strategies, direct introduction of CF_3 group by substitution of hydrogen or functional groups or using CF_3-containing building blocks [4]. Prakash and Yudin have carried out significant work in this area by developing novel fluorinating and fluoromethylating agents [5]. Introduction of trifluoromethyl group through building block strategy also represents an attractive method for the synthesis of trifluoromethylated compounds [6].

Flavonoids continue to attract the interest of scientists in many different aspects due to their structural diversity and biological activities [7]. Among them, dihydrochalcones that are widely present in nature display a broad spectrum of bioactivities such as anticancer, antifungal, antibacterial, antiviral, antioxidant and anti-inflammatory properties [9]. Phloretin **1** and phloridzin **2** are dihydrochalcone flavonoids having potent antioxidant activities [8]. Phloretin and phloridzin are abundantly found in apples [9]. Cytotoxic dihydrochalcones uvaretin **3**, isouvaretin **4** and diuvaretin **5** isolated from *Uvaria acuminate*, displayed growth inhibitory effects against human promyelotic leukemia HL-60 cells [10]. Davidigenin **6** and DHC **7** isolated from *Artemisia dracunculus* have antidiabetic activity [11]. The DHC **8** as a main metabolite

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extracted from a traditional Amazonian medicinal plant *Iryanthera juruensis* shows cytotoxic activity against a panel of cancer cell lines as well as significant anti-*Trypanosoma cruzi* activity *in vitro* [12]. Chromeno dihydrochalcones **9**–**11** from *Crotalaria ramosissima*, which are very rare as plant secondary metabolites, exhibit a variety of biological activities [13]. Dihydrochalcones have also received considerable attention as food sweeteners (neohesperidine) *etc.* [14,15] (see Fig. 1).

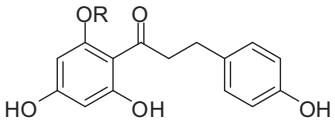
DHCs are also key intermediates for the synthesis of flavones, anthocyanin-type dyes [8b,16], quinoline derivatives as antibacterial agents [17], and phenyl indoles as plasminogen activator inhibitors [18]. The general synthesis of dihydrochalcones involves the Claisen–Schmidt condensation of acetophenone with appropriate aldehyde and subsequent reduction of the chalcone double bond [11,19]. Other methods include palladium catalyzed arylation of allyl alcohol, based on Heck coupling reaction [8b,16], transition metal catalyzed reaction of benzyl alcohol with acetophenone [20a–d], phenylacetylene [20e], 1-phenylethanol [20f], and decarboxylative coupling reaction of benzylic chloroformate with silyl enol ether [20g]. Chalcone **12** demonstrated significant chemopreventive activities against lung, breast, prostate and colorectal cancers [21]. Since aryl vinyl ketones have been widely used for the synthesis of chalcones [22a], various heterocycles [22b–i], β-amino ketones [22j], polymers [22k], and for cycloaddition reactions [22l,m], methodologies for their synthesis are of great interest. The main methods to prepare such compounds are the 1,3-rearrangement of propargyl alcohols (Meyer–Schuster rearrangement) [23a,b], palladium-catalyzed coupling reactions, reaction of alkynes with aldehydes [23c–e], and allylation of ketones [23f].

1-Indanone ring system constitutes the core structures of many biologically important compounds. 1-Indanones are present in many cytotoxic natural compounds. 1-Indanones have also been used as intermediates in the synthesis of Sulindac, a non-steroidal anti-inflammatory drug (NSAID) and other novel biologically important compounds [23g]. Knowing the importance of dihydrochalcones and aryl vinyl ketones as potential drug candidates, the economical, facile and rapid one pot synthesis of dihydrochalcones and aryl vinyl ketones carrying "CF_3" group would be highly desirable. However, synthetic methodologies reported for the synthesis of trifluoromethyl containing dihydrochalcones [24] aryl vinyl ketones [25] are quite limited. Herein, we report an efficient synthesis of trifluoromethylated dihydrochalcones and aryl vinyl ketones through superacid catalyzed Friedel–Crafts alkylation/acylation reactions of trifluoromethylated crotonic acids with arenes.

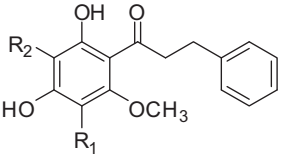
2. Results and discussion

Recently, we have carried out one-pot synthesis of trifluoromethylated arylpropanoic acids (**16**), indanones (**17**), and dihydrocoumarins (**18**) using Friedel–Crafts alkylation and cyclicacylation of arenes/phenols with 2-(trifluoromethyl)acrylic acid (**15**) under superacidic conditions using trifluoromethanesulfonic acid (Scheme 1) [26]. It is important to notice that the selective preparation of trifluoromethylated propanoic acid (**16**) or indanones (**17**) has been achieved from the same arene substrate by properly tuning and optimizing the reaction conditions. The formation of propanoic acid (**16**) occurs by intermolecular Friedel–Crafts alkylation while the indanones (**17**) are formed by subsequent Friedel–Crafts intramolecular cyclicacylation at a higher temperature.

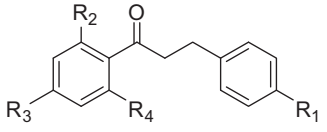
Intrigued by these results, we have now probed to carry out the condensation of 4,4,4-trifluorocrotonic acid (**19a**) and 3-(trifluoromethyl)crotonic acid (**19b**) with arenes under similar conditions as a one-pot protocol toward the direct access of trifluoromethylated dihydrochalcones (**20**), aryl vinyl ketones (**21**) and indanones (**22**). To our delight, it has been found that 4,4,4-trifluorocrotonic acid (**19a**) undergoes intermolecular Friedel–Crafts acylation and alkylation to afford trifluoromethylated dihydrochalcones (DHCs, **20**) as the main product in a single step whereas 3-(trifluoromethyl)crotonic acid gives aryl vinyl ketones (**21**) and indanones (**22**) in most cases (Scheme 2). Nucleophilic attack occurs at the less substituted position of the olefinic group, leading to *anti*-Markovnikov addition giving the favored conjugate addition product. 4,4,4-Trifluorocrotonic acid (**19a**) with benzene at 55 °C



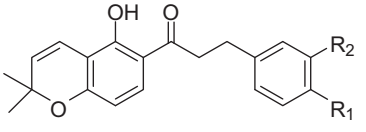
Phloretin **1**, R = H
Phloridzin **2**, R = D-glucose



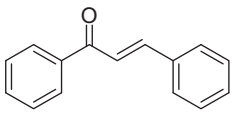
Uvaretin **3**, R_1 = H, R_2 = 2-hydroxybenzyl
Isouvaretin **4**, R_1 = 2-hydroxybenzyl, R_2 = H
Diuvaretin **5**, R_1 = R_2 = 2-hydroxybenzyl



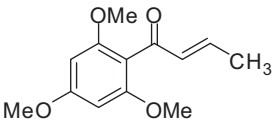
6, R_1 = OH, R_2 = R_3 = OH, R_4 = H
7, R_1 = OMe, R_2 = R_3 = OH, R_4 = H
8, R_1 = OMe, R_2 = R_3 = OH, R_4 = OMe



9, R_1 = OCH_3, R_2 = H
10, R_1 = OH, R_2 = H
11, R_1 = OH, R_2 = OH



12 (chalcone)



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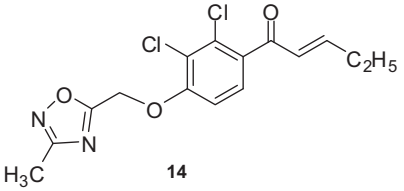

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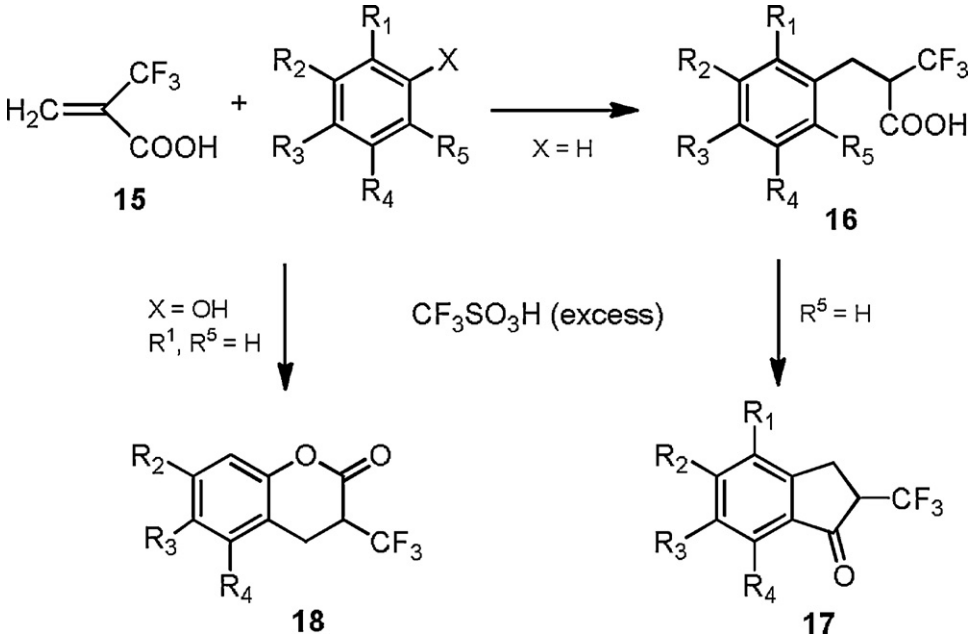
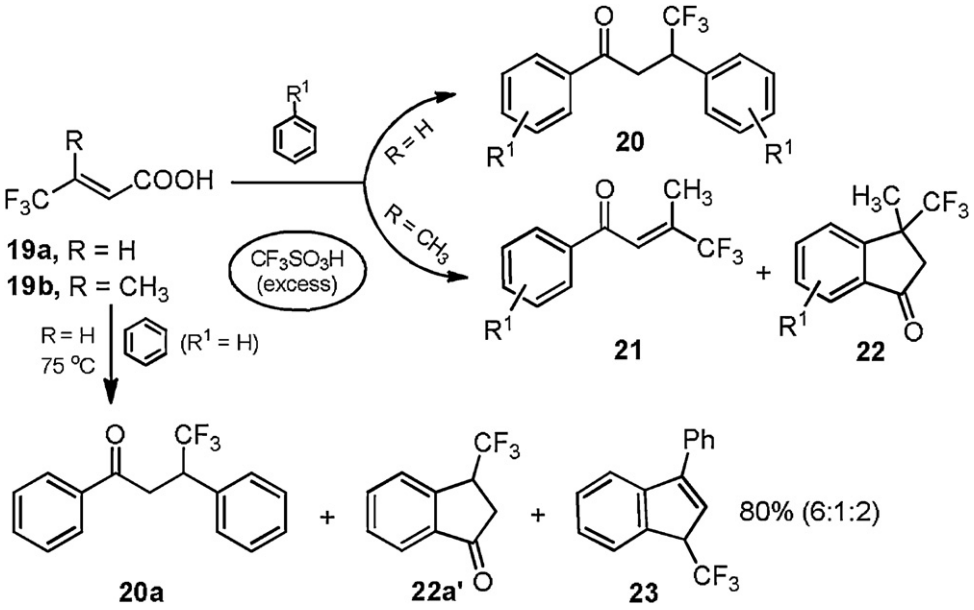
Fig. 1. Biologically active dihydrochalcones and aryl vinyl ketones.



Scheme 1. Triflic acid catalyzed Friedel–Crafts alkylation and alkylation/cycliacylation of arenes with 2-(trifluoromethyl)acrylic acid (**15**).

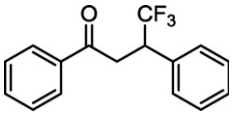
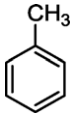
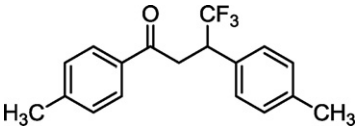
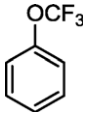
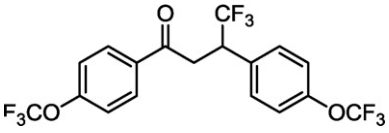
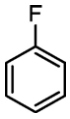
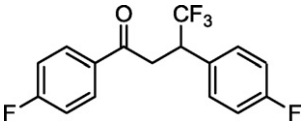
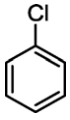
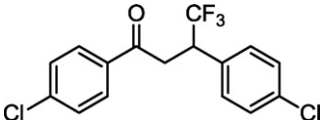
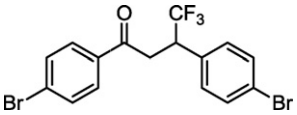
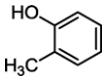
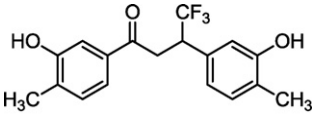
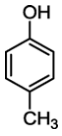
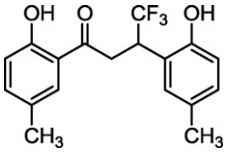
afforded trifluoromethylated dihydrochalcone (**20a**) as the only product in 80% yield. Interestingly, no desired product has been isolated using less acidic sulfuric acid or trifluoroacetic acid as catalysts implying the higher acidity requirement for this reaction. Condensation of toluene with 4,4,4-trifluorocrotonic acid at 45 °C gives *p*,*p*′-substituted DHC (**20b**) exclusively in 75% yield. In the case of benzene, increase in temperature (75 °C) has resulted in a mixture of trifluoromethylated DHC (**20a**), indanone (**22a**′) and indene (**23**) in the ratio 6:1:2 (*vide infra*) whereas toluene gives a mixture of unidentified products (not easily separable) possibly due to transalkylation and isomerization followed by Friedel–Crafts acylation and alkylation. Reaction with trifluoromethoxybenzene yields the *p*,*p*′-substituted DHC (**20c**) with high regioselectivity. No product has been observed with *p*-xylene possibly due to the presence of two methyl groups and the enhanced steric effect at the *ortho* position to the four equivalent reaction centers. Condensation of halobenzenes with 4,4,4-trifluorocrotonic acid also yield the corresponding trifluoromethylated DHCs (**20d**–**f**) in good yields. Unlike as reported earlier in the case of 2-(trifluoromethyl)acrylic acid [26], phenols undergo condensation reaction with 4,4,4-trifluorocrotonic acid to afford the corresponding DHCs as the only product rather than 3,4-dihydrocoumarin derivatives (**18**, Scheme 1). Therefore, the position of trifluoromethyl group is powerful handle having a dramatic effect on the direction of the reaction and nature of the products.

In the presence of excess triflic acid, reaction of 3-(trifluoromethyl)crotonic acid (**19b**) with arenes gives trifluoromethylated aryl vinyl ketones and indanones in a single step (Table 2) depending on the reaction conditions. At room temperature,



Scheme 2. Triflic acid catalyzed Friedel–Crafts alkylation/acylation/cyclialkylation of arenes with 4,4,4-trifluorocrotonic acid (**19a**) and 3-(trifluoromethyl)crotonic acid (**19b**).

Table 1
Triflic acid catalyzed synthesis of trifluoromethylated dihydrochalcones (**20a**–**h**) from 4,4,4-trifluorocrotonic acid (**19a**).[a]

Entry	Arene	Temp (°C)	Products		Yield (%)
a[b]		55			80
b		45		(*p*,*p*′-):other regioisomers 92:8	75
c		55			66
d		60			70
e		70		(*p*,*p*′-):other regioisomers 78:22	65
f		80		(*p*,*p*′-):other regioisomers 73:27	85
g		50			85
h		55			85

[a] Reaction time – 24 h.
[b] With excess of benzene.

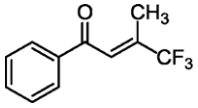
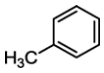
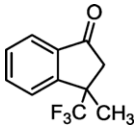
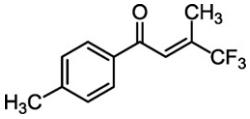
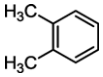
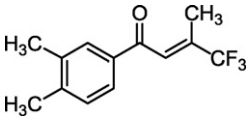
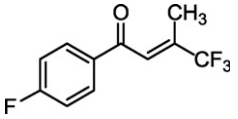
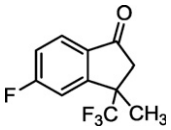
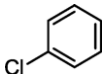
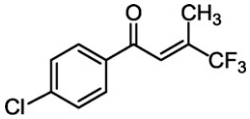
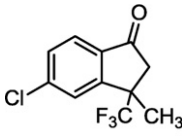
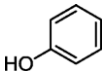
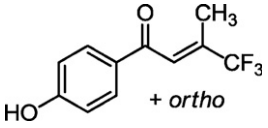
intermolecular Friedel–Crafts acylation of benzene occurs with **19b** giving (*E*, *Z*)-4,4,4-trifluoro-3-methyl-1-phenyl-2-buten-1-one (**21a**) as the only product. When the temperature is increased to 120 °C indanone is formed through intramolecular Friedel–Crafts alkylation. In contrast, reaction of 2-(trifluoromethyl)acrylic acid (**15**) with arenes gives 2-trifluoromethyl-3-phenyl propanoic acids (**16**) followed by intramolecular acylation to form indanone products **17** [26]. Again, this is a clear manifestation of trifluoromethyl group acting as a control group depending on its position in propenoic acids **15** and **19** (acrylic or crotonic acids), leading the reaction regioselectively. With toluene, *o*-xylene as well as fluorobenzene and chlorobenzene 3-(trifluoromethyl)crotonic acid **19b** has yielded the corresponding aryl vinyl ketones, with only the *para*-derivatives. However, the indanone products **22** are achieved by increasing the temperature as required (Table 2). Interestingly, the reaction of phenol with 3-(trifluoromethyl)crotonic acid at 50 °C yields the corresponding aryl vinyl ketone product unlike the formation of 3,4-dihydrocoumarins with 2-(trifluoromethyl)acrylic acid (**15**) as reported before [26].

2.1. Comparative study of structures and energies of protonated 4,4,4-trifluorocrotonic acid, protonated 3-(trifluoromethyl)crotonic acid, and their acyl cations (oxocarbenium ions) by ab initio *methods*

To rationalize the formation of the products, calculations of possible protonated/protosolvated 4,4,4-trifluorocrotonic acid species were performed using the Gaussian 09 program [27]. The geometry optimizations were performed at the MP2/6-31G** level. Vibrational frequencies at the MP2/6-31G**//MP2/6-31G** level were used to characterize stationary points as minima (number of imaginary frequency (NIMAG) = 0)) and to evaluate zero point vibrational energies (ZPE) which were scaled by a factor of 0.95 [28]. For MP2/6-31G** structures further geometry optimizations were carried out at the MP2/cc-pVTZ level. Final energies were computed at the MP2/cc-pVTZ//MP2/cc-pVTZ + ZPE level.

Two structures of protonated 4,4,4-trifluorocrotonic acid, oxygen protonated **24**, C=C protonated **25**, were found to be minima on the potential energy surface at the MP2/6-31G** and

Table 2
Synthesis of 4,4,4-trifluoro-3-methyl-1-aryl-2-buten-one (**22**) and 3-methyl-3-(trifluoromethyl)indanone (**23**) from 3-(trifluoromethyl)crotonic acid.

Entry	Arene	Temp (°C)	Time (h)	Products	Yield[a] (%)
a		RT	24		80
		120	24		50
b		RT	6		85
c		RT	5		90
d		RT	10		75
		130	24		60
e		60	24		69
		150	24		55
f		50	24		36, 7

[a] Only *para*-products are formed in the case of toluene, fluorobenzene and chlorobenzene.

MP2/cc-pVTZ levels (Fig. 2). The Cα carbon protonated structure does not correspond to a minimum and converted into **25** upon optimization without any activation barrier. Similarly, the Cβ carbon protonated structure also does not correspond to a minimum and converted into same **25** upon optimization. The structure **24** is 42.3 kcal/mol more stable than structure **25** (Table 3). The calculated Cα=Cβ and Cα–C(CO) distances of **25** are 1.339 Å and 1.441 Å, respectively. The structure **25** is a hydrogen-bridged structure involving a hydrogen and two carbon atoms.

Two isomeric structures, **26** and **27** were located as minima for diprotonated 4,4,4-trifluorocrotonic acid dications (Fig. 2). The structure **26** was characterized as O,O-diprotonated dication. The structure **27** contains a difluorocarbenium unit and a carboxononium unit separated by two carbon atoms and can be characterized as carbenium–carboxononium dication. However, the structure **27** is 34.9 kcal/mol more stable than **26** (Table 2). The central Cα=Cβ bond length of 1.362 Å in **26** is slightly shorter than the Cα–C(CO) bond length of **1** by about 0.04 Å. This is due to extended conjugation between Cα=Cβ double bond, Cα–C(CO) bond and the C=O bond in **26**. Thus, both dications **26** and **27** can be considered as superelectrophiles [29] with greatly increased electrophilic reactivity compared to their parent monoprotonated monocation. Structures of oxocarbenium ion of 4,4,4-trifluorocrotonic acid **28** and its oxygen protonated superelectrophilic **29** were also found to be minima at the MP2/cc-pVTZ level (Fig. 2).

For comparison we have also calculated the structures of protonated 3-(trifluoromethyl)crotonic acid at the same level. Two structures, O-protonated **30** and Cα carbon protonated structure **31** were found to be viable minima on the potential energy surface (Fig. 2). No hydrogen-bridged structure could be located as a minimum. The structure **30** is 33.8 kcal/mol more stable than **31** (Table 3). The structure **31** is in fact a carboxyl, trifluoromethyl substituted tertiary cation.

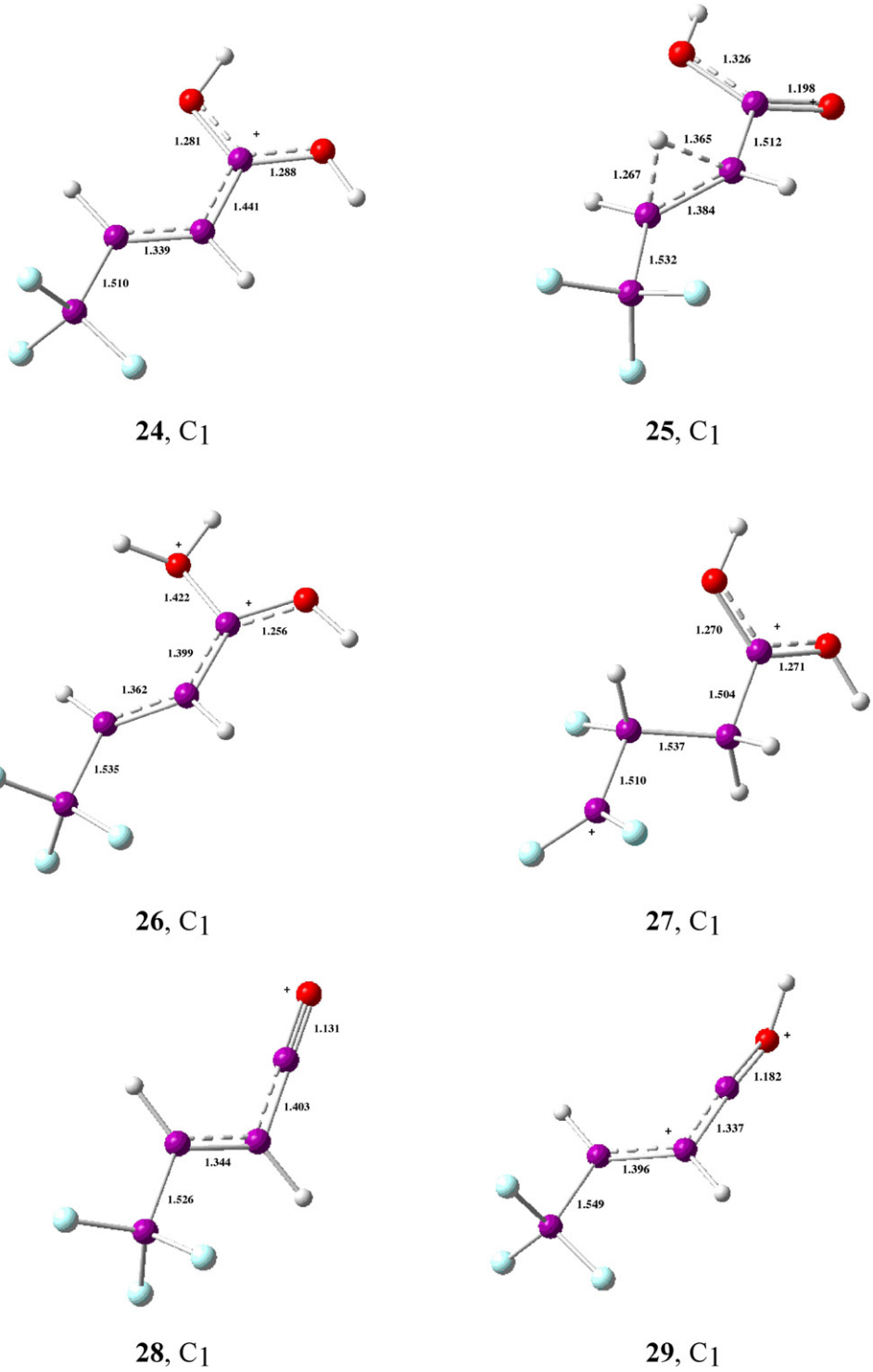


Fig. 2. MP2/cc-pVTZ calculated structure of **24**–**29**.

Two isomeric diprotonated dications, O,O-diprotonated **32** and O-protonated **33** containing a hydrogen-bridged unit were located as minima (Fig. 2). The structure **32** is substantially less stable than the structure **33** by 20.5 kcal/mol (Table 3). The structure **33** contains a protonated ethyl cation unit and a carboxonium ion unit separated by a CH_2 unit. Thus, the structure can be considered as a carbonium–carboxonium dication.

Structures of oxocarbenium ion of 3-(trifluoromethyl)crotonic acid **34** and its oxygen protonated superelectrophilic **35** were also found to be minima at the MP2/cc-pVTZ level (Fig. 3).

2.2. Plausible mechanism

The nature of the products and the results from calculational studies clearly indicate that the possible mechanistic pathway involves protosolvation of crotonic acids leading to superelectrophilic dications **38** through protonation, subsequent dehydration and further protosolvation. Intermolecular Friedel–Crafts acylation leads to the formation of aryl vinyl ketone **21**. Further protosolvation of **21** leads to the superelectrophile **40**, which can either initiate intermolecular Friedel–Crafts alkylation with arene

Table 3
Total energies (-au), ZPE[a] and relative energies (kcal/mol).[b]

	MP2/6-31G**	ZPE (kcal/mol)	MP2/cc-pvtz	Rel. energy
24	602.96737	51.9	603.63974	0.0
25	602.89842	49.4	603.56839	42.3
26	603.01423	57.5	603.68228	34.9
27	603.07050	59.2	603.74065	0.0
28	526.68989	33.7	527.26596	0.0
29	526.67468	39.1	527.24772	16.9
30	642.16300	69.0	642.87484	0.0
31	642.10732	66.3	642.81671	33.8
32	642.22422	74.3	642.93263	20.5
33	642.25828	74.1	642.96505	0.0
34	565.89358	50.8	566.51242	0.0
35	565.90488	55.4	566.51907	0.4

[a] Zero point vibrational energies (ZPE) at MP2/6-31G**//MP2/6-31G** scaled by a factor of 0.95.
[b] Relative energy at MP2/cc-pVTZ//MP2/cc-pVTZ + ZPE level.

toward the formation of dihydrochalcones **20** or undergo intramolecular cycli-alkylation (Nazarov cyclization) leading to indanones **22** depending on the crotonic acid substrate **19a** or **19b** (Scheme 3). Formation of indene **23**, isolated in the case of benzene, can be rationalized by further protonation/protosolvation of the dihydrochalcone **20a** followed by intramolecular cyclodehydration [30].

3. Conclusion

In summary, we have developed a novel and highly efficient direct synthetic route to trifluoromethylated dihydrochalcones, aryl vinyl ketones and indanones based on Friedel–Crafts reaction of 4,4,4-trifluorocrotonic acid **19a** and 3-(trifluoromethyl)crotonic acid **19b** with arenes in superacidic conditions. 4,4,4-Trifluorocrotonic acid and 3-(trifluoromethyl)crotonic acid are found to be highly useful synthetic precursors for the synthesis of a variety of new potent biologically active trifluoromethylated compounds.

4. Experimental

4.1. General

Unless otherwise mentioned, all chemicals were purchased from commercial sources. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on Varian NMR at 400 MHz. ^{1}H NMR chemical shifts were determined relative to internal tetramethylsilane at 0.0 ppm, ^{13}C NMR chemical shifts were determined relative to ^{13}C signal of $CDCl_3$ at 77.0 ppm. ^{19}F NMR chemical shifts were determined relative to internal $CFCl_3$ at 0.0 ppm. HRMS data were obtained from a high resolution Micromass GCT (GC–MS TOF) spectrometer at the Mass Spectrometry Facility, Department of Chemistry, University of Arizona.

4.2. General procedure for the synthesis of trifluoromethylated dihydrochalcones, aryl vinyl ketones and indanones

4,4,4-Trifluorocrotonic acid or 3-(trifluoromethyl)-crotonic acid (2 mmol) was mixed with excess of arene (10 mmol) in a pressure tube. The mixture was cooled to 0 °C and TfOH (3 mL, 34 mmol) was added slowly. The mixture was stirred for the required period of time and temperature (Tables 1 and 2). Progress of the reaction was monitored by TLC (4:1 hexane/ethyl acetate) and ^{19}F NMR spectroscopy. After the reaction was complete the mixture was poured over ice/water (≈25 g) and extracted with CH_2Cl_2 (3× 15 mL). The organic extracts were combined, washed with water and dried over anhydrous Mg_2SO_4. The solvent was removed by vacuum evaporation. The products were characterized by spectral analysis (NMR, GC–MS and HRMS).

*4,4,4-Trifluoro-1,3-diphenyl-1-butanone (**20a**)*

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.58 (dd, J = 17.76, 4.03 Hz, 1H), 3.68 (dd, J = 17.76, 9.16 Hz, 1H), 4.23 (pd, J = 9.52, 4.03 Hz, 1H), 7.27–7.35 (m, 3H), 7.39–7.47 (m, 4H), 7.54–7.59 (m, 1H), 7.91–7.94 (m, 2H); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 38.24 (q, $^{3}J_{(C-F)}$ = 1.2 Hz), 44.76 (q, $^{2}J_{(C-F)}$ = 27.47 Hz),126.94 (q, $^{1}J_{(C-F)}$ = 279.62 Hz), 127.70, 128.01, 128.27, 128.67, 128.70, 129.00, 133.54, 136.25, 195.25; ^{19}F NMR (376 MHz, $CDCl_3$): δ −70.14 (d, $J_{(H-F)}$ = 9.15 Hz); HRMS (EI) m/z calcd. for $C_{16}H_{13}F_3O$ 278.0918, found 278.0913.

*4,4,4-Trifluoro-1,3-bis(*p*-tolyl)butan-1-one (**20b**)*

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.30 (s, 3H), 2.39 (s, 3H), 3.53 (dd, J = 17.70, 4.1 Hz, 1H), 3.65 (dd, J = 17.70, 9.3 Hz, 1H), 4.20 (pd, J = 9.60, 4.06 Hz, 1H), 7.13 (d, J = 7.8, 2H), 7.22–7.28 (m, 4H), 7.82 (dt, J = 8.2, 1.73 Hz, 2H); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 21.034, 21.61, 38.02 (q, $^{3}J_{(C-F)}$ = 1.0 Hz), 44.40 (q, $^{2}J_{(C-F)}$ = 27.47 Hz),126.94 (q, $^{1}J_{(C-F)}$ = 279.8 Hz), 128.13, 128.82, 129.34, 131.57 (q, $^{3}J_{(C-F)}$ = 1.4 Hz), 133.85, 137.96, 144.40, 194.98; ^{19}F NMR (376 MHz, $CDCl_3$): δ −70.27 (d, $J_{(H-F)}$ = 9.7 Hz); HRMS (EI) m/z calcd. for $C_{18}H_{17}F_3O$ 306.1232, found 306.1220.

*4,4,4-Trifluoro-1,3-bis(4-trifluoromethoxyphenyl)butan-1-one (**20c**)*

^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.56–3.70 (m, 2H), 4.26 (pd, J = 9.4, 4.6 Hz, 1H), 7.19 (d, J = 8.1 Hz, 2H), 7.28 (d, J = 8.1 Hz, 2H), 7.43 (d, J = 8.7 Hz, 2H), 7.95–8.00 (m, 2H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ = 38.30 (d, $^{3}J_{(C-F)}$ = 1.6 Hz), 44.17 (q, $^{2}J_{C-F}$ = 27.9 Hz), 120.21 (q, $^{1}J_{(C-F)}$ = 259.1 Hz), 120.35 (q, $^{1}J_{(C-F)}$ = 257.5 Hz), 120.46 (d, J = 1.0 Hz), 121.07 (s), 126.59 (q, $^{1}J_{(C-F)}$ = 279.4 Hz), 130.06 (s), 130.45 (s), 133.00 (d, J = 1.8 Hz), 134.19 (s), 149.15 (d, J = 1.8 Hz), 153.03 (q, J = 1.7 Hz), 193.42 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ = −57.80 (s), −58.00 (s), −69.83 (d, $^{3}J_{(H-F)}$ = 9.5 Hz). HRMS calcd. for $C_{18}H_{11}F_9O_3$ 446.0564, found 446.0561.

*4,4,4-Trifluoro-1,3-bis(4-fluorophenyl)butan-1-one (**20d**)*

^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.37–3.54 (m, 2H), 4.09 (pd, J = 9.5, 4.2 Hz, 1H), 6.83 (t, J = 8.7 Hz, 2H), 6.92 (t, J = 8.6 Hz, 2H), 7.21 (dd, J = 8.6, 5.3 Hz, 2H), 7.77 (dd, J = 8.9, 5.3 Hz, 2H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ = 38.12 (d, $^{3}J_{(C-F)}$ = 1.3 Hz), 44.18 (q, $^{2}J_{(C-F)}$ = 27.7 Hz), 115.61 (d, $^{2}J_{C-F}$ = 21.6 Hz), 115.78 (d, $^{2}J_{(C-F)}$ = 22.0 Hz), 122.70 (d, J = 1.0 Hz), 124.34 (d, J = 3.7 Hz), 126.86 (q, $^{1}J_{(C-F)}$ = 279.3 Hz), 130.06 (d, $^{3}J_{(C-F)}$ = 8.6 Hz), 130.66 (d, $^{3}J_{(C-F)}$ = 9.5 Hz), 162.59 (d, $^{1}J_{(C-F)}$ = 247.2 Hz), 165.99 (d, $^{1}J_{(C-F)}$ = 255.6 Hz), 193.48 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ = −69.96 (dd, J = 9.5, 1.5 Hz), −104.15 (m), −113.69 (m). HRMS calcd. for $C_{16}H_{11}F_5O$ 314.0730, found 314.0740.

*4,4,4-Trifluoro-1,3-bis(4-chlorophenyl)butan-1-one (**20e**)*

^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.59 (qd, J = 17.9, 6.7 Hz, 2H), 4.20 (m, 1H), 7.32 (s, 4H), 7.46–7.41 (m, 2H), 7.83–7.88 (m, 2H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ = 38.11 (s), 44.23 (q, $^{2}J_{C-F}$ = 27.7 Hz), 126.56 (q, $^{1}J_{(C-F)}$ = 279.4 Hz), 128.94 (s), 129.08 (s), 129.38 (s), 130.28 (s), 132.81 (d, $^{3}J_{(C-F)}$ = 1.9 Hz), 140.23 (s), 193.78 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ = −70.21 (d, $^{3}J_{(H-F)}$ = 9.5 Hz). HRMS calcd. for $C_{16}H_{11}Cl_2F_3O$ 346.0139, found 346.0123.

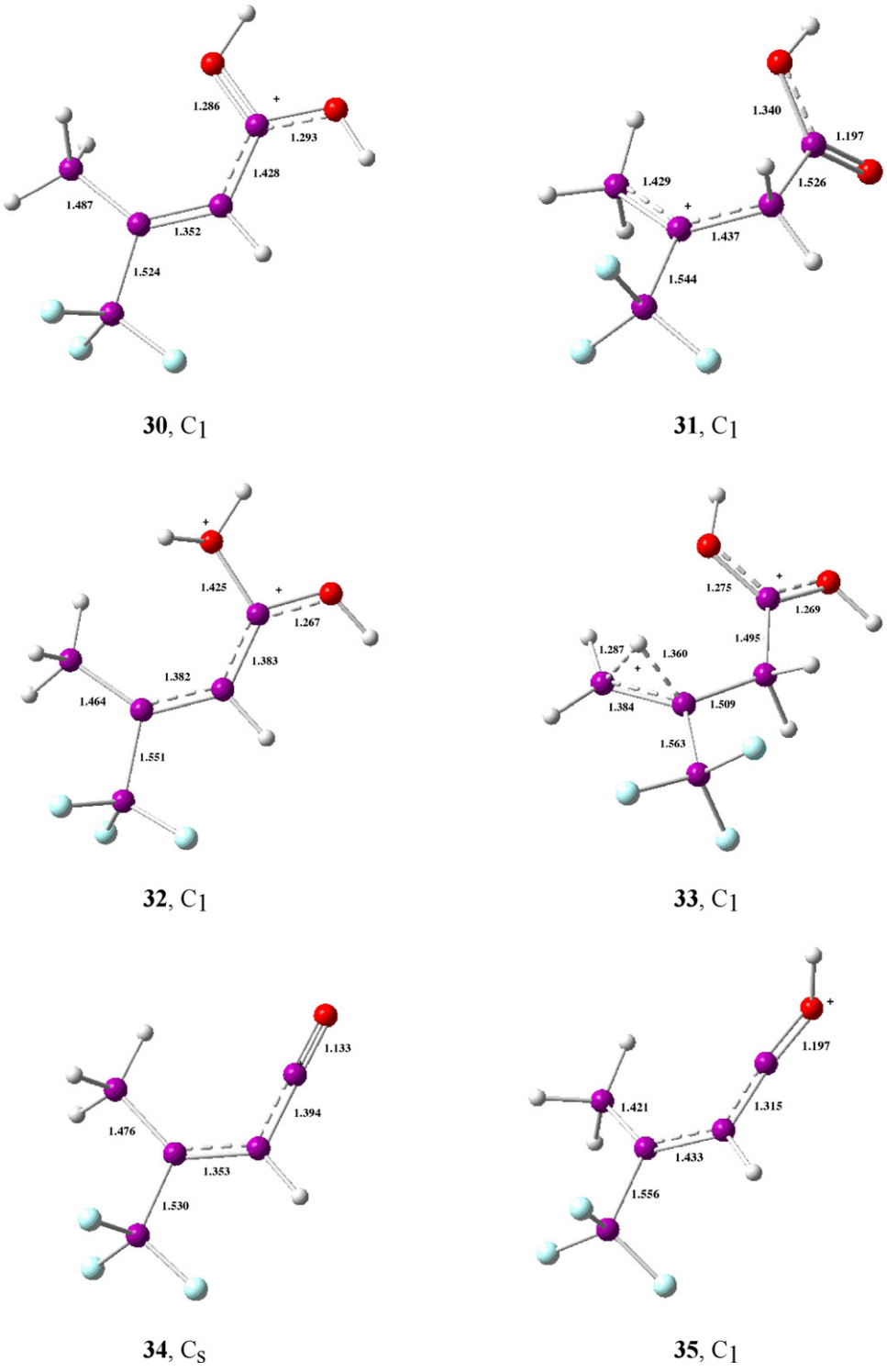


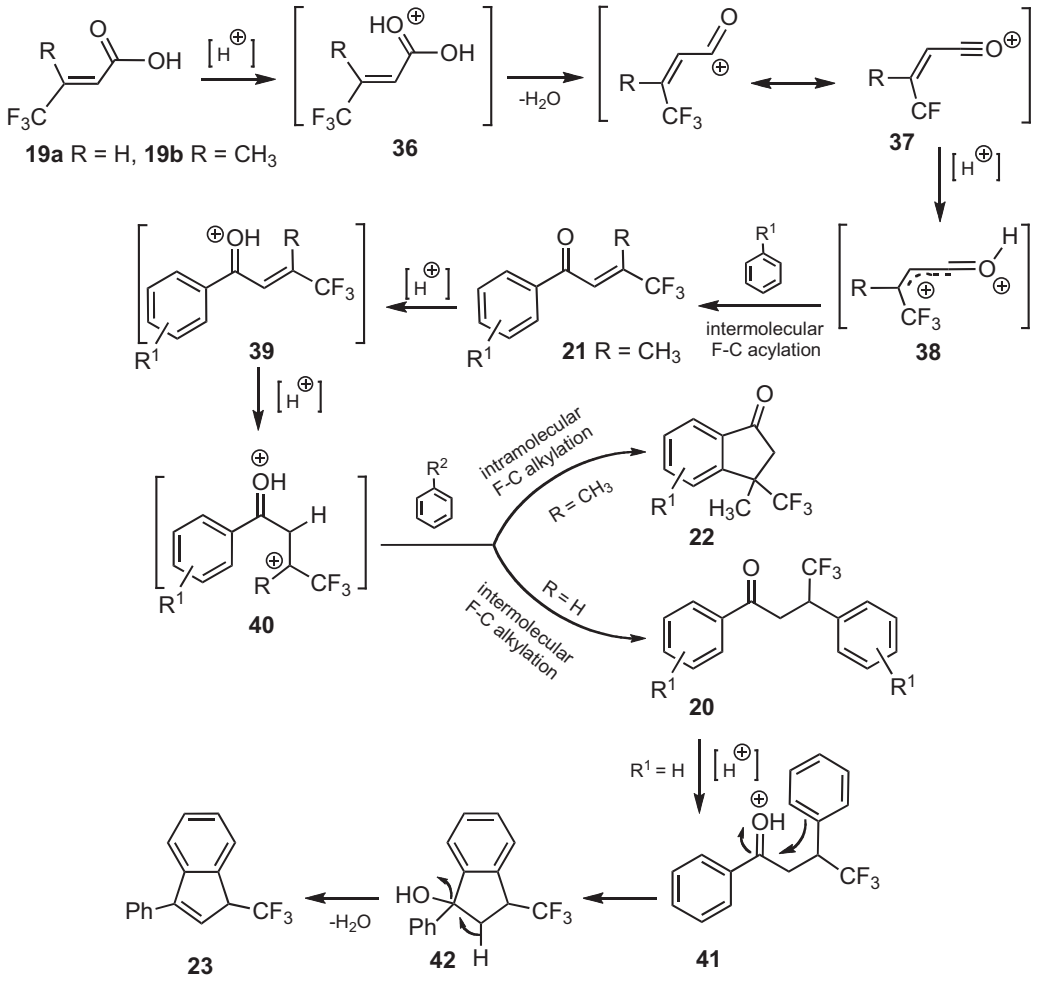
Fig. 3. MP2/cc-pVTZ calculated structure of **30**–**35**.

*4,4,4-Trifluoro-1,3-bis(4-bromophenyl)butan-1-one (**20f**)*

^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.51–3.65 (m, 2H), 4.18 (pd, J = 9.4, 4.4 Hz, 1H), 7.23–7.29 (m, 2H), 7.44–7.49 (m, 2H), 7.57–7.62 (m, 2H), 7.74–7.79 (m, 2H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ = 38.05 (d, J = 1.5 Hz), 44.31 (q, J = 27.8 Hz), 122.58 (s), 122.94–129.21 (q, $^1J_{(C-F)}$ = 281 Hz), 129.02 (s), 129.50 (d, J = 2.5 Hz), 130.63 (s), 131.92 (s), 132.10 (s), 133.34 (d, J = 1.8 Hz), 134.73 (s), 193.98 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ = −70.17 (d, $^3J_{(H-F)}$ = 9.5 Hz). HRMS calcd. for $C_{16}H_{11}Br_2F_3O$ 433.9129, found 433.9150.

*4,4,4-Trifluoro-1,3-bis(3-hydroxy-4-methylphenyl)butan-1-one (**20g**)*

^{1}H NMR (399 MHz, acetone-d_6) δ = 2.01 (s, 3H), 2.06 (s, 3H), 3.35 (dd, J = 17.5, 4.0 Hz, 1H), 3.64 (dd, J = 17.5, 9.4 Hz, 1H), 3.95–4.08 (m, 1H), 6.63 (d, J = 8.3 Hz, 1H), 6.74 (d, J = 8.4 Hz, 1H), 6.96 (dd, J = 8.2, 1.7 Hz, 1H), 7.05 (s, 1H), 7.60 (dd, J = 8.4, 2.2 Hz, 1H), 7.68 (d, J = 1.6 Hz, 1H), 8.16 (s, 1H), 9.05 (s, 1H); ^{13}C NMR (100.5 MHz, acetone-d_6) δ = 15.32 (s), 15.45 (s), 37.15 (s), 44.10 (q, $^2J_{(C-F)}$ = 26.9 Hz), 114.46 (s), 114.64 (s), 124.33 (s), 124.62 (s),



Scheme 3. Suggested mechanism for the formation of dihydrochalcones **20**, aryl vinyl ketones **21**, indanones **22**, and indene **23**.

125.63 (d, $^{3}J_{(C-F)}$ = 1.8 Hz), 127.54 (s), 127.68 (q, $^{1}J_{(C-F)}$ = 278.9 Hz), 128.16 (s), 128.74 (s), 131.49 (s), 131.75 (s), 155.23 (s), 160.34 (s), 193.93 (s); ^{19}F NMR (376 MHz, acetone-d_6) δ = −70.23 (d, $^{3}J_{(H-F)}$ = 10.1 Hz). HRMS calcd. for $C_{18}H_{17}F_3O_3$ 338.1101, found 337.10570 (M^+−H)

*4,4,4-Trifluoro-1,3-bis(2-hydroxy-5-methylphenyl)butan-1-one (**20h**)*

^{1}H NMR (400 MHz, acetone-d_6) δ = 2.17 (s, 3H), 2.26 (s, 3H), 3.76 (dd, *J* = 17.8, 4.9 Hz, 1H), 3.97 (dd, *J* = 17.8, 8.9 Hz, 1H), 4.89 (pd, *J* = 9.8, 4.9 Hz, 1H), 6.76–6.83 (m, 2H), 6.92 (ddd, *J* = 8.2, 2.2, 0.6 Hz, 1H), 7.25 (s, 1H), 7.29 (ddd, *J* = 8.5, 2.1, 0.4 Hz, 1H), 7.89 (d, *J* = 1.3 Hz, 1H), 8.58 (s, 1H), 11.82 (s, 1H); ^{13}C NMR (100 MHz, acetone-d_6) δ = 19.50 (s), 19.71 (s), 36.60 (dd, *J* = 54.2, 26.5 Hz), 37.00 (d, *J* = 1.9 Hz), 115.36 (s), 117.71 (s), 118.91 (s), 120.70 (d, *J* = 1.8 Hz), 127.55 (q, $^{1}J_{(C-F)}$ = 279.5 Hz), 128.17–128.28 (m), 128.54 (s), 129.04 (s), 129.54 (s), 130.18 (s), 137.58 (s), 153.47 (s), 160.18 (s), 202.49 (s); ^{19}F NMR (376 MHz, acetone-d_6) δ = −69.98 (d, $^{3}J_{(H-F)}$ = 9.9 Hz). HRMS calcd. for $C_{18}H_{17}F_3O_3$ 338.1101, found 337.1057 (M^+−H).

*4,4,4-Trifluoro-3-methyl-1-phenyl-2-buten-1-one (**21a**)*

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.15 (d, *J* = 1.46 Hz, 3H), 7.23 (Hept, *J* = 1.46 Hz, 1H), 7.17–7.20 (m, 2H), 7.47–7.52 (m, 2H), 7.60 (tt, *J* = 7.32, 1.55 Hz, 1H), 7.92–7.95 (m, 2H); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 12.50 (q, $^{3}J_{(C-F)}$ = 1.5 Hz), 123.60 (q, $^{1}J_{(C-F)}$ = 273.9 Hz), 126.0 (q, $^{3}J_{(C-F)}$ = 5.1 Hz), 128.70, 129.10, 134.05, 137.40, 139.40 (q, $^{2}J_{(C-F)}$ = 30.2 Hz), 191.81; ^{19}F NMR (376 MHz, $CDCl_3$): δ −71.33; HRMS (ESI), *m*/*z* calcd. for $C_{11}H_9F_3O$ 214.0605, found 214.0600.

*4,4,4-Trifluoro-3-methyl-1-*p*-tolyl-2-buten-1-one (**21b**)*

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.13 (d, *J* = 1.2 Hz, 3H), 2.42 (s, 3H), 7.20 (Hept, *J* = 1.40 Hz, 1H), 7.29 (d, *J* = 8.2 Hz, 2H), 7.83 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 12.54 (q, $^{3}J_{(C-F)}$ = 1.4 Hz), 21.50 123.42 (q, $^{1}J_{(C-F)}$ = 273.9 Hz), 125.89 (q, $^{3}J_{(C-F)}$ = 5.1 Hz), 128.60, 129.45, 134.62, 138.48 (q, $^{2}J_{(C-F)}$ = 30.2 Hz), 144.77, 190.51; ^{19}F NMR (376 MHz, $CDCl_3$): δ −70.91; HRMS (EI) *m*/*z* calcd. for $C_{12}H_{11}F_3O$ 228.0762, found 228.0757.

*4,4,4-Trifluoro-1-(3,4-dimethylphenyl)-3-methyl-2-buten-1-one (**21c**)*

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.13 (d, *J* = 1.4 Hz, 3H), 2.33 (s, 6H), 7.20 (Hept, *J* = 1.40 Hz, 1H), 7.25 (d, *J* = 8.1 Hz, 1H), 7.66 (dd, *J* = 7.7, 1.9 Hz, 1H), 7.71 (d, *J* = 1.4 Hz, 1H); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 12.56 (q, $^{3}J_{(C-F)}$ = 1.5 Hz), 19.57, 19.94, 123.43 (q, $^{1}J_{(C-F)}$ = 273.9 Hz), 126.08 (q, $^{3}J_{(C-F)}$ = 5.2 Hz), 126.33, 129.49, 129.97, 134.94, 137.28, 138.26 (q, $^{2}J_{(C-F)}$ = 30.2 Hz), 143.63, 190.89; ^{19}F NMR (376 MHz, $CDCl_3$): δ −71.26; HRMS (EI) *m*/*z* calcd. for $C_{13}H_{13}F_3O$ 242.0918, found 242.0920.

*4,4,4-Trifluoro-1-(4-fluorophenyl)-3-methyl-2-buten-1-one (**21d**)*

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.16 (d, J = 1.3 Hz, 3H), 7.15–7.21 (m, 3H), 7.95–7.99 (m, 2H); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 12.77 (q, $^3J_{(C-F)}$ = 1.5 Hz), 116.06 (d, $^2J_{(C-F)}$ = 22.1 Hz), 123.31 (q, $^1J_{(C-F)}$ = 273.9 Hz), 125.36 (q, $^3J_{(C-F)}$ = 5.2 Hz), 131.27 (d, $^3J_{(C-F)}$ = 9.5 Hz), 133.55 (d, $^4J_{(C-F)}$ = 2.9 Hz), 139.37 (q, $^2J_{(C-F)}$ = 30.2 Hz), 166.10 (d, $^1J_{(C-F)}$ = 256.2 Hz), 189.42; ^{19}F NMR (376 MHz, $CDCl_3$): δ −71.37 (d, $J_{(H-F)}$ = 1.4 Hz), −103.96 (m); HRMS (ESI), m/z calcd. for $C_{11}H_8F_4O$ 232.0511, found 232.0512.

*4,4,4-Trifluoro-1-(4-chlorophenyl)-3-methyl-2-buten-1-one (**21e**)*

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.16 (d, J = 1.6 Hz, 3H), 7.19 (Hept, J = 1.50 Hz, 1H), 7.46 (dt, J = 8.8, 2.2 Hz, 2H), 7.87 (dt, J = 8.8, 2.2 Hz, 2H); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 12.75 (q, $^3J_{(C-F)}$ = 1.5 Hz), 123.28 (q, $^1J_{(C-F)}$ = 274.13 Hz), 125.04 (q, $^3J_{(C-F)}$ = 5.4 Hz), 129.15, 129.87, 135.47, 139.95 (q, $^2J_{(C-F)}$ = 30.2 Hz), 140.30, 189.59; ^{19}F NMR (376 MHz, $CDCl_3$): δ −71.34; HRMS (ESI), m/z calcd. for $C_{11}H_8ClF_3O$ 248.0216, found 248.0205.

*4,4,4-Trifluoro-1-(4-hydroxyphenyl)-3-methyl-2-buten-1-one (**21f**)*

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.12 (d, J = 1.5 Hz, 3H), 6.41 (br, 1H), 7.46 (dt, J = 8.8, 2.4 Hz, 2H), 7.18 (Hept, J = 1.4 Hz, 1H), 7.89 (dt, J = 8.9, 2.4 Hz, 2H); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 12.75 (q, $^3J_{(C-F)}$ = 1.5 Hz), 115.78, 123.39 (q, $^1J_{(C-F)}$ = 273.8 Hz), 126.21 (q, $^3J_{(C-F)}$ = 5.2 Hz), 130.05, 131.52, 138.30 (q, $^2J_{(C-F)}$ = 30.2 Hz), 161.13, 190.35; ^{19}F NMR (376 MHz, $CDCl_3$): δ −71.27; HRMS (ESI), m/z calcd. for $C_{11}H_9F_3O_2$ 230.0555, found 230.0566.

*3-Methyl-3-(trifluoromethyl)-2,3-dihydro-1*H*-inden-1-one (**22a**)*

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.67 (s, 3H), 2.56 (d, J = 18.9 Hz, 1H), 3.10 (d, J = 19.1 Hz, 1H), 7.51–7.55 (m, 1H), 7.67–7.72 (m, 2H), 7.60 (d, J = 7.8, 1H); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 21.62 (q, $^3J_{(C-F)}$ = 2.20 Hz), 45.47 (q, $^3J_{(C-F)}$ = 1.4 Hz), 47.12 (q, $^2J_{(C-F)}$ = 27.3 Hz),123.92, 125.50, 127.58 (q, $^1J_{(C-F)}$ = 281.33 Hz), 129.56, 135.39, 136.67, 152.64, 202.03; ^{19}F NMR (376 MHz, $CDCl_3$): δ −76.03; HRMS (EI) m/z calcd. for $C_{11}H_9F_3O$ 214.0605, found 214.0596.

*6-Chloro-3-methyl-3-(trifluoromethyl)-2,3-dihydro-1*H*-inden-1-one (**22e**)*

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.65 (s, 3H), 2.57 (d, J = 19.1 Hz,1H), 3.10 (d, J = 19.1 Hz, 1H), 7.41 (dd, J = 8.2, 1.7 Hz, 1H), 7.62 (s, 1H), 7.66 (d, J = 8.2, 1H); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 22.02 (q, $^3J_{(C-F)}$ = 2.20 Hz), 45.77 (q, $^3J_{(C-F)}$ = 1.5 Hz), 47.28 (q, $^2J_{(C-F)}$ = 27.46 Hz),125.04, 125.88, 127.21 (q, $^1J_{(C-F)}$ = 281.20 Hz), 130.35, 135.03, 141.94, 153.92 (q, $^3J_{(C-F)}$ = 1.5 Hz), 202.32; ^{19}F NMR (376 MHz, $CDCl_3$): δ −76.01; HRMS (ESI), m/z calcd. for $C_{11}H_8ClF_3O$ 248.0216, found 248.0205.

*3-(Trifluoromethyl)-2,3-dihydro-1*H*-inden-1-one (**22a′**)*

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.78 (dd, J = 19.23, 3.66 Hz, 1H), 2.91 (dd, J = 19.23, 8.42 Hz, 1H), 4.08 (qd, J = 8.79, 3.66 Hz, 1H), 7.49–7.53 (m, 1H), 7.64–7.68 (m, 2H), 7.80 (d, J = 7.69 Hz, 1H); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 36.93 (q, $^3J_{(C-F)}$ = 2.20 Hz), 42.52 (q, $^2J_{(C-F)}$ = 29.70 Hz), 124.18, 126.25 (q, $^1J_{(C-F)}$ = 278.3 Hz), 127.05, 129.71, 135.28, 137.50, 147.08, 202.09; ^{19}F NMR (376 MHz, $CDCl_3$): δ −70.78 (d, $J_{(H-F)}$ = 9.15 Hz); HRMS (EI) m/z calcd. for $C_{10}H_7F_3O$ 200.0449, found 200.0442.

*1-(Trifluoromethyl)-3-phenyl-1*H*-indene (**23**)*

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.24 (qd, J = 9.4, 2.15 Hz, 1H), 6.42 (d, J = 2.3 Hz, 1H), 7.32 (td, J = 7.5, 0.8 Hz, 1H), 7.36–7.50 (m, 4H), 7.55–7.60 (m, 3H), 7.66 (d, J = 7.4 Hz, 1H); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 52.59 (q, $^2J_{(C-F)}$ = 29.4 Hz), 121.16, 124.72 (q, $^3J_{(C-F)}$ = 5.1 Hz), 124.80, 126.10 (q, $^1J_{(C-F)}$ = 278.3 Hz), 126.32, 127.72, 128.41, 128.51, 128.73, 134.50, 138.66 (q, $^3J_{(C-F)}$ = 2.3 Hz), 144.10, 149.28; ^{19}F NMR (376 MHz, $CDCl_3$): δ −67.78 (d, $J_{(H-F)}$ = 9.15 Hz); HRMS (EI) m/z calcd. for $C_{16}H_{11}F_3$ 260.0813, found 260.0814.

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