organics

MDPI

Review

Synthesis of 1-Trifluorometylindanes and Close Structures: A Mini Review

Olesya V. Khoroshilova [1] and Aleksander V. Vasilyev [1,2,*]

[1] Department of Organic Chemistry, Institute of Chemistry, Saint Petersburg State University, Universitetskaya nab., 7/9, 199034 Saint Petersburg, Russia; o_khorosh@mail.ru
[2] Department of Chemistry, Saint Petersburg State Forest Technical University, Institutsky per., 5, 194021 Saint Petersburg, Russia
* Correspondence: aleksvasil@mail.ru

Abstract: This review describes methods for the synthesis of 1-trifluomethylindanes and close structures, which are still quite rare and scarcely available compounds. There are two main approaches to obtain 1-CF_3-indanes. The first one is the construction of an indane system from CF_3 precursors; the main methods are acid-mediated Friedel–Crafts cyclization, transition metal-catalyzed [3+2] annulation, and free-radical transformations. The second approach is the trifluoromethylation of a ready-made indane core by various CF_3 sources, such as Ruppert–Prakash or Togni reagents. Many of these synthetic procedures possess high regio- and stereo-selectivity, allowing the preparation of unique 1-CF_3-indane structures. In recent years, great attention has been paid to the synthesis of 1-CF_3-indanes, due to the discovery of important biologically active properties for these compounds.

Keywords: 1-trifluorometylindanes; trifluorometylation; indanes; organic synthesis; biologically active properties

Citation: Khoroshilova, O.V.; Vasilyev, A.V. Synthesis of 1-Trifluorometylindanes and Close Structures: A Mini Review. *Organics* **2021**, *2*, 348–364. https://doi.org/10.3390/org2040019

Academic Editor: Stéphane P. Roche

Received: 23 August 2021
Accepted: 16 September 2021
Published: 8 October 2021

1. Introduction

Organofluorine compounds are widely used and are of great importance in chemistry, biology, medicine, agriculture, materials science, and other fields of science and technology. The presence of fluorine atoms in organic molecules significantly changes their chemical (reactivity), physical (high electronegativity), and pharmokinetic (lipophilicity, bioavailability, and metabolic activity) properties. Fluorinated compounds are intensively explored as drugs, agrochemicals, liquid crystals, sensors, nanomaterials, etc. (see books [1–13] on these topics).

One of the most important types of organic compounds is indanes, which possess various valuable practical properties including biological activity. There are several reviews on the synthesis and use of indanes [14–18]. The introduction of a trifluorometyl group CF_3 in the indane core may bring new, important properties for these compounds. For instance, we have recently found that *trans*-1,3-diaryl-1-trifluoromethyl indanes are very good ligands for cannabinoid receptors of CB_1 and CB_2 types. The most potent compound showed sub-micromolar affinity for both receptor subtypes, with six-fold selectivity toward the CB_2 receptor and with no appreciable cytotoxicity toward SHSY5Y cells (Figure 1) [19]. Apart from this, various 1-CF_3-substituted indanes have been tested for the inhibition of monoacylglycerol lipase (MAGL) and anandamide (AEA) uptake; the latter can be related to the low-micromolar inhibition of fatty acid amide hydrolase (FAAH) [20].

Thus, 1-trifluoromethyl indanes are extremely promising objects for medicinal chemistry. The development of novel methods of synthesis of CF_3-indane derivatives and investigation of their biologically active properties is an important goal for chemistry, biology, and medicine. Moreover, these fluorinated derivatives must find broad application in material science and many other fields. However, to the best of our knowledge, CF_3-indanes are still rare compounds. Their synthesis has not yet been developed. This

mini review is focused on current methods of the synthesis of 1-CF_3-indanes including trifluoromethylatedindanols and indanones to show the main approaches to the preparation of these compounds.

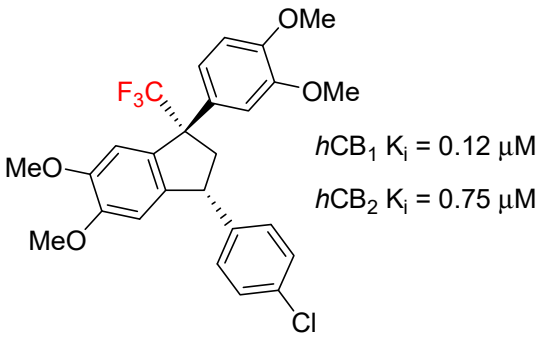


Figure 1. Cannabinoid receptor (CB_1 and CB_2 types) ligand properties of the CF_3-indane (data from ref. [19]).

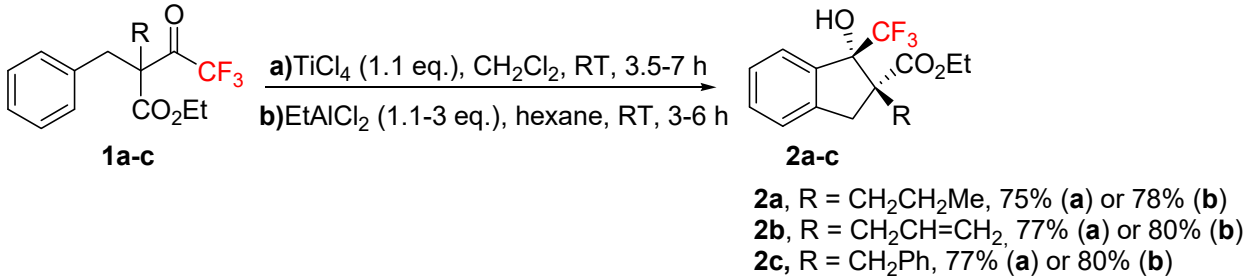
2. Discussion

One may classify the methods for the synthesis of trifluoromethyl indanes into two main approaches. The first one is the construction of an indane system from CF_3 precursors, including acid-mediated electrophilic Friedel–Crafts cyclization, transition metal-catalyzed [3+2] annulation, free-radical transformations, and some other procedures. The second approach is thetrifluoromethylation of suitable indane scaffolds or the reduction of trifluoromethylindene compounds. All these methods are considered in this mini review.

2.1. Construction of Trifluoromethylindane Core from CF_3 Precursors

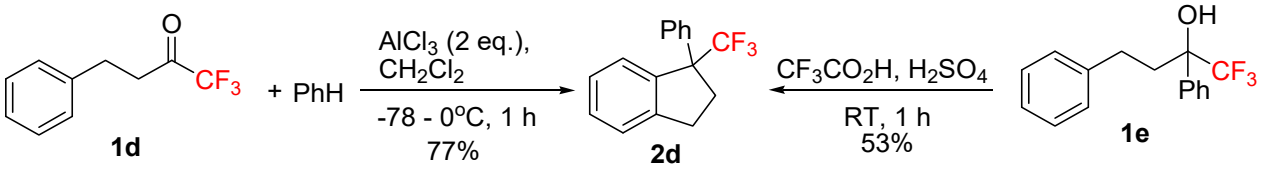
In this type of CF_3-indane synthesis, one of the most effective methods is electrophilic Friedel–Crafts cyclization with the participation of various aromatic substrates having trifluoromethyl substituents.

One of the first reports in this field was published by Béguéet al.in 1989 [21]. The authors described the cycloalkylation of trifluoromethylated β-phenyl ketones, non-enolizable β-keto esters, and alcohols. In this work, the series of 1-trifluoromethylindanes has been prepared by intramolecular Friedel–Crafts alkylation. The best results have been demonstrated by electrophilic activation of the ketone carbonyl group of CF_3-β-keto esters **1a-c** under the action of $TiCl_4$ (conditions **a**) or $EtAlCl_2$ (conditions **b**), which gives 1-trifluoromethylindan-1-ols **2a-c** in excellent yield and perfect stereoselectivity; only one diastereomer was obtained (Scheme 1).



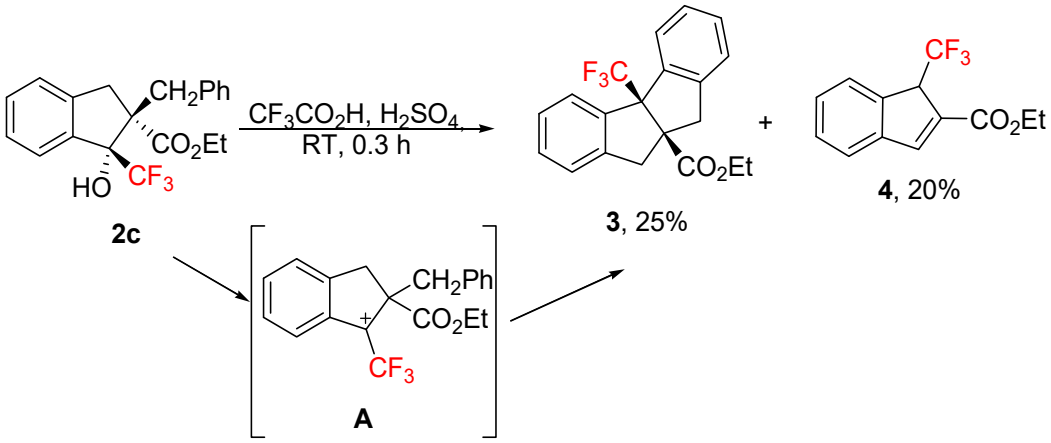
Scheme 1. $TiCl_4$ or $EtAlCl_2$-induced stereoselective synthesis of 1-CF_3-indanes **2a-c** from CF_3-β-keto esters **1a-c**.

Apart from this, in the presence of benzene, as a good trap for intermediate cationic species, the Lewis acid $AlCl_3$-promoted cycloalkylation of β-phenyl CF_3-ketone **1d** furnishes 1-phenyl-1-trifluoromethylindane **2d** in a good yield of 77% (Scheme 2) [21]. Meanwhile, Friedel–Crafts alkylation of tertiary alcohol **1e** in Brønsted acids (CF_3CO_2H, H_2SO_4) affords compound **2d** in a lower yield of 53%.



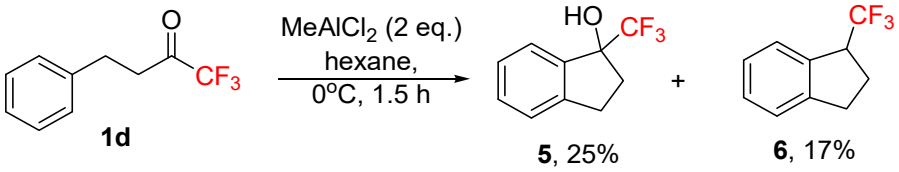
Scheme 2. Synthesis of 1-CF_3-indane **2d** from CF_3-ketone **1d** or from CF_3-alcohol **1e**.

Remarkably, indanol **2c** under the same protosolvolytic conditions in CF_3CO_2H, H_2SO_4, as for alcohol **1e**, is transformed into intermediate cation **A,** which is cyclized to tetracyclic compound **3** (condensed bis-indane structure) and partially undergoes fragmentation to CF_3-indene **4** (Scheme 3).



Scheme 3. Transformation of 1-CF_3-indane **2c** into compounds **3** and **4** in CF_3CO_2H, H_2SO_4.

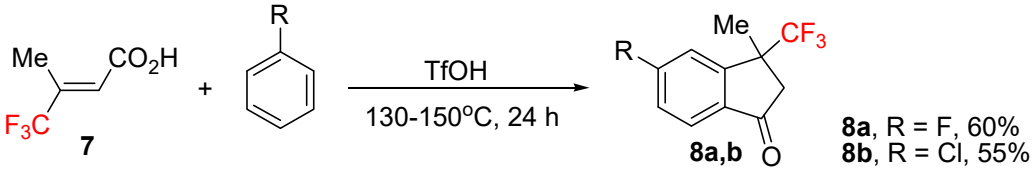
In the absence of benzene at 0 °C, CF_3-ketone **1d** reacts very slowly with $AlCl_3$,affording polymeric materials, and does not react with $TiCl_4$. However, in the presence of $MeAlCl_2$, ketone **1d** is cyclized into a mixture of indanol **5** and the reduced indane **6** in low yields [21] (Scheme 4).



Scheme 4. $MeAlCl_2$-promoted synthesis of 1-CF_3-indan-1-ol **5** and 1-CF_3-indan **6** from CF_3-ketone **1d**.

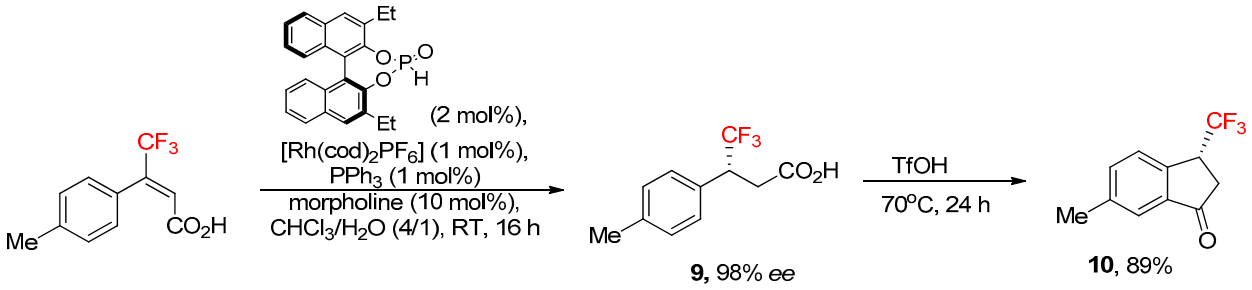
Later on, the same scientific group developed Lewis acid ($TiCl_4$ or $EtAlCl_2$)-induced ene-cyclization of ω-olefinic CF_3-ketones into trifluoromethyl carbocycles [22]. However, in this reaction, phenyl substituted substrate **1b** gives 1-CF_3-indanol **2b** (see in Scheme 1), rather than the expected cyclopentanes, as products of the cyclization of the carbonyl group onto the alkene bond.

Prakash et al. have shown the formation of CF_3-indanones **8a,b** by the reaction of 3-(trifluoromethyl)crotonic acid **7** with haloarenes in neat Brønsted superacid, triflic acid TfOH (CF_3SO_3H), at 130–150 °C for 24 h (Scheme 5) [23]. This reaction initially proceeds at room temperature as the Friedel–Crafts acylation of arenes by acid **7**, leading to the corresponding 1-aryl-3-CF_3-butenones, which may be intermolecularly cyclized into CF_3-indanones at higher temperatures under superacidic reaction conditions.



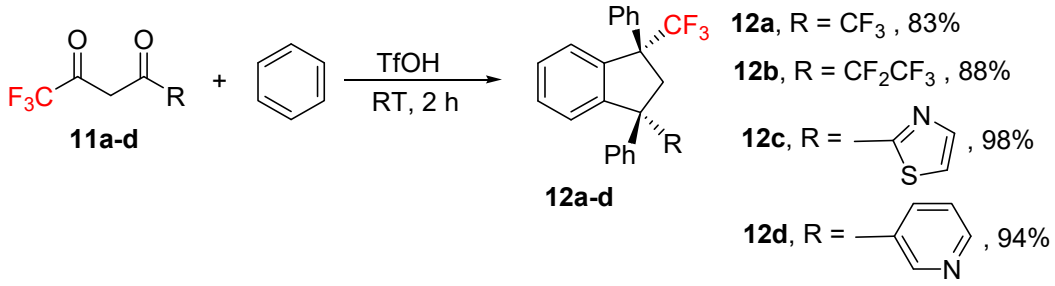
Scheme 5. Reaction of 3-CF_3-crotonic acid **7** with arenes in neat TfOH, resulting in CF_3-indanones **8a,b**.

Similar cyclization of enantiomeric CF_3-acid **9** into indanone **10** in TfOH has been described in work [24] (Scheme 6). The starting compound **9** was obtained by rhodium(I)-catalyzed asymmetric hydrogenation of the corresponding β-CF_3-substituted acrylic acid.



Scheme 6. Cyclization of CF_3-acid **9** into CF_3-indanone **10** in TfOH.

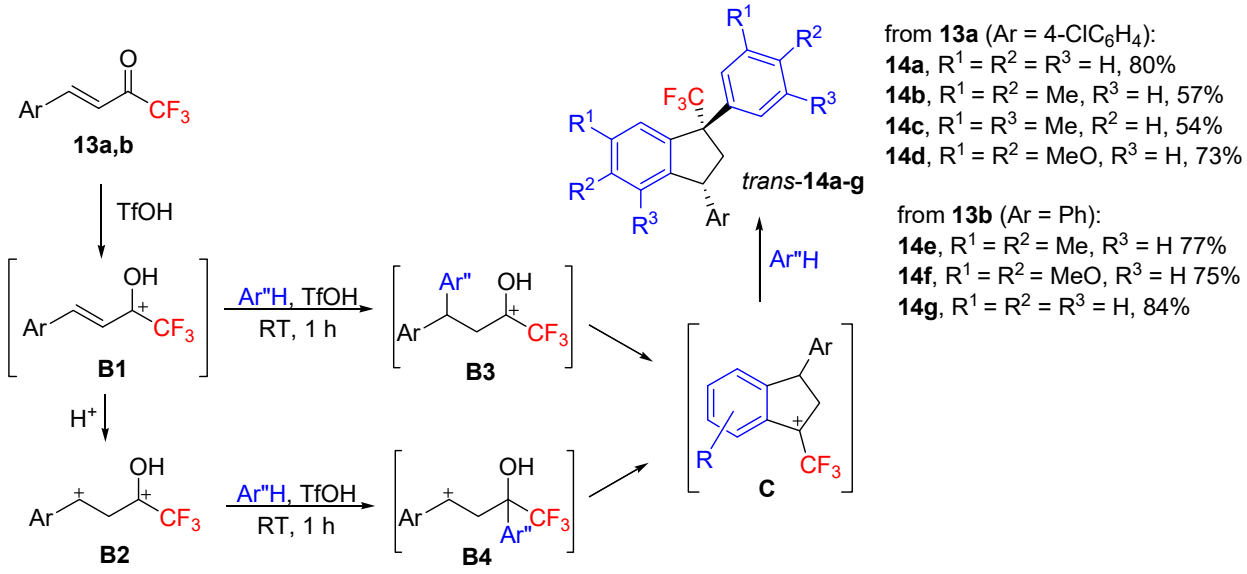
Fruitful CF_3 precursors for the building of an indane core under electrophilic activation conditions are trifluoromethyl ketones. Thus, CF_3-β-diketones bearing trifluoroalkyl or heterocyclic substituents **11a-d** in reaction with benzene in neat TfOH give stereoselective 1-CF_3-indanes **12a-d** having phenyl groups in the *cis*-position relative to the indane plane [25] (Scheme 7). There is an electrophilic activation of carbonyl carbons in diketones **11a-d** due to the protonation of carbonyl oxygens and heteroatoms (for **11c,d**) in Brønsted superacid TfOH. The generated cationic species react, in a cascading manner, with three molecules of benzene, leading finally to CF_3-indanes **12a-d**. The authors have explained the reaction's stereoselectivity by possible cation π-stacking stabilization between phenyl groups in intermediate cations [25].



Scheme 7. Synthesis of 1-CF_3-indanes **12a-d** by reaction of CF_3-β-diketones **11a-d** with benzene in TfOH.

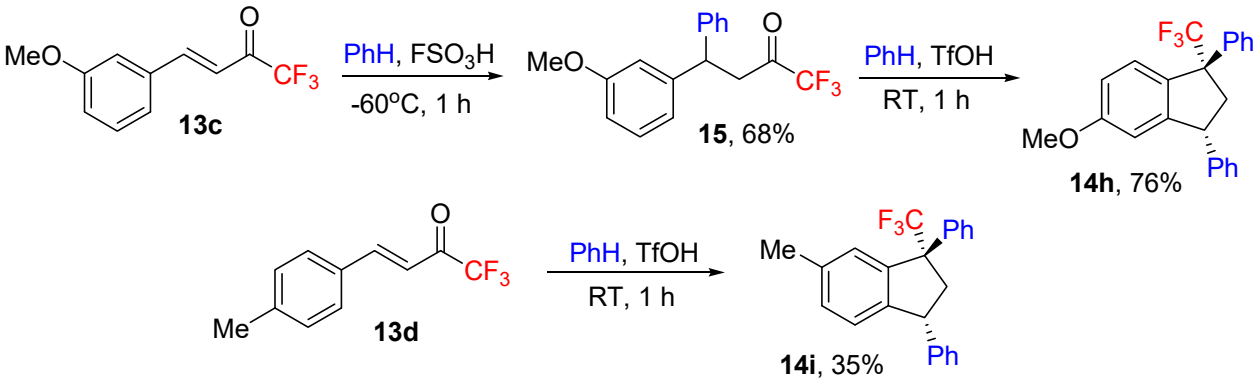
A similar approach has been used in works [19,26] for the cyclization of CF_3-enones, 1,1,1-trifluorobut-3-en-2-ones **13a,b**, in their reaction with arenes in TfOH, affording 1,3-diaryl-substituted 1-trifluoromethylindanes **14a-g** with an exclusively *trans*-configuration of aryl groups (Scheme 8). Protonation of the enone system of **13a,b** may give rise to either monocationic species **B1** or dications **B2**, which further interact in two pathways with two molecules of arene, forming indanes **14a-g** through the intermediate formation of cations **B3** or **B4**, and **C**. The excellent stereoselectivity of this reaction may be explained by the intermediate formation of cation **C**, which reacts with an arene molecule, which gives a more stable *trans*-orientation of bulky aromatic rings. It should be noted that the high sensitivity to steric effects of substituents in arenes in this transformation results also in the

formation of an unexpected product of electrophilic attack to position 5 of m-xylene for compound **14c** [19].



Scheme 8. Stereoselective synthesis of *trans*-1-CF_3-indanes **14a-g** from CF_3-enones **13a,b** and arenes in TfOH.

Running this reaction in another Brønsted superacid FSO_3H at a low temperature of −60 °C for enone **13c** and benzene, the authors have been able to obtain intermediate ketone **15**, as a product of the initial addition of benzene to the double carbon–carbon bond (Scheme 9) [19]. Then, compound **15** is cyclized into 1-CF_3-indane **14h** in reaction with benzene in TfOH at room temperature. The cyclization results in a more nucleophilic methoxy-substituted aromatic ring; the same regioselectivityis observed upon the formation of indane **14i** from enone **13d**.



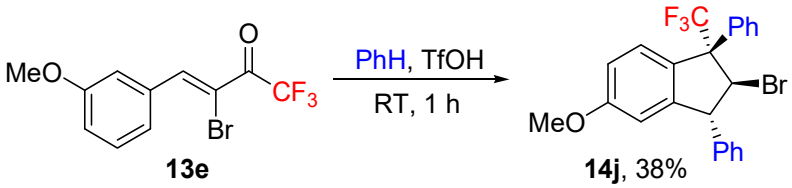
Scheme 9. Synthesis of 1-CF_3-indanes **1h,i** from CF_3-enones **13c,d** and benzene.

It has been found that these diaryl-substituted *trans*-1-CF_3-indanes **14** show high activity towards cannabinoid receptors of CB_1 and CB_2 types [19] (see Introduction).

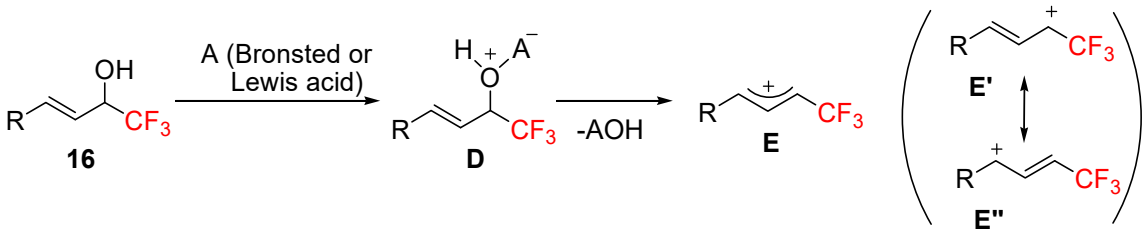
Under similar superelectrophilic activation conditions in TfOH, bromo-substituted CF_3-enone **13e** in reaction with benzene is stereoselectively transformed into 1-CF_3-bromoindane **14j** in moderate yield (Scheme 10) [27].

In the series of papers [19,28–30], it has been demonstrated that trifluoromethylatedallyl alcohols and their trimethylsilyl (TMS) ethers are good precursors for the preparation of 1-CF_3-indanes. The protonation of oxygen of CF_3-allyl alcohols with Brønsted acid or coordination of oxygen with Lewis acid gives rise to species **D**; dehydroxylation of the latter affords CF_3-allyl cations **E**, having two resonance forms **E′** and **E″**, with electrophilic centers on the ends of the allylic system. Both species **D** and **E** (**E′**↔**E″**) may take part in

interaction with aromatic nucleophiles, which depends on substituents in species **D** and **E** and the nucleophilicity of arenes (Scheme 11).

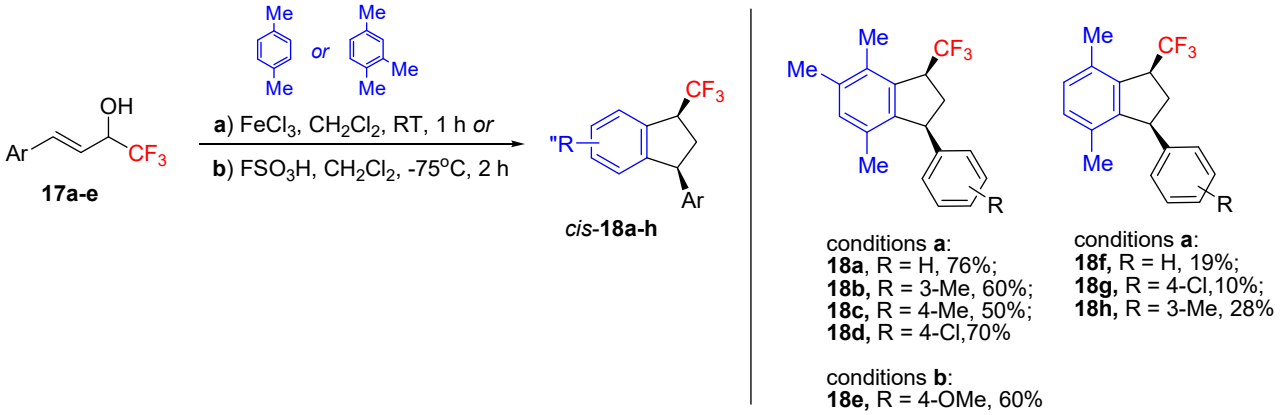


Scheme 10. Synthesis of 1-CF_3-indane **14j** from bromo-CF_3-enone **13e** and benzene in TfOH.



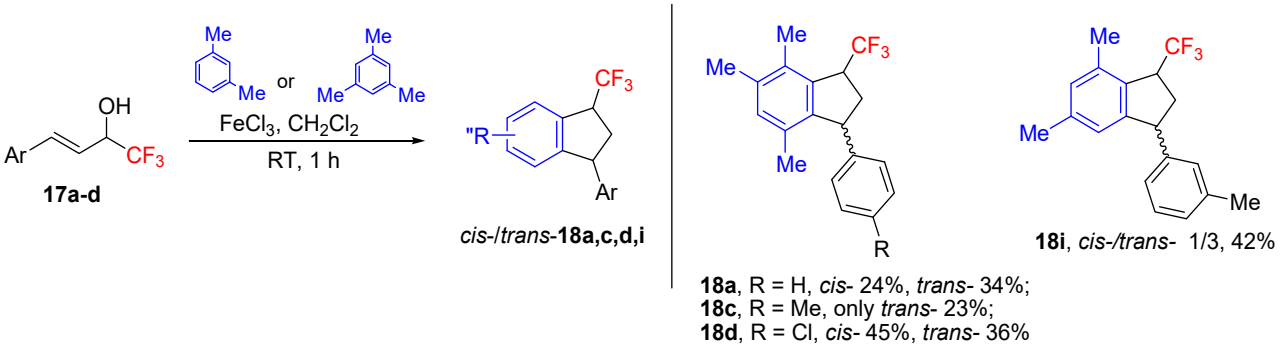
Scheme 11. Generation of species **D** and **E** (**E′**↔**E″**) from CF_3-allyl alcohols **16** under the action of Brønsted or Lewis acids.

Thus, the reaction of CF_3-allyl alcohols **17** with electron-donating arenes under the action of Lewis acid $FeCl_3$ at room temperature or Brønsted superacid FSO_3H at −75 °C can be used to obtain monoarylatedtrifluoromethylindanes **18a-h** (Scheme 12) [28]. Reactions with *p*-xylene and pseudocumene demonstrate high stereoselectivity, affording only *cis*-CF_3-indanes **18a-h**. More striking results are obtained for the reactions with pseudocumene, leading to 50–76% yields of target products. However, the interaction with *p*-xylene gives alkenes [Ar(2,5-$Me_2C_6H_3$)CHCH=$CHCF_3$] as major products.



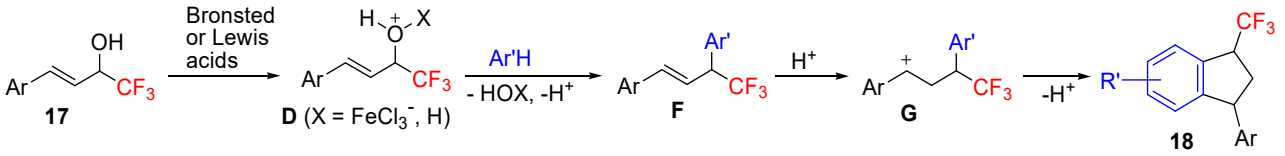
Scheme 12. Stereoselective synthesis of *cis*-1-CF_3-indanes **18a-h** from CF_3-allyl alcohols **17a-e** and donating arenes under the action of Lewis acid $FeCl_3$ or Brønsted superacid FSO_3H.

The use of mesitylene results in the formation of the same indanes **18a-d** (Scheme 13), as in the case of pseudocumene (Scheme 12), due to the methyl group shift during the electrophilic aromatic substitution step. However, both the yields of the target reaction products and stereoselectivity are lower compared to the reaction with pseudocumene (compare Schemes 12 and 13). The formation of a *cis*-/*trans*-isomeric mixture for indane **18i** is also observed in reaction with *m*-xylene (Scheme 13) [28].



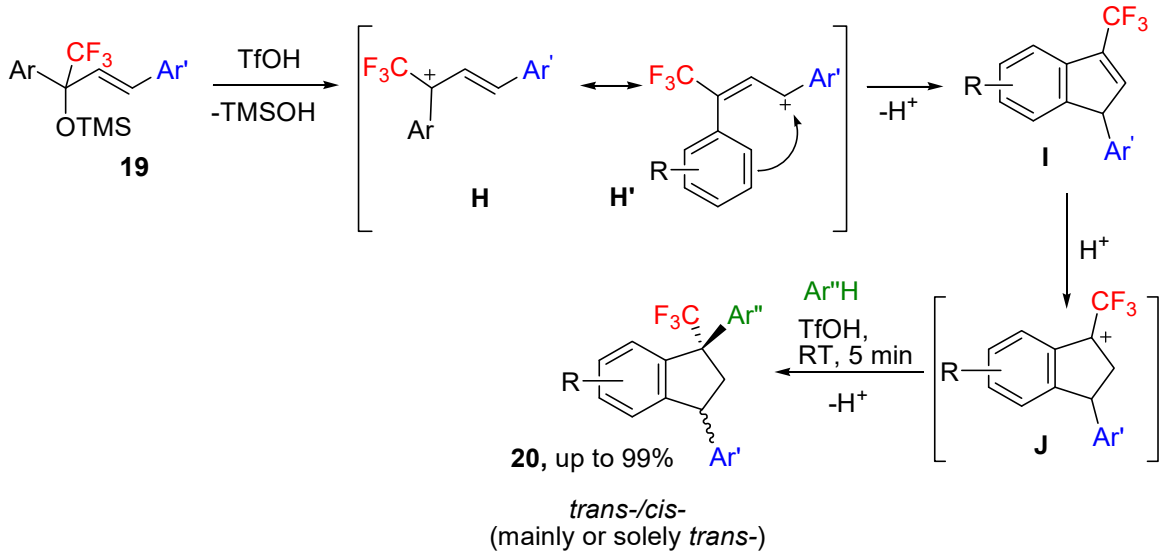
Scheme 13. Synthesis of 1-CF_3-indanes **18a,c,d,i** from CF_3-allyl alcohols **17a-d** and arenes.

A plausible mechanism of Brønsted or Lewis acid-promoted formation of 1-CF_3-indanes **18** from CF_3-allyl alcohols **17** and arenes includes the initial generation of species **D** (Scheme 14). The latter possesses a sufficiently electrophilic reactive center on allylic carbon to interact with polymethylatedπ-donating arenes, giving alkenes **F**, which are protonated to form cations **G**. Cyclization of the latter furnishes finally indanes **18** [28].



Scheme 14. Possible mechanism of acid-promoted formation of 1-CF_3-indanes **18** from CF_3-allyl alcohols **17** and arenes.

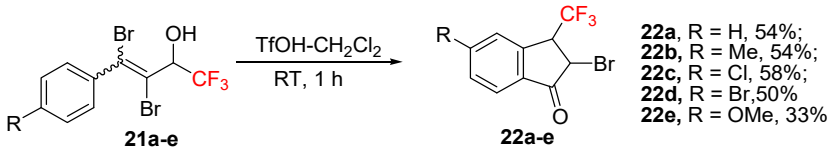
The same approach of superelectrophilic activation of TMS-ethers of diaryl-substituted CF_3-allyl alcohols **19** in TfOH has been applied in the synthesis of 1-CF_3-indanes **20** (Scheme 15) [29]. This reaction has been studied for a broad series of starting alcohols **19**. The reaction proceeds very rapidly, within just 5 min, at room temperature, and leads mainly to indanes **20** with *trans*-configuration of aryl groups in high yields. At the first stage of this transformation, there is an intermediate generation of allyl cation **H**↔**H′**, which is cyclized into indene **I**. Protonation of the latter gives rise to cation **J**, which reacts with the arene, forming 1-CF_3-indane **20**. The predominant formation of *trans*-indanes **20** is probably explained by sterical hindrance between aryl moieties Ar′ and Ar″ at the last stage of the reaction (Scheme 15) [29].



Scheme 15. TfOH-promoted synthesis of 1-CF_3-indanes **20** from CF_3-allyl alcohols **19** and arenes.

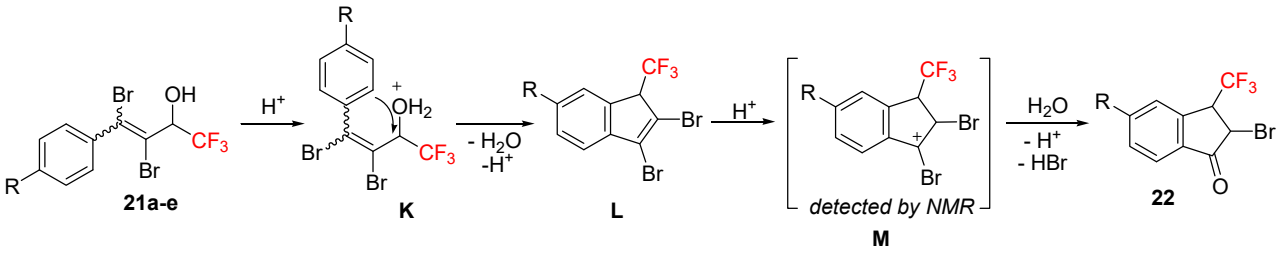
Apart from this, the TfOH-promoted reaction of TMS-ethers **19** and their corresponding alcohols with arenes have been used for the stereoselective synthesis of several *trans*-1-CF_3-indanes **20** to study their biologically active properties [20] (see Introduction).

Cyclization of dibromo-CF_3-allyl alcohols **21a-e** into CF_3-indanones **20a-e** in TfOH-CH_2Cl_2 has been described in work [30] (Scheme 16). This reaction is in concurrence with the formation of 2,3-dibromo-1-CF_3-indenes. It has been found that prolongation of the reaction to1 h leads to the exclusive or predominant formation of indanones **22**.



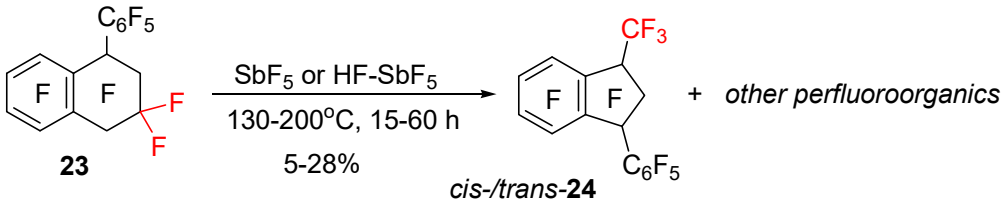
Scheme 16. Cyclization of dibromo-CF_3-allyl alcohols **21a-e** into CF_3-indanones **22a-e** in TfOH-CH_2Cl_2.

A plausible mechanism of the cyclization includes the formation of O-protonated cation **K**, which is cyclized into indene **L** (Scheme 17). Subsequent protonation of the formed indene gives rise to cation **M**, which has been studied by NMR in TfOH. The quenching of the reaction mixture with water leads to CF_3-indanone **22** along with 2,3-dibromo-1-CF_3-indenes; the latter are formed at the deprotonation of species **M** [30].



Scheme 17. Plausible mechanism of cyclization of dibromo-CF_3-allyl alcohols **21a-e** into CF_3-indanones **22a-e** in TfOH-CH_2Cl_2.

Karpov et al., in their study on the synthesis and reactions of perfluorinated aromatics, have found an interesting transformation of perfluoro-1-phenyltetralin **23** into 1-CF_3-perfluoroindane **24**, along with other perfluoroorganics, under the action of SbF_5or the system HF-SbF_5underharshconditions at 130–200 °C in a nickel autoclave (Scheme 18) [31]. The authors explain the formation of indane **24** by multi-step cationic transformations of starting tetralin **23**, in which one of the CF_2 groups is transformed into a CF_3-substituent of **24** under a ring contraction process. Later on, the same group developed the synthesis of perfluorofluorenes, containing a 1-CF_3-indane structural fragment, by the reaction of perfluoro-1,1-diphenylalkanes with SbF_5 [32].

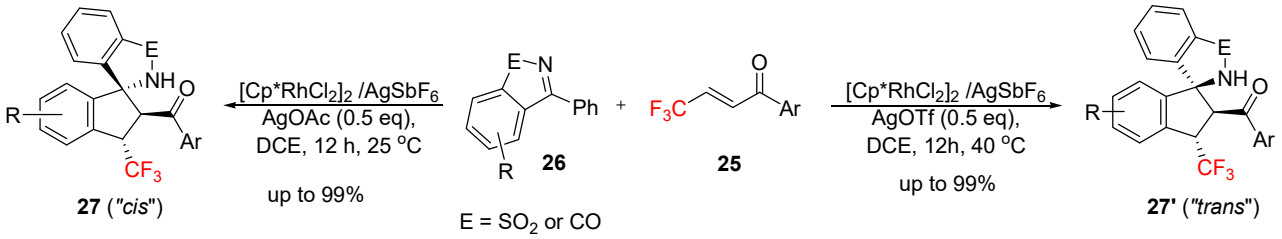


Scheme 18. Synthesis of 1-CF_3-perfluoroindane **24** from perfluoro-1-phenyltetralin **23** under the action of SbF_5 and HF.

One more promising approach to the building of a 1-CF_3-indane core is the transition metal-catalyzed [3+2] annulation of various CF_3 precursors.

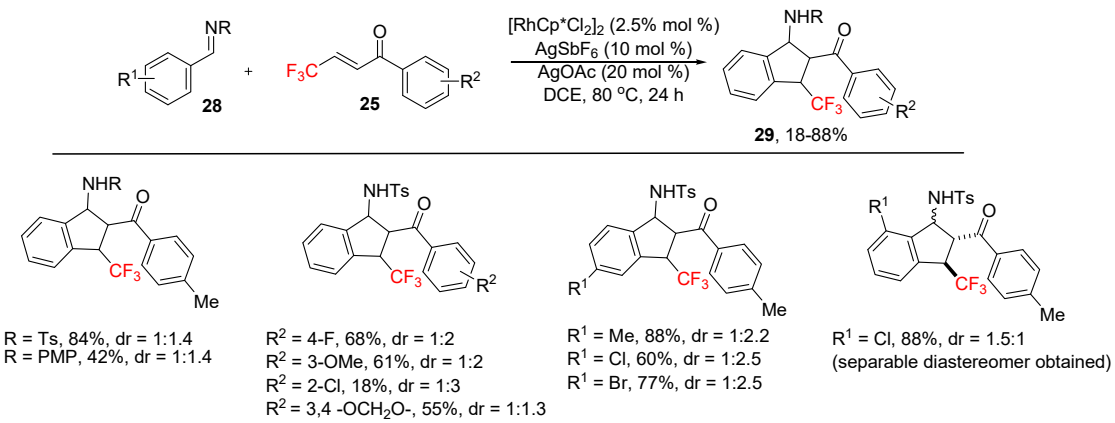
Trifluoromethyl-substituted enones containing a CF_3 group at the carbon–carbon double bond have found successful application in Rh(III)-catalyzed [3+2] annulation via

C-H activation. Thus, Li et al. have investigated reactions of cyclic-*N*-sulfonyl and *N*-acyl ketimines **26** with *β*-CF_3-enones **25** (Scheme 19) [33]. This coupling furnishes a set of diverse spirocycles **27** and **27′** with three stereogenic centers, stereochemistry of which can be regulated by silver additives. For *N*-sulfonyl ketimines, it has been found that the use of AgOAc increases the yield of diastereomer **27** with the*cis*-orientation of CF_3 and NH groups. Meanwhile, the application of AgOTf shifts thediastereomer ratio in favor of another isomer **27′** with *trans*-orientation of these moieties. In contrast to this, for the annulation of *N*-acyl ketimines, the use of a AgTFA additive increases the yields of diastereomers, and diastereomer **27′** is formed in a predominant amount. The authors have extensively studied the scope and limitations of this reaction. The yields of target products **27** and **27′** are increased by electron-donating groups in the *para*-position of *N*-sulfonyl and *N*-acyl ketimines, such as the methoxy group, and decreased by electron-withdrawing groups, such as fluorine. It is worth mentioning that the use of the *N*-sulfonyl ketimine with the *o*-methoxyphenyl substituent resulted in the formation of only one diastereomer **27′** due to steric hindrance affected by the transition state during the insertion of the imine group. The reaction results in a broad range of CF_3-enones **25**. In this way, substrates bearing both electron acceptors (4-NO_2, 2-CF_3, halogens) and donors (4-OMe, 2-Me, 3-Me-, 2,4-Me_2 or 3,4-OMe_2) in the aryl ring of **25** demonstrate moderate to excellent yields of the target products and high stereoselectivity [33].



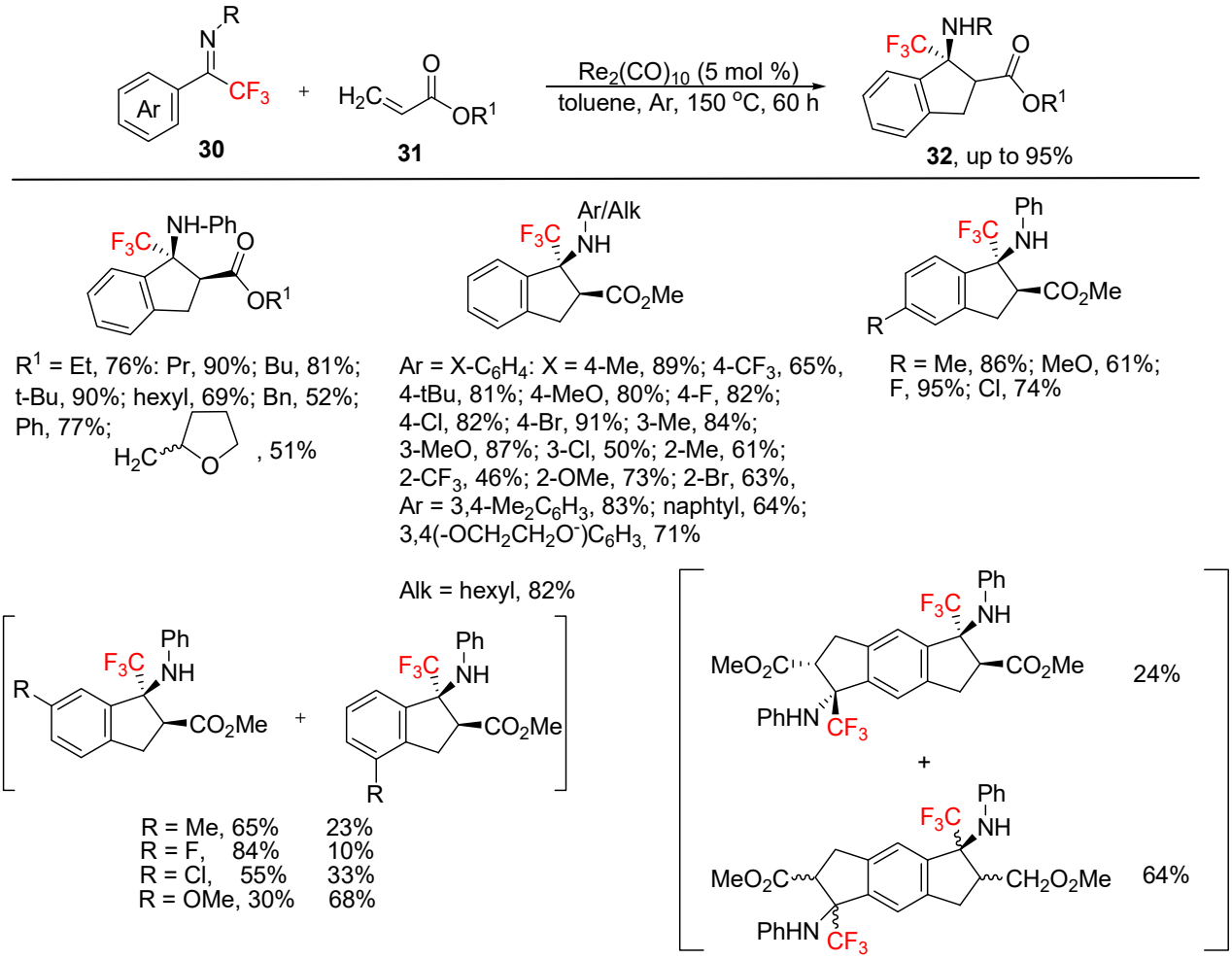
Scheme 19. Synthesis of 1-CF_3-indanespirocycles **27** and **27′** by Rh(III)-catalyzed [3+2] annulation of *β*-CF_3-enones **25** with cyclic-*N*-sulfonyl and *N*-acyl ketimines **26**.

The substrate scope of Rh(III)-catalyzed [3+2] annulation with participation of *β*-CF_3-enones **25** has been expended to acyclic aldimines **28** by Sharma et al. (Scheme 20) [34]. This reaction affords an inseparable diastereomeric mixture of CF_3-aminoindanes **29**. Contrary to cyclic ketimines **26** (Scheme 19), such high diastereoselectivity in reactions of aldimines **28** has not been observed, presumably due to the lower steric hindrance for non-cyclic compounds **28**. Various tosylaldimines and N-(*p*-methoxyphenyl)aldimine, in contrast to tosylhydrazone, have been successfully involved in this coupling. At the same time, the reaction with *β*-CF_3-enones **25**, containing electron-rich aryl rings, gives CF_3-aminoindanes **29** in moderate to high yields, whereas the use of compounds **25** with electron-withdrawing substituents in the aryl moiety leads to the target products **29** in lower yields.



Scheme 20. Synthesis of CF_3-aminoindanes **29** by Rh(III)-catalyzed [3+2] annulation of *β*-CF_3-enones **25** with aldimines **28**.

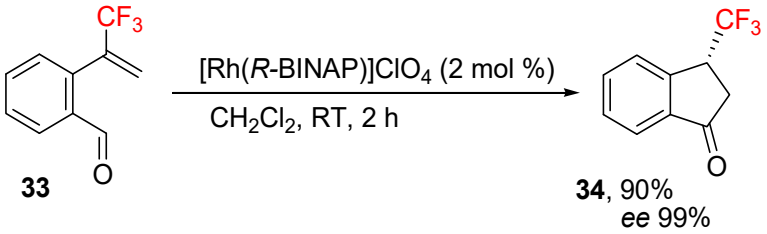
Another type of fluorinated substrate for transition metal-catalyzed [3+2] annulationvia C−H activation is CF_3-ketimines **30** (Scheme 21). Xiong, Zhang et al. [35] have found that the Re-catalyzed reaction of CF_3-ketimines **30** with alkyl acrylates **31** results in the formation of compounds **32**, having geminal trifluoromethyl and amino substituents along with a vicinal ester group in the indane core. CF_3-aminoindanes **32** are important precursors for the synthesis of fluorinated *β*-amino acids. CF_3-ketimines **30** bearing both electron-rich and -poor aromatic substituents as well as an alkyl group in the amine part can be successfully involved in this coupling. The reaction is also tolerated by various *para*- and *meta*-substituents in the aryl group in the ketone part of **30**. Remarkably, due to steric factors, only one regioisomer **32** with *cis*-configuration is formed. It is worth mentioning that *meta*-substituted ketimines **30** give two regioisomers of desirable products in excellent general yields. Moreover, the interaction of diketimine with acrylate affords two regioisomers of the tricyclic skeleton, bearing two CF_3-amino-esterindane moieties in high yield.



Scheme 21. Synthesis of CF_3-aminoindanes **32** by Re-catalyzed [3+2] annulation of CF_3-ketimines **30** with alkyl acrylates **31**.

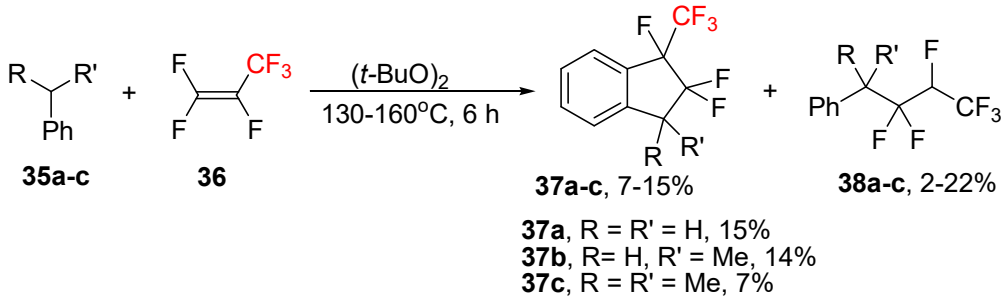
One more example of the transition metal-catalyzed construction of a 1-CF_3-indane core is the stereoselective Rh(I)-catalyzed intramolecular hydroacylation of 2-(1-CF_3-ethenyl)benzaldehyde **33**, furnishing CF_3-indanone **34** in high yield and with high *ee* value (Scheme 22) [36].

There are some methods forbuilding CF_3-indane systems on the basis of free-radical transformations.



Scheme 22. Stereoselective synthesis of CF_3-indanone **34** by Rh(I)-catalyzed intramolecular hydroacylation of 2-(1-CF_3-ethenyl)benzaldehyde **33**.

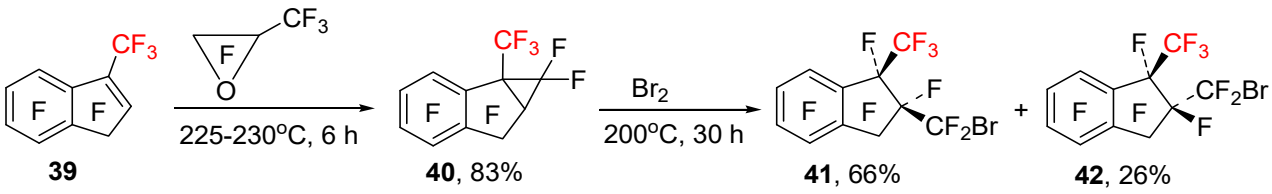
Kimoto et al. have studied di-*t*-butylperoxide-induced reactions of alkylbenzenes **35a-c** with hexafluoropropene **36** under harsh conditions (130–160 °C, 6 h) (Scheme 23) [37]. One of the reaction products is fluorinated 1-CF_3-indanes **37a-c**, along with fluoroalkyl arenes **38a-c** and other unidentified substances. However, the yields of the obtained compounds are rather low. The initial step in the reaction is the generation of a phenylmetyl radical, which is added to the double bond of **36**, and then transformations of secondary radical species lead to 1-CF_3-indanes **37a-c**. Later on, this scientific group, using the same radical reaction between hexafluoropropene **36** and benzaldehyde, prepared 2,2,3-trifluoro-3-trifluoromethylindan-one, which was transformed to other 1-CF_3-indanes by reactions onto carbonyl group [38].



Scheme 23. Synthesis of 1-CF_3-indanes **37a-c** by free radical reaction of alkylbenzenes **35a-c** with hexafluoropropene **36**.

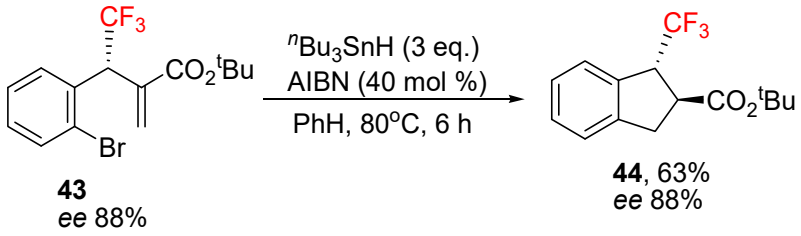
The reaction between substrates **35** and **36** has been also investigated by Haszeldine et al. under thermal conditions at 250 °C without the addition of any peroxide for the initiation; however, target 1-CF_3-indanes **37** have been obtained in very low yields [39].

The synthesis of diastereomeric 1-CF_3-indanes **41** and **42** has been described in work [40] (Scheme 24). Starting 1-CF_3-perfluoroindene **39** is subjected to cyclopropanation by difluorocarbene generated from hexafluoropropylene oxide that gives compound **40**. The latter is brominated under thermal conditions (intermediate free-radical species generation) with the formation of 1-CF_3-indanes **41** and **42** in a ratio of 2.5 : 1 in a good general yield.



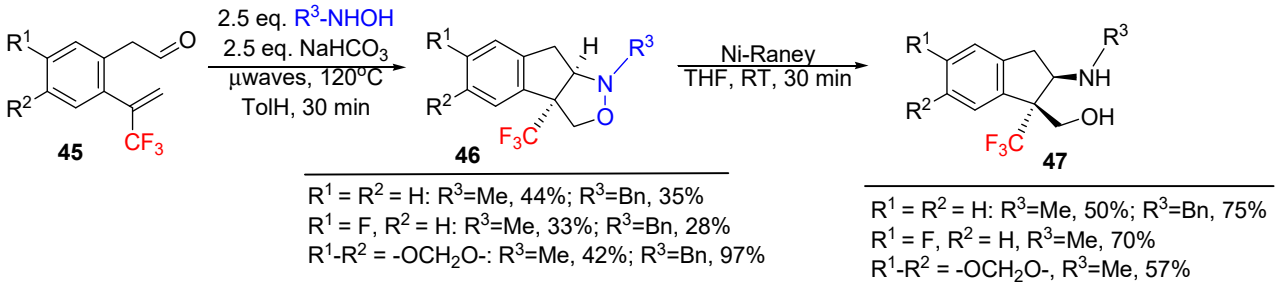
Scheme 24. Synthesis of 1-CF_3-indanes **41** and **42** by bromination of compound **40**.

Intramolecular radical cyclization has been used in the stereoselective synthesis of 1-CF_3-indane **44** from compound **43** in the presence of (n-Bu)$_3$SnH and AIBN (Scheme 25) [41].



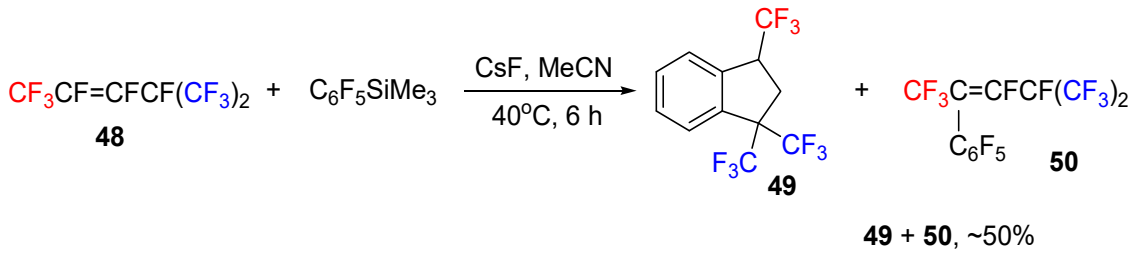
Scheme 25. Stereoselective synthesis of 1-CF_3-indane **44** by intramolecular radical cyclization of compound **43**.

Pozo, Fustero et al. have used intramolecular 1,3-dipolar nitrone cycloaddition to construct a 1-CF_3-indane core from compounds **45** (Scheme 26) [42]. The reaction of the aldehyde group of substrates **45** with *N*-alkylhydroxylamines gives rise to the intermediate formation of the corresponding nitrones, which are spontaneously cyclized into isoxazolidines **46** adjacent to the trifluoromethylindane fragment. It should be especially emphasized that the regioselectivity of the cycloaddition is determined by the presence of the CF_3 group in styrenes **45**. Analogous methylstyrenes do not give desirable isoxazolidines. At the final stage, the tricyclicisoxazolidine ring in **46** may be easily opened by Raney Ni, leading to 1-CF_3-aminoindanes **47**.



Scheme 26. Synthesis of 1-CF_3-aminoindanes **47** from compounds **45** by intramolecular 1,3-dipolar nitrone cycloaddition followed by reduction with Raney Ni.

Among all approaches to the synthesis of trifluoromethylindanes, there is an example of a complex nucleophilic process to create a 1-CF_3-indane structure [43]. The reaction of perfluoro-4-methyl-pent-2-ene **48** with trimethylsilylpentafluorobenzene under the action of CsF in MeCN results in the formation of two compounds **49** and **50** in a general yield of ~50% (Scheme 27). The authors provide a multi-step mechanism of this nucleophilic transformation, according to which trifluoromethyl groups form the structure of tri-CF_3-indane **49** from starting alkene **48** [43].

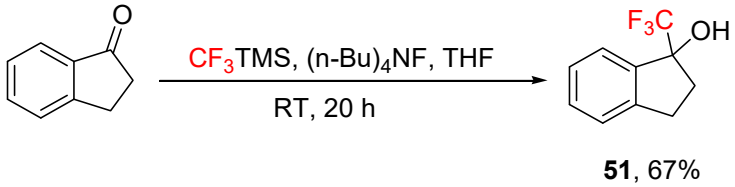


Scheme 27. Synthesis of tri-CF_3-indane **49** from perfluoro-4-methyl-pent-2-ene **48** and trimethylsilylpentafluorobenzene under the action of CsF in MeCN.

2.2. Trifluoromethylation of Indane Scaffolds

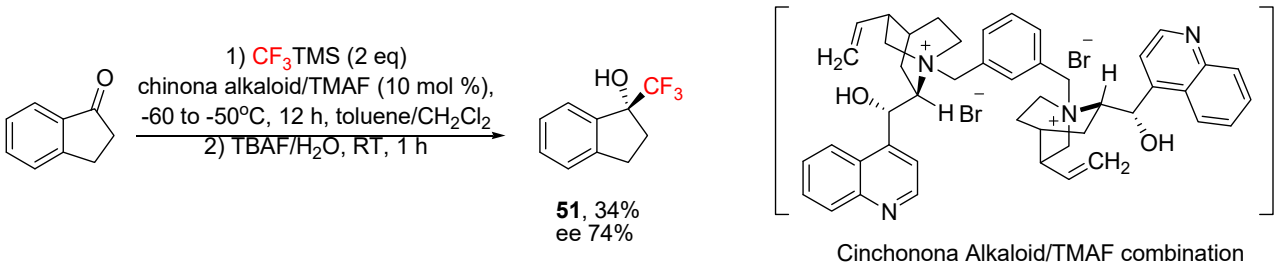
The next group of synthesis methods of trifluoromethylindanes is based on the introduction of a CF_3 group into a suitable indane carcass.

One of the simplest approaches in these methods is the trifluoromethylation of the carbonyl group by Ruppert–Prakash reagent CF_3SiMe_3 (CF_3TMS). Thus, Gassman et al. carried out the synthesis of 1-CF_3-indan-1-ole **51** from indan-1-one using CF_3TMS and tetra-*n*-butylammonium fluoride as a catalyst (Scheme 28) [44].



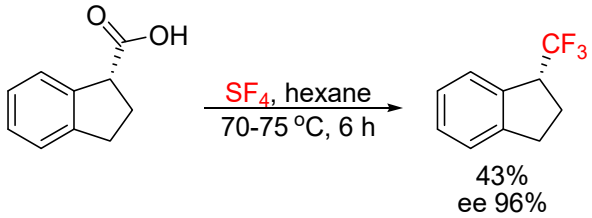
Scheme 28. Synthesis of 1-CF_3-indan-1-ole **51** from indan-1-one using Ruppert–Prakash reagent CF_3TMS.

Enantioselective Ruppert–Prakash reagent trifluoromethylation of indan-1-one has been conducted with chiral ammonium salts derived from cinchona alkaloids by Shibata, Toru et al. [45]. The target1-CF_3-indan-1-ole **51** has been obtained in a yield of 34% and 74% enantiomeric excess [45] (Scheme 29).



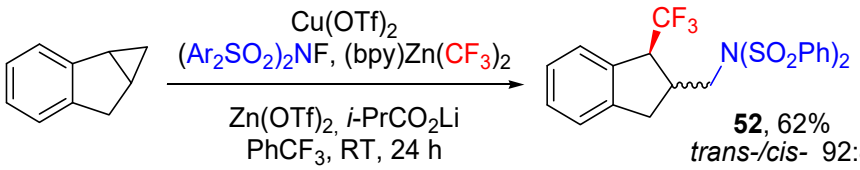
Scheme 29. Enantioselective synthesis of 1-CF_3-indan-1-ole **51** from indan-1-one by Ruppert–Prakash trifluoromethylation.

Sulfur tetrafluoride SF_4 can be also used for the introduction of a CF_3 group into theindane core. The reaction of enantio-enriched indan carboxylic acid with SF_4 at 70–75 °C for 6 h affords 1-CF_3-indane in a moderate yield 43% and perfect enantiomeric excess of 96% (Scheme 30) [46].



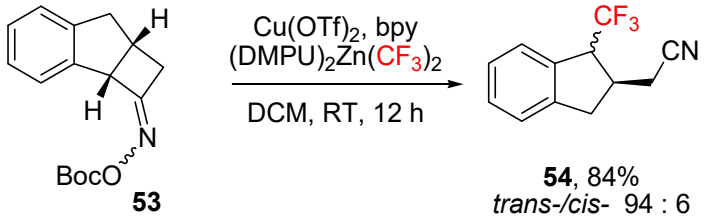
Scheme 30. Synthesis of 1-CF_3-indane from indan carboxylic acid under the action of SF_4.

Copper-catalyzed radical trifluoromethylation may be also used to access CF_3-indanes. Very recently, in 2021, Fang, Zhu, Li et al. have successfully developed ring-opening 1,3-aminotrifluoromethylation of the wide series of arylcyclopropanes including indane derivatives [47]. The radical reaction of tetrahydrocyclopropa[*a*]indene with trifluoromethylating agent (bpy)$Zn(CF_3)_2$ under the action of $Cu(OTf)_2$ as a catalyst leads to 1-CF_3-indane **52** in a good yield of 62% and high stereo- and chemoselectivity (Scheme 31).



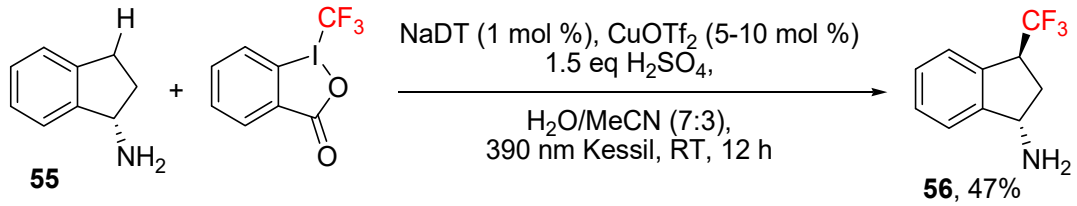
Scheme 31. Copper-catalyzed radical trifluoromethylation of tetrahydrocyclopropa[*a*]indene leading to 1-CF_3-indane **52**.

Earlier, the same scientific group described the copper-catalyzed ring-opening radical trifluoromethylation of cycloalkanone oxime derivatives [48]. In this reaction, copper(II) triflate and bipyridyl act as catalysts, and $Zn(CF_3)_2$ complex is a reagent. Oxime derivative **53** affords 1-CF_3-indane **54** in a high yield of 84% and with good stereoselectivity with a *trans-/cis-* isomeric ratio of 94:6 (Scheme 32).



Scheme 32. Copper-catalyzed radical trifluoromethylation of compound **53** leading to 1-CF_3-indane **54**.

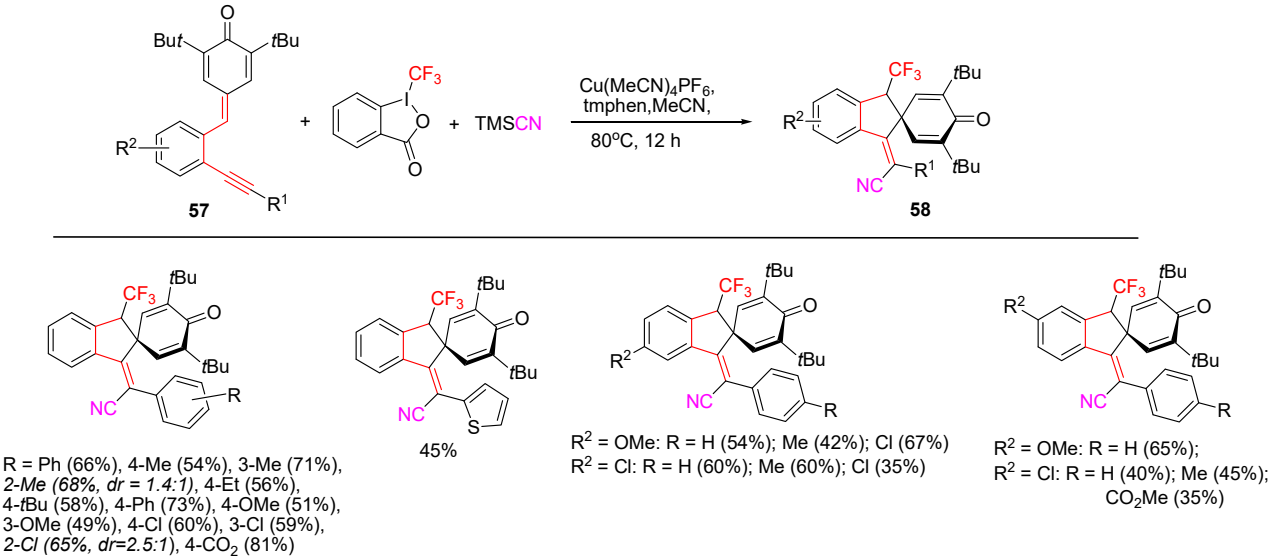
Several recent works have been devoted to metal-catalyzed trifluoromethylation with hypervalent iodine-based reagents. Thus, MacMillan et al. [49] reported ametallaphotoredox methodology including sodium decatungstate(NaDT)-photocatalyzed hydrogen atom transfer and copper catalysis, which allows the conversion of C–H bonds into the corresponding C(sp^3)–CF_3 one using Togni reagent II. This provides the transformation of unprotected amine **55** into a single regioisomer of 1-CF_3-indane **56** with good stereoselectivity (Scheme 33).



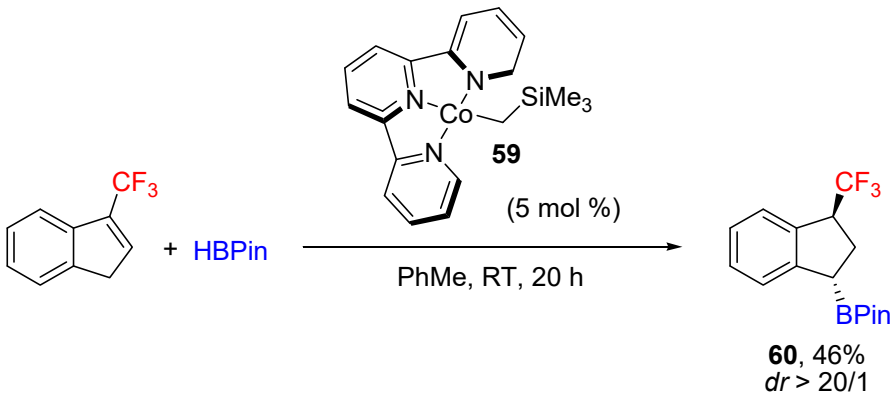
Scheme 33. Metallaphotoredox trifluoromethylation of compound **55** by Togni reagent II leading to 1-CF_3-aminoindane **56**.

Togni reagent II and TMSCN have been also applied for the copper-catalyzed spiroannulation–cyanotrifluoromethylation of 1,5-enynes **57** for the synthesis of spiro-1-CF_3-indanes **58** (Scheme 34) [50]. The set of substituents R^1 in the acetylene moiety of compounds **57** includes a wide range of electron-rich and electron-poor aryl groups. However, starting enynes**57** bearing alkyl or cycloalkyl groups R^1 do not converge into target compounds **58**. Remarkably, 1,5-enynes containing an *ortho*-substituted aryl group give inseparable diastereomeric mixtures; otherwise, only *Z*-products are obtained in good yields.

One more synthetic approach to 1-CF_3-indanes is the reduction of 1-CF_3-indenes. In this area, it is worth mentioning the recent work by Chirik et al. [51], which focused on the diastereoselective cobalt-catalyzed hydroboration of substituted indenes, including trifluoromethylated ones. Thus, the reduction of 1-CF_3-indene by HBP in the presence ofcobalt catalyst **59** results in the stereoselective formation of *trans*-1,3-disubstituted CF_3-indanyl boronate ester **60** (Scheme 35).



Scheme 34. Copper-catalyzed spiroannulation–cyanotrifluoromethylation of 1,5-enynes **57** into spiro-1-CF_3-indanes **58**.



Scheme 35. Cobalt-catalyzed reduction of 1-CF_3-indene by HBPin leading to 1-CF_3-indane **60**.

3. Conclusions

This survey of methods for the synthesis of 1-trifluoromethylindanes and close substances reveals that existing approaches allow these compounds to be obtained in regio- and stereoselective ways by two main procedures: the construction of a 1-CF_3-indane core from CF_3 precursors and the trifluoromethylation of indane structures. The latter method needs further deep investigation, since the regio- and stereoselective introduction of a CF_3 group into an indane core allows novel structures of this series to be obtained.

The combination of an indane scaffold, which is suitable for the creation of asymmetric carbons, along with a lipophilic CF_3 group, in various 1-CF_3-indane containing structures, makes these compounds extremely important for medicinal chemistry, as the basisfor the search for novel biologically active substances. In the near future, one should expect further intensive research on the development of the synthesis of 1-CF_3-indanes and the discovery of new methods in this area.

Funding: This research was funded by the Russian Scientific Foundation (grant no. 21-13-00006).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Acknowledgments: This work was supported by the Russian Scientific Foundation (grant no. 21-13-00006).

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Hiyama, T. *Organofluorine Compounds. Chemistry and Applications*; Springer: Berlin, Germany, 2000.
2. Chambers, R.D. *Fluorine in Organic Chemistry*; Blackwell: Oxford, UK, 2004.
3. Kirsch, P. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*; Wiley-VCH: Weinheim, Germany, 2004.
4. Uneyama, K. *Organofluorine Chemistry*; Blackwell: Oxford, UK, 2006.
5. Theodoridis, G. Fluorine-Containing Agrochemicals: An Overview of Recent Developments. In *Advances in Fluorine Science*; Tressaud, A., Ed.; Elsevier: Amsterdam, The Netherlands, 2006; Volume 2, pp. 121–175.
6. Begue, J.P.; Bonnet-Delpon, D. *Bioorganic and Medicinal Chemistry of Fluorine*; Wiley: Hoboken, NJ, USA, 2008.
7. Tressaud, A.; Haufe, G. (Eds.) *Fluorine and Health: Molecular Imaging, Biomedical Materials and Pharmaceuticals*; Elsevier: Amsterdam, The Netherlands, 2008.
8. Petrov, V.A. (Ed.) *Fluorinated Heterocyclic Compounds: Synthesis, Chemistry, and Applications*; Wiley: Hoboken, NJ, USA, 2009.
9. Nenajdenko, V.G. (Ed.) *Fluorine in Heterocyclic Chemistry*; Springer: Berlin, Germany, 2014.
10. Prakash, R.V. *Organofluorine Compounds in Biology and Medicine*; Elsevier: Amsterdam, The Netherlands, 2015.
11. Westwell, A.D. (Ed.) *Fluorinated Pharmaceuticals: Advances in Medicinal Chemistry*; Future Science Ltd.: London, UK, 2015.
12. Groult, H.; Leroux, F.R.; Tressaud, A. (Eds.) *Modern Synthesis Processes and Reactivity of Fluorinated Compounds. Progress in Fluorine Science*; Elsevier: Amsterdam, The Netherlands, 2017.
13. Postigo, A. (Ed.) *Late-Stage Fluorination of Bioactive Molecules and Biologically-Relevant Substrates*; Elsevier: Amsterdam, The Netherlands, 2018.
14. Prasher, P.; Sharma, M. Medicinal chemistry of indane and its analogues: A mini review. *ChemistrySelect* **2021**, *6*, 2658. [CrossRef]
15. Gabriele, B.; Mancuso, R.; Veltri, L. Recent advances in the synthesis of indanes and indenes. *Chem. Eur. J.* **2016**, *22*, 5056. [CrossRef] [PubMed]
16. Borie, C.; Ackermann, L.; Nechab, M. Enantioselective syntheses of indanes: From organocatalysis to C-H functionalization. *Chem. Soc. Rev.* **2016**, *45*, 1368. [CrossRef]
17. Kuck, D. Three-dimensional hydrocarbon cores based on multiply fused cyclopentane and indane units: Centropolyindanes. *Chem. Rev.* **2006**, *106*, 4885. [CrossRef] [PubMed]
18. Ganellin, C.R. Indane and indene derivatives of biological interest. *Adv. Drug Res.* **1967**, *4*, 163.
19. Iakovenko, R.O.; Kazakova, A.N.; Muzalevskiy, V.M.; Ivanov, A.Y.; Boyarkaya, I.A.; Chicca, A.; Petrucci, V.; Gertsch, J.; Krasavin, M.; Starova, G.L.; et al. Reactions of CF_3-enones with arenes under super-lectrophilic activation: A pathway to trans-1,3-diaryl-1-CF_3-indanes, new cannabinoid receptor ligands. *Org. Biomol. Chem.* **2015**, *13*, 8827. [CrossRef]
20. Iakovenko, R.O.; Chicca, A.; Nieri, D.; Reynoso-Moreno, I.; Gertsch, J.; Krasavin, M.Y.; Vasilyev, A.V. Synthesis of various arylatedtrifluoromethyl substituted indanes and indenes, and study of their biological activity. *Tetrahedron* **2019**, *75*, 624. [CrossRef]
21. Aubert, C.; Begue, J.-P.; Bonnet-Delpon, D.; Mesureur, D. Access to trifluoromethylindanes; cycloalkylation of β-phenyl trifluoromethyl ketones, β-keto esters, and alcohols. *J. Chem. Soc. Perkin Trans. 1* **1989**, *3*, 395. [CrossRef]
22. Abouadbellah, A.; Aubert, C.; Begue, J.-P.; Bonnet-Delpon, D.; Guilhem, J. Lewis acid-induced ene-cyclization of ω-olefinictrifluoromethyl ketones: Access to alicyclic compounds bearing a CF_3 group. *J. Chem. Soc. Perkin Trans. 1* **1991**, *6*, 1397. [CrossRef]
23. Prakash, G.K.S.; Paknia, F.; Narayanan, A.; Rasul, G.; Mathew, T.; Olah, G.A. Efficient synthesis of trifluoromethylateddihydrochalcones, aryl vinyl ketones and indanones by superelectrophilic activation of 4,4,4-trifluoro/3-(trifluoromethyl)crotonic acids. *J. Fluor. Chem.* **2012**, *143*, 292. [CrossRef]
24. Dong, K.; Li, Y.; Wang, Z.; Ding, K. Catalytic asymmetric hydrogenation of α-CF_3- or β-CF_3-substituted acrylic acids using rhodium(I) complexes with a combination of chiral and achiral ligands. *Angew. Chem. Int. Ed.* **2013**, *52*, 14191. [CrossRef]
25. O'Connor, M.J.; Boblak, K.N.; Topinka, M.J.; Kindelin, P.J.; Briski, J.M.; Zheng, C.; Klumpp, D.A. Superelectrophiles and the effects of trifluoromethyl substituents. *J. Am. Chem. Soc.* **2010**, *132*, 3266. [CrossRef] [PubMed]
26. Iakovenko, R.O.; Muzalevskiy, V.M.; Nenajdenko, V.G.; Vasilyev, A.V. Reactions of 1,1,1-trifluoro-4-phenylbut-3-en-2-one with arenestrifluoromethanesulfonic acid. *Russ. J. Org. Chem.* **2015**, *51*, 436. [CrossRef]
27. Iakovenko, R.O.; Kazakova, A.N.; Boyarkaya, I.A.; Gurzhiy, V.V.; Adontceva, M.S.; Panikorovskiy, T.L.; Muzalevskiy, V.M.; Nenajdenko, V.G.; Vasilyev, A.V. Superacid-promoted synthesis of CF_3-indenes using brominated CF_3-enones. *Eur. J. Org. Chem.* **2017**, *37*, 5632. [CrossRef]
28. Kazakova, A.N.; Iakovenko, R.O.; Boyarskaya, I.A.; Nenajdenko, V.G.; Vasilyev, A.V. Acid-promoted reaction of trifluoromethylatedallyl alcohols with arenes. Stereoselective synthesis of CF3-alkenes and CF3-indanes. *J. Org. Chem.* **2015**, *80*, 9506. [CrossRef]
29. Zerov, A.V.; Bulova, A.A.; Khoroshilova, O.V.; Vasilyev, A.V. TfOH-promoted transformations of TMS-ethers of diarylsubstituted CF_3-allyl alcohols with arenes into CF_3-indanes. *Org. Chem. Front.* **2019**, *6*, 3264. [CrossRef]
30. Kazakova, A.N.; Iakovenko, R.O.; Boyarskaya, I.A.; Ivanov, A.Y.; Avdontceva, M.S.; Zolotarev, A.A.; Panikorovsky, T.L.; Starova, G.L.; Nenajdenko, V.G.; Vasilyev, A.V. Brominated CF_3-allyl alcohols as multicentered electrophiles in TfOH promoted reactions with arenes. *Org. Chem. Front.* **2017**, *4*, 255. [CrossRef]
31. Sinyakov, V.R.; Mezhenkova, T.V.; Karpov, V.M.; Platonov, V.E. The alicyclic ring contraction of perfluoro-1-phenyltetralin in reaction with antimony pentafluoride. *J. Fluor. Chem.* **2004**, *125*, 49. [CrossRef]

32. Mezhenkova, T.V.; Karpov, V.M.; Zonov, Y.V. Formation of polyfluorofluorenes in the reactions of perfluoro-1,1-diphenylalkanes with antimony pentafluoride. *J. Fluor. Chem.* **2018**, *207*, 59. [CrossRef]
33. Liu, B.; Hu, P.; Zhang, Y.; Li, Y.; Bai, D.; Li, X. Rh(III)-catalyzed diastereodivergentspiroannulation of cyclic imines with activated alkenes. *Org. Lett.* **2017**, *19*, 5402. [CrossRef]
34. Chaudhary, B.; Autim, P.; Shinde, S.D.; Yakkala, P.A.; Giri, D.; Sharma, S. Rh(III)-catalyzed [3+2] annulations via C–H activation: Direct access to trifluoromethyl substituted indenamines and aminoindanes. *Org. Lett.* **2019**, *21*, 2763. [CrossRef]
35. Hu, T.; Xu, Y.; Zhang, S.; Xiong, H.-Y.; Zhang, G. Synthesis of β-amino esters with an undane backbone by rhenium-catalyzed [3+2] annulations. *Org. Lett.* **2020**, *22*, 8666. [CrossRef]
36. Kundu, K.; McCullagh, J.V.; Morehead, A.T. Hydroacylation of 2-vinyl benzaldehyde system: An afficient method for the synthesis of chiral 3-substituted indanones. *J. Am. Chem. Soc.* **2005**, *127*, 16042. [CrossRef] [PubMed]
37. Kimoto, H.; Muramatsu, H.; Inukai, K. Synthesis of fluorine-containing indanes and indenes: A novel radical cycloaddition of alkylbenzenes and hexafluoropropene. *Chem. Lett.* **1974**, *3*, 791. [CrossRef]
38. Kimoto, H.; Muramatsu, H.; Inukai, K. Synthesis and reactions of fluorine-containing aromatic ketones. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1642. [CrossRef]
39. Haszeldine, R.N.; Mitchinson, A.J.; Rowland, R.; Tipping, A.E. Fluoro-olefin chemistry. Part IX. Thermal insertion of hexafluoropropene into carbon-hydrogen bonds in alkylbenzenes. *J. Chem. Soc. Perkin Trans. 1* **1976**, *5*, 517. [CrossRef]
40. Chuikov, I.P.; Karpov, V.M.; Platonov, V.E.; Yakobson, G.G. Cyclization of difluorocarbene to perfluoro-3-methylindene and perfluoro-1-methylindane. Thermolysis and bromination of the resultant cyclopropane derivatives. *Russ. Chem. Bull.* **1988**, *37*, 1645. [CrossRef]
41. Furukawa, T.; Nishimine, T.; Tokunaga, E.; Hasegawa, K.; Shiro, M.; Shibata, N. Organocatalyzed region- and enantioselectiveallylictrifluoromethylation of Morita-Baylis-Hilman adducts using Ruppert-Prakash reagent. *Org. Lett.* **2011**, *13*, 3972. [CrossRef]
42. Rabasa-Alcaniz, F.; Asensio, A.; Sanchez-Rosello, M.; Escolano, M.; del Poza, C.; Fustero, S. Intramolecular nitronecycloaddition of α-(trifluoromethyl)styrenes. Role of the CF_3 group in the regioselectivity. *J. Org. Chem.* **2017**, *82*, 2505. [CrossRef]
43. Bardin, V.V.; Petrov, V.A.; Stennikova, I.V.; Furin, G.G.; German, L.S. Formation of perfluoro-1,1,3-trimethylindane in the reaction of trimethylsilylpentafluorobenzene with perfluoro-4-methyl-2-pentene. *Russ. Chem. Bull.* **1989**, *38*, 420. [CrossRef]
44. Gassman, P.G.; Ray, J.A.; Wenthold, P.G.; Mickelson, J.W. Synthesis of perfluoroalkeylatedindenes. *J. Org. Chem.* **1991**, *56*, 5143. [CrossRef]
45. Muzita, S.; Shibata, N.; Akiti, S.; Fujimoto, H.; Nakamura, S.; Toru, T. Cinchona alkaloids/TMAF combination-catalyzed nucleophilic enentioselectivetrifluoromethylation of aryl ketones. *Org. Lett.* **2007**, *9*, 3707. [CrossRef] [PubMed]
46. Lorentzen, R.J.; Brewster, J.H.; Smith, H.E. Application of the bezene sector and the benzene chirality rulus to perhydrobenzocycloalkenes and related compounds. *J. Am. Chem. Soc.* **1992**, *114*, 2181. [CrossRef]
47. Zhang, H.; Xiao, H.; Jiang, F.; Fang, Y.; Zhu, L.; Li, C. Copper-catalyzed ring-opening 1,3-amonotrifluoromethylation of arylcyclopropanes. *Org. Lett.* **2021**, *23*, 2268. [CrossRef] [PubMed]
48. Liu, Z.; Shen, H.; Xiao, H.; Wang, Z.; Zhu, L.; Li, C. Copper-catalyzed ring-opening radical trifluoromethylation of cycloalkanoneoximes. *Org. Lett.* **2019**, *21*, 5201. [CrossRef] [PubMed]
49. Sarver, P.J.; Bacauanu, V.; Schultz, D.M.; DiRocco, D.A.; Lam, Y.; Sherer, E.C.; NacMillan, D.W.C. The merger of decatungstate and copper catalysis to enable aliphatic C(sp^3)–H trifluoromethylation. *Nat. Chem.* **2020**, *12*, 459. [CrossRef] [PubMed]
50. Zuo, H.-D.; Cui, C.-C.; Gui, C.; Hao, W.-J.; Tu, S.-J.; Jiang, B. Metal-catalyzed spiroannulation-fluoromethylfunctionalization of, 1,5-enynes for the synthesis of stereodefined (Z)-epiroindenes. *Chem. Asian J.* **2020**, *15*, 4070. [CrossRef]
51. Leonard, N.G.; Palmer, W.N.; Friedfield, M.R.; Bezdek, M.J.; Chirik, P.J. Remote, diastereoselective cobalt-catalyzed alkene isomerization-hydroboration: Access to stereodefined 1,3-difunctionalyzed indanes. *ACS Catal.* **2019**, *9*, 9034. [CrossRef]