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Fluorine-containing agrochemicals in the last decade and approaches for fluorine incorporation

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ABSTRACT

In this review, the methodologies for fluorine incorporation of 40 fluorine-containing agrochemicals that received an international standardization organization (ISO) name during the last decade are described. The predominant approach for fluorine introduction of these agrochemicals is to use a fluorine-containing building block. Here we present how the fluorine-containing building blocks are introduced into these agrochemicals. The synthetic methods of fluorine-containing building blocks that are not easily available are also specifically discussed. Fluoroarenes, difluomethylarenes and trifluomethylarenes are the main building blocks that have been used in this review. Fluorine-containing small molecules, such as alcohol, amine, ketoester, olefin are also widely used. The only example of late-stage fluorination is the synthesis of fungicide quinofumelin. We believe the fluorine introduction methods described here can provide ideas for the development of new and economical pesticide synthetic routes, and stimulate researchers to develop new fluorine incorporation methods and create new pesticides.

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1. Introduction

Fluorine has the second smallest atomic radius, the highest electronegativity and it forms the strongest single bond with carbon. The introduction of fluorine into a bioactive molecule can dramatically modify its physico-chemical properties, such as acidity, lipophilicity and stability [1-4]. These modifications usually enhance the biological activity by affecting any parameters, such as binding to target receptors or enzymes and transporting bioactive molecules from the point of application to the target site, as well as preventing metabolic deactivation.

Even though there are so many advantages of fluorine-containing molecules, the introduction of fluorine into a molecule always causes a significant increase in cost. This is because of the lack of simple, efficient and cheap fluorine introduction method in agrochemical industry. As we all know, the most common method for fluorine introduction is to use fluorine-containing building blocks [5].

The dramatic effect of fluorine on the biological activity of agrochemicals such as fungicides, insecticides, herbicides, acaricides, and nematicides has earned fluorine a unique place in the toolbox of the agrochemical chemist [6-10]. Recently, Shibata and coworkers reviewed almost all the existing fluorine-containing agrochemicals by subdividing them into several categories, including agrochemical type, chemotype, mode of action, heterocycle and chirality [11]. However, the fluorine introduction methods of these pesticides have not been properly discussed. We believe the discussion of this issue is very critical, because it may provide ideas for the development of new and economical pesticide synthetic routes, and it may also promote agricultural chemists to develop new fluorine introduction methods and create new pesticides.

This review aims to present the fluorine introduction approaches for the agrochemicals that received an ISO name during the last decade (January 2011 to December 2020) [12]. In fact, it is basically equivalent to summarize the introduction methods of fluorine-containing building blocks that have been used for these agrochemicals. There are 54 fluorine containing molecules that received an ISO name in that period, we selected 40 of them based on diversity of chemical or synthetic methods.

Since the authors pay more attention to the fluorine introduction step, the complete synthetic route is sometimes not presented in this review. For example, the synthesis of fluorine-free building blocks is not included in this review. In most cases, the exact synthetic route of an agrochemical is not fully disclosed by the manu-

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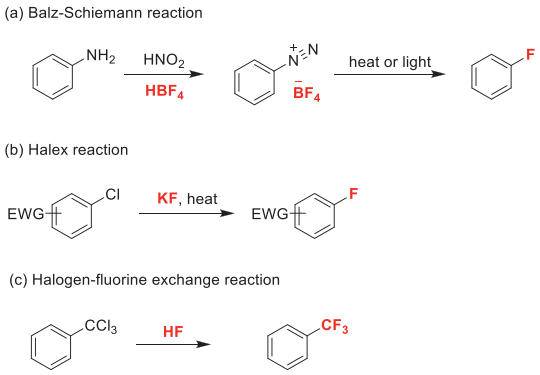
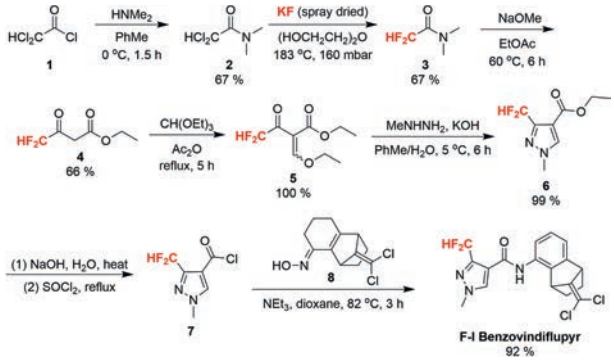


Scheme 1. The general methods for preparing fluorobenzene and trifluoromethylbenzene derivatives.



Scheme 2. Fluorine introduction of benzovindiflupyr **(F-I)**.

facturer. The authors extracted synthetic routes from published papers or patents. Consequently, the fluorine introduction methods described herein might be close to the manufacturing methods, but will unlikely be exactly the same. Nevertheless, this review intends to show the type and scope of fluorine-containing building blocks and small molecules most likely to be used for the synthesis of latest agrochemicals, as well as how exactly they have been used.

Generally, the synthesis of easily available fluorine-containing building blocks, such as fluorobenzene, trifluoromethylbenzene derivatives and small nonaromatic raw materials will not be discussed in this review. The general method for preparing fluorobenzene derivatives is the Balz-Schiemann reaction [13], in which a primary aromatic amine is transformed to an aryl fluoride *via* a diazonium tetrafluoroborate intermediate by using HBF_4 as fluorine source (Scheme 1a). Alternatively, the Halex reaction [14] has been widely used to convert electron poor aromatic chlorides to the corresponding aromatic fluorides by using spray-dried KF as a fluorine source (Scheme 1b). Though there are a number of approaches for the preparation of the trifluoromethylbenzene derivatives, the most common industrial approach is the halogen exchange reaction involving the conversion of trichloromethylbenzene (Scheme 1c).

This review is classified by type of agrochemical, including fungicides, herbicides, insecticides, acaricides and nematicides. In the fungicide section, fluorine introduction methods of 15 representative fungicides are described (Fig. 1).

2. Fungicides

2.1. Benzovindiflupyr (*F-I*)

Benzovindiflupyr (**F-I**) was developed by Syngenta and received its ISO name in 2011. It is a pyrazole carboxamide fungicide, belongs to the class of succinate dehydrogenase inhibitors (SDHIs) [15]. It is active on a broad spectrum of diseases in cereals, especially efficient for soybean rust. The key step of the synthesis of benzovindiflupyr is the combination of oxime **8** and 3-(difluoromethyl)-1-methyl-1*H*-pyrazole-4-carbonyl chloride **7** *via* Semmler-Wolff type aromatization and amidation (Scheme 2) [16]. Since 4,4-difluoroacetoacetate **4** is not available in bulk quantities, the preparation of **7** starts from dichloroacetyl choloride **1**. The fluorine introduction is achieved by Halex reaction of dichloroacetamide **2** with KF [17]. Then the difluoroacetamide **3** is converted to the ketoester **4** through an amido-Claisen approach discovered by Syngenta researchers. The reaction of **4** with triethyl orthoformate gives a mixture of the vinylether **5** in excellent yield [18], which reacts with methylhydrazine to obtain the pyrazolate **6** [19]. Compound **6** can be transferred to acid chloride **7** through sequential hydrolysis and chlorination. Intermediates **6** and **7** are both

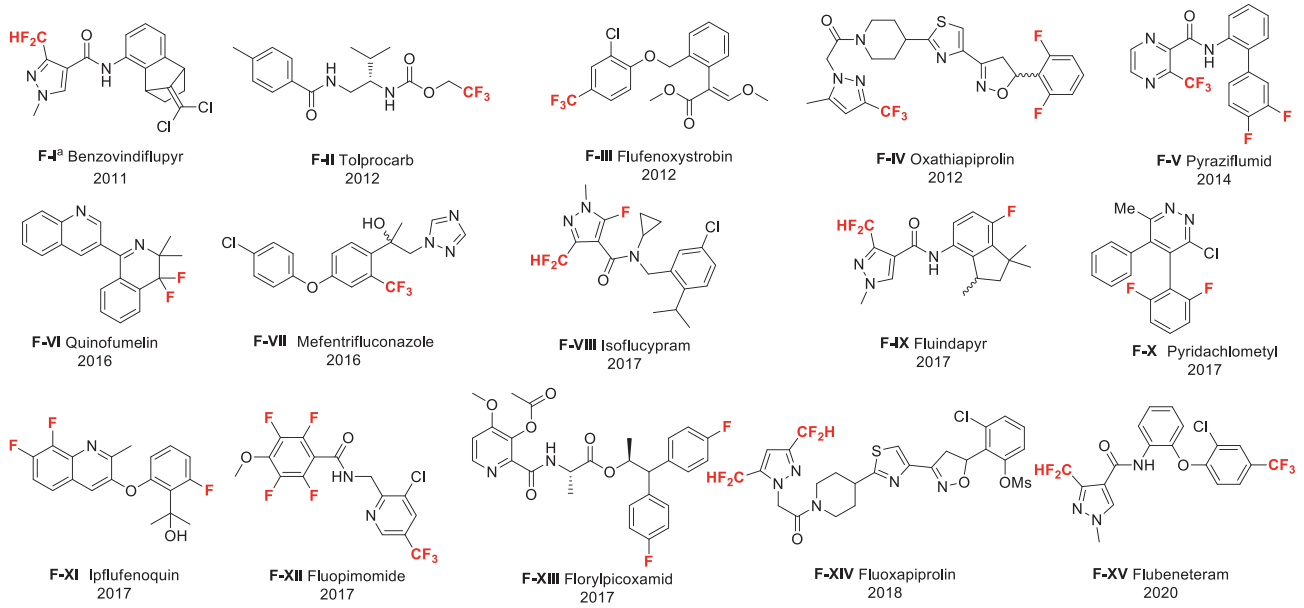
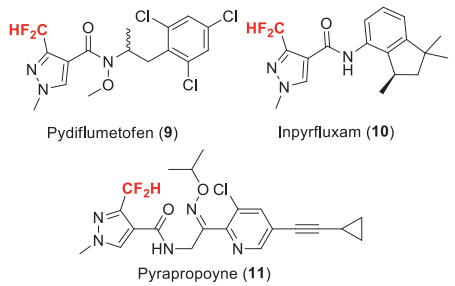
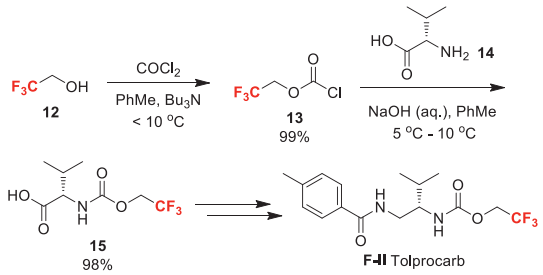


Fig. 1. Structure of 15 fungicides featured in this review. [a] **F-I** means fungicide I.



Scheme 3. Representative fungicides containing difluoromethyl pyrazole carboxamide moiety.



Scheme 4. Fluorine introduction of tolprocarb **(F-II)**.

useful fluorine-containing building blocks in the synthesis of agrochemicals containing difluoromethyl pyrazole carboxamide moiety, such as pydiflumetofen, inpyrfluxam and pyrapropoyne (Scheme 3) [20-22].

2.2. Tolprocarb (*F-II*)

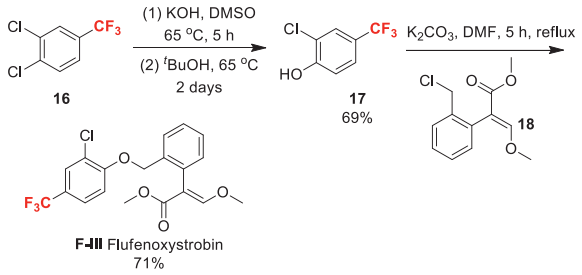
Tolprocarb (**F-II**) was developed by Mitsui Chemicals and received its ISO name in 2012. It is a carbamate fungicide developed for controlling rice blast, which is caused by the fungal pathogen *Magnaporthe grisea*. It is been recognized as a melanin biosynthesis polyketide synthase inhibitor (MBI-P) [23,24]. The synthesis of tolprocarb starts from 2,2,2-trifluoroethanol **12**, which is a commercially available fluorine source in bulk quantities (Scheme 4). The transformation from **12** to trifluoroethyl chloroformate **13** can be considered as the fluorine introduction step [25]. The carbamate coupling of valine **14** with trifluoroethyl chloroformate **13** affords **15** followed by a couple of transformations finally lead to tolprocarb [26].

2.3. Flufenoxystrobin (*F-III*)

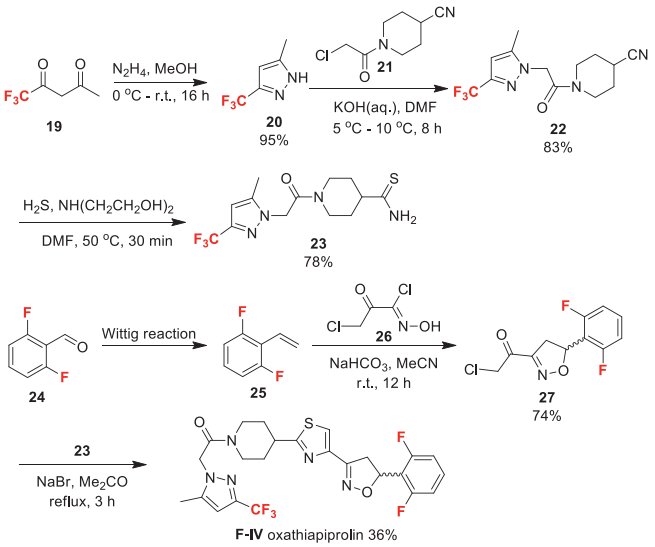
Flufenoxystrobin (**F-III**) was developed by Shenyang Research Institute of Chemical Industry (SYRICI) and received its ISO name in 2012. It belongs to the group of strobilurin analogues, is a quinone outside inhibitor (QoI) fungicide [27]. Flufenoxystrobin exhibits excellent fungicidal activity against *Erysiphe graminis* and moderately high acaricidal activity against *Tetranychus cinnabarinus* [28]. Flufenoxystrobin is synthesized by alkylation of 2-chloro-4-(trifluoromethyl)phenol **17** with intermediate **18** (Scheme 5) [29]. Compound **17** can be manufactured by hydroxyl substitution of easily available building block 3,4-dichlorobenzotrifluoride **16** [30].

2.4. Oxathiapiprolin (*F-IV*)

Oxathiapiprolin (**F-IV**) was developed by DuPont and received the ISO name in 2012. It belongs to the class of piperidinyl thiazole isoxazolines, and has extremely high efficacy against oomycete plant pathogens. Its mode of action involves binding to the oxysterol-binding protein in oomycetes [27]. Oxathiapiprolin has



Scheme 5. Fluorine introduction of flufenoxystrobin **(F-III)**.

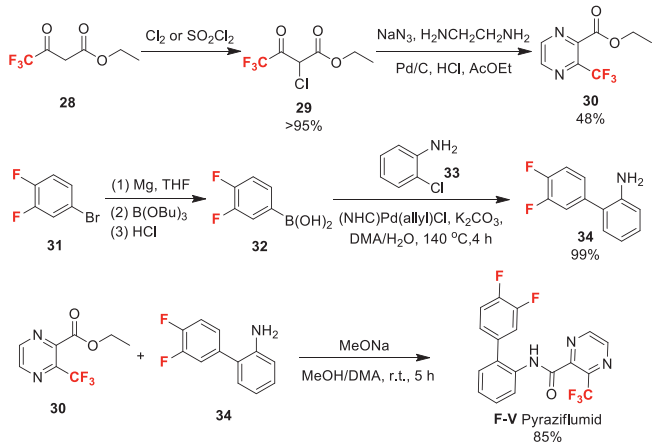


Scheme 6. Fluorine introduction of oxathiapiprolin **(F-IV)**.

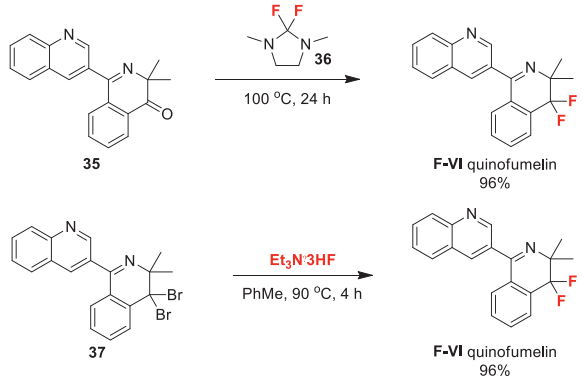
two fluorine-containing moieties [31,32]. Trifluoromethyl group is introduced through condensation of trifluoroacetylacetone **19** with hydrazine, in which trifluoromethyl pyrazole **20** can be obtained in excellent yield (Scheme 6). The alkylation of **20** followed by nitrile group conversion affords the important intermediate **23**. Compound **23** reacts with the chloroacetylisoxazoline derivative **27** to yield oxathiapiprolin. The required intermediate **27** is obtained in two steps from 2,6-difluorobenzaldehyde **24**. First, the Wittig reaction of **24** affords styrene **25**. Then, **25** undergoes a 1,3-dipolar cycloaddition with oxime **26** to obtain intermediate **27**. Trifluoroacetylacetone **19** and difluorobenzaldehyde **24** used in the synthesis are both easily available raw materials.

2.5. Pyraziflumid (*F-V*)

Pyraziflumid (**F-V**) was discovered by Nihon Nohyaku and received the ISO name in 2014. It has unique pyrazine carboxamide skeleton, belongs to the class of succinate dehydrogenase inhibitors (SDHIs). Pyraziflumid shows excellent biological activity against ascomycete and basidiomycete fungi and exhibits good controlling activity against many diseases in the field [33]. Pyraziflumid also contains two different fluorinated moieties (Scheme 7). Trifluoromethyl group is introduced to the pyrazine moiety by cyclization and aromatization of **29** with ethylenediamine. Compound **29** can be synthesized through chlorination of raw material trifluoroacetoacetate **28** [34]. On the other hand, fluorine-containing building block **31** is first converted to boronic acid **32**. The Suzuki coupling between **32** and 2-chloroaniline **33** leads to biphenyl amine intermediate **34** in excellent yield [35]. Finally, the amidation reaction between two fluorinated moieties **30** and **34** gives pyraziflumid [36].



Scheme 7. Fluorine introduction of pyraziflumid (**F-V**).



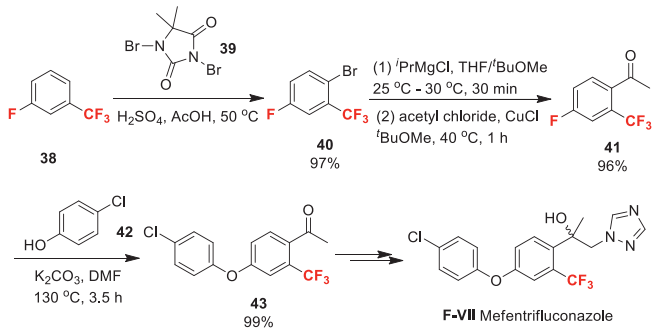
Scheme 8. Fluorine introduction of quinofumelin (**F-VI**).

2.6. Quinofumelin (*F-VI*)

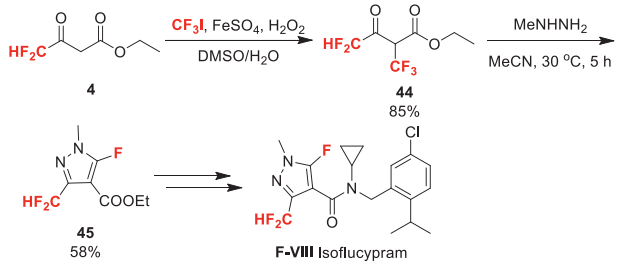
Quinofumelin (**F-VI**) was discovered by Mitsui Chemicals Agro and received its ISO name in 2016. It is a novel quinoline fungicide with excellent ability to control *Botrytis cinerea, Sclerotinia sclerotiorum*, blast disease, and anthracnose. Its mode of action is unknown. The fluorine introduction of quinofumelin is a late-stage fluorination (Scheme 8). The deoxofluorination of ketone intermediate **35** with 2,2-difluoro-1,3-dimethylimidazolidine (DFI) **36** [37] affords quinofumelin in excellent yield [38]. Alternatively, the debromofluorination of 1,1-dibromo-substituted intermediate **37** with triethylamine trihydrofluoride also yields quinofumelin in the same yield [39].

2.7. Mefentrifluconazole (*F-VII*)

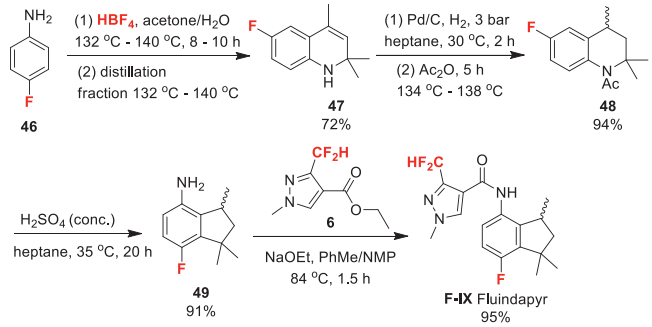
Mefentrifluconazole (**F-VII**) was developed by BASF and received the ISO name in 2016. It is the first isopropanol triazole fungicide that belongs to sterol demethylation inhibitor (DMI) group. Mefentrifluconazole is used in several crops for the control of a broad range of important pathogens. It is active against different fungal stages both on the plant surface and in the plant tissue. Very recently, it has been reported to exhibit excellent protective and curative efficacy against *Botrytis cinerea* on detached leaves of cucumber [40]. The synthesis of mefentrifluconazole starts from fluorine-containing raw material *meta*-fluorobenzotrifluoride **38** (Scheme 9). First of all, compound **38** is converted to bromobenzene **40** by electrophilic bromination [41]. Then the debromoacetylation of **40** gives acetophenone **41** in excellent yield [42]. The defluoroetherification of **41** leads to key intermediate **43** which can be transferred to mefentrifluconazole eventually.



Scheme 9. Fluorine introduction of mefentrifluconazole (**F-VII**).



Scheme 10. Fluorine introduction of isoflucypram (**F-VIII**).



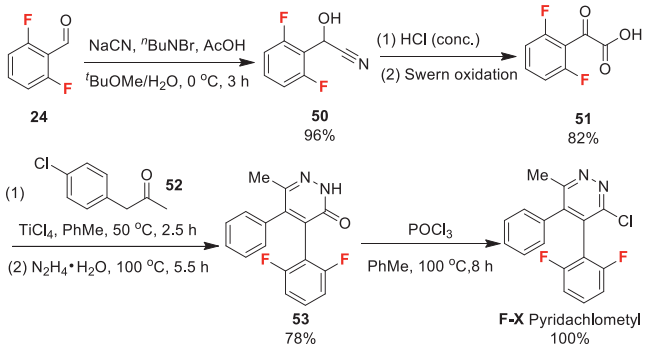
Scheme 11. Fluorine introduction of fluindapyr (**F-IX**).

2.8. Isoflucypram (*F-VIII*)

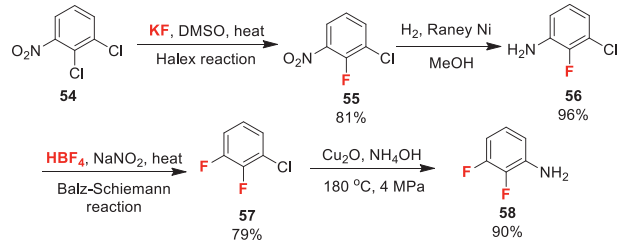
Isoflucypram (**F-VIII**) was developed by Bayer and received its ISO name in 2017. It belongs to SDHI fungicide, exhibits long-lasting efficacy in controlling leaf spot diseases on a large range of crops [43]. The difluoromethyl group is introduced by using building block 4,4-difluoroacetoacetate **4** whose synthesis has been discussed in Scheme 2. Compound **4** is first converted to trifluoromethylated intermediate **44** with CF_3I. The novel cyclization process of **44** and methyl hydrazine developed by Bayer, can afford 3-difluoromethyl-5-fluoropyrazole carboxylate **45** in moderate yield (Scheme 10). Finally, **45** can be transferred to isoflucypram [44].

2.9. Fluindapyr (*F-IX*)

Fluindapyr (**F-IX**) was originally discovered by Isagro, now has been jointly developed by FMC and Isagro under a 2012 research and development collaboration agreement. It belongs to the succinate dehydrogenase inhibitor (SDHI) class of compounds. It has high levels of efficacy to a variety of crops, especially for Asian soybean rust (ASR) when used in certain premixed formulations. The key step of the synthesis of fluindapyr is the coupling of two fluorine-containing building blocks, pyrazole carboxylate **6** and aminoindane **49** (Scheme 11). The construction of compound **6** has been discussed in Scheme 2. The preparation of compound **49**



Scheme 12. Fluorine introduction of pyridachlometyl **(F-X)**.



Scheme 13. Fluorine introduction of 2,3-difluoroaniline **58**.

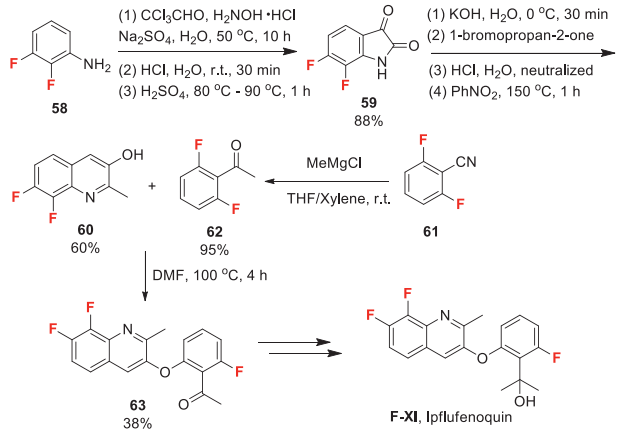
starts from cheap raw material 4-fluoroaniline **46**. Compound **46** undergoes cyclization with acetone at high temperature to afford **47**. Then **47** is reduced by hydrogenation and protected by acetylation to give **48**. Finally, the rearrangement of **48** promoted by sulfuric acid produces the key intermediate **49** in excellent yield [45].

2.10. Pyridachlometyl (*F-X*)

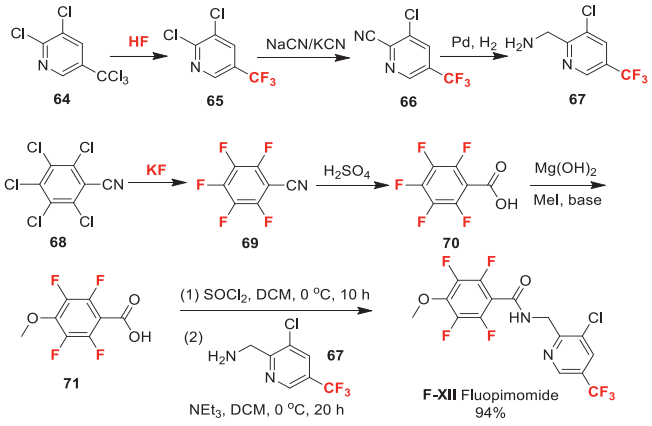
Pyridachlometyl (**F-X**) is a pyridazine fungicide from Sumitomo Chemical. A recent research showed that pyridachlometyl had a novel anti-tubulin mode of action which could be useful in anti-resistance management [46]. Pyridachlometyl exhibites potent antifungal activity against a broad range of fungal species belonging to the *Ascomycota* and *Basidiomycota*. The difluorobenzene moiety of pyridachlometyl comes from difluorobenzaldehyde **24** (Scheme 12). Compound **24** is first converted to cyano **50**. Then **51** is obtained through hydrolysis and oxidation of **50**. Next, **51** undergoes sequential Knoevenagel reaction with **52** and hydrazine promoted condensation reaction to afford precursor **53**, which can be finally transferred to pyridachlometyl by phosphoryl chloride [47, 48].

2.11. Ipflufenoquin (*F-XI*)

Ipflufenoquin (**F-XI**) was developed by Nippon-Soda. It has stable efficacy against a wide range of plant diseases, such as gray mold, scab and rice blast. Its mode of action is unknown. Ipflufenoquin is synthesized by coupling of two fluorinated intermediates **60** and **62**. The quinoline intermediate **60** can be synthesized from isatin **59** which is made from 2,3-difluoroaniline **58** *via* Sandmeyer methodology [49]. The synthesis of compound **58** can be diverse. Here we present one possible manufacturing way (Scheme 13) [50]. The synthesis is based on Halex reaction and Balz-Schiemann reaction to introduce two fluorine atoms respectively. The acetophenone intermediate **62** can be simply synthesized by Grignard reaction of easily available 2,6-difluorobenzonitrile **61** [51]. Then the defluoroetherification between **60** and **62** affords precursor **63** which can be finally converted to ipflufenoquin (Scheme 14) [52].



Scheme 14. Fluorine introduction of ipflufenoquin **(F-XI)**.



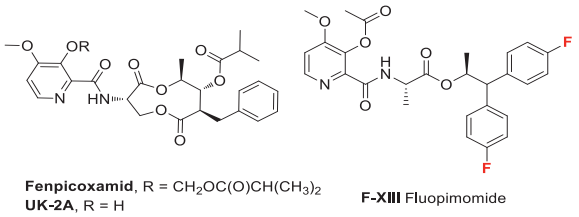
Scheme 15. Fluorine introduction of fluopimomide **(F-XII)**.

2.12. Fluopimomide (*F-XII*)

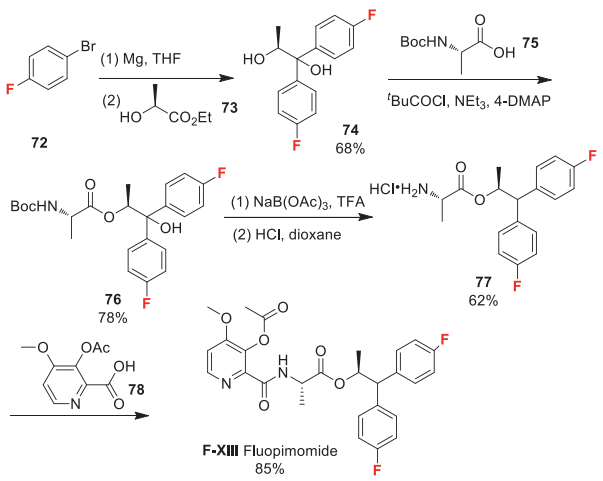
Fluopimomide (**F-XII**) is an innovative nicotinamide fungicide developed by Sino-Agri Union (Shandong Sino-Agri Union Biotechnology). It is a broad-spectrum fungicide used for management of *Oomycetes* and *Rhizoctonia* diseases [53]. Its mode of action is under development [54]. Fluopimomide is synthesized by coupling of trifluoromethyl pyridine **67** and tetrafluorobenzoic acid **71**. For compound **67**, the fluorine introduction is completed by halogen exchange with **64** as starting material [55]. Then **65** undergoes dechlorocyanation [56] and subsequent hydrogenation [57] to give **67**. On the other hand, the fluorine introduction of **71** is based on Halex reaction of **68** [58]. The hydrolysis of cyano group of **69** followed by defluorohydroxylation of **70** affords **71** [59,60]. In the end, the coupling of intermediates **67** and **71** gives fluopimomide in excellent yield [61].

2.13. Fluopimomide (*F-XIII*)

Fluopimomide (**F-XIII**) is a neopicolinamide fungicide developed by Corteva Agriscience. Florylpicoxamid is the second member of the quinone outside inhibitors (QiI) class of picolinamide fungicides, joining fenpicoxamid [62]. While fenpicoxamid was obtained through derivatization of the natural product UK-2A, florylpicoxamid was discovered using UK-2A as an inspirational starting point (Scheme 16). Florylpicoxamid controls a wide range of pathogens including *Septoria* spp., powdery mildew, *Botrytis* spp., Anthracnose, Alternaria, scab, *Monilinia*, and others [27]. The fluorobenzene part of fluopimomide is introduced by Grignard reaction using easily available 1-bromo-4-fluorobenzene **72** as start-



Scheme 16. Structures of fenpicoxamid and UK-2A.



Scheme 17. Fluorine introduction of fluopimomide (**F-XIII**).

ing material [63]. The compound **74** can be easily converted to **76** by reaction with Boc-L-alanine **75**. The dehydroxylation of **76** produced **77**, which finally reacts with **78** to form fluopimomide (Scheme 17).

2.14. Fluoxapiprolin (*F-XIV*)

Fluoxapiprolin (**F-XIV**) is a new piperidinyl thiazole isoxazoline fungicide developed by Bayer Crop Science in 2012. It is effective against Phytophthora rot and downy mildew. Its mode of action has not been reported, but seems to be oxysterol binding protein inhibitors (OSBPI) in chemical structure. Recently, the resistance risk of *Phytophthora capsici* to fluoxapiprolin was investigated to be moderate [64]. Fluoxapiprolin is synthesized by the alkylation of bis-difluoromethyl pyrazole **82** (Scheme 18) [65]. Compound **82** can be produced by two different ways from the same raw material 1,1-difluoroacetone **79** [66]. For example, **79** can react with hydrazine to give bis(1,1-difluoropropan-2-ylidene)hydrazine **80**, which then reacts with amine **81** to afford **82** [67]. Alternatively, **79** can also react with hydrazone **83** to get **84**, which yields **82** by reaction with difluoroacetic anhydride **85** [68].

2.15. Flubeneteram (*F-XV*)

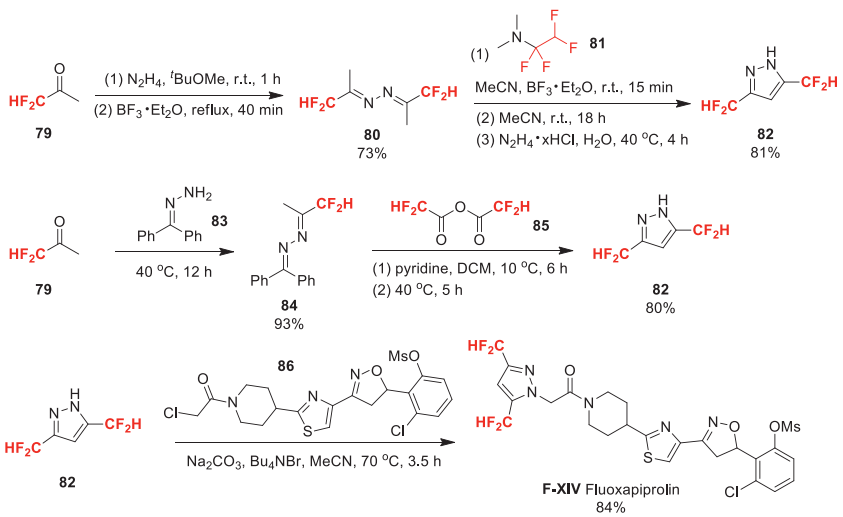
Flubeneteram (**F-XV**) is a promising fungicide candidate recently discovered in China in 2017. It contains a pyrazole carboxamide diphenyl ether moiety and is considered to be an SDHI based on its chemical structure. Flubeneteram displays excellent protection activity against *Rhizoctonia solani* and *Sphaerotheca fuliginea* [69]. Recently, the carbon-silicon switch strategy was used in the design and synthesis of a series of flubeneteram-silyl derivatives and the new silyl compound showed comparable and even higher fungicidal activities compared to flubeneteram lead compound [70]. For the synthesis of flubeneteram, its trifluoromethyl phenol moiety is made through the defluoroetherification of raw material **87** (Scheme 19). Compound **90** can be synthesized from pyrazole carboxylate **6** via simple transformations. The coupling of **89** and **90** affords flubeneteram in good yield [71].

3. Insecticides

In the insecticide section, fluorine introduction methods of 12 representative insecticides are discussed (Fig. 2).

3.1. Flupyradifurone (*I-I*)

Flupyradifurone (**I-I**) was developed by Bayer Crop Science and received its ISO name in 2011. Flupyradifurone is used as an alternative insecticide for controlling sucking pest species, such as aphids, psyllids, stink bugs, and white flies. Although flupyradifurone is chemically classified as a butenolide, many scientists might regard it as a neonicotinoid. Both flupyradifurone and neonicotinoids have the same mode of action involving activation of the nicotinic acetylcholine receptor (*i.e.*, nAChR agonist) and very similar chemical structures [72]. The difluoromethyl group of flupyradifurone is introduced by using difluoroethyl amine **91** as building



Scheme 18. Fluorine introduction of fluoxapiprolin (**F-XIV**).

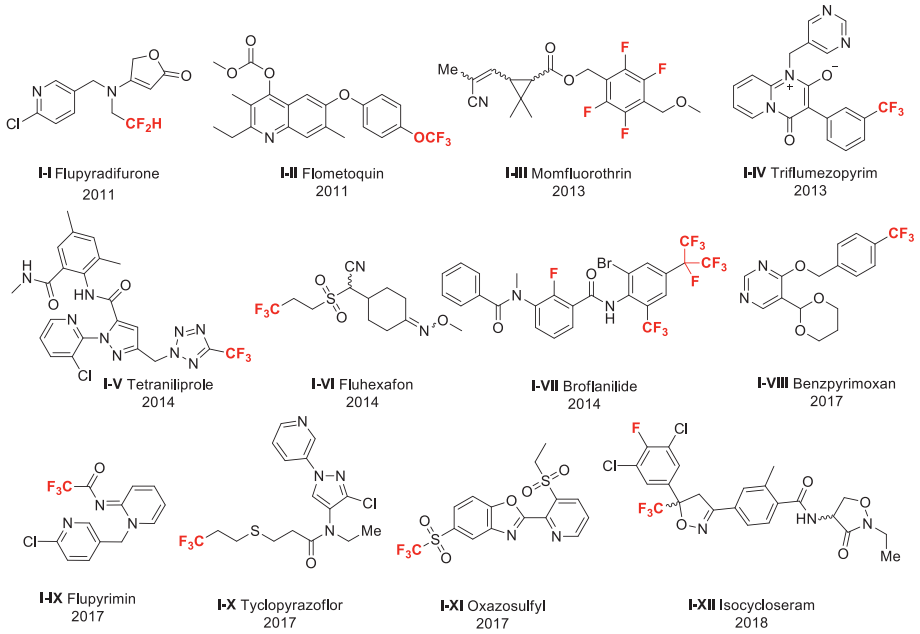
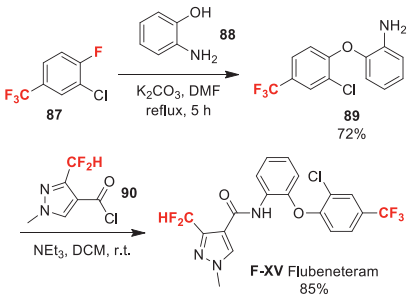
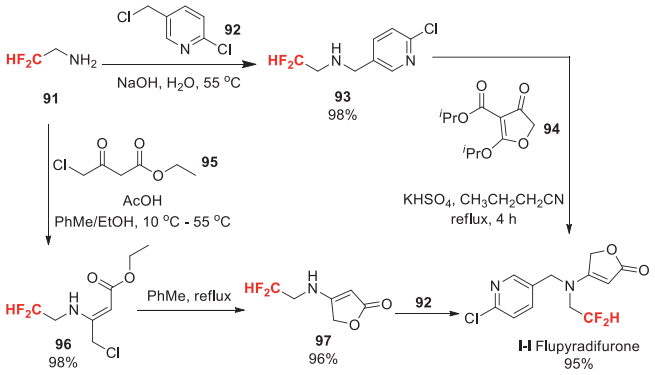


Fig. 2. Structures of 12 insecticides featured in this review. **I-I** means insecticide I.

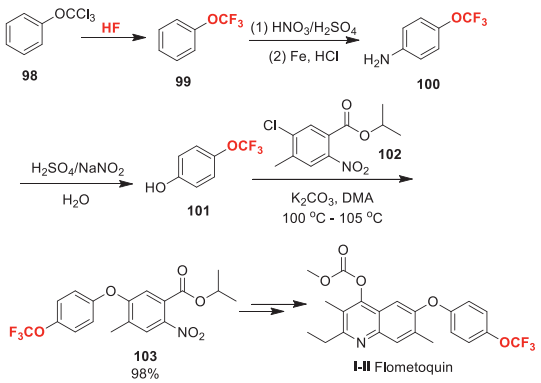


Scheme 19. Fluorine introduction of flubeneteram **(F-XV)**.



Scheme 20. Fluorine introduction of flupyradifurone **(I-I)**.

block (Scheme 20). Bayer reported two different synthetic routes. One route starts with alkylation of **91** with chloromethyl pyridine **92** [73]. The obtained intermediate **93** reacts with **94** to afford the target product in high yield [74]. Another route starts with alkylation of **91** with 4-chloroacetoacetate **95**. Then the cyclization of **96** gives **97**, which is finally alkylated with **92** to afford flupyradifurone [75].



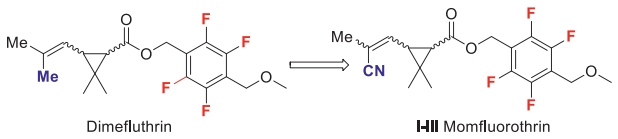
Scheme 21. Fluorine introduction of flometoquin **(I-II)**.

3.2. Flometoquin (*I-II*)

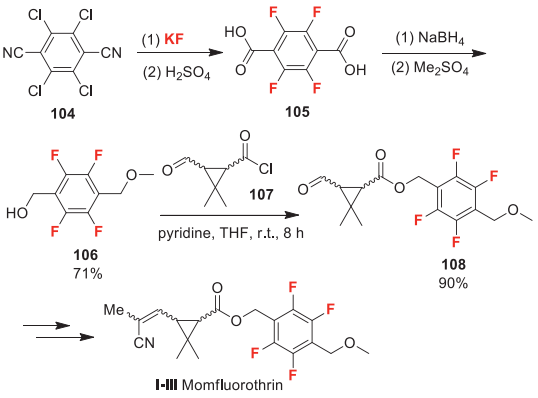
Flometoquin (**I-II**) has been presented by Nippon Kayaku as a new insecticide, which is active on controlling lepidoptera, diptera, hemiptera, and mites. It belongs to insect mitochondrial electron transport complex (III) inhibitor, acts on complex III Qi site [76]. In the synthetic route for flometoquin reported by Nippon Kayaku, 4-(trifluoromethoxy)phenol **101** is used directly. Here, we present a possible manufacturing way for the synthesis of compound **101** (Scheme 21) [77]. The trifluoromethoxy group is introduced by halogen exchange of **98**. Then the *para*-selective nitration of **99** and the subsequent reduction yields 4-(trifluoromethoxy)aniline **100**. Finally, the Sandmeyer reaction of **100** produces **101**. The etherification reaction between **101** and **102** affords key intermediate **103** which can be converted to flometoquin eventually [78].

3.3. Momfluorothrin (*I-III*)

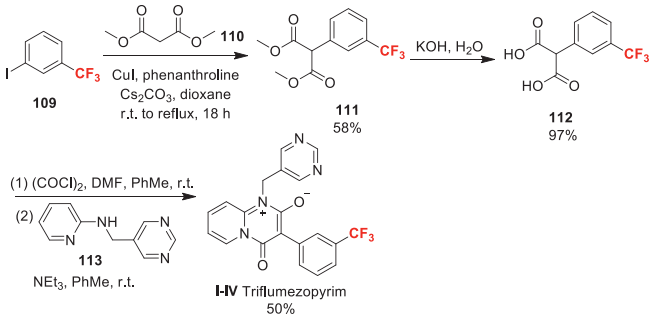
Momfluorothrin (**I-III**) was announced by Sumitomo Chemical as a new synthetic pyrethroid and received its ISO name in 2013. It is developed by introducing a cyano group to the acid moiety of the tetrafluorobenzyl ester type pyrethroid dimefluthrin (Scheme 22). Momfluorothrin exhibits excellent knockdown effi-



Scheme 22. Transformation of dimefluthrin to momfluorothrin.



Scheme 23. Fluorine introduction of momfluorothrin **(I-III)**.



Scheme 24. Fluorine introduction of triflumezopyrim **(I-IV)**.

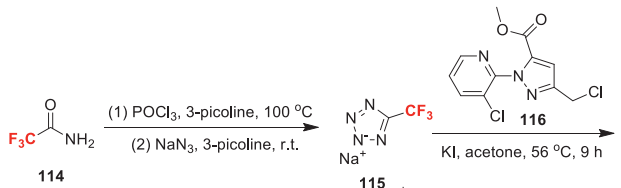
cacy against the housefly and German cockroach [79]. The synthesis of key fluorine-containing building block **106** is completed in a similar way as compound **71** (Scheme 15). The difference is intermediate **105** is further converted to alcohol **106** through reduction and methylation (Scheme 23) [80]. The esterification of **106** with acid chloride **107** affords cyclopropane carboxylate **108** which can be finally converted to momfluorothrin [81].

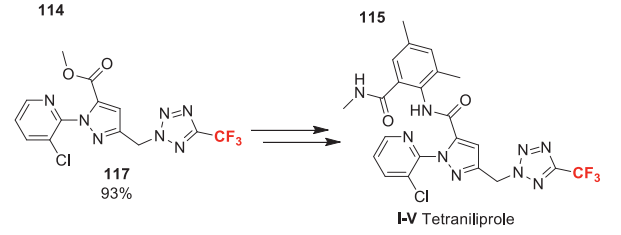
3.4. Triflumezopyrim (*I-IV*)

Triflumezopyrim (**I-IV**) was discovered by DuPont as a novel and highly potent insecticide to control hoppers in rice. This compound has been found to have a very favorable environmental profile with minimal effects on fish, aquatic invertebrates, avian species, earthworms, beneficial arthropods, or honeybees. Triflumezopyrim belongs to the novel class of mesoionic insecticides, and binds to the orthosteric site of the nicotinic acetylcholine (nAChR) receptor and acts primarily *via* inhibition of the binding site [82]. Trifluoromethyl group is introduced through the coupling between 1-iodo-3-(trifluoromethyl)benzene **109** and dimethyl malonate **110** (Scheme 24). The obtained compound **111** is then hydrolyzed to give malonic acid derivative **112**. Finally, the condensation of **112** and **113** produces triflumezopyrim [82].

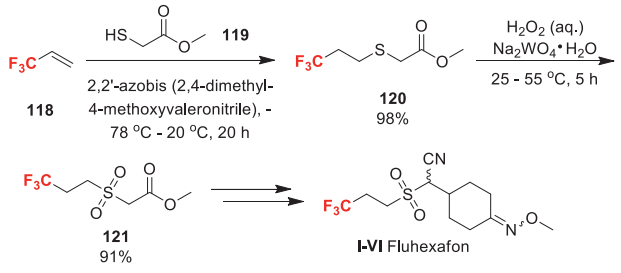
3.5. Tetraniliprole (*I-V*)

Tetraniliprole (**I-V**) was announced by Bayer Crop Science as a new diamide insecticide. It exhibits excellent control performance





Scheme 25. Fluorine introduction of tetraniliprole **(I-V)**.



Scheme 26. Fluorine introduction of fluhexafon **(I-VI)**.

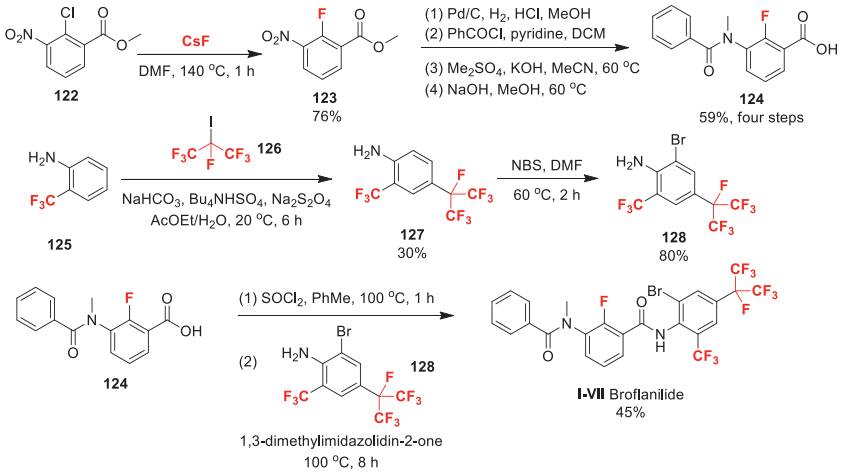
on lepidopteran pests. Tetraniliprole has a novel mode of action involving activation ryanodine receptor, which plays an important role in the muscle function of insects [83]. The trifluoromethyl tetrazole moiety is introduced through alkylation of **115** with **116** (Scheme 25). Compound **115** can be generally made from easily available 2,2,2-trifluoroacetamide **114** [84]. This transformation involves dehydration of **114** and subsequent 1,3-dipolar cyclization with sodium azide [85].

3.6. Fluhexafon (*I-VI*)

Fluhexafon (**I-VI**) was developed by Sumitomo Chemical for controlling aphids and hoppers [86]. It has also been reported to be able to control cockroaches, house flies, and mosquitoes [86]. The mode of action has not yet been reported. The trifluoromethyl group is introduced through a novel radical addition reaction of methyl thioglycolate **119** to trifluoropropene **118** [87]. The obtained compound **120** is oxidized to sulfonyl acetate **121**, which can be further converted to fluhexafon by a couple of steps [88].

3.7. Broflanilide (*I-VII*)

Broflanilide (**I-VII**) was announced by Mitsui Chemicals Agroin and received the ISO name in 2014. It has a unique *meta*-diamide chemical structure and exhibits high activity against various pests, including lepidopteran, coleopteran, and thysanopteran pests. Because broflanilide has a novel mode of action, the Insecticide Resistance Action Committee (IRAC) classified it as a member of a new group: Group 30 [89]. Broflanilide is classified as a negative allosteric modulator of insect γ-aminobutyric acid receptors (GABARs) as desmethyl-broflanilide allosterically inhibits the GABA-induced responses [90, 91]. The synthesis of broflanilide is completed by the coupling of two fluorine-containing building blocks **124** and **128** (Scheme 27) [92]. Compound **124** is synthesized from **122**, which is first fluorinated through Halex reaction [92]. Compound **123** undergoes sequential reduction, benzoylation, methylation and hydrolysis to obtain **124** in good yield [92]. In

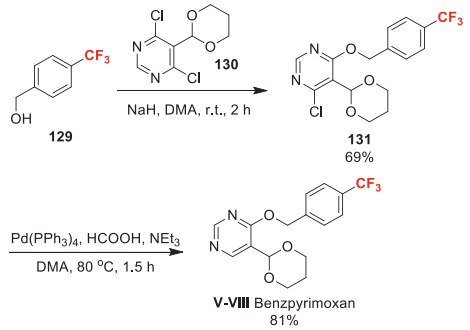


Scheme 27. Fluorine introduction of broflanilide **(I-VII)**.

the other hand, compound **128** is prepared by sequential radical alkylation of easily available 2-trifluoromethyl aniline **125** with heptafluoro-2-iodopropane **126** and bromination of **127** with NBS [93].

3.8. Benzpyrimoxan (*I-VIII*)

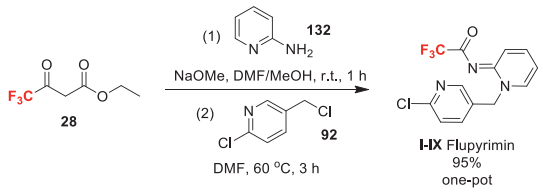
Benzpyrimoxan (**I-VIII**) was developed by Nihon Nohyaku as a novel insecticide structurally characterized by a pyrimidine derivative substituted with 1,3-dioxanyl and 4-trifluoromethylbenzyloxy groups [94]. Benzpyrimoxan exhibits excellent activity against nymphal stages of rice plant hoppers, including strains resistant to existing insecticides [95]. Furthermore, benzpyrimoxan has low adverse effects on pollinators and beneficial arthropods. The study on its mode of action is undergoing. For the synthesis of benzpyrimoxan, 4-trifluoromethyl benzyl alcohol **129** is employed as raw material to introduce trifluoromethyl group (Scheme 28). The dechloroetherification of **130** with **129** leads to **131**, which then undergoes palladium-catalyzed dechlorohydrogenation to afford benzpyrimoxan [94].



Scheme 28. Fluorine introduction of benzpyrimoxan **(I-VIII)**.

3.9. Flupyrimin (*I-IX*)

Flupyrimin (**I-IX**) was developed by Meiji Seika Pharma as a novel neonicotinoid insecticide. It exhibits remarkable biological properties featuring outstanding potency to neonicotinoid-insensitive rice insect pests and superior safety toward pollinators [96]. Intriguingly, flupyrimin acts on the insect nAChRs as an antagonist via a recognition manner different from those of the other nicotinic insecticides [97]. Flupyrimin is synthesized through trifluoroacetylation of **132** with trifluoroacetoacetate **28** and subsequent alkylation with 2-chloro-5-(chloromethyl)pyridine **92** in one-pot (Scheme 29) [98].



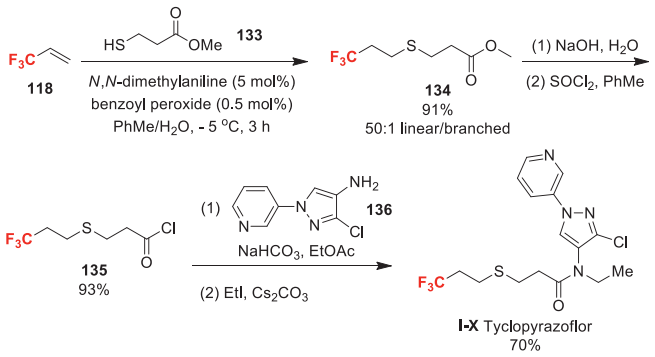
Scheme 29. Fluorine introduction of flupyrimin **(I-IX)**.

3.10. Tyclopyrazoflor (*I-X*)

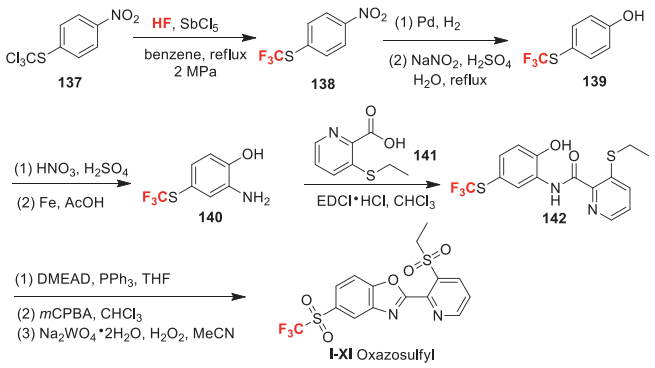
Tyclopyrazoflor (**I-X**) was developed by Dow (Corteva Agriscience) and received its ISO name in 2017. It is a pyrazole-containing insecticidal candidate with excellent activities against sap-feeding pests [99]. The synthesis of tyclopyrazoflor is based on the amidation of advanced pyridinylpyrazole derivative **136** with acid chloride **135**. A radical strategy is applied for the synthesis of intermediate **134** with trifluoropropene **118** as raw material. Its synthesis is similar as the preparation of **120** in Scheme 26. The major challenge of this radical thiol−ene chemistry is the regioselectivity between the linear and branched products. Recently, Gray and coworkers reoptimized this transformation and developed a two-component initiator system consisting of benzoyl peroxide and *N,N*-dimethylaniline, which improved the overall yield and selectivity of the radical thiol−ene reaction from 78% yield and 11:1 selectivity with azobis(isobutyronitrile) to 91% yield and 50:1 selectivity (Scheme 30) [100].

3.11. Oxazosulfyl (*I-XI*)

Oxazosulfyl (**I-XI**) was developed by Sumitomo Chemical as the first representative of a novel sulfyl class of insecticides [101]. It exhibits broad-spectrum control of insect pests, such as hemiptera, lepidoptera and coleoptera. Especially, this compound is effective in controlling major rice insects, including the three planthopper species, *Nephotettix cincticeps, Cnaphalocrocis medinalis* and *Oulema oryzae* [89]. Even though, its mode of action is unclear, Suzuki and Yamato recently discovered that the mechanism of oxazosulfyl involved the state-dependent blockage of voltage-gated sodium channels [102]. Oxazosulfyl can be synthesized as described in Scheme 31 [101]. The trifluoromethylthio group is introduced by halogen exchange of **137**. Then the obtained compound **138** undergoes reduction and Sandmeyer reaction to afford **139**. Com-



Scheme 30. Fluorine introduction of tyclopyrazoflor **(I-X)**.

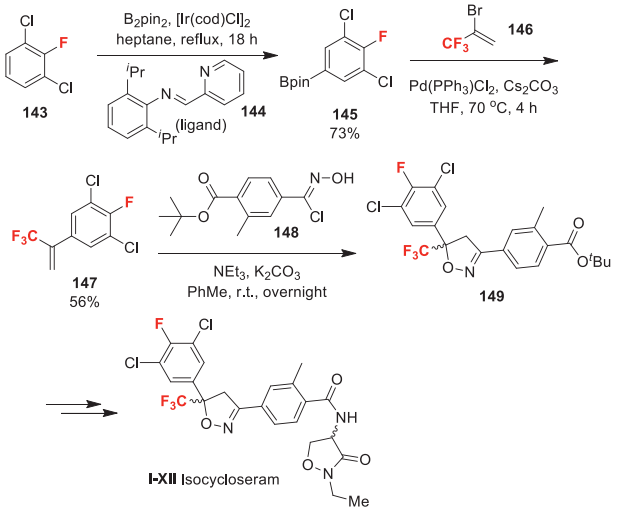


Scheme 31. Fluorine introduction of oxazosulfyl **(I-XI)**. DMEAD = bis(2-methoxyethyl)azodicarboxylate.

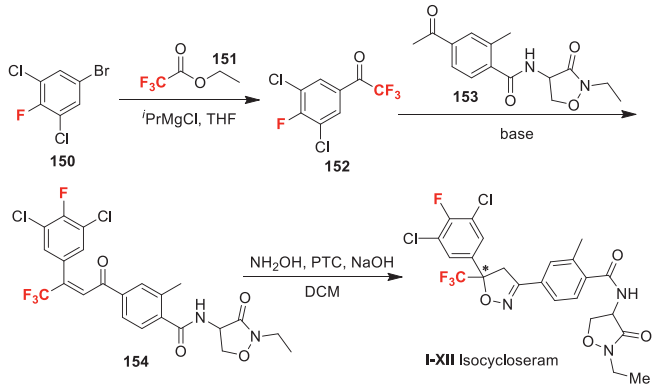
pound **139** can produce key intermediate **140** through nitration and reduction processes [103]. Next, the condensation between aminophenol **140** and carboxylic acid **141** generates benzoxazole intermediate **142**. In the end, cyclization of **142** and subsequent oxidation of trifluoromethylthio group and ethylthio group give oxazosulfyl.

3.12. Isocycloseram (*I-XII*)

Isocycloseram (**I-XII**) was announced by Syngenta Crop Protection as a new member of the isoxazoline class of insecticides [103]. It exhibits broad control of a range of crop-damaging pests, in particular order lepidoptera, hemiptera, coleoptera, thysanoptera, diptera, and acari [103]. There is now a consensus that isoxazoline insecticides act as unique modulators of the invertebrate GABA-gated chloride channels mainly present in the insect central nervous system. The key step of the synthesis of isocycloseram is the construction of trifluoromethyl substituted isoxazoline ring which can be completed in two different routes. In Scheme 32, a [3+2] dipolar cyclization approach is shown. First of all, the *para*-selective borylation of fluorobenzene **143** affords **145**. The Suzuki coupling of **145** and bromotrifluoropropene **146** produces key building block **147** [104]. Then the [3+2] dipolar cyclization of **147** and **148** affords trifluoromethyl isoxazoline **149**, which can be finally converted to isocycloseram [105]. Alternatively, the isoxazoline core structure can also be assembled by the condensation of chalcone derivative **154** and hydroxylamine catalyzed by chiral phase transfer catalyst [103]. This synthetic breakthrough enabled an efficient access to highly enantioenriched mixtures of the desired compound [106]. The chalcone precursor **152** is made through Grignard reaction between **150** and trifluoroacetate **151** (Scheme 33).



Scheme 32. Fluorine introduction of isocycloseram **(I-XII)**.



Scheme 33. Alternative fluorine introduction method of isocycloseram **(I-XII)**. PTC means phase transfer catalyst.

4. Herbicides

In the herbicide section, fluorine introduction methods of 7 representative herbicides are discussed (Fig. 3).

4.1. Tiafenacil (*H-I*)

Tiafenacil was developed by Farm Hannong as a new pyrimidinedione herbicide. It is a new protoporphyrinogen IX oxidase (PPO)-inhibiting herbicide, with IC_{50} values of 22-28 nmol/L for various plant species, including amaranth (*Amaranthus tuberculatus*), soybean (*Glycine max*), arabidopsis (*Arabidopsis thaliana*), and rapeseed (*Brassica napus*) [107]. The key step for preparing tiafenacil is the condensation between 2-fluorophenyl carbamate **156** and ethyl 3-amino-4,4,4-trifluorocrotonate **157** to afford the pyrimidinedione core structure **158** (Scheme 34) [108]. The precursor **156** can be made from easily available 4-chloro-2-fluoroaniline **155**. It is worth noting that compound **157** is a useful raw material, which is generally made from the amidation of trifluoroacetylacetate **28**.

4.2. Trifludimoxazin (*H-II*)

Trifludimoxazin was developed by BASF as a new 1,3,5-triazinane herbicide. It is intended for the non-selective pre-plant knockdown and selective pre-emergence residual control of a range of broadleaf weeds and suppression of key grass weeds prior

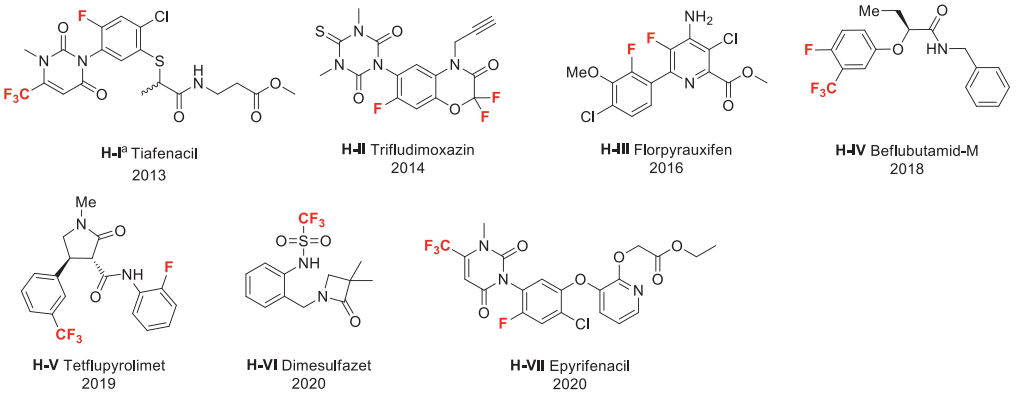
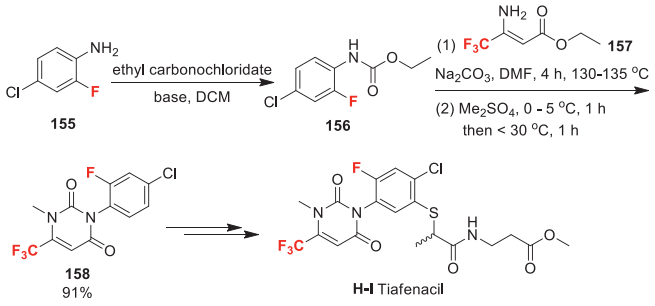
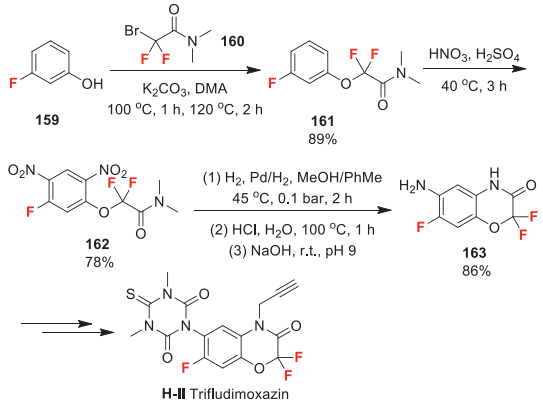


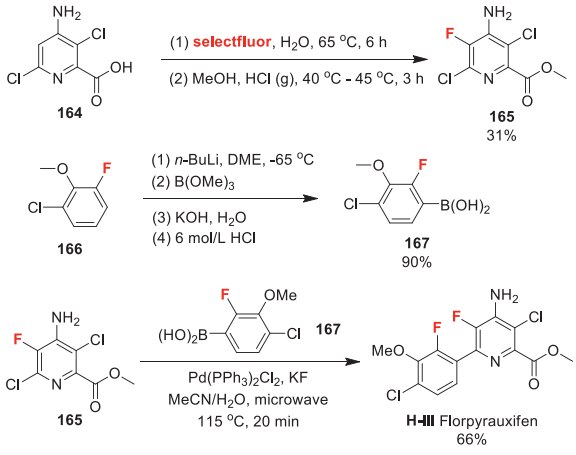
Fig. 3. Structure of 7 herbicides featured in this review. [a] **H-I** means herbicide I.



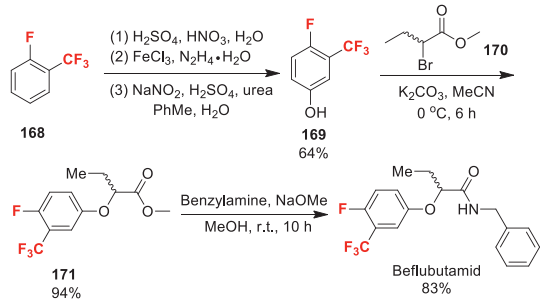
Scheme 34. Fluorine introduction of tiafenacil (**H-I**).



Scheme 35. Fluorine introduction of trifludimoxazin (**H-II**).



Scheme 36. Fluorine introduction of florpyrauxifen (**H-III**).



Scheme 37. Fluorine introduction of beflubutamid.

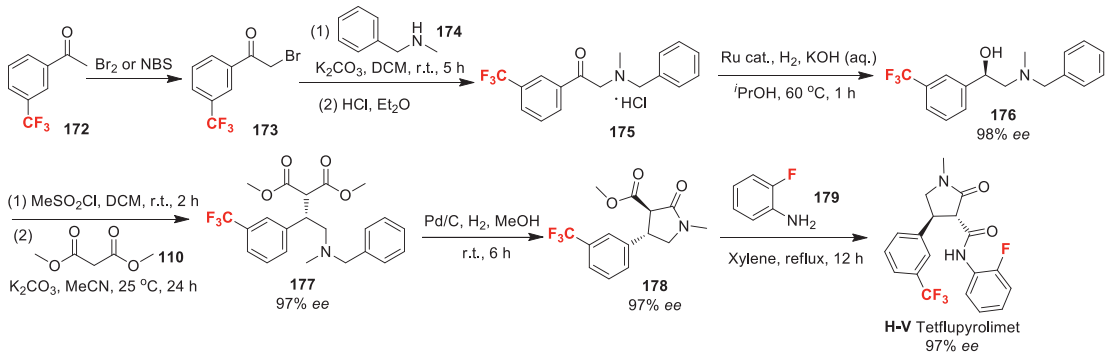
to planting of cereal crops [109]. Trifludimoxazin inhibits the protoporphyrinogen oxidase (PPO) enzyme, ultimately interfering with the chlorophyll biosynthetic pathway [109]. The fluorine introduction of trifludimoxazin is achieved by coupling of 3-fluorophenol **159** and 2-bromo-2,2-difluoroacetamide **160** (Scheme 35). The obtained intermediate **161** undergoes double-nitration to yield compound **162**. Then **162** occurs reduction and intramolecular cyclization to obtain *gem*-difluoro-benzoxazinone intermediate **163**, which can be finally converted to trifludimoxazin by a couple of transformations [110].

4.3. Florpyrauxifen (*H-III*)

Florpyrauxifen was developed by Corteva Agriscience as an auxin-like herbicide, which structurally characterized by arylpicolinate. It is usually used as a benzyl derivative with various applications including controlling of grass, sedge and broadleaf weed in rice, as well as managing freshwater aquatic vegetation and invasive freshwater aquatic vegetation [111]. The specific mode of action of synthetic auxins is actually not fully known, but the possible effects on plants include alterations in cell wall elasticity and gene expression [111]. For the synthesis of florpyrauxifen, compound **165** is applied as a fluorine-containing building block. It can be made through the electrophilic fluorination of **164** with selectfluor [112] and subsequent methylation process. Another fluorine-containing building block **167** is prepared by borylation of raw material **166** [113]. In the end, the Suzuki coupling of **165** and **167** affords florpyrauxifen in good yield (Scheme 36) [114].

4.4. Beflubutamid-M (*H-IV*)

Beflubutamid was developed in the nineties by Ube Industries as a phenoxybutanamide herbicide. It is a soil herbicide for pre- and early post-emergence control of dicotyledonous weeds in ce-



Scheme 38. Fluorine introduction of tetflupyrolimet (**H-V**). Ru cat. = dichloro[(5)-(-)-2,2′,6,6′-tetramethoxy-4,4′-bis(di(3,5-xylyl)phosphino)-3,3′-bipyridine][(15,2*S*)-(-)-l,2-diphenylethylenediamine]ruthenium(II) (CAS Registry No. 821793-37-7).

reals [115]. Beflubutamid consists of a pair of enantiomers and is marketed as racemates. However, the biotests have shown that (-)-beflubutamid has at least 1000-fold higher activity than (+)-beflubutamid [116]. So, the (-)-beflubutamid has received an ISO name as beflubutamid-M in 2018. Beflubutamid inhibits the enzyme phytoene-desaturase, which is involved in the biosynthesis of carotenoids. The chiral beflubutamid-M was isolated by high-performance liquid chromatography (HPLC) [116]. The synthesis of the racemic beflubutamid is shown in Scheme 37. First of all, fluorine is introducted by using 1-fluoro-2-(trifluoromethyl)benzene **168** as raw material. It undergoes nitration, reduction and Sandmeyer reaction to afford compound **169** [117]. Then the coupling of **169** and **170** gives ester intermediate **171** [118]. Finally, the amidation of **172** produces the racemic beflubutamid [119].

4.5. Tetflupyrolimet (*H-V*)

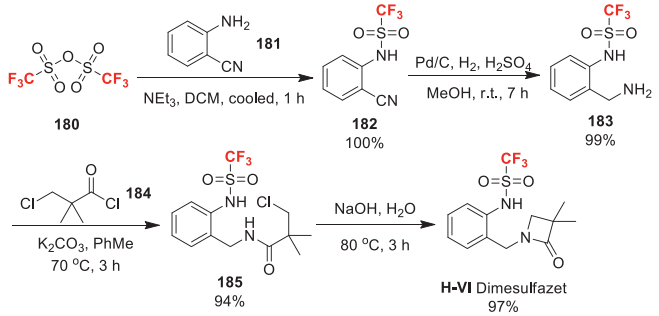
Tetflupyrolimet was developed by FMC Corporation as an aryl pyrrolidinone anilide herbicide. It provides season-long control of important grass weeds in the rice market, as well as key hard-to-control broadleaf weeds and sedges. Tetflupyrolimet is a new mode of action herbicide for the first time in last three decades, it interferes with *de novo* pyrimidine biosynthesis *via* the inhibition of dihydroorotate dehydrogenase (DHODH) [120]. The FMC Corporation reported a synthetic route for tetflupyrolimet (Scheme 38) [121]. The synthesis starts from the coupling of 2-bromoacetophenone **173** and amine **174**, in which **173** can be usually made by bromination of raw material **172**. The obtained amine hydrochloric acid salt **175** undergoes asymmetric hydrogenation to produce alcohol **176** with R configuration. Compound **176** is then converted to **177** by sequential mesylation and alkylation. Next, the debenzylation followed by intramolecular cyclization affords lactam **178**. Finally, the 2-fluoroaniline moiety is introduced by amidation of **178** to obtain tetflupyrolimet in high *ee* value.

4.6. Dimesulfazet (*H-VI*)

Dimesulfazet was developed by Nissan Chemical as a haloalkylsulfonanilide herbicide used in paddy fields. Its mode of action is presumed to inhibit a very-long-chain fatty acid synthesis (VLCFAS) [122]. The fluorine introduction is achived by trifluoromethanesulfonylation of **181** with trifluoromethanesulfonic anhydride **180** (Scheme 39). Then the obtained compound **182** is reduced to **183**. The amidation of **183** and **184** gives **185**. Finally, the intramolecular cyclization of **185** promoted by base yields dimesulfazet [123].

4.7. Epyrifenacil (*H-VII*)

Epyrifenacil was developed by Sumitomo Chemical as a phenyluracil herbicide with excellent activity [124]. It is a protoporphyrinogen oxidase (PPOX) inhibitor. The key intermediate of the synthesis of epyrifenacil is phenylether **193**, which can be made in different routes. Here, we select one route that has been reported by Syngenta [125]. The synthesis starts with the alkylation of fluoring-containing raw material **186** with **187**. The obtained **188** undergoes cyclization with 1,1,3,3-tetramethoxypropane **189** to produce phenylether **190**. Then the O-alkylation of **190** with diazo compound **191** affords **192**. The nitration and subsequent reduction of **192** yields **193**. Next, the trifluoromethyl group is introduced by amidation between **193** and trifluoroacetoacetate **28** to obtain **194** [126]. In the end, the uracil moiety is assembled by the condensation of **194** and potassium cyanate (Scheme 40).



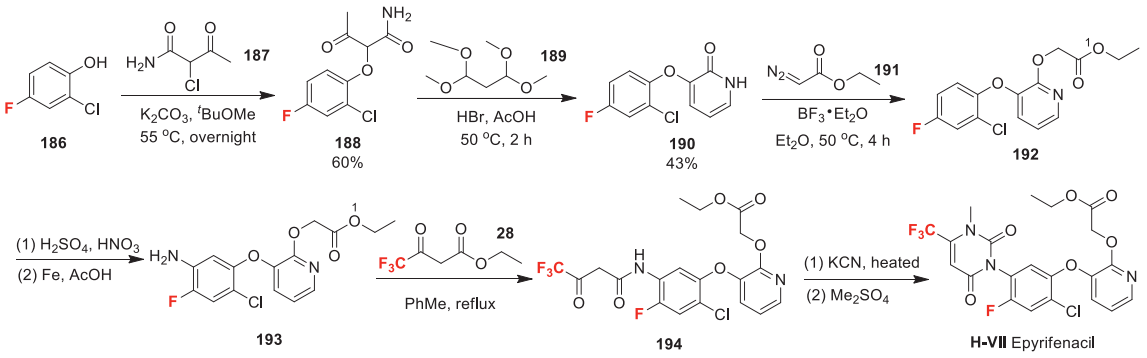
Scheme 39. Fluorine introduction of dimesulfazet (**H-VI**).

5. Acaricides and nematicides

In this section, fluorine introduction methods of 4 acaricides and 2 nematicides are discussed (Fig. 4).

5.1. Pyflubumide (*A-I*)

Pyflubumide was developed by Nihon Nohyaku as a novel carboxanilide acaricide which has a unique methoxyhexafluoroisopropyl substituent on the aniline [127]. It exhibits high activity against phytophagous mites, including populations of spider mites that have developed resistance to conventional acaricides. Pyflubumide is a novel inhibitor of mitochondrial complex II on the respiratory chain [127]. The fluorine moiety is introduced by employing heptafluoro-2-iodopropane **126** as raw material (Scheme 41). It undergoes a radical reaction with aniline **195** to obtain **196**. Then the defluoromethoxylation of **196** with sodium methoxide affords **197** [128]. Finally, **197** undergoes twice amidation reactions with acid chloride **198** and **199** to yield pyflubumide [129].



Scheme 40. Fluorine introduction of epyrifenacil **(H-VII)**.

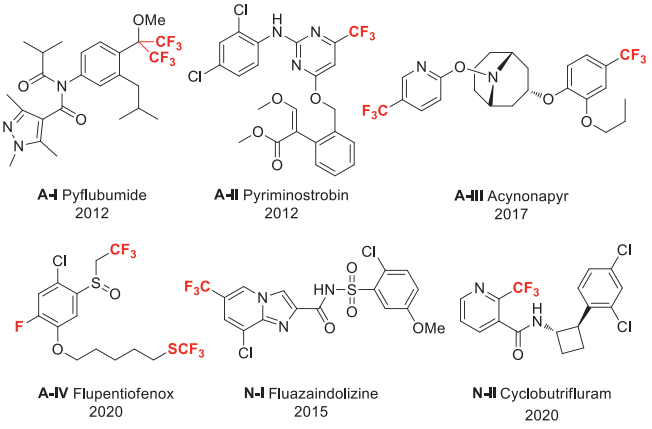
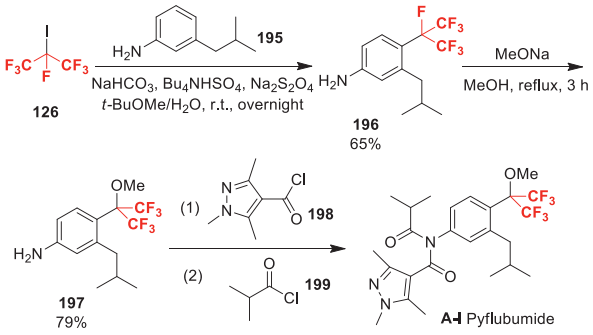
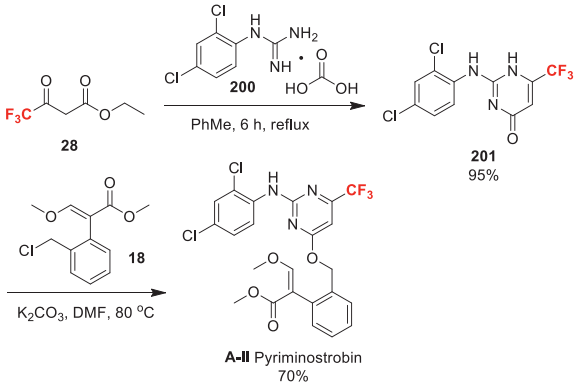


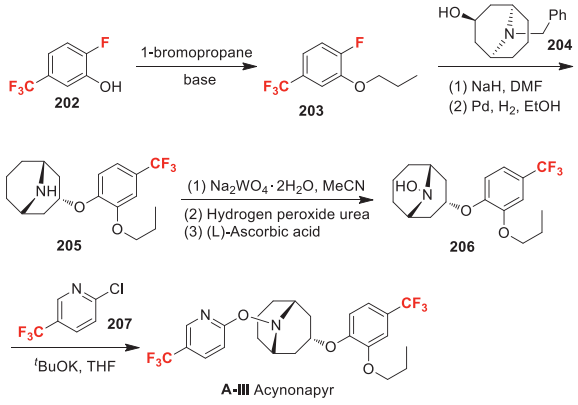
Fig. 4. Structures of 4 acaricides and 2 nematicides featured in this review. **A-I** means acaricide I. **B-I** means nematicide I.



Scheme 41. Fluorine introduction of pyflubumide **(A-I)**.



Scheme 42. Fluorine introduction of pyriminostrobin **(A-II)**.



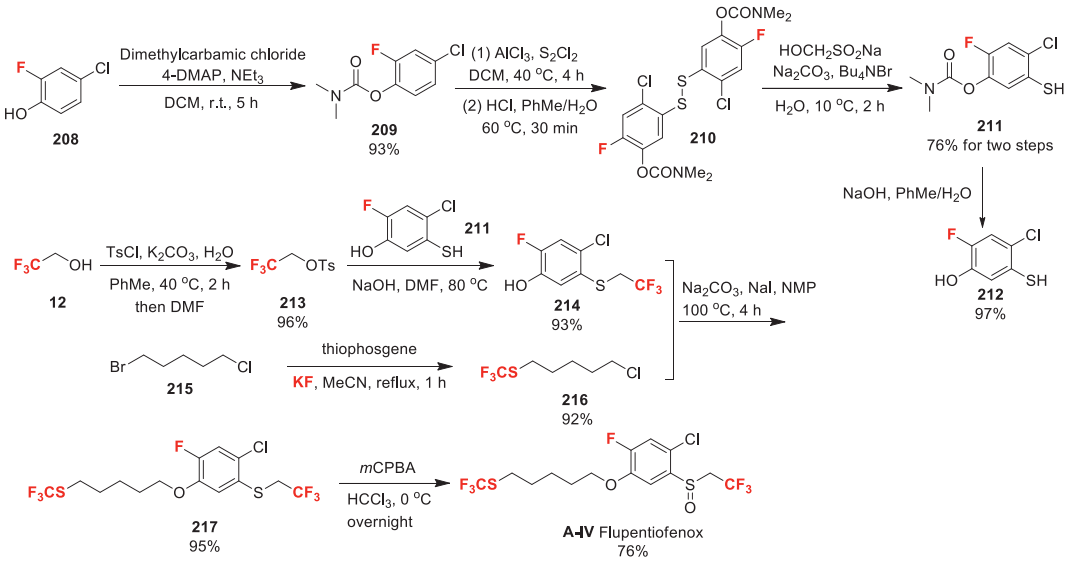
Scheme 43. Fluorine introduction of acynonapyr **(A-III)**.

5.2. Pyriminostrobin (*A-II*)

Pyriminostrobin was announced by Shenyang Research Institute of Chemical Industry (SYRICI) as a novel methoxyacrylate strobilurin acaricide. It exhibits notable control of *Tetranychus cinnabarinus* [130]. The acaricidal potency of pyriminostrobin is higher than that of fluacrypyrim in greenhouse application, and is comparable with those of commercial acaricides such as spirodiclofen and propargite in field trials [130]. For the synthesis of pyriminostrobin, trifluoroacetoacetate **28** is used for the construction of pyrimidine moiety (Scheme 42). The condensation of **28** and phenyl guanidine **200** affords intermediate **201** in excellent yield [131]. Then the *O*-alkylation of compound **201** with **18** produces pyriminostrobin.

5.3. Acynonapyr (*A-III*)

Acynonapyr was developed by Nippon Soda as a new acaricide, which structurally characterized by an azabicyclo ring. It exhibits a selective effect on spider mites of tetranychus and panonychus. Its application is currently being expanded to fruit, tea, vegetables, and flowering fields. Acynonapyr has been reported to act on glutamate receptors and interfere neurotransmission [27]. The synthesis of acynonapyr starts with the alkylation of raw material **202** to obtain compound **203** (Scheme 43). The defluoroetherification of **203** with azabicycle **204** and subsequent debenzylation process produces intermediate **205**. Then **205** is oxidized to hydroxylamine **206** [132]. The final *O*-arylation of **206** affords acynonapyr with trifluoromethyl pyridine **207** as aromatic source [133]. Compound **207** can be easily prepared in the same way as compound **65** (Scheme 15) by halogen exchange.



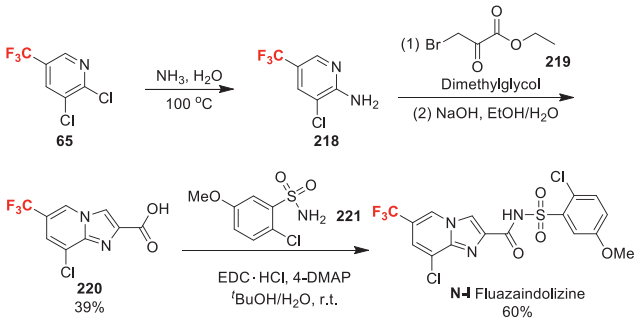
Scheme 44. Fluorine introduction of flupentiofenox **(A-IV)**.

5.4. Flupentiofenox (*A-IV*)

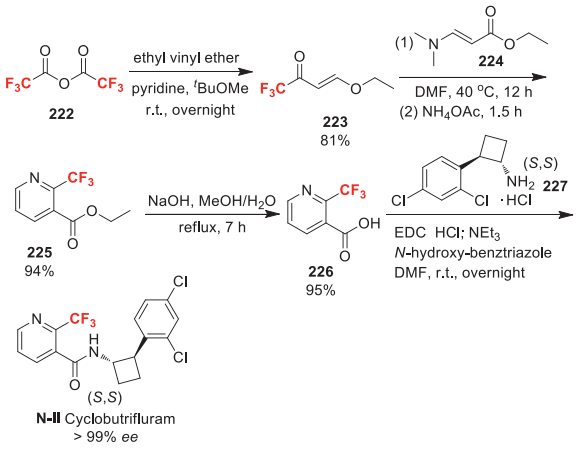
Flupentiofenox was developed by Kumiai Chemical Industry as an alkylphenylsulphide acaricide candidate [134]. It has three different fluorine-containing functional groups. The fluorobenzene moiety is introduced by using 4-chloro-2-fluorophenol **208** as starting material (Scheme 44). It can be transferred to fluorobenzenethiol **212** by sequential *O*-protection, Friedel-Crafts-type thiolation, radical reduction and *O*-deprotection [135]. Then compound **212** is converted to **214** by alkylation with **213** which comes from trifluoroethanol **12**. In this step, the trifluoromethyl group is introduced. On the other hand, the trifluoromethylthiolation of **215** produces **216** by *in situ* generated trifluoromethylthio anion [136]. Next, the coupling between **214** and **216** yields compound **217**, in which all the three fluorine-containing functional groups are assembled [137]. In the end, **217** is converted to flupentiofenox by oxidation with *m*CPBA [138].

5.5. Fluazaindolizine (*N-I*)

Fluazaindolizine was developed by DuPont Company as a new member of the class of imidazopyridine nematicides [139]. Fluazaindolizine exhibits excellent control of plant parasitic nematodes and the damage they cause to plant roots. Specificity for nematodes coupled with absence of activity against the target sites of commercial nematicides suggests that fluazaindolizine has a novel mode of action. The core trifluoromethyl imidazopyridine structure (**220**) of fluazaindolizine is constructed by condensation of 2-aminopyridine **218** and ketoester **219** (Scheme 45) [140]. Compound **218** is obtained via amination of **65** [141], the synthesis of which has been shown in Scheme 15. The coupling of **220** and **221** produces imidazopyridine in good yield.



Scheme 45. Fluorine introduction of fluazaindolizine **(N-I)**.



Scheme 46. Fluorine introduction of cyclobutrifluram **(N-II)**.

5.6. Cyclobutrifluram (*N-II*)

Cyclobutrifluram was announced by Syngenta as a novel nematicides. It contains 80%–100% of the (1*S*,2*S*)-enantiomer and 20%–0% of the (1*R*,2*R*)-enantiomer. It is a novel multi-use pesticide that offers control of a broad spectrum of nematode pests and diseases across all major crops. Cyclobutrifluram is presumed to be an inhibitor of the mitochondrial electron transport chain complex II based on its similarity in chemical structure to fluopyram [27]. The Syngenta Company reported a route for the synthesis of (1*S*,2*S*) enantiomer of cyclobutrifluram [142]. In this synthesis, the key step is the coupling of chiral cyclobutylamine **227** and 2-trifluoromethyl nicotinic acid **226** (Scheme 46). Here, we present a general synthetic approach for preparing compound **226** [143]. First of all, trifluoroacetic anhydride **222** reacts with ethyl vinyl ether to obtain compound **223**. Then the addition of **224** to **223** followed by cyclization affords 2-trifluoromethyl nicotinic acid ethyl ester **225**. Finally, **225** is hydrolyzed to produce acid **226**.

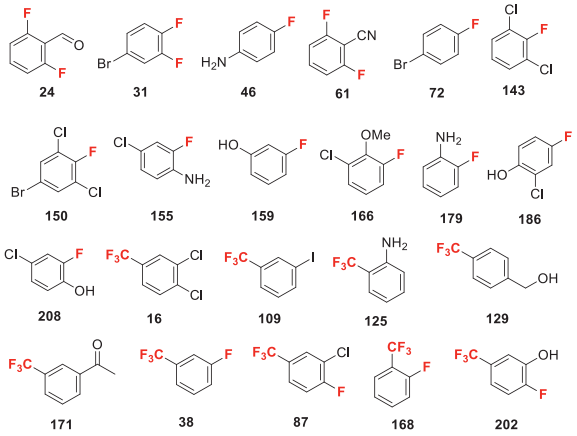


Fig. 5. Fluoroarene and trifluoromethylarene building blocks used directly.

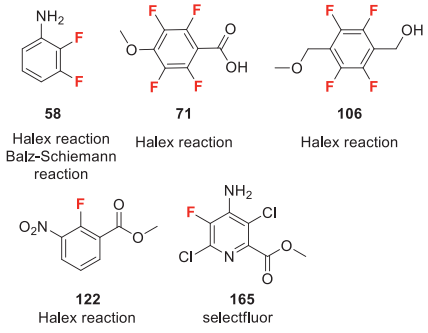


Fig. 6. Fluoroarene building blocks synthesized.

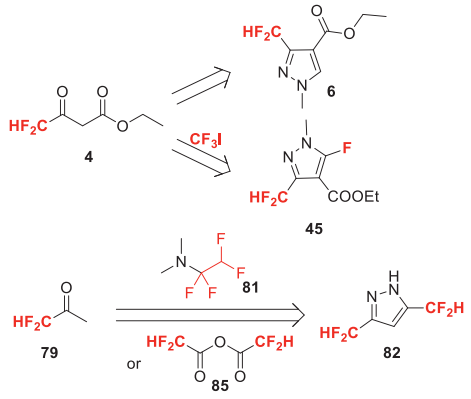


Fig. 7. Difluoromethylarene building blocks synthesized.

Here we summarize all the fluorine-containing building blocks that have been used in this review (Figs. 5-9). There are 22 fluorobenzene and trifluoromethyl benzene building blocks that have been used directly (Fig. 5). Their colorful reaction pathways for being introduced into the final agrochemicals are described in the main text.

The fluorine introduction method of five representative and not easily available fluoroarene building blocks are discussed in this review (Fig. 6). These methods include Halex reaction, Balz-Schiemann reaction and electrophilic fluorination with selectfluor.

Difluoromethyl pyrazoles are usually used for the synthesis of fungicides. They are made by condensation of fluorine-containing ketones with hydrazines or hydrazones (Fig. 7).

Trifluoromethyl cyclic building blocks include aromatic and non-aromatic structures. They are usually made through cyclization of small fluorine-containing molecules, except trifluoromethyl

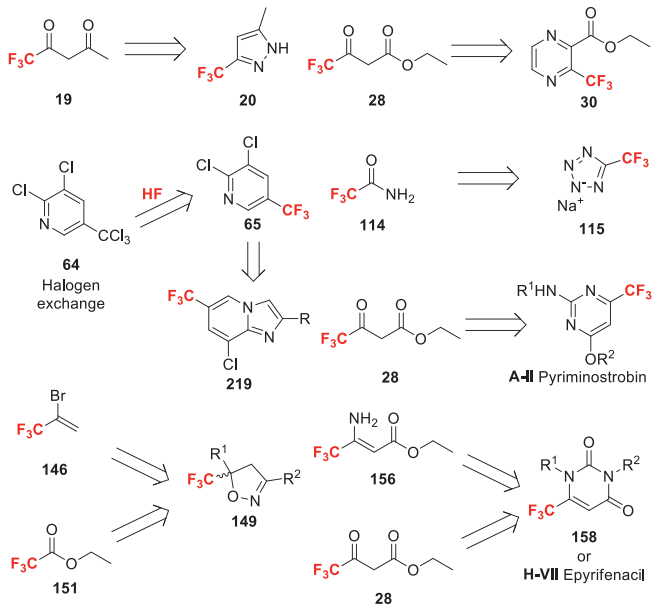


Fig. 8. Trifluoromethyl cyclic building blocks synthesized.

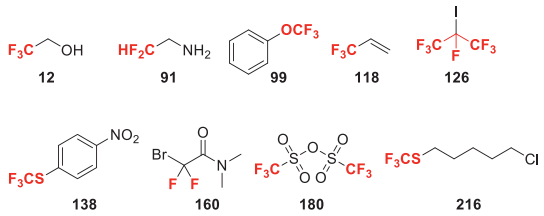


Fig. 9. Other fluorine-containing building blocks.

pyridine **65**, which is obtained by halogen exchange (Fig. 8). It is worth noting that imidazopyridine **220** is made from **65**.

There are also some other fluorine-containing building blocks that have been used in this review (Fig. 9). Some of them are used directly, like alcohol **12**, amine **91**, olefin **118**, alkyl iodide **126**, amide **160** and sulfonic anhydride **180**. The trifluoromethyl ether **99** and trifluoromethyl thioether **138** are made by halogen exchange, and alkyl chloride **216** is made by nucleophilic substitution *via in situ* generated trifluoromethylthio anion.

It is worth noting that there is only one example of late-stage fluorination. The final fluorine introduction of fungicide quinofumelin can be completed either by deoxofluorination with DFI or debromofluorination with triethylamine trihydrofluoride (Scheme 8).

6. Conclusion

This review has showcased the fluorine introduction methods of 40 agrochemicals in the last decade. It can be seen throughout this review that fluoroarenes, difluomethylarenes and trifluomethylarenes are most widely used building blocks for the synthesis of agrochemicals. Fluorine-containing small molecules, such as alcohol, amine, ketoester, olefin, etc., are also widely used, either for the synthesis of more complex cyclic fluorine-containing building blocks or used directly in the final agrochemicals. Here we have not only shown the introduction of fluorine and fluorine-containing functional groups into representative building blocks, but also have revealed how exactly these building blocks were assembled into the final agrochemicals. We think the chemistries showed here can spark ideas for the development of new and economical pesticide synthesis routes, and stimulate researchers to

develop new fluorine incorporation methods and creat new pesticides.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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