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Alkyne chemistry in crop protection ☆

Clemens Lamberth *

Syngenta Crop Protection AG, Crop Protection Research, Chemistry, Schaffhauserstr. 101, CH-4332 Stein, Switzerland

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Dedicated to the memory of Prof. Mark Bednarski.

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ABSTRACT

An overview is given of the significance of alkyne derivatives in crop protection chemistry. The main herbicidally, fungicidally, insecticidally and acaricidally active alkyne classes are presented, together with their synthetic routes, their mode of action and their biological efficacies. Also the importance of alkynes as intermediates in the preparation of agrochemicals is demonstrated.

1. Introduction

The alkyne function is a common structural motif in organic chemistry, linking linearily different moieties of the molecule's scaffold as well as allowing its transformation. The carbon–carbon triple bond is in this regard one of the most important functional groups in organic chemistry,[2] because there are many reactions known, in which new compounds are formed via the transformation of acetylenic groups, such as the Sonogashira-,[3] Castro-Stephens-,[3b] Glaser-[4] and Cadiot-Chodkiewicz[5] couplings, the Pauson-Khand[6] and Nicholas[7] reactions, the Bergman,[8,9] Moore[9] and Myers[9] cyclizations, the Rautenstrauch rearrangement[10] and the Huisgen 1,3-dipoar cycloaddition (click chemistry).[11] The explosive growth of alkyne chemistry has particularly benefited from the recent development of new synthetic methodology based on transition metal catalysts and metal acetylides. Acetylenic functions are also readily found in a series of natural products and exhibit a broad distribution especially in plant species.[12] This review deals with the agrochemical aspects of alkyne chemistry.

2. Herbicides bearing an alkyne group

2.1. PPO (protox) inhbitors

One of the most important herbicidal mode of actions is the inhibition of protoporphyrinogen-IX oxidase (PPO, protox), which is the last enzyme in the porphyrin pathway that is common to both chlorophyll and heme synthesis. In treated tissues, protox inhibitors cause the accumulation of protoporphyrin IX. This tetrapyrrole is known to be a potent photosensitizer, generating high levels of singlet oxygen in the presence of sunlight. This oxygen modification induces peroxidation of unsaturated fatty acids in cell membranes, resulting in membrane leakage, pigment breakdown and finally necrosis of the leaf. Therefore PPO inhibitors are also called peroxidizing herbicides.[13]

The propargyl group seems to be a magic substituent for PPO inhibition, because it is present in many peroxidizing herbicides. This is probably due to the fact, that the propargylated moiety of the inhibitor mimics successfully the vinyl-substituted hydrophobic region of protoporphyrin IX. Some propargylated PPO herbicides, which have been commercialized, are shown in Figure 1. Oxadiargyl (**1**) has been developed for the pre- and early post-emergent control of broadleaf weed, grass and annual sedge in rice and sugarcane,[14] pyraclonil (**2**) is currently under development as a rice herbicide.[15] The benzoxazinone flumioxazin (**3**) is specialized in the pre-emergent control of annual broad-leaved weeds in soybean and peanut.[16] Thidiazimin (**4**)[17] and flumipropyn (**5**)[18] are

☆ See Ref. 1.

* Tel.: +41 61 323 2373; fax: +41 61 323 8726.
E-mail address: clemens.lamberth@syngenta.com

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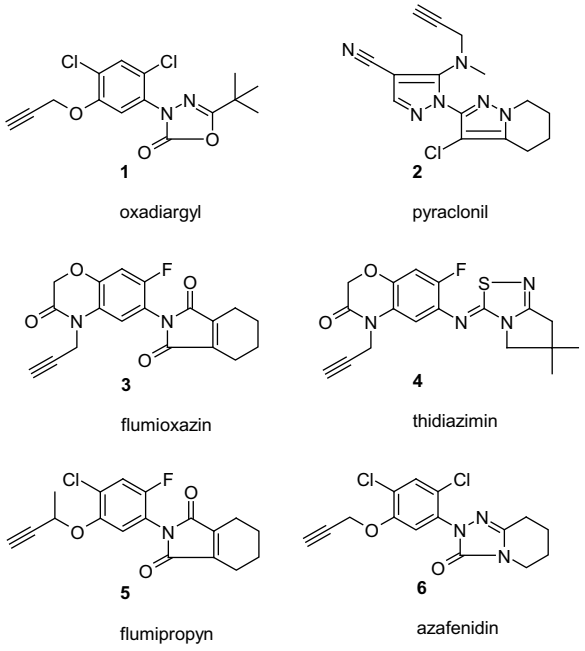


Figure 1. Acetylenic PPO inhibitors on the herbicide market.

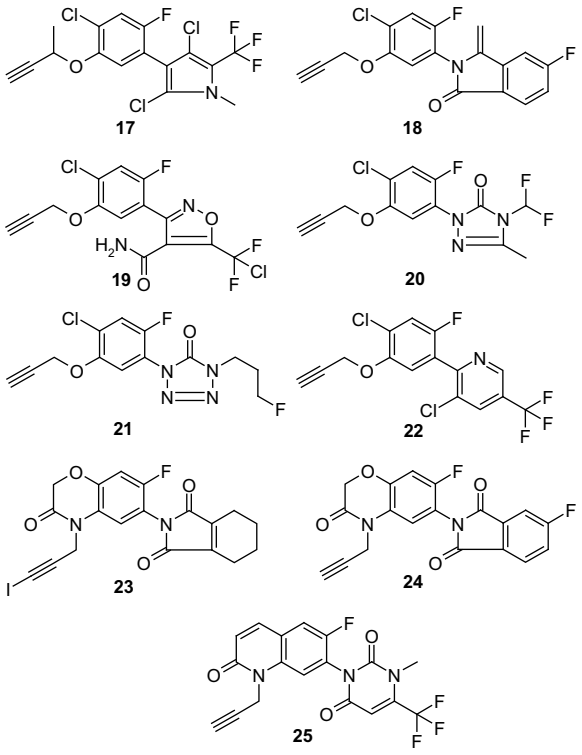
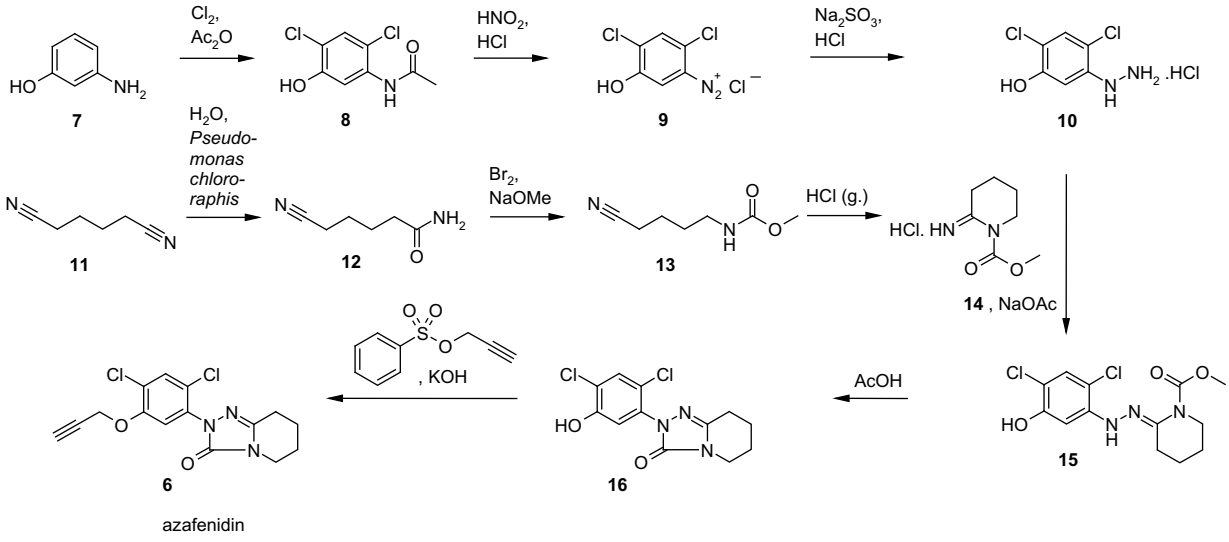


Figure 2. Different types of PPO inhibitors with alkyne functions.

used as post-emergent herbicide in cereals, whereas azafenidin (**6**) has been developed for weed control in vineyards, citrus and olive orchards.[19]

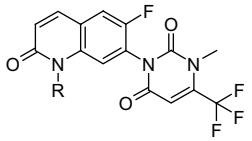
The interesting technical synthesis of azafenidin has been recently reported (Scheme 1).[20] 3-Aminophenol (**7**) could be converted in three steps under the conditions of the Fischer hydrazine synthesis to 2,4-dichloro-5-hydroxyphenylhydrazine (**10**). This building block is condensed with the iminopiperidine salt **14**, which is available in three steps from the inexpensive Nylon intermediate adiponitrile (**11**) via enzyme-catalyzed selective monohydration, Hofmann rearrangement and subsequent Pinner-type cyclization. The obtained amidrazone **15** is then converted by intramolecular 3 + 2 cyclocondensation to the triazolone **16**, which is finally propargylated with propargyl benzenesulfonate to obtain azafenidin (**6**).[20]

Several further propargylated PPO inhibitors with interesting properties have been described in the literature (Fig. 2). The pentasubstituted pyrrole **17** completely controls *Amaranthus retroflexus* (redroot pigweed) and *Solanum nigrum* (common nightshade).[21] The key step in the synthesis of the herbicidally active isoindolone **18** is a unique condensation of an *ortho*-acetylbenzoate with an aniline.[22] The isoxazole **19** showed excellent efficacy against *Abutilon theophrasti* (velvetleaf), *Ipomoea purpurea* (morning glory) and *Echinochloa crus-galli* (barnyard grass).[23] Due to only marginal crop tolerance the trizazolone **20**[24] and the tetrazolone **21**[25] could not be developed, although they are highly active against, for example, *Abutilon theophrasti* (velvetleaf) and *Setaria viridis* (green foxtail). The pyridine **22** possesses strong activity against both grass and broadleaf weeds.[26] The flumioxazin derivative **23**, which is iodin-



Scheme 1. Synthesis of azafenidin (**6**).

Table 1
Preemergent herbicidal activity of different N-substituted quinolinone-based PPO inhibitors against *Abutilon theophrasti and Ipomoea purpurea*



Compound	R	ED_{85} (g/ha)	
		Abutilon theophrasti (velvetleaf)	*Ipomoea purpurea* (morning glory)
26	H	30	30
27	CH_3	10	10
28	CH_2CH_3	3	10
29	$CH_2CH_2CH_3$	10	30
30	$CH_2CH{=}CH_2$	1	3
25	$CH_2C{\equiv}CH$	1	3
31	CH_2CN	10	30
32	$CH_2CO_2CH_3$	10	100
33	$CH_2CH(CH_3)_2$	10	30

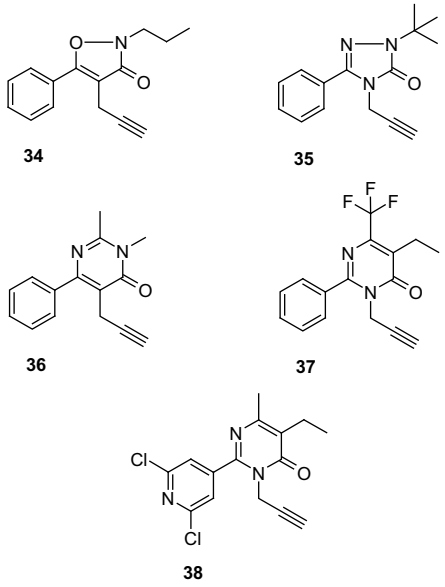


Figure 3. Different types of ZDS inhibitors with alkyne functions.

ated at the terminal alkyne position, is a powerful post-emergent herbicide with better crop selectivity than flumioxazin (**3**) at the same dosage rate.[27] The combination of high efficacy against several weeds, such as *Abutilon theophrasti* (velvetleaf), *Amaranthus ascedense* (redroot pigweed) and *Digitaria sanguinalis* (crabgrass) and a crop selectivity comparable to the structurally related flumioxazin (**3**) is also the strength of the phthalimide **24**.[27] Out of several substituents which have been attached to the nitrogen atom of the quinolinone ring of the PPO inhibitor **25**, the propargyl but also the allyl group gave by far the best herbicidal results (Table 1).[28]

2.2. ZDS inhibitors

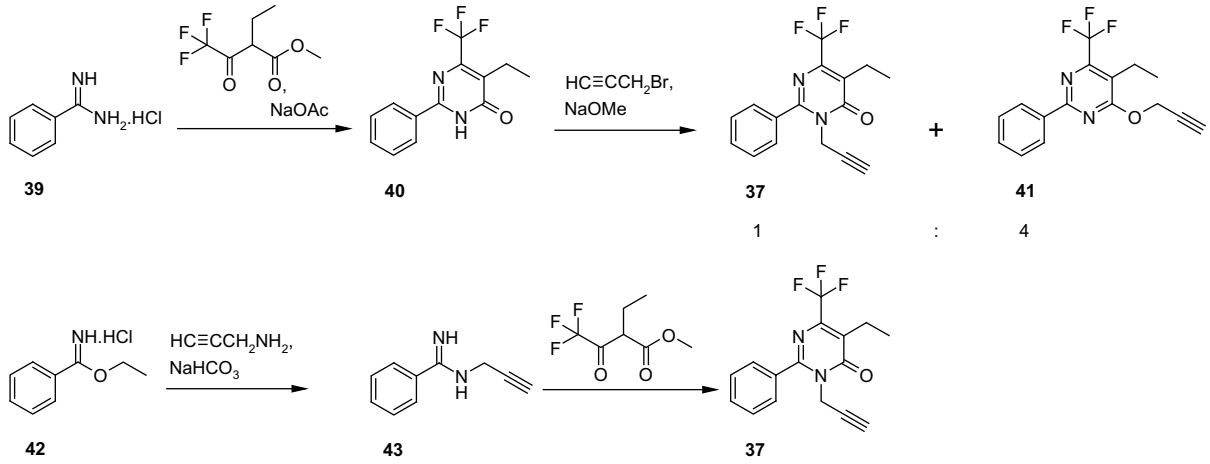
Herbicides, which block the enzyme ζ-carotene desaturase (ZDS) inhibit the accumulation of both chlorophyll and β-carotene and concomitantly induce the accumulation of the β-carotene precursors phytoene, phytofluene and, in particular, ζ-carotene.[29] As a result, newly growing leaf tissue is white, because it emerges devoid of any photosynthetic pigments. Therefore ZDS inhibitors belong to the so-called bleaching herbicides.[30]

Typical examples of this class of pre-emergent herbicides, which control a broad range of mono- and dicotyledonous weeds, are the phenyl- and propargyl-substituted isoxazolone **34**,[31] triazolone **35**[31] as well as the two regioisomeric pyrimidinones **36**[31] and **37**.[32,33] Regarding herbicidal efficacy, it does not seem to play a role if the propargyl group is linked to a ring carbon or nitrogen atom. Also the dichloropyridyl-substituted pyrimidinone **38** displays good herbicidal activity[32,34] (Fig. 3).

The original synthesis of **37** was troubled by selectivity problems during the propargylation. The reaction sequence started with the condensation of benzamidine hydrochloride (**39**) with methyl 2-trifluoroacetylbutanoate to afford the pyrimidinone **40**. The propargylation of this intermediate proceeds in high yield, but with unfavourable selectivity, delivering predominantly the inactive O-propargyl product **41**.[32,33] The formation of this undesired regioisomer could be completely avoided by introduction of the propargyl function before the ring closure. Therefore the *N*-propargyl benzamidine **43** was prepared first by reaction of ethyl benzimidate hydrochloride (**42**) with propargylamine under basic conditions. Subsequent condensation with the same β-ketoester of the original approach reliably delivers the bleaching herbicide **37**[32,33] (Scheme 2).

2.3. Miscellaneous acetylenic herbicides

Several further commercial herbicides bear an alkyne function. The aryloxyphenoxypropionate herbicide clodinafop (**44**), which



Scheme 2. Synthesis of **37**.

inhibits the chloroplastic acetyl-CoA carboxylase (ACC), is mainly used for the selective control of *Alopecurus myosuroides* (black grass), *Poa trivialis* (roughstalk bluegrass) and other stubborn annual grasses in cereals.[35] Only its R-enantiomer is herbicidally active. The antimitotic propyzamide (**45**) is very active against the monocotyledonous weeds *Lolium perenne* (ryegrass) and *Setaria faberii* (foxtail).[36] Prynachlor (**46**), belonging to the class of chloroacetamides, has been used as selective herbicide in soybean and vegetables.[37] The two elder herbicides buturon (**47**) and barban (**48**) have been specialized on grass control in cereals. The urea derivative buturon (**47**) was mainly used as post-emergent herbicide,[38] the strength of the carbamate barban (**48**) was clearly its high herbicidal activity against *Avenua fatua* (wild oat)[39] (Fig. 4).

The aryl-dione herbicide **49** is a potent inhibitor of the cytosolic acetyl-CoA carboxylase (ACC).[40] The propargylated thiatriazin-1,1-dioxide **50** possesses activity against *Cyperus esculentes* (yellow nutsedge), *Amaranthus retroflexus* (redroot pigweed) and *Solanum nigrum* (black nightshade).[41] *N*-Methyl-*N*-propargyl-*N*′-(3,4-dichlorophenyl)urea (**51**) displayed in field trials high pre-emergent activity against *Echinochloa crus-galli* (barnyardgrass) and *Setaria viridis* (green foxtail), while showing an excellent crop tolerance for corn and cotton.[42] Good rice selectivity combined with herbicidal activity against the rice weeds *Echinochloa oryzicola* (early watergrass) and *Cyperus serotinus* (water nutgrass) has been reported for the isoxazolinone **52**.[43] The benzodiazepindione **53** bears herbicidal properties,[44] the phenylpropargyloxy derivative **54** is very efficient against *Stellaria media* (chickweed) and *Amaranthus retroflexus* (redroot pigweed).[45] Also the two pyrazole derivatives **55**[46] and **56**[47] are herbicidally active, the propargyloxy derviative **55** especially against *Echinochloa crus-galli* (barnyard grass),[46] the phenylacetylene derivactive **56** mainly against *Solanum nigrum* (black nightshade), *Amaranthus retroflexus* (redroot pigweed) and *Abutilon theophrasti* (velvetleaf)[47] (Fig. 5).

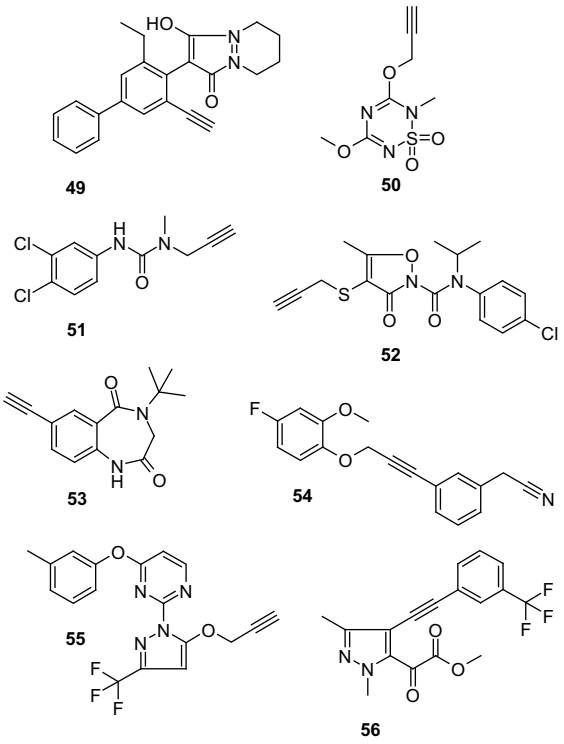


Figure 5. Miscellaneous herbicidally active alkynes.

3. Fungicides bearing an alkyne group

3.1. CAA fungicides

The carboxylic acid amide (CAA) fungicides are a group of structurally diverse compounds, which share the same, so far unknown mode of action.[48] They are mainly active against oomycetes diseases, such as *Phytophthora infestans* (potato and tomato late blight) and *Plasmopara viticola* (grape downy mildew). From this fungicide family, so far cinnamides, valinamides and with mandipropamid (**57**)[49,50] also the first mandelamide reached the market.[48] The double-propargylated mandipropamid is highly effective in preventing spore germination of most foliar oomycete pathogens, but also inhibits mycelial growth and sporulation.[51] Being rapidly absorbed into the wax layer of the plant surface, it provides a rainfast and long-lasting barrier to fungal diseases.[51] Also other α-propargyloxycarboxamides, such as the heterocyclic mandelamide **58** and the glyceric acid amide **59**, are highly active against *Phytophthora infestans* and *Plasmopara viticola*[49,52] (Fig. 6).

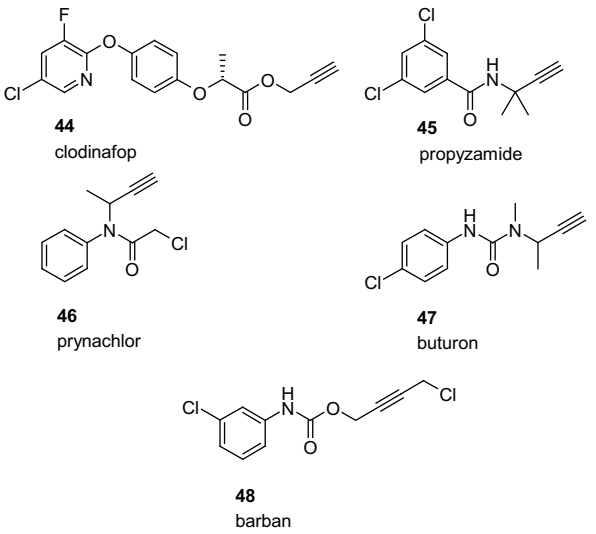


Figure 4. Miscellaneous alkynes on the herbicide market.

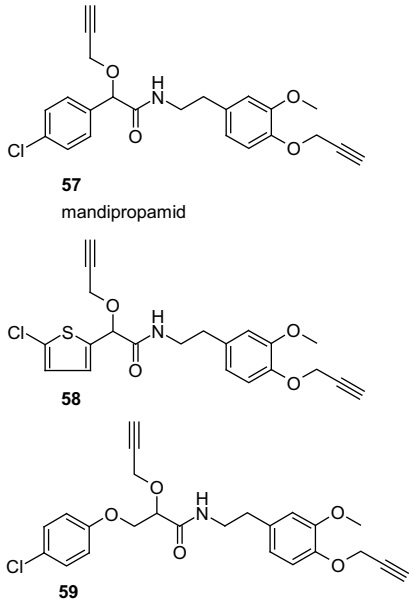
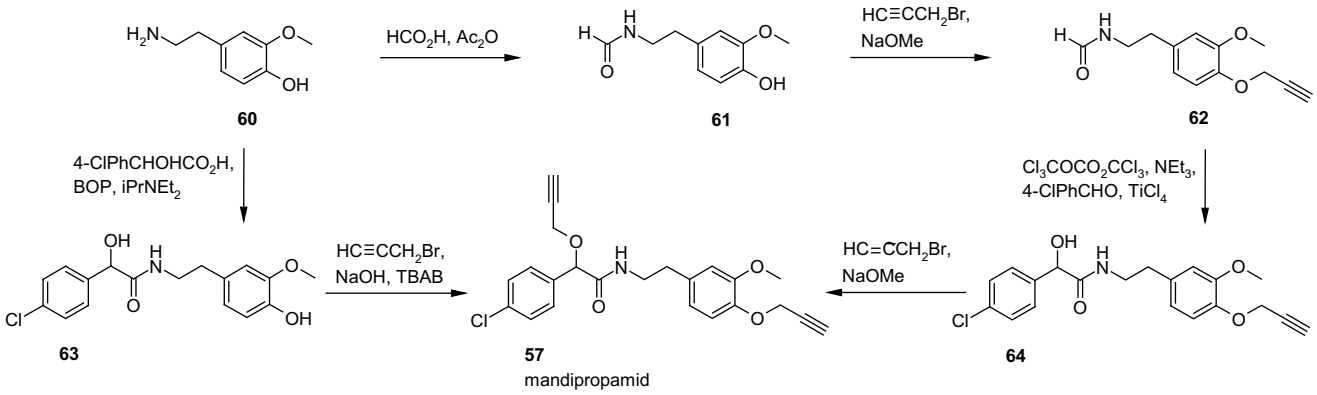


Figure 6. Fungicidally active α-propargyloxycarboxamides.

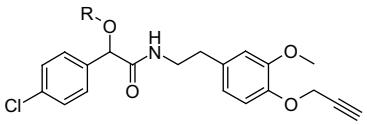


Scheme 3. Synthesis of mandipropamid (**57**).

There are several possibilities for the synthesis of mandipropamid (**57**), two of which are shown in Scheme 3.[48–50] The starting material for both approaches is 3-methoxytyramine (**60**), which is available in two steps from vanillin.[48,53] It can be converted by standard N-formylation and O-propargylation into the propargylated formamide **62**. This intermediate can then be directly transformed into the mandelamide **64** by Seebach's modification of the Passerini reaction. The introduction of a second propargyl group into the hydroxy function of the mandelic moiety of **64** delivers mandipropamid.[48–50] Alternatively, 3-methoxytyramine (**60**) can be reacted with 4-chloromandelic acid, which is available in two steps either from 4-chlorobenzaldehyde or from 4-chloroacetophenone, under peptide coupling conditions with Castro's reagent and Hünig's base. The resulting mandelamide **63**, which bears an alcoholic as well as a phenolic hydroxy function. Both OH groups can be simultaneously propargylated with propargyl bromide under phase-transfer conditions to deliver mandipropamid (**57**).[48,50]

Table 2 shows the influence of the hydroxy substituent in the mandelic acid moiety of mandelamide fungicides on the anti-oomycetic activity.[50] The alkylation of the free hydroxy function of mandelamide **65** generally leads to an increase in fungicidal activity. In this connection, especially C_2 (e.g., **67**) and C_3 units (e.g., **57**) seem to possess the best potential. A comparison between the propargylated mandipropamid **57** and its allyl (**71**) and propyl derivatives (**69**) reveals that the biological activity increases with enhanced degree of unsaturation in the linear C_3 chain. The introduction of additional methyl groups in the propargylic (**72**) or in the terminal position (**73**) of the alkyne reduces the anti-oomycetic activity. Acylation of the free hydroxy group results in surprisingly good efficacy (see **74** and **75**). The introduction of a carbonate function (as in **76**) instead of the successful ether and ester groups leads to a dramatic drop in biological activity. In conclusion, the presence of an alkyne function in form of a propargyl ether in the benzylic position of a mandelamide fungicides leads to the optimum biological results.[50]

Table 2
Fungicidal activity of different O-substituted mandelamides against *Phytophthora infestans and Plasmopara viticola*



Compound	R	EC_{80} (mg/L)	
		Phytophthora infestans (tomato late blight)	*Plasmopara viticola* (grape downy mildew)
65	H	34.6	10.4
66	CH_3	9.7	3.5
67	CH_2CH_3	4.6	2.0
68	CH_2CH_2F	4.7	8.9
69	$CH_2CH_2CH_3$	5.4	31.0
70	$CH(CH_3)_2$	3.1	10.1
71	$CH_2CH{=}CH_2$	44.1	18.6
57	$CH_2C{\equiv}CH$	0.1	1.2
72	$C(CH_3)_2C{\equiv}CH$	4.9	3.5
73	$CH_2C{\equiv}CCH_3$	18.3	14.0
74	$C(=O)CH_2CH_3$	4.2	2.8
75	$C(=O)CH_2CN$	3.1	4.9
76	$C(=O)OCH_3$	38.6	109.5

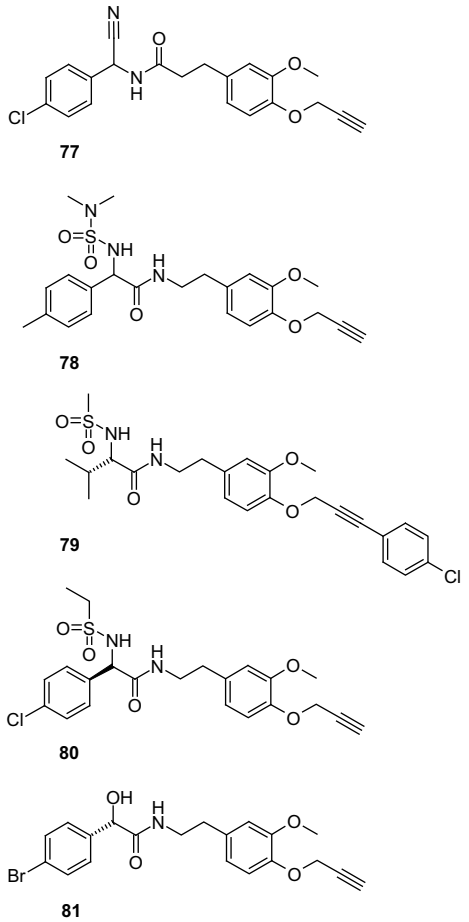


Figure 7. Miscellaneous CAA fungicides with alkyne functions.

The hydroferulic acid amide **77**, which is a mandipropamid derivative with an inverted amide function, possesses powerful fungicidal activity (Fig. 7).[48] Also the alkynylated *N*-sulfonyl amino acid amides, such as the phenylglycinamide **78** and the valinamide **79**, are highly active against oomycetes diseases.[48,49,53] The asymmetric synthesis of the (*R*)-phenylglycinamide **80**[49] and the (*S*)-mandelamide **81**[54] could be achieved via diastereoselective multicomponent reactions with a glycosylamine as chiral inducing amine component or a glycuronic acid as acid component, respectively.

3.2. Triazoles

Several 1,2,4-triazole derivatives show broad fungicidal activity. These compounds are inhibitors of sterol biosynthesis, typically inhibiting sterol 14α-demethylase.[55] Hereby, the triazole group acts as ligand for the Fe atom of cytochrome P450 of different oxidases. Also a few triazole fungicides with alkyne functions have been described in the literature. The compound **82** showed very good activity against *Puccinia recondita* (cereal brown rust), *Erysiphe graminis* (cereal powdery mildew), *Botrytis cinerea* (grey mould) and *Cercospora arachidicola* (peanut early leaf spot).[56] The similar triazole derivative **83** with a silylated alkyne function is only weakly active against *Rhizoctonia solani* (rice sheath blight).[57] The bis-phenylacetylene derivative **84** was more effective in inhibiting the radial mycelial growth of *Botrytis cinerea* (grey mould) than the highly active fungicide cyproconazole.[58] The O-propargylated triazole derivative **85** showed in vitro activity against *Cercospora beticola* (sugar beet leaf spot) and *Ustilago maydis* (corn smut),[59] whereas the N-propargylated compound **86** strongly controls *Erysiphe graminis* (cereal powdery mildew) in vivo[60] (Fig. 8).

3.3. Strobilurins

The strobilurins are an important class of agrochemical fungicides, the discovery of which was inspired by a group of naturally occuring fungicidally active derivatives of β-methoxyacrylic acid, for example, strobilurin A, oudemansin A and myxothiazol A.[61] The fungicidal efficacy of the strobilurins results from their ability to inhibit mitochondrial respiration by binding to the Q_o site of cytochrome *b*. Cytochrome *b* is part of the cytochrome bc_1 complex (complex III), located in the inner mitochondrial membrane of fungi and other eucaryotes. When a strobilurin binds, it blocks electron transfer between cytochrome *b* and cytochrome c_1, which, in turn, disrupts the energy cycle within the fungus by stopping the oxidative phosphorylation and therefore the production of ATP[61] (Fig. 9).

In almost all commercially available strobilurine fungicides, a phenyl ring bearing the toxophore (in most cases β-methoxyacrylate) and another phenyl ring in the sidechain are linked together by a more or less flexible bridge. Many different spacers have been tested and several of them give good fungicidal results, as it is also the case for a simple ethynyl bridge as in **87**.[62] Compound **88** is very similar to **87**, only the ring substituted with the β-methoxyacrylate-toxophore is exchanged from a phenyl to a cyclopentene.[63] The strobilurin derivative **89** possesses a diphenyl ether scaffold, which is substituted with a methoxyiminoacetamide toxophore in one of the phenyl rings as well as with a *meta*-propargyloxy group in the other phenyl. It is highly active against *Pyricularia oryzae* (rice blast), whereas its closely related benzyl phenyl ether analogue **90** efficiently controls *Pseudoperonospara cubensis* (cucumber downy mildew).[64] The kresoxim methyl analogue **91**, which bears instead of a methoxyiminoacetate a *N*-propargylcarbamate toxophore, inhibits the mitochondrial respiration of fungal phytopathogens in vitro as well as in vivo.[65]

3.4. Miscellaneous acetylenic fungicides

Mepanipyrim (**92**) is a commercial fungicide belonging to the class of anilinopyrimidines, which are considered to be inhibitors of methionine biosynthesis (Fig. 10).[66,67] It is highly active against *Botrytis cinerea* (grey mould). Efficacy against this disease is also reported for the squalene epoxidation inhibitor terbinafine (**93**), although it is primarily applied as an anti-mycotic pharmaceutical,[68] as well as for the anti-microtubular pyridylcarbamate **94**.[69] The 7-azaindole **95**[70] as well as the two *scytalone dehydratase* inhibitors **96**[71] and **97**[72] have shown some effects against *Magnaporthe grisea* (rice blast).

The synthesis of mepanipyrim (**92**) is possible via several different pathways, an interesting approach is displayed in Scheme 4.[66] The condensation of phenylguanidine (**98**) with dehydroacetic acid leads to the anilinopyrimidine **99**. The propan-2-one function of **99** can be transformed by chlorination and elimination of hydrogen chloride to the propynyl substituent of mepanipyrim (**92**).[66]

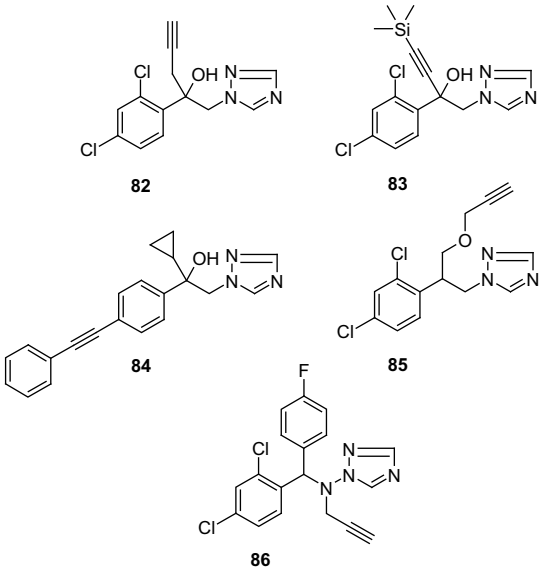


Figure 8. Fungicidally active triazoles with an alkyne function.

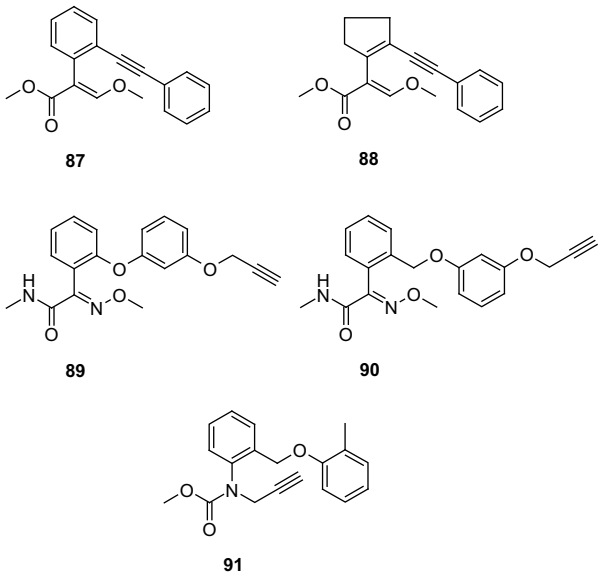


Figure 9. Fungicidally active strobilurins with an alkyne function.

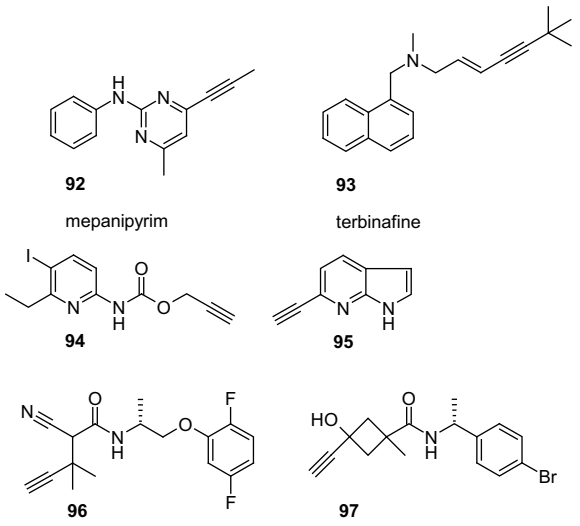


Figure 10. Miscellaneous fungicidally active alkynes.

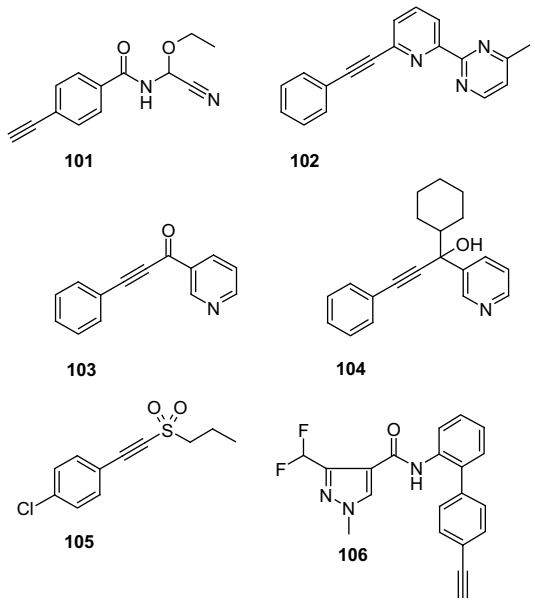
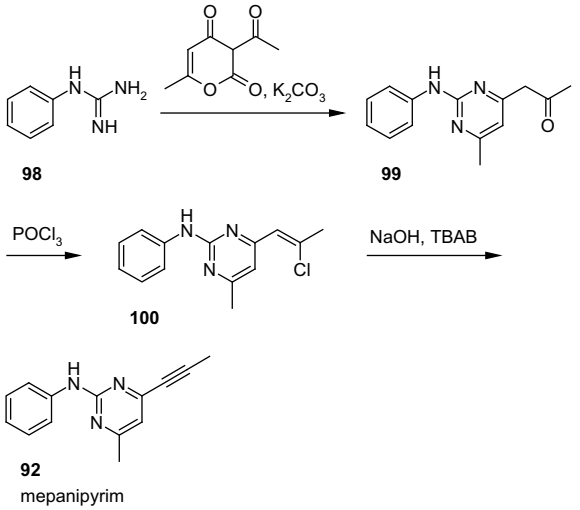


Figure 11. Miscellaneous fungicidally active alkynes.

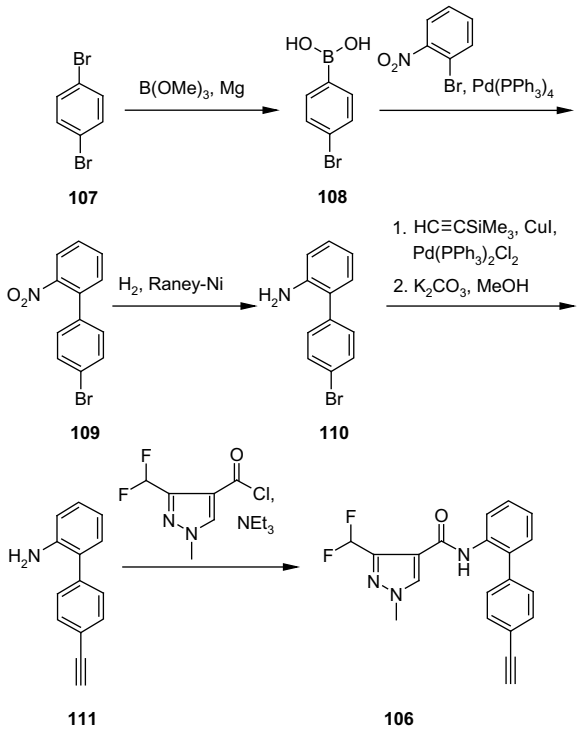
The hemiaminal ether **101** displayed efficacy against both oomycetes diseases *Phytophthora infestans* (potato and tomato late blight) and *Plasmopara viticola* (grape downy mildew).[73] The pyridylpyrimidine **102** owes it potent fungicidal activity to its ability to cycle copper through fungal cell membranes, where it accumulates internally to toxic levels.[74] The related phenylacetylene derivatives **103**[75] and **104**[76] are both active against *Sphaerotheca fuliginea* (cucumber powdery mildew). The alkynyl sulfone **105** possesses in vitro activity against *Botrytis allii* (onion neck rot).[77] The respiration inhibitor **106**, blocking *succinate dehydrogenase* (mitochondrial complex 2), is highly active against *Puccinia recondita* (cereal brown rust)[78] (Fig. 11).

Two consecutive palladium-catalyzed cross-coupling reactions are the key steps for the synthesis of the amine moiety **111** of the *succinate dehydrogenase* inhibitor **106**.[78] The boronic acid **108**, available in one step from 1,4-dibromobenzene (**107**), undergoes a Suzuki-Miyaura coupling with bromo-2-nitrobenzene to the biphenyl derivative **109**. After the reduction of the nitro function of **109**, the Sonogashira coupling of the resulting **110** with trimethylsilylacetylene delivers **111**, which is then converted with the required pyrazolecarboxylic acid chloride to the highly active fungicide **106**[78] (Scheme 5).



Scheme 4. Synthesis of mepanipyrim (**92**).

Several acetylenic natural products possess fungicidal properties.[75,77,79] Capillin (**112**),[75,77,79] isolated from the essential oil of *Artemisia capillaris*, and agrocybin (**113**),[80] found in the edible mushroom *Agrocybe cylindracea*, both display remarkable fungitoxic efficacy. Wyerone (**114**) was isolated in seedlings of *Vicia faba* (broad bean) and is active against *Botrytis cinerea* (grey mould),[81] *Alternaria brassicicola* (cabbage leaf spot)[79] and *Uromyces fabae* (bean rust).[79] Cellocidin (**115**), obtained from *Streptomyces chibaensis*, has a protective effect against *Xanthomonas oryzae* (bacterial rice leaf blight).[82] A common feature of all these fungicidally active, naturally occuring alkyne derivatives is the conjugation of the C–C



Scheme 5. Synthesis of **106**.

triple bond to an adjacent carbonyl or carboxamide function. Although there is no evidence of a definite mechanism of action, it is believed that the conjugated carbonyl functions can be attacked more easily by nucleophilic reactive groups in enzymes, such as amino or thiol. Fischerellin A (**116**), found in the cyanobacterium *Fischerella muscicola*, strongly inhibits the growth of *Uromyces fabae* (bean rust).[83] Finally, the bithienyl **117**, which was isolated from *Echinops sphaerocephalus*, displays a photo-induced fungicidal activity against *Pythium aphanidermatum* (pepper root rot)[84] (Fig. 12).

4. Insecticides and acaricides bearing an alkyne group

4.1. Pyrethroids: voltage-dependent sodium channel blockers

Powders derived from the flower *Tanacetum cinerariaefolium* (also known as *Chrysanthemum cinerariaefolium* or *Pyrethrum cinerariaefolium*) have been used for centuries against a broad range of insects, because they contain the six closely related insecticidal compounds pyrethrin I and II, jasmolin I and II and cinerin I and II. Pyrethorids are synthetic analogs of these natural products with enhanced insecticidal efficacy and photostability.[85] Typical features of pyrethroids, which act on the central nervous system of insects by blocking their voltage-dependent sodium channel, are a rapid insecticidal 'knockdown' effect at low doses, low toxicity against warm-blooded animals and a low vapor pressure. Responsible for this low vapor pressure is their relatively lipophilic molecular structure, which is why the alkyne function is frequently present in several biologically active pyrethroids. Figure 13 shows the five so far commercialized acetylenic pyrethroids prallethrin (**118**),[86] imiprothrin (**119**),[87] furamethrin (prothrin, **120**),[86a,88] kikuthrin (**121**)[89] and empenthrin (**122**).[90] All these products are esters, which contain the same naturally occuring acid moiety, chrysanthemic acid, linked to different alcohols. Especially the household insecticide prallethrin is very similar to pyrethrin I, whose pentadienyl function has been replaced by a propargyl group as only structural difference.

The two cis-3-(2,2-dibromovinyl)-2,2-dimethylcyclo-propanecarboxylates **123** and **124** both showed a higher insecticidal

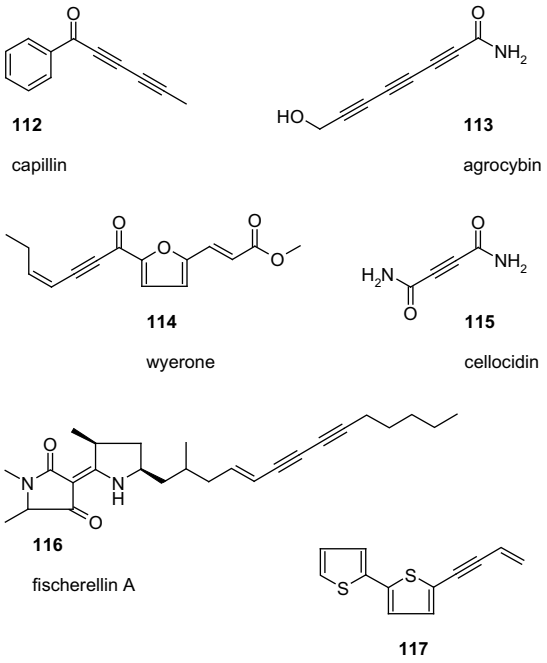


Figure 12. Fungicidally active natural products with alkyne functions.

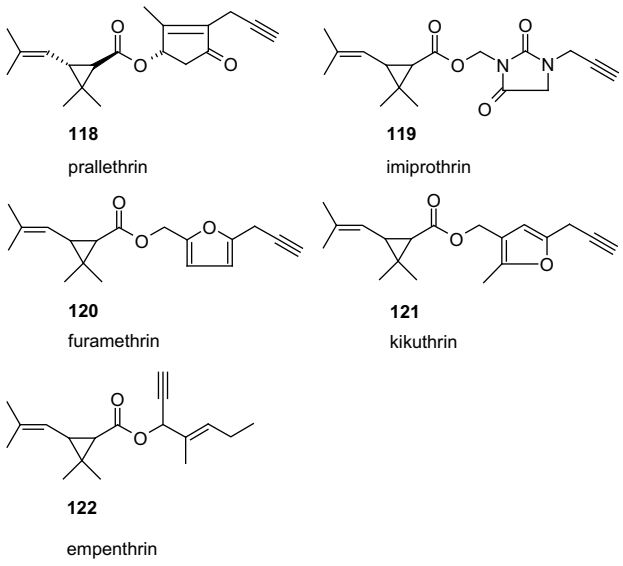


Figure 13. Acetylenic pyrethroids on the insecticide market.

efficacy than the commercial pyrethroid bioresmethrin, **123** against *Musca domestica* (housefly),[91] **124** against *Phaedon cochleariae* (mustard beetle).[92] The 3-propargyloxyphenyl derivative **125** is highly active against *Heliothis virescens* (tobacco budworm),[93] whereas the related phenylacetylene derivative **126** combines an interesting insecticidal performance against *Nilaparvata lugens* (brown plant hopper) and *Lissorhoptrus oryzophilus* (rice water weevil) with rather low fish toxicity, a combination of features which is very important for the application in paddy rice fields.[94] The imiprothrin analog **127** possesses a higher knockdown efficacy against several house insects than the commercial pyrethroid tetramethrin.[95] The *N*-allylpyrazole derivative **128** is very active against *Culex pipiens pallens* (Northern house mosquito) and *Blatella germanica* (German cockroach).[96] Finally with **129**, bearing no cyclopropyl group anymore, a selective pyrethroid was found, which exhibits strong acaricidal efficacy against *Tetranychus urticae* (two-spotted spider mite) without having any insecticidal properties at all[97] (Fig. 14).

The alcohol moiety of the enantiomerically pure experimental pyrethroid **126** can be prepared enantioselectively by asymmetric addition of 2-phenylethynylzinc bromide to the aldehyde **130** in the presence of a chiral amino alcohol, the lithium salt of (−)-*N*-methylephedrine (Scheme 6).[94,98]

4.2. GABA-gated chloride channel blockers

Several phenylacetylene derivatives possess highly efficient broad-spectrum insecticidal activity, because they act as non-competitive antagonistic inhibitors of the γ-aminobutyric acid (GABA)-gated chloride channel in the membrane of insect nerve fibers, causing neuronal cell hyperexcitability (Fig. 15).[99] The trioxabicyclooctane EBOB (**132**) is highly toxic to both insects and mammals and was therefore intensively used to study this mode of action class.[100] The trimethylsilyl-protected EBOB-derivative **133** possesses a much better toxicological selectivity than EBOB (**132**) itself. The metabolic oxidative desilylation, which transforms this proinsecticide into its biologically active form EBOB, takes place in *Musca domestica* (housefly), but not in mouse.[101] The bicycloorthobenzoate **134** is one of the most potent GABA receptor antagonists known to date.[102,103] Its cyano substituent interacts favorably with the receptor but also increases the hydrolytic stability of the 2,6,7-trioxabicyclo[2.2.2]octane nucleus. The highly

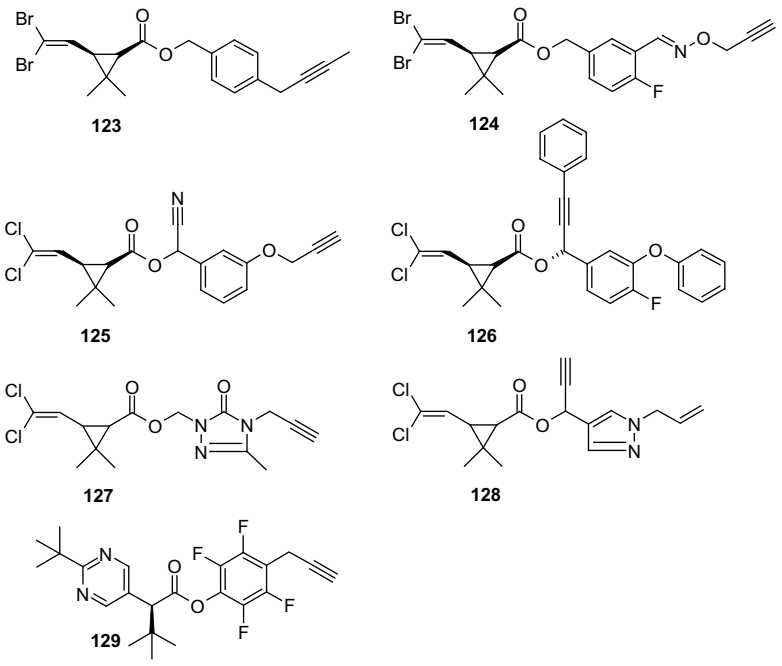
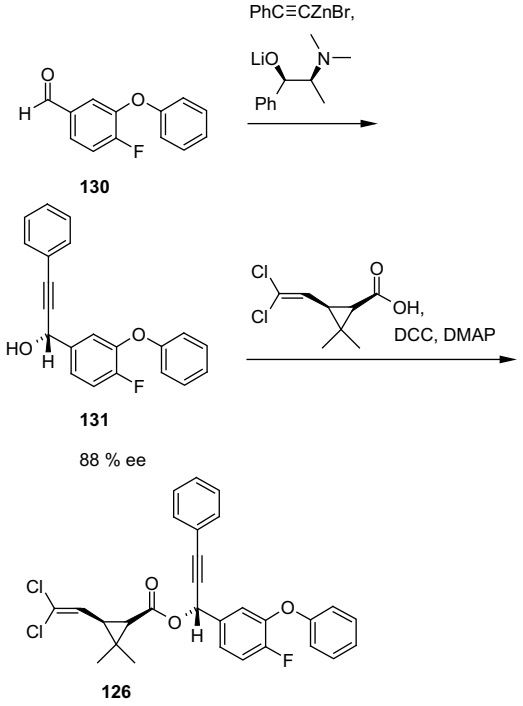


Figure 14. Insecticidally active pyrethroids with an alkyne function.

active hexynyl substituted trioxabicyclooctane **135** allows the alkynyl function to occupy the same position at the binding site as when present at the 4-position of the benzene ring of EBOB.[104] Also the two EBOB analogs **136**[105] and **137**,[106] in which the six-membered ring of the trioxabicyclooctane is replaced by a seven- or eight-membered ring, respectively, are both active against *Musca domestica* (housefly). Also 1,3-dithianes and their sulfur oxidation products are appropriate replacements for the trioxabicyclooctane moiety of GABA-gated chloride channel blockers.[99] The 1,3-dithiane 1,1-dioxide **138** is highly active against *Musca domestica* (housefly).[107] Also several other insecticidal 1,3-dithiane derivatives have been reported, in which the terminal carbon of the ethynyl function in **138** bears various carbon, nitrogen, oxygen, phosphorous or sulfur substituents.[108] Also some aromatic heterocycles, such as the pyrimidine **139**[109] or the pyrazole **140**,[102] a close analog of the commercial insecticide fipronil, possess interesting housefly activities.

The synthesis of EBOB (**132**) starts from the triol **141**, which is converted with diethyl carbonate via pyrolysis of the intermediate carbonate ester into the 3,3-disubstituted oxetane **142** (Scheme 7). Its acylation with 4-iodobenzoyl chloride delivers the oxetane ester **143**, which undergoes upon treatment with boron trifluoride



Scheme 6. Synthesis of **126**.

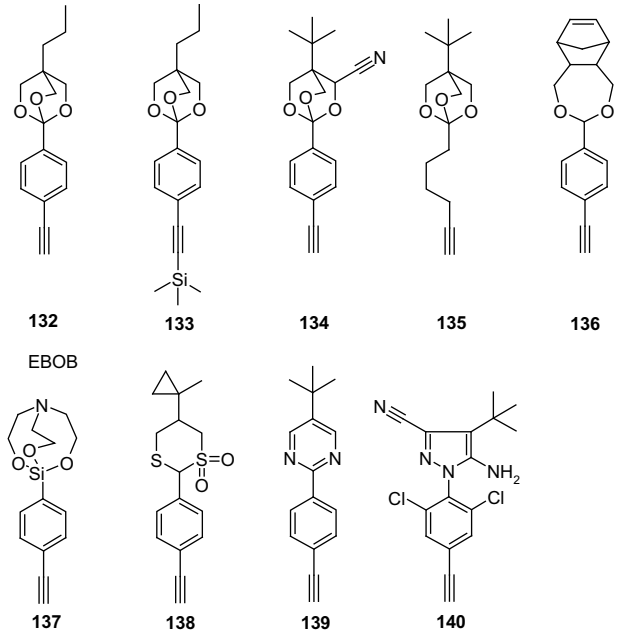
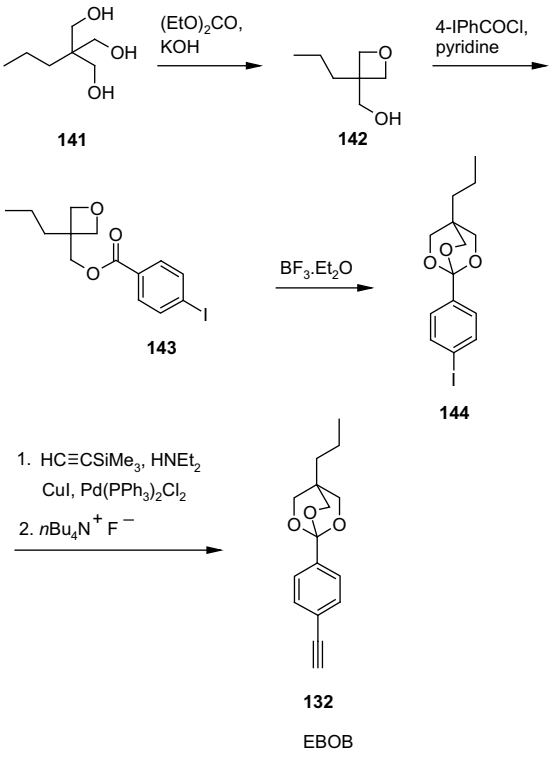


Figure 15. Insecticidally active GABA-gated chloride channel blockers with an alkyne function.



Scheme 7. Synthesis of EBOB (**132**).

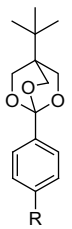
etherate a Lewis acid catalyzed rearrangement to the trioxabicyclooctane **144**. Finally the Sonogashira cross coupling between **144** and (trimethylsilyl)acetylene and subsequent desilylation affords EBOB (**132**).[100b,104]

In comparison to other substituents in the *para*-position of the phenyl ring of bicycloorthobenzoates **145**–**148**, the ethynyl function gives rise to the highest topical toxicity against *Musca domestica* (housefly) (Table 3).[100b,104,110]

4.3. Miscellaneous acetylenic insecticides and acaricides

Several alkyne derivatives possess potent activities against spider mites (Fig. 16). The commercial acaricide propargite (**149**) inhibits mitochondrial ATPase.[111] The propargyl ester kinoprene (**150**) is a potent insect/mite growth regulator with juvenile hormone activity.[112] Also the hydroquinone ether **151**[113] and the

Table 3
Insecticidal activity of different phenyl-substituted bicycloorthobenzoates against *Musca domestica*



Compound	R	LD_{50} (μg/g) of *Musca domestica* (housefly)	
		Alone	With synergist (piperonyl butoxide)
145	Cl	10	1.5
146	Br	3.5	0.83
147	C≡N	4.8	0.23
148	C≡CH	0.087	0.011

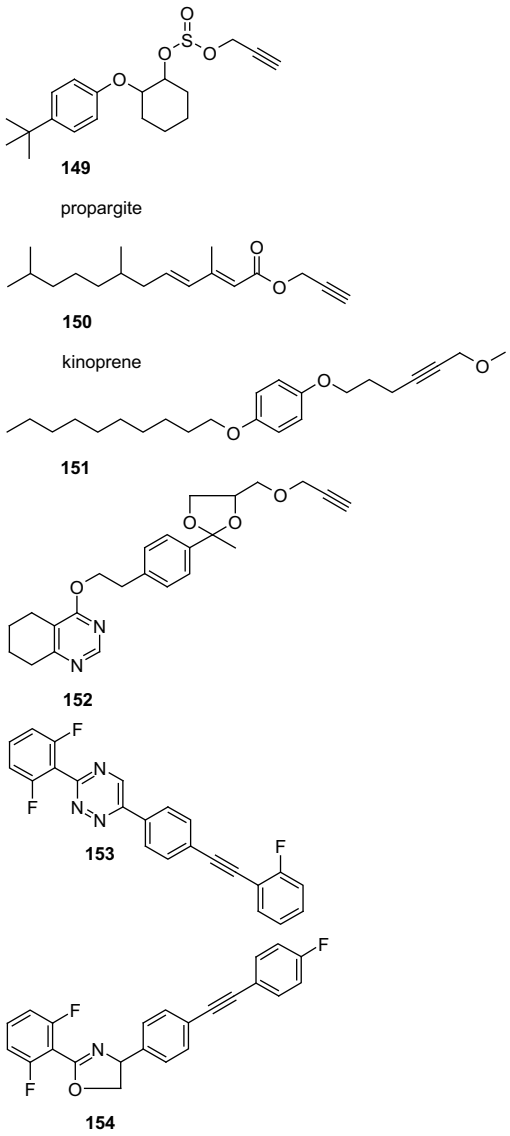
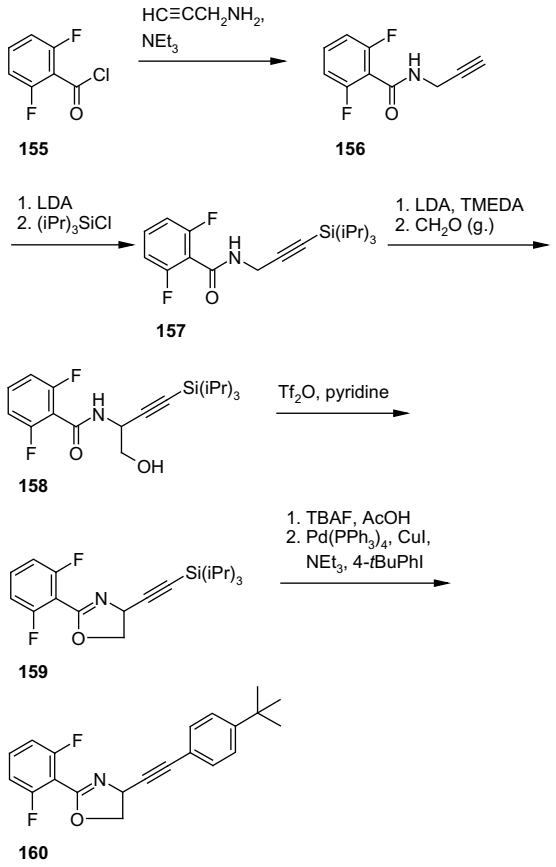


Figure 16. Miscellaneous insecticidally and acaricidally active alkynes.

glycerol ketal **152**[114] display at low concentrations powerful ovidical activity against eggs of *Tetranychus urticae* (two-spotted spider mite). The mode of action of **151** is unknown, whereas **152** interrupts the mitochondrial electron transport by inhibition of NADH:ubiquinone oxidoreductase (complex 1).[113] Finally, also the chitin biosynthesis inhibiting insect/mite growth regulators **153**[115] and **154**[116] are highly efficient acaricides, but in addition also active against key lepidopteran pests such as *Spodoptera littoralis* (cotton leafworm), *Spodoptera frugiperda* (fall armyworm), *Heliothis virescens* (tobacco budworm), *Plutella xylostella* (diamondback moth) and *Trichoplusia ni* (cabbage looper).

In addition to the 2,4-diaryl substituted oxazoline **154**, there are also other insecticidally active analogs known, in which the phenyl substituent in position 4 is omitted, which means that the alkyne function is directly linked to the oxazoline ring, leading to 4-alkynyloxazolines such as **160**. Its synthesis starts from 2,6-difluorobenzoyl chloride (**155**), which is converted by amidation with propargyl amine and silylation with chlorotriisopropylsilane into **157** (Scheme 8).[117] Lithiation of this TIPS protected alkyne with LDA in the presence of TMEDA followed by the introduction of formaldehyde gas delivers the hydroxymethyl intermediate **158**, which is then converted into the desired final product **160**



Scheme 8. Synthesis of **160**.

by intramolecular oxazoline formation, desilylation and Sonogashira coupling. The oxazoline **160** completely controlled larval stages of *Tetranychus urticae* (two-spotted spider mite) and *Spodoptera frugiperda* (fall armyworm) at 1 ppm.[117]

The benzophenone hydrazone **161** is very active against eggs and early larval stages of *Heliothis virescens* (tobacco budworm).[118] The formamidine **162** showed good activity against *Blattella germanica* (German cockroach).[119] The N-propargylated imidacloprid and chromafenozide derivatives **163**[120] and **164**[121] both possess a weaker insecticidal efficacy than their commercial parent compounds. The propargyl ether **165** shows potent toxicity to larvae of *Culex quinquefasciatus* (mosquito) at 1 mg L^{-1} [122] (Fig. 17).

There are also several natural products bearing alkyne functions with interesting insecticidal activities. The 1,2-dithiin thiarubrine C (**166**), isolated from the flower *Rudbeckia hirta* (black-eyed Susan) is highly toxic against larvae of *Aedes atropalpus* (mosquito) and *Manduca sexta* (tobacco hornworm).[123] Tonghaosu (**167**) was isolated from the Chinese vegetable *Chrysanthemum segetum* L. (tonghao). This spiroketal enol ether possesses potent antifeeding activity against *Pieris brassicae* (large white butterfly) and insecticidal activity against *Culex quinquefasciatus* (mosquito).[124] Anacyclin (**168**) was isolated from the roots of *Anacyclus pyrethrum*. This amide itself is only weakly active against *Tenebrio molitor* (yellow mealworm), but becomes very potent after stereospecific reduction of the diyne system to a (*Z*),(*Z*)-diene.[125] Finally, the triol **169**, found in the unripe fruit of *Persea americana* (avocado),[126] and the two triynes **170**, isolated from *Chrysanthemum silvaticum*, and **171**, obtained from *Bidens pilosa*, are all highly toxic against larvae of *Aedes aegypti* (yellow fever mosquito)[127] (Fig. 18).

Oxidative metabolism mediated by cytochrome-P450 monooxygenases is one of the most important detoxification routes of

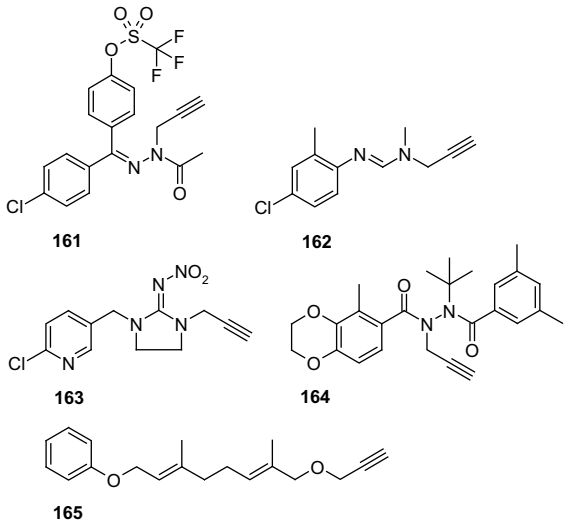


Figure 17. Miscellaneous insecticidally active alkynes.

insecticides in insects. So called synergists, which inhibit this metabolic detoxification, generally increase the potency of many insecticides, such as carbamates, pyrethroids and neonicotinoids, without having intrinsic insecticidal activity itself. Several alkynes are powerful synergists (Fig. 19). The presence of verbutin (**172**) increases the efficacy of carbofuran against *Musca domestica* (housefly) 35-fold.[128] Also the naphthalene **173**,[128a] the 2,2-dimethyldihydrobenzofuran **174**,[128a] the piperonal oxime **175**,[129] the pyrene **176**[130] and the phosphonate **177**[131] show high factors of synergism.

5. Alkynes as functional groups for the preparation of agrochemicals

5.1. Acetylenic building blocks in herbicide synthesis

The *N*-propargylaniline **178** is the starting material for a two-step synthesis of the bleaching herbicide **181**, which can be used

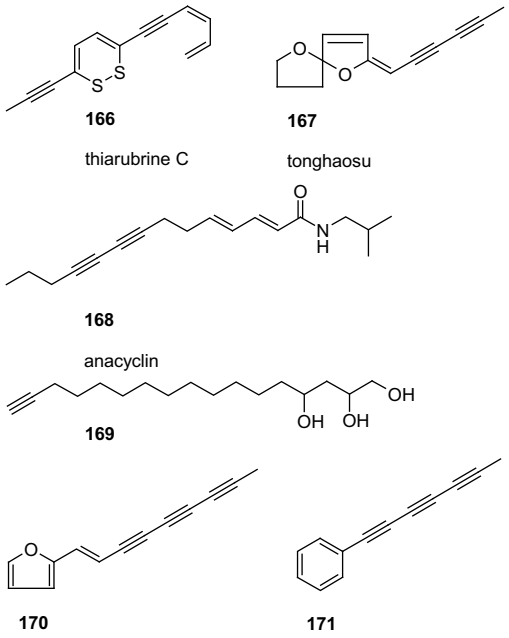


Figure 18. Insecticidally active natural products with alkyne functions.

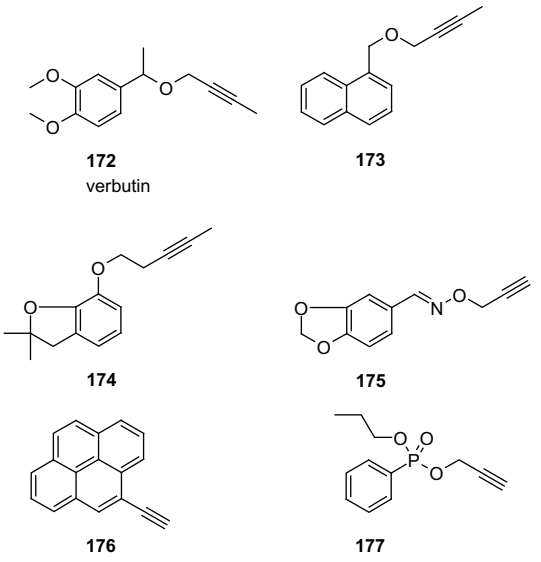
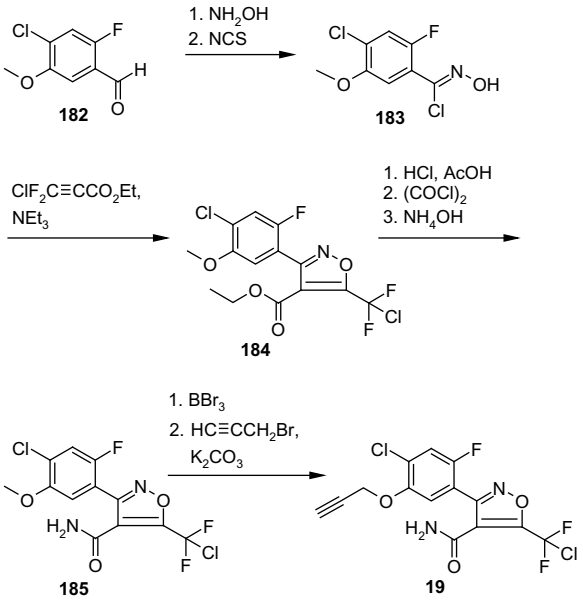


Figure 19. Insecticide synergists with alkyne functions.



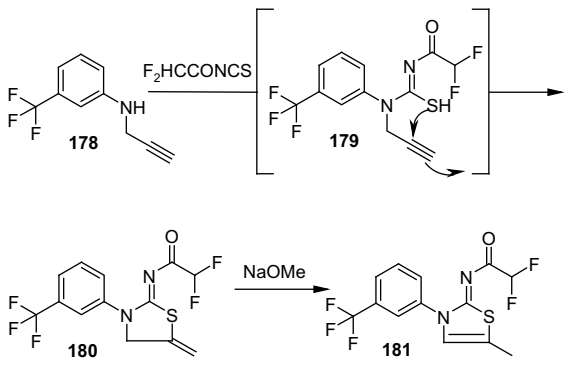
Scheme 10. Synthesis of **19**.

for pre-emergent grass and broadleaf weed control in cotton (Scheme 9). Treatment of **178** with difluoroacetylisothiocyanate furnishes the thiazolidine **180**. This cyclization proceeds through the formation of the thiourea **179**, followed by the nucleophilic attachment of the sulfur atom onto the electrophilic carbon atom of the C–C triple bond. The conversion of the thiazolidine **180** into the desired thiazoline **181** is achieved with sodium methoxide.[132]

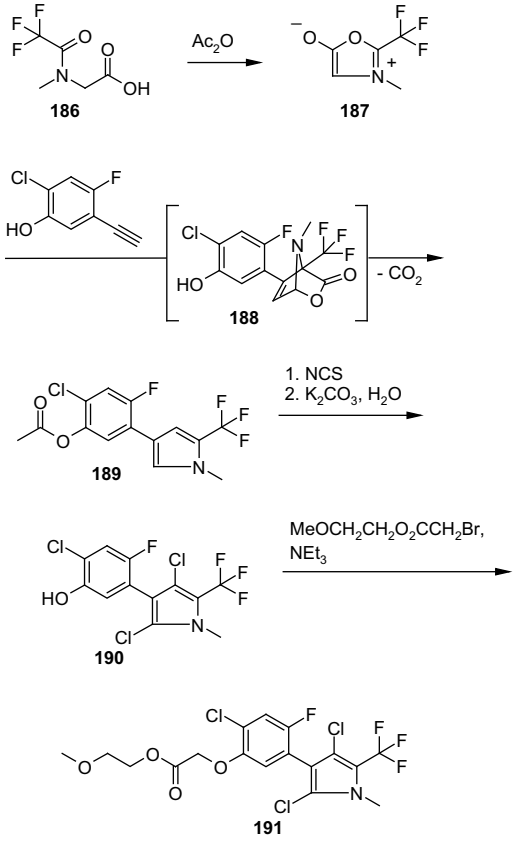
Scheme 10 shows the synthesis of the PPO inhibitor **19**, whose herbicidal activity is already described in Section 2.1. The benzohydroximinoyl chloride **183**, easily available from the aldehyde **182**, is converted under elimination of hydrochloride acid into the corresponding nitrile oxide, which reacts with ethyl 4-chloro-4,4-difluorobut-2-ynoate via 1,3-dipolar cycloaddition to the trisubstituted isoxazole **184**. Subsequently, the ester function of **184** is transformed into the primary amide **185**. Finally, the replacement of the methoxy group by a propargyl function leads to the PPO inhibitor **19**.[23]

Another 1,3-dipolar cycloaddition is also the key step in the synthesis of the PPO inhibitor **191**, which efficiently controls *Ipomoea purpurea* (morning glory), *Sida spinosa* (prickly sida) and *Amaranthus retroflexus* (redroot pigweed) in soybeans. The mesoionic 2-trifluoromethyl-3-methyl-1,3-oxazolium-5-olate (**187**), which can be obtained by cyclodehydration of *N*-trifluoroacetylsarcosine (**186**), adds to 2-chloro-5-ethynyl-4-fluorophenol under formation of the instable bicyclic intermediate **188**, which under carbon dioxide evolution and aromatisation reacts to **189**. Dichlorination and ester saponification leads to the per-substituted pyrrole **190**, which is alkylated to the highly active post-emergent soybean-selective herbicide **191**[13a,21] (Scheme 11).

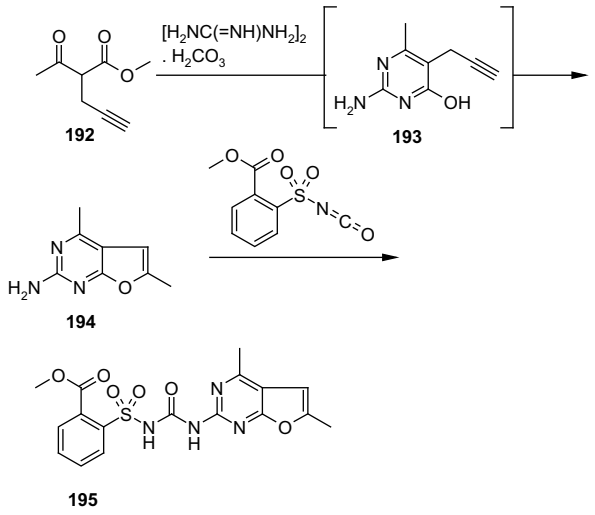
A concise synthesis to the sulfonylurea herbicide **195** starts from methyl 2-propargylacetoacetate (**192**). Condensation of this starting material with guanidine carbonate directly delivers the furo[2,3-*d*]pyrimidine **194** via the tetrasubstituted pyrimidine



Scheme 9. Synthesis of **181**.



Scheme 11. Synthesis of **191**.

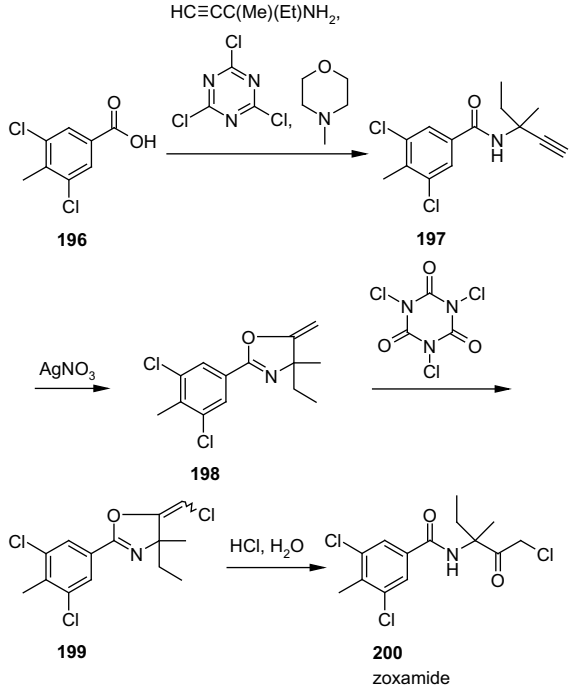


Scheme 12. Synthesis of **195**.

intermediate **193** (Scheme 12). Further conversion of this biheterocyclic amine with 2-carbomethoxybenzenesulfonyl isocyanate furnishs the sulfonylurea herbicide **195**, which is a highly active inhibitor of *acetolactate synthase* (ALS).[133]

5.2. Acetylenic building blocks in fungicide synthesis

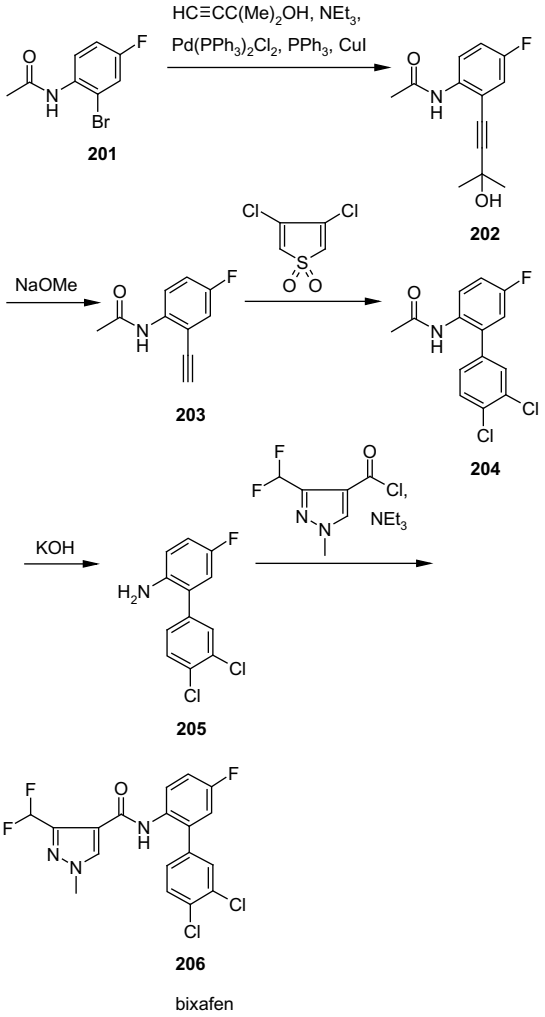
The tubulin polymerization (microtubule assembly) inhibitor zoxamide (**200**) is a modern fungicide, which is used for the control of the oomycetes diseases *Phytophthora infestans* (potato late blight) and *Plasmopara viticola* (grape downy mildew). Its synthesis starts with the formation of the amide **197** from 3,5-dichloro-4-methylbenzoic acid (**196**) and 3-amino-3-methyl-1-pentyne (Scheme 13). This alkynyl amide is then ring-closed to the oxazoline **198**, whose exocyclic methylene function is chlorinated with trichloroisocyanuric acid to obtain **199**. The oxazoline **199** is then finally transformed to zoxamide (**200**) by acid-catalyzed hydrolysis. Interestingly, with cyanuric chloride and trichloroisocyanuric acid, two different triazine-based chlorination agents are applied in this synthesis of zoxamide.[134]



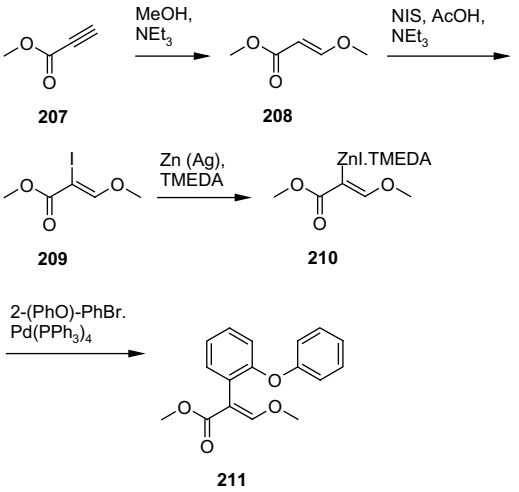
Scheme 13. Synthesis of zoxamide (**200**).

The disubstituted anilide **201** is the starting material for a short access to bixafen (**206**), the novel developmental fungicide of Bayer CropScience (Scheme 14). Compound **201** is converted with 2-methylbut-3-yn-2-ol in a Sonogashira reaction to the alkyne **202**, which is cleaved to the phenylacetylene **203** under basic conditions. A tandem Diels–Alder cycloaddition–cycloreversion transformation of **203** with 3,4-dichlorothiophene 1,1-dioxide furnishs the biphenyl derivative **204**, which after deacetylation and amidation leads to bixafen (**206**), an inhibitor of *succinate dehydrogenase* (mitochondrial complex 2).[135]

A concise reaction sequence starting from methyl propynoate (**207**) allows the flexible introduction of the β-methoxyacrylate toxophore of strobilurins (see Section 3.3) into various aromatic systems. Addition of methanol to **207** gives the acrylate **208**, which is transformed by halogenation into methyl (*Z*)-2-iodo-3-methoxypropenoate (**209**). This iodo derivative is then converted with an activated Zn/Ag couple in the presence of tetramethylenediamine (TMEDA) into the ethenyl zinc iodide **210**, which reacts in a palladium-catalyzed Negishi cross-coupling with 1-bromo-2-phenoxybenzene to the strobilurine fungicide **211**[63] (Scheme 15).



Scheme 14. Synthesis of bixafen (**206**).



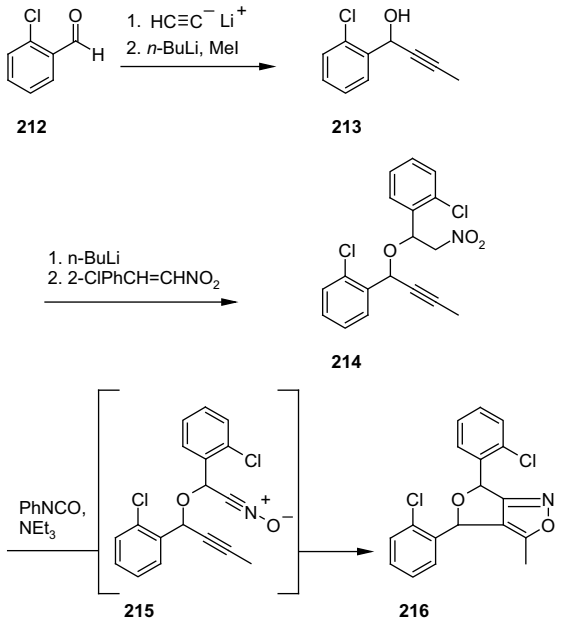
Scheme 15. Synthesis of **211**.

The furo[3,4-c]isoxazole derivative **216** is highly active against *Pyricularia oryzae* (rice blast). It is easily prepared by the Michael addition of the alkynol **213** to 2-chloronitrostyrene. The resulting Michael adduct **214** undergoes in the presence of phenylisocyanate an intramolecular 1,3-dipolar cycloaddition to the fungicidally active furoisoxazole **216** via the nitrile oxide intermediate **215**[136] (Scheme 16).

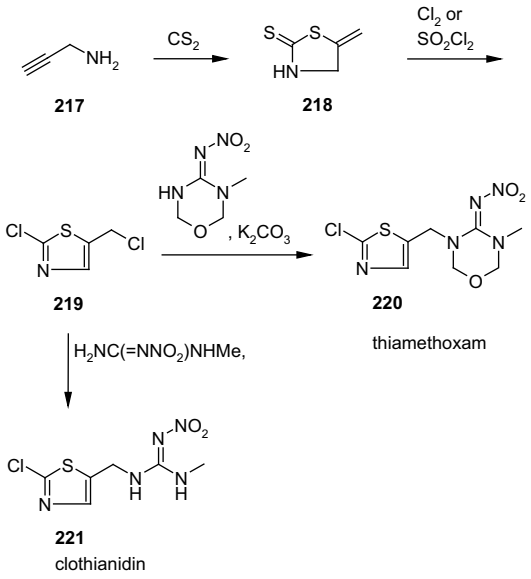
5.3. Acetylenic building blocks in insecticide and acaricide synthesis

2-Chloro-5-chloromethylthiazole (**219**) is an important building block required for the technical synthesis of both neonicotinoid insecticides thiamethoxam (**220**) and clothianidin (**221**). It can be prepared in two steps from propargyl amine (**217**) with the inexpensive reagents carbon disulfide and chlorine (Scheme 17).[137]

Chromafenozide (**228**) is a non-steroidal agonist of the insect molting hormone 20-hydroxyecdysone. Its synthesis starts from



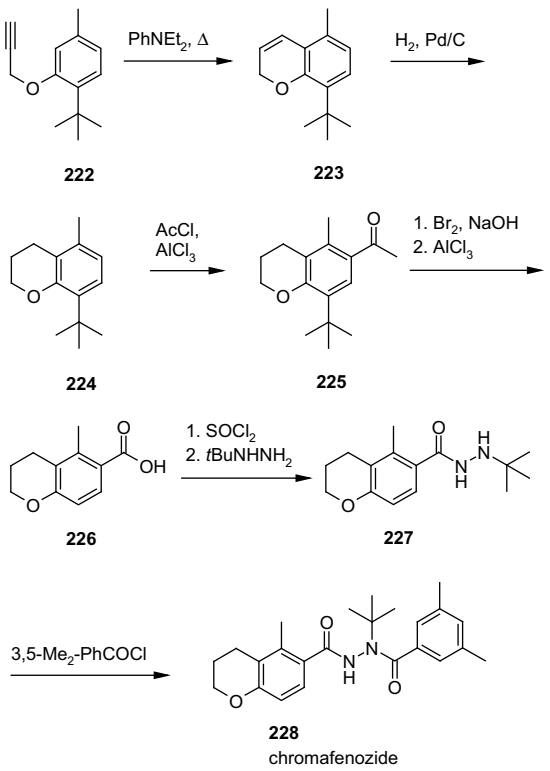
Scheme 16. Synthesis of **216**.



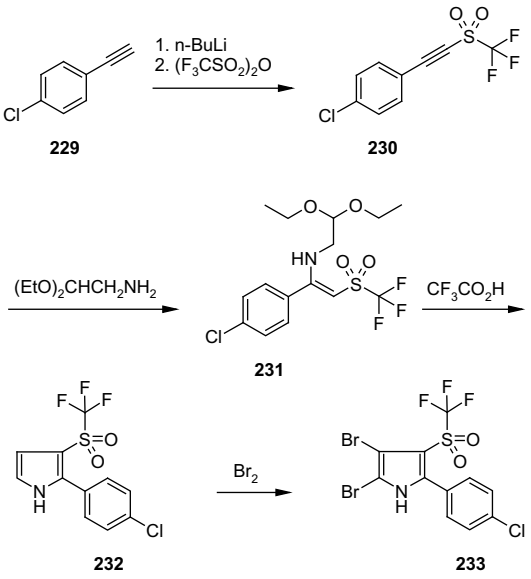
Scheme 17. Synthesis of thiamethoxam (**220**) and clothianidin (**221**).

1-*t*-butyl-4-methyl-2-propargyloxybenzene (**222**), which can be efficiently cyclized to the chromene **223** in refluxing *N*,*N*-diethylaniline (Scheme 18). Catalytic hydrogenation affords the chroman **224**, which is converted by Friedel–Crafts acylation, bromination, hydrolysis and de-*t*-butylation to the carboxylic acid **226**. Finally, two consecutive amidation steps lead to the bisacylhydrazine insecticide chromafenozide (**228**).[138]

The pyrrole insecticide **233** can be prepared in only four steps from 1-chloro-4-ethynylbenzene (**229**). This phenylacetylene derivative is converted to the triflate-substituted alkyne **230**, which



Scheme 18. Synthesis of chromafenozide (**228**).



Scheme 19. Synthesis of **233**.

undergoes a Michael addition with aminoacetaldehyde diethyl acetal to afford the enamine **231**. Intramolecular cyclization of **231** leads to the disubstituted pyrrole **232**, which is transformed to **233** by double-bromination with bromine. The pyrrole **233**, structurally related to chlorfenapyr, is highly active against *Spodoptera eridania* (Southern army worm), *Heliothis virescens* (tobacco budworm), *Empoasca abrupta* (Western potato leafhopper) and *Tetranychus urticae* (two-spotted spider mite)[139] (Scheme 19).

6. Conclusion

Many alkyne derivatives play important roles in the control of weeds, insects and fungal diseases. Their structural diversity is impressive as well as the wide range of different modes of action involved. The ability of several acetylenes to cross biological membranes benefits from their lipophilic, rigid and linear attributes. Also several naturally occuring alkynes display interesting herbicidal, fungicidal and insecticidal activity, some of them only after UV-A light activation (phototoxicity). Furthermore, alkynes are key intermediates in the synthesis of many agrochemicals.

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Clemens Lamberth was born in 1961 and studied chemistry at the Technical University of Darmstadt, Germany, where he obtained his Ph.D. under the supervision of Prof. Bernd Giese in 1990. Subsequently he spent one and a half years as a postdoctoral fellow in the group of Prof. Mark Bednarski at the University of California at Berkeley, USA, who died much too young at the age of 47 and to whose memory this review is dedicated. In 1992 he joined the agrochemical research department of Sandoz AG, Switzerland, which is today, after two mergers, part of Syngenta AG. Since 16 years he is specialized in fungicide discovery. He is the author of more than 90 publications and patents and the inventor of Syngenta's novel fungicide mandipropamid, which is described in Section 3.1 of this review.