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Fascinating Ambimobile Aryldiones in Crop Protection: Managing Grass Weeds and Harmful Sucking Insects

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Abstract: This review examines the innovation journeys, developments, and properties of two ambimobile crop protection compounds containing a 2-aryl-1,3-dione pharmacophoric motif: pinoxaden for post-emergence broad-spectrum grass weed control in cereals, and spiropidion for protecting multiple crops against damaging and difficult to control piercing and sucking pests. Both active ingredients function as propesticides, hydrolyzing *in planta* to release their bioactive aryldione forms, which inhibit acetyl-CoA carboxylase and disrupt fatty acid metabolism. As weak acids with specific physicochemical properties, these aryl cyclic diones demonstrate ambimobility in plants, enabling them to access both long-distance translocation pathways in plant vasculature, xylem, and phloem. This systemic translocation is crucial for both herbicidal and insecticidal applications.

Keywords: Acetyl-CoA carboxylase · Ambimobility · Aryldiones · Pinoxaden · Spiropidion

Michel Muehlebach graduated from the University of Neuchâtel (CH, 1987), obtained his PhD in chemistry at the University of Bern (CH, 1992, Prof. M. Neuenschwander), and did postdoctoral research at Stanford University (USA, Prof. P. A. Wender). In 1994, he joined Ciba (now Syngenta) in Crop Protection research, working on various weed control drug discovery projects. Since 2004, he has specialized in insecticide chemistry at Syngenta Crop Protection with a focus on design, synthesis, and optimization of new active ingredients. Contributing to the discovery of development candidates, he has authored and co-authored about 190 patent applications and scientific papers.

1. Inhibitors of Acetyl-CoA Carboxylase

Acetyl-CoA carboxylase (ACCase) is a commercially important target site for herbicide and insecticide action. In 2023, sales of ACCase-inhibiting herbicides accounted for $2.4 billion, which represents a 7.6% share of the total herbicide sales performance.[1] In insect control, the market is dominated by modes of action targeting nerves and muscles. Nevertheless, the non-neuronal acting ACCase insecticides reached sales of $395 million (1.8% share of the total 2023 insecticide sales).

ACCase is a crucial enzyme in the biosynthesis of fatty acids, it catalyzes the biotin-dependent carboxylation of acetyl-CoA to produce malonyl-CoA.[2] This conversion proceeds *via* two half reactions: the ATP-dependent carboxylation of enzyme-bound biotin, followed by the transfer of the carboxyl group to acetyl-CoA. ACCases are multi-subunit enzymes in prokaryotes, whereas in most eukaryotes, ACCase is a single polypeptide consisting of three major functional domains: the biotin carboxylase (BC), the biotin carboxyl-carrier protein (BCCP), and the carboxyltransferase (CT) domain.

Amongst crop protection compounds, there are four classes of commercial ACCase inhibitors known to bind to the CT domain active site. These include the aryloxyphenoxypropionate (AOPP or FOPs)[3] and the cyclohexanedione oxime ether (CHD or DIMs)[4] herbicides, known since the mid-1970s.[5] Syngenta innovated in 2006 with the launch of pinoxaden (**1**), the first and, so far, only representative of the DEN (phenylpyrazoline) herbicide subclass.[6] The members of these three distinct subgroups are categorized as Group 1 by the Herbicide Resistance Action Committee (HRAC).[7]

In contrast, tetronic and tetramic acids form a fourth class of compounds acting on ACCase with acaricidal and insecticidal action,[8] classified as Group 23 by the Insecticide Resistance Action Committee (IRAC).[9] With the recent market introduction of spiropidion (**2**) in this class,[10] Syngenta has uniquely developed active ingredients for both weed and insect control indications.

Pinoxaden (**1**) and spiropidion (**2**) share a common pharmacophoric motif: the 2-aryl-1,3-dione unit **3** (Fig. 1).[11] Both active ingredients are propesticides, the pivaloyl ethoxycarbonyl groups are cleaved *in planta* to release the bioactive aryldiones **4** and **5**, respectively, which are ultimately responsible for the target site binding. 2-Aryl-1,3-dione **4** is referred to as 'pinoxaden dione' herein (alternative citation as pinoxaden acid in the literature) and similarly tetramic acid **5** is named 'spiropidion dione' (in contrast to spiropidion enol).

Binding at the active site of the CT domain was elucidated by Tong.[2] X-ray crystallographic structures of the CT domain of yeast ACCase in complexes with representatives from all three commercial classes of herbicides were published in the 2004–2010 timeframe.[12] Despite their chemical structural differences, the binding modes of haloxyfop (an AOPP representative), tepraloxydim (a CHD), and the active principle of pinoxaden **4** revealed two common key anchoring points of interaction. The X-ray crystallographic data indicates that pinoxaden dione (**4**) binds to the CT domain site in its deprotonated enol form.[12c]

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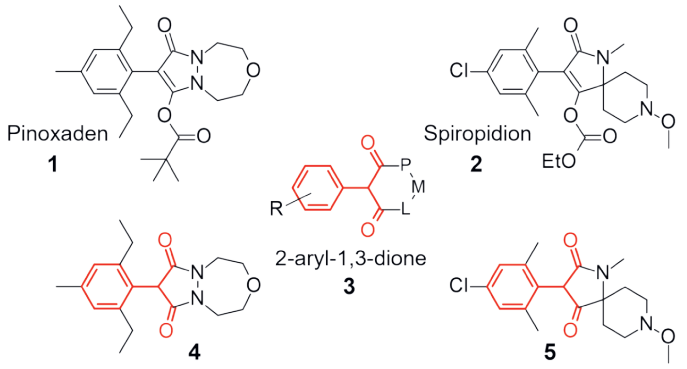


Fig. 1. Pharmacophoric motif **3** of crop protection aryldione compounds typified by pinoxaden (**1**) and spiropidion (**2**), and structures of their active principles **4** and **5**.

Cross-species sequence conservation around the active site, combined with the above structural binding information from the yeast CT domain, can serve as a basis to build homology models for further study of the binding interactions of newly designed aryldione herbicides and insecticides.[13]

Herein, we review our compelling journey towards the discovery of the 2-aryl-cyclic-1,3-dione derivatives pinoxaden (**1**), spiropidion (**2**), and related analogs, which are effective for managing grass weeds and harmful insects. Our discovery approach relied almost exclusively on ligand-based design principles, predating the structural studies by Tong and others that later validated our work. Aspects of the chemical scope and encountered challenges in the development of such novel aryldiones are summarized in Fig. 2.

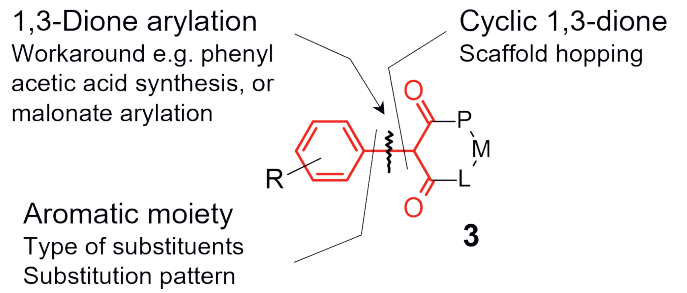


Fig. 2. Scope and challenges.

2. Aryldiones for Grass Weed Control

ACCase-inhibiting compounds from the AOPP and CHD classes are selective herbicides used primarily to control grass weeds in broadleaf crops such as soya, cotton, oilseed rape and sugar beet. The selectivity of these herbicides is based on the inherent insensitivity of dicot ACCase enzymes to these compounds, resulting in broadleaf crop tolerance.[5a] Distinct from the above classes, pinoxaden (**1**) is used for broad-spectrum grass weed management in cereal (monocot) crops.

2.1 *Discovery of Pinoxaden*

Durden and coworkers[14a] (representative 2-phenyl-indane-1,3-dione **6**, Union Carbide, 1970s) and Babczinski and Fischer[14b] (2-phenyl-tetrahydro-indolizine-1,3-dione **7**, Bayer, 1990s) disclosed 2-aryl-1,3-diones exhibiting herbicidal and miticidal effects. Compound **7** was reported to inhibit plastidic ACCase in corn. Inspired by this background, Cederbaum *et al.*[15a] (Ciba, now Syngenta) found a patentable entry for the class of 4-aryl-pyrazolidine-3,5-diones **8**, incorporating a cyclic hydrazine moiety, and quickly establishing mesityl derivative **9** as a first lead with herbicidal activity (Fig. 3). Scientists at Bayer CropScience had essentially the same discovery idea,[15b] their patent application encompassing an almost identical scope was published only two days later!

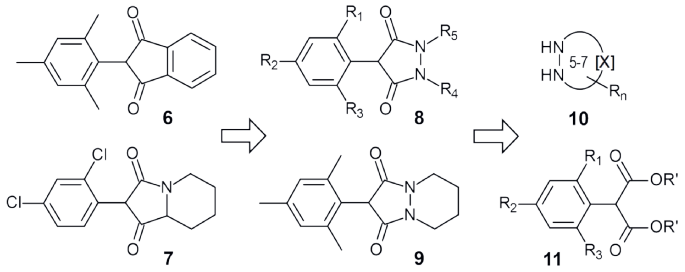
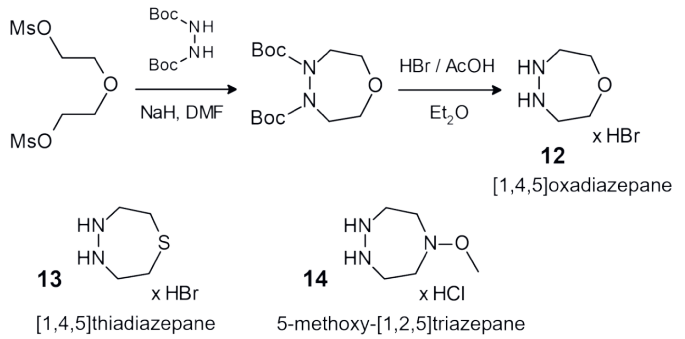


Fig. 3. Inspiring prior art and discovery path.

Further exploration work prompted us to investigate the preparation of optionally substituted 5- to 7-membered cyclic hydrazines **10**.[16] Condensation of those with aryl malonates **11** warranted the construction of an array of novel 4-aryl-pyrazolidine-3,5-diones **8** to probe for graminicidal efficacy and crop safety. This condensation approach enabled rapid diversification and efficient optimization of both aryl and hydrazine moieties.

Worth mentioning is the facile preparation of previously unprecedented 7-membered cyclic hydrazine reagents incorporating heteroatoms (Scheme 1), including [1,4,5]oxadiazepane (**12**),[16] its thio analog **13**[16] and 5-methoxy-[1,2,5]triazepane **14**.[17]

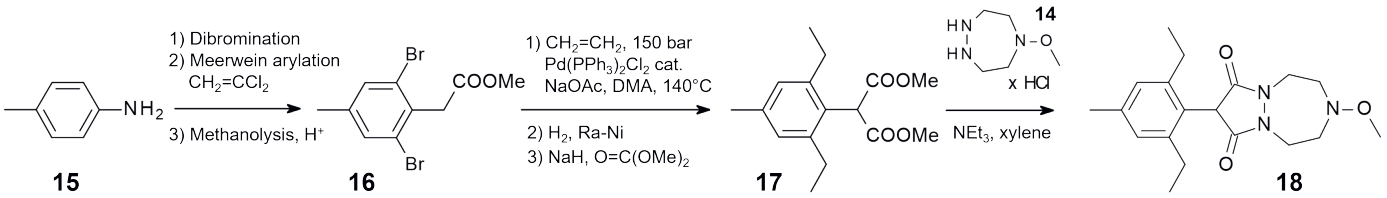


Scheme 1. Synthesis of [1,4,5]oxadiazepane (**12**) *via N,N'*-alkylation of a protected form of hydrazine. Structure of related di- and triazepanes **13** and **14**.

Functionalizable phenylacetic acid derivatives (*e.g.* **16**) were particularly useful starting materials for the synthesis of aryldione targets. They served as precursors to the corresponding malonates (*e.g.* **17**) and allowed the introduction of bulky substituents in the *ortho* positions (R_1/R_3 in **11**, Fig. 3).

While an alternative first-generation approach to aryl malonate **17** required eight tedious steps,[16] an improved methodology based on a palladium-catalyzed Heck olefination of **16** with pressurized ethylene, in combination with a subsequent hydrogenation, permitted a 2-step shorter assembly from inexpensive *p*-toluidine **15** (Scheme 2).[18] State of the art metal-catalyzed conditions for a direct arylation of cyclic diones were either not yet available at the time of our work, or showed (very) limited success when handling hindered di-*ortho* substituted aryl substrates.

A general synthetic approach to aryldione analogs such as **18** is represented by the thermal cyclocondensation of malonate **17**



Scheme 2. A Heck olefination approach to hindered aryl malonate **17**, and representative thermal cyclocondensation with triazepane **14** toward aryl-dione **18**.

with cyclic hydrazine **14**, under concomitant off-distillation of the formed alcohol. In light of physicochemical, biochemical and biological characterization, the 4-aryl-pyrazolidine-3,5-dione **18**, incorporating a 5-methoxy-[1,2,5]triazepane ring, was identified as bioisosteric to pinoxaden dione (**4**).[17]

A series of key modifications in the 4-aryl-pyrazolidine-3,5-dione scaffold **8**, in both the aryl (substituents R_1, R_2, R_3) and the cyclic hydrazine (fragment R_4N-NR_5, Fig. 3) parts, and analysis of the structure-activity relationships (SAR) allowed rationalization of the structural factors impacting weed control efficacy against grasses and crop tolerance in cereals.[16–18] Functionalization of the aryl moiety was mainly achieved through cross-coupling and directed *ortho*-metalation strategies.[18] A 2,4,6-substitution pattern proved highly beneficial for herbicidal activity. Notably, an optimal structural fragment combination associating a 2,6-diethyl-4-methyl-phenyl part with a [1,4,5]oxadiazepane ring unveiled pinoxaden dione (**4**) with high post-emergence graminicidal activity and tolerance to both wheat and barley (Fig. 4).

The multiparameter optimization also encompassed the use of an appropriate adjuvant, which significantly boosted the biological efficacy through enhanced *in planta* bioavailability.[18,19] With a pK_a of about 3.8, the 2-aryl-1,3-dione unit **3** of compound **4** is further suited for prodrug formation with the aim to improve cuticular penetration. Final enol pivaloate proherbicide formation ultimately revealed pinoxaden (**1**) as an exciting novel crop protection development candidate.[20,21]

To ensure excellent crop tolerance and secure substantial selectivity margin under agronomical relevant application conditions, pinoxaden (**1**) was further evaluated in combination with safeners by Glock *et al.*[20a,22] In particular, this evaluation included the incorporation of the proprietary safener cloquintocet-mexyl into the formulation. The safener was shown by Hall and coworkers[18,21] to facilitate faster and higher levels of detoxification within the crop in the form of oxidations at benzylic positions. The specific pinoxaden plus safener combination consequently provided very good tolerance in wheat, barley, and other economically important cereal crops, without any significant antagonism on weed control.[6,18] Effects of aryl pattern, adjuvant response, safener inclusion, and type of cyclic hydrazine on activity against grass weeds and selectivity in small grain cereals is summarized in Fig. 5.

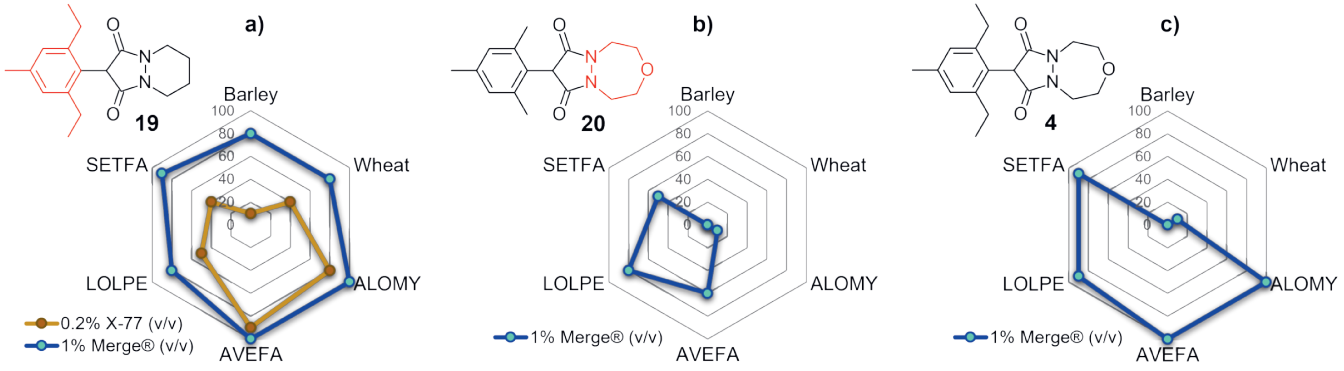


Fig. 4. Summary of the aryl pyrazolidinedione optimization demonstrating key fragment contributions to the activity level against grass weed species (aryl moiety) and to tolerance in cereal crops (hydrazine moiety). Post-emergence crop damage and grass control (%) at 30 g ha^{-1} of compounds **19**, **20** and **4** formulated as WP25:[16] a) significant impact of adjuvant Merge® (1% v/v) over X-77 (0.2% v/v) leading to improved graminicidal performance of **19**, but with unacceptable crop injury. b) [1,4,5]Oxadiazepane containing mesityl derivative **20** showing good cereal selectivity, yet insufficient control of grasses. c) Pinoxaden dione (**4**) exerting promising tolerance to both wheat and barley and excellent efficacy against cold climate grasses. Definitions of the grass weeds in Table 1 below.

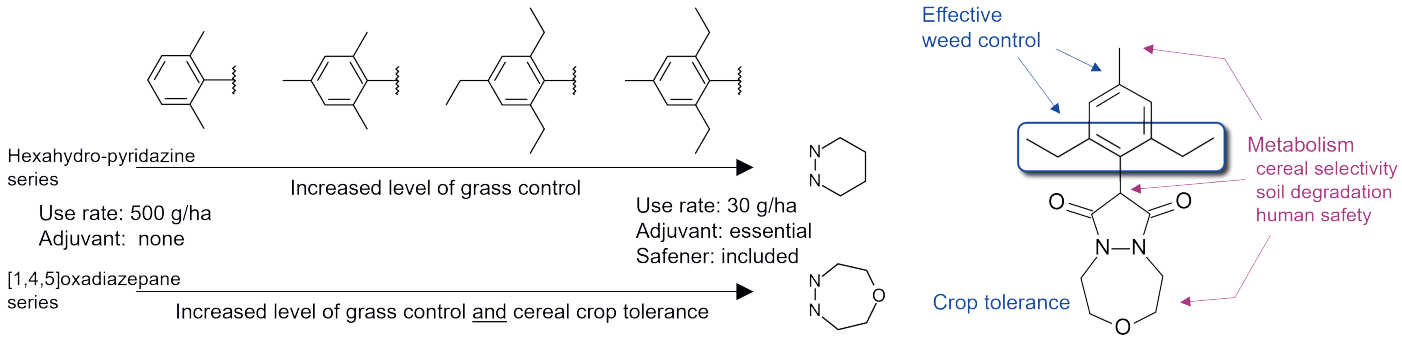
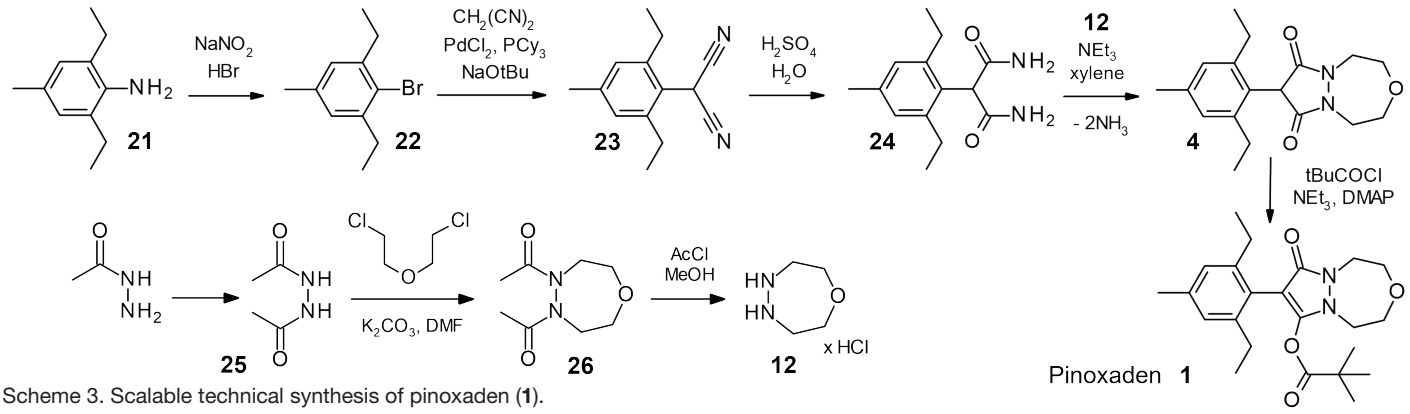


Fig. 5. Multiparameter optimization and their impact on performance and metabolism.



Scheme 3. Scalable technical synthesis of pinoxaden (**1**).

Pinoxaden (**1**) is prepared effectively in a total of eight steps from 2,6-diethyl-toluidine **21** (Scheme 3).[20a] Impressively, this short, convergent and economical third-generation approach (5 steps in the longest linear sequence) is cutting in half the number of steps implemented in the discovery route.[16] Process research work by Schnyder *et al*.[23] uncovered the palladium-catalyzed coupling reaction of malononitrile with hindered aryl bromide **22**, delivering aryl malononitrile **23**. Maetzke *et al*.[24] further submitted its malonamide hydrolysis product **24** to a thermal condensation reaction with [1,4,5]oxadiazepane (**12**) to form pinoxaden dione (**4**) effectively. Ostensibly, aryl malonamide **24** can be considered as a synthetic equivalent of malonate **17** in its ability to cyclocondense with cyclic hydrazines under extrusion of ammonia. Finally, aryldione **4** was esterified to pinoxaden (**1**) with pivaloyl chloride under standard conditions. The structure of pinoxaden (**1**) was unambiguously confirmed by a single crystal X-ray structure analysis (CCDC 706870).

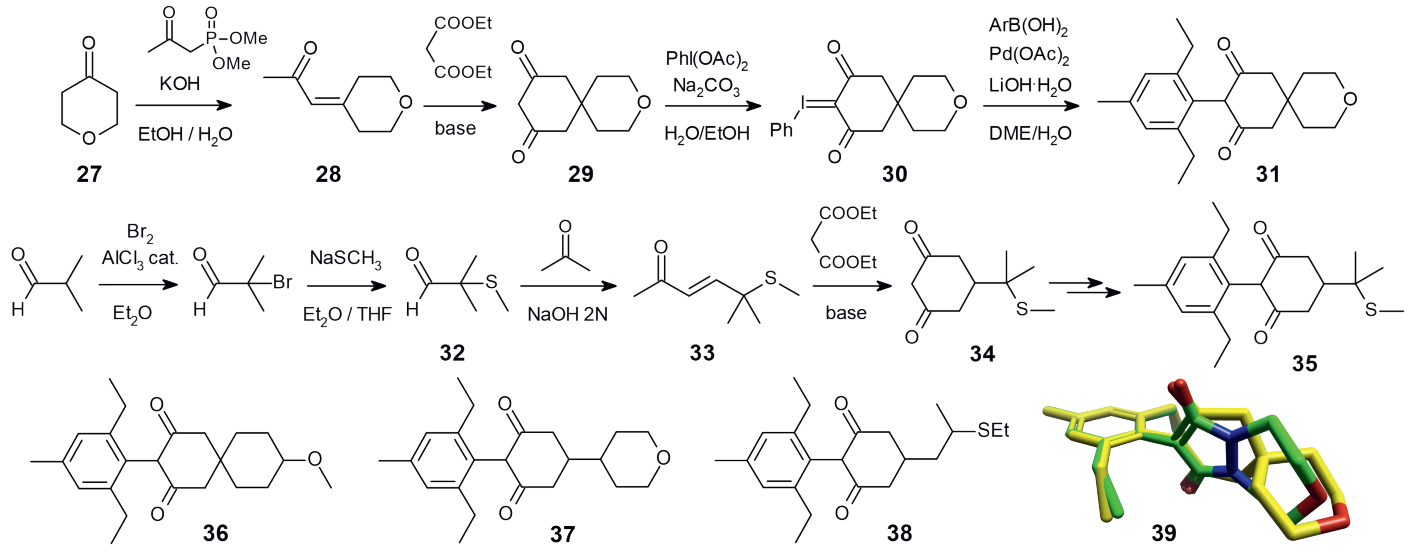
The technical sequence to [1,4,5]oxadiazepane (**12**) includes *N*,*N*'-bisalkylation of diacetyl hydrazine **25** with bis(chloroethyl) ether, followed by deprotection in the presence of dry hydrochloric acid.[25]

The AXIAL® product brand family, based on pinoxaden (**1**), was first commercialized in 2006.[6] AXIAL® is for post-emergence broad-spectrum cold climate grass weed management use in cereal crops. The weed spectrum covers a wide range of key annual grass species such as *Alopecurus myosuroides* (blackgrass), *Apera spica-venti* (silky bent grass), *Avena spp*. (wild oats), *Lolium spp*. (ryegrass), *Phalaris spp*. (canary grass), *Setaria spp*. (foxtails) and other monocot weeds commonly found in cereals.

2.2 *Aryl Cyclohexanediones and Aryl Tetrahydropyrandiones*

A range of five- and six-membered cyclic 1,3-diones have been investigated by crop protection companies over the last three decades.[21] When combined with optimized aryl moieties, the cyclic dione part may not only impact graminicidal activity, but also crop selectivity. Biocidal carbocyclic 2-aryl-1,3-diones were first reported in the late 1970s by Wheeler at Union Carbide.[26] Dione scaffold hopping led us to consider alternative approaches to prepare novel aryl cyclohexanediones and aryl tetrahydropyrandiones.

The methodology for the preparation of 5-substituted 2-aryl-cyclohexane-1,3-dione derivatives **31** and **35** builds on a reliable ring synthesis of the cyclohexanedione building blocks **29** and **34** from α,β-unsaturated precursors **28** and **33** and ethyl malonate.[5b] Enone **28** was obtained from tetrahydropyran-4-one **27** under modified Wadsworth-Emmons condensation conditions,[27] while thioether **33** resulted through an aldol condensation between aldehyde **32** and acetone.[28] Availability of cyclohexanediones **29** and **34** allowed for a late-stage aryl coupling approach to the targets.[29] Representatively, iodonium ylide **30**



Scheme 4. Preparation of 5-substituted 2-aryl-cyclohexane-1,3-diones **31** and **35** *via* palladium-catalyzed cross-coupling of iodonium ylides with aryl boronic acids. Structures of related aryl cyclohexanediones **36**, **37** and **38**. Superposition **39** of the minimized energy conformation of **31** in its enolate form (yellow) onto the bioactive conformation of deprotonated pinoxaden dione (**4**) (green; PDB code 3PGQ[12c]).

was first readily formed from cyclic-1,3-dione **29** and (diacetoxy) iodobenzene in aqueous ethanol.[30] A Suzuki-like cross-coupling reaction of ylide **30** with an aryl boronic acid then afforded the spiro-linked aryldione **31** under mild conditions (Scheme 4).[31,32]

In contrast, 4-aryl-tetrahydropyran-3,5-dione derivatives such as **45** were accessed through a cycloisomerization-rearrangement strategy. Deprotonation of 2-methylbut-3-yn-2-ol **40** and *O*-alkylation with methyl bromoacetate **41** provided an acetylene substrate able to undergo a Sonogashira cross-coupling with aryl bromide **42**. Silver-catalyzed cycloisomerization (a 6-*exo*-dig cyclization) of the formed alkynoic acid derivative **43** was achieved in good yields using silver carbonate in acetonitrile.[33] Final enol-lactone **44** to pyrandione **45** rearrangement was performed under basic conditions using catalytic potassium cyanide and triethylamine in acetonitrile (Scheme 5).[34]

Worth a mention, but not detailed herein, is an alternative and robust method for the direct coupling of hindered aryls to cyclic 1,3-diones, in the form of an atypical aryl lead cross-coupling reaction using refined conditions reported by Morgan and Pinhey.[35] The involved aryl lead triacetate reagents must be prepared from their corresponding aryl boronic acid precursors.[29,34]

Greenhouse biological profiles of the above representative aryl cyclohexanediones and tetrahydropyrandiones are outlined in Table 1. Post-emergence weed control efficacy and trends toward crop tolerance were evaluated on whole plants under standard screening conditions.[32a] Some of the new aryldiones were highly active against both cool- and warm-season grasses. Cyclohexanediones **37** and **38** can be seen as hybrid compounds which incorporate structural fragments of pinoxaden (**1**) and DIM cyclohexanedione oxime ethers.[4] The crossover molecule design gratifyingly resulted in potent sensitive grass killers. Unfortunately, the extent of crop damage in cereals was too severe, safening with cloquintocet-mexyl was not effective enough. Conversely, observed glasshouse trends for a safe use in dicotyledonous crops prompted a number of evaluations in small plot field trials. For example, the performance of aryl cyclohexanedione analogs **31**, **35** and **37** was benchmarked in oilseed rape, soybean and cotton to validate potency, spectrum, crop safety, residuality and soil behavior.

Other starting points for chemical optimization involved *meta*-biaryl diones typified by *meta*-biphenyl dimethylpyrandione **45**. Remarkably, minimal structural modifications on essentially inactive **45** led to the discovery of the *meta*-biphenyl tetramethylpyrandiones **47** and **48** by Scutt and coworkers.[34] Both compounds displayed high activity levels against warm climate grasses, in particular with excellent control of *Echinochloa crus-galli*, and promising rice selectivity.[29]

3. Aryldiones for the Protection of Crops from Damaging Sucking Insects

Cross-indication screening was at the origin of the discovery of tetronic acid derivatives acting as ACCase inhibitors at Bayer. Phenotypic screening-driven optimization resulted in the launch of the first-in-class acaricide spirodiclofen in 2002.[36] Further refinements within this cyclic ketoenol structural class (IRAC group 23) led to an expanded pest spectrum controlled by spiromesifen (whiteflies and mites) and spirotetramat (a tetramic acid with broad-spectrum activity against sucking insects and mites).

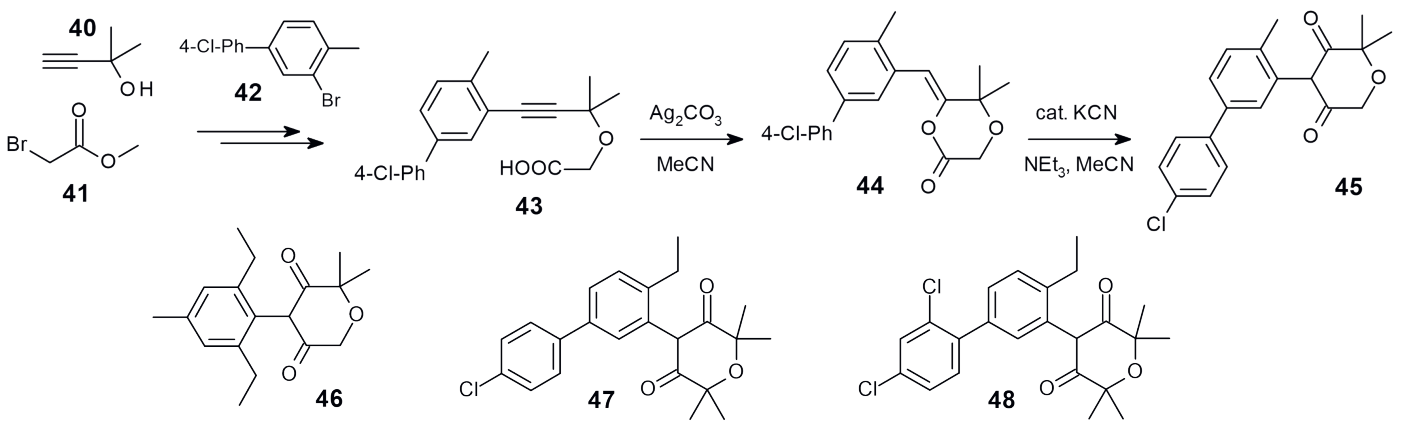
Intrigued by certain properties of this class of compounds and keen to investigate a different, non-neuronal post-neonicotinoid mode of action for the control of sap feeding pests, we embarked in an insecticidal aryldione project around 2005. The discovery of spiropidion (**2**) emerged from multiple cross-functional contributions, including chemical design and in-house expertise from weed control aryldione programs.

3.1 *Discovery of Spiropidion*

N-alkylpiperidones, and later 1-methoxypiperidin-4-one (**49**),[37] acted as synthetic precursors in the development of simplified morphine derivatives, specifically the phenylpiperidinol class (prodines) of opioid analgesics. This *N*-methoxy piperidone building block **49** remained underutilized thereafter, until its thoughtful reconsideration and incorporation into the pharmacophoric 2-aryl-1,3-cyclic dione scaffold **3** of the IRAC group 23 chemical family of ACCase inhibitors by Zambach *et al*.[38] Despite an already extensive body of published research, novel chemistry in the spiro-linked *N*-alkoxy-piperidine class **50** of tetramic acids was thereby successfully identified, yielding compounds with both insecticidal and acaricidal properties (Fig. 6).[39,40]

A Strecker-Dieckmann route to the spirofused 3-aryl-pyrrolidine-2,4-dione framework **51** was envisaged.[36,39,40] Optimization of the spirocyclic piperidine *N*-substituent (NOR) rapidly revealed *N*-methoxy (R = CH_3) as most effective. Notably, this structural feature proved crucial for establishing novel intellectual property and significant insecticidal efficacy within the tetramic acid class. Accordingly, the flexible and powerful Strecker methodology[41] applied on ketone intermediate **49** enabled the synthesis of cyclic α-amino nitrile adducts **52**, and their corresponding α-amino acid derivatives **53**, in which A is either hydrogen, alkyl, oxy or amino (Fig. 7). Overall, the approach capitalized on the ease of synthetic access to 1-methoxypiperidin-4-one (**49**) from readily available starting materials, namely *O*-methyl hydroxylamine **54** and methyl acrylate **55**.[37]

A representative Strecker-Dieckmann path is outlined in Scheme 6.[39] Acylation of the Strecker α-amino ester intermediate **53** with activated aryl acetic acids led to amido-esters **56**.



Scheme 5. A cycloisomerization-rearrangement strategy toward the preparation of 2,2-dimethyl-4-(*meta*-biphenyl)-tetrahydropyran-3,5-dione **45**. Structures of related aryl tetrahydropyrandiones **46**, **47** and **48**.

Table 1. Post-emergence herbicidal activity at a rate of 60 g ha^{-1} of selected aryl cyclohexanediones and aryl tetrahydropyrandiones[a]

Compound	ALOMY	AVEFA	BROTE	LOLPE	SETFA	PANMI	SORVU	DIGSA	ECHCG
31	100	90	80	90	100	100	100	90	100
35	90	90	90	90	100	100[b]	70	70	70
36	80	30	40	80	10	10	30	30	20
37	90	90	80	90	80	100	60	90	100
38	80	50	60	80	90	100	80	90	80
45	0	0	0	40	10	0	0	10	50
46	60	70	0	70	70	90[b]	70	70	80
47	60	70	30	90	100	100	100	100	100
48	30	70	0	70	100	100	60	100	100

[a]Greenhouse post-emergence grass control (%) at 60 g ha^{-1} on whole plants of formulated compounds with 0.2% adjuvant X-77.[32a] Test evaluation 14-15 DAA (100 = total damage to plant; 0 = no damage to plant; DAA = days after application). Grass weeds: *Alopecurus myosuroides* (ALOMY), *Avena fatua* (AVEFA), *Bromus tectorum* (BROTE), *Lolium perenne* (LOLPE), *Setaria faberi* (SETFA), *Panicum miliaceum* (PANMI), *Sorghum bicolor* (SORVU), *Digitaria sanguinalis* (DIGSA), *Echinochloa crus-galli* (ECHCG). [b]*Panicum dichotomiflorum* (PANDI)

Ring closure through treatment with base afforded the key cyclic 3-aryl-pyrrolidine-2,4-diones **51a**. In a final step, tetramic acid derivatives **51a** were acylated with ethyl chloroformate to yield proinsecticides **57**.

Excitingly, compounds **57** demonstrated translaminar distribution through leaf tissues and systemic translocation to new growth, providing extended protective activity. Subsequent SAR investigations focused on adjusting the aryl substitution pattern (R_1 to R_4 in **51a**/**57**) and probing the substituent space at the lactam nitrogen position (group A) of the spirofused aryl-pyrrolidinedione framework (Fig. 8).[39,40] Initial optimization of insecticidal efficacy and target spectrum identified a preferred 2,4,6-substitution pattern, demonstrating strong control of several pest species including aphids, whiteflies, scales, and mites following foliar application. Succeeding refinements focused on enhancing crop compatibility, bee safety and other properties, mainly by adapting the substituents R_2 and A.

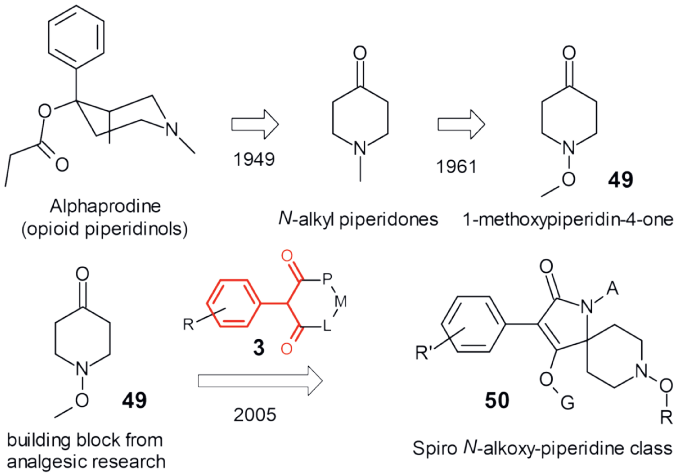


Fig. 6. Invention path toward the spiro-linked *N*-alkoxy-piperidine class **50** of tetramic acids.

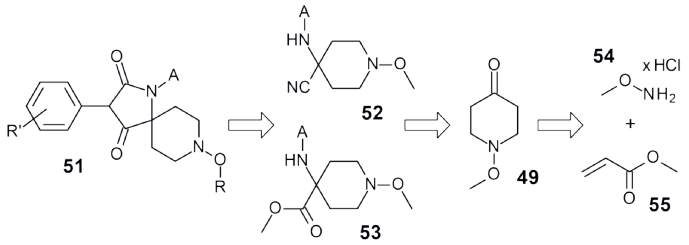
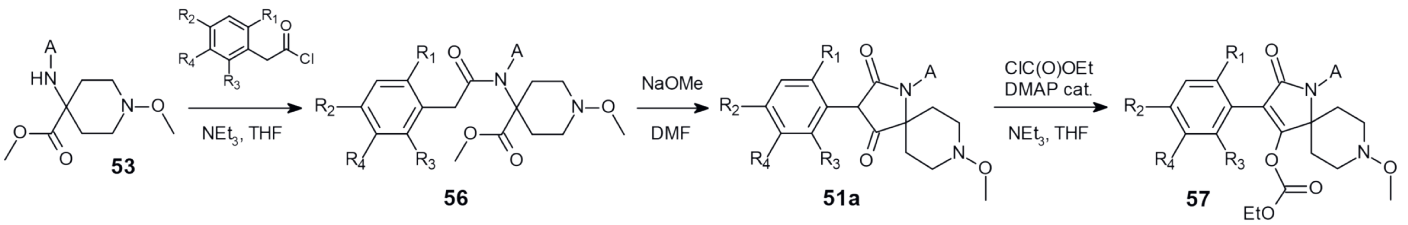


Fig. 7. Strecker α-amino nitrile **52** and α-amino ester **53** intermediates.

Advanced tetramic acid derivatives (in the three *N*-unsubstituted,[38] *N*-alkyl[42a] and *N*-alkoxy[42b] lactam subclasses) featuring a 2,6-dimethyl-4-halo aromatic motif provided the broadest pest spectrum, good curative efficacy (Fig. 9), crop compatibility (A ≠ H) and systemic translocation in plants. The comprehensive optimization process resulted in the discovery of spiropidion (**2**), a 2-aryl-1,3-dione proinsecticide featuring a spiro *N*-methoxy piperidine, which was selected for global development.

A scalable synthesis of spiropidion dione (**5**) *via* the Strecker-Dieckmann pathway is shown in Scheme 7. The seven-step convergent sequence enabled multi-kg amount preparation.[39,40] 2-(4-Chloro-2,6-dimethyl-phenyl)acetic acid (**58**) was obtained from 4-chloro-2,6-dimethylaniline in three steps: Sandmeyer reaction, a malononitrile arylation[23,43] (utilizing insights from the pinoxaden technical route, see Scheme 3), and hydrolysis.[43] The acid chloride of **58** was then reacted with the *N*-methyl amino nitrile Strecker product **52** derived from 1-methoxypiperidin-4-one (**49**). The resulting amide **59** underwent methanolysis of the nitrile



Scheme 6. Representative Strecker-Dieckmann path to 3-aryl-pyrrolidine-2,4-diones **51a**, and corresponding formation of proinsecticides **57** as enol ethyl carbonates.

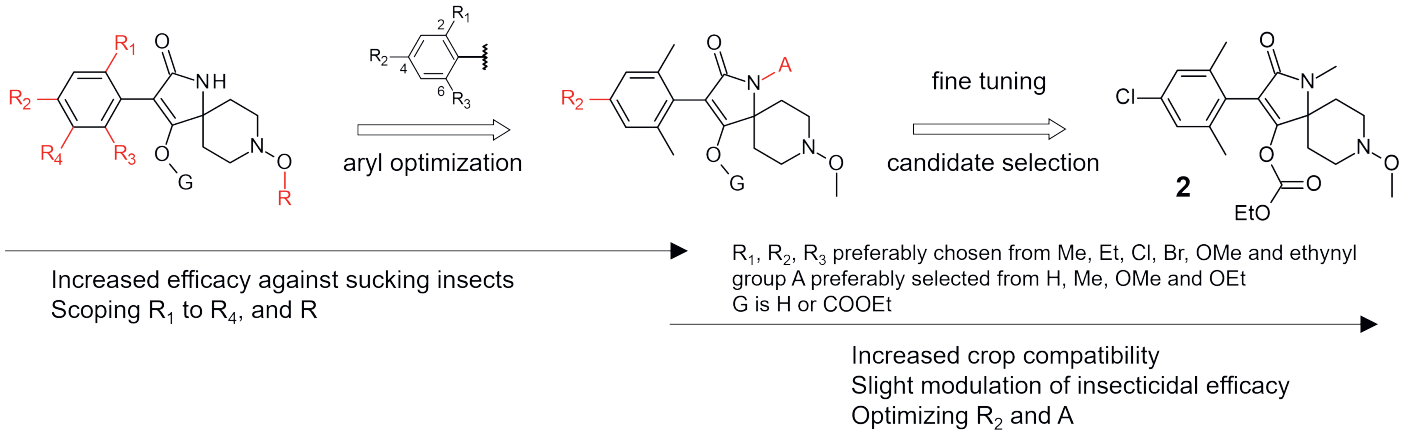
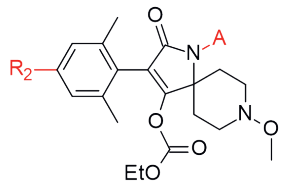


Fig. 8. Chemistry-driven and phenotypic screening-guided optimization leading to spiropidion (**2**).

group to yield methyl ester **60**, which was subsequently efficiently converted to target aryldione **5** through the base-mediated Dieckmann-type cyclization.

Final acylation of spiropidion dione (**5**) with ethyl chloroformate under standard conditions afforded spiropidion (**2**), the structure of which was unequivocally confirmed by a single crystal X-ray structure analysis (CCDC 1962940).

A practical alternative route to spiropidion dione (**5**) utilized an Ugi four-component reaction (Ugi-4CR), notably with superior convergence. In this approach, *N*-methoxy piperidone **49**, phenylacetic acid **58**, methylamine, and phenyl isocyanide (Ph-N$^+$≡C$^-$) condensed simultaneously to form the expected α-acylamino amide product **61**. Spiropidion dione (**5**) was then obtained expeditiously through direct post-condensation of this Ugi-adduct under basic, Dieckmann-like conditions. The cyclization efficiency proved highly dependent on both reaction conditions and isocyanide selection[44] (Fig. 10). Notably, phenyl isocyanide emerged as the optimal choice, offering both cost-effectiveness and superior step economy, as demonstrated through careful process research work by Godineau, Smejkal and coworkers.[45]



R_2	A	EC_{90} [mg L^{-1}]
Br	H	<1.5
Br	OMe	10.6
Br	Me	3.7
Cl	Me	2.8

Fig. 9. Curative aphicidal efficacy data (EC_{90}, effective concentration with at least 90% efficacy) against cowpea aphids (mixed age population) shown for representative advanced candidates with a preferred 2,6-dimethyl-4-halo substitution pattern.[39]

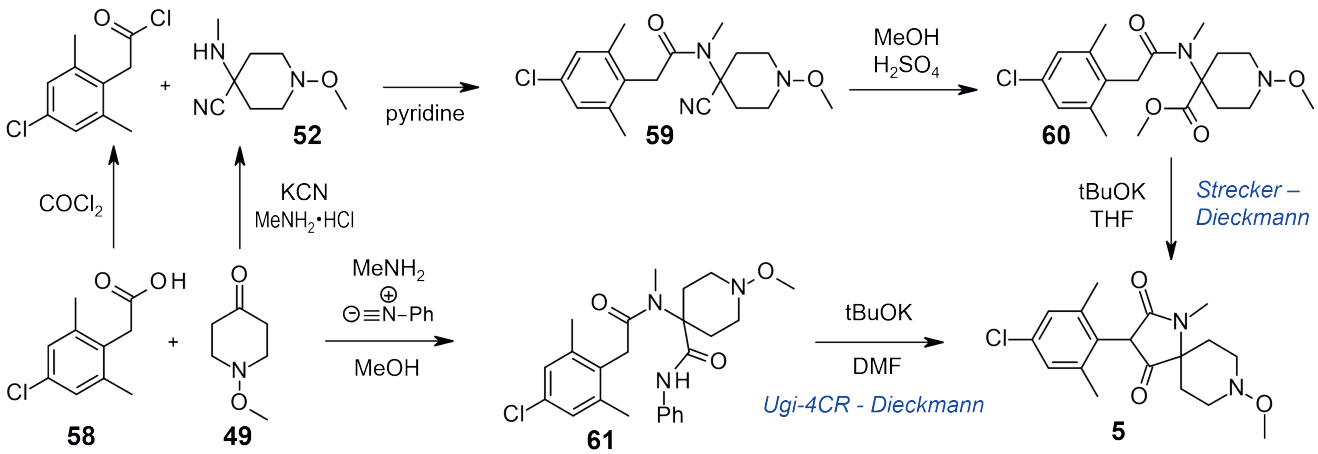
Products containing spiropidion (**2**) (active ingredient trademarked as TINIVION® technology; ELESTAL® product brand family) offer long-lasting protection against many damaging and difficult to control piercing and sucking pests, such as aphids, whiteflies, psyllids and scales, and various types of mites. TINIVION® technology, introduced to the marketplace in the 2020/21 season, is for use in field crops (soybean, cotton), specialty crops (citrus, pome, and stone fruits) and vegetables (tomato, pepper, and eggplant).

4. Properties and Ambimobility

Owing to the ACCase mode of action involved, *in planta* bioavailability of active ingredients **1** and **2** is essential for achieving effective control of both weeds and pests. Parameters that improve spray retention on leaf surfaces after foliar application, increase penetration across leaf cuticles and enhance systemic distribution in plant tissues are key determinants of treatment success.

For comprehensive visualization of plant distribution patterns, a combination of radiolabeled compounds and phosphor imaging techniques was employed. After a single leaf application, both [^{14}C]-pinoxaden[6,18] and [^{14}C]-spiropidion[39] demonstrated rapid foliar uptake, systemic distribution in leaves, and translocation across the whole plant.

The physicochemical properties of the active ingredients – their neutral character, a log P_{ow} value of 3.2 (both compounds **1** and **2**) and moderate-good water solubilities (200 mg L^{-1} for **1**, 46



Scheme 7. Convergent approaches to spiropidion dione (**5**) *via* Strecker-Dieckmann and Ugi-Dieckmann pathways.

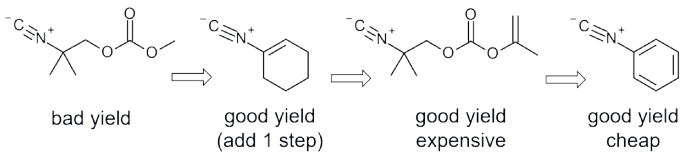


Fig. 10. Evolution of the used isocyanides.

mg L^{-1} for **2**, at 25 °C) – favor good foliar uptake. Suitable adjuvants can further enhance leaf cuticle penetration.[19,22,46]

Once within plant tissues, propesticides **1** and **2** undergo rapid hydrolysis to release the bioactive compounds pinoxaden dione (**4**) and spiropidion dione (**5**), respectively (hydrolytic stability $t_{1/2}$ at pH 7: 20.6 h at 50 °C for **1** and 34.9 h at 40 °C for **2**).[18,39] The enolate forms of these compounds subsequently bind to the CT domain active site of ACCase.[12c] The molecular weight, molar volume and weak acidity of these aryldiones (pK_a values of 3.82 for **4** and 5.53 for **5**), among other factors, are essential features that govern systemic distribution in plants.[18,39] The varying pH milieus across plant cellular compartments, combined with the weak acid character of these compounds, define their enolate-neutral form equilibrium, lipophilicity (log D), and water solubility.

In the context of insecticidal applications, efficacy also depends on exposure, *i.e.* the foliar bioavailability, to target pests in relation to their feeding behavior. *In planta* systemicity provides significant advantages, particularly for selectively controlling sucking pests that feed on leaf undersides, typically sheltered from direct spray contact. This means that, next to cuticle penetration and translaminar distribution, the oral accessibility from the vascular system is very important, especially for sap feeding insects (Fig. 11).[47] Specifically, aphids (*Aphis craccivora* and *Myzus persicae*) and whiteflies (*Bemisia tabaci*) feed predominantly within the vascular system.[48]

As demonstrated experimentally by Buchholz and coworkers,[39,47] the weak acid spiropidion dione (**5**) exhibited comprehensive systemicity in plant tissues, including translaminar distribution in treated foliage and significant basipetal movement from a treated leaf to the stem, thereby protecting untreated growing tissues through translocation within the phloem. In basic compartments such as the phloem (pH *ca.* 8), the enolate form of **5** predominates, exhibiting lower lipophilicity and enhanced water solubility. The reduced membrane permeability of the deprotonated form leads to accumulation in the basic phloem sap, resulting in increased exposure of target pests to spiropidion enolate during feeding.[47]

Due to its ability to be translocated within both vascular systems, xylem and phloem, spiropidion (**2**)-based chemistry exhibits full systemic properties (ambimobility). Depending on the application site, the compound may move acropetally within the xylem following the transpiration stream or within the phloem, becoming translocated to growing tissues (shoots and roots). This unique quality enables true whole-plant protection, as foliage growing after application remains protected.

Similarly, the ambimobility of pinoxaden (**1**)-based chemistry is crucial for robust herbicidal performance. Effective grass weed control relies on thorough *in planta* distribution of the active principle **4**, in particular translocation to the site of action in the meristematic growing tissues.[6,18]

5. Conclusion

Our chemical investigations into diverse ACCase-inhibiting aryl cyclic 1,3-diones spanned both herbicidal and insecticidal classes. The synthetic approaches showcased diverse methodologies including malonate-hydrazine cyclocondensations and iodonium ylide cross-couplings, alongside cycloisomerization-rearrangement strategies and Strecker/Ugi-Dieckmann pathways. Notable innovations included the first reported use of [1,4,5]oxadiazepane (**12**) as a reagent and a strategic exploitation of the underutilized 1-methoxypiperidin-4-one (**49**) building block.

Collaborative work with process research experts leveraged further key advances: malononitrile arylation of hindered substrates, cyclocondensation of aryl malonamides with cyclic hy-

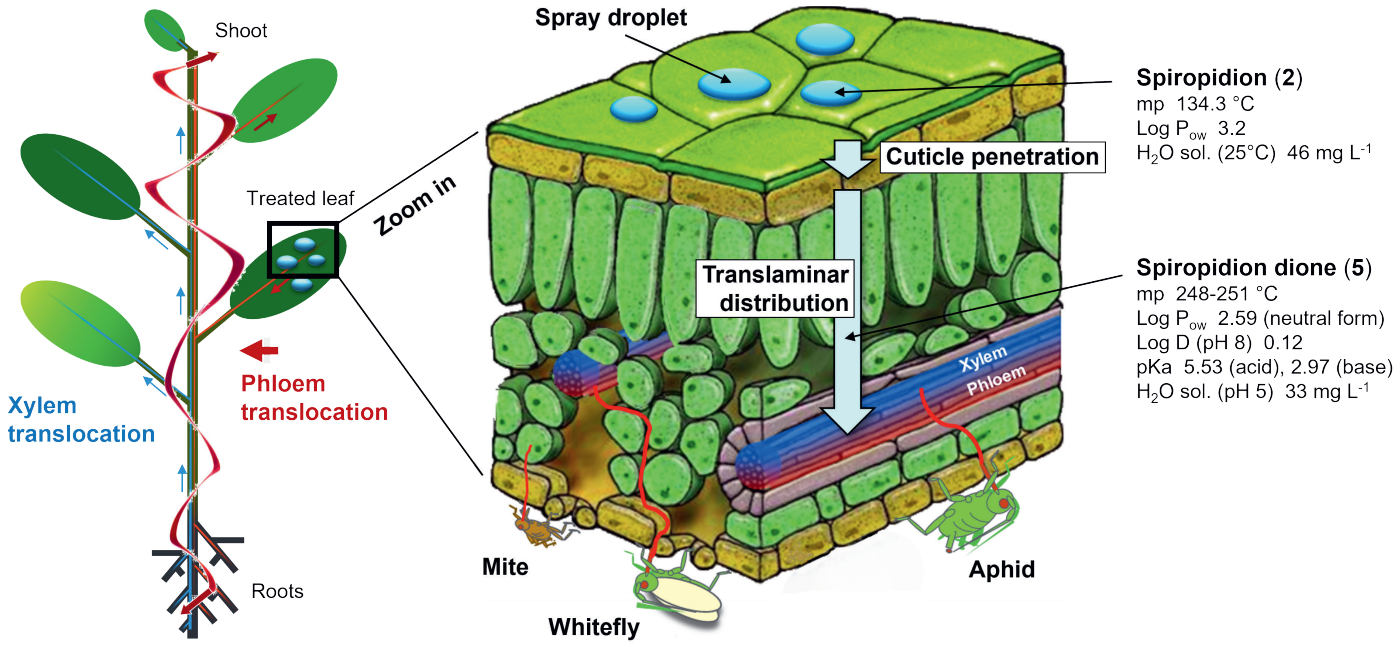


Fig. 11. Schematic illustration (left) of the two systemic translocation pathways within plants (xylem and phloem mobility). Leaf cross-section (right) showing key uptake and translocation events determining the bioavailability of foliar-applied active ingredients. The weakly basic phloem sap (pH ~8) promotes ion trapping of spiropidion dione **5** (pK_a 5.53) through its deprotonation, enhancing phloem mobility. As a result, sucking pests encounter elevated concentrations of spiropidion-enolate at their preferred phloem feeding sites. Modified from Buchholz *et al.*[47,48a] (mp = melting point, H_2O sol. = water solubility).

drazines, and direct Dieckmann-like post-condensation of Ugi adducts, demonstrating the value of methodology innovation in agrochemical discovery.

Building on synthetic achievements, a crucial interplay of active ingredient with safener technology and adjuvant science established pinoxaden (**1**) as an effective selective graminicide for use in both wheat and barley. In a distinct development, the ambimobility of spiropidion (**2**)-based chemistry provided full plant protection and unique long-lasting control against sap-feeding pests.

Crop protection research on ACCase-inhibiting aryldione chemistry continues at Syngenta and other institutions. Scutt *et al*.[49] reported metproxybicyclone, a novel carbocyclic aryldione for post-emergence control of both sensitive and ACCase-inhibitor resistant grass weeds in soybean, cotton, and other dicotyledonous crops. In parallel developments, spidoxamat is set to enter the marketplace as the fifth member of the tetronic/tetramic acid insecticidal class.[50]

The increasing prevalence of resistance to ACCase inhibitors, combined with stringent regulatory requirements as well as safety and sustainability challenges,[51] underscores the necessity of ongoing research in this field.

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