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Sedaxane, Isopyrazam and Solatenol™: Novel Broad-spectrum Fungicides Inhibiting Succinate Dehydrogenase (SDH) – Synthesis Challenges and Biological Aspects[1]

Harald Walter*, Hans Tobler, Denis Gribkov, and Camilla Corsi

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Abstract: Sedaxane (SDX) **1**, isopyrazam (IZM) **2** and Solatenol™ (STL) **3** are broad-spectrum pyrazole carboxamides, which originate from novel chemical classes of fungicides. Their mode of action (MoA) is inhibition of succinate dehydrogenase (SDH), which was recognized for a long time to deliver only compounds with a narrow biological spectrum. This view changed with the market introduction of BASF's boscalid in 2003.[2] All major agro-companies subsequently worked in parallel on this MoA successfully and recently introduced new compounds to the market. Syngenta entered the SDHI area in 1998 and was able to introduce three complementary compounds to the market between 2010 and 2012. In this short review some synthesis challenges and biological effects of SDX **1**, IZM **2** and STL **3** will be covered. New cost-efficient synthesis strategies for the preparation of *o*-biscyclopropyl-aniline, new benzonorbornene intermediates and the key pyrazole carboxylic acid intermediate which is essential for all three Syngenta SDHIs, will be in the focus of this review

Keywords: *o*-Biscyclopropylaniline · Isopyrazam · SDHI · Sedaxane · Solatenol™

Harald Walter

Hans Tobler

Denis Gribkov

Camilla Corsi

*Correspondence: Dr. H. Walter
Syngenta Crop Protection AG
Building 5.6.150, CH-4058 Basel
Tel.: + 41 62 866 03 31
E-mail: harald.walter@syngenta.com

Harald Walter *studied chemistry and mathematics at the University of Tübingen and received a PhD in organic chemistry from the University of Tübingen, Germany (Prof. Dr. M. Hanack) in 1985. In 1986 he started his industrial career at the dyestuff division of former Ciba-Geigy AG. In 1990 he joined the agro division of Ciba-Geigy and worked there as a team respective project leader in the fungicide area. After several mergers (Ciba-Geigy + Maag AG + Sandoz AG + Zeneca (agro part)), Syngenta Crop Protection AG was formed in 2000. Within Syngenta he worked as a senior project leader and was appointed to Syngenta Fellow (member of the scientific career ladder of Syngenta) in 2003. He was appointed to leader of the portfolio strategy team fungicides in 2008 and is currently research portfolio manager for fungicides and new technologies. Harald Walter has published more than 135 journal papers and patent applications (major topics: heterocyclic chemistry, new agrochemical fungicides), three chapters in books (a fourth chapter in progress), topics: complex I inhibitors and SDHIs (complex II inhibitors).*

Hans Tobler *was born in 1946 in Münsterlingen/Thurgau and graduated in chemistry and natural sciences from ETHZ in 1970. This was followed by a postgraduate stay with Prof. Barton at Imperial College in London (1970/71). From 1971 to 1976 he undertook PhD studies with Oskar Jeger and Camille Ganter at ETHZ (synthesis of Wurtzitane (Iceane)). In 1976 he joined the agro division of Ciba-Geigy AG, where he was engaged in many herbicide-, plant growth regulator- and insecticide projects until 2000 (within Ciba-Geigy and Novartis, which was the product of the merger of Ciba-Geigy AG and Sandoz AG). In 1993/94 he was granted a sabbatical leave with P. Magnus at Texas University at Austin. After a further merger (agro divisions of Novartis and Astra Zeneca in 2000) he worked as a senior scientist in the fungicide research team of Syngenta Crop Protection AG and was part of the SDHI-inhibitor optimisation project team until his retirement in 2008. Hans Tobler has published 79 journal papers and patent applications (major topics: new fungicides, herbicides, insecticides and plant growth regulators).*

Denis Gribkov *studied chemistry at the Moscow State University and received a PhD in organic chemistry from the University of Erlangen-Nuremberg (Dr. K. Hutzsch/Prof. Dr. J. A. Gladysz) in 2005. From 2005 to 2007 he was a postdoc at the Columbia University (New York – Prof. D. Sames) and from 2007 to 2008 he added a*

second postdoc stay at the Albert-Ludwigs-University of Freiburg (Prof. B. Breit). In 2008 he started his industrial career at Syngenta Crop Protection Muenchwilen AG as a team leader in process chemistry. In 2012 he moved to the production site of Monthey, where he stayed for one year. In 2013 he returned to Muenchwilen as a team leader in process chemistry. Denis Gribkov has published 24 journal papers and patent applications (major topics within Syngenta: new processes for agrochemicals (fungicides/insecticides/herbicides)).

Camilla Corsi *graduated in Chemistry from Florence University with a PhD and Postdoc in Organic Chemistry obtained from University College London (London, UK, 2002) and Ecole Polytechnique (Palaiseau, France, 2003) respectively. In 2004, she joined Syngenta as Chemistry Team Leader. From 2004-2008, she has been working in fungicide and insecticide research before being appointed Fungicide Chemistry Group Leader. After a few years in this role, she became Head of Abiotic Stress Management and Seed Care Chemistry in 2011. In 2012, Camilla was appointed Head of Global Crop Protection R&D Portfolio. From 1st March to July 2014, Camilla was Head of Chemistry Crop Protection R&D before her last appointment to Head of Chemical Research Crop Protection R&D. Camilla Corsi has published more than 40 scientific papers and patents.*

Introduction

Carboxin, the first succinate dehydrogenase inhibitor (SDHI) compound to reach the market, was introduced in 1966 by Uniroyal.[3] This heterocyclic carboxamide showed a narrow biological spectrum (smuts and bunts) and was used for seed treatment only. For a very long time no real breakthroughs in the SDHI area in terms of spectrum and efficacy were made. This situation changed when BASF and Monsanto incorporated *o*-substituted anilines and better optimized the carboxylic acid moiety (Fig. 1) (for example pyrazole and pyridine acid components turned out to be especially of interest in combination with appropriate *o*-substituted aniline partners[4,5]).

Some of the new compounds that were studied, especially the bisphenyl-type pyrazole carboxamides, showed interesting potential for the control of cereal diseases including the most interesting cereal disease *Septoria tritici*. Although BASF researchers filed further patents covering pyrazole-4-carboxamides based on bisphenyl-type amines, between 1994 and 1997,[6,7] they either didn't realize the full potential of the bisphenyl-type pyrazole-4-carboxamides at that time or perhaps their first priority was not to discover a marketable compound targeting cereal diseases. Boscalid (**50**), a pyridine carboxylic acid amide of the bisphenyl-type was introduced in 2003, which mainly filled BASF's *Botrytis* gap,[2] but also covered other important diseases such as *Alternaria* spp. and *Sclerotinia* spp.

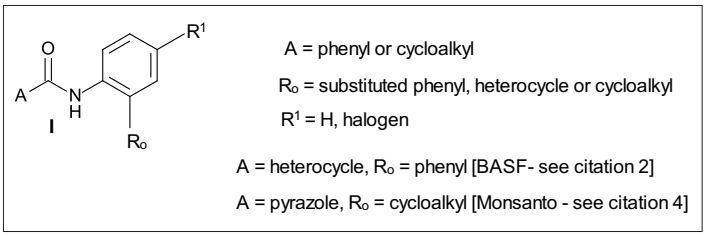


Fig. 1. General formula **I** of compounds covered by breakthrough patents of BASF and Monsanto.

The promising spectrum and potency of some new representatives of the pyrazole carboxamide class convinced chemists at Syngenta Crop Protection AG to put more emphasis into the SDHI area.

The Major Syngenta Contributions

The structures of the Syngenta market compounds are shown in Fig. 2. It is obvious that these structures are unique in the agro market place and clearly differentiated from the competitor SDHIs. The disease control spectra and uses of the Syngenta compounds are complementary and each of them has their place in the market. In the following chapters the chemistry challenges and some biological aspects will be discussed in more detail.

Sedaxane (SDX, 1)

The starting points for sedaxane (**1**) were Monsanto's *o*-cycloalkylaniline-type and BASF's bisphenyl-type SDHIs.[4,5] Monsanto's patent only specifically covered pyrazole-4-carboxamides, whereas the BASF patent covered heterocyclic acids more broadly, with a focus on pyridine carboxamides (the structure of boscalid (**50**) was first revealed here). An in-depth analysis of the IP landscape around the Monsanto and BASF SDHIs, which was carried out in 2000, showed that there were still some gaps left around the *o*-cycloalkyl-substituted and the *o*-phenyl-substituted anilines. In addition, the pyrrole acid was identified as a significant gap in more or less all competitor patents, including the Monsanto and BASF breakthrough patents published in the early 1990s. Follow up of the pyrrole carboxylic acid gap proved to be successful and the best pyrrole carboxamides (amines of the Monsanto as well as the BASF type used) found by Syngenta researchers showed broad spectrum and good efficacy in the glasshouse, comparable to the better pyrazole carboxamides.[8] The most interesting disease, *Septoria tritici* was also covered, but in field trials the pyrroles turned out to be inferior to the comparable pyrazole carboxamides (rate per rate comparison). Syngenta researchers soon realized that there were two product-concept streams that could be followed up. The first priority at the beginning of the project (2000/2001) was to find a compound with a complete cereal spectrum (with *Septoria tritici* as key driver disease). The second priority was to find a broad-spectrum seed treatment compound (with *Ustilago nuda* as key driver disease). The leads shown in Fig. 3 could be seen as starting points for both types of products being on the marketing organisation's wish list. As systemicity is a key

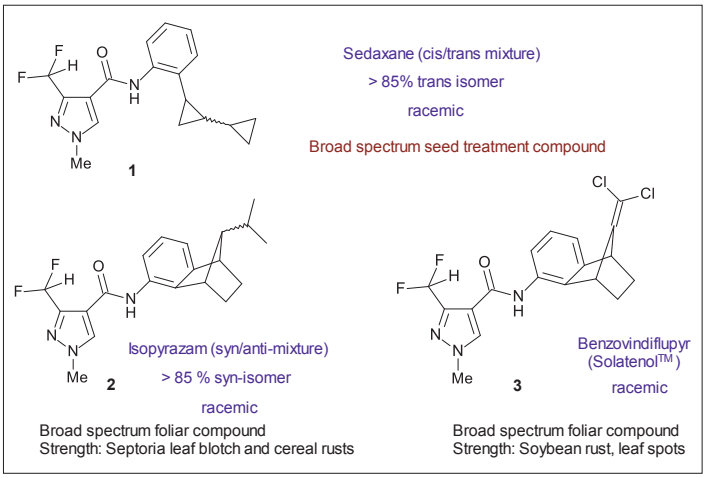


Fig. 2. The Syngenta SDHI market compounds introduced between 2010 and 2012.

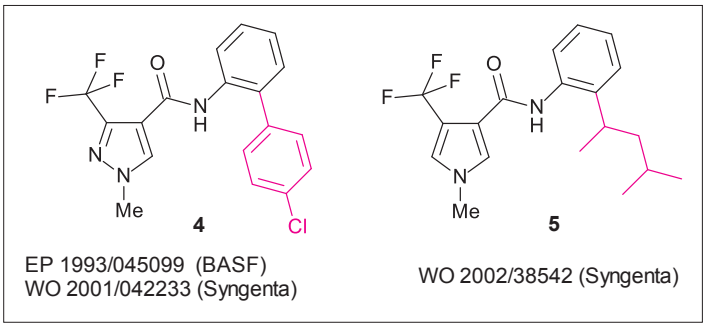


Fig. 3. The first *Ustilago* leads for sedaxane **1**.[9,10]

characteristic for seed treatment use, compounds with lower logP (range 2.0–3.5) and higher water solubility (at least 10 ppm) were the focus of the synthesis optimisation program. From the IP analysis, specifically substituted *o*-cyclobutyl- and *o*-cyclopropyl-substituted ring systems looked favourable and therefore were studied more thoroughly (Fig. 4).[11,12]

The predicted physical chemical properties needed for seed treatment use favoured the cyclopropyl-substituted cyclobutanes and biscyclopropyl substituents as *o*-substituents of the aniline moiety. Optimisation of the *o*-cyclopropyl and *o*-cyclobutyl substituent revealed a simple rule for optimal potency and spectrum: the C_6/C_7 rule suggested that 6 to 7 carbon atoms in the *ortho*-position are preferred. This leads to the conclusion then to consider the option of either a cyclopropyl-substituted cyclobutane as the *ortho*-substituent or to have a biscyclopropyl *ortho*-substituent, where one of the cyclopropane rings can bear a further methyl group (of course, halo-groups such as fluorine and chlorine were still allowed). As we considered the *o*-biscyclopropyl substituent to be more attractive (simplicity of chemistry was one reason to go this way), we soon realized that there was big potential in this class and with compound **1**, we discovered a very good compound, suitable for further progression. The follow-up of the *o*-cyclobutyl-substituted anilines revealed that compound **1** was the compound of choice to take forward as it showed broad-spectrum activity, including *Ustilago nuda*. The synthesis of SDX **1** on a larger scale in the earlier phase of the project turned out to be challenging. The first hurdle was to prepare the difluoromethyl-substituted pyrazole acid **12** efficiently in kg quantities. Since 4,4-difluoro-3-oxobutyric acid alkyl esters **9a,b** (preferred alkyl groups are: Me: **9a** or Et: **9b**) were not available in bulk when we started the project, a route for the preparation of 4,4-difluoro-oxobutyric acid alkyl esters **9a** and **9b** had to be developed. The synthesis of the β-ketoester mixture **9a,b** was achieved by starting with the cheap chloroacetylchloride **6** and then using a Halex reaction with potassium fluoride at higher temperatures followed by a new protocol, the so-called amido-Claisen approach, discovered by Syngenta researchers, which led to the mixture of 4,4-difluoro-3-oxobutyric acid alkyl esters **9a,b** in satisfactory yield. The reaction of **9a,b** with trimethyl orthoformate gave a mixture of the vinylether cyclisation precursors **10a,b** in excellent yield, which after reaction with methylhydrazine gave the pyrazole acid ester mixture **11a,b** (as outlined in Scheme 1). The crude mixture of esters **11a,b** was hydrolysed under standard conditions and after recrystallisation 3-difluoromethyl-1-methyl-4-pyrazole carboxylic acid **12** was obtained in pure form in satisfactory yield.

For the synthesis of *o*-biscyclopropylaniline, two favourable routes were taken into account for upscaling. The first one described here is the Kishner approach, in which we started the synthesis with the very cheap 2-chlorobenzaldehyde **13** (see Scheme 2).

The reaction of the cheap aldehyde **13** with methylcyclopropylketone **14** under basic conditions (crossed Aldol reaction) followed by reaction with hydrazine gave the pyrazoline intermediate **15** in very good yields.[14] Heating up the crude pyrazoline **15** under basic conditions (T >190 °C) in diethylene glycol resulted in the loss of nitrogen with formation of the 1-chloro-2-biscyclopropylbenzene **16** in good yields (*trans*/*cis* mixture: ratio *ca.* 2:1).[14,15] For the introduction of the amino group, several technologies were tested, including the Cu-catalysed direct amination of chloro- and bromophenyl starting materials in an autoclave,[16] the direct amination with ammonia *via* a Pd-catalysed process using Josiphos as the ligand[17] and the Pd-catalysed benzylamination of the chlorobenzene precursor **16** in the presence of an appropriate ligand. It turned out that the most favourable methodology with the best chances for scaling up was a Pd-catalysed amination in the presence of

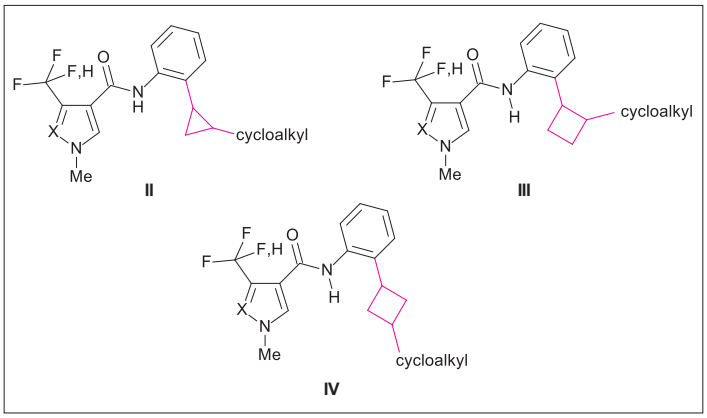
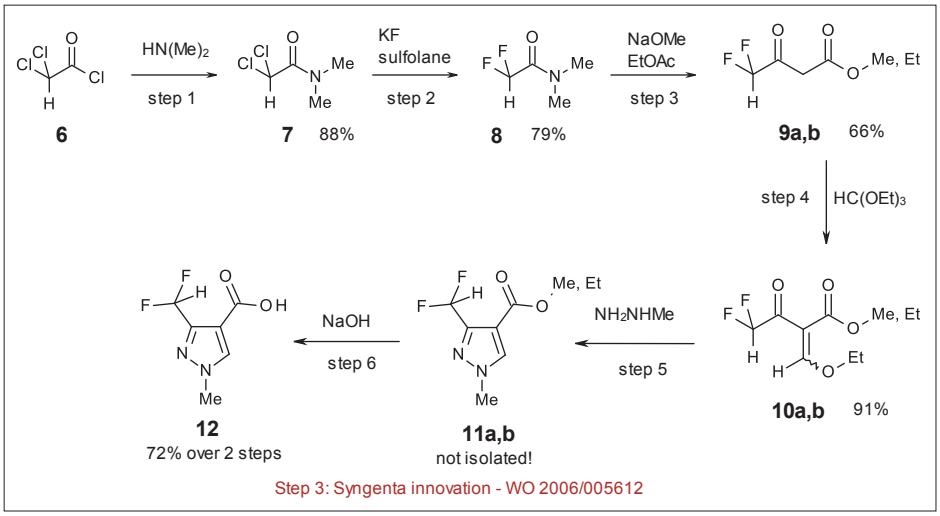
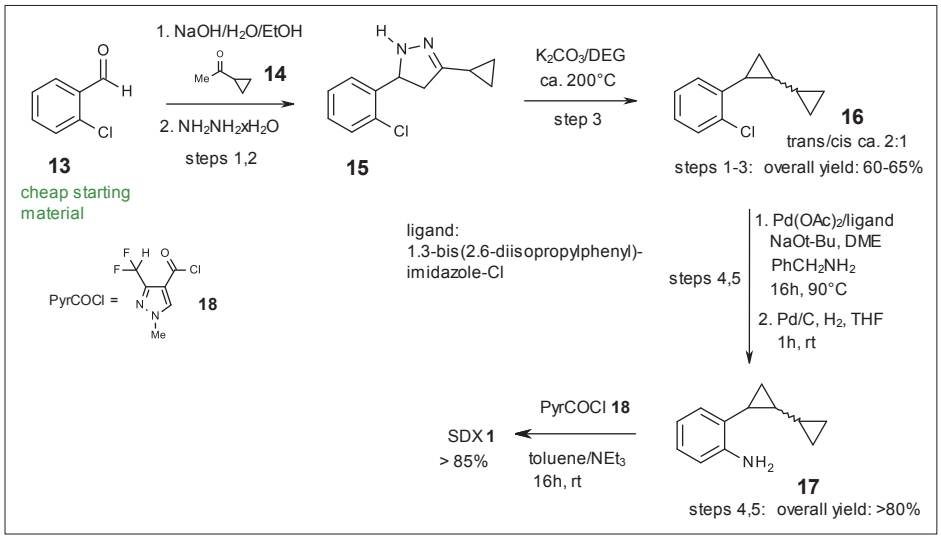


Fig. 4. General formulae **II**, **III** and **IV** of novel pyrazole carboxamides derived from new *o*-cyclobutyl/cyclopropyl-substituted anilines.[11,12]



Scheme 1. Synthesis of 3-difluoromethyl-1-methyl-4-pyrazole carboxylic acid **12** using new Syngenta technology.[13]



Scheme 2. Synthesis of SDX **1** using the Kishner route.[11,13–18]

a carbene ligand.[18] After catalytic cleavage of the protecting group, *o*-biscyclopropylaniline **17** was obtained in excellent yields (Scheme 2). The preparation of the amide is straightforward and the standard reaction of the carboxylic acid chloride **18** with the aniline in the presence of a cheap base such as triethylamine gave sedaxane (**1**) in very good yields (>85%).

The second approach described here is the so-called 1,3-cyclisation approach (Scheme 3), starting from an appropriate *o*-halomethylnitrobenzene (halo is bromo or chloro),[19] which could be transferred to the *o*-substituted nitrobenzene intermediate **19** using well-known procedures.[20,21] The reduction of the keto group (present in the *o*-substituent) with sodium borohydride gave the alcohol **20** in excellent yields. The reaction of **20** with methylsulfonylchloride (intermediate used as raw material for the next step) followed by treatment with an appropriate base, gave *o*-biscyclopropylnitrobenzene **21** in reasonable yields (Scheme 3). The 1,3-cyclisation was best performed using a stronger base such as powdered potassium hydroxide in dimethylformamide (DMF) or dimethylsulfoxide (DMSO). The yields of *ortho*-biscyclopropylnitrobenzene **21** varied between 65 and 85% (depending on the cyclisation reaction conditions). One advantage of the second route was the higher stereoselectivity (a *trans*/*cis* ratio of 7.7:1 could be achieved), but overall the route was judged to be less attractive (more expensive) than the Kishner route and therefore no further optimisation work on this route was done.

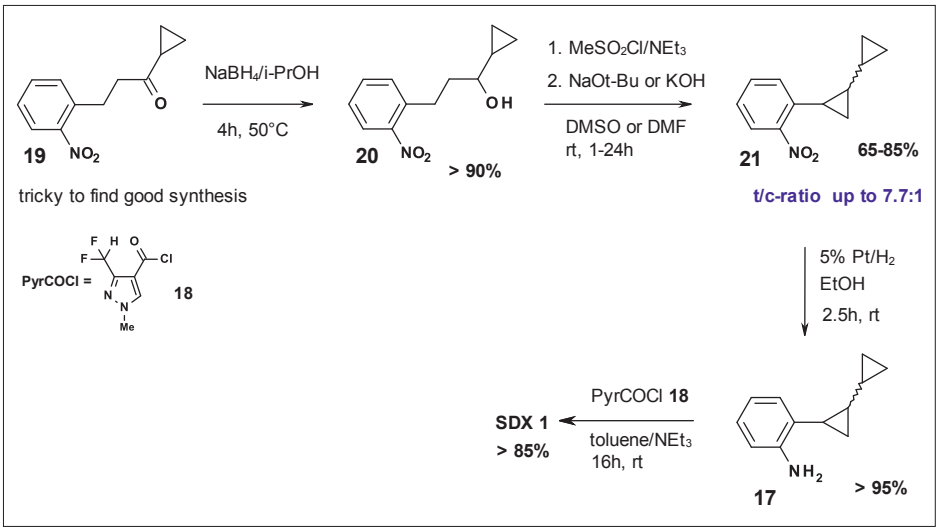
Biological properties of SDX (1)

Sedaxane (**1**) is a broad-spectrum seed treatment compound covering some very important diseases in major crops. It offers a very good cereal spectrum with excellent activity against *Microdochium nivale*, *Rhizoctonia solani*, *Tilletia caries* and *Ustilago nuda* and good activity against *Puccinia recondita* and *Pyrenophora graminea*. A specific strength is the control of *Rhizoctonia spp*. (best in class seedcare compound) in cereals and also in many other crops. There are other market opportunities such as control of *Macrophomina* in soybean, *Phoma* in canola and soybean as well as *Sclerotium spp*. (peanut and soybean), which have already been followed up by Syngenta.

Isopyrazam (IZM, 2)

When we started to work in the SDHI area, the top priority of the Syngenta business was to look for a cereal compound covering the major diseases including *Septoria tritici*. As a starting point we choose furametpyr (**22**), a compound with a narrow spectrum (sheath blight, rice) and interesting physical chemistry properties (high water solubility – potential for systemicity), where we saw plenty of options for optimisation and could touch new ground with the use of more complex cyclic amines. Another advantage was that we could more easily generate IP protection for the new classes planned. Bridged furametpyr-type compounds of the general formula **V** showed very weak activity against *Septoria tritici* as long as a heteroatom was present in the 9-position of the bicyclic system and also generally showed weak overall fungicidal activity (Fig. 5)

The breakthrough could be achieved by introducing aminobenzonorbornenes as the amine components. Carboxamides



Scheme 3. Synthesis of SDX **1** using the 1,3-cyclisation route.[19–21]

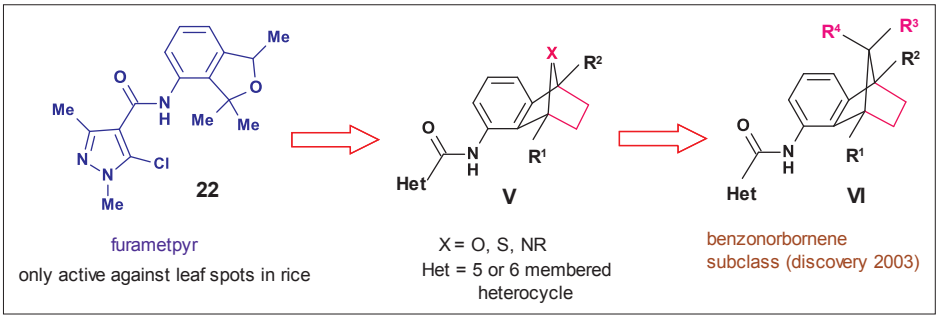
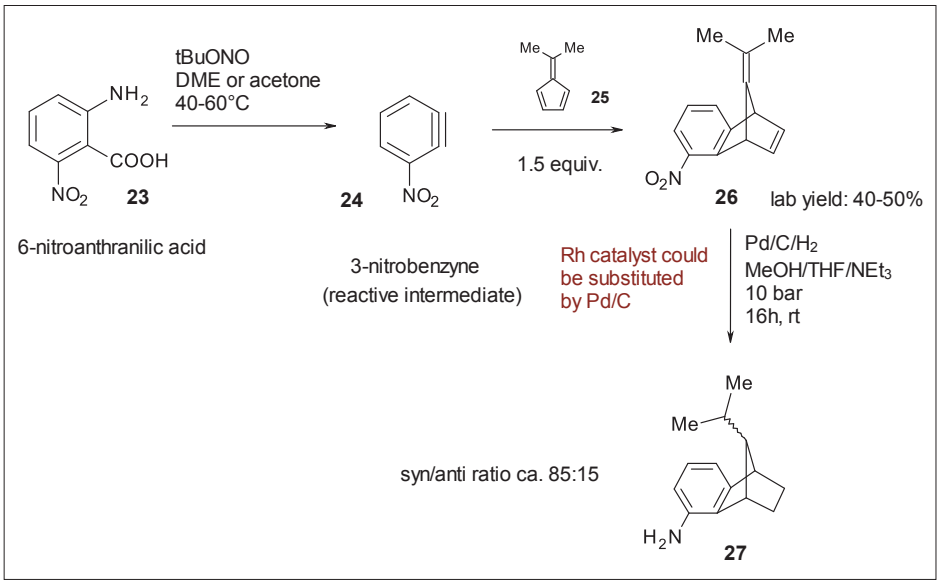


Fig. 5. Structure of furametpyr **22** and general structure of bicyclic heterocyclic amides **V** and **VI**, including the benzonorbornene amide subclass.

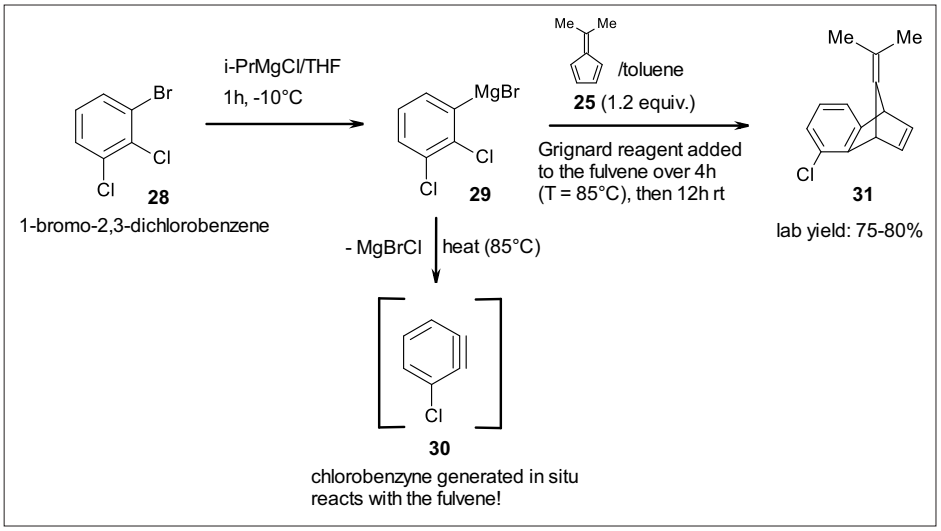
derived from the new benzonorbornene amines showed an interesting spectrum and activity level. Here we saw clear progress in term of potency and also came closer to our biological spectrum of choice. As we were interested in getting a really good cereal spectrum, we had to cover at least *Puccinia recondita* and *Septoria tritici*. Analysing the biological glasshouse data carefully led to the conclusion that C_1-alkyl to C_4-alkyl in 9-position could deliver what we were interested in.

An optimal balance between rust- and *Septoria* activity was achieved by using the isopropyl group in the 9-position of the benzonorbornene ring combined with the 3-difluoromethyl-1-methyl-4-carboxylic acid **12** , leading finally to isopyrazam (IZM, **2**). Carboxylic acids other than the pyrazoles (but even in the pyrazoles the substitution pattern has to be optimised) only led to weak rust- and *Septoria* activity levels and the trifluoromethyl-substituted pyrazole carboxamides as well as other amides were clearly inferior to the corresponding difluoro-methyl-substituted pyrazole carboxamides as far as the biological efficacy was concerned. Isopyrazam (**2**) turned out to be a broad-spectrum fungicide, which could also be used in crops other than cereals. Especially pronounced was the activity against powdery mildew diseases in the fruit and vegetable segments. As always in industry, we had the following commercial challenge: is the compound really producible for a price that gives us a chance to be competitive in the market place? Isopyrazam (**2**) is a complex molecule and was the first benzonorbornene compound designed for the agro market. As the pyrazole carboxylic acid is the same as in sedaxane (**1**), we already knew that the pyrazole carboxylic acid **12** contributed significantly to the cost of IZM (**2**). The synthesis of the aminobenzonorbornene intermediate **27** therefore had to be done in a very cost effective way. In order to construct the benzonorbornene skeleton, a cycloaddition approach seemed to be the best option.[22,23] In the research phase we used a route that started from dimethylfulvene **25**.[24] Dimethylfulvene **25** was prepared from cyclopentadiene **38** (obtained by cracking of the dimer **37**), followed by a base-catalysed reaction with acetone in good overall yields. As the diene partner for the cycloaddition reaction we choose 3-nitrobenzyne **24**, which was generated *in situ* from 6-nitroanthranilic acid **23** (Scheme 4).[24–26] The cycloadditon reaction worked out reasonably well in the laboratory and gave nitrobenzonorbornadiene intermediate **26** in yields of *ca.* 50%. The final step, a complex hydrogenation, could be optimised and we were able to use the cheaper catalyst palladium instead of rhodium, which we used in an earlier phase of the project. After some laboratory optimisation work, we were able to isolate the desired 9-isopropylsubstituted aminobenzonorbornene amine **27** in yields of >90% with satisfying *syn*/*anti* isomer ratio (7:3 until 9:1, the ratio depending on the hydrogenation conditions used).[24,27,28] The multistep sequence outlined in Scheme 4 clearly shows that this process might not be the best one for scaling up and doesn't have the best chance for matching the cost target. However, for the preparation of the field amounts needed for global biological field-testing (up to 100 g material or even more) this route was good enough and used for a longer time in research.

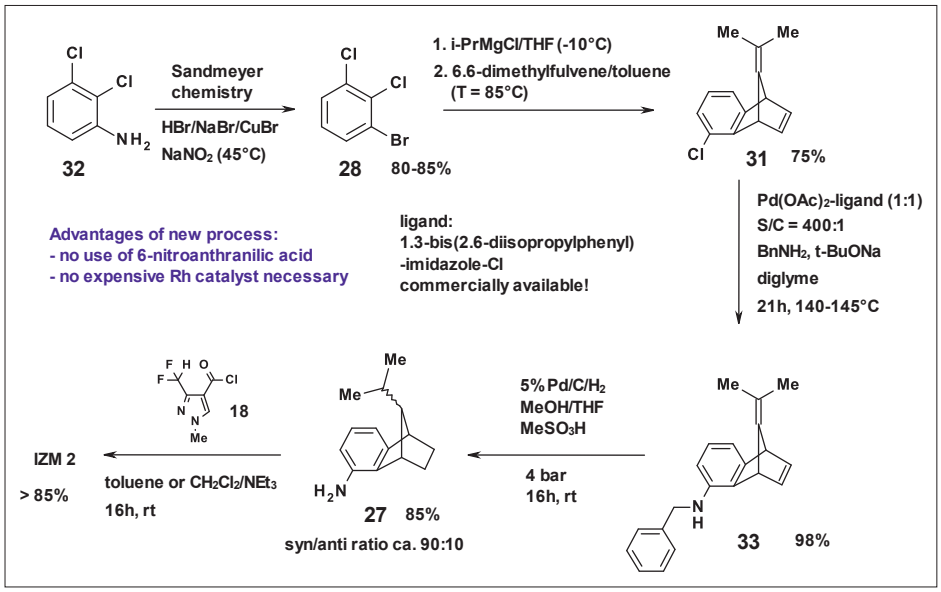
As the research team realized that the project would go forward more readily with an improved and more cost-effective route, the team worked on a simplification of the nitrobenzyne route. In our opinion, the most critical step was the cycloaddition using 3-nitro-benzyne **24** (generated *in situ*) and dimethylfulvene **25** as reaction partners. In fact, this reaction leads to by-products including tars, which are difficult to remove from the product. In the laboratory the pure material was obtained by use of column chromatography, but this is of course not practical for purification on a production scale. To avoid by-products in the cycloaddition step, one idea was to use chlorobenzyne **30,** generated *in situ* from 1-bromo-2,3-dichlorobenzene **28** by reaction with isopropyl magnesium chloride (Scheme 5). In the laboratory we soon saw that this approach gave higher yields (fewer by-products, less tar formation) and the chlorosubstituted benzonorbornadiene **31** could be isolated in yields of 75–80%[29,30] (Scheme 5).



Scheme 4. Preparation of the aminobenzonorbornene part **27** of IZM (**2**) using the nitrobenzyne route.[24–28]



Scheme 5. A breakthrough in the synthesis of IZM **2**: the cycloaddition reaction of *in situ* generated chlorobenzyne **30** with dimethylfulvene **25**.[29,30]



Scheme 6. Preparation of IZM (**2**) using the chlorobenzyne approach – the whole sequence.[29,30]

The transformation of the chlorobenzonorbornadiene **31** into the final aminobenzonorbornene **27** required the development of new technology. The best approach we found in the laboratory was to use a palladium-catalysed benzylamination in the presence of an appropriate ligand, leading to 4-benzyl-9-isopropylidenebenzonorbornadiene **33**. Subsequent hydrogenation of the double bonds and concomitant deprotection (loss of toluene) using a heterogeneous palladium-catalysed approach, leads to the amine **27** in good yield. The reduction /deprotection step was optimised to a degree that it could be handed over directly to the process technology group for further optimisation (Scheme 6). The direct amination approach using a Pd-catalysed, Josiphos catalyst and ammonia[30] was inferior to the benzylamination approach and therefore not followed up.

Biological Properties of Isopyrazam (IZM, 2)

IZM (**2**) is a broad-spectrum fungicide which can be used in important crops such as apple, banana, cereals, cotton, oilseed rape (OSR), turf and vegetables. As this compound was designed mainly for use in cereals, it is no surprise that control *of Septoria tritici*, *Puccinia recondita*, *Puccinia striiformis* and *Ramularia collo-cygni* are all strengths of IZM (**2**). The control of powdery mildews and certain leaf spots in fruit and vegetables as well as the control of black sigatoka (*Micosphaerella fijiensis*) in bananas, offers additional market opportunities for this fungicide.

Benzovindiflupyr/Solatenol™ (STL, 3)

Solatenol™ (ISO common name: benzovindiflupyr) is Syngenta's second benzonorborne containing SDHI and is derived from the structure of isopyrazam (IZM, **2**). As Syngenta was the only player in the benzonorbornene field and had a very favourable patent position in the area, we tried to exploit further the potential of the benzonorbornene amide class. The final goal was to improve the efficacy as well as the spectrum of IZM (**2**). As an additional goal we wanted to reduce the complexity of the IZM structure (fewer stereocentres). At the time we discovered IZM (**2**), Asian soybean rust (ASR) was not in the focus of the Syngenta research. Subsequently, ASR increased in importance and has become a major threat for Brazilian farmers. After building-up a glasshouse screening cascade for ASR, we could more reliably test the SDHI compounds. IZM (**2**) turned out to be a good lead for control of ASR in the glasshouse and we therefore decided to optimise the benzonorbornene part towards ASR activity, keeping in mind the objective to reduce the complexity of the IZM structure. The most obvious approach was to eliminate the problem posed by the presence of geometric (*syn/anti*) isomers. To achieve this goal, we checked two options (Fig. 6): 1) two substituents of the same type in 9-position (*e.g.* two methyl groups- see general formula **VIII**) or 2) a methylidene system having the same substituents (see general formula **VII**).

We checked the two options carefully and realized that for the optimisation of the ASR activity, the methylidene approach was the more successful one. We discovered that compounds with dihalomethylidene substituents in 9-position combined with an appropriate pyrazole carboxylic acid, looked very promising in the glasshouse and this activity could also be confirmed in Brazilian field trials. After the second field season in Brazil, it was clear that the compound having the dichloromethylidene substituent was the most preferred one. From the cost of goods perspective this substituent was also the most favoured one. The pyrazole part of choice again turned out to be the 3-difluoromethyl-1-methyl-4-pyrazole carboxylic acid **12**. The structure of the newly discovered compound **3**, which was later called Solatenol™, only has two stereocentres (no more *syn/anti* isomers) and therefore at a first glance looks simpler than IZM (**2**). However, when we started to brainstorm about synthesis options that are amendable for production, we realised that the synthesis of STL (**3**) was even more challenging than the synthesis of IZM (**2**). As the biological potential was clearly proven, we started to investigate new synthetic routes. In the research phase we commenced to use an intermediate we already knew from the first IZM research route (benzyne route). The intermediate, 4-nitro-9-isopropylidene-benzonorbornadiene **26** was prepared by our colleagues in the process technology group during the up-scaling of our first IZM route and was therefore available in kg quantities. Starting from

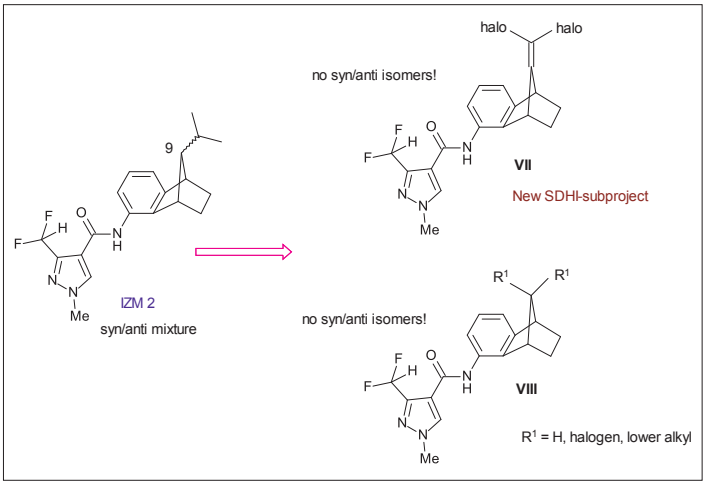
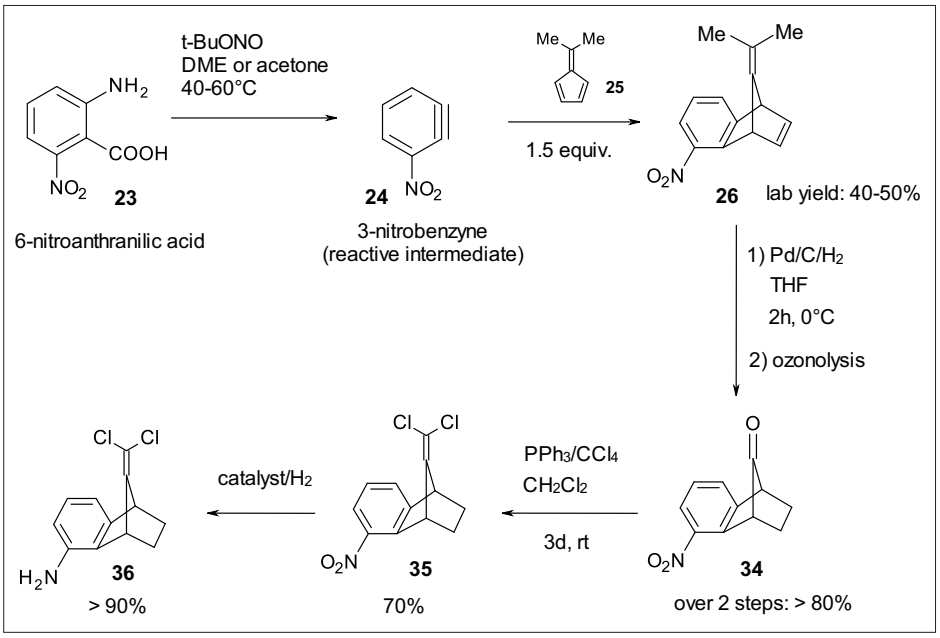


Fig. 6. Optimisation of the IZM lead structure towards soybean rust activity whilst simplifying the structure.[31]



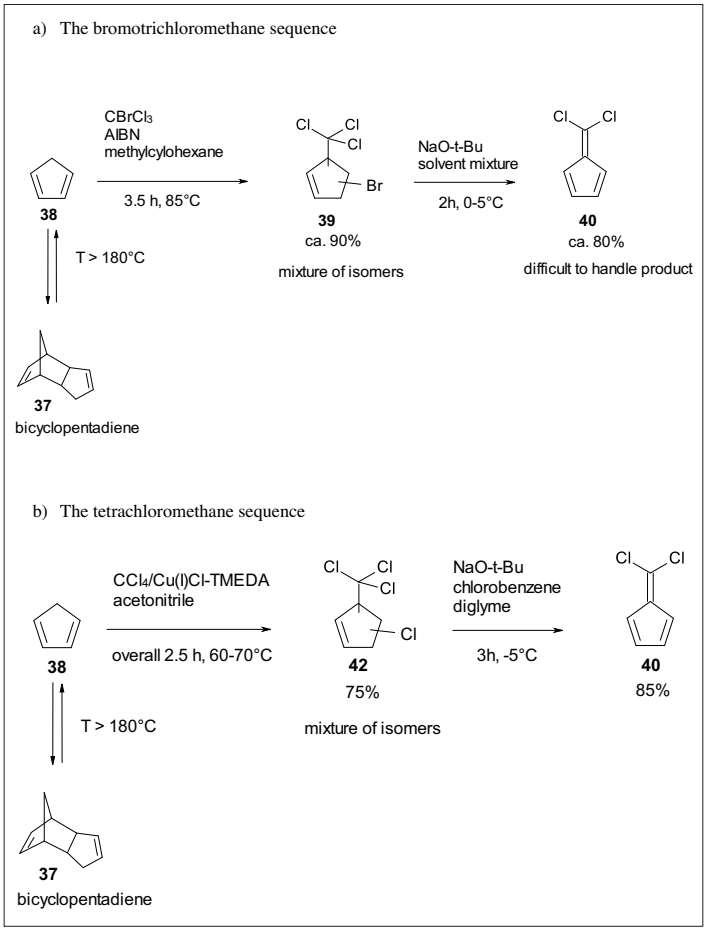
Scheme 7. The research route (*via* ozonolysis) used for the synthesis of the aminobenzonorbornene part of STL (**3**).[32,33]

this compound, we only had four steps to go to prepare STL (**3**) (Scheme 7)

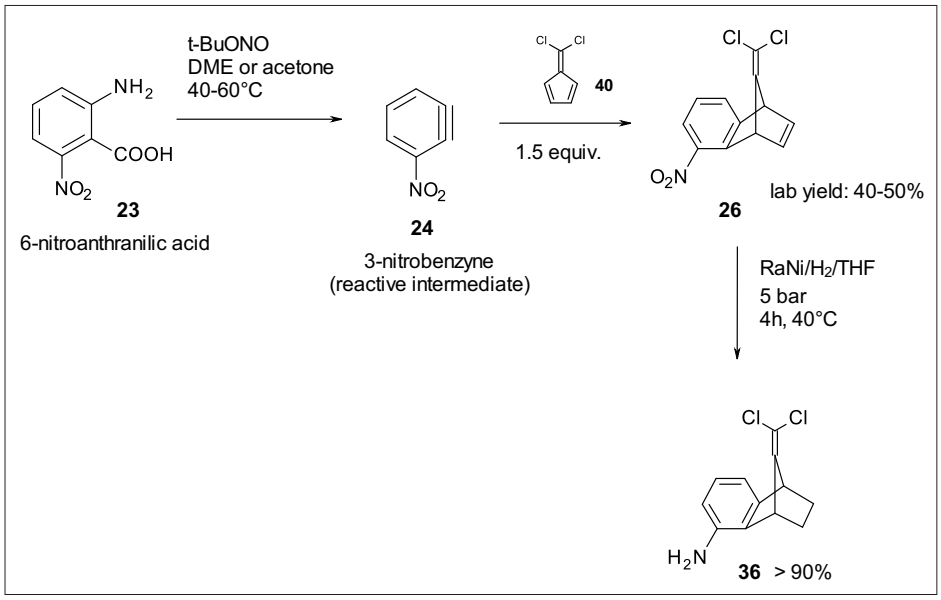
Before performing the ozonolysis step, the double bond in the benzonorbornadiene system has to be reduced using a palladium-catalysed reduction in the presence of hydrogen at lower temperature. The ozonolysis of the isopropylidenebenzonorbornene intermediate **26** under standard conditions led to the ketone **34** in good yields. Introduction of the dichloro-methylidene group could then be achieved by using Wittig type technology (reaction with triphenylphosphine/CCl_4-reagent).[33] The final step, reduction of the nitro group, could be achieved by using a Raney-Ni catalyst in the presence of hydrogen. With the described route, we were able to produce the needed field amounts of STL (**3**) (50–150 g quantities) in the research synthesis laboratories. The team soon realized that this route was not the one that can be used for scaling up: 1) ozonolysis is not the technology of choice for upscaling and 2) the use of the expensive triphenylphosphine needed in the Appel-Wittig reaction is unfavourable. The research and process technology groups joined up efforts to identify and investigate new synthesis options that could provide viable solutions to the challenge above. To avoid ozonolysis as well as Appel-Wittig type chemistry, the best strategy was to start from dichlorofulvene **40** again using cycloaddition technology. But the first hurdle was to find a cheap process for the large scale production of dichlorofulvene. Going through several optimisation cycles, the colleagues from the process technology group found a promising solution: the radical addition of either bromotrichloromethane or tetrachloromethane to cyclopentadiene **38** in the presence of an appropriate radical starter (Scheme 8).[32,34] From a cost perspective the sequence using tetrachloromethane is clearly preferred (Scheme 8b). The reaction of tetrachloromethane with cyclopentadiene **38** gave the cyclopentene isomer mixture **42** , which after treatment with a base (preferred: a stronger base such as potassium-tert. butanolate) led to dichlorofulvene **40** in good yields.

The next challenge in the synthesis of STL (**3**), was to find a suitable cycloaddition partner for dichlorofulvene **40**. The first reaction partner we tried was nitrobenzyne **24**. The yields of the new cycloaddition leading to the nitrobenzonorbornadiene **26** turned out be in the range of 50% in the laboratory. Trying to upscale the reaction of the unstable dichlorofulvene **40** with nitrobenzyne **24** turned out to be very challenging and the yields on larger scale dropped significantly. The following reduction of the double bond using a Ra-Ni catalyst was straightforward and the aminobenzonorbornene **36** could be obtained in high yields (Scheme 9).

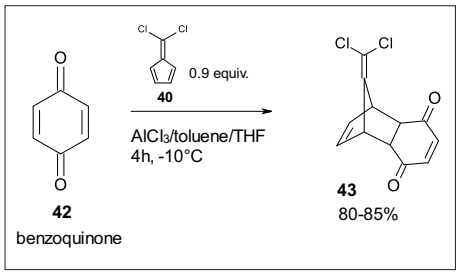
The problems in upscaling the cycloaddition between nitrobenzyne **24** and dichlorofulvene **40**, forced the chemists in the process technology group to look for alternative reaction partners for dichlorofulvene **40**. In laboratory trials, benzochinone **42** turned out to be a good reaction partner for dichlorofulvene **40**. The $AlCl_3$ catalysed cyloaddition reaction of the unstable dichlorofulvene **40** with benzochinone **42** at lower temperature (–10 °C) turned out to be fast enough to avoid



Scheme 8. Synthesis of dichlorofulvene **40** following a radical reaction sequence.[32,34]



Scheme 9. The first new route for the synthesis of the aminobenzobornene part of STL (**3**) using the novel cycloaddition reaction of nitrobenzyne **24** with dichlorofulvene **40**.[32,34]



Scheme 10. An important breakthrough in the synthesis of STL (**3**): the cycloaddition reaction of benzochinone **42** with dichlorofulvene **40**.[38,39]

formation of polymeric tars and other by-products, which could lower the yields and complicate the work-up. The yields in the new cyloaddition reaction were also generally much higher in comparison to the yields that could be achieved in the reaction of nitrobenzyne **24** with dichlorofulvene **40** and usually are between 80 and 85% (Scheme 10).

Another problem we had to solve was to convert the cyclohexenone moiety, which is present in the intermediate **44**, to an aniline or directly to the final product STL (**3**) (Schemes 11,12). The Semmler-Wolff approach[35–37] was taken into account to deliver a solution for this problem using oxime **45** as starting point.[39] The conversion of the ketone **44** into the oxime **45** was the first step required, then several options were tested to activate the oxime **45**: reactions of the oxime **45** with an acid chloride (lower alkyl carboxylic acid chlorides) or a chloroformic acid ester. Adding an acid such as HCl to the activated oxime derivatives **46** or **47** in the presence of the carboxylic acid chloride **18** leads to STL (**3**) in good yields, which was a clear breakthrough in preparing STL (**3**). The described sequence, discovered by the process technology group in Muenchwilen (CH), is highly innovative and this is the first time it had been used in the synthesis of any SDHI product. This route was used as a basis to prepare STL (**3**) on larger scale.

In Scheme 12 the complete multistep synthesis of STL (**3**) is outlined. The first step is the earlier discussed cycloaddition of benzochinone **42** with dichlorofulvene **40** in the presence of $AlCl_3$. The reduction of the resulting intermediate **43** with a rhodium catalyst gave the 1,4-diketo intermediate **48** in good yields. Selective reduction of one keto group by using sodium borohydride gave an isomer mixture of alcohols **49a,b**, which after elimination of water gave the annelated cyclohexenone intermediate **44**. Formation of the oxime **45** followed by application of the Semmler Wolff technology (as described earlier) leads to STL (**3**) in good yields.

Biological Properties of STL (3)

Solatenol™ is a broad-spectrum fungicide for use in a broad range of crops (*e.g.* apple, bean, chilli, cereals, corn, curcurbits, grape, peanut, potato, soybean, tomato). The clear strength, where STL differentiates from the current SDHIs, is the outstanding control of soybean rust (best in class compound). It also offers a full cereal disease spectrum (*Septoria tritici*, *Puccinia spp.* and *Pyrenophora teres*) with outstanding activity against *Puccinia spp.* (better than known standards). The compound is also very strong in controlling *Venturia ineaequalis* (apples), *Uncinula necator* (grapes) and *Alternaria solani* (potatoes, tomatoes). Other opportunities have been or will be scoped in the field.

Conclusions

With sedaxane, isopyrazam, and Solatenol™, it has been possible for Syngenta to introduce three complementary compounds to the market. Sedaxane is a broad-spectrum seed treatment compound which in mixtures (all SDX-based Syngenta offers are sold under the brand Vibrance®) offers unique benefits to the farmer including higher and more reliable average yields in a broad range of commercially relevant crops. With IZM, Syngenta has developed the first SDHI product that controls *Septoria tritici* and some other important cereal diseases. IZM is a broad-spectrum compound and as such offers other market opportunities such as control of black sigatoka in bananas and control of powdery mildews in the fruit and vegetable segments. STL is a second-generation benzonorbornene carboxamide active at low rates against key market diseases and offering a unique solution in controlling soybean rust at very low rates.

The importance of the SDHI class is clearly demonstrated by the rise in sales over the last two years. The 2013 figures available from Phillips McDougall revealed that SDHIs are already the third most important MoA class with further significant potential for sales growth in the next five years (structures of the major competitor SDHIs are shown in Fig. 7). The major mixing partners for the SDHIs are the triazoles (sterol biosynthesis inhibitors–DMIs) and strobilurins (complex III inhibitors–QoIs). The SDHIs will play a very important role in building up effective anti-resistance strategies in a broad range of crops in the next 5–10 years.

Acknowledgements

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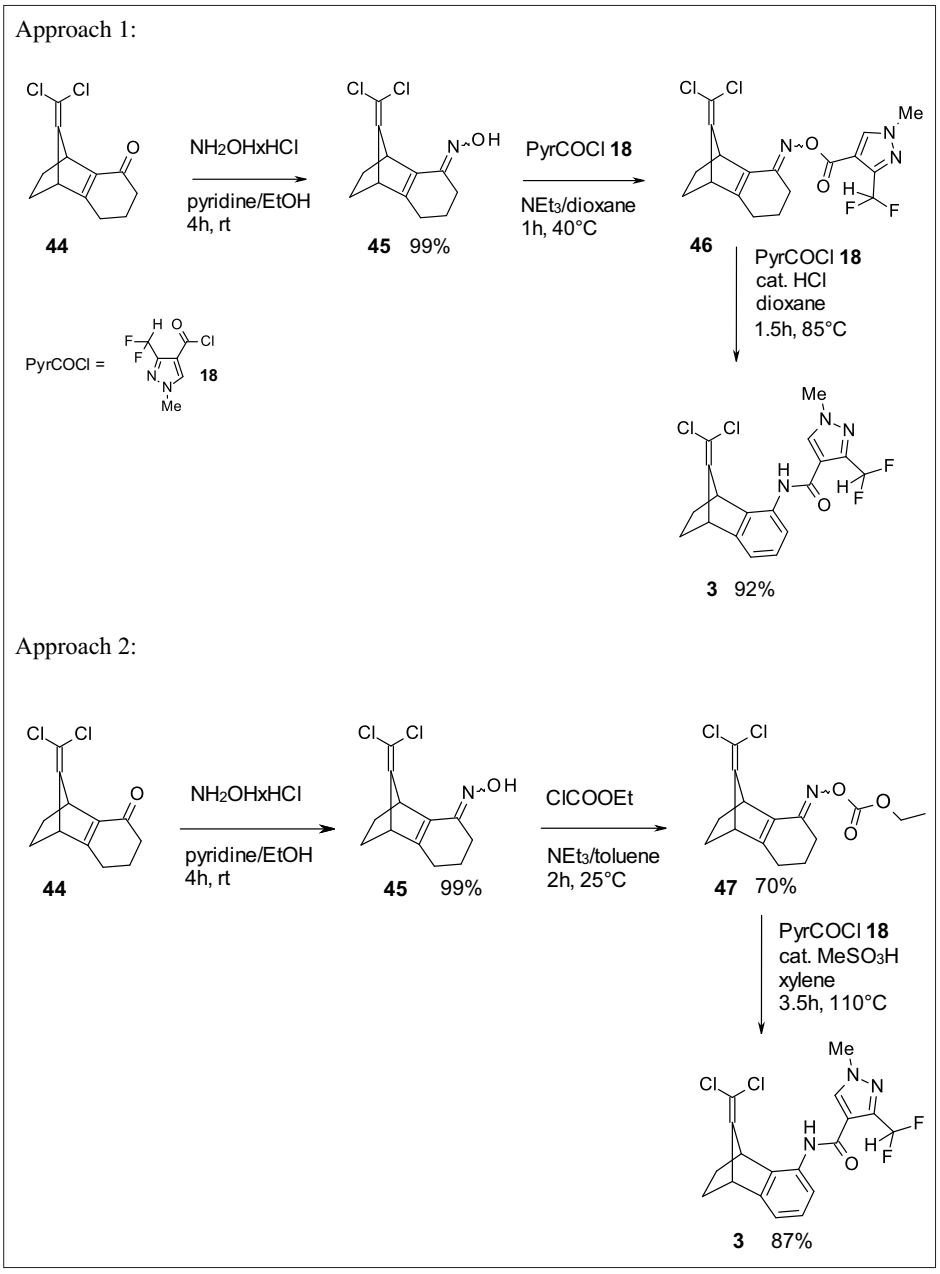
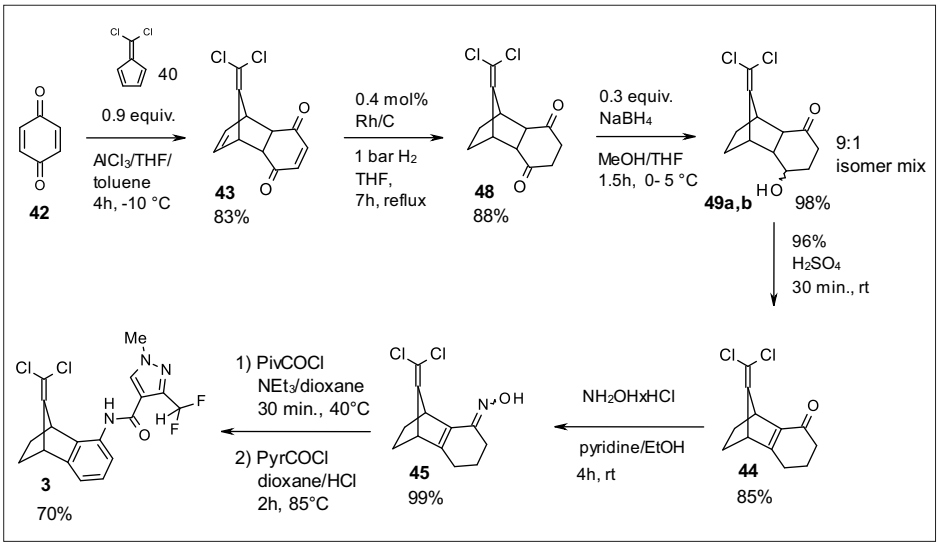


Scheme 11. Two approaches using the Semmler-Wolff aromatisation as the final step of the STL synthesis.[39]



Scheme 12. Complete synthesis of STL (**3**) following the benzochinone route.[38,39]

[1] a) Presented in part at the Fall Meeting of the SCS (Sandmeyer Award Lecture), Zürich, Switzerland, September 11, **2014**; b) For a general review on the pyrazole carboxamide SDHI class, see: H. Walter in 'Bioactive Heterocyclic Compound Classes', Ed. C. Lamberth, J. Dinges, Wiley VCH Weinheim, **2012**, pp. 175–193.

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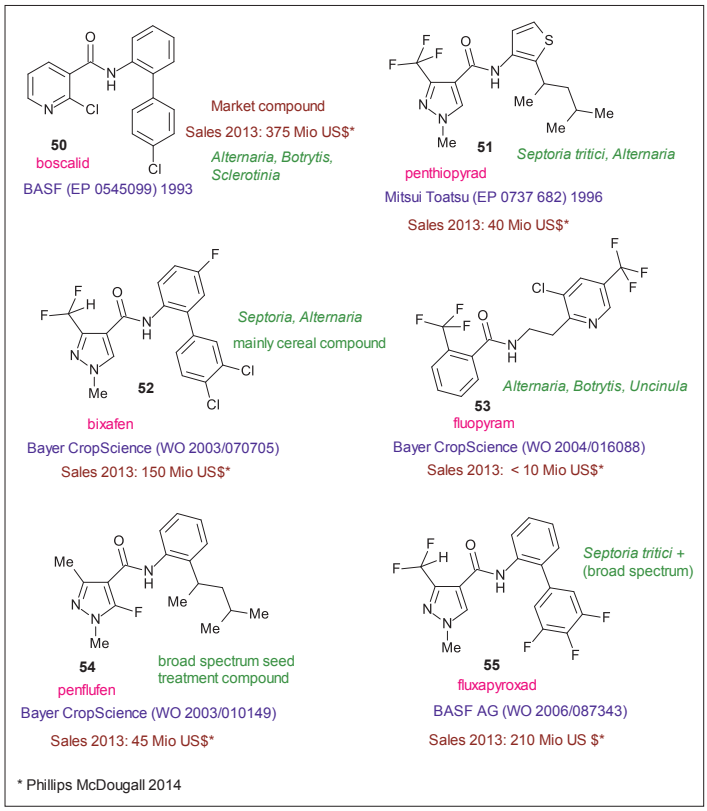

Fig. 7. Structures of the most important competitor SDHI market compounds.

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