THE CHEMISTRY OF 3-NITROCHROMENES

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Abstract. *A large variety of natural products and medicinal drugs have chromene and chromane cores incorporated in their structures. Because of their high and versatile reactivity, and simple synthesis, 3-nitrochromenes are regarded as an easily available and highly functional constituent for the preparation of chromene and chromane derivatives. In the present review, the synthesis of the 3-nitrochromene scaffold is briefly discussed. The multifaceted reactivity of 3-nitrochromenes is highlighted and divided into different subjects in which emphasis is mainly placed on recent advances in literature from 2013 up until now.*

Contents

1. Introduction

Chromenes (2*H*-benzo[*b*]pyrans) have been of considerable interest for a long period of time and remain omnipresent in various fields such as medicinal chemistry and natural products.[1-4] Characterization of natural products proved that chromenes are common patterns in many biological systems.[3] Some important examples of naturally occurring chromenes and chromanes are α-tocopherol (one out of eight compounds featuring vitamin E activity),[5-8] tetrahydrocannabinol (THC),[9-12] arahypin-5,[13,14] calanone[15] and seselin[16] (Figure 1). Furthermore, the medicinal uses of chromenes are remarkably widespread. Examples of chromene analogs with biological activities ranging from anticancer to antiviral properties are well documented, *e.g.* daurichromenic acid,[17] extracted from dried leaves of the *Rhododendron dauricum*, that showed significant anti-HIV activity, and methoxy substituted chromene **1** blocking the production of TNF-α which is a pro-inflammatory cytokine secreted by a variety of cells[18] (Figure 1).

As the chromene core is a common essential structure, the synthesis of chemical products containing a chromene core has been a matter of high interest. In this regard, 3-nitro-2*H*-1-benzopyrans, yet more commonly described as 3-nitrochromenes **2** (Figure 1), have been shown to be privileged precursors for further derivatization of the chromene core.[19] The main reactivity of 3-nitrochromenes is dictated by the nitroalkene part which offers a multitude of possible reactions and transformations in synthetic chemistry. The effect on the reactivity is accompanied by a considerable effect of the potentially present substituents on the 2-position.[19] Furthermore, 3-nitrochromenes by themselves have shown promising and interesting prospects, such as their valuable medicinal,[20-27] radioprotective[28] and non-linear optical[29] properties. The development of novel reactions with 3-nitrochromenes is still a highly valued topic in current research projects, due to their accessibility and wide applicability.[19]

2. Synthesis of 3-nitrochromenes

The first description of the synthesis of 3-nitrochromene derivatives was given in 1938 by Hahn and Stiehl, starting from the reaction between 2-(1-hydroxy-2-nitroethyl)phenol and salicylaldehyde with methylamine.[30] In 1978 Sakakibara *et al.* outlined the synthesis of 2-aryl-3-nitrochromenes starting from

readily available salicylaldehyde **3** and β-nitrostyrene **4** in the presence of triethylamine at room temperature (Scheme 1) while simultaneously *trans*,*trans*-4-hydroxy-3-nitro-2-phenyl-2*H*-chromene **6** was observed in equimolar amounts.[31]

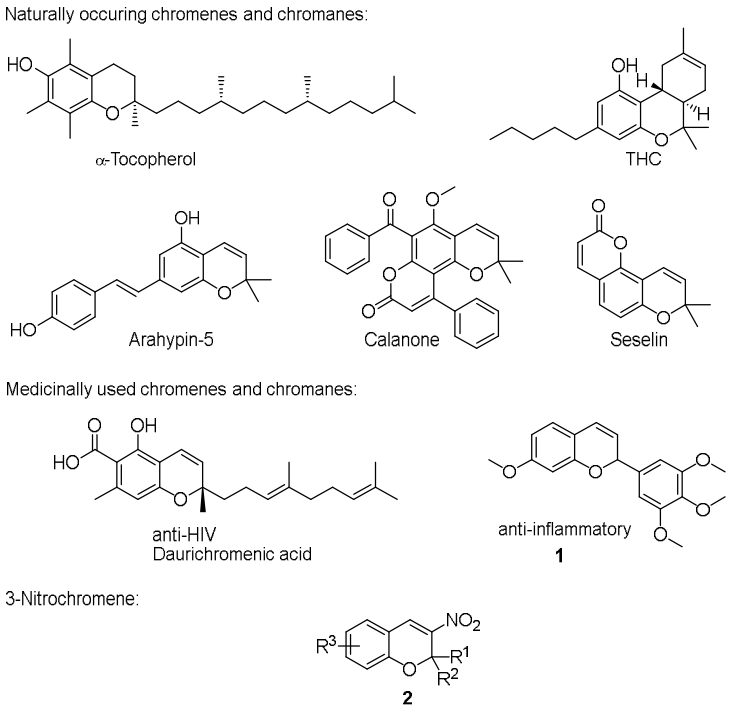
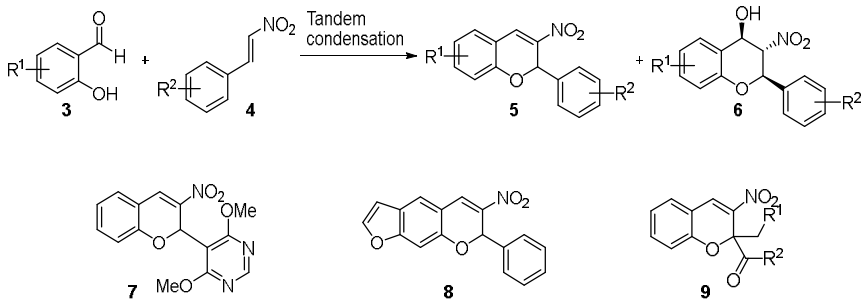


Figure 1. Examples of naturally occurring chromenes and chromanes (top), chromenes **1** used in medicinal applications (middle) and general structure of 3-nitrochromene **2** (bottom).

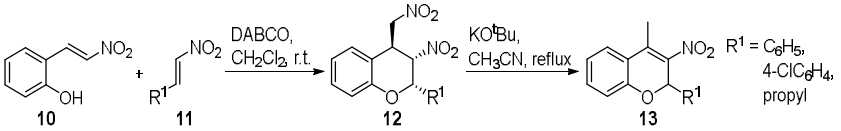


Scheme 1. Synthesis of 3-nitrochromene **5** starting from salicylaldehydes **3** and nitroalkenes **4** as firstly described by Sakabari *et al.* (top); nitrochromenes **7**, furochromenes **8** and 2-alkyl-2-acyl nitrochromenes **9** (bottom).

The reaction proceeds *via* a cascade oxa-Michael-Henry-dehydration reaction. Since then, a tremendous amount of modifications have been published in order to optimize the reaction and synthesize specific 2-aryl/alkyl-substituted 3-nitrochromene targets **5**, discussed in clear detail in the review of Korotaev *et al.*[19] These modified methods provide complete dehydration of the formed chromanol intermediates by performing the reaction under heating,[32,33] with triethylamine in a melt at room

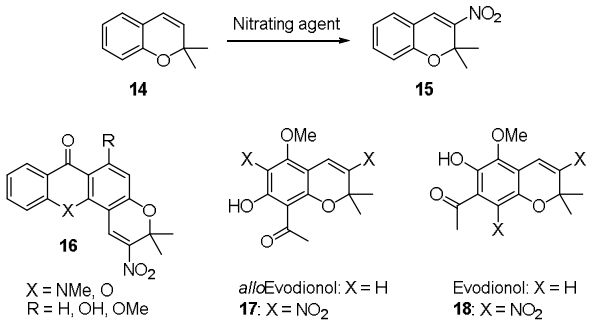
temperature,[34] basic alumina or Al_2O_3 as dehydrating agents under ultrasonicating conditions,[28,35,36] catalytic amount of L-proline and triethylamine in toluene under reflux,[25] or preactivated neutral alumina under solvent-free conditions[37]. Specific targets such as 2-pyrimidine-appended nitrochromenes **7**, furochromenes **8** and 2-alkyl-2-acyl nitrochromenes **9** were prepared according to specific procedures, *i.e.* reaction between sodium 2-formylphenoxide and 2-nitrovinylpyrimidines in DMSO,[31] reaction of furan fused salicylaldehydes and nitroalkenes under KOH in various solvents under heating,[38] and the treatment of salicylaldehydes with KO^{t}Bu at 0°C, followed by the addition of nitroalkenes, acetic acid and finally SiO_2 at 50 °C as dehydrating agent,[39] respectively. The (modified) Sakakibara method with triethylamine failed to deliver the desired products **7**-**9**.[31,38,39] Yet another modification which employs DABCO under solvent-free conditions at 40 °C has been disclosed by Yao *et al.*, by which an easy and improved method is provided.[40-42] Herein DABCO is proposed to be the better catalyst compared to triethylamine regarding yields and *via* this way it is possible to prepare 2-mono-, 2,2-disubstituted and 2,2-spiro-fused 3-nitrochromenes. The use of a catalyst combination of pyrrolidine and benzoic acid in boiling ethanol also provides 2-aryl-3-nitrochromenes in yields up to 83%.[43] As the preparation of 3-nitrochromenes **5** is commonly performed in the absence of solvents, the ball milling technique has been proven to be a highly effective tool in the construction of 3-nitrochromenes **5**. This powerful technique offers a green procedure resulting in high yields and decreased reaction times under mild mechanochemical conditions (25 Hz) and K_2CO_3 as solid base.[44]

A variant on the oxa-Michael-Henry-dehydration reaction was disclosed by Yao and coworkers. Herein, nitroolefins **11** are reacted with (*E*)-(2-hydroxyphenyl)-1-nitroethylenes **10** using DABCO as a catalyst, resulting in the formation of 3-nitrochromans **12** (Scheme 2). The consecutive treatment of the formed 3-nitrochromans **12** with KO^{t}Bu in refluxing acetonitrile yields 4-methyl substituted 3-nitrochromenes **13** in yields of up to 40%.[45]



Scheme 2. Oxa-Michael-Henry-dehydration reaction starting from nitroolefins and (*E*)-(2-hydroxyphenyl)-1-nitroethylenes.

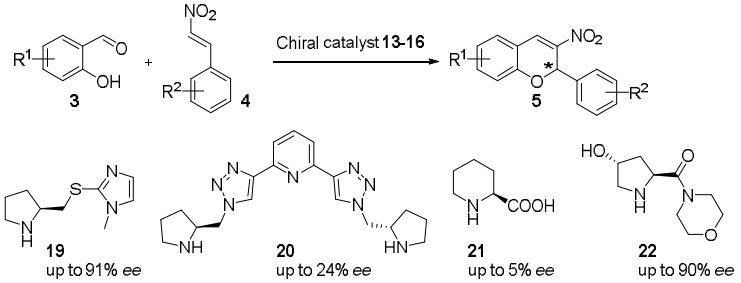
Another method to synthesize 3-nitrochromenes starts from the parent chromene **14** using various nitrating agents (Scheme 3). These nitration methods are mainly essential for the conversion of natural product analogs containing a chromene core into various 3-nitrochromene building blocks. This enables an easy access for the derivatization of chromenes obtained from natural sources. Nitration is possible by using nitrogen monoxide and Al_2O_3 for 4-unsubstituted 3-nitrochromenes,[46] or the use of $Cu(NO_3)_2$ in combination with acetic anhydride for 4-substituted 3-nitrochromenes.[47]



Scheme 3. Nitration of 2,2-disubstituted chromenes **14** (top); natural product analogs **16**-**18** (bottom).

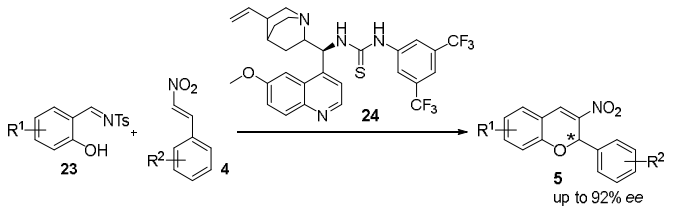
Furthermore, treatment of various pyranoacridone alkaloids with nitric acid in acetic acid led to nitrochromene derivatives **16**,[21,48] and 2,2-dimethylchromene derivatives extracted from Australian plants (*i.e.* evodionol and *allo*evodionol) have been nitrated by means of nitric acid in boiling ethanol yielding doubly nitrated 3-nitrochromene species **17** and **18**.[49]

The resolution and enantioselective synthesis of optically active 3-nitrochromenes **5** have been well studied and documented[19,50] since chiral chromenes are present in diverse scaffolds and natural products like daurichromenic acid.[17,51] A number of strategies were employed for the enantioselective construction of 3-nitro-2*H*-chromenes **5**. The enantioselective synthesis of 3-nitro-2*H*-chromenes **5** starting from salicylaldehydes **3** and β-nitrostyrenes **4** mainly proceeds by means of a chiral secondary amine catalyst *via* an organocatalytic iminium activation (Scheme 4). Xu *et al.* disclosed the first enantioselective synthesis in 2008, in which pyrrolidine-thioimidazole catalyst **19** and salicylic acid as cocatalyst furnished 3-nitro-2*H*-chromenes **5** in reasonable yields and enantioselectivity of up to 91% *ee* at room temperature.[52] Another pyrrolidine-triazole-based C_2 symmetric organocatalyst **20**, derived from L-proline, was tested but showed poor enantioselectivities (% *ee* up to 24) and chemical yields.[53] The domino-Michael/aldol reaction catalyzed by L-pipecolic acid **21** proceeded smoothly at 80 °C in toluene, resulting in 81% yield and low chiral induction of 5% *ee*.[54] An improved one-pot enantioselective procedure was developed by Chen and coworkers in 2013, in which *trans*-4-hydroxy-L-prolinamide **22** as asymmetric organocatalyst and 4-nitrophenol as a cocatalyst are employed.[55] The respective 3-nitro-2*H*-chromenes **5** were prepared in yields of up to 99% and 90% *ee*.



Scheme 4. Asymmetric synthesis of 3-nitro-2*H*-chromenes starting from salicylaldehydes **3**, β-nitrostyrenes **4** and chiral catalysts **19**-**22** with corresponding enantioselectivities.

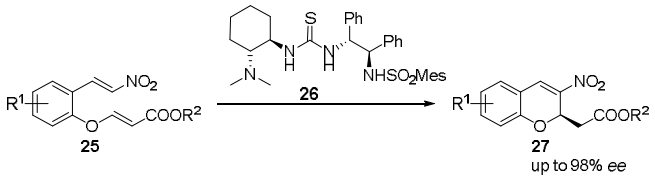
Furthermore, some modifications were explored, one of which was published by Schreiner in which salicyl *N*-tosylimines **23** were chosen as salicylaldehyde surrogates and a bifunctional non-covalent hydrogen-bonding quinine-thiourea catalyst **24** (Scheme 5).[56] The enantioselective oxa-Michael-aza-Henry-desulfonamidation reaction showed a kinetically controlled desulfonamidation step and resulted in high enantioselectivities (up to 92% *ee*) at 0 °C.



Scheme 5. Enantioselective synthesis starting from salicyl *N*-tosylimines **23** and β-nitrostyrenes **4**.

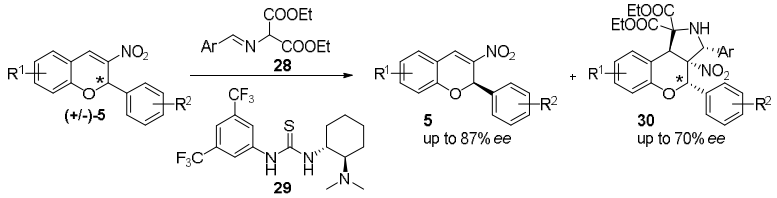
Finally, *via* an enantioselective crossed intramolecular Rauhut-Currier reaction of nitroolefin enoates **25** in the presence of the proper chiral thiourea catalyst **26** and nucleophilic promotor (*i.e.* benzyl *tert*-butoxycarbonyloxycarbamate), an excellent enantioselectivity of up to 98% *ee* of product **27** was reached (Scheme 6).[57] Related to this, Yuan and Ren *et al.* studied a one-pot domino

Henry-Michael-dehydration reaction *via* a dual-electrophile/dual-nucleophile approach with nitromethane, alkyl 2-formylphenoxy acrylates and Takemoto's thiourea bifunctional organocatalyst **29**.[27] High enantioselectivities (up to 93% *ee*), but low yields (up to 30%) were obtained *via* this methodology, and additionally the compounds exhibited good potency in a wide range of antibacterial activities.



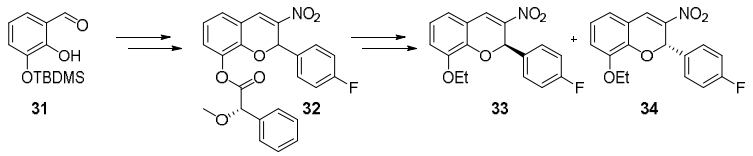
Scheme 6. Enantioselective Rauhut-Currier reaction towards 3-nitro-2*H*-chromenes **27**.

Less explored strategies for the assembly of enantiopure 3-nitro-2*H*-chromenes **5** are kinetic resolution and chemical resolution. The former is used in the asymmetric kinetic resolution of 3-nitro-2*H*-chromenes **5** *via* a [3+2]-cycloaddition of racemic nitrochromenes with azomethine ylides derived from **28** under the asymmetric effect of Takemoto's catalyst **29**, as reported by Xie *et al.* in 2010 (Scheme 7).[58] Herein, moderate yields for both, and moderate to good enantioselectivies are acquired for 3-nitro-2H-chromenes **5** (up to 87% *ee*) and chromeno pyrrolidines **30** (up to 70% *ee*), respectively.



Scheme 7. Kinetic resolution of racemic 3-nitro-2*H*-chromenes **5**.

Racemic S14161, pichromene or 8-ethoxy-2-(4-fluorophenyl)-3-nitro-2*H*-chromene and its analogs, have been identified as potent phosphoinositide 3-kinase inhibitors, rendering it effective as antileukemia and antimyeloma agent.[23,59] The optimized preparation of the racemic product S14161 employed L-proline as catalyst and triethylamine as cocatalyst in toluene at 90 °C.[25] Yet, Liu *et al.* designed an efficient synthesis of both (*R*)- and (*S*)-isomers of S14161 **33** and **34** *via* chiral resolution and derivatization (Scheme 8).[60] Oxa-Michael-Henry reaction between 3-(*tert*-butyldimethylsilyloxy)salicylaldehyde **31** and *trans*-4-fluoro-β-nitrostyrene under the optimized conditions for racemic S14161 afforded TBDMS-protected 3-nitrochromene, which was subsequently silyl deprotected and coupled with enantiomerically pure (*S*)-α-methoxyphenylacetic acid. The two obtained diastereomers were separated, followed by removal of the chiral auxiliary with methylamine and ethylation, without affecting the enantiomeric excess of both (*R*)- and (*S*)-isomers **33** and **34**.



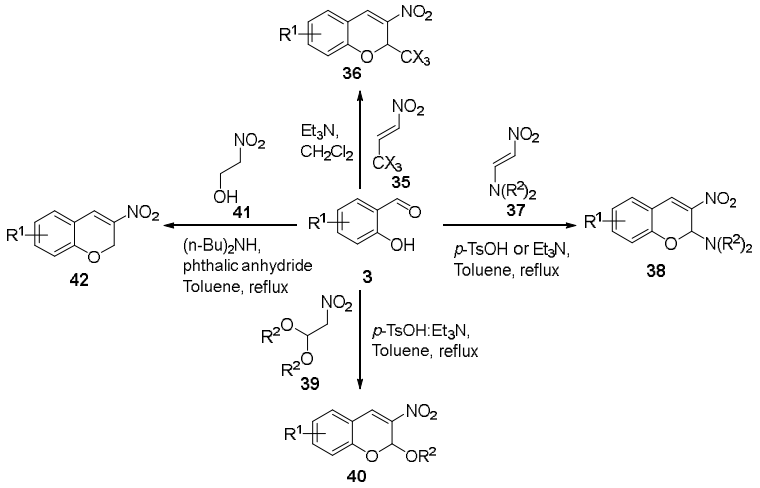
Scheme 8. Chemical resolution and derivatization towards both enantiomerically pure forms of S14161 **33** and **34**.

Although 2-aryl/alkyl-substituted 3-nitrochromenes **5** are the largest target group, other substituents on the 2-position have been well described. The synthesis of 2-trihalomethyl-3-nitro-2*H*-chromenes **36** is

similar as the above mentioned Sakakibara method,[31] and starts from salicylaldehydes **3** and trihalonitropropenes **35** in the presence of triethylamine in dichloromethane at room temperature (Scheme 9), without the observation of chromanol intermediate.[61] 1-Bromo-1-nitro-3,3,3-trichloropropene has also been used and yields chromanol intermediate with one equivalent of triethylamine, but solely gives 2-trichloromethyl-3-nitro-2*H*-chromenes **35** when two equivalents of triethylamine are employed.[62] Furthermore, 4-methyl substituted derivatives were obtained from ketimines and trihalonitropropenes **35** in dichloromethane under the influence of DABCO while heating at reflux.[63]

2-Substituted 3-nitrochromene derivatives containing a directly linked heteroatom, such as 2-amino- and 2-alkoxy-3-nitro-2*H*-chromenes **38** and **40**, have been reported by Royer *et al.* in 1982.[64,65] 2-Dialkylamino-3-nitrochromenes **38** have been prepared from β-nitroenamines **37** and salicylaldehydes **3** in refluxing toluene in the presence of a catalyst, *i.e. p*-toluenesulfonic acid[64] or triethylamine[66] (Scheme 9). 2-Arylamino-derivatives are subsequently synthesized *via* a transamination reaction with two equivalents of aniline (or pyrazole as sole example of a heteroaromatic structure) together with 2-morpholino-3-nitro-2*H*-chromene as a common precursor, and (+)-10-camphorsulfonic acid as the acid catalyst.[20] For the synthesis of 2-alkoxy-3-nitro-2*H*-chromenes **40**, β-nitroacetaldehyde dialkylacetals **39** are used as precursors of β-nitroalkoxyethylenes in the presence of *p*-toluenesulfonic acid:triethylamine salt (Scheme 9).[65] Alternatively, 2-ethoxy-3-nitro-4-alkoxy-2*H*-chromenes were prepared starting from 3-nitrochromone and diazoalkanes in chloroform containing 5% ethanol.[67]

Finally, 2-unsubstituted-3-nitro-2*H*-chromenes **42** can be prepared from salicylaldehydes **3** and 2-nitroethanol **41** (Scheme 9). Several modifications on this approach have been reported, mainly on the dehydration of 2-nitroethanol **41** to nitroethylene considering the low stability of the latter. Hence, methods employ either 2-nitroethanol **41** and dibutylamine:hydrochloride salt in isoamyl acetate under reflux,[68] freshly produced nitroethylene and dibutylamine in chloroform at 80 °C,[69] or dibutylamine, 2-nitroethanol **41** and phthalic anhydride (for the *in situ* preparation of nitroethylene) in toluene.[25,69,70,71] A solvent-free microwave-assisted protocol, which starts from salicylaldehydes **3**, 2-nitroethanol **41**, phthalic anhydride and a catalytic amount of tetrabutylammonium bromide adsorbed on dry potassium carbonate, was developed by Koussini.[72] Furthermore, 2-unsubstituted chromenes have been selectively nitrated by means of tetranitromethane,[73] and recently *via* $NaNO_2$ with I_2 in NMP as a safer alternative.[74]



Scheme 9. Synthesis of 2-trihalomethyl-, 2-dialkylamino-, 2-alkoxy- and 2-unsubstituted 3-nitro-2*H*-chromenes **36**, **38**, **40** and **42**.

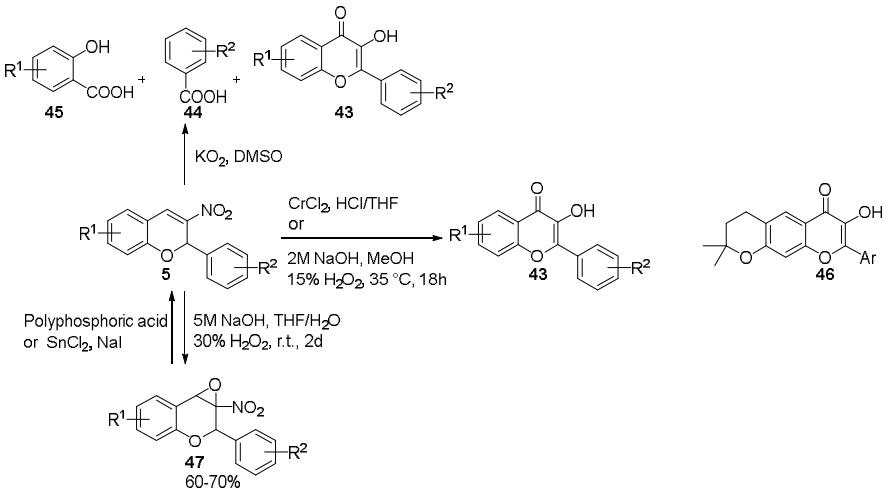
3. Reactivity of 3-nitrochromenes

3-Nitrochromenes are considered as privileged structures for the derivatization of the chromene core. The reactivity of 3-nitrochromenes is well investigated and is mainly governed by the nitroalkene function as

an electrophilic moiety, which opens up a broad scope of various reactions.[19] In this section, we subdivide the numerously reported reactions in different categories, *i.e.* oxidations, reductions, conjugate additions and cycloaddition reactions, and primarily focus is set on recent literature from 2013 onwards. For earlier work we refer to the review article of Sosnovskikh *et al.*[19]

3.1. Oxidations

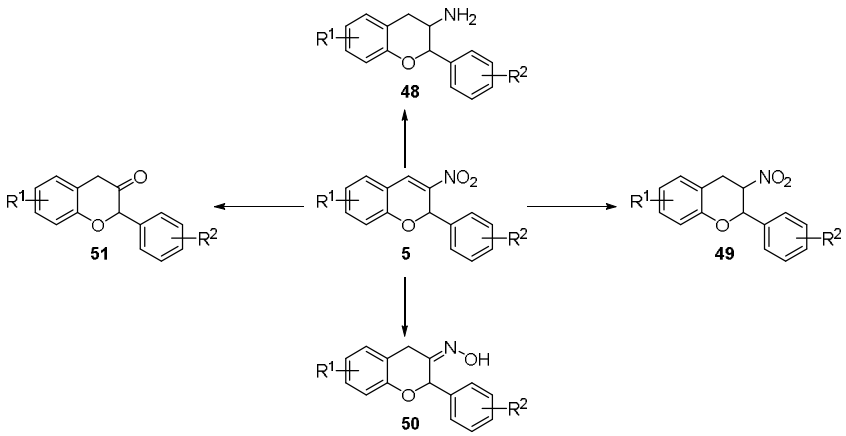
The variety on the outcome of the oxidation reactions of 3-nitro-2*H*-chromenes **5** is fairly narrow and hence there is only minor research interest in the further development of this kind of reactions. A few reports, dating back to the 1980s, describe several methodologies (Scheme 10). The use of 15% hydrogen peroxide and 2M aqueous NaOH in methanol at 35 °C for 18 h[75] or $CrCl_2$ in HCl and THF[76] led to the formation of flavonols **43** as the main product. Furthermore, potassium superoxide was also employed, resulting mainly in cleavage towards benzoic acids **44** and **45**, and flavonols **43** in diminished yields (10-15%).[77] The former method, employing 15% hydrogen peroxide, is used for the preparation of biologically relevant dihydropyranoflavanols **46** and the mechanism is assumed to go *via* a base-catalyzed rearrangement of the formed epoxide, which however could not be isolated.[78] Yet, in 2015 Ahmed and Pathe disclosed a very similar reaction as reported above, in which the synthesis of nitrochromene epoxides **47** were successfully conducted with 5M aqueous NaOH, 30% hydrogen peroxide in THF/H_2O, and their subsequent eliminative deoxygenation towards **5** by using polyphosphoric acid[79] or $SnCl_2$ and NaI in boiling ethanol[80] is reported. The peculiar usage of reducing agent chromous chloride in an (overall) oxidation reaction is considered to involve the formation of α-hydroxy oximes as intermediates.[76]



Scheme 10. Oxidation reactions of 3-nitro-2*H*-chromenes **5**.

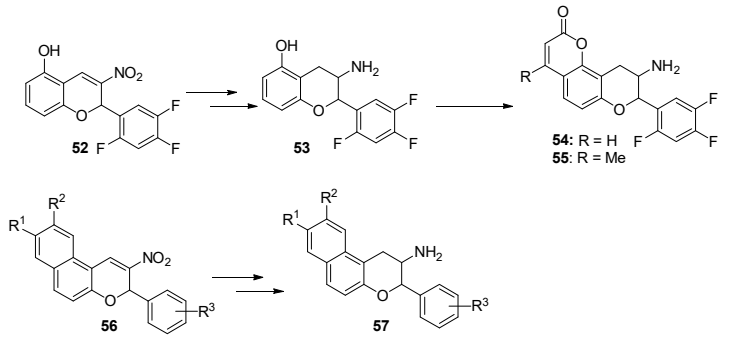
3.2. Reductions

The reduction of 3-nitrochromene **5** offers a larger variety of product outcomes (Scheme 11). The full reduction of the nitroalkene part towards 3-aminochromanes **48** has been accomplished by using several methodologies, such as lithium aluminium hydride,[81] borane in THF and sodium borohydride,[54,82,83] sodium borohydride followed by Raney nickel and hydrazine[21,74,84-86] or hydrogen on Pd/C,[48] or copper(II)acetate with sodium borohydride.[48] Furthermore, the selective reduction of the nitroalkene double bond towards 3-nitrochromane **49** was effected by sodium borohydride[21,24,48,74,82,84-87] or baker's yeast.[88] Oximes **50** serve as interesting functionalities and they are possible product outcomes when 3-nitrochromene **5** is treated with stannous chloride,[89] tin in combination with hydrochloric acid[48] or Raney nickel together with hydrazine.[90] A final possibility is the formation of 3-oxo-chromanes **51** *via* the employment of chromous chloride,[91] or titanium(III)chloride and ammonium chloride in dioxane-acetic acid.[92]



Scheme 11. Reduction reactions of 3-nitro-2*H*-chromenes **5**.

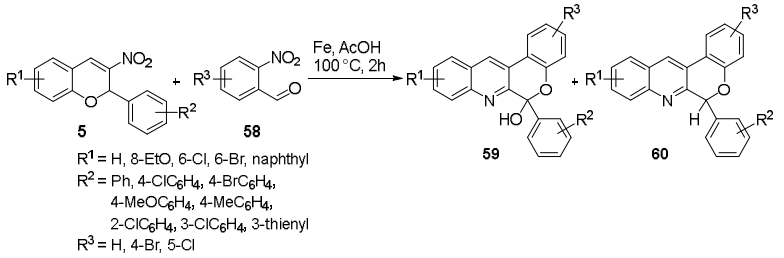
Recently, Gusev *et al.* presented the reduction of 2-trifluoromethyl-3-nitro-2*H*-chromenes, resulting in a library of 3-aminochromanes, mediated by B_2H_6 in THF and sodium borohydride, together with their promising biological activity.[83] Other fully reduced 3-aminochromene analogs **54, 55** and **57** were identified as dipeptidyl peptidase 4 inhibitors for the use as antidiabetic agent (Scheme 12).[93] 3-Aminochromenes **53** and **57** are prepared by treatment of the corresponding nitrochromene **52** and **56** with sodium borohydride to yield nitrochromane, and the subsequent reduction with zinc in 6N HCl. 3-Aminochromane **53** was further derivatized with ethyl acetoacetate or ethyl propiolate in order to yield racemic dihydropyrano[2,3-*f*]chromen-2(8*H*)-one **54** and **55**, respectively. The *cis*- and *trans*-isomers of **53** are readily separated *via* column chromatography, yet the *cis*- and *trans*-racemic products **54** and **55** are separated *via* chiral column chromatography resulting in four different isomers. The biological tests showed that only one single stereoisomer was the most active, and the structure was deduced as one of the enantiomers of the *trans*-isomeric pair. Hence, for the derivatization of 2-phenyl-3,4-dihydro-2*H*-benzo[*f*]chromen-3-amine **57** only the *trans*-isomers were isolated and enantiomers were separated solely for the most active compounds. The designed compounds resulted in a 7400-fold increase (IC_{50}≈2.0 nM) in activity compared to the lead compound, isodaphnetin.[93]



Scheme 12. Reduction reactions of 3-nitrochromenes **52** and **56** towards antidiabetic agents 3-aminochromans **54**, **55** and **57**.

Quinolin-6-ol- and quinoline-annulated chromenes **59** and **60** have been prepared *via* a reductive cyclization reaction commencing from 3-nitrochromenes **5** and 2-nitrobenzaldehydes **58**, mediated by iron as reducing agent in acetic acid (Scheme 13).[94] In total 19 examples of quinolin-6-ol derivatives **59** and 13

examples of chromeno[3,4-*b*]quinolones **60** as a by-product have been prepared in yields of up to 92% and 21%, respectively. The reaction offers a wide substrate scope starting from easily available reactants and for both derivatives the X-ray structures have been elucidated, clearly proving the aryl/hydroxyl or solely aryl compositions. A reaction mechanism is proposed in which both nitroalkene and nitro moieties are sequentially reduced (and hydrolyzed) to 3-oxo-chromane **51** and 2-aminobenzaldehyde, respectively. The reaction proceeds further *via* aldol condensation, intramolecular addition, and nucleophilic addition of water or dehydration to yield a mixture of **59** and **60**.[94]

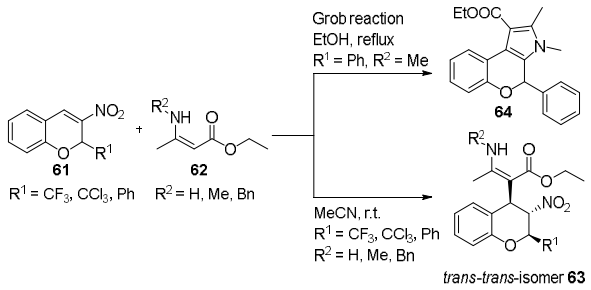


Scheme 13. Synthesis of 6*H*-chromeno[3,4-*b*]quinolin-6-ol derivatives **59** and **60** from 3-nitrochromenes **5** and 2-nitrobenzaldehydes **58**.

3.3. Conjugate additions

The nitro group conjugated to the alkene makes the nitroalkene moiety of 3-nitrochromenes excellent Michael acceptors and therefore the resulting reactions are often called nitro-Michael additions.[19] In general, all the reactions use a nucleophile to attack the double bond, and a generous amount of examples have been reported because of the wide applicability of this reaction. Several nucleophiles have been employed such as carbon nucleophiles, *i.e.* organolithium[70] and -magnesium[95] species, enolates,[96-102] enamines,[103-108] indoles[57,109-114] and pyrroles,[110,113] and other carbon-,[101,115-117] nitrogen-,[102,118,119] sulfur-[102,118] and phosphorus-centered[120] nucleophiles. Subsequent cyclization (domino-Michael-cyclization) leads to interesting structural derivatives of natural products.[70,103-105] The recent trends in this field are stereoselective additions of enamines, newly developed axially chiral structures, the exploration of novel reactions leading to hybrid structures, and domino-Michael-cyclizations towards multicyclic chromenes and chromanes, frequently performed in an enantioselective and diastereoselective fashion.

A major part of the recent research theme consisting of the stereoselective addition of enamines was investigated by Korotaev and Sosnovskikh *et al.* The study of the properties of various push-pull enamines in conjugate additions (Scheme 14) was initiated by performing nucleophilic additions with primary and secondary *Z*-enamines **62** (R^2=H, Me and Bn) of acetoacetic esters in acetonitrile at room temperature.[121]

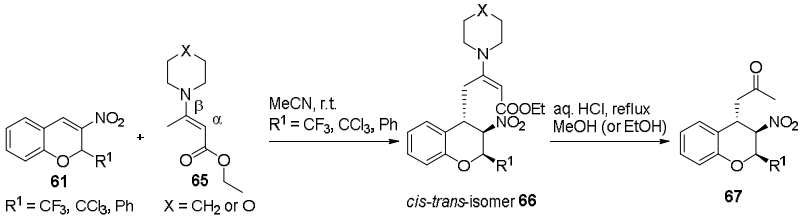


Scheme 14. Use of primary and secondary push-pull enamines of acetoacetic ester **62** to 3-nitrochromenes **61**.

Addition took place *via* the nucleophilic α-carbon and the obtained compound was proven to be *trans-trans*-isomer **63** with *Z*-configuration of the alkene *via* ^{1}H NMR, showing ^3J coupling constants of

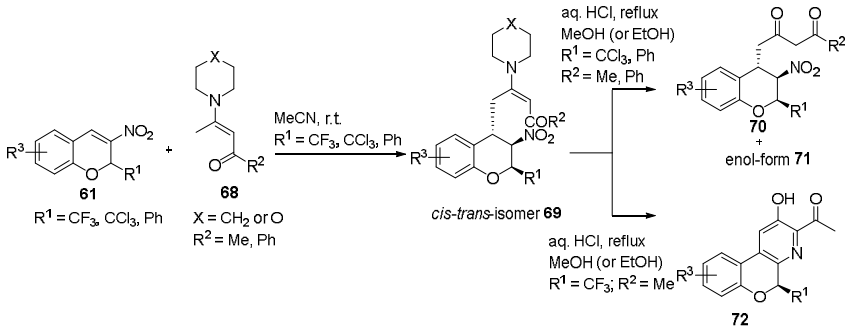
8-11 Hz proving that the three bulky substituents are in equatorial positions, and by means of an X-ray structure determination. The *Z*-configuration is maintained by stabilization *via* an intramolecular hydrogen bonding interaction. Grob pyrrole reaction in ethanol resulted in the formation of chromeno[3,4-*b*]pyrrole **64**, although exclusively for β-methylaminocrotonate and 2-phenyl-3-nitro-2*H*-chromenes.[121]

Interestingly, the reaction of tertiary *E*-enamines **65** proceeds smoothly with 2-trifluoromethyl, 2-trichloromethyl- and 2-phenyl-3-nitro-2*H*-chromenes **61** *via* the vinylogous β-methyl position, through isomerization to the kinetic, less sterically encumbered enamine (Scheme 15).[122] These reactions yield *cis-trans*-isomers **66** with *E*-configuration of the enaminone confirmed by ^3J values of 1,5 Hz and X-ray diffraction data. The subsequent hydrolysis in methanol or ethanol and hydrochloric acid resulted in acetonyl derivatives **67**. Retention of the configuration was observed, except for when the hydrolysis was performed in ethanol for the CCl_3 products in which partial or total epimerization was seen at the 3-position next to the nitro group.[122]



Scheme 15. Addition of tertiary push-pull enamines of acetoacetic ester **65** in the stereoselective addition to 3-nitrochromenes **61** and acid hydrolysis.

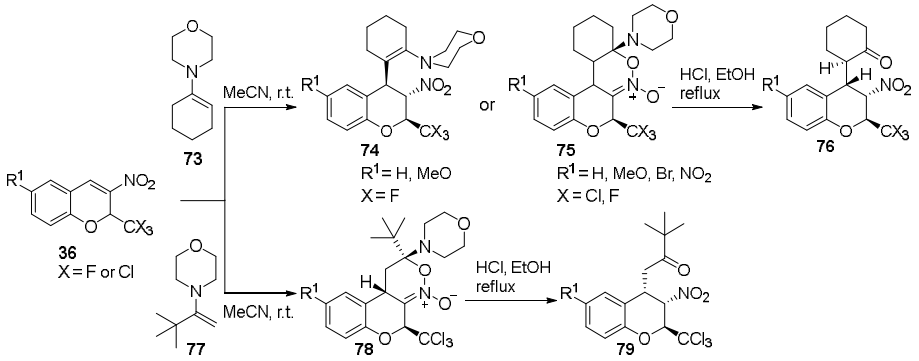
Push-pull enamines derived from cyclic amines and acetylacetone **68** were also examined and were found to behave in a similar fashion as tertiary enamines derived from acetoacetic esters **65**, reacting *via* the vinylogous β-methyl group and resulting mainly in the diastereoselective formation of *cis-trans*-isomers **69** and *E*-configuration of the double bond, as proven by NMR coupling constants (^3J≈2 Hz) and an X-ray diffraction study (Scheme 16).[123,124] Few exceptions were isolated as single diastereomeric *trans-cis*-isomers, using 2-trichloromethylchromenes. 2-Trifluoromethyl groups seemed to be leading to higher reactivity compared to 2-trichloromethyl and 2-phenyl substituted 3-nitrochromenes **61**, and showed some distinguishable characteristics in the acidic hydrolysis. Hydrolysis of enamino ketones, bearing CCl_3 and Ph at the R^1-position and Me or Ph at the R^2-position of **69**, in methanol gave a mixture of diketones **70** and a majority of the enol form **71** with in most cases retention of the configuration, although some exceptions were observed. For example, when doing the hydrolysis in boiling ethanol, some benzoylacetone derivatives showed substantial epimerization at the 3-position.



Scheme 16. Use of tertiary push-pull enamines of acetylacetones **68** in 1,4-additions to 3-nitrochromenes **61**.

CF_3 bearing derivatives at the R^1-position of **69** gave under the same hydrolysis conditions chromeno[3,4-*b*]pyridines **72**, with the exception when Ph at the R^2-position and/or NO_2 at the R^3-position were present only diketone derivatives **70** were obtained, showing the substituent sensitivity of this reaction. NO_2 containing derivative **70** precipitated from the mixture, but could be converted into pyridine fused derivatives **72** (R^1=CF_3). Presumably, fluorinated derivatives of **69** have a higher acidity of H-2, initiating the cyclization *via* an easier formation of the *aci*-form *via* a [1,4]-H shift. Dehydration into a nitrosoalkene intermediate, intramolecular nucleophilic attack of the enol, and aromatization lead to chromeno[3,4-*b*]pyridines **72**.[123,124]

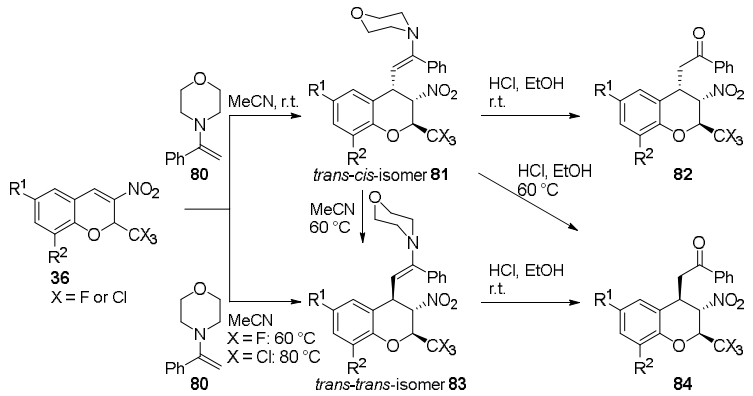
Stereoselective 1,4-additions of enamines to 3-nitrochromenes were further examined with morpholine derived enamines. The reaction between 3-nitrochromenes **36** and *N*-cyclohexenylmorpholine **73** primarily gave the formation of 1,2-oxazine *N*-oxides **75** in the case of 3-nitro-2-trichloromethyl-chromenes and exclusively with electron withdrawing groups (R^1=Br or NO_2) in the case of the trifluoromethyl analog (Scheme 17).[125] This formal [4+2]-cycloadduct **75** was formed *via* diastereoselective Michael addition and subsequent addition of the nitronate onto the iminium. The importance of the trihalomethyl group on the 2-position was illustrated by the fact that 3-nitro-2-phenyl-chromenes did not yield product **75** under these conditions and since trifluoromethyl analogs **75** showed a decrease in stability in solution, resulting in the formation of hydrolyzed starting materials. Furthermore, this was exemplified by the use of trifluoromethyl-chromenes bearing H or MeO at the R^1-position emerging in the construction of tetrasubstituted enamine adduct **74** in which all three bulky substituents were in equatorial positions. Interestingly, restricted rotation about the newly formed bond could be deduced *via* broadening of the aliphatic NMR signals. 1-*Tert*-butyl-1-morpholinoethene **77**, derived from morpholine and pinacolone, reacted smoothly under the same conditions with 3-nitro-2-trichloromethyl-chromenes **36** (X=Cl) with the formation of single diastereomer **78** under kinetic control. Trichloromethyl nitronates **75** and **78** were subjected to hydrolysis with hydrochloric acid in ethanol, yielding the anticipated ring-opened ketone products **76** and **79**.[125]



Scheme 17. Conjugate addition of cyclohexanone and pinacolone enamines **73** and **77** to 3-nitro-2*H*-chromenes **36**.

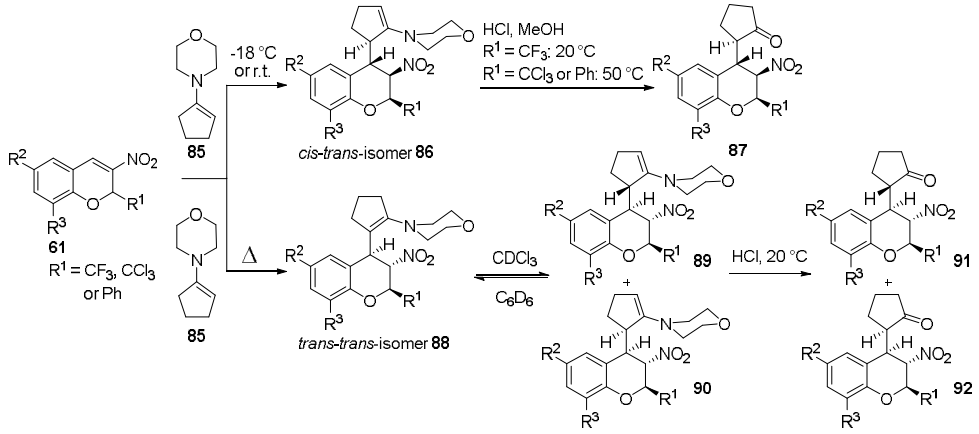
The reaction between α-morpholinostyrene **80** and 3-nitrochromenes **36** (Scheme 18) in acetonitrile at room temperature resulted in Michael adducts **81** with in most cases *trans-cis*-configuration, and not into 1,2-oxazine *N*-oxides derivatives **75** and **78** as described above for enamines **73** and **77**.[126] Mixtures of *trans-cis*- and *trans-trans*-, and *cis-trans*- and *trans-trans*-isomers were analyzed in some cases *via* coupling constant values and deducing the molecular structure *via* X-ray analysis. The selective formation of the *trans-trans*-isomer **83** was obtained when reactions were performed at elevated temperatures or when isolated *trans-cis*-trifluoromethyl-product **81** was heated in acetonitrile at 60 °C. This indicates that *trans-cis*-isomer **81**, formed at lower temperature, is the kinetic product which can be isomerized at C-4 to the thermodynamic *trans-trans*-product **83** *via* a retro-Michael reaction followed by thermodynamically controlled addition at elevated temperatures. The influence of the 2-phenyl-substituent was explored with

low observed diastereoselectivity under the same conditions, showing that the earlier observed diastereoselective addition is due to the steric bulk of the trihalomethyl groups. Acid hydrolysis of isomers **81**, **83** and 2-phenyl-substituted analogs at room temperature resulted, as expected, in ketone products **82**, **84** and 2-phenyl-compounds without changing the configuration of the pyran ring. Epimerization at C-4 was observed when enamine **81** was hydrolyzed to **84** at 60 °C.[126]



Scheme 18. Conjugate addition of α-morpholinostyrene **80** to 3-nitro-2*H*-chromenes **36**.

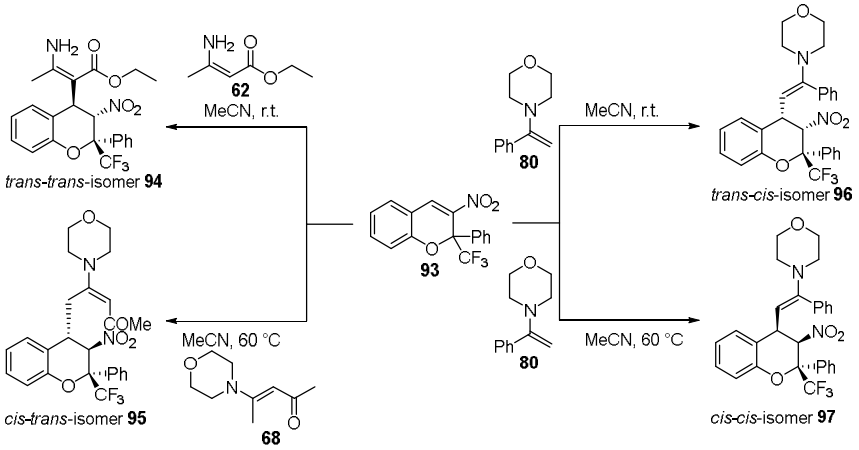
An extended study of conjugate additions of 1-morpholinocyclopentene **85** onto 3-nitro-2*H*-chromenes **61** under various conditions was executed (Scheme 19).[127] The kinetically favored *cis-trans*-product **86** derived from trisubstituted enamine was obtained in a stereoselective fashion for 2-trihalomethyl-chromenes **61** at -18 °C and for 2-phenyl-substituted-chromenes **61** at 20 °C. The products were easily obtained after precipitation and hence the yields for the trifluoromethyl derivatives **86** were lower than the yields of trichloromethyl bearing compounds **86** because of the increased solubility of the 2-CF_3-analogs in acetonitrile. The thermodynamic *trans-trans*-products **88**, with tetrasubstituted enamine moiety and all bulky substituents at equatorial positions, were synthesized in methanol at 35 °C for CF_3-analogs, again showing decreased yields in acetonitrile. However, for the production of *trans-trans*-isomers of 2-CCl_3- and 2-phenyl-chromanes **88**, higher temperatures of 40 °C and 60 °C were needed in methanol or acetonitrile, respectively. Interesting equilibrium mixtures of tautomers **88**, and epimers **89** and **90** were established in deuterated chloroform and benzene.



Scheme 19. Conjugate addition 1-morpholinocyclopentene **85** to 3-nitro-2*H*-chromenes **61**.

Chromanoenamine **88** was favored in C_6D_6 with the composition of each component given as approximately 61:27:12% for **88**:**89**:**90** and the corresponding structures were all determined by NMR and single-crystal X-ray measurements. Hydrolysis of *cis-trans*-chromanes **86** were performed in methanol at 20 °C for CF_3-ketone-analogs **87** and at 50 °C for CCl_3- and Ph-ketone-analogs **87** with retention of the configuration. CF_3-chromanoenamines **86** hydrolyzed at 50 °C showed substantial retro-Michael reaction. Moreover, hydrolysis experiments conducted under non-epimerization conditions at 20 °C on **88** resulted in the formation of epimers **91** and **92**, in which **91** was the major component with *anti*-configuration of the hydrogens. It is postulated that this is due to the presence of the tautomers **88**-**90** in solution. Epimerization of the less stable chromane **92** was observed when heating was applied, resulting in the formation of stable epimer **91**.[127]

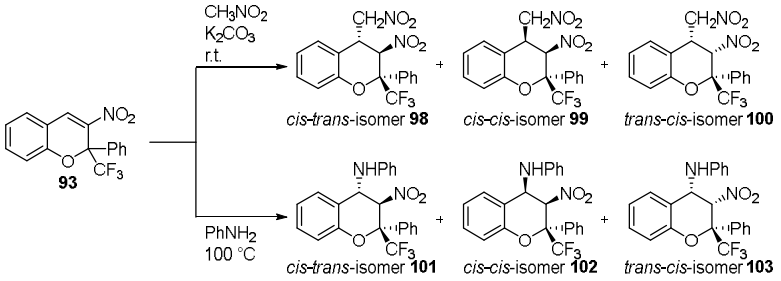
The above described nucleophilic additions with push-pull and regular enamines were carried out with 3-nitro-2-phenyl-2-(trifluoromethyl)-2*H*-chromenes **93**, and reported together with the Michael addition of other C- and N-nucleophiles.[128] 2-Phenyl-2-trifluoromethyl-chromenes **93** were prepared *via* tandem condensation of salicylaldehyde **3** and (*E*)-3,3,3-trifluoro-1-nitro-2-phenylprop-1-ene with triethylamine in dichloromethane. Push-pull enamines displayed similar reactivity in the Michael addition onto 3-nitro-2-phenyl-2-trifluoromethylchromenes **93** as described above for 2-monosubstituted 3-nitrochromenes **61** (Scheme 20). Primary enamines **62** attacked *via* the most nucleophilic α-carbon, forming tetrasubstituted chromanes **94** as single *trans-trans*-diastereomer with *Z*-configuration of the enamine double bond, which is favored due to intramolecular hydrogen bonding. Tertiary *E*-enaminoketones **68** approached *via* the vinylogous β-methyl part resulting in the exclusive formation of *cis*,*trans*-isomer **95**. In addition, reactions of 3-nitro-2-phenyl-2-trifluoromethyl-2*H*-chromene **93** and α-morpholinostyrene **80** gave *trans-cis*-isomer **96** and *cis-cis*-isomer **97** under kinetically (acetonitrile, room temperature) and thermodynamically (acetonitrile, 60 °C) controlled conditions, respectively. Under kinetic control, a 3:1-mixture of isomers **96** and **97** was obtained, from which major isomer **96** was easily isolated *via* recrystallization in dichloromethane-hexane. X-ray studies and NMR spectroscopy were used to illustrate the stereochemistry, in which the kinetic product **96** bears the most sterically encumbered enamine substituent equatorially, and CF_3 and NO_2 are in trans-diaxial configuration, whilst in thermodynamic product **97** the equatorial positions are occupied by both bulky enamine and CF_3 groups.[128]



Scheme 20. 1,4-Additions of push-pull and regular enamines to 3-nitro-2-phenyl-2-(trifluoromethyl)-chromene **93**.

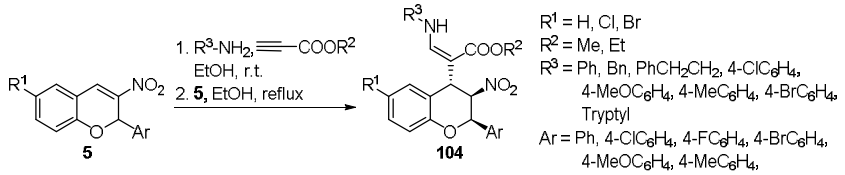
Diastereoselective Michael reactions were observed when enamine nucleophiles were used in these studies. However, the use of nitromethane and aniline as nucleophiles in the conjugate additions to 3-nitro-2-phenyl-2-trifluoromethyl-2*H*-chromene **93** produced mixtures of isomers (Scheme 21).[128] The ratios of isomeric nitromethane adducts were determined as *cis-trans* **98**, *cis-cis* **99** and *trans-cis* **100** in

44%, 38% and 18%, respectively, and the configuration of each isomer was determined by NMR coupling constants. The obtained diastereomers in the reaction of 3-nitro-2-phenyl-2-trifluoromethyl-2*H*-chromene **93** with aniline showed the same stereochemistry, although in different amounts, *i.e. cis-trans* **101**, *cis-cis* **102** and *trans-cis* **103** in 9%, 36% and 55%, respectively.[128]



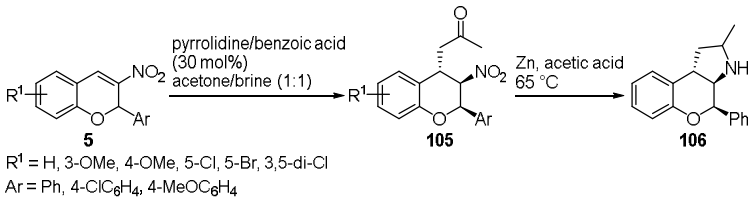
Scheme 21. 1,4-Additions of nitromethane and aniline to 3-nitro-2-phenyl-2-(trifluoromethyl)-chromenes **93**.

Similar to the enamine work presented by Korotaev and Sosnovskikh *et al.*, Yan and coworkers reported a one-pot sequential β-enaminoester formation and Michael addition (Scheme 22).[129] Initial trials for the domino reaction of amines, propiolate and 3-nitrochromenes **5** at 20 °C in ethanol for both steps of the sequence offered good yields (80%), but poor diastereoselectivity as observed from the NMR spectrum. Intermediate β-enaminoesters can be formed in both *Z*- or *E*-configuration depending on various factors, hence when the reaction is performed in ethanol at reflux, only one diastereomer is formed, *i.e.* cis-trans-isomer **104** with *Z*-configuration of the enamine double bond as illustrated by the X-ray crystal structures. The scope was examined, starting from available reagents *i.e.* amines, propiolates and 3-nitrochromenes **5**, resulting in good to excellent yields (69-92%).[129]



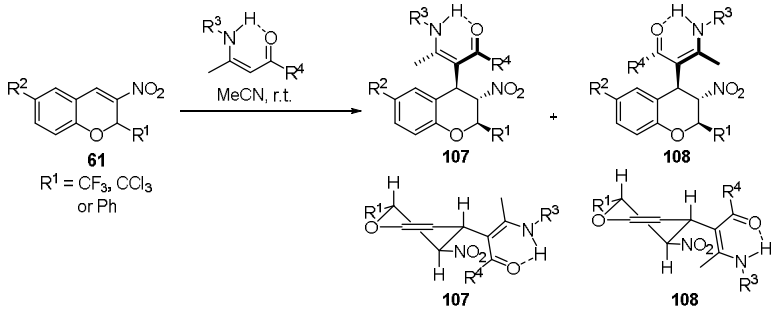
Scheme 22. One-pot β-enaminoester formation and conjugate additions to 3-nitrochromene **5**.

The conjugate addition between 3-nitrochromenes **5** and acetone was mediated by the same catalytic system as used for the synthesis of the 3-nitrochromenes **5**, *i.e.* 30 mol% of pyrrolidine and benzoic acid (Scheme 23).[43] Unfortunately, a one-pot protocol generated a complex mixture, yet the best results for acetone-adducts **105** were achieved by performing the reaction in the presence of acetone and brine allowing yields of up to 86% and excellent stereoselectivity (>99%). A *cis-trans*-relationship on the pyran ring was observed *via* NMR and X-ray analysis. Further reduction of the nitro group under the influence of zinc in acetic acid directly generated tricyclic pyrrolidine-fused chromane **106** in 92% yield on gram-scale.[43]



Scheme 23. 1,4-Addition of acetone and reductive amination towards fused pyrrolidine **106**.

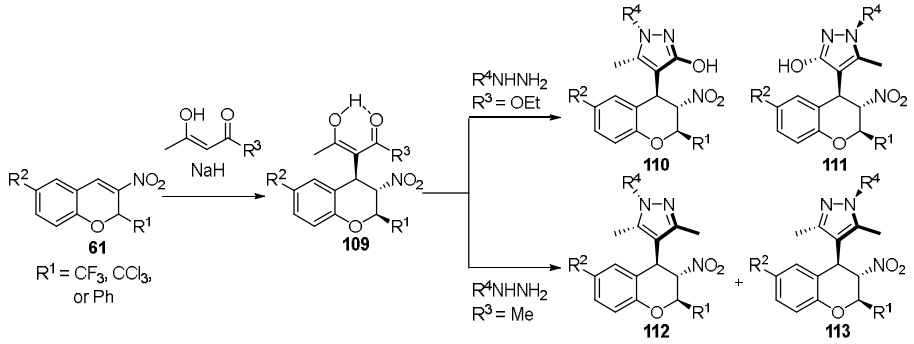
Closely related to the previously discussed topic, in which we reviewed the stereoselective conjugate additions to 3-nitrochromenes, is the field covering the synthesis of axially chiral trisubstituted chromanes from 3-nitrochromenes. The addition products of primary and secondary push-pull enamines, derived from acetoacetic esters (R^4=OEt), to 3-nitrochromenes **61** were synthesized earlier[121] (Scheme 14) and the ones derived from acetylacetone (R^4=Me) were synthesized in a study concerning the axial chirality of the prepared compounds (Scheme 24).[130] The latter *trans*,*trans*-isomers, obtained from acetylacetone (R^4=Me), formed two isomeric compounds **107** and **108** in a 3:2 ratio with R^3=H, while when R^3=alkyl, isomer **107** is only a minor compound. The difference in NMR chemical shifts and coupling constants together with 2D NMR and 1D NOE (together with the exchange processes) provided further data to assume atropoisomers **107** with *anti* orientation and **108** with *syn* orientation as a result of the hindered rotation about the C(sp^3)-C(sp^2) axis of the C(4)-C(3') bond. This kind of atropoisomerism is less frequently seen. It is important to note that the type of enamine is important in obtaining atropoisomers, since only primary or secondary push-pull enamines form *trans*,*trans*-isomers and attack *via* the α-carbon in order to get sufficient sterical hindrance. The *trans-trans*-configuration is imperative, after all this brings the equatorial 3-nitro and the pseudoequatorial 4-enamino groups in closer proximity. Variable-temperature NMR studies did not show coalescence of the signals, rather decomposition of the products, and separation of the atropoisomers (R^4=Me) was not possible. Yet, the same derivative from acetoacetic esters (R^4=OEt) was produced as a single atropoisomer, showing an *anti* oriented **107** derived from 2D NOESY. The fact that the nitro and ethoxy groups are in closer proximity in atropoisomer **107** than in isomer **108**, results in a strongly enhanced stereoselectivity for acetoacetic esters (R^4=OEt) derivatives, and has been hypothesized to be due to the secondary interactions between the nitro and ethoxy groups and so the bulkiness of the present moieties is not the decisive aspect.[130]



Scheme 24. Preparation of axially chiral *trans*,*trans*-trisubstituted chromans **107** and **108**.

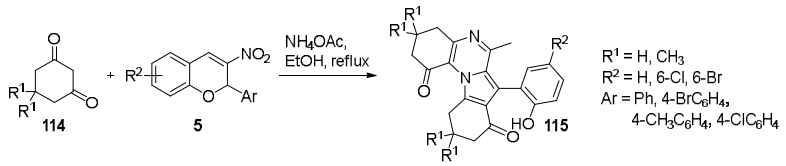
The analogous addition of 1,3-dicarbonyl compounds (*i.e.* acetylacetone (R^3=Me) and ethyl acetoacetate (R^3=OEt)) results in the formation of ketoenol derivatives **109** (Scheme 25).[131] Chroman **109** (R^3=OEt) existed solely in its enol form and 2D NOESY provided evidence for the existence of **109** as single atropoisomer in the *anti* orientation. These compounds served as available starting materials for the preparation of pyrazoles, yet two atropoisomeric forms **110** and **111** (with R^4=H) were found as a consequence of the lowered rotational barrier concomitant with the formation of the pseudoequatorial five-membered pyrazole, even though starting from one stable atropoisomer **109**. The free energy barrier for rotation of **112** (R^4=H) was determined *via* variable-temperature NMR and a coalescence was observed of the methyl peaks at 290K. Hence, the rotational barrier was calculated with the help of line shape simulations to obtain a value of 13.5 kcal/mol at the coalescence temperature. Additionally, the *N*-methylpyrazoles **110**-**113** (R^4=Me) were obtained from methylhydrazine, and interestingly a rotameric ratio of 2:1 was observed for **112** and **113** upon cooling. Again the configurations were determined *via* 2D NOESY illustrating that isomer **112** is the major isomer. It is critical to note that the additions of 2-substituted indoles did not give atropoisomers, since the obtained adducts result in *cis*,*trans*- and *trans*,*cis*-configurations in which the indole is placed in a pseudoaxial direction with less hindrance about

the chiral axis. Finally, the *trans*,*trans*-2-phenyl-2-(trifluoromethyl)-2*H*-chromene isomers **94** presented itself as stable atropoisomer in the *anti*-configuration (Scheme 20).[131]



Scheme 25. Preparation of pyrazole derived atropoisomers **110-113**.

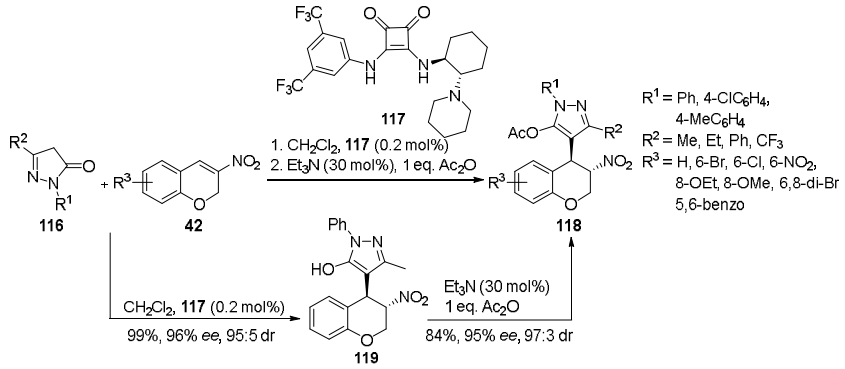
The exploration of novel reactions resulted in a variety of hybrid structures starting from 3-nitrochromenes. Yan *et al.* developed a straightforward synthesis of 3,4,10,11-tetrahydroindolo[1,2-*a*]quinoxalines **115** starting from 1,3-cyclohexanediones **114** and 3-nitro-2-phenyl-2*H*-chromenes **5** by means of excess of ammonium acetate in ethanol at reflux (Scheme 26).[132] Functionalized derivatives **115** were prepared in good yields (64-72%) and single crystal X-ray studies confirmed the polycyclic tetrahydroindolo[1,2-*a*]quinoxaline core. A mechanism is postulated involving the conjugate addition of the *in situ* formed β-enaminone *via* the α-carbon and subsequent nucleophilic attack at C-2 of a second molecule of β-enaminone *via* the amine moiety, in which the pyran core ring-opens. An intramolecular substitution of the free amine of the first β-enaminone species results in the formation of a dihydropyrrole intermediate, subsequent intramolecular attack of the amino group of the dihydropyrrole onto the second β-enaminone species and finally aerial oxidation yields 3,4,10,11-tetrahydroindolo[1,2-a]quinoxalines **115**.[132]



Scheme 26. Reaction towards highly functionalized hybrid 3,4,10,11-tetrahydroindolo[1,2-*a*]quinoxalines **115**.

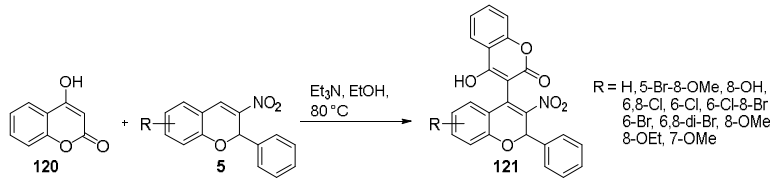
The study of the enantio- and diastereoselective 1,4-addition of pyrazolin-5-ones **116** to 3-nitro-2*H*-chromenes **42** was enabled by various squaramides (Scheme 27).[133] A mixture of tautomers was observed, hence the model reaction was adjusted by successively acetylating in the presence of triethylamine to yield pyrazole **118**. Under the optimized conditions, (1*S*,2*S*)-cyclohexane-1,2-diamine-appended squaramide **117** in CH_2Cl_2 at -15 °C with a reduced amount of catalyst loading of 0.2 mol%, an excellent yield, diastereomeric ratio and enantioselectivity were obtained of up to 99%, 99:1 and 96% *ee*, respectively. The utility of the reaction was displayed by a broad substrate scope and a gram-scale preparation in similar yields and stereoselectivities. In an experiment where intermediate **119** was isolated without the loss of yield and stereoselectivity in the first step, the second acetylation step exhibits a significant decrease in yield due to the low stability of tautomeric product **119**. Crystallographic data showed the absolute stereochemistry (3*S*,4*S*) and with this information in hand the role of the chiral catalyst was specified. *Re* face nucleophilic attack of the pyrazole substrate, deprotonated by the amine moiety of the (1*S*,2*S*)-cyclohexane-1,2-diamine part of **117**, is guided *via* hydrogen-bonding of the squaramide part of bifunctional catalyst **117** to

3-nitro-2*H*-chromene **42**. Nitronate protonation and possible epimerization, as a result of the high acidity, yields an *anti* diastereomer formation (3*S*,4*S*)-configuration by thermodynamic control. *In situ* enolization and treatment with acetic anhydride and triethylamine yields 3-nitrochromanyl-pyrazolyl acetates **118** under excellent control.[133]



Scheme 27. Asymmetric Michael addition of pyrazolin-5-ones **116** to 3-nitro-2*H*-chromenes **42**.

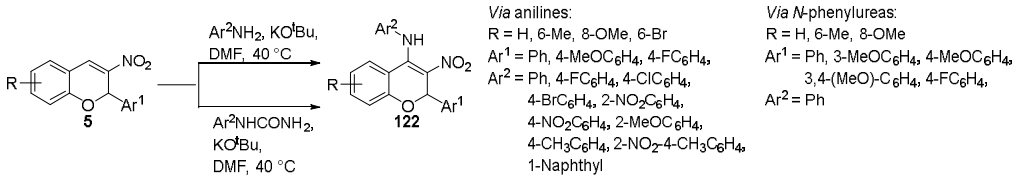
The combination of Michael addition followed by an aerobic oxidation yields 4-substituted-3-nitrochromenes. The first example used 4-hydroxy coumarin **120** as a nucleophile followed by air oxidation, rendering 4-hydroxycoumarin-3-nitrochromene conjugates **121** with triethylamine in ethanol at 80 °C (Scheme 28).[134] A small study, in which solely the 3-nitrochromene core is changed, furnished hybrid structures **121** in good to excellent yields (68-88%). A straightforward isolation, in which the product precipitated from ethanol, increases the utility of this methodology. The extended conjugation of the 4-hydroxycoumarin to the nitroalkene drives the dehydrogenation step.[134]



Scheme 28. Michael addition-oxidation of 4-hydroxycoumarin **120** to 3-nitro-2-phenyl-2*H*-chromenes **5**.

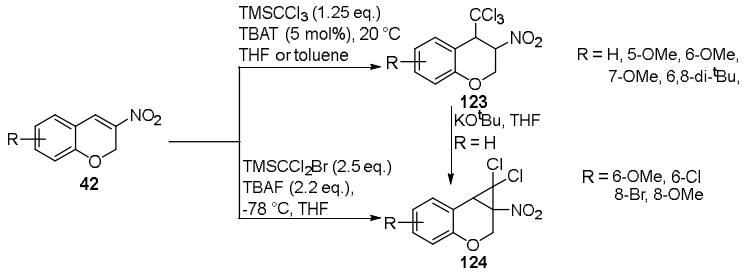
A second example of entailing a sequential conjugate addition-dehydrogenation was disclosed by Ahmed *et al*. where 4-anilino-3-nitrochromenes **122** were received (Scheme 29).[135] Only strong bases in polar, aprotic solvents gave appreciable yields above 80%, which resulted in the optimized conditions by applying 2 equivalents of KO^{t}Bu in DMF at room temperature (35-40 °C) for 10 minutes. The reaction tolerated a wide variety of 3-nitrochromenes **5** and anilines, exhibiting substantial effect of electronic and steric factors. In general, electron-withdrawing groups on the chromene core and 2-aryl group of 3-nitrochromenes **5**, and anilines resulted in improved yields of up to 86%. The reaction displayed some limitations, *e.g.* sterically hindered 2-aminobiphenyl, aliphatic amines and (sulfon)amides were ineffective under the reaction conditions. Furthermore, *N*-phenylureas served as excellent aniline precursors *via* basic hydrolysis, resulting in yields of up to 80% under the previously mentioned optimal conditions with various 3-nitrochromenes **5**. Numerous mechanistic studies were executed starting with the influence of the solvent and aerial conditions, which proved that both air and DMF are acting as oxidants. Competition experiments showed that aniline reacted faster than *N*-phenylurea, and experiments in the presence of TEMPO and investigation of an single-electron transfer mechanism demonstrated a non-free-radical mechanism. Hence, the reaction proceeds *via* the formation of deprotonated aniline as a soft nucleophile under the influence of KO^{t}Bu, followed by conjugate addition to 3-nitrochromenes **5**. Aerial oxidation is proposed to continue

through a hydroperoxide radical-nitronate species and finally elimination. Further exploration of the reaction was effected on gram-scale in good yield (81%).[135]



Scheme 29. Michael addition-oxidation of anilines or *N*-phenylureas to 3-nitro-2-phenyl-2*H*-chromenes **5**.

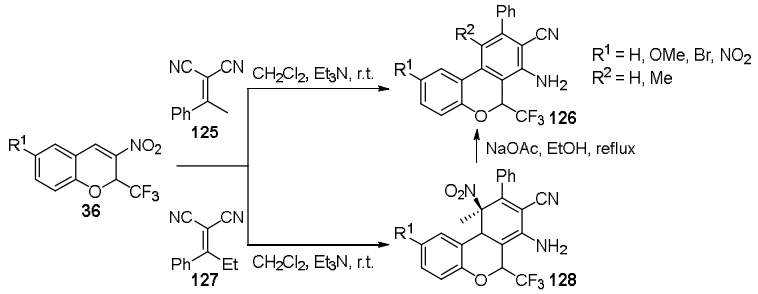
A final subject in the 1,4-additions to 3-nitrochromenes are the domino-Michael-cyclization reactions. Herein, the first group of reactions result in the formation of carbocyclic fused chromenes. The 1,4-addition of trimethyl(trichloromethyl)silane ($TMSCCl_3$) to 3-nitrochromenes **42**, promoted by silylophilic promotors is disclosed by Woodward *et al.* (Scheme 30).[136] This reaction gave access towards new 4-CCl_3-substituted 3-nitrochromanes **123** in which $TMSCCl_3$ is prepared in substantial quantities *via* addition of LiHMDS to chloroform and TMSCl as a co-solvent. Comparison of the efficacy of various promotors (5 mol%) proved that tetrabutylammonium salts soluble in organic solvents, with slowest rate for NBuBr and highest for $NBu_4Ph_3SiF_2$, were very potent in THF and toluene. A small range of 3-nitrochromenes **42** were employed furnishing **123** in yields of 61%-95%, and X-ray analysis showed *anti* arrangement in the substitution pattern. The authors proposed a catalytic cycle in which coordination of $TMSCCl_3$ to the nitro moiety results in the formation of a 4-CCl_3-nitronate species after attack of a nucleophilic promotor. The nitronate could both play the role of promotor or provide product **123**. Furthermore, treatment of **123** with KO^{t}Bu in THF instantly produced dichlorocyclopropane derivative **124** in 54% yield. Inspired by this, Woodward *et al.* discovered the use of $TMSCCl_2Br$, synthesized similarly as described above with bromodichloromethane instead of chloroform, for the direct cyclopropanation of 3-nitrochromenes **42** towards **124**.[137] Stoichiometric amounts of TBAF at -78 °C gave excellent chemoselectivity and yields of 76-86% of **124**. Halogen containing 3-nitrochromene derivatives **42** needed TEMPO to give appreciable yields.[136,137]



Scheme 30. Dichlorocyclopropanation of 3-nitro-2*H*-chromenes **42**.

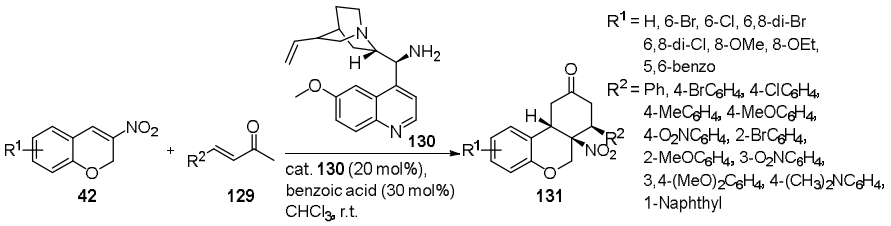
The reaction between 3-nitro-2-(trifluoromethyl)-2*H*-chromenes **36** and 2-(1-phenylalkylidene)malononitriles **125** and **127** is reported and furnished 6-(trifluoromethyl)-6*H*-dibenzo[*b*,*d*]pyrans **126** (Scheme 31).[138] The reaction went smooth with 2-(1-phenylethylidene)malononitrile **125** under the influence of triethylamine in dichloromethane at room temperature in which 7-amino-9-phenyl-6-(trifluoromethyl)-6*H*-benzo[*c*]chromene-8-carbonitrile **126** (R^2=H) was isolated *via* filtration of the formed precipitate. The reaction proceeded *via* a Michael addition, cyclization and tautomerization, followed by elimination of HNO_2 in the aromatization step. Formal [4+2]-cycloadduct **126** (R^2=H) was obtained in reasonable yields (33-64%), yet in the case of 2-(trichloromethyl)-2*H*-chromenes no product could be obtained. Interestingly, the employment of 2-(1-phenylpropylidene)malononitrile **127** resulted in the absence of spontaneous aromatization, a [1,5]-sigmatropic nitro-shift and under the same reaction conditions as described above, intermediate **128**

precipitated as a single diastereomer from the reaction mixture in yields of 45-70%. The configuration of diastereomer **128** was confirmed by ^{1}H NMR and X-ray analysis bearing the CF_3 in an axial and the NO_2 in an equatorial position, insinuating a stereospecific suprafacial sigmatropic rearrangement. Although **128** was a stable solid, equilibrium studies of **128** in DMSO-d_6 at ambient conditions for 6-7 minutes showed three different compounds, namely **128**, isomeric compound before the [1,5] nitro-shift and aromatized product **126** (R^2=Me). The proportions were strongly dependent on the R^1-group and the solvent, showing that electron-donating groups and polar solvents (*e.g.* DMSO-d_6) facilitate the aromatization step. With this in mind, intermediate **128** was treated with NaOAc in refluxing ethanol to afford dibenzo[*b*,*d*]pyrans **126** (R^2=Me) in good to excellent yields (72-89%).[138]



Scheme 31. Addition of 2-(1-phenylalkylidene)malonitriles **125** and **127** towards 6-(trifluoromethyl)-6*H*-dibenzo[*b*,*d*]pyrans **126** and **128**.

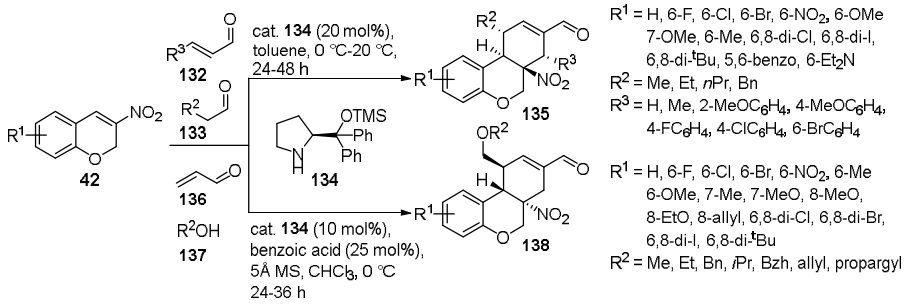
The first asymmetric organocatalyzed double Michael addition of α,β-unsaturated ketones **129** on 3-nitro-2*H*-chromenes **42** was presented by Du *et al.* (Scheme 32).[139] Under optimal conditions, the cascade double Michael addition was effected with quinine **130** (20 mol%) bearing a primary amine and benzoic acid (30 mol%) as an additive in chloroform at room temperature. The primary amine of **130** forms a dienamine intermediate with α,β-unsaturated ketones **129**, which engages in an intermolecular Michael addition with 3-nitro-2*H*-chromenes **42**. The nitronate-iminium intermediate then undergoes an intramolecular Michael addition resulting in chroman derivative **131**. Variation of the 3-nitro-2*H*-chromenes **42** and α,β-unsaturated ketones **129** eventuated in a broad scope of tricyclic chromane derivatives **131** resulting in overall good yields and enantioselectivities (45-90%, 65-83% *ee*), and excellent diastereoselectivities (>25:1). The absolute configuration could be deduced from the X-ray crystal structure determination as being (6a*R*,7*S*,10a*S*). Interestingly, a low enantiomeric excess (26% *ee*) was obtained when 2-nitro-3*H*-benzo[*f*]chromene was used as the substrate. However, the pseudo-enantiomer of **130** provided the inverted enantiomer (*ent*-isomer) in good enantioselectivities (78% *ee*).[139]



Scheme 32. Enantioselective cascade double conjugate addition of acyclic enones **129**.

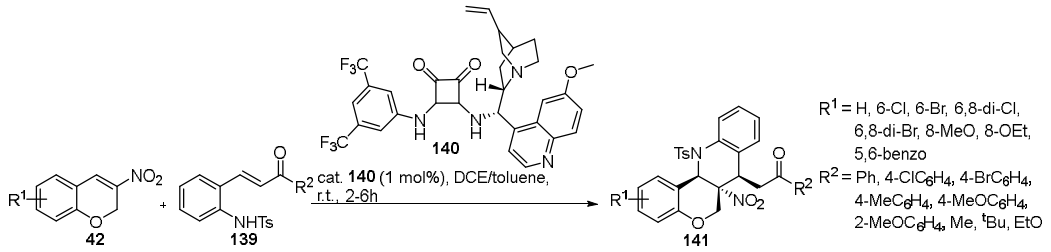
An elegant organocatalytic asymmetric triple domino reaction was developed by Enders and coworkers towards tricyclic chromanes **135** displaying four neighboring stereocenters (Scheme 33).[140] The domino Michael/Michael/aldol condensation was successfully conducted in toluene at 0 °C to room temperature under the influence of (*S*)-TMS-diarylprolinol catalyst **134** with a range of 3-nitrochromenes **42**,

α,β-unsaturated aldehydes **132** and aliphatic aldehydes **133**. Good to excellent stereoselectivities (99% *ee*, 9:1 to >20:1 dr) and moderate to good yields (20-66%) were obtained. The highly functionalized tricyclic chromane **135** was synthesized in gram-scale and X-ray analysis unambiguously determined the relative and absolute configurations. Closely related, the same group published a novel asymmetric one-pot four-component quadruple oxa-Michael/Michael/Michael/aldol condensation by employing TMS-protected prolinol catalyst **134**.[141] Substrate modification of 3-nitro-2*H*-chromenes **42** and aliphatic alcohols **137** resulted in excellent stereoselectivities (99% *ee*, >20:1 dr) and moderate to good yields (30-70%). The absolute configuration, obtained from X-ray crystal determination, was (*S*,*S*,*S*) for the three contiguous stereocenters. The robustness of both reactions was proven by scale-up reactions and modifications of the prepared tricyclic chromane cores **135** and **138**, *e.g.* transformation of the aldehyde into a dithioacetal, alcohol and olefin.[140,141]



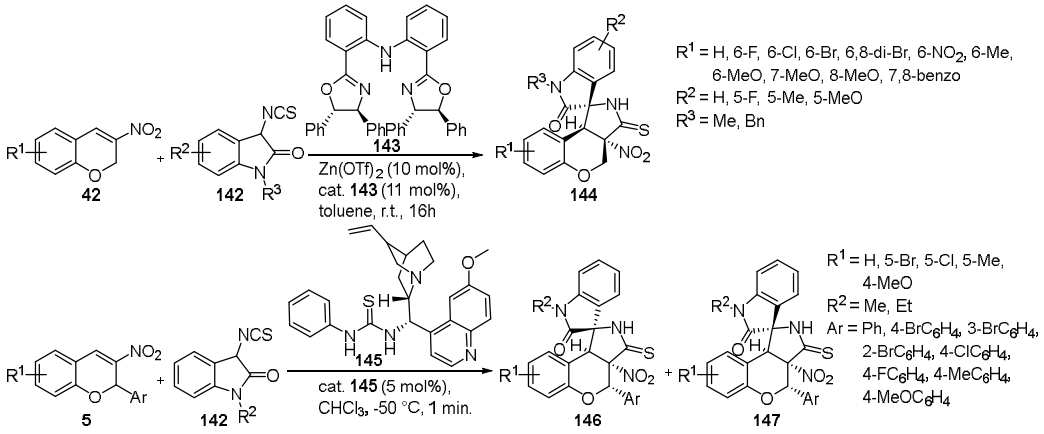
Scheme 33. Organocatalytic asymmetric triple and quadruple domino reaction.

A second group of domino-Michael additions, followed by cyclization results in the formation of heterocyclic fused chromenes. The synthesis of tetrahydrochromanoquinoline derivatives **141** bearing a quaternary stereocenter was accomplished under excellent stereocontrol by means of an organocatalytic cascade aza-Michael/Michael addition (Scheme 34).[142] Quinine-appended squaramide **140** was employed in low catalyst loading (1 mol%) in DCE/toluene mixture at room temperature, which established excellent diastereo- and enantioselectivities (>99:1 dr, 88-99% *ee*), and superb yields (90-99%) for a variety of synthesized derivatives **141**. The obtained (2*R*,3*S*,4*R*)-configuration was unquestionably proven *via* X-ray analysis, which entails a plausible transition state model. Simultaneous deprotonation of the sulfonamide with the basic nitrogen of the quinuclidine part of **140**, and coordination through hydrogen bonding of the squaramide with the sulfonamide encompasses the intermolecular aza-Michael addition *via* the *Re* face. Intramolecular Michael addition through the *Re* face permits the formation of tetrahydrochromanoquinolines **141**. The value of the procedure was featured by performing gram-scale synthesis with lowered catalyst loading (0.5 mol%), and synthetic transformations of **141** towards amine and sulfonyl-deprotected γ-lactam by means of hydrogen with Pd/C and $NiCl_2$ with sodium borohydride followed by magnesium, respectively.[142]



Scheme 34. Asymmetric aza-Michael-Michael addition towards tetrahydrochromanoquinolines **141**.

There are some reports related to the enantioselective reaction between 3-nitro-2*H*-chromenes **42** and **5**, and 3-isothiocyanato oxindoles **142**, leading to polycyclic spirooxindoles **144** or **146**.[143,144] Firstly, a chiral $Zn(OTf)_2$/(*S*,*S*)-**143** complex gave **144** in toluene at room temperature in excellent yields (72-99%) with good diastereo- and outstanding enantioselectivities (>95:5dr, 91->99% *ee*) for a range of 3-nitro-2*H*-chromenes **42** and 3-isothiocyanato oxindoles **142** (Scheme 35).[143] Gram-scale synthesis allowed the use of substantially lowered amounts of catalyst system (1 mol% $Zn(OTf)_2$ and 1.1 mol% **143**) and isolation of compound **144** was facilitated by filtration of the product without significantly hampering the yield and stereoselectivities. Crystallographic analysis provided the absolute configuration (1*S*,11*S*,12*S*) from which a model could be proposed. The chiral zinc catalyst serves a twofold role, namely zinc acts as Lewis acid and activates the 3-nitrochromene **42** through coordination with the nitro moiety, and the nitrogen of the *NH* of the oxazoline catalyst **143** acts as Lewis base to direct the Michael addition from the *Re* face through hydrogen bonding. The reaction advances through cyclization *via* addition of the nitronate onto the isothiocyanate. Synthetic transformation of the thiolactam towards the lactam, and reduction of the nitro towards the amine have been conducted in good yields and without loss of the stereoselectivities. Secondly, independently Xie and colleagues developed an organocatalytic asymmetric synthesis of tetracyclic spirooxindoles **146** and **147** (Scheme 35).[144] The reaction is finished in less than one minute at -50 °C in chloroform with the use of quinine-adjoined thiourea organocatalyst **145** (5 mol%). The reaction resulted in poor diastereoselectivity, but good enantioselectivities and good combined yield of the easily separable diastereomers **146** (39-56%, 67-84% *ee*) and **147** (37-60%, 51-86% *ee*) for a range of 3-nitro-2*H*-chromenes **5** and 3-isothiocyanato oxindole **142**. The bifunctional thiourea catalyst **145** activates the nitroalkene through hydrogen bonding with the thiourea and simultaneously the quinuclidine tertiary amine acts as base in the conjugate addition, in which the proposed transition state favors *Re* face attack. The structures were undoubtedly proven *via* the single crystal structure and interestingly, diastereomer **147** could be converted in isomer **146** by means of DABCO with a slight improvement of enantioselectivity.[143,144]

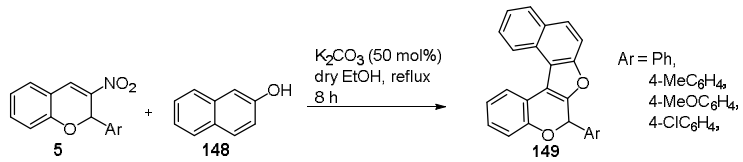


Scheme 35. Enantioselective domino reaction of 3-isothiocyanato oxindoles **142** and 3-nitro-2*H*-chromenes **42** and **5**.

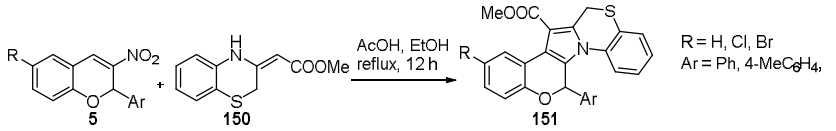
A small series of 6-aryl-substituted dioxa[5]helicenes **149** were made in fair yields (41-48%) *via* a straightforward one-pot procedure entailing 3-nitro-2H-chromenes **5**, β-naphthol **148** and potassium carbonate as basic promoter in dry ethanol at reflux (Scheme 36).[145] The mechanism is proposed to follow a base-promoted conjugate addition of β-naphthol *via* the C-nucleophilic center, followed by intramolecular cyclization of the naphthol onto the nitronate, and finally aromatization as a result of the elimination of water and nitroxyl (HNO).[145]

The annulation reaction between methyl 2-(benzo[*b*][1,4]thiazin-3-ylidene)acetate **150** and 3-nitrochromenes **5** in the presence of acetic acid in refluxing ethanol was described by the group of Yan and Sun (Scheme 37).[146] Polycyclic benzo[*b*]chromeno[4',3':4,5]pyrrolo[1,2-*d*][1,4]thiazines **151** were obtained

for a variety of 3-nitrochromenes **5** in reasonable yields (52-67%). Crystal structure determination showed that the developed procedure presents itself as an efficient route towards highly fused N,O,S-containing compounds. The cyclic β-enamino ester **150** undergoes nucleophilic conjugate addition onto 3-nitrochromene **5**, which delivers a nitroalkane in the presence of acetic acid. Intramolecular substitution and oxidation in air results in the formation of **151** *via* a dihydropyrrole.[146]

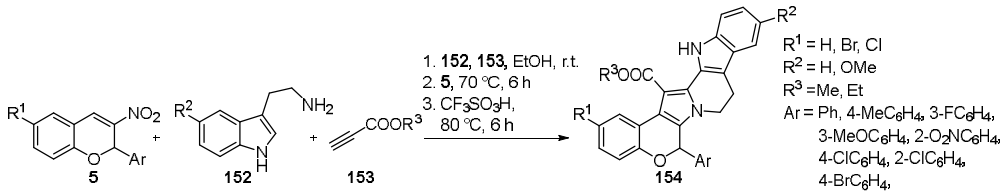


Scheme 36. Preparation of dioxa[5]helicenes **149** from 3-nitro-2-aryl-2*H*-chromenes **5**.



Scheme 37. Benzo[*b*]chromeno[4',3':4,5]pyrrolo[1,2-*d*][1,4]thiazine **151** synthesis from methyl 2-(benzo[*d*][1,4]thiazin-3-ylidene) acetate **150**.

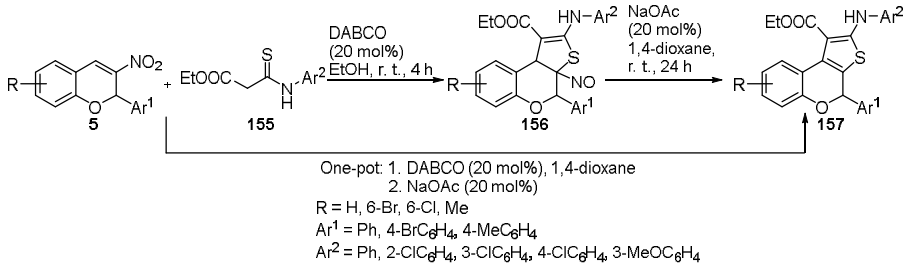
Another methodology towards dihydroindolizine-fused chromenes has been disclosed by the Yan group (Scheme 38).[147] Herein, a one-pot step-by-step procedure was acquired by reacting tryptamines **152** with propiolates **153** in ethanol at room temperature. The *in situ* furnished β-enamino ester was further reacted with 2-aryl-3-nitro-2*H*-chromenes **5** at 70 °C and yields the Michael addition product, which was cyclized under strong acid (triflic acid) and heating conditions, and finally furnished the polycyclic tetrahydrochromeno[4',3':2,3]indolizino[8,7-*b*]indoles **154**. This final step comprises the nucleophilic addition of the indole onto the enamino ester, *i.e.* an acid-mediated Pictet-Spengler cyclization, followed by substitution of the nitro by the amino group and aromatization. The structure of the linear polycyclic core was nicely proven *via* X-ray analysis. The convenience of this novel method was exemplified by a substrate scope for various 2-aryl-3-nitrochromenes **5**, tryptamines **152** and alkyl propiolates **153** with yields ranging from 62% to 89%.[147]



Scheme 38. Synthesis of tetrahydrochromeno[4',3':2,3]indolizino[8,7-*b*]indoles **154** *via* a one-pot domino reaction.

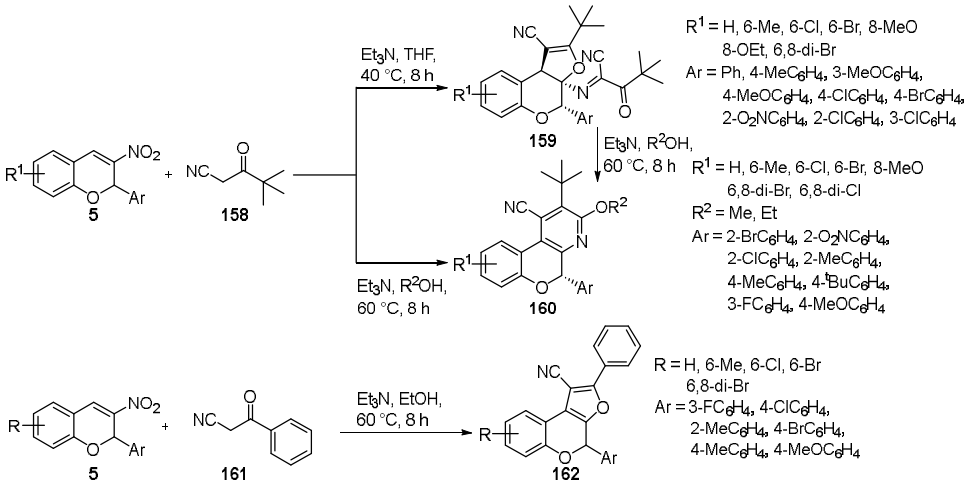
A facile one-pot domino protocol towards (dihydro)thieno[2,3-*c*]chromenes **156** and **157** was recently discovered (Scheme 39).[148] The procedure towards nitrosodihydrothiophene-fused chromenes **156** employed an oxidative umpolung strategy starting from 3-nitro-2*H*-chromenes **5** and thioamides **155** by means of DABCO (20 mol%) in ethanol at room temperature with excellent diastereoselectivity (>99:1 dr). Pleasingly, this method enables smooth access towards dihydrothieno[2,3-*c*]chromenes **156** in good to excellent yields (76-96%) under ambient conditions. In addition, the authors described the conversion of nitrosodihydrothiophene-fused chromenes **156** towards thieno[2,3-*c*]chromene **157** in 61% yield when **156** is treated with sodium acetate in 1,4-dioxane at room temperature. Hence, a one-pot protocol was developed in which multiple thieno[2,3-*c*]chromene derivatives **157** were successfully prepared in moderate yields

(32-52%), furthermore the structure was proven *via* the X-ray crystal structure. The domino reaction is initiated by a Michael addition of **155** onto **5**. The formed nitronate undergoes nucleophilic addition on the α-carbon by the S-atom of the thioamide. The cyclization is initially followed by dehydration towards nitrosodihydrothiophene-fused chromenes **156**. Loss of nitroxyl initiates the formation of the wanted thieno[2,3-*c*]chromenes **157**.[148]



Scheme 39. Domino Michael addition/intramolecular cyclization reaction between 3-nitro-2*H*-chromenes **5** and thioamides **155**.

Finally, the annulation reaction of 2-aryl-3-nitrochromenes **5** and α-cyanoketones **158** and **161** under various conditions showed peculiar differences in reaction outcomes (Scheme 40).[149] When 2-aryl-3-nitrochromenes **5** are treated with pivaloylacetonitrile **158** in THF and triethylamine at 40 °C, a range of imino-substituted dihydrofuro[2,3-*c*]chromenes **159** were obtained in excellent yields (76-95%). On the basis of single-crystal X-ray diffraction and ^{1}H NMR studies of various obtained compounds, the reaction with pivaloylacetonitrile **158** in THF resulted in high diastereoselectivities, rendering the furan fused to the chromane, and the aryl and the imine moiety both in the *cis*-configuration as the relative configuration of **159**. Surprisingly, when the reaction was performed in methanol or ethanol under reflux, chromeno[3,4-*b*]pyridines **160** were found to be formed in good to excellent yields (65-91%). The difference in reaction outcome is explained by the authors in a proposed mechanism. Starting from the conjugate addition of **158** onto 3-nitrochromene **5**, double deprotonation leads to an enolate-nitronate-adduct which undergoes cyclization by attack of the enolate-oxygen onto the nitronate-carbon resulting in a dihydrofuran intermediate. Under the influence of base a second molecule of pivaloylacetonitrile **158** attacks and forms imino-substituted dihydrofuro[2,3-*c*]chromenes **159** after dehydration.



Scheme 40. Annulation reaction of 3-nitro-2*H*-chromenes **5** and α-cyanoketones **158** and **161**.

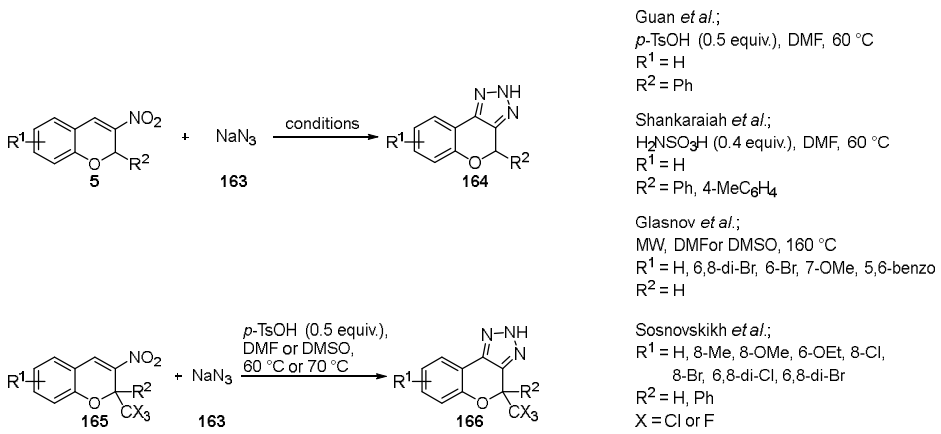
When the reaction is performed in alcohol solvents, in a next step the alcohol will attack the carbonyl carbon of the imine proceeding into a ring-opened enol. After loss of cyanide, tautomerization to the imine, cyclization of the imine onto the pivaloyl carbonyl carbon and aromatization by loss of pivalic acid eventually result in the formation of chromeno[3,4-*b*]pyridines **160**. Hence, alcohol substances acted as solvents and nucleophile. Furthermore, this formation mechanism is supported by a control experiment in which imino-substituted dihydrofuro[2,3-*c*]chromenes **159** were successfully converted into chromeno[3,4-*b*]pyridines **160** by treatment of **159** with triethylamine in the appropriate alcohol solvents. Remarkably, the use of benzoylacetonitriles **161** in ethanol resulted in the formation of furo[2,3-*c*]chromenes **162** in good yields (49-80%), the structures of which were proven *via* NMR and X-ray structure analysis.[149]

3.4. Cycloaddition reactions

The nitro group present in 3-nitrochromenes activates the double bond in such a way that it can act in cycloaddition reactions with 1,3-dipoles, *e.g.* azomethine ylides,[58,150-152] diazo compounds,[33,153-155] azides[156] and nitrones[157] resulting in the formation of a variety of five-membered (hetero)cyclic rings. Additionaly, enantioselective [4+2]-cycloadditions with 2-vinyl-1*H*-indoles,[158] hetero-Diels-Alder reactions with the nitroalkene participating with four electrons[159] and tandem [4+2]/[3+2]-cycloadditions[159] are described. Furthermore, although not really a cycloaddition reaction, the photocatalyzed electrocyclization of 3-nitro-2-phenyl-chromenes is reported and this reaction belongs to the group of pericyclic reactions additionally being the sole example of its kind in 3-nitrochromene chemistry.[160] Recent literature emphasizes on 1,3-dipolar cycloadditions resulting in the synthesis of triazole-fused chromenes, and reactions of 3-nitrochromenes with a variety of thiazolium and isoquinolinium salts, diazoalkanes, and azomethine ylides.

The preparation of chromeno[3,4-*d*]triazoles is most commonly described by the 1,3-dipolar cycloaddition reaction of azides with 3-nitrochromenes. The synthesis of *NH*-triazole annulated chromenes **164** has been investigated extensively, resulting in various procedures towards these highly interesting fused scaffolds (Scheme 41). Early reports with 3-nitrochromenes **5** did not mention the use of a catalyst, solely elevated temperatures (80 °C in DMSO) were applied to cause the reaction with sodium azide **163**.[156] In 2014, Guan *et al.* developed a general method for the conversion of nitroolefins into *NH*-1,2,3-triazoles **164** by means of *p*-toluenesulfonic acid (*p*-TsOH, 0.5 equivalents) and azide anion at 60 °C in DMF.[161] The role of *p*-TsOH is thought to be the protonation of the oxygen of the nitro group, resulting in further activation of the double bond. In their work, one example of a *NH*-1,2,3-triazole fused to chromene **164**, namely 4-phenyl-3,4-dihydrochromeno[3,4-*d*][1,2,3]triazole, was prepared in excellent yields (95%). Furthermore, sulfamic acid was found to be an efficient catalyst.[162] The use of sulfamic acid accelerated the reaction considerably and resulted in excellent yields (92-93%) for a limited amount of examples of **164**. The reason for the increased reactivity could be the hydrogen-bonding with the nitro moiety, activating the nitroalkene. Lastly, the effect of microwave irradiation was investigated by Glasnov without the aid of additional catalyst.[163] Under microwave radiation at 160 °C for 1 minute in DMF or DMSO, good yields (63-89%) were obtained for a selected amount of *NH*-triazole-fused products **164**. Specific caution should be given when using these methods since highly volatile, explosive and toxic hydrazoic acid is released.[164]

The research group of Sosnovskikh used *p*-TsOH in reactions of 3-nitro-2-(trihalomethyl)-2*H*-chromenes **165** with sodium azide **163** for the preparation of CX_3-containing *NH*-triazole-fused chromenes **166** (Scheme 41).[165] Optimized procedures use 0.5 equivalents of *p*-TsOH in DMSO or DMF at 60 °C or 70 °C, depending on the 3-nitro-2-(trihalomethyl)-2*H*-chromene substrates **165**. Reactions towards 4-CF_3-chromenotriazoles **166** finished within a couple of minutes and the products were obtained in excellent yields (84-96%) in both DMSO and DMF by filtration of the precipitated product. Under the same conditions CCl_3-containing *NH*-triazole-fused chromenes **166** needed slightly elongated reaction times (10-90 minutes) and were isolated in lower yields (37-64%), probably due to more decomposition. Finally, 4-phenyl-4-(trifluoromethyl)chromeno[3,4-*d*]triazoles **166** were prepared in decent yields (60-78%), even though the reaction proceeded slower. The CF_3-group was shown to be needed for the reaction to proceed, since 3-nitro-2,2-diphenyl-2*H*-chromene showed no reactivity towards sodium azide **163**. Crystal structure determination of CF_3-containing derivatives **166** showed that the hydrogen of the *NH*-tautomer is placed at the *N*2-position.[165]

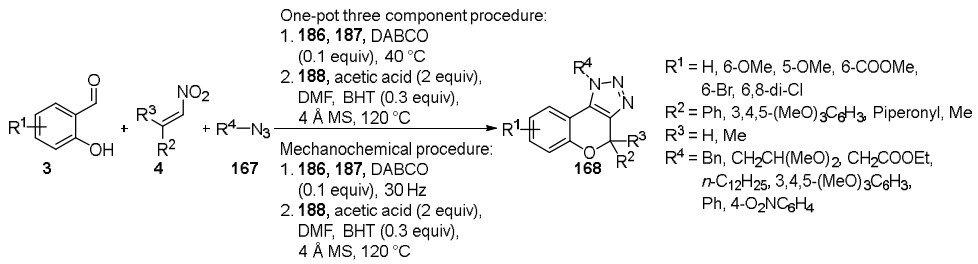


Scheme 41. 1,3-Dipolar cycloaddition of sodium azide **163** towards *NH*-triazole-annulated chromenes **164** and **166**.

In our research program towards the assembly of triazole-fused (hetero)cycles,[166-173] we recently developed a regioselective one-pot three-component reaction starting from salicylaldehydes **3**, nitroalkenes **4** and organic azides **167** (Scheme 42).[173] *Via* this methodology, the isolation of the intermediate 3-nitrochromenes is no longer mandatory, facilitating purification of the triazole-fused chromenes **168** and circumventing an additional reaction set-up and purification step. In the same context, we recently reported the preparation of triazolocoumarins using a three-component reaction, although the regiochemistry was not as predicted.[166] Hence, the regioselectivity of the reaction needed to be verified, and we started by the regiospecific synthesis of both regioisomers **168** and the complementary isomeric product from the cycloaddition reaction. Three additional pathways were used. *NH*-triazole-fused chromenes **164**, prepared *via* the method of Guan *et al.*,[161] were alkylated with benzyl bromide furnishing mainly 2-alkylated triazolochromene in 39% yield and an unseparable mixture of the two plausible regioisomers of our novel one-pot three-component reaction. *Via* our in-house developed regiospecific triazolization methodology[168] we were able to prepare regioisomer **168** and the complementary regioisomer, in low yields (3 and 26%, respectively), by starting from the ketones 2-phenyl-3-chromone **51**, prepared *via* reduction of 3-nitro-2-phenyl-2*H*-chromene **5** with $TiCl_3$, and commercially available flavanone. NMR comparison showed a clear distinction in diastereotopic splitting of the benzylic protons for the three regioisomers, due to the variation in proximity of the benzylic group to the stereocenter, giving us unambiguous proof for the regioselectiviy of our one-pot three-component reaction. The product with the benzylic group closest to the stereocenter showed a strong AX splitting pattern, the 2-alkylated derivative displayed an AB splitting pattern, while the prepared regioisomer **168** from flavanone and our one-pot three-component reaction clearly showed no splitting (A_2 pattern). This made it clear that the one-pot three-component reaction was regioselective, since also NMR analysis of the crude reaction mixture only showed regioisomer **168**. With this regiochemistry clearly established, a two-step synthesis was performed in which first 3-nitrochromene is prepared, and then in a second step is reacted with benzyl azide furnishing triazolochromene **168** in 48% overall yield. Furthermore, the reaction was adapted to a one-pot three-component reaction, and with the optimized conditions in hand the generality of the reaction was explored in which all three starting materials **3**, **4**, and **167** were varied and a range of products were obtained in low to good yields (3-60%). Compared to the two-step synthesis (48% yield) a clear improvement was observed for the one-pot synthesis (54% yield), both regarding yields and labor intensiveness. Solid salicylaldehydes needed an adjusted procedure, with triethylamine as base, liquefying the mixture, mainly resulting in strongly reduced yields.

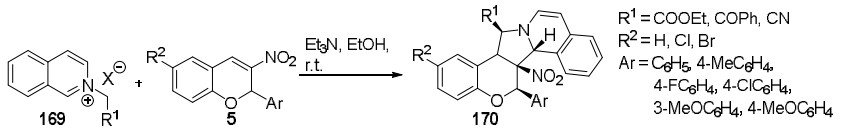
Hence, a two-pot mechanochemical procedure was applied by using a ball milling apparatus, in which the salicylaldehydes **3** were diversified, resulting in significantly increased yields for solid salicylaldehydes, but slightly decreased yields for liquid salicylaldehydes. This mechanochemical procedure led to a complementary route towards triazolochromenes **168** for solid salicylaldehydes. The applicability of these

two methods was shown by performing gram-scale syntheses without significant loss of yield and by performing post-functionalizations towards interesting biological structures and building blocks. 6-Bromotriazolochromene derivative **168** was easily converted *via* Buchwald-Hartwig amination with *N*-phenylpiperazine and *via* Suzuki-Miyaura coupling with 3,5-dimethoxyphenylboronic acid to possibly biologically relevant chromenes. Dimethyl acetal connected to the *N*1-position of the 1,2,3-triazole was quantitatively deprotected to the aldehyde and triazolium annulated chromene was synthesized by simple methylation at the *N*3-position of the triazolochromene.[173]



Scheme 42. Synthesis of fully substituted triazole-fused chromenes **168** *via* a one-pot three component reaction or mechanochemical synthesis.

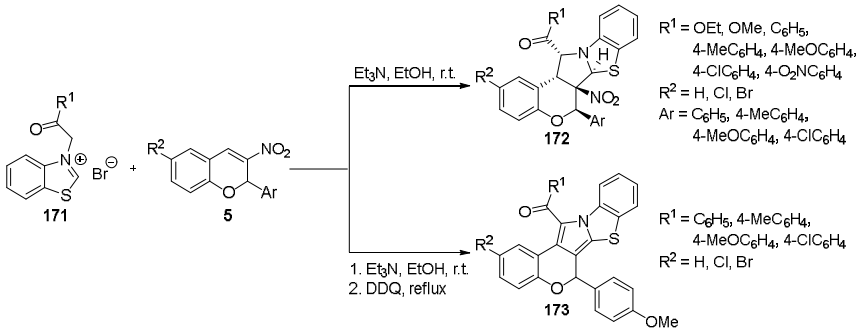
The group of Yan reported a number of cycloaddition reactions between heteroaromatic *N*-ylides and 3-nitrochromenes. In this regard, isoquinolinium salts **169** have been used as valuable precursors for isoquinolium ylides in the 1,3-dipolar cycloaddition reactions with 3-nitrochromenes **5**, resulting in the synthesis of 6a,6b,13,13a-tetrahydro-6*H*-5-oxa-12a-azadibenzo[*a*,*g*]fluorenes **170** (Scheme 43).[174] *N*-ethoxycarbonylmethyleneisoquinolinium bromide **169** smoothly reacted in the presence of triethylamine in ethanol at ambient temperature with a variety of 3-nitrochromenes **5** yielding the desired product **170** in excellent yields (83-96%) as pure compounds after precipitating from the reaction mixture. Only a single diastereomer was present in each reaction, which was deduced *via* the NMR spectra that showed only a single set of signals. Crystallographic analysis of compounds **170** clearly showed a *cis*-relation between the 6-aryl group, nitro group and ester moiety, while a *trans*-orientation is visualized in the dihydroisoquinoline substructure. Other electron-withdrawing R^1-groups were explored, *i.e. N*-phenacylisoquinolinium bromides and *N*-cyanomethyleneisoquinoline chlorides **169**. The same conditions were applied and derivatives **170** were easily furnished *via* this procedure in yields ranging from 83 to 91% for cyano and phenacyl derivatives **170**, again in excellent diastereoselectivity and the same configuration as described above for the ethoxycarbonyl derivatives.[174]



Scheme 43. Cycloaddition reaction between 3-nitrochromenes **5** and isoquinolinium salts **169**.

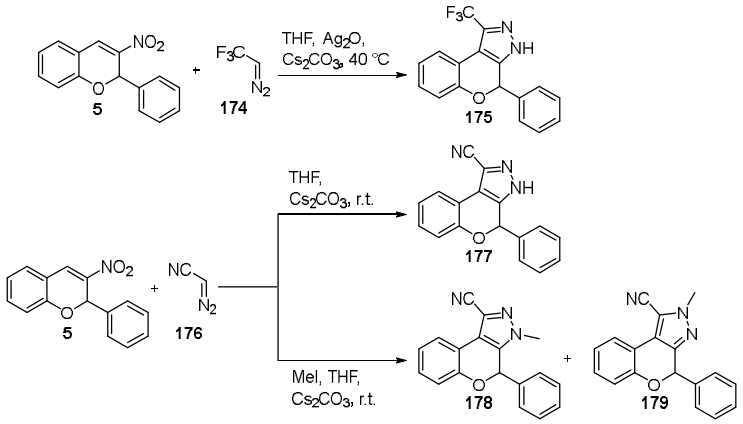
Furthermore, Yan *et al.* disclosed the synthesis of the polycyclic (tetrahydro)benzo[*d*]chromeno[3',4':3,4]pyrrolo[2,1-*b*]thiazoles **172** and **173** (Scheme 44).[175] Similar reaction conditions as described for the isoquinolinium salts were applied for phenacyl-appended benzothiazolium salts **171** in which product **172** conveniently precipitated from the reaction in satisfactory yields (83-95%). NMR analysis and X-ray determination of multiple compounds provided proof for the excellent diastereoselectivity. It is proposed that the *endo* transition state goes through the *anti* form of the ylide formed from **171**, resulting in a highly diastereoselective procedure. Slightly lower yields (69-76%) are achieved by changing from phenacyl to alkoxycarbonylbenzothiazolium salts **171**, yet the triethylamine promoted reaction still resulted in a single diastereomer with identical configuration for ester functionalized

172. A one-pot dehydrogenation reaction was developed by employment of DDQ after the 1,3-dipolar cycloaddition, in which benzo[*d*]chromeno[3',4':3,4]pyrrolo[2,1-*b*]thiazoles **173** were easily prepared after aromatization of the pyrrolidine ring (67-83%).[175]



Scheme 44. Reaction of 3-nitrochromenes **5** and benzothiazolium salts **171**.

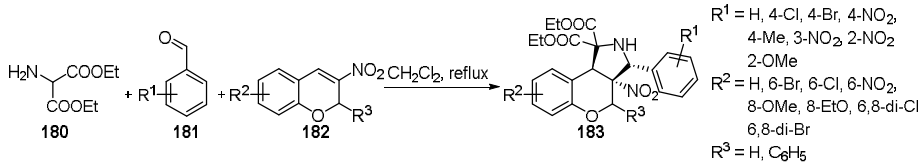
Two reports by Ma and coworkers described the 1,3-dipolar cycloaddition of nitroolefins with trifluorodiazoethane[176] **174** and diazoacetonitrile[177] **176** towards trifluoromethyl- and cyanopyrazoles (Scheme 45). Firstly, under the influence of Ag_2O, Cs_2CO_3 at 40 °C in THF, 3-nitro-2-phenyl-2*H*-chromene **5** has been converted into trifluoromethylpyrazole fused chromene **175** in 99% yield.[176] A second method involved the *in situ* generation of trifluorodiazoethane **174** from 2,2,2-trifluoroethylamine and *tert*-butyl nitrite in the presence of acetic acid in THF at 55 °C, and the subsequent one-pot reaction with 3-nitrochromene **5** furnishing pyrazole **175** in 72% yield. Mechanistic studies suggested the preparation of a silver trifluorodiazoethylide species by means of Ag_2O and Cs_2CO_3. Addition to the nitroalkene moiety, followed by nitrite elimination generates trifluoromethylpyrazole fused chromene **175** after hydrolysis of the silver pyrazolyl intermediate. On the other hand, direct cycloaddition of trifluorodiazoethane **174** onto 3-nitrochromene **5** furnishes dihydropyrazole, which could also be converted to the silver pyrazolyl intermediate. Secondly, transition-metal-free protocols were established for the conversion of diazoacetonitrile **176** in fused cyanopyrazole derivatives **177**-**179**.[177] The [3+2]-cycloaddition reaction of 3-nitrochromene **5** with diazoacetonitrile **176** in the presence of Cs_2CO_3 in THF at room temperature resulted in the formation of *NH*-pyrazole fused chromene **177** in 85% yield. This reaction was further developed in a one-pot three component reaction with methyl iodide providing regioisomers **178** and **179** in poor selectivity with yields of 48% and 31%, respectively.[176,177]



Scheme 45. Preparation of trifluoromethyl- and cyanopyrazole-fused chromenes **175**, **177**-**179**.

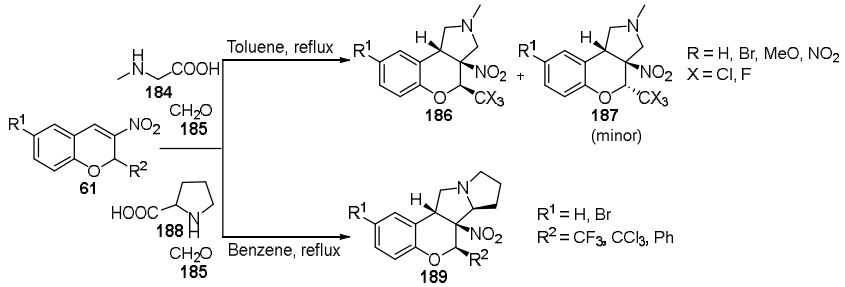
A final group of compounds undergoing 1,3-dipolar cycloaddition reactions with 3-nitrochromenes are the azomethine ylides. Further subdivision can be made, *i.e.* the use of miscellaneous azomethine ylides resulting in highly interesting fused pyrrolidine and pyrazolidine chromane derivatives, isatin-based azomethine ylides yielding spirooxindole nitrochromanes, and the combination of various azomethine ylides with glyco 3-nitrochromenes.

The combination of diethyl 2-aminomalonate **180**, benzaldehydes **181** and 3-nitro-2*H*-chromenes **182** translated into the development of a catalyst-free one-pot 1,3-dipolar cycloaddition reaction towards pyrrolidine-fused nitrochromanes **183** (Scheme 46).[178] The reaction proceeded smoothly in boiling dichloromethane for a range of benzaldehydes **181** and 3-nitro-2*H*-chromenes **182** in excellent yields (83-99%) and diastereoselectivities (6:1>20:1). Crystal structure determination resolved the conformation of the major diastereomer, showing *cis* relation between the nitro and the phenyl group. This indicates that the 1,3-dipolar cycloaddition proceeds *via* the *endo* transition state.[178]



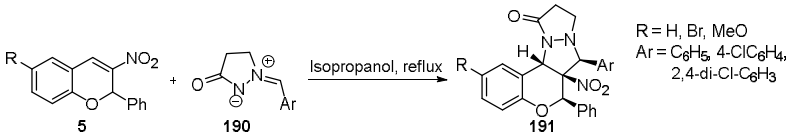
Scheme 46. One-pot three-component reaction of diethyl 2-aminomalonate **180**, benzaldehydes **181** and 3-nitro-2*H*-chromenes **182**.

Sosnovskikh and coworkers investigated the reaction of 3-nitro-2-trihalomethyl-2*H*-chromenes **61** with azomethine ylides derived from sarcosine **184** or proline **188** and paraformaldehyde **185** (Scheme 47).[179] The former combination reacted smoothly affording pyrrolidine chromanes **186** and **187**, with a high preference of *cis*-adduct **186** in high yields (77-97%). The CX_3-group was deemed to increase the reactivity and the *cis*-free base pyrrolidine **186** was isolated by crystallization, while the *trans*-isomer **187** was only observed in the NMR spectra of the crude mixture. The structure was ascertained *via* crystallographic analysis and 2D NMR measurements, clearly visualizing the *cis*-conformation between the CX_3-group and the nitro-moiety. The latter combination between proline **188** and paraformaldehyde **185** resulted in highly diminished yields of cycloaddition product **189** (11-34%) and lower selectivity. Only *cis*-isomer **189** was isolated by recrystallization and the structure proven by 2D NMR and X-ray analysis.[179]



Scheme 47. 1,3-Dipolar cycloaddition of nonstabilized azomethine ylides to 3-nitro-2-trihalomethyl-2*H*-chromenes **61**.

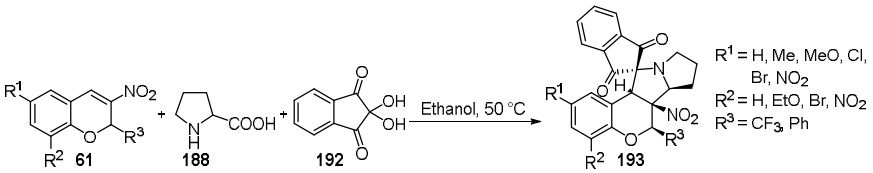
The applicability of stabilized *N*,*N*'-cyclic azomethine imines **190**, prepared from benzaldehydes, methyl acrylate and hydrazine, in 1,3-dipolar cycloadditions with 3-nitrochromenes **5** was illustrated in the report by Sosnovskikh (Scheme 48).[180] In isopropanol at 50 °C, the reaction resulted in yields between 42% and 81% for a small range of derivatives of **191**. The reaction towards tetrahydrochromeno[4,3-*c*]pyrazolo[1,2-*a*]pyrazol-11-ones **191** led to the formation of a single all-*cis*-diastereomer, as proven by crystallographic analysis.



Scheme 48. Reaction of stabilized *N*,*N*'-cyclic azomethine imines **190** towards tetrahydrochromeno[4,3-*c*]pyrazolo[1,2-*a*]pyrazol-11-ones **191**.

The authors propose a non-concerted alternative to the 1,3-dipolar cycloaddition, yielding the nitro- and phenyl-group in a *cis*-relationship by going through the addition *via* the *Z*-configured azomethine imine **190** due to approach *via* the smaller hydrogen group and finally resulting in the synthesis of pyrazolidine chromane derivatives **191** after addition of the nitronate to the iminium. Importantly to state is the fact that the inversion to the product where the aryl- and nitro-group are *trans* does not happen under these conditions.[180]

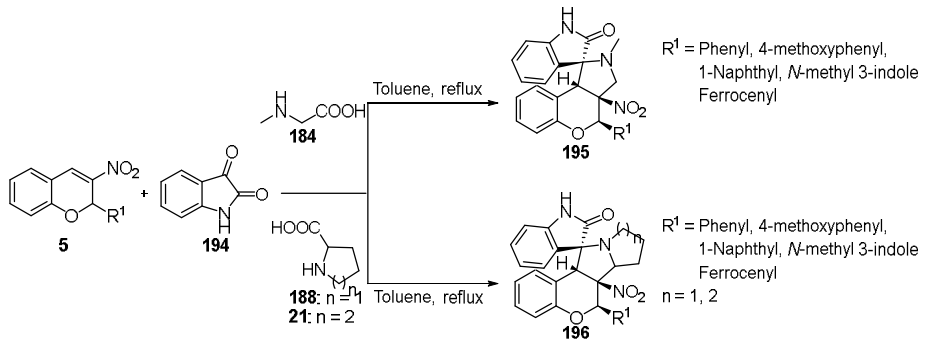
The *in situ* generation of azomethine ylides derived from ninhydrin **192** and proline **188** was applied successfully to the preparation of spiro[chromeno[3,4-*a*]pyrrolizidine-11,2'-indene]-1',3'-diones **221**, resulting in high yields (80-90%) for both 2-CF_3 and 2-phenyl analogs (Scheme 49).[181] Moreover, an excellent regio- and stereoselectivity were obtained in the form of *endo* product **193** with the nitro-group and 2-substituent in *cis*-relation. This is the result of the azomethine ylides approaching *via* the less hindered pseudoequatorial 2-hydrogen side. Interestingly, the difference in stability showed to be a problem for the CF_3-analogs of **193**, while the 6-phenylchromenopyrrolizidines were stable in DMSO. CF_3-appended **193** appeared as an equilibrium mixture in DMSO-d_6 existing of product **193** versus the starting chromenes and azomethine ylides in different ratios. Sterically encumbered 3-nitro-2-phenyl-2-(trifluoromethyl)-2*H*-chromenes and 2-CCl_3-analogs did not undergo the cycloaddition reaction, the latter displaying low stability under these conditions as was also observed in the cycloaddition reactions with sodium azide.[165,181]



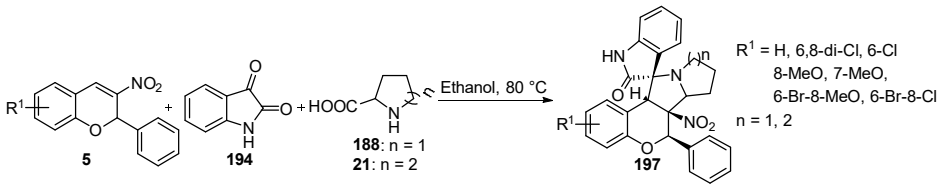
Scheme 49. 1,3-Dipolar cycloaddition of *in situ* generated azomethine ylides derived from ninhydrin **192** and proline **188**.

The utilization of isatin **194** and its derivatives in the preparation of azomethine ylides led to interesting and highly complex spirooxindole nitrochromanes **195** and **196** when reacted with 3-nitrochromenes **5**. Azomethine ylides were obtained from the thermal decarboxylative reaction between isatin **194** and sarcosine **184**, proline **188** or pipecolic acid **21** in toluene with removal of water.[182] High yields of **195** (75-85%) were obtained for reactions performed with sarcosine-derived azomethine ylides, exhibiting one single regioisomer with a high degree of stereoselectivity with the R^1 and nitro-group, and the phenyl of the oxindole in *cis*-relation (Scheme 50). Additionally, cyclic secondary amino acids proline- and pipecolic acid-derived azomethine ylides were examined for their application in 1,3-dipolar cycloaddition reaction with 3-nitrochromenes **5**, furnishing the similar isomers **196** in good yields (77-87%).[182]

As reported above, spirooxindole-pyrrolidine/piperidine fused nitrochromanes **197** were prepared by using an eco-friendly protocol (Scheme 51).[183] The reactions were performed in ethanol at 80 °C for a short period of time. Furthermore, the products were easily isolated since they rapidly precipitated as a single isomer **197** from the reaction mixture and in this report a variety of 3-nitrochromenes **5** were utilized resulting in good yields for pyrrolidine (81-88%) and pipecolic acid (78-89%) derived products **197**. The produced spirooxindole nitrochromanes **197** showed a *cis* orientation as the relative stereoconformation of the 2-substituent and nitro group.[183]

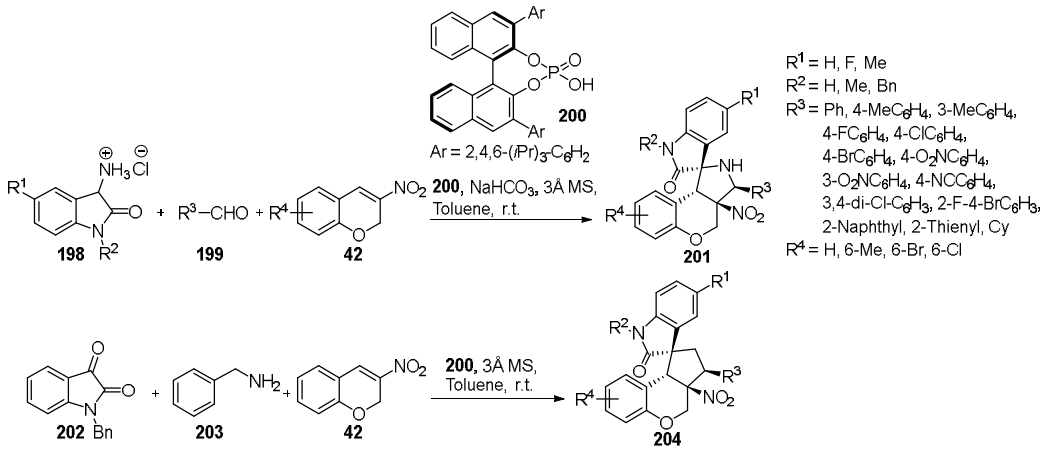


Scheme 50. 1,3-Dipolar cycloaddtion of azomethine ylides towards spirooxindole based chromanes **195** and **196**.



Scheme 51. Green synthesis of spirooxindole-pyrrolidine-piperidine derived nitrochromans **197**.

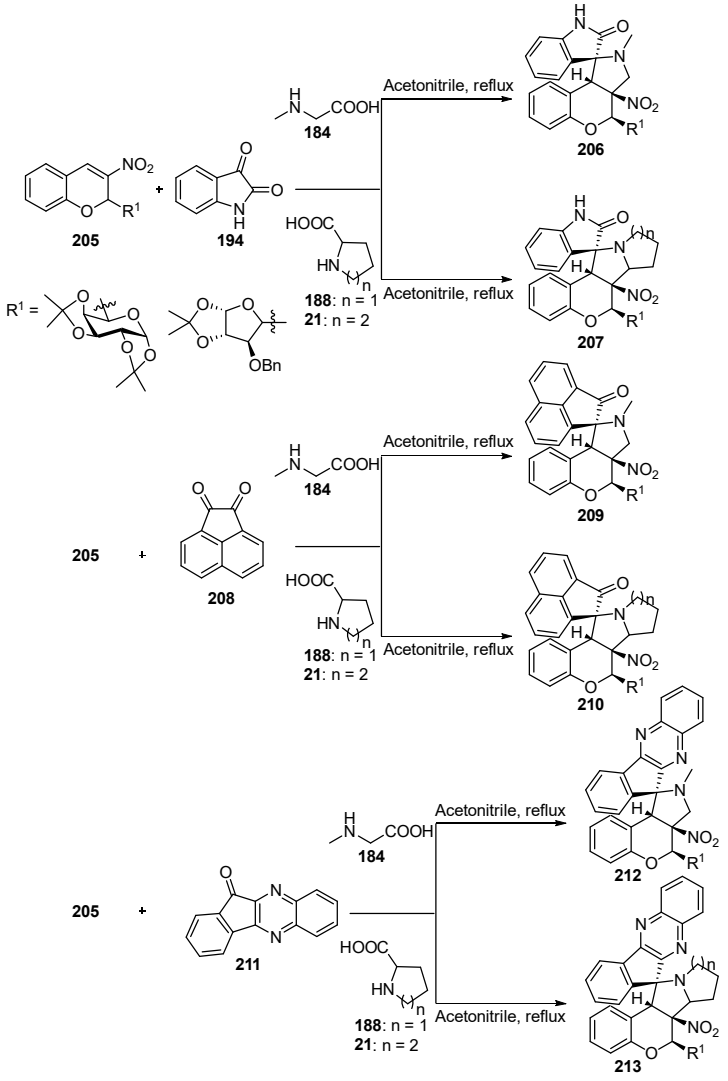
The group of Wang presented an enantioselective three-component reaction of 3-aminooxindoles **198**, aldehydes **199**, and 3-nitro-2*H*-chromenes **42** towards highly functionalized polycyclic spirooxindole-chromane **201** bearing four neighboring chiral centers (Scheme 52).[184] The enantioselectivity is induced by means of 20 mol% of chiral phosphoric acid catalyst **200**, which exhibited enhanced performance regarding both yield and stereoselectivity when compared to guanidine, thiourea and squaramide-based catalysts. *N*-unsubstituted aminooxindoles **198** exhibited lower reactivity than *N*-substituted ones. Furthermore, the authors demonstrated the wide scope of the reaction by changing all components **198**, **199** and **5**, resulting in good to excellent yields (82-99%), diastereo- (15:1->20:1 dr) and enantioselectivities (50-96% *ee*) of **201**.



Scheme 52. Enantioselective [3+2]-cycloaddition of 3-nitrochromenes **42** and oxindole-based azomethine ylides.

This was not the case when starting the reaction with the aliphatic aldehyde cyclohexanecarbaldehyde, in which a lower diastereo- (12:1 dr) and a tremendously low enantioselectivity (6% *ee*) was obtained. The comparison was made with the reaction of isatin **202**, benzylamine **203** and 3-nitro-2*H*-chromene **42** under the same conditions, resulting in 98% yield and low stereoselectivity (7:1 dr, 65% *ee*). The advantageous approach of the methodology was further displayed by performing a large scale preparation of **201** and post-functional transformations, *i.e.* oxidation with DDQ towards 2*H*-pyrrole derivative and reduction by means of zinc and TMSCl in order to reduce the nitro group. Excellent regio- and stereocontrol, induced by chiral phosphoric acid **200**, is proposed to be a result from the combination of hydrogen-bonding and activation of the nitroalkene, followed by *endo* cyclization.[184]

Raghunathan *et al.* focused on the application of glyco 3-nitrochromenes **205** with a variety of azomethine ylides for the exploration towards carbohydrate-based heterocycles (Scheme 53).[185]



Scheme 53. The reactivity of carbohydrate based 3-nitrochromenes **205** towards azomethine ylides.

Azomethine ylides derived from sarcosine **184**, proline **188** or pipecolic acid **21** were applied in the 1,3-dipolar cycloaddition with glyco 3-nitrochromenes **205** resulting in yields ranging from 81 to 86% with excellent regio- and stereoselectivity for **206** and **207**. Additionally, the reactions of carbohydrate derived 3-nitrochromenes **205** with azomethine ylides prepared from acenaphthylene-1,2-dione **208** and indenoquinoxalinone **211** resulted in the formation of 3-nitrochromane fused pyrrolidinyl spiroacenaphthylenones **209** and **210**, and 3-nitrochromane hybrid pyrrolidinyl spiro indenoquinoxalines **212** and **213**, respectively. The reactions were performed in refluxing acetonitrile, resulting in excellent yields (80-87%), and regio- and stereoselectivities due to approach of the ylide from the least hindered side.[185]

4. Conclusions

In this chapter, we summarized the varied chemistry related to 3-nitrochromenes, mainly focusing on recent advances in the field. Reports before 2013 were briefly mentioned, and we refer to the review of Sosnovskikh *et al.*[19] for more details on older work. The synthesis of 3-nitrochromenes with variations at the 2-position, ranging from aryl and alkyl to groups linked *via* a heteroatom, have been well established. These methodologies have led up to interesting and complementary protocols by starting from available starting materials or nitration and functionalization of natural products. However, still new methods, such as the mechanochemical preparation of 3-nitrochromenes, have recently arisen as an effective tool. Furthermore, enantioselective preparations were successfully conducted with the aid of chiral catalysts or *via* resolution. The chemical reactivity of 3-nitrochromenes, governed by the nitroalkene moiety, has been extensively investigated and resulted in 3-nitrochromenes undergoing oxidation and reduction reactions, conjugate additions and cycloadditions, the latter two types of reactions being the most elaborately studied furnishing highly functionalized chromane and chromene derivatives.

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