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Part I: Nitroalkenes in the synthesis of heterocyclic compounds†

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The applications of nitroalkenes in the synthesis of three- to five-membered O, N and S-heterocycles, including natural products are investigated in this review. These heterocyclic compounds were synthesized from nitroalkenes with a variety of substituents at the α and β-positions and those that were part of common and medium rings *via* a wide variety of reactions such as Michael addition reactions, epoxidation, [3 + 2] cycloaddition and many cascade/domino/tandem reactions. In addition, the potential of nitroalkenes to take part in multi-component and cascade reactions, particularly, in diastereo- and enantioselective versions is reviewed. The high reactivity of nitroalkenes and their potential to coordinate with the metal catalysts as well as organocatalysts signify them as efficient precursors in synthetic organic chemistry. Also, the flexibility of the nitro group in functional group manipulations has expanded the scope of the nitro group, in general, and nitroalkenes, in particular, in organic synthesis.

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† Dedicated to Professor Mohammad Reza Saidi on the occasion of his 70th birthday.

Azim Ziyaei Halimehjani was born in 1979 at Halimehjan, a small village in the Roudbar of Guilan, north of Iran. He obtained his B.Sc. in pure chemistry in 2001 from Shiraz University. After completing his M.Sc. in Organic Chemistry from Sharif University of Technology in 2003 under the supervision of Prof. M. R. Saidi and M. Tafazzoli, immediately he started his Ph.D. under the supervision of Prof. M. R. Saidi and advisor of Prof. J. Ipaktschi in the same University. During his Ph.D., he had two research visits from the research group of Prof. Ipaktschi (2005) and Prof. Peter R. Schreiner (2006) at Justus-Liebig-Universität Gießen, Germany. After completing the Ph.D. in 2007, he began his academic career as Assistant Prof. of Organic Chemistry at Kharazmi University, Tehran, Iran. He has published over 35 publications. He works in the area of synthetic organic chemistry and coordination chemistry with emphasis on the chemistry of dithiocarbamates, nitroalkenes and development of new synthetic methodologies as well as green chemistry.

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1. Introduction

Conjugated nitroalkenes constitute a unique class of electron deficient alkenes owing to their ability to take part in a wide range of organic reactions.[1] These include aldol reactions,[2] Michael addition reactions,[3] Mannich reactions,[4] (*m* + *n*) cycloadditions,[5] Morita–Baylis–Hillman reactions[6] and even metal mediated coupling reactions,[7] to name a few. The reactivity umpolung of the nitro group as an acyl anion equivalent and nitroalkene as an acyl methyl cation equivalent is well documented in the literature.[1] The exceptional ability of the nitro group to activate electrophiles and stabilize nucleophiles *via* co-ordination with Lewis and Bronsted acids as well as the ability of nitroalkenes to undergo Lewis base activation have elevated nitroalkenes as the substrates of choice in asymmetric reactions.[3,8] The flexibility of nitro group in functional group manipulations has expanded the scope of nitro group, in general, and nitroalkenes, in particular, in synthetic organic chemistry.[9] Among these, transformation to carbonyl compounds *via* Nef reaction, oximes, hydroxylamines and amines *via* reduction, nitriles *via* dehydration and reactive 1,3-dipoles such as nitrones, nitrile oxides and silyl nitronates with the intervention of various reagents are the prominent ones.

The pivotal role of nitroalkenes as substrates in new methodology development[1–8,10] and in targeted synthesis,[11] is also attributable to the ability of nitro group to survive hostile reagents and reaction conditions. The directing influence of nitro group is amply evident even in reactions where nitro group ultimately undergoes substitution or elimination (*vide infra*). The easy accessibility of nitroalkenes *via* nitro-aldol condensation and other methods such as direct nitration, nitrodecarboxylation *etc.* also contributed to the phenomenal growth of nitroalkene chemistry in recent decades.[12]

The versatility of nitroalkenes in organic synthesis has featured in numerous reviews.[1–12] However, since the literature on nitroalkene chemistry currently grows by leaps and bounds, a comprehensive coverage of all the recent developments in one review article is a challenging task. Therefore, we recently reviewed the participation of nitroalkenes in the synthesis of carbocycles.[13] This report surveys the central role of nitroalkenes as substrates in the synthesis of 3–5 membered O, N and S-heterocycles, including natural products. The succeeding part (part II) features the 6-membered heterocycles derived from conjugated nitroalkenes. To our knowledge, a focused review on nitroalkenes in the synthesis of heterocycles appeared 28 years ago.[14]

Seyyed Emad Hooshmand was born in Bandar Lengeh/Hormozgan, Iran, in 1988. He received his B.Sc. in chemistry from Bu-Ali Sina University, Hamedan, Iran in 2011, and his M.Sc. in organic chemistry from Kharazmi University, Tehran, Iran, under the supervision of Dr Azim Ziyaei Halimehjani, in 2013. His research interests include synthesis of novel biologically active compounds based on dithiocarbamates and synthesis of novel acid organic salts and their applications as catalyst in organic transformations. Now, he is a Ph.D. student at Shahid Beheshti University in Tehran, Iran.

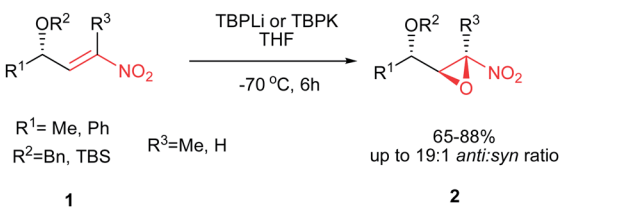
2. Synthesis of three-membered heterocycles

2.1. Epoxide derivatives

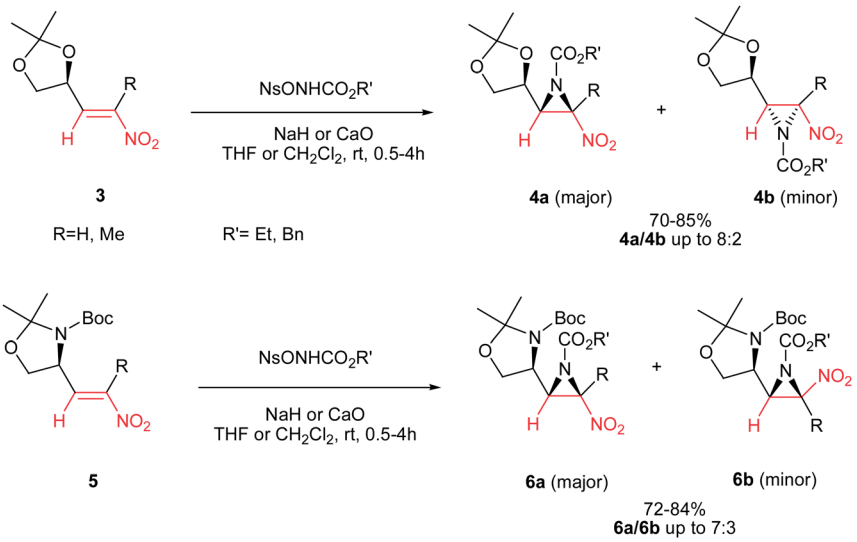
Rodríguez *et al.* found a versatile procedure for stereoselective epoxidation of chiral nitroalkenes **1** to provide the chiral nitroepoxides **2** (dr up to 19 : 1), which are useful intermediates for synthesis of a variety of biologically active compounds. The reactions were carried out using lithium *tert*-butylperoxide or potassium *tert*-butylperoxide as the oxidizing reagent in THF as solvent at −70 °C. Nitroalkene **1** with a methyl group on the double bond also gave the corresponding product, but in lower diastereoselectivity (dr of 3.5 : 1). In addition, better selectivity can be enriched using potassium *tert*-butylperoxide as oxidant (Scheme 1).[15]

2.2. Aziridine derivatives

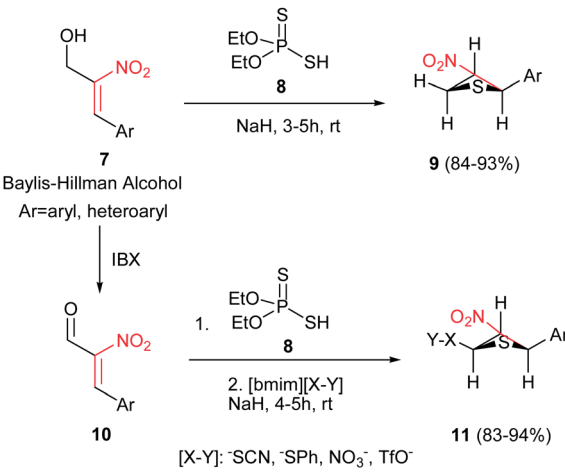
Fioravanti *et al.* reported an efficient protocol for asymmetric synthesis of chiral nitroaziridines **4** and **6** from optically active (*E*)-nitroalkenes **3** and **5** bearing a 1,3-dioxolane or 1,3-oxazolidine residue and carbamates ($NsONHCO_2Et$ or $NsONHCO_2Bn$) *via* a stereoselective aza-Michael initiated ring closure reactions catalyzed by an inorganic base such as CaO or NaH. The reaction was carried out both in solution (in CH_2Cl_2 or THF) and solvent-free conditions with similar results. Interestingly, while nitroalkenes generated from (*R*)-2,2-dimethyl-1,3-dioxolane-4-carboxaldehyde **3** provided the aziridines **4a**/**b** as products in up to 8 : 2 ratio, nitroalkene **5** gave stereoisomers **6a**/**b** in up to 7 : 3 ratio under the same reaction conditions. Complete retention of configuration of substrates was observed during the reaction condition. Also, nitroalkenes **3** shows higher dr than **5** (Scheme 2).[16]



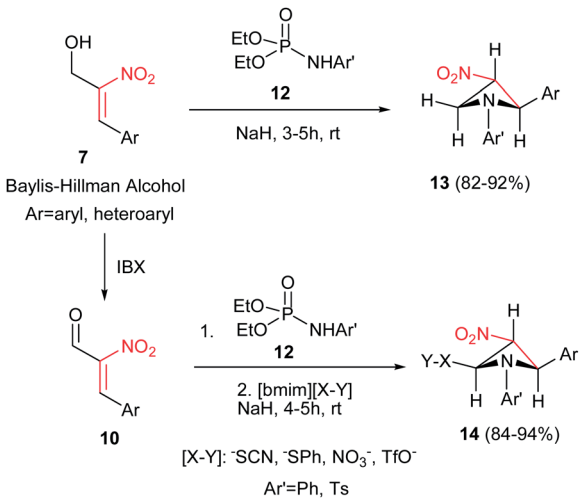
Scheme 1 Stereoselective epoxidation of chiral nitroalkenes.



Scheme 2 Asymmetric synthesis of chiral nitroaziridines from optically active (*E*)-nitroalkenes.



Scheme 3 Nitroalkenes in the synthesis of substituted thietanes.



Scheme 4 Nitroalkenes in the synthesis of substituted 3-nitroazetidines.

3. Synthesis of four-membered heterocycles

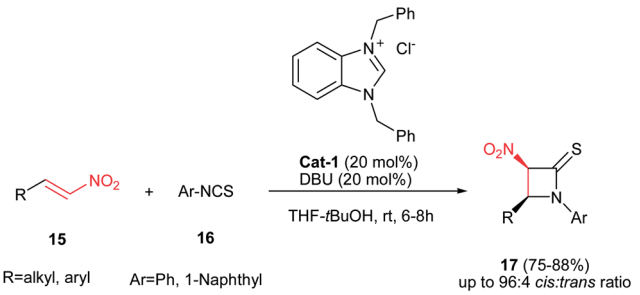
3.1. Substituted thietanes and azetidines

Reaction of Baylis–Hillman alcohols **7** and their aldehydes **10** with either O,O-diethyl hydrogen phosphorodithioate **8** or O,O-diethyl hydrogen phosphorodithioate in combination with a task-specific ionic liquid [bmim]X–Y afford the corresponding 2,3-di- or 2,3,4-trisubstituted thietanes **9** or **11**, respectively, with complete diastereoselectivity in favor of the *trans* isomers as confirmed by NOE (Scheme 3).[17] Diverse nucleophiles such as SCN, PhS, NO_3 and TfO anions can be applied in this protocol with excellent yields. The authors have also shown that the nucleophilicty of SCN or PhS anion is considerably higher in [bmim]SCN or [bmim]SPh compared to that from KSCN or PhSNa. Another point in this report is using IBX as a mild oxidant and compatible with a variety of functional groups.

Also, the same group described that by using *N*-aryl/tosylphosphoramidates **12** instead of **8** under similar reaction conditions, the corresponding substituted 3-nitroazetidines **13** or **14** can be synthesized in high to excellent yields. The reaction proceeded *via* domino Michael/cyclization reaction (Scheme 4).[18]

3.2. β-Thiolactam derivatives

Yadav and Awasthi reported an efficient procedure for synthesis of β-thiolactams **17** from nitroalkenes **15** and aryl isothiocyanates **16** catalyzed by N-heterocyclic carbene **Cat-1** (Scheme 5).[19] The optimal conditions for this reaction involved stirring **15** and **16** in the presence of 20 mol% precatalyst **Cat-1** and DBU, in THF-*t*BuOH at room temperature for 6–8 hours under a nitrogen atmosphere. Under these conditions, the β-thiolactams **17** were obtained in excellent yields with high



Scheme 5 N-Heterocyclic carbene-catalyzed synthesis of thiolactams from aryl isothiocyanates and nitroalkenes.

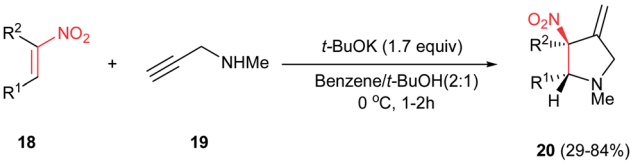
diastereoselectivity (up to 96 : 4) in favor of the *cis* isomer. Aromatic and aliphatic nitroalkenes were compatible in this process.

4. Synthesis of five-membered heterocycles

4.1. Synthesis of N-heterocyclic compounds

4.1.1. Pyrrolidine derivatives. Pyrrolidine rings are present in the structure of numerous natural products, pharmaceuticals, and bioactive molecules with different biological activities.[20] Also, they have a wide range of applications as organocatalysts, building blocks in organic synthesis, chiral auxiliaries, and ligands for asymmetric synthesis.[21] Many syntheses of pyrrolidines have been reported.

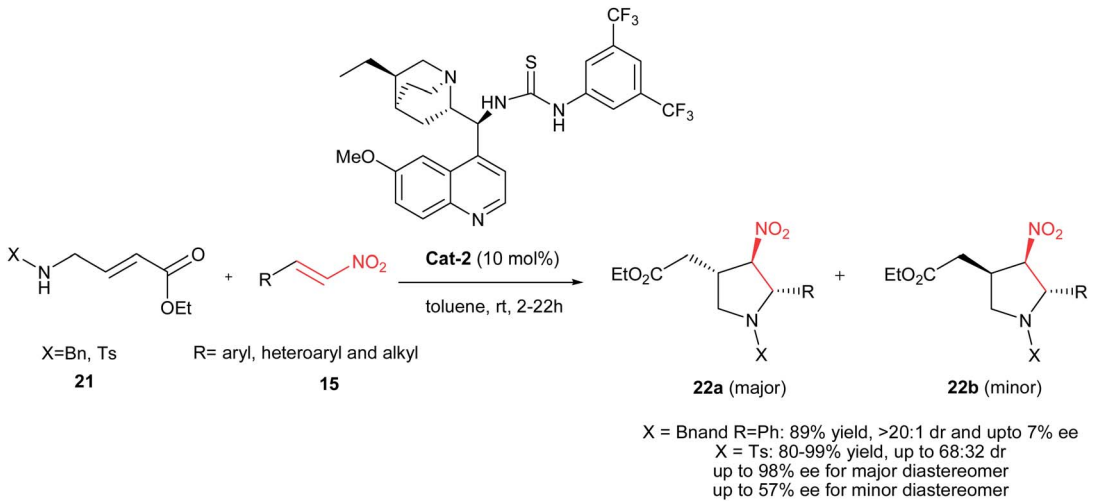
Nitroalkenes were applied as efficient starting materials for synthesis of pyrrolidine derivatives. In this context, reaction of nitroalkenes **18** and *N*-methylprop-2-ynyl amine **19** was investigated by Rodriguez *et al.* for the regio- and distereoselective synthesis of the 3-methylenepyrrolidines **20** *via* Michael addition/5-*exo* intramolecular nucleophilic carbocyclization cascade (Scheme 6).[22]



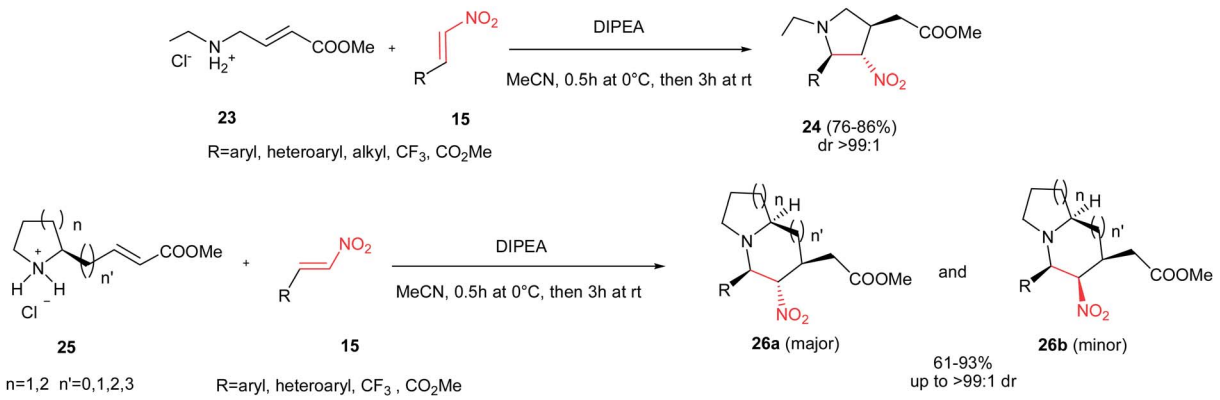
Scheme 6 3-Methylenepyrrolidines *via* Michael addition/5-*exo* intramolecular nucleophilic carbocyclization cascade

Kanger *et al.* demonstrated a new asymmetric synthesis of chiral pyrrolidines **22** with three stereocenters from 4-aminocrotonate **21** and nitroolefins **15** in the presence of 10 mol% bifunctional thiourea catalyst **Cat-2**.[23] The selectivity of the reaction is highly dependent on the substituent on the nitrogen atom of the aminocrotonate. While, the reaction with *N*-benzyl substituted reagent proceeds in high diastereoselectivity (>20 : 1) toward **22** with low enantioselectivity (ee up to 7%), the *N*-tosyl crotonate affords products with moderate diastereoselectivity (**22a : 22b** up to 68 : 32) but with high enantioselectivity in the case of major *trans–trans*-isomers **22a** (ee from 92% to 98%) and ee up to 57% for the minor *trans–cis*-isomers **22b** (Scheme 7). Aromatic, heteroaromatic and aliphatic nitroalkenes work equally well in this procedure. The absolute configuration of both isomers was examined *via* derivatization with Mosher's and mandelic acids, with the relative stereochemistry being determined *via* NMR analysis.

The same strategy was applied by Shi *et al.* for preparation of substituted pyrrolidines **24** through the reaction of amine **23** and nitroalkenes **15** with high yields and excellent diastereoselectivities (up to >99 : 1 dr) using Hünig's base (DIPEA) (Scheme 8).[24] The reaction proceeded *via* aza-Michael/Michael reaction cascade. By using a cyclic amine **25**, the 5-5, 5-6, 6-5 or 6-6 bicyclic structures **26** can readily be prepared in good to excellent yields. Although the products were obtained with four stereogenic centers, the reaction exhibited excellent stereoselectivity with only two stereoisomers isolated (**26a** and **26b**) in a diastereomeric ratio of up to >99 : 1. The relative



Scheme 7 Synthesis of trisubstituted chiral pyrrolidines.



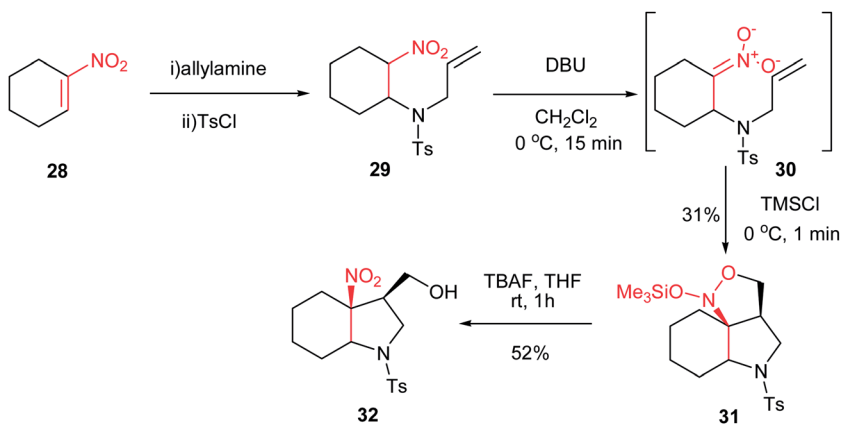
Scheme 8 Synthesis of pyrrolidine rings *via* cascade aza-Michael/Michael reaction.

stereochemistry was verified by NMR and confirmed by X-ray crystallography. β-Triflouromethylnitroethene **27** ($CF_3CH{=}CHNO_2$) also gave the similar cyclization products in excellent yields, which provided an interesting strategy to incorporate the CF_3 group into the N-heteroycles. The formation of 7- and 8-*exo*-trig cyclization products is also possible with poor isolated yields (<25%).

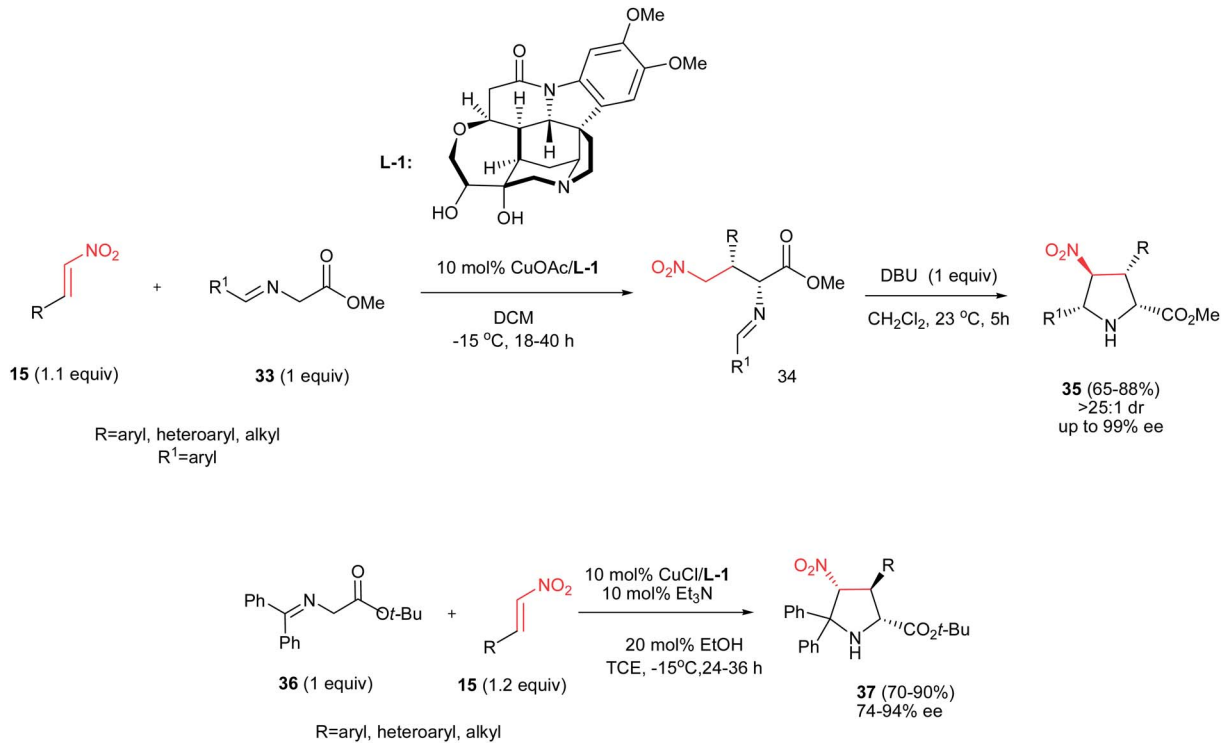
In 2005, Dulcere *et al.* reported a diastereoselective procedure for synthesis of fused 3-nitro-4-hydroxymethylpyrrolidine **32**. They described that silylation of nitronate **30**, prepared by an aza Michael addition of tosylallylamine to nitroalkene **28**, provided *N*-(silyloxy)-isoxazolidine **31** in 31% yield, which was then diastereoselectively converted to 3-nitro-4-hydroxymethylpyrrolidine **32** in 52% yield after desilylation (Scheme 9).[25]

Nitroalkenes were extensively applied in [3 + 2] cycloaddition reactions for synthesis of substituted chiral pyrrolidines with different stereogenic centers. In this context, a stepwise one-pot [3 + 2] cycloaddition reaction of glycine(ket)imines **33** or **36** with nitroalkenes **15** is investigated by Oh *et al.* as outlined in Scheme 10.[26] They described that Michael addition of glycine imines **33** to nitroalkenes **15** afforded exclusively *syn*-adducts **34** with excellent stereoselectivity (>25 : 1 dr, 97−99% ee) at −15 °C in CH_2Cl_2 when 10 mol% of CuOAc was used in combination with multidentate amino alcohol **L-1** as ligand. Intramolecular Mannich reaction of the crude reaction mixture of *syn*-adducts **34** in the presence of 1 equiv. of DBU at 23 °C afforded the *exo*-selective chiral pyrrolidines **35** in high yields and excellent diastereo- and enantioselectivities (>25 : 1 dr, 93−99% ee). Surprisingly, performing the reaction with the glycine ketimines **36** instead of glycine imines in the presence of 10 mol% CuCl/**L-1** and Et_3N, affords the *endo*-selective pyrrolidines **37** in high yield (65–88%) and enantioselectivity (74–93% ee). The reaction is applicable to a wide range of aromatic, heteroaromatic, and aliphatic nitroalkenes.

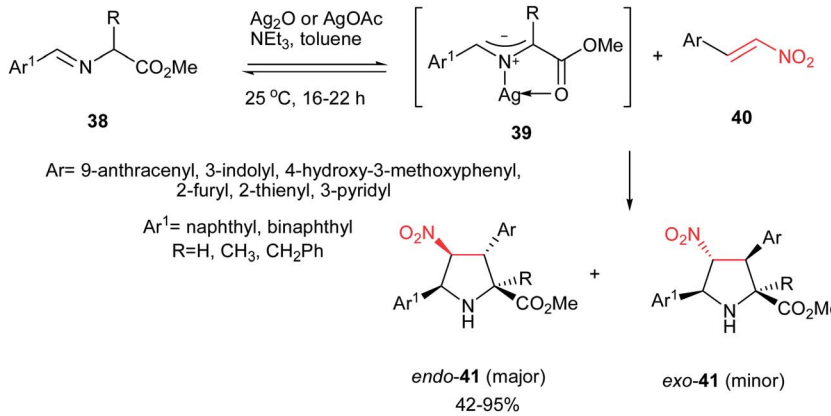
In 2008, Grigg *et al.* described that 1,3-dipolar cycloaddition reaction of imines **38**, prepared from natural aminoacids and aldehydes, with nitroalkenes **40** in the presence of 10 mol% of AgOAc or Ag_2O and NEt_3 afforded the *endo*-selective pyrrolidine adducts **41** in high to excellent yields (Scheme 11).[27] The reactions occurred *via* concerted cycloaddition of the *in situ* generated argento azomethine ylides **39** to *E*-nitroalkenes **40** *via endo*-transition states. Imines generated from glycine, alanine, and phenylalanine were used successfully in this process. Nitroalkenes with aromatic and heteroaromatic groups are well tolerated. With using the cyclic imine **43**, prepared from homoserine lactone **42**, the corresponding spiro nitropyrrolidines **45** were obtained in good to high yields as mixture of diastereomers **45a** and **45b** (Scheme 12).



Scheme 9 Diastereoselective synthesis of fused 3-nitro-4-hydroxymethylpyrrolidine.



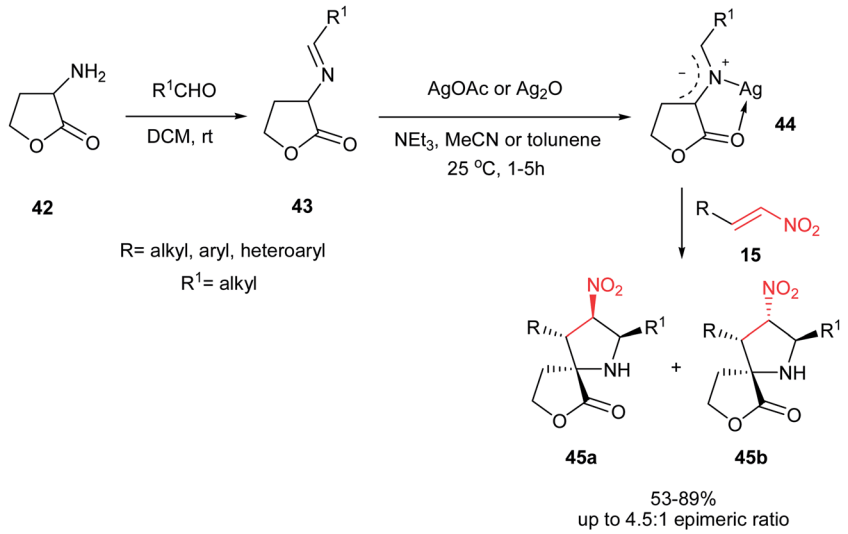
Scheme 10 Cu(I)-catalyzed asymmetric synthesis of pyrrolidine derivatives.



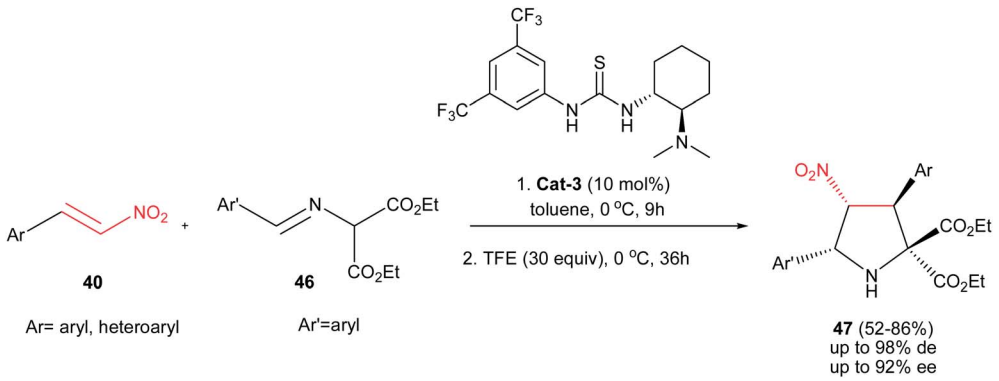
Scheme 11 Ag(I)-catalysed azomethine ylide cycloadditions with nitroalkenes.

Better yields and stereoselectivities (up to 98 : 1 : 1 dr and 92% ee) were obtained in the reaction of azomethine ylides **46** with nitroalkenes **40** using Takemoto catalyst **Cat-3** (Scheme 13).[28] The reaction proceeds in a stepwise manner consisting of Michael addition and subsequent intramolecular aza-Henry reaction. While the first step accelerated by thiourea catalyst (10 mol%) in ethanol at 0 °C, the later step was promoted by addition of 2,2,2-trifluoroethanol (30 equiv.) to the reaction mixture and completed after stirring for additional 36 h at the same temperature. Without TFE, the reaction stopped in the first step. Although the electronic nature of substituents on the phenyl ring of nitroalkenes does not have significant effect on the outcome of the reaction, lower ee's were observed with increasing the electron-donating properties of the substituents on the imines.

The one-pot three-component asymmetric [3 + 2] cycloaddition of aldehydes **47**, diethyl α-aminomalonate **48**, and nitroalkenes **40** is also investigated by Chen *et al.* affording highly substituted pyrrolidines **49** in high to excellent yields and stereoselectivities (Scheme 14) using 20 mol% of chiral thiourea catalyst **Cat-4**.[29] The reaction proceeded *via in situ* formation of azomethine ylides from the aminomalonate and the aldehyde, followed by 1,3-dipolar cycloaddition with the nitroalkene with complete endo selectivity (>99 : 1). It is notable that aliphatic aldehydes do not participate in this reaction.



Scheme 12 Ag(I)-catalysed asymmetric synthesis of spiro nitropyrrolidines.



Scheme 13 Asymmetric synthesis of functionalized pyrrolidines with Takemoto's bifunctional chiral thiourea.

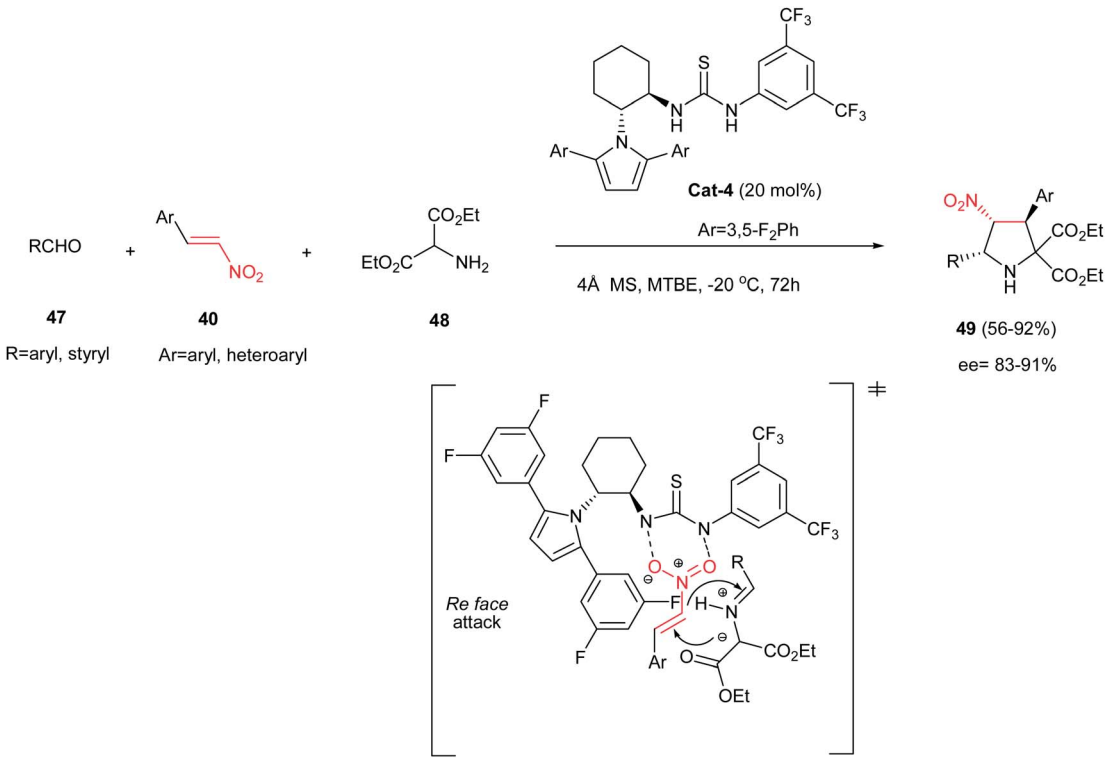
In another report, Gong *et al.* described the synthesis of highly substituted pyrrolidines **50** with diastereoselectivities of up to >99 : 1 and moderate enantioselectivities. The authors found that among the several cinchona alkaloid thiourea derivatives that were able to catalyze the reaction, catalyst **Cat-5** afforded the best results in terms of catalytic activity, diastereo- and enantioselectivities. It is notable that this method is limited to the use of only the imine of benzophenone derivatives (Scheme 15).[30]

In this context, Fukuzawa *et al.* have shown that AgOAc engaged with the chiral ferrocenyltriazole-based *P*,*S*-ligand **L-2** is another efficient catalytic system for asymmetric synthesis of pyrrolidine products **50** with the same starting materials (Scheme 16).[31] The pyrrolidine products **50** (major) were obtained as sole diastereomer in good yields with high enantioselectivities (up to 96% ee) along with Michael adducts as minor products.

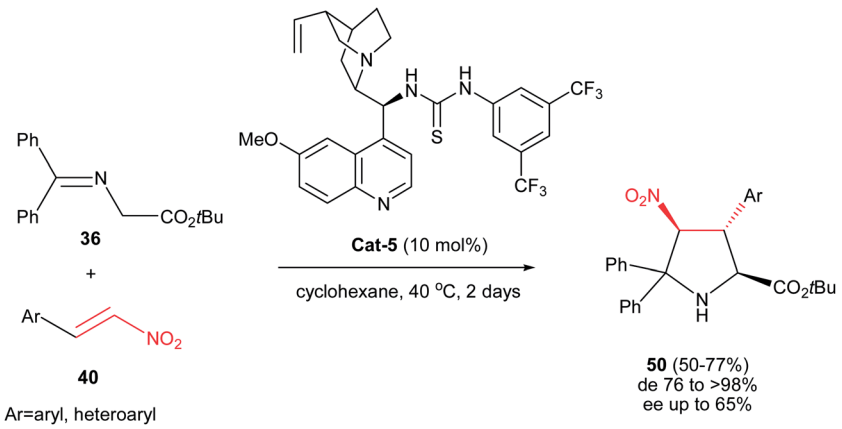
Hou *et al.* have shown that 10 mol% of $CuClO_4$ in combination with a chiral *P*,*N*-ferrocene ligand **L-3** is an efficient catalytic system for the asymmetric 1,3-dipolar cycloaddition of azomethine ylides **33** to nitroalkenes **15**. They confirmed that by varying the groups on the phosphorus in ligands, dramatic variations in diastereoselectivity can be observed. In this context, while *P*,*N*-ferrocene ligands with electron-rich aryl group on the P atom afford *exo*-selective pyrrolidine adducts *exo*-**51**, the corresponding ligands with electron-deficient aryl groups provide *endo*-selective adducts **51**. Aliphatic and aromatic nitroalkens gave similar results. The authors also examined that the Ag salts gave somewhat higher yields of the *endo* product compared to Cu salts, but in lower enantioselectivity (Scheme 17).[32]

Also, the same group described that 3-(fluoromethyl)-4-nitroproline derivatives **53** can be prepared in high yields and stereoselectivities (*exo* : *endo* up to 27 : 1; up to 97% ee) from azomethine ylides **52** and fluoromethyl-substituted nitroalkenes **15** in the presence of copper(I) perchlorate and a commercially available chiral Walphos ligand **L-4** (Scheme 18).[33] They have also shown that the products can be facilely reduced with $NaBH_4/NiCl_2$ into the corresponding 4-amino-3-(fluoromethyl)proline derivatives with retention of the enantioselectivity.

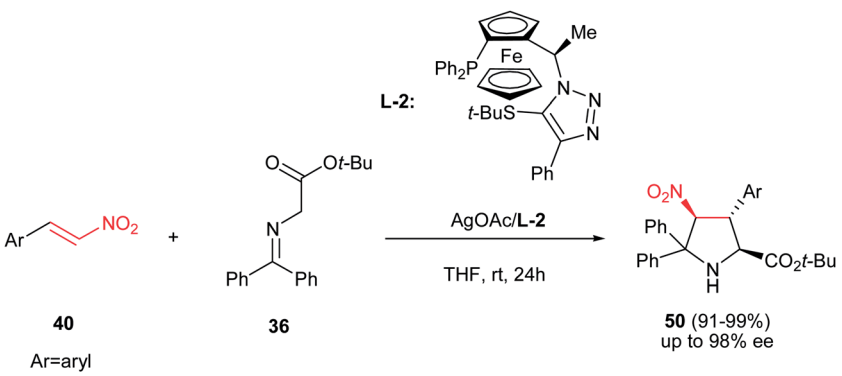
Recently, Xu *et al.* described that AgOTf (5 mol%) in combination with chiral bipyrrolidine-derived phosphine **L-5** as



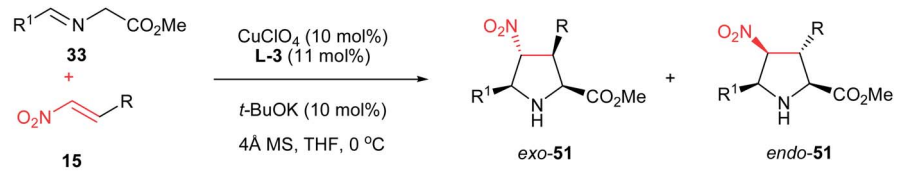
Scheme 14 Enantioselective three-component synthesis of polysubstituted pyrrolidines.

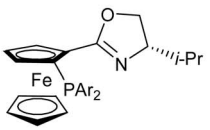


Scheme 15 The 1,3-dipolar cycloadditions of azomethine ylide generated from imine **36** with nitroalkenes **40** catalyzed by **Cat-5**.



Scheme 16 AgOAc/ferrocenyl triazole-based *P,S*-ligand for asymmetric synthesis of functionalized pyrrolidines.



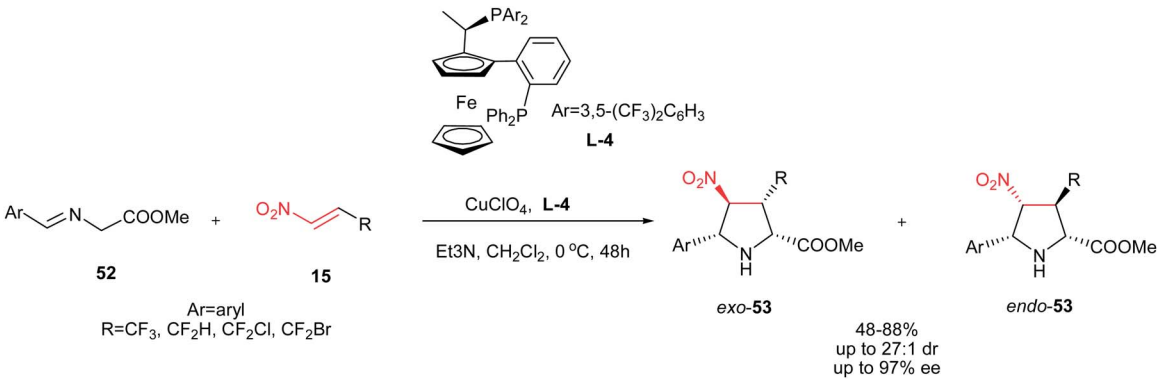


L-3a Ar=Ph
L-3b Ar=4-$CF_3C_6H_4$
L-3c Ar=4-$MeOC_6H_4$
L-3d Ar=3,5-$Me_2C_6H_3$
L-3e Ar=3,4-$(CF_3)_2C_6H_3$

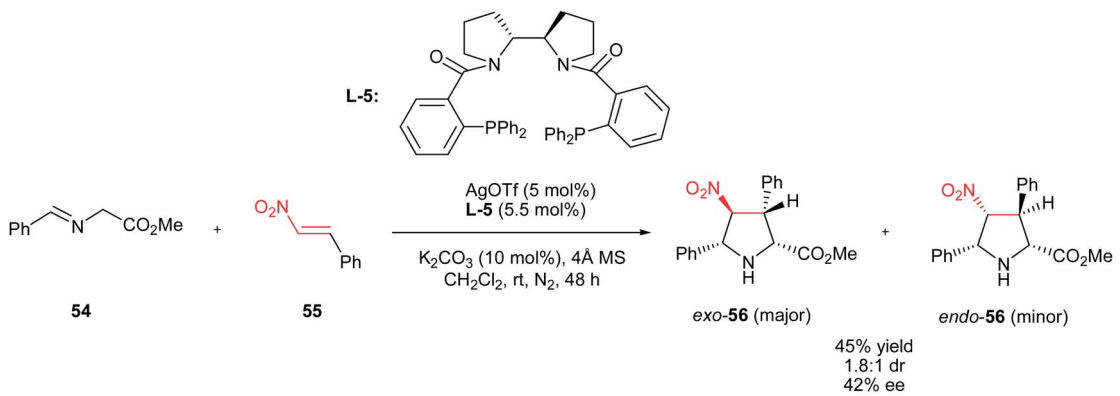
Reaction of **33** (R^1=Ph) and **15** (R=Ph) in the presence of different ligands

entry	ligand	yield (%)	*exo/endo*	ee (%)
1	**L-3a**	58	only *exo*	97
2	**L-3b**	67	73:27	95
3	**L-3c**	65	only *exo*	98
4	**L-3d**	49	only *exo*	98
5	**L-3e**	62	18:82	88

Scheme 17 Synthesis of chiral pyrrolidines promoted by $CuClO_4$ in combination with a chiral *P,N*-ferrocene ligand.



Scheme 18 Asymmetric synthesis of 3-(halogenated methyl)-4-nitroproline derivatives.



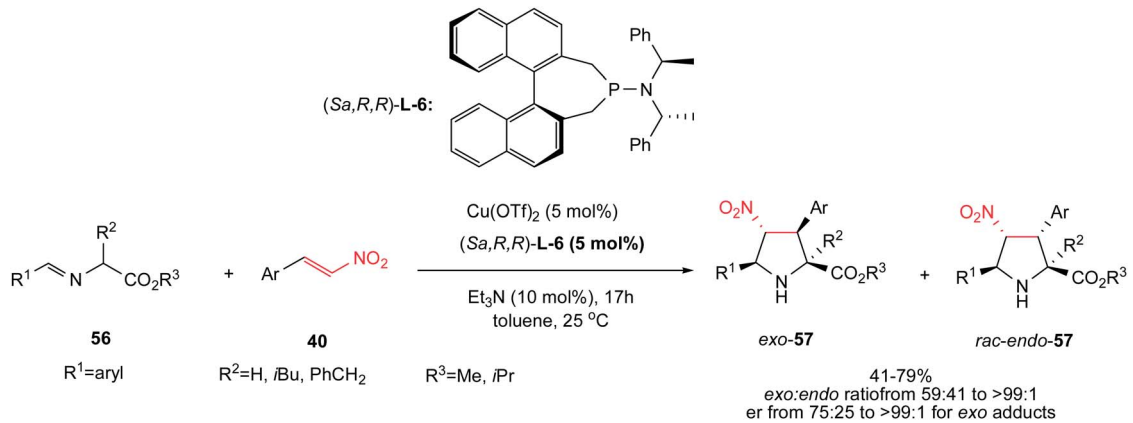
Scheme 19 Ag(I)/chiral bipyrrolidine-derived phosphine ligand for asymmetric [3 + 2] cycloaddition of azomethine ylide with nitroalkene.

ligand can also be applied for this transformation to give highly substituted pyrrolidines **56** in good yields with moderate diastereoselectivities and enantioselectivities (Scheme 19).[34]

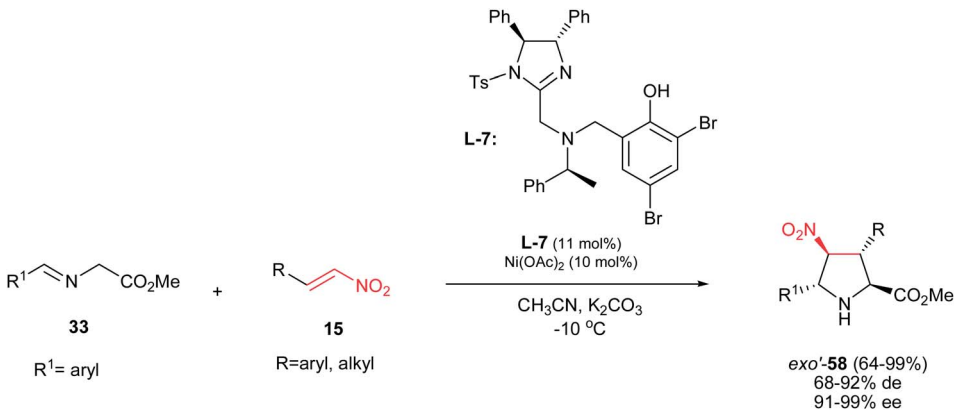
Another asymmetric protocol for synthesis of tetrasubstituted proline esters **57** is reported by Sansano and co-workers using $Cu(OTf)_2$ as catalyst, (S_a,*R*,*R*)-phosphoramidite **L-6** as chiral ligand and Et_3N as external base.[35] This chiral complex efficiently catalyzed the 1,3-dipolar cycloaddition reactions of azomethine ylides **56** and nitroalkenes **40** to give mainly the *exo*-cycloadducts *exo*-**57** (up to >99 : 1) in high er (75 : 25 to >99 : 1) at room temperature (Scheme 20). According to the authors suggestion, obtaining the Michael adducts at low temperatures supported a stepwise mechanism in this protocol. Aromatic substituents in both components are compatible in this procedure. When the imino ester of leucine and phenylalanine were applied, enantiomerically enriched *exo*-cycloadducts (>99 : 1 ee) were obtained in moderate yields without further recrystallization. When the enantiomeric ligand (R_a,*S*,*S*)-**L-6** was employed, the corresponding enantiomer of *exo*-**57** was mainly isolated.

When a *trans* nitroalkene is used in the [3 + 2] cyclization, the stereoconjunction between the 3- and 4-positions is fixed in a *trans* conformation, and four diastereomers are possible, classified as *endo*, *exo*, *endo*′, and *exo*′ isomers. In contrast to previous reports, the first *exo*′-selective synthesis of pyrrolidine derivatives **58** is reported by Arai *et al.* by using the $Ni(OAc)_2$ and ligand **L-7** in the reaction of nitrostyrenes **15** and iminoesters **33**. The products were obtained in high to excellent yields (64–99%), high diastereoselectivities (68–92%) and excellent ee's (91–99%) (Scheme 21).[36]

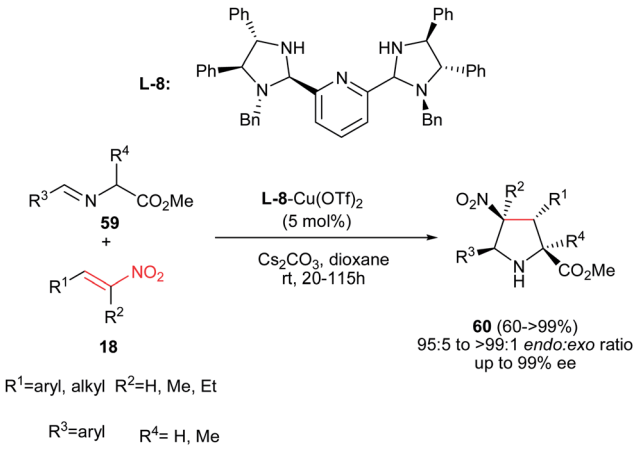
An *endo*-selective route for synthesis of pyrrolidine derivatives **60** was reported by Arai *et al. via* 1,3-dipolar cycloaddition of imino esters **59** with nitroalkenes **18** in the presence of *bis*(imidazolidine)pyridine (**L-8**)–$Cu(OTf)_2$ complex and a basic additive. The best reaction conditions were examined using 5 mol% of **L-8**-$Cu(OTf)_2$ chiral complex and Cs_2CO_3 in dioxane to afford the *endo*-selective pyrrolidines **60** in high to excellent yield.[37] Electron-donating and –withdrawing substituents on the phenyl ring of both R^1 and R^3 were equally effective in this procedure. Aliphatic nitroalkenes also gave similar results. Furthermore, trisubstituted nitroalkenes were also well tolerated to give the corresponding products having chiral quaternary carbon centers in 99% ee. The chiral quaternary carbon center at the 2-position of the pyrrolidine ring was also generated using alanine-derived imino ester. The stereochemistry of products was assigned as (2*S*,3*R*,4*S*,5*S*) by using (*S*,*S*,*S*,*S*)-pyridine–$Cu(OTf)_2$ catalyst (Scheme 22).



Scheme 20 $Cu(OTf)_2$ in combination with (S_a,*R*,*R*)-phosphoramidite for asymmetric synthesis of pyrrolidines.



Scheme 21 Ligand **L-7**/$Ni(OAc)_2$-catalyzed *exo*′-selective [3 + 2] cycloadditions.



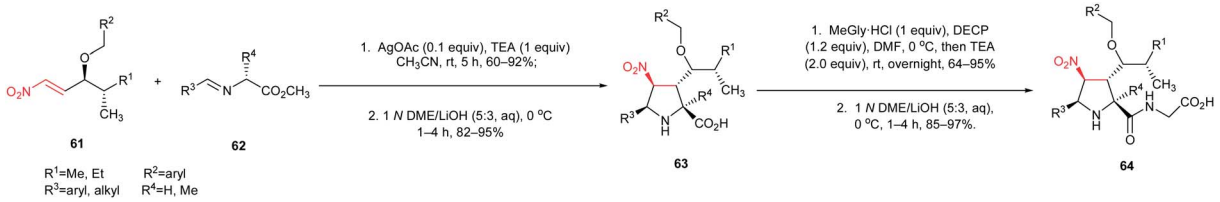
Scheme 22 Bis(imidazolidine)pyridine–Cu(OTf)$_2$ complex promoted an *endo*-selective synthesis of pyrrolidines.

The [3 + 2] cycloaddition of azomethine ylides with nitroalkenes was successfully applied for total synthesis of inhibitors of $\alpha_4\beta_1$-integrin-mediated hepatic melanoma metastasis **64** by Cossio and coworkers.[38] As shown in Scheme 23, the key step in the synthetic route is the formal [3 + 2] cycloaddition between *E*-nitroalkenes **61** and imines **62** to yield pyrrolidines **63** which is simply converted to biologically active compound **64**.

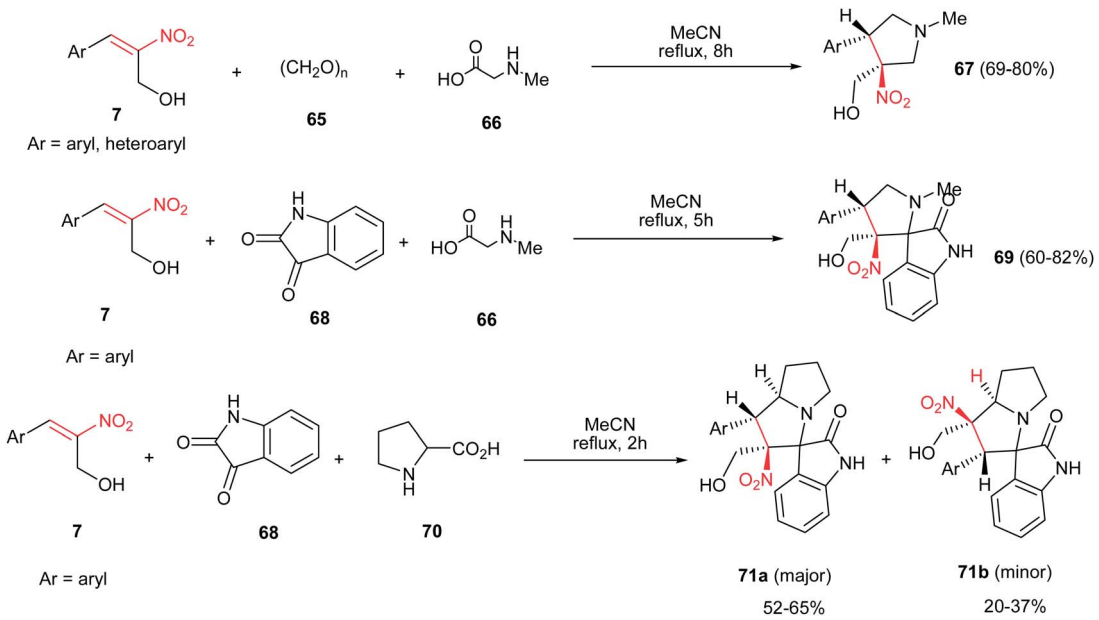
[3 + 2]-Cycloaddition reaction of (*E*)-2-nitro-3-phenylprop-2-en-1-ol **7**, with dipoles generated from paraformaldehyde **65** and sarcosine **66** gave the desired *N*-methylpyrrolidines **67** in 69–80% yields under catalyst-free conditions in refluxing acetonitrile (Scheme 24).[39] When isatin **68** was applied as carbonyl source, the corresponding desired 3-spiropyrrolidines **69** were obtained in very good yields (60–82%). In addition, the reaction of **7** with dipole generated from isatin **68** and proline **70** under the same reaction conditions provided the corresponding 3-spiropyrrolizidines **71a/b**.

Rios and Crovetto reported another catalyst-free route toward synthesis of 2,3,4,5-tetrasubstituted pyrrolidine derivatives **73** in high yields (76–99%) and in high diastereoselectivities (>25 : 1) from nitroolefins **15**, diethyl 2-aminomalonate **48**, and different aromatic aldehydes **72** (Scheme 25).[40] This is a simple and metal-free route for synthesis of pyrrolidine rings with three stereocenters. Surprisingly, the reaction in the presence of different additives such as triethylamine, thiourea, and chiral thioureas gave low diastereoselectivities.

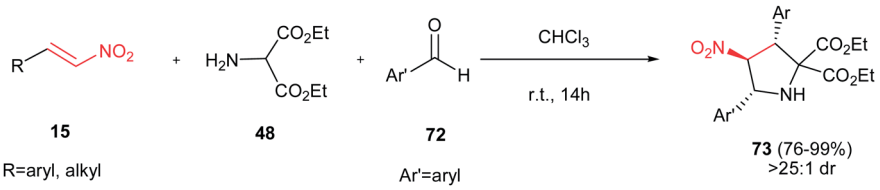
Also, Sarrafi *et al.* described that a one-pot *endo*-selective [1,3]-dipolar cycloaddition of nitrostyrenes **76** with 1,3-dipoles,



Scheme 23 Synthesis of inhibitors of $\alpha_4\beta_1$-integrin-mediated hepatic melanoma metastasis **64** starting with a nitroalkene.



Scheme 24 (*E*)-2-Nitro-3-phenylprop-2-en-1-ol in [3 + 2]-cycloaddition reaction.



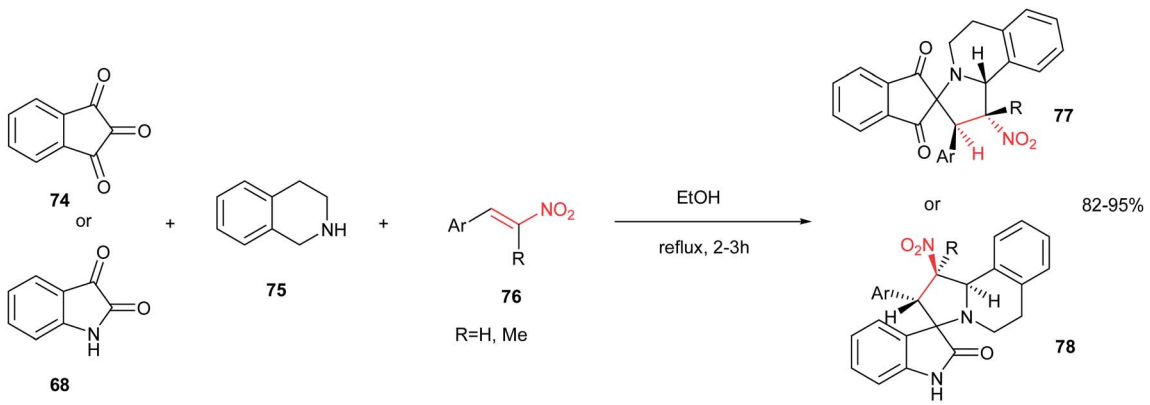
Scheme 25 Catalyst-free route toward synthesis of 2,3,4,5-tetrasubstituted pyrrolidines.

generated *in situ* from isatin **68** or ninhydrin **74** with 1,2,3,4-tetrahydroquinoline **75**, afforded a new series of spiroindolizidines **77–78** in high yield and stereoselectivity. The reaction was performed by stirring an equimolar amount of starting materials in ethanol at reflux temperature for 2–3 h (Scheme 26).[41]

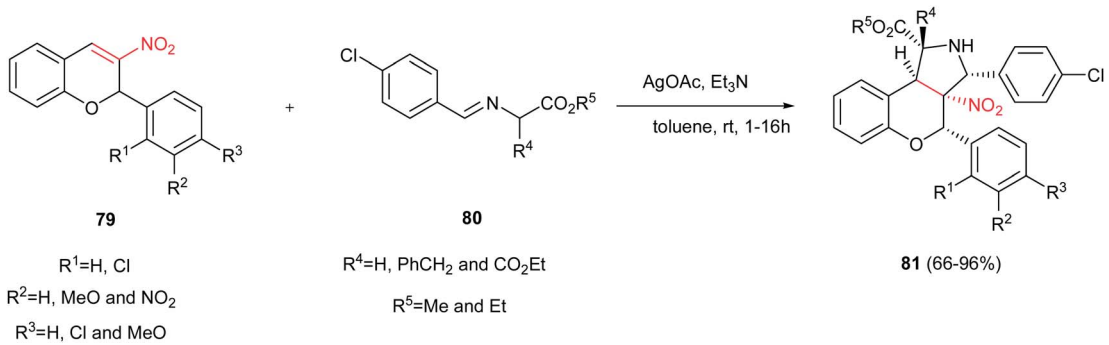
3-Nitrochromenes **79** were used as 2π components in the 1,3-dipolar cycloaddition reactions with various azomethine ylides **80** to achieve polysubstituted benzopyrano[3,4-*c*]-pyrrolidines **81** in the presence of AgOAc/Et_3N as catalyst (Scheme 27).[42] It is notable that the one-pot three-component reactions of 3-nitrochromenes, sarcosine or *N*-benzylglycine and aldehydes also afforded the corresponding cycloaddition products in refluxing toluene in high to excellent yields.

Recently, Xie *et al.* demonstrated that the kinetic resolution of 3-nitro-2*H*-chromenes **82** catalyzed by Takemoto's bifunctional chiral thiourea **Cat-3** afforded the enantioenriched (*R*)-3-nitro-2*H*-chromene derivatives (*R*)-**82** with moderate- to -good enantioselectivities (≤87% ee), along with the corresponding fused functionalized pyrrolidines **84** possessing four vicinal chiral carbon centers, with moderate enantioselectivities (≤70% ee), as shown in Scheme 28.[43]

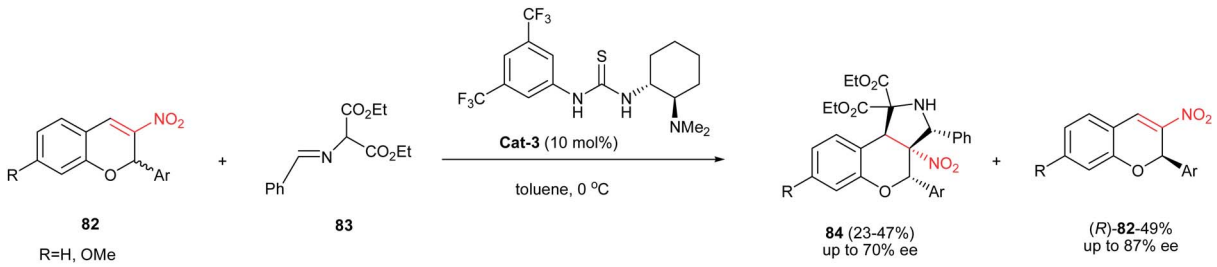
Finally, Du *et al.* reported a one-pot 1,3-dipolar cycloaddition of diethyl 2-aminomalonate **48**, benzaldehyde derivatives **85** and 3-nitro-2*H*-chromenes **86** in refluxing CH_2Cl_2 to give polysubstituted benzopyrano [3,4-*c*]-pyrrolidines **87** in excellent yields (83–99%) and high diastereoselectivities (up to >20 : 1) under catalyst-free conditions (Scheme 29).[44] It seems that the electronic and steric factors of substituent on the starting materials didn't have significant influence on the reaction yield. The configuration of the major isomer of products was determined with X-ray crystallographic analysis as *cis* for NO_2 group and benzene ring.



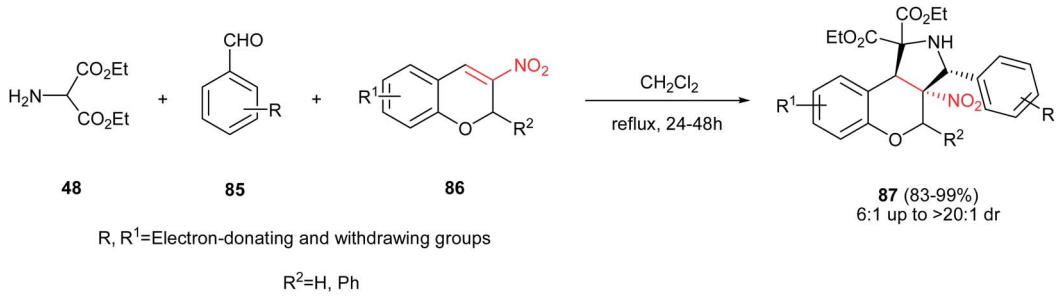
Scheme 26 Regioselective synthesis of spiroindolizidine.



Scheme 27 3-Nitrochromenes were used as 2π components in the 1,3-dipolar cycloaddition reactions with various azomethine ylides.



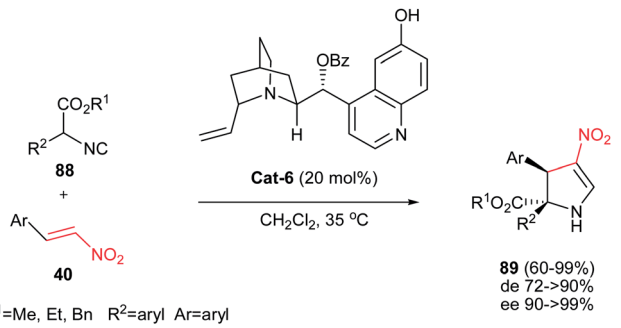
Scheme 28 Kinetic resolution of 3-nitro-2*H*-chromenes catalyzed by Takemoto's bifunctional chiral thiourea.



Scheme 29 One-pot 1,3-dipolar cycloaddition of diethyl 2-aminomalonate, benzaldehydes and 3-nitro-2*H*-chromenes.

4.1.2. Dihydropyrrole derivatives. There are three kinds of pyrrolines: 1-pyrrolines, 2-pyrrolines and 3-pyrrolines. There are numerous naturally and synthetically occurring biologically active compounds containing these pyrrolines.[45] Pyrrolines are versatile synthetic intermediates for synthesis of diversity of biologically active compounds especially pyrroles and pyrrolidines.[46] Several methods for construction of pyrroline derivatives were reported including 1,3-dipolar cycloaddition,[47] the reaction of α,β-diketones with acetamides,[48] ring-closing metathesis of diallyl amines,[49] nucleophilic addition of organometallic reagents,[50] selective oxidation or reduction of pyrrolinones and maleimide derivatives,[51] transition-metal-catalyzed coupling, oxidative or tandem process,[52] domino Heck-aza-Michael[53] and organocatalytic tandem Michael/cyclization sequence.[54]

Gong *et al.* reported an asymmetric tandem Michael-CH insertion process (formal [3 + 2] cycloaddition) for the synthesis of dihydropyrroles from nitroolefins and α-aryl isocyanoacetates catalyzed by 20 mol% of cinchona alkaloid **Cat-6**.[55] The corresponding chiral 2-pyrrolines were obtained in excellent enantioselectivity (90 to >99% ee) and useful diastereoselectivity. Several alkyl- and aryl-substituted nitroalkenes were examined and the best diastereoselectivity (up to 20 : 1) was obtained with electron-deficient aryl substituents (Scheme 30).

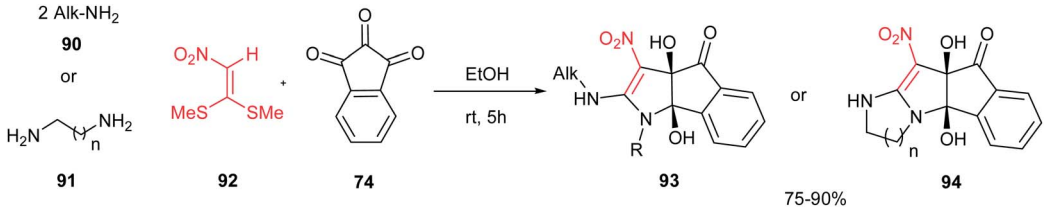


Scheme 30 [3 + 2] Cycloaddition of α-substituted isocyanoesters and nitroolefins catalysed by cinchona alkaloid.

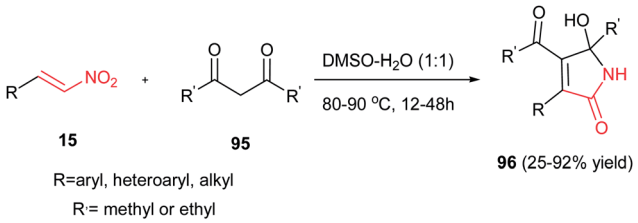
In 2011, an efficient approach for the synthesis of dihydroindeno[1,2-*b*]pyrroles **93** and indeno[2′,1′:4,5]pyrrolo[1,2-*a*]-fused 1,3-diazaheterocycles **94** was reported by Alizadeh *et al.* *via* a new and one-pot reaction between primary amines **90** or 1,*n*-diamines **91**, 1,1-bis-(methylthio)-2-nitroethene **92** and ninhydrin **74** in aqueous ethanol under mild conditions (Scheme 31).[56] The merits of this protocol are access to fairly high yields of the products without any catalyst, the ready availability of the starting materials, simple reaction conditions such as aqueous media at room temperature.

Usually, the reaction of 1,3-dicarbonyl compounds with nitroethylenes gave the Michael adducts and the hydroxyimino-substituted dihydrofuran derivatives. Surprisingly, Yu *et al.* demonstrated that heating the starting materials **15** and **95** in DMSO–H_2O (1 : 1) at 80–90 °C for 12–48 h under catalyst-free conditions affords 5-hydroxy-1,5-dihydro-2*H*-pyrrol-2-ones **96** as major products (Scheme 32).[57] They confirmed that aromatic nitroalkenes gave higher yields compared to aliphatic nitroalkenes.

4.1.3. Pyrrolidine-2-one and pyrroloindoles. Compounds containing the 2-pyrrolidinone (γ-lactam) rings have found significant applications in the treatment of epilepsy,[58] HIV,[59] viral hepatitis,[60] Alzheimer,[61] neurodegenerative diseases and depression.[62] Among the methods reported for the synthesis of



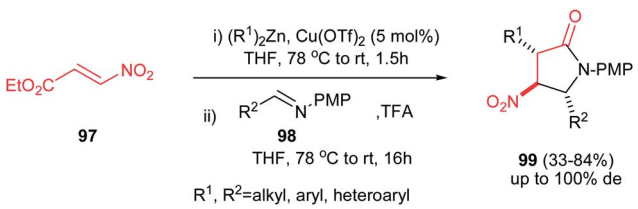
Scheme 31 Synthesis of dihyroindeno[1,2-*b*]pyrroles and indeno[2′,1′:4,5]pyrrolo[1,2-*a*]-fused 1,3-diazaheterocycles.



Scheme 32 A novel process for the synthesis of 5-hydroxy-1,5-dihydro-2*H*-pyrrol-2-ones.

2-pyrrolidinones, intramolecular amide bond formation,[63] expansion or contraction of a previously formed ring,[64] radical cyclization,[65] ring-closing metathesis,[66] cycloaddition reactions,[67] condensation of imines and cyanosuccinic anhydride[68] and reaction of *N*-arylidene-*N*-alkylamines with succinic anhydride are the most applicable approaches.[69]

Recently, Anderson *et al.* reported an efficient procedure for synthesis of 1,3,5-trisubstituted 4-nitropyrrolidin-2-ones **99** *via* $Cu(OTf)_2$-catalyzed Michael addition of diorganozinc reagents to nitroacrylate **97** followed by a subsequent aza-Henry/lactamization reaction with *N*-*p*-(methoxy)phenyl protected aldimines **98** (Scheme 33).[70] Different *N*-*p*-(methoxy)phenyl protected aldimines **98** derived from alkyl, aryl, and heteroaryl aldehydes were examined with high to excellent yields. Using the more electron-withdrawing protecting group such as *N*-Boc prevents the cyclization step due to the decreased availability of the nitrogen loan pair in the β-nitro-amine product. Also an enantioselective version of this reaction was performed in the presence of chiral BINOL ligand **L-9** and $Cu(OTf)_2$ to give the corresponding product **100** in high yield (74–80%) and enantioselectivity (89% ee) which could be recrystallized to afford enantiopure product in high yields (99% ee) (Scheme 34). Also, reduction of the nitro group and its protection was also performed to give the compound **101** in high yields.



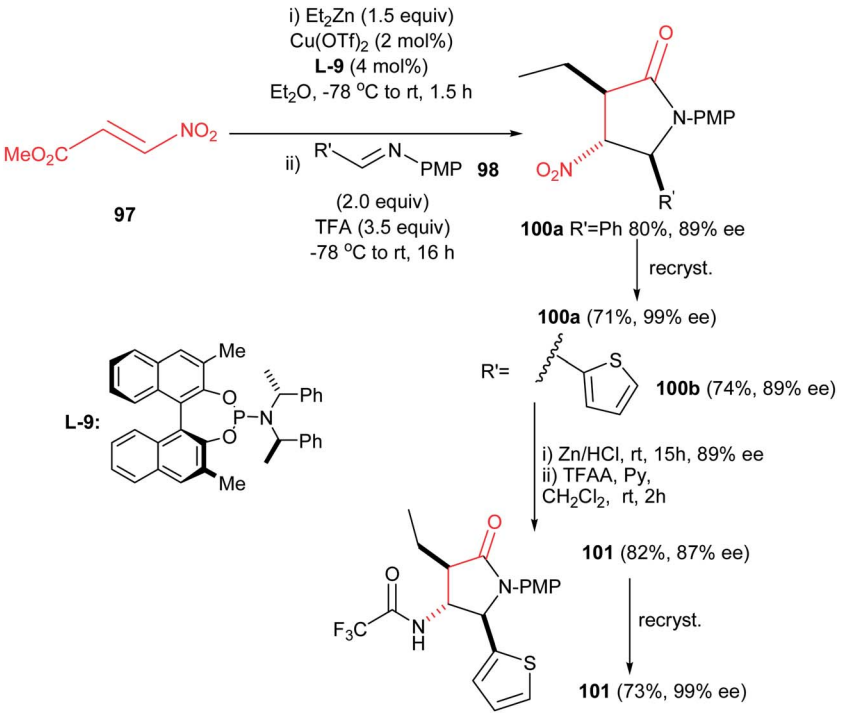
Scheme 33 Synthesis of 1,3,5-trisubstituted 4-nitropyrrolidin-2-ones.

Also, 1,2-*cis*-disubstituted 1*H*-pyrrolo[1,2a]indol-3(2*H*)-ones **106** have been synthesized in moderate to good overall yields (49–68%) by Enders *et al. via* a one-pot Michael addition–hemiaminalization–oxidation reaction employing simple aldehydes **102** and 2-nitrovinyl-substituted indoles **103** as substrates (Scheme 35).[71] This process is promoted by 15 mol% of (*R*)-diphenylprolinol TMS-ether **Cat-7** and AcOH (20 mol%) as additive with very high asymmetric induction to produce the stereoisomerically pure products (>98% de, >99% ee).

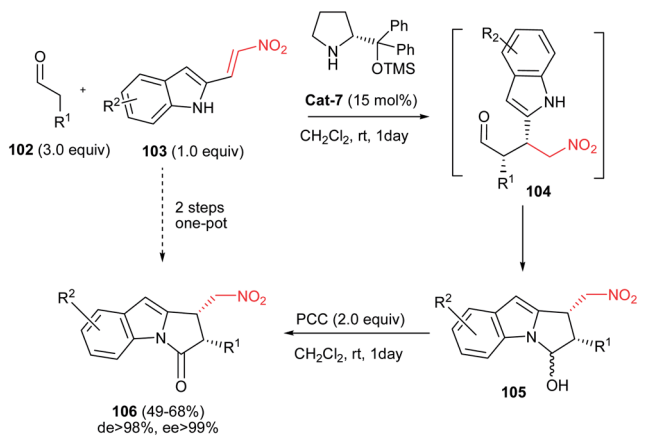
4.1.4. Pyrrole derivatives. Pyrroles are an important class of heterocycles present in the structure of many natural and synthetic bioactive molecules[72] with a wide range of applications in medicinal chemistry as antibacterial,[73] antiviral,[74] anti-inflammatory,[75] antitumour,[76] antioxidant[77] and antifungal[78] agents. Also, recently pyrroles have found extensive applications in the field of materials chemistry and as structural elements in molecular recognition studies.[79] As a result, a large number of methods have been reported for synthesis of pyrroles. Classical methods for synthesis of these nitrogen heterocycles include the Knorr,[80] Hantzsch,[81] and Paal–Knorr[82] reactions. Several other useful routes such as 1,3-dipolar cycloadditions of acetylenes with azomethine ylides,[83] metal-catalyzed,[84] reductive coupling,[85] aza-Wittig[86] and multicomponent reactions[87] were also developed for synthesis of highly substituted pyrroles.

Nitroalkenes were proved to be efficient starting materials for synthesis of pyrroles with different substitution pattern. In this context, the Ishii group reported a new approach to various tri- and tetrasubstituted pyrrole derivatives **108** from nitroalkenes **15** and imines **107** with using 5 mol% of $Sm(Oi\text{-}Pr)_3$ in refluxing THF (Scheme 36).[88] The nitro-group plays a double role in this transformation as activator of the alkene moiety toward Michael addition and as a leaving group during the aromatization step.

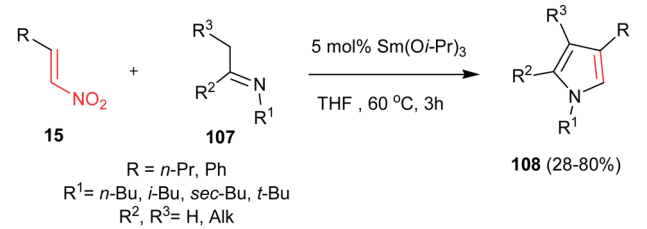
Guan *et al.* reported a simple and efficient procedure for synthesis of 2,3,4,5-tetra-substituted pyrroles **111** in good yields from enamine **109** and nitroalkenes **110** promoted by $FeCl_3$ (Scheme 37).[89] According to the proposed mechanism, the reaction proceeds *via* Michael addition of **109** to **110** to furnish the adduct **112**, which undergoes cyclization into intermediate **113**. Finally elimination of HNO and water provides tetrasubstituted pyrroles **111** bearing a variety of aryl substituents at the C4 atom. The one-pot four-component fashion of this work is also developed by Jana and co-workers with using $FeCl_3$ as catalyst[90] and by Pal and co-workers with using $(PPh_3)_2PdCl_2$.[91] They have used a nitroalkane and a carbonyl group instead of nitroalkenes.



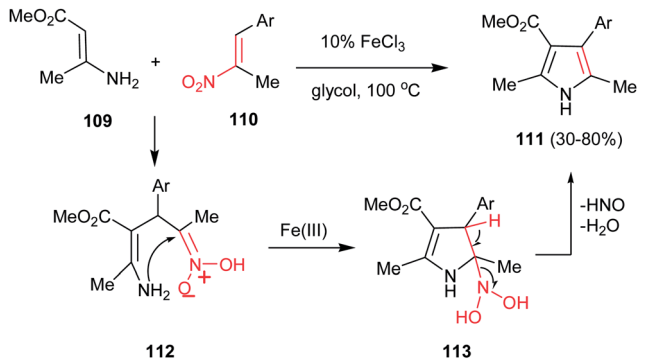
Scheme 34 Enantioselective conjugate addition/nitro-Mannich/lactamization reactions.



Scheme 35 Asymmetric synthesis of pyrrolo[1,2a]indolones from aldehyde and 2-nitrovinyl 1-substituted indoles.



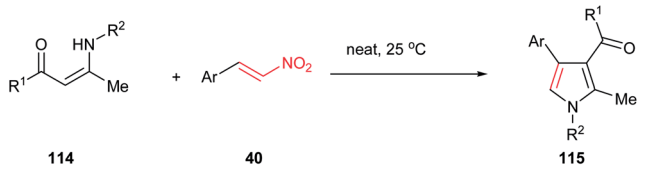
Scheme 36 $Sm(O\textit{i}\text{-}Pr)_3$-promoted synthesis of functionalized pyrroles from imines and nitroalkenes.



Scheme 37 $FeCl_3$-catalyzed synthesis of functionalized pyrroles from enamines and nitroalkenes.

In addition, an eco-friendly procedure for synthesis of 1,2,3,4-tetrasubstituted pyrroles **115** from enaminones **114** and β-nitrostyrenes **40** under solvent- and catalyst-free conditions is developed by Yavari *et al.* The products were obtained in high to excellent yields (Scheme 38).[92] Very recently, these products were also prepared in 68–93% yield by using Ph_3PAuCl and AgOTf in methanol. This protocol tolerated enamines derived from both aliphatic and aromatic amines.[93]

Another environmentally benign procedure for synthesis of fully substituted pyrroles **117** is reported by Guan *et al. via* condensation of nitroalkenes **76** and enaminoesters **116** in CH_3OH at 120 °C without using any catalyst (Scheme 39).[94] Diversities of nitroalkenes and enaminoesters were applied in this protocol to give the corresponding products in high to excellent yields. This protocol allows preparation of *N*-aryl,



Scheme 38 A catalyst-free procedure for synthesis of 1,2,3,4-tetra-substituted pyrroles.

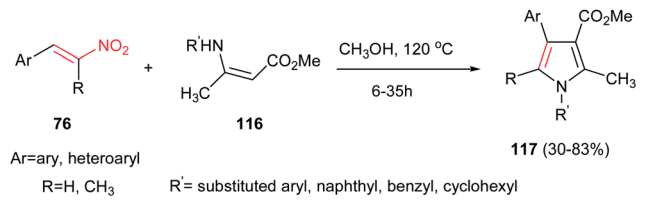
benzyl or cyclohexyl substituted pyrroles in high to excellent yields. The authors confirmed that electron-rich enaminoesters and nitroalkenes gave better results compare to electron-deficient ones. Also, enaminones gave lower yield than enaminoesters under similar conditions.

In this context, Ballini *et al.* described another green procedure for synthesis of pyrroles **120** in high to excellent yield with acceptable *E*-factor from β-nitroacrylates **118** and β-enaminones **119** under solvent- and catalyst-free conditions (Scheme 40).[95] They examined that varieties of nitroacrylates with different alkyl substituents are tolerated in this protocol. Also, this procedure gave higher yield for enaminones compared to previous one.

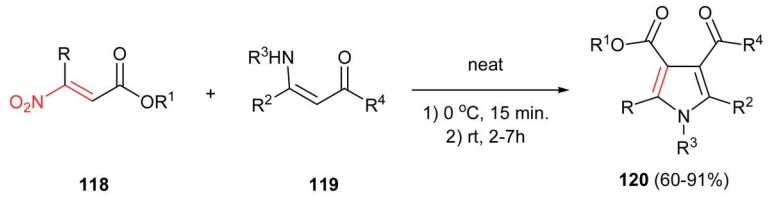
In 2012, Paul and Das described the coupling of nitroalkenes **40** with 4-aminocoumarin **121** to give the coumarin fused pyrrole derivatives **122** in high yields using PEG–SO_3H, as a biodegradable, polymer supported catalyst in methanol at 80 °C (Scheme 41).[96] The catalyst efficiently promoted the Michael addition and intramolecular cyclisation with the concomitant removal of the nitro group. The catalyst was recycled for five times without loss of catalytic activity. Also a wide variety of Lewis or Bronsted acids such as $ZnCl_2$, $AlCl_3$, I_2, $FeCl_3$, $InCl_3$, *p*-toluenesulphonic acid were used, but the results were less impressive when compared to PEG–SO_3H catalyzed reaction. This approach can be also applied to 6-aminouracil for synthesis of the corresponding uracil fused pyrroles. In addition, they proved that three component coupling reaction of 4-aminocoumarin, benzaldehyde and nitromethane using nitromethane as solvent is not very much efficient.

Sosnovskikh and co-workers reported an efficient approach for synthesis of 8,9-dihydro-6*H*-chromeno[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinoline derivatives **126**, as main skeleton of lamellarin alkaloids, from the reaction of 3-nitro-2-(trifluoromethyl)-2*H*-chromenes **123** and 1-methyl(benzyl)-3,4-dihydroisoquinolines **124** (Scheme 42).[97] Two routes were developed for this transformation; the first path is mixing of the starting materials in toluene at room temperature to give the Michael adducts **125** and refluxing the isolated Michael adducts in isobutanol, and the second procedure is direct refluxing the starting materials in isobutanol. The first route gave higher yield compared to second one. With replacing the CF_3 group with CCl_3 or aryl groups, the Michael adducts were isolated as diastereomeric mixtures even in refluxing isobutanol. When benzofused chromenes **127a,b** were used in the reaction with **124** (R^4 = 4,5-$(MeO)_2C_6H_3$), only **127a** gave the desired product in 94% yield and no product was obtained with **127b**, which may be the result of unfavourable steric interactions between the R^4 and benzene ring in **127b**.

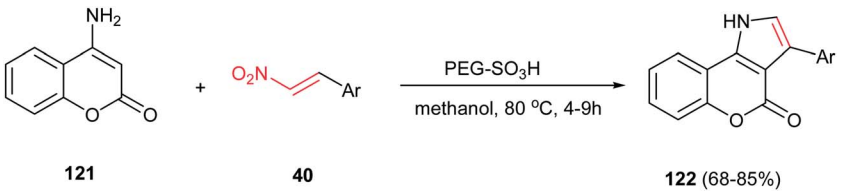
A one-pot three-component reaction of pyridinium/isoquinolinium ylide, generated *in situ* from pyridine/isoquinoline **129a/b** with bromoacetonitrile or ethyl bromoacetate **128**, with β-nitrostyrenes **40** in the presence of Et_3N at ambient temperature is investigated by Perumal *et al.* (Scheme 43).[98] They ascribed that while **128** (X = CN) afforded the 1-nitro-2-aryl-3-indolizine carbonitriles **130a** and 1-nitro-2-arylpyrrolo[2,1-*a*]isoquinoline-3-carbonitrile **130b** *via* reaction with pyridine and isoquinoline, respectively, the **128** (X = CO_2Et) provided the ethyl 2-aryl-1-nitroindolizine-3-carboxylates **131a** and ethyl 2-arylpyrrolo[2,1-*a*]isoquinoline-3-carboxylates **131b**. Different bases such as Et_3N, DBU, DMAP, piperidine and K_2CO_3 were examined in this procedure and the maximum yields (44–80%) were obtained employing a molar equivalent of Et_3N. Nitrostyrenes with different substitutions on the phenyl ring were used successfully in this reaction. It is very interesting to note that other regioisomers were not observed. Notably, these products displayed good activity against Mycobacterium tuberculosis H37Rv.



Scheme 39 Catalyst-free synthesis of fully substituted pyrroles from nitroalkenes and enaminoesters.

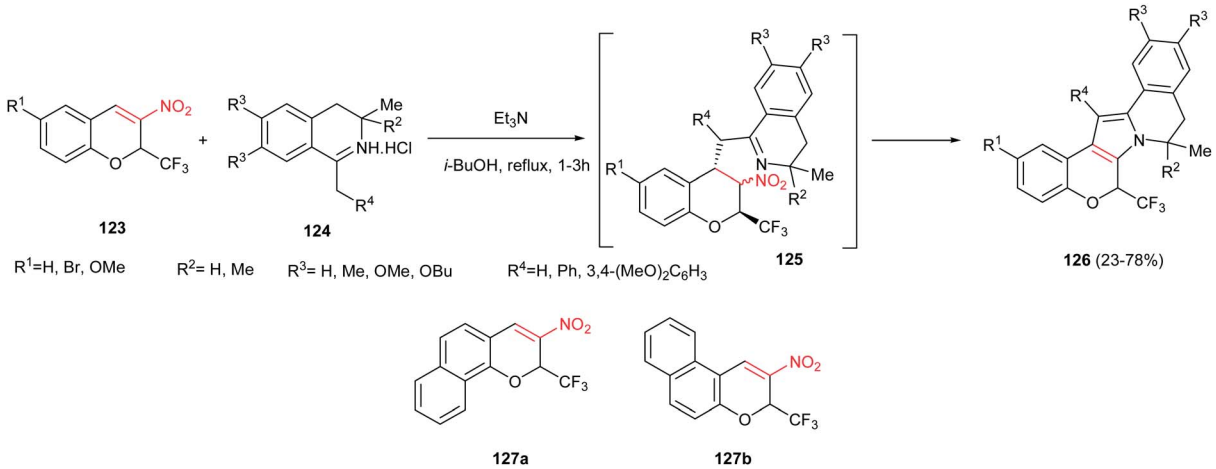


Scheme 40 Synthesis of pyrroles from β-nitroacrylates and β-enaminones under solvent- and catalyst-free conditions.



121 40 **122** (68-85%)

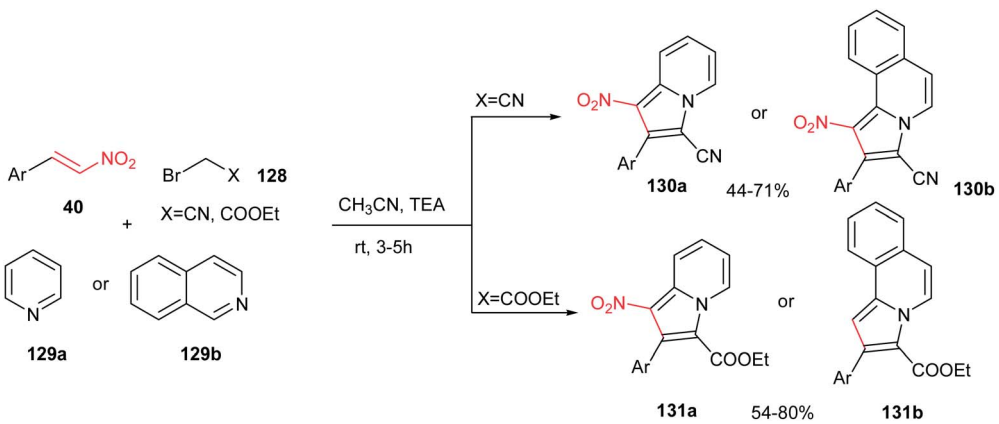
Scheme 41 PEG–SO_3H promoted synthesis of pyrrole core containing coumarins.



123 124 125 **126** (23-78%)

127a **127b**

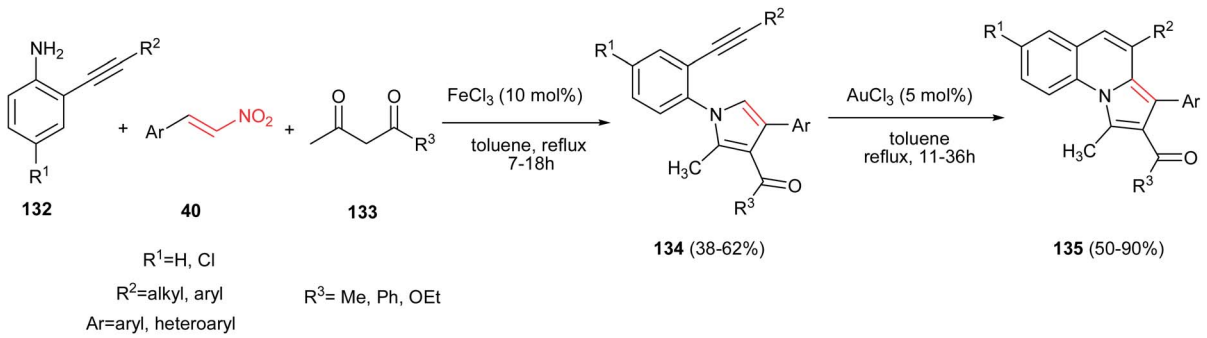
Scheme 42 Synthesis of the pentacyclic lamellarin skeleton.



Scheme 43 Synthesis of indolizines and pyrrolo[2,1-*a*]isoquinolines.

A two step procedure for synthesis of pyrrolo[1,2-*a*]-quinoline derivatives **135** is reported by Jana and coworkers. The first step is a one-pot three-component synthesis of *N*-(2-alkynylaryl)pyrroles **134** from anilines **132**, 1,3-dicarbonyl compounds **133** and nitroalkenes **40** promoted by 10 mol% of $FeCl_3$ and the second step is transformation of the pyrrol adducts **134** to pyrrolo[1,2-*a*]-quinoline derivatives **135** *via* treatment with 5 mol% of $AuCl_3$ in toluene at reflux temperature (Scheme 44).[99] The products exhibited fluorescence activity in a range from 452 to 465 nm with quantum efficiencies (Φ) ranging from 0.033 to 0.067.

In addition, 2,3,4,5-tetrasubstituted *NH*-pyrroles **138** were synthesized by Guan *et al.* *via* condensation of the Blaise reaction intermediate **137** and nitroolefins **76** catalyzed by 20 mol% $FeCl_3$ in THF at reflux temperature.[100] The reaction was carried out by formation of the Blaise intermediate by nucleophilic addition of an *in situ* generated Reformatsky reagent to an alkyl (aryl)nitrile **136** in THF, followed by addition of nitroalkenes **76** and $FeCl_3$ (20 mol%) and refluxing the mixture for additional times until completion (Scheme 45). Other iron salts such as $FeCl_2$, $FeCl_3$, $FeSO_4$, $Fe(acac)_2$ and $Fe(acac)_3$ and other Lewis acids such as $ZnBr_2$, $Cu(OTf)_2$ and $Yb(OTf)_3$ were also examined and afforded lower yield than $FeCl_3$. While this protocol is insensitive to electronic effects of the aromatic nitriles and nitroalkenes, steric effects in nitriles (*ortho*



Scheme 44 Two-step synthesis of pyrrolo[1,2-*a*]-quinolines.

substituted benzonitriles) had a significant influence on the reaction yield. Vinyl nitriles and aliphatic nitriles are suitable substrates for this transformation. Nitrostyrene gave lower yield (42%) than α-substituted nitroolefins.

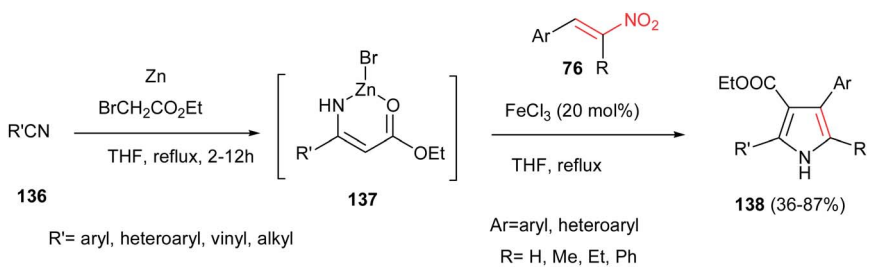
Accordingly, Lu, Wang, and co-workers reported the synthesis of highly substituted pyrroles **141** with acyl group on the C-2 position from α-diazoketones **139**, nitroalkanes **18**, and amines **140** in the presence of 10 mol% of CuOTf (Scheme 46).[101] The authors proposed that N–H insertion of α-diazoketone **139** with amine **140** furnished intermediate **A**, which underwent oxidative dehydrogenation by Cu(I) under aerobic conditions to generate the azomethine ylide **B**. Subsequent [3 + 2] cycloaddition of the formed azomethine ylide **B** with nitroalkene **18** afforded the pyrrolidine ring **C**. Finally, thermal extrusion of HNO_2 and dehydrogenative aromatization of the pyrrolidine ring gave the corresponding products **141**.

Ranu *et al.* developed another approach to substituted pyrroles **142** by coupling of an aldehyde/ketone **102/143**, an amine **90** and an α,β-unsaturated nitroalkene **76** on the surface of alumina without any solvent under MW irradiation (Scheme 47).[102] In this procedure, the presence of α-substituent on nitroalkene seems to be crucial for completion of reaction, since its absence takes the reaction along different pathways. It is also examined that open chain ketones led to different reaction products. Cyclic ketones **143** are suitable in this procedure to generate the fused pyrroles **144** in high yields. Also, the same group developed another approach for synthesis of these compounds in molten tetrabutylammonium bromide at 105 °C.[103]

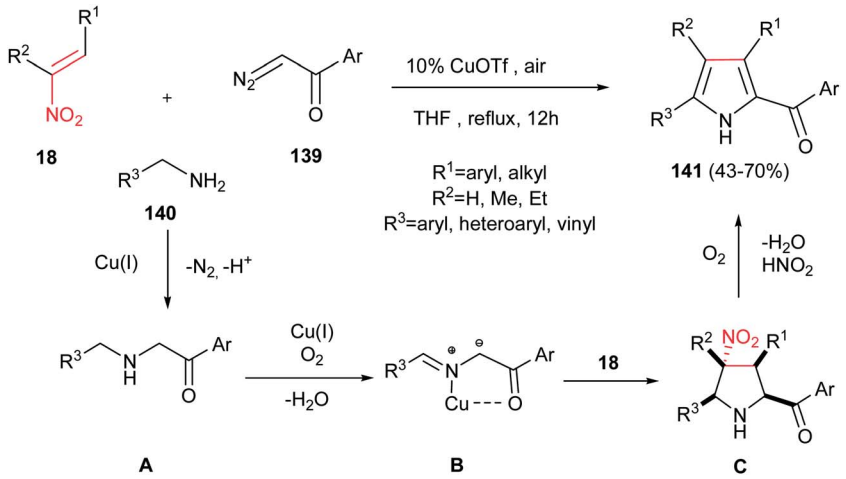
Very recently, Telvekar *et al.* introduced (diacetoxyiodo)-benzene (DIB) as efficient catalyst for synthesis of 1,2,3,4-tetrasubstituted pyrroles **147** from amines **145**, nitrostyrenes **40** and acetylacetone **146**. The reaction was performed by stirring the mixture of an aniline (2 equiv.), a nitroalkene (1 equiv.), and acetylacetone (1.2 equiv.) in ethanol for 10 min, followed by addition of DIB (1 equiv.) and refluxing for 3–4 h (Scheme 48).[104] Anilines, benzyl amines and cyclohexylamine were employed to afford the corresponding products in high to excellent yields. Electronic nature of the substituents on the nitrostyrenes had no effect on yields.

Microwave-assisted synthesis of highly substituted pyrroles **148** from nitroalkenes **18**, 1,3-dicarbonyl compounds **133** and amines **145** using inexpensive $CeCl_3 \cdot 7H_2O$ as catalyst is reported by Silveria, Kaufman and co-workers (Scheme 49).[105] Other Ce^{III} salts such as $Ce(NO_3)_3$, $Ce(OTf)_3$ and $(NH_4)_2Ce(NO_3)_6$ gave lower yield in this protocol. Nitroalkenes with electron-donating group on benzene ring afforded higher yield than those with electron-withdrawing groups. Cyclic 1,3-dicarbonyls such as dimedone, Meldrum's acid and 1,3-cyclohexanedione did not afford the expected products. With aliphatic amines, lower yields were achieved.

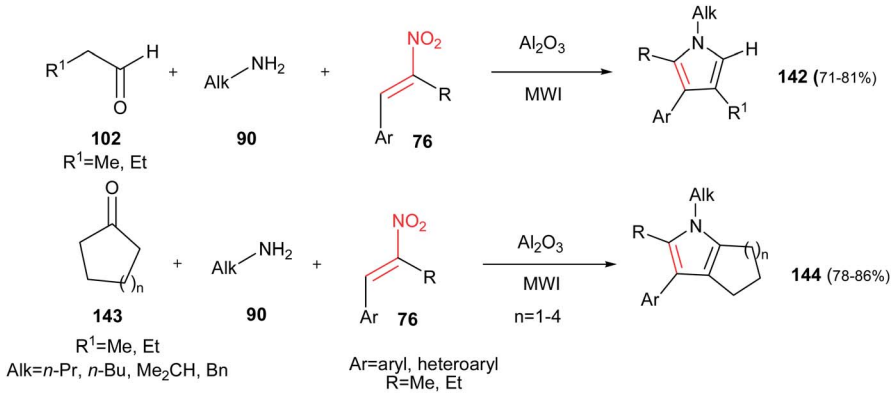
Fully substituted pyrrole derivatives **151** with a carboxamide group on the C-3 position were prepared by Alizadeh *et al. via* a one-pot four-component operation from primary amines **90/90′**, diketene **150** and nitrostyrenes **149** (Scheme 50).[106] The reaction proceeds *via* formation of an enaminone from two primary amines and diketene, followed by condensation of this enaminone with nitrostyrene. Not only linear amines, but also *iso*-butyl amine and *tert*-butyl amine were examined with excellent yields. The merits of this method are performing the reaction under neutral and catalyst-free conditions, simple workup, ambient reaction temperature, and excellent yields.



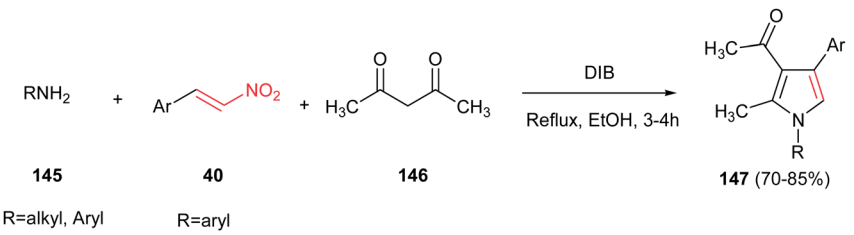
Scheme 45 2,3,4,5-Tetrasubstituted *NH*-pyrroles from Blaise reaction intermediate and nitroolefins.



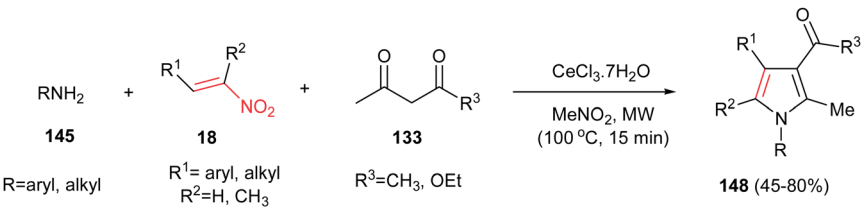
Scheme 46 CuOTf-catalyzed synthesis of substituted pyrroles from nitroalkenes, α-diazoketones and amines.



Scheme 47 Substituted pyrroles from an aldehyde/ketone, an amine and a nitroalkene.



Scheme 48 Hypervalent iodine-promoted three-component direct synthesis of substituted pyrroles.



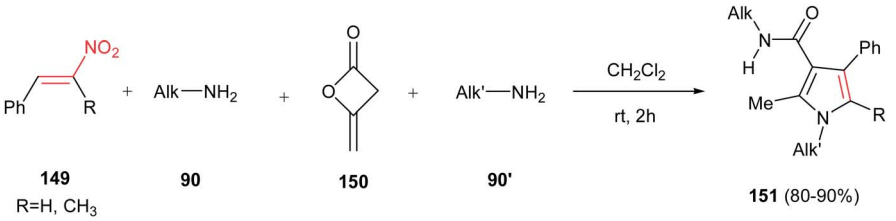
Scheme 49 $CeCl_3 \cdot 7H_2O$ promoted synthesis of highly substituted pyrroles.

1,3-Dipolar cycloaddition of munchnones **152** and β-nitrostyrenes **40** was investigated by Gribble *et al.* for synthesis of substituted pyrroles **154**. The reaction proceeds *via* 1,3-dipolar cycloaddition, followed by aromatization *via* elimination of CO_2 and HNO_2 to give the corresponding products in excellent yields and high regioselectivities using *N*,*N*′-diisopropylcarbodiimide (DIPC)in THF (Scheme 51). The reaction is insensitive to electronic nature of substituents on the phenyl ring of nitroalkenes.[107]

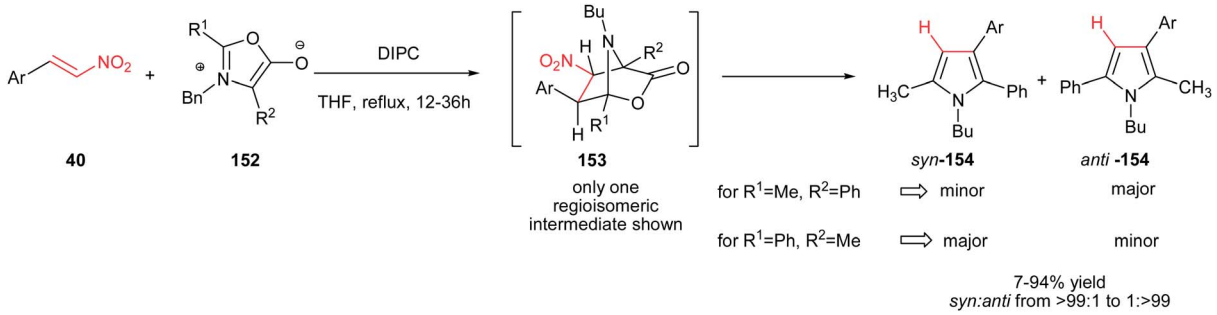
In this context, 2-, 3-, 4-pyridyl(quinolyl)pyrroles **157** were prepared by Gribble and Lopchuk from *in situ* prepared symmetrical and unsymmetrical münchnones **152** and nitroalkenes **155** *via* 1,3-dipolar cycloaddition. The Munchnones **152** were prepared *in situ* from their precursor **156** *via* treatment with DIPC. The reactions showed good regioselectivity of up to >99 : 1 toward *syn* or *anti* regioisomer when unsymmetrical munchnones were employed (Scheme 52).[108]

A concise route for synthesis of 2,3,4-substituted pyrroles **160–162** *via* a base-induced [3 + 2] cycloaddition of readily available polarized ketene *S*,*S*- and *N*,*S*-acetals **92** and **158** or **159** with activated methylene isocyanides was reported by Ila and coworkers (Scheme 53).[109] A number of functional groups such as tosyl, carbalkoxy, aryl, cyano, nitro, acetyl, benzoyl, cyclic amines, *etc.* can be introduced at the three positions of the pyrrole ring with proper selection of starting materials. The optimized conditions for this reaction are when **92** was reacted with **158** or **159** in the presence of DBU in DMF at 120 °C. Compared to previous reports on the reaction of nitroalkenes with ethyl isocyanoacetate, the nitro group is retained in the 4-position of the pyrrole adducts **160–162** with elimination of the methylthio group which allow further constructions.

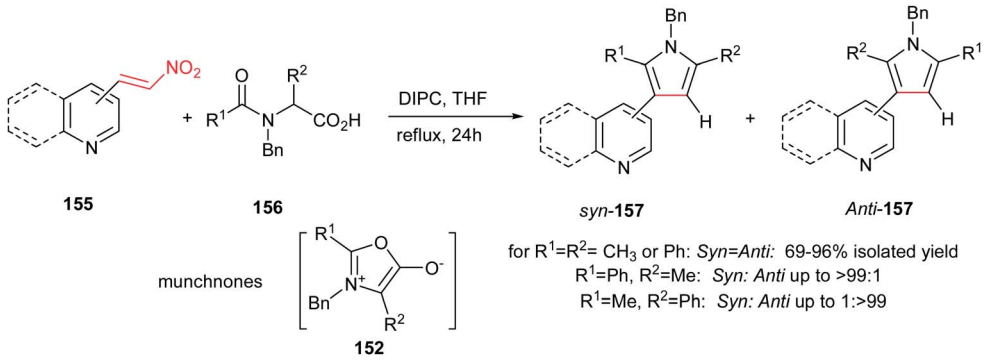
Also, Ley *et al.* reported a facile procedure for synthesis of nitro-substituted pyrroles **163** *via* a one-pot three-component reaction of tosyl isocyanide **159**, ethyl chloroformate and nitrostyrenes **40** in good yield (Scheme 54).[110] In this protocol,



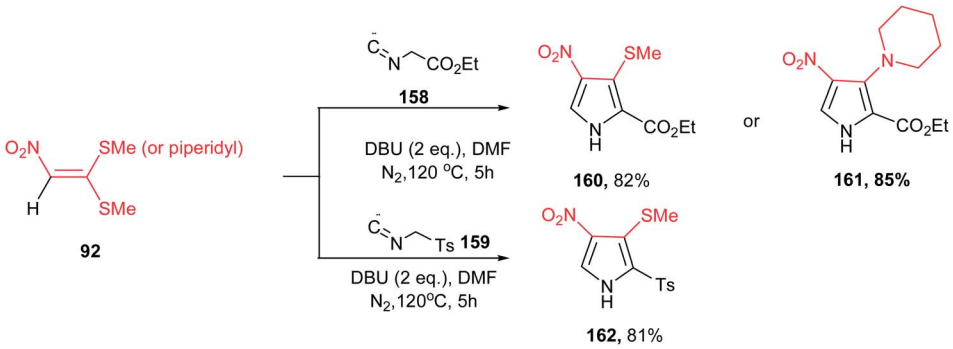
Scheme 50 Fully substituted pyrroles *via* a one-pot four-component condensation of primary amines, diketene and nitrostyrenes.



Scheme 51 Synthesis of pyrroles *via* 1,3-dipolar cycloaddition of munchnones and β-nitrostyrenes.



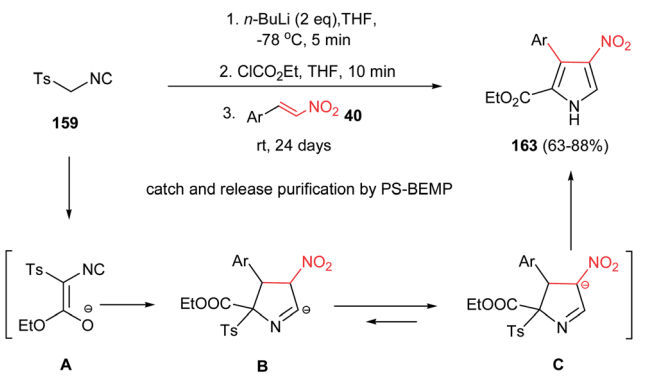
Scheme 52 2-,3-,4-Pyridyl(quinolyl)pyrroles from symmetrical and unsymmetrical münchnones and nitroalkenes.



Scheme 53 Synthesis of 2,3,4-substituted pyrroles *via* condensation of ketene *S,S*- and *N,S*-acetals with activated methylene isocyanides

treatment of **159** with ethyl chloroformate in the presence of butyl lithium generates the intermediate isocyanoacetate **A**, which easily attacks nitroalkene **40** to form cyclic compound **B** or its isomer **C**. Subsequent elimination of *p*-toluenesulfinate from **B** or **C** and [1,5]-proton shift provides the corresponding nitropyrroles **163.** The NO_2 group is retained as masked amine in the target molecule. The products were isolated in good to excellent yields (63–88%) using a polymer-assisted catch-and-release workup and purification protocol using PS-BEMP (2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine on polystyrene 2%). In general, under usual workup and column chromatography conditions, the yields do not exceed 40%.

Very recently, Zou and co-workers reported a high yielding protocol for synthesis of substituted 3-pyrrolines **166** from the cascade reactions of nitroallylic acetates **164** with methanesulfonyl 2-aminoethanones **165** in the presence of a base (Scheme 55).[111] Several bases and solvents were screened from which K_2CO_3 in THF at room temperature was selected as optimal conditions. No reaction was observed without a base. Under optimal conditions, the 3-pyrrolines were isolated with *cis* configuration as proved by NOESY. Electron-deficient nitroallylic acetates showed higher yields than electron-rich ones. Also, aliphatic nitroallylic acetates and methanesulfonyl 2-aminoethanones gave lower yields than aromatic substrates. In addition, it is notable that the products could be simply transformed *in situ* to pyrroles **167** by adding DMF to the reaction mixture and heating at 85 °C for 8 h.



Scheme 54 Synthesis of nitro-substituted pyrroles from tosyl isocyanide, ethyl chloroformate and nitrostyrenes.

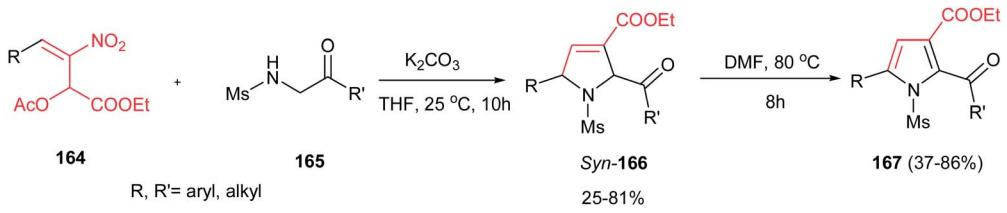
Tetrasubstituted pyrroles **169** were obtained in good to high yields from oxime-enoates **168** and nitroolefins **15** by Takasu and coworkers (Scheme 56).[112] The reaction proceeds *via* a double Michael addition promoted by a strong base such as NaOEt, followed by dehydrative aromatization. Only ethanol was proven as suitable solvent for this reaction. In the presence of the weaker bases, such as Na_2CO_3 or DBU, the reaction did not proceed, even in longer reaction time. The reaction is not feasible with oxime ether. The geometry of the nitrogen lone pair of **168** is important for the formation of the pyrrole and only *syn* isomer provided the product.

The 1,2,3,5-tetrasubstituted pyrroles **173** were synthesized by Dell'Erba in three steps from primary amines and activated dinitrobutadienes **170.**[113] The reaction proceeded *via* an unusually favored 5-*endo-trig* ring closure to give the corresponding pyrrolidine **171** as pure all-*trans* diastereomer. Then, **171** was treated with pyridinium *p*-toluenesulfonate (PPTS) in dichloromethane at room temperature to generate the nitropyrroline **172** *via* elimination of alkylamine group. Subsequent oxidation of **172** using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) affords corresponding nitropyrrole **173** (Scheme 57).

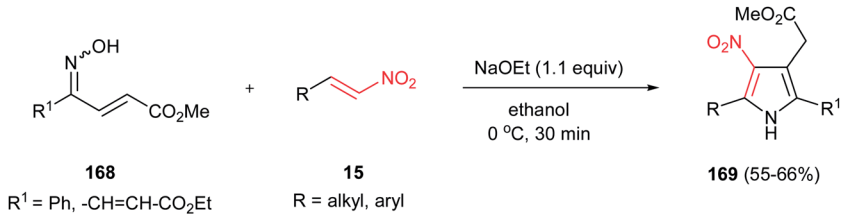
Nishiwaki *et al.* described that reaction of the enamine of nitromalondialdehyde **174** with glycine ethyl ester hydrochloride **175** afforded ethyl 4-nitropyrrole-2-carboxylate **176** in 56% yield (Scheme 58).[114]

Also, the same group reported another approach for synthesis of 1,2,3,4-tetrasubstituted pyrroles **179** from nitroisoxazolone **177** and various β-ketoesters **178.** The nitroisoxazolone **177** was considered by the authors as the hidden form of the substituted nitroenamine (Scheme 59).[115]

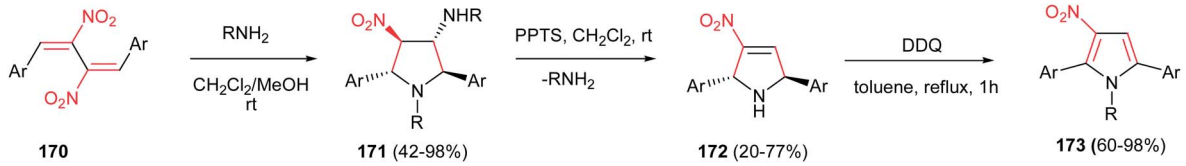
Finally, Moradi and co-workers reported a one-pot three-component synthesis of pyrrolo[1,2-*a*]pyrazines **181** from ethylenediamine **91**, acetylenic esters **180** and nitrostyrene derivatives **40** (Scheme 60).[116] The reaction was performed *via* initial stirring of the ethylenediamine **91** (1.2 equiv.) and an acetylenic ester **180** (1 mmol) in CH_3CN at room temperature, followed by addition of a β-nitrostyrene **40** (1 mmol) and sulfamic acid (SA, 20 mol%), then refluxing the mixture for 24 h. Diversity of nitroalkenes with electron-donating and



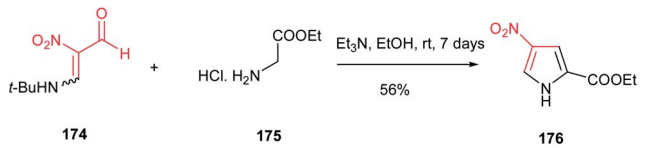
Scheme 55 Synthesis of 3-pyrrolines and pyrroles.



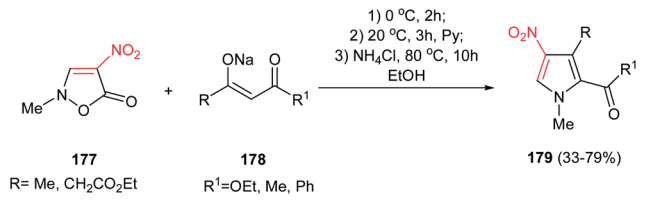
Scheme 56 Base-promoted synthesis of tetrasubstituted pyrroles from oxime-enoates and nitroolefins.



Scheme 57 1,2,3,5-Tetrasubstituted pyrroles from primary amines and dinitrobutadienes.



Scheme 58 Synthesis of pyrroles from enamine of nitromalondialdehyde and glycine ethyl ester. hydrochloride.



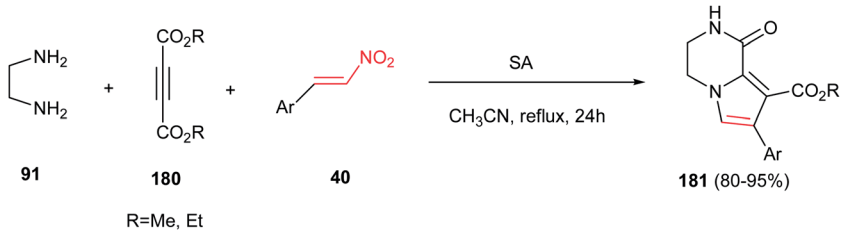
Scheme 59 Synthesis of 1,2,3,4-tetrasubstituted pyrroles from nitroisoxazolone and the enolate of various β-ketoesters.

-withdrawing groups on the phenyl ring gave similar yields in this protocol.

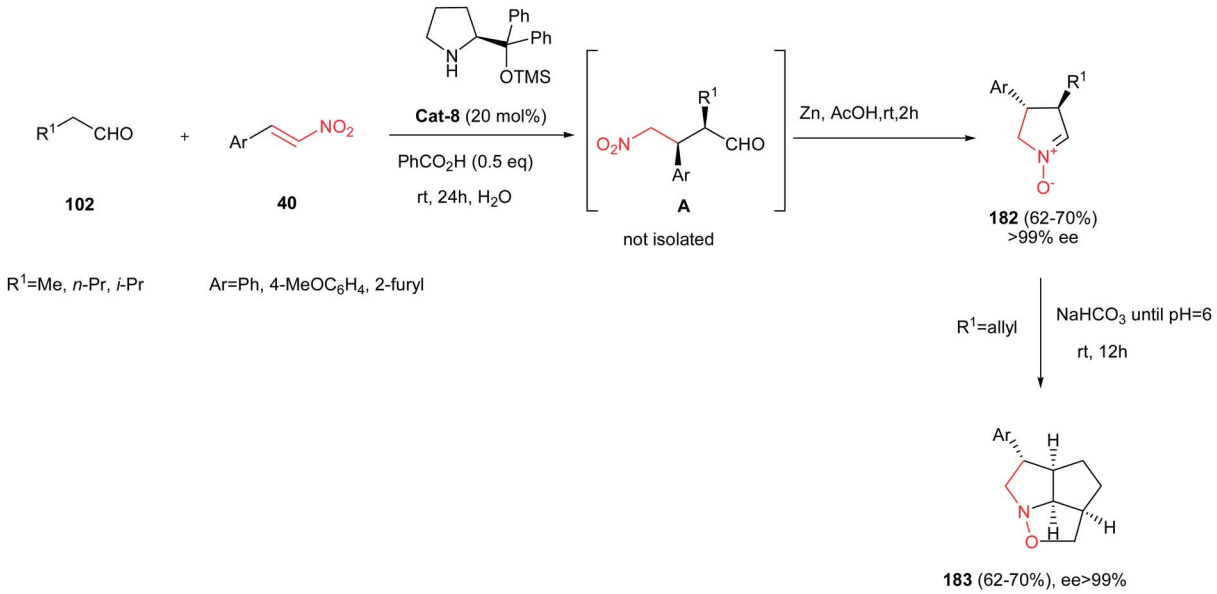
4.1.5. Five-membered cyclic nitrones. Cyclic nitrones have been used as advanced intermediates in organic synthesis for the preparation of various natural and biologically active compounds.[117] Nitrones possess one of the largest dipole moments known for any functional group type (3.37–3.47 D) making them potentially useful for non-linear optic applications and control of molecular orientation. Many routes are available for synthesis of these nitrones including the oxidation of cyclic amines or hydroxylamines,[118] intramolecular condensation of ω-hydroxylamino-carbonyl derivatives,[119] intramolecular cyclization of a suitable leaving group (halide, epoxide, or mesylate) by the oxime nitrogen atom,[120] and cyclizations of ω-unsaturated oximes.[121]

Reductive cyclizations of γ-nitrocarbonyl derivatives have found wide applications in synthesis of cyclic nitrones. In this context, Merino *et al.* reported a one-pot synthesis of enantiomerically pure five-membered cyclic nitrones **182** through the organocatalytic Michael addition of aliphatic aldehydes **102** to *trans*-nitroalkenes **40** and *in situ* Zn-promoted reductive cyclization by using water as a solvent (Scheme 61).[122] This methodology were also applied successfully for preparation of alkenyl cyclic nitrones (**182**, R^1 = allyl) that undergo spontaneous intramolecular 1,3-dipolar cycloaddition to provide tricyclic derivatives **183** in water with excellent ee values (ee > 99%).

In 2012, Dong *et al.* demonstrated that cinchonine-squaramide **Cat-9** is an efficient catalyst for asymmetric Michael addition of ketosulfones **184** to nitroalkenes **15**. The Michael adducts **185** were used for subsequent transformation to chiral cyclic *trans* nitrones **186** *via* reduction with Zn/NH_4Cl system with excellent results (up to 85% yield and >99% ee) (Scheme 62).[123] Diverse of nitroalkenes including aliphatic, aromatic and heteroaromatic ones afforded the products in



Scheme 60 One-pot three-component synthesis of pyrrolo[1,2-*a*]pyrazines.



Scheme 61 Synthesis of cyclic nitrones from aldehydes and nitroolefins and their application in the synthesis of tricyclic compounds.

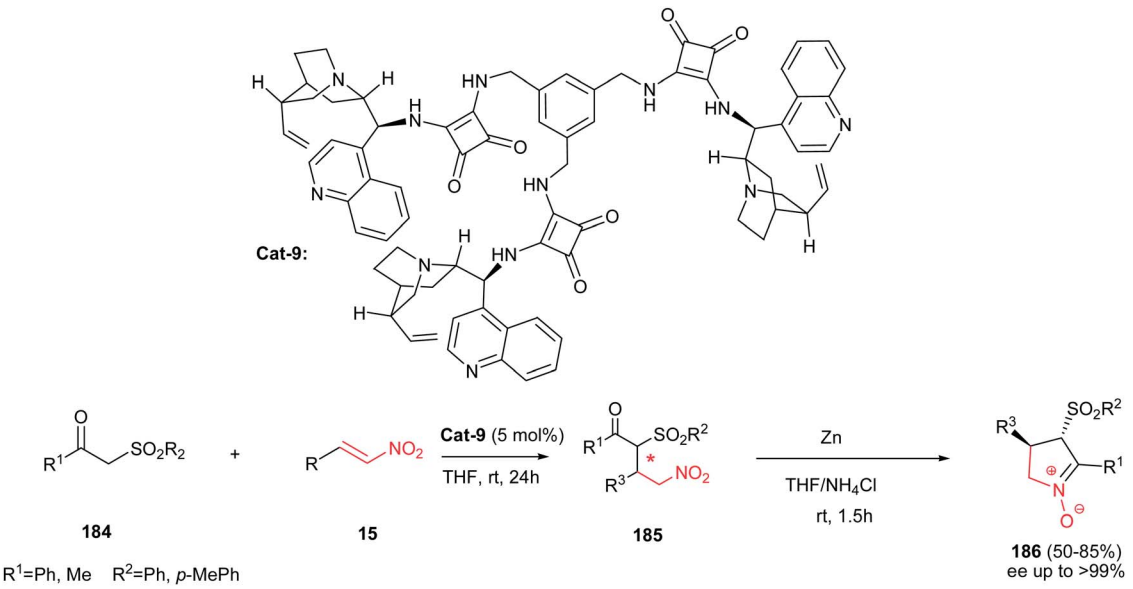
high yields. Also, it is notable that the catalyst can be recovered and reused for six cycles without losing activity and selectivity.

4.1.6. Indole derivatives. Indole derivatives are prevalent in numerous natural products and are extremely important in medicinal chemistry.[124] According to the wide applications of indole derivatives, many reviews are published about indole synthesis[125] as there are several name reactions associated with indole synthesis including Fischer, Bischler, Hinsberg, Reissert, Nenitzescu, Madelung, Bartoli, Hemetsberger, Julia, Larock, Leimgrubere-Batcho, and Sundberg approaches.[126]

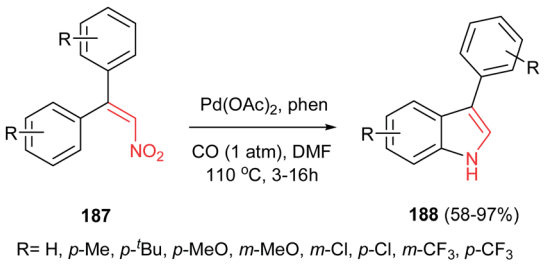
Pd-catalyzed reductive cyclization of diaryl nitroalkenes **187** with carbon monoxide as an inexpensive reductant is reported by Hsieh and Dong to give 3-arylindoles **188** in high to excellent yields (Scheme 63).[127] The reactions were performed using 2 mol% $Pd(OAc)_2$, 4 mol% 1,10-phenanthroline (phen), 1 atm of CO in DMF at 110 °C. Other transition-metal salts such as $Fe_3(CO)_{12}$, $Rh_6(CO)_{16}$, and $PtCl_2(PPh_3)_2$ were also proved to be efficient for this transformation, albeit with lower yield. The reaction is sensitive to the electronic nature of substitution on the phenyl ring of nitroalkenes. Electron-rich nitroalkenes gave higher yields in shorter reaction times compared to nitroalkenes containing electron-withdrawing groups such as Cl and CF_3. Nitroalkenes containing *meta*-substituted phenyl groups afforded both the 5- and 7-substituted indoles in excellent yields.

Ishikawa group also described that condensation of cyclohexane-1,3-dione **189** with the nitroalkene **149** (R = Me) provided the fused pyrrole **190** after exchange with benzylamine. Aromatization of **190** with acetic anhydride in the presence of oxygen gave the 4-oxygenated indole **191** (Scheme 64).[128] In this context, very recently, Qi *et al.* reported another green approach for synthesis of tetrahydro-4*H*-indol-4-one derivatives from the same starting materials using 10 mol% of proline in water.[129]

Although Pelkey and Gribble described that thermolysis of β-nitro-styrylazides **192** in xylene at 140 °C produced the 2-nitroindole **193b** as the major product,[130] recently, Driver *et al.* described that a fundamental change in reactivity of **192** can be achieved using catalytic amount of $Rh_2(esp)_2$ (1 mol%) [esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropionate] in toluene at 76 °C to give the 3-nitroindoles **193a** as major products *via* migration of the nitro group (Scheme 65).[131] The reaction gave excellent yield toward preparation of **193b**. Only with an R^4 substituent on azides, the 2-nitroindole **193b** formation became a competitive process. This strategy is also applicable for synthesis of different 3-substituted indoles by replacing the nitro group with other electron-withdrawing groups such as ketones, esters, amides, sulfones.



Scheme 62 A two-step synthesis of substituted chiral cyclic *trans* nitrones.

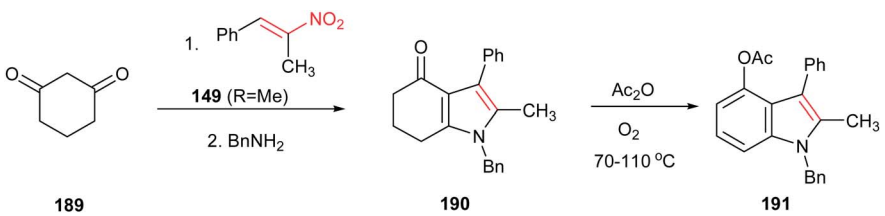


Scheme 63 Pd-catalyzed synthesis of indoles from nitroalkenes.

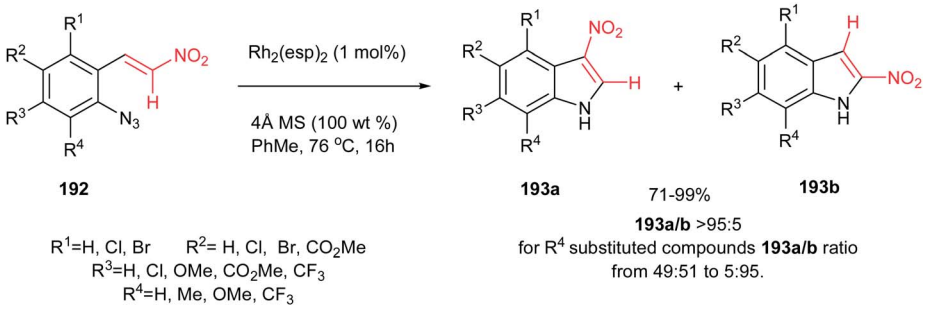
Finally, a one-pot two-step synthesis of polysubstituted indoles **197** is reported by Ballini *et al.* *via* the reaction of pyrroles **194** with β-nitroacrylates **195** under solvent- and catalyst-free conditions, followed by *in situ* treatment with Amberlyst 15 in refluxing isopropyl alcohol (Scheme 66).[132] The reaction initiated with intermolecular Friedel–Crafts alkylation, followed by intramolecular Friedel–Crafts alkylation of the amberlyst activated oxonium cation, and subsequent losing of a molecule of both ethylene glycol and nitrous acid. It is notable that this strategy allowed synthesis of indoles **197** with different functionalities in both rings.

4.1.7. Imidazole derivatives. An efficient, environmentally benign and high yielding procedure for synthesis of 4,5-unsymmetrically substituted 1-*H* imidazoles **199** was developed by Majee, Hajra and coworkers *via* nano In_2O_3-catalyzed reaction of an amidine hydrochloride **198** and a substituted nitroalkene **18** (Scheme 67).[133] The reaction proceeds *via* heating an equimolar amount of the starting materials in the presence of 5 mol% of In_2O_3 and an equivalent of K_2CO_3 in ethanol at 70 °C. The use of a base is necessary for progress of reaction. The catalyst can be recovered and reused for four subsequent runs without any significant loss of the activity. Other catalysts such as $In(OTf)_3$, $InCl_3$, nano ZnO and CuO afforded the products in lower yields under similar conditions. Also, fully substituted imidazoles were prepared by Chen *et al.* from the reaction of nitroalkenes and N-substituted amidines catalyzed by 20 mol% $FeCl_3$ in DMF at 90 °C.[134]

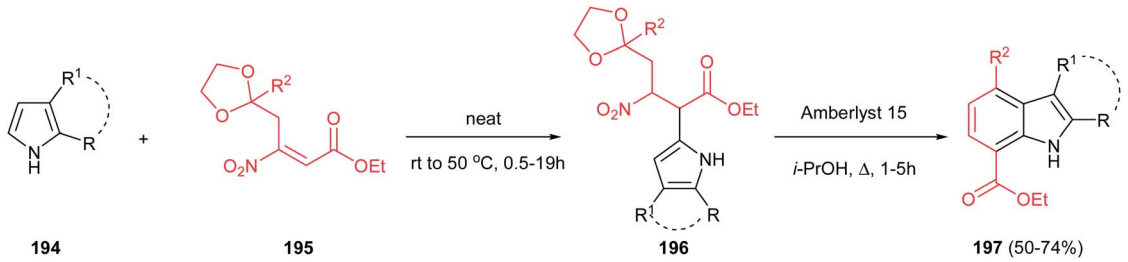
In 2012, a green procedure for synthesis of imidazo[1,2-*a*]-pyridines **201** from 2-aminopyridines **200** and nitroolefins **40** was developed by Yan, Huang and co-workers using air as oxidant and 10 mol% CuBr as catalyst (Scheme 68).[135] Among the several copper salts such as CuBr, CuCl, CuOTf, $Cu(OAc)_2$,and $Cu(OTf)_2$ examined for this process, CuBr afforded the highest yield. It is notable that electron-rich nitroolefins or aminopyridines showed better reactivity and gave higher



Scheme 64 Synthesis of indole from cyclohexane-1,3-dione and nitroalkene.



Scheme 65 Synthesis of indoles from β-nitro-styrylazides.



Scheme 66 A one-pot two-step synthesis of poly substituted indoles.

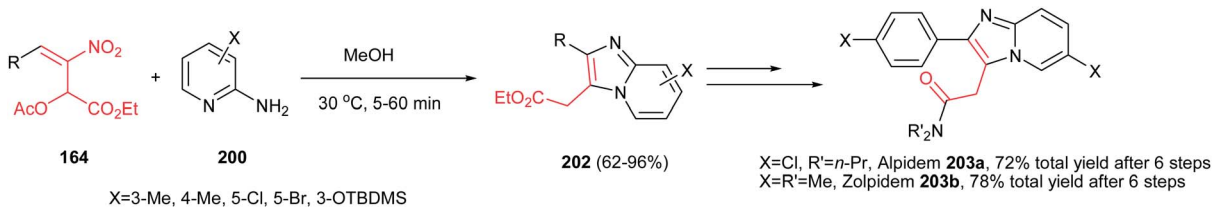
Scheme 67 Synthesis of imidazoles *via* tandem cyclization between amidine and nitroolefins.

yields than electron-deficient ones. More recently, Hajra *et al.* developed another catalytic route for this reaction by performing the reaction of nitroalkenes with 2-aminopyridines in the presence of 20 mol% $FeCl_3$ in DMF at 80 °C.[136]

The method for synthesis of functionalized imidazo[1,2-*a*]-pyridines **202** from reaction of MBH acetates of nitroalkenes **164** and 2-aminopyridines **200** was reported by Namboothiri *et al.* (Scheme 69).[137] The reaction was conducted in methanol at room temperature under catalyst-free conditions to give the corresponding products in high to excellent yields (63–96%) *via* cascade inter-intramolecular double aza-Michael addition. While MBH acetates with unsubstituted and weakly deactivating aromatic rings gave excellent yields of products, lower yields were encountered in the case of MBH acetates with strongly electron withdrawing aromatic substituent and nitrodiene derived MBH acetates. Also aminopyridines with a substitution on the 3-position gave lower yield than those with substitution on the 4- or 5-position. In addition, aminoheterocycles such as aminopyrimidine, aminopyrazine and aminothiazole examined in this protocol, were unreactive under the above reaction conditions. This strategy was successfully applied for total synthesis of anxiolytic drug Alpidem **203a** and hypnotic drug Zolpidem **203b** in six steps with 72 and 78% overall yields, respectively.

Scheme 68 Cu-catalyzed synthesis of imidazo[1,2-*a*]pyridines.

4.1.8. Pyrazoles, pyrazolidines and pyrazolines. Pyrazoles are an important class of heterocyclic compounds with diverse biological activities as antimicrobial, antiparasitic, anti-inflammatory, antidepressant, antiviral, A_{2A} receptor antagonist, CB1 receptor antagonist, DNA intercalating and anti-tumor.[138] Pyrazole-containing compounds such as the blockbuster drugs Viagra, Celebrex, and Acomplia have been successfully commercialized. Also, pyrazoles have been employed as ligands for the transition-metal-catalyzed cross-

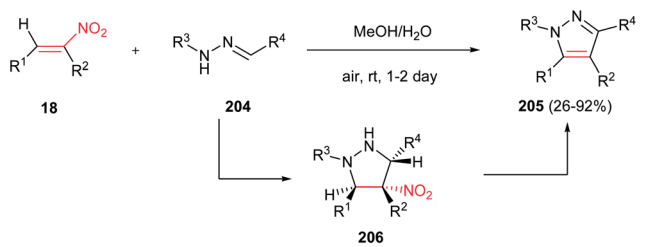


Scheme 69 Synthesis of imidazo[1,2-*a*]pyridines from 2-aminopyridine and MBH acetates of nitroalkenes.

coupling reactions.[139] The most general and convenience methods for synthesis of pyrazole derivatives are the condensation of substituted hydrazines with 1,3-dicarbonyl compounds or their derivatives (Knorr reaction)[140] and the 1,3-dipolar cycloaddition of diazoalkanes or nitrile imines with olefins or alkynes.[141]

Pyrazoline and pyrazolidine derivatives also exhibit wide range of biological activities such as anti bacterial,[13] anti depressant,[14] anti tubercular[15] anti amoebic[16] anti inflammatory,[17] herbicidal, insecticidal[18] and cardiovascular[19] activities.[142] The most applied procedure for synthesis of pyrazolines is based on the reaction of α,β-unsaturated aldehydes and ketones with hydrazines.[143] Pyrazolidines usually are accessible *via* reduction of pyrazolines[144] or pyrazolium salts[145] and by the reactions of hydrazine with 1,3-dibromides[146] or phenylhydrazones with electron-deficient alkenes.[147]

Deng and Mani developed an efficient, simple and regioselective procedure for synthesis of highly substituted pyrazoles **205** from N-substituted hydrazones **204** and nitroalkenes **18** (Scheme 70).[148] This reaction is quite broad in scope, generating a diverse set of pyrazole products in moderate to excellent yields. Solvent screening showed that polar protic solvents are suitable for this transformation, while polar aprotic solvents (except dichloromethane), furnished the Michael adducts. The reaction yield is tolerated with electronic and steric effects of substituents on the hydrazone component. Hydrazones with electron deficient group on parent aldehyde favored the formation of a Michael addition product. Moreover, hydrazones with bulky group on nitrogen gave low yield. Either aryl or alkyl groups at the R^3 position afford corresponding pyrazoles in excellent yields. Substitution at the R^4 position of nitroolefins is also well tolerated. Mechanism study by authors revealed that the reaction proceeded *via* intermediate **206** which was successfully confirmed by NMR, IR and mass spectroscopy. Also, the same group developed two more practical procedures



Scheme 70 Synthesis of pyrazole derivatives in aqueous methanol.

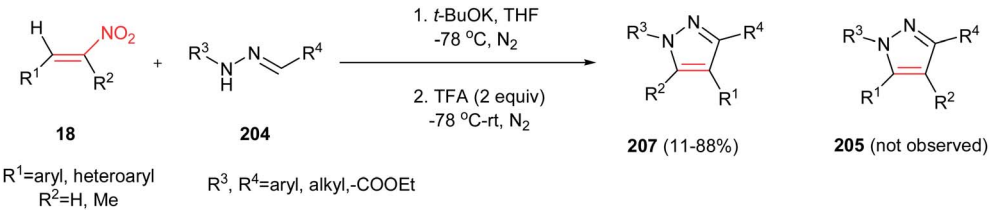
for synthesis of 1,3,5-tri- and 1,3,4,5-tetrasubstituted pyrazoles from the same starting materials. The first protocol is heating the starting materials in ethylene glycol at 120–150 °C for 16 h, while the second procedure is stirring the starting materials in triflouroethanol in the presence of 10 equiv. of TFA for two days.[149]

By performing the same reaction in the presence of *t*-BuOK at −78 °C and under atmosphere of N_2, reverse regioselectivity in the pyrazoles (1,3,4-regioselectivity **207** instead of 1,3,5-regioselectivity **205**) can be obtained compared to earlier protocols (Scheme 71).[150] Fortunately, hydrazones with electron deficient groups on the parent aldehydes also provided high yield. In addition, 1-nitrocyclohexene gave fused pyrazole ring in 63% isolated yield.

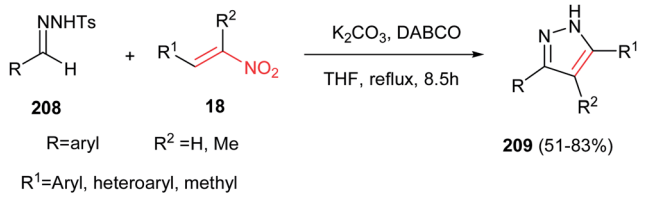
Although the previous methods provided the N-protected pyrazoles, Tang *et al.* described that by using tosylhydrazones **208** in the reactions with nitroalkenes **18**, the corresponding 3,4,5-substituted pyrazoles **209** can be obtained in good to high yields (Scheme 72).[151] Different reaction conditions were examined and the use of tosylhydrazones **208** (0.4 mmol), nitroalkenes **18** (0.8 mmol), K_2CO_3 (0.4 mmol) and DABCO (0.24 mmol) in THF (4 ml) under reflux temperature was selected as optimum conditions. It is noteworthy that aromatic, heteroaromatic and aliphatic nitroalkenes reacted equally in this protocol. Two mechanisms were proposed for this reaction; the first one is initiated by aza-Michael addition of deprotonated tosylhydrazone to nitroalkene, followed by sequential intramolecular cyclization, nitro-elimination and 1,3-H shift, while the second one proceeded *via* sequential Baylis–Hillman reaction/intramolecularcyclization/nitro-elimination and 1,3-H Shift.

An environmentally benign procedure for synthesis of highly substituted pyrazoles **213** was reported by Xie *et al.* from different nitroalkenes **210** and ethyl diazoacetate **212** (Scheme 73).[152] The reaction was carried out by stirring of a mixture of nitroalkenes **210** (1 equiv.) with an excess amount of ethyl diazoacetate **212** (5 equiv.) in THF for 48–96 h. α-Carbethoxy-1-nitrostyrenes gave higher yields in shorter reaction time compare to simple nitrostyrenes. Reaction of 3-nitrocumarines **211** with **212** also afforded the fused pyrazole rings **214** in high yields. By using α-bromonitroalkenes in this protocol, the nitro group could be retained in the structure of products *via* elimination of bromide and the corresponding nitropyrazoles could be obtained in good yields.

Kaufmann *et al.* approved that the complex ketones **218**, which was prepared from polyhalogenated nitrobutadiene **215**



Scheme 71 Reverse regioselectivity in the synthesis of pyrazoles by using *t*-BuOK as catalyst.

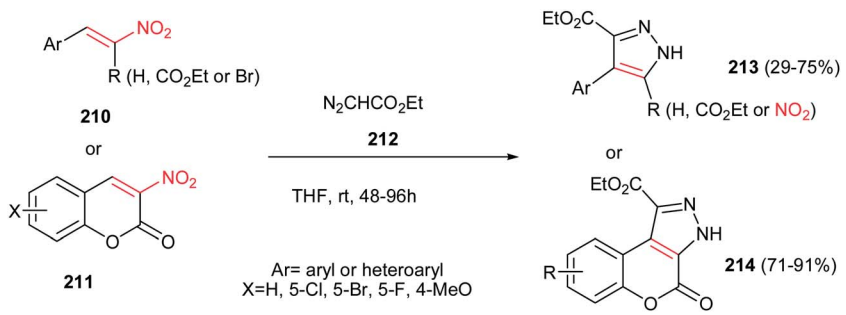


Scheme 72 Synthesis of 3,4,5-substituted pyrazoles from tosylhydrazones and nitroalkenes.

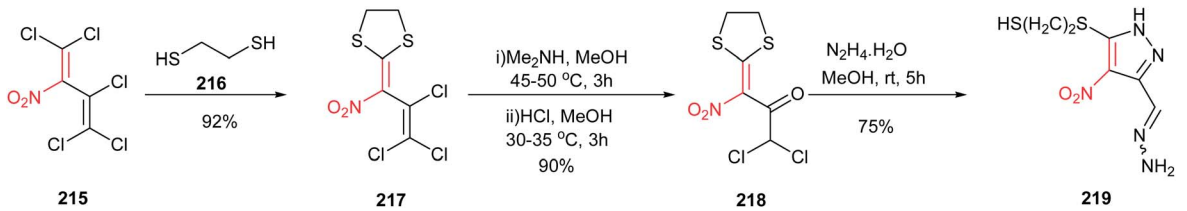
in two steps, is a suitable building block for synthesis of pyrazole ring **219** (Scheme 74). An unexpected reaction between **218** and hydrazine in MeOH at room temperature provide the structurally interesting pyrazole **219** in 75% isolated yield.[153]

In 2007, Namboothiri and co-workers suggested an interesting one-pot route to phosphonylpyrazoles **221**, based on the 1,3-dipolar cycloaddition of the anion of diethyl 1-diazomethylphosphonate, generated *in situ* from diethyl 1-diazo-2-oxopropylphosphonate (Bestmann–Ohira reagent) **220**, with conjugated nitroalkenes **15** (Scheme 75).[154] Reactions were promoted by NaOEt/EtOH at room temperature for 15 min to afford the regioisomerically pure 4-substituted 3-phosphonylpyrazoles **221** in moderate to good yields. Heteroaromatic nitroalkenes gave lower yield when compared to aromatic nitroalkenes. Also, phosphonylpyrazole with dimethyl amino group could be synthesized in 64% yield using *N*,*N*-dimethyl-2-nitroethenamine. When the 3-nitro-2*H*-chromene or 2-nitronaphthalene **222** was used in this protocol, the corresponding fused phosphonylpyrazole was obtained with same yields, albeit in longer reaction time. Morita–Baylis–Hillman adducts of conjugated nitroalkenes with various electrophiles **223–226** also included as partner with Bestmann–Ohira reagent. It is notable that the nitro group could be retained in the structure of phosphonylpyrazoles by using α-bromonitroalkenes **210** in the same protocol.

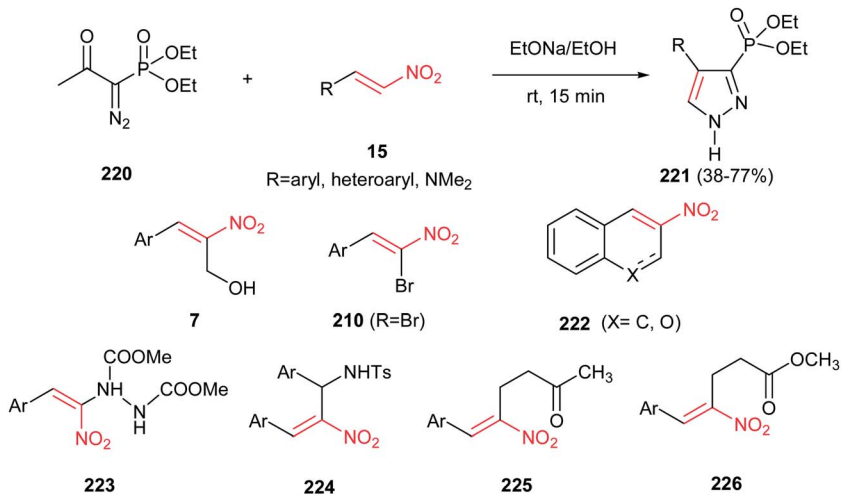
Furthermore, the same group also demonstrated that α-diazo-β-ketosulfones **227** are suitable substrates for synthesis of substituted sulfonylpyrazoles **228** in the reaction with nitroalkenes **18** (Scheme 76).[155] The sulfonyl group could be simply removed *via* reduction with Na/Hg in methanol to give the corresponding substituted pyrazoles **229**. It is notable that different groups such as aryl, heteroaryl, styrenyl, alkyl, hydroxymethyl, and hydrazinyl groups could be introduced on the pyrazole ring by the appropriate choice of nitroalkenes.



Scheme 73 Synthesis of highly substituted pyrazoles from nitroalkenes and ethyl diazoacetate.



Scheme 74 Synthesis of substituted pyrazoles starting with polyhalogenated nitrobutadiene.

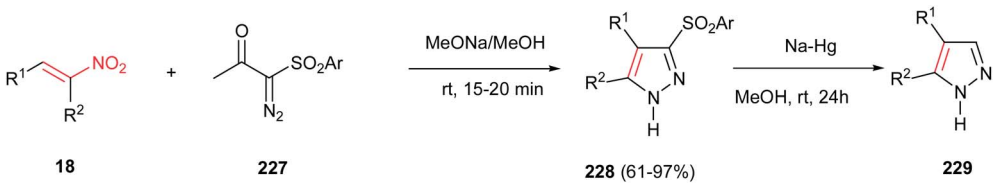


Scheme 75 Synthesis of phosphonylpyrazole from diethyl 1-diazomethylphosphonate and nitroalkenes.

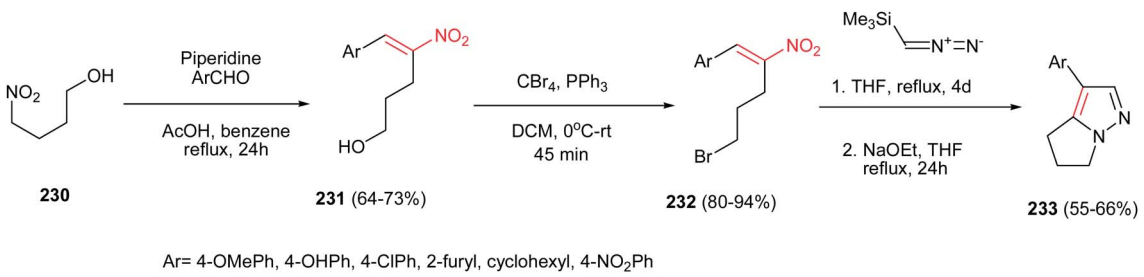
Also, reactions of bromonitroalkenes **232** with commercially available $TMSCHN_2$ were carried out by Namboothiri *et al.* for synthesis of pyrazole-based withasomnine alkaloids **233** and their non-natural analogues. This one-pot protocol proceeds *via* 1,3-dipolar cycloaddition-elimination cascade, followed by intramolecular alkylation in the presence of NaOEt in THF at reflux temperature (Scheme 77). Bromo compound **232** was prepared in two steps from 4-nitro-1-butanol **230** *via* Henry condensation, followed by conversion of the OH group to Br using CBr_4 and Ph_3P. An overall yield of 39% was obtained for Ar = Ph from the corresponding nitroalcohol **230**.[156]

Very recently, an efficient route for regioselective synthesis of pyrazoles **235** was developed by Zou group *via* reaction of a nitroallylic acetate **164** and *N*-tosyl hydrazine **234** in methanol for 30 min, followed by addition of Na_2CO_3 (10 mol%) and refluxing the mixture for 2 h at 65 °C (Scheme 78).[157] Aromatic, heteroaromatic and aliphatic nitroallylic acetates are compatible with this protocol to provide high to excellent yields of the products. Performing the reaction under base-free condition afforded the S_N2 adducts of nitrogen attack to electrophilic γ-site. With these results in hands, the authors proposed a cascade S_N2-Michael addition–aromatization mechanism for this transformation.

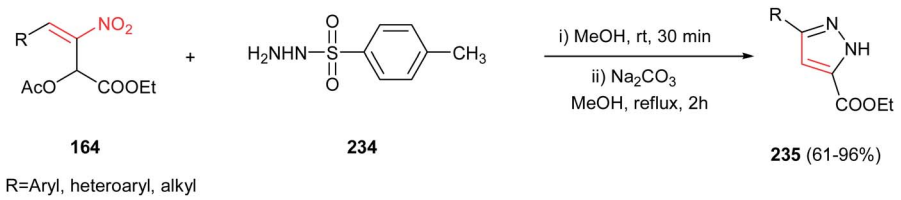
In addition, Sosnovskikh *et al.* demonstrated a high yielding procedure for synthesis of pyrazolidines **238** from the reaction of 3-nitro-2-trichloromethyl-2*H*-chromenes **123** with an equimolar amount of 60% hydrazine hydrate in ethanol at room temperature (Scheme 79).[158] The corresponding products were obtained as a single, most thermodynamically stable 3,4-*trans*, 4,5-*trans*-3-(2-hydroxyaryl)-4-nitro-5-trichloromethylpyrazolidines **238** in 56–73% yields. Phenylhydrazine does not react with chromenes **123** under these conditions. If the amount of hydrazine is increased,



Scheme 76 Synthesis of substituted sulfonylpyrazoles from α-diazo-β-ketosulfones and nitroalkenes.



Scheme 77 Synthesis of pyrazole-based withasomnine alkaloids from bromonitroalkenes and $TMSCHN_2$.



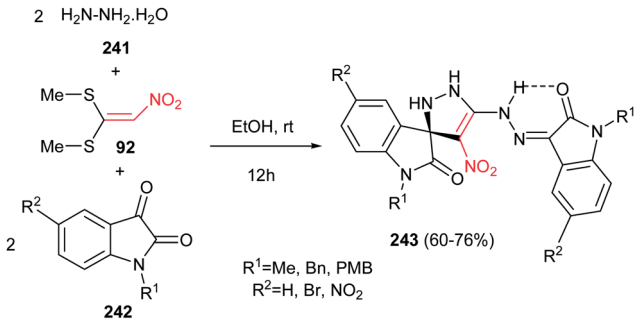
Scheme 78 Regioselective synthesis of pyrazoles from nitroallylic acetates and *N*-tosyl hydrazine.

or if the reaction is carried out in boiling ethanol, intermediate **237** decomposes to give hydrazone **240** as the predominant product.

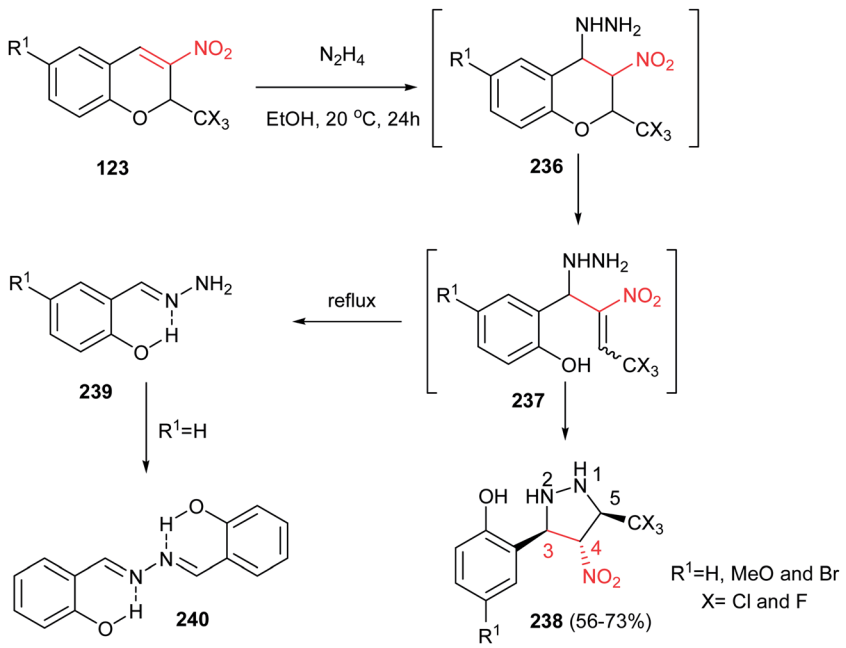
Finally, Alizadeh and Zohreh developed a novel method for preparation of spirooxindole-pyrazoline derivatives **243** in high yields *via* a one-pot pseudo-five-component reaction of hydrazine hydrate **241**, 1,1-*bis*(methylthio)-2-nitroethylene **92**, and isatin derivatives **242** (Scheme 80).[159] The products are polynitrogen compounds with potential synthetic and pharmacological interest that will be suitable for further elaboration. The products are strongly colored with high heat resistance. The proposed mechanism shows that the reaction is initiated by formation of 1,1-*bis*(hydrazine)-2-nitroethylene intermediate from the addition of aqueous hydrazine to 1,1-*bis*(methylthio)-2-nitroethylene **92**, followed by trapping this intermediate by two equivalents of isatin derivatives to give the title compounds.

4.1.9. Pyrrolizines, pyrrolizidines and pyrrolizidinones. Pilipecz *et al.* described that reaction of 2-nitromethylenpyrrolidine **244** with phenylglyoxal in EtOAc at room temperature for 2 h afforded product **245** in 92% yield. These adducts were then transformed to substituted dihydro-1*H*-pyrrolizines **246** in 75–87% yields by heating in various alcohols in the presence of conc. HCl. Interestingly, by heating of **245** in molten phenol in the presence of HCl, 4-hydroxyphenyl substituted pyrrolizines **247** was obtained in 41% yield *via* Friedel–Crafts type electrophilic aromatic substitution occurred at C-4 of phenol. Performing this reaction in 2,2,2-trifluoroethanol/HCl solution afforded the chloro derivative **248** in 88% yield (Scheme 81).[160]

Reaction of phenylglyoxal with β-nitrostyrene **40**(Ar = Ph) and an equimolar amount of L-proline (*S*)-**70** in *i*-PrOH at room temperature affords substituted pyrrolizidine **249** in 80% yield



Scheme 80 A one-pot approach for synthesis of spirooxindole-pyrazolines.



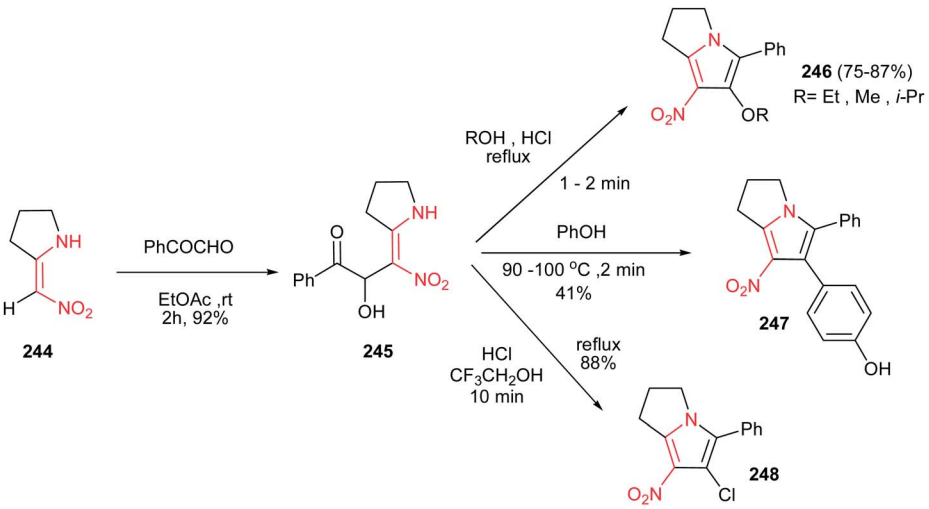
Scheme 79 Synthesis of pyrazolidines from 3-nitro-2-trichloromethyl-2*H*-chromenes and hydrazine hydrate.

as a single regioisomer. The reaction proceeds *via in situ* generation of 1,3-azomethine ylide **A** from phenylglyoxal and (*S*)-**70** by decarboxylation, then 1,3-dipolar cycloaddition reaction with **40** (Scheme 82).[161]

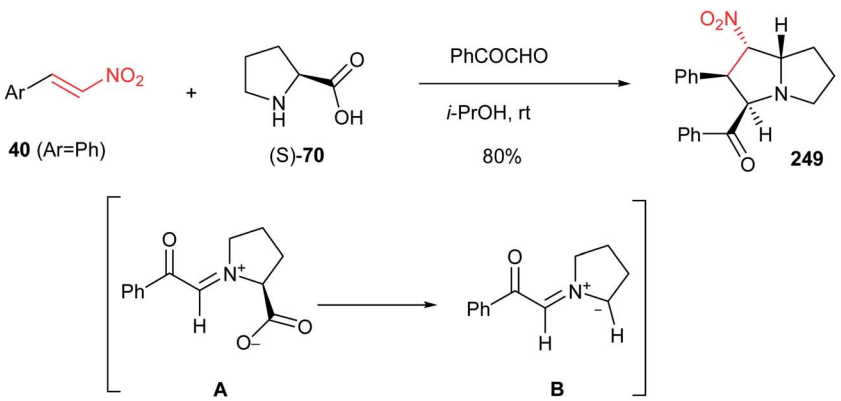
[4 + 2] Cycloaddition reaction of nitroalkene **250** to ethyl vinyl ether **251** was applied as key step for racemic synthesis of GlaxoSmithKline's highly potent PDE IVb inhibitor **253** (Scheme 83).[162] Subsequent hydrogenation of nitronate **252** with Adams catalyst (PtO_2/AcOH) under 20 bar H_2 at 50–60 °C for 4 h afforded the racemic product **253** in high yield and diastereoselectivity. Reduction with other catalytic systems such as Ra–Ni, 5% Pd–C, 0.5% Pd/Al_2O_3, 5% $Pd/CaCO_3$, 5%Rh/Al_2O_3 and $Rh(PPh_3)_3Cl$ gave only low diastereoselectivity of **253**. Also, the asymmetric version of this protocol was carried out with using a vinyl ether containing a chiral auxiliary group to give the cyclic nitronate **252** in 8.3 : 1 diatereomeric ratio. Subsequent reduction of the major diastereomer with Adams catalyst provided the corresponding **253** in 7 : 1 diastereomeric ratio.

4.1.10. 1,2,3-Triazole derivatives. 1,2,3-Triazoles are an important class of heterocycles with considerable interest due to their wide applications in many pharmaceuticals and their usefulness in synthetic organic chemistry. A large number of 1,2,3-triazoles exhibit various biological activities as antiviral,[163] antimicrobial,[164] antifungal,[165] anticancer,[166] anti-HIV,[167] β3-selective adrenergic receptor agonists[168] and kinase inhibitors.[169] However, the scope of triazole chemistry is not confined to drug discovery. They have found wide applications in numerous other areas of modern chemical sciences, such as bioconjugation,[170] supramolecular chemistry,[171] and polymer sciences.[172] In addition, they are commercially employed as anticorrosive agents, agrochemicals, photostabilizer photographic materials, and dyes.[173] Substituted 1,2,3-triazoles are commonly prepared by Huisgen's 1,3-dipolar cycloaddition between organic azides and substituted alkynes.[174]

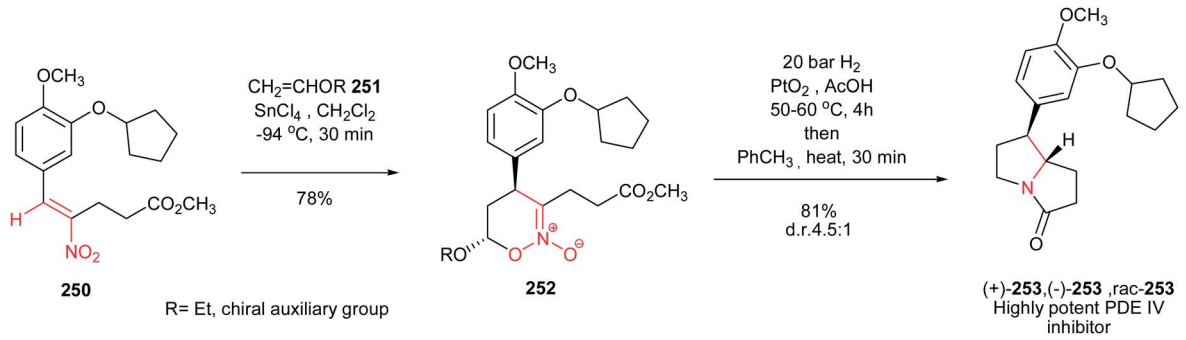
Shi *et al.* developed a one-pot three-component condensation of a β-alkyl nitroalkene **254**, an aldehyde **255** and sodium azide catalyzed by L-proline for synthesis of *NH*-1,2,3-triazole derivatives **256** (Scheme 84).[175] A large number of aryl aldehydes and β-alkyl nitroalkenes **254a–e** were used for this transformation and more than 25 new (*NH*)-triazoles **256** were prepared in good to excellent yields under mild conditions. Substituted azides (*n*-hexanyl azide and phenyl azide) are not



Scheme 81 Synthesis of dihydropyrrolizines from nitroalkenes.



Scheme 82 Substituted pyrrolizidine from nitroalkene.



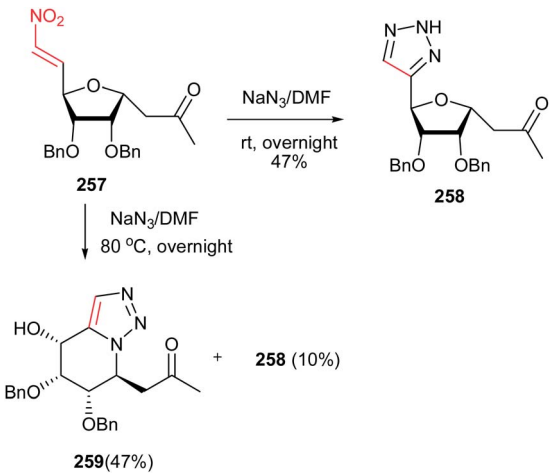
Scheme 83 [4 + 2] cycloaddition reaction of nitroalkene as key step for synthesis of GlaxoSmithKline's highly potent PDE IVb inhibitor **253**.

suitable for this cascade process. The presence of vinyl group on the C-4 position allows further elaboration to diversity of other functionalized triazole derivatives. Proposed mechanism by the authors revealed that Henry reaction between nitroalkene **254** and aryl aldehyde **255** furnished the 2-nitro-1,3-diene, which underwent 1,3-dipolar cycloaddition with N_3^-. Finally aromatization occurred by elimination of NO_2^-.

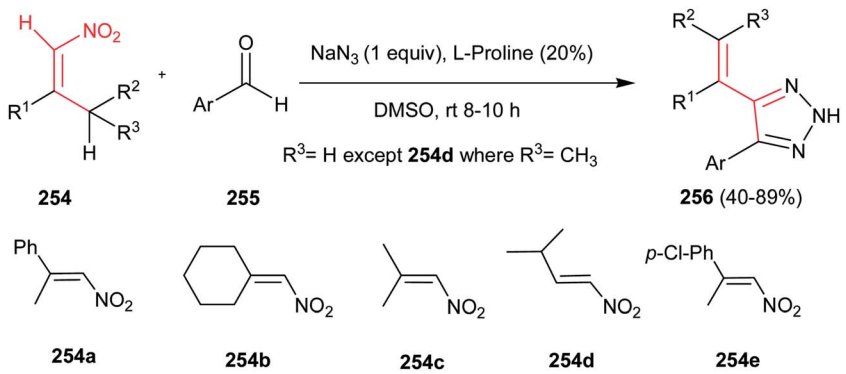
In 2009, reaction of nitroalkene-containing *C*-glycosides **257** with sodium azide was investigated by Zou *et al.*[176] They described that while at room temperature only the 1,3-dipolar cycloaddition products **258** were obtained, at elevated reaction temperature, the 1,5-disubstituted triazole-fused sugars **259** was obtained as major product in good yield *via* a tandem β-elimination/cycloaddition/Michael addition (Scheme 85).

4-Aryl-5-cyano- or 4-aryl-5-carbethoxy-1*H*-1,2,3-triazoles **260** were synthesized by Fringuelli and coworkers *via* a [3 + 2] cycloaddition reaction of 2-aryl-1-cyano- or 2-aryl-1-carbethoxy-1-nitroethenes **210** with $TMSN_3$ catalyzed by TBAF under solvent-free conditions (Scheme 86).[177] This protocol affords good to excellent yields (70–90%) of products. While (*E*)-2-aryl-1-cyano-1-nitroethene gave high to excellent yield (75–90%) in the presence of 0.1 equiv. of TBAF at 30 °C with $TMSN_3$ (2.0 equiv.) under SFC conditions in less than 3 h, the 2-aryl-1-carbethoxy-1-nitroethene needs 4 equiv. of $TMSN_3$ and higher temperatures (50–80 °C) and longer reaction times (4–12 h) to afford the product in comparable yield. This procedure does not require anhydrous or inert atmosphere.

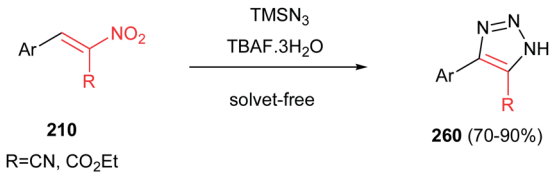
In 2005, Zard *et al.* have shown that reaction of nitroalkenes **40** and **262** or vicinal acetoxy nitro derivatives (as nitroalkene precursor) with sodium azide in hot dimethyl sulfoxide (80–90 °C) gave the corresponding 1,2,3-triazoles **261** in excellent yields (Scheme 87).[178] Aliphatic and aromatic niroalkenes were compatible with this protocol. They reported that the amount of sodium azide is crucial for this reaction and in the presence of at least 4 eq. of sodium azide, the triazole was the only product.



Scheme 85 Reaction of nitroalkene-containing *C*-glycosides with sodium azide.



Scheme 84 Synthesis of *NH*-1,2,3-triazoles from β-alkyl nitroalkenes, aldehydes and sodium azide.



Scheme 86 Synthesis of 4-aryl-5-cyano- or 4-aryl-5-carbethoxy-1*H*-1,2,3-triazoles.

Very recently, condensation of 2-alkynyl nitroolefin **264** (obtained from 2-alkynylbenzaldehyde) and sodium azide in DMSO at 100 °C was introduced by Kundu *et al.* as an efficient route for synthesis of tricyclic triazoloisoquinolines **265** in excellent yields (Scheme 88).[179] The reaction proceeded *via* a domino [3 + 2] cycloaddition/extrusion of the nitro group/regioselective 6-*endo* cyclization sequence. Using other solvents such as DMF, toluene, toluene : H_2O and CH_3CN : H_2O (9 : 1) gave trace to low yield of products. No variation in yield was observed by varying the R^1 and R^2 groups, except for R^2 = CN, in which case no product was observed.

4.1.11. Tetrazole derivatives. Kaufmann *et al.* demonstrated that the reaction of 1,1,2-trichloro-2-nitroethene **266** with excess benzotriazole (BztH) affords 1,1-bis(benzotriazol-1-yl)-2-chloro-2-nitroethene **267** in excellent yields. Then, transamination of **267** with different aniline derivatives provides the corresponding 1-(arylimino)-1-(benzotriazolyl)ethanes **268**, which produces the product **269** *via* cycloaddition with sodium azide. By using the arenediamines instead of aniline derivatives, the corresponding *bis* tetrazoles were also obtained in excellent yields. The tetrazoles **269** are valuable precursors for further constructions on the side chain (Scheme 89).[180]

4.2. Synthesis of O-heterocyclic compounds

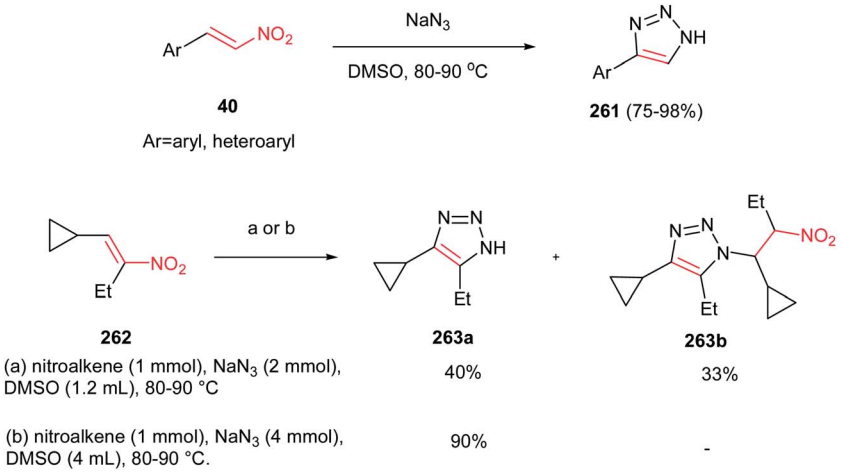
4.2.1. Tetrahydrofurans derivatives. Nitroalkenes were used as efficient starting materials for synthesis of several tetrahydrofuran lignans which have found diverse biological activity in recent years. In this context, highly functionalized 4-(1-haloalkyl)-3-nitrotetrahydrofurans **273a–d** were prepared by an oxidative tandem process consisting of conjugate addition reaction of lithium allyloxides of **270** to nitroalkenes **271** followed by single electron transfer oxidation of the resulting nitronates **272** in moderate to good yield and moderate to very good diastereoselectivity (Scheme 90).[181] The authors found that the optimal conditions for the tandem reactions consist of using butyl lithium as the base in dimethoxyethane and using cupric halides as single electron transfer oxidants. The nitro- and chloride functionalities in the structure of products can be easily modified to other interesting structures. Also this methodology should be easily applicable to other Michael acceptors such as α,β-unsaturated esters, amides or nitriles.

R^1= 1,2-$(OMe)_2$, 4-MeO, 4-F

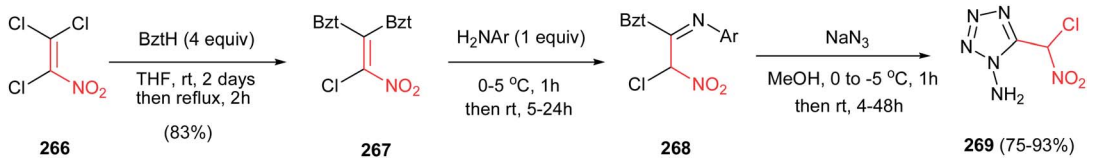
R^2= aryl, alkyl, $SiMe_3$

Scheme 88 Synthesis of tricyclic triazoloisoquinolines from 2-alkynyl nitroolefin.

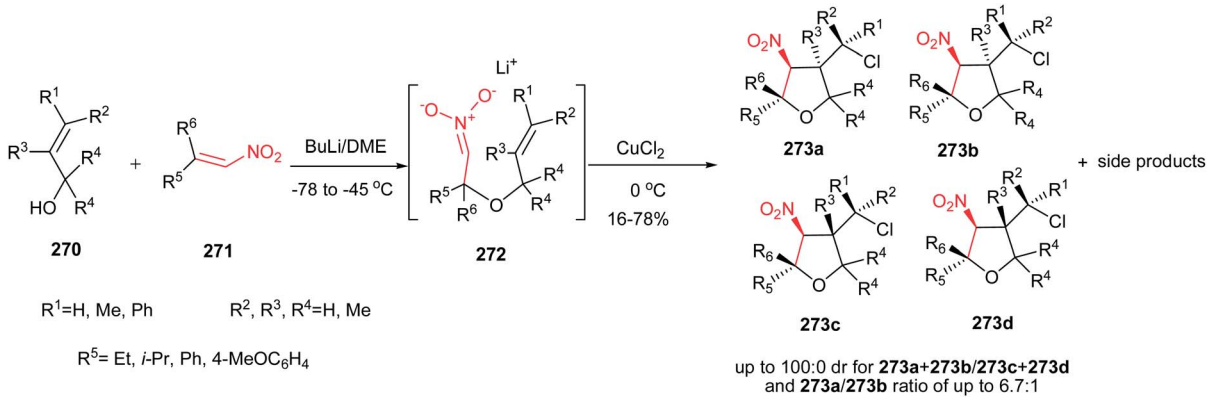
The same strategy was applied by the same authors for synthesis of Galgravin **277a** and Veraguensin **277b** in only three or four steps from nitroalkenes **274** and allylic alcohols **275**.[182] While the corresponding bromo derivatives **276** can be directly reduced and denitrated by excess Bu_3SnH/AIBN at reflux in toluene in good yield, the chloro derivatives need two steps for halide and nitro removal *via* treatment with Bu_3SnH/AIBN followed by reduction with $LiAlH_4$. Also β-nitro ethers **278**, simply prepared from the starting materials using BuLi, undergo reductive radical cyclizations with Bu_3SnH/AIBN to afford Galbelgin **279a** and Ganschisandrin **279b** as major products (Scheme 91).



Scheme 87 Catalyst-free synthesis of triazoles from nitroalkenes and NaN_3.



Scheme 89 Synthesis of tetrazoles starting with 1,1,2-trichloro-2-nitroethene.



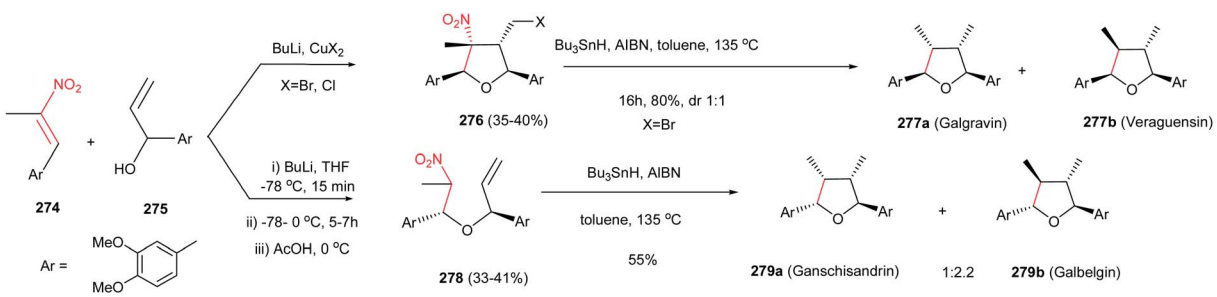
Scheme 90 Tandem alkoxide conjugate addition/radical cyclization.

Namboothiri *et al.* demonstrated that the Michael addition reaction of a *O*-, *S*-, *N*-, and *C*-centered nucleophiles possessing unsaturated tether **281** to β-furyl nitroethylene **280** furnish a suitable building block **282** for further construction *via* intramolecular Diels–Alder reaction of furan diene to give five- and six-membered carbocycles and heterocycles **283** fused to an easily cleavable oxabicycloheptene moiety. Cleavage of the oxa-bridge in the cycloadducts with $BF_3 \cdot OEt_2$ (path A) and Ac_2O/H_2SO_4 (path B) afford novel multifunctional fused tetrahydofurans **284** and **285** in 51% and 73%, respectively (Scheme 92).[183]

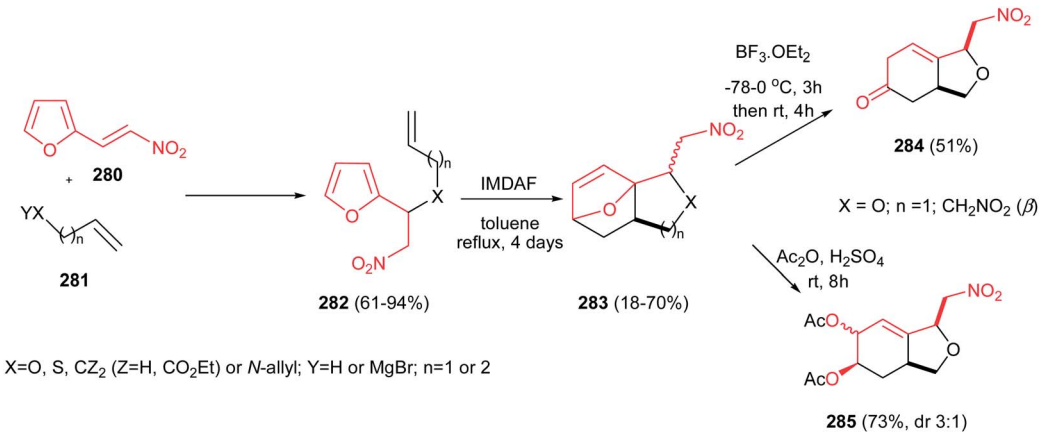
Rodrigues *et al.* described that addition of nitroalkenes **18** to a solution of prop-2-ynyl alcohols **286** in a mixture of benzene and *t*-BuOH containing *t*-BuOK, led to formation of 3-methylenetetrahydrofurans **287a** in moderate to good yields and high diastereoselectivities, which in some cases were accompanied by the formation of corresponding dihydropyrans **287b** (Scheme 93).[22] The reaction proceeded with total diastereoselectivity due to allylic 1,3-strain. Among other bases examined in this transformation (BuLi, NaH, KH, K_2CO_3 and Cs_2CO_3), only Cs_2CO_3 gave similar results but in lower yield.

In 2001, Dulcere *et al.* developed a two-step protocol for the construction of a series of vinylidene tetrahydrofurans **290** as a single diastereomer in high yield *via* KO*t*-Bu mediated oxy-Michael addition of propargyl alcohols **288** to nitroalkenes **18** followed by S_Ni' ring-closure (Scheme 94).[184] Different leaving groups such as chloride, bromide, and alkysulfonate examined, provided comparable results. The *trans* relationship between the nitro and the alkyl substituent R^2 is due to conformer **289** which is favored to avoid allylic strain.

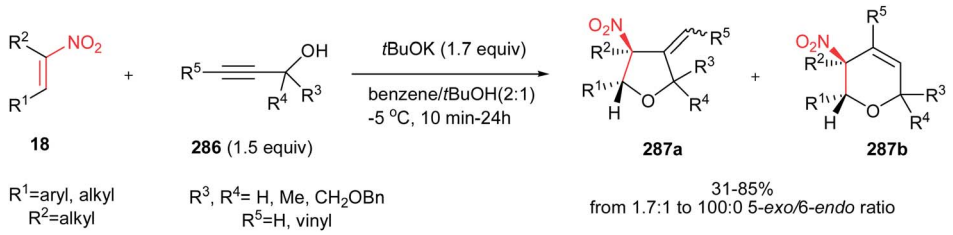
Alexakis *et al.* reported an enantioselective procedure for synthesis of chiral nitrosubstituted tetrahydrofuranyl ethers **294** *via* a tandem Michael/acetalisation/cyclisation reaction using combination of **Cat-8** and a gold complex as catalytic system (Scheme 95).[185] The reaction occurred between alkyne-tethered nitroalkenes **291** and aldehyde **292** to generate the corresponding products **294** in good yields and high diastereo- and enantioselectivities of up to 94% de and >99% ee,



Scheme 91 Tetrahydrofuran lignans *via* tandem oxidative anionic–radical processesor reductive radical cyclizations.



Scheme 92 Fused tetrahydrofurans *via* Michael-initiated intramolecular Diels–Alder furan reaction.



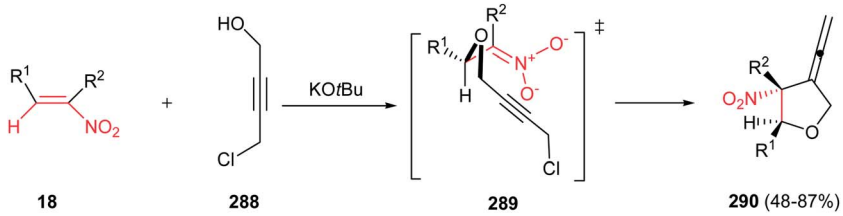
Scheme 93 Synthesis of 3-methylenetetrahydrofurans *via* Michael addition/cyclization sequence.

respectively. In this work, the reaction initiated with amine-catalyzed Michael addition followed by sequential addition of Au(I) complex to achieve acetalisation/cyclisation sequence. It is notable that *p*-TsOH was used to prevent deactivation of the Au(I) catalyst by the secondary amine catalyst.

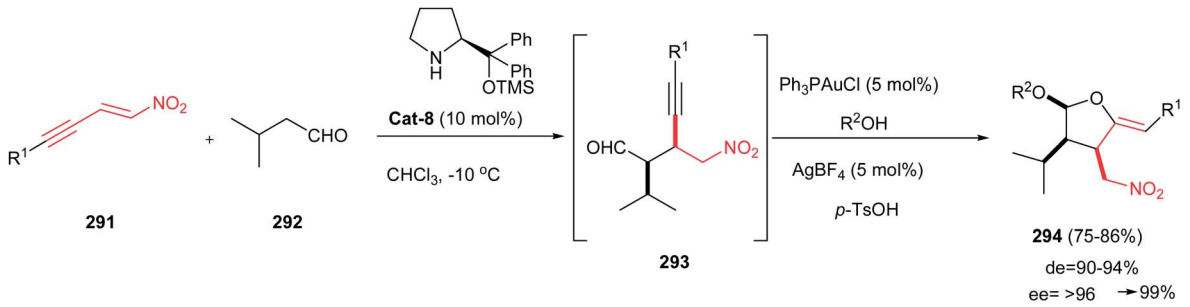
In addition, Hou and coworkers reported another asymmetric procedure for synthesis of substituted tetrahydrofurans **296** in high yields and stereoselectivities *via* [3 + 2]-cycloaddition reaction of vinyl epoxide **295** and nitroalkenes **15** using Pd/1,1′-ferrocene-*P*,*N*-ligand (**L-10**) (Scheme 96). Aliphatic nitroalkenes afford the products in similar yields and enantioselectivities compared to aromatic niroalkenes, but in lower diastereoselectivities.[186]

Another approach for synthesis of tetrahydrofurans is [3 + 2] cycloaddition reaction of carbonyl ylides with alkenes.[187] In this context, the $Rh_2(OAc)_4$-catalyzed reaction of a nitrostyrene **40** with dimethyl diazomalonate **297** and an aldehyde **85** was investigated by Nair *et al.* to afford tetrahydrofurans **298** in 76% yield as a single diastereomer (Scheme 97).[188] These transformations proceed *via* Rh-catalyzed generation of a carbonyl ylide **299** from the diazo compound and the aldehyde, which then undergoes a [3 + 2] dipolar cycloaddition with the nitroalkene. It is notable that these transformations are only effective with electron-poor alkenes.

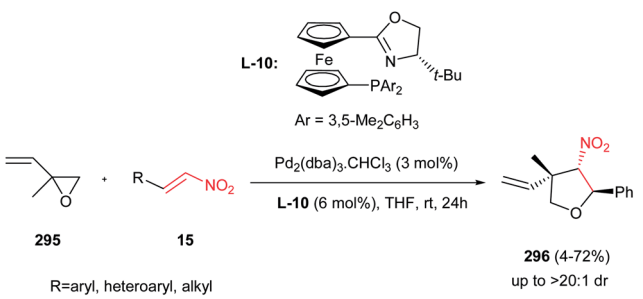
4.2.2. Furans and dihydrofurans. Furans and their derivatives are an important class of compounds due to their widespread occurrence in nature and versatile applications in medicinal chemistry and pharmaceutical industry.[189] The biological activities such as anti-microbial,[190] anticancer,[191] and tubulin binding properties[192] of furan containing compounds are well-documented in the literature. The classical methods for synthesis of furan derivatives are cyclocondensation of 1,4-dicarbonyl compounds (Paal–Knorr synthesis)[193] and that of α-haloketones or analogous compounds with β-dicarbonyl



Scheme 94 Sequential Michael addition-S_Ni' displacement.



Scheme 95 Chiral nitrosubstituted tetrahydrofuranyl ethers *via* tandem Michael/acetalisation/cyclisation reaction.



Scheme 96 Pd/1,1′-ferrocene-*P,N*-ligand catalyzed [3 + 2]-cycloaddition reaction of vinyl epoxide and nitroalkenes.

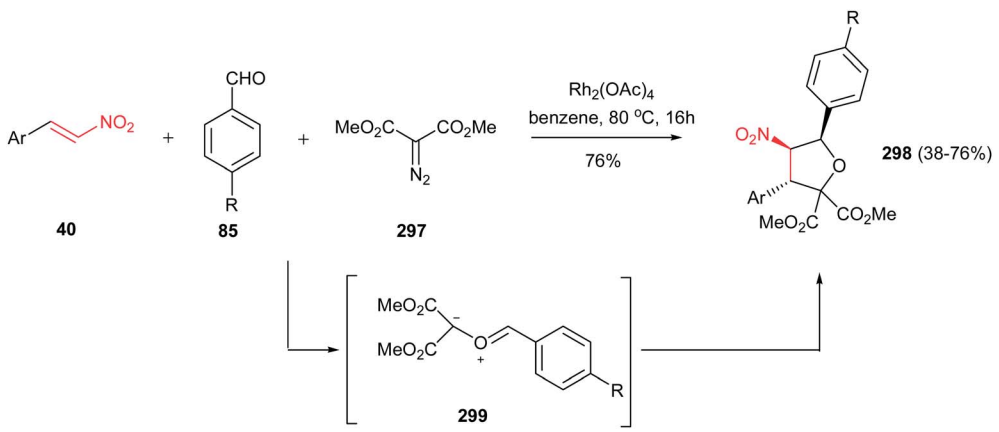
compounds (Feist–Benary synthesis).[194] Recently, transition metal-mediated cycloisomerization of alkynyl and allenyl substrates[195] and feasible cascade processes[196] have emerged as an efficient strategy for the synthesis of highly substituted furanes.

Dihydrofuran derivatives have also shown pharmacological properties, such as antibacterial,[197] antifungal[198] and anticancer activities.[199] Also they are valuable potential intermediates in the synthesis of many biologically active compounds.[200]

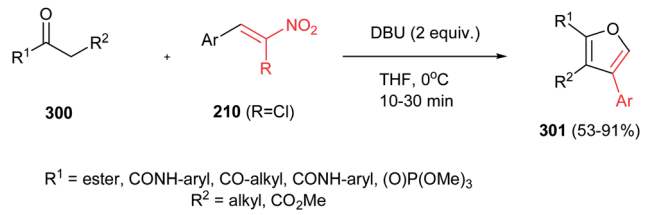
Very recently, Rodriguez *et al.* reported a simple and one-pot procedure for synthesis of substituted furans **301** starting with a nitroalkene **210**. The furan ring is formed *via* a formal [3 + 2] cycloaddition of a 1,2-dicarbonyl or 2-ketophosphonate ester **300** and an α-halo-α-nitroalkene **210** in one pot manner using DBU as the base in excellent yields (51–92%) in a relatively short time (10–30 min) (Scheme 98). The cycloaddition with ketophosphonate is particularly attractive because ketophosphonates can serve as synthetic handles in cross-coupling reactions.[201]

Namboothiri *et al.* described a highly regioselective cascade reactions of β-dicarbonyl compounds **303** with Morita–Baylis–Hillman acetates of nitroalkenes **164** and **302** for preparation of functionalized and fused furans **304–305** in high yields (Scheme 99).[202] The reaction promoted by DABCO and proceeded in a cascade Michael-5-*exo*-trig-oxa-Michael fashion in the case of open chain **303a** and six-membered **303b** cyclic β-dicarbonyl compounds afforded fused furans **304–305**. For five-membered cyclic β-dicarbonyl compounds such as cyclopentane-1,3-dione **303c**, a cascade Michael-5-*endo*-trig-oxa-Michael reaction takes place to afford fused 4*H*-pyrans **306**. A proposed mechanism for preparation of these products is given in Scheme 100. However, Meldrum's acid and barbitoric acid did not give the corresponding products.

A one-pot synthesis of tetrasubstituted furan derivatives **308** has been developed by Palmieri *et al.* starting with α-functionalized carbonyl derivatives **307** and β-nitroacrylates **118**, catalyzed by acidic alumina under catalyst-free conditions (Scheme



Scheme 97 Rh-promoted synthesis of tetrahydrofurans from nitrostyrenes, dimethyl diazomalonate and aldehydes.



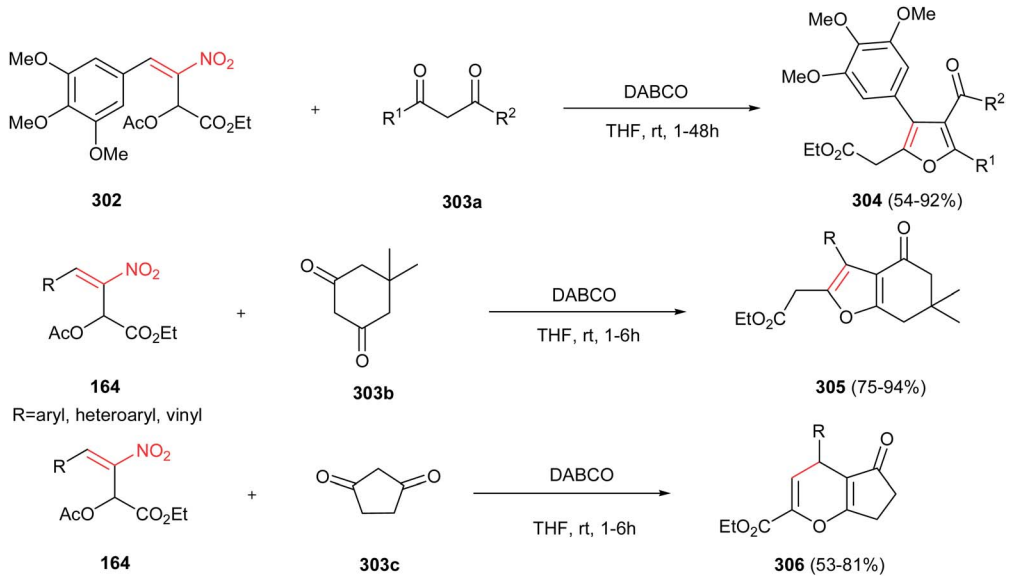
Scheme 98 Synthesis of substituted furans *via* [3 + 2] cycloaddition of a 1,2-dicarbonyl or 2-ketophosphonate ester and an α-halo-α-nitroalkene.

101).[203] This process gives at least the presence of two powerful functionalities in the 3- and 4-positions of furan rings.

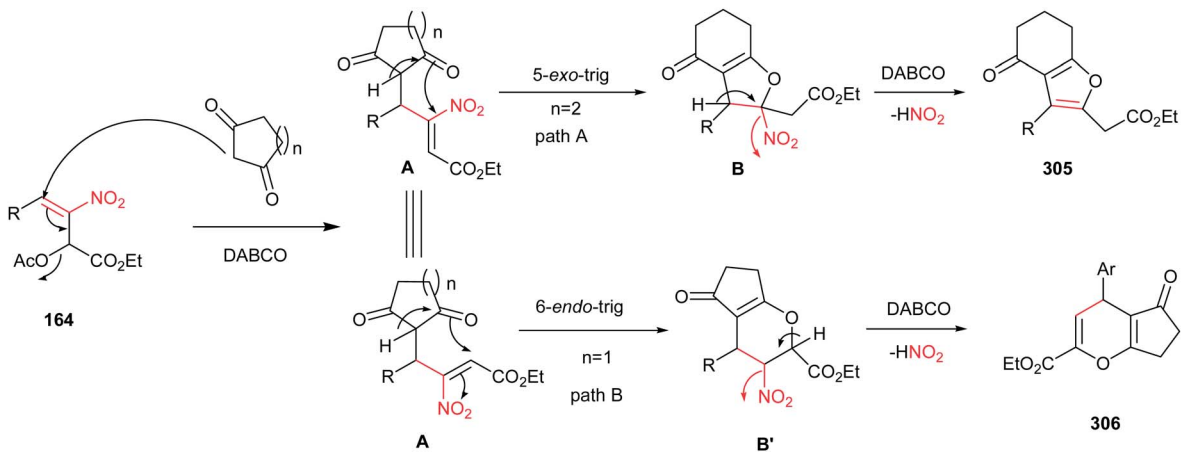
Sosnovskikh *et al.* demonstrated that reaction of 1,3-dicarbonyl compounds **309** with (*E*)-1,1,1-trifluoro-3-nitrobut-2-ene **310** in the presence of NaOAc in ethanol at rt, afforded β-(trifluoromethyl)furans **311** in good yields (Scheme 102). Meldrum's acid and its derivatives did not react with **310** under the same conditions which may be because of the lack of enolic form in solution.[204]

Shi *et al.* developed a highly efficient cascade synthesis of dihydrofurans *via* the same strategy as outlined in Scheme 84, but with using 1,3-diketone/β-keto-esters instead of sodium azide (Scheme 103).[205] Proline (5 mol%) was examined as efficient catalyst for this approach to provide dihydrofurans in excellent yields (up to 95%) and diastereoselectivity (only *trans* isomers). Since one equivalent of HNO_2 would be generated in this process, application of 1.0 equiv. of base (0.5 equiv. of K_2CO_3) significantly improves the reaction yield. With proper selection of starting materials, substituted groups on all the four positions of furan could be controlled.

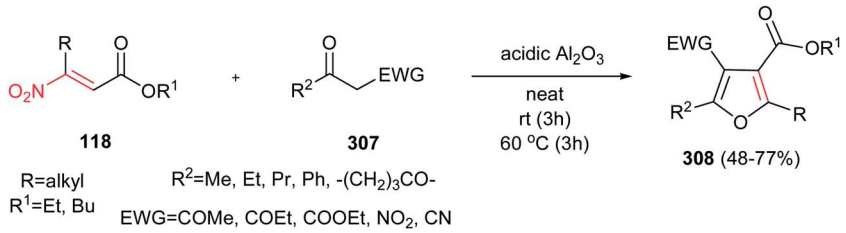
Reactions of curcumins **315** with α-bromonitroalkenes **210** afford dihydrofurans **316** with two contiguous chiral centers



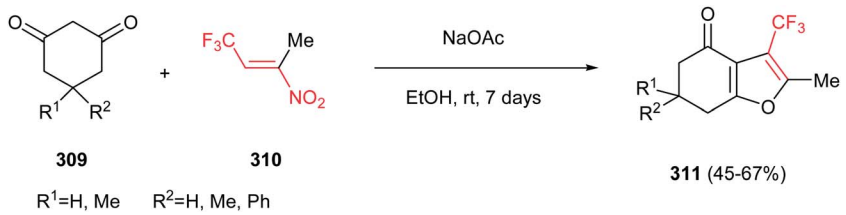
Scheme 99 Synthesis of furans and pyrans from β-dicarbonyl compounds and Morita–Baylis–Hillman acetates of nitroalkenes.



Scheme 100 Proposed mechanism for preparation of furans and pyrans.



Scheme 101 Acidic alumina-catalyzed synthesis of tetrasubstituted furans from α-functionalized carbonyl derivatives and β-nitroacrylates.

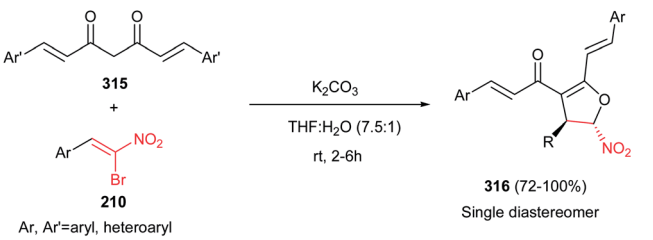


Scheme 102 Synthesis of fused β-(trifluoromethyl)furans from (*E*)-1,1,1-trifluoro-3-nitrobut-2-ene and 1,3-dicarbonyl compounds.

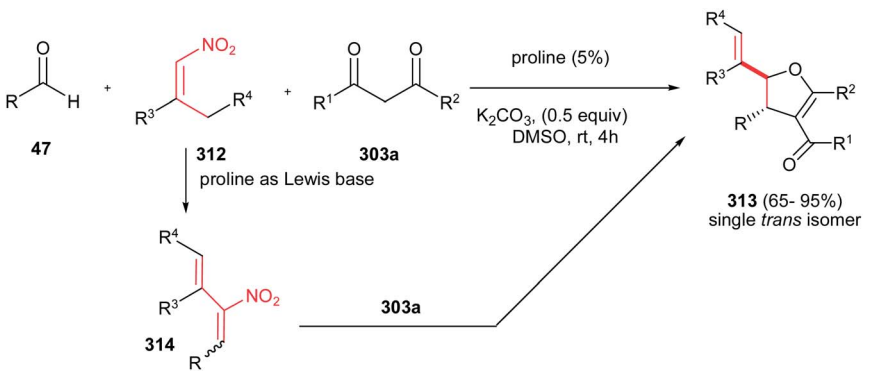
through an intermolecular Michael addition-intramolecular nucleophilic substitution (*O*-alkylation), which is analogous to an 'interrupted' Feist–Benary reaction. No double Michael adducts were isolated in these reactions. The products were obtained as single diastereomers in excellent yields (Scheme 104).[206]

A one-pot asymmetric synthesis of tetronic acid derivatives **318** in good yields and with excellent enantioselectivities was reported by Yan *et al.* in 2012.[207] The reaction proceeds *via* asymmetric conjugate addition of ethyl 4-chloro-3-oxobutanoate **317** to nitroalkenes **15** catalysed by 6′-dimethyl quinine **Cat-10** and subsequent intramolecular cyclization promoted by AcOLi. Various β-aryl, heteroaryl, and alkyl nitroalkenes are generally applicable in the reaction (Scheme 105). The absolute configuration of the products was assigned as *R* by X-ray diffraction analysis. Furthermore, the products are synthetically useful for the preparation of chiral aza-mimics of prostaglandins and γ-lactams.

Very recently, reactions of 4-hydroxycoumarin **319** and nitroolefins **40** were investigated by Wang *et al.* to afford the 2,3-dihydrofuro[3,2-*c*]-coumarin type adducts **320** (fused dihydrofurans) in moderate yields (53–75%) and satisfactory enantioselectivities (64–90% ee) (Scheme 106).[208] The reaction proceeded *via* domino Michael addition–intramolecular cyclization, followed by dehydration and tautomerization in the presence of chiral bifunctional thiourea **Cat-11** (20 mol%) and 2,6-difluorobenzoic acid (20 mol%) as additive in 1,4-dioxane for 5 days. The electronic feature and position of the substituents on the aromatic ring of nitroalkenes have only slight effects



Scheme 104 Dihydrofurans from curcumins and α-bromonitroalkenes.

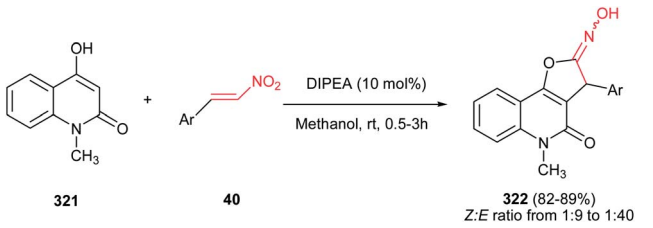


Scheme 103 Proline-catalyzed synthesis of dihydrofurans from 1,3-diketone/β-keto-esters, aldehydes and nitroalkenes.

on the yields, while striking effects on enantioseletivities. In this context, Yao and coworkers described that by using 4-hydroxy-*N*-methylquinolinone **321** instead of **319**, the corresponding fused 5-hydroxyimino-4,5-dihydrofurans **322** can be obtained as inseparable mixture of *E* : Z isomers (*E* : *Z* ratio of up to 40 : 1) (Scheme 107).[209]

Wang and co-workers described a four-component protocol for the direct synthesis of 2-arylideneamino-3-aryl-4*H*-furo[3,2-*c*]-chromen-4-ones **323** from substituted nitrostyrenes **40**, aromatic aldehydes **72**, coumarins **319**, and ammonium acetate (Scheme 108).[210] Different reaction conditions were tested and the best results were obtained when a mixture of a nitroalkene **40** (1 equiv.), 4-hydroxy coumarin (1 equiv.), and piperidine (50 mol%) were stirred in EtOH at room temperature for 12 h, followed by addition of an aldehyde **72** (1 equiv.) and ammonium acetate (1 equiv.) and stirring for 12 h at the same temperature, then refluxing the final mixture for 3 h. Nitrostyrenes and aromatic aldehydes with both electron-donating and -withdrawing groups were amenable for this reaction providing the products in moderate to good yields.

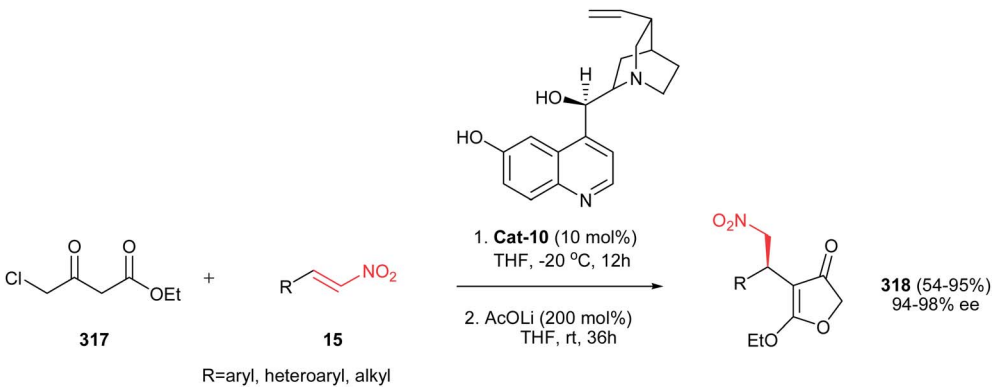
Furthermore, Parra *et al.* demonstrated a facile and efficient protocol for the synthesis of *trans*-dihydroarylfuran derivatives **325** from (*Z*)-bromonitroalkenes **210** and naphthol or phenol derivatives **324** in good yields and excellent enantioselectivities by using squaramide catalysis **Cat-12** (Scheme 109).[211] The reaction proceeds *via* a Michael–Friedel–Crafts reaction followed by a nucleophilic substitution on the bromide carbon. The use of a base for neutralization of generated HBr is a key



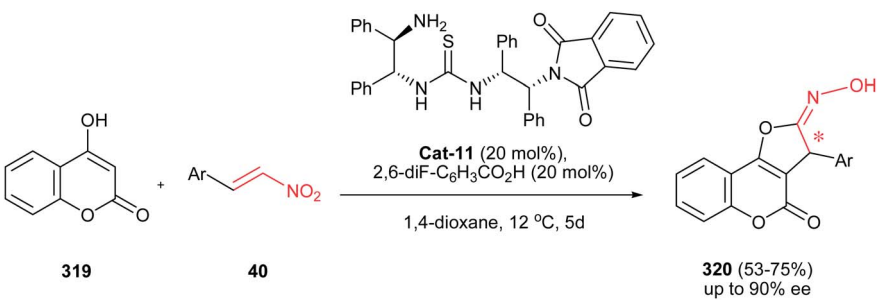
Scheme 107 Synthesis of fused 5-hydroxyimino-4,5-dihydrofurans from 4-hydroxy-*N*-methylquinolinone and nitroalkenes.

point in this reaction. Nitroalkenes with bulkier alkyl groups on the β position were not compatible, due to the steric hindrance of the first step. The absolute configuration of products was determined as (1*S*,2*S*).

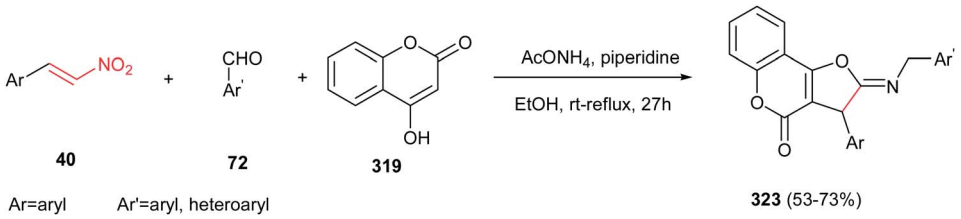
In 2011, Yu *et al.* reported a biocatalytic route for synthesis of 5-hydroxyimino-4,5-dihydrofurans and their fused derivatives **327a** *via* a coupling reaction between β-nitrostyrenes **40** and 1,3-dicarbonyl compounds **326** catalyzed by the lipase derived from porcine pancreas (PPL) (Scheme 110).[212] Aromatic and heteroaromatic nitroalkenes with different substitutions were successfully applied in this protocol to give the corresponding products in high yields and stereoselectivity (*Z*/*E* up to 99 : 1), along with the Michael adducts **327b** as minor products. 1,3-Cyclohexanedione **326** ($n = 1$) showed better reactivity and lower stereoselectivity compared to linear 2,4-pentanedione **326** ($n = 0$) under similar reaction conditions. However, 1,3-



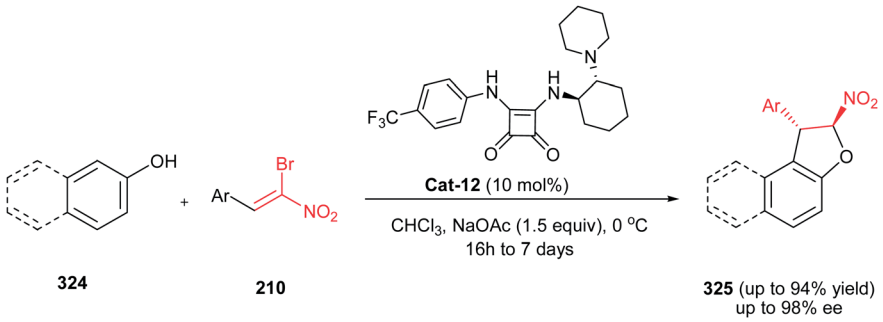
Scheme 105 Synthesis of tetronic acid derivatives.



Scheme 106 Asymetric addition of 4-hydroxycoumarin to nitroalkenes.



Scheme 108 A four-component protocol for the direct synthesis of 2-arylideneamino-3-aryl-4*H*-furo[3,2-*c*]chromen-4-ones.



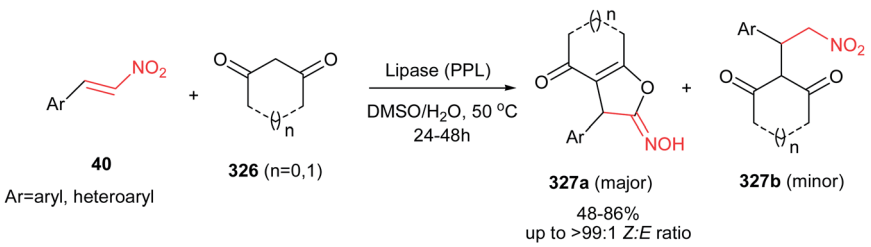
Scheme 109 Synthesis of *trans*-dihydroarylfurans from (*Z*)-bromonitroalkenes and naphthols or phenols.

cyclopentanedione, ethyl acetoacetate, and diethylmalonate could not give the corresponding cyclic products and the Michael adducts were only achieved.

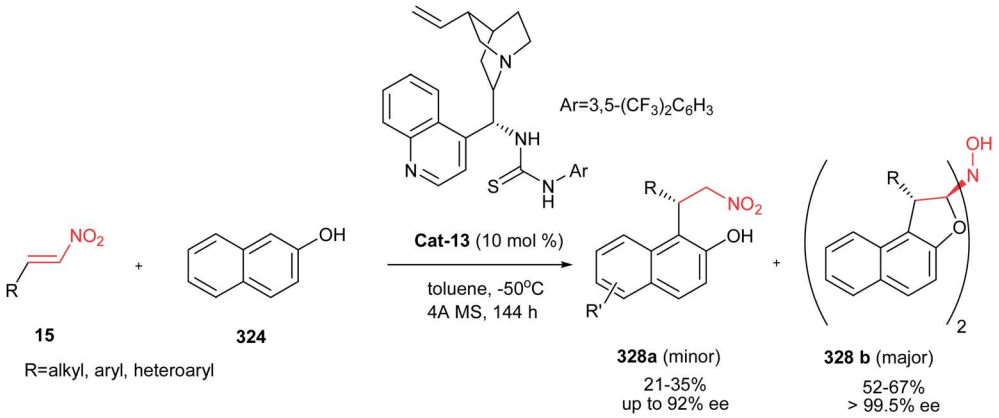
Although reaction of 2-naphthols **324** with simple nitroalkenes **15** gave the Michael adducts **328a** in the presence of thiourea–tertiary amine organocatalysts at −50 °C for 96 h, surprisingly, Chen *et al.* reported that by expanding the reaction time to 144 h, optically pure dimeric 1,2-dihydronaphtho[2,1-*b*]-furanyl-2-hydroxylamine derivatives **328b** can be obtained as major product (Scheme 111).[213]

Finally, reaction of ethyl 4,4,4-trifluoro-3-oxobutanoate **329** and nitroalkenes **40** were investigated by Song *et al.* to prepare trifluoromethyl-substituted furan derivatives **330a** (major product) and **330b** (minor product) (Scheme 112).[214] The reaction proceeded *via* Michael addition followed by intramolecular cyclization reaction. While treatment of **330a** with 1.2 equivalents of TsOH in refluxing *t*-BuOH afforded ethyl 2-hydroxy-5-imino-4-aryl-2-(trifluoromethyl)-2,5-dihydrofuran-3-carboxylates **330d** in good yields, with less sterically hindered alcohols such as EtOH and MeOH, ethyl 2-alkoxy-5-oxo-4-aryl-2-(trifluoromethyl)-2,5-dihydrofuran-3-carboxylates **330c** was formed as major products. In *i*-PrOH, **330c** and **330d** could be obtained in approximately equal amount. Furthermore, they proved that **330d** could be directly synthesized by one-pot, tandem reaction of **329** with **40** in *t*-BuOH.

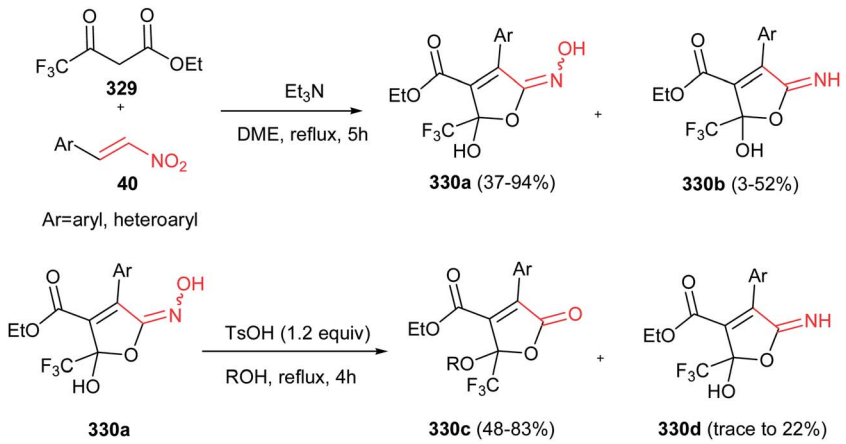
4.2.3. Benzofurans, naphthofurans and their reduced derivatives. The presence of nitro group in the structure of benzofurans allows further constructions leading to formation of many biologically active compounds. In this context, Liu *et al.* reported a two-step synthesis of various 3-alkyl-2-nitrobenzo[*b*]-furans **333** starting with 2-((*E*)-2-nitrovinyl)phenols **331** *via* a hypervalent iodine-induced oxidative cyclization, with good to excellent yields (Scheme 113).[215] The reaction start with Michael addition of a Grignard reagent to 2-((*E*)-2-nitrovinyl)phenols **331** to generate the alkylated 2-(2-nitroethyl)phenols **332**. Oxidative cyclization of **332** were achieved using $PhI(OAc)_2$/TBAI. The best results were obtained when 2.5 equiv. of TBAI were used with 3.0 equiv. of $PhI(OAC)_2$ in acetonitrile at 35 °C in the presence of 2 equiv. of triethylamine. Also, indole was used instead of Grignard reagent as nucleophile in the first step to give the 3-(2-nitrobenzofuran-3-yl)-1*H*-indole in 52% yield.



Scheme 110 A biocatalytic route for synthesis of 5-hydroxyimino-4,5-dihydrofurans.



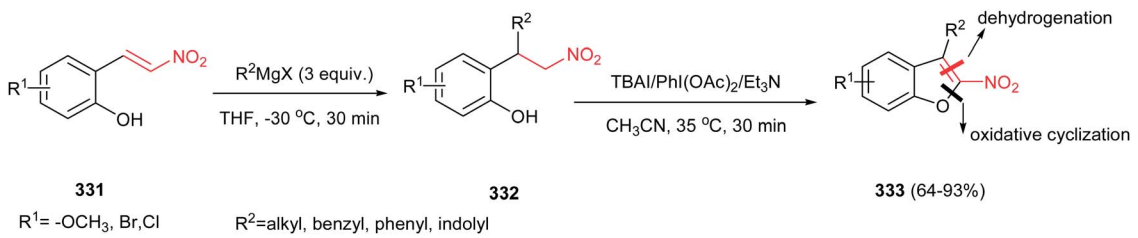
Scheme 111 Asymmetric Friedel–Crafts/cascade reaction of 2-naphthols and nitroalkenes.



Scheme 112 Reaction of ethyl 4,4,4-trifluoro-3-oxobutanoate and nitroalkenes.

In 2005, Ishikawa *et al.* developed the synthesis of 4-acetoxy-2-amino-3-arylbenzofurans **336** from nitroalkenes **15** and cyclohexane-1,3-diones **334**.[216] This one-pot two-step process provided first the cyclic oxime intermediates **335** in THF in the presence of catalytic amount of Et_3N (10 mol%), which was then converted to the corresponding products **336** *via* treatment with acetic anhydride (Ac_2O), triethylamine(Et_3N), and 4-(*N*,*N*-dimethylamino)pyridine (DMAP) at room temperature (Scheme 114). Is it notable that aliphatic nitroalkenes gave lower yield compared to aromatic nitroalkenes. Unsymmetrical cyclohexane-1,3-diones afforded the 5-alkyl4-acetoxy-2-amino-3-arylbenzofurans in combination with their regioisomer, 7-alkyl 4-acetoxy-2-amino-3-arylbenzofurans. In this context, Yao *et al.* demonstrated that similar yields and selectivity in the synthesis of **335** can be achieved using silica gel as mild acidic catalyst in combination with microwave irradiation at 60 °C in methanol.[217]

Very recently, Namboothiri *et al.* investigated the reaction of Morita–Baylis–Hillman acetates of nitroalkenes **164** with different arenols such as β-naphthol **324**, α-naphthols **337**, and substituted phenols **338** under basic conditions to give the corresponding arenofurans **339–341** as single regioisomers in good to excellent yield (Scheme 115).[218] Several organic and inorganic bases were screened in this protocol and, finally,



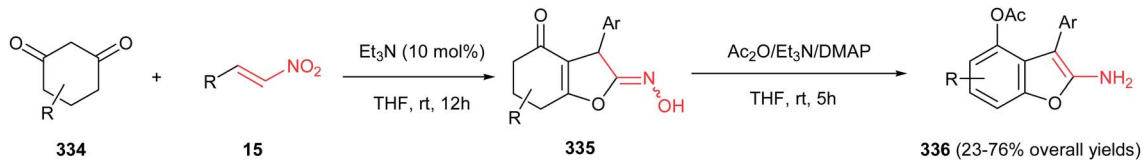
Scheme 113 Synthesis of 3-alkyl-2-nitrobenzo[*b*]furans starting with 2-((*E*)-2-nitrovinyl)phenols.

K_2CO_3 in toluene at room temperature was selected as optimal conditions with regard to yields and reaction times. While the reaction of **164** with β-naphthol **324** is not sensitive to the electronic nature of substituents on the aryl group in the acetates, for 1-naphthols, acetates**164** with strongly electron donating aryl groups afforded greater yield than those with weak electron donating ability. In addition, phenols with strongly electron donating alkoxy groups reacted well with **164** and afforded the corresponding furans **341** in good to excellent yields (22–82%). Simple phenol gave the Michael adduct as the only product. Proposed mechanism by the authors involved an S_N2' reaction/intramolecular oxa-Michael addition reaction cascade. Furthermore, this strategy was successfully employed for the total synthesis of an anti fungal agent isoparvifuran **342** in six steps from nitrostyrene with 47% overall yield.

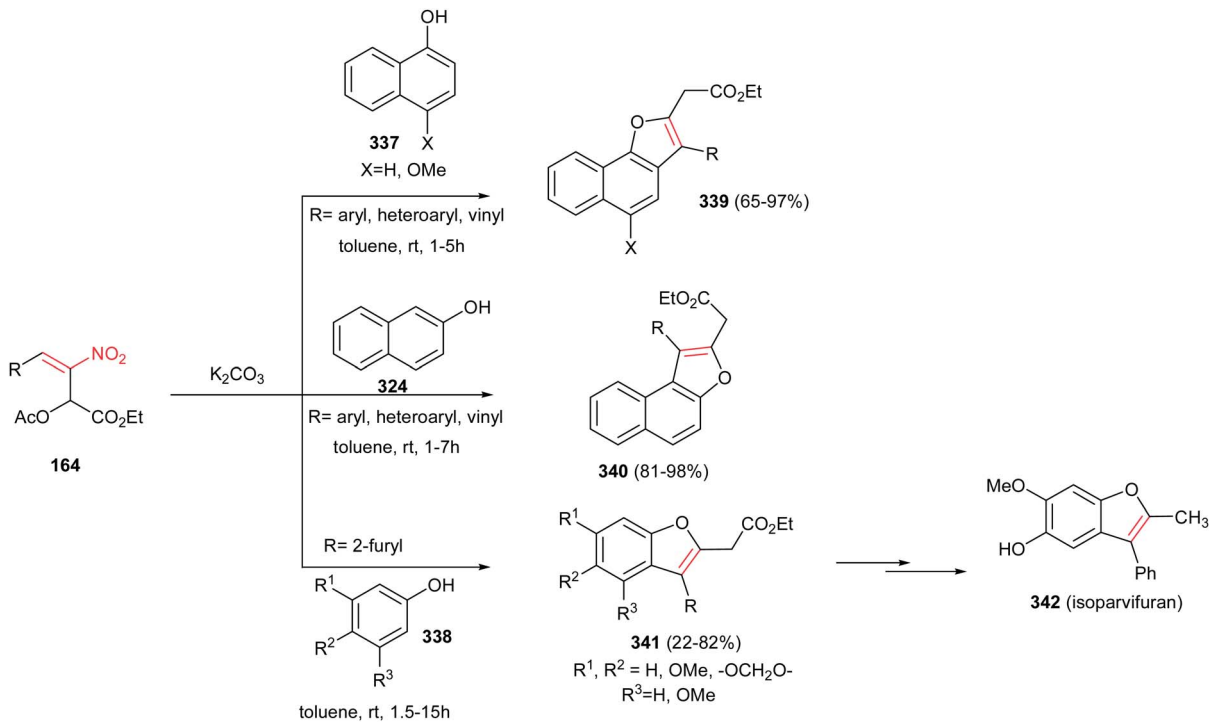
Hajra and co-workers described the reaction of naphthols/phenol **337**/**324** with nitroalkenes **18** in the presence of indium(III) triflate to give the benzofuran and naphthofuran derivatives **343a/b** in high yields (Scheme 116).[219] The reaction was performed by stirring an equimolar amount of starting materials and 5 mol% of In $(OTf)_3$ in DCE at reflux temperature with a $CaCl_2$ moisture guard tube. Aliphatic nitroalkenes were used successfully in this transformation, albeit with lower yields compared to aromatic nitroalkenes. Under the reaction conditions, no Michael adduct was observed.

As shown in Scheme 117, a one-pot four-component reaction between β-nitrostyrenes **40**, aromatic aldehydes **85**, ammonium acetate, and cyclohexane-1,3-diones **344** for synthesis of polysubstituted 3-aryl-2-arylmethylene amino-4-hydroxybenzofurans **345** was described by Wang *et al.*[220] The reaction was carried out by slow addition of a cyclohexane-1,3-dione **334** to a mixture of a β-nitrostyrene **40**, an aromatic aldehyde **85**, ammonium acetate, and piperidine in DMF at room temperature, and refluxing this mixture for 7 h to afford the titled compounds **345** in 46–73% yields. Variety of aromatic aldehydes and nitroalkenes were successfully used in this protocol.

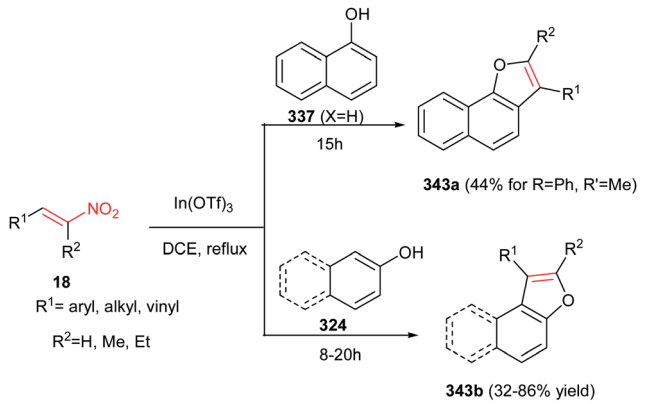
A series of functionalized 2,3-dihydrobenzofurans **347** was prepared by Xie and coworkers starting with 2-hydroxyarylnitroalkenes **331** and diethyl α-bromomalonate **346** *via* a domino oxa-Michael/aldol alkylation reaction catalyzed by K_2CO_3 under mild conditions (Scheme 118).[221] Other bases such as KOH, KOAc and DABCO gave lower yields compared to K_2CO_3. The best yield was obtained when 120 mol% of K_2CO_3 was used in acetone at room temperature for 3 h. Also, using ethyl 2-



Scheme 114 Formation of 4-acetoxy-2-amino-3-arylbenzofurans from 1-aryl-2-nitroethylenes and cyclohexane-1,3-diones.



Scheme 115 Synthesis of naphthofurans and benzofurans.



Scheme 116 Reaction of naphthols/phenols with nitroalkenes in the presence of indium(III) triflate.

chloroacetoacetate instead of **346** afforded the corresponding product in high yield and excellent diastereselectivity (>99 : 1).

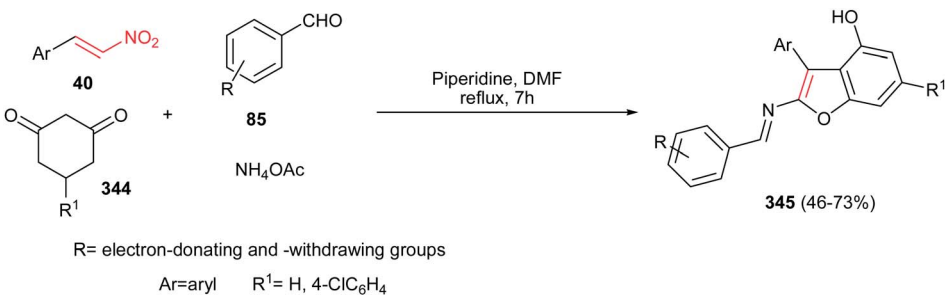
Very recently, Yao *et al.* described the synthesis of substituted 2-amino-3-phenylnaphtho[2,3-*b*]furan-4,9-dione derivatives **349** in moderate to good yields *via* the NH_4OAc-catalyzed reaction of 2-hydroxy-1,4-naphthoquinone **348** (1 equiv.) and nitroalkenes **40** (2 equiv.) in water at 100 °C (Scheme 119).[222] Nitroalkenes with electron-donating groups afforded higher yields than those with electron-withdrawing groups. Other bases such as TEA, basic Al_2O_3, $(NH_4)_2CO_3$, NaOAc, NH_4HCO_3, KOAc, K_2CO_3 and *t*-BuOK resulted in the same products in lower yields. Performing the reaction at temperatures up to 80 °C produced the Michael adducts. Mechanistic studies revealed that the ammonium acetate is not the source of the amino group in the products and the reaction proceeded *via in situ* reduction of the nitro group to the amino functionality without using any reducing agents during the process. Also, a one-pot three-component version of this reaction using an aldehyde **255**, 2-hydroxy-1,4-naphthoquinone **348** and nitromethane **350** was developed by the same authors. Under similar conditions, the yields of the products obtained from multicomponent reactions are less than those obtained from the direct condensation of nitroalkenes and 2-hydroxy-1,4-naphthoquinone.

Finally, 3-aryl-5,6-dihydrobenzofuran-7(4*H*)-ones **352** are prepared by Hunt and Simpkins through the reaction of β-nitrostyrenes **76** and 1,2-cyclohexanedione **351** promoted by 10 equiv. of K_2CO_3 as a base in DMF at 80 °C. The products were obtained in good yields (40–84%). Also, this process is highly dependent on the base stoichiometry (Scheme 120).[223]

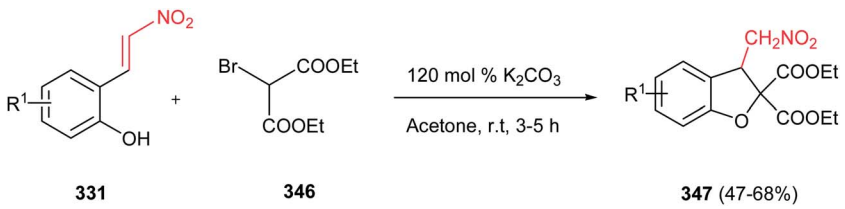
4.3. Synthesis of S-heterocyclic compounds

4.3.1. Thiophenes, dihydrothiophenes and tetrahydrothiophenes. Thiophene derivatives form an integral part of many natural products and pharmaceuticals.[224] They have wide applications in advanced materials such as conjugated polymers,[225] organic conductors,[226] semiconductors,[227] and light emitting devices.[228] Generally, formation of thiophenes can be divided in four main categories; (1) reaction of the 1,4-difunctional compounds with sulfides (Paal–Knorr strategy); (2) reaction of unsaturated compounds with sulfides (Gewald reaction); (3) reaction of 1,2-difunctional compounds with thiodiacetic acid and esters; and (4) reaction of aryl methyl ketones with sulfides.[229] In addition, dihydro- and tetrahydrothiophenes have found extensive applications in the structure of many biologically active compounds[230] and are important intermediates that form thiophene derivatives through dehydration and aromatization.

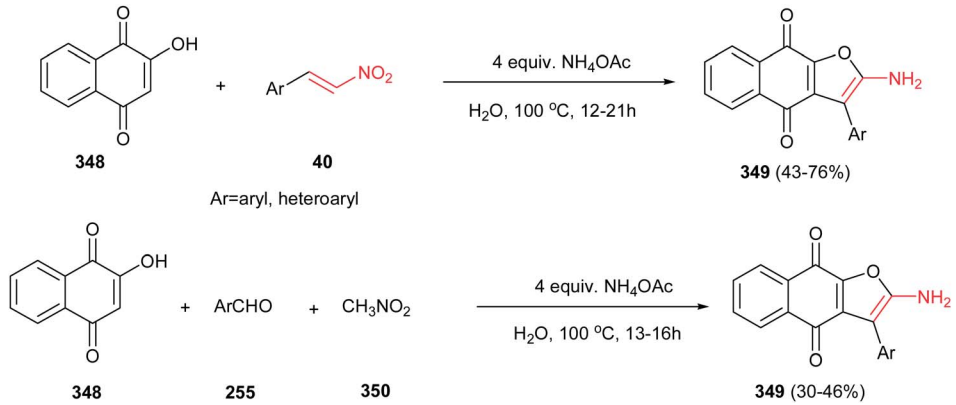
Southern and coworkers developed an efficient approach to 3-nitro-2-substituted thiophenes **357** in two steps starting with



Scheme 117 Synthesis of polysubstituted 3-aryl-2-arylmethylene amino-4-hydroxybenzofurans.



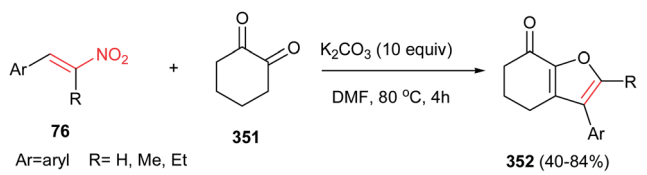
Scheme 118 Synthesis of 2,3-dihydrobenzofurans starting with 2-hydroxyarylnitroalkenes and diethyl α-bromomalonate.



Scheme 119 NH_4OAc-catalyzed preparation of 2-amino-3-phenylnaphtho[2,3-*b*]furan-4,9-dione derivatives in water.

commercially available 1,4-dithane-2,5-diol **353** and nitroalkenes **15**.[231] The reaction proceeds *via* formation of the thiolate anion **354** from dithiane **353** with a catalytic amount of triethylamine, and subsequent Michael addition-intramolecular Henry reaction to generate the tetrahydrothiophenes (THTs) **356** in excellent yields (Scheme 121). Subsequent dehydration and oxidation of THTs using 20 equiv. (w/w) of acidic alumina with 1.5 equiv. of chloranil under microwave irradiation (with the maximum temperature set to 125 °C and maximum power set to 200 W) form 3-nitro-2-substituted thiophenes **357** bearing a wide range of substituents (aromatic, heterocyclic, aliphatic, H, CH_2OTBS) at the 2-position. Alternative dehydration and oxidation systems such as SiO_2/DDQ and TFA/DDQ were also used, but gave lower yield. Both aromatic and aliphatic nitroalkenes are compatible with this protocol. Also, reactions of 1,4-dithiane-2,5-diol **353** with 2-nitroethylacetates **358**, used as stable precursors for the corresponding nitroalkenes, were investigated by Risi *et al.* for synthesis of 4-nitrotetrahydrothiophen-3-ol scaffolds **359** (Scheme 122).[232]

Very recently, Tao *et al.* reported that the same reaction can be efficiently catalyzed by a tertiary amine immobilized fiber **Cat-14** to give the THTs **360a/b** in high to excellent yields (75–93%) (Scheme 123).[233] The catalyst **Cat-14** was synthesized *via* reaction of PANF and ethylenediamine followed by alkylation with 3-dimethylaminopropylchloride hydrochloride in the presence of K_2CO_3. The fiber catalyst exhibits excellent recyclability and reusability (up to 10 times) without any additional treatment.

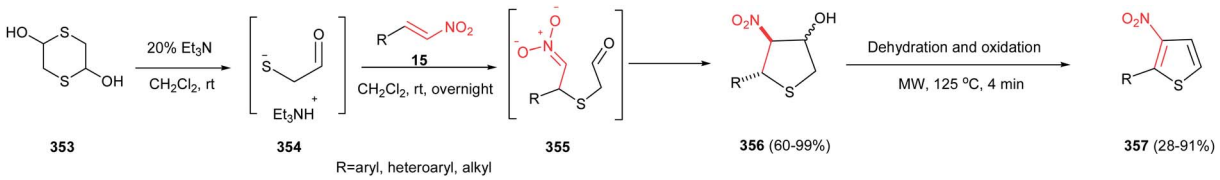


Scheme 120 K_2CO_3-promoted synthesis of 3-aryl-5,6-dihydrobenzofuran-7(4*H*)-ones.

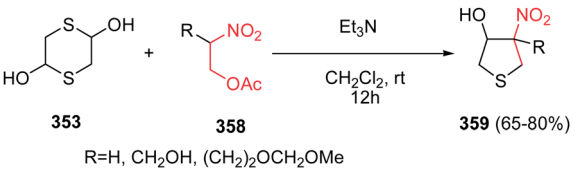
A novel asymmetric domino thia-Michael/Michael addition reaction between nitroalkenes **15** and *trans*-ethyl 4-mercapto-2-butenoate **361** was employed by Wang *et al.* for synthesis of trisubstituted THTs **362** (Scheme 124).[234] Different organocatalysts, solvents and reaction temperatures were screened and using 20 mol% of Takemoto amine thiourea catalyst **Cat-15** for the reaction of 1.2 mmol of **361** with 1 mmol of **15** in chloroform at −40 °C for 72 h was selected as optimum condition. Under this condition, one C–S and one C–C bond and three stereogenic centers were generated in a "one pot" fashion with high enantioselectivity (92–97% ee) and good diasteriomeric ratios (6 : 1 to >30 : 1). Notably, aromatic, heteroaromatic and aliphatic nitroalkenes afforded similar results in this transformation. Mechanistic studies by the authors revealed that the stereochemical outcomes are the results of an unprecedented activation mode of cooperative direct stereocontrol and dynamic kinetic resolution by catalyst.

In 2007, Chunikhin *et al.* established that the reaction of nitrostyrenes **40** with cyanothioacetamide **363** in the presence of catalytic amount of a base such as tetramethylethylenediamine (TMEDA) or morpholine in ethanol at room temperature afford compounds **364** in high yields (Scheme 125).[235]

Reaction of *trans*-β-nitrostyrene **55** with mesoionics **365**, prepared by the reaction of thioureas and α-chlorophenylacetic acid chloride in the presence of triethylamine, afforded a



Scheme 121 Tandem Michael addition-intramolecular Henry reaction for generation of tetrahydrothiophenes and their oxidation to thiophenes.



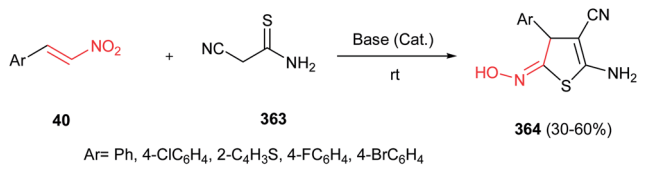
Scheme 122 Synthesis of 4-nitrotetrahydrothiophen-3-ols from 1,4-dithiane-2,5-diol and 2-nitroethylacetates.

diastereomeric mixture of racemic dihydrothiophenes **367a/b** in CH_2Cl_2 at room temperature for 48 h, which can be separated by flash chromatography (Scheme 126).[236] The reaction proceeds *via* the bicyclic intermediate **366a** and **366b**, which were evidenced by NMR experiments in $CDCl_3$ at 0 °C.

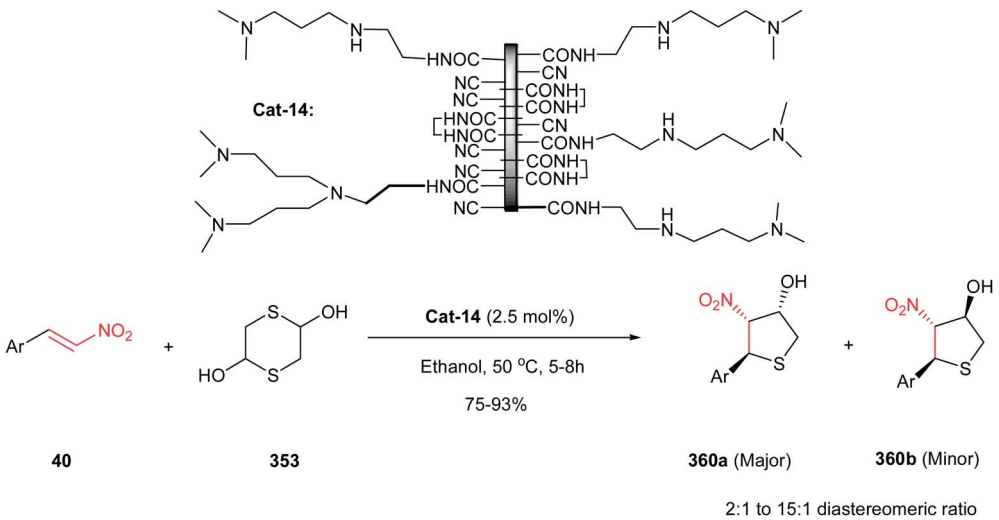
Finally, Bogdanowicz-Szwed and Gil in 2004 carried out the reaction of cyclic 3-oxoacid thioanilides with β-nitrostyrenes to achieve the functionalized spiro[cycloalkano-2,3-thiophenes] in boiling anhydrous ethanol in the presence of catalytic amounts of piperidine in moderate to good yields (41–86%).[237] Reaction of the obtained products with acetic anhydride yielded the corresponding oxime acetates. Any attempt for transformation of the products into nitrogen heterocycles *via* Dimroth or Beckmann rearrangements under acidic conditions was unsuccessful (Scheme 127).

4.4. N,O-Heterocyclic compounds

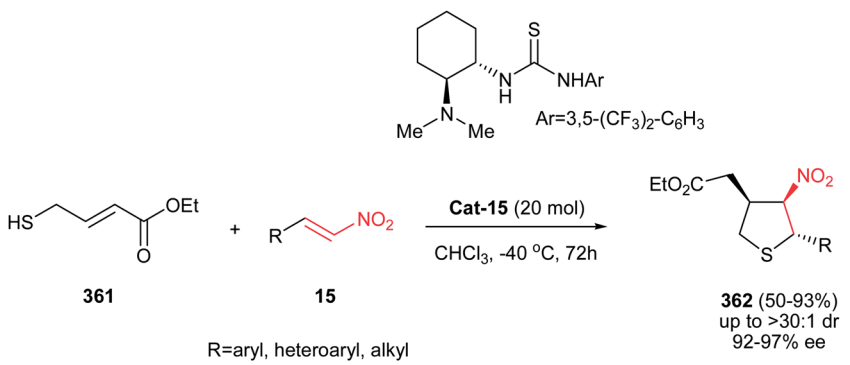
4.4.1. Isoxazole, Isoxazoline and isoxazolidine. Isoxazole and its reduced forms have served as useful building blocks in organic synthesis in the total synthesis of several natural and unnatural biologically active compounds such as β-lactam antibiotics, quinolizidine and indolizine tricycles, testosterone, sarkomycin, and biotin.[238] In addition, these compounds can be simply transformed into a variety of 1,3-bifunctional organic compounds such as β-hydroxy ketones, α,β-unsaturated ketones



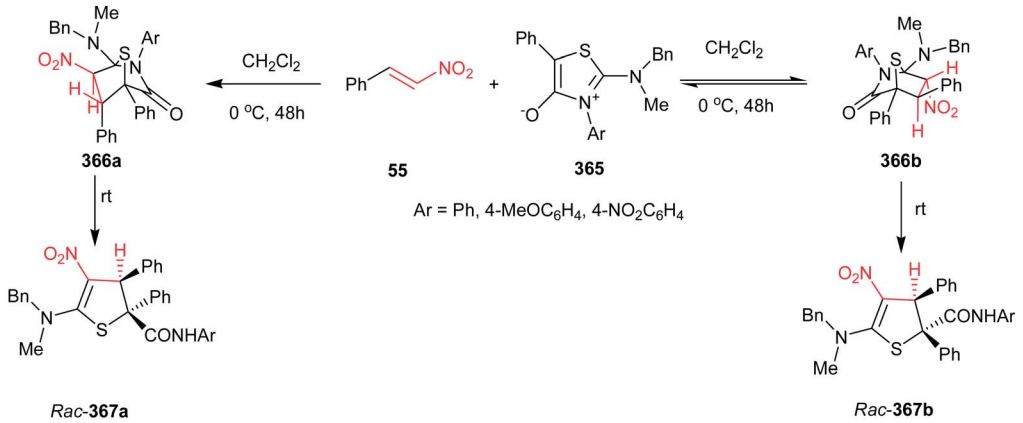
Scheme 125 Reaction of nitrostyrenes with cyanothioacetamide.



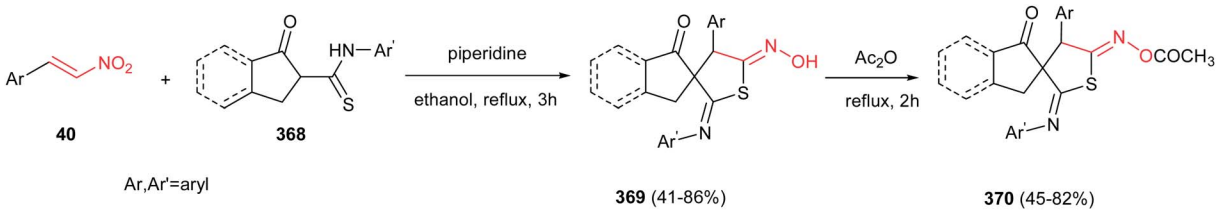
Scheme 123 Synthesis of substituted THTs from nitroalkenes and 1,4-dithiane-2,5-diol.



Scheme 124 Asymmetric domino thia-Michael/Michael addition approach for synthesis of THTs.



Scheme 126 Formation of dihydrothiophenes from thioisomunchnones and *trans*-β-nitrostyrene.



Scheme 127 Functionalized spiro[cycloalkanono-2,3-thiophenes] from cyclic 3-oxoacid thioanilides and β-nitrostyrenes.

and γ-amino alcohols.[239] 1,3-dipolar cycloaddition reactions[240] and condensation of hydroxylamine with 1,3-dicarbonyl compounds and α,β-unsaturated carbonyl compounds[241] are the most applied procedures for synthesis of isoxazole and its reduced derivatives.

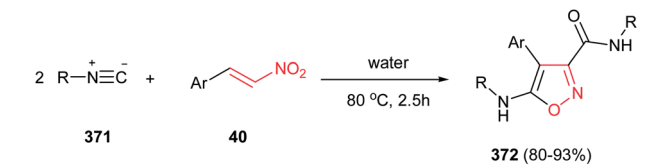
Although, the base-catalyzed reaction of nitroalkenes with isocyanoacetate is known as the Barton–Zard pyrrole synthesis, recently, Adib and co-workers demonstrated that by heating two equiv. of an isocyanide **371** with nitrostyrenes **40** in water at 80 °C, 5-(alkylamino)-4-aryl-3-isoxazolecarboxamides **372** could be obtained in 83–93% isolated yields (Scheme 128).[242] This protocol is well tolerated for aromatic and heteroaromatic nitroalkenes.

In 2010, Perumal and co-workers reported the synthesis of isoxazolobenzoxepanes **376** starting with nitroalkenes **373** derived from *O*-propargyl salicylaldehyde (Scheme 129).[243] They have shown that Michael addition of an indole **374** to the nitroalkene moiety of **373** in the presence of $KHSO_4$ in water afforded the corresponding nitroalkane **375**, which can be simply transformed to the isoxazolobenzoxepane **376** *via* intramolecular nitrile oxide cycloaddition upon treatment with $(Boc)_2O$/DMAP in methanol at 90 °C. Notably, replacing the terminal alkynes with internal alkynes gave similar yields.

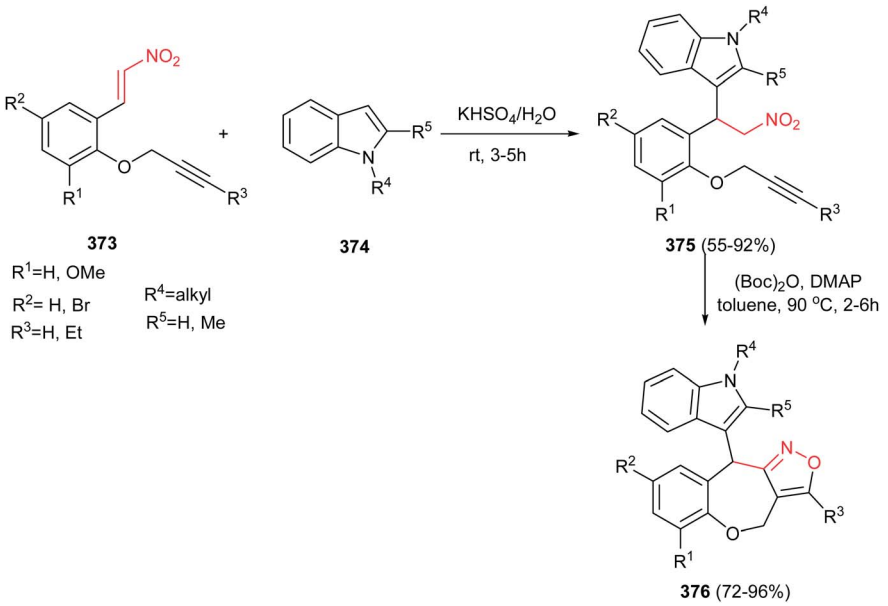
Gao *et al.* reported that the bicyclic isoxazoles **378** can be prepared from nitroalkenes **15** and prop-2-ynylmalonate **377a** or prop-2-ynylmalononitrile **377b** *via* a one-pot tandem Michael addition–dehydration-[3 + 2] cycloaddition reactions in the presence of *t*-BuOK and TCT or TCT/$ZnCl_2$ (Scheme 130).[244] The rate of cycloaddition of nitroalkenes **15** with prop-2-ynylmalonate **377a** is faster than with prop-2-ynylmalononitrile **377b**, because the presence of the bulky dimethoxy carbonyl groups enables the dipolarphile to be closer to the nitrile oxide to more easily undergo the intramolecular cycloaddition.

Also, the same group described that reaction of allyl malonate **379** with nitroalkenes **15** in the presence of *t*-BuOK at −78 °C gave the nitronates **380** which can be simply transformed to corresponding nitrile oxides **381** *via* treatment with 3 eq. of TCT. Then, intramolecular [3 + 2] cyclization of the nitrile oxide with the alkene moiety produces the bicyclic isoxazolines **382** in 84–97% yield (Scheme 131).[244]

Furthermore, highly substituted isoxazolines **386** were synthesized by Whittle and coworkers *via* a one-pot four-component condensation of TMSCN **383**, epoxides **384**, nitroalkenes **15** and methylacrylate **385**. They proposed that reaction of trimethylsilyl cyanide **383** with epoxide **384** in the presence of $Pd(CN)_2$ generates isonitrile **A** which undergoes [1 + 4] cycloaddition reaction with nitroalkenes in lithium perchlorate



Scheme 128 Synthesis of 5-(alkylamino)-4-aryl-3-isoxazolecarboxamides from isocyanides and nitrostyrenes in water.

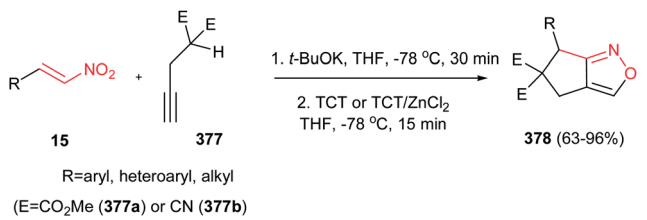


Scheme 129 Synthesis of isoxazolobenzoxepanes starting with nitroalkenes derived from *O*-propargyl salicylaldehyde.

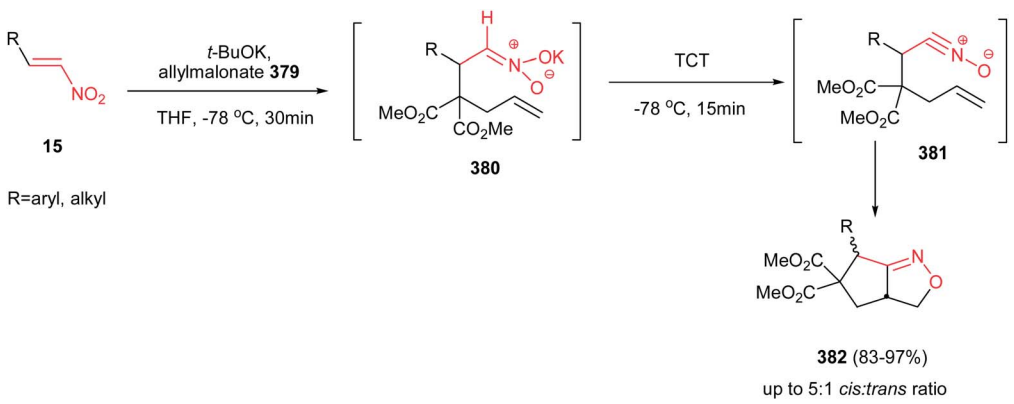
medium to form *N*-(isoxazolylidene)alkylamines **B**. After fragmentation to nitrile oxides **C**, it can undergo intermolecular 1,3-dipolar cycloadditions with methyl acrylate to produce substituted isoxazolines **386** in one synthetic operation with moderate yields (Scheme 132).[245]

Very recently, Sabbasani and Lee reported an efficient method for synthesis isooxazolidinone derivatives **390** in good yields from α-nitro-α,β-unsaturated silyloximes **389** *via* treatment with TBAF. The oximes **389** were prepared by reaction of silylallenes **387** and nitrogen dioxide radical, generated from $NaNO_2$ and AcOH (Scheme 133).[246]

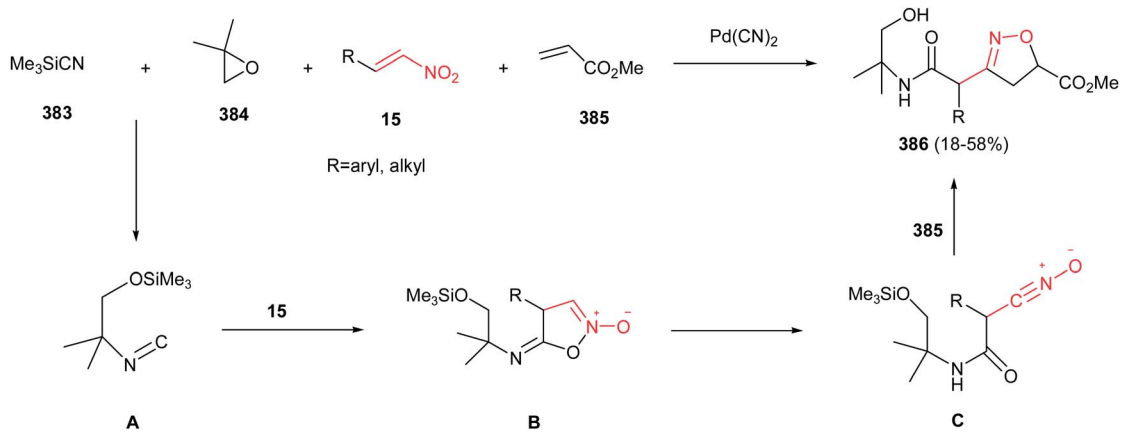
A two-step protocol for synthesis of fused isoxazolidines **394** starting with nitrolakenes is developed by Kamimura *et al.* in 2008. The first step is Michael addition of the pretreated *N*-(4-pentenyl)formamide **391** with *t*-BuOK to nitroalkenes **15** in THF at −50 °C to give the corresponding adducts in 48–85% isolated yields. The second step is treatment of these Michael adducts **392** with phenyl isocyanate in the presence of Et_3N in THF at reflux temperature to afford the bicycloazepines **393** in 50–71% as diastereomeric mixtures in favor of *cis* isomer (*cis* : *trans* ratio of up to 96 : 4). The N-formyl group simply removed from the structure of products **393** *via* treatment with ethanolic diluted HCl solution without significant epimerization. In addition, they have shown that performing these two reactions in a one-



Scheme 130 Isoxazoles prepared from nitroalkenes and prop-2-ynylmalonate or prop-2-ynylmalononitrile.



Scheme 131 One-pot and two-step synthesis of isoxazolines.



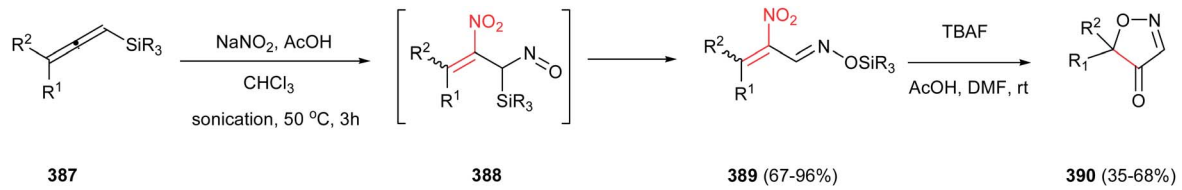
Scheme 132 One-pot four-component synthesis of substituted isoxazolines.

pot manner gave the corresponding products in moderate yields (Scheme 134).[247]

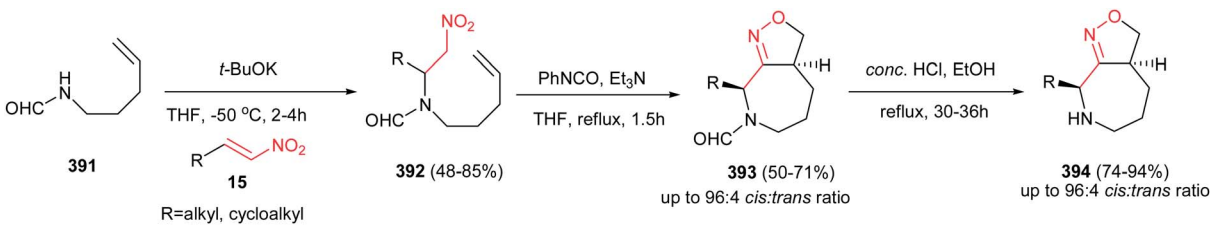
Reaction of 7-oxohept-2-enoate derivatives **395** with nitroolefins **15** were investigated by Zhong *et al.* to give highly stereoselective bicyclic isoxazolidines **396** bearing five stereogenic centers (Scheme 135).[248] The reaction proceeded *via* domino Michael addition/nitrone formation/intramolecular [3 + 2] nitrone-olefin cycloaddition catalysed by 10 mol% of chiral α,α-diphenyl prolinol trimethylsilyl ether **Cat-8** and AcOH (20 mol%) as an additive. The products were obtained in good-to-excellent yields with excellent diastereo- and enantioselectivities of up to 94% de and >99% ee, respectively. While the yields and diastereoselectivities affected by substituents on the nitroolefins, for almost all nitroalkenes tested, the enantioselectivities were higher than 98% ee. Moreover, the products are valuable intermediates for preparation of α-hydroxy-γ-amino-acid derivatives, which could have potential applications in both synthetic chemistry and the pharmaceutical industry.

Asymmetric 1,3-dipolar cycloaddition of nitrones **397** with β-alkyl nitroolefins **15** was reported by Chen *et al.* in 2008. Among the several thiourea organocatalysts examined for this reaction, **Cat-4** derived from (*R*,*R*)-1,2-diaminocyclohexane exhibited excellent diastereoselectivities (generally >99 : 1 dr) and moderate to high enantioselectivities (up to 88% ee). The cycloadducts **398** can be simply converted to protected 2,3-diaminopropanol derivatives **399** with three contiguous chiral centers *via* reduction with $NiCl_2/NaBH_4$ and subsequent protection with $(Boc)_2O$ in excellent yield and enantioselectivity (Scheme 136).[249]

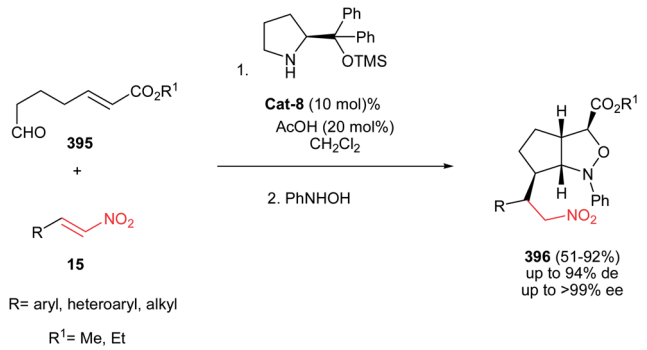
Gottlieb *et al.* described a one-pot procedure for synthesis of α-dialkylaminoaldoximes **400** from nitroalkenes **18** and secondary amines (as solvent and reagent) in the presence of tin(II) chloride. Alkyl and aryl substituted nitroalkenes undergo this transformation, however better yields were obtained with β-nitrostyrenes containing electron donating substituents. When a secondary allylamine was used, the corresponding α-allylamino aldoxime underwent an efficient intramolecular oxime–



Scheme 133 Synthesis of isooxazolidinone derivatives from α-nitro-α,β-unsaturated silyloximes.



Scheme 134 Synthesis of isoxazoline fused to azepines.



Scheme 135 Stereoselective synthesis of bicyclic isoxazolidines bearing five stereogenic centers.

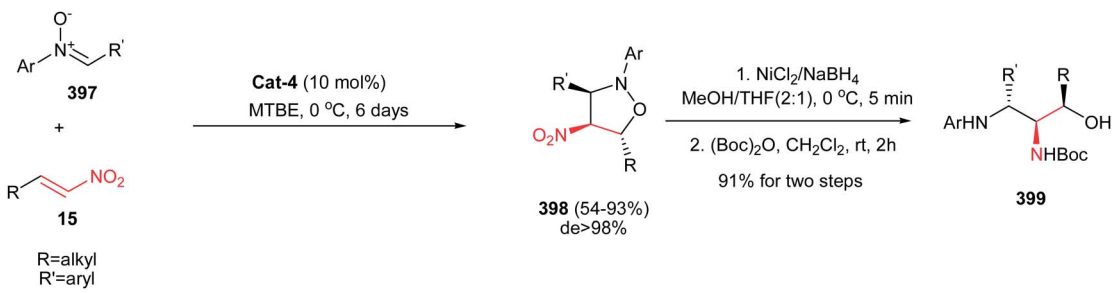
olefin cycloaddition in toluene under nitrogen at 110 °C to give bicyclic isoxazolidines **401** in good to high yields (Scheme 137).[250]

Finally, [2 + 3] cycloadditions between camphor-derived oxazoline *N*-oxide **403** and α,β-substituted nitroalkenes **18** afforded stereoselectively adducts **404** with isoxazolidine cycle in the structure. Denitration of products with Bu_3SnH (D) in the presence of AIBN gave compounds **405** in good yield and stereoselectivity (Scheme 138).[251]

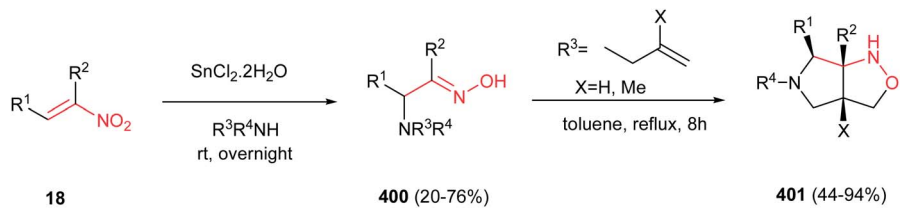
4.4.2. Isoxazoline *N*-oxide derivatives. Recently nitroalkenes have found wide applications in the synthesis of isoxazoline *N*-oxides. In this context, Shi *et al.* reported a catalytic cascade one-step synthesis of isoxazoline-*N*-oxide **407** from nitroalkenes **254** and vinyl esters **406** (as aliphatic aldehyde analogue) (Scheme 139).[252] This approach provides only *trans* isomers with good to excellent yields. The best results were obtained when 20 mol% of proline and 1 equiv. of NaOAc were used in DMSO at room temperature. Lewis bases such as DMAP and PPh_3 were also used and resulted in lower yield with significant amounts of polymerization. While various 2,2-disubstituted nitroalkenes were suitable for this transformation, monoalkyl substituted nitroalkenes gave only trace amount of the desired products with a significant amount of polymerization adducts.

In another report, the same group also described that a one-pot condensation of nitroalkene (**254a**)-aldehyde (**255**)- sulfur ylide **408e/f** in the presence of proline and K_2CO_3 afford the fully substituted isoxazoline-*N*-oxides **410** in high to excellent yields. The phosphine ylide **408c** and amine ylide **408d** also generate the desired product **410** but with significant competition reaction for homo-condensation and production of **409** (Table 1).[253] This strategy was successfully used for stereoselective gram-scale total synthesis of clausenamide **415** in five steps from nitroalkene as shown in Scheme 140.

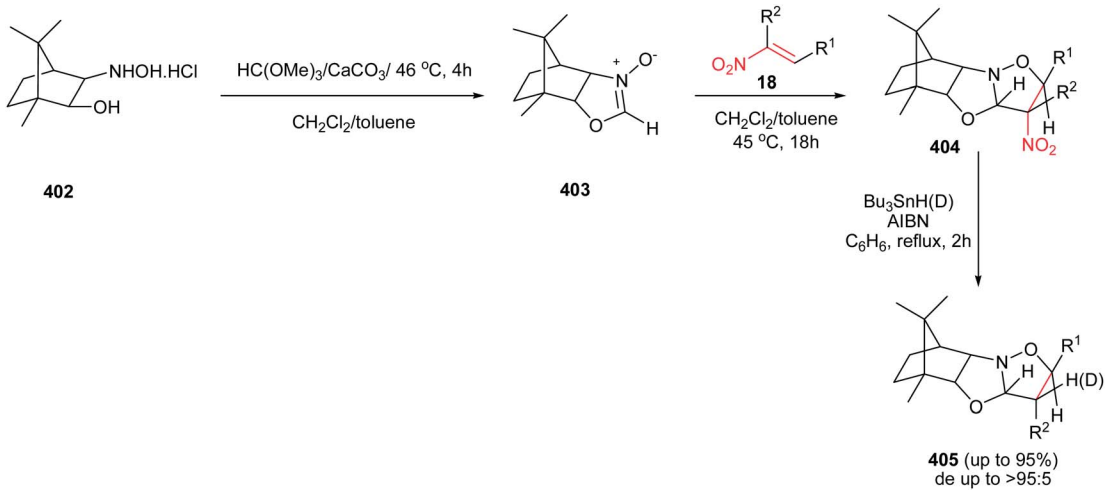
Also, Tang *et al.* developed an efficient protocol for synthesis of isoxazoline *N*-oxides **418a/b** in excellent yield (79–99%) and diastereomeric ratios of higher than 99/1 in favor of *trans* isomer from sulfonium salt **416** and substituted nitroalkenes **417** (Scheme 141).[254] The reaction proceeds well in CH_3CN in the presence of both inorganic bases (Cs_2CO_3, K_2CO_3, KOH, and KO*t*Bu) and organic base (iPr_2NH). No cyclopropanes formation was observed. Comparison to Shi's work, this protocol is applicable for ammonium ylides. The asymmetric version of this reaction was also investigated by the same group using cinchona alkaloid-derived ammonium salts **419a** and **419b** and higher than 96% ee values are achieved for products, albeit in opposite configurations. The enantiomeric excesses are nearly independent of the substituents of the aryl and heteroaryl groups. Aliphatic nitroalkene were used as well as aromatic nitroalkenes in asymmetric version with excellent ee, although both the yield and the diastereoselectivity decreased.



Scheme 136 [3 + 2] Cycloaddition of nitrones and nitroalkenes.



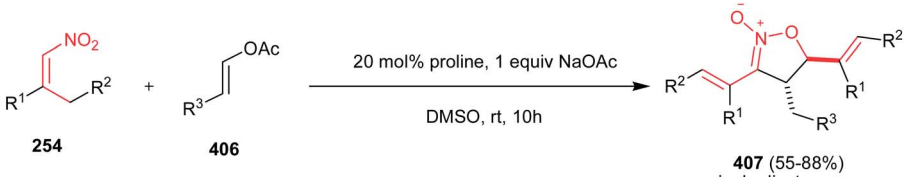
Scheme 137 $SnCl_2 \cdot 2H_2O$ catalyzed synthesis of bicyclic isoxazolidines from nitroalkenes and secondary amines.



402 **403** **404**

405 (up to 95%)
de up to >95:5

Scheme 138 [2 + 3] Cycloaddition reactions between camphor-derived oxazoline *N*-oxide and α,β-substituted nitroalkenes.



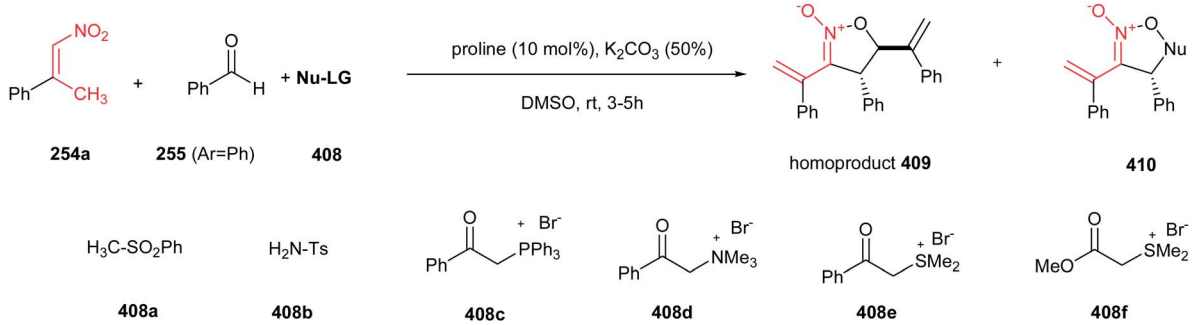
254 **406**

407 (55-88%)
single diastereomer

R^1= Ph, *p*-CH_3-Ph, *p*-Cl-Ph, 2-naphthalene, CH_3; R^2= H and CH_3; R^3=H, Me, Et, CH_2Ph and R^1;R^2= -$(CH_2)_3$- and -$(CH_2)_4$-

Scheme 139 A catalytic cascade one-step synthesis of isoxazoline-*N*-oxide from nitroalkenes and vinyl esters.

Table 1 Substrate screening for three-component condensation in the synthesis of isoxazoline-*N*-oxide[a]



254a **255** (Ar=Ph) **408** homoproduct **409** **410**

408a **408b** **408c** **408d** **408e** **408f**

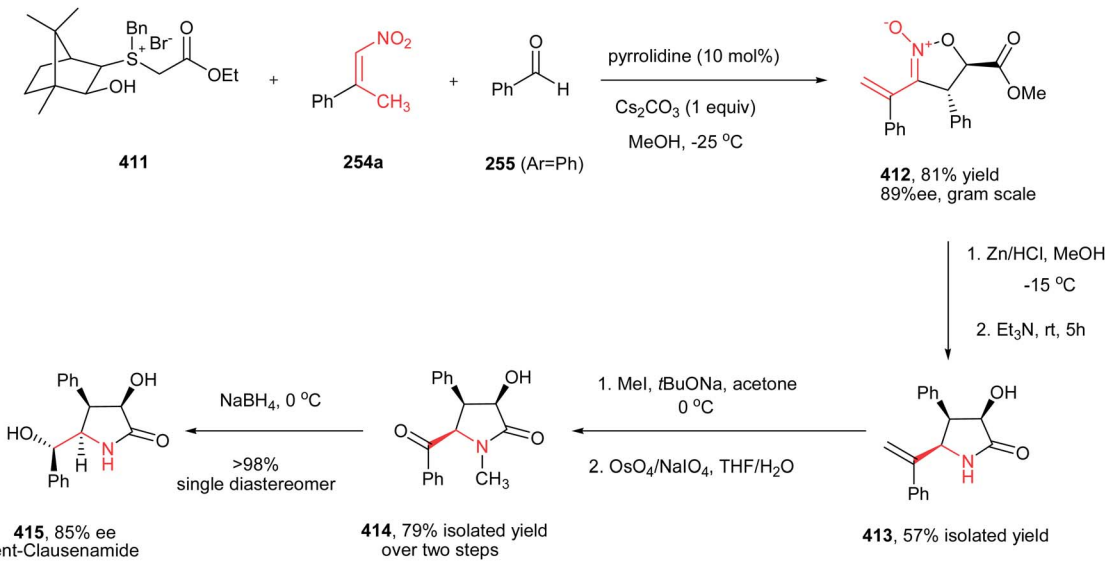
Entry	Nu-LG	Product	
		409 (%)	**410** (%)
1	**408a**	76[b]	<5
2	**408b**	85[b]	<5
3	**408c**	58[b]	35[b]
4	**408d**	74[b]	18[b]
5	**408e**	<5[b]	91[c]
6	**408f**	<5[b]	92[c]

[a] Reaction condition: **254a** (1.0 equiv.), **255** (1.0 equiv., 0.75 M), and catalyst were mixed in solvents. [b] NMR yield with 1,3,5-trimethoxybenzene as internal standard. [c] Isolated yield.

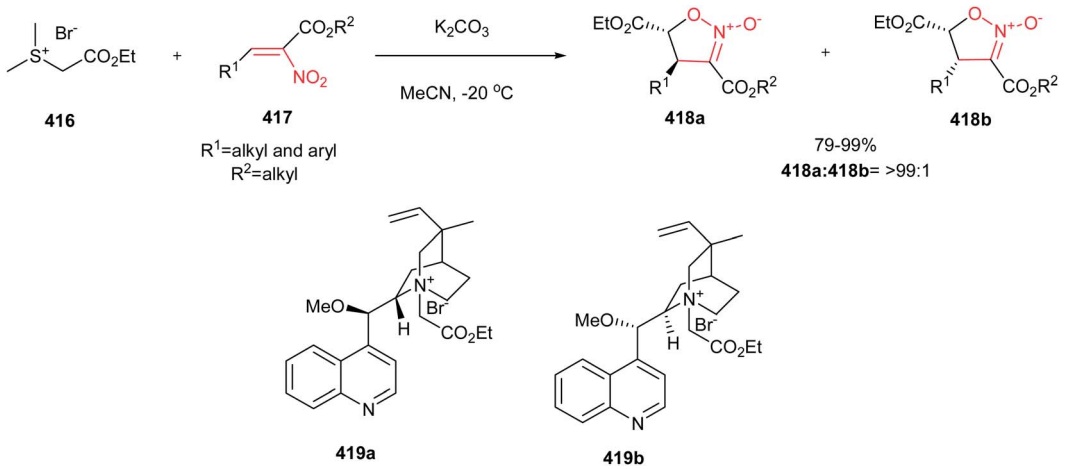
Although it is well-known that the reaction of alkyl 2-bromomalonate **420** with β-nitroalkenes **18** afforded the cyclopropane rings, in 2011, Marouka *et al.* have shown that various chiral isoxazoline-*N*-oxides **421** having a tetrasubstituted carbon can be obtained in high to excellent yields and high ee's (72–87%) by asymmetric conjugate addition of bromomalonate **420** to α,β-substituted nitroolefins **18** in the presence of 70 mol% of Cs_2CO_3 and 1 mol% of (*R*,*R*)-**Cat-16** as chiral phase-transfer catalyst (Scheme 142).[255] The reaction was initiated by Michael addition, and followed by subsequent ring-closing *O*-alkylation.

4.4.3. Oxazolidinone derivatives. Xiao *et al.* reported a new protocol for synthesis of oxazolidin-2-ones **423** from sulfur ylides **422** and nitroalkenes **15** *via* [4 + 1] annulations/rearrangement cascade sequentially catalyzed by thiourea and DMAP.[256] The best results were obtained when 1.25 equiv. of sulfur ylide **422** reacted with 1 equiv. of nitroolefin **15** in the presence of 10 mol% of 1-(2-chlorophenyl)thiourea **Cat-17** and DMAP in chloroform at room temperature for 24 h. Both aromatic and aliphatic nitroalkenes are compatible with this protocol to produce the corresponding oxazolidin-2-ones **423** in high yields (70–89%) (Scheme 143). The authors proposed that the reaction proceeded *via* intermediate **A**. Also, they have shown that by performing the same reaction in the presence of 50 mol% of the chiral *bis*-urea catalyst **Cat-18**, enantioenriched 4,5-substituted oxazolidinones were obtained in moderate to excellent isolated yields (65–96%) with excellent stereocontrol (up to more than 95 : 5 dr and 97 : 3 er).[257] Accordingly, Toy *et al.* developed another catalytic system for this reaction using 10 mol% of bifunctional polymeric organocatalyst **Cat-19** which contain both amine and thiourea catalytic groups.[258]

In addition, the same authors developed another asymmetric method for this transformation by using stable chiral BINOL-derived sulfur ylides **424** and nitroalkenes **15**.[259] The stereochemistry of the reaction is controlled by the chiral sulfur



Scheme 140 Total synthesis of clausenamide.



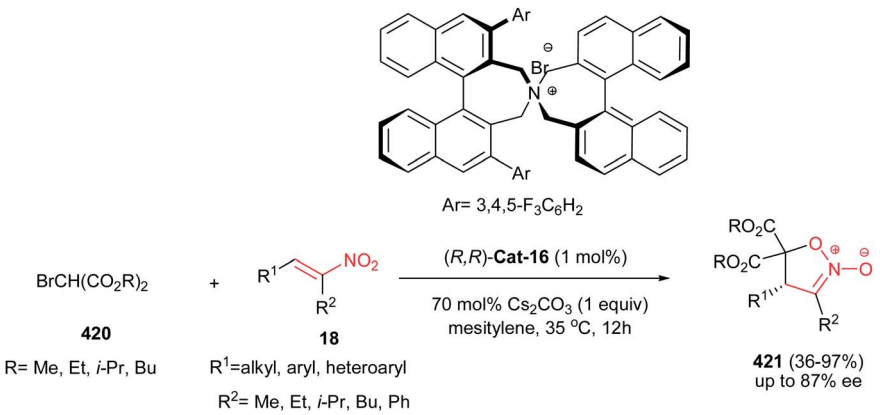
Scheme 141 Synthesis of isoxazoline *N*-oxides from sulfonium salt and substituted nitroalkenes.

ylide. This approach provides chiral oxazolidinones **425** in good yields and high stereoselectivities (up to 96 : 4 er and >95 : 5 dr) (Scheme 144). The absolute configuration of oxazolidinones **425** was confirmed to be (4*S*,5*R*) by X-ray crystallographic analysis. This protocol was also successfully applied to the asymmetric [4 + 1]/[3 + 2] cycloaddition cascade of sulfur ylides **424** with acrylate-tethered β-nitrostyrene **426** to afford the enantioenriched fused heterocycles **427** (up to 87 : 13 er and >95 : 5 dr) in good to excellent yields (54–95% yields) (Scheme 145).

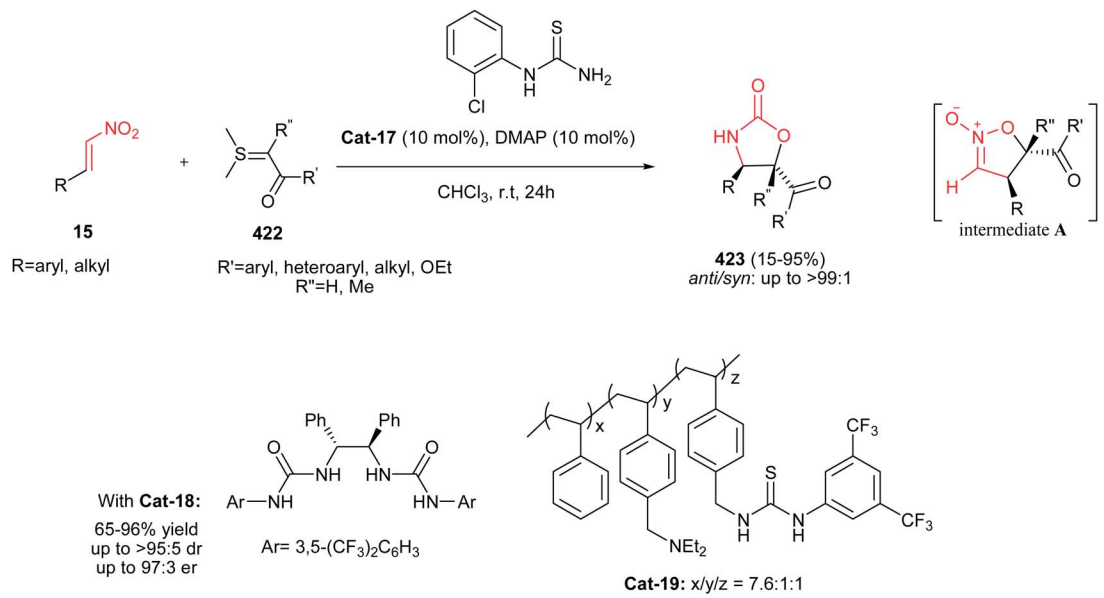
In 2007, Evans *et al.* developed an efficient procedure for the synthesis of optically active *cis*-oxazolidinone **430** from chiral 3-amino-substituted-1-arylthio-1-nitroalkene **428**. The reaction initiated with epoxidation of **428** by *t*-BuO_2Li to furnish the intermediate **429**. Then, in the presence of SiO_2, the intramolecular epoxide ring opening initiated by the carbamate group led to subsequent elimination of the nitro group, followed by migration of the thioester group to give corresponding products **430** in high yields (Scheme 146).[260]

4.4.4. Nitrosoacetal derivatives. The nitrosoacetals are suitable intermediates for synthesis of diversity of biologically active compounds such as pyrrolizidin-3-ones, amino acids and alkaloids.[261] These compounds can be simply prepared *via* tandem [4 + 2]/[3 + 2] nitroalkene cycloaddition with unactivated olefins or enol ethers as dienophiles and electron-deficient alkenes as 1,3-dipolarophiles. The inter- or intamolecular fashion of this method has been investigated extensively by Denmark group and others.[262] In this part, we wish to describe some of the recent key publications in the synthesis of nitrosoacetals.

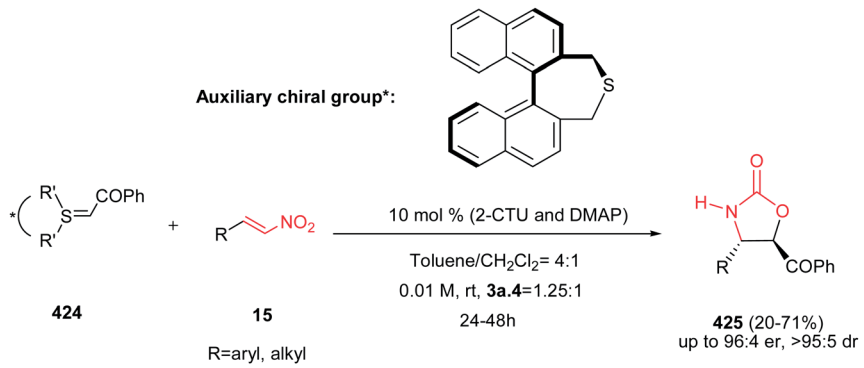
Domino hetero-Diels–Alder/1,3-dipolar cycloaddition reaction of 3,3,3-trichloro(trifluoro)-nitroethylenes **431** (or **27**) with 2,3-dihydrofuran **432** was investigated by Sosnovskikh *et al.*[263] They described that compound **431** (or **27**) play a dual role as the heterodiene and the dipolarophile in the reaction. The trichloromethylated nitroolefin **431** gave tricyclic nitroso acetal **434** as a single regio- and stereoisomer in 45% isolated yield,



Scheme 142 Asymmetric synthesis of isoxazoline-*N*-oxides.



Scheme 143 Organocatalyzed cascade reaction of sulfur ylides with nitroalkenes.

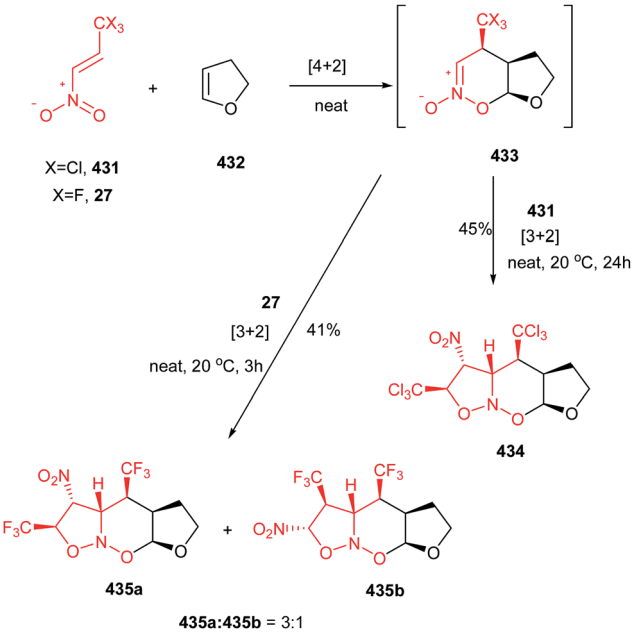


Scheme 144 Nitroolefins for the enantioselective cascade [4 + 1] annulation/rearrangement reaction.

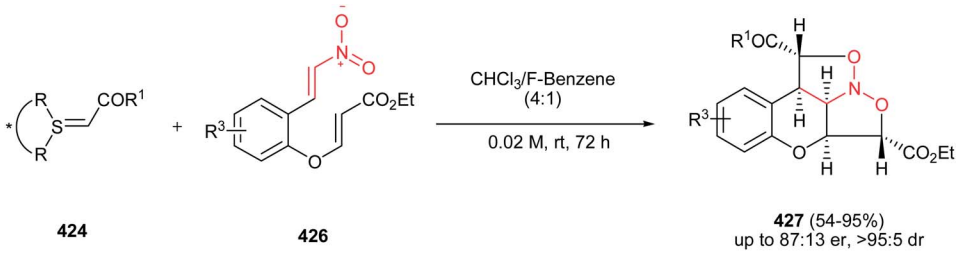
while the trifluoromethylated derivative **27** afforded a 3 : 1 mixture of two regioisomeric cycloadducts **435a** and **435b** in 41% total yield (Scheme 147).

Giommi *et al.* demonstrated that reaction of substituted 4-nitroisoxazoline **436** with a large excess of ethyl vinyl ether **351** in anhydrous CH_2Cl_2 at 40 °C for 4 days afforded 5 : 1 mixture of the diasteremeric spiro nitrosoacetal **439a/b** in excellent yield.[264] By performing the reaction in refluxing chloroform, surprisingly 3 : 2 mixture of the diasteromeric isoxazolo-oxepines **437a/b** was obtained in 54% yield. Treatment of the mixture of **439a/b** in $CHCl_3$ also afforded the products **437a/b** in same yield and diastereomeric ratio (Scheme 148).

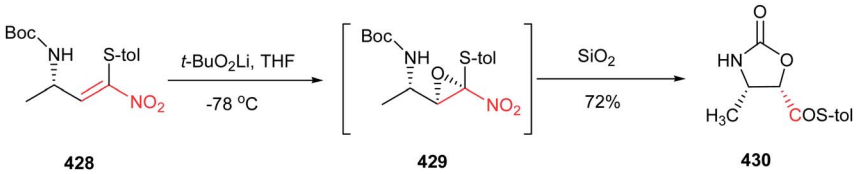
A one-pot domino (4 + 2)/(4 + 2)/(3 + 2) cycloaddition reaction of 2-methoxy buta-1,3-diene **440** with a dienophile, β-nitro-styrene and a dipolarophile under high pressure conditions gives tri, tetra and pentacyclic nitroso acetals. The reaction of **440** with 3 eq. of nitroalkenes **55** gave tricyclic nitrosoacetals as two regioisomers **441** and **442** (**441/442a/442b** : 0.2/0.6/0.2). (Scheme 149a), while reaction of **440** with maleimide **443** in the presence of 2 eq. of niroalkene **55** gave two regioisomeric tetracyclic nitrosoacetal **444a/b** and **445** (1 : 1 ratio) in 64% yield in which both regioisomers consisted of two diastereomers in a



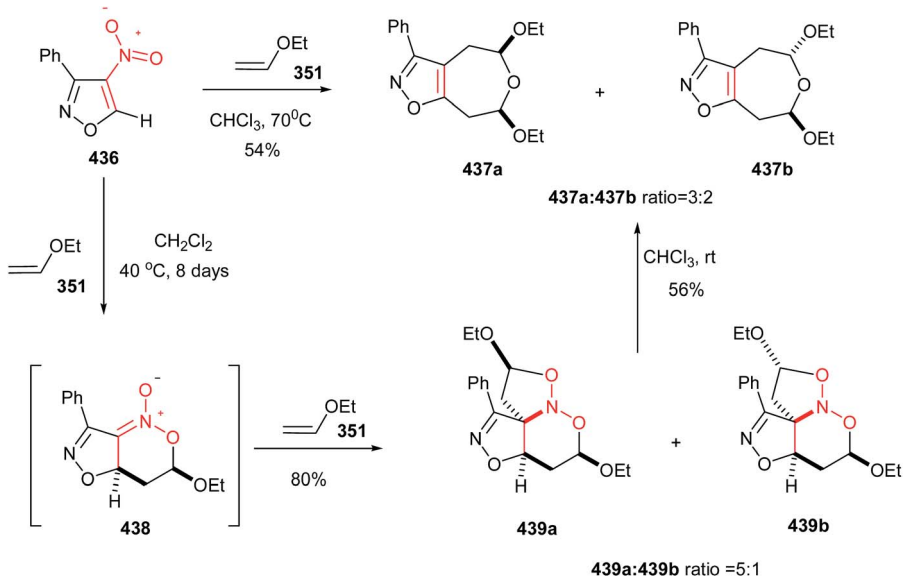
Scheme 147 Domino hetero-Diels–Alder/1,3-dipolar cycloaddition reaction of 3,3,3-trichloro(trifluoro)-nitroethylenes with 2,3-dihydrofuran.



Scheme 145 Enantioselective [4 + 1]/[3 + 2] cascade reactions.



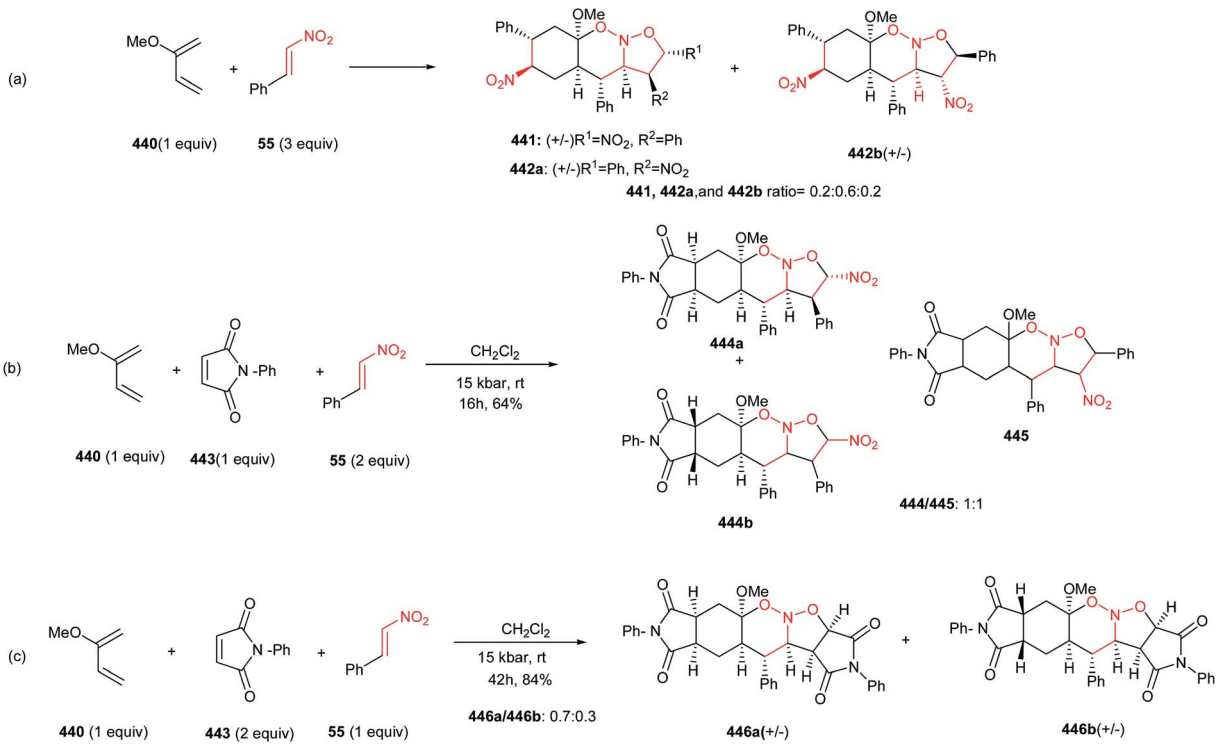
Scheme 146 Synthesis of optically active *cis*-oxazolidinone from chiral 3-amino-substituted-1-arylthio-1-nitroalkene.



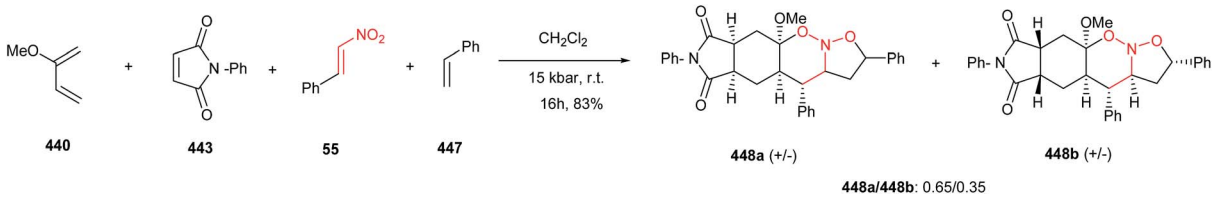
Scheme 148 Reaction of substituted 4-nitroisoxazoline with a large excess of ethyl vinyl ether.

ratio of 0.65/0.35 (Scheme149b). The configuration of one of the stereoisomers was assigned by 2D-NOESY analysis. In addition, reaction of **440** with nitroalkene **55** and 2 eq. of maleimides **443** gave pentacyclic nitrosoacetals **446a/b** (Scheme 149c). In this novel domino reaction up to six bonds and up to eight stereogenic centers are created in one step in good yield and good stereoselectivity. The results showed that *N*-phenylmaleimide **443** was more reactive than β-nitrostyrene **55** toward 2-methoxybuta-1,3-diene **440**.[265]

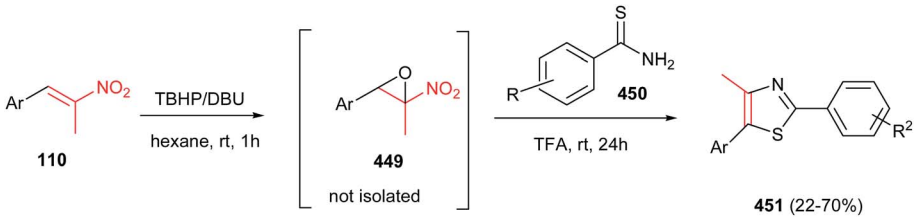
Finally, they have examined that mixing of an equimolar of 2-methoxybuta-1,3-diene **440** (as a diene), *N*-phenyl maleimide **443** (as a dienophile), β-nitrostyrene **55** (as a heterodiene), and



Scheme 149 Highly functionalized polycyclic nitrosoacetals *via* a one-pot domino (4 + 2)/(4 + 2)/(3 + 2) cycloaddition reactions.



Scheme 150 A one-pot four-component route for synthesis of nitrosoacetals.



Scheme 151 One-pot two-step process for synthesis of 1,3-thiazoles from nitroalkenes.

styrene **447** (as a dipolarophile) at 15 kbar and room temperature for 16 h yielded in 83% a mixture of two diastereomeric nitrosoacetals **448a** and **448b** (Scheme 150).[265]

4.5. Synthesis of N,S-heterocyclic compounds

Tsogoeva *et al.* reported a one-pot two-step procedure for synthesis of 1,3-thiazoles **451** starting with nitroalkenes **110**. Epoxidation of **110** with TBHP/DBU (*t*-BuOOH/1,8-diazabicyclo [5.4.0] undec-7-ene) gave α-nitroepoxides **449** which undergo cyclization with thioamides **450** in the presence of TFA to afford fully substituted 1,3-thiazoles **451** in good to high yields (Scheme 151).[266]

5. Conclusions

Nitroalkenes are elegant substrates for the facile synthesis of 3–5 membered heterocycles. Small ring heterocycles such as epoxides, aziridines, azetidines and thietanes can be synthesized with high stereoselectivity *via* a Michael addition-intramolecular cyclization strategy involving nitroalkenes and an *O*, *N* or *S*-nucleophile bearing a suitable leaving group. Five-membered aromatic heterocycles such as pyrrole, pyrazole, imidazole, triazole, tetrazole, isoxazole, furan and thiophene are conveniently accessible using nitroalkenes as the key substrates. Synthesis of saturated heterocycles such as pyrrolidine, tetrahydrofuran and tetrahydrothiophene is also feasible, often with excellent functional group diversity and stereoselectivity.

Abbreviations

AcOH	Acetic acid
Ac	Acyl
acac	Acetylacetonate
AIBN	Azobisisobutyronitrile
Alk	Alkyl
Ar	Aryl
BINOL1	1′-Bi-2-naphthol
bmim	1-Butyl-3-methylimidazolium
Bn	Benzyl
Boc	*t*-Butyloxy carbonyl
Bu	Butyl
Bz	Benzoyl
BztH	Benzotriazole
2-CTU	1-(2-Chlorophenyl)thiourea
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	Dichloroethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
de	Diastereomericexcess
DECP	Diethylcyanophosphonate
DIB	(Diacetoxyiodo)benzene
DIPC	*N*,*N*′-Diisopropylcarbodiimide
DIPEA	*N*,*N*-Diisopropylethylamine
DMAP	4-(*N*,*N*-Dimethylamino)pyridine
DME	1,2-Dimethoxyethane
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
dr	Diastereomeric ratio
ee	Enantiomeric excess
eq	Equivalent
er	Enantiomeric ratio
esp	α,α,α′,α′-Tetramethyl-1,3-benzenedipropionate
Et	Ethyl
IBX	2-Iodoxybenzoicacid
MBH	Morita–Baylis–Hillman
MeGly	Glycine methyl ester
Ms	Methanesulfonyl
MTBE	Methyl tertiary-butyl ether
MW	Microwave
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
NOESY	Nuclear Overhauser effect spectroscopy
Ns	4-Nitrobenzenesulfonyl
PANF	Polyacrylonitrile fiber

PCC	Pyridinium chlorochromate
PEG	Polyethylene glycol
Ph	Phenyl
Phen	1,10-Phenanthroline
PMB	*p*-Methoxybenzyl
PMP	*p*-Methoxyphenyl
PPL	Porcine pancreas lipase
PPTS	Pyridinium *p*-toluenesulfonate
PS-BEMP	2-*tert*-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine on polystyrene
SA	Sulfamic acid
SFC	Solvent-free conditions
TBAI	Tetrabutylammonium iodide
TBAF	Tetrabutylammonium fluoride
TBHP	*tert*-Butyl hydroperoxide
t-BuO	*tert*-Butoxide
TBPLi	Lithium *tert*-butylperoxide
TBPK	Potassium *tert*-butylperoxide
TBS	Tributylsilyl
TCT	2,4,6-Trichloro-1,3,5-triazine
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
TFE	2,2,2-Trifluoroethanol
Tf	Trifluoromethanesulfonyl
TEA	Triethylamine
THF	Tetrahydrofuran
THTs	Tetrahydrothiophenes
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl
Ts	Tosyl
TLC	Thin-layer chromatography

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