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Developments and applications of α-bromonitrostyrenes in organic syntheses

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The presence of the bromo and nitro groups in the structure of α-bromonitrostyrene makes them highly reactive and versatile reagents in organic syntheses. α-Bromonitrostyrenes act as an effective dielectrophile in the reaction with various nucleophiles. In these reactions, the bromo and nitro groups behave as good leaving groups for the assembly of a diverse range of heterocyclic compounds, such as dihydrofurans, dihydropyranes, furans, pyrroles, pyrazoles, isooxazolines, spiropyrrolidines, *etc.* In the current review, we have focused on the transformations of α-bromonitrostyrenes under organocatalysis, metal catalysis, and base-catalysis systems as well as catalyst-free conditions, since 2010.

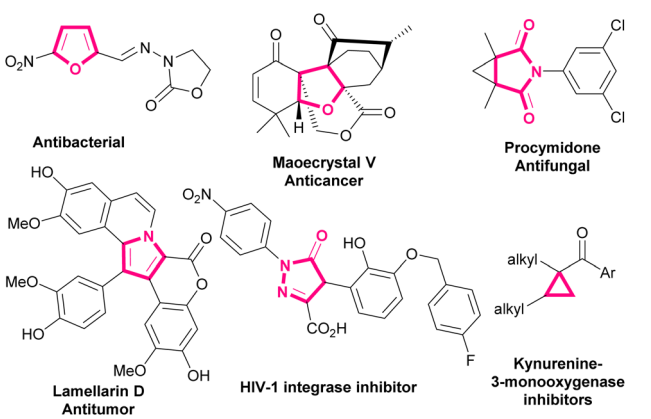
1. Introduction

Bromonitroalkenes, especially bromonitrostyrenes are versatile building blocks for the construction of biological and pharmaceutical molecules and optically active compounds, such as dihydrofurans,[1,2] pyrroles,[3–6] and pyrazoles.[7–9] Selected examples of biologically active molecules containing pyrrole, furan, dihydrofuran, or cyclopropane cores are shown in Scheme 1.

Due to the presence of both nitro and bromo groups, α-bromonitrostyrenes exhibit peculiar properties in comparison with nitrostyrenes and bromostyrenes.[10–14] These substituents can behave as good leaving groups in the nucleophilic substitution reactions. Because of this feature, α-bromonitrostyrenes can easily be used in Michael addition reactions as a dipolarophile to make various functionalized dihydrofurans, pyrroles, pyrazoles, bicyclic oximes, triazoles, imidazoles, cyclopropanes, *etc.*[15] In such reactions, α-bromonitroalkenes act as a 1,2-bielectrophile in a diverse range of cascade reactions with binucleophiles, such as 1,3-dicarbonyl compounds, enamines, aldehydes, alkenes, phenols, diazo compounds and other miscellaneous reagents.

Michael addition reactions of α-bromonitroalkenes can be performed in the presence of organocatalysts, metal catalysts, and bases, as well as catalyst-free systems. Among them, advances in enantioselective organocatalytic Michael reactions have provided various enantiomerically enriched compounds and biologically active molecules.[16–19] On the other hand, domino Michael/Henry reactions are known as powerful methods for rendering complex molecular architectures through constructing the carbon–carbon bonds in a one-pot procedure without isolating intermediates.[20,21] Recently, progress in asymmetric domino reactions utilizing chiral organocatalysts has been well revealed and interesting achievements has been gained.[22–24]

Recently, various research teams, such as Jakubec,[25] Gao,[26] Lee,[27] Halimehjani,[28] Shen,[29] and Zhang[30] reported the organic transformations of nitrostyrenes. In this review, we have specifically discussed the use of α-bromonitrostyrenes in various types of catalytic systems, such as organocatalysis, metal catalysis and base catalysis as well as catalyst-free reactions. We have also highlighted important features of the reactions and mechanisms to familiarize the readers with the reactivity and behavior of α-bromonitrostyrenes in organic syntheses.



Scheme 1 Selected examples of biologically active molecules containing pyrrole, furan, dihydrofuran, or cyclopropane rings.

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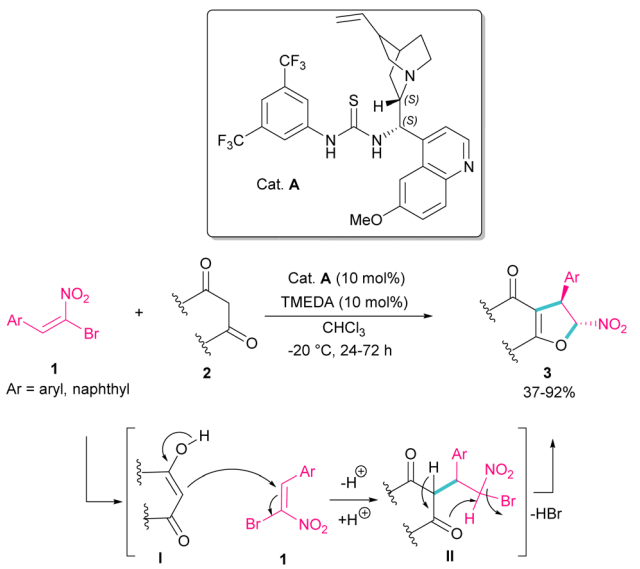
2. Transformations of bromonitrostyrenes

2.1. Organocatalyst-catalyzed transformations of bromonitrostyrenes

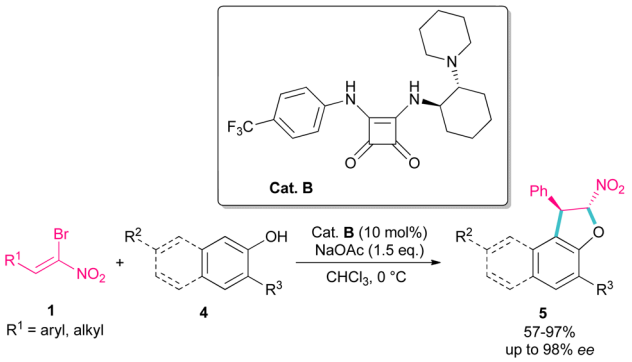
In 2010, Rueping *et al.* used (*E*)-β-bromonitrostyrenes **1** for the synthesis of dihydrofurans **3** from 1,3-dicarbonyl compounds **2** (Scheme 2).[31] In this reaction, the chiral thiourea catalyst **A** can close two substrates together by hydrogen-bonding interaction and facilitate Michael addition of diketone **2** as a dinucleophile to bromonitrostyrene **1** as an electrophile to generate intermediate **II**. Then, an intramolecular nucleophilic addition delivered product **3** by the release of HBr. The same organocatalyst was used in the reaction of bromonitrostyrene, as a dielectrophile and 1,3-indandione as a dinucleophile to make spironitrocyclopropane in 57% yield with 35% ee.[32]

Parra and co-workers used an organocatalysis system to synthesize enantioselective dihydroarylfuran derivatives **5** from the cyclization reaction between (*Z*)-bromonitroalkenes **1** and naphthol **4** (Scheme 3).[33] The hydrogen bonding interaction of chiral organocatalyst **B** with both substrates was responsible for the suitable orientation for Michael–Friedel–Crafts reaction and subsequent S_N2 reaction on the carbon attached bromide. It should be noted that HBr resulting from the reaction can be neutralized with a stoichiometric amount of a base.

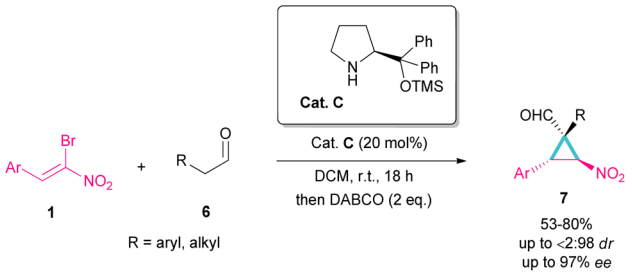
Another organocatalyst was used in the reaction of bromonitroalkenes **1** and alkyl aldehydes **6** (Scheme 4).[34] A series of enantioenriched cyclopropanes **7** with quaternary carbon centers were prepared in the presence of a chiral pyrrolidine catalyst **C**. As illustrated in Scheme 5, the reaction started with the condensation of pyrrolidine with aldehyde to form imine **I**, followed by a 1,3-H shift to enamine **II**. The attack of bromonitrostyrene to the alkene moiety produced intermediate **III**. By release of the catalyst and subsequent intramolecular S_N2 reaction, cyclopropane **7** was provided along with the elimination of bromide. It seems that the formation of two diastereomers **7** and **7′** from two configurations **IV** and **V** is possible. The configuration at C2 is generated from the intramolecular attack of the anion with DABCO, while the configuration at C4 is from the acidic proton at this C-atom, providing the thermodynamically stable product. In this case, the NO_2 group is at the *trans* position to the aryl ring at C3.



Scheme 2 Organocatalysis reaction of (*E*)-β-bromonitrostyrenes with 1,3-dicarbonyl compounds.



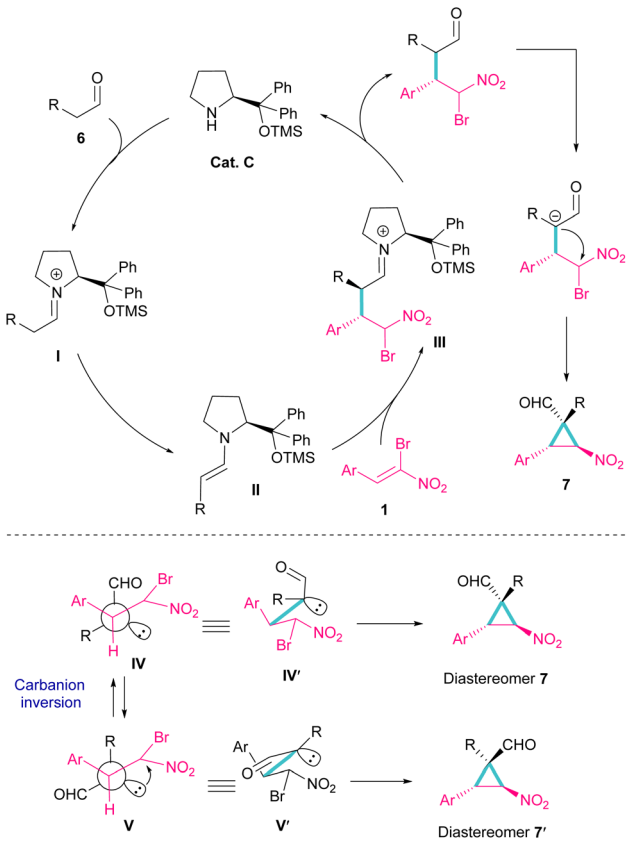
Scheme 3 Reaction of (*Z*)-bromonitroalkenes and naphthols catalyzed by a chiral organocatalyst.



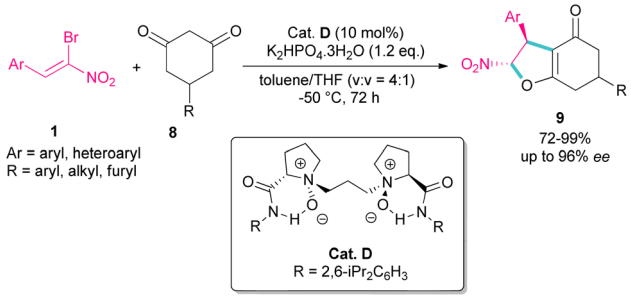
Scheme 4 Reaction of bromonitroalkenes and alkyl aldehydes catalyzed by chiral organocatalyst.

A domino Michael-alkylation reaction was reported by Feng and co-workers for the synthesis of dihydrofurans **9** from bromonitrostyrene **1** (Scheme 6).[35] For this purpose, they treated bromonitrostyrene **1** and cyclohexane-1,3-diones **8** in the presence of the organocatalyst **D**. For dimedone, two stereocenters of the bicyclic 2,3-dihydrofurans were obtained with high diastereo- and enantioselectivity, while three stereocenters of the bicyclic 2,3-dihydrofurans were prepared from prochiral 5-monosubstituted cyclohexane-1,3-dione products *via* the desymmetrization reaction.

In 2016, Feng *et al.* introduced a chiral organocatalyst **E** for the asymmetric synthesis of dihydrofurans **11** from (*Z*)-bromonitrostyrenes **1** and α-substituted cyano ketones **10** (Scheme 7).[36] In this regard, a domino Michael addition-alkylation between bromonitrostyrene and α-substituted cyano ketone in the presence of chiral *N*,*N*′-dioxide **E** was conducted under very mild reaction conditions. The authors found that the use of proton sponge, added in six equal parts, could enhance enantioselectivity and also the performance of the reaction in a very low temperature prevent the formation of the cyclopropane



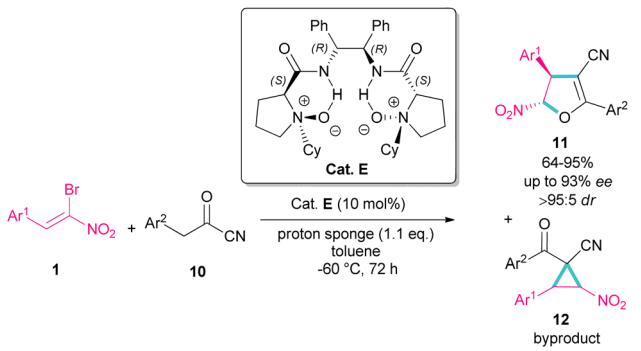
Scheme 5 Putative mechanism for reaction of bromonitroalkenes and alkyl aldehydes.



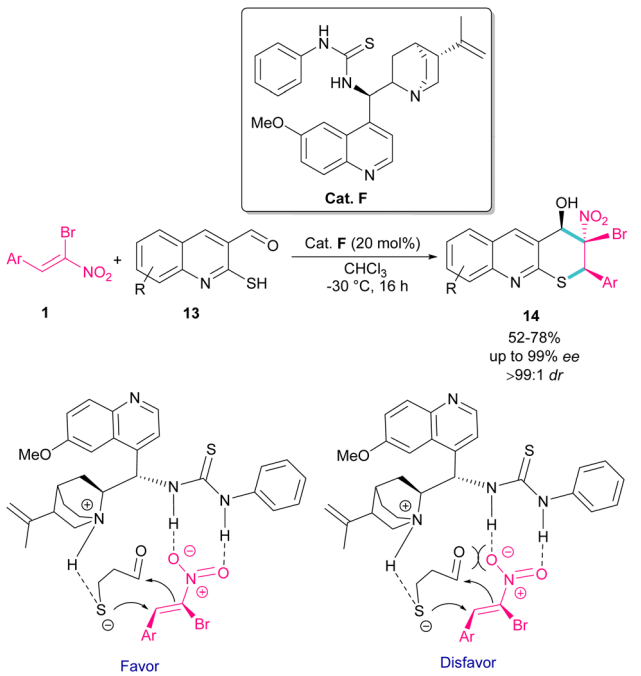
Scheme 6 Reaction of cyclohexane-1,3-dione and bromonitrostyrenes catalyzed by organocatalyst.

compound as a byproduct and thus increasing the yield of dihydrofuran **11**. In addition to excellent enantioselectivity, high diastereo- and regioselectivity were also observed in this reaction.

The use of α-bromonitroalkenes **1** in the synthesis of 3,4-dihydro-2*H*-thiopyrano[2,3-*b*]quinolines **14** was reported by Xie and co-workers in 2018 (Scheme 8).[37] An organocatalysis system was proposed for this synthetic method, which started with the deprotonation of 2-mercaptoquinoline-3-carbaldehyde **13** by tertiary amine of catalyst **F**, and the activation of α-bromonitroalkene **1** by the thiourea moiety of **F** through the formation of two hydrogen bonds. The subsequent domino Michael/Henry



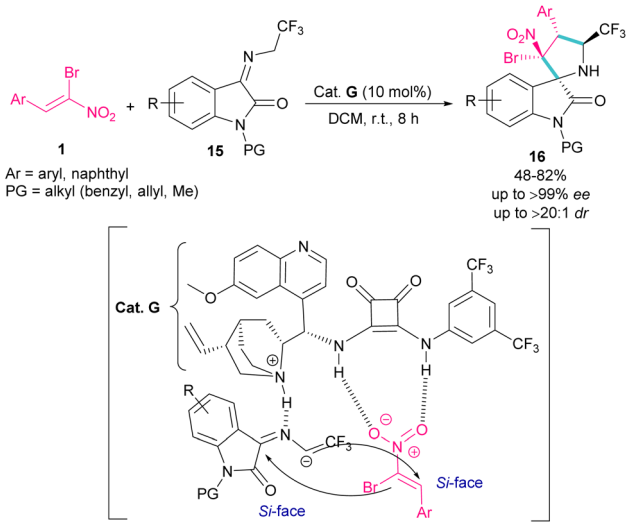
Scheme 7 Organocatalysis reaction of (*Z*)-bromonitrostyrenes and α-substituted cyano ketones.



Scheme 8 Organocatalyst-catalyzed reaction of 2-mercaptoquinoline-3-carbaldehyde and α-bromonitroalkene.

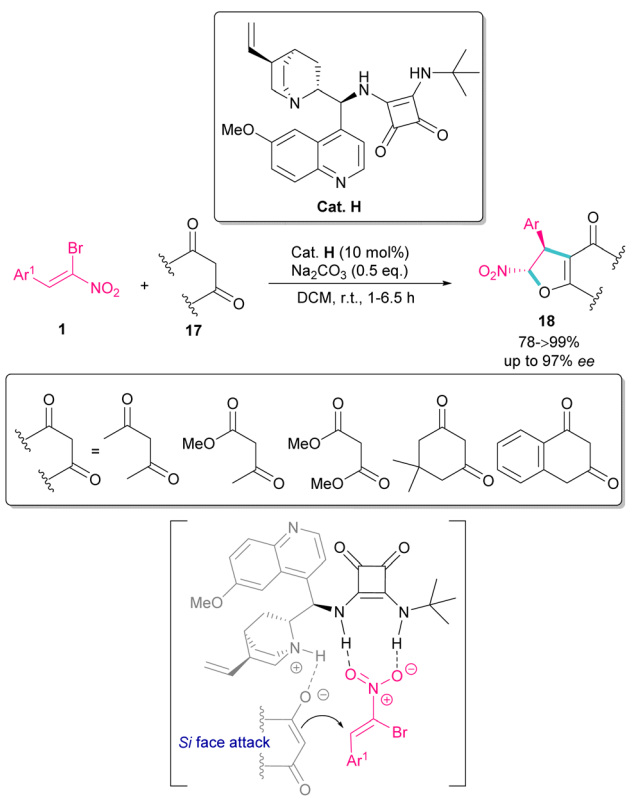
reaction resulted in product **14**. This method had the advantages of excellent enantio- and dieastereoselectivity, mild reaction conditions, and the ability of 3,4-dihydro-2*H*-thiopyrano[2,3-*b*]quinolines to undergo further organic transformations. In addition, salicylaldehyde can also act as a coupling partner in the cyclization with bromonitroalkene.

In 2020, an organocatalysis system was developed to prepare pyrrolidinyl spiro-oxindoles bearing quaternary carbon centers **16** (Scheme 9).[38] Han and co-workers designed a (3 + 2)-cycloaddition reaction between isatin-derived ketimine **15** and (*Z*)-α-bromonitroalkene **1** in the presence of cinchonidine-derived squaramide **G**. This bifunctional organocatalyst can control the stereoselectivity by the hydrogen bonding interactions with both substrates blocking one side of each substrate, allowing nucleophilic attack from the *Si*-face.



Scheme 9 Reaction of isatin-derived ketimine and (*Z*)-α-bromonitroalkene catalyzed by cinchonidine-derived squaramide.

In 2022, Tanyeli and co-workers extended a new organocatalysis system for the synthesis of chiral dihydrofurans **18** from bromonitroalkenes **1** and 1,3-dicarbonyl compounds **17** (Scheme 10).[39] Their reaction proceeded through domino type Michael-S_N2 reactions in the presence of a quinine-derived sterically encumbered squaramide **H**. The main advantages of this method that differentiates it from previous methods was the performance of the reaction in room temperature at short reaction times, while other similar reactions required cryogenic conditions and longer times to proceed. As shown in transition state, the quinoline moiety of the catalyst **H** activates the nucleophile **17** by hydrogen bonding. At the same time, the electrophile **1** is also activated by double hydrogen bonding with the squaramide group of **H**. Consequently, the nucleophilic attack of **17** from the *Si*-face of **1** afforded product with excellent enantioselectivity.

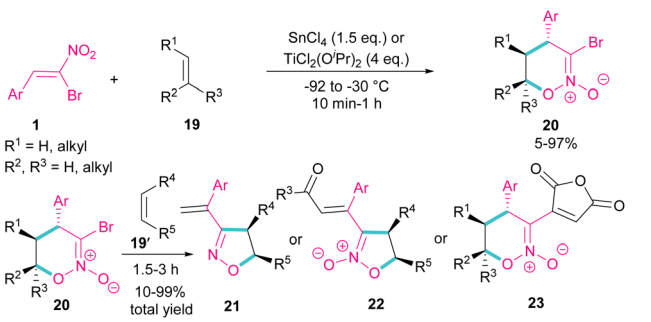


Scheme 10 Squaramide-catalyzed reaction of bromonitroalkenes and 1,3-dicarbonyl compounds.

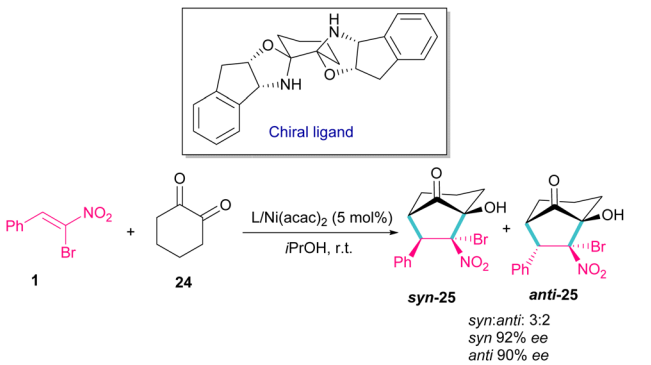
2.2. Metal-catalyzed transformations of bromonitrostyrenes

Bromonitrostyrenes can be applied for the construction of 3-bromo-5,6-dihydro-4*H*-1,2-oxazine *N*-oxides (Scheme 11).[40] An alkene was used as a coupling partner and the cyclization reaction was performed in the presence of $SnCl_4$ or $TiCl_2(O^iPr)_2$ as a Lewis acid catalyst. (4 + 2)-Cycloaddition of alkene to bromonitrostyrene was sensitive to the reaction conditions, where an increase in temperature or time led to 3-chloro-1,2-oxazine *N*-oxide as byproduct. In the next stage, (3 + 2)-cycloaddition of the obtained 3-bromo-5,6-dihydro-4*H*-1,2-oxazine *N*-oxides **20** with another alkene reactant **19′** was performed and three products, including 3-vinyloxazole **21**, isoxazole *N*-oxide **22**, and 3-functionalized 1,2-oxazine *N*-oxide **23** were obtained in different ratios.

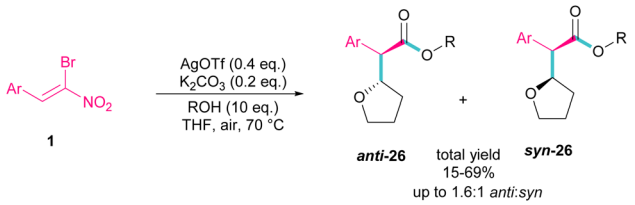
In 2014, a chiral bisoxazolidine in the combination with $Ni(acac)_2$ catalyst was used for the preparation of optically active



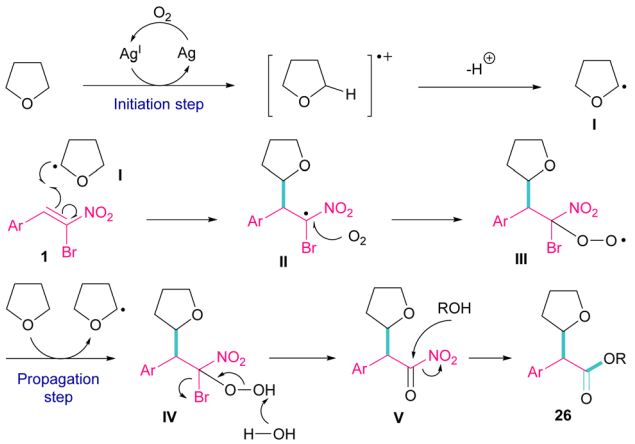
Scheme 11 Reaction of bromonitrostyrenes with alkenes in the presence of $SnCl_4$.



Scheme 12 Ni-catalyzed reaction of bromonitrostyrenes with 1,2-cyclohexadione.



Scheme 13 Ag-catalyzed addition of THF radicals to β-bromonitrostyrenes.



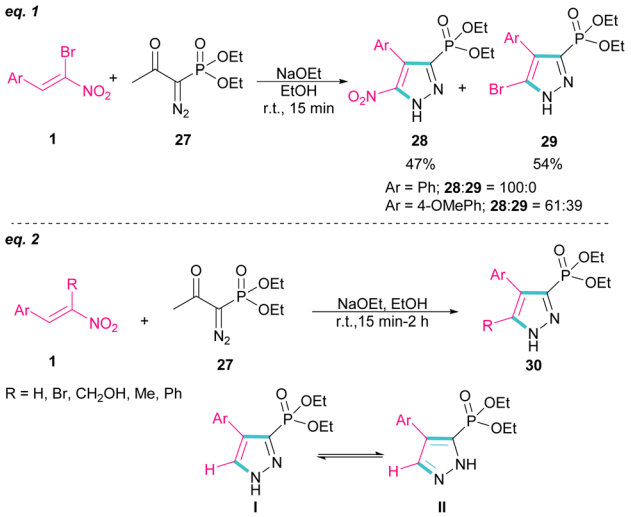
Scheme 14 Plausible mechanism for Ag-catalyzed addition of THF radicals to β-bromonitrostyrenes.

bicycle[3,2,1] octane of 1,2-diones **25** from nitroalkenes and **1** 1,2-cyclohexadione **24** (Scheme 12).[41] α-Bromonitroalkene **1** in a domino Michael–Henry reaction with diketone **24** can furnish product **25** with two *syn* and *anti* isomers. In this reaction, excellent enantioselectivity was observed (98% ee), but diastereoselectivity was relatively lower (2 : 1 dr) in comparison with other nitroalkenes as coupling reactants (up to 99% ee, up to 7 : 1 dr).

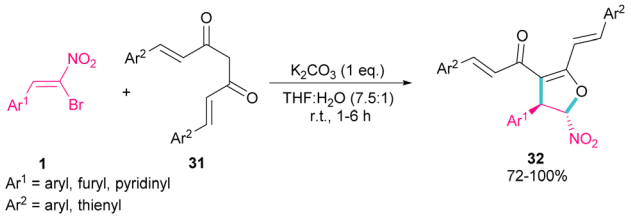
Silver triflate can catalyze the three-component reaction of tetrahydrofuran, β-bromonitrostyrene and alcohol *via* a radical pathway (Scheme 13).[42] The reaction was initiated by the formation of radical **I** from the interaction of Ag(I) with THF, which attacked β-bromonitrostyrene **1** to form intermediate **II**. Further attack of O_2 on **II** led to the peroxy radical **III**. Then, **III** abstracted a hydrogen from THF to give hydroperoxide **IV**. The cleavage of the O–O bond by H_2O resulted in intermediate **V** with the release of bromide. In this step, the nucleophilic attack of alcohol to the carbonyl group along with the removal of the second leaving group (NO_2) led to product **26**. It is noteworthy that only less hindered alcohols can attack intermediate **V** (Scheme 14).

2.3. Base-mediated transformations of bromonitrostyrenes

In 2007, Namboothiri and co-workers reported the synthesis of phosphonylpyrazoles **28** and **29** from diethyl 1-diazo-2-oxopropylphosphonate **27** with α-bromonitroalkenes **1** under basic conditions (Scheme 15, eqn (1)).[43] The elimination of the leaving group in the final product depended on the substituent at the aryl ring of bromonitroalkene substrate. When Ar = Ph,



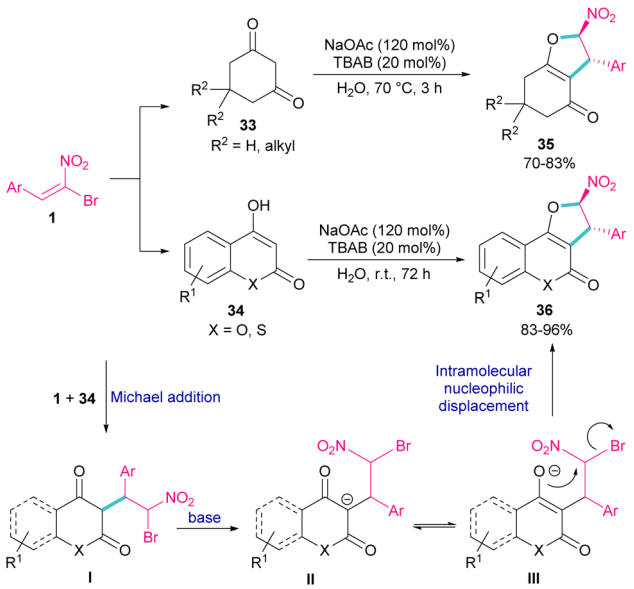
Scheme 15 Reaction of diethyl 1-diazo-2-oxopropylphosphonate and α-bromonitroalkenes.



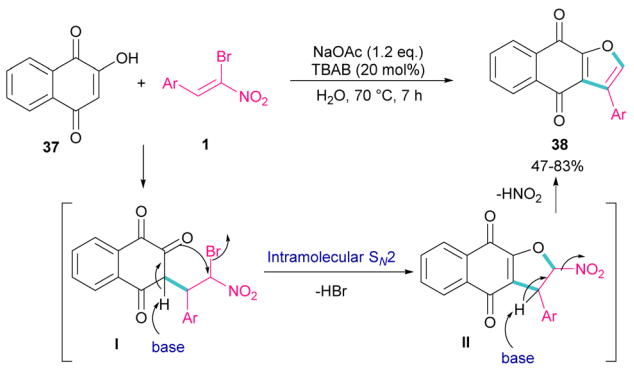
Scheme 16 Base-mediated reaction of α-bromonitroalkenes with curcumins.

product **28** was the major product, while products **28** and **29** were obtained in a ratio of 61 : 39 if bromonitrostyrene contained a 4-OMePh moiety. In a similar work, by dynamic NMR investigation, the Namboothiri group showed that two tautomers **I** and **II** are presented in such a reaction mixture that have a small energy difference but a high barrier to interconversion (Scheme 15, eqn (2)).[44] Also, they could extend the substrate scope of bromonitrostyrenes in this work. Namboothiri *et al.* also reported the reaction of α-bromonitroalkenes **1** with curcumins **31** in the presence of a base (Scheme 16).[45] Single diastereomer of dihydrofurans **32** was obtained in a Michael addition–alkenylation cascade reaction.

In 2011, Xie *et al.* developed a method for the assembly of dihydrofurans from domino reaction of bromonitrostyrenes with 4-hydroxycoumarins or 1,3-carbonyl compounds (Scheme 17).[46] In this work, tricyclic 2,3-dihydrofurans **36** and bicyclic 2,3-dihydrofurans **35** were obtained in high yields under basic conditions in a aqueous solution. In all cases, only the *trans* isomer of products was isolated, showing excellent diastereoselectivity of this method. Regarding the mechanism, Michael addition of bromonitroalkene **1** to 1,3-dicarbonyl compounds **33** gave intermediate **I**, which was converted to the enolate **II** under basic conditions. Finally, product **36** was formed *via* an intramolecular nucleophilic displacement in **III**. Similar reaction conditions were used by Jianwu and co-workers



Scheme 17 Reaction of bromonitrostyrenes with 4-hydroxycoumarins mediated by base.

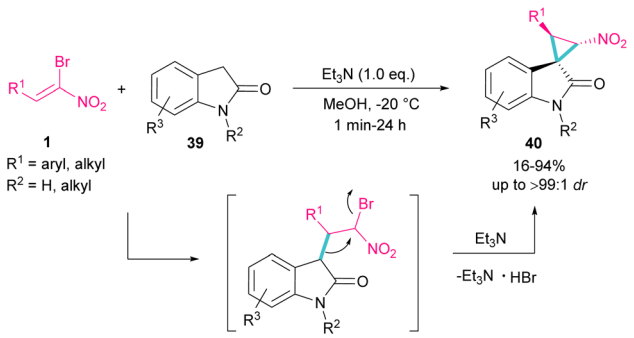


Scheme 18 Reaction of α-bromonitroalkenes and 2-hydroxynaphthalene-1,4-diones under basic conditions.

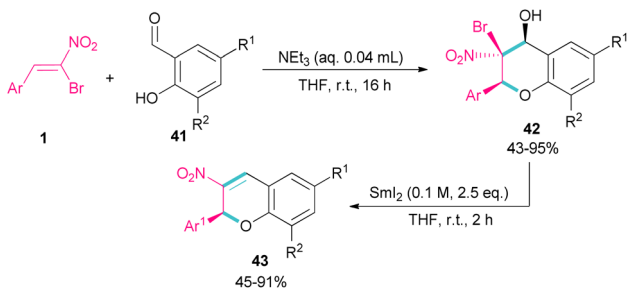
for the synthesis of furan structures (Scheme 18).[47] In their reaction, α-bromonitroalkenes **1** and 2-hydroxynaphthalene-1,4-diones **37** were applied as starting materials to form 3-phenylnaphtho[2,3-*b*]furan-4,9-diones **38** *via* Michael addition and subsequent intramolecular S_N2 reaction. At last, the absorption properties of the obtained products were determined by UV-Vis spectra and fluorescence spectroscopy.

Spirocyclopropyl oxindole frameworks **40** were constructed in high yield with excellent diastereoselectivity from the reaction of bromonitroalkene **1** and *N*-protected indolin-2-ones **39** (Scheme 19).[48] Due to high reactivity of indolin-2-one under ambient temperature and consequently low diastereoselectivity of the obtained product, a very low temperature was necessary for this reaction. The formation of cyclopropane was accomplished by the abstraction of a proton by a base and the liberation of bromide. Not only *N*-protected indolin-2-one but also *N*-H indolin-2-one was included in this transformation.

Soengas *et al.* established a two-step procedure for the preparation of 2-*C*-glycosyl-3-nitrochromenes **43** starting from



Scheme 19 Reaction of bromonitroalkene with *N*-protected indolin-2-ones.

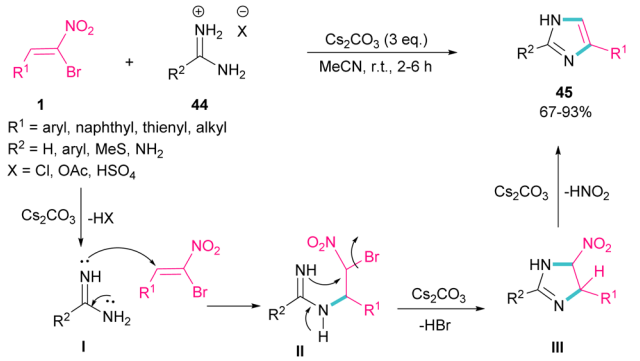


Scheme 20 NEt_3-catalyzed reaction of bromonitroalkene with *ortho*-hydroxybenzaldehydes.

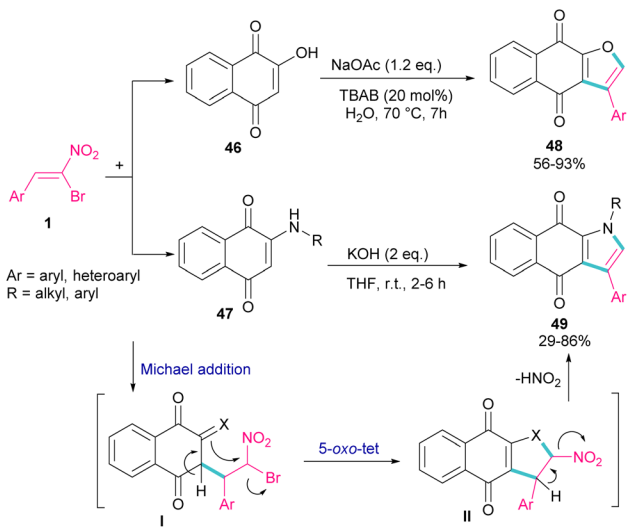
bromonitrostyrenes **1** and *ortho*-hydroxybenzaldehydes **41** (Scheme 20).[49] For this purpose, first, they treated bromonitrostyrenes **1** with *ortho*-hydroxybenzaldehydes **41** under basic conditions to achieve (2*S*,3*S*,4*S*)-3-bromo-3,4-dihydro-4-hydroxy-3-nitro-2*H*-1-benzopyrans **42** in moderate to excellent yields. In the next stage, the reaction was conducted in the presence of 0.1 M solution of SmI_2 in THF for couple hours to form 3-nitrochromenes **43**. SmI_2 can promote the β-elimination in benzopyran **42** with complete stereoselectivity. All steps were performed under mild conditions and all products were obtained with enantiomeric purity.

In 2015, again the Namboothiri research team synthesized imidazole scaffolds **45** through the reaction of amidine hydrochloride **44** with α-bromonitroalkenes **1** (Scheme 21).[50] For the assembly of 2,5-disubstituted imidazoles from α-bromonitroalkenes, 3.0 equivalents of Cs_2CO_3 were required to promote all steps of this imidazole synthesis. First, Cs_2CO_3 promoted the formation of amidine **I** by the elimination of HX form **44**. Michael addition of **1** to **I** gave intermediate **II**, which underwent an intramolecular S_N2 process *via* a 5-*exo-tet* fashion to provide nitroimidazoline **III** along with the removal of HBr in the presence of Cs_2CO_3. Subsequent elimination of HNO_2 by Cs_2CO_3 led to product **45**. Moreover, the authors reported potential anti-parasitic activity of the resulting imidazoles.

In 2018, Namboothiri and co-workers used α-bromonitroalkene **1** in the reaction with lawsone **46** and 2-aminonaphthoquinone **47** to produce furan and pyrrole fused quinonoid compounds **48** and **49** using two different basic



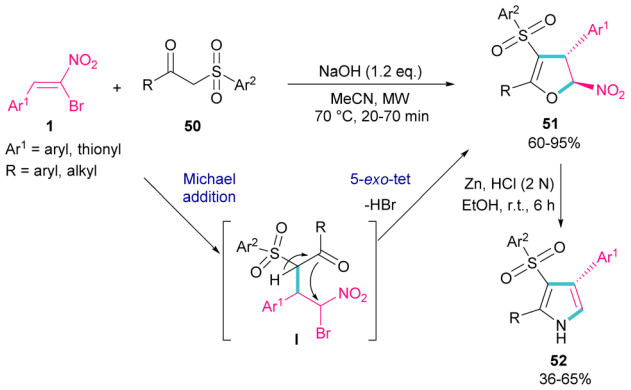
Scheme 21 Cs_2CO_3-promoted reaction of bromonitroalkene with amidines.



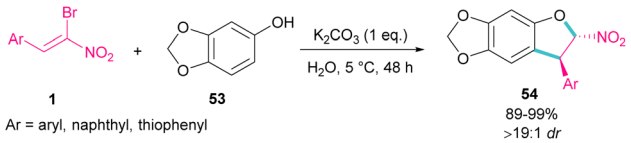
Scheme 22 Reaction of bromonitroalkene with lawsone and 2-aminonaphthoquinone under basic conditions.

conditions (Scheme 22).[51] The transformations were performed *via* Michael addition of **1** to **47** to form intermediate **I**, followed by S_N2 reaction in a 5-*exo-tet* manner to obtain intermediate **II**. Finally, pyrrole or furan frameworks were furnished after HNO_2 removal. The authors also studied the anticancer activity of the obtained products. After a while, Namboothiri proposed a similar mechanism involving Michael addition/5-*exo-tet* reaction for the construction of dihydrofuran derivatives **51** from α-bromonitroalkenes **1** and β-ketosulfones **50** (Scheme 23).[52] They could provide a series of pyrroles **52** by the reduction of dihydrofuran **51** in the presence of zinc powder under acidic conditions.

In 2020, Feng *et al.* presented a protocol for the construction of diastereoselective *trans*-3-aryl-2-nitro-2,3-dihydrobenzofurans **54** under basic conditions (Scheme 24).[53] A diverse range of (*Z*)-bromonitrostyrenes **1**, containing aryl, naphthyl and thiophenyl moieties reacted smoothly with sesamol **53** in water as a green solvent to form dihydrofurans in excellent yields. All products were purified only by a simple filtration procedure and could also be synthesized in the Gram-scale (1.20 g, 94%). In the same year,



Scheme 23 Reaction of bromonitroalkene with β-ketosulfones.



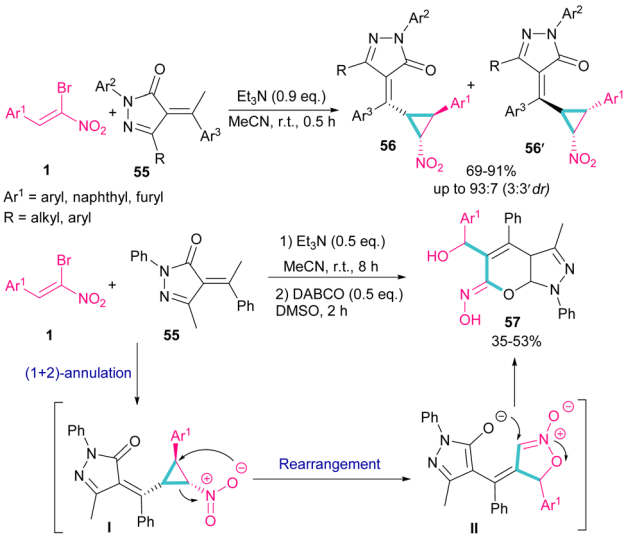
Scheme 24 Reaction of (*Z*)-bromonitrostyrenes and sesamol in the presence of K_2CO_3.

the synthesis of the oxazole rings from α-halo-β-naphthol and nitroalkenes was carried out.[54] Bromonitroalkene as a coupling partner gave the desired product in 82% with >20 : 1 diastereoselectivity.

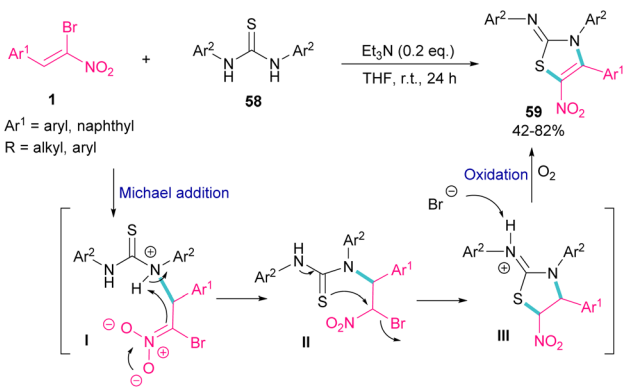
A chemoselective annulation of bromonitrostyrenes with α-alkylidene pyrazolones was established by Han and co-workers in 2021 (Scheme 25).[55] A novel library of pyrazole-fused pyranone oximes were obtained, where α-alkylidene pyrazolone **55** acted as C1 synthon and react in (2 + 1)-cycloaddition with bromonitrostyrene **1** to provide vinylcyclopropane-based pyrazolone **56** and **56′** in the presence of a base. The formation of diastereoisomer **56** was favored due to the less steric hindrance between the aryl and nitro groups. In another stage, the authors conducted this reaction in two steps, in which Et_3N was served as a base to obtain the cyclopropane product. Then, the addition of second base resulted in an intramolecular rearrangement towards the synthesis of pyrazole-fused pyranone oximes **57**.

The synthesis of 2-iminothiazolines **59** can be obtained from the cyclization of 1,3-disubstituted thioureas **58** with 1-bromo-1-nitroalkenes **1** (Scheme 26).[56] At first, Michael addition between 1-bromo-1-nitroalkenes **1** and 1,3-diphenylthiourea **58** produced intermediate **II**, which then underwent a tautomerism and nucleophilic substitution to afford the five-membered ring intermediate **III**. The deprotonation of **III** by bromide anion, followed by the oxidation yielded product **59**. It should be noted that using the suitable amount of the base and the performance of the reaction under air is crucial for this reaction to proceed.

A new class of cyclopenta[*c*]furo[3,2-*b*]furan-5,6-diones, containing three carbon stereocenters were constructed by Yavari *et al.* in 2022 (Scheme 27).[57] A three-component reaction, including β-bromo-β-nitrostyrenes **1**, 3-acetyl-2*H*-chromen-2-

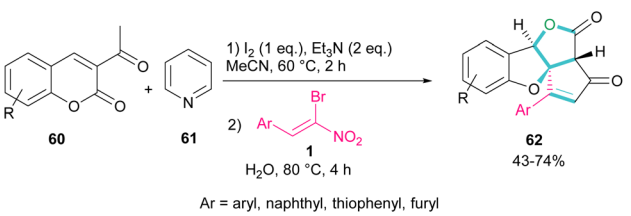


Scheme 25 Reaction of bromonitrostyrenes with α-alkylidene pyrazolones mediate by Et_3N.

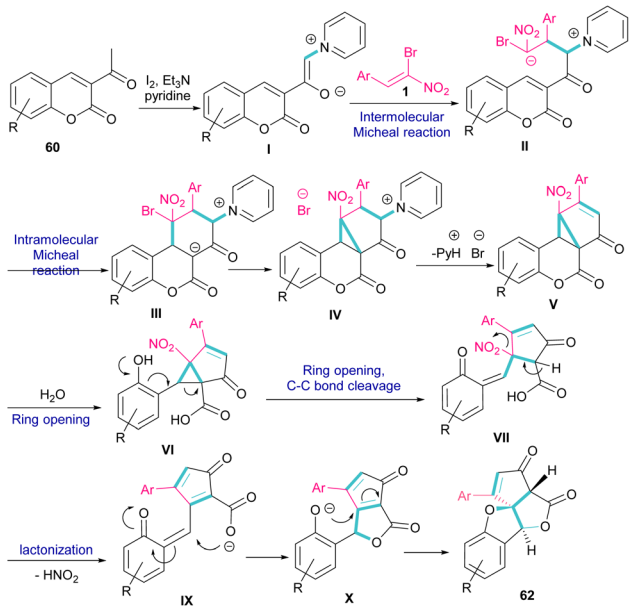


Scheme 26 Et_3N-promoted reaction of 1,3-disubstituted thioureas with 1-bromo-1-nitroalkenes.

ones **60**, and pyridine **61** was carried out through three steps intermolecular and intramolecular Michael additions. Initially, the C–H bond functionalization of 3-acetyl-2*H*-chromen-2-one **60** with pyridine **61** in the presence of I_2 and Et_3N furnished pyridinium ylide **I**. Then, sequentially intermolecular Michael addition of **1** with **I**, and intramolecular Michael reaction gave intermediate **II**, which was converted to cyclopropane **III**. Intermediate **IV** was obtained *via* the elimination of pyridinium



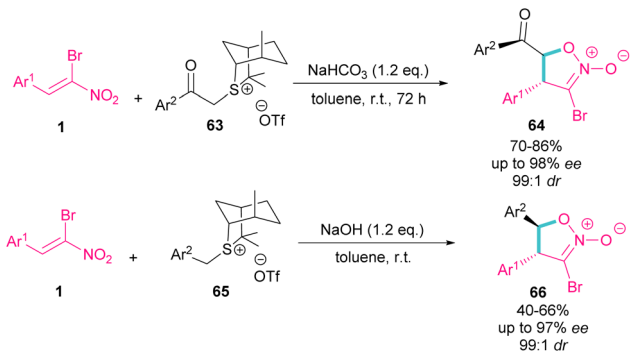
Scheme 27 Three-component reaction of β-bromo-β-nitrostyrenes, 3-acetyl-2*H*-chromen-2-ones, and pyridine.



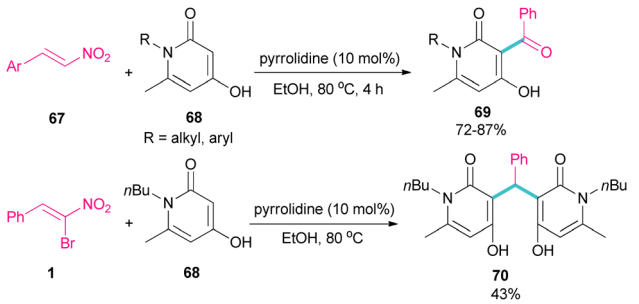
Scheme 28 Possible mechanism for reaction of β-bromo-β-nitrostyrenes, 3-acetyl-2*H*-chromen-2-ones, and pyridine.

bromide in **III**, followed by two steps cyclopropane ring-opening and rearrangement to produce **VI**. The release of HNO_2 gave **VII**, which underwent an intramolecular lactonization to render **IX**. Another intramolecular Michael addition of the phenoxide ion with the C=C bond gave product **62** (Scheme 28).

In the same year, the Xie group designed a (4 + 1) ylide annulation between chiral sulfonium salts **63** and **65** with α-bromonitroalkenes **1** access to enantioenriched isoxazoline *N*-oxides **64** and **66** (Scheme 29).[58] Two types of chiral sulfonium salts, such as α-benzoyl sulfonium triflate salts **63** and α-benzyl sulfonium triflate salts **65** could smoothly generate the sulfonium ylide intermediates, which served as C1 synthon in (4 + 1)-annulation with bromonitroalkene as a 4-atomic synthon. All products were obtained in high yields with excellent enantio- and diastereoselectivity. Also, changing the anions of sulfonium salts from OTf^- to Br^-, ClO_4^- and BF_4^-, showed that the type of anion has a great effect on the activity, and enantioselectivity in this asymmetric annulation.



Scheme 29 Reaction of sulfonium salts and substituted α-bromonitroalkenes.



Scheme 30 Pyrrolidine-catalyzed reaction of 1-butyl-4-hydroxy-6-methylpyridin-2(1*H*)-one and nitroalkenes.

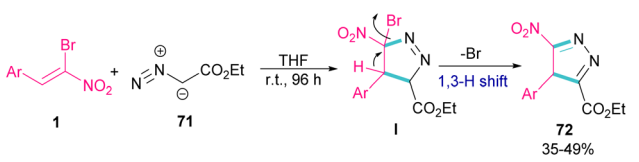
In 2023, Li *et al.* investigated the application of pyrrolidine as a catalyst in the reaction of 1-butyl-4-hydroxy-6-methylpyridin-2(1*H*)-one **68** and nitroalkenes **67** (Scheme 30).[59] They achieved an open ring product **69**, when α-bromonitrostyrene **1** was used as a coupling reactant, while the reaction of other nitroalkenes led to 4-hydroxy-3-benzoylpyridin-2(1*H*)-ones **70** as the main product. This may be because of the high steric hindrance in α-bromonitrostyrene, which inhibits the formation of product **69**.

2.4. Catalyst-free transformations of bromonitrostyrenes

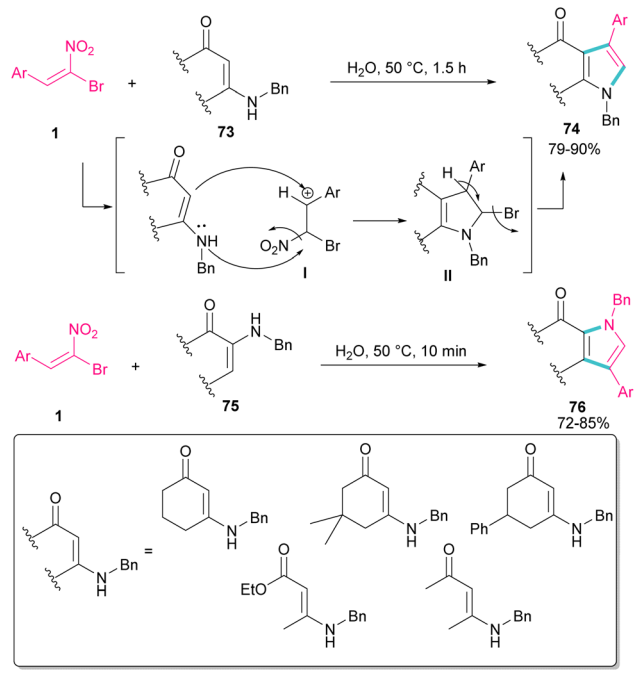
In 2009, Xie and co-workers reported the synthesis of pyrazoles **72** from 1,3-cycloaddition of α-bromo-α-nitroalkenes **1** with ethyl diazoacetate **71** under catalyst-free conditions (Scheme 31).[60] In general, the reaction involved the nucleophilic addition of **71** to **1** to form intermediate **I**, followed by the elimination of bromide along with the 1,3-H shift to furnish the final pyrazole product **72**.

In 2010, Rueping and Parra treated (*E*)-β-bromonitrostyrenes **1** with enaminones **73** to synthesize pyrrole derivatives **74** (Scheme 32).[61] The main advantages of their reaction were the performance of the reaction in water as a green solvent, very short reaction time, and excellent product yields. In this reaction, bromonitrostyrenes **1** acted as a trifunctional synthon and reacted well with both enaminone **73** and *N*-benzylenaminone **75** as binucleophilic synthons. First, the nucleophilic attack of nitrogen to the carbon atom in **I** concomitant with removal of a leaving group produced **II**. Next, the deprotonation and the release of another leaving group afforded the desired product **74**.

Deng *et al.* showed that depending on the type of nitrostyrenes and the reaction solvent, two different pyrazole products could be obtained under acidic conditions (Scheme 33).[62] When β-chloro-β-nitrostyrenes **77** were used as reactants in the



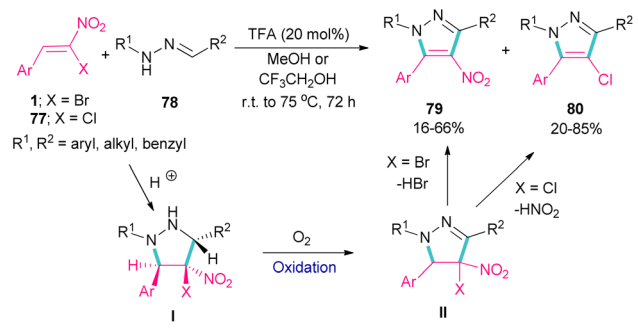
Scheme 31 Reaction of α-bromo-α-nitroalkenes with ethyl diazoacetate under catalyst-free conditions.



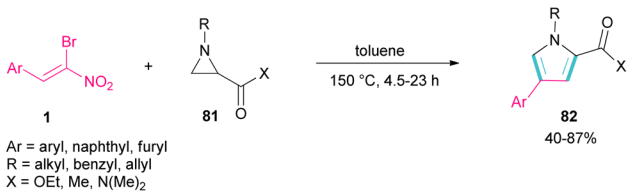
Scheme 32 Catalyst-free reaction of (*E*)-β-bromonitrostyrenes with enaminones.

reaction with hydrazones **78**, the elimination of HNO_2 occurred to produce 4-chloro-tetrasubstituted pyrazoles **80** in MeOH as a solvent. Whereas, 4-nitro-tetrasubstituted pyrazoles **79** were obtained from β-bromo-β-nitrostyrenes **1** and hydrazones **78** as starting materials in MeOH. In this case, the removal of HBr was favored over HNO_2, which could be due to the easy cleavage of the C–Br bond compared to the C–Cl bond. In fact, the leaving-group abilities of functional groups can be classified as Br > NO_2 > Cl. In general, the reactions involved pyrazolidine intermediate **I**, which was subjected to oxidation and elimination steps. It should be noted that when a more acidic alcoholic solvent like CF_3CH_2OH was utilized, the formation of 4-bromo-tetrasubstituted pyrazoles was also observed in the reaction mixture.

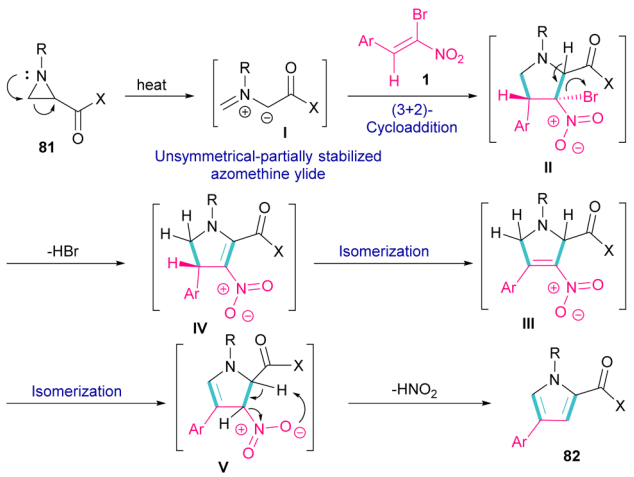
Another domino reaction was carried out by the Khan research team to construct 1,2,4-trisubstituted pyrrole



Scheme 33 TFA-catalyzed reaction of bromonitrostyrenes with hydrazones.

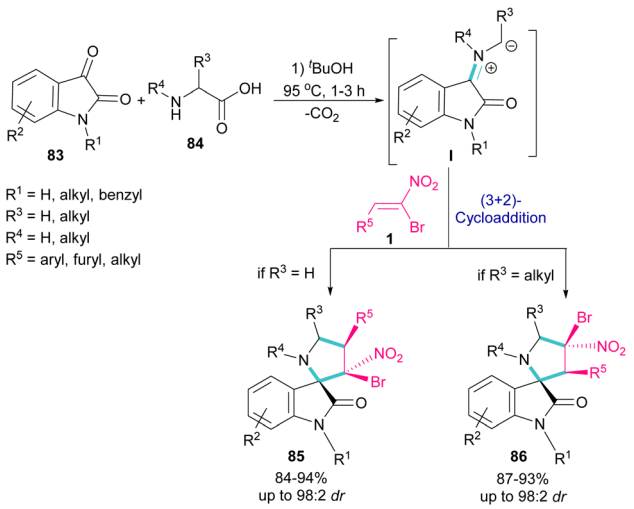


Scheme 34 Catalyst-free reaction of unactivated aziridines with β-bromo-β-nitrostyrenes.



Scheme 35 Plausible mechanism for reaction of unactivated aziridines with β-bromo-β-nitrostyrenes.

derivatives **82** from 1,3-dipolar cycloaddition of unactivated aziridines **81** with β-bromo-β-nitrostyrenes **1** (Scheme 34).[63] This reaction involved *in situ* generated unsymmetrical azomethine ylide from aziridine, followed by a cascade elimination and aromatization step. As shown in Scheme 35, the mechanism started with simultaneous cleavage of the C–C bond of aziridine **81** under heat to afford azomethine ylide **I**. The interaction of **I** with β-bromo-β-nitrostyrene **1** resulted in the unstable cycloadduct **II**, which readily underwent E2 elimination of HBr to render **III**. In this step, **III** was isomerized to **IV** and then **V**, followed by the elimination of HNO_2 to form product **82**.



Scheme 36 Reaction of oxindole, bromonitrostyrenes and α-amino acids.

In 2019, Ganesh and co-workers developed a multicomponent reaction, including oxindoles **83**, bromonitrostyrenes **1** and α-amino acids **84** to generate tetra-substituted α-spiropyrrolidine structures **85** and **86** (Scheme 36).[64] In the first step, azomethine ylide **I** was formed from the condensation of oxindole and α-amino acid. Next, (3 + 2)-cycloaddition of bromonitrostyrene with **I** provided spiropyrrolidine. Two diastereomers could be obtained depending on the substituent at the α-position of amino acid. If R^3 = H, diastereomer **85** was the major product, while spiropyrrolidine **86** was obtained as a major diastereomer when R^3 = alkyl. The diastereoselectivity may be due to the steric effects in transition states of azomethine ylides.

3. Conclusions

In this review, we have described the advances in the synthesis of carbocyclic and heterocyclic compounds from the reaction of α-bromonitrostyrenes with various coupling reactants in straightforward and atom economical manners. Organocatalytic domino Michael reactions offer a direct and sustainable route for the synthesis of diastereo- and enantioselective bioactive products under mild reaction conditions. Although it seems that the use of Lewis acid metal catalysts and bases as promoters in the reactions of α-bromonitrostyrenes could be studied further. Considering the great potential of α-bromonitrostyrene as a reactive dipolarophile with good leaving groups (bromo and nitro), the use of this synthon in the cross-coupling reactions, as well as regio- and stereoselective syntheses can provide useful insights for further researches in this field. In our opinion, α-bromonitrostyrenes can be considered as a simple and accessible building block for the construction of more complex organic molecules.

Conflicts of interest

There are no conflicts to declare.

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