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Morita-Baylis-Hillman and Rauhut-Currier Reactions of Conjugated Nitroalkenes

Kirandeep Kaur and Irishi N. N. Namboothiri*

Abstract: α-Functionalization of conjugated nitroalkenes and nitrodienes using various electrophiles in the presence of amine catalysts such as imidazole and DMAP and the synthetic applications of the products are reviewed. The electrophiles include formaldehyde, activated non-enolizable carbonyl compounds, activated imines, azodicarboxylates as well as activated alkenes such as nitroalkenes, MVK and acrylate. Reports on synthetic applications of the products, though only appearing in the last three years, highlight the potential of these multi-functional scaffolds to take part in diverse transformations such as Michael addition, cycloaddition and many cascade reactions leading to complex molecules including natural products.

Keywords: DMAP · Imidazole · Morita-Baylis-Hillman reaction · Nitroalkenes · Rauhut-Currier reaction

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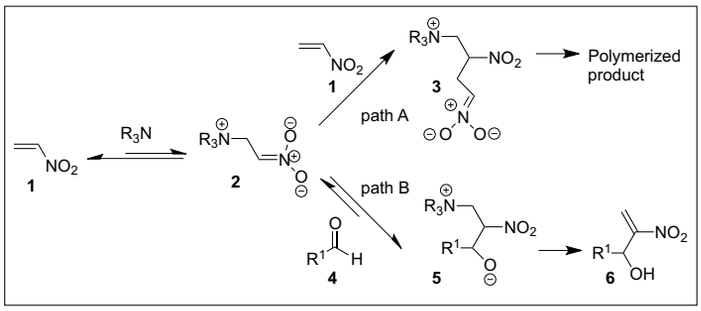
1. Introduction

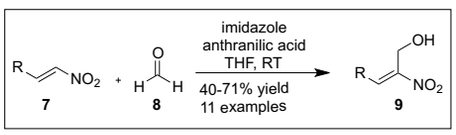
The Morita-Baylis-Hillman (MBH) reaction, in general, is a C–C bond forming reaction of an α,β-unsaturated carbonyl compound with an aldehyde mediated by an organic nucleophilic base resulting in an allylic alcohol. Since this reaction embodies atom economy and generation of functional groups in a one-pot three-step three-component fashion, it is regarded as an important process for the formation of carbon–carbon bonds. While the phosphine-catalyzed reaction was reported by Morita in 1968,[1] the corresponding amine-catalyzed version was disclosed by Baylis and Hillman in 1972.[2] Ignored for a long time after its invention, the reaction was resurrected in the 1980s when organic chemists led by Basavaiah started exploring different facets of this fabulous reaction.[3] Although the original process involved the use of an aldehyde as electrophile in a Michael-aldol-elimination sequence, replacement of the aldehyde by an imine led to the formation of α-aminoalkylated products. The aminoalkylation strategy, which involves a Michael-Mannich-elimination sequence, leads to very useful β-methylene-β-amino products and, in particular, to β-amino esters when an acrylate is used as Michael acceptor. This has now developed into a subarea of MBH reaction and is often called the aza-MBH reaction.[4] Further variation of the electrophile to electron deficient alkenes in a Michael-Michael-elimination sequence leads to homo- and heterodimerization which is also the vinylogous version of the MBH reaction and is currently termed the Rauhut-Currier reaction.[5]

Detailed mechanistic studies have shed light onto the role of catalysts and solvents in this equilibrium-controlled reaction.[3,6] The scope of the reaction has been extensively investigated in recent decades by employing numerous substrates, electrophiles, catalysts and conditions.[3,7] Intramolecular[3] and asymmetric[8] versions have given a fresh impetus towards expanding the scope and applications of this fascinating reaction. The immense potential of this reaction as a key step in the synthesis of complex molecules including natural products is evident from the number of reviews appeared on the synthetic applications of MBH reaction in the past decade.[9] Biological properties of the MBH adducts,[10] formation of unexpected products in the MBH reaction[11] and formation of MBH adducts through other reactions[12] have also become the subject matter of recent reviews.

In this short review we have focused exclusively on the MBH and RC reactions of nitroalkenes and their synthetic applications reported by us and closely related work by others. Although Baylis and Hillman have reported in their patent that nitroethylene **1** reacted with acetaldehyde **4** ($R^1 = CH_3$) in the presence of DABCO to afford the MBH adduct **6**, there were no further reports or experimental data in the literature (Scheme 1).[2] Our attempts to carry out the reaction proved futile as we observed only polymerization of nitroethylene **1**. We attributed the reluctance of nitroethylene **1** to undergo the MBH reaction to instant reversibility of the initial conjugate addition of the tertiary amine catalyst to nitroethylene **1** and/or Michael addition of the initially formed nitronate **2** to another molecule of nitroethylene **1** to form the intermediate **3**, instead of addition to the aldehyde **4** in an aldol fashion to form the desired product **6** through the intermediate **5**. It is presumed that the intermediate **3** further reacts with nitroethylene **1** leading to polymerized product.



Scheme 1.



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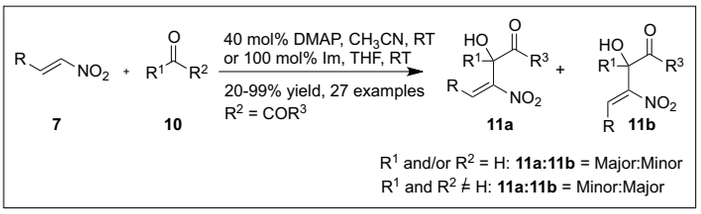
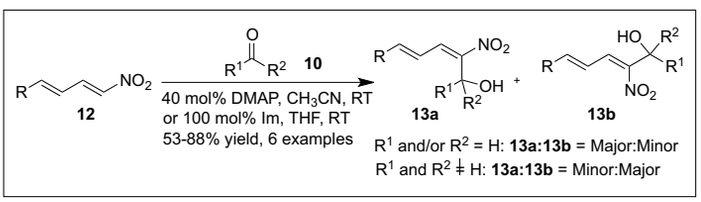


Scheme 3.



Scheme 4.

In light of the above, we turned to β-substituted nitroethylenes in anticipation that these would be less prone to polymerization. Surprisingly, there has been no report, besides the mention made by Baylis and Hillman in their patent,[2] of the MBH reaction of nitroalkenes when we initiated our program in early 2001. This is despite the well-documented status of nitroalkenes as synthetic chameleons because of their diverse reactivity as Michael acceptors, dienophiles, dipolarophiles and 1,3-dipoles.[13] However, besides the difficulties encountered in employing nitroethylene **1** as a substrate in the MBH reaction, the well-established fact that β-substituted electron-deficient alkenes, in general, do not react or react only sluggishly in the MBH reaction may have dissuaded various research groups from directing their efforts towards developing a viable strategy for the MBH reaction of nitroalkenes.

2. Hydroxyalkylation

Initially, we investigated the α-hydroxymethylation of various aromatic and heteroaromatic nitroalkenes **7** with formaldehyde **8** (Scheme 2).[14] Our optimization studies have revealed that stoichiometric amounts of imidazole in the presence of catalytic amounts of anthranilic acid in THF at room temperature would provide the hydroxymethylated adducts of nitroalkenes **9** in good yields.

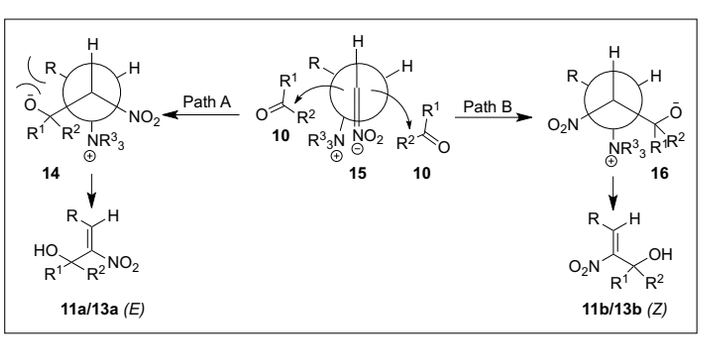
Anthranilic acid was superior to aniline and benzoic acid as co-catalyst suggesting its involvement in the dual activation of nitroalkene **7** and aldehyde **8**. The α-hydroxymethylated nitroalkenes **9** were subsequently screened for their anticancer activity and some of them were found to inhibit cervical cancer (HeLa) cell proliferation at low micromolar concentrations with half-maximal inhibitory concentrations in the range of 1–2 μM. It was shown that the hydroxymethylated nitroalkenes **9** exert their antiproliferative activity at least in part by depolymerizing cellular microtubules through tubulin binding.[15]

Since the MBH reactions of nitroalkenes **7** with various aliphatic and aromatic aldehydes were not immediately feasible, we employed activated nonenolizable carbonyl compounds **10** as electrophiles for reaction with various conjugated nitroalkenes **7** (Scheme 3).[16] The substrate scope of this reaction showed that ethyl 2-oxopropanoate (**10a**) and ethyl phenyl glyoxylate (**10b**) were not suitable electrophiles for reaction with nitroalkenes **7**. But, ethyl glyoxylate (**10c**), methyl 3,3,3-trifluoro-2-oxopropanoate (**10d**), ketomalonate **10e** and pyruvaldehyde **10f** reacted with a variety of nitroalkenes **7** under the optimized conditions, *i.e.* 40–100 mol% of DMAP in CH_3CN or 100 mol% of imidazole in $CHCl_3$ or THF, and provided the MBH adducts **11** in high yields. Among the cyclic activated carbonyl compounds, α-dicarbonyl compounds were inactive while the tricarbonyl compound, ninhydrin **10g**, provided good yields of the MBH adducts **11**.

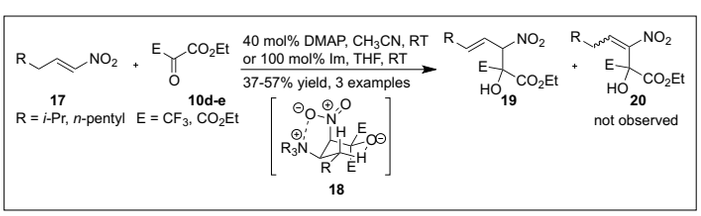
The MBH reactions of nitroalkenes **7** and nitrodienes **12** with formaldehyde **8** and α-dicarbonyl compounds **10**, *e.g.* ethyl glyoxylate **10c** and pyruvaldehyde **10f**, gave *E* isomers **11a/13a** as the major or exclusive products whereas *Z* isomers **11b/13b** were obtained in the cases of trifluoropyruvate **10d** and ninhydrin **10g** (Schemes 3 and 4).[17]

The above selectivities were explained on the basis of transition state models. In case of electrophiles **10** having R^1 and/or R^2 as H, their approach is tolerated from the hindered side of nitronate **15** leading to *E* isomer (path A, Scheme 5).[17] This is because there are no severe steric interactions between the alkoxide and the β-substituent R in the intermediate **14** and hence *E* isomer **11a** or **13a** is formed (Scheme 5). But in the case of electrophiles, where R^1 and $R^2 \neq H$, approach from the less hindered side of the nitronate **15** avoiding any possible steric interaction between the alkoxide and the β-substituent R in the intermediate **16** gives rise to *Z* isomer **11b** or **13b**.

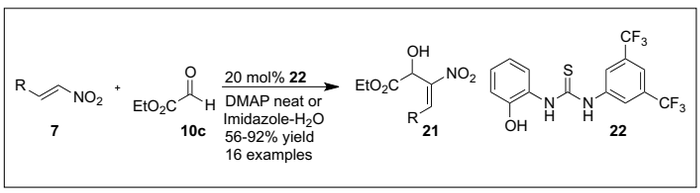
The reaction between nitroalkenes **17** and ketoesters **10d**,**e** gave β,γ-unsaturated nitro compounds **19** instead of the expected MBH adducts **20** (Scheme 6).[17] This was



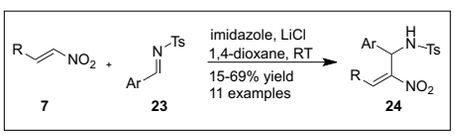
Scheme 5.



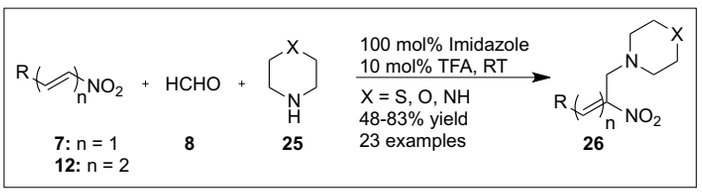
Scheme 6.



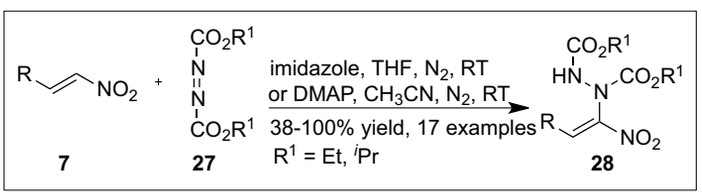
Scheme 7.



Scheme 8.



Scheme 9.



Scheme 10.

attributed to the γ-hydrogen abstraction by the alkoxide through a chair-like conformation adopted by the transition state **18**, which was devoid of 1,3-diaxial interaction of NO_2 group with the substituent R.

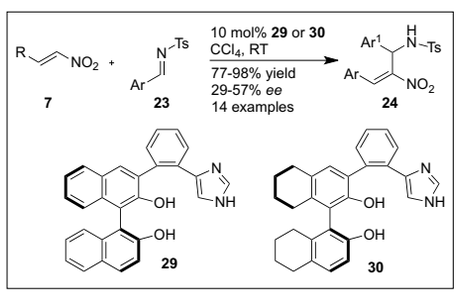
Recently, Chen *et al*. have reported an efficient thiourea **22** promoted MBH reaction of various conjugated nitroalkenes **7** with ethyl glyoxylate **10c** in the presence of DMAP (20 mol%) under solvent free conditions or imidazole (100 mol%) in aqueous medium (Scheme 7).[18]

3. Aminoalkylation/Hydrazination

The aza-MBH reaction of nitroalkenes **7** appeared an attractive approach for the synthesis of novel 1,2-nitramines, 1,2-diamines and α-aminoketones. Since activated imines, particularly *N*-sulfonylimines **23**, have been successfully employed for aminoalkylation of α,β-unsaturated ketones, esters, and aldehydes,[4] we proposed that such imines would be suitable electrophiles for α-aminoalkylation of nitroalkenes **7** as well (Scheme 8). Our catalyst screening suggested that imidazole as catalyst in conjunction with LiCl as co-catalyst in dioxane would constitute suitable conditions for obtaining the aza-MBH adducts **24** in moderate to good yields (15–69%, Scheme 8).[19] The role of LiCl, besides its 'salting out' ability and Lewis acidic nature, is reminiscent of the R_3N-LiCl combination in the Roush-Masamune variant of the Horner-Wadsworth-Emmons reaction. Some of the aminoalkylated products **24** exhibited anti-cancer properties by inhibiting human cervical cancer (HeLa) cell proliferation at low micromolar concentrations (1–10 μM). The activity was attributed to perturbation of microtubule assembly *in vitro* and in cells by tubulin binding.

It appeared possible to employ iminium species, generated *in situ* from an aldehyde and a secondary amine, as electrophiles for aminoalkylation of nitroalkenes **7** and nitrodienes **12**. Thus facile aminoalkylation at the β-position of nitroalkenes **7** possessing aryl, heteroaryl, and alkyl substituents at the β-position as well as δ-substituted nitrobutadienes **12** could be achieved by treating them with formaldehyde **8** and a secondary amine **25** in the presence of imidazole as catalyst and trifluoroacetic acid as co-catalyst (Scheme 9).[20] The scope of this reaction was investigated by using different cyclic secondary amines such as morpholine, piperidine and thiomorpholine and in all the cases the products were obtained in moderate to high yields (48–83%) and excellent stereoselectivity. Multiple roles have been proposed for TFA as Brønsted acid in this reaction. These include activation of the nitroalkene **7**/nitrodiene **12** towards conjugate addition of imidazole, stabilization of the so-formed nitronate *via* hydrogen bonding, activation of the aldehyde in the iminium formation and activation of the iminium towards addition of the nitronate by stabilizing the counter ion.

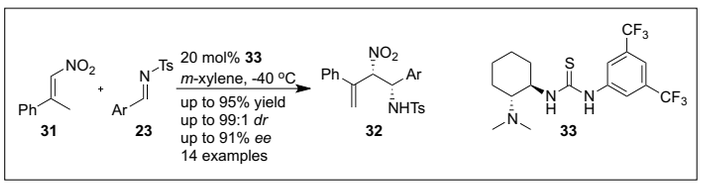
Having developed the C–C bond forming methods, viz hydroxyalkylation and aminoalkylation, *via* the MBH reaction of nitroalkenes, we turned our attention to C-hetero atom bond formation. In particular, azodicarboxylates, by virtue of their ability to react as electrophilic aminating agents, appeared excellent candidates for C–N bond formation under MBH conditions. Thus the MBH reactions of nitroalkenes **7** with azodicarboxylates **27** proceeded smoothly with imidazole or DMAP as the catalyst at room temperature and provided novel α-hydrazino-α,β-unsaturated nitroalkenes **28** in excellent yields (4–5 h, up to 98%, Scheme 10).[21] Our catalyst and solvent screening confirmed that the most appropriate solvents were THF for imidazole and acetonitrile for DMAP. The nature of substrates on the aromatic ring of nitroalkenes **7** (R = Ar) had no effect on the efficiency of the reaction. Both diethyl- and diisopropyl azodicarboxylate (DEAD and DIAD) were equally effective as electrophilic agents but the corresponding diamide remained unreactive. The geometry of the hydrazinodicarboxylates **28** was assigned to be *E* by analysis of the ^{1}H-^{1}H NOESY spectrum and single crystal X-ray analysis of a representative compound.



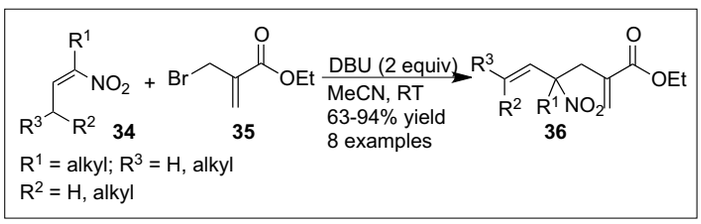
Scheme 11.

The asymmetric version of the aminoalkylation of nitroalkenes described in Scheme 8 has been developed by Sasai *et al.* using a new class of chiral imidazoles **29** and **30** (Scheme 11).[22] The bifunctional Lewis base-Brønsted acid chiral BINOLate organocatalysts **29** and **30** were instrumental in delivering the aza-MBH adducts **24** in good yields but with moderate enantioselectivities (up to 60% *ee*). But nevertheless, the cooperativity of acidic phenolic hydroxy groups in activating nitroalkenes and basic imidazole unit in acting as a nucleophilic Lewis base, thus creating an environment for asymmetric induction, has been elegantly demonstrated by the authors in this reaction.

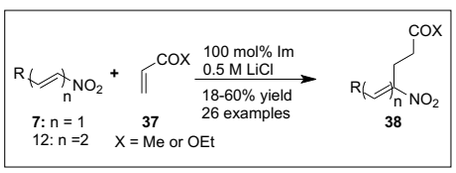
Xu *et al.* have reported an aza-MBH-type reaction of *N*-tosylimines **23** and nitroalkene **31** in the presence of (1*R*,2*R*)-diaminocyclohexane-thiourea **33** as the chiral catalyst.[23] The products, β-nitro-γ-enamines **32** were isolated in good yields (up to 95%) and high diastereo- (up to 99:1 *dr*) and enantioselectivities (up to 91% *ee*, Scheme 12). However, the products are not α,β-unsaturated nitroalkenes and the applicability of the catalyst **33** has been limited to trisubstituted β-nitrostyrene as no reaction was observed when disubstituted nitroalkenes were employed as substrates.



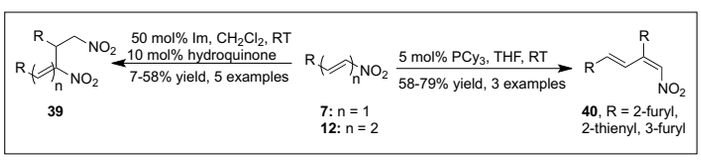
Scheme 12.



Scheme 13.



Scheme 14.



Scheme 15.

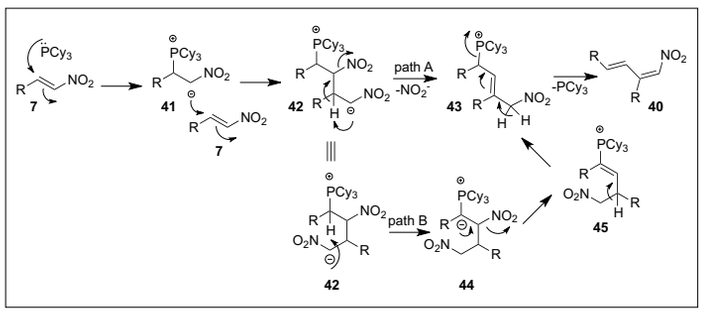
4. Vinylogous MBH Reaction/ Rauhut-Currier Reaction

Ballini *et al.* have described a reaction between aliphatic nitroalkenes **34** and ethyl-2-bromomethylacrylate **35** under DBU-catalyzed conditions (Scheme 13).[24] Although the products are not conjugated nitroalkenes (see also Schemes 6 and 12) and elimination of bromide takes place thereby undermining the atom economy, it appears to be the first example of a vinylogous MBH-type reaction or Rauhut-Currier (RC)-type reaction of nitroalkenes. According to the mechanism proposed by the authors, the nitronate arising from Michael addition of DBU to nitroalkene **34** adds to acrylate **35** in a second Michael reaction. This second Michael addition, which is overall a vinylogous S_N2 reaction (S_N2'), is facilitated by activation of the allylic position *via* substitution of bromide by DBU. Finally, β,γ-elimination completes the sequence.

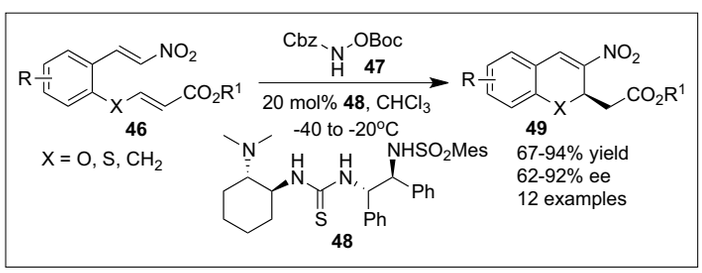
The imidazole-LiCl catalyst system we employed in the aminoalkylation of nitroalkenes (Scheme 8) was originally employed for the RC reaction of nitroalkenes **7** and nitrodienes **12** with methyl vinyl ketone (MVK) and acrylate **37** (Scheme 14).[25,26] While the RC adducts of nitroalkenes **7** and nitrodienes **12** with MVK were isolated in moderate to good yield (28–60%), the yields were relatively lower with acrylate (18–27%). One of the RC adducts was found to inhibit HeLa cell proliferation at low micromolar (<5 μM) concentrations by binding to tubulin.

Having developed a method for the hetero-coupling of nitroalkenes with other electron-deficient alkenes such as MVK and acrylate **37**, we investigated the more challenging self-dimerization of nitroalkenes **7** and nitrodienes **12** (Scheme 15).[26] Under the optimized conditions, *i.e.* in the presence of 50 mol% imidazole and 10 mol% hydroquinone in CH_2Cl_2, four nitroalkenes and a nitrodiene dimerized to provide the RC adducts **39** in varying yields. Interestingly, when the reaction was carried out in the presence tricyclohexylphosphine, the heteroaromatic nitroalkenes formed nitrodienes **40** through self-dimerization and an abnormal nitro group elimination.

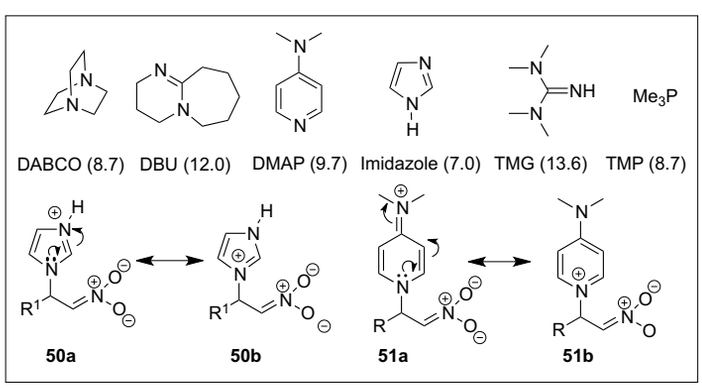
The proposed mechanism identifies a common intermediate **42** for the formation of normal RC adduct **39** and the abnormal one **40** that arises *via* nitro group elimination (Scheme 16).[26] In the normal pathway (not shown) **42** undergoes intramolecular proton transfer followed by elimination of the catalyst to afford dimer **39**. However, transformation of **42** to **40** directly *via* intermediate **43** (path A) or through more likely ylide **44** in which HNO_2 was eliminated prior to the elimination of phosphine was proposed in the abnormal pathway.



Scheme 16.



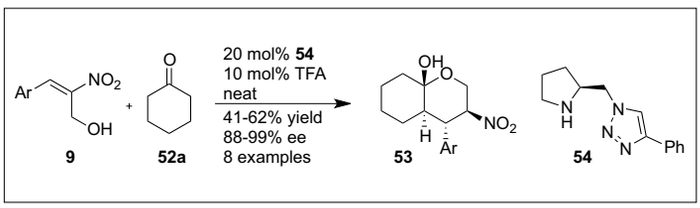
Scheme 17.



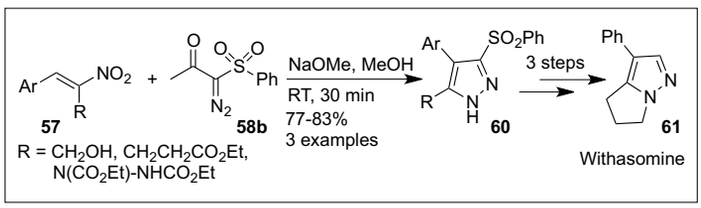
Scheme 18.

Xiao *et al.* have developed a highly enantioselective and atom economical crossed RC reaction of nitroalkenes with tethered α,β-unsaturated esters **46** by merging nucleophilic activation by **47** and hydrogen-bonding catalysis through **48**, providing highly functionalized 2*H*-chromenes, 2*H*-thiochromenes, and 1,2-dihydronaphthalenes **49** (Scheme 17).[27] Computational investigations indicated that the stereoselectivity of the RC reaction was determined by the intramolecular-Michael addition step and the rate-determining step was the retro-aza-Michael addition.

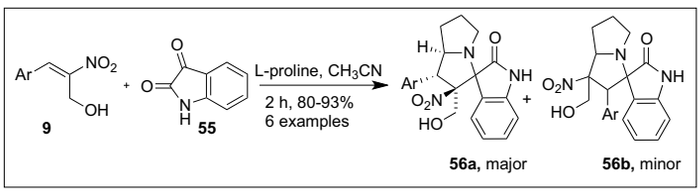
In most of the MBH and RC reactions of nitroalkenes discussed above, the nucleophilic Lewis base that worked satis-



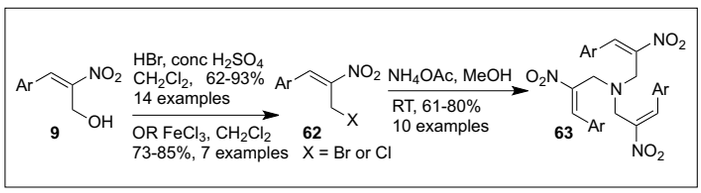
Scheme 19.



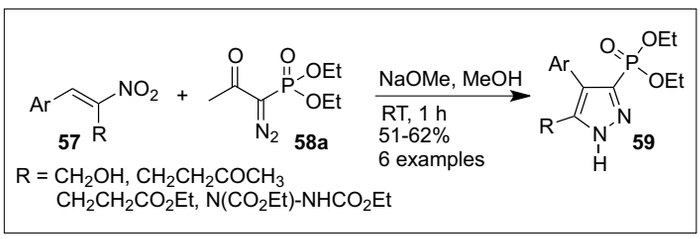
Scheme 22.



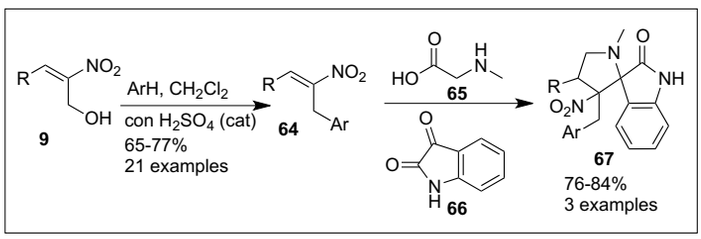
Scheme 20.



Scheme 23.



Scheme 21.



Scheme 24.

factorily was either imidazole or DMAP. Other amine bases such as DABCO, DBU and TMG and a phosphine base such as TMP were totally ineffective in catalyzing the MBH and RC reactions of nitroalkenes (for exceptions, see Schemes 12, 13 and 17). This is despite the fact that DABCO has been the catalyst of choice for the vast majority of MBH reactions known in the literature. Interestingly, the pKa's of these bases did not correlate with their catalytic activity. For instance, while both imidazole and DMAP with pKa's 7.0 and 9.7, respectively, catalyzed the MBH reaction of nitroalkenes, DABCO and TMP with an intermediate pKa (8.7) were ineffective (Scheme 18). Those amine bases with high pKa's such as DBU and TMG were also not suitable for our purpose. This prompted us to propose that sterically less hindered bases such as imidazole and DMAP with the possibility of resonance stabilization of the positive charge in the initial Michael adducts, *e.g.* **50** and **51**, are the best catalysts for the MBH reaction of nitroalkenes.[17]

5. Synthetic Applications of MBH and RC adducts

The MBH adducts and their derivatives such as carbonates and acetates, owing to their functional group diversity, have become excellent scaffolds for the synthesis of novel complex molecules and natural products. Novel multi-component and cascade reactions that rely on the multifunctionality of the MBH adducts have emerged in recent years.[9] Although studies on the synthetic applications of MBH and RC adducts of nitroalkenes are still in their infancy, we discuss below the progress made thus far to enable the reader to appreciate the enormous potential of these multi-functional adducts.

Chandrasekhar *et al.* have reported a highly enantioselective Michael-ketalization cascade reaction of MBH alcohols **9** with cyclohexanone **52a** in the presence of 20 mol% of organocatalyst **54** (Scheme 19).[28] The fused bicyclic cyclohexylpyran derivatives **52** were isolated in moderate to good yields (41–62%) and good to excellent enantioselectivities (88–99% *ee*). The proposed mechanism involves a cascade enamine Michael addition to MBH alcohol **9** followed by intramolecular ketalization.

Bakthadoss *et al.* have reported a simple methodology for the regio- and stereoselective synthesis of 3-spiropyrrolizidines **56** from the MBH adducts **9** (Scheme 20).[29] An intermolecular [3+2] cycloaddition between 9 and a 1,3-dipole derived *via* decarboxylation of proline based imine of isatin **54** afforded spiropyrrolizidines **56** in good to excellent yield, but as a mixture of regio-isomers. The Ar and NO_2 groups are presumably *trans* in the minor regioisomer as well, though the authors have not assigned the stereochemistry of the minor isomer. Similar reaction with sarcosine-based imines provided spiropyrrolidines in 60–82% yield.

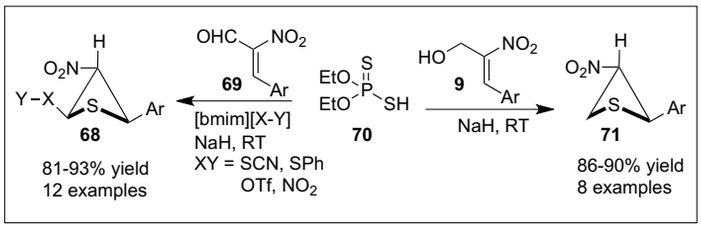
We have employed various MBH and RC adducts of nitroalkenes **57** as cycloaddition partners with Bestmann-Ohira reagent (BOR) **58a** in the regioselective synthesis of phosphonylpyrazoles **59** (Scheme 21).[30] The reaction involves nucleophilic alkoxide base-mediated deacylation of BOR **58a** to form diazomethylphosphonate anion and its reaction as a 1,3-dipole with MBH and RC adducts of nitroalkenes **56**.

Similar one-pot reaction of MBH and RC adducts **57** with diazosulfone **58a** delivers sulfonylpyrazoles **60** as single regioisomers (Scheme 22).[31] The synthetic utility of this methodology was demonstrated by transforming a pyrazole analog **60**, derived from RC adducts of nitroalkenes with acrylate (see Scheme 14), to withasomnine (**61**), a bioactive pyrazole alkaloid, in three steps.

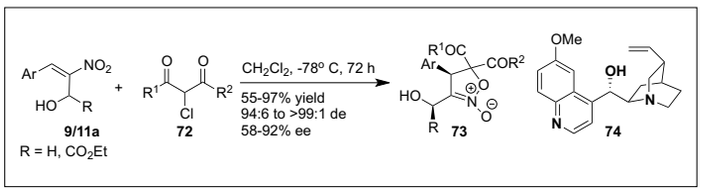
Bakthadoss *et al.* have also converted the MBH adducts **9** into a novel class of building blocks, the α-bromo- and β-chloromethylated nitroalkenes **62**, in very good yields *via* S_N2 reaction under simple conditions (Scheme 23). These compounds were further transformed into amines **63**, prospective dendrimer cores, in good yields.[32]

Later, Bakthadoss *et al.* carried out conc H_2SO_4-mediated Friedel-Crafts reaction of the MBH adducts **9** with a variety of arenes such as benzene, *p*-xylene and naphthalene affording nitro-1,3-diarylpropenes **64** in good yields, which were further employed for the synthesis of pyrrolidines and 3-spiropyrrolidines **67** (Scheme 24).[33]

Rai and Yadav have utilized the MBH adducts **9** for the synthesis of thietanes



Scheme 25.



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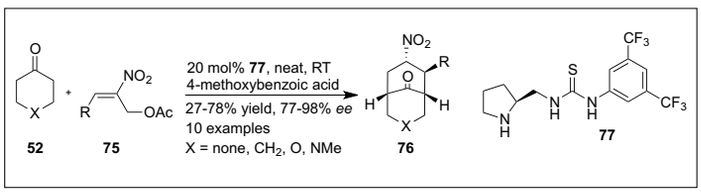
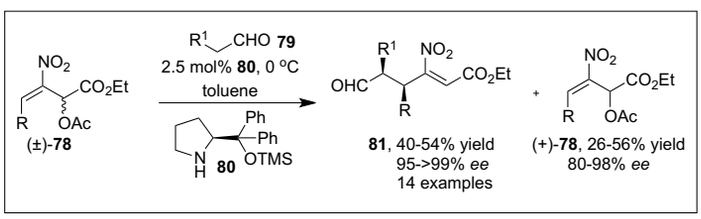
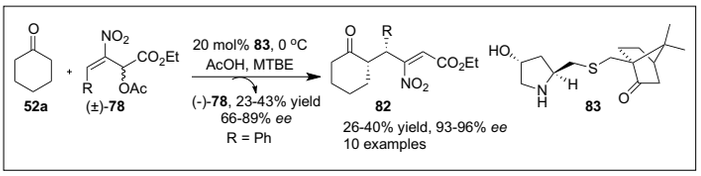


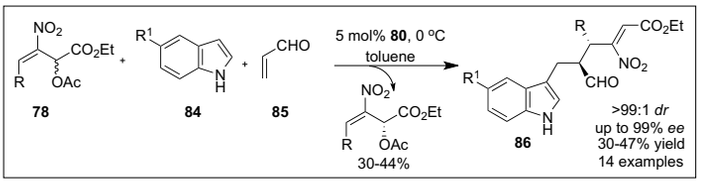
Scheme 27.



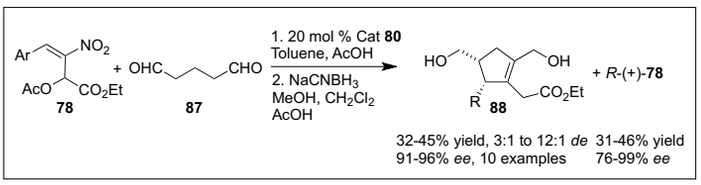
Scheme 28.



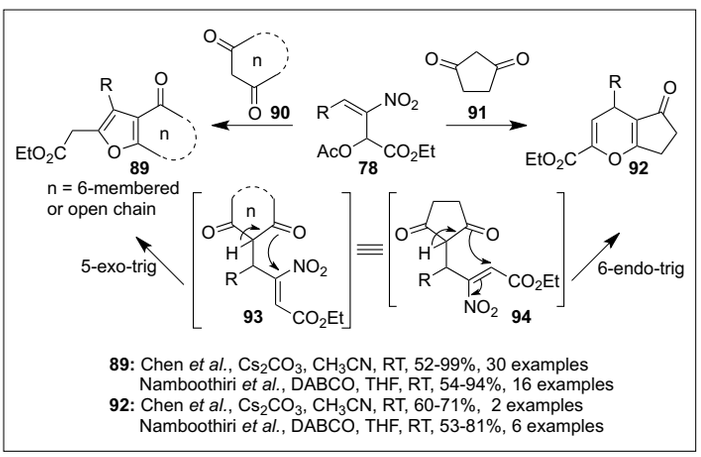
Scheme 29.



Scheme 30.



Scheme 31.



Scheme 32.

68 and **71**. In a one-pot procedure, thia-Michael addition of *O*,*O*-diethyl hydrogen phosphorodithioate **70**, in the presence of a task-specific ionic liquid [bmim][X-Y], to MBH alcohols **9** and their aldehydes **69**, followed by anion-induced cyclization afforded 2,3-di- or 2,3,4-trisubstituted thietanes **68** and **71**, respectively, with complete diastereoselectivity (Scheme 25).[34]

Zhu *et al.* have reported synthesis of isoxazoline N-oxides **73** through a [4+1] annulation of MBH alcohols **9/11a** with 2-halo-1,3-dicarbonyl compounds **72** (Scheme 26).[35] The reaction catalyzed by quinidine **74** afforded the products **73** in good to excellent yield, diastereo- and enantioselectivities.

Tang *et al.* have reported the reaction of cyclic ketones **52** with MBH acetates **75** in the presence of pyrrolidine-thiourea catalyst **77** (Scheme 27).[36] The bicyclic products **76** bearing at least four chiral centers were formed with up to 98% *ee* and in moderate to high yields. The cooperative effects of both enamine, formed from ketone **52** and catalyst **77**, and the Brønsted acidic thiourea moiety in **77** were crucial for the high reactivity and enantioselectivity of this S_N2'-Michael cascade reaction.

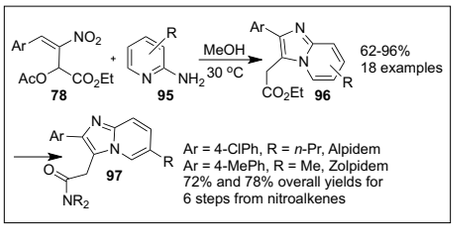
Reddy and Chen have reported a novel and efficient organocatalytic kinetic resolution of a variety of MBH acetates **78** with aldehydes **79** in the presence of Jørgensen catalyst (**80**) (2.5 mol%) *via* conjugate addition-elimination (S_N2') sequence (Scheme 28). The densely functionalized products **81** were obtained with excellent enantioselectivities (up to >99% *ee*), and the unreacted enantiomer of **78** was also recovered with good to excellent optical purity (up to 98% *ee*).[37]

Chen *et al.* have also employed ketones, *e.g.* **52a**, in the organocatalyst **83** (20 mol%) mediated kinetic resolution of MBH acetates **78** (Scheme 29).[38] The transformation presumably took place *via* S_N2' reaction of chiral enamine, formed *in situ* from ketone **52a** and catalyst **83**, with MBH acetate **78**, leading to the formation of densely functionalized products **82** in good chemical yields and excellent stereoselectivities (up to >99:1 *dr* and >99% *ee*).

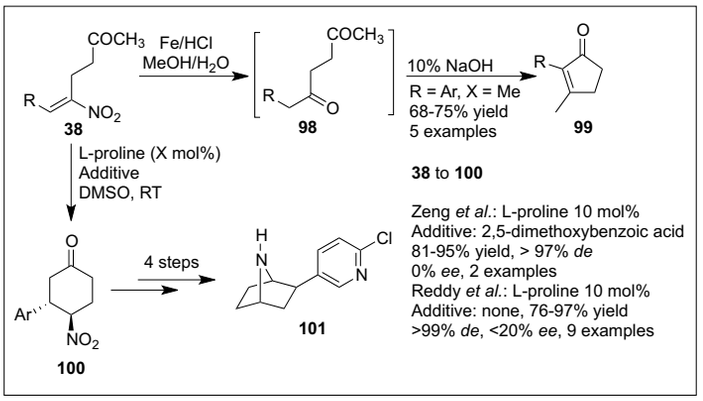
Later, Roy and Chen reported kinetic resolution of the MBH acetates **78** *via* an asymmetric three-component coupling involving indoles **84**, acrolein **85**, and MBH acetate **78** catalyzed by TMS-prolinol **80** (5 mol%, Scheme 30).[39] The reaction proceeded *via* a Friedel-Crafts/S_N2' process involving a sequential iminium/enamine catalysis. The recovered MBH acetate **78** and the products **86** were typically obtained in high chemical yield and in good to excellent enantiopurity.

Yet another method for the kinetic resolution of MBH acetate **78** *via* cascade S_N2'-Michael process using dialdehyde **87** has been reported by Chen *et al.* (Scheme 31).[40] The reaction involves addition of enamine of aldehyde **87** to MBH acetate **78**, intramolecular enamine addition to the resulting S_N2' adduct and HNO_2 elimination. The product was further reduced *in situ* to cyclopentenediol **88**.

Chen *et al.* and we have independently developed an efficient strategy for the synthesis of fused and functionalized furans **89** and pyrans **92** by taking advan-



Scheme 33.



Scheme 34.

tage of the bi-electrophilic character of MBH acetates **78** (Scheme 32).[41,42] The reaction sequence involves the displacement of acetate in **78** by the 1,3-dicarbonyl compound **90** or **91** in S_N2' fashion to form intermediates **93** or **94** followed by intramolecular oxa-Michael addition and elimination of HNO_2. While Chen *et al.* employed Cs_2CO_3 as base, we found amine base DABCO to be suitable for this transformation. Interestingly, an unusual switching of selectivity in the intramolecular oxa-Michael addition from 5-exo-trig to 6-endo-trig was observed when the β-dicarbonyl compound was changed from acyclic or six-membered ring cyclic **90** to five-membered ring cyclic system **91**.[41,42]

Very recently, we have exploited the bielectrophilic character of MBH acetate **78** in the one-pot reagent-free synthesis of imidazopyridines **96** (Scheme 33).[43] This reaction takes place *via* S_N2'-aza-Michael-HNO_2 elimination cascade in MeOH at room temperature affording potentially biologically active functionalized imidazopyridines **96** in good to excellent yields (62–96%). A practical application of this methodology was demonstrated by synthesis of imidazopyridine drugs Alpidem and Zolpidem **97** from **96** through simple transformations.

An application of the Rauhut-Currier adducts **38** of nitroalkenes with MVK (see Scheme 14) was developed by transforming them in one pot into 2,3-disubstituted cyclopentenones **99** with a quaternary benzylic center in high yields (Scheme 34).[26] The protocol included metal-acid reduction of nitro group in RC adduct **38** to enamine, hydrolysis of the resulting enamine to diketone **98** followed by intramolecular aldol condensation under basic workup conditions.

Recently, Zeng *et al.* and Reddy *et al.* have reported intramolecular cyclization of RC adduct **38** using L-proline (10 mol%) as the catalyst (Scheme 34).[44,45] Both the authors have reported high yields and diastereoselectivities, but poor or no enantioselectivities in this reaction. Our own results after catalyst screening and considerable optimization of reaction conditions suggest that L-proline/DMSO is the combination that gives good yield and diastereoselectivity, though with poor enantioselectivity.[46]

6. Conclusions and Outlook

For almost half a century, phosphine- and amine-catalyzed dimerization of electron-deficient alkenes (Rauhut-Currier reaction) has been known in the literature. α-Functionalization of electron-deficient alkenes using aldehydes, imines *etc.* under similar conditions (Morita-Baylis-Hillman reaction) has also been known for over 40 years. Surprisingly, nitroalkenes have not been employed as substrates in such reactions until eight years ago despite the fact that nitroalkenes are excellent Michael acceptors and the first step in the above reactions is the Michael addition of the nucleophilic amine/phosphine catalyst. This scenario has been attributed to reversibility in the initial conjugate addition of the amine/phosphine catalyst and polymerization of the substrate. However, reports in the last eight years reassure that MBH and RC reactions of nitroalkenes are indeed feasible with appropriate choice of the catalyst. Thus nitroalkenes have been successfully reacted with activated aldehydes, ketones, imines and azodicarboxylates as well as other electron deficient alkenes such as MVK and acrylate to afford the MBH/RC adducts primarily under the influence of imidazole or DMAP. Possible exploitation of these multi-functional adducts as novel scaffolds in organic synthesis have received considerable attention in the last three years. Future challenges include use of simple aliphatic and aromatic aldehydes as electrophiles, newer intramolecular and asymmetric versions as well as development of multi-component and cascade reactions using MBH/RC adducts or their derivatives as the key substrates.

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