Efforts towards Michael addition of isobutyraldehyde to *β*-methyl-*β*-nitrostyrenes

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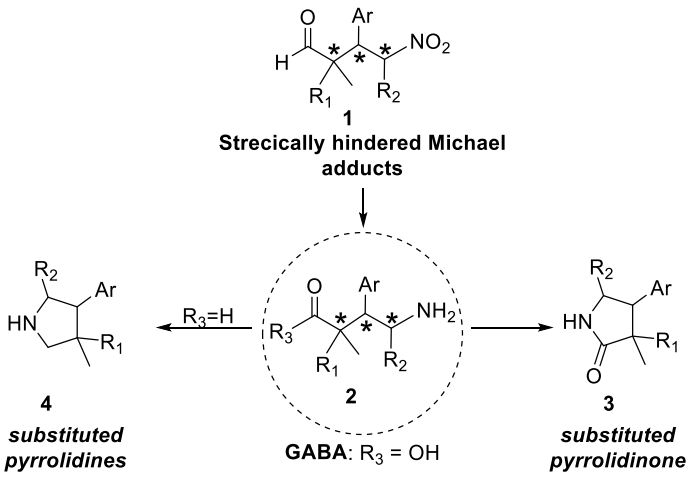
Abstract

This article describes the attempt towards racemic Michael addition reaction of isobutyraldehyde with branched nitrostyrenes. The reactions yield the Michael adduct in part but mostly undergo an undesired reverse reaction due to nucleophilic attack of pyrrolidine on the nitrostyrene. A detailed discussion reasoning for the poor forward reaction and the kinetics of the reverse hydrolysis of the nitrostyrene has been documented.

1.1 Introduction

The carbon-carbon bond formation is generally regarded as the backbone of synthetic organic chemistry. There are enormous number of paths present for this type of transformation to generate ample natural products, intermediates and different synthetic moieties. The popular and efficient C–C bond formation can be achieved by Michael addition reactions.[1] In recent years, much effort has been made for the development of asymmetric variants of this reaction as the demand for optically active compounds has soared to new heights. Organocatalytic asymmetric Michael reaction is one of the most important tools to provide such type of transformations (Scheme 1) with high enantiomeric purity. *γ*-aminobutyric acid (GABA)[2] analogues exhibit a range of pharmacological activities and can be potent drugs in the treatment of neurodegenerative disorders. *γ*-aminobutyric acid is a potential inhibitory neurotransmitter in the mammalian central nervous system, which plays a principal role in reducing neuronal excitability. Many GABA derivatives, derived from Michael adducts are capable of crossing the blood-brain barrier have been used clinically to prevent or treat neurodegenerative diseases.[3] An appropriate approach towards the synthesis of structurally versatile compounds containing the GABA moiety and choosing a suitable catalyst could open the door for drug development process. Indeed, substituted pyrrolidine and

pyrrolidinone derivatives of GABA are fundamental units of many biologically active molecules and ligands (Figure 1).



Scheme 1. Possible applications of the Michael adduct to GABA derivatives, substituted pyrrolidine and substituted pyrrolidinone moeities

The huge application of γ-aminobutyric acid draws attention of the scientific community to take a dive in the sea of opportunities present. There are plethora of natural products containing pyrrolidine, pyrrolidinone backbones (Figure 1), which can be derived from corresponding γ-aminobutyric acid derivative, which in turn can be synthesized using organocatalytic Michael reaction as a key step (Scheme 1).[4,5]

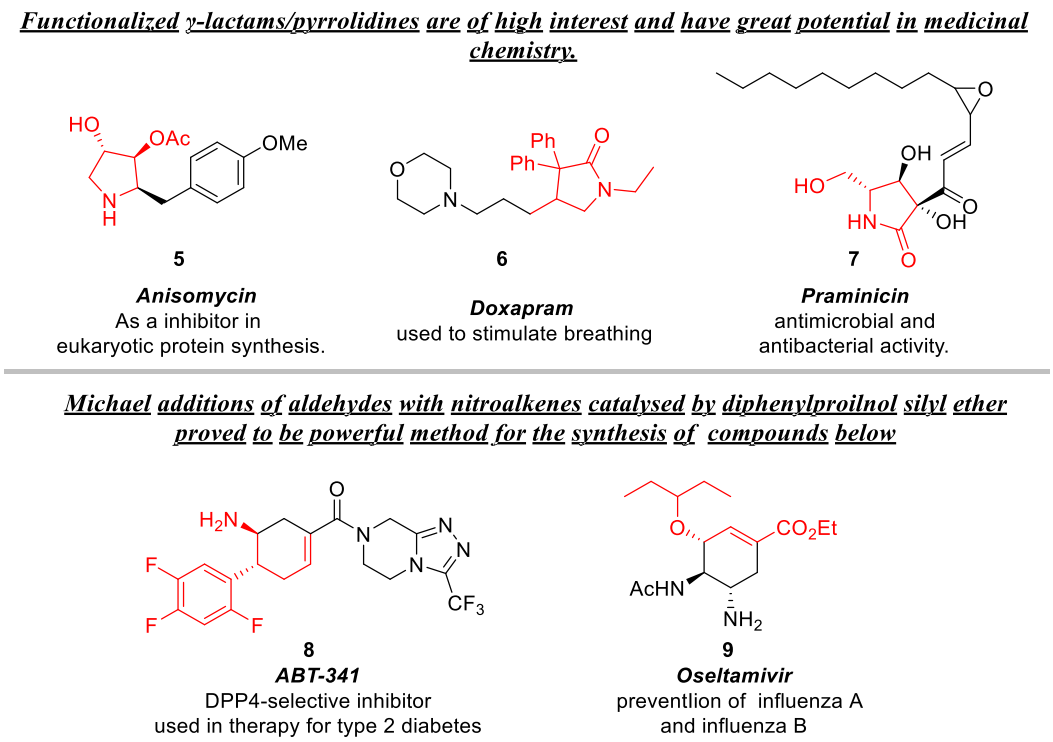


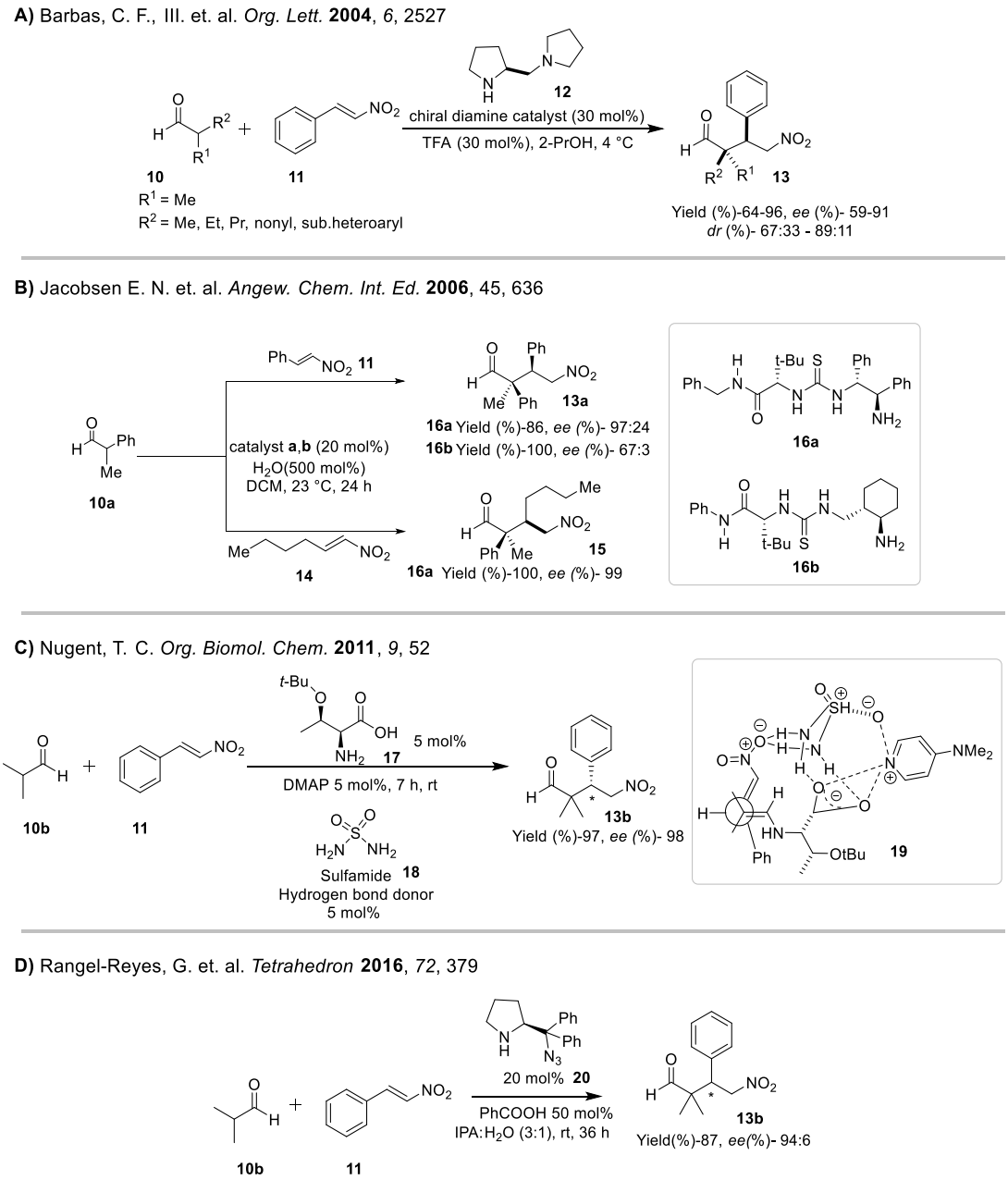
Figure 1. Pharmacological applications of GABA derivatives

From past to present there have been a few strategies, which have been online for Michael reactions of α-monosubstituted or α,α-disubstituted aldehydes and ketones with sterically hindered nitroalkenes. Individually Seebach group, Hayashi group, Blackmond group and Pihko group investigated thoroughly the kinetics and mechanistic studies of the intermediates formed during the organocatalytic Michael reaction of straight chain aldehydes with α-unsubstituted and α-substituted nitroalkenes. In the early 1980's, Seebach reported the reaction of achiral amines with β-nitroalkene yielding Michael adducts in good yield. In 2001, the first catalytic version of this transformation was reported by Benjamin list, Betancort and Barbas-III. The organocatalytic version of this transformation was independently reported by Jørgensen and Hayashi in the year 2005. Later in 2012, Wennemers group and Pihko group reported the reactions of linear aldehydes with branched β-nitroalkenes using peptide catalyst and Hayashi-Jørgensen catalyst respectively, with excellent yields and selectivity. Further, the synthesis of organocatalytic all carbon quaternary centre is considered challenging in synthesis. Scientific reports have been unfolded towards the organocatalytic Michael addition reactions of unbranched aldehydes or ketones with nitroalkenes to generate α-all carbon quaternary γ-aminobutyric aldehydes.

Literature gap

Few reported reactions of α,α-dialkyl aldehydes with β-nitroalkenes

Above in Scheme 2 are among the various reported reactions of branched aldehydes with *β*-nitroalkene which have yielded the desired Michael adducts in enantio-pure form using various activation modes and different types of catalyst. Barbas III and co-worker's in 2004 reported the Michael addition reaction of *α,α*-dialkyl aldehydes with (*E*)-*β*-nitroalkene using chiral diamine catalyst (*S*)-(+)-1-(2-pyrrolidinylmethyl) pyrrolidine and trifluoroacetic acid as the acid co-catalyst with excellent yields (up to 96%) and enantioselectivities (up to 91% *ee*) (Scheme 2A).[6]



Scheme 2. Few selected reports on enantioselective Michael addition reactions of *α,α*-dialkyl aldehydes with *β*-nitroalkene

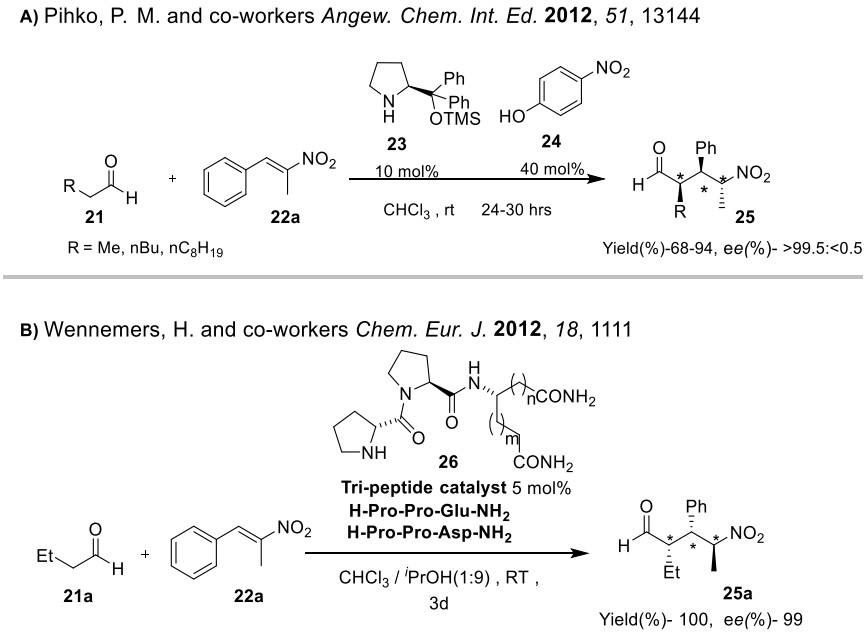
Later in 2006, Jacobsen group reported chiral primary amine thiourea catalysts (**7**,**8**) as highly effective in the addition of α,α-disubstituted aldehydes to nitroalkenes (Scheme 2B), which suggested the dual-activation catalysis with simple bi-functional organic frameworks.[7]

In 2011, Nugent and co-workers reported a three-component catalyst system including an amino acid (O-^{t}Bu-L-threonine), a hydrogen bond donor (sulfamide), and an amine base (DMAP) which allows addition of α-branched aldehydes with nitroalkenes which yielded the adduct in higher yields and excellent enantiomeric excess. The amino acid forms the enamine with the aldehyde while the carboxylate-sulfamide assembly activates the nitroalkene and brings it into bonding distance proximity of the β-carbon of the enamine through hydrogen bonding. The carboxylate-sulfamide assembly also increases the rate of enamine formation by forming a suitable conformation in the amino acid structure (Scheme 2C).[8]

Rangel *et al*. in 2016 emphasized on the improved reaction conditions for the substitution of the hydroxyl group in (*S*)-diphenyl (pyrrolidin-2-yl) methanol by the azide group, which is further reduced to the diamine derivative. The enantiopure diamine can be further treated with borane in order to afford the diazaborolidine precatalyst for the asymmetric reduction of carbonyl compounds. The target compounds were used as bifunctional organocatalysts in the asymmetric Michael and Mannich addition reactions which indicates that the azide catalyst affords the highest yields and stereoselectivity, especially when employing a mixture of isopropanol-water (3:1) as solvent (Scheme 2D).[9]

Reported reactions of linear aldehydes with *β*-substituted *β*-methyl *β*-nitroalkene

Very few reports have been published for reactions of linear aldehydes with β-alkyl β-nitroalkene in the recent years. Pihko and co-workers in 2012 (Scheme 3A) have reported that the rate determining step of these Michael addition reactions involve the protonation of a downstream intermediate, dihydrooxazine oxide (OO) species formed from the combination of the Michael precursors with the amine catalyst. They reported that the sluggish reaction rates observed with increase in steric hindrance is due to the stability of the OO species rather than the lower reactivity of the nitroalkene as propose by Wennemers (Scheme 3B).



Scheme 3. Michael addition reactions of aldehydes to α-alkyl nitroalkenes

Wennemers and co-workers in the same year reported tripeptides H-Pro-Pro-D-Gln-OH and H-Pro-Pro-Asn-OH as effective catalysts for the conjugate addition reactions by stabilizing the resulting nitronate by coordinating with the carboxylic acid moiety of the catalyst (Scheme 3B).

Finding suitable organocatalyst for Asymmetric Michael addition of Jumbo precursors

The information gained from previous reports, reveals the challenges/sluggishness of reactions faced with steric crowding of the substrates. Till date there have been no reports of the Michael addition of α,α-disubstituted aldehydes and/or ketones with α-substituted-β-nitroalkene to the best of our knowledge (Figure 2).

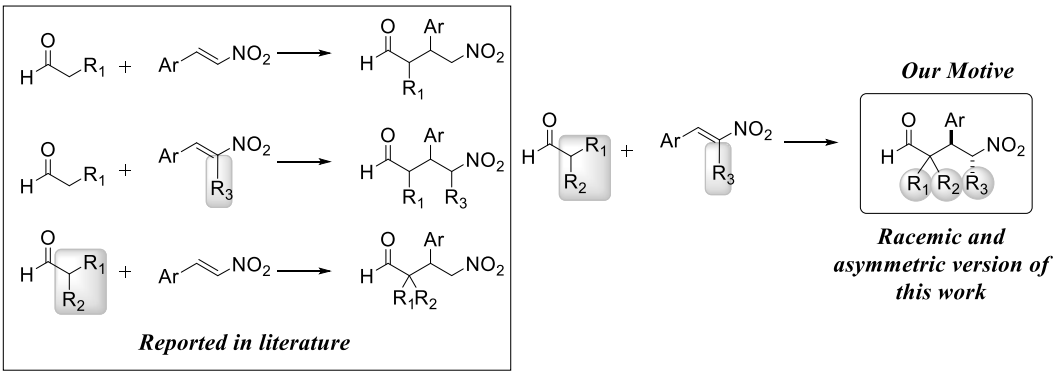


Figure 2. Reports till date for Michael additions of α-di/monosubstituted aldehydes with β-substituted/unsubstituted β-nitroalkenes

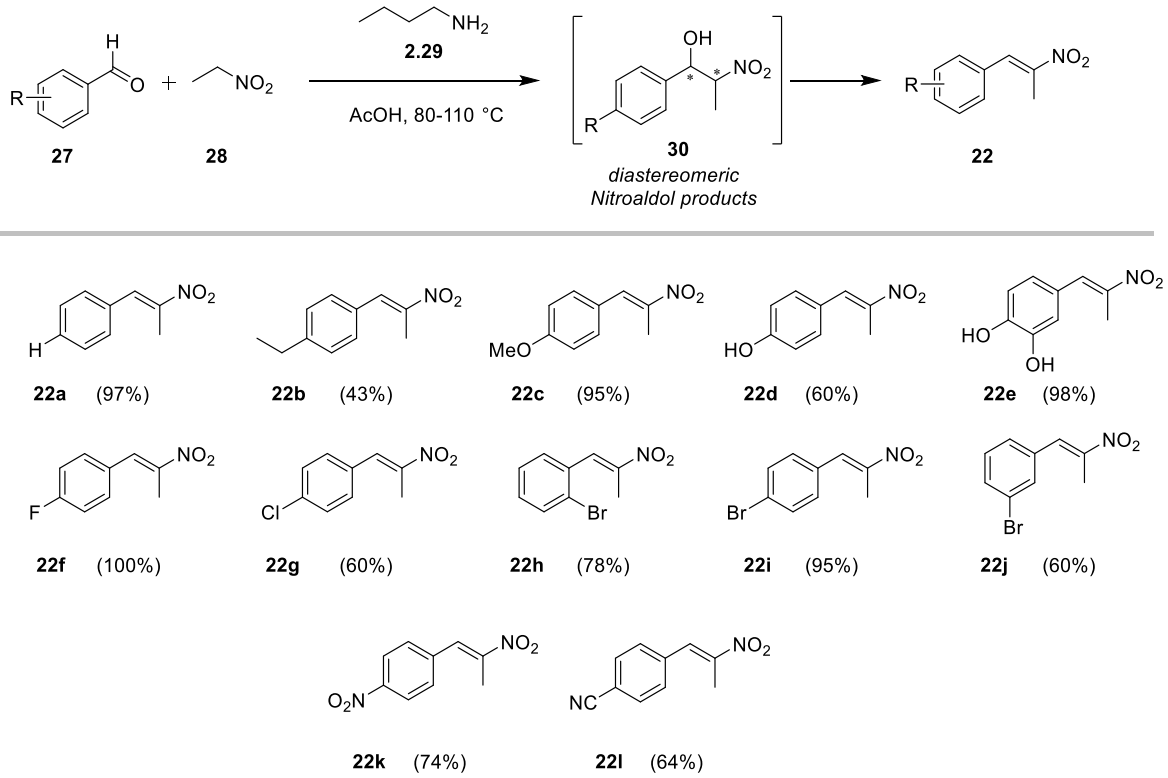
The interesting chemistry/intriguing mechanistic explanation for such sluggishness with steric crowding motivated our group to study the effect of steric crowding on both aldehyde and nitroalkene partners.

Therefore, we have initiated the investigation towards organocatalytic Michael reaction of α, α-disubstituted aldehydes and β-methyl-β-nitrostyrenes. This method provides a direct access to chiral γ-nitro aldehydes with two stereogenic centres and a quaternary carbon, which could be versatile precursors for chiral γ-aminobutyric acid derivatives. These GABA analogues have a varied range of pharmacological uses,[10] that include anti-depressants, anti-convulsants, anti-anxiety etc. The γ-nitro aldehydes can further be transformed to other value-added chemicals and key intermediates to a plethora of natural products. Herein we aim to investigate the direct organocatalytic Michael addition reactions of α,α-disubstituted aldehydes with β-alkyl substituted β-nitrostyrenes.

1.2 Results and discussion

Synthesis of β-alkyl substituted β-Nitrostyrenes: Henry Nitroaldol Reaction

Although β-methyl-β-nitrostyrenes are commercially available, its derivatives at the aromatic ring are either expensive or not available. Therefore, the nitrostyrenes **22(a-l)** were synthesized after few optimizations with excellent yields in the laboratory respectively (Scheme 4).[11]

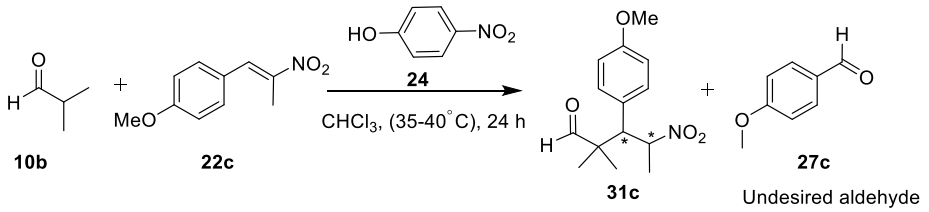


Scheme 4. Synthesis of various substrates of *β*-methyl-*β*-nitrostyrenes (**22**)

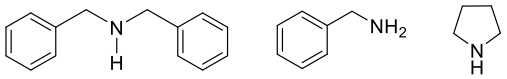
Racemic Michael addition reactions of Isobutyraldehyde to *β*-methyl-*β*-nitrostyrenes:

After successfully synthesizing different *β*-methyl-*β*-nitrostyrenes, the racemic Michael addition reaction was examined first. Literature precedence for Michael addition reactions of aldehydes to nitrostyrenes, both preparatory and mechanistic studies are not encouraging towards the success of the present case of both hindered Michael precursors. Hence, at first the racemic reaction was examined to find the possible amine backbone, which might shed some light on the chiral amine source for the asymmetric reaction.

Table 1. Optimization of Michael addition reaction



Achiral catalysts screened



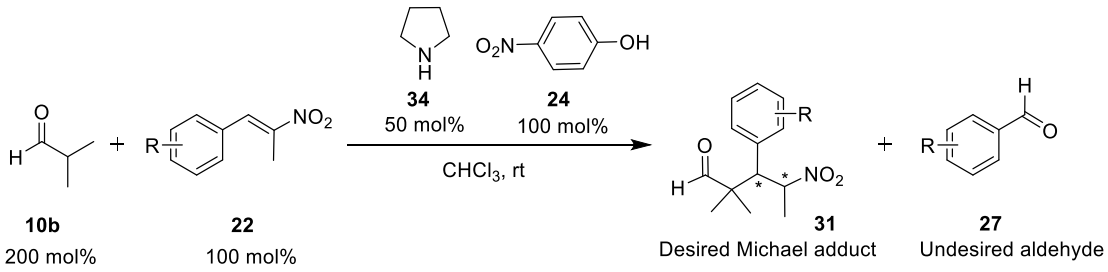
32 **33** **34**

Entry	Amine (mol%)	24 (mol%)	(%) Conversion[a] 31c	Ratio (27c:31c)
1	**32** (50)	100	13	100:0
2	**33** (50)	100	10	100:0
3	**34** (50)	-	95	71:29
4	**34** (20)	100	23	61:39

a) Conversion values represent the consumption of the nitrostyrene towards Michael adduct and the reverse hydrolysis product

The racemic reactions were performed with benzylamine (**33**, a primary amine), dibenzylamine (**32**, a secondary acyclic amine), pyrrolidine (**34**, secondary cyclic amine). Pihko and co-workers have reported *p*-nitrophenol (**24**) as the optimized proton source for the hindered Michael precursors. While the acyclic amines (**32** and **33**) were not successful towards the formation of Michael adduct **31c** (Table 1, entries 1 and 2), it was encouraging to see the formation of Michel addition product in presence of pyrrolidine (**34**, 50 mol%) (Table 1, entry 3) in 28% conversion. However, the reaction furnished 67% of an undesired aldehyde (precursor aldehyde **27** used for the synthesis of nitrostyrene **22**). With reactions employing 20 mol% of pyrrolidine and 100 mol% of acid co-catalyst *p*-nitro phenol (**24**) the product conversion dropped to 9 %, with majority of unreacted nitrostyrene (Table 1, entry 4). This clearly suggested that without the acid co-catalyst the forward Michael addition reaction was unfavourable and rather favoured an undesired side reaction. Also lowering the amine equivalent hindered the reactivity. Thus by taking the *β*-methyl-*β*-nitrostyrene **22(a-l)**, reactions were attempted with isobutyraldehyde (**10b**) in presence of pyrrolidine and *p*-nitro phenol (Table 2).

Table 2. Screening of various *β*-methyl-*β*-nitrostyrene substrates for Michael addition reaction with isobutyraldehyde



Entry	Nitrostyrene (22)	Time (days)	(%) Conversion[a]	Ratio (27:31)	31 *dr*
1	4-H (**22a**)	5	83	7:93	33:67
2	4-Et (**22b**)	5	54	25:75	29:71
3	4-OMe (**22c**)	5	57	36:64	37:63
4	4-OH (**22d**)	5	40	60:40	62:38
5	3,4-di-OH (**22e**)	4	-	-	-
6	4-F (**22f**)	4	79	33:77	52:48
7	4-Cl (**22g**)	5	64	9:91	51:49
8	4-Br (**22h**)	4	41	31:69	31:69
9	2-Br (**22i**)	5	20	14:86	49:51
10	3-Br (**22j**)	5	64	9:91	51:49
11	4-NO_2 (**22k**)	4	47	26:74	57:43
12	4-CN (**22l**)	5	75	11:89	49:51

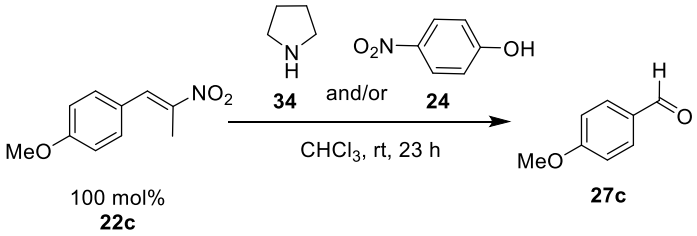
a) Conversion values represent the consumption of the nitrostyrene towards Michael adduct and the reverse hydrolysis product; *dr* values were calculated from crude reaction mixture via ^{1}H NMR spectrum

The best conversion to the product **31a** was obtained with unsubstituted *β*-methyl-*β*-nitrostyrene (**22a**, Table 2, entry 1). With *β*-methyl-*β*-nitrostyrenes having electron withdrawing substituents in the aromatic ring such as 4-fluoro (**22f**), 4-chloro (**22g**), 3-bromo (**22j**) and 4-cyano (**22l**), (Table 2, entries 6, 7, 10 and 12) showed decent conversion the Michael adduct respectively. The conversions dropped with 4-bromo nitrostyrene (**22h**, Table 2, entry 8, 28%) which could be attributed to the +R effect of this directing group which could also explain poor conversions with 2-bromo nitrostyrene (**22i**, Table 2, entry 9). This could also be due to the steric factor which could prevail due to the presence of substitution at the ortho position. 4-nitro *β*-methyl-*β*-nitrostyrene (**22k**) also furnished poor product conversion

(Table 2, entry 11) as compared to other electron withdrawing group substituted nitrostyrenes. With *β*-methyl-*β*-nitrostyrenes having electron-donating substituents in the aromatic ring such as 4-ethyl (**22b**), 4-methoxy (**22c**), 4-hydroxy (**22d**), the conversions were relatively poor (Table 2, entries 2, 3 and 4). With 3, 4-dihydroxy (**22e**) substituted nitrostyrene the reaction does not proceed (Table 2, entry 5). Despite poor conversions to the desired product, what was imperative to be addressed here was that the reaction furnished back the precursor aldehydes **27** used to synthesize the nitrostyrenes. The initial assumption was, the source of this reverse hydrolysis of the *β*-methyl-*β*-nitrostyrene could be the H_2O liberated in the catalytic cycle of the Michael reaction (Scheme 5, pathway 1).

This rose concern that reactants involved along with the reaction conditions (moisture) might play an effective role in the formation of the desired Michael adduct or the undesired precursor aldehyde. In order to explore the reactivity of the reverse reaction in nitrostyrenes, a set of controlled experiments were conducted to establish the exact mechanism and reagent involved in the process.

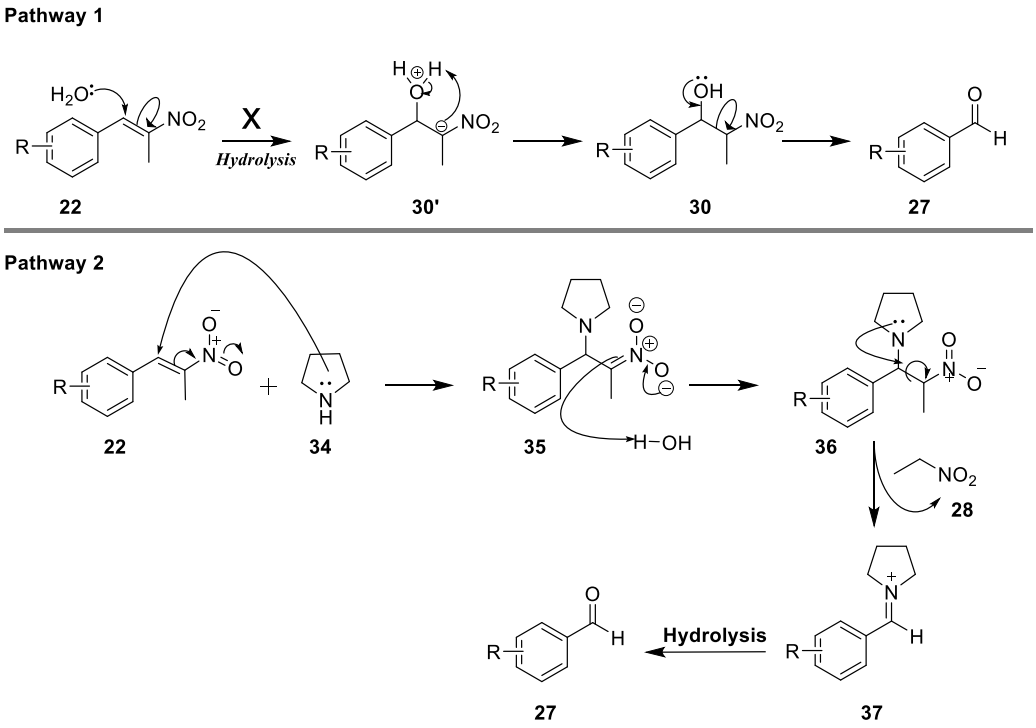
Table 3. Controlled experiments of nitrostyrene (**22**) with different reagents involved in Michael addition reaction to find the reason for the aldehyde **(27)** formation



Reagent / Entry	34/mol%	24/mol%	H_2O/mol%	Ratio (27c:22c)
1	×	×	✓/100	No formation of **27c**
2	✓/20	×	×	49:51
3	✓/20	×	✓/100	44:55
4	✓/50	✓/100	×	40:60
5	×	✓/100	×	No formation of **27c**

A set of controlled experiments were conducted to establish the exact reagent and condition, where it could be concluded that pyrrolidine was the prime/only reagent initiating the

hydrolysis with the help of H_2O/moisture present in used pyrrolidine. On reacting the nitrostyrene with H_2O only (100 mol%, Table 3, entry 1) there was no formation of anisaldehyde (**27c**) which clearly proved that moisture alone was not sufficient for the formation of aldehyde **27c** (Scheme 5). When the reaction was performed with pyrrolidine (20 mol%, Table 3, entry 2) 49% of anisaldehyde formation was seen. Similarly, in Table 3, entries 3 and 4 the reaction of nitrostyrene with pyrrolidine in presence of moisture and *p*-nitro phenol, anisaldehyde formation was 44% and 40% respectively. The similarity among the Table 3 entries 2-4, is the presence of pyrrolidine which was responsible for the undesired side product and the presence of moisture or *p*-nitro phenol did not seem to affect the side product formation much. The reactions without involving pyrrolidine (Table 3, entries 1 and 5) did not provide any undesired aldehyde **27c**. This undoubtedly pointed out the role of pyrrolidine in the formation of anisaldehyde (**27c**) though a nucleophilic attack (Scheme 5).

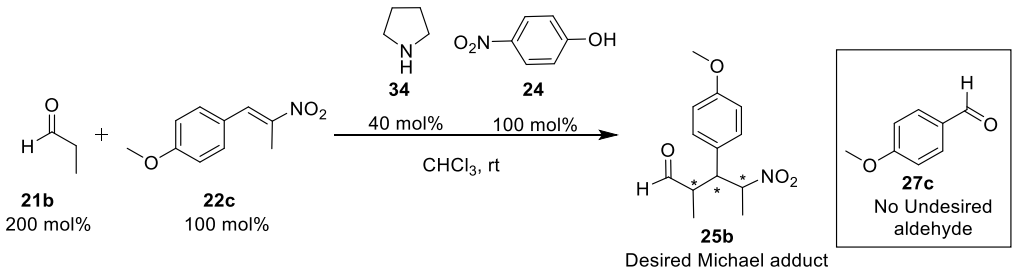


Scheme 5. Plausible pathways for the formation of precursor aldehyde from nitrostyrene in presence of pyrrolidine

It was envisioned that the most plausible pathway was where pyrrolidine could efficiently make a nucleophilic attack on to the nitrostyrene which could result in a retro-aldol reaction forming the iminium followed by hydrolysis to form the precursor aldehyde **27** (Scheme 5, pathway 2).

Comparative study showing reverse reaction for straight-chain aldehyde (propanal)

A control experiment was tried with *β*-methyl-*β*-nitrostyrene **22c** and propanal **21b**, using 40 mol% of pyrrolidine and 100 mol% of *p*-nitro phenol (**24**) in a NMR tube using $CDCl_3$ as solvent (Scheme 6). Here with the use of a linear aldehyde no undesired aldehyde **27c** peak was seen, rather the reaction showed a steady decrease in nitrostyrene peaks furnishing the three diastereomers of the Michael addition product **25b** (Figure 3). It suggested that the forward reaction was favoured even in presence of pyrrolidine (**34**) due to the lesser steric hindrance of propanal (**21b**). Therefore, it was safe to assume that the unwanted nucleophilic reaction of pyrrolidine with nitrostyrene is the result of incompetent forward Michael addition reaction due to the bulkier appendages of the reactants.



Scheme 6. Michael addition reaction of propanal **21b** with *β*-methyl-*β*-nitrostyrene **22c**

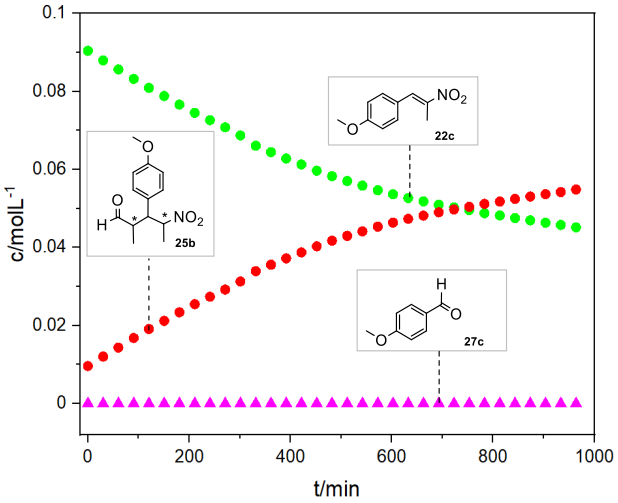


Figure 3. a) A plot of concentration versus time for different species in the reaction between **22c** and **34** in $CDCl_3$ with excess of **21b**; The conc. of **25b** includes all diastereomers of the Michael adduct.

Kinetic studies of nucleophilic addition of pyrrolidine on various *β*-methyl-*β*-nitrostyrenes

In order to investigate the reverse reactions similar control experiments were tried with various *β*-methyl-*β*-nitrostrene **22** using pyrrolidine as the amine catalyst. A real time analysis of the reversal of nitrostyrene to its parent aldehyde **27** and nitro-ethane **28** via vic-nitroamine intermediate **36** was observed as shown in Scheme 5.

In an NMR tube, *β*-methyl-*β*-nitrostyrene (**22**, 50 μmols, 100 mol%) was dissolved in chloroform-*d* (0.5 mL). The tube was inserted into the magnet. The ^{1}H NMR spectrum of nitrostyrene was recorded. The sample was removed from the magnet and pyrrolidine (**34**, 50 μmols, 100 mol%) was added. The NMR tube was shaken well to allow to ensure a homogenous solution and the sample was reinserted into the magnet. The ^{1}H NMR spectra were recorded at regular intervals (either 15 min or 30 min). The figures below (Figure 4-Figure 8) shows the reaction profile diagrams for the reaction between *β*-methyl-*β*-nitrostyrene and pyrrolidine as a plot of concentration vs. time.

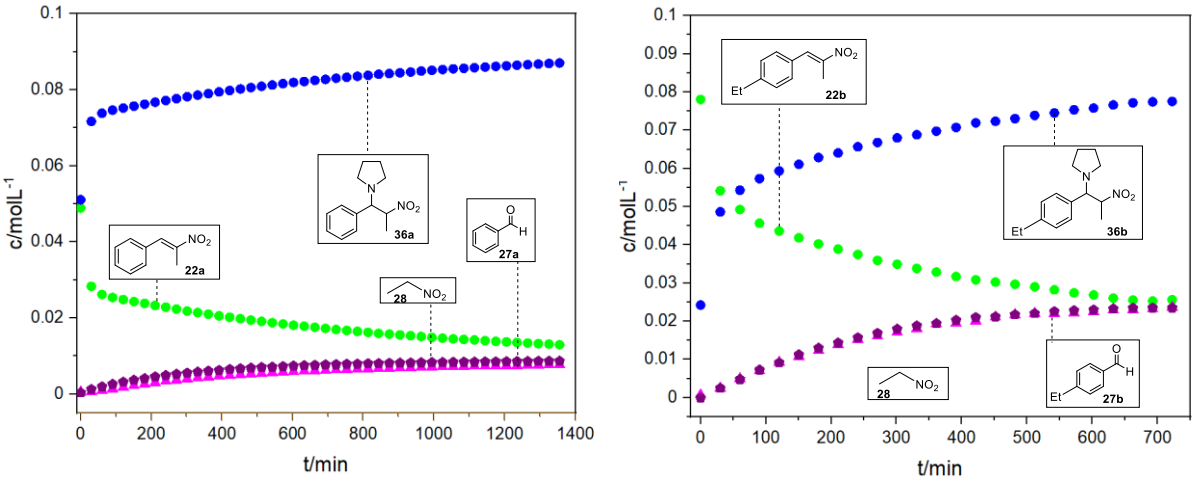


Figure 4. a) A plot of concentration versus time for different species in the reaction between **22a** and **34** in $CDCl_3$; b) A plot of concentration versus time for different species in the reaction between **22b** and **34** in $CDCl_3$

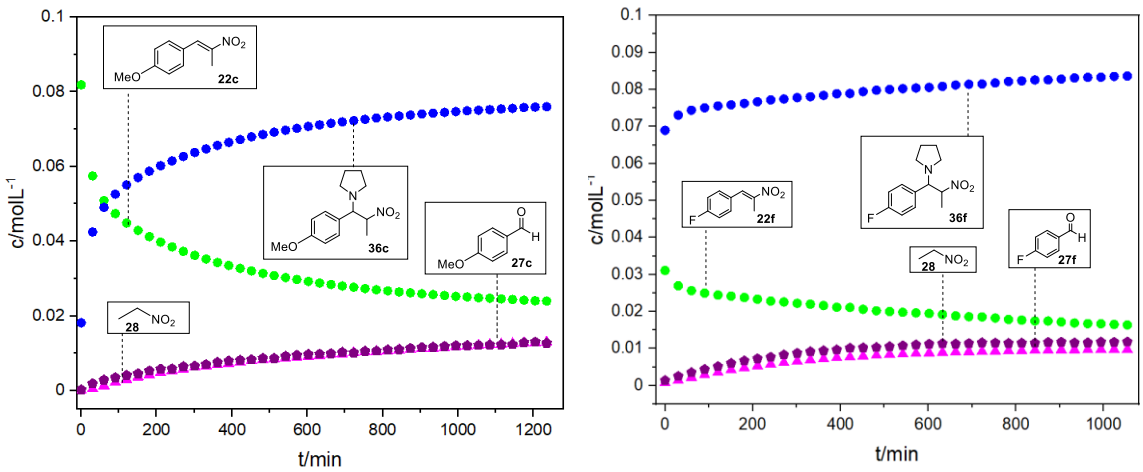


Figure 5. a) A plot of concentration versus time for different species in the reaction between **22c** and **34** in $CDCl_3$; b) A plot of concentration versus time for different species in the reaction between **22f** and **34** in $CDCl_3$

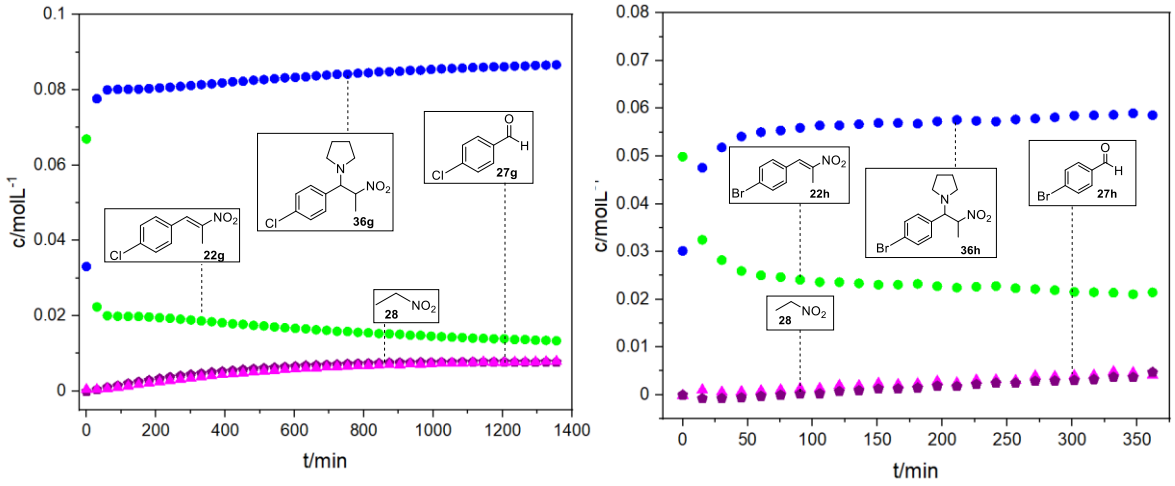


Figure 6. a) A plot of concentration versus time for different species in the reaction between **22g** and **34** in $CDCl_3$; b) A plot of concentration versus time for different species in the reaction between **22h** and **34** in $CDCl_3$ (total concentration of the reaction was 0.08M).

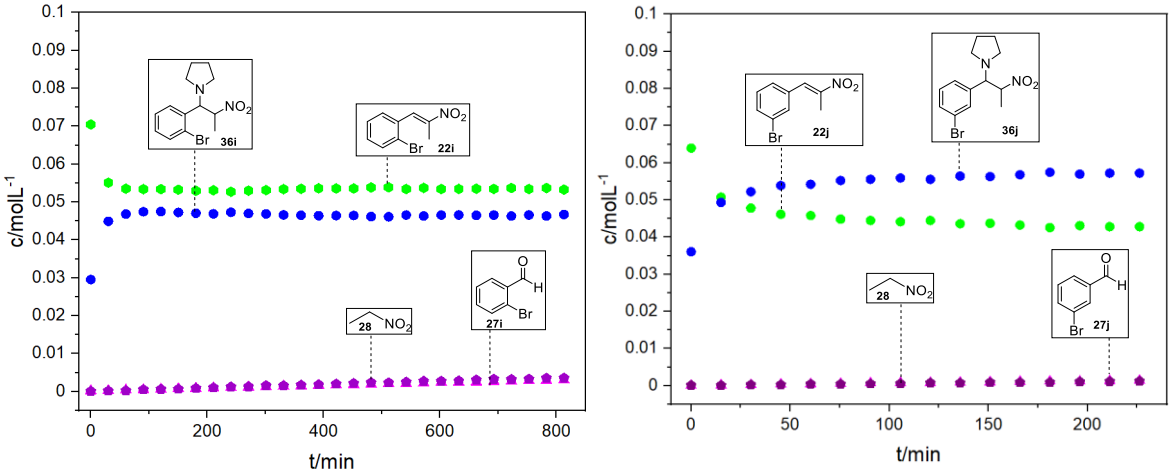


Figure 7. a) A plot of concentration versus time for different species in the reaction between **22i** and **34** in $CDCl_3$; b) A plot of concentration versus time for different species in the reaction between **22j** and **34** in $CDCl_3$

The vic-nitroamine **36** formation was observed immediately after the addition of pyrrolidine in all the *β*-methyl-*β*-nitrostyrenes **22** screened. As seen in the reaction profile diagrams a gradual decrease in concentration of *β*-methyl-*β*-nitrostyrene along with increase in concentration of precursor aldehyde **27**, nitro-ethane **28** and diastereomers of the vic-

nitroamine intermediate **36**. Interestingly, both the diastereomers start forming at the same time; but with increase in reaction time a steady drop in concentration one diastereomer and synchronous increase in the other diastereomer is observed.

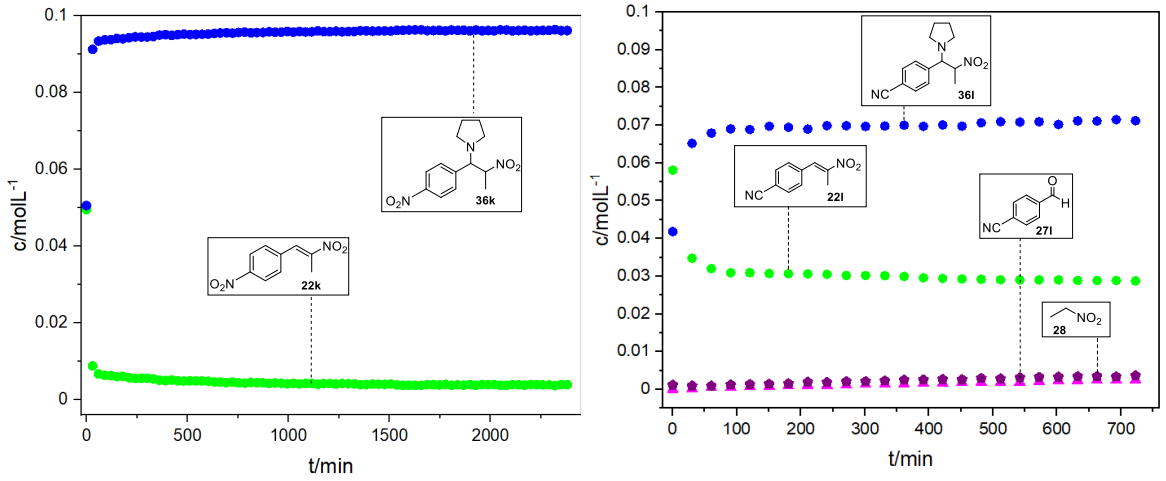


Figure 8. a) A plot of concentration versus time for different species in the reaction between **22k** and **34** in $CDCl_3$; b) A plot of concentration versus time for different species in the reaction between **22l** and **34** in $CDCl_3$

With *β*-methyl-*β*-nitrostyrene having, electron-withdrawing groups on the aromatic ring exhibited faster reversal to the vic-nitroamine intermediate **36** as compared to those having electron donating groups. With *β*-methyl-*β*-nitrostyrene (4-H) **22a** the vic-nitroamine intermediate formation at [**36**]t_0 = 0.01, whereas with groups having +R effect such as **22b** (4-ethyl) and with **22c** (4-methoxy) the vic-nitroamine concentration is [**36**]t_0 = 0.02 (Figure 4B and Figure 5A). With electron withdrawing groups such as halogens, the vic-nitroamine concentration was relatively higher. With, **22i** (2-bromo)- [**36**]t_0 = 0.03, **22h** (4-bromo)- [**36**]t_0 = 0.03, **22j** (3-bromo)- [**36**]t_0 = 0.035, **22g** (4-chloro)- [**36**]t_0 = 0.075, **22f** (4-fluoro)- [**36**]t_0 = 0.07. With **22f** (4-fluoro) and **22g** (4-chloro) the reversal to vic-nitroamine was higher as the +R effect of these halogens is weaker as compared to that of bromine. Vic-nitroamine formation with nitrostyrene having substitutions of **22l** (4-cyano)- are [**36**]t_0 = 0.04 and **22k** (4-nitro)- [**36**]t_0 = 0.08.

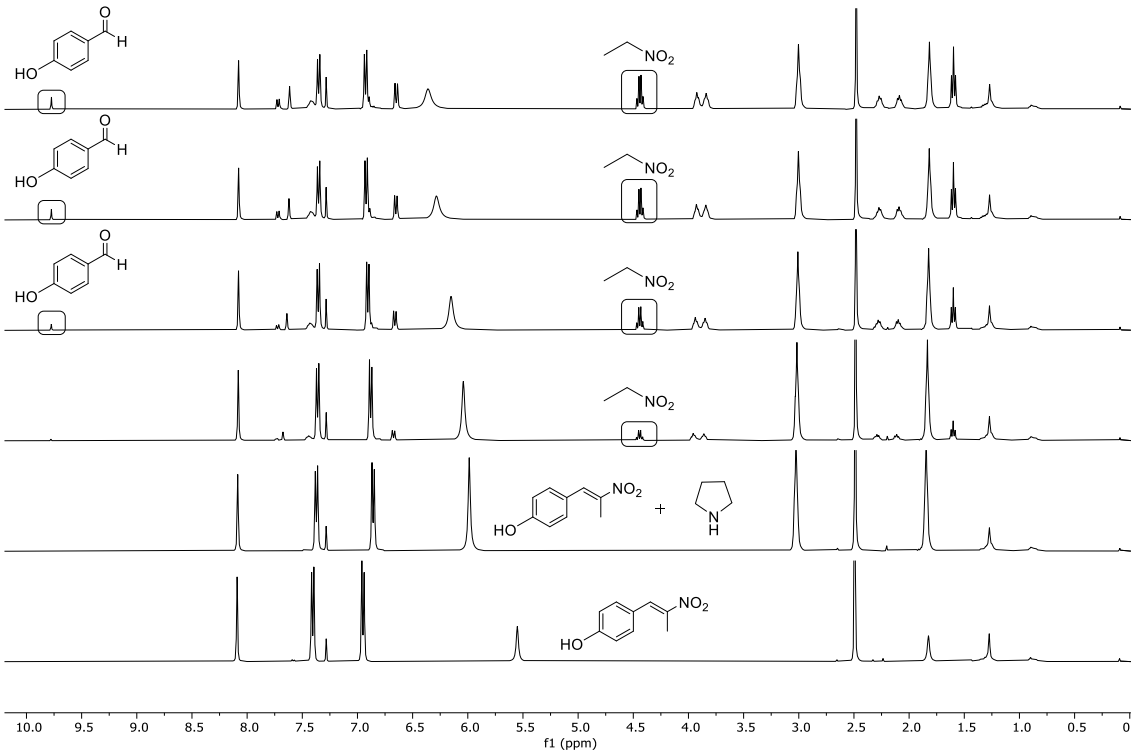
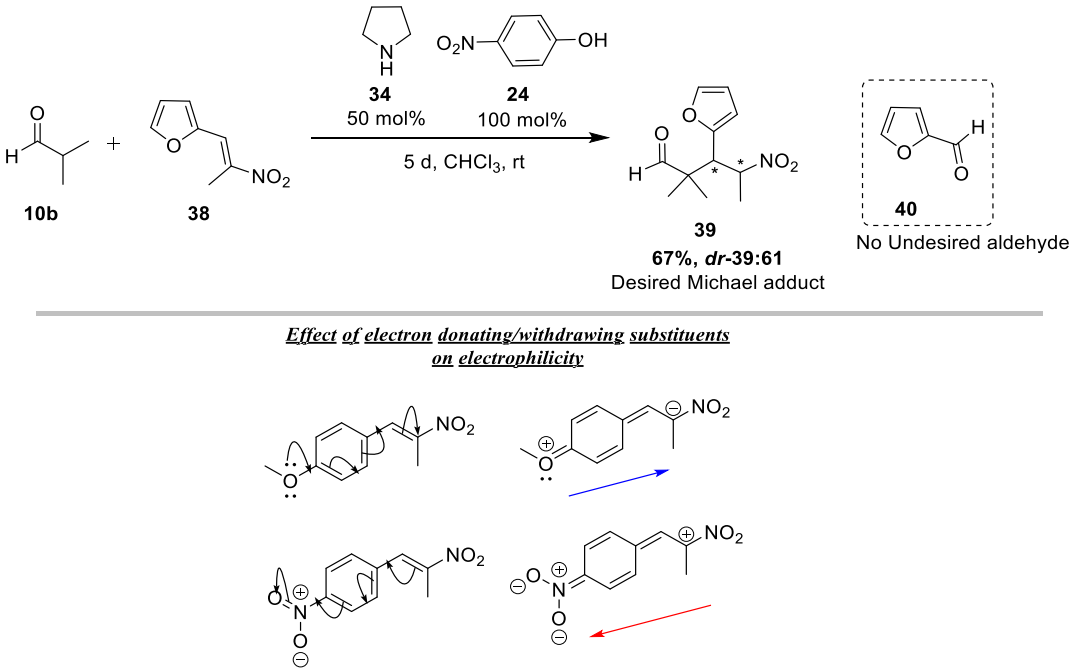


Figure 9. Stacked NMR spectra of reaction between 4-hydroxy nitrostyrene **22d** and pyrrolidine at different time intervals

The reaction between 4-hydoxy nitrostyrene **22d** and pyrrolidine (**34**) did not furnish any vic-nitroamine intermediate **36d** rather showed very minor aldehyde peaks (**27d**) over prolonged reaction time. Similarly, with 3, 4-di hydroxy nitrostyrene **22e** no reversal to the vic-nitroamine intermediate **36e** or the precursor aldehyde **27e** was seen. It could be that the strong electron donating ability of the hydroxy group decreases the electrophilicity of the nitrostyrene **22d** and **22e** which ceases any reverse reaction (Figure 9) or any forward reaction (Table 2 entries 4 and 5).

Surprisingly when the racemic Michael addition of isobutyraldehyde was tried with nitrostyrene **38,** (Scheme 7) the reaction did not give any undesired side products. With (*E*)-2-(2-nitroprop-1-en-1-yl)furan no reversal to the precursor aldehyde **40** (furfural) was seen and Michael adduct (**39**) was obtained in 67% conversion.

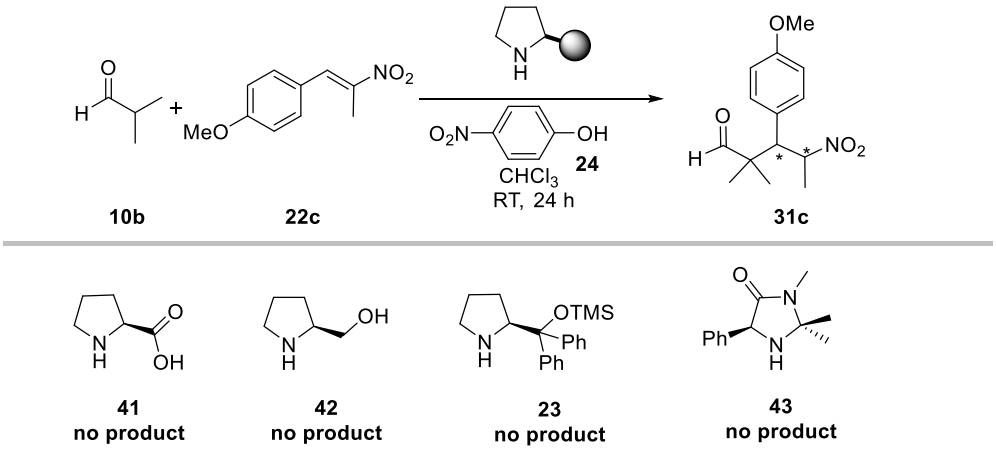


Scheme 7. Racemic Michael addition reaction of isobutyraldehyde to (*E*)-2-(2-nitroprop-1-en-1-yl)furan

It led to the conclusion that not only the amine catalyst structure (pyrrolidine) but the structure of the aryl nitrostyrene also might play a significant role in the reactivity. Although the exact reason for the same has not been established, we believe that the suboptimal conjugation in case of furan like heterocyclic aryl systems diminishes the undesired reverse hydrolysis to the aldehyde **40**. Further studies into the structure activity relationship might be helpful but it would fall out of the scope of the present study of reactions with nitrostyrenes.

Catalyst screening for asymmetric Michael addition reaction

For the asymmetric version of the Michael addition, in-house available catalysts starting from L-Proline (**38**), L-Prolinol (**39**), Hayashi-Jørgensen catalyst (**23**), and MacMillan's imidazolidinone catalyst (**40**) were employed separately instead of pyrrolidine (Scheme 8). None of the catalysts were successful towards the endeavour as there was no formation of the Michael adduct, also interestingly there was no back hydrolysis of the nitrostyrene. The observations towards the reversal of the reaction could be explained based on nucleophilicity. Unlike pyrrolidine, the nucleophilicity of the catalysts might be somehow decreased or restricted by the presence of the substituents/bulky appendage (Scheme 8).



Scheme 8. Screening of chiral pyrrolidine based organocatalysts **41**, **42**, **23** and imidazolidinone **43** for Michael addition reactions

Earlier successful reports of Michael addition of aldehydes with nitroalkenes catalysed by Hayashi-Jørgensen catalyst (**23**), show relative stronger/harsher conditions like acid co-catalyst, higher temperature etc. employed for bulkier substrates. In this present case, the reaction with all-bulky coupling partners with pyrrolidine as catalyst furnished the racemic product, along with the precursor aldehyde **27** probably due to the slower reactivity owing to steric hindrance of the starting material. However, with Hayashi-Jørgensen catalyst (**23**), probably the bulkier appendage in the pyrrolidine ring hindered the reaction all together. Hence it was assumed that an intermediate prolinol derived catalyst with suitable steric in the ring might be needed for the transformation where there would not be any compromise towards the yield and selectivity.

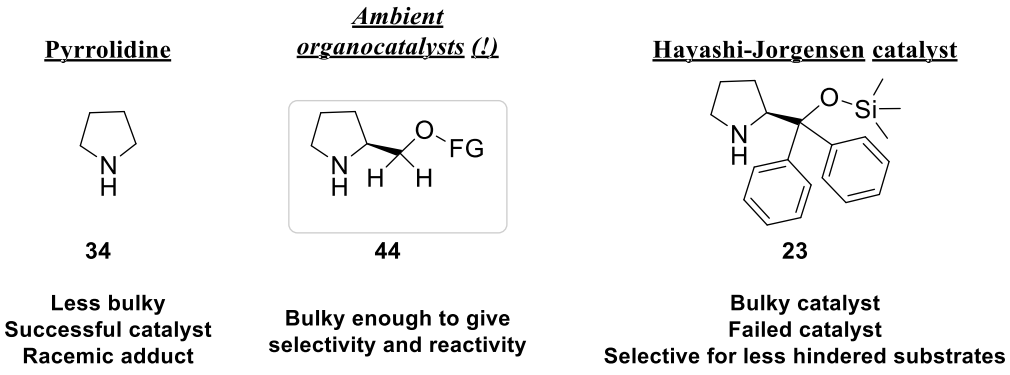


Figure 10. Designing an intermediate prolinol derived catalyst with suitable steric in the ring for the transformation of hindered Michael adducts

1.2 Conclusion

In this report we have synthesized the racemic Michael adducts of isobutyraldehyde with different substrates of *β*-methyl-*β*-nitrostyrene **22**. Although the conversions are not satisfactory, the reason behind the poor forward reactions was investigated. The real time monitoring of these reactions led to the observation of vic-nitroamine intermediates **36** which form as a result of the nucleophilic addition of amine on the *β*-methyl *β*- nitrostyrenes. Also the synthesis of an ambient organocatalyst with steric and electronic modifications to ensure the reactivity towards hindered Michael adducts was envisioned.

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