# Stereo-electronic effect of partial charge over oxygen atom in prolinol ether catalysts in Michael addition reactions of Propanal to *β*-Nitrostyrenes

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## Abstract

In this article, the utility of the synthesized prolinol derived organocatalysts in the Michael addition reaction of propanal with differently substituted *β*-nitrostyrenes has been discussed. The effect of the catalyst substitution on the reactivity of the reactions is studied along with the varying reactivity while using different electrophiles (in this case nitrostyrene).

## 1.1 Introduction and background study

Michael addition reaction of propanal to *β*-nitrostyrenes has been vastly reported in literature, employing various catalysts, which have been successful through various modes of activation. Figure 1 showcases a few of the various catalysts employed in the Michael addition of propanal to *β*-nitrostyrenes via various modes of activation. Barbas and Alexakis in the early millennium have employed pyrrolidine-derived organocatalysts for asymmetric Michael addition of aldehydes to *β*-nitrostyrenes where reaction progresses via enamine formation. Wennemers[1] in 2012 introduced tripeptides as effective organocatalysts in similar Michael addition reactions via covalent activation through enamine formation and non-covalent activation of the nitrostyrene by glutamic acid moiety. Later Lecouvey[2] in 2017 employed similar catalysts by replacing the carboxylic acid with a phosphonic acid moiety with excellent selectivity.

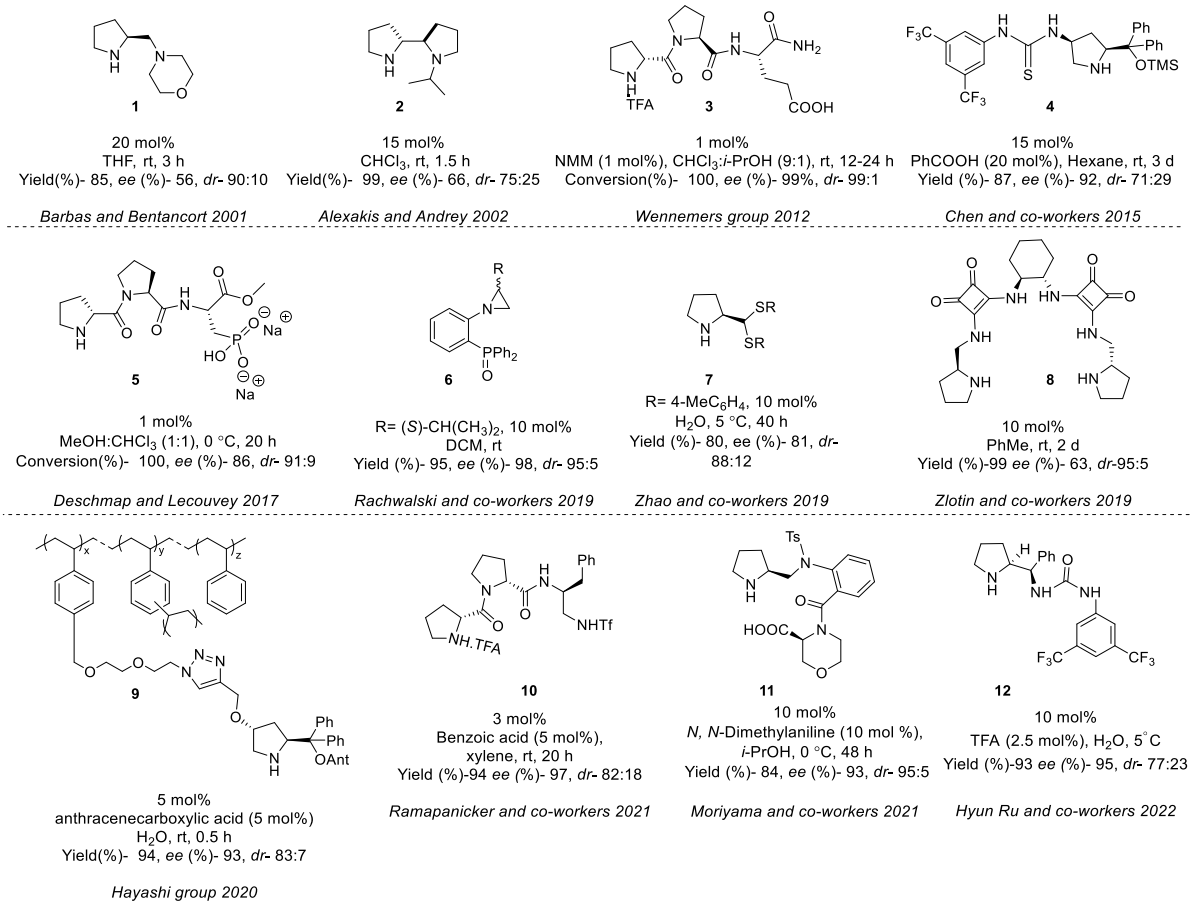



**Figure 1.** Catalysts employed in the Michael addition of propanal to *β*-nitrostyrene

Diarylprolinol silyl ether-derived bifunctional thiourea catalysts[3] have also yielded Michael adducts with excellent selectivity. Few new class of catalysts have also been employed in the recent years such as phosphinoyl aziridines (H-bonding catalysis),[4] prolinol dithioacetals(enamine catalysis),[5] C2-symmetric *N,N´*-bis-[(pyrrolidin-2-ylmethyl)squaramides] (H-bonding catalysis),[6] diphenylprolinol anthrylmethyl ether supported on PS-PEG resin(enamine catalysis),[7] peptide-based triflicamide organocatalyst (*S*)-*N*-(D-prolyl-L-prolyl)-1-triflicamido-3-phenylpropan-2-amine(H-bonding catalysis),[8] chiral anthranilic pyrrolidine catalyst as a custom-made amine catalyst(H-bonding catalysis),[9] proline-based bi-functional organocatalysts PHU (1-(3,5-Bis(trifluoromethyl)phenyl)-3-((*R*)-phenyl((*S*)-pyrrolidin-2-yl)methyl)urea),[10] etc. Figure 1 shows that a single reaction can be optimized and carried out successfully through various catalysts which are essential for the specific reaction condition. Therefore, catalysts development for substrate specific reactions is an essential part of reaction development (Figure 2). For that reason, the following study is focused on the study of successful employment of synthesized organocatalysts in Michael addition reactions of propanal to *β*-nitrostyrenes.

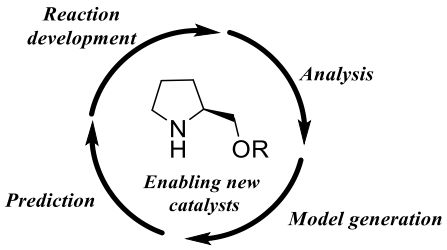
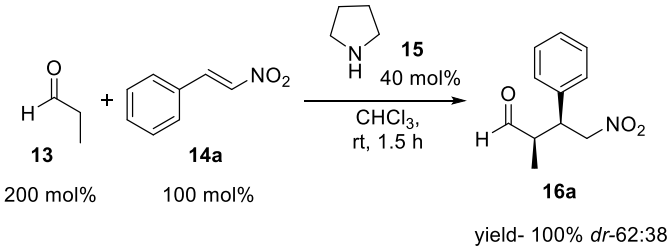



**Figure 2.** Processes involved in the development of substrate-specific catalysts

## 1.2 Application of organocatalysts in Michael addition reaction of aldehydes to *β*-nitrostyrenes

### Michael addition reaction of propanal to *β*-nitrostyrenes

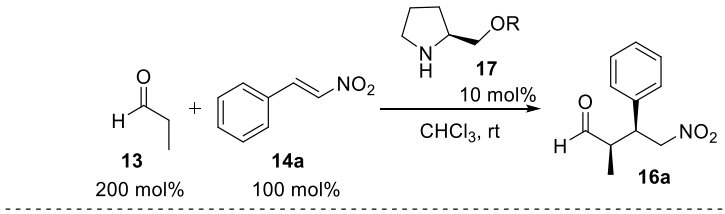
We planned to study the reactivity and selectivity of the newly synthesized compact prolinol ether catalysts in the addition reactions of aldehydes to *β*-nitrostyrenes. Initially a racemic reaction of propanal with unsubstituted *β*-nitrostyrenes was tried with 40 mol% pyrrolidine as catalyst which resulted in the Michael adduct in just 5 h (Scheme 1). Further screening reactions were performed with unsubstituted *β*-nitrostyrenes and propanal employing prolinol derived organocatalysts to check the selectivity and reactivity in each case (Table 1).

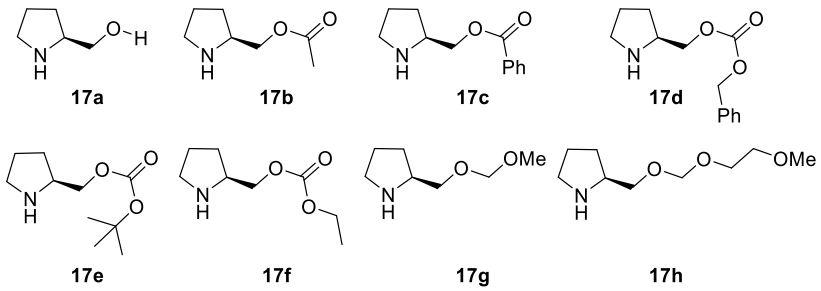



**Scheme 1.** Racemic reaction of propanal with *β*-nitrostyrene using pyrrolidine as catalyst

**Table 1. Screening of prolinol derived organocatalysts**

The reaction with prolinol as catalyst gave poor conversion of only 16% to the Michael adduct although with good diastereoselectivity of 78:22. With **17b** as a catalyst the reaction conversion was very poor (14%); whereas with **17c**, **17d**, and **17e** the conversions were also inadequate. These reactions did not furnish any other side-products in the course of the reaction and consisted of unreacted starting material in case of incompletion. The complete conversion was obtained with catalysts **17f**, **17g** and **17h**.




| Entry | Catalyst | Time (h) | (Product 16a) % conversion | *dr* ratio[a] |
|---|---|---|---|---|
| 1 | **17a** | 56 | 16 | 78:22 |
| 2 | **17b** | 24 | 14 | 64:36 |
| 3 | **17c** | 115 | 32 | 69:31 |
| 4 | **17d** | 111 | 50 | 61:39 |
| 5 | **17e** | 42 | 42 | 69:31 |
| 6 | **17f** | 144 | 100 | 67:33 |
| 7 | **17g** | 47 | 100 | 60:40 |
| 8 | **17h** | **28** | **100** | **63:37** |

a) The *dr* ratio was calculated from crude reaction mixture via $^{1}$H NMR spectrum; *ee* to be calculated from HPLC

While all three catalysts gave 100% conversion, the reactions with **17g** and **17h** were completed in a relatively lesser reaction time. The optimum reaction condition was obtained using O-MEM functionalized prolinol (**17h**) where the reaction was complete in 28 h and therefore further reaction screenings with substituted *β*-nitrostyrenes were screened employing **17h** catalyst (Table 2).

An interesting observation was made from the above Table 1; the reactions employing catalysts where the oxygen atom attains a partial positive charge (like when O lone pair remains in conjugation with a carbonyl group) showed poor conversions. Conversely, the catalyst structures with electron-donating groups attached to the oxygen atom of the prolinol backbone showed excellent reactivity towards the Michael adduct; like in catalysts **17g** and **17h**. In these catalysts, the oxygen atom would be electron dense.

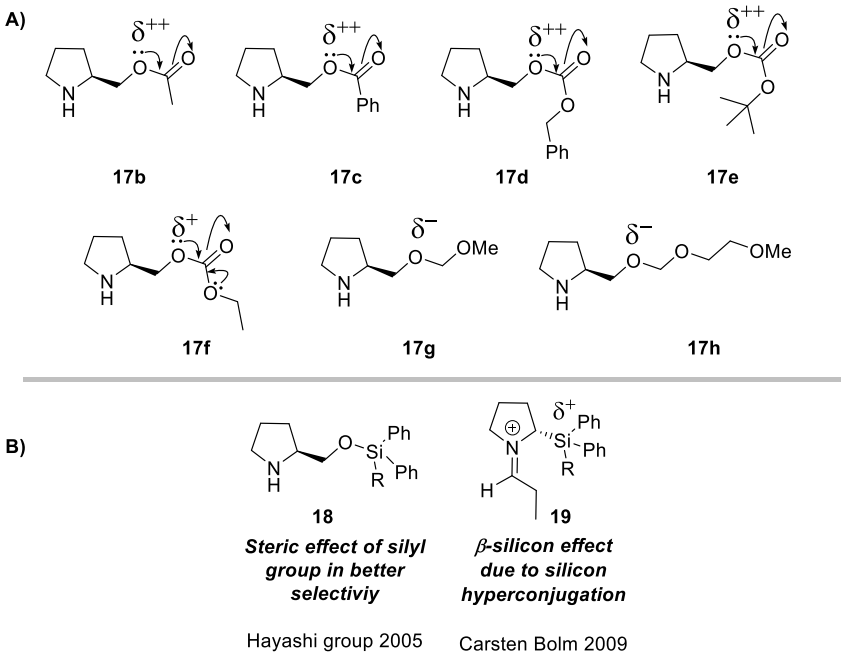


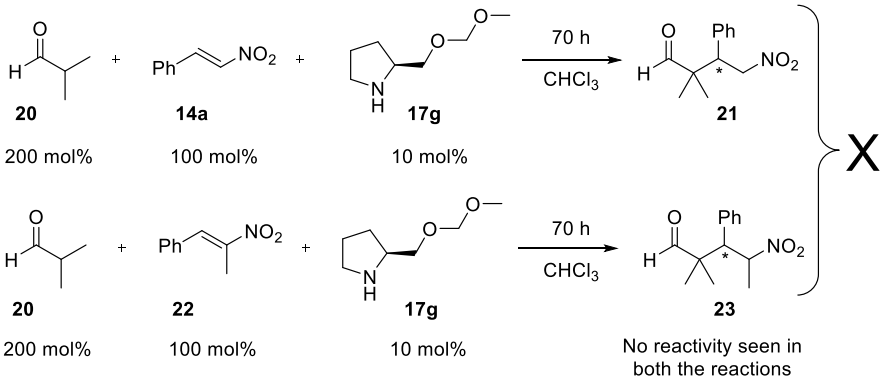

**Figure 3.** Effect of electron density on the oxygen atom of catalyst structure on the Michael addition reactivity

Comparing **17b** and **17f**, the ether oxygen of catalyst **17f** also remains in conjugation with the carbonyl thereby the partial positive charge on the other oxygen atom is relatively less as compared to **17b** resulting in better conversion. In the case of catalysts **17d** and **17e**, the presence of the bulky benzyl and $^{t}$Bu group could result in poor reactivity (Figure 3A).

Earlier reports by Hayashi group[11] suggested the presence of silyl group in the catalyst structure led to faster reactions with minimal catalyst loadings owing to better solubility of the catalyst in organic solvents. But the association of the nature of the silyl atom;[12] like the stabilization of charge in the vicinity of the electropositive silyl group is yet to be discussed. Likewise, Bolm group in 2009[13] reported that the silicon group attached at the $\alpha$-position of the nitrogen atom of the heterocyclic core helped in the stabilization of positive charge and thereby assisted in the iminium formation (Figure 3B). Although at this point the role of partial charge on the oxygen atom (in catalysts **17**) of the prolinol backbone is unclear, computational studies might be helpful in determining the stereo-electronic effect of these catalysts on the reactivity of Michael addition reaction of aldehydes to $\beta$-nitrostyrenes.

## Application of organocatalysts in Michael addition reaction of isobutyraldehyde to *β*-nitrostyrenes

After the successful implementation of the catalysts **17** with propanal, the reactivity of Michael addition reactions of isobutyraldehyde to *β*-nitrostyrene was evaluated by screening the reactions with O-MOM prolinol catalyst **17g**. As the reactants involved are sterically hindered **17g** was used instead of **17h**. Although the above Michael adducts have been reported in literature we wanted to showcase the utility of these catalysts in synthesizing the same, with efficient reactivity (Scheme 2).



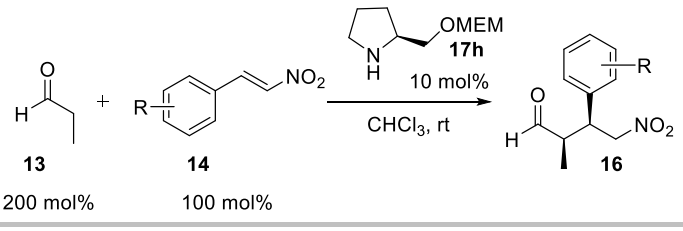

**Scheme 2.** Reaction of isobutyraldehyde with *β*-nitrostyrene and *β*-methyl-*β* nitrostyrene using **17g** as catalyst

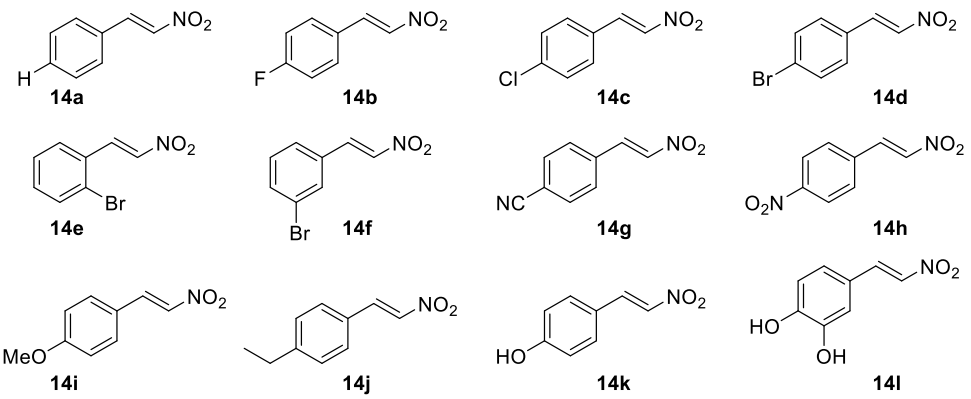
The reactions of isobutyraldehyde with *β*-methyl substituted/unsubstituted *β*-nitrostyrenes did not furnish the Michael adduct when reacted with **17g** as catalyst. This suggested that the reactions with branched aldehydes needed an even more compact catalyst for the reaction to proceed through the stable intermediate species.[14]

## Michael addition reaction of propanal to various substituted *β*-nitrostyrenes using 17h as catalyst

Although the reactions with branched aldehydes and branched nitrostyrenes employing catalysts **17** were not successful, the Michael addition reaction of propanal with various *β*-nitrostyrenes (various substitution in the aromatic ring) was screened which successfully furnished various substituted Michael adducts. After establishing O-MEM prolinol **17h** to be the optimum catalyst, the reactions were screened with various *β*-nitrostyrenes (Table 2).

**Table 2. Substrate scope with various *β*-nitrostyrenes**




| Entry | Nitrostyrene(14) | Time (h) | 16 (% conversion) | 16 Yield[b] (%) | *dr* ratio[a] |
|---|---|---|---|---|---|
| 1 | 4-H | 28 | **16a**/100 | 95 | 61:39 |
| 2 | 4-F | 28 | **16b**/100 | 90 | 64:36 |
| 3 | 4-Cl | 23 | **16c**/100 | 92 | 60:40 |
| 4 | 4-Br | 20 | **16d**/100 | 96 | 59:41 |
| 5 | 2-Br | 18 | **16e**/100 | 87 | 58:42 |
| 6 | 3-Br | 18 | **16f**/100 | 91 | 61:39 |
| 7 | 4-CN | 18 | **16g**/100 | 90 | 61:39 |
| 8 | 4-$NO_2$ | 30 | **16h**/100 | 94 | 60:40 |
| 9 | 4-OMe | 113 | **16i**/100 | 95 | 64:36 |
| 10 | 4-Et | 77 | **16j**/100 | 91 | 59:41 |
| 11 | 4-OH | 53 | 0 | - | *nd* |
| 12 | 3,4-di OH | 107 | 0 | - | *nd* |

a) The *dr* ratio was calculated from crude reaction mixture via $^1$H NMR spectrum; *ee* to be calculated from HPLC b) NMR yield

The reaction with all the *β*-nitrostyrenes (Table 2, entries 1-10) gave complete conversion to the desired Michael adduct except **14k** and **14l** (Table 2, entries 11 and 12). The reactions of propanal with *β*-nitrostyrenes having electron-withdrawing substituents in the phenyl ring gave faster reactions (Table 2, entries 2-8) as compared to reactions with electron-donating

substituents (Table 2, entries 9 and 10) in the phenyl ring. The electron-withdrawing substituents could enhance the electrophilicity of the *β*-nitrostyrene favouring the nucleophilic attack from the enamine (formed from aldehyde **13** and catalyst **17**); whereas with electron-donating substituents, the attack would be slower owing to the increased electron density over the double bond of the *β*-nitrostyrene. In this regard, reactions with *β*-nitrostyrene having hydroxy group, as substituents 14 k and **14l** (Table 2, entries 11 and 12) did not furnish any Michael adduct. The catalyst peaks were also disintegrated in the crude NMR spectra which could indicate the decomposition of the ether catalyst in the presence of phenolic protons in the *β*-nitrostyrene.

### 1.3 Conclusion

Summarizing this report, we have employed various synthesized prolinol ether catalysts in successful racemic and asymmetric Michael addition reactions of propanal with various *β*-nitrostyrenes. The best reactivity obtained was with catalysts **17g** and **17h** (MOM and MEM substituted prolinol ether catalysts). The diastereoselectivities of the obtained products **16** were nearly comparable in case of all catalysts and not much difference in selectivity was seen. Although there are still issues with these catalysts generalizability we plan to analyze these catalyst structures via computational chemistry to understand the steric and stereo-electronic effects. This would give us insight into a predictive model in terms of steric as well as stereo electronic effect; which would be best suited to accelerate reaction conditions for superior reactivity as well as selectivity.

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