Studies on the Organocatalytic Enantioselective Michael Addition of Cyclic Ketones and α,α-Disubstituted Aldehydes to α-Nitrostyrenes

Ritesh A. Annadate, Moorthy N. V. G. and Sunil V. Pansare*

Department of Chemistry, Memorial University, St. John’s, NL, A1B 3X7, Canada

Abstract: Background: The catalytic asymmetric Michael addition of carbonyl compounds to nitrostyrenes is of interest because the reaction establishes two adjacent stereocenters in one step and the product γ-nitrocarbonyl compounds are synthetically useful intermediates. This reaction has been exhaustively investigated with β-nitrostyrenes as the Michael acceptors but the use of α-nitrostyrenes, for establishing nonadjacent stereocenters in the product, is not well studied.

Objective: The aim of this study was to investigate the organocatalytic asymmetric, enamine mediated, Michael addition of cyclic ketones and α,α-disubstituted aldehydes to in situ generated α-nitrostyrenes and to optimize the diastereoselectivity and the enantioselectivity of the reaction.

Method: The Michael addition reactions of a series of ketones and aldehydes with a variety of α-nitrostyrenes, that were generated in situ form nitroacetates, were conducted in a selection of solvents in the presence of chiral pyrrolidine catalysts and protic acid additives. Conditions that provided the highest asymmetric induction were identified.

Results: Under optimized conditions, γ-nitroketones (up to 99% ee) and γ-nitroaldehydes (up to 79% ee) were obtained. The synthetic utility of the γ-nitroldehyde was demonstrated by converting a representative Michael adduct into a functionalized pyrrolidine.

Conclusion: The enamine mediated Michael addition of cyclic ketones and α,α-disubstituted aldehydes to in situ generated α-nitrostyrenes proceeds with moderate to good levels of 1,3-asymmetric induction. The methodology complements the well-known Michael addition reactions of β-nitrostyrene, and provides access to enantiomerically enriched γ-aryl-γ-nitro ketones and γ-aryl-γ-nitro aldehydes.

Keywords: Aldehydes, ketones, Michael addition, organocatalysis, α-nitrostyrene, carbonyl compounds.

1. INTRODUCTION

Organocatalytic, asymmetric carbon-carbon and carbon-heteroatom bond forming reactions have been extensively investigated in recent years [1-5] and the organocatalyzed Michael addition reaction has attracted significant attention [6-18]. The enamine mediated conjugate addition of aldehydes and ketones to nitroalkenes is particularly interesting since it generates two stereocenters in a single step.

Within this category, the utility of a variety of Michael acceptors has been documented, among which the β-nitrostyrenes ((2-nitrovinyl) arenes) have been extensively investigated [19]. However, the isomeric α-nitrostyrenes ((1-nitrovinyl) arenes) have received very little attention, and only a few studies with α-nitroalkenes ((1-nitrovinyl)alkenes) as Michael acceptors are reported [20-22]. In a broader context, the stereoselective Michael addition of an aldehyde or a ketone nucleophile to an α-nitrostyrene is subject to 1,3 asymmetric induction (generation of α,γ stereocenters, Fig. 1). In contrast to catalytic 1,2 asymmetric induction (generation of α,β or β,γ stereocenters), catalytic versions of 1,3-asymmetric induction processes are less established and all of the current efforts in this area are directed towards the construction of γ-quaternary stereocenters [23-31].

Herein, we report details of our studies on the catalytic asymmetric Michael addition of cyclic ketones and α,α-disubstituted aldehydes to α-nitrostyrenes, involving the enantioselective protonation of a nitronate as the crucial step.

2. RESULTS AND DISCUSSION

At the outset, we noted that α-nitrostyrenes can be unstable and prone to polymerization [32] and isomerization [33] reactions which are generally not an issue with β-nitrostyrene. We, therefore, chose to generate α-nitrostyrenes in situ rather than attempting to prepare and isolate them, and our studies were conducted with 2-nitro-2-arylethyl acetates (5-
Fig. (1). Organocatalytic 1,2 and 1,3-asymmetric induction in nitroalkene Michael addition reactions.

Fig. (2). Organocatalyzed reaction of ketones (1-4) and 2-nitro-2-arylethyl acetates (5-9) with selected catalysts (10, 11) and acid additives (12-20).

The focus of our initial studies [37] was the reaction of cyclohexane 1,4-dione monoethylene ketal (1) and 2-(3,4-dimethoxyphenyl)-2-nitroethyl acetate (5) to generate the γ-nitroketone 21 [37] as the product of a Michael addition of 1 to the α-nitrostyrene obtained in situ from 5 (Scheme 1). The S-proline-derived catalysts 10 [38] and 11 [38] were examined for their ability to promote the required Michael addition in the presence of a selection of protic acid additives (12-20, Fig. 2).
Notably, the required Michael adduct 21 was obtained when 10 or 11 was used as the catalyst at ambient temperature. This indicated that 10 and 11 were capable of generating the α-nitrostyrene from 5 as well as participating in enamine formation from the ketone 1. Initial studies also indicated that 21 was always obtained as a mixture of diastereomers (21 and 22) with a preference for 21. In the absence of the acid additive, the yield and the enantioselectivity of the Michael addition reaction were low. Optimization studies were therefore conducted with selected combinations of the catalysts 10 or 11 with one of the acids 12-20 in equimolar amounts, with the objective of maximizing the diastereomeric excess of 21 and also the enantiomeric excess of 21 and 22 if both are obtained.

Initial investigations revealed that the diamine 11 was more efficient than the triamine 10 as a catalyst. For example, when a combination of 10 and pTsOH (12) was used in DMF or CHCl$_3$, none of the required 21 was obtained (entries 1 and 3, Table 1). However, with catalyst 11 and pTsOH in DMF, 21 was obtained as a mixture of diastereomers (49%, entry 5, Table 1).
Fig. (3). Formation of the γ-nitro ketone 21 and 22 from 1 using the catalyst 11.

1). Similarly, although the 10/MsOH (13) combination in EtOAc provided 21 in low yield (34%, entry 4, Table 1) the use of 11+13 in EtOAc provided 21 in higher yield (49%, entry 6, Table 1). The enantiomeric excess of the individual diastereomers 21 and 22 is also higher with the 11+13 catalyst system. Hence, most of the optimization studies were conducted with the diamine 11. Simultaneous with a full survey of acid additives with the catalyst 11, the effect of solvents on the 11+13 catalyst system was briefly examined (entries 6-9, Table 1). These studies indicated that EtOAc, DMF and CH₂Cl₂ were suitable solvents (entries 6-8, Table 1) and that CHCl₃ was not beneficial (entry 9, Table 1). However, parallel studies also indicated that EtOAc and CH₂Cl₂ were unsuitable solvents with the chiral acid additive 1S-camphorsulfonic acid (15) (entries 13 and 14, Table 1), and hence the acid additive survey was conducted with DMF as the solvent.

From this survey, the combination of diamine 11 and 1S-camphorsulfonic acid (15) in DMF at 0°C emerged as the optimum catalyst system. Under these conditions, the Michael adducts 21 and 22 were obtained in a good combined yield (81%), dr (21/22) = 1.7/1, major diastereomer 21 with 92% ee. The absolute configuration of 21 was assigned by X-ray crystallographic analysis [37]. It may be noted that the configuration of the acid additive 15 also influences the yield, the diastereomeric excess, and the enantiomeric excess of 21. Thus, when 1R-camphorsulfonic acid (ent-15) is used as the additive with diamine 11, the Michael adducts 21 and 22 are obtained in only 48% combined yield, dr (21/22) = 1/1, 21 obtained with 88% ee (compare entries 12 and 16, Table 1).

Since the formation of 22 could not be prevented, we considered if it was being formed by epimerization of the benzylc methine proton, which is also α to the nitro group, in 21. In order to test this hypothesis, pure 21 (92% ee) was subjected to the reaction conditions under which it is formed (ketone 1 (5 equiv), catalyst 11 (20 mol %) and 1S-camphorsulfonic acid (15, 20 mol%), DMF, 0°C, 72 h). Analysis of 21 recovered after workup of the reaction indicated that there was no change in its enantiomeric excess. More importantly, the minor diastereomer 22 could not be detected at any time during the course of this reaction. These observations provide two important clues to the reaction mechanism: 1) since 22 was not formed, the Michael adduct 21 does not generate the ketone 1 and the corresponding nitroalkene via a retro-Michael process and 2) the minor diastereomer 22 is not obtained by the epimerization of 21 under the reaction conditions. Clearly, 22 is formed by
competing reaction pathways that involve the enamine intermediate obtained from 1 and the α-nitrostyrene derived from 5. Although the full mechanistic details for the formation of 21 and 22 are not established, a proposed mechanism is shown in Fig. (3).

It is plausible that the Michael addition of the enamine, derived from 1 and the catalyst 11, to the α-nitrostyrene derived from 5 proceeds via the hydrogen-bonded [39] intermediate A Fig. (3) in which the nitroalkene is delivered to the re face of the enamine (Fig. 3 Path A). This step establishes the α stereocenter in the ketone as R, and it probably generates the 1,2-oxazine N-oxide intermediate B. Similar intermediates have been characterized [40, 41] in stoichiometric reactions of achiral enamines with α-nitrostyrene. Subsequent opening of the oxazine produces the nitronate C, which is protonated stereoselectively to generate D which has the R benzylic stereocenter in 21. The reason for the high stereoselectivity of the protonation of C, which leads to the formation of R,R-21, is not known at present. However, since one of the stereocenters is established prior to the protonation step, the observed influence of the chirality of the acid additive on the stereoselectivity of protonation is reasonable. The low diastereoselectivity of the Michael addition may be due to two reasons: 1) the inherently high reactivity of the α-nitrostyrene enables a competing non-hydrogen-bonded addition to the si face of the enamine to generate intermediate B' (Fig. 3 Path B) which, via C', would provide ent-22 with S stereochemistry at the ring stereocenter, and 2) the unselective protonation of intermediate C (Fig. 3 Path C) provides a small amount 22 with S stereochemistry at the benzylic stereocenter. Although the factors that control the formation of 22 and ent-22 are not known at this time, the low enantiomeric excess of 22 suggests that both Path B and Path C (Fig. 3) are operative.

Having established the optimized set of conditions for the conjugate addition reaction, the utility of the diamine catalyst 11 was examined for Michael addition reactions of the cyclic ketones 1-4 to selected, in situ generated, α-nitrostyrenes that are obtained from the nitroacetates 5-9 (Fig. 4). These reactions proceeded with moderate diastereoselectivity (1.1:1 to 2.3:1) but the major diastereomers (21, 23-36) were easily isolated by chromatography and were obtained in synthetically useful enantiomeric excess (up to 99% ee, Fig. 4). The stereochemistry of the major γ-nitroketone product is assigned by the observed trend in chemical shift and the multiplicities of the distinctive benzylic proton in 23-36 by comparison to that for 21. The highest levels of diastereoselectivity and enantiomeric excess are obtained with the ketone 1 which suggests that the spirocyclic ring system is beneficial for stereoselectivity.

Fig. (4). γ-Aryl γ-nitroketones 21 and 23-36 obtained by the Michael addition of cyclic ketones 1-4 to α-nitrostyrenes generated from 5-9.
The Michael addition of α,α-disubstituted aldehydes and cyclic ketones to α-nitrostyrenes was also investigated. In contrast to the reactions with ketones, S-proline was found to be the most suitable catalyst for these reactions. The yields and enantioselectivities of the reactions examined were moderate. Within the series, reactions with cyclohexane carboxylic aldehyde provided products with higher enantiomeric excess (52-79% ee). At this stage, the stereochemistry of the major enantiomer of the γ-aryl γ-nitroaldehyde Michael adduct was assigned by analogy to the products obtained from the cyclic ketones. These results are summarized in Fig. (5).

The synthetic utility of the γ-nitro aldehydes was demonstrated by the conversion of 41 into a functionalized pyrrolidine (Scheme 2). Reduction of 41 to the nitroalcohol followed by mesylation provided the nitro mesylate 47. This was converted into the N-acetyl pyrrolidine 48 [42] by reductive cyclization with Fe, followed by acetylation. The R configuration of 48 confirmed the stereochemical assignment for the nitroaldehyde 41 and, by analogy, the configurations of 42-46.

**CONCLUSION**

In conclusion, the first detailed study of the organocatalytic enantioselective Michael addition of α,α-disubstituted aldehydes and cyclic ketones to α-nitrostyrenes was undertaken and a procedure for the synthesis of enantiomerically enriched γ-aryl-γ-nitro ketones and γ-aryl-γ-nitro aldehydes was developed. The stereoselectivity of the Michael addition reactions is moderate, presumably due to the inherent reactivity of the α-nitrostyrene. In view of the high electrophilicity of α-nitro styrenes, it is notable that the organocatalysts employed in this study are not deactivated by N-alkylation with the nitrostyrene. The reactions described here complement the well-known Michael addition reactions of β-
Dalko, P.I.; Moisan, L. In the golden age of organocatalysis. [64x303]

Liu, J.; Wang, L. Recent advances in asymmetric reactions catalysis. [64x267]

Nayak, S.; Panda, P.; Bhakta, S.; Mishra, S.K.; Mohapatra, S. Current advances in organocatalysis. [92x222]

Vicario, J.L.; Reyes, E.; Carrillo, L.; Uria, U. Organocatalytic enamine catalysis. [359x240]

REFERENCES

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

These investigations were supported by the Natural Sciences and Engineering Research Council of Canada and the Canada Foundation for Innovation.

SUPPLEMENTARY MATERIAL

Experimental methods and spectroscopic data for all compounds.

Supplementary material is available on the publisher’s website along with the published article.

REFERENCES


Desmarchelier, A.; Cofeard, V.; Moreau, X.; Greck, C. Asymmetric organocatalytic functionalization of α-disubstituted aldehydes through enamine activation. Tetrahedron, 2014, 70, 2491-2513.


Kunetsky, R.A.; Dilman, A.D.; Struchkova, M.I.; Tartakovsky, V.A.; Ioff, S.L. Novel synthesis of a-nitroalkanes from nitroalkanes...


