The Nitro-Mannich Reaction

Adam Noble[†] *and James C. Anderson,*[*,†]

†Department of Chemistry, University College London, 20 Gordon Street, London, WC1H 0AJ, U.K.

CONTENTS

1. INTRODUTION

Reactions that utilize the addition of active C–H nucleophiles to C=X bonds represent some of the most fundamental carbon–carbon bond forming processes in organic chemistry. Of these reactions, the well known aldol,[1] nitroaldol (Henry)[2] and Mannich[3] have been studied extensively. The nitro-Mannich (or aza-Henry) reaction, involving the nucleophilic addition of a nitronate species to an imine electrophile, is another member of this family of carbon–carbon bond forming reactions, but is one that has been studied to a far lesser extent (Figure 1). Although this reaction has been known for over a century[4] real interest from the synthetic community only began around the turn of the century and it has since received considerable attention. This has resulted in the rapid development of a wide range of novel methodologies. The interest in the nitro-Mannich reaction arises from the value of the *β*-nitroamine products,

which possess vicinal nitrogen containing functionalities in differing oxidation states, providing the opportunity for selective manipulation of either. Furthermore, the versatility of the nitro group allows access to other important structural motifs such as 1,2-diamines (via nitro reduction), mono-amines (via reductive denitration) and α-aminocarbonyls (via Nef reaction).[5]

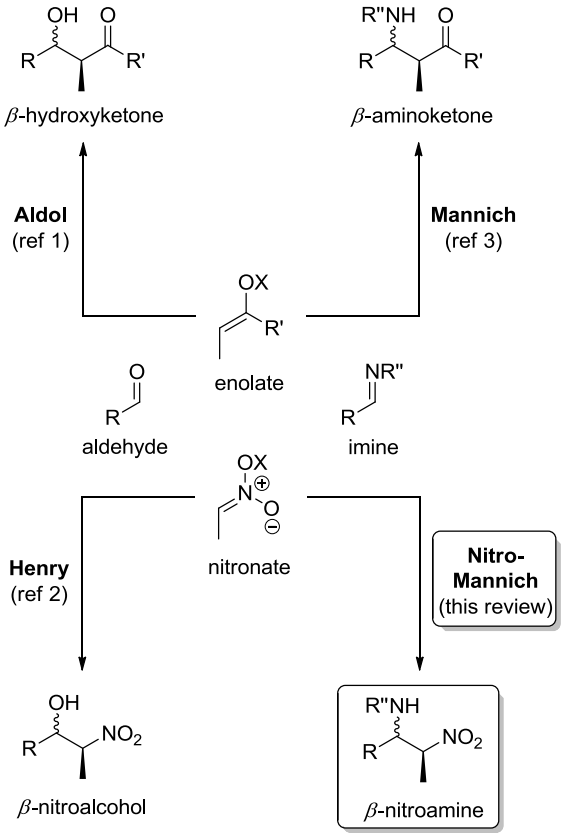


Figure 1. The Addition of Active C–H Nucleophiles to C=X Bonds.

Significant interest in the nitro-Mannich reaction began with the introduction of the first acyclic diastereoselective reactions, reported in 1998.[6] Prior to this, reports of nitro-Mannich reactions were limited to non-selective, uncatalyzed examples. However, since then many protocols have been developed that provide access to a wide variety of β-nitroamines with high levels of stereoselectivity, including both organocatalyzed and metal-catalyzed examples.

Furthermore, the utility of this reaction has recently begun to be demonstrated through its successful application to target synthesis.

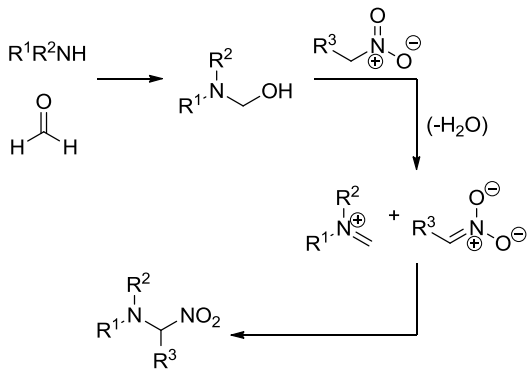
Although the nitro-Mannich reaction has not previously been reviewed in its entirety,[7] selected aspects of this reaction have appeared in reviews on related subjects. These include reviews on multimetallic multifunctional catalysts,[8–12] asymmetric additions to C=N bonds,[13–15] organocatalysis,[16–20] *N*-acyl imines,[21] and the synthesis of α,β-diamino acids.[22] There have also been a number of smaller reviews that have focused specifically on asymmetric nitro-Mannich reactions.[23–24] The most recent of these was in 2009 and contains a good review of the asymmetric methodology up to that point.[24] The aim of this review is to present a comprehensive survey of the nitro-Mannich literature spanning the 116 years from the initial report to the spring of 2012. It encompasses the past history, more recent rapid developments over the past 14 years and applications to synthesis. We try to show the key contributions from the 20th century that have led to many of the developments concerning asymmetric control in the 21st century.

2. EARLY DEVELOPMENTS

The early examples of nitro-Mannich reactions consisted mainly of unselective non-catalyzed methods with the majority of reactions being performed on imines derived from formaldehyde. These imines were generated *in situ* by dehydration of water from the hemiaminal products of the reaction between formaldehyde and an amine (Scheme 1). The iminium intermediate is then free to react with a nitronate species in a nitro-Mannich coupling to form a β-nitroamine product. It was this chemistry that was used by the first groups who developed the early nitro-Mannich reactions and many others prior to the 21st century. There were, however, a number of examples of nitro-Mannich reactions being performed with pre-formed imines derived from substituted

aldehydes. It was these reactions that lay the foundations for the highly selective catalytic methodologies that were later developed.

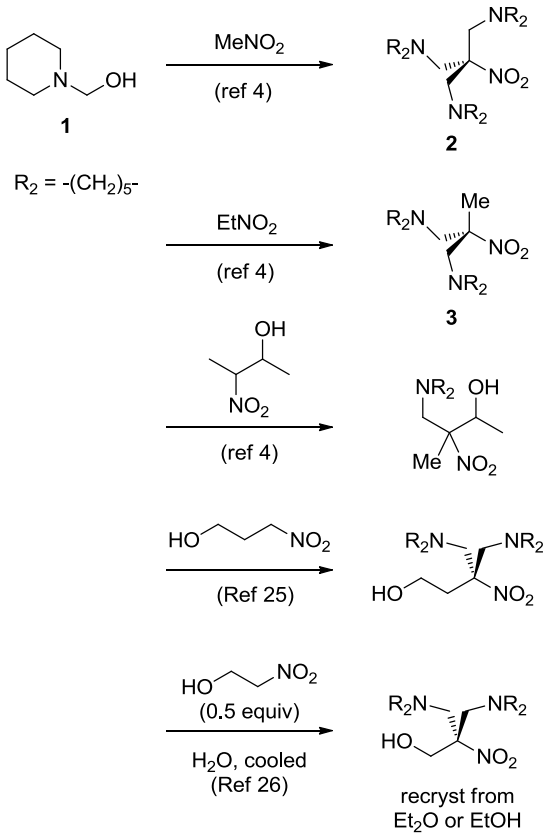
Scheme 1. The Mechanism of Early Nitro-Mannich Reactions



2.1. The First Reports

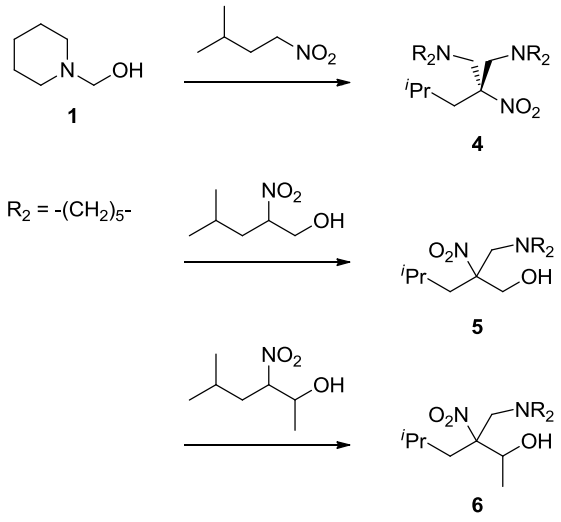
The first report of a nitro-Mannich reaction was by Louis Henry in 1896.[4] He described the reaction of methanolamine **1**, derived from formaldehyde and piperidine, with nitromethane and nitroethane to form the tri- and di-piperidines **2** and **3** (Scheme 1). He also successfully performed the reaction with 3-nitro-2-butanol, the product of a Henry reaction between nitroethane and acetaldehyde. This substrate was used because he was unable to obtain 2-nitropropane at the time. No yields or procedures were given in this first report. Henry later reported several other reactions involving other nitroalcohols (Scheme 2). Yields were still not reported but a rough experimental procedure was given.[25–26]

Scheme 2. The First Reported Nitro-Mannich Reactions



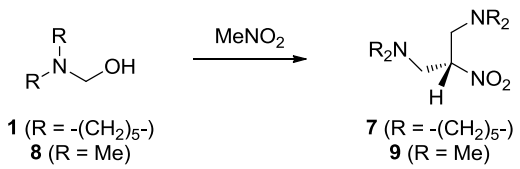
The next contribution came from Mousset in 1901.[27] Having recently synthesized nitroisopentane he investigated its properties through its application in both Henry and nitro-Mannich reactions. He demonstrated that nitroisopentane, and its products formed from Henry reactions with formaldehyde and acetaldehyde, would undergo nitro-Mannich reactions with methanolamine **1** when using the same procedures reported by Henry (Scheme 3). Although the structure of dipiperidine compound **4** was supported by elemental analysis, compounds **5** and **6** were described as "syrupy liquids" that could not be purified for analysis. Therefore, the structures of these compounds are only postulated and were not supported by any analytical methods.

Scheme 3. Nitro-Mannich Reactions Reported by Mousset



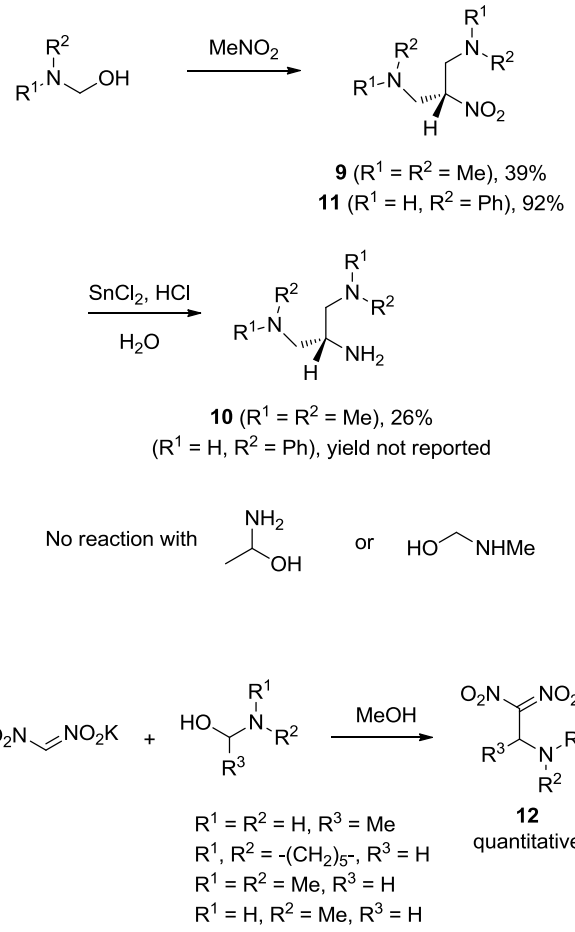
In the early 20th century, after receiving a query from Duden *et al.* regarding his original structural assignment of nitroamine **2**, Henry published a revised structure of the product of the reaction between methanolamine **1** and nitromethane (Scheme 4).[28] It was found that nitromethane reacted with only two molecules of **1**, not three as was originally suggested, to form dipiperidine product **7**. The original incorrect assignment was made due to similarities between the elemental composition of the two compounds. This new assignment was also supported by the reaction of nitromethane with dimethylaminomethanol **8**, which led to the formation of nitrodiamine product **9**. These observations lead Henry to the theory that nitromethane will react with only two molecules of secondary amine and two molecules of formaldehyde, leaving one free C–H α to the nitro group in the product.

Scheme 4. Reassignment of the Product of Nitro-Mannich Reactions with Nitromethane



In the following article of the same journal issue, Duden *et al.* published the results of their investigations into the nitro-Mannich reaction.[29] They further supported the work performed by Henry by independently synthesizing nitrodiamine product **9** in 39% yield (Scheme 5). Due to the instability of **9** it was reduced using stannous chloride and HCl to give 1,2,3-triamine **10**. This was the first application of the nitro-Mannich reaction to the synthesis of polyamines. They also extended the work of Henry by performing similar reactions with the aminomethanol derived from aniline and formaldehyde, forming nitrodiamine **11** in excellent yield. Limitations of this early procedure were highlighted by the failure of the reaction to proceed when using the aminomethanol derived from methylamine and formaldehyde and also that derived from ammonia and acetaldehyde. The authors also investigated the reaction of the potassium salts of dinitromethane with a variety of amines and aldehydes to form dinitroamines **12**. The yields were reported as near quantitative for all examples given. Using this method, the authors reported the first examples of nitro-Mannich reactions of imines derived from acetaldehyde and ammonia.

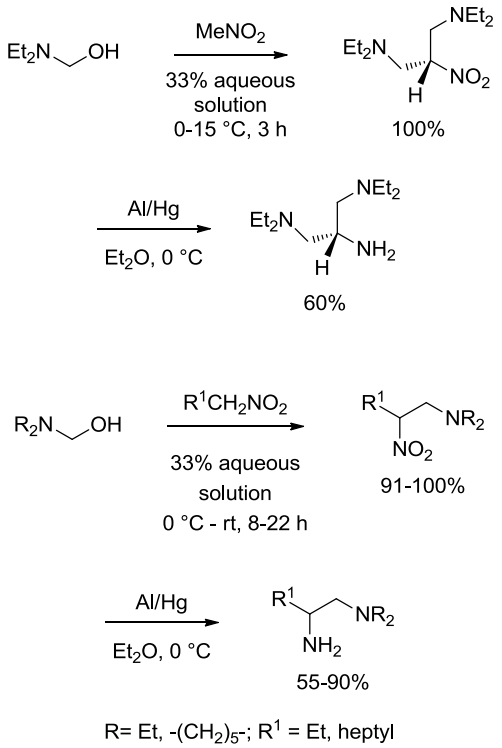
Scheme 5. Nitro-Mannich Reactions Described by Duden *et al.*



The next contribution did not come until almost 30 years later, when Cerf de Mauny published a more detailed study of the original experiments performed by Henry.[30–32] His aim was to provide general procedures for the reactions of nitromethane with one, two and three molecules of aminomethanol. Although he was unsuccessful in this endeavor, as under all the conditions he tried the same product of a double addition was formed, he did provide more detailed experimental procedures and extend the scope of the nitro-Mannich reaction to higher order nitroalkanes (Scheme 6). He was able to form the nitroamine products in excellent yield by careful regulation of the temperature and concentration of the reactions. He also provided an improved reduction protocol using aluminium amalgam to provide the di- or tri-amine products in good to excellent yield. Based on his observations, and the original theory made by Henry,[28]

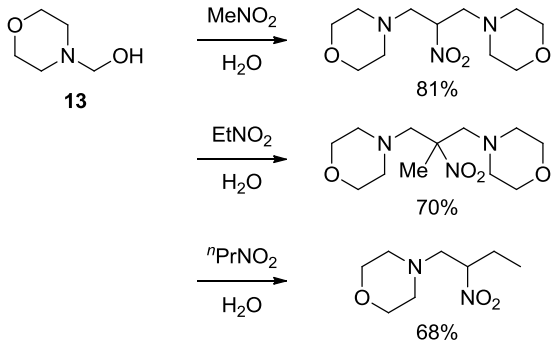
he concluded that a general rule could be applied to the reaction of nitroalkanes with methanolamines. He stated that for a nitroalkane of general formula $R_{3-n}H_nCNO_2$ the number of molecules of methanolamine that it reacts with is n-1. This rule contradicted some of the earlier results obtained by Henry and Mousset, however, no attempts to replicate the early results of these groups was made.

Scheme 6. Nitro-Mannich Reactions Described by Cerf de Mauny



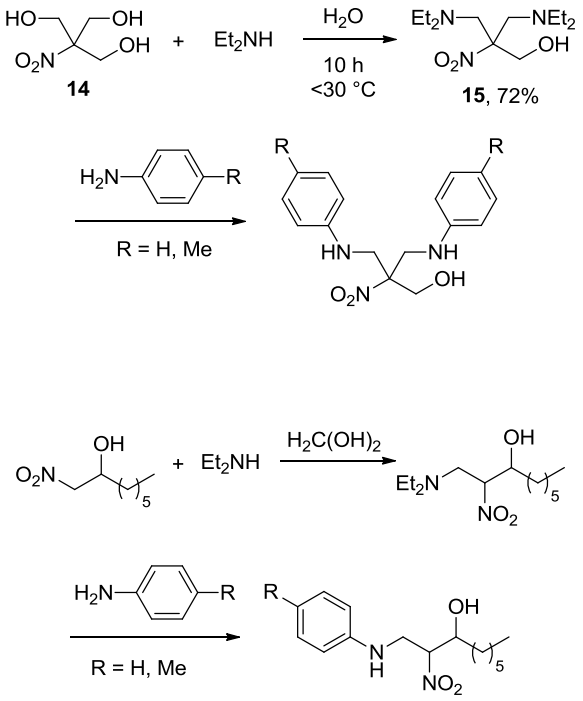
Cerf de Mauny's rule was later proved not to apply to nitro-Mannich reactions involving nitroethane by Zief and Mason (Scheme 7).[33] They found that the reaction of morpholinylmethanol **13** with nitroethane gave the double addition product, as it did with nitromethane, whereas with nitropropane only a single addition was observed, the predicted product based on Cerf de Mauny's rule.

Scheme 7. Nitro-Mannich Reactions Described by Zief and Mason



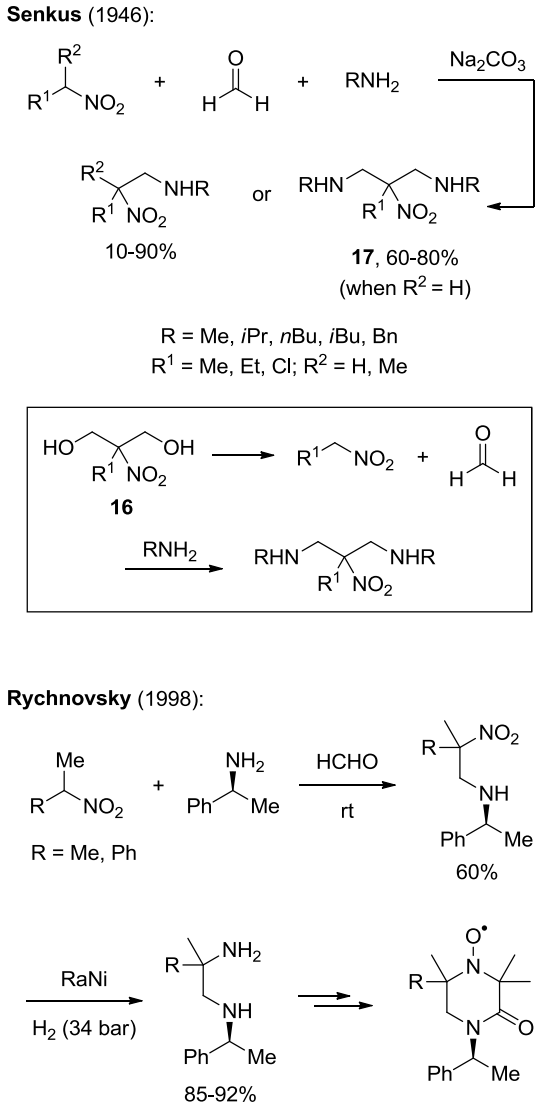
In 1944, Cerf de Mauny published a novel nitro-Mannich reaction of nitroalcohols (Scheme 8).[34] The nitro-Mannich reaction of nitro-triol **14** with diethylamine proceeded via a double retro-Henry/nitro-Mannich sequence. The diethylamine nitro-Mannich product **15** was then converted to the corresponding arylamine products through reactions with a number of anilines. This substitution reaction presumably proceeds via a double retro-nitro-Mannich/nitro-Mannich sequence to form the more stable arylamine product. Similar reactions were also performed on the Henry product of nitromethane and 1-heptanal.

Scheme 8. Nitro-Mannich Reactions of Nitroalcohols



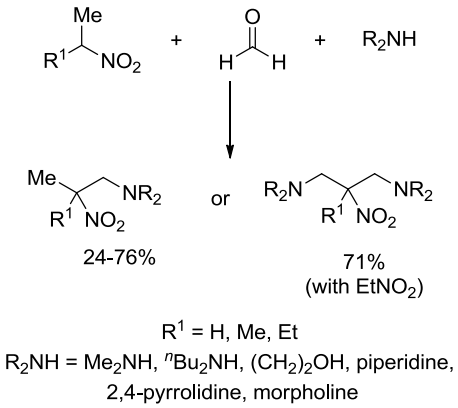
The next contributions came independently from Senkus and Johnson in 1946.[35–37] Senkus demonstrated the reaction of a variety of nitroalkanes with formaldehyde and a range of primary amines (Scheme 9).[35] He also demonstrated that the same products could be formed in comparable yields by the reaction of 1,3-dihydroxy-2-nitropropanes **16** with primary amines, via initial retro-Henry reaction, forming two molecules of formaldehyde and the nitroalkane, followed by the standard nitro-Mannich reaction. These reactions are similar to those originally reported of Cerf de Mauny.[34] However, the formation of double addition products **17** showed that Cerf de Mauny's rule does not apply when using primary amines. Senkus also demonstrated that the nitroamines products could be readily converted to the corresponding polyamines by hydrogenation over Raney nickel. Rychnovsky *et al.* later used this chemistry for the synthesis of chiral nitroxides (Scheme 9).[38] The reaction of (*S*)-1-phenylethylamine with formaldehyde and a number of secondary amines proceeded with good yield. The products were hydrogenated over RaNi to yield the diamine products, which were then converted to the respective chiral nitroxides.

Scheme 9. Nitro-Mannich Reactions of Primary Alkylamines



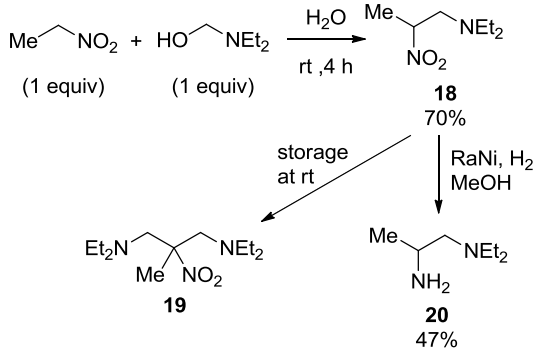
Johnson published his findings from investigations into the scope of the nitro-Mannich reactions with secondary alkylamines (Scheme 10).[36] The reactions proved to be general for a range of secondary amines, providing the products in moderate to good yields. The products were also reduced to the corresponding polyamines in 23-95% yield by hydrogenation over RaNi. Grillot and Bashford later used Johnson's procedures during their investigations into Mannich reactions of optically active nitroalkanes.[39]

Scheme 10. Nitro-Mannich Reactions of Secondary Alkylamines



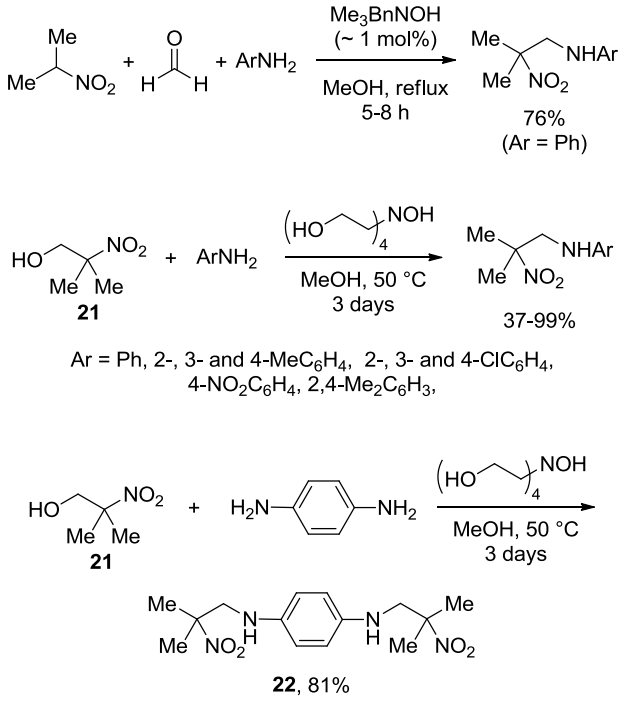
Lambert and Rose investigated the use of this chemistry for the selective mono-addition of aminomethanols to nitroethane, which typically undergoes double addition. They successfully performed the mono-addition reaction of diethylaminomethanol with nitroethane (Scheme 11).[40] This was accomplished by using equimolar quantities of each reagent and performing the reactions over a short period of time at ambient temperature. The nitro-monoamine product **18** could not be obtained in pure form as decomposition to nitrodiamine **19** occurred on storage. Consequently, reduction of crude **18** was carried out by hydrogenation over RaNi to yield 1,2-diamine **20** in moderate yield.

Scheme 11. Selective Mono-Nitro-Mannich Reaction of Nitroethane



Johnson also extended the scope of the nitro-Mannich reaction to include primary arylamines.[37] Unlike the reactions of alkylamines, the reactions of arylamines required the addition of a basic catalyst to achieve acceptable yields (Scheme 12). The author used tetraalkyl ammonium hydroxides for the formation of a variety of nitro-Mannich products. The products could be formed in higher yields by using the retro-Henry/nitro-Mannich reaction of 2-nitroethanol **21**. In the same communication, Johnson also reported the first example of a nitro-Mannich reaction of a diamine to form dinitrodiamine product **22**. The products were again reduced using hydrogenation over RaNi to yield the polyamine products in 48-98% yield.

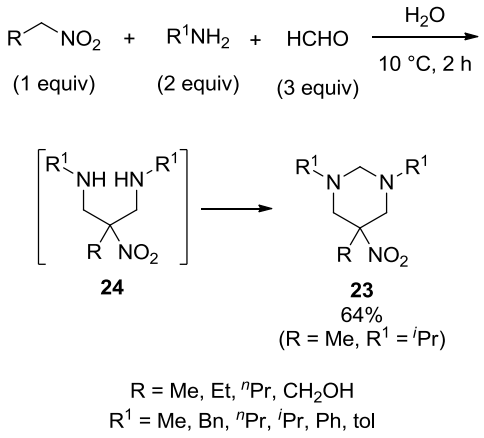
Scheme 12. Nitro-Mannich Reactions of Primary Arylamines



2.2. Heterocycle Synthesis

These early nitro-Mannich methodologies have been used by a number of groups for the synthesis of a variety of heterocyclic products. Senkus demonstrated that his nitro-Mannich reactions of primary alkylamines could be used for the synthesis of 5-nitro-hexahydropyrimidines **23** (Scheme 13).[41] By using an additional equivalent of formaldehyde the nitrodiamine intermediates **24** underwent cyclization via condensation with formaldehyde to form the 5-nitro-hexahydro-1,3-pyrimidines **23**. This methodology was later expanded by Shakirov *et al.* to include the reaction of methyl nitroacetate.[42] Similar reactions have also been reported by Cichra and Adolph.[43]

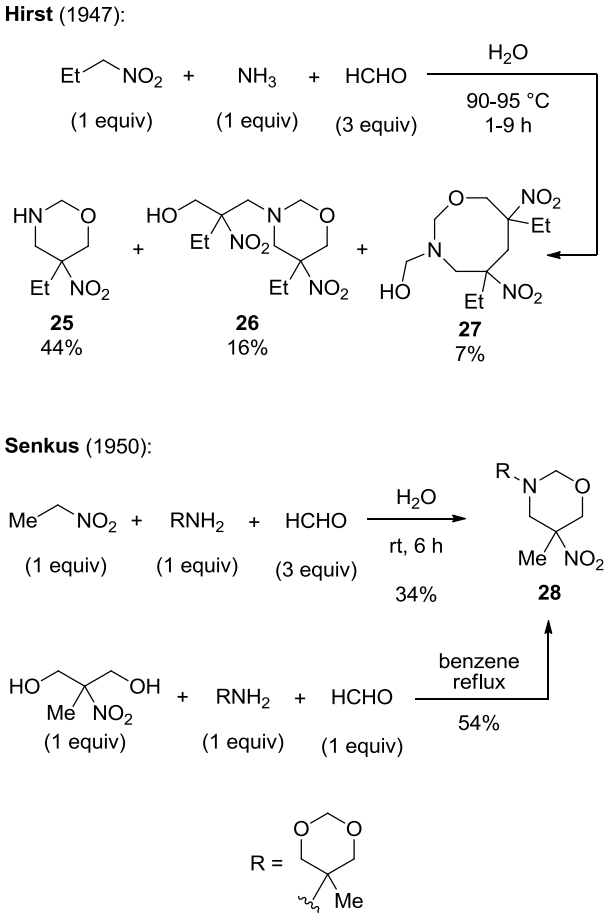
Scheme 13. Synthesis of 5-Nitro-hexahydropyrimidines



Hirst *et al.* showed that similar chemistry could be used for the synthesis of 5-nitro-tetrahydro-1,3-oxazines **25** (Scheme 14).[44] They performed the reaction of nitropropane, ammonia and excess formaldehyde and isolated a number of products including the major product 5-nitro-tetrahydro-1,3-oxazine **25**, oxazine **26** and eight-membered ring **27**. These products were isolated from a complex mixture of other oligomers and no investigation into improving the selectivity for each product was reported. Senkus later reported an improved general procedure for the synthesis of 5-nitro-tetrahydro-1,3-oxazines **28** (Scheme 14).[45] He demonstrated the synthesis

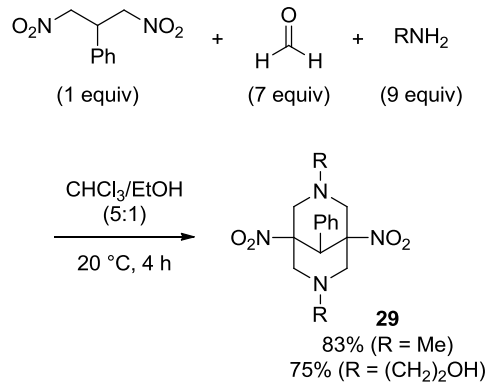
with a wide variety or primary alkylamines. The reaction could be performed by mixing the amine, formaldehyde and the nitroalkane in water at room temperature, however, improved yields were obtained when starting from 2-nitro-1,3-propanediol and with azeotropic removal of water under Dean-Stark conditions. The scope of the synthesis of 5-nitro-tetrahydro-1,3-oxazines using this method was subsequently extended, mainly by the group of Urbański, to include the use of a wide variety of primary nitroalkanes and primary amines. These investigations have been discussed in a review by Eckstein and Urbański.[46]

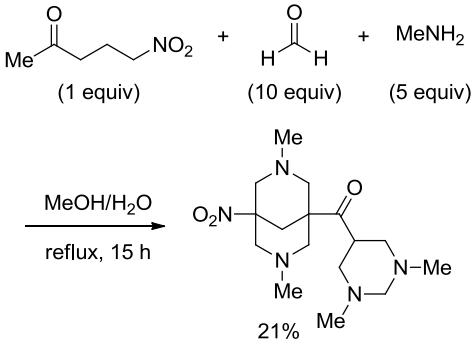
Scheme 14. Synthesis of 5-Nitro-tetrahydro-1,3-oxazines

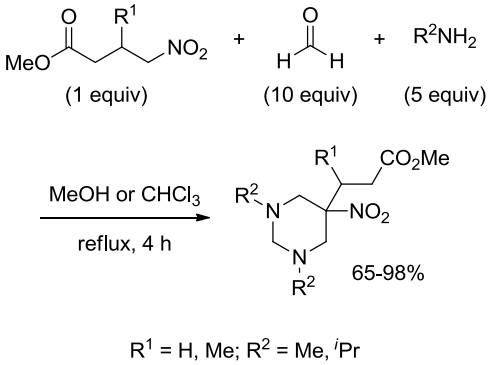


More recently, in 2001, Yarmukhamedov *et al.* reported the reaction of 1,3-dinitro-2-phenylpropane with formaldehyde and primary amines to form 1,5-dinitro-3,7-diazabicyclo[3.3.1]nonanes **29** in excellent yield (Scheme 15).[47] The same group later reported that a similar reactions could be performed on *γ*-nitroketones and *γ*-nitroesters to form a range of cyclic compounds (Scheme 15).[48] The products of the reactions with unsubstituted *γ*-nitroesters were formed in excellent yields, however, substitution on the *γ*-nitroesters resulted in reduced reaction rates and substitution on the *γ*-nitroketone prevented any reaction taking place.

Scheme 15. Yarmukhamedov's Synthesis of Heterocyclic Products

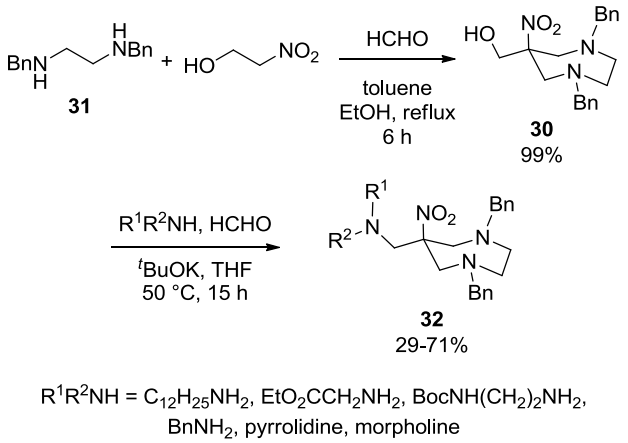






In 2009, Tei *et al.* reported a high yielding synthesis of 6-nitroperhydro-1,4-diazepines **30** via a double nitro-Mannich reaction between *N*,*N*'-dibenzylethylenediamine (**31**), formaldehyde and 2-nitroethanol (Scheme 16).[49] The same group later demonstrated that further functionalization of these products could be achieved via a base-mediated retro-Henry/nitro-Mannich reaction to form *β*-nitroamines **32** in moderate to good yields.[50]

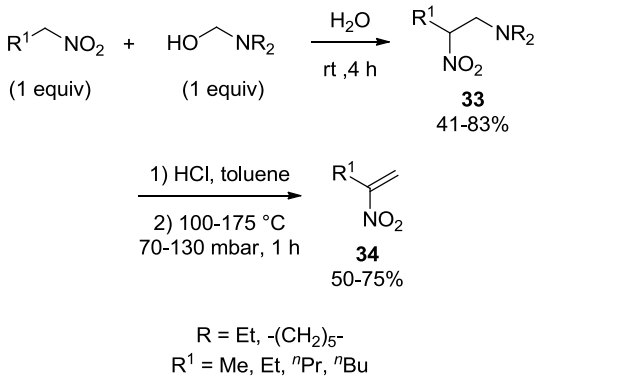
Scheme 16. Synthesis of 6-Nitroperhydro-1,4-diazepines



2.3. Nitroalkene Synthesis

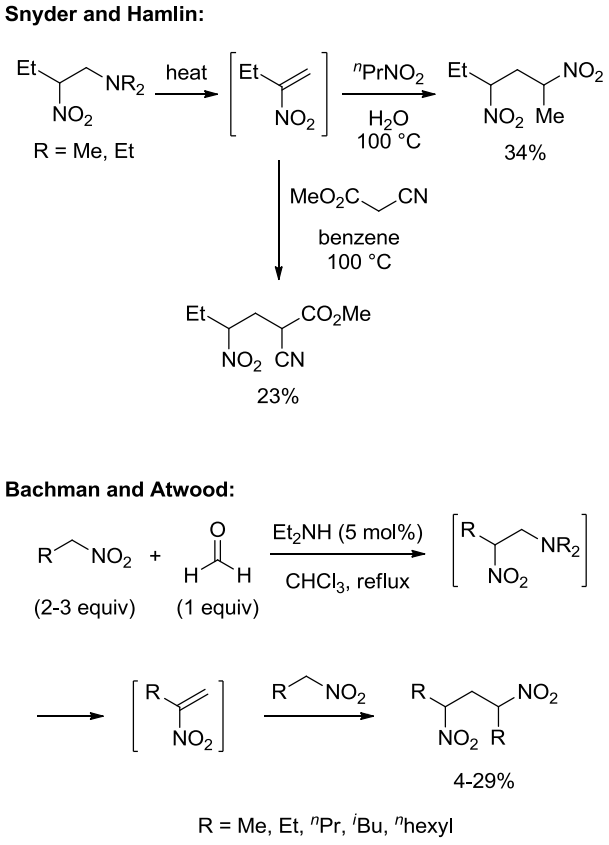
There are also a number of examples of nitro-Mannich chemistry being used for the synthesis of nitroalkenes, via elimination of the amine group from the *β*-nitroamine products. Blomquist and Shelley demonstrated that this kind of nitroalkene synthesis was possible by pyrolysis of the hydrochloride salts of nitro-Mannich products **33** (Scheme 17).[51] Elimination of the amine group afforded the nitroalkene products **34** in good yield.

Scheme 17. Synthesis of Nitroalkenes by Pyrolysis of Nitro-Mannich Products



The subsequent use of such nitroalkene products was demonstrated by Snyder and Hamlin.[52] They performed tandem elimination conjugate addition reactions with a variety of nucleophiles including nitroalkanes and cyanoacetates (Scheme 18). The products were, however, formed in low yield. This work was later extended by Bachman and Atwood who were able to perform nitro-Mannich/elimination/conjugate addition sequences in a single reaction flask (Scheme 18).[53] Although the yields were poor, this kind of tandem reaction sequence demonstrates the usefulness of the nitro-Mannich reaction and also represents an early form of organocatalysis. The reaction was higher yielding for larger nitroalkanes and in several cases separation of the diastereomers was possible, although these were isolated in approximately 1:1 ratios.

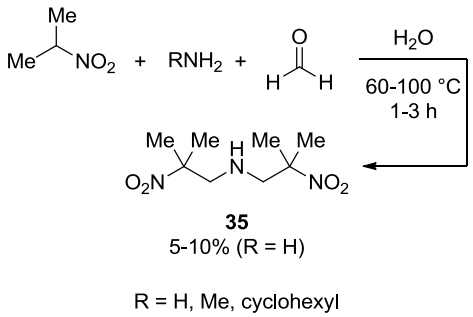
Scheme 18. Tandem Nitroalkene Synthesis/Michael Addition Reaction



2.4. Synthesis of Dinitroamines

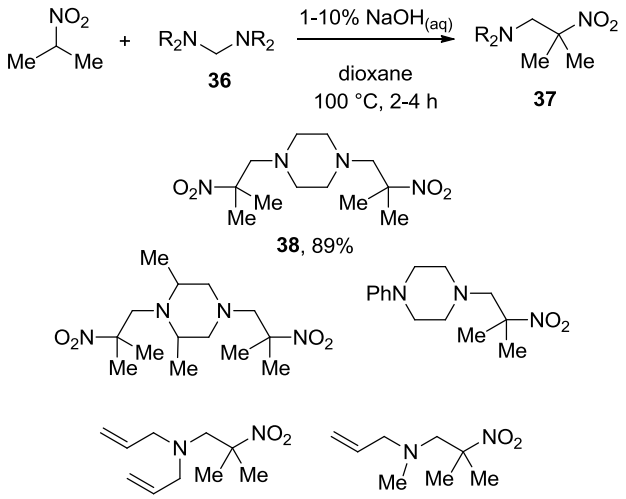
Through variation of the stoichiometry of the starting materials in these early nitro-Mannich reactions the formation of a variety of different products was possible. For example, the use of excess nitroalkane in the reactions with primary amines can lead to the formation of dinitroamines. Similarly, the reactions with diamines, originally reported by Johnson,[37] can lead to the formation of dinitro-diamines. Jones and Urbański formed dinitroamines **35** through the reaction of 2-nitropropane with formaldehyde and primary alkylamines or ammonia (Scheme 19).[54] The yields with ammonia were, however, very low and no purified yields were reported for the reactions with primary alkyl amines.

Scheme 19. Synthesis of Dinitroamines



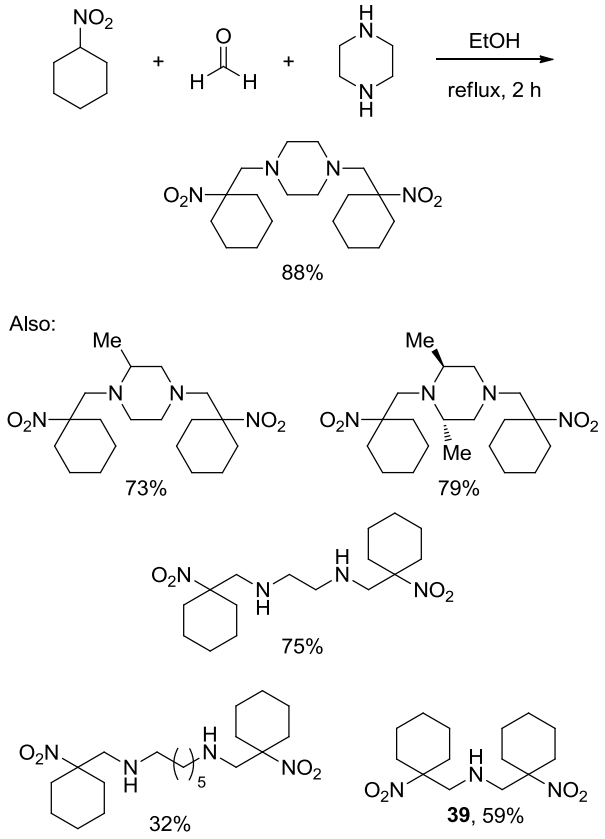
While investigating the nitro-Mannich reactions of 2-nitropropane with bis(alkylamino)methanes **36** Butler synthesized a range of dinitro-diamines from cyclic diamines (Scheme 20).[55] The reactions of bis(alkylamino)methanes **36** required more forcing conditions than those performed with aminomethanols but the product *β*-nitroamines **37** were formed in excellent yields. Although the author only reported a single yield for the dinitro-diamine products (89% for **38**) the yields for the remaining nitroamine products were described as "good".

Scheme 20. Nitro-Mannich Reactions of Bis(alkylamino)methanes



Smiley extended the scope of the dinitro-diamine synthesis by demonstrating the reaction of a range of diamines with nitrocyclohexane (Scheme 21).[56] The author also reported the formation of dinitroamine **39** by using ammonia in the reaction. This demonstrated the first use of nitrocyclohexane in a nitro-Mannich reaction. The products were formed in moderate to excellent yield and were subsequently reduced to their respective tetra-amine products in good yield.

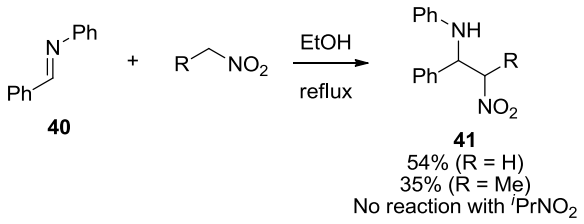
Scheme 21. Synthesis of Dinitro-Diamines



2.5. Reactions with Pre-Formed Imines

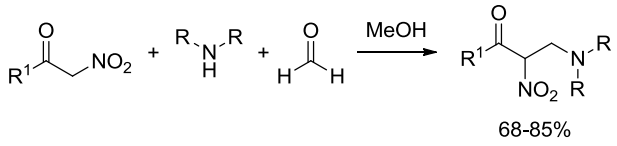
All of the nitro-Mannich reactions mentioned up until this point have involved the *in situ* formation of imines. The first nitro-Mannich reaction of a pre-formed imine was performed by Hurd and Strong in 1950.[57] They successfully reacted nitromethane and nitroethane with benzylidineaniline (**40**) by refluxing in ethanol, forming the corresponding *β*-nitroamines **41** in moderate yields (Scheme 22). These results were in contrast to the observations made by Hass and Riley who stated that the reactions of aromatic aldehydes with nitroalkanes and amines resulted in the formation of nitroalkenes due to elimination of the amine after the initial nitro-Mannich reaction.[58]

Scheme 22. The First Nitro-Mannich Reactions with Pre-Formed Imines

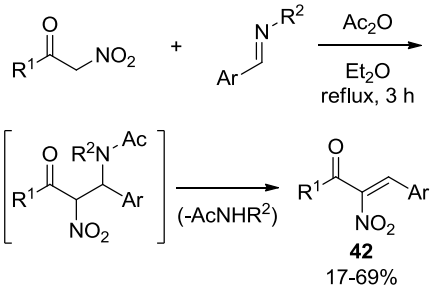


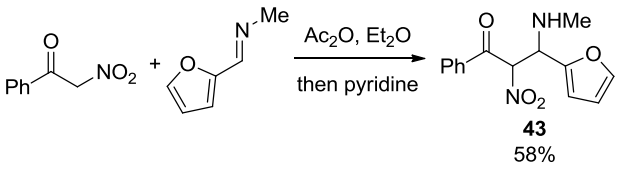
Dornow *et al.* later reported high yielding nitro-Mannich reactions of nitroacetophenone and nitroacetone with a variety of methanolamines formed from secondary amines and formaldehyde (Scheme 23).[59–60] They also demonstrated that nitroacetophenone and nitroacetone react with pre-formed aryl imines in the presence of acetic anhydride. By refluxing the reaction mixture elimination of the alkylacetamide occurred to form nitroalkenes **42** in low to good yields. However, addition of pyridine to the reaction resulted in deacetylation which prevented elimination and enabled isolation of *β*-nitroamine **43** in good yield. The same group later extended the scope of these reactions to include arylidene nitroacetones.[61]

Scheme 23. Nitro-Mannich Reactions of Nitroacetophenone and Nitroacetone



R_2NH = piperidine, morpholine, Me_2NH, Et_2NH



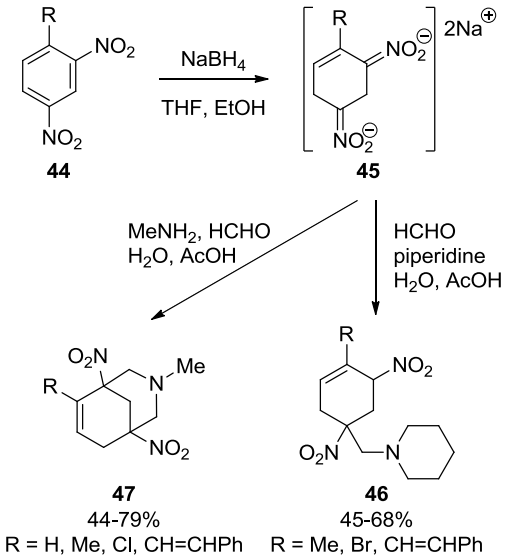


R^1 = Ph, Me
R^2 = Me, Et, Bn
Ar = Ph, 4-MeO-C_6H_4, 4-Cl-C_6H_4, 4-NO_2-C_6H_4, 2-furyl

2.6. Conjugate Addition Nitro-Mannich Reactions

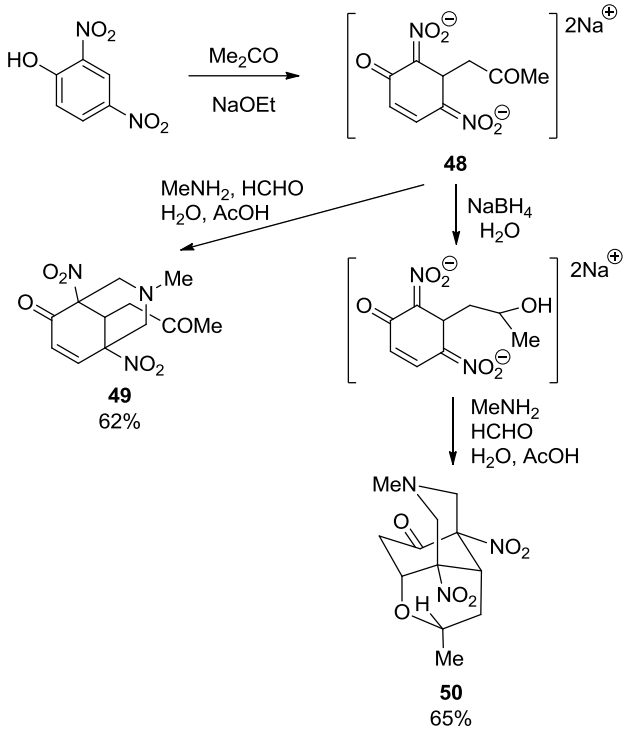
In 1963, Severin *et al.* demonstrated that $NaBH_4$ reacts with *meta*-dinitrobenzenes **44** to form the disodium salt of bis(nitronate)cyclohexenes **45** (Scheme 24).[62] These isolable dinitronate salts could then undergo nitro-Mannich reactions with formaldehyde and a variety of amines in the presence of acetic acid. This reductive nitro-Mannich reaction formed *β*,*δ*-dinitroamines **46** with piperidine and bicylic products **47** with methylamine, which were formed in good yields for a number of substituted dinitrobenzenes. The same group also demonstrated that similar reactions could be performed using Grignard reagents in the place of $NaBH_4$.[63] This methodology has since been extended to a variety of other *meta*-dinitroaromatic, dinitrobicycloaromatic and dinitroheteroaromatic rings.[64–69]

Scheme 24. Reductive Nitro-Mannich Reactions of *meta*-Dinitrobenzenes



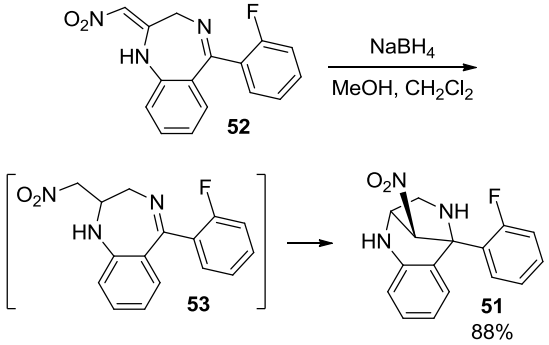
In 1965, the same group went on to demonstrate that, instead of $NaBH_4$, the addition of acetone to 2,4-dinitrophenol could be promoted by sodium ethoxide to form the bis(nitronate)cyclohexenone **48** (Scheme 25)[70] This underwent similar reactions to dinitronate **45**. Reaction with formaldehyde and methylamine yielded bicyclic product **49** in 62% yield. The authors also performed the reaction with cyclohexanone instead of acetone to give the respective product in 48% yield. The alternative bridged tricyclic product **50** was obtained in 65% yield by first reduction of the methyl ketone moiety in **48** with $NaBH_4$. This nitro-Mannich chemistry has since been extended to the use of a variety of other primary alkylamines and acetophenone by the group of Shakhkel'dyan.[71–72]

Scheme 25. Conjugate Addition Nitro-Mannich Reactions of 2,4-Dinitrophenol



There was also a report of another reductive nitro-Mannich reaction by Walser and co-workers (Scheme 26).[73] During their investigations into the synthesis of pharmacologically active benzodiazepines the authors observed the unexpected formation of *β*-nitroamine **51**. The reduction of nitroalkene **52** with $NaBH_4$ generated nitroamine **53**. This then underwent a spontaneous intramolecular nitro-Mannich reaction to form **51** in 88% yield, the structure of which was confirmed by single crystal X-ray analysis.

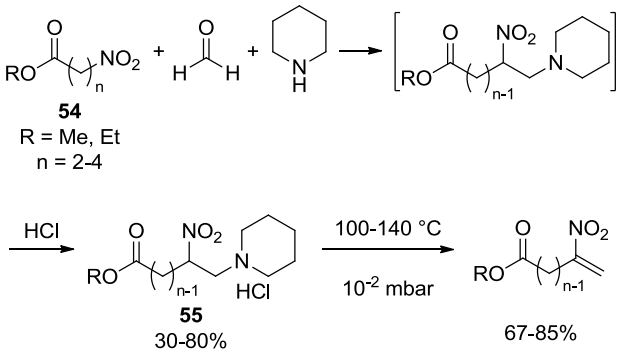
Scheme 26. Unexpected Intramolecular Reductive Nitro-Mannich Reaction



2.7. Reactions of Nitroesters

There were also a number of early reports of nitro-Mannich reactions of nitroesters. These were first investigated by Mühlstädt and Schulze who demonstrated that reactions of *β*-, *γ*-and *δ*-nitroesters **54** with formaldehyde and piperidine provided the representative nitroamino esters **55** in moderate to good yields (Scheme 27).[74] They also demonstrated that these *β*-nitroamines could be used to form the corresponding nitroalkenes by elimination of piperidine hydrochloride under pyrolysis conditions.

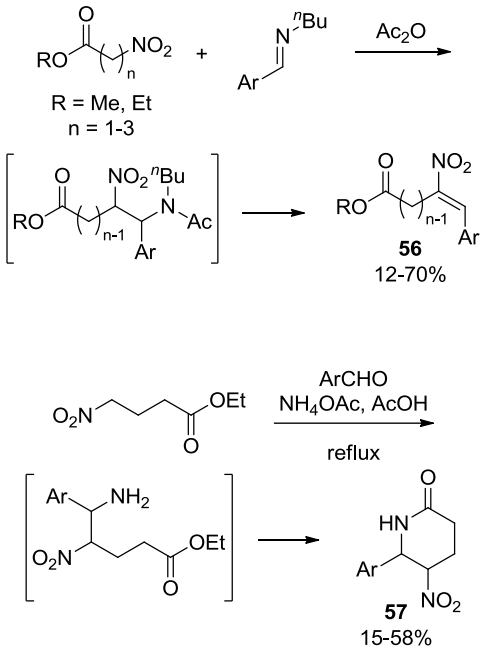
Scheme 27. Nitro-Mannich Reactions of Nitroesters



Inspired by the work of Dornow *et al.* on acetic anhydride-mediated nitro-Mannich reactions with pre-formed imines, Mühlstädt and Schulze extended their nitroalkene synthesis to include those formed from pre-formed aryl imines (Scheme 28).[75] They formed nitroalkenes **56** derived from a wide variety of aryl imines in low to good yields. They also demonstrated that when ammonium acetate was used instead of butylamine in the reaction of ethyl 4-nitrobutanoate the products formed were 5-nitropiperidin-2-ones **57**. This was the first reported example of a nitro-Mannich/lactamization cascade reaction. No diastereomeric ratios (*dr*) were reported, however,

based on subsequent studies by Jain *et al.* it is likely that the products were formed with high *trans* selectivity.[76]

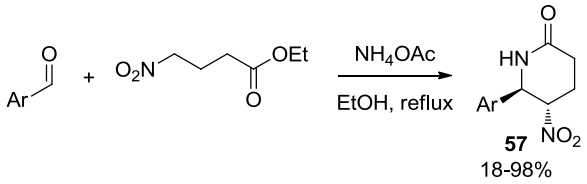
Scheme 28. Nitro-Mannich Reactions of Nitroesters with Pre-Formed Imines and Nitro-Mannich/Lactamizations



Independently of Mühlstädt and Schulz, Jain *et al.* also developed the nitro-Mannich/lactamization reaction.[76] He demonstrated an improved substrate scope and provided a number of different experimental procedures (Scheme 29). The reaction of a variety of aryl aldehydes, ethyl 4-nitrobutanoate and ammonium acetate gave 5-nitropiperidin-2-ones **57** in low to excellent yields. The products were confirmed to possess *trans* stereochemistry by ^{1}H NMR. The use of benzylammonium acetate was also demonstrated, however, this gave the desired product in only 5% yield. This report by the group of Jain represents the first examples of

diastereoselective nitro-Mannich reactions, most probably aided by the formation of a piperidinone ring.

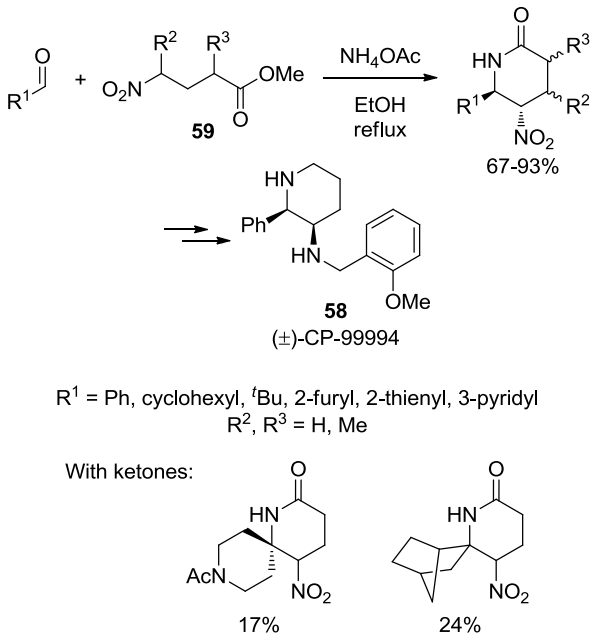
Scheme 29. Nitro-Mannich/Lactamization Reactions



Ar = Ph, 1-naphthyl, 2-naphthyl, 3,4-$(MeO)_2C_6H_3$, 2,3-$(MeO)_2C_6H_3$, 4-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 3-indolyl

There were also two reports by the group of Desai which utilized the nitro-Mannich/lactamization methodology developed by the groups of Mühlstädt, Schulz and Jain for the synthesis of analogues of CP-99994 (**58**), a potent substance P antagonist (Scheme 30).[77–78] Their aim was to develop a versatile synthesis of CP-99994 (**58**) that would allow the easy generation of analogues, whose biological activities could then be assessed. They demonstrated that the nitro-Mannich/lactamization reactions worked well for a range of heteroaryl and alkyl aldehydes, cyclic ketones and substituted ethyl 4-nitrobutanoates (**59**).

Scheme 30. Synthesis of Analogues of CP-99994 (**58**) Using Nitro-Mannich/Lactamizations



3. NON-CATAYLTIC REACTIONS

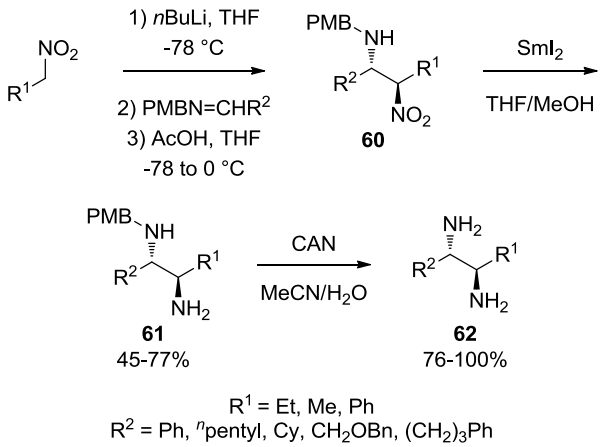
The next development in nitro-Mannich chemistry came when the first acyclic diastereoselective reactions were reported in 1998.[6] It was after this that interest in this reaction began to increase significantly. New developments reported around the turn of the century involved a number of diastereoselective non-catalytic methods that involved the use of stoichiometric amounts of base for the formation of reactive nitronate species.

3.1. Base-Mediated Reactions

The first acyclic diastereoselective nitro-Mannich reaction was reported by Anderson *et al.* in 1998.[6] The authors formed lithium nitronates by deprotonation of a range of nitroalkanes with ^{n}BuLi. Introduction of an imine and acetic acid promoted the desired nitro-Mannich reactions. A range of *N-para*-methoxybenzyl (PMB)-imines and nitroalkanes provided *β*-nitroamines **60** in high yield and, in certain cases, high *anti*-diastereoselectivity (Scheme 31). Due to the instability of *β*-nitroamines **60** the group went on to synthesize the corresponding 1,2-diamines **61** by

reduction of the nitro group with SmI_2. Removal of the amine protecting group with ceric ammonium nitrate (CAN) furnished the bis-primary amines **62**. The presence of acetic acid was found to be crucial for the nitro-Mannich reaction to occur. This is because the addition of a nitronate anion to an imine is thermodynamically disfavored, primarily due to the difference in pK_a values between the nitronate (pK_a 9) and the aza-anion product (pK_a 35). This report represented an important turning point for the development of the nitro-Mannich reaction as it provided a method for the reliable formation of *β*-nitroamines with high levels of diastereoselectivity and demonstrated that they could be converted easily into 1,2-diamines.

Scheme 31. The First Acyclic Diastereoselective Nitro-Mannich Reactions

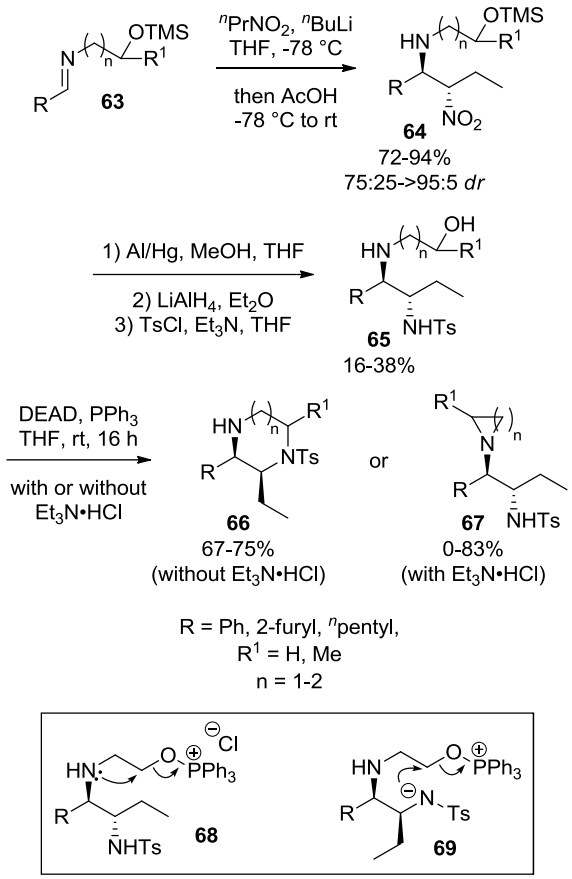


The same group later reported an improvement to this nitro-Mannich protocol by replacing the *N*-PMB-imines with *N*-*ortho*-methoxylbenzyl (OMB)-imines. Using the OMB-protected imines led to improved yields and a higher substrate scope for the reaction.[79] In another report, they expanded the scope of this nitro-Mannich reaction with respect to the imine protecting group and also demonstrated a convenient reduction of unstable *β*-nitroamines using aluminium amalgam.[80]

In 2007, Anderson *et al.* reported the nitro-Mannich reaction of imines derived from ethanolamines and propanolamines, the hydroxyl group of which could later be displaced under

Mitsunobu conditions to form a variety of nitrogen heterocycles including piperazines, 1,4-diazepanes and aziridines (Scheme 32).[81] The AcOH-promoted reaction of imines **63** with the lithium nitronate of 1-nitropropane yielded *β*-nitroamines **64** in good to excellent yields and diastereoselectivities. Reduction of the nitro group using aluminium amalgam and $LiAlH_4$, which simultaneously caused cleavage of the TMS group, followed by tosylation of the primary amine yielded the 1,2-diamines **65**. Under Mitsunobu conditions 1,2-diamines **65** underwent 6-*exo*-tet cyclization to form piperazines **66** (when n = 1) and 1,4-diazepanes (when n = 2) in good yield. Addition of an equivalent of triethylamine hydrochloride was found to reverse the regioselectivity of the reaction to favor 3-*exo*-tet cyclizations, forming aziridines **67** (when n = 1) in good yields. Unfortunately the formation of the four-membered ring analogue (when n = 2) could not be achieved under the reaction conditions. Also, cyclization of secondary alcohols (when R^1 = Me) gave the aziridine products under both sets of reaction conditions. They explain that the change in regioselectivity to favor aziridine formation is due to the $Et_3N{\cdot}HCl$ providing a proton for the formation of intermediate **68**. The most nucleophilic nitrogen in **68** then reacts to form aziridine **67**. In the absence of the proton source deprotonation of the sulfonamide occurs forming intermediate **69** and results in reaction of the nitrogen anion to form a piperazine ring.

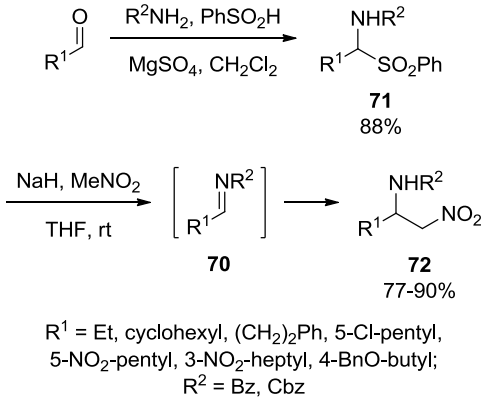
Scheme 32. Piperazine and Aziridine Syntheses



3.2. Reactions of *α*-Amido Sulfones

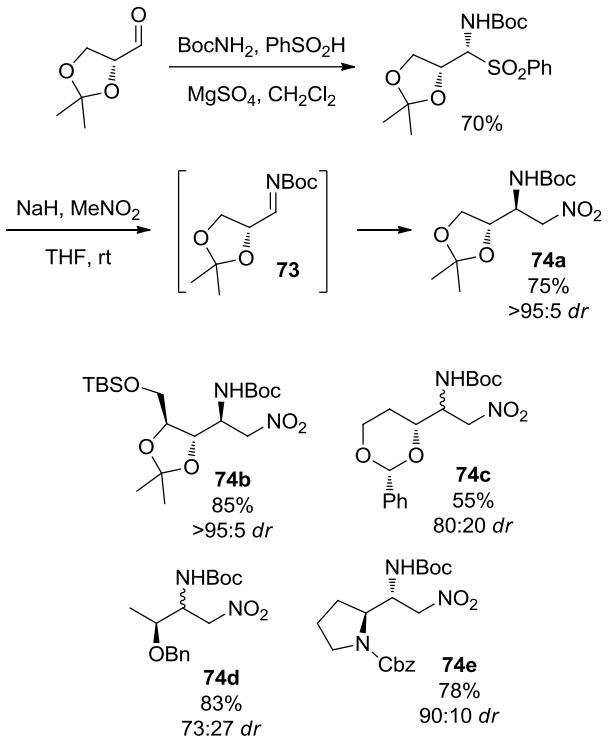
In 1999, Petrini *et al.* investigated the reaction of *in situ* formed *N*-acyl imines **70** with sodium methanenitronate, formed by the reaction of nitromethane with sodium hydride (Scheme 33).[82] Under the basic reaction conditions *α*-amidosulfones **71** eliminate phenylsulfinic acid to form imines **70** which can then undergo nitro-Mannich reactions. The *β*-nitroamide products **72** were formed in excellent yield for a range of alkyl imines and for a number of *N*-acyl protecting groups. The products were also successfully converted to the corresponding amino acid derivatives via Nef reactions. The same group also demonstrated that the same method could be used for the synthesis of *α*,*α*-dipeptides by utilizing *N*-acyl imines derived from amino acids.[83]

Scheme 33. Reactions of α-Amidosulfones with Sodium Methanenitronate



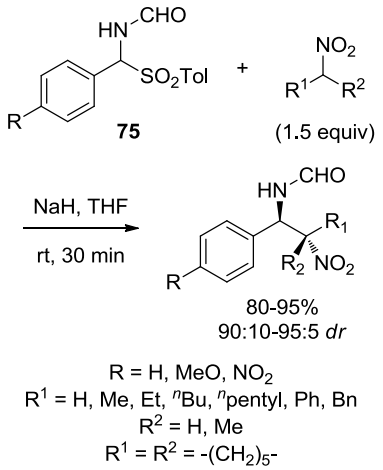
The same group later extended this work to investigate the effect of imines bearing *α*-chiral centres on the diastereoselectivity of the nitro-Mannich reactions (Scheme 34).[84] Optically active *N*-acyl imines **73**, formed from the corresponding *α*-amidosulfones, were reacted with the sodium methanenitronate. Although the *β*-nitroamine products **74** were formed in good yields, the diastereoselectivity of the reaction was found to be highly dependent on the steric influence of the chiral centre *α* to the reaction centre. This was particularly evident in the acyclic product **74d**, which was formed with low diastereoselectivity. Nonetheless, when sterically demanding cyclic structures were in close proximity to the reaction centre the products were formed in excellent yield and diastereoselectivity.

Scheme 34. Nitro-Mannich Reactions of Imines Bearing α Chiral Centres



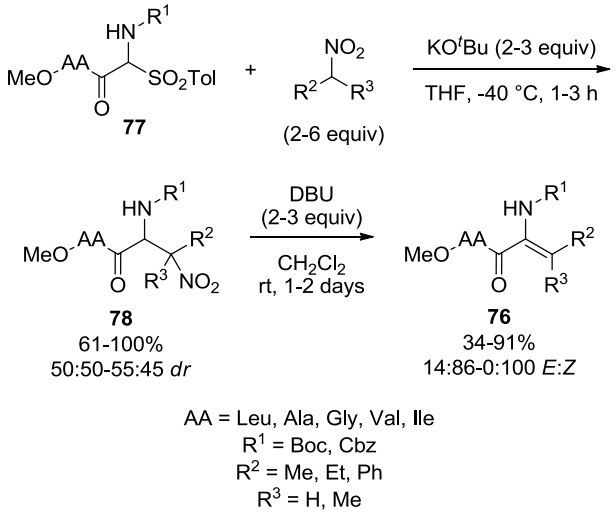
In 2006, Petrini *et al.* published an extension to their sodium hydride mediated nitro-Mannich reactions to include larger nitroalkanes, including both primary and secondary (Scheme 35).[85] The reactions involved the use of *N*-formyl-imines generated *in situ* from *α*-formamidoaryl sulfones **75**. The use of the *N*-formyl-imines provided increased reactivity over the previously used *N*-carbamoyl-imines to allow for short reaction times even when the reactions were performed with sterically hindered tertiary nitroalkanes. The products were formed in excellent yields and with high *anti* diastereoselectivities for a range of aryl imines and nitroalkanes.

Scheme 35. *Anti*-Selective Nitro-Mannich Reactions of *α*-Amidosulfones



In 2004, Kinoshita *et al.* used similar chemistry in the synthesis of *α*,*β*-dehydroamino acids **76** through a nitro-Mannich reaction and subsequent elimination of nitrous acid (Scheme 36).[86] They performed nitro-Mannich reactions between a variety of dipeptide-derived *N*-Boc and *N*-Cbz imines, formed *in situ* from the corresponding *α*-amidosulfones **77**, and a number of nitroalkanes. The *β*-nitroamine products **78** were formed in good to excellent yields, albeit with very low levels of diastereoselectivity. These nitro adducts were then treated with 1,8-diazabicycloundec-7-ene (DBU) to effect elimination of nitrous acid and give the desired of *α*,*β*-dehydroamino acids **76** in good yields and *Z*-selectivity.

Scheme 36. Synthesis of *α*,*β*-Dehydroamino Acids

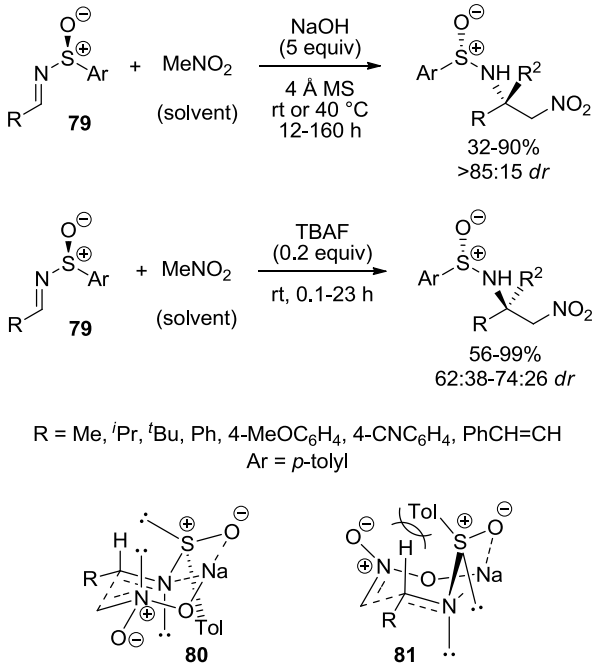


3.3. Auxiliary Controlled Stereoselective Reactions

Other non-catalytic nitro-Mannich reactions reported since 1998 include several asymmetric protocols that make use of imines bearing a chiral auxiliary. The group of Ruano and Cid demonstrated the first use of chiral *N*-sulfinyl imines in nitro-Mannich reactions (Scheme 37). They applied chiral *N*-*p*-tolylsulfinyl imines (**79**) in highly diastereoselective NaOH-mediated nitro-Mannich reactions.[87] The reactions with nitromethane proved to be highly diastereoselective for a range of alkyl and aryl imines. The group also found that the use of substoichiometric amounts of tetrabutylammonium fluoride (TBAF) in the place of NaOH caused a drastic increase in the reaction rate and provided the product in the opposite diastereomeric form. However, the diastereoselectivities were much lower than those obtained for the opposite diastereomer with NaOH. In the same article, the authors also demonstrated the application of their methodology to chiral *N*-sulfinyl ketimines (see Section 7.2.). They account for the high diastereoselectivity of the reaction with NaOH by proposing Na-coordinated six-membered ring transition states. Transition state (TS) **80** is favored due to the destabilizing steric interactions of the bulky *p*-tolyl group in TS **81**. They suggest that the increased reactivity in the

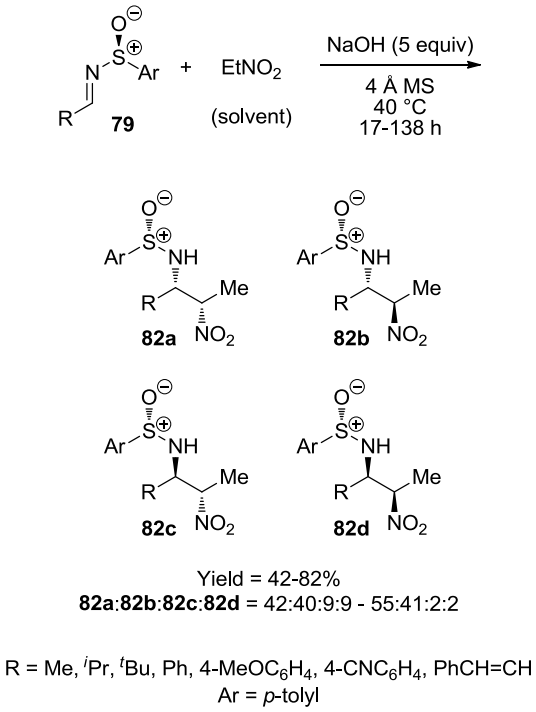
reactions performed with TBAF results from a dual activation of both nitromethane and the imine. This, they say, also prevents the formation of TS **80**, thereby accounting for the change in diastereoselectivity of the reaction.

Scheme 37. Auxiliary Controlled Nitro-Mannich Reactions with Nitromethane



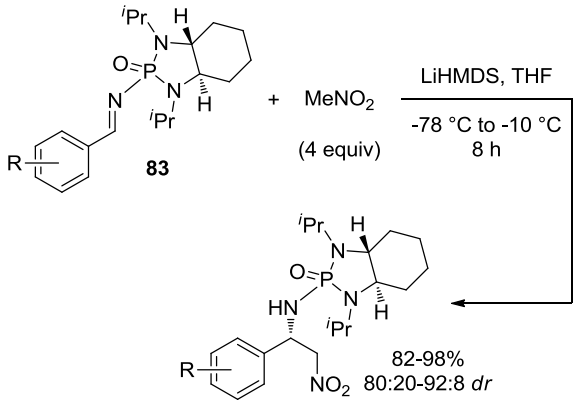
In a later paper, the same group applied their nitro-Mannich conditions to the reaction of nitroethane (Scheme 38).[88] The products **82** were formed in moderate to high yields for a range of *N*-*p*-tolylsulfinyl-imines but with only poor diastereoselectivities. The low diastereoselectivities were found to result from epimerization of the position α to the nitro group under the reaction conditions. Imines derived from ketones failed to undergo any reaction with nitroethane.

Scheme 38. Auxiliary Controlled Nitro-Mannich Reactions with Nitroethane



An alternative chiral imine protecting group was reported by Li *et al.* who used chiral *N*-phosphinoyl imines **83** derived from 1,2-diaminocyclohexane in lithium hexamethyldisilazide (LiHMDS)-mediated nitro-Mannich reactions (Scheme 39).[89–90] The products were formed in excellent yields and good diastereoselectivities for a range of aryl imines. Furthermore, the auxiliary could be removed by treatment with excess aqueous hydrogen bromide and the chiral 1,2-diaminocyclohexane recovered. The recovery of the chiral auxiliary represents an advantage of this method over the use of chiral *N*-sulfinyl imines, which suffer from destruction of the chiral centre in the sulfoxide during removal.

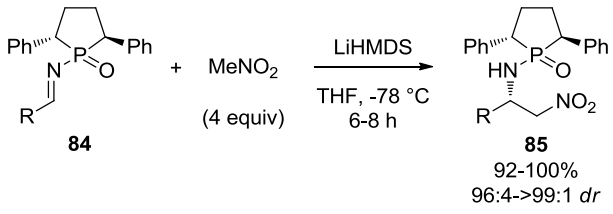
Scheme 39. Auxiliary Controlled Nitro-Mannich Reactions of *N*-Phosphinoyl Imines



R = H, 4-MeO, 2-Me, 4-Me, 4-F, 2-Cl, 4-Cl, 2-Br, 4-Br, 4-CN

In 2011, Li *et al.* reported the use of an improved chiral phosphinoyl auxiliary for use in nitro-Mannich reactions, which enabled efficient purification of the *β*-nitroamine products and easy deprotection and recovery of the auxiliary for reuse (Scheme 40).[91] The use of *N*-phosphinoyl imines **84** instead of **83** enabled the easy preparation of alkyl imines and also ketimines, thereby improving the scope of this auxiliary controlled nitro-Mannich reaction. Under similar conditions to those described in Scheme 39, the new *N*-phosphinoyl imines **84** were transformed into *β*-nitroamines **85** in excellent yields and diastereoselectivities.

Scheme 40. Auxiliary Controlled Nitro-Mannich Reactions of *N*-Phosphinoyl Imines

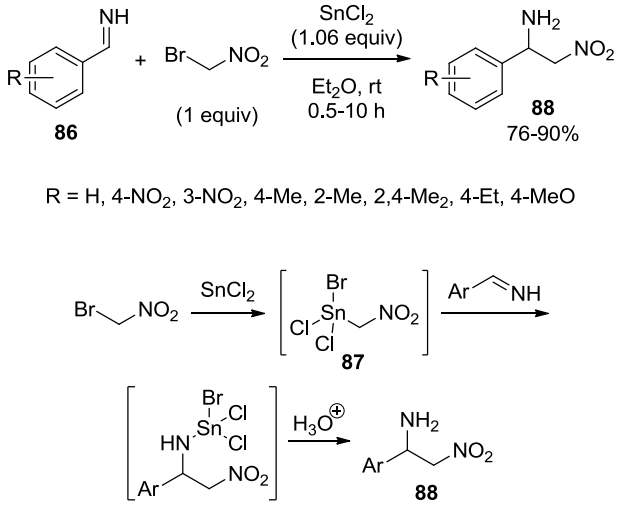


R = Ph, 4-$NO_2C_6H_4$,2-FC_6H_4, 4-FC_6H_4, 2-BrC_6H_4, 4-BrC_6H_4, 2-furyl, 2-MeC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, ^{t}Bu

3.4. Reformatsky-Type Reactions

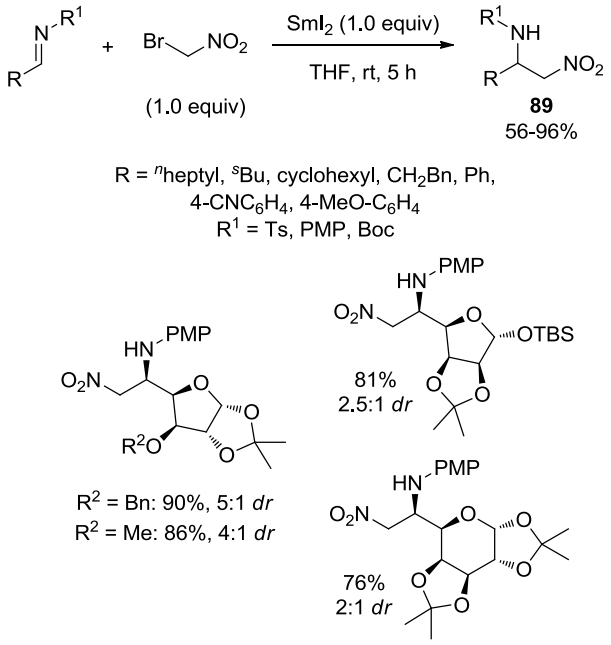
In 2005, the group of Mahasneh published a $SnCl_2$-mediated nitro-Mannich reaction of bromonitromethane with unprotected imines **86** (Scheme 41).[92] They propose a mechanism that proceeds via initial oxidative addition of bromonitromethane to the Sn-centre to form alkyl tin species **87**, similar to a Reformatsky-type reagent. This then undergoes nucleophilic addition to the imine to form *β*-nitroamines **88** upon acidic aqueous workup. The products were formed in good yield for a range of aryl imines.

Scheme 41. Tin-Mediated Reformatsky-Type Nitro-Mannich Reactions



Another Reformatsky-type nitro-Mannich reaction was reported by the group of Rodríguez-Solla in 2012, which involved a SmI_2-mediated reaction of bromonitromethane with a variety of imines (Scheme 42).[93] The reaction gave excellent yields of the *β*-nitroamine products **89** for a range of *N*-tosyl, PMP- and Boc-imines, including those derived from aryl and alkyl aldehydes. Furthermore, they demonstrated that *N*-PMP-imines bearing *α*-chiral centres reacted to give the products in moderate to good diastereoselectivities and with no epimerization.

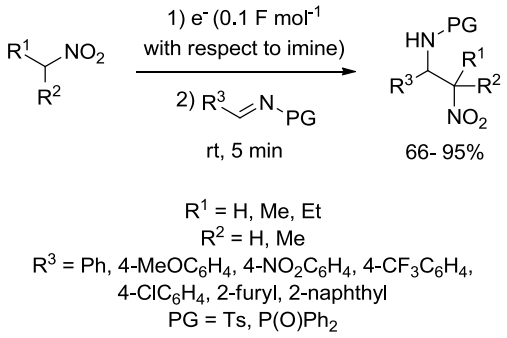
Scheme 42. Samarium-Mediated Reformatsky-Type Nitro-Mannich Reactions



3.5. Electrochemically Induced Nitro-Mannich Reactions

In 2007, the group of Rossi and Inesi reported the only example of an electrochemically induced nitro-Mannich reaction (Scheme 43).[94] The reactions of a variety of *N*-tosyl and *N*-phosphinoyl aryl imines with nitromethane, 1-nitropropane and 2-nitropropane were found to proceed with good to excellent yield under catalyst-, supporting electrolyte- and base-free conditions. The group also claims the reaction to be under solvent-free conditions but they use in excess of 90 equivalents of nitroalkane with respect to imine, therefore the nitroalkane can be regarded as the solvent. The reaction proceeds via initial electrochemical reduction of the nitroalkane and subsequent addition of the imine to the electrochemical cell. The resulting nitro-Mannich reaction then occurs within five minutes at room temperature. The group did not report any diastereoselectivity for the reaction with 1-nitropropane.

Scheme 43. Electrochemically Induced Nitro-Mannich Reactions

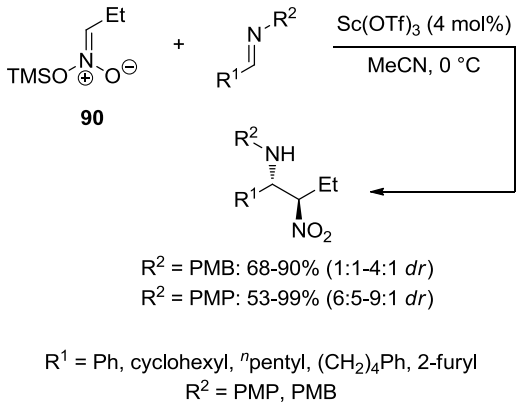


4. INDIRECT METAL-CATALYZED REACTIONS

4.1. Racemic Reactions

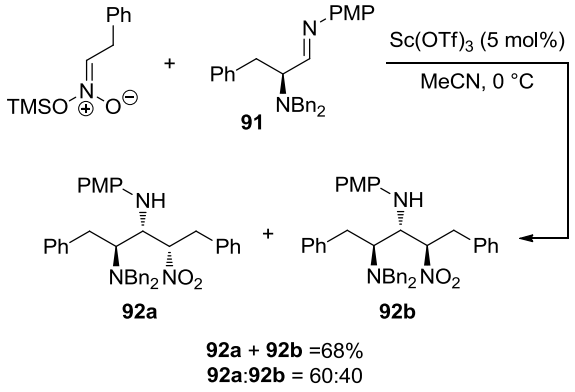
In 2000, the group of Anderson published the first indirect nitro-Mannich reaction.[95] The report detailed their preliminary results in the development of an asymmetric nitro-Mannich reaction, in which they planned to utilize trimethylsilyl (TMS)-nitronates **90** in Lewis acid catalyzed reactions. The use of Lewis acids in the nitro-Mannich reaction of lithium-nitronates only gave acceptable yields when stoichiometric quantities of Lewis acid were used. This was suggested to be a result of the product aza-anion binding too tightly to the Lewis acid. The use of TMS-nitronates allowed the use of catalytic quantities of Lewis acid, thereby providing the opportunity to use a chiral ligand to induce asymmetry into the reaction. The group found $Sc(OTf)_3$ to be an effective Lewis acid for the reaction of TMS-nitronates **90** with a number of alkyl and aryl imines (Scheme 44). The use of *N-para*-methoxyphenyl (PMP)-imines was found to give increased diastereoselectivity and yield in several cases. In a later publication, the same group expanded the substrate scope of this reaction and also provided similarly successful procedures catalyzed by $Cu(OTf)_2$ and $Ti(O^iPr)_4$.[79]

Scheme 44. Lewis Acid Catalyzed Reactions of TMS-Nitronates



This $Sc(OTf)_3$-catalyzed indirect nitro-Mannich reaction was subsequently used by Ricci *et al.* during their investigations into the synthesis of HIV protease inhibitors (Scheme 45).[96] The reaction was performed using *N*-PMP-imine **91** with an *α* chiral centre which could control the stereochemistry of the newly formed stereocentres. Although nitrodiamine **92** was formed in good yield, the reaction was poorly selective with a *dr* of only 60:40 in favor of the *anti*,*syn*-product **92a**.

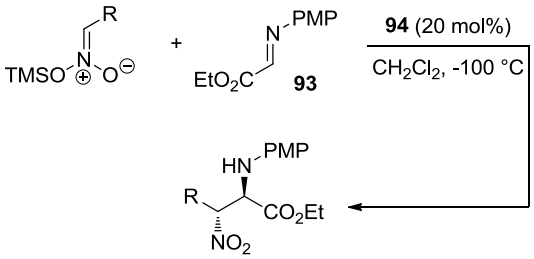
Scheme 45. Synthesis of HIV Protease Inhibitors Using a Lewis Acid Catalyzed Indirect Nitro-Mannich Reaction



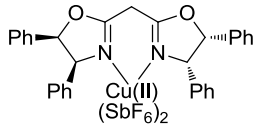
4.2. Asymmetric Reactions

In the year following the initial report of a Lewis acid catalyzed indirect nitro-Mannich reaction, the group of Jørgensen published the first asymmetric nitro-Mannich reactions of TMS-nitronates with ethylglyoxylate-*N*-PMP-imine **93** (Scheme 46).[97] They used Cu(II)-*cis*-DiPh-BOX catalyst **94**, to achieve excellent yields, enantio- and diastereoselectivities. The communication gives several examples to demonstrate the scope of the reaction with respect to the TMS-nitronate but appears to be limited to imines derived from ethylglyoxylate. They account for the stereochemical induction by proposing a mechanism that involves binding of the α-iminoester to the catalyst in a bidentate fashion followed by coordination of the TMS-nitronate to the copper centre.

Scheme 46. Asymmetric Lewis Acid Catalyzed Indirect Nitro-Mannich Reactions

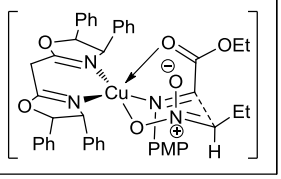


R = Et: 94%, 25:1 *dr*, 95% *ee*
R = ^{n}pentyl: 99%, 39:1 *dr*, 83% *ee*



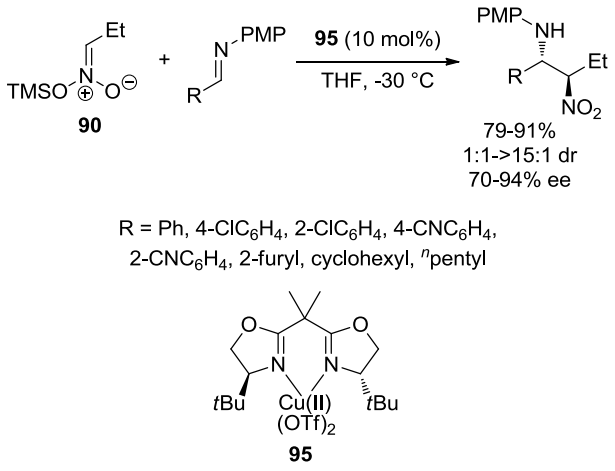
94

Proposed transition state:



In 2005, Anderson *et al.* reported an improved asymmetric Cu-catalyzed indirect nitro-Mannich procedure that used a lower catalyst loading and demonstrated a broad substrate scope with respect to the imine used.[98] The use of Cu(II)-*t*Bu-BOX catalyst **95** promoted the nitro-Mannich reactions to form a range of *β*-nitroamines in excellent yields, diastereo- and enantioselectivities (Scheme 47). They demonstrated that the use of imines capable of bidentate coordination to the catalyst (such as *N*-OMB-imines) prevented the bidentate coordination of the chiral ligand, thereby compromising the stereoinducing effect. The use of *N*-PMP-imines (only capable of monodentate binding to the catalyst) greatly enhanced the stereoselectivity of the reaction.

Scheme 47. Asymmetric Lewis Acid Catalyzed Indirect Nitro-Mannich Reactions



5. DIRECT METAL-CATALYZED REACTIONS

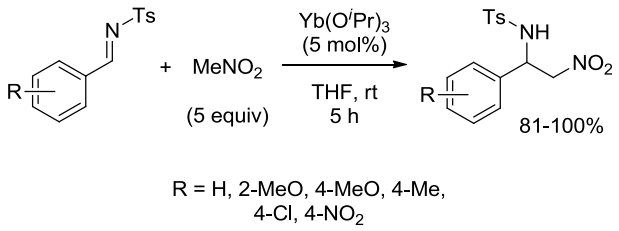
Although the indirect metal-catalyzed nitro-Mannich reactions provide efficient access to *β*-nitroamines in high yield and stereoselectivity, the requirement to preform the silyl-nitronates limits their synthetic utility. A more attractive method would allow the direct coupling of

nitroalkanes with imines via *in situ* nitronate formation. There have to date been a considerable number of reports of both racemic and asymmetric direct metal catalyzed nitro-Mannich reactions, providing ready access to a range of *β*-nitroamines with high levels of diastereo- and enantioselectivity.

5.1. Racemic Reactions

Qian *et al.* reported the first examples of racemic direct metal catalyzed nitro-Mannich reactions in 2001, after the first report of an asymmetric direct metal-catalyzed process by Shibasaki *et al.* in 1999 (see section 5.2). The reaction of nitromethane with *p*-toluenesulfonyl (Ts) imines was effectively catalyzed by $Yb(O^iPr)_3$ (Scheme 48).[99] The products were formed in excellent yield for a range of aryl imines.

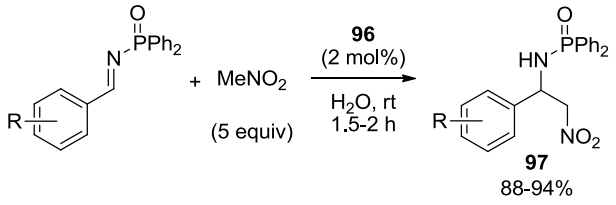
Scheme 48. Ytterbium-Catalyzed Direct Nitro-Mannich Reactions

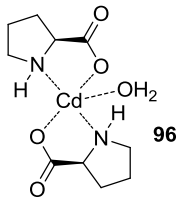


In 2008, the group of Bai and Pan published the only example of a metal catalyzed nitro-Mannich reaction that is performed using water as the solvent (Scheme 49).[100] The reaction of *N*-phosphinoyl aryl imines with nitromethane was effectively catalyzed by Cd-proline complex **96**. Even when low catalyst loadings were used *β*-nitroamines **97** were formed in excellent yields. The authors also demonstrated that the Cd-complex **96**, which acts as a phase transfer catalyst, could be easily recycled as it remained in the aqueous solvent when the reaction products were extracted into EtOAc. Although the catalyst is enantiopure they do not report any

enantioselectivies for the nitro-Mannich reactions, they merely state that when the same Cd-complex is used to catalyze Henry reactions "the *ee* value of the products is very low".

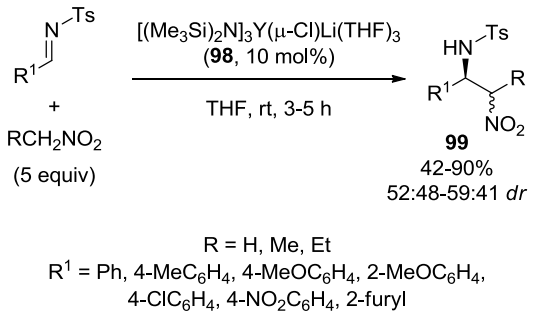
Scheme 49. Cd-Proline Complex-Catalyzed Direct Nitro-Mannich Reactions





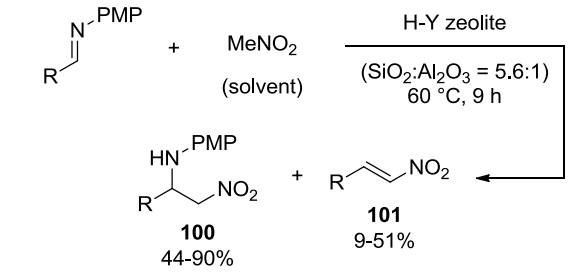
In 2009, Wang *et al.* reported the use of heterobimetallic lanthanide-amide complex **98** to catalyze the reaction of a variety of *N*-tosyl aryl imines with nitromethane, nitroethane and 1-nitropropane (Scheme 50).[101] When using nitromethane the *β*-nitroamine products **99** were formed in good yields (60-90%). However, when the reaction was performed with larger nitroalkanes the yields were significantly lower (42-49%) and very low levels of diastereoselectivity were achieved. Also, the reaction failed to proceed when applied to alkyl imines.

Scheme 50. Lanthanide-Amide-Catalyzed Nitro-Mannich Reactions

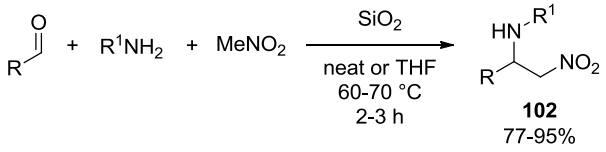


In 2010, Komura *et al.* reported the nitro-Mannich reaction of *N*-PMP aryl imines with nitromethane promoted by a heterogeneous H-Y zeolite catalyst (Scheme 51).[102] The *β*-nitroamine products **100** were isolated in moderate to good yields for a range of aryl and heteroaryl imines. However, problems did arise due to the formation of the corresponding *β*-nitrostyrenes **101**, via elimination of *p*-anisidine, which in some cases were formed as the major product. They propose that the zeolite acts as a Brønsted acid causing activation of the imine. The catalyst could be easily recycled by filtration and showed a similar level of reactivity after three recycles. Reactivation of the catalyst by calcination at 550 °C under air flow restored its activity. Similarly, the group of Mahasneh reported a silica gel-mediated nitro-Mannich reaction between nitromethane and a variety of aldehydes and arylamines (Scheme 51).[103] The products **102** were formed in good yields (Scheme 51).

Scheme 51. Nitro-Mannich Reactions Promoted by Silica-Based Heterogeneous Catalysts



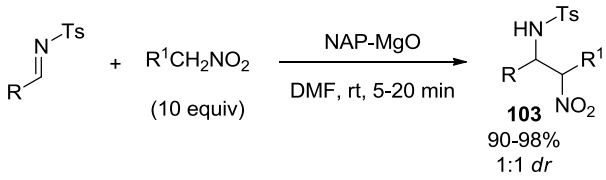
R = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-$NO_2C_6H_4$, 2-furyl, 2-thienyl



R = H, Ph, 2-MeC_6H_4, 4-EtC_6H_4, 3-$NO_2C_6H_4$, 4-HOC_6H_4, 4-$MeOC_6H_4$, 2,4-$Cl_2C_6H_3$, 1-naphthyl, 2-naphthyl
R^1 = Ph, 4-BrC_6H_4, 4-$NO_2C_6H_4$, 4-MeC_6H_4

In 2011, Kantam *et al.* reported the reaction of nitroalkanes with *N*-tosyl imines catalyzed by nanocrystalline magnesium oxide (NAP-MgO) (Scheme 52).[104] This heterogeneous catalyst enabled the formation of *β*-nitroamines **103** in excellent yields for a number of aryl and heteroaryl imines and simple nitroalkanes, although no diastereoselectivity was observed in the reactions of nitroethane and 1-nitropropane. The group also demonstrated that the catalyst could be effectively recovered by centrifugation and reused three times with consistent activity.

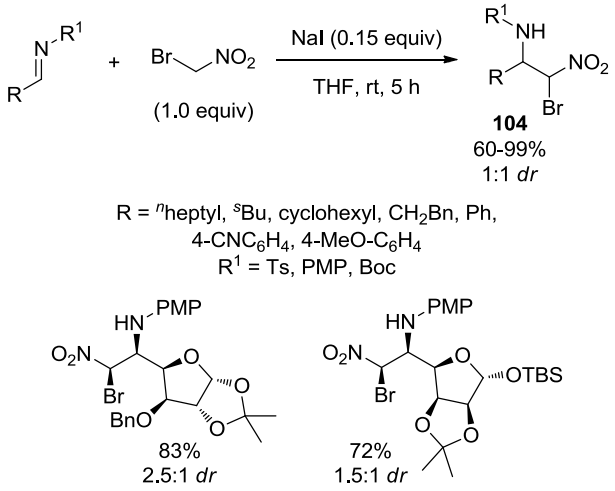
Scheme 52. Nitro-Mannich Reactions Catalyzed by Nanocrystalline Magnesium Oxide



R = Ph, 4-ClC_6H_4, 4-$NO_2C_6H_4$, 4-$MeOC_6H_4$, 4-$CF_3C_6H_4$, 2-furyl
R^1 = H, Me, Et

In the same article in which they reported their SmI_2-mediated Reformatsky-type nitro-Mannich reactions, Rodríguez-Solla *et al.* also demonstrated that catalytic sodium iodide could be used to promote the nitro-Mannich reaction of bromonitromethane with a variety of imines (Scheme 53).[93] The product *β*-bromo-*β*-nitroamines **104** where formed in good to excellent yields for *N*-tosyl-, PMP- and Boc-imines derived from aryl and alkyl aldehydes, albeit with low to no diastereoselectivity. The reaction was also demonstrated to be applicable to *N*-PMP-imines bearing *α*-chiral centres, with the products formed in moderate diastereoselectivities.

Scheme 53. Sodium Iodide-Catalyzed Nitro-Mannich Reactions

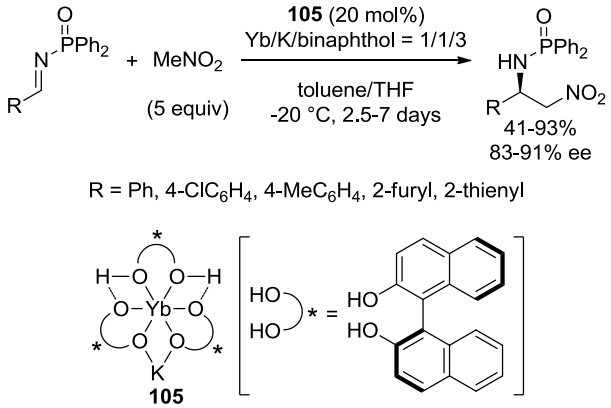


5.2. Asymmetric Reactions

The first example of an asymmetric direct metal-catalyzed nitro-Mannich reaction was reported by Shibasaki *et al.* in 1999.[105] They used the Yb/K heterobimetallic complex **105**, which contains both Lewis acidic and Brønsted basic sites, for the reaction between nitromethane and a variety of *N*-phosphinoyl-aryl imines (Scheme 54). The catalyst successfully promoted the nitro-Mannich reaction in excellent enantioselectivities, however, the catalyst failed to promote

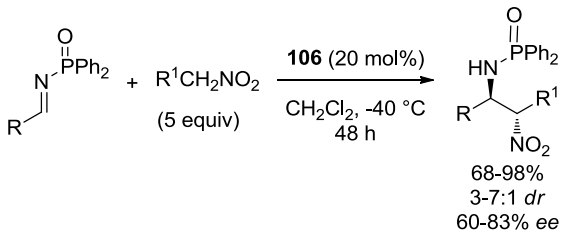
the reaction of higher homologues of nitromethane, such as nitroethane. Furthermore, for optimal selectivity the use of 60 mol% of the chiral ligand was required.

Scheme 54. Direct Nitro-Mannich Reactions Catalyzed by Yb/K/Binaphthoxide-Catalyst **105**

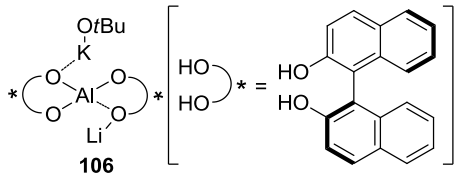


In 2001, the same group reported the use of Al/Li/binaphthoxide-KO*t*Bu catalyst **106** to promote the reaction of larger nitroalkanes with *N*-phosphinoyl-aryl imines (Scheme 55).[106] The larger binding pocket of **106** compared to **105** was proposed to be responsible for the increased reactivity with larger nitroalkanes. The *β*-nitroamines were formed in excellent yield and good diastereo- and enantioselectivity.

Scheme 55. Direct Nitro-Mannich Reactions Catalyzed by Al/Li/Binaphthoxide-KO*t*Bu Catalyst **106**



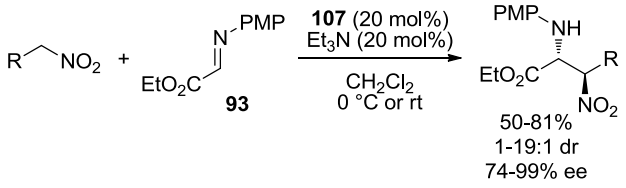
R = Ph, 4-MeOC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$
R^1 = Me, Et, (CH$_2$)$_2$OBn



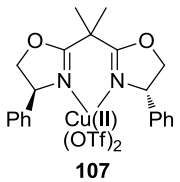
106

In the same year, Jørgensen *et al.* reported an improvement to their Cu(II)-*cis*-DiPh-bis(oxazoline) (BOX) (**94**)-catalyzed nitro-Mannich reactions of TMS-nitronates (see Scheme 46). The use of TMS-nitronates was avoided through the use of catalytic amounts of organic base in the reaction (Scheme 56).[107] They used Cu(II)-Ph-BOX catalyst **107** with catalytic triethylamine to promote the direct nitro-Mannich between a variety of nitroalkanes and *α*-iminoester **93**. The reaction gave moderate to good yields and stereoselectivities, however, only imine **93** was compatible with the reaction conditions, therefore, limiting its substrate scope.

Scheme 56. Direct Nitro-Mannich Reactions Catalyzed by Et$_3$N and Cu(II)-Ph-BOX **107**



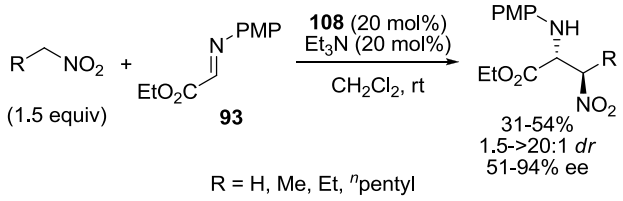
R = Me, Et, ^{n}pentyl, Bn, Ph

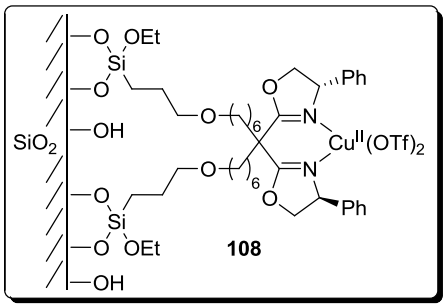


107

In 2004, Hyeon *et al.* reported a modified procedure to that reported by Jørgensen *et al.* which involved the use of the silica-grafted Cu(II)-BOX catalyst **108** (Scheme 57).[108] They aimed to generate a protocol that uses a catalyst immobilized on a solid support, thereby allowing the expensive chiral BOX ligand to be recycled. They used their silica-Cu(II)-BOX catalyst **108** under the same conditions that were described by Jørgensen *et al*. However, their heterogeneous reactions failed to provide the same high yields and selectivities, with only modest yields and moderate to good stereoselectivities. The catalyst could be easily recovered and after it was recycled five times a comparable level of yield of the product was maintained for each of the nitroalkanes investigated. However, considerable drops in diastereo- and enantioselectivity were observed upon each recycling of the catalyst.

Scheme 57. Asymmetric Silica-Cu-BOX-Catalyzed Nitro-Mannich Reaction

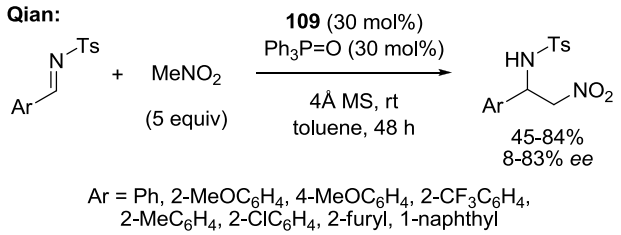


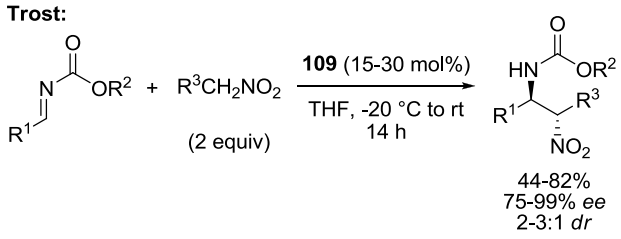


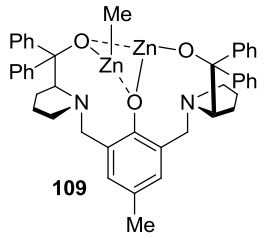
In 2006, Qian *et al.* reported the enantioselective reaction between *N*-tosyl imines and nitromethane catalyzed by binuclear zinc complex **109** (Scheme 58).[109] The product *β*-nitroamines were formed in moderate to good yields and enantioselectivities for a range of aryl imines. In the following year, Trost *et al.* reported an improved procedure that utilized the same

binuclear zinc complex **109** (Scheme 58).[110] They found that the nitro-Mannich reaction of a variety of *N*-carbamate-imines and nitroalkanes was effectively catalyzed by **109** providing *β*-nitroamines in high levels of enantioselectivity. The scope of the reaction was also extended to larger nitroalkanes, which gave the products in modest diastereoselectivities. Although the reactions of enolizable imines were not reported due to their instability, the group extended the scope of the nitro-Mannich reaction to a variety of *α*,*β*-unsaturated imines. The products of these reactions were formed in lower yields than with aryl imines due to the instability of the *α*,*β*-unsaturated imines, but the enantioselectivities were uniformly high. The authors proposed a catalytic cycle that highlights the dual Lewis acid/Lewis basic functionality of catalyst **109**, including initial deprotonation of nitromethane to form a zinc nitronate intermediate, followed by binding of the imine and subsequent attack by the nitronate.

Scheme 58. Nitro-Mannich Reactions Catalyzed by Dinuclear Zinc Complex **109**

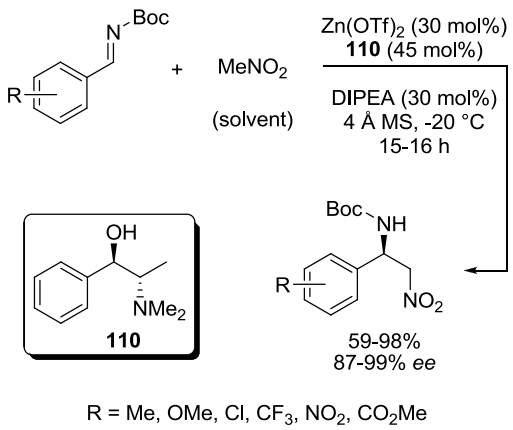






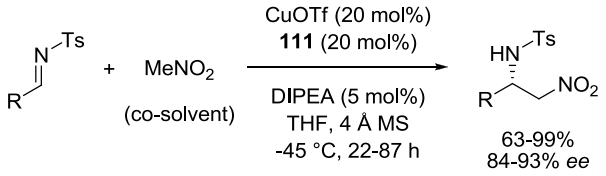
Palomo *et al.* reported the use of a much simpler cooperative catalyst system consisting of *N*-methylephedrine (**110**), diisopropylethylamine (DIPEA) and $Zn(OTf)_2$.[111] This catalyzed the reaction between nitromethane and a number of *N*-Boc-aryl-imines to give the products in good yields and with high enantioselectivities (Scheme 59). However, the authors failed to report the nitro-Mannich reaction with any nitroalkanes other than nitromethane and high catalyst loadings were required to achieve good selectivities. Furthermore, the use of the nitroalkane as the solvent limits this method to the use of simple nitroalkanes.

Scheme 59. $Zn(OTf)_2$/*N*-Methylephedrine-Catalyzed Nitro-Mannich Reaction

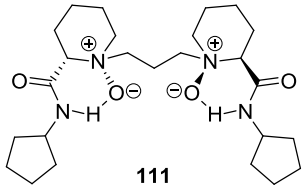


In 2007, Feng *et al.* reported the enantioselective nitro-Mannich reaction of *N*-tosyl-aryl-imines and nitromethane catalyzed by a chiral *N*,*N*'-dioxide **111**-Cu(I) complex and DIPEA (Scheme 60).[112] The optimized conditions gave excellent yields and enantioselectivities for a range of aryl and heteroaryl imines. However, the reaction failed to give satisfactory results for *α*,*β*-unsaturated imines and alkyl imines. They proposed a catalytic cyclic proceeding via complex **112**, which involves coordination of the imine to the Lewis acidic Cu(I)-centre and a hydrogen-bonding interaction between a nitronate species and an amide group of the catalyst. This directs the nitronate to the *Re* face of the imine to give the observed (*S*)-enantiomer of the *β*-nitroamine product.

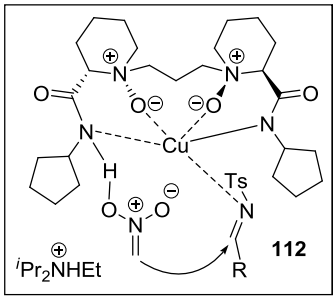
Scheme 60. Chiral *N*,*N*'-dioxide **111**-Cu(I)-Catalyzed Nitro-Mannich Reactions



R = Ph, 1-naphthyl, 2-naphthyl, 2-MeC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 2-furyl, 3,4-$(OCH_2O)C_6H_4$



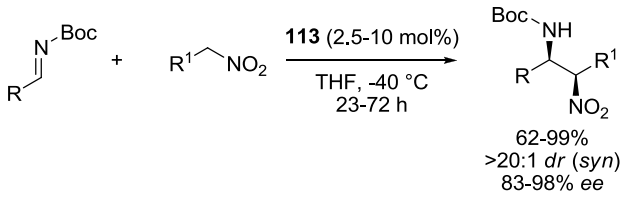
111



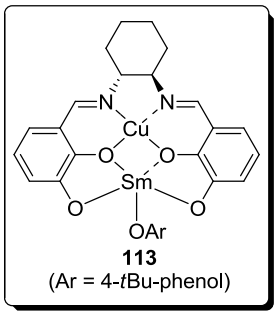
112

The most successful direct metal-catalyzed nitro-Mannich reaction to date is an improved procedure from the group of Shibasaki.[113] Through the use of heterobimetallic Cu-Sm-Schiff base complex **113** the group were able to perform highly *syn*-selective nitro-Mannich reactions between a range of *N*-Boc-aryl and alkyl imines and nitroethane and 1-nitropropane (Scheme 61). The *syn*-*β*-nitroamines were obtained in excellent yield and enantio- and diastereoselectivities. The excellent *syn*-selectivities obtained from this method are in stark contrast to all previously reported methods, and most published since, which are generally highly selective for the *anti*-diastereomer.

Scheme 61. Heterobimetallic Cu-Sm-Schiff Base (**113**) Catalyzed *syn*-Selective Nitro-Mannich Reactions



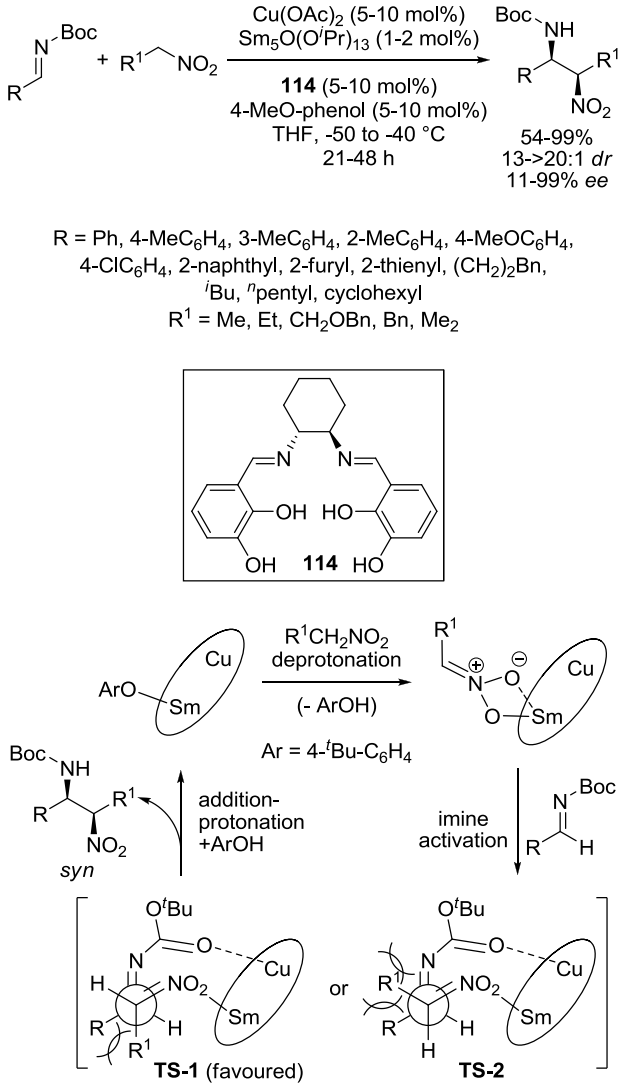
R = Ph, 1-naphthyl, 2-furyl, 3-MeC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, CH_2Bn
R^1 = Me, Et



113
(Ar = 4-*t*Bu-phenol)

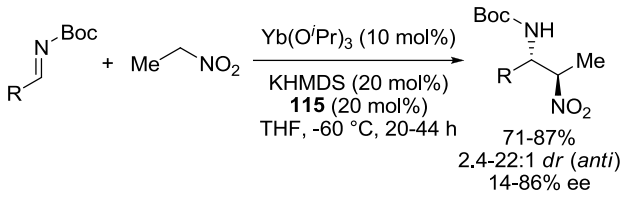
In a later publication the same group reported the development of a second generation catalyst formed from the reaction of Schiff base **114**, $Cu(OAc)_2$, $Sm_5O(O^iPr)_{13}$ and 4-methoxyphenol (Scheme 62).[114] This catalyst system demonstrated greater activity and an improved substrate scope, especially with respect to *N*-Boc alkyl imines. The authors also carried out extensive mechanistic studies and determined the active catalyst to be a trimeric species. Cooperative dual activation of both the nitroalkane and imine by Sm and Cu are crucial for the *syn*-selectivity. The Sm-aryl oxide moiety in the catalyst acts as a Brønsted base to generate a Sm-nitronate, while the Cu(II) acts as a Lewis acid to control the position of the Boc-imine. The group proposes the reaction to proceed via sterically less hindered **TS-1**, which would be favored over **TS-2**, to give the *syn*-product upon protonation with 4-^{t}Bu-phenol.

Scheme 62. Second Generation Catalyst and Proposed Mechanism of Shibasaki's *syn*-Selective Nitro-Mannich Reactions

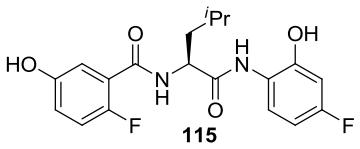


The same group also published a complimentary *anti*-selective nitro-Mannich using a heterobimetallic catalyst derived from amide **115** (Scheme 63).[115] Although this catalyst system provided good yields and diastereoselectivities, the enantioselectivities failed to match those of their *syn*-selective protocol.

Scheme 63. Heterobimetallic Yb/K/Amide **115**-Catalyzed *anti*-Selective Nitro-Mannich Reactions



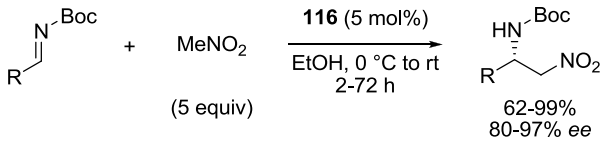
R = Ph, 2-naphthyl, 3-MeC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-$CF_3C_6H_4$



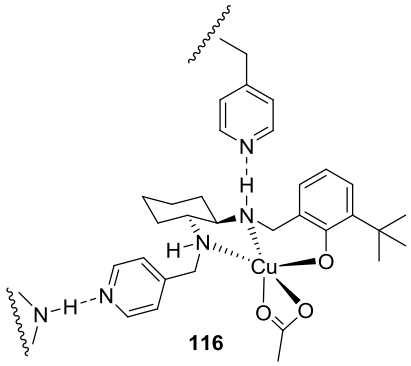
115

In 2009, Woggon *et al.* reported the use of supramolecular Cu(II) complex **116** for the nitro-Mannich reactions of *N*-Boc aryl imines with nitromethane (Scheme 64).[116] The reaction of chiral diamine ligands with $Cu(OAc)_2$ generated complexes that formed helical supramolecular structures via hydrogen bonds between the pyridine nitrogen and the N–H group adjacent to the phenolate. When applied to the nitro-Mannich of *N*-Boc imines with nitromethane the *β*-nitroamine products were formed in good to excellent yields and enantioselectivities. The same complex also gave excellent results when applied to Henry reactions of aryl- and alkyl-aldehydes with nitromethane.

Scheme 64. Nitro-Mannich Reactions Catalyzed by Supramolecular Cu(II) Complex **116**



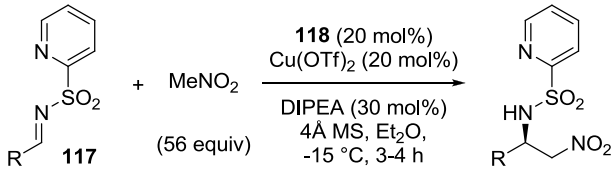
R = Ph, 4-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 2-$NO_2C_6H_4$, 4-$MeO_2CC_6H_4$, 4-CNC_6H_4, 1-naphthyl, 3-pyridyl, 4-MeC_6H_4, 2-MeC_6H_4, 4-$CF_3C_6H_4$, 4-$MeOC_6H_4$, 3-$MeOC_6H_4$, 4-ClC_6H_4,



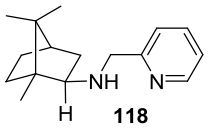
116

In 2012, the group of Blay and Pedro reported the enantioselective Cu-catalyzed nitro-Mannich reactions of *N*-(2-pyridyl)sulfonyl imines **117** with nitromethane (Scheme 65).[117] They used chiral amino-pyridine ligand **118** in combination with $Cu(OTf)_2$ and DIPEA to form the *β*-nitroamine products in moderate to good yields and enantioselectivities. No examples of the use of alkyl imines were given and no diastereoselective reactions with larger nitroalkanes were reported. The authors went on to demonstrate that an advantage of the *N*-(2-pyridyl)sulfonyl group is that it can be removed under milder conditions than other *N*-sulfonyl groups. They found that treatment with magnesium in MeOH-THF provided a good yield for this transformation.

Scheme 65. Cu(II)-Catalyzed Nitro-Mannich Reactions of *N*-(2-Pyridyl)sulfonyl Imines



R = Ph, 2-$MeOC_6H_4$, 3-$MeOC_6H_4$, 4-$MeOC_6H_4$, 2-MeC_6H_4, 3-MeC_6H_4, 3-MeC_6H_4, 2-ClC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, 3-thienyl, 3-furyl



118

6. ORGANOCATALYTIC REACTIONS

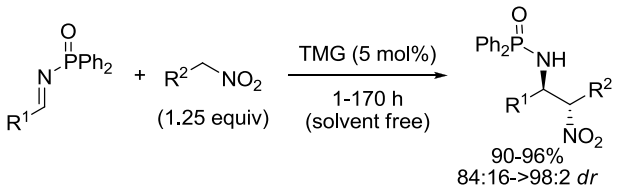
Small molecule organocatalysis has emerged as an extremely powerful tool for asymmetric synthesis, and has been successfully applied to a whole host of C–C bond forming processes.[16–20] Consequently, a number of different organocatalysts have been developed for use in nitro-Mannich reactions. These include a variety of different chiral thioureas, Brønsted acids and phase transfers catalysts that are able to catalyze highly stereoselective reactions. There have also been a number of examples of racemic nitro-Mannich reactions using achiral organocatalysts.

6.1. Racemic Reactions

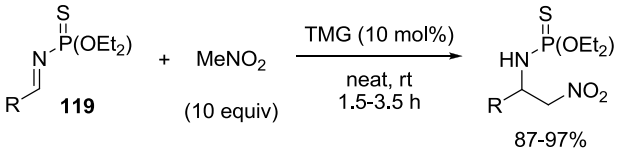
In 2004, the group of Bernardi and Ricci published a nitro-Mannich reaction of *N*-phosphinoyl imines catalyzed by 1,1,3,3-tetramethylguanidine (TMG) (Scheme 66).[118] The products were formed in excellent yields and with excellent *anti*-diastereoselectivities. Their aim was to develop a more environmentally friendly nitro-Mannich protocol, which was achieved by performing the reactions under solvent free conditions and with only a slight excess of nitroalkane. Furthermore, the use of solvents was avoided during workup by distilling off the catalyst and excess nitroalkane from the crude reaction mixture to yield spectroscopically pure

product. They were also able to perform a one-pot nitro-Mannich/reduction/deprotection sequence to yield the corresponding free 1,2-diamines in good yield. In 2009, Zhou *et al.* reported another TMG-catalyzed nitro-Mannich reaction. They demonstrated the first use of *N*-thiophosphoryl imines **119** in organocatalyzed nitro-Mannich reactions with nitromethane (Scheme 66).[120] These reactions were efficiently catalyzed by TMG under solvent-free conditions to give the *β*-nitroamine products in excellent yield.

Scheme 66. TMG-Catalyzed Nitro-Mannich Reactions



R^1 =Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$, 2-furyl, 2-thienyl, ^{t}Bu
R^2 = H, Et, ^{n}pentyl, Bn

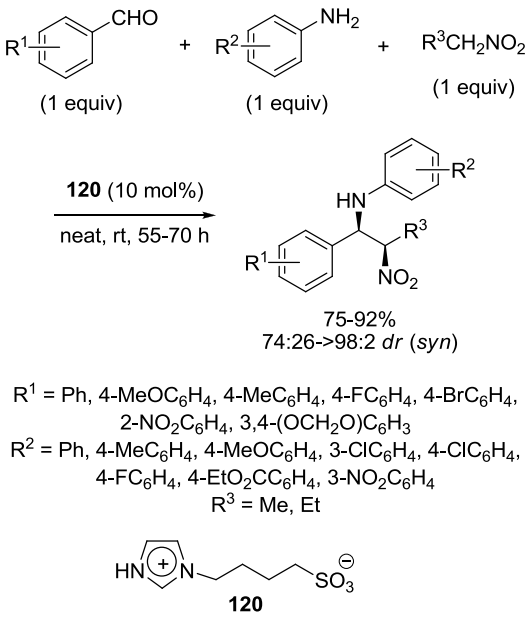


R = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 3-$MeOC_6H_4$, 2-$MeOC_6H_4$, 2-ClC_6H_4, 2-$CF_3C_6H_4$, 3-FC_6H_4, 2-furyl

In 2009, Hajra *et al.* reported the first example of a nitro-Mannich reaction promoted by a zwitterionic-type molten salt (Scheme 67).[119] They used imidazole-based catalyst **120** to catalyze the diastereoselective three-component reaction of a variety of benzaldehydes and anilines with nitroethane and 1-nitropropane. The reactions were performed under solvent- and metal free conditions, at ambient temperature, and with all the substrates used in equimolar amounts making this a relatively environmentally friendly method. Furthermore, the product *β*-nitroamines were formed with very rare *syn*-diastereoselectivity (confirmed by X-ray crystal

analysis) in high diastereoselectivity. The reaction gave excellent yields and good to excellent *syn*-diastereoselectivities for a range of aryl aldehydes and amines. However, reactions with alkyl aldehydes and amines were found to proceed sluggishly and none of the desired products could be isolated. They also investigated the recovery and reusability of catalyst **120** and found that it could be easily recovered and demonstrated similar activity, in terms of yield and diastereoselectivity, after five recycles.

Scheme 67. Zwitterionic Molten Salt **120**-Catalyzed Nitro-Mannich Reactions



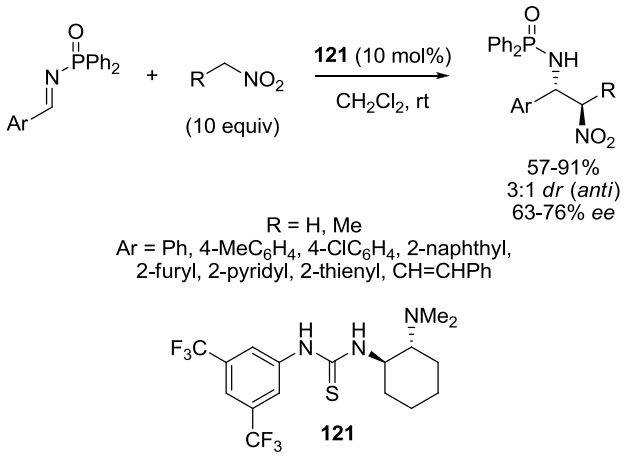
6.2. Asymmetric Reactions

6.2.1. Urea/Thiourea Catalysts

The first asymmetric organocatalyzed nitro-Mannich reaction was reported by the group of Takemoto in 2004.[121] The group applied thiourea catalyst **121**, previously developed for use in asymmetric Michael additions,[122] to the reaction of nitromethane and a range of *N*-phosphinoyl-

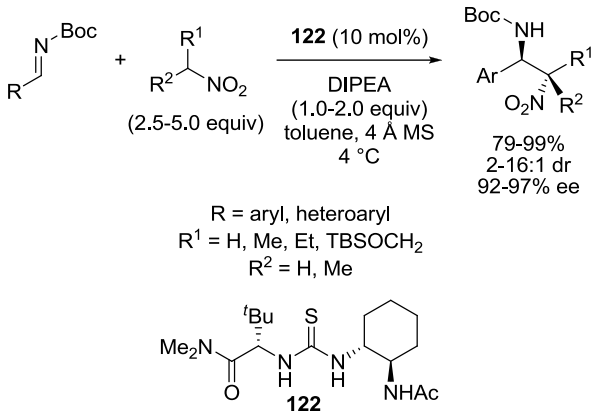
aryl imines (Scheme 68). The reactions were high yielding but only gave moderate enantioselectivities. Only a single diastereoselective example was given by using nitroethane to form the product in a modest 3:1 *dr* in favor of the *anti*-diastereomer.

Scheme 68. The First Asymmetric Organocatalytic Nitro-Mannich Reaction



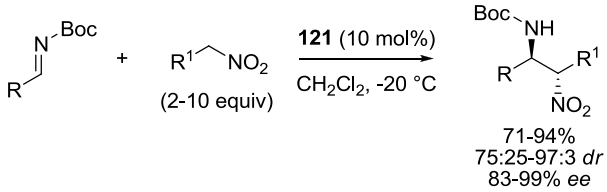
In 2005, Jacobsen *et al*. demonstrated the use of thiourea catalyst **122** as a very efficient catalyst for the nitro-Mannich reaction between nitroethane and *N*-Boc-aryl-imines (Scheme 69).[123] Although the yields and stereoselectivities were comparable to those obtained using Takemoto's protocol, the lack of a basic functionality in the catalyst required the addition of an equivalent of a tertiary amine base for the reaction to reach completion.

Scheme 69. Jacobsen's Thiourea Catalyzed Nitro-Mannich Reactions

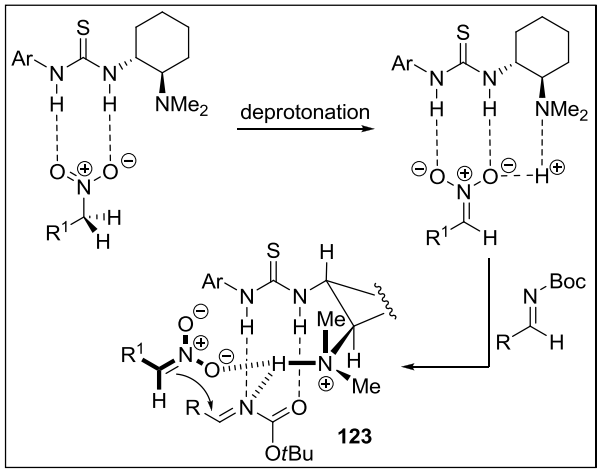


Inspired by the excellent results obtained by other groups when using *N*-Boc-aryl-imines, Takemoto's group later reported an improvement to their thiourea-catalyzed method by using *N*-Boc-imines (Scheme 70).[124] While still using catalyst **121**, changing from *N*-phosphinoyl-imines to *N*-Boc-imines enabled the formation of *β*-nitroamines with much higher enantioselectivities. They also demonstrated an improved scope of the reaction with respect to the nitroalkane used, with good to excellent diastereoselectivities achieved for a range of functionalized nitroalkanes. Their proposed mechanism proceeds via ternary complex **123** consisting of the imine and nitronate coordinated to the thiourea and tertiary amino group of catalyst **121** by hydrogen bonding. The thiourea moiety functions both to activate the *N*-Boc-imine and also to aid in the deprotonation of the nitroalkane.

Scheme 70. Thiourea **121**-Catalyzed Nitro-Mannich Reactions of *N*-Boc-Imines



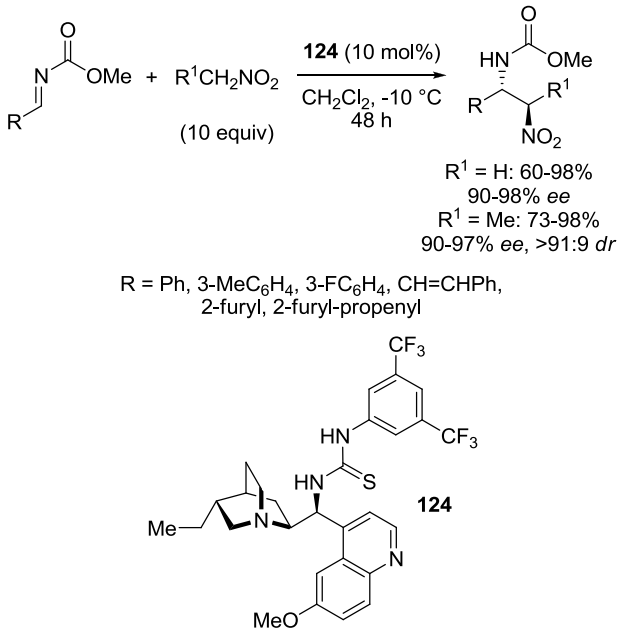
R = Ph, 4-$CF_3C_6H_4$, 4-MeC_6H_4, 4-$MeOC_6H_4$, 1-naphthyl, 2-naphthyl, 2-furyl, 2-thienyl, 3-pyridyl
R^1 = H, Me, ^{n}Bu, Bn, CH_2OBn, $(CH_2)_2OBn$, $(CH_2)_3OBn$, $(CH_2)_2OH$, $(CH_2)_2OTf$



Since the reports by Takemoto[121,124] and Jacobsen[123] on the application of thiourea-based organocatalysts to asymmetric nitro-Mannich reactions, there have been a large number of publications from other groups demonstrating the use of thioureas bearing various chiral scaffolds. These include catalysts derived structures including from cinchona alkaloids,[125–126] chiral sulfonamides,[127] glycosides[128] and steroids.[129]

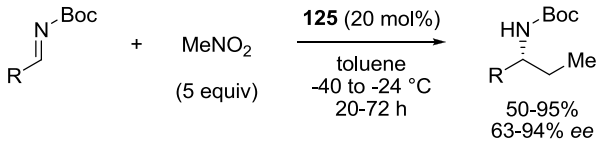
In 2006, Schaus *et al.* published an asymmetric nitro-Mannich reaction catalyzed by hydroquinine-based thiourea **124** (Scheme 71).[125] The reaction of a variety of methyl carbamate aryl imines with nitromethane and nitroethane was accomplished in excellent yields and diastereo- and enantioselectivities. The authors also modelled the transition states leading to both enantiomeric products and found a 1.6 kcal/mol energy difference in favor of the observed *Si*-facial attack of nitromethane.

Scheme 71. Hydroquinine-Based Thiourea **124**-Catalyzed Nitro-Mannich Reactions

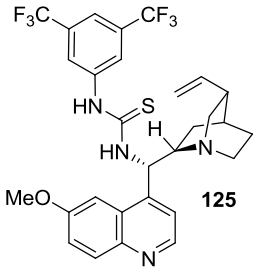


In the month following the report by the group of Schaus, Ricci *et al.* published a similar nitro-Mannich reaction catalyzed by quinine-based thiourea **125** (Scheme 72).[126] The group used *N*-Boc-aryl imines in nitro-Mannich reactions with nitromethane to form *β*-nitroamines in good to excellent yields and enantioselectivities. The reactions were also shown to be high yielding and enantioselective with a variety of other *N*-acyl protecting groups, including Cbz and Fmoc.

Scheme 72. Quinine-Based Thiourea **125**-Catalyzed Nitro-Mannich Reactions



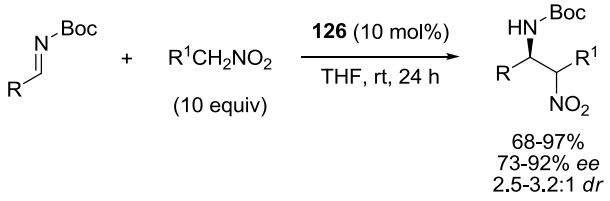
R = Ph, 1-naphthyl, 2-naphthyl, 4-ClC_6H_4, 2-BrC_6H_4, 4-$MeOC_6H_4$, 2-furyl, 2-thienyl



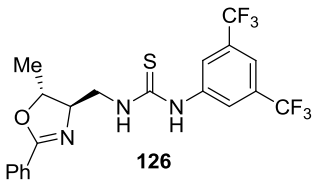
125

In 2007, Chang *et al.* reported the use of the chiral oxazoline-thiourea catalyst **126** in asymmetric nitro-Mannich reactions of nitromethane with a number of *N*-Boc-aryl imines (Scheme 73).[130] The *β*-nitroamine products were formed in excellent yields and good to excellent enantioselectivities. The authors also reported the reactions of nitroethane and nitropropane, which gave the products in excellent yield and enantioselectivity but only modest diastereoselectivity. The authors also failed to report the relative stereochemistry of the major diastereomers.

Scheme 73. Oxazoline-Thiourea **126**-Catalyzed Nitro-Mannich Reactions



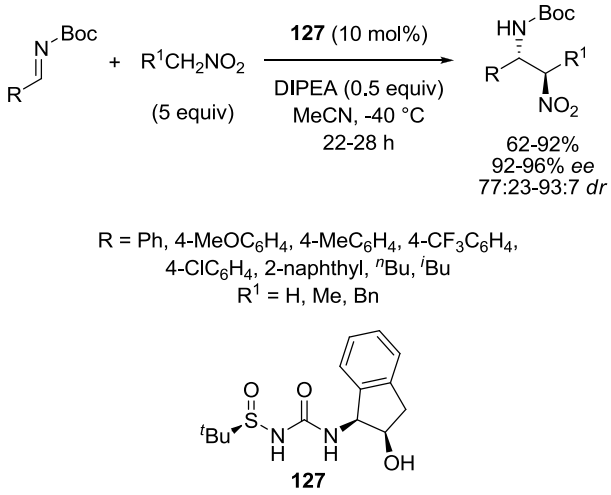
R = Ph, 2-MeC_6H_4, 4-MeC_6H_4, 3-$MeOC_6H_4$, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-$F_3CC_6H_4$, 4-$NO_2C_6H_4$, 4-$NO_2C_6H_4$
R^1 = H, Me, Et



126

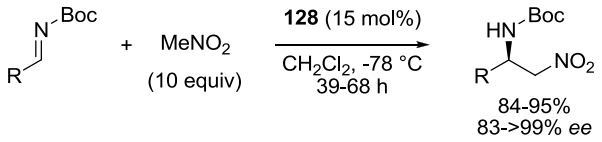
In the same year, Ellman *et al.* reported the use chiral *N*-sulfinyl-urea **127** to catalyze the reaction of *N*-Boc-imines with a number of nitroalkanes (Scheme 74).[127] The products were formed in good yields and diastereoselectivities and excellent enantioselectivities. The reaction was also successfully performed with a number of enolizable imines, the use of which had not previously been demonstrated in hydrogen-bonding catalysis.

Scheme 74. *N*-Sulfinyl-Urea **127**-Catalyzed Nitro-Mannich Reactions

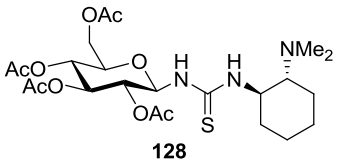


In 2008, Zhou *et al.* reported the use of glycosyl-based thiourea **128** in the highly enantioselective nitro-Mannich reactions of *N*-Boc aryl imines with nitromethane (Scheme 75).[128] The *β*-nitroamine products were formed in excellent yields and enantioselectivities for a range of aryl imines. The catalyst also provided high enantioselectivity for nitro-Mannich reactions with nitroethane. Good *anti*-diastereoselectivity was achieved with the benzaldehyde-derived imine but when substituted aryl imines were utilized the diastereoselectivities were very low.

Scheme 75. Glycosyl-Based Thiourea **128**-Catalyzed Nitro-Mannich Reactions



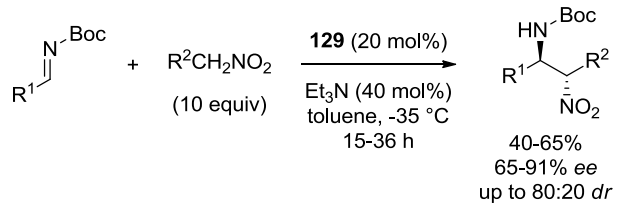
R = Ph, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-ClC_6H_4, 2-ClC_6H_4, 4-$CF_3C_6H_4$, 3-$CF_3C_6H_4$, 2-$CF_3C_6H_4$, 2-furyl, 1-naphthyl



128

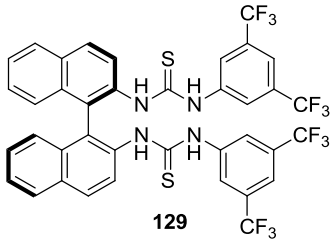
In the same year, Wulff reported the use of BINAP-based bis-thiourea catalyst **129** in the nitro-Mannich reaction of *N*-Boc aryl imines with a number of nitroalkanes (Scheme 76).[131] The product *β*-nitroamines were formed in moderate yields and moderate to good enantioselectivities. The yield and enantioselectivities obtained in the reactions with nitroethane and nitropropane were similar to those obtained with nitromethane but the diastereoselectivities were only moderate, with a maximum *dr* of 80:20 in favor of the *anti* diastereomer. Due to the lack of a basic functionality in the catalyst the addition of sub-stoichiometric triethylamine was required to achieve acceptable yields. The authors proposed a mechanism that involves simultaneous hydrogen-bonding interactions between the two thiourea groups and the imine and nitronate species.

Scheme 76. BINAP-Based Bis-thiourea **129**-Catalyzed Nitro-Mannich Reactions



R^1 = Ph, 4-ClC_6H_4, 3-ClC_6H_4, 2-ClC_6H_4, 4-BrC_6H_4, 4-$MeOC_6H_4$, 2-$MeOC_6H_4$, 4-MeC_6H_4, 1-naphthyl, 3-pyridyl

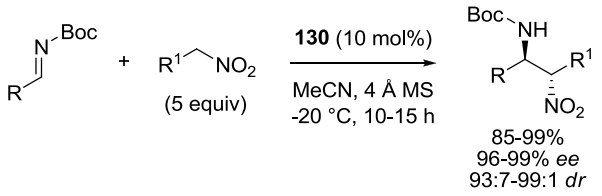
R^2 = H, Me, Et



129

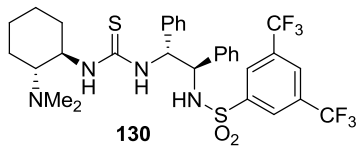
One of the most efficient organocatalytic nitro-Mannich protocols reported to date was presented by C. Wang *et al.* in 2008.[132] They used chiral thiourea **130** to catalyze the nitro-Mannich reaction between a range of *N*-Boc-imines and a number of nitroalkanes (Scheme 77). Near quantitative yields were obtained in the majority of cases, accompanied by exceptional stereoselectivities. The conditions were also found to have a high tolerance for alkyl imines, demonstrated by the use of the *N*-Boc-imine derived from isobutyraldehyde, which gave comparable yields and selectivities to aryl imines. Although a relatively large excess of nitroalkane is required, the high yields and stereoselectivities obtained make this methodology the most effective *anti*-selective organocatalytic direct nitro-Mannich reaction reported so far. It is complementary to the highly *syn*-selective heterobimetallic Cu-Sm-Schiff base complex-catalyzed reactions reported by Shibasaki *et al.* (see Schemes 61 and 62).[113–114]

Scheme 77. Wang's Thiourea **130**-Catalyzed Nitro-Mannich Reactions



R = Ph, 4-MeC_6H_4, 2-$MeOC_6H_4$, 4-$MeOC_6H_4$, 4-ClC_6H_4, 2-ClC_6H_4, 4-FC_6H_4, 4-$CF_3C_6H_4$, 1-naphthyl, 2-naphthyl, 2-furyl, 3-pyridyl, ^{i}Bu

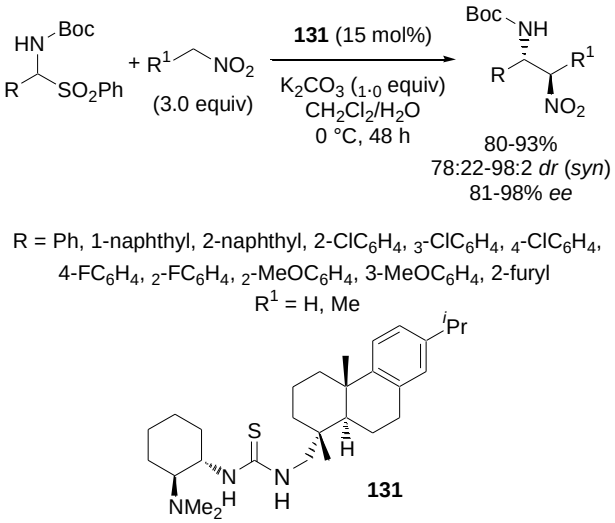
R^1 = H, Me, Et, Bn



130

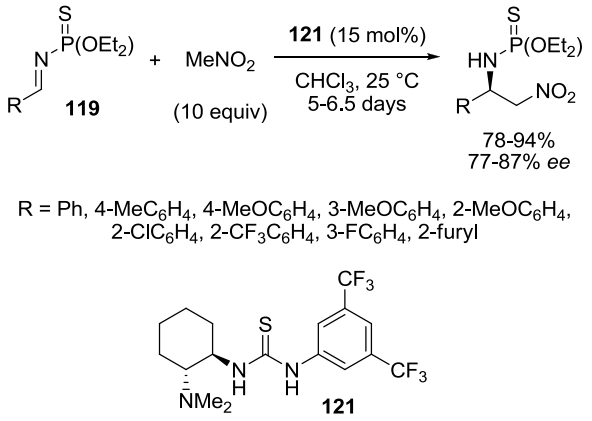
In 2009, R. Wang *et al.* published the only report of a direct asymmetric *syn*-selective organocatalytic nitro-Mannich reaction.[129] They used the rosin-derived thiourea **131** in the reaction of nitromethane and nitroethane with aryl and heteroaryl *N*-Boc-imines formed *in situ* by treatment of *α*-amidosulfones with K_2CO_3 (Scheme 78). They found that the use of a biphasic (water/dichloromethane) solvent system was crucial for achieving high enantioselectivity. The group also demonstrated that the 1,2-diaminocyclohexane group in the catalyst was responsible for the stereochemical control as switching to the (*R*)-enantiomer provided efficient reversal of stereoselectivity in the nitro-Mannich reactions. Excellent yields and enantioselectivities were obtained in the reactions of nitromethane with aryl and heteroaryl imines. However, the yields dropped dramatically when the reaction was performed with the imine derived from cyclohexane carboxaldehyde. Several examples of reactions with nitroethane were reported to give high selectivity for the *syn*-diastereomers. The authors, however, failed to elaborate on this remarkably high *syn*-selectivity and offered no explanation for the observed diastereoselectivity. A private communication to us by the authors has revealed that the representations of the diastereoisomers in the paper are wrong and that the real structures are in fact the *anti*-diastereoisomers (corrected structures appear in Scheme 78).

Scheme 78. *Syn*-Selective Thiourea-Catalyzed Nitro-Mannich Reactions



As was mentioned in Section 6.1, Zhou *et al.* reported the first use of *N*-thiophosphoryl imines **119** in TMG-catalyzed nitro-Mannich reactions with nitromethane (see Scheme 66).[120] In the same article the authors also reported an asymmetric variant of this reaction. The reaction of a variety of *N*-thiophosphoryl imines **119** was efficiently catalyzed by thiourea **121** to give the *β*-nitroamine products in good to excellent yields and enantioselectivities (Scheme 79). The authors observed that they obtained the opposite enantiomeric products (*R*) to those obtained by Takemoto *et al.* (*S*) in their reactions of *N*-phosphinoyl imines catalyzed by thiourea **121** (see Scheme 68).[121] This indicates the important effect the *N*-protecting group can have on the stereochemical outcome of nitro-Mannich reactions. The *R*-configuration is the same as that reported by Takemoto *et al.*[124] for their nitro-Mannich reactions of *N*-Boc-imines (see Scheme 70). As a result, Zhou *et al.* proposed a similar TS for their reactions with *N*-thiophosphoryl imines **119**.

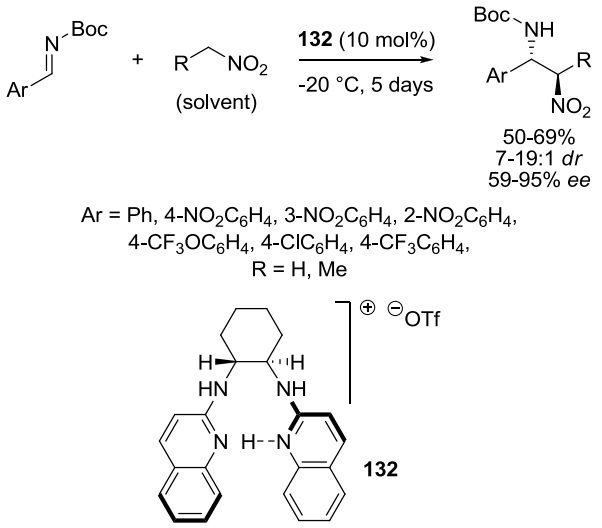
Scheme 79. Asymmetric Organocatalyzed Nitro-Mannich Reactions of *N*-Thiophosphoryl Imines



6.2.2. Brønsted Acid Catalysts

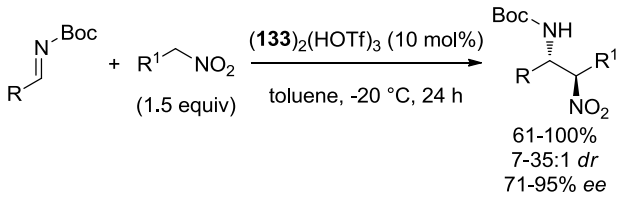
Less than a week after the initial report by Takemoto *et al.*[121] in 2004, the group of Johnston published the use of an alternative organocatalyst in asymmetric nitro-Mannich reactions.[133] They implemented the use of chiral proton catalyst **132** for the enantio- and diastereoselective nitro-Mannich reactions of *N*-Boc-aryl-imines with nitromethane and nitroethane (Scheme 80). They speculate that the bis-amidine ligand sequesters the proton from solvent interactions, thereby preventing achiral solvent-coordinated Brønsted acid catalysis, to create a chiral proton coordination complex capable of inducing enantioselectivity. The method, however, suffered from long reaction times and only demonstrated limited substrate scope as it required the use of electron-poor aryl imines to achieve high enantioselectivities. Furthermore, the use of the nitroalkane as the solvent limits the applicability of this method to more complex nitroalkanes.

Scheme 80. Enantioselective Chiral Proton-Catalyzed Nitro-Mannich Reactions



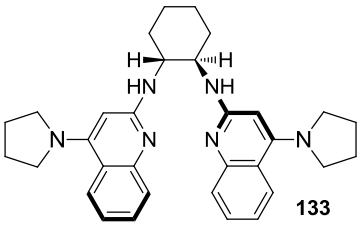
Johnston *et al.* later reported the use of bis-amidine catalyst **133**, which demonstrated improved efficiency in nitro-Mannich reactions (Scheme 81).[134] The reactions with the new catalyst system gave higher yields and stereoselectivities over a wide range of *N*-Boc-aryl imines and several nitroalkanes. The reactions were complete in 24 hours using just 1.5 equivalents of nitroalkane, demonstrating a drastic improvement over their previous report, which required 5 days and used the nitroalkane as the solvent.[133] They rationalize that the increased Brønsted basicity of **133** compared to the free base of **132** is responsible for the increased reactivity of the catalyst. They also uncovered an interesting effect caused by the amount of TfOH used in the reaction and found that a 2:3 ratio of **133**:TfOH provided the optimum yield and stereoselectivity.

Scheme 81. Chiral Proton-Catalyzed Nitro-Mannich Reactions



R = 4-ClC_6H_4, 4-$MeOC_6H_4$, 3,4-$(MeO)_2C_6H_3$, 2-naphthyl, 4-MeC_6H_4, 2-MeC_6H_4, 1-naphthyl, 4-FC_6H_4, 4-$MeO_2CC_6H_4$, 2-naphthyl, 2-furyl, 2-thienyl, 3-thienyl, $PhSC_6H_4$, allylOC_6H_4

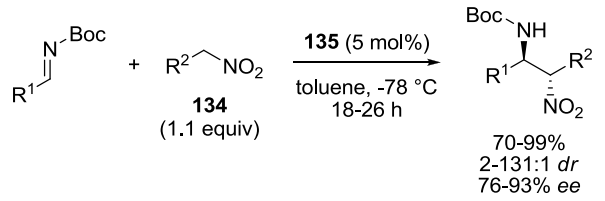
R^1 = Me, Et, ^{n}Pr, ^{i}Pr, Me_2 $CH_2C_6H_{11}$



133

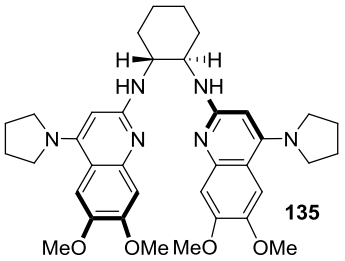
The group of Johnston further extended the scope of their nitro-Mannich methodology to include the reaction of aryl nitromethanes **134** (Scheme 82), a relatively unexplored substrate in nitro-Mannich chemistry.[135] Due to the challenges associated with this substrate, which in previous examples generally resulted in low stereoselection,[107,136] the development of bisamidine **135** was required to provide the high levels of stereoselectivity. The *β*-nitroamine products were formed in excellent yields, enantioselectivities and *anti*-diastereoselectivities for a range of aryl nitromethanes **134** and *N*-Boc aryl imines. The reaction of electron deficient aryl nitromethanes (R^2 = 4-$NO_2C_6H_4$), however, resulted in lower levels of stereoselectivity due to the acidity of the product rendering it susceptible to epimerization at the nitro-substituted carbon. Nonetheless, this represents a useful method for the synthesis of *cis*-stilbene diamines, which the authors utilized in the synthesis of (-)-nutlin-3 (see Section 14).

Scheme 82. Bisamidine-Catalyzed Nitro-Mannich Reactions of Aryl Nitromethanes



R^1 = 4-ClC_6H_4, 4-allylOC_6H_4, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-FC_6H_4, 4-$CF_3C_6H_4$, 4-PhC_6H_4, 2-naphthyl

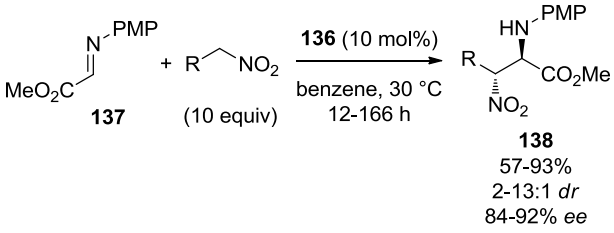
R^2 = Ph, 4-ClC_6H_4, 3-BrC_6H_4, 2-naphthyl, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$



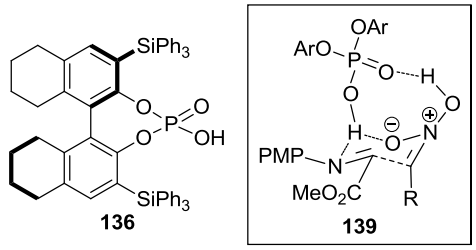
135

In 2008, Rueping *et al.* described the first direct organocatalytic Brønsted acid-catalyzed nitro-Mannich reaction of *α*-iminoesters.[136] They were able to use the BINOL-derived phosphoric acid **136** to catalyze the reaction of a variety of nitroalkanes with *N*-PMP-*α*-iminoester **137** to form a range of *β*-nitro-*α*-amino acid esters **138** (Scheme 83). The yields were good to excellent and the products were obtained in high enantio- and diastereoselectivities in favor of the *anti*-product. The protocol offers very good nitroalkane scope, however, the large excess required (10 equiv) limits the practicability of this method if more complex nitroalkanes were required. Furthermore, the procedure suffers from long reaction times and has only been applied to the reaction of a single imine. The authors proposed that the catalyst has a bifunctional role in which it activates *α*-iminoester **137** by protonation and also accelerates the nitroalkane/nitronic acid equilibrium. The reaction then proceeds via TS **139** with the catalyst is acting both as a Brønsted acid and a Lewis base.

Scheme 83. Chiral Phosphoric Acid-Catalyzed Nitro-Mannich Reactions



R = Me, Et, ^{n}pentyl, CH_2Ph, $CH_2(4\text{-}BrC_6H_4)$, $CH_2(4\text{-}MeOC_6H_4)$, CH_2(2-thienyl), $(CH_2)_3Ph$, $4\text{-}MeC_6H_4$

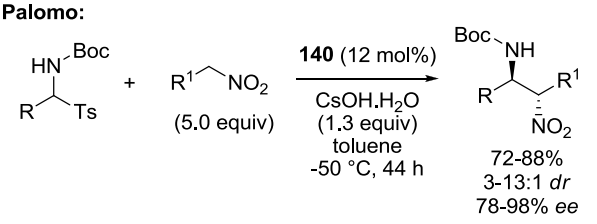


6.2.3. Phase Transfer Catalysts

The groups of Palomo and Hererra independently reported the use of cinchona-derived phase-transfer-catalyst (PTC) **140** in the nitro-Mannich reaction of α-amidosulfones with nitroalkanes (Scheme 84).[137–138] Both groups gave near identical conditions, with the exception of the inorganic base used for the *in situ* formation of the *N*-Boc-imines from the α-amidosulfones. The β-nitroamine products were formed in excellent yields and enantioselectivities. The method is particularly useful for imines derived from enolizable aldehydes as the formation of the *N*-Boc-imines *in situ* avoids the need to isolate these unstable substrates. Herrera *et al.* also demonstrated that the method was not restricted to Boc-protected substrates and could be extended to other carbamoyl protecting groups such as Cbz. However, they failed to give any examples of reactions involving higher order nitroalkanes, whereas Palomo *et al.* reported reactions with nitroethane giving moderate to high *anti*-diastereoselectivities.

Scheme 84. Phase Transfer Catalyzed Nitro-Mannich Reactions

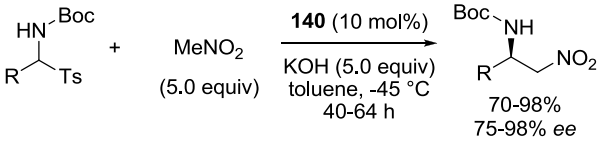
Palomo:



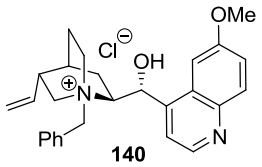
R = Ph, 4-$MeOC_6H_4$, 4-$ClOC_6H_4$, 4-$CF_3C_6H_4$, 3-$NO_2C_6H_4$, 2-furyl, 1-naphthyl, CH_2Bn, cyclohexyl, ^{n}Pr, ^{n}hexyl, ^{i}Bu, ^{i}Pr, Et

R^1 = H, Me

Hererra:



R = Ph, 2-BrC_6H_4, 4-$MeOC_6H_4$, 1-naphthyl, 2-furyl, CH_2Bn, cyclohexyl, ^{i}Pr, Et, Me

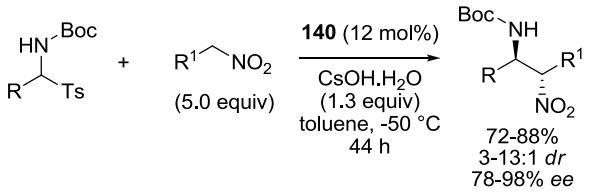


140

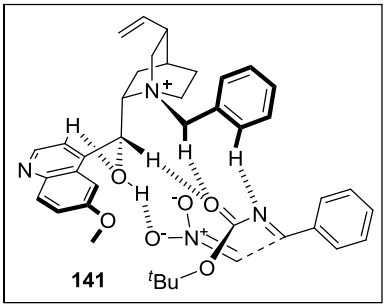
Palomo *et al.* went on to expand the scope of this reaction with respect to both nitroalkanes and *α*-amidosulfones (Scheme 85).[139] The nitro-Mannich reactions of a range of functionalized nitroalkanes gave the corresponding *β*-nitroamines in excellent yields and stereoselectivities. The reaction of 2-nitropropane was also demonstrated to proceed in good yield, albeit with low enantioselectivities. The authors also reported a detailed mechanistic study of this nitro-Mannich reaction. Through the use of computational methods to calculate the energies of the possible transition states they proposed that the mechanism proceeds via TS **141**. A hydrogen-bonding network creates a stable complex resulting in high enantioselectivity. This consists of a hydrogen bond between the O–H of the catalyst and the nitronate anion, which was confirmed by the drastically lower reactivity of catalysts bearing protected alcohols, and three additional hydrogen bonds between the carbamate of the imine and a number of C–H bonds of the catalyst. Binding of the imine in this orientation, with the *tert*-butyl group orientated away from the catalyst's bicycle,

results in nucleophilic attack of the nitronate from the *Si* face of the imine. The authors did not offer any explanation for the high *anti*-diastereoselectivity obtained with higher order nitroalkanes.

Scheme 85. Phase Transfer Catalyzed Nitro-Mannich Reactions and Proposed TS

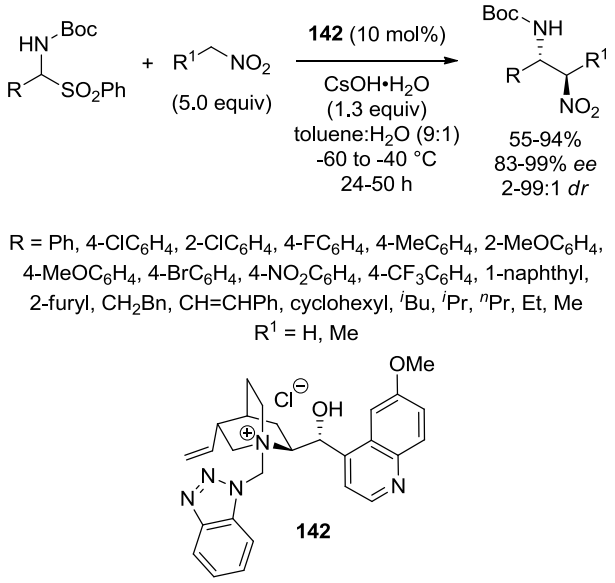


R = Ph, 4-$MeOC_6H_4$, 4-$ClOC_6H_4$, 4-MeC_6H_4, 3-MeC_6H_4, 3-$NO_2C_6H_4$, 2-furyl, CH_2Bn, Et, ^{i}Bu, ^{i}Pr, cyclohexyl
R^1 = Me, Et, ^{n}Bu, $CH_2{=}CH(CH_2)_2$, $(EtO)_2CH$, EtO_2CCH_2, 4,4-dimethyl-2,6-dioxanyl



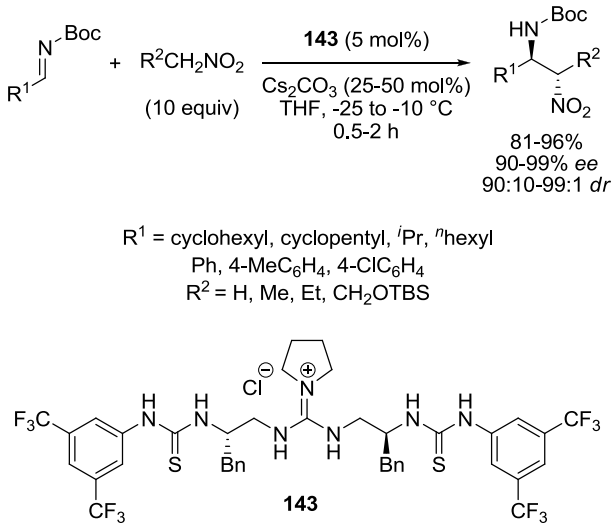
In 2012, He *et al.* reported the use of a similar PTC for the reaction of *α*-amidosulfones with nitroalkanes (Scheme 86).[140] The *N*-benzotriazole-cinchona-based chiral ammonium salt **142** was used to catalyze the reactions of a wide range of *in situ* formed aryl, heteroaryl and alkyl *N*-Boc-imines with nitromethane and nitroethane. The products were formed in good yields and diastereoselectivities and excellent enantioselectivities. Interestingly, by changing the *N*-benzyl group in **140** to an *N*-benzotriazole group complete reversal of enantioselectivity of the *β*-nitroamine products was observed, even when using the same chiral source quinine. Consequently, this catalyst system is complementary to that developed by the groups of Palomo and Herrera.[137–139]

Scheme 86. Nitro-Mannich Reactions catalyzed by PTC **142**



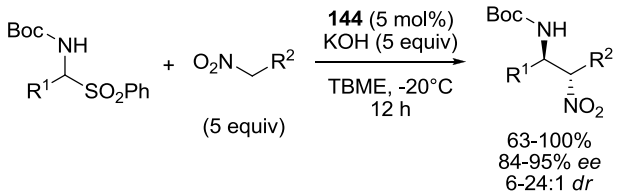
In 2009, Nagasawa reported the use of an alternative bis-thiourea PTC in highly stereoselective nitro-Mannich reactions (Scheme 87).[141] They used guanidine-based bis-thiourea **143** to catalyze the reaction of a variety of *N*-Boc aryl and alkyl imines with a number of nitroalkanes. The *anti*-*β*-nitroamine products were formed in excellent yields, diastereo- and enantioselectivities. This methodology demonstrates one of the broadest substrate scopes with respect to *N*-Boc-alkyl imines that has been reported to date. This is likely to be a result of the short reaction times minimizing the amount of imine degradation that can occur. The same catalyst was later used by the group of Peng and Han in the nitro-Mannich reactions of a variety of functionalized nitroalkanes with *N*-Boc-imines formed *in situ* from the reaction of *α*-amidosulfones with K_2CO_3.[142] The reactions could be carried out with fewer equivalents of nitroalkane (2.0 equiv) and the products were formed in good yields and excellent enantioselectivities but with lower diastereoselectivities to those reported by Nagasawa.[141]

Scheme 87. Bis-Thiourea Phase Transfer Catalyzed Nitro-Mannich Reactions

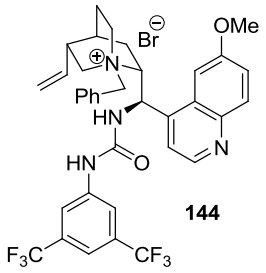


In 2012, Dixon *et al.* reported the use of a new family of cinchonium/H-bond donor bifunctional phase transfer catalysts in asymmetric nitro-Mannich reactions (Scheme 88).[143] They used quinidinium-urea catalyst **144** to perform highly enantioselective reactions between a range of aryl, heteroaryl and alkyl *N*-Boc-imines, generated *in situ* from *α*-amidosulfones, and nitroalkanes. The product *β*-nitroamines were formed in good to excellent yields and *anti*-diastereoselectivities.

Scheme 88. Bifunctional Quinidinium-Urea-Catalyzed Nitro-Mannich Reactions



R^1 = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-FC_6H_4, 4-$CF_3C_6H_4$, 2-naphthyl, 3-pyridyl, ^{t}Bu, cyclohexyl, ^{i}Bu
R^2 = H, Me, Et, $CH_2CH{=}CH_2$

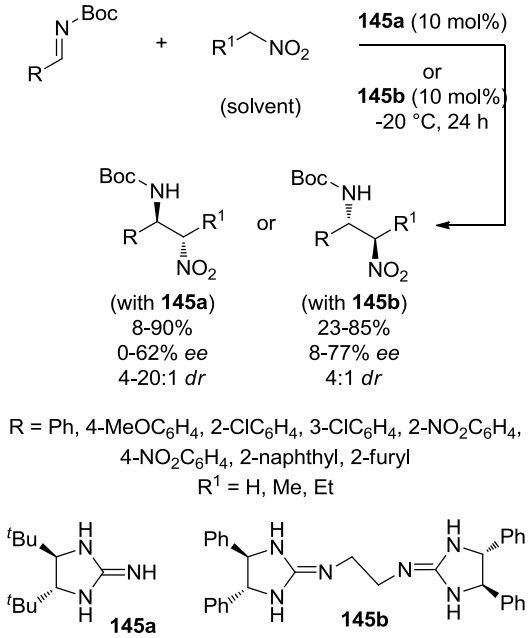


144

6.2.4. Brønsted Base Catalysts

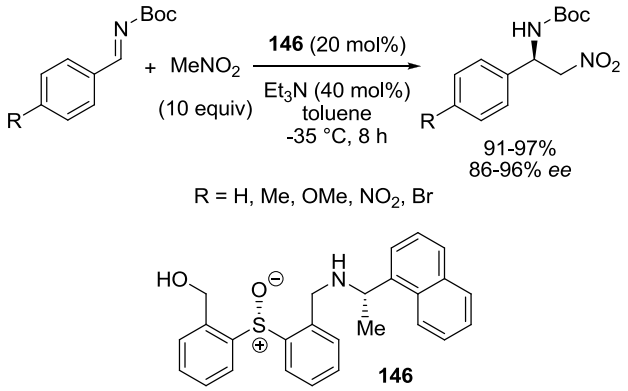
In 2009, Michael *et al.* reported the use of mono- and bis-guanidine catalysts **145a** and **145b** for the enantioselective nitro-Mannich reactions of *N*-Boc aryl imines with nitromethane, nitroethane and 1-nitropropane (Scheme 89).[144] The group observed a reversal in enantioselectivity when switching between mono-guanidine **145a** and bis-guanidine **145b** catalysts. However, the enantioselectivities were moderate at best, with mono-guanidine **145b** providing racemic products for half of the analogues investigated. Low to good yields were achieved and the reactions with larger nitroalkanes gave moderate to excellent *anti*-diastereoselectivities.

Scheme 89. Chiral Guanidine-Catalyzed Nitro-Mannich Reactions



In 2011, Rachwalski *et al.* reported the use of an alternative chiral sulfoxide organocatalyst for the highly enantioselective nitro-Mannich reactions of nitromethane with a number of *N*-Boc-aryl imines (Scheme 90).[145] The group used tridentate ligand **146** along with catalytic triethylamine to promote the reaction. The *β*-nitroamine products were formed in excellent yields and enantioselectivities. However, a very limited substrate scope was presented and no insight into the mechanism of the reaction was given.

Scheme 90. Chiral Sulfoxide-Catalyzed Nitro-Mannich Reactions



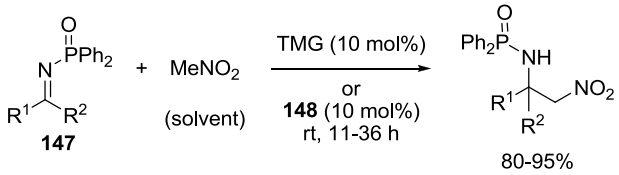
7. REACTIONS OF KETIMINES

As a result of their lower electrophilicities compared to aldimines there has been far fewer reported examples of nitro-Mannich reactions involving ketimines. There have, however, been a number of reports that show promising results with these difficult substrates. Methods now include both metal catalyzed and organocatalyzed protocols that provide *β*-nitroamines containing a quaternary chiral centre in excellent levels of enantioselectivity. The following section will detail the advances that have been made in this area.

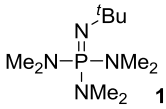
7.1. Racemic Reactions

In 2007, Terada *et al.* reported the first organocatalyzed nitro-Mannich reactions of ketimines (Scheme 91).[146] The authors demonstrated that the reaction of *N*-phosphinoyl-ketimines **147** with nitromethane could be catalyzed by TMG to give the *β*-nitroamine products in excellent yields. The group also performed a single diastereoselective example with nitroethane to give the product in excellent yield but only moderate *dr*. The relative stereochemistry of the major diastereomer was not given. The reaction was also found to be efficiently catalyzed by phosphazene **148** to give the products in comparable yields to those achieved with TMG. The reaction of chiral *N*-sulfinyl ketimines was also effectively catalyzed by TMG and phosphazene **148**, although TMG failed to provide any diastereoselectivity and phosphazine **148** only gave a moderate *dr*.

Scheme 91. Nitro-Mannich Reactions with *N*-Phosphinoyl-Ketimines



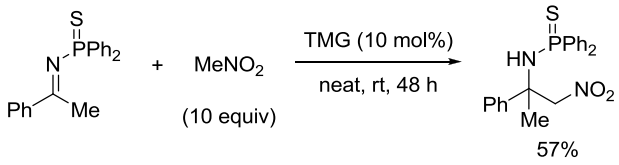
R^1 =Ph, 4-ClC_6H_4, 4-MeC_6H_4,4-$MeOC_6H_4$, 1-naphthyl, CH_2Bn
R^2 = Me, Et, ^{i}Pr, ^{n}Pr, 4-ClC_6H_4



148

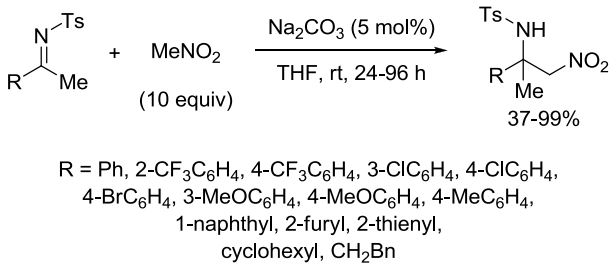
In their previously mentioned report on nitro-Mannich reactions of *N*-thiophosphoryl imines (see Schemes 66 and 79), Zhou and coworkers also gave a single example of the use of an *N*-thiophosphoryl ketimine (Scheme 92).[120] The product *β*-nitroamine was formed in substantially lower, but still acceptable, yield than those formed from aldimines.

Scheme 92. Nitro-Mannich Reactions with *N*-Thiophosphoryl Ketimines



In 2008, Feng *et al.* reported the inorganic base-catalyzed nitro-Mannich reaction of *N*-tosyl ketimines with nitromethane (Scheme 93).[147] The reaction was effectively catalyzed by sodium carbonate to give the *β*-nitroamine products in moderate to excellent yields for a range of aryl, heteroaryl and alkyl imines.

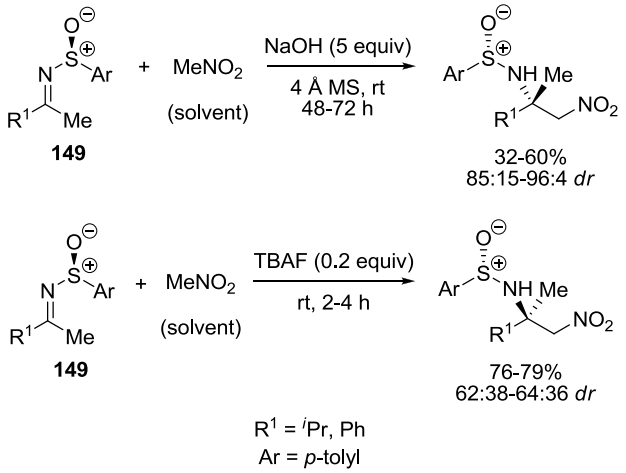
Scheme 93. Nitro-Mannich Reactions with *N*-Tosyl Ketimines



7.2. Auxiliary Controlled Reactions

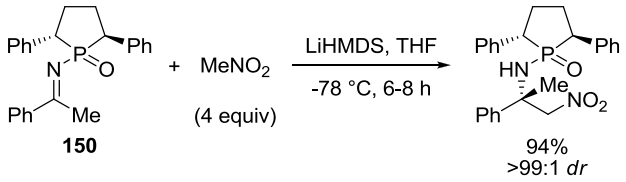
In the report by the group of Ruano and Cid on nitro-Mannich reactions of chiral *N*-sulfinyl imines **79** (see Scheme 37) the authors also demonstrated the application of their methodology to chiral *N*-sulfinyl ketimines **149** (Scheme 94).[87] The NaOH-mediated nitro-Mannich reactions with a number of ketimines were demonstrated to proceed with moderate to good yields and with excellent diastereoselectivities. However, their lower reactivity compared to aldimines necessitated the addition of an equivalent of $Yb(O^iPr)_3$ to increase the reaction rate and provide the products in acceptable yields. The group also found that their TBAF-mediated protocol provided the desired products in good yields and in the opposite diastereomeric form, albeit with low *dr*.

Scheme 94. Auxiliary Controlled Nitro-Mannich Reactions with Ketimines



In the same report by Li *et al.* in which they demonstrated the use of chiral *N*-phosphinoyl imines **84** (see Scheme 40), the authors also reported a single example of a reaction of a chiral *N*-phosphinoyl ketimine (Scheme 95).[91] The reaction of *N*-phosphinyl ketimine **150** generated the *β*-nitroamine product in excellent yield and diastereoselectivity, demonstrating that their methodology still performs well with these less reactive substrates.

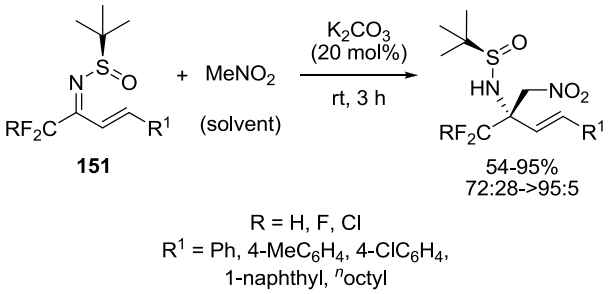
Scheme 95. Auxiliary Controlled Nitro-Mannich Reactions of *N*-Phosphinoyl Ketimines



In 2011, Liu *et al.* reported the K_2CO_3-catalyzed nitro-Mannich reaction of *α*,*β*-unsaturated *N*-*tert*-butanesulfinyl ketimines **151** with nitromethane (Scheme 96).[148] The *β*-nitroamine products were formed in good to excellent yields and moderate to excellent diastereoselectivities. The authors found that the presence of the strongly electron-withdrawing perfluoroalkyl group was crucial for the success of this reaction. This was apparent from the reaction of difluoromethyl analogue (R = H), which gave significantly lower yields and diastereoselectivities; and the non-fluorinated analogue, which failed to undergo any reaction. Surprisingly, the reaction of

heptafluoropropyl analogue (R = $CF_2CF_2CF_3$) resulted in a 1,4-addition reaction, with no 1,2-addition product observed. This methodology represents the first example of a nitro-Mannich reaction of perfluorinated imines and also the first investigation into the use of *N-tert*-butanesulfinyl ketimines.

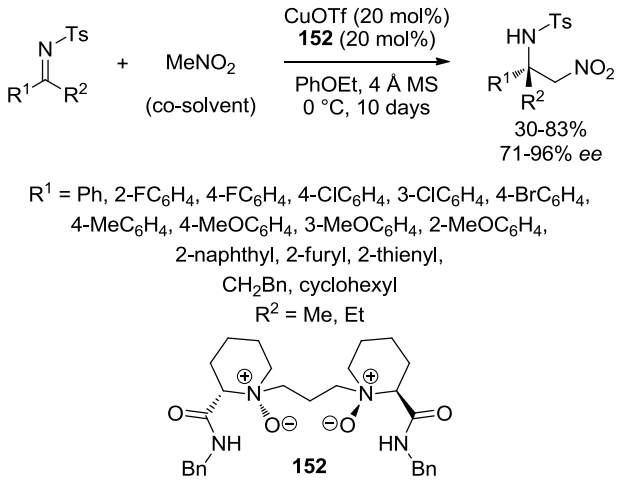
Scheme 96. Nitro-Mannich Reactions of *α,β*-Unsaturated *N-tert*-Butanesulfinyl Ketimines



7.3. Catalytic Enantioselective Reactions

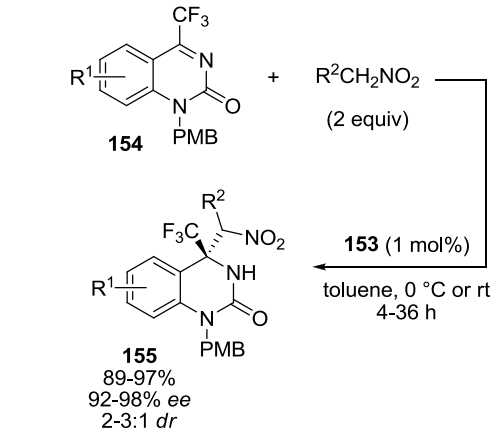
In 2008, Feng *et al.* reported the first catalytic enantioselective nitro-Mannich reactions of ketimines.[149] These involved the use a chiral *N,N*'-dioxide **152**-Cu(I) complex catalyst system which effectively catalyzed the reactions of a number of *N*-tosyl-ketimines with nitromethane (Scheme 97). The *β*-nitroamine products were formed in low to moderate yields and with good to excellent enantioselectivities for a range of aryl ketimines as well as several alkyl ketimines. The reaction of larger nitroalkanes, such as nitroethane and nitropropane, was also attempted but these only resulted in trace amounts of the desired products. One drawback of this methodology is the very long reaction times, which were necessary due to the poor reactivity of the ketimines. Nonetheless, this protocol still represents an important development in nitro-Mannich chemistry as the catalytic enantioselective reaction of ketimines had not previously been reported.

Scheme 97. The First Catalytic Enantioselective Nitro-Mannich Reactions of Ketimines



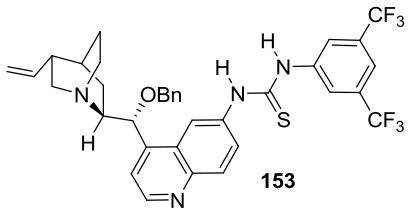
In 2011, W. Wang *et al.* reported the first organocatalytic enantioselective nitro-Mannich reactions of ketimines (Scheme 98).[150] They used thiourea **153** to catalyze the reactions of a number of cyclic trifluoromethyl ketimines **154** and nitroalkanes for the synthesis of trifluoromethyl dihydroquinazolinones **155**. The reactions with nitromethane gave the products **155** in excellent yields and enantioselectivities. The products of the reactions with larger nitroalkanes required lower temperatures to obtain high yields and enantioselectivities but only showed modest levels of diastereoselectivity. Impressively, thiourea **153** could be used with loadings as low as 1 mol% and still retain high activity. However, the authors found that the reaction was limited to trifluoromethyl ketimines as no reaction occurred when the trifluoromethyl group was replaced with a methyl or phenyl group, resulting from the low reactivity of these substrates.

Scheme 98. The First Organocatalytic Enantioselective Nitro-Mannich Reactions of Ketimines



R^1 = H, 6-Cl, 6-Br, 6-I, 6-F, 6-PMB, 5-MeO, 6-MeO

R^2 = H, Me, Et



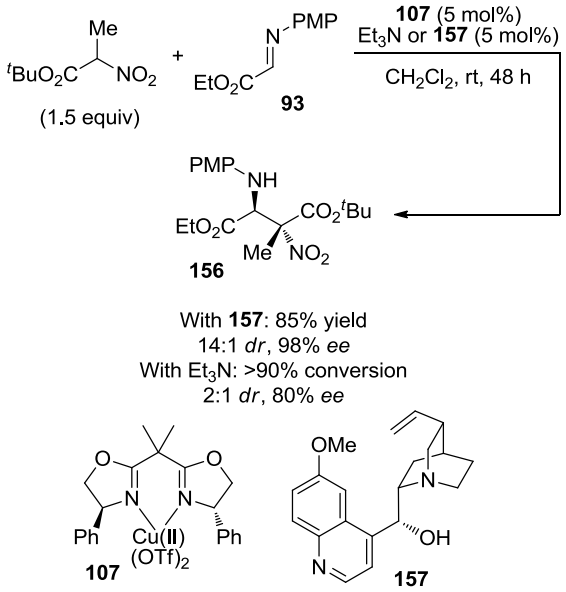
8. REACTIONS OF *α*-NITROESTERS

The use of *α*-nitroesters in nitro-Mannich reactions has also been studied by a number of different groups. The interest in these substrates arises from the importance of the *α*-nitro-*β*-aminoester products, which can be conveniently converted into the corresponding *α*,*β*-diamino acid derivatives.

Jørgensen *et al.* demonstrated that their Cu(II)-BOX-catalyzed nitro-Mannich methodology (see Scheme 56[107]) could be applied to the synthesis of *α*-nitro-*β*-aminoacid derivatives **156** bearing quaternary chiral centres.[151] This involved the reaction of 2-nitropropanoic acid *tert*-butyl ester with ethyl glyoxylate imine **93** (Scheme 99). Using the conditions that proved successful for the reaction of primary nitroalkanes with imine **93** (Cu(II)-BOX **107** and triethylamine) resulted in good enantioselectivity but poor diastereoselectivity. They then investigated the effect of a series of cinchona alkaloids as substitutes for triethylamine. The use of quinine (**157**) as a co-

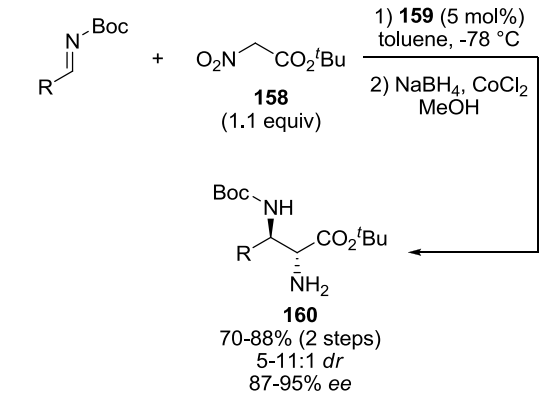
catalyst resulted in a drastic improvement in diastereoselectivity. They state that the chiral Lewis acid is responsible for the high enantioselectivity whereas the cinchona alkaloid controls the diastereoselectivity. Therefore, a combination of both is essential to achieve highly stereoselective reactions.

Scheme 99. Nitro-Mannich Reaction of 2-Nitropropanoic Acid *tert*-Butyl Ester

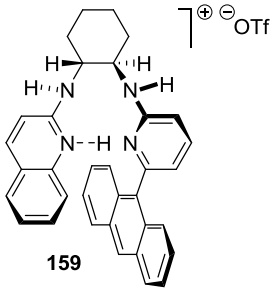


In 2007, Johnston *et al.* reported the use of a another bis-amidine catalyst in the nitro-Mannich reaction of *N*-Boc aryl imines with secondary *α*-nitroesters **158** (Scheme 100).[152] Although the reaction was effectively catalyzed by other bis-amidine catalysts, to obtain both high enantio- and diastereoselectivities the use of the unsymmetric anthracene-containing bis-amidine **159** was required. Due to the high basicity of the proton *α* to the nitro group in the *β*-nitroamine products, reduction of the nitro group was required to avoid epimerization. The *α*,*β*-diamino acid derivatives **160** were formed in excellent yields, enantio- and diastereoselectivies for a range of aryl imines.

Scheme 100. Bis-Amidine Catalyzed Reaction of Secondary α-Nitroesters

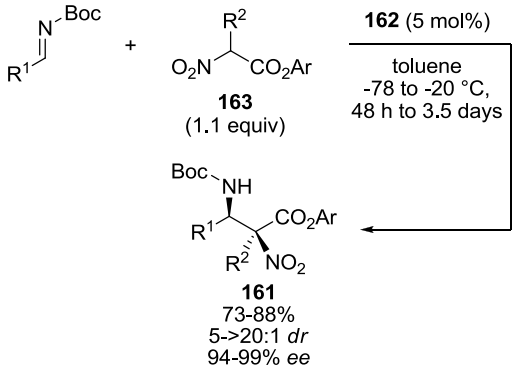


R = 4-ClC_6H_4, 3-ClC_6H_4, 4-FC_6H_4, 4-$AcOC_6H_4$, 4-$CF_3C_6H_4$, 4-MeC_6H_4, 3-$PhOC_6H_4$, 4-$MeO_2CC_6H_4$, 2-naphthyl

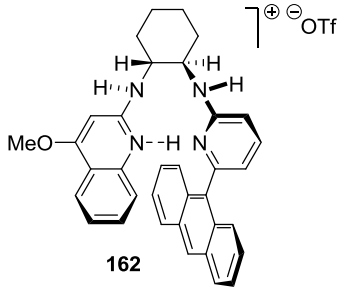


In the following year, Johnston *et al.* reported another nitro-Mannich reaction of α-nitroesters with *N*-Boc-imines for the selective synthesis of *syn*-α-nitro-β-amino acid esters **161** (Scheme 101).[153] The authors found that bis-amidine catalyst **162** catalyzed the reaction of a variety of *N*-Boc aryl imines and tertiary α-nitroesters **163** to give the α-nitro-β-amino acid esters **161** in good yields, excellent enantioselectivities and good to excellent *syn*-diastereoselectivities. Due to the lower reactivity of the tertiary α-nitroesters **163** over secondary α-nitroesters **158** the use of the more active methoxy-substituted catalyst **162** was required to achieve good levels of conversion. Furthermore, they found that the use of the bulky arylesters (Ar = 2,6-^{i}Pr$_2$C$_6$H$_4$) enabled a drastic increase in the diastereoselectivity of the reactions. Although they demonstrated a good substrate scope, the reaction of *N*-Boc alkyl imines failed to give any of the desired products due to decomposition of these imines under their reaction conditions.

Scheme 101. Bis-Amidine-Catalyzed Reactions of Tertiary α-Nitroesters



R^1 = 4-ClC_6H_4, 4-$MeSC_6H_4$, 4-$PhSC_6H_4$, 4-MeC_6H_4, 4-$MeOC_6H_4$, 2-naphthyl, 2-furyl
R^2 = Me, Et, ^{n}Pr, ^{n}Bu
Ar = 2,6-$^i Pr_2C_6H_3$

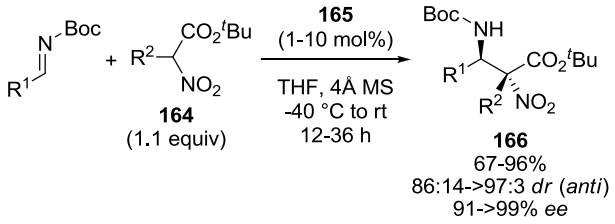


162

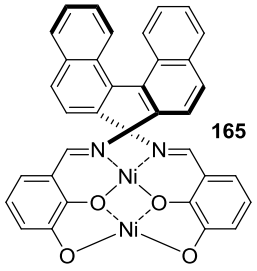
Shibasaki *et al.* have also published a highly enantioselective nitro-Mannich protocol for the reaction of *N*-Boc-imines with α-nitroesters **164** (Scheme 102).[154] They found that their Cu-Sm-Schiff base complex **113**, which had successfully catalyzed nitro-Mannich reactions of simple nitroalkanes (see Scheme 61),[113–114] resulted in poor stereoselectivity. They instead found that the homodinuclear Ni_2-Schiff base complex **165** was a very efficient catalyst that enabled the formation of *anti*-α-nitro-β-amino acid esters **166** in excellent yields, diastereo- and enantioselectivities. The reactions gave uniformly high yields and selectivities for a range of aryl, heteroaryl and alkyl imines, although the reactions of enolizable alkyl imines needed to be performed at lower temperatures. This *anti*-selective synthesis of α-nitro-β-amino acid esters **166**

provides a complementary method to Johnston's bis-amidine **162**-catalyzed synthesis of *syn*-α-nitro-β-amino acid esters **161**.

Scheme 102. Homobimetallic Ni_2-Schiff Base Complex-Catalyzed Nitro-Mannich Reactions of Tertiary α-Nitroesters

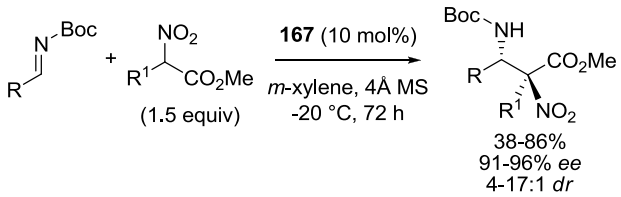


R^1 = Ph, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 3-thienyl, CH_2Bn, ^{n}Bu, ^{i}Bu
R^2 = Me, Et, ^{n}Pr, Bn



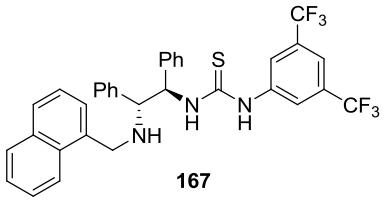
In 2008, Chen *et al.* reported the highly enantioselective reaction of tertiary α-nitroesters with *N*-Boc-aryl imines catalyzed by thiourea **167** (Scheme 103).[155] The reaction proceeded with moderate to good yields to give a range of α-nitro-β-amino acid esters in moderate to good *anti* diastereoselectivities and with excellent enantioselectivities. The authors also reported some preliminary work into the elucidation of the mechanism of the reaction.

Scheme 103. Thiourea-Catalyzed Nitro-Mannich Reactions of Tertiary α-Nitroesters



R = Ph, 4-$CF_3C_6H_4$, 3-ClC_6H_4, 2-ClC_6H_4, 4-MeC_6H_4, 3-MeC_6H_4, 2-furyl, 2-thienyl

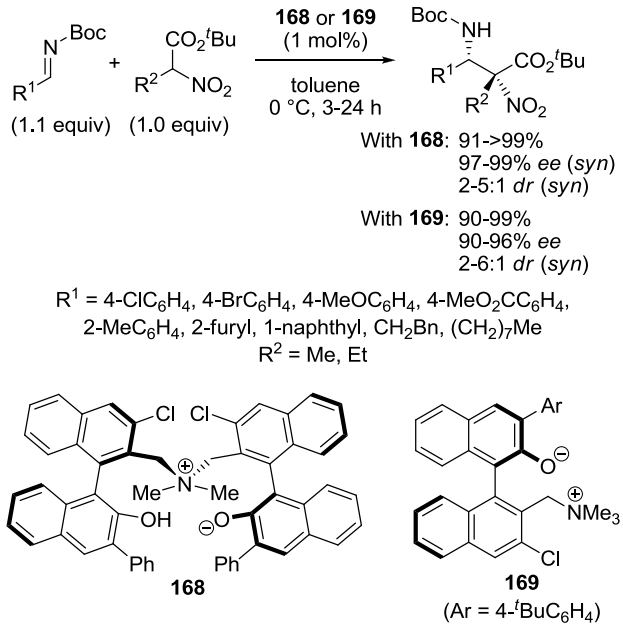
R^1 = Me, Bn, ^{i}Pr



167

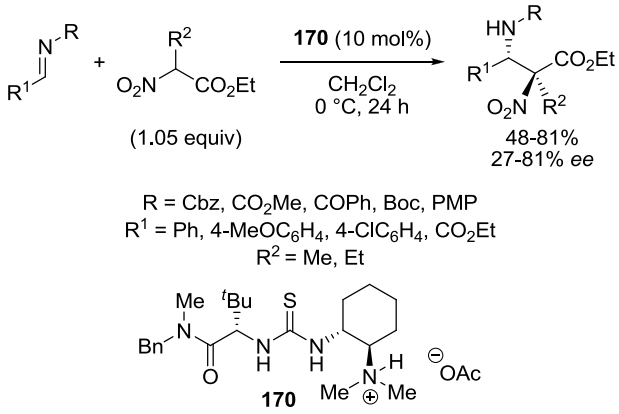
There have also been a number of reports of nitro-Mannich reactions of *α*-nitroesters promoted by phase transfer catalysts. In 2008, Ooi *et al.* reported the use of chiral ammonium betaine **168** to catalyze the reaction between *α*-nitroesters and *N*-Boc aryl imines (Scheme 104).[156] The product *β*-nitroamines were formed in excellent yield and enantioselectivities for a range of aryl and alkyl imines. Although the *syn* diastereoselectivities failed to compete with those reported by Johnston *et al*.[153] the level of enantiocontrol was excellent for both the *syn*- and *anti*-diastereomers. The same group went on to report that simplified catalyst **169** could be used to catalyze the same reactions (Scheme 104).[157] Very similar results to those obtained with catalyst **168** were achieved with the *α*-nitro-*β*-amino acid esters being formed in excellent yields, enantioselectivities and with moderate *syn*-diastereoselectivities. However, no examples of *N*-Boc-alkyl imines were given with the reactions catalyzed by **169**.

Scheme 104. Phase Transfer Catalyzed Nitro-Mannich Reactions of α-Nitroesters



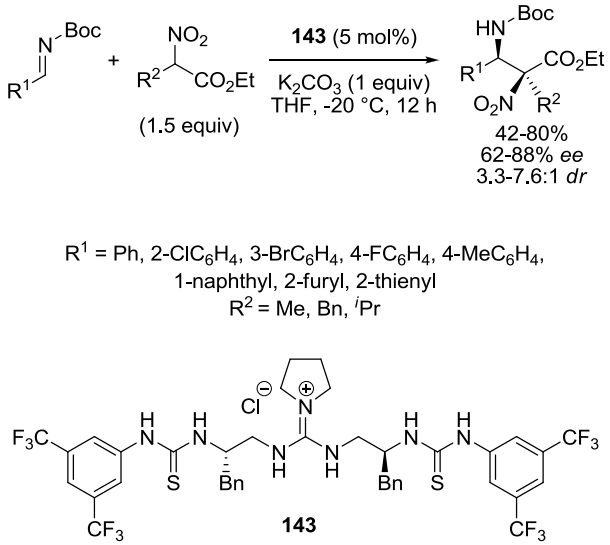
In 2009, the group of Puglisi and Benaglia reported the use of protonated thiourea catalyst **170** in the reaction of a variety of *N*-protected imines with *α*-nitroesters (Scheme 105).[158] Although this catalyst gave a good yield and enantioselectivity for the reaction of *N*-Boc-phenyl imine with ethyl 2-nitropropionate (81%, 81% *ee*), all other protecting groups and imine substituents resulted in only moderate yields and enantioselectivities. Furthermore, the reactions only displayed very poor, if any, diastereoselectivity (no diastereomeric ratios were reported for the majority of examples).

Scheme 105. Nitro-Mannich Reactions of *α*-Nitroesters Catalyzed by Protonated Thiourea **170**



In 2011, the group of Huang and Dong reported the use of the bis-thiourea catalyst **143**, developed by Nagasawa *et al*.,[141] in asymmetric nitro-Mannich reactions of *N*-Boc aryl imines with *α*-nitroesters (Scheme 106).[159] The products were formed in moderate to good yields, enantioselectivities and *anti*-diastereoselectivities.

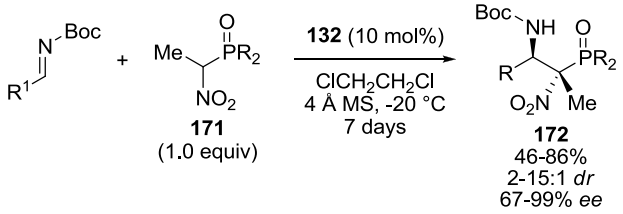
Scheme 106. Bis-Thiourea-Catalyzed Nitro-Mannich Reactions of *α*-Nitroesters



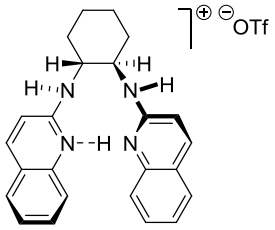
9. REACTIONS OF *α*-NITROPHOSPHONATES

In 2008, Johnston *et al.* reported the first stereoselective nitro-Mannich reactions of *α*-nitrophosphonates **171** with *N*-Boc aryl imines for the synthesis of *anti*-*α*-nitro-*β*-aminophosphonates **172** (Scheme 107).[160] The use of a sterically large phosphonate esters (R = OCH^iPr_2) was found to be essential to achieve simultaneously high enantio- and diastereoselection in the reactions. Bis-amidine catalyst **132** was used to form *anti*-*α*-nitro-*β*-aminophosphonates **172** in good yields and moderate to excellent diastereo- and enantioselectivities. The authors also demonstrated that the products could be easily converted to the corresponding *anti*-*α*,*β*-diaminophosphonic acids.

Scheme 107. The First Nitro-Mannich Reactions of *α*-Nitrophosphonates



R^1 = Ph, 4-ClC_6H_4, 3,4-$(MeO)_2C_6H_3$, 4-$MeOC_6H_4$, 4-$PhOC_6H_4$, 4-allyloxyC_6H_4, 4-MeC_6H_4, 4-MeO-3-MeC_6H_3, 4-MeO-3-BrC_6H_3, 4-$MeSC_6H_4$, 4-$PhSC_6H_4$, 4-PhC_6H_4, 2-naphthyl, 4-$AcOC_6H_4$
R = OCH^iPr_2

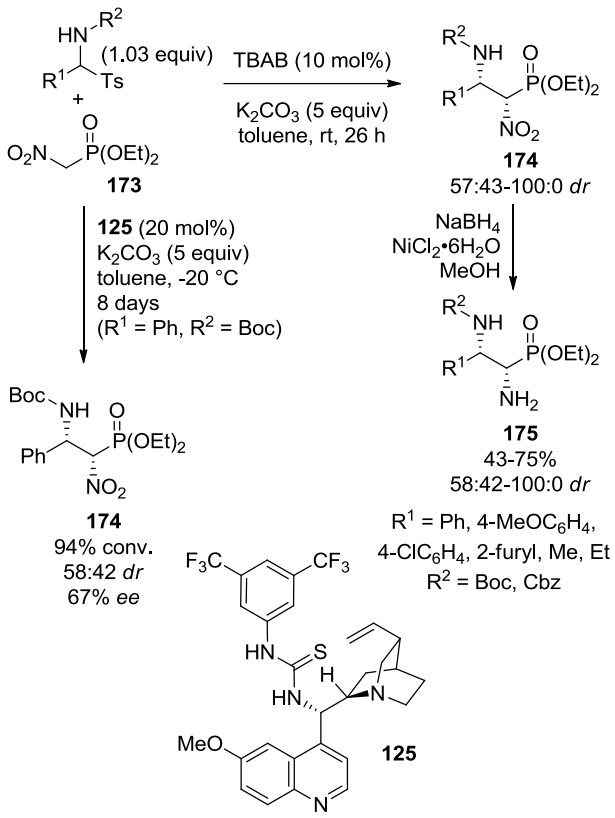


132

In 2010, Gajda *et al.* reported a racemic nitro-Mannich reaction of diethyl nitromethanephosphonate (**173**) (Scheme 108).[161] The authors demonstrated that tetrabutylammonium bromide (TBAB) was an effective PTC for the reaction of diethyl nitromethanephosphonate (**173**) with *N*-carbamoyl imines formed *in situ* from *α*-amidosulfones.

They used TBAB in combination with K_2CO_3 for the synthesis of a range of *syn*-*α*-nitro-*β*-aminophosphonates **174**, which could be isolated in good yields (79-88%). However, due to rapid epimerization during purification the diastereoselectivities were low. To overcome this problem reduction to the corresponding corresponding *syn*-*α*,*β*-diaminophosphonates **175** was performed. The reduction products were formed in moderate yields for a range of aryl and alkyl imines. Although the diastereoselectivities were excellent for the aryl imines, the alkyl imines suffered from much lower selectivities. The authors also attempted the nitro-Mannich reaction of larger homologues of diethyl nitromethanephosphonate but these were found to be unreactive under their reaction conditions. In the same article, Gajda reported the second example of an asymmetric nitro-Mannich reaction of *α*-nitrophosphonates. The authors reported a single example of an asymmetric reaction catalyzed by thiourea **125** (Scheme 108). The *syn*-*α*-nitro-*β*-aminophosphonate **175** was formed in excellent conversion but with only moderate enantioselectivity and low diastereoselectivity.

Scheme 108. TBAB- and Thiourea-Catalyzed Nitro-Mannich Reactions of Diethyl Nitromethanephosphonate



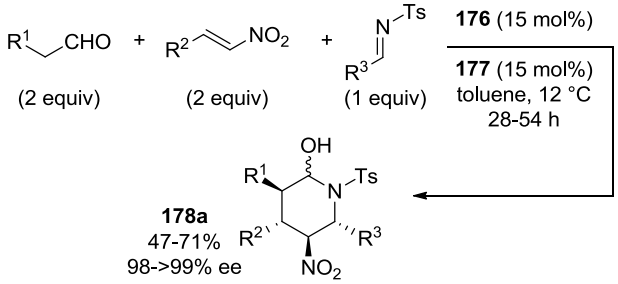
10. CONJUGATE ADDITION NITRO-MANNICH REACTIONS

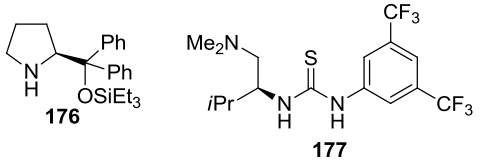
In Section 2.6 a number of early examples of conjugate addition/nitro-Mannich reactions were discussed. These reactions involved the conjugate addition of either hydride or carbon nucleophiles to nitroalkenes to form nitronate species that subsequently react in nitro-Mannich reactions. Since these early reports there have been a variety of novel conjugate addition/nitro-Mannich reactions developed to provide access to a variety of different products, including piperidines, pyrrolidines, cyclobutanes and acyclic *β*-nitroamines. The benefit of these tandem processes is that they enable greater levels of structural diversity to be achieved in fewer synthetic steps and from simpler starting materials.

10.1. Organocatalytic Reactions of Carbon Nucleophiles

Conjugate addition/nitro-Mannich/hemiaminalization cascade reactions have been demonstrated to provide easy access to highly enantioenriched substituted piperidines. The first examples of such reactions were reported independently by the groups of Xu,[162] Hayashi[163] and Barbas III.[164] These groups used similar chemistry for the synthesis of a 3-nitropiperidines, via the asymmetric organocatalyzed conjugate addition of aldehydes to nitroalkenes and subsequent reaction of the resulting nitroalkane with an imine in a nitro-Mannich reaction. The *β*-nitroamine products then undergo a hemiaminalization reaction to form the piperidine products (Schemes 109 to 111). Xu *et al.* utilized two organocatalysts, prolinol **176** to catalyze the conjugate addition and thiourea **177** to catalyze the nitro-Mannich/hemiaminalization, in a one-pot three-component cascade reaction sequence (Scheme 109).[162] Hemiaminals **178** were formed with excellent enantio- and diastereoselectivities but only moderate yields. The reaction also failed to give acceptable results when it was applied to alkyl imines.

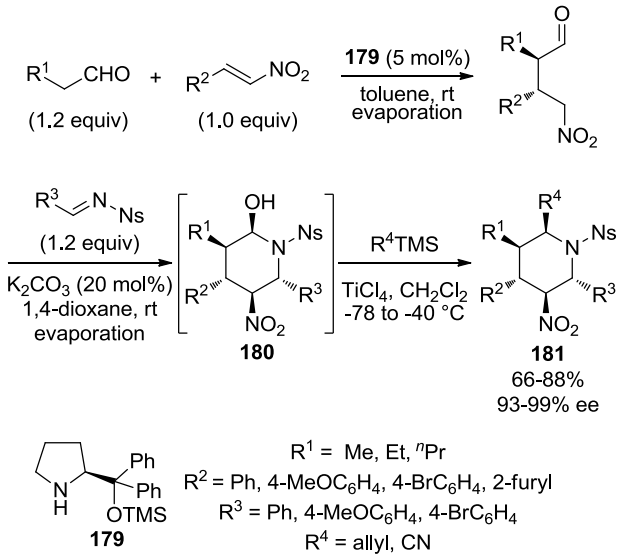
Scheme 109. One-Pot Three-Component Conjugate Addition/Nitro-Mannich Reactions





Hayashi *et al.* used prolinol **179** to catalyze the conjugate addition reaction (Scheme 110).[163] In order to affect the desired nitro-Mannich/hemiaminalization reaction a solvent swap to 1,4-dioxane, before introduction of the imine and catalytic K_2CO_3, was required. The authors also demonstrated that the hemiaminals **180** could be substituted with allyltrimethylsilane or trimethylsilylcyanide, furnishing piperidines **181** in good yields and excellent enantio- and diastereoselectivities. The drawback of this method is that it requires two solvent swaps to achieve good yields and selectivities.

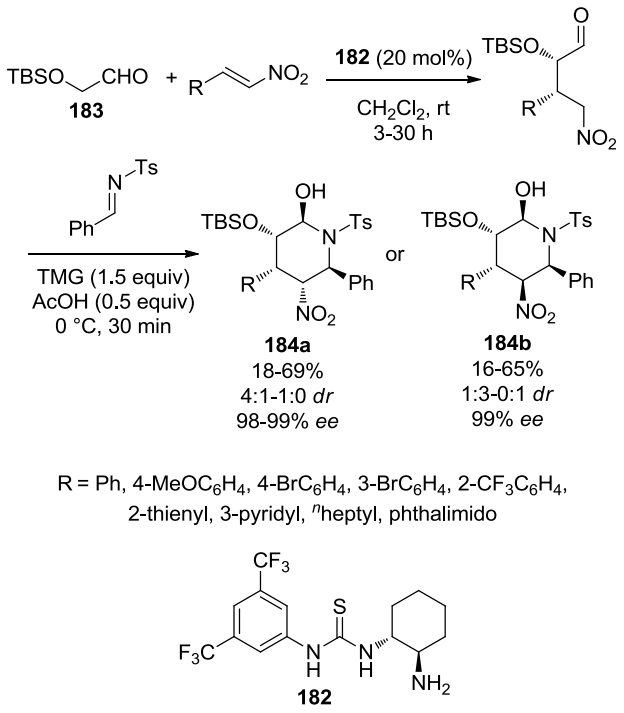
Scheme 110. Prolinol-Catalyzed Conjugate Addition/Nitro-Mannich/Hemiaminalization Reactions



Barbas III *et al.* used primary amine-containing thiourea catalyst **182** to promote the conjugate addition of silyloxy acetaldehyde **183** (Scheme 111).[164] Although no solvent swaps were required, the addition of TMG and acetic acid was required to achieve good yields of hemiaminals **184**. The products were formed in excellent enantioselectivities and with moderate to excellent diastereoselectivities. The relative stereochemistry of the products was found to be

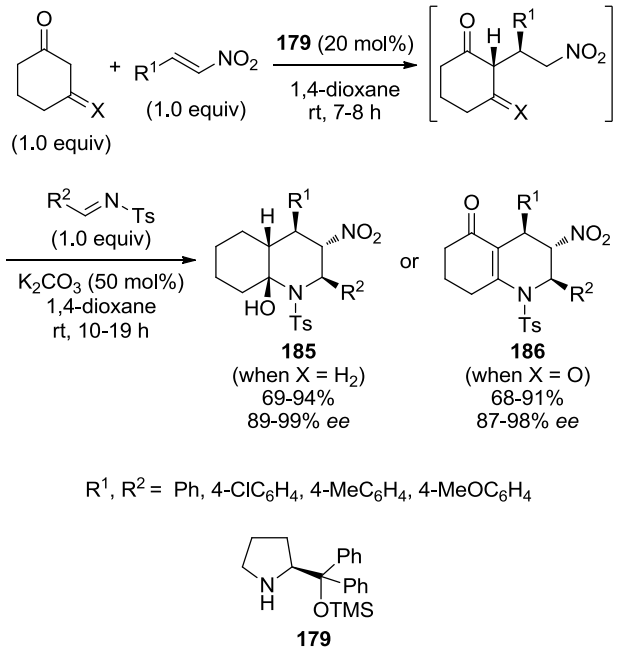
highly dependent on the nitroalkene substituent as with several analogues, especially electron-deficient analogues, the C-5 epimer **184b** was isolated as the major product. This was believed to be due to an epimerization process after the initial formation of **184a**.

Scheme 111. Thiourea-Catalyzed Conjugate Addition/Nitro-Mannich/Hemiaminalization Reactions



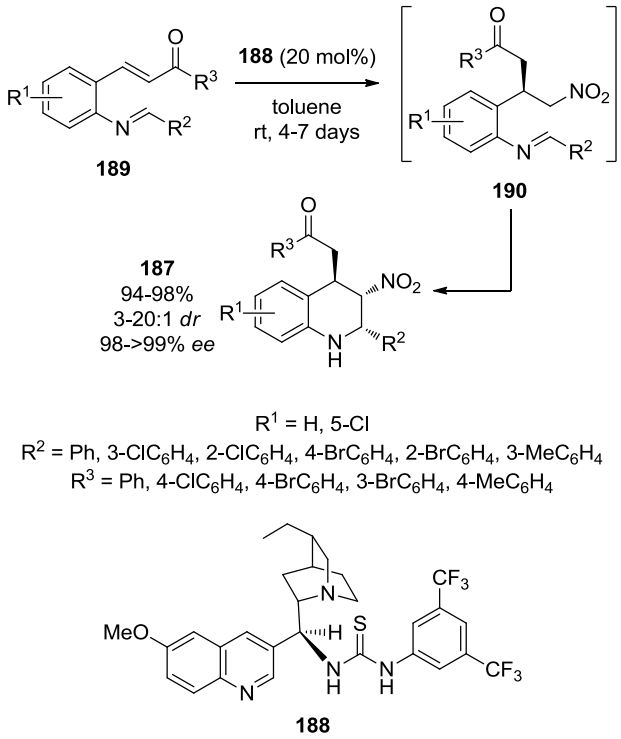
Several other examples of conjugate addition/nitro-Mannich/hemiaminalization reactions were reported by Yadav *et al.* (Scheme 112).[165–166] They extended the scope of this reaction to the conjugate addition of cyclohexanone and 1,3-cyclohexanedione. Using prolinol based catalyst **179** they formed a range of *cis*-decahydroquinolines **185** from cyclohexanone,[165] and octahydroquinolines **186** from 1,3-cyclohexanedione.[166] The products were formed in good to excellent yields and with excellent diastereo- and enantioselectivities.

Scheme 112. Synthesis of Hydroquinolines via Conjugate Addition/Nitro-Mannich Reactions



In 2011, Xu *et al.* published an alternative organocatalyzed conjugate addition/nitro-Mannich reaction (Scheme 113).[167] They reported an asymmetric synthesis of 3-nitrotetrahydroquinolines **187** catalyzed by thiourea **188**. The cascade sequence proceeds via initial conjugate addition of nitromethane to enone **189** and subsequent intramolecular nitro-Mannich reaction of nitroimine **190**. Tetrahydroquinolines **187** were formed in excellent yields and enantioselectivities, and moderate to good diastereoselectivities for a range of different imine substituents. The reaction did, however, fail for alkyl imine analogues such as those derived from ethyl glyoxylate (R^2 = CO_2Et). Also, the reaction relies on the use of aromatic ketones (R^3 = aryl), as alkyl ketones and esters failed to produce any of the desired products under the reaction conditions.

Scheme 113. Synthesis of 2-Nitrotetrahydroquinolines



10.2. Reactions with Organometallic Nucleophiles

There have also been a number of reports of conjugate addition/nitro-Mannich reactions which involve the use of organometallic reagents as nucleophiles in the conjugate addition. In 2011, Anderson *et al.* reported the application of asymmetric conjugate additions of dialkylzincs to nitroalkenes to conjugate addition/nitro-Mannich reactions (Scheme 114).[168] They implemented asymmetric dialkylzinc additions to nitroalkenes, developed by the groups of Hoveyda[169] and Charette,[170] to form zinc nitronates **191**. They were then able to perform highly diastereoselective nitro-Mannich reactions by the introduction of *N*-PMP-imines and trifluoroacetic acid (TFA). Selective formation of either the *anti*-*β*-nitroamines **192a** and **192b** or the rare *syn*-*β*-nitroamines **193a** and **193b** with excellent stereocontrol over three contiguous stereocentres was achieved by variation of the solvent used in the nitro-Mannich reaction and the ligand (**194** or **195**) used in the conjugate addition reaction. The procedures gave uniformly high yields and

stereoselectivities for a range of aryl and heteroaryl nitroalkenes and aryl, heteroaryl and alkyl imines. The authors postulate that the observed diastereoselectivity arises from the differing solubility of $Zn(O_2CCF_3)_2$, formed upon addition of TFA to the reaction mixture, in THF and Et_2O. When the reactions were performed in THF the $Zn(O_2CCF_3)_2$ remained in solution. Coordination of the nitronate and imine to the Zn^{2+} species enables the formation of closed chair-like TS **196** and, with the chiral nitronate side chain occupying an equatorial orientation, leads to the *syn*,*anti*-diastereomers **192a** and **192b** (Figure 2) The poor solubility of $Zn(O_2CCF_3)_2$ in Et_2O resulted in precipitation of this species from the reaction. With no Zn^{2+} species available to form a coordinated complex, the reaction proceeds via open TS **197**, leading to the *syn*,*syn*-diastereomers **193a** and **193b**.

Scheme 114. Asymmetric Dialkylzinc-Mediated Conjugate Addition/Nitro-Mannich Reactions

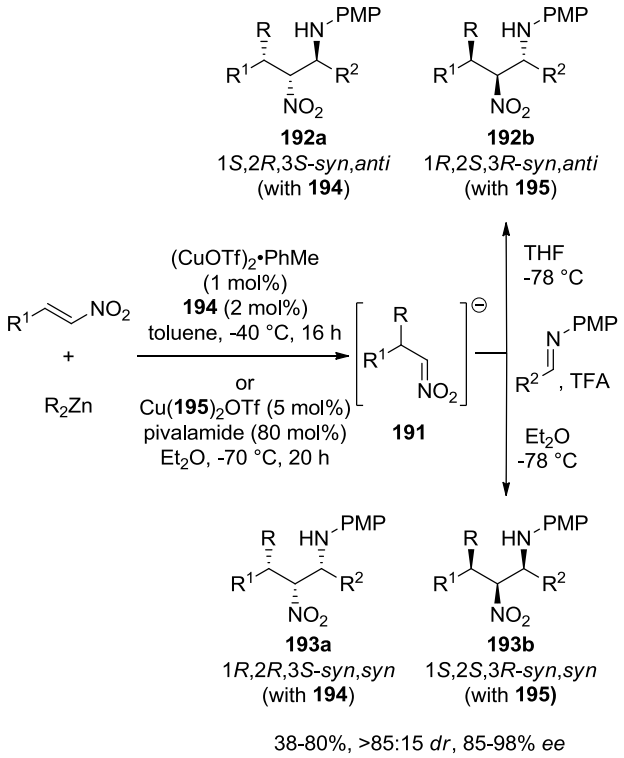
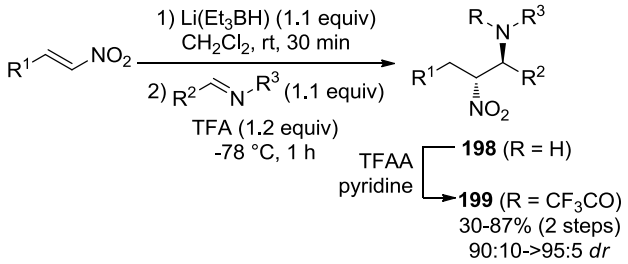


Figure 2. Proposed Transition States Leading to *Syn* and *Anti* Products.

The Anderson group have since expanded the scope of their conjugate addition nitro-Mannich methodology to include the use of hydride nucleophiles (Scheme 115).[171] This was achieved through the use of Li(Et_3BH) (Superhydride™) in the conjugate addition reaction, which forms a nitronate that can subsequently be trapped by the addition of an imine and a Brønsted acid. The authors showed that this reductive nitro-Mannich reaction was applicable to a range of nitroalkenes and aryl, heteroaryl and alkyl *N*-OMB and *N*-PMP imines. To prevent retro-addition the *β*-nitroamine products **198** were protected by treatment with trifluoroacetic anhydride (TFAA) to form *β*-nitroacetamides **199** in good to excellent yields and high *anti*-diastereoselectivities. The authors went on to demonstrate that *β*-nitroacetamides **199** could be reduced to differentially protected 1,2-diamines in excellent yields by using a zinc hydrochloride reduction.

Scheme 115. Li(Et_3BH)-Mediated Reductive Nitro-Mannich Reactions

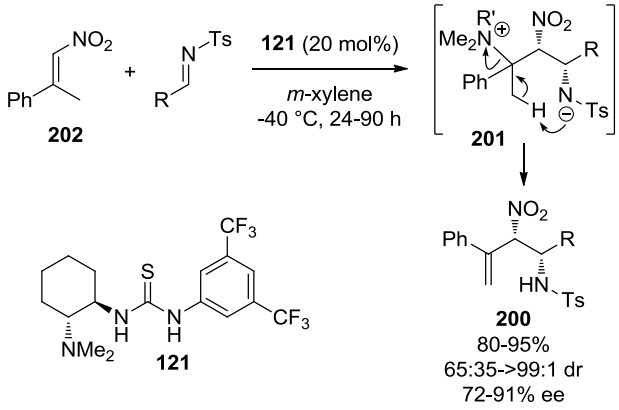


R^1 = ^{n}pentyl, cyclohexyl, ^{t}Bu, Ph, Bn, 4-$MeOC_6H_4$, 2-$MeOC_6H_4$, 4-$CF_3C_6H_4$, 2-$CF_3C_6H_4$, 4-MeC_6H_4, 2-MeC_6H_4, 2-furyl, 2-pyridyl, *N*-Me-2-pyrrole, *N*-Ts-2-pyrrole
R^2 = Ph, ^{n}pentyl, cyclohexyl, 2-furyl, 4-$MeOC_6H_4$, 3-$MeOC_6H_4$, 2-$MeOC_6H_4$, 4-$CF_3C_6H_4$, 2-$CF_3C_6H_4$, 2-MeC_6H_4, 2-pyridyl, 3-pyridyl, *N*-Ts-2-pyrrole, *N*-Ts-3-indole
R^3 = OMB, PMP

10.3. Aza-Morita-Baylis-Hillman Reactions

Another example of a conjugate addition/nitro-Mannich reaction is the aza-Morita-Baylis-Hillam reaction of nitroalkenes. This was first reported by Xu *et al.*[172] who used Takemoto's thiourea catalyst **121** in highly enantio- and diastereoselective aza-Morita-Baylis-Hillman-type reactions for the synthesis of *β*-nitro-*γ*-enamines **200** (Scheme 116). The reaction proceeds via a conjugate addition of the tertiary amine catalyst and subsequent nitro-Mannich reaction forming intermediate **201**. Intramolecular proton shift and *β*-elimination reforms **121** and generates the observed product **200**. Good to excellent yields and enantioselectivities were obtained for the reaction of a number of aryl, heteroaryl and alkyl *N*-tosyl-imines with nitroalkene **202**. The reactions were highly selective for the *syn*-diastereomers (confirmed by X-ray crystal analysis), however, no explanation of the origin of this rare relative stereochemistry was given.

Scheme 116. Aza-Morita-Baylis-Hillman-Type Reactions

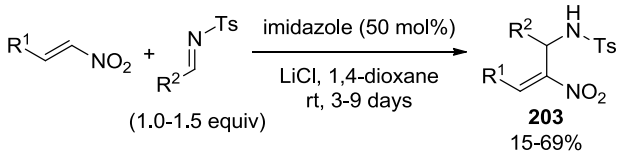


R = Ph, 2-MeC_6H_4, 2-BrC_6H_4, 2-FC_6H_4, 3-MeC_6H_4, 3-ClC_6H_4, 4-MeC_6H_4, 4-BrC_6H_4, 4-ClC_6H_4, 4-$NO_2C_6H_4$, 4-CNC_6H_4, 4-$MeOC_6H_4$, 2-furyl, ^{n}Pr

A number of other aza-Morita-Baylis-Hillman reactions involving nitroalkenes have also been reported. Namboothiri *et al.* reported the imidazole-catalyzed reaction of nitroalkenes with *N*-tosyl-imines (Scheme 117).[173] The reactions were, however, sluggish and the nitroallyl amine products **203** were formed in low to moderate yields. The same group also reported similar

higher yielding reactions of imines generated *in situ* from formaldehyde and cyclic secondary amines.[174]

Scheme 117. Imidazole-Catalyzed Aza-Morita-Baylis-Hillman Reactions

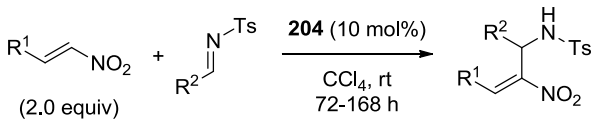


R^1 = 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 4-$MeOC_6H_4$, 3,4-$(MeO)_2C_6H_3$, 3,4-$(OCH_2O)C_6H_4$

R^2 = Ph, 2-furyl, 4-$MeOC_6H_4$

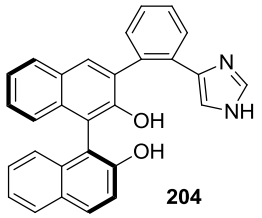
The group of Takizawa and Sasai later reported an enantioselective variant of this reaction utilizing the chiral BINOL-derived imidazole **204** (Scheme 118).[175] The nitroallyl amine products **203** were formed in moderate to excellent yields and with moderate enantioselectivities. The reaction demonstrated good scope with respect to the imine but relied on electron rich nitroalkenes to achieve good yields. The authors also reported the use of a similar catalyst to generate **203** in the opposite enantiomeric form with similar levels of selectivity.

Scheme 118. Enantioselective Aza-Morita-Baylis-Hillman Reactions



203
16-98%
21-57% *ee*

R^1 = 2-furyl, 4-$MeOC_6H_4$, 3,4-$(MeO)_2C_6H_3$
R^2 = Ph, 4-FC_6H_4, 4-ClC_6H_4, 4-$MeOC_6H_4$, 4-CNC_6H_4, 4-BrC_6H_4, 2-naphthyl

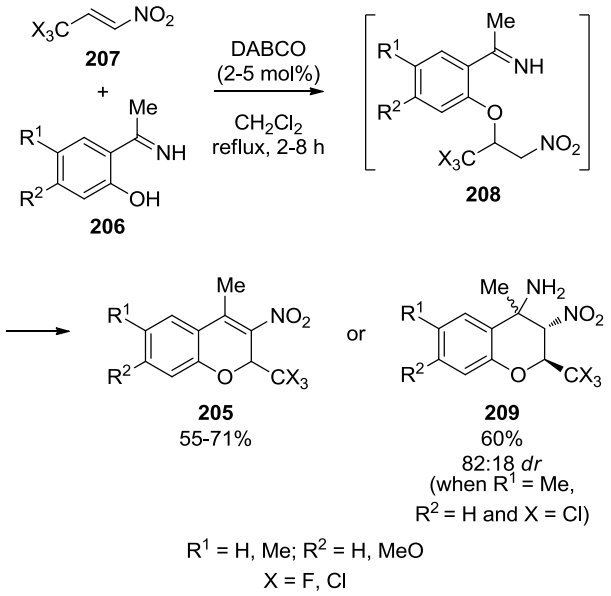


204

10.4. Synthesis of 3-Nitrochromene Derivatives

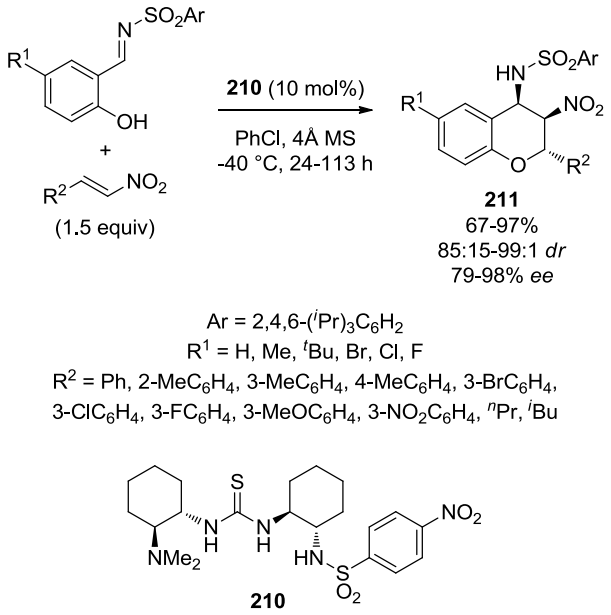
The use of oxygen nucleophiles has also been demonstrated in conjugate addition/nitro-Mannich reactions. Sosnovskikh *et al.* reported the first tandem oxy-Michael/nitro-Mannich reactions for the synthesis of 3-nitro-2*H*-chromenes **205** (Scheme 119).[176] The reaction of unsubstituted imines of 2-hydroxyacetophenones **206** with trihaloethylidene nitromethanes **207** in the presence of catalytic 1,4-diazabicyclo[2.2.2]octane (DABCO) proceeded via initial oxy-Michael addition to form *β*-nitroether **208**. Subsequent intramolecular nitro-Mannich reaction followed by elimination of ammonia formed chromenes **205** in moderate yields. The reaction was found to be sensitive to the substituents on the aromatic ring, as when R^1 was a methyl group the elimination of ammonia did not occur, resulting in isolation of *β*-nitroamine **209**. Furthermore, electron withdrawing groups or *ortho*-substituents on the aromatic ring inhibited the reaction, generally resulting in aza-Michael addition. The reaction was also found to be sensitive to the solvent used, with reactions performed in benzene favoring aza-Michael over oxy-Michael addition.

Scheme 119. DABCO-Catalyzed Synthesis of 3-Nitro-2*H*-chromenes



An enantioselective organocatalytic synthesis of 3-nitro-2*H*-chromenes of type **205** catalyzed by a quinine-based thiourea catalyst was later developed by Schreiner and co-workers but they only achieved low to moderate enantioselectivities.[177] An improved procedure was later reported by Peng *et al.*[178] They used chiral thiourea **210** to catalyze the oxy-Michael/nitro-Mannich reaction cascade (Scheme 120). Their method also prevented elimination of the amino group, thereby allowing the synthesis of a range of 4-amino-3-nitrobenzopyrans **211**. The oxy-Michael/nitro-Mannich cascade reactions of *N*-sulfonyl-salicylaldimines with a variety of aryl and alkyl nitroalkenes proceeded in excellent yields, enantio- and diastereoselectivities. The authors then went on to demonstrate that the products could be used in high yielding syntheses of 3,4-diaminochromanes via reduction of the nitro group.

Scheme 120. Organocatalytic Enantioselective Synthesis of 4-Amino-3-nitrobenzopyrans



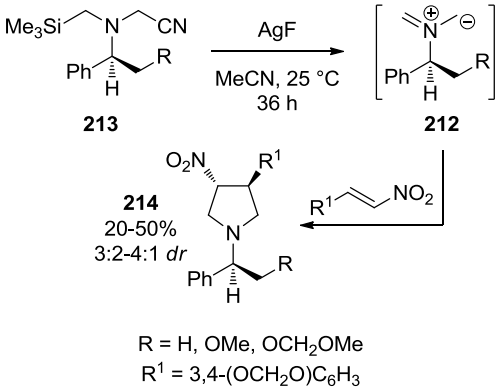
10.5. [3+2] Cycloadditions

The [3+2] cycloaddition of azomethine ylides with nitroalkenes provides a method for the expedient synthesis of 3-nitropyrrolidines. Due to nitroalkenes being highly π-deficient they behave as Michael acceptors and the majority of these [3+2] cycloaddition reactions actually consist of tandem conjugate addition/nitro-Mannich reaction sequences, rather than proceeding through a concerted mechanism. This stepwise mechanism has been supported through a number of mechanistic studies by the group of Cossío,[179–182] although a concerted mechanism is also possible, depending on the substituents on the dipole and dipolarophile.[180]

The first [3+2] cycloaddition reactions of azomethine ylides with nitroalkenes were reported by Padwa *et al.* in 1985 (Scheme 121).[183] The authors formed chiral azomethine ylides **212** *in situ* by the treatment of *α*-cyanoaminosilanes **213** with silver fluoride. These then reacted with a variety of electron deficient alkenes, including nitroalkenes, in [3+2] cycloadditions to form a range of pyrrolidines. The 3-nitropyrrolidine products **214** were formed in low to moderate yields and diastereoselectivities. The group of Tőke performed similar reactions but formed their

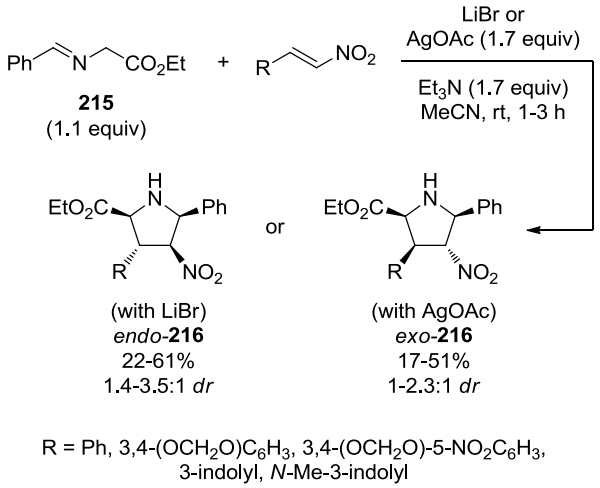
azomethine ylides by a decarboxylative condensation of *N*-methylglycine with paraformaldehyde.[184–185]

Scheme 121. AgF-Mediated [3+2] Cycloaddition Reactions



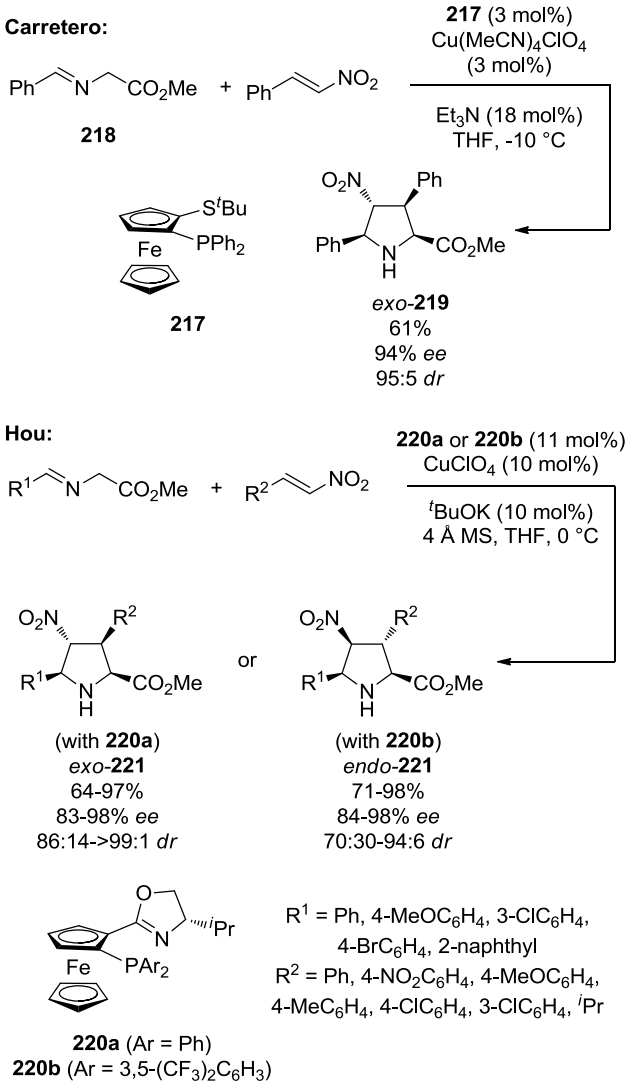
The group of Tőke also broadened the scope of these [3+2] cycloaddition reactions by using glycine-derived imines **215** as azomethine ylides (Scheme 122).[186–187] They found that selective formation of both *exo* and *endo* cycloadducts was possible by using either AgOAc or LiBr, respectively. The pyrrolidine products **216** were formed in low to good yields and with moderate diastereoselectivities. Cossío *et al.* later reported a more detailed study into the effect of using lithium and silver salts on the *exo*/*endo* selectivity of these [3+2] cycloaddition reactions.[179] A number of other groups have also reported the use of similar conditions.[188–189]

Scheme 122. *Exo* and *Endo* Selective [3+2] Cycloaddition Reactions



The first enantioselective catalytic [3+2] cycloaddition reaction of a nitroalkene was reported by Carretero *et al.* in 2005 (Scheme 123).[190–191] They used planar chiral ferrocene-phosphine ligand **217** in the Cu-catalyzed [3+2] cycloaddition of azomethine ylide **218** with a variety of electron deficient alkenes, including a single example with a nitroalkene. The 3-nitropyrrolidine product **219** formed in good yield and excellent enantio- and *exo*-selectivity. The use of a similar ferrocene-based ligand was later reported by the group of Hou, who demonstrated a broad substrate scope and developed both *exo*- and *endo*-selective procedures by simple variation of the electronics of chiral ferrocene-phosphine ligand **220** (Scheme 123).[192] Excellent yields and enantioselectivities were achieved for both the *endo*- and *exo*-products **221**. The same group later utilized this methodology in the synthesis of 3-trifluoromethyl proline derivatives.[193] There have since been a number of other transition metal catalyzed [3+2] cycloaddition reactions reported, including highly *endo*-selective Cu-catalyzed and *exo*'-selective Ni-catalyzed reactions by Arai *et al.*,[194–195] and *endo*- and *exo*-selective Cu-catalyzed reactions by Oh *et al.*[196]

Scheme 123. Enantioselective Cu-Catalyzed [3+2] Cycloaddition Reactions

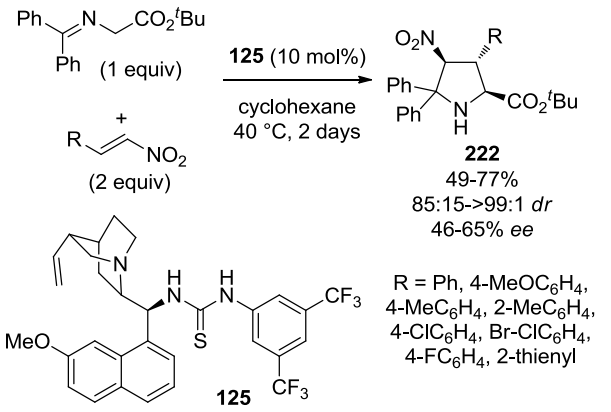


A number of asymmetric organocatalytic [3+2] cycloaddition reactions have also been reported. In 2008, the groups of Zhang, Chen and Takemoto all reported organocatalyzed *endo*-selective [3+2] cycloaddition reactions (Scheme 124).[197–199] Zhang *et al.* used cinchona-derived thiourea **125** to promote the formation of pyrrolidines **222** in moderate to good yields and enantioselectivities and excellent diastereoselectivities.[197] Chen *et al.* used thiourea **223** to promote the three-component [3+2] cycloaddition reaction between α-aminomalonate **224** and a number of aldehydes and nitroalkenes.[198] The products were formed in good to excellent yields and enantioselectivities and with excellent *endo*-selectivity. During their investigations into

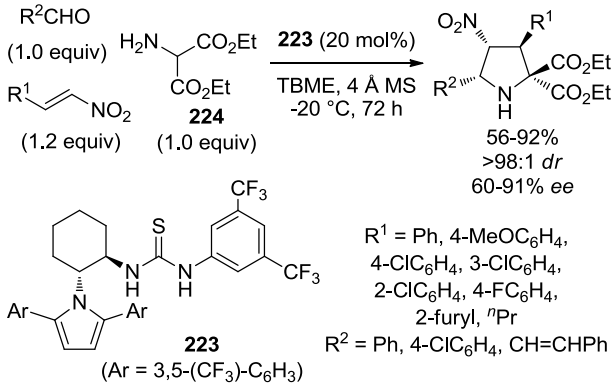
similar three-component organocatalytic [3+2] cycloaddition reactions, the group of Rios found the same reaction could be performed in the absence of a catalyst to form the [3+2] adducts with excellent levels of *exo*-selectivity.[200] Takemoto *et al.* found that thiourea **121** efficiently catalyzed the conjugate addition of α-amino-malonate imines to nitroalkenes but the addition of 2,2,2-trifluoroethanol (TFE) to the reaction after completion of the conjugate addition was required to affect the desired nitro-Mannich reaction. They observed that the intramolecular nitro-Mannich reaction required both thiourea **121** and TFE to proceed, indicating that a cooperative reactivity between **121** and TFE is involved. The reaction gave excellent results for a range of aryl nitroalkenes but the presence of an electron withdrawing group on the imine substituent was required to achieve high enantioselectivities.

Scheme 124. Enantioselective Organocatalyzed [3+2] Cycloaddition Reactions

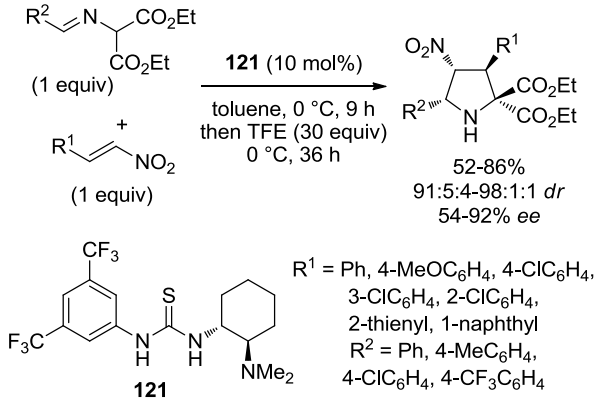
Zhang:



Chen:



Takemoto:

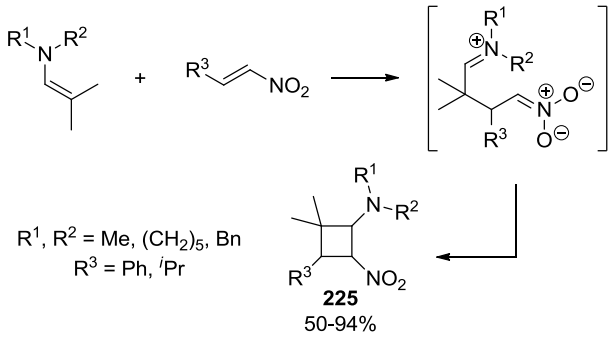


10.6. [2+2] Cycloadditions

The formal [2+2] cycloaddition reaction of enamines and nitroalkenes, proceeding via a conjugate addition/nitro-Mannich reaction sequence, has also been reported. In 1964, the group

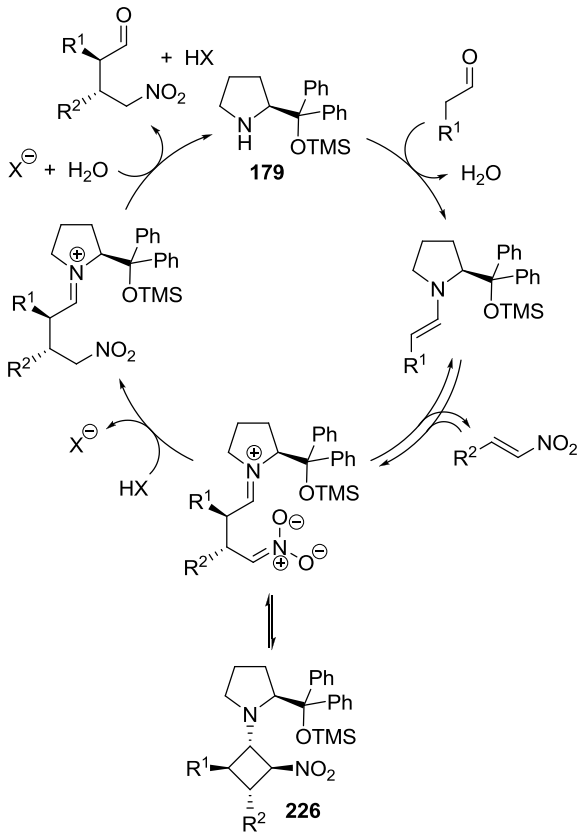
of Brannock synthesized a number of cyclobutanes **225** while investigating the conjugate addition of enamines to nitroalkenes (Scheme 125).[201] The reaction of a number of enamines derived from secondary amines and isobutyraldehyde with nitroalkenes gave the cyclobutane products **225** in moderate to good yields. Other groups have also reported the isolation of similar products as intermediates in conjugate additions of enamines to nitroalkenes.[188,202–204]

Scheme 125. Formal [2+2] Cycloadditions of Enamines with Nitroalkenes



More recently, the groups of Blackmond and Seebach independently investigated the mechanism of diarylprolinol TMS-ether **179**-catalyzed Michael additions of aldehydes to nitroalkenes.[205–206] Both groups discovered that cyclobutane **226**, formed by a conjugate addition/nitro-Mannich reaction sequence, was formed reversibly as an off-cycle resting state of the catalyst, a so-called "parasitic" catalytic species (Scheme 126). Blackmond also suggested that this species played a role in the maintenance of high stereoselectivity in these Michael addition reactions. In a later publication, Blackmond *et al.* reported further mechanistic studies and proposed that cyclobutane **226** actually forms as an on-cycle catalyst resting state.[207]

Scheme 126. Formation of [2+2] Cycloaddition Intermediates in Organocatalyzed Conjugate Addition Reactions



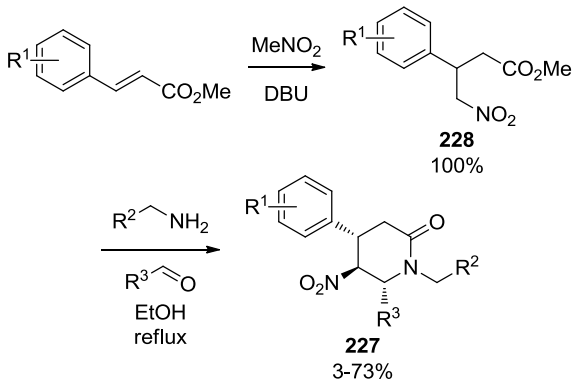
11. CASCADE REACTIONS

11.1. Nitro-Mannich/Lactamization Cascades

As was mentioned earlier, the groups of Mühlstädt and Jain reported the synthesis of 5-nitropiperidin-2-ones using nitro-Mannich/lactamization cascades (see Schemes 28 and 29).[75–76] Subsequent reports by Desai demonstrated that this methodology was useful for the rapid synthesis of a range of piperidinones whose biological activities could then be assessed.[77–78] Consequently, this methodology has since been used by a number of other groups for investigations into the pharmacological effects of novel piperidine structures. Kanda *et al.* synthesized a series of 5-nitro-piperidin-2-ones **227** and discovered them to be potent farnesyltransferase inhibitors (Scheme 127).[208–209] They generated a number of substituted methyl 4-nitrobutanoates **228** via a Michael addition of nitromethane to the corresponding cinnamate

derivative. The subsequent nitro-Mannich lactamizations were performed with a variety of aryl aldehydes and benzylamines to give the products in excellent diastereoselectivities and low to good yields.

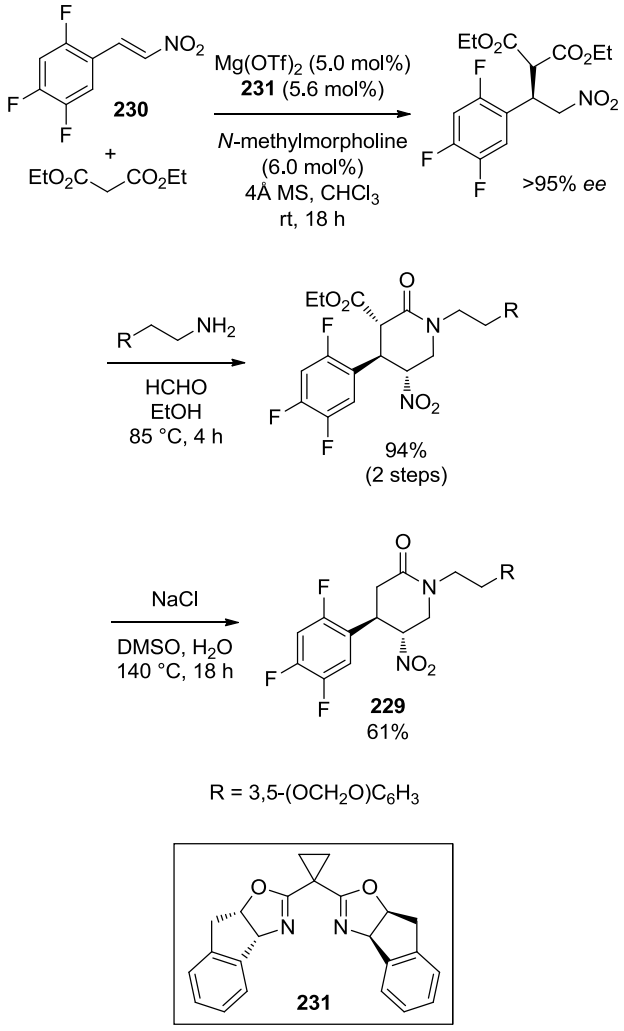
Scheme 127. Synthesis of Potent 5-Nitropiperidin-2-one Farnesyltransferase Inhibitors



R^1 = H, Br, Cl, Me
R^2 = 3-pyridyl, 4-pyridyl,
R^3 = 4-HOC_6H_4, 4-$MeOC_6H_4$, 3,4-$(HO)_2C_6H_3$,
3-NH_2-4-HOC_6H_3

In 2007, Pei *et al.* used similar chemistry to synthesize a range novel piperidinones and piperidines, which were used to investigate structure-activity relationships in dipeptidyl peptidase IV inhibition.[210] The group also demonstrated an asymmetric synthesis of piperidinones **229** by performing a highly enantioselective Michael addition of diethylmalonate to nitroalkene **230** using chiral BOX-ligand **231** (Scheme 128). Subsequent nitro-Mannich/lactamization, with a number of primary alkylamines and formaldehyde, and decarboxylation yielded the piperidinones **229** in good yields and excellent *trans* diastereoselectivities. The group of Xu has since used a similar procedure for the synthesis of other dipeptidyl peptidase IV inhibitors.[211]

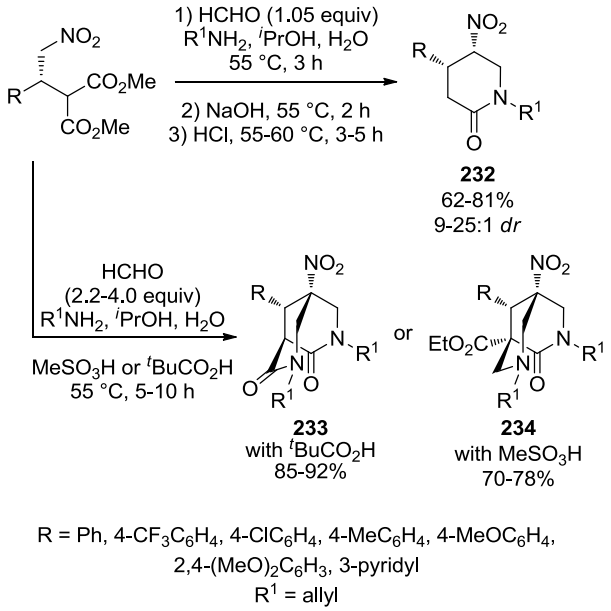
Scheme 128. Asymmetric Synthesis of Piperidinone Dipeptidyl Peptidase IV Inhibitors



In 2007, Xu *et al.* published similar results to those obtained by the group of Pei. The group were able to develop a one-pot protocol for the synthesis of piperidinones **232** that involved nitro-Mannich/lactamization and decarboxylation steps (Scheme 129).[212] Piperidinones **232** were formed in good yield and high *cis* diastereoselectivity, which is in contrast to the *trans* selectivity observed by Pei *et al.*[210] The switch in selectivity was found to result from an epimerization process that occurred under the acidic decarboxylation conditions. The *trans* diastereomer could be obtained selectively from *cis*-**232** via a base-catalyzed dynamic crystallization-driven process. The group also reported that reactions with excess formaldehyde enabled the synthesis of bispidines **233** and **234** by additional nitro-Mannich/lactamization or nitro-Mannich/Mannich

sequences, respectively. Each product could be formed selectively by varying the acid used in the reaction. The presence of a strong acid, such a methanesulfonic acid ($MeSO_3H$), prevented lactamization by protonation of an amine intermediate, therefore resulting in a Mannich reaction to form bispidine **234**. The presence of a weak acid, such as pivalic acid ($^tBuCO_2H$), enabled efficient lactamization, therefore favoring the formation of bispidine **233**.

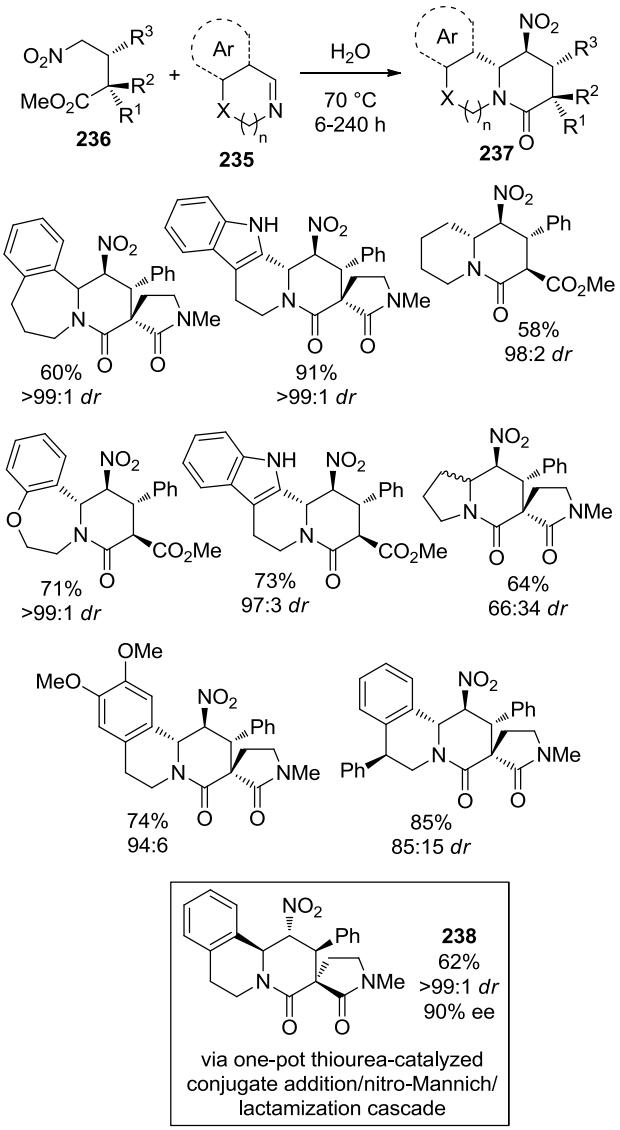
Scheme 129. Nitro-Mannich/Lactamizations for the Synthesis of Piperidinones and Bispidines



In 2008, Dixon *et al.* expanded the scope of the nitro-Mannich/lactamization methodology developed by the groups of Pei[210] and Xu[211–212] to include a variety of cyclic imines **235** (Scheme 130).[213] The reaction of a number of *γ*-nitroesters **236** with a range of cyclic imines **235** gave polycyclic products **237** in moderate to good yields and with excellent diastereoselectivities over four contiguous stereocentres. The authors found that the use of water as the solvent was crucial to obtaining high yields for the reactions. The synthesis was shown to be tolerant of five-, six- and seven-membered ring imines. However, the diastereoselectivities were lower for the reaction with a five-membered ring imine. The authors proposed that the high diastereoselectivities arise

from the differential rates of lactamization of the diastereomeric intermediates, which are formed by a reversible nitro-Mannich reaction. The authors went on to demonstrate that a one-pot asymmetric conjugate addition/nitro-Mannich/lactamization sequence could be performed to generate the highly enantioenriched polycyclic lactam **238** in high yield and diastereoselectivity, from the corresponding nitroalkene, malonate and cyclic imine. The same group later further expanded the scope of this methodology to a range of acyclic imines and they also presented a more detailed discussion with regards to the observed diastereoselectivity of the reactions.[214]

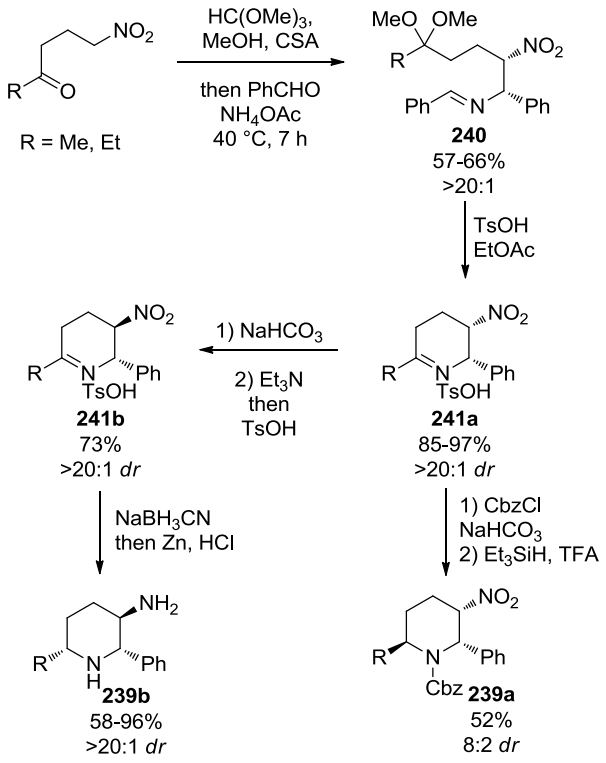
Scheme 130. Synthesis of Polycyclic Lactams via Nitro-Mannich/Lactamizations of Cyclic Imines



In 2009, the group of Humphrey and O'Neill reported a variation on the nitro-Mannich/lactamization methodology that allowed the synthesis of all four possible diastereomers of 2,3,6-trisubstituted piperidines **239** (Scheme 131).[215] The synthesis proceeded via a nitro-Mannich reaction between *γ*-nitroketones, benzaldehyde and ammonium acetate to yield *β*-nitroamine **240**. The authors found that prior protection of the ketone moiety as an acetal was required so as to avoid undesired Mannich side reactions. The product could be formed in excellent diastereoselectivity by using a thermodynamically driven crystallization process. Treatment of *β*-nitroamine **240** with *p*-toluenesulfonic acid (TsOH) affected the hydrolysis of the

imine and cyclization to form tetrahydropyridine **241a** as a single *cis*-diastereomer. Base catalyzed epimerization of **241a** enabled the formation of the *trans*-diastereomer **241b** in excellent diastereoselectivity. The group then demonstrated that selective reduction of **241a** and **241b** to give either the 2,6-*trans*-piperidines **239a** or the 2,6-*cis*-piperidines **239b** was possible by varying the reduction protocol. This enabled the selective synthesis of all four possible diastereomers of piperidines **239**.

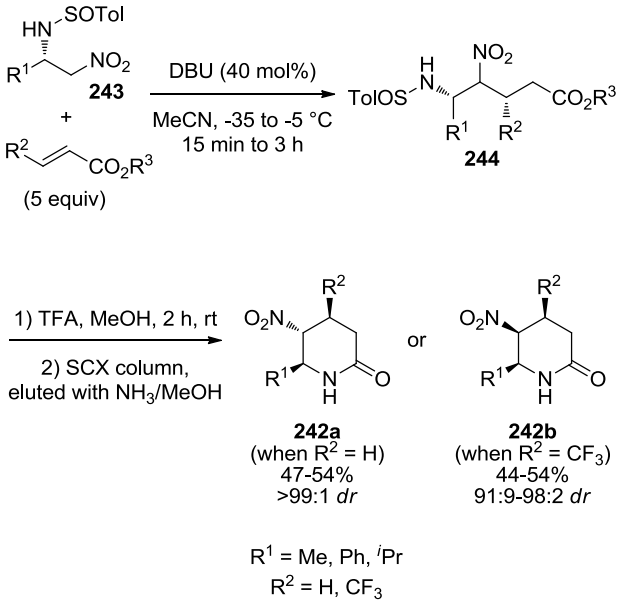
Scheme 131. Diastereoselective Synthesis of 2,3,6-Trisubstituted Piperidines



In 2008, the group of Ruano and Cid published an alternative synthesis of 5-nitropiperidinones **242** via the reaction of *N*-*p*-tolylsulfinyl-*β*-nitroamines **243** with *α*,*β*-unsaturated esters (Scheme 132).[216] The reaction of **243**, generated using their previously reported method,[87] involved a DBU-mediated Michael addition to *α*,*β*-unsaturated esters forming *γ*-nitro-*δ*-amino acid esters

244. These were then treated with TFA to affect the tandem desulfinylation/lactamization sequence to generate a range of enantiopure 5-nitropiperidinones **242** in moderate yields over three steps. The products could be obtained in excellent diastereoselectivities after epimerization of stereocentre α to the nitro group during purification by strong cation exchange (SCX) chromatography. The relative stereochemistry of the products was found to be highly dependent on the α,β-unsaturated ester substituent (R^2), as when β-trifluoromethyl ethyl acrylate ($R^2 = CF_3$, R^3 = Et) was used the piperidinone products **242b** were found to possess a *cis*,*cis*-configuration. The authors also demonstrated the synthetic utility of this methodology as one analogue (R^1 = Ph, R^2 = H) represented a formal synthesis of CP-99994 (**58**).

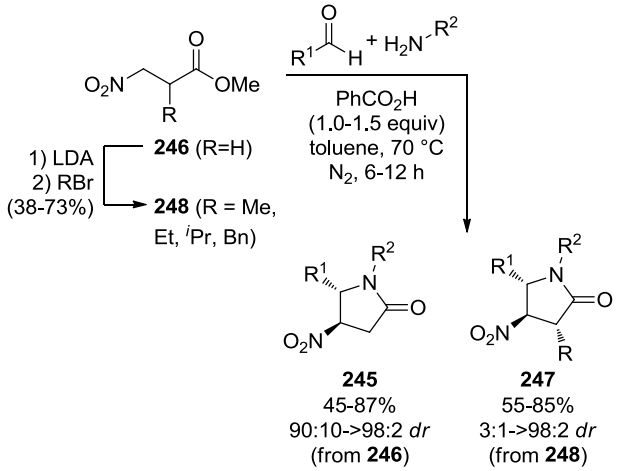
Scheme 132. Michael Addition/Desulfinylation/Lactamization Sequence for the Synthesis of 5-Nitropiperidinones



Dixon's group later expanded the nitro-Mannich/lactamization methodology to the synthesis of pyrrolidinones **245** by utilizing methyl-3-nitropropanoate (**246**) and a variety of *in situ* formed alkyl and aryl imines (Scheme 133).[217–218] Unlike their reactions for the formation of

piperidinones,[213] no reaction occurred when using water as a solvent. The optimum conditions were found to be with degassed toluene, under an atmosphere of N_2 and with an equivalent of benzoic acid. A wide variety of aldehydes and amines were tolerated, with pyrrolidinones **245** being formed in moderate to good yields and excellent diastereoselectivities. The reaction was also applicable to cyclic imines but the stereoselectivities were found to be lower. In a later publication, the authors also reported a synthesis of 1,3,5-trisubstituted 4-nitropyrrolidin-2-ones **247** (Scheme 133).[218] This was achieved by alkylating **246**, forming **248**, prior to the nitro-Mannich/lactamization cascade. Alkylation prior to the nitro-Mannich/lactamization was found to be necessary to introduce functionality α to the carbonyl as all attempts to alkylate **245** failed.

Scheme 133. Pyrrolidinone Synthesis Using Nitro-Mannich/Lactamization Cascades

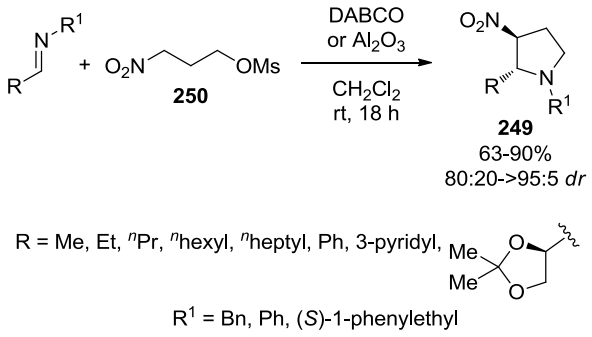


R^1 = ^{i}Pr, ^{n}pentyl, 3-cyclohexenyl, 1-phenylethyl, 4-ClC_6H_4, 2-$MeOC_6H_4$, 3-$MeOC_6H_4$, 4-$MeOC_6H_4$, 2-$NO_2C_6H_4$, 4-$TMSCCC_6H_4$, 2-pyridyl, 2-furyl, 3-furyl, 2-thienyl
R^2 = ^{n}Bu, ^{i}Pr, allyl, Bn, CH_2(2-naphthyl), CH_2CO_2Et, $(CH_2)_2$-1-cyclohexenyl, $(CH_2)_2$-3-$MeOC_6H_4$, $(CH_2)_2$-3-indolyl, $(CH_2)_3Cl$, $(CH_2)_5OH$, $(CH_2)_3CH(OEt)_2$

In 2004, Benetti *et al.* demonstrated a tandem nitro-Mannich/alkylation reaction sequence for the synthesis of 2-substituted 3-nitropyrrolidines **249** (Scheme 134).[219] The reaction of a variety

of imines with 3-nitro-1-propanol methanesulfonate **250** was promoted by either basic alumina or catalytic amounts of DABCO to form the corresponding 3-nitropyrrolidines **249** in good to excellent yields and high selectivity for the *trans* diastereomers. They also performed the reaction with a number of enantiopure imines and amines to form the pyrrolidine products in enantioenriched form.

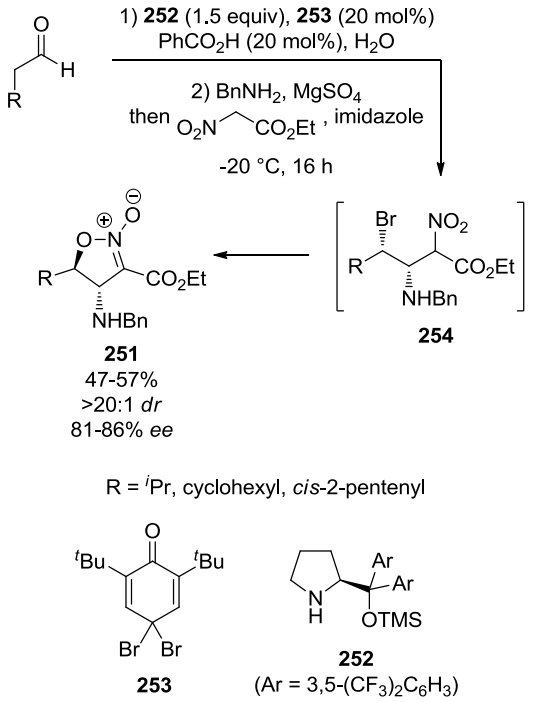
Scheme 134. Pyrrolidine Synthesis Using a Nitro-Mannich/Alkylation Cascade



11.2. Other Cascade Reactions

In 2009, Jørgensen *et al.* reported the synthesis of 4-amino-isoxazoline-*N*-oxides **251** via an enantioselective *α*-bromination/imination/nitro-Mannich/cyclization sequence. (Scheme 135).[220] The sequence begins with an enantioselective *α*-bromination reaction of an aldehyde using the TMS-protected prolinol catalyst **252** and bromination reagent **253**. The *α*-bromoaldehyde product then undergoes imination with benzylamine and reacts with ethyl nitroacetate in a base-induced nitro-Mannich reaction to form *β*-amino-*α*-nitroester **254**. Subsequent deprotonation *α* to the nitro group and intramolecular S_N2-type *O*-alkylation furnished **251** in moderate yields and excellent diastereo- and enantioselectivities.

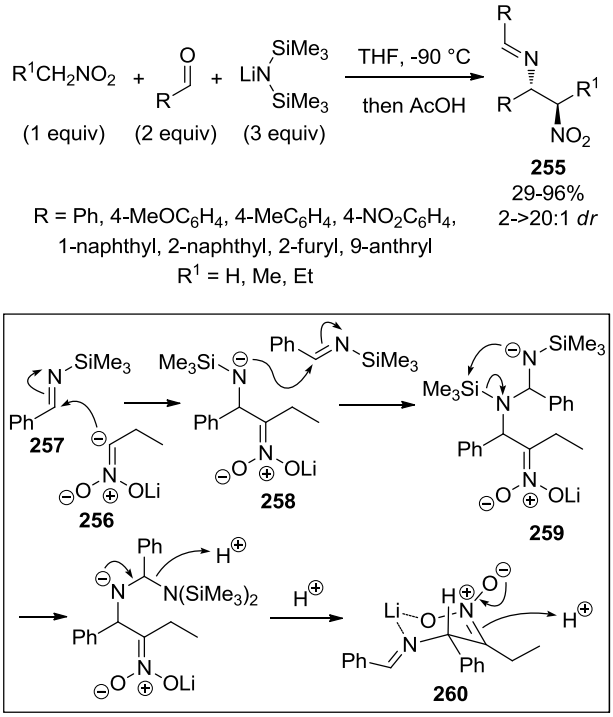
Scheme 135. Enantioselective Synthesis of 4-Amino-isoxazoline-*N*-oxides



In 2008, Tanaka *et al.* reported a "double" nitro-Mannich reaction for the synthesis of nitroimines **255** (Scheme 136).[221] The reaction involves a four-component coupling of LiHMDS, a nitroalkane and two equivalents of an aryl aldehyde. The product nitroimines **255** were formed in moderate to excellent yields and with low to good *anti* diastereoselectivities. The reaction proceeds via initial double deprotonation of the nitroalkane to form nitro-dianion **256**. The resulting hexamethyldisilane reacts with an aldehyde to form silyl imine **257**. After the initial nitro-Mannich reaction the resulting aza anion **258** undergoes a Mannich-type reaction with another equivalent of **257** to form intermediate **259**, which then eliminates hexamethyldisilane upon quenching with acid. The observed diastereoselectivity arises from the chelated six-membered ring complex **260**, which undergoes protonation from the least hindered face to give the observed *anti* products. The authors found that protonation at low temperatures (-90 °C) was required to achieve good selectivity. The same group later reported a modification of this

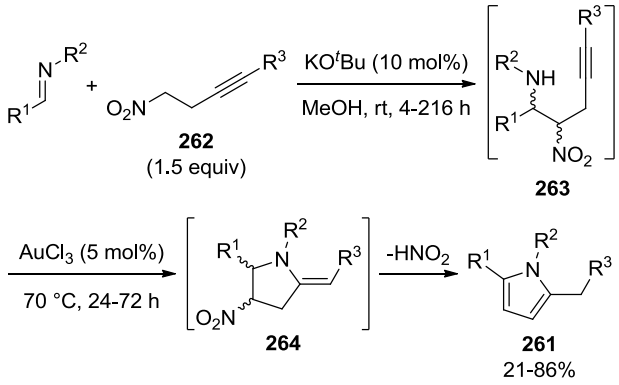
reaction that involved a retro-Henry/nitro-Mannich/Mannich cascade of *β*-nitroalcohols to give the same nitroimine products **255**.[222]

Scheme 136. Nitro-Mannich/Mannich Cascade Reactions



In 2011, Dixon *et al.* reported a one-pot nitro-Mannich/hydroamination cascade reaction for the synthesis of 2,5-disubstituted pyrroles **261** (Scheme 137).[223] The reaction proceeds via initial KO^{t}Bu-catalyzed nitro-Mannich reaction between 4-nitro-1-butyne (**262**) and an imine to form *β*-nitroamines **263**, followed by $AuCl_3$-catalyzed hydroamination and elimination of nitrous acid from dihydropyrrole **264** to form pyrroles **261**. The products were formed in moderate to good yields for a range of *N*-tosyl aryl imines. The reaction also tolerated *N*-nosyl imines but *N*-Boc imines were less reactive and led to reduced yields. Substituted alkynes (R^3 = Me) were unreactive under their reaction conditions but the authors found that the desired product could be obtained, albeit in low yield, by switching to a $Au(PPh_3)Cl$/AgOTf catalyst system.

Scheme 137. Synthesis of Pyrroles via Nitro-Mannich/Hydroamination Cascade Reactions



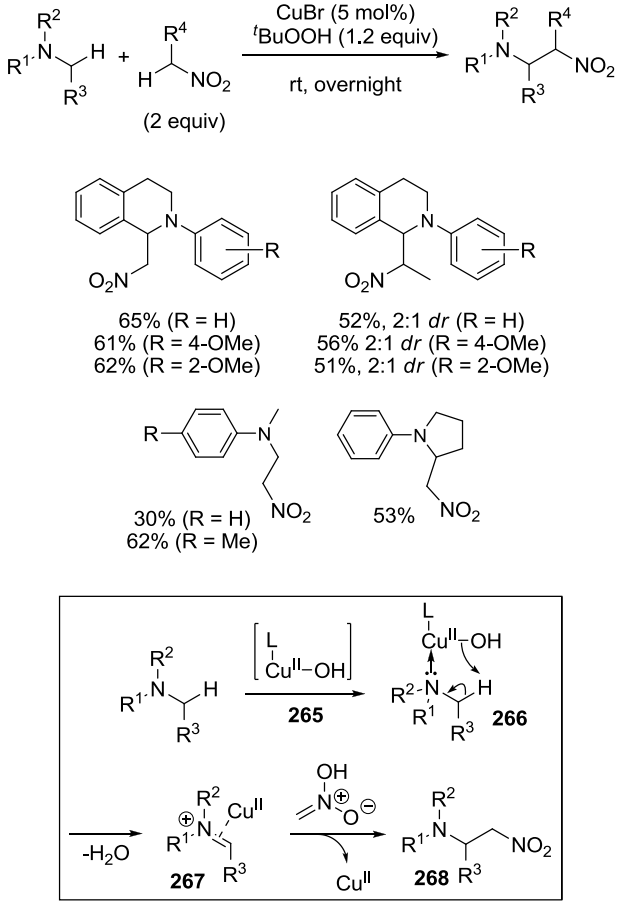
R^1 = Ph, 2-MeOC$_6$H$_4$, 3-MeOC$_6$H$_4$, 4-MeOC$_6$H$_4$, piperonyl, 2-FC$_6$H$_4$, 3-FC$_6$H$_4$, 4-FC$_6$H$_4$, 3,5-F$_2$C$_6$H$_3$, 4-CF$_3$C$_6$H$_4$, 2-NO$_2$C$_6$H$_4$, 4-MeO$_2$CC$_6$H$_4$, 4-MeC$_6$H$_4$, 2-thienyl
R^2 = Ts, Ns, Boc
R^3 = H, Me

12. CROSS DEHYDROGENATIVE COUPLING REACTIONS

Cross dehydrogenative coupling (CDC) reactions involve the direct coupling of active C–H nucleophiles with C–H bonds *α* to tertiary amines, effectively demonstrating the direct coupling of two sp^3 centres. As a result of their high reactivities, nitroalkanes have been used by many groups as substrates in CDC reactions. These reactions, proceeding via initial oxidation of the tertiary amine to an iminium species, can be considered as oxidative nitro-Mannich processes. The first use of CDC chemistry for nitro-Mannich reactions was reported by Li *et al.* in 2005.[224] They used a simple Cu(I)-catalyst in combination with *tert*-butylhydroperoxide (TBHP) to achieve CDC reactions between a number of cyclic and acyclic tertiary amines and simple nitroalkanes to form *β*-nitroamines in moderate to good yields (Scheme 138). The authors later reported an improved procedure that used fewer equivalents of nitroalkane to give the same products in improved yields.[225] They propose an ionic mechanism that begins with oxidation of

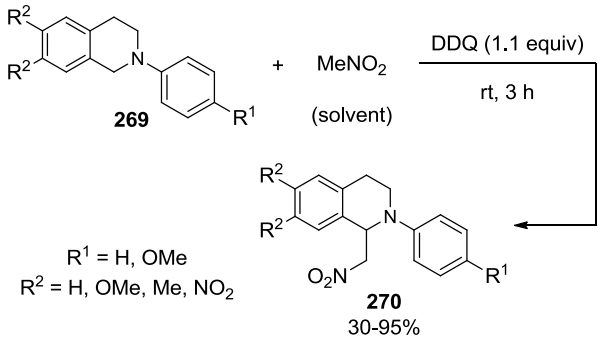
the copper catalyst to oxy-copper species **265** by TBHP. This highly Lewis acidic species coordinates to the nitrogen forming intermediate **266**. Iminium **267** is then formed by elimination of water through a five-membered ring TS. Nucleophilic attack of iminium **267** by a nitronic acid species forms *β*-nitroamine **268**. The same group later reported a safer and more atom economical CuBr-catalyzed CDC reaction that was performed in water and with molecular oxygen as the oxidant, which replaced the potentially explosive peroxide.[226] The new protocol gave slightly improved yields compared to those obtained in the TBHP-mediated reactions. Li *et al.* also demonstrated that the oxygen-mediated process could be performed in ionic liquids, which enabled easy recycling of the copper catalyst; or electrochemically, to eliminate the need to use a metal catalyst.[227] The group of Klussmann has since performed studies into the mechanism of these oxygen and TBHP-mediated Cu-catalyzed CDC reactions.[228]

Scheme 138. CDC Reactions of Tertiary Amines and Nitroalkanes



In 2009, Todd *et al.* reported an alternative metal-free CDC reaction of *N*-aryl tetrahydroisoquinolines **269** and nitromethane mediated by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (Scheme 139).[229] The reactions yielded the *β*-nitroamine products **270** in moderate to excellent yields. In 2011, Su *et al.* reported a solvent-free variant of this DDQ-mediated CDC reaction achieved through the use of high speed ball milling.[230] The products were formed in comparable yields to those obtained under stirring conditions and benefitted from shorted reaction times and required fewer equivalents of nitroalkane. Liang *et al.* have also reported a high yielding metal-free CDC reaction of *N*-aryl tetrahydroisoquinolines **269** and nitroalkanes mediated by hypervalent iodine(III) reagent $PhI(OAc)_2$.[231]

Scheme 139. DDQ-Mediated CDC Reactions of Tetrahydroisoquinolines and Nitroalkanes



In 2010, Stephenson *et al.* reported an alternative CDC nitro-Mannich reaction that utilized visible-light photoredox catalysis (Scheme 140).[232] They implemented Ir(III)-catalyst **271** in high yielding reactions of a variety of *N*-aryl tetrahydroisoquinolines **269** with nitromethane and nitroethane. The reaction of *N*-phenylpyrrolidine was also investigated but, as it is a non-benzylic amine, the reaction was markedly slower and only resulted in an isolated yield of 27% after 72 hours. The authors proposed a mechanism involving initial excitation of the iridium catalyst by visible light to affect reduction of the tertiary amine to form radical cation **272** (the presence of visible light was found to be necessary as no conversion was observed when the reaction was performed in the dark). Proton extraction then leads to iminium **273** which reacts with nitromethane to give *β*-nitroamine **274**. The same group later reported the use of a Ru photocatalyst that efficiently catalyzed the same CDC nitro-Mannich reactions when using $BrCCl_3$ as a stoichiometric oxidant,[233] a process that was later also successfully performed in a flow reactor.[234] The group of Lin reported similar photoredox reactions catalyzed by Ru and Ir complexes incorporated into porous cross-linked polymers (PCP).[235–237] These heterogeneous catalysts showed comparable reactivity to their homogeneous counterparts and also enabled efficient recycling of the catalysts. In 2011, König *et al.* reported that eosin Y (**275**, Figure 3), a cheap and environmentally friendly organic dye, could be used instead of expensive and toxic Ir and Ru complexes as an effective photoredox catalyst for oxidative nitro-Mannich reactions.[238]

Good yields, although slightly lower than those obtained by Stephenson *et al.*,[232] were reported for the reaction of a number of *N*-aryl tetrahydroisoquinolines **269** with nitromethane, nitroethane and 1-nitropropane. This use of eosin Y (**275**) as an organophotocatalyst for CDC nitro-Mannich reactions was later extended by the group of Wu.[239] They found that the bis-tetrabutylammonium salt of eosin Y is an efficient catalyst for the reaction.

A variety of other metal catalysts have also been used to catalyze similar CDC nitro-Mannich reactions. These include examples catalyzed by vanadium,[240] gold,[241] ruthenium,[242] platinum,[243] iron[244] and titanium.[245]

Scheme 140. Visible-Light Photoredox Catalyzed CDC Reactions

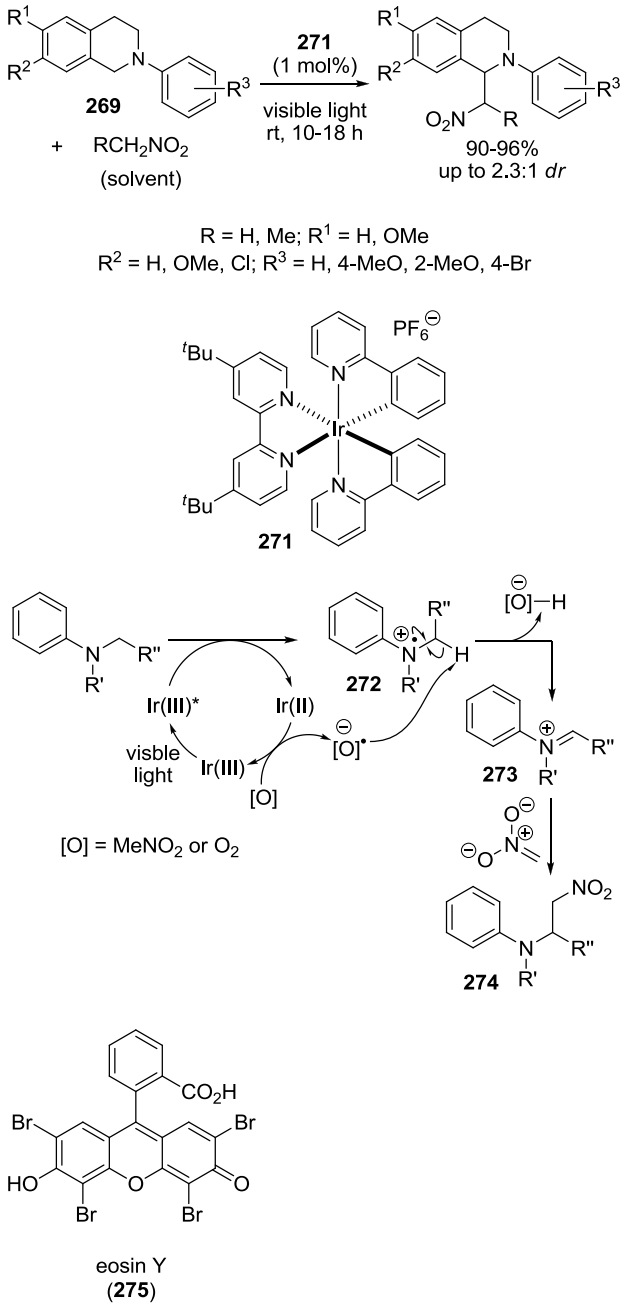


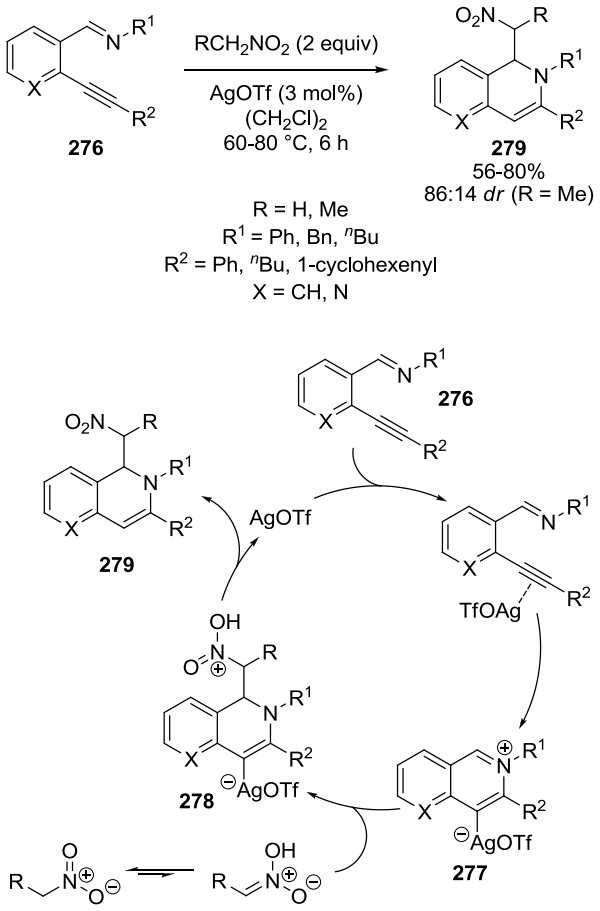
Figure 3. Organic Dye Photoredox Catalyst

13. MISCELLANEOUS REACTIONS

13.1. Reactions of Isoquinolines

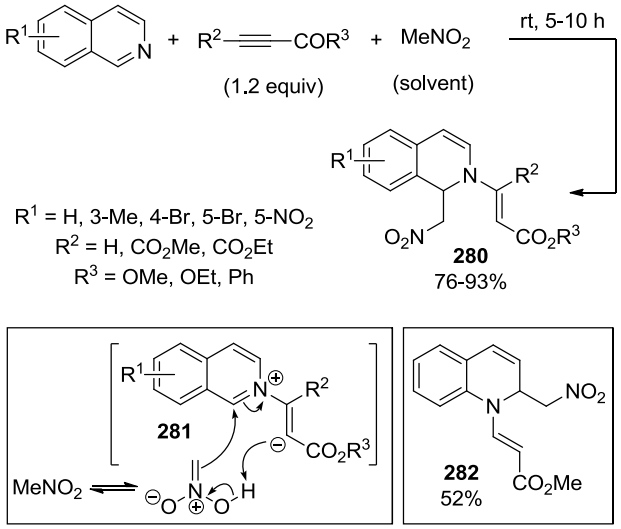
In 2005, Asao *et al.* reported the AgOTf-catalyzed tandem hydroamination/nitro-Mannich reaction of *ortho*-alkynylaryl aldimines **276** with nitromethane (Scheme 141).[246] The reactions proceed via attack of AgOTf-coordinated alkyne by the nitrogen atom of the imine in **276** to form isoquinolinium intermediate **277**. Addition of the nitronic acid tautomer of nitromethane to this iminium species results in a nitro-Mannich reaction to form intermediate **278**, which after proto-demetallation forms dihydroisoquinoline **279**. The products were formed in good yields for a range of substrates. The majority of examples given included the reaction of nitromethane, however, a single example involving nitroethane gave the product in a good *dr* of 86:14.

Scheme 141. AgOTf-Catalyzed Dihydroquinoline Synthesis



In 2009, Yadav *et al.* reported a synthesis of 1-(nitromethyl)-1,2-dihydroisoquinolines **280** via a three component coupling of isoquinolines, activated alkynes and nitromethane (Scheme 142).[247] They proposed that the reaction proceeded via initial aza-Michael reaction of the isoquinoline with the activated alkyne to form zwitterionic intermediate **281**, which undergoes a nitro-Mannich reaction to form the desired product **280**. The reactions proceed smoothly at 25 °C without the need of a catalyst and were found to be high yielding for a range of substrates. Furthermore, the reaction was also applicable to the reaction of quinoline to form 2-(nitromethyl)-1,2-dihydroquinoline **282**, albeit in moderate yield.

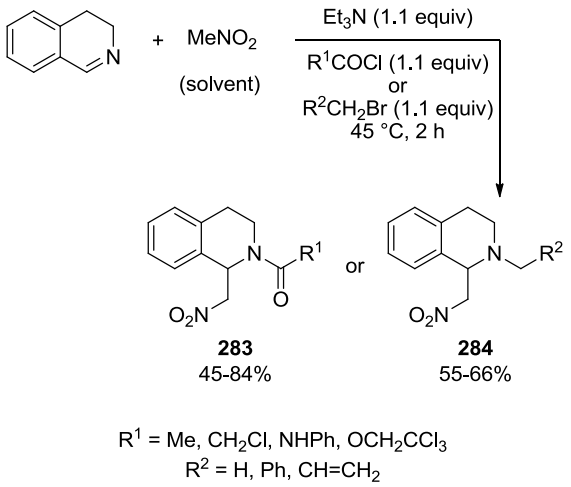
Scheme 142. Three Component Coupling Reactions of Isoquinolines, Activated Alkynes and Nitromethane



In 2010, Todd *et al.* reported the nitro-Mannich reaction of 3,4-dihydroisoquinoline with nitromethane (Scheme 143).[248] The reaction was found to proceed smoothly in the presence of triethylamine to give 1-nitromethyl-tetrahydroisoquinolines in excellent yield. However, this product was found to be unstable as it underwent a retro-addition process to reform 3,4-dihydroisoquinoline and nitromethane. To overcome this instability issue the authors performed

in situ acylations and alkylations, which enabled the isolation of *N*-substituted-1-nitromethyl-tetrahydroisoquinolines **283** and **284** in good yields. The formation of *N*-alkylated products **284** is similar to a report by Robinson and Malan in 1927, which included a single example of a nitro-Mannich reaction of a dihydroisoquinolinium salt with nitromethane.[249]

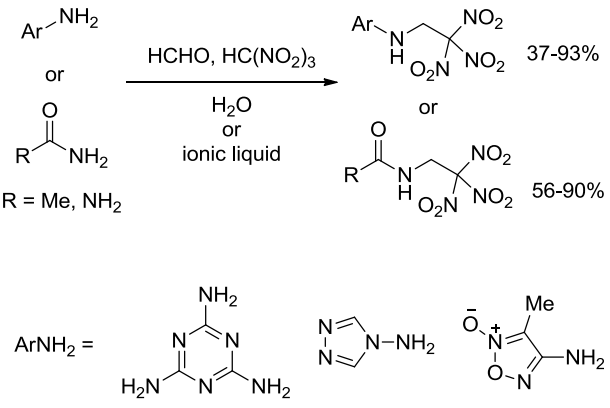
Scheme 143. Nitro-Mannich Reactions of Dihydroisoquinolines



13.2. Reactions of Trinitromethane

In 2005, Makhova *et al.* reported the nitro-Mannich reactions of a number of primary amides and heterocyclic primary amines with formaldehyde and trinitromethane (Scheme 144).[250] The products were formed in good to excellent yields under mild aqueous conditions. The same group later extended this methodology to the use of ionic liquids as the reaction solvent.[251] The products were formed in comparable yields to those obtained previously under aqueous conditions[250,252] and the ionic liquid could be reused to provide the products in similar yields after four cycles.

Scheme 144. Nitro-Mannich Reactions of Trinitromethane

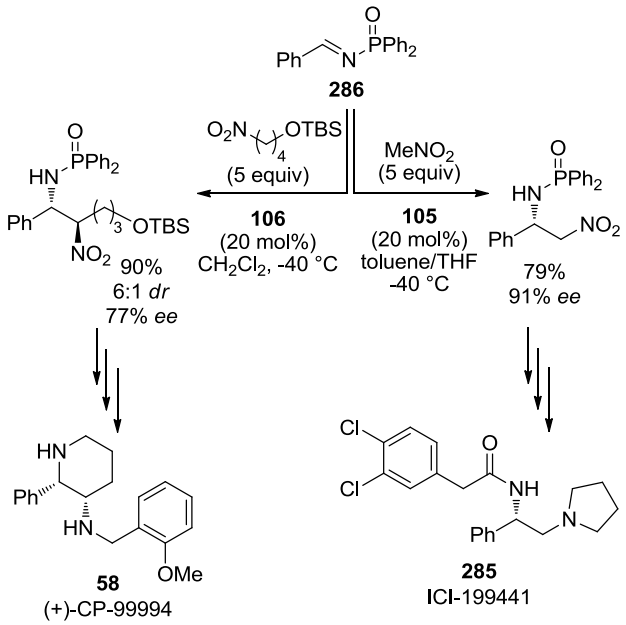


14. APPLICATIONS TO SYNTHESIS

The efficiency of the nitro-Mannich reaction and the versatility of the *β*-nitroamine products have unsurprisingly resulted in its application to the synthesis of a number of natural products and pharmaceuticals. These have been performed using a variety of different nitro-Mannich protocols ranging from base mediated diastereoselective reactions to highly enantioselective metal-catalyzed and organocatalytic reactions responsible for creating the key stereogenic centres found in the final product.

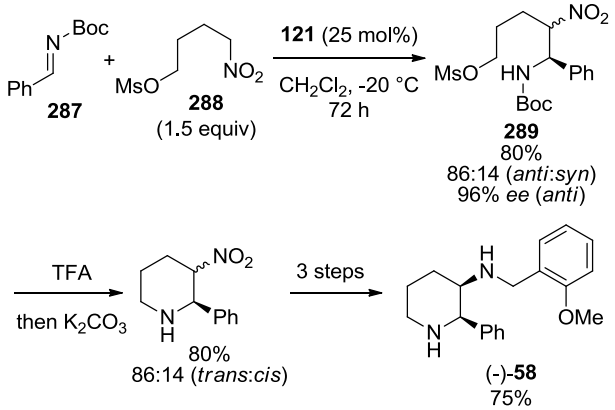
In 2002, Shibasaki *et al.* demonstrated the use of his asymmetric nitro-Mannich reactions to the synthesis of ICI-199441 (**285**) and CP-99994 (**58**) (Scheme 145).[253] The nitro-Mannich reactions of *N*-phosphinoyl phenyl imine **286** were performed using their heterobimetallic binaphthoxide-derived catalysts **105** and **106** (see Schemes 54 and 55). The use of the appropriate nitroalkane gave the desired key *β*-nitroamine intermediates in excellent yields and stereoselectivities.

Scheme 145. Synthesis of ICI-199441 (**285**) and CP-99994 (**58**)



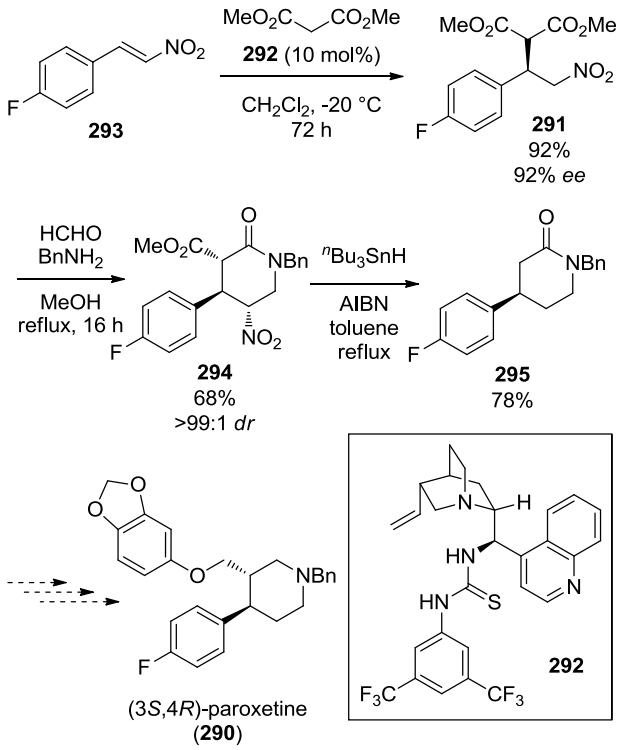
In 2006, Takemoto *et al.* reported an improved synthesis of (-)-CP-99994 (**58**) using their thiourea **121** catalyzed nitro-Mannich reaction (Scheme 146).[124] They performed a nitro-Mannich reaction between *N*-Boc-phenyl imine **287** and nitroalkane **288** to form *β*-nitroamine **289** in excellent yield and enantioselectivity. The synthesis of (-)-CP-99994 (**58**) was completed in four further steps in an overall yield of 48%.

Scheme 146. Takemoto's Synthesis of CP-99994 (**58**)



In 2008, Dixon *et al.* used the nitro-Mannich/lactamization cascades developed by the group of Pei[210] in an enantioselective formal synthesis of (3*S*,4*R*)-paroxetine (**290**) (Scheme 147).[254] The group used *γ*-nitroester **291**, formed in a thiourea **292**-catalyzed asymmetric Michael addition of dimethylmalonate to nitroalkene **293**, in a nitro-Mannich/lactamization cascade to form piperidinone **294**. Simultaneous reductive denitration and decarboxylation provided piperidinone **295** and completed the formal synthesis. Similar nitro-Mannich/lactamization chemistry was also used by the group of Jørgensen in a formal synthesis of (3*S*,4*R*)-paroxetine (**290**).[255]

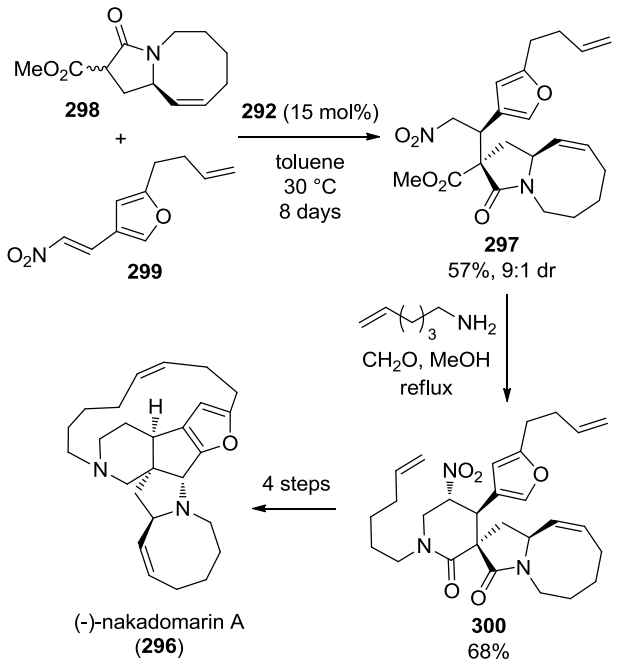
Scheme 147. Synthesis of (3*S*,4*R*)-Paroxetine (**290**)



In 2009, Dixon *et al.* utilized the same nitro-Mannich/lactamization cascade chemistry to synthesize the piperidine core of (-)-nakadomarin A (**296**) (Scheme 148).[256] They formed *γ*-nitroester **297** through a diastereoselective Michael addition of malonate **298** to nitroalkene **299**, catalyzed by thiourea **292**. Heating **297** in the presence of formaldehyde and hex-5-enamine led

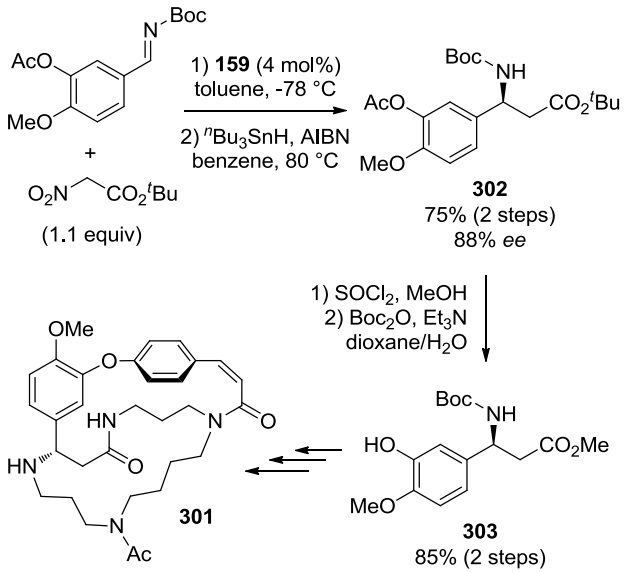
to the formation of 5-nitropiperidin-2-one **300** in good yield and excellent diastereoselectivity. This was subsequently converted to (-)-nakadomarin A (**296**) in four further steps. More recently, the Dixon *et al.* utilized the same nitro-Mannich/lactamization chemistry in two further total syntheses of (-)-nakadomarin A (**296**).[257–258]

Scheme 148. Synthesis of (-)-Nakadomarin A (**296**)



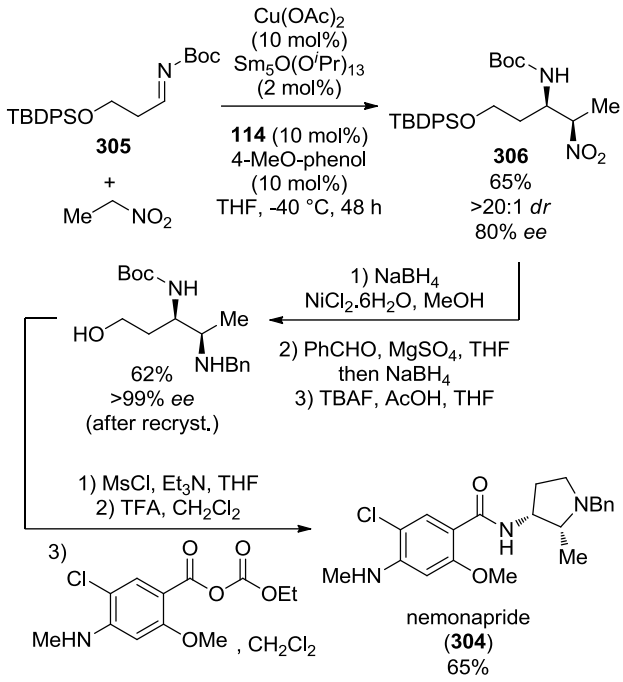
In 2008, Johnston *et al.* utilized their methodology for the asymmetric nitro-Mannich reactions of *α*-nitroesters with *N*-Boc imines (see Scheme 100) in a formal enantioselective synthesis of (+)-chaenorhine (**301**) (Scheme 149).[259] They demonstrated that highly enantioselective nitro-Mannich/denitration sequences could be used to form a variety of *β*-amino acid esters in good yields. This was then applied to the synthesis of *β*-amino acid ester **302**, which was converted to phenol **303** to complete the formal synthesis of (+)-chaenorhine (**301**).

Scheme 149. Synthesis of (+)-Chaenorhine (**301**)



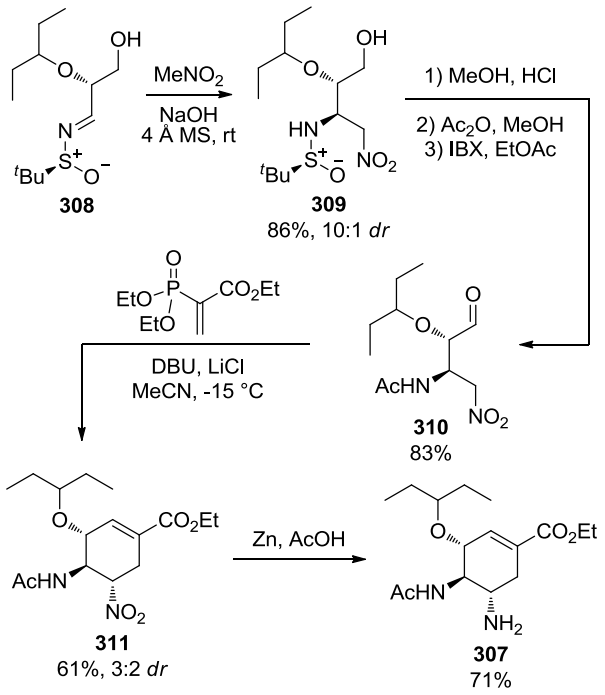
In 2010, Shibasaki *et al.* demonstrated the synthetic utility of their *syn*-selective nitro-Mannich methodology (see Scheme 62) to the synthesis of the antipsychotic agent nemonapride (**304**) (Scheme 150).[114] The nitro-Mannich reaction between *N*-Boc alkyl imine **305** and 1-nitropropane gave the *syn*-*β*-nitroamine **306** in 65% yield and with no observed *anti*-diastereomer. The synthesis of nemonapride (**304**) was completed in six further steps.

Scheme 150. Shibasaki's Synthesis of Nemonapride (**304**)



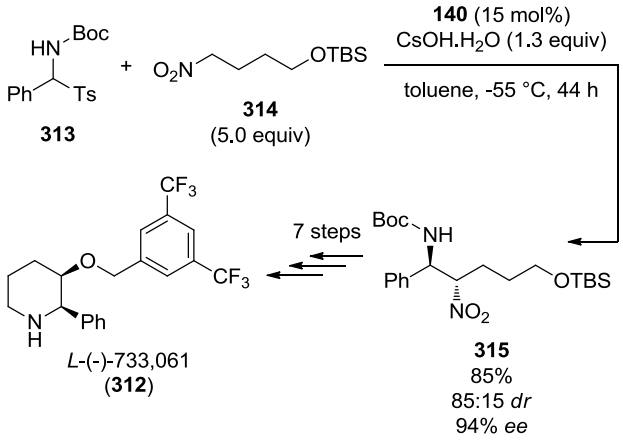
In 2010, the group of Lu reported a synthesis of oseltamivir (**307**), the free amine of Tamiflu™, using a nitro-Mannich reaction of chiral *N*-*tert*-butylsulfinyl imine **308**.[260] The highly diastereoselective base mediated nitro-Mannich reaction between nitromethane and **308** generated *β*-nitroamine **309** in excellent yield (Scheme 151). Four further steps including a Michael/Horner-Wadsworth-Emmons cascade of nitroaldehyde **310** and reduction of the resulting cyclic *β*-nitroamine **311** provided oseltamivir (**307**).

Scheme 151. Lu's Synthesis of Oseltamivir (**307**)



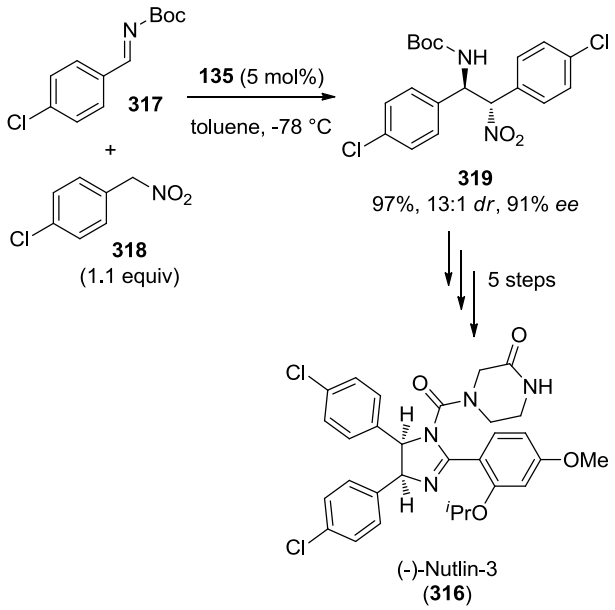
In 2011, Kumaraswamy *et al.* reported an enantioselective synthesis of the highly potent Substance P antagonist L-(-)-733,061 (**312**) (Scheme 152).[261] They utilized the phase transfer catalyzed nitro-Mannich methodology developed by Palomo *et al.*[137,139] (see Schemes 84 and 85) for the key stereodetermining step. The reaction of *α*-amidosulfone **313** with nitroalkane **314**, catalyzed by cinchona-based catalyst **140**, provided *β*-nitroamine **315** in excellent yield, diastero- and enantioselectivity. The synthesis was completed in seven further steps. In the same article, the authors also reported the use of this nitro-Mannich chemistry for the synthesis of methyl 3-aminopiperidine-2-carboxylate. In a later report, the same group demonstrated that similar chemistry could be implemented in the formal synthesis of a number of alkaloid natural products.[262]

Scheme 152. Kumaraswamy's Synthesis of L-(-)-733,061 (**312**)



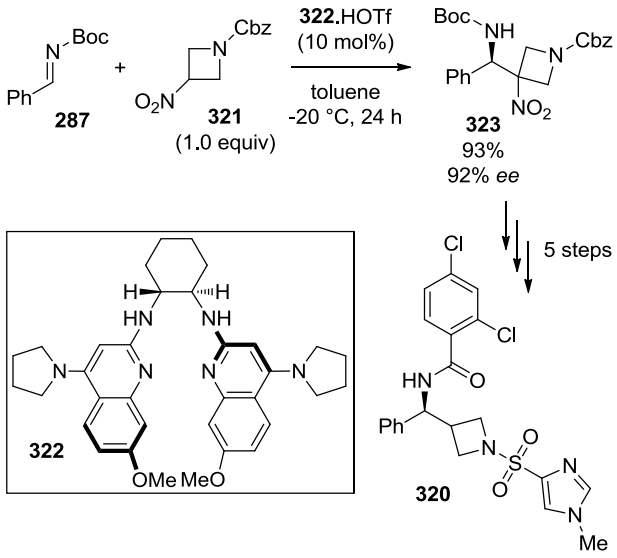
In 2011, Johnston *et al.* published their synthesis of the potent p53/MDM2 inhibitor (-)-nutlin-3 (**316**), originally discovered by Hoffmann-La Roche (Scheme 153).[135] They used chiral bis-amidine catalyst **135** (see Scheme 82) to catalyze the reaction between *N*-Boc aryl imine **317** and aryl nitromethane **318**. The resulting *β*-nitroamine **319** was formed in exceptional yield and stereoselectivity, providing the desired *anti*-diastereomer in 13:1 *dr* and 91% ee. Reduction of the nitro group followed by a series of amide bond formations and cyclization to form the imidazoline ring furnished (-)-nutlin-3 (**316**) in 42% yield over five steps.

Scheme 153. Johnston's Synthesis of (-)-Nutlin-3 (**316**)



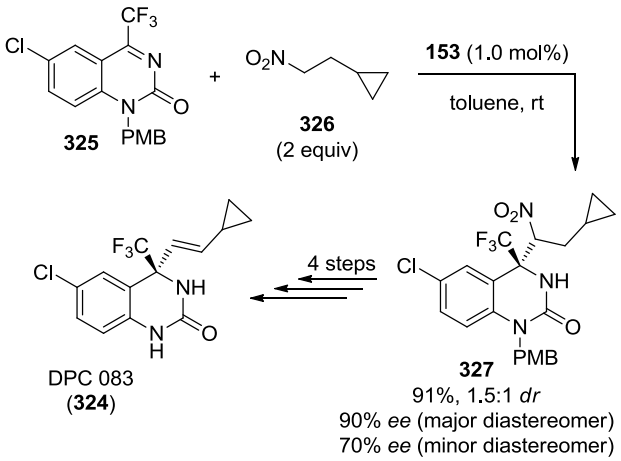
The following year, Johnston *et al.* further demonstrated the utility of their bis-amidine-catalyzed nitro-Mannich reactions through its application to the synthesis of azetidine **320**, a potent GlyT1 inhibitor (Scheme 154).[263] The key step in the synthesis was a nitro-Mannich reaction between *N*-Boc phenyl imine **287** and 3-nitroazetidine **321** catalyzed by bis-amidine **322**. The *β*-nitroamine product **323** was formed in excellent yield and enantioselectivity. This is a rare example of a nitro-Mannich reaction of a functionalized secondary nitroalkane. Reductive denitration and a number of amide bond formations enabled the synthesis of **320** in five further steps.

Scheme 154. Johnston's Synthesis of Azetidine **320**



In 2011, W. Wang *et al.* applied their thiourea **153**-catalyzed nitro-Mannich reaction of cyclic trifluoromethyl ketimines (see Scheme 98) to the synthesis of the anti-HIV drug DPC 083 (**324**).[150] The nitro-Mannich reaction between cyclic ketimine **325** and nitroalkane **326** proceeded in excellent yield giving *β*-nitroamine **327** in 91% yield, albeit in poor diastereoselectivity (Scheme 155). Completion of the synthesis of DPC 083 (**324**) was accomplished in a further four steps.

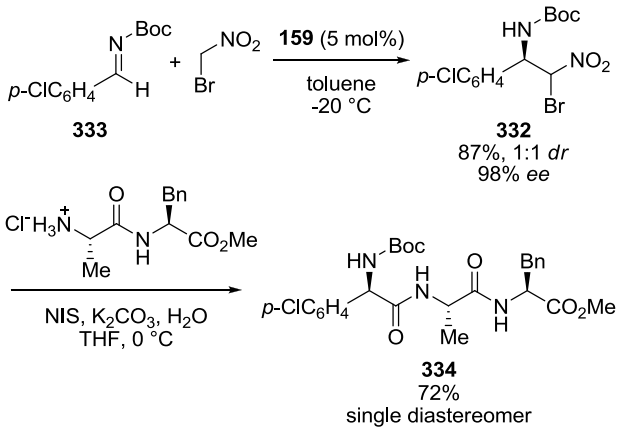
Scheme 155. Wang's Synthesis of DPC 083 (**324**)



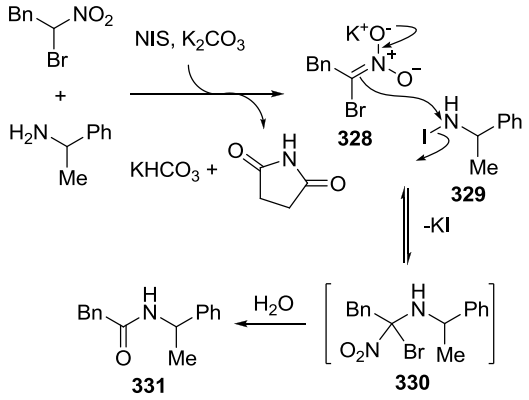
14.1. Peptide Synthesis

The group of Johnston published a novel method for the synthesis of amides and peptides that uses the direct coupling of bromonitroalkanes and amines in the presence of an electrophilic iodine source (NIS).[264] The construction of the amide bond results from the nucleophilic attack of nitronate **328** onto an electrophilic *N*-iodoamine **329**. Hydrolysis of the resulting *α*-bromo-*α*-nitroamine **330** gives the amide product **331** (Scheme 156). The bromonitroalkanes function as nucleophilic acyl anion equivalents, demonstrating the first use of umpolung reactivity in amide bond formation. The group went on to demonstrate that *β*-nitroamine **332**, the product from a nitro-Mannich reaction between bromonitromethane and *N*-Boc aryl imine **333** catalyzed by bis-amidine **159**, could be subjected to the umpolung chemistry with a range of amino acid derivatives to form the corresponding peptides **334** (Scheme 156). The peptide products were obtained in good yields and no epimerization of the *α*-carbonyl positions was observed.

Scheme 156. Umpolung Amide Bond Formation Using Bromonitroamines



Mechanism:



15. SUMMARY

The nitro-Mannich reaction belongs to a formidable suite of carbon-carbon bond forming reactions, the aldol, Mannich and Henry reactions that are all well understood and used routinely in molecular construction. They are all linked by the common addition of a stabilised anion to a carbonyl derivative. It seems peculiar that one permutation of this set of reactions, the addition of a nitronate anion to an imine (nitro-Mannich or aza-Henry reaction) has lagged behind its congeners. The likely explanation is due to the fact that the β-nitro amine products from the nitro-Mannich reaction are often prone to retro-addition if they do not contain an electron withdrawing group on the amine nitrogen. In early experiments with imines derived from

ammonia or aliphatic/aromatic amines this complicated their isolation, purification and impeded further transformations. Experiments in the early 20th century consisted mainly of unselective, non catalysed, thermal methods with simple amines and nitroalkanes with formaldehyde. They relied upon the natural formation of nitronic acid or deprotonation to nitronate species. The use of the nitro-Mannich reaction as a tool to prepare other functionality was recognised as far back as 1943 by Zief and Mason who prepared polyamines by reduction of the product β-nitro amines (Scheme 7).[33] However, this disconnection was rarely used throughout the whole of the 20th Century. Notable exceptions include the synthesis of polyamines by Johnson in 1946 (Scheme 10)[36] and Rychnovsky's use of the disconnection in a synthesis of chiral nitroxides as late as 1998 (Scheme 9).[38] Studies which characterised the diastereoselectivity of the reaction were rare and limited to cyclic products formed from lactamisation by using nitroesters. Building on a reaction characterised by Muhlstadt and Schulze (Scheme 28),[75] Jain was the first to show that in the formation of piperidinones a *trans* relationship between the two new chiral centres was formed in the key nitro-Mannich reaction (Scheme 29).[76] The *trans*-selectivity of this reaction has subsequently persisted throughout all, but a very few examples (vide infra) of the nitro-Mannich reaction. The publication of the first diastereoselective nitro-Mannich reactions in 1998 formulated some mechanistic understanding that the reaction was proton centred, was inherently *trans*-selective and that this appeared to be kinetic diastereoselectivity (Scheme 31).[6] In this comprehensive review there are 55 publications before that paper that detail a nitro-Mannich reaction or nitro-Mannich product, where as in the last 14 years there has been over 200 reports of the same reaction. The recognition that the reaction was proton centred invited the use of chiral Lewis acids to catalyse the nitro-Mannich reaction. [6] At the time there was incredible activity in the field of asymmetric catalysis and a surge of workers reported asymmetric catalytic nitro Mannich reactions. The first of these was by Shibasaki in 1999 using a mixed Lewis

acid/Brønsted base catalysts (Scheme 54).[105] Racemic Lewis acid catalysed reactions in 2000 (Scheme 44)[79] were followed by Jørgensen's studies using bis-oxazoline chiral copper triflate Lewis acid complexes in 2001 (Schemes 46 and 56).[97,107] The field dramatically widened from then on to include not only other asymmetric metal centred systems (Section 4.2 and 5.2), but a host of organocatalysts relying on chiral hydrogen bond donors, chiral Bronsted acids, phase transfer catalysts and Bronsted base catalysts (Section 6). Ingenious methods of conducting the reaction have been reported using electrochemistry (Scheme 43)[94] and cross dehydrogenative coupling (Section 12). The catalytic asymmetric studies necessitated and stimulated investigations into the substrate scope of the reaction. Although the reaction is tolerant of a wide range of aromatic and heteroaromatic aldimines, with neutral or electron withdrawn groups on nitrogen, there are relatively few reports of nitronate additions to ketimines. Fundamentally ketimines are less electrophilic than aldimines, the resultant β-nitroamine products from the nitro-Mannich reaction are less stable due to their natural tendancy to *retro*, which in this case is exacerbated by steric compression. Also the stereoselective facial addition to ketimines, like asymmetric nucleophilic addition to ketones, is much more difficult due to the relative sizes of the substituents on carbon and inherently more complex because of the fluctionality of *E* and *Z* isomers across the C=N double bond, which is complicated even more when complexed to a Lewis acid. More success has been realised with 2° nitroalkanes, but these are in the majority α-nitroesters or α-nitrophosphonates (Sections 8 and 9), but examples are still limited mainly to forming α,α-disubstituted amino acids.[22] There is a real need for the development of reaction protocols for these more hindered nitro-Mannich reactions to make tertiary substituted amine products, which will require some clever solutions and a high degree of optimisation. A relatively simple set of on the whole commercially available nitroalkanes have been used in the

nitro-Mannich reaction, with more complex examples being provided by conjugate addition to nitroalkenes (Section 10) and cascade reactions (Section 11). Indeed the early results of Muhlstadt and Schulze,[75] and Jain[76] in using the nitro-Mannich reaction for the synthesis of various heterocycles through spontaneous cyclisation has led to some ingenious tandem cyclisation reactions. More recent examples have utilised a separate cyclisation step after an initial stereoselective nitro-Mannich reaction.[265,266] There is wide scope for the nitro-Mannich to trigger subsequent reactions due to the formation of a nucleophilic amine and the fact that the nitro group may still possess an acidic proton. Future research will no doubt uncover more varied multicomponent coupling reactions. The nitro-Mannich has already found considerable use in target synthesis, either for the synthesis of natural products or potential drug molecules (Section 14). These syntheses comprise of using the β-nitro amine products as stereodefined building blocks or using the nitro-Mannich reaction as a key bond forming event during the synthesis. There are examples of using both functionalities of the β-nitroamines or denitration has been used to remove the nitro group to leave a chiral amine. Inspiring work originating from Desai (Scheme 30)[77,78] and then Shibasaki (Scheme 145)[253] concering the synthesis of CP-99994 and analogues has been followed by many applications to drug molecules including oseltamivir, the free amine of Tamiflu™ (Scheme 151).[260] The nitro-Mannich reaction has been used in the synthesis of more complex molecules, such as (-)-Nakadomarin A by Dixon (Scheme 148).[256-8] A particularly ingenious and alternative disconnection for the amide bond has been published by Johnson which relies upon the umploung reactivity of a bromonitroamines formed from a nitro-Mannich reaction catalysed by a chiral bis-amidine base (Scheme 156).[264] The nitro-Mannich reaction should continue to be effective in target synthesis as it's use becomes more widespread.

We hope that this revue has demonstrated the diversity and efficiency of the nitro-Mannich reaction to inform other scientists of the ease and versatility of this particular bond construction, so it may take its rightful place amongst its powerful carbon-carbon bond forming cousins, the aldol, Mannich and Henry reactions. For example, medicinal chemists have become aware that drug molecules which possess more saturated carbon atoms and especially chiral centres have a greater chance of becoming a successful drug candidate (Escape from flatland).[267] The vast majority of pharmaceuticals do not include chiral vicinal diamines - not so much because they would not be effective, but because they are difficult to make. Chiral vicinal diamines are readily prepared from the reduction of β-nitroamines from the nitro-Mannich reaction. The nitro-Mannich reaction has the promise to become a foundation reaction in organic synthesis that will be of value to the wider synthetic chemistry community. Continued creative development of this reaction will enable the catalytic asymmetric synthesis of a range of complex β-nitro amines, from readily available starting materials, which can be transformed into a range of other amine functionality.

AUTHOR INFORMATION

Corresponding Author

* j.c.anderson@ucl.ac.uk.

ACKNOWLEDGMENT

We thank the EPSRC and GlaxoSmithKline for funding.

REFERENCES

(1) (a) Trost, B.M.; Brindle, C.S. *Chem. Soc. Rev.* **2010**, *39*, 1600. (b) *Modern Aldol Reactions*, ed. R. Mahrwald, R. Wiley-VCH, Berlin **2004**. (c) Palomo, C.; Oiarbide, M.; Garci, J. M. *Chem. Eur. J.* **2002**, *8*, 36. (d) Machajewski, T. D.; Wong, C.-H. *Angew. Chem. Int. Ed.* **2000**, *39*, 1352. (e) Wurtz, A. *Bull. Soc. Chim. Fr*. **1872**, *17*, 436.

(2) (a) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471 (b) Palomo, C.; Oiarbide, M.; Laso, A. *Eur. J. Org. Chem.* **2007**, *2007*, 2561. (c) Boruwa, J.; Gogoi, N.; Pratim, Saikia, P.P.; Barua, N.C. *Tetrahedron: Asymmetry* **2006**, *17*, 3315.

(3) (a) Verkade, J.M.M.; van Hemert, L.J.C.; Quaedflieg, P.J.L.M.; Rutjes, F.P.J.T. *Chem. Soc. Rev.* **2008**, *37*, 29–41. (b) Luzzio, F. A. *Tetrahedron* **2001**, *57*, 915. (c) Kobayashi, S.; Mori, Y.; Fossey, J. S.; Salter, M. M. *Chem. Rev.* **2011**, *111*, 2626

(4) Henry, L. *Bull. Acad. R. Belg.* **1896**, *32*, 33.

(5) Ono, N. *The Nitro Group in Organic Synthesis*, John Wiley & Sons, New York, **2001**.

(6) Adams, H.; Anderson, J. C.; Peace, S.; Pennel, A. M. K. *J. Org. Chem.* **1998**, *63*, 9932.

(7) Baer, H. H.; Urbas, L. In *The Chemistry of the Nitro and Nitroso Groups*, Part II, Feurer, H., Eds.; Interscience: New York, 1970; pp 117.

(8) Shibasaki, M. *Chemtracts* **1999**, *12*, 979.

(9) Shibasaki, M.; Kanai, M. *Chem. Pharm. Bull.* **2001**, *49*, 511.

(10) Shibasaki, M.; Matsunaga, S.; Kumagai, N. *Synlett* **2008**, 1583.

(11) Matsunaga, S.; Shibasaki, M. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 60.

(12) Shibasaki, M.; Kanai, M.; Matsunaga, S.; Kumagai, M. *Top Organomet. Chem.* **2011**, *37*, 1.

(13) Vilaivan, T.; Bhanthumnavin, W.; Sritana-Anant, Y. *Curr. Org. Chem.* **2005**, *9*, 1315.

(14) Weinreb, S. M.; Orr, R. K. *Synthesis* **2005**, 1205.

(15) Friestad, G. K.; Mathies, A. K. *Tetrahedron* **2007**, *63*, 2541.

(16) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999.

(17) Ting, A.; Schaus, S. E. *Eur. J. Org. Chem.* **2007**, 5797.

(18) Bernardi, L.; Fini, F.; Fochi, M.; Ricci, A. *Chimia* **2007**, *61*, 224.

(19) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713.

(20) Takemoto, Y. *Chem. Pharm. Bull.* **2010**, *58*, 593.

(21) Petrini, M.; Torregiani, E. *Synthesis* **2007**, 159.

(22) Arrayás, R. G.; Carretero, J. C. *Chem. Soc. Rev.* **2009**, *38*, 1940.

(23) Westermann, B. *Angew. Chem. Int. Ed.* **2003**, *42*, 151.

(24) Marquéz-López, E.; Merino, P.; Tejero, T.; Herrera, R. P. *Eur. J. Org. Chem.* **2009**, 2401.

(25) Henry, L. *Bull. Acad. R. Belg.* **1897**, *33*, 412.

(26) Henry, L. *Bull. Acad. R. Belg.* **1899**, *37*, 162.

(27) Mousset, T. *Bull. Acad. Roy. Belg.* **1901**, 622.

(28) Henry, L. *Ber.* **1905**, *38*, 2027.

(29) Duden, P.; Bock, K.; Reid, H. J. *Ber.* **1905**, *38*, 2036.

(30) Cerf de Mauny, H. *Compt. Rend.* **1932**, 1084.

(31) Cerf de Mauny, H. *Bull. Soc. Chim. Fr.* **1937**, *4*, 1451.

(32) Cerf de Mauny, H. *Bull. Soc. Chim. Fr.* **1937**, *4*, 1460.

(33) Zief, M.; Mason, P. J. *J. Org. Chem.* **1943**, *8*, 1.

(34) Cerf de Mauny, H. *Bull. Soc. Chim. Fr.* **1944**, *11*, 281.

(35) Senkus, M. *J. Am. Chem. Soc.* **1946**, *68*, 10.

(36) Johnson, H. G. *J. Am. Chem. Soc.* **1946**, *68*, 12.

(37) Johnson, H. G. *J. Am. Chem. Soc.* **1946**, *68*, 14.

(38) Rychnovsky, S. D.; Beauchamp, T.; Vaidyanathan, R.; Kwan, T. *J. Org. Chem.* **1998**, *63*, 6363.

(39) Grillot, G. F.; Bashford, R. I. *J. Am. Chem. Soc*. **1951**, *73*, 5598.

(40) Lambert, A.; Rose, J. D. *J. Chem. Soc.* **1947**, 1511.

(41) Senkus, M. *J. Am. Chem. Soc.* **1946**, *68*, 1611.

(42) Shakirov, R. R.; Dokichev, T. V.; Biglova, R. Z.; Vlasova, N. M.; Baibulatova, N. Z.; Talipov, R. F. *Chem. Heterocycl. Compd.* **2008**, *44*, 43.

(43) Cichra, D. A.; Adolph, H. G. *J. Org. Chem.* **1982**, *47*, 2474.

(44) Hirst, E. L.; Jones, J. K. N.; Minahan, S.; Ochynski, F. W.; Thomas, A. T.; Urbański, T. *J. Chem. Soc.* **1947**, 924.

(45) Senkus, M. *J. Am. Chem. Soc.* **1950**, *72*, 2967.

(46) Eckstein, Z.; Urbański, T. *Advan. Heterocyclic Chem.* **1963**, *2*, 311.

(47) Yarmukhamedov, N. N.; Baibulatova, N. Z.; Dokichev, V. A.; Tomilov, Y. V.; Yunusov, M. S. *Russ. Chem. Bull. Int. Ed.* **2001**, *50*, 753.

(48) Shakirov, R. R.; Vlasova, L. I.; Shishkin, D. V.; Yarmukhamedov, N. N.; Baybulatova, N. Z.; Semesko, D. G.; Dokichev, V. A.; Tomilov, Y. V. *Russ. Chem. Bull. Int. Ed.* **2005**, *54*, 1737.

(49) Gugliotta, G.; Botta, M.; Giovenzana, G. B.; Tei, L. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3442.

(50) Martinelli, J.; Gugliotta, G.; Tei, L. *Org. Lett.* **2012**, *14*, 716.

(51) Blomquist, A. T.; Shelley, T. H. *J. Am. Chem. Soc.* **1948**, *70*, 147.

(52) Snyder, H. L.; Hamlin, W. E. *J. Am. Chem. Soc.* **1950**, *72*, 5082.

(53) Bachman, G. B.; Atwood, M. T. *J. Am. Chem. Soc.* **1956**, *78*, 484.

(54) Jones, J. K. N.; Urbański, T. *J. Chem. Soc.* **1949**, 1766.

(55) Butler, G. B. *J. Am. Chem. Soc.* **1956**, *78*, 482.

(56) Smiley, R. A. *J. Org. Chem.* **1958**, *23*, 1115.

(57) Hurd, C. D.; Strong, J. S. *J. Am. Chem. Soc.* **1950**, *72*, 4813.

(58) Hass, H. B.; Riley, E. F. *Chem. Rev.* **1943**, *32*, 373.

(59) Dornow, A.; Müller, A.; Lüpfert, S. *Ann. Chem.* **1955**, *594*, 191.

(60) Dornow, A.; Sassenberg, W. *Ann. Chem.* **1957**, *602*, 14.

(61) Dornow, A.; Sassenberg, W. *Ann. Chem.* **1957**, *606*, 61.

(62) Severin, T.; Schmitz, R.; Adam, M. *Chem. Ber.* **1963**, *96*, 3076.

(63) Severin, T.; Adam, M. *Chem. Ber.* **1964**, *97*, 186.

(64) Severin, T.; Loske, J.; Scheel, D. *Chem. Ber.* **1969**, *102*, 3909.

(65) Wall, R. T. *Tetrahedron* **1970**, *26*, 2107.

(66) Blackall, K. J.; Hendry, D.; Pryce, R. J.; Roberts, S. M. *J. Chem. Soc. Perkin Trans. 1* **1995**, 2767.

(67) Yakunina, I. E.; Shakhkeldyan, I. V.; Atroshenko, Y. M.; Borbulevich, O. Y.; Nesterov, V. V.; Kopyshev, M. B.; Troitskii, N. A.; Efremov, Y. A.; Alifanova, E. N.; Subbotin, V. A. *Russ. J. Org. Chem.* **2004**, *40*, 239.

(68) Yakunina, I. E.; Shakhkel'dyan, I. V.; Atroshchenko, Y. M.; Rybakova, A. S.; Troitskii, N. A.; Shuvalova, E. V. *Russ. J. Org. Chem.* **2005**, *41*, 1238.

(69) Asadulina, E. M.; Bastrakov, M. A.; Kachala, V. V.; Starosotnikov, A. M.; Shevelev, S. A. *Mendeleev Commun.* **2008**, *18*, 213.

(70) Severin, T.; Temme, H.-L. *Chem. Ber.* **1965**, *98*, 1159.

(71) Leonova, O. V.; Shakhkel'dyan, I. V.; Grudtsyn, Y. D.; Atroshchenko, Y. M.; Alifanova, E. N.; Gitis, S. S.; Chudakov, P. V.; Nikiforova, E. G.; Alekhina, N. N.; Kaminskii, A. Y. *Russ. J. Org. Chem.* **2001**, *37*, 395.

(72) Shakhkel'dyan, I. V.; Leonova, O. V.; Atroshchenko, Y. M.; Boikova, O. I.; Borbulevych, O. Y.; Grintselev-Knyazev, G. V.; Yakunina, I. E.; Shchukin, A. N.; Alifanova, E. N.; Subbotin, V. A. *Russ. J. Org. Chem.* **2003**, *39*, 1593.

(73) Walser, A.; Benjamin, L. E.; Flynn, T.; Mason, C.; Schwartz, R.; Fryer, R. I. *J. Org. Chem.* **1978**, *43*, 936.

(74) Mühlstädt, V. M.; Schulze, B. *J. Prakt. Chem.* **1971**, *313*, 745.

(75) Mühlstädt, M.; Schulze, B. *J. Prakt. Chem.* **1975**, *317*, 919.

(76) Bhagwatheeswaran, S. P.; Gaur, S. P.; Jain, P. C. *Synthesis* **1976**, 615.

(77) Desai, M. C.; Thadeio, P, F.; Lefkowitz, S. L. *Tetrahedron Lett.* **1993**, *34*, 5831.

(78) Desai, M. C.; Lefkowitz, S. L.. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2083.

(79) Anderson, J. C.; Blake, A. J.; Howell, G. P.; Wilson, C. *J. Org. Chem.* **2005**, *70*, 549.

(80) Anderson, J. C.; Chapman, H. A. *Synthesis* **2006**, 3309.

(81) Anderson, J. C.; Chapman, H. A. *Org. Biomol. Chem.* **2007**, *5*, 2413.

(82) Ballini, R.; Petrini, M. *Tetrahedron Lett.* **1999**, *40*, 4449.

(83) Petrini, M.; Seri, M. *Tetrahedron* **2006**, *62*, 960.

(84) Foresti, E.; Palmieri, G.; Petrini, M.; Profeta, R. *Org. Biomol. Chem.* **2003**, *1*, 4275.

(85) Petrini, M.; Torregiani, E. *Tetrahedron Lett.* **2006**, *47*, 3501.

(86) Shiraishi, Y.; Yamauchi, H.; Takamura, T.; Kinoshita, H. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 2219.

(87) Ruano, J. L. G.; Topp, M.; López-Cantarero, J.; Alemán, J.; Remuinán, M. J.; Cid, M. B. *Org. Lett.* **2005**, *7*, 4407.

(88) Ruano, J. L. G.; López-Cantarero, J.; Haro, T. D.; Alemán, J.; Cid, M. B. *Tetrahedron* **2006**, *62*, 12197.

(89) Kattuboina, A.; Li, G. *Tetrahedron Lett.* **2008**, *49*, 1573.

(90) Kattuboina, K.; Kaur, P.; Ai, T.; Li, G. *Chem. Biol. Drug Res.* **2008**, *71*, 216.

(91) Pindi, S.; Kaur, P.; Shakya, G.; Li, G. *Chem. Biol. Drug Des.* **2011**, *77*, 20.

(92) Mahasneh, A. S.; Qaraqe, H. *Z. Naturforsch.* **2005**, *60b*, 797.

(93) Rodríguez-Solla, H.; Concellón, C.; Alvaredo, N.; Soengas, R. G. *Tetrahedron* **2012**, *68*, 1736.

(94) Rossi, L.; Bianchi, G.; Feroci, M.; Inesi, A. *Synlett* **2007**, 2505.

(95) Anderson, J. C.; Peace, S.; Pih, S. *Synlett*, **2000**, 850.

(96) Bernardi, L.; Bonini, B. F.; Dessole, G.; Fochi, M.; Comes-Franchini, M.; Gavioli, S.; Ricci, A.; Varchi, G. *J. Org. Chem.* **2003**, *68*, 1418.

(97) Knudsen, K. R.; Risgaard, T.; Nishiwaki, N.; Gothelf, K. V.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2001**, *123*, 5843.

(98) Anderson, J. C.; Howell, G. P.; Lawrence, R. M.; Wilson, C. S. *J. Org. Chem.* **2005**, *70*, 5665.

(99) Qian, C.; Gao, F.; Chen, R. *Tetrahedron Lett.* **2001**, *42*, 4673.

(100) Wang, J.; Lu, Z.-J.; Wang, L.-Y.; Bai, J.; Pan, Y. *Lett. Org. Chem.* **2008**, *5*, 286.

(101) Zhang, L.; Wu, H.; Su, S.; Wang, S. *Chin. J. Chem.* **2009**, *27*, 2061.

(102) Komura, K.; Taninaka, Y.; Ohtaki, Y.; Sugi, Y. *App. Catal., A* **2010**, *388*, 211.

(103) Mahasneh, A. S. *Z. Naturforsch.* **2006**, *61b*, 1162.

(104) Chakrapani, L.; Kantam, M. L. *Synth. Commun.* **2011**, *41*, 3442.

(105) Yamada, K.-I.; Harwood, S. J.; Gröger, H.; Shibasaki, M. *Angew. Chem. Int. Ed.* **1999**, *38*, 3504.

(106) Yamada, K.-I.; Moll, G.; Shibasaki, M. *Synlett* **2001**, 980.

(107) Nishiwaki, N.; Knudsen, K. R.; Gothelf, K. V.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2001**, *40*, 2992.

(108) Lee, A.; Kim, W.; Lee, J.; Hyeon, T.; Kim, B. M. *Tetrahedron: Asymmetry* **2004**, *15*, 2595.

(109) Gao, F.; Zhu, J.; Tang, Y.; Deng, M.; Qian, C. *Chirality* **2006**, *18*, 741.

(110) Trost, B. M.; Lupton, D. W. *Org. Lett.* **2007**, *9*, 2023.

(111) Palomo, C.; Oiarbide, M.; Halder, R.; Laso, A.; López, R. *Angew. Chem. Int. Ed.* **2006**, *45*, 117.

(112) Zhou, H.; Peng, D.; Qin, B.; Hou, Z.; Liu, X.; Feng, X. *J. Org. Chem.* **2007**, *72*, 10302.

(113) Handa, S.; Gnanadesikan, V.; Matsunga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 4900.

(114) Handa, S.; Gnanadesikan, V.; Matsunga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 4925.

(115) Nitabaru, T.; Kumagai, N.; Shibasaki, M. *Molecules* **2010**, *15*, 1280.

(116) Zhang, G.; Yashima, E.; Woggon, W.-D. *Adv. Synth. Catal.* **2009**, *351*, 1255.

(117) Blay, G.; Escamilla, A.; Hernández-Olmos, V.; Pedro, J. R.; Sanz-Marco, A. *Chirality* **2012**, *24*, 441.

(118) Bernardi, L.; Bonini, B. F.; Capitò, E.; Dessole, G.; Comes-Franchini, M.; Fochi, M.; Ricci, A. *J. Org. Chem.* **2004**, *69*, 8168.

(119) Kundu, D.; Debnath, R. K.; Majee, A.; Hajra, A. *Tetrahedron Lett.* **2009**, *50*, 6998.

(120) Hu, K.; Wang, C.; Ma, X.; Wang, Y.; Zhou, Z.; Tang, C. *Tetrahedron: Asymmetry* **2009**, *20*, 2178.

(121) Okino, T.; Nakamura, S.; Furukawa, T.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 625.

(122) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672.

(123) Yoon, T. P.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2005**, *44*, 466.

(124) Xu, X.; Furukawa, T.; Okino, T.; Miyabe, H.; Takemoto, Y. *Chem. Eur. J.* **2006**, *12*, 466. The enantiomers depicted in this paper are correct, but many of the reported optical rotations are missing a '-'ve sign. Private communication from Prof Takemoto 25th Oct 2012.

(125) Bode, C. M.; Ting, A.; Schaus, S. E. *Tetrahedron* **2006**, *62*, 11499.

(126) Bernardi, L.; Fini, F.; Herrera, R. P.; Ricci, A.; Sgarzani, V. *Tetrahedron* **2006**, *62*, 375.

(127) Robak, M. T.; Trincado, M.; Ellman, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 15110.

(128) Wang, C.; Zhou, Z.; Tang, C. *Org. Lett.* **2008**, *10*, 1707.

(129) Jiang, X.; Zhang, Y.; Wu, L.; Zhang, G.; Liu, X.; Zhang, H.; Fu, D.; Wang, R. *Adv. Synth. Catal.* **2009**, *351*, 2096.

(130) Chang, Y.-W.; Yang, J.-J.; Dang, J.-N.; Xue, Y.-X. *Synlett*, **2007**, 2283.

(131) Rampalakos, C.; Wulff, W. D. *Adv. Synth. Catal.* **2008**, *350*, 1785.

(132) Wang, C.-J.; Dong, X.-Q.; Zhang, Z.-H.; Xue, Z.-Y.; Teng, H.-L. *J. Am. Chem. Soc.* **2008**, *130*, 8606.

(133) Nugent, B. M.; Yoder, R. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 3418.

(134) Davis, T. A.; Wilt, J. C.; Johnston, J. N. *J. Am. Chem. Soc.* **2010**, *132*, 2880.

(135) Davis, T. A.; Johnston, J. N. *Chem. Sci.* **2011**, *2*, 1076.

(136) Rueping, M.; Antonchick, A. P. *Org. Lett.* **2008**, *10*, 1731.

(137) Palomo, C.; Oiarbide, M.; Laso, A.; López, R. *J. Am. Chem. Soc.* **2005**, *127*, 17622.

(138) Fini, F.; Sgarzani, V.; Pettersen, D.; Herrera, R. P.; Bernardi, L.; Ricci, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 7975.

(139) Gomez-Bengoa, E.; Linden, A.; López, R.; Múgica-Mendiola, I.; Oiarbide, M.; Palomo, C. *J. Am. Chem. Soc.* **2008**, *130*, 7955.

(140) Wei, Y.; He, W.; Liu, Y.; Liu, P.; Zhang, S. *Org. Lett.* **2012**, *14*, 704.

(141) Takada, K.; Nagasawa, K. *Adv. Synth. Catal.* **2009**, *351*, 345.

(142) Huang, W.; Peng, C.; Guo, L.; Hu, R.; Han, B. *Synlett* **2011**, 2981.

(143) Johnson, K. M.; Rattley, M. S.; Sladojevich, F.; Barber, D. M.; Nuñez, M. G.; Goldys, A. M.; Dixon, D. J. *Org. Lett.* **2012**, *14*, 2492.

(144) Lovick, H. M.; Michael, F. E. *Tetrahedron Lett.* **2009**, *50*, 1016.

(145) Rachwalski, M.; Leśniak, S.; Kielbasiński, P. *Tetrahedron: Asymmetry* **2011**, *22*, 1087.

(146) Pahadi, N. K.; Ube, H.; Terada, M. *Tetrahedron Lett.* **2007**, *48*, 8700.

(147) Wang, L.; Tan, C.; Liu, X.; Feng, X. *Synlett* **2008**, 2075.

(148) Zhang, F.; Liu, Z.-J.; Liu, J.-T. *Org. Biomol. Chem.* **2011**, *9*, 3625.

(149) Tan, C.; Liu, X.; Wang, L.; Wang, J.; Feng, X. *Org. Lett.* **2008**, *10*, 5305.

(150) Xie, H.; Zhang, Y.; Zhang, S.; Chen, X.; Wang, W. *Angew. Chem. Int. Ed.* **2011**, *50*, 11773.

(151) Knudsen, K. R.; Rahbek, K.; Jørgensen, K. A. *Org. Biomol. Chem.* **2005**, *3*, 1362.

(152) Singh, A.; Yoder, R. A.; Shen, B.; Johnston, J. N. *J. Am. Chem. Soc.* **2007**, *129*, 3466.

(153) Singh, A.; Johnston, J. N. *J. Am. Chem. Soc.* **2008**, *130*, 5866.

(154) Chen, Z.; Morimoto, H.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 2170.

(155) Han, B.; Liu, Q.-P.; Li, R.; Tian, X.; Xiong, X.-F.; Deng, J.-G.; Chen, Y.-C. *Chem. Eur. J.* **2008**, *14*, 8094.

(156) Uraguchi, D.; Koshimoto, K.; Ooi, T. *J. Am. Chem. Soc.* **2008**, *130*, 10878.

(157) Uraguchi, D.; Koshimoto, K.; Sanada, C. Ooi, T. *Tetrahedron: Asymmetry* **2010**, *21*, 1189.

(158) Puglisi, A.; Raimondi, L.; Benaglia, M.; Bonsignore, M.; Rossi, S. *Tetrahedron Lett.* **2009**, *50*, 4340.

(159) Han, B.; Huang, W.; Xu, Z. R.; Dong, X. P. *Chin. Chem. Lett.* **2011**, *22*, 923.

(160) Wilt, J. C.; Pink, M.; Johnston, J. N. *Chem. Commun.* **2008**, 4177.

(161) Blaszczyk, R.; Gajda, A.; Zawadzki, S.; Czubacka, E.; Gajda, T. *Tetrahedron* **2010**, *66*, 9840.

(162) Wang, Y; Yu, D.-F.; Liu, Y.-Z.; Wei, H.; Luo, Y.-C.; Dixon, D. J.; Xu, P.-F. *Chem. Eur. J.* **2010**, *16*, 3922.

(163) Urushima, T.; Sakamoto, D.; Ishikawa, H.; Hayashi, Y. *Org. Lett.* **2010**, *12*, 4588.

(164) Imashiro, R.; Uehara, H.; Barbas III, C. F. *Org. Lett.* **2010**, *12*, 5250.

(165) Rai, A.; Singh, A. K.; Singh, S.; Yadav, L. D. S. *Synlett* **2011**, 335.

(166) Rai, A.; Singh, A. K.; Singh, P.; Yadav, L. D. S. *Tetrahedron Lett.* **2011**, *52*, 1354.

(167) Jia, Z.-X.; Luo, Y.-C.; Xu, P.-F. *Org. Lett.* **2011**, *13*, 832.

(168) Anderson, J. C.; Stepney, G. J.; Mills, M. R.; Horsfall, L. R.; Blake, A. J.; Lewis, W. *J. Org. Chem.* **2011**, *76*, 1961.

(169) Mampreian, D. M.; Hoveyda, A. H. *Org. Lett.* **2004**, *6*, 2829.

(170) Côté, A.; Lindsay, V. N.; Charette, A. B. *Org. Lett.* **2007**, *9*, 85.

(171) Anderson, J. C.; Blake, A. J.; Koovits, P. J.; Stepney, G. J. *J. Org. Chem.* **2012**, *77*, 4711.

(172) Wang, X.; Chen, Y-F.; Niu, L.-F.; Xu, P.-F. *Org. Lett.* **2009**, *11*, 3310.

(173) Rastogi, N.; Mohan, R.; Panda, D.; Mobin, S. M.; Namboothiri, I. N. N. *Org. Biomol. Chem.* **2006**, *4*, 3211.

(174) Rajesh, K.; Shanbhag, P.; Raghavendra, M.; Bhardwaj, P.; Namboothiri, I. N. N. *Tetrahedron Lett.* **2010**, *51*, 846.

(175) Takizawa, S.; Horii, A.; Sasai, H. *Tetrahedron: Asymm.* **2010**, *21*, 891.

(176) Korotaev, V. Y.; Sosnovskikh, V. Y.; Kutyashev, I. B.; Barkov, A. Y.; Matochkina, E. G.; Kodess, M. I. *Tetrahedron* **2008**, *64*, 5055.

(177) Zhang, Z.; Jakab, G.; Schreiner, P. R. *Synlett* **2011**, 1262.

(178) Hou, W.; Zheng, B.; Chen, J.; Peng, Y. *Org. Lett.* **2012**, *14*, 2378.

(179) Ayerbe, M.; Arrieta, A.; Cossío, F. P. *J. Org. Chem.* **1998**, *63*, 1795.

(180) Vivanco, S.; Lecea, B.; Arrieta, A.; Prieto, P.; Morao, I.; Linden, A.; Cossío, F. P. *J. Am. Chem. Soc.* **2000**, *122*, 6078.

(181) Zubia, A.; Mendoza, L.; Vivanco, S.; Aldaba, E.; Carrascal, T.; Lecea, B.; Arrieta, A.; Zimmerman, T.; Vidal-Vanaclocha, F.; Cossío, F. P. *Angew. Chem. Int. Ed.* **2005**, *44*, 2903.

(182) Arrieta, A.; Otaegui, D.; Zubia, A.; Cossío, F. P.; Díaz-Ortiz, A.; de la Hoz, A.; Herrero, M. A.; Prieto, P.; Foces-Foces, C.; Pizarro, J. L.; Arriortua, M. I. *J. Org. Chem.* **2007**, *72*, 4313.

(183) Padwa, A.; Chen, Y.-Y.; Chiacchio, U.; Dent, W. *Tetrahedron* **1985**, *41*, 3529.

(184) Nyerges, M.; Balázs, L.; Kádas, I.; Bitter, I.; Kövesdi, I.; Tőke, L. *Tetrahedron* **1995**, *51*, 6783.

(185) Virányi, A.; Marth, G.; Dancsó, A.; Blaskó, G.; Tőke, L.; Nyerges, M. *Tetrahedron* **2006**, *62*, 8720.

(186) Nyerges, M.; Bitter, I.; Kádas, I.; Tóth, G.; Tőke, L. *Tetrahedron Lett.* **1994**, *35*, 4413.

(187) Nyerges, M.; Rudas, M.; Tóth, G.; Herényi, B.; Kádas, I.; Bitter, I.; Tőke, L. *Tetrahedron* **1995**, *51*, 13321.

(188) Felluga, F.; Nitti, P.; Pitacco, G.; Valentin, E. *J. Chem. Soc. Perkin Trans. 1* **1992**, 2331.

(189) Alcaide, B.; Almendros, P.; Alonso, J. M.; Aly, M. F. *J. Org. Chem.* **2001**, *66*, 1351.

(190) Cabrera, S.; Arrayás, R. G.; Carratero, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 16394.

(191) Cabrera, S.; Arrayás, R. G.; Martín-Matute, B.; Cossío, F. P.; Carratero, J. C. *Tetrahedron* **2007**, *63*, 6587.

(192) Yan, X.-X.; Peng, Q.; Zhang, Y.; Zhang, K.; Hong, W.; Hou, X.-L.; Wu, Y.-D. *Angew. Chem. Int. Ed.* **2006**, *45*, 1979.

(193) Li, Q.; Ding, C.-H.; Li, X.-H.; Weissensteiner, W.; Hou, X.-L. *Synthesis* **2012**, *44*, 265.

(194) Arai, T.; Mishiro, A.; Yokoyama, N.; Suzuki, K.; Sato, H. *J. Am. Chem. Soc.* **2010**, *132*, 5338.

(195) Arai, T.; Yokoyama, N.; Mishiro, A.; Sato, H. *Angew. Chem. Int. Ed.* **2010**, *49*, 7895.

(196) Kim, H. Y.; Li, J.-Y.; Kim, S.; Oh, K. *J. Am. Chem. Soc.* **2011**, *133*, 20750.

(197) Xue, M.-X.; Zhang, X.-M.; Gong, L.-Z. *Synlett* **2008**, 691.

(198) Liu, Y.-K.; Liu, H.; Du, W.; Yue, L.; Chen, Y.-C. *Chem. Eur. J.* **2008**, *14*, 9873.

(199) Xie, J.; Yoshida, K.; Takasu, K.; Takemoto, Y. *Tetrahedron Lett.* **2008**, *49*, 6910.

(200) Crovetto, L.; Rios, R.; *Synlett* **2008**, 1840.

(201) Brannock, K. C.; Bell, A.; Burpitt, R. D.; Kelly, C. A. *J. Org. Chem.* **1964**, *29*, 801.

(202) Kuehne, M. E.; Foley, L. *J. Org. Chem.* **1965**, *30*, 4280.

(203) Colonna, F. P.; Valentin, E.; Pitacco, G.; Risaliti, A. *Tetrahedron* **1973**, *29*, 3011.

(204) Felluga, F.; Nitti, P.; Pitacco, G.; Valentin, E. *Tetrahedron* **1989**, *45*, 5667.

(205) Burés, J.; Armstrong, A.; Blackmond, D. G. *J. Am. Chem. Soc.* **2011**, *133*, 8822.

(206) Patora-Komisarska, K.; Benohoud, M.; Ishikawa, H.; Seebach, D.; Hayashi, Y. *Helv. Chim. Act.* **2011**, *94*, 719.

(207) Burés, J.; Armstrong, A.; Blackmond, D. G. *J. Am. Chem. Soc.* **2012**, *134*, 6741.

(208) Nara, S.; Tanaka, R.; Eishima, J.; Hara, M.; Takahashi, Y.; Otaki, S.; Foglesong, R. J.; Hughes, P. F.; Turkington, S.; Kanda, Y. *J. Med. Chem.* **2003**, *46*, 2467.

(209) Tanaka, R.; Rubio, A.; Harn, N. K.; Gernert, D.; Grese, T. A.; Eishima, J.; Hara, M.; Yoda, N.; Ohashi, R.; Kuwabara, T.; Soga, S.; Akinaga, S.; Nara, S.; Kanda, Y. *Bioorg. Med. Chem.* **2007**, *15*, 1363.

(210) Pei, Z.; Li, X.; von Geldern, T. W.; Longenecker, K.; Pireh, D.; Stewart, K. D.; Backes, B. J.; Lai, C.; Lubben, T. H.; Ballaron, S. J.; Beno, D. W. A.; Kempf-Grote, A. J.; Sham, H. L.; Trevillyan, J. M. *J. Med. Chem.* **2007**, *50*, 1983.

(211) Xu, F.; Corley, E.; Zacuto, M.; Conlon, D. A.; Pipik, B.; Humphrey, G.; Murry, J.; Tschaen, D. *J. Org. Chem.* **2010**, *75*, 1343.

(212) Xu, F.; Corley, E.; Murry, J. A.; Tschaen, D. M. *Org. Lett.* **2007**, *9*, 2669.

(213) Jakubec, P.; Helliwell, M.; Dixon, D. J. *Org. Lett.* **2008**, *10*, 4267.

(214) Jakubec, P.; Cockfield, D. M.; Helliwell, M.; Raftery, J.; Dixon, D. J. *Beilstein J. Org. Chem.* **2012**, *8*, 567.

(215) Humphrey, J. M.; Arnold, E. P.; Chappie, T. A.; Feltenberger, J. B.; Nagel, A.; Simon, W.; Suarez-Contreras, M.; Tom, N. J.; O'Neill, B. T. *J. Org. Chem.* **2009**, *74*, 4525.

(216) Ruano, J. L. G.; de Haro, T.; Singh, R.; Cid, M. B. *J. Org. Chem.* **2008**, *73*, 1150.

(217) Pelletier, S. M.-C.; Ray, P. C.; Dixon, D. J. *Org. Lett.* **2009**, *11*, 4512.

(218) Pelletier, S. M.-C.; Ray, P. C.; Dixon, D. J. *Org. Lett.* **2011**, *13*, 6406.

(219) Baricordi, N.; Benetti, S.; Biondini, G.; De Risi, C.; Pollini, G. P. *Tetrahedron Lett.* **2004**, *45*, 1373.

(220) Jiang, H.; Elsner, P.; Jensen, K. L.; Falcicchio, A.; Marcos, V.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2009**, *48*, 6844.

(221) Tanaka, S.; Oguma, Y.; Tanaka, Y.; Echizen, H.; Masu, H.; Yamaguchi, K.; Kishikawa, K.; Kohmoto, S.; Yamamoto, M. *Tetrahedron* **2008**, *64*, 1388.

(222) Tanaka, S.; Kochi, K.; Ito, H.; Mukawa, J.; Kishikawa, K.; Yamamoto, M.; Kohmoto, S. *Synth. Commun.* **2009**, *39*, 868.

(223) Barber, D. M.; Sanganee, H.; Dixon, D. J. *Chem. Commun.* **2011**, *47*, 4379.

(224) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 3672.

(225) Li, Z.; Bohle, D. S.; Li, C.-J. *Proc. Nat. Acad. Sci.* **2006**, *103*, 8928.

(226) Baslé, O.; Li, C.-J. *Green Chem.* **2007**, *9*, 1047.

(227) Baslé, O.; Borduas, N.; Dubois, P.; Chapuzet, J. M.; Chan, T.-H.; Lessard, J.; Li, C.-J. *Chem. Eur. J.* **2010**, *16*, 8162.

(228) Boess, E.; Schmitz, C.; Klussmann, M. *J. Am. Chem. Soc.* **2012**, *134*, 5317.

(229) Tsang, A. S.-K.; Todd, M. H. *Tetrahedron Lett.* **2009**, *50*, 1199.

(230) Su, W.; Yu, J.; Li, Z.; Jiang, Z. *J. Org. Chem.* **2011**, *76*, 9144.

(231) Shu, X.-Z.; Xia, X.-F.; Yang, Y.-F.; Ji, K.-G.; Liu, X.-Y.; Liang, Y.-M. *J. Org. Chem.* **2009**, *74*, 7464.

(232) Condie, A. G.; González-Gómez, J. C.; Stephenson, R. J. *J. Am. Chem. Soc.* **2010**, *132*, 1464.

(233) Freeman, D. B.; Furst, L.; Condie, A. G.; Stephenson, C. R. J. *Org. Lett.* **2012**, *14*, 94.

(234) Tucker, J. W.; Zhang, Y.; Jamison, T. F.; Stephenson, C. R. J. *Angew. Chem. Int. Ed.* **2012**, *51*, 4144.

(235) Xie, Z.; Wang, C.; deKrafft, K. E.; Lin, W. *J. Am. Chem. Soc.* **2011**, *133*, 2056.

(236) Wang, C.; Xie, Z.; deKrafft, K. E.; Lin, W. *J. Am. Chem. Soc.* **2011**, *133*, 13445.

(237) Wang, C.; Xie, Z.; deKrafft, K. E.; Lin, W. *ACS Appl. Mater. Interfaces* **2012**, *4*, 2288.

(238) Hari, D. P.; König, B. *Org. Lett.* **2011**, *13*, 3852.

(239) Liu, Q.; Li, Y.-N.; Zhang, H.-H.; Chen, B.; Tung, C.-H.; Wu, L.-Z. *Chem. Eur. J.* **2012**, *18*, 620.

(240) Alagiri, K.; Prabhu, K. R. *Org. Biomol. Chem.* **2012**, *10*, 835.

(241) Xie, J.; Li, H.; Zhou, J.; Cheng, Y.; Zhu, C. *Angew. Chem. Int. Ed.* **2012**, *51*, 1252.

(242) Yu, A.; Gu, Z.; Chen, D.; He, W.; Tan, P.; Xiang, J. *Catal. Commun.* **2009**, *11*, 162.

(243) Shu, X.-Z.; Yang, Y.-F.; Xia, X.-F.; Ji, K.-G.; Liu, X.-Y.; Liang, Y.-M. *Org. Biomol. Chem.* **2010**, *8*, 4077.

(244) Zeng, T.; Song, G.; Moores, A.; Li, C.-J. *Synlett* **2010**, 2002.

(245) Rueping, M.; Zoller, J.; Fabry, D. C.; Poscharny, K.; Koenigs, R. M.; Weirich, T. E.; Mayer, J. *Chem. Eur. J.* **2012**, *18*, 3478.

(246) Asao, N.; Yudha, S. S.; Nogami, T.; Yamamoto, Y. *Angew. Chem. Int. Ed.* **2005**, *44*, 5526.

(247) Yadav, J. S.; Reddy, B. V. S.; Yadav, N. N.; Gupta, M. K. *Synthesis* **2009**, 1131.

(248) Ahamed, M.; Thirukkumaran, T.; Leung, W. Y.; Jensen, P.; Schroers, J.; Todd, M. H. *Eur. J. Org. Chem.* **2010**, 5980.

(249) Malan, J.; Robinson, R. *J. Chem. Soc.* **1927**, 2653.

(250) Ovchinnikov, I. V.; Kulikov, A. S.; Epishina, M. A.; Makhova, N. N.; Tartakovsky, V. A. *Russ. Chem. Bull.* **2005**, *54*, 1346.

(251) Epishina, M. A.; Ovchinnikov, V.; Kulikov, A. S.; Makhova, N. N.; Tartakovsky, V. A. *Mendeleev Commun.* **2011**, *21*, 21.

(252) Avdonin, V. V.; Volkov, G. A.; Galkin, P. V.; Grebennikov, V. N.; Eremenko, L. T.; Kirpichev, E. P.; Korepin, A. G.; Nazin, G. M.; Rubtsov, Y. I. *Russ. Chem. Bull.* **1992**, *41*, 1447.

(253) Tsuritani, N.; Yamada, K.-I.; Yoshikawa, N.; Shibasaki, M. *Chem. Lett.* **2002**, 276.

(254) Hynes, P. S.; Stupple, P. A.; Dixon, D. J. *Org. Lett.* **2008**, *10*, 1389.

(255) Jensen, K. L.; Poulsen, P. H.; Donslund, B. S.; Morana, F.; Jørgensen, K. A. *Org. Lett.* **2012**, *14*, 1516.

(256) Jakubec, P.; Cockfield, D. M.; Dixon, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 16632.

(257) Jakubec, P.; Kyle, A. F.; Calleja, J.; Dixon, D. J. *Tetrahedron Lett.* **2011**, *52*, 6094.

(258) Kyle, A. F.; Jakubec, P; Cockfield, D. M.; Cleator, E.; Skidmore, J.; Dixon, D. J. *Chem. Commun.* **2011**, *47*, 10037.

(259) Shen, B.; Johnston, J. N. *Org. Lett.* **2008**, *10*, 4397.

(260) Weng, J.; Li, Y.-B.; Wang, R.-B.; Li, F.-Q.; Liu, C.; Chan, A. S. C.; Lu, G. *J. Org. Chem.* **2010**, *75*, 3125.

(261) Kumaraswarmy, G.; Pitchaiah, A. *Tetrahedron* **2011**, *67*, 2536.

(262) Kumaraswarmy, G.; Pitchaiah, A. *Helv. Chim. Act.* **2011**, *94*, 1543.

(263) Davis, T. A.; Danneman, M. W.; Johnston, J. N. *Chem. Commun.* **2012**, *48*, 5578.

(264) Shen, B.; Makley, D. M.; Johnston, J. N. *Nature* **2010**, *465*, 1027.

(265) Anderson, J.C.; Noble, A.; Tocher, D.A. *J. Org. Chem.* **2012**, *77*, 6703

(266) Barber, D. M.; Sanganee, H. J.; Dixon, D. J. *Org. Lett.* **2012**, *14*, 5290.

(267) Lovering, F.; Bikker, J.; Humblet, C. *J. Med. Chem.* **2009**, *52*, 6752