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Enantioselective methodologies using *N*-carbamoyl-imines

Jan Vesely[a] and Ramon Rios†*[b]

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Nucleophilic addition to carbon–nitrogen double bonds (imines) represents one of the most common strategies for the synthesis of amine derivatives. In order to circumvent the problem associated with low reactivity of imines in nucleophilic addition, various imines with electron-withdrawing groups at nitrogen have been studied, and many of them were successfully applied in asymmetric methodologies. Especially *N*-carbamoyl imines were found to be useful in the enantioselective synthesis of various organic compounds, due to their increased reactivity toward nucleophiles as well as limited difficulties connected with the removal of the carbamoyl moiety in target molecules. The aim of this review is to cover enantioselective methods based on *N*-carbamoyl imines, focusing on synthetically useful protocols.

1. Introduction

In the last decade, the stereoselective formation of carbon–nitrogen bonds has emerged as one of the most important topics in organic chemistry. One of the most common strategies for the synthesis of nitrogen derivatives is the nucleophilic addition to carbon–nitrogen double bonds. However, given the low reactivity of imines in nucleophilic addition, several approaches have been explored to enhance their reactivity. These approaches include coordination of the Lewis acid through the nitrogen lone electron, which has a beneficial effect on reactivity, but is not compatible with several nucleophilic reagents (amines, alcohols, *etc.*).[1] Another approach has been the use of electron-withdrawing substituents at the

[a] *Department of Organic Chemistry, Charles University, Hlavova 2030, 128 43 Praha 2, Czech Republic. E-mail: jxvesely@natur.cuni.cz*
[b] *School of Chemistry, University of Southampton, Southampton, SO17 1BJ, UK. E-mail: R.Rios-Torres@southampton.ac.uk*
† Dedicated to Dr Martin C. Grossel on occasion of his retirement.

Jan Vesely

Jan Veselý obtained his PhD in 2005 under the supervision of Prof. Tomáš Trnka (Charles University in Prague) and Dr Miroslav Ledvina (IOCB, AS CR) for his work on the synthesis of linear and cyclic oligosaccharides. Then, he worked for one year as a postdoc in the group of Stefan Oscarson, and for one and a half years in the group of Armando Córdova (both at Arrhenius Laboratories, Stockholm University). After his return, he started an independent research career at the Charles University in Prague, where he currently holds the position of an assistant professor. His research interests are stereoselective preparation of glycoconjugates and sugar-derived units, as well as the development of new asymmetric methodologies based on organocatalysis and their application in total synthesis.

Ramon Rios

Ramon Rios obtained his PhD degree from the University of Barcelona in 2000. He has enjoyed several postdoctoral and research positions with Prof. Greg C. Fu (MIT, Boston, MA, 1999), Prof. Patrick Walsh, Prof. Benjamin List, Armando Córdova and Prof. Jose Ma Alvarez-Pez as well as industrial experience (J. C. Uriach S. A., Barcelona, Spain, 2002–2004). He began his independent career as ICREA Researcher in 2008 at the University of Barcelona. In 2011 he was visiting Professor at the Nagoya Institute of Technology after being awarded a JSPS invitational fellowship. In 2012 he was appointed as a Reader of Organic Chemistry at the University of Southampton (UK). He is the author of more than 100 papers and several chapters in chemistry books and has been the editor of two books. His research interests are the development of new asymmetric methodologies based on organocatalysis and/or organometallic chemistry and their application in total synthesis.

nitrogen atom, which significantly enhances the reactivity of imino derivatives. Nitrones,[2] *N*-sulfinylimines like Ellman auxiliary,[3] *N*-tosylimines[4] and *N*-phosphinoylimines[5] are some of the most commonly used electron withdrawing groups. However, there are drawbacks to using these compounds, such as difficulty in the cleavage of the activating group of the nitrogen. In order to circumvent this problem, *N*-carbamoyl has become a powerful option.

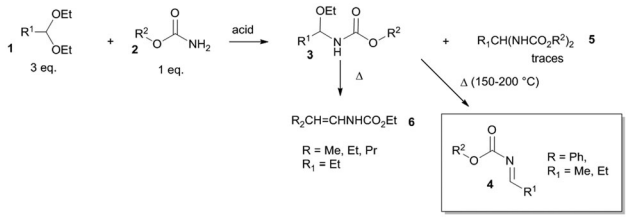
Cation stabilization is stronger in *N*-carbamoyl-imines because of the increased availability of the carbamate nitrogen lone pair. However, these compounds are quite unstable (hydroscopic) and some precaution should be taken to store them for longer periods. The advantages of *N*-carbamoyl imines compared to other imines lie in their higher reactivity (*N*-aryl imines, *N*-hydroxylimines, *etc.*), their enhanced stability compared to *N*-acylimines and their ease of deprotection (*N*-sulfinylimines, nitrones or acylimines).

The initial synthesis of these types of compounds was reported by Stavrovskaya *et al.* in 1970 in a reaction of diethyl-acetals with methyl carbamates that yielded *N*-carbamoyl-imine **4** (Scheme 1).[6]

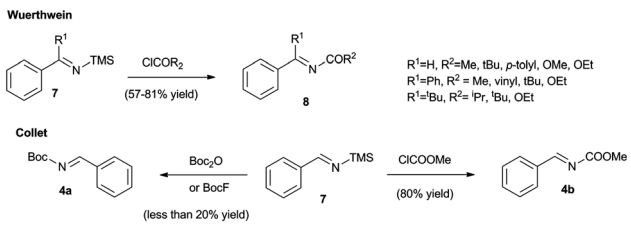
Further improvements in their synthesis were made by Wuerthwein *et al.* using silyl imines as the starting compound.[7] However, these initial syntheses were focused on methyl carbamates, which are not commonly used due to the difficulty of deprotection.

In order to bypass this important limitation, Collet and co-workers reported the synthesis of *N*-Boc imines for the first time in 1993 (Scheme 2).[8]

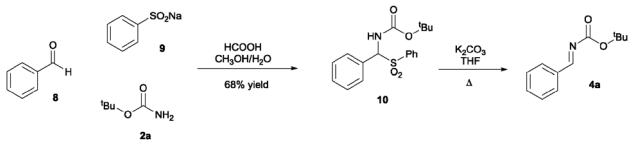
They found that it was beneficial to use more conventional protecting groups, such as Boc, Fmoc, or Cbz, which were already being used in peptide chemistry. In 1994, Greene reported the use of these compounds in the preparation of the Taxotere side chain, with excellent results.[9] These results were not only applicable to the synthesis of these types of compounds, but also resulted in the development of a new strategy for their synthesis, a strategy that is still used today. Aromatic aldehydes react with



Scheme 1 First synthesis of *N*-carbamoyl imines (1970).



Scheme 2 Synthesis of *N*-carbamoyl imines reported by Wuerthwein and Collet.



Scheme 3 Synthesis of *N*-Boc imines reported by Greene.

benzenesulfinate **9** and tertbutyl carbamate **2a** to yield a highly stable compound known as *N*-(tertbutoxycarbonyl)-α-phenyl-sulfonylbenzylamine (**10**). Next refluxing compound **10** in THF in the presence of potassium carbonate affords the *N*-Boc imine **4a**. This new preparation technique was easy to scale-up and most importantly in the following years several chemists were able to prepare "*in situ*" the *N*-Boc imines from the intermediate **10**, opening a new window for the development of enantio-selective methodologies (Scheme 3).[10]

The first example of enantioselective reaction using *N*-Boc imines was reported by Lipton and co-workers in 1996.[11] Since then, several research groups have devoted their efforts to the development of new methodologies based on *N*-carbamoyl imines.

The aim of this review is to cover enantioselective methods based on *N*-carbamoyl imines, focusing on synthetically useful protocols. Wherever possible, working mechanistic models are also presented.

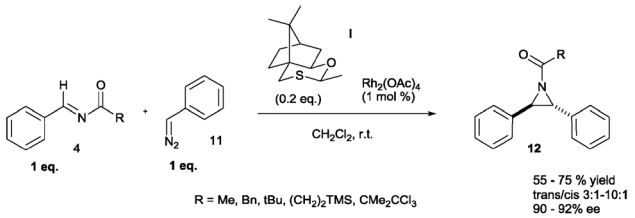
This review is organized according to the nature of the catalyst: organometallic and organocatalytic processes. We first discuss organometallic reactions and catalysis reactions based on *N*-carbamoyl imines. We will deal with Mannich reaction, aza-Henry reaction, *etc.* In Section 3, we describe the most important organocatalytic methodologies, which include Mannich, aza-Henry, Friedel–Crafts, and Strecker reactions. Although several reviews dealing with specific aspects (processes, reaction conditions, catalyst and reagent types, mechanisms) of *N*-carbamoyl imines have been published in the past few years, few have described their use in enantioselective methodologies.[12] The coverage of the present review extends generally until December 2012, although selected more recent references have been included.

2. Organometallic approaches

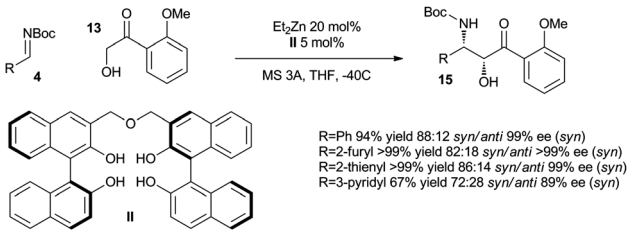
Organometallic chemistry has been established as one of the most important approaches for the development of enantioselective methodologies. The first reported example was the aziridination of imines mediated by sulfur ylides, which was developed by Aggarwal *et al.* in 2001.[13] As shown in Scheme 4 the aziridination of *N*-carbamoyl imines using diazo compounds and catalytic amounts of metal salts and sulfides resulted in good yields and stereoselectivities of the final products.

2.1 Mannich reaction

In 2004, Shibasaki and co-workers reported one of the first enantioselective Mannich reactions between *N*-Boc aldimines (**4**) and hydroxyketones (**13**).[14] The reaction was promoted by Et_2Zn/(*S*,*S*)-linked-BINOL (**II**) complexes yielding the *syn* adducts in good yields and enantioselectivities (Scheme 5).



Scheme 4 Aziridination reported by Aggarwal.



Scheme 5 Mannich reaction developed by Shibasaki.

The nature of the protecting group of the amine determines the diastereoselectivity of the reaction. *N*-Diphenylphosphinoyl (DPP) imines gave the *anti* β-aminoalcohols adducts in contrast with *N*-Boc imines; this feature is explained by the transition states outlined in Fig. 1. To avoid steric repulsion between the DPP group and the zinc-enolate, the Mannich reaction proceeded *via* transition state **A**. When using less sterically demanding *N*-Boc aldimines the facial selectivity of the imine should be opposite in order to avoid steric repulsions between the substituent of the imine and the zinc-enolate (transition state **B**, Fig. 1).

Sodeoka and co-workers reported the use of palladium(II) complexes as catalyst for the enantioselective addition of β-ketoesters (**17**) to *N*-Boc imines (**4**).[15] The use of (*R*)-segphos (**IV**) as a ligand rendered final adducts with excellent yields and enantioselectivities. The palladium complex activated the ketoester forming Pd-enolate, while trifluoromethanesulfonic acid (TfOH) formed concomitantly with the Pd-enolate to activate the imine, thereby promoting C–C bond formation. In 2008 the same research group expanded the scope of the reaction by using malonates. This time the reaction was catalyzed by BINAP–Pd(II) aqua complexes. The reaction afforded the desired β-aminocarbonyl compounds in good yield with high to excellent stereoselectivity (up to 96 : 4 d.r., 95–99% ee in most cases) (Scheme 6).[16]

Zhou and co-workers reported the use of silver acetate as a catalyst for the Mannich reaction of *N*-Boc aldimines with several dicarbonylic compounds.[17] Silver acetate works as a bifunctional catalyst, in which the acetate plays the role of a base while the metal acts as a Lewis acid. Chiral ferrocene derived *P*,*S* or *P*,*N*

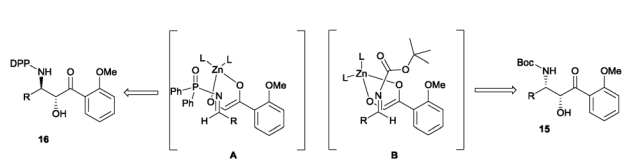
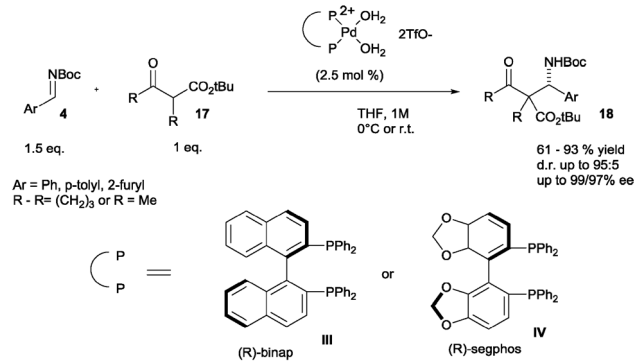


Fig. 1 Transition state models.



Scheme 6 β-Ketoester addition to *N*-Boc imines reported by Sodeoka.

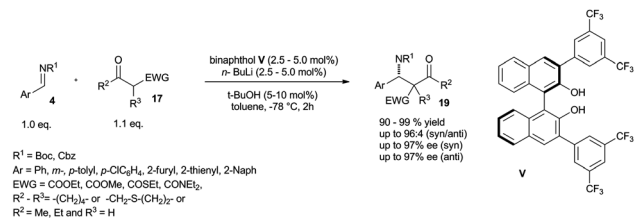
ligands were used in the reactions with excellent results. As nucleophiles the authors tested acetoacetates, ketoesters, malonates and α,α-dicyanoolefins; in the first three examples (acetoacetates, ketoesters and malonates) the reaction affords the amine derivatives in excellent yields and enantioselectivities. However, with α,α-dicyanoolefins the reaction only affords moderate enantioselectivities.

Years later, Ishihara and co-workers reported similar Mannich reactions catalyzed by lithium(I) binaphtholate (**V**).[18] Acetoacetates and β-ketoesters react with *N*-Boc or *N*-Cbz aromatic aldimines with excellent yields (91–99%), good diastereoselectivities (up to 97 : 3 d.r.) and excellent enantioselectivities (87–95%) as shown in Scheme 7.

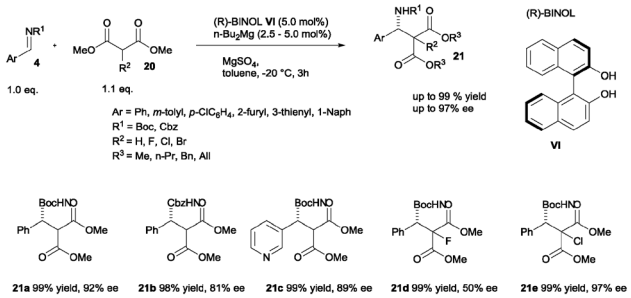
However, this catalytic system cannot promote the reaction with less reactive dicarbonylic compounds such as malonates. For this reason, the same authors developed a similar strategy using magnesium(II)-binaphtholate as a chiral catalyst to promote the reaction (Scheme 8).[19] With this catalyst, the reaction between aromatic or heteroaromatic *N*-Boc aldimines and malonates takes place in excellent yields (94–99%) and enantioselectivities (81–92%).

The same research group tested calcium phosphates as catalysts to promote the Mannich reaction between aromatic or heteroaromatic *N*-Boc aldimines and β-ketothioesters with excellent results.[20] The use of chiral calcium complexes as a suitable catalyst for the addition of malonates to *N*-Boc aldimines was also reported by Kobayashi and co-workers in 2010 (Scheme 9).[21] The best results were obtained when using the calcium-pybox (pyridinebisoxazoline) complex (**VII**) at −20 °C, resulting in final *N*-Boc-amine derivatives in good yields (75–99%) and moderate enantioselectivities (43–73%).

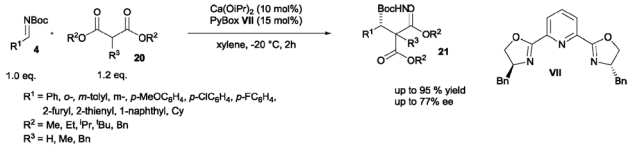
Rueping and co-workers reported the addition of cyclic 1,3-dicarbonylic compound to *N*-Boc aldimines catalyzed by



Scheme 7 Addition of β-ketoesters to *N*-Boc imines reported by Ishihara.



Scheme 8 Addition of malonates to *N*-Boc imines catalyzed by Mg salts.



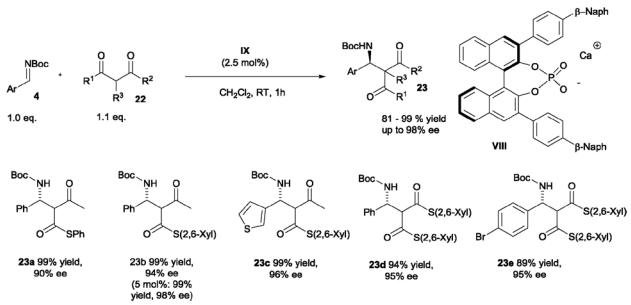
Scheme 9 Addition of malonates to *N*-Boc imines catalyzed by Ca–Pybox complexes.

calcium phosphates derived from BINOL, with good yields and moderate to good enantioselectivities (Scheme 10).[22]

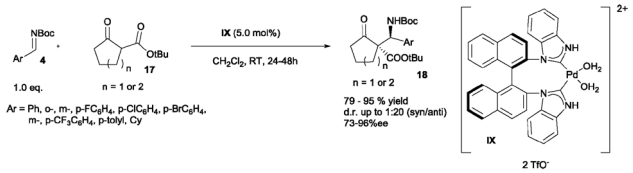
Shi and co-workers demonstrated that chiral C_2-symmetric cationic Pd^{+2} N-heterocyclic carbene diaqua complexes catalyze the addition of cyclic β-ketoesters to *N*-Boc aldimines.[23] The reaction affords amine derivatives **18** in good yields and enantioselectivities, albeit with moderate diastereoselectivities (Scheme 11).

Shibasaki and co-workers reported the Mannich reaction between α-cyanoketones and *N*-Boc aldimines catalyzed by scandium complexes.[24] They used a simple chiral amide ligand (**X**). They hypothesized that this imine should mimic a metalloenzyme to reproduce a highly ordered transition state. The high coordination mode and unpredictable coordination mode will allow a variety of assembled structures depending of the reaction conditions, substrate, *etc.* In the optimized condition the ligand **X** and scandium tris-isopropoxide mixture in the ratio of 2 : 1 catalyzed the addition of 2-cyanocyclopentanone **18** and *N*-Boc aldimines (**4**) in excellent yields and stereoselectivities (Scheme 12).

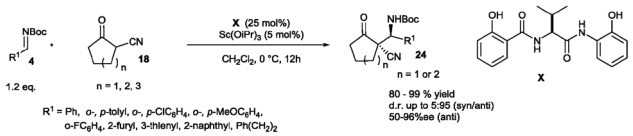
In 2009, Kim and co-workers reported the same reaction as Shibasaki but this time catalyzed by Pd(II) complexes using diphosphines as chiral ligands.[25] The room temperature reaction rendered the amine derivatives in moderate to good yields



Scheme 10 Addition of malonates to *N*-Boc imines catalyzed by Mg salts.



Scheme 11 Addition of β-ketoesters to *N*-Boc aldimines catalyzed by Pd–NHC complexes.



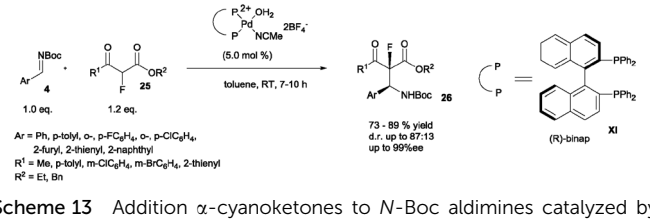
Scheme 12 Addition α-cyanoketones to *N*-Boc aldimines catalyzed by scandium complexes.

(71–95%) with good diastereo- (up to 100 : 1) and enantioselectivities (70–91%). Following this work the same research group developed the addition of fluorinated ketoesters to *N*-Boc aldimines catalyzed by chiral Pd(II) catalysts using BINAP (**XI**) as a ligand.[26] Under optimized conditions the reaction rendered the β-fluoroamine derivatives with good yields (73–89%), moderate diastereoselectivities (up to 87 : 13) and excellent enantioselectivities (93–99%) (Scheme 13).

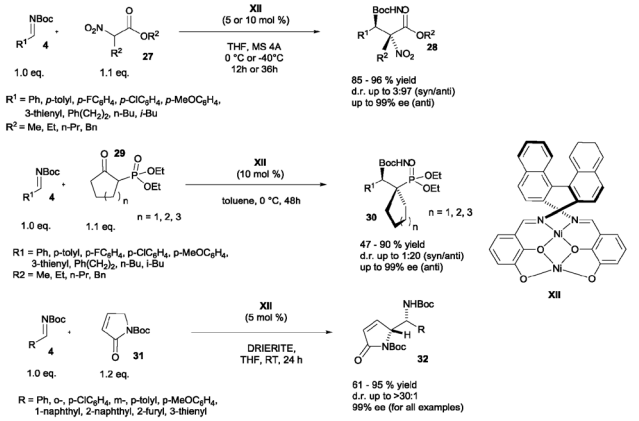
In 2008, Shibasaki and Matsunaga reported the addition of α-substituted nitro esters (**28**)[27] and β-ketophosphonates (**29**)[28] to *N*-Boc aldimines (**4**) promoted by a homo dinuclear Ni_2-Schiff base (**XII**). Under optimized conditions the reaction afforded the desired Mannich adducts with excellent yields, diastereoselectivities and enantioselectivities (Scheme 14). In 2010, the same research group reported the Mannich reaction between α,β-unsaturated γ-butyrolactams (**31**) and *N*-Boc aldimines promoted by the same catalyst.[29] The reaction with aromatic and heteroaromatic *N*-Boc aldimines rendered the Mannich adducts with excellent yields (61–95%), diastereoselectivities (up to >30 : 1 d.r.) and enantioselectivities (99% ee).

Kobayashi and co-workers reported the addition of sulfonylimidates to *N*-Boc aldimines catalyzed by alkaline earth metals.[30] As it is well known, alkaline earth metals display dual properties, with both Lewis acid and Bronsted base characters. The authors only reported a single enantioselective example using a chiral bissulfonylamine ligand affording the amine derivatives in good yield (85%) and moderate diastereoselectivity (83 : 17 *syn* : *anti*) and enantioselectivity (57%).

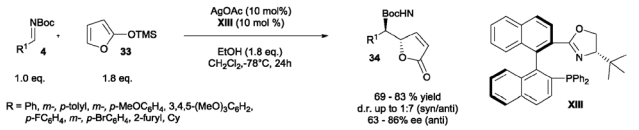
The addition of trimethylsiloxyfuran to *N*-Boc aldimines promoted by silver salts was reported by Shi in 2011.[31] In this work,



Scheme 13 Addition α-cyanoketones to *N*-Boc aldimines catalyzed by scandium complexes.



Scheme 14 Additions to *N*-Boc imines developed by Shibasaki and Matsunaga.



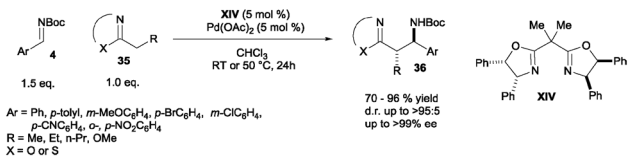
Scheme 15 Addition of trimethylsiloxyfuran to *N*-Boc imines.

axially chiral phosphine-oxazolines (**XIII**) were used as chiral ligands achieving amino derivatives **34** in good yields (79–97%) and good diastereo- (up to 7 : 1) and enantioselectivities (63–86%). The reaction is run at −78 °C and is limited to *N*-Boc aldimines (Scheme 15).

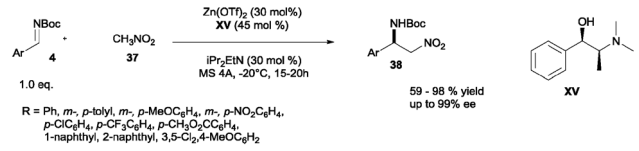
Recently, Lam and co-workers reported a Mannich addition between 2-alkylazaarenes **35** and *N*-Boc aldimines.[32] The reaction is promoted by Pd(II) bisoxazoline complexes (**XIV**) that activate the azaarene lowering the pK_a of the benzylic position. The reaction produced amine derivatives in good yields (70–95%) and excellent diastereo- (up to >95 : 5 d.r.) and enantioselectivities (88–98% ee). The reaction presented several limitations, including a need for incorporation of electron withdrawing groups into the azaarenes, and the fact that the reaction was only tested with aromatic *N*-Boc aldimines (Scheme 16).

2.2 Aza-Henry reaction

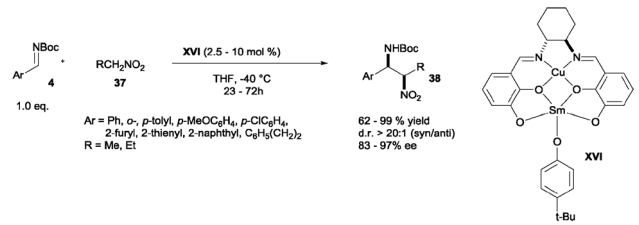
Palomo and co-workers employed Zn(II)-(−)-*N*-methylephedrine (**XV**) complexes as catalysts for the aza-Henry reaction.[33] In this work, they tried different imines, but the best results were obtained with *N*-Boc-imines. The reaction rendered the final amine derivatives with good yields (59–95%) and excellent enantioselectivities (87–99%). *N*-Cbz aldimines rendered the final amine derivatives with slightly lower enantioselectivities. However, the reaction was limited to the use of nitromethane (Scheme 17).



Scheme 16 Reaction reported by Lam.



Scheme 17 Aza-Henry reaction reported by Palomo.



Scheme 18 Aza-Henry reaction reported by Shibasaki.

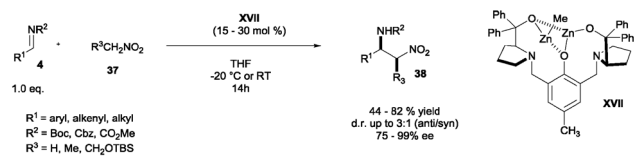
Shibasaki and co-workers overcame this limitation by using a heterobimetallic Cu–Sm–Schiff base complex (**XVI**) as catalyst (Scheme 18).[34] The importance of this reaction lies in the fact that this is the first *syn* selective aza-Henry reaction. As shown in Scheme 17 the reaction provided synthetically versatile nitroamines in good to excellent yields (99–62%) and excellent diastereo- (>20 : 1 d.r.) and enantioselectivities (99–83%). Despite the lack of mechanistic evidence, the use of Cu–Sm bimetallic catalysts was essential for high *syn*-selectivity, as the use of other metals resulted in lower diastereo- and enantioselectivities. The same authors later reported a similar catalytic system using Yb/K as a bimetallic catalyst with slightly worse results.[35]

At approximately the same time, Trost and co-workers reported the use of dinuclear Zn catalysts for the enantioselective aza-Henry reaction.[36] The dual Lewis acid/Lewis base functionality of catalyst **XVII** should facilitate the formation of the nitronate anion and at the same time activate the imine. In this work, *N*-Boc aldimines reacted with nitromethane affording nitroamine compounds in moderate yields (48–82%) and good to excellent enantioselectivities (82–96%). The type of carbamate group of the azomethine was also investigated. The use of Moc-protected imines led to similar results, whereas when Cbz-protected imines were used, the enantioselectivity decreased (Scheme 19).

Chiral supramolecular metal–organic frameworks assembled from copper complexes have been used as suitable catalysts for the aza-Henry reaction between aromatic *N*-Boc aldimines and nitromethane.[37] The reaction renders the final nitro-amines in excellent yields and enantioselectivities.

2.3 Other reactions

Trost and co-workers developed the palladium catalyzed [3+2] cycloaddition of trimethylene methane with *N*-Boc imines



Scheme 19 Aza-Henry reaction reported by Trost.

(Scheme 20).[38] 3-Acetoxy-2-trimethylsilylmethyl-1-propene (**39**) reacted with *N*-Boc aldimines (**4**) to afford chiral pyrrolidines as shown in Scheme 18. Chiral phosphoramidites **XVIII** were use as chiral ligands rendering the final pyrrolidines **40** in good to excellent yields (60–96%) and excellent enantioselectivities (85–93%).

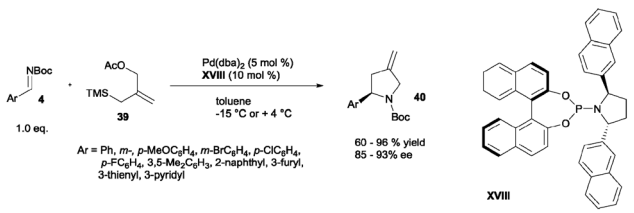
In 2008, Ishihara reported a single example of the alkynylation of *N*-Boc aldimines catalyzed by copper salts. This reaction afforded the desired propargyl amine derivative in low yield (16%) and low enantioselectivity (29%).[39]

The same year, an interesting reaction was reported by Falck regarding the stannation of *N*-Boc imines using ethyl(tri-*n*-butylstannyl)zinc (**41**) and an aminoalcohol **XIX** as catalysts.[40] Despite only one single example being shown (with moderate ee), this reaction opened a new window for the synthesis of chiral α-aminoalkylstannanes (Scheme 21).

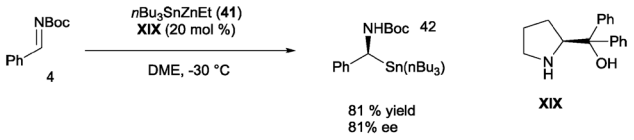
The addition of diethylzinc to *N*-Boc aldimines catalyzed by copper salts was reported by Alexakis in 2008 (Scheme 22).[41] Phosphorimidite **XX** was used as a chiral ligand rendering the final amines **44** in good yields (83–90%) and enantioselectivities (83–90%).

Chai and Seayad reported a titanium catalyzed Strecker reaction between imines and TMSCN.[42] The catalyst was a partially hydrolyzed titanium alkoxide using a readily available *N*-salicyl-β-aminoalcohol as a ligand. They tested the reaction with different imines (Bn, benzhydril and *N*-Boc aldimines) with excellent results at room temperature.

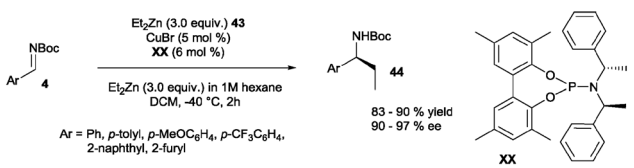
Ohkuma and co-workers reported a Strecker reaction between *N*-carbamoyl imines and HCN catalyzed by a ruthenium complex or a bimetallic Ru–Li complex (**XXI**).[43] The reaction required very low catalyst loadings (0.2 mol%) rendering cyanated amines **46** in excellent yields and enantioselectivities (Scheme 23).



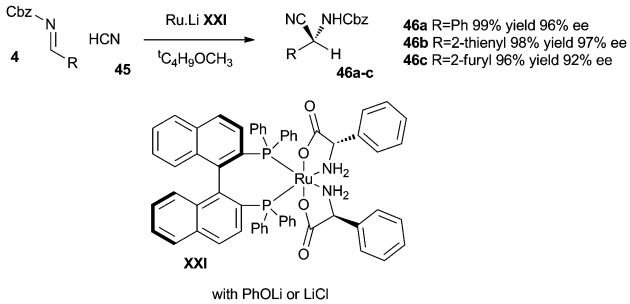
Scheme 20 3+2 cycloaddition reported by Trost.



Scheme 21 Aza-Henry reaction reported by Shibasaki.



Scheme 22 Et_2Zn addition to *N*-Boc imines.



Scheme 23 HCN addition to *N*-carbamoyl imines.

3. Organocatalytic approaches

Since the rediscovery of proline as a catalyst for aldol reactions by List, Lerner, and Barbas,[44] and the pioneering work of MacMillan on iminium activation in 2000,[45] organocatalysis has emerged as a useful tool for synthetic organic chemists.

The use of *N*-carbamoyl imines has been extensively studied due to their high reactivity and utility as precursors for the synthesis of chiral amines. During the last decade several organocatalytic methodologies have been developed: Strecker, Mannich, aza-Henry, aza Baylis–Hillman, *etc*.

Two different approximations have been used in order to organocatalyze these reactions: the first approximation relies upon activation of the nucleophile: secondary amine catalysts to activate the nucleophile *via* an enamine formation, chiral bases to deprotonate the nucleophile or phase transfer catalysts to form highly active ionic pairs have been used with high success. The second approximation involves the activation of the *N*-carbamoyl imines: using (thio)ureas (or related compounds) to activate the imine *via* hydrogen bond donation (Fig. 2b) or acidic compounds (phosphoric acids, dicarboxylic acids, sulfonamides, *etc*.) that protonate the imine forming a highly reactive iminium intermediate (Fig. 2a). Finally, some groups have developed bifunctional catalysts that activate both nucleophile and *N*-carbamoyl imines (Fig. 2c).

In this section we will disclose the most important approximations reported.

3.1 Organocatalytic Strecker reactions

As stated in the introduction the first example of the use of *N*-carbamoyl imines in enantioselective reactions was demonstrated by Lipton in 1996.[11] In this pioneering work, Lipton reported the addition of hydrogen cyanide to several imines catalyzed by dipeptide **XXII**. There is only one example of the

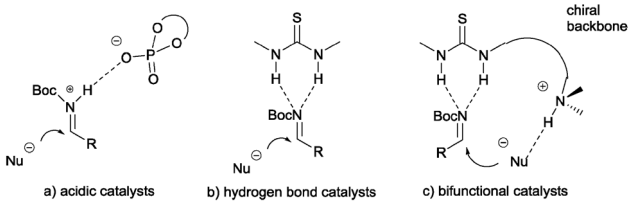
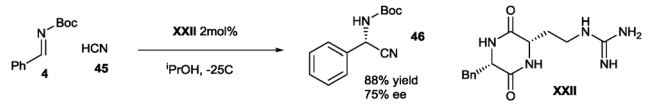


Fig. 2 *N*-Carbamoyl imine activations.



Scheme 24 First HCN addition to *N*-carbamoyl imines developed by Lipton.

use of Boc imines and with moderate ee, but this is the first enantioselective reaction with *N*-carbamoyl imines and should be considered the starting point for the development of the chemistry of *N*-carbamoyl imines (Scheme 24).

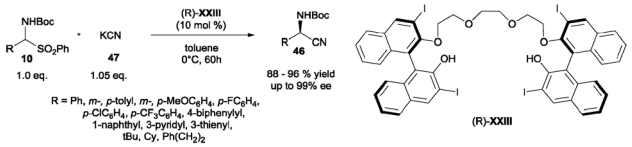
Very recently, Choong Eui Song and co-workers reported a chiral cyanide generator that promotes the Strecker reaction between *N*-Boc aldimines (**4**) and KCN.[46] The reaction use a chiral variant of oligoethylene glycols based on the 1,1′-binaphthol backbone (**XXIII**) as a catalyst. This type of compound brings insoluble potassium salts into the organic solution by forming a chiral ion pair. The resulting chiral ion pair then mediates an asymmetric Strecker reaction. The authors tested the Strecker reaction with *N*-Boc aldimines and KCN affording the amine derivatives **46** in low yields and moderate enantioselectivities. However, when they applied the same conditions with the stable amido-sulfone precursors, the reaction rendered the final compounds in excellent yields and enantioselectivities (Scheme 25).

3.2 Organocatalytic Mannich reactions

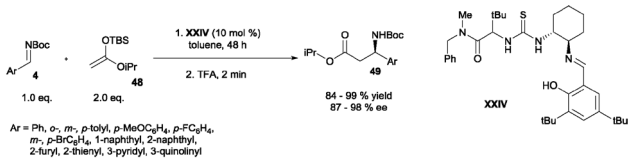
In 2002, Jacobsen reported the first organocatalytic Mannich reaction with *N*-carbamoyl imines catalyzed by thiourea catalyst **XXIV**.[47] Thiourea acts as a hydrogen bond donor that activates imine. As a suitable nucleophile for the reaction Jacobsen used silyl ketene acetals (**48**). The reaction requires low temperatures, but the final Mannich adducts (**49**) were obtained in excellent yields and enantioselectivities. However the reaction seems to be restricted to the use of *N*-Boc imines, as other *N*-carbamoyl imine derivatives tested gave moderate to low enantioselectivities under the same reaction conditions (Scheme 26).

In 2004, Terada reported the first enantioselective Mannich reaction between *N*-Boc imines and acetylacetone (**22**) catalyzed by a chiral phosphoric acid (**XXV**) obtaining excellent results (Scheme 27).[48] The phosphoric acid protonates the imine forming a highly active ion pair, which is readily attacked by the acetylacetone. Later, the same research group reported the use of phosphodiamidic acid as catalyst for the addition of 1,3-dicarbonyl compounds to *N*-carbamoyl imines.[49]

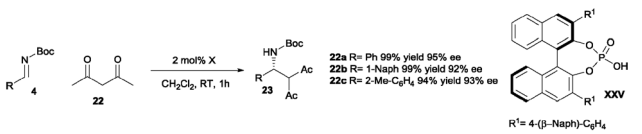
The addition of methyleneaminopyrrolidines to *N*-Boc aldimines was reported by Dixon in 2005.[50] This Mannich-type reaction was promoted by chiral Bronsted acid catalysts derived from BINOL



Scheme 25 Strecker reaction developed by Song.



Scheme 26 Mannich reaction reported by Jacobsen.



Scheme 27 Acetylacetate addition to *N*-Boc imines.

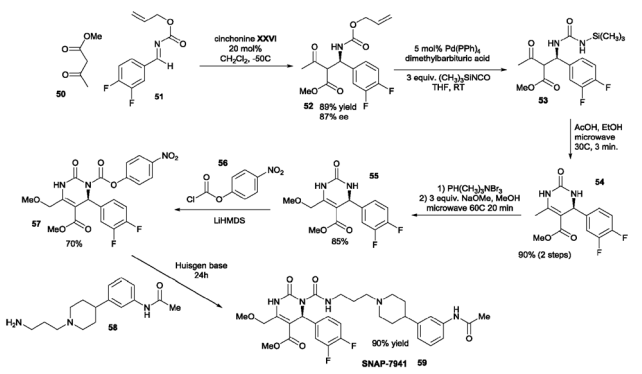
affording the final amino-hydrazone compounds in good yields and moderate to good enantioselectivities.

Schaus and co-workers reported the addition of β-ketoesters to *N*-carbamoyl imines catalyzed by cinchonine.[51] In this work they tested different *N*-carbamoyl imines obtaining the best result with methoxycarbamoylimines, achieving Mannich adducts up to 97% yield and up to 95% ee. The same research group also reported the addition of malonates to methylacylimines catalyzed by hydroquinine-derived thiourea with excellent results.[52] They applied this methodology to the synthesis of SNAP-7941, an inhibitor of MCH1-R (Scheme 28).[53]

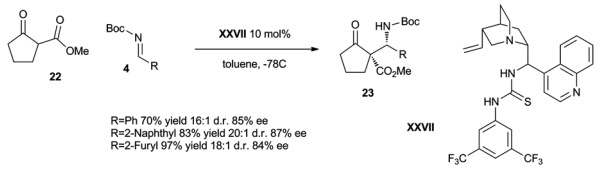
In 2006, Deng and co-workers reported the Mannich reaction between malonates and *N*-Boc imines catalyzed by thioureas derived from cinchona alkaloids.[54] The reaction afforded, after decarboxylation, the highly valuable β-amino acids with good yields (99–55%) and enantioselectivities (88–99%) when quinine or quinidine derived thioureas were used as catalysts. An important drawback of this reaction is that in order to get good enantioselectivities, the reaction requires extremely low temperatures (−60 °C).

Almost at the same time, Dixon and co-workers independently reported the same reaction as Deng using a cinchonine derived thiourea (**XXVII**) as a catalyst.[55] Dixon *et al.* expanded the scope of the reaction using β-ketoesters and *N*-Cbz aldimines obtaining slightly worse results than Deng's group (Scheme 29).

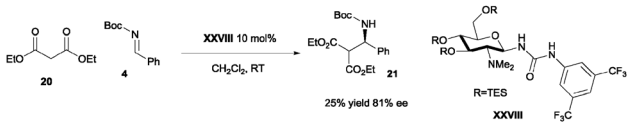
Benaglia *et al.* reported the addition of acetoacetate and malonates to *N*-Cbz imines catalyzed by chiral bifunctional



Scheme 28 Synthesis of SNAP-7941.



Scheme 29 Mannich reaction reported by Dixon.



Scheme 30 Mannich reaction reported by Benaglia.

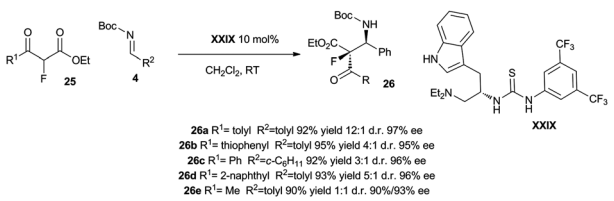
tertiary amine:thiourea catalysts with moderate enantioselectivities.[56] In 2011 the same research group reported a single example of the malonate addition to *N*-Boc phenylimine catalyzed by a carbohydrate-based bifunctional tertiary amine–urea catalyst **XXVIII** with low yields and moderate enantioselectivities (Scheme 30).[57]

A similar approximation was reported by Kim and co-workers based on the Mannich reaction between cyclic β-ketoesters and *N*-Boc aldimines, catalyzed by bifunctional (thiourea–tertiary amine) BINOL derived catalysts.[58] The reaction was conducted at −78 °C rendering the final amino derivatives in good yields and excellent enantio- (97–99%) and diastereoselectivities (up to 100 : 1 d.r.).

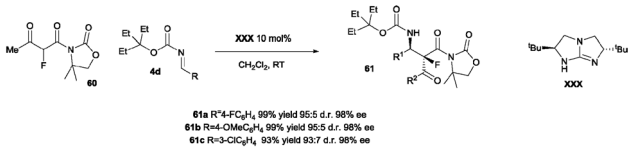
Lu and Huang reported the addition of fluorinated ketoesters to *N*-Boc aldimines catalyzed by a tryptophan-derived bifunctional thiourea catalyst **XXIX** (Scheme 31).[59] The reaction afforded the β-fluoroamines **26** in good yields and enantioselectivities. The reaction with aliphatic *N*-Boc aldimines rendered the final compounds with slightly worse enantioselectivity.

Years later, Kim's research group reported the addition of fluoromalonates[60] or α-fluoroketoesters[61] to aromatic and heteroaromatic *N*-Boc aldimines. The reaction is catalyzed by bifunctional tertiary amine–thiourea catalysts, affording the β-fluoro amines in good yields (81–94%) and excellent enantioselectivities (93–97%).

A similar strategy for the synthesis of β-fluoro amines was reported by Tan, Jiang and co-workers.[62] Fluoro carbon nucleophiles such as α-fluoroketoesters, α-fluoro-β-keto-acyloxazolidinones (**60**), α-fluoroketosulfones or α-fluoro-α-nitro-1-phenylsulfonylmethane react with aromatic *N*-3-ethylpentan-3-yloxycarbonylimines catalyzed by chiral guanidine **XXX** achieving the desired β-fluoro-amino derivatives **61** in excellent yields and enantioselectivities (Scheme 32).



Scheme 31 Addition of fluoro β-ketoesters to *N*-Boc imines.



Scheme 32 Addition of fluoro β-ketoesters to *N*-Boc imines reported by Tan.

The same research group developed an allylic addition of *N*-aryl alkylidene-succinimides (**62**) to *N*-carbamoyl imines promoted by bicyclic guanidines.[63] Amine derivative **66** was the only product formed by an α-addition followed by a 1,3-proton shift. Importantly, no product resulting from the γ-addition was observed (Fig. 3).

The reaction rendered the final amine derivatives with excellent yields (81–92%) and good enantioselectivities (71–85%) when aromatic *N*-3-ethylpentan-3-yloxycarbonylimines **4d** were used (Scheme 33). Wang and co-workers reported a related reaction based on the addition of lactones to *N*-Boc aldimines catalyzed by bifunctional rosin-derived amine thiourea catalysts.[64] The reaction requires low temperatures (−60 °C) but affords the final amine derivatives in excellent yields (80−92%), excellent diastereoselectivities (>20 : 1 d.r. in all the examples) and good to excellent enantioselectivities (75–99%). Malononitriles also proved their efficacy in the addition to *N*-Boc aldimines promoted by cinchonine, affording the amine derivatives in excellent yields and moderate to good enantioselectivities.[65]

In 2012, Lu reported the addition of phthalides to *N*-Boc and *N*-Cbz aldimines catalyzed by bifunctional tertiary amine–thiourea catalysts.[66] Under optimized conditions, the reaction afforded the desired amine derivatives in excellent yields (71–93%), good diastereoselectivities (up to 92 : 8 d.r.) and excellent enantioselectivities (80–97% ee). Remarkably, *N*-Cbz aldimines gave better results than *N*-Boc aldimines in terms of stereoselectivity. When aliphatic *N*-Cbz aldimines were used, the enantioselectivity of the reaction dropped dramatically (55–62% ee).

Dixon's research group studied the reaction between preformed enamines (**87**) and *N*-Boc aldimines (**4**) catalyzed by chiral

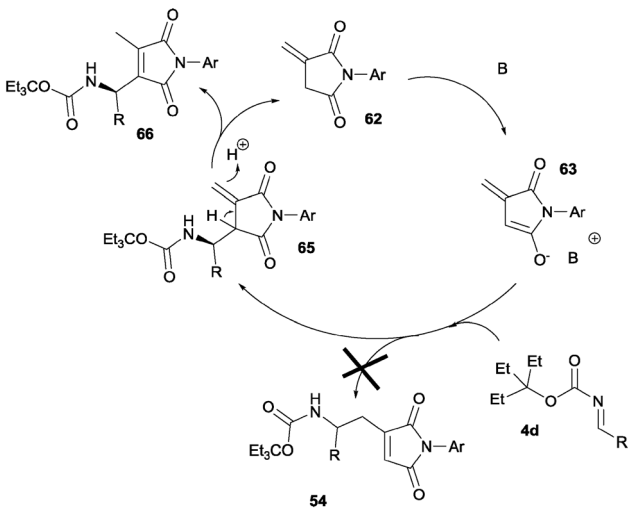
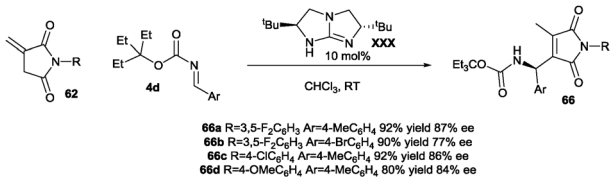


Fig. 3 Mechanism of the addition of *N*-aryl alkylidene-succinimides.



Scheme 33 Addition of *N*-aryl alkylidene-succinimides reported by Tan.

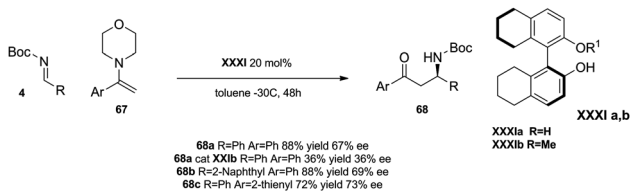
hydrogen bond donors such as diols.[67] The authors chose BINOL as a good catalyst scaffold (**XXXI**), and proved the importance of both hydroxyls for the efficacy of the catalyst (Scheme 34). The reaction was tested with aromatic morpholinoenamines and aromatic and heteroaromatic *N*-Boc aldimines achieving the final ketoamines in moderate to good yields (45–98%) and moderate enantioselectivities (60–84%).

Ishihara and co-workers reported the use of pyridinium 1,1′-binaphthyl-2,2′-disulfonate as a suitable catalyst for the Mannich reaction between acetoacetates and *N*-carbamoyl aldimines.[18b,68] The use of chiral organic salts, which consist of a Bronsted acid and a Bronsted base, as catalysts presented several advantages such as flexible design and ease of modification. The authors used simple BINOL derived disulfonic acid in the presence of a bulky pyridine to catalyze the Mannich reaction with excellent yields (91–99%) and enantioselectivities (84–98%). It is worth noting that *N*-Boc imines rendered better results, but the use of *N*-Cbz as a protecting group only gave slightly worse enantioselectivities. The same research group reported the addition of 1,3-dicarbonylic compounds to *N*-Boc aldimines catalyzed by chiral phosphoric acids affording the *anti* amine derivatives with excellent results (Scheme 35).

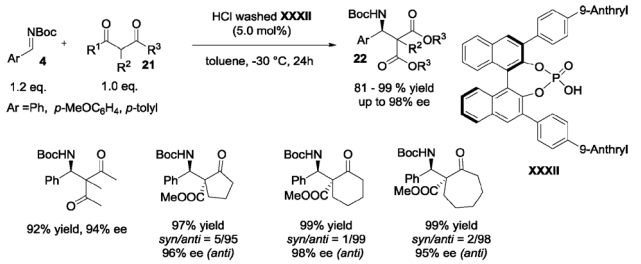
The Mannich reaction between 2,2-dimethyl-1,3-dioxan-5-one and *N*-Boc aldimines catalyzed by proline was reported by Enders in 2006 as an efficient biomimetic $C_3 + C_N$ entry to amino sugars.[69] The reaction furnishes highly functionalized ketoamines with excellent yields and enantioselectivities.

In 2007, List[70] and Cordova[71] independently reported the Mannich reaction between aldehydes (**69**) and *N*-Boc imines (**4**). The reaction is efficiently catalyzed by proline, rendering the final *syn* amino aldehydes in high yields and stereoselectivities. The importance of this reaction lies in the fact that after oxidation of the amino aldehyde chiral β-amino acids can be easily synthesized (Scheme 36).

Soon afterwards, List and co-workers expanded the scope of the reaction by using acetaldehyde as an electrophile in similar reaction conditions.[72] This methodology allows the synthesis of β3-amino acids, which are highly valuable targets. Next they described the double Mannich reaction of acetaldehyde with *N*-Boc aldimines with excellent results.[73]



Scheme 34 Mannich reaction reported by Dixon.

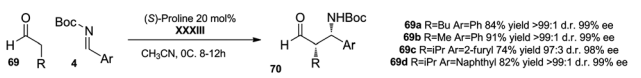


Scheme 35 *Anti* Mannich reaction reported by Ishihara.

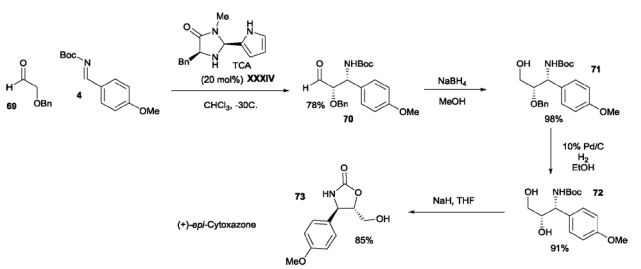
Several research groups have synthesized pharmaceutical or natural compounds using as a key step the Mannich reaction between aldehydes and *N*-Boc aldimines: for example, Cordovas's group applied this reaction to the synthesis of the Taxotere side chain;[74] Rao and co-workers reported the synthesis of *N*-Boc safingol (an inhibitor of sphingosine kinase) which started with the addition of protected α-hydroacetaldehyde to *N*-Boc phenylimine catalyzed by (*R*)-proline;[75] Kim and co-workers reported the synthesis of (+)-*epi*-cytoxazone (**73**)[76] (Scheme 37); and Chandrasekhar's research group reported the synthesis of (−)-lasubine II.[77]

Maruoka and co-workers reported the *anti* Mannich reaction between aldehydes and *N*-Boc aldimines using BINOL derived sulfonamide **XXXV** as catalyst.[78] Aromatic, heteroaromatic and aliphatic *N*-Boc aldimines were used affording the final *anti* products in excellent yields and enantioselectivities (Scheme 38). Peng and co-workers also developed a highly enantioselective *anti* Mannich reaction between aliphatic aldehydes and *N*-Boc aldimines promoted by an amino-thiourea organocatalyst derived from 3-hydroxypyrrolidine.[79]

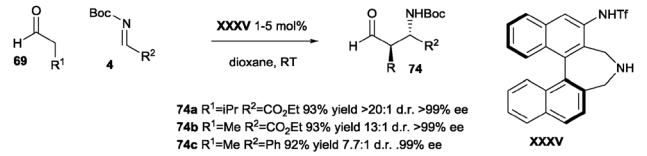
In 2012, Maruoka and co-workers expanded the scope of the Mannich reaction to the synthesis of vicinal diamines based on the reaction of *N*-Boc or *N*-Cbz protected aminoacetaldehydes with *N*-Boc aldimines.[80] The diastereoselectivity (*syn*:*anti*) of the reaction could be controlled by choosing the right catalyst. Proline **XXXIII** promoted the reaction between protected aminoacetaldehyde and *N*-Boc imines affording the *syn* adducts in good yields and excellent enantioselectivities; on the other hand, the amino



Scheme 36 Mannich reaction reported by List.



Scheme 37 Synthesis of (+)-*epi*-cytoxazone (**73**).



Scheme 38 Mannich reaction reported by Maruoka.

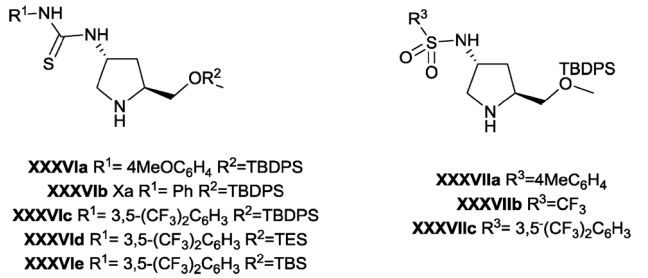


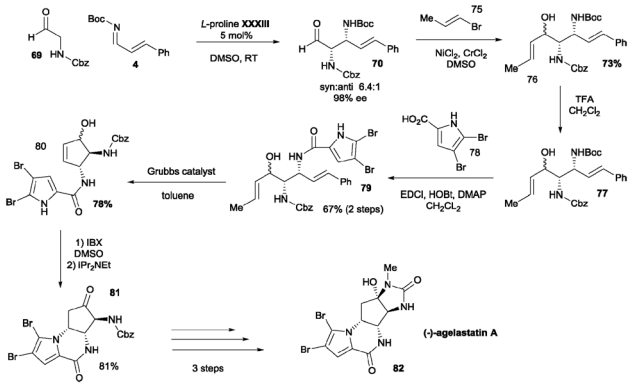
Fig. 4 Organocatalysts developed by Peng.

sulfonamide **XXXV** rendered the *anti*-adducts in similar yields and enantioselectivities. They demonstrated the utility of this reaction by synthesizing (−)-agelastatin A (Scheme 39).

In 2009, Carter and co-workers expanded the scope of the Mannich reaction of *N*-Boc aldimines with ketones, using a *p*-dodecylphenylsulfonamide proline mimetic as a catalyst with excellent results.[81]

A few years later, Peng and co-workers reported an *anti*-Mannich reaction between *N*-carbamoyl aldimines and aldehydes catalyzed by pyrrolidine derivatives.[82] The main advantage of this methodology was the possibility of using heavily substituted aldehydes as substrates. The authors synthesized a pool of catalysts based on a pyrrolidine scaffold bearing various H-bond donors at the 4-position to activate electrophiles and a cooperative stereocontrol silyl ether group at the 2-position of the pyrrolidine ring (Fig. 4). The reactions were performed at 0 °C affording the amino derivatives in good yields (82–94%) and excellent diastereo- (up to 96 : 4 d.r.) and enantioselectivities (92–>99% ee). Several *N*-carbamoyl imines were tested such as Boc, Cbz or CO_2Et without a significant loss of stereoselectivity.

Chen and co-workers reported the Mannich reaction between oxindoles and *N*-Boc aldimines.[83] The reaction was efficiently catalyzed by bifunctional thiourea–tertiary amine catalysts affording amino oxindole derivatives in good to excellent yields (60–95) and excellent diastereo- (up to >19 : 1 d.r.) and enantioselectivities (82–95%). The reaction worked with aromatic and heteroaromatic *N*-Boc aldimines, and the only limitation was the use of *N*-Boc protected oxindoles in order to get high enantioselectivities. One year later Maruoka reported the same reaction but this time it was promoted by chiral phosphonium salts as a phase transfer catalyst.[84] The reaction afforded the corresponding amino oxindoles with excellent yields (95–99%), excellent diastereoselectivities (up to 99 : 1 d.r.) and moderate enantioselectivities (56–88%).

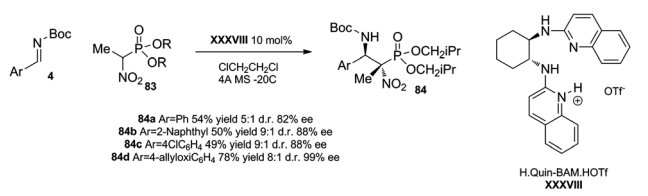


Scheme 39 Synthesis of (−)-agalastatin reported by Maruoka.

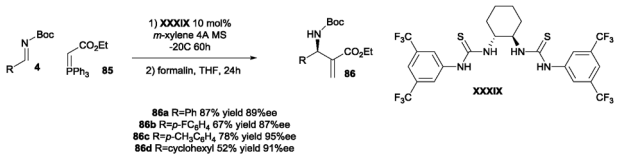
Johnston *et al.* applied their own catalyst (QUIN-BAM-HOTf) to the synthesis of α-substituted-*anti*-α,β-diaminophosphonic acid derivatives **84** with good results.[85] They reported the reaction between *N*-Boc aldimines and α-substituted-nitrophosphonates **83** promoted by chiral proton catalysts (Scheme 40). The size of the phosphonate ester became crucial in order to get high diastereo- and enantioselectivity; bigger substituents such as CH^iPr_2 rendered the best selectivities. The scope of the reaction was limited to aromatic aldimines and α-methylnitrophosphonates. In the optimized condition the reaction led to *anti* α-methyl-β-amino-nitrophosphonate derivatives **84** in moderate to good yields (48–86%), moderate to good *anti* selectivities (up to 15 : 1 d.r.) and good to excellent enantioselectivities (67–99%).

Chen and co-workers reported an enantioselective Mannich-type reaction between *N*-Boc aldimines and phosphorous ylides **85** to render *N*-Boc-β-amino-α-methylene carboxylic esters **86**.[86] The reaction was efficiently promoted by bisthiourea catalyst **XXXIX**, resulting in final compounds with good yields and enantioselectivities. The scope of the reaction was limited to *N*-Boc aromatic or highly substituted aliphatic aldimines, with linear aliphatic or heteroaromatic *N*-Boc aldimines rendering the final compounds in lower yields and enantioselectivities. The use of less substituted phosphorous ylides instead of triphenyl phosphine ylides gave faster reaction rates but lower selectivities (Scheme 41).

Rui Wang and co-workers reported a similar reaction, this time using the highly reactive Horner–Wadsworth–Emmons (HWE) reagent.[87] First a Mannich addition between HWE reagent and *N*-Boc or *N*-Cbz aldimine took place, catalyzed by bifunctional thiourea–tertiary amine catalyst (*N*-Boc imines give generally slightly lower enantioselectivities than those provided by their Cbz counterparts). Next, treatments with base and an aldehyde rendered the desired *N*-Boc/Cbz-β-amino-α-methylene carboxylic esters in excellent yields and enantioselectivities. Remarkably, the type of base in this last reaction determines diastereoselectivity in the double bond. When NaOMe



Scheme 40 Mannich reaction reported by Johnston.



Scheme 41 Cascade Mannich–Wittig reaction reported by Chen.

is used as a base *Z* products were found to be dominant, whereas when proazaphosphatrane served as a base the *E* isomer was the major product.

In 2009, Jorgensen and co-workers reported the addition of β-keto benzothiazolesulfones to *N*-Boc protected aldimine.[88] The importance of this reaction relies on the ease of transformation of the amine derivatives to allylic amines or β-ketoamine compounds. The reaction is efficiently catalyzed by thiourea catalyst **XL**, affording the final amino derivatives in good yields and stereoselectivities (Scheme 42).

A similar approach was reported by Palomo and co-workers based on the addition of phenylsulfonylacetonitrile to *N*-Boc aldimines.[89] The advantage of β-phenylsulfonylacetonitrile is the ease of removal of the sulfonyl group, resulting in a formal acetonitrile addition. The reaction was catalyzed by bases derived from cinchona alkaloids achieving the amine derivatives in good yields (72–92%) and moderate enantioselectivities (40–83%).

Two years later, Ooi and co-workers expanded this reaction by using substituted phenylsulfonylacetonitriles.[90] The reaction is efficiently catalyzed by chiral 1,2,3-triazolium ions through their anion recognition ability. The reaction between *N*-Boc aldimines and α-cyano α-sulfonyl carbanions renders the final amino derivatives in good to excellent yields (96–99%), moderate to good d.r. (up to >95 : 5 d.r.) and excellent enantioselectivities for the major diastereomer (84–97%). The reaction allowed the use of aromatic, heteroaromatic and aliphatic *N*-Boc aldimines with similar results; however the d.r. of the reaction is highly dependent on the substituent in the α-position of the phenylsulfonylnitrile.

In 2007 Kunz and co-workers reported a single example of the addition of silyl ketene acetals to *N*-Boc aldimines catalyzed by glucosamine derived urea affording the amino ester derivative in 73% yield and 58% ee under optimized conditions.[91]

In 2009, Smith and co-workers designed a new type of catalyst (**XLI**) based upon hydrogen bonding through positive cooperativity.[92] The catalyst was based on a preorganized hydrogen-bonded turn structure that allowed the use of low catalyst loadings with higher stereoselectivities. As a test reaction Smith used the Mannich reaction between silyl ketene acetal **48** and *N*-Boc aldimines. The reaction was conducted at −40 °C in the presence of 5 mol% catalyst and rendered the final amino acid derivatives in excellent yields and enantioselectivities (Scheme 43).

A similar catalyst design was developed by Pihko a few years later for the addition of malonates to *N*-Boc aldimines with excellent results.[93]

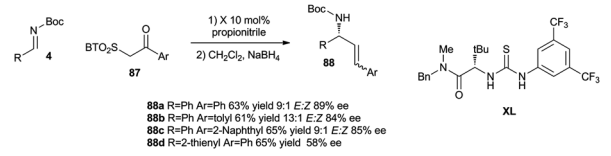
In 2011, Akiyama and co-workers reported the addition of difluoroenol silyl ether to *N*-Boc aldimines catalyzed by chiral phosphoric acids.[94] This reaction led to the synthesis of highly valuable β-amino-α,α-difluoro carbonyl compounds. Under the optimized conditions, aromatic and heteroaromatic *N*-Boc aldimines reacted with difluoro silyl ethers, promoted by chiral phosphoric acid, affording the β-amino-α,α-difluoro carbonyl derivatives in good yields (56–91%) and excellent enantioselectivities (80–93%). One of the limitations of the present methodology is that aliphatic aldimines did not give the desired product. Another key aspect of this reaction is the need to use MS 3A as an additive in order to get good results.

Kobayashi in 2009 reported the addition of 9-fluorenylidendeaminoalkanes to *N*-Boc aldimines catalyzed by chiral PTC catalysts.[95] A single enantioselective example was reported, rendering as a major compound the *syn* 1,2-diamine (78 : 22 *syn* : *anti*) in good yields and moderate enantioselectivities.

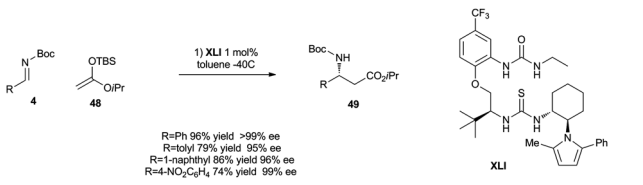
The first organocatalytic enantioselective α-cyanoketone addition to *N*-Boc aldimines was reported in 2009 regardless of the early metal catalyzed examples reported in the literature.[96] Kim and co-workers used a chiral bifunctional (tertiary amine–urea) catalyst to promote the reaction with excellent yields (81–99%), diastereoselectivity (up to 100 : 0 *syn* : *anti* selectivity) and enantioselectivity (88–99%). Once again, the reaction is limited to aromatic or heteroaromatic *N*-Boc aldimines.

Rueping developed the first imino-azaenamine reaction. The addition of methyleneaminopyrrolidine to *N*-Boc aldimines catalyzed by phosphoric acid derivatives afforded amino derivatives in good yields and enantioselectivities.[97] One year later, Maruoka and co-workers expanded this reaction by using arylaldehyde *N*,*N*-dialkylhydrazones as an acyl anion equivalent.[98] The imino aza-enamine reaction was promoted by axially chiral dicarboxylic acids derived from BINOL, achieving the final amine derivatives in moderate yields and good enantioselectivities.

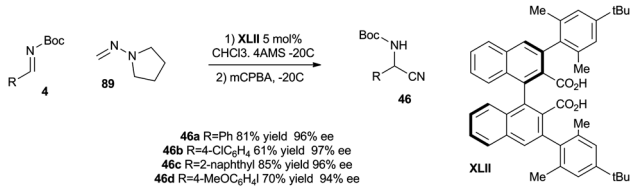
In 2010, based on this concept, Maruoka developed a formal Strecker reaction by asymmetric aza-enamine addition to *N*-Boc aldimines and later oxidation.[99] The imino aza-enamine reaction was promoted by axially chiral dicarboxylic acid **XLII** derived from BINOL, achieving, after oxidation, the final Strecker adducts in good yields (61–88%) and excellent enantioselectivities (92–97%). The reaction was only tested with aromatic or heteroaromatic *N*-Boc aldimines (Scheme 44).



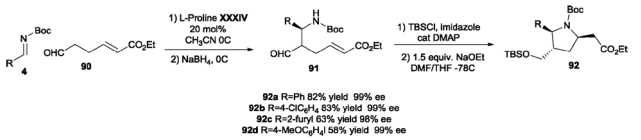
Scheme 42 Synthesis of allyl amines developed by Jorgensen.



Scheme 43 Mannich reaction reported by Smith.



Scheme 44 Formal Strecker reaction reported by Maruoka.



Scheme 45 Tandem reaction reported by Schneider.

Following this work, the same research group reported a formal alkenylation of imines using vinylogous aza-enamines.[100] Aza-enamines could be easily prepared by condensation of enals and *N*,*N*-dialkylhydrazines; these compounds are a class of umpolung species which exhibit a nucleophile character at the C^3 position. After initial addition to *N*-carbamoyl imines, the reaction is understood to proceed *via* the initial formation of the ionic intermediate and successive deprotonation to regenerate the alkene moiety. Axially chiral dicarboxylic acid derived from BINOL promoted the reaction in high yields with high enantioselectivities when aromatic *N*-benzoyl imines are used. Remarkably in the conditions tested the use of *N*-Boc aldimines led to low reaction rates of almost racemic compounds.

3.2.1 Tandem reactions based on Mannich additions. Schneider and co-workers reported a sequential Mannich, aza-Michael reaction for the synthesis of highly substituted pyrrolidines.[101] The reaction started with the addition of aldehyde **90** to *N*-Boc aldimines catalyzed by proline, followed by an intramolecular aza-Michael reaction catalyzed by base. The final pyrrolidines **92** were obtained in good yields, good d.r. and excellent enantioselectivities as depicted in Scheme 45.

Enders and co-workers developed a cascade reaction for the synthesis of pyrrolidines based in a domino Mannich–aza-Michael reaction.[102] γ-Malonate substituted α,β-unsaturated esters react with *N*-Boc aldimines promoted by bifunctional tertiary amine–thiourea catalysts rendering the 2,5-*cis* configured polysubstituted pyrrolidines in good to excellent yields (76–99%), diastereoselectivities (de > 95%) and enantioselectivities (75–94%).

Jorgensen and co-workers also developed a tandem reaction based on the addition of propargylated malononitriles to *N*-Boc imines.[103] They reported the synergistic combination between organo- and gold catalysis for the enantioselective synthesis of dihydropyrrole derivatives. The Mannich reaction between malononitriles and aromatic *N*-Boc aldimines was catalyzed by bifunctional thiourea catalyst. Next, a gold catalyzed hydroamination took place between the formed amine and the triple bond to afford the dihydropyrrole derivatives in moderate to good yields (45–93%) and moderate to good enantioselectivities (58–88%).

Another tandem reaction was reported by Yan and co-workers for the synthesis of *O*-alkylated tetronic acids.[104] The tandem reaction consisted of a Mannich reaction between *N*-Boc aldimines and ethyl-4-chloro-3-oxobutanoate and a subsequent intramolecular cyclization. The Mannich reaction was catalyzed by a bifunctional tertiary amine–thiourea catalyst while the subsequent intramolecular cyclization was catalyzed by a base. The tandem reaction rendered the tetronic acid derivatives in good yields (65–88%) and excellent to good enantioselectivities (60–91%). Only *N*-Boc aldimines were tested in this reaction; other imines such as PMP or tosyl aldimines gave worst results.

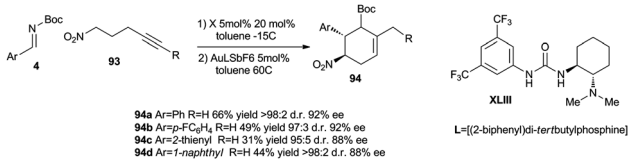
Dixon and co-workers developed an enantioselective synthesis of tetrahydropyridines **94** by a cascade reaction where the first step was an aza Mannich reaction followed by a gold catalyzed hydroamination.[105] The reaction cascade utilized a combination of gold and bifunctional base/H bonding catalysis to afford the desired pyrrolidines. Bifunctional thiourea:tertiary amine catalyst **XLIII** promotes the initial Mannich reaction between *N*-Boc aldimines and 5-nitropent-1-yne (**93**). Next [(2-biphenyl)di-*tert*-butylphosphine] gold(I) hexafluoroantimonate is added to promote the intramolecular hydroamination. The final piperidines **94** were obtained in moderate to good yields (31–72%) and excellent diastereo- (up to >98 : 2 d.r.) and enantioselectivities (86–94%) (Scheme 46).

Terada and co-workers reported a tandem aza-ene-aminal cyclization cascade reaction for the synthesis of enantioenriched piperidines.[106] The reaction consists of an initial addition of *N*-Cbz enecarbamates to *N*-Boc imines catalyzed by chiral phosphoric acid. Next another *N*-Cbz enecarbamate reacts with the resulting imine. Finally aminal cyclization takes place to form the piperidine. The reaction tolerated aromatic, heteroaromatic and aliphatic *N*-Boc imines rendering piperidine compounds in good yields (99–68%) and excellent diastereo- (up to 95 : 5 d.r.) and enantioselectivities (99–97%).

3.3 Aza-Henry reactions

In 2004, Johnston and co-workers reported the first aza-Henry reaction using *N*-Boc imines as an aza counterpart. The reaction was catalyzed by a Bronsted acid salt that was synthesized as a single enantiomer by the reaction of HQuin-BAM (**XXXIX**) and trifluoromethane sulfonic acid.[107] The reaction afforded the *cis* diastereomer with good enantioselectivities (Scheme 47). The importance of this reaction was shown as a key step for the synthesis of (−)-Nutlin-3, a potent p53/MDM2 inhibitor,[108] and VNI, a potent CYP51 inhibitor.[109]

The same group expanded the scope of the reaction using cyclic secondary nitroalkanes (3-nitroazetidines) as a key step to synthesize a potent GlyT1 inhibitor.[110] This time the reaction was catalyzed by (MeO)PBAM·HOTf catalyst, rendering the final



Scheme 46 Tandem reaction reported by Dixon.

nitroamine derivative in good yields and enantioselectivities. Next they synthesized the GlyTy inhibitor in good yields in 4 steps. In 2007 they expanded the scope of the reaction using nitroacetic acid derivatives as glycine equivalents with excellent results,[111] and later they applied this reaction to the synthesis of (+)-chaenorhine.[112]

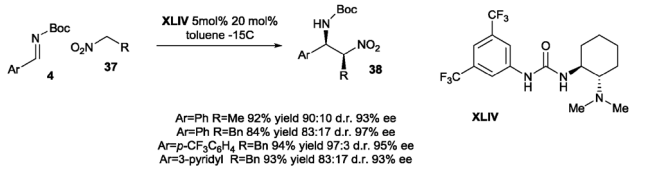
In 2008 the same research group developed a highly diastereo- and enantioselective synthesis of α-substituted *syn*-α,β-amino acids.[113] Catalyst **XXXIX** promotes the addition of substituted α-nitroesters to *N*-Boc aldimines affording the *syn* adducts in good yields (59–88%), good to excellent diastereoselectivities (up to >20 : 1 d.r.) and excellent enantioselectivities (94–99% ee). At the same time, Chen and co-workers independently reported the same reaction catalyzed by bifunctional thiourea/secondary amine catalysts with slightly worse stereoselectivities.[114]

In 2005, Ricci and co-workers reported a different approach to the aza-Henry reaction between *N*-Boc aldimines and nitromethane using cinchona alkaloid derivatives as catalysts. The quinine derived thiourea gave the best results. However the reaction was only tested with nitromethane.[115] At about the same time, a similar reaction was reported by Schaus using methylacyl imines and nitroalkanes.[52] This reaction was catalyzed by hydroquinine-derived thiourea affording the final amino derivatives in good yields (73–96%) and excellent diastereo- (82–97 d.e.) and enantioselectivities (91–97% ee).

Xue and co-workers reported the same reaction with similar results although they used oxazoline–thiourea catalysts.[116] At about the same time, Jacobsen and co-workers reported the aza-Henry reaction between *N*-Boc imines and nitromethane catalyzed by thiourea catalysts.[117] In this reaction, thiourea catalysts are better than urea catalyst giving higher reaction rates with similar enantioselectivities. The reaction is compatible with aromatic and heteroaromatic *N*-Boc imines affording amino-nitro derivatives in excellent yields (99–79%) and enantioselectivities (97–92%). It is worth noting that the reaction with other nitroalkenes rendered the amine product in excellent yields and enantioselectivities and moderate to good diastereoselectivities (1-nitropropane: 99% yield, 95% ee, 7 : 1 d.r.).

One year later, Takemoto and co-workers applied their own catalyst (**XLIV**) to the aza-Henry reaction between *N*-Boc imines and nitromethane achieving the final amine compounds in good yields (71–89%) and enantioselectivities (98–83%).[118] They studied the scope of the reaction with different nitroalkenes achieving high yields and stereoselectivities (94–75% yield, up to 97 : 3 d.r. and 99–89% ee). Moreover, they applied this methodology to the synthesis of (−)CP-99994, a potent neurokinin1 (NKN-1) receptor antagonist (Scheme 48).

Wulff and co-workers designed a new bis thiourea catalyst (**XLV**, Fig. 5) for the addition of nitroalkanes to *N*-Boc aldimines.[119]



Scheme 48 Aza-Henry reaction developed by Takemoto.

The reactions were carried out at low temperatures (−35 °C) and were limited to aromatic or heteroaromatic *N*-Boc aldimines. The reaction with nitromethane rendered the desired nitroamines in moderate yields (40–65%) and good enantioselectivities (74–91%). When substituted nitromethanes were used the reaction rendered similar yields and enantioselectivities but moderate diastereoselectivities (4 : 1 d.r.).

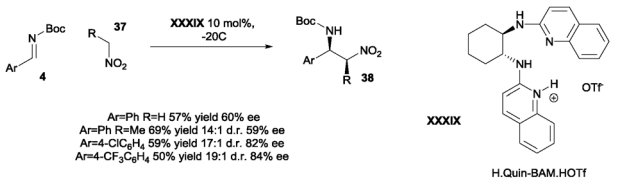
Ellman and co-workers reported the use of *N*-sulfonyl ureas (**XLVI**, Fig. 5) as organocatalysts for the aza-Henry reaction between nitroalkanes and *N*-Boc imines.[120] The reaction was carried out at −40 °C and afforded the nitroamine derivatives in good yields (92–62%), moderate to good *syn* diastereoselectivities (up to 93 : 7 d.r.) and excellent enantioselectivities (96–92% ee).

Zhou and co-workers reported the use of sugar derived thioureas (**XLVII**, Fig. 5) for the same reaction affording the nitroamines in good yields (84–95%) and excellent enantioselectivities (83–99%).[121] However the reaction seems to be limited to the use of nitromethane, as other nitroalkenes such as nitroethane proved to be much less reactive, and the reaction with nitropropane did not proceed at all.

The first highly enantioselective *anti*-aza-Henry reaction was reported by Wang and co-workers in 2008.[122] In this work *N*-Boc aldimines reacted with nitroalkanes promoted by bifunctional amine–thiourea catalysts bearing multiple hydrogen bonding donors (catalyst **XLVIII**). The reaction showed good scope in terms of nitroalkanes and in terms of *N*-Boc aldimines (aromatic, heteroaromatic and aliphatic imines were used with excellent results). The desired *anti*-nitroamines were obtained in good yields and excellent enantioselectivities as shown in Scheme 49.

An interesting alternative to the aza-Henry reaction of *N*-Boc aldimines was developed by Michael.[123] In this work, the authors used chiral guanidines as catalysts, and reported reversal of stereoselectivity in the reaction by using mono or bisguanidine catalysts. The reaction afforded the nitroamine derivatives in moderate to good yields and moderate enantioselectivities when nitromethane was used as a nucleophile; however, when longer nitroalkanes were used the enantioselectivity of the reaction dropped dramatically.

Nagasawa developed a similar approach but using bifunctional acyclic guanidine–thiourea catalysts.[124] Using these catalysts



Scheme 47 Aza-Henry reaction developed by Johnston.

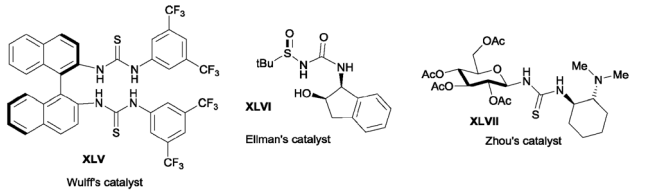
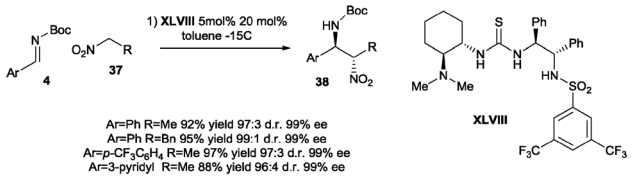


Fig. 5 Bifunctional catalysts.



Scheme 49 *Anti* aza-Henry reaction developed by Wang.

the reaction afforded the nitroamine derivatives in excellent yields (82–96%), diastereoselectivities (up to 99 : 1) and enantioselectivities (90–99%).

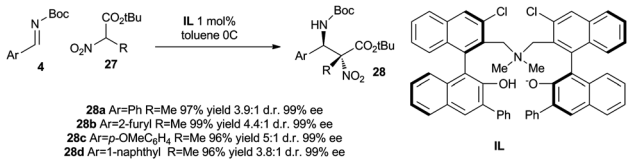
The addition of α-nitrocarboxylates to *N*-Boc imines was reported by Ooi and co-workers in 2008.[125] Chiral ammonium betaines could work as bifunctional organocatalysts to promote the cited reaction with excellent yields and stereoselectivities. The ammonium betaine is capable of deprotonating the α-nitrocarboxylate **27** to furnish an onium ion as its conjugate acid form. The acidic proton thus generated could direct the counterionic nucleophile at a defined position through the hydrogen-bonding interaction, thereby affording a highly structured intermolecular ion pair. Using catalyst **IL**, the reaction gave the desired amino nitro carboxylates **28** in excellent yields (91–99%), moderate diastereoselectivities (up to 5 : 1 d.r.) and excellent enantioselectivities (97–99%) as shown in Scheme 50.

Later, the same research group tested C_1-symmetric chiral ammonium betaines as a suitable catalyst for the addition of nitroacetates to *N*-Boc aldimines, achieving the highly substituted amine derivatives in good yields and enantioselectivities.[126]

Almost the same reaction was reported by Benaglia, one year later, using this time bifunctional thiourea–tertiary amine catalysts.[127] In this report, 1 : 1 mixtures of diastereomers with lower yields (48–77%) and enantioselectivities (27–81%) were obtained. The authors studied different carbamoyl imines (*t*Bu, Me, Bn, *etc.*), with *N*-Boc aldimines giving the best results.

Dong and co-workers reported the same reaction but catalyzed by bifunctional thiourea–guanidine catalysts.[128] The reaction required the use of 1 equiv. of K_2CO_3, and rendered the final nitro-amine derivatives bearing contiguous tertiary and quaternary stereocenters in moderate yields (42–77%), good diastereoselectivities (up to 7.6 : 1 d.r.) and moderate enantioselectivities (62–88%).

In 2011, Rachwalski reported the use of hydroxy-amine-sulfinyl compounds as suitable catalysts for the addition of nitromethane to *N*-Boc-aldimines.[129] These catalysts bearing two stereogenic centers (one located on the sulfonyl sulfur atom and the other on the carbon atom of the amine) are very easy to synthesize and exhibit good enantioinduction in the aza-Henry reaction. Under the optimized conditions the addition of nitromethane to several *N*-Boc aldimines rendered the final nitro-amine derivatives in excellent yields (91–98%) and enantioselectivities (86–95%).



Scheme 50 Aza-Henry reaction developed by Ooi.

3.4 Aza-Friedel–Crafts reaction

In 2004, Terada and co-workers reported the first aza-Friedel–Crafts reaction using *N*-Boc imines catalyzed by chiral phosphoric acid **L** (Scheme 51). The reaction is limited, in this case, to furan derivatives achieving the final compounds with good yields and excellent enantioselectivities.[130] In 2007 the same research group expanded the scope of the reaction developing the aza-Friedel–Crafts reactions of indoles.[131]

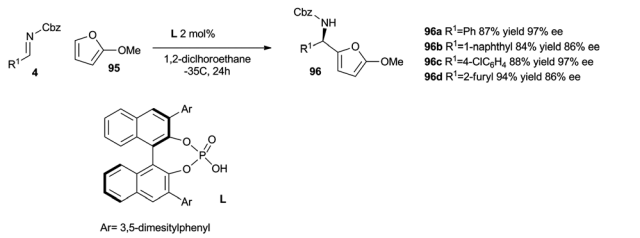
Ishihara and co-workers reported the use of chiral ammonium 1,1-binaphthyl-2,2-disulfonates (**LI**) as suitable catalysts for the Friedel–Crafts reaction of *N*-Cbz aldimines and *N*-benzylpyrroles (Scheme 52).[132] The chiral ammonium 1,1-binaphthyl-2,2-disulfonates acted as dynamic Bronsted acid–Bronsted base catalysts. Acid–base combined salts present several advantages regarding the flexibility in the design of their dynamic complexes. These types of catalysts were very active and promoted the reaction between *N*-Cbz aldimines and *N*-benzyl pyrroles in good yields (59–92%) and moderate to good enantioselectivities (67–92%).

3.5 Other reactions

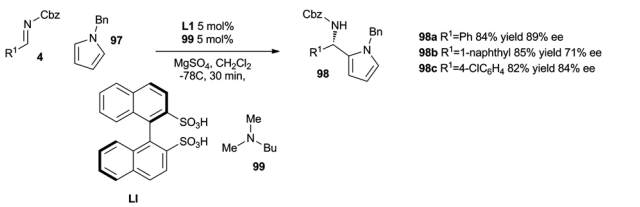
In 2005, Antilla and co-workers developed an enantioselective synthesis of aminals based on the addition of sulfonamides to *N*-Boc imines. The reaction is catalyzed by chiral phosphoric acids derived from BINOL and (*S*)-VAPOL achieving the aminals in good yields and excellent enantioselectivities (Scheme 53).[133]

Years later, the same research group expanded the scope of the reaction by reacting simple imides with *N*-Boc imines using VAPOL phosphoric acids as catalysts to form chiral aminals with excellent results.[134] Ishihara and co-workers applied pyridinium 1,1′-binaphthyl-2,2′-disulfonate as a suitable catalyst for the addition of amides to *N*-Cbz aldimines.[135] The reaction afforded the aminal derivatives in good yields (80–99%) and good enantioselectivities (71–87%).

Soon after, Shibasaki and co-workers developed the addition of glycine Schiff bases **102** to *N*-Boc imines promoted by tartrate derivative diammonium salts **LIII** as a phase transfer catalyst.[136]



Scheme 51 Aza-Friedel–Craft reaction reported by Terada.



Scheme 52 Aza-Friedel–Craft reaction reported by Ishihara.

The reaction requires low temperatures in order to achieve high *syn* diastereoselectivities (>20 : 1 d.r.) and good enantioselectivities (90–69% ee). The synthetic utility of this reaction was proved by synthesizing the antipsychotic agent Nemonapride as shown in Scheme 54.

Years later Kobayashi expanded this reaction by using fluorenone imines of glycine esters or their phosphonic acid derivatives. The reaction was promoted by chiral guanidines affording the final diamine derivatives in good yields and excellent diastereo- (up to >99 : 1 d.r.) and enantioselectivities (90–98% ee).[137]

In 2006, Pettersen, Fini and co-workers reported the first addition of diethyl phosphite to *N*-Boc imines catalyzed by quinine.[138] The reaction afforded the highly valuable α-amino-phosphinic acids in moderate to good yields (50–83%) and good to excellent enantioselectivities (48–94%). There are some limitations for the present reaction: the use of *N*-Cbz imines gave lower enantioselectivities, or the use of other phosphites such as dimethylphosphite or diisopropylphosphite lowered the reactivity and selectivity of the reaction.

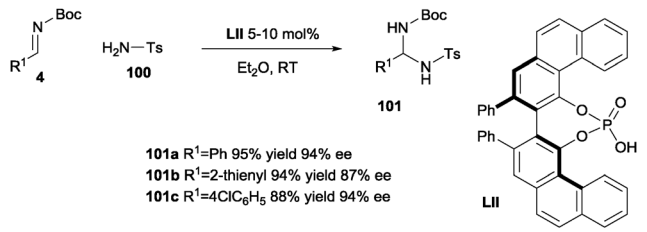
Maruoka and co-workers reported in 2007 the addition of diazoacetates to *N*-Boc imines catalyzed by axially chiral dicarboxylic acids.[139] 3,3′-Diaryl-1,1′-binaphthyl-2,2′-dicarboxylic acids catalyze the reaction in good yields and excellent enantioselectivities. It is worth noting the importance of molecular sieves 4A as an additive in order to achieve high yields. The reaction is limited to aromatic and heteroaromatic imines. The authors explored the scope of the reaction by using diazomethylphosphonates and tolyl(diazomethyl)sulfones[140] obtaining similar results. Peng and co-workers reported a similar reaction in 2012 using di-*tert*-butyl diazomethylphophonates and *N*-Boc aldimines (Scheme 55).[141] In this case the reaction was promoted by phosphoric acid derivatives with excellent yields (82–95%) and enantioselectivities when aromatic or heteroaromatic *N*-Boc aldimines were used (98–99% ee). Remarkably the substituent pattern on the imine influenced the reactivity: *ortho* substituents in the aromatic ring of the *N*-Boc aldimines dramatically reduce reactivity. *N*-Cbz aldimines were also tested giving similar results but in longer reaction times.

In 2008, Maruoka's research group reported the synthesis of aziridines by the reaction of *N*-Boc aldimines and diazoacetamides catalyzed by 3,3′-diaryl-1,1′-binaphthyl-2,2′-dicarboxylic acids.[142] The rationale behind the reaction is that by lowering the acidity of the α-proton of diazocarbonyl the formation of the aziridine is favoured. The reaction gave the *N*-Boc protected *trans*-aziridines in excellent yields and enantioselectivities. Taking advantage of the precedent methodology Maruoka and co-workers rationalized that by using a stronger acid the reaction between *N*-Boc aldimines and α-substituted-α-diazocarbonyl compounds will lead to the formation of trisubstituted aziridines (Scheme 56). α-Diazocarbonyl compounds bearing oxazolidinones as key templates emerged as a perfect counter partner to *N*-Boc aldimines for the aziridine synthesis.[143] The need for a strong Bronsted acid led the authors to use *N*-trifyl phosphoramide (**LV**) decorated with two phenyl rings at 3 and 3′ positions in order to get high enantioselectivities. The reaction under the optimized condition renders the aziridine derivatives in good yields (69–91%) and excellent diastereo- (*trans* : *cis* 20 : 1) and enantioselectivities (74–95%). In the same work highly active ketimines such as *N*-Boc-α-ketiminoesters (**108**) were reacted with α-diazocarbonyl compounds in the same reaction conditions achieving the *trans*-trisubstituted aziridines with excellent yields (74–92%) and enantioselectivities (84–98%).

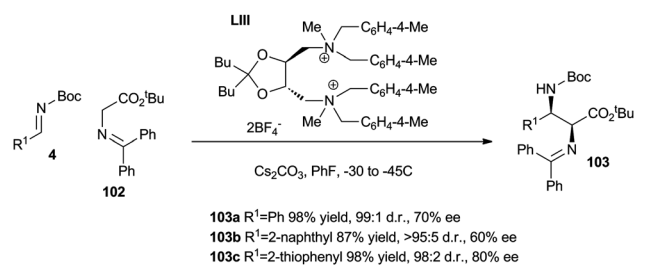
Almost at the same time, Wulff and co-workers reported the same reaction but catalyzed by chiral polyborate Bronsted acid catalysts derived from VANOL or VAPOL.[144] The reaction was conducted at −78 °C affording only the *trans* trisubstituted aziridines in good yields and excellent enantioselectivities. Once again the use of α-diazo-*N*-acyloxazolidinones is crucial in order to get good results (Scheme 57).

In 2009, Zhong developed an aziridination reaction based on the reaction of *N*-Boc aldimines with diazoacetamides catalyzed by chiral Bronsted acids.[145] The reaction was catalyzed by chiral phosphoric acid and afforded the final *trans* aziridines in good yields (71–90%) and excellent enantioselectivities (88–96%). The only limitation is the use of aromatic *N*-carbomoyl aldimines; thus the use of *N*-Cbz-aldimines also gives the aziridines in excellent yields and enantioselectivities.

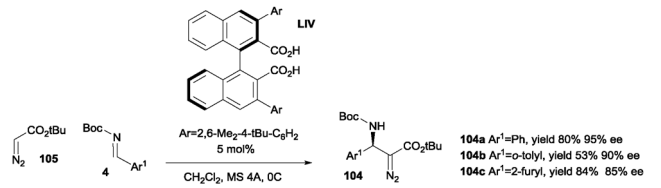
In 2007, Cordova and co-workers reported the enantioselective aza-Morita–Baylis–Hillman reaction between enals and *N*-Boc aldimines.[146] The reaction was catalyzed by a combination of proline and DABCO affording the amino aldehydes in moderate yields and



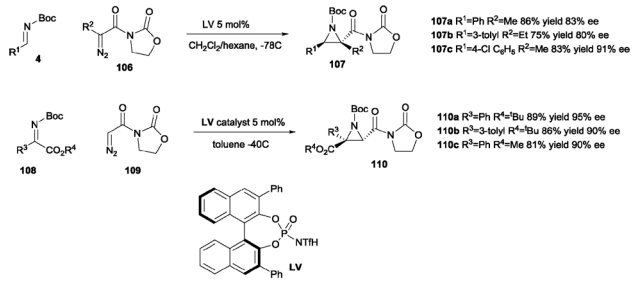
Scheme 53 Imine amidation reported by Antilla.



Scheme 54 Mannich reaction reported by Maruoka.



Scheme 55 Mannich reaction reported by Maruoka.



Scheme 56 Synthesis of *trans* trisubstituted aziridines reported by Maruoka.

diastereoselectivities and excellent enantioselectivities (Scheme 58). The use of a nucleophilic organic base (DABCO) was essential for the outcome of the reaction. First proline reacted with the enal to form the iminium species, next the enal was activated by the nucleophilic amine (DABCO) forming a chiral enamine that subsequently reacted with the *N*-Boc aldimine. After the addition took place elimination of the nucleophilic base afforded the final amino aldehyde. In 2011, they expanded the scope of the reaction by using *N*-Cbz imines with slightly worse enantioselectivities.[147]

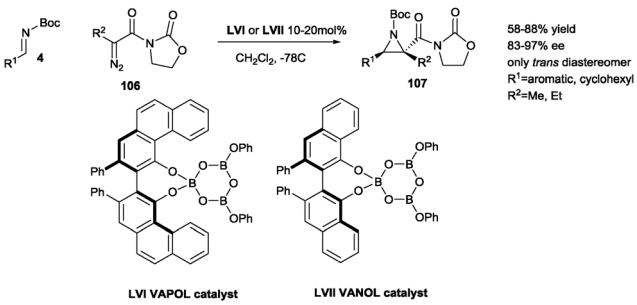
In 2010, a closely related aza-Morita–Baylis–Hillman reaction with *N*-Boc aldimines was reported by Shi.[148] The reaction between alkyl vinyl ketones and *N*-Boc aldimines was catalyzed by β-isocupreidine, rendering the desired allylamines in moderate yields (38–82%) and good enantioselectivities (86–95%).

A similar approach was developed by Xu using nitroalkenes and bifunctional tertiary amine–thiourea catalysts.[149] Only one example was reported using *N*-Boc aldimines with good yields and moderate enantioselectivities.

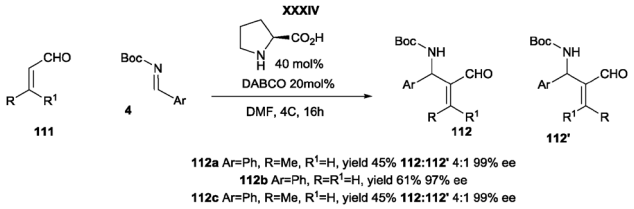
An important feature of the reaction is the role of the β-alkyl substituent: deliver a proton to the intermediate amide ion in an intramolecular fashion to give the final product and regenerate the catalyst.

Ooi reported a similar reaction based on the addition of β,β-disubstituted nitroolefines (**113**) to *N*-Boc aldimines catalyzed by chiral ammonium betaine **LVIII** (Scheme 59).[150] The reaction gave the final nitroamine derivatives in excellent yields (87–99%), diastereoselectivities (>20 : 1 d.r. in all the examples) and enantioselectivities (95–99%).

Ye and co-workers developed a Staudinger reaction between *N*-Boc aldimines and ketenes (**115**) catalyzed by chiral N-heterocyclic carbene **LIX.**[151] The scope of the reaction is limited to



Scheme 57 Synthesis of *trans* trisubstituted aziridines reported by Wulff.

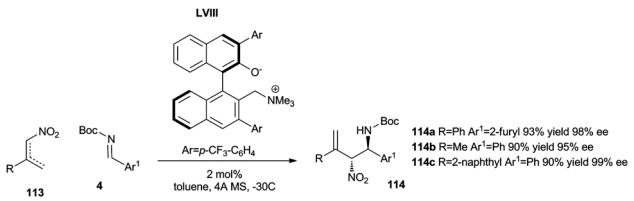


Scheme 58 Aza-Morita–Baylis–Hillman reaction reported by Cordova.

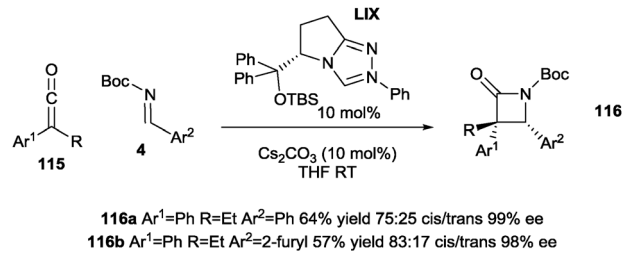
aromatic *N*-Boc aldimines affording the β-lactam derivatives (**116**) in moderate to good yields, good diastereoselectivities and excellent enantioselectivities (Scheme 60).

Rovis and co-workers developed the first cross-aza-benzoin reaction between aliphatic aldehydes and *N*-Boc aldimines catalyzed by chiral N-heterocyclic carbenes.[152] Thiazolidine catalyst **LX** in combination with cesium acetate and 4A MS as additive provided the desired α-aminoketone derivatives **117** in good yields (72–93%) and excellent enantioselectivities (92–96%). One of the limitations of this reaction is the use of linear aliphatic aldehydes, with β-branched aldehydes giving the reaction with low yield while α-branched aldehydes are almost unreactive. In terms of the imine, only *N*-Boc aldimines were tested with excellent results with *para* or *meta* substituted aromatic aldimines. *Ortho* substituted aromatic *N*-Boc aldimines did not show any reactivity and heteroaromatic *N*-Boc aldimines gave low enantioselectivities (Scheme 61).

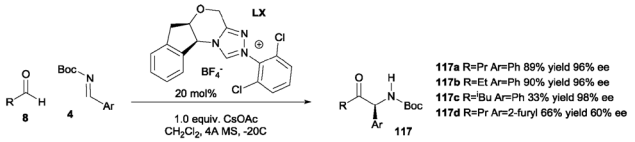
A three component cascade reaction was developed by Chen for the synthesis of spirocyclic oxindoles.[153] In this reaction methylene-oxindoles **118** reacted with propionaldehyde (**8**); next, the furnished intermediate was trapped by *N*-Boc aldimines *via* a Mannich reaction. Finally an intramolecular hemiaminal formation took place to render the final spirocycle **119**. Only two examples were reported with moderate yields and excellent enantio and diastereoselectivities (Scheme 62).



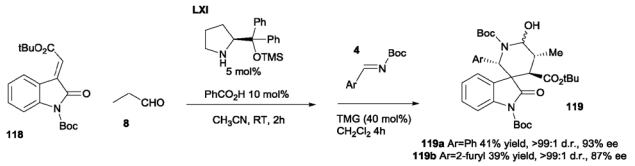
Scheme 59 Synthesis of nitroamines developed by Ooi.



Scheme 60 Staudinger reaction reported by Ye.



Scheme 61 Cross aza-benzoin reaction reported by Rovis.



Scheme 62 Multicomponent spirocyclization reported by Chen.

4. Conclusions

N-Boc carbamoyl imines have recently emerged as one of the most useful compounds for the synthesis of chiral amines. Their improved reactivity towards classical imines, ease of synthesis, and ease of removal of the carbamoyl group make them a logical platform for the development of new powerful transformations. Moreover, the orthogonal reactivity of the different carbamoyl groups (Boc, Cbz, FMoc, *etc.*) allows synthetic chemists to plan highly ambitious syntheses with a high degree of freedom. As we have shown in this review, organometallic and organocatalytic methodologies have been developed: Mannich, Henry, Friedel–Crafts, tandem reactions, *etc.* Clearly, the highlighted methodologies have several drawbacks, including poor structural diversity and limited group compatibility. Yet, the achievements with these methodologies have been immense. In the future, many improvements are expected, such as new multicomponent reactions and their application in total synthesis, the use of supported catalysts, application in flow chemistry, the study of new carbamoyl groups like FMOC, new photolabile carbamoyl groups, *etc.* Thus, we envision a bright future for these reagents; probably the only limit is the imagination.

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