ChemComm

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Journal:	*ChemComm*
Manuscript ID	CC-FEA-07-2015-005891.R1
Article Type:	Feature Article
Date Submitted by the Author:	24-Sep-2015
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Journal Name

ARTICLE

Cyclic enaminones. Part I: Stereocontrolled synthesis using diastereoselective and catalytic asymmetric methods

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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Cyclic enaminones are versatile intermediates to construct a variety of azacyclic frameworks and have been widely used in alkaloid synthesis. Here, we summarize three approaches for stereoselective syntheses of cyclic enaminones and their functionalized derivatives. These include chiral substrates (chirons) as starting materials, syntheses employing non-catalytic (stoichiometric) reagents, and catalytic asymmetric methods.

1. Introduction

1.1 About enaminones

Nitrogen containing molecules, especially the alkaloids are ubiquitous in nature. They are invariably endowed with a variety of pharmacologically relevant activity ranging from toxins to medicinal agents. Among the many methods to construct the core motifs of azacyclic compounds, few have been more useful than cyclic enaminones which can be functionalized in a variety of ways to incorporate the required substituents needed to achieve the intended target structure.

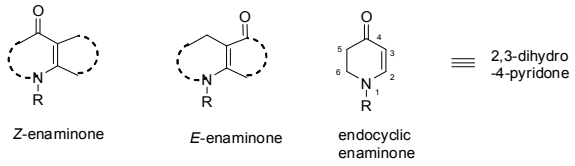

Figure 1: Cyclic enaminones.

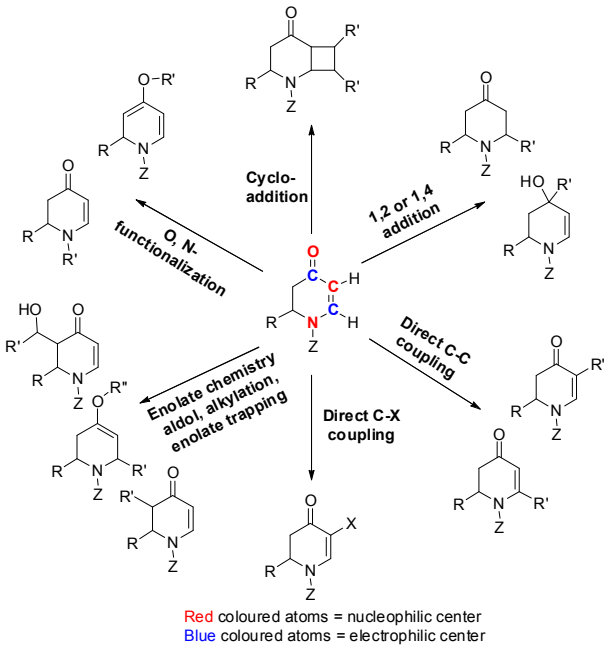

Figure 2: Reactive sites and possible transformations of cyclic enaminones.

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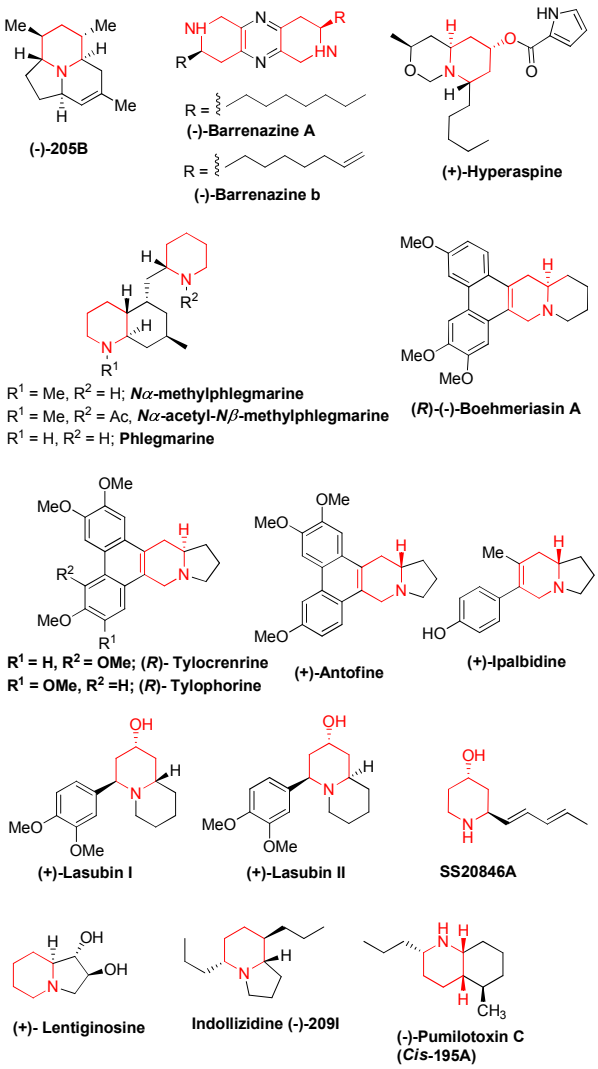


Figure 3: Selected azacyclic natural products. Red coloured indicates original enaminone embedded in the core structure.

The word enaminone[1] consists of three sub-words "ene", "amine" and "one". An enaminone can be considered as a β-acyl enamine or an amide with an interpolated alkene. The term enaminone is used to indicate any compound containing the conjugated system N-C=C=O. Enaminones can be cyclic or acyclic. A cyclic enaminone can be best represented by two possible structures, shown in Figure 1. Endocyclic enaminones exist only in a *cisoid* form which is formally exemplified by a 2,3-dihydro-4-pyridone,[2] whereas bicyclic enaminones may be either *cis* or *trans*. Enaminones combine the modest nucleophilicity of enamines and the modest electrophilicity of enones. They are a special kind of push-pull olefin in which the amine group pushes the electron density and the carbonyl pulls the electron density. The reactivity and stability of an enaminone is quite different from an enamine and an enone individually. Enamines can be readily decomposed by hydrolysis and oxidation, whereas enaminones are quite stable and easily isolable under atmospheric conditions. The reactive sites and the possible transformations are shown in Figure 2. The most common transformations are conjugate additions[3], direct C-C[4] or C-X bond formation[5], enolate chemistry[6], *O*- or *N*-functionalization,[7,8] and cycloaddition[9] reactions (Figure 2).

In this brief review, we summarize selected methods for the enantioselective synthesis of cyclic enaminones and their functionalized variants.

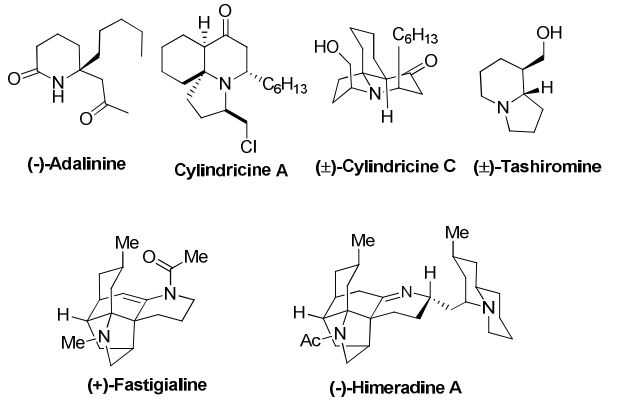


Figure 4: Selected natural products where enaminones were used as intermediates in the course of a synthesis.

1.2 Versatile building blocks and intermediates in natural products synthesis

A variety of natural products related to alkaloids have been synthesized in enantiopure form or as racemates using cyclic enaminones as building blocks as well as intermediates represented in Figure 3-4. A detailed description of these total syntheses is reported separately (See Part II). [10]

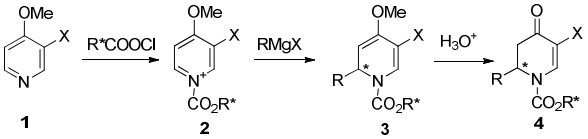
2. Stereoselective syntheses of cyclic enaminones

The most common synthetic strategies to obtain enaminones in highly enantioenriched (or enantiopure) form are classified in three major categories. First, from chiral substrates, where enaminones are synthesized either using an optically pure chiral auxiliary or from amino acid precursors. Second, is the non-catalytic approach, where enantiopure enaminones are synthesized *via* the use of stoichiometric amounts of a Lewis acid-ligand complex. In the third, and most straightforward method, optically active enaminones are synthesized by means of catalytic (0.1 to 10 mol %) amounts of catalyst-ligand complexes.

2.1. From chiral substrates

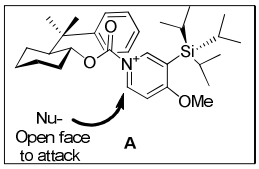
2.1.1. From pyridinium salts

Synthesis of dihydropyridones from chiral pyridinium salts *via* addition of carbon nucleophiles is one of most practical and reliable strategies to access enantioenriched (or enantiopure) substituted cyclic enaminones. The wide applicability of this method makes it an attractive method in alkaloids synthesis.



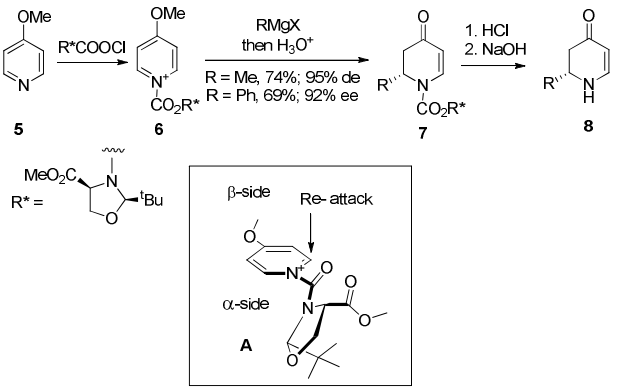
X = silyl, stannyl, H
R* = (-/+)-menthol
(-/+)-8-phenylmenthol
(-/+)-*trans*-2-(α-cumyl)cyclohexanol

Yield and de of compund **4** (X = TIPS)
R* = (-)-menthol, R = Ph; 87%, 44% de
R* = (-)-8-phenylmenthol, R = Me, ^{i}Bu, ^{n}Pr, vinyl, Ph, *o*-MeC$_6$H$_4$, *p*-OMeC$_6$H$_4$, *p*-MeC$_6$H$_4$, cyclohexyl; 77-90%; 60-94% de
R* = (-/+)-*trans*-2-(α-cumyl)cyclohexanol, R = Ph, ^{n}Pr; 90-98%; 90-92% de



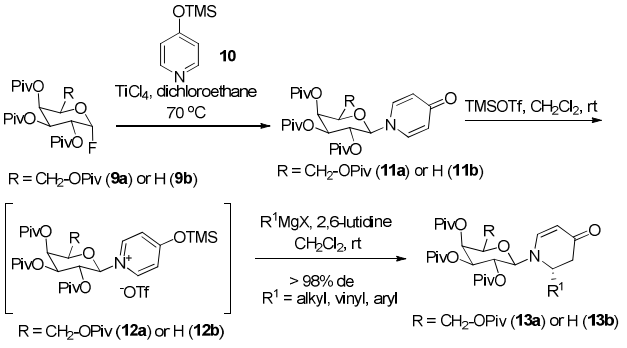
Scheme 1: Comins' synthesis of cyclic enaminones.

In 1990, Comins' and co-workers[11] reported a Grignard addition reaction to chiral 1-acyl-4-methoxy-pyridinium salts **2**, prepared *in situ* from 4-methoxypyridine **1** and a chiral chloroformate. An aqueous-acid hydrolysis of the intermediate **3** afforded dihydropyridones **4** with high diasteroselectivity. The choice of chiral auxiliary was found to be vital for implementation of high asymmetric induction in these reactions. Excellent diastereoselectivity was observed with 8-phenylmentyl or *trans*-2-(α-cumyl)cyclohexyl pyridinium salts. The trialkylsilyl substituent at C-3 effectively prevents attack at the adjacent C-2 of the 1-acylpyridinium ion **2**, leading to site selectivity at C-5 towards Grignard reagents. The stereoselectivity was found to be solvent dependent. The best yield and stereoselectivity were obtained when pyridinium salts **2** in toluene were treated with the Grignard reagent in THF. The diastereoselectivity of the reaction was dependent on the steric and electronic nature of the Grignard reagent. It was believed that the aryl substituent of the chiral auxiliary effectively blocked one face of the pyridinium salt, thus favoring nucleophilic attack from the opposite face (Scheme 1, **A**). The scope of the reaction was further extended towards the use of metallo enolates[12] instead of Grignard reagents. The application of this methodology was demonstrated by various total syntheses and found to be a reliable method.

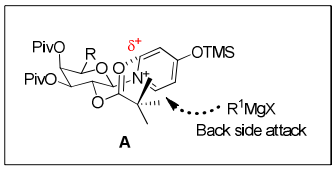


Scheme 2: Streith's synthesis of cyclic enaminones.

In 1994, Streith and co-workers[13] reported a diastereoselective 1,2-methyl conjugate addition to optically active pyridinium salts **6** derived from Seebach's (2*R*, 4*S*) oxazolidine auxiliary (Scheme 2). This reaction no longer required the bulky and expensive triisopropylsilyl C-3 substituent in the pyridinium salt to ensure site selectivity. It was assumed that the high diasteroselectivity in the absence of a trialkylsilyl group may be due to chelation of the alkylating agent to the urea carbonyl followed by face-selective attack (Scheme 2, **A**). The scope of the reaction is limited since only MeMgBr and PhMgBr were reported.



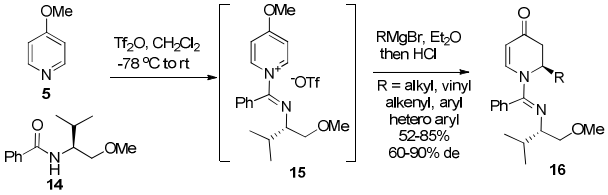
Yield and de of compound **13**
R = CH_2OPiv, R^1 = Me, ^{n}Pr, ^{i}Pr, ^{n}Bu, ^{n}Dec, vinyl, *m*-OMeC$_6$H$_4$, Ph; 30-89%; 80-100% de
R = H, R^1 = Me, ^{n}Pr, ^{n}Bu, Ph; 37-100%; 76-100% de;



Scheme 3: Kunz's synthesis of cyclic enaminones.

In 1998, the Kunz group[14] first reported a desymmetrizing 1,2-conjugate addition of Grignard reagents to

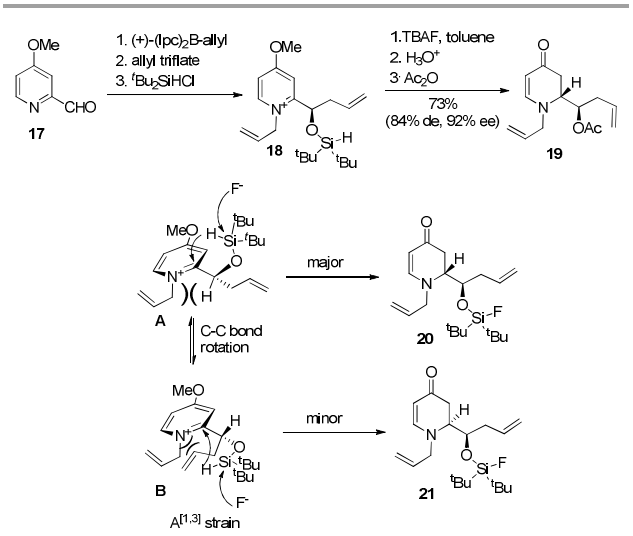
enantiopure 4-siloxypyridinium salts **12a**-**b** generated *in situ* from *O*-pivaloylated *N*-D-galactopyranosyl-pyrid-4-ones (**11a**) and *N*-L-arabinopyranosyl-pyrid-4-ones (**11b**) (Scheme 3). The reaction proceeded with high asymmetric induction, leading to the formation of *N*-protected-2-substituted dihydropyridones. The starting 4-pyridone **11a**-**b** was synthesized *via* *N*-glycosylation using $TiCl_4$ as Lewis acid. Activation of **11a-b** by *O*-silylation with TMSOTf, provided the intermediate chiral pyridinium ion **12a**-**b** to give products such as **13a**-**b,** which was reacted with different Grignard reagents with excellent diastereoselectivity. The absolute configuration of several enaminone derivatives such as **13a**-**b**, was confirmed by X-ray analysis. It was postulated that in intermediate **12a**-**b**, the front side of the pyridinium ion was effectively shielded by the 2-pivaloyl group in addition to a participation of the carbonyl oxygen atom of the 2-pivaloyl group that could block one face. (Scheme 3, **A**) This methodology was successfully applied toward the synthesis of (*S*)-coniine.



Scheme 4: Charette's synthesis of cyclic enaminones.

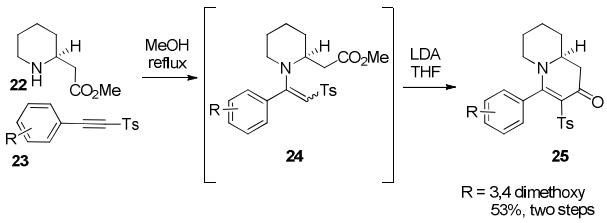
In 2006, the Charette group[15] reported a stereoselective synthesis of enantioenriched cyclic enaminones *via* nucleophilic addition of Grignard reagents to chiral pyridinium salts derived from 4-methoxypyridine **5** (Scheme 4). Previously, the same group reported a new method for the generation of pyridinium salts from pyridine, a secondary amide and triflic anhydride as an activator.[16] 4-Treatment of methoxypyridine **5** with *N*-benzoyl-*O*-methyl-L-valinol **14** in presence of triflic anhydride led to the chiral pyridinium salt **15**, which underwent a highly diastereo- and regioselective 1,2-conjugate addition reaction with carbon nucleophiles. The diastereoselectivity of the reaction was best achieved using dichloromethane as solvent. The reaction proceeded with good to excellent yields in presence of simple Grignard reagents and also with bulkier nucleophiles, ensuring wide applicability. According to the report, the amidine auxiliary can be easily cleaved using BBr_3, *via* cleavage of the methoxy group on the amidine motif and spontaneous fragmentation. This method was applied to synthesis of (-)-barrenazine A and B (See Part II).

Recently Donohoe and co-workers[17] reported a novel synthesis of enantiopure substituted dihydropyridones *via* an intramolecular hydride addition onto substituted pyridinium salts **18** (Scheme 5). The authors described conversion of 4-methoxy pyridine-2-carboxaldehyde **17** to pyridinium ion **18**, bearing an exocyclic silyl protected hydroxyl group, capable of an intramolecular hydride transfer reaction in presence of TBAF with fluoride as a nucleophile, which allowed the silicon atom to transfer its hydride. The reaction preceded with good yield and selectivity in non-polar solvents compared to polar solvents like THF. It was hypothesized that the loss of an alkoxide from the pentavalent silicon intermediate might be disfavored in non-polar solvents. The high diastereoselectivity was explained based on a transition state model, where conformation **B** was disfavored by $A^{[1,3]}$ allylic strain (Scheme 5, **A** and **B**). The use of a silane as an internal hydride source for 1,2-conjugate reduction of pyridinium salts is worth mentioning.



Scheme 5: Donohoe's synthesis of cyclic enaminones.

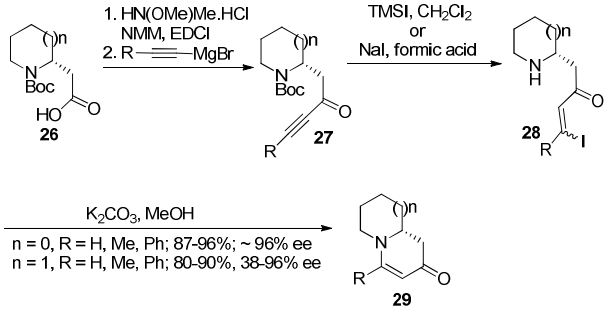
2.1.2. From amino acids



Scheme **6**: Back's synthesis of cyclic enaminones.

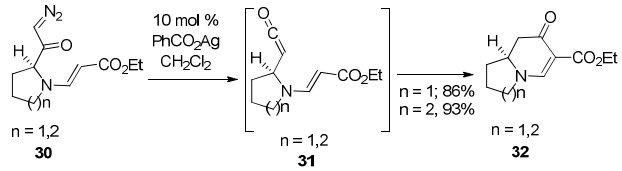
In 1999, Back and Nakajima[18] reported the synthesis of various azacyclic compounds *via* conjugate additions of cyclic or acyclic secondary amines bearing β- or γ- halo substitutents to acetylenic sulfones, followed by intramolecular ring formation. The methodology was further successfully extended to β-amino esters leading to the formation of cyclic enaminones[19] (Scheme 6). The reactions involved a Michael-type addition of an amino ester **22** to an

acetylenic sulfone **23**, followed by treatment of the crude product **24** with LDA, to afford bicyclic enaminone **25** in moderate yield. The feasibility of this method was further demonstrated by various total syntheses reported by the same group (See Part II).



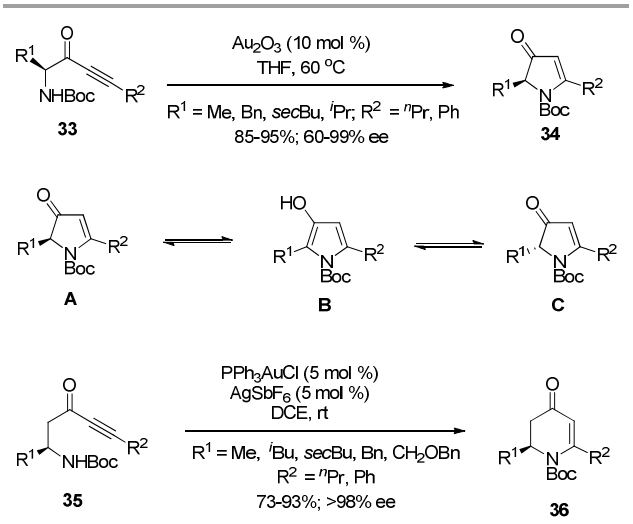
Scheme 7: Georg's synthesis of cyclic enaminones.

Georg and co-workers[20] first reported a novel synthetic route to enaminones from β-amino acids *via* intramolecular ring formation (Scheme 7). The reaction sequence involved conversion of an *N*-Boc-β-amino acid **26** to the corresponding ynone **27**, followed by *in situ* Boc-deprotection and subsequent 6-*endo*-*trig* ring closure of a vinyliodo intermediate **28**. A variety of enantiopure five- and six-membered as well as open chain β-amino ynones were subjected to the standard reaction conditions, to afford annelated six- or seven-membered cyclic enaminones **29** with good yields and selectivities. The yield of the cyclization process strongly depends on the choice of the solvent and MeOH was found to be best during the intramolecular cyclization. This method was successfully applied to construct an array of monocyclic and bicyclic azacycles, which was eventually used in the synthesis of a variety of alkaloids (See Part II).



Scheme 8: Georg's synthesis of cyclic enaminones.

In 2010, Seki and Georg[21] disclosed a synthetic strategy to prepare mono-, bi-, tricyclic enaminones from amino acids *via* Wolf rearrangement using vinylogous amides as carbon nucleophiles (Scheme 8). When diazoketone **30** was treated in presence of 10 mol % of silver benzoate, it formed a ketene intermediate **31**, which underwent a 6-*exo*-*dig* cyclization to afford enaminone **32** in good yield and enantioselectivity. The rare 6-*exo*-*dig* cyclization using a ketene as the electrophile is noteworthy.



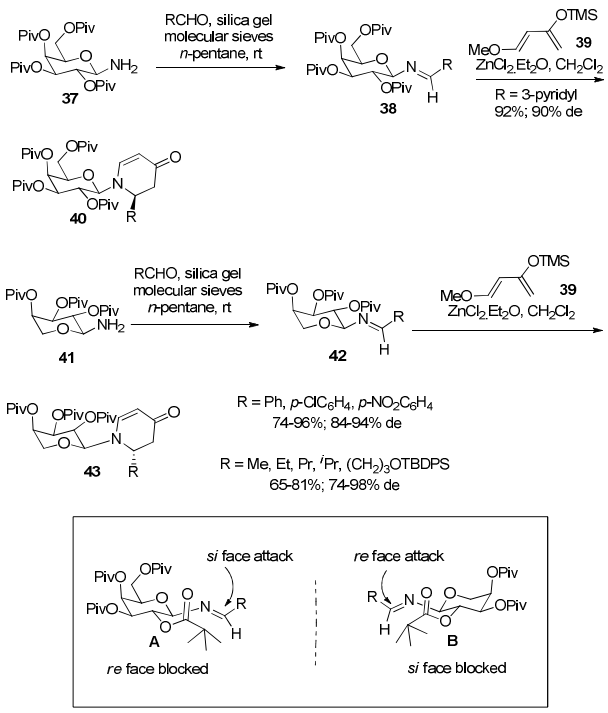
Scheme 9: Gouault's synthesis of cyclic enaminones.

In 2009, Gouault and co-workers[22] reported an extended version of the Georg method, where gold-catalyzed cyclizations of various α-amino-ynone **33** derivatives were studied (Scheme 9). According to the authors, a moderate to total stereocontrol during the cyclization process was observed when gold (III) oxide was used as a catalyst. The use of AuCl, resulted in partial epimerization due to formation of HCl, resulting in a keto-enol equilibrium (Scheme 9, **A**-**C**). Decrease of catalyst loading from 10 to 1 mole % only affected the reaction time without any change in product yield.

This methodology was further extended to β-amino ynones **35**, and led to enantiospecific syntheses of dihydropyridones[23] **36** (Scheme 9). During this process, a variety of gold catalysts and co-catalysts were screened. The use of PPh_3AuCl in presence of equal amounts of silver salts in dichloroethane at room temperature was advantageous over others gold catalysts. No reaction was observed when gold or silver catalysts were used independently. The variation of the substitutents (R^1 or R^2) provided a variety of protected dihydropyridones which was further diversified to the corresponding piperidine analogs.

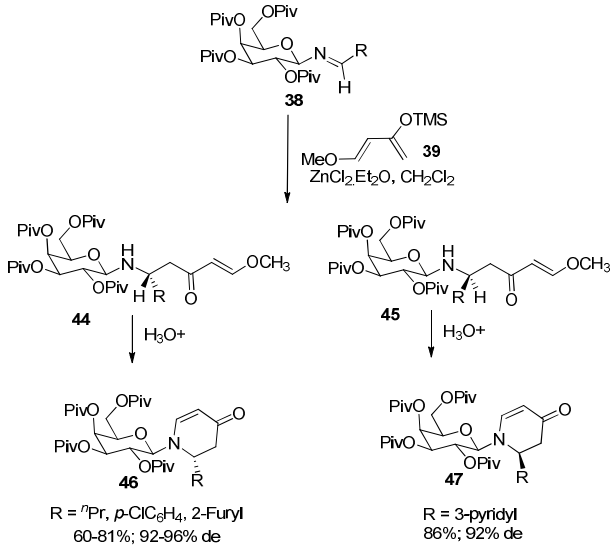
2.1.3. Aza-Diels-Alder and tandem Mannich-Michael sequence

Danishefsky and co-workers[24] reported that unactivated aliphatic or aromatic imines react smoothly with electron rich dienes in presence of a Lewis acid to give azacyclic compounds. Subsequent reports using ((4-methoxybuta-1,3-dien-2-yl)oxy)trimethylsilane (Danishefsky's diene), have led to 2,3-dihydro-4-pyridone derivatives.



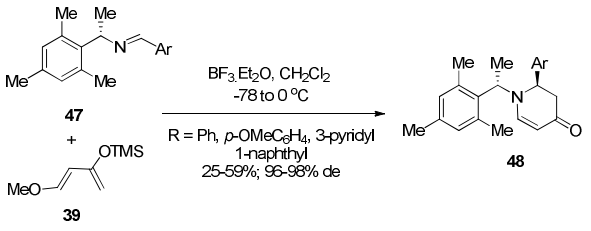
Scheme 10: Kunz's synthesis of cyclic enaminones.

In 1989, the Kunz group[25,26] first reported a diastereoselective aza-Diels-Alder reaction using tetra-*O*-pivaloyl-β-D-galactopyranosylamine **37** as the chiral appendage and Danishefsky's diene. A couple of years later, the reaction was further extended with tri-*O*-pivaloyl-α-D-arabinopyranosylamine **41**, which was almost the mirror image of the D-galactosylamine homologue **37** (Scheme 10). The reaction involved a $ZnCl_2.Et_2O$ promoted hetero Diels-Alder reaction between Schiff bases of a variety of aromatic and heteroaromatic aldehydes such as **38** with Danishefsky's diene **39**. The reactions proceeded with good yields and moderate to high diastereoselectivities. Schiff bases of aromatic and heteroaromatic aldehydes were obtained as crystalline solids and existed mostly in the β-anomeric form. Imines of aliphatic aldehydes underwent anomerization at temperatures above -10°C. The high diastereoselectivity of the reaction was controlled by the bulky pivaloyl group at C-2 of the tetra-*O*-pivaloyl-β-D-galactopyranosylamine auxiliary **38**, which effectively shields the *re* face of the imine group. (Scheme 10, **A**) In contrast, the pivaloyl group of the tri-*O*-pivaloyl-α-D-arabinopyranosylamine **41** blocked the *si* face of the aldimines **42**, and led to protected dihydropyridones **43** bearing the opposite configuration at the C-2 position (Scheme 10, **B**). The absolute configuration of the *N*-arabinosyl dihydropyridones **43** was proved by X-ray analysis. The absolute configuration of the *N*-galactosyl dihydropyridones **40** was proved through the synthesis of known alkaloid (*S*)-anabasin. Use of a sugar motif as a chiral inducing agent in hetero Diels-Alder reactions and recycling of the auxiliary *via* detachment from the chiral piperidine derivatives is notable.



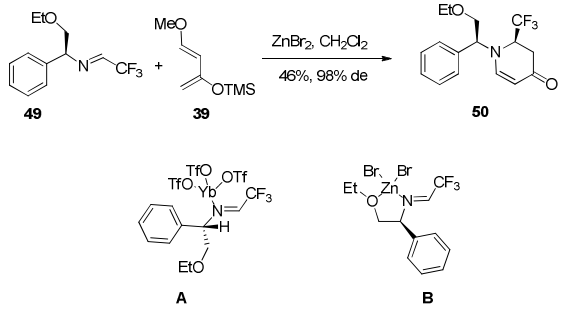
Scheme 11: Kunz's synthesis of cyclic enaminones

When Schiff base **38** was treated with Danishefsky's diene **39** in THF at -20 °C in presence of $ZnCl_2$ as a Lewis acid, the reaction followed a Mannich/Michael tandem sequence instead of the aza-Diels-Alder reaction[27] (Scheme 11). When the reaction was stopped at half way quenching with NH_4Cl solution, the Mannich compounds **44**-**45** were isolated as the exclusive product. On the other hand, the Michael addition products **46**-**47** were isolated when direct hydrolysis with 1N HCl was used as a work-up procedure. In this sequence, the Lewis acid $ZnCl_2$ first coordinates to the Schiff base nitrogen as well as the carbonyl oxygen of the pivaloyl group in the 2-position. The Mannich reaction was assumed to be initiated due to the latent nucleophilicity of the silyl dienol ether in **39**.



Scheme 12: Hashimoto and Saigo's synthesis of cyclic enaminones.

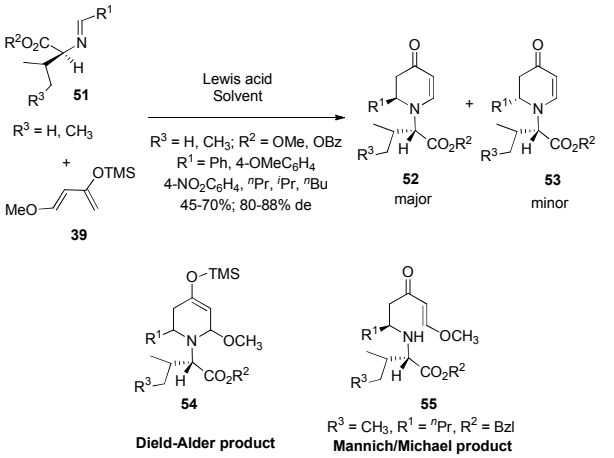
Hashimoto, Saigo and co-workers[28] reported a new variation of the Kunz method, where they used a non-natural auxiliary to induce chirality during the aza-Diels-Alder reaction (Scheme 12). Aldimine **47**, derived from enantiopure 1-(*S*)-methyl mesitylethylamine and aromatic aldehydes, reacted with Danishefsky's diene **39** in the presence $BF_3.Et_2O$, to afford 2,3-dihydro-4-pyridones **48** with high diastereoselectivity but moderate yield. The relative configuration of one of the major products was determined by X-ray analysis. The high *anti* selectivity was achieved due to the steric effect of the *ortho* methyl substituents in the benzene ring.



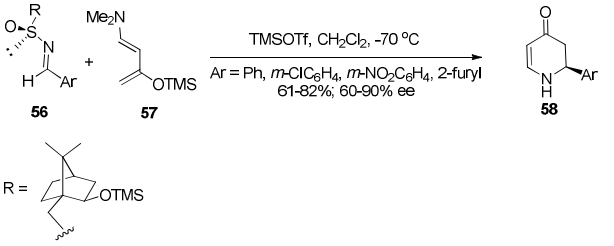
Scheme 13: Kagawa's synthesis of cyclic enaminones.

In 2013, Kagawa and co-workers[29] reported an aza-Diels-Alder reaction, where an optically active trifluoromethyl 2-ethoxy-1-phenylethyl-1-imine **49** reacted with Danishefsky's diene **39** in presence of variety of Lewis acids (Scheme 13). In the case of $Yb(OTf)_3$ and $BF_3.Et_2O$, low diastereoselectivity (9-27%) was observed, whereas zinc dihalides offered excellent diasteroselectivity. Chelation of $Yb(OTf)_3$ and $BF_3.Et_2O$ with the nitrogen atom, prevented the ethoxymethyl group to effectively shield the α-face in the coordinated intermediate, hence the low diastereoselectivity. (Scheme 13, **A**) On the other hand, Zn-dihalides formed a stable five-membered chelated intermediate (**B**) which led to a more shielded α-face (Scheme 13, **B**). This method suffered mostly from low product yield.

In 1990, Waldmann and co-workers[30] reported the use of easily accessible amino acid esters as a chiral auxiliary in the Lewis acid mediated reaction of non-activated imine **51** with Danishefsky's diene **39** (Scheme 14). Imines derived from valine and isoleucine uniformly provided cyclic enaminones with moderate to high yield and stereoselectivity. No significant effect in stereoselectivity and product yield was observed while varying the steric bulk of the ester moiety, as well as the substituents of the aldehyde group, bearing the imine. Aliphatic aldimines led to good results with aluminium Lewis acids in dichloromethane, whereas for aromatic aldimines the best catalyst system was $ZnCl_2$ in THF at lower temperature. The chiral auxiliary was easily removed *via* a one-pot multistep process. According to Waldmann and co-workers the reaction progressed *via* a tandem Mannich-Michael mechanism instead of a hetero Diels-Alder reaction. In neither case, a Diels-Alder intermediate **54** was isolated. On the other hand, when isoleucine benzoate ester was used as a chiral auxiliary with propionaldehyde, a Mannich intermediate **55** was isolated. The potential of this method was shown by the synthesis of a yohimbine-type alkaloid in enantiomerically pure form. The use of less expensive and easily accessible amino acids as a chiral auxiliary is notable in this transformation.

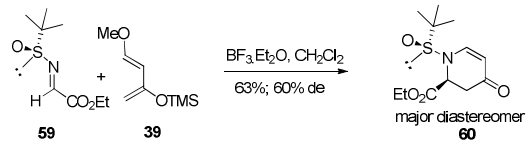


Scheme 14: Waldmann's synthesis of cyclic enaminones.



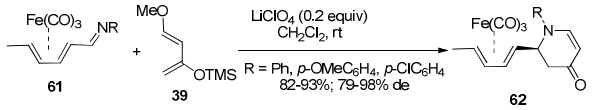
Scheme 15: Kawęcki's synthesis of cyclic enaminones.

In 2006, Kawęcki[31] reported a TMSOTf-catalyzed aza-Diels-Alder reaction of optically active sulfinimines **56** with the more reactive Rawal diene **57** (Scheme 15). Best results were obtained when 10-isobornylsufinimines were used as a chiral auxiliary. The steric effect of the TMS group had a profound influence on product selectivity. The reaction proceeded with moderate yield and diastereoselectivity. The cleavage of the sulfinyl template occurred during the workup of the reaction mixture. No reaction was observed with the relatively less reactive Danishefsky's diene **39**. The use of optically active sulfinimines is noteworthy in this type of reaction.



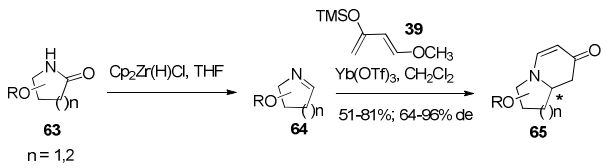
Scheme 16: Gautun's synthesis of cyclic enaminones.

Gautun and co-workers[32] reported an improved version of the Kawecki's method, where *N*-*tert*-butanesulfinyl α-imino esters such as **59** were treated with activated and non-activated dienes in presence of $BF_3.Et_2O$ (Scheme 16). The aza-Diels-Alder product **60** was isolated in moderate yields and diastereoselectivity.



Scheme 17: Iwata's synthesis of cyclic enaminones.

In 1996, Iwata and Takemoto[33] reported a new method for dihydropyridone synthesis using aza-Diels-Alder strategy, where an optically active iminedienophile $Fe(CO)_3$ complex **61** reacted with Danishefsky's diene **39** in presence $LiClO_4$ as Lewis acid (Scheme 17). The reaction required catalytic amounts of $LiClO_4$ and dichloromethane solvent for high yield and stereoselectivity especially with electron rich aldimine complexes. It was assumed that the stereoselectivity might result due to the coordinating ability of the aldimine nitrogen atom. The applicability of this methodology was demonstrated with an asymmetric total synthesis of SS20846A (See Part II). The use of [Fe(azatriene)$(CO)_3$] complex as a chiral template is noteworthy for this type of reaction.

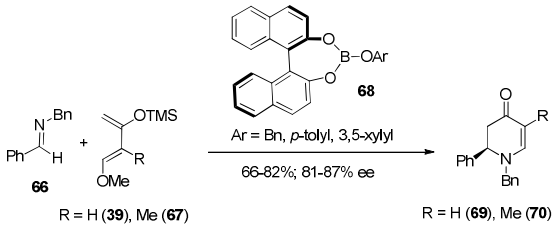


Scheme 18: Stecko and Furman's synthesis of cyclic enaminones.

Most recently, Stecko, Furman and their co-workers[34] reported a straightforward approach to the synthesis of indolizidine and quinolizidine core units **65**, using sugar derived imines with activated dienes *via* a Mannich/Michael tandem reaction sequence (Scheme 18). The one-pot sequence involved reduction of a sugar lactam **63** with Schwartz's reagent followed by a stereoselective Mannich-Michael reaction between the resulting imine **64** and Danishefsky's diene **39** in presence of $Yb(OTf)_3$ as a Lewis acid catalyst. A variety of five- and six- membered sugar lactams were used to generalize the efficiency of this process.

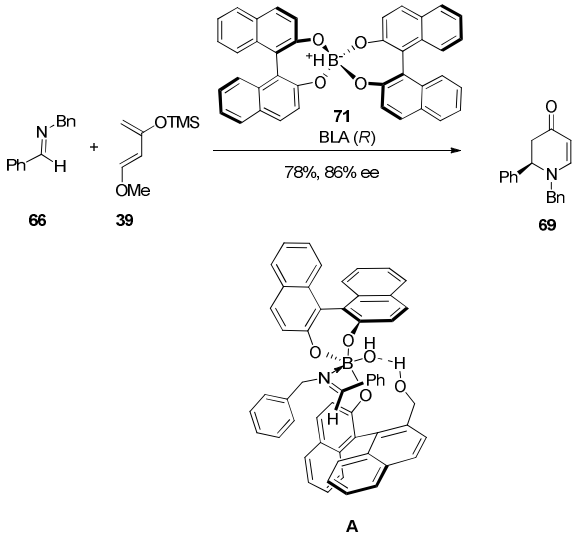
2.2. Non-catalytic asymmetric synthesis

2.2.1. Aza-Diels-Alder reaction



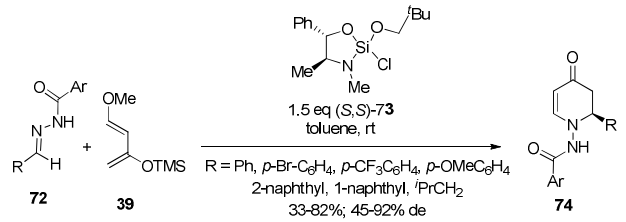
Scheme 19: Yamamoto's synthesis of cyclic enaminones.

In 1992, the Yamamoto group[35] first reported an asymmetric aza-Diels-Alder reaction of an imine **66** with an activated diene **39**/**67** in presence of a stoichiometric chiral boron complex **68**, generated *in situ* from 1:1 molar mixture of $B(OPh)_3$ and optically active binaphthol (Scheme 19). The reaction proceeded with good yield and enantioselectivity in the presence of 4-Å molecular sieves at -78 °C. A slight improvement in the optical yield was observed with more bulky aryloxy reagents. High enantioselectivity was only observed in dichloromethane as a solvent, rather than tetrahydrofuran or propionitrile. The efficiency of this new method was illustrated by the synthesis of (-)-anabasine.



Scheme 20: Yamamoto's synthesis of cyclic enaminones.

In later years, the same group reported an asymmetric BrØnsted acid-assisted chiral Lewis acid (BLA) mediated aza-Diels-Alder reaction between aromatic imines and activated dienes, to provide direct access of optically pure cyclic enaminoes[36] (Scheme 20). The BLA (**71**) was prepared from a 1:2 molar ratio of $B(OMe)_3$ and optically pure (*R*) or (*S*)-binaphthol. The aza-Diels-Alder reaction of benzylidenebenzylamine **66** with Danishefsky's diene **39** in presence of BLA **71**, afforded (*R*)-*N*-benzyl-2,3-dihydro-2-phenyl-4-pyridone (**69**) with 78% yield and 86% ee. The high enantioselectivity in this process was explained *via* a model, in which an intramolecular hydrogen bonding interaction with the BrØnsted acid effectively blocked the *si* face of the imine complex (Scheme 20, **A**).



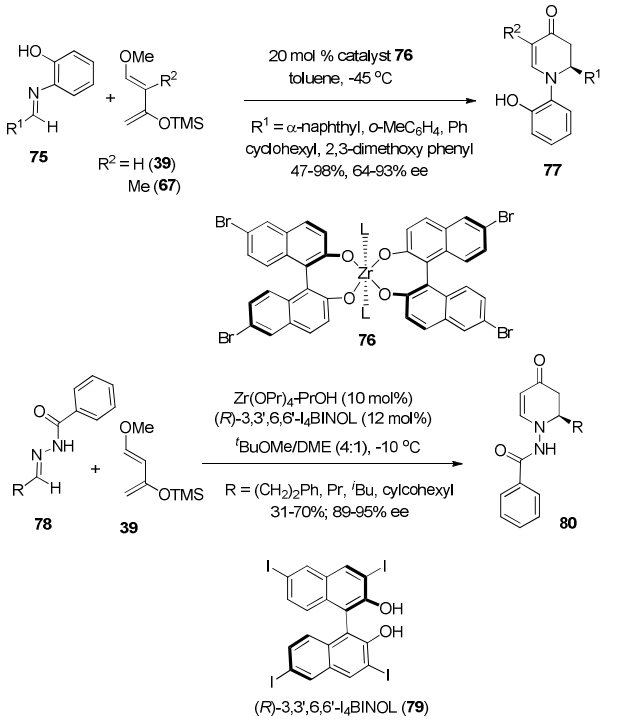
Scheme 21: Leigton's synthesis of cyclic enaminones.

In 2010, Leighton and co-workers reported[37] a chiral silicon Lewis acid **73** promoted highly enantioselective [4+2] cycloaddition reaction of acylhydrazones **72** with Danishefsky's diene **39** to construct optically pure cyclic enaminones **74** (Scheme 21). The reaction was highly solvent dependent and toluene provided the best selectivity for aromatic aldehydes, whereas for aliphatic aldehydes, dichloromethane afforded cyclic enaminones with opposite enantioselectivity. The unusual solvent-dependent reversal effect of enantioselectivity was not explained. The method had been successfully applied to the synthesis of casopitant, a neurokinin 1 receptor antagonist.

2.3. Catalytic asymmetric synthesis

2.3.1 Aza-Diels-Alder reaction

In 1998, Kobayashi and co-workers[38] reported the first catalytic, enantioselective aza-Diels-Alder reaction of imino dienophiles **75** with Danishefsky's diene **39** to obtain optically pure 2,3-dihydro-4-pyridones **77** (Scheme 22). The chiral zirconium complex **76** was prepared *in situ* in toluene from one equivalent of $Zr(O^tBu)_4$, two equivalents of (*R*)-6,6'-dibromo-1,1'-binaphthol and three equivalents of ligand at room temperature. *N*-Methylimidazole was found to be the best ligand in this transformation. In most of the cases, good yields and enantioselectivities were obtained in the presence of 20% of catalyst loading. *Ortho*-substituted arene aldehydes provided good yields of 2,3-dihydro-4-pyridone derivatives.

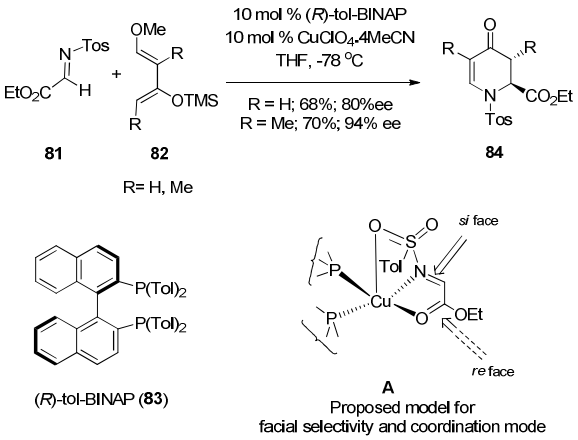


Scheme 22: Kobayashi's synthesis of cyclic enaminones.

Another variation of catalytic asymmetric aza-Diels-Alder reactions was reported with aldimines **78**, derived from acyl hydrazines and aliphatic aldehydes.[39] The use of new chiral zirconium complex, derived from zirconium propoxide and 3,3',6,6'-I_4BINOL **79**, provided cyclic enaminones **80** with moderate to good yield and excellent enantioselectivity. The method was applied toward the synthesis of coniine (Scheme 22).

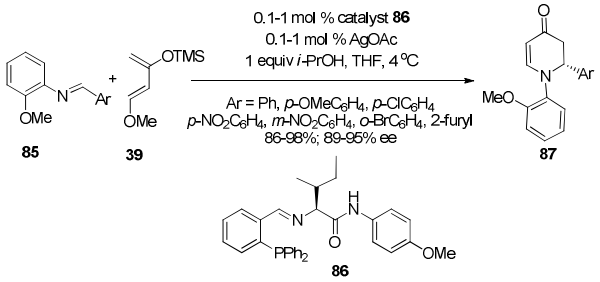
In the same year, Jørgensen and co-workers[40] reported a catalytic enantioselective [4+2] cycloaddition reaction between *N*-tosyl-α-imino esters **81** with different reactive dienes **82** (Scheme 23). Various chiral ligands, in combination with Lewis acid complexes were screened for this transformation. Excellent yields and diastereoselectivities were obtained when BINAP-copper (I) complexes were used as catalyst. The catalyst complex was prepared by mixing equal amounts of (*R*)-tol-BINAP (**83**) and $CuClO_4$.4MeCN in anhydrous THF at room temperature. An excellent enantioselectivity was observed even with 1 mol % catalyst loading at -78 °C in THF as a solvent, making this transformation highly efficient. The high enantioselectivity and plausible coordination mode in this process was explained based on a suitable model[40b] (Scheme 23, **A**). The *N*-tosyl *α*-imino ester has several possible coordination modes to the Tol-BINAP-(*R*).$CuClO_4$ catalyst. In comparison with bidentate coordination, the tridentate coordination of the *N*-tosyl α-imino ester to chiral Cu-catalyst leads to a change in the face-

shielding of the imine. In this proposed model two phosphorous atoms of the BINAP ligand (**83**) are coordinated *cis* and the remaining three coordination sites are occupied by the imine *N* and *O* atoms. The *re*-face of the imine is effectively shielded by one of the tolyl substitutent of the ligand, leaving the *si*-face more accessible for an attack.

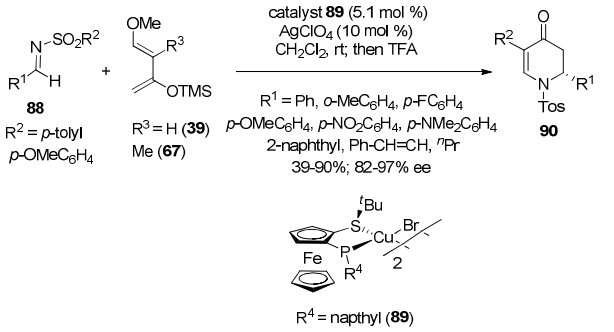


Scheme 23: Jørgensen's synthesis of cyclic enaminones.

In 2003, Hoveyda, Snapper and co-workers[41] reported the efficient Ag-catalyzed asymmetric [4+2] cycloaddition reactions of non-activated aryl imines **85** with Danishefsky's diene **39** to give 2,3-dihydro-4-pyridone derivatives **87** in excellent yield and enantioselectivity (Scheme 24). In this transformation an inexpensive phosphine ligand **86** was used as a catalyst. Even 0.1 mol % of catalyst loading was sufficient to complete the transformation with 98% yield albeit with slightly diminished enantioselectivity. According to the report, *o*-anisaldehyde imine underwent aza-Diels-Alder reactions most efficiently. The presence of an OMe group in the imine substrate was mandatory to get high enantioselectivity. Cycloaddition reactions are also possible in absence of solvent but the use of *i*-PrOH as additive was necessary to obtain good yield and selectivity.

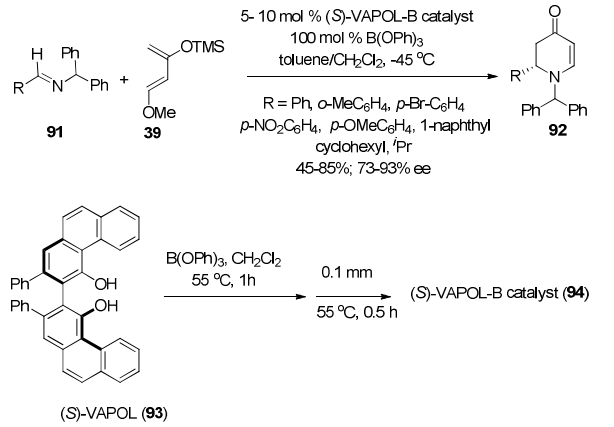


Scheme 24: Hoveyda and Snapper's synthesis of cyclic enaminones.



Scheme 25: Carretero's synthesis of cyclic enaminones.

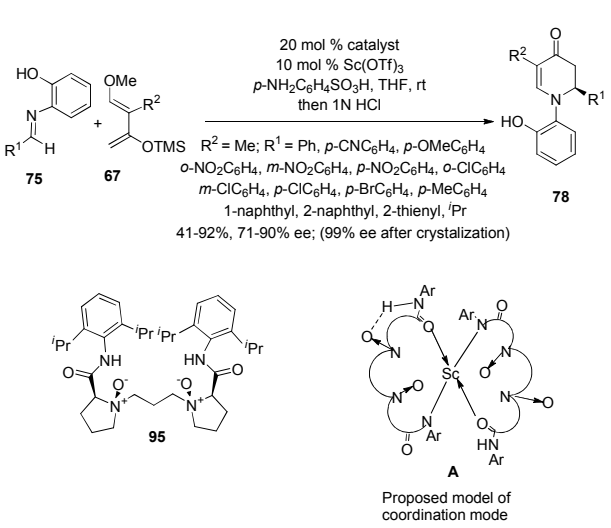
The Carretero group[42] disclosed an aza-Diels-Alder reaction between activated tosyl imines **88** and Danishefsky's diene **39** in presence of chiral phosphinosulfenyl ferrocene copper (I) bromide dimeric complex **89** to give enantiopure cyclic enaminones **90** (Scheme 25). In this transformation $AgClO_4$ was used as a halogen scavenger which furnished the product with higher selectivity. The reaction was highly dependent on the substitution at the phosphorus atom and the α-naphthyl group was found to be the best to obtain high yields and selectivity. The reaction followed a tandem Mannich-Michael sequence to afford substituted 2,3 dihydro-4-pyridones **90**. The low LUMO energy of the *N*-sulfonyl imines and highly crystalline nature of adducts make this transformation attractive with respect to reactivity and ease of handling.



Scheme 26: Wulff's synthesis of cyclic enaminones.

In 2007, Wulff and co-workers[43] reported a catalytic version of Yamamoto's aza-Diels-Alder reaction using (*S*)-VAPOL **93** and $B(OPh)_3$ as a catalyst duo. In this transformation, 10 mol % of the (*S*)-VAPOL catalyst and a sub-stoichiometric amount of $B(OPh)_3$ were used, assuming that at least 20 turnovers could be achieved (Scheme 26). The

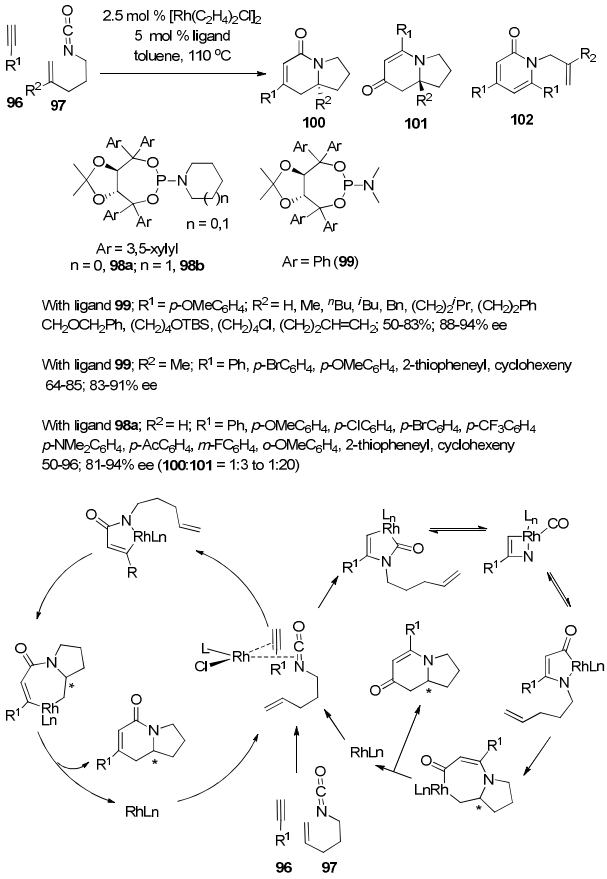
rationale behind this approach was that an excess non-chiral catalyst could free up the chiral catalyst to turn over the reaction, as the product was more basic than the starting imine. The cycloadditions were highly efficient in terms of product yield and selectivity for aromatic and α-branched aliphatic aldimines. NMR analysis showed that the VAPOL-B catalyst **94** binds to the imine seven times stronger than $B(OPh)_3$, but only about twice as strongly to the products. This result showed the higher reaction rate of the imine **91** with the chiral catalyst **94** over the non-chiral catalyst. The use of dual catalysts in the aza-Diels-Alder reaction is noteworthy.



Scheme 27: Feng's synthesis of cyclic enaminones.

Feng and co-workers[44] developed an enantioselective aza-Diels-Alder reaction between aldimines **75** and reactive dienes **67** catalyzed by $Sc(OTf)_3$ and L-proline derived *N*,*N*'-dioxide complex **95** (Scheme 27). The reactions proceeded with moderate to good yields and high enantioselectivities at room temperature. The product selectivity was highly dependent upon the steric effect of *ortho* substituent's on the amide moiety of ligand **95** and best results were obtained when 2,6-diisopropyl benzene was used. Like the other methods, THF was found to be the most suitable for this purpose. The *ortho* hydroxy group of the imine is mandatory for high enantioselectivity as well as for product formation. This method was almost equally efficient for aromatic and aliphatic imines and found to be practical. A plausible coordination mode and catalyst structure was investigated by ^1H NMR analysis and the positive nonlinear effect study. It was concluded that the ligand coordinated with scandium in a 2:1 manner, in which the ligand provided a carbonyl oxygen and an amide nitrogen for coordination (Scheme 27, **A**). From the NMR analysis it was assumed that among all the hydrogen atoms of complex **A** in the catalyst system, only some were affected by intramolecular hydrogen bond interaction. The molar ratio of these two types of hydrogens was 3:7 and this intramolecualr hydrogen bonding was totally disrupted when an external acid source was added. The relationship between chiral ligand and enantiomeric excess of the product was studied and a strong positive nonlinear effect was observed, which further supports the existence of 2:1 ligand-metal complex.

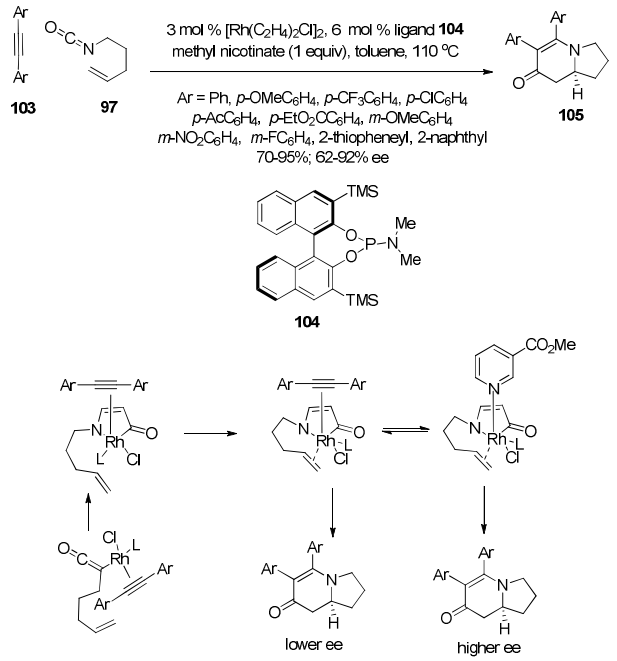
2.3.2. [2+2+2] Cycloaddition reactions



Scheme 28: Rovis' synthesis of cyclic enaminones.

During the period 2006 to 2009, Rovis and co-workers[45] reported several rhodium catalyzed [2+2+2] cycloaddition reactions of alkenyl isocyanates and terminal alkynes, to provide lactam products and substituted cyclic enaminones. A high level of enantioselectivity, regioselectivity and product yields were obtained by using different modified phosphoramidite ligands, although in all cases a small amount of pyridone side-product was also observed. In 2008, Lee and Rovis revealed an enantioselective synthesis of bicyclic enaminones **101** with angular substituted quaternary

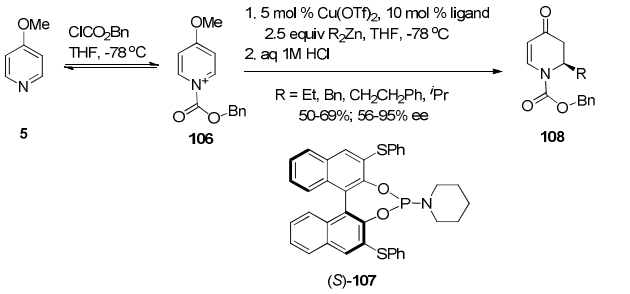
stereocentres *via* rhodium-catalyzed [2+2+2] cycloaddition of substituted alkenyl isocyanates **97** and terminal alkynes **96**.[46, 45a] In presence of phosphoramidite ligand **98** aliphatic aldehydes provided bicyclic enaminone **101** along with minor amounts of lactam products **100**. Whereas, using ligand **99** aromatic aldehydes led exclusively to bicyclic enaminones. The ratio of lactam **100** and cyclic enaminone products **101** were independent of the steric and electronic properties of the alkene substituents but highly dependent on the alkyne substituent. With an increase in steric size of the alkyne substituent, the yield of vinylogous amide was decreased. The reaction is highly efficient and works in presence of only 2.5 mol% of $[Rh(C_2H_4)_2Cl]_2$ and 5 mol % of phosphoramidite ligands **98b**. The authors proposed a plausible mechanism for a [2+2+2] cyloaddition reaction as shown in Scheme **28**.



Scheme 29: Rovis' synthesis of cyclic enaminones.

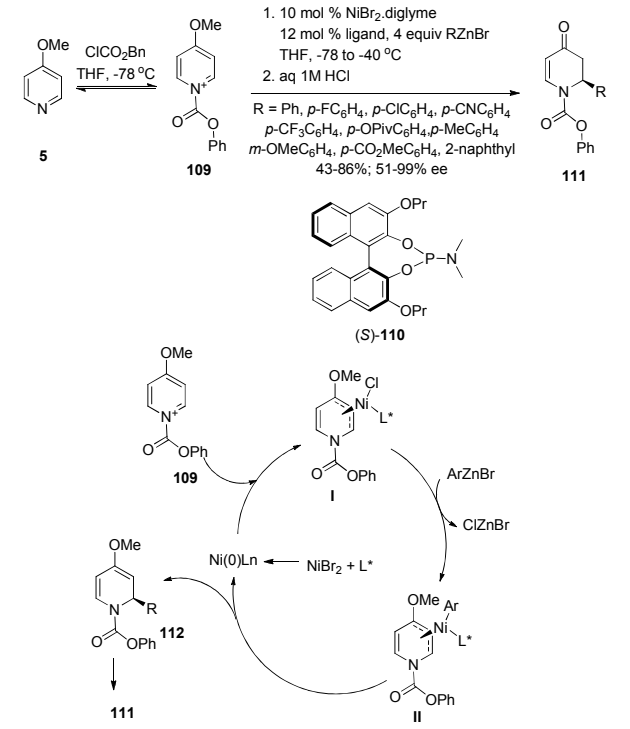
The following year, the Rovis group[47] reported an interesting example of substrate-dependency on product selectivity during the cycloaddition reaction (Scheme 29). Since excess alkyne **103** participates as a ligand during the reaction process they screened a variety of additives. The use of methyl nicotinate as additive influenced the substrate electronics by affecting the ligand environment for the rhodium (III) intermediate. It was found that the use of stoichiometric levels of the additives provided high enantioselectivity, whereas no noticeable change in selectivity was observed with sub-stoichiometric amounts of additive. The proposed mechanism and role of the additive is shown in Scheme **29**.

2.3.3. Nucleophilic addition



Scheme 30: Minnaard and Feringa's synthesis of cyclic enaminones.

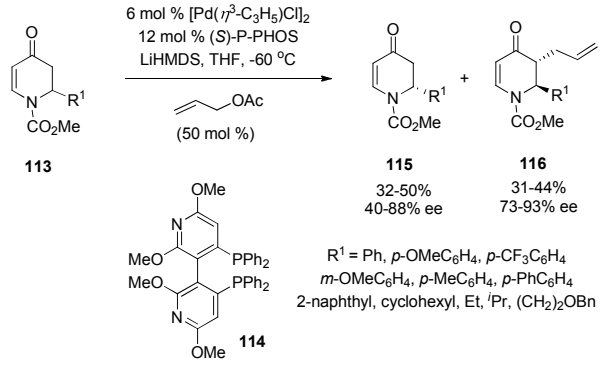
In 2009, Minnaard, Feringa and co-workers[48] reported the first catalytic enantioselective addition of organometallic reagents to *N*-acylpyridinium salts **106** in presence of copper/phosphoramidite catalyst, to give optically pure 2,3-dihydro-4-pyridone derivatives **108** (Scheme 30). A combination of $Cu(OTf)_2$ and (*S*)-phosphoramidite ligand **107** in THF at -78 °C was found to be the best catalyst combination for this transformation. A variety of dialkyl zinc reagents were added to pyridinium salts with good yields and excellent enantioselectivity. The synthesis of chiral 2,3-dihydro-4-pyridones, from optically inactive pyridinium salts in a single step is noteworthy.



Scheme 31: Doyle's synthesis of cyclic enaminones.

In 2013, Doyle and co-wokers[49] developed an iminium ion activation strategy for the enantioselective synthesis of 2,3-dihydro-4-pyridones **111** *via* a Negishi cross-coupling with *N*-acyl pyridinium ions **109** (Scheme 31). The use of 10 mol % of $NiBr_2$.diglyme along with 12 mol % of phosphoramidite ligand **110** in THF at -40 °C, was found to be the best conditions for the Negishi reaction. *Ortho-*, *meta-*, and *para-* substituted zinc nucleophiles provided good yields and selectivities, when electron withdrawing substituents were used. According to the proposed catalytic cycle, Ni(0) first oxidatively adds onto the C-N π-bond of the pyridinium salt, followed by a transmetallation with ArZnBr, which undergoes a reductive elimination to regenerate the Ni(0) catalyst before releasing the product (Scheme 31). Engaging an iminium ion in transition–metal-catalyzed C-C bond construction is worth mentioning.

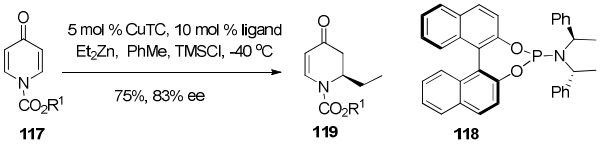
2.3.4. Kinetic resolution



Scheme 32: Ding and Hou's kinetic resolution of cyclic enaminones.

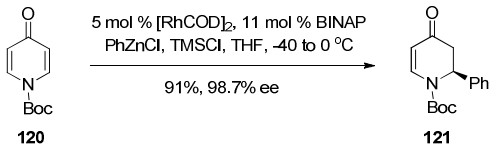
In 2014, Ding, Hou and co-wokers[50] disclosed a kinetic resolution of 2-substituted 2,3-dihydro-4-pyridones **113** using a palladium-catalyzed asymmetric allylic alkylation strategy[51] to give optically pure derivatives (Scheme 32). Under optimized reaction conditions, racemic pyridones **113** were subjected to 6 mol % of $Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 12 mol % (*S*)-P-PHOS ligand **114**, allyl acetate and LiHMDS in THF at -60 °C to obtain maximum enantiocontrol. The enantioselectivity of the resolved products **116** was almost unaltered with the electronic nature of the *meta-*, *para-* substituents of the aryl group, whereas the ee of the recovered dihydropyridones **115** was strongly affected by the nature of the substituents. The method was successfully applied for the total synthesis of alkaloid (-)-209I (See Part II). The use of asymmetric allylic alkylation in the kinetic resolution of a nucleophile is noteworthy.

2.3.5. Conjugate addition to 4-pyridones



Scheme 33: Dieter's synthesis of cyclic enaminones.

In 2009, Dieter and Guo[52] reported an asymmetric conjugate addition reaction to *N*-carbamoyl-4-pyridones **117** with a variety of organozinc compounds to afford 2-substituted-2,3-dihydro-4-pyridones **119** (Scheme 33). A chiral phosphoramidite ligand **118** promoted the copper catalyzed conjugate addition of diethylzinc to *N*-carbamoyl-4-pyridone **119** with good yield and enantioselectivity. The synthesis of optically pure 2-substituted 2,3-dihydro-4-pyridones in a single step is noteworthy.



Scheme 34: Corey's synthesis of cyclic enaminones.

In the same year, Corey and co-workers[53] utilized Hayashi's[54] protocol to synthesize optically enriched 5-substituted 2,3-dihydro-4-pyridones **121** during the enantioselective synthesis of a chiral C_3-symmetric bridgehead amine. Upon treatment with PhZnCl and TMSCl in presence of 5 mol % $[RhCODCl]_2$ and 11 mol % (*S*)-BINAP in THF, 4-pyridone **120** afforded **121** in 91% yield and 98.7 % ee (Scheme 34). This method provides a direct route to synthetically important 2,3-dihydropyridone derivatives.

Conclusion

The last 25 years has witnessed a plethora of methods developed toward the synthesis of enantiopure or enantioenriched cyclic enaminones, which are highly versatile and practically useful intermediates for the synthesis of azabicyclic natural products and heterocyclic compounds of biologically interest. In this brief review, we have attempted to highlight diverse synthetic methods leading to enantioenriched substituted 2,3-dihydro-4-pyridones using cyclic enaminones as versatile tools. The availability of asymmetric processes relying on substrate and reagent control to achieve high diastereo- and enantioselectivity offers a powerful arsenal of methods towards functionalized 2,3-dihydro-4-pyridones. The advent of catalytic methods, especially in aza-Diels-Alder cycloadditions and site-directed substitutions auger well for

future innovations in the field. These and related advances applying catalysis will heighten the immense potential of cyclic enaminones toward the asymmetric synthesis of complex azacyclic target compounds of biological relevance.

References

1 (a) A. S. Shawali *Arkivoc*, 2012, 383; (b) B. Govindh, B. S. Diwakar and Y. L. N. Murthy, *Org*. *Commun*., 2012,105; (c) C. M. Kascheres, J. Braz. Chem. Soc., 2003, **14**, 945; (d) J. P. Michael, C. B. de Koning, D. Gravestock, G. D. Hosken, A. S. Howard, C. M. Jungmann, R. W. M. Krause, A. S. Parsons, S. C. Pelly and T. V. Stanbury, *Pure Appl*. *Chem*., 1999, **71**, 979; (e) J. P. Michael and D. Gravestock, *Pure Appl*. *Chem*., 1997, **69**, 583; (f) J. V. Greenhill, *Chem*. *Soc*. *Rev*., 1977, **6**, 277.

2 (a) S. Joseph and D. L. Comins, Current opinion in drug discovery and development, 2002, **5**, 870; (b) D. L. Comins, *J. Heterocyclic Chem*., 1999, **36**, 1491.

3 (a) Y. Nakao, J. Chem, H. Imanaka, T. Hiyama, Y. Ichikawa, W. L. Duan, R. Shintani and T. Hayashi, *J. Am*. *Chem*. *Soc*., 2007, **129**, 9137; (b) R. Sebesta, M. G. Pizzuti, A. J. Boersma, A. J. Minnaard and B. L. Feringa, *Chem*. *Commun*, 2005, 1711; (c) D. L. Comins and M. O. Killpack, *J. Am*. *Chem*. *Soc*., 1992, **114**, 10972.

4 (a) Y. W. Kim and G. I. Georg, *Org*. *Lett*., 2014, **16**, 1574; (b) Y. W. Kim, M. J. Niphakis and G. I. Georg, *J. Org*. *Chem*., 2012, **77**, 9496; (c) L. Bi and G. I. Georg, *Org*. *Lett*., 2011, **13**, 5413; (d) Y.-Y. Yu, M. J. Niphakis and G. I. Georg, *Org*. *Lett*., 2011, **13**, 5932.

5 (a) X. Wang, B. J. Turunen, M. W. Leighty and G. Georg, *Tetrahedron Lett*., 2007, **48**, 8811; (b) S. Knapp, C. Yang, S. Pabbaraga, B. Rempel, S. Reid and S. G. Withers, *J. Org*. *Chem*., 2005, **70**, 7715.

6 (a) M. J. Niphakis and G. I. Georg, *J. Org*. *Chem*., 2010, **75**, 6019; (b) M. M. Martínez, L. A. Sarandeses and J. P. Sestelo, *Tetrahedron Lett*., 2007, **48**, 8536; (c) B. H. Wolfe, A. H. Libby, R. S. Al-awar, C. J. Foti and D. L. Comins, *J. Org*. *Chem*., 2010, **75**, 8564.

7 (a) E. Klegraf, S. Knauer and H. Kunz, *Angew*. *Chem*. *Int*. *Ed*., 2006, **45**, 2623; (b) R. Shintani, N. Tokunaga, H. Doi and T. Hayashi, *J. Am*. *Chem*. *Soc*., 2004, **126**, 6240.

8 (a) M. O. Garcia, A. R. Gomez, J. Adrio and J. C. Carretero, *J. Org*. *Chem*., 2007, **72**, 10294; (b) M. Ege and K. T. Wanner, *Org*. *Lett*., 2004, **6**, 3553.

9 D. L. Comins, X. Zheng and R. R. Goehring, *Org*. *Lett*., 2002, **4**, 1611.

10 See Part II. Accompanying article.

11 (a) D. L. Comins, S. P. Joseph and R. R. Goehring, *J. Am*. *Chem*. *Soc*., 1994, **116**, 4719; (b) D. L. Comins, R. R. Goehring, S. P. Joseph and S. O'Connor, *J. Org*. *Chem*., 1990, **55**, 2574.

12 D. L. Comins, J. T. Kuethe, H. Hong and F. J. Lakner, *J. Am*. *Chem*. *Soc*., 1999, **121**, 2651.

13 J. Streith, A. Boiron, T. Sifferlen, C. Strehler and T. Tschamber, *Tetrahedron Lett*., 1994, **35**, 3927.

14 (a) E. Klegraf, M. Follmann, D. Schollmeyer and H. Kunz, *Eur*. *J. Org*. *Chem*., 2004, 3346; (b) M. Follmann and H. Kunz, *Synlett*, 1998, 989.

15 T. Focken and A. B. Charette, *Org*. *Lett*., 2006, **8**, 2985.

16 (a) A. Lemire and A. B. Charette, *Org*. *Lett*., 2005, **7**, 2747; (b) A. Lemire, M. Grenon and A. B. Charette, *J. Org*. *Chem*., 2005, **70**, 2368.

17 T. J. Donohoe, M. J. Connolly, A. H. Rathi and L. Walton, *Org*. *Lett*., 2011, **13**, 2074.

18 (a) T. G. Back, and K. Nkajima *J. Org*. *Chem*., 2000, **65**, 4543; (b) T. G. Back, and K. Nkajima, *Org*. *Lett*., 1999, **1**, 261.

19 T. G. Back and M. D. Hamilton, *Org*. *Lett*., 2002, **4**, 1779.

20 (a) H. Seki and G. I. Georg, *Org*. *Lett*., 2011, **13**, 2147; (b) M. J. Niphakis, B. J. Turunen and G. I. Georg, *J. Org*. *Chem*., 2010, **75**, 6793; (c) B. J. Turunen and G. I. Georg, *J. Am*. *Chem*. *Soc*., 2006, **128**, 8702.

21 H. Seki and G. I. Georg, *J. Am*. *Chem*. *Soc*., 2010, **132**, 15512.

22 N. Gouault, M. L. Roch, C. Cornée, M. David and P. Uriac, *J. Org*. *Chem*., 2009, **74**, 5614.

23 N. Gouault, M. L. Roch, A. Chelgnon, P. Uriac and M. David, *Org*. *Lett*., 2011, **13**, 4371.

24 (a) S. Danishefsky and C. Vogel, *J. Org*. *Chem*., 1986, **51**, 3915; (b) S. Danishefsky, M. Langer and C. Vogel, *Tetrahedron Lett*., 1985, **26**, 5983; (c) Jr. J. Kervin and S. Danishefsky, *Tetrahedron Lett*., 1982, **23**, 3739.

25 W. Pfrengle and H. Kunz, *J. Org*. *Chem.,* 1889, **54**, 4263.

26 B. Kranke and H. Kunz, *Can*. *J*. *Chem*., 2006, **84**, 625.

27 H. Kunz and W. Pfrengle, *Angew*. *Chem*. *Int*. *Ed*., 1989, **28**, 1067.

28 T. Kohara, Y. Hashimoto, R. Shioya and K. Saigo, *Tetrahedron*: *Asymmetry*, 1999, **10**, 4831.

29 T. Kagawa, K Fujita and K. Kawada, *J. Fluorine Chem*., 2013, **152**, 77.

30 (a) H. Waldmann and M. Braun, *J. Org. Chem*., 1992, **57**, 4444. (b) H. Waldmann, M. Braun and M. Dräger, *Angew*. *Chem*. *Int*. *Ed*., 1990, **29**, 1468.

31 R. Kawęcki, *Tetrahedron*: *Asymmetry*, 2006, **17**, 1420.

32 T. Andreassen, T. Håland, L. K. Hansen and O. R. Gautun, *Tetrahedron Lett*., 2007, **48**, 8413.

33 C. Iwata and Y. Takemoto, *Chem*. *Commun*., 1996, 2497.

34 P. Szczésniak, S. Stecko, E. Maziarz, O. Staszewska-Krajewska and B. Furman, *J. Org*. *Chem*., 2014, **79**, 10487.

35 (a) K. Hattori and H. Yamamoto, *J. Org. Chem*., 1992, **57**, 3264; (b) K. Hattori and H. Yamamoto, *Tetrahedron*, 1993, **49**, 1749.

36 K. Ishihara, M. Miyata, K. Hattori, T. Tada and H. Yamamoto, *J. Am*. *Chem*. *Soc*., 1994, **116**, 10520.

37 S. K. Lee, U. K. Tambar, N. R. Perl and J. L. Leighton, *Tetrahedron*, 2010, **66**, 4769.

38 S. Kobayashi, S. Komiyama and H. Ishitani, *Angew*. *Chem*. *Int*. *Ed*., 1998, **37**, 979.

39 Y. Yamashita, Y. Mizuki and S. Kobayashi, *Tetrahedron Lett*., 2005, **46**, 1803.

40 (a) S. Yao, M. Johannsen, R. G. Hazell and K. A. JØrgensen, *Angew*. *Chem*. *Int*. *Ed*., 1998, **37**, 3121; (b) S. Yao, S. Saaby, R. G. Hazell and K. A. Jørgensen, *Chem*. *Eur*. *J*. 2000, **6**, 2435.

41 N. S. Josephsohn, M. L. Snapper and A. H. Hoveyda, *J. Am*. *Chem*. *Soc*., 2003, **125**, 4018.

42 O. G. Mancheño, R. G. Arrayás and J. C. Carretero, *J. Am*. *Chem*. *Soc*., 2004, **126**, 456.

43 C. A. Newman, J. C. Antilla, P. Chen, A. V. Predeus, L. Fielding and W. D. Wulff, *J. Am*. *Chem*. *Soc*., 2007, **129**, 7216.

44 D. Shang, J. Xin, Y. Liu, X. Zhou, X. Liu and X. Feng, *J. Org*. *Chem*., 2008, **73**, 630.

45 (a) D. M. Dalton, K. M. Oberg, R. T. Yu, E. E. Lee, S. Perreault, M. E. Oinen, M. L. Pease, G. Malik and T. Rovis, *J. Am*. *Chem*. *Soc*., 2009, **131**, 15717; (b) R. T. Yu and T. Rovis, *J. Am*. *Chem*. *Soc*., 2006, **128**, 2782.

46 E. E. Lee and T. Rovis, *Org*. *Lett*., 2008, **10**, 1231.

47 M. E. Oinen, R. T. Yu and T. Rovis, *Org*. *Lett*., 2009, **11**, 4934.

48 M. Á. Fernández-Ibáñez, B. Maciá, M. G. Pizzuti, A. J. Minnaard and B. L. Feringa, *Angew*. *Chem*. *Int*. *Ed*., 2009, **48**, 9339.

49 S. T. Chau, J. P. Lutz, K. Wu and A. G. Doyle, *Angew*. *Chem*. *Int*. *Ed*., 2013, **52**, 9153.

50 B.-L. Lei, Q.-S. Zhang, W.-H. Yu, Q.-P. Ding, C.-H. Ding and X.-L. Hou, *Org*. *Lett*., 2014, **16**, 1944.

51 (a) Z. Lu and S. Ma, *Angew*. *Chem*. *Int*. *Ed*., 2008, **47**, 258; (b) B. M. Trost and M. L. Crawley, *Chem*. *Rev*., 2003, **103**, 2921.

52 R. K. Dieter and F. Guo, *J. Org*. *Chem*., 2009, **74**, 3843.

53 X. Gao, R. P. Sing and E. J. Corey, *Org. Lett.*, 2010, **12**, 1812.
54 (a) R. Shintani, N. Tokunaga, H. Doi and T. Hayashi, *J. Am. Chem. Soc.*, 2004, **126**, 6240; (b) R. Shintani, T. Yamagami, T. Kimura and T. Hayashi, *Org. Lett.*, 2005, **7**, 5317.

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