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Review

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A concise review on the stereoselective synthesis of chiral α-bisamides using stereoselective Ugi-type reaction

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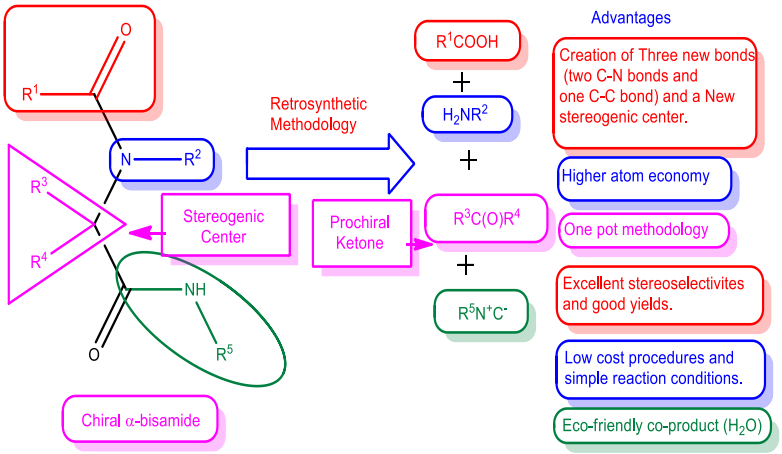
Abstract

To ensure a sustainable development, the "twelve principles of green chemistry" have been proposed for the field of synthetic organic chemistry. The stereoselective Ugi reaction is one of the most widely used reactions with high atom economy to prepare chiral α-bisamides and this reaction satisfies many of the green chemistry principles. The recent achievements in this reaction include one pot synthetic methodology, aqueous phase transformations and solvent free transformations even at ambient conditions. This review summarizes the progress recorded in this field over the past 20 years.



Retrosynthetic methodology for the synthesis of Chiral α-bisamide

Keywords: α-Bisamides, stereoselective Ugi reaction, green chemical transformations, multicomponent reaction, one pot synthesis, atom economy

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1. Introduction

The Ugi reaction involves a one-pot condensation of four components, an aldehyde or a ketone, an isocyanide, an amine, and a carboxylic acid to furnish **α-bisamides**.[1,2] In addition to three new bonds (two C-N bonds and one C-C bond) a new stereogenic center may be generated in this reaction by using a prochiral ketone / aldehyde having enantiotopic / diastereotopic faces. As one stereocenter can be generated, the search for its stereoselective version has become a much-desired goal among synthetic organic chemists. However, achieving the control of chirality in this reaction is still an extremely difficult task. This reaction can be carried out using one pot synthetic methodology and hence unnecessary derivatization steps such as protecting or deprotecting reactions can be avoided. To prevent waste or to maximize atom economy, these kinds of multicomponent reactions are to be encouraged not only in academic laboratories but also in industry. The recent developments in this field include the usage of aqueous phase transformations and solvent free transformations at ambient conditions. It offers high atom economy and low-cost production to access complex heterocycles within a short period of time using simple procedures. The control of stereochemical outcome is still a long-standing challenge. In case of its asymmetric version, the genesis of chirality is achieved by using chiral non-racemic compounds. In the past few years, stereoselective approaches have been realized by employing chiral catalysts, chiral substrates or chiral auxiliaries to obtain optically pure asymmetric chiral Ugi products. A wide range of natural products and pharmacologically relevant **α-bisamides** can be synthesized directly by using asymmetric version of the Ugi reaction.
Some examples are as follows:

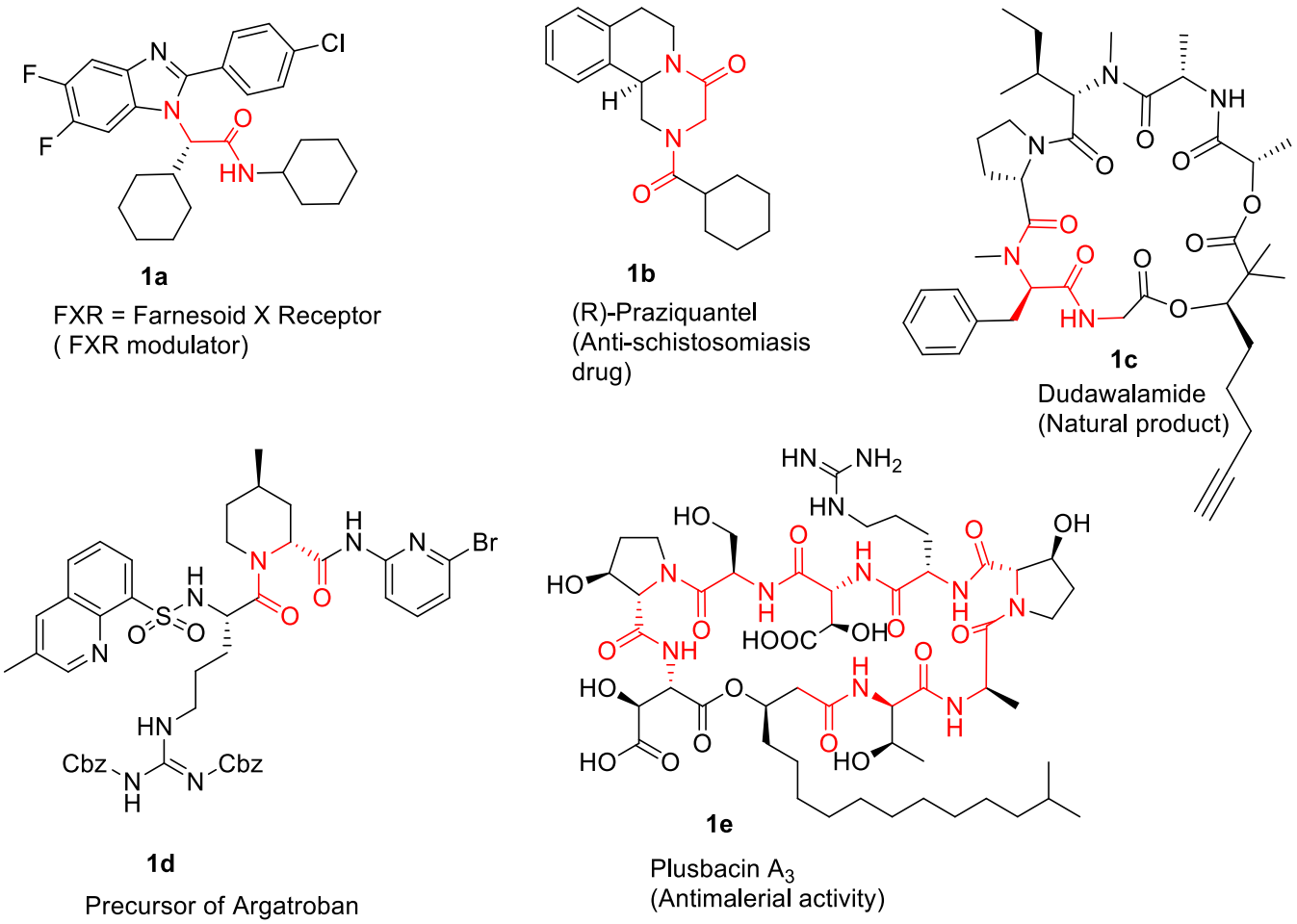
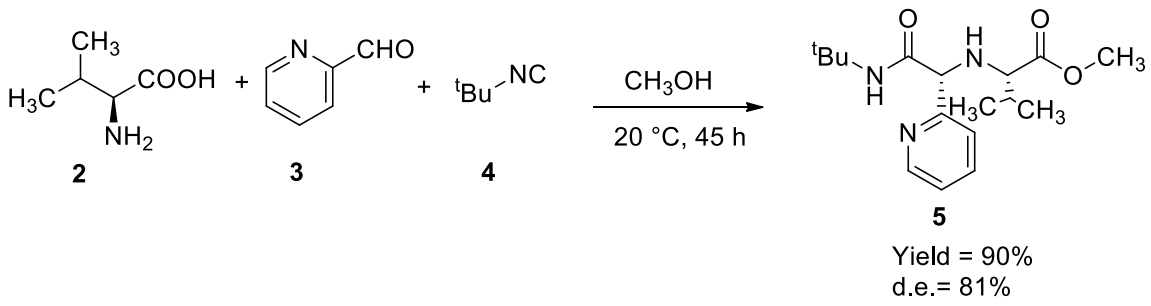


Figure 1

2. Asymmetric Ugi Reactions Involving Chiral Substrates

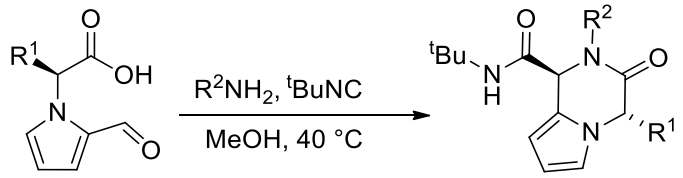
2.1. Chiral amino acid derivatives as substrate

In 2002, Dyker[3] and his group reported the synthesis of novel chiral ligands from amino acids by employing the Ugi reaction (Scheme 1). The amino acid L-valine **2** on condensation with pyridine-2-aldehyde **3** and *tert*-butyl isocyanide **4** in anhydrous methanol at room temperature afforded the Ugi product 1,1′-iminodicarboxylic acid derivative **5** in good yield and excellent diastereoselectivity. It is one of the first examples of an asymmetric Ugi reaction based on chiral amino acid as substrate. Ugi products can be further used as efficient ligands for enantioselective transition metal catalysis.



Scheme 1

In 2007, Nenajdenko[4] and his co-workers described the stereoselective outcome of a three component Ugi reaction involving chiral 2-(2-formyl-1*H*-pyrrol-1-yl) acetic acids **6a-c** prepared from natural L-amino acids **7a-c**, amines and tert-butyl isocyanide resulting in chiral substituted 3-oxo-1,2,3,4-tetrahydropyrrolo[1,2-α]pyrazines **7a** and **7b** which can act as effective aldol protease inhibitors (Scheme 2).

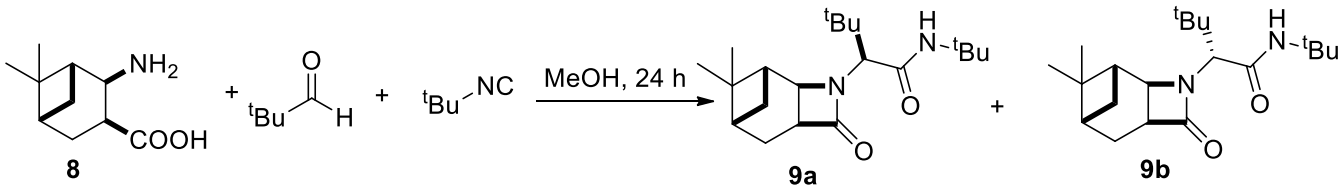


6a-c **7a-c**

	Yield (%)	d.r.
a : R^1= H , R^2= (1*R*)-PhEt	67	1.3:1
b : R^1= ^{s}Bu, R^2= (1*S*)-PhEt	62	3.6:1.
c : R^1= ^{s}Bu, R^2= (1*R*)-PhEt	65	4.0:1

Scheme 2

In 2009, Szakonyi[5] and his co-workers reported a stereoselective four centered three component Ugi reaction starting from (1*R*,2*R*,3*S*,4*R*)-2-Amino-6,6-dimethylbicyclo [3.1.1]heptane-3-carboxylic acid **8**, aldehyde and isocyanide in methanol to synthesize enantiomerically pure β-lactams **9a** and **9b** (Scheme 3). Reaction proceeds smoothly to give a mixture of diastereomers, which can be separated easily.



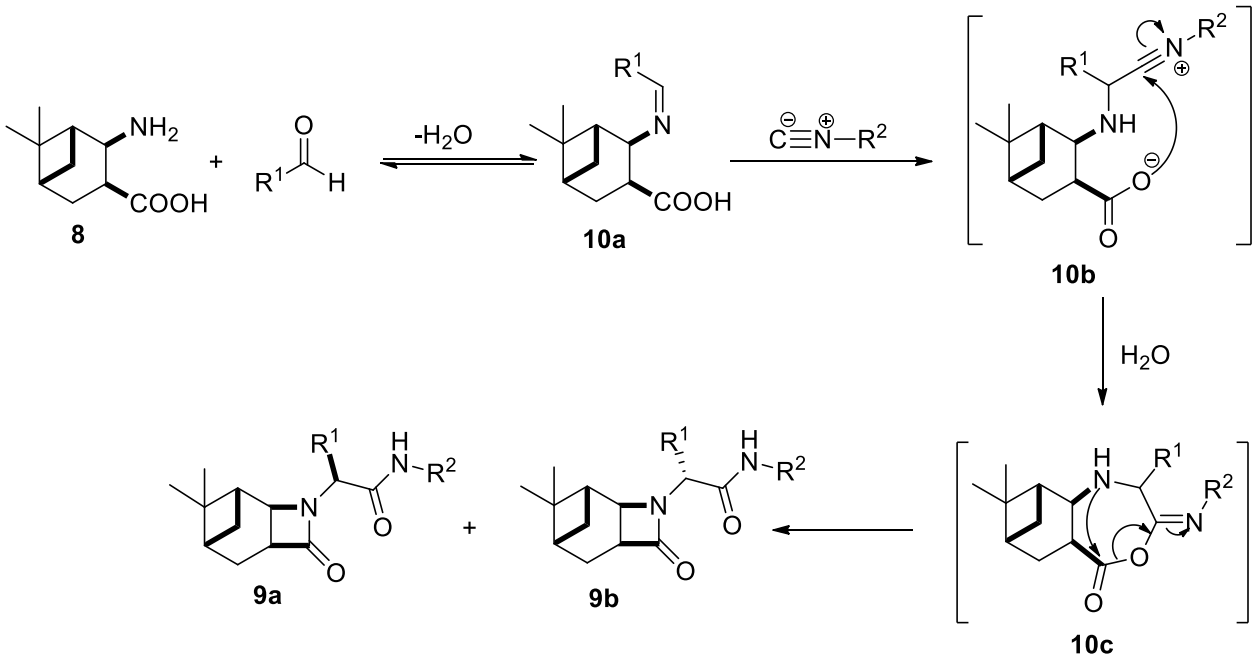
8 **9a** **9b**

d.r.= 100:0
yield = 75%

Scheme 3

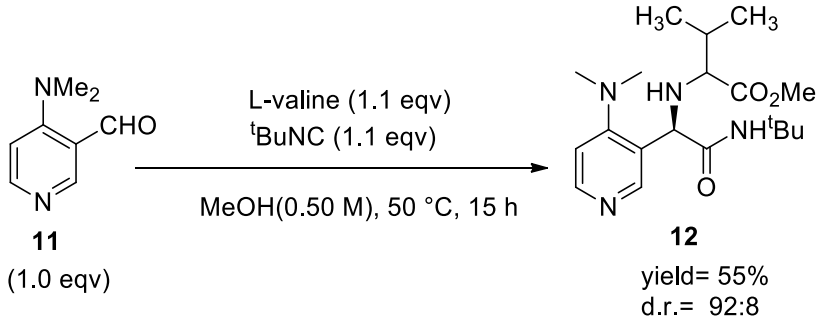
Plausible mechanism

β-Lactam ring generation starts through the formation of Schiff base intermediate **10a**. The next step includes nucleophilic addition of isocyanide on to the intermediate **10a**, followed by generation of product **9a** and **9b**. The approach of the isocyanide from the *Si* face is sterically hindered by existing dimethylmethylene bridge of **10a** resulting a minor product **9b**. Steric interactions are absent for *Re* face mediated nucleophilic addition process and hence it proceeds preferentially resulting the major product **9a** (Scheme 4).



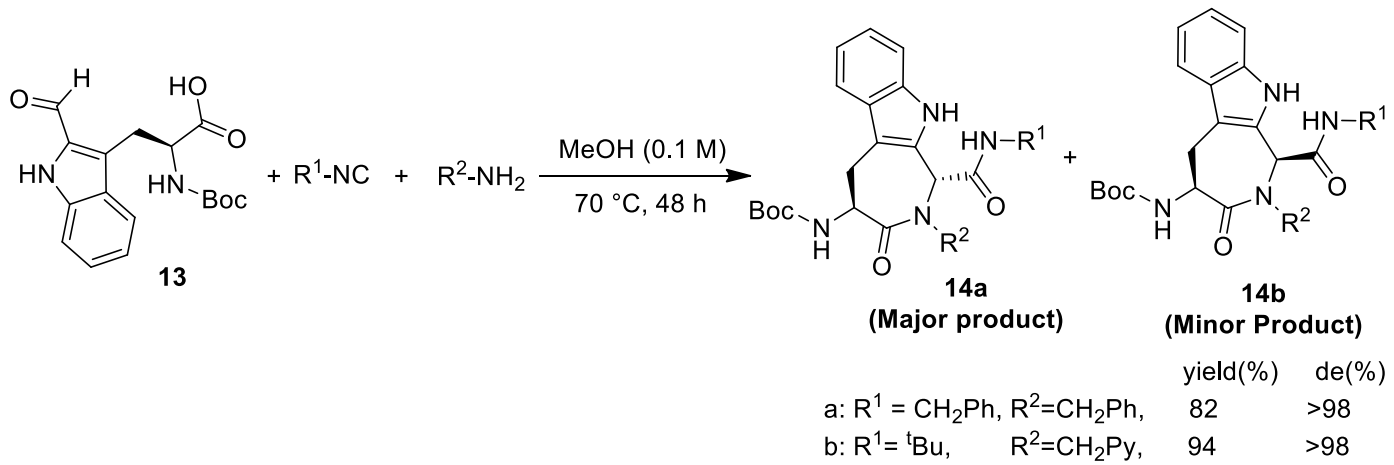
Scheme 4

In 2011, Mondai[6] reported a diastereoselective Ugi reaction of 4-(dimethylamino)nicotinaldehyde **11** with α-amino acids and *tert*-butyl isocyanide to obtain (1*R*) *N*-(1-(*N*-*tert*-butylcarbamoyl)-1-(4-(dimethylamino)pyridyn-3-yl)methyl)-L-valine methyl ester **12** in moderate yield and 92:8 diastereoselectivity (Scheme 5). These DMAP derivatives are of interest as they are potential enantioselective organocatalysts for asymmetric transformations.



Scheme 5

A new diastreoselective Ugi three component reaction involving 2-formyl-L-tryptophan **13** as a bifunctional unit, isocyanide and amine to synthesize 1-carbamoyl-4-amino-1,2,4,5-tetrahydroindolo[2,3-c]azepin-3-one derivatives **14a-b** was described by Jida[7] and his group in the year 2013 (Scheme 6). The desired seven membered heterocyclic products are obtained in high yield and excellent diastereomeric excess (de >98%).



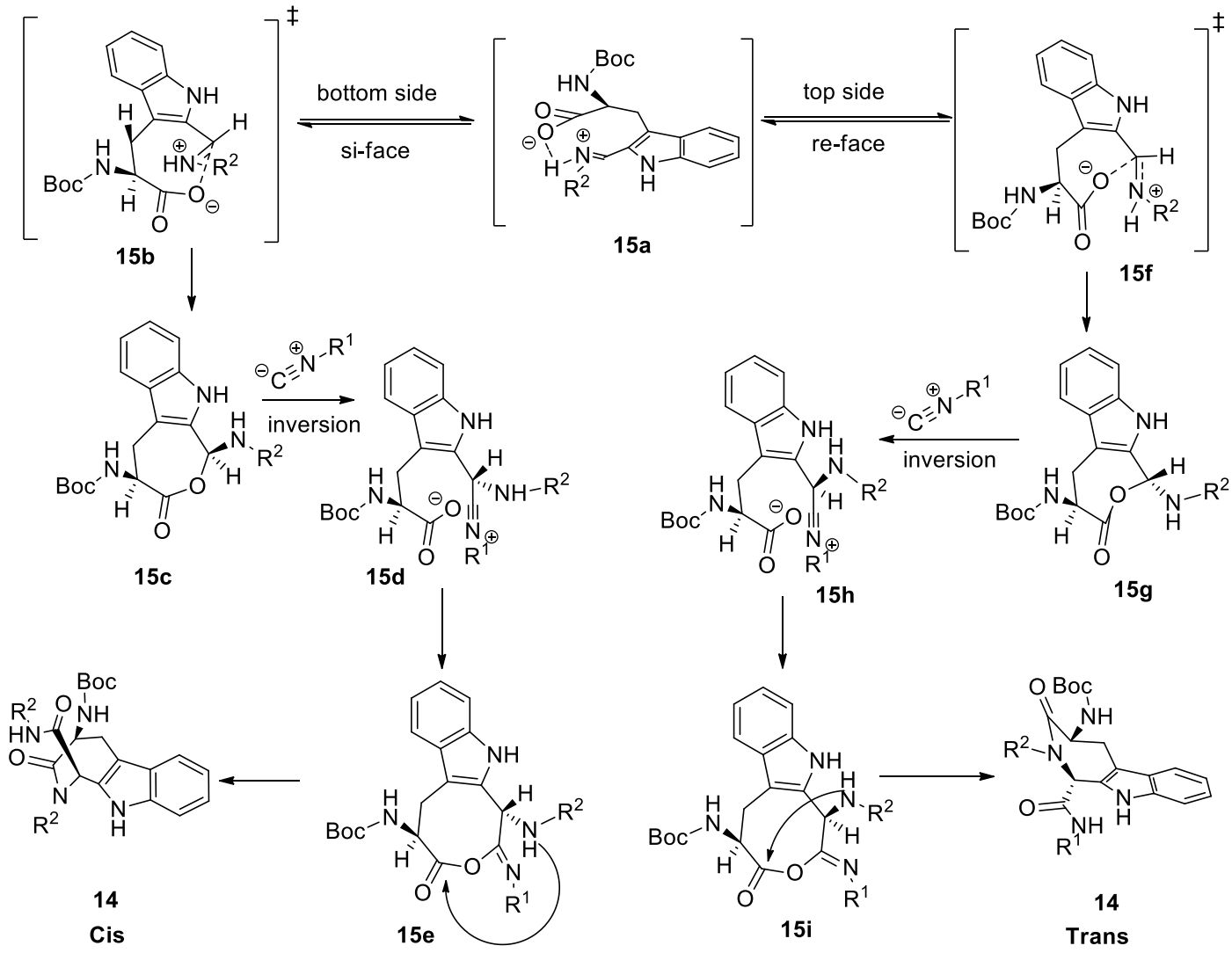
	yield(%)	de(%)
a: R^1 = CH_2Ph, R^2=CH_2Ph,	82	>98
b: R^1= ^tBu, R^2=CH_2Py,	94	>98

Scheme 6

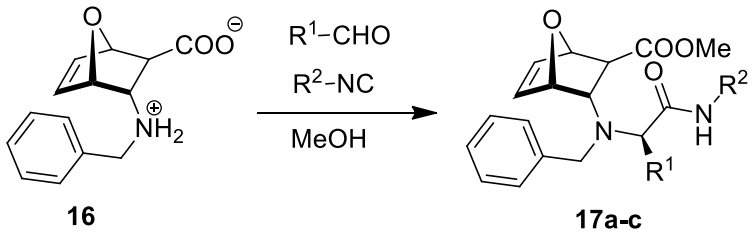
Mechanism

A plausible mechanism for this protocol (Scheme 7) proceeds via intermediate **15a.** Formyltryptophan **13** and amine react to give an iminium ion which then gets protonated intramolecularly by carboxylic acid to generate pseudocyclic intermediate **15a**. In the next step, carboxylate can then attack from the *Re* face giving a transition state **15f** in which the substituent on nitrogen is in pseudoequatorial position where unfavorable allylic strain with indole N-H is absent. Substitution by isocyanide leads to inversion of configuration giving an intermediate **15h** which then rearranges to **15i** followed by acyl transfer to give trans isomer as major product. Alternatively, carboxylate can attack **15a** from the *Si* face giving an unfavorable transition state **15b**. Attack of isocyanide and acyl transfer in later steps results in *cis* isomer as minor product.

In 2012, Banfi[8] and his co-workers reported an asymmetric Ugi reaction of oxanorbornene β-amino acid derivative **16** leading to a bicyclic peptidomimetics **17a-c** with moderate to high yield and diastereo selectivities (Scheme 8). The generality and postulated mechanism for this reaction has been described.



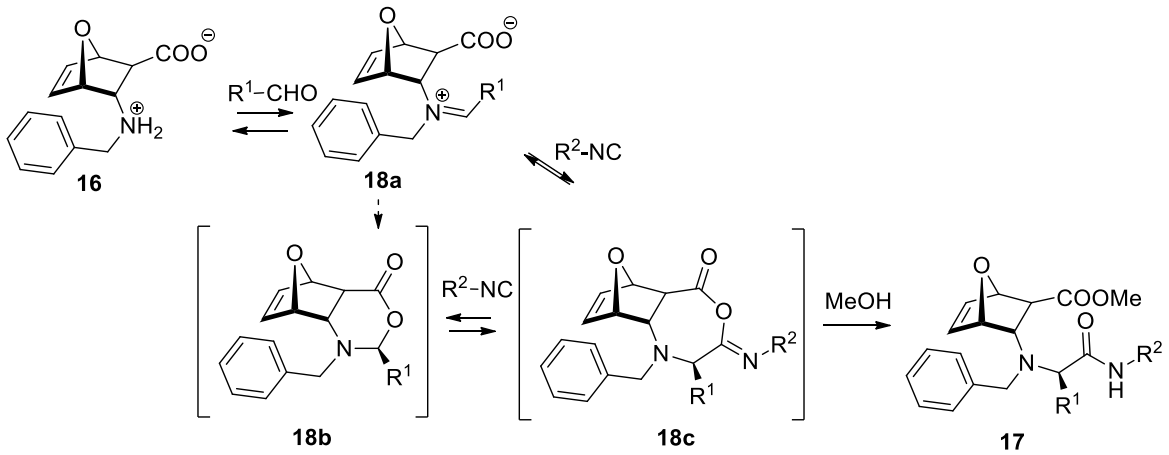
Scheme 7



			d.r.	Yield
a:	R^1=Ph	R^2=^{n}Bu	83:17	97%
b:	R^1=Et	R^2=^{n}Bu	>95:5	80%
c:	R^1=Ph	R^2=cHex	83:17	98%

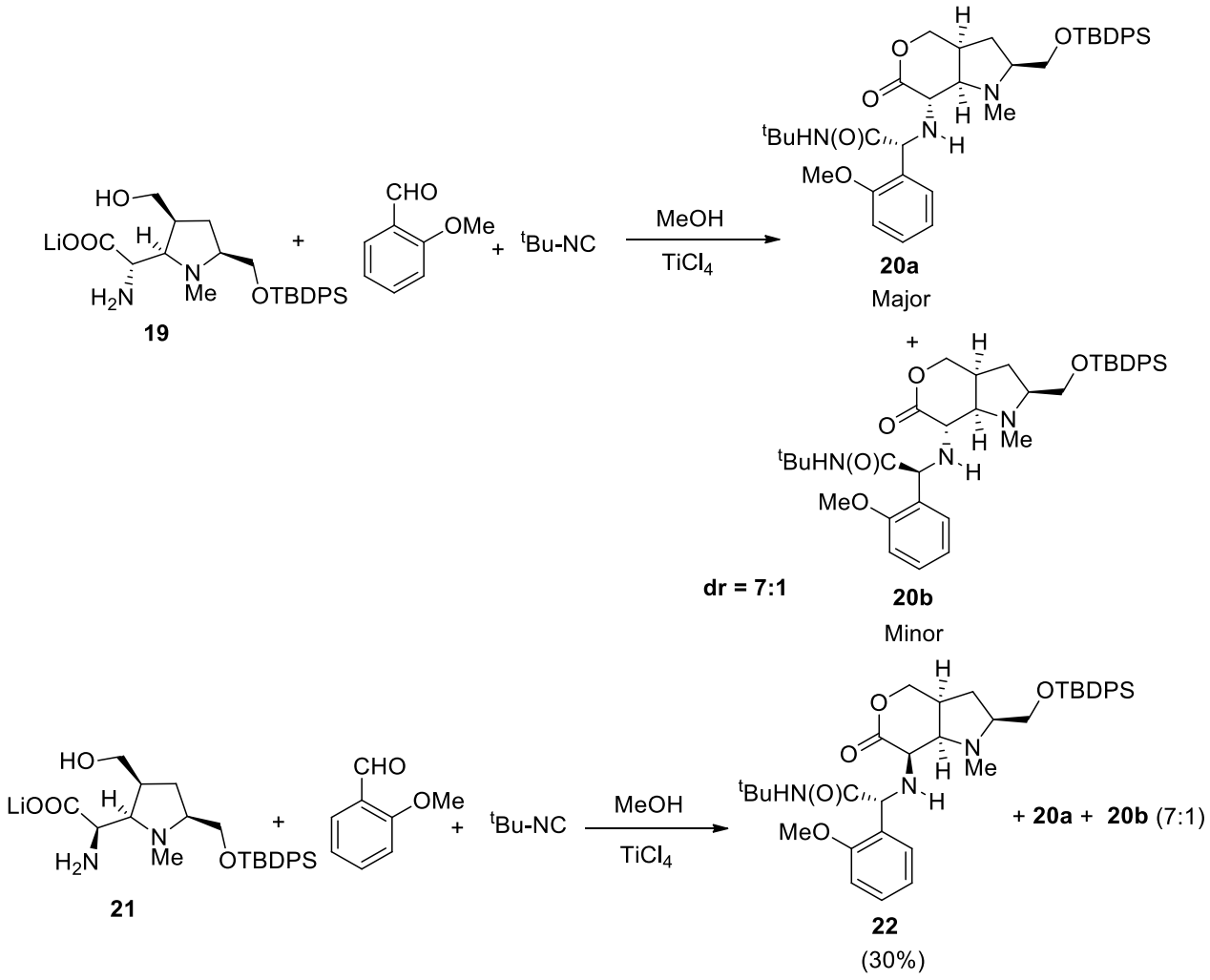
Scheme 8

Mechanism



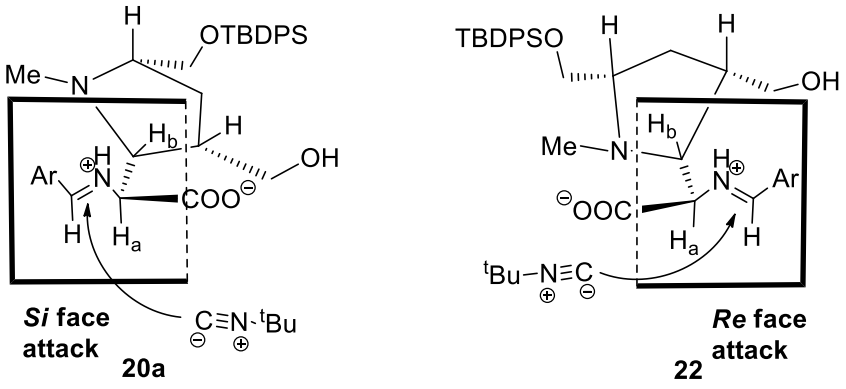
Scheme 9

In 2012, Turner[9] and his co-workers reported a stereoselective Ugi reaction of carboxylate salt of amino acids **19** and **21**, aromatic aldehyde, and isocyanides in presence of catalytic amount of titanium (IV) chloride for synthesis of peptide mimics **20** and **22** (Scheme 10). A nonchelated model (Scheme 11) has been proposed to explain mechanism of this reaction.



Scheme 10

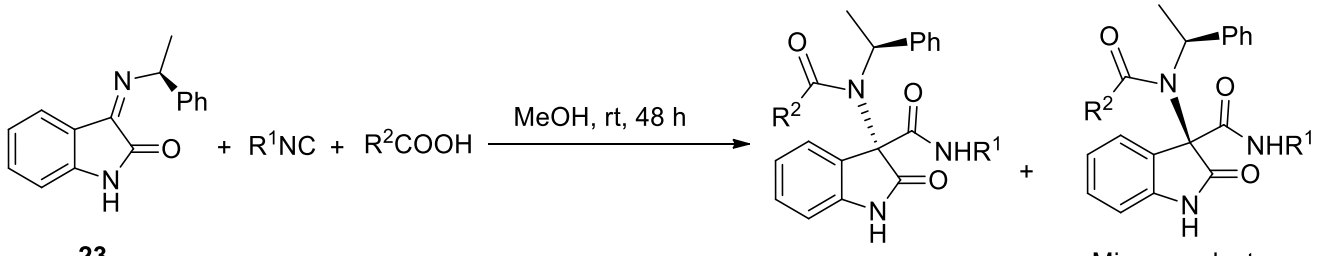
Proposed Mechanism:



Scheme 11

2.2 Chiral imine as substrate

A novel protocol for the synthesis of chiral 3,3-disubstituted 3-amino-2-oxindoles **24a-c** using (*S*,*Z*)-3-((1-phenylethyl)imino)indolin-2-one **23**, various isocyanide and acid components as precursor using methanol as solvent has been described by Lesma[10] and his co-workers in 2014 (Scheme 12). This one pot Ugi reaction represents the first example of isocyanide based multicomponent reaction involving an isatin-derived ketimine. Chiral 3,3-disubstituted 3-aminooxoindole motifs are present in various natural products and biologically active molecules.

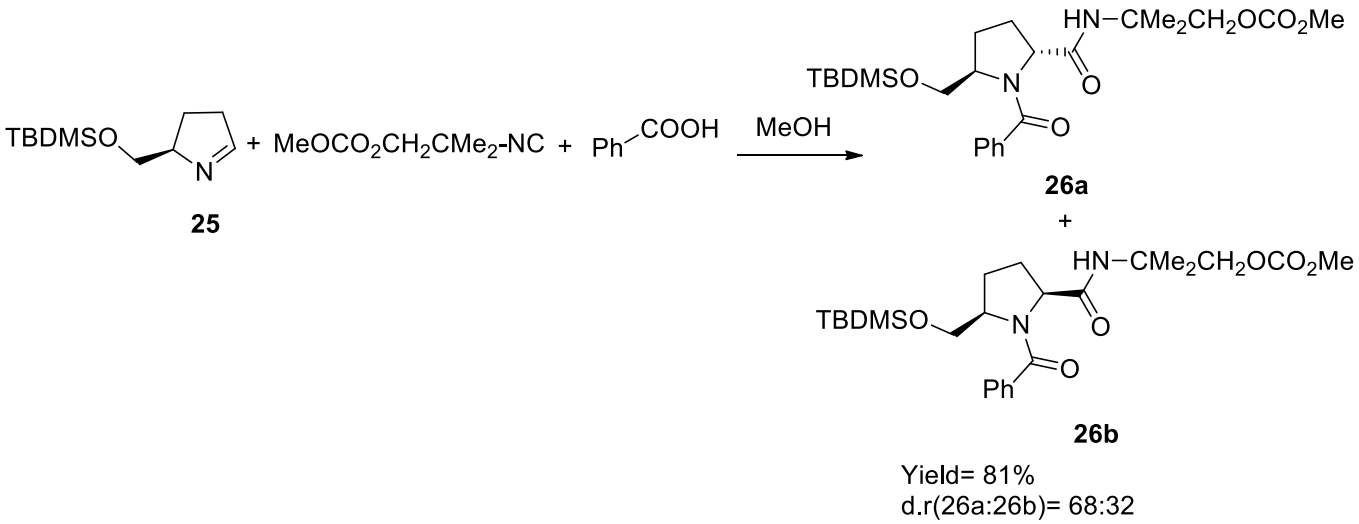


24a-c

	Yield,	d.r.
a:R^1=^{t}Bu, R^2=CF_3	77%	89:11
b:R^1=CH_2COOMe, R^2=CF_3	70%	63:37
c:R^1=Bn, R^2=HCOOH	70%	64:36

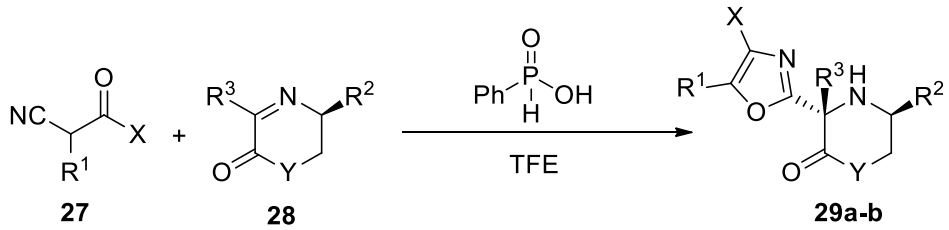
Scheme 12

A new efficient enantioselective and diastereoselective synthesis of *N*-acyl-2,5-disubstituted pyrrolidine **26a** and **26b** through a multicomponent Ugi reaction has been described by Banfi[11] and co-workers in 2008, using pyrrolines **25** as cyclic imine, 2-isocyano-2-methylpropyl methyl carbonate and 2-phenylacetic acid (Scheme 13). Pyrrolidines can be further used as substrate for synthesis of many bicyclic derivatives.



Scheme 13

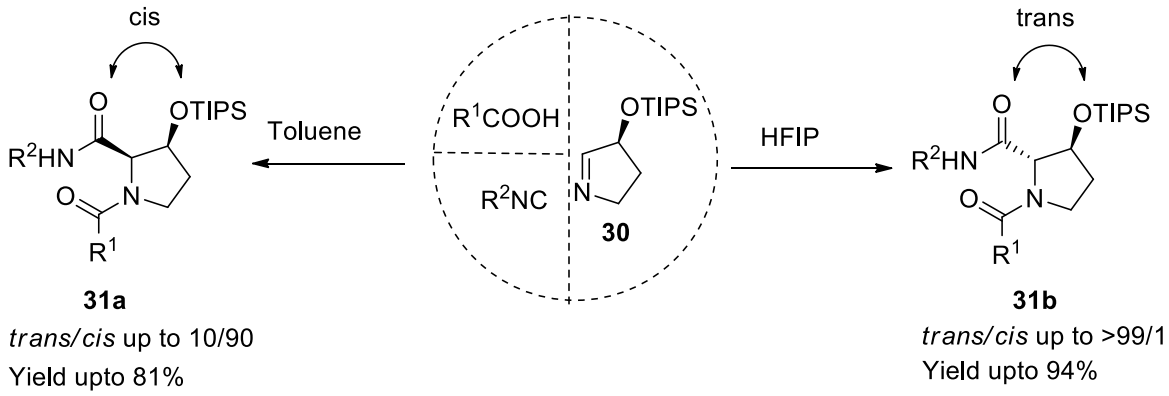
A new catalytic Ugi-type condensation of α-isocyanoacetamide **27** and chiral cyclic imine **28** has been developed by Chen[12] and his co-workers in 2012 where a combination of phenyl phosphilic acid and trifluoroethanol was used as catalytic system to promote the aforementioned reaction. Under mild conditions, the reaction of **27** and **28** proceeded quickly to give 3-oxazolyl-morpholin or piperazine-2-one derivatives **29a-b** in excellent yield and good diastereoselectivity (Scheme 14).



				Yield (%)	D.r.
a: R^1=H,	R^2=Bn, R^3=Me	Y=O	X=morpholinyl	86	14:1
b: R^1=Me,	R^2=Bn, R^3=Me	Y=O	X=morpholinyl	92	single

Scheme 14

In 2016, Katsuyama[13] and his group investigated on the effect of solvents on diastereoselectivity of Joullié-Ugi reaction of cyclic α-siloxyimine **30**, isocyanides and acids affording 3-hydroxyproline derivative (Scheme 15). It was observed that cis and trans isomers were obtained in toluene and 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) respectively.



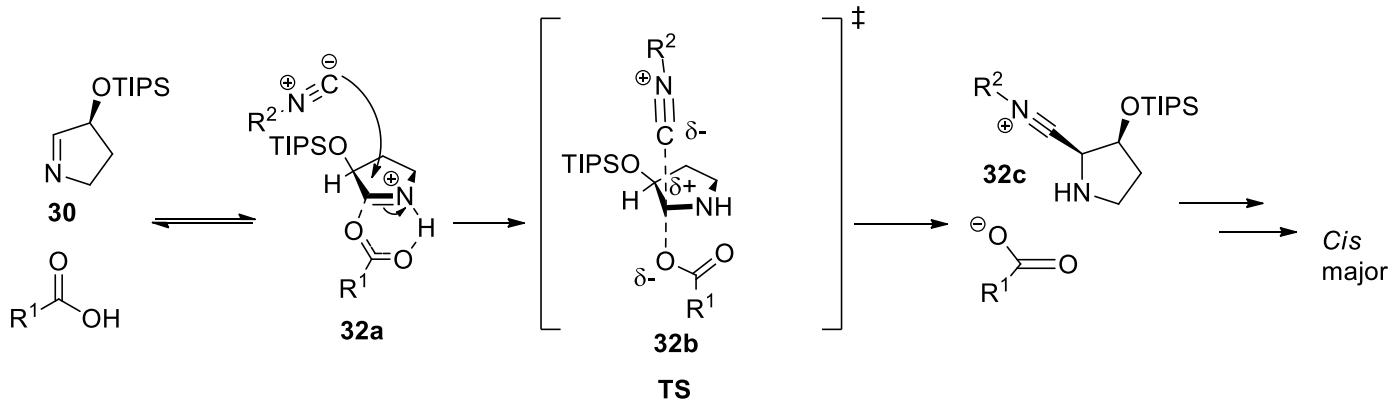
Scheme 15

Mechanism

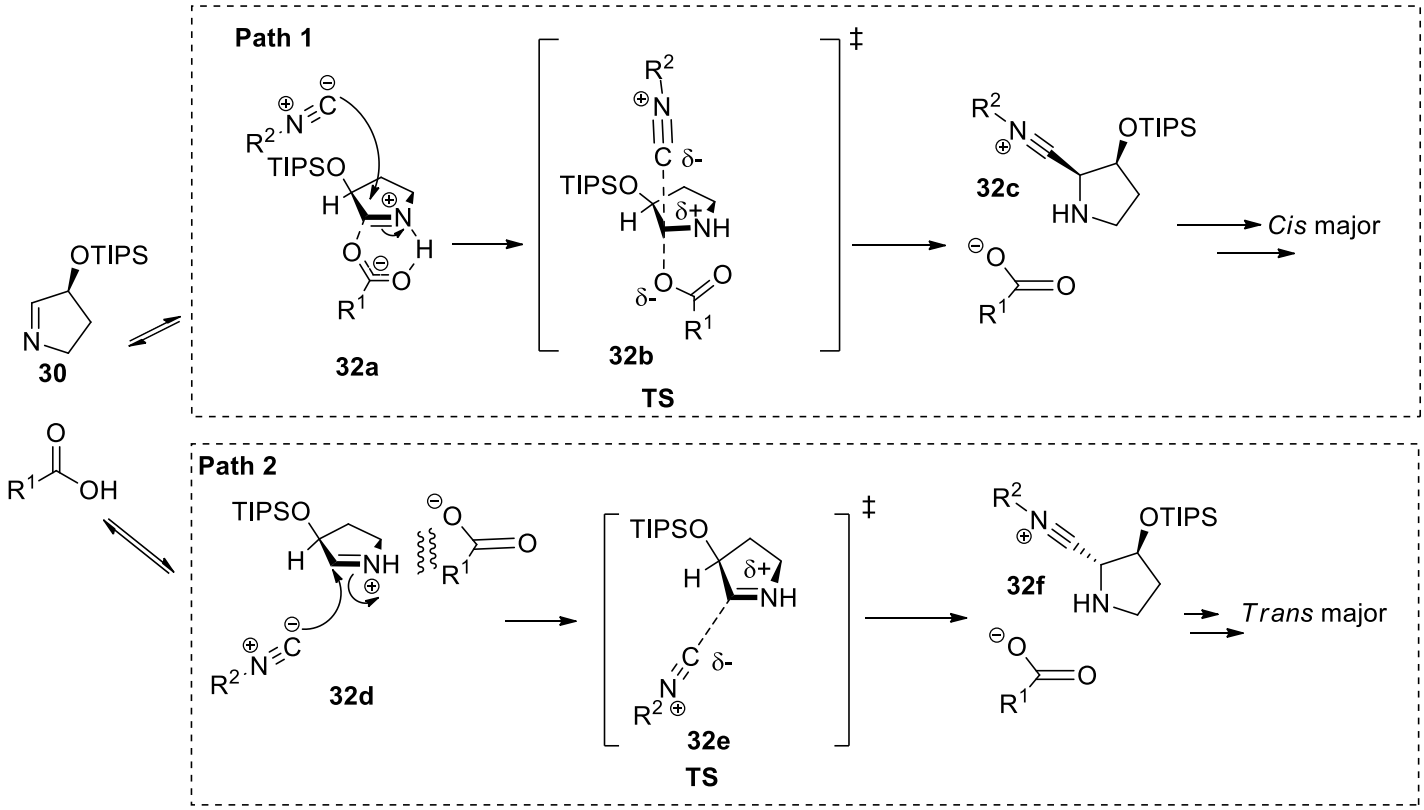
The stereochemical outcome can be explained in terms of two different structures of ion pair as intermediate in Joullié-Ugi three component reactions (Scheme 16). In non-polar solvent like toluene, imine **30** gets protonated by carboxylic acid to form a contact-oriented ion pair **32a**, which is stabilized by coulombic forces prominent in non-polar solvents. This results in an S_N2-type transition state **32b** in which positive charge is stabilized by carboxylate ion giving *cis* isomer as major product. However, in polar solvents like HFIP, a solvent-separated ion pair **32d** also exist along with contact-oriented ion pair **32a**. Therefore, when isocyanide reacts with the former, isocyanide attacks iminium ion from opposite side of bulky siloxy group forming an S_N1-type transition state **32e** where positive charge is not stabilized by carboxylate ion, thus it affords the *trans* isomer and on reaction with **32a** it results in *cis* isomer as in non-polar solvent.

In 2017, Zarezin[14] and his group reported a diastereoselective azido-Ugi reaction employing 2-(*tert*-butyl)pyrrolidine **33**, isobutyraldehyde, benzyl isonitrile and trimethylsilyl azide as substrates in an alcoholic solvent. This protocol provides a short and efficient route for synthesis of tetrazole derivatives **34** with high control of diastereoselectivity (d.r. up to 100:0) and excellent yield (≤ 98%). Tetrazoles are of interest due to their broad applicability in medicinal chemistry (Scheme 17)[15].

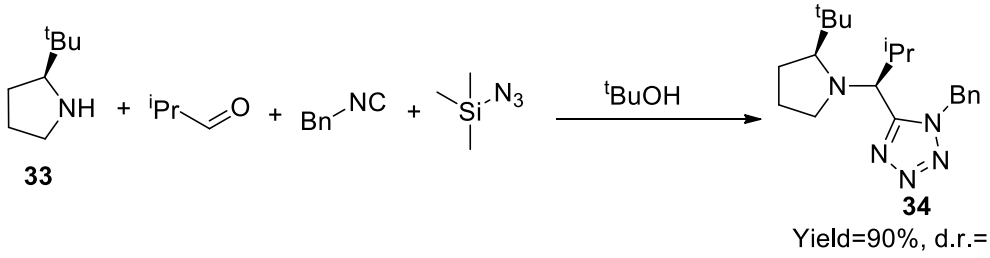
(a) In toluene solvent



(b) In HFIP solvent

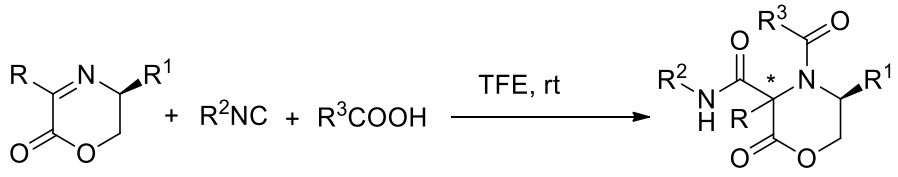


Scheme 16



Scheme 17

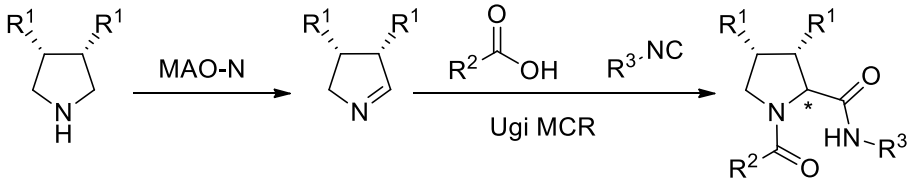
Zhu[16] and his co-workers developed a new asymmetric three-component Ugi reaction of cyclic ketoimines **35** with isocyanides and carboxylic acids to afford novel morpholin-2-one-3-carboxamide **36a-c** in the year 2010 (Scheme 18). Cyclic imines show great potential for stereoinduction of new chiral center in the desired Ugi products. Morpholin-2-one-3-carboxamide is important in medicinal and pharmaceutical chemistry[17].



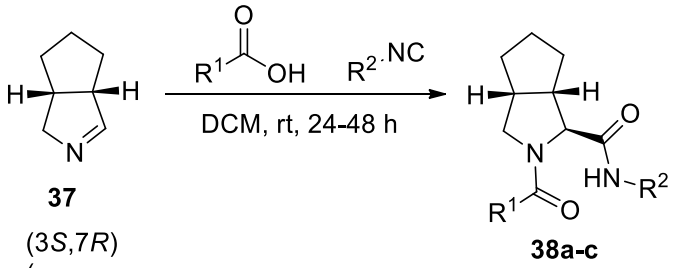
					Yield	D.r.
a: R^1=Ph	R=Me	R^2=^{t}Bu	R^3=H		76%	3.9:1
b: R^1=Ph	R=Me	R^2=^{n}Bu	R^3=H		81%	8.2:1
c: R^1=Ph	R=Me	R^2=Cy	R^3=H		86%	4.6:1

Scheme 18. Synthesis of 5-substituted morpholin-2-one-3-carboxamide derivatives from ketoimines

The absolute configuration of the major diastereomer was determined through a NOESY experiment.
In 2010, Znabet[18] and his group developed an efficient combination of desymmetrization of meso-pyrrolidines using monoamine oxidase (MAO-N) as biocatalyst with Ugi multicomponent reaction for stereoselective synthesis of 3,4-substituted prolyl peptides which are important in medicinal chemistry (Scheme 19).

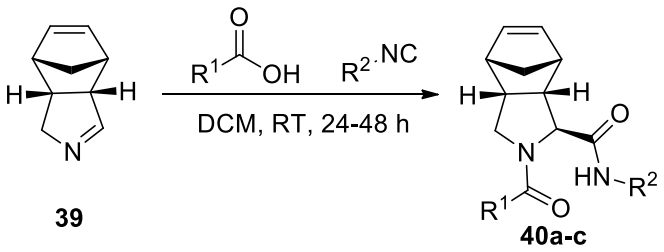


Scheme 19



			Yield (%)	d.r.	ee (%)
a: R^1=Me,	R^2=^{t}Bu		73	93:7	95
b: R^1=Ph,	R^2=^{t}Bu		80	93:7	94
c: R^1=Ph,	R^2=Bn		81	92:8	97

Scheme 20

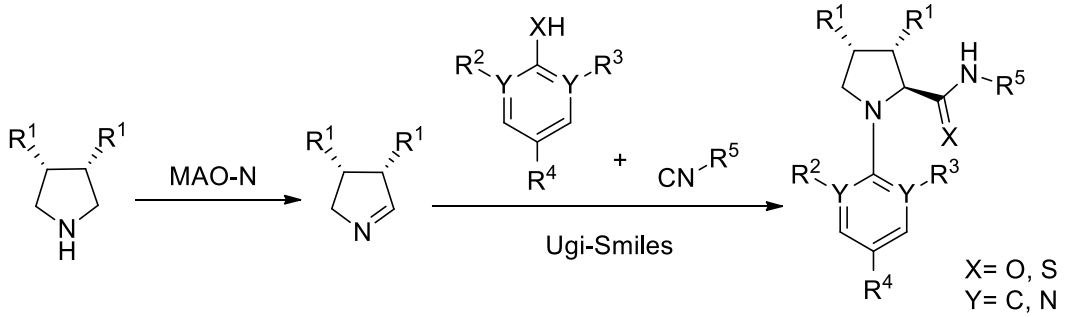


39 **40a-c**

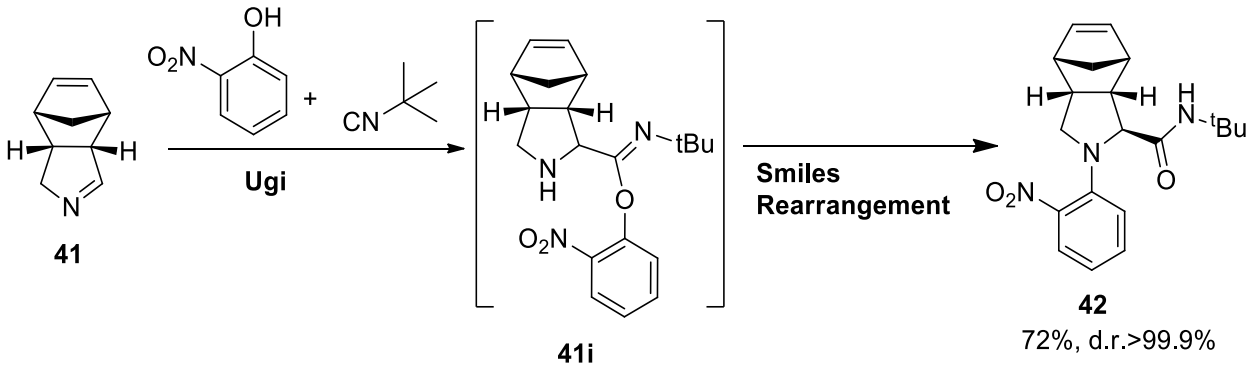
.	Yield (%)	d.r.	ee (%)
a:R^1=Me, R^2=^{t}Bu	83	>99:1	>99
b:R^1=Ph, R^2=^{t}Bu	82	>99:1	>99
c:R^1=furyl, R^2=^{i}Pr	75	>99:1	>99

Scheme 21

In 2012, Znabet[19] and his group developed an efficient combination of MAO-N-catalyzed desymmetrization of cyclic meso-amines with Ugi-Smiles multicomponent reaction to synthesize chiral N-aryl proline amides (Scheme 22).



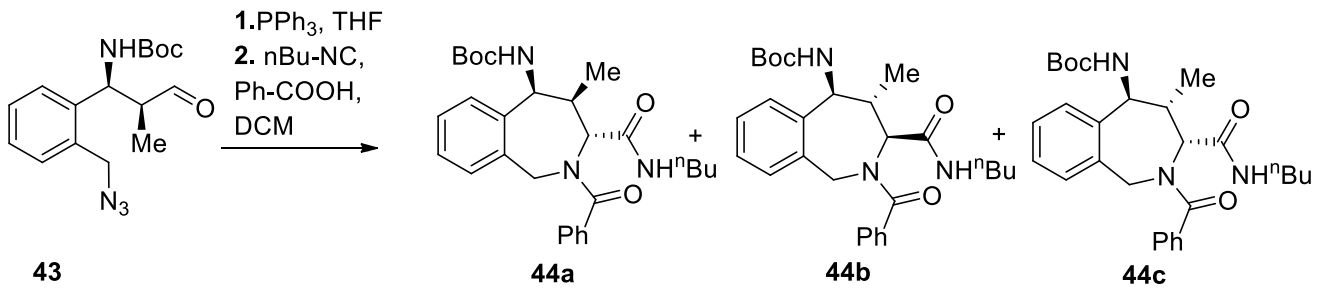
Scheme 22



41 **41i** **42**
72%, d.r.>99.9%

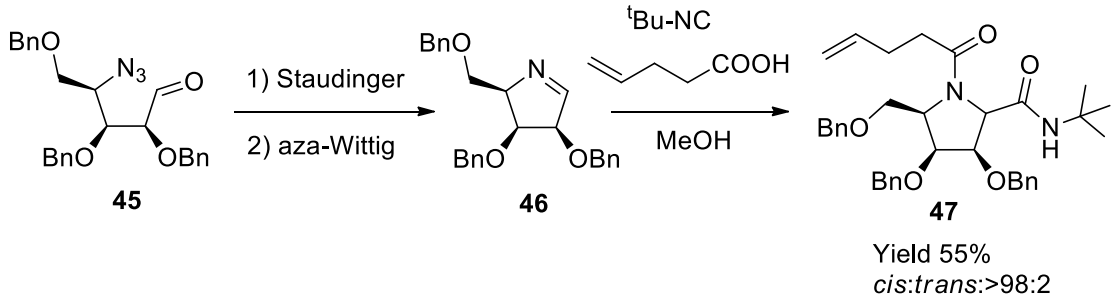
Scheme 23

In 2014, Moni[20] and his group synthesized an optically pure aldehyde **43** and employed it in Staudinger/aza-Wittig/Ugi-Joullié reaction sequence leading to diastereomeric mixture of 4,5-dihydro-1*H*-benzo[c]azepines **44a**, **44b** and **44c** in modest to good yield and diastereoselectivities (Scheme 24).



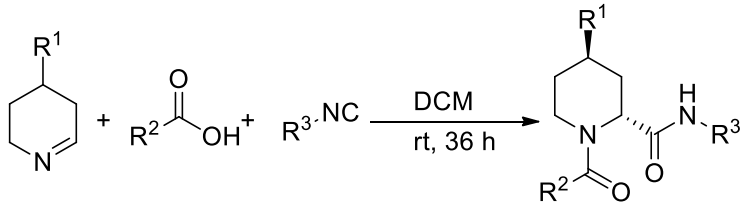
Scheme 24

In 2013, Rijsel[21] and his group reported an Ugi reaction involving chiral pyrroline **46** formed from Staudinger-aza-Wittig reaction of a D-pentose-derived 4-azido aldehyde **45** leading to pyrrolidine derivative **47** in moderate yield and high diastereoselectivities favoring the cis isomer (Scheme 25).



Scheme 25

In 2019, van der Heijden[22] and his co-workers reported a highly diastereoselective Ugi reaction of Δ^1-piperideines, various isocyanides and carboxylic acids for the synthesis of pipecolic amides **49a-b** (Scheme 26).



Yield

a: R^1=Ph, R^2= CH_3, R^3=^{t}Bu, 95%

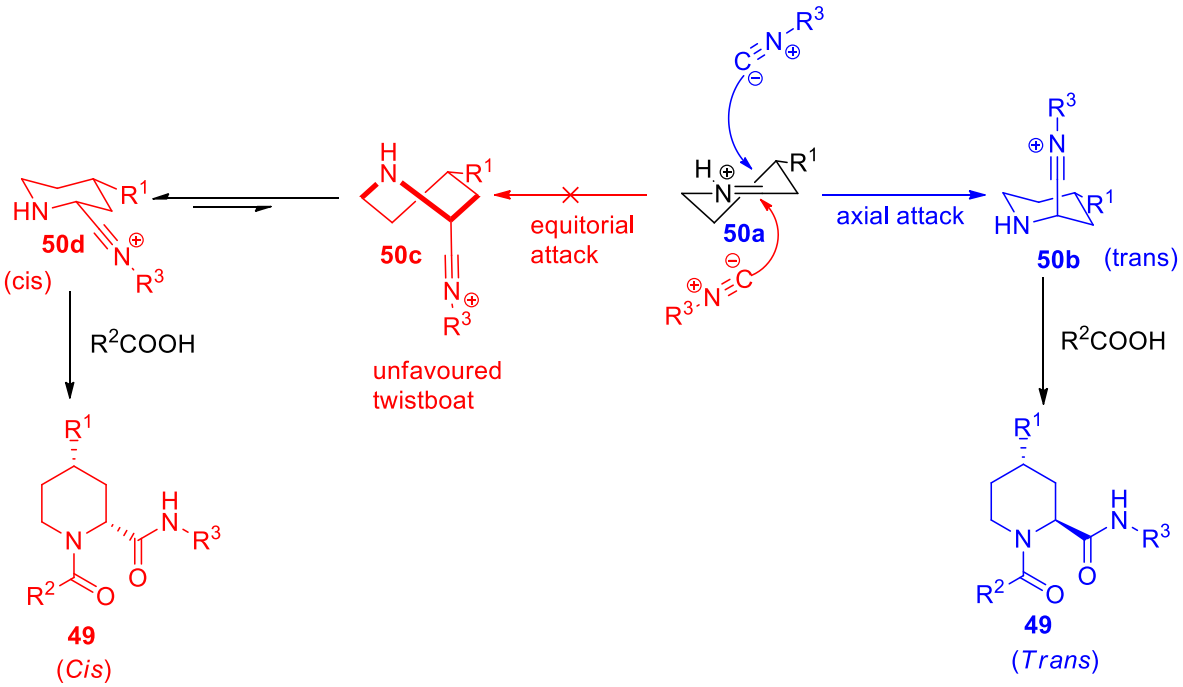
b: R^1=Et, R^2=^{t}Bu, R^3=Cy, 79%

Scheme 26

Mechanism

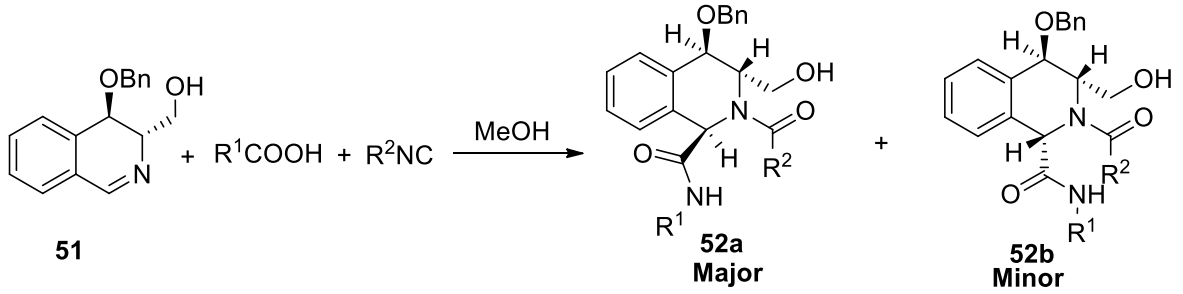
The observed diastereoselectivity can be explained by Fürst-Plattner rules. Δ^1-piperideine on protonation by carboxylic acid affords an iminium ion having half chair conformation **50a** where alkyl substituent occupies a

pseudo-equatorial position. In the next step, since equatorial attack of isocyanide gives an unfavorable twist-boat conformation, so it attacks from top face (axial attack) giving a more favorable chair conformation **50b**. As a result, trans-pipecolic amide **49** is formed exclusively (Scheme 27).



Scheme 27

In 2015, Ramanivas[23] and his co-workers reported a highly diastereoselective Ugi reaction of 3,4-dihydroisoquinolines (DHIQs) **51**, isocyanides and carboxylic acids leading to optically pure 1,2,3,4-tetrahydroisoquinolines (THIQs) **52a-b**. Computational studies demonstrated that the relative stereochemistry at C-2 and C-3 in DHIQ controls the addition if isocyanide at C-1 giving rise to efficient diastereoselectivity in THIQs (Scheme 28).

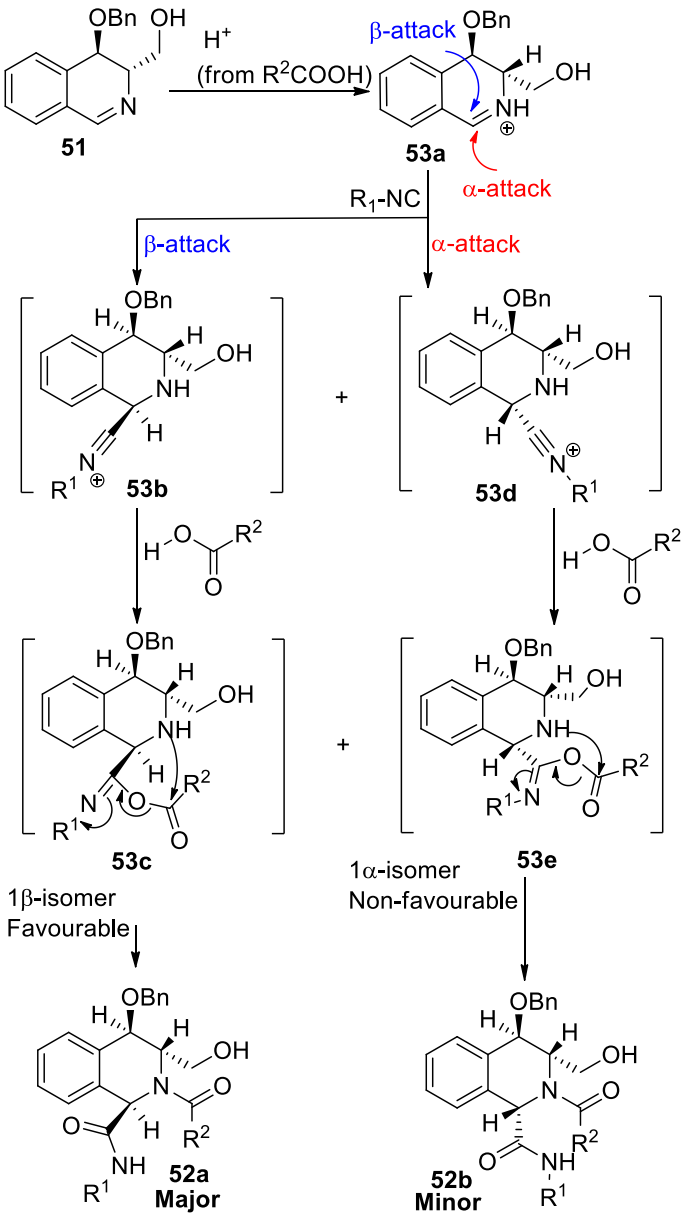


52a-b	Yield,	d.r.
a: R^1=Ph-NO_2, R^2= ^{t}Bu	89%	89:11
b: R^1=CH_2Ph NO_2, R^2= ^{t}Bu	61%	95:5

Scheme 28

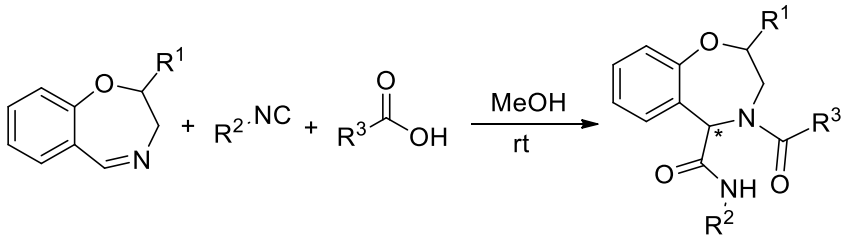
Mechanism

Imine **51** gets protonated by carboxylic acid to give iminium ion **53a**. From computational studies it was found that isocyanide prefers to attack from more favorable *Si* face resulting intermediate **53b** followed by reaction with acid to give more stable intermediate **53c** which then rearranges to final product **52** as major diastereomers.



Scheme 29

In 2011, Banfi[24] and his co-workers reported Ugi reaction of 2-substituted dihydrobenzoxazepines **54** leading to synthesis of tetrahydrobenzoxazepine derivative **55a-c** using methanol as solvent at room temperature (Scheme 30). It is the first example of asymmetric Ugi reaction involving seven membered cyclic imines.

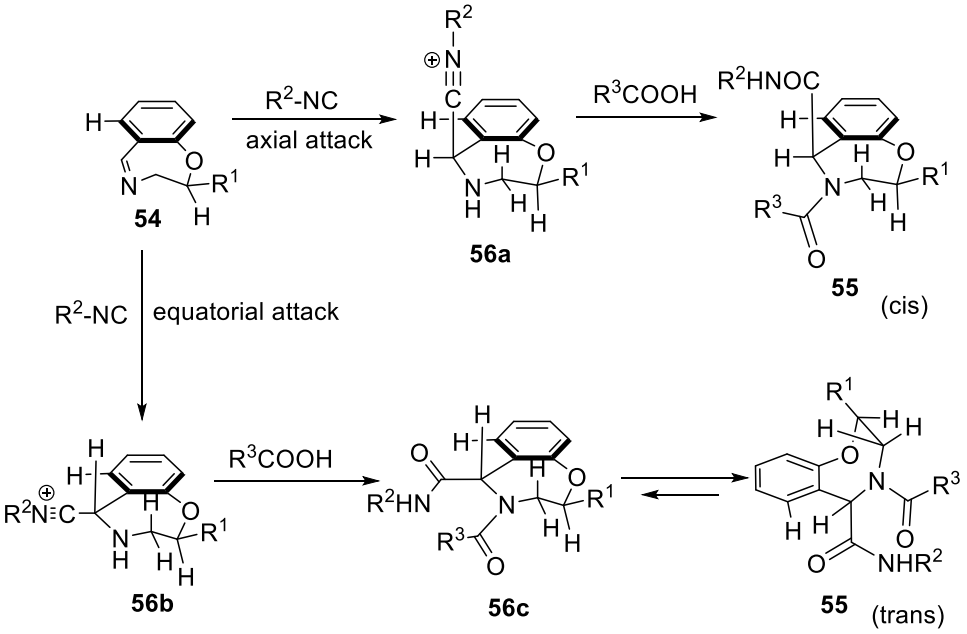


	Yield	d.r.
a:R^1=Me, R^2=Cy, R^3=Et	70%	85:15
b:R^1=^{i}Bu, R^2=^{t}Bu, R^3=5-Cl-2-thienyl	78%	89:11
c:R^1=^{i}Bu, R^2=4-BnOC$_6$H$_4$CH$_2$CH$_2$, R^3=CH$_2$OMe	56%	90:10

Scheme 30

Mechanism

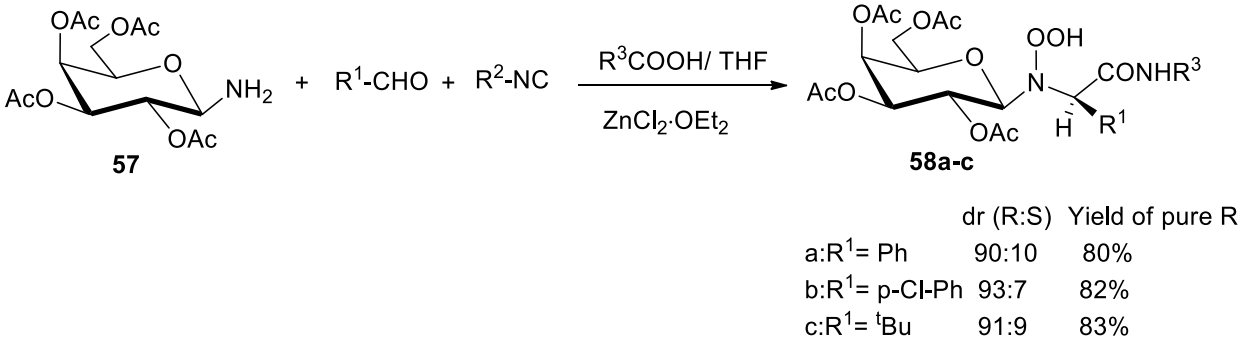
The observed diastereoselectivity can be explained by the fact that, equatorial attack of isocyanide leads to an intermediate **56b** which is unfavorable due to peri-interactions so that the *trans* isomer is obtained as a minor product. In contrast, axial attack of isocyanide gives *cis* isomer as major product.



Scheme 31

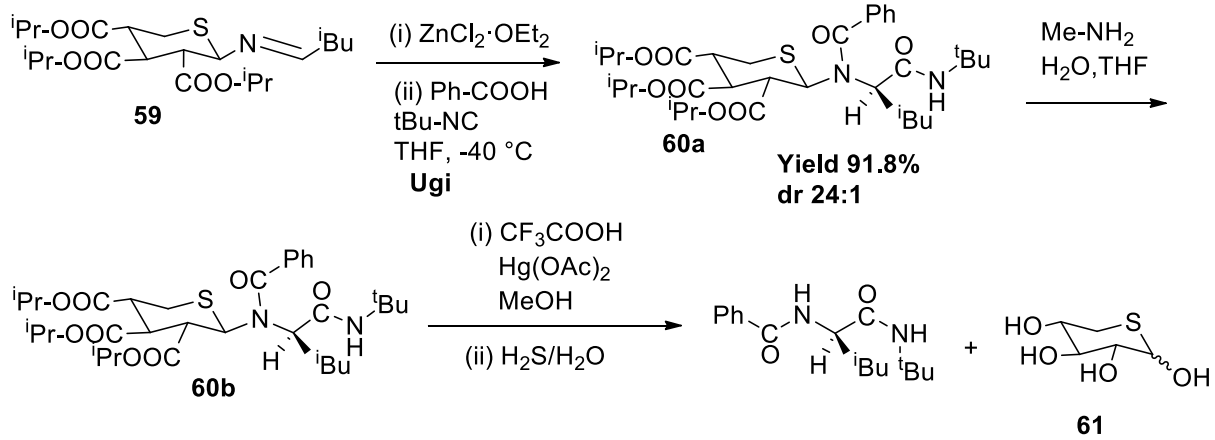
2.3 Chiral amine as substrates

In 1988, Kunz[25] and his group reported a stereoselective synthesis of *N*-galactosyl-amino acid amide derivative **58a-c** via Ugi reaction of *β*-D-galactopyranosylamines **57**, aldehydes and isocyanides in presence of catalytic amount Lewis acid (Scheme 32). The reaction proceeded smoothly to give product with satisfactory yields and high diastereoselectivity.



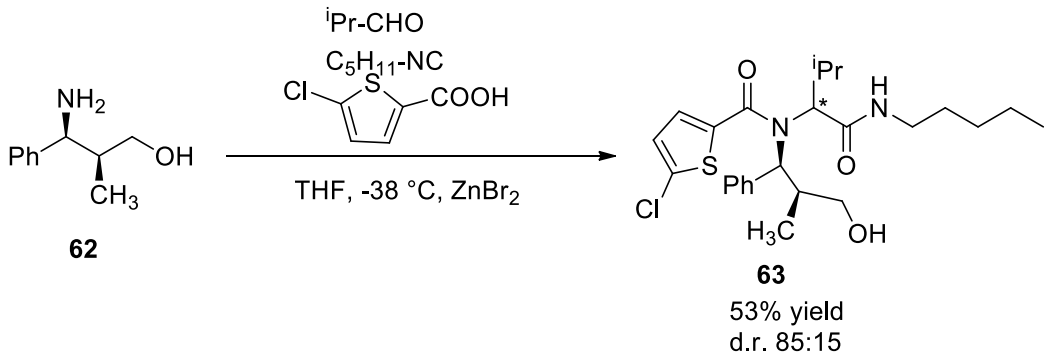
Scheme 32

In 2002, Ross[26] and his group reported a stereoselective Ugi reaction of 1-amino-5-desoxy-5-thio-2,3,4-O-isobutanoyl-β-D-xylopyranose **59** to furnish various peptide derivatives (Scheme 33). Excellent yields, stereoselectivities and easy removal of chiral auxiliary after the Ugi reaction are the merits of this protocol. However, the versatility of this reaction in terms of the substrate scope has not been explored by the authors.



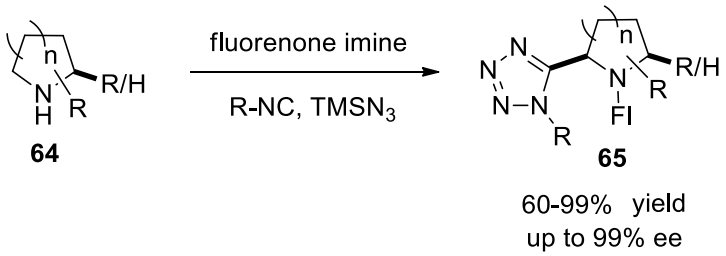
Scheme 33

In 2016, Basso[27] and his co-workers reported Ugi reaction employing β-amino alcohol **65** as a chiral template to access complex heterocycles **63** in presence of Lewis acid catalysts (Scheme 34). Products with three adjacent stereogenic centers were obtained in high yield and stereoselectivities. The diversity of this reaction has been explored by varying amino alcohols, aldehyde, acid, isocyanide and conditions.

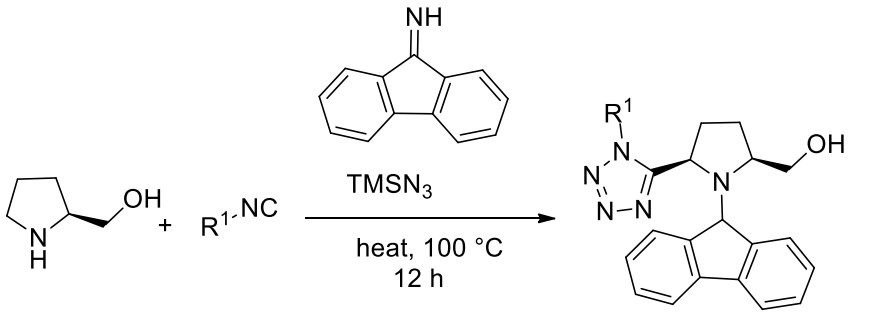


Scheme 34

Surajit Haldar[28] and his group reported a metal free stereoselective synthesis of α-tetrazolyl pyrrolidines via an azido-Ugi reaction in 2013 (Scheme 35). Structurally diverse chiral amines and isocyanides were employed to afford the desired skeleton with good yield and up to >99% ee. Enantioenriched prolinol **66** upon reaction with various isocyanides under standard conditions furnished tetrazole derivatives **67a-c** (Scheme 36). Pyrrolidine **68** was treated with isocyanoethyl benzene **69** in presence of fluorenimine to give enantioenriched tetrazole **70a** and **70b** which then subjected to standard hydrogenolysis to obtain (*S*)-2-tetrazolyl pyrrolidine **70c** and (*R*)-2-tetrazolyl pyrrolidine respectively **70d** (Scheme 37).

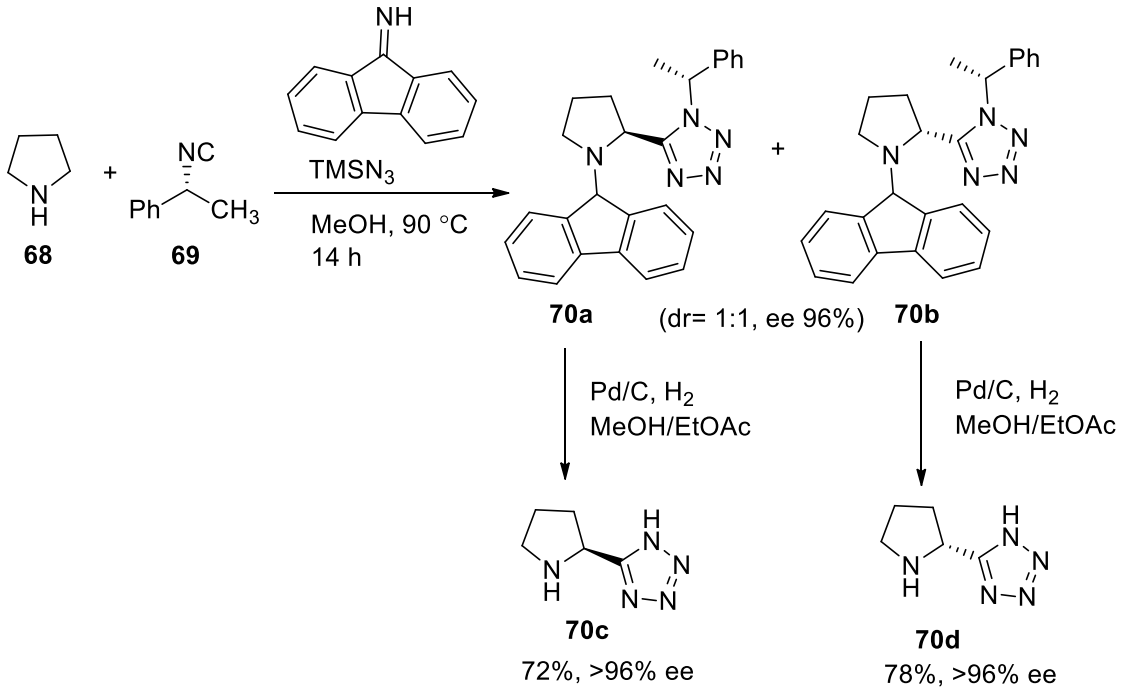


Scheme 35



	Yield (%)	Ee (%)
a: R^1=Bn	54	>99
b: R^1=p-Cl-Bn	56	>99
c: R^1=Ph	50	>99

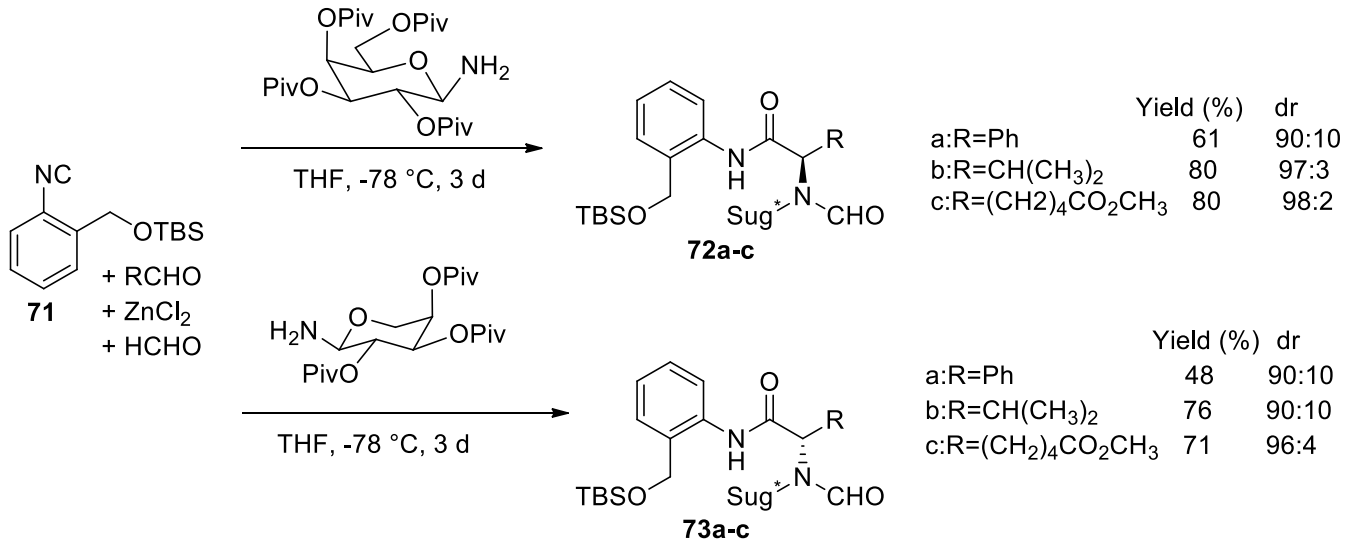
Scheme 36



Scheme 37

The absolute configurations of products were determined from crystallographic studies.

Lindermann[29] and his co-workers developed a convertible isonitrile and applied in asymmetric Ugi reaction in 1999. Both aliphatic and aromatic aldehydes can be tolerated in this reaction leading to optically pure amino acids with noteworthy diastereoselectivity (Scheme 38).



	Yield (%)	dr
a:R=Ph	61	90:10
b:R=$CH(CH_3)_2$	80	97:3
c:R=$(CH2)_4CO_2CH_3$	80	98:2

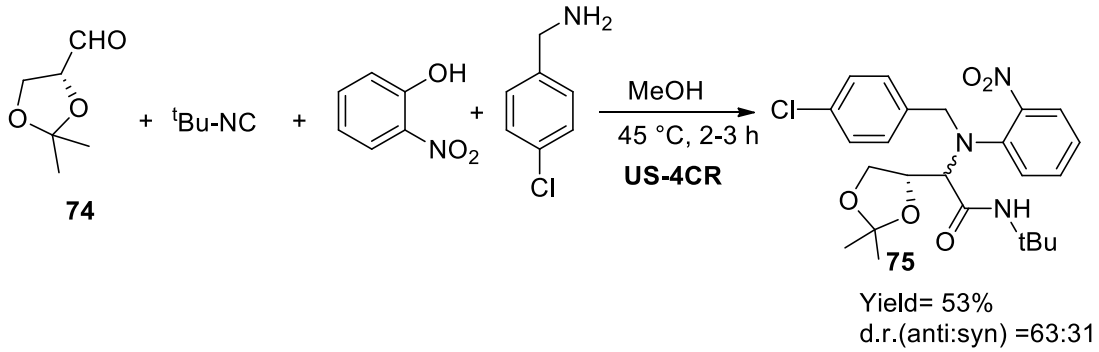
	Yield (%)	dr
a:R=Ph	48	90:10
b:R=$CH(CH_3)_2$	76	90:10
c:R=$(CH_2)_4CO_2CH_3$	71	96:4

Scheme 38

2.4. Chiral aldehydes as substrate

The first diastereoselective N-arylative Ugi-Smiles (US-4CR) reaction using a chiral aldehyde **74** to afford N-aryl amides **75** was reported by Radhakrishna[30] and his group in 2014 (Scheme 39). The reaction proceeds

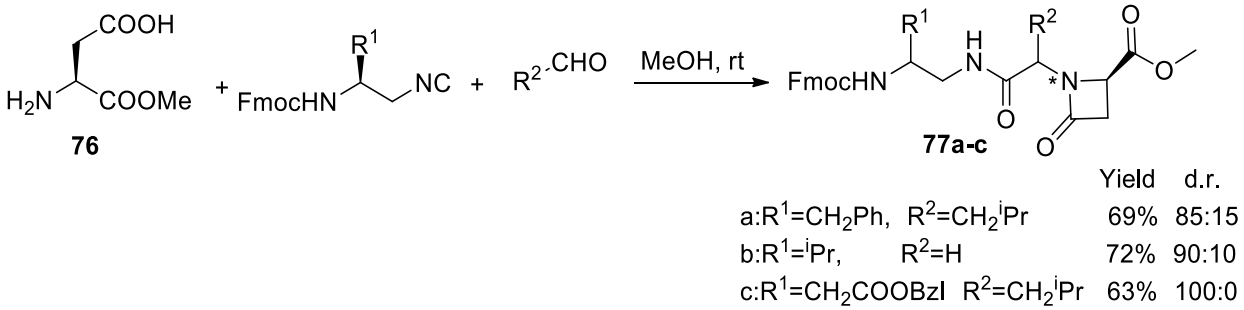
smoothly under optimized conditions to give N-aryl amides in moderate to good yield and diastereomeric ratios.



Scheme 39

2.5. Chiral isocyanides as substrates

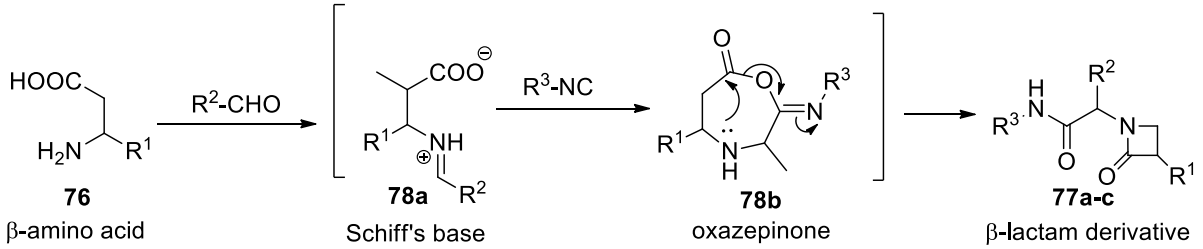
In 2011, Viswanatha[31] and his co-workers reported a stereoselective Ugi reaction of chiral N$^{\beta}$-Fmoc amino alkyl isonitriles, L-aspartic acid **76** and α-methyl ester to synthesize β-lactam peptidomimetics **77a-c** (Scheme 40). β-Lactam peptidomimetics are potential antibacterial and are important in medicinal chemistry[32].



Scheme 40

Mechanism

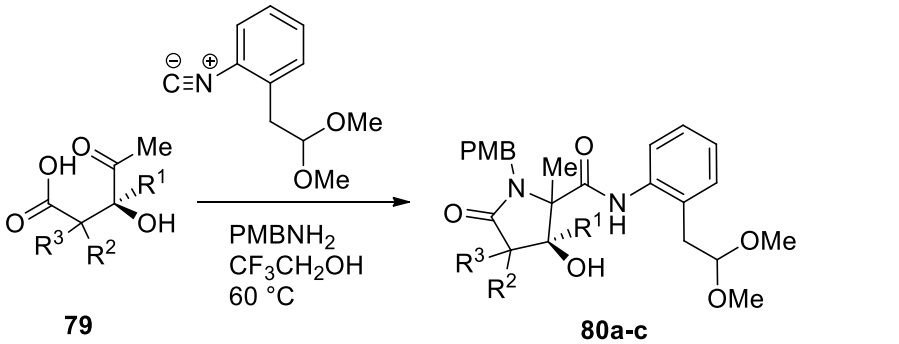
A general mechanism for the formation of β-lactam derivatives has been represented below. aminoacid **76** condenses with aldehyde to afford Schiff's base followed by reaction with isocyanide to give oxazepinone intermediate **78b**. In the next step, intramolecular N,O-acyl migration results in synthesis of β-lactam derivatives (Scheme 41). The origin of selectivity in the formation of products **77** a-c is based on the usage of chiral substrates such as chiral amino acid **76** and chiral isocycnides.



Scheme 41

2.6. Chiral keto acid as substrate

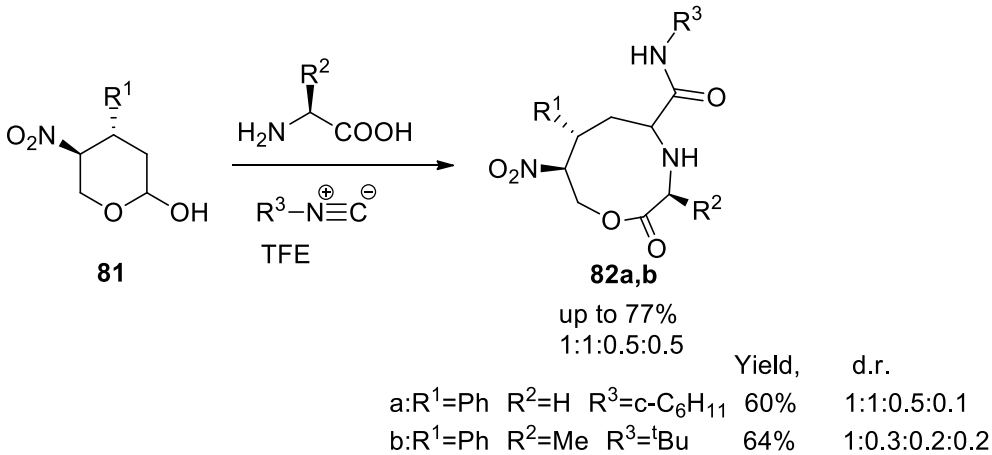
In 2008, Kobayashi[33] and his group investigated the stereoselectivity of Ugi-4C-3CR involving chiral levulinic acid derivatives **79** as starting material. The resulting pyroglutamic acids **80a-c** were obtained in good yield and stereoselectivities (Scheme 42).



Scheme 42

2.7 Chiral cyclic hemiacetals as substrates

In 2015, de la Torre[34] and his group developed a new strategy for synthesis of cyclic depsipeptide mimics **82a,b** employing 4,5-disubstituted 2-hydroxytetrahydropyrans **81** as chiral substrate by means of an Ugi five centered three component reaction (Scheme 43). Products were obtained in good yields and low diastereoselectivities (d.r. up to 1:1:0.5:0.5).

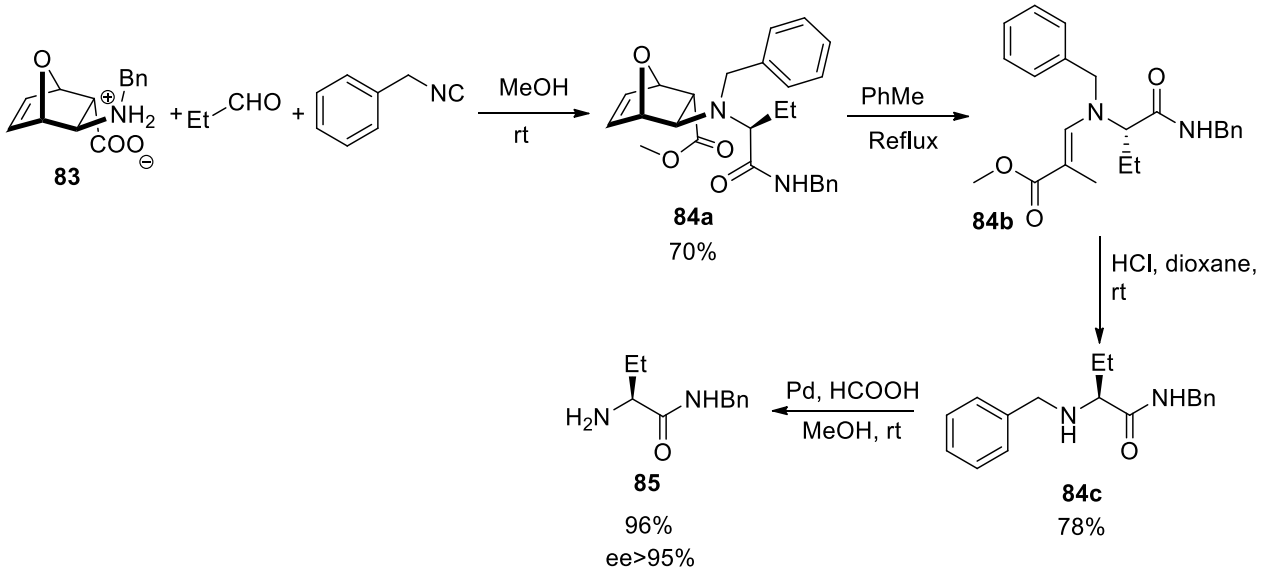


Scheme 43

3. Asymmetric Ugi reactions involving chiral auxiliary

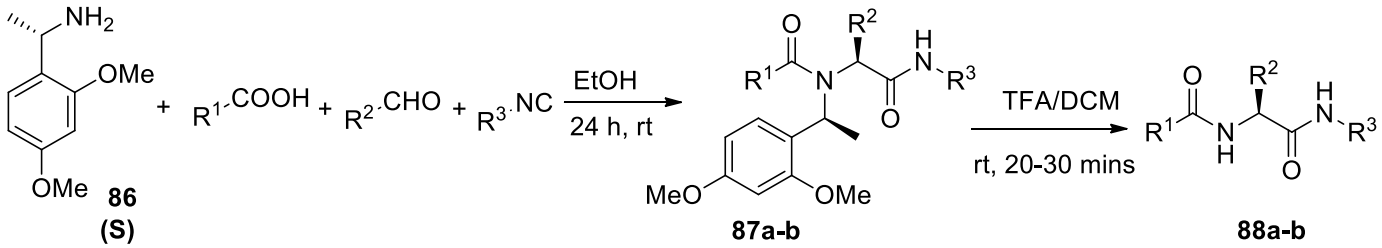
In 2005, Basso[35] and his group reported the application of β-amino acids derivative **83** as a novel chiral auxiliary in Ugi reactions for the preparation of optically pure α-amino acid derivatives **85** in both D- and L-

form (Scheme 44). It was suggested that the stereoselectivity is due to the conformation of the cyclic intermediate formed from condensation of **83** and aldehyde followed by attack of isocyanide from the side opposite to the carboxylic oxygen. The origin of selectivity in the formation of products **84a** is based on the usage of chiral substrate **83**.



Scheme 44

In 2014, Klossowski[36] and his group synthesized a new chiral auxiliary α-(2,4-dimethoxyphenyl)ethylamine **86** from α-phenylethylamine and employed it for preparation of peptidomimetics **87a-b** in a stereoselective manner by means of Ugi reaction (Scheme 45). Broad substrate scope and easy removal of auxiliary from product makes this reaction attractive.

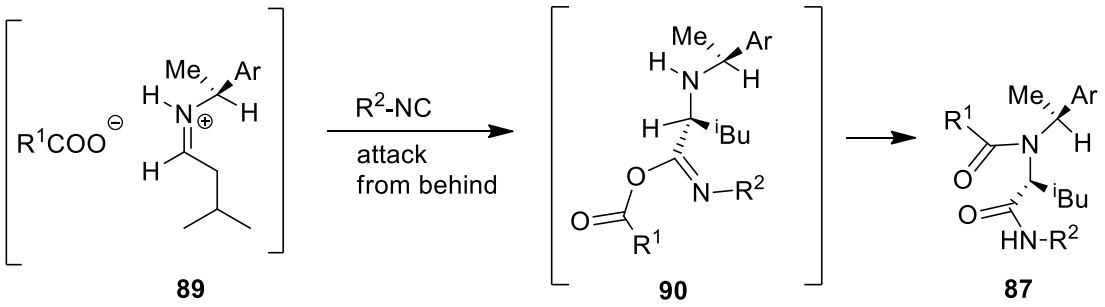


	Yield	d.r.
a: R^1=Ph, R^2=CH_2-^{i}Pr, R^3=Cy	77%	2:1
b: R^1= CH_2-NH-$COCH_3$, R^2=Ph-NO_2, R^3=Cy	87%	2:1

Scheme 45

Plausible mechanism of the Ugi reaction

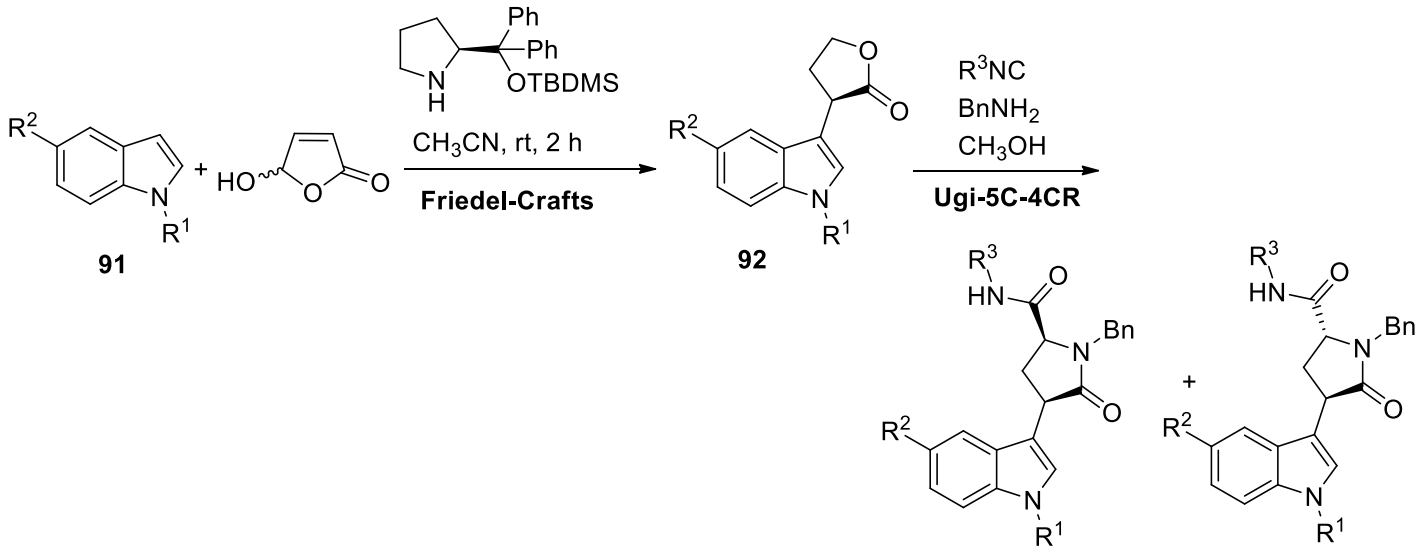
Condensation of aldehyde and amine gives an imine, which on protonation by carboxylic acid leads to iminium ion **89**. Attack of isocyanide from less hindered side results in intermediate **90** to finally afford the desired product **87** in an intramolecular acyl migration (Mumm rearrangement).



Scheme 46

4. Asymmetric Ugi reactions involving chiral catalysts

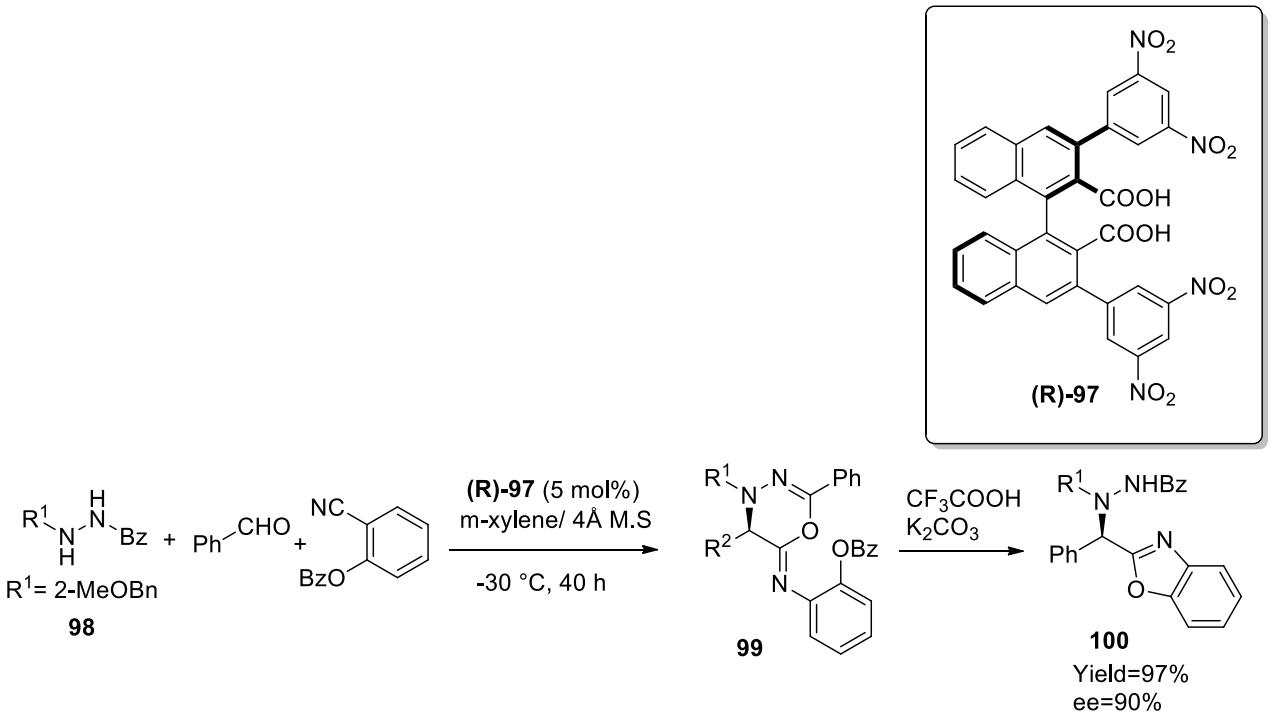
In 2011, Riguet[37] reported an enantioselective Friedel-Crafts reaction of indole **91** with 5-hydroxyfuran-2(5*H*)-one using a diphenylprolinol silyl ether as catalyst to afford chiral indoyl oxo-carboxylic acid **92** which was further employed as a chiral synthon in Ugi reaction leading to *γ*-lactams **93-96** (Scheme 47). This one pot synthetic methodology was developed on the basis of a green chemistry approach consisting of sequential reactions such as enantioselective organocatalytic Friedel-Crafts alkylation reaction of indoles and Ugi 4-center 3-component reaction resulting chiral five-membered lactams **93-96** in high yields and enantioselectivities.



			Compound	Yield (%)	er	Compound	Yield (%)	er
R^1=Me	R^2=H	R^3=^{t}Bu	**93a**	43	94:6	**93b**	34	94:6
R^1=Me	R^2=H	R^3=Cy	**94a**	44	92:8	**94b**	38	94:6
R^1=Me	R^2=H	R^3=Bn	**95a**	42	94:6	**95b**	35	94:6
R^1=H	R^2=F	R^3=^{t}Bu	**96a**	29	91:9	**96b**	30	nd

Scheme 47

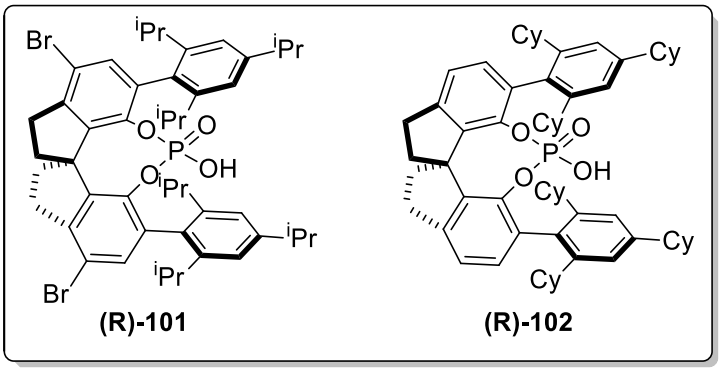
In 2012, Hasimoto[38] and his group reported a new asymmetric Ugi reaction involving N' alkylbenzohydrazide **98**, benzaldehydes and various isocyanides using axially chiral dicarboxylic acid **(R)-97** as catalyst (Scheme 48). This reaction proceeded through an azomethine imine intermediate.

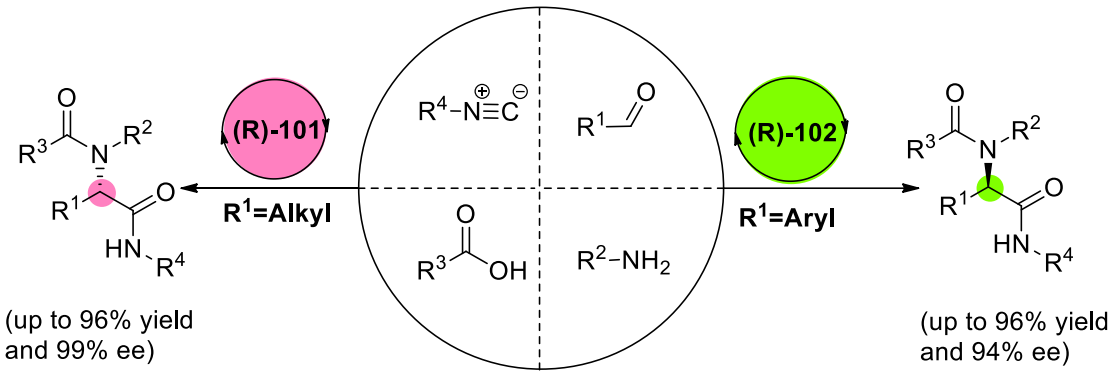


Scheme 48

In 2018, Zhang[39] and his group reported an asymmetric four component Ugi reaction catalyzed by chiral phosphoric acid derivatives **(R)-101** and **(R)-102** leading to optically pure *α*-acylaminoamides from achiral building blocks (Scheme 49). *α*-Acylaminoamides were obtained in excellent yield (up to 96%) and enantiomeric excess (up to 99%). Non-covalent interactions such as intermolecular hydrogen bonding restricts the approach of the isocyanide to only one enatiotopic face of the iminium ion.

Catalyst

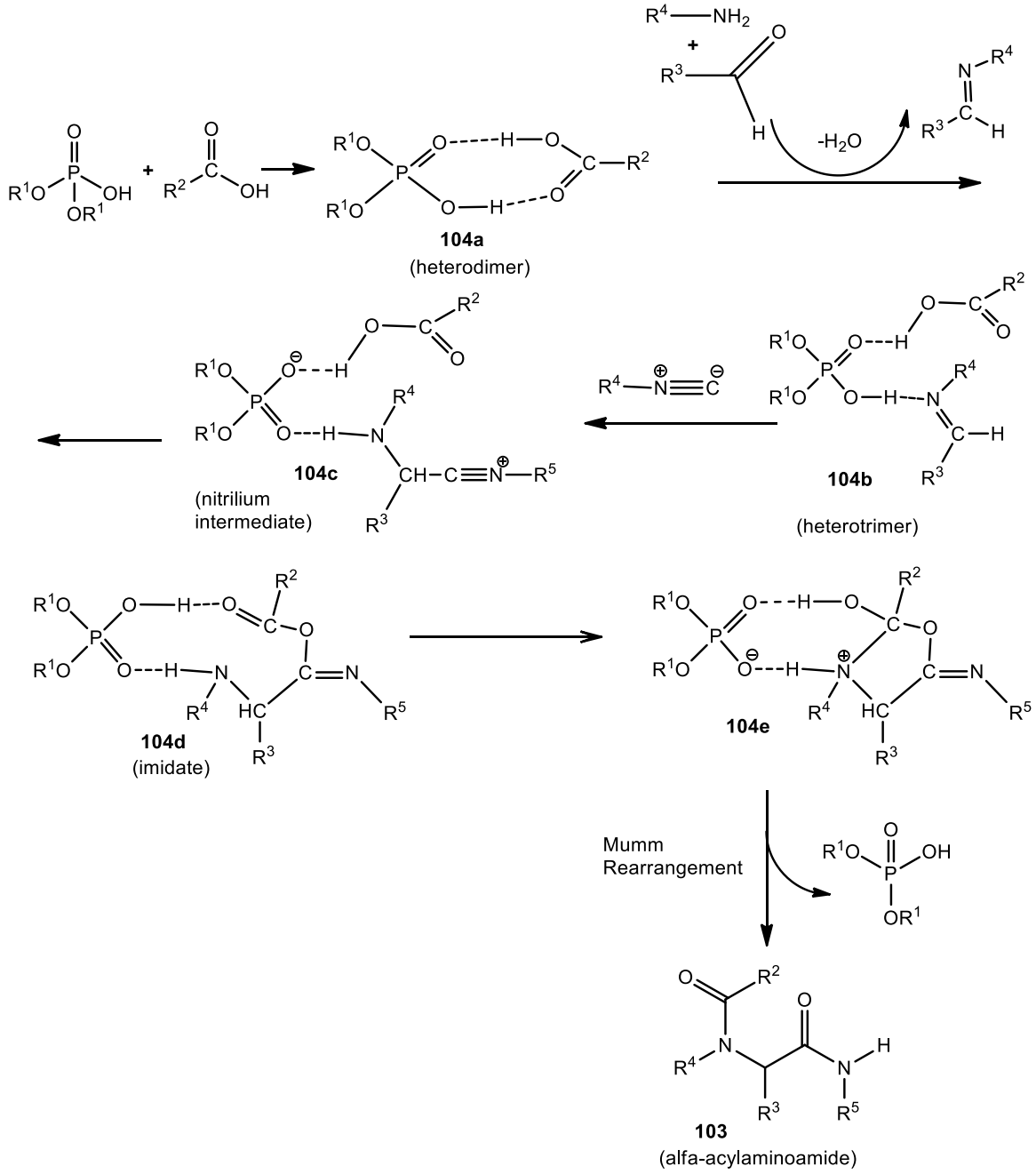




Scheme 49

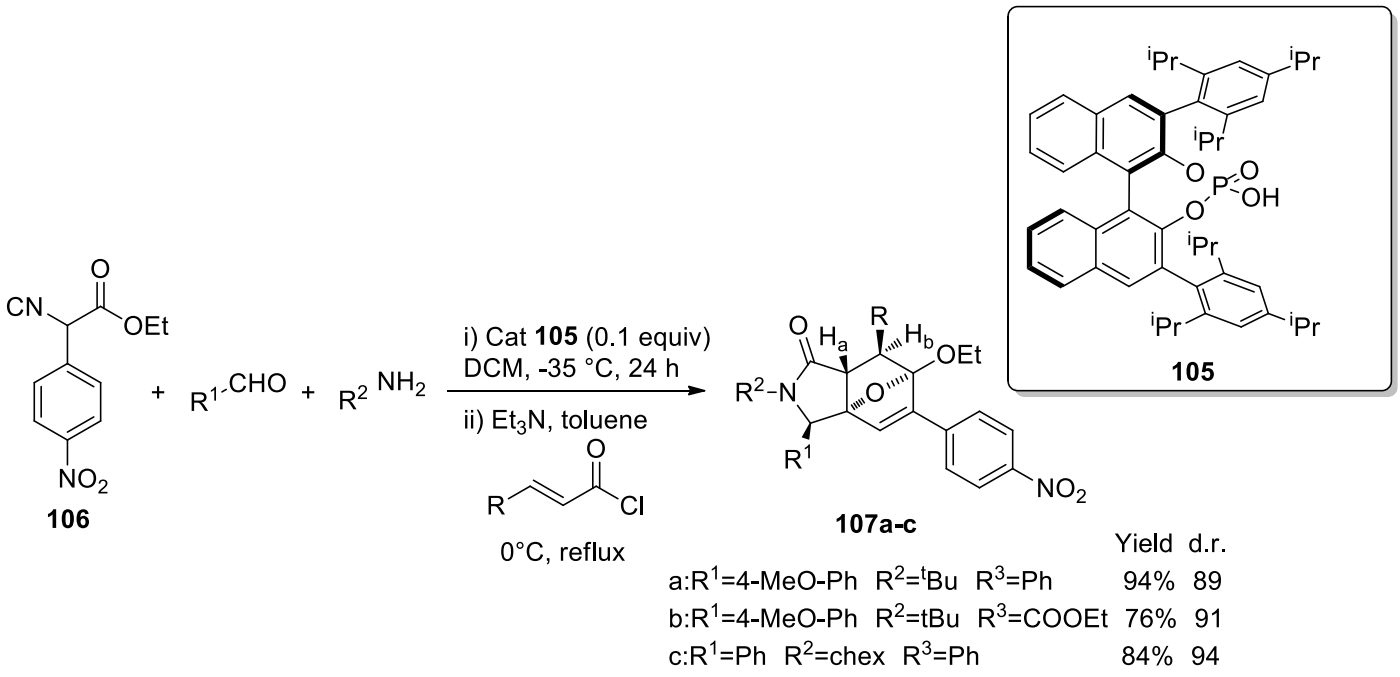
Mechanism

From Density Functional Theory calculations and control experiments, the mechanism of this reaction has been proposed as presented below (Scheme 50). At first, phosphoric acid and carboxylic acid form a relatively stable heterodimer **104a** which then co-ordinates with imine formed from aldehyde and amine to generate a heterotrimer **104b**. In the next step, nucleophilic attack of isocyanide results in a nitrilium intermediate 104c followed by attack of carboxylate to nitrilium carbon to give imidate intermediate **104d**. Phosphoric acid promotes Mumm rearrangement to afford final product α-acylaminoamide **103** accompanied by regeneration of catalyst. The α-addition of isocyanide to imine is the enantio-determining step.



Scheme 50

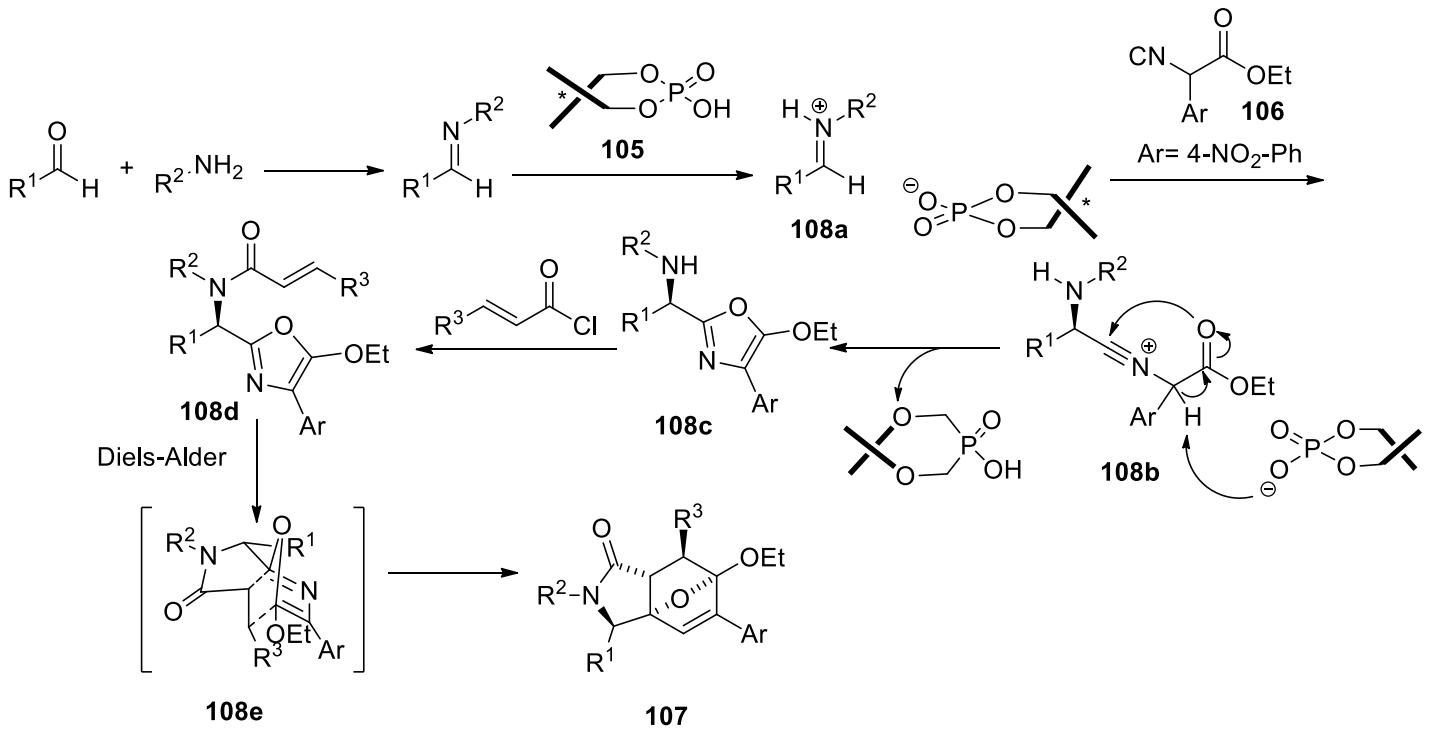
In 2012, Su[40] and his co-workers reported an enantioselective Ugi four component reaction of isocyanoacetate **106**, aldehydes and amine catalyzed by chiral phosphoric acid derivative **105** for synthesis of *epoxy*-tetrahydropyrrolo[3,4-b]pyridine-5-ones **107** in moderate to high yield (up to 94%) and enantioselectivities (*ee* up to 94%) (Scheme 51).



Scheme 51

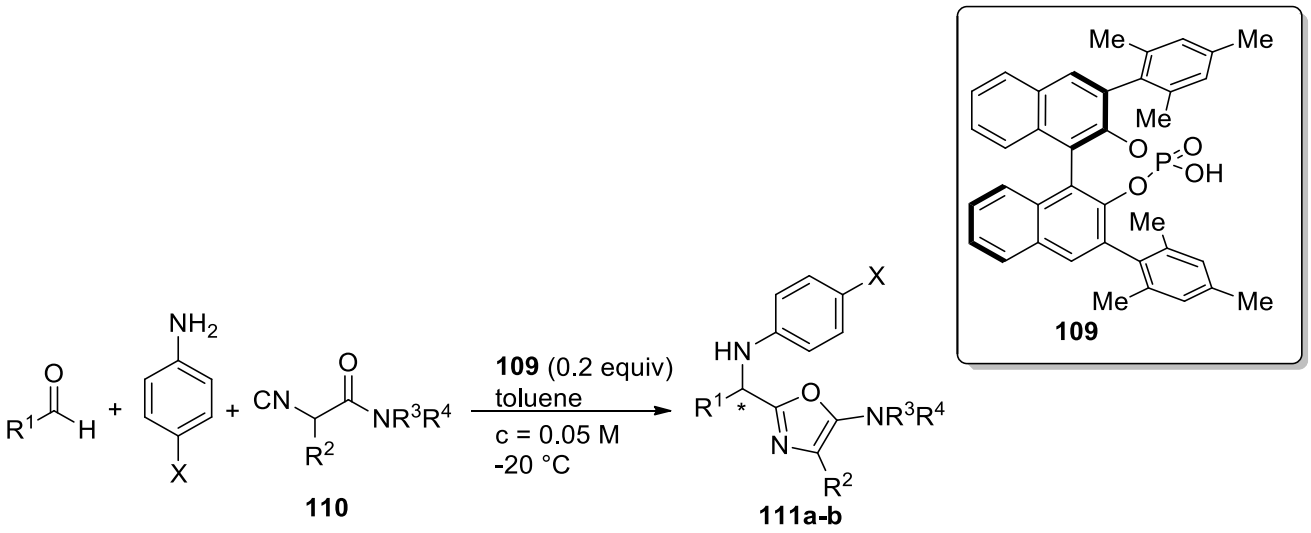
Mechanism

A possible reaction mechanism (Scheme 52) for formation of heterocycle **107** has been shown below. At first aldehyde and amine condenses to give imine which gets protonated by chiral phosphoric acid **105** to give iminium ion **108a** followed by nucleophilic attack of isocyanide to the Si-face of iminium ion leads to nitrilium intermediate **108b**. Then, deprotonation of α-proton by phosphate and simultaneous attack of resulting enolate oxygen to nitrilium carbon affords oxazole **108c** with regeneration of catalyst **105**. In the next step, addition of acyl chloride and triethylamine, followed by acylation of secondary amine results in **108d** which then undergoes an intramolecular Diels-Alder reaction to furnish epoxy-tetrahydropyrrolo[3,4-b]pyridine-5-ones **107**.



Scheme 52

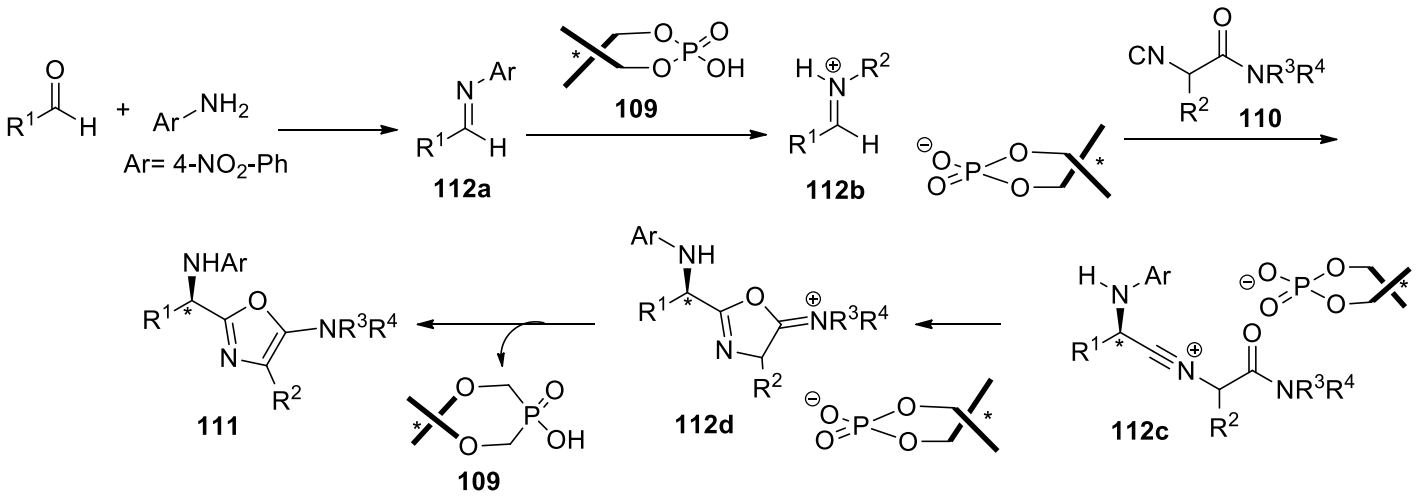
In 2009, Yue[41] and co-workers investigated the three-component reaction between the aldehydes, anilines and α-isocyanoacetamides catalyzed by chiral phosphoric acid derivative **109** for the synthesis of 2-(1-aminoalkyl)-5-aminoxazoles **111a-b** (Scheme 53). A possible reaction pathway was proposed for this protocol (Scheme 54). Protonation of imine **112a** by chiral phosphoric acid **109** leads to the formation of iminium ion **112b** followed by attack of isonitrile **110** from the *Si* face to give an intermediate **112c**. The intermediate **112c** then undergoes intramolecular cyclisation to furnish **112d** which on deprotonation by the phosphate ion afforded 5-aminooxazole **111** with regeneration of the catalyst **109**.



	Yield	ee
a:R^1=^{i}Pr, R^2=Ph, NR^3R^4=Piperidine, X=Cl,	68%,	74%

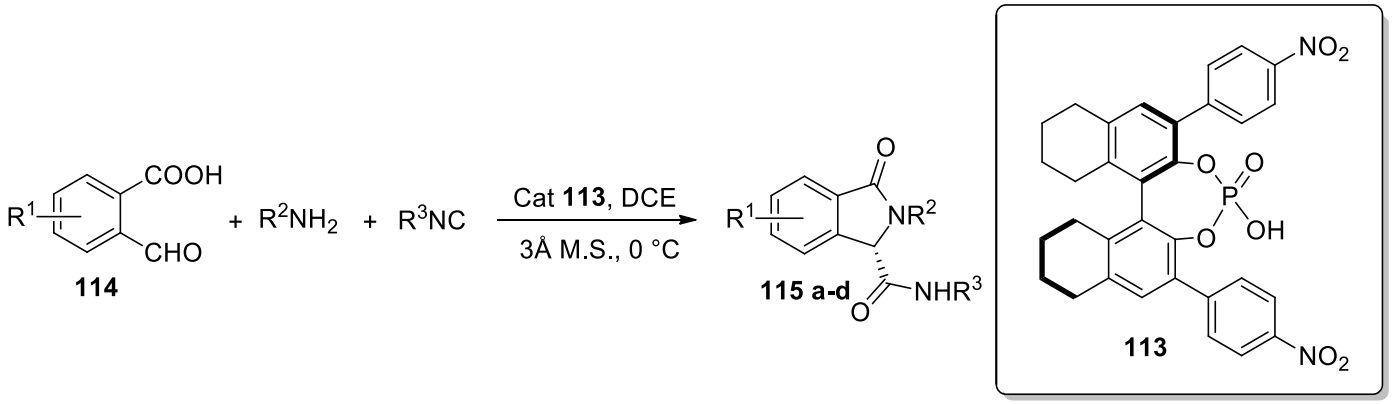
Scheme 53

Mechanism



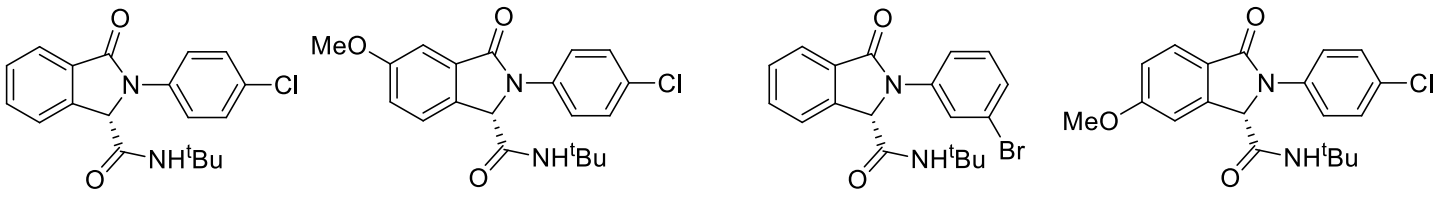
Scheme 54

In 2016, Zhang[42] and his group reported an enantioselective Ugi three component reaction between 2-formylbenzoic acid **114**, anilines, and isocyanides in presence of a binol derived chiral phosphoric acid **113** acting as catalyst to give structurally diverse heterocycles **115a-d** with excellent yield and enantiomeric excess (Scheme 55).



Scheme 55

Substrate Scope



115a
yield 97%
ee 90%

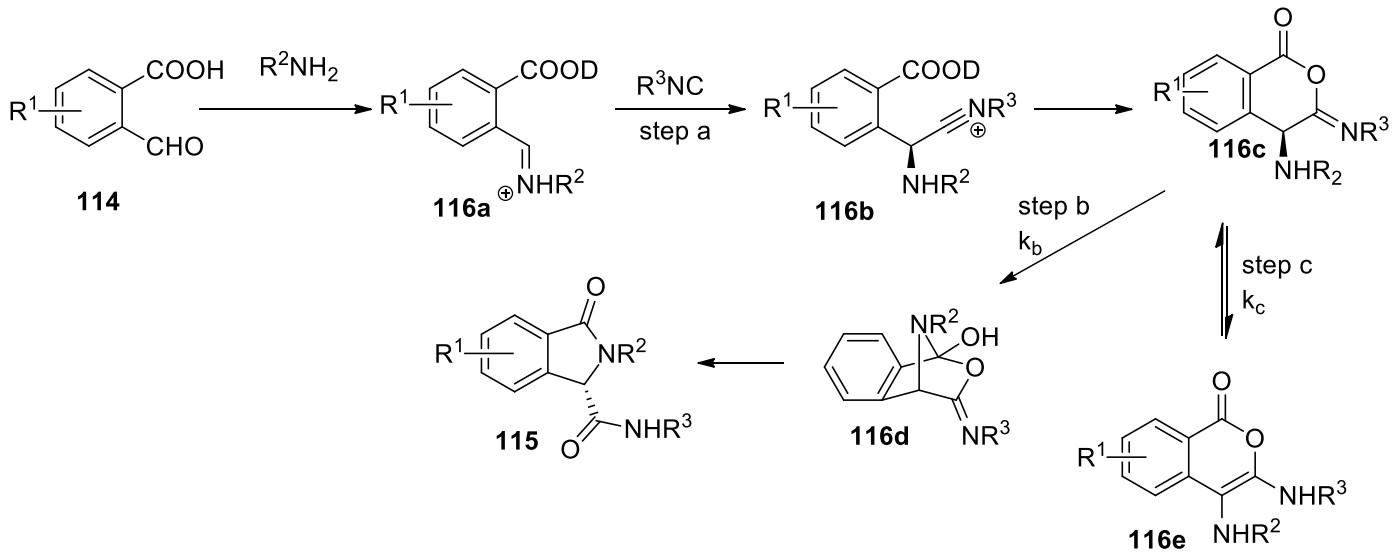
115b
yield 97%
ee 90%

115c
yield 91%
ee 87%

115d
yield 92%
ee 86%

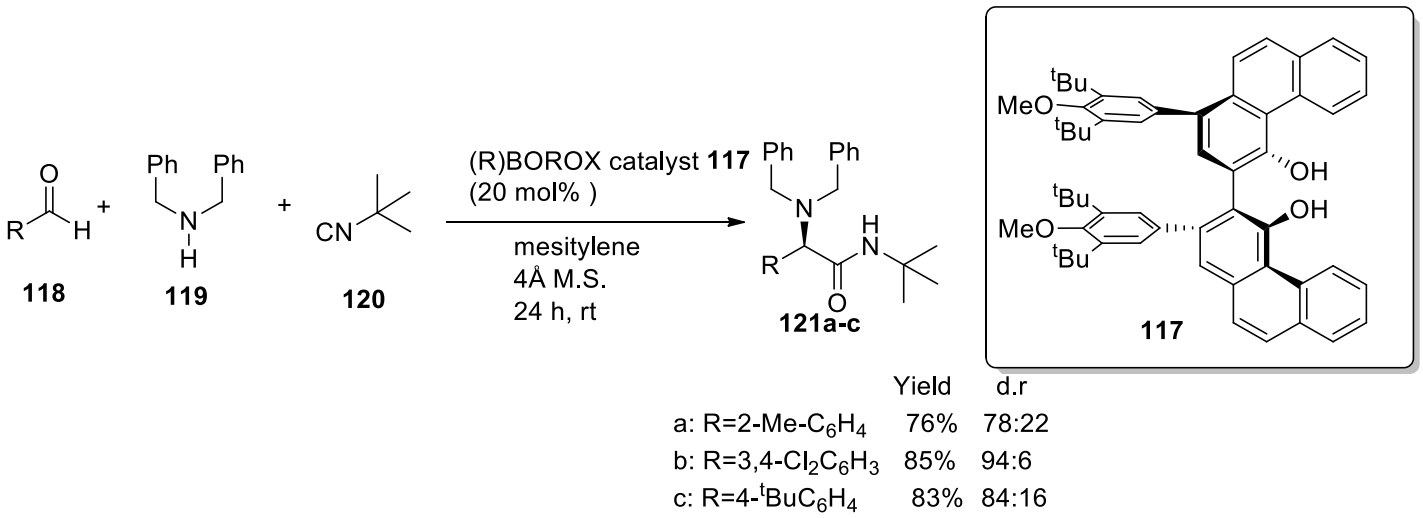
Mechanism

A plausible mechanism (Scheme 56) for the enantioselective synthesis of 3-oxoisoindoline-1-carboxamides **115** via Ugi reaction has been elucidated as depicted below. Condensation of formyl benzoic acid **114** with amine affords iminium salt **116a**. In the next step, nucleophilic addition of isocyanide carbon to iminium ion results in formation of nitrilium intermediate and is trapped by carboxylate to give **116c**. Mumm rearrangement of **116c** via bridged intermediate **116d** affords isoindolinone**115**. However, **116c** can undergo isomerization to give isocoumarin**116e**. Now, there are two possibilities for accounting observed enantioselectivity: a) Mumm rearrangement (step b) is faster than the imine– enamine isomerization (step c/d; $k_b >> k_c, k_d$). In this case, the C-C bond-forming step (step a) leading to **116b** would determine the absolute configuration of the final adduct; b) imine– enamine isomerization (step c/d) is much faster than the Mumm rearrangement (step b; k_c, $k_d >> k_{b)}$. In this case, the DKR (Dynamic Kinetic Resolution) of **116e** would be responsible for the observed enantioselectivity. Control experiments and mechanistic studies indicate that observed enantioselectivity results from a DKR of the primary Ugi adduct rather than from the C-C bond-forming process.



Scheme 56

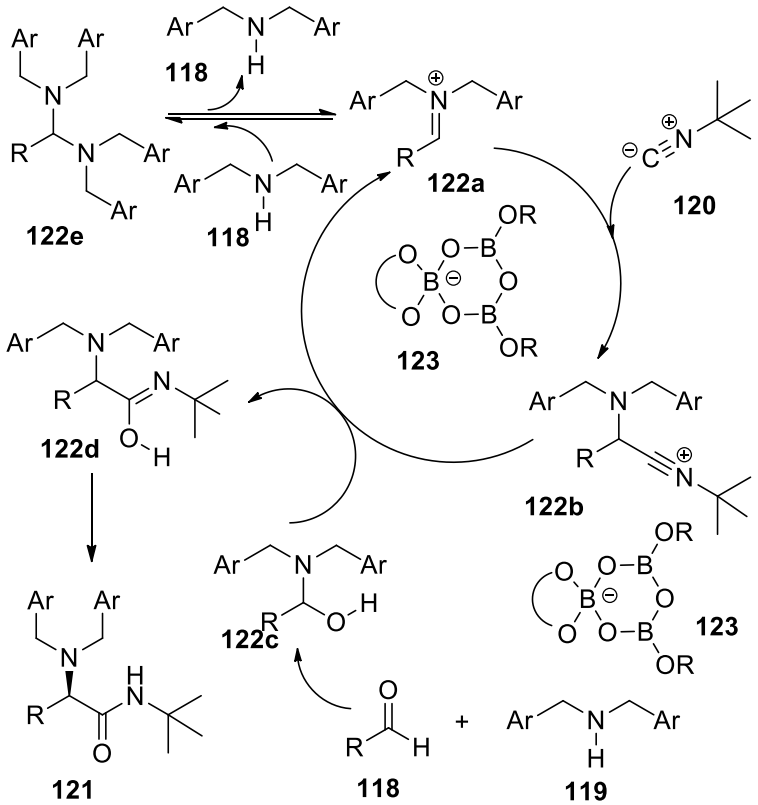
In 2014, Zhao[43] and his group investigated the catalytic property of various BOROX catalysts bearing functional groups of different electronic properties and found **117** to provide optimum selectivity. In presence of catalytic amount of this R-BOROX catalyst **117**, the Ugi three component reaction of aldehyde **118**, amine **119** and isocyanide **120** leads to synthesis of enantio-enriched α-amino amide **121a-c** in good yields (Scheme 57).



Scheme 57

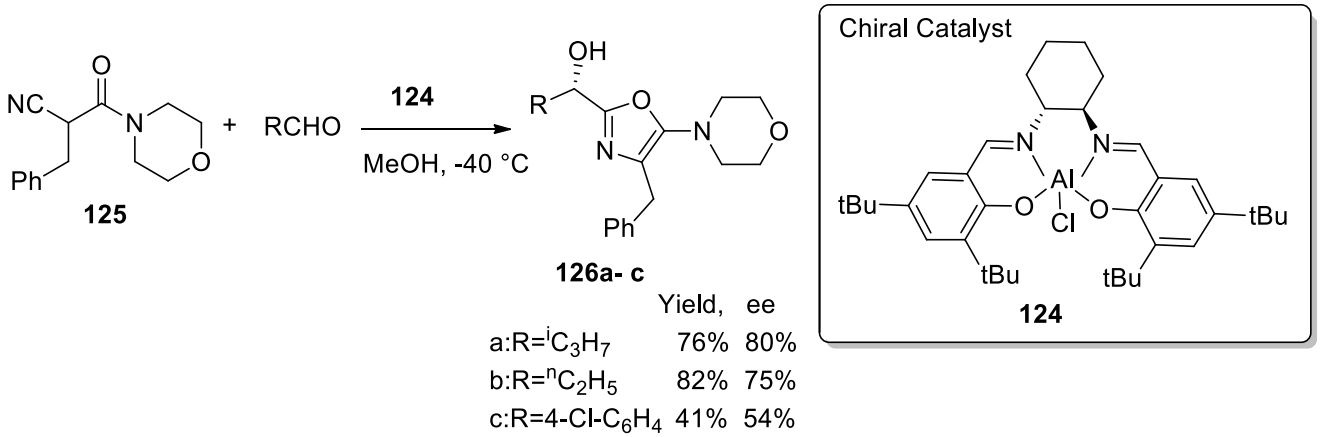
Mechanism

The proposed mechanism (Scheme 58) for this reaction involves addition of isonitrile **120** to iminium ion **122a** to give nitrilium cation **122b** which remain as ion pair with BOROX catalyst **123**. In the next step exchange of OH group between the nitrilium cation **122b** and hemiaminal **122c** to refurnish iminium ion **122a** accompanied by simultaneous formation of final product **121**.



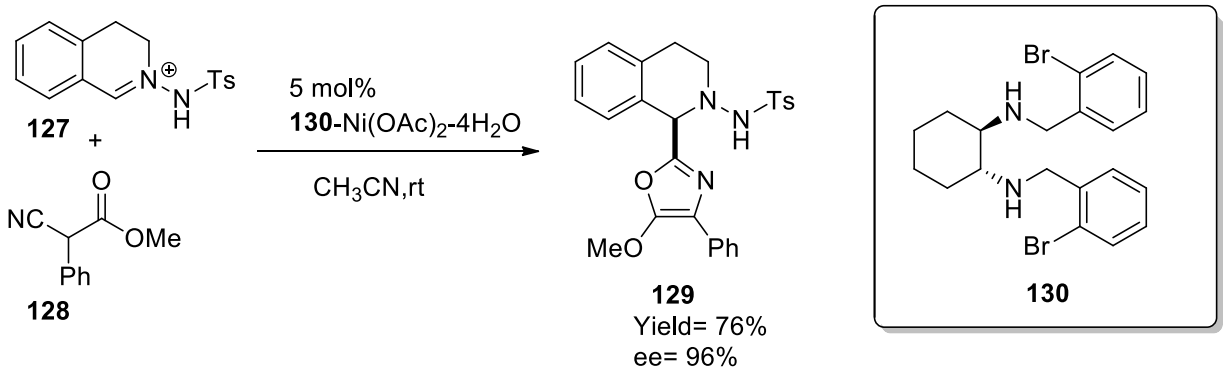
Scheme 58

In 2007, Wang[44] and his group reported an Ugi type reaction of α-isocyanoacetamides **125** and aldehydes catalyzed by a chiral salen-aluminium complex **124** for synthesis of 2-(1-hydroxyalkyl)-5-aminooxazoles **126a-c** (Scheme 59). It offers a large substrate scope and structural diversity of product in high yield and low to moderate enantiomeric excess (up to 80%).



Scheme 59

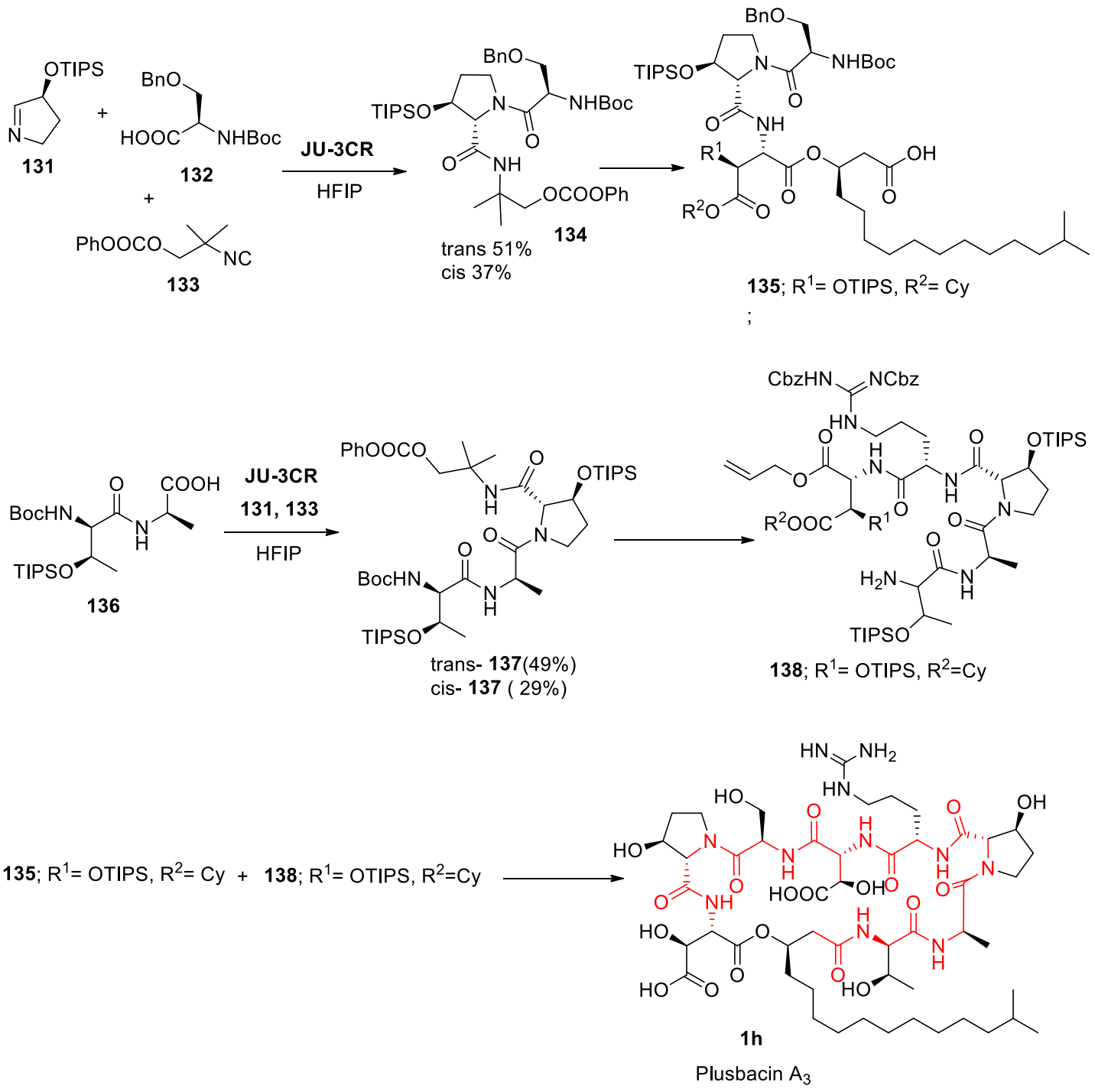
A nickel complex of **130** catalyzed enantioselective Ugi reaction of cyclic azomethine imines **127** and methyl 2-cyano-2-phenylacetate **128** was reported by List[45] and co-workers in the year 2017 (Scheme 60). This reaction proceeds efficiently to furnish (*R*)-*N*-(1-(5-methoxy-4-phenyloxazol-2-yl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-4-methylbenzenesulfonamide **129** with high yield and excellent enantiomeric excess.



Scheme 60

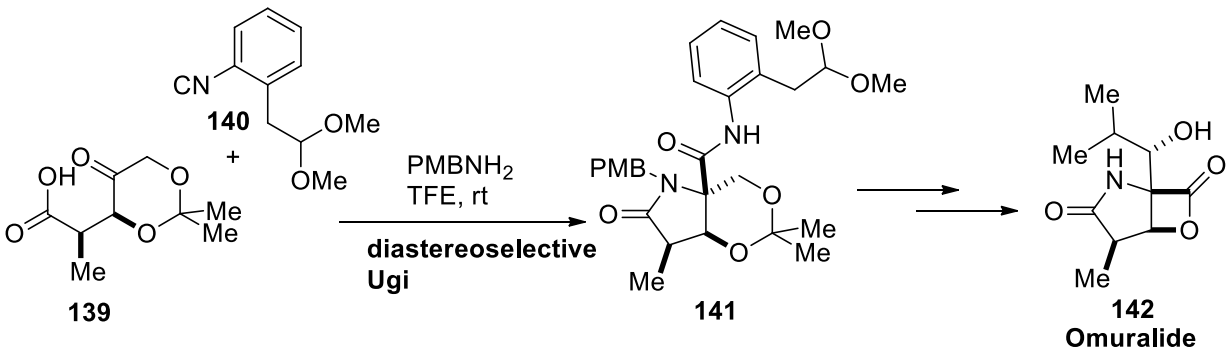
5. Applications

5.1. Plusbascin A_3 (**1h**) is a potential antimicrobial agent against methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin resistant Enterococci (VRE). It has been reported that **1h** also inhibits lipid II polymerization.It can be synthesized employing a solvent dependent diastereoselective Ugi reaction. Two peptide derivatives **135** and **138** derived from asymmetric Ugi reaction react to give Plusbacin A_3 (**1h**)[46] (Scheme 61).



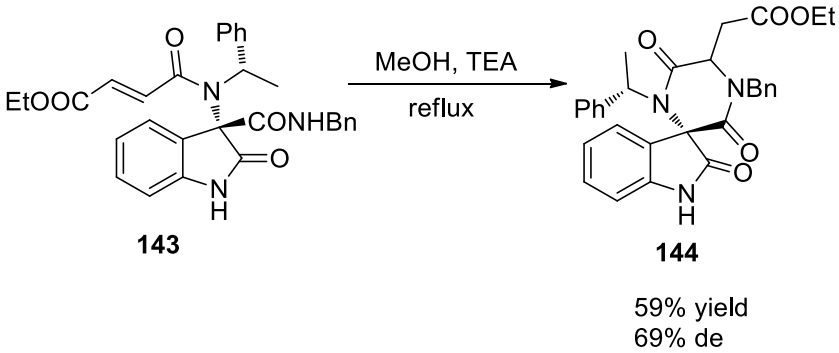
Scheme 61

5.2. The Ugi reaction can be used for total synthesis of Omuralide[47] (Scheme 62.). It is obtained from natural product lactacystin and is a selective inhibitor of the 20S proteasome present in mammalian and bacterial cells. Proteasome inhibition has been reported to be a novel cancer therapy.



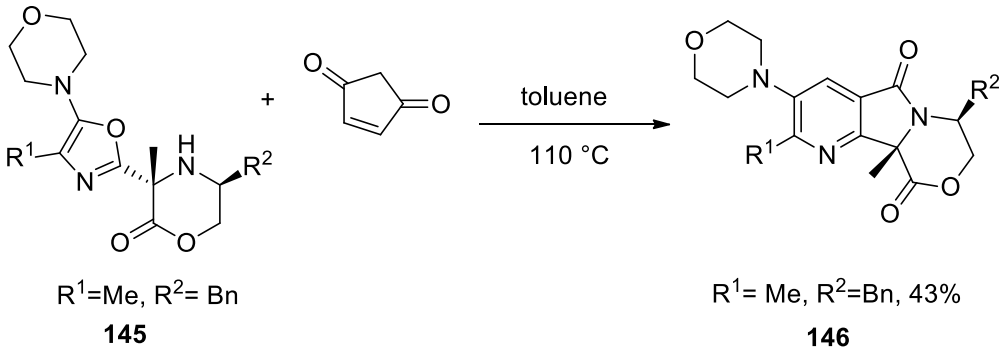
Scheme 62

5.3. Ugi adducts can afford the spiro-diketopiperazine scaffold by means of intramolecular aza-Michael reaction. Spiro-diketopiperazines are of interest because of their peptidomimetic properties and are abundant in many natural products such as verruculogen, spirotryprostatin B and brevianamide F [10] (Scheme 63).



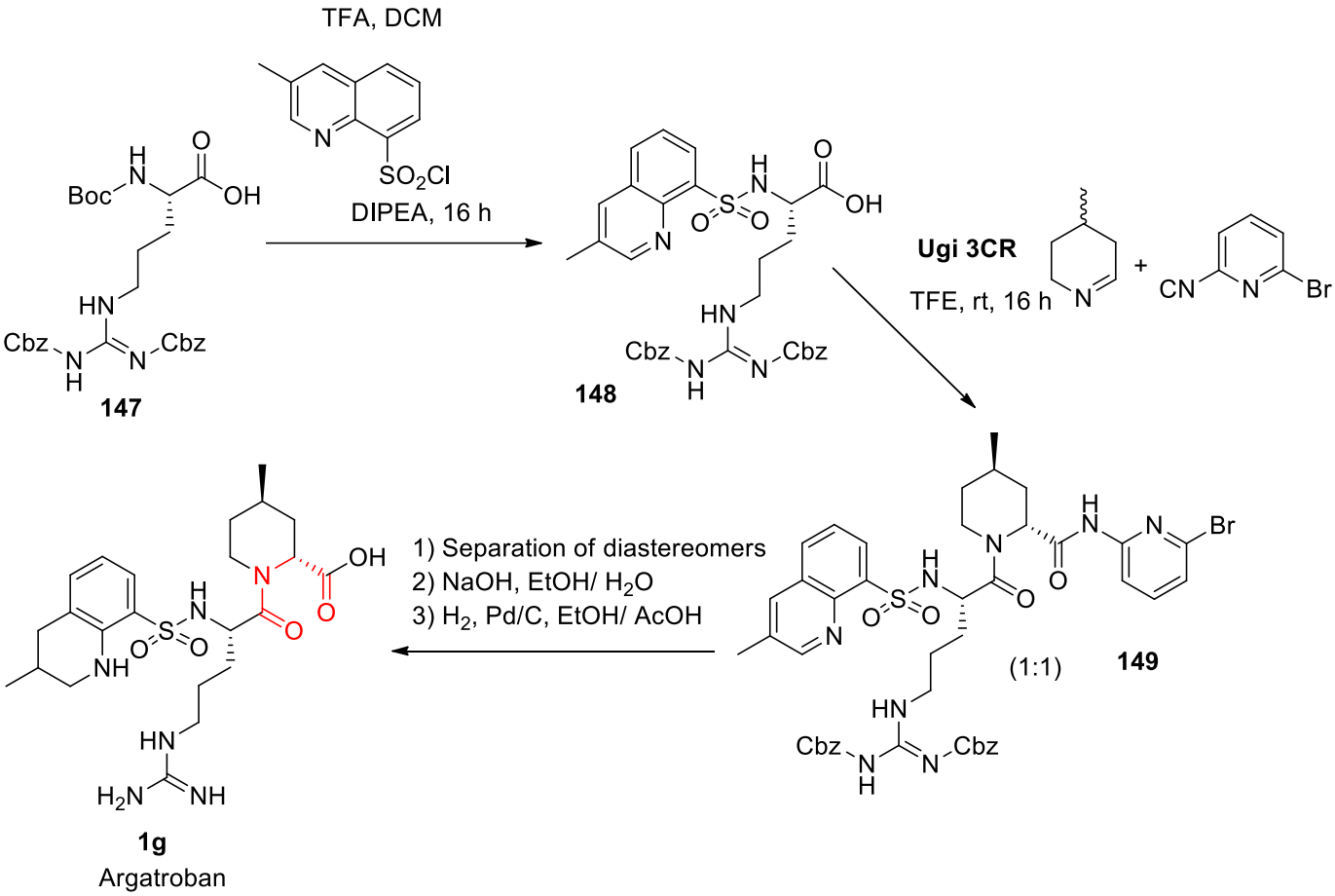
Scheme 63

5.4. The reaction of oxazole with maleic anhydride leads to synthesis of a novel fused tricyclic framework which contains a morpholinone unit as well as pyrrolopyridine unit[12] (Scheme 64). The pyrrolopyridine, having an analogous structure to the isoindolinones, nicotinamide, etc., is a potential pharmacophore and synthetic intermediate (mechanistic studies were under progress).



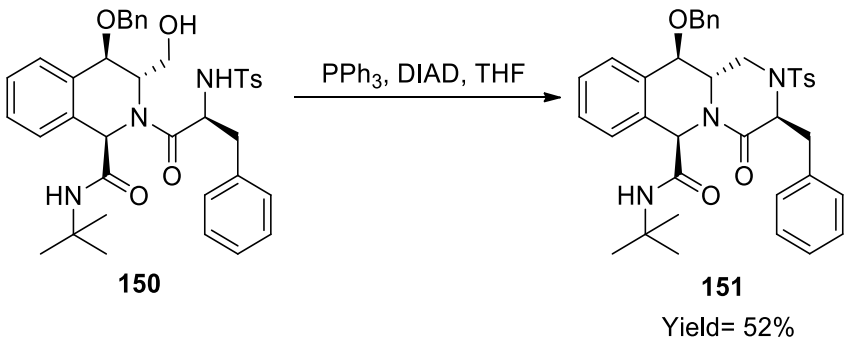
Scheme 64

5.5. Argatroban which is an effective anticoagulant indicated for prophylaxis or treatment of thrombosis can be synthesized from Ugi product [22] (Scheme 65). Argatroban is an anticoagulant that directly inhibits the thrombin enzyme, which is responsible for the blood clotting in thrombosis. This drug is mainly given to patients suffering from coronary artery disease (CAD) or stroke, when the conventional antithrombotic drug heparin results in heparin-induced thrombocytopenia (HIT) or platelet deficiency.



Scheme 65

5.6 Hexahydro-pyrazino isoquinolinone, can be synthesized from Ugi products by means of intramolecular Mitsunobu reaction[23] (Scheme 66). Hexahydro-pyrazino isoquinolinone is a key component in many natural products such as ecteinascidine 743, saframycin and naphthyridinomycin.



Scheme 66

6. Conclusions

In conclusion, this work highlights on various strategies to achieve higher stereoselectivity in Ugi reactions by employing chiral substrates, chiral auxiliaries and chiral catalysts as stereodiscriminating elements. Chiral amino acids and amines provide high yield and stereoselectivity (up to 99%ee or 99%de) whereas in case of chiral isocyanide and acid substrates it is found to be relatively low. This protocol offers efficient and very short routes to diverse complex molecules having bioactive properties. However, a precise mechanism to explain stereoinduction in this reaction is yet to be fully discovered.

References

1. Ingold, M.; Colella, L.; Dapueto, R.; López, G. V.; Porcal, W. World J. Chem. Educ. 2017, 5, 153-157. https://doi.org/10.12691/wjce-5-5-2
2. Ramos-Tomillero, I.; Pérez-Chacon, G.; Somovilla-Crespo, B.; Sánchez-Madrid, F.; Cuevas, C.; Zapata, J. M.;
3. Domínguez, J.M.; Rodríguez, H.; Albericio, F. ACS Omega 2020, 5(13), 7424-7431. https://doi.org/10.1021/acsomega.0c00099
4. Dyker, G.; Breitenstein, K.; Henkel, G. Tetrahedron Asymm. 2002, 13(17), 1929-1936. https://doi.org/10.1016/S0957-4166(02)00530-X
5. Nenajdenko, V. G.; Reznichenko, A. L.; Balenkova, E. S. Tetrahedron 2007, 63(14), 3031-3041. https://doi.org/10.1016/j.tet.2007.01.056
6. Szakonyi, Z.; Sillanpää, R.; Fülöp, F. Mol. Divers. 2010, 14(1), 59-65. https://doi.org/10.1007/s11030-009-9143-y
7. Mandai, H.; Irie, S.; Mitsudo, K.; Suga, S. Molecules 2011, 16(10), 8815-8832. https://doi.org/10.3390/molecules16108815
8. Jida, M.; Betti, C.; Urbanczyk-Lipkowska, Z.; Tourwe, D.; Ballet, S. Org. Lett. 2013, 15(22), 5866-5869. https://doi.org/10.1021/ol402940x
9. Banfi, L.; Basso, A.; Chiappe, C.; De Moliner, F.; Riva, R.; Sonaglia, L. Org. Biomol. Chem. 2012, 10(19), 3819-3829. https://doi.org/10.1039/C2OB25060H
10. Turner, C. D.; Ciufolini, M. A. Org. Lett. 2012, 14(18), 4970-4973. https://doi.org/10.1021/ol302379a
11. Lesma, G.; Meneghetti, F.; Sacchetti, A.; Stucchi, M.; Silvani, A. Beilstein J. Org. Chem. 2014, 10(1), 1383-1389. https://doi.org/10.3762/bjoc.10.141
12. Banfi, L.; Basso, A.; Guanti, G.; Merlo, S.; Repetto, C.; Riva, R. Tetrahedron 2008, 64(6), 1114-1134. https://doi.org/10.1016/j.tet.2007.10.058
13. Li, S.; Chen, R.; Liu, X.; Pan, L.; Xia, L.; Chen, X. Synlett 2012, 23(13), 1985-1989. https://doi.org/10.1055/s-0032-1316549
14. Katsuyama, A.; Matsuda, A.; Ichikawa, S. Org. Lett. 2016, 18(11), 2552-2555. https://doi.org/10.1021/acs.orglett.6b00827
15. Zarezin, D. P.; Khrustalev, V. N.; Nenajdenko, V. G. J. Org. Chem. 2017, 82(12), 6100-6107. https://doi.org/10.1021/acs.joc.7b00611
16. Ostrovskii, V. A.; Trifonov, R. E.; Popova, E. A. Russ. Chem. Bull. 2012, 61(4), 768-780. https://doi.org/10.1007/s11172-012-0108-4

17. Zhu, D.; Xia, L.; Pan, L.; Li, S.; Chen, R.; Mou, Y.; Chen, X. J. Org. Chem. 2012, 77(3), 1386-1395. https://doi.org/10.1021/jo2021967
18. Raparti, V.; Chitre, T.; Bothara, K.; Kumar, V.; Dangre, S.; Khachane, C.; Gore, S.; Deshmane, B. *Eur. J. Med. Chem*. **2009**, *44*(10), 3954-3960. https://doi.org/10.1016/j.ejmech.2009.04.023
19. Znabet, A.; Ruijter, E.; de Kanter, F. J.; Köhler, V.; Helliwell, M.; Turner, N. J.; Orru, R. V. *Angew. Chem. Int. Ed.* **2010**, *49*(31), 5289-5292. https://doi.org/10.1002/ange.201001592
20. Znabet, A.; Blanken, S.; Janssen, E.; de Kanter, F. J.; Helliwell, M.; Turner, N. J.; Ruijter, E.; Orru, R. V. *Org. Biomol. Chem.* **2012**, *10*(5), 941-944. https://doi.org/10.1039/C1OB06699D
21. Moni, L.; Banfi, L.; Basso, A.; Galatini, A.; Spallarossa, M.; Riva, R. *J. Org Chem.* **2014**, *79*(1), 339-351. https://doi.org/10.1021/jo402527w
22. van Rijssel, E. R.; Goumans, T. P.; Lodder, G.; Overkleeft, H. S.; van der Marel, G. A.; Codée, J. D. *Org. Lett.* **2013**, *15*(12), 3026-3029. https://doi.org/10.1021/ol4012053
23. van der Heijden, G.; van Schaik, T. B.; Mouarrawis, V.; de Wit, M. J.; Velde, C. M. V.; Ruijter, E.; Orru, R. V. *Eur. J. Org. Chem.* **2019**, *2019*(31-32), 5313-5325. https://doi.org/10.1002/ejoc.201900399
24. Ramanivas, T.; Gayatri, G.; Priyanka, D.; Nayak, V. L.; Singarapu, K. K.; Srivastava, A. K. *RSC Adv.* **2015**, *5*(90), 73373-73380. https://doi.org/10.1039/C5RA11144G
25. Banfi, L.; Basso, A.; Cerulli, V.; Rocca, V.; Riva, R. *Beilstein J. Org. Chem.* **2011**, *7*(1), 976-979. https://doi.org/10.3762/bjoc.7.109
26. Kunz, H.; Pfrengle, W. *Tetrahedron* **1988**, *44*(17), 5487-5494. https://doi.org/10.1016/S0040-4020(01)86054-3
27. Ross, G. F.; Herdtweck, E.; Ugi, I. *Tetrahedron* **2002**, *58*(30), 6127-6133. https://doi.org/10.1016/S0040-4020(02)00484-2
28. Caputo, S.; Basso, A.; Moni, L.; Riva, R.; Rocca, V.; Banfi, L. *Beilstein J Org. Chem.* **2010,** *12*(1), 139-143. https://doi.org/10.3762/bjoc.12.15
29. Haldar, S.; Saha, S.; Mandal, S.; Jana, C. K. *Green Chem.* **2018**, *20*(15), 3463-3467. https://doi.org/10.1039/C8GC01544A
30. Linderman, R. J.; Binet, S.; Petrich, S. R. *J. Org. Chem.* **1999,** *64*(2), 336-337. https://doi.org/10.1021/jo994009z
31. Radha Krishna, P.; Dayaker, G.; Venkata Ramana, D.; Kunde, R. *Helv. Chim. Acta* **2014**, *97*(8), 1076-1087. https://doi.org/10.1002/hlca.201300317
32. Vishwanatha, T. M.; Narendra, N.; Sureshbabu, V. V. *Tetrahedron Lett.* **2011**, *52*(43), 5620-5624. https://doi.org/10.1016/j.tetlet.2011.08.090
33. Sperka, T.; Pitlik, J.; Bagossi, P.; Tozser, J. *Bioorg. Med. Chem. Lett.* **2005**, *15*(12), 3086-3090. https://doi.org/10.1016/j.bmcl.2005.04.020
34. Gilley, C. B.; Kobayashi, Y. *J. Org. Chem.* **2008**, *73*(11), 4198-4204. https://doi.org/10.1021/jo800486k
35. de la Torre, A. F.; Rivera, D. G.; Concepcion, O.; Echemendia, R.; Correa, A. G.; Paixao, M. W. *J. Org. Chem.* **2016**, *81*(3), 803-809.

https://doi.org/10.1021/acs.joc.5b02158
36. Basso, A.; Banfi, L.; Riva, R.; Guanti, G. *J. Org. Chem.* **2005**, *70*(2), 575-579. https://doi.org/10.1021/jo048389m
37. Klossowski, S.; Brodzka, A.; Zysk, M.; Ostaszewski, R. *Tetrahedron Asymm.* **2014**, *25*(5), 435-442. https://doi.org/10.1016/j.tetasy.2014.01.016
38. Riguet, E. *J. Org. Chem.* **2011**, *76*(20), 8143-8150. https://doi.org/10.1021/jo201184p
39. Hashimoto, T.; Kimura, H.; Kawamata, Y.; Maruoka, K. *Angew. Chem. Int. Ed.* **2012**, *51*(29), 7279-7281. https://doi.org/10.1002/ange.201201905
40. Zhang, J.; Yu, P.; Li, S. Y.; Sun, H.; Xiang, S. H.; Wang, J. J.; Houk, K.N.; Tan, B. *Science* **2018**, *361*(6407). https://doi.org/10.1126/science.aas8707
41. Su, Y.; Bouma, M. J.; Alcaraz, L.; Stocks, M.; Furber, M.; Masson, G.; Zhu, J. *Chem. Eur. J.* **2012**, *18*(40), 12624-12627. https://doi.org/10.1002/chem.201202174
42. Yue, T.; Wang, M. X.; Wang, D. X.; Masson, G.; Zhu, J. *Angew. Chem. Int. Ed.* **2009**, *48*(36), 6717-6721. https://doi.org/10.1002/anie.200902385
43. Zhang, Y.; Ao, Y. F.; Huang, Z. T.; Wang, D. X.; Wang, M. X.; Zhu, J. *Angew. Chem. Int. Ed.* **2016**, *55*(17), 5282-5285. https://doi.org/10.1002/anie.201600751
44. Zhao, W.; Huang, L.; Guan, Y.; Wulff, W. D. *Angew. Chem. Int. Ed.* **2014**, *53*(13), 3436-3441. https://doi.org/10.1002/anie.201310491
45. Wang, S. X.; Wang, M. X.; Wang, D. X.; Zhu, J. *Org. Lett.* **2007**, *9*(18), 3615-3618. https://doi.org/10.1021/ol7014658
46. Li, D.; Yang, D.; Wang, L.; Liu, X.; Wang, K.; Wang, J.; Wang, P.; Liu, Y.; Zhu, H.; Wang, R. *Chem. Eur. J.* **2017,** *23*(29), 6974-6978. https://doi.org/10.1002/chem.201700970
47. Katsuyama, A.; Yakushiji, F.; Ichikawa, S. *J. Org. Chem.* **2018,** *83*(13), 7085-7101. https://doi.org/10.1021/acs.joc.8b00038
48. Gilley, C. B.; Buller, M. J.; Kobayashi, Y. *Org. Lett.* **2007**, *9*(18), 3631-3634. https://doi.org/10.1021/ol701446y

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