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Recent Advances in Synthesis of 3,4-Dihydroisoquinolin-1(2*H*)-one

Mahesh R. Kulkarni and Nitin D. Gaikwad*[a]

The 3,4-dihydroisoquinolin-1(2*H*)-one motifs found in many natural products, synthetic molecules with a diverse range of the biological activities and represent a privilege scaffold. Thereby the number of the innovative synthetic methodologies has been reported for constructions of this scaffold, which includes metal catalyzed and metal free method, multicomponent, domino one pot protocol, oxidation, Friedel-Crafts type of cyclization. In the recent years many general protocols for the construction of this scaffold were reported in the literature and there is no focussed individual review for the 3,4-dihydroisoquinolin-1(2*H*)-one since 2001. This review focuses on the reports describing the new method for the synthesis of 3,4-dihydroisoquinolin-1(2*H*)-one, published since 2001 to till date. In this review, we approach method of the synthesis of 3,4-dihydroisoquinolin-1(2*H*)-one according to the strategy used for its synthesis, which includes, the intramolecular cyclization of carbamate/ urea/ thiourea/ isocyanate/ azidoamide, carbonylation/ carbomylation/ carbonyl insertion, metal catalyzed protocols by C–H activation by directing group, metal free domino procedures and oxidations of isoquinoline derivatives that were included in recent publications. Moreover, the reports published since 2001 for the synthesis of the chiral 3,4-dihydroisoquinolin-1(2*H*)-one are included.

1. Introduction

The 3,4-dihydroisoquinolin-1(2*H*)-one **1** belongs to class of nitrogen containing heterocyclic compound with six membered lactam ring fused together with benzene ring. It resembles likes to the rigidly fixed amino acid, which gives characteristics of biomimetic.[1] It is also called as isocarbostyril. Due to its pharmacological properties plethora of literature was available for this scaffold (Figure 1).

3,4-Dihydroisoquinolin-1(2*H*)-one core is more common in natural products and it belongs to the isoquinolinone alkaloid family. The molecular structures of representative isoquinolinone alkaloids such as, coryaldine (**2**), *N*-methyl coryaldine (**3**),[2] dorianine (**4**),[3] thalflavine (**5**),[4] (+)-plicamine (**7**),[5] isoquinolinone analogues isolated from a genus of nigella (**6**),[6] etc. is represented in Figure 2.

3,4-Dihydroisoquinolin-1(2*H*)-one core containing compounds possess wide range of biological activities such as anti-HIV,[7] antidepressant,[8] anticancer,[9] H3 receptor antagonist for treatment of neuropathic pain,[10] EZH2 inhibitor,[11] PARP inhibitor,[12] steroidomimetic,[13] cyclin-dependent kinase inhibitor,[14] anti-hypertension, anti-arrhythmia, antioxidant,[15] inhibitor of cholesterol biosynthesis,[16] anti-thrombotic,[17] antiinflammatory,[8] antibacterial,[18] PET imaging of s2 receptors.[19] The molecular structure of representative 3,4-dihydroisoquinolin-1(2*H*)-one's of biological importance is illustrated in Figure 3.

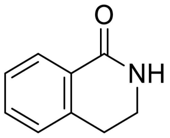

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Figure 1. Molecular structure of 3,4-dihydroisoquinolin-1(2*H*)-one

Palnosetron (**8**) is marketed 5-H3 agonist used to prevent nausea and omitting induced by chemotherapy.[20] The dihydroisoquinolinone **9** is a potent GSK-3 inhibitor and **10** was studied for the treatment of the thromboembolic disorder.[21]

With the abundance of this core in the natural products and growing interest in medicinal chemistry, several new synthetic methodologies were reported for its synthesis in the recent years. The methods for the synthesis of 3,4-dihydroisoquinolin-1(2*H*)-one up to 2001 have been described in details.[22] V. A. Glushkov and Yu. V. Shklyaev were published the first report on the methods of synthesis for isoquinolinone's (3,4-dihydroisoquinolin-1(2*H*)-one, isoquinolin-1(2*H*)-one, 1,2-dihydroisoquinolin-3(4*H*)-one, isoquinolin-3(2*H*)-one) in science of synthesis. This report covered the literature from 2004–2015 and few selected literature reports of 2016 towards the synthesis of 3,4-dihydroisoquinolin-1(2*H*)-one.[23] However, there is no focussed individual review for the 3,4-dihydroisoquinolin-1(2*H*)-one since 2001. This review is focusses on the reports describing the new methods for the synthesis of 3,4-dihydroisoquinolin-1(2*H*)-one, published since 2001 to till date. In this review, we approach method of the synthesis of 3,4-

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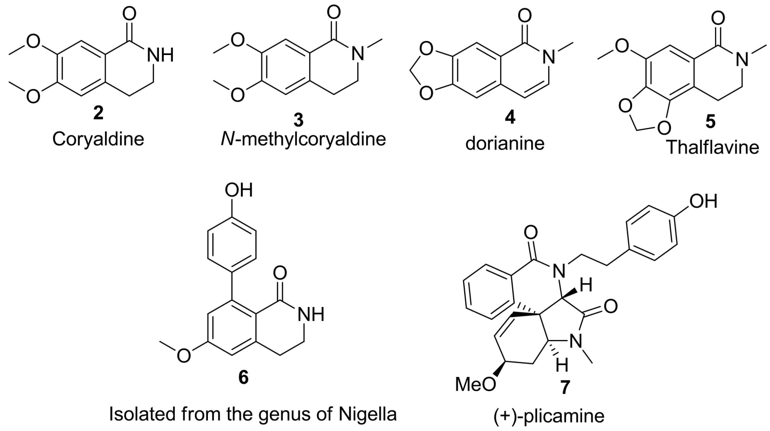


Figure 2. Molecular structure for representative natural 3,4-dihydroisoquinolin-1(2*H*)-one

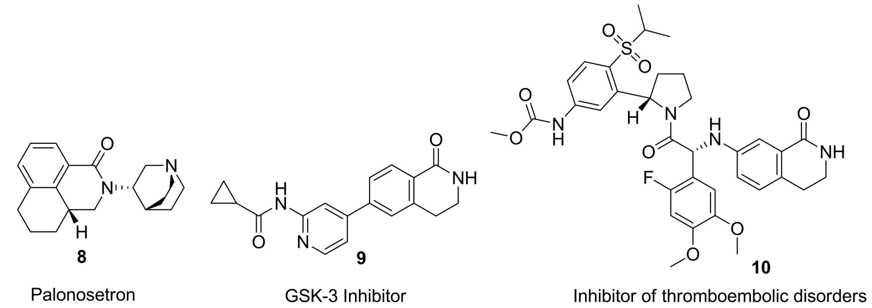


Figure 3. Molecular structure of representative 3,4-dihydroisoquinolin-1(2*H*)-one drugs

Dr. Nitin D. Gaikwad was born in 1978 in Nashik, Maharashtra, India. He obtained his post graduate degree in Organic Chemistry and received his Ph.D. degree in Chemistry from Savitribai Phule Pune University in 2012. In 2003 he was appointed as assistant professor and in 2018 he became Associate Professor at K.R.T. Arts, B.H. Commerce and A.M. Science (K.T.H.M.) College, Nashik. Currently, he serves as Associate Professor and Research Guide of the Doctoral Course in Chemistry at K.R.T. Arts, B.H. Commerce and A.M. Science (K.T.H.M.) College, Nashik. His major research interests are in synthetic organic chemistry, Heterocyclic chemistry, Method development and biological evaluation. His current research interest focuses on the development of novel heterocyclic molecules acting as anticancer agents.

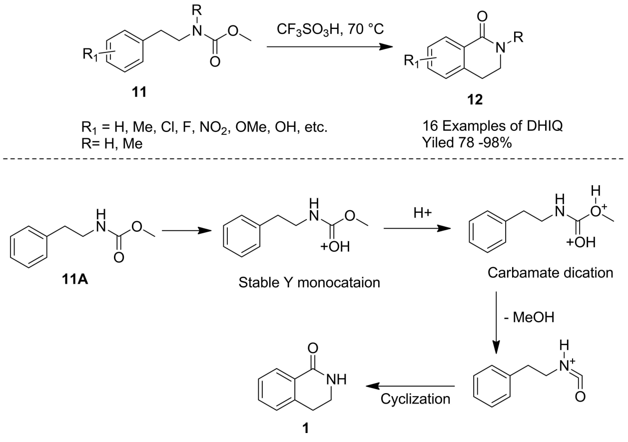
Dr. Mahesh R. Kulkarni obtained his B. Sc. and M. Sc. in chemistry from Swami Ramanand Teerth Marathwada University Nanded, Maharashtra, India in 2004. He has worked for two years with Cipla Ltd. Kurkumbh, Dist. Pune as a process development chemist. In 2008 started his career with Piramal Life sciences Ltd. Mumbai (formerly known as Nicholas Piramal Research Center) in the medicinal chemistry department. In 2013 he has selected for industrial Ph. D. program and completed his Ph. D. in chemistry, from Savitribai Phule Pune University in 2019 under supervision Dr. Nitin D. Gaikwad. Presently he is working as a Senior Research Scientist in Route finding team of the Piramal discovery solutions, Ahmedabad, Gujarat, India. His current research interest is in the field of development of new synthetic methodologies for construction of medicinally important scaffolds and medicinal chemistry.

dihydroisoquinolin-1(2*H*)-one according to the strategy used for its synthesis. The type of the approach used for the construction of 3,4-dihydroisoquinolin-1(2*H*)-one includes, the intramolecular cyclization of carbamate/ urea/ thiourea/ isocyanate/ azidoamide, carbonylation/ carbomylation/ carbonyl insertion, metal catalyzed protocols/ C–H activation by a directing group, metal free domino procedures and oxidations of isoquinoline derivatives that were included in recent publications. Moreover, the reports published since 2001 for the synthesis of the chiral 3,4-dihydroisoquinolin-1(2*H*)-one are included.

2. Intramolecular cyclization of carbamate/ urea/ thiourea/ isocynate/ azidoamide

The cyclization of arylethylcarbamates to dihydroisoquinolinones was known in literature using various reagents such as $POCl_3$, PPA, Tf_2O, PCl_5, etc., however these methods limited for the synthesis of the natural products and the electron rich substrates. Tomohiko Ohwada and co-workers synthesized the 3,4-dihydroisoquinolin-1(2*H*)-one **12** in high yield by the cyclization of the arylethyl carbamate **11** in the presence of the strong acid such as methane sulfonic acid. They found out that acid strength is the key factor for the cyclization of carbamate to 3,4-dihydroisoquinolin-1(2*H*)-one. On using the low concentration of the acid only the formation of the intermediate mono protonated carbamate was observed, which does not under goes cyclization on heating also. However, further on increasing in the acid strength, cyclization to 3,4-dihydroisoquinolin-1(2*H*)-one started. Use of the strong acid in high concentration led to the formation of carbamate dicataion, which is dissociated to the protonated isocyanate which further cyclized to 3,4-dihydroisoquinolin-1(2*H*)-one (Scheme 1).[24]

Additionally, the same research group demonstrated that the phenyl ethyl carbamate bearing ortho salicylate (**13**) as an ether group accelerates the rate for the formation of the protonated isocyanate which underwent subsequent electrophilic cyclization to 3,4-dihydroisoquinolin-1(2*H*)-one. They found out ortho salicylate helps in accelerating the C–O bond dissociation which facilitates the formation of the isocyanate cation. The phenyl ethyl carbamte bearing O-salicylate **13** cyclized to 3,4-dihydroisoquinolin-1(2*H*)-one **14** at room temperature and the reaction time reduced drastically as compared the cyclization methyl phenethylcarbamate which took several hour heating at 70 °C. Furthermore, the reaction proceeds with same efficiency on the chiral substrate without loss in chirality (Scheme 2. Examples **14a** to **14c**).[25]

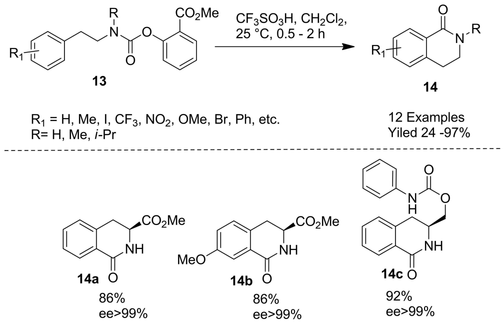


Scheme 1. Methanesulfonic acid mediated cyclization of arylethylcarbamates to 3,4-dihydroisoquinolin-1(2*H*)-one

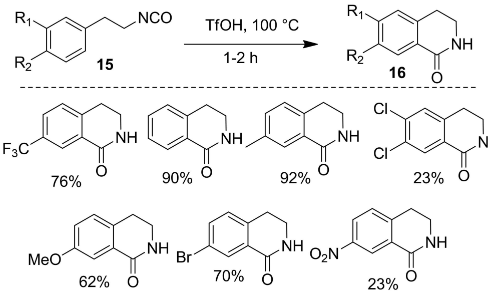
Ryo Murashige and co-workers established intramolecular Friedel-Crafts cyclization of 1-(2-iso-cyanatoethyl)benzene derivatives (**15**) in the presence of trifluoromethane sulfonic acid. Trifluoromethane sulfonic acid serves as an efficient catalyst for the cyclization of 1-(2-iso-cyanatoethyl)benzene **15** rather the other tested Lewis/ Bronsted acid catalyst (Scheme 3).[26]

L. Caggiano *et al.* developed one pot protocol for the synthesis of the 3,4-dihydroisoquinolin-1(2*H*)-one by the reaction of the 3,4-Methylenedioxydihydrocinnamic (**17**) acid with DPPA in toluene. The evaporation of the solvent followed by treatment of the generated isocyanate with borontrifluride etherate gave 3,4-dihydroisoquinolin-1(2*H*)-one (**18 a-c**) analogues in 55–81% yield. Notably, under the optimized conditions, the reaction of the trimethoxyhydrocinnamic acid **19** gave the 8-hydroxy-6,7-dimethoxy-3,4-dihydroisoquinolin-1(2*H*)-one **20** in which one methoxy group was deprotected (Scheme 4).[27]

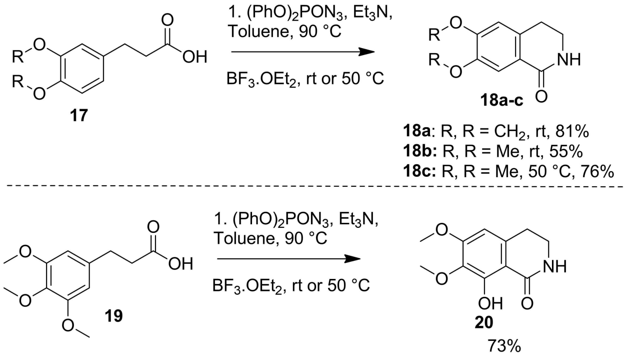
N-Boc-protected (β-arylethyl)carbamates **21** on reaction with 2-chloropyridine and triflic anhydride in the presence of



Scheme 2. Cyclization of arylethylcarbamates bearing ortho salicylate to 3,4-dihydroisoquinolin-1(2*H*)-one

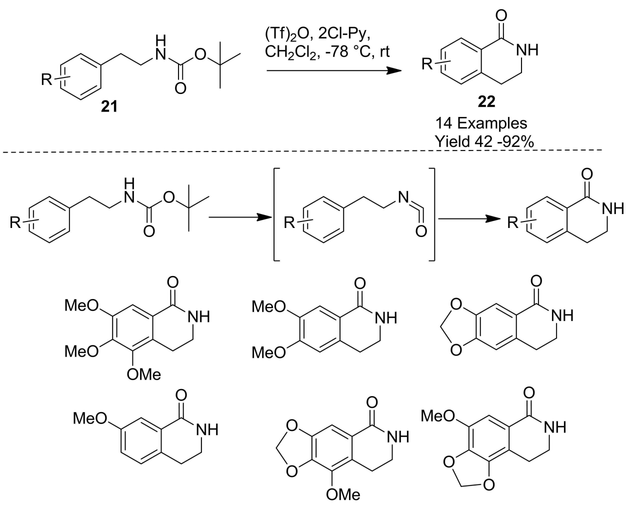


Scheme 3. Friedel-Crafts-type cyclization of arylethylisocynate to 3,4-dihydroisoquinolin-1(2*H*)-one

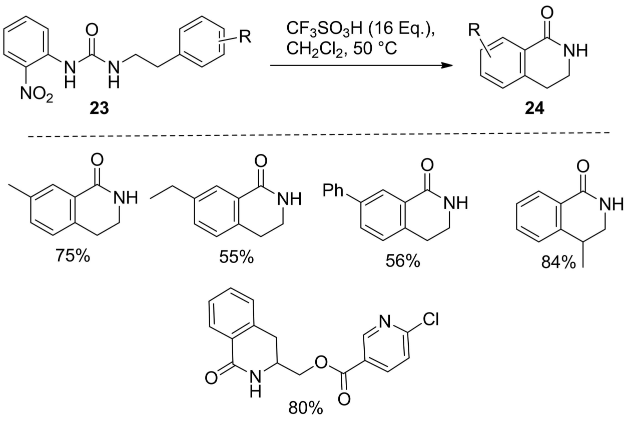


Scheme 4. One pot synthesis of 3,4-dihydroisoquinolin-1(2*H*)-one

the Lewis acid such as boron trifluoride etherate yields 3,4-dihydroisoquinolin-1-ones **22** in 42–92% yield. The reaction proceeds via the formation of the isocyanate as reactive intermediate which undergoes Friedel-Crafts-type cyclization (Scheme 5).[28]



Scheme 5. Cyclization of *N*-Boc-protected (β-arylethyl)carbamates to 3,4-dihydroisoquinolin-1(2*H*)-one



Scheme 6. Intramolecular cyclization of the *O*-Nitro urea/thiourea to 3,4-dihydroisoquinolin-1(2*H*)-one

Douglas A. Klumpp and co-workers demonstrated that urea and thiourea participates in Friedel-Craft types of the reaction in the presence of super acids. The O-Nitro urea/thiourea (**23**) are the best starting materials for the synthesis of 3,4-dihydroisoquinolin-1(2*H*)-ones (**24**) and related thiones. Methanesulfonic acid serves as the best catalyst for the intramolecular Friedel Crafts cyclization (Scheme 6).[29]

Metin Balci *et al.* synthesized 3,4-dihydroisoquinolinone core starting form methyl 2-(3-methoxy-3-oxopropyl)benzoate **25**. This method involves the conversion of the ester group adjacent to the methylene to isocyanate **29** which on reaction with aniline yields urea. The intermediate urea cyclized to 3,4-dihydroisoquinolin-1(2*H*)-one **31** in the presence of the sodium hydride (Scheme 7).[8]

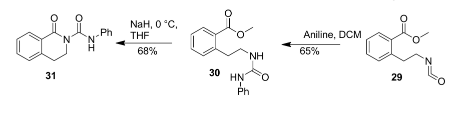
The radical cyclization is the powerful technique for the constructions of the many heterocycles, it involves the formation of the C–C and the carbon Nitrogen bond. Luisa Benati *et al.* constructed the 3,4-dihydroisoquinolin-1(2*H*)-one/ lactams by intramolecular cyclization of acyl radical onto the azido group **34**. The azidacyl radical is generated by the homolytic fission of the thioester **32** which is cyclized to the lactam/ 3,4-dihydroisoquinolin-1(2*H*)-one **35** (Scheme 8).[30]

Staudinger type of the reductive cyclization of azido amide **36** was investigated by Chang-Woo Cho group (Scheme 9). This method gives access to 3,4-dihydroisoquinolin-1(2*H*)-one **1** by direct lactamization of azido amide **36** under mild reaction conditions.[31]

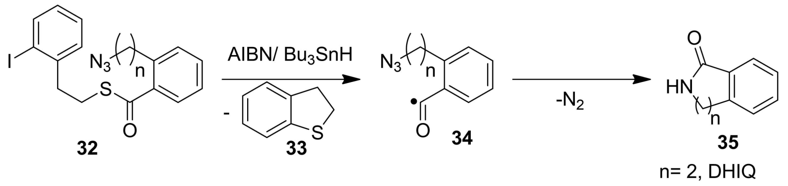
Additionally, the same research group also developed the procedure for the cyclization of azidoamide **36** to 3,4-dihydroisoquinolin-1(2*H*)-one **1** in presence of the tributyltin hydride. This procedure produces 3,4-dihydroisoquinolin-1(2*H*)-one **1** in 92% yield (Scheme 10).[32]

3. Carbonylation/ carbamoylation and carbonyl insertion

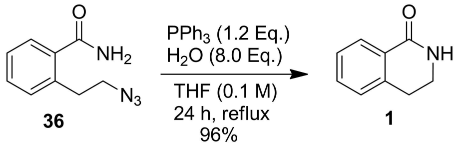
The palladium catalyzed β-C(SP^2)H bond in oxalylamide protected aromatic amine **37** with carbon monoxide serves an efficient protocol for the synthesis of 3,4-dihydroisoquinolinones **38.** This is an efficient protocol for synthesis of 3,4-dihydroisoquinolinones with a wide range of the substituent (Scheme 11).[33]



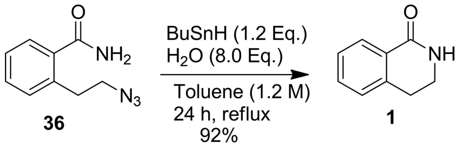
Scheme 7. Intramolecular cyclization of the methyl benzoate bearing *o*-urea to 3,4-dihydroisoquinolin-1(2*H*)-one



Scheme 8. Radical cyclization to 3,4-dihydroisoquinolin-1(2*H*)-one



Scheme 9. Reductive cyclization of azido amide under Staudinger condition



Scheme 10. Reductive cyclization of azido amide using tributyl tin hydride

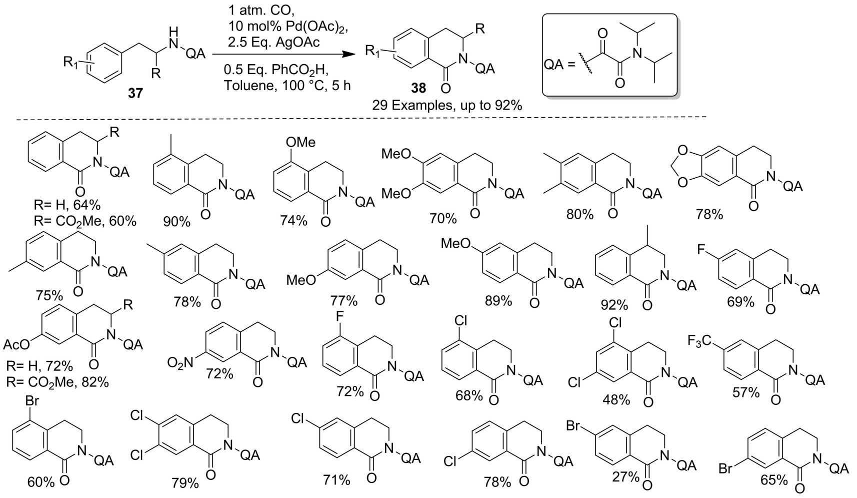
Pd(II)-catalyzed NH_2 directed carbonylation of quaternary aromatic α-amino esters **39** yields 3,4-dihydroisoquinolin-1(2*H*)-one **40** in moderate to good yield. The reaction proceeds via the formation of ortho-palladation complex by Pd(II) which could be isolable and the oxidant benzoquinone is necessary for regeneration Pd(II) from Pd(0). Notably, the bulky substituents around the amino group were favourable for the carbonylation. The quaternary carbon of the α-amino ester plays an important role in cyclopalladation reaction (Scheme 12).[34]

Cobalt catalyzed C–H carbonylation of phenylethylamine **41** using the traceless directing group serves as a method for synthesis of 3,4-dihydroisoquinolin-1(2*H*)-one **42** in 65% yield (Scheme 13).[35]

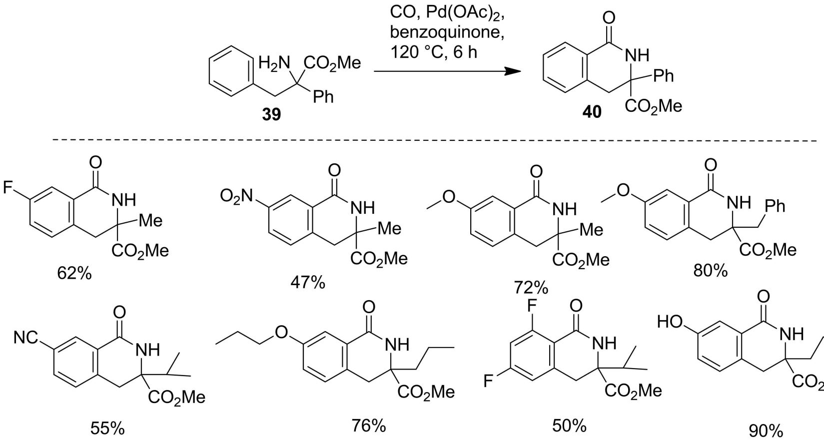
Carbamoylation of aryl halide by metal reagent gives access to the amide. The intramolecular carbamoylation reaction yields lactam. Motoki Yamane *et al.* developed palladium catalyzed carbamoylation of the aryl halide to amide using aminopentacarbonyltungsten **43**.[36] This method can be applied for intramolecular carbamoylation to 3,4-dihydroisoquinolin-1(2*H*)-one **1** in 57% yield (Scheme 14).

Furthermore, Motoki Yamane and co-worker demonstrated $Mo(CO)_6$ catalyzed carbamoylation of aryl iodide **44** to 3,4-dihydroisoquinolin-1(2*H*)-one **1** in 70% yield. The advantage of this procedure over previously reported procedure by the same research group is, here no need to synthesis of aminopentacarbonyltungsten intermediate and reduced the reaction time drastically. Moreover, this method does not require the use of the carbon monoxide gas, which was used in excess in case of the traditional methods (Scheme 15).[37]

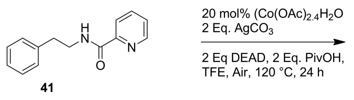
S. Chung and co-workers used the aromatic tosylate for amino carbonylation for the synthesis of the carboxymide using palladium catalyst. The condition identified can be used for synthesis of 3,4-dihydroisoquinolin-1(2*H*)-one using intramolecular carbonylation in 81% yield. The cyclization to lactam with the cleavage of Boc group was reported (Scheme 16).[38]



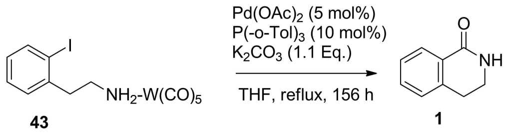
Scheme 11. Palladium-catalyzed carbonylation of β-arylethylamide



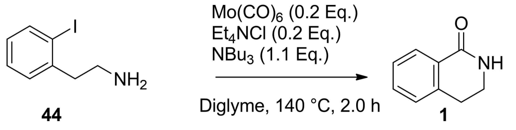
Scheme 12. Pd(II)-catalyzed NH_2 directed carbonylation of quaternary aromatic α-amino esters



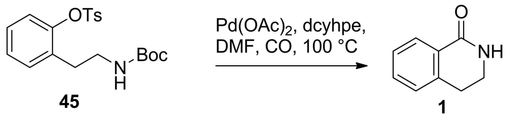
Scheme 13. Cobalt catalyzed *C-H* carbonylation of phenylethylamine



Scheme 14. Palladium catalyzed carbamoylation of aryl halide



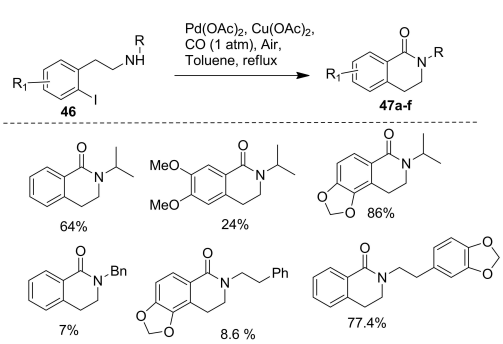
Scheme 15. Intramolecular carbamoylation catalyzed by $Mo(CO)_6$



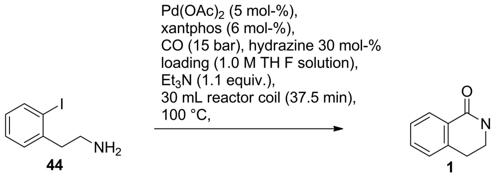
Scheme 16. Palladium catalyzed carbamoylation of aryl tosylate

Kazuhiko Orito and co-workers synthesized dihydroisoquinolinones **47** by palladium (II) catalyzed direct carbonylation of arylethylamine **46** using $Pd(OAc)_2$ and $Cu(OAc)_2$ in an CO atmosphere containing air. This is an example of the phosphine ligand free protocol for carbonylation (Scheme 17).[39]

The continuous flow, palladium catalyzed method for carbonyl insertion was developed by M. O'Brien *et al.* Using this protocol the 3,4-dihydroisoquinolin-1(*2H*)-one **1** is synthesized in 95% yield (Scheme 18).[40]



Scheme 17. Synthesis of the dihydroisoquinolinones by the phosphine ligand free palladium catalyzed direct carbonylation

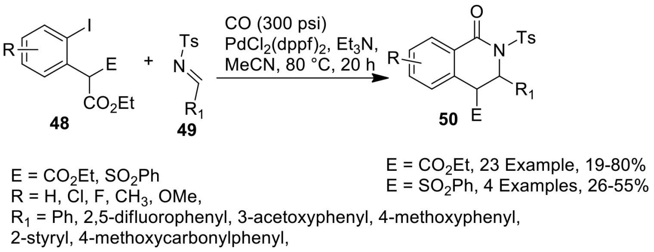


Scheme 18. Continuous flow Palladium catalyzed carbamoylation of aryl halide

Kazumi Okuro and Howard Alper constructed the 3,4-dihydroisoquinolin-1(*2H*)-one by palladium catalyzed carbonylation of the 2-(iodoaryl)malonates (**48**) with *N*-tosylimine (**49**). This procedure involves the one pot Mannich condensation/ decarboxylation / carbonylation reactions. Notably, this protocol gives access to the trans- diastereoisomer of the 3,4-dihydroisoquinolin-1(*2H*)-one (**50**) derivatives in moderate to good yield (Scheme 19).[41]

4. Metal catalyzed reaction by C-H activation/ domino protocol

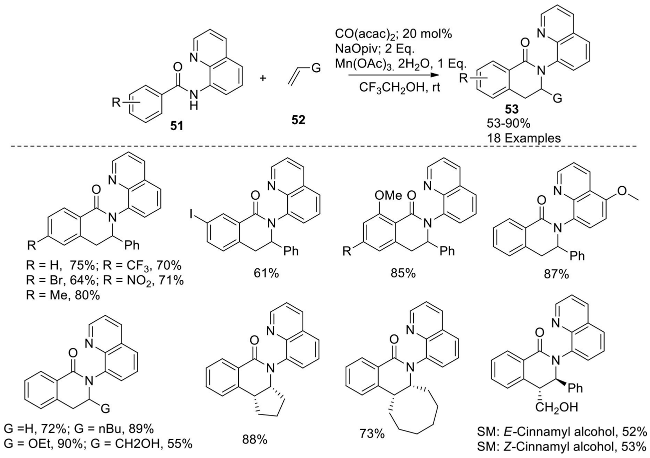
The cobalt catalyzed reaction of aminoquinoline directed ortho sp^2 C–H bond of arylamide **51** with alkene **52** gives access to



Scheme 19. Synthesis of 4-alkoxycarbonyl/phenylsulfonyl-3,4-dihydroisoquinolin-1(2*H)*-ones

3,4-dihydroisoquinolin-1(2*H*)-one (**53**) at room temperature in moderate to good yield. Mn(OAc)$_3$ serves as co-catalyst, the reaction proceeds smoothly in trifluoroethanol solvent and the oxygen from the air is serves as an oxidant. The reactions proceeds with the same efficiency on mono, di-substituted and cyclic alkene with tolerance of both electrons withdrawing and donating substituent on aryl amide (Scheme 20).[42]

N. Chatani *et al.* developed the method for 3,4-dihydroisoquinolin-1(2*H*)-one synthesis using the rhodium catalyzed alkylation of aromatic amide **54** with *N*-Vinylphthalimide **55** followed by cyclization. 8-aminoquinoline is acting as the directing group. The deuterium labelling experiment gave an evidence that reactions proceeds through the carbine mechanism (Scheme 21).[43]



Scheme 20. Cobalt catalyzed reaction of aminoquinoline directed ortho sp^2 C–H bond of arylamide with alkene

Nicolas Guimond *et al.* developed the protocol for the synthesis of *N*-heterocycles using a rhodium catalyst.[44] 3,4-Dihydroisoquinolin-1(2*H*)-one **60** was synthesized in good to excellent yield at room temperature using rhodium catalyzed internal oxidant directed synthesis with low catalyst loading (0.5 mol%). This protocol is an example of C–H bond functionalization at room temperature with very low catalyst loading (Scheme 22).

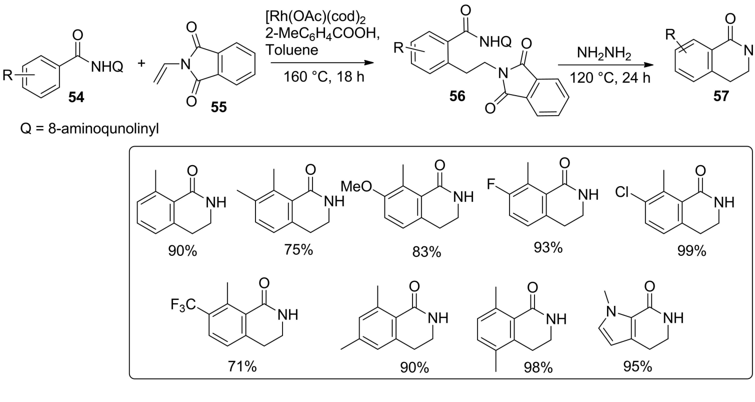
Y. Wang *et al.* reported the synthesis of 3,4-dihydroisoquinolin-1(2*H*)-one **63** by rhodium catalyzed [4 + 2] annulation of *N*-methoxybenzamides (**61**) and the β-alkyl substituted ketenamines (**62**) (Scheme 23). The annulation product further undergoes Cu catalyzed intramolecular C–N coupling to yield benzo[4,5]imidazo[1,2-*b*]isoquinolin-11-ones in one pot (**64**) (Scheme 24).[45]

Frank Glorius *et al.* optimized the protocol for the Rh(III) catalyzed oxidative olefination of the directed C–H bond activation of *N*-methoxy benzamide **65**. Changing the substituents on the directing/oxidizing group resulted in the synthesis of library of 3,4-dihydroisoquinolin-1(2*H*)-one **66** (Scheme 25).[46]

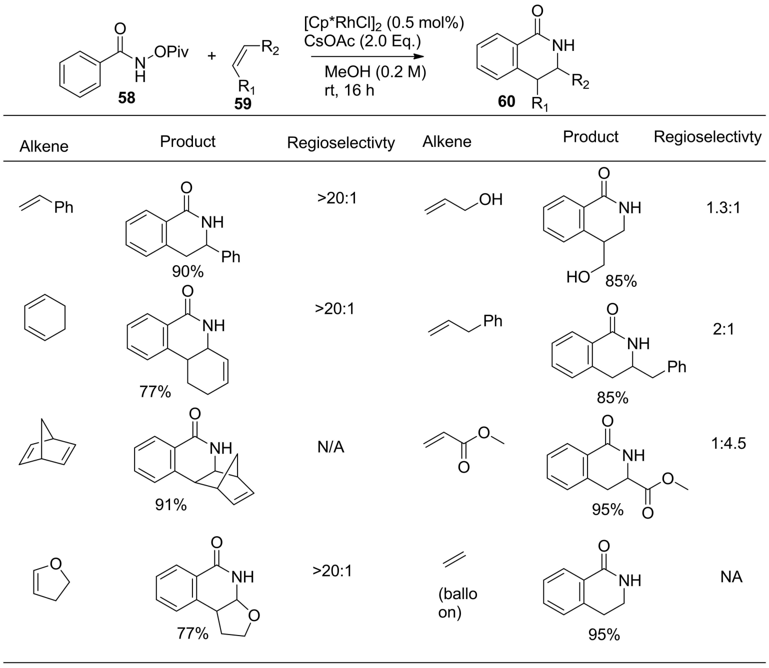
Tomislav Rovis *et al* demonstrated the regioselective synthesis of dihydroisoquinolinone form aliphatic alkene and O-pivalyl hydraxamic acid (**67**) in presence of the Rh(III) catalyst bearing the bulky substituent on the ligand. Notably, the catalyst having ligand with sterically bulky substituent (Cp*t*) provides excellent regioselectivity over the Cp* ligand (Scheme 26).[47]

Tomislav Rovis *et al* synthesized the dihydroisoquinolinones **71** by Rh(III)-catalyzed intramolecular amidoarylations of via *C-H* activation of directed amide **70** (Scheme 27).[48]

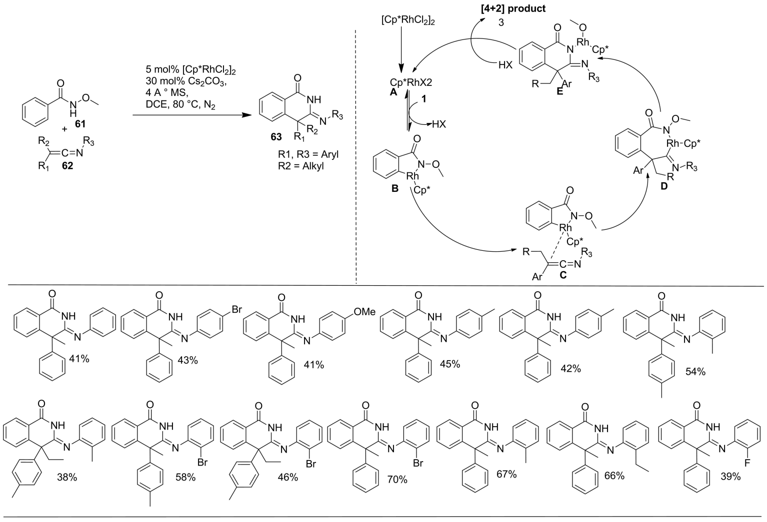
Due to the attractive pharmacological properties fluorinated heterocycles in the medicinal chemistry and agrochemicals, synthesis of these remains demanded. In this direction are Jia-Qiang Wu *et. al.* reported the synthesis of gem-difluorinated dihydroisoquinolin-1(2*H*)-ones **73**. The author has synthesized



Scheme 21. Rhodium catalyzed alkylation of aromatic amide having 8-aminoquinoline as directing group with *N*-Vinylphthalimide



Scheme 22. Rhodium catalyzed synthesis of 3,4-dihydroisoquinolin-1(2*H*)-one



Scheme 23. Rhodium catalyzed [4 + 2] annulation of *N*-methoxybenzamides to 3,4-dihydroisoquinolin-1(2*H*)-one.

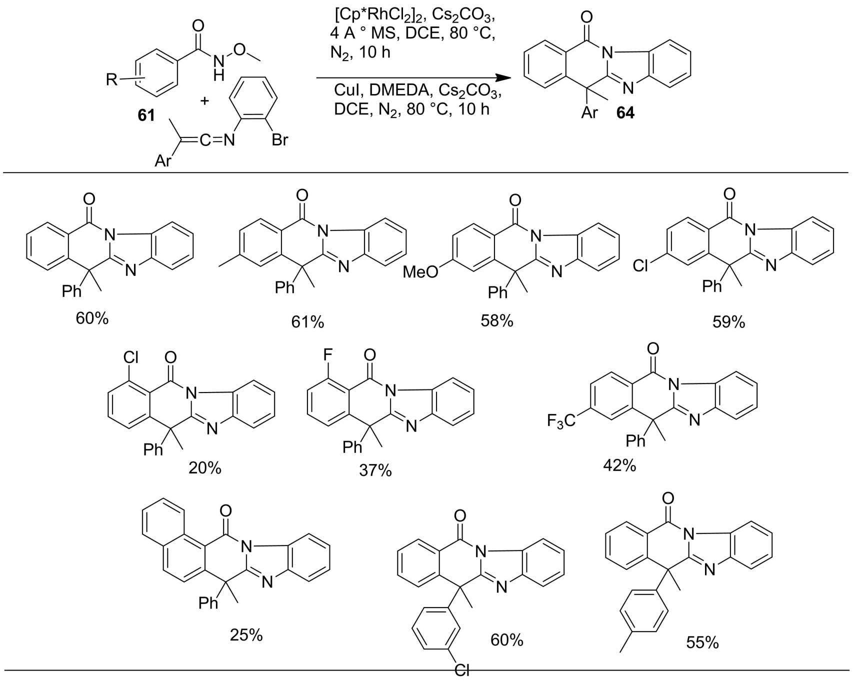
the gem-difluorinated dihydroisoquinolin-1(2*H*)-ones **73** via Rh (III) catalyzed C–H activation of aryls **67**, alkenes followed by coupling with difluorovinyl tosylate **72** (Scheme 28).[49]

Moreover, G. A. Molander group synthesized 4-Trifluoroboratotetrahydroisoquinolones (**75**) by using Rh(III) catalyzed annulation of the benzamide derivative (**67**) and the coupling partner used is vinyltrifluoroborate (**74**) (Scheme 29).[50]

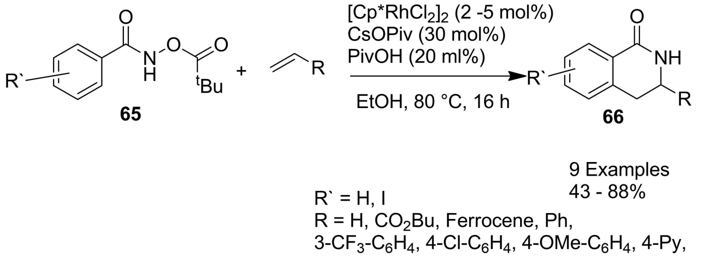
The 4-Trifluoroboratotetrahydroisoquinolones derivatives (**75**) further *N*-arylated to get corresponding *N*-substituted analogues (**77**) with retention of the boron substituent which was converted to 4-OH dihydroisoquinolinone by treatment with Oxone in acetone at rt (Scheme 30).

Using this method the natural product Corydildine **2** can be synthesized as below (Scheme 31),

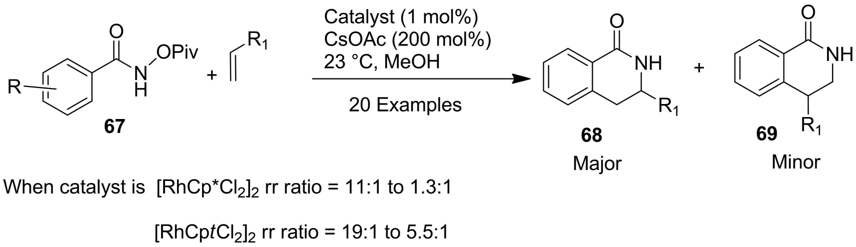
A. B. Charette and co-workers have optimized the protocol for the synthesis ethyl 1,2,3,4-tetrahydroisoquinolone-3-carboxylates. This involves the intramolecular palladium catalyzed $\beta-$ functionalization of the cyclopropyl $\alpha-$amino-acid-derived benzamides. The optimized protocol provide the access to ethyl 1,2,3,4-tetrahydroisoquinolone-3-carboxylates without use of the silver or pivalate additives. However, in some challenging substrates the use of these additive may be beneficial (Scheme 32).[51]



Scheme 24. One-pot preparation of benzo[4,5]imidazo[1,2-*b*]isoquinolin-11(6*H*)-ones



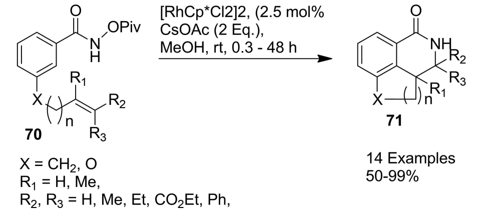
Scheme 25. Rh(III)-Catalyzed directed C–H olefination using an oxidizing directing group:



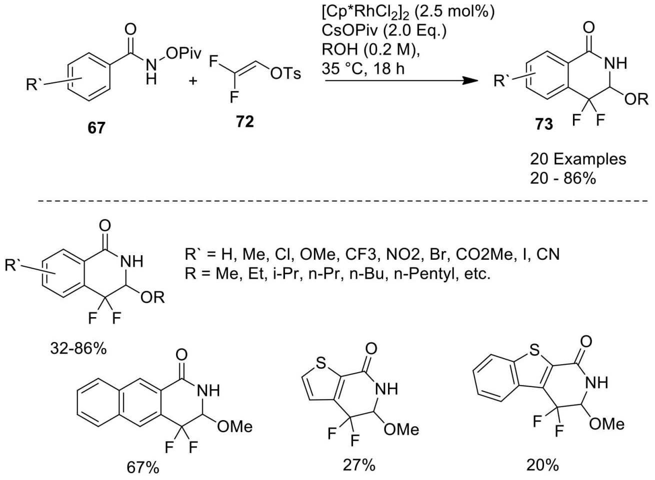
Scheme 26. Ligand control synthesis of dihydroisoquinolinones

Frank Glorius *et al.* synthesized the olegocyclic dihydroisoquinolinones (**81**) by Rhodium(III) catalyzed intramolecular cyclization of the alkene via *C-H* activation. Using this methodology variety of the olegocyclic dihydroisoquinolinones (**81**) of biological importance were prepared. The reaction proceeds at room temperature without use of the external oxidant. Notably, the less favoured *C-H* bond activated and functionalized under the reaction condition (Scheme 33).[52]

The regioselectivity during the synthesis of the dihydroisoquinolinones by C–H functionalization of the aryl hydroxycarbamate using Rh(III) mainly depends on the substrates. Nicolai Cramer and co-workers developed the method for regioselective synthesis of the 3 and 4- substituted dihydroisoquinolinone where, the regioselectivity is controlled fully by the catalyst. Author have performed study towards the examination of contributing factors of the different catalyst towards the



Scheme 27. Synthesis of dihydroisoquinolinones via Rh(III)-catalyzed intramolecular amidoarylations



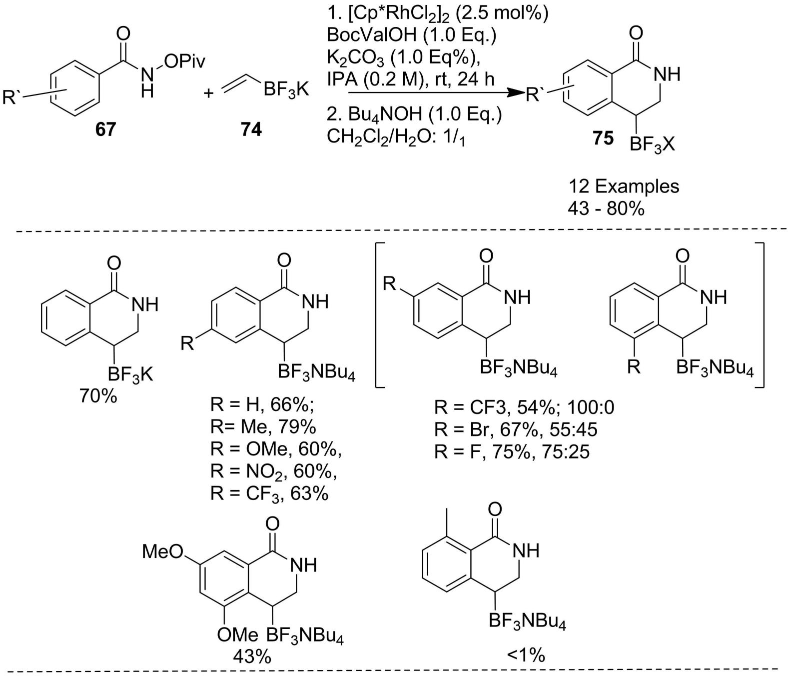
Scheme 28. Synthesis of 4,4-Difluoro-3-alkoxy-3,4-dihydroisoquinolin-1(2*H*)-ones

regioselectivity by computational and experimental approach. From their study they reach to the conclusions, the stability of the styrene-rhodium complex, ability of migratory insertion and differences in activation energies are the key factors for the regioselective synthesis of 3,4-dihydroisoquinolin-1(2*H*)-one using this methodology (Scheme 34).[53]

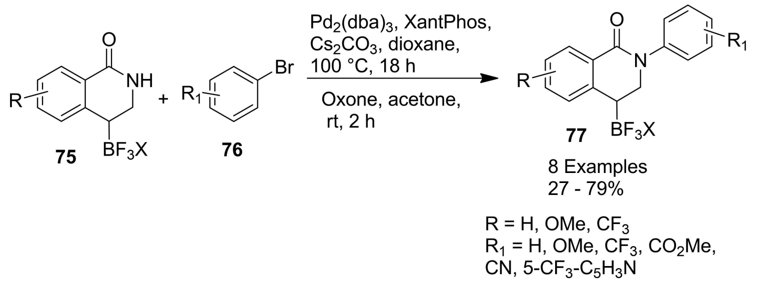
Tandem catalysis involves the two or more sequential bond forming reactions by two or more catalysts in a single flaks. The protocols involving the use of tandem catalysis advantages over the traditional methods in terms of the reaction time, efforts, waste minimization, utilizations of the diverse relativities of the catalyst and synthesis of complex molecules from the simple starting materials. In this directions Shang-Shi Zhang *et al.* developed a protocol for the synthesis of 3,4-dihydroisoquinolin-1(2*H*)-one by Rh(III)/Pd(II) tandem catalysis. The reaction proceeds under mild conditions with a good substrate scope with high regio and stereo selectivity (Scheme 35).[54]

Dmitry S. Perekalin and co-workers synthesized the 4-substituted dihydroisoquinolinones in the regioselective manner by rhodium(III) catalyst complexed with bulky cyclopentadinyl ligand. The bulky cyclopentadinyl ligand gives access to 4-dihydroisoquinoline **90**. The reaction proceeds with C–H activation of the arylhdroxamic acid **89**. This protocol gives access to the 4- substituted dihydroisoquinolinones **90** with excellent regio selectivity. The bulky ligand of the rhodium (III) catalyst $[(C_5H_2tBu_2CH_2tBu)RhCl_2]_2$ is synthesized by the 2+2+1-cyclotrimerization of *tert*-butylacetylene (Scheme 36).[55]

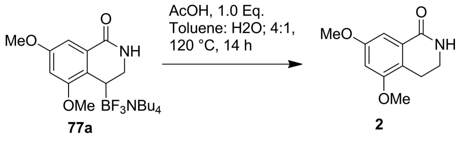
Rh catalyzed *C-H* functionalization of O-pivalyl benzhydroxamic acids **67** with propelene **91** gas gives access to 4-methyl substituted dihydroisoquinolinones **92**. This protocol gives access to the 4-methyl substituted dihydroisoquinoli-



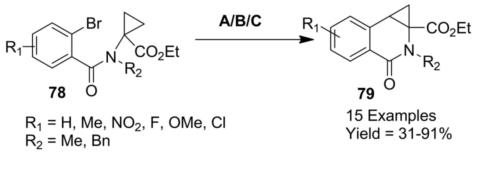
Scheme 29. Synthesis of 4-Trifluoroboratotetrahydroisoquinolones derivatives



Scheme 30. Synthesis of *N*-arylated –4-Trifluoroboratotetrahydroisoquinolones derivatives

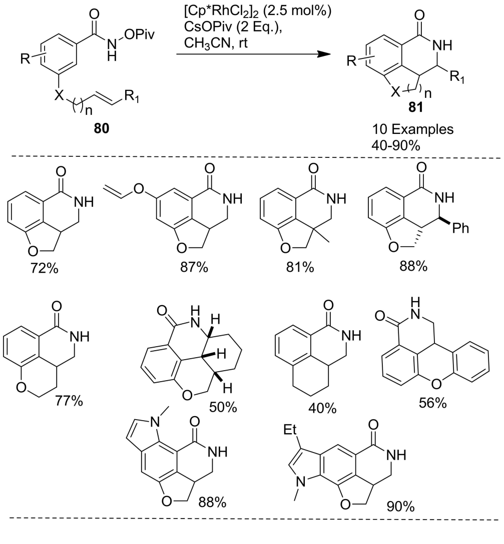


Scheme 31. Synthesis of Corydildine from 4-Trifluoroboratotetrahydroisoquinolones derivatives



Reaction Conditions:
Conditions A: $Pd(OAc)_2$ (5 mol %), PCy_3 (5 mol %), K_2CO_3 (1.5 eq.), toluene [0.2 M],110 °C, 16 h;
Conditions B: $Pd(OAc)_2$ (5 mol %), $PtBu_2MeoHBF_4$ (5 mol %), CsOPiv (0.3 eq.), K_3PO_4 (1.5 eq.), toluene [0.2 M], 110 °C, 16 h;
Conditions C: $Pd(OAc)_2$ (5 mol %), PCy_3 (5 mol %), Ag_3PO_4 (0.3 eq.), K_2CO_3 (1.5 eq.), toluene [0.2 M], 110 °C, 16 h.

Scheme 32. Synthesis of ethyl 3-oxo-1a,2,3,7b-tetrahydro-1*H*-cyclopropa[*c*]isoquinoline-1*a*-carboxylate derivatives



Scheme 33. Synthesis of olegocyclic dihydroisoquinolinones

nones **92** with good regioselectivity and tolerated with for the various substituent on aryl group and on alkene (Scheme 37).[56]

The ruthenium catalyzed reaction of the *N*-methoxybenzamide **86** with styrene **83** or norbornadiene **94** in the presence of sodium acetate in trifluoroethanol at 50 °C gives access to the 3-substituted dihydroisoquinolinone **93** and fused dihydroisoquinolinone **95**. This is an example of C–H bond olefination by ruthenium catalyst. Alkene with electron withdrawing groups other than aryl gives olefinated un-cyclized product (Scheme 38).[57]

M. Jeganmohan *et. al* developed the method O-allylation of benzamide **86** using allylic acetate **96** using Ruthenium(II) catalyst at rt. This protocol can be used for the synthesis of dihydroisoquinolinone **97** in moderate yield (Scheme 39).[58]

David C. Rees *et. al* synthesized the 3,4-dihydroisoquinolin-1(*2H*)-one **98** / **99** for fragment based drug discovery by using the ruthenium catalyzed reaction of the hydraxamic acid derivative with alkene (Scheme 40).[59]

Grigg R. *et al.* synthesised the dihydroisoquinolinones (**102**) in good yield by the palladium catalyzed multicomponent domino reaction of substituted allene **101**, ammonium tartarate and 2-Iodobenzoate **100** (Scheme 41).[60]

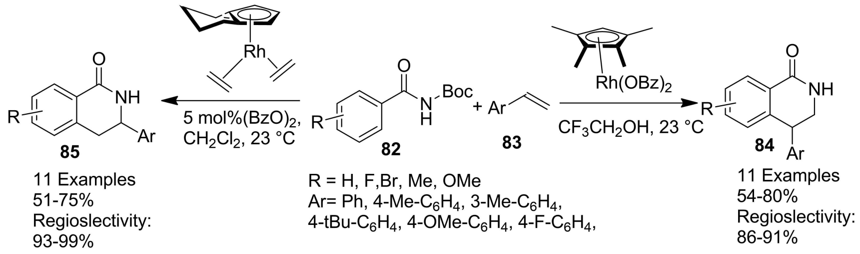
5. Metal free domino protocols

Zhau *et al.* synthesized 4-hydroxyalkyl-substituted 3,4-dihydroisoquinolin-

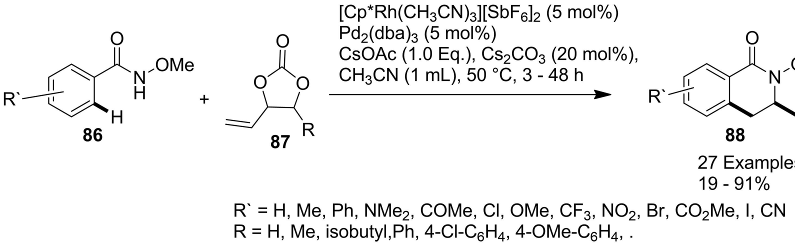
1(2*H*)-one derivatives (**105**) by the reaction of *N*-allybenzamides (**103**) with alcohols (**104**) which acts as radical partner (Scheme 42).[61]

Yi Pan *et al.* synthesized 4-alkyl-substituted dihydroisoquinolin-1(2*H*)-ones (**108**) by oxidative alkylarylation reactions of substituted *N*-allylbenzamide (**106**). Herein, used cycloalkane **107** as a radical partner instead of alcohols.The reaction proceeds through a sequence of alkylation followed by intramolecular cyclization (Scheme 43).[62]

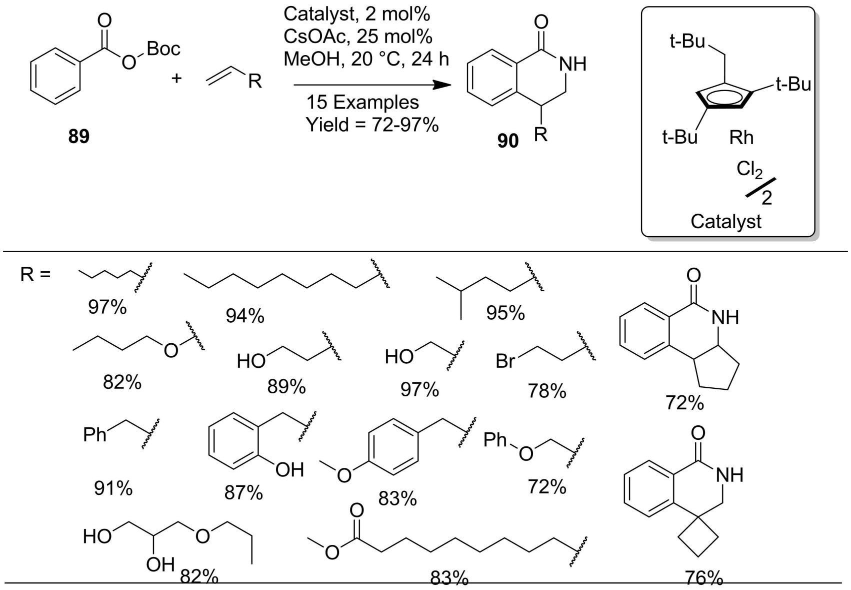
Changduo Pan and co-workers constructed the chloromethyl substituted dihydroisoquinolinones (**111**) by cascade radical chloromethylation/ arylation of the *N*-allyl benzamide (**109**) by CH_2Cl_2. The reaction involves the direct functionalization of SP^3 C–H of CH_2Cl_2 with SP_2 C–H of the phenyl ring. Under the optimized conditions the $CHCl_3$ serves as trichloromethylating reagent. The author has proposed the radical mechanism for this transformation. The *tert*-butyl radical generated in reaction



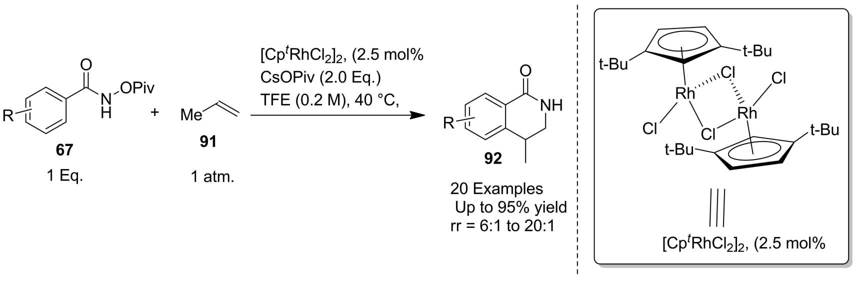
Scheme 34. Catalyst controlled regioselective synthesis of dihydroisoquinolinones



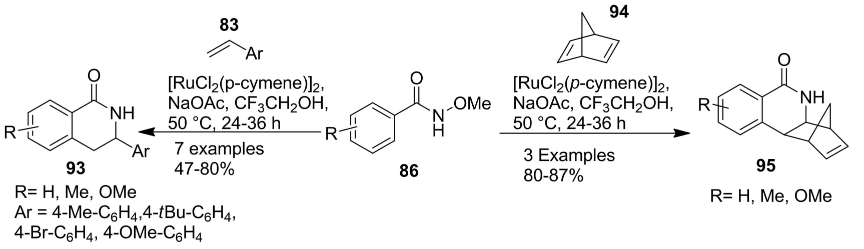
Scheme 35. Tandam catalysis approach to synthesis of 3,4-dihydroisoquinolin-1(2*H*)-ones



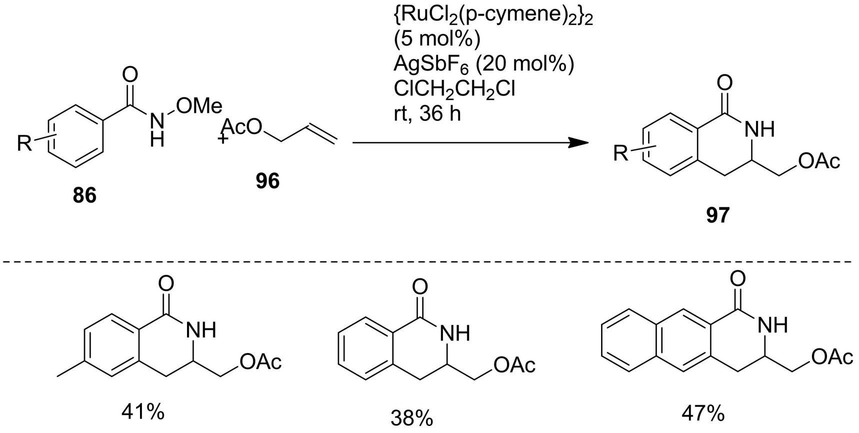
Scheme 36. Synthesis of 4-substituted dihydroisoquinolones



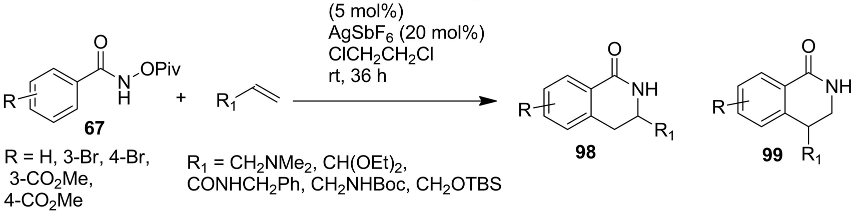
Scheme 37. Synthesis of 4-methyl substituted dihydroisoquinolinones



Scheme 38. Ruthenium-Catalyzed Oxidative C–H Olefination with Phenylethylene and 2,5-Norbornadien



Scheme 39. Ruthenium-Catalyzed Oxidative C–H Olefination with allylic acetate



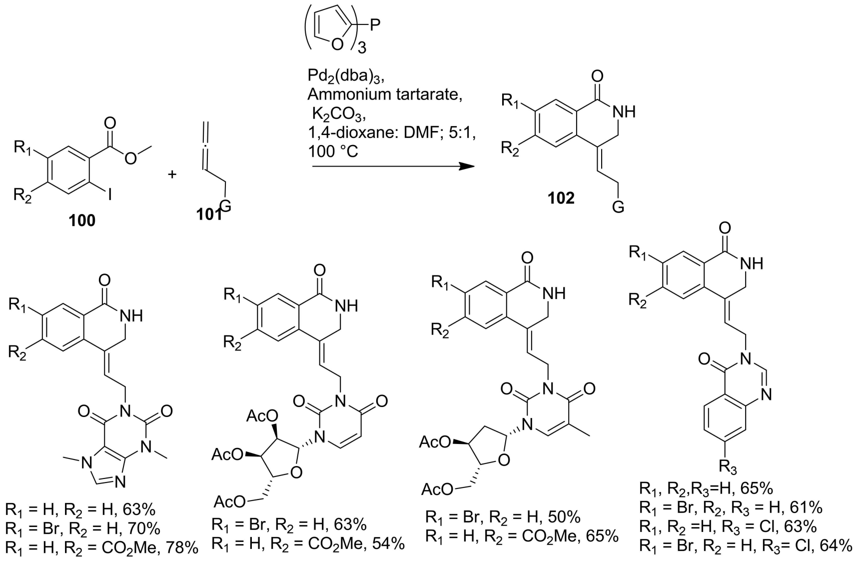
Scheme 40. Ruthenium-Catalyzed synthesis of 3,4-dihydroisoquinolin-1(*2H*)-one

by homolytic fission of the DTBP, acts as initiator reacts with CH_2Cl_2 and produces the radical dichloromethyl. The dichloromethyl radical adds to the allylic double bond and generate new radical which undergoes addition cyclization followed by oxidation yields the chloromethyl substituted dihydroisoquinolinones (**111**) (Scheme 44).[63]

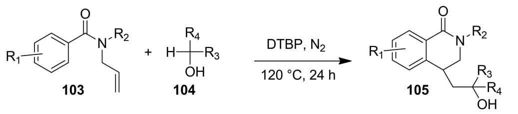
Yue-Ming Li *et al.* constructed the 3,4-dihydroisoquinolin-1(*2H*)-one by metal free oxidative tandem coupling of *N*-allylbenzamide **112** with aryl aldehydes **113** in the presence of DTBP. Author optimized the tandem coupling of C(SP^2)-H bonds of carbonyl with C(SP^2)-H of the aryl and directed their efforts in order to understand the reaction mechanism by radical trapping experiment and DFT calculation studies. Author proposed the radical addition cyclization mechanism which started with the formation of the tert-butoxyl radical formed by the homolytic fission of the DTBP. Which acts as an initiator resulted in the formation of alkyl radical via series of the reaction which under goes the intramolecular cyclization to 3,4-dihydroisoquinolin-1(*2H*)-one (**114**). Using the optimized reaction conditions variety of the 3,4-dihydroisoquinolin-1(*2H*)-one's were synthesized in moderate to good yield. The aldehydes with electron withdrawing substituent gives lower yield of the products 3,4-dihydroisoquinolin-1(*2H*)-one (Scheme 45).[64]

6. Oxidation to dihydroisoquinolinones

Gold nanoclusters stabilized by poly(*N*-vinyl-2-pyrrolidone) (Au:PVP) serves as selective catalysts for oxidation of α carbon to the nitrogen atom of secondary amine **115** under aerobic conditions. The reaction proceeds smoothly in water with



Scheme 41. Synthesis of the dihydroisoquinolinones by the palladium catalyzed multicomponent reaction of the substituted allene, ammonium tartrate and 2-iodobenzoate.



Scheme 42. Synthesis 4-hydroxyalkyl-substituted 3,4-dihydroisoquinolin-1(2*H*)-one

catalyst loading of 5 and 10 atom% and gave the oxidation product **1** up to 99% yield (Scheme 46).[65]

Molecular oxygen mediated α-CH_2 oxygenation of secondary cyclic amines is a useful method for synthesis of lactam. The cyclic amine **116** under goes oxidation to 3,4-dihydroisoquinolin-1(2*H*)-one **118** in 76 to 82% yield in presence of 9-Fluorene-imine **117** under oxygen at reflux (Scheme 47).[66]

N. J. Turner *et al.* synthesized the 3,4-dihydroisoquinolin-1(2*H*)-one **1** by enzymatic oxidation of amino alcohol **119** using the Galactose Oxidase. The reaction proceed at 37 °C, at buffer pH = 7.0 (Scheme 48).[67]

Moreover, N. Mizuno and co-workers used alumina supported Gold nanoparticles as catalyst for synthesis of the 3,4-dihydroisoquinolin-1(2*H*)-one analogues (**118**) by α- oxygenation of the cyclic amines (**116**). This is the green procedure, as the reaction produces water as by-products and the heterogeneous catalyst can be recycled. O_2 is serves as the source of oxygen (Scheme 49).[68]

Kiyoshi Tomioka *et al.* demonstrated that synthesis of the 3,4-dihydroisoquinolin-1(2*H*)-one (**1**, **121**, **123**) can be achieved under Pinnic oxidation conditions from the cyclic imine (**120**, **122**). The oxidations proceed smoothly by sodium chlorite under buffer condition.at ambient temperature (Scheme 50).[69]

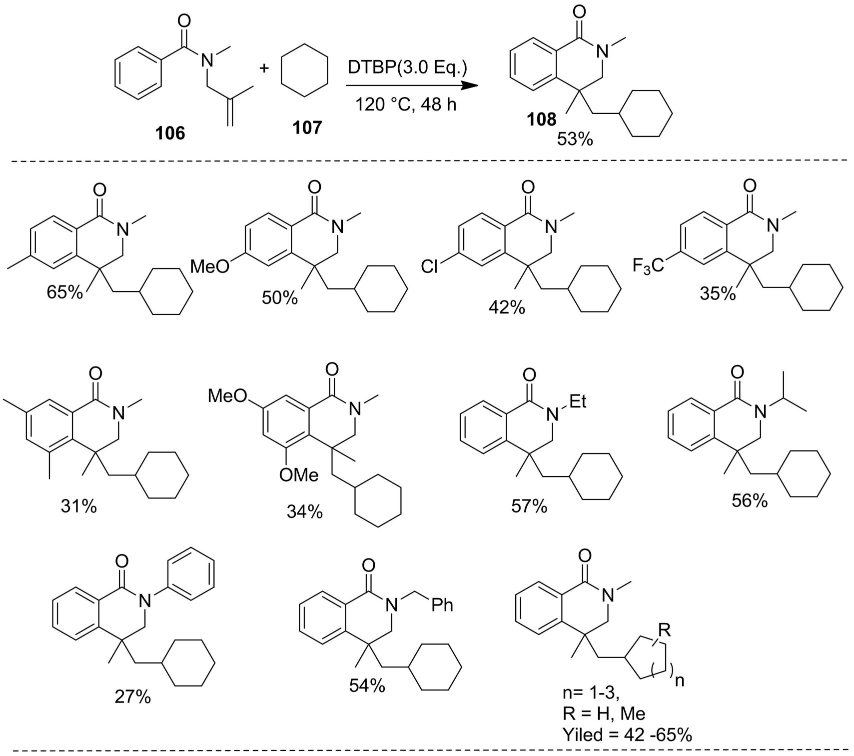
Catalytic bio–chemo and bio–bio tandem oxidations of cyclic amine (**124**) yields the lactam in moderate to good yields. This protocol gives easy access to lactam under aqueous conditions at ambient temperature using bio–chemo and bio–bio approach. Both the procedures involve the first's use of A. niger monoamine oxidase (MAO–N D9) as catalyst for the oxidation of the cyclic amine to the imine/iminium. The second step uses either chemo catalysis (H_2O_2/cat. CuI) or bio catalysis (xanthine dehydrogenase (XDH)/electron acceptor) to yield the desired lactam **125** (Scheme 51).[70]

7. Synthesis of Asymmetric Dihydroisoquinolinones

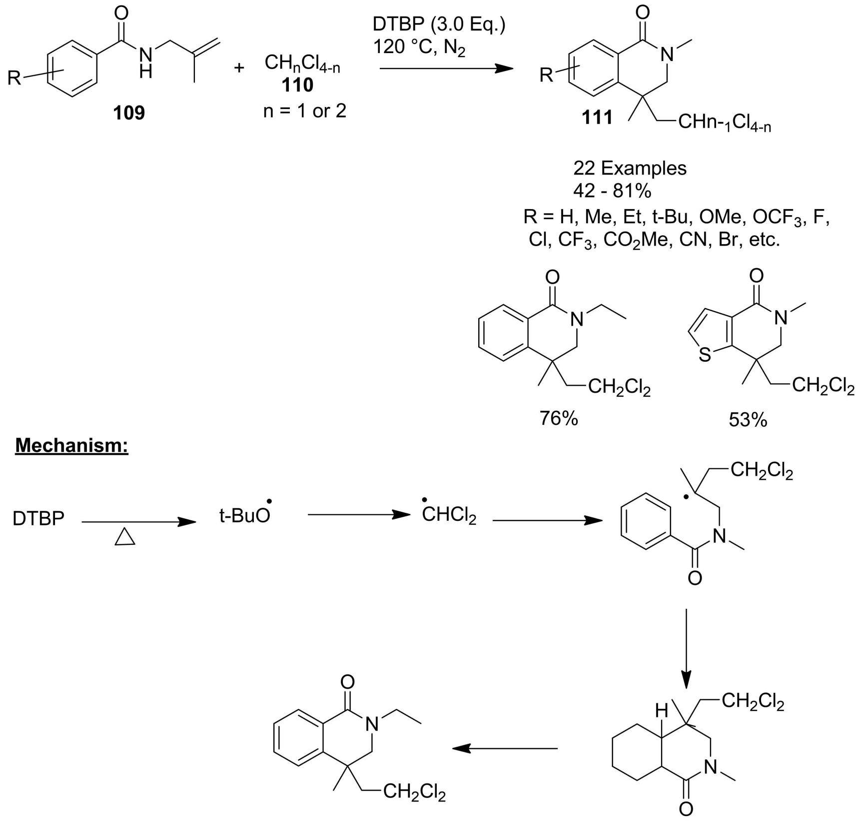
The reaction of 2-(nitromethyl)benzaldehydes **126** and various *N*-protected aldimines (**127**) in the presence of 5 mole % of quinine based squarimide organo catalyst **129** yield single diastereoisomer of dihydroisoquinolinones (**128**) in moderate to good yield. This is an example of one pot synthesis via an aza-Henry–hemiaminalization–oxidation sequence (Scheme 52).[71]

Castagnoli–Cushman reaction proceeds smoothly without any additive and bases however, many variations suggested in literature in order to improve the substrate scope, selectivity and yield of the reaction. Spencer Knapp and co-worker have demonstrated that the addition of the 2 equivalent of *N*-methylimidazole improves the overall atom economy of the reaction of homophthalic anhydride and pyridine-3-carboxaldehyde-*N*-trifluoroethylimine. In absence of the *N*-Methyl imidazole observed the formation of the elimination by product as major one (Scheme 53).[72]

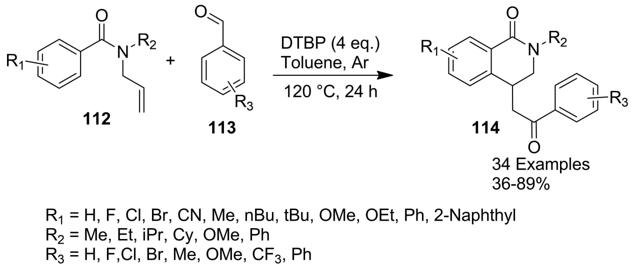
Ionic liquid can act as both solvent and catalyst for the multicomponent reaction of the aldehyde, amine and homophthalic anhydride for the synthesis of the cis-isoquinolonic acid derivative's. The ionic liquid $[bmim]BF_4$ or $[bmim]PF_6$ serves as suitable ionic liquid for this conversion (Scheme 54).[73]



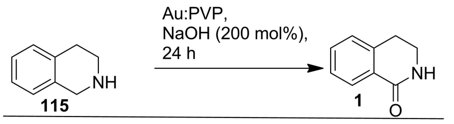
Scheme 43. Synthesis of 4-alkyl-substituted dihydroisoquinolin-1(2*H*)-ones by oxidative alkylarylation reactions of substituted *N*-allylbenzamide



Scheme 44. Cascade radical chloromethylation/ arylation of the *N*-allyl benzamide to chloromethyl substituted dihydroisoquinolinones



Scheme 45. Tandem coupling of *N*-allylbenzamide with aryl aldehydes to 3,4-dihydroisoquinolin-1(*2H*)-one



Au:PVP (Atom %)	Solvent	Temperature	Yield
10	*t*-BuOH: H_2O; 2:1	100 °C	85%
10	H_2O	90 °C	99%
10	H_2O	80 °C	84%
5	H_2O	90 °C	97%

Scheme 46. Oxidation to 3,4-dihydroisoquinolin-1(2H)-one by Gold nanoclusters stabilized by poly(*N*-vinyl-2-pyrrolidone) (Au:PVP)

A base catalyzed Mannich type of the reaction of enolizable cyclic anhydride **130** with the *N*-sulfonylimine (**135**) gives the access to the 3,4-dihydroisoquinolin-1(*2H*)-one (**136**) up to 95% yield and anti diastereoselectivity up to 95:5 (Scheme 55).[74]

M. Krasavin *et al.* constructed 3,4-dihydroisoquinolin-1(*2H*)-one (**138**) by using Castagnoli–Cushman reaction of homophthalic anhydride **130** with aldazine (**137**). The reaction proceeds smoothly at room temperature and yields predominately kinetic *cis* product which converted to its *trans* isomer by heating in DMSO or by treatment with base imidazole (Scheme 56).[75]

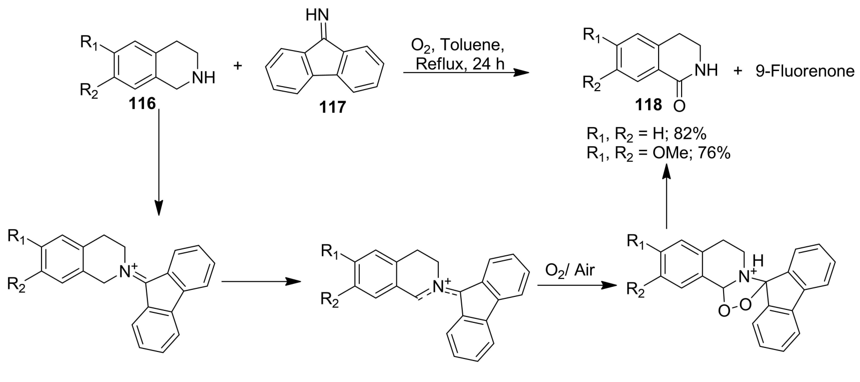
Unsymmetrical aldizine gives the mixture of 3,4-dihydroisoquinolin-1(*2H*)-one **136** and **137**, scheme 57.

M. Krasavin and co-workers developed one pot three component approach for synthesis of the trans-configured 3,4-dihydroisoquinolinone (**146**). This protocol serves as an example of the Castagnoli-Cushman reaction of homophthalic acid **143**, amine (**145**) and aldehyde (**144**) (Scheme 58).[76]

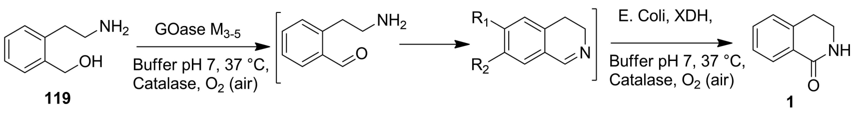
Later on, M. Krasavin and co-workers studied the Castagnoli – Cushman reaction in combinatorial fashion for the construction of the structurally diverse γ- and δ-lactam carboxylic acids with high diastereoselectivity. This three component reaction involved the reaction of the amine, aldehyde and homophthalic acid in presence of the acetic anhydride as dehydrating agent, to affords the 2,3 substituted 1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid in 38–77% (Scheme 59).[77]

Furthermore, M. Krasavin research group extended the scope of the Castagnoli–Cushman reaction for the synthesis of the cyclic hydroxamic acid derivatives. The homophthalic anhydride and oxime on heating at 110 °C in toluene or in neat gives access to the *N*-hydroxy lactam in moderate to good yield (Scheme 60).[78]

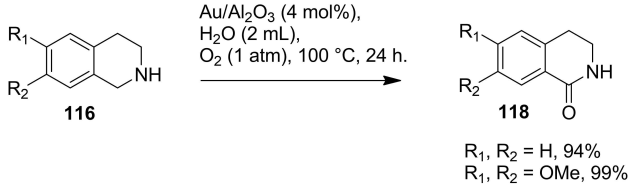
Additionally, M. Krasavin and co-workers carried out the synthesis of the cyclic hydroxamic acid derivative using the multicomponent approach. This three component reaction involve, the reaction of the homophthalic acid, hydroxylamine acetate/ O-benzylhydroxylamine and aldehyde (Scheme 61).[79]



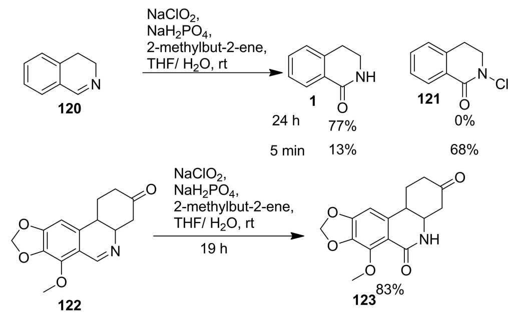
Scheme 47. α-CH_2 oxygenation of secondary cyclic amines by molecular oxygen



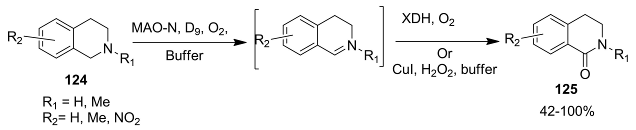
Scheme 48. Synthesis of 3,4-dihydroisoquinolin-1(*2H*)-one by oxidation of amino alcohol Galactose Oxidase



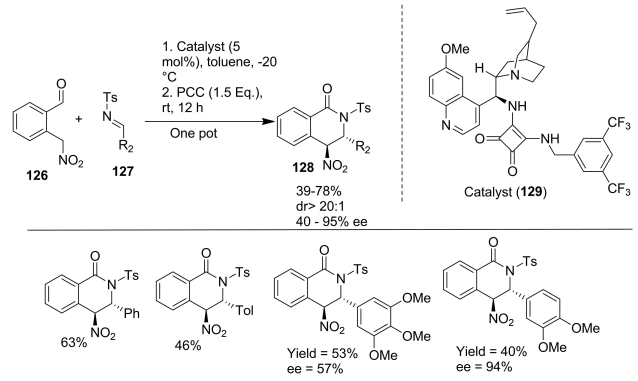
Scheme 49. α- Oxygenation of the cyclic amines using the alumina supported Gold nanoparticles.



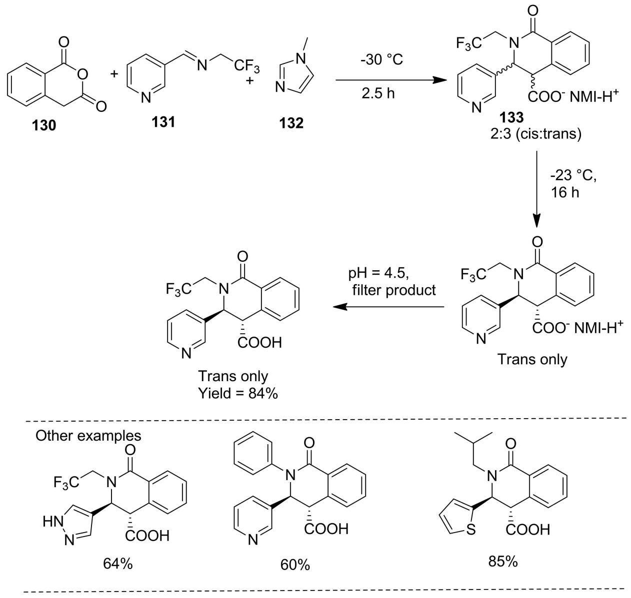
Scheme 50. Synthesis of 3,4-dihydroisoquinolin-1(*2H*)-one by oxidation of cyclic imine by sodium chlorite



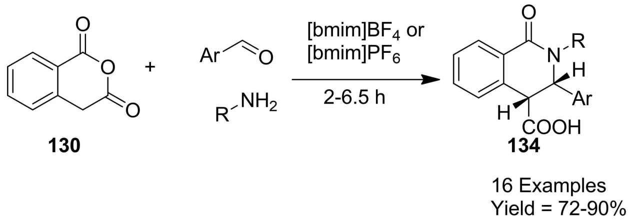
Scheme 51. Green synthesis of 3,4-dihydroisoquinolin-1(*2H*)-one by catalytic bio–chemo and bio–bio tandem oxidation



Scheme 52. One pot synthesis of chiral dihydroisoquinolinones via an aza-Henry–hemiaminalization–oxidation sequence



Scheme 53. Castagnoli–Cushman reaction of homophthalic anhydride and pyridine-3-carboxaldehyde-*N*-trifluoroethylimine

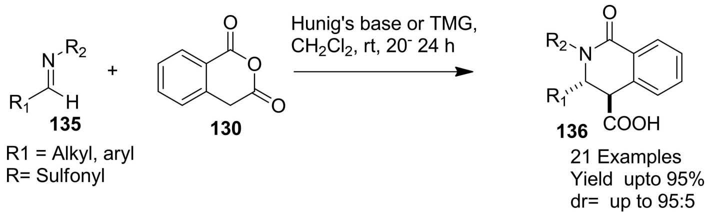


Scheme 54. Castagnoli–Cushman reaction in ionic acid

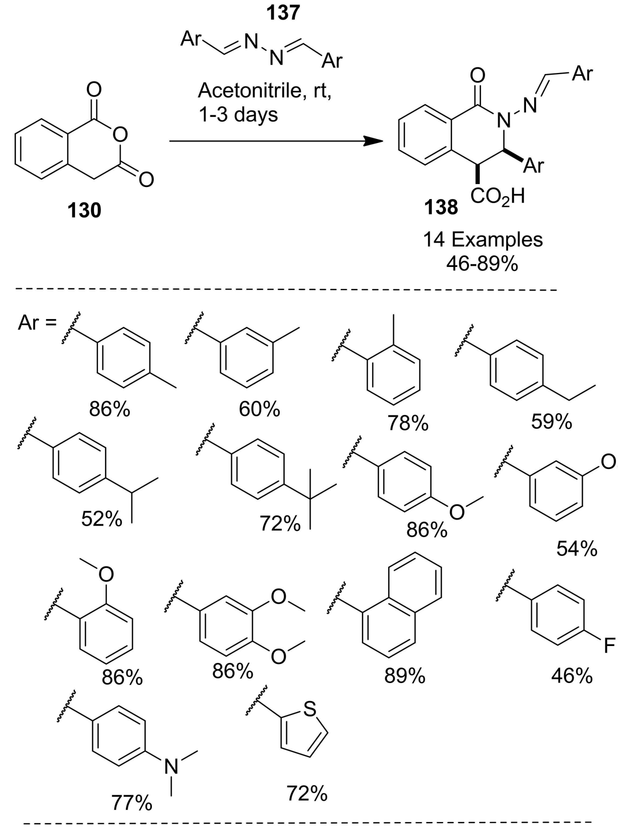
The hexahydropyrrolo[1,2-*b*]isoquinoline core is present in many natural products such as tylophorine, lycorine, zephyranthine, galantine and many alkaloids. Due to the diverse range of the biological activities this scaffold is considered as privileged scaffold. M. Krasavin and co-workers extended the scope of the Castagnoli–Cushman reaction towards the synthesis of the hexahydropyrrolo[1,2-*b*]isoquinoline derivatives, this includes the variation in the imine partner. The reaction of the cyclic imine that is indolenines with homophthalic anhydride at room temperature in acetonitrile gives access to the hexahydropyrrolo[1,2-*b*]isoquinoline derivatives in moderate to good yield (Scheme 62).[80]

Synthesis of the chiral 3,4-dihydroisoquinolinone **155** is achieved by o-tolylamide **152** and SMAP or RAMP hydrazine (**153**). This protocol involves one pot 1,2-addition and ring closer reaction sequence followed by removal of the chiral auxiliary using the conditions for *N-N* bond cleavage (Scheme 63).[81]

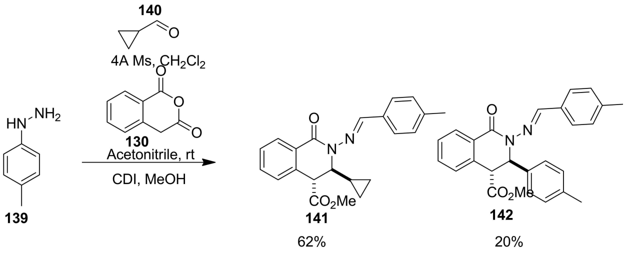
Axel Couture *et al.* provided the new route for an asymmetric isoquinolinone **164** form the aromatic enehydrazide **162**. The aromatic enehydrazide **162** undergo the stereo selective 6 electrons photochemical conrotatary ring closure followed by suprafacial [1,5]-*H* shift to yield the SMAP-isoquinolinone **163**. The SMAP is removed by treatment with Magnesium monoperoxyphthalate hexahydrate (MMPP) in methanol at rt.to gives the unprotected dihydroisoquinolinone **164** (Scheme 64).[82]



Scheme 55. Base catalyzed AMR of *N*-Sulfonyl Imine and homophthalic anhydride to dihydroisoquinolinone.

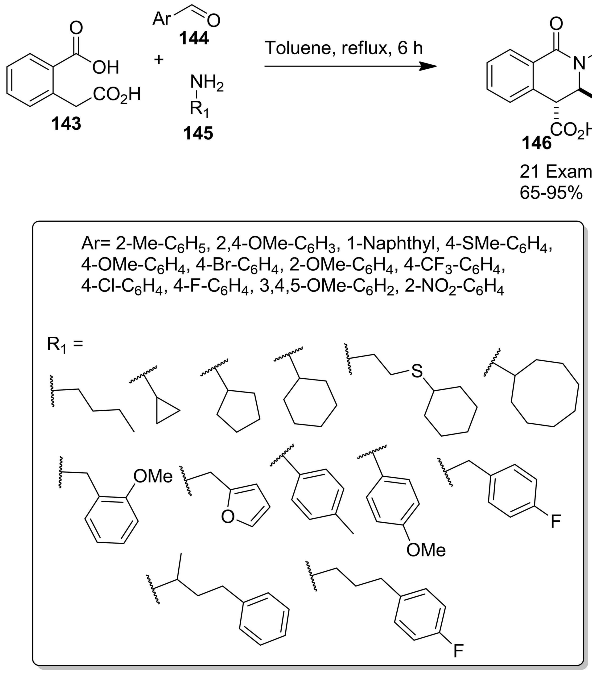


Scheme 56. Synthesis of 3,4-dihydroisoquinolin-1(2*H*)-one by CCR of aldazine

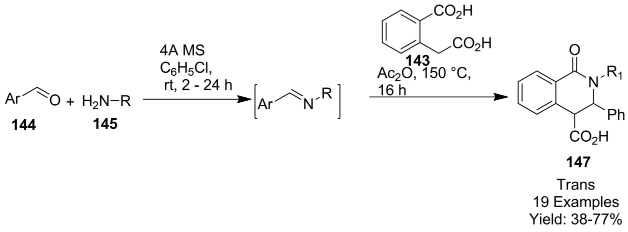


Scheme 57. CCR product distribution obtained with a non-symmetrical aldazine

Y. Lu *et al.* developed the method for the synthesis of chiral isoquinolinone **170** by the Mannich reaction of phthalide **165** using chiral quinidine catalyst **167** (Scheme 65).[83]



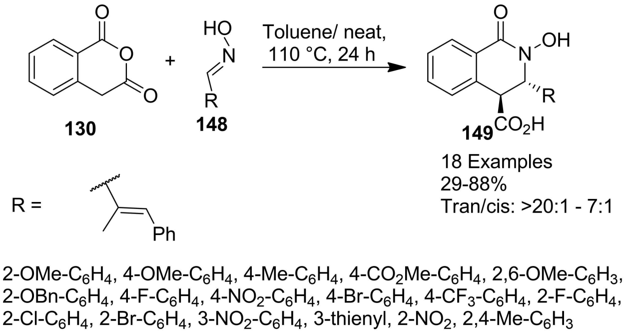
Scheme 58. Synthesis of 3,4-dihydroisoquinolin-1(2*H*)-one by three-component CCR of homophthalic acid



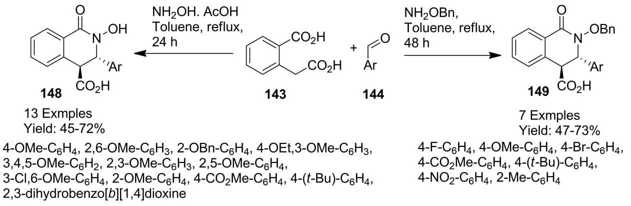
Scheme 59. Synthesis of 1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid

Wanli Chen *et al.* synthesized trans-3,4-dihydroisoquinolin-1(2*H*)-ones and (*E*)-4-(1-alkenyl)isoquinolin-1(2*H*)-ones (**176**) by DBU-promoted cyclization of ortho-(3-hydroxy-1-alkynyl)benzamide (**175**). By this method trans-3,4-dihydroisoquinolin-1(2*H*)-ones and (*E*)-4-(1-alkenyl)isoquinolin-1(2*H*)-ones synthesized in good to moderate yields with a variety of substituents on aliphatic ring (Scheme 66 and 67).[84]

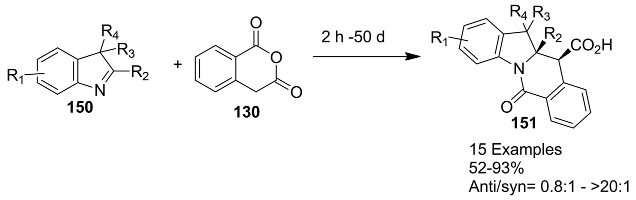
Ji-Bao Xia *et al.* synthesized the chiral isoquinolinone by palladium catalyzed enantioselective *C-H* aminocarbonylation



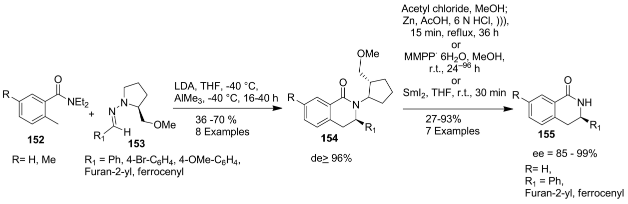
Scheme 60. Synthesis of 1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid



Scheme 61. Castagnoli – Cushman reaction of homophthalic acid

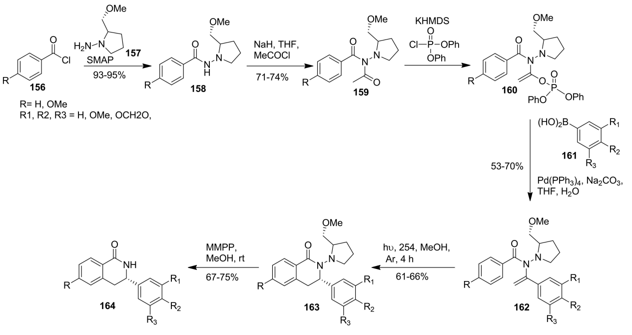


Scheme 62. Castagnoli – Cushman reaction for synthesis of hexahydropyrrolo[1,2-*b*]isoquinoline



Scheme 63. Synthesis of the 3-Substituted dihydro-2*H*-isoquinolin-1-ones *via* 1,2-Addition/Ring Closure

reactions. L-pyroglutamic acid serve as a chiral ligand for Pd catalyzed *C-H* carbonylation by desymmetrization. The chiral isoquinolinone (**180**) obtained in good yield with high enantioselectivity. The synthesized chiral isoquinolinone (**180**) transferred to the useful compounds without the loss of the chiral purity (Scheme 68).[85]



Scheme 64. Stereo selective photochemical synthesis of 3-Substituted dihydro-2*H*-isoquinolin-1-ones *via* conrotatary ring closure followed by suprafacial [1,5]-*H* shift

Jianguo Yang *et al.* synthesized the chiral 3,4-dihydroisoquinolin-1(2*H*)-one by asymmetric palladium catalyzed *C-H* functionalization by cascade approach. Intramolecular asymmetric allylation of *N*-Sulfonylbenzamide **181** with 1,3-dines **182** in the presence of the Pd(II) catalyst and pyrax ligand gives access to chiral 3,4-dihydroisoquinolin-1(2*H*)-one **183**. This methodology tolerated to the wide variety substituent both on sulfonylarylamide **181** and diene **182**, and obtained product **183** up to 96% ee (Scheme 69).[86]

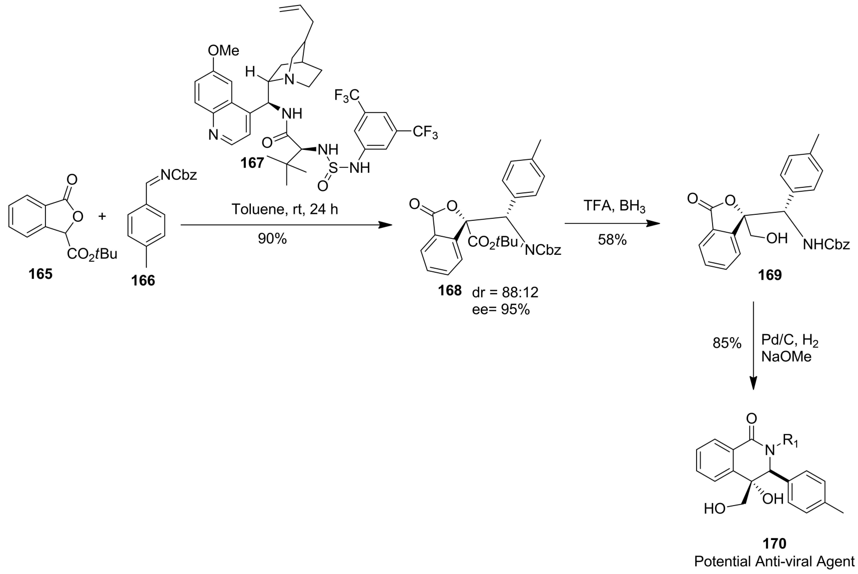
M. Murakami *et al.* optimized the method for enantioselective synthesis the of the 3,4-dihydroisoquinolin-1(2*H*)-ones. The *N*-substituted-1,2,3-benzotriazin-4(3*H*)-one undergoes the denitrogenative coupling with allene in the presence of the $Ni(cod)_2$ and 1,2-bis(diphenylphosphino)benzene (Dppbenz) in THF yield the 3,4-Dihydroisoquinolin-1(2*H*)-ones **188** and **187**. The net reaction partner is the azanickelacycle (**189**) which is formed by the reaction of the *N*-tolyl-1,2,3-benzotriazin-4(3*H*)-one (**185 a**) with stoichiometric amounts of the $Ni(cod)_2$ and 1,2-bis (diphenylphosphino)benzene (Dppbenz) in THF at 25–30 °C in 2 h. The azanickelacycle (**189**) on reactions with different allenes **186** yields the 3,4-dihydroisoquinolin-1(2*H*)-ones **188** (major) and **187** (minor). The 3,4-dihydroisoquinolin-1(2*H*)-ones **188** is the major isomer but notably the bulky substituent on the allene reverse the ratio of isomers **188** and **187**. In the isomer **188** the Z isomer formed as major one (Scheme 70).[87]

This protocol further extended for the synthesis of the chiral 3,4-dihydroisoquinolin-1(2*H*)-one by using the chiral ligand in combination with $Ni(COD)_2$ catalyst. The highest regio- and enantioselectivities were achieved when the phosphino-oxazoline ligand (*S,S*)-i-Pr-FOXAP used. This protocol gives access to 3,4-dihydroisoquinolin-1(2*H*)-one with overall yield up to 99% and *ee* up to 97%.

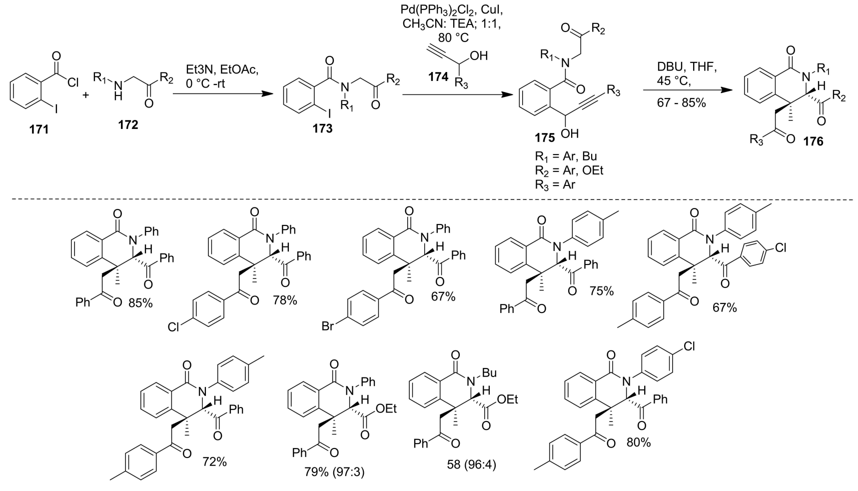
Baihua Ye *et al.* synthesized the chiral 3,4-dihydroisoquinolin-1(2*H*)-one by chiral cyclopentadienyl ligands based Rh(III) catalyst **193** as a as symmetric *C–H* functionalization agent for hydroxamic acid derivative (**190**). The reaction proceed at room temperature with great enantioselectivity and high yield (Scheme 71).[88]

Herbert Waldmann *et. al* constructed the chiral dihydroisoquinolinones by enantioselective *C-H* activation by Rh(III) catalyst having highly efficient cyclopentadienyl ligand (Scheme 72).[89]

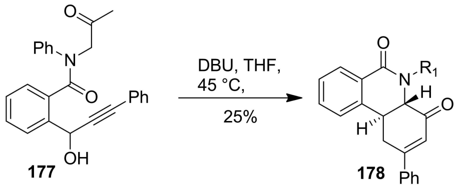
Nicolai Cramer *et. al* demonstrated that use of the 3-d-chiral cyclopentadienyl Cobalt(III) complexes **199** for the asymmetric



Scheme 65. Chiral quinidine catalyst catalyzed stereo selective synthesis of 3,4-dihydroisoquinolin-1(2*H*)-ones



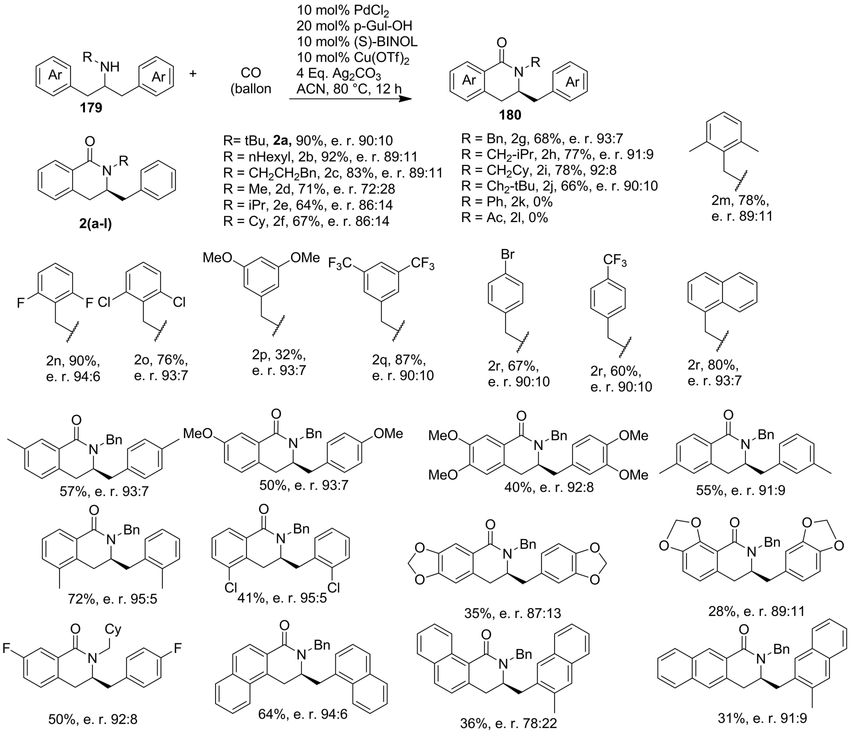
Scheme 66. DBU-promoted cyclization of ortho-(3-hydroxy-1-alkynyl)benzamide to anti-dihydroisoquinolin-1(2*H*)-ones



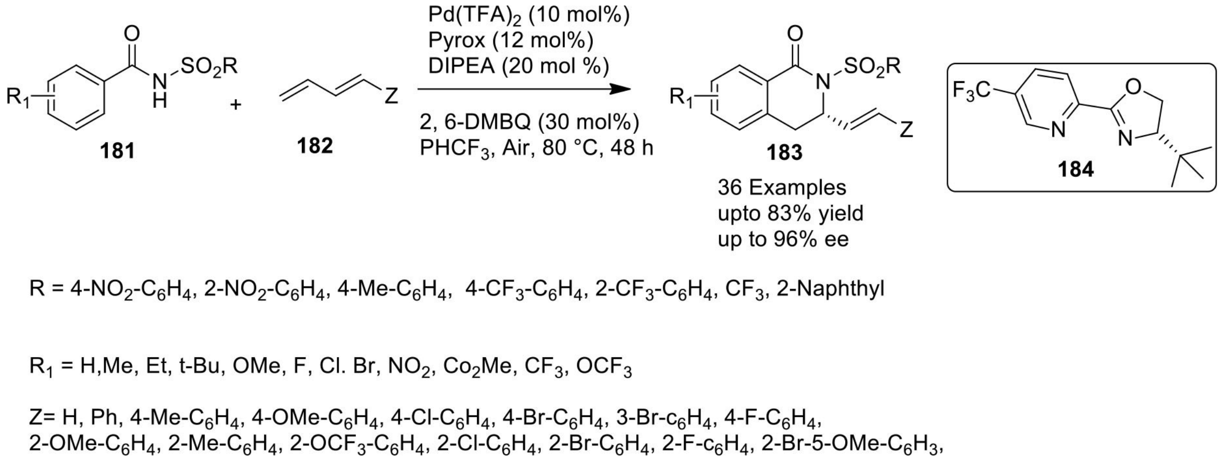
Scheme 67. DBU-promoted cyclization of ortho-(3-hydroxy-1-alkynyl)benzamide to (4aS,10bS)-2-phenyl-1,4a,5,10b-tetrahydrophenanthridine-4,6-dione

C-H functionalization for the synthesis of the dihydroisoquinolinones **197** and **198** in high enantio/ diastereoselectivity. They have shown that the 3d metal catalyzed asymmetric *C-H* functionalization of the *N*-chlorobenzamide **196** with a variety of alkene's including challenging alkyl alkenes proceeds smoothly under optimized conditions to yield the dihydroisoquinolinones in high regio and enantioselectivities (Scheme 73).[90]

J. Clayden and co-worker developed the potassium iodide carbonative cyclization reaction of imidazolidinone derivatives to generate a library of dihydroisoquinolinones with good yield. The starting material *trans N*-chloroformylimidazolidinones were synthesized with excellent trans diastereoselectivity, from their corresponding amino acid pivaldimine precursors **200**. The trans phenylalanine-derived carbamoyl chloride **200** on treatment with potassium iodide and 2,6-lutidine under microwave irradiation in acetonitrile at 150 °C for 5 min produces dihydroisoquinolinones. The cyclized product (3S,10aS)-3-(tert-butyl)-2-methyl-2,3,10,10a-tetrahydroimidazo [1,5-*b*]isoquinoline-1,5-dione can be used to get the functionalized dihydroisoquinolinones via the by regio- and diastereose-



Scheme 68. Palladium catalyzed enantioselective *C-H* aminocarbonylation reactions for synthesis of chiral isoquinolinone

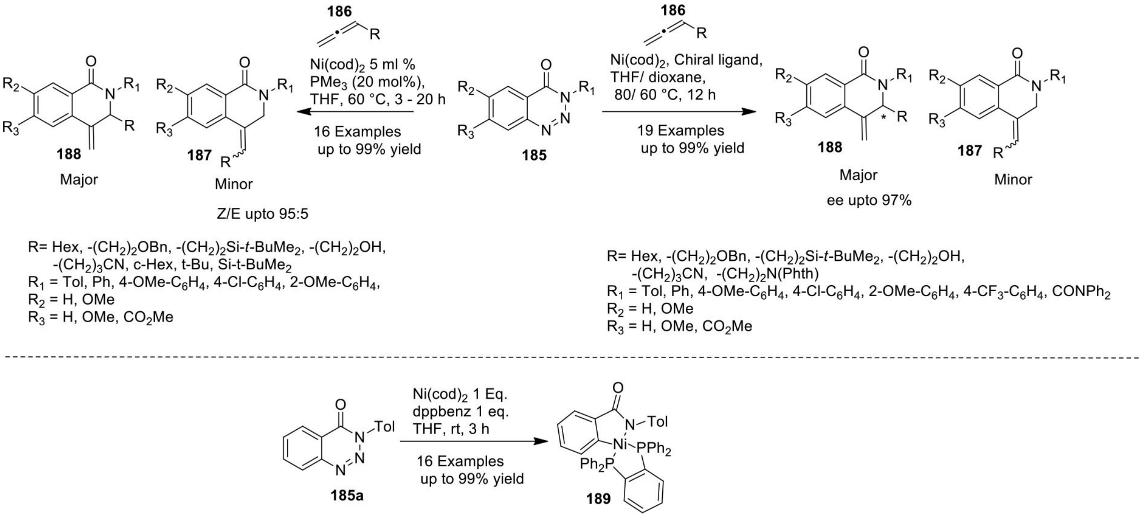


Scheme 69. Palladium catalyzed intramolecular asymmetric allylation of *N*-sulfonylbenzamide with 1,3dines to chiral 3,4-dihydroisoquinolin-1(*2H*)-one

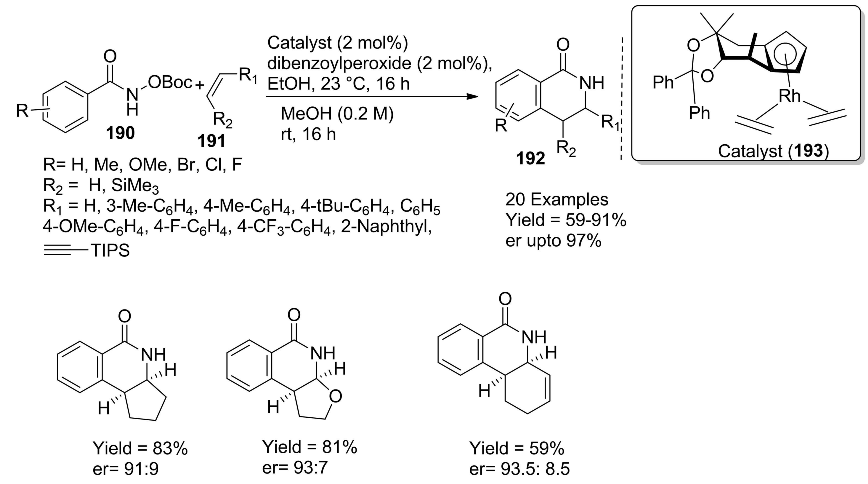
lective alkylation followed by the acidic hydrolysis of the imidazolidinones to get enantiopure dihydroisoquinolinones carboxylic acids (Scheme 74).[91]

S. Cui *et al.* demonstrated the silver catalyzed cascade phosphorylation/cyclization of propene having *N*-cyanamide to dihydroisoquinolinones. The propene containing *N*-acylcyanamides on treatment with diphenylphosphineoxide in presence of the 1 equivalent of silver nitrate cyclized to phosphorous incorporated dihydroisoquinolinones. This cyclization is in accordance with the Baldwin Rule (Scheme 75).[92]

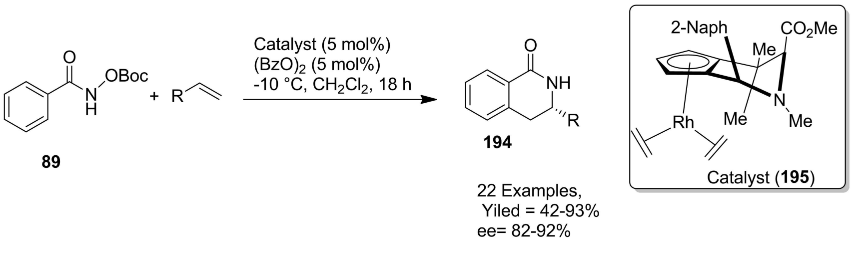
Y. Zhang and co-workers have developed the protocol for the enantioselective synthesis of quaternary 3,4-dihydroisoquinolines (**206**). This involves the carbon monoxide free palladium-catalyzed enantioselective intramolecular carbonylative Heck reaction. For this conversion the formate esters is used as CO source and reaction proceeds well in presence of the phosphine ligand **207** from the screened ligand. Wide variety of the substituent tolerated under the reaction condition gives access to the functionalized 3,4-dihydroisoquinolines **206** in good yield with good enantioselectivities (Scheme 76).[93]



Scheme 70. Enantioselective synthesis the of the 3,4-Dihydroisoquinolin-1(2*H*)-ones by denitrogenative coupling of *N*-substituted-1,2,3-benzotriazin-4(3*H*)-one with allene



Scheme 71. Chiral cyclopentadienyl ligands based Rh(III) catalyzed enantioselective synthesis the of the 3,4-dihydroisoquinolin-1(2*H*)-ones

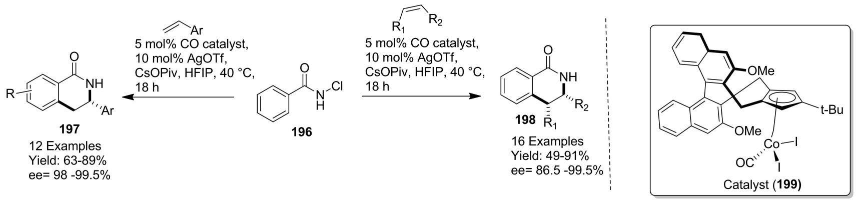


Scheme 72. Synthesis of chiral dihydroisoquinolinones by enantioselective *C-H* activation using Rh(III) catalyst with cyclopentadienyl ligand.

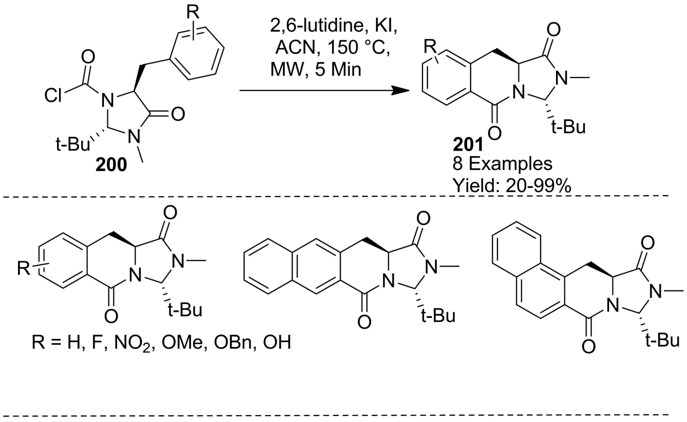
8. Miscellaneous to dihydroisoquinolinones

Many reports are available for the synthesis of 3,4-dihydroisoquinolin-1(2*H)*-ones using the Schmidt and Beckman rearrangement conditions. The indinone oxime (**208**) undergoes rearrangement to 3,4-dihydroisoquinolin-1(2*H)*-ones in presence of acid catalyst such as Conc. HCl, H_2SO_4, MsOH (Scheme 77).[94]

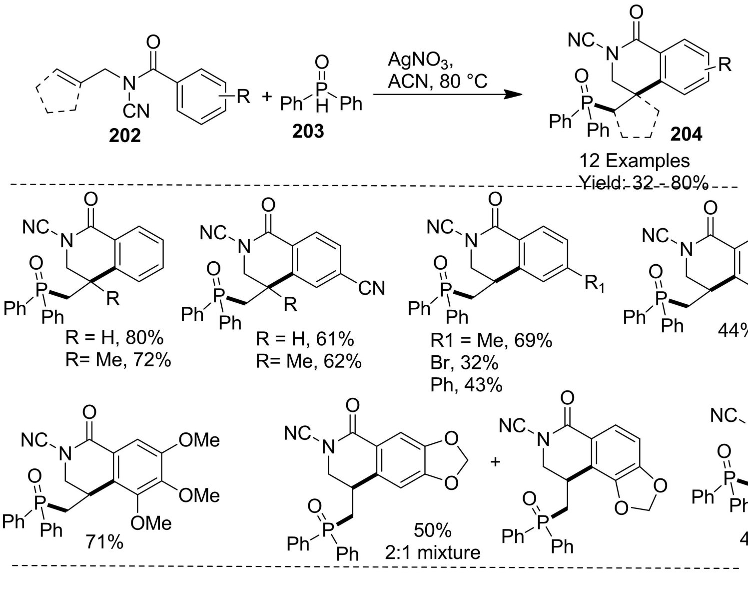
The cyclic ketone bound with the vinyl azide group undergoes Schmidt reaction and afford the secondary lactam in regioselective manner. If the cyclic ketone is five membered



Scheme 73. Synthesis of chiral dihydroisoquinolinones by enantioselective *C-H* activation using 3-d-chiral cyclopentadienyl cobalt (III) complexes



Scheme 74. Synthesis of enantiopure chiral dihydroisoquinolinones from imidazolidinones



Scheme 75. Synthesis of spirocyclic dihydroisoquinolinone

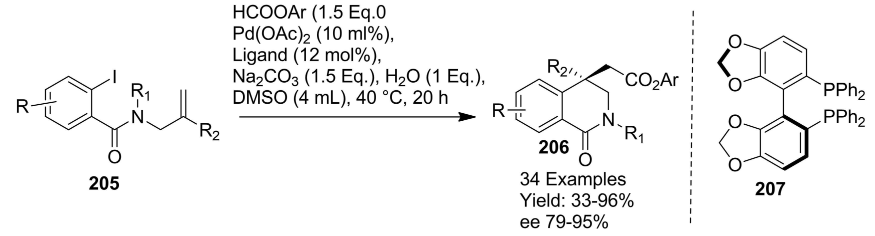
gives access to dihydroisoquinolinones in moderate to good yield (Scheme 78).[95]

Hydrogenation of the isoquinolinone **196** using 20% Pd/C in acetic acid for 20 h yield 3,4-dihydroisoquinolin-1(*2H*)-one **1** in 86% yield (Scheme 79).[12]

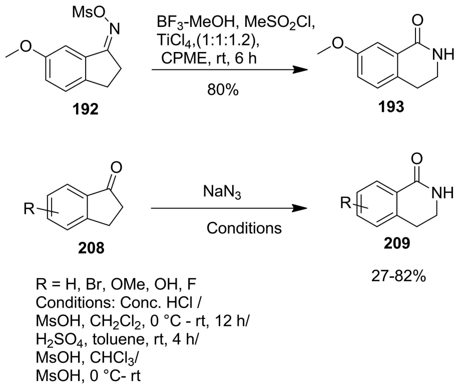
Minoru Tanaka and co-workers have developed synthetic procedure for the synthesis of the *N*-substituted 3,4-dihydroisoquinolinone's **214** having the substituents at the 3-position. This strategy involve synthesis of the iminium salt **213** by alkylation of the imine **212** followed by oxidation using $K_4Fe(CN)_6$ to get dihydroisoquinolinones in good yield as per the reaction sequence depicted in Scheme 80.[96]

The synthesis of the imine **212** is achieved as per the reaction sequence depicted in Scheme 81.

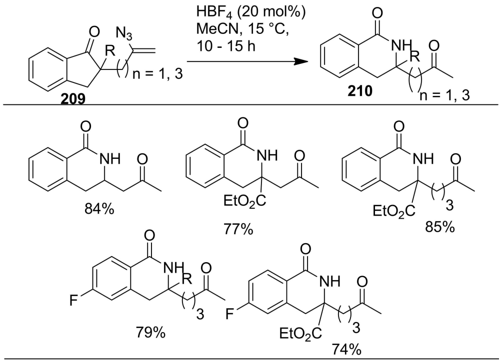
Shuai Zou, *et al.* developed method for photo catalytic synthesis of 3-position substituted 3,4-dihydroisoquinolin-



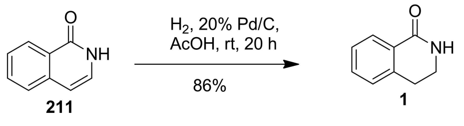
Scheme 76. Synthesis of palladium-catalyzed enantioselective intramolecular carbonylative Heck reaction



Scheme 77. Synthesis of dihydroisoquinolinones by Beckmann rearrangement



Scheme 78. Synthesis of dihydroisoquinolinones by intramolecular Schmidt reaction of vinyl azides with cyclic ketone and hydrolysis of vinyl azides



Scheme 79. Hydrogenation of the isoquinolinone to 3,4-dihydroisoquinolin-1(2*H*)-ones

1(2*H*)-one derivatives **224** using an organic dye photo catalyst EosinY Na. The protocol was tested on a wide variety of substrates with applicability on gram scale synthesis. The proposed mechanism for the reaction is the radical reaction (Scheme 82).[97]

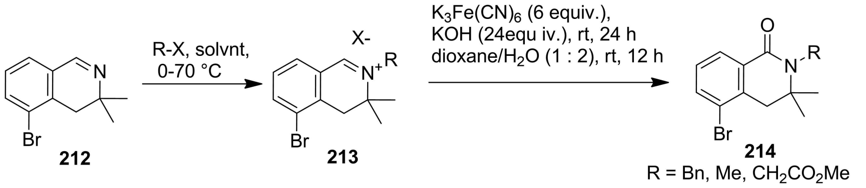
Eng-Chi Wang *et al.* synthesized 3,4-dihydroisoquinolinone **231** by the reaction of o-oxiranylmethylbenzonitrile **230** with tetra-*n*-butylammonium bromide and sodium cyanide. This involves the chemo selective ring opening of epoxide followed by formation of iminoisochroman ring. Which again opened by the nitrile and re-cyclized to 3,4-dihydroisoquinolinone in one pot. The starting material o-oxiranylmethylbenzonitrile **230** was synthesized from isovanillin **225** as per the reaction sequence depicted in Scheme 83.[98]

9. Synthesis of representative 3,4-dihydroisoquinolin-1(2*H*)-one Building Blocks of Natural Products and Pharmaceutics

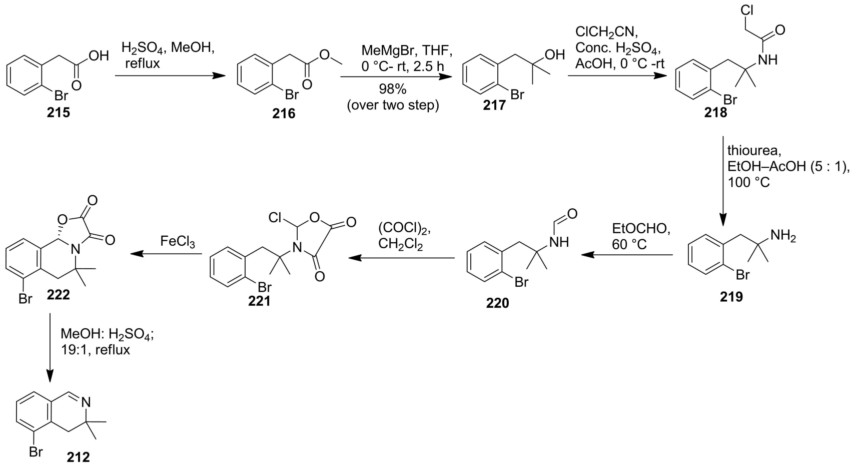
The 3,4-dihydroisoquinolin-1(2*H*)-one derivative **244** is BTK (Bruton's Tyrosine Kinase) inhibitor. J.-B. Hong and co-workers developed the scalable route for the synthesis of the **244**, this involved scalable synthesis of the 6-dimethylaminodihydroisoquinolinone core **242**, which was prepared via a $AlCl_3$ mediated regioselective cyclization of an isocyanate. Additionally, this optimization involved the fine tune of the process of all key intermediates including the procedure for the palladium catalyzed amidation and Suzuki-Miyaura coupling. This route is suitable for the large scale production in required quantity, this gives 42% overall yield from 3-fluorophenethylamine (**240**) (Scheme 84).[99]

(+)-Pancratistatin

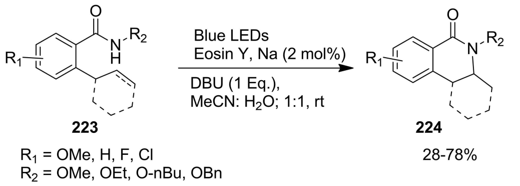
(+)-Pancratistatin is an Amaryllidaceae alkaloid with potential candidate in anticancer drug discovery. It is having the functionalized cyclohexane ring with continuous stereo genic centres. Due to the wide biological activities and potential use medicinal chemistry, the synthesis of (+)-Pancratistatin is attracted by synthetic organic community. The efforts towards the total synthesis of (+)-Pancratistatin published in the literature and reviewed time to time.[100] Here we have illustrated the interesting synthetic approach developed by D. Sarlah research group (Scheme 85). This does not required the protection-deprotection to achieve the total synthesis of (+)-Pancratistatin from benzene. D. Sarlah and co-worker synthesized the (+)-Pancratistatin in seven steps with overall yield of 12% starting from benzene. The key step towards this synthesis involves the development of an enantioselective, catalytic, dearomative trans-carboamination of benzene to



Scheme 80. Synthesis of alkylated 3,4-dihydroisoquinolin-1(2*H)*-ones



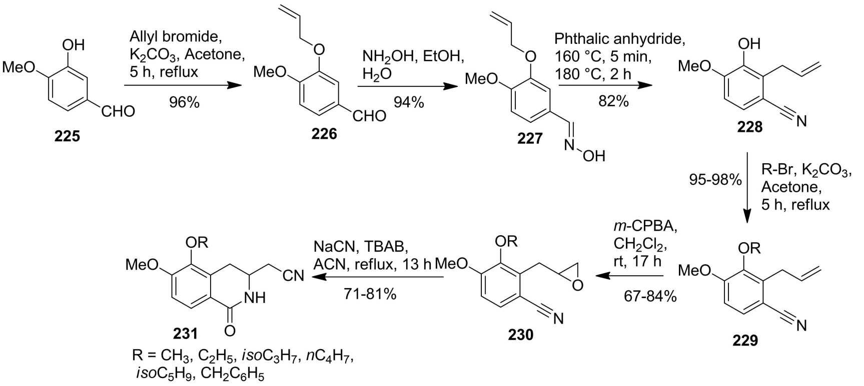
Scheme 81. Synthesis of imine **212**



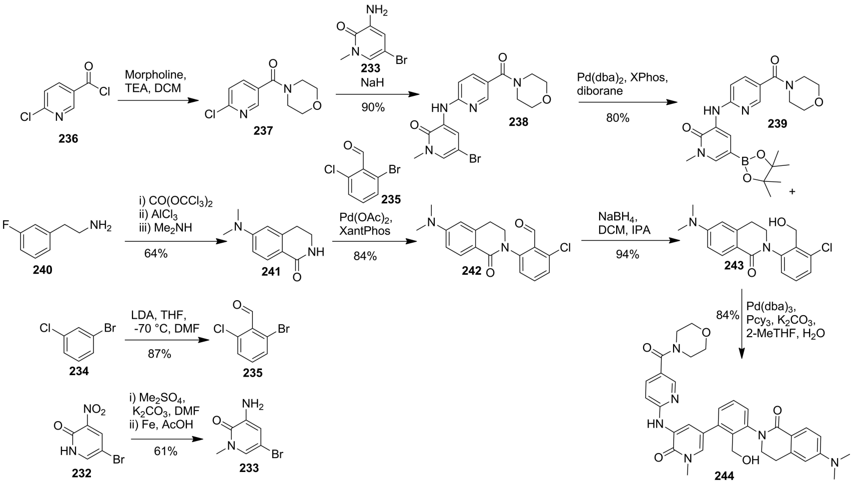
Scheme 82. Photo catalytic synthesis of 3,4-dihydroisoquinolin-1(2*H*)-one derivatives

yields cyclohexadiene with two required stereo centres in Pancratistatins. Further the diene, selectively converted into an epoxide which underwent hydrolysis to give the trans-diol. Followed by cis- dihydroxylation of remaining alkene and the reduction of the urazole using $LiAlH_4$ to afford aminotetraol. This intermediate on bromination and cyclocarbonylation using $Na[Co(CO)_4]$ catalyst to give (+)-7-deoxypancratistatin.

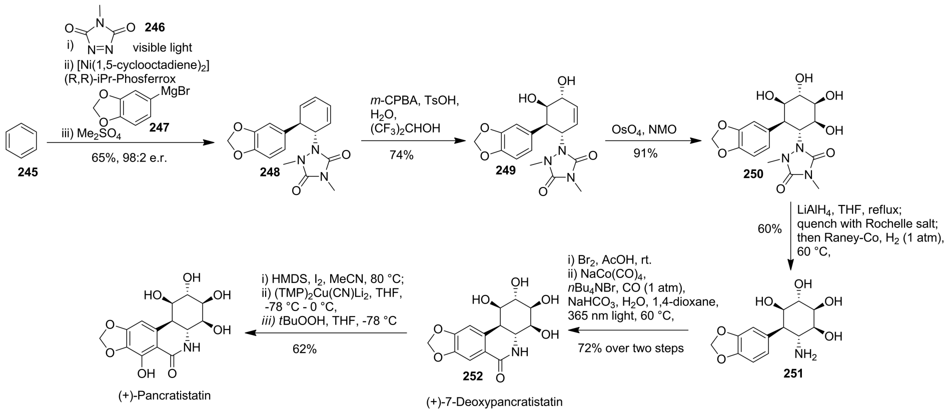
The final C-7 hydroxylation was achieved by reaction of (+)-7-deoxypancratistatin **252** with $HN(SiMe_3)_2$ and a catalytic amount of iodine which gave a fully O- silylated intermediate, which on treatment C-7 cupration with $Li_2[TMP_2Cu(CN)]$ and oxidation with *tert*-butylhydroperoxide affords (+)-pancratistatins. This methodology for the synthesis of (+)-pancratistatins



Scheme 83. Synthesis of the 3-cyanomethyl-(3,4)-dihydro-2*H*-isoquinolin-1-ones from isovanillin.



Scheme 84. Scalable Synthesis of a BTK Inhibitor



Scheme 85. Synthesis of (+)-pancratistatins and (+)-7-deoxypancratistatin from benzene

offer the advantage over other methods is that it does not require the protection deprotecton.[101]

Summary and outlook

In this review, we have summarized the methods of the synthesis of 3,4-dihydroisoquinolin-1(2*H*)-one which is a privilege scaffold in medicinal chemistry. Due to its smaller size, contains a strong hydrogen bonding motif in the form of the cis-amide, resembles likes to the rigidly fixed amino acid, which gives characteristics of biomimetic and the space available for incorporation of substituent the number of the methods reported for its synthesis in recent years. Over the year the traditional approaches are replaced with the new methods, the ligand controlled transition metal catalyzed asymmetric synthesis methods becomes more popular. Mostly the procedure for the synthesis 3,4-dihydroisoquinolin-1(2*H*)-one's involve cyclization of carbamate/ urea/ thiourea, isocyanate, reductive cyclization of azidoamide. Metal catalyzed protocols such as carbonylation, carbomylation/ carbonyl insertion, transition metal catalyzed by *C-H* activation aryl amide. The Castagnoli–Cushman protocol and the ligand controlled transition metal catalyst give the access to chiral 3,4-dihydroisoquinolin-1(2*H*)-one.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Carbonylation · Cyclization · 3 · 4-Dihydroisoquinolin-1(2*H*)-one · Lactam

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