Mini-Review

InCl$_3$: A Versatile Catalyst for Synthesizing a Broad Spectrum of Heterocycles

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ABSTRACT: This review deals with the recent applications of the indium trichloride (InCl$_3$) catalyst in the synthesis of a broad spectrum of heterocyclic compounds. Over the years, a number of reviews on the applications of InCl$_3$-catalyzed organic synthesis have appeared in the literature. It is evident that InCl$_3$ has emerged as a valuable catalyst for a wide range of organic transformations due to its stability when exposed to moisture and also in an aqueous medium. The most attractive feature of this review is the application of the InCl$_3$ catalyst for synthesizing bioactive heterocyclic compounds. The study of InCl$_3$-catalyzed organic reactions has high potential and better intriguing aspects, which are anticipated to originate from this field of research.
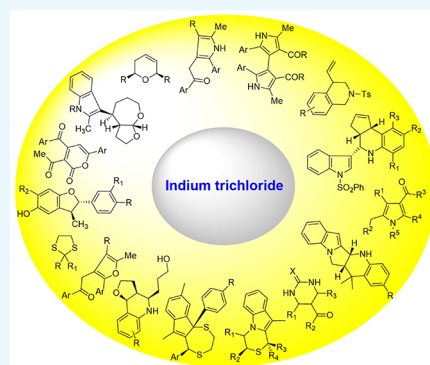
1. INTRODUCTION

Lewis acid catalysis has brought a radical change in the approach toward the synthesis of a large number of important organic intermediates and heterocyclic compounds having significant biological activity.[1a] The common Lewis acids which are generally used for various organic transformations include AlCl$_3$, BF$_3$·Et$_2$O, ZnCl$_2$, TiCl$_4$, and SnCl$_2$. Although indium (In) belongs to the same group in the periodic table as boron (B) and aluminum (Al), the study of indium and its salts was unexplored until recently.[1b] Indium and its salts have found applications in the preparation of alloys to be used as medical diagnostic agents for the health sector and equipment for the electronic industry.[2a−d] The ability of indium(III) salts to react with organic compounds to form an in situ organoindium species has largely eliminated the use of sensitive, toxic, and explosive organometallics.[3a] The effectiveness of InCl$_3$ as a Lewis acid catalyst has sustained immense interest due to its moisture compatibility, which enhances its use in a wide range of solvents including water. Moreover, nontoxicity, abundance, recyclability, and excellent catalytic activity[3b] of InCl$_3$ afforded high chemo- and regioselectivity in various organic transformations.[2a−d] These advantages of InCl$_3$ inspired us to write a review highlighting its catalytic applications in the synthesis of a broad range of heterocycles.
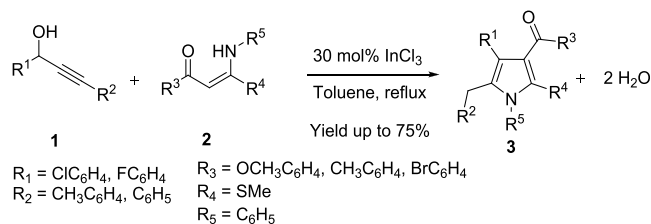
2. SYNTHESIS OF N-HETEROCYCLES

N-Heterocycles constitute the core scaffolds of many natural products and pharmaceutical agents. The syntheses of these N-heterocycles are very challenging, and the development of methodologies for their synthesis provided us with unique metal catalysts, but many of them are hazardous and expensive. Among them, InCl$_3$ was found to be inexpensive, moisture friendly, and reactive even in mild conditions.[2a−d,3a,b]

Nandi et al.[3c] accomplished a one-pot synthesis of highly substituted pyrrole **3** directly by reacting propargylic alcohol **1** with β-ketoimide **2** in the presence of InCl$_3$ catalyst (Scheme 1) in good yields.

Scheme 1. InCl$_3$-Catalyzed Synthesis of Tetrasubstituted Pyrroles from Propargyl Alcohol and Ketoimide

R$_1$ = ClC$_6$H$_4$, FC$_6$H$_4$
R$_2$ = CH$_3$C$_6$H$_4$, C$_6$H$_5$

R$_3$ = OCH$_3$C$_6$H$_4$, CH$_3$C$_6$H$_4$, BrC$_6$H$_4$
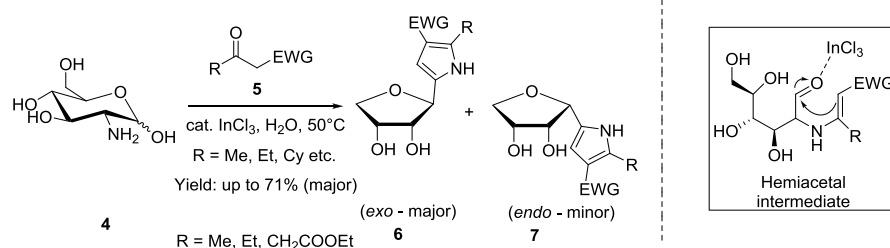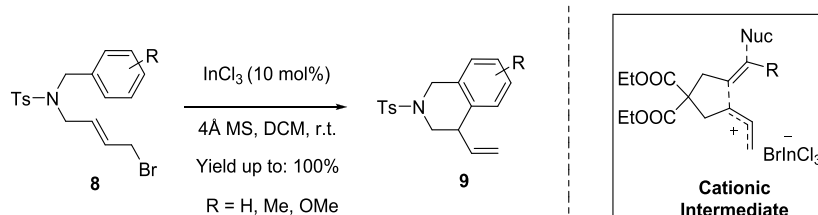R$_4$ = SMe
R$_5$ = C$_6$H$_5$

In 2011, Meng et al.[3d] reported the synthesis of various C-pyrrolyl glycoside **6** in moderate to good yields through a tandem (hemiacetal intermediate) condensation of aminosugar

Scheme 2. InCl$_3$-Catalyzed Synthesis of *C*-Pyrrolyl Glycosides

Scheme 3. InCl$_3$-Catalyzed Synthesis of Substituted *N*-Tosyl Isoquinolines

Scheme 4. InCl$_3$-Catalyzed Synthesis of Cyclopentane-Fused Hydroquinolines
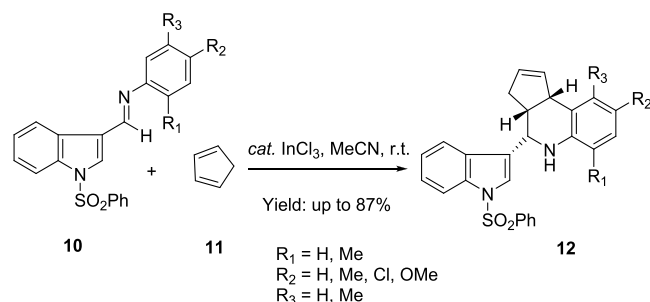
(D-glucosamine and D-galactosamine) **4** and carbonyl compound **5** in water in the presence of InCl$_3$ (Scheme 2).

Cook et al.[4a] disclosed the catalytic activity of InCl$_3$ to favor an intramolecular Friedel−Crafts reaction of simple arenes incorporated with allylic bromides **8** to give the corresponding arene-fused heterocycle **9** (Scheme 3).

Perumal et al.[4b] reported the synthesis of quinoline derivatives **12** and **14**. The reaction proceeds via an imino Diels−Alder reaction of *N*-arylaldimine **10** or **13** with cyclopentadiene **11** in the presence of the InCl$_3$ catalyst (Schemes 4 and 5). They have

also demonstrated that 3,4-dihydro-2*H*-pyran and indene underwent a Diels−Alder reaction under the same condition.

The tetrahydro-3*H*-cyclopenta[*c*]quinoline **14** (Scheme 5) was achieved from the Schiff base **13**, which had been derived from 4,4′-diaminodiphenylmethane, and an excess of cyclopentadiene **11**.[4b]

Menéndez et al.[4c] reported the synthesis of C-4-substituted 1,2,3,4-tetrahydroquinoline **17** by reacting aromatic imine **15** and methacrolein dimethyl hydrazone **16** in the presence of 10 mol % of InCl$_3$ catalyst in acetonitrile (Scheme 6).

Raghunathan et al.[4d] disclosed an efficient synthesis of diastereomeric *cis*-tetrahydroquinoline **20** and *trans*-tetrahydroquinoline **21** by reacting substituted aromatic amine **18** with *N*-allylindole-2-carbaldehyde **19** in the presence of 20 mol % of InCl$_3$ catalyst (Scheme 7).

Again, the synthesis of pyrrolo[2,3-*d*]pyrimidine-annulated tetrahydroquinoline derivatives **24** and **25** were synthesised from aldehyde **22** and amine **18** via intramolecular aza-Diels−Alder cyclization (Scheme 8). The products were obtained as diastereomeric mixtures, which were enriched with the *cis*-isomer.[4d]

The same group also reported[4e] an excellent catalytic activity of InCl$_3$ in acetonitrile or impregnated in silica gel toward the synthesis of diastereomeric pyrano/thiopyranoquinoline derivatives
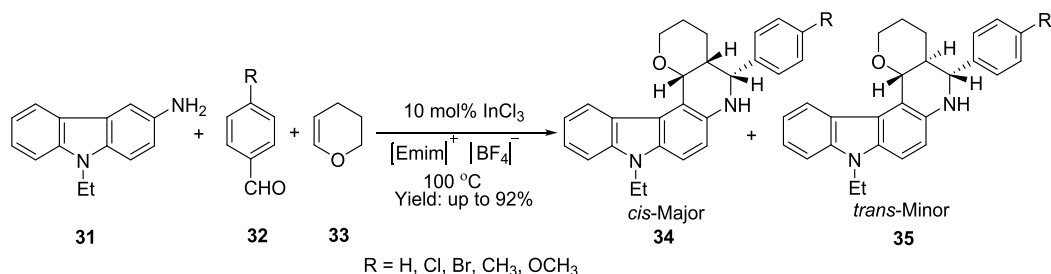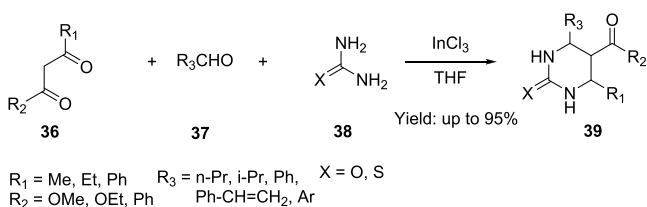
Scheme 5. InCl$_3$-Catalyzed Synthesis of 6,6′-Bishydroquinolinyl Methane
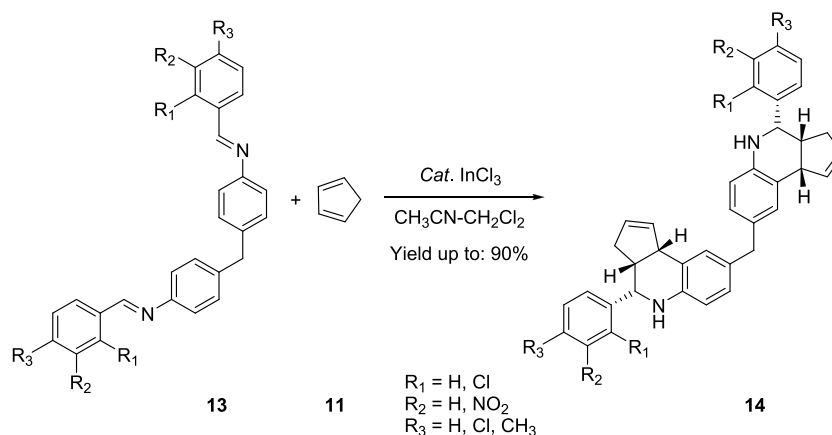
Scheme 6. InCl₃-Catalyzed Synthesis of C-4-Substituted 1,2,3-Trihydroquinolines

R₁ = H, CH₃, OCH₃
R₂ = OCH₃, CH₃, H
R₃ = H, Cl, OCH₃, CH₃, Br
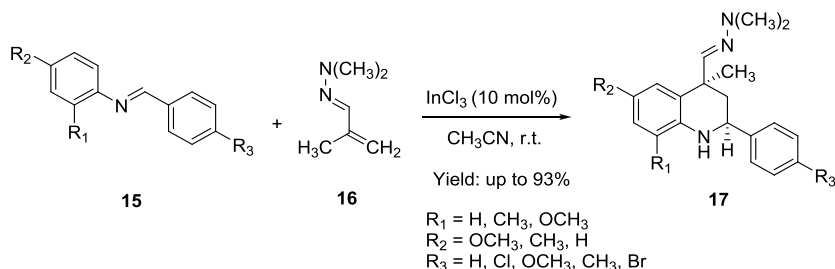
Scheme 7. InCl₃-Catalyzed Synthesis of Fused Hydroquinolines
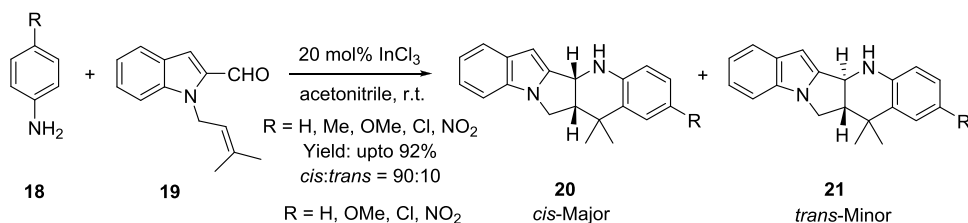
Scheme 8. InCl₃-Catalyzed Synthesis of Pyrimidine-Annulated Fused Hydroquinolines

R₁ = CH₃, H
R₂ = CH₃, C₆H₅

R = H, OMe, Cl, NO₂
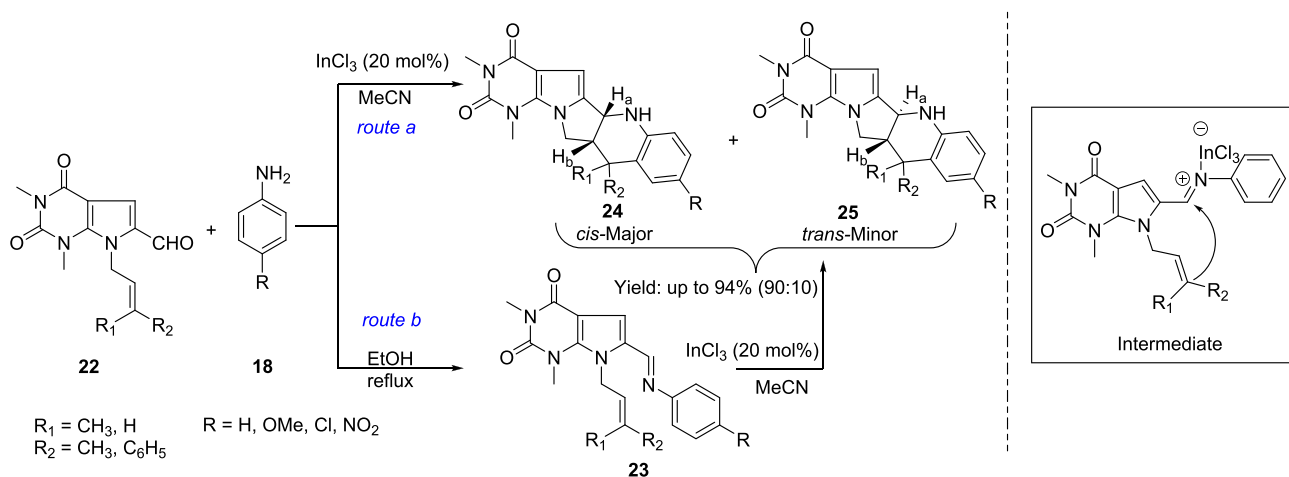
Scheme 9. InCl₃-Catalyzed Synthesis of Thiopyranoquinolines via Intramolecular Imino–Diels–Alder Reaction

R' = H, Me, OMe, Cl, Br, NO₂
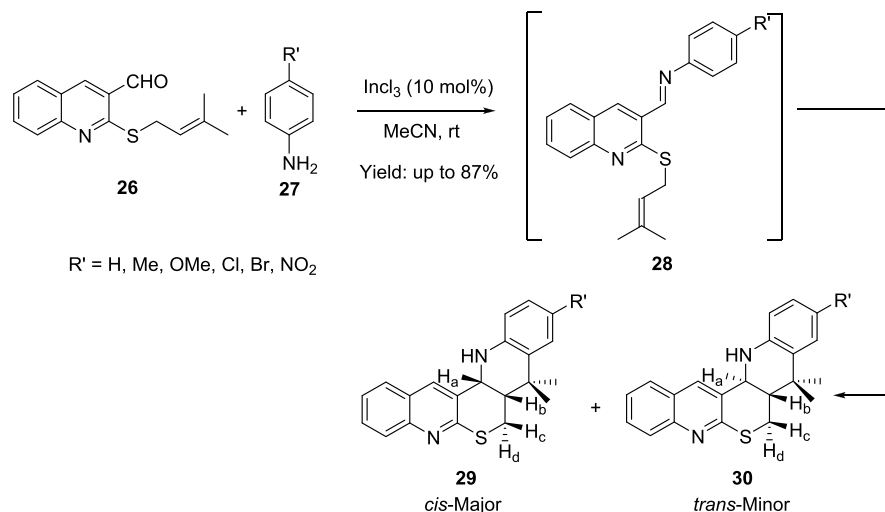
29 and **30** through an intermolecular imino-Diels–Alder reaction (Scheme 9).

An efficient three-component one-pot synthesis of diastereomeric ellipticine derivatives was reported by Nagarajan et al.[4f]

through an imino-Diels–Alder reaction of 3-aminocarbazole **31** and substituted benzaldehyde **32** with an electron-rich alkene **33**, such as 3,4-dihydro-2*H*-pyran, 2,3-dihydrofuran, or ethyl vinyl ether in the presence of 10 mol % of InCl₃ catalyst in an
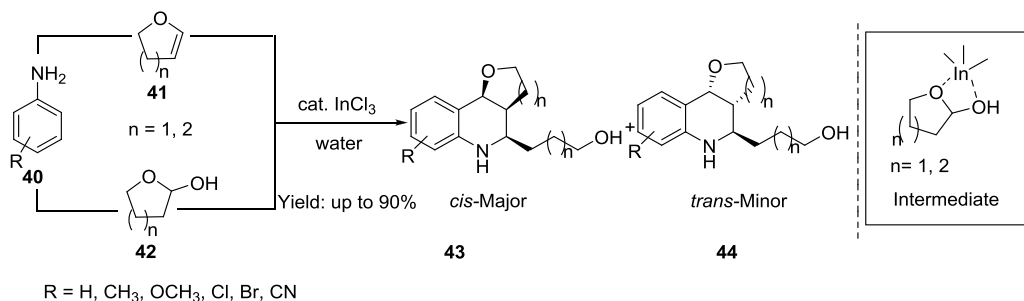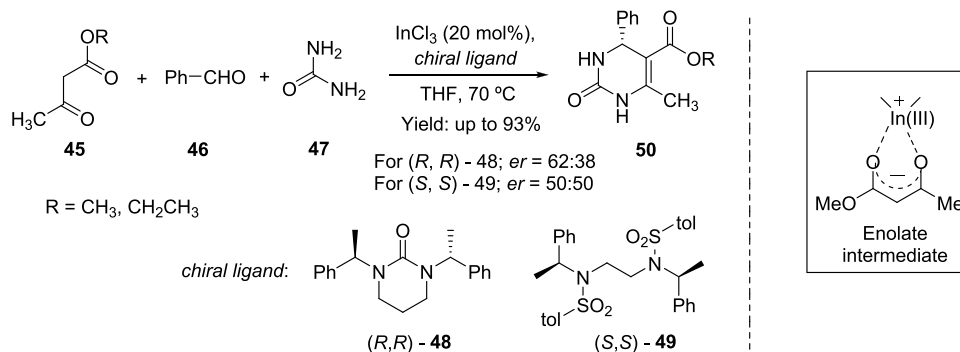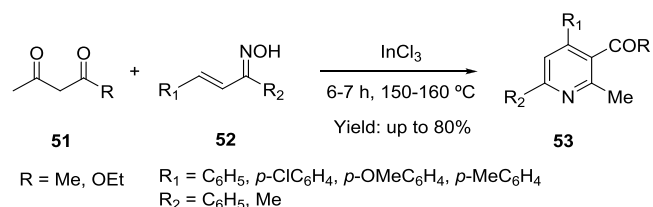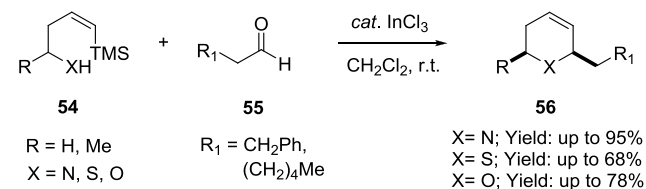
Scheme 10. InCl₃-Catalyzed Synthesis of Ellipticine Derivatives

R = H, Cl, Br, CH₃, OCH₃

Scheme 11. InCl₃-Catalyzed Synthesis of Dihydropyrimidines

R₁ = Me, Et, Ph   R₃ = n-Pr, i-Pr, Ph,   X = O, S
R₂ = OMe, OEt, Ph   Ph-CH=CH₂, Ar

Scheme 14. InCl₃-Catalyzed Synthesis of Tetrasubstituted Pyridines

R = Me, OEt   R₁ = C₆H₅, p-ClC₆H₄, p-OMeC₆H₄, p-MeC₆H₄
R₂ = C₆H₅, Me

Scheme 15. InCl₃-Catalyzed Synthesis of Unsaturated Heterocycles from Silylated Homoallyl Alcohols

R = H, Me   R₁ = CH₂Ph,
X = N, S, O   (CH₂)₄Me

X= N; Yield: up to 95%
X= S; Yield: up to 68%
X= O; Yield: up to 78%

ionic liquid at 100 °C (Scheme 10). In the case of substituted benzaldehydes, reductive amination was also observed.

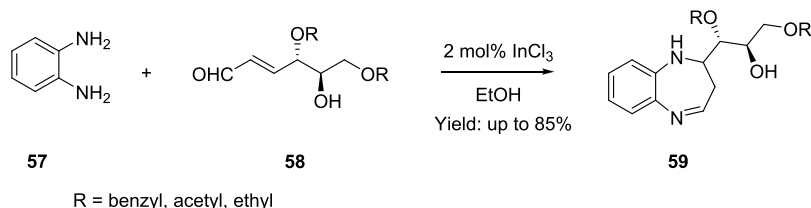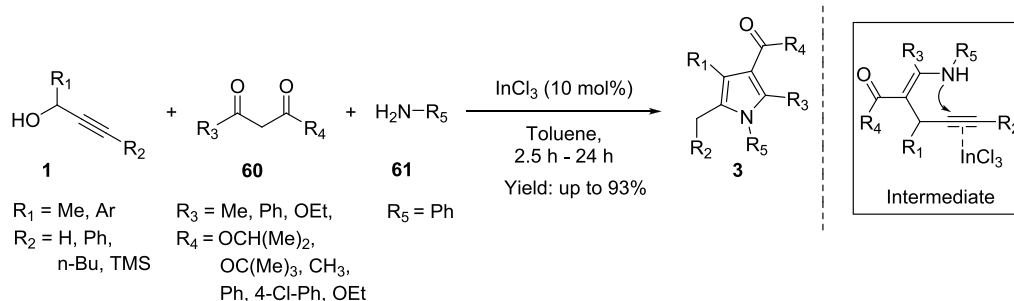Ranu et al.[3e] demonstrated the InCl₃-catalyzed three-component one-pot synthesis of dihydropyrimidin-2(1*H*)-one **39** in good to excellent yields by reacting 1,3-dicarbonyl **36**, aldehyde **37**, and urea/thiourea **38** (Scheme 11).

Li et al.[4g] synthesized diastereoselective tetrahydroquinolines by reacting aromatic amine **40** and cyclic enol ether **41** or 2-hydroxy cyclic ether **42** in the presence of a catalytic amount of InCl₃ in water. The reaction followed an aza-Diels−Alder path to yield *cis*-selective tetrahydroquinolines as major products (Scheme 12).

Juaristi et al.[5a] have reported the asymmetric synthesis of *R*-selective 4-phenyldihydropyrimidinone derivative **50** in a

one-pot Biginelli condensation by reacting acetoacetate ester **45** with benzaldehyde **46** and urea **47** in THF in the presence of a catalytic amount of InCl₃ and chiral ligands (Scheme 13).

Scheme 12. InCl₃-Catalyzed Synthesis of Fused Tetrahydroquinolines

R = H, CH₃, OCH₃, Cl, Br, CN

Scheme 13. InCl₃-Catalyzed Synthesis of Aryl-Substituted Chiral Dihydropyrimidinones

R = CH₃, CH₂CH₃

For (*R*, *R*) - **48**; *er* = 62:38
For (*S*, *S*) - **49**; *er* = 50:50

chiral ligand:

(*R*,*R*) - **48**   (*S*,*S*) - **49**

Enolate intermediate

Scheme 16. InCl$_3$-Catalyzed Synthesis of 1,5-Benzodiazepine

R = benzyl, acetyl, ethyl

Scheme 17. InCl$_3$-Catalyzed Multicomponent Synthesis of Polysubstituted Pyrroles

R$_1$ = Me, Ar
R$_2$ = H, Ph,
     n-Bu, TMS

R$_3$ = Me, Ph, OEt,
R$_4$ = OCH(Me)$_2$,
     OC(Me)$_3$, CH$_3$,
     Ph, 4-Cl-Ph, OEt

R$_5$ = Ph

Scheme 18. InCl$_3$-Catalyzed Synthesis of Substituted 1,8-Naphthiridines

R$_1$ = H, Me
R$_2$ = H, Br, Me
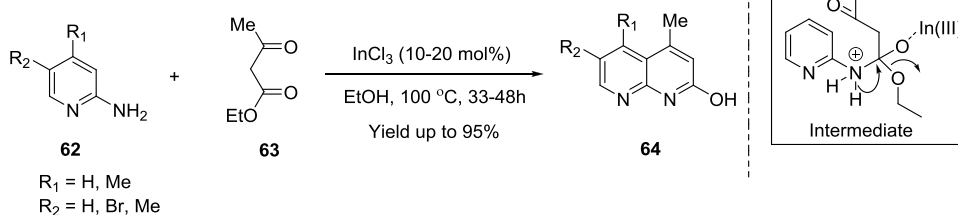
Scheme 19. InCl$_3$-Catalyzed Synthesis of Substituted Tetrahydroquinolines

R = H, Cl, Br, F, Me, OMe
R$_1$ = H, Cl, Me
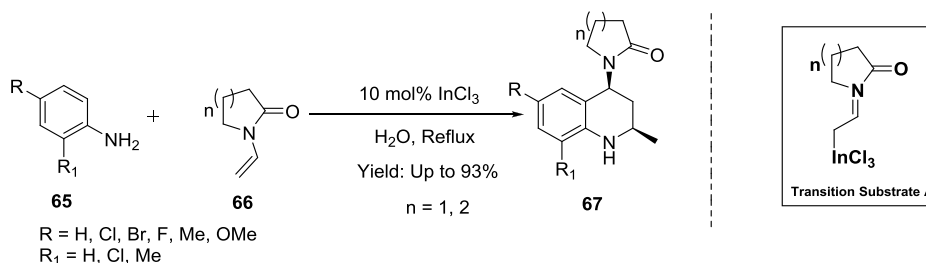
Scheme 20. InCl$_3$-Catalyzed Synthesis of Pyridopyrimidine Derivatives

R = 4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-OHC$_6$H$_4$, 4-O$_2$NC$_6$H$_4$, 2-Thiophenyl, (CH$_3$)$_2$CH
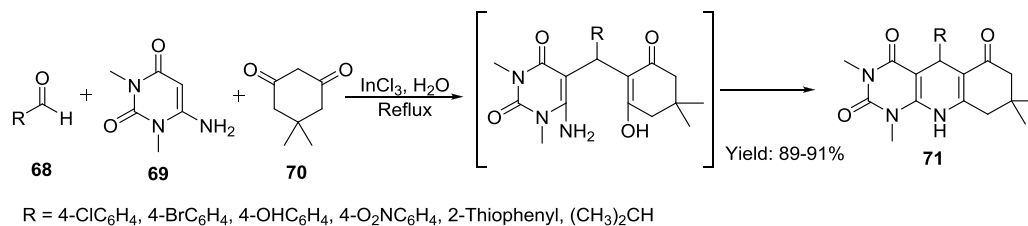
The enantiomeric ratio (er) of the product was found to be 62:38 (for *R,R*-**48**) with an excellent yield of up to 93%.

Prajapati et al.[5b] have developed an InCl$_3$-catalyzed neat synthesis of tetra-substituted pyridine derivative **53** via Michael addition of 1,3-dicarbonyl **51** with α,β-unsaturated oxime **52** followed by a ring-closing reaction (Scheme 14).

Dobbs et al.[5c] reported the cyclization reaction of silylated homoallyl alcohol **54** and aldehyde **55** (even epoxides) in the presence of a catalytic amount of InCl$_3$ to yield diastereoselective unsaturated heterocycle **56** (Scheme 15).

Yadav et al.[5d] have reported an InCl$_3$-catalyzed condensation of *o*-phenylenediamine **57** with 4,6-di-*O*-alkyl-2,3-dideoxyaldehyde-D-*erythro-trans*-hex-2-enose **58** followed by cyclization under mild conditions to afford 1,5-benzodiazepine **59** in good yield (Scheme 16).

A mild, efficient InCl$_3$-catalyzed multicomponent one-pot synthesis of highly substituted pyrroles was developed by Liu et al.[5e]

Scheme 21. InCl₃ catalyzed synthesis of polysubstituted pyrroles from azidochalcones

R₁ = R₂ = H, Me, Cl, Br, NO₂, OMe

R₃ = Me
R₄ = Me, CF₃, Ph, OEt

Scheme 22. InCl₃-Catalyzed Synthesis of Substituted Tetrahydroquinolines

R₁ = Me, CH₂Ph
R₂ = CN, CO₂Me, CONH₂

Scheme 23. InCl₃-Catalyzed Synthesis of Substituted Pyrazole Derivatives

R₁ = H, p-OMeC₆H₄, m-OMeC₆H₄, p-FC₆H₄, m-BrC₆H₄, m-CF₃C₆H₄
R₂ = CO₂Me, CO₂Et

Scheme 24. InCl₃-Catalyzed Synthesis of 2,3,4-Substituted Quinolines

R = H, O-Me, m-Me, p-Me, O-OMe, p-OMe, m-OH, m-Cl, p-Br, m-Cl
R₁ = H, Me, n-Pr
R₂ = H, Et
R₃ = Me, p-OMeC₆H₄

Scheme 25. InCl₃-Catalyzed Synthesis of Quinolones from Coumarins

R = H, NEt₂

R₁ = C₆H₅, o-FC₆H₄, m-IC₆H₄, p-ClC₆H₄, o/p-Cl₂C₆H₃, p-OCH₃C₆H₄, cyclohexyl, isopropyl, isobutyl

in the presence of a catalytic amount of InCl₃ in ethanol at 100 °C for 33−48 h (Scheme 18).

Mahadevan and co-workers[6a] reported an advanced efficient method for the synthesis of various cis-2-methyl-4-amido-1,2,3,4-tetrahydroquinoline derivative 67 by reacting aromatic amine 65 and N-vinyl caprolactam or N-vinyl pyrrolidone 66 in the presence of a catalytic amount of InCl₃ in an aqueous medium in good to excellent yields. These 2,4-disubstituted tetrahydroquinolines showed cis diastereoselectivity (Scheme 19).

Khurana et al.[5g] reported an appealing synthetic protocol which utilized water as the solvent and InCl₃ as the promoter for the three-component combinatorial synthesis of a variety of bioactive pyrimidine and pyrazole derivatives. The latter derivatives were synthesized from aldehyde 68, electron-rich amino heterocycles such as 6-amino-1,3-dimethyl uracil 69 and 3-methyl-1-phenyl-1H-pyrazol-5-amine, and 1,3-dicarbonyl compound 70 under refluxing conditions. Following the same reaction conditions, the synthesis of a new class of pyrimidine derivative 71 was also reported. The reactions were environmentally benign; the reaction product could be isolated easily, and the catalyst could be recycled (Scheme 20).

A facile and regioselective synthesis of polysubstituted pyrroles 73 have been reported by Muthusubramanian and co-worker[6b] from azido chalcones 72 and 1,3-dicarbonyl compounds 60 via an InCl₃ catalyst in water under microwave irradiation (Scheme 21).

Lavilla et al.[4h] achieved a successful InCl₃-catalyzed three-component reaction of dihydropyridine 74, aldehyde 75, and p-methylaniline 76 to afford a diastereomeric mixture of highly substituted tetrahydroquinolines which contained cis-isomer 77 as the major product (Scheme 22).

Interestingly, they found that the reaction involved propargylation, amination, followed by cycloisomerization in a single step to afford pyrrole 3 from propargyl alcohol 1, 1,3-dicarbonyl 60, and primary amine 61 in very good yields (Scheme 17).

Adimurthy et al.[5f] developed a highly efficient and regioselective method for the synthesis of 1,8-naphthyridine 64 directly from substituted 2-aminopyridine 62 and ethyl acetoacetate 63
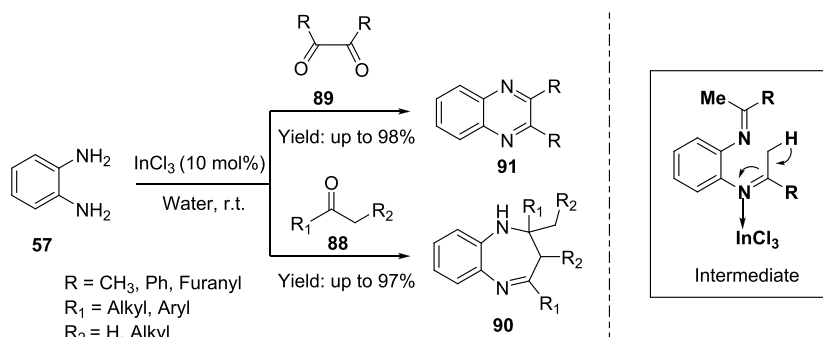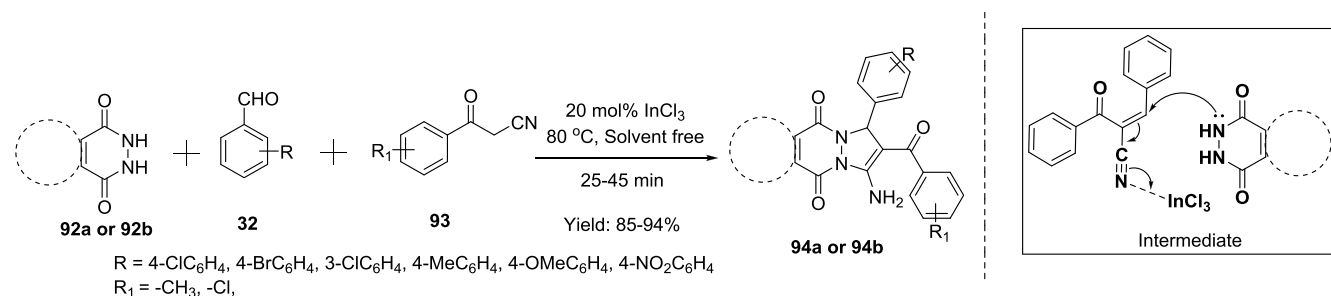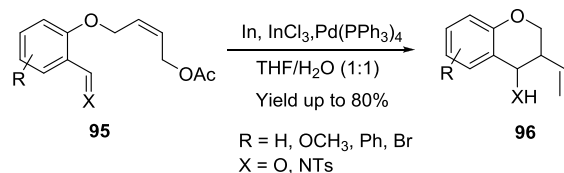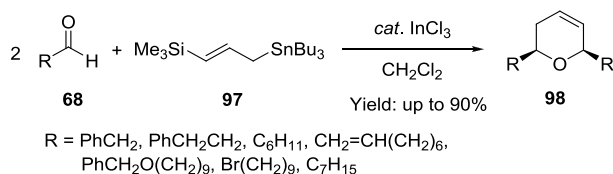
Scheme 26. InCl$_3$-Catalyzed Synthesis of 1,5-Benzodiazepines and Quinoxalines from 1,2-Aminobenzene

Scheme 27. InCl$_3$-Catalyzed Synthesis of Pyrazole Derivatives

R = 4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$, 3-ClC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-OMeC$_6$H$_4$, 4-NO$_2$C$_6$H$_4$
R$_1$ = -CH$_3$, -Cl,

Scheme 28. InCl$_3$-Catalyzed Synthesis of Benzopyran Derivatives

Scheme 29. InCl$_3$-Catalyzed Synthesis of Substituted Dihydropyrans

R = PhCH$_2$, PhCH$_2$CH$_2$, C$_6$H$_{11}$, CH$_2$=CH(CH$_2$)$_6$,
PhCH$_2$O(CH$_2$)$_9$, Br(CH$_2$)$_9$, C$_7$H$_{15}$

Scheme 30. InCl$_3$-Catalyzed Synthesis of 4-Chlorotetrahydropyrans via Prins Cyclization

R = PhCH$_2$CH$_2$, Ph, Cy, Et$_2$CH, CH$_3$(CH$_2$)$_7$, BnO(CH$_2$)$_2$
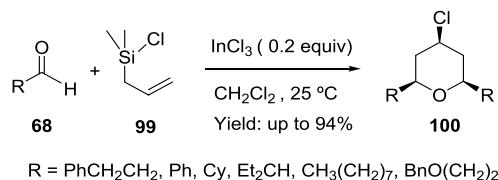
Li et al.[4i] reported an intermolecular 1,3-dipolar cycloaddition of methyl α-diazoacetate **79** with alkyne **80** in water in the presence of InCl$_3$ catalyst to afford substituted pyrazole compounds **81** and **82** in good yields (Scheme 23).

Ranu et al.[3f–g] developed a one-pot synthesis of quinoline **84** by reacting aniline **40** with alkyl vinyl ketone **83** on the solid surface of silica gel impregnated with InCl$_3$ under microwave irradiation (Scheme 24). The products were obtained in excellent yields.

An efficient and eco-friendly synthesis of structurally diversified 2-quinolinones **87** from coumarin-3-carboxylic acid **85** and primary amine **86** in the presence of a catalytic amount of InCl$_3$ in aqueous medium at ambient temperature was reported by Mahadevan et al.[4j] (Scheme 25).

Gogoi et al.[7a] reported an InCl$_3$-catalyzed condensation of o-phenylenediamine **57** with ketone **88** and 1,2-dicarbonyl **89** to afford various 1,5-benzodiazepine **90** and quinoxaline **91**, respectively, with excellent yields (Scheme 26).

Very recently, Jeong et al.[7b] reported a synthesis of novel 3-amino-2-benzoyl-1-aryl-1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione derivative **94a** via a one-pot three-component reaction of phthalhydrazide **92a**, aldehyde **32**, and arylacetonitrile **93** in the presence of InCl$_3$ (20 mol %) catalyst under solvent-free environmentally friendly conditions. Similarly, they reported the synthesis of 3-amino-2-benzoyl-1-aryl-1*H*-pyrazolo[1,2-*a*]pyridazine-5,8-dione **94b** derivatives but used maleic hydrazide **92b** instead of **92a** (Scheme 27).

3. SYNTHESIS OF O-HETEROCYCLES

Indium and its salts have been extensively used for alkylation, allylation, and alenylation reactions in water.[8a,b] Therefore, InCl$_3$-catalyzed synthesis of bioactive compounds in water is the decent choice for researchers for the development of pharmaceutical agents with less or no toxicity. Among various O-heterocycles, chromanes were found in many important natural products and were reported to have significant biological importance.[9] Synthesis of these compounds in water has been a topic of interest to medicinal chemistry researchers.

Kang et al.[10] reported an intramolecular allylation of carbonyl/imine **95** to chromane **96** in the presence of In, InCl$_3$, and Pd(PPh$_3$)$_4$ in water with high yield (Scheme 28). The main advantage of using indium along with InCl$_3$ was to generate active InCl, which was responsible for the generation of an organoindium complex via transmetalation from an organo-palladium complex followed by allylation.

Scheme 31. InCl$_3$-Catalyzed Synthesis of 2,3-Dihydrobenzofuran Derivatives

101   102   103

R = H, OCH$_3$, OCH$_2$O   R$_2$ = H, Me
R$_1$ = OCH$_3$, OCH$_2$O
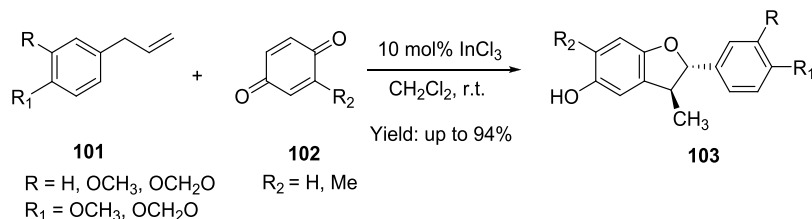
Scheme 32. InCl$_3$-Catalyzed Rearrangement of Dihydropyran to Furan

104   105
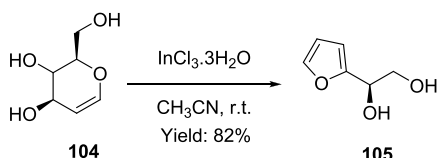
Li et al.[11a] demonstrated InCl$_3$-mediated highly diastereoselective tandem carbonyl allylation−Prins cyclization of aldehyde **68** with 3-trimethylsilylallyltributylstannane **97** to afford 2,6-dialkyl-5,6-dihydropyran **98** with a *cis* diastereoselectivity (Scheme 29).

Loh et al.[11b] accomplished a one-pot Prins cyclization of aldehyde **68** with allylchlorosilane **99** to afford corresponding 2,4,6-trisubstituted tetrahydropyran **100** in the presence of InCl$_3$ catalyst (Scheme 30). They also observed that α,β-unsaturated aldehydes also respond to the reaction equally.
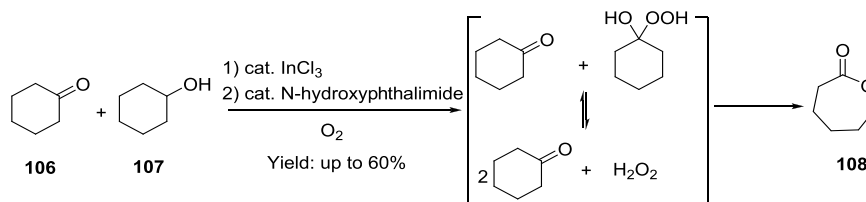
Yadav et al.[12a] found that, in the presence of 10 mol % of InCl$_3$, 1,4-benzoquinone **102** could react with electron-rich alkene **101** to afford the corresponding 2,3-dihydrobenzofuran **103** in excellent yield. It was noted that the reaction underwent a [3 + 2] cycloaddition pathway to produce a *trans*-selective product (Scheme 31).

Balasubramanian et al.[11c] reported the synthesis of 2-(D-glycero-1,2-dihydroxyethyl)furan **105**, an optically active furandiol from glucal **104** in the presence of a catalytic amount of InCl$_3$·3H$_2$O in acetonitrile at room temperature (Scheme 32).

Ishii et al.[11d] have developed a catalytic Baeyer−Villiger oxidation of KA-oil (a mixture of cyclohexanone **106** and cyclohexanol **107**) with molecular oxygen. The reaction has been done in the presence of a catalytic amount of InCl$_3$ and *N*-hydroxyphthalimide to afford ε-caprolactone **108** (Scheme 33).

An efficient InCl$_3$-catalyzed synthesis of substituted pyran **110** was demonstrated by Lee et al.[11e] by reacting 1,3-dicarbonyl **70** with α,β-unsaturated aldehyde **109** in acetonitrile under refluxing conditions with moderate yields (Scheme 34).

Perumal et al.[11f] developed InCl$_3$-catalyzed cyclization of *o*-hydroxyaldimine **111** with vinyl enol ether **41**, resulting in the formation of diastereoselective benzopyran derivatives (*syn*-**112** and *anti*-**113**) at ambient temperature with excellent yield and high diastereoselectivity (Scheme 35).

Scheme 34. InCl$_3$-Catalyzed Synthesis of Substituted Pyrans

70   109   110
R$_1$ = R$_2$ = H, Me
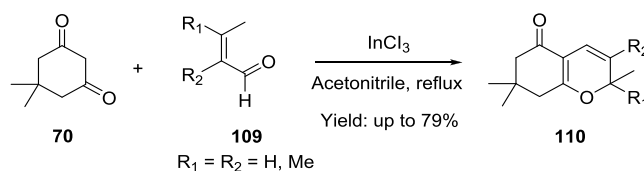
Scheme 35. Diastereoselective Synthesis of Furano/Pyranobenzopyran Derivatives

111   41   *syn*-Major   *anti*-Minor
n = 1,2   112   113

R = C$_6$H$_5$, 4-MeC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-O$_2$NC$_6$H$_4$
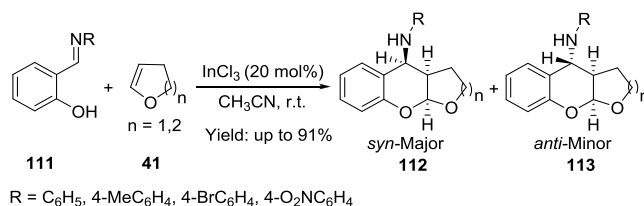
Scheme 36. InCl$_3$-Catalyzed C-Alkylation of Indoles with Cyclic Enol Ether

114   115   116

R = H, Me, CH$_2$Ph, Ethyl, *t*-butoxycarbonyl, allyl;
R$_1$ = OMe, Br

117   33   118
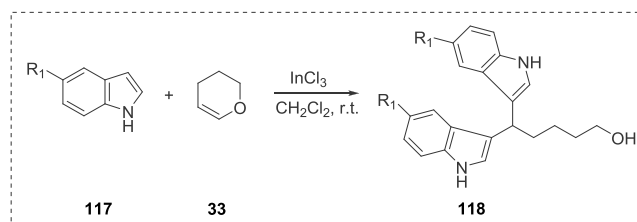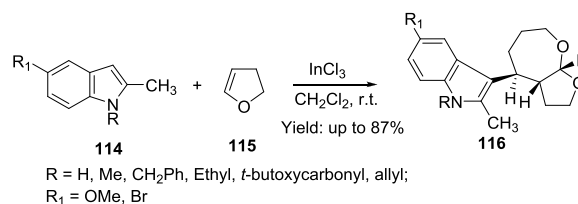
Scheme 37. InCl$_3$-Catalyzed Synthesis of Substituted Coumarins

119   120   121

X = oxygen substituent   R = H, Ph

Scheme 33. InCl$_3$-Catalyzed Baeyer−Villiger Oxidation of KA-Oil to ε-Caprolactone

106   107   108
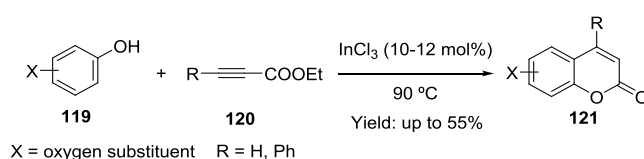
Scheme 38. InCl$_3$-Catalyzed Synthesis of Dioxolanes

R = alkyl, aryl
R$_1$ = H, alkyl, aryl

n = 1, 2
Yield: up to 98%

Scheme 42. InCl$_3$-Catalyzed Cyclotrimerization of Aldehydes to Trioxanes

R = CH$_3$, (CH$_3$)$_2$CH, (CH$_3$)$_3$C, Ph, PhCH$_2$, etc.
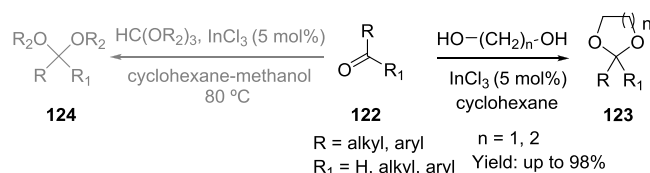
Yadav and co-workers[12b] also developed the methodology for the synthesis of 2-methyl-3-perhydrofuro[2,3-b]oxepin-4-yl-1H-indole derivative 116 by reacting substituted 2-methylindole 114 with 2,3-dihydrofuran 115 in the presence of a catalytic amount of InCl$_3$ under mild reaction conditions. The yield and diastereoselectivities of the products were found to be excellent. On the other hand, 5,5-di(1H-3-indolyl)-1-pentanol derivative 118 was formed in high yields when indole 117 and 3,4-dihydro-2H-pyran 33 were reacted under similar reaction conditions (Scheme 36).

Kalyanam et al.[11g] synthesized coumarin 121 in a single step with a condensation reaction of substituted phenol 119 and acetylenic ester 120 in the presence of a catalytic amount of InCl$_3$ under solvent-free conditions (Scheme 37).

Ranu et al.[13a] developed an easy and efficient methodology that demonstrated InCl$_3$-catalyzed masking of carbonyl 122 to 1,3-dioxolane 123 and dialkyl acetal 124 with good to excellent yields (Scheme 38).

Tocco et al.[13b] reported that 2,2′-dihydroxybiphenyl 125 and bis(2-hydroxyphenyl)methane 127 reacted with carbonyl 122 to afford dibenzo(d,f)-(1,3)dioxepine 126 and 12H-dibenzo-

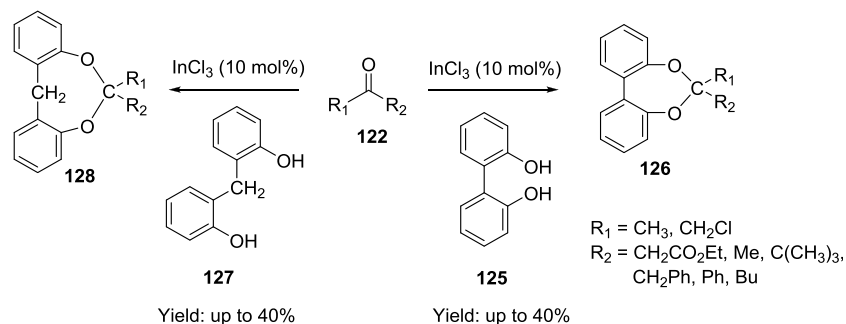(d,g)-(1,3)dioxocin 128, respectively, in the presence of a catalytic amount of InCl$_3$ (Scheme 39).

van Lier et al.[11h] have shown a facile oxidation of 2′-hydroxy-chalcone 129 and hydroflavanone 130 to afford the corresponding flavone 131 in the presence of silica gel impregnated with 15−20 mol % of InBr$_3$ or InCl$_3$ under solvent-free conditions (Scheme 40).

Chen and co-workers[11i] reported an InCl$_3$-catalyzed three-component reaction of arylglyoxal monohydrate 132, phenol 133, and p-toluenesulfonamide 134 to afford 2-aryl-3-amino-benzofuran 135 in good to excellent yields (Scheme 41).

Raghunathan et al.[13c] reported the InCl$_3$-catalyzed synthesis of 1,3,5-trioxane 136 by the cyclotrimerization of aldehyde 68 in excellent yields under solvent-free conditions (Scheme 42).

Prajapati and Gohain have synthesized a cis−$trans$ mixture of pyrano[2,3-d]pyrimidines 140 and 141 from a multicomponent domino Knoevenagel/hetero-Diels−Alder reaction of 1,3-dimethyl barbituric acid 137 and an aromatic aldehyde 138 followed by vinyl ether 139 addition, in the presence of 1 mol % of InCl$_3$ (Scheme 43).[13d]

Yadav et al.[12c] also reported that hexose sugar 142 underwent a coupling reaction with 1,3-dicarbonyl 143 in the presence of

Scheme 39. InCl$_3$-Catalyzed Synthesis of Dibenzodioxepines and -dioxocins

Yield: up to 40%　　　　　Yield: up to 40%

R$_1$ = CH$_3$, CH$_2$Cl
R$_2$ = CH$_2$CO$_2$Et, Me, C(CH$_3$)$_3$,
　　　CH$_2$Ph, Ph, Bu

Scheme 40. InCl$_3$-Catalyzed Oxidation of Hydroxychalcones and Dihydroflavones to Flavone Derivatives

R = H, OH, OMe; R$_1$ = H, Cl, OH, OMe, Br, F, NO$_3$
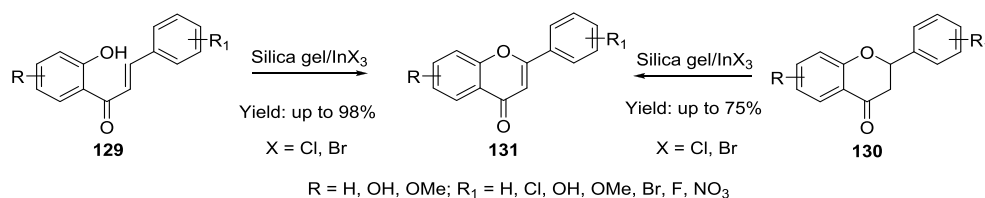
Scheme 41. InCl$_3$-Catalyzed Synthesis of Substituted Benzofurans

R$_1$ = H, Cl, OMe

R$_2$ = H, ^{t}Bu, Ph, OMe, F, Cl, Br
R$_3$ = H, ^{t}Bu

10 mol% InCl$_3$
CH$_2$Cl$_2$, reflux
6-16 h
Yield: up to 86%
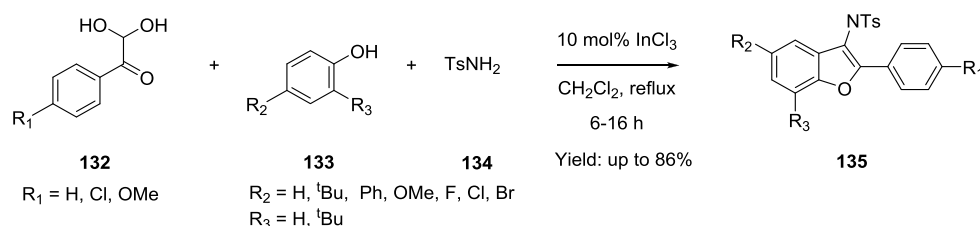
Scheme 43. InCl₃-Catalyzed Synthesis of Pyranopyrimidines

137   138

Ar = C₆H₅, 4-ClC₆H₄, 4-MeC₆H₄, 4-OMeC₆H₄, 4-NO₂C₆H₄

Yield: up to 99%   140   141

trans-isomer   *cis*-isomer
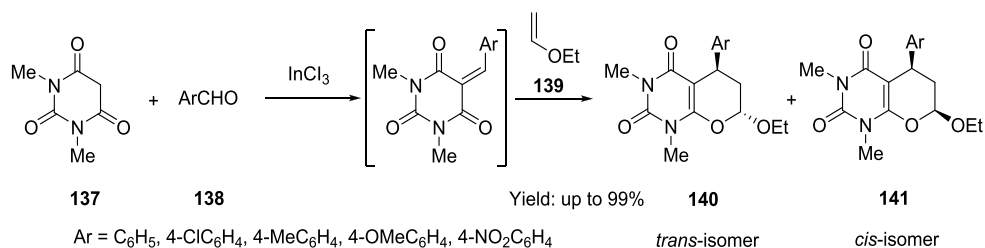
Scheme 44. InCl₃-Catalyzed Synthesis of Furyl Glycosides

142   143   144

R = alkoxy, alkyl   Yield: up to 93%
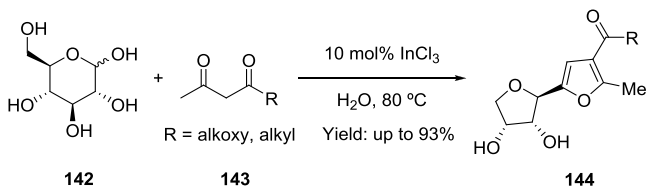
10 mol % of InCl₃ in water at 80 °C to afford *C*-furyl glycosides **144** in high yields (Scheme 44). The pentose sugars with 1,3-dicarbonyls gave the corresponding furan derivatives, and reaction of cyclic ketones with hexose sugars gave the corresponding tetrahydrobenzofuranyl glycoside derivatives.

Perumal et al.[2a] developed an InCl₃-catalyzed three-component one-pot synthesis of spirooxindoles under both conventional and solvent-free microwave irradiation conditions. Isatin **145** first

Scheme 45. Synthesis of Spirooxindoles from Isatin and Malonitriles

MW reaction, Yield: up to 90%
Reflux condition, Yield: up to 75%

145   146a/b   147c/d   148   149

R = H, CH₃   **a**, X = CN   **c**, Y = OH, Z = H
               b, X = COOEt **d**, Y = H, Z = OH

Scheme 46. InCl₃-Catalyzed Synthesis of Amino Chromenes

150   151   152   153

X = H, CH₃, OMe, Br, Cl

Yield: up to 87%
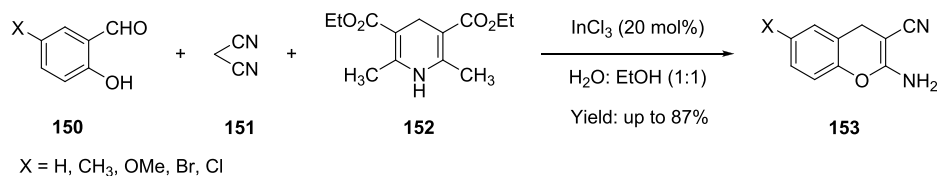
Scheme 47. InCl₃-Catalyzed Synthesis of Naphthapyranopyrimidines

154   155   156   157

R = H, OMe, Me, OH, Br, Cl, F, NO₂

InCl₃, 120 °C
Solvent-free
Yield: up to 83%

ortho-quinonemethide
intermediate
(o-QM)
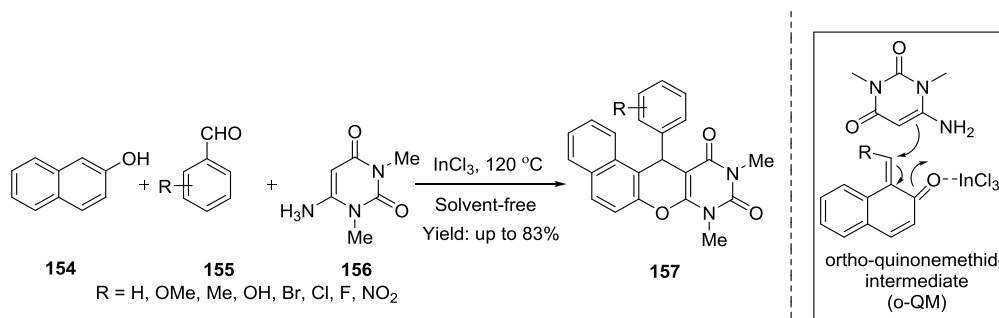
Scheme 48. InCl₃-Catalyzed Synthesis of Dihydropyranochromenediones

158   159   70   160

Incl₃ (10 mol%)
120 °C
Yield = 90%
R = H, Me, OMe, OPh, Cl, F
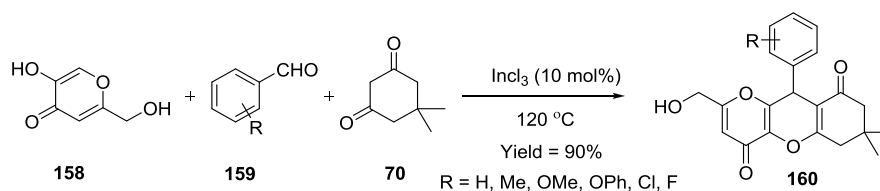
Scheme 49. InCl₃-Catalyzed Synthesis of Pyranoquinolines
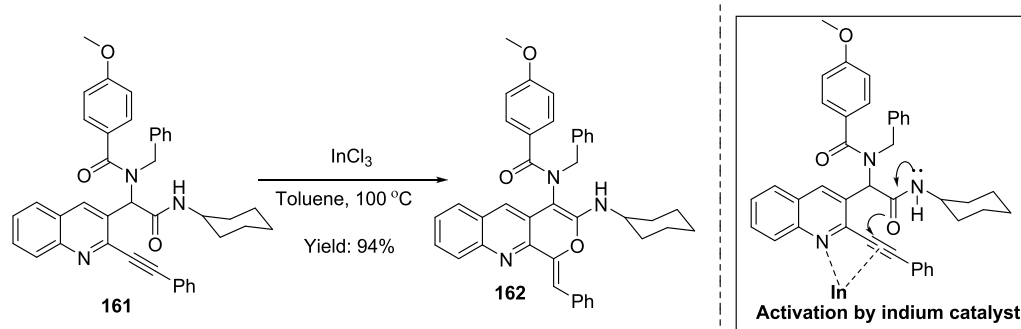
Scheme 50. InCl₃-Catalyzed Synthesis of Dithiolanes

R₁ = H, CH₃; R₂ = CH₃,C₆H₅, OMeC₆H₄, MeC₆H₄, OHC₆H₄, O₂NC₆H₄, CH₂CO₂Et
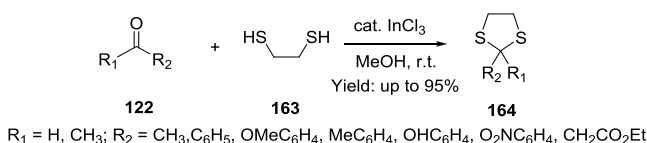
Scheme 51. InCl₃-Catalyzed Thioacetalization of Ketals

R₁ = H
n = 2, 3
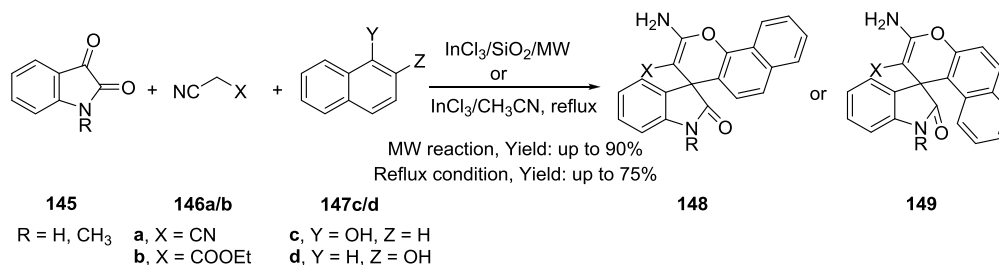R₂ = C₆H₅, MeC₆H₄, OMeC₆H₄,O₂NC₆H₄,
ClC₆H₄, O-allylC₆H₄, alkyl
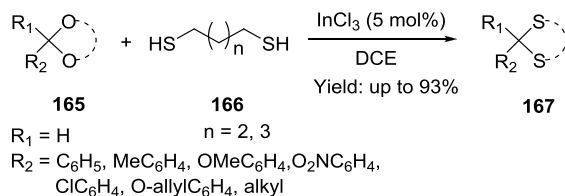
Scheme 52. InCl₃-Catalyzed Synthesis of Indenodithiepines and Dithiocines

R = H, CH₃, Cl, F

Ar = C₆H₅, MeC₆H₄, OMeC₆H₄,
ClC₆H₄, CF₃C₆H₄, NMe₂C₆H₄, naphthyl
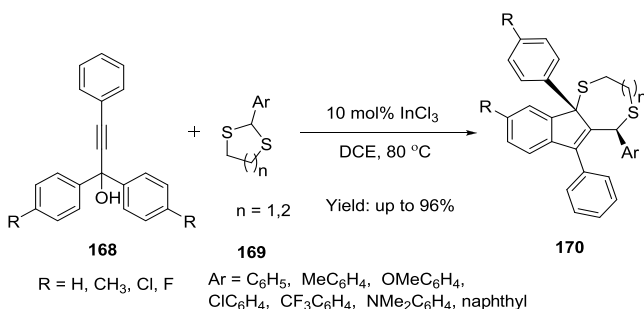
condenses with malononitrile **146a** or ethyl cyanoacetate **146b** to form α,β-unsaturated nitrile or acetate derivatives which undergo a C-alkylation reaction with 1-naphthol **147c** or 2-naphthol **147d** followed by nucleophilic addition of the phenolic OH group onto the cyano moiety, affording spirooxindoles **148** and **149**, respectively (Scheme 45).
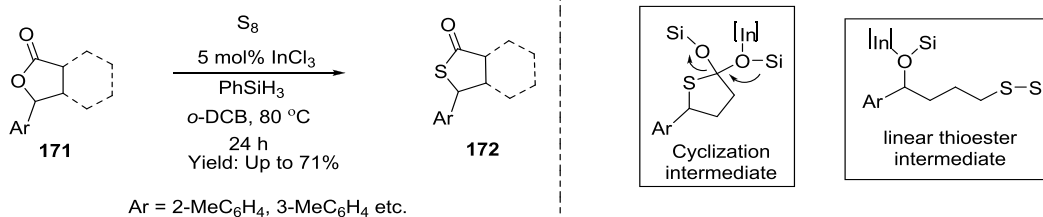
The same group further reported a convenient three-component one-pot synthesis of 2-aminochromene **153** from salicylaldehyde **150**, malononitrile **151**, and Hantzsch dihydropyridine ester **152** in aqueous ethanol using InCl₃ catalyst (Scheme 46).[13e]

Singh et al.[14] have reported an InCl₃-catalyzed three-component one-pot coupling of β-naphthol **154**, aldehydes **155**, and 6-amino-1,3-dimethyluracil **156** under solvent-free conditions to give 8,10-dimethyl-12-aryl-12H-naphtho[1′,2′:5,6]pyrano-[2,3-d]pyrimidine-9,11-dione **157** in high yields (Scheme 47).

Reddy et al.[15] reported a novel three-component one-pot synthesis of dihydropyrano[3,2-β]chromenedione derivative **160** from kojic acid **158**, aldehyde **159**, and dimedone **70** in the presence of 10 mol % of InCl₃ under solvent-free conditions at 120 °C. The product 2-(hydroxymethyl-7,7-dimethyl-10-phenyl-7,8-dihydroxypyrano[3,2-β]-chromene-4,9(6H,10H)-dione (**160**) was obtained in 90% yield (Scheme 48).

Balalaie et al.[16] reported an efficient approach for the synthesis of pyranoquinoline **162** through InCl₃-catalyzed activation of alkyne **161**. Intramolecular hydroamidation of alkynes can proceed through alkyne activation by indium(III) chloride and then 6-exo-dig cyclization, leading to a fused pyran ring with high selectivity, high atom economy, and good yields (Scheme 49).

4. SYNTHESIS OF S-CONTAINING HETEROCYCLES AND OTHERS

Muthusamy et al.[18] reported an InCl₃-catalyzed synthesis of 1,3-dithiolane **164** by reacting carbonyl **122** with 1,2-ethanedithiol **163** in methanol at room temperature in excellent yields (Scheme 50).

Ranu et al.[17] also developed a method for trans-thioacetalization of O,O-acetal **165** by thiol **166** in 1,2-dichloroethane (DCE) to afford **167** in the presence of a catalytic amount of InCl₃ in good yields (Scheme 51).

Muthusamy et al.[18] reported an InCl₃-catalyzed atom-economical diastereoselective synthesis of indenodithiepines and indenodithiocines via a domino reaction of propargylic

Scheme 53. InCl₃-Catalyzed Conversion of Lactones to Thiolactones

Ar = 2-MeC₆H₄, 3-MeC₆H₄ etc.

Scheme 54. InCl$_3$-Catalyzed Synthesis of Nitrogen-Fused Thiazinoindole Derivatives

R$_1$ = H; R$_2$ = Ph, Me
R$_1$ = R$_2$ =CH$_2$(CH$_2$)$_2$CH$_2$

R$_3$ = H;
R$_4$ = Ph, MeC$_6$H$_4$, OMeC$_6$H$_4$, O$_2$NC$_6$H$_4$, benzyl, alkyl
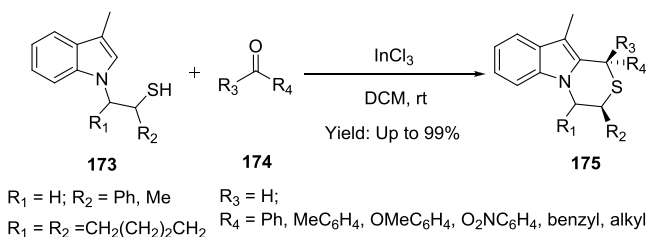
alcohol **168** and dithioacetal **169** (Scheme 52). The reaction works efficiently with remarkable accessibility of a wide variety of indene-fused sulfur heterocycles **170** (e.g., functionalized dithiepines and dithiocines) with good to excellent yields (up to 96%).

Sakai et al.[19] reported the direct conversion of lactone **171** into thiolactone **172** with elemental sulfur (S8) catalyzed by InCl$_3$/PhSiH$_3$ in a one-pot reaction (Scheme 53). This catalytic system was successfully applied to the novel preparation of selenolactones from lactones and selenium.

Gharpure and co-workers[20] reported an inter- as well as intramolecular thia-Pictet−Spengler cyclization of N-tethered thiol **173** and carbonyl compound **174** to yield nitrogen-fused thiazinoindole derivative **175** in excellent yields (Scheme 54).

The strategy was extended to a one-pot, sequential Friedel−Crafts alkylation/Pictet−Spengler cyclization and the synthesis of thiazinooxepinoindole.[20]

Scheme 58. InCl$_3$-Catalyzed Synthesis of Broad Spectrum of Heterocycles

Ar = Ph, 4-Me-Ph, 4-Cl-Ph, 4-Br-Ph, 3-Cl-4-Me-Ph
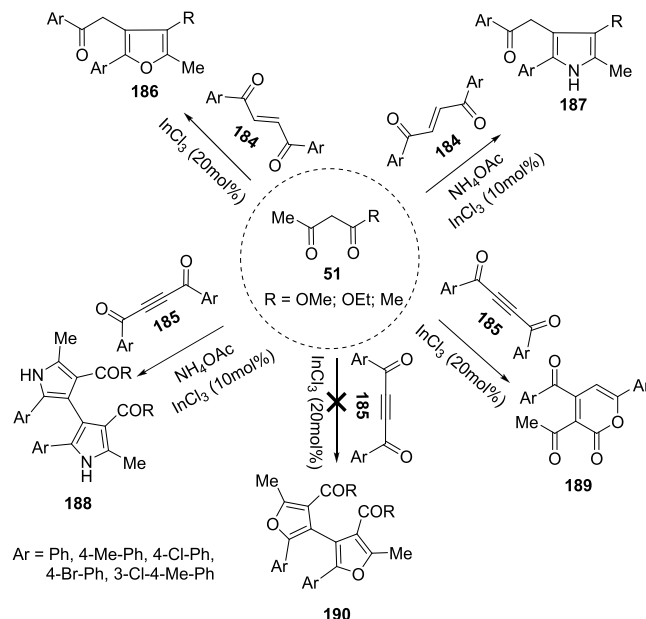
Perumal et al.[2a] have discovered the intramolecular imino Diels−Alder reaction of aldimines derived from aromatic amines **40** and O-allyl salicylaldehydes **176** to give a diastereomeric

Scheme 55. InCl$_3$ catalyzed synthesis of tetrahydrochomanoquinolines

R = H, Me, OMe, Br, NO$_2$, COOH, CN; R$_1$ = H, OMe, Cl
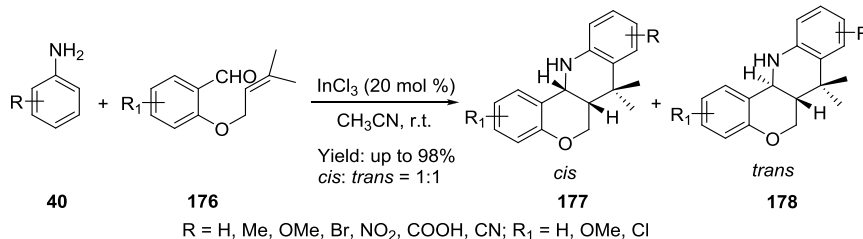
Scheme 56. InCl$_3$ catalyzed synthesis of oxazoloquinolines

X = H, OMe, Cl, F, NO$_2$, Me, Ph, CF$_3$
R$_1$ = H, SMe, SBn, SAll
R$_2$ = H, Me, iPr, c-Pr
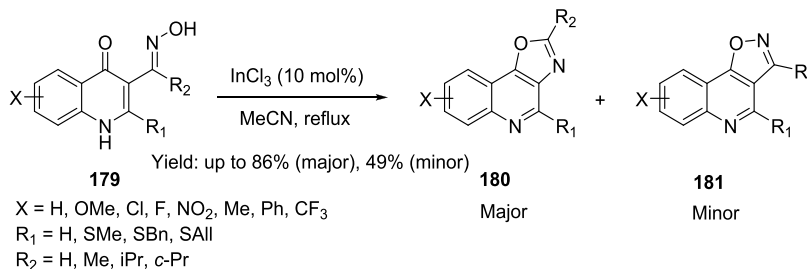
Scheme 57. InCl$_3$-Catalyzed Synthesis of Oxa-Aza Bicyclononene Derivatives

R = Me, OMe
R$_1$ = Me, acetyl, allyl
R$_2$ = Me, OMe, aryl, halogen
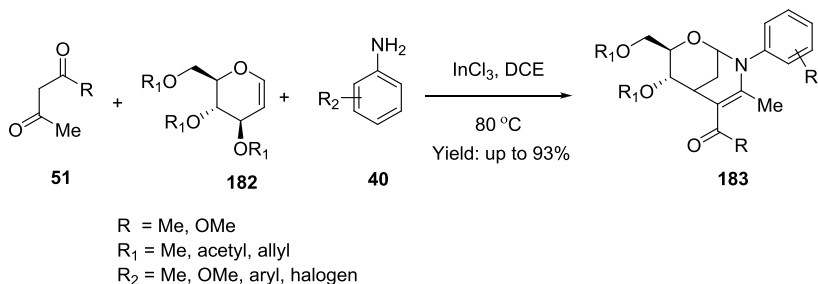
Scheme 59. InCl$_3$-Catalyzed Synthesis of Oxa-Aza Bicycles

Ar = C$_6$H$_5$, FC$_6$H$_4$, ClC$_6$H$_4$, MeC$_6$H$_4$, OMeC$_6$H$_4$, OCH$_2$OC$_6$H$_4$,
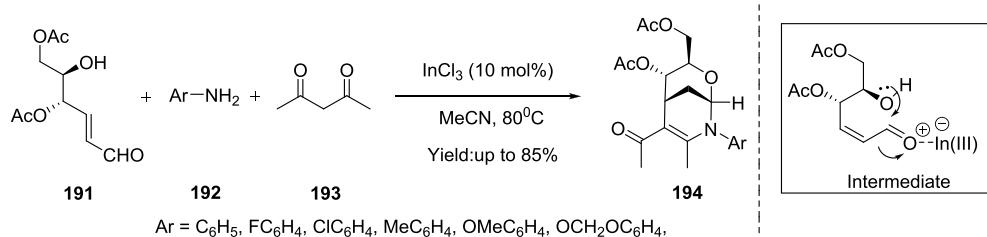
Scheme 60. InCl$_3$-Catalyzed Synthesis of Fused Tetrahydroquinolines

R = H, Me, Cl, Br; R$_1$ = H, Me, Cl
R$_2$ = H, Me, Cl, Br, F, Ph
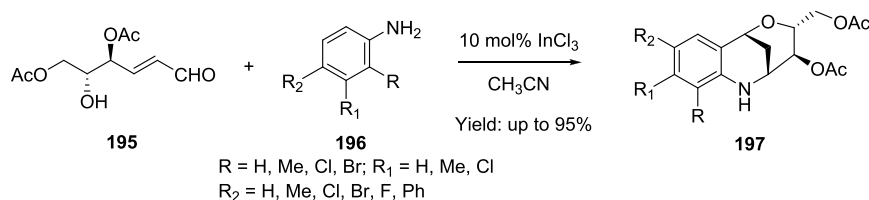
Scheme 61. InCl$_3$-Catalyzed Synthesis of 3-Pyrrolylindolones

R$_1$ = H, Me, Cl, Br; R$_2$ = H, Me, CH$_2$Ph
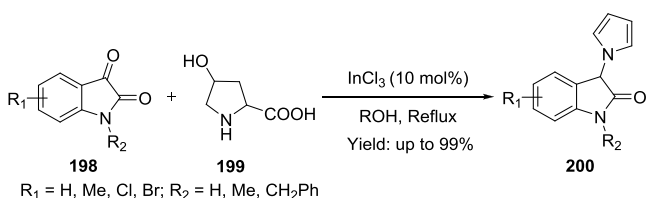
mixture of tetrahydrochromano[4,3-b]quinolines in the presence of InCl$_3$ catalyst in excellent yields under mild reaction conditions (Scheme 55). The products were obtained as a mixture of *cis* 177 and *trans* 178 isomers in 1:1 ratio.

Pak et al.[21] reported an InCl$_3$ catalyzed Beckmann rearrangement of 3-acyl-4-quinolinone ketoximes 179 to obtain predominantly an oxazoloquinoline 180 as the major product; an isooxazoloquinoline 181 was isolated as a minor product without rearrangement (Scheme 56).

Yadav et al.[12d] developed a synthetic methodology for the synthesis of oxa-aza bicyclononene scaffolds which have presumed importance in the field of drug discovery. They have demonstrated a three-component coupling (3CC) of glycal 182,

1,3-dicarbonyl compound 51, and arylamine 40 in the presence of 10 mol % of InCl$_3$ in DCE under refluxing conditions. This reaction afforded oxa-aza bicyclononene 183 in 93% isolated yield and high stereoselectivity (Scheme 57).

For more than a decade, our group also worked on the InCl$_3$-catalyzed synthesis of heterocycles.[22] We explored the use of the InCl$_3$ catalyst in the synthesis of four different types of heterocyclic compounds, which included substituted furans, pyrroles, bipyrroles, and pyrones. We reacted 1,2-diaroylethylene 184 with various β-dicarbonyls 51 in the presence of a catalytic amount of InCl$_3$, which resulted in the formation of tetrasubstituted furan 186. In the presence of ammonium acetate (NH$_4$OAc), the reaction between 51 and 184 yielded substituted pyrrole 187. The treatment of diaroylacetylene 185 with 51 and NH$_4$OAc yielded (±)-3,3′-bipyrrole 188. In the absence of NH$_4$OAc, 51 reacted with 185 to afford substituted 2-pyrone 189 in very good yield and not the expected(±)-3,3′-bifuran 190 (Scheme 58).

Reddy et al.[23] developed a novel one-pot synthesis of oxa-aza bicycle 194 from the δ-hydroxy-α,β-unsaturated sugar aldehyde (Perlin aldehyde) 191, arylamine 192, and 1,3-dicarbonyl compound 193 in the presence of 10 mol % of InCl$_3$ in acetonitrile at 80 °C. Initially, the aryl amine reacted with the

Scheme 62. InCl$_3$-Catalyzed Synthesis of Pyranoquinolines

R = H, Cl, Br, F, CN, CH$_2$CN, OMe, NO$_2$
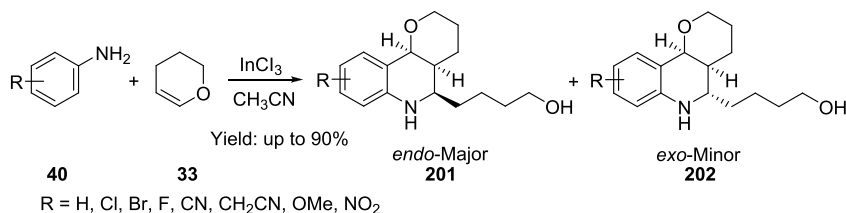
Scheme 63. InCl$_3$-Catalyzed Synthesis of Pyrazole-Fused Thiopyranoquinolines

R = H, Me, OMe, Cl, NO$_2$; R$_1$ = Me, Ph
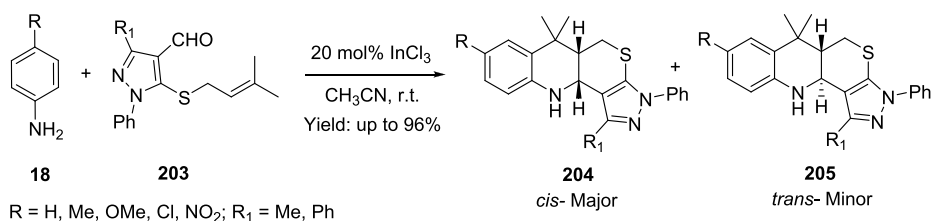
1,3-dicarbonyl to form β-enamino ketones, which subsequently coupled with the Perlin aldehyde to produce oxa-aza bicycles in good yields with high selectivity (Scheme 59).

Yadav et al.[12e] found that in the presence of a catalytic amount of InCl$_3$ a tandem Michael addition and intramolecular Friedel–Crafts-type cyclization occurred under mild conditions between δ-hydroxy-α,β-unsaturated aldehyde **195** and arylamine **196** to afford fused heterocycle **197** in good yield and excellent stereoselectivity (Scheme 60).

A systematic and comprehensive study on the synthesis of 3H-(pyrrol-1-yl)indolin-2-one **200** was reported by Ji et al.[24] Various isatin derivatives **198** and 4-hydroxyproline **199** were reacted in the presence of 10 mol % of InCl$_3$ under ambient reaction conditions to afford the products in excellent yields up to 99% (Scheme 61).

Yadav et al.[12f] described a cycloaddition reaction of aryl amine **40** with 3,4-dihydro-2H-pyran **33** in the presence of the InCl$_3$ catalyst under mild reaction conditions to afford the corresponding pyrano[3,2-c]quinoline **201** with high diastereoselectivity (Scheme 62).

Raghunathan et al.[25] demonstrated the synthesis of tetrahydropyrazolo[4′,3′:5,6]thiopyrano[4,3-b]quinolines catalyzed by InCl$_3$ under mild conditions (Scheme 63). The products were obtained as a diastereomeric mixture of cis-isomer **204** as the major product and the $trans$-isomer **205** as the minor product.

5. CONCLUSIONS

This review encompasses catalytic applications of InCl$_3$ for synthesizing a wide range of heterocycles. It is evident from the above discussion that InCl$_3$ is a valuable Lewis acid catalyst for the synthesis of many heterocyclic scaffolds. The most attractive feature of this review is the application of InCl$_3$ to catalyze reactions in both organic and/or aqueous media with almost equal feasibility. It exhibits unique activity in this area owing to its high coordination number and fast coordination–dissociation equilibrium maintenance. In contrast, the application of InCl$_3$ along with a chiral auxiliary in asymmetric synthesis is still largely unexplored. Thus, the future of this area lies in the development of an enantioselective InCl$_3$ catalyst which may be air- and water-insensitive. Hence, InCl$_3$-catalyzed reactions have a huge potential for application in organic synthesis and green chemistry.

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Notes

Biographies

Sanjit K. Mahato completed his Ph.D. (Organic Chemistry) from Jadavpur University in 2012 under the supervision of Prof. Parasuraman Jaisankar at the CSIR-Indian Institute of Chemical Biology, India, in the area of heterocyclic synthesis using catalysts. During his doctoral program, he also worked with Prof. Marek Zaidlewicz on borane-based oxazaborolidine asymmetric catalysis. He did postdoctoral training (November 2012 to October 2013) with Prof. K. Mallick at the University of Johannesburg on catalysis. Further postdoctoral training was with Prof. Emeritus Eli Breuer (November 2013 to January 2014) at the Institute for Drug Research, School of Pharmacy, Hebrew University of Jerusalem, Israel, where he worked on the design and synthesis of carbamoylphosphonic-based autotoxin inhibitors. He also worked at the Career Point University Hamirpur, India (August 2014 to July 2016) as an Assistant Professor in organic chemistry, and on deputation from this University, he served as a position of visiting scientist at Council for Scientific and Industrial Research in Pretoria, South Africa, and the Indian Institute of Technology in Bombay, India, under the joint supervision of Prof. A. Maity and Prof. Debabrata Maiti on catalysis funded by UNISA, South Africa (March 2015 to March 2016). This was followed by as a position of Research Scientist at TCG Lifesciences Pvt. Ltd. Kolkata, India (July 2016 to August 2018). Currently, he is working on the C−H activation reaction in the laboratory of Professor Naoto Chatani as a Specially Appointed Researcher (since September 2018) at the Department of Applied Chemistry, Osaka University, Japan.

Chiranjit Acharya obtained his B.Sc. in 2005 and his M.Sc. in 2007 from Vidyasagar University, Midnapore, West Bengal, India. He then moved to the CSIR-Indian Institute of Chemical Biology, Jadavpur, Kolkata, India, in 2009 and joined the group of Prof. Parasuraman Jaisankar as a junior research fellow (JRF) in the field of synthetic organic chemistry

and chemical biology. He was also awarded a Senior Research Fellowship (SRF) in 2011 by the University Grant Commission (UGC). He also had an opportunity to work with Prof. Hiroshi Sugiyama at Kyoto University in Japan during his Ph.D. internship program in the field of DNA-catalyzed asymmetric Diels−Alder reactions in 2013. He was awarded the Ph.D. (Chemistry) degree by Jadavpur University in 2015 followed by a Research Associate (RA) award from CSIR in 2017. In the same year, he was also awarded the National Postdoctoral Fellowship (N-PDF) from DST in chemical science for continuing his postdoctoral research at the CSIR-Indian Institute of Chemical Technology, Hyderabad. He was recently awarded the prestigious Royal Society−SERB Newton International Fellowship by the Royal Society, UK, to pursue postdoctoral research at Liverpool John Moores University, UK.

Kevin W. Wellington obtained his Ph.D. (Chemistry) degree from Rhodes University, Grahamstown, South Africa, in 1999 under the supervision of Prof. Perry T. Kaye with whom he was also a postdoctoral fellow in 2000 in the area of asymmetric synthesis. He then joined the group of Prof. Kelly Chibale as a postdoctoral fellow at the University of Cape Town, South Africa, where he conducted research on the discovery of antimycobacterial agents with GlaxoSmithkline (2001− 2002). In the USA, he worked as a postdoctoral associate with Prof. Steven A. Benner at the University of Florida and the Foundation of Applied Molecular Evolution in Gainesville, Florida, USA (2003− 2006) in the area of nucleic acid chemistry for application in synthetic biology. He joined the Biosciences unit at the Council for Scientific and Industrial Research, Pretoria, South Africa, in January 2007. His research has been on the development of green methods (biocatalysis) for the synthesis of anticancer and antimicrobial agents and on the discovery of bioactive natural products from plants for application in human and animal health.

Pinaki Bhattacharje completed his B.Sc. in 2010 and M.Sc. in 2012 from North Bengal University, Darjeeling, West Bengal, India. He received

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Parasuraman Jaisankar was born on May 20, 1966 in Vinayagapuram Village, Tiruvannamalai Dist. Tamil Nadu, India, and did his M.Sc. (Chemistry) degree from Presidency College, Madras University, in 1989 and the Ph.D. degree from Jadavpur University, Kolkata, in 1995. He pursued his postdoctoral research (DAAD Fellowship; 1996− 1998) on antisense oligonucleotides in association with Prof. Seliger of Ulm University, Germany, and has achieved a rare accomplishment of having worked with the group of Nobel Laureates, Prof. Ryoji Noyori and Prof. Masato Kitamura of Nagoya University, Japan, in the field of asymmetric catalysis. His research career started by joining CSIR-Indian Institute of Chemical Biology (January 1990), Kolkata, and presently he is the head of the department and holding permanent position as "Chief Scientist and Professor of Chemical Sciences, AcSIR, New Delhi". He was the visiting Scientist to the Laboratory of Prof. Marek Zaidlewicz of Nicolaus Copernicus University in Toruń, Poland, during 2007−2008. He was awarded the "Raman Research Fellowship (RRF)" by CSIR for the year 2010 to visit Prof. Masato Kitamura's Laboratory of Nagoya University, Japan, and again the DAAD fellowship (German Academic Exchange Service) under a reinvitation program in 2013 to the laboratory of Prof. Lukas Hintermann, Technical University of Munich (TUM), Germany. He is the recipient of the prestigious "Bharat Seva Ratan GOLD MEDAL" Award by Global Economic Progress & Research Association (GEPRA), New Delhi, for the year 2014. Recently, he was awarded the INSA International Fellowship award to NCUE, Taiwan, in the year 2015. He is the elected Fellow of West Bengal Academy of Science and Technology (FAScT) and Fellow of Institution of Chemists India (FIC). He is one of the founders and Secretary of Chemical Biology Society (CBS), India. He has supervised 21 Ph.D. and more than 26 masters and bachelor theses. Currently, he is continuing his research on catalysis and chemical biology with a 10-member team. Prof. Jaisankar has published over 100 research articles, filed 13 national and international patents, and is the author of three book chapters.

■ ACKNOWLEDGMENTS

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