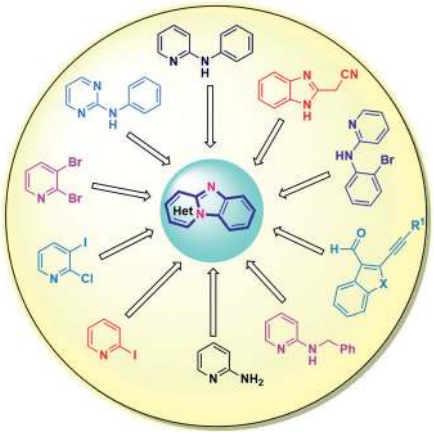
Synthesis R. Khajuria et al. Review

Recent Developments in the Synthesis of Pyrido[1,2-*a*]benzimidazoles

Rajni Khajuria[a,b] ◊
Sk. Rasheed[c,d] ◊
Chhavi Khajuria[e]
Kamal K. Kapoor[*a]
Parthasarathi Das[*c,d,f]

[a] Department of Chemistry, University of Jammu, Jammu 180006, India
kamalkka@gmail.com
[b] Department of Chemistry and Chemical Sciences, Central University of Jammu, Jammu 181143, India
[c] Academy of Scientific and Innovative Research (AcSIR), New Delhi 110001, India
partha@iiim.ac.in
[d] Medicinal Chemistry Division, Indian Institute of Integrative Medicine (CSIR), Jammu 180001, India
[e] Department of Chemistry, Guru Nanak Dev University, Amritsar 143005, India
[f] Department of Applied Chemistry, Indian Institute of Technology (Indian School of Mines), Dhanbad 826004, India

◊ These authors contributed equally to this work.



Received: 03.01.2018
Accepted after revision: 21.02.2018
Published online: 24.04.2018
DOI: 10.1055/s-0036-1589533; Art ID: ss-2018-e0009-r

Abstract Pyrido[1,2-*a*]benzimidazole is one of the most important azaheterocyclic compounds consisting of three fused aromatic rings. Molecules containing this core have displayed a wide range of applications in the field of medicinal chemistry. The synthesis of pyrido[1,2-*a*]benzimidazole and its derivatives has attracted organic chemists because of its tremendous utility in interdisciplinary branches of chemistry. In this context, this review discusses the main advances in the synthesis of pyrido[1,2-*a*]benzimidazoles via metal-mediated and metal-free reactions from 2000 to 2016.

Key words azaheterocyclic compounds, pyrido[1,2-*a*]benzimidazoles, transition-metal mediated, metal-free reactions, nitrogen heterocycles

1 Introduction

Pyrido[1,2-*a*]benzimidazole is one of the most important heterocyclic systems because of its occurrence as a synthon in various bioactive molecules and materials. This core exhibits remarkable biological properties such as antimalarial, anticancer, antiproliferative, antitumor, antifungal, antiviral, and antipyretic activities (Figure 1).[1] Pyrido[1,2-*a*]benzimidazole was initially prepared in the late 1930s,[2] but has received attention only during the past decade, when some of its derivatives were found to have pharmaceutical applications.[3] Moreover, the difficulties associated with the preparation of this heterocyclic system, often comprising of laborious and low-yielding methods, became the point of concern for organic chemists.[4] The important biological properties shown by pyrido[1,2-*a*]benzimidazole and its derivatives have inspired organic chemists to develop simple and convenient synthetic methods. The review presented here on synthetic strategies for pyrido[1,2-*a*]benzimidazoles is organized according to whether the reaction is metal-catalyzed (type I) or metal-free (type II).

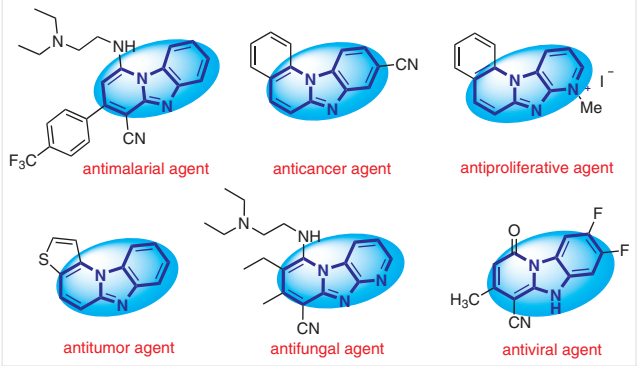


Figure 1 Pyrido[1,2-*a*]benzimidazole based bioactive molecules

2 Synthetic Approaches to Pyrido[1,2-a]benzimidazoles

2.1 Type I: Transition-Metal-Catalyzed Methods

Transition-metal-catalyzed reactions have been studied since the very beginning of the past century and represent a great success in organic chemistry along with the birth and growth of organometallic chemistry.[5] Transition-metal-catalyzed coupling reactions, which were initiated in the 1960s as a major topic in organometallic chemistry, have

Biographical Sketches

Rajni Khajuria received her M.Sc. (2010) from the Department of Chemistry, University of Jammu, India and M.Phil. (2012) at the same university under the guidance of Prof. Kamal K. Kapoor. She then worked on the synthesis of novel aza-heterocyclic compounds as antimicrobial agents in the same laboratory and obtained her Ph.D. in 2016. Presently, she works as an assistant professor on contract basis in the Department of Chemistry and Chemical Sciences, Central University of Jammu. Her main research interests include the development of greener synthetic methods to access biologically active heterocycles and coupling reactions for C–C and C–X bond formation.

Sk. Rasheed received his M.Sc. (2009) in organic chemistry from Osmania University, Hyderabad, India and in 2010 he joined the Indian Institute of Integrative Medicine (CSIR-IIIM), Jammu as a CSIR Junior Research Fellow. In 2011, he registered with the Academy of Scientific and Innovative Research (AcSIR) for a Ph.D. program under the supervision of Dr. Parthasarathi Das on the research topic 'Transition-Metal-Catalyzed C–C and C–N Bond Formation: Synthesis of Carbazoles and Aza-Fused Heterocycles' and received his degree in 2017. Presently, he is working as a senior research associate at Gland Pharma Ltd., Hyderabad, India.

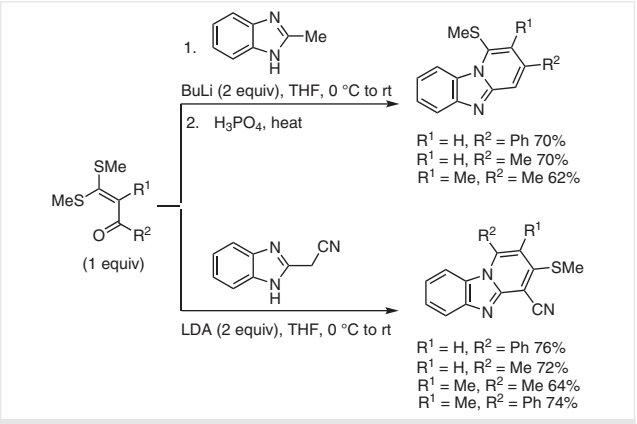
Chhavi Khajuria is an undergraduate student of integrated BSc. Honors in chemistry at the Department of Chemistry, Guru Nanak Dev University, Amritsar, India. She wishes to pursue her career in synthetic and biological chemistry.

Kamal K. Kapoor received his Ph.D. (1996) from IIT, Kanpur, India. He joined the University of Jammu as lecturer in December 1995, where he is professor at present. His research interests include the synthesis of novel heterocyclic compounds having significance in scaffold hopping, biology, and material science. He was awarded DST-BOYSCAST and INSA Royal Society fellowships for visiting Japan and UK, respectively. He has served as lead scientist in Dabur Research Foundation, Sahibabad (UP) and Sphaera Pharma, IMT Manesar (Haryana), as advisory consultant to Curadev Pharma Pvt Ltd, Noida, and also as adjunct professor at the Central University of Jammu.

Parthasarathi Das received his Ph.D. (1999) from NCL Pune, India. After completing postdoctoral studies at RWTH-Aachen, Germany, Tohoku University, Japan, and Harvard University, USA, he returned to India to join Dr. Reddy's Laboratories Ltd. (2004) and worked in the medicinal chemistry group with a research focus on various therapeutic areas (oncology, metabolic disorder, and antibacterial). In 2012, he shifted to academia and joined the CSIR-Indian Institute of Integrative Medicine Jammu, India. Recently, he moved to the Indian Institute of Technology (ISM) Dhanbad. His research interests include medicinal chemistry, the development of new synthetic tools, and the synthesis of biologically active natural products.

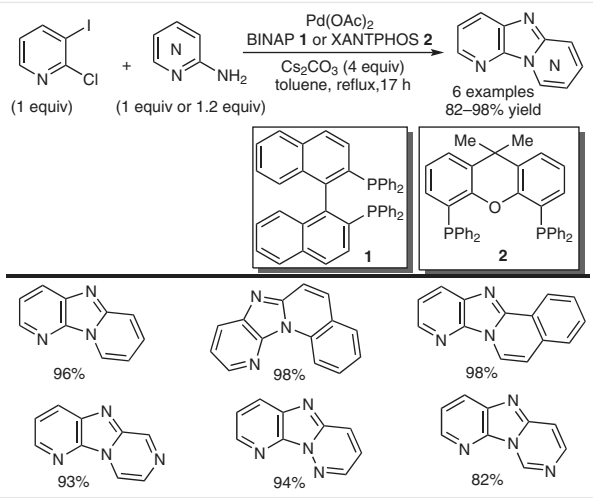
made significant progress in the last half century and become one of the most efficient and direct strategies for carbon–carbon bond formation.[6] The extensive variations and modifications of transition-metal-catalyzed coupling reactions have enabled wide applications in organic synthesis and have been regarded as the most reliable, accurate, and powerful tools in the chemist's arsenal.[7] Many named reactions have been assigned and are well known nowadays, together with the development of novel chemical reagents. The great success and significance of transition-metal-catalyzed coupling reactions were highlighted by the 2010 Nobel Prize in chemistry.[8]

In 2003, Junjappa et al. reported a dexterous method for the preparation of 1,2- and 2,3-substituted/annulated pyrido[1,2-*a*]benzimidazoles via regioselective annulation of 2-methylbenzimidazole or 2-(cyanomethyl)benzimidazole dianions with α-oxo ketene dithioacetals involving [3+3] cyclocondensation (Scheme 1).[9] The dianion derived from 2-methylbenzimidazole undergoes 1,2-addition with α-oxo ketene dithioacetals, followed by intramolecular cyclocondensation in the presence of phosphoric acid to provide the corresponding 1-(methylthio)-2,3-substituted pyrido[1,2-*a*]benzimidazoles. The dianion of 2-(cyanomethyl)benzimidazole is involved in a one-pot 1,4-addition–elimination and cyclocondensation with α-oxo ketene dithioacetals to form 4-cyano-3-(methylthio)-1(or 1,2)-substituted pyrido[1,2-*a*]benzimidazoles.



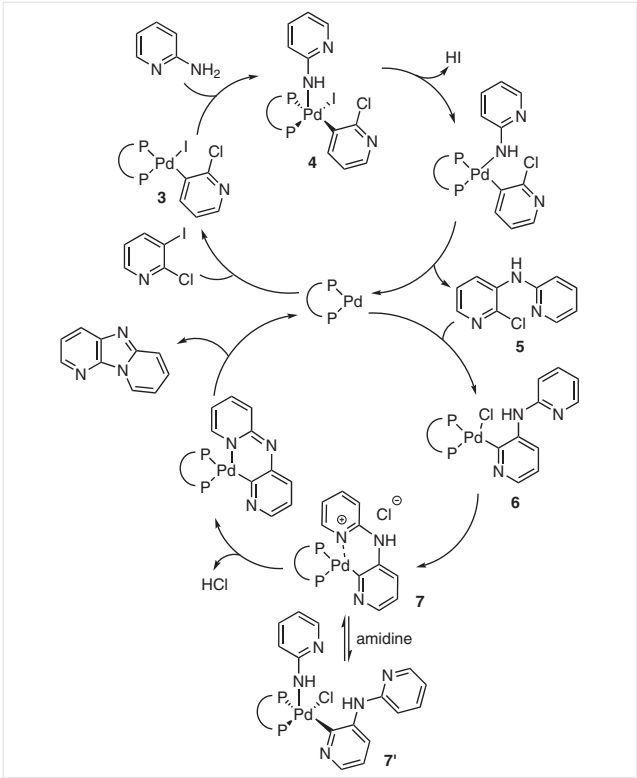
Scheme 1 Regioselective synthesis of 1,2- and 2,3-substituted/annulated pyrido[1,2-*a*]benzimidazoles

In 2004, Maes et al. reported a tandem palladium-catalyzed Buchwald–Hartwig amination reaction for the synthesis of benzo and aza analogues of dipyrido[1,2-*a*:3′,2′-d]imidazole (Scheme 2).[10] The regio- and chemoselective one-pot inter- and intramolecular Buchwald–Hartwig amination of 2-chloro-3-iodopyridine with aminoazines/aminodiazines using Pd(BINAP)/Pd(XANTPHOS) catalysts in combination with an excess of Cs_2CO_3 base in toluene under reflux conditions afforded the corresponding dipyrido[1,2-*a*:3′,2′-d]imidazole derivatives in excellent yields.



Scheme 2 Synthesis of benzo and aza analogues of dipyrido [1,2-*a*:3′,2′-*d*]imidazole

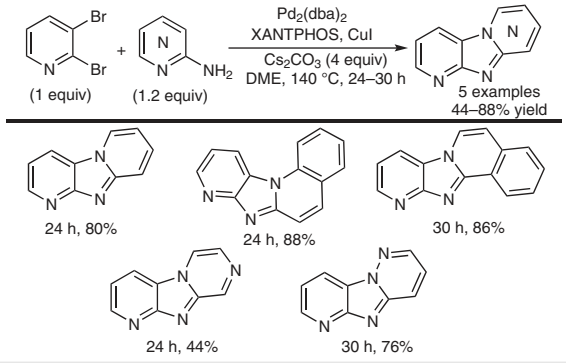
The catalytic cycle proposed for the tandem double palladium-catalyzed amination of 2-chloro-3-iodopyridine with 2-aminopyridine (Scheme 3) starts with the oxidative addition of 2-chloro-3-iodopyridine to Pd(0), forming an organopalladium(II) complex **3**. Insertion of 2-aminopyridine into intermediate **3** generates another intermediate **4**,



Scheme 3 Plausible mechanism for the tandem double palladium-catalyzed synthesis of dipyrido[1,2-*a*:3′,2′-d]imidazole

which upon deprotonation followed by reductive elimination gives *N*-(2-chloropyridin-3-yl)pyridine-2-amine (**5**). Then **5** undergoes oxidative addition to Pd(0) forming another organopalladium(II) complex **6**. Coordination of the pyridine ring nitrogen with the metal center occurs, forming a palladacycle **7** over the competitive formation of palladium(II)–amine complex **7′**. Deprotonation of **7** and subsequent reductive elimination gives the final desired product, along with the regeneration of the palladium catalyst.

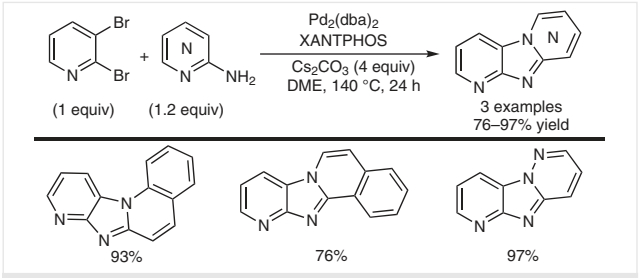
Two years later, the same group reported the regioselective orthogonal (Pd- and Cu-catalyzed) or auto-tandem (Pd-catalyzed) inter- and intramolecular Buchwald–Hartwig amination reaction for the expedient synthesis of dipyrido[1,2-*a*:2′,3′-*d*] imidazole and its benzo and aza analogues by using 2,3-dibromopyridine and amino(di)azines as starting materials (Schemes 4 and 5).[11] The orthogonal tandem-catalyzed amination is based on a chemoselective oxidative addition, which involves consecutive Pd-catalyzed intermolecular amination and Cu-catalyzed intramolecular amination steps (Scheme 4).



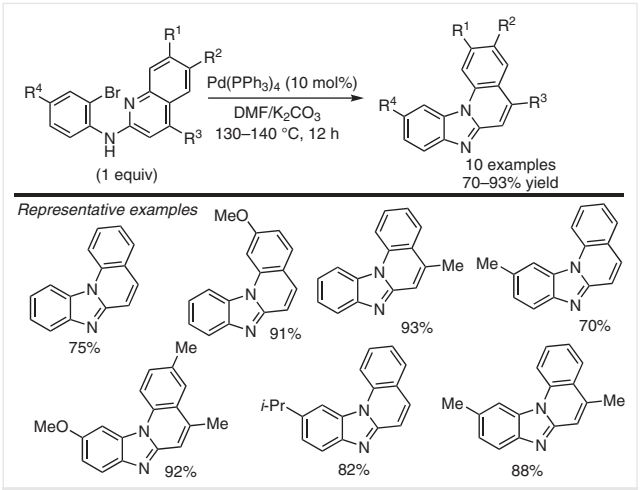
Scheme 4 Orthogonal tandem Pd- and Cu-catalyzed amination of 2,3-dibromopyridine with amino(di)azines

In addition, an auto-tandem inter- and intramolecular Pd-catalyzed amination by a simple alteration of the reaction temperature was also presented. The auto-tandem Pd-catalyzed amination was performed at 140 °C (Scheme 5) and at refluxing temperature. Double amination of 2,3-dibromopyridine at 140 °C occurred smoothly with 2-aminoisoquinoline, 1-aminoquinoline and 3-aminopyridazine to give the corresponding dipyrido[1,2-*a*:2′,3′-*d*]imidazoles, whereas the same reaction of all amino(di)azines performed under reflux conditions gives only the respective intermediates, i.e. *N*-(3-bromopyridin-2-yl)azaheteroaryl amines.

In 2006, H. Ila and co-workers presented an efficient method for the synthesis of diversely substituted benzimidazo[1,2-*a*]quinolines in high yields (Scheme 6).[12] They described the $Pd(PPh_3)_4$-catalyzed Buchwald–Hartwig intramolecular N-arylation of readily accessible 2-(2-bromoanilino)quinolines, using K_2CO_3 as a base in DMF at 130–140 °C. The requisite starting materials, i.e. 2-(2-bromoanilino)quinolines, were in turn prepared from 2-(methylsulfonyl)quinolines and various 2-bromoanilines under reflux conditions.[13]



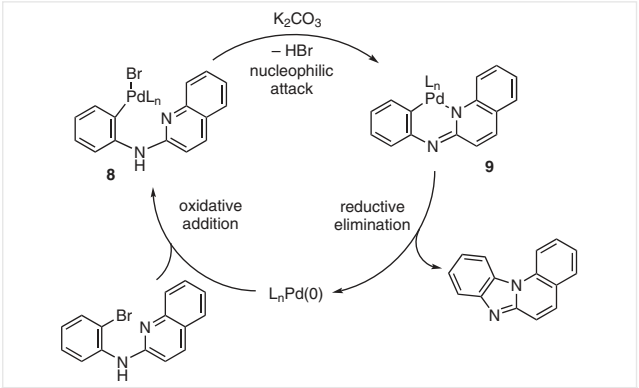
Scheme 5 Auto-tandem Pd-catalyzed inter- and intramolecular amination of 2,3-dibromopyridine with amino(di)azines at 140 °C



Scheme 6 $Pd(PPh_3)_4$-catalyzed synthesis of benzimidazo[1,2-*a*]quinolines

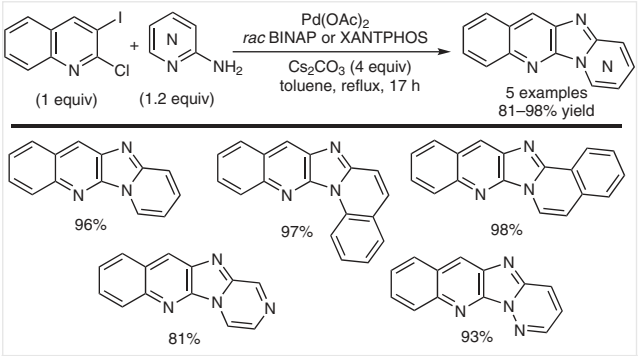
A plausible mechanism for the formation of benzimidazo[1,2-*a*]quinoline from 2-(2-bromoanilino)quinoline using $Pd(PPh_3)_4$ as a catalyst is presented in Scheme 7. Intermediate **8**, formed by the oxidative addition of Pd(0) to 2-(2-bromoanilino)quinoline, undergoes an intramolecular nucleophilic attack at the basic quinoline nitrogen; this is followed by the elimination of HBr to give the six-membered palladacycle intermediate **9**. Palladacycle **9**, upon subsequent reductive elimination and N–C bond formation steps, yields the corresponding benzimidazo[1,2-*a*]quinoline.

One year later, the Maes group reported the application of their previously developed regioselective auto-tandem (Pd-catalyzed) and orthogonal-tandem (Pd- and Cu-catalyzed) protocols for the effective aminations of dihaloquinolines with amino(benzo)(di)azines (Schemes 8 and 9).[14] The synthesis of pyrido[2′,1′:2,3] imidazo[4,5-*b*]quinoline and its benzo and aza analogues was achieved via $Pd(OAc)_2$–*rac*-BINAP/XANTPHOS-catalyzed amination of 2-chloro-3-iodoquinoline with various amino(benzo)(di)azines (Scheme 8). In the orthogonal-tandem amina-

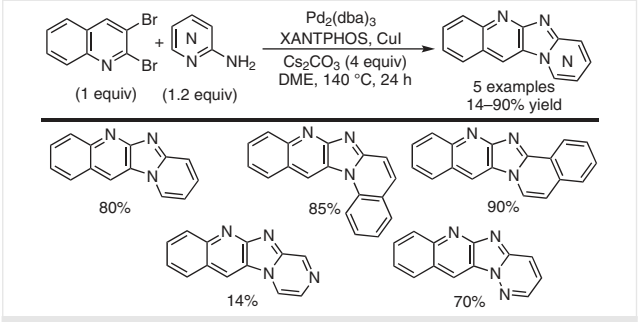


Scheme 7 $Pd(PPh_3)_4$-catalyzed mechanism for the formation of benzimidazo[1,2-*a*]quinoline from 2-(2-bromoanilino)quinoline

tion, the $Pd_2(dba)_3$–XANTPHOS and CuI combination gave an easy access to various benzo and aza analogues of pyrido[1′,2′:1,2]imidazo[4,5-*b*]quinoline using amino(benzo)(di)azines and 2,3-dibromoquinoline as starting materials (Scheme 9).



Scheme 8 Synthesis of pyrido[2′,1′:2,3]imidazo[4,5-*b*]quinoline and its benzo and aza analogues via $Pd(OAc)_2$ auto-tandem amination



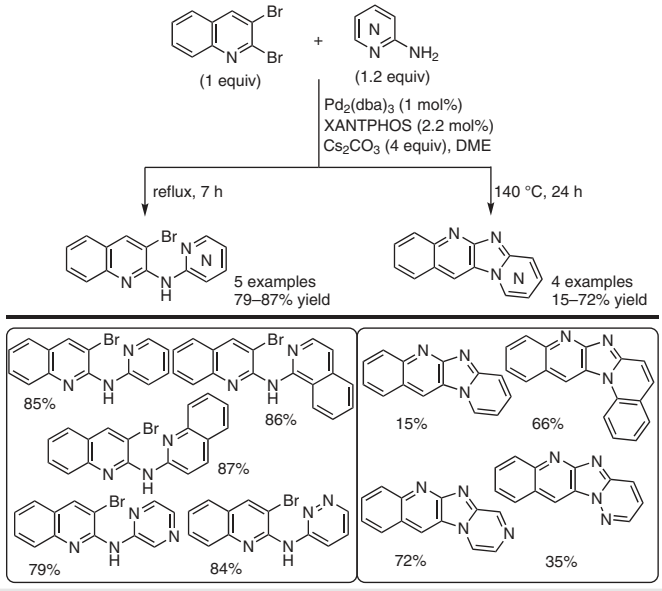
Scheme 9 Synthesis of pyrido[1′,2′:1,2]imidazo[4,5-*b*]quinoline and its benzo and aza analogues via $Pd_2(dba)_3$-CuI orthogonal-tandem amination

Subsequently, they reported that by controlling the reaction temperature of the $Pd_2(dba)_3$–XANTPHOS-catalyzed auto-tandem reaction, selective C-2 intermolecular amination of 2,3-dibromoquinoline with amino(benzo)(di)azines could be achieved to provide the corresponding *N*-(3-bromoquinolin-2-yl)azaheteroaryl amines as the sole products in good yields (Scheme 10).[14]

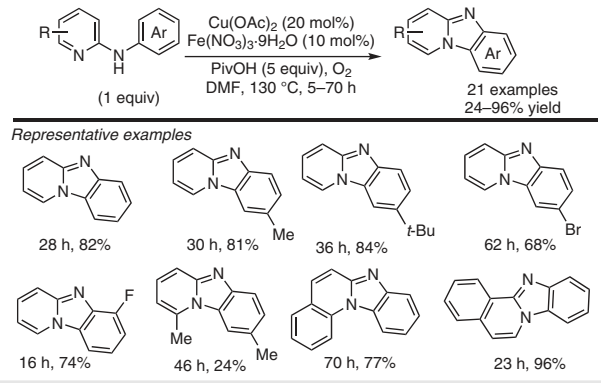
The Zhu group developed a novel strategy for the synthesis of pyrido[1,2-*a*]benzimidazoles through the direct intramolecular aromatic C–H amination of *N*-aryl-2-aminopyridines, in which the pyridine moiety serves as a directing group as well as an intramolecular nucleophile (Scheme 11).[15] The reaction is co-catalyzed by $Cu(OAc)_2$ and $Fe(NO_3)_3{\cdot}9H_2O$ in DMF under an O_2 atmosphere to provide good to excellent yields of diversely substituted pyrido[1,2-*a*]benzimidazoles. The presence of electron-withdrawing groups at any position of the pyridine ring and in the *meta* position of aniline ring was found to be unfavorable for the reaction under the optimized reaction conditions. $Fe(NO_3)_3{\cdot}9H_2O$ itself does not promote the reaction, but increases the yield of the reaction significantly due to its ability to facilitate the formation of more electrophilic Cu(III) species, which readily undergo the SEAr (electrophilic aromatic substitution) process. Pivalic acid is used as an additive for this reaction to improve the yields of the final products.

The following mechanism was proposed by Zhu et al. for the $Cu(OAc)_2$–$Fe(NO_3)_3{\cdot}9H_2O$ co-catalyzed preparation of pyrido[1,2-*a*]benzimidazole from *N*-phenyl-2-aminopyridine (Scheme 12).[15] In the absence of Fe(III) salt, the Cu(II) salt forms intermediate **11** from the initially formed Cu(II) adduct **10** through electrophilic aromatic substitution, followed by reversible protonation. In the presence of oxygen, intermediate **12** is converted into a more reactive Cu(III) intermediate **13** through oxidation; upon subsequent reductive elimination, the requisite product is produced along with the formation of Cu(I). In the presence of Fe(III) salt, the initially formed adduct **10** is oxidized to a more electrophilic Cu(III) intermediate **14**. Then **14** undergoes electrophilic aromatic substitution to generate intermediate **13** through the formation of the six-membered transition state **15**. Reductive elimination takes place very quickly, before reversible protonation, to yield the desired product. The formed Cu(I) is oxidized into Cu(II) in the presence of O_2, thus completing the catalytic cycle.

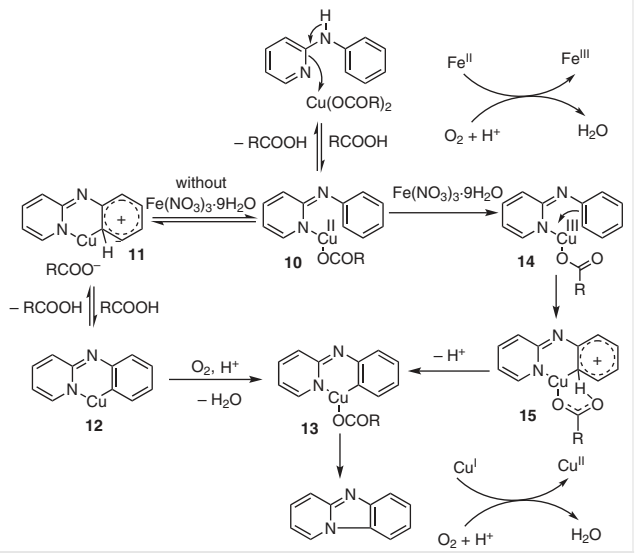
In 2010, Maes and co-workers reported further studies of the scope of their well-established methodology of auto-tandem and orthogonal-tandem double aminations of dihalopyridines, i.e. 2-chloro-3-iodopyridine and 2,3-dibromopyridine, with unexplored benzodiazinamines, i.e. phthalazin-1-amine, quinoxalin-2-amine and quinazolin-4-amine as coupling partners (Schemes 13 and 14).[16] The requisite benzodiazinamines were prepared by using the literature method of Hara and van der Plas.[17] They observed that their previously developed auto-tandem double amination protocol for the coupling of 2-chloro-3-iodopyridine could not be generally applied for benzodiazinamines, whereas the orthogonal-tandem double amination protocol for the cou-



Scheme 10 Temperature-dependent $Pd_2(dba)_3$–XANTPHOS-catalyzed auto-tandem amination of 2,3-dibromoquinoline with amino(benzo)(di)azines



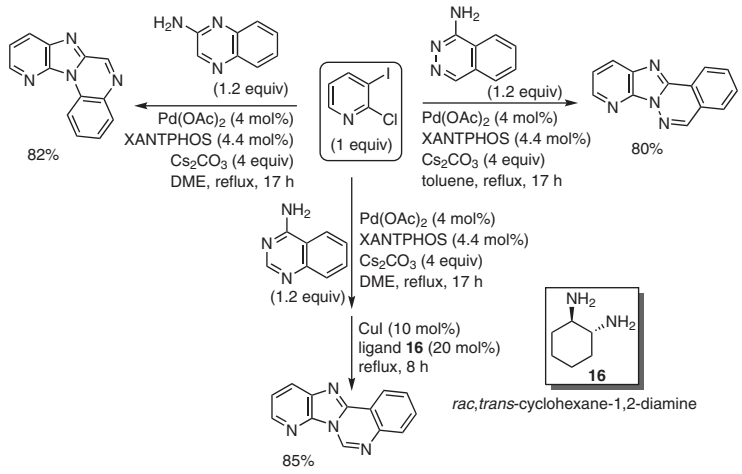
Scheme 11 Synthesis of diversely substituted pyrido[1,2-*a*]benzimidazoles via $Cu(OAc)_2$–$Fe(NO_3)_3·9H_2O$ co-catalyzed intramolecular C–H amination of *N*-aryl-2-aminopyridines



Scheme 12 Mechanism proposed for the $Cu(OAc)_2$-catalyzed intramolecular C–H amination of *N*-phenyl-2-aminopyridine, with and without Fe(III) salt

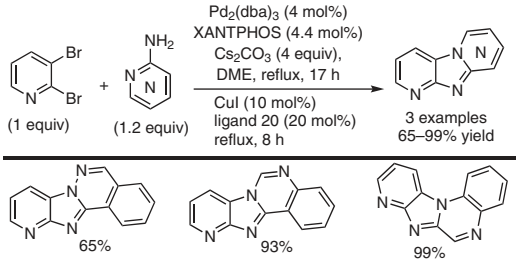
pling of 2,3-dibromopyridine with benzodiazinamines revealed unexpected Smiles rearrangement at high temperature. To prevent this undesired rearrangement step, the *rac*,*trans*-cyclohexane-1,2-diamine ligand was used for the copper catalyst to achieve the intermolecular and intramolecular reactions for ring closure in a sequential manner.

The auto-tandem $Pd(OAc)_2$–XANTPHOS-catalyzed double amination of 2-chloro-3-iodopyridine with benzodiazinamine in refluxing toluene gave the desired pyrido[3′,2′:4,5]imidazo [2,1-*a*]phthalazine in 80% yield (Scheme 13). Applying the same reaction conditions to phthalazin-1-amine and quinoxalin-2-amine did not give the desired products. Instead, the reactions stopped at the intermolecular amination step, with no further intramolecular C–N bond formation. However, the synthesis of pyrido[3′,2′:4,5]imidazo[1,2-*a*]quinoxaline was successfully achieved under the optimized auto-tandem double amination reaction conditions by simply replacing toluene with DME as solvent under reflux conditions (Scheme 13). For the coupling of 2-chloro-3-iodopyridine with quinazolin-4-amine, a one-pot approach was developed consisting of a $Pd(OAc)_2$–XANTPHOS-catalyzed intermolecular amination step, followed by the addition of CuI in combination with the *rac*,*trans*-cyclohexane-1,2-diamine ligand in a ratio of



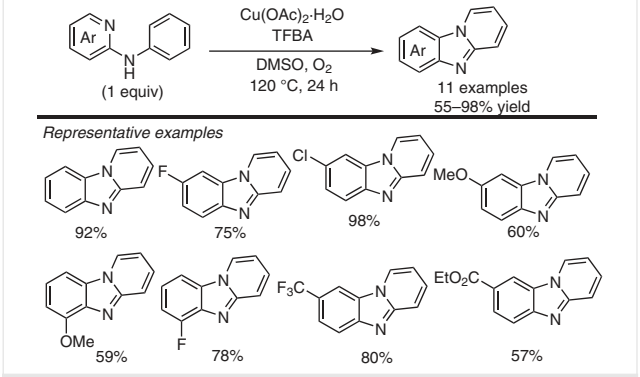
Scheme 13 Auto-tandem and orthogonal-tandem double aminations of 2-chloro-3-iodopyridine with benzodiazinamines

1:2, upon completion of the first amination, to access the desired pyrido[3′,2′:4,5]imidazo[1,2-*c*]quinazoline (Scheme 13). The one-pot method was also developed for the coupling of 2,3-dibromopyridine with benzodiazinamines, by replacing $Pd(OAc)_2$ with $Pd_2(dba)_3$ as a catalyst for orthogonal-tandem double amination (Scheme 14).



Scheme 14 Orthogonal-tandem double amination of 2,3-dibromopyridine with benzodiazinamines

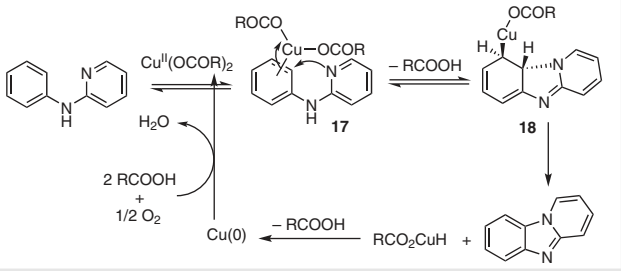
One year later, the same group investigated the role of an acid additive in the synthesis of diverse pyrido[1,2-*a*]benzimidazoles by direct $Cu(OAc)_2{\cdot}H_2O$-catalyzed amination of *N*-arylpyridin-2-amines in DMSO in the presence of O_2 at 120 °C (Scheme 15).[18] They studied the influence of the structure of the acid additive and the result showed that carboxylic acids such as acetic acid, pivalic acid, butyric acid, benzoic acid, and 3,4,5-trifluorobenzoic acid (TFBA) produced the desired products in good efficiency. Non-carboxylic acids such as HCl were also found useful when used in catalytic amounts. Among the various acid additives screened, 3,4,5-trifluorobenzoic acid was clearly found to be a superior additive and this acid also provided a faster reaction and complete conversion of the starting materials when used in an equimolar amount relative to the catalyst.



Scheme 15 $Cu(OAc)_2{\cdot}H_2O$–TFBA-catalyzed synthesis of diversely substituted pyrido[1,2-*a*]benzimidazoles

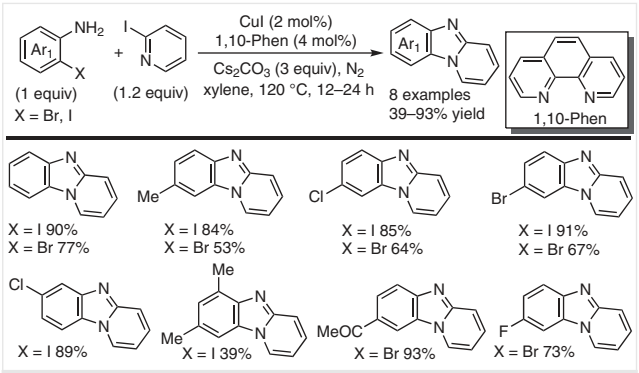
The mechanism proceeding via a Cu(II)/Cu(0) catalytic cycle was proposed in accordance with their findings and control experiments (Scheme 16).[18] The first step is the coordination of $Cu^{II}(OCOR)_2$ with *N*-phenylpyridin-2-amine, leading to the formation of intermediate **17**, followed by intramolecular nucleophilic attack of its amidine nitrogen on the activated phenyl ring to give the σ-alkyl–Cu(II) intermediate **18**. Subsequent β-hydride elimination of **18** gives the corresponding product and $RCO_2Cu(II)H$. Reductive elimination of RCOOH from $RCO_2Cu(II)H$ yields Cu(0), which is reoxidized to $Cu(II)(OCOR)_2$ with RCOOH in the presence of O_2, thus completing one catalytic cycle.

Subsequently, Wu et al. developed a simple method for the expeditious synthesis of diversely substituted pyrido[1,2-*a*]benzimidazoles through a CuI–1,10-Phen-catalyzed inter- and intramolecular C–N coupling cascade process using haloanilines and halopyridines as the coupling partners in xylene at 120 °C (Scheme 17 and Scheme 18).[19] Various substituted haloanilines and halopyridines bearing electron-donating and electron-withdrawing substituents

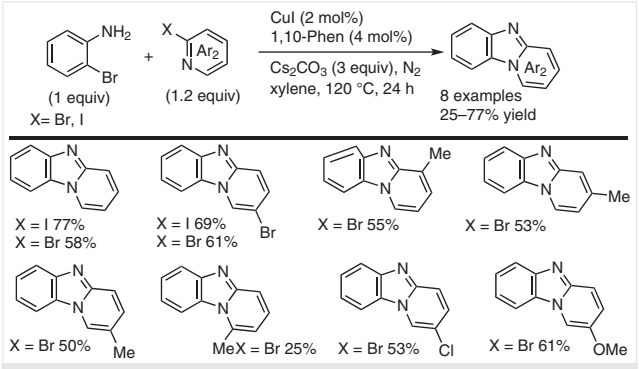


Scheme 16 Plausible mechanism for the intramolecular C–H amination of *N*-phenylpyridin-2-amine

were well tolerated under the optimized reaction conditions to afford the corresponding pyrido[1,2-*a*]benzimidazoles in good to excellent yields.

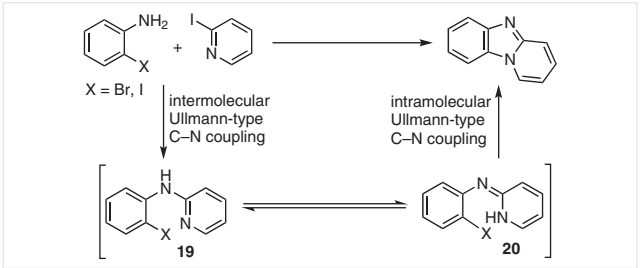


Scheme 17 CuI–1,10-Phen-catalyzed coupling of various substituted 2-haloanilines with 2-iodopyridine



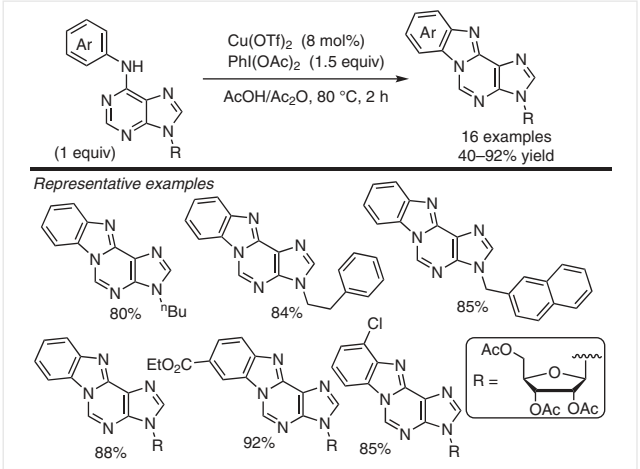
Scheme 18 CuI–1,10-Phen-catalyzed coupling of 2-bromoaniline with various substituted 2-halopyridines

They have proposed the following plausible reaction pathway for the CuI–1,10-Phen catalyzed inter- and intramolecular amination of 2-iodopyridine with haloanilines (Scheme 19). The 2-haloaniline couples intermolecularly with 2-iodopyridine via an Ullmann-type C–N bond formation, due to the electron-deficient nature of the pyridine ring, to give intermediate **19**. Subsequent isomerization of intermediate **19** into **20** followed by intramolecular Ullmann-type C–N coupling leads to the formation of the desired product, as shown in Scheme 19.



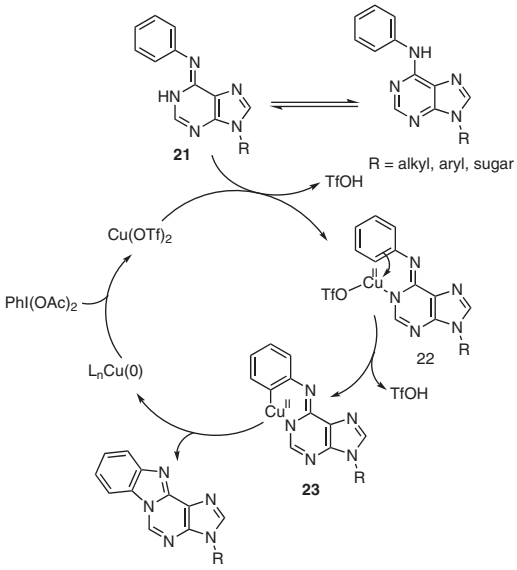
Scheme 19 Proposed mechanism for the CuI–1,10-Phen-catalyzed pyrido[1,2-*a*]benzimidazole synthesis

In 2012, Fossey and co-authors reported a Cu(OTf)$_2$-catalyzed intramolecular C–H bond amination reaction of purine and its derivatives, by employing PhI(OAc)$_2$ as an oxidant in a 1:1 mixture of acetic acid and acetic anhydride as a solvent, for the efficient synthesis of purine-fused polycyclic compounds (Scheme 20).[20] This was the first report on the utility of intramolecular C–H activation/amination reaction protocols for the synthesis of purine nucleosides, which offers an easy alternative access to many useful multi-fused ring purine heterocyclic compounds.



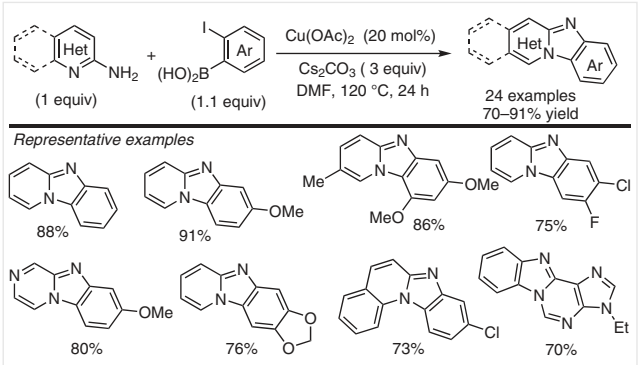
Scheme 20 Cu(OTf)$_2$-catalyzed synthesis of multi-fused ring purine heterocyclic compounds

The mechanism for the Cu(OTf)$_2$-assisted intramolecular C–H bond activation and amination of 6-anilinopurine based substrates is outlined in Scheme 21. Oxidative addition of substrate **21** to Cu(OTf)$_2$ yields intermediate **22**, which undergoes an electrophilic substitution process to form Cu(II) intermediate **23**. The final step is the reductive elimination of **23** to give the desired product, along with the regeneration of Cu(OTf)$_2$ to complete the Cu(II)/Cu(0) catalytic cycle.



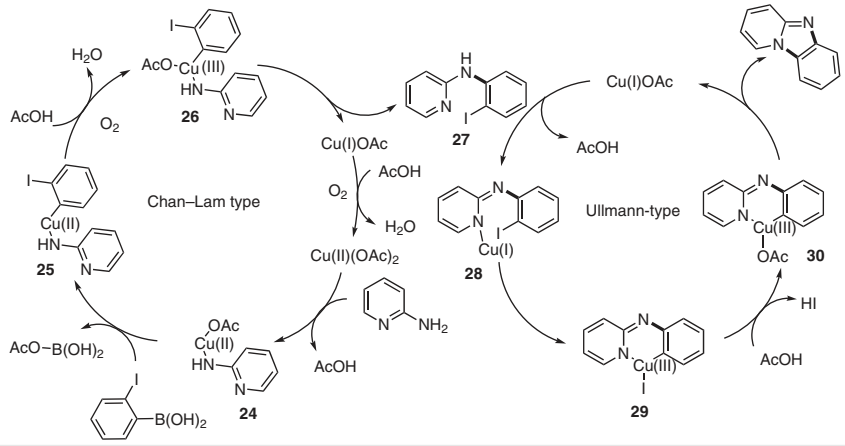
Scheme 21 Plausible mechanism for $Cu(OTf)_2$-catalyzed intramolecular C–H bond activation and amination of 6-anilinopurine-based substrates

In 2015, Das et al. described a ligand-free Cu(II)-catalyzed, inter/intramolecular C–N bond formation for the synthesis of various benzimidazole-fused heteroaromatic compounds (Scheme 22).[21] The robustness of this method was demonstrated by the synthesis of a series of benzimidazole-fused heterocycles, e.g., pyrido[1,2-*a*]benzimidazole, benzimidazo[1,2-*a*]quinolines, benzimidazo[1,2-*a*]pyrazine, directly from 2-aminoheteroarenes and 2-iodoarylboronic acids in one pot. The novel cascade protocol for C–N bond formation represents a distinctive example of a sole combination of Chan–Lam- and Ullmann-type coupling reactions.



Scheme 22 Benzimidazole-fused heteroaromatics preparation via Cu(II)-catalyzed consecutive Chan–Lam- and Ullmann-type coupling reactions

The following plausible catalytic cycle was proposed for the formation of pyrido[1,2-*a*]benzimidazole as shown in Scheme 23. In the Chan–Lam type of coupling, the first step is the rapid coordination of the Cu(II) complex with 2-aminopyridine, forming **24**, which subsequently enters into a transmetalation step with 2-iodophenylboronic acid to afford complex **25**. Then Cu(II) complex **25** undergoes air oxidation to provide the higher oxidation Cu(III) complex **26**, facilitating the smooth reductive elimination to furnish N-arylated product **27** (intermediate I). In the Ullmann-type coupling, the first step involves the smooth coordination of **27** with Cu(I) to form complex **28**, which upon intramolecular oxidative addition with aryl iodide furnishes complex **29**, which subsequently converts into complex **30**. As far as the oxidation state of copper is concerned, these types of reactions are supposed to proceed via Cu(I) and Cu(III) intermediates. Thus, Cu(III) complex **30**, on smooth reductive elimination, furnishes the final cyclized product with concurrent formation of Cu(I). Finally, Cu(II) is generated by aerial oxidation to complete the catalytic cycle.

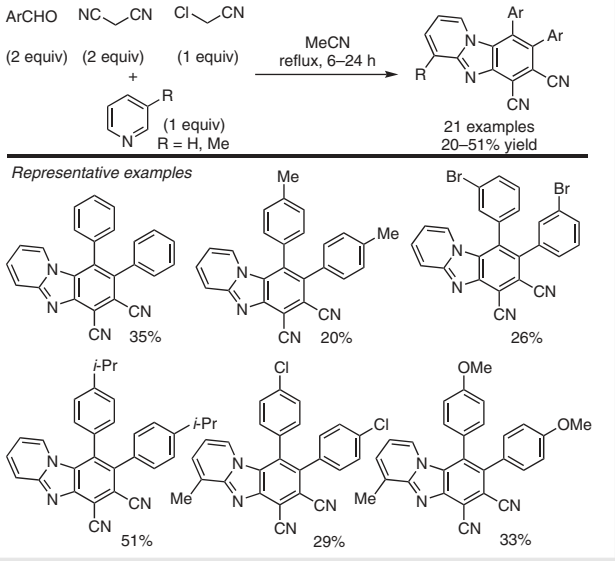


Scheme 23 Mechanism proposed to explain the Cu(II)-catalyzed Chan–Lam coupling followed by Ullmann-type coupling of 2-aminopyridine with 2-iodophenylboronic acid to access pyrido[1,2-*a*]benzimidazole

2.2 Type II: Metal-Free Approaches

Nevertheless, transition-metal-catalyzed coupling reactions are still limited in applications and confront challenges to some extent, owing to the innate drawbacks of the catalytic systems. First, most of the transition-metal catalysts are normally very expensive[22] and the supporting ligands are usually even more expensive and sometimes difficult to prepare. Second, most of the transition metals are toxic to different extents, and removal of trace amounts of transition-metal residues from the desired products is quite costly and challenging, while crucial, especially in the pharmaceutical industry.[23] Third, many transition-metal catalysts are usually sensitive to oxygen (O_2) and moisture; thus, very strict manipulation is indispensable. Fourth, in many cases, special additives and co-catalysts are also critical to promote the efficiency and selectivity of transformations.[24] Last but not least, the large consumption of transition metals does not indeed meet the requirement of sustainable development.[25] Obviously, alternative pathways to construct C–C bonds under transition-metal-free conditions to fulfill the classic transition-metal-catalyzed coupling reactions are highly appealing. Thus, studies on transition-metal-free coupling reactions are of great significance to provide a better understanding of how the reactions work with or without transition metals.

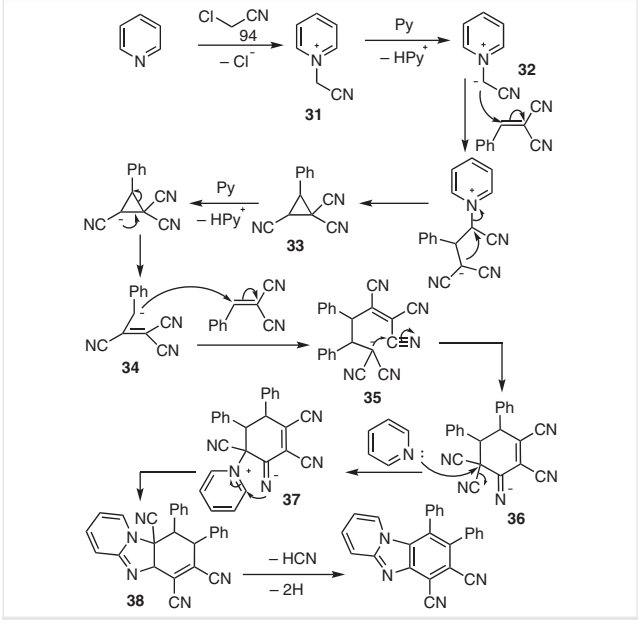
In 2009, the Yan group reported a one-pot, four-component method to afford diversely substituted pyrido[1,2-*a*]benzimidazoles, by employing aromatic aldehydes, malononitrile, chloroacetonitrile, and pyridine or 3-picoline as starting materials in refluxing acetonitrile (Scheme 24).[26] A library of pyrido[1,2-*a*]benzimidazole derivatives with broad substrate scope was synthesized in moderate to good yields.



Scheme 24 One-pot, four-component method of preparation of polysubstituted pyrido[1,2-*a*]benzimidazoles

The postulated mechanism (Scheme 25) begins with the formation of two reaction intermediates: the *N*-cyanomethylpyridinium salt **31**, formed by the addition of chloroacetonitrile to pyridine, and the benzylidenemalononitrile, formed by the pyridine-promoted Knoevenagel condensation of malononitrile with benzaldehyde. In the second step, the pyridinium ylide **32**, formed by the pyridine-assisted deprotonation of the *N*-cyanomethylpyridinium intermediate **31**, undergoes Michael addition with benzylidenemalononitrile to give an activated cyclopropane derivative **33**. Upon subsequent deprotonation and ring-opening, **33** yields an allylic carbanionic intermediate **34**, which reacts with the second molecule of benzylidenemalononitrile to form a cyano-stabilized carbanionic intermediate **35**. The intramolecular nucleophilic addition of carbanion **35** to one of its cyano groups affords a fully substituted six-membered cyclic intermediate **36**. The substitution of one cyano group in intermediate **36** by pyridine occurs to form another pyridinium ion **37**. Pyridinium ion **37** experiences an intramolecular attack of an amino group on the *ortho* positive center of pyridine to form a cyclic pyridine derivative **38**, from which one molecule of hydrogen cyanide and two hydrogen atoms are eliminated to form the desired pyrido[1,2-*a*]benzimidazole. In this mechanism, pyridine plays a multifaceted role, by acting as a tertiary amine to yield pyridinium cation, as a base to form the carbanion intermediate and as a nucleophilic reagent.

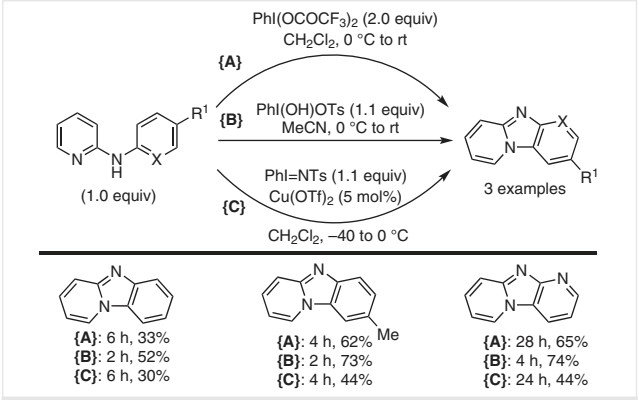
In 2011, the Kutsumura group reported a versatile method for the synthesis of pyrido[1,2-*a*]benzimidazoles via intramolecular dehydrogenative C–N coupling between



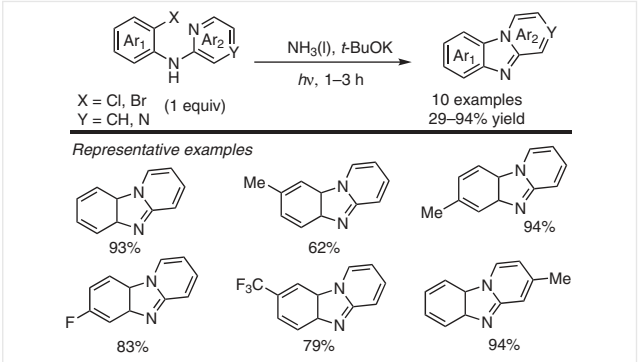
Scheme 25 Proposed mechanism for the catalyst-free synthesis of pyrido[1,2-*a*]benzimidazole

aryl C–H and N–H bonds of *N*-pyridin-2-ylanilines by using hypervalent iodine reagents under mild reaction conditions (Scheme 26).[27]

The synthesis of pyrido[1,2-*a*]benzimidazoles in moderate to excellent yields via photo-stimulated cyclization of 2-(2-halophenylamino)pyridines in liquid ammonia and in the presence of potassium *tert*-butoxide was reported by Rossi and co-workers (Scheme 27).[28] The reaction procedure involves the photo-stimulated SRN_1 mediated C–N bond formation in 2-(2-halophenylamino)pyridines. Various substituents were well tolerated on both the phenyl and pyridine rings of the starting materials.

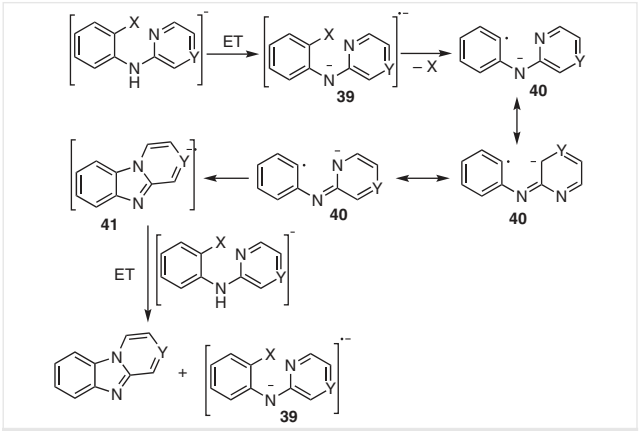


Scheme 26 Hypervalent iodine-assisted intramolecular dehydrogenative C–N coupling reactions of *N*-pyridin-2-ylanilines



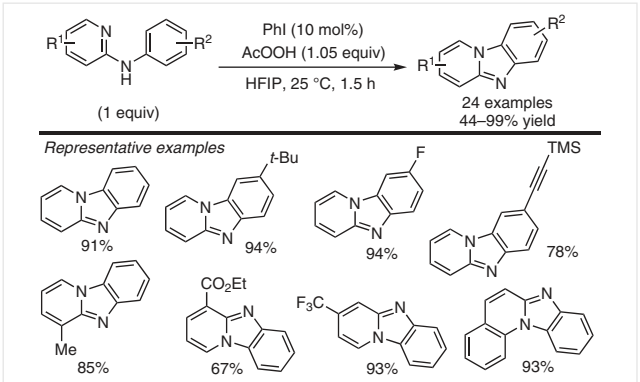
Scheme 27 Photo-stimulated cyclization of 2-(2-halophenyl amino)-pyridines to afford the corresponding pyrido[1,2-*a*]benzimidazole derivatives

The mechanism proposed for the photo-stimulated cyclization of 2-(2-halophenylamino)pyridine is shown in Scheme 28. The first step involves the generation of the radical dianion **39** of the substrate by a photo-induced electron transfer (ET) reaction. This radical dianion **39** upon fragmentation yields the distonic radical anion **40** and the halide anion, followed by the cyclization of the resonance distonic radical anion **40** to give the conjugated radical anion **41**. Finally, an electron transfer from radical anion **41** to the anion of 2-(2-halophenylamino)pyridine leads to the formation of the final product, along with the intermediate **39**, to continue the propagation cycle.



Scheme 28 Photo-stimulated SRN_1 cyclization of 2-(2-halophenylamino)pyridine

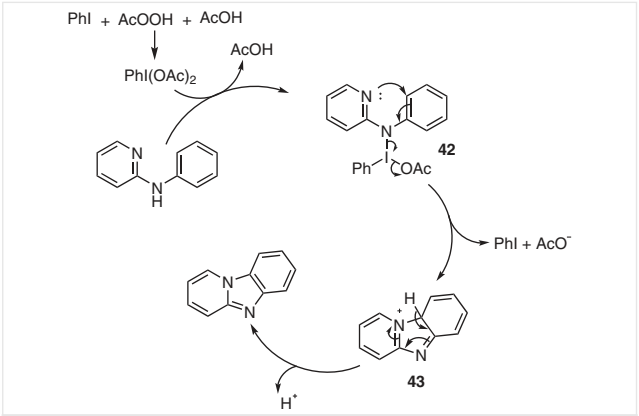
In 2013, a hypervalent iodine(III)-catalyzed C–H cycloamination reaction of *N*-aryl-2-aminopyridines was reported by Zhu et al. for the easy and efficient synthesis of various pyrido[1,2-*a*]benzimidazoles in good to excellent yields (Scheme 29).[29] The hypervalent iodine(III) reagent phenyliodine diacetate (PIDA) was generated in situ from a catalytic amount of iodobenzene and a stoichiometric amount of peracetic acid. Various electron-donating and electron-withdrawing groups were well tolerated under the optimized reaction conditions to provide more diversified pyrido[1,2-*a*]benzimidazole derivatives.



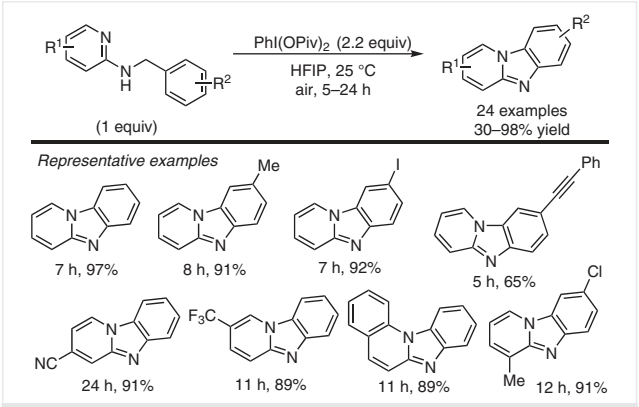
Scheme 29 PIDA-catalyzed synthesis of pyrido[1,2-*a*]benzimidazole derivatives

The authors proposed the followed reaction pathway (Scheme 30) for the C–H cycloamination reaction of *N*-phenyl-2-aminopyridine catalyzed by an in situ generated hypervalent iodine(III) reagent. The reaction starts with the formation of phenyliodine diacetate (PIDA) by the oxidation of iodobenzene with peracetic acid in the presence of acetic

acid, followed by nucleophilic substitution of the aniline nitrogen of *N*-phenyl-2-aminopyridine on the iodine(III) center in PIDA to form intermediate **42**, bearing an electrophilic *N*-iodo moiety. Subsequent nucleophilic attack from the pyridine nitrogen onto the aniline ring produces intermediate **43** along with the simultaneous release of PhI and acetate ion. The released PhI enters the catalytic cycle again upon its reoxidation by peracetic acid, which is used as a stoichiometric oxidant. In the final step, the deprotonative rearomatization of intermediate **43** takes place, leading to the formation of the desired final product, along with the generation of one molecule each of acetic acid and water as byproducts.



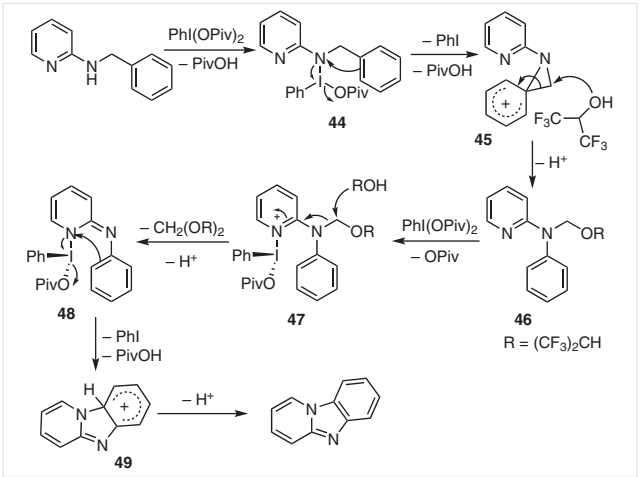
Scheme 30 Mechanism for the PIDA-catalyzed C–H cycloamination reaction of *N*-phenyl-2-aminopyridine



Scheme 31 PhI(OPiv)$_2$ promoted C–H cycloamination of *N*-benzyl-2-aminopyridines to access pyrido[1,2-*a*]benzimidazoles

Subsequently, the same group developed another mild and highly efficient, metal-free method for the oxidative, tandem demethylative C–H cycloamination of *N*-benzyl-2-aminopyridines using PhI(OPiv)$_2$ as a stoichiometric oxidant to afford the corresponding pyrido[1,2-*a*]benzimidazoles in high yields (Scheme 31).[30] This process involves PhI(OPiv)$_2$-mediated tandem C–C bond activation and intramolecular C–N bond formation steps.

The mechanism proposed for this transformation (Scheme 32) begins with the coordination of PhI(OPiv)$_2$ with *N*-benzyl-2-aminopyridine, leading to the formation of an electrophilic *N*-iodo species **44**, which undergoes *ipso* SEAr on the phenyl ring to furnish the delocalized carbocation **45** (Wheland intermediate). C–C bond cleavage in **45** occurs upon its nucleophilic addition by HFIP at the benzylic carbon, giving intermediate **46**, which upon reaction with a second equivalent of PhI(OPiv)$_2$ produces the active complex **47**. A second nucleophilic addition by HFIP to **47** results in C–N bond cleavage to give an activated electrophilic iodo species **48**, along with the release of a methylene group in the form of an acetal. Electrophilic annulation on the pyridine nitrogen of **48** forms intermediate **49**, which is deprotonated to the corresponding pyrido[1,2-*a*]benzimidazole in the final step.

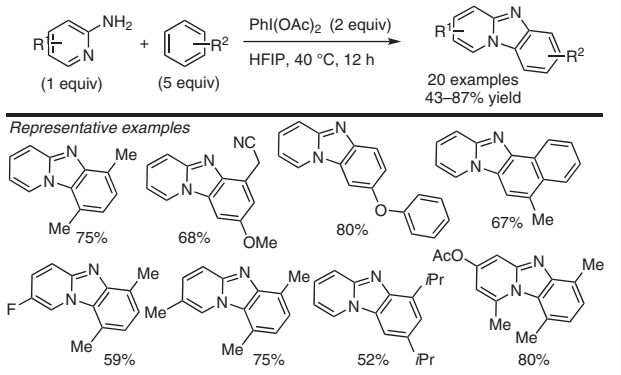


Scheme 32 Proposed reaction mechanism for the PhI(OPiv)$_2$-promoted C–H cycloamination of *N*-benzyl-2-aminopyridine

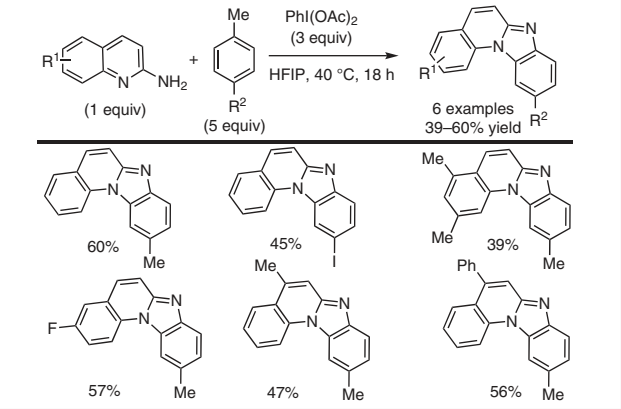
In 2014, Antonchick et al. reported a metal-free annulation reaction between various substituted 2-aminopyridines/2-aminoquinolines and arenes to get an easy access to diversified pyrido[1,2-*a*]benzimidazoles (Scheme 33) and quinolino[1,2-*a*]benzimidazoles (Scheme 34) under mild reaction conditions.[31]

A plausible mechanism for the formation of pyrido[1,2-*a*]benzimidazole is outlined in Scheme 35. It begins with a ligand exchange between 2-aminopyridine and PhI(OAc)$_2$ to form intermediate **50**, followed by nucleophilic attack of *p*-xylene, forming N-arylated 2-aminopyridine **51**. Subsequent oxidation of **51** with a second equivalent of PhI(OAc)$_2$ and nucleophilic attack of the pyridine nitrogen on xylene produces another intermediate **53**, which upon rearomatization gives the final annulated product.

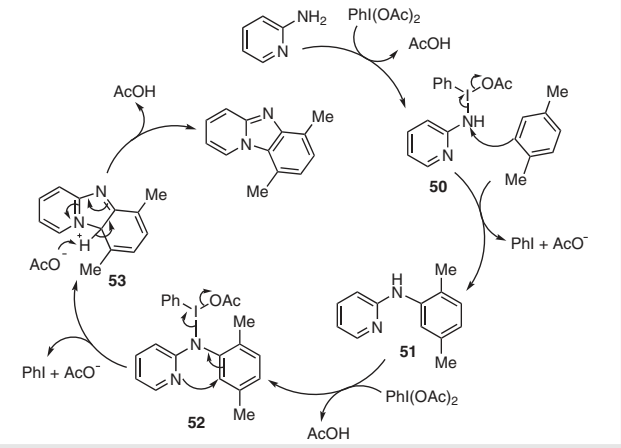
To be highlighted in this report is the in situ synthesis of benzylic amine **56** via an unprecedented participation of the methyl group of methylarene as a traceless, non-chelat-



Scheme 33 Synthesis of pyrido[1,2-*a*]benzimidazoles via metal-free annulations of 2-aminopyridines with arenes

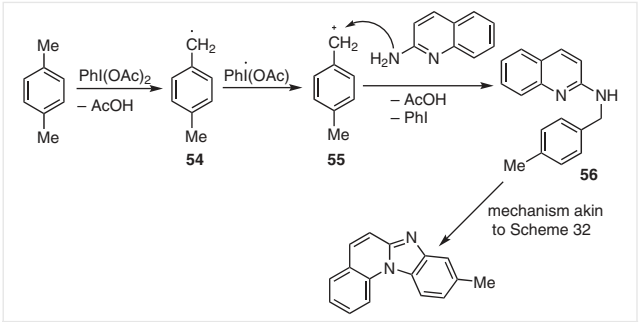


Scheme 34 Synthesis of quinolino[1,2-*a*]benzimidazoles via metal-free annulations of 2-aminoquinolines with arenes



Scheme 35 Proposed mechanism for the PhI(OAc)$_2$-mediated annulation of 2-aminopyridine with *p*-xylene

ing and highly regioselective directing group in its cross-annulation reaction with 2-aminoquinoline (Scheme 36). To obtain the requisite starting material **56**, xylene was

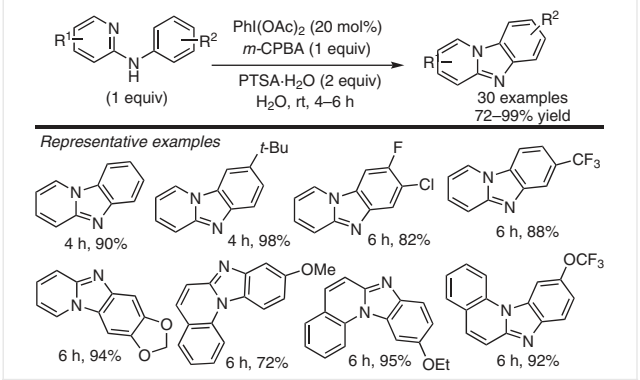


Scheme 36 Proposed mechanism explaining the PhI(OAc)$_2$-mediated annulation of 2-aminoquinoline with *p*-xylene

treated with PhI(OAc)$_2$ to form benzylic radical **54**, which was subsequently converted into cation **55** by the PhI(OAc) free-radical species. Nucleophilic attack of 2-aminoquinoline onto cation **55** gave benzylic amine **56**, which was converted into the final product via a mechanism akin to that described in Scheme 32.

In the same year, Das et al. reported a hypervalent iodine(III) [PhI(OH)OTs, Koser's reagent] catalyzed, regioselective C–H cycloamination reaction of various *N*-aryl-2-aminopyridines for the synthesis of pyrido[1,2-*a*]benzimidazoles in excellent yields (Scheme 37).[32] Hypervalent iodine(III) was generated in situ by using iodosobenzene diacetate in a catalytic amount and *p*-toluenesulfonic acid monohydrate and *m*-chloroperbenzoic acid in stoichiometric amounts. Use of water as a solvent and open-flask chemistry makes the protocol greener and more significant for large-scale synthesis of diversified pyrido[1,2-*a*]benzimidazole derivatives.

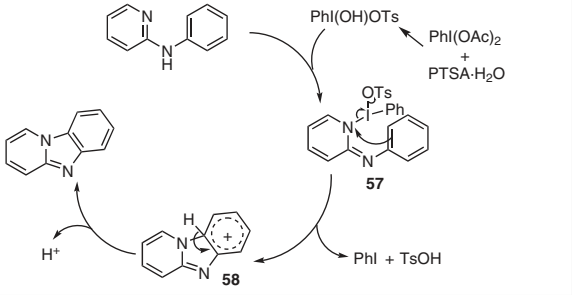
The following plausible mechanism was proposed for the PhI(OH)OTs-catalyzed oxidative C–N bond-formation reaction of *N*-phenyl-2-aminopyridine (Scheme 38). The reaction starts with the interaction of in situ generated PhI(OH)OTs with *N*-phenyl-2-aminopyridine, generating the electrophilic *N*-iodo species **57**. The formation of intermediate **58** occurs next by electrophilic annulation on the



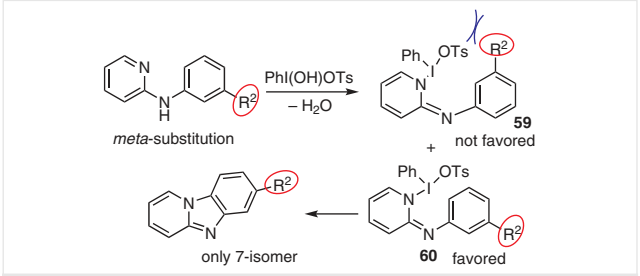
Scheme 37 Koser's reagent catalyzed, regioselective C–H cycloamination of *N*-aryl-2-aminopyridines

pyridine nitrogen of *N*-iodo species **57**, followed by deprotonation of **58** to give the final product. The eliminated PhI enters the catalytic cycle upon its oxidation by *m*-CPBA in the presence of PTSA·H_2O to generate the reactive iodine(III) PhI(OH)OTs, thus completing the catalytic cycle. Further, the rationale behind the high regioselectivity of this method is the favored formation of intermediate **60** over **59** due to steric effects (Scheme 39), to afford one regioisomer exclusively.

The Patel group reported a one-pot, three-component cyclocondensation reaction of (aryloxy)pyrazole-4-carbaldehyde, malononitrile, and 2-(cyanomethyl)benzimidazole catalyzed by piperidine to give newer (aryloxy)pyrazole-substituted pyrido[1,2-*a*]benzimidazole derivatives (Scheme 40).[33] This methodology allows an easy and expedient assimilation of two promising bioactive nuclei, namely (aryloxy)pyrazole and pyrido[1,2-*a*]benzimidazole into a single molecule for antimicrobial screening.



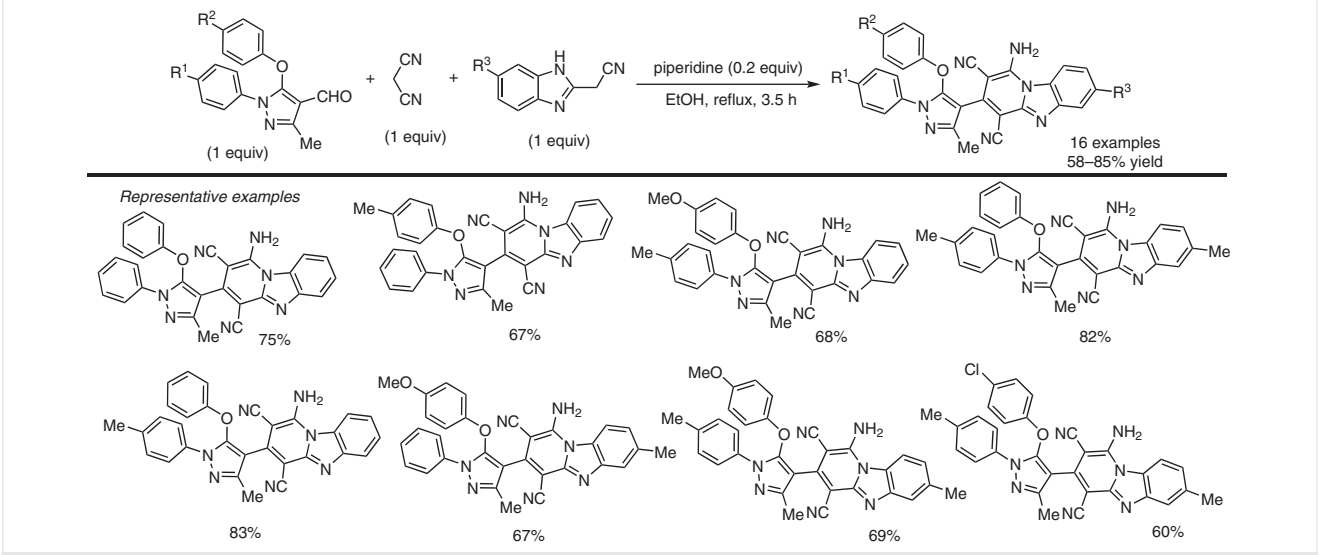
Scheme 38 Plausible mechanism for Koser's reagent catalyzed, regioselective C–H cycloamination of *N*-phenyl-2-aminopyridine



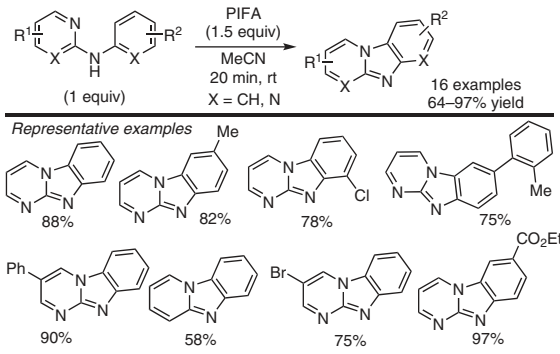
Scheme 39 Reaction path for the regioselective C–H cycloamination of *meta*-substituted *N*-phenyl-2-aminopyridine

In 2014, the Xu group described the use of hypervalent iodine(III) in the expedient preparation of imidazo[1,2-*a*]pyrimidine derivatives in good yields from readily available *N*-aryl-2-aminopyrimidines (Scheme 41).[34] This process involves the intramolecular C(sp^2)–H bond cycloamination reaction of *N*-aryl-2-aminopyrimidines promoted by hypervalent iodine(III) formed in situ from stoichiometric iodobenzene bis(trifluoroacetate) (PIFA). Various *N*-aryl-2-aminopyrimidines were employed to establish the wide scope of this method.

The authors proposed two mechanistic pathways to explain the hypervalent iodine(III)-catalyzed cycloamination of *N*-phenyl-2-aminopyrimidine (Scheme 42). A nucleophilic substitution reaction of the aniline nitrogen onto the iodine(III) center of PIFA forms intermediate **61**. In path A, intermediate **61** is transformed into nitrenium ion **62** through an oxidative process, followed by the nucleophilic addition of the pyrimidyl nitrogen atom on the carbon center of the carbocationic form **63** of intermediate **62** to give a cyclic intermediate **64**. Upon deprotonative rearomatiza-

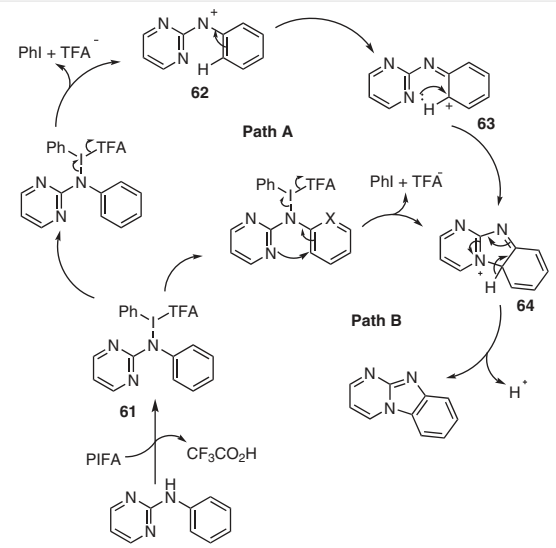


Scheme 40 One-pot, three-component synthesis of various (aryloxy)pyrazole-substituted pyrido[1,2-*a*]benzimidazole compounds



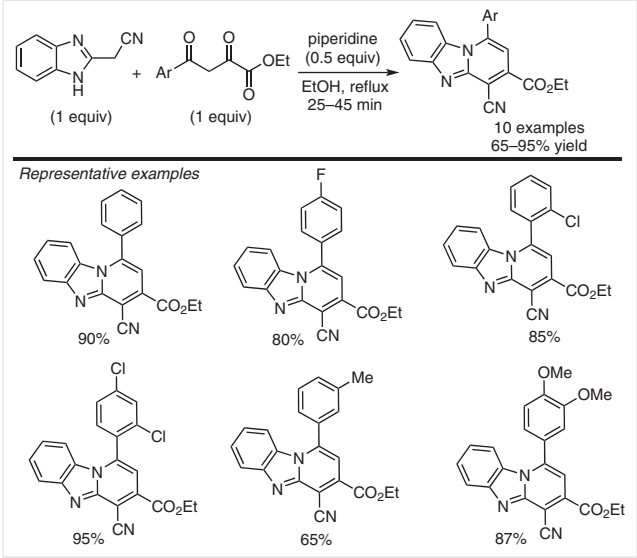
Scheme 41 PIFA-catalyzed intramolecular cycloamination of *N*-aryl-2-aminopyrimidines

tion of **64**, the desired product is produced. Alternatively, the direct nucleophilic substitution of the pyrimidyl nitrogen on the aniline ring of intermediate **61** affords the cyclic intermediate **64**, along with the release of one molecule each of PhI and CF_3COO^-.



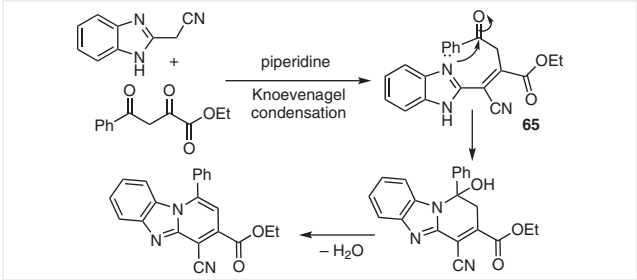
Scheme 42 Mechanism proposed for the intramolecular C(sp^2)–H bond cycloamination of *N*-phenyl-2-aminopyrimidine catalyzed by PIFA

Foroumadi and his group synthesized a series of pyrido[1,2-*a*]benzimidazole derivatives by the reaction between 2-(1*H*-benzo[*d*]imidazol-2-yl)acetonitrile and ethyl 2,4-dioxo-4-arylbutanoates, using piperidine as a base in refluxing EtOH (Scheme 43).[35] Various ethyl 2,4-dioxo-4-arylbutanoates were used to establish the substrate scope of the method. Mild reaction conditions, short reaction times and easy purification of the obtained compounds are the significant advantages of this reaction from a synthetic point of view.



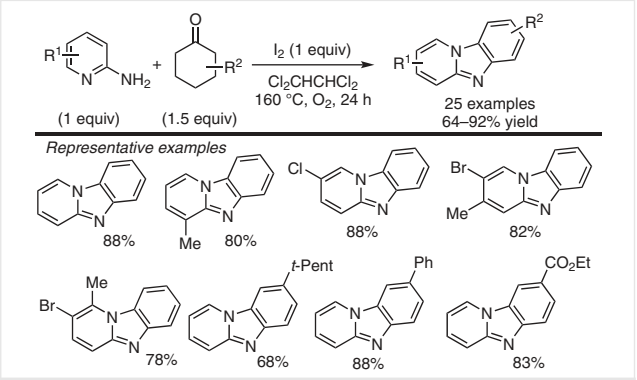
Scheme 43 Piperidine-catalyzed synthesis of pyrido[1,2-*a*]benzimidazole derivatives

The mechanism that explains this conversion (Scheme 44) starts with the formation of intermediate **65** by a Knoevenagel condensation reaction between 2-(1*H*-benzo[*d*]imidazol-2-yl)acetonitrile and ethyl 2,4-dioxo-4-phenylbutanoate. Intramolecular nucleophilic addition of the benzimidazole ring nitrogen on the carbonyl carbon occurs, followed by dehydration to give the desired pyrido[1,2-*a*]benzimidazole derivative.



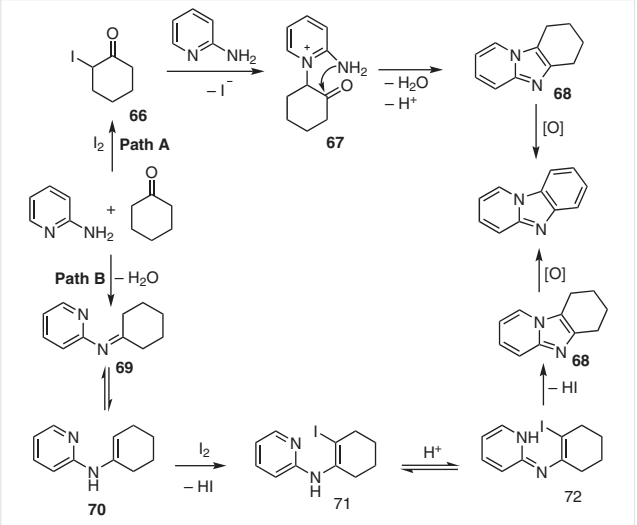
Scheme 44 Proposed mechanism for the synthesis of diversely substituted pyrido[1,2-*a*]benzimidazoles

Subsequently, Deng and his group developed an expedient, molecular iodine-mediated preparation of pyrido[1,2-*a*]benzimidazole derivatives, using 2-aminopyridines and non-aromatic cyclohexanones as starting materials under metal-free conditions (Scheme 45).[36] Molecular oxygen was employed as a green oxidant for the dehydrogenation–aromatization of non-aromatic cyclohexanones which were used as an aryl source in this protocol. A library of pyrido[1,2-*a*]benzimidazoles was prepared in good to excellent yields by using various 2-aminopyridines and cyclohexanones to establish the general applicability of this method.

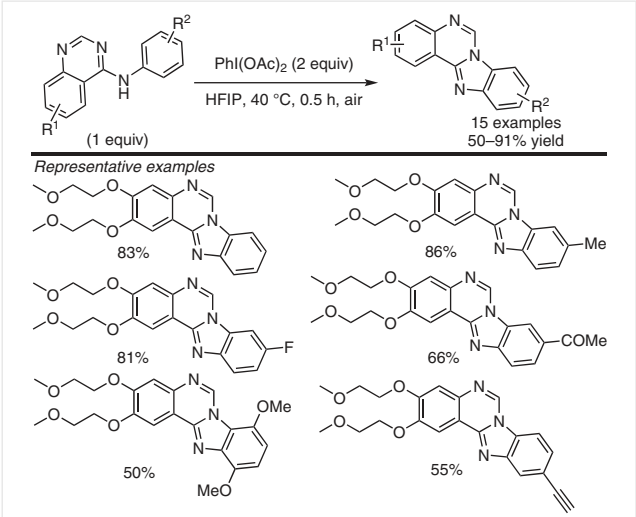


Scheme 45 I_2-catalyzed synthesis of pyrido[1,2-*a*]benzimidazole derivatives from 2-aminopyridines and non-aromatic cyclohexanones

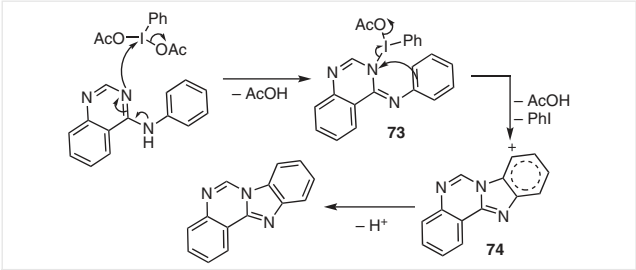
Two plausible reaction pathways were proposed to explain the metal-free synthesis of pyrido[1,2-*a*]benzimidazole, as shown in Scheme 46. Iodination of cyclohexanone forms 2-iodocyclohexanone (**66**), which, upon nucleophilic substitution by 2-aminopyridine, generates the second intermediate **67**. Subsequent intramolecular cyclization of **67** followed by deprotonation and dehydration leads to 6,7,8,9-tetrahydrobenzo[4,5]imidazo[1,2-*a*]pyridine intermediate **68** (path A). Molecular oxygen assisted dehydrogenation of **68** forms the final product. In an alternative pathway, the initial step is the condensation of 2-aminopyridine with cyclohexanone to give imine intermediate **69**, which is subsequently isomerized to intermediate **70** (path B). Iodination of **70** forms intermediate **71**, which is isomerized into another intermediate **72**. Intramolecular substitution of the iodo group with amine in **72** also affords intermediate **68**.



Scheme 46 Plausible reaction pathways for the I_2-mediated synthesis of pyrido[1,2-*a*]benzimidazole



Scheme 47 Synthesis of benzimidazo[1,2-*c*]quinazolines via metal-free C–N coupling of 4-anilinoquinazolines

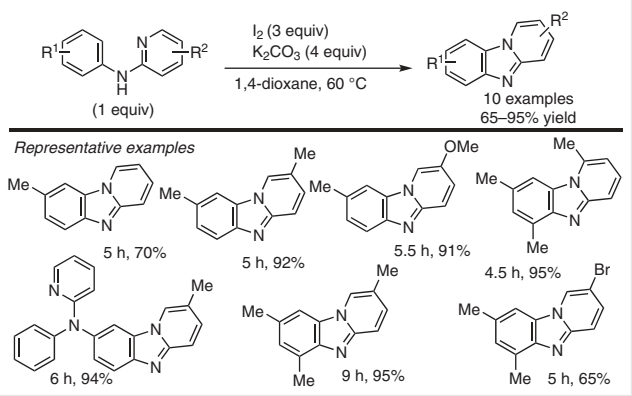


Scheme 48 Plausible mechanism for the $PhI(OAc)_2$-promoted cycloamination of 4-anilinoquinazoline

In 2016, Zhang et al. reported a phenyliodine(III) diacetate (PIDA) mediated intramolecular C(sp^2)–H bond cycloamination reaction of 4-anilinoquinazolines using mild reaction conditions to afford erlotinib drug-related benzimidazo[1,2-*c*]quinazoline derivatives in appreciable yields (Scheme 47).[37] This metal-free C–N coupling protocol was found tolerable to both electron-donating and electron-withdrawing groups at various substitution positions of the aniline fragment of the starting materials used.

A plausible mechanism (Scheme 48) involves initiation by the interaction of $PhI(OAc)_2$ with 4-anilinoquinazoline to give intermediate **73** that contains the electrophilic *N*-iodo moiety, with the subsequent loss of a molecule of acetic acid. Electrophilic annulation on the pyridine nitrogen through the cleavage of the N–I bond leads to the formation of another intermediate **74** along with the concurrent release of one molecule each of PhI and acetic acid. In the final step, the deprotonative rearomatization of intermediate **74** occurs, leading to the formation of the desired product.

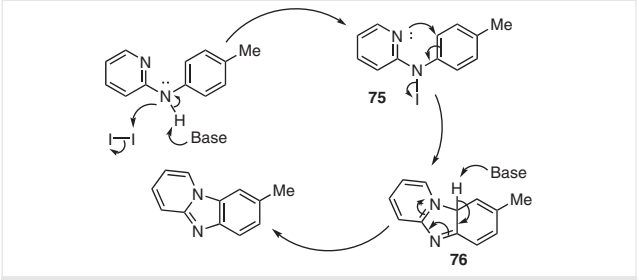
During the same year, Yu and his group demonstrated the use of molecular iodine as an oxidant for the intramolecular C(sp^2)–H bond cycloamination of *N*-arylpyridin-2-amines to construct a diverse range of pyrido[1,2-*a*]benzimidazoles, employing K_2CO_3 as a base under mild reaction conditions (Scheme 49).[38] The optimized reaction conditions worked well with various substituted *N*-arylpyridin-2-amines.



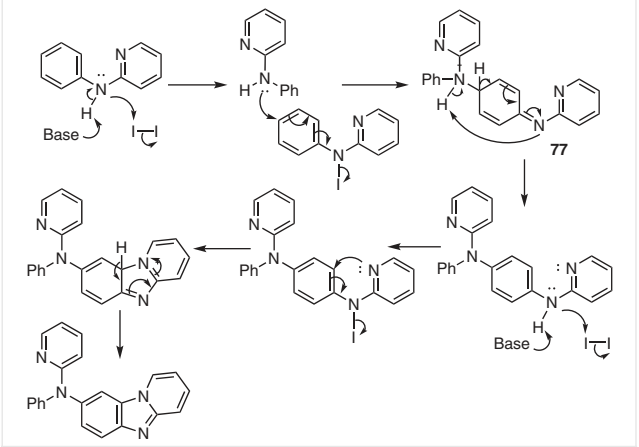
Scheme 49 I_2-mediated intramolecular aryl C–H amination of *N*-arylpyridin-2-amines to access pyrido[1,2-*a*]benzimidazoles

Depending upon the substitution on the aryl ring of the *N*-arylpyridin-2-amines, three plausible mechanisms (Schemes 50–52) were proposed for their direct I_2-mediated C–H cycloamination. The substrates with methyl substitution at the *para* position of the *N*-phenyl ring undergo base-mediated oxidative iodination to produce the electrophilic *N*-iodo species **75**, followed by N–I bond cleavage and subsequent intramolecular C–N bond formation to generate intermediate **76**, which undergoes deprotonative rearomatization to form the corresponding final product (Scheme 50). When *N*-phenylpyridin-2-amine is used as the starting material, the initial step is the attack of a molecule of *N*-phenylpyridin-2-amine on the *para* position of its *N*-iodo form to give dimer **77**; subsequent I_2-mediated oxidative cycloamination affords the product (Scheme 51). 2,4,6-Trimethylphenyl-bearing substrates undergo intramolecular nucleophilic substitution of the pyridine nitrogen onto the aryl ring carbon to give intermediate **78**. Iodide-ion-assisted demethylation of **78** yields the corresponding final product (Scheme 52).

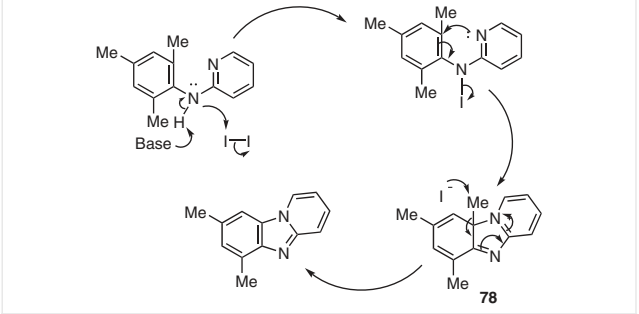
Verma and co-workers recently described an eco-benign tandem method of preparation of various benzimidazo-fused heterocyclic compounds, namely benzimidazo-fused benzofuro[3,2-*c*]pyridines, benzimidazo-fused benzofuro/benzothieno[2,3-*c*]pyridines, and benzimidazo-fused benzoindolo[3,2-*c*]pyridines, by using functionally varied alkynyl aldehydes and *o*-phenylenediamines as starting materials in aqueous medium under transition-



Scheme 50 I_2-mediated intramolecular aryl C–H amination of *p*-methyl-substituted *N*-phenylpyridin-2-amine



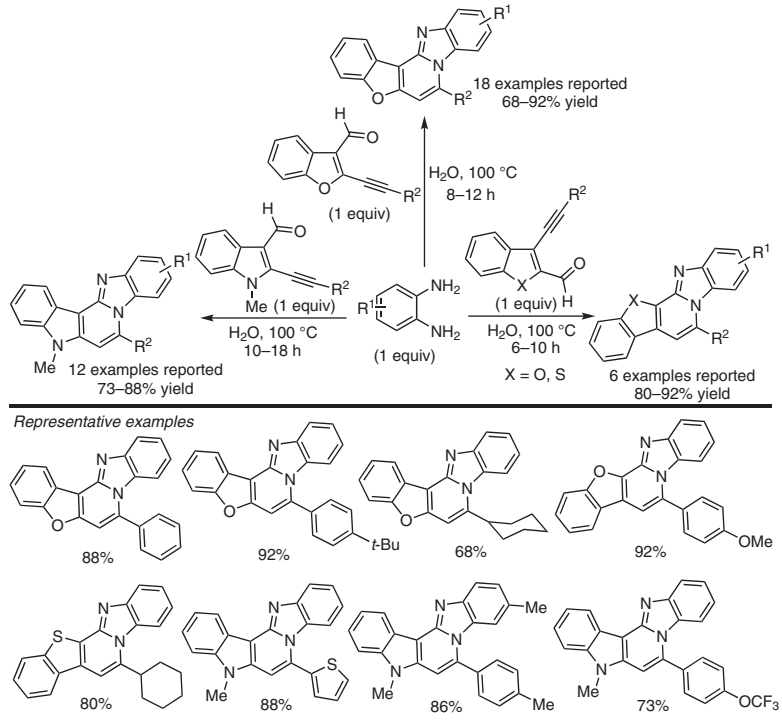
Scheme 51 I_2-mediated intramolecular aryl C–H amination of *N*-phenylpyridin-2-amine



Scheme 52 I_2-mediated intramolecular aryl C–H amination of 2,4,6-trimethyl-substituted *N*-phenylpyridin-2-amine

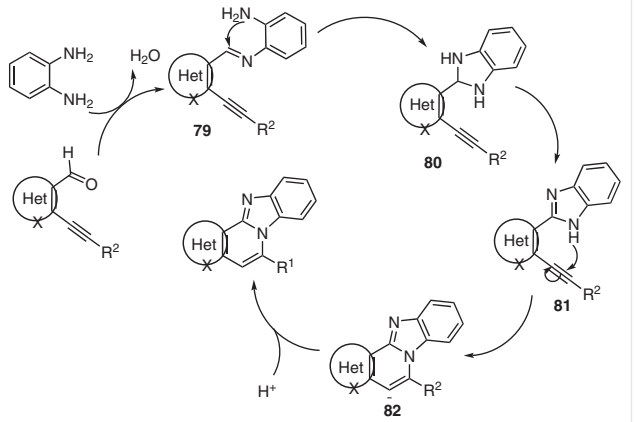
metal-free conditions (Scheme 53).[39] The reaction occurs through a one-pot inter- and intramolecular C–N bond formation via regioselective 6-*endo*-*dig* cyclization.

A plausible mechanism for the formation of benzimidazo-fused polyheterocycles (Scheme 54) involves the initial reaction between the alkynyl aldehyde and *o*-phenylenediamine to furnish the corresponding imine intermediate **79**. Subsequent intramolecular nucleophilic attack of the amino group on the imine bond generates the cyclic intermediate **80**, which upon auto-oxidation forms the benzimidazole-



Scheme 53 Metal-free synthesis of various benzimidazo-fused heterocyclic compounds from alkynyl aldehydes and *o*-phenylenediamines

fused intermediate **81**. A second intramolecular nucleophilic attack by the benzimidazole ring nitrogen on the electrophilic alkyne bond produces the unstable vinylic anion **82**, which is protonated to give the final product.



Scheme 54 Mechanistic explanation for the metal-free synthesis of benzimidazo-fused heterocyclic compounds

3 Conclusion

In summary, pyrido[1,2-*a*]benzimidazole and its analogues have taken a leading role in the recent literature, because of their wide variety of applications in various disciplines such as medicinal chemistry and materials science. Several novel synthetic routes have been developed to produce these scaffolds, involving mainly construction of the imidazole ring on the pyridine nucleus and scantly the opposite. These newer synthetic routes are based on the combination of several interesting strategies such as multicomponent reactions, tandem sequences, and C–H activation. As is evident from the discussion in this review, these synthetic procedures offer easy access to pyrido[1,2-*a*]benzimidazole from simple and readily available precursors without the need of any prefunctionality. The development of these synthetic procedures is very useful, especially for medicinal and materials chemists.

Acknowledgement

Sk.R. thanks CSIR-New Delhi for his research fellowship.

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