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Advances in transition metal-catalyzed C–H amination strategies using anthranils

Yogesh N. Aher,† Nilanjan Bhaduri † and Amit B. Pawar *

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Modern times have witnessed an uprise in the synthesis and derivatization of nitrogen-containing fused heterocycles. Amination reactions involving nitrene chemistry have always been the most convenient choice for the incorporation of a nitrogen atom in a molecule. The utilization of an open nitrene species harnesses harsh conditions. Hence, transition metal-catalyzed C–H amination reactions using aminating agents have been an attractive choice. Electrophilic aminating agents for C–H amination reactions are well exploited due to their desirable reaction conditions. Out of all, anthranils have paved the way forward due to their utility in simultaneously forming two new functional groups (amine and carbonyl). Amination using anthranils follows a metal-nitrenoid pathway. Often, the amination has been followed by a Lewis acid or transition metal-mediated intramolecular cyclization to directly produce fused heterocycles. This review broadly demonstrates the utilization of anthranils as an aminating agent for transition metal-catalyzed C–H amination reactions. The focus has been given to the scope, limitations, and mechanistic understanding of using such an electrophilic aminating agent, anthranil, with transition metals.

1. Introduction

C–H activation/amination has emerged as an efficient tool for organic transformations over time. C–H activation has further promoted the concepts of green chemistry and reduced the number of steps required for any transformation, even in milder conditions.[1] Such a concept has allowed researchers to come up with a wide range of catalytic systems optimized for carrying out a particular transformation. Synthetically, all the transformations in organic chemistry involve C–H and C–C bond-breaking or bond-making. Apart from the chemistry involving C–H and C–C bonds, C–N bond formation is also of high industrial importance due to its presence in a variety of natural products and agrochemical moieties.[2] Traditional

School of Chemical Sciences, Indian Institute of Technology Mandi, Himachal Pradesh, 175075, India. E-mail: amitpawar@iitmandi.ac.in
†Authors contributed equally.

Yogesh N. Aher

Yogesh N. Aher was born and raised in Maharashtra, India. He received his Master's in Organic Chemistry from the University of Pune in 2017. He then worked as a project assistant at the CSIR-Indian Institute of Chemical Technology in Hyderabad from 2017 to 2019. He is presently pursuing his Ph.D. at the School of Chemical Sciences, IIT Mandi, under the guidance of Dr Amit B. Pawar. His research focuses on redox-neutral C–H functionalization/annulation reactions under transition metal catalysis, assisted by oxidizing directing groups and coupling partners.

Nilanjan Bhaduri

Nilanjan Bhaduri was born in Belgharia (North 24 Parganas), West Bengal, in 1999. He obtained his B.Sc. from Maharaja Manindra Chandra College, University of Calcutta, and is currently pursuing his M.Sc. at IIT Mandi under the supervision of Dr Amit B. Pawar. His research interest lies broadly in the domain of sustainable catalysis via C–H activation/functionalization.

approaches for the construction of a C–N bond include amination/annulation reactions and coupling reactions. Owing to the high demands for the synthesis of N-heterocycles, the synthetic community has developed catalytic systems for transition metal-catalyzed amination/annulation reactions with a suitable directing group.[3] The directing group directs an aminating agent, through its nitrogen or oxygen atom, to a particular reaction site. This allows the functionalization of activated as well as inert C–H bonds for C–N bond formation. Broadly, aminating agents could be of two types: electrophilic or nucleophilic. The charm of using electrophilic aminating agents lies in their inherent reactivity with redox-neutral behavior. A variety of aminating agents, such as chloramines,[4] *N*-nosyloxycarbamate,[5] aryl oxycarbamates,[6] organic azides,[7] aryl nitroso,[8] dioxazolones,[9] anthranil,[10] amidobenziodoxolones,[11] *N*-tosyloxyphthalimide,[12] and *N*-methoxybenzamide,[13] *etc*., have been developed (Fig. 1). Over time, anthranil as an aminating agent has been particularly attractive in this domain due to the incorporation of two functionalities (amine and carbonyl) in a single transformation.

Anthranils, or 2,1-benzisoxazoles, are highly aromatic and bench-stable compounds. In general, anthranils generate an aryl nitrene species at a very high temperature. The utilization of nitrene species has always been the top choice for organic chemists for the incorporation of a nitrogen atom in a molecule.[14] However, the use of a sole nitrene species in a reaction demands harsh conditions. The involvement of transition metal catalysts with anthranils has tuned their reactivity in terms of the requirement of milder conditions and the site-selectivity of the product. Transition metal catalysts activate the anthranil moiety and generate metal-nitrenoid species *via* an electrocyclic ring-opening (Fig. 2). So far, transition metals

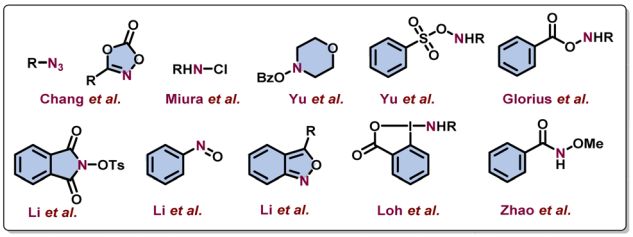


Fig. 1 Representative examples of electrophilic C–H aminating agents.

such as rhodium, iridium, copper, and cobalt have been successfully merged with anthranils for amination reactions. Interestingly, C–H activation strategies involving anthranils for amination reactions follow a redox-neutral pathway. It is to be believed that the requirement of no external oxidant is due to the presence of a cleavable N–O bond in the upcoming coupling partner, *i.e.*, anthranil. Mostly, the amination with anthranils follows an inner sphere mechanism,[15] wherein the metal catalyst forms a metallacycle with the substrate, and then the coupling partner (anthranil) is directed towards a specific site.

The general mechanism of C–N bond formation with anthranils (Fig. 2) as an aminating agent involves the formation of a metallacycle with the assistance of a suitable directing group. Next, with anthranil, a metal-nitrenoid intermediate is generated, followed by the migratory insertion of the coordinated anthranil into a metal–carbon bond to furnish a tridentate metal-coordinated intermediate. The last step includes protonolysis to furnish the aminated product. In general, 3-substituted anthranils generate an aryl nitrene species, whereas unsubstituted anthranils lead to aryl ketene species at high temperatures (probably due to the electronic effect), and the metal-catalyzed amination reactions using anthranil lead to *ortho* C–H bond activation for C–N bond formation.

However, few approaches have additionally utilized the Lewis acidity of rhodium or cobalt catalysts for intramolecular cyclization to unveil fused heterocycles such as acridines, indoloindolones, *etc*. Mostly, such reactivities of anthranils are governed by the substituent at its 3-position. Specifically, aliphatic substituents at the 3-position of anthranils have promoted such *in situ* cyclization as compared to the aryl substituents.

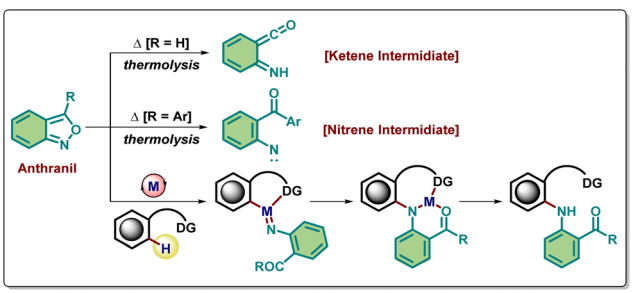


Fig. 2 General reactivity of anthranils in the presence or absence of a transition metal catalyst.

Amit B. Pawar

Dr Amit B. Pawar completed his M.Sc. in Organic Chemistry at the University of Pune in 2007. He obtained his Ph.D. from the Indian Institute of Science, Bangalore, under the supervision of Prof. Kavirayani R. Prasad in 2012. He was awarded first prize from Eli-Lily for the "2012 Lilly Asia Outstanding Thesis Award". He carried out his post-doctoral work with Prof. Sukbok Chang at KAIST, South Korea, in the area of C–H bond functionalizations (2013–2015). Later, he worked as a DST-Inspire faculty member at CSIR-IICT, Hyderabad, from April 2015 to October 2019. Currently, he is working as an Assistant Professor in the School of Basic Sciences at IIT Mandi, Himachal Pradesh, India. His research is focused on the utilization of first-row transition metals for C–H functionalization and the development of mild C–H activation reactions.

The amination reactions with anthranils are assisted by either strong nitrogen-atom-containing directing groups or weak oxygen-/sulphur-containing directing groups. Apart from cascade cyclization, the charm of anthranil also lies in the installation of the carbonyl functionality along with the amino group, which can be successfully implemented for diverse modifications of the synthesized molecules.

Due to the presence of a cleavable N–O bond, anthranils are also widely found in a variety of cross-coupling reactions, ring-opening reactions, and dipolar additions, which are also significantly important in the synthesis of N-heterocycles. This could be found in the previous literature review by Hu *et al.*[16] and Kapur *et al.*[17] However, such reactions are beyond the scope of this review and will not be discussed here. In this review, we have critically summarized all the developments made until August 2023 in the transition metal-catalyzed amination reactions domain using anthranils as an aminating agent. This review is mainly classified based on transition metal catalysts, and the focus has been entirely given to the accessibility, scope, failures, and mechanistic understanding of the available amination strategies with anthranils. We have also listed the various methods for the synthesis of anthranils available in the literature.

2. Preparation of anthranils or 2,1-benzisoxazoles

Anthranils, or 2,1-benzisoxazoles, have emerged as a privileged structural motif in organic synthesis that can be synthesized by several methods (Fig. 3). The initial report was from Eckroth and co-workers in 1970, who prepared an anthranil from 2-nitrophenylacetic acid in the presence of concentrated sulfuric acid.[18]

Later in 1986, Phillips *et al.* developed a method for the synthesis of anthranils by the reduction of *ortho*-nitrobenzaldehyde in the presence of stannous chloride in concentrated hydrochloric acid.[19] After this, Fletcher and co-workers developed a synthetic method by changing the reaction condition.[20] Additionally, in 1997, Kim *et al.* reported that 2-bromo-2-nitropropane with zinc metal promoted the reductive cyclization of 2-nitrobenzaldehyde towards anthranils in a methanolic solution.[21] Moreover, 3-substituted anthranils can be synthesized by various methods. (i) Li and co-workers reported the 3-substituted anthranils *via* treatment of a stoichiometric amount of $PhI(OAc)_2$ with 2-aminophenyl ketones.[22] (ii) Corma *et al.* reported a reductive heterocyclization of 2-nitrophenyl ketones using Pt-supported nanoparticles.[23] (iii) Driver and co-workers reported the Fe-catalyzed intramolecular heterocyclization of 2-azidophenyl ketones for the synthesis of 3-substituted anthranils.[24] (iv) Pizzini *et al.* reported the condensation of acrylacetonitriles with substituted aromatic nitro compounds in the presence of a base in a methanolic solution.[25] (v) Recently, Arcadi and co-authors reported a chemoselective oxidation cyclization of 2-aminoacyl benzene with oxones for the synthesis of 3-substituted anthranils.[26]

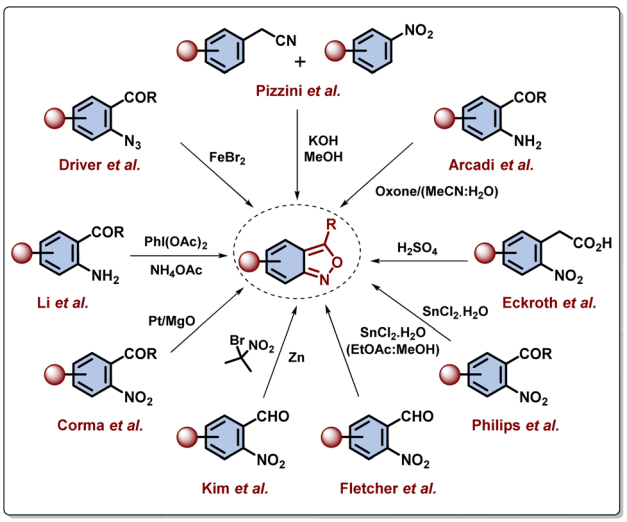


Fig. 3 Synthetic approaches for anthranils or 2,1-benzisoxazoles.

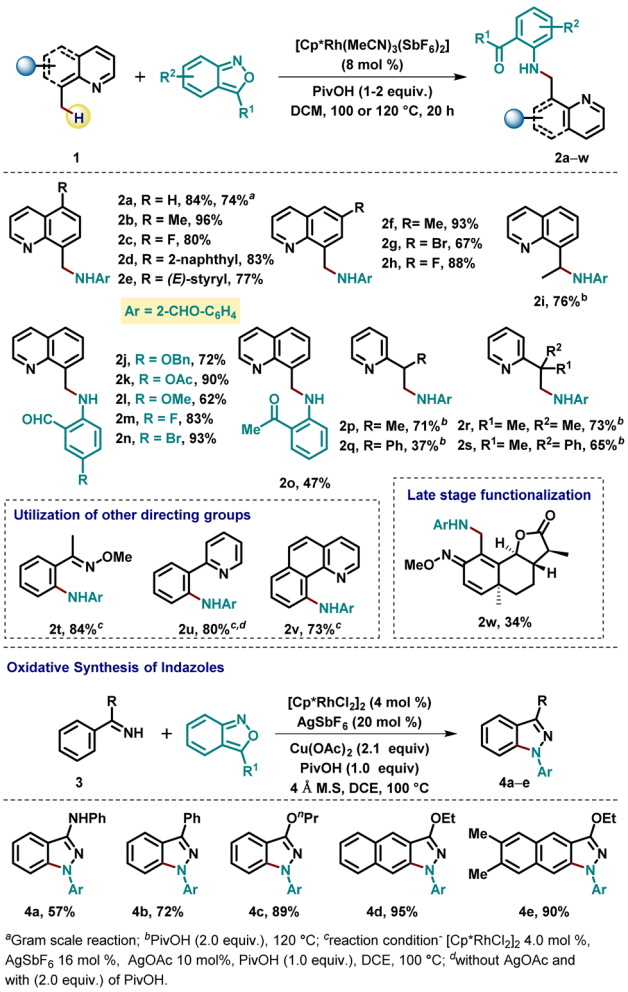
3. Transition metal-catalyzed C–H amination using anthranils

In this section, we have summarized various C–H amination protocols using anthranil as an aminating agent based on the transition metal catalysts.

3.1. Rhodium catalysis

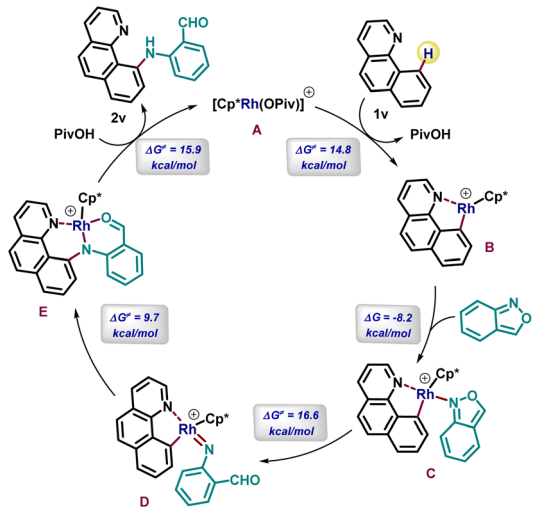
In 2016, Li and co-workers developed the first Cp*Rh(III)-catalyzed amination strategy for sp^2 and sp^3 carbon centers using anthranils as an aminating agent (Scheme 1).[10] For amination at the sp^3 center, 8-methylquinoline **1** was used in the presence of PivOH additive in DCM solvent at 100 °C. The protocol could tolerate a variety of alkyl **2b**, aryl **2d**, alkenyl **2e**, and halo-substituted quinolines **2c**. Interestingly, the amination could also be further extended to 8-ethylquinoline **2i** as the starting material. A variety of substituted anthranils (**2j–2n**) could also furnish the desired aminated product in good yields; however, electron-withdrawing coupling partners were found to be more effective than electron-donating ones. In addition, 3-substituted anthranils **2o** gave expected products with a ketonic group. The added advantage to this protocol was its applicability for substrates with pyridine as the directing group to furnish a wide range of desymmetric products (**2p–2s**). Apart from the sp^3 methyl centers, the group also extended the protocol to tertiary and quaternary centers as well. Low yields were observed for 2-ethylpurines. The driving force of the reaction could be aromatization, which is well understood from the failure of a simple isoxazole as a coupling partner.

For amination at the sp^2 carbon center, a variety of directing groups such as pyridine **2u**, pyrimidine **2v**, and oxime ethers **2t** on the arenes could be used. The protocol required $AgSbF_6$ salt, AgOAc base, and PivOH additive in DCE

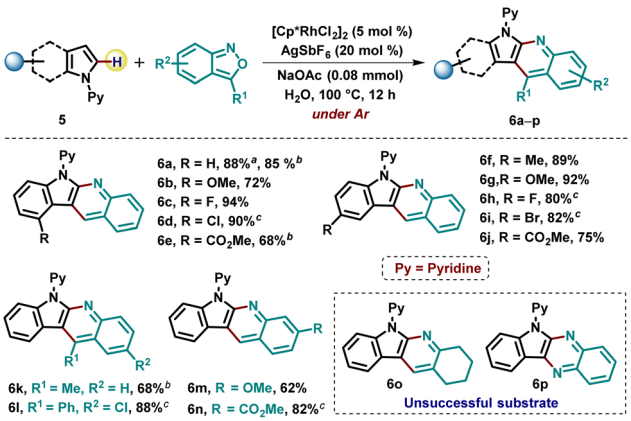


aGram scale reaction; bPivOH (2.0 equiv.), 120 °C; creaction condition: [Cp*RhCl2]2 4.0 mol %, AgSbF6 16 mol %, AgOAc 10 mol%, PivOH (1.0 equiv.), DCE, 100 °C; dwithout AgOAc and with (2.0 equiv.) of PivOH.

Scheme 1 Cp*Rh(III)-catalyzed C–H amination of 8-methylquinoline and arenes with anthranils (ref. 10).



Scheme 2 Proposed mechanism for Cp*Rh(III)-catalyzed C–H amination of 8-methylquinoline and arenes with anthranils.



aGram scale synthesis; bUsing THF as solvent; cReaction performed at 120 °C

Scheme 3 Cp*Rh(III)-catalyzed C–H amination/annulation of indoles with anthranils for the synthesis of indoloquinolines (ref. 27).

solvent at 100 °C. Upon modifying the reaction conditions with the same rhodium catalyst, anthranils could also be used as an aminating agent for the synthesis of indazoles (**4a–4e**). A functionalizable –NH group is used to assist the reaction. Lastly, the group has extended the protocol for the oxime ether-directed late-stage amination of (–)-santonin **2w**.

The proposed catalytic cycle (Scheme 2) began with the formation of the active species **A**. Next, a five-membered metallacycle intermediate **B** is generated with the assistance of pivalic acid. The weak coordination of the nitrogen atom of anthranil with the rhodium center gave intermediate **C**, which further generated the rhodium-nitrenoid intermediate **D**. Next, the migratory insertion of the nitrene into the Rh–C bond gave intermediate **E**. Lastly, the aminated product **2v** was furnished with the assistance of pivalic acid. The entire cycle was depicted on the basis of DFT calculations.

During the same period, Wang and co-workers also demonstrated the Cp*Rh(III)-catalyzed amination strategies using anthranils (Scheme 3).[27] The amination/annulation of indoles **5** to furnish indoloquinoline derivatives **6a–p** was carried out in the presence of $AgSbF_6$ salt and NaOAc base in water as solvent at 100 °C. A variety of functional groups (**6a–6j**), regardless of their substitution positions, furnished the product with good yield. Interestingly, 2-(1*H*-pyrrol-1-yl)pyridine could also be used to furnish pyrroloquinoline **6a** as a product. The protocol could tolerate a variety of coupling partners (**6k–6n**), though the reaction was dependent on the electronic nature of the substituents.

Similar to Li's report, electron-withdrawing coupling partners were found to be more effective than electron-donating ones. The reaction failed with benzo[*c*][1,2,5]oxadiazole **6p** and 4,5,6,7-tetrahydrobenzo-[*c*]isoxazole **6o** as the coupling partners.

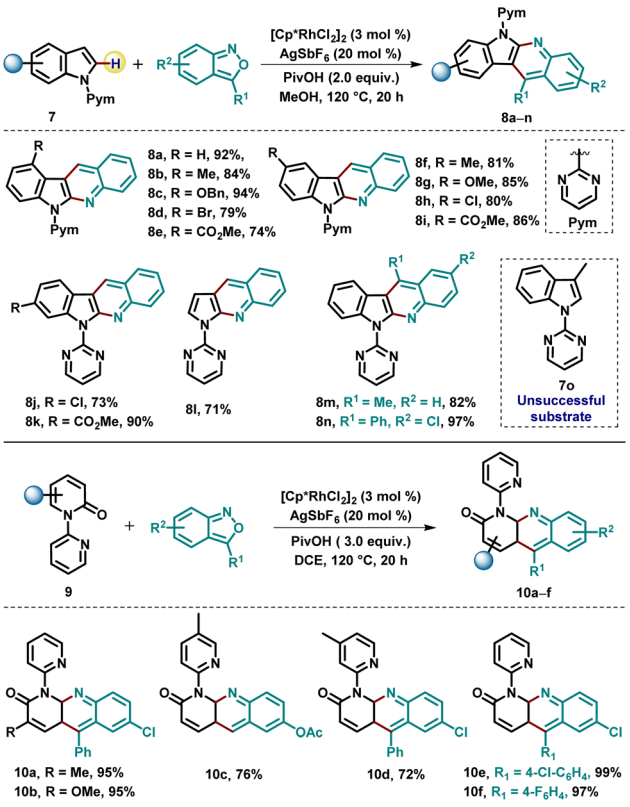
Furthermore, the group also synthesized open-chain products by employing 2-phenylpyridine or 2-(thiophene-2-yl)pyridine as a starting material in modified reaction conditions.

In the same year, Li reported another Cp*Rh(III)-catalyzed amination strategy for the synthesis of quinoline-fused heterocycles **8a–n** (Scheme 4).[28] The protocol required $AgSbF_6$ salt and PivOH additive in MeOH solvent at 120 °C for 20 h for the amination/annulation of indoles. *N*-Pyrimidinylindoles with both electron-donating and electron-withdrawing substituents worked efficiently (**8a–8k**). A pyridyl group was also used as a directing group for furnishing desired products from bromo- and benzyl ether-substituted indoles. Notably, no aminated product was observed for 3-methyl-1-(pyrimidin-2-yl)-1*H*-indole **7o**. The scope of anthranils as a coupling partner was vast, as both electron-donating **8m** and electron-withdrawing groups **8n** on the anthranil furnished the desired products. The group also reported rhodium-catalyzed amination/annulation of 2-pyridones under modified conditions, *i.e.*, $AgSbF_6$ salt and PivOH additive in DCE solvent at 120 °C for 20 h. The protocol could be used for the synthesis of benzo[*b*][1,8]naphthyridin-2-ones. A wide range of electron-donating substituents at various positions of the 2-pyridone derivatives (**10a** and **10b**) could also furnish the product with good yields. The substrate scope could be extended to isoquinolones to furnish a highly conjugated heterocycle. Like the previous case, the scope of anthranil (**10e** and **10f**) was broad.

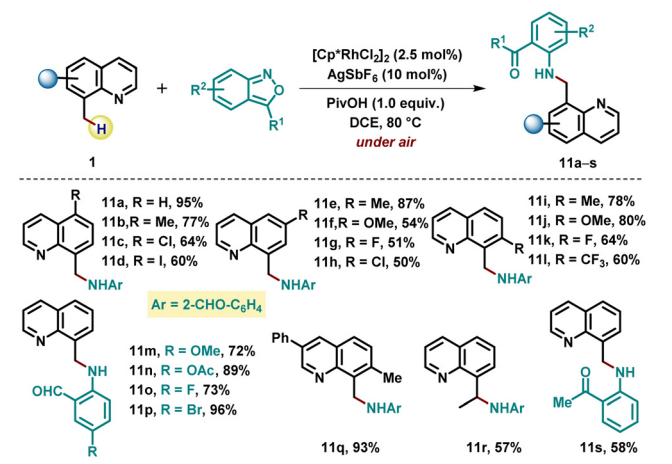
Similarly, Jiao and co-workers reported a Cp*Rh(III) amination strategy for the amination of 8-methylquinoline **1** using anthranils (Scheme 5).[29] The protocol required $AgSbF_6$ salt and PivOH additive in DCE solvent at 80 °C. The protocol could tolerate a variety of sensitive functional groups (**11a–11l**) on 8-methylquinoline. Few products, so formed, could be used in cross-coupling reactions such as Suzuki–Miyaura coupling, Buchwald–Hartwig coupling, and Heck coupling. Multi-substituted substrates such as 5,8-dimethyl-3-phenylquinoline and 7,8-dimethyl-3-phenylquinoline also worked smoothly. Apart from unactivated primary sp^3 carbon centers, the protocol even worked for secondary sp^3 carbon centers as in 8-ethylquinoline **11r**; however, the protocol failed for tertiary sp^3 carbon centers as in 8-isopropylquinoline. The scope of anthranil (**11m–11p**) in this protocol was also very broad. Interestingly, methyl-substituted anthranil led to the formation of the *o*-aminoacetophenone fragment **11s**.

The proposed catalytic cycle (Scheme 6) began with the formation of active rhodium species, which, on metalation, gave five-membered rhodacycle intermediate **A**. The weak coordination of anthranil with the rhodium atom gave intermediate **B**. Next, the breakage of the N–O bond resulted in the rhodium–nitrene species **C**. Following, the insertion of nitrene into the Rh–C bond gave amido-rhodium complex **D**. Lastly, the aminated product **11a** is furnished by a protodemetalation process along with the regeneration of active rhodium species.

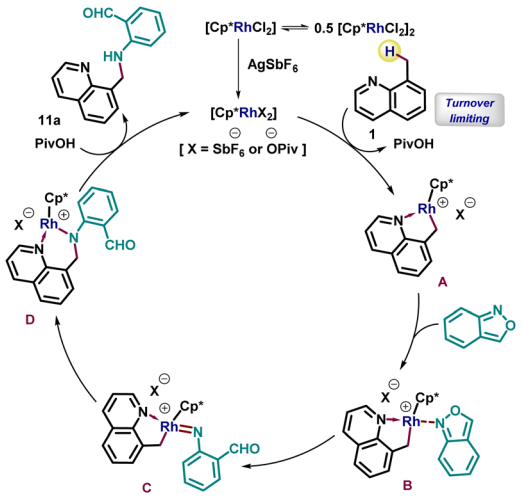
The same group also reported a Cp*Rh(III)-catalyzed amination strategy for the synthesis of 2-acyl diarylamines **13a–p**, starting from acetophenone *O*-methyl oxime **12**, which constitutes various bioactive compounds (Scheme 7).[30] The protocol required $AgNTf_2$ salt and PivOH additive in DCE solvent at 85 °C for 24 h. A variety of desired products (**13a–13d**) could be furnished for electron-donating and electron-withdrawing substituted oximes. Halo-substituted substrates **13e** also resulted in the desired aminated products in good yield. The protocol could also tolerate cyclic oxime ethers **13f** and oxime ethers derived from diaryl ketones **13g** or phenyl alkyl ketones **13h**. Notably, halo-substituted anthranils (**13i** and **13j**) could also furnish unprotected 2-acyl diarylamine derivatives with moderate yields. Also, N-heterocycles (**13l–13p**) such as quinoline,



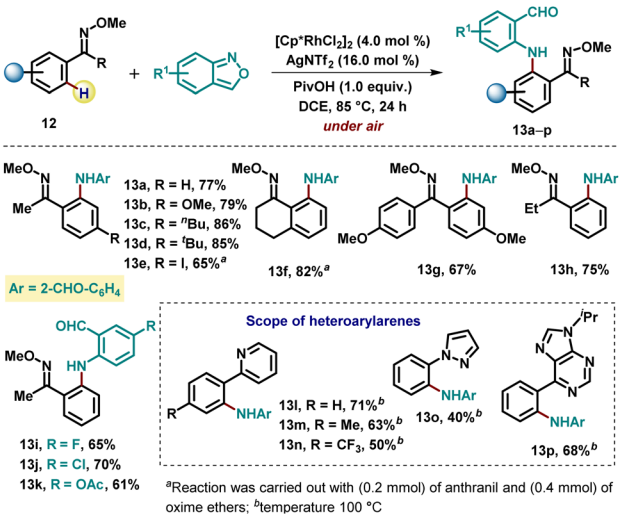
Scheme 4 Cp*Rh(III)-catalyzed C–H amination/annulation of indoles and 2-pyridones with anthranils (ref. 28).



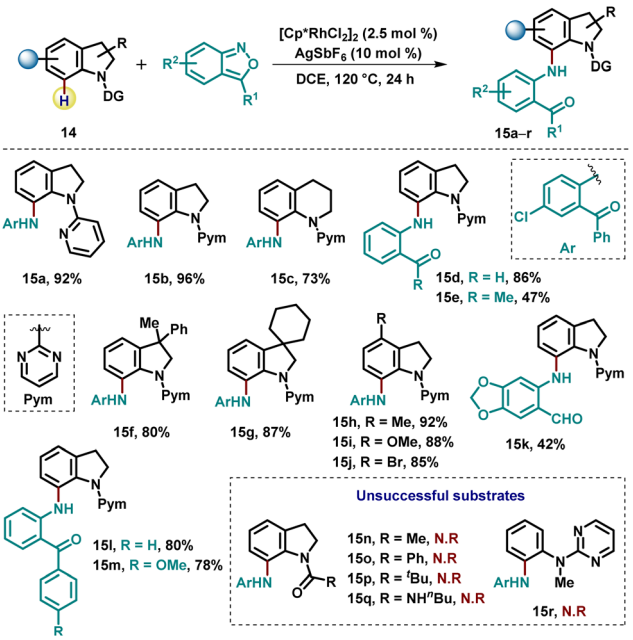
Scheme 5 Cp*Rh(III)-catalyzed C–H amination of 8-methylquinoline with anthranils (ref. 29).



Scheme 6 Proposed mechanism for Cp*Rh(III)-catalyzed C–H amination of 8-methylquinoline with anthranils.



Scheme 7 Cp*Rh(III)-catalyzed C–H amination of acetophenone *O*-methyl oxime with anthranils (ref. 30).



Scheme 8 Cp*Rh(III)-catalyzed C–H amination at the C7 position of indolines with anthranils (ref. 31).

pyridine, purine, and pyrazole could also be used as the directing groups for the amination reaction.

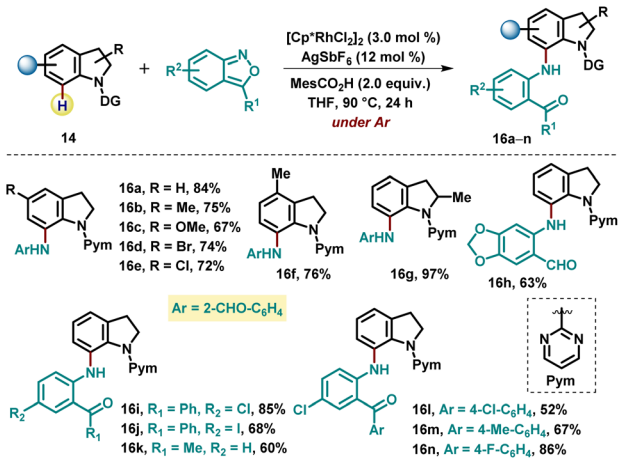
Furthermore, the group also demonstrated the synthesis of polycyclic aza-aromatic compounds by the reaction of the aminated product(s) with ethyl diazoacetate or using $In(OTf)_3$ catalysis, *etc*.

In 2017, Kim and co-workers reported Cp*Rh(III)-catalyzed direct amination of indolines **14** at the C7 position with anthranils as an aminating agent (Scheme 8).[31] The protocol required $AgSbF_6$ additive in DCE solvent at 120 °C for 24 h. This amination strategy was highly specific with pyridine **15a** or pyrimidine (**15b** and **15c**) as the directing group, as the strategy failed with other carbonyl (**15n–15p**) or carbamoyl directing groups **15q**. A wide range of C2-, C3-, C4-, and C5-substituted indolines furnished the desired product in good to excellent yields; however, only a low yield was found for fluoro-substituted indoline at the C6-position. Interestingly, the amination strategy worked for tetrahydroquinoline **15c** but failed for *N*-methyl aniline **15r**. The anthranil scope was found to be diverse, with substituted aryl rings at the C3-position (**15d** and **15e**) furnishing desired products in high yields. Moderate-to-good yields were also found for C5- and C6-substituted anthranils. Notably, the unsubstituted anthranil furnished 2-formyl aniline derivatives **15k** in good yield.

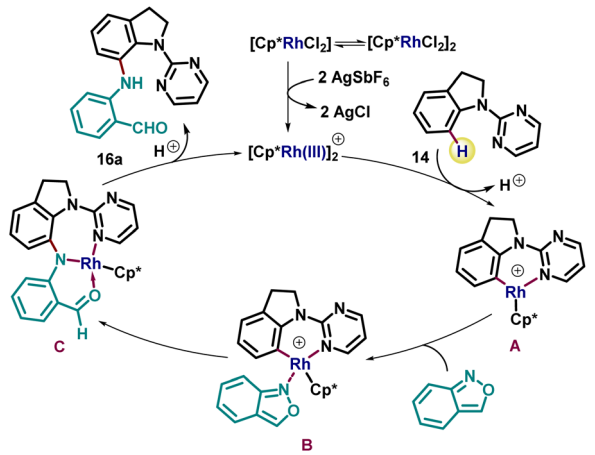
During the same period, Xu and Yang also reported a similar Cp*Rh(III)-catalyzed direct amination of indolines **14** at the C7 position with anthranils as an aminating agent (Scheme 9).[32]

The protocol required $AgSbF_6$ salt and $MesCO_2H$ additive in THF solvent at 90 °C for 24 h. The substrate scope and coupling partner scope are very broad. Halo-substituted indolines furnished the desired products (**16d** and **16e**) in moderate yields. Methyl-substituted C2-, C3-, C4-, and C5-indolines also furnished the desired product. A low yield was found for $-NO_2$-substituted indolines at the C5-position. Similarly, halo-substituted anthranils also furnished the desired product (**16i–16n**) in good yield. The group also demonstrated the amination of 9-(pyrimidin-2-yl)-9*H*-carbazole, which has a similar structural motif to indoline; only a mono-aminated product was found for the carbazole derivative in low yield. The protocol fails with an acetyl-directing group.

The catalytic cycle (Scheme 10) was proposed to begin with the formation of a cationic Rh(III) species. Then it reacted with the indoline **14** to form a six-membered rhodacycle intermediate **A**, followed by the formation of anthranil-coordinated intermediate **B**. After this, intermediate **C** was formed by the



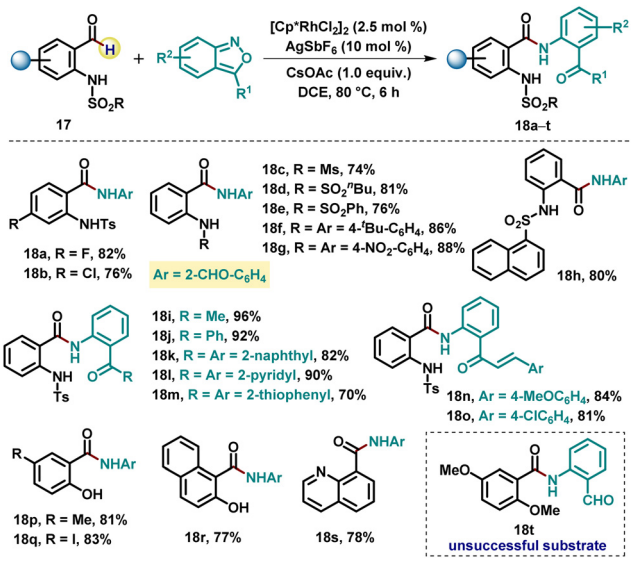
Scheme 9 Cp*Rh(III)-catalyzed C7 amination of indolines with anthranils (ref. 32).



Scheme 10 Proposed mechanism for Cp*Rh(III)-catalyzed C–H amination at the C7 position of indolines with anthranils.

migratory insertion of anthranil into the Rh–C bond, followed by the cleavage of the N–O bond of anthranil. Finally, protonolysis resulted in the formation of the product **16a**, along with the regeneration of the Cp*Rh(III) catalyst.

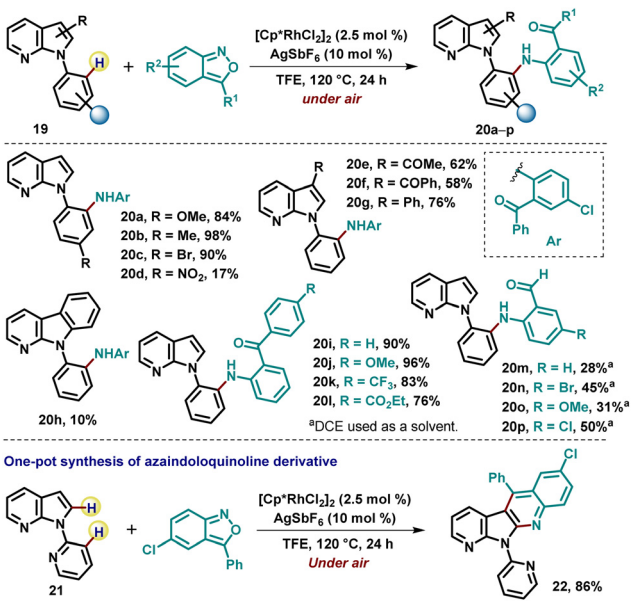
In 2017, Maji and co-workers reported a Cp*Rh(III)-catalyzed C–H amination of *N*-sulfonyl-2-aminobenzaldehyde **17** using anthranils as an aminating agent (Scheme 11).[33] The protocol required $AgSbF_6$ salt and CsOAc additive in DCE solvent at 80 °C for 6 h. The substrate scope was very broad, with halo-substituted substrates (**18a** and **18b**) furnishing desired products in good yield. Apart from aromatic sulfonyl chlorides, amine-protected aliphatic sulfonyl chlorides (**18c–18e**) also worked in this protocol. The substrate scope could be extended to other aryls (**18f** and **18g**) and heteroarenes **18h**. The reaction failed upon using other amine-protecting groups such as acetate, pivaloyl, or *t*-butoxycarbonyl. The protocol worked with anthranils containing alkyl **18i**, aryl (**18j** and **18k**), and alkenyl substituents (**18n** and **18o**) in good to excellent yields.



Scheme 11 Cp*Rh(III)-catalyzed C–H amination of *N*-sulfonyl-2-aminobenzaldehyde with anthranils (ref. 33).

Substituents such as pyridine **18l** and thiophene substituents **18m** on anthranils also furnished the desired product. Under the same conditions, the group also successfully demonstrated the C–H amination of 2-hydroxyarenecarbaldehydes (**18p–18r**) through *o*-hydroxy group assistance. Furthermore, the scope could also be extended to aldehydes containing quinoline units **18s**.

In 2017, Kim and Mishra reported a site-selective Cp*Rh (III)-catalyzed C–H amination of 7-azaindoles **19** to furnish pharmaceutically valuable heterocycles (Scheme 12).[34]



Scheme 12 Cp*Rh(III)-catalyzed C–H amination of 7-azaindoles with anthranils (ref. 34).

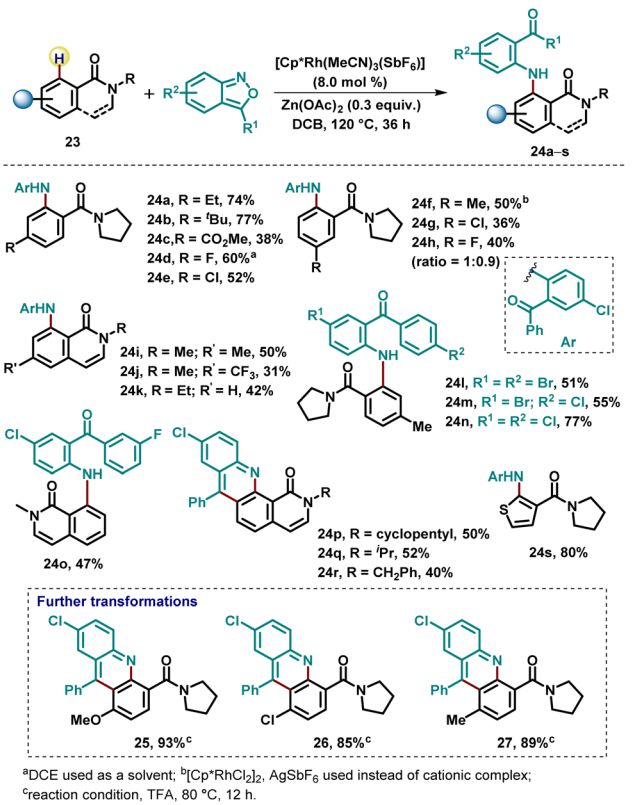
The protocol required $AgSbF_6$ additive in TFE solvent at 120 °C for 24 h. A wide range of electron-donating and electron-withdrawing groups on the *ortho*-substituted substrates furnished the desired product in good yield. A single regioisomer is obtained for *meta*-OMe-substituted substrate **20a**, which was further confirmed by ^1H–^1H TOCSY analysis. The reaction failed for sterically hindered substrates. The protocol also works with C3-substituted azaindoles (**20e–20g**) and *N*-aryl-α-carboline **20h**. The electron-donating substituents **20j** on anthranils furnished the desired product in a higher yield as compared to the electron-withdrawing ones (**20k** and **20l**). The protocol was also compatible with anthranil-containing pyridinyl and naphthyl groups. A low yield was observed for the unsubstituted and C3-substituted anthranils (**20m–20p**). To depict the site-selectivity of the protocol, the group demonstrated the synthesis of azaindoloquinoline derivatives **22** starting from *N*-pyridinyl azaindole **21**. The formation of a single product in high yield could be probably due to the bidentate chelation by the N-atoms on the pyridinyl group and 7-azaindole, resisting the formation of a simple five-membered rhodacycle.

In the same year, Li and Wang reported a Cp*Rh(III)-catalyzed amination/annulation strategy of arenes **23** with anthranils (Scheme 13).[35]

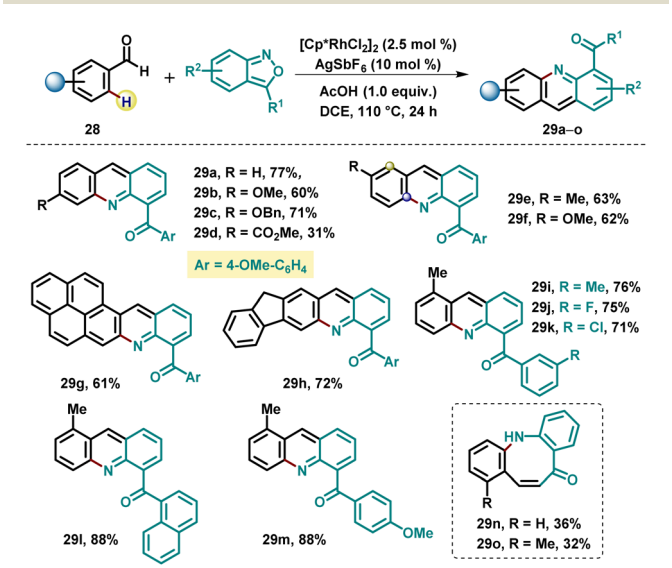
The protocol worked with *N*-benzoylpyrrolidines/isoquinolone derivatives in the presence of $Zn(OAc)_2$ additive in DCB solvent at 120 °C for 36 h. A wide range of *para*-substituted benzamides (**24a–24e**) furnished products in good yield. However, slightly lower yields were observed for the electron-withdrawing groups (**24c–24e**) at the *para*-position. The amination reaction was also feasible with *meta*-substituted substrates (**24f–24h**). However, a 2 : 1 regioisomeric ratio was found for *meta*-flouro-substituted benzamides **24h**, probably due to the secondary interactions. The substrate scope was further extended to heterocyclic amides such as that of thiophene **24s**. Upon changing the substrate to *N*-methyl **24o** or *N*-ethylisoquinolones, the amination took place at the C8 position. Interestingly, an amination–annulation reaction took place for *N*-cyclopentyl **24p**, *N*-isopropyl **24q**, and *N*-benzyl-substituted isoquinolones **24r**. The stark difference in product formation is due to the steric and electronic effects of the substituted N-atom. A strong electron-donating substituent on the N-atom furnished fused acridines (**24p–24r**) *via* cyclization. The protocol worked with a variety of anthranils with both *N*-benzoylpyrrolidines and isoquinolone derivatives. The presence of a free halogen-atom was beneficial for further transformation (**25–27**).

In 2018, Kim *et al.* reported a cationic Rh(III)-catalyzed coupling of benzaldehydes **28** with anthranils to furnish 2-acyl acridines **29a–o** (Scheme 14).[36] The protocol required $AgSbF_6$ salt with AcOH additive in DCE solvent at 110 °C for 24 h and utilized anthranils as both an aminating agent and a transient directing group. *para*-Substituted benzaldehydes (**29a–29d**) furnished the desired products in good yield. The structure of 2-acyl acridine was confirmed by X-ray crystallography. However, the lower yield of 4-carbomethoxybenzaldehydes in this protocol could be because of the ineffective *ortho*-bond activation owing to its electron-withdrawing nature.

The substrate scope was further extended to highly conjugated benzaldehydes **29g** and fluorene-2-carboxaldehyde **29h**.



Scheme 13 Cp*Rh(III)-catalyzed C–H amination/annulation of weakly coordinating amides with anthranils (ref. 35).

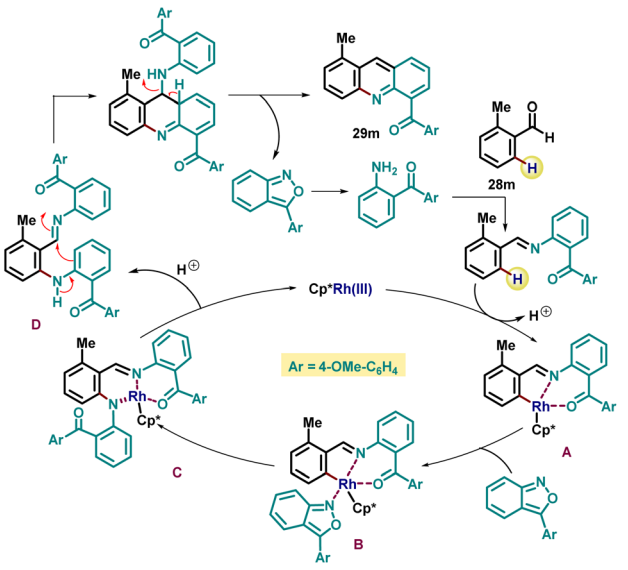


Scheme 14 Cp*Rh(III)-catalyzed C–H amination/annulation of benzaldehydes with anthranils (ref. 36).

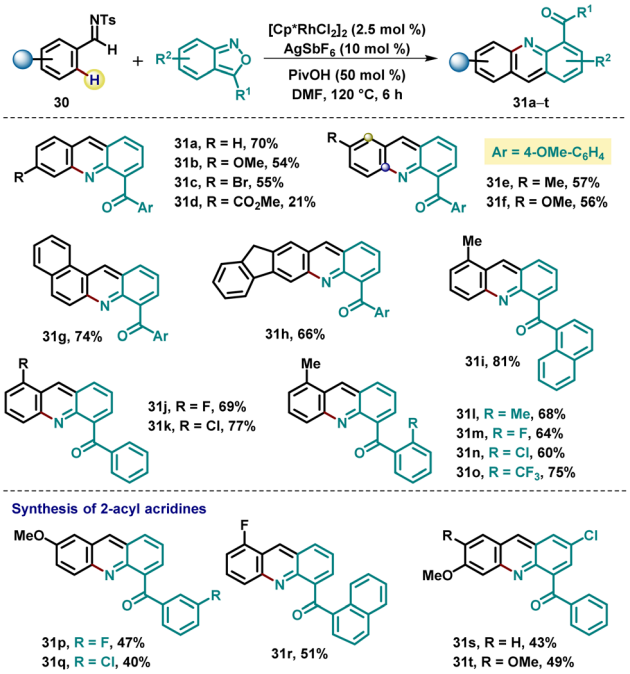
The vast coupling scope of anthranils was examined with *o*-tolualdehyde. C3-substituted anthranils (**29i–29k**) readily furnished the desired products in good yield. Notably, 6-chloro-3-phenylbenzo[*c*]isoxazole could be efficiently utilized as a coupling partner in this strategy. The group also reported the synthesis of dibenzoazocinones (**29n** and **29o**), starting from *ortho*-substituted benzaldehydes and C3-methyl-substituted anthranils under the same conditions. The formation of an 8-membered ring rather than 2-acetyl acridines could be explained by the intramolecular aldol condensation between the aldehyde group and the free acetyl group of the aminated product.

The catalytic cycle (Scheme 15) began with the formation of aldimine from aldehyde **28m** and 2-benzoylaniline under acidic conditions. Then, a 5-membered rhodacycle intermediate **A** was formed upon C–H activation. Furthermore, the coordination of the N-atom of the anthranil with the rhodium center furnished intermediate **B**. A migratory insertion furnished intermediate **C**, which, upon protonolysis, gave the active catalyst back with intermediate **D**. Finally, the intramolecular electrophilic cyclization followed by rearomatization furnished 2-acyl acridine **29m** as the product with 2-benzoylaniline, which continued the catalytic cycle.

In 2018, Ku and Kim reported a similar strategy for the synthesis of 2-acyl acridines **31a–t** *via* Cp*Rh(III)-catalyzed coupling of aldimines **30** with anthranils (Scheme 16).[37] The protocol required $AgSbF_6$ salt with PivOH additive in DMF solvent at 120 °C for 6 h. *para*- (**31a–31d**), *meta*- (**31e** and **31f**), and *ortho*-substituted aldimines (**31j** and **31k**) furnished products in good yield. However, the less sterically hindered product was furnished for *meta*-substituted aldimines. The reaction could also tolerate highly conjugated **31g** and fused polycyclic aldimines **31h**. The coupling partner scope was broad. A variety of substituted and highly conjugated anthranils (**31l–31o**) could



Scheme 15 Proposed mechanism for Cp*Rh(III)-catalyzed C–H amination/annulation of benzaldehydes with anthranils.



Scheme 16 Cp*Rh(III)-catalyzed C–H amination/annulation of aldimines with anthranils (ref. 37).

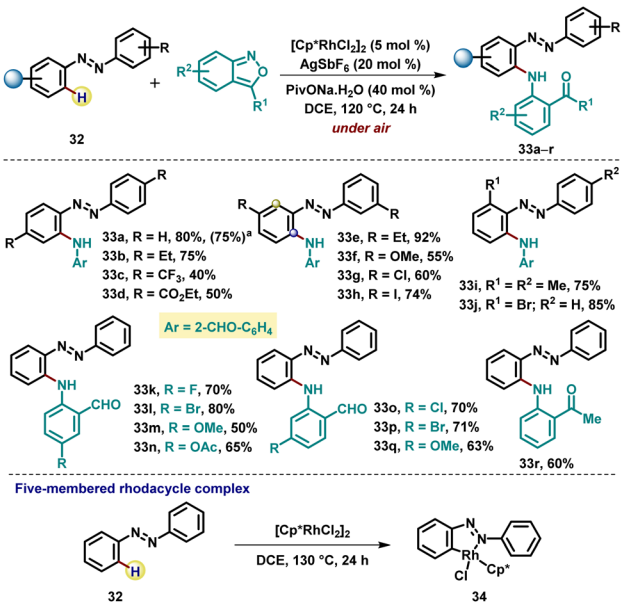
be utilized in this strategy. Many of the synthesized compounds were successfully screened for their anti-cancer activity.

In the same year, Zhou *et al.* reported a Cp*Rh(III)-catalyzed amination strategy of azobenzenes **32** with anthranils as an aminating agent (Scheme 17).[38]

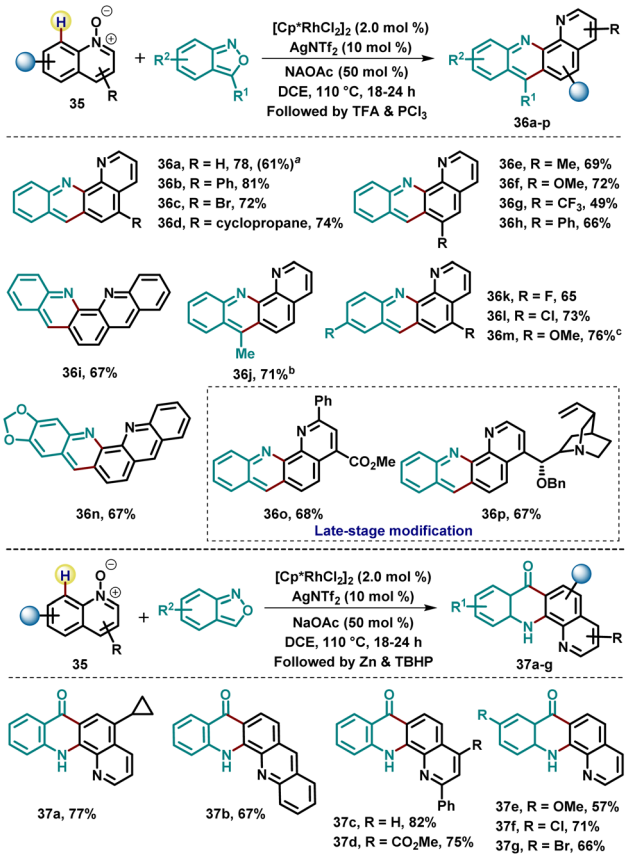
The protocol required $AgSbF_6$ salt with PivOH additive in DCE solvent at 120 °C for 24 h. The substrate scope was broad, and the protocol was highly compatible with *para*- (**33a–33d**), *meta*- (**33e–33h**), and *ortho*-substituted substrates (**33i** and **33j**). A variety of substituted anthranils (**33k–33q**) were also compatible with this protocol. Interestingly, the group could also isolate the five-membered rhodacycle **34** under the standard reaction conditions.

In 2019, Samanta *et al.* illustrated the development of an economically novel methodology for the synthesis of benzophenanthroline derivatives **36a–p** *via* Cp*Rh(III)-catalyzed aryl amination followed by annulation (Scheme 18).[39] Commercially available starting materials, such as quinoline *N*-oxide and anthranils, were used. The protocol required $AgNTf_2$ salt with NaOAc additive in DCE solvent at 110 °C for 24 h. However, TFA and PCl_3 were used to enhance the yield of the reaction. The substrate scope (**36a–36h**) revealed that electron-donating, electron-withdrawing, and halo-substituted quinoline *N*-oxide, furnished products in moderate-to-good yields. The substituted anthranils gave a better yield compared to the unsubstituted ones. Furthermore, the group also demonstrated the synthesis of benzophenanthrolinone **37a–g** under standard reaction conditions.

However, rather than TFA and PCl_3, Zn and TBHP were used to promote deoxygenation, followed by oxidative coup-



Scheme 17 Cp*Rh(III)-catalyzed C–H amination/annulation of azobenzenes with anthranils (ref. 38).



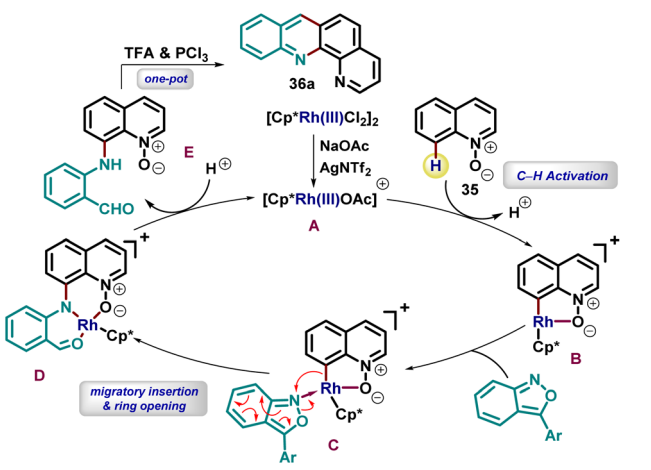
Scheme 18 Cp*Rh(III)-catalyzed C–H amination/annulation of quinoline *N*-oxide with anthranils (ref. 39).

ling. Late-stage functionalization (**36o** and **36p**) was also carried out on more complex bioactive scaffolds.

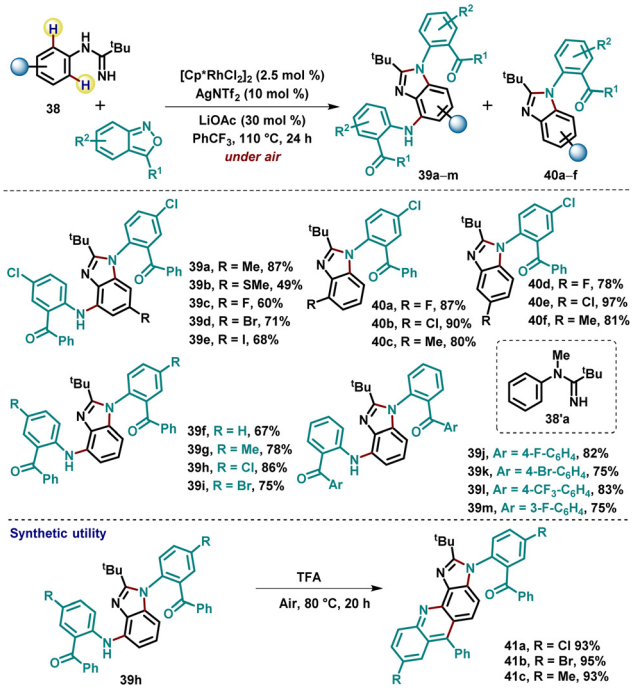
The plausible mechanism (Scheme 19) began with the formation of active catalytic species **A**, which, upon C–H activation, furnished five-membered rhodacycle intermediate **B**. Next, the coordination of anthranil *via* its N-atom with the metal center furnished intermediate **C**. A ring-opening process, followed by metal-nitrenoid insertion into the Rh–C bond, furnished intermediate **D**, which, on protodemetallation, furnished the annulated product **E** and regenerated the active catalytic species. In one case, TFA-assisted annulation followed by PCl_3-assisted deoxygenation led to the formation of benzophenanthroline **36a**, whereas in the other case, Zn-mediated deoxygenation, followed by TBHP-assisted oxidative coupling, led to the formation of benzophenanthrolinone **37**.

In 2019, Cui and co-workers reported the synthesis of benzimidazoles *via* a Cp*Rh(III)-catalyzed C–H amination/annulation of *N*-phenylpivalimidamide **38** with anthranils as both an aminating agent and an internal oxidant (Scheme 20).[40] The protocol required $AgNTf_2$ salt with LiOAc additive in trifluorotoluene solvent at 110 °C for 24 h. A variety of substituted *N*-arylimidamide and anthranils were compatible with this protocol, including **39a–m** and **40a–f**. From the mechanistic study, it was revealed that *N*-methyl-*N*-phenylpivalimidamide could not yield the desired product **38′a**, suggesting that the amine group of *N*-phenylpivalimidamide might assist the C–H amination process. Furthermore, the authors also conducted synthetic utility and photo-physical studies that revealed dual fluorescence spectra for substituted benzimidazole products, which could be used in biosensors and OLEDs **41a–c**.

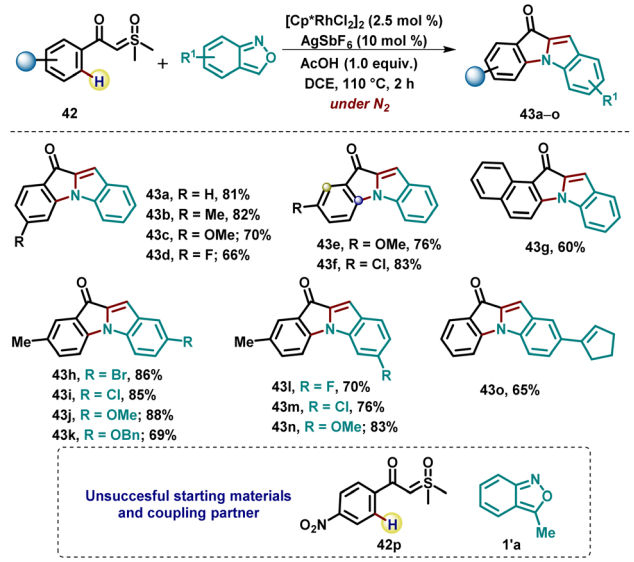
In the same year, Cheng and co-workers reported a Cp*Rh(III)-catalyzed synthesis of indoloindolones **43a–o**, starting from aroyl sulfoxonium ylides **42** and anthranils *via ortho* C–H amination/annulation (Scheme 21).[41] The protocol required $AgSbF_6$ salt with AcOH additive in DCE solvent at 110 °C for 2 h under inert conditions. Most substrates smoothly furn-



Scheme 19 Proposed mechanism for Cp*Rh(III)-catalyzed C–H amination/annulation of quinoline *N*-oxide with anthranils.



Scheme 20 Cp*Rh(III)-catalyzed C–H amination/annulation of *N*-phenylpivalimidamide with anthranils (ref. 40).



Scheme 21 Cp*Rh(III)-catalyzed C–H amination/annulation of aroyl sulfoxonium ylides with anthranils (ref. 41).

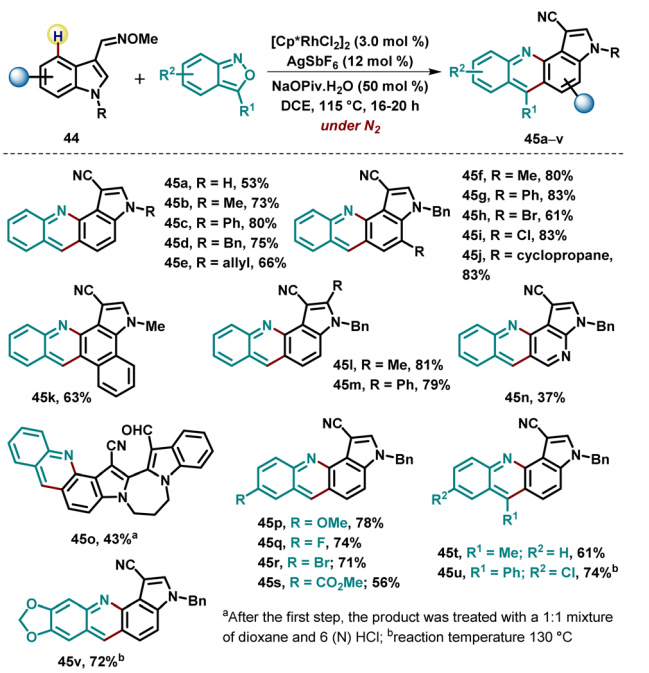
ished the desired product (**43a–43g**) in moderate-to-good yields.

A variety of halo-substituted anthranils (**43h–43i** and **43l–43m**) were compatible in this protocol. Anthranils substituted with protected hydroxy (**43j** and **43k**) and unsaturated functional groups **43o** also furnished the desired products in good yield.

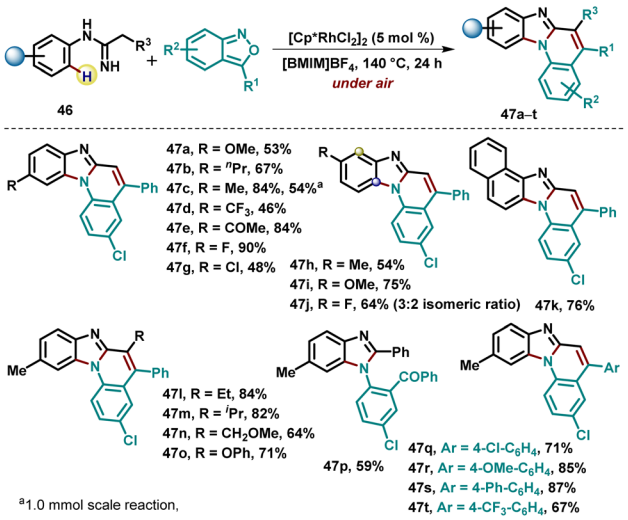
Furthermore, the X-ray crystallography results demonstrated that the carbonyl group in the final product was derived from the sulfoxonium ylide rather than anthranils.

In 2019, another report from Samanta and co-workers demonstrated the synthesis of indoloquinoline derivatives **45a–v** *via* Cp*Rh(III)-catalyzed C4-arylamination/annulation of indole derivatives **44** (Scheme 22).[42] The protocol required $AgSbF_6$ salt with PivOH additive in DCE solvent at 115 °C for 16–20 h under a nitrogen atmosphere. The protocol could furnish a variety of indoloquinolines from substituted anthranils and different derivatives of indoles. A wide range of indoles, irrespective of substituents in either of the rings (**45a–45n**), could be tolerated in this protocol. The reactions with bis-indole aldoximines **45o** furnished mono-annulated products. Phenyl and halo-substituted anthranils **45u** furnished the desired product in good yield. Electron-withdrawing substituents on the anthranil (**45q–45s**) could also be tolerated in this protocol. A controlled study revealed that azacycle was crucial in the formation of cyano functionality. Lastly, the group also studied the photophysical properties of the synthesized indoloquinoline moieties.

During the same period, Wu and co-workers reported Cp*Rh(III)-catalyzed C4-arylamination/annulation of imidamides **46** for the synthesis of benzimidazo[1,2-*a*]quinolines **47a–t** (Scheme 23).[43] The protocol did not require any additives. 1-Butyl-3-methylimidazolium tetrafluoroborate solvent was used at 140 °C for 24 h. A wide range of *N*-arylimidamides, irrespective of the distinct substituents present on the phenyl ring (**47a–47k**), could be tolerated in this protocol. However, only a corresponding benzimidazole was found when employ-



Scheme 22 Cp*Rh(III)-catalyzed C4-arylamination/annulation of indole aldoximines with anthranils (ref. 42).



Scheme 23 Cp*Rh(III)-catalyzed C–H amination/annulation of imidamides with anthranils (ref. 43).

ing *N*-(*p*-tolyl)benzimidamide as a substrate. This could probably be due to the unavailability of the α-H atom of the imine groups, accounting for no intramolecular Knoevenegal condensation. Similarly, various substituted anthranils (**47p–47t**) also furnished the desired products with good yield.

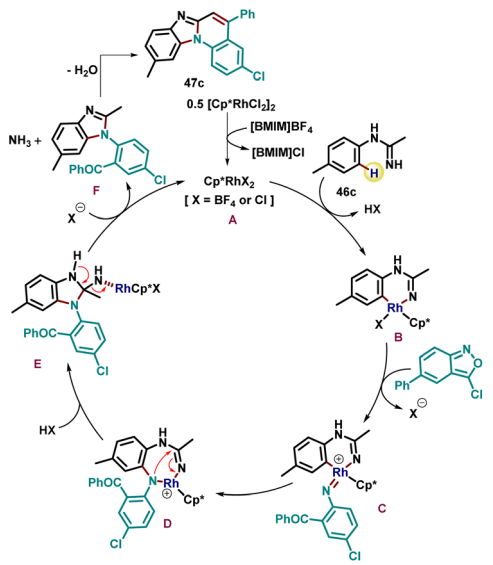
The proposed catalytic cycle (Scheme 24) began with the formation of active rhodium species **A** *via* the [BMIM] BF_4-assisted anion-exchange step from the commercially available Cp*Rh(III)-catalyst.

The *ortho* C–H bond activation furnished the six-membered rhodacycle intermediate **B**. Next, the anthranil coordinated with the rhodium center and formed nitrene species **C**. The insertion of nitrene into the Rh–C bond gave intermediate **D**. Further migratory insertion of the Rh–N bond into the C=N bond gave amido intermediate **E**. Subsequently, the loss of an ammonia molecule generated the active catalyst back with intermediate **F**, which furnished the fused product **47c** *via* an intramolecular Knoevenagel condensation.

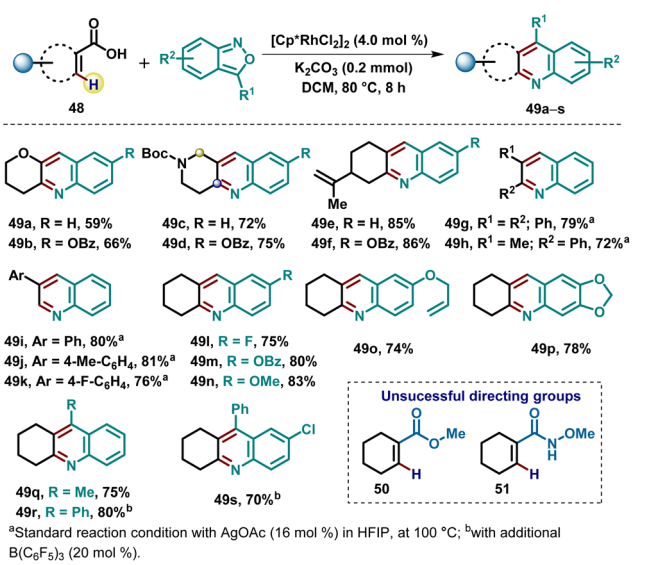
In 2020, Gao *et al.* reported a Cp*Rh(III)-catalyzed synthesis of polysubstituted quinolines **49a–s** *via* C–H amination/annulation of acrylic acids **48** with anthranils as an aminating agent (Scheme 25).[44] The protocol utilized carboxylic acid as a weakly coordinating directing group, which could be easily removed *in situ* for cyclization.

The protocol required K_2CO_3 salt in DCM solvent at 80 °C for 8 h. However, in some cases, AgOAc as an additive in HFIP solvent at 100 °C for 8 h also served as a better reaction condition. Both cyclic (**49a–49f**) and acyclic acrylic acids (**49g–49k**) demonstrated compatibility under standard reaction conditions. Similarly, different substituted anthranil analogues (**49l–49r**) were well tolerated under the optimized reaction conditions. Moreover, the group also demonstrated the potential application of the protocol. The control experiments revealed the importance of the –COOH group since the reaction did not proceed with changing the directing group to the ester **50** or carboxamide group **51**.

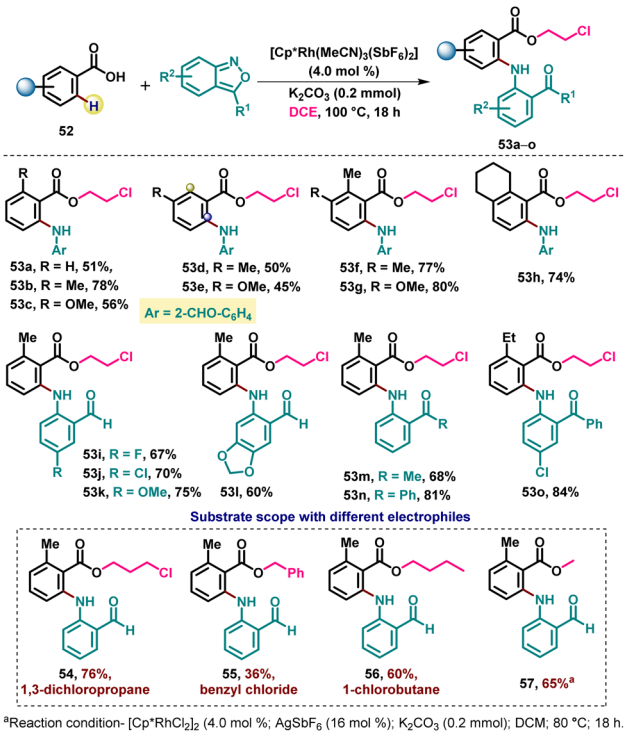
In 2020, the same group reported a Cp*Rh(III)-catalyzed C(sp^2)–H amination strategy for the synthesis of anthranilic acid derivatives **53a–o**, starting from the substituted benzoic acids **52** with anthranils (Scheme 26).[45] The protocol utilized a weakly coordinating carboxylic acid group as a directing group for *ortho* C–H amination. The protocol required [Cp*Rh$(MeCN)_3(SbF_6)_2]_2$ catalyst with K_2CO_3 salt in DCE solvent at 100 °C for 18 h. The product obtained was an esterification product due to the involvement of the solvent as an electrophile. A variety of desired products (**53a–53g**) could be



Scheme 24 Proposed mechanism for Cp*Rh(III)-catalyzed arylamination/annulation of imidamides with anthranils.



Scheme 25 Cp*Rh(III)-catalyzed C–H amination/annulation acrylic acids with anthranils (ref. 44).



[a]Reaction condition- $[Cp^*RhCl_2]_2$ (4.0 mol %; $AgSbF_6$ (16 mol %); K_2CO_3 (0.2 mmol); DCM; 80 °C; 18 h.

Scheme 26 Cp*Rh(III)-catalyzed C–H amination of benzoic acid with anthranils (ref. 45).

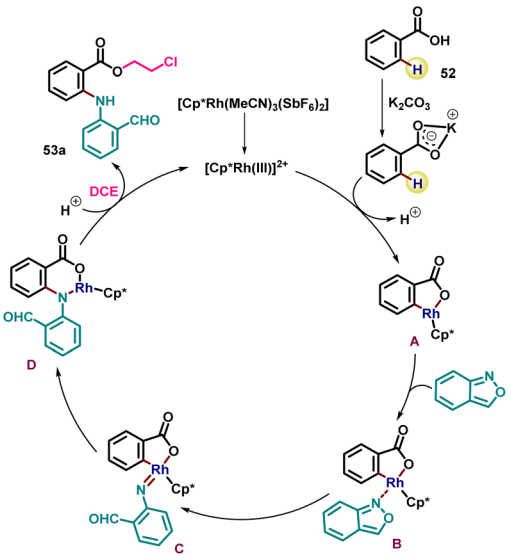
obtained for the electron-donating and electron-withdrawing substituted benzoic acids.

Halo-substituted (**53i** and **53j**) and fused substrates **53h** also furnished the desired aminated products in moderate-to-high yield.

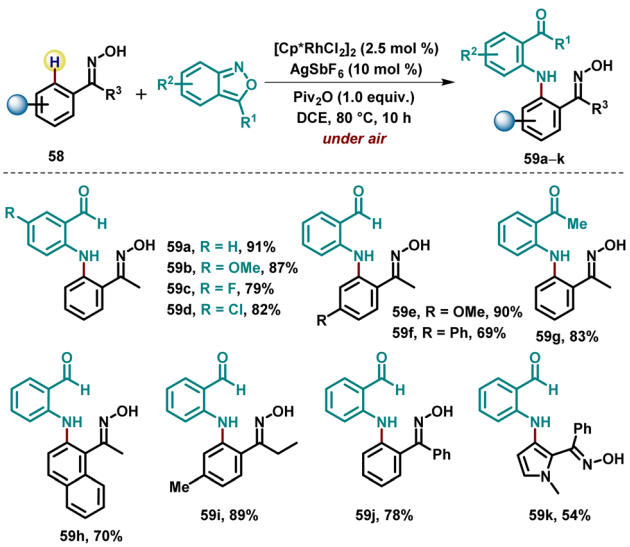
However, the protocol failed for heterocyclic carboxylic acids. Interestingly, this three-component strategy for C–H amination was also applicable to the different electrophiles (**54–57**). Furthermore, the group also demonstrated the synthetic utility of the synthesized moieties. The reaction mechanism followed a concerted pathway: first C–H amination then electrophilic substitution occurred.

The proposed catalytic cycle (Scheme 27) began with the reaction of potassium-benzoate with Cp*Rh(III) catalyst to form the five-membered rhodacycle species **A** through *ortho*-selective C–H metalation. Next, the anthranil-coordinated intermediate **B** was formed. After this, rhodium nitrenoid intermediate **C** was formed by the cleavage of the N–O bond of anthranil. Lastly, the insertion of the nitrogen atom of anthranil into the Rh–C bond furnished intermediate **D**. Protonolysis resulted in the regeneration of the active Cp*Rh(III) catalyst, along with the formation of the final product **53a**, through electrophilic substitution.

In 2021, Wu *et al.* reported a Cp*Rh(III)-catalyzed *ortho* C–H amination of ketoximes **58** with anthranils as an aminating agent. The protocol required $AgSbF_6$ salt with Piv_2O promoter in DCE solvent at 80 °C for 10 h (Scheme 28).[46] The protocol could tolerate a wide range of substituted ketoximes (**59e–59j**).



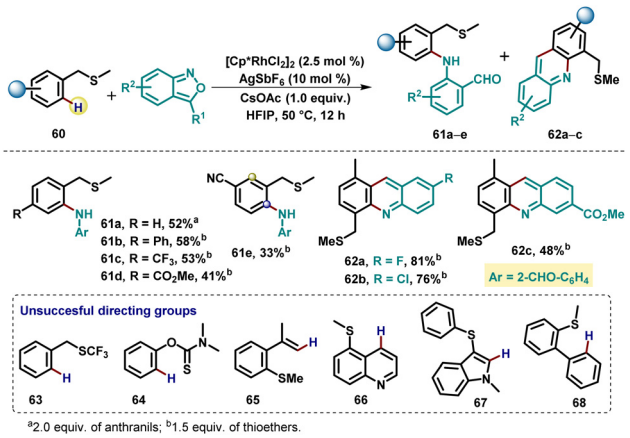
Scheme 27 Proposed mechanism for Cp*Rh(III)-catalyzed C–H amination of benzoic acid with anthranils.



Scheme 28 Cp*Rh(III)-catalyzed C–H amination of ketoximes with anthranils (ref. 46).

Pyrole-containing oximes **59k** also furnished the desired product in good yield. The scope of anthranil in this protocol was vast (**59a–59d**). Apart from halo-substituted anthranils, dioxolane-fused anthranils were also tolerated in this protocol.

In 2021, Zhang *et al.* reported a unique amination strategy of arenes **60** using anthranils as an aminating agent *via* Cp*Rh (III) catalysis (Scheme 29).[47] The uniqueness of the protocol lies in the utilization of the thioether group as the directing group. The protocol required $AgSbF_6$ salt with CsOAc additive in HFIP solvent at 50 °C for 12 h. *para*-Substituted arenes (**61a–61d**) furnished the desired product in good yield; however, the reaction was sluggish for electron-withdrawing



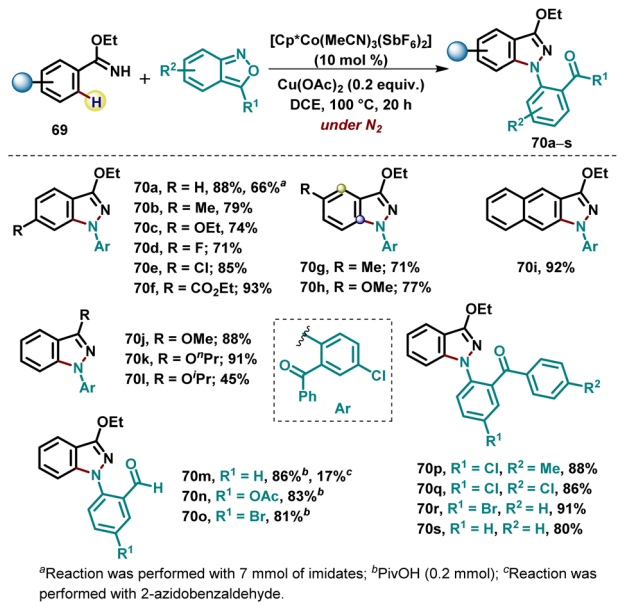
a2.0 equiv. of anthranils; b1.5 equiv. of thioethers.

Scheme 29 Cp*Rh(III)-catalyzed C–H amination of arene with anthranils using thioether as a directing group (ref. 47).

substituents (**61c** and **61d**). Less sterically hindered products **61e** were obtained for *meta*-substituted substrates. Interestingly, amination followed by annulation to furnish acridines was observed for *para*-methyl-substituted substrates. A variety of anthranils (**62a–62c**) could also be tolerated in this protocol. The group could also successfully identify certain unsuccessful thioether directing groups (**63–68**).

3.2. Cobalt catalysis

In 2016, Li *et al.* reported the synthesis of substituted 1H-indazoles **70a–s** from imidate esters **69** and anthranils as aminating agents as well as organic oxidants *via* a C–H activation pathway under a synergistic cobalt/copper-catalyzed system in the absence of a metal oxidant (Scheme 30).[48] The amination/



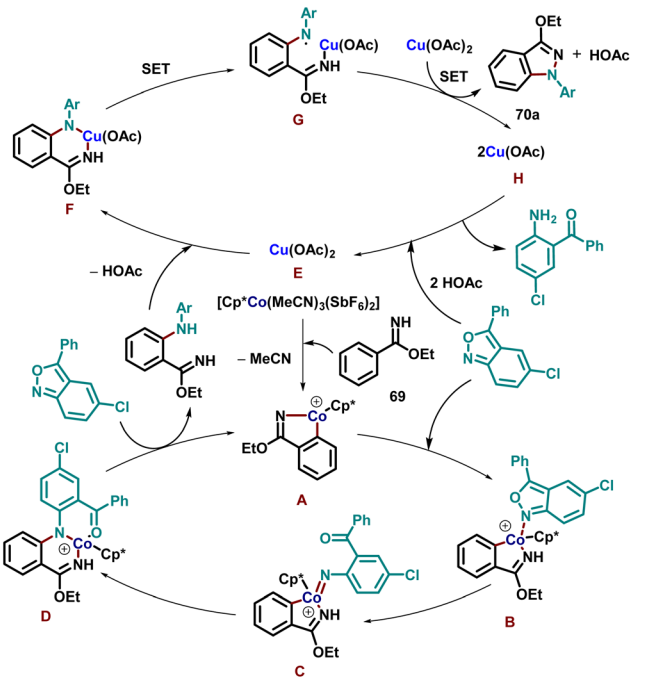
aReaction was performed with 7 mmol of imidates; bPivOH (0.2 mmol); cReaction was performed with 2-azidobenzaldehyde.

Scheme 30 Synergistic Co(III)/Cu(II)-catalyzed C–H amination of imidate esters with anthranils (ref. 48).

annulation of imidate esters furnished 1H-indazole derivatives by the $[Cp^*Co(MeCN)_3(SbF_6)_2]$ cationic complex with $Cu(OAc)_2$ in DCE solvent at 100 °C for 20 h. The *para*-substituted imidates bearing both electron-donating (**70a–70c**) and electron-withdrawing substituents (**70d–70f**) were coupled in excellent yield. For *meta*-substituted imidates (**70g** and **70h**), C–H activation took place at the less hindered position in moderate-to-good yields. Various 3-substituted anthranils (**70p–70s**) could also furnish the desired aminated product in good yields; however, the reaction was sluggish for non-substituted anthranils **70m**. The poor yields in amination with 2-azidobenzaldehyde **70m** justified the intrinsic reactivity of the anthranils. Based on control experiments, N–N bond formation was likely to be involved in the nitrogen-radical species.

The proposed mechanism (Scheme 31) operated with two simultaneous catalytic cycles. The cobalt-catalytic cycle began with the formation of cobaltacycle intermediate **A**. Next, the coordination of anthranil to the metal center generated intermediate **B**, which led to the formation of cobalt-nitrene intermediate **C**.

The migratory insertion of nitrene into the Co–C bond furnished intermediate **D**. The coordination of an imidate, followed by an activation step, furnished the mono-aminated product along with the generation of cobalt catalyst. The mono-aminated product underwent a sequential copper-catalytic cycle coordinated with the copper(II) catalyst **E** to generate intermediate **F**. Next, two simultaneous single electron transfer processes occurred that furnished the indazole product **70a** *via* the nitrogen-radical species **G**. Probably, the copper(I) system



Scheme 31 Proposed mechanism for synergistic Co(III)/Cu(II)-catalyzed C–H amination of imidate esters with anthranils.

H so produced was oxidized back to the copper(II) system by a molecule of anthranil.

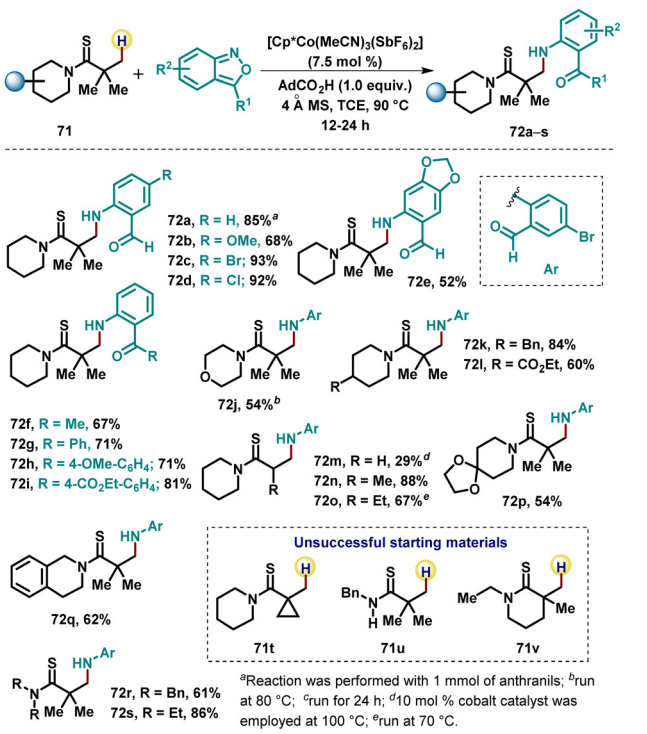
In 2019, Loh *et al.* developed the first Cp*Co(III)-catalyzed unactivated C(sp^3)–H amination of thioamides **71** using synthetically versatile bifunctional amino sources, anthranils, under redox-neutral conditions (Scheme 32).[49] Specifically, this strategy provided higher selectivity, even for the less reactive and more challenging primary and secondary alkyl thioamides. This protocol required $[Cp^*Co(MeCN)_3(SbF_6)_2]$ cationic complex with $AdCO_2H$ as an additive in TFE solvent at 90 °C for 12–24 h. A variety of substituted anthranils furnished the desired aminated product in good yields; however, electron-withdrawing coupling partners (**72c** and **72d**) were found to be more effective than the electron-donating ones (**72b**). In addition, 3-substituted anthranils provided expected products with a ketonic group (**72f–72i**). Subsequently, the scope of *N*-substituted thiopivalamide was not restricted to the piperidine derivatives; various other aza-cyclic-containing starting materials such as morpholine, pyrrolidine, piperazine, and azepane were productive directing groups for this transformation.

Similarly, all of them readily reacted with substituted anthranils to access desired products in moderate-to-good yields. Interestingly, challenging substrates (**72r** and **72s**) such as isopropyl and sec-butyl thioamides were applicable for this transformation, offering moderate yields. However, this protocol could not afford the aminated product in the cases of cyclopropane-thioamide **71t**, benzyl thioamide **71u**, and piperidine-2-thione **71v**. Studies suggested that the reaction probably involved an electrophilic-type cobaltation manifold.

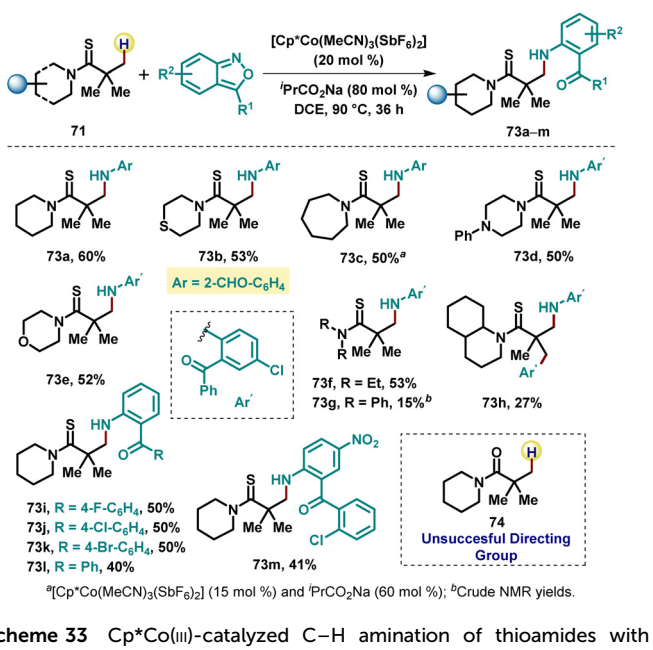
During the same period, Li and co-workers also reported a similar thioamide **71**-assisted Cp*Co(III)-catalyzed direct C(sp^3)–H amination using anthranils as an electrophilic aminating source (Scheme 33).[50]

The protocol required the $[Cp^*Co(MeCN)_3(SbF_6)_2]$ cationic complex with i-$PrCO_2Na$ as an additive in DCE solvent at 90 °C for 36 h. The substrate scope of thioamides and the coupling partner scope were very broad (**73a–73m**). Halo-substituted thioamides delivered the desired animo-ketones and aldehyde in moderate yields. Furthermore, heteroatom-containing five, seven-membered rings of thioamides obtained modest yields of the desired amino products **73b–73e**. A low yield was found by replacing the methyl with ethyl and phenyl groups (**73f** and **73g**). Similarly, halo-substituted anthranils also furnished the desired product in good yields (**73i–73k**). The protocol failed with an acetamide-directing group **74**.

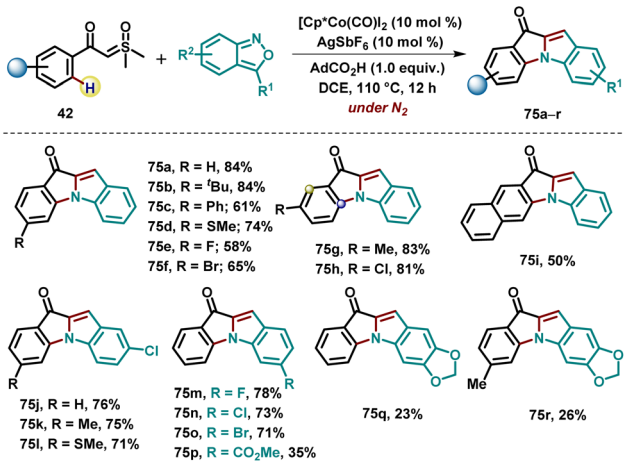
In 2021, Aher and Pawar reported the first example of Cp*Co(III)-catalyzed [4 + 1] C–H amination/annulation of aryl sulfoxonium ylides **42** with bifunctional anthranils, wherein the dual functionalities of anthranils, *viz.*, amine and aldehyde, were exploited for the synthesis of tetra-cyclic indoloindolone derivatives **75a–r** (Scheme 34).[51] The protocol required $AgSbF_6$ salt and $AdCO_2H$ additive in DCE solvent at 110 °C for 12 h. A wide range of substituents at the *para*-positions of the sulfoxonium ylide derivatives (**75a–75f**) could also furnish the product with good yields. Similarly, the halo-substituted sulfoxonium ylides (**75e** and **75f**) provided the desired products in moderate yields. In addition to this, C–H amination/annulation was observed to occur at the less hindered site, furnishing a single regioisomer of the desired product when the reactions



Scheme 32 Cp*Co(III)-catalyzed sp^3 C–H amination of thioamides with anthranils (ref. 49).



Scheme 33 Cp*Co(III)-catalyzed C–H amination of thioamides with anthranils (ref. 50).

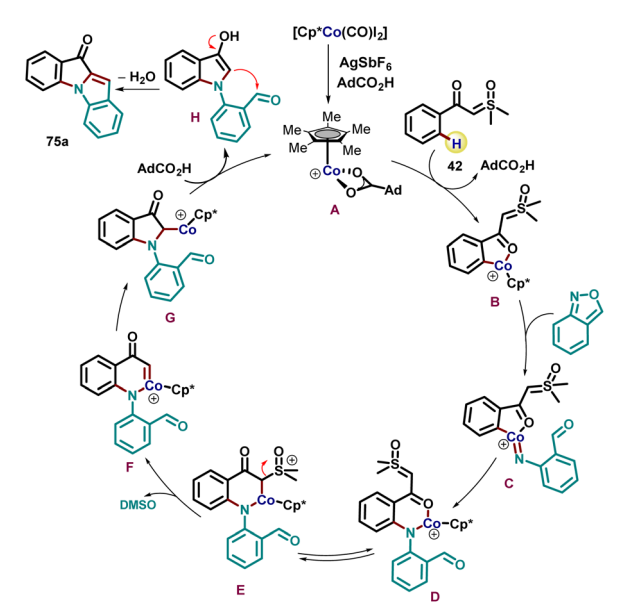


Scheme 34 Cp*Co(III)-catalyzed C–H amination/annulation of aryl sulfoxonium ylides with anthranils (ref. 51).

were performed with *meta*-substituted ylides (**75g** and **75h**). Additionally, site-selectivity was detected in a 2-naphthalene substrate **75i** in moderate yield. A variety of desired products (**75m**–**75p**) could be furnished for electron-donating and electron-withdrawing substituted anthranils. However, a lower yield was obtained for piperonal substituted anthranils (**75q** and **75r**).

The catalytic cycle (Scheme 35) began with the generation of cationic Co(III) species **A**, which underwent activation to form a five-membered cobaltacycle **B**.

The insertion of anthranil in species **B** generated the cobalt-nitrene intermediate **C**. Next, species **D** and **E** were formed by the migratory insertion of anthranil into the Co–C bond. The cobalt carbene species **F** was formed by the release of DMSO from intermediate **E**. After this, the insertion of the N-atom of anthranil in the cobalt-carbene generated the five-membered intermediate **G**, which, on protodemetalation, generated intermediate **H**, along with the regeneration of the active catalyst. Lastly, an intermolecular aldol condensation furnished the required product **75a**.

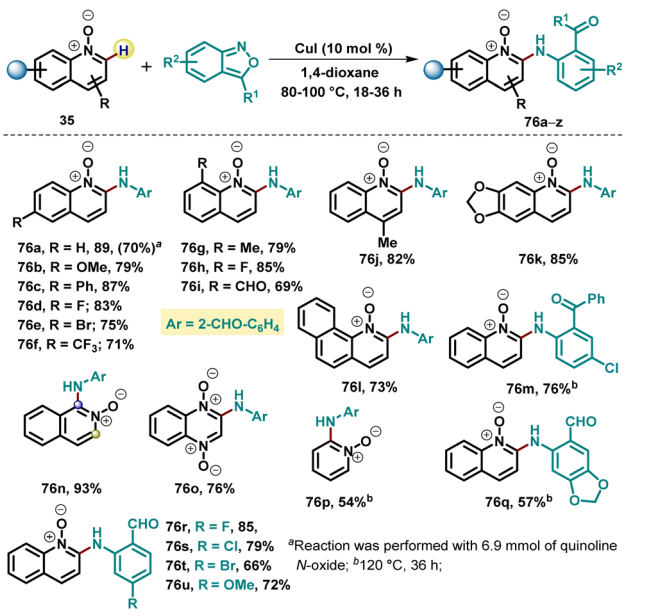


Scheme 35 Proposed mechanism for Cp*Co(III)-catalyzed C–H amination/annulation of aryl sulfoxonium ylides with anthranils.

3.3. Copper catalysis

In 2017, Samanta *et al.* reported a Cu(I)-catalyzed direct aryl amination of various heterocyclic *N*-oxide **35** *via* cross-coupling reactions with anthranils under redox-neutral conditions to furnish a regioselective product **76a–z** (Scheme 36).[52] The protocol required Cu(I) catalyst without any additives in the 1,4-dioxane solvent at 80–100 °C for 18–36 h. In general, a wide range of electron-donating and electron-withdrawing substituents at different positions of the *N*-oxides (**76a–76k**) were well tolerated. Similarly, the alkyl and halo-substituted *N*-oxides at the C6 position gave the desired product an excellent yield. In addition to this, the sensitive acetal group **76k** was cleaved during the operation to provide the corresponding product-bearing double aldehyde groups. Next, the scope of polyaromatic hydrocarbons such as benzo[*h*]quinoline **76l** and other isomeric heterocycles, *i.e.*, isoquinoline **76n**, pyridine **76p**, and quinoxaline-*N*-oxide **76o**, were also afforded in moderate-to-good yields with high regioselectivity. Subsequently, the substituted anthranils (**76q–76u**) bearing electronic and steric features also afforded the desired product in moderate yields.

Furthermore, the group also demonstrated the post-synthetic modification of the synthesized moieties. Notably, without the *N*-oxides, the decomposition of anthranil was observed with the use of only a stoichiometric amount of



Scheme 36 Cu(I)-catalyzed C–H amination of heterocyclic *N*-oxide with anthranils (ref. 52).

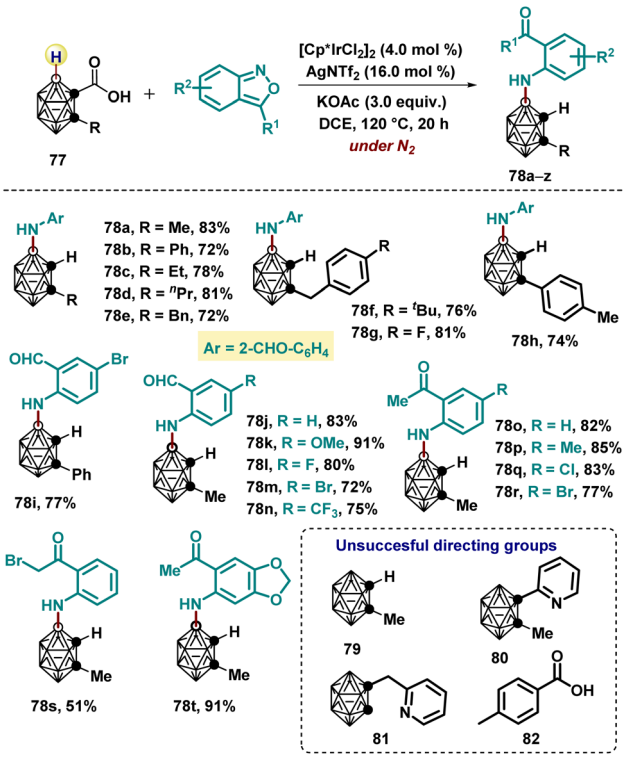
Cu(I). Apart from anthranils, a simple aniline did not deliver an isolable C2-arylaminated product.

The catalytic cycle began (Scheme 37) with Cu(I) coordinating with the nitrogen atom of anthranil to form intermediate **A**. Next, migration of the metal center followed by the dissociation of the N–O bond led to the formation of a copper-nitrenoid intermediate **B**. Subsequently, the migratory insertion of nitrenoid into the Cu(III)–C bond formed species **C**. Lastly, protodemetalation of **D** furnished the desired product **76a** along with the regeneration of the Cu(I) catalyst.

3.4. Iridium catalysis

Apart from C–H functionalization, the scientific community has often shown high intent towards B–H functionalization.[53] The most commonly targeted molecules in this plethora have been the boron–carbon cages, specifically *o*-carboranes, due to their wide applications in radiochemistry, coordinate chemistry, and medicinal chemistry. The functionalization of the boron atoms in the boron–carbon cage structures, such as those in *o*-carboranes, is often very challenging, as compared to the carbon atoms. In this section, we have summarized the sole example of the formation of a B–N bond with anthranils.

In 2022, Zhang and Xie reported oxidant-free Cp*Ir(III)-catalyzed selective B(4)–H amination of *ortho*-carboranes **77** with anthranils as an aminating agent under mild reaction conditions (Scheme 38).[54] In this protocol, carbonyl groups played a crucial role in determining regioselectivity as well as serving as a traceless directing group. The protocol required $AgNTf_2$ and KOAc additives in DCE solvent at 120 °C for 20 h under a nitrogen atmosphere. The substrate scope for anthranils was very broad and tolerated various functional groups (**78a–78e**). Halo, electron-donating, and electron-withdrawing at different positions of anthranils (**78j–78t**) furnished the desired products in medium to high yields. Similarly, different substituted C2-benzylated o-carboranyl acid analogues (**78f–78i**) were well tolerated under the optimized reaction conditions. The control experiment revealed the importance of the COOH group, as the reaction did not proceed when the COOH group of C2-benzylated o-carboranyl acids was replaced by pyridine **80**, benzoic acid **82**, or without the COOH group (**79** and **81**).

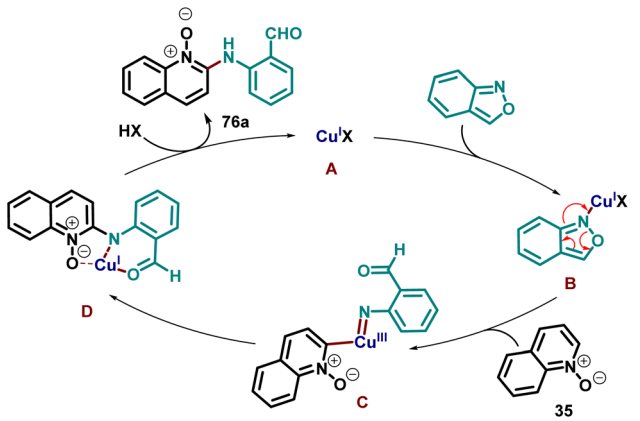


Scheme 38 Cp*Ir(III)-catalyzed selective B(4)–H amination of *o*-carboranes with anthranils (ref. 53).

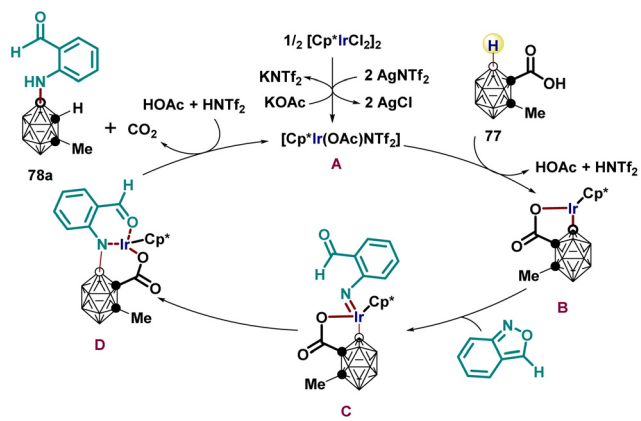
The authors proposed the catalytic cycle (Scheme 39) to begin with the formation of active Ir(III) species (**A**).

Subsequently, A reacted with o-carboranyl acid to generate the five-membered intermediate (**B**), followed by the generation of the Ir(V)-nitrene intermediate (**C**) by the insertion of anthranil.

Next, the insertion of nitrene into the Ir–B bond furnished a metalacyclic intermediate (**D**). Finally, protonation and de-



Scheme 37 Proposed mechanism for Cu(I)-catalyzed C–H amination of heterocyclic *N*-oxide with anthranils.



Scheme 39 Proposed mechanism for Cp*Ir(III)-catalyzed selective B(4)–H amination of *o*-carborane with anthranil.

carboxylation of intermediate (**D**) resulted in the regeneration of the active Cp*Ir(III) catalyst, along with the formation of the final product **78a**.

4. Conclusion

In this review, we have summarized all the reports on transition metal-catalyzed amination reactions using an electrophilic aminating agent, anthranil, for the synthesis of a variety of nitrogen-containing heterocycles. Important classes of biologically relevant N-heterocycles, such as acridines, benzophenanthrolines, indoloindolones, *etc*., could be easily synthesized utilizing the outlined strategies. Additional efforts have been made to outline the scope and mechanistic understanding of the entire amination pathway. The review focuses on the modern methods of amination reactions in milder conditions. So far, all the reports also utilize the redox-neutral concept, which transcends the generation of by-products due to the inutility of co-oxidants. Furthermore, the review depicts a variety of methodologies that are implemented to promote the synthesis of nitrogen-containing heterocycles in a greener and more economical way. Though there has been remarkable progress, a few challenges remain in this field. Most of the reports involving anthranils as aminating agents have utilized Cp*Rh (III)-catalytic systems as the prime choice of the transition metal catalyst. There is still scope for the utilization of cost-intensive, non-toxic, and non-noble 3d metals to unveil other classes of N-heterocycles. Only a handful of reports have utilized cascade cyclization for the synthesis of fused N-heterocycles. In general, an amination has led to *ortho*-amination products for aryl systems. The directing groups or template designs might be inclined towards *meta*-aminated products followed by an intramolecular cyclization to generate more flexible rings. The methodologies for the amination of heterocycles have only involved indoles. The plethora could be shifted towards the amination of non-nitrogen-containing heterocycles. We believe that this review will encourage non-specialists to make an impact in this domain and allow its readers to take up these challenges.

Conflicts of interest

There are no conflicts to declare.

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References

1 For selected recent reviews on C–H activation/functionalization. See. (*a*) P. Gandeepan and L. Ackermann, *Chem*, 2018, **4**, 199–222; (*b*) S. Rej, Y. Ano and N. Chatani, *Chem. Rev.*, 2020, **120**, 1788–1887; (*c*) U. Dhawa, N. Kaplaneris and L. Ackermann, *Org. Chem. Front.*, 2021, **8**, 4886–4913; (*d*) W. Ali, G. Prakash and D. Maiti, *Chem. Sci.*, 2021, **12**, 2735–2759; (*e*) T. Dalton, T. Faber and F. Glorius, *ACS Cent. Sci.*, 2021, **7**, 245–261; (*f*) S. K. Sinha, S. Guin, S. Maiti, J. P. Biswas, S. Porey and D. Maiti, *Chem. Rev.*, 2022, **122**, 5682–5841.

2 (*a*) R. Hili and A. K. Yudin, *Nat. Chem. Biol.*, 2006, **2**, 284–287; (*b*) E. Vitaku, D. T. Smith and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 10257–10274; (*c*) R. D. Taylor, M. MacCoss and A. D. G. Lawson, *J. Med. Chem.*, 2014, **57**, 5845–5859; (*d*) J. Shearer, J. L. Castro, A. D. G. Lawson, M. MacCoss and R. D. Taylor, *J. Med. Chem.*, 2022, **65**, 8699–8712.

3 (*a*) S. H. Cho, J. Y. Kim, J. Kwak and S. Chang, *Chem. Soc. Rev.*, 2011, **40**, 5068–5083; (*b*) T. A. Ramirez, B. Zhao and Y. Shi, *Chem. Soc. Rev.*, 2012, **41**, 931–942; (*c*) H. Kim and S. Chang, *ACS Catal.*, 2016, **6**, 2341–2351; (*d*) Y.-L. Feng and B.-F. Shi, *Chin. J. Org. Chem.*, 2021, **41**, 3753–3770.

4 (*a*) T. Kawano, K. Hirano, T. Satoh and M. Miura, *J. Am. Chem. Soc.*, 2010, **132**, 6900–6901; (*b*) K.-H. Ng, Z. Zhou and W.-Y. Yu, *Org. Lett.*, 2012, **14**, 272–275.

5 K. H. Ng, A. S. C. Chan and W. Y. Yu, *J. Am. Chem. Soc.*, 2010, **132**, 12862–12864.

6 C. Grohmann, H. Wang and F. Glorius, *Org. Lett.*, 2013, **15**, 3014–3017.

7 (*a*) J. Y. Kim, S. H. Park, J. Ryu, S. H. Cho, S. H. Kim and S. Chang, *J. Am. Chem. Soc.*, 2012, **134**, 9110–9113; (*b*) J. Ryu, K. Shin, S. H. Park, J. Y. Kim and S. Chang, *Angew. Chem., Int. Ed.*, 2012, **51**, 9904–9908; (*c*) K. Shin, Y. Baek and S. Chang, *Angew. Chem., Int. Ed.*, 2013, **52**, 8031–8036; (*d*) J. Ryu, J. Kwak, K. Shin, D. Lee and S. Chang, *J. Am. Chem. Soc.*, 2013, **135**, 12861–12868.

8 B. Zhou, J. Du, Y. Yang, H. Feng and Y. Li, *Org. Lett.*, 2013, **15**, 6302–6305.

9 Y. Park, K. T. Park, J. G. Kim and S. Chang, *J. Am. Chem. Soc.*, 2015, **137**, 4534–4542.

10 S. Yu, G. Tang, Y. Li, X. Zhou, Y. Lan and X. Li, *Angew. Chem., Int. Ed.*, 2016, **55**, 8696–8700.

11 X. H. Hu, X. F. Yang and T. P. Loh, *ACS Catal.*, 2016, **6**, 5930–5934.

12 S. Yu, B. Wan and X. Li, *Org. Lett.*, 2013, **15**, 3706–3709.

13 (*a*) G. Ju, G. Li, G. Qian, J. Zhang and Y. Zhao, *Org. Lett.*, 2019, **21**, 7333–7336; (*b*) C. Zhou, J. Zhao, W. Guo, J. Jiang and J. Wang, *Org. Lett.*, 2019, **21**, 9315–9319.

14 (*a*) G. Dequirez, V. Pons and P. Dauban, *Angew. Chem., Int. Ed.*, 2012, **51**, 7384–7395; (*b*) T. Shimbayashi, K. Sasakura, A. Eguchi, K. Okamoto and K. Ohe, *Chem. – Eur. J.*, 2019, **25**, 3156–3180.

15 (*a*) Y. Park, Y. Kim and S. Chang, *Chem. Rev.*, 2017, **117**, 9247–9301; (*b*) B. Du, C. M. Chan, C. M. Au and W. Y. Yu, *Acc. Chem. Res.*, 2022, **55**, 2123–2137.

16 Y. Gao, J. Nie, Y. Huo and X. Q. Hu, *Org. Chem. Front.*, 2020, **7**, 1177–1196.
17 S. Madhavan, S. K. Keshri and M. Kapur, *Asian J. Org. Chem.*, 2021, **10**, 3127–3165.
18 D. R. Eckroth and T. G. Cochran, *J. Chem. Soc. C*, 1970, 2660–2661.
19 B. T. Phillips and G. D. Hartman, *J. Heterocycl. Chem.*, 1986, **23**, 897–899.
20 J. Chauhan and S. Fletcher, *Tetrahedron Lett.*, 2012, **53**, 4951–4954.
21 B. H. Kim, Y. M. Jun, T. K. Kim, Y. S. Lee, W. Baik and B. M. Lee, *Heterocycles*, 1997, **45**, 235–240.
22 D. Zhao, Q. Shen and J. X. Li, *Adv. Synth. Catal.*, 2015, **357**, 339–344.
23 L. Marti, L. M. Sanchez, M. J. Climent, A. Corma, S. Iborra, G. P. Romanelli and P. Concepcion, *ACS Catal.*, 2017, **7**, 8255–8262.
24 B. J. Stokes, C. V. Vogel, L. K. Urnezis, M. Pan and T. G. Driver, *Org. Lett.*, 2010, **12**, 2884–2887.
25 R. B. Davis and L. C. Pizzini, *J. Org. Chem.*, 1960, **25**, 1884–1888.
26 M. Chiarini, L. Del Vecchio, F. Marinelli, L. Rossi and A. Arcadi, *Synthesis*, 2016, 3017–3030.
27 L. Shi and B. Wang, *Org. Lett.*, 2016, **18**, 2820–2823.
28 S. Yu, Y. Li, X. Zhou, H. Wang, L. Kong and X. Li, *Org. Lett.*, 2016, **18**, 2812–2815.
29 C. Tang, M. Zou, J. Liu, X. Wen, X. Sun, Y. Zhang and N. Jiao, *Chem. – Eur. J.*, 2016, **22**, 11165–11169.
30 M. Zou, J. Liu, C. Tang and N. Jiao, *Org. Lett.*, 2016, **18**, 3030–3033.
31 N. K. Mishra, M. Jeon, Y. Oh, H. Jo, J. Park, S. Han, S. Sharma, S. H. Han, Y. H. Jung and I. S. Kim, *Org. Chem. Front.*, 2017, **4**, 241–249.
32 H. Li, J. Jie, S. Wu, X. Yang and H. Xu, *Org. Chem. Front.*, 2017, **4**, 250–254.
33 S. Debbarma and M. S. Maji, *Eur. J. Org. Chem.*, 2017, 3699–3706.
34 M. Jeon, J. Park, P. Dey, Y. Oh, H. Oh, S. Han, S. H. Um, H. S. Kim, N. K. Mishra and I. S. Kim, *Adv. Synth. Catal.*, 2017, **359**, 3471–3478.
35 M. Wang, L. Kong, F. Wang and X. Li, *Adv. Synth. Catal.*, 2017, **359**, 4411–4416.
36 S. Kim, S. H. Han, N. K. Mishra, R. Chun, Y. H. Jung, H. S. Kim, J. S. Park and I. S. Kim, *Org. Lett.*, 2018, **20**, 4010–4014.
37 S. Kim, A. Kundu, R. Chun, S. H. Han, A. K. Pandey, S. Yoo, J. Park, H. S. Kim, J.-M. Ku and I. S. Kim, *Asian J. Org. Chem.*, 2018, **7**, 2069–2075.
38 T. Fu, J. Yang, H. Sun, C. Zhang, H. Xiang and X. Zhou, *Asian J. Org. Chem.*, 2018, **7**, 1844–1848.
39 A. Biswas, S. Sarkar and R. Samanta, *Chem. – Eur. J.*, 2019, **25**, 3000–3004.
40 S. Huang, H. Li, X. Sun, L. Xu, L. Wang and X. Cui, *Org. Lett.*, 2019, **21**, 5570–5574.
41 X. Wu, Y. Xiao, S. Sun, J. T. Yu and J. Cheng, *Org. Lett.*, 2019, **21**, 6653–6657.
42 A. Biswas, S. Bera, P. Poddar, D. Dhara and R. Samanta, *Chem. Commun.*, 2020, **56**, 1440–1443.
43 Y. Hu, T. Wang, Y. Liu, R. Nie, N. Yang, Q. Wang, G.-B. Li and Y. Wu, *Org. Lett.*, 2020, **22**, 501–504.
44 Y. Gao, J. Nie, Y. Li, X. Li, Q. Chen, Y. Huo and X. Q. Hu, *Org. Lett.*, 2020, **22**, 2600–2605.
45 Y. Gao, J. Nie, Y. Li, G. Liao, Y. Huo and X. Hu, *ChemCatChem*, 2020, **12**, 2721–2725.
46 W. Chen, C. Li, H.-J. Li and Y.-C. Wu, *Asian J. Org. Chem.*, 2021, **10**, 838–844.
47 H. Xie, M. Zhong, X.-T. Wang, J.-Q. Wu, Y.-Q. Cai, J. Liu, B. Shu, T. Che and S.-S. Zhang, *Org. Chem. Front.*, 2021, **8**, 635–642.
48 L. Li, H. Wang, S. Yu, X. Yang and X. Li, *Org. Lett.*, 2016, **18**, 3662–3665.
49 R.-H. Liu, Q.-C. Shan, X.-H. Hu and T.-P. Loh, *Chem. Commun.*, 2019, **55**, 5519–5522.
50 L. Liu, Z. Zhang, Y. Wang, Y. Zhang and J. Li, *Synthesis*, 2020, 3881–3890.
51 Y. N. Aher and A. B. Pawar, *Chem. Commun.*, 2021, **57**, 7164–7167.
52 A. Biswas, U. Karmakar, S. Nandi and R. Samanta, *J. Org. Chem.*, 2017, **82**, 8933–8942.
53 (*a*) S. Duttwyler, *Pure Appl. Chem.*, 2018, **90**, 733–744; (*b*) Y. Quan and Z. Xie, *Chem. Soc. Rev.*, 2019, **48**, 3660–3673; (*c*) Y. K. Au and Z. Xie, *Bull. Chem. Soc. Jpn.*, 2021, **94**, 879–899; (*d*) H. Jia and Z. Qiu, *Chin. J. Org. Chem.*, 2023, **43**, 1045.
54 L.-B. Zhang and Z. Xie, *Org. Lett.*, 2022, **24**, 7077–7081.

