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Directing group migration strategy in transition-metal-catalysed direct C–H functionalization

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Very recently, directing group (DG) migration has emerged as a practical strategy for transition-metal-catalysed direct C–H activation, resulting in a highly atom-economical process and enabling the reusage of DG. Therefore, great progress has been made in developing multitasking DGs. In this tutorial review, we present the rapid advances of this novel strategy by analyzing and comparing the different types of migratable DGs (including N–O, N–C, N–N or O–C bond cleavage to trigger DG migration). The related mechanisms, as well as synthetic applications, are also mentioned.

Key learning points

1. N–O bond cleavage triggers DG migration based on a TM(III)/TM(I) or TM(III)/TM(V) catalytic cycle pathway (TM: Transition Metal).
2. N–C or O–C bond cleavage triggers DG migration based on a metal- or alkali-promoted N-to-N, N-to-C, or O-to-C 1,4-migration pathway.
3. N–N bond cleavage triggers DG migration based on an acid-promoted protonation/nucleophilic capture pathway.
4. Scope, related mechanisms, as well as synthetic applications.
5. Currently, only a relatively few examples of CHA/DG migration have been implemented. This may represent a challenge and inspire modifying DGs and developing new migration mechanisms, resulting in the discovery of novel methods for complex molecule synthesis.

1 Introduction

Transition-metal-catalysed direct C–H bond activation (CHA) has become an important synthetic strategy in terms of high step- and atom-economy.[1–3] The direct functionalization of 'inert (non-activated)' C–H bonds is one of the most straightforward approaches to increase molecular complexity in organic synthesis. In this regime, directing groups (DGs) not only enhance reactivity, but also solve the problem of regioselectivity in organic molecules containing multiple C–H bonds. Nevertheless, they always bring chemical traces in products, which limit the structural diversity.[4] For example, DGs for C(sp^2)–H functionalization reactions are typically linked to aromatic substrates *via* stable C–C, C–O, or C–N bonds, which are difficult to cleave. For the sake of overcoming the disadvantage, we developed N–O as a traceless oxidizing DG,[5] in which the N–O group plays the dual role of DG and an internal oxidant and allows convenient removal after C–H functionalization. This research has attracted the attention of international peers. So far, various oxidative DGs, such as O–O,[7] N–O,[5,6,8–12] and N–N groups,[13] have been developed. Despite the success in the design of C–H activation systems using an internal oxidizing DG, a small molecule is eliminated as a by-product (alcohol, water, carboxylic acid, or amide) as a result of N–O, O–O or N–N bond cleavage. In fact, DG can not only work as an internal oxidant, but also serves as central building blocks to increase molecular complexity and realize a highly atom-economical process. Consequently, some strategies have been devised to address this problem, including the incorporation of DG into the product *via* CHA/DG migration.[14] Various migrating groups, such as oxy, amido, phthaloyl, heteroaryl, carbamoyl, and nitroso groups, have been developed. DG migration usually takes mainly the following three chemical transformations after C–H functionalization (Scheme 1): (1) cyclometallated intermediates undergo reductive elimination/oxidative addition to achieve DG migration, in which DGs act as the internal oxidant (through a TM(III)/TM(I) or TM(III)/TM(V) catalytic cycle); (2) either nucleophilic substitution of the Ms (migration site: C or N)–[TM] bond (TM: Transition Metal) or base-mediated deprotonation/nucleophilic substitution; (3) acid-promoted protonation/nucleophilic capture. In this review, we summarize recent investigations to

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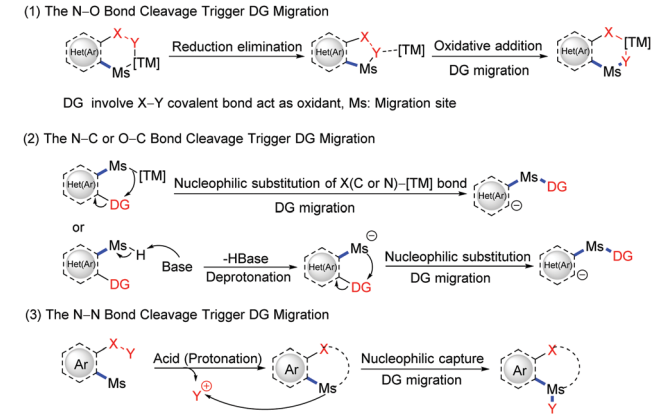

Scheme 1 Directing group migration strategy.

enhance the interest in the development of efficient and versatile migratable DGs for C–H functionalization, and the related mechanisms are discussed. DG migration is also briefly summarized.

2 N–O bond cleavage-triggered DG migration

2.1 The *O*-linked moiety as a migratable group

The N–O group is widely known as an efficient directing group for CHA reactions. In 2005, Fagnou and group pioneered the direct arylation of pyridine *N*-oxides with aryl bromides.[15] Then, Hiyama[16] and Chang[17] successively developed methods for the alkenylation and arylation of aza-heterocycle *N*-oxides *via* CHA. The *N*-oxide group played the role of an efficient directing group in these procedures. Subsequently, we

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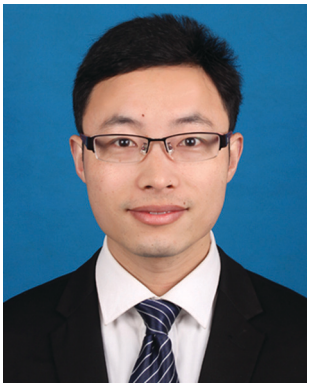

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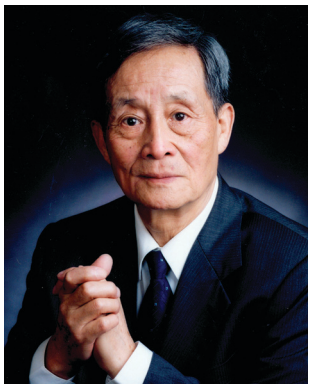

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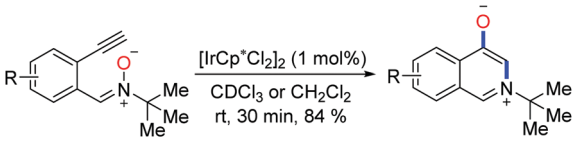
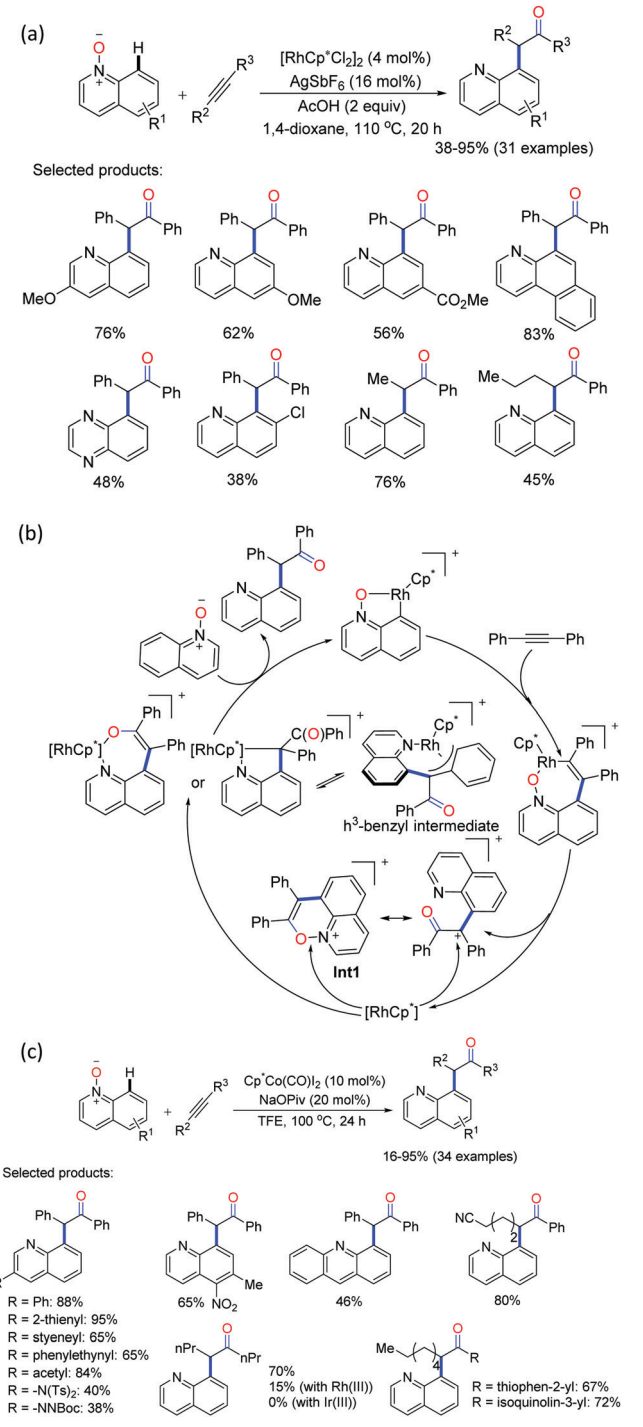


Scheme 2 [IrCp*Cl_2]$_2$-catalysed intramolecular O-atom transfer.

disclosed a palladium(II)-catalysed CHA reaction for the preparation of *ortho*-alkenylated quinolines under external-oxidant free conditions,[5] in which the *N*-oxide served the dual roles of an inducing platform to realize regioselectivity and an internal oxidant to regenerate the active catalyst. The oxygen atom was liberated as waste through N–O bond cleavage. As early as 2011, Li and co-workers realized [IrCp*Cl_2]$_2$-catalysed intramolecular O-atom transfer (OAT) from nitrone to a proximal terminal alkyne, which cast a new light on this subject (Scheme 2).[18] Isolable azomethine ylides were generated with low catalyst loading (1 mol%) at room temperature. Although the reaction had little to do with CHA, [IrCp*Cl_2]$_2$ is a typical CHA catalyst. Thus the combination of CHA and OAT would be possible.

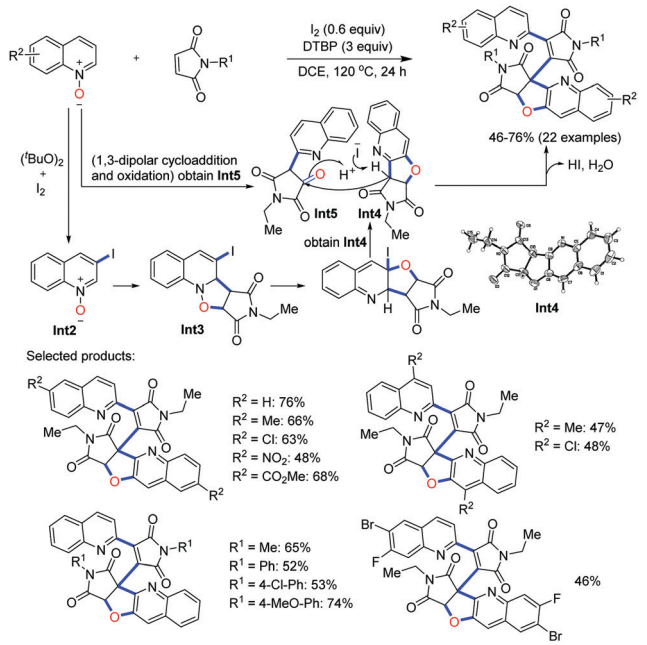
2.1.1 Quinoline *N*-oxide. As a proof of this concept, Li[19] and Chang[20] independently realized the Rh(III)-catalysed coupling reaction of quinoline *N*-oxides with alkynes, which successfully integrated CHA with OAT and led to the efficient synthesis of α,α-disubstituted acetophenones with 100% atom utilization in 2014 (Scheme 3a). Li and co-workers pinpointed that C8–H activation was an irreversible rate-limiting step through deuterated experiments and kinetic isotope effect (KIE, k_H/k_D = 3.6–4.0) studies. The thermodynamically stable η^3-benzyl intermediate was successfully isolated, which was established as the resting state of the catalyst. Moreover, the authors proved that C–H activation occurred prior to OAT. Chang and co-workers revealed that the *N*-oxide of the substrates delivered an oxygen atom to form a carbonyl group *via* an ^{18}O labelled experiment. A pathway involving an Rh(III)–Rh(I)–Rh(III) catalytic cycle was proposed (Scheme 3b). The seven-membered rhodacycle underwent reductive C–O bond elimination to obtain an Rh(I) species and a cationic heterocyclic intermediate (**Int1**), followed by the oxidative addition of **Int1** to regenerate the Rh(III) species and realize OAT. Moreover, Sundararaju and co-workers developed a Co(III)-catalysed C–H and C–O coupling system *via* the CHA/OAT reaction of quinoline *N*-oxide with an internal alkyne that allowed for a wide substrate range (Scheme 3c).[21] This protocol showed that Co(III) displayed better reactivity as a catalyst for aliphatic alkynes compared with Rh(III) and Ir(III). Mechanistic studies suggested that a Co(III)–Co(I)–Co(III) catalytic cycle was likely involved, which is conceptually consistent with the mechanism proposed by Li and Chang.

In 2019, we first developed an efficient I_2-mediated synthetic process for polyheterocycles bearing furoquinoline and maleimide through a tandem iodization/[3+2] cycloaddition/nucleophilic addition reaction of quinoline *N*-oxides and maleimides (Scheme 4).[22] In this reaction, I_2 acted as a halogenating agent to promote the subsequent [1,5]-Sigma rearrangement, in which the oxygen atom underwent 1,3-migration from the N atom to the C atom. Two C–O



Scheme 3 (a) Rh(III)-Catalysed tandem C–H activation/oxygen atom transfer for the synthesis of α,α-disubstituted acetophenones. (b) Proposed catalytic cycle for C–H activation with subsequent oxygen atom transfer. (c) Co(III)-Catalysed tandem C–H activation/oxygen atom transfer for the synthesis of α,α-disubstituted acetophenones.

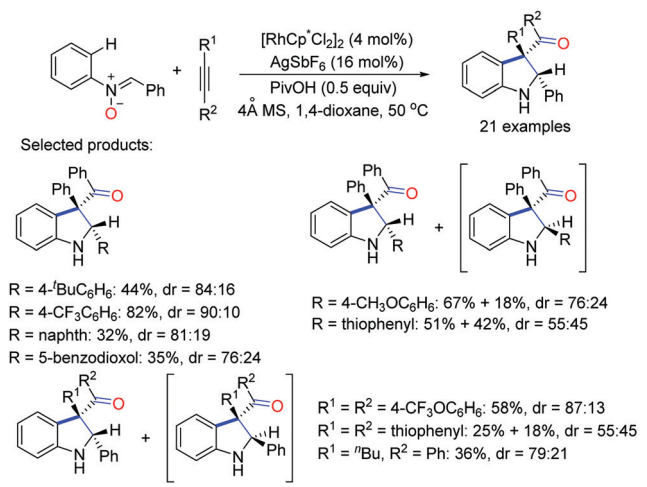
bonds, a quaternary carbon centre and three C–C bonds were formed in one pot reaction. In this transformation, **Int2** was generated through the iodination reaction at the C3 position of quinoline *N*-oxides in the presence of I_2, followed by the 1,3-dipolar cycloaddition of maleimide with **Int2** to deliver **Int3**.



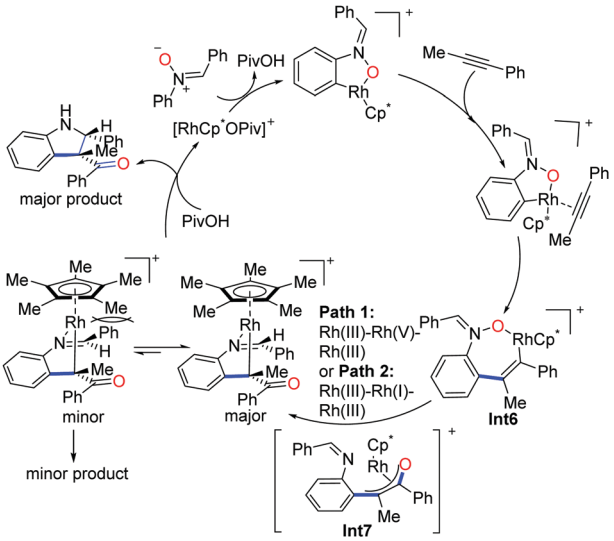
Scheme 4 I_2-Mediated tandem iodization/[3+2]cycloaddition/nucleophilic addition for the synthesis of polyheterocycles.

Int5 was obtained through the 1,3-dipolar cycloaddition and oxidation of maleimide with quinoline *N*-oxides. Subsequently, [1,5] Sigma rearrangement, aromatization and dehydroiodide afforded **Int4** (as confirmed by X-ray single-crystal diffraction analysis). Finally, the nucleophilic addition of **Int4** to **Int5** gave the final products *via* dehydration.

2.1.2 Arylnitrones. In 2015, Chang[23] and Li[24] successfully applied the CHA/OTA strategy to synthesize 3-acylindolines in a stereoselective manner through the Rh(III)-catalysed direct C–H functionalization of simple phenylnitrone with internal alkynes that set the *O*-linked moiety as the migratable group (Scheme 5). A new C=O bond was formed at the C3-position of the indoline skeleton. In addition, the N–O bond acted as an internal oxidant and a carbonylation reagent to meet the requirement of green chemistry. The *para*-CF_3-substituted aryl groups were found to be more stereoselective and efficient than *para*-CH_3O-substituted aryl groups. O-Atom transfer (OAT) was proposed to be involved through two pathways (Scheme 6): (1) cleavage of the N–O bond to form an Rh(v) oxo species that undergoes reductive elimination to afford an Rh(III)-enolate (**Int7**); (2) reductive elimination of **Int6** to form a benzoxazine and Rh(I), followed by the oxidation of Rh(I) to Rh(III) *via* N–O cleavage, leading to the formation of Rh(III)-enolate (**Int7**).

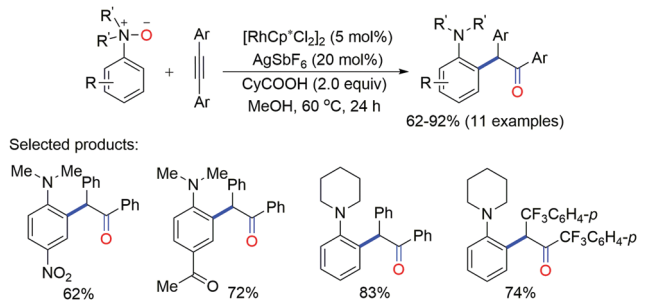


Scheme 5 Rh(III)-Catalysed tandem C–H activation/oxygen atom transfer using arylnitrones as substrate.



Scheme 6 Reaction mechanisms for C–H activation/oxygen atom transfer.

2.1.3 Tertiary aniline *N*-oxides. One year later, the N–O group, as migratable DG, was extended to tertiary anilines. Rh(III)-catalysed chemoselective C–H functionalization of tertiary aniline *N*-oxides with alkynes was reported by You and co-workers, including an OAT process *via* the sequential formation of C–C and C=O bonds to afford acetophenones (Scheme 7).[12] This redox-neutral process did not only avoid an external oxidant, but also improved the reactivity and selectivity under mild reaction conditions. Both tertiary aniline *N*-oxides bearing strong electron-withdrawing groups (such as nitro and acetyl) and various cyclic arylamines worked well.



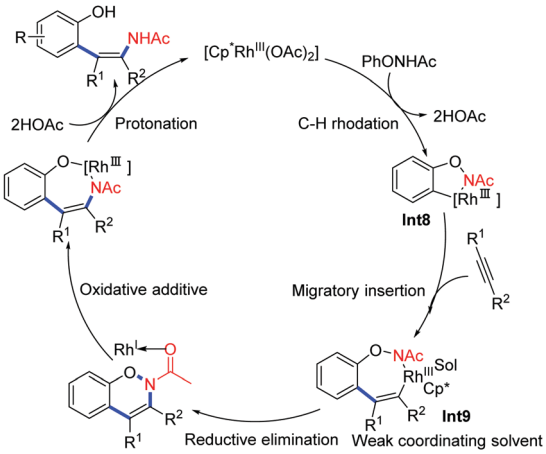
Scheme 7 Rh(III)-Catalysed tandem C–H activation/oxygen atom transfer using tertiary aniline *N*-oxides as the substrate.

2.2 The *N*-linked moiety as a migratable group

2.2.1 *N*-Phenoxyacetamides. It is well-known that *N*-phenoxyacetamides are powerful internal oxidizing DGs in transition-metal-catalysed direct C–H functionalization.[25] In this strategy, O–NHAc acts as an internal oxidant by allowing the cleavage of the oxidized bond (O–N) with the liberation of the cleaved unit "NHAc" as waste. From both atom-economy and synthesis points of view, it is worth investigating the function of endowing acetamide group that directly migrates to the product after C–H functionalization. Subsequently, chemists used *N*-phenoxyacetamides to react with various alkynes, alkenes, and diazo compounds as coupling partners to synthesize a series of linear and cyclized products. In these reactions, the O–NHAc group of *N*-phenoxyacetamides could serve as internal oxidants, DGs, as well as acetamidation agents, for sequential *ortho* C–H activation/C–N bond formation. In addition, a DG migration strategy for the transition-metal-catalysed intramolecular C–H functionalization of *N*-phenoxyacetamides was developed.[26,27] These methods do not only enrich the structural diversity of the products greatly, but also cater to the development of green chemistry.

2.2.1.1 Alkynes as coupling partners. In 2013, Lu and Liu successfully expanded N–O to O–NHAc as migratable DGs for the synthesis of *ortho*-hydroxyphenyl-substituted enamides through the Rh(III)-catalysed direct C–H functionalization of *N*-phenoxyacetamides with alkynes (Scheme 8).[28] The O–NHAc group acted as a DG, internal oxidant, and an acetamidation reagent. In this transformation, *N*-phenoxyacetamides that bear various groups (such as CH_3O, CF_3 and Cl) on the benzene ring reacted smoothly with various alkynes, such as prop-1-yn-1-ylbenzene, 3-phenylprop-2-yn-1-ol and methyl 3-(2-oxooxazolidin-3-yl)propiolate, to provide *ortho*-hydroxyphenyl-substituted enamides with moderate to excellent yields. 3-Trifluoromethyl-substituted *N*-phenoxyacetamide gave a mixture of two regioisomers. This protocol provided high atom-economy and highly functional products under mild reaction conditions.

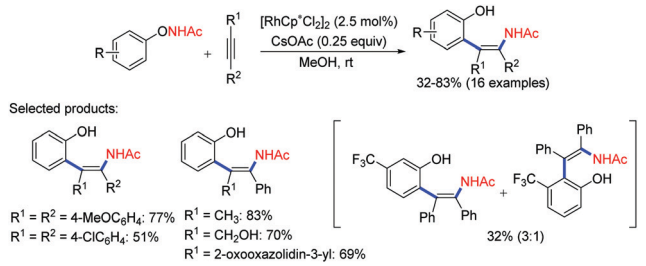
Furthermore, the kinetic isotope effect (KIE, k_H/k_D = 1.4) revealed that the C–H bond cleavage process might not be the rate-determining step. In this transformation, the acetate anion was crucial for the formation of the five-membered rhodacycle (**Int8**), and weak coordinating solvents (such as MeOH) could stabilise the seven-membered rhodacycle (**Int9**). Subsequently, **Int9** could undergo reductive elimination/oxidative addition to realize acetamido migration and provide enamide as the main product (Scheme 9).



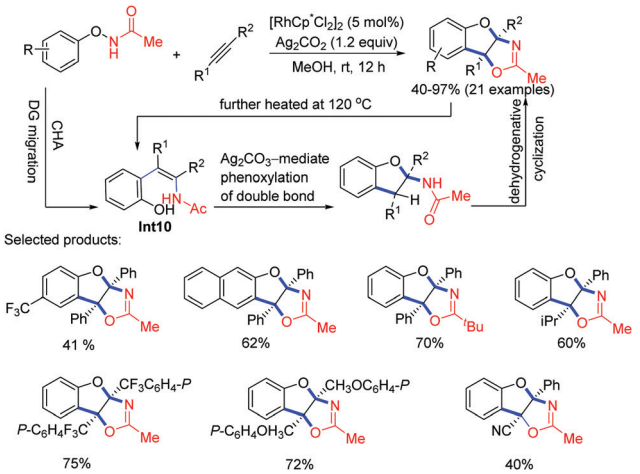
Scheme 9 Proposed catalytic cycle for C–H activation with acetamido migration.

In 2014, Chen and Wang reported an Rh(III)-catalysed oxidative double ring-closure reaction of *N*-phenoxyacetamides with internal alkynes, in which the O–NHAc group was used as the oxidising agent and migrating group (Scheme 10).[29] This domino reaction afforded dihydrobenzofuro[2,3-*d*]oxazoles bearing two adjacent quaternary stereogenic centers. Mechanistic studies revealed that the olefins (**Int10**) participated in an enamine-directed deoxygenation cascade reaction in the presence of Ag_2CO_3 (1.2 equiv.). Moreover, the final product could be reversed to get the initial olefin (**Int10**) when further heated to 120 °C. The reaction exhibited excellent chemoselectivity and tolerated a wide substrate scope under mild reaction conditions.

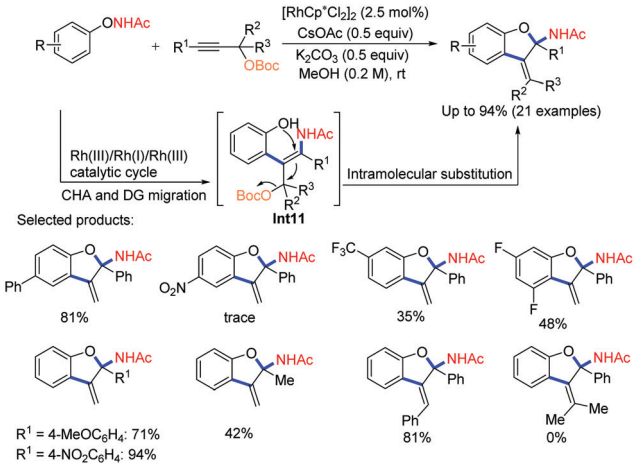
In 2015, the efficient synthetic process for 3-alkyl-idene dihydrobenzofurans was developed by Lu and Liu through the Rh(III)-catalysed cycloaddition of *N*-phenoxyacetamides with carbonates containing alkynes (Scheme 11),[30] in which the C–C, C–N, and C–O bonds were formed in one pot.



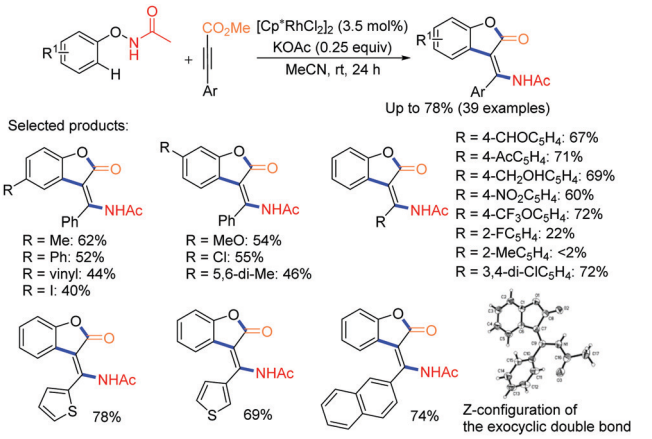
Scheme 8 Rh(III)-Catalysed cascaded C–H activation/acetamido migration for the preparation of *ortho*-hydroxyphenyl-substituted enamides.



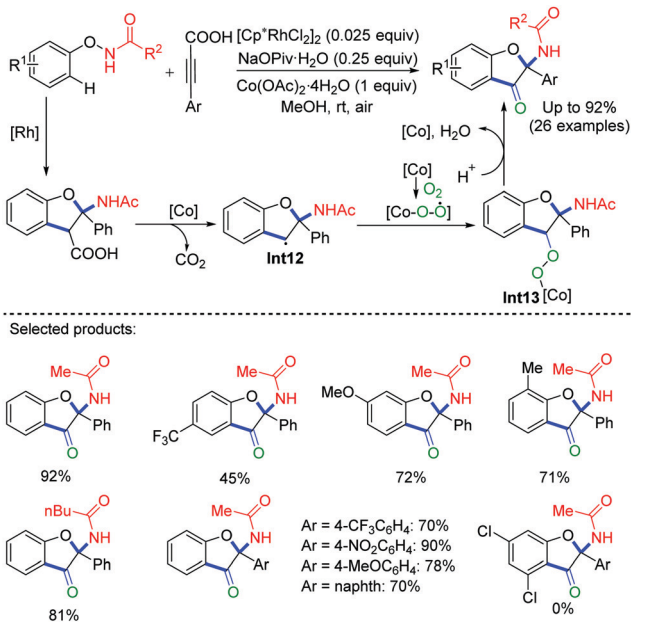
Scheme 10 Rh(III)-Catalysed cascaded C–H activation/acetamido migration/dioxygenation for the preparation of dihydrobenzofuro[2,3-*d*]oxazole skeleton.



Scheme 11 Rh(III)-Catalysed cascaded C–H activation/acetamido migration/cycloaddition for the preparation of 2-acetamido-substituted dihydrobenzofuran derivative.



Scheme 12 Rh(III)-Catalysed cascaded C–H activation/acetamido migration/isomerization/lactonization for the preparation of benzofuran-2(3*H*)-ones.



Scheme 13 Rh(III)-Catalysed cascaded C–H activation/acetamido migration and [Co]-mediated decarboxylation/radical coupling for the preparation of benzofuran-3(2*H*)-ones.

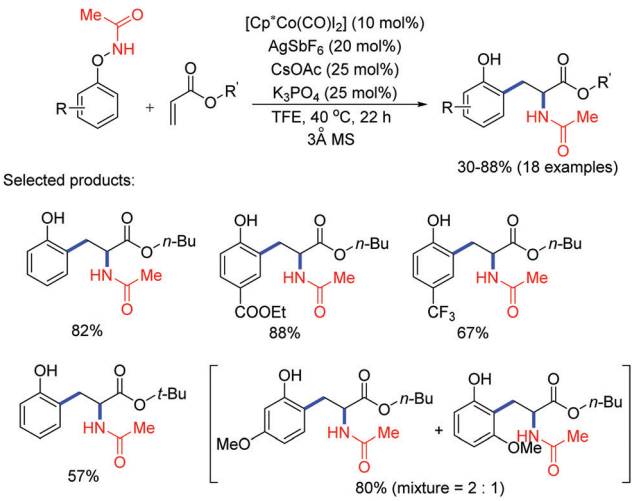
Deuterium-labelling experiments implied that C–H activation might be irreversible. Further, the KIE data (k_H/k_D = 1.8) indicated that the C–H bond cleavage process was not involved in the rate-determining step, which was consistent with their previous work.[27] For this transformation, mechanistic studies showed that the installation of "–OBoc" as the leaving group on alkynes was the key step to form the C–O and exocyclic double bonds through an intramolecular substitution of enamide (**Int11**).

Moreover, Zhang and Pan described an efficient method for the synthesis of benzofuran-2(3*H*)-ones containing exocyclic amino motifs with an exclusive *Z*-configuration by the Rh(III)-catalysed redox-neutral cascade [3+2] annulation of *N*-phenoxyacetamides with acetylene esters in 2018 (Scheme 12).[31] O–NHAc was used as both internal oxidative DG and acetamide reagent. The *Z*-configuration of the exocyclic double bond in the products was confirmed by X-ray diffraction analysis and was thought to be stabilised by the hydrogen bond (N–H···O type intramolecular interaction). Mechanistic investigations revealed that C–H bond activation was largely reversible and might not be involved in the rate-determining step. In addition, deuterium-labelling experiments illustrated that C–C bond formation was not reversible. The cascade reaction was a consecutive process, including C–H functionalization, isomerization, and lactonization, which endowed the method with excellent functional group compatibility, broad substrate scope, and mild reaction conditions. One year later, Zhao and co-workers achieved Co(III)-catalysed carbonamination of propiolates with bicyclic alkenes through non-annulative redox-neutral coupling.[32]

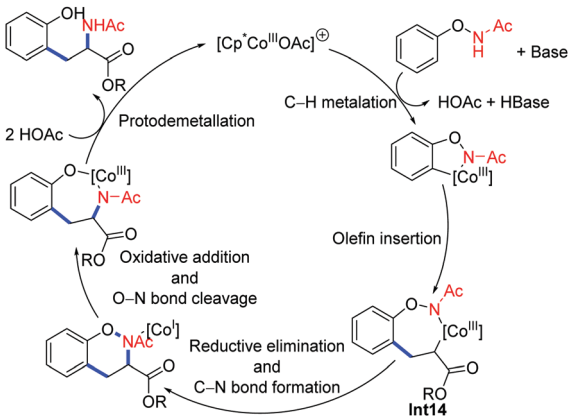
In 2019, Li and co-workers disclosed a novel approach, comprising the Rh/Co relay-catalysed C–H activation/annulation of simple *N*-aryloxyacetamides with propiolic acids to afford valuable benzofuran-3(2*H*)-ones with a quaternary center.[33] In this method, the acetamide group released from O–N bond cleavage migrated to the exocyclic olefin to construct a new C(sp^2)–N bond (Scheme 13). The reaction featured the simultaneous construction of a benzofuran motif containing a C2 quaternary center and a C3 carbonyl group. The KIE data (k_H/k_D = 2.5) indicated that the C–H bond cleavage process was involved in the rate-determining step. Additionally, the results of control reactions suggested that $Co(OAc)_2{\cdot}4H_2O$ could play a key role in cyclization and decarboxylation. The authors proposed a reasonable amide group migration mechanism, involving a catalytic cycle of Rh(III), Rh(V) and Rh(III). Moreover, the oxygen atom of the benzofuran-3(2*H*)-one C3 carbonyl group derived from molecular oxygen was involved in a [Co]-mediated decarboxylation to generate a free radical intermediate (**Int12**), which subsequently trapped the [Co–O–O•] species that was generated from [Co] under the air to form the hydroperoxide species (**Int13**).

2.2.1.2 Alkenes act as the coupling partners. In 2016, the study on the amide group migration approach was extended to alkenes that acted as the coupling partners by Glorius and co-workers.[34] Using Cp*Co(III) as the catalyst, the reaction of a variety of acrylates – with phenoxyacetamide gave carboamination products with good yields under mild reaction conditions (Scheme 14). This method achieved the regioselective construction of the C–N bond by the migration of DG on olefins. Both KIE of 2.1 (competition experiment) and k_H/k_D = 1.5 (parallel experiment) indicated that the C–H bond cleavage process was involved partly in the rate-determining step. The reaction mechanism was conceptually consistent with the Co(III)–Co(I)–Co(III) catalytic pathway described in Scheme 15. The C(sp^3)-metal-species (**Int14**) underwent reductive elimination to form the desired C–N bond with the concomitant generation of Cp*Co(I), avoiding alkenylated products through β-H-elimination and reflecting the complementary reactivity of Cp*Co(III) to Cp*Rh(III).

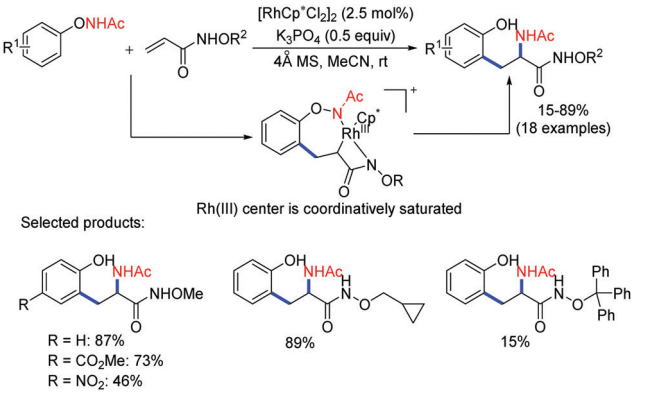
Rhodium(III)-catalysed C–H functionalization of *N*-phenoxyacetamides by employing *N*-alkoxyacrylamides as coupling partners to produce 2-hydroxyphenylalanines (*o*-tyrosine) under redox-neutral and mild reaction conditions was developed by Liu and co-workers (Scheme 16).[35] In this reaction, the amido group was formally transferred from the oxidising directing group (–ONHAc) to the alkene. According to mechanistic studies, due to the nitrogen atom in *N*-alkoxyacrylamide, it might act as an anion ligand after deprotonation, and the metal center was coordinatively saturated. As a result, β-H elimination was suppressed, and no C–H olefination product was observed. Subsequently, acylamino migration (O–N bond cleavage) took place to afford a seven-membered rhodacycle(III) intermediate, which then underwent tandem reductive elimination/oxidation addition/protonation to afford the final products.



Scheme 14 Co(III)-Catalysed cascaded C–H activation/acetamido migration for the direct carboamination of alkenes.



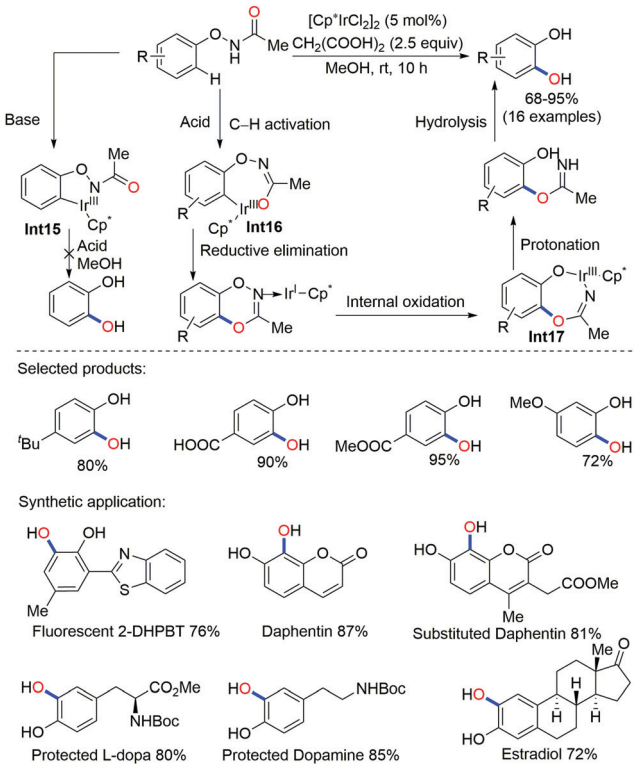
Scheme 15 Proposed catalytic cycle for C–H activation with subsequent acetamido migration.



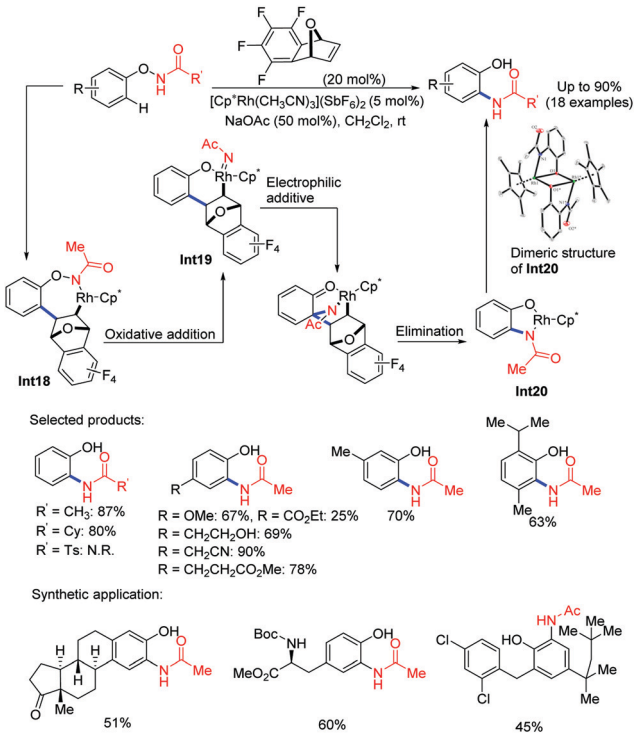
Scheme 16 Rh(III)-Catalysed cascaded C–H activation/acetamido migration for the direct carboamination of alkenes.

2.2.1.3 Intramolecular reaction. In 2017, efficient rhodium(III)-catalysed intramolecular CHA and OTA was described for the synthesis of catechols from phenols through the formation of *N*-phenoxyacetamide intermediates by Wu and co-workers (Scheme 17),[26] in which the oxyacetamide group could function as a directing group, internal oxidant, and oxygen source simultaneously. The authors confirmed that the oxygen in the product came from the carbonyl moiety of the O–NHAc group based on isotope labelling experiments and HRMS analysis. The acid additives ($CH_2(COOH)_2$) might play important roles, such as preventing the generation of inactive **Int15**, promoting the formation of seven-membered [Ir(III)] (**Int16**) and protonating **Int17**. Furthermore, theoretical calculations revealed that $CH_2(COOH)_2$ could significantly reduce the free energy of **Int16** (from 22.4 to 2.1 kcal mol^{-1}), highlighting the crucial role of the acid in stabling **Int16** and protonation. As for the reaction mechanism, seven-membered [Ir(III)] (**Int16**) could be the active intermediate, which underwent the reductive elimination process to form a C–O bond and [Ir(I)]. Subsequently, catechols were obtained through oxidative addition, protonation and hydrolysis.

Interestingly, Glorius and co-workers also developed a Cp*Rh(III)/bicyclic olefin co-catalysed intramolecular *ortho*-C–H amidation reaction of *N*-phenoxyacetamides under mild and neutral conditions (Scheme 18).[27] The O–NHAc group could



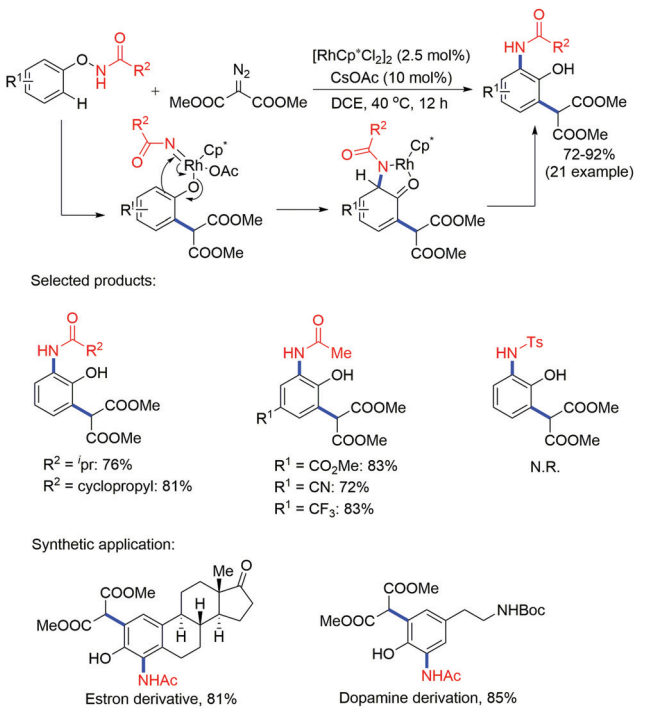
Scheme 17 Ir(III)-Catalysed cascaded intramolecular C–H activation/OTA for the synthesis of catechols.



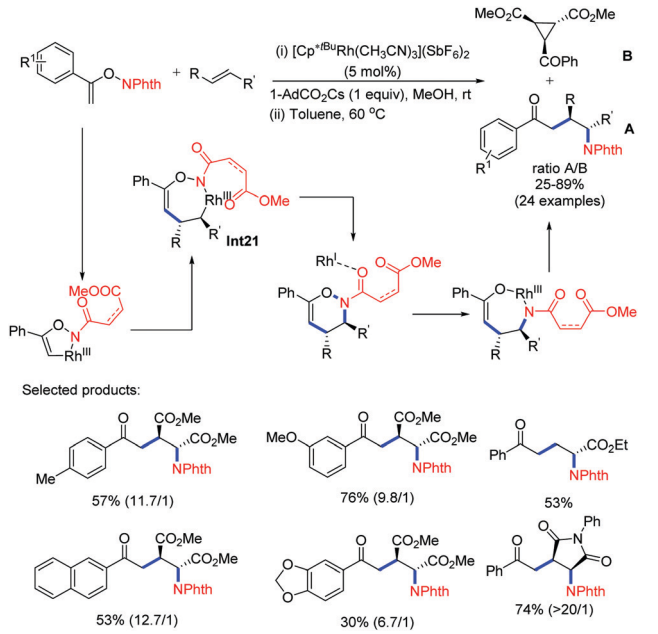
Scheme 18 Rh(III)/bicyclic olefin co-catalysed intramolecular *ortho*-C–H amidation for the synthesis of *O*-amidophenol.

act as an intramolecular amidation reagent by DG migration. The bicyclic 7-oxa-(tetrafluorobenzo) norbornadiene, which acted as a co-catalyst, facilitated the insertion and stabilised **Int18** by inhibiting β-H elimination. Consecutively, the Rh(V) nitrenoid species (**Int19**) was formed by the oxidative addition of Rh into the O–N bond. Subsequently, **Int19** underwent an electrophilic *ortho*-nitrenoid addition and generated a spirocyclic dearomatised intermediate, while simultaneously reducing Rh. This was followed by aromatization and reductive elimination accompanied by the removal of the olefin, forming **Int20**, which was confirmed by X-ray crystallography. Moreover, **Int20** was protonated by HOAc to release the desired product and regenerate the active Rh(III) species.

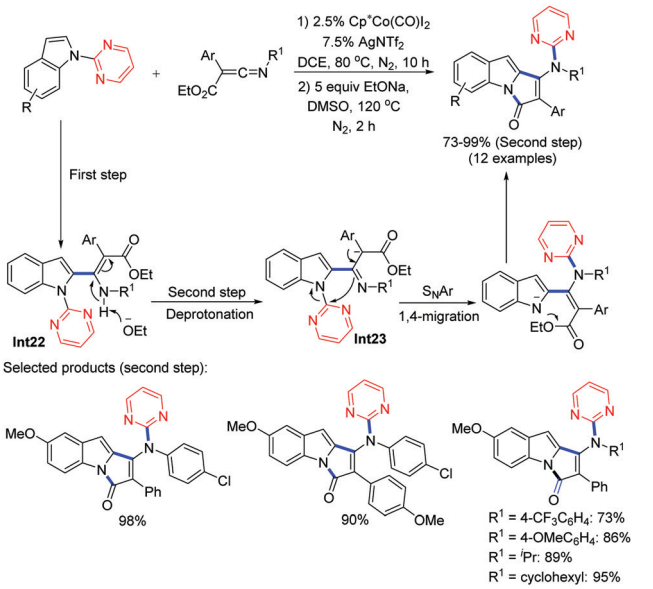
2.2.1.4 Diazo compounds as the coupling partners. Shortly after that, Zhou and Zhu *et al.* further expanded the coupling reaction to diazo compounds, disclosing an Rh(III)-catalysed intermolecular asymmetrical *ortho*-C–H difunctionalization reaction under mild and redox-neutral conditions (Scheme 19).[36] The acetamide group could function as the directing group to facilitate *ortho*-C–H functionalization and also as an essential coupling partner for the second *ortho*-C–H amidation *via* an intramolecular DG migration strategy. In contrast to the work by Glorius,[27] the clear advantage of this protocol was that norbornene was not required as a ligand. Mechanistic studies and density functional theory (DFT) calculations supported a stepwise reaction mechanism. Firstly, an initial Rh(III)-catalysed *ortho*-C–H alkylation of *N*-phenoxyacetamides happens, and subsequently, the processes of tandem intramolecular oxidative addition, electrophilic nitrenoid addition, protonation,



Scheme 19 Rh(III)-catalysed tandem *ortho*-C–H alkylation/amidation using diazo compounds as coupling partners.



Scheme 20 *syn*-Carboamination of disubstituted alkenes through the Rh(III)-catalysed cascaded C–H activation/phthalimide migration.



Scheme 21 Co(III)-Catalysed C–H alkenylation and base-promoted pyrimidinyl migration for the preparation of 3*H*-pyrrolo[1,2-*a*]indol-3-one scaffolds.

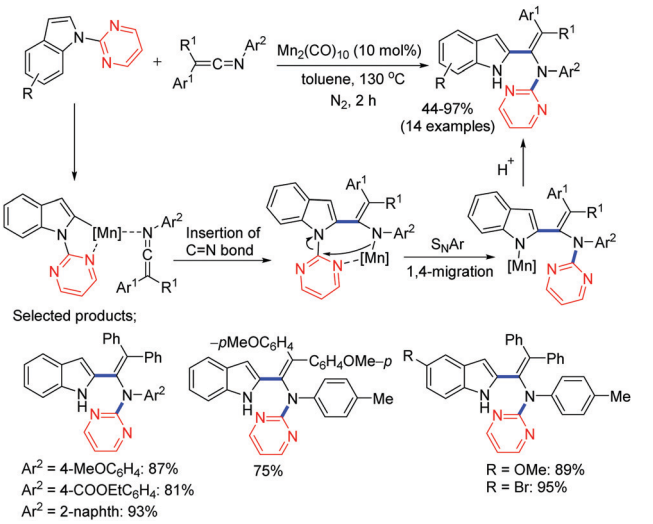
isomerisation, and DG migration of the amide group at the *ortho* position of phenol (electrophilic addition to the second *ortho* position of the phenol) occur.

2.2.2 *N*-Enoxyphthalimide. In 2015, Piou and co-workers successfully applied the CHA and DG migration strategy in the stereoselective intermolecular *syn*-carboamination of disubstituted alkenes through Rh(III)-catalysed C–H activation (Scheme 20).[37] This protocol highlighted the utility of the *O*-phthalimide group as a DG, internal oxidant, and amination reagent, which provided high atom-economy and highly functional products. The phthalimide group could reversibly open to form a bidentate DG in the presence of methanol and a base. Moreover, β-H-elimination could be inhibited by the saturated coordination complex C(sp^3)–Rh **Int21**. As for the reaction mechanism, the active Rh(III) catalyst underwent irreversible C–H activation for the synthesis of a five-membered rhodacycle, and subsequent migratory insertion of the alkene generated the saturated Rh(III) coordination complex **Int21** *via* coordination of the ester group with the metal. Then, **Int21** underwent reductive elimination and oxidative addition of the N–O bond to give Rh(I), followed by protonation/tautomerisation of the enol to afford product **A**.

3 N–C or O–C bond cleavage-triggered DG migration

3.1 Heteroaryl group migration by N–C bond cleavage

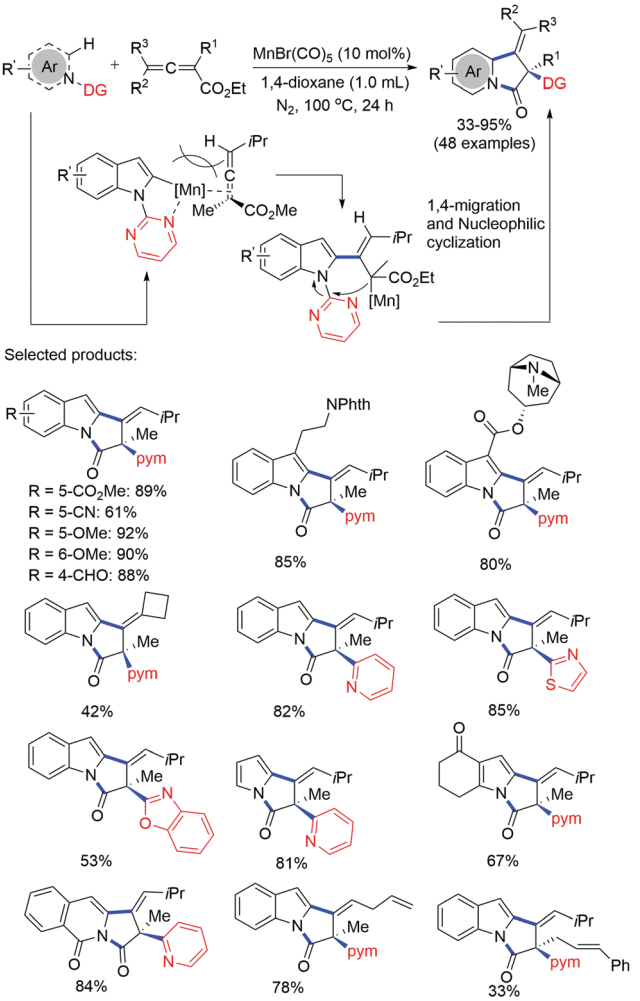
In 2016, Wang and Lu *et al.* firstly applied pyrimidinyl as a migratable group, which was introduced in Co(III)-catalysed *ortho* C–H activation to synthesize 3*H*-pyrrolo[1,2-*a*]indol-3-one (Scheme 21).[38] This reaction involved the enaminylation of *N*-pyrimidinylindoles with ketenimines using the pyrimidine group as a DG and the subsequent base (EtONa)-promoted migration of the pyrimidine group. This method represents a promising sustainable chemical process with a high atom-economy. The authors proposed a possible reaction mechanism, involving the treatment of **Int22** with EtONa, resulting in deprotonation to provide the anion **Int23**. Then, **Int23** underwent a sequence of nucleophilic aromatic substitutions (S_NAr: N-to-N 1,4-migration of the directing group) and aminolysis of the ester to liberate the products. Additionally, in 2018, Wang and Lu developed the synthesis of 2-enaminylated indoles from 1-(pyrimidin-2-yl)-1*H*-indoles with ketenimines involving $MnBr(CO)_5$-catalysed C–H activation (Scheme 22).[39] Compared to their previous report on the [Co(III)]–$AgNTf_2$ catalytic system,



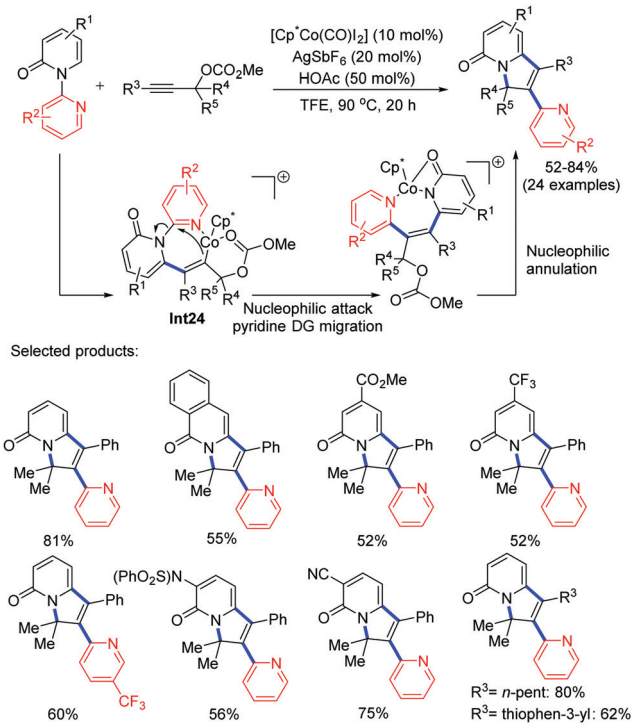
Scheme 22 Mn(I)-Catalysed C–H alkenylation/pyrimidinyl migration for the preparation of 2-enaminylated indoles.

this reaction achieved the migration of the directing group using Mn(I) as the Lewis acid in the absence of external additives. Furthermore, the directing group (pyrimidinyl) failed to migrate when ester-substituted ketenimines were used as the coupling partners. In the cases when R^1 = aryl, DG migration could be achieved through the intramolecular nucleophilic aromatic substitution (S_NAr: N-to-N 1,4-migration of the directing group) of the N–Mn(I) bond.

A similar process was simultaneously achieved by Wang[40] and Rueping.[41] Mn(I)-Catalysed cascaded C–H activation/Smiles rearrangement reaction of 1-(pyrimidin-2-yl)-1*H*-indoles with tri-substituted allenyl esters was developed under additive-free and redox-neutral conditions (Scheme 23). Moreover, bicyclic or tricyclic heterocycles bearing an exocyclic double bond were afforded with moderate to excellent yields. The KIE data (k_H/k_D = 1.1) indicated that the C–H bond cleavage process was not involved in the rate-determining step. As for the reaction mechanism, the strong nucleophilicity of the C(sp^3)–Mn bond could lead to the N-to-C 1,4-migration of the directing group (Smiles rearrangement). The final cyclized products



Scheme 23 Mn(I)-Catalysed C–H alkenylation/pyrimidinyl migration/cyclization for the synthesis of tricyclic heterocycle scaffolds.



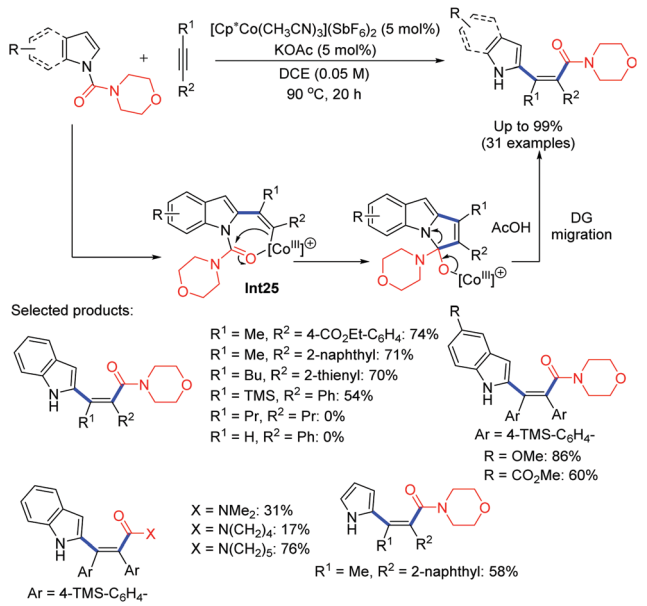
Scheme 24 Co(III)-Catalysed cascaded C–H activation/pyridyl migration/cyclization for the synthesis of indolizinone scaffolds.

were obtained accompanied by an intramolecular displacement of the ethoxyl group. Based on a similar mechanism, subsequently, Sharma and co-workers developed an alkylation process for indoles at the C2 position with β-CF_3-substituted enones using Rh(III) as the catalyst, providing access to novel migration products.[42] In this reaction, the pyrimidine group acted as the DG. This protocol provided high atom-economy, broad functional group compatibility, as well as excellent regio- and chemoselectivity.

Recently, Ackermann and co-workers achieved a Co(III)-catalysed domino reaction of C–H bond activation/pyridine directing group migration/alkyne annulation reaction of pyridones with propargylic carbonates, affording indolizinone alkaloids in a single operation (Scheme 24).[43] The author proposed that the C–H bond cleavage occurred *via* a base-assisted intramolecular electrophilic-type substitution (BIES) mechanism rather than a concerted metallation/deprotonation (CMD) mechanism based on detailed Wiberg bond order analysis. Besides, density functional theory (DFT) calculations showed that the activation barrier for pyrimidine group migration increased significantly because of the key nucleophilic attack of the metal–C bond when the cobalt in **Int24** was replaced by manganese. As for the reaction mechanism, the nucleophilicity of the preferred C(sp^2)–Co bond led to the chemoselective migration of the pyridine group in the key intermediate Co (**Int24**) rather than β-oxygen elimination.

3.2 Carbamoyl group migration by N–C bond cleavage

In 2017, Matsunaga and Yoshino developed a Cp*Co(III)-catalysed carbamoyl-protected indole/pyrrole C–H alkenylation/DG migration reaction with alkynes for the preparation of tetra-substituted olefins

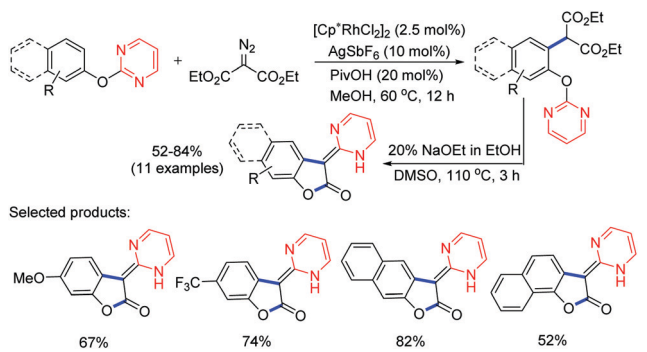


Scheme 25 Co(III)-Catalysed C–H activation/carbamoyl migration for the synthesis of tetra-substituted olefins.

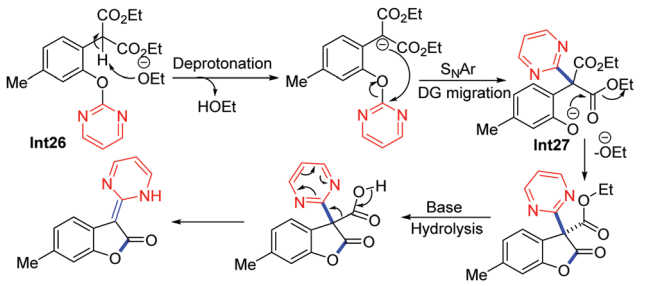
under relatively mild reaction conditions (Scheme 25).[44] The carbamoyl group, which was typically liberated after C–H functionalisation, served as an internal amino acylating agent and migrated to the alkene moiety of **Int25**. The migration of the directing group was realised with the Cp*Co(III) catalyst, while the related Cp*Rh(III) catalyst failed to realise the migration process. As for the mechanism, a concerted metalation-deprotonation (CMD) occurred in the first step, and subsequently, the seven-membered cobalt cycle was formed through alkyne migration insertion (**Int25**). The tetra-substituted alkene was obtained by nucleophilic addition and elimination of indole, accompanied by the migration of the DG (carbamoyl group), in which [Co(III)] cation acted as the Lewis acid and coordinated with oxygen to promote the cleavage of the N–C bond.

3.3 Heteroaryl group migration by O–C bond cleavage

In 2017, Swamy and co-workers discovered Rh(III)-catalysed *ortho*-alkylation of 2-phenoxypyridine/2-phenoxypyrimidines using the pyrimidine group as the DG (Scheme 26),[45] and the



Scheme 26 Rh(III)-Catalysed C–H alkylation and base-promoted pyrimidinyl migration for the preparation of benzofuran-2(3*H*)-one scaffolds.

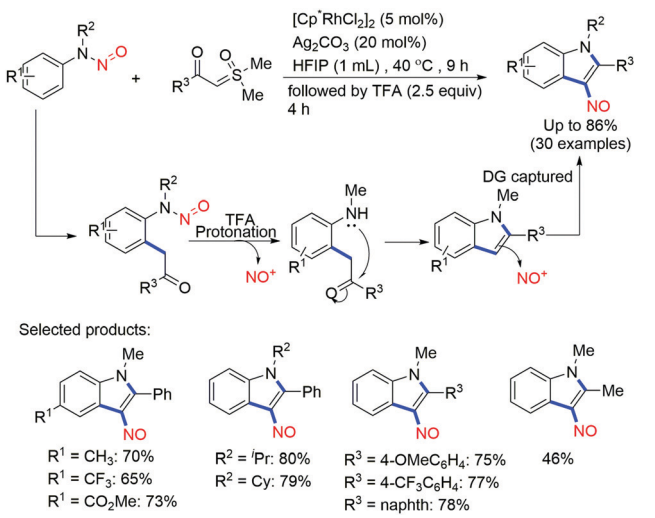


Scheme 27 Reaction mechanism of base-promoted pyrimidinyl migration in the second step.

reaction was achieved by employing the two-step two-pot procedure. The migration of pyrimidine was promoted by a base (NaOEt). The difference from the pyrimidinyl group migration reported by Wang and Lu[38] is that its aromaticity was destroyed. Experimental investigations revealed that sodium ethoxide (NaOEt) abstracted a proton from **Int26**, followed by the migration of the pyrimidine group to afford the anion **Int27**. Finally, the product was obtained through the electrophilic cyclisation/protonation/dearomatisation process (Scheme 27).

4 N–N bond cleavage-triggered DG migration

More recently, we firstly applied Rh(III)-catalysed tandem acylmethylation/cyclization/nitroso migration of *N*-nitrosoanilines with sulfoxonium ylides in one pot to afford 3-nitrosoindole derivatives (Scheme 28).[46] In this reaction, the N–NO group acted as a versatile DG and an internal nitrosation reagent. The salient features of this protocol included high atom economy, good functional group tolerance, and mild reaction conditions. Moreover, the desired products could proceed smoothly with further chemical transformations.



Scheme 28 Rh(III)-Catalysed tandem C–H acylmethylation and acid-mediated nitroso migration for the preparation of 3-nitrosoindoles.

Rh(III)-Catalysed *ortho*-acylmethylation of *N*-nitrosoanilines with sulfoxonium ylides was involved. Subsequently, the *N*-nitroso group was protonated with TFA (trifluoroacetic acid) to release NO^+, and then, nucleophilic addition and dehydration afforded *N*-methylindole derivatives, which were substituted by NO^+ at the electron-rich C3 position, giving the nitroso products.

5 Conclusion

In summary, great progress has been made recently in the area of directing group (DG) migration strategy for transition-metal-catalysed direct C–H functionalization. This type of reaction has numerous advantages, such as realising a highly atom-economical process, incorporating the DGs in the final products, and enriching the diversity of the product structure. Furthermore, the strategy usually involves multi-step tandem reactions starting from simple and easily available substrates to rapidly generate relatively complex molecules in one shot. This review focuses on the migration of various groups that act as DGs and the related mechanistic insights to date through analysis and comparison. We expect that the DG migration strategy will stimulate further innovative studies with modified DGs and new migration mechanisms, resulting in the discovery of novel methods for the synthesis of complex molecules.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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