Transition-Metal-Catalyzed Decarbonylative Functionalization of Phthalimides

Ying-Ying Liu, a,b Shao-Han Sun, a,b Xiang-Ting Min, a Boshun Wan a Qing-An Chen a

a Dalian Institute of Chemical Physics, Chinese Academy of Sciences, 457 Zhongshan Road, Dalian, 116023, P. R. of China
b University of Chinese Academy of Sciences, Beijing, 100049, P. R. of China

Abstract Phthalimide derivatives are prevalent in a wide array of biologically important molecules, including drugs, fungicides, and anticancer molecules. Thus, catalytic methods that directly edit the phthalimide moiety, in particular, decarbonylation and derivatization, could be strategically valuable for the modification of existing phthalimide molecular scaffolds. In recent years, considerable efforts have been devoted to emulating the transition-metal-catalyzed phthalimide decarbonylative reaction. A set of elegant strategies, including decarbonylative addition reactions with alkynes, alkenes, and benzynes, decarbonylative polymerization, alkylation, arylation, and protodecarbonylation, have been demonstrated. This review aims to highlight these advances and discusses the mechanism issues, to further extend application and promote developments in this field.

1 Introduction

As the most well-known and studied phthalimide derivative, thalidomide has been used as a sedative-hypnotic since 1958. Although it was banned in 1962 as a consequence of its unexpected dominant teratogenicity, the bioactivities of thalidomide toward other diseases have been discovered gradually.1 So far, phthalimide derivatives have shown some pharmaceutical applications and been used as scaffolds for drugs such as amphotalide,2 otezla,3 pomalyst,4 and discusses the mechanism issues, to further expand application and promote developments in this field.

1 Introduction

As the most well-known and studied phthalimide derivative, thalidomide has been used as a sedative-hypnotic since 1958. Although it was banned in 1962 as a consequence of its unexpected dominant teratogenicity, the bioactivities of thalidomide toward other diseases have been discovered gradually.1 So far, phthalimide derivatives have shown some pharmaceutical applications and been used as scaffolds for drugs such as amphotalide,2 otezla,3 pomalyst,4 and discusses the mechanism issues, to further expand application and promote developments in this field.

1 Introduction

As the most well-known and studied phthalimide derivative, thalidomide has been used as a sedative-hypnotic since 1958. Although it was banned in 1962 as a consequence of its unexpected dominant teratogenicity, the bioactivities of thalidomide toward other diseases have been discovered gradually.1 So far, phthalimide derivatives have shown some pharmaceutical applications and been used as scaffolds for drugs such as amphotalide,2 otezla,3 pomalyst,4 and discusses the mechanism issues, to further expand application and promote developments in this field.

1 Introduction

As the most well-known and studied phthalimide derivative, thalidomide has been used as a sedative-hypnotic since 1958. Although it was banned in 1962 as a consequence of its unexpected dominant teratogenicity, the bioactivities of thalidomide toward other diseases have been discovered gradually.1 So far, phthalimide derivatives have shown some pharmaceutical applications and been used as scaffolds for drugs such as amphotalide,2 otezla,3 pomalyst,4 and discusses the mechanism issues, to further expand application and promote developments in this field.
taltrimide,\(^5\) and talmetoprim\(^6\) (Figure 1). Recently, phthalimide derivatives have been used as anticancer and antitumor drugs.\(^7\) The prevalence of the phthalimide scaffold in pharmaceutical and fine chemical libraries has attracted extensive interest for site-selective derivatization to access new chemicals.\(^8\)

![Figure 1 Selected drugs containing the phthalimide moiety](image)

Recently, transition-metal-catalyzed decarbonylation of amides or imides has garnered significant attention because it provides a new and creative synthetic strategy using carbonyl groups as ‘traceless handles’ for amide modification.\(^9\) Thus, a decarbonylative functionalization reaction of phthalimides that directly edits the phthalimide moiety could be strategically valuable for the modification of existing phthalimide molecular scaffolds. In addition, phthalimides are electronically activated amides, in which N\(_{\text{lp}}\) delocalization (lp = lone pair) is possible through the amide bond as well as the aromatic ring.\(^10\)

Theoretically, there are substantial challenges for the transition-metal-catalyzed decarbonylation of phthalimides. In general, they can be summarized as two aspects: (1) As a result of the strong π\(_{\text{back}}\)-*C=O conjugation, direct oxidative addition of the C–N bond with transition metals has always been a challenging topic.\(^11\) (2) Because of the π-back-bonding between the CO p* orbitals and metal center d orbitals, breaking the metal–carbonyl bond is another challenge (Scheme 1).\(^12,13\)

Historically, the field of Ni-catalyzed decarbonylative addition reactions of phthalimides with alkynes was launched by the Matsubara and Kurahashi group in 2008.\(^14\) They also found that 1,3-dienes\(^15\) and trimethylsilyl-substituted alkynes\(^16\) were suitable substrates in Ni-catalyzed decarbonylative addition reactions with phthalimides. Apart from nickel catalysts, in the past decade, Pd\(^17\), Rh\(^18\), Co\(^19\), and Ru\(^20\) have been developed for use in decarbonylation and derivatization reactions of phthalimides by our group and others. In some cases, the reactions are not only facilitated by the typical reactivity of phthalimides but also enabled by a directing group on the phthalimides. At present, transition-metal-catalyzed decarbonylation of phthalimides represents an attractive method for the construction of a wide variety of polysubstituted amides.

In this Short Review, we mainly focus on recent advances in transition-metal-catalyzed decarbonylation and derivatization reactions of phthalimides. For a better discussion and understanding, this review is arranged by the type of addition or coupling components. Throughout the review, we give special attention to the reaction mechanism to reveal versatile achievements, especially in the decarbonylation step. Furthermore, we summarize the unique synthetic advantages of the developed decarbonylation reactions, which will definitely further expand their application and promote development in this field.

## 2 Decarbonylative Addition Reaction with Alkynes

### 2.1 Nickel Catalysis

In 2008, the Kurahashi and Matsubara group reported the first example of a nickel-catalyzed decarbonylative addition reaction of phthalimides with alkynes (Scheme 2).\(^14\) With the oxidative addition of nickel into the N–C(O) bond of phthalimide, decarbonylation and alkyne insertion steps subsequently took place. Overall, the nickel–catalyzed intermolecular carboamination of alkynes had been developed in a single step by forming the C–C and C–N bonds simultaneously. In fact, direct oxidative addition of an Ni(0) catalyst into a C–N bond generated the active species, which was the main challenge. The authors postulated that in-
creasing the nucleophilicity of the nickel catalyst and the electrophilicity of the carbonyl group of the imide would conquer the obstacles. In particular, electron-donating PMe3 ligands promoted the transformation and gave the desired product in 18% isolated yield. In addition, trace or lower amounts of 1 were obtained by using PbBu3, PCy3, and PPh3 in place of PMe3 (17%, 11%, and 8% yields, respectively) (Scheme 2a). Furthermore, the reaction of N-phenylphthalimides 2 possessing an electron-withdrawing group afforded the correspondingly product in 34% yield. Subsequently, they found that electron-deficient N-arylphthalimides 3–5 could react with alkynes efficiently and gave the desired products in approximately 90% yields (Scheme 2a).

Interestingly, different types of alkynes exhibited various reactivities. Unsymmetrical dialkyl alkynes 6 and 7 gave products in excellent yields but with low regioselectivities (1:1 to 2:1). Symmetrical diphenyl alkene 8 reacted slowly and gave the corresponding isoquinoline in moderate yield. Terminal phenylacetylene 9 failed to participate in the reaction, presumably because of rapid oligomerization (Scheme 2b).

A plausible mechanism for the nickel-catalyzed decarbonylative addition reaction of phthalimides with alkynes is depicted in Scheme 3. Firstly, with the help of the electron-rich phosphine ligand, Ni(0) undergoes oxidative addition to give the nickelacycle 10. Subsequent decarbonylation and insertion of alkynes to the C–Ni bond leads to the seven-membered nickelacycle complex 12, which undergoes reductive elimination to give desired product 13 with regeneration of the initial Ni(0) complex.20

![Scheme 3 Plausible pathway for Ni-catalyzed decarbonylative addition](image)

In subsequent research, a distinct decarbonylative addition reaction was reported by the Kurahashi and Matsubara group in 2010.15 An unprecedented nickel and Lewis acid cocatalyzed decarbonylative reaction pattern occurred in this reaction. It provided isoindolinone products instead of isoquinolones when the Lewis acid methylaluminum bis(2,6-di-tert-butyl-4-methylphenoxide) (MAD) was added as a cocatalyst (Scheme 4).

![Scheme 4 Selectivity for synthesis of isoquinolones or isoindolinones affected by Lewis acids](image)

For this decarbonylative alkylidenation reaction, the Lewis acids and ligands played major roles in selective regulation. These effects are summarized in Scheme 5a. According to the previous vicinal addition conditions, when phthalimide 14 and alkene 15 were treated in the presence of Ni(cod)2 (10 mol%) and PMe3 (40 mol%) for 2 h, only a trace amount of isoindolinone 16 was observed (entry 1). However, 16 could be obtained in 20% yield in the presence of 20 mol% trimethylaluminum (entry 2). The addition of a catalytic amount of MAD, a sterically bulky and monomeric homogeneous Lewis acid, gave the best results and afforded 16 in 56% yield (entry 3). Finally, 16 was obtained in 82% yield by decreasing the loading of ligands to 20 mol% (entry 4).

© 2022. Thieme. All rights reserved. Synthesis 2022, 54, 2561–2573
Intermediate groups and the phosphine ligands on the nickel provides in-...silylindolinone products and regenerates the initial Ni(0) cata-

...tively (Scheme 5b).

As shown in Scheme 6, the proposed mechanism began with the oxidative addition of an Ni(0) complex to an imide N–(CO) bond with the help of MAD. Subsequent decarbonylation, coordination, and isomerization gives cyclic cation-

...natively (Scheme 5b).

As shown in Scheme 6, the proposed mechanism began with the oxidative addition of an Ni(0) complex to an imide N–(CO) bond with the help of MAD. Subsequent decarbonylation, coordination, and isomerization gives cyclic cationic nickel complex 25. The electron-rich phosphate ligands play very important roles in the stability of 25. Nucleophilic addition of alkynes then takes place to afford cationic nickel disubstituted vinylidene intermediate 26 via a silyl group [1,2]-shift. Finally, reductive elimination furnishes the iso-

...[20 mol%] 16/17: 82%/7%/3%
5 P(10 mol%) MAD 16/17: 35%/3%/8%

Scheme 5 Nickel-catalyzed decarbonylative alkyldenation of phthalimides with trimethylsilyl-substituted alkynes

With the best conditions in hand, the researchers investigated the effects of substituents on the alkyne. A wide range of substituted alkynes were compatible with the reaction conditions and produced the correspondingly substituted isoindolinones 18–23 in moderate yields. Electron-donating methoxy-substituted alkynes reacted with 14 to afford 22 and its isomer 23 in 53% and 21% yields, respectively (Scheme 5b).

As shown in Scheme 6, the proposed mechanism began with the oxidative addition of an Ni(0) complex to an imide N–(CO) bond with the help of MAD. Subsequent decarbonylation, coordination, and isomerization gives cyclic cationic nickel complex 25. The electron-rich phosphate ligands play very important roles in the stability of 25. Nucleophilic addition of alkynes then takes place to afford cationic nickel disubstituted vinylidene intermediate 26 via a silyl group [1,2]-shift. Finally, reductive elimination furnishes the isoindolinone products and regenerates the initial Ni(0) catalyst. Notably, steric hindrance between the trimethylsilyl groups and the phosphine ligands on the nickel provides intermediate 27, rather than 27'.
GC-MS with silver oxide added as the oxidant. Carbon dioxide was detected as the major gas component, which suggested that the silver oxide acted as a CO scavenger in the cobalt-catalyzed decarbonylation. The corresponding alkyne insertion and cyclization product was not detected when nitro-group-substituted 36 was treated under the standard conditions. Only decarbonylative product 37 was obtained in 45% yield. Product 37 could be obtained in 90% yield with external water as an additive (Scheme 8a).

A proposed cobalt catalytic cycle is depicted in Scheme 8b. Firstly, Co(II) undergoes disproportionation to form the active Co(I) species. By means of oxidative addition, Co(I) activates the C–N bond of the phthalimide to form Co(III) intermediate 38. Subsequent decarbonylation leads to cobalt complex 39. As a CO scavenger, external oxidant Ag₂CO₃ facilitates the formation of active aryl-Co intermediate 40. The alkyne undergoes coordination and migratory insertion to afford seven-membered cobaltacycle complex 41. The final reductive elimination process produces the desired isoquinolone product and regenerates the Co(I) catalyst.

2.3 Rhodium Catalysis

The pioneering work on RhCl(PPh₃)₃ mediated decarbonylative reactions of aldehydes was done by Tsuji and Ohno.¹⁻²¹ In this reaction, π-backbonding between CO and Rh impeded the ligand dissociation step to regenerate the Wilkinson’s catalyst under mild conditions. To solve this problem, scientists were forced to adopt the thermal dissociation (usually at 110–200 °C) of CO from the resting state of the catalyst to facilitate catalytic regeneration. Therefore, it was of great interest to develop mild conditions for the catalytic decarbonylation.

In 2020, Chen and co-workers reported a Rh catalyzed decarbonylative addition reaction using visible light to promote the decarbonylation process (Scheme 9).¹⁻²⁸ An initial investigation suggested the functional group on the nitrogen atom of the imide played an important role in the reaction outcomes (Scheme 9a). Under thermal-induction conditions (150 °C), low yields (11–45%) could be obtained with pyridyl or quinolinyl as the functional group. Under photoinduced conditions (450–455 nm, 40 °C), a dramatic functional group effect was observed in that only the quinoline-substituted substrates delivered the expected cross-addition products in 80% yield. These initial results indicated that the functional group played a bifunctional role as a directing group and an energy-transfer promoter.
The generality of the alkyne and phthalimide substrates was subsequently investigated. A series of terminal alkynes could be well tolerated and delivered isoquinolones 45–48 in 28–42% yields, which were unusual because of the existence of a dominant [2+2+2] cycloaddition side reaction. Furthermore, unsymmetrical phthalimides possessing a methoxy group on the 6-position of the quinoline ring successfully furnished the regiospecific products 49 and 50 in 75–81% yield, which constituted an important complement to the reported C–H activation strategies for 5-substituted isoquinolinone synthesis (Scheme 9b).

To elucidate the role of visible light, the researchers performed some control experiments (Scheme 10a). After light irradiation and subsequent purification, the reaction of [RhCl(C₂H₄)₂]₂ with phthalimide slowly generated the unexpected saturated coordination complex 51 (18-electron). In the absence of visible light irradiation, no Rh complexes were formed and only phthalimide 33 was recovered in 72%. The UV/Vis absorption spectra of 51 showed a strong absorbance in the region of 390–420 nm. No desired product was observed in the absence of light. Under light irradiation, 44 was obtained in 95% yield. Overall, the above results suggest that the rhodium complex simultaneously served as the catalytic center and a photosensitizer for decarbonylation.

A plausible mechanism is depicted in Scheme 10b. The reaction is initiated from the oxidative addition of the Rh(I) species into the phthalimide C–N bond to form Rh(III) intermediate 52. Subsequent deinsertion of carbon monoxide breaks the C–C bond to give Rh complex 53. Under visible light irradiation, the excited state Rh complex 53* is generated, in which the transfer of an electron from the anti-bonding Rh–CO orbital into the antibonding orbital decreases the bond dissociation energy of the Rh–CO bond. This leads to subsequent CO extrusion under mild conditions to give the Rh intermediate 54 with a vacant coordination site. The coordination and migratory insertion of the alkyne delivered the seven-membered Rh complex 55, which underwent reductive elimination to form the isoquinoline and regenerated the Rh(I) catalyst.

Notably, during the process of the Chen group’s study,18b a thermally induced decarbonylative addition of imides with alkynes was reported by Xu et al.18a It should be noted that high temperature (140 °C) and a high catalyst loading (5 mol%) were essential for this reaction (Scheme 11).
3 Decarbonylation Additive Reaction with Alkenes

3.1 Nickel Catalysis

Similar to the Ni-catalyzed decarbonylation cycloaddition of phthalimides with alkynes, the Kurahashi and Matsubara group reported a decarbonylation cycloaddition of phthalimides with 1,3-dienes in 2010, which provided 3-vinylidihydroisoquinolones regioselectively. The reaction presented an unprecedented replacement reaction of a carbon monoxide by a C–C single bond of a readily available heterocyclic compound (Scheme 12). In this reaction, screening of ligands showed that PMe₃ gave the highest yield. Pyrrolyl as the N-substituent group gave a higher reaction yield than other groups.

4 Decarbonylation Additive Reaction with Benzyne

4.1 Palladium Catalysis

Inspired by the Ni(0)-catalyzed decarbonylation additive reaction of phthalimides with alkynes, in situ formed aryynes were chosen as additive partners. In 2019, Meng, Xu and co-workers reported the first palladium-catalyzed decarbonylation annulation reactions of phthalimides with aryynes for the synthesis of phenanthridinones, which are widely present in various bioactive natural products and pharmaceuticals (Scheme 14a). The reactions gave moderate to high yields under the optimized conditions. Both electron-donating and electron-withdrawing groups were tolerated with phthalimides and aryynes. However, the optimized conditions could not control the regioselectivity satisfactorily when unsymmetric phthalimides or aryne precursors were used as substrates (e.g., 70 and 70') (Scheme 14a).
To gain insight into the reaction mechanism, the reaction of Pd(PPh₃)₄ with phthalimides and Kobayashi benzyne precursor 71 was performed. As expected, the stable Pd(II) complex 72 was formed, for which the structure and relative stereochemistry were rigorously confirmed by X-ray crystallography (Scheme 14b).

Based on the X-ray crystallography result of intermediate 72 and previous research reported by the Matsubara and Kurahashi group, a plausible mechanism was proposed and is shown in Scheme 15. The decarbonylative process is similar to the pathways mentioned in previous research. Elimination of the TMS and OTf groups in 71 generates an active benzyne species, which undergoes insertion of the C–C triple bond into the Pd–aryl complex. A final reductive elimination of 75 leads to the product.

### 5 Decarbonylative Polymerization

#### 5.1 Nickel Catalysis

Decarbonylative annulations of phthalimides with alkynes could also be applied as an elementary step for polymerization. In 2012, Takeuchi et al. managed to synthesize polyisoquinolones by using alkynyl-substituted phthalimides as original monomers (Scheme 16). A methoxy moiety was introduced at the ortho position of the amide to serve as a directing group in regioselective oxidative addition of Ni(0). Single monomer products of polyisoquinolones were successfully obtained by using this strategy (Scheme 16b).
6 Decarbonylative Alkylation

6.1 Nickel Catalysis

In 2011, Johnson and co-workers discovered that nickel-mediated cross-coupling of phthalimides with diorganozinc reagents could proceed via a decarbonylative process to produce ortho-alkyl-substituted benzamides (Scheme 17).\(^{26}\) Significantly, the yields of these reactions were closely matched to the nickel loading, suggesting a failure of nickel catalytic turnover. No desired products were observed when the reactions were performed in the absence of ligands or nickel catalysis (entries 2 and 3). In addition, Ni(COD)\(_2\) also proved to be a viable metal source for the reaction (entry 4).

Furthermore, the ketamide product anticipated from direct coupling of the imide and diethylzinc was not observed. It was presumed that an Ni–CO complex was formed after one catalytic cycle, which indicated that the strong Ni–CO bond prevented regeneration of the Ni(0) species. To circumvent this problem, the authors tried using various π-accepting ligands combined with different solvents. However, none of the conditions led to the expected decarbonylative coupling products. Based on previous studies about the influences of N-protecting groups, the authors chose electron-withdrawing groups on N-substituents (84–87), which enabled the reaction to proceed with a catalytic amount of nickel catalysis (Scheme 18a).\(^{27}\) The results indicated that CO dissociation was prior to N dissociation from the metal center. Apart from electron-withdrawing N-protecting groups, electron-deficient ortho substituents would also facilitate the catalytic process and only a single regioisomer was formed when o-fluorinated phthalimide was used as the substrate.

The proposed mechanism is presented in Scheme 18b. Firstly, the active Ni(0) complex undergoes oxidative addition to generate metallacycle intermediate 88, which undergoes decarbonylation and transmetalation to generate complex 90. Reductive elimination and acid workup give the ortho-substituted benzamides and regenerated Ni–CO complex. In a potential alternative, 88 could undergo transmetalation prior to decarbonylation, which would generate complex 91.

7 Decarbonylative Arylation

7.1 Palladium Catalysis

In 2019, Samanta and Biswas reported the Pd-catalyzed decarbonylative arylation of phthalimide with aryl halides (Scheme 19).\(^{172}\) No ligands were required for this transformation. On the contrary, introduction of a ligand into the system led to decreased yields. The base and solvent had a significant impact on the reactivity, because they could participate in the regeneration of the catalytically active Pd(0) species.

A wide range of substituted phenyl and heterocyclic halides were well tolerated in this system, and the reactivity of aryl iodide was slightly better than aryl bromide (Scheme 19). A sterically demanding aryl N-protecting group was also tolerated. However, an N-protecting group

© 2022. Thieme. All rights reserved. Synthesis 2022, 54, 2561–2573
containing a strong coordinating atom inhibited the reaction by forming a stable Pd(II) complex.

Based on several control experiments, the authors proposed a mechanism (Scheme 20). Firstly, Pd(II) is reduced to Pd(0) by DMF and base. The Pd(0) species is then inserted into the amide C–N bond by oxidative addition. After thermal decarbonylation, the aryl halide reacts with Pd(II) species 99 via oxidative addition to generate Pd(IV) species 100. The product is obtained from intermediate 101 and the Pd(0) is regenerated in the presence of DMF.

7.2 Nickel Catalysis

In 2020, Johnson and co-workers reported Ni(0)-mediated decarbonylative coupling of phthalimides with aryl boronic acids. Relative to diorganozinc as the transmetalation reagent, aryl boronic acid was more compatible with active groups such as ketones and esters (Scheme 21). In addition, the steric effect of aryl boronic acid had almost no effect on the reactivity. The proposed mechanism was similar to that of the Ni-catalyzed alkylation reported by the same group in 2016. However, similar to their previous report in 2011, this reaction required a stoichiometric amount of Ni(0), which might indicate that the strong binding force of Ni–CO inhibited the catalytic cycle. Introduction of electron-withdrawing groups to the N atom of the phthalimide also failed to facilitate dissociation of the CO ligand.

8 Protodecarbonylation

8.1 Ruthenium Catalysis

In 2020, Gramage-Doria and co-workers reported an unexpected protodecarbonylation of phthalimides into amides. These Ru-catalyzed decarbonylative transformations were achieved in high yields and short reaction times (113–124). However, satisfactory results were not achieved with selective decarbonylation of phthalimide substituted with aromatic rings (125 and 126) (Scheme 22a). Notably, the reaction with the six-membered-ring phthalimide 127 did
not proceed under standard conditions, indicating that the ring strain released in the six-membered-ring phthalimide was probably the driving force for the initial step of the catalytic cycle. Furthermore, substrates 128–130 bore structural resemblance to phthalimides that did not react in the protodecarbonylation reaction (Scheme 22b).

To gain insight into the reaction mechanism, the gas phase of the reaction mixture was analyzed by GC. Differently from the traditional decarbonylation reaction mechanism, CO was not formed in this system. Instead, H2 and CO2 were detected by GC. The reaction only gave 8% yield of product when 1 bar of H2 was introduced into the system, which indicated that H2 did not participate in the catalytic cycle. Full incorporation of deuterium at the ortho position of the product suggested that H2O was the proton source. Interestingly, the reaction without H2O also achieved 56% yield. The authors argued that a trace amount of water in K2CO3 might still serve as a proton source and the use of overnight-dried K2CO3 powder led to a slightly decreased yield, which supported this opinion to a certain extent.

A mechanism is tentatively postulated in Scheme 23. Firstly, a ruthenium chloride-free species is formed after the reaction of [RuCl2(p-cymene)]2 with K2CO3. N- or O-coordination of the Ru species to 131 led to 133 or isomers. After ring opening, 134 was formed. Hydroxylolation followed by release of a proton or hydrogen leads to 135. After decarbonylation, ruthenacycle complex 136 was formed. Finally, 137 was obtained after protonolysis of 136, and the Ru catalyst was regenerated.

Later, the authors discovered that using KOH instead of K2CO3 led to the formation of the hydrolysis product. DFT calculations were applied to explain this phenomenon (Scheme 24). However, according to the DFT results, CO2 was generated by K2CO3, which seemed to contradict the role of H2O as the source of H2 proposed in their previous report.

Ruthenium-catalyzed protodecarbonylation of phthalimide derivatives into secondary amides needed to release two molecules of CO2. One came from the carbonyl group of the substrate, and the other came from K2CO3. Moreover, the potassium cations were relevant for stabilizing all of the intermediates via weak interactions. When the base additive was switched to KOH, high temperature led to the formation of secondary amides, and low temperature yielded the phthalamic acid derivative products. Interestingly, it was found that the ruthenium center exhibited an oxidation state of +2 through the whole catalytic cycle.

Phthalimides, and N-aryl phthalimides in particular, are prone to hydrolysis followed by decarboxylative coupling. Some examples discussed likely involve hydrolysis or a decarboxylative coupling mechanism. In terms of the net transformation, this is a protodecarbonylation process.

9 Conclusion and Outlook

To conclude, transition-metal-catalyzed decarboxylative reactions of phthalimides have exhibited unique and diverse chemical reactivities over the past decades. Initially, Matsubara group reported the first example of nickel-catalyzed decarboxylative addition of phthalimides to alkynes. In recent years, decarboxylative processes with other transition-metal catalysts, including Rh, Pd, Ru, and Co catalysts.
Phthalimides with other units under mild conditions require electron-withdrawing N-protecting groups or directing groups on the phthalimides. The innovative designs of more efficient catalyst systems to solve these limitations continue to be important issues in this area.

Although studies of the transition-metal-catalyzed decarbonylative reactions of phthalimides have been described, the synthetic application of these protocols is still in its infancy and needs profound explorations. Phthalimides can also react with other unsaturated congeners, such as allenes, cyanides, isocyanides, and azide compounds. Their chemoselectivities and regioselectivities need careful regulation as well. This Short Review is intended to be a foundation for the further developments of novel strategies to achieve decarbonylative derivatizations by using mild and sustainable conditions.

**Conflict of Interest**

The authors declare no conflict of interest.

**Funding Information**

Financial support from the National Natural Science Foundation of China (Grant Nos. 21971234, 21772194, and 21572225) is acknowledged.

**References**


3. (a) Keating, G. M. Drugs 2017, 77, 459. (b) Deeks, E. D. Drugs 2020, 80, 181.


